



**Tivozanib Hydrochloride  
in  
Advanced Renal Cell Carcinoma**

**ADVISORY COMMITTEE BRIEFING MATERIALS:  
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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Expanded Term
$\lambda_z$	terminal disposition rate constant
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
BP	blood pressure
CI	confidence interval
CL/F	apparent oral clearance
C <sub>max</sub>	maximum concentration
C <sub>min</sub>	minimum concentration
CR	complete response
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DR	duration of response
DS	duration of stable disease
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EQ-5D	European Quality of Life 5-Domain Scale
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	Food and Drug Administration
FKSI-DRS	Functional Assessment of Cancer Therapy - Kidney Symptom Index
HFS	hand-foot syndrome
HR	hazard ratio
IC <sub>50</sub>	half-maximal inhibitory concentration
IFN- $\alpha$	interferon-alpha
IRR	independent radiological review

<b>Abbreviation</b>	<b>Expanded Term</b>
ITT	intent-to-treat
IVRS	interactive voice response system
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDGFR	platelet-derived growth-factor receptor
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PopPK	population pharmacokinetics
PP	per protocol
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient -reported outcome
QTc	QT interval corrected for heart rate
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SBP	systolic blood pressure
SD	stable disease
SMQ	Standardized MedDRA Query

<b>Abbreviation</b>	<b>Expanded Term</b>
sVEGFR-2	soluble VEGF receptor-2
$t_{1/2}$	terminal elimination half-life
TKI	tyrosine kinase inhibitor
Tmax	time to maximum concentration
TSH	thyroid stimulating hormone
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel-Lindau

## **1. INTRODUCTION AND EXECUTIVE SUMMARY**

### **1.1. Introduction**

AVEO Pharmaceuticals Inc. (“AVEO”) submitted a New Drug Application (NDA) to the FDA on 28 September 2012 to support the approval of tivozanib hydrochloride (hereinafter referred to as tivozanib) for the treatment of patients with advanced renal cell carcinoma (RCC).

Tivozanib, an oral tyrosine kinase inhibitor (TKI), was developed by AVEO for the treatment of RCC because of its high potency and selectivity for all 3 vascular endothelial growth factor receptors (VEGFR-1, -2, and -3), relative to its inhibition of non-VEGF tyrosine kinases, and its long half-life. High potency and selectivity for the VEGFRs may lower the incidence of adverse events unrelated to VEGF inhibition, allowing more patients to remain on an effective dose.

Overall, 785 subjects with advanced RCC have received single-agent tivozanib at the proposed dose and regimen, 1.5 mg daily for 3 weeks followed by 1 week off treatment. The NDA includes data from a proof-of-concept Phase 2 study 201 that tested the proposed dose and schedule, which were subsequently used in the pivotal Phase 3 study 301. In study 301, tivozanib produced a statistically significant and clinically meaningful increase in progression-free survival (PFS) in patients with advanced RCC relative to sorafenib, an approved TKI. In extension study 902, 156 subjects who had documented progressive disease on sorafenib while in study 301 were treated with next-line tivozanib. The safety profile across development is consistent with the high VEGF selectivity relative to other kinase inhibition.

### **1.2. Renal Cell Carcinoma: Disease and Treatment**

In 2012, there were about 59,500 new cases of RCC with more than 12,000 deaths in the US.<sup>1</sup> As of 2007, RCC was the seventh most frequently diagnosed cancer in the US and the third leading urologic cancer.<sup>2</sup> The incidence of RCC is greatest after age 55 and twice as high in males as in females. Other risk factors include smoking, obesity, chronic renal failure, family history of RCC, and rare hereditary conditions.<sup>3</sup>

At initial diagnosis, approximately 25% of patients with RCC have locally advanced or metastatic disease.<sup>4</sup> RCC tends to metastasize to the lung, lymph nodes, bone, brain, liver, and adrenal glands. In general, treatment for locally advanced or metastatic disease consists of nephrectomy (either partial or complete) followed by systemic therapy.<sup>1,3,5</sup> Survival rates are strongly correlated with clinical stage at diagnosis. Five-year survival is 91% in patients with localized disease compared with 12% in patients with metastatic disease.<sup>6</sup>

Prior to 2005, systemic treatment options for RCC were limited to cytokines (interferon-alpha and interleukin-2 in selected patients) because of the resistance of RCC to conventional cytotoxic chemotherapy. Since 2005, three VEGFR TKIs – sorafenib, sunitinib, and pazopanib – have been approved for the treatment of advanced RCC,<sup>7-9</sup> the indication sought in the NDA submitted for tivozanib. A fourth TKI, axitinib, was

approved for the treatment of advanced RCC after failure of one prior systemic therapy. The effectiveness of TKIs in RCC is believed to be due to VEGF inhibition, with mechanistic studies confirming that RCC is highly sensitive to VEGF modulation.<sup>10-12</sup> Clear cell RCC, the most common type of RCC, is associated with inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene. Lack of VHL activity leads to stabilization of hypoxia-inducible factor 2-alpha, which results in overexpression of the angiogenic factor VEGF, explaining the hypervascular nature of clear cell RCC and its sensitivity to VEGF-targeted agents.<sup>13</sup>

Each of the 3 VEGFR TKIs approved broadly for use in advanced RCC (Table 1) was approved based on registration studies which included PFS as the primary endpoint and either placebo or interferon-alpha (IFN- $\alpha$ ) as the comparator.<sup>7-9</sup>

**Table 1: Early VEGFR Tyrosine Kinase Inhibitor Approvals were Based on Benefit Compared with Placebo or Interferon Alpha**

VEGFR TKI	Study Population	Median PFS (Months)	PFS HR	p-value	Year of Approval
Sorafenib (vs placebo)	Prior cytokines	5.5 vs 2.8 <sup>1</sup>	0.44	<0.001	2005
Sunitinib (vs IFN- $\alpha$ )	Treatment-naïve	10.9 vs 5.1 <sup>2</sup>	0.42	<0.000001	2006
Pazopanib (vs placebo)	Treatment naïve-prior cytokines	9.2 vs 4.2 <sup>3</sup>	0.46	<0.001	2009

Source: 1. Escudier et al. 2007 NEJM;<sup>14</sup> 2. Sutent [prescribing information] 2012<sup>9</sup>; 3. Sternberg et al. 2010 J Clin Oncol.<sup>15</sup>

HR = hazard ratio; IFN- $\alpha$  = interferon alpha; PFS = progression-free survival; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

The availability of new RCC treatment options in both first and subsequent lines of therapy has corresponded with improvements in median overall survival from 10 months in 1999 to approximately 28 months currently.<sup>16</sup> In the US, treatment with multiple lines of targeted therapy has become the standard of care.<sup>5</sup>

Clinical trial data support the concept that multiple lines of targeted therapy can improve overall survival. The RECORD-1 study, a placebo-controlled Phase 3 trial, evaluated everolimus, an mTOR inhibitor, in patients with metastatic RCC who had received prior VEGF therapy. In this study, the median PFS for patients treated with everolimus versus placebo was 3.9 versus 1.8 months in patients who had received prior sunitinib and 5.9 versus 2.8 months for patients who had received prior sorafenib, showing the efficacy benefit for subsequent therapy vs. placebo after an initial VEGF targeted agent. In a post-hoc, exploratory analysis, after adjusting for patients who crossed over from placebo to the active agent, the overall survival was shown to be 1.9-fold longer if treated with everolimus than if treated with placebo (i.e. never treated). This analysis indicated that receipt of a second targeted therapy after an initial VEGF targeted therapy could result in

4 months additional OS benefit, compared with patients who did not receive a second targeted therapy.<sup>17</sup>

Recent retrospective analyses of survival patterns for patients with RCC support the concept that sequential therapies are associated with longer overall survival. A study by Harrison et al.<sup>18</sup> presented data from a registry of 255 RCC patients across 11 community oncology centers in the US. The patients had been diagnosed since January 2007, not enrolled in a trial and were aged 65 ± 11 yrs. 62% had clear cell histology (25% unknown) with a MSKCC risk breakdown of 28% good, 63% intermediate, and 10% poor. Patients were grouped by treatment sequence, reflecting up to 3 exposures based on drug mechanism of action (VEGFR TKI or mTOR). The authors concluded that only patients treated with 2 TKI exposures approached the OS seen in recent clinical trials.

A second study by Xie et al,<sup>19</sup> looked retrospectively at 2161 mRCC patients treated with targeted therapy. 152 patients who survived 4 years or more after the initiation of targeted therapy (long-term survivors) were compared with 218 patients who survived 6 months or less (short-term survivors) over the same time period (2004-2007). In a multivariate analysis that controlled for prognostic factors, long term survival was associated with response to targeted therapy and use of second-line targeted therapy.

In clinical trials, while sunitinib showed a strong trend in improved overall survival, none of the approved TKIs has demonstrated a statistically significant improvement in this endpoint (Table 2), likely due to the confounding effects of crossover to subsequent therapies in the clinical trial setting.<sup>20</sup>

**Table 2: Improvement in Overall Survival has been Difficult to Demonstrate**

VEGFR TKI	Comparator	Study Population	Median OS (Months)	OS HR (95% CI)	p-value
Sorafenib <sup>1</sup>	Placebo	Prior cytokines	17.8 vs. 15.2	0.88	0.146
Sunitinib <sup>2</sup>	IFN- $\alpha$	Treatment-naïve	26.4 vs. 21.8	0.82	0.051
Pazopanib <sup>3</sup>	Placebo	Treatment-naïve, Prior cytokines	22.9 vs. 20.5	0.91	NR <sup>6</sup>
Axitinib <sup>4</sup>	Sorafenib	Treatment-naïve	20.1 vs. 19.2	0.97	NS
Pazopanib <sup>5</sup>	Sunitinib	Treatment-naïve	28.4 vs. 29.3	0.91	0.275

Source: 1. Escudier et al. 2009 J Clin Oncol<sup>21</sup>; 2. Motzer et al. 2009 J Clin Oncol<sup>22</sup>; 3. Sternberg et al. 2013 Eur J Cancer<sup>23</sup>; 4. Inlyta [prescribing information] 2012<sup>24</sup>; 5. Motzer et al. 2012 ESMO<sup>16</sup>. 6. Omitted from publication and listed as ‘not mature.’

HR = hazard ratio; NR = not reported; NS = not significant; OS = overall survival; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

While VEGFR TKIs have become the mainstay of treatment for advanced RCC, they are associated with a range of toxicities, including toxicities related and unrelated to VEGF inhibition (Table 3).

**Table 3: Toxicities Commonly Associated with VEGFR Inhibition (Treatment Emergent)**

VEGFR TKI	Adverse Events (All Grades)				Laboratory Abnormalities (≥Grade 3)		
	Hypertension (%)	HFS (%)	Diarrhea (%)	Fatigue (%)	ALT Increased (%)	Thrombocytopenia (%)	Anemia (%)
Sunitinib <sup>1</sup>	34	29	66	62	2	9	8
Sorafenib <sup>2</sup>	17	20	43	37	-	1	2
Pazopanib <sup>3</sup>	40	6	52	19	10	<1	-
Axitinib <sup>4</sup>	40	27	55	39	<1	<1	<1

Source: 1. Sutent [prescribing information] 2012<sup>9</sup>. 2. Nexavar [prescribing information] 2012<sup>7</sup>. 3. Votrient [prescribing information] 2012<sup>8</sup>. 4. Inlyta [prescribing information] 2012.<sup>24</sup>  
HFS = hand-foot syndrome, ALT= alanine aminotransferase; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

One of the best-documented and frequently observed on-target effects of agents that target the VEGF pathway, hypertension is related to the effect of these drugs on the vasculature.<sup>25</sup> Hypertension is recognized as a pharmacodynamic marker of VEGF inhibition and has been correlated with the efficacy of anti-VEGF agents in RCC.<sup>26-28</sup>

### 1.3. Unmet Medical Need in Treatment of Renal Cell Carcinoma

Toxicities not clearly linked to VEGF inhibition (“off-target toxicities”) such as hand-foot syndrome (also known as of palmar plantar erythrodysesthesia), fatigue and diarrhea, in particular, can be difficult for patients to tolerate, and can hinder the ability of patients to remain on full-dose therapy, as evidenced by the high rates of dose reduction, interruption and discontinuation seen in studies of these agents (Table 4).

**Table 4: Dose Modifications and Discontinuations in Clinical Studies of Tyrosine Kinase Inhibitors**

VEGFR TKI	Dose Reductions (%)	Dose Interruptions (%)	Discontinuations (%)
Axitinib <sup>1,2,3,4</sup>	25-31	50-54	9-NR
Pazopanib <sup>5,6,7,8</sup>	36-44	42-60	14-24
Sorafenib <sup>1,9</sup>	13-52	21-63	10-13
Sunitinib <sup>5,6,10</sup>	51-52	54-63	19-20

Source: 1 Inlyta [prescribing information]. 2012<sup>24</sup>; 2 Rini et al. 2011 Lancet<sup>27</sup>; 3 Rini et al, 2011 ASCO<sup>29</sup>; 4 Hutson et al. 2013 ASCO GU<sup>30</sup>; 5 Motzer R, et al. 2012 ESMO<sup>16</sup>; 6 Eisen et al, 2012 ESMO 2012<sup>31</sup>; 7 Votrient [prescribing information] 2010<sup>32</sup>; Sternberg 2010 J Clin Oncol<sup>15</sup>; 9 Escudier et al. 2007 N Eng J Med<sup>14</sup>; 10 Sutent [prescribing information]. 2011.<sup>33</sup>

Patient perspectives with regard to the relative importance of these symptomatic off-target toxicities are informative. Results from a recent survey conducted with 272 US RCC patients from the Kidney Cancer Association member panel concluded that patients place a high value on avoiding severe forms of symptomatic toxicities such as fatigue, mucositis, stomach problems, and hand foot syndrome.<sup>34</sup>

Outside of the setting of controlled clinical trials, reports suggest that clinicians find these toxicities associated with approved VEGFR TKIs to be difficult to manage and maintaining patients on therapy to be challenging. For example, a retrospective review of cases from 17 clinical oncology practices affiliated with the US Oncology Network examined outcomes for patients with advanced RCC.<sup>35</sup> Patients who started first-line therapy with sunitinib, the most commonly prescribed first-line agent, between June 1, 2007 and May 31, 2011 were studied. Of 134 patients identified, 45 patients had dose reductions primarily due to toxicity. Of the 131 patients who discontinued after completing at least 1 cycle, 17% discontinued due to toxicity. Sixty-seven percent of all dose reductions occurred early in the course of therapy, preventing patients from receiving full dose therapy. This is particularly noteworthy in light of analyses which demonstrate that higher exposure to sunitinib is significantly associated with objective response, longer time to progression, and overall survival.<sup>36</sup>

Finally, administration of the approved agents can be complicated due to their interactions with CYP3A4 inhibitors. Sunitinib, pazopanib and axitinib are subject to drug-drug interactions with strong CYP3A4 inhibitors, which lead to increased serum concentrations of TKI and may lead to an increased risk of associated toxicities.<sup>8, 9, 24</sup> Strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole as well as grapefruit should be avoided (or the dose of the TKI should be reduced) for patients receiving sunitinib, pazopanib or axitinib. Other CYP3A4 inhibitors of relevance to RCC patients include the following agents: ciprofloxacin, atorvastatin, amlodipine, alprazolam, fluoxetine, cimetidine, and ranitidine.

Great strides have been made over the last decade in the treatment of RCC. For many patients RCC has become a chronic condition requiring therapy over years rather than months. The toxicity profiles of approved agents vary, each providing different challenges for patients and physicians, and often preventing patients from receiving full-dose therapy. There is no single therapy choice that has emerged as the optimal choice for all patients, and many patients will receive multiple different therapies during the course of their disease. Despite this progress, there remains a significant need in the RCC community for efficacious agents with differentiated safety profiles.

#### **1.4. Overview of Clinical Development Program for Tivozanib**

At the time of the application, data from 17 clinical studies (Phase 1, 2 and 3) sponsored by AVEO were available. In addition, 2 Phase 1 clinical studies (1 study in subjects with hepatic impairment and 1 combination therapy study) were ongoing. Since the application was filed, 2 studies have been initiated (1 in breast cancer and 1 in RCC).

At the time of the 120-day safety update, pertinent safety data were available for the following groups of subjects:

- >1000 subjects (healthy volunteers and subjects with various solid tumors) who have received tivozanib as a single agent or in combination with other therapies.
- 894 subjects with various solid tumors (including RCC) who have received single agent tivozanib.
- 785 subjects with advanced RCC who have received single agent tivozanib 1.5 mg in a 3 weeks on/1 week off dosing cycle in the 4 core RCC monotherapy studies (studies 201, 202, 301, and 902) (Table 5).
- 259 subjects with advanced RCC who have received single-agent tivozanib in study 301.

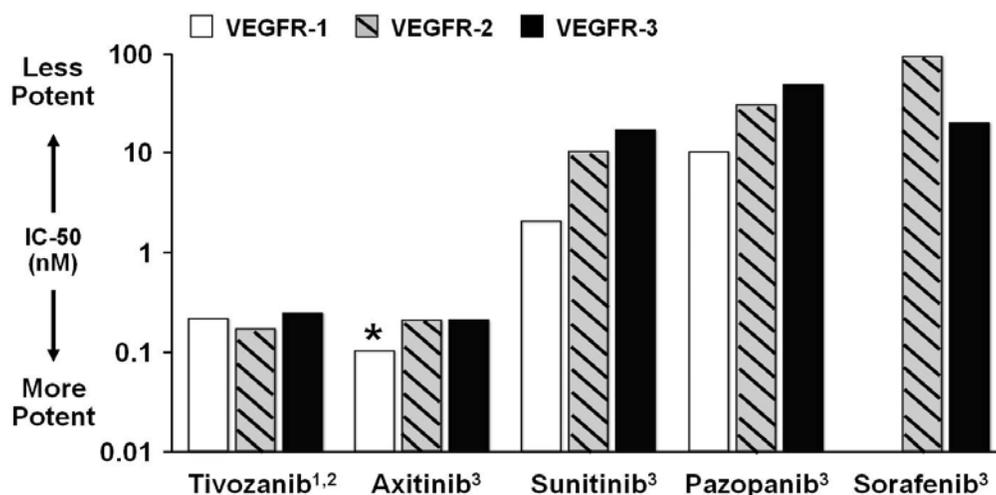
**Table 5: Core Renal Cell Carcinoma Monotherapy Studies**

<b>Study Number</b>	<b>Study Title</b>
301	A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib (AV-951) to Sorafenib in Subjects With Advanced Renal Cell Carcinoma
201	A Phase 2, Placebo-Controlled, Randomized, Discontinuation Trial of Tivozanib (AV-951) in Patients With Renal Cell Carcinoma
202	A Phase 2 and Biomarker Study of Tivozanib in Subjects With Advanced Renal Cell Carcinoma
902	An Extension Treatment Protocol for Subjects who have Participated in a Phase 3 Study of Tivozanib vs. Sorafenib in Renal Cell Carcinoma (Protocol 301)

### 1.4.1. Background and Pharmacological Characteristics of Tivozanib

Tivozanib was selected for development in RCC because nonclinical studies have shown that tivozanib blocks the activation of all 3 VEGFRs (VEGFR-1, -2, and -3) more potently (Figure 1) and selectively (Figure 2) than earlier-generation TKIs. More potent and selective inhibition of the VEGFRs offered the potential of efficacy with a reduced rate of toxicities that are not clearly mediated by VEGF inhibition such as hand-foot syndrome, diarrhea and fatigue.

**Figure 1: Tivozanib is a Potent VEGFR Inhibitor: Comparison of IC<sub>50</sub> Values of VEGFR Inhibitors**

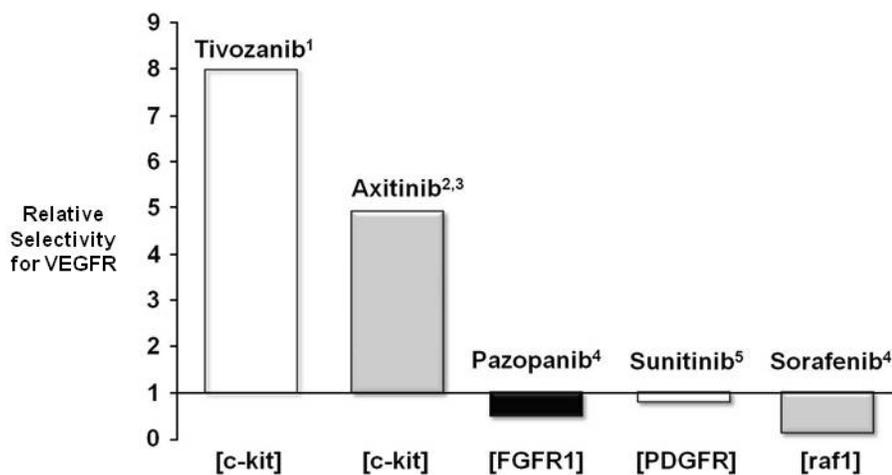


Source: 1. Eskens et al.<sup>37</sup>; 2. Nakamura et al.<sup>38</sup>; 3. Escudier et al. 2011<sup>39</sup>

\* Approximate: Adjustment in consideration of 2.3% BSA.

IC<sub>50</sub> = half-maximal inhibitory concentration; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor

**Figure 2: Tivozanib Exhibits Greater Selectivity for the VEGF Receptors than Other VEGFR TKIs**



Note: Comparisons were made using the average  $IC_{50}$  values of each agent for VEGFR-1, -2, and -3 in relation to the  $IC_{50}$  values for the most potently inhibited non-VEGFR kinase.

Source: 1. Nakamura K, et al. 2006.<sup>38</sup>; 2. Axitinib data for VEGFR-2 are from an ELISA assay; all other axitinib data are from an immunoprecipitation assay. In addition, Chow et al. reported an axitinib selectivity of 2.9 (Chow et al. 2007)<sup>40</sup>; 3. Hu-Lowe et al. 2008.<sup>41</sup>; 4. Chow et al. 2007.<sup>40</sup>; 5. Escudier B, et al 2011.<sup>39</sup>

$IC_{50}$  = half-maximal inhibitory concentration; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor

The clinical pharmacology profile of tivozanib has been characterized based on data from multiple clinical studies. Results from these studies support the following conclusions:

- Tivozanib has a half-life of 4.5 to 5.1 days, enabling once-daily dosing, with serum drug levels well in excess of VEGFR inhibitory concentrations throughout the 7-day rest period.
- Food has no effect on the overall AUC of tivozanib, indicating that tivozanib can be administered in both the fed and fasted states.
- Tivozanib can be dosed concomitantly with CYP3A4 inhibitors, unlike other approved TKIs.
- Similar to other approved TKIs, coadministration with inducers of the CYP3A4 enzyme is likely to result in decreased tivozanib serum concentrations.
- Tivozanib itself is not an inducer or inhibitor of CYP enzymes, is not an inhibitor of UGT enzymes, and is not a substrate or inhibitor of the P-glycoprotein transporter, suggesting that tivozanib has a low likelihood of perpetrating a drug-drug interaction (DDI) via these mechanisms.

Based on these results, it is apparent that tivozanib has a pharmacological profile that is differentiated from existing approved agents, and may provide a useful additional option for clinicians who treat RCC.

#### **1.4.2. Clinical Efficacy of Tivozanib for the Treatment of RCC**

Study 201 was a 272-patient randomized discontinuation Phase 2 study of tivozanib that was conducted in treatment-naïve patients and patients who had received prior cytokine treatment. The primary objective for the randomization period was met: in the randomized 12-week double-blind period of the study, the progression-free rate at 12 weeks post-randomization was 49.2% for tivozanib compared to 21.1% for placebo ( $p=0.001$ ) by IRR assessment. The median PFS in all treated subjects throughout the study was 11.7 months (95% CI 8.3-14.3 months) by independent radiological review (IRR) assessment. The median PFS in subjects with clear cell histology and prior nephrectomy was 14.8 months (95% CI 10.3-19.3 months) by IRR assessment. Among 272 subjects, the ORR for all treated subjects throughout the 16-week open-label period was 18.0% (95% CI: 13.6%, 23.1%) by IRR assessment. The ORR for all treated subjects throughout the study was 24.3% (95% CI 19.3%-29.8%) by IRR assessment. Based on the anti-tumor activity demonstrated in study 201, a determination was made to proceed to a Phase 3 trial using the same dose and regimen as in Phase 2, in clear cell and nephrectomized advanced RCC patients.

Study 301 was the first pivotal trial to compare an investigational agent to an approved targeted agent in patients with RCC who had not received prior targeted therapy. It was a multinational, randomized, active-controlled, open-label pivotal Phase 3 study that compared the efficacy and safety of tivozanib with that of sorafenib in RCC. Sorafenib is a multikinase inhibitor that is approved for the treatment of advanced RCC in the US and other countries. According to the NCCN guidelines, sorafenib is recommended for the treatment of cytokine-pretreated patients and for selected treatment-naïve patients. Study 301 was designed to detect an approximate 3-month increase in PFS attributable to tivozanib relative to sorafenib. Five hundred seventeen patients were randomized in a 1:1 ratio to tivozanib or sorafenib.

Study drug (tivozanib or sorafenib) was administered orally in 4-week cycles. Tivozanib 1.5 mg was taken once daily for 3 weeks followed by 1 week off treatment. Sorafenib 400 mg was taken twice daily continuously (1 cycle = 4 weeks on; no break between cycles).

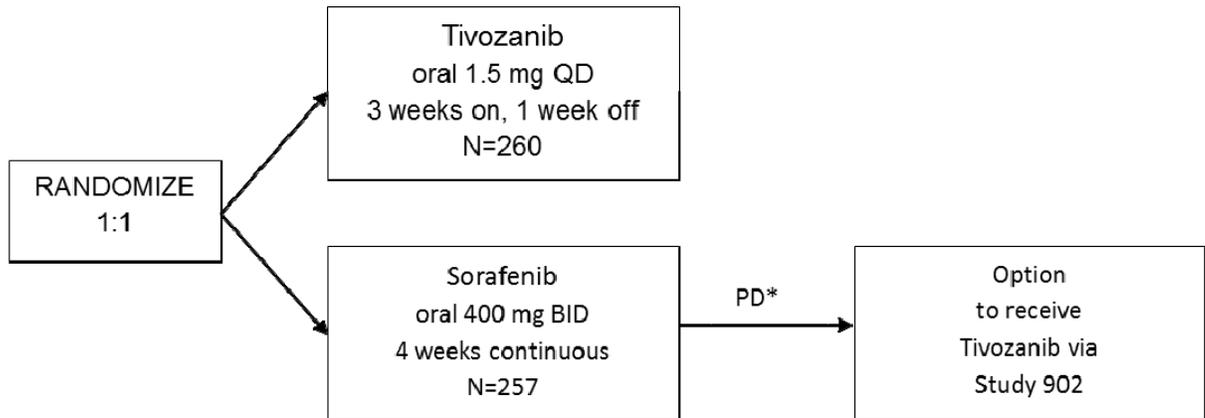
The primary efficacy endpoint was PFS, with all imaging assessed by blinded centralized IRR. The primary efficacy analysis compared PFS between treatment arms in the intent-to-treat (ITT) population using a stratified log-rank test where the stratification factors were number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or  $\geq 2$ ). After completion of the primary analysis, a larger proportion of subjects was observed in the stratum for  $\geq 2$  metastatic sites/organs than had been seen in other RCC development programs,<sup>15</sup> raising concerns that stratification had been based upon the number of metastatic sites rather than the number of involved organs. Review of individual patient data confirmed that the number of sites rather than organ number was used for stratification in many cases, due to imprecise language in the protocol and IRR charter. To address this concern, a second post-hoc blinded IRR review was conducted

for all subjects to determine the number of involved organs at baseline, consistent with the original intent and in line with other VEGFR inhibitor pivotal trials in RCC. Based upon a request from the FDA during the NDA review, data from the second review for number of involved organs were used in subgroup analyses and a sensitivity analysis as a revised stratification factor to evaluate the potential impact upon the primary analysis.

The primary analysis of PFS was to be conducted after approximately 310 PFS events had been observed. The study was designed to have 90% power with two-sided  $\alpha$  of 0.05. The hazard ratio (HR) for treatment and the corresponding 95% CI were estimated using the sorafenib arm as the reference group in a Cox proportional hazards regression model. Secondary efficacy endpoints included: objective response rate (ORR) by IRR, duration of response (DR) by IRR, duration of stable disease (DS) by IRR, overall survival (OS), and patient-reported outcome (PRO) of quality of life.

For subjects randomized to sorafenib who met Response Evaluation Criteria In Solid Tumors (RECIST) (v 1.0) for progressive disease (PD), subsequent treatment with tivozanib was offered as an option in extension study 902. Subjects treated with tivozanib who had PD were discontinued from study drug. Subjects who discontinued study drug in either treatment arm for reasons other than PD could receive subsequent cancer treatment at the discretion of their physician (Figure 3). The final OS analysis was to be conducted when the last patient enrolled had 2 years of follow-up as specified by protocol.

**Figure 3: Study Design for Study 301**



\* Radiographic evidence of progression of disease needed to enter Study 902

Subjects were enrolled primarily from Central and Eastern Europe (88%). Access to second-line targeted therapies in this geographic region was limited. Very few patients who discontinued study drug on study 301 had access to effective second-line therapy, except for those with documented progressive disease on sorafenib who subsequently received tivozanib on study 902.

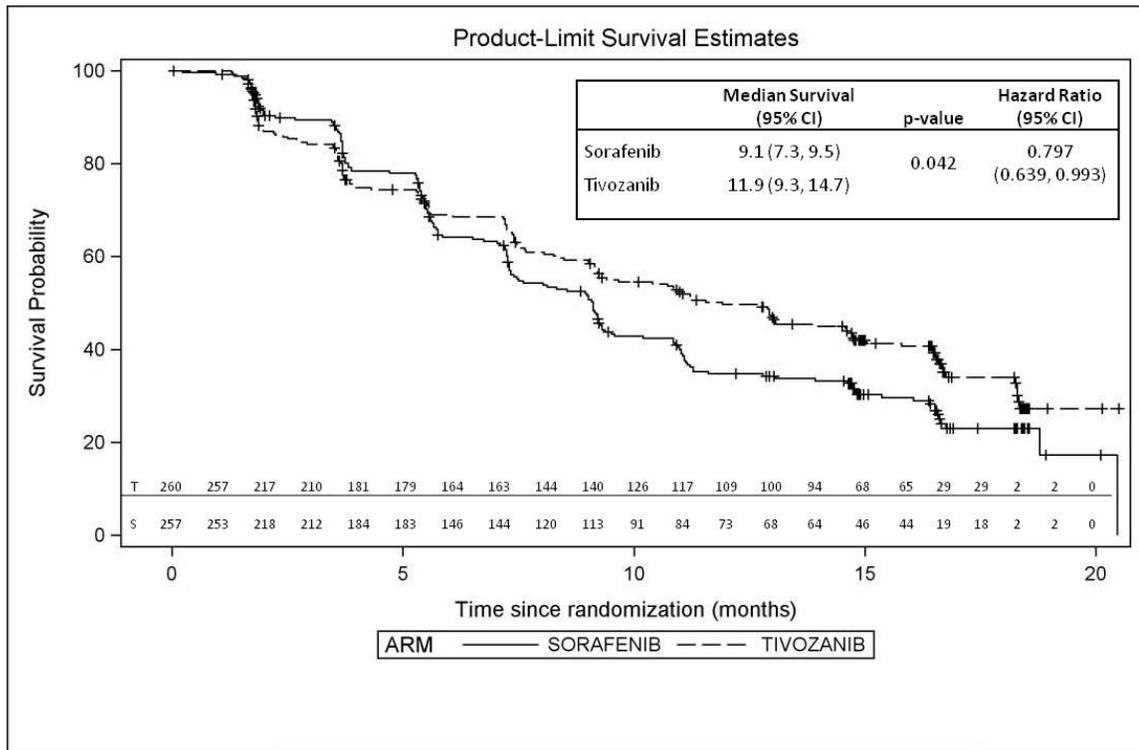
Baseline characteristics for patients enrolled in the study were consistent with populations studied in prior RCC pivotal trials. The two arms were generally well balanced except for Eastern Cooperative Oncology Group performance status (ECOG PS), which had a significant imbalance with a higher proportion of ECOG PS 0 patients

in the sorafenib arm. Consistent with this imbalance, there were also more patients with favorable MSKCC and Heng prognostic criteria at baseline in the sorafenib arm.

The efficacy data from study 301 and extension study 902 support the following conclusions:

- Study 301 met its primary objective of demonstrating improved PFS for tivozanib over sorafenib ( $p=0.042$  with a hazard ratio of 0.797 [95% CI: 0.639, 0.993], indicating a 20% lower risk of progression or death. The median PFS was 11.9 months in the tivozanib arm and 9.1 months in the sorafenib arm (Figure 4).

**Figure 4: Study 301 Met its Primary Endpoint of Progression-Free Survival**



- Applying the corrected site/organ count for stratification purposes, the p-value for the primary endpoint, PFS, decreased to  $p=0.006$  and the hazard ratio decreased to 0.736 (95% CI: 0.589, 0.919).
- Median OS estimates of 28.8 months in the tivozanib arm and 29.3 months in the control arm are comparable to OS medians in recent trials of other TKIs.
  - The HR for OS was 1.245 (95% CI: 0.954, 1.624). The log-rank p value was 0.105. The trend for longer survival in the control arm is likely due to the greater proportion of patients in the control arm who had access to and were treated with next-line targeted RCC treatment (63% in the sorafenib arm v. 13% in the tivozanib arm), primarily in extension study 902. This result is consistent with other observations that two consecutive targeted

agents are associated with longer overall survival than treatment with only one line of targeted therapy.<sup>18, 19</sup>

- Overall Response Rate (by IRR) in study 301 was significantly higher for tivozanib than for sorafenib (33.1% vs. 23.3%, p=0.014).
- Analysis of Quality of Life (QoL) endpoints in study 301 affirmed that the increase in PFS and resulting longer treatment with tivozanib was not associated with lowered QoL in the tivozanib group compared to sorafenib.
- In extension study 902, tivozanib showed evidence of anti-tumor activity as next-line crossover therapy for patients who experienced disease progression on sorafenib in study 301 (n=156). Median PFS was 8.4 months (95% CI: 5.5-12.4 months). ORR for confirmed responses was 13.5% (95% CI: 8.5%-19.8%).

### 1.4.3. Clinical Safety of Tivozanib

The safety profile of tivozanib is based on data from the entire tivozanib program, including data from studies of tivozanib in combination with other therapies (N = >1000 subjects or patients who received at least one dose of tivozanib), pooled safety data from the pivotal and supportive single-agent RCC studies (N = 785) and comparative safety data from study 301 (N = 259 treated with tivozanib and N = 257 treated with sorafenib).

The safety data support the following conclusions:

- The median duration of therapy was 12.0 months in the tivozanib arm and 9.5 months in the sorafenib arm.
- The overall incidence of adverse events (AEs) was 91% in the tivozanib arm and 97% in the sorafenib arm. Some were more frequent in the tivozanib arm than the sorafenib arm, including hypertension (44 % vs. 34%), dysphonia (21% vs. 5%) and back pain (14% vs. 8%). Others were more frequent in the sorafenib arm than in the tivozanib arm, including hand-foot syndrome (54% vs 14%), diarrhea (33% vs 23%) and alopecia (21% vs 2%).
- Adverse events  $\geq$  Grade 3 occurred in 61.4% in the tivozanib arm and in 69.6% in the sorafenib arm. The most frequent  $\geq$  Grade 3 AE in the tivozanib arm was hypertension (25.5%, compared with 17.5% in the sorafenib arm). The most frequent  $\geq$  Grade 3 AEs in the sorafenib arm were hypertension and hand-foot syndrome (16.7%, compared with 1.9% in tivozanib arm).
- 25.9% of tivozanib subjects had at least one SAE compared to 21.4% of sorafenib subjects.
- Fewer subjects in the tivozanib group required a dose reduction and/or interruption due to an AE (24.7% tivozanib subjects compared with 52.1% of sorafenib subjects). The most frequent adverse events leading to dose reduction and/or interruptions were hypertension in the tivozanib arm (7.7%,

compared with 6.2% in the sorafenib arm) and hand-foot syndrome in the sorafenib arm (23.3% compared with 3.1% in the tivozanib arm).

- The incidence of discontinuation of therapy due to adverse events was comparable in the two arms (13.1% on tivozanib vs. 12.5% on sorafenib).
- Deaths within 30 days of last dose of study drug occurred in 21 subjects (8.1%) on the tivozanib arm and 14 (5.4%) on the sorafenib arm. Of these, deaths due to adverse events other than progressive disease occurred in 13 subjects on the tivozanib arm and 12 on the sorafenib arm, and deaths due to progressive disease occurred in 8 subjects on the tivozanib arm and 2 on the sorafenib arm.
- High serum tivozanib exposure is not associated with an increased incidence of fatal adverse events.

## **1.5. Benefit-Risk in the Context of Approved Agents**

Despite significant advances in the treatment of RCC over the past decade, the existing approved agents can often be difficult for patients to tolerate. Symptomatic toxicities such as fatigue, diarrhea and hand foot syndrome are important to patients and often lead to high rates of dose reductions and interruptions, raising concern that many patients may be receiving a suboptimal dose of these agents. A significant unmet medical need remains in the RCC community for efficacious agents with a differentiated safety profile.

### **1.5.1. Benefit**

Tivozanib has demonstrated a statistically significant and clinically meaningful improvement in PFS when compared to sorafenib, an approved targeted agent. The robustness of the PFS improvement is confirmed by various sensitivity analyses. The PFS results are consistent across prespecified subgroups and are consistent with the PFS results from a large Phase 2 trial in RCC.

Although the overall survival hazard ratio indicates a trend that favors the control arm, this result can be explained due to a confluence of factors including: 1) adoption of an active comparator, 2) a high rate of utilization of next-line tivozanib by patients in the control arm and 3) limited access to next-line therapy for patients in the tivozanib arm.

A one-way crossover to tivozanib was offered to patients who experienced disease progression on sorafenib in study 301. This crossover resulted in a major imbalance in utilization of next line targeted cancer therapies for patients enrolled in study 301. A total of 63% of sorafenib patients who discontinued sorafenib therapy in study 301 were treated with next line targeted cancer therapy, nearly all with tivozanib in study 902. Data from study 902 demonstrate that tivozanib has antitumor activity in this setting. Only 13% of tivozanib patients who discontinued therapy in study 301 were treated with next line targeted cancer therapy, owing to the fact that access to next-line therapies was severely limited in the countries where the great majority of patients in study 301 were enrolled.

This imbalance in the utilization of next line cancer therapies is the most plausible explanation for the trend toward longer overall survival in patients originally randomized to sorafenib in study 301, most of whom were subsequently treated with tivozanib upon progression. The comparison of overall survival for patients enrolled in study 301 is essentially a comparison of outcomes for two groups of patients: those who received a single-line of therapy (tivozanib) vs. those who received two lines of therapy (sorafenib followed by tivozanib). Given published observations that patients who receive multiple lines of therapy have longer overall survival when compared to patients who receive only a single line of therapy, the results of the overall survival analysis are unsurprising.

### **1.5.2. Risk**

The safety profile of tivozanib has been well characterized and demonstrates a profile consistent with a highly selective VEGF receptor inhibitor. The most frequently reported adverse event is hypertension, an effect that is commonly seen with other TKIs and is familiar to oncologists who treat patients with RCC. Hypertension in tivozanib-treated subjects was managed with anti-hypertensive medications as directed in the study protocols and infrequently led to dose modification.

Tivozanib is associated with certain Grade 3-4 toxicities that are seen with other VEGFR TKIs. In the pivotal trial these occurred at rates that were comparable to what was observed for sorafenib, with the exception of hemorrhage, for which tivozanib may have a slightly higher rate than sorafenib. Deaths due to adverse events occurred at comparable rates for tivozanib and sorafenib and are consistent with reports from other TKI trials. There is no indication of a safety signal contributing to the observed trend in overall survival.

## **1.6. Tivozanib Benefit-Risk in the Context of TKIs Approved for Use in RCC**

Since their introduction into clinical practice in 2005, VEGFR TKIs have become a mainstay of treatment for patients with advanced RCC. The benefit of these agents has been consistently demonstrated in clinical trials by improvements in PFS. In early studies this benefit was demonstrated relative to placebo or interferon. Tivozanib has built upon these early successes by now demonstrating PFS benefit over another TKI, sorafenib.

Cross-study comparisons have limitations; however, it is of interest that the median PFS for tivozanib in the ITT population appears comparable to both sunitinib and pazopanib, with a median PFS of 11.9 months for tivozanib compared to 11.1 months for sunitinib and 9.2 months for pazopanib based on data from each of their registration trials. In addition, the ORR for tivozanib was comparable to both sunitinib and pazopanib (33% vs. 28% and 30%, respectively) in their respective Phase 3 RCC studies. Tivozanib efficacy also appears comparable to sunitinib and pazopanib in the treatment-naïve population with a median PFS of 12.7 months for tivozanib compared to 11.1 months for sunitinib and 11 months for pazopanib based on data from each of their registration trials. An analysis of available prognostic data (e.g., ECOG PS score and MSKCC criteria) do

not indicate that patients in study 301 had more favorable prognostic criteria than those in the registration studies of sunitinib or pazopanib.

While PFS has served as the approval endpoint for all VEGFR TKIs approved in RCC to date, prolongation of overall survival remains the ultimate goal of therapy in this disease. In this regard, the median estimates in both arms of the tivozanib pivotal trial are among the longest reported in RCC. Of particular note, tivozanib achieved this overall survival benefit despite the fact that fewer patients on the tivozanib arm of study 301 received any subsequent targeted therapy relative to reports from other trials (Table 6).

**Table 6: Median Overall Survival in Pivotal Studies of VEGFR-targeted Therapies in Advanced Renal Cell Carcinoma**

	<b>Median OS in Months</b>	<b>95% CI</b>	<b>Percent on Subsequent Targeted Therapy</b>
Tivozanib	28.8	22.5, NA	13%
Sorafenib	29.3	29.3, NA	63%
Sorafenib <sup>a</sup>	17.8	NR	NR
Placebo	15.2	NR	NR
Bevacizumab+Interferon <sup>b</sup>	23.3	NR	35%
Interferon	21.3	NR	37%
Pazopanib <sup>c</sup>	22.9	19.9, 25.4	22%
Placebo	20.5	15.6, 27.6	63%
Sunitinib <sup>d</sup>	26.4	23.0, 32.9	42%
Interferon	21.8	17.9, 26.9	NR
Pazopanib <sup>e</sup>	28.4	26.2, 35.6	NR
Sunitinib	29.3	25.3, 32.5	NR

NR = not reported

<sup>a</sup> Escudier, et al. 2009<sup>21</sup>

<sup>b</sup> Escudier, et al. 2010<sup>42</sup>

<sup>c</sup> Sternberg, et al. 2013<sup>23</sup>

<sup>d</sup> Motzer, et al. 2009<sup>22</sup>

<sup>e</sup> Presentation by Motzer, et al. at the European Society for Medical Oncology, 2012

Despite the recognition of the importance of overall survival as a therapeutic goal, its utilization as a clinical trial endpoint can often be confounded by the utilization of multiple lines of treatment. Such was the case in the tivozanib pivotal trial.

The absence of an overall survival trend in favor of the control arm in previous trials of VEGF TKIs can be explained by the fact that in each case where such trials permitted a crossover, the control arm was either placebo or a minimally active agent (e.g., IFN-a). Thus, these trials essentially compared outcomes of patients who received an active agent

vs. patients who received placebo or a minimally active agent followed by an active agent.

Given the improvements in overall survival, many patients are remaining on therapy for a period of years. For many patients RCC has become a chronic disease. Furthermore, many of the patients living with this disease are relatively young and active. As a result, clinicians and patients are becoming increasingly sensitized to the need for agents that are not only effective but which have a safety profile which can be matched to the needs of individual patients, thereby maximizing individual patients' abilities to live full and productive lives.

Tivozanib has a distinctive safety profile. While the safety profile of tivozanib has some similarity to that of sorafenib and other VEGF TKIs, some important differences are also observed between tivozanib and data reported for these other agents. Tivozanib is associated with an incidence of hypertension (an adverse event that correlates with efficacy) that is higher than sorafenib and higher than reported for sunitinib, but comparable to that reported for pazopanib and axitinib. With respect to symptomatic toxicities that are important to patients, tivozanib appears to have lower rates of fatigue than sunitinib and axitinib, lower rates of hand-foot syndrome than sorafenib, sunitinib and axitinib and lower rates of diarrhea than all four approved TKIs.

Tivozanib is associated with lower rates of dose reductions and interruptions than have been reported for all four approved TKIs, an indicator of patient tolerability. Tivozanib has shown no evidence of serious hepatotoxicity, which has been reported for patients taking sunitinib and pazopanib. Tivozanib does not have pharmacokinetic interactions with potent inhibitors of CYP3A4 and is therefore unlike sunitinib, pazopanib and axitinib, for which reduction of the TKI dose or avoidance of concomitant CYP3A4 inhibitors is recommended.

## **1.7. Conclusions**

A favorable risk-benefit profile for tivozanib was demonstrated by a clinically meaningful and statistically significant prolongation of PFS and improvement in ORR over an approved VEGFR TKI, sorafenib. Tivozanib has also demonstrated antitumor activity when used in patients following radiographic progression on sorafenib.

Tivozanib has a well-characterized and manageable safety profile that is distinct from other approved TKIs. Overall, tivozanib represents a valuable addition to the treatment armamentarium for advanced RCC.

## **2. OVERVIEW OF TIVOZANIB DEVELOPMENT PROGRAM**

### **2.1. Regulatory Interaction Regarding the Phase 3 Pivotal Trial and Clinical Pharmacology Development Plan**

In December 2008, AVEO met with FDA to discuss the clinical development of tivozanib, which was followed-up with an end-of-Phase-2 meeting in May 2009. At these meetings, the basic design of the Phase 3 trial was discussed and deemed acceptable. A Type C meeting was held in January 2011 to discuss the clinical pharmacology development program. In May 2012, AVEO held a pre-NDA meeting with the FDA where agreement was reached on the format and content of the NDA. At this meeting, the FDA raised concern about the overall survival trend. In September 2012, the NDA was submitted to the FDA, and was accepted for review in November 2012.

### **2.2. Overview of Clinical Development in RCC**

At the time of the application, data from 17 clinical studies (Phase 1, 2 and 3) conducted by the Sponsors were available. In addition, a Phase 1 study in subjects with hepatic impairment and a Phase 2 combination therapy study in subjects with metastatic colorectal cancer were ongoing. Since the application was filed, 2 additional Phase 2 studies (one in breast cancer and one in RCC) have been initiated.

Safety data in the 120-day safety update consisted of information over 1,000 subjects who have received tivozanib as a single agent or in combination with other therapies, including: 894 subjects with various solid tumors (including RCC) who have received single-agent tivozanib, 106 subjects who received tivozanib in combination with other cancer therapies, and 97 healthy volunteers in pertinent pharmacology studies.

Of the 894 subjects with solid tumors, a total of 785 subjects (in studies 201, 301, 902, 202) with advanced RCC have received single-agent tivozanib (1.5 mg in a 3 weeks on/1 week off dosing cycle). These 4 studies are considered the core RCC monotherapy studies:

- Study 201: A proof of concept Phase 2 randomized discontinuation study in RCC patients that included a placebo-controlled double-blind 12 week observation period (272 tivozanib subjects).
- Study 301: A Phase 3, randomized, controlled multicenter, open-label study that compared tivozanib to sorafenib in RCC (259 tivozanib subjects).
- Study 902: An extension study for subjects who participated in study 301 providing data on next line tivozanib treatment in subjects who had PD while on sorafenib (149 tivozanib subjects).
- Study 202: A Phase 2 and biomarker study of tivozanib in subjects with advanced RCC from the US and Canada (105 tivozanib subjects).

The following sections of this briefing book summarize the pharmacology, efficacy, and safety experience across the tivozanib clinical development program.

The clinical pharmacology section of this document provides a summary of the mechanism of action and pharmacological properties of tivozanib ([Section 3](#)). In addition, data regarding drug-drug interactions (DDIs), the lack of food-effect, population pharmacokinetic (PopPK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses, and the dose rationale are presented.

The efficacy portion of this document presents results from studies 201, 301, and 902. Study 201, the proof-of-concept study, provided initial evidence of antitumor activity in subjects with advanced RCC ([Section 4](#)). Study 301, the Phase 3 pivotal trial, met its primary endpoint, demonstrating longer PFS in subjects with advanced RCC treated with tivozanib as compared with sorafenib ([Section 5](#)). Study 902, the extension study for study 301, demonstrated the activity of tivozanib in patients with documented progressive disease on sorafenib.

The safety portion of this document focuses on the safety results from study 301, with additional supporting data from the core RCC monotherapy studies ([Section 6](#)). These results include the overall AE profiles observed in each treatment arm in study 301. An analysis of AEs in patient subgroups and a review of AEs of interest are also provided.

### **3. SUMMARY OF CLINICAL PHARMACOLOGY**

#### **3.1. Tivozanib Mechanism of Action**

Tivozanib hydrochloride is a potent vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor. The chemical name of tivozanib is 1-{2-chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-3-(5-methylisoxazol-3-yl)urea hydrochloride hydrate.

The anti-tumor activity of tivozanib is derived from its anti-angiogenic actions resulting from the blocked activation of the VEGF pathway. The VEGF pathway is a dominant mediator of tumor angiogenesis, which is essential for tumor development, growth and maintenance.<sup>10-12</sup> In vitro studies have shown that tivozanib potently and selectively blocks the activation of all 3 VEGF receptors (VEGFR-1, -2, and -3) (Table 7). By blocking VEGF ligand-induced VEGFR activation, tivozanib inhibits angiogenesis and vascular permeability in tumor tissues, leading to inhibition of tumor growth in vivo.

**Table 7: Selectivity of Inhibition of Phosphorylation of RTKs by Tivozanib Hydrochloride in Cell-Based Assays**

RTK	Cell	IC <sub>50</sub> (nmol/L)	95% CI (nmol/L)	Fold Selectivity vs VEGFR-2 <sup>a</sup>
VEGFR-2	HUVEC	0.16	0.13–0.20	1
VEGFR-1	Flt-1-3T3 <sup>b</sup>	0.21	0.16–0.30	1.3
VEGFR-3	HUVEC	0.24	0.16–0.34	1.5
c-Kit	KU812F	1.63	1.13–2.35	10
PDGFRβ	NHDF	1.72	1.39–2.13	11
FGFR1	NHDF	299	214–417	1870
Flt3	EOL-1	422	342–522	2640
c-Met	A431	1360	730–2540	8500
EGFR	A431	ND <sup>c</sup>	ND	ND
IGF-1R	HT29	ND <sup>c</sup>	ND	ND

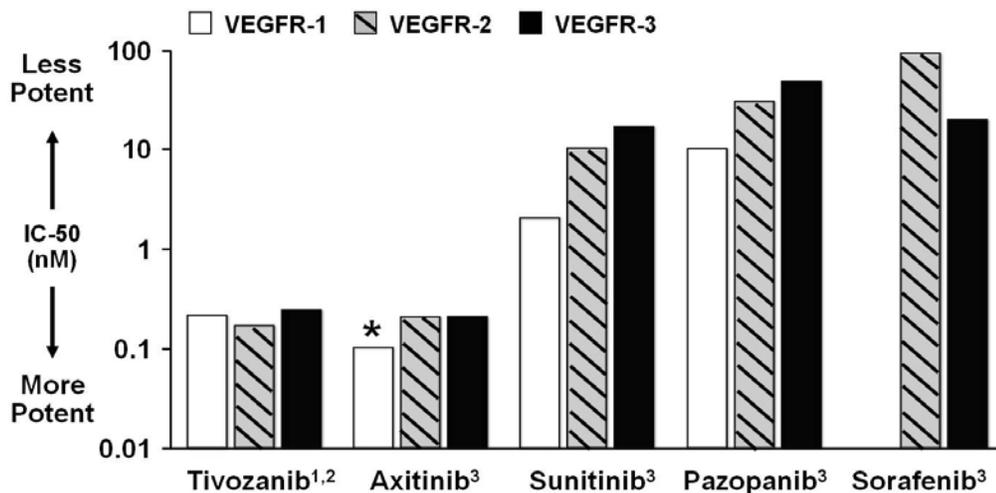
Source: Nakamura et al. 2006.<sup>38</sup>

- Ratio for the IC<sub>50</sub> obtained with a given RTK compared to that achieved vs VEGFR-2.
- Flt-1-transfected NIH3T3.
- Cellular IC<sub>50</sub> value could not be determined because tivozanib was apparently insoluble in the medium at the concentrations tested. The tivozanib hydrochloride concentrations tested in these studies ranged from 3 to 100 μmol/L.

CI = confidence interval; c-Kit = mast/stem cell growth factor receptor; c-Met = met proto-oncogene/hepatocyte growth factor receptor; EGFR = epidermal growth factor receptor; FGFR-1 = fibroblast growth factor receptor; Flt-3 = FMS-like tyrosine kinase 3; HUVEC = human umbilical vein endothelial cells; IC<sub>50</sub> = half maximal inhibitory concentration; IGF-1R = insulin-like growth factor 1 receptor; ND = not determined; NHDF = normal human dermal fibroblasts; PDGFR = platelet-derived growth factor receptor; SC = saturation concentration of tivozanib hydrochloride in serum-free medium; RTK = receptor tyrosine kinase; VEGFR = vascular endothelial growth factor receptor.

Four other VEGFR TKIs (sorafenib, sunitinib, pazopanib, and axitinib) have been approved for the treatment of RCC. Each of these agents has demonstrated efficacy in patients with RCC. A comparison of the potency of VEGFR inhibition for each of the previously approved agents and tivozanib, using reported half maximal inhibitory concentration (IC<sub>50</sub>) values for each VEGFR, demonstrates that tivozanib is more potent than sunitinib, pazopanib and sorafenib, and similar in potency to axitinib (Figure 5).<sup>39</sup> It is important to note that the assays used for these analyses were performed using slightly different methods.

**Figure 5: Comparison of Potency (IC<sub>50</sub>) of VEGFR Inhibition Demonstrated by Tivozanib and other VEGFR TKIs**



Source: 1. Eskens et al.<sup>37</sup>; 2. Nakamura et al.<sup>38</sup>; 3. Escudier et al. 2011<sup>39</sup>

\* Approximate: Adjustment in consideration of 2.3% BSA.

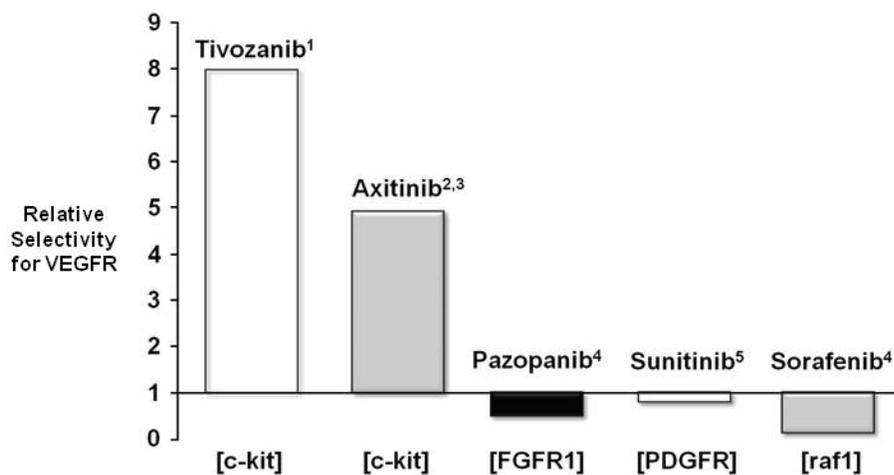
IC<sub>50</sub> = half-maximal inhibitory concentration; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor

Nonclinical studies confirmed the antitumor activity of tivozanib. These in vivo studies, conducted across a broad panel of models, including human RCC tumor xenograft models, demonstrated marked antitumor effects of tivozanib ranging from significant tumor inhibition to complete tumor regression.

A comparison of the IC<sub>50</sub> values across several kinases indicated that tivozanib also demonstrated a greater selectivity for the 3 VEGF receptors than other VEGFR TKIs (Figure 6). Tivozanib inhibition of the VEGF receptors is approximately 8-fold more potent than tivozanib inhibition of c-kit, the second most potently inhibited kinase. The VEGFR IC<sub>50</sub> values for tivozanib are similar to the reported IC<sub>50</sub> values for axitinib, which demonstrated a 5-fold or greater selectivity for the VEGF receptors over other kinases.<sup>39</sup> In comparison sorafenib, sunitinib, and pazopanib more potently inhibit kinases other than the VEGFRs. For example, pazopanib inhibits FGFR1 more potently than it inhibits VEGFR-2 or -3. Inhibition of platelet-derived growth-factor receptor (PDGFR) by sunitinib and inhibition of raf1 by sorafenib are also more potent than inhibition of VEGFR-2 and -3 by the same agents.<sup>39</sup>

Again, it is important to note that the assays used for these analyses were performed using slightly different methods.

**Figure 6: Tivozanib Exhibits Greater Selectivity for the VEGF Receptors than Other VEGFR TKIs**



Note: Comparisons were made using the average IC<sub>50</sub> values of each agent for VEGFR-1, -2, and -3 in relation to the IC<sub>50</sub> values for the most potently inhibited non-VEGFR kinase.

Source: 1. Nakamura K, et al. 2006.<sup>38</sup>; 2. Axitinib data for VEGFR-2 are from an ELISA assay; all other axitinib data are from an immunoprecipitation assay. In addition, Chow et al. reported an axitinib selectivity of 2.9 (Chow et al. 2007)<sup>40</sup>; 3. Hu-Lowe et al. 2008.<sup>41</sup>; 4. Chow et al. 2007.<sup>40</sup>; 5. Escudier B, et al 2011.<sup>39</sup>

IC<sub>50</sub> = half-maximal inhibitory concentration; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor

The high level of selectivity demonstrated in vitro provided the rationale to advance tivozanib into clinical development. It was anticipated that due to the higher selectivity of tivozanib, it would effectively inhibit tumor angiogenesis while limiting the toxicities observed with agents that inhibit the other kinases. For example, hand-foot syndrome may be caused by combined inhibition of multiple pathways,<sup>43,44</sup> and has been observed in subjects receiving pazopanib, sunitinib, and sorafenib.<sup>45,46</sup>

Another pharmacologic feature that differentiates tivozanib from the other VEGFR TKIs is its long half-life ( $t_{1/2}$ ). Tivozanib has a longer half-life (~108 to 123 hours) than sunitinib (40 to 60 hours),<sup>9</sup> pazopanib (30.9 hours),<sup>8</sup> sorafenib (25 to 48 hours),<sup>7</sup> and axitinib (2.5 to 6.1 hours).<sup>24</sup> The long  $t_{1/2}$  of tivozanib allows for once daily dosing with serum levels well in excess of VEGFR inhibitory concentrations throughout the break period.

### 3.2. Clinical Pharmacological Properties

The pharmacokinetics (PK) of tivozanib have been evaluated in 128 healthy volunteers and in 463 subjects with solid tumors. Studies involving healthy volunteers assessed mass balance and in vivo metabolism, drug-drug interactions (DDIs) (ketoconazole and rifampin), bioequivalence and food effect. In addition the PK of tivozanib were assessed in 5 monotherapy and 3 combination therapy studies conducted in subjects in solid

tumors. One of the monotherapy studies conducted in subjects with solid tumors evaluated QT interval corrected for heart rate (QTc).

Population pharmacokinetic analyses evaluated the potential effect of intrinsic patient characteristics (ie, gender, body weight, age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine and race) on the PK of tivozanib. Additionally, pharmacokinetic/pharmacodynamic (PK/PD) analyses were completed using data from the Phase 2 and 3 studies conducted in subjects with RCC (studies 201 and 301) to evaluate potential relationships between tivozanib serum exposure and soluble VEGFR-2 (sVEGFR-2), blood pressure (BP), incidence of hand-foot syndrome, tumor growth, and progression-free survival (PFS).

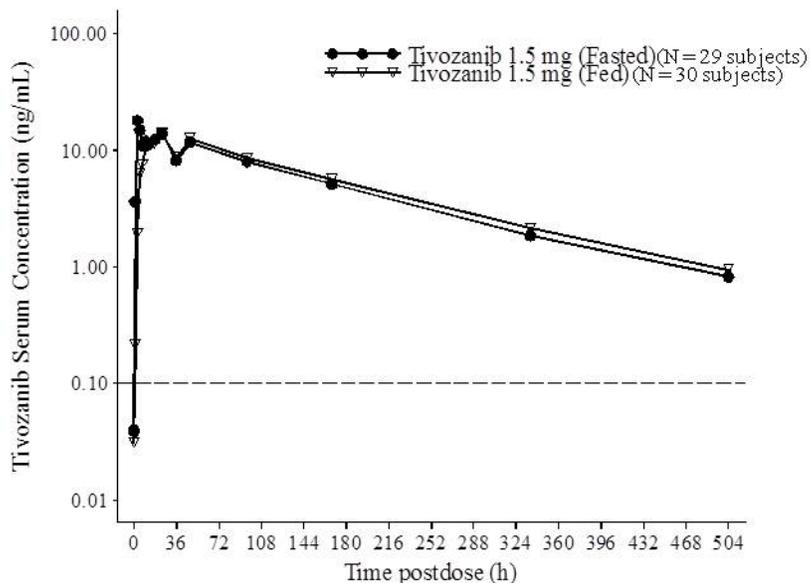
### **3.2.1. Absorption, Distribution, Metabolism, and Excretion**

The overall disposition of tivozanib is driven by its low clearance (CL/F) (mean ~0.593 to 0.698 L/hr), which contributes to its long half-life ( $t_{1/2}$ ) of ~4.5 to 5.1 days. The time to maximum concentration ( $T_{max}$ ) of tivozanib is typically within the first 24 hours after drug administration. This parameter is variable due to enterohepatic recirculation of tivozanib, which results in multiple peaks of similar magnitude in the concentration-time profile. The maximum peak may occur anywhere between 2 to 24 hours after dosing, however, the differences in the multiple peaks typically vary by only a few nanograms per milliliter (Figure 7).

Exposure (maximum concentration [ $C_{max}$ ] and area under the concentration-time curve [AUC]) of tivozanib generally increased in a dose-proportional manner across the dose range evaluated (0.5 mg to 2.0 mg). The mean  $C_{max}$ , following a single 1.5 mg dose, was 10.2 to 25.2 ng/ml across studies in healthy volunteers and subjects with solid tumors. When 1.5 mg was administered daily for 21 or 28 days in subjects with solid tumors,  $C_{max}$  was 67.5 to 94.3 ng/mL and AUC<sub>0-24</sub> was 1180 to 1641 ng·hr/mL. Tivozanib is highly bound to plasma proteins (> 99%). Accumulation at steady state is approximately 6- to 7-fold the exposure observed at single-dose levels, which is consistent with the long  $t_{1/2}$  of tivozanib.

After a high-fat meal, absorption of tivozanib was delayed and  $C_{max}$  was decreased by 23% compared to the fasted state (Figure 7). However, food had no effect on the overall AUC of tivozanib, indicating that tivozanib can be administered in the fed and fasted state.

**Figure 7: Arithmetic Mean ( $\pm$  STD) Concentration-Time Profiles for Tivozanib (Free Base) (Fed versus Fasted)**



----- Lower limit of quantification  
STD = standard deviation.

In vitro metabolism studies have shown that only CYP1A1 and CYP3A4 are capable of metabolizing tivozanib to some extent and that tivozanib does not undergo primary metabolism via the UDP glucuronosyltransferase (UGT) class of enzymes. Additional in vitro studies showed that tivozanib itself is not an inducer or inhibitor of CYP, is not an inhibitor of UGT enzymes, and is not a substrate or inhibitor of the P-glycoprotein transporter. Overall, these data suggest that tivozanib has a low likelihood of perpetrating a drug-drug interaction (DDI) via these mechanisms.

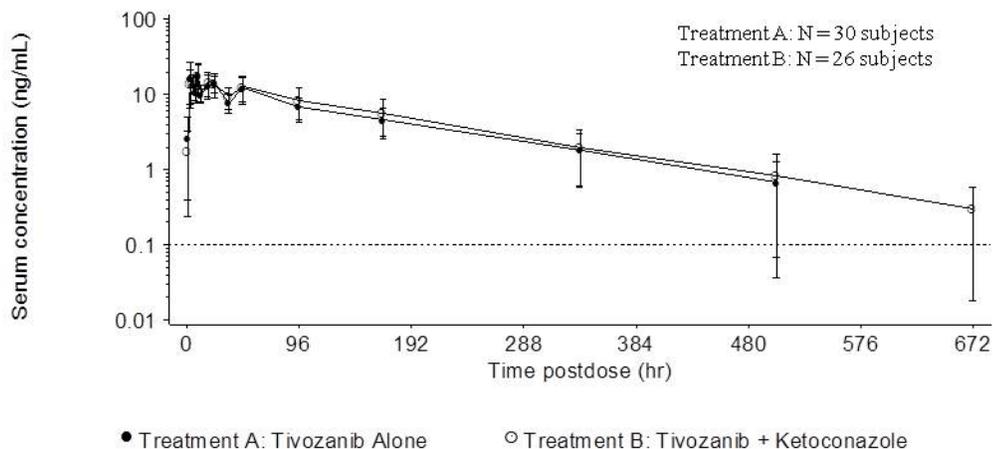
The excretion properties of tivozanib were characterized in a mass-balance study. This study demonstrated that after a single dose of radiolabeled tivozanib, unchanged tivozanib was the major circulating form of the molecule, and there were no major metabolites detected in serum at exposure levels  $\geq 10\%$  of the total radioactivity exposure. Mean radioactivity recovered from the feces was 79.3%, parent compound and metabolites were both detected. Mean radioactivity recovered from the urine was 11.8%. No detectable parent compound was found in the urine, but various metabolites were detected.

### 3.2.2. Drug-Drug Interactions

Two clinical DDI studies were conducted in healthy volunteers, both evaluating the potential for agents to interfere with the CYP3A4-mediated metabolism of tivozanib. One DDI study demonstrated that concomitant ketoconazole, a potent CYP3A4 inhibitor, did not cause a clinically significant change in the PK of tivozanib, indicating that tivozanib can be dosed concomitantly with CYP3A4 inhibitors (Figure 8).

**Figure 8: Arithmetic Mean ( $\pm$  STD) Serum Concentration Profiles of Tivozanib (Free Base) Following Administration of Tivozanib Hydrochloride Alone or Tivozanib Hydrochloride with Ketoconazole**

Semi-logarithmic scale

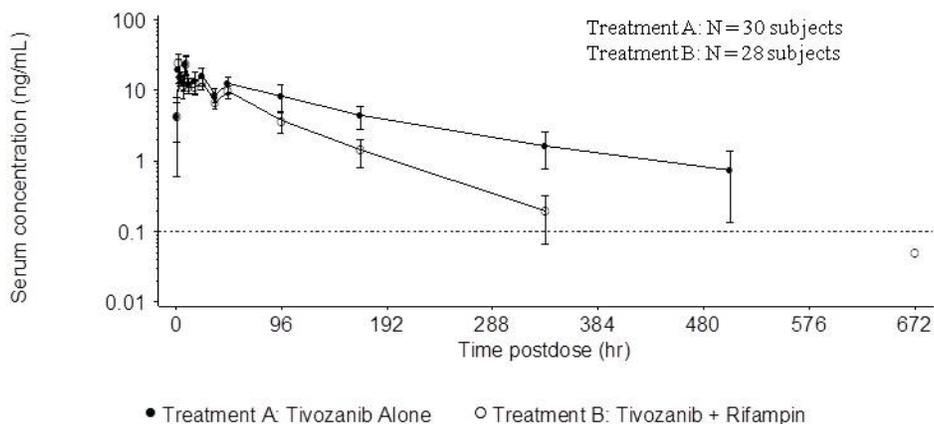


---Lower limit of quantification (0.1 ng/mL)  
STD = standard deviation.

Conversely, a second DDI study evaluating coadministration of tivozanib with a potent CYP3A4 inducer, rifampin, resulted in increased CL/F of tivozanib by ~50% (geometric mean increased from 0.583 to 1.21 L/hr), leading to a similar decrease in the  $t_{1/2}$  of tivozanib by ~55% (decreased from 121 to 54.0 hours) (Figure 9).

**Figure 9: Arithmetic Mean ( $\pm$  STD) Concentration Profiles for Tivozanib (Free Base) Following Administration of Tivozanib Hydrochloride Alone or Tivozanib Hydrochloride with Rifampin**

Semi-logarithmic scale



----Lower limit of quantification (0.1 ng/mL)  
STD = standard deviation.

### 3.2.3. Pharmacokinetics in Special Populations

Based on results of a population PK (PopPK) analysis, estimates of tivozanib CL/F were different between males and females, with females having mean values of CL/F that were 25.6% lower. Gender differences in CL/F were most likely responsible for the longer  $t_{1/2}$  determined for females (122 hours) compared to males (104 hours). The clearance differences between males and females were independent of weight.

Volume of distribution was found to increase nearly proportionally with body weight. This was not a surprising finding since volume of distribution generally scales linearly with body weight.

Other parameter-covariate relations that were evaluated and not found to affect the PK of tivozanib included age, ALT, AST, creatinine and race on CL/F, and albumin and gender on volume of distribution.

A Phase 1 study evaluating the effect of various degrees of hepatic impairment on the PK of tivozanib is currently underway. A renal impairment study has not been conducted.

A comparison of serum exposure results from subjects in North America/Western Europe versus Central/Eastern Europe was conducted. Serum exposure was similar between regions.

The PK and efficacy of tivozanib in pediatric patients have not been evaluated.

The effect of tivozanib on the QT interval was assessed as part of an uncontrolled, open-label study in subjects with solid tumors. Fifty subjects received 1.5 mg tivozanib once daily for 21 days. Triplicate ECGs were collected prior to and at various time points

post-dose on Day 1, Day 8 and Day 21. The mean maximum change in QTcF (corrected QT by the Fridericia method) was 9.3 ms (90% CI: 5, 13.6) occurring 2.5 hours after dosing on Day 21. None of the subjects in the study had a QTcF (corrected QT by the Fridericia method) >500 msec, although one subject had an increase in QTcF >60 msec from baseline.

#### **3.2.4. Pharmacokinetic/Pharmacodynamic Analysis**

Pharmacokinetic/pharmacodynamic analyses evaluated potential relationships between exposure, efficacy and adverse events in studies 201 and 301. Relationships between tivozanib exposure parameters and sVEGFR-2, incidence of hand-foot syndrome, change in tumor size, PFS, and OS were found. Increased tivozanib serum levels were associated with longer PFS and OS, an increased incidence of hand-foot syndrome, decreased levels of s-VEGFR-2, and more rapid tumor shrinkage. No significant association was observed between tivozanib exposure and BP measurements; however, the study was not designed to rigorously assess relationships between PK and blood pressure and therefore insufficient data were available for a thorough analysis.

Additional details on the relationship between tivozanib serum exposure and safety parameters are provided in [Section 6.3.4.5](#).

A post-hoc analysis of overall survival confirmed that higher exposures of tivozanib do not correlate with an increased incidence of death. Details of this analysis are provided in [Section 6.3.3.5](#).

### **3.3. Selection of Dose and Schedule for Clinical Study**

The proposed dose of 1.5 mg/day oral tivozanib in 4-week cycles (3 weeks of treatment followed by a 1-week break) for the treatment of patients with advanced RCC was determined based on various factors.

The dose level of tivozanib (1.5 mg) was selected based on the results of the First-in-Human (FIH) study. This study evaluated doses of 1.0, 1.5, and 2.0 mg/day. Results from the FIH study identified 1.5 mg as the recommended Phase 2 dose based on safety and tolerability in subjects with solid tumors. Additionally, PD analyses from this study demonstrated dose-dependent increases in serum VEGF-A levels, dose-dependent decreases in serum soluble VEGFR-2 (sVEGFR-2) levels, and dose-dependent reduction in tumor perfusion.

The dosing regimen for tivozanib (3 weeks of treatment followed by a 1-week break) was selected based on the results of the FIH study as well as additional considerations. The FIH study dosing regimen was a 6-week cycle (4 weeks of treatment followed by a 2-week break). This regimen was modeled on the dosing regimen used for sunitinib, another VEGFR TKI, which utilized a 2-week break to allow patients time to recover from drug-induced toxicities. However, there was concern that the longer 2-week break in treatment might result in recurrence of disease-related symptoms, as has been observed in other VEGFR inhibitors.<sup>47</sup> Furthermore, the 1.5 mg dose of tivozanib was well tolerated in the FIH study, indicating that a shorter treatment break would be acceptable. Based on this information, the 4-week cycle (3 weeks of treatment followed by a 1-week

break) was selected for the proof-of-concept study 201. In addition, it was anticipated that the 4-week cycle would provide greater flexibility for coadministration of tivozanib with other cancer therapies.

The selected dose and regimen (1.5 mg for 3 weeks of treatment followed by a 1-week break) was shown to be safe and effective in both the proof-of-concept study 201 and the Phase 3 pivotal study 301. In addition, this dose and regimen have been evaluated in other studies conducted in healthy volunteers and in subjects with solid tumors.

## **4. STUDY DESIGN AND EFFICACY FINDINGS IN STUDY 201 (PROOF OF CONCEPT)**

### **4.1. Summary of Study Design and Efficacy Findings in Study 201**

- Study 201 was a placebo-controlled randomized discontinuation study in 272 patients with RCC with various histological types. Following an initial 16-week open-label treatment with tivozanib, subjects with at least 25% tumor shrinkage on tivozanib were not randomized and continued tivozanib for 12 weeks. Subjects with tumor progression were discontinued. The remaining subjects were randomized to tivozanib or placebo and monitored for tumor response in a 12-week double-blind period. All imaging was read by independent radiological review (IRR).
- The primary endpoint for the randomization period was met: in the randomized 12-week double-blind period of the study, the progression-free rate at 12 weeks post-randomization was 49.2% for tivozanib compared to 21.1% for placebo (p=0.001) by IRR assessment.
- The ORR for all treated subjects throughout the 16-week open-label period was 18.0% (95% CI: 13.6%, 23.1%) by IRR assessment. The ORR for all treated subjects throughout the study was 24.3% (95% CI 19.3%-29.8%) by IRR assessment.
- The median PFS in all treated subjects throughout the study was 11.7 months (95% CI: 8.3, 14.3) by IRR assessment. The median PFS in the 176 subjects with clear cell histology and prior nephrectomy was 14.8 months (95% CI: 10.3, 19.3) by IRR assessment.

### **4.2. 201 Study Design**

Study 201 ([Figure 10](#)) was an international proof of concept randomized discontinuation study. Enrolled subjects had recurrent or metastatic RCC, or primary RCC that was not amenable to surgical intervention, and no more than 1 prior systemic treatment for RCC. Subjects with prior treatment with VEGF binding agents or VEGFR TKI therapy were excluded.

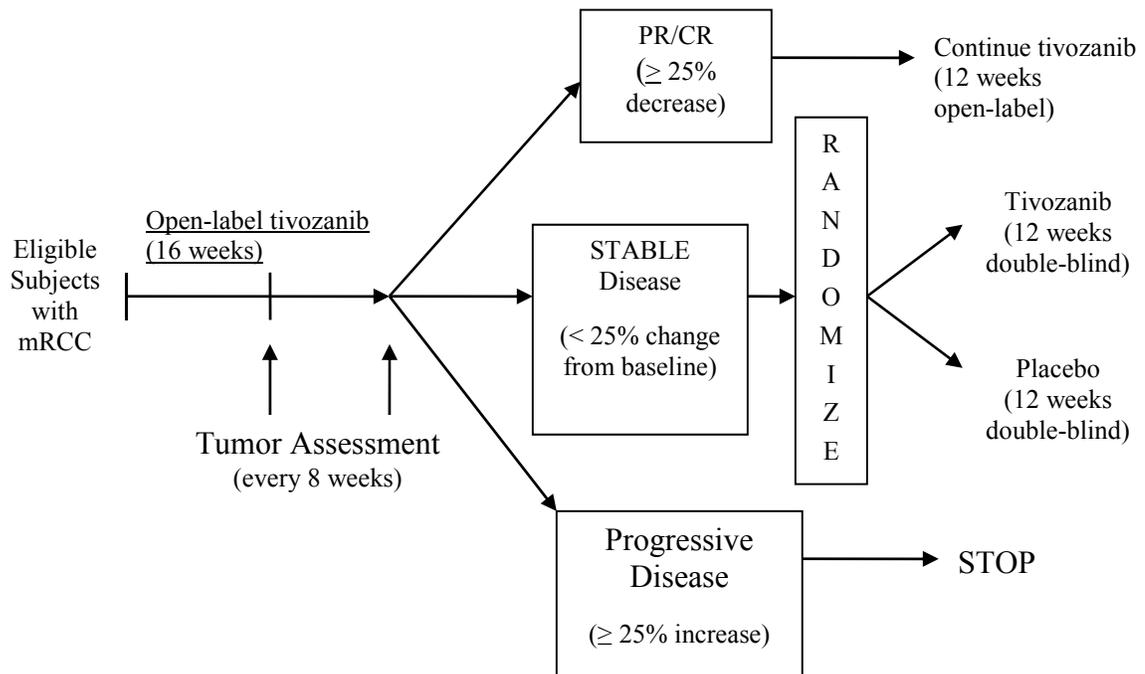
Subjects were treated with tivozanib in an initial 16-week open-label treatment period, with tivozanib administered at a dose of 1.5 mg daily in cycles of 3 weeks on treatment followed by 1 week off treatment. After the 16-week open-label period, tumor response to tivozanib was assessed by the investigator and the subset of subjects selected for randomized assignment to tivozanib or placebo for a 12-week double-blind period, was determined as follows:

- Subjects with  $\geq 25\%$  tumor shrinkage (decrease in sum of longest diameters) compared to baseline continued dosing with open-label tivozanib (1.5 mg/day or current dose) for an additional 12 weeks as long as there was no evidence of disease progression or unacceptable toxicity.

- Subjects with  $< 25\%$  tumor change (increase or decrease in sum of longest diameters) from baseline were randomly assigned to receive either tivozanib (1.5 mg/day or current dose) or placebo for 12 weeks in a double-blind treatment period. Subjects underwent scheduled disease assessments every 4 weeks during the double-blind phase. Those with disease progression had their treatment unblinded; subjects receiving tivozanib were discontinued from the study, while subjects receiving placebo were given the option to re-start tivozanib or discontinue from the study.
- Subjects with  $\geq 25\%$  tumor growth (increase in sum of longest diameters) compared to baseline or other evidence of progression were discontinued from the study.

Subjects receiving tivozanib who completed the 12-week double-blind period or the 12-week open-label continuation period with documented stable disease or an objective response could continue to receive tivozanib for up to 1 year from their first dose, or longer at the Sponsor or investigator's discretion, as long as tolerability was acceptable. Thereafter, tivozanib subjects could continue therapy by enrolling in an extension study. Subjects receiving placebo who completed the 12-week double-blind period were given the option to re-start treatment with tivozanib.

**Figure 10: Study Design for Study 201**



All imaging studies to determine disease response were assessed by both the investigator and in a retrospective review by an independent panel of radiologists who were blinded to treatment assignment. The key efficacy analyses in this study were based on results from the IRR.

The key efficacy variables were defined as follows:

- ORR following the initial 16-week open-label period
- Progression-free rate (defined as the percentage of subjects remaining progression-free) at 12 weeks post-randomization.
- Overall PFS (from start of treatment)
- PFS throughout study for the following subgroups:
  - Memorial Sloan Kettering Cancer Center (MSKCC) Risk (favorable, intermediate, or poor)
  - Histopathology (clear cell or other)
  - Nephrectomy status (yes or no)

### **4.3. Subject Enrollment, Disposition and Subject Characteristics**

A total of 272 subjects entered the study and began treatment with tivozanib in the 16-week open-label period. Of the 272 subjects, 76 discontinued (50 subjects due to PD and 26 subjects for other reasons). Of the 196 subjects completing the 16-week open-label period without progression, 78 had tumor response and continued to receive open-label tivozanib. Of the 118 remaining subjects, 61 were randomized to tivozanib and 57 to placebo in the 12-week double-blind period. A total of 148 subjects completed both the 16-week and 12-week treatment periods and continued or resumed tivozanib.

Subjects ranged in age from 26 years to 79 years (mean 56 years). The majority of subjects were male (70.2%) and white (93.4%). Subjects randomized to tivozanib and placebo were similar with respect to age, gender, race, ethnicity, and body mass index and had similar characteristics to those in the total population entering the study.

The mean time since initial diagnosis of RCC was 2.3 years. Previous treatments for RCC included surgery/tumor embolization (92.3%), medication (46.3%), and radiotherapy (13.2%). The majority of subjects had  $\leq 1$  prior systemic medication for RCC: 53.7% had no prior systemic treatments and 42.6% had 1 prior systemic treatment. The majority of subjects underwent prior nephrectomy (73.2%). The majority of RCC cases had a clear cell histopathology (83.1%) and were metastatic (95.6%).

### **4.4. Efficacy Findings**

#### **4.4.1. Objective Response Rate following the 16-Week Open-Label Period (Primary Endpoint)**

Among 272 subjects, the ORR (defined as the sum of the confirmed complete response and partial response rates (ie at least 30% tumor shrinkage per RECIST 1.0) for all treated subjects throughout the 16-week open-label period was 18.0% (95% CI: 13.6%, 23.1%) by IRR assessment.

Of note, the ORR for all treated subjects throughout the study was 24.3% (95% CI 19.3%-29.8%) by IRR assessment.

**4.4.2. Progression-Free Rate at 12 Weeks Post-Randomization (Primary Endpoint)**

The percentage of subjects remaining progression-free after completion of the 12-week double-blind period favored tivozanib. In the ITT population, the progression-free rates were 49.2% for tivozanib compared to 21.1% for placebo by IRR assessment (p=0.001).

**4.4.3. Progression-Free Survival from the 12-Week Double-Blind Period**

PFS from the 12-week double-blind period was measured from the date of randomization rather than from the date of first dose, with subjects in the placebo arm not censored at the time of unblinding. The median PFS by IRR was 10.3 months in the tivozanib arm compared to 3.3 months in the placebo arm (p=0.010).

**4.4.4. Progression-Free Survival Throughout the Study**

Median PFS throughout the study in all treated subjects (including those that received placebo) was 11.7 months (95% CI: 8.3, 14.3) by IRR assessment.

**4.4.5. Subjects with Clear Cell Histology and Prior Nephrectomy**

In the subset of 176 subjects (out of 272 enrolled) with clear cell histology and prior nephrectomy, the median PFS throughout the study was 14.8 months (95% CI: 10.3, 19.2) by IRR. Because of the longer PFS in subjects with clear cell histology and prior nephrectomy, these characteristics were selected as eligibility criteria in study 301.

## **5. STUDY DESIGN AND EFFICACY FINDINGS IN STUDY 301 (PIVOTAL PHASE 3 STUDY)**

### **5.1. Summary of study design and efficacy findings in study 301**

- The pivotal Phase 3 study (study 301) was an open-label, randomized, active-controlled study comparing tivozanib to sorafenib in subjects with recurrent or metastatic RCC with a clear cell component who had undergone prior nephrectomy.
- The primary endpoint was PFS based upon imaging assessed by IRR. The median PFS in the tivozanib arm was 11.9 months compared to 9.1 months in subjects randomized to sorafenib. Based upon the log-rank test statistic by the primary stratified analysis in the ITT population, Study 301 met its pre-defined primary objective of showing significantly longer PFS in the tivozanib arm compared to the sorafenib arm ( $p=0.042$ ), with a hazard ratio (HR) of 0.797 (95% CI: 0.639, 0.993).
- All pre-specified sensitivity analyses for PFS supported the findings in the primary analysis. In an exploratory sensitivity analysis requested by FDA, applying the corrected site/organ count for stratification purposes, the p-value for the primary endpoint, PFS, decreased to  $p=0.006$  and the hazard ratio decreased to 0.736 (95% CI: 0.589, 0.919).
- Analysis of PFS by subgroups confirmed the consistency of findings. In the subgroup of subjects with no prior therapy for metastatic RCC (70% of subjects), the PFS with tivozanib was 12.7 months compared to 9.1 months for sorafenib (HR: 0.756,  $p=0.037$ ).
- Median OS estimates of 28.8 months in the tivozanib arm and 29.3 months in the control arm are comparable to OS medians in recent trials of other TKIs.
  - The HR for OS was 1.245 (95% CI: 0.954, 1.624). The log-rank p value was 0.105. The trend for longer survival in the control arm is likely due to the greater proportion of patients in the control arm who had access to and were treated with next-line targeted RCC treatment (63% in the sorafenib arm v. 13% in the tivozanib arm), primarily in extension study 902. This result is consistent with other observations that two consecutive targeted agents are associated with longer overall survival than treatment with only one line of targeted therapy.<sup>18, 19</sup>
- The ORR by IRR assessment was significantly higher for tivozanib subjects compared to sorafenib subjects (33.1% vs. 23.3%,  $p=0.014$ ). Duration of response by IRR assessment was not statistically significant. Duration of stable disease by IRR assessment was significantly longer in the tivozanib arm compared with sorafenib ( $p=0.026$ ).

- Analysis of patient-reported outcome (quality of life, QoL) endpoints showed that the increase in PFS was not associated with lowered QoL in the tivozanib arm compared to the sorafenib arm. In each QoL domain evaluated, there was no clinically or statistically significant decrease from baseline for either arm.

## 5.2. 301 Study Design

Study 301 was a randomized, parallel-arm, active-controlled, open-label, multinational study that compared tivozanib efficacy and safety with that of sorafenib, an approved VEGFR TKI for the treatment of advanced RCC. This was the first pivotal study ever conducted in RCC subjects who had not been treated with a prior targeted therapy to utilize an active targeted agent as its comparator. Enrolled subjects had recurrent or metastatic RCC with a clear cell component and had undergone prior nephrectomy (complete or partial) for excision of the primary tumor. Subjects with documented stable disease or an objective response could continue therapy as long as tolerability was acceptable and disease did not progress. Subjects who discontinued sorafenib treatment in study 301 due to radiographically-documented progressive disease could elect to receive tivozanib as next-line treatment in study 902 (Figure 11). Subjects who discontinued sorafenib for reasons other than progressive disease (or who had progressive disease and chose not to cross-over to tivozanib) and subjects who discontinued tivozanib for any reason were treated at the discretion of their physician.

Subjects were required to have no prior therapy or no more than 1 prior systemic therapy for metastatic RCC. Prior systemic therapy could include immunotherapy, chemotherapy, hormonal therapy or an investigational agent, but subjects treated with prior VEGF-directed therapy or an agent targeting the mTOR pathway were excluded.

Scans for disease assessment were performed at baseline and approximately every 8 weeks (2 cycles) of treatment, and reduction in tumor size consistent with a CR or PR was confirmed by repeat evaluation performed at least 4 weeks later (per RECIST 1.0).

The primary endpoint was pre-specified as PFS as determined by blinded IRR, consistent with the use of PFS as an endpoint in registration studies for other VEGFR inhibitors. The study was designed to detect an approximately 3 month increase in PFS attributable to tivozanib relative to sorafenib. IRR assessment of imaging for the primary analysis was performed on a rolling basis throughout the study, without any transmission of these findings to the investigator.

Subjects were randomized in a 1:1 ratio to tivozanib or sorafenib, with the randomization stratified as follows:

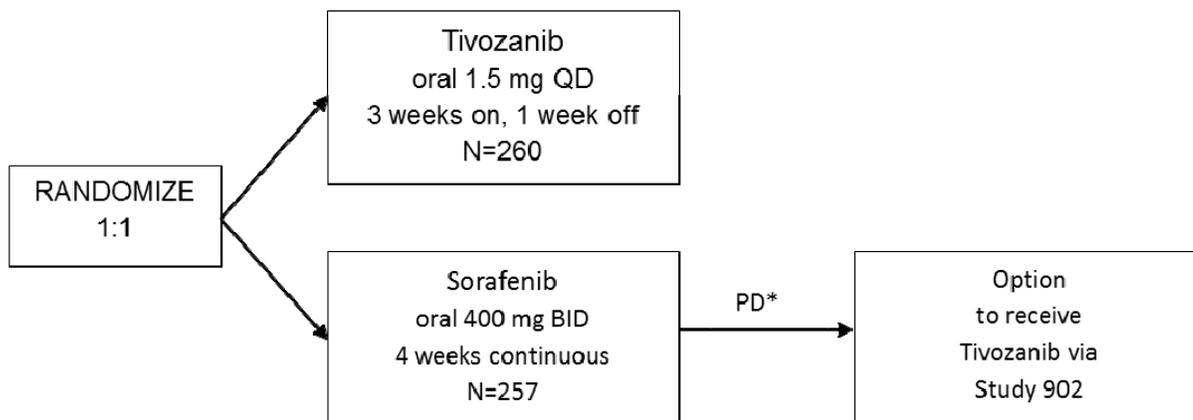
- geographic region (North America/Western Europe, Central/Eastern Europe, or rest of the world)
- number of prior treatments for metastatic RCC (0 or 1)
- number of metastatic sites/organs involved (1 or  $\geq 2$ ) as determined by IRR.

Stratification by number of metastatic sites/organs was determined by IRR, prior to randomization, using the baseline scans. After completion of the primary analysis, a larger proportion of subjects was observed in the stratum for  $\geq 2$  metastatic sites/organs

than had been seen in other RCC development programs,<sup>15</sup> raising concerns that stratification had been based upon the number of metastatic sites rather than the number of involved organs. Review of individual subject data confirmed that the number of sites rather than organ number was used for stratification in many cases, due to imprecise language in the protocol and IRR charter. To address this concern, a second post-hoc blinded IRR was conducted for all subjects to determine the number of involved organs at baseline, consistent with the original intent and in line with other VEGFR inhibitor pivotal trials in RCC. In response to a request from the FDA during the NDA review, data from the second review for number of involved organs were used in subgroup analyses and a sensitivity analysis as a revised stratification factor to evaluate the potential impact upon the primary analysis.

A secondary endpoint was OS. Survival follow-up included all experience in a given subject who had been randomized to tivozanib or sorafenib, including experience after discontinuation of study drug. In particular, in subjects randomized to sorafenib who had radiographically-documented PD and then were treated with tivozanib as next-line treatment in study 902 (Figure 11), the survival experience in study 902 was included in the analysis of OS for study 301. By protocol, the final analysis of survival was to be conducted when all subjects in follow-up had been on study for at least 2 years (the criteria were met on 27 August 2012).

**Figure 11: Study Design for Study 301**



\* Radiographic evidence of progression of disease needed to enter Study 902

### 5.2.1. Justification for Active-Control, Open-Label Study Design, and Use of PFS as the Primary Efficacy Endpoint

Study 301 was the first pivotal study ever conducted in RCC subjects who had not been treated for metastatic disease with a prior targeted therapy to utilize an active targeted agent as its comparator. Given the availability of approved effective targeted treatments for RCC, a placebo-controlled study in subjects with recurrent or metastatic RCC was not feasible or ethical. Sorafenib inhibits tumor cell proliferation and angiogenesis and is approved for treatment of RCC in the US and many other countries, based on data

showing positive findings on PFS as compared to placebo observed in a large randomized Phase 3 study in subjects with advanced RCC who had received 1 prior systemic therapy. Sorafenib is also the only VEGFR inhibitor that had been extensively studied in a pivotal study in RCC subjects with no prior therapy as well as prior therapy with cytokines and chemotherapy. Since study 301 was designed to assess PFS for tivozanib compared to sorafenib, the active-controlled design provides a high standard for establishing efficacy.

An open-label design was chosen for this study because tivozanib and sorafenib have different toxicity profiles and it was felt that a double-blind design would not be any more effective in preventing investigator bias than an open-label design. In addition, managing a double-dummy design would have placed a significant burden on the subjects and physicians, given the different dosing schedules and rules for dose management for the 2 drugs, and could have potentially put the subjects at risk for a dosage error (including overdosage) or contributed to noncompliance. The open-label design was discussed with both the FDA and the Committee for Medicinal Products for Human Use (CHMP).

In order to strengthen the open-label design, all imaging studies were read by 2 blinded, independent radiologists with a third blinded, independent radiologist performing adjudication in the event there was a difference in opinion between the 2 primary reviewers. Adjudication was triggered due to differences in best response, date of first response, or date of PD. As an additional feature to limit the potential for bias in investigator assessments for this open-label study, the study design incorporated a separate independent 48-hour review of investigator-determined progression, as described in Section 5.2.2. Further measures, including the use of a blinded programming team at the vendor that was responsible for the analysis of the data, as well as restrictions placed on the Sponsor study team, were intended to further safeguard the integrity of the study.

PFS was chosen as the primary efficacy endpoint for study 301 because several agents for the treatment of advanced RCC have recently been approved by US and European regulatory agencies based on statistically significant and clinically meaningful improvement in PFS in large, well-controlled Phase 3 studies. In particular, angiogenesis inhibitors targeting the VEGF pathway, including sunitinib, sorafenib (the comparator for study 301), pazopanib, and axitinib, were all approved by the FDA and the European Commission based on improvement in PFS.

### **5.2.2. Study Drug Administration and Discontinuation**

Tivozanib was administered in 4-week cycles consisting of daily oral 1.5 mg tivozanib for 3 weeks followed by a 1-week rest period. Sorafenib was administered continuously as 400 mg twice daily for 4 weeks with no rest period. Subjects continued to receive their assigned treatment until they experienced disease progression, unacceptable toxicity, death, or another reason to discontinue study drug. Subjects underwent disease assessment at screening, after Cycle 2, and after every subsequent even-numbered cycle. Response was determined by RECIST, Version 1.0.

Investigators continued administering study drug to subjects who in their judgment had radiological evidence of PD until it was confirmed by independent radiological review

within 48 hours. The 48-hour independent review was separate from the rolling IRR review to assess imaging for PFS and other efficacy analyses. Once progression was confirmed by the 48 hour independent review, subjects were discontinued from study drug. Verification of PD by the 48 hour independent review was not required prior to subject discontinuation in the following circumstances:

- Greater than 50% increase in measurable disease (sum of longest diameters of target lesions) per RECIST as assessed by the investigator
- Appearance of new lesions, at least one of which measured > 20 mm by computed tomography (CT) scan or > 10 mm by spiral CT scan as assessed by the investigator
- Significant clinical deterioration indicative of progressive disease, as assessed by the investigator (subjects in this group who had been randomized to sorafenib were not allowed to receive tivozanib in the extension study 902)

### 5.2.3. Drug Modifications/Discontinuations

Dose reductions and/or dose interruptions were recommended for subjects who experienced study drug related adverse events (AEs).

Dose reductions were allowed for sorafenib-related AEs (other than skin toxicity) that were  $\geq$  Grade 3, as follows:

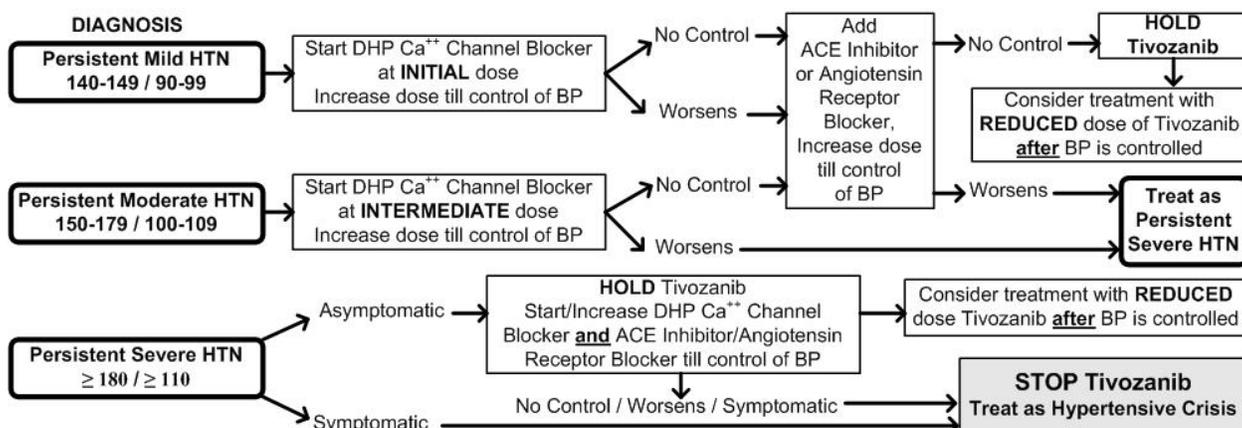
- Initially the dose was reduced from 400 mg twice daily to 400 mg once daily.
- If the AE persisted, the dose was further reduced to 400 mg once every other day.
- If the sorafenib-related AE persisted at this dose, treatment was interrupted.
- If the sorafenib-related AEs resolved to  $\leq$  Grade 1, the dose could be re-escalated to the previous level at the discretion of the investigator.

Dose reductions (from 1.5 mg/day to 1.0 mg/day) were allowed for tivozanib-related AEs (other than hypertension) that were  $\geq$  Grade 3. If the tivozanib-related AE persisted at the 1.0 mg/day dose, the treatment was interrupted. The dose of tivozanib could not be re-escalated following a dose reduction.

Subjects were excluded from study 301 if they had uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg on 2 or more antihypertensive medications, documented on 2 consecutive measurements taken at least 24 hours apart). Blood pressure on the study was measured at baseline, Cycle 1 Days 1 and 15, the first day of every subsequent cycle, at the end of treatment and 30 days later, and for unscheduled visits. Specific procedures were recommended for the management of hypertension associated with tivozanib (Figure 12). Persistent mild hypertension (140-149/90-99) and persistent moderate hypertension (150-179/100-109) were treated with a calcium channel blocker starting with the recommended initial dose or intermediate dose, respectively. The dose was increased as needed until blood pressure was controlled. If blood pressure was not adequately controlled, a second antihypertensive could be added. Persistent severe hypertension ( $\geq 180/\geq 110$ ) was treated

by holding tivozanib and initiating or increasing the calcium channel blocker in conjunction with another antihypertensive until blood pressure was controlled.

**Figure 12: Management of Hypertension, Study 301**



#### 5.2.4. Inclusion and Exclusion Criteria

The key inclusion criteria were as follows:

- At least 18 years of age.
- Recurrent or metastatic RCC.
- Prior nephrectomy (complete or partial) for excision of the primary tumor.
- Histologically or cytologically confirmed RCC with a clear cell component.
- Measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, Version 1.0.
- Treatment-naïve status, or no more than 1 prior systemic treatment (immunotherapy including interferon-alpha or interleukin 2 based therapy, chemotherapy, hormonal therapy or an investigational agent) for metastatic RCC.
- ECOG PS of 0 or 1, and life expectancy of at least 3 months.

The key exclusion criteria were as follows:

- Any prior VEGF-directed therapy including VEGF antibody (eg, bevacizumab), VEGF receptor tyrosine kinase inhibitor (eg, sunitinib, sorafenib, axitinib, pazopanib), VEGF trap (eg, aflibercept), or any other agent or investigational agent targeting the VEGF pathway.
- Any prior therapy with an agent targeting the mTOR pathway (eg, temsirolimus, everolimus).
- Primary central nervous system malignancies or metastases.

- Specified hematologic, serum chemistry (including liver function test), cardiovascular, thromboembolic, vascular, bleeding, wound healing, or organ system abnormalities; inadequate recovery from surgery, increased risk of gastrointestinal perforation, requirement for hemodialysis or peritoneal dialysis, life-threatening illness, currently active second primary malignancy, or serious infection.

## **5.2.5. Statistical Methods**

### **5.2.5.1. Efficacy Endpoints**

The primary endpoint was PFS as determined by IRR.

Secondary endpoints included: objective response rate (ORR) by IRR, duration of response (DR) by IRR, duration of stable disease (DS) by IRR, overall survival (OS), change from baseline in target (measured) lesions, and patient reported outcome (PRO) (quality of life assessments).

Definitions of these endpoints are provided below in the relevant analysis sections.

### **5.2.5.2. Sample Size**

Study 301 was designed to have at least 90% power to detect a statistically significant difference between treatment arms in the primary endpoint of PFS as assessed by IRR. Randomizing 500 subjects (250 per treatment arm) with a total number of 310 events (deaths or progression) would yield 90% power to detect a treatment difference, assuming a median PFS of 6.7 months for subjects receiving sorafenib and 9.7 months for subjects receiving tivozanib and a dropout rate of 3% per treatment arm.

### **5.2.5.3. Analysis Populations**

The intent-to-treat (ITT) population was defined as all randomized subjects. For the ITT population, the treatment arm was designated according to the initial randomization, regardless of whether the subjects received the assigned study drug. The ITT population was used for the analysis of the primary and secondary efficacy endpoints.

The per protocol (PP) population was defined as all randomized subjects who remained in the study for at least 8 weeks (2 cycles) (unless discontinued due to death or disease progression) and had no major protocol violations that would confound the effects of treatment in the judgment of the Sponsor's medical monitor. The PP population was used as a sensitivity analysis for the assessment of the primary efficacy endpoint.

The safety population was defined as all randomized subjects who received at least 1 dose of either study drug. For the safety population, the treatment arm was designated according to the actual study treatment received. This population was used for all safety analyses. Please refer to [Section 6](#) for further details regarding safety assessments and results.

### **5.2.5.4. Analysis of Primary Endpoint**

The primary endpoint was PFS as determined by IRR and based on a data snapshot as of 15 December 2011. PFS was defined as the time from randomization to first

documentation of objective tumor progression (PD) or death due to any reason, whichever came first. The primary efficacy analysis compared PFS between treatment arms in the ITT population using a stratified log-rank test. For this analysis, the stratification factors (as entered into the IVRS) were number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or  $\geq 2$ ), and the analysis was considered positive if the 2-sided stratified log-rank test was significant at the 5% level. The HR for treatment and the corresponding 95% CI were estimated using the sorafenib arm as the reference group in a proportional hazards model. Kaplan Meier (KM) plots of the survival distribution function by treatment arm were presented for all PFS analyses. PFS data were censored on the day following the date of last tumor assessment documenting absence of PD in the following subjects:

- Subjects who did not have objective tumor progression and were still on study at the time of the analysis.
- Subjects who were treated with anti-tumor treatments other than study drug.
- Subjects who were removed from treatment follow-up prior to documentation of objective tumor progression.

Subjects with missing imaging at baseline were censored at the date of randomization. Subjects who had no tumor assessments after randomization also had their PFS data censored on the date of randomization, unless they died within 140 days of randomization (ie, after 2 or more missed assessments, where 20 weeks was chosen to be the midpoint between the second and third planned assessments during the first year on study). If PD or death occurred more than 140 days after the last assessment (ie, after 2 or more missed assessments), the subject was censored on the day following the date of the last assessment before the gap.

### **Sensitivity Analyses for PFS**

In addition to analyzing PFS in the per protocol population using the IRR assessment, four additional sensitivity analyses were pre-specified.

- Sensitivity Analysis 1: Performed using the investigator assessment of response and adding in any clinical PDs specified by the investigator. A clinical PD was defined as treatment failure not meeting the criteria for PD but considered by the investigator to require removal of the subject from the study. Sensitivity analysis 1 was repeated using the ITT and PP population.

The following sensitivity analyses were conducted using the ITT population:

- Sensitivity Analysis 2: For this analysis, initiation of new anticancer treatment was considered an event. All deaths or PDs (based on the IRR assessment) were events, even those occurring after 2 or more missed tumor assessments.
- Sensitivity Analysis 3: For this analysis, discontinuation of therapy and initiation of new anticancer treatment were considered events. All deaths or PDs (based on the IRR assessment) were events, even those occurring after 2 or more missed tumor assessments.

- Sensitivity Analysis 4: This analysis used the IRR assessments and backdated any PD events that occurred immediately after missing or not evaluable (NE) assessments. If the PD occurred immediately after a NE assessment (or series of NE assessments), the PD date was the date of the first NE assessment preceding the PD. If the PD occurred immediately after a missing assessment (or series of missing assessments), the PD date was the date of the first missing assessment preceding the PD.

In addition, sensitivity analyses based upon the full stratified model that included all stratification factors in randomization and unstratified model were examined for consistency of the findings.

#### **5.2.5.5. Analysis of Secondary Endpoints**

The secondary efficacy endpoints were analyzed using the ITT population (OS, ORR, DR, and DS).

#### **Overall Survival**

OS was defined as the time from the date of randomization to date of death due to any cause, irrespective of use of subsequent therapy. In the absence of confirmation of death, survival time was censored at the last date the subject was known to be alive or 27 August 2012, whichever was sooner. For subjects with no data beyond randomization, survival times were censored on the date of randomization.

OS was compared between the 2 treatment arms using a stratified log-rank test, where the stratification matched that used in the primary analysis for PFS. An interim OS analysis was carried out at the time of the final PFS analysis. The final OS analysis was based on vital status follow-up as of 27 August 2012, when all subjects in follow-up were on the study for at least 2 years. Subjects treated with other therapy after discontinuing study drug in study 301 were included in the analysis (including subjects randomized to sorafenib who were treated with tivozanib in study 902).

The distribution of OS was estimated using the KM method. The HR for treatment was estimated using the Cox proportional hazard regression model. An unstratified analysis was also conducted, as well as a stratified log-rank test where the stratification included the factors used to stratify randomization. KM plots of the survival distribution function by treatment arm were produced.

#### **Objective Response Rate**

Confirmed ORR was defined as the proportion of subjects with confirmed complete response (CR) or confirmed partial response (PR) per RECIST criteria, relative to the total population of randomized subjects. For the overall analysis, the confirmed ORR was compared between the 2 treatment arms using the Cochran-Mantel-Haenszel test, where the stratification matched that used in the primary PFS analysis. The estimate of the odds ratio for treatment (using the sorafenib arm as the reference treatment) and corresponding 95% CI were presented.

### **Duration of Response and Duration of Stable Disease**

DR was defined as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any reason. DR was calculated only for subjects who had an objective tumor response. Duration of SD was defined as the time from first dose of study drug to the first time the RECIST criteria for progression were met, taking as reference the smallest measurements recorded since study treatment started. DR and DS were analyzed in a similar manner as PFS and OS. Results of the analysis stratified by the randomization stratification factors were also presented. KM plots of the survival distribution function by treatment arm were produced.

### **Patient-reported Outcomes (Quality of Life) Analyses**

Quality of life (QoL) was assessed using three validated self-reported PRO instruments: one generic instrument, the European Quality of Life 5-Domain Scale (EQ-5D), and two cancer-specific instruments, the Functional Assessment of Cancer Therapy-General (FACT-G) and the Functional Assessment of Cancer Therapy - Kidney Symptom Index's Disease Related Symptoms subscale (FKSI-DRS). These instruments were administered on Day 1 of each cycle until Cycle 24 and upon discontinuation from the study drug. For all three instruments, higher scores indicate better quality of life or fewer symptoms.

The PRO results were summarized in the ITT population. The preplanned analysis was to investigate changes from baseline (Cycle 1 Day 1 assessment) in PRO scores. Mixed-effects repeated measures models (MMRM) of change from baseline in PRO scores were used to test whether there was a difference between treatment arms across the different timepoints. The results were interpreted using previously established minimally important differences (MIDs) for each PRO instrument (EQ-5D utility index: MID = 0.08, EQ-5D VAS: MID = 7,<sup>48</sup> FACT-G total score: MID = 5-6,<sup>49</sup> FACT-G subscales: MID = 2-3,<sup>50</sup> and FKSI-DRS = 2-3).<sup>51</sup>

Two post-hoc exploratory analyses of the cancer-specific instruments were conducted: time to first QoL deterioration and percentage of subjects reporting a clinically meaningful improvement from baseline at any time during treatment.

#### **5.2.5.6. Subgroup and Exploratory Analyses**

##### **Protocol-Specified Subgroup Analyses**

In these analyses, PFS was compared between the 2 treatment arms, including pre-specified subgroups defined by the following variables: age group (< 65 years, ≥ 65 years), sex (male, female), race (white, non-white), screening ECOG PS (0, 1), time since diagnosis (< 1 year, ≥ 1 year), number of prior systemic therapies for metastatic disease (0, 1), and geographic region (North America/Western Europe, Central/Eastern Europe, rest of world). The analyses for the pre-specified subgroups of number of metastatic sites/organs involved (1, ≥ 2) are presented together with those of an exploratory analysis for number of involved organs (1, ≥2).

### Exploratory Analyses

PFS was also compared between the 2 treatment arms in exploratory subgroup analyses defined by the following variables: MSKCC prognostic group (favorable, intermediate, poor), Heng prognostic group (favorable, intermediate, poor), and location of involved organ (any liver metastases, lung only metastases, and metastases in other organs).

In order to examine the relationship between PFS and pharmacokinetics (tivozanib exposure), a pharmacokinetics/pharmacodynamics analysis was performed using clinical data from study 301 and tivozanib exposure data, with exposure parameters taken from the population pharmacokinetics model.

Additional survival analyses were performed in order to fully describe the OS results. These analyses examined the association between tivozanib serum exposure and OS, the influence of baseline prognostic factors on OS (in particular ECOG PS and organ versus site stratification), differential use of next-line targeted therapy, and post-progression overall survival.

### 5.3. Subject Enrollment and Disposition At the Time of the Primary Efficacy Analysis

Overall, study 301 included 260 subjects randomized to tivozanib (1 subject was randomized but not treated) and 257 subjects randomized to sorafenib (Table 8). At the time of the primary efficacy analysis, the study drug discontinuation rate was lower with tivozanib than with sorafenib (59.2% compared to 74.7%). For both treatment arms, the most common reason for study drug discontinuation was progressive disease.

**Table 8: Disposition of Subjects in Study 301 at the Time of the Primary Efficacy Analysis**

	<b>Tivozanib</b>	<b>Sorafenib</b>
Subjects Randomized [n]	260	257
Subjects Treated [n (%) <sup>a</sup> ]	259 (99.6)	257 (100.0)
Subjects Randomized but Not Treated [n (%) <sup>a</sup> ]	1 (0.4)	0 (0.0)
Subjects with study drug ongoing [n (%) <sup>a</sup> ]	106 (40.8)	65 (25.3)
Subjects discontinued [n (%) <sup>a</sup> ]	154 (59.2)	192 (74.7)

**Table 8: Disposition of Subjects in Study 301 at the Time of the Primary Efficacy Analysis**

	Tivozanib	Sorafenib
Primary reason for study drug discontinuation [n (%)]		
Investigator-assessed progressive disease	107 (41.2)	153 (59.5)
Adverse event	19 (7.3)	18 (7.0)
Death	12 (4.6)	9 (3.5)
Subject withdrawal of consent	5 (1.9)	3 (1.2)
Lack of efficacy	4 (1.5)	3 (1.2)
Noncompliance	0	1 (0.4)
Other	7 (2.7)	5 (1.9)

NA=not achieved

<sup>a</sup> Percent of all randomized subjects.

<sup>b</sup> Calculated as the date of discontinuation from the study drug minus the date of first dose plus 1.

Subjects who were missing a discontinuation reason were censored on their last visit date.

Note: Reasons for discontinuation were based on the end-of-treatment electronic Case Report Form page.

The majority of the subjects enrolled were from Central/Eastern Europe (88.1% of subjects randomized to tivozanib and 88.7% randomized to sorafenib). Overall, 8.5% of subjects in tivozanib arm and 7.0% in sorafenib arm were from North America/Western Europe.

#### 5.4. Baseline Demographics and Medical History

The majority of subjects enrolled were males (71% and 74% in the tivozanib and sorafenib arms, respectively), and approximately 75% of the enrolled subjects were less than 65 years old (Table 9). Baseline characteristics, with the exception of ECOG PS, were similar between the treatment arms (Table 10). Fewer subjects in the tivozanib arm had an ECOG PS score of 0 at baseline (44.6%) compared to that in sorafenib arm (54.1%;  $p = 0.035$ , Fisher exact test). The differential in ECOG PS favored the sorafenib arm, which had a higher percentage of subjects with a higher level of function at baseline. Consistent with this imbalance, there were also more patients with favorable MSKCC and Heng prognostic criteria at baseline in the sorafenib arm.

**Table 9: Demographics, Study 301 (ITT Population)**

	<b>Tivozanib (N=260)</b>	<b>Sorafenib (N=257)</b>
<b>Gender [n (%)]</b>		
Male	185 (71.2)	189 (73.5)
Female	75 (28.8)	68 (26.5)
<b>Age (years)</b>		
Mean (STD)	58.2 (9.96)	58.4 (9.57)
Median	59.0	59.0
Range	23-83	23-85
<b>Age group [n (%)]</b>		
< 65 years	195 (75.0)	193 (75.1)
≥ 65 years	65 (25.0)	64 (24.9)
<b>Race [n (%)]</b>		
White	249 (95.8)	249 (96.9)
Asian	10 (3.8)	8 (3.1)
Black or African American	1 (0.4)	0 (0.0)
<b>Ethnicity [n (%)]</b>		
Not Hispanic or Latino	254 (97.7)	244 (94.9)
Unknown	4 (1.5)	4 (1.6)
Hispanic or Latino	2 (0.8)	9 (3.5)
<b>Geographic Region<sup>a</sup> [n (%)]</b>		
Central/Eastern Europe	229 (88.1)	228 (88.7)
North America/Western Europe	22 (8.5)	18 (7.0)
Rest of world	9 (3.5)	11 (4.3)

ITT = Intent-to-treat; STD = standard deviation

<sup>a</sup> Geographic region was a randomization stratification factor.

**Table 10: Baseline Characteristics, Study 301**

<b>Characteristic</b>	<b>Tivozanib (N=260)</b>	<b>Sorafenib (N=257)</b>
<b>Weight (kg)</b>		
Mean (STD)	80.70 (17.091)	80.08 (16.042)
Median	79.00	79.20
Range	44.0-137.0	43.0-138.8
<b>Height (cm)</b>		
Mean (STD)	171.41 (8.465)	171.33 (9.151)
Median	173.00	172.00
Range	145.0-190.0	145.0-203.0
<b>Body mass index (kg/m<sup>2</sup>)</b>		
Mean (STD)	27.38 (5.123)	27.28 (5.037)
Median	26.95	26.50
Range	17.0-47.8	16.3-49.2
<b>Baseline SBP [n (%)]</b>		
SBP ≤ 140 mmHg	243 (93.5)	233 (90.7)
SBP > 140 mmHg	17 (6.5)	24 (9.3)
<b>Baseline DBP [n (%)]</b>		
DBP ≤ 90 mmHg	254 (97.7)	238 (92.6)
DBP > 90 mmHg	6 (2.3)	19 (7.4)
<b>Antihypertensive Medication at Baseline</b>		
Subjects with 1 HTN medication	41 (15.8)	45 (17.5)
Subjects with ≥ 2 HTN medications	37 (14.2)	44 (17.1)
<b>ECOG performance status [n (%)]</b>		
0	116 (44.6)	139 (54.1)
1	144 (55.4)	118 (45.9)

HTN = hypertension, ITT = Intent-to-treat; STD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure; ECOG = Eastern Cooperative Oncology Group

All of the subjects had a diagnosis of clear cell or clear cell component RCC based on local pathology reports, and all of them had a prior complete or partial nephrectomy. Baseline medical and RCC characteristics were similar between treatment arms (Table 11). All of the subjects had a prior complete or partial nephrectomy. Nearly all of the subjects had stage IV (metastatic) RCC, with the majority having at least ≥ 2 metastatic

sites or organs involved as determined by the independent radiologist. Overall, 27% of subjects had their classification change with the second post-hoc, blinded IRR, with most of them initially classified into the  $\geq 2$  stratum when in fact they had single organ involvement. The distribution of metastatic sites was similar in the treatment arms. Fewer subjects in the tivozanib arm had a favorable MSKCC prognosis. A similar number had favorable Heng prognosis, but fewer tivozanib subjects had intermediate Heng prognosis and slightly more tivozanib subjects had a poor Heng prognosis.

**Table 11: Cancer History Characteristics, Study 301**

	<b>Tivozanib (N=260)</b>	<b>Sorafenib (N=257)</b>
<b>Time since diagnosis (months)</b>		
n	246	242
Mean (STD)	29.9 (36.20)	35.7 (48.63)
Median	14.7	16.6
Q1, Q3	4.0, 40.8	4.4, 47.7
Range	0.5-168.6	1.0-264.3
<b>Time since diagnosis</b>		
< 1 year since diagnosis (n)	109	105
> 1 year since diagnosis (n)	137	137
<b>Time since most recent relapse or staging (months)</b>		
n	242	235
Mean (STD)	6.0 (13.13)	5.3 (8.86)
Median	2.1	2.0
Range	0.2- 144.2	0.1- 56.8
<b>Pathological diagnosis [n (%)]</b>		
Clear cell	246 (94.6)	244 (94.9)
Clear cell component	14 (5.4)	13 (5.1)
<b>Diagnosis confirmed by [n (%)]</b>		
Histology	258 (99.2)	256 (99.6)
Cytology	2 (0.8)	1 (0.4)
<b>Stage at screening [n (%)]</b>		
Stage IV (metastatic)	259 (99.6)	254 (98.8)
Local recurrence	1 (0.4)	3 (1.2)

**Table 11: Cancer History Characteristics, Study 301**

	<b>Tivozanib (N=260)</b>	<b>Sorafenib (N=257)</b>
<b>Number of metastatic sites or organs involved [n (%)]</b>		
1	16 (6.2)	17 (6.6)
≥ 2	244 (93.8)	240 (93.4)
<b>Number of involved organs <sup>a</sup> [n (%)]</b>		
1	76 (29.2)	88 (34.2)
≥ 2	184 (70.8)	169 (65.8)
<b>Metastatic sites of disease [n (%)]</b>		
Lung	212 (81.5)	204 (79.4)
Lymph nodes	182 (70.0)	166 (64.6)
Other	110 (42.3)	106 (41.2)
Adrenal gland	78 (30.0)	57 (22.2)
Liver	67 (25.8)	49 (19.1)
Bone	61 (23.5)	52 (20.2)
Soft tissue	42 (16.2)	31 (12.1)
Opposite kidney	33 (12.7)	34 (13.2)
Brain	8 (3.1)	8 (3.1)
Spine	8 (3.1)	2 (0.8)
Colon	2 (0.8)	1 (0.4)
Rectum	0 (0.0)	1 (0.4)
<b>Number of prior treatments for metastatic disease [n (%)]</b>		
0	181 (69.6)	181 (70.4)
1	78 (30.0)	76 (29.6)
<b>Prior chemotherapy setting [n (%)]</b>		
Metastatic/unresectable therapy	49 (18.8)	55 (21.4)
Adjuvant	23 (8.8)	22 (8.6)
Other	7 (2.7)	6 (2.3)
Unknown	5 (1.9)	3 (1.2)
Neo-adjuvant	1 (0.4)	0 (0.0)

**Table 11: Cancer History Characteristics, Study 301**

	<b>Tivozanib (N=260)</b>	<b>Sorafenib (N=257)</b>
<b>Prior radiation indication [n (%)]</b>		
Pre-operative	3 (1.2)	1 (0.4)
Post-operative	12 (4.6)	13 (5.1)
Palliative	20 (7.7)	18 (7.0)
<b>Prior nephrectomy [n (%)]</b>		
Complete nephrectomy	249 (95.8) <sup>c</sup>	247 (96.1)
Partial nephrectomy	11 (4.2)	10 (3.9)
Other	1 (0.4) <sup>c</sup>	0 (0.0)
<b>MSKCC prognostic group [n (%)]</b>		
Favorable	70 (26.9)	87 (33.9)
Intermediate	173 (66.5)	160 (62.3)
Poor	17 (6.5)	10 (3.9)
<b>Heng score [n (%)]</b>		
Favorable	41 (15.8)	45 (17.5)
Intermediate	137 (52.7)	152 (59.1)
Poor	78 (30.0)	59 (23.0)

Geographic region, number of prior treatments, and number of metastatic sites/organs involved are the randomization stratification factors.

<sup>a</sup> Based on post-hoc, blinded IRR review<sup>c</sup>

## 5.5. Primary Endpoint

### 5.5.1. Progression-Free Survival

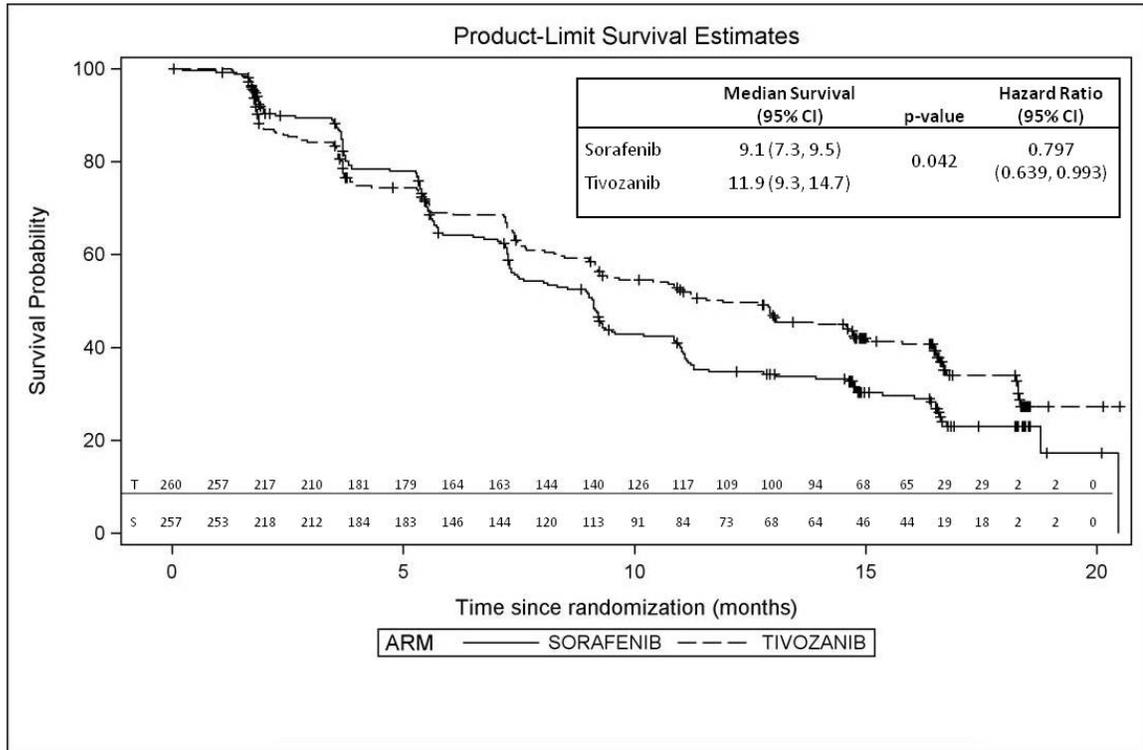
The primary efficacy endpoint was PFS as determined by IRR and analyzed in the ITT population. In subjects randomized to tivozanib, median PFS was significantly longer (11.9 months) than in sorafenib subjects (9.1 months) (p=0.042, using the primary stratified analysis). The hazard ratio was 0.797 (95% CI: 0.639, 0.993) using the stratified Cox proportional hazards model (Table 12 and Figure 13).

**Table 12: Progression-Free Survival as Determined by Independent Radiological Review, Study 301 (ITT Population)**

	<b>Tivozanib (N=260)</b>	<b>Sorafenib (N=257)</b>
Subjects who had disease progression or died, n (%)	153 (58.8)	168 (65.4)
Event by disease progression	139 (53.5)	156 (60.7)
Event by death without disease progression	14 (5.4)	12 (4.7)
Subjects with censored endpoints, n (%)	107 (41.2)	89 (34.6)
PFS (months), estimated quartile and 95% CI		
25%	4.0 (3.7, 5.6)	5.4 (3.8, 5.6)
50%	11.9 (9.3, 14.7)	9.1 (7.3, 9.5)
75%	NA (18.3, NA)	16.6 (14.8, 20.4)
Log-rank test statistic (p-value) for tivozanib as compared with sorafenib by primary stratified analysis <sup>a</sup>	4.123 (0.042)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by stratified Cox proportional hazards model	0.797 (0.639, 0.993)	

<sup>a</sup> Primary stratified analysis includes the following stratification factors, as entered into the IVRS: number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥ 2)

**Figure 13: Primary Endpoint of Study 301: Progression-Free Survival as Determined by Independent Radiological Review (ITT Population)**



**5.5.2. Pre-specified Sensitivity Analyses of PFS**

The primary efficacy analysis of PFS was performed using the pre-specified stratification factors (as entered into the IVRS) for number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥ 2). Additional sensitivity analyses were conducted that included an unstratified analysis and an analysis stratified by all stratification factors at randomization (as entered into the IVRS) by geographic region (North America/Western Europe, Central/Eastern Europe, or rest of the world), number of prior treatments (0 or 1), and number of metastatic sites/organs involved (1 or ≥ 2) (full stratified analysis). The results from the unstratified analysis (HR 0.785 [95% CI: 0.630, 0.978], p=0.030) and the full stratified analysis (HR 0.810 [95% CI: 0.648, 1.012], p=0.062) supported the primary findings.

A comparison of PFS using IRR assessment in the per protocol population was also performed and, as expected, strengthened the inference. Median PFS in the PP population for the tivozanib subjects was 12.9 months (95% CI: 10.4, 15.0), compared with 9.1 months (95% CI: 7.3, 10.2) for sorafenib subjects, with a hazard ratio of 0.751 (95% CI: 0.592, 0.953) (p = 0.018) for the primary stratified analysis.

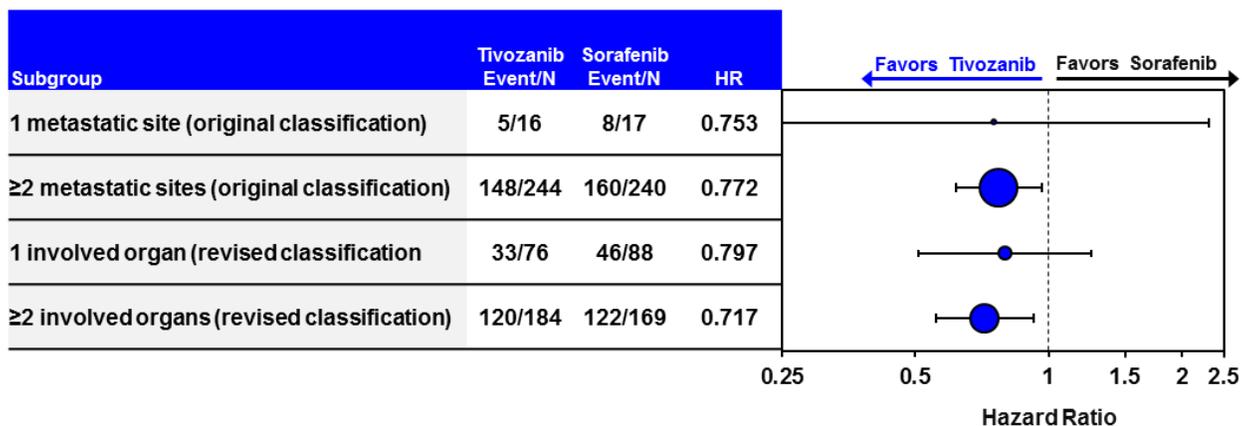
Median PFS by investigator assessment for the tivozanib subjects was 14.7 months (95% CI: 10.4, 16.6) compared with 9.6 months (95% CI: 9.0, 11.0) for sorafenib subjects, with an HR of 0.722 (95% CI: 0.580, 0.899) and p=0.003 by the primary stratified analysis.

### 5.5.3. Exploratory Sensitivity and Subgroup Analysis of PFS Based upon Stratification by Involved Organ Number

Based upon a request from the FDA during the NDA review, data from the second review for number of involved organs were used in a sensitivity analysis to evaluate the potential impact upon the primary analysis. In this exploratory post-hoc analysis that repeated the primary analysis with organ number substituted for number of sites, the statistical evidence and the hazard ratio were both substantially strengthened. The p-value in the primary stratified analysis for PFS decreased from p=0.042 to p=0.006, and the hazard ratio decreased from 0.797 (95% CI: 0.639, 0.993) to 0.736 (95% CI: 0.589, 0.919).

In addition, PFS was assessed for each category of site/organ number, with hazard ratios as shown in the Forest Plot in Figure 14.

**Figure 14: Forest Plot of PFS Hazard Ratios by IRR Assessment for Exploratory Sensitivity Analysis Regarding Number of Involved Sites/Organs, Study 301 (ITT Population)**



### 5.5.4. Pre-Specified and Exploratory Analyses of PFS by Subject Subgroup

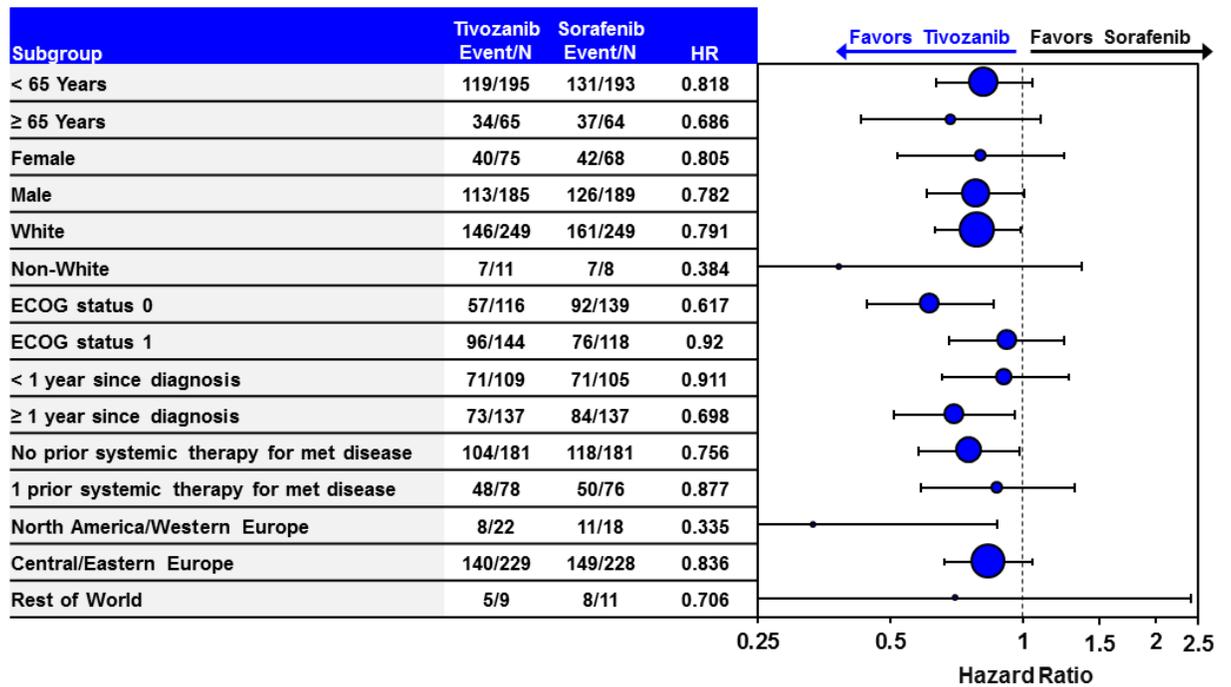
HRs for the effect of tivozanib on PFS were examined across pre-specified subject subgroups. In all subgroups presented in Figure 15, HRs were less than 1 (favoring tivozanib), indicating that the trend observed with PFS was consistent with that observed in the primary analysis.

In the subgroup of 70% of subjects with no prior therapy for metastatic disease, median PFS was 12.7 months (95% CI: 9.1, 15.0) for tivozanib as compared to 9.1 months for sorafenib (95% CI: 7.3, 10.8), with an HR of 0.756 (95% CI: 0.580, 0.985) and p=0.037, indicating that tivozanib is particularly effective in subjects with no prior therapy. The findings in the subgroup of no prior systemic therapy are consistent with the primary analysis. In the US, the overwhelming majority of RCC patients present without prior treatment.

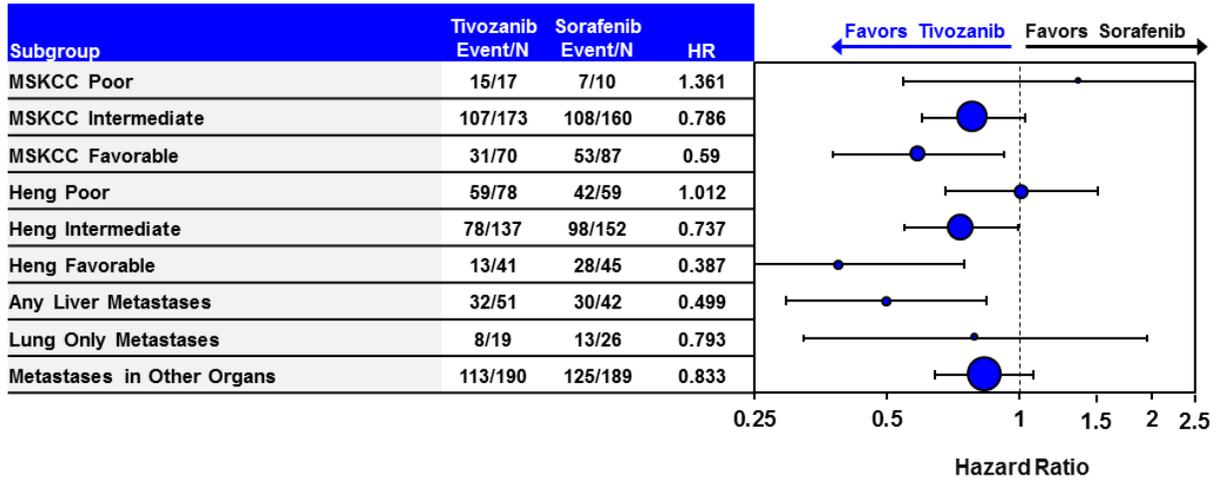
Findings by exploratory subgroup analyses also support the consistency of the primary findings, with all HRs less than 1 (favoring tivozanib) except in the subgroup of 27 subjects in the poor MSKCC prognosis category (Figure 16). Subjects in the

favorable MSKCC or Heng subgroups had a particularly favorable HR. Slightly more subjects on the tivozanib arm had liver metastases at baseline, whereas slightly more subjects on the sorafenib arm had metastases present only in the lungs at baseline. This suggested that subjects randomized to the tivozanib arm may have had worse underlying disease characteristics, consistent with the higher proportion of subjects in the tivozanib arm with an unfavorable (ie, intermediate or poor) MSKCC prognosis at baseline as well as the statistically significant imbalance in ECOG PS at baseline. The subgroup of subjects with any liver metastases demonstrated a statistically significant improvement in PFS for tivozanib compared with sorafenib (median PFS of 9.7 months versus 5.5 months,  $p = 0.007$ ).

**Figure 15: Forest Plot of PFS Hazard Ratios by IRR Assessment for Pre-Specified Subgroups, Study 301 (ITT Population)**



**Figure 16: Forest Plot of PFS Hazard Ratios by IRR Assessment for Exploratory Subgroups, Study 301 (ITT Population)**



**5.5.5. Exploratory Analysis of PFS by On-Study Hypertension**

An exploratory analysis of median PFS by maximum blood pressure on study was also performed for study 301 (Table 13). The proportion of subjects with elevated blood pressure (as measured by SBP > 140 mmHg or DBP > 90 mmHg) was similar, about 40%, in subjects from each treatment arm. In both treatment arms, subjects who developed elevated blood pressure on study had a longer median PFS than subjects who did not. However, regardless of the development of elevated blood pressure, tivozanib subjects had longer median PFS than sorafenib subjects, consistent with the results of the overall population.

**Table 13: Exploratory Kaplan-Meier Analysis of Progression-Free Survival by Maximum Post-Baseline Blood Pressure Subgroup, by IRR, Study 301**

	Event, n/N		Median PFS, months (95% CI)		Unstratified Analysis, Tivozanib vs. Sorafenib
	Tivozanib	Sorafenib	Tivozanib	Sorafenib	Hazard Ratio <sup>a</sup> (95% CI)
<b>All blood pressures:</b>	153/260	168/257	11.9 (9.3, 14.7)	9.1 (7.3, 9.5)	0.785 (0.630, 0.978)
<b>By blood pressure group:</b>					
Maximum SBP on study, mmHg					
≤ 140	97/144	100/140	9.0 (7.2, 11.3)	5.8 (5.5, 9.0)	0.811 (0.613, 1.074)
> 140	56/115	67/116	16.7 (12.9, 18.3)	11.1 (9.2, 14.7)	0.726 (0.508, 1.037)
Unstratified Analysis, SBP ≤ 140 vs. SBP > 140 mmHg					
Hazard Ratio <sup>b</sup> (95% CI)			0.543 (0.390, 0.756)	0.559 (0.409, 0.763)	
Maximum DBP on study, mmHg					
≤ 90	106/158	116/169	9.1 (7.5, 12.7)	7.3 (5.7, 9.1)	0.826 (0.633, 1.077)
> 90	47/101	51/87	18.3 (12.9, NA)	11.0 (9.3, 16.4)	0.751 (0.504, 1.117)
Unstratified Analysis, DBP ≤ 90 vs. DBP > 90 mmHg					
Hazard Ratio <sup>b</sup> (95% CI)			0.553(0.391, 0.781)	0.581(0.417, 0.810)	

CI = confidence interval, DBP = diastolic blood pressure, PFS = progression-free survival, SBP = systolic blood pressure

<sup>a</sup> Hazard ratio for tivozanib arm vs sorafenib arm of study 301 based on Cox proportional hazards model. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of tivozanib.

<sup>b</sup> Hazard ratio for the 2 blood pressure groups based on Cox proportional hazards model. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of the group with elevated maximum blood pressure.

## 5.6. Secondary Endpoints

### 5.6.1. Overall Survival

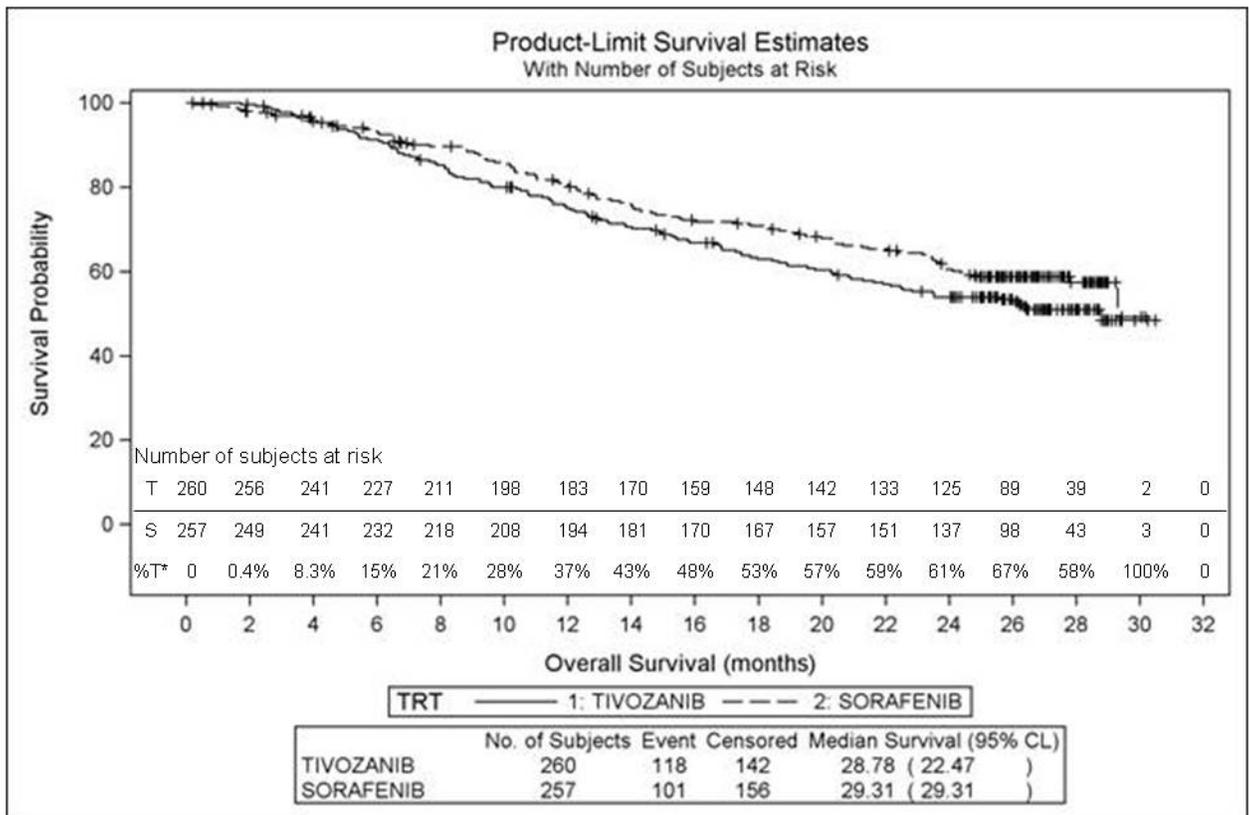
OS was defined as the time from the date of randomization to date of death due to any cause, irrespective of use of subsequent therapy. Given that the majority of sorafenib subjects in study 301 received next-line tivozanib in study 902, results from both studies are considered for OS analyses.

#### 5.6.1.1. Final Overall Survival Results

OS was compared between the tivozanib and control arms in the ITT population as of 27 August 2012, when all subjects in follow-up had been on study for at least 2 years. A trend was observed for longer OS in the control arm (Figure 17 and Table 14). In the tivozanib arm, 45.4% of subjects died compared with 39.3% in the control arm.

The HR by the primary stratified analysis was 1.245 for tivozanib compared with the control (95% CI: 0.954, 1.624; p= 0.105). All subjects had been followed for approximately 24 to 30 months, with the estimates of median OS in both arms within this range (28.8 months for tivozanib and 29.3 months for the control).

**Figure 17: Kaplan-Meier Plot of Final Overall Survival (ITT Population)**



**Table 14: Final Overall Survival (ITT Population)**

	<b>Tivozanib N=260</b>	<b>Control N=257</b>
Subjects who died, n (%)	118 (45.4)	101 (39.3)
Subjects who survived, n (%)	142 (54.6)	156 (60.7)
OS (months), estimated quartile and 95% CI		
25%	12.1 (10.4, 15.0)	14.1 (12.3, 19.3)
50%	28.8 (22.5, NA)	29.3 (29.3, NA)
75%	NA	NA
Log-rank test statistic (p-value) for tivozanib as compared with control by primary stratified analysis <sup>a</sup>	2.621 (0.105 <sup>b</sup> )	
Hazard ratio (95% CI) for tivozanib as compared with control by stratified Cox proportional hazards model <sup>a</sup>	1.245 (0.954, 1.624)	
Log-rank test statistic (p-value) for tivozanib as compared with control by unstratified analysis	2.460 (0.117)	
Hazard ratio (95% CI) for tivozanib as compared with control by unstratified Cox proportional hazards model	1.236 (0.948, 1.613)	

NA = Not achieved

<sup>a</sup> Stratification factors for the primary stratified analysis are number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or  $\geq 2$ )

<sup>b</sup> P-value is not adjusted for multiple looks. Adjusting for 2 interim looks at 64% information (141/219 deaths) and 89% information (194/219 deaths) using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary yields an adjusted p-value of 0.108.

Applying the corrected stratification factor for number of organs in an exploratory analysis resulted in a lower HR (1.158, 95% CI: 0.887, 1.513) and a higher p-value (0.279) compared to stratification by number of metastatic sites (HR 1.245 [95% CI: 0.954, 1.624], p= versus 0.105).

An additional exploratory analysis to adjust for the imbalance in baseline ECOG PS between the arms, an unstratified Cox proportional hazards model that included baseline ECOG PS (0 or 1) and treatment as explanatory variables, resulted in an HR of 1.186 (95% CI: 0.908, 1.548; p=0.211). Inclusion of the treatment by ECOG PS interaction was statistically significant (p=0.014).

### **5.6.1.2. Differential Use of Next-line VEGFR Inhibitor Therapy**

As the OS ITT analysis included OS data from all randomized subjects, including those randomized to sorafenib who developed radiographic evidence of progression and then received next-line tivozanib, the OS results are confounded by differential use of subsequent treatment. As shown in [Table 15](#), of the subjects randomized to sorafenib in study 301, 63% (162/257) received next-line targeted therapy outside of study 301, with

almost all of them receiving tivozanib in study 902. In contrast, 13% (34/260) of the subjects randomized to tivozanib received a next-line targeted therapy.

**Table 15: Summary of Next-line Therapy for Subjects in Study 301**

	Tivozanib N=260		Sorafenib N=257	
	n	%	n	%
Subjects who discontinued assigned therapy <sup>a</sup>	190 <sup>b</sup>	(73.1)	226	(87.9)
Subjects with next-line therapy	68	(26.2)	168	(65.4)
VEGFR inhibitor	18	(6.9)	158	(61.5)
Tivozanib	0		156	(60.7)
mTOR	16	(6.2)	4	(1.6)
Cytokines	14	(5.4)	3	(1.2)
Radiotherapy	10	(3.8)	2	(0.8)
Other	10	(3.8)	1	(0.4)

<sup>a</sup> On/before 27 August 2012

<sup>b</sup> Subject 186-006 erroneously appears as “discontinued”, but was ongoing. Therefore, there were actually 189 subjects who discontinued therapy.

mTOR = mammalian target of rapamycin; PD = progressive disease; VEGFR = vascular endothelial growth factor receptor.

The differential use of next-line therapy between treatment groups reflected the location of the investigative sites and the availability of additional therapy. A larger than anticipated proportion of subjects was enrolled from Central and Eastern Europe where subjects had limited access to effective next-line treatment options for RCC. Subjects randomized to sorafenib who discontinued due to PD, however, had access to tivozanib in study 902. In subjects from the North American/Western European region, a trend toward longer OS was noted in the tivozanib arm compared with the control arm (HR = 0.503, 95% CI: 0.174, 1.451). This result should be interpreted with caution given the small number of subjects enrolled in North America/Western Europe (n=40) and the small number of events on which it is based (14 events).

### **5.6.2. Anti-tumor Activity of Next-line Tivozanib After Progression on Sorafenib**

Tivozanib has demonstrated anti-tumor activity after disease progression on sorafenib. In the ongoing study 902, at the time of the final overall survival analysis for study 301, the median PFS of the 156 subjects who received next-line tivozanib was 8.4 months (95% CI: 5.5, 12.4) and the confirmed overall response rate by investigator assessment was 13.5% (95% CI: 8.5, 19.8). A waterfall plot of individual subjects’ tumor measurements indicates that 74.5% of patients with measurable disease had some degree of tumor regression on tivozanib in study 902 (Figure 18).



**Table 16: Summary of Overall Response, Independent Radiological Review, Study 301 (ITT Population)**

	<b>Tivozanib N=260</b>	<b>Sorafenib N=257</b>
Confirmed Overall Response, n (%)		
Complete Response (CR)	3 (1.2%)	2 (0.8%)
Partial Response (PR)	83 (31.9%)	58 (22.6%)
Stable Disease (SD)	134 (51.5%)	168 (65.4%)
Progressive Disease (PD)	34 (13.1%)	19 (7.4%)
Not evaluable (NE)	6 (2.3%)	10 (3.9%)
Missing	0	0
Overall confirmed ORR (CR+PR)	86 (33.1%)	60 (23.3%)
95% CI for ORR	(27.4, 39.2)	(18.3, 29.0)
Primary stratified analysis		
p-value	0.014	
Odds ratio	1.625	
95% CI for odds ratio	(1.103, 2.395)	

#### 5.6.4. Duration of Response

By IRR assessment, the median duration of response was 14.8 months in the tivozanib arm (86 responding subjects) and 13.0 months with sorafenib (58 responding subjects),  $p=0.486$  by the primary stratified analysis.

#### 5.6.5. Duration of Stable Disease

The median duration of stable disease was significantly longer for the tivozanib arm (9.3 months, in 134 subjects) than for the sorafenib arm (8.5 months, in 168 subjects) based on IRR assessment,  $p=0.026$

#### 5.6.6. Patient-reported Outcomes (Quality of Life)

Completion rates for all three PROs for patients remaining in the study at each assessment timepoint ranged between 95.7% and 100% for measurements corresponding to the first 12 months (Cycle 13) and between 68.8% and 100% for the remaining measurements. Baseline PRO scores were well balanced between the two arms.

Quality of life (QoL) was maintained during the first 12 months of treatment in both arms, i.e. decrease in scores did not meet the pre-established criteria for clinically meaningful changes.<sup>48, 51, 55</sup> No clinically or statistically significant differences were observed for the change from baseline between arms for any of the PRO scores (Table 17).

**Table 17: Mean Change from Baseline and Treatment Difference for PRO Measures (across 13 cycles), Study 301**

Domain	Adjusted Mean Change From Baseline (95% CI)		
	Tivozanib (n=258)	Sorafenib (n=251)	Treatment Difference
FACT-G			
Physical well-being	-1.54 (-2.25, -0.84)	-2.08 (-2.77, -1.39)	0.53 (-0.18, 1.24)
Functional well-being	-0.73 (-1.52, 0.07)	-1.02 (-1.79, -0.25)	0.29 (-0.51, 1.10)
Emotional well-being	0.59 ( 0.02, 1.15)	0.40 (-0.15, 0.95)	0.19 (-0.38, 0.77)
Social/Family well-being	-0.79 (-1.57, -0.02)	-0.35 (-1.10, 0.41)	-0.45 (-1.24, 0.34)
Total score	-2.83 (-4.88, -0.78)	-3.10 (-5.10, -1.10)	0.27 (-1.88, 2.42)
FKSI-DRS			
Total score	-0.94 (-1.59, -0.29)	-0.93 (-1.56, -0.30)	-0.01 (-0.67, 0.64)
EQ-5D			
EQ-5D utility index	-0.05 (-0.08, -0.01)	-0.06 (-0.09, -0.03)	0.01 (-0.02, 0.05)
EQ-5D VAS score	0.34 (-1.71, 2.40)	-1.96 (-3.96, 0.03)	2.31 ( 0.19, 4.42)

FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: FACT–Kidney Symptom Index Disease Related Symptoms.  
Minimally important differences: FACT-G subscales and FKSI-DRS=2–3; FACT-G total score=5–6; EQ-5D utility index=0.08; EQ-5D VAS score=7.

Two post-hoc exploratory analyses of the cancer-specific instruments were conducted: time to first QoL deterioration and percentage of subjects reporting a clinically meaningful improvement from baseline at any time during treatment. While in general there was no statistically significant difference between the arms in either analysis, trends favored the tivozanib arm. The only exception was the FACT-G physical well being subscore, for which significantly more subjects in the tivozanib arm showed an improvement compared to sorafenib. Physical well-being is the most sensitive of the domains for detecting drug toxicities. The findings are consistent with the improved tolerability of tivozanib as compared with sorafenib.

In conclusion, no detrimental effect on QoL was evident for tivozanib compared with sorafenib when assessed with the FACT-G, FKSI-DRS and EQ-5D instruments. The prolongation of PFS for tivozanib compared with sorafenib was not associated with lowered QoL in the tivozanib arm compared to sorafenib.

## 6. CLINICAL SAFETY ACROSS DEVELOPMENT

### 6.1. Summary of Safety

#### Adverse Events

- Adverse events (AEs) were reported in 91% in the tivozanib arm and 97% in the sorafenib arm. Hypertension (44%), dysphonia (21%) and back pain (14%) were more frequent on tivozanib. Palmar-plantar erythrodysesthesia (hand-foot syndrome, 54%), diarrhea (33%) and alopecia (21%) were more frequent on sorafenib.
- Adverse events  $\geq$  Grade 3 occurred in 61.4% in the tivozanib arm and in 69.6% in the sorafenib arm. The most frequent  $\geq$  Grade 3 AE in the tivozanib arm was hypertension (25.5%). The most frequent  $\geq$  Grade 3 AEs in the sorafenib arm were hypertension (17.5%) and palmar-plantar erythrodysesthesia (16.7%).
- 25.9% of tivozanib subjects had at least one SAE compared to 21.4% of sorafenib subjects.
- Dose reductions and/or interruptions due to an AE were about half as common for tivozanib compared with sorafenib (24.7% vs 52.1%). The most frequent adverse event leading to dose modification in the tivozanib arm was hypertension (7.7%) and hand-foot syndrome in the sorafenib arm (23.3%).
- The percentage of subjects with AEs leading to study drug discontinuation was similar in each treatment arm (13.1% on tivozanib vs. 12.5% on sorafenib).
- Deaths due to adverse events other than progressive disease occurred in 13 subjects on the tivozanib arm and 12 on the sorafenib arm. Deaths due to progressive disease occurred in 8 subjects on the tivozanib arm and 2 on the sorafenib arm.
- High serum tivozanib exposure is not associated with an increased incidence of fatal adverse events.

#### Adverse Events of Interest

- One case of PRES occurred in the 894 subjects with solid tumors who received tivozanib.
- In study 301, arterial thromboembolic events  $\geq$  Grade 3 occurred in 9 (3.5%) subjects on the tivozanib arm and 7 (2.7%) on the sorafenib arm.
- In study 301, hemorrhage events  $\geq$  Grade 3 occurred in 7 (2.7%) subjects on the tivozanib arm and 3 (1.2%) on the sorafenib arm.

- Across the tivozanib development program, no subjects administered tivozanib have met the criteria for Hy's law. One event of reversible cholestatic liver injury was reported. Tivozanib is associated with fewer  $\geq$  Grade 3 liver function test elevations compared with sorafenib.

## **6.2. Overview of Safety Populations**

For the briefing book, the safety experience with tivozanib is reviewed and discussed in the following study populations:

- Study 301: Subjects treated as randomized to tivozanib or sorafenib
- 4 RCC monotherapy studies: studies 201, 301, 902, and 202
- Adverse events of interest: A summary of all experience focused on AEs of interest that may be associated with tivozanib treatment.

## **6.3. Safety Experience in 301**

### **6.3.1. Disposition of Subjects**

At the time of the 120-day safety update analyses for study 301 ([Table 18](#)), a lower percent of subjects in the tivozanib arm discontinued study drug compared with the sorafenib arm (70.0% compared to 85.6%). The most common reason for study drug discontinuation in each treatment arm was progressive disease, with a lower incidence of discontinuations in the tivozanib arm than the sorafenib arm (48.8% compared to 67.3%).

**Table 18: Subject Disposition for Study 301 (Safety Analyses)**

	Tivozanib (n=260) n (%)		Sorafenib (n=257) n (%)	
Subjects randomized/enrolled [n]	260		257	
Subjects treated [n, (%)]	259	(99.6)	257	(100.0)
Subjects randomized but not treated	1	(0.4)	0	
Subjects ongoing <sup>a</sup>	78	(30.0)	37	(14.4)
Subjects who discontinued study drug treatment	182	(70.0)	220	(85.6)
Primary reason for study drug discontinuation				
Death	13	(5.0)	8	(3.1)
Adverse event	22	(8.5)	20	(7.8)
Investigator-assessed progressive disease	127	(48.8)	173	(67.3)
Lack of efficacy <sup>b</sup>	4	(1.5)	3	(1.2)
Significant protocol deviation	1	(0.4)	0	
Noncompliance	0		2	(0.8)
Subject withdrawal of consent	5	(1.9)	5	(1.9)
Treatment interruption >2 weeks	2	(0.8)	1	(0.4)
Other	8	(3.1)	8	(3.1)

<sup>a</sup> Subjects who were continuing to receive study drug at the time of the 120-day safety update analyses.

<sup>b</sup> Lack of efficacy was meant to capture clinical progression in the absence of radiographic evidence.

### 6.3.2. Extent of Exposure and Relative Dose Intensity

At the time of the 120-day safety update analyses for study 301, the median number of days of treatment was 365 for the tivozanib arm and 288 for the sorafenib arm (Table 19). In the tivozanib arm, 70.3% of subjects were treated for longer than 6 months and 52.9% of subjects were treated for longer than 12 months. In the sorafenib arm, 70.0% of subjects were treated longer than 6 months and 43.6% of subjects were treated longer than 12 months.

Relative dose intensity is defined as the actual dose relative to the initial prescribed dose of study drug (1.5 mg tivozanib once daily for 3 weeks on/1 week off and 400 mg sorafenib twice daily for 4 weeks). In study 301 (Table 19), the mean relative dose intensity for tivozanib-treated subjects was 94.2% (median 100%), higher than for sorafenib-treated subjects (mean 79.4%, median 89.3%).

**Table 19: Exposure to Study Drug: Duration of Exposure and Relative Dose Intensity for Study 301 (Safety Analyses)**

	Tivozanib (N=259)		Sorafenib (N=257)	
Duration of exposure, days <sup>a</sup>				
Quartile, n (95% CI)				
25%	159	(118, 187)	168	(113, 171)
50%	365	(280, 497)	288	(264, 337)
75%	699	(672, 721)	548	(448, 624)
Subjects dosed by number of cycles, n (%)				
≤ 6	77	(29.7)	77	(30.0)
> 6 to ≤ 12	45	(17.4)	68	(26.5)
> 12 to ≤ 24	135	(52.1)	99	(38.5)
> 24	2	(0.8)	13	(5.1)
Total dose administered, mg				
N	259		257	
Mean (std)	450.90	(294.99)	232174.3	(172217.85)
Median	409.50		185600.0	
Q1, Q3	172.00, 756.00		91200.00, 319600.0	
Min, Max	21.00, 945.00		800.00, 648800	
Relative dose intensity, %				
N	259		257	
Mean (std)	94.18	(9.53)	79.41	(21.55)
Median	100.00		89.29	
Q1, Q3	92.00, 100.00		64.29, 96.30	
Min, Max	54.52, 100.00		3.57, 100.00	

<sup>a</sup> The measurement of exposure by days includes the 7-day rest period in each cycle.  
CI = confidence interval.

### 6.3.3. Adverse Events

Presentation of adverse event information focuses on study 301. For certain analyses, data from the 4 core RCC monotherapy studies were used. In general, the safety profile of tivozanib in study 301 is representative of that seen across the tivozanib program.

#### 6.3.3.1. Treatment Emergent Adverse Events

##### Adverse Events: All Grades

In study 301, the frequency of AEs was 90.7% in the tivozanib arm and 96.9% in the sorafenib arm (Table 20).

**Table 20: Summary of Adverse Events (Study 301)**

Category of AE	Tivozanib (N=259) n (%)		Sorafenib (N=257) n (%)	
Any AE	235	(90.7)	249	(96.9)
AE ≥ Grade 3	159	(61.4)	179	(69.6)
AE with an outcome of death within 30 days of last dose of study drug	20	(7.7)	14	(5.4)
SAE	67	(25.9)	55	(21.4)
AE leading to discontinuation of study drug	34	(13.1)	32	(12.5)
AE leading to study drug interruption and/or reduction	64	(24.7)	134	(52.1)

For all AEs and SAEs, subjects are included only once, even if they experienced multiple events.  
AE = adverse event; SAE = serious adverse event.

In study 301 (Table 21), palmar-plantar erythrodysesthesia, alopecia, and diarrhea occurred more frequently in the sorafenib arm. Hypertension, dysphonia, nausea, and back pain occurred more frequently in the tivozanib arm.

**Table 21: Most Common Adverse Events in Study 301 ( $\geq 10.0\%$  of Subjects in Either Treatment Arm)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
Any Adverse Event	235	(90.7)	249	(96.9)
Hypertension	113	(43.6)	88	(34.2)
Diarrhea	59	(22.8)	84	(32.7)
Dysphonia	55	(21.2)	12	(4.7)
Fatigue	50	(19.3)	41	(16.0)
Weight decreased	47	(18.1)	53	(20.6)
Asthenia	40	(15.4)	43	(16.7)
Palmar-plantar erythrodysesthesia	36	(13.9)	139	(54.1)
Back pain	35	(13.5)	21	(8.2)
Nausea	31	(12.0)	19	(7.4)
Stomatitis	29	(11.2)	23	(8.9)
Dyspnea	29	(11.2)	22	(8.6)
Decreased appetite	27	(10.4)	24	(9.3)
Alopecia	6	(2.3)	55	(21.4)

For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

### Adverse events: $\geq$ Grade 3

In study 301,  $\geq$  Grade 3 AEs occurred in 61.4% of subjects in the tivozanib arm compared with 69.6% of subjects in the sorafenib arm. The most common  $\geq$  Grade 3 AEs in the tivozanib arm were hypertension (25.5%), fatigue (5.4%), and asthenia (3.9%). Each of these AEs occurred more frequently in the tivozanib arm than in the sorafenib arm (Table 22). The most common  $\geq$  Grade 3 AEs in the sorafenib arm were hypertension (17.5%), palmar-plantar erythrodysesthesia (16.7%), and lipase increased (9.3%). With the exception of hypertension, each of these events occurred more frequently in the sorafenib arm. The incidence of palmar-plantar erythrodysesthesia events was 8-fold higher in the sorafenib arm than in the tivozanib arm.

**Table 22: Adverse Events  $\geq$  Grade 3 in Study 301 ( $\geq$  1.0% of Subjects in Either Treatment Arm)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
<b>Any Adverse Event <math>\geq</math> Grade 3</b>	<b>159</b>	<b>(61.4)</b>	<b>179</b>	<b>(69.6)</b>
Hypertension	66	(25.5)	45	(17.5)
Fatigue	14	(5.4)	9	(3.5)
Asthenia	10	(3.9)	7	(2.7)
Disease progression	8	(3.1)	2	(0.8)
Lipase increased	8	(3.1)	24	(9.3)
Back pain	8	(3.1)	5	(1.9)
Amylase increased	7	(2.7)	6	(2.3)
Weight decreased	7	(2.7)	9	(3.5)
Anemia	7	(2.7)	9	(3.5)
Hyperkalemia	7	(2.7)	2	(0.8)
Diarrhea	6	(2.3)	17	(6.6)
Blood potassium increased	5	(1.9)	3	(1.2)
Dyspnea	5	(1.9)	5	(1.9)
Palmar-plantar erythrodysesthesia	5	(1.9)	43	(16.7)
Hypertensive crisis	4	(1.5)	0	
Gamma-glutamyltransferase increased	4	(1.5)	6	(2.3)
Proteinuria	4	(1.5)	6	(2.3)
Spinal pain	3	(1.2)	0	
Aspartate aminotransferase increased	3	(1.2)	7	(2.7)
Ischemic stroke	3	(1.2)	0	
Cerebrovascular accident	3	(1.2)	3	(1.2)
Metastatic pain	3	(1.2)	1	(0.4)
Alanine aminotransferase increased	2	(0.8)	6	(2.3)
Blood phosphorus decreased	2	(0.8)	10	(3.9)
Myocardial infarction	2	(0.8)	4	(1.6)
Neutropenia	1	(0.4)	3	(1.2)
Pneumonia	1	(0.4)	3	(1.2)
White blood cell count decreased	0		1	(0.4)

**Table 22: Adverse Events  $\geq$  Grade 3 in Study 301 ( $\geq$  1.0% of Subjects in Either Treatment Arm)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
Pleural effusion	0		4	(1.6)
Hyponatremia	0		3	(1.2)
Hypophosphatemia	0		4	(1.6)
Cholecystitis acute	0		3	(1.2)

For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

### 6.3.3.2. Adverse Events Leading to Discontinuation of Study Drug

In study 301, the incidence of AEs leading to with study drug discontinuation was similar in each treatment arm (13.1% tivozanib versus 12.5% sorafenib) (Table 23). In the tivozanib arm, 3 subjects (1.2%) discontinued study drug due to AEs of ischemic stroke. In the sorafenib arm, 3 subjects (1.2%) discontinued study drug due to AEs of back pain. All other AEs resulting in study drug discontinuation occurred in  $\leq$  2 subjects.

The 7 events in tivozanib subjects of ischemic stroke, cerebrovascular accident, and hemiparesis occurred in 6 subjects. One subject had both ischemic stroke and hemiparesis events leading to study drug discontinuation.

**Table 23: Adverse Events Leading to Discontinuation of Study Drug ( $\geq$  2 Subjects in Either Treatment Arm) (Study 301)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
<b>Any AE leading to discontinuation of study drug</b>	<b>34</b>	<b>(13.1)</b>	<b>32</b>	<b>(12.5)</b>
Ischemic stroke	3	(1.2)	0	
Cerebrovascular accident	2	(0.8)	2	(0.8)
Hemiparesis	2	(0.8)	0	
Fatigue	2	(0.8)	1	(0.4)
Pulmonary embolism	2	(0.8)	2	(0.8)
Hypertension	2	(0.8)	1	(0.4)
Acute myocardial infarction	2	(0.8)	1	(0.4)
Asthenia	1	(0.4)	2	(0.8)

**Table 23: Adverse Events Leading to Discontinuation of Study Drug  
(≥ 2 Subjects in Either Treatment Arm) (Study 301)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
Back pain	1	(0.4)	3	(1.2)
Myocardial infarction	0		2	(0.8)

For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

### 6.3.3.3. Adverse Events Leading to Dose Reduction and/or Interruption

In study 301, more than twice as many sorafenib subjects had dose reductions and/or interruptions (134 subjects, 52.1%) compared with tivozanib subjects (64 subjects, 24.7%)(Table 24). In both arms, the most common reasons for dose reduction and/or interruption were hypertension (7.7% of tivozanib subjects and 6.2% of sorafenib subjects), diarrhea (3.9% of tivozanib subjects and 7.8% of sorafenib subjects), and palmar-plantar erythrodysesthesia (3.1% of tivozanib subjects and 23.3% of sorafenib subjects).

**Table 24: Adverse Events Leading to Dose Reduction and/ or Interruption  
(≥ 3 Subjects in Either Treatment Arm) (Study 301)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
<b>Any AE Resulting in Dose Reduction and/or Interruption</b>	<b>64</b>	<b>(24.7)</b>	<b>134</b>	<b>(52.1)</b>
Hypertension	20	(7.7)	16	(6.2)
Diarrhea	10	(3.9)	20	(7.8)
Palmar-plantar erythrodysesthesia	8	(3.1)	60	(23.3)
Vomiting	5	(1.9)	6	(2.3)
Asthenia	5	(1.9)	5	(1.9)
Amylase increased	3	(1.2)	2	(0.8)
Proteinuria	3	(1.2)	3	(1.2)
Anemia	3	(1.2)	0	(0.0)
Fatigue	2	(0.8)	6	(2.3)
Lipase increased	2	(0.8)	9	(3.5)
Abdominal pain	2	(0.8)	3	(1.2)
Stomatitis	1	(0.4)	4	(1.6)

**Table 24: Adverse Events Leading to Dose Reduction and/ or Interruption (≥ 3 Subjects in Either Treatment Arm) (Study 301)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
Blood creatinine increased	1	(0.4)	3	(1.2)
Rash erythematous	1	(0.4)	4	(1.6)
Weight decreased	1	(0.4)	3	(1.2)
Nausea	0		3	(1.2)
Alanine aminotransferase increased	0		3	(1.2)
Aspartate aminotransferase increased	0		4	(1.6)
Rash pustular	0		3	(1.2)
Cholecystitis acute	0		3	(1.2)
Constipation	0		3	(1.2)
Hyperemia	0		3	(1.2)
Pruritus generalized	0		3	(1.2)
Rash maculo-papular	0		3	(1.2)

For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

#### 6.3.3.4. Serious Adverse Events

In study 301, the incidence of SAEs was 25.9% in the tivozanib arm and 21.4% in the sorafenib arm (Table 25), largely attributable to more events of disease progression reported as SAEs in the tivozanib arm. In the tivozanib arm, 8 subjects (3.1%) had SAEs of disease progression and 4 subjects (1.5%) had SAEs of anemia. In the sorafenib arm, 4 subjects (1.6%) had SAEs of myocardial infarction, 4 subjects (1.6%) had SAEs of anemia, and 4 subjects (1.6%) had SAEs of pleural effusion.

**Table 25: Serious Adverse Events (≥ 3 Subjects in Either Treatment Arm) (Study 301)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
<b>Any Serious Adverse Event</b>	<b>67</b>	<b>(25.9)</b>	<b>55</b>	<b>(21.4)</b>
Disease progression	8	(3.1)	2	(0.8)
Anemia	4	(1.5)	4	(1.6)
Fatigue	3	(1.2)	1	(0.4)
Ischemic stroke	3	(1.2)	0	
Cerebrovascular accident	3	(1.2)	3	(1.2)
Pulmonary embolism	3	(1.2)	2	(0.8)
Hypertension	3	(1.2)	2	(0.8)
Myocardial infarction	2	(0.8)	4	(1.6)
Dyspnea	2	(0.8)	3	(1.2)
Pleural effusion	0		4	(1.6)
Cholecystitis acute	0		3	(1.2)

For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

#### **6.3.3.5. Adverse Events with an Outcome of Death Within 30 Days of Last Dose of Study Drug**

In study 301, adverse events with an outcome of death within 30 days of last dose of study drug were more frequent in the tivozanib arm (7.7%) than the sorafenib arm (5.4%) (Table 26). In addition, there was one death in the tivozanib group that occurred within 30 days of last dose, for which no AE was recorded. This occurred in a subject who had been lost to follow-up but subsequent information obtained during a sweep for overall survival revealed that they had died within 30 days of last dose. Cause of death was unknown.

There were 21 deaths that occurred within 30 days of last dose on the tivozanib arm and 14 deaths that occurred on the sorafenib arm. Deaths due to progressive disease (including terms for progressive disease, renal cancer, metastases to central nervous system, neoplasm progression, and spinal cord compression) occurred in 8 subjects on the tivozanib arm and 2 on the sorafenib arm.

Deaths due to adverse events other than progressive disease occurred in 13 subjects on the tivozanib arm and 12 on the sorafenib arm.

The death due to dyspnea on the tivozanib arm occurred in the setting of pancreatitis with jaundice.

**Table 26: All Adverse Events with an Outcome of Death Within 30 Days of Last Dose of Study Drug (Study 301)**

Preferred Term	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
<b>Any AE with an outcome of death within 30 days of last dose of study drug</b>	<b>20</b>	<b>(7.7)</b>	<b>14</b>	<b>(5.4)</b>
Disease progression	4	(1.5)	2	(0.8)
Myocardial infarction	2	(0.8)	0	
Arteriosclerosis coronary artery	1	(0.4)	1	(0.4)
Cardiac arrest	1	(0.4)	0	(0.0)
Cardiac failure	1	(0.4)	1	(0.4)
Cardiac failure acute	1	(0.4)	1	(0.4)
Renal cancer	1	(0.4)	0	
Metastases to central nervous system	1	(0.4)	0	
Neoplasm progression	1	(0.4)	0	
Pulmonary embolism	1	(0.4)	2	(0.8)
Apnea	1	(0.4)	0	
Dyspnea	1	(0.4)	0	
Cerebrovascular accident	1	(0.4)	3	(1.2)
Spinal cord compression	1	(0.4)	0	
Aortic aneurysm rupture	1	(0.4)	0	
Hypertension	1	(0.4)	0	
Coronary artery insufficiency	0		1	(0.4)
Acute respiratory distress syndrome	0		1	(0.4)
Pleural effusion	0		1	(0.4)
Jaundice	0		1	(0.4)
Post procedural hemorrhage	0		1	(0.4)

Note that 1 subject in the sorafenib arm had 2 adverse events with an outcome of death within 30 days of last dose: pulmonary embolism and acute cardiac failure.

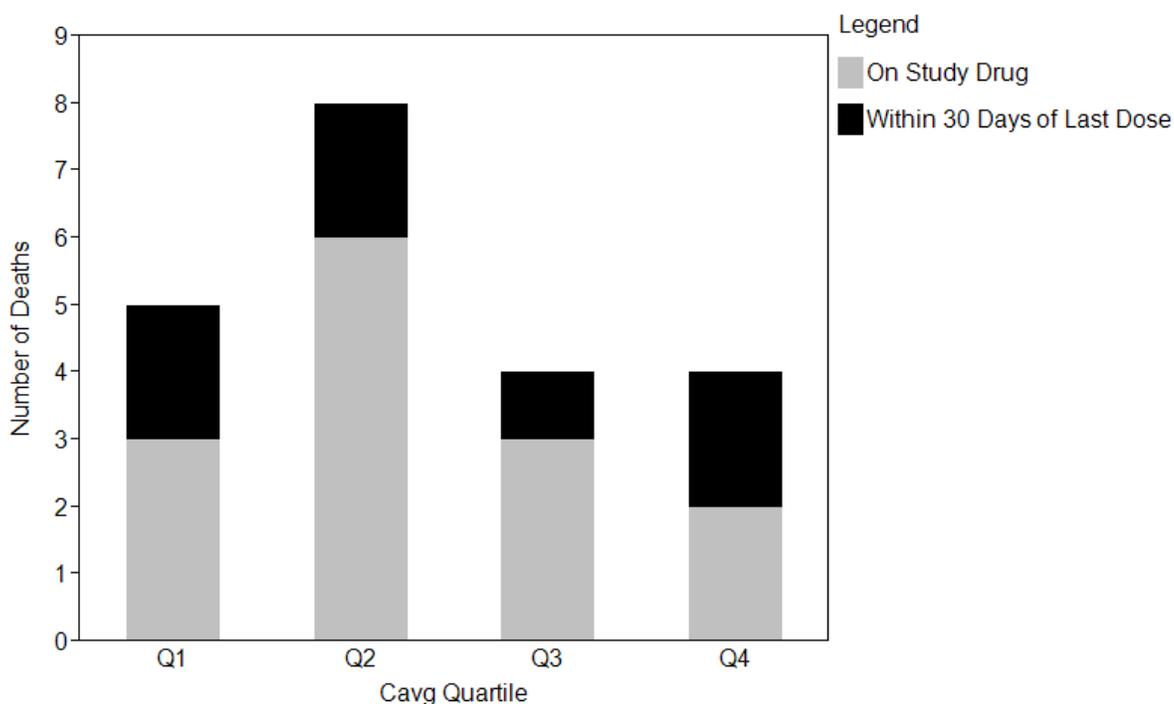
Note that there was 1 subject in the tivozanib arm who died within 30 days of last dose for whom no AE was recorded. The patient had been lost to follow-up but information obtained during a sweep for overall survival revealed the death (cause unknown).

An exploratory analysis was performed to examine whether or not high serum levels were associated with mortality. The exposure measure,  $C_{avg}$ , the average concentration of

tivozanib over an entire 4-week steady-state treatment cycle, including rest period, was utilized. The  $C_{avg}$  was calculated using sparse serum concentration data that was collected for each subject and then entered into a population PK model developed for tivozanib. All subjects were then categorized into exposure quartiles (Q) determined by  $C_{avg}$ . The  $C_{avg}$  ranges for each quartile were: Q1: 18 to 43 ng/mL; Q2: 43 to 57 ng/mL; Q3: 57 to 73 ng/mL; Q4: 73 to 180 ng/mL.

As illustrated in Figure 19, which presents the number of tivozanib-treated subjects who died while on study drug or within 30 days of last dose by exposure quartile, higher exposure to tivozanib was not associated with short-term mortality.

**Figure 19: Subject Deaths That Occurred During Tivozanib Treatment and Up to 30 Days Following Last Dose of Study Drug, Presented by Exposure Quartile**



Note:  $C_{avg}$  ranges for each quartile were: Q1: 18 to 43 ng/mL; Q2: 43 to 57 ng/mL; Q3: 57 to 73 ng/mL; Q4: 73 to 180 ng/mL.

### 6.3.4. Adverse Events by Patient Subgroup

#### 6.3.4.1. Age

A subgroup analysis evaluated AEs (all grades) and SAEs that occurred in subjects aged < 65 years compared to subjects  $\geq 65$  years in the core RCC monotherapy studies. The overall incidence of AEs and SAEs was similar between age groups. The most common AEs in both age groups were hypertension and dysphonia. Serious adverse events included disease progression (14 subjects [2.4%] < 65 years compared with 5 subjects [2.5%]  $\geq 65$  years), ischemic stroke (4 subjects [0.7%] < 65 years compared with

3 subjects [1.5%]  $\geq$  65 years), and anemia (7 subjects [1.2%]  $<$  65 years compared with 0 subjects  $\geq$  65 years).

#### **6.3.4.2. Gender**

A subgroup analysis evaluated AEs (all grades) and SAEs that occurred in male and female subjects in the core RCC monotherapy studies. Overall, the incidence of AEs and SAEs was similar between males and females. Some AEs were more frequent in females than males, such as hypertension (females 45.3%; males 41.3%), palmar-plantar erythrodysesthesia (females 13.5%; males 9.3%), stomatitis (females 13.9%; males 8.2%), cough (females 14.3%; males 9.4%), nausea (females 15.2%; males 11.6%), and headache (females 12.6%; males 7.7%). Serious adverse events included disease progression (14 males [2.5%] compared with 5 females [2.2%]), cerebrovascular accident (1 male [0.2%] compared with 3 females [1.3%]), and anemia (4 males [0.7%] compared with 3 females [1.3%]).

The higher incidence of some AEs in females is consistent with the population PK analysis, which indicated that females had clearance values 25.6% lower than those of males and therefore had higher exposure to tivozanib. The proposed label does not require dose adjustments for females.

#### **6.3.4.3. Race**

Although small numbers of nonwhites were enrolled in study 301, a subgroup analysis evaluated AEs  $\geq$  Grade 3 reported by race (white and nonwhite). The incidence of AEs  $\geq$  Grade 3 was similar in whites (152 tivozanib subjects, 61.3% and nonwhites (7 of 11 tivozanib subjects, 63.6%).

#### **6.3.4.4. Geographic Region**

A subgroup analysis evaluated AEs, AEs  $\geq$  Grade 3, and AEs with an outcome of death within 30 days of last dose of tivozanib reported by geographic region (North America/Western Europe and Central/Eastern Europe) across the core monotherapy studies. The incidence AEs was higher in subjects from North America/Western Europe (99.3%) than in Central/Eastern Europe (83.8%). The incidence of AEs  $\geq$  Grade 3 was also higher in subjects in North America/Western Europe (73.5%) than Central/Eastern Europe (51.1%).

Notably, the incidence of AEs with an outcome of death within 30 days of last dose was higher in Central/Eastern Europe (19 subjects, 8.3%) than in North America/Western Europe (0 subjects). This was largely due to the incidence of fatal AEs of disease progression in this region (19 subjects, 3.1%).

These trends were similar across both the tivozanib and sorafenib arms in study 301.

#### **6.3.4.5. Relationship between Tivozanib Serum Exposure and Adverse Events**

The PK/PD analysis ([Section 3.2.4](#)), which was conducted using data from study 201 and study 301 (as of the 15 December 2011 data snapshot date), evaluated potential relationships between tivozanib serum exposure and 2 safety parameters; incidence of palmar-plantar erythrodysesthesia syndrome and changes in BP. As tivozanib exposure

increased, the incidence of hand-foot syndrome increased. No significant finding was observed between tivozanib exposure and BP measurements; however, due to infrequent BP measurements, insufficient data were available to conduct a thorough analysis.

Even though a correlation between tivozanib and recorded blood pressures was not observed, a separate analysis examining the relationship between exposure and AEs across the core monotherapy studies indicated that increased tivozanib exposure resulted in an increase in the incidence of hypertension AEs. This analysis reviewed the incidence of AEs by tivozanib serum exposure quartile. Exposure quartiles (Q) were determined by average concentration over an entire steady-state treatment cycle, including rest period ( $C_{avg}$ ). The  $C_{avg}$  ranges for each quartile were: Q1: 18 to 43 ng/mL; Q2: 43 to 57 ng/mL; Q3: 57 to 73 ng/mL; Q4: 73 to 180 ng/mL.

Adverse events that occurred more frequently in subjects with higher exposure were hypertension (Q1 33.8%, Q2 44.6%, Q3 39.1%, Q4 56.9%), diarrhea (Q1 12.3%, Q2 20.0%, Q3 28.1%, Q4 30.8%), and palmar-plantar erythrodysesthesia (Q1 3.1%, Q2 16.9%, Q3 14.1%, Q4 21.5%). However these associations were not seen consistently for all AEs. In AEs  $\geq$  Grade 3, the only notable trends observed were the incidence of hypertension (Q1 16.9%, Q2 26.2%, Q3 23.4%, Q4 35.4%) and fatigue (Q1 3.1%, Q2 4.6%, Q3 4.7%, Q4 9.2%), both of which increased with exposure.

## **6.4. Adverse Events of Interest Across Development**

AEs of interest were defined by the pharmacology of tivozanib, events observed throughout the clinical development of tivozanib, and events reported for similar agents. Standard Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) were used to select AEs reported for each type of event to ensure an established, systematic clustering of AE terms was employed to facilitate identification of cases. For categories of AEs for which SMQs do not exist (wound healing and proteinuria), medical judgment was used to choose the applicable preferred terms. AEs of interest are reported for study 301 and across the core monotherapy studies.

### **6.4.1. Hypertension Events**

One of the best-documented and frequently observed on-target effects of agents that target the VEGF pathway, hypertension is related to the effect of these drugs on the vasculature.<sup>25</sup> Hypertension is considered to be a pharmacodynamic effect of anti-angiogenic agents.<sup>26</sup> Hypertension in tivozanib-treated subjects was managed with anti-hypertensive medications as directed in the study protocols and infrequently led to dose modification or discontinuation. Hypertension events in the tivozanib clinical development program were graded using NCI-CTCAE version 3.0 criteria.

In study 301, hypertension SMQ events were more common in the tivozanib arm (46.3%) than in the sorafenib arm (36.2%) (Table 27). The incidence of  $\geq$  Grade 3 hypertension AEs with tivozanib was 27.4% compared to 18.3% with sorafenib. One tivozanib-treated subject, a 75-year-old male, had a fatal AE of uncontrolled hypertension in the setting of a possible overdose of tivozanib (3 x 1.5 mg capsules were suspected but could not be confirmed).

**Table 27: Hypertension AEs (Study 301)**

<b>MedDRA Preferred Term</b>	<b>Tivozanib (N=259) n (%)</b>	<b>Sorafenib (N=257) n (%)</b>
<b>All Adverse Events</b>	<b>120 (46.3)</b>	<b>93 (36.2)</b>
<b>All ≥ Grade 3 Adverse Events</b>	<b>71 (27.4)</b>	<b>47 (18.3)</b>
Hypertension	66 (25.5)	45 (17.5)
Hypertensive crisis	4 (1.5)	0
Blood pressure increased	2 (0.8)	1 (0.4)
Labile hypertension	1 (0.4)	0
Retinopathy hypertension	0	1 (0.4)

For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

Blood pressure measurements were assessed to determine the number of subjects who had maximum blood pressure readings that were elevated (Table 28). The same number of subjects in both treatment arms had elevated SBP readings: 54 subjects treated with tivozanib (20.8%) and 54 subjects treated with sorafenib (21.0%) had SBP >150 mmHg. There were more subjects treated with tivozanib who had elevated DBP: 20 tivozanib subjects (7.7%) and 12 sorafenib subjects (4.7%) had DBP >100 mmHg. There were 15 tivozanib subjects (5.8%) and 8 sorafenib subjects (3.1%) who had SBP >150 mmHg and DBP >100 mmHg at the same reading.

**Table 28: Subjects with Maximum Blood Pressure Measurements Above Normal Limits (Study 301)**

<b>Maximum Blood Pressure</b>	<b>Tivozanib (N=259) n (%)</b>	<b>Sorafenib (N=257) n (%)</b>
SBP > 150 mmHg	54 (20.8)	54 (21.0)
DBP > 100 mmHg	20 (7.7)	12 (4.7)
SBP > 150 mmHg and DBP > 100 mmHg	15 (5.8)	8 (3.1)

SBP = systolic blood pressure; DBP = diastolic blood pressure

#### 6.4.2. Posterior Reversible Encephalopathy Syndrome (PRES)

Case reports of posterior reversible encephalopathy syndrome (PRES) possibly preceded by severe acute hypertension have been reported in patients treated with agents that target the VEGF pathway<sup>56,57,58</sup>. While inhibition of VEGF signaling is implicated in the pathophysiology of PRES due to anti-angiogenic or hypertension-inducing effects, the

syndrome has other contributing factors and the precise mechanism of PRES by agents that target the VEGF pathway has not been established.<sup>59</sup>

There has been 1 reported case of PRES in the 894 subjects with solid tumors who received tivozanib monotherapy (785 subjects in the core RCC monotherapy studies and 109 subjects in the other monotherapy studies). This subject, with serous carcinoma, had no known medical history of hypertension, cardiovascular disease, or relevant concomitant medication. The subject initially received tivozanib hydrochloride 1.5 mg. Tivozanib was reduced to 1 mg due to worsening hypertension, which was managed medically. The subject was admitted to the hospital during Cycle 2 with mental status changes, with SBP of > 200 mmHg, and DBP of 100-120 mmHg. Brain magnetic resonance imaging (MRI) revealed Grade 4 PRES. Study drug was permanently discontinued due to PRES, which was considered possibly treatment-related. The event resolved.

### 6.4.3. Arterial Embolic and Thrombotic Events

Arterial thromboembolic events have been reported with VEGFR inhibitors.<sup>60</sup> Adverse events in the Embolic and Thrombotic Events, Arterial SMQ are presented in Table 29 for study 301. Arterial thromboembolic events  $\geq$  Grade 3 occurred in 9 (3.5%) subjects on the tivozanib arm and 7 (2.7%) on the sorafenib arm. Two of the events on the tivozanib arm were fatal myocardial infarctions.

In the 4 core RCC monotherapy studies (n=785) there were two additional fatal arterial thromboembolic events, both ischemic strokes.

**Table 29: Arterial Embolic and Thrombotic AEs (Study 301)**

<b>System Organ Class Preferred Term</b>	<b>Tivozanib (N=259) n (%)</b>	<b>Sorafenib (N=257) n (%)</b>
<b>Any Adverse Event</b>	<b>12 (4.6)</b>	<b>8 (3.1)</b>
<b>Any Adverse Event <math>\geq</math> Grade 3</b>	<b>9 (3.5)</b>	<b>7 (2.7)</b>
Ischemic stroke	3 (1.2)	0
Acute myocardial infarction	2 (0.8)	2 (0.8)
Myocardial infarction	2 (0.8)	4 (1.6)
Transient ischemic attack	1 (0.4)	0
Retinal artery thrombosis	1 (0.4)	0
Pulmonary artery thrombosis	0	1 (0.4)

Only treatment-emergent adverse events are summarized.

For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.

Note: SMQ terms are from MedDRA 15.0.

#### **6.4.4. Cardiac Failure AEs**

Cardiac failure events are likely related to endothelial cell dysfunction and have been observed in some RCC patients administered anti-angiogenic TKIs. Reduced left ventricular ejection fraction (LVEF) of more than 20% occurred in 4.7% of sunitinib-treated patients.<sup>61</sup> Cardiac ischemia or infarction was reported in 3.0% of patients treated with sorafenib.<sup>14</sup>

In study 301, 3 (1.2%) subjects in each arm experienced  $\geq$  Grade 3 AEs in the cardiac failure SMQ, 2 of which were fatal in each arm.

#### **6.4.5. Venous Embolic and Thrombotic Events**

Inhibition of tumor angiogenesis by agents that target the VEGF pathway affects endothelial cell homeostasis which may result in venous thromboembolic events such as pulmonary embolism and deep vein thrombosis.<sup>59, 62 63</sup>

In study 301, venous embolic and thrombotic SMQ events were more frequent in the tivozanib arm (6 subjects, 2.3%) than in the sorafenib arm (2 subjects, 2 of whom had events  $\geq$  Grade 3). Tivozanib subjects experienced AEs of pulmonary embolism (3 subjects), vena cava thrombosis (2 subjects), and thrombophlebitis (1 subject). One pulmonary embolus was fatal on the tivozanib arm and both pulmonary embolus events on the sorafenib arm were fatal.

#### **6.4.6. Hemorrhage**

Bleeding complications have been reported with other VEGFR inhibitors.<sup>64</sup> The mechanism of VEGFR inhibition on bleeding is due to disruption of endothelial cell-platelet interactions, loss of vascular integrity, and exacerbation of pro-coagulant activity.<sup>59</sup> Bleeding complications (regardless of causality) were reported in as many as 35% of patients treated with bevacizumab,<sup>65</sup> 37% of patients treated with sunitinib,<sup>9</sup> and 15% of patients treated with sorafenib.<sup>7</sup>

In study 301, hemorrhage SMQ events were more frequent in the tivozanib arm (31 subjects, 12.0%) than in the sorafenib arm (16 subjects, 6.2%).  $\geq$ Grade 3 hemorrhage AEs were also more frequent in the tivozanib arm (7 subjects, 2.7%) than in the sorafenib arm (3 subjects, 1.2%) (Table 30). One tivozanib-treated subject experienced a fatal AE of aortic aneurysm rupture and 1 sorafenib-treated subject experienced a fatal AE of post-procedural hemorrhage, which occurred after a pleurocentesis for a malignant pleural effusion.

**Table 30: Hemorrhage AEs (Safety Population)**

MedDRA Preferred Term	Tivozanib (N=259) n (%)	Sorafenib (N=257) n (%)
<b>All Adverse Events</b>	<b>31 (12.0)</b>	<b>16 (6.2)</b>
<b>All Grade 3 or Higher Adverse Events</b>	<b>7 (2.7)</b>	<b>3 (1.2)</b>
Aortic aneurysm rupture	1 (0.4)	0
Hematemesis	1 (0.4)	0
Hemorrhagic stroke	1 (0.4)	0
Hemorrhoidal hemorrhage	1 (0.4)	0
Postmenopausal hemorrhage	1 (0.4)	0
Purpura	1 (0.4)	0
Small intestine hemorrhage	1 (0.4)	0
Epistaxis	0	2 (0.8)
Post procedural hemorrhage	0	1 (0.4)

For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

In the core RCC monotherapy studies (n=785) one additional fatal hemorrhage occurred (pulmonary hemorrhage).

#### **6.4.7. Hepatic AEs**

Hepatotoxicity may be a severe and fatal toxicity associated with some VEGFR pathway inhibitors. Pazopanib and sunitinib both agents have black box warnings for hepatotoxicity.<sup>8,9</sup> Across the 894 subjects with solid tumors receiving tivozanib monotherapy (including 785 subjects in the core RCC monotherapy studies and 109 subjects in the other monotherapy studies), systematic review of the clinical database has not identified any subjects who potentially met the criteria for Hy's Law.

In study 301, the incidence of all grade and  $\geq$  Grade 3 laboratory abnormalities for high ALT, AST and bilirubin are lower for tivozanib than for sorafenib ([Section 6.5.2](#)).

One tivozanib subject in the extension study 901 was reported to have reversible cholestatic drug-related liver toxicity as evidenced by elevated transaminases, bilirubin, and alkaline phosphatase, with positive dechallenge and re-challenge with tivozanib. Tivozanib was discontinued after positive re-challenge and the subject's symptoms and liver function tests normalized.

One subject in 894 subjects with solid tumors who received tivozanib monotherapy died of hepatic failure in the setting of extensive hepatic involvement with progressive metastatic breast cancer.

#### 6.4.8. Acute Renal Failure

Although the majority of advanced RCC subjects in the core RCC monotherapy studies (and all the subjects in study 301) had a nephrectomy, putting them at increased risk of renal failure following a nephrotoxic event, the incidence of acute renal failure was low.

In study 301, 1 (0.4%) subject in each treatment arm experienced an acute renal failure SMQ event; both events were  $\geq$  Grade 3. Neither event was fatal.

#### 6.4.9. Proteinuria

The presence of excess proteins in the urine has been observed with other VEGF targeting agents.<sup>66</sup>

In study 301, the frequency of events in this category was similar in the 2 treatment arms (23 tivozanib subjects [8.9%] and 21 sorafenib subjects [8.2%]). Four (1.5%) tivozanib subjects and 6 (2.3%) sorafenib subjects experienced AEs  $\geq$  Grade 3. None of these events was fatal.

#### 6.4.10. Thyroid Dysfunction AEs

Elevated thyroid stimulating hormone (TSH) concentrations indicative of hypothyroidism have been observed with other VEGF targeting agents.<sup>66</sup>

In study 301, thyroid function tests (TSH, T3 and T4) were measured on even numbered cycles. The incidence of hypothyroidism SMQ events was higher in the tivozanib arm (13 subjects, 5.0%) than in the sorafenib arm (6 subjects, 2.3%). None of these adverse events was  $\geq$  Grade 3.

In study 301, TSH levels that were normal prior to dosing but increased to  $>10$  mIU/L during treatment were reported for 30.1% of tivozanib subjects and 7.0% of sorafenib subjects (Table 31). A smaller number of tivozanib subjects had low T3 or free T4 on or after the date that the elevations in TSH were observed (8.9% with low T3; 1.9% with low free T4), consistent with the occurrence of hypothyroidism AEs.

**Table 31: Thyroid Function Assessments in Study 301**

Parameter	Tivozanib (N=259)		Sorafenib (N=257)	
	n	(%)	n	(%)
TSH $<$ ULN before treatment and TSH $>$ 10mIU/L after treatment	78	(30.1)	18	(7.0)
Decreased T3 $<$ LLN	23	(8.9)	5	(1.9)
Decreased freeT4 $<$ LLN	5	(1.9)	2	(0.8)

ULN=upper limit of normal range. LLN=lower limit of normal range  
Thyroid assessments were graded using NCI-CTCAE version 3.0.

#### **6.4.11. Gastrointestinal Perforation and Fistula Formation AEs**

Gastrointestinal perforation is a rare but potentially life-threatening event during anti-VEGF therapy. Disruption of normal endothelial cell homeostasis by VEGF inhibition may be one mechanism for the development of gastrointestinal perforations.<sup>59</sup>

In study 301, 1 (0.4%) subject in each treatment arm experienced a gastrointestinal perforation and fistula formation SMQ events. The tivozanib subject experienced a Grade 4 AE of abdominal abscess. The sorafenib subject experienced Grade 4 large intestine perforation and Grade 3 peritonitis. The sorafenib subject underwent several abdominal surgeries and died of acute respiratory distress syndrome 2 days after the last surgery.

#### **6.4.12. Wound Healing**

Angiogenesis is a necessary step in wound healing.<sup>67</sup> As such, impairment of revascularization may lead to insufficient vessel growth resulting in delayed or disordered healing. Wound healing AEs have been reported during anti-VEGF therapy.<sup>66</sup>

In study 301, 1 (0.4%) subject in each treatment arm experienced a wound healing complication AE. None of the events in the tivozanib arm was  $\geq$  Grade 3. The event in the sorafenib arm was Grade 3.

#### **6.4.13. Acute Pancreatitis AEs**

Acute pancreatitis events have been reported for other VEGFR TKIs.<sup>66</sup>

In study 301, 2 (0.8%) subjects in the tivozanib arm and 1 (0.4%) subject in the sorafenib arm experienced AEs in this category. Both tivozanib subjects experienced AEs of pancreatitis acute, one of which was Grade 4. The sorafenib subject also experienced a Grade 4 event of pancreatitis acute.

In study 301, the tivozanib subject who died of dyspnea did so in the setting of underlying pancreatitis with jaundice.

### **6.5. Clinical Laboratory**

#### **6.5.1. Hematology**

In study 301, 149 (57.5%) subjects in the tivozanib arm demonstrated a hematology toxicity compared with 158 (61.5%) subjects in the sorafenib arm (Table 32). Of these, 18 (6.9%) subjects in the tivozanib arm and 14 (5.4%) subjects in the sorafenib arm had a  $\geq$  Grade 3 hematology toxicity.

**Table 32: Incidence of Hematology Laboratory Abnormalities: All Grades and  $\geq 3$  Grades (Study 301)**

Parameter	Tivozanib (N=259)				Sorafenib (N=257)			
	All Grades		$\geq 3$ Grades		All Grades		$\geq 3$ Grades	
	n	(%)	n	(%)	n	(%)	n	(%)
Any low hematology toxicity	149	(57.5)	18	(6.9)	158	(61.5)	14	(5.4)
Low hemoglobin	107	(41.3)	9	(3.5)	126	(49.0)	8	(3.1)
Low leukocytes	30	(11.6)	4	(1.5)	38	(14.8)	3	(1.2)
Low neutrophils	28	(10.8)	6	(2.3)	27	(10.5)	5	(1.9)
Low platelets	47	(18.1)	1	(0.4)	31	(12.1)	0	

Hematology assessments were graded using NCI-CTCAE version 3.0.

### 6.5.2. Chemistry

In study 301, 250 (96.5%) subjects in the tivozanib arm demonstrated a chemistry toxicity compared with 253 (98.4%) subjects in the sorafenib arm (Table 33). Of these, 55 (21.2%) subjects in the tivozanib arm and 126 (49.0%) subjects in the sorafenib arm had a  $\geq$  Grade 3 chemistry toxicity. The difference between the arms is primarily due to lower incidences of  $\geq$  Grade 3 low phosphate, as well as transaminase and lipase elevation on the tivozanib arm.

**Table 33: Incidence of Selected Chemistry Laboratory Abnormalities: All Grades and  $\geq 3$  Grades (Study 301)**

Parameter	Tivozanib (N=259)				Sorafenib (N=257)			
	All Grades		$\geq 3$ Grades		All Grades		$\geq 3$ Grades	
	n	(%)	n	(%)	n	(%)	n	(%)
Any chemistry toxicity	250	(96.5)	55	(21.2)	253	(98.4)	126	(49.0)
High ALT	73	(28.2)	2	(0.8)	89	(34.6)	9	(3.5)
High AP	91	(35.1)	5	(1.9)	86	(33.5)	1	(0.4)
High amylase	104	(40.2)	12	(4.6)	135	(52.5)	17	(6.6)
High AST	97	(37.5)	5	(1.9)	131	(51.0)	10	(3.9)
High bilirubin	32	(12.4)	2	(0.8)	38	(14.8)	3	(1.2)
High lipase	119	(45.9)	29	(11.2)	164	(63.8)	63	(24.5)
High creatinine	155	(59.8)	0		117	(45.5)	2	(0.8)
Low calcium	65	(25.1)	4	(1.5)	73	(28.4)	5	(1.9)
Low phosphate	95	(36.7)	11	(4.2)	199	(77.4)	67	(26.1)
Low albumin	89	(34.4)	0		68	(26.5)	0	

Chemistry assessments were graded using NCI-CTCAE version 3.0.

## **7. BENEFIT-RISK CONCLUSION**

Despite significant advances in the treatment of RCC over the past decade, the existing approved agents can often be difficult for patients to tolerate. Symptomatic toxicities such as fatigue, diarrhea, and hand foot syndrome are important to patients and often lead to high rates of dose reductions and interruptions, raising concern that many patients may be receiving a suboptimal dose of these agents. A significant unmet medical need remains in the RCC community for efficacious agents with a differentiated safety profile

### **7.1. Benefit**

Tivozanib has demonstrated a statistically significant and clinically meaningful improvement in PFS when compared to sorafenib, an approved targeted agent. The robustness of the PFS improvement is confirmed by various sensitivity analyses. The PFS results are consistent across prespecified subgroups and are consistent with the PFS results from a large Phase 2 trial in RCC.

Although the overall survival hazard ratio indicates a trend that favors the control arm, this result can be explained due to a confluence of factors including: 1) adoption of an active comparator, 2) a high rate of utilization of next-line tivozanib by patients in the control arm and 3) limited access to next-line therapy for patients in the tivozanib arm.

A one-way crossover to tivozanib was offered to patients who experienced disease progression on sorafenib in study 301. This crossover resulted in a major imbalance in utilization of next line targeted cancer therapies for patients enrolled in study 301. A total of 63% of sorafenib patients who discontinued sorafenib therapy in study 301 were treated with next line targeted cancer therapy, nearly all with tivozanib in study 902. Data from study 902 demonstrate that tivozanib has antitumor activity in this setting. Only 13% of tivozanib patients who discontinued therapy in study 301 were treated with next line targeted cancer therapy, owing to the fact that access to next-line therapies was severely limited in the countries where the great majority of patients in study 301 were enrolled.

This imbalance in the utilization of next line cancer therapies is the most plausible explanation for the trend toward longer overall survival in patients originally randomized to sorafenib in study 301, most of whom were subsequently treated with tivozanib upon progression. The comparison of overall survival for patients enrolled in study 301 is essentially a comparison of outcomes for two groups of patients: those who received a single-line of therapy (tivozanib) vs. those who received two lines of therapy (sorafenib followed by tivozanib). Given published observations that patients who receive multiple lines of therapy have longer overall survival when compared to patients who receive only a single line of therapy, the results of the overall survival analysis are unsurprising.

### **7.2. Risk**

The safety profile of tivozanib has been well characterized and demonstrates a profile consistent with a highly selective VEGF receptor inhibitor. The most frequently reported

adverse event is hypertension, an effect that is commonly seen with other TKIs and is familiar to oncologists who treat patients with RCC. Hypertension in tivozanib-treated subjects was managed with anti-hypertensive medications as directed in the study protocols and infrequently led to dose modification.

Tivozanib is associated with certain Grade 3-4 toxicities that are seen with other VEGFR TKIs. In the pivotal trial, these occurred at rates that were comparable to what was observed for sorafenib, with the exception of hemorrhage, for which tivozanib may have a slightly higher incidence than sorafenib. Deaths due to adverse events occurred at comparable incidences for tivozanib and sorafenib and are consistent with reports from other TKI trials. There is no indication of a safety signal contributing to the observed trend in overall survival.

### **7.3. Tivozanib Benefit-Risk in the Context of TKIs Approved for Use in RCC**

Since their introduction into clinical practice in 2005, VEGFR TKIs have become a mainstay of treatment for patients with advanced RCC. The benefit of these agents has been consistently demonstrated in clinical trials by improvements in PFS. In early studies, this benefit was demonstrated relative to placebo or interferon. Tivozanib has built upon these early successes by now demonstrating PFS benefit over another TKI, sorafenib.

Cross-study comparisons have limitations; however, it is of interest that the median PFS for tivozanib in the ITT population appears comparable to both sunitinib and pazopanib, with a median PFS of 11.9 months for tivozanib compared to 11.1 months for sunitinib and 9.2 months for pazopanib based on data from each of their registration trials. In addition, the ORR for tivozanib was comparable to both sunitinib and pazopanib (33% vs. 28% and 30%, respectively) in their respective Phase 3 RCC studies. Tivozanib efficacy also appears comparable to sunitinib and pazopanib in the treatment-naïve population with a median PFS of 12.7 months for tivozanib compared to 11.1 months for sunitinib and 11 months for pazopanib based on data from each of their registration trials. An analysis of available prognostic data (e.g., ECOG PS score and MSKCC criteria) do not indicate that patients in study 301 had more favorable prognostic criteria than those in the registration studies of sunitinib or pazopanib.

While PFS has served as the approval endpoint for all VEGFR TKIs approved in RCC to date, prolongation of overall survival remains the ultimate goal of therapy in this disease. In this regard, the median estimates in both arms of the tivozanib pivotal trial are among the longest reported in RCC. Of particular note, tivozanib achieved this overall survival benefit despite the fact that fewer patients on the tivozanib arm of study 301 received any subsequent targeted therapy relative to reports from other trials ([Table 34](#)).

**Table 34: Median Overall Survival in Pivotal Studies of VEGF-targeted Therapies in Advanced Renal Cell Carcinoma**

	<b>Median OS in Months</b>	<b>95% CI</b>	<b>Percent on Subsequent Targeted Therapy</b>
Tivozanib	28.8	22.5, NA	13%
Sorafenib	29.3	29.3, NA	63%
Sorafenib <sup>a</sup>	17.8	NR	NR
Placebo	15.2	NR	NR
Bevacizumab+Interferon <sup>b</sup>	23.3	NR	35%
Interferon	21.3	NR	37%
Pazopanib <sup>c</sup>	22.9	19.9, 25.4	22%
Placebo	20.5	15.6, 27.6	63%
Sunitinib <sup>d</sup>	26.4	23.0, 32.9	42%
Interferon	21.8	17.9, 26.9	NR
Pazopanib <sup>e</sup>	28.4	26.2, 35.6	NR
Sunitinib	29.3	25.3, 32.5	NR

NR = not reported

<sup>a</sup> Escudier, et al. 2009<sup>21</sup>

<sup>b</sup> Escudier, et al. 2010<sup>42</sup>

<sup>c</sup> Sternberg, et al. 2013<sup>23</sup>

<sup>d</sup> Motzer, et al. 2009<sup>22</sup>

<sup>e</sup> Presentation by Motzer, et al. at the European Society for Medical Oncology, 2012

Despite the recognition of the importance of overall survival as a therapeutic goal, its utilization as a clinical trial endpoint can often be confounded by the utilization of multiple lines of treatment. Such was the case in the tivozanib pivotal trial.

The absence of an overall survival trend in favor of the control arm in previous trials of VEGF TKIs can be explained by the fact that in each case where such trials permitted a crossover, the control arm was either placebo or a minimally active agent (e.g., IFN-a). Thus, these trials essentially compared outcomes of patients who received an active agent vs. patients who received placebo or a minimally active agent followed by an active agent.

Given the improvements in overall survival, many patients are remaining on therapy for a period of years. For many patients, RCC has become a chronic disease. Furthermore, many of the patients living with this disease are relatively young and active. As a result, clinicians and patients are becoming increasingly sensitized to the need for agents that are not only effective but which have a safety profile which can be matched to the needs of individual patients, thereby maximizing individual patients' abilities to live full and productive lives.

Tivozanib has a distinctive safety profile. While the safety profile of tivozanib has some similarity to that of sorafenib and other VEGF TKIs, some important differences are also observed between tivozanib and data reported for these other agents. Tivozanib is associated with an incidence of hypertension (an adverse event that correlates with efficacy) that is higher than sorafenib and higher than reported for sunitinib, but comparable to that reported for pazopanib and axitinib. With respect to symptomatic toxicities that are important to patients, tivozanib appears to have lower rates of fatigue than sunitinib and axitinib, lower rates of hand-foot syndrome than sorafenib, sunitinib and axitinib and lower rates of diarrhea than all four approved TKIs.

Tivozanib is associated with lower incidences of dose reductions and interruptions than have been reported for all four approved TKIs, an indicator of patient tolerability. Tivozanib has shown no evidence of serious hepatotoxicity, which has been reported for patients taking sunitinib and pazopanib. Tivozanib does not have pharmacokinetic interactions with potent inhibitors of CYP3A4 and is therefore unlike sunitinib, pazopanib and axitinib, for which reduction of the TKI dose or avoidance of concomitant CYP3A4 inhibitors is recommended.

#### **7.4. Conclusions**

A favorable risk-benefit profile for tivozanib was demonstrated by a clinically meaningful and statistically significant prolongation of PFS and improvement in ORR over an approved VEGFR TKI, sorafenib. Tivozanib has also demonstrated antitumor activity when used in patients following radiographic progression on sorafenib. Tivozanib has a well-characterized and manageable safety profile that is distinct from other approved TKIs. Overall, tivozanib represents a valuable addition to the treatment armamentarium for advanced RCC.

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