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 significant cardiovascular disease, uncontrolled hypertension, or myocardial infarction being exclusion criteria. Further studies of this combination at the full recommended phase 2 dose are ongoing.

Objectives

We aimed to determine the safety, tolerability, and maximum tolerated dose (MTD) of the combination of weekly paclitaxel with Tivozanib in women with hormone-refractory metastatic breast cancer (MBC) with no prior exposure to VEGFR inhibitors.

Methods

Key Eligibility Criteria

- Age of 18 years with MBC
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2
- Adequate hematologic and organ function
- No prior treatment with VEGFR inhibitors
- No concurrent use of investigational new agents or non-steroidal anti-inflammatory drugs (NSAIDs)
- No significant cardiovascular disease, uncontrolled hypertension, or myocardial infarction

Study Design

Phase 1, open-label, ascending study of treatment with weekly paclitaxel

Results

Patients

16 patients with MBC were enrolled between February 2009 and December 2009 (median age, 57 years; range, 35-72 years; median ECOG PS, 1; range, 0-2). All had hormone-refractory MBC and were pretreated with endocrine therapy.

Safety

- Grade 3 or 4 non-hematologic adverse events (AEs) were observed in 8 patients (50%); the most frequent was fatigue (25%) followed by nausea (20%), vomiting (20%), and diarrhea (13%).
- Two patients experienced grade 5 non-hematologic AEs (13%), both due to grade 4 neutropenia.

Efficacy

- No patients achieved a partial response (PR) or complete response (CR).
- Median time to disease progression (TDPP) was 22.6 weeks (95% CI, 18.8-31.4).
- One patient had stable disease (SD) lasting ≥ 6 months.

References


Acknowledgments

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Conclusions

The MTD of 1.5 mg/day of tivozanib plus paclitaxel was 90 mg/m². No dose-limiting toxicities were observed, and one patient had SD lasting ≥ 6 months. Additional phase 1 studies are ongoing to determine the role of this combination in breast cancer.

Authors

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Figure 1. Treatment schedule.

Figure 2. Efficacy measures: waterfall plot of maximum tumor change.

Table 2. Treatment-emergent adverse events (31% of patients).

Table 3. Treatment-emergent adverse events (45% of patients).

Table 4. Best overall response.

Table 5. Serum concentrations of tivozanib on Cycle 1, Day 22.

Table 6. Study endpoints.

Table 7. Patient demographics.

Figure 3. 104 weeks of therapy.

Figure 4. Progression-free survival.