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Current Perspective

Current perspective: Bevacizumab in colorectal cancer – A time for reappraisal?

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ABSTRACT

Bevacizumab was the first anti-angiogenic drug to be licensed in malignant disease, based on the results of a randomised trial in advanced colorectal cancer, in which the addition of bevacizumab to chemotherapy with irinotecan plus fluorouracil/leucovorin (IFL) significantly improved tumour response, progression-free survival (PFS) and overall survival (median 15.6–20.3 months, $p < 0.001$). A subsequent randomised trial of bevacizumab combined with fluoropyrimidine and oxaliplatin (FOLFOX or CAPOX) confirmed an improvement in PFS, but without a survival benefit, probably due to the limited duration of bevacizumab treatment. However, in the second-line setting a randomised trial of bevacizumab combined with FOLFOX showed a significant improvement in survival, similar to that observed with IFL in the first-line. A benefit from the use of bevacizumab plus chemotherapy beyond progression remains unproven but data from non-randomised trials are encouraging. In contrast, bevacizumab monotherapy has limited efficacy in advanced disease and currently there are no data to support maintenance monotherapy. Bevacizumab is recognised to cause hypertension, arterial and venous thrombosis, intestinal perforation and impairment of wound healing but can be safely used in patients undergoing surgery, particularly when the timing of surgery is controlled. At the 2009 ASCO annual meeting, the first adjuvant study to report its primary end-point, NSABP protocol C-08, failed to demonstrate an improvement in 3-year disease-free survival from the addition of bevacizumab to modified FOLFOX6 for resected stage II/III disease.

Health economics have unfortunately limited the universal use of bevacizumab, but it is hoped that the future identification of predictive biomarkers may enhance the benefits and thereby improve cost-effectiveness.

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1. Rationale for bevacizumab

Bevacizumab is a humanised monoclonal antibody targeting vascular endothelial growth factor (VEGF)-A, one of the family of circulating pro-angiogenic growth factors. The actions of VEGF-A, mediated principally via the VEGF receptors 1 and 2, include the regulation of vascular permeability and neovascularisation.[1] Angiogenesis is critical to tumour growth and metastatic potential,[2] but is also thought to be an early event in tumour development, as the transformation of a pre-malignant tumour to a malignant tumour, the angiogenic switch, involves the expression and secretion of pro-angio-

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genic factors.[3] The mechanism of action of bevacizumab is complex and unlikely to be limited to the inhibition of tumour angiogenesis. Postulated actions include the induction of epithelial cell apoptosis, sensitising tumour endothelial cells to chemotherapy-induced apoptosis, inhibition of the VEGF-mediated mobilisation of endothelial progenitor cells, vasoconstriction via inhibition of nitric oxide and prostacyclin, normalisation of tumour vasculature allowing improved chemotherapy and oxygen delivery, immune modulation via inhibition of dendritic cell function, counteracting chemotherapy and radiotherapy-induced VEGF signalling and direct effects on tumour cells.[4]

2. What are the benefits of adding bevacizumab to chemotherapy for advanced disease?

Bevacizumab was licensed for use in metastatic colorectal cancer (mCRC) in the United States (US) in February 2004 and in Europe in January 2005 after efficacy in the first-line setting was demonstrated by Hurwitz et al. in a phase III randomised, placebo controlled study of 813 patients treated with irinotecan/bolus 5-fluorouracil (5-FU)/leucovorin (IFL) plus bevacizumab or placebo. A statistically significant increase in median overall survival (OS) was reported, corresponding to an absolute increase in median survival of 4.7 months from 15.6 to 20.3 months ($p < 0.001$), with significant increases also demonstrated in progression-free survival (PFS) and response rate (RR).[5] On the basis of these results, bevacizumab rapidly became established as a routine component of the first-line treatment of mCRC in the US and Europe. Since that time, globally, many thousands of patients have received bevacizumab as part of their treatment for mCRC. However, the magnitude of survival benefit demonstrated in this study has not been confirmed in subsequent first-line studies, although there has been a consistent prolongation of PFS. Nevertheless, a meta-analysis of five randomised studies of bevacizumab, comprising 3103 patients with mCRC demonstrated that OS as well as PFS and overall RR were increased from the addition of bevacizumab to chemotherapy (HR 0.66, 0.77 for PFS and OS, respectively; relative risk of response 1.5)[6] albeit, the improvement in survival was strongly influenced by the Hurwitz study. This meta-analysis included two phase II studies which evaluated the addition of bevacizumab to 5-FU and leucovorin and which were not individually powered to detect a difference in survival, but a combined analysis of the two studies demonstrated a statistically significant improvement in response, PFS and survival from 14.6 to 17.9 months (HR 0.74, $p = 0.008$).[7]

The randomised phase III NO16966 study, initially designed to demonstrate non-inferiority for capecitabine plus oxaliplatin (CAPOX) compared to 5-FU and oxaliplatin (FOLFOX) with PFS as the primary end-point,[8] was modified to a 2 by 2 factorial design to evaluate the addition of bevacizumab compared to placebo to oxaliplatin-based chemotherapy.[9] The study met the initial primary end-point, demonstrating that the oral fluoropyrimidine-based regimens were non-inferior for PFS and survival. On the other hand, whilst the addition of bevacizumab resulted in a modest prolongation of median PFS (9.4 versus 8.0 months, HR 0.83; $p = 0.0023$), there was no significant difference in median OS (21.3 versus 19.9 months, HR 0.89, $p = 0.077$) or RR (38% with bevacizumab or placebo). The use of second-line chemotherapy was comparable in all arms and therefore cannot explain the lack of a significant survival difference. Equally, the use of first-line oxaliplatin-based (rather than irinotecan-based) regimens cannot explain the lack of survival benefit, because in the second-line setting, the addition of bevacizumab to FOLFOX4 results in a statistically significant survival benefit: The Eastern Cooperative Oncology Group (ECOG) Study E3200 randomised 829 patients with mCRC previously treated with irinotecan and a fluoropyrimidine, to receive FOLFOX4 with or without bevacizumab, or bevacizumab monotherapy. Median OS for patients treated with FOLFOX4, with or without bevacizumab was 12.9, and 10.8 months, respectively, and 10.2 months for patients in the monotherapy arm.[10] The hazard ratios for death demonstrated a greater magnitude of benefit than seen from the addition of bevacizumab to an oxaliplatin/fluoropyrimidine doublet in the first-line NO16966 study (0.75 and 0.89, respectively). This may be because the expected OS from chemotherapy alone in the second line is shorter than in the first line, therefore the beneficial effect of bevacizumab is magnified. Additionally, the impact of subsequent chemotherapy is lessened in the second-line setting, as fewer patients will receive further treatment.

How can we explain the inconsistency between the two large phase III studies in first-line mCRC? A possible explanation is a comparatively longer duration of chemotherapy and bevacizumab in the IFL trial by Hurwitz et al.[5] than in the NO16966 trial.[9] In the former study, treatment was continued until disease progression or unacceptable toxicity and patients received a median of 40.4 weeks in the IFL/bevacizumab arm, 27.6 weeks in the IFL alone arm.[5] In contrast, although patients were permitted to receive treatment until progression in NO16966, the median duration of treatment was 27.1 weeks in those treated with bevacizumab and 25.1 in those receiving placebo, with most discontinuation events occurring due to chemotherapy rather than bevacizumab-related toxicity.[9] Only 3% of patients in NO16966 received further bevacizumab with second-line chemotherapy, therefore this reduced duration of exposure to bevacizumab may explain the difference in the survival between this and the Hurwitz trial. By inference, if patients are given a fixed duration of treatment of chemotherapy with bevacizumab, when reintroducing the same chemotherapy it is likely to be important to re-combine it with the anti-angiogenic agent. Given the relatively low toxicity of bevacizumab as a single agent, maintenance monotherapy is an attractive option, although in the E3200 trial bevacizumab monotherapy appeared to have limited efficacy.[10] A phase II study has demonstrated the feasibility of delivering maintenance bevacizumab in patients responding to initial treatment with capecitabine, irinotecan and bevacizumab[11] but at present there are no supporting phase III data. A randomised phase III trial by the Swiss Group for Clinical Cancer Research is in progress to evaluate maintenance bevacizumab. The impact upon the cost-effectiveness ratio of bevacizumab will be

determined by the degree of benefit, if any, as well as the duration of maintenance therapy required.

Based on the randomised studies of bevacizumab added to IFL[5] and 5-FU,[12,13] combination with 5-FU/folinic acid with or without irinotecan for mCRC was not recommended by the UK National Institute for Clinical Excellence (NICE) in a guidance document issued in January 2007, due to inadequate cost-effectiveness. A review of bevacizumab with oxaliplatin-based chemotherapy is in progress. Where funding for bevacizumab is available, it remains a useful addition to first- or second-line chemotherapy, with maximal efficacy likely achieved by continuation until disease progression.

3. Is there a role for bevacizumab beyond disease progression?

An effort was made to evaluate the strategy of bevacizumab beyond disease progression in the non-randomised, observational BRiTE study. The 1953 patients registered to the study achieved a median survival of 25.1 months (95% confidence interval (CI) 23.4–27.5 months). In the 1445 patients who had documented disease progression, continuation of bevacizumab beyond disease progression was significantly associated with a prolonged survival (HR 0.48; $p < 0.001$) on multivariate analysis. Median OS was 12.6 months in the 253 patients that had no further treatment, 19.9 months in the 531 who had further treatment without bevacizumab and 31.8 months in the 642 patients who received further chemotherapy with bevacizumab.[14] Within this context, receiving bevacizumab may have been an epiphenomenon or alternatively, physicians may only have continued bevacizumab in those patients who had an initial favourable response to the treatment; but in fact, the two treatment groups were similar with regard to response rates (43.8% versus 48.1%) and PFS (8.7 versus 8.9 months), respectively. Therefore the BRiTE study provides suggestive but not definitive data supporting the use of bevacizumab beyond disease progression, with subsequent lines of chemotherapy. This strategy would impact on the cost of treatment and may not be as effective as introducing alternative growth factor pathway modulators such as anti-epidermal growth factor receptor (EGFR) antibodies, although these agents are now limited to the 60% of patients with *KRAS* wild-type tumours and it is likely that there will be further refinement of patient selection, excluding mutations in *BRAF* and possibly *PTEN*.[15] Furthermore, additional data are required to determine whether prolonged use of bevacizumab may select for resistant, more aggressive clones and a rebound effect of tumour flare following discontinuation.

4. Bevacizumab and surgery: rationale and efficacy

Selected patients with initially unresectable mCRC may be suitable for secondary resection, usually of liver-only metastases, following down-sizing of the metastases by first-line chemotherapy. The proportion of patients that can be converted from unresectable to resectable disease varies markedly between studies from 0.8% to 15% in phase III studies of unselected mCRC[16–21] to 26.4% to 45% in small phase II studies of patients with liver-only metastases.[22–25] This strategy allows selected patients with initially unresectable disease to undergo potentially curative surgery.[26] The choice of regimen, as for any first-line mCRC, may be oxaliplatin or irinotecan-based, with or without a monoclonal antibody such as bevacizumab or cetuximab.

An analysis of clinical trials reporting resection rate in mCRC demonstrated a correlation with RR to chemotherapy.[27] In view of this, the addition of monoclonal antibodies to combination chemotherapy may increase resection rates; however, the actual impact of bevacizumab on radiological RR to chemotherapy is inconsistent (Table 1). Of interest, a retrospective histopathological study of liver resection specimens demonstrated that there were fewer viable tumour cells in the samples from patients treated with oxaliplatin-based chemotherapy plus bevacizumab, compared to those treated with neo-adjuvant chemotherapy alone.[28] These data require further prospective validation, ideally within the context of a randomised study. The use of functional imaging such as 18-FDG-PET has also been explored in small retrospective series and appears to correlate better with the pathological response to chemotherapy plus bevacizumab, than CT scanning.[29,30]

Retrospectively collected data on resection rate within the NO16966 study have shown similar resection rates in patients receiving oxaliplatin-based chemotherapy with or without bevacizumab (8.4% and 6.1%, respectively).[31] These numbers are small, but are comparable to the curative-intent hepatic metastasectomy rate in the non-randomised First Bevacizumab Expanded Access Trial (BEAT) which was 7.6%.[32]

In contrast, cetuximab increases the response to both oxaliplatin[33] and irinotecan-based[34] chemotherapies and therefore may have a useful role added to conversion chemotherapy. In a randomised phase II study of cetuximab plus FOLFOX or FOLFIRI chemotherapy in 81 patients with unresectable liver-only metastases, the 75% RR (85% in patients with wild-type *KRAS*) and 36% R0 resection rate were encouraging.[35] In the CRYSTAL study in unselected patients with mCRC, RR was increased from 38.7% with FOLFIRI alone to 46.9% with FOLFIRI/cetuximab ($p = 0.004$) in the overall study population, with corresponding secondary resection rates of 3.7% and 7%, respectively. Complete resection (R0) was achieved in 1.7% and 4.8%, respectively. In patients with wild-type *KRAS* the difference in RR was more marked at 59.3% and 43.2% in the investigational and standard arms, respectively.[34] Similar response rates were seen in the OPUS trial in the *KRAS* wild-type patient subset treated with FOLFOX/cetuximab versus FOLFOX alone (61% versus 37%; odds ratio 2.54; $p = 0$ .011) and R0 resection rates were correspondingly higher in this group (9.8% versus 4.1%).[33] Based on these data, many clinicians may elect to use chemotherapy plus cetuximab in patients with initially unresectable *KRAS* wild-type disease, but as resection rates are comparable to the NO16966 study of oxaliplatin-based chemotherapy plus bevacizumab,[31] neither antibody has a clear advantage over the other in this group. Of note, cetuximab was recently approved in this indication by the UK organisation, NICE. In patients with *KRAS* mutations, cetuximab is not effective. As the subset of patients who respond to EGFR targeted treatment is fur-

Table 1 – Randomised Trials evaluating the addition of bevacizumab to chemotherapy in mCRC.

Study	Regimens (no. of patients)	Response rate (%)	PFS/TTP (months)	HR for progression (with versus without bevacizumab)	OS (months)	HR for death (with versus without bevacizumab)
Hurwitz et al.[5]	IFL/placebo (402)	34.8	6.2	0.54 ($p < 0.001$)	15.6	0.66 ($p < 0.001$)
	IFL/bevacizumab (411)	44.8	10.6		20.3	
NO16966 Saltz et al.[9], Cassidy et al.[8]	XELOX/placebo (350)		7.3	0.83 ($p = 0.0023$)		0.89 ($p = 0.077$)
	FOLFOX/placebo (351)	38	7.7		19.9	
	XELOX/bevacizumab (350)		9.3			
	FOLFOX/bevacizumab (349)	38	9.4		21.3	
E3200[a] Giantonio et al.[10]	FOLFOX4 (291)	8.6	4.7	0.61 ($p < 0.001$)	10.8	0.75 ($p = 0.0011$)
	FOLFOX4/bevacizumab (286)	22.7	7.3		12.9	
	bevacizumab (243)	3.3	2.7		10.2	
Kabbinavar et al.[12]	5-FU/LV (36)	17	5.2	0.45 ($p = 0.003$)	13.8	0.86
	5-FU/LV/bevacizumab 5mg/kg (35)	40	9.0		21.5	
	5-FU/LV/bevacizumab 10mg/kg (33)	24	7.2		16.1	
Kabbinavar et al.[13]	5-FU/placebo (105)	15.2	5.5	0.50 ($p = 0.0002$)	12.9	0.79 ($p = 0.16$)
	5-FU/bevacizumab (104)	26.0	9.2		16.6	

PFS = progression-free survival; OS = overall survival; TTP = time to progression.
a Second-line mCRC.

ther refined, the proportion of patients suitable to receive cetuximab will be reduced, but the relative efficacy will also be increased. Response to bevacizumab is not altered by the presence or absence of *KRAS* mutations.[36]

The current randomised phase III trials of bevacizumab added to adjuvant chemotherapy are summarised in Table 2. The first to report efficacy results is the NSABP C-08 study of adjuvant-modified FOLFOX6 with or without bevacizumab in 2710 patients with resected stage II/III colon cancer, which failed to achieve the primary end-point of a prolonged 3-year disease-free survival (DFS).[37] At a median follow-up of 36 months, the 3-year DFS was 75.5% and 77.4% in the control and investigational arms, respectively (HR 0.89, 95% CI 0.76–1.04, $p = 0.15$). In an unplanned sub-set analysis, no heterogeneity of treatment effect was seen in patients with stage II or III disease. These results cannot be explained by any excess toxicity preventing adequate dose intensity of chemotherapy, as the regimen was well tolerated in the adjuvant setting. In fact, more patients treated with bevacizumab than chemotherapy alone received the protocol-specified oxaliplatin dose (34% versus 27%, $p < 0.01$) and 5-FU dose (median 30,800 versus 29,540 mg/m^2, $p < 0.01$) although there was no significant difference in dose density for either agent.[38] Of interest, due to an apparent early separation of the survival curves, an exploratory analysis was undertaken to determine the hazard ratio for DFS at 6 monthly intervals from the completion of maintenance bevacizumab. A significant benefit from bevacizumab was seen at 1-year (HR 0.6, $p = 0.0004$), but this benefit steadily deteriorated over time. As bevacizumab was given for a total of 12 months to patients in the investigational arm, the investigators suggested that future trials might be designed to include longer periods of maintenance bevacizumab,[37] for up to 2–3 years, although the risk of cumulative toxicity could be increased by this approach. The next adjuvant study to report is AVANT, which may confirm or refute the lack of efficacy in this setting. At this time, bevacizumab cannot be recommended as an adjuvant following surgery for early colorectal cancer outside the context of clinical trials.

5. What are the potentially adverse effects of bevacizumab and how can they be modified?

The rates of serious bevacizumab-related toxicities, in particular, arterial and venous thromboembolism, bleeding, hypertension, proteinuria, visceral perforation and impaired wound healing, are relatively low when administered in combination with chemotherapy both in the phase III clinical trial setting[5,9,10] and within large expanded access studies.[39,40] These data are summarised in Table 3. The major overlapping toxicity with the chemotherapy agents used in mCRC is thromboembolism. A pooled analysis of five trials had suggested that the risk of arterial thromboembolic events may be doubled (HR 2.0, 95% CI 1.05–3.75) with bevacizumab added to chemotherapy in patients with advanced disease with a positive association with prior arterial events ($p < 0.001$) and age $\geqslant 65$ ($p = 0.01$) for arterial events.[41] A recent meta-analysis of 15 randomised controlled trials of bevacizumab in solid tumours has defined the relative risk of venous thromboembolism as

Table 2 – Current randomised phase III studies evaluating the addition of bevacizumab to adjuvant chemotherapy.

Study	Planned *n* (status)	Eligibility	Regimens
TOSCA (GISCAD)	4100 (open)	High-risk stage II/stage III resected colon cancer	Arm A: FOLFOX × 3 months Arm B: FOLFOX4 × 6 months High risk stage III (node positive T4 or any N2 disease) randomised to ±bevacizumab
ECOG E5202	3610 (recruitment suspended)	Resected stage II colon cancer	High risk (MSI and/or 18q LOH): Arm I: mFOLFOX × 12 weeks or Arm II: mFOLFOX/bevacizumab × 12 weeks then bevacizumab maintenance × 24 weeks Low risk assigned to Arm III: observation only
AVANT (Jonsson Comprehensive Cancer Centre)	3450 (completed accrual)	Stage III and high risk stage II resected CRC	Arm A: FOLFOX × 24 weeks Arm B: FOLFOX/bevacizumab × 24 weeks then bevacizumab maintenance × 24 weeks Arm C: CAPOX/bevacizumab × 24 weeks then bevacizumab maintenance × 24 weeks
NSABP C-08	2632 (completed accrual)	Stage II/III resected adenocarcinoma of the colon	Arm I: FOLFOX × 24 weeks Arm II: FOLFOX/bevacizumab × 24 weeks then bevacizumab maintenance × 24 weeks
QUASAR2	2240 (open)	Stage III and high risk stage II resected CRC	Arm A: Capecitabine × 24 weeks Arm B: Capecitabine/bevacizumab × 24 weeks then bevacizumab maintenance × 24 weeks
NSABP-ECOG E5204	2100 (completed accrual)	Stage II or III rectal cancer treated with neo-adjuvant chemoradiation then surgery	Arm I: FOLFOX × 24 weeks Arm II: FOLFOX + bevacizumab × 24 weeks

1.33 (95% CI 1.13–1.56, $p < 0.001$), which was not dose related. The overall incidence of grade $\geqslant 3$ venous thromboembolism was 7.3% (95% CI 5.0–10.5) when the analysis was limited to the six mCRC trials.[42] Of note, the rate of venous thrombosis in the adjuvant NSABP C-08 study was 4.6% with FOLFOX and 6.3% with FOLFOX plus bevacizumab, a difference which was not statistically significant. The rates of cardiac, cerebrovascular and peripheral arterial ischaemia were also similar in the two arms.

GI perforation is associated with both high morbidity and mortality, therefore is of particular concern. The rate of perforations reported in randomised phase III studies in mCRC is up to 2.3%.[5,9,10,43] Similarly, the reported rate was 2% in First BEAT,[44] in which the site of perforation was the primary tumour in 50% of patients who had not undergone previous resection of the primary.[45] Similarly, in the BRiTE study, perforations occurred in 34/1968 patients (1.7%), a median of 2.1 months after commencing bevacizumab and having an in situ primary tumour was a non-statistically significant risk factor for GI perforation; 2.6% versus 1.6% in those with the resected primary tumours. Other possible risk factors identified were acute diverticulitis, bowel obstruction, previous abdominal or pelvic radiotherapy, intra-abdominal abscess or abdominal carcinomatosis.[46] In contrast, in the adjuvant NSABP C-08 study, the perforation rate was 0.3% with adjuvant FOLFOX plus bevacizumab and 0.2% with FOLFOX alone.[38] These data demonstrate that administration of bevacizumab is safer in patients with resected primary tumours. Whilst the use of bevacizumab in patients with the primary tumour in situ is not contraindicated, particular caution should be applied, especially in those with more than one potential risk factor.

The pathogenesis of perforations due to bevacizumab may be due to impairment of visceral healing and ulceration may be the first event: an analysis of patients treated with chemotherapy plus bevacizumab in the phase III randomised CAIRO2 study reported that 4 out of 8 reported GI perforations were at the site of ulcers and the overall rate of ulceration (1.3%) was relatively high, leading the authors to hypothesise that ulceration; whether gastroduodenal or tumour related, may precede perforation.[47] Of concern, 4/7 patients with gastric or duodenal perforations were taking proton pump inhibitors (PPIs), 2 with concomitant non-steroidal anti-inflammatory drugs (NSAIDs), suggesting that PPIs may be less effective in protection against ulcers/perforations in this setting. The concomitant use of corticosteroids or NSAIDs with bevacizumab should be avoided due to the risk of peptic ulceration.

Careful planning of the timing of surgery in relation to chemotherapy is important to minimise the risk of complications and a minimum 4-week delay has been suggested.[48] Due to the relatively long half-life of bevacizumab,[49] precipitating concerns that wound-healing, bleeding, liver regeneration and overall operative complication rates could be adversely affected, in clinical trials of bevacizumab; eligible patients are required to have completed any surgery a minimum of 4 weeks before treatment. No increase in wound healing complications in patients receiving bevacizumab

Table 3 – Safety in Selected trials of chemotherapy plus bevacizumab for mCRC.

Study and regimen (*n*)	Rate of bevacizumab-related toxicities (%)					
	Any grade thrombo-embolism	Grade ⩾ 3 bleeding	GI perforation	Grade ⩾ 3 wound healing complications	Grade ⩾ 3 proteinuria	Grade ⩾ 3 hypertension
Hurwitz et al.[5]						
IFL/placebo (402)	16.2	2.5	0.0	3.4%	0.8	2.3
IFL/bevacizumab (411)	19.4	3.1	1.5	placebo 13% bevacizumab (50)	0.8	11.0
Kabbinavar et al., 2005 (13)						
5-FU/placebo (105)	18	3	0		–	3
5-FU/bevacizumab (104)	18	5	2			16
NO16966[8,9]						
XELOX or FOLFOX + placebo (701)	6	1	<1	<1	0	1
XELOX or FOLFOX + bevacizumab (699)	10	2	<1	<1	<1	4
E3200[10]						
FOLFOX4/bevacizumab (286)	3.4	3.4	1.0	–	0.7	6.2
FOLFOX4 (291)	2.5	0.4	0		0	1.8
Bevacizumab (243)	0.4	2.1	1.2		0	7.3
First BEAT[44]						
Chemotherapy + bevacizumab (1914)	–	3	2	1	1	5

compared to those recieving placebo was observed in patients commencing treatment 28–60 d after resection of their primary tumour in a combined analysis of two studies. However, an increased rate of grade 3/4 wound-healing events was demonstrated in patients requiring unplanned major surgery during study treatment including bevacizumab compared to placebo (13% versus 3.4%). This effect was observed whether surgery was undertaken within 30 d or within 31–60 d of receiving bevacizumab.[50]

Impaired liver regeneration via VEGF inhibition is a potential concern with the use of peri-operative bevacizumab for liver resections. However, in a prospective phase II study of neo-adjuvant CAPOX plus bevacizumab, there was only one case of impaired liver function and regeneration reported in 52 patients (1.9%) undergoing liver surgery.[51] Similarly, Adam and colleagues demonstrated no significant difference in short-term liver recovery following hepatic resection in a retrospective analysis of patients treated with neo-adjuvant chemotherapy with or without bevacizumab.[52] Early retrospectively collected data have suggested that bevacizumab may protect against oxaliplatin-induced sinusoidal dilatation[28,53], but this requires prospective validation. Bleeding is a relatively uncommon complication with bevacizumab.

6. Can EGFR monoclonal antibodies be added to chemotherapy plus bevacizumab?

Given the emerging role for anti-EGFR antibodies in mCRC, panitumumab was evaluated in combination with bevacizumab plus chemotherapy in the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study. This four-drug combination resulted in increased diarrhoea, infections and pulmonary emboli, leading to early closure of both dual inhibition arms. Efficacy was also compromised; PFS was significantly lower in the patients receiving dual VEGF/EGFR inhibition and retrospective analysis by *KRAS* status failed to explain these data, as no association was demonstrated.[54] The unexpected deleterious effect of the combination may relate to toxicity precipitating delays and early cessation of not only the investigational antibody, but also the chemotherapy/bevacizumab combination. In contrast, there was no excess grade 3/4 toxicity reported in the investigational arm of the phase III CAIRO2 study of CAPOX/bevacizumab, with or without cetuximab in first-line mCRC, other than the expected skin toxicity related to EGFR inhibition.[55] Despite this, a statistically significant reduction in median PFS was observed in the investigational arm compared to CAPOX/bevacizumab alone and quality of life scores were also reduced. Of interest, the detrimental effect was greatest in patients with *KRAS* mutations, who are now known not to benefit from EGFR inhibition.[56] The safety concerns raised by PACCE were also not reported in the smaller phase II Bowel Oncology with Cetuximab Antibody (BOND)-2 study evaluating bevacizumab plus cetuximab, with or without irinotecan in chemotherapy-refractory mCRC. Efficacy data according to KRAS status have not been reported for this study.[57] The cause and mechanism of the adverse effect of combining bevacizumab with an anti-EGFR monoclonal antibody has not been fully elucidated. As a result of these data, dual inhibition should not currently be considered in patients with *KRAS* mutations and cannot be recommended in *KRAS* wild-type outside the context of a clin-

Table 4 – Efficacy Results in dual VEGF/EGFR trials.

Study, setting	Regimen (*n*)	Response rate			Median PFS/months			Median OS/months		
		All Pts	KRAS WT	KRAS mutant	All Pts	KRAS WT	KRAS mutant	All Pts	KRAS WT	KRAS mutant
PACCE Hecht et al., [54] 1st line mCRC	Oxaliplatin/ bevacizumab/ panitumumab (413)	46%	50%	47%	8.8	9.8	10.4	19.4	20.7	19.3
	Oxaliplatin/ bevacizumab (410)	48%	56%	44%	10.5 (HR 1.44, 95% CI 1.13–1.85, $p = 0.004$)	11.5	11.0	24.5 (HR 1.43, 95% CI 1.11–1.83)	24.5	19.3
	Irinotecan/ bevacizumab/ panitumumab (115)	43%	54%	30%	10.1	10.0	8.3	20.7	Not estimable	17.8
	Irinotecan/ bevacizumab (115)	40%	48%	38%	11.9 (HR 1.57, 95% CI 0.71–3.46)	12.5	11.9	20.5 (HR 1.42, 95% CI 0.77–2.62)	19.8	20.5
CAIRO2 Tol et al.,[56] 1st line mCRC	CAPOX/bevacizumab/ Cetuximab (377)	52.7	61.4	45.9	9.4	10.5	8.1	19.4	21.8	17.2
	CAPOX/bevacizumab (378)	50.0	50.0	59.2	10.7	10.6	12.5	20.3	22.4	24.9
		$p = 0.49$	$p = 0.06$	$p = 0.03$	HR 1.22 (95% CI 1.04–1.43) $p = 0.01$	$p = 0.30$	$p = 0.003$	HR 1.15, $p = 0.16$	$p = 0.64$	$p = 0.03$
BOND2 Saltz et al.,[57] Chemotherapy refractory mCRC	Cetuximab/ bevacizumab/ irinotecan (43)	37%	–	–	7.3	–	–	14.5	–	–
	Cetuximab/ bevacizumab (40)	20%			4.9			11.4		

WT = wild type.

ical trial. Efficacy results from VEGF/EGFR dual inhibition trials are summarised in Table 4.

7. Biomarkers of efficacy and resistance

The discovery and subsequent confirmation of KRAS mutations as a marker of resistance to EGFR inhibitors was one of several observations that will contribute to the quest for a personalised approach to cancer treatment. As yet, no marker of resistance has been identified for bevacizumab. A retrospective analysis of samples from the phase III study by Hurwitz and colleagues showed that response to bevacizumab is not altered by the presence of *KRAS*, *BRAF* or *P53* mutations.[36] However, it should not be concluded from these data that all patients benefit from the addition of bevacizumab; rather that we have simply not yet identified the relevant predictive biomarker (s).

Circulating VEGF level has been evaluated as a surrogate marker of angiogenic activity[3] but the association has not been reliably demonstrated in the clinical trial setting. Quantification of circulating endothelial cells (CECs) in the peripheral blood has also been evaluated as a potential marker of tumour control,[58,59] but larger confirmatory studies are required.

8. Other anti-angiogenic agents

The VEGF receptor tyrosine kinase inhibitor (TKI), valatanib, was evaluated in a placebo-controlled randomised study, CONFIRM 2. Of interest, the addition of valatanib to second-line FOLFOX4 chemotherapy resulted in a modest prolongation in PFS (5.5 versus 4.1 months, HR 0.83, $p = 0.026$) but no significant difference in OS (12.1 versus 11.8 months, HR 0.94; $p = 0.511$).[60] An exploratory sub-group analysis demonstrated a significant survival benefit in patients with high LDH, but the efficacy in this sub-group was inadequate for licensing purposes and development in colorectal cancer has ceased. Other agents currently in phase III testing include the TKI, cediranib in combination with FOLFOX, the multikinase inhibitor, sunitinib with FOLFIRI in the first-line setting and aflibercept, a soluble VEGF trap, added to FOLFIRI in the second-line setting.

9. The future of bevacizumab and VEGF inhibition

The future use of bevacizumab in mCRC may be influenced by whether or not predictive biomarkers, to allow selection of patients who will attain the greatest benefit, can be identified. More stringent patient-selection criteria will enhance the cost-effectiveness of the drug and could further refine its role in the metastatic disease setting. Future prospective clinical trials will also determine whether bevacizumab added to conversion chemotherapy improves resection rate and long-term survival in patients with initially unresectable disease. Whether there is a role for selected patients in the adjuvant setting will be determined by the on-going phase III trials; although this is again likely to be dependent upon the identification and validation of a predictive biomarker to define the appropriate patient group.

10. Conclusions

Bevacizumab is the first anti-angiogenic drug to be used in metastatic colorectal cancer, and now has an established role with predictable and generally manageable toxicities. The true overall impact of bevacizumab on survival of patients with this disease has been difficult to quantify, although it seems probable that its use throughout the period of chemotherapy may maximise the benefit. As with many of the new anti-cancer agents, relative cost-effectiveness has been a barrier to the universal use of this agent in clinical practice and thus the discovery of biomarkers for patient selection would be extremely valuable.

Conflict of interest statement

Dr. Okines received an honorarium from Roche for a presentation. Professor Cunningham has received research funding from Roche.

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REFERENCES

1. Rosen L. Clinical experience with angiogenesis signaling inhibitors: focus on vascular endothelial growth factor (VEGF) blockers. *Cancer Control* 2002;**9**(2 Suppl.):36–44.
2. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005;**23**(5):1011–27.
3. Ronnie Tung-Ping Poon S-TF, John Wong. Clinical implications of circulating angiogenic factors in cancer patients. *J Clin Oncol* 2001;**19**(4):1207–25.
4. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer* 2008;**8**(8):579–91.
5. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;**350**(23):35–2342.
6. Cao Y, Tan A, Gao F, et al. A meta-analysis of randomized controlled trials comparing chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer. *Int J Colorectal Dis* 2009;**24**(6):677–85.
7. Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005;**23**(16):3706–12.
8. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008;**26**(12):2006–12.
9. Saltz LB, Clarke S, Diaz-Rubio E, et al. 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**(12):2013–9.
10. Giantonio BJ, Catalano PJ, Meropol NJ, et al. 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**(12):1539–44.
11. Ardavanis A, Kountourakis P, Mantzaris I, et al. Bevacizumab added to the irinotecan and capecitabine combination for advanced colorectal cancer: a well-tolerated, active and convenient regimen. *Anticancer Res* 2008;**28**(5B):3087–92.
12. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. 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**(1):60–5.
13. Kabbinavar FF, Schulz J, McCleod M, et al. 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**(16):3697–705.
14. Grothey A, Sugrue MM, Purdie DM, et al. 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**(33):5326–34.
15. Wong R, Cunningham D. Using predictive biomarkers to select patients with advanced colorectal cancer for treatment with epidermal growth factor receptor antibodies. *J Clin Oncol* 2008;**26**(35):5668–70.
16. De Gramont AAC, Andre T, Figer A, et al. OPTIMOX study: FOLFOX 7/LV5FU2 compared to FOLFOX 4 in patients with advanced colorectal cancer, 2004 ASCO annual meeting proceedings (post-meeting edition). *J Clin Oncol* 2004:3525.
17. Falcone A, Ricci S, Brunetti I, et al. 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**(13):1670–6.
18. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;**22**(2):229–37.
19. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer – a GERCOR study. *J Clin Oncol* 2006;**24**(3):394–400.
20. Delaunoit T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol* 2005;**16**(3):425–9.
21. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;**22**(1):23–30.
22. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005;**23**(36):9243–9.
23. Pozzo C, Basso M, Cassano A, Quirino M, Schinzari G, Trigila N, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004;**15**(6):933–9.
24. Ychou M, Viret F, Kramar A, et al. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases. *Cancer Chemother Pharmacol* 2007.
25. De La Cámara JJR, Rotellar F, Viudez A, et al. Triplet therapy with oxaliplatin, irinotecan, 5-fluorouracil and folinic acid within a combined modality approach in patients with liver metastases from colorectal cancer, 2004 ASCO annual meeting proceedings (post-meeting edition). *J Clin Oncol* 2004:3593.
26. Watkins DJJC, Chua YJ, Chong G, et al. A prospective study of oxaliplatin and capecitabine (CapOx) in metastatic colorectal cancer (MCRC) with baseline stratification according to resectability status, 2007 ASCO annual meeting proceedings, part I. *J Clin Oncol* 2007:4024.
27. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005;**16**(8):1311–9.
28. Ribero D, Wang H, Donadon M, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. *Cancer* 2007;**110**(12):2761–7.
29. Goshen E, Davidson T, Zwas ST, Aderka D. PET/CT in the evaluation of response to treatment of liver metastases from colorectal cancer with bevacizumab and irinotecan. *Technol Cancer Res Treat* 2006;**5**(1):37–43.
30. Funaioli C, Pinto C, Di Fabio F, et al. 18FDG-PET evaluation correlates better than CT with pathological response in a metastatic colon cancer patient treated with bevacizumab-based therapy. *Tumori* 2007;**93**(6):611–5.
31. Cunningham DKA, Berry S, Rivera F, et alon behalf of the First BEAT investigators. Efficacy and safety of surgery with curative intent in patients treated with first-line bevacizumab for mCRC: first BEAT. In: *Gastrointestinal Cancers Symposium; 2008*. Chicago: Proc Am Soc Clin Oncol; 2008. p. 445.
32. Van Cutsem E, Rivera F, Berry S, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol* 2009.
33. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009;**27**(5):663–71.
34. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;**360**(14):1408–17.
35. Folprecht GGT, Hartmann JT, Lordick F, et al. Randomized multicentre study of cetuximab plus FOLFOX or plus FOLFIRI in neoadjuvant treatment of non-resectable colorectal liver metastases (CELIM-study), 33rd ESMO congress, Stockholm, Sweden. *Ann Oncol* 2008. abstract 510PD.
36. Ince WL, Jubb AM, Holden SN, et al. Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab. *J Natl Cancer Inst* 2005;**97**(13):981–9.
37. Wolmark NYG, O'Connell MJ, Sharif S, et al. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: results of NSABP Protocol C-08. In: *ASCO annual meeting, Orlando*; 2009. p. LBA4.
38. Allegra CJ, Yothers G, O'Connell MJ, et al. Initial Safety Report of NSABP C-08: A Randomized Phase III Study of Modified FOLFOX6 With or Without Bevacizumab for the Adjuvant Treatment of Patients With Stage II or III Colon Cancer. *J Clin Oncol* 2009.
39. Hedrick E, Hainsworth J, Badarinath S, et al. Safety of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRiTE), 2006 ASCO annual meeting proceedings part I, 2006 June 20. *J Clin Oncol* 2006:3536.
40. Van Cutsem EMM, Berry S, Dibartolomeo M, et al. Preliminary safety and efficacy of bevacizumab with first-line FOLFOX,

XELOX, FOLFIRI, and capecitabine for mCRC: First BEATrial. In: *ASCO*; 2007.
41. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007;**99**(16):1232–9.
42. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *Jama* 2008;**300**(19):2277–85.
43. Hochster HS, Hart LL, Ramanathan RK, et al. 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**(21):3523–9.
44. Van Cutsem ERF, Berry S, Kretzschmar A, et alCunningham D on behalf of the First BEAT investigators. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol* 2009.
45. Kretzschmar ADC, Berry S, DiBartolomeo M, et al., First BEAT Investigators. Incidence of gastrointestinal perforations and bleeding in patients starting bevacizumab treatment in first-line mCRC without primary tumour resection: Preliminary results from the first BEATrial. In: *Gastrointestinal cancers symposium*; 2006. p. abstract 248.
46. Sugrue MMK, Hainsworth J, Badarinath S, et al. Risk factors for gastrointestinal perforations in patients with metastatic colorectal cancer receiving bevacizumab plus chemotherapy, ASCO annual meeting, 2006 ASCO annual meeting proceedings part I, vol. 24, no. 18S (June 20 supplement). *J Clin Oncol* 2006. abstract 3535.
47. Tol J, Cats A, Mol L, Koopman M, et al. Gastrointestinal ulceration as a possible side effect of bevacizumab which may herald perforation. *Invest New Drugs* 2008;**26**(4):393–7.
48. Welsh FK, Tilney HS, Tekkis PP, John TG, Rees M. Safe liver resection following chemotherapy for colorectal metastases is a matter of timing. *Br J Cancer* 2007;**96**(7):1037–42.
49. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J Clin Oncol* 2001;**19**(3):843–50.
50. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol* 2005;**91**(3):173–80.
51. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008;**26**(11):1830–5.
52. Adam RWDA, de Haas RJ, Lévi F, et al. Postoperative liver function recovery after hepatic resection for colorectal metastases previously treated with bevacizumab, ASCO annual meeting, 2009; Orlando. *J Clin Oncol* 2009. abstract 4093.
53. Klinger M, Eipeldauer S, Hacker S, et al. Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. *Eur J Surg Oncol* 2009;**35**(5):515–20.
54. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009;**27**(5):672–80.
55. Tol J, Koopman M, Rodenburg CJ, et al. A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. *Ann Oncol* 2008;**19**(4):734–8.
56. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009;**360**(6):563–72.
57. Saltz LB, Lenz H-J, Kindler HL, et al. Randomized phase ii trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the bond-2 study. *J Clin Oncol* 2007. JCO.2007.12.0949.
58. Davis DW, Kurzrock R, Naing A, et al. Circulating tumor and endothelial cells as pharmacodynamic biomarkers in a phase I clinical trial of intravenous bevacizumab in combination with escalating doses of oral cediranib for patients with advanced malignancies, ASCO annual meeting, 2009, Orlando. *J Clin Oncol* 2009;**27**(15). abstract 3525.
59. Farace F, Adenis A, Boucher E, et al. Circulating endothelial cell (CEC) monitoring in metastatic colorectal cancer (mCRC) patients (pts) treated with first-line bevacizumab (BEV)-based combination regimens: Results of the randomized phase II FNCLCC-ACCORD 13/0503 trial, ASCO annual meeting, 2009, Orlando. *J Clin Oncol* 2009;**27**(15s). abstract 4071.
60. Kohne C EB, E. Lin, J. W. Valle, E. Van Cutsem, J. R. Hecht, M. Moore, C. J. Germond, G. Meinhardt, C. Jacques. Final results of CONFIRM 2: A multinational, randomized, double-blind, phase III study in 2nd line patients (pts) with metastatic colorectal cancer (mCRC) receiving FOLFOX4 and PTK787/ZK 222584 (PTK/ZK) or placebo. In: ASCO; 2007: Journal of Clinical Oncology; 2007. p. 4033.