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A Phase 1b Study of Escalating Doses of Vascular Endothelial Growth Factor (VEGF) Tyrosine Kinase Inhibitor Tivozanib and FOLFOX6 in Patients With Advanced Gastrointestinal (GI) Tumors

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Introduction

- Tivozanib (AV-951) is a highly potent and selective small-molecule pan-vascular endothelial growth factor receptor (VEGFR) inhibitor with activity against VEGFR-1, -2, and -3 at subnanomolar concentrations (IC_{50} of 0.21, 0.16, and 0.24 nM, respectively)[1]
- Preclinical studies have demonstrated antitumor activity with tivozanib against a variety of tumor cell lines, including colon and renal cancers[2]
- Results from a phase 1 study determined a maximum tolerated dose (MTD) of 1.5 mg/day tivozanib, with responses observed in patients with renal cell carcinoma (RCC), colorectal cancer (CRC), and other tumor types[1]
- A phase 2 randomized discontinuation trial demonstrated antitumor activity and a favorable safety profile with single-agent tivozanib in patients with RCC[3]
- 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
- Tivozanib has shown additive antitumor activity with 5-FU in preclinical studies (Lin, et al. EORTC-NCI-AACR 2010. Poster #PP20.)
- This phase 1b study investigated whether tivozanib may be combined 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 in combination with FOLFOX6 in patients with advanced GI tumors
- To assess the antineoplastic activity and pharmacokinetic (PK) profile of the combination of tivozanib and FOLFOX6 in this patient population

Methods

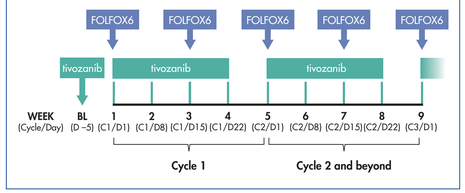
Key Eligibility Criteria

- 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 and life expectancy ≥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 trial
- Sequential cohorts of 0.5, 1.0, and 1.5 mg/day oral tivozanib for 3 weeks, followed by a 1-week break (1 cycle = 4 weeks), using standard "3 + 3" dose escalation guidelines (**Figure 1** and **Table 1**)
- FOLFOX6 (leucovorin 400 mg/m^2 + 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 continuous infusion over 46 hours + oxaliplatin 85 mg/m^2) was administered intravenously every 14 days

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.

- Treatment was continued for a minimum of 4 weeks (or until disease progression or unacceptable toxicity) for assessment of tolerability, and a minimum of 8 weeks (2 consecutive dosing cycles) for assessment of antitumor activity
  - Patients who discontinued FOLFOX6 were allowed to continue tivozanib

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 patients have been enrolled, have received at least 1 dose of study medication, and are evaluable (**Table 2**)

Safety

- Four patients experienced dose-limiting toxicities during the study
  - Cohort 1 (0.5 mg/day tivozanib): reversible grade 3 diarrhea (n = 1) and reversible grade 3 and 4 transaminase elevations (n = 1)
  - Cohort 3 (1.5 mg/day tivozanib): grade 3 grand mal convulsion (n = 1) and reversible grade 3 dizziness (n = 1)

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 (4)
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.

- The most common treatment-emergent adverse events (all grades and grade 3/4) are shown in **Table 3**
  - 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 3. Treatment-emergent Adverse Events (>15% of Patients)

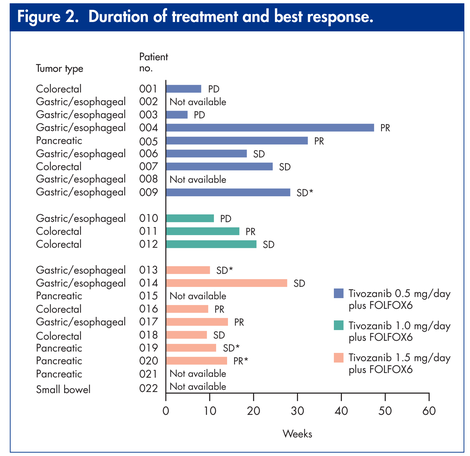
Adverse event, n (%)	All grades	Grade 3/4
Nausea	16 (73)	0
Fatigue	12 (55)	3 (14)
Vomiting	11 (50)	0
Constipation	9 (41)	0
Decreased appetite	9 (41)	0
Peripheral sensory neuropathy	9 (41)	0
Headache	7 (32)	0
Stomatitis	7 (32)	0
Diarrhea	6 (27)	1 (5)
Dysphonia	6 (27)	0
Hypertension	4 (18)	2 (9)
Neutropenia	4 (18)	2 (9)

- Four patients discontinued tivozanib during the study due to adverse events, including 1 case each of diarrhea, increased transaminase levels, malignant ascites, and dizziness
- Five patients required dose interruptions of tivozanib; 4 patients required dose interruptions and 8 required dose reductions of FOLFOX6

Efficacy

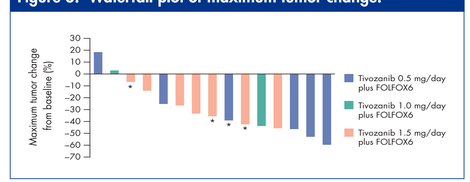
- Median duration of treatment was 8.1 weeks (range, 0.1–43.1 weeks; **Figure 2**)
- Partial response (confirmed and unconfirmed) has been achieved by 6 (27%) patients as of the data cutoff date; an additional 8 patients maintained stable disease (disease control rate, 63%; **Figures 2** and **3**)

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.

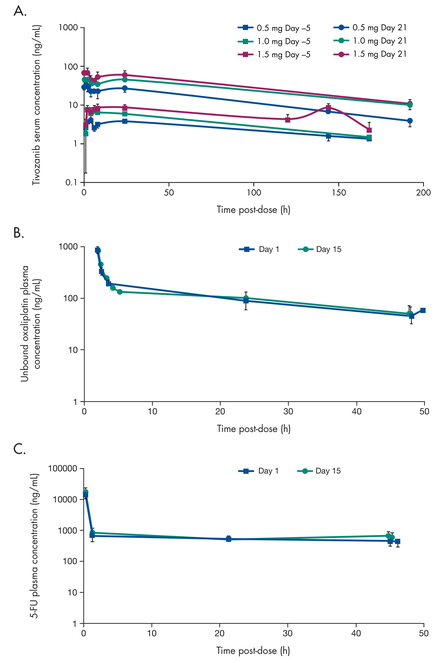


*Indicates patients who are still receiving treatment.
Maximum tumor change from baseline was not available for 7 patients.

Pharmacokinetics

- Mean tivozanib serum concentrations at steady state do not appear to be influenced by FOLFOX treatment and are similar to levels observed in tivozanib monotherapy studies (**Figure 4A**)
- Unbound platinum and 5-FU plasma concentrations are similar on Days 1 and 15 (**Figure 4B** and **C**)

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 safely be combined at the full recommended dose (1.5 mg/day) with the standard FOLFOX6 chemotherapy regimen**
- **The combination of tivozanib and FOLFOX6 shows encouraging tumor responses in patients with advanced GI malignancies**
- **Pharmacokinetic data indicated no influence of FOLFOX on tivozanib serum concentrations and no influence of circulating tivozanib on unbound platinum or 5-FU plasma concentrations**
- **The clinical activity observed with this combination merits further exploration in GI tumors, including CRC, and these studies are currently being planned**

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