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

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Study Design

- **Objective:** The maximum tolerated dose was determined to be 1.5 mg/day in a Phase I study, and the sprouting of new blood vessels (angiogenesis) is an essential process required to sustain tumor growth.
- **Method:** A Myeloid Mutigene Biomarker Is Associated with Tivozanib Resistance – Analysis of 21 samples from patients enrolled in the tivozanib Phase II RCC trial
- **Results:** The median progression-free survival (PFS) was 11.7 months in all patients and 14.8 months in patients with renal cell carcinoma (RCC) using a randomized discontinuation design.
- **Conclusion:** Tivozanib inhibits phosphorylation of VEGFRs 1, 2, and 3 at picomolar concentrations (half-maximal effective concentration (IC50) ≤ 10 pM), and other examined kinases were more than 100-fold less potently inhibited compared with VEGFR inhibitors. VEGFR inhibitors represent a promising therapeutic option for controlling tumor growth.

Study Objectives

**Primary Objectives**
- Correlation of biomarkers in blood and oncthetic tissue samples with clinical activity and/or outcome

**Secondary Objectives**
- Safety and tolerability

**Key Eligibility Criteria**

- **Inclusion Criteria:**
  - Patients with measurable locally recurrent or metastatic RCC (clear cell or non-clear cell) or metastatic renal cell carcinoma (RCC) (clear cell or non-clear cell) with a history of exposure to anti-VEGF therapy
  - Patients with measurable locally recurrent or metastatic RCC (clear cell or non-clear cell), or metastatic renal cell carcinoma (RCC) (clear cell or non-clear cell) with a history of exposure to anti-VEGF therapy who have a median progression-free survival (PFS) of ≤ 6 months
  - Patients with measurable locally recurrent or metastatic RCC (clear cell or non-clear cell), or metastatic renal cell carcinoma (RCC) (clear cell or non-clear cell) with a history of exposure to anti-VEGF therapy who have a median PFS of ≤ 6 months and are on a background of exploratory therapy, chemotherapeutic agent, or as investigational agent for RCC treatment
  - Patients with metastatic RCC (clear cell or non-clear cell) treated after progression on another anti-angiogenesis therapy
  - Patients with measurable locally recurrent or metastatic RCC (clear cell or non-clear cell), or metastatic renal cell carcinoma (RCC) (clear cell or non-clear cell) with a history of exposure to anti-VEGF therapy who have a median PFS of ≤ 6 months and are on a background of exploratory therapy, chemotherapeutic agent, or as investigational agent for RCC treatment

- **Exclusion Criteria:**
  - Patients with measurable locally recurrent or metastatic RCC (clear cell or non-clear cell) or metastatic renal cell carcinoma (RCC) (clear cell or non-clear cell) with a history of exposure to anti-VEGF therapy
  - Patients with measurable locally recurrent or metastatic RCC (clear cell or non-clear cell), or metastatic renal cell carcinoma (RCC) (clear cell or non-clear cell) with a history of exposure to anti-VEGF therapy who have a median progression-free survival (PFS) of ≤ 6 months
  - Patients with measurable locally recurrent or metastatic RCC (clear cell or non-clear cell), or metastatic renal cell carcinoma (RCC) (clear cell or non-clear cell) with a history of exposure to anti-VEGF therapy who have a median PFS of ≤ 6 months and are on a background of exploratory therapy, chemotherapeutic agent, or as investigational agent for RCC treatment

**Study Endpoint Evaluations**

- **Assessments for primary and secondary endpoints:**
  - Overall survival and updated results for sunitinib compared with IFN-α in metastatic RCC. J Clin Oncol 2010;28:2137–2143.
  - Best response % change in tumor volume
  - Worst response % change in tumor volume
  - Time to progression
  - Overall median = –23.8%
  - Myeloid high median = –13.7%
  - Myeloid low median = –3.8%
  - 6-month PFS rate
  - 80 72–87%
  - 70 61–79%
  - Patients per treatment cycle
  - Cycles are repeated every 4 weeks
  - After screening, patients receive tivozanib orally at 1.5 mg/day, beginning on Day 1 of Cycle 1.
  - Patients are stratified by histology (clear cell vs non-clear cell)
  - One hundred evaluable patients from approximately 20–30 sites in the United States and Canada

**Background**

- The maximum tolerated dose was determined to be 1.5 mg/day in a Phase I study, and the sprouting of new blood vessels (angiogenesis) is an essential process required to sustain tumor growth.
- Vascular endothelial growth factor (VEGF) heavily regulates a critical role during tumor development. VEGF stimulation results in the advancement process of endothelial cell proliferation, migration, and survival.
- Tivozanib was representative of a promising agent for vascular endothelial growth factor.
- Tivozanib is a small, potent, selective, and long-lasting orally active receptor tyrosine kinase inhibitor targeting VEGFRs 1, 2, and 3.
- Tivozanib inhibits phosphorylation of VEGFRs 1, 2, and 3 at picomolar concentrations (half-maximal effective concentration (IC50) ≤ 10 pM), and other examined kinases were more than 100-fold less potently inhibited compared with VEGFR inhibitors.
- VEGFR inhibitors represent a promising therapeutic option for controlling tumor growth.
- Other examined kinases were more than 100-fold less potently inhibited compared with VEGFR inhibitors.

**Statistical Considerations**

- 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 patient selection and critical clinical endpoints to facilitate compliance.

**References**