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REVIEW

Anti-angiogenic agents in metastatic colorectal cancer

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Abstract

Colorectal cancer (CRC) is a major public health concern being the third leading cause of cancer mortality in the United States. The availability of better therapeutic options has led to a decline in cancer mortality in these patients. Surgical resection should be considered in all stages of the disease. The use of conversion therapy has made surgery a potentially curative option even in patients with initially unresectable metastatic disease. In this review we discuss the role of various anti-angiogenic agents in patients with metastatic CRC (mCRC). We describe the mechanism of action of these agents, and the rationale for their use in combination with chemotherapy. We also review important clinical studies that have evaluated the safety and efficacy of these agents in mCRC patients. Despite the discovery of several promising anti-angiogenic agents, mCRC remains an incurable disease with a median overall survival of just over 2 years in patients exposed to all available treatment regimens. Further insights into tumor biology and tumor microenvironment may help improve outcomes in these patients.

Key words: Anti-angiogenic agents; Metastatic colorectal cancer; Targeted agents; Conversion therapy; Colorectal metastasectomy

Core tip: Colorectal cancer is a major health concern and a leading cause of cancer mortality worldwide. New innovations have provided improved survival in recent years. In this review, we outline the novel anti-angiogenic agents and their respective roles in metastatic colorectal cancer. In addition to three agents approved by the Food and Drug Administration, several alternative anti-angiogenic agents hold promise for use in the metastatic setting.

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INTRODUCTION

The past decade has seen a significant decline in the incidence rate and cancer mortality in patients with colorectal cancer (CRC) in the United States. The decrease in cancer deaths appears to be due largely to the widespread use of screening colonoscopy and the availability of better treatment options. However, from a public health perspective, CRC remains a major concern, with 136830 new cases estimated to be diagnosed and over 50000 deaths predicted to occur in the United States alone in 2014. Today, CRC is the third leading cause of cancer mortality in the United States, surpassed only by lung cancer, breast cancer in women and prostate cancer in men[1].

Surgery remains the mainstay of treatment in patients with early stage and locally-advanced CRC and should be considered for those with metastatic CRC (mCRC) with liver-only or lung-only metastases. Though only 10%-20% of patients with liver-only metastases are resectable at the time of diagnosis[2], the use of conversion therapy can make up to 61.9% of tumors resectable[3].

Since the discovery of 5-fluorouracil (5-FU) in 1957[4], several chemotherapeutic agents have been approved for the treatment of mCRC, including capecitabine, oxaliplatin, and irinotecan. Insights into the molecular mechanisms of disease led to the discovery of biologic agents targeting tumor vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). This review focuses on the anti-angiogenic agents used in the treatment of mCRC.

BIOLOGICAL BASIS OF ANTI-ANGIOGENIC THERAPY

Tumor cells and endothelial cells are inter-dependent for their growth *via* a carefully regulated system[5]. Pre-clinical studies have shown that implanted tumor cells can only grow to a size of 2-3 mm without neovascularization. They can remain dormant for several years or switch to an angiogenic phenotype[6]. Tumor cells with the angiogenic phenotype release growth factors (pro-angiogenic factors) which stimulate endothelial proliferation, migration, and formation of new capillaries. This process is called tumor angiogenesis and leads to tumor perfusion, growth, and metastases[5,7]. Hematopoietic stem cells and circulating endothelial progenitor cells (CEPs), which are bone marrow derived rapidly proliferating cells, are also thought to contribute to tumor angiogenesis[8].

Vascular endothelial growth factor (VEGF) is one of the most extensively studied pro-angiogenic factors. It is produced by normal and certain neoplastic cells (such as CRC cells)[9]. The human VEGF family is primarily composed of 5 glycoproteins (VEGF A, B, C, D, and platelet derived growth factor, or PlGF). These proteins exert their effects by binding to receptor tyrosine kinases (VEGFR1, R2, and R3)[9-11]. VEGF-A is commonly referred to as VEGF or vascular permeability factor (VPF) and is first discovered by Senger *et al*[12].

Tissue hypoxia (*via* hypoxia inducible factor), growth factors (*e.g.*, epidermal growth factor, insulin like growth factor-1), and oncogenes (*e.g.*, c-Src proto-oncogene) increase VEGF expression[9,13,14]. VEGF then exerts its angiogenic effects predominantly *via* VEGFR2; however, the role of VEGFR1 remains unclear[15]. VEGF promotes tumor angiogenesis by increasing permeability of post-capillary venules, which subsequently leads to the leakage of plasma proteins such as fibrinogen and clotting factors into the extracellular matrix (ECM). Fibrinogen is converted to fibrin in the ECM which leads to increased endothelial cell migration and proliferation[16]. VEGF is also an endothelial cell mitogen[13] and causes endothelial cell proliferation by activating members of the MAP kinase and protein kinase C pathways[9]. Other pro-angiogenic factors include hepatocyte growth factor (HGF), axon guidance factors, interleukins (IL-1, 6, 8, and stromal cell derived factor 1), fibroblastic growth factors (FGF 1 and 2), angiopoietins, and pro-angiogenic chemokines[17]. Another important regulator of angiogenesis is the tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2) expressed primarily on endothelial cells. TIE2 interacts with angiopoietin 1, angiopoietin 2, VEGF, and FGF to cause maturation of immature blood vessels[18].

The use of anti-angiogenic therapy to arrest tumor growth and thereby make these tumors more susceptible to chemotherapy and cell-mediated immunity was first proposed by Folkman[5] in 1971. Angiogenesis inhibitors can be broadly classified into 2 groups, direct and indirect anti-angiogenic agents. Direct angiogenic inhibitors act on endothelial cells of the microvasculature, thus inhibiting their response to angiogenic stimuli. Indirect angiogenic inhibitors on the other hand target pro-angiogenic stimuli either at the level of the ligand (*e.g.*, VEGF inhibition) or at the level of the receptor (*e.g.*, VEGFR inhibition)[19].

ANTI-ANGIOGENIC AGENTS IN THE TREATMENT OF UNRESECTABLE mCRC

Bevacizumab is an IgG1 monoclonal antibody against the VEGF-A ligand that was developed by humanization of the murine anti-human VEGF antibody A.4.6.1[20,21]. It was the first anti-angiogenic agent to be FDA-approved in the treatment of mCRC in combination with chemotherapy[22]. Adverse effects include hypertension, proteinuria, hemorrhage, GI perforation, delayed wound healing, and arterial and venous thromboembolism[23,24]. Hypertension is a common side effect of bevacizumab therapy, with more than half of the patients requiring pharmacologic intervention. It has been hypothesized

Table 1 Bevacizumab in the first-line setting in metastatic colorectal cancer

Ref.	Regimen	PFS (mo)	*P* value	OS (mo)	*P* value
Kabbinavar *et al*[26]; Phase Ⅱ	[1]Bolus 5-FU/LV ± bevacizumab	9 *vs* 5.2 (TTP[3])	NA	21.5[2] *vs* 13.8	NA
Kabbinavar *et al*[27]; Phase Ⅱ	[1]Bolus 5-FU/LV + bevacizumab *vs* bolus 5-FU/LV + placebo	9.2 *vs* 5.5	0.0002	16.6 *vs* 12.9	0.16
Hochster *et al*[35]; Phase Ⅱ (TREE-1)	mFOLFOX6/bFOL/CapeOX	8.7/6.9/5.9 (TTP[3])	N/A[4]	19.2/17.9/17.2 18.2 (overall)	N/A[4]
Hochster *et al*[35]; Phase Ⅱ (TREE-2)	mFOLFOX6 + bevacizumab/bFOL + bevacizumab/CapeOX + bevacizumab	9.9/8.3/10.3 (TTP[3])		26.1/20.4/24.6 23.7 (overall)	
Hurwitz *et al*[22]; Phase Ⅲ	IFL + bevacizumab *vs* IFL + placebo	10.6 *vs* 6.2	< 0.001	20.3 *vs* 15.6	< 0.001
Stathopoulos *et al*[115]; Phase Ⅲ	IFL ± bevacizumab	NA	NA	22 *vs* 25	0.1391
Saltz *et al*[29]; Phase Ⅲ	FOLFOX/CapeOX + bevacizumab *vs* FOLFOX/CapeOX + placebo	9.4 *vs* 8	0.0023	21.3 *vs* 19.9	0.077

[1]Roswell Park regimen: LV 500 mg/m^2 over 2 h and FU 500 mg/m^2 as a bolus midway through the LV infusion; [2]Data presented is on patients who received chemotherapy plus low-dose bevacizumab; [3]Time to progression; [4]Comparison between outcomes of TREE-1 and TREE-2 is not possible as they were sequential cohorts. 5-FU: 5-Fluorouracil; LV: Leucovorin; PFS: Progression-free survival; OS: Overall survival; mFOLFOX6: Three fluoropyrimidine regimens-infusional 5FU/LV; bFOL: Bolus FU/LV; CapeOX: Capecitabine; FOLFOX: 5-FU/LV/oxaliplatin; NA: Not available; N/A: Not applicable.

that VEGF inhibition leads to a decrease in nitric oxide synthase, leading to inhibition of vasodilation. In addition, bevacizumab decreases arteriolar and capillary perfusion leading to increased peripheral vascular resistance and hypertension[25]. The hemorrhage and thrombosis paradox of bevacizumab therapy can be explained by the disruption in hemostasis secondary to VEGF inhibition. VEGF inhibition leads to apoptosis of quiescent endothelial cells, which in turn leads to activation of the extrinsic coagulation pathway. This mechanism lends credence to the prothrombotic properties of bevacizumab. Inhibition of angiogenesis and platelet function are thought to contribute to hemorrhage and impaired wound healing related to bevacizumab therapy. Proteinuria as a consequence of bevacizumab therapy is common and is secondary to renal thrombotic microangiopathy leading to glomerular endothelial injury[25].

Bevacizumab in treatment-naive patients

Bevacizumab has been extensively studied in several clinical trials with favorable results (Table 1). The combination of bevacizumab and bolus 5-FU/leucovorin (LV) chemotherapy was compared to bolus 5-FU/LV alone in treatment-naive mCRC patients in a phase Ⅱ randomized study by Kabbinavar *et al*[26] in the year 2003. The addition of low-dose bevacizumab led to higher response rates (40% *vs* 17%), longer time to disease progression (9 mo *vs* 5.2 mo), and a longer median overall survival (OS) (21.5 mo *vs* 13.8 mo) in these patients[26]. In another phase Ⅱ trial comparing first-line bevacizumab plus chemotherapy (bolus 5-FU/LV) to chemotherapy alone in mCRC patients who were poor candidates for irinotecan therapy, a 3.7 mo progression-free survival (PFS) advantage was noted in the group that received bevacizumab (9.2 mo *vs* 5.5 mo; HR, 0.50; *P* = 0.0002). There was a trend toward a longer median OS in the bevacizumab-containing group; however; this difference was not statistically significant (16.6 mo *vs* 12.9 mo; HR, 0.79; *P* = 0.16)[27].

Subsequently, a large randomized phase Ⅲ trial compared the use of bevacizumab plus irinotecan, bolus 5-FU/LV (IFL) *vs* IFL plus placebo as front-line therapy. The addition of bevacizumab not only conferred a benefit in median OS (20.3 mo *vs* 15.6 mo; HR, 0.66; *P* < 0.001) and PFS (10.6 mo *vs* 6.2 mo; HR, 0.54; *P* < 0.001), but also led to higher response rates (44.8% *vs* 34.8%; *P* = 0.004) and more durable responses (10.4 mo *vs* 7.1 mo; *P* = 0.001)[22]. The results of this trial led to the FDA approval of bevacizumab for use as a first-line agent in mCRC patients in combination with chemotherapy. In a combined analysis of 2 phase Ⅱ (53, 54) and 1 phase Ⅲ study[22], patients in the 5-FU/LV/bevacizumab arm had a statistically significant improvement in median OS (17.9 mo *vs* 14.6 mo; HR, 0.74; *P* = 0.008) and median PFS (8.8 mo *vs* 5.6 mo; HR, 0.63; *P* ≤ 0.0001) when compared to the chemotherapy-only arm (patients receiving 5-FU/LV or IFL)[28]. However, in another phase Ⅲ randomized trial comparing IFL with and without bevacizumab, the addition of bevacizumab did not confer an OS advantage (22 mo in the IFL-bevacizumab arm *vs* 25 mo in the IFL arm; *P* = 0.1391)[28]. With the emergence of combination chemotherapy regimens [5-FU/LV/oxaliplatin (FOLFOX), and 5-FU/LV/irinotecan (FOLFIRI)], subsequent studies focused on testing the efficacy and safety of these regimens in combination with bevacizumab. In a randomized phase Ⅲ study by Saltz *et al*[29], untreated mCRC patients were randomized to receive either bevacizumab or placebo in combination with chemotherapy (FOLFOX-4 or Cape-OX). Though the effect size was small, a PFS advantage was seen in the bevacizumab-containing arm (9.4 mo *vs* 8 mo; HR, 0.83; *P* = 0.0023), however there was no statistically significant difference in median OS between the two groups (21.3 mo *vs* 19.9 mo; HR, 0.89; *P* = 0.077). An interesting observation in this study that the authors effectively point out is the similar median treatment duration of

patients receiving bevacizumab and placebo (approximately 6 mo), in contrast to the significantly longer PFS (as noted above) in the bevacizumab arm. The early discontinuation of bevacizumab (prior to disease progression) probably explains the absence of a survival advantage in the bevacizumab-containing arm. The authors concluded that continuation of bevacizumab until disease progression is critical for a meaningful clinical benefit[29].

A randomized head-to-head comparison of FOLFIRI with and without bevacizumab has not been done to date. However, sufficient evidence to justify the use of FOLFIRI plus bevacizumab in untreated mCRC patients exists. In a pooled analysis on 29 published trials, patients who received FOLFIRI-bevacizumab had a median PFS of 10.8 mo (95%CI: 8.9-12.8) and a median OS of 23.7 mo (95%CI: 18.1-31.6)[30]. In an open-label, phase Ⅳ AVIRI study, patients who received first-line FOLFIRI plus bevacizumab had a PFS of 11.1 mo and a median OS of 22.2 mo[31]. A phase Ⅲ trial of 285 patients compared efficacy of CapeIri plus bevacizumab with FOLFIRI plus bevacizumab. There was no difference in PFS (10.2 mo *vs* 10.8 mo; P = 0.74), or median OS (20.0 mo *vs* 25.3 mo, P = 0.099) between the two groups[32].

After the Gruppo Oncologico Nord Ovest (GONO) group showed that 5-FU/LV/oxaliplatin/irinotecan (FOLFOXIRI) improved response rate (RR), PFS, and OS in treatment-naive unresectable mCRC patients in a phase Ⅲ randomized trial[33], the addition of bevacizumab to FOLFOXIRI was compared to FOLFIRI plus bevacizumab by the same group of investigators. The latter trial was also a phase Ⅲ randomized trial (TRIplet plus BEvacizumab, or TRIBE), which showed that patients receiving triplet chemotherapy (FOLFOXIRI) plus bevacizumab had a longer PFS (primary end point; 12.1 mo *vs* 9.7 mo; HR, 0.75; P = 0.003) and better objective response rate (65% *vs* 53%; P = 0.006) when compared to those receiving FOLFIRI plus bevacizumab. Though patients in the FOLFOXIRI arm had a longer median OS when compared to those in the FOLFIRI arm, this difference was not statistically significant (31.0 mo *vs* 25.8 mo; HR, 0.79; P = 0.054). Not surprisingly, patients who received the triplet chemotherapy regimen plus bevacizumab had a significantly higher incidence of grade 3-4 neutropenia, diarrhea, stomatitis, and peripheral neuropathy when compared to the FOLFIRI plus bevacizumab arm[34].

The Three Regimens for Eloxatin Evaluation (TREE) study was initially designed to evaluate the efficacy and safety of Oxaliplatin (Eloxatin) in combination with three fluoropyrimidine regimens- infusional 5FU/LV (mFOLFOX6), bolus FU/LV (bFOL), and Capecitabine (CapeOX). When the trial was nearing completion of accrual, data on the efficacy of bevacizumab in mCRC began to emerge. The study was therefore modified to include 2 sequential cohorts of patients- the initial cohort of patients who did not receive bevacizumab (TREE-1) and a subsequent cohort of patients who received bevacizumab in combination with one of the above three chemotherapy regimens (TREE-2). The incidence of serious (grade 3/4) treatment related AEs in the first 12 wk of therapy in each of the patient groups in the TREE-2 cohort (primary end point) were 59% (mFOLFOX6/bevacizumab), 51% (bFOL/bevacizumab), and 56% (CapeOX/bevacizumab), with neutropenia, diarrhea, and nausea/vomiting being the most common AEs in each of the treatment groups respectively. The respective incidence of grade 3/4 AEs in the TREE-1 cohort were 59% (mFOLFOX6), 36% (bFOL), and 67% (Cape-OX). The overall median OS was nearly 2 years (23.7 mo) in the TREE-2 cohort, and 18.2 mo in the TREE-1 cohort[35].

Two randomized phase Ⅲ trials (FIRE-3 and CALGB 80405) compared the efficacy of cetuximab *vs* bevacizumab in combination with chemotherapy in previously untreated KRAS WT mCRC patients. The FIRE-3 study randomized patients with KRAS WT exon 2 tumors to receive either cetuximab plus FOLFIRI or bevacizumab plus FOLFIRI as front-line therapy. Though the objective response (CR/PR; primary end point) and median PFS were similar between the two groups, median OS favored the cetuximab-containing group (28.7 mo *vs* 25.0 mo; HR, 0.77; P = 0.017)[36]. The CALGB 80405 trial randomized untreated mCRC patients with KRAS WT (codons 12 and 13) tumors to receive either cetuximab or bevacizumab in combination with chemotherapy (FOLFIRI or mFOLFOX6). The OS (primary end point) and PFS were similar in both groups and the authors concluded that either regimen would be an appropriate option in these patients. It is important to note that in contrast to the FIRE-3 study, most patients (73.4%) in the CALGB 80405 study received mFOLFOX6 as their combination chemotherapy regimen[37].

Bevacizumab as maintenance therapy

Maintenance treatment in advanced CRC for the Treatment of Digestive Tumors (MACRO TTD) was the first randomized phase Ⅲ study undertaken to evaluate the role of bevacizumab alone in the maintenance setting. Patients were randomized to receive either bevacizumab alone *vs* bevacizumab plus maintenance chemotherapy (Cape-OX), after completion of induction therapy (Cape-OX + bevacizumab, or Cape-OX-B). The primary end point was PFS and the prespecified non-inferiority limit of HR for PFS was set at 1.32. After a median follow-up of 29 mo, median PFS in patient receiving maintenance Cape-OX-B *vs* Bevacizumab alone was 10.4 mo and 9.7 mo respectively. The HR for PFS was 1.10 with a 95%CI: 0.89-1.35. The study thus did not confirm non-inferiority of bevacizumab maintenance when compared to Cape-OX-B as the upper limit of the 95%CI of HR for PFS exceeded the pre-specified limit of 1.32. However, there was no statistically significant difference in PFS,

Table 2 Phase Ⅲ trials using bevacizumab in the second-line setting

Ref.	Regimen	PFS (mo)	*P* value	OS (mo)	*P* value
Giantonio *et al*[41]; (E3200)	FOLFOX4 ± bevacizumab	7.3 *vs* 4.7	< 0.0001	12.9 *vs* 10.8	0.0011
Bennouna *et al*[45]; (ML18147)	Chemotherapy ± bevacizumab	5.7 *vs* 4.1	< 0.0001	11.2 *vs* 9.8	0.0062
Masi *et al*[46]; (BEBYP)	Chemotherapy ± bevacizumab	6.8 *vs* 5.0	0.010	14.1 *vs* 15.5[1]	0.043[1]

[1]The lower median OS in the bevacizumab arm was due to intersection of curves; adjusted HR was 0.77 (stratified log-rank *P* = 0.043) and favored the bevacizumab arm. PFS: Progression-free survival; OS: Overall survival.

OS, and response rate between the two arms, with a significantly lower frequency of grade 3-4 sensory neuropathy in the bevacizumab alone group (8% *vs* 26%; *P* < 0.0001)[38].

Subsequently, the role of bevacizumab maintenance therapy in patients who had stable disease/partial response (PR)/complete response (CR) after bevacizumab-containing induction chemotherapy was evaluated in a multicenter retrospective analysis of treatment-naive mCRC patients. The study results favored bevacizumab maintenance over no maintenance therapy (PFS: 13 mo *vs* 8 mo; *P* < 0.0001). An OS advantage was only seen in those patients who received bevacizumab maintenance after they had an objective response to induction chemotherapy[39].

More recently, the role of bevacizumab plus chemotherapy as maintenance therapy was investigated in the phase Ⅲ CAIRO3 trial. After completion of six cycles of Cape-OX-B, patients were randomized to either receive maintenance therapy with capecitabine plus bevacizumab (Cape-B) or receive no further therapy. Irrespective of randomization, patients who had first progression (PFS1) received Cape-OX-B until second progression (PFS2). After a median follow-up of 2 years, maintenance therapy conferred a PFS advantage (PFS1: 8.5 mo *vs* 4.1 mo; *P* < 0.0001; PFS2: 11.7 mo *vs* 8.5 mo; *P* < 0.0001)[40]. In patients with baseline synchronous metastases and resected primary tumor, an OS benefit was noted as well (25 mo *vs* 18 mo; *P* < 0.0001)[40].

An ongoing randomized phase Ⅲ trial (NCT00973609) is evaluating three treatment strategies in mCRC patients. All patients will receive induction (and re-induction) with a 5-FU, oxaliplatin, and bevacizumab-based chemotherapy for a period of 6 mo. Induction therapy will be followed by maintenance therapy with a fluoropyrimidine and bevacizumab (active comparator), or bevacizumab alone (experimental arm) or no maintenance therapy (experimental arm).

Bevacizumab in the second-line setting

A multi-center, randomized phase Ⅲ E3200 study was pivotal in bevacizumab's approval in previously treated mCRC patients (Table 2). This study randomized patients who were previously treated with fluoropyrimidine and irinotecan to received FOLFOX-4 plus bevacizumab (group 1), FOLFOX-4 alone (group 2), or bevacizumab alone (group 3). Patients in group 1 had a longer median OS and a better PFS when compared to patients in group 2 (group 1 *vs* group 2; OS: 12.9 mo *vs* 10.8 mo; *P* = 0.0011; PFS: 7.3 mo *vs* 4.7 mo; *P* < 0.0001) and group 3 (group 1 *vs* group 3; OS: 12.9 mo *vs* 10.2 mo; PFS: 7.3 mo *vs* 2.7 mo)[41].

Bevacizumab beyond progression: The rationale behind continuing bevacizumab despite progression on bevacizumab-containing chemotherapy is that the mechanisms of resistance to cytotoxic chemotherapy and to bevacizumab differ significantly and may not necessarily occur concomitantly[42,43]. Changes in tumor cell biology and genetic instability *via* mutations in tumor suppressor genes or of drug targets, contribute to chemotherapy resistance. As anti-VEGF therapy targets the genetically stable tumor microvasculature, emergence of resistance to bevacizumab requires development of alternative proangiogenic signaling[43]. Thus, it is not unreasonable to assume that progression of disease on a combination treatment regimen (cytotoxic chemotherapy plus bevacizumab) may be secondary to resistance to chemotherapy alone and continuation of bevacizumab beyond progression in combination with a different chemotherapy regimen may be an option. This hypothesis was validated by two large observational studies[42,44] and large phase Ⅲ study (ML 18147)[45]. The BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) study was a large observational cohort study undertaken to evaluate the role of bevacizumab continuation beyond disease progression. The study enrolled 1445 mCRC patients who had progression on a first-line bevacizumab-containing treatment regimen. Patients who had received "Bevacizumab Beyond Progression" (BBP: *n* = 642) had a significantly longer median OS when compared to those who discontinued bevacizumab (no-BBP; n, 531) therapy (median OS: 31.8 mo *vs* 19.9 mo; HR, 0.49; *P* < 0.001). As would have been expected, patients in the BBP group had a higher rate of hypertension requiring medication compared to the no-BBP group or to the overall study population (24.6% *vs* 19.2%), however, the risk of serious AEs including arterial thromboembolic events, grade 3 or 4 bleeding, and GI perforation were similar between the two groups[42].

The ARIES study was another observational study that confirmed that findings of the BRiTE study. In this study, a total of 1105 patients survived longer that 2 mo after first progression, and were included in the modified ITT analysis. The median post-progression

survival was higher in the BBP group when compared to the no-BBP group [14.4 mo *vs* 10.6 mo; multivariable HR (95%CI): 0.84 (0.73-0.97)]. Protocol-specified adverse events were higher in the BBP group *vs* the no-BBP group (13% *vs* 8.5%)[44].

In order to validate the results of the BRiTE and ARIES studies, a multinational phase Ⅲ trial (ML18147) randomized mCRC patients with POD within 3 mo of discontinuation of 1st line bevacizumab plus chemotherapy, to receive 2nd line chemotherapy while continuing BBP *vs* chemotherapy alone. A total of 819 patients were included in the ITT analysis. After a median follow-up of 11.1 and 9.6 mo in the chemotherapy plus BBP group and chemotherapy alone group respectively, the median OS (primary end point) significantly favored the bevacizumab containing arm [11.2 mo *vs* 9.8 mo; HR (95%CI): 0.81 (0.69-0.94); unstratified log-rank test, 0.0062] (Table 2). Patients receiving BBP had a higher rate of grade 3-5 bleeding (2% *vs* < 1%), GI perforation (2% *vs* < 1%), and VTE (5% *vs* 3%), but as is evident from the frequency of these AE, the difference between the two arms was not considerable. Neutropenia (16% *vs* 13%), diarrhea (10% *vs* 8%), and asthenia (6% *vs* 4%) were the most common grade 3-5 adverse events and were comparable between the two arms. Also, the rate of arterial thromboembolism was not increased in the BBP group when compared to the no-BPP group. Thus, continuation of bevacizumab beyond first progression in mCRC patients significantly improved median OS without substantially increasing serious AEs[45].

The Bevacizumab Beyond Progression (BEBYP) trial (Table 2) was a phase Ⅲ, prospective, multicenter Italian study that evaluated the efficacy and safety of continuation or reintroduction of bevacizumab after first progression in patients with unresectable mCRC. The sample size was much smaller when compared to the ML18147 trial, but also included patients with POD beyond 3 mo of discontinuation of first-line therapy. PFS was the primary end point and 184 patients were included in the ITT analysis. After a median follow-up of 45.3 mo, the median PFS was noted to be significantly higher in the bevacizumab group when compared to the chemotherapy-only group (6.8 mo *vs* 5.0 mo; HR, 0.70; stratified log-tank $P = 0.010$). PFS benefit persisted when patients were stratified based on the bevacizumab-free interval (≤ 3 mo *vs* > 3 mo). An OS advantage was also noted in the bevacizumab group (adjusted HR, 0.77; stratified log-rank $P = 0.043$), though responses were comparable between the two arms (17% in the chemotherapy arm *vs* 21% in the bevacizumab arm; $P = 0.573$). Consistent with the safety data of the ML18147 trial, grade 3-4 AEs were similar between both arms[46].

Bevacizumab-based chemotherapy in the elderly

The efficacy and tolerability of bevacizumab in the elderly has been studied both in the first- and second-line settings. The BRiTE study was a large observational cohort study of 1953 untreated mCRC patients with 896 patients ≥ 65 years of age. PFS in the elderly patients was similar to their younger counterparts though median OS declined with increasing age[47]. Interestingly however, in another large observational cohort study of 1777 treatment-naive German mCRC patients, those ≥ 75 years of age had a significantly lower PFS and median OS when compared to those < 75 years of age (PFS: 10.5 mo *vs* 8.9 mo; $P = 0.00019$; OS: 25.8 mo *vs* 20.8 mo; $P < 0.0001$)[48]. In a multicenter phase Ⅱ study by the Hellenic Oncology Research Group, the combination of capecitabine, oxaliplatin, and bevacizumab (AVELOX) was proven to be safe and effective in the first-line treatment of elderly patients (≥ 70 years old)[49].

In a pooled analysis of 439 untreated mCRC patients ≥ 65 years old, bevacizumab-based chemotherapy produced a PFS and OS advantage when compared to chemotherapy alone[50]. In another retrospective pooled analysis of 4 RCTs (3 RCTs in the first-line setting and 1 RCT in the second-line setting), the addition of bevacizumab conferred a PFS and OS advantage in elderly patients (≥ 65 and ≥ 70 years old) when compared to chemotherapy alone. Patients receiving bevacizumab had more arterial thromboembolic events; however, there was no increase in ≥ grade 3 adverse events with increasing age[51].

More recently, the safety of bevacizumab-based chemotherapy was studied in a multi-national phase Ⅲ randomized trial (AVEX) in which 280 patients with a median age of 76 years were randomized to receive bevacizumab plus capecitabine *vs* capecitabine alone. Progression free survival favored the bevacizumab-containing arm (9.1 mo *vs* 5.1 mo; $P < 0.0001$). Overall, the percentage of patients who had any grade treatment related adverse events was similar in both groups (84% *vs* 81% in the bevacizumab-containing arm *vs* the chemotherapy alone arm). However, a higher percentage of patients in the bevacizumab plus chemotherapy group had grade 3 or greater treatment-related adverse events when compared to the chemotherapy alone group (40% *vs* 22%). Not surprisingly, bevacizumab-specific any grade adverse effects such as hypertension, proteinuria, and venous thromboembolism were greater in the bevacizumab containing arm[52].

Ziv-aflibercept (VEGF trap): A human recombinant soluble decoy protein that was engineered by the fusion of the second immunoglobulin (Ig) domain of VEGFR1 and the third Ig domain of VEGFR2 with the constant region (Fc) of human IgG1[53]. The drug binds to VEGF-A, VEGF-B, and placental growth factor (PlGF) with high affinity, thus preventing these ligands from binding to their respective endogenous receptors[54]. This leads to tumor growth and angiogenesis inhibition as shown in *in-vitro* and *in-vivo* studies[53]. When compared to bevacizumab, in addition to inhibiting

endothelial cell migration, ziv-aflibercept has a much greater binding affinity to VEGF-A and more potent inhibition of VEGFR1 and VEGFR2 activation[54]. Adverse effects include fatigue, headache, hemorrhage, nausea, diarrhea, hypertension, and proteinuria[55-57].

The efficacy of ziv-aflibercept in mCRC patients was evaluated in a large randomized phase Ⅲ trial (VELOUR). The study included all mCRC patients who progressed after prior oxaliplatin-based therapy for metastatic disease or who relapsed within 6 mo of adjuvant oxaliplatin-based chemotherapy. Prior bevacizumab therapy was not an exclusion criterion, though prior irinotecan therapy was not allowed. Patients who received prior bevacizumab therapy constituted 30.6% of the intent to treat (ITT) population. Patients were randomized to receive FOLFIRI plus ziv-aflibercept (ziv-aflibercept arm) *vs* FOLFIRI plus placebo (control arm). After a median follow-up of 22.28 mo, patients in the ziv-aflibercept arm had a significantly longer median OS (13.50 mo *vs* 12.06 mo; $P = 0.0032$) and PFS (6.90 mo *vs* 4.67 mo; HR, 0.758, $P < 0.0001$) when compared to the control arm. Neither prior bevacizumab use nor ECOG PS had an interaction with treatment for OS or PFS. OS and PFS advantage with ziv-aflibercept *vs* placebo was noted regardless of prior bevacizumab exposure [prior bevacizumab therapy: median OS: 12.5 mo *vs* 11.7 mo; HR (95%CI): 0.862 (0.673-1.104); median PFS: 6.7 mo *vs* 3.9 mo; HR (95%CI): 0.661 (0.399-1.095); no prior bevacizumab therapy: Median OS: 13.9 mo *vs* 12.4 mo; HR (95%CI): 0.788 (0.669-0.927); Median PFS: 6.9 mo *vs* 5.4 mo; HR (95%CI): 0.797 (0.58-1.096)]. Grade 3 and 4 adverse events that were higher in the ziv-aflibercept arm included hypertension, hemorrhage, thromboembolic events (arterial and venous)[56]. In a post-hoc subset analysis of the VELOUR trial, patients with liver-only metastases had a greater OS and PFS benefit from ziv-aflibercept in comparison to patients with no liver metastasis or liver plus other organ metastases. Prior bevacizumab therapy did not have an influence on treatment effect[58]. Ziv-aflibercept in combination with FOLFIRI is FDA approved for use in the treatment of mCRC patients who have progressed through or following a first-line oxaliplatin-based regimen.

Regorafenib: A biaryl-urea compound which functions as an oral multikinase inhibitor of angiogenic (VEGF R1-3, tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains, or TIE2), stromal (PDGF-β, fibroblast growth factor receptor 1), and oncogenic (RET, KIT, BRAF) receptor tyrosine kinases[18,59]. The safety and efficacy of regorafenib was first demonstrated in humans in a phase Ⅰ dose-escalation study which enrolled 53 patients with advanced and refractory solid tumors. The maximum tolerated dose was determined to be 160 mg daily, with a 3 wk on, 1 wk off schedule every 4 wk. More than half of the patients (66%) had either partial response or stable disease per RECIST criteria. The most common drug-related adverse events noted were voice changes, hand-foot syndrome (HFS), mucositis, diarrhea, and hypertension. Most patients (83%) developed at least 1 treatment related AE. The most frequently observed grade 3 or 4 drug-related AEs were hand-foot skin reaction (HFS), skin rash, hypertension, and diarrhea[60].

Another phase Ⅰ dose-escalation and extended cohort trial enrolled 37 patients with advanced or mCRC refractory to standard therapy and 1 patient with treatment-naive disease who refused standard therapy. Of the 27 patients evaluable for response, 19 had stable disease and 1 had partial response. The median PFS was 107 d (95%CI: 66-161). As in the prior phase 1 trial, most patients (84%) had treatment-related AEs (HFS, skin rash/desquamation, fatigue, fatigue, voice changes, diarrhea), though most of the AEs were grade 3 or lower. HFS was the most common grade 3 or greater treatment related AE. More than half of the patients (66%) required dose reduction or treatment interruption due to AEs with HFS being the most common AE requiring dose reduction[61].

The efficacy and safety of regorafenib in combination with FOLFOX or FOLFIRI chemotherapy in the 1st or 2nd line setting was evaluated in a phase Ib trial of 45 mCRC patients. Of the 38 patients evaluable for treatment response, either partial response or stable disease was noted in 33 patients. Median TTP for the study population was 119 d (FOLFOX group: 116 d; FOLFIRI group: 186.5 d). Most patients (71%) had treatment related AEs that were grade 3 or higher, of which neutropenia was the most common AE. Common any grade AEs included diarrhea, mucositis, neutropenia, HFS, alopecia, and fatigue. Interestingly the area under the curve (AUC) of irinotecan and its active metabolite (SN-38) were significantly higher in cycle 2 when compared to cycle 1 prior. Overall, regorafenib was shown to have acceptable tolerability in combination with chemotherapy in this study[62].

The CORRECT trial was a randomized multinational phase Ⅲ trial evaluating the benefit and tolerability of regorafenib in previously treated mCRC patients after failure of standard licensed therapy. A total of 760 patients were randomized in a 2:1 ratio to receive regorafenib plus BSC or placebo plus BSC. The mean treatment duration was 2.8 mo in the regorafenib arm and 1.8 mo in the placebo arm. Either partial response or stable disease was achieved in 41% of patients in the regorafenib group compared to 15% of patients in the placebo arm ($P < 0.0001$). Median OS was 6.4 mo *vs* 5 mo (HR, 0.77; $P = 0.0052$) and median PFS was 1.9 mo *vs* 1.7 mo (HR, 0.49; $P < 0.0001$) in the regorafenib group *vs* placebo arm, respectively. Though the magnitude of OS benefit with regorafenib *vs* placebo appears small, the HR of 0.77 would imply a 23% reduction in the risk of death during the study period. When stratified based on the primary site

of disease, patients with colon cancer who received regorafenib had a significant OS advantage with an HR of 0.70 and 95%CI: 0.56-0.89, when compared to the placebo arm, however this benefit was not seen in patients with rectal cancer [HR (95%CI), 0.95 (0.63-1.44)]. PFS favored the regorafenib arm in colon, rectal, and colon and rectal cancer subgroups with an HR of 0.55, 0.45, and 0.35 respectively. The apparent lack of an OS advantage despite a PFS advantage in patients with rectal cancer could be attributed to the higher percentage of patients in the placebo group and the smaller proportion of patients in the regorafenib group went on to receive further anti-cancer therapies post-study. Ninety three percent of patients in the regorafenib group *vs* 61% of those in the placebo group had treatment-related adverse events. Hand-foot syndrome, fatigue, diarrhea, hypertension, skin rash or desquamation were the most frequent toxicities that were ≥ grade 3. Hepatotoxicity with elevated liver transaminases and bilirubin (mostly grade 1-2) was noted to be more common in the regorafenib group when compared to placebo. A fatal case of liver injury in a 62-year-old male with liver metastases was noted in the regorafenib arm 43 d after treatment initiation. Health-related quality of life and health outcomes were measured using standard scoring systems and showed no difference in deterioration in the regorafenib *vs* placebo arms. Regorafenib monotherapy appears to be a reasonable option in patients with refractory mCRC who have exhausted all other systemic treatment options[63].

Ramucirumab: A human IgG1 monoclonal Ab against the extracellular domain of VEGFR2, thereby preventing the interaction between VEGF and VEGFR2[64]. The efficacy and safety of Ramucirumab was initially reported in a phase Ⅰ study of 37 advanced solid tumor patients, of whom 6 had a primary CRC (refractory to standard therapy). After at least 12 wk of therapy, three of the six (50%) CRC patients experienced SD for 30 (dose level: 2 mg/kg), 31 (dose level: 4 mg/kg), and 15 wk (dose level: 10 mg/kg) respectively. Overall, 22 patients (60%) developed grade 3-5 AEs, with hypertension, abdominal pain, anorexia, vomiting, increased blood alkaline phosphatase, headache, proteinuria, dyspnea, and deep venous thrombosis being the common serious AE[65]. Subsequently, a phase Ⅱ study enrolled 42 treatment-naive mCRC patients to receive Ramucirumab (at a dose of 8 mg/kg) in combination with mFOLFOX6 every 2 wk. The combination was shown to be efficacious with a median PFS of 11.5 mo and a median OS of 20.4 mo (Table 3). Neutropenia, hypertension, and neuropathy were the most commonly reported serious (grade 3-4) AEs[66]. The benefit of the addition of Ramucirumab to FOLFIRI in the second-line setting was recently evaluated in a large, randomized double-blind phase Ⅲ study (RAISE). The trial enrolled a total of 1072 patients who had POD during or after first line therapy with a combination of bevacizumab, fluoropyrimidine, and oxaliplatin, were randomized in a 1:1 design to receive FOLFIRI plus Ramucirumab *vs* FOLFIRI plus placebo. Patients in the Ramucirumab arm had a longer median OS (primary end-point; 13.3 mo *vs* 11.7 mo; HR, 0.84; log-rank $P = 0.0219$) and a longer PFS (5.7 mo *vs* 4.5 mo; HR, 0.79; log-rank $P = 0.0005$). The commonly reported serious AE (≥ grade 3) included neutropenia, hypertension, diarrhea, and fatigue[67]. Ramucirumab in combination with FOLFIRI is a promising second-line treatment option in patients with unresectable mCRC.

Famitinib: A small molecule multi-tyrosine kinase inhibitor with predominantly antiangiogenic properties[68]. The drug inhibits VEGFR2 and VEGFR3, PDGFR, stem cell factor receptor c-KIT, FMS-like tyrosine kinase-3 receptor (FLT3), and the proto-oncogene tyrosine-protein kinase inhibitor RET[69,70]. The tolerability of famitinib in patients with advanced solid tumor malignancies was evaluated in a phase Ⅰ study of 44 patients, including 7 patients with advanced CRC. The most common grade 3-4 toxicities at occurring in the first 8 wk of therapy dose levels of 24, 25, and 27 mg included hypertension, bone marrow suppression leading to leukopenia, neutropenia, thrombocytopenia, and anemia, HFS, hypertriglyceridemia, and proteinuria. The authors recommended a dose of 25 mg for a phase Ⅱ trial. The efficacy data in patients with advanced CRC was not reported in this study[69]. More recently, the efficacy and safety of famitinib in the third or later line setting was studied in a multicenter phase Ⅱ, randomized, double-blind study of 154 advanced CRC patients. Patients were randomized in a 2:1 design to receive either famitinib or placebo. Patients who received famitinib have a longer median PFS (primary end point; 2.8 mo *vs* 1.5 mo; HR, 0.58; $P = 0.0034$) and a better disease control rate (57.58% *vs* 30.91%; $P = 0.0023$) when compared to the placebo arm. The most commonly reported AEs were predominantly grade 1-2 and included neutropenia, thrombocytopenia, hypertension, proteinuria, and HFS. There was no significant difference in serious AEs between the two arms. Famitinib was thus noted to be efficacious and safe in mCRC patients who have failed second or later line therapies[68]. The results will however require further validation with a phase Ⅲ trial.

OTHER ANTI-ANGIOGENIC AGENTS

Several other antiangiogenic agents have been studied in patients with advanced CRC with disappointing results.

Sorafenib is an orally administered small molecule multi-tyrosine kinase inhibitor which targets the RAF/MEK/ERK pathway in addition to inhibiting several receptor tyrosine kinases including VEGFR2, VEGFR3, PDGR beta, c-KIT, FLT3, and tyrosine kinase colony-

Table 3 Other anti-angiogenic agents

Ref.	Regimen (line of treatment)	Sample size	Objective response (%)	PFS (mo)	OS (mo)	Serious AE (grade 3-4)[5]
Samalin *et al*[73]; Phase Ⅰ/Ⅱ	Sorafenib/irinotecan (NEXIRI) (2nd or later line KRAS mutated)	10 (phase Ⅰ) 54 (phase Ⅱ)	64.9 (DCR)	3.7	8	Asthenia, diarrhea, neutropenia, HFS
Tabernero *et al*[74]; Phase Ⅱb	Sorafenib/mFOLFOX *vs* Placebo/mFOLFOX (1st line)	198	NA	9.1 *vs* 8.7 HR, 0.88 $P = 0.46$	17.6 *vs* 18.1 HR, 1.13 $P = 0.51$	Neutropenia, peripheral neuropathy, HFS
Starling *et al*[116]; Phase Ⅰ	Sunitinib/FOLFIRI (1st line)	37	57.9	NA	NA	Febrile neutropenia neutropenia, anemia, diarrhea, mucosal inflammation, stomatitis, vomiting, lethargy, pyrexia, thrombotic events
Yoshino *et al*[117]; Phase Ⅰ	Sunitinib/mFOLFOX6 (1st line)	12 (6 + 6)[3]	66.7 in each arm	NA	NA	Neutropenia, leukopenia, thrombocytopenia
Saltz *et al*[118]; Phase Ⅱ	Sunitinib (refractory setting)	43 (prior bevacizumab)	2.4	2.2 (TTP; prior bevacizumab)	7.1	Fatigue, diarrhea, nausea, vomiting, and anorexia (most common any grade toxicities)
		41 (no prior bevacizumab)	0	2.5 (TTP; no prior bevacizumab)	10.2	
Tsuji *et al*[75]; Phase Ⅱ	Sunitinib/FOLFIRI (1st line)	71	36.6[1]/42.3[2]	6.7[1]/ 7.2[2]	NR due to early study closure	Neutropenia, leukopenia, thrombocytopenia diarrhea, nausea decreased appetite and fatigue (most common any grade)
Carrato *et al*[119]; Phase Ⅲ	Sunitinib/FOLFIRI *vs* Sunitinib/placebo (1st line)	768	NA	7.8 *vs* 8.4 HR 1.095 one-sided stratified log-rank $P = 0.807$	20.3 *vs* 19.8 HR, 1.171 $P = 0.916$	Diarrhea, stomatitis/oral syndromes, fatigue, HFS, neutropenia, thrombocytopenia, anemia, febrile neutropenia
Michael *et al*[79]; Phase Ⅰ	Vandetanib/mFOLFOX6 (1st or 2nd line)	9 (100 mg/d dose)	44.44	NA	NA	Diarrhea, nausea and lethargy (most common any grade toxicities)
		8 (300 mg/d dose)	NA	NA	NA	
Saunders *et al*[80]; Phase Ⅰ	Vandetanib/FOLFIRI (1st or 2nd line)	11 (100 mg/d dose)	18.18	NA	NA	Diarrhea, nausea fatigue (most common any grade toxicities; were grade 1-2)
		10 (300 mg/d dose)	NA	NA	NA	
Yang *et al*[81]; Phase Ⅱ	Vandetanib/mFOLFOX6 *vs* Placebo/mFOLFOX6	32 (100 mg/d dose)[4] 35 (300 mg/d dose)[4]	NA	NA	NA	Diarrhea, nausea, thrombocytopenia, peripheral sensory neuropathy (most common any grade toxicities)
Van Cutsem *et al*[84]; Phase Ⅲ	FOLFOX 4/Vatalanib *vs* FOLFOX4/placebo (2nd line)	855	NA	5.6 *vs* 4.2 HR, 0.83 $P = 0.013$	13.1 *vs* 11.9 HR, 1.0 $P = 0.957$	Neutropenia, HTN, diarrhea, fatigue, nausea, vomiting, dizziness
Hecht *et al*[85]; Phase Ⅲ	FOLFOX4/Vatalanib *vs* FOLFOX4/placebo (1st line)	1168	NA	7.7 *vs* 7.6 HR, 0.88 $P = 0.118$	21.4 *vs* 20.5 HR, 1.08 $P = 0.260$	Neutropenia, HTN, diarrhea, fatigue, nausea, vomiting

[1]By independent review; [2]Investigator initiated review; [3]Six patients received sorafenib 2 wk on, 2 wk off and another 6 patients received sorafenib 4 wk on, 2 wk off; [4]Progression events (objective/clinical progression/death) in vandetanib 100 mg arm *vs* placebo: 72% *vs* 65% (HR, 1.21; 2-sided $P = 0.53$); vandetanib 300 mg arm *vs* placebo: 77% *vs* 65% (HR, 1.41; 2-sided $P = 0.25$); [5]In study drug containing arm. DCR: Disease control rate; NA: Not available; NR: Not reached; PFS: Progression-free survival; OS: Overall survival; mFOLFOX6: Three fluoropyrimidine regimens-infusional 5FU/LV; HFS: Hand-foot syndrome.

stimulating factor 1 receptor (c-Fms)[71]. Adverse effects include HFS, fatigue and diarrhea[72]. In a phase Ⅰ/Ⅱ trial evaluating the benefit of sorafenib plus irinotecan in previously treated mCRC patients, the combination was shown to be well tolerated in both phases of the trial. In phase 2, an encouraging response rate of 64.9% was noted with a PFS of 3.7 mo and a median OS of 8 mo[73]. However, in a subsequent phase Ⅱb study of 198 treatment naive mCRC patient, the combination of sorafenib and mFOLFOX4 was shown to offer no PFS or OS advantage over placebo (Table 3)[74].

Sunitinib is an oral multi-tyrosine kinase inhibitor targeting VEGFR1, VEGFR2, VEGFR3, PDGFR alpha and beta, FLT3, stem cell factor receptor, colony stimulating factor receptor, and glial cell line-derived neurotrophic factor[75]. The efficacy and tolerability of sunitinib as monotherapy and in combination with chemotherapy was studied without significant benefit (Table 3). Common side effects include fatigue, HFS, diarrhea, mucositis, hypothyroidism, yellow discoloration of skin, and cardiotoxicity[76].

Vandetanib is an antiangiogenic agent that inhibits VEGFR2 and VEGFR3 in addition to targeting EGFR,

and several tyrosine and serine-threonine kinases[77]. Common side effects include diarrhea, rash, dermatitis, nausea/vomiting, hypertension, fatigue, abdominal pain, decreased appetite, and QT prolongation[78]. After early phase trials[79,80] demonstrated safety of vandetanib in combination with chemotherapy in advanced CRC patients, a phase Ⅱ trial randomized patients to receive chemotherapy plus vandetanib *vs* chemotherapy plus placebo[81]. In this study the frequency of progression events - defined as objective or clinical progression or death from any cause- were noted to be higher in the vandetanib containing arm when compared to placebo (vandetanib 100 mg arm *vs* placebo: 72% *vs* 65%; HR, 1.21; 2-sided $P = 0.53$; vandetanib 300 mg arm *vs* placebo: 77% *vs* 65%; HR, 1.41; 2-sided $P = 0.25$)[81].

Vatalinib is an orally active antiangiogenic agent that blocks all VEGFR tyrosine kinase mediated signaling by competitively inhibiting the binding of ATP to the receptor kinase[82]. Adverse effects include lightheadedness, ataxia, nausea, vomiting, and hypertension[83]. Despite a tolerable toxicity profile in phase 1 studies[83], Vatalinib showed no survival advantage over placebo in two phase Ⅲ randomized trials studies in mCRC patients (Table 3)[84,85].

ANTI-ANGIOGENIC THERAPY IN INITIALLY AND POTENTIALLY RESECTABLE mCRC

Carefully selected patients can be cured, if not at least provided with improved survival benefits, with resection of their metastases. Improved 5-year OS after liver resection was found in up to 46% of patients with up to 25% resected patients considered cured[86-90]. The 5-year survival rate of patients treated with pulmonary metastasectomies was found to be 55%-67%[91,92]. The median disease-free survival (DFS) and OS for those who had both hepatic and pulmonary resection has been shown to be 13-19.8 mo and up to 87 mo, respectively[93,94].

Bevacizumab is the only anti-angiogenic agent that has been extensively studied in the setting of resectable (or potentially resectable) mCRC. Small phase Ⅱ studies have shown that when used either as preoperative therapy or as conversion treatment, bevacizumab in combination with Cape-OX or FOLFOX is associated with improved pathologic response, PFS, and OS in these patients[3,95,96]. Additionally, the combination of Cape-OX and bevacizumab rendered 40% of initially unresectable patients resectable in the BOXER (bevacizumab, oxaliplatin, capecitabine in unresectable liver metastases) study. This regimen provided objective responses in 78% of patients (95%CI: 63% to 89%) with 9% of patients (4 patients) achieving complete radiologic responses. These 4 patients remained in remission for 18-30 mo[97]. However, the sample sizes of these studies are too small to draw meaningful conclusions. Furthermore, the similar response rates (38% *vs* 38%; OR, 1.00; $P = 0.99$) between the bevacizumab and placebo arms when added to oxaliplatin-containing chemotherapy, in conjunction with a similar proportion of patients undergoing attempted curative intent metastasectomies (8.4% *vs* 6.1%) in a large phase Ⅲ study by Saltz *et al*[29] argue against the use of bevacizumab in combination with oxaliplatin-based chemotherapy as conversion therapy. Several studies have demonstrated benefit with an irinotecan-containing regimen in combination with bevacizumab. In a retrospective study evaluating histopathologic features of resected liver tissue samples of 42 patients with mCRC who received FOLFOXIRI/Cape-irinotecan (Cape-IRI) with or without bevacizumab in the pre-operative setting, a significantly higher pathological response was noted in patients who received bevacizumab plus chemotherapy *vs* chemotherapy alone (63% *vs* 28%; $P = 0.033$)[98]. In a phase Ⅱ study evaluating the efficacy and safety of preoperative bevacizumab plus FOLFIRI, patients with resectable liver metastases had a median PFS of 14 mo (95%CI: 11-24 mo), median OS of 38 mo (95%CI: 28-NA mo), an objective response rate of 66.7% (95%CI: 49.8% to 80.9%) and an R0 resection rate of 84.6%[99]. Masi *et al*[100] showed a conversion rate to R0 resection of 26% and up to 40% in those with liver-only metastatic disease after treatment with FOLFOXIRI and bevacizumab. Osterlund *et al*[101] also showed that bevacizumab plus cytotoxic chemotherapy was able to convert unresectable patients to resectable candidates in the 1st- and 2nd-line setting. Finally, Loupakis *et al*[34] found a response rate of 53.1% in the FOLFOX and bevacizumab arm compared to 65.1% in the FOLFOXIRI and bevacizumab arm with an odds ratio of 1.64 (95%CI: 1.15-2.35, $P = 0.006$) in the phase Ⅲ TRIBE trial. However, there was no difference in the rate of R0 metastasectomy (12% *vs* 15%, respectively, $P = 0.33$)[34].

More recently, the OLIVIA trial provided further support for use of FOLFOX or FOLFOXIRI with bevacizumab. It also provided further evidence that while FOLFOXIRI with bevacizumab resulted in increased toxicities, it also offered improved resection rates and PFS compared to the FOLFOX and bevacizumab regimen. Thirty-nine patients with initially unresectable disease were assigned to the FOLFOX with bevacizumab arm and 41 patients received FOLFOXIRI with bevacizumab. The overall resection rate was 49% (95%CI: 32-65) and 61% (95%CI: 45-76), respectively. R0 resection was accomplished in 23% and 49% of patients, respectively. Median overall survival was 32.2 mo in the FOLFOX and bevacizumab group. It has not yet been reached in the FOLFOXIRI and bevacizumab group. Median PFS was 11.5 mo (95%CI: 9.6-13.6) in the FOLFOX and bevacizumab group compared to 18.6 mo (95%CI: 12.9-22.3) in the FOLFOXIRI and bevacizumab group.

Table 4 Bevacizumab plus chemotherapy as conversion therapy

Ref.	Regimen	Rate of conversion (%)	Overall response (%)	Median PFS (mo)	Median OS (mo)
Bertolini *et al*[95]; Phase Ⅱ	FOLFOX6 + bevacizumab	61.9	57.1	12.9	22.5
Wong *et al*[97]; Phase Ⅱ	CAPE-OX + bevacizumab	40	78 (95%CI: 63-89)	NA[1]	NA[1]
Nasti *et al*[99]; Phase Ⅱ	FOLFIRI + bevacizumab	N/A	66.7 (95%CI: 49.8-80.9)	14 (95%CI: 11-24)	38 (95%CI: 28 to NA)
Klinger *et al*[3]; Meta-analysis/phase Ⅱ	CAPE-OX/FOLFOX + bevacizumab	N/A	38 *vs* 10 (P < 0.001)	NA[2]	67 (95%CI: 8.4-125.6)[2]
Gruenberger *et al*[96]; Phase Ⅱ	CAPE-OX + bevacizumab	N/A	73.2	NA	NA
Gruenberger *et al*[102]; Phase Ⅱ	FOLFOX/FOLFOXIRI + bevacizumab	49% (FOLFOX), 61% (FOLFOXIRI)	62% (95%CI: 45-77) (FOLFOX), 81% (95%CI: 65-91) (FOLFOXIRI)	11.5 (95%CI: 9.6-13.6) (FOLFOX), 18.6 (95%CI: 12.9-22.3) (FOLFOXIRI)	32.2 (FOLFOX), not yet reached (FOLFOXIRI)
Masi *et al*[100]; Phase Ⅱ	FOLFOXIRI + bevacizumab	26	NA	NA	NA
Loupakis *et al*[34]; Phase Ⅲ	FOLFOX/FOLFOXIRI + bevacizumab	53.1 (FOLFOX), 65.1 (FOLFOXIRI)	12 (FOLFOX), 15 (FOLFOXIRI)	NA	NA
Saltz *et al*[29]; Phase Ⅲ	FOLFOX/Cape-OX + bevacizumab *vs* FOLFOX/Cape-OX + placebo	8.4 *vs* 6.1 P = NA	38 *vs* 38 P = 0.99	9.4 *vs* 8 P = 0.0023	21.3 *vs* 19.9 P = 0.077
Loupakis *et al*[98]; meta-analysis	FOLFOXIR/Cape-IRI ± bevacizumab	NA	63 *vs* 28 P = 0.033	NA[3]	NA
Osterlund *et al*[101]; retrospective analysis	FOLFIRI + bevacizumab	9	42%	8.8	18.4

[1]Though median PFS and OS were not specifically reported by Wong *et al*[97], the 12-mo PFS was 50% (95%CI: 34%-64%) and 12-mo OS was 86% (95%CI: 70%-94%); [2]The OS in this study was not reported as a single parameter given its sample population. Instead, it was reported as a function of tumor regression grade, or TRG. The median OS of 67 mo cited in this table was found in those patients with lower TRGs (histologically with more fibrosis/necrosis than tumor, or major histological response). This OS decreases to 44 mo (95%CI: 14.1-73.8) in those with higher TRGs (histologically with more tumor than fibrosis/necrosis, or no histological response). Though the median PFS was not reported in this study, the 5-year PFS was 34% in lower TRGs and 9% in higher TRGs; [3]Again, the PFS was reported in this study as a function of TRGs. There was a PFS benefit in those with lower TRGs compared to those with higher TRGs such that for every 10 units in the percentage of necrosis, there was a 0.83 HR reduction (95%CI: 0.7-0.99, P = 0.04). NA: Not available; N/A: Not applicable; PFS: Progression-free survival; OS: Overall survival.

Most common grade 3-5 toxicities included diarrhea (14% with FOLFOX, 30% with FOLFOXIRI) and neutropenia (35% and 50%, respectively)[102].

Table 4 summarizes some of the currently available clinical data in this patient population.

Multiple studies have now established that the use of bevacizumab in combination of cytotoxic chemotherapy given preoperatively neither affects the recovery of liver function nor its regeneration. The anti-VEGF activity likely persists after preoperative cessation for at least 6 wk but does not seem to affect postoperative liver recovery. Furthermore, it was found not to increase the rate of complications if discontinued at least 5 wk prior to resection[96,103-111]. In fact, there is evidence that bevacizumab, when added to oxaliplatin-based chemotherapy, may protect against sinusoidal dilatation or sinusoidal obstruction syndrome[3,112,113].

Despite the efficacy of bevacizumab plus chemotherapy in the neoadjuvant setting, it was not found to provide either a PFS or OS benefit when used as adjuvant therapy after liver metastasectomy[114].

CONCLUSION

Anti-angiogenic therapy has assumed a vital role in the management of patients with mCRC. A total of three anti-angiogenic agents are currently approved in the treatment of these patients: bevacizumab, ziv-aflibercept, and regorafenib. The choice of agents differs based on tumor resectability and line of therapy. Patients with potentially resectable liver metastases have been shown to have an improved pathological response with the addition of bevacizumab to neo-adjuvant chemotherapy. Studies have refuted concerns about hepatotoxicity and liver regeneration in patients treated with bevacizumab in the neoadjuvant setting.

Bevacizumab in combination with irinotecan-based chemotherapy has also been used as conversion therapy with a resection rates up to 61% in combination with FOLFOXIRI though at the expense of increased toxicities. In patients with treatment-naive unresectable mCRC, the addition of bevacizumab to cytotoxic chemotherapy achieves better and more durable responses, in addition to an advantage in PFS and OS when compared to chemotherapy alone. The beneficial role of bevacizumab in combination with a fluoropyrimidine in the maintenance setting, and the benefits of continuing bevacizumab beyond progression have been confirmed in multiple studies.

The use of bevacizumab in the first-line setting in patients with KRAS WT unresectable mCRC has been challenged by the FIRE-3 and CALGB 80405 studies, and cetuximab-based chemotherapy appears to be a viable option in these patients. More recently,

two new anti-angiogenic agents were added to the armamentarium of targeted agents approved for use in mCRC. Ziv-aflibercept improved survival when used in the second-line setting in combination with an irinotecan-based chemotherapy in patients who have failed oxaliplatin-based therapy, and Regorafenib improved survival when compared to placebo in the treatment of patients with refractory mCRC. Another antiangiogenic agent, Ramucirumab has shown to improve survival in the second-line setting when used in combination with chemotherapy, and awaits FDA approval.

Despite these advances, mCRC remains an incurable disease with a median OS of approximately over 2 years in patients exposed to all available treatment regimens. Further insights into tumor biology and tumor microenvironment may help improve outcomes in these patients.

REFERENCES

1 **Siegel R**, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; **64**: 9-29 [PMID: 24399786 DOI: 10.3322/caac.21208]
2 **Wicherts DA**, de Haas RJ, Adam R. Bringing unresectable liver disease to resection with curative intent. *Eur J Surg Oncol* 2007; **33** Suppl 2: S42-S51 [PMID: 17981429 DOI: 10.1016/j.ejso.2007.09.017]
3 **Klinger M**, Tamandl D, Eipeldauer S, Hacker S, Herberger B, Kaczirek K, Dorfmeister M, Gruenberger B, Gruenberger T. Bevacizumab improves pathological response of colorectal cancer liver metastases treated with XELOX/FOLFOX. *Ann Surg Oncol* 2010; **17**: 2059-2065 [PMID: 20177795 DOI: 10.1245/s10434-010-0972-9]
4 **Heidelberger C**, Chaudhuri NK, Danneberg P, Mooren D, Griesbach L, Duschinsky R, Schnitzer RJ, Pleven E, Scheiner J. Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature* 1957; **179**: 663-666 [PMID: 13418758]
5 **Folkman J**. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971; **285**: 1182-1186 [PMID: 4938153 DOI: 10.1056/NEJM197111182852108]
6 **Folkman J**. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; **1**: 27-31 [PMID: 7584949]
7 **Folkman J**, Shing Y. Angiogenesis. *J Biol Chem* 1992; **267**: 10931-10934 [PMID: 1375931]
8 **Rafii S**, Lyden D, Benezra R, Hattori K, Heissig B. Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy? *Nat Rev Cancer* 2002; **2**: 826-835 [PMID: 12415253 DOI: 10.1038/nrc925]
9 **Hicklin DJ**, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005; **23**: 1011-1027 [PMID: 15585754 DOI: 10.1200/jco.2005.06.081]
10 **Holmes DI**, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome Biol* 2005; **6**: 209 [PMID: 15693956 DOI: 10.1186/gb-2005-6-2-209]
11 **Lee JJ**, Chu E. Sequencing of antiangiogenic agents in the treatment of metastatic colorectal cancer. *Clin Colorectal Cancer* 2014; **13**: 135-144 [PMID: 24768040 DOI: 10.1016/j.clcc.2014.02.001]
12 **Senger DR**, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 1983; **219**: 983-985 [PMID: 6823562]
13 **Ferrara N**, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev* 1997; **18**: 4-25 [PMID: 9034784 DOI: 10.1210/edrv.18.1.0287]
14 **Dimova I**, Popivanov G, Djonov V. Angiogenesis in cancer - general pathways and their therapeutic implications. *J BUON* 2014; **19**: 15-21 [PMID: 24659637]
15 **Goel HL**, Mercurio AM. VEGF targets the tumour cell. *Nat Rev Cancer* 2013; **13**: 871-882 [PMID: 24263190 DOI: 10.1038/nrc3627]
16 **Dvorak HF**, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol* 1995; **146**: 1029-1039 [PMID: 7538264]
17 **Gacche RN**, Meshram RJ. Angiogenic factors as potential drug target: efficacy and limitations of anti-angiogenic therapy. *Biochim Biophys Acta* 2014; **1846**: 161-179 [PMID: 24836679 DOI: 10.1016/j.bbcan.2014.05.002]
18 **Wilhelm SM**, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH, Zopf D. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011; **129**: 245-255 [PMID: 21170960 DOI: 10.1002/ijc.25864]
19 **Abdollahi A**, Lipson KE, Sckell A, Zieher H, Klenke F, Poerschke D, Roth A, Han X, Krix M, Bischof M, Hahnfeldt P, Grone HJ, Debus J, Hlatky L, Huber PE. Combined therapy with direct and indirect angiogenesis inhibition results in enhanced antiangiogenic and antitumor effects. *Cancer Res* 2003; **63**: 8890-8898 [PMID: 14695206]
20 **Presta LG**, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, Winkler M, Ferrara N. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res* 1997; **57**: 4593-4599 [PMID: 9377574]
21 **Elamin YY**, Rafee S, Toomey S, Hennessy BT. Immune effects of bevacizumab: killing two birds with one stone. *Cancer Microenviron* 2015; **8**: 15-21 [PMID: 25326055 DOI: 10.1007/s12307-014-0160-8]
22 **Hurwitz H**, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-2342 [PMID: 15175435 DOI: 10.1056/NEJMoa032691]
23 **Hurwitz HI**, Tebbutt NC, Kabbinavar F, Giantonio BJ, Guan ZZ, Mitchell L, Waterkamp D, Tabernero J. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. *Oncologist* 2013; **18**: 1004-1012 [PMID: 23881988 DOI: 10.1634/theoncologist.2013-0107]
24 **Cartwright TH**. Adverse events associated with antiangiogenic agents in combination with cytotoxic chemotherapy in metastatic colorectal cancer and their management. *Clin Colorectal Cancer* 2013; **12**: 86-94 [PMID: 23562587 DOI: 10.1016/j.clcc.2012.12.001]
25 **Higa GM**, Abraham J. Biological mechanisms of bevacizumab-associated adverse events. *Expert Rev Anticancer Ther* 2009; **9**: 999-1007 [PMID: 19589038 DOI: 10.1586/era.09.68]
26 **Kabbinavar F**, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003; **21**: 60-65 [PMID: 12506171]
27 **Kabbinavar FF**, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, Mass R, Perrou B, Nelson B, Novotny WF. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005; **23**: 3697-3705 [PMID: 15738537 DOI: 10.1200/jco.2005.05.112]
28 **Kabbinavar FF**, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005; **23**: 3706-3712 [PMID: 15867200 DOI: 10.1200/JCO.2005.00.232]
29 **Saltz LB**, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer:

a randomized phase III study. *J Clin Oncol* 2008; **26**: 2013-2019 [PMID: 18421054 DOI: 10.1200/jco.2007.14.9930]

30 **Petrelli F**, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Maspero F, Sauta MG, Beretta GD, Barni S. FOLFIRI-bevacizumab as first-line chemotherapy in 3500 patients with advanced colorectal cancer: a pooled analysis of 29 published trials. *Clin Colorectal Cancer* 2013; **12**: 145-151 [PMID: 23763824 DOI: 10.1016/j.clcc.2013.04.006]

31 **Sobrero AF**, Young S, Balcewicz M, Chiarra S, Perez Carrion R, Mainwaring P, Gapski J, Clarke S, Langer B, Ackland S. Phase IV study of first-line bevacizumab plus irinotecan and infusional 5-FU/LV in patients with metastatic colorectal cancer: AVIRI. *ASCO Meeting Abstracts* 2007; **25** (18_suppl): 4068

32 **Pectasides D**, Papaxoinis G, Kalogeras KT, Eleftheraki AG, Xanthakis I, Makatsoris T, Samantas E, Varthalitis I, Papakostas P, Nikitas N, Papandreou CN, Pentheroudakis G, Timotheadou E, Koutras A, Sgouros J, Bafaloukos D, Klouvas G, Economopoulos T, Syrigos KN, Fountzilas G. XELIRI-bevacizumab versus FOLFIRI-bevacizumab as first-line treatment in patients with metastatic colorectal cancer: a Hellenic Cooperative Oncology Group phase III trial with collateral biomarker analysis. *BMC Cancer* 2012; **12**: 271 [PMID: 22748098 DOI: 10.1186/1471-2407-12-271]

33 **Falcone A**, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; **25**: 1670-1676 [PMID: 17470860 DOI: 10.1200/jco.2006.09.0928]

34 **Loupakis F**, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, Chiara S, Carlomagno C, Boni C, Allegrini G, Boni L, Falcone A. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014; **371**: 1609-1618 [PMID: 25337750 DOI: 10.1056/NEJMoa1403108]

35 **Hochster HS**, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, Wong L, Fehrenbacher L, Abubakr Y, Saif MW, Schwartzberg L, Hedrick E. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol* 2008; **26**: 3523-3529 [PMID: 18640933 DOI: 10.1200/JCO.2007.15.4138]

36 **Heinemann V**, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M, Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A, Stintzing S. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; **15**: 1065-1075 [PMID: 25088940 DOI: 10.1016/s1470-2045(14)70330-4]

37 **Venook AP**, Niedzwiecki D, Lenz HJ, Innocenti F, Mahoney MR, O'Neil BH, Shaw JE, Polite BN, Hochster HS, Atkins JN, Goldberg RM, Mayer RJ, Schilsky RL, Bertagnolli MM, Blanke CD; Cancer, Leukemia Group B S, ECOG. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). *ASCO Meeting Abstracts* 2014; **32** (18_suppl): LBA3

38 **Díaz-Rubio E**, Gómez-España A, Massutí B, Sastre J, Abad A, Valladares M, Rivera F, Safont MJ, Martínez de Prado P, Gallén M, González E, Marcuello E, Benavides M, Fernández-Martos C, Losa F, Escudero P, Arrivi A, Cervantes A, Dueñas R, López-Ladrón A, Lacasta A, Llanos M, Tabernero JM, Antón A, Aranda E. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. *Oncologist* 2012; **17**: 15-25 [PMID: 22234633 DOI: 10.1634/theoncologist.2011-0249]

39 **Moscetti L**, Nelli F, Fabbri MA, Sperduti I, Alesini D, Cortesi E, Gemma D, Gamucci T, Grande R, Pavese I, Franco D, Ruggeri EM. Maintenance single-agent bevacizumab or observation after first-line chemotherapy in patients with metastatic colorectal cancer: a multicenter retrospective study. *Invest New Drugs* 2013; **31**: 1035-1043 [PMID: 23417697 DOI: 10.1007/s10637-013-9936-9]

40 **Koopman M**, Simkens L, May AM, Mol L, van Tinteren H, Punt CJA. Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine bevacizumab versus observation after induction treatment with chemotherapy bevacizumab in metastatic colorectal cancer (mCRC). *ASCO Meeting Abstracts* 2014; **32** (15_suppl): 3504

41 **Giantonio BJ**, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; **25**: 1539-1544 [PMID: 17442997 DOI: 10.1200/JCO.2006.09.6305]

42 **Grothey A**, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E, Kozloff M. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). *J Clin Oncol* 2008; **26**: 5326-5334 [PMID: 18854571 DOI: 10.1200/jco.2008.16.3212]

43 **Giantonio BJ**. Targeted therapies: Goldie-Coldman and bevacizumab beyond disease progression. *Nat Rev Clin Oncol* 2009; **6**: 311-312 [PMID: 19483736 DOI: 10.1038/nrclinonc.2009.66]

44 **Grothey A**, Flick ED, Cohn AL, Bekaii-Saab TS, Bendell JC, Kozloff M, Roach N, Mun Y, Fish S, Hurwitz HI. Bevacizumab exposure beyond first disease progression in patients with metastatic colorectal cancer: analyses of the ARIES observational cohort study. *Pharmacoepidemiol Drug Saf* 2014; **23**: 726-734 [PMID: 24830357 DOI: 10.1002/pds.3633]

45 **Bennouna J**, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, Steffens CC, Alonso-Orduña V, Schlichting C, Reyes-Rivera I, Bendahmane B, André T, Kubicka S. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013; **14**: 29-37 [PMID: 23168366 DOI: 10.1016/s1470-2045(12)70477-1]

46 **Masi G**, Salvatore L, Boni L, Loupakis F, Cremolini C, Fornaro L, Schirripa M, Cupini S, Barbara C, Safina V, Granetto C, Fea E, Antonuzzo L, Boni C, Allegrini G, Chiara S, Amoroso D, Bonetti A, Falcone A. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. *Ann Oncol* 2015; **26**: 724-730 [PMID: 25600568 DOI: 10.1093/annonc/mdv012]

47 **Kozloff MF**, Berlin J, Flynn PJ, Kabbinavar F, Ashby M, Dong W, Sing AP, Grothey A. Clinical outcomes in elderly patients with metastatic colorectal cancer receiving bevacizumab and chemotherapy: results from the BRiTE observational cohort study. *Oncology* 2010; **78**: 329-339 [PMID: 20733336 DOI: 10.1159/000320222]

48 **Hofheinz R**, Petersen V, Kindler M, Schulze M, Seraphin J, Hoeffkes HG, Valdix AR, Schroeder J, Herrenberger J, Stein A, Hinke A, Arnold D. Bevacizumab in first-line treatment of elderly patients with metastatic colorectal cancer: German community-based observational cohort study results. *BMC Cancer* 2014; **14**: 761 [PMID: 25311943 DOI: 10.1186/1471-2407-14-761]

49 **Vamvakas L**, Matikas A, Karampeazis A, Hatzidaki D, Kakolyris S, Christophylakis C, Boukovinas I, Polyzos A, Georgoulias V, Souglakos J. Capecitabine in combination with oxaliplatin and bevacizumab (AXELOX) as 1st line treatment for fit and vulnerable elderly patients (aged & gt; 70 years) with metastatic colorectal cancer (mCRC): a multicenter phase II study of the Hellenic Oncology Research Group (HORG). *BMC Cancer* 2014; **14**: 277 [PMID: 24755296 DOI: 10.1186/1471-2407-14-277]

50 **Kabbinavar FF**, Hurwitz HI, Yi J, Sarkar S, Rosen O. Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials. *J Clin Oncol* 2009; **27**: 199-205 [PMID: 19064978 DOI: 10.1200/jco.2008.17.7931]

51 **Cassidy J**, Saltz LB, Giantonio BJ, Kabbinavar FF, Hurwitz HI, Rohr UP. Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies. *J Cancer Res Clin Oncol* 2010; **136**: 737-743 [PMID: 19904559 DOI: 10.1007/s00432-009-0712-3]

52 **Cunningham D**, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, Jonker D, Osborne S, Andre N, Waterkamp D, Saunders MP. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; **14**: 1077-1085 [PMID: 24028813 DOI: 10.1016/S1470-2045(13)70154-2]

53 **Holash J**, Davis S, Papadopoulos N, Croll SD, Ho L, Russell M, Boland P, Leidich R, Hylton D, Burova E, Ioffe E, Huang T, Radziejewski C, Bailey K, Fandl JP, Daly T, Wiegand SJ, Yancopoulos GD, Rudge JS. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci USA* 2002; **99**: 11393-11398 [PMID: 12177445 DOI: 10.1073/pnas.172398299]

54 **Papadopoulos N**, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, Pyles EA, Yancopoulos GD, Stahl N, Wiegand SJ. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012; **15**: 171-185 [PMID: 22302382 DOI: 10.1007/s10456-011-9249-6]

55 **Lockhart AC**, Rothenberg ML, Dupont J, Cooper W, Chevalier P, Sternas L, Buzenet G, Koehler E, Sosman JA, Schwartz LH, Gultekin DH, Koutcher JA, Donnelly EF, Andal R, Dancy I, Spriggs DR, Tew WP. Phase I study of intravenous vascular endothelial growth factor trap, aflibercept, in patients with advanced solid tumors. *J Clin Oncol* 2010; **28**: 207-214 [PMID: 19949018 DOI: 10.1200/jco.2009.22.9237]

56 **Van Cutsem E**, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; **30**: 3499-3506 [PMID: 22949147 DOI: 10.1200/jco.2012.42.8201]

57 **Tang PA**, Cohen SJ, Kollmannsberger C, Bjarnason G, Virik K, MacKenzie MJ, Lourenco L, Wang L, Chen A, Moore MJ. Phase II clinical and pharmacokinetic study of aflibercept in patients with previously treated metastatic colorectal cancer. *Clin Cancer Res* 2012; **18**: 6023-6031 [PMID: 22977191 DOI: 10.1158/1078-0432.ccr-11-3252]

58 **Chau I**, Joulain F, Iqbal SU, Bridgewater J. A VELOUR post hoc subset analysis: prognostic groups and treatment outcomes in patients with metastatic colorectal cancer treated with aflibercept and FOLFIRI. *BMC Cancer* 2014; **14**: 605 [PMID: 25142418 DOI: 10.1186/1471-2407-14-605]

59 **Tabchi S**, Ghosn M. Regorafenib: start low and go slow. *Target Oncol* 2014; Epub ahead of print [PMID: 25548130 DOI: 10.1007/s11523-014-0352-7]

60 **Mross K**, Frost A, Steinbild S, Hedbom S, Büchert M, Fasol U, Unger C, Krätzschmar J, Heinig R, Boix O, Christensen O. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. *Clin Cancer Res* 2012; **18**: 2658-2667 [PMID: 22421192 DOI: 10.1158/1078-0432.ccr-11-1900]

61 **Strumberg D**, Scheulen ME, Schultheis B, Richly H, Frost A, Büchert M, Christensen O, Jeffers M, Heinig R, Boix O, Mross K. Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. *Br J Cancer* 2012; **106**: 1722-1727 [PMID: 22568966 DOI: 10.1038/bjc.2012.153]

62 **Schultheis B**, Folprecht G, Kuhlmann J, Ehrenberg R, Hacker UT, Köhne CH, Kornacker M, Boix O, Lettieri J, Krauss J, Fischer R, Hamann S, Strumberg D, Mross KB. Regorafenib in combination with FOLFOX or FOLFIRI as first- or second-line treatment of colorectal cancer: results of a multicenter, phase Ib study. *Ann Oncol* 2013; **24**: 1560-1567 [PMID: 23493136 DOI: 10.1093/annonc/mdt056]

63 **Grothey A**, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 303-312 [PMID: 23177514 DOI: 10.1016/s0140-6736(12)61900-x]

64 **Spratlin JL**, Mulder KE, Mackey JR. Ramucirumab (IMC-1121B): a novel attack on angiogenesis. *Future Oncol* 2010; **6**: 1085-1094 [PMID: 20624120 DOI: 10.2217/fon.10.75]

65 **Spratlin JL**, Cohen RB, Eadens M, Gore L, Camidge DR, Diab S, Leong S, O'Bryant C, Chow LQ, Serkova NJ, Meropol NJ, Lewis NL, Chiorean EG, Fox F, Youssoufian H, Rowinsky EK, Eckhardt SG. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; **28**: 780-787 [PMID: 20048182 DOI: 10.1200/jco.2009.23.7537]

66 **Garcia-Carbonero R**, Rivera F, Maurel J, Ayoub JP, Moore MJ, Cervantes A, Asmis TR, Schwartz JD, Nasroulah F, Ballal S, Tabernero J. An open-label phase II study evaluating the safety and efficacy of ramucirumab combined with mFOLFOX-6 as first-line therapy for metastatic colorectal cancer. *Oncologist* 2014; **19**: 350-351 [PMID: 24674871 DOI: 10.1634/theoncologist.2014-0028]

67 **Tabernero J**, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, Ciuleanu TE, Portnoy DC, Van Cutsem E, Grothey A, Prausová J, Garcia-Alfonso P, Yamazaki K, Clingan PR, Zagonel V, Kim TW, Simms L, Chang SC, Nasroulah F, Yoshino T, Investigators TRS. RAISE: A randomized, double-blind, multicenter phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab (RAM) or placebo (PBO) in patients (pts) with metastatic colorectal carcinoma (CRC) progressive during or following first-line combination therapy with bevacizumab (bev), oxaliplatin (ox), and a fluoropyrimidine (fp). *ASCO Meeting Abstracts* 2015; **33** (suppl_3): 512

68 **Xu RH**, Shen L, Wang K, Wu G, Shi C, Ding K, Lin L, Wang J, Xiong J, Wu C, Li J, Liu Y, Wang D, Ba Y, Feng J, Bai Y, Bi J, MA L, Lei J, Yu H. A randomized, double-blind, parallel-group, placebo-controlled, multicenter, phase II clinical study of famitinib in the treatment of advanced metastatic colorectal cancer. *ASCO Meeting Abstracts* 2015; **33** (3_suppl): 513

69 **Zhou A**, Zhang W, Chang C, Chen X, Zhong D, Qin Q, Lou D, Jiang H, Wang J. Phase I study of the safety, pharmacokinetics and antitumor activity of famitinib. *Cancer Chemother Pharmacol* 2013; **72**: 1043-1053 [PMID: 24043137 DOI: 10.1007/s00280-013-2282-y]

70 **Xie C**, Zhou J, Guo Z, Diao X, Gao Z, Zhong D, Jiang H, Zhang L, Chen X. Metabolism and bioactivation of famitinib, a novel inhibitor of receptor tyrosine kinase, in cancer patients. *Br J Pharmacol* 2013; **168**: 1687-1706 [PMID: 23126373 DOI: 10.1111/bph.12047]

71 **Chappell WH**, Steelman LS, Long JM, Kempf RC, Abrams SL, Franklin RA, Bäsecke J, Stivala F, Donia M, Fagone P, Malaponte G, Mazzarino MC, Nicoletti F, Libra M, Maksimovic-Ivanic D, Mijatovic S, Montalto G, Cervello M, Laidler P, Milella M, Tafuri A, Bonati A, Evangelisti C, Cocco L, Martelli AM, McCubrey JA. Ras/Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR inhibitors: rationale and importance to inhibiting these pathways in human health. *Oncotarget* 2011; **2**: 135-164 [PMID: 21411864]

72 **Di Marco V**, De Vita F, Koskinas J, Semela D, Toniutto P, Verslype C. Sorafenib: from literature to clinical practice. *Ann Oncol* 2013; **24** Suppl 2: ii30-ii37 [PMID: 23715941 DOI: 10.1093/annonc/mdt055]

73 **Samalin E**, Bouché O, Thézenas S, Francois E, Adenis A, Bennouna J, Taieb J, Desseigne F, Seitz JF, Conroy T, Galais MP, Assenat E,

Crapez E, Poujol S, Bibeau F, Boissière F, Laurent-Puig P, Ychou M, Mazard T. Sorafenib and irinotecan (NEXIRI) as second- or later-line treatment for patients with metastatic colorectal cancer and KRAS-mutated tumours: a multicentre Phase I/II trial. *Br J Cancer* 2014; **110**: 1148-1154 [PMID: 24407191 DOI: 10.1038/bjc.2013.813]

74 **Tabernero J**, Garcia-Carbonero R, Cassidy J, Sobrero A, Van Cutsem E, Köhne CH, Tejpar S, Gladkov O, Davidenko I, Salazar R, Vladimirova L, Cheporov S, Burdaeva O, Rivera F, Samuel L, Bulavina I, Potter V, Chang YL, Lokker NA, O'Dwyer PJ. Sorafenib in combination with oxaliplatin, leucovorin, and fluorouracil (modified FOLFOX6) as first-line treatment of metastatic colorectal cancer: the RESPECT trial. *Clin Cancer Res* 2013; **19**: 2541-2550 [PMID: 23532888 DOI: 10.1158/1078-0432.ccr-13-0107]

75 **Tsuji Y**, Satoh T, Tsuji A, Muro K, Yoshida M, Nishina T, Nagase M, Komatsu Y, Kato T, Miyata Y, Mizutani N, Hashigaki S, Lechuga MJ, Denda T. First-line sunitinib plus FOLFIRI in Japanese patients with unresectable/metastatic colorectal cancer: a phase II study. *Cancer Sci* 2012; **103**: 1502-1507 [PMID: 22537162 DOI: 10.1111/j.1349-7006.2012.02320.x]

76 **Heng DY**, Kollmannsberger C. Sunitinib. *Recent Results Cancer Res* 2010; **184**: 71-82 [PMID: 20072832 DOI: 10.1007/978-3-642-01222-8_6]

77 **Wedge SR**, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res* 2002; **62**: 4645-4655 [PMID: 12183421]

78 **Vozniak JM**, Jacobs JM. Vandetanib. *J Adv Pract Oncol* 2012; **3**: 112-116 [PMID: 25031937]

79 **Michael M**, Gibbs P, Smith R, Godwood A, Oliver S, Tebbutt N. Open-label phase I trial of vandetanib in combination with mFOLFOX6 in patients with advanced colorectal cancer. *Invest New Drugs* 2009; **27**: 253-261 [PMID: 19002384 DOI: 10.1007/s10637-008-9182-8]

80 **Saunders MP**, Wilson R, Peeters M, Smith R, Godwood A, Oliver S, Van Cutsem E. Vandetanib with FOLFIRI in patients with advanced colorectal adenocarcinoma: results from an open-label, multicentre Phase I study. *Cancer Chemother Pharmacol* 2009; **64**: 665-672 [PMID: 19184020 DOI: 10.1007/s00280-008-0914-4]

81 **Yang TS**, Oh DY, Guimbaud R, Szanto J, Salek T, Thurzo L, Vieitez JM, Pover GM, Kim TW. Vandetanib plus mFOLFOX6 in patients with advanced colorectal cancer (CRC): A randomized, double-blind, placebo-controlled phase II study. *ASCO Meeting Abstracts* 2009; **27** (15S): 4084

82 **Hess-Stumpp H**, Haberey M, Thierauch KH. PTK 787/ZK 222584, a tyrosine kinase inhibitor of all known VEGF receptors, represses tumor growth with high efficacy. *Chembiochem* 2005; **6**: 550-557 [PMID: 15742376 DOI: 10.1002/cbic.200400305]

83 **Thomas AL**, Morgan B, Drevs J, Unger C, Wiedenmann B, Vanhoefer U, Laurent D, Dugan M, Steward WP. Vascular endothelial growth factor receptor tyrosine kinase inhibitors: PTK787/ZK 222584. *Semin Oncol* 2003; **30**: 32-38 [PMID: 12802793]

84 **Van Cutsem E**, Bajetta E, Valle J, Köhne CH, Hecht JR, Moore M, Germond C, Berg W, Chen BL, Jalava T, Lebwohl D, Meinhardt G, Laurent D, Lin E. Randomized, placebo-controlled, phase III study of oxaliplatin, fluorouracil, and leucovorin with or without PTK787/ZK 222584 in patients with previously treated metastatic colorectal adenocarcinoma. *J Clin Oncol* 2011; **29**: 2004-2010 [PMID: 21464401 DOI: 10.1200/jco.2010.29.5436]

85 **Hecht JR**, Trarbach T, Hainsworth JD, Major P, Jäger E, Wolff RA, Lloyd-Salvant K, Bodoky G, Pendergrass K, Berg W, Chen BL, Jalava T, Meinhardt G, Laurent D, Lebwohl D, Kerr D. Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. *J Clin Oncol* 2011; **29**: 1997-2003 [PMID: 21464406 DOI: 10.1200/jco.2010.29.4496]

86 **Kopetz S**, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, Grothey A, Vauthey JN, Nagorney DM, McWilliams RR. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009; **27**: 3677-3683 [PMID: 19470929 DOI: 10.1200/jco.2008.20.5278]

87 **Viganò L**, Russolillo N, Ferrero A, Langella S, Sperti E, Capussotti L. Evolution of long-term outcome of liver resection for colorectal metastases: analysis of actual 5-year survival rates over two decades. *Ann Surg Oncol* 2012; **19**: 2035-2044 [PMID: 22219066 DOI: 10.1245/s10434-011-2186-1]

88 **Wicherts DA**, de Haas RJ, Andreani P, Ariche A, Salloum C, Pascal G, Castaing D, Adam R, Azoulay D. Short- and long-term results of extended left hepatectomy for colorectal metastases. *HPB* (Oxford) 2011; **13**: 536-543 [PMID: 21762296 DOI: 10.1111/j.1477-2574.2011.00321.x]

89 **Adam R**, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, Ducreux M, Azoulay D, Bismuth H, Castaing D. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 2009; **27**: 1829-1835 [PMID: 19273699 DOI: 10.1200/jco.2008.19.9273]

90 **Van Cutsem E**, Nordlinger B, Adam R, Köhne CH, Pozzo C, Poston G, Ychou M, Rougier P. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 2006; **42**: 2212-2221 [PMID: 16904315 DOI: 10.1016/j.ejca.2006.04.012]

91 **Blackmon SH**, Stephens EH, Correa AM, Hofstetter W, Kim MP, Mehran RJ, Rice DC, Roth JA, Swisher SG, Walsh GL, Vaporciyan AA. Predictors of recurrent pulmonary metastases and survival after pulmonary metastasectomy for colorectal cancer. *Ann Thorac Surg* 2012; **94**: 1802-1809 [PMID: 23063195 DOI: 10.1016/j.athoracsur.2012.07.014]

92 **Cho JH**, Hamaji M, Allen MS, Cassivi SD, Nichols FC, Wigle DA, Shen KR, Deschamps C. The prognosis of pulmonary metastasectomy depends on the location of the primary colorectal cancer. *Ann Thorac Surg* 2014; **98**: 1231-1237 [PMID: 25086943 DOI: 10.1016/j.athoracsur.2014.05.023]

93 **Gonzalez M**, Robert JH, Halkic N, Mentha G, Roth A, Perneger T, Ris HB, Gervaz P. Survival after lung metastasectomy in colorectal cancer patients with previously resected liver metastases. *World J Surg* 2012; **36**: 386-391 [PMID: 22167262 DOI: 10.1007/s00268-011-1381-3]

94 **Shah SA**, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, Taylor BR, Langer B, Gallinger S, Wei AC. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. *J Am Coll Surg* 2006; **202**: 468-475 [PMID: 16500252 DOI: 10.1016/j.jamcollsurg.2005.11.008]

95 **Bertolini F**, Malavasi N, Scarabelli L, Fiocchi F, Bagni B, Del Giovane C, Colucci G, Gerunda GE, Depenni R, Zironi S, Fontana A, Pettorelli E, Luppi G, Conte PF. FOLFOX6 and bevacizumab in non-optimally resectable liver metastases from colorectal cancer. *Br J Cancer* 2011; **104**: 1079-1084 [PMID: 21386839 DOI: 10.1038/bjc.2011.43]

96 **Gruenberger B**, Tamandl D, Schueller J, Scheithauer W, Zielinski C, Herbst F, Gruenberger T. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 1830-1835 [PMID: 18398148 DOI: 10.1200/jco.2007.13.7679]

97 **Wong R**, Cunningham D, Barbachano Y, Saffery C, Valle J, Hickish T, Mudan S, Brown G, Khan A, Wotherspoon A, Strimpakos AS, Thomas J, Compton S, Chua YJ, Chau I. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. *Ann Oncol* 2011; **22**: 2042-2048 [PMID: 21285134 DOI: 10.1093/annonc/mdq714]

98 **Loupakis F**, Schirripa M, Caparello C, Funel N, Pollina L, Vasile E, Cremolini C, Salvatore L, Morvillo M, Antoniotti C, Marmorino F, Masi G, Falcone A. Histopathologic evaluation of liver metastases from colorectal cancer in patients treated with FOLFOXIRI plus bevacizumab. *Br J Cancer* 2013; **108**: 2549-2556 [PMID: 23703247 DOI: 10.1038/bjc.2013.245]

99 **Nasti G**, Piccirillo MC, Izzo F, Ottaiano A, Albino V, Delrio

P, Romano C, Giordano P, Lastoria S, Caracò C, de Lutio di Castelguidone E, Palaia R, Daniele G, Aloj L, Romano G, Iaffaioli RV. Neoadjuvant FOLFIRI+bevacizumab in patients with resectable liver metastases from colorectal cancer: a phase 2 trial. *Br J Cancer* 2013; **108**: 1566-1570 [PMID: 23558891 DOI: 10.1038/bjc.2013.140]

100 **Masi G**, Loupakis F, Salvatore L, Fornaro L, Cremolini C, Cupini S, Ciarlo A, Del Monte F, Cortesi E, Amoroso D, Granetto C, Fontanini G, Sensi E, Lupi C, Andreuccetti M, Falcone A. Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. *Lancet Oncol* 2010; **11**: 845-852 [PMID: 20702138 DOI: 10.1016/s1470-2045(10)70175-3]

101 **Osterlund P**, Peltonen R, Alanko T, Bono P, Isoniemi H. A single-institution experience with bevacizumab in the treatment of metastatic colorectal cancer and in conjunction with liver resection. *Onco Targets Ther* 2014; **7**: 1177-1184 [PMID: 25061319 DOI: 10.2147/ott.s63739]

102 **Gruenberger T**, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S, Lasserre S, Hermann F, Waterkamp D, Adam R. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol* 2015; **26**: 702-708 [PMID: 25538173 DOI: 10.1093/annonc/mdu580]

103 **Dede K**, Mersich T, Besznyák I, Zaránd A, Salamon F, Baranyai ZS, Landherr L, Jakab F, Bursics A. Bevacizumab treatment before resection of colorectal liver metastases: safety, recovery of liver function, pathologic assessment. *Pathol Oncol Res* 2013; **19**: 501-508 [PMID: 23420304 DOI: 10.1007/s12253-013-9608-2]

104 **Cvetanovic A**, Vrbic S, Filipovic S, Pejcic I, Milenkovic D, Milenkovic N, Zivkovic N. Safety and efficacy of addition of bevacizumab to oxaliplatin-based preoperative chemotherapy in colorectal cancer with liver metastasis- a single institution experience. *J BUON* 2013; **18**: 641-646 [PMID: 24065477]

105 **Lubezky N**, Winograd E, Papoulas M, Lahat G, Shacham-Shmueli E, Geva R, Nakache R, Klausner J, Ben-Haim M. Perioperative complications after neoadjuvant chemotherapy with and without bevacizumab for colorectal liver metastases. *J Gastrointest Surg* 2013; **17**: 527-532 [PMID: 23299220 DOI: 10.1007/s11605-012-2108-y]

106 **Millet G**, Truant S, Leteurtre E, Hebbar M, Zerbib P, Huet G, Boleslawski E, Pruvot FR. Volumetric analysis of remnant liver regeneration after major hepatectomy in bevacizumab-treated patients: a case-matched study in 82 patients. *Ann Surg* 2012; **256**: 755-761; discussion 761-762 [PMID: 23095619 DOI: 10.1097/SLA.0b013e31827381ca]

107 **Starlinger P**, Alidzanovic L, Schauer D, Maier T, Nemeth C, Perisanidis B, Tamandl D, Gruenberger B, Gruenberger T, Brostjan C. Neoadjuvant bevacizumab persistently inactivates VEGF at the time of surgery despite preoperative cessation. *Br J Cancer* 2012; **107**: 961-966 [PMID: 22850548 DOI: 10.1038/bjc.2012.342]

108 **Kesmodel SB**, Ellis LM, Lin E, Chang GJ, Abdalla EK, Kopetz S, Vauthey JN, Rodriguez-Bigas MA, Curley SA, Feig BW. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. *J Clin Oncol* 2008; **26**: 5254-5260 [PMID: 18854565 DOI: 10.1200/jco.2008.17.7857]

109 **Constantinidou A**, Cunningham D, Shurmahi F, Asghar U, Barbachano Y, Khan A, Mudan S, Rao S, Chau I. Perioperative chemotherapy with or without bevacizumab in patients with metastatic colorectal cancer undergoing liver resection. *Clin Colorectal Cancer* 2013; **12**: 15-22 [PMID: 23021126 DOI: 10.1016/j.clcc.2012.07.002]

110 **Kitamura H**, Koike S, Nakazawa K, Matsumura H, Yokoi K, Nakagawa K, Arai M. A reversal in the vascularity of metastatic liver tumors from colorectal cancer after the cessation of chemotherapy plus bevacizumab: contrast-enhanced ultrasonography and histological examination. *J Surg Oncol* 2013; **107**: 155-159 [PMID: 22903532 DOI: 10.1002/jso.23244]

111 **Reddy SK**, Morse MA, Hurwitz HI, Bendell JC, Gan TJ, Hill SE, Clary BM. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. *J Am Coll Surg* 2008; **206**: 96-106 [PMID: 18155574 DOI: 10.1016/j.jamcollsurg.2007.06.290]

112 **van der Pool AE**, Marsman HA, Verheij J, Ten Kate FJ, Eggermont AM, Ijzermans JN, Verhoef C. Effect of bevacizumab added preoperatively to oxaliplatin on liver injury and complications after resection of colorectal liver metastases. *J Surg Oncol* 2012; **106**: 892-897 [PMID: 22552819 DOI: 10.1002/jso.23142]

113 **Rubbia-Brandt L**, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, Brezault C, Soubrane O, Abdalla EK, Vauthey JN, Mentha G, Terris B. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. *Histopathology* 2010; **56**: 430-439 [PMID: 20459550 DOI: 10.1111/j.1365-2559.2010.03511.x]

114 **Turan N**, Benekli M, Koca D, Ustaalioglu BO, Dane F, Ozdemir N, Ulas A, Oztop I, Gumus M, Ozturk MA, Berk V, Kucukoner M, Uner A, Balakan O, Helvaci K, Ozkan S, Yilmaz U, Buyukberber S. Adjuvant systemic chemotherapy with or without bevacizumab in patients with resected liver metastases from colorectal cancer. *Oncology* 2013; **84**: 14-21 [PMID: 23076023 DOI: 10.1159/000342429]

115 **Stathopoulos GP**, Batziou C, Trafalis D, Koutantos J, Batzios S, Stathopoulos J, Legakis J, Armakolas A. Treatment of colorectal cancer with and without bevacizumab: a phase III study. *Oncology* 2010; **78**: 376-381 [PMID: 20798560 DOI: 10.1159/000320520]

116 **Starling N**, Vázquez-Mazón F, Cunningham D, Chau I, Tabernero J, Ramos FJ, Iveson TJ, Saunders MP, Aranda E, Countouriotis AM, Ruiz-Garcia A, Wei G, Tursi JM, Guillen-Ponce C, Carrato A. A phase I study of sunitinib in combination with FOLFIRI in patients with untreated metastatic colorectal cancer. *Ann Oncol* 2012; **23**: 119-127 [PMID: 21447616 DOI: 10.1093/annonc/mdr046]

117 **Yoshino T**, Yamazaki K, Hamaguchi T, Shimada Y, Kato K, Yasui H, Boku N, Lechuga MJ, Hirohashi T, Shibata A, Hashigaki S, Li Y, Ohtsu A. Phase I study of sunitinib plus modified FOLFOX6 in Japanese patients with treatment-naive colorectal cancer. *Anticancer Res* 2012; **32**: 973-979 [PMID: 22399619]

118 **Saltz LB**, Rosen LS, Marshall JL, Belt RJ, Hurwitz HI, Eckhardt SG, Bergsland EK, Haller DG, Lockhart AC, Rocha Lima CM, Huang X, DePrimo SE, Chow-Maneval E, Chao RC, Lenz HJ. Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. *J Clin Oncol* 2007; **25**: 4793-4799 [PMID: 17947727 DOI: 10.1200/jco.2007.12.8637]

119 **Carrato A**, Swieboda-Sadlej A, Staszewska-Skurczynska M, Lim R, Roman L, Shparyk Y, Bondarenko I, Jonker DJ, Sun Y, De la Cruz JA, Williams JA, Korytowsky B, Christensen JG, Lin X, Tursi JM, Lechuga MJ, Van Cutsem E. Fluorouracil, leucovorin, and irinotecan plus either sunitinib or placebo in metastatic colorectal cancer: a randomized, phase III trial. *J Clin Oncol* 2013; **31**: 1341-1347 [PMID: 23358972 DOI: 10.1200/jco.2012.45.1930]

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