Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial

Aimery de Gramont, Eric Van Cutsem, Hans-Joachim Schmoll, Josep Tabernero, Stephen Clarke, Malcolm J Moore, David Cunningham, Thomas H Cartwright, J Randolph Hecht, Fernando Rivera, Seock-Ah Im, György Bodoky, Ramon Salazar, Frédérique Maindrault-Goebel, Einat Shacham-Shmueli, Emilio Bajetta, Martina Makrutzki, Aijing Shang, Thierry André, Paulo M Hoff

Summary

Background Bevacizumab improves the efficacy of oxaliplatin-based chemotherapy in metastatic colorectal cancer. Our aim was to assess the use of bevacizumab in combination with oxaliplatin-based chemotherapy in the adjuvant treatment of patients with resected stage III or high-risk stage II colon carcinoma.

Methods Patients from 330 centres in 34 countries were enrolled into this phase 3, open-label randomised trial. Patients with curatively resected stage III or high-risk stage II colon carcinoma were randomly assigned (1:1:1) to receive FOLFOX4 (oxaliplatin 85 mg/m², leucovorin 200 mg/m², and fluorouracil 400 mg/m² bolus plus 600 mg/m² 22-h continuous infusion on day 1; leucovorin 200 mg/m² plus fluorouracil 400 mg/m² bolus plus 600 mg/m² 22-h continuous infusion on day 2) every 2 weeks for 12 cycles; bevacizumab 5 mg/kg plus FOLFOX4 (every 2 weeks for 12 cycles) followed by bevacizumab monotherapy 7·5 mg/kg every 3 weeks (eight cycles over 24 weeks); or bevacizumab 7·5 mg/kg plus XELOX (oxaliplatin 130 mg/m² on day 1 every 2 weeks plus oral capecitabine 1000 mg/m² twice daily on days 1–15) every 3 weeks for eight cycles followed by bevacizumab monotherapy 7·5 mg/kg every 3 weeks (eight cycles over 24 weeks). Block randomisation was done with a central interactive computerised system, stratified by geographic region and disease stage. Surgery with curative intent occurred 4–8 weeks before randomisation. The primary endpoint was disease-free survival, analysed for all randomised patients with stage III disease. This study is registered with ClinicalTrials.gov, number NCT00112918.

Findings Of the total intention-to-treat population (n=3451), 2867 patients had stage III disease, of whom 955 were randomly assigned to receive FOLFOX4, 960 to receive bevacizumab–FOLFOX4, and 952 to receive bevacizumab–XELOX. After a median follow-up of 48 months (range 0–66 months), 237 patients (25%) in the FOLFOX4 group, 280 (29%) in the bevacizumab–FOLFOX4 group, and 253 (27%) in the bevacizumab–XELOX group had relapsed, developed a new colon cancer, or died. The disease-free survival hazard ratio for bevacizumab–FOLFOX4 versus FOLFOX4 was 1·17 (95% CI 0·98–1·39; p=0·07), and for bevacizumab–XELOX versus FOLFOX4 was 1·07 (0·90–1·28; p=0·44). After a minimum follow-up of 60 months, the overall survival hazard ratio for bevacizumab–FOLFOX4 versus FOLFOX4 was 1·27 (1·03–1·57; p=0·02), and for bevacizumab–XELOX versus FOLFOX4 was 1·15 (0·93–1·42; p=0·21). The 573 patients with high-risk stage II cancer were included in the safety analysis. The most common grade 3–5 adverse events were neutropenia (FOLFOX4: 477 [42%] of 1126 patients, bevacizumab-FOLFOX4: 416 [36%] of 1145 patients, and bevacizumab–XELOX: 74 [7%] of 1135 patients), diarrhoea (110 [10%], 135 [12%], and 181 [16%], respectively), and hypertension (12 [1%], 122 [11%], and 116 [10%], respectively). Serious adverse events were more common in the bevacizumab groups (bevacizumab–FOLFOX4: 297 [26%]; bevacizumab–XELOX: 284 [25%]) than in the FOLFOX4 group (226 [20%]). Treatment-related deaths were reported in one patient receiving FOLFOX4, two receiving bevacizumab–FOLFOX4, and five receiving bevacizumab–XELOX.

Interpretation Bevacizumab does not prolong disease-free survival when added to adjuvant chemotherapy in resected stage III colon cancer. Overall survival data suggest a potential detrimental effect with bevacizumab plus oxaliplatin-based adjuvant therapy in these patients. On the basis of these and other data, we do not recommend the use of bevacizumab in the adjuvant treatment of patients with curatively resected stage III colon cancer.

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Hôpital Saint Antoine, Paris, France (Prof A de Gramont MD, F Maindrault-Goebel MD, T André MD); **University Hospital Gasthuisberg, Leuven, Belgium** (Prof E Van Cutsem MD); **University Clinic Halle (Saale), Germany** (Prof H-J Schmoll MD); **Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain** (J Tabernero MD); **University of Sydney and Sydney Cancer Centre, Sydney, Australia** (Prof S Clarke FRACP); **Department of Medical Oncology, Princess Margaret Hospital and University of Toronto, Toronto, ON, Canada** (Prof M J Moore MD); **Royal Marsden Hospital, Sutton, UK** (Prof D Cunningham MD); **Ocala Oncology, Ocala, FL, USA** (T H Cartwright MD); **UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA, USA** (Prof J R Hecht MD); **University Hospital Marqués de Valdecilla, Santander, Spain** (F Rivera MD); **Seoul National University Hospital, Seoul, South Korea** (Prof S-A Im MD); **St László Hospital, Department of Oncology, Budapest, Hungary** (Prof G Bodoky MD); **Institut Catala d'Oncologia (IDIBELL), Barcelona, Spain** (Prof R Salazar MD); **Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel** (E Shacham-Shmueli MD); **Istituto di Oncologia-Policlinico di Monza, Monza, Italy** (Prof E Bajetta MD); **F Hoffmann-La Roche, Basel, Switzerland** (M Makrutzki MD, A Shang MD); **and Instituto do Cancer do Estado de São Paulo,**

Introduction

The prognosis of colorectal cancer is dependent on disease stage. The rate of 5-year survival is more than 60% in individuals with lymph node involvement, but less than 5% in those with distant metastases.[1–7] As metastatic disease is generally incurable, the concept of adjuvant chemotherapy was developed to allow patients with high-risk primary colon tumours the best chance of cure.

The survival benefits of adjuvant therapy in patients with resected, node-positive colon cancer were established in the 1990s.[8–10] A 6-month course of bolus fluorouracil and leucovorin emerged as the standard of

Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
(Prof P M Hoff FACP)

Correspondence to:
Prof Aimery de Gramont, Hôpital Saint Antoine, Rue du Faubourg Saint-Antoine, 75012 Paris, France
aimery.de-gramont@sat.aphp.fr

care;[9,10] it was later superseded in trials by infusional fluorouracil and leucovorin regimens, which had an improved safety profile.[2,11] Further changes to adjuvant treatment have since been made after the finding that adding oxaliplatin to fluoropyrimidines reduces the relative risk of recurrence by 20–23%.[4,12,13]

VEGF is a crucial regulator of normal and pathological angiogenesis.[14] VEGF inhibition with bevacizumab, a humanised anti-VEGF monoclonal antibody, has direct antivascular effects in human tumours,[15] improving outcomes when given with chemotherapy in patients with metastatic colorectal cancer.[16–18]

National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 investigated the efficacy of bevacizumab plus adjuvant oxaliplatin-based chemotherapy in patients in the USA with stage II/III colon cancer.[19] Adding bevacizumab did not increase disease-free survival (DFS) significantly after a median follow-up of 3 years (hazard ratio [HR] 0·89, 95% CI 0·76–1·04; p=0·15). However, a significant, but transient, effect was seen in the experimental group during bevacizumab exposure and at up to 3 months after completion of bevacizumab.

This article reports the primary efficacy findings from the AVANT trial (BO17920). This study was designed to show the superiority of bevacizumab added to oxaliplatin in combination with fluorouracil and leucovorin (FOLFOX4) or capecitabine (XELOX) compared with FOLFOX4 in terms of DFS in patients who had undergone surgery with curative intent for stage III colon carcinoma.

Methods

Study design and patients

AVANT was a prospective, multicentre, randomised, parallel, three-arm, phase 3 trial. The results of several phase 3 trials have shown that FOLFOX and XELOX are equivalent in the setting of metastatic colorectal cancer.[16–18] As a result, rather than using a 2×2 factorial trial design, which would have required an equivalency hypothesis between the arms making the trial inefficient in terms of patient number, we used a parallel three-arm design. This study was done in accordance with the declaration of Helsinki. Protocol approval was obtained from the ethics review committees or institutional review boards at participating sites. Patients provided written informed consent before study participation.

Eligible patients were 18 years or older with histologically confirmed stage III or high-risk stage II colon carcinoma (defined by the American Joint Cancer Committee/Union Internationale Contre le Cancer). Surgery with curative intent was done 4–8 weeks before randomisation. Key exclusion criteria included: evidence of remaining tumour; carcinoembryonic antigen levels of more than 1·5 times the upper normal limit after surgery; previous antiangiogenic treatment; major surgical procedure, open biopsy, or significant traumatic injury less than 28 days before study treatment; and abnormal haematological, liver, or renal function.

Randomisation and masking

Randomisation was done after surgery using a centralised interactive computerised system and stratified according to geographic region (n=8) and disease stage (high-risk stage II *vs* stage III [N1] *vs* stage III [N2]). A block design randomisation procedure (block size of six) was used. The study had an open-label design. Patients were randomly assigned 1:1:1 to one of three treatment options: FOLFOX4 for 24 weeks followed by observation for 24 weeks; bevacizumab–FOLFOX4 for 24 weeks followed by bevacizumab monotherapy for 24 weeks; or bevacizumab–XELOX for 24 weeks followed by bevacizumab monotherapy for 24 weeks.

In February, 2006, recruitment was halted temporarily after the data and safety monitoring board recommended a review of 60-day safety data. In May 2006, the board concluded that the safety profile was consistent with other adjuvant colon cancer studies and recommended restarting of recruitment.

Procedures

Treatment regimens were as follows: FOLFOX4 consisted of oxaliplatin (85 mg/m² intravenous infusion) given with leucovorin (200 mg/m² intravenously) and fluorouracil (400 mg/m² bolus then 600 mg/m² 22-h continuous infusion) on day 1. On day 2, leucovorin (200 mg/m² intravenous infusion) was followed by fluorouracil (400 mg/m² bolus then 600 mg/m² 22-h continuous infusion). Cycles were repeated every 2 weeks for 12 cycles (24 weeks). This was followed by 24 weeks of observation only in the FOLFOX4 group. Patients in the bevacizumab–FOLFOX4 group received bevacizumab (5 mg/kg intravenous infusion) on day 1 followed by oxaliplatin (85 mg/m² intravenously) with leucovorin (200 mg/m² intravenously), followed by fluorouracil (400 mg/m² bolus then 600 mg/m² 22-hour continuous infusion). On day 2, patients received leucovorin (200 mg/m² intravenously), fluorouracil (400 mg/m² bolus then 600 mg/m² 22-h continuous infusion), with cycles repeated every 2 weeks for 12 cycles (24 weeks). This was followed by bevacizumab 7·5 mg/kg on day 1 every 3 weeks for a further 24 weeks (eight cycles). Bevacizumab–XELOX consisted of bevacizumab (7·5 mg/kg intravenous administration) followed by oxaliplatin (130 mg/m² intravenous administration) on day 1 every 3 weeks and capecitabine (1000 mg/m² twice daily, orally, with first dose in the evening of day 1 and last dose in the morning of day 15) every 3 weeks for eight cycles (24 weeks). This was followed by bevacizumab (7·5 mg/kg intravenous administration) on day 1 every 3 weeks for a further 24 weeks (eight cycles).

Bevacizumab was administered by 30-min to 90-min intravenous infusion on day 1 before oxaliplatin. If capecitabine or fluorouracil was discontinued because of toxicity, patients could continue bevacizumab but not oxaliplatin.

The primary endpoint, DFS, was defined as the time between randomisation and recurrence, new occurrence of colorectal cancer, or death from any cause. Event-free patients at the clinical cutoff date were censored at the last date at which they were known to be disease-free. Recurrences or new occurrences were based on investigator tumour assessments, and pre-scheduled every 6 months after randomisation until year 4, then annually thereafter. A scheduled tumour assessment mandatorily contained carcinoembryonic antigen measurement, abdominal and pelvic CT/MRI or ultrasound, and chest CT/MRI or radiograph. Suspicious lesions detected by ultrasound or chest radiograph required confirmation by CT/MRI. Any recurrence of the original cancer or appearance of a new colorectal cancer should have been proven by cytology or histology when possible. An isolated event of increased carcinoembryonic antigen, or unexplained clinical deterioration, was not considered to be evidence of recurrence without support of other objective measurements (eg, radiology, histology, and cytology). The date of recurrence was defined as the date of definitive assessment by objective measurements.

Overall survival was defined as time from randomisation to death. Patients who were still alive at the clinical cutoff date were censored at the date at which they were last confirmed to be alive. Survival status was assessed every 6 months in the first 4 years after randomisation, then annually thereafter.

Adverse events were monitored until at least 28 days after the last dose of study treatment or end of observation phase. Adverse events of special interest to bevacizumab (hypertension, proteinuria, wound-healing complications, and fistulae or intra-abdominal abscesses) were monitored for 6 months, and related serious adverse events indefinitely. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

Statistical analysis

Statistical analyses were done with SAS version 8.2. Efficacy analysis was based on all randomised patients with stage III disease. The AVANT trial was event-driven, time-driven, or both. The study continued until either around 836 events had occurred in patients with stage III disease or 36 months after the last patient was randomly assigned, whichever occurred first. No interim efficacy analyses were planned. Assuming that patients with stage III disease would have a 23% reduction in the hazard rate with bevacizumab–FOLFOX4 versus FOLFOX4 or bevacizumab–XELOX versus FOLFOX4, we calculated that 2880 patients (960 in each group) would provide 836 events, sufficient to yield 80% power for a two-sided log-rank test at an alpha level of 0·025. This also guaranteed 80% power for a two-sided log-rank test at an alpha level of 5% using a closed test procedure (adjustment for multiplicity).[20] Primary study objectives were tested only if the global hypothesis, which assessed differences in distribution of DFS between all treatment groups at the 5% alpha level, was rejected. Additional patients

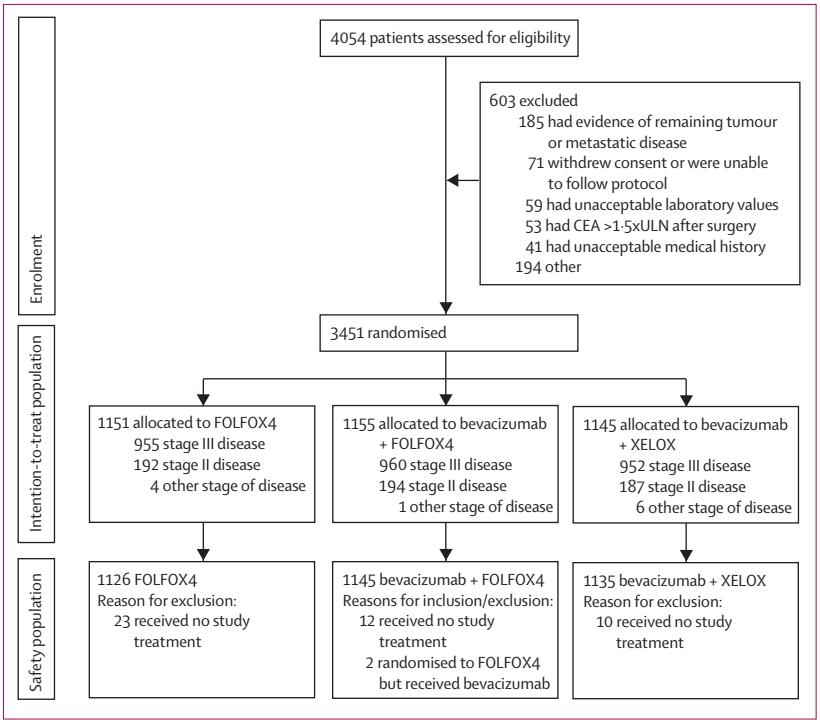

Figure 1: **Trial profile**
CEA=carcinoembryonic antigen. ULN=upper limit of normal.

	FOLFOX4 (N=1151)	Bevacizumab plus FOLFOX4 (N=1155)	Bevacizumab plus XELOX (N=1145)
Disease stage			
Stage III	955 (83%)	960 (83%)	952 (83%)
N1	585 (51%)	590 (51%)	572 (50%)
N2	370 (32%)	370 (32%)	380 (33%)
Stage II (high-risk)	192 (17%)	194 (17%)	187 (16%)
Age (years)	58 (20–83)	58 (19–82)	58 (19–82)
Sex			
Men	656 (57%)	587 (51%)	625 (55%)
Women	495 (43%)	568 (49%)	520 (45%)
ECOG performance status			
0	994 (86%)	987 (85%)	978 (85%)
1	156 (14%)	166 (14%)	165 (14%)
Ethnic origin			
White	956 (83%)	976 (85%)	963 (84%)
Asian	158 (14%)	138 (12%)	138 (12%)

Data are n (%) or median (range). Percentages subject to rounding error. Patient numbers for disease stage do not add up to total intention-to-treat population because 11 patients had other stages of disease (I, II, IV). ECOG=Eastern Co-operative Oncology Group. FOLFOX4=fluorouracil, leucovorin, and oxaliplatin. XELOX=capecitabine plus oxaliplatin.

Table 1: **Baseline characteristics (intention-to-treat population)**

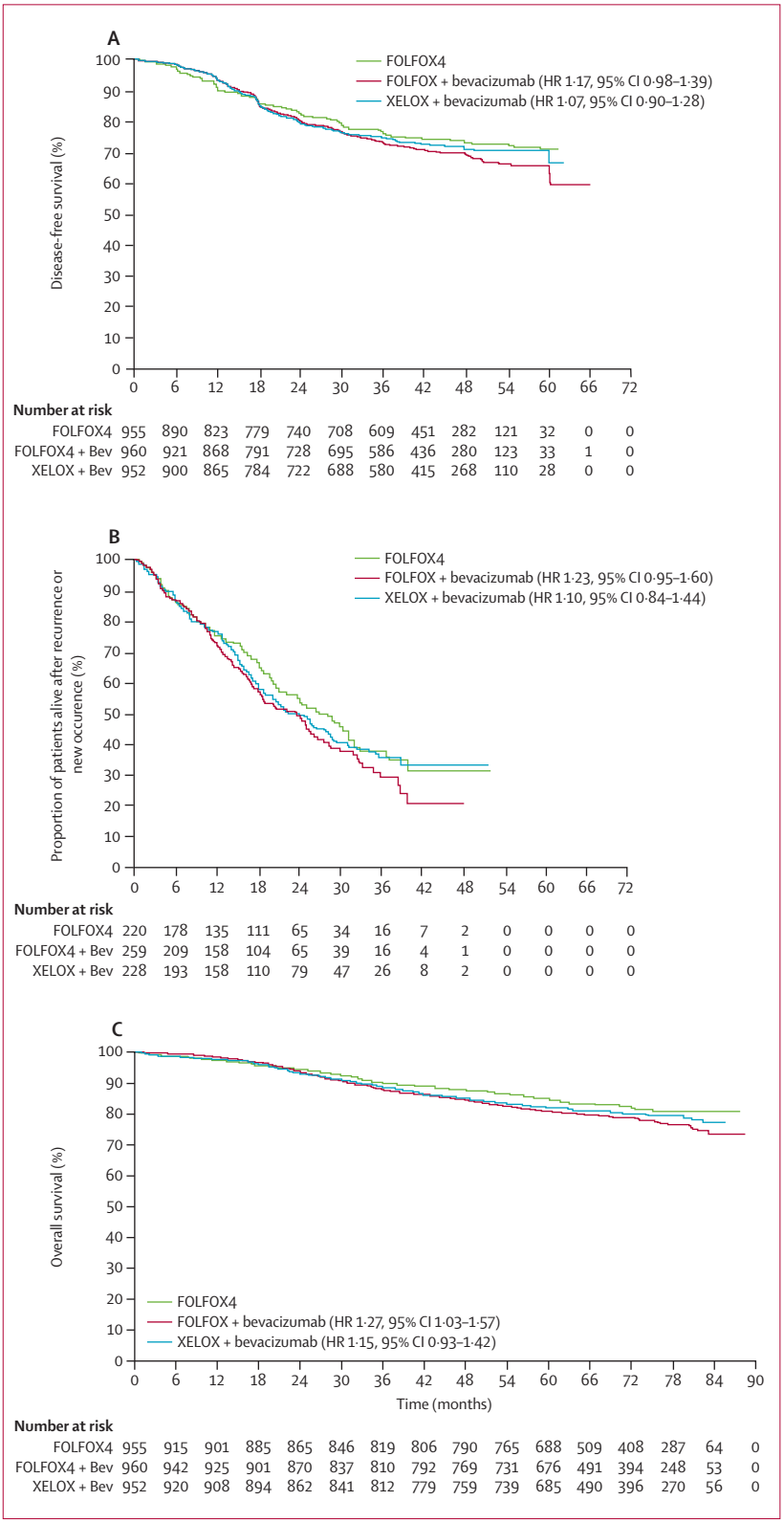

Figure 2: **Disease-free survival (A), time from disease recurrence/new occurrence to death (B), and overall survival (C) in patients with stage III disease**
Bev=bevacizumab.

with high-risk stage II disease (16% of total) were recruited for exploratory analyses, giving a planned total sample size of 3450 randomised patients. The cutoff date for the primary analysis was June 30, 2010, and the cutoff date for the overall survival follow-up analysis was June 30, 2012.

Kaplan-Meier methodology was used to analyse time-to-event endpoints. Estimates of treatment effect were expressed as HRs including 95% CIs. Based on NSABP C-08,[19] cumulative HRs over time were analysed prospectively and calculated based on patients with stage III disease from randomisation to fixed timepoints. Patients who were event-free at a given timepoint were censored at that timepoint.

The safety population comprised all patients who received at least one dose of study treatment. Patients who received at least one dose of bevacizumab were assigned to the bevacizumab group. Safety data were analysed descriptively.

This study is registered with ClinicalTrials.gov as NCT00112918.

Role of the funding source

The study sponsor was involved in study design, data interpretation, and the decision to submit the report for publication in conjunction with the authors. Employees of the sponsor collected and managed the data, and undertook data analysis. The principal investigator (AdG) had full access to all study data and had final responsibility for the decision to submit for publication.

Results

From Dec 20, 2004, to June 8, 2007, 3451 patients from 330 centres in 34 countries worldwide were randomly assigned to receive FOLFOX4 (n=1151), bevacizumab–FOLFOX4 (n=1155) or bevacizumab–XELOX (n=1145; figure 1). Of the 3451 patients enrolled, 2867 (83%) had stage III disease (FOLFOX4, n=955; bevacizumab–FOLFOX4, n=960; bevacizumab–XELOX, n=952). Baseline demographic and clinical characteristics were balanced between groups (table 1).

Median duration of oxaliplatin treatment was 5·3 months (range 0–8·8) in the FOLFOX4 group, 5·2 months (0–9·0) in the bevacizumab–FOLFOX4 group, and 4·9 months (0–7·9) in the bevacizumab–XELOX group. Median duration of fluorouracil or capecitabine treatment was 5·6 months (0–8·8) in the FOLFOX4 group, 5·4 months (0–9·0) in the bevacizumab–FOLFOX4 group, and 5·3 months (0–8·3) in the bevacizumab–XELOX group. Median duration of bevacizumab treatment was 10·6 months (0–13·8) in the bevacizumab–FOLFOX4 group and 10·4 months (0–12·9) in the bevacizumab–XELOX group.

There were some imbalances between groups in use of therapy after disease recurrences or new occurrences (appendix). Bevacizumab was given to 77 (35%) of 220 patients with recurrence or new occurrence of colon

cancer in the FOLFOX4 group, 41 (16%) of 259 patients in the bevacizumab–FOLFOX4 group, and 48 (21%) of 228 patients in the bevacizumab–XELOX group.

For patients with stage III disease, median follow-up duration for patients who did not have DFS events at the clinical cutoff date (June 30, 2010) was 48·5 months (range 0–62·3) in the FOLFOX4 group, 48·3 months (0–66·0) in the FOLFOX4 plus bevacizumab group and 48·3 months (0–65·7) in the XELOX plus bevacizumab group. The hypothesis for the DFS global test was not rejected (p=0·2024); therefore, all subsequent analyses are exploratory only.

At the cutoff date, 237 (25%) of 955 patients in the FOLFOX4 group had relapsed, developed a new colon cancer, or died, compared with 280 (29%) of 960 patients in the bevacizumab–FOLFOX4 group and 253 (27%) of 952 patients in the bevacizumab–XELOX group. The HR for bevacizumab–FOLFOX4 versus FOLFOX4 was 1·17 (95% CI 0·98–1·39; p=0·07), and for bevacizumab–XELOX versus FOLFOX4 was 1·07 (0·90–1·28; p=0·44; figure 2A). 3-year DFS rate was 76% (95% CI 74–79) for patients in the FOLFOX4 group, 73% (71–76) for those in the bevacizumab–FOLFOX4 group, and 75% (72–78) for those in the bevacizumab–XELOX group. Findings were consistent across all patient subgroups (appendix).

Most DFS events in the three treatment groups were recurrences (219 [23%] of 955 patients in the FOLFOX4 group, 252 [26%] of 960 in the bevacizumab–FOLFOX4 group, and 223 [23%] of 952 in the bevacizumab–XELOX group), with a few new colon cancer occurrences (three [<1%], eight [<1%], and six [<1%] patients, respectively) and deaths (17 [2%], 21 [2%], and 25 [3%] patients, respectively). The rate of tumour recurrences at various sites seemed to be similar in all groups (table 2). There were no meaningful differences between groups regarding modalities used to confirm recurrences or the timepoints at which these checks were done (data not shown).

1 year after randomisation, the cumulative DFS HR for bevacizumab–FOLFOX4 versus FOLFOX4 was 0·63 (95% CI 0·45–0·89) and 0·61 (0·43–0·86) for bevacizumab–XELOX versus FOLFOX4. Thereafter, cumulative HRs exceeded 1·00 for the remaining observation period (figure 3).

The median time from recurrence or new occurrence to death was 27·0 months (95% CI 21·4–32·2) in the FOLFOX4 group, 23·8 months (18·5–26·4) in the bevacizumab–FOLFOX4 group, and 22·4 months (19·0–29·0) in the bevacizumab–XELOX group. Survival after recurrence or new colon cancer occurrence is presented in figure 2B. The HR for bevacizumab–FOLFOX4 versus FOLFOX4 was 1·23 (0·95–1·60; p=0·1208), and for bevacizumab–XELOX versus FOLFOX4 was 1·10 (0·84–1·44; p=0·4892).

At the final cutoff date for overall survival (June 30, 2012), of the randomised patients with stage III colorectal cancer, 161 (17%) in the FOLFOX4 group had died, compared with 202 (21%) in the bevacizumab–FOLFOX4 group and 182 (19%) in the bevacizumab–XELOX group. The overall survival HR for bevacizumab–FOLFOX4 versus FOLFOX4 was 1·27 (95% CI 1·03–1·57; p=0·02) and for bevacizumab–XELOX versus FOLFOX4 was 1·15 (0·93–1·42; p=0·21; figure 2C). 5-year survival rates were 85% (95% CI 83–87) in the FOLFOX4 group, 81% (78–83) in the bevacizumab–FOLFOX4 group, and 82% (80–85) in the bevacizumab–XELOX group. Most deaths were due to disease progression (appendix).

Subgroup analyses were done to identify prognostic factors for DFS within the stage III population (appendix). No subgroup, defined on baseline characteristics including age, sex, ethnic origin, T stage, number of analysed lymph nodes, and the number of metastatic

	FOLFOX4 (n=955)	Bevacizumab plus FOLFOX4 (n=960)	Bevacizumab plus XELOX (n=952)
Patients with tumour recurrence	219 (23%)	252 (26%)	223 (23%)
Local	39 (4%)	42 (4%)	47 (5%)
Regional lymph nodes	19 (2%)	22 (2%)	21 (2%)
Distant lymph nodes	36 (4%)	31 (3%)	30 (3%)
Liver	82 (9%)	87 (9%)	62 (7%)
Lung	45 (5%)	63 (7%)	57 (6%)
Other	62 (6%)	88 (9%)	64 (7%)
Number of sites involved			
1	164 (17%)	192 (20%)	177 (19%)
>1	55 (6%)	60 (6%)	46 (5%)

Data are n (%). FOLFOX4=fluorouracil, leucovorin, and oxaliplatin. XELOX=capecitabine plus oxaliplatin.

Table 2: **Site of tumour recurrence in patients with stage III disease (intention-to-treat population)**

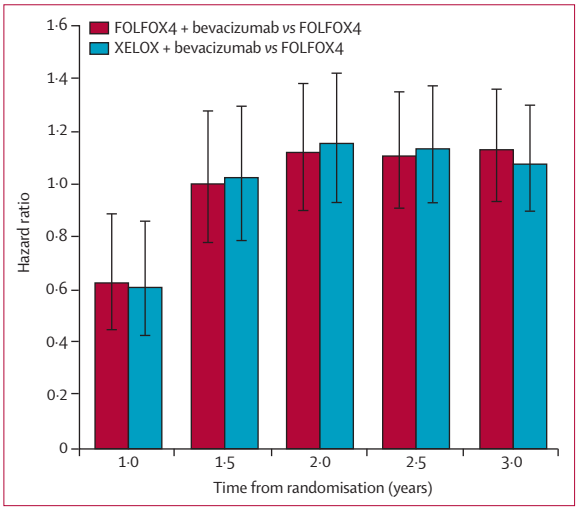

Figure 3: **Cumulative hazard ratios for disease-free survival in patients with stage III disease (intention-to-treat population)**

See **Online** for appendix

	FOLFOX4 (n=1126)			Bevacizumab plus FOLFOX4 (n=1145)			Bevacizumab plus XELOX (n=1135)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Adverse events									
Any*	741 (66%)	205 (18%)	9 (<1%)	780 (68%)	214 (19%)	6 (<1%)	712 (63%)	57 (5%)	11 (1%)
Neutropenia	315 (28%)	162 (14%)	0	272 (24%)	144 (13%)	0	71 (6%)	3 (<1%)	0
Diarrhoea	105 (9%)	5 (<1%)	0	133 (12%)	2 (<1%)	0	172 (15%)	9 (<1%)	0
Vomiting	22 (2%)	1 (<1%)	0	41 (4%)	0	0	57 (5%)	0	0
Nausea	18 (2%)	0	0	41 (4%)	0	0	57 (5%)	0	0
Hand-foot syndrome	6 (<1%)	0	0	13 (1%)	0	0	96 (8%)	0	0
Peripheral neuropathy†	157 (14%)	2 (<1%)	0	152 (13%)	3 (<1%)	0	138 (12%)	3 (<1%)	0
Adverse events of special interest to bevacizumab‡									
Any*	82 (7%)	18 (2%)	5 (<1%)	243 (21%)	42 (4%)	2 (<1%)	190 (17%)	25 (2%)	2 (<1%)
Venous thromboembolic events	51 (5%)	11 (1%)	1 (<1%)	77 (7%)	17 (1%)	0	39 (3%)	12 (1%)	1 (<1%)
Arterial thromboembolic events	4 (<1%)	4 (<1%)	3 (<1%)	7 (<1%)	10 (<1%)	0	10 (<1%)	5 (<1%)	0
Hypertension	12 (1%)	0	0	118 (10%)	4 (<1%)	0	112 (10%)	4 (<1%)	0
Bleeding/haemorrhage	5 (<1%)	1 (<1%)	0	10 (<1%)	3 (<1%)	1 (<1%)	3 (<1%)	0	1 (<1%)
Gastrointestinal perforation	0	0	1 (<1%)	4 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
Proteinuria	1 (<1%)	0	0	10 (<1%)	0	0	11 (1%)	1 (<1%)	0
Wound-healing complications	4 (<1%)	0	0	3 (<1%)	0	0	4 (<1%)	1 (<1%)	0
Fistula/abscess	3 (<1%)	1 (<1%)	0	12 (1%)	4 (<1%)	0	9 (<1%)	1 (<1%)	0

Data are n (%). FOLFOX4=fluorouracil, leucovorin, and oxaliplatin. XELOX=capecitabine plus oxaliplatin. *Some patients had more than one event. †Peripheral neuropathy also includes paraesthesia and peripheral sensory neuropathy. ‡Event onset within 183 days after last treatment.

Table 3: **Most common grade 3–5 adverse events (≥5%) and grade 3–5 adverse events of special interest to bevacizumab (safety population, including patients with stage III and high-risk stage II disease)**

lymph nodes, derived benefit from the addition of bevacizumab to chemotherapy. Furthermore, preliminary analysis of an ancillary biomarker study in selected centres has shown that baseline plasma levels of VEGF-A or VEGF receptors 1 or 2 could not identify a subgroup that could have either a potential benefit or a potential detriment from bevacizumab (appendix).

The safety population consisted of 3406 patients (1126 in the FOLFOX4 group, 1145 in the bevacizumab–FOLFOX4 group, and 1135 in the bevacizumab–XELOX group; figure 1). Grade 3–5 adverse events were reported in 824 (73%) patients in the FOLFOX4 group, 869 (76%) in the bevacizumab–FOLFOX4 group, and 733 (65%) in the bevacizumab–XELOX group (table 3); 772 (69%), 829 (72%), and 675 (60%), respectively, were deemed to be treatment related. Adverse events resulted in fluorouracil dose delays, interruptions, or reductions in 829 (74%) patients in the FOLFOX4 group and 801 (70%) patients in the FOLFOX4 and bevacizumab group; capecitabine doses were delayed, interrupted or reduced in 683 (60%) patients in the XELOX plus bevacizumab group. Oxaliplatin doses were delayed, interrupted, or reduced as a result of adverse events in 838 (74%) patients in the FOLFOX4 group, 808 (71%) patients in the FOLFOX4 plus bevacizumab group, and 615 (54%) patients in the XELOX plus bevacizumab group. Bevacizumab doses were delayed, interrupted, or reduced as a result of adverse events in 771 (67%) patients in the FOLFOX4 plus bevacizumab group and 569 (50%) patients in the XELOX plus bevacizumab group. The most common grade 3–5 adverse events were neutropenia, diarrhoea, peripheral neuropathy and hypertension (table 3).

Adding bevacizumab seemed to cause no clinically relevant increase in chemotherapy-related toxicity, with the possible exceptions of diarrhoea and nausea or vomiting (table 3). Grade 3–5 events of special interest to bevacizumab occurred in 264 (23%) patients in the bevacizumab–FOLFOX4 group, 203 (18%) in the bevacizumab–XELOX group, and 99 (9%) in the FOLFOX4 group (table 3); the difference between groups was mainly attributable to a higher incidence of hypertension and proteinuria with bevacizumab. Grade 3–5 venous thromboembolic events were noted in 5–8% of patients (table 3). All other grade 3–5 events of special interest occurred infrequently (≤1·5% of patients).

The proportion of patients with serious adverse events was greater in the bevacizumab-treated groups (297 [26%] patients in the bevacizumab–FOLFOX4 group; 284 [25%] in the bevacizumab–XELOX group) than in the FOLFOX4 group (226 [20%]).

Deaths related to study treatment occurred in one patient receiving FOLFOX4 (myocardial ischaemia), two of those receiving bevacizumab–FOLFOX4 (sudden death, n=1; lower gastrointestinal haemorrhage, n=1), and five receiving bevacizumab–XELOX (sudden death, n=3; sudden cardiac death, n=1; febrile neutropenia, n=1). Mortality within 60 days after starting treatment was low, affecting two patients in the FOLFOX4 group,

four patients in the FOLFOX4 plus bevacizumab group, and six patients in the XELOX and bevacizumab group.

Discussion

AVANT did not show a significant DFS improvement after a minimum of 3 years' follow-up with the addition of bevacizumab to either FOLFOX4 or XELOX in patients with resected stage III disease. After a minimum of 5 years' follow-up, overall survival data, unlike those from NSABP C-08,[19] suggest a potential detrimental effect with bevacizumab plus oxaliplatin-based adjuvant therapy (numerically more relapses and deaths due to disease progression were seen in both bevacizumab groups).

Bevacizumab seemed to have a transient favourable effect in the first year (figure 2), as in NSABP C-08 (panel).[19] However, in AVANT the effect became unfavourable from 1·5 years onwards in both experimental groups. Baseline prognostic factors and plasma levels of VEGF-A or VEGF receptors 1 or 2 could not identify a subgroup which could have either a potential benefit or a potential detriment from bevacizumab.

Several hypotheses could explain the failure of bevacizumab in the adjuvant setting. First, despite a strong preclinical rationale supporting the hypothesis that tumour angiogenesis is a key factor for growth of metastases in colorectal cancer, a biological model showing benefit with bevacizumab in early-stage disease is lacking.[21] On the basis of Gompertz's principle,[22] micrometastases tend to grow faster than macrometastases, and are therefore more sensitive to cytotoxic therapy. This principle might explain why adjuvant fluorouracil and leucovorin leads to a 10% absolute improvement for stage III patients in 8-year overall survival,[1] but only offers modest efficacy in patients with metastatic disease. However, this effect might not be the case for agents like bevacizumab. The apparent transient DFS benefit seen in the first year might be due to an effect of bevacizumab on already-present undetectable metastases. If this hypothesis is true, prolongation of bevacizumab administration beyond 1 year would not further increase DFS, since this effect of bevacizumab plus chemotherapy lasts about a year or less.[16,17]

Additionally, mechanisms underlying resistance to antiangiogenic therapy involve evasive resistance and intrinsic or pre-existing indifference,[23] and even increased invasiveness phenotype.[24] Up-regulation of other pro-angiogenic factors has been postulated as one of the resistance phenomena that block the effects of anti-angiogenic therapy, potentially inducing VEGF rebound once anti-VEGF treatment is stopped.[25] A rebound effect after withdrawal of an antiangiogenic agent has been shown in preclinical studies and in glioblastoma.[21] However, discontinuation of bevacizumab in metastatic patients, including those with colorectal cancer, does not seem to affect disease progression patterns.[26] We believe that such a conclusion could be extrapolated to the adjuvant setting, since there was no difference in survival after recurrence in either AVANT or NSABP C-08.[19] Furthermore, the proportion of patients with more than one site of recurrence and the organ distribution of recurrences were also similar in both studies. Reducing the cycling potential of tumour cells or inducing pro-survival pathways might also facilitate tumour resistance.[27–29]

Another possible explanation for the lack of bevacizumab efficacy in the adjuvant setting could be tumour cell dormancy. Adjuvant therapies can suppress antiangiogenic vascularisation of micrometastases and thus tumour growth,[30] but the early benefit seen in bevacizumab trials is lost when cells that acquire resistance or are quiescent start to proliferate again in the absence of chemotherapy. Interestingly, arrested angiogenesis is a component of cell dormancy and bevacizumab can increase this effect.[31] A consequence of dormancy could be resistance to chemotherapy.[32]

No new or unexpected safety signals were recorded that could explain our findings. The safety of bevacizumab in combination with FOLFOX4 and XELOX is consistent with what has been documented in patients with metastatic colorectal cancer.[17]

Panel: Research in context

Systematic review

We searched PubMed for original research articles published in English before July 30, 2012, regarding the adjuvant treatment of patients with colon cancer using bevacizumab plus chemotherapy. We used the keywords "colon", "carcinoma", and "bevacizumab" and limited our search to randomised controlled trials. We identified one randomised controlled trial comparing bevacizumab plus chemotherapy versus chemotherapy alone, NSABP C-08, which investigated the efficacy of bevacizumab plus adjuvant oxaliplatin-based chemotherapy in patients with resected stage II/III colon cancer.[19] NSABP C-08 showed that adding bevacizumab to oxaliplatin-based adjuvant chemotherapy did not increase disease-free survival significantly after a median follow-up of 3 years. However, a significant, but transient, effect was seen in the bevacizumab-containing group during bevacizumab exposure. The AVANT trial is the second trial to investigate whether or not the addition of bevacizumab to oxaliplatin-containing chemotherapy is superior to chemotherapy alone after curative surgery in patients with stage II/III colon cancer.

Interpretation

The AVANT trial shows that the addition of bevacizumab to FOLFOX4 or XELOX does not prolong disease-free survival in patients with resected stage III colon cancer compared with FOLFOX4 alone. Overall survival data suggest a potential detrimental effect with bevacizumab plus oxaliplatin-based adjuvant therapy in this patient population. Bevacizumab should not be used in the adjuvant treatment of patients with curatively resected stage III colon cancer.

Bevacizumab is not the first drug to show efficacy in metastatic colorectal cancer but not early-stage disease. Irinotecan and cetuximab, which are approved for treating metastatic disease, failed to show convincing benefits in adjuvant trials.[33–37] Unless all three drugs have a common mechanism, these results might suggest that the biological behaviour of early-stage tumours and its drivers are different from those of metastatic cancer. Although AVANT was adequately powered to answer the question of whether bevacizumab in combination with adjuvant chemotherapy significantly prolongs DFS in patients with stage III colon cancer, the results are not generalisable outside the adjuvant treatment of colon cancer. An active research programme is continuing with bevacizumab as adjuvant therapy for other tumour types.

In conclusion, bevacizumab does not prolong DFS when added to adjuvant chemotherapy in patients with stage III colon cancer, with more relapses and deaths due to disease progression being seen in both bevacizumab groups compared with the control group. Consequently, bevacizumab should not be used in the adjuvant treatment of patients with curatively resected stage III colon cancer.

Contributors

The principal investigator (AdG) had full access to all study data and had final responsibility for the decision to submit for publication. All other authors were involved in study design, data collection, data analysis, data interpretation, manuscript writing and approval prior to submission (equal contribution).

Conflicts of interest

AdG has acted as a consultant for and received honoraria from Roche-Genentech. H-JS has acted as a consultant for and received honoraria from Roche and Merck. JT has acted as a consultant for and received honoraria from Sanofi-Aventis, Roche, and Genentech. DC has acted as a consultant for and received honoraria from Roche, Sanofi-Aventis, Merck-Serono, and Amgen. THC has acted as a consultant for and received honoraria from Roche-Genentech. FR has acted as a consultant for and received travel grants and honoraria from Roche. ES-S has received travel grants from Roche. TA has acted as a consultant for and received honoraria from Roche. PMH has acted as a consultant for and received travel grants from Roche. MM and AS are employed by F Hoffmann-La Roche. AS owns stock in Roche F Hoffman-La Roche. The other authors declare that they have no conflicts of interest.

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