Paclitaxel and bevacizumab with or without capecitabine as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer: a multicentre, open-label, randomised phase 2 trial

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Abstract

Background
The addition of bevacizumab to paclitaxel or capecitabine has demonstrated improved progression-free survival (PFS) and objective response rate (ORR) as compared with chemotherapy alone in patients with HER2-negative locally recurrent or metastatic breast cancer (LR/MBC). We evaluated the efficacy and safety of first-line therapy of paclitaxel and bevacizumab with or without capecitabine in patients with HER2-negative LR/MBC.

Methods
In this multicentre, open-label, randomised phase II trial, women with HER2-negative LR/MBC were randomly assigned in a 1:1 ratio to paclitaxel (90 mg/m² intravenously [IV] on days 1, 8, and 15) and bevacizumab (10 mg/kg IV on days 1 and 15) every 4 weeks for 6 cycles, followed by bevacizumab (15 mg/kg IV on day 1) every 3 weeks (AT) or to paclitaxel (90 mg/m² IV on days 1 and 8), bevacizumab (15 mg/kg IV on day 1) and capecitabine (825 mg/m² orally twice daily on days 1–14) every 3 weeks for 8 cycles, followed by bevacizumab and capecitabine at the same doses every 3 weeks (ATX). The primary endpoint was investigator-assessed PFS. Secondary endpoints included ORR, duration of response, overall survival (OS), and safety. Exploratory analyses were conducted to evaluate the impact of capecitabine on OS and to validate a novel prognostic model. This trial is registered with EudraCT, number 2006-006058-83.

Findings
Median PFS was significantly longer in ATX as compared with AT (11.2 months vs 8.4 months; stratified hazard ratio [HR], 0.52; 95% CI, 0.41–0.67; \( p < 0.0001 \)). The ORR in ATX patients with measurable disease (n = 268) was higher than that in AT (69% vs 51%; \( p = 0.01 \)). The median duration of response was 6.8 vs 5.4 months for, respectively, ATX and AT (\( p <0.0001 \)). Median OS was 24.2 months for ATX and 23.1 months for AT (\( p = 0.53 \)). The increased rate of grade 3–4 adverse events related to the addition of capecitabine, being hand-foot syndrome (34% vs 0% for AT) and neutropenia (20% vs 12% for AT), generally did not preclude continuation of treatment. Exploratory analyses indicated that 1) patients receiving capecitabine at some line for treatment have significantly improved OS and 2) a prognostic model can classify patients into three risk groups associated with OS.

Interpretation
In patients with HER2-negative LR/MBC, addition of capecitabine to paclitaxel and bevacizumab significantly improved PFS, ORR and response duration. This combination was reasonably well tolerated and may be considered of use as first-line treatment in rapidly progressive disease.
Introduction

In the past years bevacizumab, a monoclonal antibody targeting tumour angiogenesis by inhibition of VEGF-A, combined with a taxane has demonstrated to significantly improve progression-free survival (PFS) and objective response rate (ORR) as compared with taxane alone in HER2-negative LR/MBC in three phase III trials (E2100, AVADO, and RIBBON-1). Likewise, significantly improved PFS and ORR were reported for first-line capecitabine and bevacizumab as compared with capecitabine and placebo in the same patient category. Phase III AVF2119g trial data addressing the efficacy of capecitabine and bevacizumab in later-line treatment of MBC showed higher ORR, but no change in PFS. Bevacizumab with either a taxane or capecitabine has a well-established safety profile, which is generally manageable.

Several doublets of cytotoxic agents, such as capecitabine and a taxane, have demonstrated synergistic activity in vitro and may thus exert enhanced clinical benefit. Preclinical studies have shown that taxanes may induce the intratumoural activity of thymidine phosphorylase, a capecitabine-metabolising enzyme, potentially enhancing the efficacy of capecitabine. In a phase III trial in anthracycline-pretreated MBC patients, the docetaxel and capecitabine doublet showed improved ORR, time to progression (TTP) and overall survival (OS) as compared with docetaxel alone. The paclitaxel and capecitabine doublet has also demonstrated high activity in several single-arm, phase II trials. In the phase III trial of docetaxel without or with capecitabine (1,250 mg/m² twice daily), little overlapping toxicities have been reported, but the doublet had higher rates of grade 3 adverse events (AEs), primarily hand-foot syndrome. The rates of dose modification and treatment-related withdrawal were also higher in the docetaxel and capecitabine group. Exploratory subgroup analysis in the doublet group showed that early dose reduction of capecitabine led to better tolerability without compromising the efficacy (TTP and OS). In a subsequent phase II randomized post-marketing commitment trial in which docetaxel was combined with capecitabine 1,250 mg/m² or 825 mg/m², non-inferiority for PFS of the lower dose combination could not be demonstrated. Although not part of the study design, superiority for PFS of the high dose combination was also not demonstrated. For paclitaxel combined with capecitabine, the safety of a dose of 825 mg/m² twice daily has been supported by several phase II trials, all with reports of few grade 3–4 AEs and encouraging efficacy.

Collectively, it appears that paclitaxel, bevacizumab and capecitabine have a largely non-overlapping safety profile and can be co-administered with feasible tolerability. The enhanced efficacy of bevacizumab plus either paclitaxel or capecitabine as well as of the doublet paclitaxel and capecitabine support the combination of paclitaxel, bevacizumab and capecitabine as a novel first-line treatment schedule in MBC. This led us to design the present randomised, phase II ATX trial to investigate whether the previous E2100 efficacy data of paclitaxel and bevacizumab could be confirmed and whether capecitabine added...
to paclitaxel and bevacizumab might improve outcome without compromising safety as first-line treatment of patients with HER2-negative LR/MBC.

Methods

Patients
The ATX study (BOOG 2006-06) was a multicentre, open-label, randomised, phase II trial. Women with confirmed HER2-negative LR/MBC without prior palliative chemotherapy were eligible. Patients had at least one evaluable lesion; bone-only lesions were allowed. Other key eligibility criteria were: age between 18 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤1; a life expectancy of ≥12 weeks; adequate haematological, biochemical and coagulation function; (neo)adjuvant cytotoxic treatment >6 months or >12 months in case of taxanes.

Key exclusion criteria included: hormonal therapy ≤2 weeks, adjuvant radiotherapy ≤6 months, or palliative radiotherapy ≤3 weeks before randomisation; other primary tumours ≤5 years except for basal cell carcinoma of the skin or in situ cervical cancer; metastasis to the central nervous system (CNS); history of CNS disorders or pre-existing peripheral neuropathy grade ≥1; major surgery ≤28 days or minor surgery ≤24 hours before randomisation; thrombosis ≤12 months; therapeutic anti-thrombotic medication; clinically significant cardiovascular disease.

The study was conducted in accordance to the International Conference on Harmonisation Good Clinical Practice guidelines and in agreement with the Declaration of Helsinki. Approval by the local institution review boards of all participating hospitals was received. Written informed consent was obtained before study enrolment. This trial is registered with the European Union Drug Regulating Authorities Clinical Trials, number 2006-006058-83, and the Netherlands Trial Register, number NTR1348.

Randomisation
The randomisation by computer was centrally performed at the IKNL (Comprehensive Cancer Centre, Amsterdam, the Netherlands) and was stratified for institute, hormone receptor status, bone-only metastasis and measurable disease using a minimisation method.

Treatment
Patients were randomly assigned in a 1:1 ratio to the standard regimen of paclitaxel and bevacizumab (AT) or the investigational regimen of paclitaxel and bevacizumab plus capcitabine (ATX; Figure 1). Patients assigned to AT were treated with paclitaxel (weekly x3) and bevacizumab (days 1 and 15) at 4-week intervals for 6 cycles, followed by bevacizumab
at 3-week intervals for subsequent cycles. Those assigned to ATX were treated with paclitaxel (weekly x2), bevacizumab (day 1) and capecitabine at 3-week intervals for 8 cycles, followed by bevacizumab and capecitabine at the same doses at 3-week intervals for subsequent cycles. The treatment duration of paclitaxel was 24 weeks in both groups.

Treatment was continued until disease progression, unmanageable toxicity, investigator’s decision or withdrawal of consent. Criteria for paclitaxel and capecitabine dose modification, delay or interruption based on treatment-related AEs were predefined (appendix pp 3–10). Bevacizumab was temporarily or permanently withheld if predefined bevacizumab-related AEs were met. Subsequent lines of treatment were at the investigator’s discretion and were recorded.

**Assessment of endpoints**

The primary endpoint was investigator-assessed PFS, defined as the time from randomisation to disease progression or death from any cause, whichever came first. Secondary endpoints were ORR, response duration, OS (the time from randomisation to death from any cause), and safety. ORR was defined as the percentage of complete and partial response confirmed after a minimum of 4 weeks after first being reported. The response duration lasted from the time that partial response or complete response was first achieved to the date of progressive disease. Tumour assessment was performed according to Response Evaluation Criteria in Solid Tumors (RECIST 1.0) every 3 months by computed tomography or magnetic resonance imaging.

The occurrence of any AEs was recorded according to the National Cancer Institute Toxicity Criteria for Adverse Events (NCI-CTCAE version 3.0) at each contact. All AEs were followed until resolution or stabilisation and relation with the treatment medication had to be determined.

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**Figure 1.** Treatment scheme.
Post-progression therapy
Data on treatment following disease progression were collected to evaluate the effect of later-line therapy on OS. Patients assigned to AT were allowed to receive capecitabine following disease progression. Here, we analysed the impact of capecitabine-containing therapy on OS in AT-treated patients.

Prognostic factor index
We validated a novel prognostic model that has been developed with the use of ATHENA trial OS data obtained from patients with HER2-negative LR/MBC treated with first-line bevacizumab in combination with non-anthracycline-containing chemotherapy. This model included four clinical variables previously identified as prognostic factors for worse OS: disease-free interval following primary diagnosis of ≤24 months, the presence of liver metastases or ≥three metastatic organ sites, triple-negative breast cancer (TNBC), and prior (neo)adjuvant therapy with a taxane and/or an anthracycline. Patients included in the ATX trial were categorised into one of the three groups based on the number of risk factors present: none or one, two, three to four risk factors. The differences in PFS and OS among the three groups were assessed.

Statistics
This phase II trial had a randomised selection design by Simon et al. to prioritise between the two treatment groups. Based on unpublished data of E2100 trial (data cut-off: 14 April 2005, data on file), the estimated median PFS for AT was 13 months with an expected increase of 3 months for ATX. Considering an 80% power and a one-sided \( p = 0.05 \), 149 patients for AT were required to detect a median PFS of 13 months and an alternative median PFS of 16 months with approximate upper critical value of 15 months. Similarly, a total of 154 patients for ATX were required to detect a median PFS of 16 months and an alternative median PFS of 13 months with an approximate lower critical value of 14 months. The sample size assumed an exponentially distributed death time, a uniform accrual over time, an additional one year follow-up and took a cube root transformation of the hazard rate to get good small sample properties. The sample size also had 93% power and two-sided \( p = 0.05 \) to detect a difference between AT and ATX with estimated response rates of, respectively, 30% and 50%.

All patients having received at least one dose of study medication were analysed for safety. Efficacy analyses were performed according to the intention-to-treat (ITT) for all randomised patients. The duration of time-to-event was estimated using the Kaplan-Meier method. Although no formal statistical comparison between treatment groups was anticipated, distributions of time-to-event endpoints (PFS and OS) between treatment groups were compared with a stratified log-rank test. Hazard ratios (HRs) for PFS and OS were calculated with a Cox proportional hazards model adjusted for stratification factors (except for institute). PFS data were censored at the date for patients that erroneously started
non-protocol treatment before documented progressive disease and at the date of last assessment for patients without progressive disease. OS data were censored at the date of last follow-up for patients who were still alive. ORR in all eligible patients and in patients with measurable disease at baseline was compared between groups using the Chi-square test. Unplanned exploratory analyses of one-year PFS rate and two-year OS rate were performed between treatment groups by using the normal approximation method. In other exploratory analyses, the Kaplan-Meier method and unstratified log-rank testing were used. Statistical analyses were performed by using SAS (v9.2 SAS Institute, Cary, NC) and R (v2.13.2). All p values reported were two sided and 95% confidence intervals (CIs) were estimated using the method of Greenwood.

**Role of the funding source**
The sponsor of the study participated in the study design with the principle investigators (AHH, EB), but had no role in data collection, data analysis, data interpretation or the writing of the report. SWL, SMG, and HvT had access to the raw data. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

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**Figure 2. Trial profile.**

* Predominantly refused treatment for reason other than adverse event, consent withdrawal, or decisions to discontinue the study by the investigator.

** One patient did not receive treatment because of brain metastasis at baseline.

ITT=Intention-to-treat population.
Results

Patient population
Between June 2007 and December 2010, 312 patients (156 per treatment group) were enrolled at 31 sites and formed the ITT population (Figure 2). At the data cut-off date (April 26, 2013), the median follow-up duration was 41.2 months. Safety population comprised 311 patients, who received at least one dose of study medication. Demographic and disease characteristics at baseline were generally well balanced between the treatment groups (Table 1).

Table 1. Patient characteristics (intention-to-treat population).

<table>
<thead>
<tr>
<th></th>
<th>AT group (n = 156)</th>
<th>ATX group (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>56 (34–74)</td>
<td>56 (32–76)</td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>133 (85%)</td>
<td>119 (76%)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>23 (15%)</td>
<td>37 (24%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>81 (52%)</td>
<td>82 (53%)</td>
</tr>
<tr>
<td>1</td>
<td>75 (48%)</td>
<td>74 (47%)</td>
</tr>
<tr>
<td>Hormone receptor-positive</td>
<td>132 (85%)</td>
<td>133 (85%)</td>
</tr>
<tr>
<td>HER2-negative disease</td>
<td>153 (98%)</td>
<td>156 (100%)</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>137 (88%)</td>
<td>131 (84%)</td>
</tr>
<tr>
<td>Metastatic at first diagnosis</td>
<td>26 (17%)</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Disease-free interval ≥12 months*</td>
<td>125 (80%)</td>
<td>134 (86%)</td>
</tr>
<tr>
<td>Sites of metastatic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>53 (34%)</td>
<td>41 (26%)</td>
</tr>
<tr>
<td>Liver</td>
<td>89 (57%)</td>
<td>91 (58%)</td>
</tr>
<tr>
<td>Bone-only</td>
<td>11 (7%)</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>No. of metastatic sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>80 (51%)</td>
<td>94 (60%)</td>
</tr>
<tr>
<td>≥3</td>
<td>76 (49%)</td>
<td>61 (39%)</td>
</tr>
<tr>
<td>Prior adjuvant hormonal therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>80 (51%)</td>
<td>74 (47%)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>45 (29%)</td>
<td>40 (26%)</td>
</tr>
<tr>
<td>AI</td>
<td>6 (4%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Tamoxifen + AI</td>
<td>24 (15%)</td>
<td>33 (21%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Prior palliative hormonal therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>67 (43%)</td>
<td>84 (54%)</td>
</tr>
<tr>
<td>Prior (neo)adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>67 (43%)</td>
<td>66 (42%)</td>
</tr>
<tr>
<td>Anthracycline-containing</td>
<td>81 (52%)</td>
<td>78 (50%)</td>
</tr>
<tr>
<td>CMF</td>
<td>6 (4%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

ECOG PS = Eastern Cooperative Oncology Group performance score. AI = aromatase inhibitor. CMF = cyclophosphamide, methotrexate and fluorouracil.
*Disease-free interval was defined as the interval from diagnosis of primary breast cancer to first relapse.
Treatment exposure

The main reason for treatment discontinuation was disease progression (Figure 2). Median duration of treatment was 40 weeks (range 1–234) and 33 weeks (range 1–176) for, respectively, the ATX and the AT schedule. Approximately 80% of the patients received the protocol-specified 24 weeks of paclitaxel-containing regimen (125 patients in ATX and 126 patients in AT). Mean relative dose intensity of paclitaxel was 84% in ATX- and 89% in AT-treated patients. Mean relative dose intensity of bevacizumab over the first 24 weeks of treatment was 89% and 93% for, respectively, ATX and AT, and that of capecitabine was 73% in ATX-treated patients.

Efficacy

At the time of analysis, 294 (94%) PFS events and 250 (80%) death events had occurred. A total of 29 patients were censored for receiving non-protocol therapy before documented progression (17 patients in ATX and 12 patients in AT). Non-protocol therapy included hormonal therapy (n = 17), chemotherapy (n = 11) and radiotherapy of the breast (n = 1). Patients receiving ATX had a significantly prolonged PFS as compared with those receiving AT (stratified HR 0.52, 95% CI 0.41–0.67; log-rank p <0.0001). Median PFS increased from 8.4 months (95% CI 8.0–9.0) to 11.2 months (95% CI 10.0–12.0; Figure 3A). The PFS rate at one year was 41% (95% CI 33–50) for ATX and 20% (95% CI 14–27) for AT.

Similar results were observed when PFS analysis was performed without censoring for non-protocol therapy. The median PFS was 11.2 months (95% CI 10.2–12.7) for ATX and 8.4 months (95% CI 8.0–9.0) for AT (stratified HR 0.56, 95% CI 0.44–0.71; log-rank p <0.0001). The PFS rate at one year was 42% (95% CI 35–51) for ATX and 21% (95% CI 16–29) for AT.
The ORR in all eligible patients was 58% in ATX- and 45% in AT-treated patients \((p = 0.02; \text{Table 2})\). In patients with measurable disease at baseline \((n = 268)\), the ORR was 69% for ATX and 51% for AT \((p = 0.01)\). The median duration of response was 6.8 months for ATX \((95\% \text{ CI 6.2–8.3})\) and 5.4 months for AT \((95\% \text{ CI 5.1–6.0}; p <0.0001)\).

OS was similar for ATX- and AT-treated patients being, respectively, 24.2 months \((95\% \text{ CI 21.2–26.6})\) and 23.1 months \((95\% \text{ CI 21.0–26.8}; \text{stratified HR 0.92, 95\% CI, 0.72–1.19; log-rank } p = 0.53; \text{Figure 3B})\). The survival rate at two years was 51\% \((95\% \text{ CI 43–59})\) in patients treated with ATX and 47\% \((95\% \text{ CI 39–55})\) in those treated with AT.

**Table 2. Tumour response.**

<table>
<thead>
<tr>
<th></th>
<th>AT group</th>
<th>ATX group</th>
<th>(p)</th>
</tr>
</thead>
</table>
| **Best overall response**
| Complete response  | 4 (3\%)  | 6 (4\%)  |       |
| Partial response   | 88 (56\%)| 94 (60\%) |       |
| Stable disease     | 42 (27\%)| 36 (23\%) |       |
| Progressive disease| 10 (6\%) | 4 (3\%)   |       |
| Not available/evaluable** | 12 (8\%) | 16 (10\%) |       |
| **Objective response rate**† | 45\% | 58\% | 0.02 |
| Objective response rate in measurable disease§ | 51\% | 69\% | 0.01 |
| **Duration of response**
| Median, months \((95\% \text{ CI})\) | 5.4 (5.1–6.0) | 6.8 (6.2–8.3) | <0.0001 |

\(^1\text{In the intention-to-treat population (ATX group = 156, AT group = 156).}\)

\(^2\text{Best overall response observed during treatment.}\)

\(^3\text{Withdrew with insufficient tumour response evaluation after baseline. On-study patients (n = 7) were consid}

\(\text{ered not available for best overall response.}\)

\(^4\text{Objective response was defined as the proportion of patients who achieved either partial or complete res}

\text{ponse by RECIST criteria confirmed after at least 4 weeks. On-study patients who fulfilled the criteria of ORR}

\text{were considered as having ORR.}\)

\(^5\text{In patients with measurable disease at baseline (AT group, n = 137; ATX group, n = 131).}\)

**Safety**

In the safety population \((n = 311)\), a comparable number of patients discontinued study treatment due to AEs \((28 \text{ patients [18\%] in ATX vs 23 \text{ patients [15\%] in AT})\}. AEs that led to study discontinuation were diverse (appendix p 11). More patients in ATX were withdrawn from study therapy before completion of 24 weeks of paclitaxel-containing treatment than those in AT \((11 \text{ patients [3.5\%] in ATX vs 5 \text{ patients [1.6\%] in AT})\}. Delay of any study drug because of toxic effects occurred in 118 \((76\%)\) patients receiving ATX and 91 \((59\%)\) patients receiving AT. Although treatment-related SAEs occurred more often in ATX than in AT \((33 \text{ [21\%] vs 19 [12\%]})\), the treatment-related death rate was identical and was low \((3 \text{ [2\%] in both groups; Table 3})\).

Treatment-related grade 3–4 AEs were few for AT. The addition of capecitabine resulted in a \(\geq5\%\) higher rate of neutropenia grade 3 and hand-foot syndrome grade 3 relative to AT (Table 3). Bevacizumab was interrupted in 29 \((18.7\%)\) and 2 \((2.6\%)\) patients receiving, respectively, ATX and AT. Hypertension grade 3 and proteinuria grade 3 also occurred at a higher rate in ATX than in AT. However, there were more patients with a history of hyper-
tension (defined as grade ≥1) at baseline receiving ATX than those on AT (45 [29%] vs 36 [23%]). Of these, 11 of 45 ATX- and 7 of 36 AT-treated patients developed hypertension grade 3. No proteinuria grade 3 occurred within the first 24 weeks of therapy containing AT or ATX. The median time until first proteinuria grade 3 was 61 weeks (range 33–186). The rates of bleeding complications and thromboembolic events were low in both groups (<1%).

**Table 3. Summary of grade 3 and 4 treatment-related events in safety-evaluable patients.**

<table>
<thead>
<tr>
<th>Event</th>
<th>AT group (n = 156)</th>
<th>ATX group (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related SAE</td>
<td>19 (12%)</td>
<td>33 (21%)</td>
</tr>
<tr>
<td>Treatment-related death†</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td><strong>Treatment-related AEs†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11 (7%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16 (10%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (4%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12 (8%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (12%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>7 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Venous thrombotic event</td>
<td>1 (&lt;1%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>0</td>
<td>52 (34%)</td>
</tr>
<tr>
<td>Stomatitis / mucositis</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

AE = adverse event. SAE = serious adverse event.

† In the AT group, three cases of deaths were due to lung bleeding, leucopenic fever and pulmonary embolus. In the ATX group, three cases of deaths were due to gastrointestinal bleeding, neutropenic fever and sepsis.

†AEs that occur in ≥2% of patients in either group.

NOTE. National Cancer Institute Common Toxicity Criteria version 3.0 worst grade experienced per patient.
Capecitabine therapy following progression on first-line paclitaxel

The median number of chemotherapy lines following disease progression after AT was 2 (range 0–8, appendix p 12). In AT, 87 (56%) patients received capecitabine in second- or later-line following disease progression. A total of 69 patients (including 3 cases of intercurrent death) received any other therapy, of which 41 received chemotherapy other than capecitabine. Baseline characteristics were grossly similar among groups (appendix p 13). Comparison between patients given any line capecitabine post-progression therapy and those receiving any other therapy (n = 69) showed a significant better OS for the first group: median OS 25.9 months (95% CI 23.3–30.7) vs 18.7 months (95% CI 13.6–23.4; log-rank \( p = 0.01 \)). The post-progression survival (PPS), defined as the time from first disease progression to death, was also better in those receiving any line capecitabine post-progression therapy: median PPS 16.9 months (95% CI 13.6–22.1) vs 6.9 months (95% CI 3.6–10.9; log-rank \( p <0.0001 \)).

![Figure 4. The impact of capecitabine post-progression therapy on overall survival (4A, left) and post-progression survival (4B, right) of patients treated with first-line paclitaxel and bevacizumab (AT).](image)

![Figure 5. Overall survival according to the number of risk factors present (n = 312).](image)
Exclusion of 28 patients who did not receive any post-progression chemotherapy revealed similar findings of better OS and PPS for patients given capecitabine as compared with those given other chemotherapy. Median OS was, respectively, 25.9 months (95% CI 23.3–30.7) vs 20.9 months (95% CI 15.5–26.7; log-rank \( p = 0.03 \); Figure 4A) and median PPS was 16.9 months (95% CI 13.6–22.1) vs 10.9 months (95% CI 7.1–14.4; log-rank \( p < 0.001 \); Figure 4B). OS of AT-treated patients receiving capecitabine post-progression therapy was numerically similar to that of ATX-treated patients.

**Prognostic factor index**

OS was not different for patients treated with ATX or AT. A total of 83 (27%) patients had none or one risk factor, whereas 134 (43%) patients had two risk factors. In 95 (30%) patients, three to four risk factors were present (appendix p 14). Among the three risk groups, patients with none or one risk factor had the best prognosis. Median OS was 30.0 months (95% CI 23.0–37.0), while that of patients with two, and three to four risk factors was, respectively, 21.6 (95% CI 19.3–24.0) and 20.2 months (95% CI 17.8–22.6; log-rank \( p = 0.01 \); Figure 5). In addition, PFS was significantly different among the three risk groups. Patients with none or one risk factor had the longest PFS (median 11.3 months; 95%CI 10.7–11.8) as compared with those with two (median 8.8 months; 95%CI 8.0–9.7) or three to four risk factors (8.5 months; 95% CI 8.2–8.9; log-rank \( p = 0.03 \)). Stratification for treatment arms showed longer PFS in favour of ATX for all three risk groups (data not shown).

**Discussion**

In this multicentre phase II trial on first-line chemotherapy of patients with HER2-negative LR/MBC, capecitabine combined with paclitaxel and bevacizumab demonstrated a significant improvement in PFS, ORR and response duration than treatment with paclitaxel and bevacizumab. These efficacy endpoints favour the triplet combination as a promising first-line regimen for this population, albeit at the cost of additional capecitabine toxicity.

In the present trial, the combination schedule of bevacizumab and paclitaxel as reported by Miller et al. \(^1\) resulted in a median PFS of 8.6 months, which was slightly shorter than the reported median PFS varying between 9.2 and 12.9 months obtained in the E2100 \(^1\) and other phase II/III trials \(^21-23\) of first-line paclitaxel plus bevacizumab (appendix pp 15–16). The precise reason for this discrepancy remains speculative. Paclitaxel was stopped after 24 weeks as specified in our trial design, which may particularly clarify the observation of shorter PFS in our AT design. In previous bevacizumab-based trials, taxane was continued until progression, up to 9 months (AVADO) or toxicity. In general, extending chemotherapy is associated with a longer duration of PFS as compared with shorter chemotherapy duration \(^24\). Furthermore, differences with regard to clinical characteristics such as tumour...
sites and burden, tumour biology, and prior treatments might contribute to variations in efficacy endpoints across trials. These factors may also possibly clarify the higher ORR of 45% achieved for AT in our trial as compared with 36.9% in the E2100 trial.

Our study is the first randomised trial reporting efficacy and safety results of first-line paclitaxel and bevacizumab with capecitabine for HER2-negative LR/MBC (panel). Treatment with ATX resulted in an effective and long-lasting disease control in terms of longer PFS and response duration, and higher ORR as compared with AT. In previous single-arm phase II trials in early breast cancer as well as in MBC the triplet of docetaxel, bevacizumab and capecitabine has consistently shown promising activity and a manageable safety profile. In metastatic triple-negative MBC, recent preliminary data from the single-arm, phase II A-Taxel trial have demonstrated promising activity and manageable toxicity for the first-line triplet of paclitaxel, bevacizumab and intermittent capecitabine. The first-line randomised phase III trial of the German breast group (NCT01200212) on a 3-week schedule of taxane (80 mg/m² paclitaxel weekly or 75 mg/m² docetaxel three weekly) and bevacizumab with or without capecitabine (900 mg/m² twice daily), however, was prematurely discontinued due to an unfavourable risk-benefit profile for the capecitabine-treated group. These findings may advocate the 3-week dosing schedule of ATX with 90 mg/m² paclitaxel given on days 1 and 8 and the lower starting dose of capecitabine (825 mg/m² twice daily) from our trial, which is an effective regimen and has a tolerable safety profile.

Most AEs with AT or ATX were manageable and consistent with the known safety profile of individual agents. The treatment discontinuation rates in both study groups were comparable to previously reported rates of bevacizumab plus chemotherapy. The incidence of SAEs and treatment-related deaths were also in agreement with previous bevacizumab trials. As expected, we found more toxicities in ATX. Hand-foot syndrome grade 3 was the most prominent non-haematological AE, which was generally manageable by capecitabine dose reduction. Although not life-threatening, this AE may affect patient’s quality of life. Dose reduction of capecitabine, if required, does not necessarily compromise efficacy. We also recorded a higher incidence of neutropenia grade 3 in ATX, a known toxicity of both capecitabine and paclitaxel. The main non-haematological AEs increased in ATX were hypertension and proteinuria. The modest increase in hypertension grade 3 may be explained by a longer treatment duration and more patients with a history of hypertension at risk for further increase of their blood pressure. Overall, hypertension could adequately be controlled by anti-hypertensive agents preventing aggravation. Proteinuria grade 3 also occurred after prolonged bevacizumab treatment, but necessitated permanent discontinuation of bevacizumab. Collectively, the safety analysis indicated that capecitabine can safely be co-administered with paclitaxel and bevacizumab, but adequate dosing control to handle specific toxicities is warranted.

The improvements in PFS (primary endpoint), ORR and response duration (both secondary endpoints) with ATX did not translate into improved OS. There are several possible expla-
nations for the lack of survival benefit. First, this phase II trial was not powered to detect OS differences. Second and perhaps more importantly, it is well-known that subsequent lines of therapy or cross-over may affect OS and would obscure any potential effect of first-line treatment. In our trial, the chemotherapeutic regimen following first progression was chosen at investigator’s discretion. Approximately 50% of patients treated with AT received capecitabine following disease progression. Third, despite practical advantages of PFS as an endpoint for clinical trial design over OS i.e. smaller sample size and shorter follow-up, it is unclear whether PFS in advanced breast cancer provides a clinically meaningful surrogate for OS. In a meta-analysis of randomised trials testing different first-line chemotherapy duration schedules in MBC, OS was significantly improved in patients receiving long-term treatment up to progression. OS benefit, however, is not a consistent finding and comes at the cost of prolonged toxicity.

The efficacy benefit of a taxane and capecitabine given in combination or sequentially for advanced breast cancer has remained elusive due to the lack of conclusive data from randomised trials. In the exploratory analysis, median OS was numerically not different between concomitant e.g. ATX group or sequential administration of paclitaxel and capecitabine. Of interest, we detected a significantly increased OS benefit in AT-treated patients who received capecitabine post-progression therapy as compared with those receiving any other (chemo)therapy. There was no apparent imbalance in baseline characteristics among the groups, but a selection bias cannot be excluded. Although a definitive conclusion cannot be drawn from the exploratory analysis, our findings add to existing data supporting an OS benefit with capecitabine alone or in combination at any time during the course of disease.

The role of bevacizumab in the treatment of advanced breast cancer is reflected by mixed opinions of regulatory authorities concerning absence of survival benefit observed in the E2100 and subsequent AVADO and RIBBON-1 trials, albeit in the presence of PFS advantage. As a consequence, the use of bevacizumab in MBC is currently not recommended by FDA. In contrast, bevacizumab with paclitaxel or capecitabine is still indicated for MBC in most EU countries according to the approval by European Medicines Agency. Recent attention has focussed on the search for subgroups among advanced breast cancer patients deriving the greatest benefit from bevacizumab. In a search for clinical evidence, primarily retrospective of nature, a beneficial effect of bevacizumab has been suggested in advanced TNBC. A recent meta-analysis of individual patient data from E2100, AVADO and RIBBON-1 reaffirmed these earlier results showing significant improvement in PFS from a median of 5.4 to a median of 8.1 months when bevacizumab was added to first-line chemotherapy in TNBC (pooled HR 0.63, 95% CI 0.52–0.76; p <0.0001). As these data do not provide a definitive conclusion, pending results from prospective, randomised trials comparing standard chemotherapy with or without bevacizumab in TNBC have to be awaited.

In the present trial 48% of patients were alive at two years. There are presently no defined
factors to identify patients with good prognosis. To this end, we validated a novel prognostic model developed on data from the ATHENA trial and demonstrated that patients with few clinical risk factors had significantly longer OS. This model could also successfully identify patients with long PFS. International guidelines for metastatic breast cancer advice sequential single-agent therapy for patients that do not need a rapid treatment response, which allows for optimal delivery of each drug, for reduction of the risk of toxicity and for retention of quality of life. Therefore, the prognostic model may be applied to systematically classify patients according to their prognosis at the start of chemotherapy and might assist in selecting treatment for those with poor prognosis aiming at increased OS.

In conclusion, capecitabine added to paclitaxel and bevacizumab as first-line treatment provides clinical benefit in terms of prolonged PFS, increased ORR and prolonged response duration in patients with HER2-negative LR/MBC. The safety profile was generally manageable. Our findings indicate that this triplet combination is an active first-line regimen, which might specifically be of use in patients requiring an optimal chance of a treatment response.

Contributors
AHH and EB are the principle investigators. AHH, HvT, and EB designed the trial. All authors except for SWL, SMG and HvT were responsible for recruitment of patients, clinical care and data collection. SMG was involved in data management. HvT performed the main analyses. SWL, HvT and EB were involved in data interpretation. SWL and EB wrote the first draft of the report. All authors were involved in revision and finalisation of the manuscript.

Conflicts of interest
EBO has received research support funding from Roche and Novartis. SWL has received an educational grant from Roche. SCL is an advisory board member for Cergentis, Novartis, Roche, and Sanofi and has received research support funding from Amgen, AstraZeneca, Roche, and Sanofi. All other authors declare no conflicts of interest.

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Panel: Research in context.

Systematic review
The combination of cytotoxic agents with different modes/mechanisms of action or cytotoxic agents with molecular-targeted agents may improve therapeutic efficacy without incremental toxicity. We searched PubMed and abstracts of major oncology conferences for randomised trials in which patients were treated with the combination of paclitaxel and bevacizumab with or without capecitabine. We also searched ClinicalTrials.gov for ongoing studies. The search was performed with the combination of terms and their synonyms “taxane”, “paclitaxel”, “docetaxel”, “bevacizumab”, “capecitabine”, “trial”, and “breast cancer”. Studies published in English until August, 1st 2013 were included.

Interpretation
Our study was the first randomised trial to report the efficacy and safety of capecitabine added to paclitaxel and bevacizumab as first-line treatment of HER2-negative LR/MBC. We have shown that progression-free survival, objective response rate, and duration of response are significantly improved by the triplet combination as compared with paclitaxel and bevacizumab. Our findings suggest that this triplet combination could be a safe and effective first-line treatment option for women with HER2-negative LR/MBC.
REFERENCE


A RANDOMIZED PHASE II TRIAL


