

# Critical appraisal of bevacizumab in the treatment of metastatic colorectal cancer

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**Abstract:** Colorectal cancer is one of the most common cancers worldwide. The prognosis of patients with metastatic colorectal cancer in recent years has increased from 5 months with best supportive care to nearly 2 years with chemotherapy combined with bevacizumab, an antivascular endothelial growth factor monoclonal antibody. New prognostic and predictive biomarkers have been identified to guide chemotherapy in metastatic colorectal cancer, such as *KRAS* and *BRAF* oncogenes. However, the status of these oncogenes does not affect the efficacy of bevacizumab, and biomarkers predicting response to treatment with bevacizumab are still lacking. Addition of bevacizumab to regimens based on fluoropyrimidines or irinotecan has been shown to improve overall survival in treatment-naïve patients with metastatic colorectal cancer. Similarly, a significant increase in overall survival rate is achieved by adding bevacizumab to fluoropyrimidines and oxaliplatin in patients with disease progression. Bevacizumab has been found to be effective even when used as third-line therapy and later. In addition, cohort studies have shown that bevacizumab improves survival significantly despite disease progression. Finally, bevacizumab therapy in the neoadjuvant setting for the treatment of liver metastasis is well tolerated, safe, and effective.

**Keywords:** metastatic colorectal cancer, bevacizumab, chemotherapy, biomarkers, liver metastases

## Introduction

Colorectal cancer (CRC) is the fourth most common cancer site in the US and the fourth most frequent cause of cancer-related death. In 2010, the estimated number of CRC cases was 142,570, with 51,370 cancer-related deaths.<sup>1</sup> Given that the prognosis of these patients is poor, improvement of treatment remains a priority. Although surgery and chemotherapy are the mainstay of treatment for CRC, their efficacy in patients with metastatic CRC remains unsatisfactory. Based on mechanisms involved in oncogenesis, treatment of metastatic CRC includes both conventional drugs, such as 5-fluorouracil (5-FU) or capecitabine, irinotecan (CPT-11), oxaliplatin (L-OHP), and new targeted agents, such as bevacizumab, cetuximab, and panitumumab. Novel therapeutic approaches have focused on the role of angiogenesis-targeting inhibitors. Angiogenesis is a crucial mechanism for both primary tumor growth and development of metastases.<sup>2,3</sup> Tumor angiogenesis is associated with invasiveness and the metastatic potential of various cancers because of abnormalities in blood vessels supplying tumors' structure and function. Vascular endothelial growth factor (VEGF), the most potent and specific angiogenic factor, regulates normal and pathologic angiogenesis. Increased expression of VEGF has been correlated with risk of metastasis, recurrence, and poor prognosis in many cancers, including CRC.<sup>4-6</sup> Consequently, a recombinant humanized

monoclonal antibody against VEGF, ie, bevacizumab, has been introduced as an antiangiogenic therapeutic strategy in cancer.<sup>3,7</sup> It was found to inhibit the growth of several tumor types in animal models, and was well tolerated in Phase I studies.<sup>4,8</sup> Phase III clinical trials demonstrated its efficacy in different metastatic cancers.<sup>9,10</sup> In patients with metastatic CRC, bevacizumab significantly improves both the tumor response rate and progression-free survival when added to 5-FU and folinic acid (FA).<sup>3,11,12</sup> Subsequent randomized trials showed that bevacizumab increased overall survival, the median being 20.3 months versus 15.6 months when the drug was combined with 5-FU-FA-CPT-11 (IFL schedule) as initial treatment.<sup>3,13</sup> Similarly, when added to L-OHP-5-FU-FA (FOLFOX), bevacizumab increased median overall survival (12.9 months versus 10.8 months) following failure on CPT-11-containing regimens,<sup>3,14</sup> and was able to improve the response rate and progression-free survival when combined with either infusional 5-fluorouracil-bolus folinic acid-irinotecan (FOLFIRI) or FOLFOX in patients with untreated metastatic colorectal cancer.<sup>3,15</sup> The use of bevacizumab as neoadjuvant treatment is another clinically relevant issue.<sup>16</sup> In such a patient setting, addition of bevacizumab increased the objective response rate, so favoring downstaging of the disease and the switch from nonresectable to resectable CRC liver metastasis, increasing the R0 resection rate, as well as sterilization of micrometastatic disease.

Based on data emerging from Phase II, III, and IV trials involving bevacizumab, we developed this systemic review to describe better the effectiveness and tolerability of bevacizumab in combination with standard chemotherapy in the various treatment lines for patients with metastatic colorectal cancer.

## Angiogenesis and vascular endothelial growth factor

Angiogenesis is an essential mechanism for both primary tumor growth and metastasis. Indeed, tumors receive sufficient nutrients and oxygen by simple diffusion up to a size of 1–2 mm, but further growth requires a vascular supply. This process involves formation of new blood vessels which infiltrate the tumor mass.<sup>17</sup> In addition, both physiologic and tumoral angiogenesis involve recruitment of circulating endothelial precursor cells from the bone marrow to promote neovascularization.<sup>18,19</sup> Blood vessels supplying tumors have a number of abnormalities in their structure and function.<sup>20</sup> Secretion of VEGF alters the balance between endothelial cell proliferation and apoptosis, resulting in increased cell

division and angiogenesis.<sup>21,22</sup> Moreover, alterations in the walls of new blood vessels make these susceptible to losses.<sup>23</sup> This mechanism increases interstitial fluid pressure, compromising blood flow to the affected area, and has implications for drug delivery to the tumor.<sup>24</sup> Impaired barrier function also increases extravasation of tumor cells, and thus metastasis, while growth factors produced or released by blood monocytes and macrophages contribute to tumor progression.<sup>20,25</sup> The VEGF receptor is highly expressed on the endothelial cells of blood vessels supplying tumors and promotes growth of endothelial cells in arteries, veins, and lymphatic vessels.<sup>26</sup> In addition, it stimulates angiogenesis *in vivo*,<sup>27</sup> favors vascular permeability and capillary leak,<sup>28</sup> and induces expression of molecules that control adhesion of leukocytes in models of inflammation.<sup>29</sup> These effects occur through binding of VEGF to VEGF receptor-2 (also known as Flk-1 or KDR).<sup>30</sup>

## Bevacizumab and first-line treatment of metastatic CRC

Bevacizumab is a humanized monoclonal antibody that binds to and neutralizes vascular endothelial growth factor A (VEGF-A). Bevacizumab has been investigated for the treatment of different tumors, including metastatic CRC, showing interesting activity with an acceptable profile in term of toxicity. In metastatic CRC, different bevacizumab-based schedules have been developed in order to evaluate the clinical impact of this novel target agent in patients with metastatic CRC. In fact, bevacizumab was studied in diverse combinations of the two most widely used chemotherapy regimens in first-line treatment of metastatic colorectal cancer, ie, FOLFIRI and FOLFOX, and then with the fluoropyrimidine alone, which has always been the cornerstone drug for the treatment of this disease.

## Bevacizumab with fluoropyrimidines plus CPT-11 (IFL, FOLFIRI)

The efficacy and tolerability of bevacizumab in combination with bolus 5-FU-FA-CPT-11 (IFL schedule) versus 5-FU-FA-CPT-11 (IFL) alone as first-line treatment have been investigated in 813 patients with advanced colorectal cancer.<sup>13</sup> Patients were randomized to receive IFL + bevacizumab or IFL + placebo. Significant improvements in overall survival, progression-free survival, and response rate were observed with IFL + bevacizumab. In detail, median overall survival was 20.3 months versus 15.6 months (hazards ratio [HR] 0.66;  $P < 0.001$ ), median progression-free

survival was 10.6 months versus 6.2 months (HR 0.54;  $P < 0.001$ ), while the corresponding response rates were, respectively, 44.8% and 34.8% ( $P = 0.004$ ). Therefore, according to these results, bevacizumab was approved for first-line treatment of metastatic CRC by the US Food And Drug Administration in 2004. However, successive studies failed to confirm the overall survival values previously observed.<sup>31</sup> Indeed, a Phase III study randomized 222 treatment-naïve patients to either IFL + bevacizumab or IFL alone, but no significant difference was found for either overall survival or response rate.<sup>32</sup> However, use of infusional 5-FU-based regimens, such as FOLFIRI, was considered a strategy suitable to achieve better results.<sup>31,33</sup> One study randomized 117 patients to either FOLFIRI + bevacizumab or IFL + bevacizumab.<sup>33</sup> Although the median progression-free survival and response rates did not differ, the FOLFIRI + bevacizumab regimen achieved significantly longer overall survival (Table 1). The combination of IFL or

FOLFIRI + bevacizumab was generally well tolerated, with an increase only in hypertensive events in patients treated with bevacizumab.

### Bevacizumab with fluoropyrimidines + oxaliplatin (FOLFOX, Capecitabine + L-OHP [XELOX])

Results of the N9741 study demonstrated the superiority of FOLFOX4 (infusional 5-FU + L-OHP) over IFL in terms of both progression-free and overall survival.<sup>4,36</sup> Addition of bevacizumab to L-OHP-based chemotherapy achieved a higher progression-free survival as compared with placebo (median 9.4 months versus 8.0 months; HR 0.83; 97.5% confidence interval [CI] 0.72–0.95;  $P = 0.0023$ ), while both overall survival and response rate did not significantly differ. The relatively modest improvements in progression-free survival and overall survival associated with bevacizumab may be explained by the inability to continue treatment

**Table 1** Response rate, progression-free survival, and overall survival of bevacizumab in first-line treatment of metastatic colorectal cancer

Author	Phase study	Treatment	Population	Median OS (months)	HR, P value	Median PFS (months)	HR, P value	RR (%)	OR, P value
Bevacizumab with fluoropyrimidines plus irinotecan									
Hurwitz et al <sup>13</sup>	III	IFL-placebo	411	15.6		6.2		34.8	
		IFL-BV	402	20.3	0.66,	10.6	0.54,	44.8	$P = 0.004$
		5-FU-FA-BV	110	18.3	$P < 0.001$	8.8	$P < 0.001$	40	
Stathopoulos et al <sup>32</sup>	III	IFL-Placebo	108	25.0	$P = 0.1391$	NR	NR	35.2	
		IFL-BV	114	22.0		NR		36.8	
Fuchs et al <sup>33</sup>	III	FOLFIRI-BV	57	28.0	$P = 0.007$	11.2	$P = 0.28$	57.9	NR
		mIFL-BV	60	19.8		8.3		53.3	
Sobrero et al <sup>34</sup>	IV	FOLFIRI-BV	209	22.2	NR	11.1	NR	53.1	NR
Kopetz et al <sup>35</sup>	II	FOLFIRI-BV	43	31.3	NR	12.8	NR	65	NR
Bevacizumab with fluoropyrimidines plus oxaliplatin									
Saltz et al <sup>15</sup>	III	XELOX-FOLFOX4-placebo	701	19.9	0.89,	8.0	0.83,	49	0.90,
		XELOX-FOLFOX4-BV	699	21.3	$P = 0.0769$	9.4	$P = 0.0023$	47	$P = 0.31$
Hochster et al <sup>37</sup>	III	FOLFOX-BV	71	26.1	NR	NR	NR	52	NR
		bFOL-BV	70	20.4				39	
		CapeOx-BV	72	24.6				46	
Bevacizumab with fluoropyrimidines alone									
Kabbinavar et al <sup>11</sup>	II	5-FU-FA	36	13.8		NR	NR	17	NR
		5-FU-FA-BV (5 mg/g)	35	21.5	0.63			40	
		5-FU-FA-BV (10 mg/kg)	33	16.1	1.17			24	
		5-FU-FA-placebo	105	12.9	0.79,	5.5	0.50,	15	$P = 0.0552$
Kabbinavar et al <sup>12</sup>	II	5-FU-FA-BV	104	16.6	$P = 0.159$	9.2	$P = 0.0002$	26	
Tebbutt et al <sup>38</sup>	III	Capecitabine	156	18.9	0.875,	5.7	0.63,	30.3	$P = 0.16$
		Capecitabine-BV	157	18.9	$P = 0.314$	8.5	$P < 0.001$	38.1	$P = 0.006$
		Capecitabine-BV-mitomycin	158	16.4	0.942,	8.4	0.59,	45.9	
					$P = 0.642$		$P < 0.001$		

**Abbreviations:** OS, overall survival; PFS, progression-free survival; RR, response rate; HR, hazard ratio; OR, odds ratio; IFL, bolus 5-fluorouracil-folinic acid-irinotecan; BV, bevacizumab; 5-FU, 5-fluorouracil; FA, folinic acid; FOLFIRI, infusional 5-fluorouracil-bolus folinic acid-irinotecan; mIFL, modified bolus 5-fluorouracil-irinotecan; FOLFOX4, infusional 5-fluorouracil-bolus folinic acid-oxaliplatin; XELOX, capecitabine-oxaliplatin; bFOL, bolus 5-fluorouracil-oxaliplatin; CapeOx, capecitabine-oxaliplatin; NR, not reported.

until progression in the majority of patients, and has led to the hypothesis that continuing bevacizumab alone until disease progression may be necessary.<sup>15</sup> In the TREE-2 trial,<sup>37</sup> 213 untreated patients with metastatic CRC were randomly assigned to bevacizumab in combination with three different schedules of fluoropyrimidines and oxaliplatin. Bevacizumab improved the response rate, time to progression, and median overall survival for all three regimens (Table 1). Toxicities from the FOLFOX and bevacizumab combination were generally characterized by chemotherapy-related events, such as neurotoxicity, gastrointestinal toxicity, and myelosuppression, rather than events related to bevacizumab.

### Bevacizumab with fluoropyrimidines alone (5-FU-FA, capecitabine)

The efficacy of bevacizumab in addition to 5-FU-FA versus 5-FU-FA alone in patients with untreated metastatic CRC has been investigated in two randomized Phase II trials.<sup>11,12</sup> In the first trial,<sup>11</sup> 104 patients were randomly assigned to receive 5-FU-FA combined with bevacizumab 10 mg/kg, 5-FU-FA combined with bevacizumab 5 mg/kg, or 5-FU-FA alone. Bevacizumab was administered until disease progression. Irrespective of dose, improvement in both time to progression and response rate was observed following use of bevacizumab, while there was no significant improvement in median overall survival. Similarly, in the other trial,<sup>12</sup> 209 patients were randomly assigned to either 5-FU-FA + placebo or 5-FU-FA + bevacizumab. The latter regimen achieved better progression-free survival and response rates, but not for overall survival. In another Phase III study,<sup>38</sup> 407 patients with metastatic CRC received capecitabine, capecitabine + bevacizumab, or capecitabine + bevacizumab + mitomycin. Both combined regimens achieved higher progression-free survival as compared with capecitabine alone (Table 1). Bevacizumab in combination with fluoropyrimidines was moderately tolerated, with bleeding, hypertension, and thrombosis more frequently observed in the bevacizumab arm.

### Bevacizumab as second-line therapy

A randomized Phase III trial<sup>14</sup> was designed to evaluate the efficacy of bevacizumab + FOLFOX4 compared with FOLFOX4 alone as second-line therapy for patients with metastatic CRC. Patients were eligible if they had previously received CPT-11 with fluoropyrimidines for advanced disease. Overall, 829 patients were enrolled, whereby 286 received FOLFOX4 + bevacizumab, 291 patients received FOLFOX4

alone, and 243 patients received bevacizumab alone (this arm was closed early due to inferior efficacy). At a median follow-up of 28 months, patients treated with bevacizumab in combination with FOLFOX4 had a median overall survival of 12.9 months as compared with 10.8 months for those treated with FOLFOX4 alone (HR 0.75;  $P = 0.0011$ ). In addition, the combination of bevacizumab and FOLFOX4 resulted in a statistically significant improvement in progression-free survival compared with chemotherapy alone (7.3 versus 4.7 months; HR 0.61;  $P < 0.0001$ ). In addition, 22.7% and 8.6% of patients achieved a confirmed response following FOLFOX + bevacizumab as compared with FOLFOX alone, respectively ( $P < 0.000$ ). Therefore, bevacizumab was approved by the US Food And Drug Administration in 2006 as second-line treatment.<sup>39</sup>

Another study investigated the efficacy of bevacizumab + FOLFIRI in patients with metastatic CRC who failed oxaliplatin-containing regimens without bevacizumab.<sup>40</sup> A total of 115 patients received bevacizumab + FOLFIRI after failure of oxaliplatin and fluoropyrimidines (FOLFIRI + bevacizumab after L-OHP-5-FU group), and 45 patients received bevacizumab + FOLFOX after failure of CPT-11 and fluoropyrimidines (FOLFOX + bevacizumab after CPT-11-5-FU group). Median progression-free survival were 8.3 months versus 7.8 months, respectively, median overall survival was 21.6 months and 16.5 months, and the response rate was 25% and 29%. Moreover, other studies showed that bevacizumab + CPT-11 was an active and safe treatment option for patients failing L-OHP-based therapy.<sup>41-43</sup> BEVA-COLOR was a prospective Phase II trial assessing the efficacy and safety of bevacizumab combined with chemotherapy regimens commonly used in the second-line treatment of metastatic CRC. Overall, 53 patients with metastatic CRC who progressed or relapsed after first-line oxaliplatin-based or CPT-11-based treatment received bevacizumab combined with chemotherapy (FOLFIRI, FOLFOX, or capecitabine + CPT-11 [XELIRI]) until disease progression. The disease control rate was 87%, the response rate was 32%, the median progression-free survival was 6.5 months, and median overall survival was 19.3 months. These data confirmed the efficacy of bevacizumab in combination with any regimen of chemotherapy as second-line treatment in patients with metastatic CRC.<sup>44</sup>

The efficacy of bevacizumab in combination with fluoropyrimidines has been evaluated as a third-line treatment in 100 patients who failed CPT-11-based and oxaliplatin-based chemotherapy regimens.<sup>45</sup> The response rate was 4%, median progression-free survival was 3.5 months, and

median overall survival was 9 months. According to this study, use of third-line fluoropyrimidines + bevacizumab in chemoresistant patients is an ineffective treatment. However, additional reports presented different results.<sup>46</sup> Two studies evaluated the efficacy and safety of bevacizumab + FOLFIRI or FOLFOX in metastatic CRC after failure with FOLFIRI and FOLFOX, using a retrospective analysis. The data showed that bevacizumab + FOLFIRI or FOLFOX (as third-line or more therapy) has modest activity with a relatively tolerable impact.<sup>47,48</sup> A summary of the data for bevacizumab-combined chemotherapy as a second-line treatment in patients with metastatic CRC is shown in Table 2.

## Bevacizumab and neoadjuvant treatment of liver metastases

Surgical resection offers the chance of long-term survival in patients with CRC and hepatic or pulmonary metastases, with a 25%–35% survival rate at 5 years observed after complete resection.<sup>52</sup> European guidelines recommend use of perioperative chemotherapy administered 3 months before and 3 months after surgery in patients with resectable liver metastases.<sup>52</sup> Use of bevacizumab in combination with chemotherapy improves the outcomes in these patients. However, as shown in Table 3, the majority of data come from retrospective studies. Bevacizumab did not significantly improve the response rate when added to a combination of oxaliplatin and fluoropyrimidine compared with oxaliplatin or fluoropyrimidine alone,<sup>15</sup> and there was no statistically significant difference in resection rates in patients treated with bevacizumab compared with placebo.<sup>55</sup>

A recent prospective study enrolled 46 patients with only liver metastases treated with neoadjuvant chemotherapy according to the XELOX + bevacizumab regimen. The radiologic response rate was 78%, the conversion rate of nonresectable liver metastases was 40%, and the rate of surgery with curative intent was 17.7%, with an R0 of 6.52%.<sup>54</sup> Addition of bevacizumab to oxaliplatin-based chemotherapy significantly reduced the number of residual tumor cells as compared with placebo (23% versus 45%,  $P = 0.02$ ),<sup>56</sup> without increasing the complete response rate (11.3% versus 11.6%,  $P = 0.59$ ). Later, in 2010, an additional retrospective analysis<sup>57</sup> on the same two studies assessed the correlation between bevacizumab and tumor regression grade (TRG), and how TRG was associated with overall survival and disease-free survival. Metastases for 100 patients were analyzed, and the results showed an increase in pathologic responses and a reduction

**Table 2** Response rate, progression-free survival, and overall survival of bevacizumab in second-line and later-line treatment of metastatic colorectal cancer

Author	Phase study	Treatment line	Treatment	Treatment	Population	Median OS (months)	HR, P value	Median PFS (months)	HR, P value	RR (%)	OR, P value
Giantonio et al <sup>14</sup>	III	II	FOLFOX4	FOLFOX4-BV	291	12.9	0.75,	7.3	0.61,	22.7	$P < 0.001$
					289	10.8	$P = 0.0011$	4.7	$P < 0.0001$	8.6	
Yildiz et al <sup>41</sup>	Retrospective	II	BV + irinotecan-based therapy		243	10.2		2.7		3.3	
Horita et al <sup>42</sup>	II	II	FOLFIRI-BV		40	14	NR	6	NR	20	NR
Morikawi et al <sup>40</sup>	Cohort	II	FOLFIRI-BV		25	21.4	NR	11.6	NR	32	NR
					115	21.6	NR	8.3	NR	25	NR
Bennouna et al <sup>44</sup>	II	II	FOLFOX4-BV		45	16.5		7.8		29	
					53	19.3	NR	6.5	NR	32	NR
Chen et al <sup>45</sup>	II	III	oxaliplatin-based therapy		100	9.1	NR	3.7	NR	4	NR
Park et al <sup>46</sup>	Retrospective	II or later-line	BV-5-FU-FA	BV-FOLFIRI or FOLFOX4	40	14	NR	6.3	NR	7.5	NR
Lievre et al <sup>47</sup>	Retrospective	II or later-line	BV + FOLFIRI or FOLFOX4		31	18.4	NR	9.7	NR	32.2	NR
Kwon et al <sup>49</sup>	Retrospective	III	BV-FOLFIRI		14	10.9	NR	3.9	NR	28.5	NR
Kang et al <sup>48</sup>	Retrospective	III or later-line	BV-FOLFIRI or FOLFOX4		42	0.5	NR	5.3	NR	9.5	NR

**Abbreviations:** OS, overall survival; PFS, progression-free survival; RR, response rate; HR, hazard ratio; OR, odds ratio; BV, bevacizumab; 5-FU, 5-fluorouracil; FA, folinic acid; FOLFIRI, infusional 5-fluorouracil-bolus folinic acid-irinotecan; FOLFOX4, infusional 5-fluorouracil-bolus folinic acid-oxaliplatin; NR, not reported.



**Table 3** Response and resectability of liver metastatic disease treated with neoadjuvant bevacizumab + chemotherapy

Author	Phase Study	Liver metastases	Treatment	Population	RR (%)	Surgery R0 (%)	Curative intent rate (%)
Van Cutsem et al <sup>50</sup>	IV	No operable	BV-FOLFIRI BV-FOLFOX	704	NR NR	11.7 15.4	14.3 20.3
Gruenberger et al <sup>16</sup>	II	Operable	BV-XELOX	56	73.2	92.85	92.85
Bouganim et al <sup>51</sup>	Retrospective	Operable	BV-oxaliplatin BV-irinotecan	60	80	NR	100
Blazer et al <sup>52</sup>	Retrospective	No operable	BV-FOLFIRI-XELIRI BV-FOLFOX-XELOX	305	40.7 62.9	89.83 NR	8.85
Masi et al <sup>53</sup>	II	No operable	BV-FOLFOXIRI	30	NR	43	NR
Wong et al <sup>54</sup>	II	No operable	BV-CAPOX	45	78	6.52	17.7

**Abbreviations:** RR, response rate; BV, bevacizumab; FOLFIRI, infusional 5-fluorouracil-bolus folinic acid-irinotecan; FOLFOX, infusional 5-fluorouracil-bolus folinic acid-oxaliplatin; XELOX, capecitabine-oxaliplatin; CAPOX, capecitabine-oxaliplatin; NR, not reported.

of TRG in patients who received neoadjuvant treatment with bevacizumab ( $P = 0.008$ ). In that study, TRG was divided as follows: TRG1–TRG2, greater (major) histologic response; TRG3, partial histologic response; TRG4–TRG5, no pathologic (histologic) response. In the group of patients treated with bevacizumab, 34% obtained no histologic response versus 66% in the group treated with chemotherapy alone; 38% of patients treated with bevacizumab obtained a major histologic response versus 10% in the group treated with chemotherapy alone ( $P < 0.001$ ). The same percentage of partial histologic response was reached in both groups. TRG differences were then related to differences in overall survival ( $P = 0.036$ ) and disease-free survival ( $P = 0.020$ ). Median survival was 67 months in the major histologic response group and 44 months in the partial histologic response and no histologic response groups. Disease-free survival at 5 years was 34%, 20%, and 9% respectively. From the data obtained, the role of TRG is identified as an essential pathologic parameter to define the outcomes of patients with colorectal liver metastases, because it correlates with statistically significant overall and disease-free survival of patients in this setting. Liver surgery is usually feasible after administration of anti-VEGF-containing combination regimens. Complications, such as delayed wound healing, gastrointestinal perforation, or bleeding, have been reported when bevacizumab is administered, and could potentially interfere with surgery.<sup>13,15,55</sup> However, a recent report has shown that liver surgery can be safely carried out without a significant increase in postoperative complications when bevacizumab is discontinued 6–8 weeks before surgery, although 4–5 weeks may be sufficient.<sup>55</sup> Therefore, bevacizumab in

the neoadjuvant setting for treatment of liver metastasis is well tolerated, safe, and effective.

## Maintenance therapy with bevacizumab

The current standard treatment for patients with advanced CRC is administration of all available drugs either sequentially or in combination until disease progression or unacceptable toxicity.<sup>58</sup> Data on the use of bevacizumab as maintenance treatment are provided in Table 4. Management of patients with metastatic CRC with disease progression on a bevacizumab-containing regimen is challenging for the oncologist. The observational BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects) cohort study showed that changing the chemotherapy regimen (but continuing bevacizumab) after disease progression was associated with significantly greater overall survival than continuing chemotherapy without bevacizumab (31.8 months versus 19.9 months; HR 0.48,  $P < 0.001$ ).<sup>59</sup>

A study enrolling 820 patients with unresectable metastatic CRC who progressed within 3 months after discontinuation of first-line bevacizumab combined with chemotherapy were randomized to second-line fluoropyrimidine-based chemotherapy  $\pm$  weekly bevacizumab.<sup>60</sup> The choice of either L-OHP-based or CPT-11-based second-line chemotherapy was related to the first-line regimen used. The primary endpoint was overall survival, while secondary endpoints included progression-free survival, response rate, and safety. Median overall survival was 11.2 months for bevacizumab + chemotherapy and 9.8 months for chemotherapy alone (HR 0.81; 95% CI 0.69–0.94;  $P = 0.0062$ ). Median progression-free survival was 5.7 months for bevacizumab + chemotherapy

**Table 4** Overall survival, progression-free survival, and response rate of bevacizumab continued beyond first progression and in maintenance treatment

Author	Phase study	Treatment	Overall	Median OS (months)	HR, P value	Median PFS (months)	HR, P value	RR (%)	OR, P value
Grothey et al <sup>59,*</sup>	Prospective	Post progression treatment without BV	531	19.9	0.49,	NR	NR	NR	NR
		Post progression treatment with BV	642	31.8	$P < 0.001$	NR	NR	NR	NR
Andre et al <sup>60,*</sup>	III	II line CT until PD	411	9.8	0.81,	4.1	0.68,	3.9	$P = 3113$
		II line CT + BV until PD	409	11.2	$P = 0.0062$	5.7	$P < 0.0001$	5.4	
Grothey et al <sup>62,§</sup>	III	Conventional L-OHP	139	NR	NR	7.3	NR	NR	NR
		Intermittent L-OHP + BV		NR		12		NR	NR
Diaz-Rubio et al <sup>63,§</sup>	III	XELOX + BV →	239	23.3	1.05,	10.4	1.10,	47%	0.95
		XELOX + BV	241	20.0	$P = 0.65$	9.7	$P = 0.38$	49%	
		XELOX + BV → BV							
Tournigand et al <sup>64,§</sup>	III	BV + erlotinib	222	NR	NR	5.76	0.73,	NR	NR
		BV	226	NR		4.67	$P = 0.0050$	NR	
Johnsson et al <sup>65,§</sup>	III	BV + erlotinib	249	NR	NR	5.9	0.81,	NR	NR
		BV		NR		4.2	$P = 0.24$	NR	

**Notes:** \*BV continued beyond first progression; §BV used as maintenance treatment.

**Abbreviations:** OR, odds ratio; OS, overall survival; PFS, progression-free survival; BV, bevacizumab; CT, chemotherapy; HR, hazard ratio; L-OHP, oxaliplatin; XELOX, capecitabine-oxaliplatin; NR, not reported; PD, progression disease; RR, response rate.

and 4.1 months for chemotherapy alone (HR 0.68; 95% CI 0.59–0.78;  $P < 0.0001$ ). The response rate was 5.4% for bevacizumab + chemotherapy and 3.9% for chemotherapy alone ( $P = 0.3113$ ). Bevacizumab-related adverse events were not increased when continuing bevacizumab beyond progression. Subsequent subanalysis conducted on the same population assessed the benefit of continuing bevacizumab after progression in relation to *KRAS* status, and the results were that patients with wild-type and mutated *KRAS* tumors were likely to benefit from bevacizumab treatment<sup>61</sup> (Table 5).

Maintenance treatment with fluoropyrimidine and bevacizumab was evaluated in CONcePT (the Combined Oxaliplatin Neuropathy Prevention Trial).<sup>62</sup> This study was designed to monitor patients with metastatic CRC receiving oxaliplatin + bevacizumab as first-line treatment and to evaluate whether an intermittent L-OHP schedule of FOLFOX + bevacizumab reduces cumulative neurotoxicity. Progression-free survival with continuous administration was 7.3 months compared with 12.0 months with the “stop-and-go” strategy. Maintenance therapy with bevacizumab alone was compared with continuous XELOX + bevacizumab therapy in the MACRO (Spanish Maintenance in Colorectal Cancer) trial.<sup>63</sup> Median progression-free survival was 10.4 months in the continuous (control) arm and 9.7 months in the maintenance (investigational) arm, with a HR of 1.11 (95% CI 0.89–1.37); median overall survival

was 22.4 versus 21.7 months (HR 1.04), with no benefit for continuous chemotherapy in combination with bevacizumab versus bevacizumab alone. Finally, in the Phase III GERCOR DREAM trial,<sup>64</sup> 700 patients were randomized, after bevacizumab-based induction chemotherapy with FOLFOX, XELOX, or FOLFIRI, to receive either maintenance therapy with bevacizumab alone or a combination of bevacizumab + erlotinib until progression or unacceptable toxicity. After 31 months of follow-up, median progression-free survival was 4.6 months in the bevacizumab group versus 5.8 months in the bevacizumab + erlotinib group (HR 0.73; 95% CI 0.59–0.91,  $P = 0.005$ ).

## Predictive biomarkers for bevacizumab treatment

Efficacy of bevacizumab therapy is independent of *KRAS*, *BRAF*, or *p53* status.<sup>66</sup> Mutation in *KRAS* strongly predicts a lack of response to anti-epidermal growth factor receptor antibodies. Selection of *KRAS* for these analyses was based upon evidence that *KRAS* is a negative prognostic factor in patients with metastatic CRC<sup>67,68</sup> and regulates VEGF and other angiogenic factors.<sup>69,70</sup> To describe better the clinical benefit of bevacizumab according to *KRAS* mutation status in this patient population, Hurwitz et al<sup>71</sup> conducted additional statistical analyses with data from *KRAS* mutation analyses in 230 patients who were treated with IFL in combination with either bevacizumab or placebo in a randomized

**Table 5** Response rate, overall survival, and progression-free survival: comparability of results between wild-type *KRAS* versus mutated *KRAS* groups and wild-type *BRAF* versus mutated *BRAF* groups

Author	Treatment	Population	RR (%)	OR, P value	Median OS (months)	HR, P value	Median PFS (months)	HR, P value
Hurwitz et al <sup>71</sup>	IFL-placebo wt-Kras	67	37.3	$P = 0.006$	17.6	0.58,	7.4	0.44,
	IFL-BV wt-Kras	85	60	$P = 0.86$	27.7	$P = 0.04$ ;	13.5	$P < 0.0001$ ;
	IFL-placebo mut-Kras	34	41.2		13.6	0.69,	5.5	0.41,
	IFL-BV mut-Kras	44	44		19.9	$P = 0.26$	9.3	$P = 0.0008$
Price et al <sup>72</sup>	Cape wt-Kras	315	27.1	$P = 0.02$	20	NR	5.9	NR
	Cape mut-Kras		48.5		22.8		6.2	
	CB wt-Kras		41		19.8		8.8	
	CB mut-Kras		24.2		17.6	NR	8.2	NR
	CBM wt-Kras		44.7		21.4	NR	6	NR
	CBM mut-Kras		45.8		6.3		2.5	
	Cape wt-Braf	315	35.5	$P = 0.91$	20.8	NR	9.1	NR
	Cape mut-Braf		25		9.2		5.5	
	CB wt-Braf		35.6					
	CB mut-Braf		42.9					
	CBM wt-Braf		48.2					
	CBM mut-Braf		27.8					
	Tol et al <sup>73</sup>	Cape-L-OHP-BVwt-Kras	156	50	$P = 0.16$	22.4	$P = 0.82$	10.6
Cape-L-OHP-BV mut-Kras		108	59.2	$P = 0.03$	24.9	$P = 0.06$	12.5	$P = 0.04$
Cape-L-OHP-BV-C wt-Kras		158	61.4		21.8		10.5	
Cape-L-OHP-BV-C mut-Kras		98	45.9		17.2		8.1	
Hecht et al <sup>74</sup>	L-OHP-CT-BV wt-Kras	203	56	NR	24.5	HR, 1.89;	11.5	HR, 1.36;
	L-OHP-CT-BV-P wt-Kras	201	50		20.7		9.8	
	L-OHP-CT-BV mut-Kras	125	44	NR	19.3	HR, 1.02	11	HR, 1.25
	L-OHP-CT-BV-P mut-Kras	135	47		19.3		10.4	
	CPT-11-CT-BV wt-Kras	58	48	NR	19.8	HR, 1.28 to NR;	12.5	HR, 1.50;
	CPT-11-CT-BV-P wt-Kras	57	54		NR	HR, 2.14	10	
	CPT-11-CT-BV mut-Kras	39	38	NR	20.5		11.9	HR, 1.19
	CPT-11-CT-BV-P mut-Kras	47	30		17.8		8.3	
Van Cutsem et al <sup>61</sup>	II line CT wt-Kras	316	NR	NR	11.1	HR, 0.69	4.5	HR, 0.61
	II line CT + BV wt-Kras	300	NR		15.4	$P = 0.0052$ ;	6.4	$P < 0.0001$ ;
	II line CT mut-Kras		NR	NR	10	HR, 0.91	4.1	HR, 0.70
	II line CT + BV mut-Kras		NR		10.4	$P = 0.4969$	5.5	$P = 0.0027$

**Note:** All studies are Phase III.

**Abbreviations:** OS, overall survival; PFS, progression-free survival; RR, response rate; HR, hazard ratio; OR, odds ratio; IFL, bolus 5-fluorouracil-folinic acid-irinotecan; BV, bevacizumab; Cape, capecitabine; CB, capecitabine, bevacizumab; CBM, capecitabine, bevacizumab, mitomycin; wt, wild-type; mut, mutated; vs, versus; L-OHP, oxaliplatin; C, cetuximab; CPT-11, irinotecan; L-OHP-CT, oxaliplatin-based chemotherapy; CPT-11-CT, irinotecan-based chemotherapy; P, panitumumab; NR, not reported.

Phase III study.<sup>13</sup> In both wild-type *KRAS* and mutated *KRAS* groups, addition of bevacizumab to IFL chemotherapy resulted in a statistically significant longer progression-free survival time, with comparable HR for progression. In the wild-type *KRAS* group, the median progression-free survival was 13.5 months for IFL + bevacizumab versus 7.4 months for IFL + placebo (HR 0.44; 95% CI 0.29–0.67;  $P < 0.0001$ ). For the mutated *KRAS* group, median progression-free survival was 9.3 months for IFL + bevacizumab versus 5.5 months for IFL + placebo (HR 0.41; 95% CI 0.24–0.70;  $P = 0.0008$ ). In the wild-type *KRAS* group, the median overall survival was 27.7 months for IFL + bevacizumab versus 17.6 months for IFL + placebo (HR 0.58; 95% CI 0.34–0.99;  $P = 0.04$ ). For the mutated *KRAS* group, median overall survival was

19.9 months for IFL + bevacizumab versus 13.6 months for IFL + placebo (HR 0.69; 95% CI 0.37–1.31;  $P = 0.26$ ). These data suggest that *KRAS* status does not predict any clinical benefit from addition of bevacizumab to first-line IFL chemotherapy. The predictive value of *KRAS* and *BRAF* gene mutation status in patients receiving capecitabine with or without bevacizumab has been evaluated in the Phase III AGITG MAX trial.<sup>72</sup> The data showed that progression-free survival ( $P = 0.95$ ) and overall survival ( $P = 0.43$ ) did not differ significantly between patients with wild-type *KRAS* and those with mutated *KRAS*. Similarly, no difference emerged in progression-free survival ( $P = 0.46$ ) or overall survival ( $P = 0.32$ ) based on *BRAF* status. The data are summarized in Table 5.



## Bevacizumab and anti-EGFR monoclonal antibodies

Inhibition of a single signal transduction pathway is unlikely to provide optimal results and, therefore, a combination of agents appears to be a valid strategy. Some studies have suggested that blocking both VEGF and epidermal growth factor receptor pathways may increase antitumoral activity.<sup>75,76</sup> The BOND-2 study<sup>77</sup> was a Phase II trial that investigated administration of either cetuximab + bevacizumab + CPT-11 or cetuximab + bevacizumab alone in 43 patients with CPT-11-refractory CRC. Overall survival was 14.5 months versus 11.4 months, respectively, with a similar toxicity profile. The CAIRO-2 study<sup>73</sup> was a Phase III trial of capecitabine, oxaliplatin + bevacizumab ± cetuximab. There was a significant decrease in progression-free survival in the cetuximab + bevacizumab arm as compared with the bevacizumab alone arm (9.8 versus 10.7 months;  $P = 0.019$ ). Overall survival and response rates did not differ significantly between the two groups (Table 5). The PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) trial<sup>74</sup> was a randomized Phase IIIB study that evaluated the efficacy and safety of bevacizumab and chemotherapy ± panitumumab (completely humanized monoclonal antibody against epidermal growth factor receptor) in patients with untreated metastatic CRC. A total of 823 and 230 patients, respectively, were randomly assigned to the oxaliplatin and CPT-11 cohorts. Panitumumab was discontinued after a planned interim analysis of 812 oxaliplatin patients due to worse efficacy in the panitumumab arm. Indeed, addition to panitumumab to bevacizumab decreased both progression-free survival (HR 1.27; 95% CI 1.06–1.52) and overall survival (HR 1.43; 95% CI 1.11–1.83). In addition, *KRAS* analysis showed a worst outcome in the panitumumab arm in both wild-type and mutated groups (Table 5). Combination of

anti-epidermal growth factor receptor monoclonal antibody with bevacizumab and oxaliplatin-based or CPT-11-based chemotherapy achieved disappointingly low progression-free survival and overall survival (Table 6) and, consequently, such a combination is not recommended for treatment of metastatic CRC.

## Treatment-related toxicity

Addition of bevacizumab increases the risk of hypertension, proteinuria, bleeding, thromboembolic events, and treatment interruption (HR 1.47; 95% CI 1.19–1.83;  $P = 0.0004$ ),<sup>31</sup> particularly with the oxaliplatin-containing regimen.<sup>15</sup> A meta-analysis of five trials found that grade 3 or 4 adverse events were approximately 10% points higher among patients receiving chemotherapy + bevacizumab than those receiving chemotherapy alone, with a statistically significant difference (OR 1.79; 95% CI 1.52–2.11;  $P = 0.01$ ). The pooled estimate found a significantly higher incidence of grade 3 or 4 hypertension (OR 4.19; 95% CI 2.76–6.36;  $P < 0.01$ ), grade 3 or 4 thromboembolic/thrombotic events (OR 1.75; 95% CI 1.21–2.53;  $P < 0.01$ ), grade 3 or 4 bleeding (OR 1.87; 95% CI 1.10–3.12;  $P = 0.02$ ), and gastrointestinal perforation (OR 4.81; 95% CI 1.52–15.3;  $P = 0.00$ ) associated with bevacizumab. No statistically significant difference was noted in the incidence of grade 3 or 4 proteinuria, leucopenia, and diarrhea. Elderly patients seem to be at increased risk of stroke and other arterial events following therapy with bevacizumab. However, although the incidence of thromboembolic events increased with age, the increase was not statistically significant after adjustment for baseline Eastern Cooperative Oncology Group performance score and prior history of thromboembolic events.<sup>78</sup> Moreover, other studies failed to find an increased incidence of adverse events in

**Table 6** Bevacizumab and anti-epithelial growth factor receptor monoclonal antibodies

Author	Phase study	Treatment	Population	Median OS (months)	HR, P value	Median PFS (months)	HR, P value	RR (%)	OR, P value
Saltz et al <sup>77</sup>	II	CPT-11-BV-Cmab	43	14.5	NR	7.3	NR	37	NR
		BV-Cmab	40	11.4		4.9	20		
Tol et al <sup>73</sup>	III	Cape-L-OHP-BV	368	20.3	$P = 0.16$	10.7	$P = 0.01$	50	$P = 0.49$
		Cape-L-OHP-BC-Cmab	368	19.4		9.4	52.7		
Hecht et al <sup>74</sup>	IIIB	L-OHP-CT-BV	410	24.5	HR, 1.43	11.4	HR, 1.06	48	NR
		L-OHP-CT-BV-Pmab	413	19.4		10	46		
		CPT-11-CT-BV	115	20.5	HR, 1.42	11.7	HR, 1.19	46	NR
		CPT-11-CT-BV-Pmab	115	20.7		10.1	49		

**Abbreviations:** OS, overall survival; PFS, progression-free survival; RR, response rate; HR, hazard ratio; OR, odds ratio; BV, bevacizumab; Cmab, cetuximab; Pmab, panitumumab; Cape, capecitabine; L-OHP, oxaliplatin; CPT-11, irinotecan; L-OHP-CT, oxaliplatin-based chemotherapy; CPT-11-CT, CPT-11-based chemotherapy; NR, not reported.

elderly as compared with young patients.<sup>79,80</sup> Bevacizumab therapy could increase post-surgical complication rate by blocking neoangiogenesis. However, a study of 186 cases failed to demonstrate liver toxicity or increased postoperative morbidity and mortality.<sup>81</sup> Some studies found that surgical complications are more frequent in patients who underwent surgery within 8 weeks of bevacizumab therapy as compared with those stopping the antibody earlier (65.5% versus 30.4%).<sup>82</sup> Therefore, it is currently recommended to stop bevacizumab at least 6 weeks prior surgery, and to resume it after 28 days, making sure that the wound has healed well.<sup>50,83</sup> A retrospective analysis<sup>84</sup> of two Phase II studies<sup>50,85</sup> evaluated the role of bevacizumab therapy on liver parenchyma. One of the two studies enrolled 56 patients undergoing neoadjuvant chemotherapy with XELOX + bevacizumab, while in the second study, 50 patients were treated with neoadjuvant FOLFOX or XELOX. In both studies, patients underwent surgery for hepatic metastasectomy 2–5 weeks following the end of chemotherapy. Dilation of hepatic sinusoids, perisinusoidal fibrosis, and hepatocellular necrosis were reduced in patients who received bevacizumab versus those treated with chemotherapy alone (42.3% versus 52.2%,  $P < 0.05$ ). These data would suggest that bevacizumab could reduce typical hepatic toxicities of chemotherapeutic drugs used in the neoadjuvant treatment of liver metastases.

## Conclusion

Targeted agents have expanded the available treatment options for patients with metastatic CRC. Some investigations are in progress to determine genetic profiles and predictors of therapeutic success and to identify patients who may benefit from targeted agents. The best combination of these biologic drugs with standard chemotherapy agents, such as oxaliplatin, CPT-11, and fluoropyrimidines, remains to be identified. Addition of bevacizumab to fluoropyrimidine-based chemotherapy improved efficacy as compared with chemotherapy alone in both first-line and second-line treatment trials. In detail, first-line chemotherapy including bevacizumab achieved median overall survival values ranging from 16.1 to 28 months, median progression-free survival values between 8.3 and 12.8 months, and a response rate of 24%–65%. The best combination of bevacizumab with standard chemotherapy regimens (oxaliplatin, CPT-11) remains to be established. In fact, on analyzing these data, it is possible to observe high heterogeneity amongst studies. Bevacizumab-based and CPT-11-based regimens appear to be the most advantageous with regard to overall

survival, while for oxaliplatin-based therapies, there is only increased progression-free survival in the XELOX subgroup. Also, there are no randomized Phase III studies comparing FOLFOX + bevacizumab versus FOLFIRI + bevacizumab. The value of continuing bevacizumab after disease progression on bevacizumab-containing regimens is still unclear. Therefore, its use in patients with disease progression is not currently recommended outside clinical trials. Bevacizumab combined with chemotherapy achieved a pathologic complete response rate of 9%–11% and a response rate of 40.7%–80%. The rate of curative intent surgery ranged from 14.3%–100%, and an R0 of 6.52%–92.8% was reported, with a reduced incidence of perioperative complications.

*KRAS* and *BRAF* mutation status does not predict a therapeutic response to bevacizumab, and no predictive biomarkers have been identified. Caution should be exercised when combining bevacizumab with cetuximab or panitumumab until further randomized data becomes available. Finally, some trials have tested bevacizumab as a rescue therapy (third-line or more), but the actual benefit in such a setting deserves further investigation.

## Disclosure

The authors report no conflicts of interest in this work.

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