Combination of Tivozanib (AV-951) With Weekly Paclitaxel for Metastatic Breast Cancer: Results of a Phase 1 Study

E. L. Mayer,[1,*] M. E. Scheulen,[2] J. Beckman,[3] H. Richly,[2] A. Poli,[4] P. Bhargava,[1,4] A. Duarte,[4] M. M. Cotreau,[4] W. Yin,[4] A. L. Strahs,[4] W. Slichenmyer,[4] M. N. Dickler[5]

[1]*Dana-Farber Cancer Institute, Boston, MA, USA;* [2]*Innere Klinik (Tumorforshung), West German Cancer Center, University of Essen Medical School, Essen, Germany;* [3]*Brigham and Women's Hospital, Boston, MA, USA;* [4]*AVEO Pharmaceuticals, Inc., Cambridge, MA, USA;* [5]*Memorial Sloan-Kettering Cancer Center, New York, NY, USA.*

*Presenting author.

Introduction

- Tivozanib (AV-951) is an oral, potent and selective small-molecule tyrosine kinase inhibitor designed to provide optimal blockade of the vascular endothelial growth factor (VEGF) pathway by inhibiting all 3 VEGF receptors (VEGFRs)
  - In cell-based models of published data, tivozanib has inhibitory activity against the VEGFR-1, -2, and -3 kinases at subnanomolar concentrations (IC_{50} of 0.21, 0.16, and 0.24 nM, respectively)[1]
- Results from a phase 1 study[1] demonstrated clinical response to tivozanib in multiple tumor types and determined a maximum tolerated dose (MTD) to be tivozanib 1.5 mg/day
- Results from a phase 2 trial[2] indicated that tivozanib has antitumor activity and a favorable safety profile in patients with advanced renal cell carcinoma
- Weekly paclitaxel is an active and commonly used regimen in the treatment of metastatic breast cancer (MBC)
- The combination of the anti-VEGF antibody bevacizumab and weekly paclitaxel has shown efficacy in the treatment of MBC[3]

Objectives

- To determine the safety, tolerability, and MTD of tivozanib when administered in combination with weekly paclitaxel in patients with MBC
- To evaluate the activity and pharmacokinetic (PK) profile of tivozanib and weekly paclitaxel combination therapy

Methods

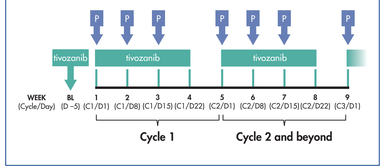
Key Eligibility Criteria

- Adults aged 18 years or older with MBC
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 with a life expectancy of at least 3 months
- Prior therapy
  - No more than 4 prior chemotherapy regimens in the adjuvant and/or metastatic settings
  - Only 1 prior taxane-based regimen for metastatic disease
  - No limit to the number of prior endocrine or biological treatments
  - No prior treatment with VEGFR tyrosine kinase inhibitors
  - No bevacizumab within 4 weeks prior to start of protocol
- No symptomatic central nervous system metastases and no baseline grade >1 neuropathy
- No significant cardiovascular disease, uncontrolled hypertension, or myocardial infarction within 3 months

Study Design

- Phase 1b, open-label, multicenter study of tivozanib combined with weekly paclitaxel

Figure 1. Treatment schedule.



P, paclitaxel; BL, baseline; D, day; C, cycle.

- Treatment schedule (**Figure 1**)
  - Tivozanib was administered orally once daily for 3 weeks, followed by a 1-week break (4 weeks = 1 cycle)
  - Paclitaxel was administered intravenously once weekly starting on Day 1 of Cycle 1 and continuing on Days 8 and 15, followed by a 1-week break
  - A single dose of tivozanib was administered 5 (± 2) days prior to the start of combination dosing to characterize the tivozanib PK
- A standard 3 + 3 dose escalation design was used (**Table 1**); enrollment to the next dose level occurred only after acceptable tolerability was demonstrated

Table 1. Dose Levels

Dose level	Tivozanib dose	Paclitaxel dose	No. of patients enrolled
1	0.5 mg/day	90 mg/m^2 weekly	7
2	1.0 mg/day	90 mg/m^2 weekly	4
3	1.5 mg/day	90 mg/m^2 weekly	7

- The MTD was defined as the maximum dose at which no more than 1 patient experienced a dose-limiting toxicity (DLT), defined as
  - Grade 3 non-hematologic toxicity lasting more than 3 days despite supportive care or any grade 4 non-hematologic toxicity
  - Grade 3 aminotransferase elevation lasting at least 1 week
  - Grade 3/4 neutropenia associated with fever and requiring antibiotics or grade 4 neutropenia lasting more than 5 days
  - Toxicity of any grade that results in treatment interruption for more than 2 weeks
- Weekly paclitaxel 90 mg/m^2 has been validated in MBC.[3,4] To reduce hypersensitivity reactions with paclitaxel, patients were pretreated with corticosteroids, antihistamines, and/or H_2 receptor antagonists

Study Endpoints

- Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0
- Antitumor activity was evaluated using standard Response Evaluation Criteria In Solid Tumors (RECIST) criteria, version 1.0
  - Patients were evaluable for efficacy if they received at least 2 cycles of treatment or discontinued due to progressive disease prior to completion of Cycle 2
  - Disease assessment was repeated after every 2 cycles, and responses were confirmed by a repeat evaluation at least 4 weeks after the criteria were first met
- Blood samples for PK analyses were collected at baseline for tivozanib (Day –5, prior to tivozanib dosing and at 1, 2, 4, 8, and 24 hours post-dose), and during Cycles 1 and 2 for both tivozanib and paclitaxel (Days 1, 2, 8, 15, and 22 for Cycle 1; Days 1, 15, and 22–28 for Cycle 2)

Results

Patients

- A total of 18 patients with MBC were enrolled between February 2009 and December 2009, received at least 1 dose of study medication, and were evaluable for both toxicity and efficacy assessments (**Table 2**)

Safety and Tolerability

- Two patients experienced DLTs during the study
  - Dose level 1 (tivozanib 0.5 mg/day): grade 1 palpitations
  - Dose level 3 (tivozanib 1.5 mg/day): grade 2 asymptomatic pneumoperitoneum
  - The MTD was identified as tivozanib 1.5 mg/day with paclitaxel 90 mg/m^2 weekly

Table 2. Patient Demographic

Characteristic	N = 18
Median age (range), y	48 (32–65)
Race, n (%)	
White	16 (89)
Other	2 (11)
ECOG Performance Status, n (%)	
0	13 (72)
1	5 (28)
2	0
Median time since diagnosis (range), y	4.5 (1.5–21)
Receptor status,[a] n (%)	
ER/PR-positive	10 (56)
HER2-positive	4 (22)
ER-negative/PR-negative/HER2-negative	7 (39)
Median no. of prior metastatic regimens (range)	2 (0–4)
Prior treatment, n (%)	
Taxanes	18 (100)
Adjuvant	11 (61)
Neoadjuvant	3 (17)
Metastatic	4 (22)
Bevacizumab	10 (56)
Trastuzumab/lapatinib	5 (28)
Radiotherapy	14 (78)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.
[a]Three patients were ER/PR-positive and HER2-positive.

- The most commonly reported treatment-emergent adverse events for all grades and cohorts are shown in **Table 3**
  - The incidence of rash was low, with 1 patient each experiencing follicular rash, papular rash, and urticaria

Table 3. Treatment-emergent Adverse Events in ≥20% of Patients, Any Causality

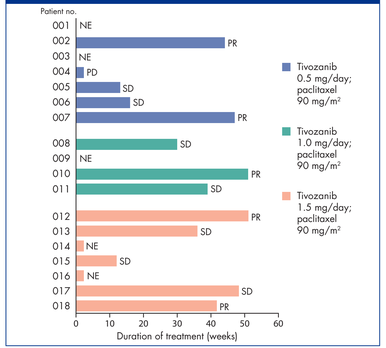
Adverse event, n (%)	All grades (N = 18)	Grade ≥3 (N = 18)
Fatigue	14 (78)	3 (17)
Alopecia	9 (50)	1 (6)
Diarrhea	8 (44)	2 (11)
Nausea	8 (44)	0
Peripheral sensory neuropathy	8 (44)	0
Cough	7 (39)	0
Hypertension	7 (39)	2 (11)
Vomiting	7 (39)	0
Stomatitis	6 (33)	1 (6)
Headache	5 (28)	0
Neutropenia	5 (28)	3 (17)
Back pain	4 (22)	2 (11)
Constipation	4 (22)	0
Dyspepsia	4 (22)	0
Epistaxis	4 (22)	0
Flatulence	4 (22)	0
Peripheral edema	4 (22)	0
Polyneuropathy	4 (22)	1 (6)
Pyrexia	4 (22)	0

- Grade 4 lumbar compression fracture and hip fracture were reported for 1 patient; no other grade 4 events were reported
- Two patients enrolled at dose level 3 developed grade 3 hypertension, leading to tivozanib dose reduction in 1 patient. Both patients were subsequently well controlled with antihypertensive medication
- Dose interruptions of tivozanib and/or paclitaxel due to adverse events were required for 7 patients
- Treatment discontinuations due to adverse events were reported for 3 patients at dose level 1 (lumbar compression fracture, palpitations, superior vena cava syndrome) and 2 patients at dose level 3 (pneumoperitoneum/increased neutrophil count, shortness of breath)
- Two deaths occurred during the study from causes unrelated to study treatment
  - One patient died due to respiratory distress and hip fracture 26 days after the last dose of study medication
  - One patient died due to tumor-related causes 68 days after the last dose of study medication

Efficacy

- Median duration of tivozanib treatment was 5.4 months (range, 0–12.0 months); individual treatment durations are shown in **Figure 2**
  - Five patients received less than 2 cycles of treatment and were not evaluable for efficacy

Figure 2. Duration of treatment.



NE, not evaluable; PR, partial response; PD, progressive disease; SD, stable disease.

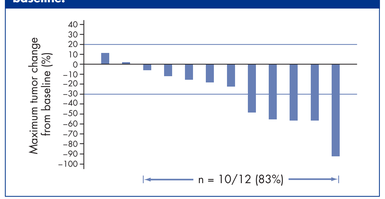
- Among the 13 patients evaluable for efficacy, the objective response rate was 38% (95% confidence interval, 13.9%–68.4%; **Table 4** and **Figure 3**)
  - Partial response was achieved by 2 of 5 evaluable patients at dose level 1, by 1 of 3 evaluable patients at dose level 2, and by 2 of 5 evaluable patients at dose level 3
- Stable disease was achieved by 54% of patients, with a median duration of 8.5 months (range, 4.2–10.7 months)

Table 4. Best Overall Response

Response,[a] n (%)	n = 13
Objective response[b]	5 (38)
Complete response	0
Partial response	5 (38)[c]
Stable disease	7 (54)
Stable disease >24 weeks	4 (31)
Progressive disease	1 (8)

[a]Using standard Response Evaluation Criteria In Solid Tumors.
[b]Objective response = complete + partial response.
[c]Unconfirmed response in 1 patient.

Figure 3. Waterfall plot of maximum tumor change from baseline.

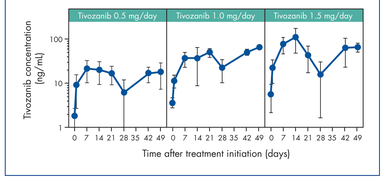


Maximum change in tumor size from baseline was not available for 6 patients, including 1 patient who was evaluable for efficacy but did not have a post-baseline assessment for change in tumor size.

Pharmacokinetics

- Because of the limited PK sampling specified in this study protocol, it was not possible to calculate PK parameters from these data, including the half-life, maximal concentration, and area under the curve
- Tivozanib serum concentrations on Day 22 of Cycle 1 in this study are similar to those reported in prior tivozanib monotherapy trials,[1,5] indicating no influence of paclitaxel on steady-state levels of tivozanib (**Table 5** and **Figure 4**)

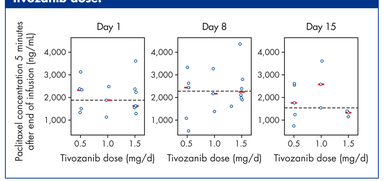
Figure 4. Mean (± SD) tivozanib concentration-time profiles after Day 1, Cycle 1.



SD, standard deviation.

- The tivozanib PK parameters obtained prior to the start of combination dosing were also consistent with previously reported values[1,5]
- Mean (± standard deviation) maximal concentrations (C_{max}) of paclitaxel were 2,032 ng/mL (± 705 ng/mL; n = 15) for Day 1; 2,311 ng/mL (± 979 ng/mL; n = 15) on Day 8; and 1,865 ng/mL (± 858 ng/mL; n = 11) on Day 15, consistent with previously reported values[6,7]
  - Tivozanib appears to have no effect on paclitaxel concentration (**Figure 5**)

Figure 5. Normalized paclitaxel concentration versus tivozanib dose.



Dashed line is overall median concentration on each visit, and short lines are the group medians. Data points are jittered to display overlapping points.

Conclusions

- **The combination of tivozanib and weekly paclitaxel was tolerable at all dose levels, supporting combination at the full dose and schedule of both agents (tivozanib 1.5 mg/day and paclitaxel 90 mg/m^2 weekly)**
- **The side effect profile was manageable; the most common adverse events included fatigue, alopecia, diarrhea, nausea, and peripheral sensory neuropathy**
- **There was no indication that drug-related adverse events associated with this combination were more frequent or severe than those observed with either tivozanib or paclitaxel alone**
- **Encouraging evidence of clinical activity was observed in this small, heavily pretreated MBC patient population, with an objective response rate of 38%**
- **The PK data suggest no influence of paclitaxel on circulating levels of tivozanib or of tivozanib on paclitaxel clearance**
- **These data support further evaluation of tivozanib plus paclitaxel at their full recommended doses in MBC**

References

1. Eskens FALM, et al. In: *Proceedings of the 99th Annual Meeting of the AACR*. Philadelphia, PA: American Association of Cancer Research; 2008. Abstract LB-201.
2. Nosov DA, et al. Poster presented at: *Annual Meeting of the American Society of Clinical Oncology*; June 3–7, 2011; Chicago, IL. Abstract 4550.
3. Miller K, et al. *N Engl J Med*. 2007;357(26):2666-2676.
4. Eniu A, et al. *Oncologist*. 2005;10(9):665-685.
5. Cotreau MM, et al. *Clin Pharmacol Ther*. 2011;89(suppl 1):S49. Abstract PII-36.
6. Mross K, et al. *Onkologie*. 2002;25(6):503-508.
7. Mross K, et al. *Cancer Chemother Pharmacol*. 2000;45(6):463-470.

Acknowledgments

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Table 5. Serum Concentrations of Tivozanib on Cycle 1, Day 22

Tivozanib dose, mg		Current study Cycle 1, Day 22 n	Current study Cycle 1, Day 22 Tivozanib concentration, ng/mL	Phase 1 study (solid tumors)[1] Cycle 1, Day 22 n	Phase 1 study (solid tumors)[1] Cycle 1, Day 22 Tivozanib concentration, ng/mL	Phase 2 study (RCC)[5] Cycle 1, Day 22 n	Phase 2 study (RCC)[5] Cycle 1, Day 22 Tivozanib concentration, ng/mL
0.5	Mean (± SEM)	4	16.6 (3.7)		Not evaluated		Not evaluated
	Range		10.6–26.5				
1.0	Mean (± SEM)	4	41.8 (8.7)	14	30.7 (3.3)		Not evaluated
	Range		19.1–56.3		16.5–57.0		
1.5	Mean (± SEM)	4	77.8 (28.8)	12	71.4 (15.6)	18	57.1 (5.5)
	Range		23.1–159.0		17.8–191.0		20.2–104.0

RCC, renal cell carcinoma; SEM, standard error of the mean.

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