Combination of Tivozanib, an Oral Inhibitor of Vascular Endothelial Growth Factor Receptors (VEGFRs), With Weekly Paclitaxel for Metastatic Breast Cancer: Preliminary Results of an Ongoing Phase 1 Study

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Introduction

- Tivozanib (AV-951) is a selective pan-vascular endothelial growth factor receptor (VEGFR) inhibitor with activity against the VEGFR-1, -2, and -3 kinases (IC_{50} of 0.21, 0.16, and 0.24 nM, respectively)[1]
- A phase 1 study demonstrated clinical responses to tivozanib in patients with multiple cancer types[1]
- Results from a phase 2 study indicated that tivozanib has antitumor activity and a favorable safety profile in patients with renal cell carcinoma[2]
- 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 maximum tolerated dose (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
- To evaluate the effect of combination therapy on vascular reactivity (flow-mediated vasodilation [FMD])

Methods

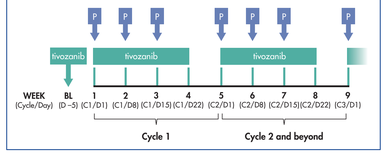
Key Eligibility Criteria

- Aged ≥18 years with MBC
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2 and life expectancy ≥3 months
- Prior therapy
  - No more than 4 prior chemotherapy treatments 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 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, multi-center 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 (1 cycle = 4 weeks)
  - 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 PKs
- 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/m² weekly	7
2	1.0 mg/day	90 mg/m² weekly	4
3	1.5 mg/day	90 mg/m² weekly	7

- MTD was defined as the maximum dose at which ≤1 patient experienced a dose-limiting toxicity (DLT), defined as
  - Grade 3 non-hematologic toxicity lasting >3 days despite supportive care or any grade 4 non-hematologic toxicity
  - Grade 3 aminotransferase elevations lasting ≥1 week
  - Grade 3 or 4 neutropenia associated with fever and requiring antibiotics or grade 4 neutropenia lasting >5 days
  - Toxicity of any grade that results in treatment interruption for >2 weeks
- Weekly paclitaxel 90 mg/m² has been validated in MBC.[3,4] To reduce DLTs with paclitaxel, patients were pretreated with corticosteroids, antihistamines, and/or H_2 receptor antagonists

Study Endpoints

- Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0
- Antitumor activity was evaluated using the standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.0. Disease assessment was repeated after every 2 cycles, and responses were confirmed by a repeat evaluation ≥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 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 ≥1 dose of study medication, and were evaluable for both toxicity and efficacy assessments (**Table 2**)

Safety

- Two patients experienced DLTs during the study
  - Dose level 1 (0.5 mg/day tivozanib): grade 1 palpitations
  - Dose level 3 (1.5 mg/day tivozanib): grade 2 asymptomatic pneumoperitoneum
  - The MTD was identified as tivozanib 1.5 mg/day with paclitaxel 90 mg/m² weekly

Table 2. Patient Demographics

Characteristic	N = 18
Median age (range), y	48 (32–65)
White race, n (%)	16 (89)
ECOG Performance Status, n (%)	
0	13 (72)
1	5 (28)
2	0
Receptor status, 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)
Metastatic	4 (22)
Neoadjuvant	3 (17)
Bevacizumab	10 (56)
Trastuzumab/lapatinib	5 (28)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

- The most commonly reported treatment-emergent AEs for all grades and cohorts are shown in **Table 3**
  - There was no indication that drug-related AEs associated with this combination were more frequent or severe than those observed with either tivozanib or paclitaxel alone

Table 3. Treatment-emergent Adverse Events (≥15% of Patients, Any Causality)

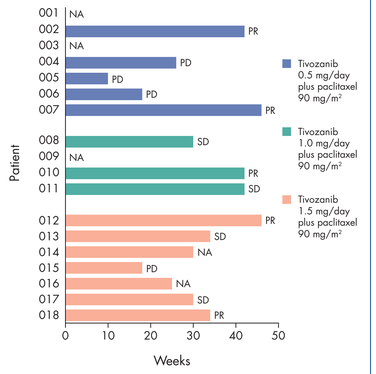
Adverse event, n (%)	All grades (N = 18)	Grade ≥3 (N = 18)
Fatigue	13 (72)	2 (11)
Diarrhea	8 (44)	2 (11)
Alopecia	8 (44)	1 (6)
Nausea	8 (44)	0
Hypertension	6 (33)	2 (11)
Cough	6 (33)	0
Vomiting	5 (28)	0
Neutropenia	4 (22)	2 (11)
Neuropathy	4 (22)	1 (6)
Constipation	4 (22)	0
Dyspepsia	4 (22)	0
Flatulence	4 (22)	0
Headache	4 (22)	0
Back pain	3 (17)	2 (11)
Leukopenia	3 (17)	1 (6)
Palpitations	3 (17)	1 (6)
Stomatitis	3 (17)	1 (6)
Bone pain	3 (17)	0
Dizziness	3 (17)	0
Dry skin	3 (17)	0
Dyspnea exertional	3 (17)	0
Epistaxis	3 (17)	0
Pyrexia	3 (17)	0

- Two patients developed grade 3 hypertension, leading to tivozanib dose reduction in 1 patient. Both patients were subsequently well controlled with anti-hypertensive medication
- Ten patients required dose interruptions of tivozanib
- Two patient deaths occurred during the study from causes not related to study treatment
  - One patient died due to grade 5 respiratory distress and grade 4 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 treatment was 22.2 weeks (5.5 cycles; range, 0.1–46.9 weeks), with 5 patients receiving ongoing therapy (**Figure 2**)

Figure 2. Duration of treatment.



NA, not available; PR, partial response; PD, progressive disease; SD, stable disease.

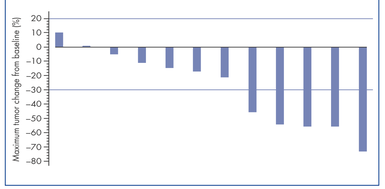
- The objective response rate was 28% and included 5 patients with confirmed partial response (**Table 4** and **Figure 3**)

Table 4. Best Overall Response

Response, n (%)	N = 18
Objective response	5 (28)
Complete response	0
Partial response	5 (28)
Stable disease ≥24 weeks	3 (17)
Clinical benefit[a]	8 (44)
Progressive disease	4 (22)
Not determined	5 (28)

[a]Clinical benefit includes patients with objective response and stable disease ≥24 weeks.

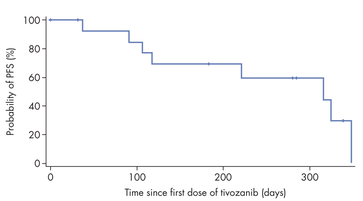
Figure 3. Waterfall plot of maximum tumor change.



Maximum tumor change from baseline was not available for 6 patients.

- Median progression-free survival was 10.4 months (316 days; range, 117–348 days; **Figure 4**)

Figure 4. Progression-free survival.



PFS, progression-free survival.

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 Cycle 1, Day 22 in this study are similar to those reported in prior tivozanib monotherapy trials,[1,2] indicating no influence of paclitaxel on steady-state levels of tivozanib (**Table 5**)

- PK data for paclitaxel were limited; however, pre-dose samples taken on Cycle 1, Days 8 and 15 were below quantitation limits (<10 ng/mL) for the majority of patients, indicating that tivozanib does not impair the clearance of paclitaxel
  - For the 2 patients with evaluable pre-dose levels on Cycle 1, Day 8 and/or Day 15, all concentrations were <20 ng/mL

Vascular Reactivity

- Prospective examination of the vascular effects of exposure to angiogenesis inhibition was performed for some patients at baseline, after 4 weeks, and after 8 weeks of therapy
- Evaluation included ultrasound assessment of brachial artery FMD after hyperemic stimulus, a validated technique to evaluate endothelium-dependent, nitric oxide-mediated vasodilation[5]
- Four patients completed the 3-part analysis; due to the small sample size, interpretation of the effects of tivozanib on vascular reactivity was not possible

Conclusions

- **The DLT criteria (2 of 6 patients) was not reached for the highest dose level evaluated; therefore, tivozanib can be combined at the full recommended dose (1.5 mg/day) with weekly paclitaxel 90 mg/m²**
- **In a heavily pretreated metastatic breast cancer patient population, the combination of tivozanib and paclitaxel demonstrated encouraging evidence of clinical activity**
- **In a limited number of patients, the PK data suggest no influence of paclitaxel on circulating levels of tivozanib or of tivozanib on paclitaxel clearance**
- **The side effect profile was manageable; the most common AEs included fatigue, diarrhea, alopecia, and nausea**
- **Further studies of this combination at the full recommended doses are warranted**

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

Tivozanib dose, mg		Current study[a] Cycle 1, Day 22 n	Current study[a] 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)[2] Cycle 1, Day 22 n	Phase 2 study (RCC)[2] 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		17.8–191.1		20.2–104

RCC, renal cell carcinoma; SEM, standard error of the mean.
[a]Data are preliminary and subject to change.

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