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Original article

Trebananib (AMG 386) plus weekly paclitaxel with or without bevacizumab as first-line therapy for HER2-negative locally recurrent or metastatic breast cancer: A phase 2 randomized study

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ABSTRACT

Introduction: This phase 2 randomized study evaluated trebananib (AMG 386), a peptide-Fc fusion protein that inhibits angiogenesis by neutralizing the interaction of angiopoietin-1 and -2 with Tie2, in combination with paclitaxel with or without bevacizumab in previously untreated patients with HER2-negative locally recurrent/metastatic breast cancer.

Methods: Patients received paclitaxel 90 mg/m^2 once weekly (3-weeks-on/1-week-off) and were randomly assigned 1:1:1:1 to also receive blinded bevacizumab 10 mg/kg once every 2 weeks plus either trebananib 10 mg/kg once weekly (Arm A) or 3 mg/kg once weekly (Arm B), or placebo (Arm C); or open-label trebananib 10 mg/kg once a week (Arm D). Progression-free survival was the primary endpoint.

Results: In total, 228 patients were randomized. Median estimated progression-free survival for Arms A, B, C, and D was 11.3, 9.2, 12.2, and 10 months, respectively. Hazard ratios (95% CI) for Arms A, B, and D versus Arm C were 0.98 (0.61–1.59), 1.12 (0.70–1.80), and 1.28 (0.79–2.09), respectively. The objective response rate was 71% in Arm A, 51% in Arm B, 60% in Arm C, and 46% in Arm D. The incidence of grade 3/4/5 adverse events was 71/9/4%, 61/14/5%, 62/16/3%, and 52/4/7% in Arms A/B/C/D. In Arm D, median progression-free survival was 12.8 and 7.4 months for those with high and low trebananib exposure ($AUC_{ss} \geq 8.4$ versus < 8.4 mg·h/mL), respectively.

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Conclusions: There was no apparent prolongation of estimated progression-free survival with the addition of trebananib to paclitaxel and bevacizumab at the doses tested. Toxicity was manageable. Exposure-response analyses support evaluation of combinations incorporating trebananib at doses > 10 mg/kg in this setting.
Trial Registration: ClinicalTrials.gov, NCT00511459

Introduction

Two receptor tyrosine kinase pathways important in induction and regulation of tumor angiogenesis are the vascular endothelial growth factor (VEGF) and angiopoietin axes [1,2]. Angiopoietin-1 and -2 influence the vasculature by binding to the Tie2 receptor [2]. Although the VEGF and angiopoietin pathways are distinct, they interact [2] and simultaneous blockade of both pathways may improve inhibition of tumor growth compared with blocking either pathway alone [3–5].

Several studies have assessed bevacizumab (an anti-VEGF-A antibody) plus chemotherapy as first-line treatment for recurrent or metastatic HER2-negative breast cancer [6–9]. In the E2100 study, bevacizumab plus paclitaxel versus paclitaxel alone significantly improved progression-free survival (PFS; 11.8 versus 5.9 months, respectively; $P < 0.001$) and objective response rate (ORR; 36.9% versus 21.2%; $P < 0.001$) in the first-line setting [8]. However, there was no significant difference in overall survival (OS) between the two treatment groups (26.7 versus 25.2 months; $P = 0.16$). Improvements in PFS have also been reported for combinations of bevacizumab with other chemotherapy regimens as first-line therapy for metastatic disease [6,7,9]. Given these improvements in PFS, but lack of concomitant improvement in OS, there has been considerable recent debate regarding the role of bevacizumab in the treatment of metastatic breast cancer [10–12].

Trebananib is an investigational, intravenously administered peptide-Fc fusion protein that binds to and inhibits the interaction of angiopoietin-1 and -2 with the Tie2 receptor. Tumor xenograft studies with trebananib have shown that dual inhibition of angiopoietin-1 and -2 in the context of concurrent VEGF blockade results in significantly better efficacy than inhibiting either target alone [1,13]. In phase 1 monotherapy and chemotherapy combination studies in patients with solid tumors, trebananib demonstrated antitumor activity and a specific toxicity profile [14,15]. In a randomized, placebo-controlled phase 2 study of trebananib plus weekly paclitaxel, patients with recurrent ovarian cancer who received trebananib demonstrated prolonged estimated PFS compared with those who received placebo with evidence of dose–response and exposure-response effects [16,17]. Treatment was tolerable, with specific and manageable toxicities. The objectives of this study were to estimate the treatment effect of trebananib (as assessed by PFS) when administered in combination with paclitaxel with or without bevacizumab in first-line treatment of locally advanced or metastatic HER2-negative breast cancer.

Methods

Patients

Eligible women (≥18 years) had histologically or cytologically confirmed HER2-negative (expression ≤ 2+ by immunohistochemistry and/or negative by fluorescence in situ hybridization) adenocarcinoma of the breast with locally recurrent (not amenable to resection with curative intent) or metastatic disease for which they had not been previously treated. Additionally, patients had Eastern Cooperative Oncology Group (ECOG) status ≤ 1; measurable/nonmeasurable disease per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [18], complete computed tomography (CT) or magnetic resonance imaging (MRI) scans and whole-body bone scintigraphy ≤ 28 days before randomization; and adequate hematologic, renal, hepatic, and cardiac function. Key exclusion criteria were inflammatory breast cancer; central nervous system metastasis; adjuvant/neoadjuvant taxane treatment within 1 year; prior radiation therapy, radiofrequency ablation, percutaneous cryotherapy, or hepatic chemoembolization ≤ 14 days before randomization; grade > 1 peripheral neuropathy; uncontrolled hypertension; history of arterial or venous thrombosis within 1 year; bleeding diathesis within 6 months; and previous treatment with VEGF or angiopoietin axis inhibitors. Patients provided written informed consent; study procedures were approved by an independent ethics committee/institutional review board at each center.

Study design and treatment

This was a randomized, placebo-controlled, 4-arm, multicenter (70 sites in four countries), phase 2 estimation study. Patients received intravenous (IV) paclitaxel 90 mg/m^2 once weekly (QW; 3-weeks-on/1-week-off) and were randomly assigned 1:1:1:1 to receive trebananib 10 mg/kg QW plus bevacizumab 10 mg/kg IV every 2 weeks (Q2W; Arm A), trebananib 3 mg/kg QW plus bevacizumab 10 mg/kg IV Q2W (Arm B), placebo plus bevacizumab 10 mg/kg IV Q2W (Arm C), or trebananib 10 mg/kg QW (Arm D). The doses of trebananib used in this study were selected based on pharmacokinetic analysis from the first-in-human monotherapy study. A maximum-tolerated dose was not reached in that study but doses greater than 3 mg/kg QW provided trough concentrations that were above the optimal biologic dose for tumor xenograft growth inhibition [1,14]. Treatment in Arms A, B, and C was double-blind; treatment in Arm D was open-label. Randomization was stratified by adjuvant taxane exposure (yes/no) and number of metastatic sites (≤3/>3). Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Doses of trebananib, bevacizumab or paclitaxel could be withheld according to protocol-specified rules. Doses of paclitaxel could be reduced to 65 mg/m^2 in the event of toxicity; dose modifications for trebananib and bevacizumab were not permitted.

The primary endpoint was PFS, defined as the time from randomization to disease progression (per RECIST) as assessed by investigators, or death. Secondary endpoints included ORR (confirmed complete response + partial response), duration of response (DOR), OS, time to response, incidence of adverse events (AEs), anti-trebananib antibody formation, and pharmacokinetics of trebananib.

Efficacy assessments

CT/MRI were performed at baseline and every 8 ± 1 weeks thereafter. Tumor response was assessed according to RECIST version 1.0 [18]. Patients who discontinued treatment without