Efficacy and safety data from patients with advanced renal cell cancer treated with tivozanib hydrochloride after progression on sorafenib

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Introduction

Tivozanib hydrochloride (tivozanib) is a potent, selective inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, with a long half-life that is designed to optimize blockade while minimizing off-target toxicity.1

Tivozanib is given orally (PO), once daily at 1.5 mg for 3 weeks followed by a one week rest

A Phase III trial (TIVO-1) in advanced renal cell carcinoma (RCC) patients failed its primary endpoint, progressive survival (PS), with a median follow-up of 19.6 months in the tivozanib arm vs 9.1 months in the sorafenib control arm (P=0.042).

It is a prespecified subgroup analysis of treatment-naive patients for metastatic disease, the PS benefit of tivozanib was 12.7 months vs 9.1 months with sorafenib (P=0.037).

- Patients who progressed on sorafenib (had documented progressive disease (PD), or for any other reason besides radiographic progressive disease, were not eligible to receive tivozanib in the extension study
- Patients who were randomized to either tivozanib or sorafenib and were not eligible to receive tivozanib in the extension study were not eligible to receive tivozanib.
- Patients who did not tolerate sorafenib and previously discontinued for adverse events (AEs), or for any other reason besides radiographic progressive disease, were not eligible to receive tivozanib in the extension study
- Patients who were to have been no more than 4 weeks from last dose of sorafenib until enrollment in the extension study

Objectives

- The primary objectives of the study were:
  - To allow long-term access to either tivozanib or sorafenib for patients who participated in TIVO-1 and experienced clinical benefit and acceptable tolerability within their randomly assigned treatment arm
  - To allow access to tivozanib for patients who participated in TIVO-1 and failed sorafenib treatment (progressive disease (PD) per RECIST (Version 1.0)) in TIVO-1 and were offered tivozanib
  - To allow access to tivozanib for patients who participated in TIVO-1 and failed sorafenib treatment (progressive disease (PD) per RECIST (Version 1.0)) in TIVO-1 and were offered tivozanib
  - To determine the anti-tumor activity of tivozanib in patients who received tivozanib after progression on sorafenib by this date
  - To determine ORR, PFS, overall survival (OS), and AEs were evaluated in patients who received tivozanib after progression on sorafenib

Methods

- Study Design
  - This was an open-label, multinational extension study (NCT01307018) of TIVO-1 Phase III Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib to Sorafenib in Subjects With Advanced Renal Cell Carcinoma (NCT01307018)
  - Planned enrollment in this extension study was to include the following:
  - Patients who were randomized to either tivozanib or sorafenib in TIVO-1 and demonstrated clinical benefit and acceptable tolerability in TIVO-1 and were offered long-term access to their respective study drug
  - Patients who progressed on sorafenib (had documented progressive disease (PD) per RECIST (Version 1.0)) in TIVO-1 and were offered long-term access to their respective study drug
  - Patients who discontinued sorafenib because of dose reductions or discontinuation of sorafenib due to AEs, or for any other reason besides radiographic progressive disease, were not eligible to receive tivozanib in the extension study

Study Population

- Patient population was predominantly male, white, and from Central/Eastern Europe
- The confirmed ORR was 13% (95% CI: 8.5–19.8), with 28 (18%) patients achieving a confirmed partial response (PR)
- Patients who were no more than 4 weeks from last dose of sorafenib until enrollment in the extension study
- Only patients with RECIST-defined progression on sorafenib in TIVO-1 who then received tivozanib in the extension study were included in this analysis

Results

- Of the 156 patients, 101 (65%) discontinued study drug and 55 patients (35%) were ongoing at the time of the analysis
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- Patients were to have been no more than 4 weeks from last dose of sorafenib until enrollment in the extension study, and have an ECOG performance status of 0 (Table 2)

Discussion and Conclusions

- In this interim report, tivozanib has demonstrated antitumor activity after radiographic progression on sorafenib
- Concluded ORR: 13% (95% CI: 8.5–19.8)
  - Tumor shrinkage in 74% of patients
  - PFS: 8.4 months (95% CI: 5.5–12.4)
  - The anti-tumor activity of tivozanib may be contributing to the OS of patients randomized to sorafenib in TIVO-1 (see Motzer et al. Poster #350)
  - Rates of dose reduction and dose interruption due to AEs for tivozanib as compared to sorafenib were lower.
  - This was consistent with the low rates of dose reduction and interruption observed in TIVO-1 (see Motzer et al. Poster #350) as compared to sorafenib (9.3% vs 14.2%)
  - The AE profile of next-line tivozanib after sorafenib was similar to that of tivozanib as frontline therapy in TIVO-1, with the exception of hypertension
  - Hypertension on next-line tivozanib was approximately half as common as observed in TIVO-1
  - All grades in this study were 24% vs 44% in TIVO-1
  - Grade 3/4 in this study were 12% vs 26% in TIVO-1

- The long ite of reported hypertension in the extension study may be related to effective management of this classifiable on prior sorafenib
- Study is currently in progress and patient follow-up is ongoing

References


Acknowledgments

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