Tivozanib vs sorafenib targeted therapy for advanced renal cell carcinoma: final results of a Phase 3 trial (901) and efficacy results of a second line tivozanib extension study (902)

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Background

- Tivozanib is a selective oral vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI)[1], with a long half-life and activity against all 3 VEGF receptors[2]
- TIVO-1 (301) was an open label, Phase 3 multinational trial (901) in which patients with metastatic renal cell carcinoma (mRCC) were randomized to either tivozanib or sorafenib (both VEGF TKIs)
  - TIVO-1 met its primary endpoint of improved median progression free survival (PFS) over sorafenib, but overall survival (OS) was shorter[3]
- An extension (902) and open access study allowed follow-up of patients from TIVO-1
  - Patients from TIVO-1 were allowed to continue long-term access with tivozanib or sorafenib; patients who failed on sorafenib were allowed to cross over to the tivozanib treatment[4]

Objective

- The objective was to provide final follow-up results of TIVO-1 (901) first-line patients and of the second-line treatment patients from the TIVO-1 trial that crossed over from sorafenib to tivozanib

Methods

- TIVO-1 was an open-label, Phase 3, randomized, controlled, multinational, parallel-arm study
  - Patients had mRCC and had a prior nephrectomy, received ≤1 prior systemic treatment for mRCC, had no prior VEGF-targeted therapy or mammalian target of rapamycin-targeted (mTOR) therapy, and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
  - Patients received tivozanib 1.5 mg PO once daily for 3 weeks followed by 1 week off, or sorafenib 400 mg PO twice daily continuously in a 4-week cycle
- Planned enrollment in the extension included patients who demonstrated acceptable tolerability in TIVO-1 and were provided long-term access to their respective drug, and patients who progressed on sorafenib (documented progressive disease per RECIST [Version 1.0]) and were provided tivozanib
  - Patients were treated until documented progression or unacceptable tolerability on both treatments, and were followed for OS, investigator assessed PFS, and long-term safety
  - The majority of patients initially treated with sorafenib crossed over to tivozanib, while the majority of patients who received first-line tivozanib had no subsequent therapy

Results

Patients

- Almost all patients discontinued initial therapy of tivozanib or sorafenib; however, few second-line therapy options were available to patients who discontinued initial tivozanib in most of the participating countries (**Table 1**)
  - Of the 259 tivozanib patients, 69.3% received no subsequent therapy, 11.7% VEGF therapy (other than tivozanib), 9.7% mTOR inhibitor therapy, and 10.0% non-targeted therapy
  - All 257 patients discontinued initial sorafenib therapy and 168 (65.4%) went on to subsequent VEGF therapy (163/168 were treated with tivozanib), 1.2% to mTOR, 2.0% to non-targeted therapy, and 31.5% received no additional therapy

Table 1. TIVO-1 Study Follow-up Therapy

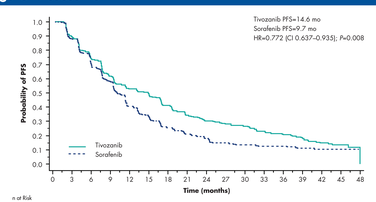
	Tivozanib	Sorafenib
Randomized to initial therapy, n	260	257
Discontinued initial therapy, n	259	257
Second-line therapy, n (%)		
VEGF	30 (11.7)	168 (65.4)
mTOR	25 (9.7)	3 (1.2)
Non-targeted	26 (10.0)	5 (2.0)
No therapy	178 (69.3)	81 (31.5)

mTOR, mammalian target of rapamycin-targeted; VEGF, vascular endothelial growth factor.

First-line analysis

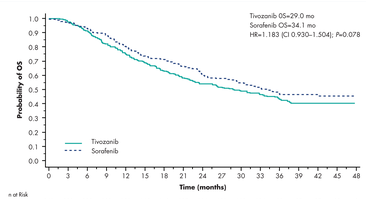
- Follow-up PFS and OS from the initial randomization of 260 patients originally receiving tivozanib and the 257 patients originally receiving sorafenib was similar to the primary analysis showing improved PFS but shorter OS
  - Median PFS was 14.6 months for tivozanib and 9.7 months for sorafenib (HR=0.77, **Figure 1**)
  - Median OS was 29.0 months for tivozanib and 34.1 months for sorafenib (HR=1.18, **Figure 2**)
  - Consistent with other RCC studies, OS improves with additional lines of therapy (**Table 2**)

Figure 1. First-line Treatment Progression-free Survival; Investigator Assessment



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 2. First-line Treatment Overall Survival; Investigator Assessment



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Table 2. Effect on Availability of Second-line Therapy on Overall Survival

Region	Patients Receiving Second-line Therapy, %		OS Hazard Ratio (*P*-value)
	Tivozanib	Sorafenib	
All N=517	36	74	1.245 (*P*=NS)
NA and EU[a] n=186	50	76	0.890 (*P*=NS)
NA and EU5[b] n=40	87	82	0.503 (*P*=NS)

[a]EU includes Bulgaria, Czech Republic, France, United Kingdom, Hungary, Italy, Poland, Romania (countries with patients enrolled in Study 301)
[b]EU5 includes UK, Italy, and France (EU5 countries with patients enrolled in Study 301)
EU, European Union; HR, hazard ratio; NA, North America; NS, not significant; OS, overall survival.

- Long-term safety assessment of patients who continued tivozanib indicated that the incidence of the most common on-target AEs (hypertension and dysphonia) decreased over time (**Table 3 and 4**)
  - Off-target AE of palmar-plantar erythrodysesthesia was more frequent in the sorafenib group
  - Diarrhea and proteinuria occurred at a higher rate after >12 months of tivozanib treatment than during the first 2 months

Table 3. Percent All-Grade Adverse Events in First-line Treatment Patients[a]

	Tivozanib			Sorafenib		
	<2 months N=259	2–12 months N=234	>12 months N=130	<2 months N=257	2–12 months N=226	>12 months N=99
Hypertension	32.0	18.8	6.2	25.7	13.7	5.1
Diarrhea	5.4	18.8	14.6	15.2	23.9	13.1
Fatigue	8.5	14.1	6.9	9.7	8.4	5.1
Palmar-plantar erythrodysesthesia syndrome	7.7	9.4	8.5	47.1	23.0	8.1
Asthenia	6.9	9.8	5.4	8.2	9.7	3.0
Dysphonia	17.4	6.4	4.6	3.9	0.9	0
Decreased appetite	5.0	6.0	3.1	4.7	5.8	1.0
Dyspnea	6.2	7.7	1.5	1.9	5.8	4.0
Peripheral edema	1.5	1.7	2.3	0.8	3.5	0
Proteinuria	3.5	7.7	9.2	3.9	6.2	6.1

[a]Data from an October 2012 data cut, analyzed by <2 months from onset of treatment, 2 to 12 months from onset of treatment, or ≥12 months from onset of treatment.
AE, adverse event.

On-target tivozanib AEs Off-target tivozanib AEs

Table 4. Percent Grade 3/4 Adverse Events in First-line Treatment Patients[a]

	Tivozanib			Sorafenib		
	<2 months N=259	2–12 months N=234	>12 months N=130	<2 months N=257	2–12 months N=226	>12 months N=99
Hypertension	20.5	7.7	3.1	13.6	4.9	4.0
Diarrhea	0	2.1	1.5	0.8	5.8	3.0
Fatigue	1.2	3.8	1.5	1.9	2.2	0
Palmar-plantar erythrodysesthesia syndrome	0.4	1.7	0.8	14.0	5.3	1.0
Asthenia	2.3	1.7	0.8	1.9	0.9	0
Dysphonia	0	0	0	0	0	0
Decreased appetite	0	0.4	0	0	0.9	0
Dyspnea	0	1.7	0.8	0	2.2	0
Peripheral edema	0	0	0	0	0	0
Proteinuria	0.4	1.7	1.5	0.8	2.2	1.0

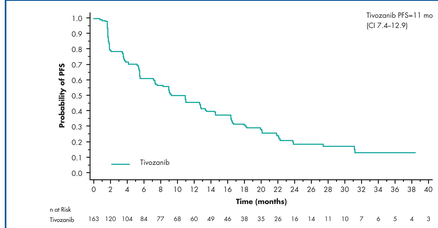
[a]Data from an October 2012 data cut, analyzed by <2 months from onset of treatment, 2 to 12 months from onset of treatment, or ≥12 months from onset of treatment.
AE, adverse event.

On-target tivozanib AEs Off-target tivozanib AEs

Second-line analysis

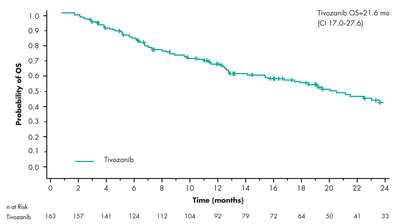
- For the 163 patients who crossed over from sorafenib to second-line tivozanib, median PFS was 11 months (CI 7.4–12.9; **Figure 3**) and median OS was 21.6 months (CI 17.0–27.6; **Figure 4**) from the start of second-line tivozanib
- The most common all-grade and grade 3/4 AE was hypertension, similar to that reported in the primary TIVO-1 study analysis (**Table 5**)

Figure 3. Second-line Tivozanib Treatment Progression-free Survival



CI, confidence interval; PFS, progression-free survival.

Figure 4. Second-line Tivozanib Treatment Overall Survival



CI, confidence interval; OS, overall survival.

Table 5. Most Frequently Reported Adverse Events Occurring in ≥5% of Second-line Tivozanib Treated Patients[a]

Adverse event, %	All-Grades	Grade 3/4
Hypertension	24	12/0
Diarrhea	13	2/0
Fatigue	12	3/0
Palmar-plantar erythrodysesthesia syndrome	10	1/0
Asthenia	9	3/0
Dysphonia	6	0
Decreased appetite	6	0
Dyspnea	5	1/0
Peripheral edema	5	0

[a]AEs are listed by MedDRA (Version 14.0) preferred term in decreasing frequency for total patients; AEs ongoing at the time of cross-over were recorded as medical history and only reported as on-study AE if severity increased (data cut Feb 4, 2013).
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Conclusions

- This long-term analysis of PFS and OS underscores the positive impact of tivozanib treatment after sorafenib failure in mRCC
- Lack of access to targeted second-line therapy in patients in the tivozanib arm due to geographical reasons (primarily from Eastern Europe) affected the trial results

References

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Acknowledgments

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