Circulating neuropilin-1 as a potential biomarker of progression-free survival benefit for tivozanib in metastatic clear cell renal cell carcinoma (RCC): post-hoc biomarker analysis of tivozanib RCC trials

Abstract Reference: A-17

Jie Lin, Michael Needle, Jeno Gyuris, Bin Feng

AVEO Oncology, Cambridge, MA, USA

Introduction

- Tivozanib hydrochloride (tivozanib) is a potent, selective inhibitor of vascular endothelial growth factor receptors (VEGFRs)-1, -2, and -3 with a long half-life that is designed to optimize blockade while minimizing off-target toxicities[1,2]
- Tivozanib has been investigated in renal cell carcinoma (RCC)
  - In the Phase 2 study of tivozanib in patients with RCC (Study 201), median progression-free survival (PFS) was 11.7 months in the intent-to-treat (ITT) population and 14.8 months in patients with clear cell renal cell carcinoma (ccRCC)[3]
  - In the TIVO-1 Phase 3 trial in patients with advanced RCC, the primary endpoint of median PFS was 11.9 months vs 9.1 months for sorafenib (hazard ratio [HR]: 0.797; 95% confidence interval [CI], 0.639–0.993; *P*=0.042)[4]
- The identification of biomarkers in targeted VEGFR cancer therapy has been challenging and neuropilin-1 (NRP-1) is a possible target candidate
  - NRP-1 is a VEGFR-2 co-receptor and is involved in the regulation of VEGFR-2 mediated angiogenesis[5,6]
- Following the completion of the 201 and TIVO-1 trials, post-hoc exploratory serum biomarkers analyses, including NRP-1, were performed to identify and validate candidate biomarkers of increased tivozanib benefit

Objective

- The objective of this study was to investigate potential biomarkers of tivozanib benefit in patients with advanced ccRCC

Methods

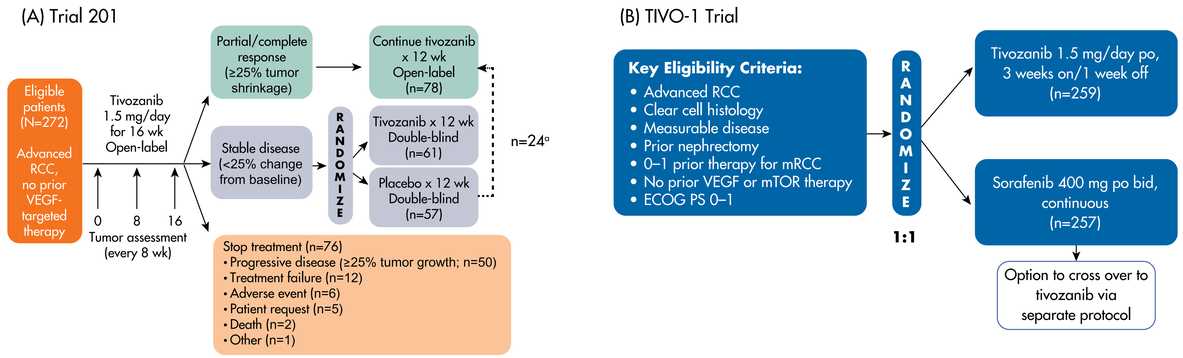
- The 201 study (NCT00502307) was a Phase 2, placebo controlled, randomized, discontinuation trial in patients with RCC (**Figure 1A**)
  - Patients had recurrent or metastatic RCC (mRCC) not amendable to surgery, no more than 1 prior systemic treatment for RCC, and no prior VEGF-targeted therapy
  - Following a 16-week open-label period in which patients were treated with tivozanib 1.5 mg once daily for 3 weeks followed by a 1-week break, patients with ≥25 tumor shrinkage continued tivozanib, subjects with tumor progression (≥25% increase) were discontinued, and the remaining patients were randomized to tivozanib or placebo
- TIVO-1 (NCT01030783) was an open-label, Phase 3, randomized, controlled, multi-national, multi-center, parallel-arm study comparing tivozanib with sorafenib in patients with mRCC (**Figure 1B**)
  - Patients had a prior nephrectomy, received ≤1 prior systemic treatment for mRCC, had no prior VEGF-targeted therapy or mammalian target of rapamycin-targeted therapy (mTOR), and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
  - Patients were randomized (1:1) to tivozanib 1.5 mg once daily for 3 weeks followed by a 1-week break, or sorafenib 400 mg twice daily continuously in a 4-week cycle
- Biomarker analyses were performed for patients in the 201 and TIVO-1 studies
  - Serum biomarker analysis was performed using Rules Based Medicine (RBM) Human Oncology 1.0 map enzyme-linked immunosorbent assay (ELISA) which measures the levels of 99 serum proteins
  - A Cox proportional hazard model was used to assess the association between potential serum biomarkers and PFS and overall survival (OS)

Results

Study 201

- Serum samples from 50 patients with ccRCC were profiled on RBM to identify and analyze serum factors that correlate with response to tivozanib
  - Maximum percent tumor reduction (MPR) and independent assessment of PFS were used to define responders; 25 responders and 25 nonresponders were chosen
    - Responders: MPR: -40.6% to -82.3%, PFS: 156 days to 838 days (n=25)
    - Non-responders: MPR: -7.8% to 174.2 %, PFS: 49 days to 144 days (n=25)
- NRP-1 was the only serum protein significantly different between responders and nonresponders (**Table 1, Figure 1**)
  - Below median levels of NRP-1 (NRP-1 low) was associated with increased clinical benefit

Figure 1. Study Design of Trial 201 (A) and TIVO-1 (B).

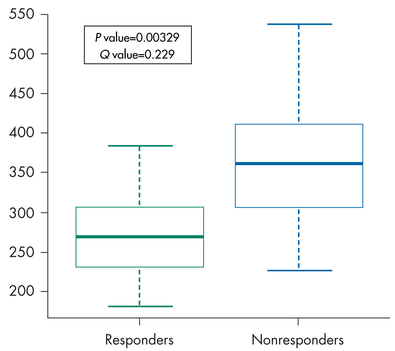


[a]Patients with progression during the double-blind phase were unblinded; those on placebo were allowed to restart tivozanib. All patients were unblinded after 12 weeks of double-blind treatment.

Table 1. Serum Protein Biomarkers Investigated in Study 201

Serum protein	*P* value	*Q* value
Neuropilin (NRP-1)	**0.0033**	**0.2289**
Leptin	0.0130	0.3664
Insulin-like growth factor binding protein 2 (IGFBP2)	0.0254	0.3664
Kallikrein 5	0.0308	0.3664
Endoglin	0.0316	0.3664
Phosphoserine aminotransferase (PSAT)	0.0362	0.3664
Insulin-like growth factor binding protein 1 (IGFBP1)	0.0368	0.3664
Interferon-gamma induced protein 10 (IP-10)	0.0449	0.3910
Monokine induced by gamma interferon (MIG)	0.0592	0.4581
Fibulin 1C (Fib-1c)	0.0708	0.4586

Figure 2. NRP-1 Levels in Tivozanib Responders vs Nonresponders



- In this exploratory analysis, controls were unavailable to determine whether NRP-1 was a potential prognostic or response biomarker
- NRP-1 was further investigated in the TIVO-1 trial

TIVO-1 Study

- Pretreatment serum samples from 240 patients treated with tivozanib were analyzed by RBM retrospectively
- Samples were classified as NRP-1 low (below the median NRP-1 level) and high (above the median)
- An increase in both PFS and OS was observed in patients with low NRP-1 levels (**Figures 3 and 4**)

Figure 3. PFS of Tivozanib-Treated Patients With High vs Low NRP-1 Levels Based on a Median Cutoff

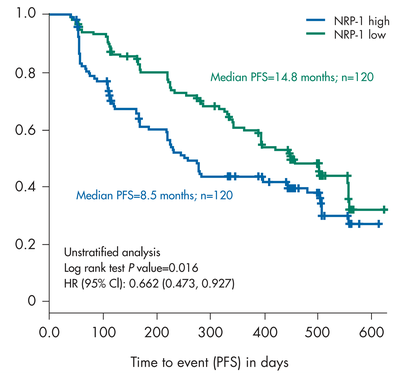
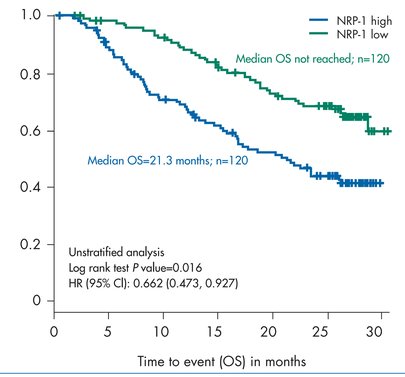


Figure 4. OS of Tivozanib-Treated Patients With High vs Low NRP-1 Levels Based on a Median Cutoff



Conclusions

- Exploratory biomarker analyses of tivozanib in Study 201 indicated NRP-1 as a potential biomarker of tivozanib efficacy in patients with ccRCC
- In TIVO-1, PFS and OS were both increased in tivozanib-treated patients with low levels of NRP-1, supporting NRP-1 as a potential tivozanib biomarker
  - The differentiation of NRP-1 as a prognostic marker vs predictive marker may be achieved by studies including a control arm

References

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