Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial

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Summary

Background Bevacizumab plus fluoropyrimidine-based chemotherapy is standard treatment for first-line and bevacizumab-naive second-line metastatic colorectal cancer. We assessed continued use of bevacizumab plus standard second-line chemotherapy in patients with metastatic colorectal cancer progressing after standard first-line bevacizumab-based treatment.

Methods In an open-label, phase 3 study in 220 centres in Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, the Netherlands, Norway, Portugal, Saudi Arabia, Spain, Sweden, and Switzerland, patients (aged ≥18 years) with unresectable, histologically confirmed metastatic colorectal cancer progressing up to 3 months after discontinuing first-line bevacizumab plus chemotherapy were randomly assigned in a 1:1 ratio to second-line chemotherapy with or without bevacizumab 2·5 mg/kg per week equivalent (either 5 mg/kg every 2 weeks or 7·5 mg/kg every 3 weeks, intravenously). The choice between oxaliplatin-based or irinotecan-based second-line chemotherapy depended on the first-line regimen (switch of chemotherapy). A combination of a permuted block design and the Pocock and Simon minimisation algorithm was used for the randomisation. The primary endpoint was overall survival, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00700102.

Findings Between Feb 1, 2006, and June 9, 2010, 409 (50%) patients were assigned to bevacizumab plus chemotherapy and 411 (50%) to chemotherapy alone. Median follow-up was 11·1 months (IQR 6·4–15·6) in the bevacizumab plus chemotherapy group and 9·6 months (5·4–13·9) in the chemotherapy alone group. Median overall survival was 11·2 months (95% CI 10·4–12·2) for bevacizumab plus chemotherapy and 9·8 months (8·9–10·7) for chemotherapy alone (hazard ratio 0·81, 95% CI 0·69–0·94; unstratified log-rank test p=0·0062). Grade 3–5 bleeding or haemorrhage (eight [2%] *vs* one [<1%]), gastrointestinal perforation (seven [2%] *vs* three [<1%]), and venous thromboembolisms (19 [5%] *vs* 12 [3%]) were more common in the bevacizumab plus chemotherapy group than in the chemotherapy alone group. The most frequently reported grade 3–5 adverse events were neutropenia (65 [16%] in the bevacizumab and chemotherapy group *vs* 52 [13%] in the chemotherapy alone group), diarrhoea (40 [10%] *vs* 34 [8%], respectively), and asthenia (23 [6%] *vs* 17 [4%], respectively). Treatment-related deaths were reported for four patients in the bevacizumab plus chemotherapy group and three in the chemotherapy alone group.

Interpretation Maintenance of VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in patients with metastatic colorectal cancer. This approach is also being investigated in other tumour types, including metastatic breast and non-small cell lung cancers.

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Introduction

In randomised clinical studies, the addition of bevacizumab, an antibody that binds to and inhibits VEGF, to standard chemotherapy regimens improved outcomes in bevacizumab-naive patients with metastatic colorectal cancer in the first-line and second-line settings.[1–4] In observational studies, addition of bevacizumab to various chemotherapy regimens in the community setting led to a median progression-free survival of 10–12 months.[5,6]

Currently, no standard treatment regimen exists for patients whose disease progresses after first-line treatment. According to treatment guidelines, second-line bevacizumab might be an option in patients who did not receive it as first-line treatment.[7] Other options are to use a different chemotherapy agent or combination as second-line treatment,[8] or chemotherapy plus an anti-EGFR agent in patients with tumours expressing wild-type *KRAS*.[9,10]

Use of antiangiogenic treatments to create an environment suitable for genetically stable endothelial cells[11] should, in principle, induce less drug resistance than do treatments directed at genetically unstable tumour cells. As a result of complementary modes of action, continued antiangiogenic treatment might be clinically effective without cumulative toxicity despite the

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development of resistance to chemotherapy.[12] Evidence from preclinical and observational studies indicates that sustained VEGF inhibition with bevacizumab can be beneficial in some patients with solid tumours. Preclinical data suggest that sustained VEGF inhibition achieves and maintains tumour regression.[13–16] In non-randomised observational studies (BRiTE and ARIES)[17,18] of patients with metastatic colorectal cancer, continued antiangiogenic treatment with bevacizumab plus chemotherapy beyond first progressive disease correlated with prolonged survival versus no continuation of bevacizumab. However, these findings have not yet been confirmed in randomised studies.

In this study, we assessed the effect on overall survival of continuing bevacizumab beyond progression of metastatic colorectal cancer in patients who had previously been given bevacizumab plus standard first-line chemotherapy.

Methods

Study design

The ML18147 trial was a prospective, intergroup, randomised, open-label, phase 3 study in 220 centres in 15 countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, the Netherlands, Norway, Portugal, Saudi Arabia, Spain, Sweden, and Switzerland). Patients (aged ≥18 years) were eligible if they had histologically confirmed, measurable metastatic colorectal cancer, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, tumour disease according to RECIST by investigator up to 4 weeks prior to start of study treatment, previous treatment with bevacizumab plus standard first-line chemotherapy including a fluoropyrimidine plus either oxaliplatin or irinotecan, and they were not candidates for primary metastasectomy. Patients were excluded if they had a diagnosis of progressive disease for more than 3 months after the last bevacizumab administration and first-line progression-free survival of less than 3 months, and if they were given less than 3 months (consecutive) of first-line bevacizumab. Detailed inclusion and exclusion criteria are shown in the appendix.

ML18147 was approved by local ethics committees, done in accordance with the Declaration of Helsinki, and adhered to Good Clinical Practice Guidelines. All patients provided written informed consent, including a separate, specific signature consenting to specimen donation.

This study was initiated in 2006 by the Arbeitsgemeinschaft Internistische Onkologie (AIO) in Germany (Aachen, Aschaffenburg, Augsburg, Berlin, Bietigheim-Bissingen, Bochum, Bremen, Chemnitz, Cologne, Darmstadt, Dessau, Dessau-Roßlau, Dortmund, Dresden, Duisburg, Eschweiler, Essen, Esslingen, Frankfurt, Fulda, Gifhorn, Gummersbach, Hamburg, Hannover, Hildesheim, Homburg/Saar, Kassel, Kiel, Köthen [Anhalt], Kronach/Oberfranken, Laatzen, Leer, Lemgo, Ludwigsburg, Magdeburg, Mainz, Mannheim, Marburg, Moers, Mönchengladbach, Mutlangen, Neustadt/Sachsen, Olpe, Regensburg, Remscheid, Rostock, Rotenburg [Wümme], Saalfeld, Schönebeck, Schwerin, Stade, Stuttgart, Troisdorf, Ulm, Velbert, Wernigerode, Wiesbaden, and Würselen) and Austria (AIO KRK 0504; Fürstenfeld, Graz, Innsbruck, Leoben, Linz, Ried im Innkreis, Salzburg, St Veit/Glan, and Waidhofen/Thaya). It was then transferred to Roche (Basel, Switzerland) in 2008 to include other countries so that the study could be done in a timely fashion and with adequate power to assess the potential benefit of bevacizumab beyond progression in the first line in terms of overall survival. Alterations to the study design (without knowledge of aggregate efficacy data results by treatment group to maintain study integrity) were: a change in the primary endpoint from progression-free survival to overall survival; sample size was increased from 572 to 810 patients to give adequate power to assess overall survival; additional study centres were included; and randomisation stratification criteria were amended. An intergroup committee was formed in coordination with Roche that included representatives from each European country.

Randomisation and masking

Patients in AIO KRK 0504 were assigned using a stratified permuted block design to ensure balance between treatment groups and the stratification factors chemotherapy backbone (irinotecan-based or oxaliplatin-based) and Köhne score (0–2 *vs* 3 or 4);[19] Gesellschaft für Studienmanagement und Onkologie (Hamburg, Germany) provided central fax randomisation for patients enrolled in AIO KRK 0504.

After the transfer to Roche, patients were randomly assigned according to the second-order minimisation algorithm of Pocock and Simon (stratified randomisation).[20] Randomisation was stratified according to first-line chemotherapy (irinotecan-based *vs* oxaliplatin-based), first-line progression-free survival (≤9 months *vs* >9 months), time from last bevacizumab dose (≤42 days *vs* >42 days), and ECOG performance status (0 or 1 *vs* 2). To pool and analyse data from patients in AIO KRK 0504 and ML18147, the stratification factors that were used in ML18147 were retrospectively obtained for patients enrolled in AIO KRK 0504. Eligible patients in ML18147 were allocated to treatment groups (bevacizumab plus chemotherapy or chemotherapy alone) and assigned an identification number by an interactive voice response system (IVRS; provided by S-Clinica, Brussels, Belgium). The patient's study identification number was uploaded automatically by the IVRS on the electronic case-report form.

The statistical and clinical study team at Roche was masked during the study and before the database lock. The data management and unmasked statistical study team (Chiltern International, Slough, UK) transferred

unmasked data to an independent statistical programmer who ensured the masking of the data. The data were analysed by Roche.

Procedures

Patients were randomly assigned in a 1:1 ratio to treatment with infusional or bolus fluorouracil or oral capecitabine at the investigator's discretion plus irinotecan or oxaliplatin with or without bevacizumab at 2·5 mg/kg per week equivalent (either 5 mg/kg intravenously every 2 weeks or 7·5 mg/kg every 3 weeks, intravenously). The choice of second-line chemotherapy was determined by the first-line regimen (ie, chemotherapy in patients who were given first-line oxaliplatin was switched with second-line irinotecan and vice versa). All standard second-line treatments based on fluoropyrimidines plus oxaliplatin or irinotecan were permitted. Treatment continued until progressive disease, unacceptable toxicity, or patient's refusal to continue.

The primary endpoint was overall survival, defined as time from randomisation to death from any cause. Secondary endpoints were: progression-free survival, defined as time from randomisation to documented disease progression or death from any cause, whichever occurred earlier; overall survival from the start of first-line treatment, defined as time from the start of first-line treatment to death from any cause; confirmed best overall response assessed with modified Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0); and safety (adverse events, laboratory data). An additional secondary endpoint was on-treatment progression-free survival, defined as time from randomisation to documented disease progression or death from any cause, whichever occurred earlier, and only if it occurred up to 28 days after the last confirmed dose of study treatment. Post-hoc analyses included assessment of disease control, defined as confirmed complete response, partial response, or stable disease by RECIST. Exploratory endpoints included evaluation of overall survival, progression-free survival, and subsequent anticancer treatments according to *KRAS* mutation status.

Tumour measurements (up to ten lesions) were taken within 28 days before the start of the study. Tumour measurements and assessments were done according to RECIST criteria using spiral or conventional CT, radiography, or MRI. Tumour assessments were done every 8–9 weeks until progressive disease. Patients discontinuing treatment before progressive disease and those who completed treatment were followed up every 3 months after the end of treatment for survival data, subsequent anticancer treatment, and study-drug-related serious adverse events. Patients discontinuing treatment before progressive disease were assessed for tumour status until progressive disease.

Adverse events and serious adverse events were assessed continuously; those of special interest in terms

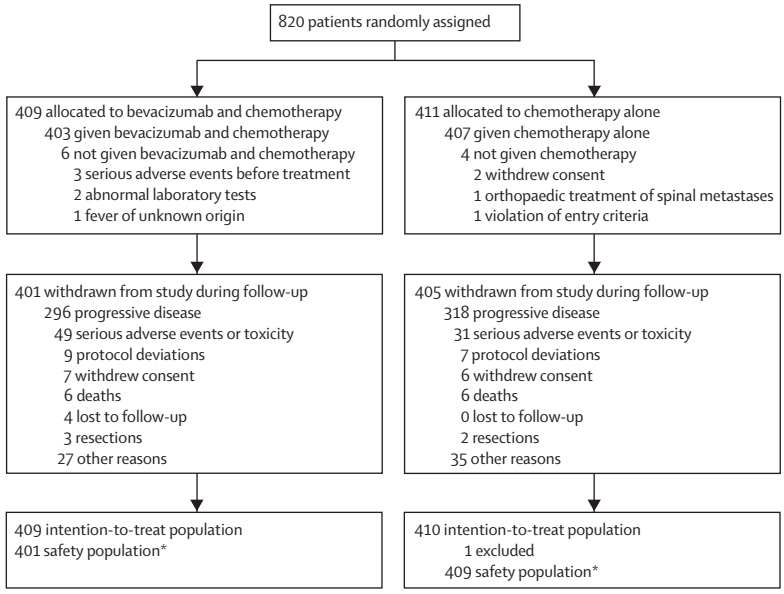

Figure 1: **Trial profile**
*Two patients in the bevacizumab plus chemotherapy group were not given bevacizumab and therefore, for the purposes of the safety analysis, were analysed in the chemotherapy alone group.

	Bevacizumab and chemotherapy (n=409)	Chemotherapy alone (n=411)
Sex		
Male	267 (65%)	259 (63%)
Female	142 (35%)	152 (37%)
Age (years)	63 (27–84)	63 (21–84)
ECOG performance status		
0	179 (44%)	178 (43%)
1	209 (51%)	212 (52%)
2	19 (5%)	19 (5%)
First-line progression-free survival (months)		
≤9	221 (54%)	229 (56%)
>9	187 (46%)	182 (44%)
Liver metastasis only		
No	300 (73%)	292 (71%)
Yes	109 (27%)	118 (29%)
Number of organs with metastases		
≤1	148 (36%)	160 (39%)
>1	261 (64%)	250 (61%)
Time from last bevacizumab dose (days)		
≤42	315 (77%)	316 (77%)
>42	94 (23%)	95 (23%)
First-line chemotherapy		
Irinotecan-based	240 (59%)	237 (58%)
Oxaliplatin-based	169 (41%)	174 (42%)

Data are number (%) or median (range). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Characteristics of patients at baseline**

of bevacizumab were followed up until return to baseline status, stabilisation, or death of the patient. Adverse events were assessed at the first treatment cycle, before each subsequent cycle, and at the end of treatment according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Dose reduction of bevacizumab was not allowed as part of this study. Skipped doses or termination of treatment were based on the actual toxicities (appendix). Instructions for the grading and management of adverse events attributable to bevacizumab were described as part of the protocol. Dose reduction or schedule modifications of chemotherapeutic regimens were based on assessment of systematic toxicity and in accordance with local standard practice. In case of toxicity-related chemotherapy dose reduction, no dose re-escalation was allowed. In the case of patients experiencing severe chemotherapy-related toxicity or progressive disease, investigators were allowed to modify or change the chemotherapy regimen as detailed in the protocol.

Statistical analysis

The AIO KRK 0504 study was originally powered at 80% to detect an increase in progression-free survival at 6 months from 25·0% to 37·5%, equivalent to an increase of 5 weeks in the median value. The following assumptions were used—5% type 1 error, exponential progression-free survival curves, 3 year recruitment and a follow-up for a minimum of 1 year or until progression, and progression-free survival at 6 months in the chemotherapy group of 25%. According to the published results of the GERCOR study,[8] progression-free survival at 6 months during second-line treatment with crossover from FOLFIRI to FOLFOX or from FOLFOX to FOLFIRI was 25% (calculated from the start of second-line treatment). The ML18147 study was subsequently designed to detect a 30% (hazard ratio [HR] 0·77) improvement in median overall survival with 90% power, assuming a two-sided 5% type 1 error and median overall survival for chemotherapy alone of 10 months. 810 patients were to be enrolled to accrue the 613 events needed for the primary analysis.

Overall survival curves were estimated with the Kaplan-Meier method. As requested by the US Food and Drug Administration, because of changes in stratification factors during the study, the primary analysis was done with unstratified log-rank tests. An unstratified Cox regression model was used to estimate the HR for overall survival, and unstratified log-rank tests were used to assess differences. Unstratified log-rank tests were also used for the analysis of progression-free survival, progression-free survival on treatment, and overall survival from the start of first-line treatment; Cox regression models were used to generate HRs. Unstratified Cox regression models were used to generate HRs and corresponding 95% CIs for all secondary endpoints, subgroup analyses, and the exploratory analyses by *KRAS* status. Unstratified χ^2 tests were used to assess between-groups differences for best overall response and the post-hoc analysis of disease control. Stratified log-rank tests and Cox regression analyses were also done but were deemed supportive in nature only. Analyses were done with SAS (version 8.2).

This study is registered with ClinicalTrials.gov, number NCT00700102.

Role of the funding source

The sponsor of the study contributed to the study design, analysis and interpretation of the data, and the writing of this report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

	Bevacizumab and chemotherapy (n=407)	Chemotherapy alone (n=407)
sFOLFIRI	64 (16%)	57 (14%)
LV5FU2 CPT11	27 (7%)	30 (7%)
FOLFOX4	37 (9%)	35 (9%)
sFOLFOX4	38 (9%)	35 (9%)
FOLFOX6	64 (16%)	53 (13%)
FUFOX	23 (6%)	37 (9%)
XELIRI	49 (12%)	49 (12%)
XELOX	58 (14%)	46 (11%)
Other regimens	47 (12%)	65 (16%)

sFOLFIRI=simplified fluorouracil 400 mg/m² intravenous bolus and 2400 mg/m² over 46 h, folinate 400 mg/m² intravenously, and irinotecan 180 mg/m² intravenously on day 1 every 2 weeks. LV5FU2 CPT11=fluorouracil 400 mg/m² intravenous bolus and 600 mg/m² (central venous line) over 22 h on days 1, 2, 15, and 16, folinate 200 mg/m² intravenously on days 1, 2, 15, and 16, and irinotecan 180 mg/m² intravenously on days 1 and 15 every 4 weeks. FOLFOX4=fluorouracil 400 mg/m² intravenous bolus and 600 mg/m² intravenously over 22 h on days 1 and 2, folinate 200 mg/m² intravenously on days 1 and 2, and oxaliplatin 85 mg/m² intravenously on day 1 every 2 weeks. sFOLFOX4=simplified folinate 400 mg/m², fluorouracil 400 mg/m² intravenous bolus, fluorouracil 2400 mg/m² continuous infusion (over 46 h), and oxaliplatin 85 mg/m² on day 1 every 2 weeks. FOLFOX6=fluorouracil 400 mg/m² intravenous bolus and 2400 mg/m² intravenously over 46 h on days 1 and 15, folinate 400 mg/m² intravenously on days 1 and 15, and oxaliplatin 100 mg/m² intravenously on days 1 and 15 every 4 weeks. FUFOX=fluorouracil 2000 mg/m² over 22 h (central venous line) on days 1, 8, 15, and 22, folinate 500 mg/m² intravenously on days 1, 8, 15, and 22, and oxaliplatin 50 mg/m² intravenously on days 1, 8, 15, and 22 every 5 weeks. XELIRI=capecitabine 800 mg/m² orally twice daily on days 1–14 and 22–35, and irinotecan 200 mg/m² intravenously on days 1 and 22 every 6 weeks. XELOX=capecitabine 1000 mg/m² orally twice daily on days 1–14 and 22–35, and oxaliplatin 130 mg/m² intravenously on days 1 and 22 every 6 weeks. *Six of 409 patients in the bevacizumab and chemotherapy group and four of 411 in the chemotherapy group were not given any treatment; however, four patients in the bevacizumab and chemotherapy group were misreported as having been given chemotherapy.

Table 2: **Chemotherapy received during the study**

Results

From Feb 1, 2006, until June 9, 2010 (data cutoff May 31, 2011), 820 patients were randomly assigned to bevacizumab plus chemotherapy (n=409) or chemotherapy alone (n=411; figure 1). One patient did not provide written informed consent; therefore, the intention-to-treat population consisted of 819 patients (figure 1). 810 patients had one or more measurable lesion at baseline, and were included in analyses of response by RECIST criteria, and the safety population consisted of 810 patients who were given at least one dose of drug. Baseline demographic and clinical characteristics were balanced between treatment groups (table 1), as were the chemotherapy regimens received during the study (table 2).

Median follow-up was 9·6 months (IQR 5·4–13·9) in the chemotherapy alone group and 11·1 months (6·4–15·6) in the bevacizumab plus chemotherapy group. Median overall survival in the bevacizumab plus chemotherapy group was 11·2 months (95% CI 10·4–12·2) versus 9·8 months (8·9–10·7) for chemotherapy (HR 0·81, 95% CI 0·69–0·94; unstratified log-rank p=0·0062; figure 2A). After the completion of randomly assigned treatment, 275 (69%) of 401 patients in the bevacizumab plus chemotherapy group and 277 (68%) of 409 in the chemotherapy alone group were given one or more subsequent anticancer treatments. 96 patients were given further bevacizumab (46 [11%] in bevacizumab plus chemotherapy group and 50 [12%] in the chemotherapy alone group); 326 patients were given subsequent anti-EGFR agents (157 [39%] and 169 [41%] patients, respectively). Of the 616 patients with known *KRAS* mutation status, five did not receive treatment and were therefore not included in the analysis of subsequent anticancer treatment, more of those with *KRAS* wild-type tumours were given subsequent EGFR inhibitors (bevacizumab plus chemotherapy, 103 [70%] of 148 patients; chemotherapy alone, 114 [69%] of 166 patients) than those with *KRAS*-mutant tumours (12 [7%] of 162 patients and 12 [9%] of 135 patients, respectively). More patients with *KRAS*-mutant tumours were given further bevacizumab (bevacizumab plus chemotherapy, 28 [17%]; chemotherapy alone, 30 [22%]) versus *KRAS* wild-type tumours (12 [8%] and 14 [8%], respectively).

Median progression-free survival was 5·7 months (95% CI 5·2–6·2) in the bevacizumab plus chemotherapy group and 4·1 months (3·7–4·4) in the chemotherapy group (HR 0·68, 95% CI 0·59–0·78; unstratified log-rank p<0·0001; figure 2B). 22 (5%) of 404 patients treated with bevacizumab plus chemotherapy with one or more measurable lesions at baseline achieved a confirmed response versus 16 (4%) of 406 treated with chemotherapy (table 3; unstratified χ^2 test p=0·31). In a post-hoc analysis, 275 (68%) patients achieved disease control in the bevacizumab plus chemotherapy group versus 220 (54%) in the chemotherapy alone group (p<0·0001).

Median overall survival from the start of first-line treatment (retrospectively documented) was 23·9 months (95% CI 22·2–25·7) with bevacizumab plus chemotherapy and 22·5 months (21·4–24·5) with chemotherapy (HR 0·90, 95% CI 0·77–1·05; unstratified log-rank p=0·17). Median progression-free survival on treatment was 5·7 months (5·2–6·2) in the bevacizumab plus chemotherapy group versus 4·0 months (3·7–4·3) for chemotherapy (HR 0·63, 95% CI 0·53–0·74; unstratified log-rank test, p<0·0001).

Prespecified subgroup analyses were generally consistent with the primary findings (figure 3). Although differences were noted in HRs for overall survival in men and women (figure 3), there was no evidence of treatment by sex interaction in the Cox model (p>0·05).

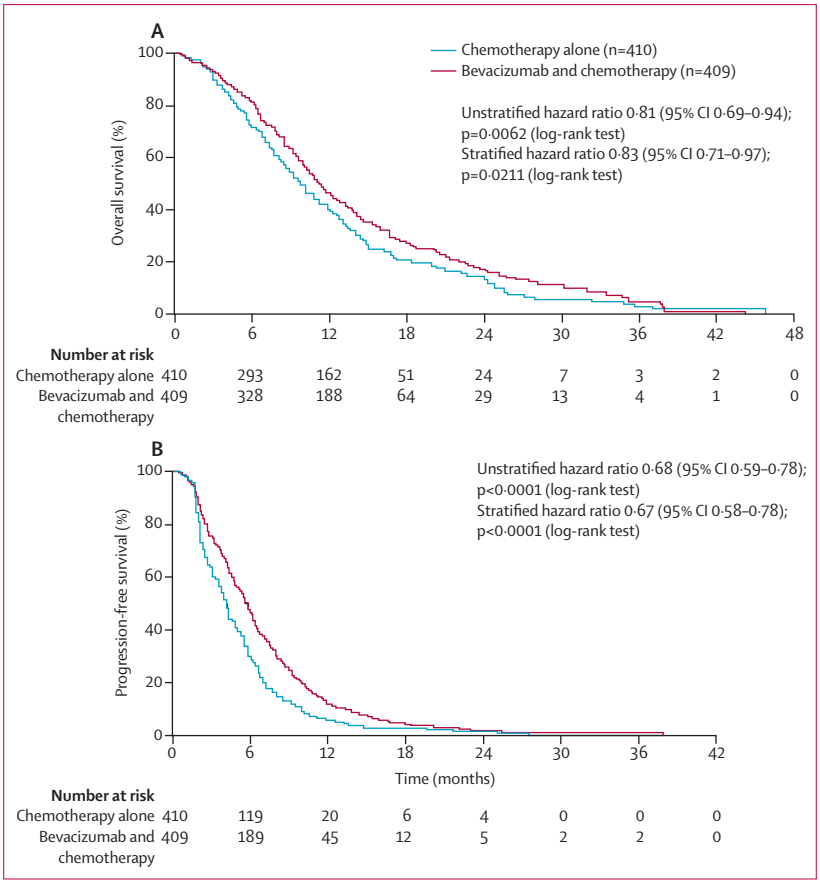

Figure 2: **Overall survival (A) and progression-free survival (B) according to treatment**
The primary analysis was unstratified. In the stratified analysis, patients were stratified by first-line chemotherapy (oxaliplatin-based *vs* irinotecan-based), first-line progression-free survival (≤9 months *vs* >9 months), time since last bevacizumab dose (≤42 days *vs* >42 days), and Eastern Cooperative Oncology Group performance status at baseline (0 *vs* ≥1).

	Bevacizumab and chemotherapy (n=404)*	Chemotherapy alone (n=406)*
Complete response	1 (<1%)	2 (<1%)
Partial response	21 (5%)	14 (3%)
Stable disease	253 (63%)	204 (50%)
Progressive disease	87 (22%)	142 (35%)
Missing or not assessable	42 (10%)	44 (11%)

Data are number (%). RECIST=Response Evaluation Criteria in Solid Tumors (version 1.0). *Includes only those patients with one or more measurable lesion at baseline.

Table 3: **Tumour response by RECIST**

The exploratory subgroup analysis according to *KRAS* status (n=616) showed benefits in terms of progression-free survival with bevacizumab and chemotherapy in patients with *KRAS* wild-type tumours and those with *KRAS*-mutant tumours (*KRAS* wild-type, HR 0·61, 95% CI 0·49–0·77; unstratified p<0·0001; *KRAS* mutant 0·70, 0·56–0·89; unstratified p=0·003). Patients with *KRAS* wild-type cancer had better overall survival with

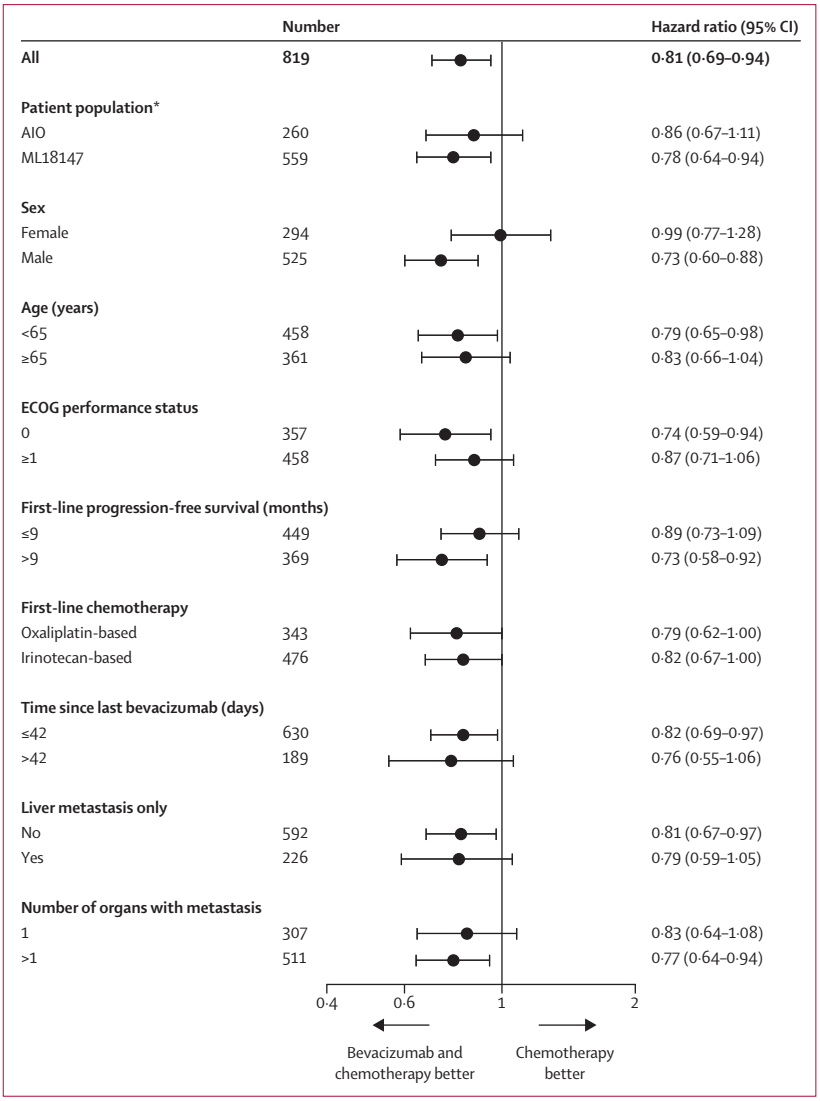

Figure 3: **Subgroup analysis of overall survival in the intention-to-treat population**
ECOG=Eastern Cooperative Oncology Group. AIO=Arbeitsgemeinschaft Internistische Onkologie. *Sequential enrolment of patients in the original AIO study and subsequent enrolment into ML18147 when the study was transferred to Roche. All patients in the AIO were included in the primary analysis.

bevacizumab and chemotherapy than with chemotherapy alone (0·69, 0·53–0·90; unstratified p=0·005); however, there was no difference in overall survival between treatment groups for those with *KRAS* mutations (0·92, 0·71–1·18; unstratified p=0·50). Nevertheless, the treatment by *KRAS* status interaction test was negative for both progression-free survival (p=0·4436) and overall survival (p=0·1266), indicating that there is no evidence that treatment effect is dependent on *KRAS* mutational status.

The results of the primary analysis were robust according to the prespecified sensitivity analyses that included stratified log-rank tests (figure 2A, B) and Cox regression analyses, various database cutoffs, and re-randomisation for the primary endpoint (appendix).

	Bevacizumab and chemotherapy (n=401)	Chemotherapy alone (n=409)
Neutropenia	65 (16%)	52 (13%)
Leucopenia	16 (4%)	12 (3%)
Asthenia	23 (6%)	17 (4%)
Fatigue	14 (3%)	10 (2%)
Diarrhoea	40 (10%)	34 (8%)
Vomiting	14 (3%)	13 (3%)
Nausea	13 (3%)	11 (3%)
Decreased appetite	5 (1%)	9 (2%)
Mucosal inflammation	13 (3%)	4 (1%)
Abdominal pain	15 (4%)	12 (3%)
Polyneuropathy	12 (3%)	6 (1%)
Peripheral neuropathy	5 (1%)	10 (2%)
Hypokalaemia	9 (2%)	8 (2%)
Dyspnoea	6 (1%)	12 (3%)
Pulmonary embolism	10 (2%)	8 (2%)
Hypertension	7 (2%)	5 (1%)
Bleeding or haemorrhage	8 (2%)	1 (<1%)
Venous thromboembolic events	19 (5%)	12 (3%)
Gastrointestinal perforation	7 (2%)	3 (<1%)
Subileus	8 (2%)	2 (<1%)

Data are number (%). *The safety population was 810 patients who were given at least one dose of study drug and were analysed according to the actual treatment given, 407 patients in the chemotherapy group and 403 in the chemotherapy plus bevacizumab group. Two patients randomly assigned to chemotherapy plus bevacizumab were not given bevacizumab and, therefore, for the purposes of all of the safety analyses, were assigned to the chemotherapy group.

Table 4: **Incidence of grade 3–5 adverse events occurring in 2% or more of patients given chemotherapy with or without bevacizumab after disease progression following first-line bevacizumab-based treatment (safety population*)**

Median overall treatment exposure was longer in the bevacizumab plus chemotherapy group (4·2 months [IQR 2·0–7·2] *vs* 3·2 months [1·7–5·2] in the chemotherapy alone group); median treatment duration with bevacizumab was 3·9 months (1·8–6·9). The duration of treatment according to chemotherapy agent is shown in the appendix.

394 (98%) patients in the bevacizumab plus chemotherapy group and 403 (99%) in the chemotherapy group had adverse events; grade 3–5 adverse events occurred in 255 (64%) and 235 (57%) patients, respectively. 11 grade 5 adverse events (ie, those resulting in death) occurred in each group. Of these deaths, four in the bevacizumab and chemotherapy group (upper gastrointestinal haemorrhage [n=1], cerebrovascular accident [n=1], sudden death [n=1], and neutropenia [n=1]) were deemed treatment related, as were three in the chemotherapy alone group (intestinal perforation [n=1], general physical health deterioration [n=1], and acute prerenal failure [n=1]). The other grade 5 events that were not judged to be treatment related were intestinal obstruction (n=1), ileus (n=1), sudden cardiac death (n=1), primary atypical

pneumonia (n=1), septic shock (n=1), pulmonary embolism (n=2), and lung disorder (n=1) in the chemotherapy group; and subileus (n=2), intestinal perforation (n=1), enteritis (n=1), multiorgan failure (n=1), and dyspnoea (n=2) in the bevacizumab and chemotherapy group. Serious adverse events occurred in 129 (32%) patients in the bevacizumab plus chemotherapy group and 137 (33%) in the chemotherapy alone group. The most commonly reported serious adverse events (>1% in either treatment group) were diarrhoea (16 [4%] *vs* 13 [3%] in the chemotherapy and chemotherapy plus bevacizumab groups, respectively), pyrexia (11 [3%] *vs* seven [2%], respectively), abdominal pain (nine [2%] *vs* six [1%], respectively), neutropenia (seven [2%] *vs* eight [2%], respectively), vomiting (four [1%] *vs* seven [2%], respectively), pulmonary embolism (four [1%] *vs* seven [2%], respectively), subileus (two [<1%] *vs* seven [2%], respectively), and drug hypersensitivity (one [<1%] *vs* five [1%], respectively).

Table 4 shows all grade 3–5 adverse events that occurred in 2% or more of patients. The most frequently reported grade 3–5 adverse events were neutropenia, diarrhoea, and asthenia. Grade 3–5 events of particular interest that were more common in the bevacizumab plus chemotherapy group than in the chemotherapy alone group were bleeding or haemorrhage, gastrointestinal perforation, and venous thromboembolic events (table 4). Arterial thromboembolic events and other notable adverse events with bevacizumab were rare. Four (1%) patients had aterial thromboembolic events in the chemotherapy group and three (<1%) patients in the chemotherapy plus bevacizumab group. Grade 3 or greater arterial thromboembolic events were reported in two patients in the chemotherapy group (grade 4 myocardial infarction and grade 3 acute myocardial infarction) and two patients in the chemotherapy plus bevacizumab group (grade 5 cerebrovascular accident and grade 3 myocardial infarction).

63 (16%) patients in the bevacizumab plus chemotherapy group discontinued any treatment because of adverse events compared with 36 (9%) patients in the chemotherapy alone group. In the bevacizumab plus chemotherapy group, 53 (13%) patients discontinued chemotherapy only or both bevacizumab and chemotherapy because of adverse events and ten (2%) patients discontinued bevacizumab because of adverse events. Deaths not related to progressive disease occurred in 23 (6%) patients in the bevacizumab plus chemotherapy group and 22 (5%) patients in the chemotherapy group (appendix).

Discussion

Our results show that bevacizumab continued beyond disease progression, while switching chemotherapy, is beneficial for patients with metastatic colorectal cancer who were previously treated with bevacizumab in the first-line setting. The continued use of bevacizumab beyond disease progression leads to a significant improvement in overall survival and progression-free survival compared with post-progression chemotherapy alone.

Resistance to chemotherapy results from changes in tumour cell biology and is often agent-specific.[21] By contrast, bevacizumab resistance, if it occurs, can result from the development of alternative angiogenesis pathways.[22] Consequently, bevacizumab resistance is unlikely to occur at the same time or through the same mechanisms as chemotherapy resistance, and thus bevacizumab can continue to be effective after the development of resistance to chemotherapy.[12]

BRiTE[17] and ARIES[18] were large, US-based observational studies in which patients were treated according to clinical practice. Their results led to a hypothesis that the use of bevacizumab after disease progression could increase survival. Our randomised trial confirms this hypothesis. However, the difference in the magnitude of the survival benefits noted in the observational studies and that seen here emphasises the shortcomings of registry studies, such as selection bias, patient attrition, and inequalities in treatment selection and that the findings of such studies cannot be cross compared with those from rigorously controlled randomised studies.

Because the choice of the doublet chemotherapy partner (irinotecan or oxaliplatin) in our study was at the discretion of investigators, patients were given a variety of chemotherapy regimens with bevacizumab, similar to real-world treatment patterns. Because the same VEGF inhibitor as used in first-line treatment was used in

Panel: Research in context

Systematic review

The complementary modes of action of anti-VEGF and chemotherapeutic agents led to the hypothesis that bevacizumab could continue to benefit patients even after resistance to chemotherapy has developed. We searched PubMed for English-language publications about randomised studies in which patients with metastatic colorectal cancer given first-line bevacizumab-containing regimens were treated again with bevacizumab plus chemotherapy after disease progression. We used the search terms "bevacizumab", "colorectal cancer" and "progression", or "second line" from Jan 1, 2000, to July 31, 2012. To our knowledge, the only studies of the use of bevacizumab after disease progression in patients with metastatic colorectal cancer who had been given bevacizumab in the first line have been the observational BRiTE[17] and ARIES[18] studies. The results of these studies suggested that continuing bevacizumab beyond disease progression was beneficial in terms of survival of the patient. However, their observational design meant that the findings could have been biased. Consequently, a rigorously controlled randomised study was needed to establish whether continuing bevacizumab with an alternative chemotherapy regimen could benefit patients who had progressed after first-line bevacizumab plus chemotherapy.

Interpretation

In this study, we have shown that overall and progression-free survival can be significantly prolonged by the continued use of bevacizumab plus chemotherapy after disease progression compared with chemotherapy alone. These findings show that maintaining VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in patients with metastatic colorectal cancer and indicates a new proof of principle in antiangiogenic treatment for cancer.

second-line treatment, at the same dose as in first-line, the survival benefits in ML18147 could be due to both persistent VEGF suppression and switching of the chemotherapy partner.

Findings from the subgroup analyses were generally consistent with those in the overall study population. Although differences in HRs were noted between men and women, they could have occurred by chance because of the number of analyses done. Furthermore, baseline characteristics by sex were balanced. The exploratory subgroup analysis by *KRAS* status showed that there is no evidence to suggest differences between the overall population and subgroups based on *KRAS* mutational status. Although the absolute difference in overall survival with bevacizumab plus chemotherapy versus chemotherapy alone from the retrospectively assessed time of starting first-line treatment was much the same as for the primary endpoint, there was no significant difference between groups for this analysis. By not randomly assigning patients from the start of first-line treatment, instead only randomly assigning those who chose to enrol after disease progression, these findings are potentially biased and cannot be compared with those of studies of overall survival from the start of first-line treatment. Moreover, care must be taken when extrapolating these results, which were obtained in the second-line setting with a prespecified first-line treatment, to the entire sequence of first-line then second-line treatment.

Response rates were low in both groups, although a greater proportion of bevacizumab-treated patients achieved disease control (post-hoc analysis) than did those given chemotherapy alone. The low response rates were not unexpected because patients had already been given first-line doublet chemotherapy plus bevacizumab and only the chemotherapy component was altered on enrolment into the study. By contrast, the response rate was 22% in bevacizumab-naive patients who were given bevacizumab as second-line treatment for metastatic colorectal cancer in the E3200 study;[4] however, importantly, in E3200 a higher bevacizumab dose was used, all patients were given an efficient fluoropyrimidine and oxaliplatin regimen, and none had previous first-line bevacizumab.[4] In accord with our results, response rates were also lower in bevacizumab-pretreated versus bevacizumab-naive patients in the second-line VELOUR study,[23] in which addition of aflibercept to chemotherapy improved survival compared with chemotherapy alone.[24]

We used bevacizumab at a dose of 2·5 mg/kg per week equivalent, in keeping with standard clinical practice for the first-line treatment of patients with metastatic colorectal cancer in the European Union. Pharmacokinetics, clinical efficacy, and safety data from studies AVF0780g[25] and AVF2107g[1] suggested that the 2·5 mg/kg per week equivalent dose of bevacizumab is well tolerated and effective in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of patients with metastatic colorectal cancer. We chose to continue this dose beyond progression to prove that any overall survival benefit was due to the continuation of bevacizumab, rather than any increase of the bevacizumab dose.

Continuing bevacizumab after disease progression raises the question of whether the risk of unacceptable toxicity is increased. Our findings indicate that the safety profile of bevacizumab plus chemotherapy was consistent with previously reported data in bevacizumab-naive patients[1–3] and did not show substantial differences in toxicity between the two treatment groups.

The biological concept of continued benefit associated with VEGF inhibition with bevacizumab after disease progression is supported by results from the CORRECT study,[26] in which treatment with regorafenib was beneficial in patients with colorectal cancer progressing after receiving all approved standard treatments. Notably, all patients in CORRECT had been given bevacizumab in an earlier treatment line. In the second-line VELOUR study,[23] subgroup analyses indicated benefits in both bevacizumab-pretreated and bevacizumab-naive patients. However, one cannot exclude the possibility that inhibition of alternative angiogenic pathways or additional tyrosine kinases (in the case of regorafenib) could account for the survival benefit in CORRECT and VELOUR. Unlike CORRECT or VELOUR (in which the biological agent was switched after progression), the results of our study suggest that continuing the same biological agent maintains treatment benefit without the potential for additional toxicities associated with inclusion of a new agent.

The findings in our study challenge the conventional definition of treatment resistance and lend support to the hypothesis that continued VEGF inhibition throughout the growth and metastasis of tumours is beneficial for patients with metastatic colorectal cancer (panel). Moreover, this result might lead to a new second-line treatment option for patients with metastatic colorectal cancer who have progressed on bevacizumab plus standard first-line chemotherapy, while maintaining an acceptable safety profile. The results from this study could serve as proof of principle that maintaining angiogenesis inhibition while switching chemotherapy from the first and second lines in colorectal cancer has clinical benefits in patients. This approach is also being investigated in studies of other tumour types, including metastatic breast and non-small-cell lung cancers.

Contributors

All authors had access to the study data, reviewed data analyses, contributed to the data interpretation, and reviewed, edited, and approved the report for publication. JB, JS, DA, PÖ, RG, EVC, RvM, JMV, OB, CB, C-CS, VA-O, CS, TA, and SK recruited patients and gathered data for the study. IRR did the statistical analyses.

Conflicts of interest

JB has received consulting fees or honoraria and travel grants from Roche and is an advisory board member for Roche and Boehringer Ingelheim; he has received payment for lectures including service on speakers' bureaus from Roche, Sanofi-Aventis, and Merck. JS has received consulting fees or honoraria and research funding from Roche. DA has received consulting fees or honoraria from Roche, Merck, and Amgen and research funding from Roche. PÖ has received consulting fees, honoraria, travel grants, or

lecturing fees from Roche, Amgen, and Merck, research funding from Roche, and is an advisory board member for Roche, Amgen, Bayer, Sanofi-Aventis, and Merck. EVC has received research funding from Roche. RvM has received consulting fees or honoraria from Roche and Novartis, research funding from Roche and Amgen, is an advisory board member for Roche, Amgen, Merck, and Novartis, and has provided expert testimony for Amgen. JMV has received research funding, payment for lectures including service on speakers' bureaus, and travel, accommodations, or meeting expenses from Roche. OB has received research funding and travel grants from Roche, payment for the development of educational presentations from Roche and Amgen, and is an advisory board member for Roche and Merck. CB has received travel grants from Roche. C-CS has received travel grants from Roche and is an advisory board member for Roche, Merck, and Amgen. IR-R is employed by Genentech and owns stock or stock options in Genentech. BB is employed by Roche and owns stock or stock options in Roche. TA has received consulting fees or honoraria and travel grants from Roche, payment for lectures or speakers' bureaus from Roche, Amgen, Merck, and Sanofi-Aventis, and is an advisory board member for Roche. SK has received consulting fees or honoraria, travel grants, and payment for lectures including service on speakers' bureaus from Roche. RG, VA-O, and CS have no conflicts of interest.

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