European Journal of Cancer (2012) **48**, 482–491

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Review

Combining capecitabine and bevacizumab in metastatic breast cancer: A comprehensive review

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Available online 16 January 2012

KEYWORDS
Bevacizumab
Capecitabine
Combination therapy
Metastatic breast cancer

Abstract Both capecitabine and bevacizumab are established agents in the treatment of metastatic breast cancer, but until recently clinical data supporting their use in combination were limited. We review available data on the capecitabine–bevacizumab combination in breast cancer, particularly results from the RIBBON-1 trial in the first-line setting, and we discuss these findings in light of previous studies. We also examine ongoing trials investigating capecitabine–bevacizumab combination therapy.
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1. Introduction

The oral fluoropyrimidine capecitabine is an established therapy in metastatic breast cancer (MBC), either alone or in combination with chemotherapeutic or biological agents. Capecitabine was initially evaluated as monotherapy in pretreated MBC, showing consistent activity in phase II and III trials.[1–7] Increasingly, capecitabine is used in the first-line setting,[8] where it has demonstrated good efficacy and tolerability.[9,10] In this review article, we will focus on data for capecitabine in combination with the anti-angiogenic agent bevacizumab.

Bevacizumab is a humanised monoclonal antibody directed specifically against all isoforms of vascular endothelial growth factor (VEGF)-A. The combination of bevacizumab with taxane therapy has demonstrated efficacy as first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative MBC, significantly improving progression-free survival (PFS) and response rate in two randomised phase III trials:

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0959-8049/$ - see front matter © 2012 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2011.12.007

E2100 (bevacizumab combined with weekly paclitaxel)[11,12] and AVADO (bevacizumab combined with 3-weekly docetaxel).[13] Until recently, bevacizumab was approved in Europe as first-line therapy for HER2-negative MBC in combination with either paclitaxel or docetaxel, but in March 2011 it was announced that the indication in combination with docetaxel has been withdrawn by the European Commission.[14] In a third phase III trial, Regimens In Bevacizumab for Breast ONcology (RIBBON) -1,[15] bevacizumab or placebo was combined with a taxane (3-weekly docetaxel, nanoparticle albumin-bound [nab]-paclitaxel) or anthracycline-based combination therapy in one cohort or with capecitabine in a second cohort. This trial is discussed in more detail later.

For patients who are ineligible for paclitaxel-based regimens or who prefer not to receive paclitaxel therapy for MBC, the combination of bevacizumab with non-taxane chemotherapy is of interest. Capecitabine is an attractive treatment choice for patients who have shown disease progression following taxane therapy, who are unwilling to receive further taxane treatment after previous experience in the adjuvant setting, who will not accept specific side-effects of taxane-based therapy, such as hair loss or neuropathy, or who have comorbidities that may predispose them to neuropathy. There are both preclinical and practical reasons for combining bevacizumab and capecitabine. In xenograft models, the combination demonstrated a synergistic inhibitory effect on tumour growth and a significant survival benefit.[16] There was no evidence that this synergy resulted from upregulation of thymidine phosphorylase, the key enzyme in the activation of capecitabine; instead the synergy appears to be attributable to the combination of anti-angiogenic and cytotoxic mechanisms of action.

2. Capecitabine–bevacizumab combination therapy for MBC

2.1. Randomised phase III trials

The most robust evidence of the efficacy of capecitabine and bevacizumab combination therapy in MBC comes from the RIBBON-1 trial mentioned briefly above.[15] This randomised phase III trial was conducted in 1237 patients with HER2-negative MBC who had received no prior chemotherapy for metastatic disease. Investigators declared their planned chemotherapy regimen for each patient (capecitabine monotherapy, taxane monotherapy or anthracycline-based combination therapy) (Fig. 1). Patients were then randomised in a 2:1 ratio to receive either bevacizumab or placebo in combination with the selected chemotherapy. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. At disease progression, all patients were able to receive bevacizumab in combination with their second-line chemotherapy. Importantly, the two cohorts were independently powered and analysed and thus RIBBON-1 was essentially two parallel trials. This trial design has important implications for interpretation: because investigators were able to choose whether patients received capecitabine, taxane or anthracycline regimens, there were marked differences in baseline characteristics between the populations. Therefore it is not appropriate to compare the results between different chemotherapy cohorts and in this summary we will focus on the cohort of patients who received capecitabine with either bevacizumab or placebo.

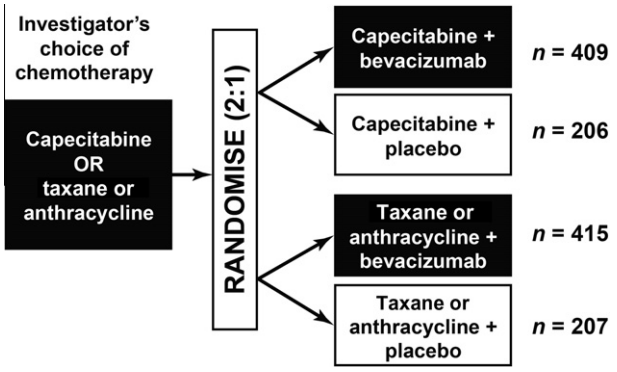

Fig. 1. RIBBON-1 trial design.[15]

The baseline characteristics were well balanced between the two treatment arms of the capecitabine cohort ($n = 615$) in RIBBON-1. The median age was 56 years in the capecitabine–bevacizumab treatment arm and 57 years in the capecitabine–placebo arm. Almost one-quarter of the patients (21% and 24%, respectively) had triple-negative disease (oestrogen receptor-, progesterone receptor- and HER2-negative) and approximately one-quarter (27% and 22%, respectively) had a disease-free interval $\leqslant$12 months. The majority of patients had received adjuvant chemotherapy. Approximately 40% of patients in each arm had received previous taxane-containing regimens, and 60% of the capecitabine–bevacizumab arm and 69% of the capecitabine–placebo arm had received anthracycline-containing therapy.

The median duration of follow-up in the capecitabine cohort was 15.6 months. The study demonstrated a significant improvement in PFS with the capecitabine–bevacizumab combination compared with capecitabine–placebo (Table 1). The hazard ratio was 0.69 (95% confidence interval [CI]: 0.56–0.84, investigator assessment; log-rank $p < 0.001$), representing a 31% reduction in the risk of disease progression or death with capecitabine–bevacizumab combination therapy versus capecitabine–placebo therapy (Fig. 2). Median PFS was 8.6 months in the capecitabine–bevacizumab arm compared with 5.7 months in the capecitabine–placebo arm. Subpopulation analyses of PFS according to

Table 1
Summary of efficacy: capecitabine cohort of the randomised RIBBON-1 trial.[15,17]

Outcome	Capecitabine–bevacizumab ($n = 409$)	Capecitabine–placebo ($n = 206$)	p-Value
Progression-free survival (investigator assessed)			
Hazard ratio (95% CI)	0.69 (0.56–0.84)		<0.001
Median, months	8.6	5.7	
Progression-free survival (IRC assessed)			
Hazard ratio (95% CI)	0.68 (0.54–0.86)		0.0011
Median, months	9.8	6.2	
Objective response rate[a]	35.4	23.6	0.0097
Median duration of response, months (95% CI)	9.2 (8.5–10.4)	7.2 (5.1–9.3)	
Hazard ratio for overall survival (stratified analysis)	0.85 (0.63–1.14)		0.27
1-year overall survival rate, %	81.0	74.4	0.076

CI = confidence interval; IRC = independent review committee.
[a] Patients with measurable disease: $n = 325$ for capecitabine–bevacizumab; $n = 161$ for capecitabine–placebo.

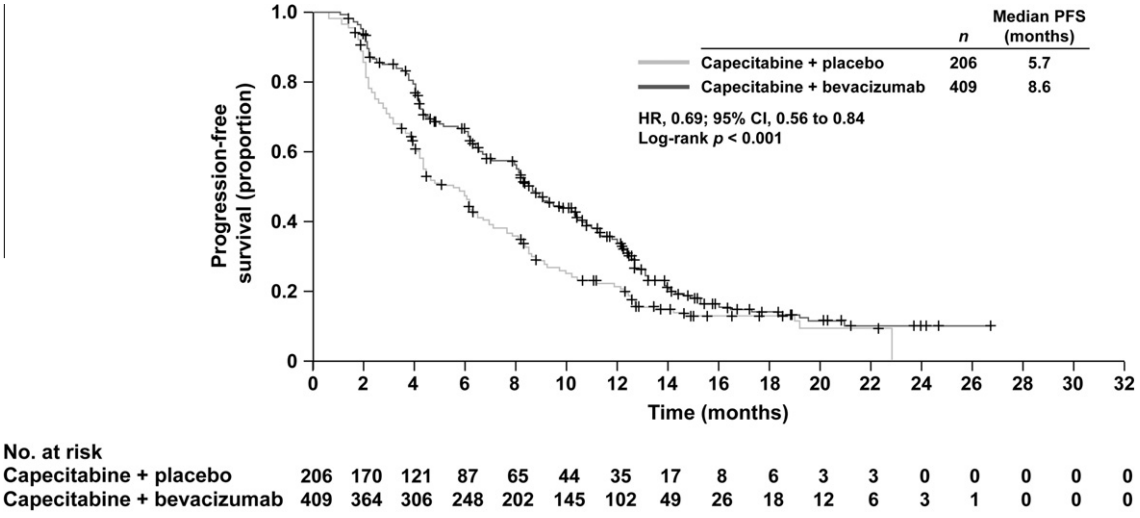

Fig. 2. RIBBON-1 trial: progression-free survival in the capecitabine cohort.[15] Reprinted with permission. ©2011 American Society of Clinical Oncology.

baseline clinical factors, such as age, hormone receptor status and number of metastatic sites, indicated a consistent benefit with capecitabine–bevacizumab therapy across all patient subgroups.[15] Response rate was also significantly superior in the capecitabine–bevacizumab arm (35% versus 24% in the capecitabine–placebo arm; $p = 0.0097$) (Table 1). There was no significant difference between the two treatments in overall survival or 1-year survival rate after events in 30% of patients, although it should be noted that the trial was not powered to show a survival difference. The stratified hazard ratio for overall survival was 0.85 (95% CI 0.63–1.14; $p = 0.27$).

RIBBON-1 is the third randomised trial to evaluate the effect of bevacizumab in combination with commonly used chemotherapy as first-line treatment for MBC. Consequently, data collection focused primarily on adverse events previously associated with bevacizumab, and detailed information on chemotherapy-related adverse events was not collected. The incidence of serious adverse events was marginally higher in the bevacizumab-containing arm than in the placebo arm (24% versus 19%, respectively), but the proportion of patients discontinuing study therapy (bevacizumab or placebo) was identical in the two arms (12%). Treatment-related deaths were reported in six patients (1.5%) in the capecitabine–bevacizumab arm compared with five patients (2.5%) in the capecitabine–placebo arm. Generally the incidence and severity of bevacizumab-associated adverse events were similar to previous experience of bevacizumab-containing therapy in the first-line setting. Bevacizumab was associated with higher incidences of grade $\geqslant 3$ hypertension (10% versus 1% in the chemotherapy-alone arm) and proteinuria (2% versus 0%, respectively). The incidence of grade $\geqslant 3$ venous thromboembolic events was slightly increased (5% versus 4%, respectively) but there was no increase in the risk of arterial thromboembolic events (1% in both arms). There were no cases of febrile

neutropenia or gastrointestinal perforation in either treatment arm.

In the second-line setting, data from the phase III RIBBON-2 trial were recently reported.[18] RIBBON-2 had an 'investigator's choice' design similar to RIBBON-1. Before randomisation, investigators selected their patient's chemotherapy regimen from the following options: weekly paclitaxel; 3-weekly paclitaxel; 3-weekly nab-paclitaxel; 3-weekly docetaxel; gemcitabine; capecitabine; or vinorelbine. After the investigator had declared the intended chemotherapy regimen, patients were randomised 2:1 to either bevacizumab or placebo. The primary objective – to show significantly improved PFS in the bevacizumab-containing arm compared with the chemotherapy alone arm – was met.[18] The hazard ratio for PFS was 0.78 (95% CI: 0.64–0.93; $p = 0.0072$), representing a 22% reduction in the risk of progression or death. Median PFS was 7.2 months in patients receiving bevacizumab versus 5.1 months in those receiving chemotherapy alone. Although the trial was not powered to detect a statistically significant difference in PFS in individual subgroups, analysis according to chemotherapy cohort was a prespecified secondary end-point. In the capecitabine cohort ($n = 144$), the hazard ratio for PFS was 0.73 (95% CI: 0.49–1.08). Median PFS was 6.9 months with capecitabine–bevacizumab ($n = 97$) compared with 4.1 months with placebo–capecitabine ($n = 47$). Interim overall survival analysis in the overall population indicated no significant difference between the arms (hazard ratio 0.90, $p = 0.374$; median 18.0 months with capecitabine–bevacizumab versus 16.4 months with capecitabine–placebo).

In the cohort of patients receiving capecitabine with bevacizumab or placebo in the RIBBON-2 trial, there was a higher incidence of adverse events leading to discontinuation of bevacizumab or placebo in the bevacizumab arm (12% versus 7%, respectively), but a lower incidence of serious adverse events (19% versus 26%, respectively) and fatal adverse events (1% versus 4%, respectively).

Before the RIBBON trials, an open-label, randomised, phase III trial of capecitabine either alone or in combination with bevacizumab (AVF2119g) was conducted in the United States of America (USA). Unlike the RIBBON-1 and RIBBON-2 trials, patients were heavily pretreated and all had disease that had progressed after treatment with both an anthracycline and a taxane.[5] Furthermore, 23% of patients had HER2-positive disease. The primary end-point of AVF2119g was PFS. Secondary end-points included response rate and overall survival. A total of 462 patients were enrolled: most patients received study therapy in the second-line setting (44%) or later (40%). The primary objective of significantly superior PFS among patients receiving capecitabine–bevacizumab was not met. The hazard ratio for PFS according to independent review facility (IRF) assessment was 0.98 (95% CI: 0.77–1.25; $p = 0.857$). The response rate was significantly higher in the bevacizumab-containing arm than in the control arm (20% versus 9%, respectively, by IRF assessment; $p = 0.001$).

The most likely and widely accepted explanation for this result is the late disease stage of the patient population. It appears from this study, especially when considered in the context of the three randomised trials of bevacizumab in the first-line setting,[12,13,15] that bevacizumab provides the greatest benefit when administered as first- or second-line treatment of metastatic disease. The number of angiogenic pathways contributing to tumour progression increases in later stages of breast cancer and because of this redundancy, inhibition of a single angiogenic pathway may not be sufficient to prevent tumour progression. Another difference between the RIBBON and AVF2119g trials is the capecitabine dose. In AVF2119g the registered dose of capecitabine (1250 mg/m^2 twice daily [bid]) was used, whereas in RIBBON-1 and RIBBON-2 patients received capecitabine 1000 mg/m^2 bid, which reflects the dose more commonly used in clinical practice that is associated with more favourable tolerability.[19] It is possible that chemotherapy may have been continued for longer in the RIBBON trials than in the AVF2119g trial. In the RIBBON-1 trial, patients received a mean of 10.3 cycles of capecitabine but corresponding data from the AVF2119g and RIBBON-2 trials have not been reported.

Despite AVF2119g not meeting its primary objective, the doubling of response rate provides an indication of activity and may be clinically meaningful to those patients. Additional important findings from the AVF2119g trial include the safety results. Although capecitabine was given at a dose higher than currently used in clinical practice, collection of chemotherapy-related adverse events was more extensive than in RIBBON-1 and therefore the trial provides a more thorough understanding of the safety profile of capecitabine–bevacizumab combination therapy. In AVF2119g, the combination of bevacizumab with capecitabine had little impact on the frequency or severity of capecitabine-related adverse effects. For example, grade 3 diarrhoea occurred in 11% of the capecitabine-alone arm versus 12% of the capecitabine–bevacizumab arm; grade 3 hand-foot syndrome occurred in 24% and 28%, respectively; and grade 2 hand-foot syndrome occurred in 36% and 42%, respectively. Consistent with the known side effects of bevacizumab, proteinuria and hypertension were more common in the combination arm but were rarely clinically significant. Grade $\geqslant 3$ hypertension was reported in 18% of patients in the combination arm compared with $<1\%$ of those receiving chemotherapy alone. Grade $\geqslant 3$ proteinuria occurred in 0.9% versus 0%, respectively. There was no difference between

the treatment arms in the incidence of grade ⩾3 thromboembolic events (0.6% versus 0.4%, respectively) or grade 4 pulmonary embolism (1.3% versus 1.4%, respectively; no grade 3 events).

2.2. Single-arm studies

In addition to the three randomised, phase III trials reported above,[5,15,18] the literature includes several single-arm studies evaluating capecitabine–bevacizumab either alone or in combination with another chemotherapeutic agent. In the first-line setting, these studies include XCALIBr,[20] North Central Cancer Treatment Group (NCCTG) NO43,[21] an Italian phase II study of metronomic therapy with bevacizumab,[22] and a subpopulation analysis of the ATHENA bevacizumab safety study.[23]

The single-arm, phase II XCALIBr study evaluated capecitabine 1000 mg/m^2 bid on days 1–14 in combination with bevacizumab 15 mg/kg every 21 days as first-line therapy in 106 patients with HER2-negative MBC.[20] The patient population was generally similar to that included in RIBBON-1, except that 46% of patients had ER-negative MBC (versus 23% with hormone receptor-negative disease in RIBBON-1). The primary objective was to demonstrate a median time to disease progression (TTP) >5.6 months. At the time of the first analysis after median follow-up of 12.7 months, median TTP was 5.7 months (95% CI: 4.9–8.4 months). The objective response rate was 38%. Final data have not yet been published. The key grade 3/4 adverse events were hand-foot syndrome, diarrhoea, hypertension and pulmonary embolism.

Further data on the combination of capecitabine and bevacizumab were generated in the ATHENA bevacizumab safety study.[23] Although the primary aim of ATHENA was to evaluate bevacizumab in combination with first-line taxane-based therapy in routine oncology practice, investigators were permitted to combine bevacizumab with alternative standard first-line chemotherapy (excluding anthracyclines) if taxane therapy was not considered their standard of care for a patient. Assessment of outcome according to chemotherapy partner was prespecified in the statistical plan. Of the 2251 patients included in the analysis, 102 (5%) received capecitabine monotherapy combined with bevacizumab. The safety profile was consistent with the known side-effects of bevacizumab. The most common grade ⩾3 adverse events characteristic of bevacizumab in the capecitabine–bevacizumab cohort were hypertension (4.4%), arterial/venous thromboembolic event (3.1%), bleeding (2.3%) and proteinuria (1.2%). Median TTP was 7.0 months and the objective response rate was 36%.

Recently, data from a single-arm US study investigating bevacizumab in combination with the novel 7/7 capecitabine regimen (7 days' treatment followed by a 7-day rest period) were published.[24] The study included 41 patients, 88% of whom were treated in the first-line setting. The overall response rate (primary end-point) was 20%. Median PFS was 8 months.

All of the studies described above have evaluated bevacizumab in combination with single-agent capecitabine. However, some investigators have studied bevacizumab administered with capecitabine-containing combination chemotherapy regimens. In a study conducted by the NCCTG, 45 patients received a 3-weekly regimen of capecitabine (825 mg/m^2 bid, days 1–14), docetaxel (75 mg/m^2, day 1) and bevacizumab (15 mg/kg, day 1) as first-line therapy for HER2-negative MBC. Each of the component doublets has shown considerable activity[13,15,25] and thus a combination of all three agents seems a logical proposition. The triplet combination demonstrated high activity: the overall response rate (primary end-point) was 49%, median PFS was 11.1 months and median overall survival was 28.4 months. Almost all patients (98%) experienced at least one grade ⩾3 adverse event, 69% experienced a grade 4 event and a considerable proportion of patients required dose reduction of docetaxel and/or capecitabine. Less than 50% of patients received the planned starting doses of docetaxel and capecitabine after cycle 2. However, there was no apparent increase in bevacizumab-related adverse events and effects typically associated with docetaxel and capecitabine were not exacerbated by bevacizumab. Recently, Italian investigators reported results from the single-arm BAT study evaluating a similar regimen.[26] Bevacizumab 15 mg/kg was combined with capecitabine 900 mg/m^2 bid on days 1–14 and docetaxel 60 mg/m^2 on day 1, repeated every 3 weeks. The overall response rate was 61% and median PFS was 11.0 months. Dose reductions were frequent: 58% of patients required capecitabine dose reduction and 37% required docetaxel dose reduction. Observations from these two studies suggest that further refinement of the schedule is necessary if this triplet regimen is to have clinical relevance. The French GINECO investigators are currently evaluating a triplet regimen comprising bevacizumab, capecitabine and paclitaxel as first-line therapy for patients with triple-negative breast cancer, a population that typically has a poor prognosis and limited treatment options. This single-arm study (ClinicalTrials.gov identifier NCT01069796) recently began recruitment. An alternative strategy, discussed later in this article, is to use active single-agent chemotherapies sequentially in combination with bevacizumab, which may provide a more appropriate and better tolerated approach.

Another group of Italian investigators evaluated an alternative triplet combination, opting for a low-dose metronomic schedule to overcome the considerable toxicity often associated with combination chemotherapy regimens. Metronomic chemotherapy appears to increase anti-angiogenic activity compared with cyclic

Table 2
Interim safety data from the capeciTabine and bevacizUmab Randomised against AvastiN anD taxOl Trial (TURANDOT): grade ⩾3 adverse events in >2 patients in either treatment arm.[35]

Grade ⩾3 adverse event, *n* (%)	Paclitaxel + bevacizumab (*n* = 163)	Capecitabine + bevacizumab (*n* = 164)
Hand-foot syndrome	0	16 (9.8)
Diarrhoea	2 (1.2)	9 (5.5)
Hypertension	5 (3.1)	7 (4.3)
Anaemia	2 (1.2)	4 (2.4)
Asthenia	3 (1.8)	1 (0.6)
Fatigue	5 (3.1)	1 (0.6)
Neutropenia	23 (14.1)	1 (0.6)
Leucopenia	7 (4.3)	0
Peripheral neuropathy	6 (3.7)	0

Three hundred and twenty seven of 561 randomised patients are eligible for safety analysis (randomised before 31st January 2010 and with sufficient post-baseline safety data).

administration at higher doses.[22] The combination of metronomic chemotherapy with anti-angiogenic agents has shown sustained tumour regression with no major toxicity in preclinical studies.[27] Based on these observations, Dellapasqua et al.[22] treated 46 patients with capecitabine 500 mg three times per day (fixed dose, not adjusted for body surface area), cyclophosphamide 50 mg daily and bevacizumab 10 mg/kg every 2 weeks. More than half of the patients (59%) were treated in the first-line setting; the remainder received study therapy in the second-line setting (24%) or later. The regimen produced a 48% response rate and disease was controlled for >6 months in 68% of patients.[22] The median TTP was 9.7 months and was achieved without incurring a major toxicity burden. The only grade 3/4 adverse events were manageable hypertension (17%), transaminitis, neutropenia, leucopenia, nausea/vomiting (each occurring in 4%) and proteinuria (2%). The median number of cycles delivered was 13 (range 2–34 cycles), with treatment ongoing in some patients at the time of publication. This favourable risk:benefit ratio suggests that metronomic chemotherapy with bevacizumab may be a valid treatment approach, offering the possibility of long-term disease control without inducing major toxicity.

In HER2-positive disease, capecitabine is widely used in combination with anti-HER2 therapy,[28] supported by results from several randomised trials.[6,29,30] There are fewer data on bevacizumab in HER2-positive MBC, although results of the phase III study of AVastin in combination with HERceptin/docetaxEL in patients with HER2-positive metastatic breast cancer (AVEREL) was presented in December 2011. [31] There is a preclinical rationale for combining bevacizumab and trastuzumab. HER2-overexpressing human breast cancer xenografts show increased angiogenic potential, mediated by VEGF, providing a rationale for combining agents that target the HER2 and VEGF pathways.[32] A single-arm phase II study evaluating the combination of trastuzumab and bevacizumab (without chemotherapy) as first-line treatment for HER2-overexpressing MBC demonstrated a response rate of 48% (95% CI: 34–62), median TTP of 7.1 months (95% CI: 5.5–12.9) and median overall survival of 43.8 months (95% CI 40.6 – not reached).[33] Recently first efficacy results from the phase II single-arm Herceptin, Avastin and Xeloda (HAX) study were reported.[34] In this study, 88 patients with HER2-positive MBC received the triplet combination of capecitabine, bevacizumab and trastuzumab as first-line therapy. The overall response rate (primary end-point) was 73% (95% CI: 62–82), including complete responses in 7% of patients. Median PFS was 14.4 months (95% CI: 10.4 – not reached) after a median follow-up of 8.8 months. Overall survival data are immature. Of note, this regimen does not produce significant alopecia and is generally well tolerated by patients. The most common grade ⩾3 adverse events were hand-foot syndrome (22%), gastrointestinal disorders (11%, including diarrhoea in 9%) and vascular disorders (8%, including hypertension in 7%).

2.3. Ongoing randomised trials in MBC

There are several ongoing trials in MBC evaluating capecitabine–bevacizumab combination regimens, predominantly as first-line therapy, with or without additional chemotherapy. In the first-line setting, the phase III capeciTabine and bevacizUmab Randomised against AvastiN anD taxOl Trial (TURANDOT) (ClinicalTrials.gov identifier NCT00600340) by the Central European Cooperative Oncology Group (CECOG) is comparing capecitabine–bevacizumab versus paclitaxel–bevacizumab in patients with HER2-negative MBC. The trial, now fully recruited, is aiming to address a question unanswered by RIBBON-1 by comparing different bevacizumab–chemotherapy combinations. The primary objective of the TURANDOT trial is to demonstrate non-inferior overall survival with the capecitabine–bevacizumab combination regimen versus paclitaxel–bevacizumab, defined as an upper limit ⩽1.33 for the two-sided CI for the overall survival hazard ratio. Secondary end-points include response rate

Table 3
Summary of ongoing randomised phase III trials of capecitabine- and bevacizumab-containing regimens in the first-line HER2-negative metastatic breast cancer setting.

Trial (identifier)	Collaborative group	Design	Control arm	Investigational arm	Primary end-point	Planned sample size	First patient entered
TURANDOT (NCT00600340)	CECOG	Capecitabine + bevacizumab versus paclitaxel + bevacizumab	Bevacizumab 10 mg/kg, d1 & 15 + paclitaxel 90 mg/m^2, d1, 8 & 15, q4w	Capecitabine 1000 mg/m^2 bid, d1–14 + bevacizumab 15 mg/kg, d1, q3w	Overall survival	560	April 2008
CARIN (NCT00868634)	AIO	Capecitabine + bevacizumab ± vinorelbine	Capecitabine 1000 mg/m^2 bid, d1–14 + bevacizumab 15 mg/kg, d1, q3w	Capecitabine 1000 mg/m^2 bid, d1–14 + bevacizumab 15 mg/kg, d1 + vinorelbine 25 mg/m^2, d1 & 8, q3w	PFS	400	February 2009
TABEA (EudraCT No. 2008-003997-17)	German Breast Group	Taxane + bevacizumab ± capecitabine	Taxane (paclitaxel 80 mg/m^2, d1, 8 & 15 OR docetaxel 75 mg/m^2, d1) + bevacizumab 15 mg/kg, d1, q3w	Taxane (paclitaxel 80 mg/m^2 d1, 8 & 15 OR docetaxel 75 mg/m^2, d1) + bevacizumab 15 mg/kg, d1 + capecitabine 900 mg/m^2 bid, d1–14, q3w	PFS	400	October 2009
NTR1348	BOOG	Paclitaxel + bevacizumab ± capecitabine	Bevacizumab 10 mg/kg, d1 & 15 + paclitaxel 90 mg/m^2, d1, 8 & 15, q4w	Bevacizumab 15 mg/kg, d1 + paclitaxel 90 mg/m^2, d1 & 8 + capecitabine 825 mg/m^2 bid, d1–14, q3w	PFS[a]	312	May 2007
SAKK 24/09	SAKK	Capecitabine + bevacizumab + cyclophosphamide versus paclitaxel + bevacizumab	Bevacizumab 10 mg/kg, d1 & 15 + paclitaxel 90 mg/m^2, d1, 8 & 15, q4w	Capecitabine 500 mg tid d1–28 + oral cyclophosphamide 50 mg od d1–28 + bevacizumab 10 mg/kg d1 & 15, q4w	Safety	142	September 2010

AIO = Arbeitsgemeinschaft für Internistische Onkologie; bid = twice daily; BOOG = Borstkanker Onderzoeks Groep; CECOG = Central European Cooperative Oncology Group; d = day; HER2 = human epidermal growth factor receptor 2; od = once daily; PFS = progression-free survival; q3w = once every 3 weeks; q4w = once every 4 weeks; SAKK = Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (Swiss Group for Clinical Cancer Research); tid = three times daily.

[a] Note added in proof: Primary endpoint reported in December 2011.

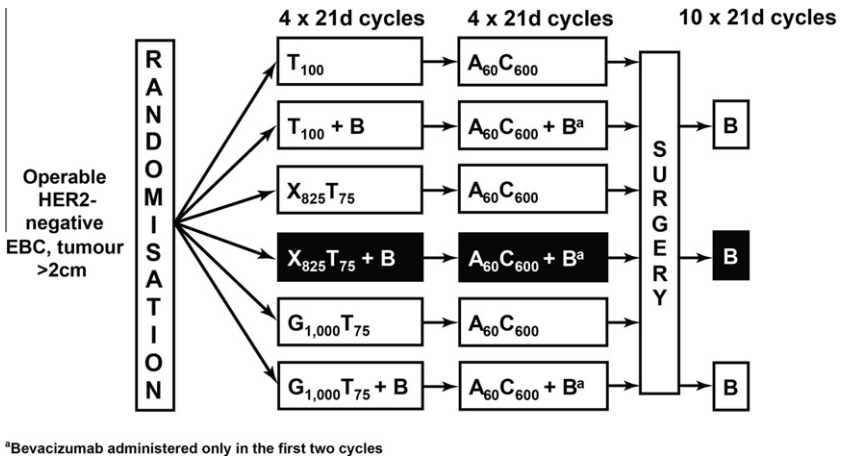

Fig. 3. Design of the National Surgical Adjuvant Breast and Bowel Project B-40 trial: randomised trial evaluating neoadjuvant chemotherapy with or without concurrent bevacizumab and adjuvant bevacizumab.[38]

(assessed using Response Evaluation Criteria in Solid Tumours), PFS, time to response, duration of response, time to treatment failure, safety and quality of life. Recently reported interim data from 327 patients eligible for safety analysis revealed safety profiles consistent with those of the component agents (Table 2).[35] The TURANDOT trial and four ongoing randomised trials evaluating bevacizumab in combination with capecitabine-containing chemotherapy doublets in the first-line setting are summarised in Table 3.

An alternative treatment strategy is being investigated in the open-label, randomised Investigation of Maintenance thErapy with XeLoDa and Avastin in mBC (IMELDA) trial (ClinicalTrials.gov identifier NCT00929240). Patients with HER2-negative MBC receive up to six cycles of bevacizumab–docetaxel as first-line induction therapy. Those without progression are then randomised to either bevacizumab–capecitabine combination therapy or bevacizumab alone as maintenance therapy until disease progression or unacceptable toxicity. The primary end-point is PFS. Capecitabine and bevacizumab are given according to the schedule used in RIBBON-1 (capecitabine 1000 mg/m^2 bid, days 1–14 in combination with bevacizumab 15 mg/kg, repeated every 3 weeks until disease progression).

The capecitabine–bevacizumab combination will also be evaluated in the (Treatment Across multiple liNes wIth Avastin (TANIA) trial (ClinicalTrials.gov identifier NCT01250379), which is designed to evaluate the role of bevacizumab beyond progression. Patients previously treated with bevacizumab in combination with chemotherapy are randomised to receive subsequent lines of single-agent chemotherapy either alone or in combination with bevacizumab. One of the permitted single-agent chemotherapy options in the TANIA trial is capecitabine, and therefore further data on this combination are anticipated.

3. Capecitabine and bevacizumab in early breast cancer

Until recently, there were limited data available for regimens combining capecitabine and bevacizumab in early breast cancer. A small pilot study ($n = 18$) of neoadjuvant capecitabine, bevacizumab and docetaxel demonstrated a pathological complete response (pCR) in four patients (22%).[36] A similar regimen is under evaluation in an ongoing single-arm, Spanish study (ClinicalTrials.gov identifier NCT00576901). In another trial, bevacizumab was combined with a neoadjuvant regimen of doxorubicin–cyclophosphamide followed by capecitabine–docetaxel, demonstrating modest activity. Bevacizumab with doxorubicin–cyclophosphamide showed an acceptable safety profile, but the bevacizumab, capecitabine and docetaxel part of the regimen was associated with substantial toxicity, particularly grade 3 mucositis and hand-foot syndrome.[37]

At the American Society of Clinical Oncology Annual Meeting 2011, the first data from a randomised trial evaluating a capecitabine- and bevacizumab-containing regimen in early breast cancer were reported from the National Surgical Adjuvant Breast and Bowel Project B-40 trial (Fig. 3).[38] The primary end-point was pCR rate. Neither capecitabine nor gemcitabine increased the pCR rate or clinical response rate when added to docetaxel, but both led to an increase in toxicity. In contrast, combining bevacizumab with chemotherapy significantly increased pCR rate (35% versus 28%, respectively; $p = 0.027$) and clinical response rate (64% versus 56%, respectively; $p = 0.006$). The incidence of grade 3/4 adverse events was higher among patients receiving bevacizumab than those treated with chemotherapy alone, influenced primarily by a higher incidence of grade 3 hypertension (10% versus <1%, respectively), grade 3 hand-foot syndrome (11% versus 8%, respectively), and grade 3 mucositis (5% versus 3%, respectively). There was no increase in the risk of

grade 3/4 left ventricular systolic dysfunction. Long-term follow-up for disease-free survival and overall survival is ongoing.

4. Conclusions

The combination of capecitabine and bevacizumab is an active first-line regimen for patients with HER2-negative MBC, significantly improving PFS (the primary end-point) and response rate versus capecitabine–placebo. No significant difference in overall survival has been shown. Data from single-arm trials show similar efficacy, notwithstanding differences in patient characteristics between studies. The positive results from the RIBBON-1 trial contrast with the lack of PFS benefit seen in the AVF2119g trial in patients with heavily pretreated disease, supporting the widely accepted hypothesis that bevacizumab provides the greatest benefit when given early in the disease course before redundancy of anti-angiogenic pathways. Numerous ongoing trials are evaluating capecitabine–bevacizumab combination therapy with or without a second chemotherapy agent (a taxane or vinorelbine). It remains to be seen whether any benefit in increased efficacy is outweighed by the likely increase in toxicity with a chemotherapy doublet.

In June 2011, the European Commission approved the combination of capecitabine and bevacizumab as first-line therapy for MBC, based on the results of the RIBBON-1 trial. This regimen provides an important treatment option for a subset of patients who are either unsuited to or prefer not to receive paclitaxel in combination with bevacizumab. Clinical trials of bevacizumab and capecitabine continue and should provide insight into currently unanswered questions, such as how to identify patients most likely to benefit from the capecitabine–bevacizumab combination and the optimal duration of therapy. Although bevacizumab combined with taxane may be expected to provide a higher response rate than bevacizumab combined with capecitabine, for some patients, paclitaxel may not be the preferred therapy and the combination of bevacizumab–capecitabine is important. In addition, the lack of alopecia with capecitabine is a key consideration for some patients.

The TURANDOT trial is designed as a non-inferiority trial. If positive, it will indicate that capecitabine–bevacizumab provides a valid alternative to paclitaxel–bevacizumab, enabling physicians and patients to choose the regimen that is most appropriate for an individual and providing an alternative treatment option.

In conclusion, the RIBBON-1 trial shows that capecitabine combined with bevacizumab is an effective and tolerable first-line regimen for patients with HER2-negative MBC, irrespective of clinical characteristics. For the considerable number of patients who may not be candidates for paclitaxel therapy or who do not wish to receive paclitaxel, capecitabine in combination with bevacizumab is an important treatment option and merits further consideration.

Role of the funding source

The study sponsors had no role in the collection, analysis or interpretation of the data or writing of the report. The decision to submit the manuscript and the critical review and approval of the final version was the responsibility of the authors. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Conflict of interest statement

D. Miles, C. Zielinski, M. Martin and E. Vrdoljak have received honoraria from Roche for speaker engagements and participation in advisory boards. N. Robert has received honoraria from Roche for lectures and consulting and also received research support from Roche.

Acknowledgement

Support for writing assistance for this manuscript was funded by F. Hoffmann-La Roche Ltd.

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