ODAC Briefing Document

NDA 204408/S000
tivozanib

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
May 2, 2013

NDA 204408/S000
tivozanib
Applicant: Aveo Pharmaceuticals, Inc.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought tivozanib to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

1. Introduction

On September 28, 2012, Aveo Pharmaceuticals submitted an application for tivozanib for the treatment of advanced renal cell carcinoma. This application was supported by a single Phase 3 trial, a randomized Phase 2 trial, and an extension/crossover study.

Tivozanib is being brought to the ODAC to discuss the findings of the Phase 3 trial. In this open label trial, 517 patients with metastatic renal cell carcinoma were randomly allocated 1:1 to either tivozanib or sorafenib. The primary endpoint was progression-free survival (PFS) as determined by an independent review committee (IRC). Overall survival (OS) was a secondary endpoint.

- PFS: The analysis of PFS showed a statistically significant improvement in PFS with tivozanib; HR = 0.80, p = 0.04. Median PFS was 11.9 mos. in the tivozanib arm and 9.1 mos. in the sorafenib arm.

- OS: The final analysis of OS showed a trend toward a detrimental effect on OS with tivozanib; HR = 1.25, p = 0.11. Median OS was 28.8 mos. in the tivozanib arm and 29.3 mos. in the sorafenib arm.

The applicant has submitted the following indication statement: Tivozanib is indicated for the treatment of advanced renal cell carcinoma.

2. Background

Tivozanib is a tyrosine kinase inhibitor with activity against a variety of receptor tyrosine kinases. Table 1 provides information on the tyrosine kinase receptors inhibited by tivozanib at nanomolar concentrations.

Table 1: IC_{50}s of Tivozanib to Receptor Tyrosine Kinases in the Nanomolar Range

	VEGFR1	VEGFR2	VEGFR3	BRK	EPHB2	PDGFRα	PDGFRβ	KIT	TIE2
IC_{50}	30 nM	6 nM	15 nM	48 nM	24 nM	40 nM	49 nM	78 nM	78 nM

The 7 drugs approved for the treatment of advanced renal cell carcinoma are all thought to act through inhibition of vascular endothelial growth factor (VEGF) or its receptor. Most of these approvals were based on an improvement in PFS. The only exception is temsirolimus, the use of which also demonstrated an improvement in the primary endpoint of OS in patients with poor prognosis. Table 2 provides information on these approvals. Data from the tivozanib trial under discussion is provided for comparison.

Table 2: FDA Approvals in Renal Cell Carcinoma				
Product	Population	Comparator	PFS[1]	Overall Survival[1]
Sorafenib	1 prior therapy (cytokines)	Placebo	5.5 vs. 2.8 mo HR 0.44, p<0.01	17.8 vs. 15.2 mo HR 0.88 (95% CI; 0.74, 1.04)[2]
Sunitinib	Newly diagnosed	Ifn-α	10.8 vs. 5.1 mo HR 0.42, p<0.01	24.5 vs. 20.4 mo HR 0.82 (95% CI; 0.67, 1.00)[2]
Temsirolimus	Newly diagnosed Poor prognosis	Ifn-α	5.5 vs. 3.1 mo HR 0.66	10.9 vs. 7.3 mo HR 0.73 (95% CI; 0.58, 0.92) p=0.008
Everolimus	Prior sorafenib, sunitinib	Placebo	4.9 vs. 1.9 mo HR 0.33, p<0.01	14.8 vs. 14.4 mo HR 0.87 (95% CI; 0.65-1.15)[2, 3]
Bevacizumab + Ifn-α	Newly diagnosed	Ifn-α	10.2 vs. 5.4 mo HR 0.60, p<0.01	23 vs. 21 mo HR 0.86 (95% CI; 0.73-1.04)[2]
Pazopanib	Newly diagnosed or prior cytokine	Placebo	9.2 vs. 4.2 mo HR 0.46, p<0.001	22.9 vs. 20.5 mo HR 0.91 (95% CI: 0.71-1.16)[2]
Axitinib	Prior anti-angio-genic or cytokine	Sorafenib	6.7 vs. 4.7 mo HR 0.67, p<0.0001	20.1 vs. 19.2 mo HR 0.97 (95% CI; 0.80-1.17)[2]
Tivozanib	Newly diagnosed or prior cytokine	Sorafenib	11.9 vs. 9.1 mo HR 0.76, p=0.02	28.8 vs. 29.3 mo HR 1.25 (95% CI; 0.95-1.62)[2]

[1]HR < 1 favors the investigational drug [2]Not statistically significant [3]Cancer 2010 116:4256

Since the relationship between progression-free survival and overall survival is of concern in the assessment of tivozanib, the use of subsequent targeted therapy was examined in the studies which led to the approval of these 7 drugs. This information is shown in Table 3 and again, tivozanib is provided for comparison.

Table 3: Use of Subsequent Therapy in Renal Cell Carcinoma				
	Number of Patients	Comparator	Crossover	All Subsequent Targeted Therapies
Sorafenib[1]	903	Placebo	48% Placebo → Sorafenib	Unknown
Sunitinib[2]	750	Ifn-α	39% Ifn-α → Sunitinib	53% Sunitinib 69% Interferon
Temsirolimus[3]	416	Ifn-α	None	Unknown
Everolimus[4]	416	Placebo	80% Placebo → Everolimus	Unknown
Bevacizumab[5]	649	Ifn-α	4% Ifn-α → Bevacizumab	54% Bevacizumab 62% Interferon
Pazopanib[6]	435	Placebo	54% Placebo → Pazopanib	22% Pazopanib
Axitinib[7]	723	Sorafenib	None	Unknown
Tivozanib	517	Sorafenib	61% Sorafenib → Tivozanib	16% Tivozanib 63% Sorafenib

[1]JCO 2009 27:3312 [2]JCO 2009 27:3584 [3]NEJM 2007 356:2271 [4]Cancer 2010 116:4256
[5]JCO 2010 28:2137 [6]Eur J Cancer Published Online 2013 [7]Lancet 2011 37:1931

Despite crossover/subsequent therapy, the point estimates for the HR for OS for the 7 approved drugs are all less than 1 and do not suggest a detrimental effect on survival with the approved product.

Regulatory History
End-of-phase 2 meetings in December 2008 and May 2009 reached agreement concerning the basic design of the Phase 3 trial. During the December 2008 meeting, the Agency and Aveo discussed several study designs and FDA stated that "a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive may be considered for regulatory decision." FDA also stated that "…a statistically significant improvement in OS is not required for regulatory approval, but a pre-specified OS analysis plan is still helpful in the regulatory decision making process." In a May 2009 meeting, the Agency and Aveo discussed the final Phase 3 protocol. Crossover was not discussed and was not included in the Phase 3 study itself (a later protocol provided crossover). A pre-NDA meeting was held in May 2012. Here, the FDA expressed concern about the adverse trend in overall survival in the single Phase 3 trial and recommended that the sponsor conduct a second adequately powered randomized trial in a population comparable to that in the US.

3. Clinical/Statistical - Efficacy

1. **AV-951-301:** A Phase 3, Randomized, Controlled, Multi-center, Open-label Study to Compare Tivozanib to Sorafenib in Subjects with Advanced Renal Cell Carcinoma

2. **AV-951-201:** Phase 2, Placebo-controlled, Randomized Discontinuation Trial of Tivozanib in Patients with Renal Cell Carcinoma

3. **AV-951-09-902:** An Extension Treatment Protocol for Subjects Who Have Participated in a Phase 3 Study of Tivozanib vs. Sorafenib in Renal Cell Carcinoma

Phase 3 Study Design (AV-951-301)

Eligibility Criteria
1. Metastatic or locally-recurrent renal cell carcinoma with a clear cell component
2. Measurable disease
3. 0-1 prior therapy; no prior anti-angiogenic therapy or prior therapy targeting the mTOR pathway
4. Prior nephrectomy

Stratification
1. Geographic region (North America/Western Europe, Central/Eastern Europe, Rest of World)
2. Number of prior therapies (0, 1)
3. Number of organs containing metastatic disease (1, $\geq$ 2).

Treatment
1. Tivozanib 1.5 mg/day PO x 21 days; 7 days off
2. Sorafenib 400 mg bid PO continuously

- Cycles were 28 days
- Tumor measurements were obtained every other cycle.

- Patients could discontinue due to progressive disease or intolerable toxicity.
- After disease progression (PD) on sorafenib, pts were offered tivozanib under Study 902. Study 902 also offered tivozanib to patients on the tivozanib arm who remained on tivozanib > 2 yrs.

Independent Review Committee (IRC)

A unique aspect of this study is that prior to discontinuation, investigator (INV)-determined PD was to be confirmed (in some patients) by independent review within 48 hours. This requirement changed during the course of the study. These changes are shown in Table 4.

Table 4: Assessment of Progressive Disease

Amendment	Date	Protocol Changes
1	8-17-2009	PD required independent review unless: • > 50% increase in measurable disease • New lesions • Significant clinical deterioration
3	6-2-2011	PD required independent review unless: • Significant clinical deterioration

The final analysis of PFS was performed by 2 radiologists. If there was disagreement, a 3rd radiologist adjudicated between the findings presented by these 2 radiologists, choosing one of these readings.

Statistical Plan

The primary endpoint was PFS as determined by an independent-review committee (IRC). PFS was defined as the time from randomization to IRC-determined progression or death from any cause. This analysis was conducted on the intent-to-treat population (all randomized patients). Data handling rules are bulleted below.

- Patients who did not have IRC-determined progression at the time of analysis and patients who discontinued study drug without IRC-determined progression were censored at the day following the date of their last tumor assessment.
- Patients whose event occurred more than 140 days after their last assessment (they missed 2 assessments) were censored at the day after their last assessment.
- Patients with no tumor assessments after randomization were censored at randomization. However, if a patient with no tumor assessments died within 140 days of randomization (after missing 2 assessments), their death was included in the primary analysis.

Progression-free survival was compared, between arms, using a stratified logrank test and a Cox regression model with treatment and randomization stratification factors as covariates was used to obtain an estimate of the hazard ratio (HR). Both tests were stratified by the number of prior treatments (0, 1) and the number of organs containing metastatic disease (1, ≥ 2). Estimates of median PFS in each arm were obtained using the Kaplan-Meier method. The primary analysis of PFS was to be performed when 310 PFS-events had occurred.

Secondary endpoints included OS, response rate by IRC, duration of response by IRC, duration of stable disease by IRC, and patient reported outcomes. An interim analysis for OS was to be conducted at the time of the final PFS analysis. OS was defined as the time from randomization to death due to any cause. Patients without a known death date at the time of analysis were censored at the last date the patient was known to be alive or the sweep date for the analysis (whichever was sooner). Patients with no data beyond randomization were censored at randomization. OS was analyzed using a stratified Cox proportional hazards model and a stratified logrank test. Median OS was estimated using the Kaplan-Meier method. At 300 events, the final analysis of OS had 70% power to detect a difference in median OS of 6 months using a 2-sided alpha of 0.05. Prior to analysis, the statistical plan was modified so that the final analysis of OS would occur after all patients had been on study for $\geq$ 2 years.

Amendments

The stratification factor, number of organs containing metastatic disease, was initially assessed by the investigator. Amendment 2 changed this to an assessment by the IRC. In the vast majority of patients, the number of organs containing metastatic disease was assessed by the IRC prior to randomization and entered into the IVRS at randomization.

Patient Disposition

The Phase 3 study was carried out at 76 sites. It was initiated in February 2010 and was ongoing at the time of submission. As shown in Table 5, most of the study sites were in Eastern Europe with potentially different standard of care and practice patterns compared to the US. Patients on the sorafenib arm of the Phase 3 study with PD could receive tivozanib on an extension/crossover study. Patients on the tivozanib arm of the Phase 3 study with PD could receive additional medications. However, the 2nd line use of targeted therapies was not considered the standard of care in many of the countries participating in the trial.

Table 5: Geographic Distribution of Patient Accrual

Geographic Region	Tivozanib N = 260	Sorafenib N = 257
Central/Eastern Europe	229 (88%)	228 (89%)
North America/Western Europe	22 (9%)	18 (7%)
Rest of World	9 (4%)	11 (4%)

Table 6 provides the patient disposition as determined by the investigator (INV). Patient disposition is shown as of October 1 (cleaned and locked dataset) and December 15 (data snapshot, date of primary analysis). At both time points, progressive disease was the most common cause of patient discontinuation. Among the 243 patients with INV-determined progression on October 1, 81/99 (82%) in the tivozanib and 110/144 (76%) in the sorafenib arm had IRC-determined progression in the primary analysis. The percentages were similar on progression assessment as of December 15.

Adverse events resulted in discontinuation in 37 patients as per the data in the disposition dataset. In the adverse event dataset (using the 10-1-11 cutoff date), 60 patients discontinued study drug due to an adverse event. Among the 20 patients in the disposition dataset who died, 18 died due to an adverse event within 30 days of their last dose of study drug.

Table 6: Patient Disposition				
Data Cutoff	October 1, 2011		December 15, 2011	
	Tivozanib	Sorafenib	Tivozanib	Sorafenib
Randomized	260	257	260	257
Treated	259	257	259	257
Ongoing	115	74	106	65
Discontinued	144	183	153	192
Progressive Disease	99	144	107	153
Adverse Event	19	18	19	18
Death	11	9	12	9
Withdrew Consent/Non-compliance/Lost to Follow Up	7	7	7	7
Lack of Efficacy[1]	4	3	5	3
Other[2]	4	2	3	2

[1]Patients discontinued w/o INV-determined PD
[2] Patients discontinued treatment, but agreed to follow up

Patient Demographics and Baseline Disease Characteristics

Baseline characteristics are shown in Table 7. The median age was 59 years in both arms and 96-97% of patients in each arm were White. Approximately, 70% of patients were male. Patients were evenly divided between performance status 0 (45% tivozanib, 54% sorafenib) and performance status 1 (55% tivozanib, 46% sorafenib). Note that a substantial number of patients had a MSKCC favorable prognosis.

Table 7: Baseline Characteristics		
	Tivozanib[3] N = 260	Sorafenib[3] N = 257
Median Time Since Diagnosis (range)	14.7 mo (0.5-168.6)	16.6 mo (1.0-264.3)
MSKCC Prognostic Group[1]		
Favorable	70 (27%)	87 (34%)
Intermediate	173 (67%)	160 (62%)
Poor	17 (7%)	10 (4%)
Metastatic Sites by IRC		
Lung Only	19 (7%)	26 (10%)
Liver	51 (20%)	42 (16%)
Median Sum of the Longest Diameter by IRC (range)	11.5 cm (1.2-36.9)	9.8 cm (1.4-38.3)
Prior Therapy		
Prior Chemotherapy/Immunotherapy for Metastatic Disease		
Interferon α/IL-2	53 (20%)	55 (21%)
Cytotoxic Chemotherapy	4 (2%)	6 (2%)
Other[2]	4 (2%)	7 (3%)
Thalidomide	1 (0.4%)	0

[1]J Clin Oncol 1999 17:2530
[2]Experimental antibody designed to elicit an immune response, tamoxifen, medroxyprogesterone
[3]There is missing data for some of these analyses.

Primary Endpoint

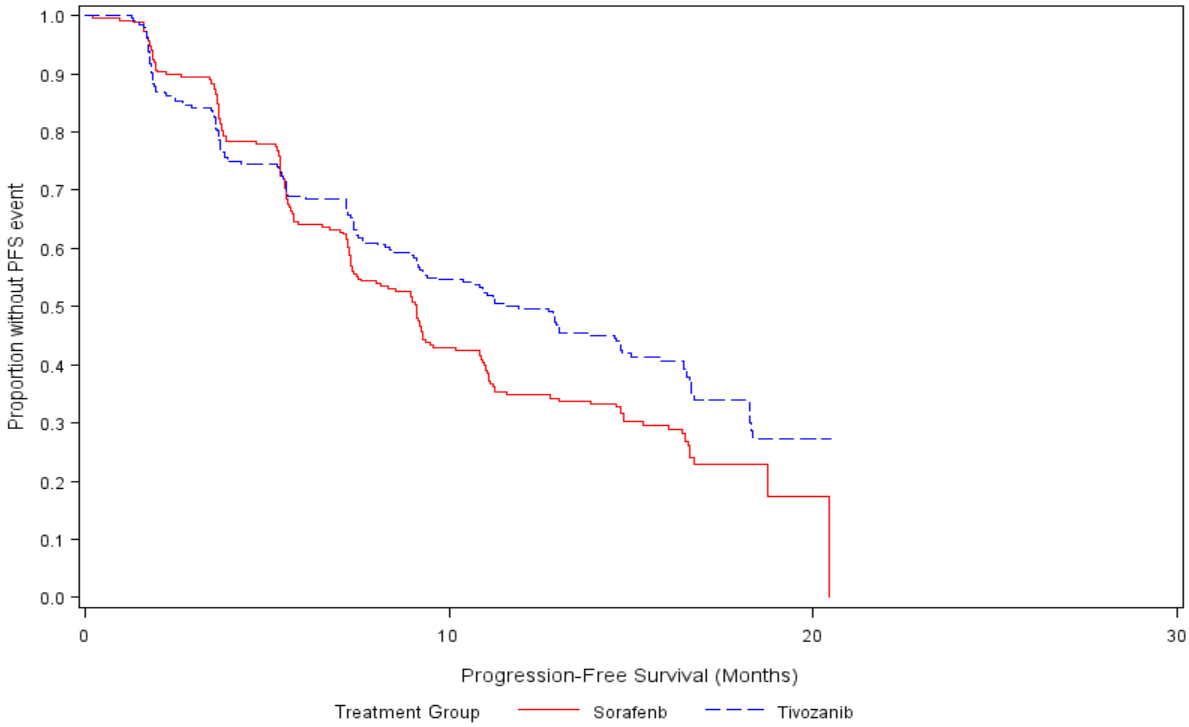
The primary analyses of IRC-determined PFS using the cutoff dates December 15, 2011, and October 1, 2011, are shown in Table 8 (see table footnotes). The analysis performed with a

cutoff of December 15, 2011, containing 321 events, is considered by the FDA as the primary analysis since the pre-specified number of events for this analysis was 310. The hazard ratio for INV-determined PFS, using a cutoff date of December 15, 2011, was 0.72.

This is a stratified analysis using the data, as entered, at the time of randomization. The applicant conducted a retrospective review of the stratification factor, number of organs containing metastatic disease. This analysis found a number of errors in recording the correct number of organs involved. Importantly, in this retrospective review, the arms were well balanced for this stratification factor.

Table 8: Primary Analysis (IRC)				
	December 15, 2011		October 1, 2011	
	Tivozanib N = 260	Sorafenib N = 257	Tivozanib N = 260	Sorafenib N = 257
Progression-free Survival Events	153 (59)	168 (65)	139 (53)	162 (63)
Median PFS (95% CI)	11.9 mos (9.3, 14.7)	9.1 mos (7.3, 9.5)	11.9 mos (9.2, 14.7)	9.1 mos (7.3, 9.5)
Hazard Ratio	0.80 (0.64, 0.99)		0.76 (0.06, 0.95)	
p-value	0.042		0.02	

Figure 1: Kaplan-Meier Plot of Progression-free Survival



Data Cutoff 12-15-11

Additional Analyses

The timing of the CT scans was similar in both arms and is shown in the stair-step pattern in the figure above. The extent of discrepancies between INV and IRC determinations of PFS was > 50%, but was similar on the two arms. Table 9 shows the extent of agreement on type (PFS-event vs. censored) and timing (date of the PFS-event). In this table, instances in which there was a difference in both type and timing were considered to be differences in type.

A unique feature of this study was the review of scans (within 48 hours) showing INV-determined progression prior to discontinuation of study drug. However, this review was not conducted for all eligible patients. Further, the radiologist who reviewed the scans within 48 hours of INV-determined progression differed from and often disagreed with the radiologists who conducted the subsequent IRC review.

Table 9: INV and IRC Discrepancies

	Tivozanib N = 260		Sorafenib N = 257	
	Type	Timing	Type	Timing
Discrepancies	60 (23%)	88 (34%)	65 (25%)	87 (34%)

Data Cutoff 12-15-11

Subsequent Therapy

Subsequent therapy is shown in Table 10. The majority of the patients on the sorafenib arm received tivozanib after the development of INV-determined PD while most of the patients on the tivozanib arm did not receive subsequent targeted therapy. The majority of patients were enrolled from sites in Central and Eastern Europe where 2nd line targeted therapy was not available. This is not consistent with the practice patterns in the US and it is, therefore, unclear whether the patients in this study were representative of those in the US.

Table 10: Subsequent Therapy

	Tivozanib N = 260	Sorafenib N = 257
Any Subsequent Targeted Therapy	41 (16%)	163 (63%)
Tivozanib	0	156

Data Cutoff 8-27-12

Overall Survival

Table 11 shows the final analysis of OS after all patients had been followed for $\geq$ 2 years. This analysis shows a trend towards decrement in survival with the use of tivozanib. Importantly, 21 patients in each arm withdrew informed consent and 6 patients in each arm were lost to follow up (54 total in an analysis with 219 events) prior to this analysis. These patients were censored at time they withdrew consent/were lost to follow up.

Table 11: Final Analysis of Overall Survival		
	Tivozanib N = 260	Sorafenib N = 257
Deaths	118 (45%)	101 (39%)
Censored	142	156
Withdrew Consent/Lost to Follow Up	21/6	21/6
Median Overall Survival (95% CI)	28.8 mos (22.5, NA)	29.3 mos (29.3, NA)
Hazard Ratio (95% CI)	1.25 (0.95, 1.62)	
p-value	0.11	

Data Cutoff 8-27-12

Response Rate
The IRC-determined response rate was 33% in the tivozanib arm and 23% in the sorafenib arm, while the median duration of response was 14.8 months in the tivozanib arm and 13.0 months in the sorafenib arm. This includes 5 patients, in both arms, with a complete response.

The 23% response rate in the sorafenib arm observed in this trial is not consistent with the observed response rates in the sorafenib arm in other randomized trials: 9.4% RR in the Phase 3 trial comparing axitinib and sorafenib and a 2% RR in the Phase 3 trial of sorafenib and placebo. The axitinib/sorafenib trial was limited to patients who had received prior anti-angiogenic therapy while the sorafenib/placebo trial enrolled only patients with a MSKCC poor or intermediate prognosis.

Supportive Study
A Phase 2 study (201) administered open label tivozanib for 16 weeks to patients with metastatic or locally advanced renal cell carcinoma who had received no prior targeted therapy. After 16 weeks, patients with a $\geq$ 25% decrease in the sum of the longest diameters (SLD) continued tivozanib while patients with a $\geq$ 25% increase in the SLD discontinued study drug. The remaining 118 patients (< 25% change in SLD) were randomized to tivozanib or placebo for 12 weeks. The primary endpoint, response rate during the first 16 weeks of therapy, by IRC, was 18%. The co-primary endpoint, the rate of PFS 12 weeks after randomization to tivozanib vs. placebo by IRC, was 49% for patients in the tivozanib arm and 21% for patients in the placebo arm. Information on subsequent therapy or OS is not available.

4. Safety

Exposure
Table 12 provides the median duration of exposure as well as the number of patients who required dose interruptions or reductions. Dose reduction, but not dose interruption, was required for grade 3 events in both arms. In addition, investigators were expected to follow the dose modifications recommended in the sorafenib package insert.

This table is notable for the differences between arms in the number of patients requiring a dose interruption or reduction. Noting this difference, other sorafenib studies were examined. In the recent axitinib/sorafenib study, 80% of patients on the sorafenib arm required a dose interruption and 52% a dose reduction. However, in the sorafenib/placebo trial, 14% of

patients on sorafenib required a dose interruption and 10% a dose reduction. Therefore, the degree of dose reduction/interruption in this trial is not consistent with other studies of sorafenib. It is important to note that the number of patients requiring permanent discontinuation of study drug in the adverse event dataset was (33 tivozanib vs. 32 sorafenib) was similar between arms.

Table 12: Exposure on the Phase 3 Trial		
	Tivozanib N = 259	Sorafenib N = 257
Median Duration (range)	12.0 mos (0.5-27.8)	9.5 mos (0.03-26.9)
Dose Interruptions	69 (27%)	180 (70%)
Dose Reductions	41 (16%)	113 (44%)

Data Cutoff 6-1-12

The safety database contains 894 patients who have received tivozanib monotherapy. The majority of patients (785) had renal cell cancer and were treated at the Phase 3 dose and schedule.

Deaths

Table 13 provides information on the number of patients who died within 30 days of study drug. The difference between arms appears to be primarily due to an increased number of patients in the tivozanib arm whose deaths were reported as progressive disease. Note that 1 patient on the tivozanib arm died due to hypertensive crisis and another patient died due to rupture of an aortic aneurysm. The patient with hypertensive crisis may have taken additional dose(s) (3 pills were unaccounted for) of tivozanib. It is unclear whether the death due to aortic aneurysm rupture was related to hypertension. The highest reported blood pressure in this patient was 140/80.

Table 13: Deaths Within 30 Days of Study Drug		
	Tivozanib N = 259	Sorafenib N = 257
All	21 (8%)	14 (5%)
Deaths due to Progressive Disease[1]	8	2
Deaths due to an Adverse Event	13	12
Cardiac Failure	2	1
Apnea/Dyspnea	2	0
Myocardial Infarction	2	0
Cerebrovascular Accident	1	3
Coronary Artery Disease	1	2
Pulmonary Embolism	1	2[2]
Aortic Aneurysm Rupture	1	0
Cardiac Arrest	1	0
Death (no additional information)	1	0
Hypertension	1	0
Adult Respiratory Distress Syndrome	0	1
Jaundice	0	1
Pleural Effusion	0	1
Post-procedural Hemorrhage	0	1

[1]Includes preferred terms spinal cord compression, metastases to CNS, and renal cell. Data Cutoff 6-1-12

[2]1 patient (counted once as PE) died due to PE and HF

Adverse Events

Grade 1-4 adverse events in > 10% of patients are shown in Table 14. The most frequent adverse event in the tivozanib arm was hypertension, but stomatitis (15%) and PPE (13%) were also seen.

Table 14: Adverse Events in > 10% of Patients on the Tivozanib Arm

	Tivozanib N = 259		Sorafenib N = 257	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	233 (90%)	145 (56%)	250 (97%)	176 (68%)
Hypertension[1]	117 (45%)	69 (27%)	90 (35%)	46 (18%)
Diarrhea	57 (22%)	5 (2%)	84 (33%)	17 (7%)
Dysphonia	54 (21%)	0	12 (5%)	0
Fatigue	50 (19%)	14 (5%)	41 (16%)	9 (4%)
Weight Decreased	47 (18%)	7 (3%)	53 (21%)	9 (4%)
All Infections	38 (15%)	4 (2%)	44 (17%)	10 (4%)
Asthenia	40 (15%)	10 (4%)	43 (17%)	7 (3%)
Stomatitis[2]	38 (15%)	2 (0.8%)	33 (13%)	2 (0.8%)
Back Pain	34 (13%)	8 (3%)	21 (8%)	5 (2%)
PPE	34 (13%)	5 (2%)	139 (54%)	43 (17%)
Abdominal Pain[3]	32 (12%)	3 (1%)	29 (11%)	2 (0.8%)
Dyspnea/Exertional Dyspnea	31 (12%)	4 (2%)	25 (10%)	5 (2%)
Nausea	31 (12%)	1 (0.4%)	20 (8%)	1 (0.4%)
Decreased Appetite	28 (11%)	1 (0.4%)	25 (10%)	2 (0.8%)

[1]Includes essential hypertension, hypertensive crisis, labile hypertension, and hypertensive retinopathy. Data Cutoff 6-1-12

[2]Includes chelitis, gingival bleeding, pain, and swelling, glossitis, glossodynia, mouth ulceration, oral mucosa erosion, oral pain, and oropharyngeal pain.

[3]Includes abdominal discomfort and gastrointestinal pain.

Adverse Events of Special Interest

Adverse events of special interest in the tivozanib arm of the Phase 3 trial include: hypertension (45%), hemorrhage (12%), proteinuria (9%), arterial embolic and thrombotic events (3%), hypothyroidism (5%), GI perforation/fistula (1%), and pancreatitis (0.8%). In the Safety Database, 1 patient developed hepatic failure and a 2nd patient developed posterior reversible encephalopathy syndrome. Note that the incidence of elevated TSH (62%) and proteinuria by dipstick (32%) along with grade 3-4 amylase (5%) and lipase (10%), was much higher than the number of reports of the corresponding adverse events. Importantly, 1 patient died due to pancreatitis.

Laboratories

Grade 3-4 neutropenia (2%) and thrombocytopenia (0.4%) were uncommon with tivozanib. Grade 1-2 creatinine elevations occurred in 58% of patients on tivozanib. However, no patient had a grade 3-4 elevation in serum creatinine.

5. Issues for ODAC

In considering the results from a single randomized trial submitted in support of marketing approval of a new molecular entity, FDA expects that the trial will be adequately designed and well conducted and that the results will be internally consistent. We are asking the ODAC's advice on whether this single trial is sufficient to support approval of tivozanib for the indication of treatment of patients with advanced renal cell cancer or whether an additional trial is necessary before considering marketing approval.