Treatment benefit of tivozanib hydrochloride vs sorafenib on health-related quality of life among patients with advanced/metastatic renal cell carcinoma (mRCC): TIVO-1 study results

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Abstract/Poster No: 355

Introduction

- A Phase III randomized open-label study (TIVO-1; NCT01030783) was conducted to compare the efficacy and safety, as well as patient reported outcomes (PROs) of tivozanib hydrochloride versus sorafenib in patients with clear cell advanced/mRCC. Patients were treatment naïve or received no more than 1 prior systemic therapy for metastatic disease
- Tivozanib demonstrated significantly prolonged progression-free survival (PFS) compared to sorafenib, in the overall study population (median 11.9 vs 9.1 months; hazard ratio [HR]=0.797, 95% confidence interval [CI]: 0.639–0.993, *P*=0.042) and in patients treatment-naïve for metastatic mRCC (12.7 vs 9.1 months; HR=0.756, 95% CI: 0.580–0.985, *P*=0.037). Tivozanib also showed a differentiated safety profile with lower rates of dose interruptions/reductions due to an adverse event versus sorafenib (18%/12% vs 35%/43%, respectively; *P*<0.001).[1] The impact of tivozanib on health-related quality of life (HRQoL), relative to sorafenib, is reported here

Methods

- In the Phase III TIVO-1 study, patients with mRCC were randomized 1:1 to receive tivozanib (1.5 mg PO once daily for 3 weeks on, 1 week off) or sorafenib (400 mg bid, continuously). HRQoL was assessed on Cycle 1/Day1 (baseline) and at the beginning of each cycle, using the Functional Assessment of Cancer Therapy–General (FACT-G), FACT–Kidney Symptom Index Disease Related Symptoms (FKSI-DRS) and EuroQol 5-dimensional (EQ-5D) questionnaires; EQ-5D scores are not reported here. Patients with baseline and ≥1 post-baseline evaluable forms were analyzed. Significance level throughout the analyses was 0.05

Change From Baseline

- Changes from baseline in FACT-G and FKSI-DRS scores over the course of the study were analyzed using mixed-effects repeated measures models (MMRM) controlling for baseline covariates. Data up to cycle 13 were used in order to remove biases introduced by high patient dropout beyond this time point. The model included the following covariates:
  - Treatment group (categorical: tivozanib or sorafenib)
  - Age (categorical: <65 or ≥65)
  - ECOG at baseline (categorical: 0 or 1)
  - Geographic region (categorical: North America/Western Europe, Central/Eastern Europe, rest of the world)
  - Number of prior treatments (categorical: 0 or 1)
  - Number of metastatic sites based on retrospective independent review (categorical: 1 or ≥2)
  - MSKCC prognostic group (categorical: good or intermediate/poor)
  - Time (months) from diagnosis to randomization (<1 year and ≥1 year)
  - Baseline value (continuous)
  - Time (categorical: Cycle 1, cycle 2, …, cycle 13)
  - Dose reduction during study (Yes; No)
- An unstructured covariance was fitted to the data. MMRM analyses utilize all data available and assume that the missing observations are missing at random (MAR) and the missing data pattern is independent of the unobserved measure conditional on the observed data. Given the potential that missing data may depend on the patient's health status and therefore missing not at random, a sensitivity analysis was performed based on missing data patterns (pattern-mixture model). Patients were stratified into groups based on time of dropout of the PRO component of the study as follows:
  - Completers before Month 12, defined as patients who completed the PRO measures at Month 12, and
  - Dropouts before Month 12, defined as patients whose last completed assessment occurred prior to Month 12
- If a patient without PRO data at Month 12 remained on-study after Month 12, s/he was classified as a "Completer." Intermittent missing data were considered to be MAR for purposes of the analyses. An MMRM was fitted within each stratum, and the estimates of the population parameters were given as the weighted averages of the estimates obtained within each pattern. Weights were estimated as the proportion of cases in each treatment group with each pattern[2]

HRQoL Improvement/Deterioration From Baseline Score

- A HRQoL improvement/deterioration from baseline at any time during the study was defined as follows:
  - FACT-G subscales and FKSI-DRS total score: 3 points
  - FACT-G total score: 6 points
- These thresholds were predefined based on existing evidence of score changes that are clinically meaningful to patients[3,4]
- The improvement rates of tivozanib versus sorafenib were compared using a stratified Cochran-Mantel-Haenszel mean score test at the two-sided 0.05 significance level with number of prior treatments (0 or 1) and number of metastatic sites based on retrospective independent review (1 or ≥2) as stratification factors

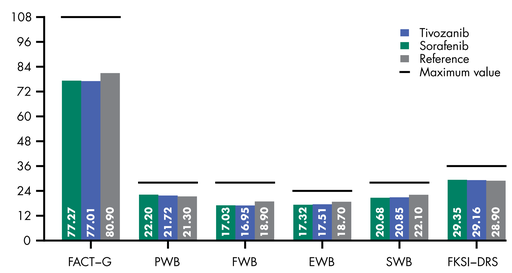
Time to First HRQoL Deterioration From Baseline Score

- The time to first HRQoL deterioration from baseline score was calculated as the duration of time from the date of randomization to the date of first HRQoL deterioration or date of death from any cause. If deterioration was observed after a missing value, it was assumed that the deterioration had occurred at the time of missing value. Patients who did not experience HRQoL deterioration from baseline score were censored at the date of the last instrument completion
- The treatment effect of tivozanib compared to sorafenib based on time to first HRQoL deterioration was tested with a stratified log-rank test and Kaplan-Meier curves were used to estimate its distribution. The stratification factors were number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥2). The effect of tivozanib compared to sorafenib was evaluated by a single HR (tivozanib/sorafenib) based on a Cox regression model

Results

- The HRQoL analysis included 509 patients: 258 in the tivozanib arm and 251 in the sorafenib arm. More than 98% of patients (tivozanib: n=257/258, 99.6%; sorafenib: n=251/251, 100%) in both treatment arms returned evaluable forms at baseline
- The average baseline HRQoL scores of the study population were similar to values reported for patients with advanced cancer **(Figure 1)**[5,6]

Figure 1. HRQoL baseline scores per treatment arm and reference values.[5,6]



EWB, emotional well-being; FACT-G, Functional Assessment of Cancer Therapy-General; FKSI-DRS, FACT–Kidney Symptom Index Disease Related Symptoms; FWB, functional well-being; PWB, physical well-being; SWB, social/family well-being.
Higher scores are associated with better health in all domains.

- Patients in both treatment arms experienced reductions in their PRO scores, except for the emotional well-being (EWB) subscale. Non-significant numeric differences usually favored tivozanib over sorafenib **(Table 1)**. Results were confirmed by the sensitivity analyses with pattern-mixture model

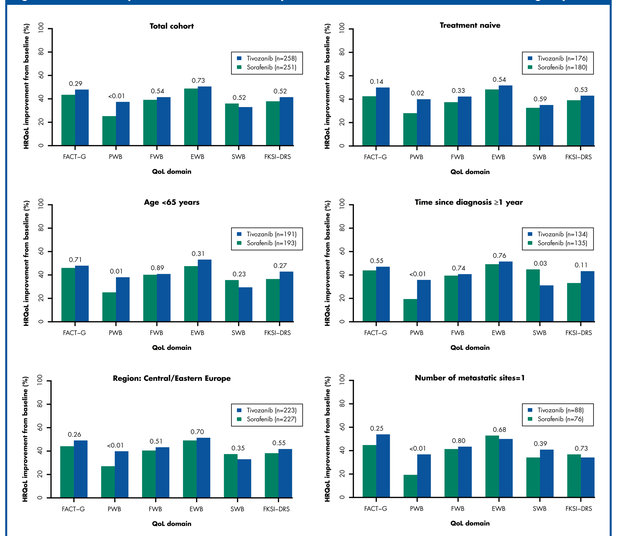
Table 1. MMRM Results on HRQoL Change From Baseline

Domain	Adjusted mean change from baseline (95% CI)			
	Tivozanib (n=258)	Sorafenib (n=251)	Difference	*P*-value
FACT-G total score	-2.83 (-4.88, -0.78)	-3.10 (-5.10, -1.10)	0.27 (-1.88, 2.42)	0.805
Physical well-being	-1.54 (-2.25, -0.84)	-2.08 (-2.77, -1.39)	0.53 (-0.18, 1.24)	0.141
Functional well-being	-0.73 (-1.52, 0.07)	-1.02 (-1.79, -0.25)	0.29 (-0.51, 1.10)	0.478
Emotional well-being	0.59 (0.02, 1.15)	0.40 (-0.15, 0.95)	0.19 (-0.38, 0.77)	0.513
Social/Family well-being	-0.79 (-1.57, -0.02)	-0.35 (-1.10, 0.41)	-0.45 (-1.24, 0.34)	0.265
FKSI-DRS	-0.94 (-1.59, -0.29)	-0.93 (-1.56, -0.30)	-0.01 (-0.67, 0.64)	0.965

FKSI-DRS, FACT–Kidney Symptom Index Disease Related Symptoms.

- Compared to sorafenib, a numerically greater percentage of patients on tivozanib reported HRQoL improvement from baseline at any time during the study for all planned comparisons with the exception of social/family well-being (SWB), which is not designed to detect drug effect. The difference for physical well-being (PWB) was statistically significant (37.4% vs 25.2%; *P*<0.01). Similar trends were observed in the following subgroups: treatment-naive, age <65, time since diagnosis ≥1 year; Central and Eastern Europe, and 1 metastatic site **(Figure 2)**

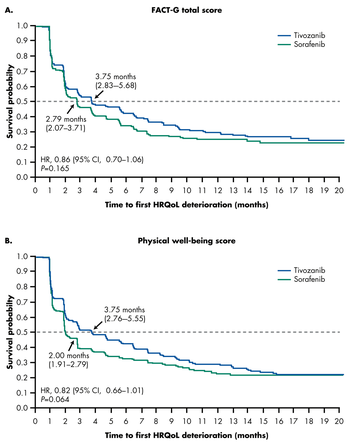
Figure 2. HRQoL improvement from baseline per treatment arm for total cohort and subgroups.



EWB, emotional well-being; FACT-G, Functional Assessment of Cancer Therapy-General; FKSI-DRS, FACT–Kidney Symptom Index Disease Related Symptoms; FWB, functional well-being; PWB, physical well-being; SWB, social/family well-being.
Numbers above bars represent P-values.

- Median time to first HRQoL deterioration was numerically longer with tivozanib (FACT-G total score: 3.75 months for tivozanib and 2.79 months for sorafenib; PWB: 3.75 months for tivozanib and 2.00 months for sorafenib) **(Figure 3)**; these results did not reach statistical significance

Figure 3. Kaplan-Meier curves for time to first HRQoL deterioration for FACT-G total score (A) and PWB score (B).



The dashed line indicates the median. HR <1 favors tivozanib.

Discussion and Conclusions

- Compared with sorafenib, tivozanib was not associated with decline in HRQoL across any scale or planned analysis, while providing significant treatment benefit on PFS and better tolerability as evidenced by fewer dose reductions and dose interruptions[1]
- HRQoL was maintained at a level comparable to the baseline level up to the analysis cut-off time point in both treatment arms (i.e., decrease in scores did not exceed the established MID)
- Numeric differences favoring tivozanib were observed regarding improvement rates across all subgroups and HRQoL scores, except SWB. Statistically significant difference in rates of improvement was observed in the PWB score for the total cohort with a consistent trend across several subgroups

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Acknowledgments

This study was sponsored by AVEO Oncology and Astellas. AVEO Oncology and Astellas are parties to a collaboration agreement for the co-development of tivozanib.
Editorial assistance was provided by Raffy M. Dakessian, PhD, Scientific Connexions, and was funded by AVEO Oncology and Astellas.

POSTER PRESENTED AT THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY GENITOURINARY CANCERS SYMPOSIUM; FEBRUARY 14-16, 2013; ORLANDO, FL

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