

Phase 1b dose-finding study of motesanib with docetaxel or paclitaxel in patients with metastatic breast cancer

Richard H. De Boer · Dusan Kotasek · Shane White · Bogda Koczwara · Paul Mainwaring · Arlene Chan · Rebeca Melara · Yining Ye · Adeboye H. Adewoye · Robert Sikorski · Peter A. Kaufman

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Abstract The purpose of this study was to investigate the safety, tolerability, and pharmacokinetics of motesanib when combined with docetaxel or paclitaxel in patients with metastatic breast cancer. In this open-label, dose-finding, phase 1b study, patients received motesanib 50 or 125-mg orally once daily (QD), beginning day 3 of cycle 1 of chemotherapy, continuously in combination with either paclitaxel 90 mg/m² on days 1, 8, and 15 every 28-day

cycle (Arm A) or docetaxel 100 mg/m² on day 1 every 21-day cycle (Arm B). Dose escalation to motesanib 125 mg QD occurred if the incidence of dose-limiting toxicities (DLTs, primary endpoint) was $\leq 33\%$. If the maximum tolerated dose (MTD) of motesanib was established in Arm B, additional patients could receive motesanib at the MTD plus docetaxel 75 mg/m². Forty-six patients were enrolled and 45 received ≥ 1 dose of motesanib. The incidence of DLTs was $< 33\%$ in all cohorts; thus, motesanib 125 mg QD was established as the MTD. Seven patients (16 %) had grade 3 motesanib-related adverse events including cholecystitis (2 patients) and hypertension (2 patients). Pharmacokinetic parameters of motesanib were similar to those reported in previous studies. The objective response rate was 56 % among patients with measurable disease at baseline who received motesanib in combination with taxane-based chemotherapy. The addition of motesanib to either paclitaxel or docetaxel was generally tolerable up to the 125-mg QD dose of motesanib. The objective response rate of 56 % suggests a potential benefit of motesanib in combination with taxane-based chemotherapy.

R. H. De Boer (✉)
Department of Medical Oncology, Royal Melbourne Hospital,
Grattan St, 2nd Floor, Parkville, Melbourne, VIC 3050, Australia
e-mail: Richard.DeBoer@wh.org.au

R. H. De Boer
Western Hospitals, Footscray, Melbourne, VIC 3050, Australia

D. Kotasek
Ashford Cancer Centre, Ashford, SA, Australia

S. White
Austin Health, Heidelberg, VIC, Australia

B. Koczwara
Flinders Medical Centre and Flinders University, Adelaide, SA,
Australia

P. Mainwaring
HOCA, Mater Private Hospital, South Brisbane, QLD 4101,
Australia

A. Chan
Mount Hospital, Perth, WA, Australia

R. Melara · Y. Ye · A. H. Adewoye · R. Sikorski
Amgen Inc., Thousand Oaks, CA, USA

P. A. Kaufman
Dartmouth-Hitchcock Medical Center and Norris Cotton Cancer
Center, Lebanon, NH, USA

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Introduction

Although there has been a significant decline in breast cancer mortality over the last decade, up to 40 % of patients will develop metastatic breast cancer (MBC), for which there remains no curative therapy. Many therapeutic agents effectively treat MBC; however, the overall duration of response remains far from ideal. The median survival

from diagnosis for triple negative MBC is approximately 2 to 3 years and for estrogen receptor-positive/progesterone receptor-positive disease, approximately 5 years [1]. Thus, the development of new therapies to treat MBC remains critically important.

Angiogenesis is essential for breast cancer development and metastasis [2], and high tumor levels of the proangiogenic cytokine vascular endothelial growth factor (VEGF) are predictive of poor clinical outcomes in patients with breast cancer [3, 4]. The VEGF signaling pathway has thus become a promising target, and agents targeting this pathway have been shown to improve outcomes in patients with MBC [5].

Motesanib is an orally administered, small-molecule antagonist of VEGF receptors (VEGFR) 1, 2, and 3; platelet-derived growth factor receptor (PDGFR); and Kit [6]. Treatment with motesanib was tolerable and showed antitumor activity when administered as monotherapy to patients with advanced solid tumors [7, 8] and in combination with either chemotherapy or an anti-epidermal growth factor receptor antibody in patients with non-small-cell lung cancer (NSCLC) [9]. In tumor xenograft models of human breast cancer, treatment with motesanib resulted in reductions in tumor growth and tumor blood vessel density [10]. Moreover, additive reductions in tumor growth were achieved when motesanib was combined with docetaxel [10], possibly as a result of VEGF pathway blockade enhancing (and/or conserving) the antiangiogenic activity of the taxane [11]. Potentially, the combination of motesanib with taxane chemotherapy may have activity in patients with MBC. The objective of this phase 1b study was to investigate the safety, tolerability, and pharmacokinetics of motesanib when combined with taxanes (docetaxel or paclitaxel) in patients with MBC.

Materials and methods

Patients

Female patients ≥ 18 years old were eligible if they had confirmed measurable or nonmeasurable [per Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 [12]] adenocarcinoma of the breast with locally recurrent or metastatic disease, Eastern Cooperative Oncology Group performance status of 0/1, and adequate organ function. Exclusion criteria included >1 prior chemotherapy regimen for MBC; taxane-containing treatment within 6 months, bevacizumab within 3 months, or VEGFR-targeted therapy within 1 month before enrollment; uncontrolled hypertension; prior malignancy (except in situ cervical cancer or nonmelanoma skin cancer); radiation therapy to >25 % of bone marrow; radiation therapy for peripheral lesions

within 14 days of enrollment; central nervous system metastases; arterial or venous thrombosis within 12 months before enrollment; bleeding diathesis or bleeding within 14 days or major surgery within 28 days before enrollment; clinically significant cardiac disease; and prior episodes of cholecystitis.

The study protocol was approved by the Institutional Review Board/Ethics Committee at each participating study site, and all patients provided written consent.

Study design

This open-label, dose-finding, multicenter study conducted at 6 centers in Australia and 1 in the United States evaluated the safety of motesanib in combination with paclitaxel or docetaxel. Patients with locally recurrent or metastatic breast cancer were assigned to receive motesanib in combination with paclitaxel (Arm A), or motesanib in combination with docetaxel (Arm B) (Fig. 1). The maximum planned sample size (if all cohorts enrolled the maximum number of patients) was 54. Four dose cohorts (2 in Arm A and 2 in Arm B) that were initially planned to test lower doses of motesanib (100 and 75 mg) were not opened because the 125-mg dose was found to be tolerable. Hence, only 46 patients were ultimately enrolled in the study. The primary endpoint was the incidence of dose-limiting toxicities (DLTs). Secondary endpoints included the incidence of adverse events (AEs); pharmacokinetics of motesanib, paclitaxel, and docetaxel; objective tumor response (per RECIST v1.0) [12]; and duration of response. Evaluation of pharmacodynamic biomarkers was an exploratory endpoint.

Maximum tolerated dose (MTD) and DLT

The MTD was defined as the highest dose of motesanib with an observed incidence of DLT in ≤ 33 % of patients per cohort.

A DLT was defined as any grade 3 or 4 hematologic or nonhematologic toxicity (except alopecia) occurring during cycle 1 that was related to motesanib or the combination of motesanib plus chemotherapy. Fatigue, nausea, diarrhea, vomiting, neutropenia, febrile neutropenia, neuropathy, thrombocytopenia, anemia, hypertension, and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations were only considered DLTs if the following conditions were met: grade 3 fatigue >7 days or grade 4 fatigue; grade 3 or 4 nausea, diarrhea, or vomiting despite maximum supportive care; grade 3 or 4 neutropenia with fever ≥ 38.5 °C; grade 4 neutropenia (absolute neutrophil count $<0.5 \times 10^9/L$) for >7 days; grade 4 thrombocytopenia (platelet count $<25 \times 10^9/L$) for >7 days; grade 4 anemia; grade 4 hypertension; or AST or ALT > 10 times the upper limit of normal.

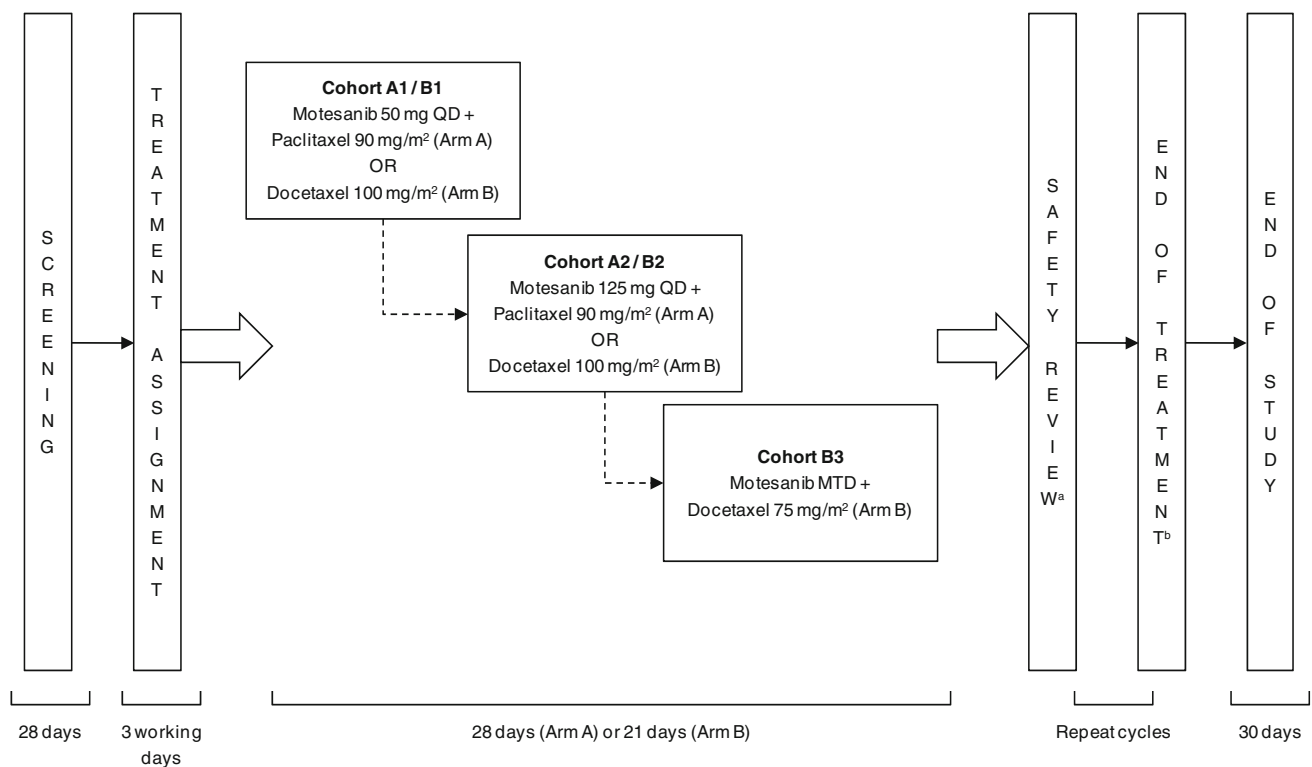


Fig. 1 Study schema. ^aThe sponsor and the principal investigators reviewed the safety data from each cohort to evaluate possible drug effects and DLTs. ^bDisease progression or motesanib intolerance

Administration of study drugs and dose escalation

Patients were assigned to receive motesanib (Amgen Inc., Thousand Oaks, CA) plus either paclitaxel or docetaxel. Motesanib 125 mg administered orally once daily (QD) was the MTD in the first-in-human single-agent motesanib study [7] and was the maximum dose for this study. Patients received 1 of 2 doses of motesanib (50 or 125 mg) self administered orally QD beginning day 3 of cycle 1, and then from day 1 of subsequent cycles (Fig. 1). Motesanib was administered with paclitaxel 90 mg/m² [intravenously (IV) over 1 h ± 15 min] on days 1, 8, and 15 every 28-day cycle (Arm A) or docetaxel 100 mg/m² or 75 mg/m² (IV over 1 h ± 15 min) on day 1 every 21-day cycle (Arm B). Patients receiving motesanib plus docetaxel 100 mg/m² received myeloid growth factor support as primary prophylaxis for febrile neutropenia.

Up to 6 patients were enrolled in each arm at the starting dose of motesanib 50 mg QD. Dose escalation to motesanib 125 mg QD was allowed if ≥4 patients completed cycle 1 with no DLTs. At least 4 patients could be enrolled into subsequent dosing cohorts, all of which could be expanded to acquire additional safety data. If >2 of 4 patients receiving motesanib 125 mg QD experienced a DLT, lower doses could be explored. If the MTD of

motesanib was established in Arm B, an additional cohort of patients could be enrolled to receive motesanib at the MTD plus docetaxel 75 mg/m², a commonly used dose of docetaxel for patients with MBC in many countries; this cohort received no myeloid growth factor support. Inpatient dose escalation was not allowed. Patients continued to receive study drugs until disease progression, withdrawal of consent, or occurrence of unacceptable toxicity.

Dose modifications

If a patient experienced a DLT, motesanib was withheld until the toxicity resolved to either grade 1 or baseline and then restarted with a 25-mg dose reduction. One dose reduction per patient was allowed with the exception of hypertension management, for which 2 dose reductions were allowed. If the patient did not recover within 3 weeks, study treatment was discontinued. A DLT in patients receiving motesanib 50 mg QD would result in the discontinuation of study treatment.

Chemotherapy could be delayed ≤3 weeks for severe toxicities. One dose reduction was allowed for paclitaxel; 2 were allowed for docetaxel. More than a 3-week delay in treatment resulted in permanent discontinuation of chemotherapy.

Blood pressure was monitored weekly for the first 6 weeks and then at each clinic visit. Investigators were permitted to use standard antihypertensive treatments. Motesanib was to be discontinued for reoccurrence of symptomatic hypertension or hypertension despite maximal doses of a 4-drug antihypertensive regimen. Motesanib was also permanently discontinued for patients with grade 4 hemorrhage, >1 grade 3 hemorrhage, grade 4 venous thrombosis, or grade 3 or 4 arterial thrombosis.

Motesanib was withheld for patients who developed a clinical diagnosis of cholecystitis or symptoms attributed to gallbladder enlargement in the absence of cholecystitis. Patients who developed hypothyroidism [elevated thyroid-stimulating hormone (TSH) levels above upper limits of normal and/or a low T4 level] and/or signs or symptoms of hypothyroidism could receive thyroid hormone replacement therapy (i.e., levothyroxine) according to standard clinical care.

AE assessments

AEs were recorded and classified according to the Medical Dictionary for Regulatory Activities and graded according to the Common Terminology Criteria for Adverse Events version 3.0 [13].

Pharmacokinetic and pharmacodynamic analyses

Plasma samples for pharmacokinetic analysis of motesanib and analysis of serum placental growth factor (PLGF) and VEGF were collected predose and at 1, 3, 6, 24 (before the next motesanib dose), and 48 h (trough) after motesanib administration on days 3 and 8 of cycle 1 in Arm A and on day 3 of cycle 1 and day 1 of cycle 2 in Arm B. Plasma samples for pharmacokinetic analysis of paclitaxel and docetaxel were collected preinfusion and at 0.5, 1, 2, 4, 6, 24, 48, and 96 h after infusion on days 1 and 8 of cycle 1 in Arm A and on day 1 of cycles 1 and 2 in Arm B. Samples were analyzed at Amgen, Inc. (Thousand Oaks, CA) for motesanib and at Bioanalytical Systems, Inc. (McMinnville, OR) for paclitaxel and docetaxel using validated analytical methods. Serum PLGF and VEGF were assessed using multiplexed electrochemiluminescent immunoassays (Meso-Scale Discovery, Gaithersburg, MD) as previously described [14].

Pharmacokinetic parameters including the area under the concentration–time curve (AUC) and the maximum and minimum observed plasma concentrations (C_{\max} and C_{\min}) were estimated using standard noncompartmental methods with WinNonlin software (version 5.1.1, Pharsight Corporation, Mountain View, CA). The effect of motesanib on exposure to paclitaxel and docetaxel was investigated by calculating the ratio point estimates for the geometric least

square mean (GLSM) values (90 % CI) of C_{\max} and $AUC_{0-\infty}$ for motesanib plus paclitaxel versus paclitaxel alone (day 8 vs. 1) and motesanib plus docetaxel versus docetaxel alone (cycle 2 vs. 1) using SAS PROC Mixed procedure (SAS for Windows, version 9.1, WIN_PRO platform; SAS Institute, Inc.). Specifically, GLSM ratios were calculated by estimating the difference in the least squares means for log-transformed C_{\max} and $AUC_{0-\infty}$; the ratios were then converted back to their original scale.

Tumor-response assessment

Tumor response was assessed with either computed tomography or magnetic resonance imaging within 28 days of enrollment and every 2 cycles: every 8 ± 1 weeks in Arm A and every 6 ± 1 weeks in Arm B. Bone scans were performed every 12 ± 1 weeks if bone metastases were present at baseline and at any time of clinical suspicion in other patients. Tumor response was assessed by investigators per modified RECIST v1.0 [12].

Statistical analyses

Safety was evaluated among all patients who received ≥ 1 dose of motesanib. Tumor responses were recorded for all patients with measurable disease at baseline. Duration of response was calculated as the time from the first objective response to disease progression or death. Patients who responded and did not progress or die while on study were censored on the date of their last assessment. Progression-free survival (PFS) was calculated as the time from the first day of study treatment and the date when disease progression was determined or death. Patients who had not died and did not have an assessment of disease progression were censored.

Results

Patients

Forty-six patients were enrolled between May 2006 and August 2008. One patient was screened but withdrew consent before receiving study treatment. Forty-five patients received ≥ 1 dose of motesanib. Patient demographics and baseline characteristics are summarized in Table 1.

Forty-two patients discontinued motesanib because of disease progression ($n = 23$, 50 %), AE ($n = 15$, 33 %), administrative decision ($n = 2$, 4 %), and withdrawal of consent ($n = 2$, 4 %). Three patients were receiving motesanib at the time of data analysis. Ten of 19 patients in cohort B2 and 8/12 patients in cohort B3 had dose

Table 1 Patient demographics and baseline characteristics

	All patients (<i>N</i> = 45)
Race, <i>n</i> (%)	
White	41 (91)
Black/African American	2 (4)
Asian	1 (2)
Other	1 (2)
Age, median (range)	51.0 (28–81)
Estrogen receptor status, <i>n</i> (%)	
Positive	14 (31)
Negative	2 (4)
Unknown	29 (64)
Progesterone receptor status, <i>n</i> (%)	
Positive	12 (27)
Negative	4 (9)
Unknown	29 (64)
HER2 status, <i>n</i> (%)	
Positive	3 (7)
Negative	15 (33)
Unknown	27 (60)
ECOG performance status, <i>n</i> (%)	
0	28 (62)
1	17 (38)
Number of sites of disease ^a , <i>n</i> (%)	
1	19 (42)
2	19 (42)
≥3	7 (15)
Patients with prior chemotherapy ^b , <i>n</i> (%)	
Adjuvant	32 (71)
For metastatic disease ^c	5 (11)
Patients with prior hormonal therapy, <i>n</i> (%)	
Adjuvant	19 (42)
For metastatic disease	14 (31)
Patients with prior radiotherapy, <i>n</i> (%)	31 (69)

Safety analysis set: all patients who received at least 1 dose of motesanib

ECOG Eastern Cooperative Oncology Group, HER2 human epidermal growth factor receptor 2

^a Per investigator assessment (data unavailable for 1 patient in Arm A)

^b No patient received prior neoadjuvant treatment

^c Patients received 1 course of prior chemotherapy

reductions during the study; dose reductions were not required in other cohorts. The median follow-up time was 29.5 weeks (range 1–94 weeks).

DLTs and MTD

Five patients received motesanib 50 mg QD plus paclitaxel 90 mg/m² (Cohort A1), and 5 received motesanib 50 mg QD plus docetaxel 100 mg/m² (Cohort B1). None of these

patients had a DLT; therefore, 5 patients were enrolled into Cohort A2 and received motesanib 125 mg QD plus paclitaxel 90 mg/m² and 19 were enrolled into Cohort B2 and received motesanib 125 mg QD plus docetaxel 100 mg/m². There were no DLTs in Cohort A2; DLTs occurred in 3 patients (16 %) in Cohort B2, 2 with grade 3 fatigue >7 days and 1 with grade 3 migraine. Motesanib 125 mg QD was, therefore, established as the MTD, and 12 additional patients were enrolled into Cohort B3 and received motesanib 125 mg QD plus docetaxel 75 mg/m²; no DLTs occurred in this cohort.

Adverse events

All 45 patients experienced ≥1 treatment-emergent AE during the study, of whom 29 (64 %), 6 (13 %), and 2 (4 %) had grade 3, 4, or 5 events, respectively. Grade 4 AEs included neutropenia (Cohort A2, 1 patient; Cohort B2, 2 patients; and Cohort B3, 1 patient), pneumonia and acute respiratory failure (Cohort B2, 1 patient), and pyrexia (Cohort B3, 1 patient). Grade 5 AEs occurred in 1 patient (Cohort B1) who experienced grade 4 thrombocytopenia, influenza, and neutropenic sepsis and later died of bronchopneumonia; and 1 in Cohort B2 who experienced grade 3 migraine, hypertension, fatigue, diplopia, asthenia, hyperbilirubinemia, and decreased level of consciousness (after a fall) and died of multiorgan failure. None of the grade 4 or 5 AEs were considered related to treatment with motesanib.

Forty patients (89 %) experienced ≥1 motesanib-related treatment-emergent AE, 19 of whom (42 %) had grade 3 motesanib-related AEs, the most common being fatigue and diarrhea (Table 2). The incidence of grade 3 motesanib-related AEs was approximately 2-fold higher among patients who received motesanib 125 mg QD versus 50 mg QD.

Twenty-seven patients (60 %) had treatment-emergent AEs of interest deemed related to motesanib, 7 of whom (16 %) had grade 3 AEs (Table 2). The patients with grade 3 cholecystitis, grade 3 decreased ejection fraction, or grade 3 increased blood amylase were removed from the study. The 2 patients with hypertension had recurrent hypertension (despite medication) and had their dose of motesanib altered. Each of these AEs occurred after the DLT assessment window.

Grade 2 hypertension deemed related to motesanib was observed in 9 patients; 2 had recurrent hypertension, and 1 was removed from the study.

Pharmacokinetics of motesanib, paclitaxel, and docetaxel

Motesanib AUC, *C*_{max}, and *C*_{min} values were comparable to those observed in previous studies (Fig. 2). Pharmacokinetic

Table 2 Motesanib-related AEs and events of interest

	Arm A Motesanib + paclitaxel 90 mg/m ²		Arm B Motesanib + docetaxel 100 mg/m ²		Arm B Motesanib + docetaxel 75 mg/m ²	All patients N = 45
	Cohort A1 50 mg QD (n = 5)	Cohort A2 125 mg QD (n = 5)	Cohort B1 50 mg QD (n = 4)	Cohort B2 125 mg QD (n = 19)	Cohort B3 125 mg QD (n = 12)	
Patients with any motesanib-related AE, n (%) ^a	4 (80)	4 (80)	4 (100)	17 (89)	11 (92)	40 (89)
Patients with any motesanib-related AE of worst grade 3, n (%) ^b	1 (20)	2 (40)	1 (25)	9 (47)	6 (50)	19 (42)
Diarrhea	0	0	0	3 (16)	3 (25)	6 (13)
Fatigue	0	1 (20)	0	3 (16)	1 (8)	5 (11)
PPES	0	0	0	2 (11)	0	2 (4)
Anticoagulation drug level elevated	0	1 (20)	0	0	0	1 (2)
Arthralgia	0	1 (20)	0	0	0	1 (2)
Eczema	0	0	0	1 (5)	0	1 (2)
Hypokalemia	0	0	0	1 (5)	0	1 (2)
Lethargy	0	0	0	1 (5)	0	1 (2)
Migraine	0	0	0	1 (5)	0	1 (2)
Patients with any motesanib-related AE of interest of worst grade 3, n (%) ^b	1 (20)	1 (20)	1 (25)	2 (11)	2 (17)	7 (16)
Cholecystitis	0	1 (20)	1 (25)	0	0	2 (4)
Hypertension	1 (20)	0	0	1 (5)	0	2 (4)
ALT increased	0	0	0	1 (5)	1 (8)	2 (4)
Deep vein thrombosis	0	1 (20)	0	0	0	1 (2)
Ejection fraction decreased	0	0	0	0	1 (8)	1 (2)
Blood amylase increased	1 (20)	0	0	0	0	1 (2)

AE adverse event, ALT alanine aminotransferase, CTCAE Common Terminology Criteria for Adverse Events, MedDRA Medical Dictionary of Regulatory Activities, PPES palmar-plantar erythrodysesthesia syndrome

^a MedDRA preferred terms, grade based on CTCAE version 3.0

^b Some AEs occurred in the same patient

parameters are shown in Table 3. Coadministration of motesanib with paclitaxel increased paclitaxel C_{max} by 23–45 % and increased paclitaxel AUC_{0-inf} by 18–28 %. Coadministration of motesanib with docetaxel did not affect docetaxel C_{max} or docetaxel AUC_{0-inf} in Cohort B2; however, the data in Cohorts B1 and B3 showed high variability (GLSM values ranging from 0.98 to 2.47) due to 1 patient in each cohort with unusually high exposures during Cycle 2. Excluding these patients from the analysis, coadministration of motesanib did not appear to markedly affect docetaxel exposure in Cohort B1, although C_{max} increased 53 % and AUC_{0-inf} decreased 19 % in Cohort B3.

Pharmacodynamic biomarkers

PLGF concentrations in the serum increased 24 h after initiation of motesanib. In all analyzed cohorts,

approximately 3-fold increases from baseline in PLGF were maintained during treatment (Fig. 3a). VEGF concentrations in the serum also increased after initiation of motesanib; however, the magnitude of this increase was smaller than the change in PLGF, and it was transient (Fig. 3b).

Tumor response

Thirty-two patients (71 %) had measurable disease at baseline, and among the 31 assessed for tumor response, 30 experienced a decrease from baseline (Fig. 4). Overall, 18 of 32 patients (56 %) achieved a confirmed partial response, 12 (38 %) had stable disease (4 for ≥ 24 weeks), and 1 had progressive disease (Table 4). A higher incidence of partial responses was observed among patients who received the highest dose of motesanib: 3 of 4 in

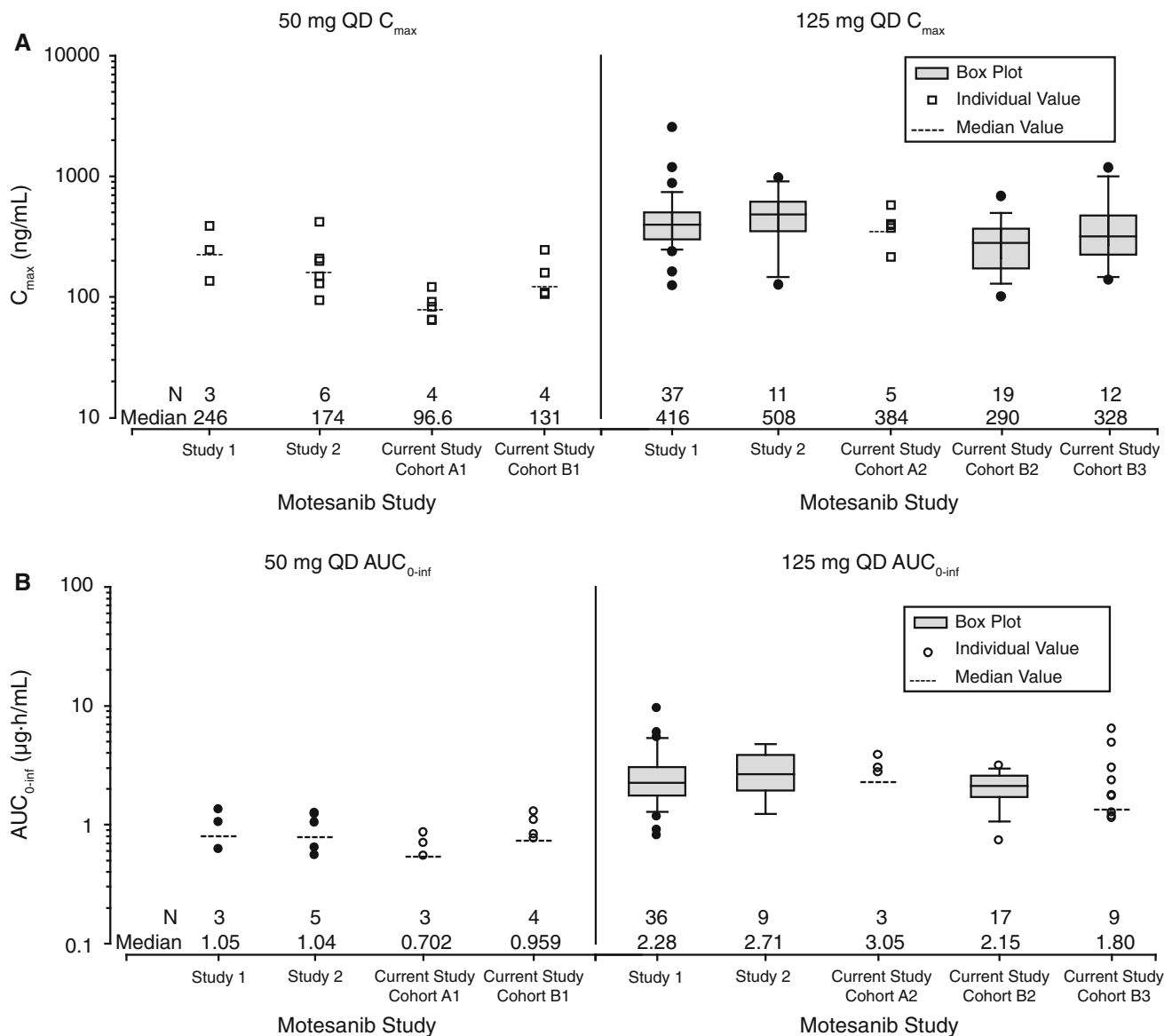


Fig. 2 Comparison of motesanib C_{max} (a) and AUC_{0-inf} (b) values during cycle 1 with C_{max} and AUC_{0-inf} values obtained from previous motesanib studies. Study 1 is the first-in-human study of motesanib in

Cohort A2, 8 of 13 in Cohort B2, and 5 of 9 in Cohort B3. The clinical benefit rate (complete response + partial response + stable disease ≥ 24 weeks) was 69 %. The Kaplan–Meier estimate of the median duration of response was between 5 and 6.3 months (Table 4). Of the 13 patients with nonmeasurable disease at baseline, 10 had stable disease, 5 with stable disease ≥ 24 weeks, and 2 had progressive disease (Table 4).

Progression-free survival

At the time of this analysis, 29 patients had had PFS events (Cohort A1, $n = 3$; A2, $n = 1$; B1, $n = 3$, B2, $n = 14$, B3, $n = 17$). The median PFS (95 % CI) was 9.3 (3.1–21.0),

patients with advanced solid tumors [7]; study 2 is the phase 1b study of motesanib in combination with chemotherapy or panitumumab in patients with NSCLC [9]

5.9 (3.4–not estimable), 6.3 (4.5–7.6), and 11.3 (5.2–12.5) months for Cohorts A1, B1, B2, and B3, respectively. Because only 1 PFS event occurred in Cohort A2 before the data cutoff, median PFS could not be evaluated for this cohort. Among the other 4 patients, 1 had a PFS event at 5.7 months, and the other 3 were on study for 5.6, 15.0, and 15.2 months without progression.

Discussion

A number of anti-VEGF pathway agents have been shown to improve outcomes for patients with MBC when used in combination with conventional chemotherapy [5]. In this

Table 3 GLSM point estimates for the ratios of paclitaxel or docetaxel C_{max} and AUC_{0-inf} in patients treated with motesanib plus paclitaxel or docetaxel, versus paclitaxel or docetaxel alone

Descriptive statistic	C_{max} (ng/mL)	AUC_{0-inf} ($\mu\text{g} \cdot \text{h/mL}$)
Cohort A1: 50 mg motesanib + 90 mg/m ² paclitaxel		
<i>N</i>	5	5
GLSM	1.23	1.18
90 % CI	0.91–1.65	1.00–1.39
Cohort A2: 125 mg motesanib + 90 mg/m ² paclitaxel		
<i>N</i>	5	4–5
GLSM	1.45	1.28
90 % CI	1.12–1.87	1.16–1.40
Cohort B1: 50 mg motesanib + 100 mg/m ² docetaxel		
<i>N</i>	3–4	3–4
GLSM	2.47 ^a	1.52 ^a
90 % CI	0.88–6.89	0.67–3.43
Cohort B2: 125 mg motesanib + 100 mg/m ² docetaxel		
<i>N</i>	14–19	14–19
GLSM	0.97	0.97
90 % CI	0.72–1.29	0.77–1.22
Cohort B3: 125 mg motesanib + 75 mg/m ² docetaxel		
<i>N</i>	12	10–11
GLSM	1.90 ^b	0.98 ^b
90 % CI	1.17–3.08	0.61–1.56

AUC area under the concentration–time curve, C_{max} maximum observed plasma concentration, *GLSM* geometric least square mean

^a High Cycle 2 mean docetaxel C_{max} and AUC_{0-inf} values and GLSM ratios were obtained from 1 patient. When this patient is excluded from the analysis, the resulting point estimates (90 % CIs) for the C_{max} and AUC_{0-inf} ratios are 1.03 (0.86–1.24) and 0.82 (0.59–1.13), respectively

^b High Cycle 2 mean docetaxel C_{max} and AUC_{0-inf} values and GLSM ratios were obtained from 1 patient. When this patient is excluded from the GLSM analysis, the resulting point estimates (90 % CIs) for C_{max} and AUC_{0-inf} ratios are 1.53 (1.16–2.01) and 0.81 (0.62–1.05), respectively

phase 1b study, 45 patients with MBC received 2 different doses of motesanib in combination with either paclitaxel or docetaxel. No new safety signals were observed beyond those already demonstrated in prior phase 1 studies with single-agent motesanib. The MTD of motesanib in combination with either paclitaxel or docetaxel was 125 mg QD, consistent with that reported for single-agent motesanib in patients with advanced solid tumors [7] and in combination with platinum-containing chemotherapy and/or panitumumab in patients with NSCLC [9].

In this study, AEs were noted that have been observed in previous motesanib clinical trials: hypertension, deep vein thrombosis, and cholecystitis. Of note, hypertension, thromboembolic events, and bleeding events are known effects of VEGF(R) inhibitors [15]. In this study, 2 patients

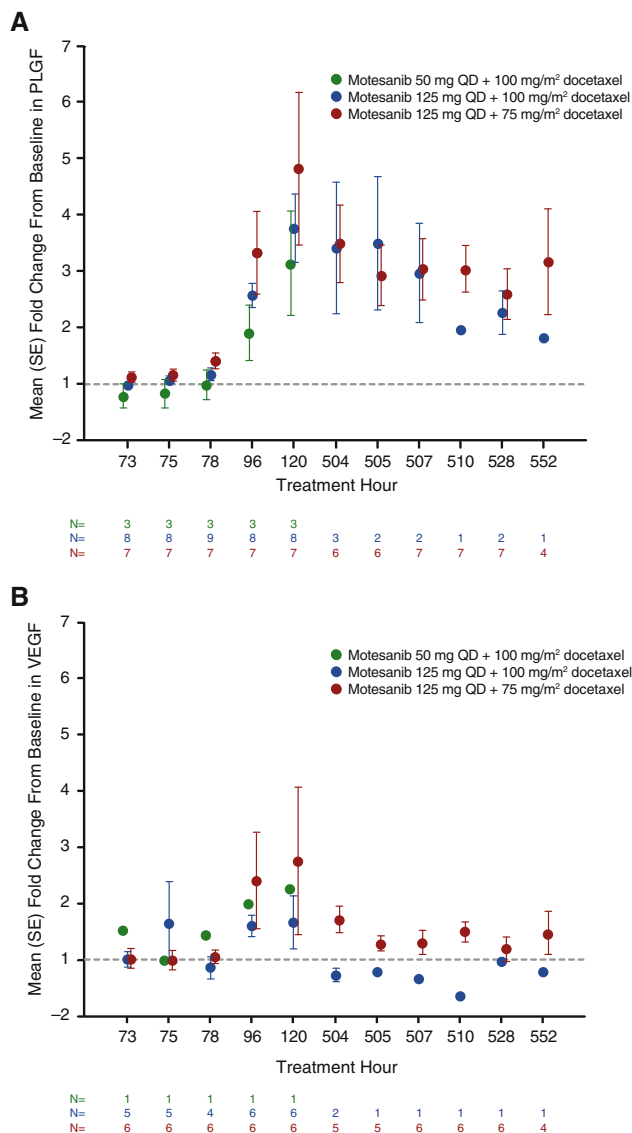


Fig. 3 Mean (\pm SE) fold change from baseline in PLGF (a) and VEGF (b) among patients receiving motesanib in combination with paclitaxel or docetaxel. No error bars are shown where only 1 or 2 samples were evaluable for a particular time point

(4 %) experienced grade 3 hypertension that resulted in dose modifications. The incidence of grade 3 hypertension was less than that observed in the motesanib phase 1b NSCLC trial [9] and in a phase 3 trial of bevacizumab combined with paclitaxel in MBC [16] and the same as that observed in a phase 2 trial of bevacizumab in combination with docetaxel in MBC [17]. The overall incidence of grade ≥ 3 thromboembolic events (2 %) was less than observed in the motesanib phase 1b NSCLC trial and similar to that observed in the aforementioned bevacizumab studies. There were no grade ≥ 3 bleeding events in the current trial; grade 1 epistaxis was observed, occurring in 22 % of patients overall.

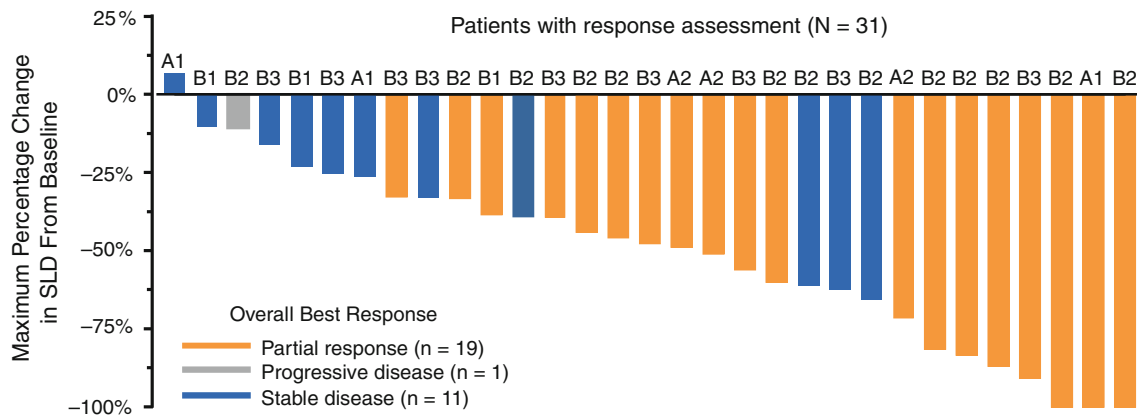


Fig. 4 Change from baseline in tumor measurements among patients with measurable disease at baseline. Cohorts: *A1* motesanib 50 mg QD + paclitaxel 90 mg/m²; *A2* motesanib 125 mg QD + paclitaxel 90 mg/m²; *B1* motesanib 50 mg QD + docetaxel 100 mg/m²; *B2* motesanib 125 mg QD + docetaxel 100 mg/m²; *B3* motesanib 125 mg QD + docetaxel 75 mg/m². One patient in Cohort *A2* had no response assessment. *SLD* sum of longest diameters

Table 4 Objective tumor response

	Arm A Motesanib + paclitaxel 90 mg/m ²		Arm B Motesanib + docetaxel 100 mg/m ²		Arm B Motesanib + docetaxel 75 mg/m ² Cohort B3 125 mg QD (n = 12)	All patients (N = 45)
	Cohort A1 50 mg QD (n = 5)	Cohort A2 125 mg QD (n = 5)	Cohort B1 50 mg QD (n = 4)	Cohort B2 125 mg QD (n = 19)		
Patients with measurable disease at baseline, n (%)	3 (60)	4 (80)	3 (75)	13 (68)	9 (75)	32 (71)
Tumor response ^a , n (%)						
Confirmed PR	1 (33)	3 (75)	1 (33)	8 (62)	5 (56)	18 (56)
SD	2 (67)	0	2 (67)	4 (31)	4 (44)	12 (38)
Durable SD ≥ 24 weeks	0	0	0	2 (15)	2 (22)	4 (13)
PD	0	0	0	1 (8)	0	1 (3)
Clinical benefit rate ^b , n (%)	1 (33)	3 (75)	1 (33)	10 (77)	7 (78)	22 (69)
Duration of response, median months ^c , (range)	5.6	NE (4.0–11.5+)	5.9	5.0 (2.3–12.7)	6.3 (2.4+ to 10.4)	5.7 (2.3–12.7)
Patients with nonmeasurable disease at baseline	2 (40)	1 (20)	1 (25)	6 (32)	3 (25)	13 (29)
Tumor response ^d , n (%)						
SD	2 (100)	1 (100)	1 (100)	5 (83)	1 (33)	10 (77)
Durable SD ≥ 24 weeks	1 (50)	1 (100)	1 (100)	2 (33)	0 (0)	5 (38)
PD	0 (0)	0 (0)	0 (0)	1 (17)	1 (33)	2 (15)
Clinical benefit rate ^b , n (%)	1 (50)	1 (100)	1 (100)	2 (33)	0 (0)	5 (38)

NE not estimable, PD progressive disease, PR partial response, QD once daily, SD stable disease

^a No response assessment data were available or response was reported as “unknown” for 1 patient in Cohort A2

^b Clinical benefit rate: PR + durable SD ≥ 24 weeks

^c Kaplan–Meier estimates. “+” indicates the value is a censoring time

^d One patient in Cohort B3 was not evaluable for tumor response

Grade 3 cholecystitis resulted in the discontinuation of treatment for 2 (4 %) patients in the study. Cholecystitis was previously reported in a phase 1b study that evaluated motesanib in NSCLC [9] and in a study with the VEGFR inhibitor sunitinib in renal cell carcinoma [18]. The etiology of this toxicity is not known, and patients should be evaluated to exclude preexisting gallbladder abnormalities before receiving motesanib and monitored for unexpected abdominal symptoms.

Paclitaxel and docetaxel had minimal effects on the pharmacokinetics of motesanib. Similarly, paclitaxel had minimal effect on motesanib pharmacokinetic parameters in patients with NSCLC [9]. In this study, paclitaxel C_{\max} and $AUC_{0-\text{inf}}$ values were generally higher (20–45 %) after exposure to motesanib. Similar results were observed at the 125-mg QD motesanib dose in patients with NSCLC [9]. This effect may be due to the mild inhibitory effects of motesanib on cytochrome P450 3A4 [19], which is involved in the metabolism of paclitaxel [20, 21]. Despite this effect, there appeared to be no impact on paclitaxel-related toxicities. Docetaxel $AUC_{0-\text{inf}}$ values were generally similar, with or without coadministration of motesanib. In contrast, docetaxel C_{\max} values were higher after exposure to motesanib in some patients likely due in part to differences in the infusion duration: the median infusion duration was slightly shorter during cycle 2 versus 1 for some patients, particularly in those in Cohort B3. Due to high interpatient variability, these results should be interpreted with caution.

The biomarker analysis showed a sustained increase in PLGF in response to motesanib treatment. These data are consistent with previous biomarker analyses of motesanib studies in various tumor types, including breast cancer [14, 22, 23]. One of those studies initially showed evidence suggesting that change in PLGF may be a predictor of response to motesanib treatment in patients with MBC [22]. However, in the large phase 3 MONET1 study of motesanib plus carboplatin/paclitaxel in patients with nonsquamous NSCLC, which prospectively assessed associations between change in PLGF and overall survival, no association between PLGF change and outcomes was identified [24].

Although the patient numbers in our study were small, the objective response rate of 56 % among patients with measurable disease is promising. To put this result into perspective, a phase 3 study of bevacizumab plus paclitaxel in previously untreated patients with MBC reported a response rate of 49.2 % among patients with measurable disease [16]. In addition, bevacizumab plus paclitaxel prolonged median PFS compared with paclitaxel alone (11.8 vs. 5.9 months) [16].

More recently, the results of 3 large phase 3 placebo-controlled trials in patients with human epidermal growth factor receptor 2-negative MBC were reported: bevacizumab or placebo plus docetaxel (AVADO) [25], bevacizumab or

placebo plus anthracycline- or taxane-based chemotherapy or capecitabine (RIBBON-1) [26], and motesanib or bevacizumab or placebo plus paclitaxel (TRIO 010) [27]. The results of AVADO and RIBBON-1 showed that the addition of bevacizumab resulted in a statistically significant, although modest (1.0–2.9 months), prolongation of PFS. In TRIO 010, the addition of motesanib did not statistically significantly improve objective response rate in comparison to paclitaxel alone, although there was a trend toward superiority, favoring motesanib plus paclitaxel (49 %) and bevacizumab plus paclitaxel (52 %) compared with single-agent paclitaxel (41 %).

Despite the somewhat disappointing results of AVADO, RIBBON-1, and TRIO 010, VEGF(R) inhibitors have proven benefit in other human cancers. Further, a benefit of antiangiogenesis therapies clearly exists in breast cancer and remains an area of active investigation. Motesanib inhibits VEGFR1, VEGFR-2, and VEGFR-3 as well as PDGFR and Kit, potentially offering additional benefit not only by blocking angiogenesis but also by reducing lymphangiogenesis, and potentially tumor growth [28–31].

In summary, in the present phase 1b study, motesanib in combination with taxanes was tolerable and showed a high response rate in this population of patients with MBC. These data warrant further exploration of motesanib in the treatment of patients with breast cancer.

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Ethical standards The experiments as described in this manuscript comply with the current laws of the countries in which they were performed.

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