2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
AVEO Pharmaceuticals, Inc.</td><td rowspan="3">Individual Study Table</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Tivozanib (AV-951)</td></tr>
<tr><td>Name of Active Ingredient:
Tivozanib (AV-951)</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 1b/2a, Open-Label, Multi-Center Study of AV-951 in Combination with Paclitaxel in Subjects with Advanced or Metastatic Breast Cancer</td></tr>
<tr><td colspan="3">Investigators and/or Study Centers:
This study enrolled subjects at 3 sites (2 sites in the United States and 1 site in Germany).</td></tr>
<tr><td colspan="3">Publications (Reference):
Mayer EL, Scheulen ME, Beckman J, et al. 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. Poster presented at the 33rd annual San Antonio Breast Cancer Symposium, December 8-12, 2010, San Antonio, Texas.
Mayer EL, Scheulen ME, Beckman J, et al. Combination of Tivozanib (AV-951) with Weekly Paclitaxel for Metastatic Breast Cancer: Reults of a Phase 1 Study. Poster to be presented at the annual meeting of the American Society of Clinical Oncology (ASCO), June 3-7, 2011, Chicago, Illinois.</td></tr>
<tr><td colspan="2">Study Period:
16 February 2009 (First Subject Dosed) – 07 January 2011 (Last Subject Last Visit)</td><td>Phase of Development:
Phase 1b/2a</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of the Phase 1b portion of the study was:
To determine the safety, tolerability, and maximum tolerated dose (MTD) of tivozanib when administered in combination with paclitaxel.
The secondary objectives were:
To characterize the pharmacokinetic (PK) profile of tivozanib and paclitaxel when administered in combination.
To evaluate the antineoplastic activity of tivozanib and paclitaxel when administered in combination.
To perform an exploratory study in a subset of subjects to evaluate:
Changes in flow-mediated vasodilation (FMD) during treatment with tivozanib.
The relationship between hypertension during tivozanib therapy, FMD, and plasma nitrotyrosine (NT) levels.
The Phase 2a study was not conducted; the planned objectives for this phase were outlined in the protocol.</td></tr>
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Methodology:

This Phase 1b/2a, open-label, multicenter, escalating dose study was planned to be conducted in approximately 30-84 subjects with confirmed advanced or metastatic breast cancer. The Phase 1b study was designed to evaluate the safety, tolerability, MTD, PK, and antineoplastic activity of tivozanib administered in combination with paclitaxel. The Phase 2a study was designed to evaluate the overall objective response rate (ORR), safety, tolerability, and pharmacogenomic activity of the MTD of the combination of tivozanib and paclitaxel established in the Phase 1b study. Investigators were informed on 21 May 2010 that the Sponsor would not proceed with the Phase 2a portion of the study.

In the Phase 1b portion, a single dose of tivozanib was administered orally 5 (± 2) days prior to the start of combination dosing in order to characterize the PK of tivozanib. Thereafter, tivozanib was administered orally once daily for 3 weeks beginning on Day 1 of Cycle 1, followed by 1 week off. Paclitaxel was administered as a 1-hour intravenous (IV) infusion on Days 1, 8 and 15 of each 4-week cycle, synchronized with tivozanib dosing (prior to treatment, subjects received a pre-treatment regimen with a corticosteroid, antihistamine, and H_2 antagonist). When dosed on the same days, tivozanib was given immediately following the paclitaxel infusion. Serial blood samples for PK analysis of tivozanib and paclitaxel were collected during Cycles 1 and 2. In addition, an exploratory evaluation of hypertension was conducted using FMD and plasma NT levels in a subset of subjects at a single site.

Three dose cohorts of tivozanib (0.5 mg/day, 1.0 mg/day, and 1.5 mg/day) were evaluated in combination with a standard 90 mg/m^2 dose of paclitaxel. Cohorts were filled sequentially. Once assigned to a cohort, subjects were treated at that dose level throughout the study. Enrollment to the next dose level occurred only after acceptable tolerability was demonstrated in Cycle 1, and only after consultation with the medical monitor. The number of dose levels enrolled and maximum dose administered depended on the observed tolerability.

Subjects were evaluated for the occurrence of adverse events (AEs) and dose-limiting toxicities (DLTs), including changes in clinical status, vital signs, and/or laboratory data, during and for 1 month after completing therapy. If AEs related to study drug were ongoing at the 1-month follow-up, safety assessments had to continue up to 3 months. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0.

Initially, 3 subjects were to have been treated at each dose level. Safety data were reviewed by the medical monitor on an ongoing basis and dose escalation occurred only after consultation with the medical monitor. Criteria for dose escalation and expansion to the next dose level were as follows:

- During Cycle 1, if any 1 of the 3 subjects within a cohort experienced a DLT, the cohort was expanded to a minimum of 6 subjects.
- If 0 of 3 or 1 of 6 of the subjects experienced a DLT during Cycle 1, the dose was escalated to the next dose level.
- If ≥ 2 of the 6 subjects at a dose level experienced a DLT during Cycle 1, dose escalation was stopped and the prior dose level was considered the MTD.
- An additional 12 subjects were planned to be enrolled at the MTD level for an expanded assessment of safety and activity.
- There was a potential to evaluate intermediate dose level(s) to further characterize the MTD.

Subjects experiencing DLTs during Cycle 1 had to be discontinued from further study participation, but could have been allowed to continue at a reduced dose if there was evidence of an objective response or other clinical benefit. Subjects experiencing DLTs at any other point during the study either received subsequent treatment with study drug at a reduced dose or were discontinued from the study. The MTD was not established until all subjects entered into the dose level under evaluation completed Cycle 1 or discontinued further study

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participation due to a DLT.

After completing the 2-cycle Response Assessment Phase of the study (8 weeks of treatment), subjects with documented stable disease (SD), an objective partial response (PR), or complete response (CR) were allowed to continue on the Maintenance Phase at the same dose and schedule previously administered. Effective with Amendment 1, this maintenance therapy could have been extended at the investigator's discretion for up to 1 year from the date of the first tivozanib dose, until either the occurrence of unacceptable toxicity or documented disease progression. After 1 year, tivozanib and paclitaxel therapy could have been continued at the discretion of the Sponsor and investigator, if there was clinical benefit and acceptable tolerability, or subjects could have returned to standard of care treatment.

Number of Subjects (Planned and Analyzed):

Approximately 30-84 subjects were planned: approximately 30 subjects in the Phase 1b dose escalation study and 19-54 in the Phase 2a study. Eighteen subjects were enrolled and analyzed in Phase 1b. The Phase 2a portion was not conducted.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Eligible subjects were females ≥ 18 years of age with histologically or cytologically documented invasive breast cancer, documented progressive disease, measurable or evaluable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and life expectancy ≥ 3 months. Subjects entered in the Phase 1b portion had to have no more than 4 prior chemotherapy treatments, and only 1 prior taxane-based regimen for metastatic disease.

Subjects were excluded if they had known hypersensitivity to paclitaxel or to any component of the paclitaxel formulation; symptomatic central nervous system metastases; protocol-defined hematologic or serum chemistry abnormalities; significant cardiovascular disease, including clinically significant symptomatic heart failure, uncontrolled hypertension, and myocardial infarction within 3 months prior to start of study drug. Subjects were also excluded if they had unhealed wounds, ulcers, and/or bone fractures; serious/active infections or infections requiring parenteral antibiotics; inadequate recovery from surgery or major surgical procedure within 6 weeks; ongoing hemoptysis or history of clinically significant bleeding within 6 months; cerebrovascular accident within 12 months; or deep vein thrombosis or pulmonary embolism within 6 months of first dose of study drug.

Test Product, Dose and Mode of Administration, Batch Number:

Tivozanib capsules, administered orally at doses of 0.5, 1.0, or 1.5 mg/day.

Batch numbers: 0.5 mg, Lot 334491, CT2567/5, 262574
1 mg, Lot 257959, 329005, CT2567/6, 298341
1.5 mg, Lot 283959

Duration of Treatment:

Treatment with the combination of tivozanib and paclitaxel was administered in 4-week cycles. After completing the 2-cycle Response Assessment Phase of the study, subjects with SD or an objective response (CR or PR) were allowed to continue in the extended Maintenance Phase of the study. Extended therapy with tivozanib and paclitaxel could have continued for up to 1 year until disease progression or the occurrence of an unacceptable toxicity. After 1 year, the medical monitor and investigator had to discuss the advisability of continued therapy based upon the subject's ongoing response status and demonstrated tolerability.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Paclitaxel 90 mg/m^2, administered intravenously once weekly for 3 weeks of each 4-week cycle (on Days 1, 8, and 15) followed by a 1-week rest.

Commercially available vials were used during the study; lot numbers were not collected.

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Criteria for Evaluation:

Safety:

Safety and tolerability were assessed by monitoring adverse events (AEs), changes from baseline in performance status, vital signs, physical examination, laboratory results, electrocardiogram (ECG), and concomitant medications/medical procedures. DLTs were any study drug-related toxicities during Cycle 1 that met the protocol-defined criteria. The MTD was defined as the maximum dose at which ≤ 1 of 3 subjects in a dose group experienced a DLT.

Disease Assessment / Response Assessment:

All subjects who received a minimum of 2 cycles of study treatment were considered evaluable for response using RECIST criteria. Disease assessment included disease classification (histological/cytological type, and stage of carcinoma) and diagnostic imaging/measurement of target lesions. The same method of assessment and the same technique was used throughout the study. Computed tomography (CT) and/or magnetic resonance imaging (MRI) was performed every 2 cycles (8 weeks) for assessing disease status. If disease progression was documented at any time, no further imaging or marker lesion measurements were required.

Subjects who developed early progressive disease (PD) (regardless of the duration of study treatment) prior to response evaluation were considered to have progressed on study. The duration of any objective response was measured from the date the initial response was observed to the date that disease progression was observed. Per RECIST criteria, to be assigned a status of CR or PR, changes in tumor measurements had to be confirmed by repeat studies performed ≥ 4 weeks after the criteria for response were first met. For SD, follow-up measurements had to meet the SD criteria at least once after study entry at an interval of 4 weeks.

Extended follow-up was to have been performed in the event of an objective response or disease stabilization at the end of treatment. Data were to have continued to be collected on duration of response or SD, as well as on the overall time to disease progression (TTP).

Pharmacokinetics:

PK parameters included maximum concentration [C_{max}], time to maximum concentration [T_{max}], and area under the curve [AUC] from Cycle 1.

Flow-Mediated Vasodilation and Plasma Nitrotyrosine Measurements:

An exploratory study of hypertension was performed in a subset of subjects enrolled at Site [redacted] only [redacted] Changes in endothelium-derived nitric oxide and endothelial function during exposure to tivozanib were evaluated using high-resolution B-mode ultrasound for FMD and a plasma sample for NT. Blood samples for NT were collected prior to dosing with paclitaxel and tivozanib. To assess endothelium-dependent FMD, brachial artery diameter was measured under basal conditions and during reactive hyperemia after 5 minutes of an ischemic stimulus. Forearm ischemia was induced by inflating a BP cuff on the upper part of the forearm to suprasystolic pressures for 5 minutes. Endothelium-independent vasodilation was assessed by measuring brachial artery diameter under basal conditions and 3 minutes after administration of sublingual nitroglycerin (0.4 mg).

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Statistical Methods:

Statistical analyses for the Phase 2a portion were planned, but this portion of the study was not conducted.

Study Populations:

The Safety Population (SAF) consisted of all subjects who received at least 1 dose of tivozanib.

The Efficacy Evaluable Population (EEF) consisted of all subjects who met the entrance criteria (or were granted a protocol exception) and received at least 2 cycles of tivozanib. Subjects withdrawn from the study before completion of Cycle 2 because of PD were also included in assessments of antineoplastic activity.

Subject Accountability:

Subject completion status, dose reductions, and study terminations were summarized for each treatment cycle and for the study overall. A listing of subjects with major protocol violations (eg, had eligibility violations or took any prohibited medications) as well as subjects with protocol exceptions and those excluded from the analyses were presented.

Demography and Baseline Characteristics:

Demography and baseline characteristics, including medical history, physical examination, vital signs, and previous medications were summarized using descriptive statistics. Baseline was defined as the last observation prior to start of tivozanib dosing on Cycle 1, Day -5 for vital signs or the Screening Visit value for all other parameters not measured at Cycle 1, Day -5.

Antineoplastic Activity:

Disease status was summarized by cycle and dose group. Tumor response was assessed according to RECIST (Version 1.0). The overall ORR, disease control rate (DCR); duration of objective response; duration of CR/PR; duration of SD, and TTP were assessed and presented.

The best overall response from the start of treatment to disease progression or end of the study was reported as assessed by the investigator in the CRF and was summarized by cohort and listed for each subject. The overall response by cycle (CR, PR) required confirmation $\geq$ 4 weeks after the response criteria were first met. If no scans were available but progression was specified as reason for study discontinuation, the subject was classified as having disease progression; otherwise, the subject was not evaluable.

ORR was defined as the proportion of evaluable subjects who had a best overall response classification of CR + PR. DCR was defined as the best overall response classification of (CR + PR + SD). A 95% confidence interval (CI) was calculated for ORR and DCR.

Duration of objective response, duration of CR/PR, duration of SD, and TTP were listed by subject. The duration of objective response (in months) in subjects with a confirmed CR or PR was defined as the time from first assessment of CR/PR to the first documentation of disease progression, the date of death due to the disease, or the start of further antitumor therapy. If a subject had not progressed, the duration of objective response was censored on the date of last disease assessment. The duration of SD (in months) was defined as the time from study entry to the first occurrence of disease progression or death due to the disease or the start of further antitumor therapy. If a subject had not progressed, the duration of SD was censored on the date of last disease assessment. Similarly to the duration of objective response, duration of PR and duration of CR were also calculated.

The TTP (in months) was defined as the time from first dose to the date of first progression. If a subject did not progress, TTP was censored on the date of the last disease assessment. If no scans were available, but progression was specified as the reason for study discontinuation, the date of last tivozanib administration was used as date of progression.

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The change from baseline in target lesion diameter (LD) was summarized using descriptive statistics for continuous data. The sum of the LD was used for all target lesions measured at each evaluation. The table was organized by cycle and dose group. The individual maximal percentage reduction in sum of LD relative to baseline was presented using a Waterfall plot.

Safety:

Safety observations and measurements included drug exposure, AEs/DLTs, safety laboratory tests, vital signs, physical examinations, ECG, ECOG performance status, and concomitant medications.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 13.1) and tabulated by system organ class (SOC) and preferred term. By-subject summary listings were presented for DLTs; serious adverse events (SAEs); AEs leading to tivozanib dose interruption, dose reduction, or study discontinuation; and death. AEs were graded according to NCI-CTCAE criteria (Version 3.0). Incidence tables showing the number and percentages of subjects were presented for:

- Treatment-emergent AEs.
- AEs by cycle (overall and by SOC, preferred term, and dose group).
- AEs by toxicity grade, using the highest toxicity per subject for multiple occurrences.
- AEs by drug relationship (separately for tivozanib and paclitaxel).
- Grade 3-4 AEs (overall and related, separately for tivozanib and paclitaxel).

All post-baseline evaluations of clinical laboratory parameters and vital sign measurements were summarized by dose group, visit, and overall using descriptive statistics. Evaluations of physical examinations, ECG, and ECOG performance status were listed. Out of range and/or abnormal laboratory values were graded and presented in listings. For selected hematology, coagulation, and biochemistry parameters, summary tables showing the shift from baseline to the worst NCI CTCAE grade on study were presented for subjects with any shift to high, any shift to low, any shift to normal, or no change. Frequencies were presented for subjects with hypertension.

Pharmacokinetics:

PK parameters were calculated using non-compartmental analysis and PK parameters (if possible, C_{max}, T_{max}, and AUC) were summarized and presented. The mean (± standard deviation [StD]) concentration-time profiles of both tivozanib and paclitaxel were presented for each dose.

Evaluations to delineate dose-response and PK parameter-response relationships were not performed.

Flow-Mediated Vasodilation and Plasma Nitrotyrosine Measurements:

An exploratory analysis of FMD and NT levels in plasma was performed in a subset of subjects from the [redacted] Changes in FMD from baseline were examined using a 1-sample two-sided Wilcoxon test at a 0.05 significance level. Mean change was calculated with 95% CI, and summary statistics from each time point were represented graphically. The median change in plasma NT levels from baseline could have been calculated with 95% CI. Plasma NT levels and the development of hypertension at each time point were summarized. Correlations between changes in FMD and NT from baseline and development of hypertension were performed.

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Summary – Conclusions:

Demographics/Baseline Disease Characteristics:

All subjects were female with a mean age of 47.7 years (range: 32 to 65 years). The majority of women were white (16 subjects, 88.9%) and not Hispanic or Latino (12 subjects, 66.7%). The mean time since breast cancer diagnosis was 76.2 months. Most subjects had histology of ductal carcinoma (14 subjects, 77.8%). There were 10 subjects (55.6%) whose tumors were positive for estrogen receptors and/or progesterone receptors; the remaining 8 subjects (44.4%) had tumors that were negative for estrogen and progesterone receptors.

Most subjects (14 subjects, 77.8%) were not assessed for human epidermal receptor protein-2 fluorescence *in situ* hybridization (HER-2 FISH). One subject (5.6%) in Cohort 1 was positive for HER-2 FISH. There were 8 subjects with a HER-2 immunochemistry score of 0 (44.4%), 6 subjects with a score of 1+ (33.3%), and 4 subjects with a score of 3+ (22.2%). There were 4 subjects who were HER-2 FISH positive and/or HER-2 immunochemistry 3+.

Antineoplastic Activity Results:

Of the 13 efficacy evaluable subjects, 4 (30.8%) had confirmed PR, 6 (46.2%) had confirmed SD, and 1 (7.7%) had confirmed PD. ORR (confirmed) was 30.8% (95% CI: 9.1 %, 61.4 %) and DCR was 76.9% (95% CI: 46.2%, 95.0 %). Four subjects had a best overall response of PR. The duration of PR ranged from 5.59 to greater than 9.36 months, and TTP ranged from 9.72 to greater than 13.14 months. Tivozanib in combination with paclitaxel is clinically active in subjects with metastatic breast cancer.

Safety Results:

The overall median duration of exposure to tivozanib for all subjects (n = 18) was 5.4 months (range: 0 to 12.0 months). The overall median duration of exposure to paclitaxel (n = 15) was 9 months (range: 0 to 12 months); 3 subjects were discontinued from the study prior to paclitaxel administration.

AEs were reported in all 18 subjects (100.0%). The most common AEs were fatigue (14 subjects, 77.8%); alopecia (9 subjects, 50.0%); and diarrhea, nausea, and peripheral sensory neuropathy (reported by 8 subjects each, 44.4%). Ten subjects (55.6%) had a total of 31 Grade 3/4 AEs. Two of these 31 AEs were Grade 4; the remaining 29 AEs were Grade 3. The Grade 4 AEs were lumbar vertebral fracture (an SAE unrelated to either drug) and hip fracture (an SAE unrelated to either study drug). The most common Grade 3 AEs were fatigue and neutropenia (3 subjects each, 16.7%). The most frequently reported Grade 3 treatment-related AEs were neutropenia (3 subjects, 16.7%), and diarrhea, fatigue, and hypertension (2 subjects each, 11.1%).

The most common AEs for the cohort of subjects (n = 7) receiving the full recommended doses of each agent, 1.5 mg/day tivozanib and paclitaxel 90 mg/m^2 per week paclitaxel, were fatigue (6 subjects), diarrhea and nausea (5 subjects each), and alopecia and stomatitis (4 subjects each). This cohort had no Grade 4 or Grade 5 AEs.

Two subjects had a DLT during the study. Subject [redacted] (Cohort 1, 0.5 mg/day) was unable to complete Cycle 1 due to Grade 1 palpitations (toxicity led to withdrawal of consent in Cycle 1), and Subject [redacted] (Cohort 3, 1.5 mg/day) was unable to complete Cycle 1 due to a Grade 2 SAE of pneumoperitoneum.

Two subjects died; one death was in Subject [redacted] (Cohort 1) who had PD (the death occurred 31 days after the last dose of study drug) and the second death occurred in Subject [redacted] (Cohort 3) and was tumor related (and occurred 54 days after the last dose of study drug). Both of these deaths were considered secondary to underlying disease and not due to study medication.

Eight subjects had a total of 10 SAEs; 7 of these subjects had a total of 8 treatment-emergent SAEs. Subject [redacted] had 2 unrelated Grade 4 SAEs of hip fracture and lumbar vertebral fracture, which was ultimately fatal. All other SAEs were Grade 2 or 3 in intensity. One of the SAEs (pneumoperitoneum in Subject [redacted] was also a DLT. Two SAEs were considered possibly related to both study drugs. These

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2 possibly related SAEs were pneumoperitoneum (Grade 2 DLT; drug discontinued; recovered) and grand mal convulsion (Grade 2; no action taken; recovered).

Five subjects had a total of 6 treatment-emergent AEs leading to discontinuation. Three of the treatment-emergent AEs leading to discontinuation were SAEs. Two subjects had tivozanib-related AEs leading to discontinuation and 2 subjects had paclitaxel-related AEs leading to discontinuation.

There were 7 subjects with a total of 20 AEs (including 2 SAEs) that resulted in tivozanib and/or paclitaxel dose interruption. No AEs leading to dose interruption were > Grade 3. Six subjects had a total of 10 AEs that resulted in tivozanib and/or paclitaxel dose reduction; none were SAEs and none were > Grade 3 in intensity.

Seven subjects had at least 1 AE of hypertension; none of the AEs of hypertension were SAEs. Three of the 7 subjects were in Cohort 3 (receiving tivozanib 1.5 mg/day and paclitaxel 90 mg/m^2 per week). Three subjects had palpitations reported as non-serious AEs, including Subject [redacted], whose palpitations were considered a DLT.

Pharmacokinetic Results:

The serum concentration profile of tivozanib following a single administration of 0.5, 1.0, or 1.5 mg was relatively flat with no discernible elimination phase in this observation period. In a significant number of subjects the observed C_{max} occurred 24 h post-dose. There was substantial variation between subjects, although there was a generally increasing trend with dose in the $AUC_{0-\tau}$ overall concentration levels in the first 24 h, and at subsequent times. There was substantial accumulation of drug after Day 1 at all doses, though it appeared that most subjects were close to or at steady-state trough levels by Day 22.

Paclitaxel exposure, estimated as C_{max} at 5 minutes after the end of the paclitaxel infusion, was consistent with previously reported data.

Flow-Mediated Vasodilation and Plasma Nitrotyrosine Measurements:

Brachial artery endothelial and vascular smooth muscle function was evaluated in a subset of subjects. Three subjects had FMD data and NT data collected at all 3 scheduled vascular assessment visits (baseline; Cycle 2, Day 1; and Cycle 3, Day 1). There was no statistically significant change from baseline in nitroglycerin-mediated, endothelium-independent vasodilation at either post-baseline assessment. Reduction in the percentage increase of flow-mediated, endothelium-dependent vasodilation did reach statistical significance at Cycle 3, Day 1 (p=0.02). Given the small sample size, this analysis of the correlations between changes in FMD and NT from baseline and the development of hypertension was inconclusive.

Conclusions:

Tivozanib and paclitaxel can safely be combined at the full recommended doses of each agent, 1.5 mg/day and 90 mg/m^2/week, respectively. The combination of tivozanib and paclitaxel was acceptably tolerated, with minimal DLTs encountered in the study.

The combination of tivozanib and paclitaxel demonstrated evidence of clinical activity in metastatic breast cancer, with 4 of 13 subjects (30.8%) achieving confirmed PR.

The systemic exposure of tivozanib and paclitaxel was consistent with previously reported values and there was no indication of any interaction between the 2 drugs.

The clinical activity and manageable side effect profile observed with this combination warrants further exploration of tivozanib in subjects with breast cancer.