Subgroup analyses of a Phase III trial comparing tivozanib hydrochloride versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC)

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Abstract/Poster No: 354

Introduction

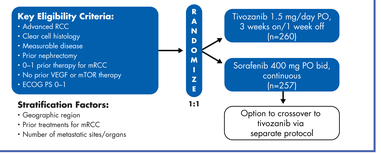
- Tivozanib hydrochloride (tivozanib) is a potent, selective inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 with a long half-life that is designed to optimize blockade while minimizing off-target toxicities[1,2]
- Tivozanib is taken orally (PO), once daily at 1.5 mg for 3 weeks followed by a one week rest
  - The half-life of 4.5–5.1 days allows once-daily administration with a consistent serum concentration[2,3]
- A Phase III trial in advanced renal cell carcinoma (RCC) patients met its primary endpoint of median progression-free survival (PFS)
  - For the subset of patients who had no prior therapy for metastatic disease, the median PFS was 12.7 months versus 9.1 months with sorafenib

Methods

Study Design

- TIVO-1 (NCT01030783) was an open-label, Phase III, randomized, controlled, multinational, multi-center, parallel-arm study comparing tivozanib with sorafenib in patients with mRCC who 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 **(Figure 1)**

Figure 1. TIVO-1: Phase III superiority study of tivozanib versus sorafenib as first-line targeted therapy for mRCC.



- Safety data were collected from consent to 30 days after last dose
- Response was assessed every 2 cycles (8 weeks)
- Eligible patients who progressed on sorafenib were given the option to receive tivozanib in an extension protocol (**see Motzer et al. Poster #364;** NCT01076010)

Analysis

- PFS was the primary endpoint, which was assessed by independent review and stratified by log-rank test with a two-sided significance level of α=0.05
- The planned trial size was N=500, giving a 90% power to detect a ≥45% improvement in median PFS from 6.7 months for sorafenib to 9.7 months for tivozanib
- PFS was compared between the 2 treatment groups for subgroups with at least 30 patients[4]
  - These included pre-specified subgroups defined by: geographic region (North America/Western Europe, Central/Eastern Europe), ECOG performance status score (0, 1), and number of prior systemic treatments for metastatic RCC (0, 1)
  - These also included exploratory subgroup analyses defined by the following variables: MSKCC (Memorial Sloan-Kettering Cancer Center) prognostic groups (intermediate and favorable), Heng prognostic groups (intermediate and favorable), and on-study blood pressure (systolic BP [SBP] ≤140 mm Hg, SBP >140 mm Hg, diastolic BP [DBP] ≤90 mm Hg, DBP >90 mm Hg)
    - MSKCC prognostic group was "favorable" for subjects with none of the following risk factors, "intermediate" with 1 or 2, and "poor" with more than 3: low Karnofsky Performance Status (KPS; <80%) (equivalent to ECOG status ≥1); high lactate dehydrogenase (>1.5 times upper limit of normal); low serum hemoglobin (<lower limit of normal); high corrected serum calcium (>10 mg/dL); absence of prior nephrectomy
    - Heng prognostic group was "favorable" for subjects with none of these risk factors, "intermediate" with 1 or 2, and "poor" with 3 to 6: low KPS (<80%) (equivalent to ECOG status ≥1); time from diagnosis to treatment with targeted therapy <1 year; low serum hemoglobin (<lower limit of normal [LLN]); high corrected serum calcium (>ULN); high neutrophils (>ULN); high platelets (>ULN)

Results

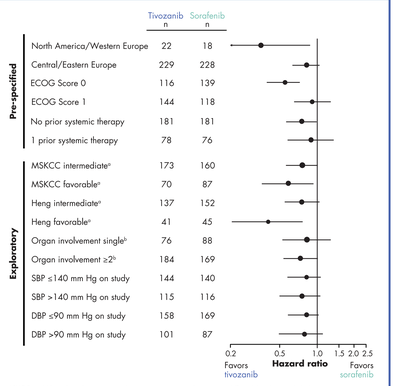
- Total of 517 patients were enrolled
- Most baseline demographics, including median age, gender, and MSKCC prognostic score, were similar between the treatment groups[4]

Table 1. Baseline Characteristics

Characteristic	Tivozanib	Sorafenib
No. of patients	260	257
Median age (range)	59 (23–85)	59 (23–85)
Gender, male (%)	71	74
ECOG score,[a] %		
0	45	54
1	55	46
Number of organs involved, %		
1	29	34
≥2	71	66
Sites of metastases, %		
Lung	82	79
Liver	26	19
Bone	24	20
MSKCC prognostic group,[a] %		
Favorable	27	34
Intermediate	67	62
Poor	7	4
Heng prognostic group, %		
Favorable	16	18
Intermediate	53	59
Poor	30	23
Prior systemic therapy for metastatic RCC, %		
0	70	70
1	30	30

ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma.
[a]Imbalance between arms. P<0.05 by Fisher exact test.

Figure 2. Forest plot of PFS hazard ratios.



[a]MSKCC and Heng "poor" prognostic subgroups were too small to estimate HR and therefore excluded.
[b]By independent radiological review assessment.

- However, ECOG performance status favored the sorafenib arm (P<0.05 by Fisher exact test; **Table 1**)
- There was a greater PFS benefit with tivozanib versus sorafenib in nearly all subgroups evaluated **(Figure 2)**
- Significant improvement in PFS by tivozanib versus sorafenib was observed for the following pre-specified subgroups:
  - North America/Western Europe region **(Figure 3)**
  - ECOG score 0 **(Figure 4)**
  - No prior systemic therapy **(Figure 5)**
- Exploratory subgroup analysis showed a significant improvement in PFS with tivozanib versus sorafenib for the following subgroups:
  - MSKCC favorable prognostic group **(Figure 6)**
  - Heng favorable and intermediate prognostic groups **(Figure 7)**
  - ≥2 organs involved **(Figure 8)**
- Within treatment arms, patients who developed elevated blood pressure (SBP >140 mm Hg or DBP >90 mm Hg, as shown in **Table 2**) on study had significantly longer PFS than patients who did not develop elevated BP (P<0.05 for within treatment arm comparison, both arms)
  - Hypertension is a recognized on-target effect of VEGF pathway inhibition[7]
- In all four subgroups of on-study BP, there was a trend toward longer PFS for tivozanib versus sorafenib **(Table 2)**
  - The longest median PFS (mPFS) was observed in patients in the tivozanib arm who developed elevated SBP (16.7 months) or elevated DBP (18.3 months)

Figure 3. PFS in North America/Western Europe and Central Europe.

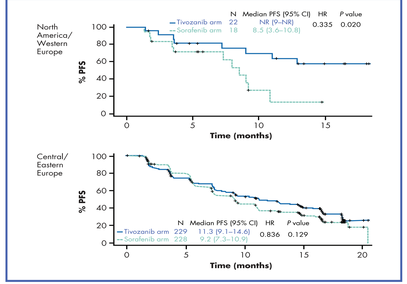


Figure 4. PFS by ECOG performance status.

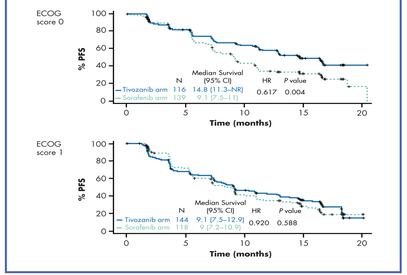


Figure 5. PFS by prior treatment history.

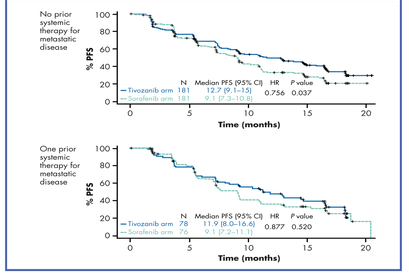
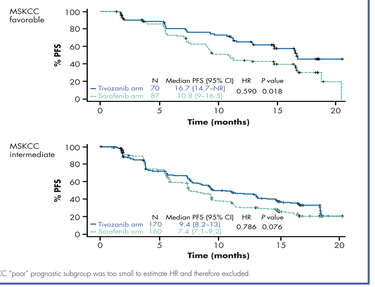
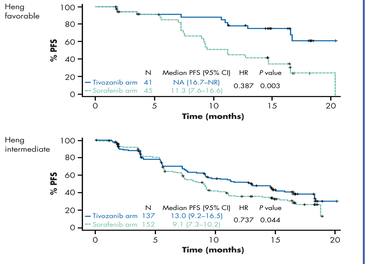


Figure 6. PFS by MSKCC favorable or intermediate score.



MSKCC "poor" prognostic subgroup was too small to estimate HR and therefore excluded.

Figure 7. PFS by Heng favorable or intermediate score.



Heng "poor" prognostic subgroup was too small to estimate HR and therefore excluded.

Figure 8. PFS by organ involvement.

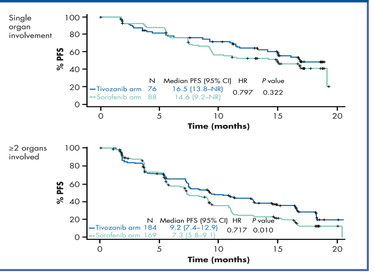


Table 2. On-study BP and PFS.

On-study BP, mm Hg	Tivozanib mPFS (95% CI)	Tivozanib n	Sorafenib mPFS (95% CI)	Sorafenib n	P value
SBP ≤140	9.0 (7.2–11.3)	144	5.8 (5.5–9.0)	140	0.142
SBP >140	16.7 (12.9–18.3)	115	11.1 (9.2–14.7)	116	0.076
DBP ≤90	9.1 (7.5–12.7)	158	7.3 (5.7–9.1)	169	0.156
DBP >90	18.3 (12.9–NR)	101	11.0 (9.3–16.4)	87	0.154

Discussion and Conclusions

- In the ITT population, tivozanib demonstrated statistically superior PFS over sorafenib
- Tivozanib was associated with a trend in longer PFS compared with sorafenib in multiple pre-specified and exploratory subset analyses
- Significant improvement by tivozanib versus sorafenib was observed for the following subgroups:
  - No prior systemic treatment
  - North America/Western Europe region
  - ECOG performance status score 0
  - MSKCC favorable prognostic group
  - Heng favorable and intermediate prognostic groups
  - Two or more organs involved
- Within treatment arms, development of elevated BP in both arms during the study was associated with significantly longer PFS than those who did not develop elevated BP

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