Disease Control Rate (DCR) With Tivozanib vs Sorafenib in Relapsed/Refractory Advanced Renal Cell Carcinoma (R/R RCC)

#N24

Sumanta K. Pal,[1]* Michael B. Atkins,[2] Thomas E. Hutson,[3] Bernard Escudier,[4] David F. McDermott,[5] Vijay Kasturi,[6] Brian I. Rini[7]

[1]Department of Medical Oncology and Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; [2]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; [3]Texas A&M College of Medicine, Bryan, TX; [4]Gustave Roussy, Villejuif, France; [5]Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; [6]Aveo Oncology, Boston, MA; [7]Vanderbilt-Ingram Cancer Center, Nashville, TN

**Presenting author.*

Background

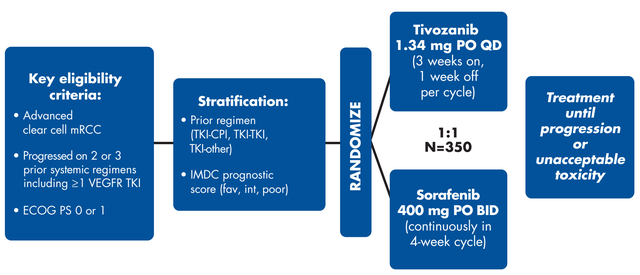
- Tivozanib is potent and highly selective vascular endothelial cell growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) with a long half-life[1-3]
- Tivozanib is approved in the United States for treatment of patients with advanced R/R RCC following ≥2 prior systemic therapies[3]
- In the phase 3 TIVO-3 trial,[1] tivozanib (vs sorafenib) was well tolerated with:
  - Significantly longer median progression-free survival (PFS; 5.6 vs 3.9 months; hazard ratio [HR], 0.73; 95% CI, 0.56-0.94; *P*=.016)[1]
  - Significantly higher overall response rate (ORR) by independent radiology review (18% vs 8%; *P*=.02)[3]
  - Numerically higher rate of 1-year duration of response (DOR, 71% vs 46%; HR, 0.60; 95% CI, 0.22-1.61; *P*=.33). The median DOR was not reached (NR; 95% CI, 12.9-NR) with tivozanib and was 5.7 months (95% CI, 5.6-NR) with sorafenib[1,3]
- The likelihood of measurable RCC tumor response diminishes after ≥2 lines of therapy (LOT), and the clinical relevance of prolonged stable disease (SD) is increasingly important[1]
- DCR is a landmark measure, defined as the sum of tumor response (complete response [CR] plus partial response [PR]) plus SD, but results vary by required duration of SD
- Previous research in advanced RCC suggests that improvement in DCR may correlate with longer-term survival and underscores the contribution of SD to patient-level outcomes[4]
- In these exploratory analyses, we assessed DCR and the probability of disease control (DC) to evaluate the magnitude of benefit with tivozanib relative to sorafenib over time

Methods

Study Design

- TIVO-3 (NCT02627963) is a phase 3, open-label study that enrolled patients with R/R RCC whose disease progressed on 2 or 3 prior systemic regimens, including ≥1 VEGFR TKI (**Figure 1**)

Figure 1. TIVO-3 Study Design



BID, twice daily; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; fav, favorable; IMDC, International Metastatic RCC Database Consortium; int, intermediate; mRCC, metastatic RCC; PO, orally; QD, once daily.

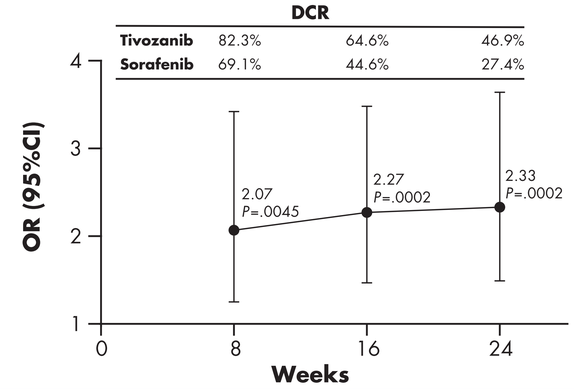
- DCR was measured as the percentage of patients who achieved CR, PR, or SD (RECIST v1.1). Investigator-assessed DCR in the intent-to-treat (ITT) population was compared between tivozanib and sorafenib, as reported at study weeks 8, 16, and 24
- Patients with unevaluable or missing scans were classified as having PD
- Odds ratios (ORs), 95% CIs, and *P* values were calculated for each time point using logistic regression; DCR across prespecified subgroups was analyzed descriptively
- ORs and 95% CIs were also calculated for subgroups stratified by number of prior LOT (2 or ≥3), previous immuno-oncology treatment (IO; yes or no), IMDC risk score (favorable, intermediate, or poor), and age group (≥65 or <65 years). *P* values were not computed for the exploratory subgroup analysis

Results

DCR in the ITT Population

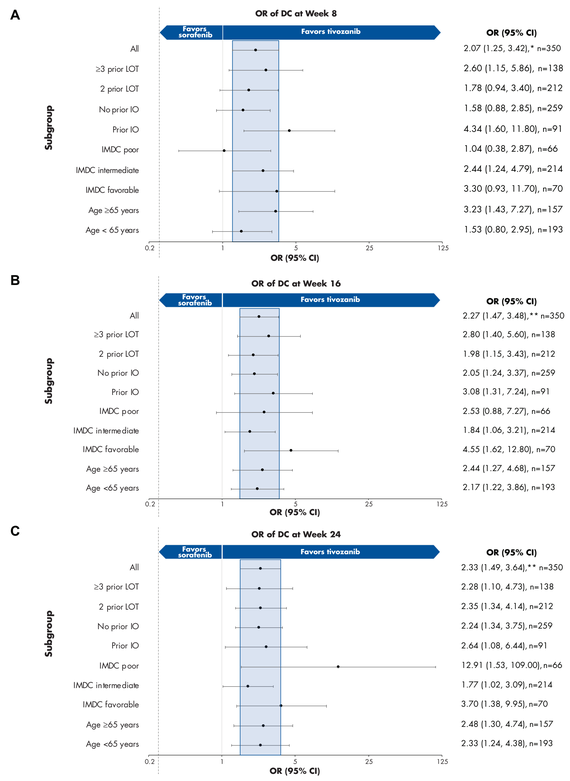
- Overall, 350 patients were randomized 1:1 to receive tivozanib (n=175) or sorafenib (n=175)
- DCR at weeks 8, 16, and 24 was consistently higher with tivozanib than with sorafenib (**Figure 2**)
- The absolute difference in DCR (tivozanib minus sorafenib) increased from 13% at week 8 to 20% at week 16 and was maintained at week 24
- Patients treated with tivozanib had more than double the odds of achieving DC than those receiving sorafenib (**Figure 2**)

Figure 2. Odds Ratio (95% CI) and DCR at Weeks 8, 16, and 24 of the TIVO-3 Trial



DCR by Age and Prior IO Subgroups

Figure 3. Odds Ratio of Achieving DC by Subgroups at (A) Study Week 8, (B) Week 16, and (C) Week 24



Blue shaded area represents the values between the lower and upper bounds of the 95% CI of the OR in the ITT (All) population. x-axes are scaled logarithmically. **P*=.0045, ***P*=.0002.

- When analyzed by subgroups, the odds of achieving DC were generally in favor of tivozanib over sorafenib across subgroups categorized by number of prior LOT, previous treatment with IO, IMDC risk, and age group (**Figure 3**)
- The 95% CIs for the ORs in all subgroups overlapped with those of the ITT (All) population, suggesting consistent DC benefit with tivozanib vs sorafenib. However, the IMDC poor-risk subgroup had an OR close to 1 at week 8, suggesting that rapid progression in this population was likely regardless of treatment received

Conclusions

- In the ITT population, DCR and the odds of achieving DC were higher with tivozanib than with sorafenib in patients with advanced R/R RCC and ≥2 prior lines oftherapy
- The odds of achieving DC with tivozanib were double those with sorafenib at week 8, increased from week 8 to 16, and were maintained to week 24, suggesting both ongoing and incremental benefit over time
- The odds of having DC generally favored tivozanib over sorafenib across subgroups categorized by prior LOT, previous IO therapy, IMDC risk score, and age group

The DCR with tivozanib was significantly higher than that with sorafenib at the first 8-week measure of response and remained so through week 24. The improved odds of DC were consistent across all subgroups, increased with additional follow-up, suggesting DC is an important endpoint for these patients with advanced R/R RCC receiving third- or fourth-line treatment.

References

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E-mail: vkasturi@aveooncology.com