Final Results of a Phase Ib Study of Tivozanib and FOLFOX6 in Patients with Advanced Gastrointestinal Tumors

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Introduction

- Tivozanib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1, 2, and 3.[1] It has a long half-life and can be administered orally.[1] Currently, tivozanib is being tested in a Phase III study in patients with renal cell carcinoma and Phase I/II studies of other solid tumors
- In a Phase I study, tivozanib's maximum tolerated dose (MTD) was found to be 1.5 mg/day, and responses were observed in patients with colorectal cancer (CRC) and other tumors[2]
- The FOLFOX6 regimen is a standard chemotherapy regimen for the treatment of patients with CRC and other gastrointestinal (GI) cancers[3]
- This open-label, Phase Ib study (NCT00660153) sought to determine the MTD, dose-limiting toxicities (DLTs), pharmacokinetics (PK), and anti-tumor activity of escalating doses of tivozanib combined with a modified FOLFOX6 (mFOLFOX6) regimen in patients with advanced GI tumors

Objectives

- The primary objective of this study was to measure the safety, efficacy, and MTD of tivozanib combined with FOLFOX6 in patients with advanced GI tumors
- Secondary objectives were to determine the PK profiles of tivozanib and FOLFOX6 when co-administered, and assess the anti-neoplastic activity of tivozanib combined with mFOLFOX6 chemotherapy

Methods

Inclusion Criteria

- Adults (≥18 years)
- Histologically or cytologically confirmed metastatic GI tumors including CRC
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2 with a life expectancy of ≥3 months

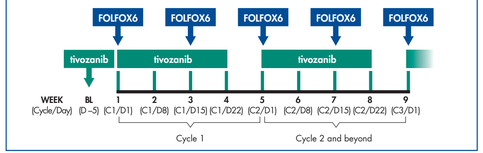
Exclusion Criteria

- More than two prior chemotherapy regimens (≥3 weeks prior) for metastatic disease, not including prior adjuvant chemotherapy with 5-fluorouracil (5-FU) and/or oxaliplatin
- Significant cardiovascular disease, uncontrolled hypertension, or myocardial infarction within 3 months
- Any central nervous system or hematologic malignancies

Study Design

- Phase Ib, open-label, dose-escalation study
- Tivozanib was administered once daily in 4-week cycles (3 weeks on/1 week off) with mFOLFOX6 administered on Days 1 and 15 of each cycle
- mFOLFOX6 consisted of 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 **(Figure 1)**

Figure 1. Design of dosing schedule.



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

- A standard '3+3' trial design was used. A cohort of 3 subjects was enrolled at each dose level (0.5 mg, 1.0 mg, or 1.5 mg). When 1 of 3 patients experienced a DLT during Cycle 1, that dose level was expanded to 6 subjects. When 0 of 3 or ≤1 of 6 patients experience a DLT during Cycle 1, escalation to the next dose took place. When ≥2 of 6 subjects experienced a DLT during Cycle 1, dose escalation was stopped, and the prior dose was considered the MTD
- Patients also received a single dose of tivozanib on Day –5 for PK analysis

Study Outcomes

- The grading of adverse events was performed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0
- Anti-neoplastic activity was assessed using standard Response Evaluation Criteria In Solid Tumors
- Blood samples for PK analyses were collected at baseline:
  - Day –5 prior to tivozanib dosing and at 1, 2, 4, 8, and 24 hours post-dose
  - Days 1, 2, 3, 8, 15, 16, 17, 21, and 22 of Cycle 1
  - Day 1 of Cycle 2, to evaluate the effects for tivozanib on 5-FU and oxaliplatin

Results

Patients' Demographics

- A total of 30 patients with a median age of 58 years were recruited and received tivozanib 0.5 mg (n=9), 1.0 mg (n=3), or 1.5 mg (n=18) and mFOLFOX6. The population was predominantly Caucasian (91%), and 60% were male. Baseline demographic characteristics are shown in **Table 1**

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	N=30
Median age (range), years	58.7 (40–75)
Male sex, n (%)	18 (60)
Race White Asian Black	 28 (93.3) 1 (3.3) 1 (3.3)
Tumor type, n (%) Esophageal Gastric Intestinal Colorectal Pancreatic	 9 (30) 4 (13) 1 (3) 6 (20) 10 (33)
ECOG performance status, n (%) 0 1 2	 10 (33.3) 19 (63.3) 1
Number of prior treatments, n (%) Neoadjuvant Adjuvant Metastatic/Unresectable therapy Other	 1 (3.3) 2 (6.7) 11 (36.7) 1 (3.3)

- Twenty-seven patients (90%) discontinued the study. Reasons for discontinuation are provided in **Table 2**

Table 2. Study Discontinuations

Parameter, n (%)	N=30
Discontinued	27 (90)
Progressive disease	15 (50)
Adverse event	6 (20)
Symptomatic deterioration	3 (10)
Other	3 (10)

- In total, 26 evaluable patients received a median of 5.2 months of treatment (range: 0.0–26.0 months)

Safety

Dose-limiting toxicities

- DLTs were observed in 2 patients (6.7%) with Grade 3/4 non-hematological toxicities. One patient was in the tivozanib 0.5 mg dose level, and the other was in the 1.5 mg dose level
- The MTD for tivozanib with mFOLFOX6 was 1.5 mg

Adverse events

- Commonly reported treatment-related adverse events are shown in **Table 3.** The adverse events most commonly reported by patients included nausea and fatigue (86.7% each) and diarrhea and vomiting (63.3% each). Grade 3/4 adverse events occurred in 28 patients (93.3%) **(Table 3)**

Table 3. Treatment-related Adverse Events (≥20% of Patients)

Adverse Event, n (%)	All Grades (N=30)	Grade 3/4 (N=30)
Fatigue	26 (86.7)	8 (26.7)
Nausea	26 (86.7)	0
Diarrhea	19 (63.3)	2 (6.7)
Peripheral sensory neuropathy	19 (63.3)	0
Vomiting	19 (63.3)	0
Decreased appetite	17 (56.7)	0
Dysphonia	17 (56.7)	0
Constipation	17 (56.7)	0
Stomatitis	17 (56.7)	0
Hypertension	15 (50)	8 (26.7)
Thrombocytopenia	13 (43.3)	1 (3.3)
Headache	12 (40)	0
Abdominal pain	11 (36.7)	2 (6.7)
Neutropenia	11 (36.7)	6 (20)
Epistaxis	9 (30)	0
Back pain	7 (23.3)	1 (3.3)
Alopecia	6 (20)	0
Anemia	6 (20)	0
Dyspepsia	6 (20)	0

- 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
- Nine patients discontinued treatment with tivozanib and/or FOLFOX6 during the study due to adverse events **(Table 4)**

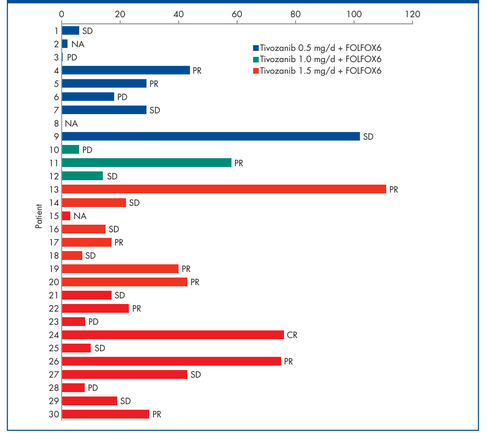
Table 4. Patient Discontinuations Due to Adverse Events

No. Patient	Event	Grade	Action Taken with Tivozanib	Action Taken with FOLFOX6	Outcome
1	Fatigue	3	Discontinued	Discontinued	Not yet recovered
2	Diahrrea	3	Discontinued	Discontinued	Recovered
	Stomatitis	1	None	Discontinued	Recovered
	Accidental 5-FU overdose		Discontinued	Discontinued	Recovered
3	Increased alanine aminotransferase	3	Discontinued	None	Recovered
	Increased aspartate aminotransferase	4	Discontinued	None	Recovered
5	Neuropathy	2	None	Discontinued	Not yet recovered
6	Thrombocytopenia	2	Interrupted	Discontinued	Recovered
9	Angina pectoris	2	Discontinued	None	Not yet recovered
11	Neutropenia	4	None	Discontinued	Recovered
14	Fatigue	2	None	Discontinued	Recovered
15	Dizziness	3	Discontinued	Discontinued	Recovered
17	Pneumothorax	2	Discontinued	Interrupted	Recovered
18	Grand mal convulsion	4	None	Discontinued	Recovered
19	Thrombocytopenia	3	None	Discontinued	Recovered
24	Peripheral sensory neuropathy	2	None	Discontinued	Recovered
25	Pulmonary embolism	2	Discontinued	Discontinued	Recovered
29	Abdominal pain	2	None	Discontinued	Recovered

Efficacy

- In total, 30.8% of patients achieved a partial response, and 42.3% achieved stable disease. No patients achieved complete response
- Median duration of exposure to tivozanib was 5.2 months (range 0–26 months)
- The duration of treatment and best response are shown by patient in **Figure 2**
- The disease control rate was 73.1%

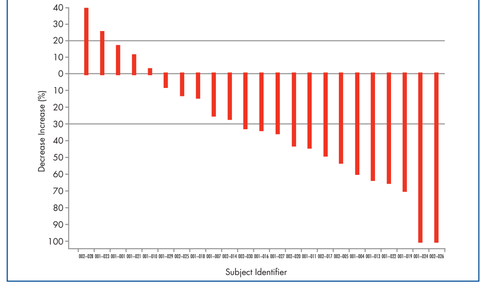
Figure 2. Treatment duration (weeks) and best overall response.



Confirmed and unconfirmed responses.
CR, complete response; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease.

- Maximum tumor change from baseline is shown by dose level in **Figure 3**

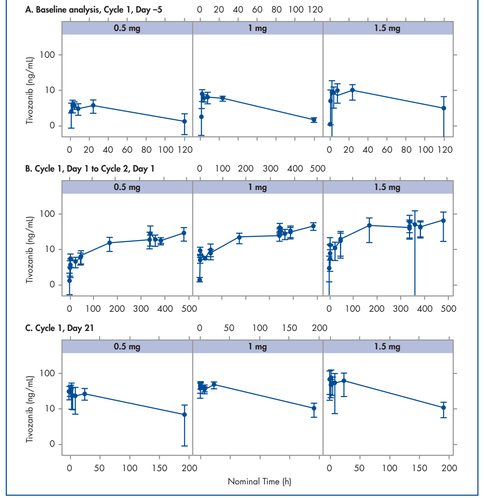
Figure 3. Maximum tumor change from baseline.



Pharmacokinetics

- PK data showed no interaction between tivozanib and mFOLFOX6. Mean tivozanib serum concentrations at steady state are not influenced by FOLFOX6 treatment **(Figure 4)**

Figure 4. Mean (± standard deviation) concentration vs time profiles for tivozanib by dose.



- Plasma concentrations of unbound platinum and 5-FU were similar on Days 1 and 15, signifying that increasing levels of tivozanib did not influence plasma concentrations of unbound platinum or 5-FU

Conclusions

- **Tivozanib can be combined at its recommended dose of 1.5 mg/day with mFOLFOX6 for patients with advanced GI tumors**
- **The combination of tivozanib and mFOLFOX6 demonstrated encouraging anti-neoplastic activity in patients with GI tumors, with 30.8% of patients achieving a partial response**
- **PK data showed that FOLFOX6 did not alter tivozanib serum concentrations, and circulating tivozanib did not influence unbound platinum or 5-FU plasma concentrations**
- **The ease of combination and improved clinical activity observed with tivozanib and FOLFOX6 deserves further studies in GI tumors. A Phase II study of this combination for mCRC is ongoing**

References

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