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A Phase II Biomarker Assessment of Tivozanib in ONcology trial in patients (pts) with advanced renal cell carcinoma (BATON RCC)

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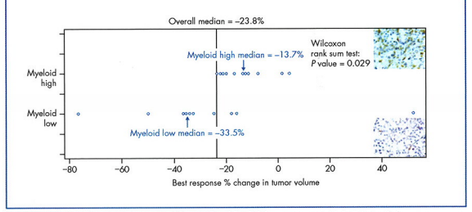
Background

- The sprouting of new blood vessels (angiogenesis) is an essential process required to sustain tumor growth[1]
- Vascular endothelial growth factor (VEGF) family members play a critical role during tumor angiogenesis via tyrosine kinase activation of VEGF receptors (VEGFRs) 1, 2, and 3, and subsequent promotion of endothelial cell proliferation, migration, and survival[2]
  - VEGFR inhibitors represent a promising therapeutic option for controlling tumor growth
- Tivozanib is a novel, potent, selective, and long half-life tyrosine kinase inhibitor targeting VEGFRs 1, 2, and 3
  - Tivozanib inhibits phosphorylation of VEGFRs 1, 2, and 3 at picomolar concentrations (half maximal inhibitory concentration [IC_{50}] of 0.21, 0.16, and 0.24 nM, respectively), and inhibits cKit and PDGFR at 10-times higher concentrations (IC_{50} of 1.63 and 1.72 nM, respectively)[3]
  - Other examined kinases were more than 100-fold less potently inhibited compared with the VEGFRs, supporting the specificity of tivozanib[3]
- The maximum tolerated dose was determined to be 1.5 mg/day in a Phase I study, and clinical activity was observed in patients with renal cell carcinoma (RCC)[4]
- RCC is characterized by a loss of function of the von Hippel-Lindau gene; this leads to overexpression of VEGF and a subsequent increase in tumor angiogenesis
  - This genetic hallmark of RCC likely underlies the robust clinical activity observed when treating RCC with VEGF pathway antagonists[5–8]
  - However, not all patients derive substantial benefit from these agents, and most patients eventually progress[5–8]
- Based on these observations, a Phase II study of tivozanib was conducted in patients with advanced RCC using a randomized discontinuation design[9]
  - Response data on all patients treated with tivozanib (N=272) demonstrated an objective response rate (ORR) of 24%; patients with clear cell RCC and a prior nephrectomy had a 30% ORR (n=176)
  - The median progression-free survival (PFS) was 11.7 months in all patients and 14.8 months in patients with clear cell RCC and nephrectomy
  - Tivozanib was relatively well tolerated in this patient population
- Despite the significant response rate of RCC patients treated with tivozanib, not all patients demonstrate an objective response
  - These clinical observations suggest that there is variation in sensitivity to tivozanib that has an impact on patient outcome

A Myeloid Mutigene Biomarker Is Associated with Tivozanib Resistance

- Preclinical studies using a population-based tumor model comprising more than 100 genetically engineered breast HER2 tumors have identified putative biological drivers of intrinsic sensitivity to tivozanib
- A novel, coherence-based bioinformatics analysis of pretreatment tumor microarray data identified a 42-gene resistance signature defining a specific tumor infiltrating myeloid population
  - Immunohistochemical quantitation of macrophage lineage markers in the tumors identified the presence of infiltrating myeloid cells with a percentage composition in the tumor correlated with both the 42-gene signature and resistance to tivozanib
  - Analysis of 21 samples from patients enrolled in the tivozanib Phase II RCC trial demonstrated a significant correlation between the percent myeloid cell composition in the tumors and clinical anti-tumor activity of tivozanib **(Figure 1)**
- The current study is designed to further validate a tivozanib-resistance biomarker, as well as to explore other biomarkers from blood and tissue that may be predictive of clinical activity and/or toxicity with tivozanib

Figure 1. Retrospective analysis from a tivozanib Phase II trial: change in median tumor volume stratified by CD68 biomarker low vs high.[10]



Twenty-one samples from a Phase II trial of tivozanib in RCC were collected, for which there was tumor material of sufficient quality for immunohistochemistry, had available tumor volume measurements, and were not randomized to the placebo arm. Quantitative CD68 immunohistochemistry on the 21 samples demonstrated CD68 composition ranging from 3–30%. Correlation of the baseline percentage CD68 infiltrate to change in target tumor volume by RECIST revealed a statistically significant correlation, with tumors exhibiting higher percentages of CD68+ cells exhibiting poorer response to tivozanib. Median percentage CD68 composition was used to classify myeloid high and low groups. RECIST, Response Evaluation Criteria In Solid Tumors.

Study Objectives

Primary Objectives

- Correlation of biomarkers in blood and archived tissue samples with clinical activity and/or treatment-related toxicity
- 6-month PFS rate

Secondary Objectives

- ORR (complete response + partial response)
- PFS
- Safety and tolerability
- Relationships between biomarker measures and serum concentration of tivozanib

Key Eligibility Criteria

Inclusion Criteria

- Patients with unresectable locally recurrent or metastatic RCC (clear cell or non-clear cell)
- Prior nephrectomy
- Measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1
- ≤1 prior systemic treatment (immunotherapy, including interferon-α– or interleukin-2–based therapy, chemotherapy, hormonal therapy, or an investigational agent) for metastatic RCC
- Eastern Cooperative Oncology Group performance status of 0 or 1, and life expectancy ≥3 months

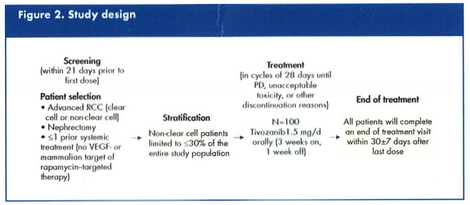
Exclusion Criteria

- Prior VEGF- or mammalian target of rapamycin-targeted therapy
- Primary central nervous system malignancies or metastases
- Significant hematologic, cardiovascular, renal, vascular, or coagulation disorders

Study Design

- Open-label, single arm, multicenter study **(Figure 2)**

Figure 2. Study design



PD, progressive disease.

- One hundred evaluable patients from approximately 20–30 sites in the United States and Canada
- Patients are stratified by histology (clear cell vs non-clear cell)
  - Enrollment of non-clear cell patients is limited to ≤30% of the entire study population
- After screening, patients receive tivozanib orally at 1.5 mg/day, beginning on Day 1 of Cycle 1
  - Patients receive tivozanib once daily for 3 weeks followed by 1 week off study drug (1 cycle = 3 weeks on, 1 week off)
  - Cycles are repeated every 4 weeks
  - Treatment with tivozanib will continue if tolerated and in the absence of disease progression
- Patients are monitored throughout the study and for follow-up safety evaluations conducted 30 days (±7 days) following the patients' last dose of tivozanib
  - An additional 90-day follow-up will be performed if an observed toxicity thought to be associated with tivozanib has not resolved by the 30-day follow-up visit to confirm that the event has resolved

Study Endpoint Evaluations

Assessments for primary and secondary endpoints

- When available, samples from archival surgical or biopsy tumor tissue (formalin-fixed, paraffin-embedded) will be collected to evaluate potential biomarkers **(Table 1)** and their correlations with clinical activity and/or treatment-related toxicity
- Blood samples will be collected from all patients to evaluate potential biomarkers and their correlations with clinical activity and/or treatment-related toxicity **(Table 1)**
  - A total of 3 whole blood samples (~10 mL each) will be collected for biomarker analyses at the following time points prior to dosing: Cycle 1, Days 1, 15; Cycle 2, Day 1

Table 1. Assessment of Biomarkers

Tumor biomarkers	CD68; HIF1/HIF2; VEGFs A, B, C, and D; HGF; CAIX; PLGF; biomarker signature based on transcriptional profiles
Blood biomarkers	VEGFs A, B, C, and D; HGF; and PLGF levels, protein expression, and metabolite patterns

CAIX, carbonic anhydrase IX; HGF, hepatocyte growth factor; HIF, hypoxia-inducible factor; PLGF, placental growth factor.

- Patients undergo disease assessment at screening (within 4 weeks prior to first dose of study drug) and following Cycle 2, and response will be determined by RECIST version 1.1
- Patients will be monitored throughout the treatment and follow-up period for occurrence of adverse events, as well as for changes in clinical status, vital signs, and laboratory data, including hematology, serum chemistry, urinalysis, thyroid function test, and coagulation parameters
  - National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 will be used for grading toxicities
- Pharmacokinetic samples will be collected to evaluate the relationship between biomarker measures and serum concentrations of tivozanib
  - Samples for tivozanib concentration determinations will be collected at the following time points prior to dosing: Cycle 1, Days 1, 15; Cycle 2, Day 1

Statistical Considerations

- Sample size (100 patients) was estimated based on clinical considerations and the precision with which 6-month PFS can be estimated, using a normal approximation to the binomial distribution **(Table 2)**

Table 2. Precision of 6-month PFS Based on Enrollment of 100 Patients

% Patients Progression Free at 6 Months	95% Confidence Interval
80	72–87%
70	61–79%
60	50–70%

- Descriptive statistics will be calculated for every variable including sample size (n), mean, median, standard deviation, minimum, and maximum for continuous variables. Categorical variables will be summarized using counts and percentages
- Two populations will be used in data analyses
  - Intent-to-treat (ITT) population
    - All enrolled patients who receive at least one dose of tivozanib
  - Per protocol (PP) population
    - All enrolled patients who remain in the study for at least 8 weeks (2 cycles), unless discontinued due to death or disease progression
    - Have no major protocol violations that will confound the effects of treatment
  - Anti-neoplastic activity will be assessed in the ITT and PP populations
  - The safety parameters will be analyzed using the ITT population
- Laboratory assessments will be summarized descriptively by visit. The change and shift (based on normal ranges) from baseline will be summarized for all post-baseline evaluations
- Correlation between biomarkers, clinical response, and treatment-related toxicity of tivozanib will be assessed
  - Correlation between dichotomous biomarkers and categorical endpoints, including objective response, may be assessed using contingency table methods
  - Correlation with time-to-event endpoints, including PFS, may be evaluated by using Cox proportional hazards regression in which the biomarker is an explanatory variable
- Confirming the association between the myeloid infiltration biomarkers and clinical activity, i.e. PFS and objective response, will be of particular interest
  - Additional biomarkers may be identified using methods similar to those described above
- Tivozanib concentration will be summarized descriptively and presented by visit
  - A linear or non-linear correlation will be attempted to characterize the relationship between the value of the marker and the serum concentration at each available time point

Discussion

- **Tivozanib has demonstrated clinical activity in RCC; however, clinical observations suggest that there is variation in sensitivity to tivozanib that may have an impact on patient outcome**
- **Tivozanib biomarkers evaluated in this study, along with those evaluated in other solid tumors, may play an important role in helping to optimize patient selection**
- **Similar studies that move forward promising biomarkers of disease response to targeted therapies will be essential to guide rational cancer therapeutic strategies and advance personalized medicine**
- **As of January 2012, the study completed enrollment of 100 patients, demonstrating a large number of patients can be enrolled in a biomarker study with well-defined candidate genes and critical inclusion criteria to facilitate compliance**

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