Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial

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Summary

Background The addition of bevacizumab to chemotherapy improves progression-free survival in metastatic breast cancer and pathological complete response rates in the neoadjuvant setting. Micrometastases are dependent on angiogenesis, suggesting that patients might benefit from anti-angiogenic strategies in the adjuvant setting. We therefore assessed the addition of bevacizumab to chemotherapy in the adjuvant setting for women with triple-negative breast cancer.

Methods For this open-label, randomised phase 3 trial we recruited patients with centrally confirmed triple-negative operable primary invasive breast cancer from 360 sites in 37 countries. We randomly allocated patients aged 18 years or older (1:1 with block randomisation; stratified by nodal status, chemotherapy [with an anthracycline, taxane, or both], hormone receptor status [negative *vs* low], and type of surgery) to receive a minimum of four cycles of chemotherapy either alone or with bevacizumab (equivalent of 5 mg/kg every week for 1 year). The primary endpoint was invasive disease-free survival (IDFS). Efficacy analyses were based on the intention-to-treat population, safety analyses were done on all patients who received at least one dose of study drug, and plasma biomarker analyses were done on all treated patients consenting to biomarker analyses and providing a measurable baseline plasma sample. This trial is registered with ClinicalTrials.gov, number NCT00528567.

Findings Between Dec 3, 2007, and March 8, 2010, we randomly assigned 1290 patients to receive chemotherapy alone and 1301 to receive bevacizumab plus chemotherapy. Most patients received anthracycline-containing therapy; 1638 (63%) of the 2591 patients had node-negative disease. At the time of analysis of IDFS, median follow-up was 31·5 months (IQR 25·6–36·8) in the chemotherapy-alone group and 32·0 months (27·5–36·9) in the bevacizumab group. At the time of the primary analysis, IDFS events had been reported in 205 patients (16%) in the chemotherapy-alone group and in 188 patients (14%) in the bevacizumab group (hazard ratio [HR] in stratified log-rank analysis 0·87, 95% CI 0·72–1·07; p=0·18). 3-year IDFS was 82·7% (95% CI 80·5–85·0) with chemotherapy alone and 83·7% (81·4–86·0) with bevacizumab and chemotherapy. After 200 deaths, no difference in overall survival was noted between the groups (HR 0·84, 95% CI 0·64–1·12; p=0·23). Exploratory biomarker assessment suggests that patients with high pre-treatment plasma VEGFR-2 might benefit from the addition of bevacizumab (Cox interaction test p=0·029). Use of bevacizumab versus chemotherapy alone was associated with increased incidences of grade 3 or worse hypertension (154 patients [12%] *vs* eight patients [1%]), severe cardiac events occurring at any point during the 18-month safety reporting period (19 [1%] *vs* two [<0·5%]), and treatment discontinuation (bevacizumab, chemotherapy, or both; 256 [20%] *vs* 30 [2%]); we recorded no increase in fatal adverse events with bevacizumab (four [<0·5%] *vs* three [<0·5%]).

Interpretation Bevacizumab cannot be recommended as adjuvant treatment in unselected patients with triple-negative breast cancer. Further follow-up is needed to assess the potential effect of bevacizumab on overall survival.

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Introduction

Triple-negative breast cancer was identified in the early 2000s as a clinically important subgroup of breast cancer characterised by an especially poor prognosis. The risk of distant recurrence was substantially higher in patients with triple-negative breast cancer than in those with non-triple-negative breast cancer, peaking 3 years after diagnosis.[1] However, less was known about outcomes for triple-negative breast cancer after adjuvant chemotherapy, and no targeted treatments were available.

Subgroup analyses of the phase 3 E2100 trial,[2] which assessed paclitaxel with or without the humanised monoclonal antibody bevacizumab in HER2-negative metastatic breast cancer, showed a similar magnitude of benefit from bevacizumab in metastatic triple-negative breast cancer as in the overall study population. However, the absolute benefit was potentially more clinically relevant in view of the poor prognosis and limited treatment options in this setting. Subsequent results of the RIBBON-2 trial in the second-line metastatic breast

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cancer setting[3] and the neoadjuvant GeparQuinto trial[4] showed promising activity in triple-negative breast cancer, although exploratory analyses of another neoadjuvant trial showed a weaker bevacizumab effect in triple-negative disease than in hormone-receptor-positive disease.[5]

There was also a biological rationale for assessing adjuvant bevacizumab in triple-negative breast cancer. Hormone-receptor-negative tumours are associated with high concentrations of VEGF,[6] the target of bevacizumab, and micrometastases seem to be dependent on angiogenesis.[7] Theoretically, targeting the anti-angiogenic switch before tumour vascularisation, when few pro-angiogenic factors are involved, might be the most appropriate time for anti-angiogenic therapy.

We therefore designed the BEATRICE trial to assess the addition of 1 year of bevacizumab to standard adjuvant chemotherapy for triple-negative breast cancer.

Methods

Study design and participants

BEATRICE is a multinational open-label randomised phase 3 trial. Eligible patients had operable primary invasive breast cancer (T1b–T3 or T1a with ipsilateral axillary node involvement) centrally confirmed as HER2-negative by fluorescence or chromogenic in-situ hybridisation and with either negative or low hormone receptor status (total Allred score 2 or 3 [intensity score 1; proportion score 1 or 2]). Definitive surgery (breast-conserving or mastectomy) had to be completed 4–11 weeks before randomisation. Patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate renal, hepatic, and haematological function, and a left-ventricular ejection fraction of 55% measured up to 3 months before randomisation, as assessed by

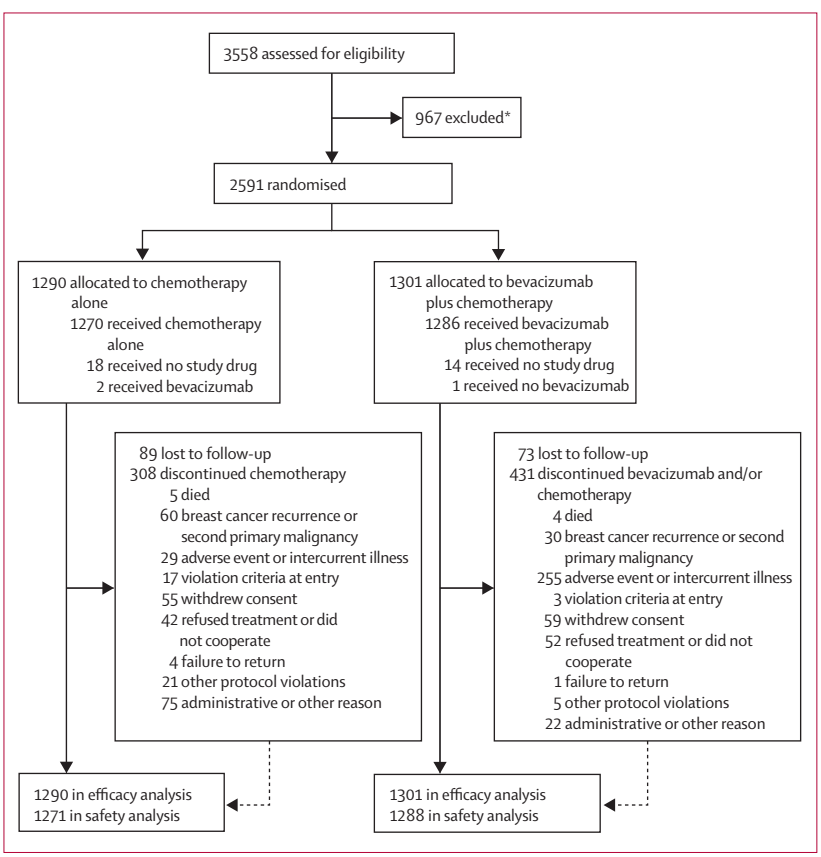

Figure 1: **Trial profile**
*Violation of at least one inclusion or exclusion criterion.

	Chemotherapy (n=1290)	Chemotherapy plus bevacizumab (n=1301)
Age		
Median age in years (range)	50 (22–80)	50 (20–84)
<40 years	253 (20%)	231 (18%)
≥40 years to <65 years	916 (71%)	952 (73%)
≥65 years	121 (9%)	118 (9%)
Premenopausal	665 (52%)	676 (52%)
ECOG performance status*		
0	1186 (93%)	1202 (92%)
1	94 (7%)	98 (8%)
2	1 (<0·5%)	0
Ethnic origin		
Asian	280 (22%)	333 (26%)
Black	32 (2%)	29 (2%)
White	968 (75%)	932 (72%)
Other	10 (1%)	7 (1%)
Tumour size†		
T1 (>0 cm to <2 cm)	457 (35%)	482 (37%)
T2 (2 cm to <5 cm)	759 (59%)	755 (58%)
T3 (≥5 cm)	71 (6%)	61 (5%)
Hormone receptor status		
Negative	1224 (95%)	1229 (94%)
Low	66 (5%)	72 (6%)
Positive axillary nodes		
0	814 (63%)	824 (63%)
1–3	326 (25%)	322 (25%)
≥4	150 (12%)	155 (12%)
Histology		
Ductal or invasive	1183 (92%)	1209 (93%)
Lobular	20 (2%)	14 (1%)
Medullary	40 (3%)	43 (3%)
Other	47 (4%)	35 (3%)
Grade 3 tumour	895 (69%)	912 (70%)
AJCC stage I	388 (30%)	382 (29%)
Breast-conserving surgery	817 (63%)	827 (64%)

Data are n (%) unless otherwise specified. AJCC=American Joint Committee on Cancer. ECOG= Eastern Cooperative Oncology Group. *Data available for 2581 patients (1281 in the chemotherapy group and 1300 in the chemotherapy plus bevacizumab group). †Data available for 2585 patients (1287 in the chemotherapy group and 1298 in the chemotherapy plus bevacizumab group).

Table 1: **Baseline characteristics**

echocardiogram (or multi-gated acquisition scan according to each institution's standard practice). Key exclusion criteria were as follows: previous systemic chemotherapy or anti-VEGF therapy; uncontrolled hypertension; history of transient ischaemic attack or cerebrovascular accident; major surgery, open biopsy, or significant traumatic injury in the 28 days before randomisation; risk of developing a venous thromboembolic event outweighing the potential benefit of trial participation; and history of abdominal fistula (including gastrointestinal perforation) within 6 months before randomisation. Before randomisation, investigators selected each patient's chemotherapy from a prespecified list of standard chemotherapy options.

All patients provided written informed consent. The study was approved by the institutional review board at each participating centre. It was done according to the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki, and other applicable local regulations. Trial conduct and progress were monitored by an international steering group, which included employees of the study funder.

Randomisation and masking

After surgical resection, eligible patients were stratified by axillary nodal status (0 *vs* 1–3 *vs* ≥4 positive lymph nodes), selected chemotherapy (anthracycline *vs* taxane *vs* anthracycline and taxane), hormone receptor status (negative *vs* low), and surgery (breast-conserving *vs*

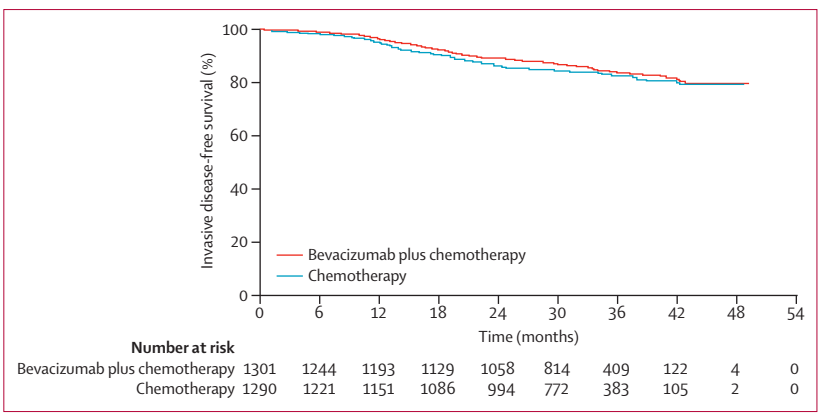

Figure 2: **Invasive disease-free survival (intent-to-treat population)**

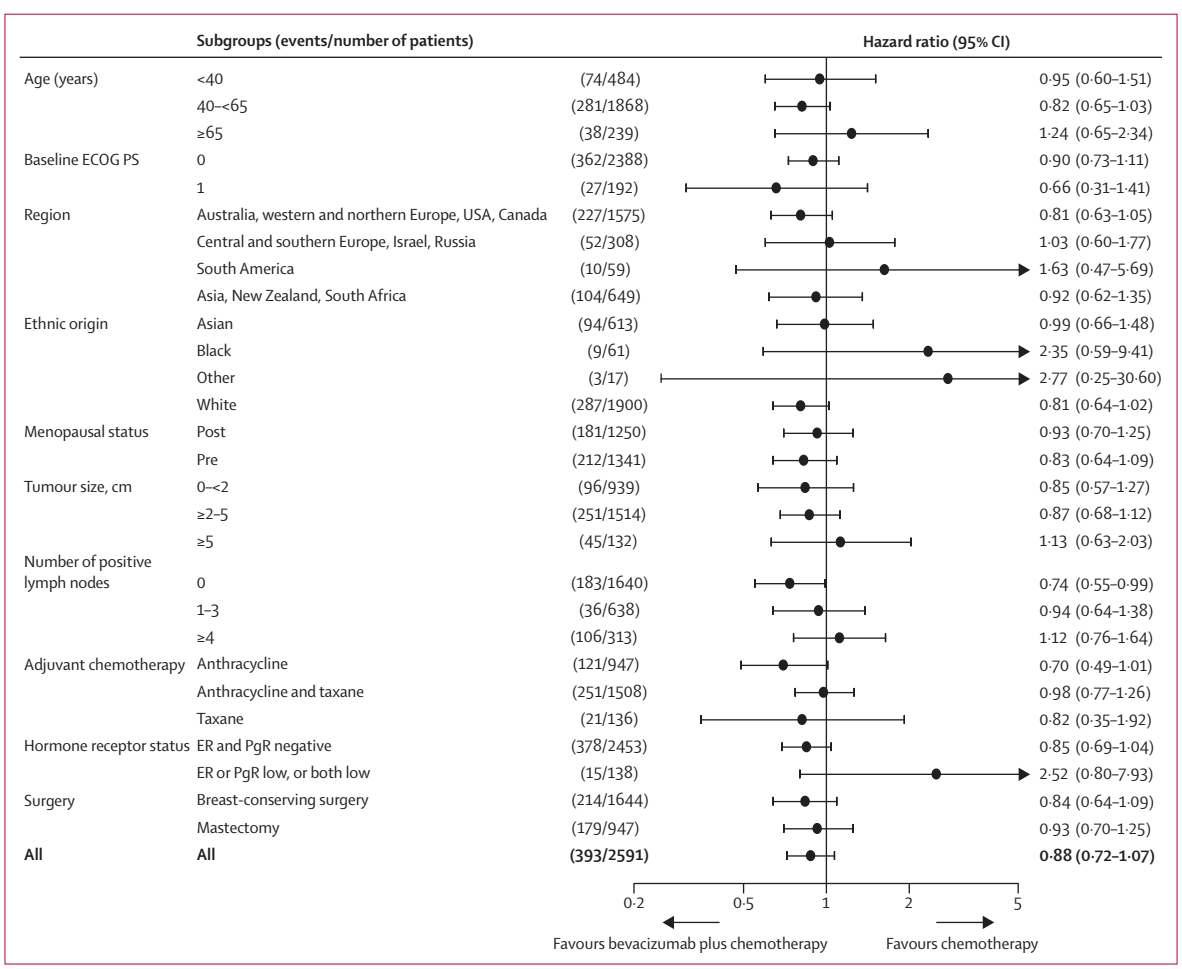

Figure 3: **Invasive disease-free survival: subgroup analyses**
ECOG PS=Eastern Cooperative Oncology Group performance status. ER=oestrogen-receptor. PgR=progesterone receptor.

	Chemotherapy (n=1290)	Chemotherapy plus bevacizumab (n=1301)	Hazard ratio (95% CI)	Log-rank p value
Disease-free survival	208 (16%)	191 (15%)	0·87 (0·72–1·07)	0·18
Breast-cancer-free interval	183 (14%)	172 (13%)	0·89 (0·72–1·10)	0·28
Distant-disease-free survival	164 (13%)	152 (12%)	0·90 (0·72–1·12)	0·33
Overall survival	107 (8%)	93 (7%)	0·84 (0·64–1·12)	0·23

Data are number of events (%) unless otherwise specified.

Table 2: **Secondary efficacy outcome measures**

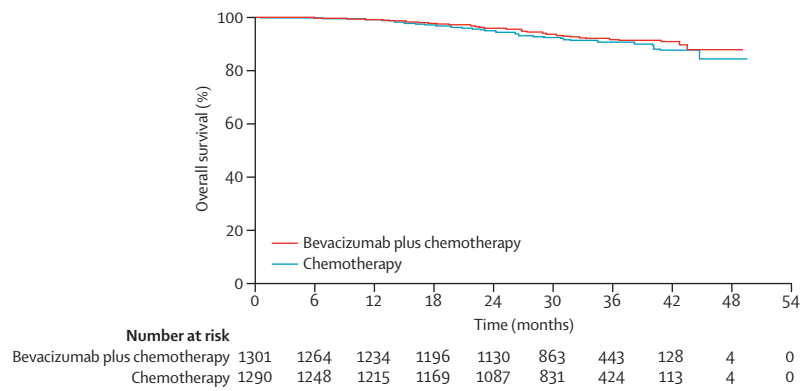

Figure 4: **Overall survival (59% of required events)**

See Online for appendix

mastectomy). Patients were randomised in a one-to-one ratio to receive either chemotherapy followed by observation or the same chemotherapy combined with bevacizumab and followed by single-agent bevacizumab. Randomisation was done centrally with an interactive voice response system and a block design randomisation procedure with random length block size.

Procedures

At screening, all patients underwent medical history and physical examinations. Patients with four or more involved axillary nodes had a baseline CT scan to exclude metastatic disease. Cardiovascular examination included assessment of risk factors for cardiovascular disease, physical examination, electrocardiogram, and left ventricular systolic function assessment (by echocardiogram or multi-gated acquisition scan). Patients received at least four cycles of anthracycline or taxane therapy, or six to eight cycles of anthracycline and taxane therapy (three or four cycles of each). Patients who underwent breast-conserving surgery received locoregional adjuvant radiotherapy either before randomisation or after completing adjuvant chemotherapy, as per local guidelines.

We gave bevacizumab at a dose equivalent to 5 mg/kg every week (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks) with the selected chemotherapy. Bevacizumab dose reduction was not allowed except for when a patient had a bodyweight change of more than 10%. Bevacizumab was interrupted or discontinued if indicated (appendix). Chemotherapy-related toxicities were treated according to local practice guidelines and in accordance with the summary of product characteristics for the relevant agent. After completing chemotherapy, patients randomly allocated to bevacizumab continued single-agent bevacizumab until they had completed 1 year of bevacizumab in total. Patients underwent clinical examination before each chemotherapy cycle. After completing chemotherapy, patients underwent clinical and laboratory assessments every 3 weeks for the first year after randomisation, although clinic visits could be alternated with telephone contact in the chemotherapy-alone group after completing chemotherapy. Thereafter, all patients underwent annual mammography with clinical review every 3 months for 2 years, then every 6 months for 2 years, and subsequently annual clinic visits coinciding with mammography. We recorded adverse events, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), at every clinic visit.

The trial included an optional translational programme assessing several candidate biomarkers as a secondary objective. Inclusion in the biomarker study required separate written informed consent. Consenting patients provided 9 mL plasma EDTA samples at baseline (after surgery, before systemic therapy), during study treatment, and at relapse. Samples were analysed centrally with immunological multi-parametric chip technology (IMPACT).[8,9]

Statistical analysis

The primary objective was to compare invasive disease-free survival (IDFS) in patients treated with chemotherapy alone versus those given chemotherapy plus bevacizumab. IDFS was defined as the interval between randomisation and first invasive recurrence of breast cancer, contralateral invasive breast cancer, second (primary) non-breast invasive cancer, or death from any cause.[10] We calculated the sample size assuming a 24-month recruitment period, 29 months' minimum follow-up, and a 5-year IDFS of 72·0% with chemotherapy alone versus 78·2% with bevacizumab (hazard ratio [HR] 0·75). To provide 80% power to detect this HR at a two-sided α of 0·05, 388 IDFS events were needed. This required 1140 patients in each group; assuming 10% dropout, the target accrual was 2530 patients.

Secondary endpoints included overall survival, breast cancer-free interval, disease-free survival (DFS), distant DFS, and safety. Overall survival analysis is prespecified to occur after 340 deaths or 5 years' median follow-up, whichever occurs first, and has 75% power to detect an HR of 0·75 at a two-sided α of 0·05. Severe cardiac events were predefined as New York Heart Association class III or IV congestive heart failure accompanied by a ten-point or more left-ventricular ejection fraction decrease from

	Chemotherapy phase						Observation or single-agent bevacizumab phase					
	Chemotherapy (n=1271)			Chemotherapy plus bevacizumab (n=1288)			Chemotherapy (n=1271)			Chemotherapy plus bevacizumab (n=1288)		
	1–2	3–4	5	1–2	3–4	5	1–2	3–4	5	1–2	3–4	5
Neutropenia or neutrophil count decreased	101 (8%)	407 (32%)	0	104 (8%)	454 (35%)	0	27 (2%)	7 (1%)	0	30 (2%)	11 (1%)	0
Febrile neutropenia	0	75 (6%)	0	1 (<0·5%)	103 (8%)	0	0	0	0	0	2 (<0·5%)	0
Leucopenia	111 (9%)	97 (8%)	0	90 (7%)	116 (9%)	0	20 (2%)	1 (<0·5%)	0	19 (1%)	4 (<0·5%)	0
Anaemia	155 (12%)	11 (1%)	0	120 (9%)	13 (1%)	0	14 (1%)	1 (<0·5%)	0	12 (1%)	0	0
Nausea	855 (67%)	17 (1%)	0	837 (65%)	35 (3%)	0	36 (3%)	0	0	63 (5%)	0	0
Stomatitis	448 (35%)	22 (2%)	0	579 (45%)	71 (6%)	0	8 (1%)	0	0	59 (5%)	0	0
Vomiting	419 (33%)	30 (2%)	0	417 (32%)	42 (3%)	0	28 (2%)	0	0	58 (5%)	0	0
Constipation	385 (30%)	3 (<0·5%)	0	420 (33%)	1 (<0·5%)	0	25 (2%)	0	0	37 (3%)	0	0
Diarrhoea	319 (25%)	13 (1%)	0	342 (27%)	22 (2%)	0	26 (2%)	0	0	91 (7%)	2 (<0·5%)	0
Dyspepsia	147 (12%)	1 (<0·5%)	0	175 (14%)	2 (<0·5%)	0	27 (2%)	0	0	26 (2%)	0	0
Alopecia	830 (65%)	0	0	804 (62%)	0	0	6 (<0·5%)	0	0	9 (1%)	0	0
Nail disorder	132 (10%)	0	0	128 (10%)	0	0	18 (1%)	0	0	53 (4%)	1 (<0·5%)	0
Fatigue	477 (38%)	26 (2%)	0	446 (35%)	37 (3%)	0	74 (6%)	0	0	88 (7%)	4 (<0·5%)	0
Asthenia	197 (15%)	14 (1%)	0	191 (15%)	13 (1%)	0	30 (2%)	1 (<0·5%)	0	46 (4%)	2 (<0·5%)	0
Pyrexia	160 (13%)	1 (<0·5%)	0	213 (17%)	2 (<0·5%)	0	14 (1%)	0	0	21 (2%)	0	0
Headache	233 (18%)	6 (<0·5%)	0	333 (26%)	14 (1%)	0	64 (5%)	1 (<0·5%)	0	163 (13%)	8 (1%)	0
Dysgeusia	222 (17%)	0	0	228 (18%)	0	0	12 (1%)	0	0	18 (1%)	0	0
Myalgia	241 (19%)	6 (<0·5%)	0	195 (15%)	6 (<0·5%)	0	39 (3%)	0	0	80 (6%)	2 (<0·5%)	0
Arthralgia	151 (12%)	4 (<0·5%)	0	180 (14%)	16 (1%)	0	108 (8%)	1 (<0·5%)	0	246 (19%)	5 (<0·5%)	0
Epistaxis	70 (6%)	0	0	409 (32%)	3 (<0·5%)	0	6 (<0·5%)	0	0	99 (8%)	0	0
Cough	117 (9%)	2 (<0·5%)	0	139 (11%)	0	0	47 (4%)	0	0	77 (6%)	0	0
Oropharyngeal pain	81 (6%)	0	0	148 (11%)	1 (<0·5%)	0	17 (1%)	0	0	40 (3%)	0	0
Hypertension	36 (3%)	5 (<0·5%)	0	139 (11%)	85 (7%)	0	16 (1%)	3 (<0·5%)	0	196 (15%)	68 (5%)	0
Hot flush	144 (11%)	6 (<0·5%)	0	139 (11%)	3 (<0·5%)	0	57 (4%)	2 (<0·5%)	0	70 (5%)	2 (<0·5%)	0
Decreased appetite	210 (17%)	4 (<0·5%)	0	238 (18%)	6 (<0·5%)	0	14 (1%)	0	0	24 (2%)	0	0
Lacrimation increased	105 (8%)	1 (<0·5%)	0	143 (11%)	0	0	3 (<0·5%)	0	0	13 (1%)	0	0
Insomnia	168 (13%)	2 (<0·5%)	0	157 (12%)	1 (<0·5%)	0	56 (4%)	0	0	30 (2%)	0	0
Proteinuria	14 (1%)	1 (<0·5%)	0	34 (3%)	8 (1%)	0	8 (1%)	0	0	132 (10%)	24 (2%)	0
Radiation skin injury	13 (1%)	0	0	7 (1%)	0	0	165 (13%)	12 (1%)	0	129 (10%)	5 (<0·5%)	0
Left ventricular dysfunction*	88 (7%)	3 (<0·5%)	0	88 (7%)	7 (1%)	0	62 (5%)	1 (<0·5%)	0	132 (10%)	12 (1%)	0
Gamma glutamyltransferase increase	35 (3%)	4 (<0·5%)	0	41 (3%)	26 (2%)	0	6 (<0·5%)	0	0	14 (1%)	5 (<0·5%)	0

Data are number of patients with events (%). *Left ventricular dysfunction according to National Cancet Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3.0); treatment decisions were made on the basis of the protocol-specified definition of severe cardiac events (as in table 4) rather than NCI CTCAE grading.

***Table 3*: Summary of adverse events occurring in more than 10% of patients (any grade) or 2% or more of patients (for grade 3 of higher)**

baseline to less than 50%, probable cardiac death (unexplained sudden death within 24 h), or definite cardiac death (from congestive heart failure, myocardial infarction, or documented primary arrhythmia). We regarded deaths with cause recorded as unknown as probable cardiac deaths.

We tested efficacy endpoints with a two-sided stratified log-rank test and plotted Kaplan-Meier estimates by treatment group. We expressed estimates of the treatment effect as HRs with 95% CIs.

Plasma VEGF-A and VEGFR-2 assessment was prespecified in the protocol to confirm previous results in metastatic breast,[8] pancreatic,[11] and gastric (VEGF-A only)[12] cancers. The biomarker-assessable population (all patients consenting to biomarker research who received any study drug and who had protein-marker concentrations measured in baseline plasma samples) was dichotomised with the median baseline concentration of each marker as the cutoff between high and low cohorts. We also did exploratory analyses by quartile. We assessed correlations between baseline concentrations of candidate biomarkers and IDFS using log-rank testing and Cox regression. We used SAS (version 8.2) for all statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT00528567.

Role of the funding source

F Hoffmann-La Roche sponsored the trial and was jointly responsible with the University of Leeds Clinical Trials

Unit for statistical analyses. The trial database was held independently from the sponsor (which had no access to efficacy data except to resolve safety queries) but was shared with the sponsor after primary analysis. Safety review was done by the sponsor. Efficacy review was done by Leeds Clinical Trials Unit. The sponsor supported medical writing assistance for this paper and had the opportunity to review the content, but the final decision to submit for publication was the responsibility of the corresponding author, in agreement with the trial steering group.

Results

Between Dec 3, 2007, and March 8, 2010, we enrolled 2591 patients from 360 sites in 37 countries (figure 1). Baseline characteristics were much the same between treatment groups (table 1). Almost two-thirds of patients in both groups had node-negative disease. Most patients received anthracycline and taxane therapy (756 [59%] of 1290 patients in the chemotherapy-alone group *vs* 752 [58%] of 1301 patients in the bevacizumab group). About a third received non-taxane anthracycline-containing chemotherapy (468 [36%] of 1290 patients in the chemotherapy-alone group *vs* 479 [37%] of 1301 patients in the bevacizumab group). 66 (5%) patients in the chemotherapy-alone group and 70 (5%) patients in the bevacizumab group were treated with a non-anthracycline taxane regimen (53 [7%] of 806 patients *vs* 56 [7%] of 834 in the subgroup of patients who were node-negative). Similar proportions of patients received radiotherapy (953 [74%] in the chemotherapy-alone *vs* 952 [73%] in the bevacizumab group) and adjuvant endocrine therapy (seven patients [1%] *vs* four patients [<0·5%]).

At the time of data cutoff (Feb 29, 2012), median duration of follow-up was 31·5 months (IQR 25·6–36·8) in the chemotherapy-alone group and 32·0 months (27·5–36·9) in the bevacizumab group. Chemotherapy was completed as planned in 1192 patients (92%) in the chemotherapy-alone group and 1205 patients (93%) in the bevacizumab group; bevacizumab was completed as planned in 887 patients (68%). The most common reasons for premature bevacizumab discontinuation were adverse events or intercurrent illness (233 patients [18%]) and withdrawal of consent (57 [4%])—30 patients (2%) discontinued bevacizumab because of breast cancer recurrence or occurrence of a second primary cancer.

At data cutoff, 205 patients (16%) in the chemotherapy alone group and 188 (14%) in the bevacizumab and chemotherapy group had had an IDFS event. There was no difference between groups in IDFS (HR 0·87 stratified log-rank analysis [95% CI 0·72–1·07]; 3-year IDFS 82·7% [95% CI 80·5–85·0] in the chemotherapy group *vs* 83·7% [81·4–86·0] in the bevacizumab group; p=0·18; figure 2). The sites of recurrence were much the same in the two treatment groups, the most common being distant recurrence (137 patients [11%] receiving chemotherapy alone *vs* 137 patients [11%] also receiving bevacizumab). The most frequent sites of distant recurrence were lung (37 [27%] of 137 distant recurrences *vs* 39 [28%] of 137 distant recurrences), liver (21 [15%] *vs* 28 [20%]), and bone (27 [20%] *vs* 23 [17%]). Distant CNS or meningeal recurrence accounted for 16 recurrences (12%) in the chemotherapy group and ten (7%) in the bevacizumab group. Subgroup analyses according to stratification factors and other clinically important characteristics showed no evidence of differences in IDFS between treatment groups (figure 3).

All secondary efficacy endpoints seemed to favour bevacizumab, but none was statistically significant (table 2). At data cutoff, 107 (8%) patients in the chemotherapy group and 93 (7%) patients in the bevacizumab group had died (HR 0·84, 95% CI 0·64–1·12; p=0·23; figure 4), with the most common cause of death being breast cancer (95 [89% of the 107] patients in the chemotherapy group and 86 [92% of the 93] in the bevacizumab group).

Almost all patients had adverse events (1252 [99%] patients in the chemotherapy group and 1274 [99%] patients in the bevacizumab group; table 3). Grade 3 or higher adverse events occurred in 722 (57%) of 1271 patients receiving chemotherapy alone and 924 (72%) of 1288 patients receiving bevacizumab. We recorded a high incidence of grade 3 or higher haematological

	Chemotherapy phase		Observation or single-agent bevacizumab phase	
	Chemotherapy (n=1271)	Chemotherapy plus bevacizumab (n=1288)	Chemotherapy (n=1271)	Chemotherapy plus bevacizumab (n=1288)
All grade 3 or higher adverse events of special interest	33 (3%)	143 (11%)	12 (1%)	122 (9%)
Arterial thromboembolic event	2 (<0·5%)	2 (<0·5%)	1 (<0·5%)	4 (<0·5%)
Venous thromboembolic event	15 (1%)	21 (2%)	4 (<0·5%)	1 (<0·5%)
Bleeding	2 (<0·5%)	8 (1%)	2 (<0·5%)	0
Severe cardiac events*	0	4 (<0·5%)	0	12 (1%)
Non-severe cardiac events†	12 (1%)	21 (2%)	8 (1%)	32 (2%)
Hypertension	6 (<0·5%)	88 (7%)	4 (<0·5%)	70 (5%)
Fistula or abscess	2 (<0·5%)	0	0	1 (<0·5%)
Gastrointestinal perforation	0	6 (<0·5%)	0	0
Proteinuria	1 (<0·5%)	8 (1%)	0	24 (2%)
Reversible posterior leucoencephalopathy syndrome	0	1 (<0·5%)	0	1 (<0·5%)
Wound-healing complication	3 (<0·5%)	3 (<0·5%)	0	1 (<0·5%)

Data are number of patients with events using MEDRA basket terms (%). LVEF=left ventricular ejection fraction; NYHA=New York Heart Association. *Predefined as NYHA class III or IV congestive heart failure accompanied by a decrease in LVEF of more than 10 percentage points to below 50%, or probable or definite cardiac death. Four deaths were counted as probable cardiac death (one in the chemotherapy group, three in the chemotherapy plus bevacizumab group) with death recorded in the survival follow-up rather than as an adverse event, but considered in a conservative approach as probable cardiac death. The remaining two patients considered to have had probable cardiac death were from multi-organ failure in one patient and coronary artery disease in one patient (both in the chemotherapy plus bevacizumab group). †Defined as LVEF below 50% together with either NYHA class I, missing NYHA but described as asymptomatic by the investigator, or NYHA class II congestive heart failure.

Table 4: **Grade 3 or higher adverse events reported in previous clinical trials of bevacizumab**

	Chemotherapy plus bevacizumab phase (n=1288)	Single-agent bevacizumab phase (n=1288)
Total	101 (8%)	128 (10%)
Vascular disorders	22 (2%)	27 (2%)
Cardiac disorders	15 (1%)	31 (2%)
Renal and urinary disorders	3 (<0·5%)	19 (1%)
Gastrointestinal disorders	16 (1%)	3 (<0·5%)

Data are number of patients (%). See appendix for a full list of adverse events leading to bevacizumab treatment discontinuation.

Table 5: **Summary of selected adverse event categories leading to bevacizumab treatment discontinuation by treatment phase**

adverse events with both treatments. Hypertension was the most common non-haematological grade 3 or worse adverse event with bevacizumab (158 [12%] of 1288 patients *vs* ten [1%] of 1271 patients in the chemotherapy-alone group over the entire treatment period). Hypertension and proteinuria were the dominant grade 3 or worse adverse events during single-agent bevacizumab treatment (table 3). The safety profile of the bevacizumab-containing regimen was generally consistent with previous phase 3 trials of bevacizumab in metastatic breast cancer (table 4).

Severe cardiac events occurring at any point during the 18-month safety reporting period were more common with bevacizumab (19 [1%] of 1288 patients given bevacizumab *vs* two [<0·5%] of 1271 patients given chemotherapy alone). All cases in the bevacizumab group occurred in patients receiving anthracycline-containing therapy. At data cutoff, 12 (86%) of 14 severe cardiac events (excluding probable cardiac deaths shown in table 4) in the bevacizumab group were regarded by the treating investigator to be resolved, although patients could have been receiving ongoing cardiac medication. Further analyses of cardiac safety, including long-term follow-up, will be reported separately.

Adverse events led to study treatment discontinuation less often in the chemotherapy group (30 [2%] of 1271 patients) than in the bevacizumab group (256 [20%] of 1288 patients). More bevacizumab discontinuations (128 [56%] of 229) occurred during the post-chemotherapy phase compared with during the chemotherapy phase (appendix). The adverse events that most commonly led to bevacizumab discontinuation were hypertension, left ventricular dysfunction, proteinuria, and left-ventricular ejection fraction decrease (table 5; appendix). Fatal adverse events occurred in three (<0·5%) patients in the chemotherapy-alone group (neutropenic sepsis, pneumonia, and shock, all during the chemotherapy period and regarded as treatment-related) and in four

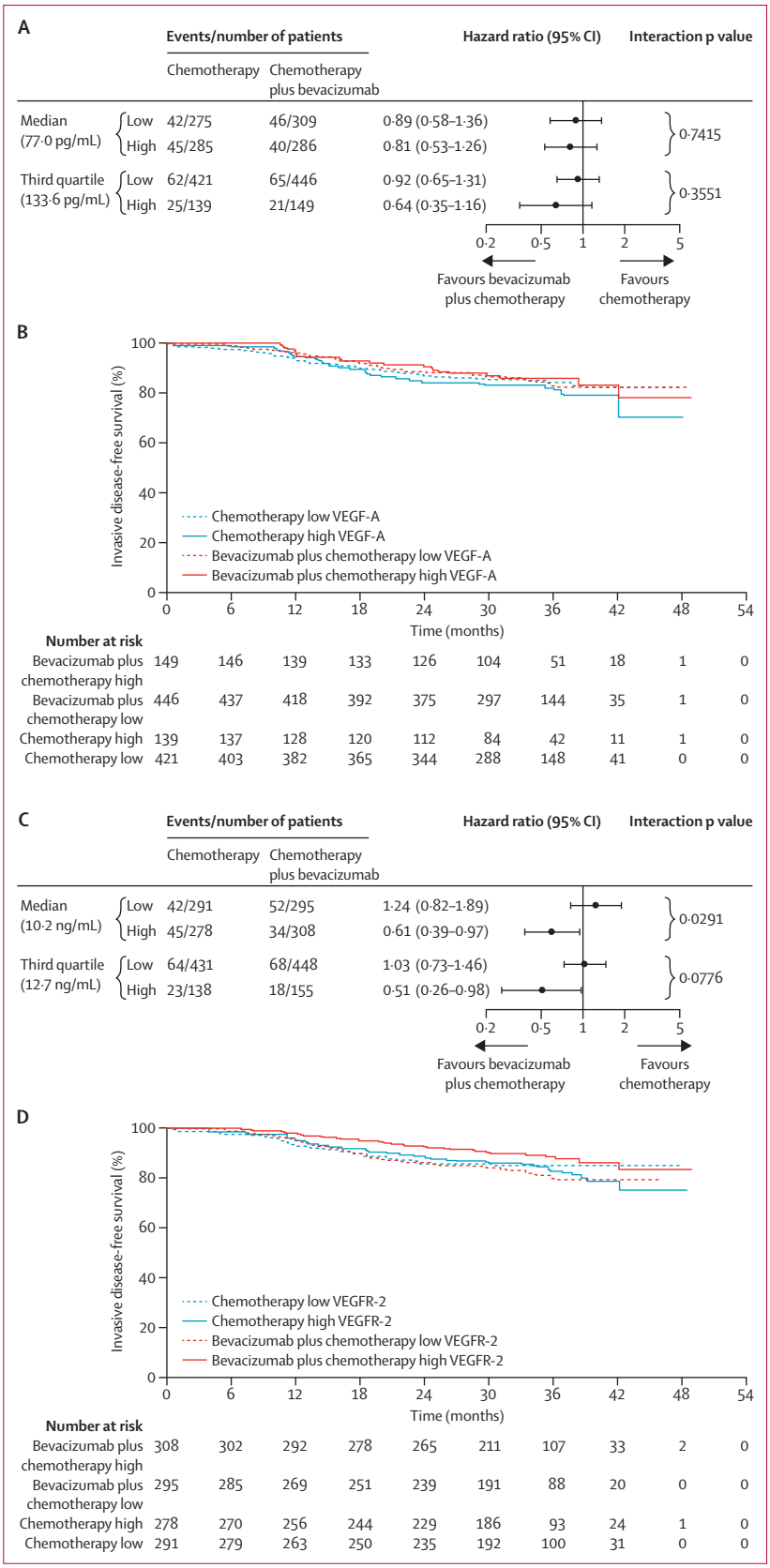

Figure 5: **Invasive disease-free survival according to pre-treatment plasma concentration of VEGF-A (A and B) and VEGFR-2 (C and D)**
Graphs show data for concentrations of VEGF-A (median *vs* third quartile cutoff; A), VEGF-A (third quartile cutoff; B), VEGFR-2 (median *vs* third quartile cutoff; C), and VEGFR-2 (median cutoff; D).

Panel: **Research in context**

Systematic review

We searched PubMed for clinical trials published in English between Jan 1, 2000, and March 1, 2013, assessing systemic therapy specifically in triple-negative breast cancer, using the search terms "triple negative", "breast", and either "adjuvant" or "neoadjuvant".

Interpretation

To our knowledge, BEATRICE is the first phase 3 trial assessing the addition of systemic therapy to standard chemotherapy for triple-negative breast cancer, and the first randomised trial to assess bevacizumab as adjuvant therapy for breast cancer. Bevacizumab did not improve IDFS, the primary endpoint, and on the basis of these data cannot be recommended as adjuvant treatment for primary triple-negative breast cancer. Longer follow-up is needed to determine the effect of bevacizumab on overall survival, a secondary outcome measure. Prespecified biomarker analyses suggested potential predictive value of pretreatment plasma VEGFR-2 concentrations on IDFS. This potential predictive effect is consistent with findings in metastatic breast cancer and pancreatic cancer.

(<0·5%) bevacizumab-treated patients (one unexplained treatment-related death on day 11, preceded by moderate diarrhoea and nausea from day 5; two treatment-related deaths during the single-agent bevacizumab period [coronary artery disease, multi-organ failure]; and one death from sepsis after stopping bevacizumab treatment but within 18 months of randomisation, which was not treatment-related).

Of the 2591 patients enrolled, 1273 (49%) consented to the biomarker study and 1178 (45%) were included in the biomarker-assessable population (573 receiving chemotherapy alone and 605 receiving bevacizumab). Overall, the baseline characteristics of the biomarker-assessable population were similar to those of the intention-to-treat population except for fewer Asian patients (141 [12%] of 1178 biomarker-assessable patients *vs* 613 [24%] of 2591 intention-to-treat patients; appendix). IDFS was similar in the biomarker-assessable and intent-to-treat populations. Baseline characteristics in the biomarker-assessable population were balanced between groups (appendix). We recorded no correlation between baseline circulating VEGFR-2 and VEGF-A concentrations (r=0·0757).

Analysis of baseline plasma VEGF-A concentration showed neither prognostic nor predictive value using the median (77·0 pg/mL) as the cutoff (figure 5). Exploratory analyses with an upper quartile cutoff (133·6 pg/mL, similar to the median cutoff values in the AVADO and AVEREL trials in metastatic breast cancer[8,13]) seemed to show a greater IDFS benefit in the subgroup with high baseline plasma VEGF-A than in those with low baseline plasma VEGF-A, but differences were not statistically significant (figure 5).

The median baseline plasma VEGFR-2 concentration was 10·2 ng/mL, similar to median values in AVADO (11·0 ng/mL)[8] and AVEREL (14·1 ng/mL).[13] Plasma VEGFR-2 concentrations showed no prognostic value but potential predictive value for bevacizumab efficacy (figure 5). We detected an IDFS benefit in only patients with high baseline plasma VEGFR-2 concentrations (figure 5).

Discussion

The addition of bevacizumab to chemotherapy during adjuvant therapy did not improve IDFS for patients with triple-negative breast cancer. To our knowledge, BEATRICE is the first randomised phase 3 trial specifically in patients with centrally confirmed early triple-negative breast cancer. The trial provides important information not only about adjuvant bevacizumab, but also about the outcomes of patients with this subtype of disease receiving standard chemotherapy (panel). 3-year IDFS in both treatment groups was higher than expected, suggesting that the prognosis for these patients is better than previously thought. The low rate of recurrences might also be attributable to the high proportion of patients with node-negative disease enrolled into BEATRICE, a finding that could have important implications for interpretation and follow-up. The timing of the primary analysis was planned with few available data for outcomes in this setting. Although the protocol-specified number of events for the primary analysis was reached, the data are arguably immature for full interpretation with 183 (56%) of 325 IDFS events in node-negative patients, who make up most of the trial population. The balance of events between patients with node-negative and node-positive disease might be expected to have altered by the time of the final analysis.

Bevacizumab had no statistically significant effect on the secondary time-related endpoints (DFS, breast cancer-free interval, distant DFS). That we recorded no difference is unlikely to be attributable to compromised chemotherapy dosing. Although conventional calculations of dose intensity are not possible because we did not record data for the planned number of chemotherapy cycles, the high and very balanced rates of chemotherapy completion in both groups suggest no detrimental effect of bevacizumab on the ability to deliver chemotherapy. Further follow-up is needed to establish any potential effect of bevacizumab on overall survival, with the prespecified overall survival analysis anticipated in early 2014.

The spectrum and incidence of adverse events with bevacizumab were consistent with the safety profile established in previous bevacizumab trials in metastatic breast cancer and other solid tumour types. We recorded no increase in the incidence of toxic deaths; this finding is in agreement with meta-analyses in metastatic breast

cancer[14,15] and contrasts with meta-analyses across a range of solid tumour types.[16] Bevacizumab discontinuation was quite frequent in BEATRICE, possibly in part owing to the open-label design and the adjuvant setting. The discontinuation rate might be indicative of patients' intolerance of treatment, attributable to either adverse effects or reluctance to attend clinic visits for regular infusions during extended treatment. The main toxicities were hypertension and proteinuria. There was a slight increase in severe cardiac events in the bevacizumab group; all cases occurred in patients receiving anthracycline-based therapy, consistent with previous experience.[17,18] Most cardiac events with bevacizumab were regarded as reversible, and therefore data are needed on the longer-term bevacizumab effects on cardiac function.

Local VEGF concentrations are important in driving tumour angiogenesis. However, assessment of VEGF bioactivity has been elusive. Tumour VEGF-A expression, assessed by immunohistochemistry or qPCR, has shown prognostic value but no correlation with anti-VEGF activity. Plasma biomarkers suggested potential predictive value for bevacizumab efficacy in the AVADO (HER2-negative metastatic breast cancer[8]), AVEREL (HER2-positive metastatic breast cancer[13]), and AViTA (advanced pancreatic cancer[11]) trials. In BEATRICE, pre-treatment plasma VEGFR-2 showed some evidence of a predictive effect, lending support to previous findings. However, the similar circulating concentrations of VEGFR-2 in the adjuvant and metastatic breast cancer settings suggest that soluble VEGFR-2 concentrations are not necessarily related to tumour burden. Further research is needed to understand factors driving plasma VEGFR-2 variance and their effect on host vascular biology and angiogenesis. It will also be important to see whether this hypothesis is substantiated on mature data for overall survival.

Plasma VEGF-A results using a median cutoff showed neither prognostic nor predictive value. Although pre-analytical factors and sample handling in BEATRICE were similar to AVADO and AVEREL, the median concentration (77·0 pg/mL) in BEATRICE was lower than seen in metastatic breast cancer (125·0 pg/mL in AVADO,[8] 129·1 pg/mL in AVEREL[13]). Tumour cells are a major source of circulating VEGF-A, and therefore the possible effect of tumour resection immediately before treatment needs further investigation, together with exploration of the effect of differing biology in the adjuvant setting.

Two previous randomised phase 3 trials assessing adjuvant bevacizumab in colon cancer (C-08[19] and AVANT[20]) showed no improvement in DFS (the primary endpoint) with 1 year of bevacizumab added to standard chemotherapy. The IDFS results of BEATRICE are consistent with the primary endpoint results of the colon cancer trials. We recorded no evidence of a difference in outcome between treatments by the end of the study period, with Kaplan-Meier curves eventually coming together after bevacizumab discontinuation in all three trials. In AVANT (but not in C-08) there was a suggestion of worse outcome in the bevacizumab group, whereas in BEATRICE the Kaplan-Meier curve favoured the bevacizumab group. This difference is maintained throughout the follow-up period and contradicts suggestions of a putative rebound effect in AVANT.[21]

The absence of a statistically significant effect of adjuvant bevacizumab in colon and breast cancers draws attention to our poor understanding of the dependency of micrometastases on angiogenesis. There has been little assessment of anti-angiogenic strategies in preclinical models of adjuvant systemic therapy, and characterisation of the mechanism of anti-VEGF treatment has focused largely on macrometastatic disease, which seems to behave differently from micrometastatic disease.[22,23] It is unclear whether bevacizumab is insufficiently active or the schedule or selection of patients was suboptimal. The transient effect of 1 year of adjuvant bevacizumab has led some to question whether longer bevacizumab exposure is needed to show an effect.[23] Indeed, the 1-year duration was arbitrarily selected. However, without improved selection of patients, assessment of a longer bevacizumab duration might be hard to justify based on the risk-benefit profile seen in the BEATRICE trial. Two further trials in early breast cancer—BETH (NSABP B-44; NCT00625898) and E5103 (NCT00433511)—are assessing adjuvant bevacizumab-containing regimens. In a broader context, the population enrolled into BEATRICE is the largest cohort of patients with triple-negative breast cancer studied to date, and therefore provides an unprecedented opportunity to improve our knowledge of the outcomes and potential prognostic factors in early triple-negative breast cancer, including sites, rates, and timing of relapse. Further analyses are ongoing in an effort to understand the different subgroups of patients included within BEATRICE and to learn more about the biology of triple-negative breast cancer. Triple-negative breast cancer is a heterogeneous group of disease entities,[24] and future assessment of therapeutic strategies for triple-negative breast cancer should differentiate between molecular subtypes.

On the basis of our findings, bevacizumab cannot be recommended as adjuvant therapy for breast cancer in the overall population of patients treated in BEATRICE. Nevertheless, biomarker results suggest that within this population, there might be subsets of patients in whom bevacizumab has an effect. Identification of those patients who stand to benefit most from bevacizumab, in both the metastatic and adjuvant settings, is a priority.

Contributors

DC, RB, GGS, CJ, and MP designed the trial. DC, JB, RD, CJ, JM, XP, GGS, TLS, MT, Y-HI, GR, VHa, OL, TP, PC, AC, PSH, and S-AI were involved in data collection. VHe and JB were involved in data analysis. All authors participated in data interpretation and revision and finalisation of the paper.

Conflictc of interest

DC's institution has received reimbursement for his advice and consultancy on Roche products, as well as from Amgen, Sanofi, AstraZeneca, Novartis, and Pfizer. DC has received travel reimbursement for conference attendance. JB has received grant and research support from Roche, AstraZeneca, Novartis, GlaxoSmithKline, Generx, and Orthobiotech. RD has received honoraria for speaker engagements from Roche, GlaxoSmithKline, Novartis, AstraZeneca, Sanofi, and Eisai, and has received honoraria for advisory boards from Roche, GlaxoSmithKline, Novartis, AstraZeneca, and Sanofi. JM is a consultant for Roche Oncology and GlaxoSmithKline Oncology and has received a speaker honorarium for CME activities from Sanofi. XP has received honoraria for speaker engagements from Sanofi and for advisory boards from Roche, Eisai, and GlaxoSmithKline. GGS has received grant and research support from Roche Austria and speaker honoraria from Roche (Basel and Austria). TMS has received grant and research support from Roche, speaker honoraria from Ratiopharm, and honoraria for advisory boards from Novar and Astex. MT has received a research grant and speaker honoraria from Chugai Pharmaceutical Company. MP's institution (Medical Research Council, UK) has received support from Roche for three trials of bevacizumab sponsored by the Medical Research Council. RL, LB-P, VHe, RJD, and CP are employees of F Hoffmann-La Roche; RL, VHe, and CP hold shares in Roche. GR's institution has received reimbursement for his advice and consultancy on Roche products; GR has received honoraria from Roche for participation in advisory boards. VHa has received research funding from Roche New Zealand and speaker honoraria from F Hoffmann-La Roche (Basel), Roche New Zealand, Chugai Pharmaceuticals (Japan), and Sanofi. PC has received speaker honoraria from Roche and Novartis, and travel reimbursement for conference attendance from Roche. AC has received research grants and honoraria for speaker engagements and advisory boards from Roche, GlaxoSmithKline, and Sanofi. S-AI has received honoraria for advisory boards from Roche, Novartis, and AstraZeneca. PSH was employed by the University of Leeds on a research grant from Roche (2008–12). RB has participated in advisory boards for Roche. CJ, Y-HI, OL, and TP declare that they have no conflicts of interest.

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