A Phase 1b, Open-label, Dose-escalation Study of Tivozanib and FOLFOX6 in Patients With Advanced Gastrointestinal Tumors

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Introduction

- Tivozanib (AV-951) is a potent and selective small-molecule pan-vascular endothelial growth factor receptor (VEGFR) inhibitor with activity against VEGFR-1, -2, and -3 at subnanomolar concentrations (half maximal inhibitory concentrations [IC_{50}] of 0.21, 0.16, and 0.24 nM, respectively)[1]
  - The high level of potency and selectivity for the VEGFRs is designed to provide an optimal blockade of the VEGF pathway with minimal "off-target" toxicities
- Preclinical studies with tivozanib have demonstrated antitumor activity against a variety of tumor cell lines, including colon and renal cancers[2]
- In a phase 1 study,[1] the maximum tolerated dose (MTD) of tivozanib was determined to be 1.5 mg/day and responses were observed in patients with renal cell carcinoma, colorectal cancer (CRC), and other tumor types
- FOLFOX6 (leucovorin, 5-fluorouracil [5-FU], and oxaliplatin) is a standard chemotherapy regimen for the treatment of patients with CRC and other gastrointestinal (GI) cancers[3]
- In preclinical studies, tivozanib has demonstrated additive antitumor activity when administered in combination with 5-FU[4]
- The current phase 1b study evaluated the combination of tivozanib with standard FOLFOX6 chemotherapy for the treatment of patients with CRC and other GI cancers

Objectives

- To determine the safety, tolerability, and MTD of tivozanib combined with FOLFOX6
- To assess the antineoplastic activity of tivozanib combined with FOLFOX6 chemotherapy in patients with advanced GI tumors
- To characterize the pharmacokinetic (PK) profiles of tivozanib and FOLFOX6 when administered together

Methods

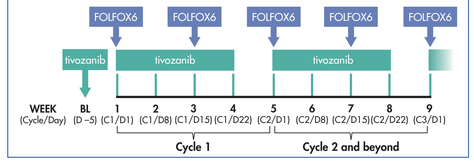
Key Eligibility Criteria

- Adults aged ≥18 years with histologically or cytologically confirmed metastatic CRC or other GI malignancy for which FOLFOX6 is a standard treatment
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2 with a life expectancy of ≥3 months
- No more than 2 prior chemotherapy regimens (≥3 weeks prior) for metastatic disease, not including prior adjuvant chemotherapy with 5-FU and/or oxaliplatin
- No significant cardiovascular disease, uncontrolled hypertension, or myocardial infarction within 3 months
- No central nervous system or hematologic malignancies

Study Design

- Phase 1b, open-label, dose-escalation study
- Tivozanib 0.5, 1.0, and 1.5 mg were administered orally once daily for 3 weeks, followed by a 1-week break (1 cycle = 4 weeks; **Figure 1**)
- FOLFOX6 (leucovorin 400 mg/m^2 + 5-FU 400 mg/m^2 bolus followed by 2,400 mg/m^2 continuous infusion over 46 hours + oxaliplatin 85 mg/m^2) was administered intravenously every 14 days
- Sequential cohorts of patients were enrolled using standard "3 + 3" dose escalation guidelines (**Table 1**)
- Treatment was continued until disease progression or intolerable adverse events
  - Patients who discontinued FOLFOX6 due to chemotherapy-related adverse events were allowed to continue tivozanib

Figure 1. Treatment schedule.



BL, baseline; C, cycle; D, day.

Table 1. Dose Levels

Cohort	Tivozanib	FOLFOX6	No. of patients
1	0.5 mg/day	Standard	9
2	1.0 mg/day	Standard	3
3	1.5 mg/day	Standard	6
MTD expansion	1.5 mg/day	Standard	12[a]

MTD, maximum tolerated dose.
[a]Data are not yet available for 8 of the 12 patients enrolled in the MTD expansion cohort.

Study Endpoints

- Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0
- Antitumor activity was evaluated using standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria
- Blood samples for PK analyses were collected at baseline (Day –5; prior to tivozanib dosing and 1, 2, 4, 8, and 24 hours post-dose); Days 1, 2, 3, 8, 15, 16, 17, 21, and 22 of Cycle 1; and Day 1 of Cycle 2 to evaluate the effects of tivozanib on oxaliplatin and 5-FU

Results

Patients

- A total of 22 evaluable patients have been enrolled who received ≥1 dose of study medication (**Table 2**)
  - Of the enrolled patients, 45% had a diagnosis of gastric/esophageal adenocarcinoma, 27% had CRC, 23% had pancreatic adenocarcinoma, and 5% had small bowel adenocarcinoma

Table 2. Baseline Patient Demographic and Clinical Characteristics

Characteristic	N = 22
Median age (range), y	58 (40–75)
Male sex, n (%)	14 (64)
Race, n (%)	
White	20 (91)
Asian	1 (5)
Black	1 (5)
Tumor type, n (%)	
Gastric/esophageal adenocarcinoma	10 (45)
Colorectal carcinoma	6 (27)
Pancreatic adenocarcinoma	5 (23)
Small bowel adenocarcinoma	1 (5)
ECOG Performance Status, n (%)	
0	7 (32)
1	14 (64)
2	1 (5)
Number of prior chemotherapy regimens, n (%)	
0	12 (55)
1	3 (14)
2	6 (27)
3	0
4	1 (5)

ECOG, Eastern Cooperative Oncology Group.

- Thirteen patients discontinued from the study; the primary reasons for study discontinuations are provided in **Table 3**

Table 3. Study Discontinuations

Parameter, n	N = 22
Discontinued	13
Progressive disease	9[a]
Adverse event	3
Withdrawal of consent	1

[a]Includes 2 patients with symptomatic deterioration that did not meet the criteria for progressive disease.

Safety

- Four patients experienced dose-limiting toxicities (DLTs) during the study
  - Cohort 1 (0.5 mg/day tivozanib): reversible grade 3 diarrhea (n = 1); reversible grade 3 and 4 transaminase elevations (n = 1)
  - Cohort 3 (1.5 mg/day tivozanib): grade 3 grand mal convulsion (n = 1); reversible grade 3 dizziness (n = 1)
- The most common treatment-related adverse events (all grades and grade 3/4) are shown in **Table 4**
  - Grade 3/4 treatment-related adverse events observed in >1 patient were fatigue, hypertension, and neutropenia (n = 2 each)
  - There was no indication that drug-related adverse events associated with this combination were more frequent or severe than those observed with FOLFOX6 or tivozanib alone

Table 4. Treatment-related[a] Adverse Events (≥15% of Patients)

Adverse event, n (%)	All grades (N = 22)	Grade 3/4 (N = 22)
Nausea	16 (73)	0
Fatigue	11 (50)	2 (9)
Vomiting	11 (50)	0
Peripheral sensory neuropathy	9 (41)	0
Decreased appetite	8 (36)	0
Stomatitis	7 (32)	0
Diarrhea	6 (27)	1 (5)
Dysphonia	6 (27)	0
Headache	4 (18)	0
Hypertension	4 (18)	2 (9)
Constipation	4 (18)	0
Neutropenia	4 (18)	2 (9)

[a]Adverse events related to treatment with tivozanib and FOLFOX6.

- Eight patients discontinued treatment with tivozanib and/or FOLFOX6 during the study due to adverse events (**Table 5**)

Table 5. Treatment Discontinuations Due to Adverse Events

Patient	Event	Grade	Action taken with tivozanib	Action taken with FOLFOX6	Outcome	DLT
002	Diarrhea	3	Discontinued	Discontinued	Recovered	Yes
003	Increased alanine transaminase	3	Discontinued	Interrupted	Recovered	Yes
	Increased aspartate transaminase	4	Discontinued	Interrupted	Recovered	Yes
004	Thrombocytopenia	1	None	Discontinued	Not yet recovered	No
005	Peripheral sensory neuropathy	2	None	Discontinued	Not yet recovered	No
006	Thrombocytopenia	2	None	Discontinued	Recovered	No
014	Fatigue	2	None	Discontinued	Recovered	No
	Malignant ascites	3	Discontinued	NA	Not yet recovered	No
015	Dizziness	3	Discontinued	Discontinued	Recovered	Yes
018	Grand mal convulsions	3	Interrupted	Discontinued	Recovered with sequelae	Yes

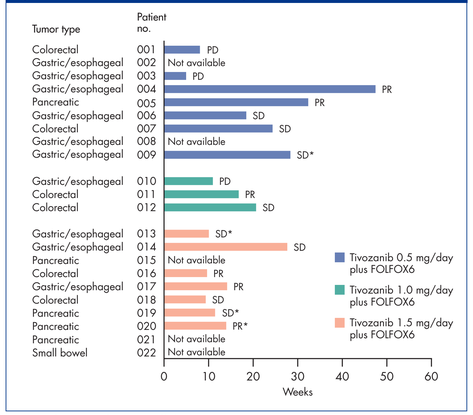
DLT, dose-limiting toxicity; NA, not applicable.

- Five patients required dose interruptions of tivozanib
- Four patients required dose interruptions of FOLFOX6, and 8 patients required dose reductions

Efficacy

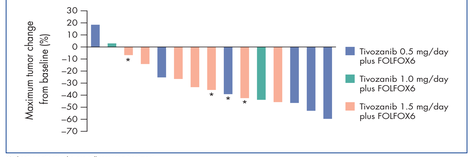
- Median duration of treatment was 8.1 weeks (range, 0.1–43.1 weeks; **Figure 2**)
- At the time of data cut-off, partial responses (confirmed and unconfirmed) have been achieved in 6 patients (27%); an additional 8 patients (36%) maintained stable disease for a disease control rate of 63% (**Figures 2** and **3**)

Figure 2. Duration of treatment and best response.



PD, progressive disease; PR, partial response; SD, stable disease.
*Indicates patients who are still receiving treatment.

Figure 3. Waterfall plot of maximum tumor change.

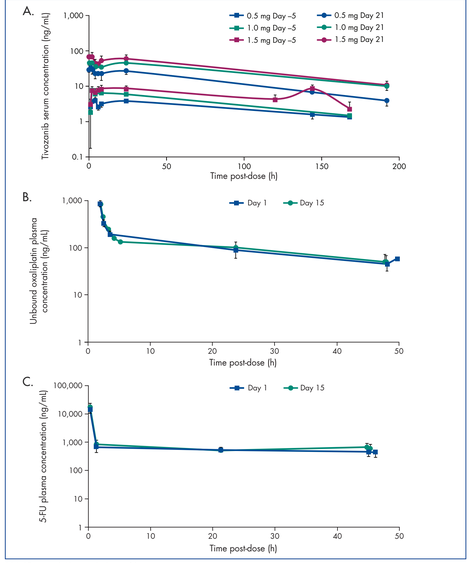


*Indicates patients who are still receiving treatment.
Maximum tumor change from baseline was not available for 7 patients.

Pharmacokinetics

- Mean tivozanib serum concentrations at steady state do not appear to be influenced by FOLFOX6 treatment and are similar to levels observed in tivozanib monotherapy studies[1,3] (**Figure 4A**)
- Unbound platinum and 5-FU plasma concentrations are similar on Days 1 and 15, indicating that increasing levels of tivozanib in the circulation did not influence plasma concentrations of unbound platinum or 5-FU (**Figures 4B** and **4C**)

Figure 4. Concentration-time profiles.[a]



5-FU, 5-fluorouracil; SEM, standard error of the mean.
[a]Values shown are mean (± SEM).

Conclusions

- **Tivozanib can be combined at the full recommended dose (1.5 mg/day) with standard-dose FOLFOX6 chemotherapy**
- **In a metastatic patient population with GI malignancies, the combination of tivozanib and FOLFOX6 demonstrated encouraging evidence of clinical activity, with 27% of patients achieving a partial response**
- **PK data indicated no influence of FOLFOX6 on tivozanib serum concentrations and no influence of circulating tivozanib on unbound platinum or 5-FU plasma concentrations**
- **The side effect profile of the combination was manageable; the most common adverse events included nausea, fatigue, vomiting, and peripheral sensory neuropathy**
- **The combinability and clinical activity observed with tivozanib and FOLFOX6 warrants further exploration in GI tumors**

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