PHASE I ACCELERATED DOSE-ESCALATING SAFETY AND PHARMACOKINETIC (PK) STUDY OF GGTI-2418, A NOVEL GERANYLGERANYLTRANSFERASE I INHIBITOR IN PATIENTS WITH REFRACTORY SOLID TUMORS.

P.J. O'Dwyer[1], M. Gallagher[1], B. Nguyen[2], M.J. Waddell[3], and E.G. Chiorean[3].,[1]University of Pennsylvania, Philadelphia, PA; [2]Tigris Pharmaceuticals, Bonita Springs, FL; [3]Indiana University, Indianapolis, IN.

ABSTRACT

Background: GGTI-2418 is a potent and selective peptidomimetic inhibitor of geranylgeranyltransferase I (IC_{50} = 9.5 nM), and has been shown to cause significant breast tumor regression in ErbB2 transgenic mice model. **Methods:** Patients (pts) with advanced solid tumors refractory to conventional therapy received GGTI-2418 as a 30-min IV infusion on Days 1-5 every 21 days. Cohorts of one patient per dose level were enrolled until a Grade 2 adverse event was observed, after which cohorts of 3-6 pts were treated. Ten additional pts will be treated at the MTD for pharmacodynamic evaluation. Inclusion criteria included age > 18 yrs, ECOG PS 0-2 and adequate organ functions. **Results:** 9 pts (8 CRC and 1 hepatocellular carcinoma) with a median age of 57 and a median of 4 prior regimens were treated at eight dose levels from 120 to 2060 mg/m²/day, one patient per dose level. LFT elevation was dose limiting toxicity observed at dose level 8 with GGTI-2418 administered at 2060 mg/m²/day. Nausea was the most common related adverse event observed (4/9), followed by fatigue (3/9), diarrhea (2/9), neutropenia (2/9), hyperbilirubinemia (2/9), AST (2/9), Alk Phos (2/9), and pruritis (2/9). Most have been grade 1 or 2 with the exception of three grade 3 events including AST, total bilirubin and Alk Phos. Preliminary PKs up to dose level 6 (1,050 mg/m²/d) of GGTI-2418 showed dose proportional with C_{max} of 360 µM and $t_{1/2}$ of about 3 hours. Two CRC patients, one treated at dose level 4 (500 mg/m²/d), and one at dose level 5 (750mg/m²/d) had stable disease for 6 and 5 cycles, respectively. **Conclusions:** Plasma concentrations of GGTI-2418 achieved in this trial exceed concentrations required for the in-vitro inhibition of geranylgeranyltransferase I, with the C_{max} at dose level 5 at 36,000 times the IC_{50}. GGTI-2418 is well tolerated with minimal side-effects to date. Expansion of patient accrual at the highest dose level is ongoing.

STUDY RATIONALE

GGTI-2418 is expected to inhibit post-translation prenylation of Rho GTPases by GGTase I, thus impacting a signal transduction pathway implicated in tumorigenesis and tumor survival. The inhibition is hypothesized to have therapeutics benefit by inhibiting tumor growth, as supported by preclinical studies, and by inducing programmed cell death (apoptosis) of tumor cells.

STUDY OBJECTIVES

- To determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD)
- To assess the safety and tolerability and pharmacokinetics
- To observe clinical response and explore correlative biomarkers predictive of GGTI-2418 efficacy

TREATMENT PLAN

GGTI-2418 is administered as a 30-minute infusion on Days 1 to 5 of a 21-Day cycle. The following dose levels are planned for this study:

Dose Level	Dose (mg/m²)
1	120
2	200
3	330
4	500

Dose Level	Dose (mg/m²)
5	750
6	1050
7	1470
8	2060

STUDY METHODS

Patient Inclusion: Patients with advanced stage, treatment-refractory solid tumors for which standard treatments have failed their disease type or for whom standard therapies are not available were considered for enrollment. Additional inclusion criteria included ≥ 18 years of age, life expectancy > 12 weeks, ECOG performance status ≤ 2, normal organ and marrow function, normal LVEF as assessed by ECHO, prior chemotherapy is allowed provided there is a 4-week washout and the patient must have full recovery from the effects of the chemotherapy agent.

Patient Exclusion criteria included pregnant females, symptomatic pulmonary disease, brain metastases, receipt of other investigational agents, history of allergy to compounds with similar structure or biologic composition, uncontrolled intercurrent illness, and patients known to be HIV positive.

Dose Limiting Toxicity: Drug related toxicities that occur during the 21-day period of Cycle 1 will be considered when determining the DLT. DLT is defined as one or more of the following:

- ≥ Grade 3 non-hematological toxicity (excluding untreated nausea or vomiting, or alopecia)
- ≥ Grade 3 nausea , vomiting or diarrhea uncontrolled by aggressive treatment
- Grade 4 granulocytopenia lasting ≥ 5 days without hematopoeitic growth factor supplement
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
- Certain Grade 2 toxicities, which, in the judgment of the investigator and sponsor are of clinical significance.

Dose Escalation Dose Escalation began with single patient cohorts and expanded to 3 patient cohorts when Grade 2 or greater toxicity was observed. Once DLT has been identified, the cohort will be expanded to 6 patients at that dose level. Dose escalation will continue until MTD is defined.

Definition of MTD: MTD is defined as the highest dose level where a maximum of 1 of 6 patients experiences a DLT.

Response: Assessed according to RECIST.

PATIENT CHARACTERISTICS (N=9)

Median Age (years)	58
Male n(%)	8 (88%)
ECOG PS 0-1 n(%)	9 (100%)
Median # prior chemo	4

DOSE ESCALATION

Dose escalation has proceeded in single patient cohorts until Dose Level 8 (2060 mg/m²) when Grade 3 increase in alkaline phosphatase and bilirubin were indentified as DLTs. This cohort will be expanded to include 5 additional patients.

The first patient dosed at DL 5 (750 mg/m2) was found to have pre-existing brain metastases on Day 2 of Cycle 1 and was taken off study. A second patient was dosed at DL 5 to replace this patient.

ADVERSE EXPERIENCES

The dose limiting toxicity was LFT elevation observed at 2060 mg/m²/day. The LFTs returned to baseline within 3 weeks of last study drug administration. Nausea (4/9) was the most common related adverse event observed (4/9), followed by fatigue (3/9), diarrhea (2/9), neutropenia (2/9), hyperbilirubinemia (2/9), elevated AST (2/9), Alk Phos (2/9), and pruritis (2/9). Most have been grade 1 or 2 with the exception of three grade 3 events including elevation in AST, total bilirubin and Alk Phos.

Incidence of Related Adverse Events (N=9)

	n (%) Grades 1 to 2	n (%) Grade 3
Nausea	4 (44%)	0
Fatigue	3 (33%)	0
Diarrhea	2 (22%)	0
Neutropenia	2 (22%)	0
Pruritis	2 (22%)	0
Anemia	1 (11%)	0
AST	1 (11%)	1 (11%)
ALT	1 (11%)	0
Alk Phos	1 (11%)	1 (11%)
Total Bilirubin	1 (11%)	1 (11%)
Anorexia	1 (11%)	0
Bruising	1 (11%)	0
Chills	1 (11%)	0
Cold sensitivity	1 (11%)	0
Pain	1 (11%)	0
Rash	1 (11%)	0
Vomiting	1 (11%)	0

PHARMACOKINETICS

Plasma concentrations of GGTI-2418 achieved in this trial exceed concentrations required for the in-vitro inhibition of geranylgeranyltransferase I, with the C_{max} at dose level 5 (1050 mg/m²/day) at 36,000 times the IC_{50}.

Individual PK Parameters

Dose (mg/m²)	Cycle	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (hr*ng/mL)	$t_{1/2,z}$ (hr)	CL (L/hr/ m²)	V_z (L/ m²)
120	1	1540	1.00	2436.76	1.22	49.25	86.74
	2	1760	1.00	2460.02	1.02	48.78	71.98
200	1	18500	0.50	14161.90	1.12	14.12	22.82
	2	26800	0.50	20356.28	1.36	9.82	19.33
330	1	17800	0.55	14211.11	1.23	23.22	41.22
	2	19000	0.67	15195.28	1.30	21.72	40.75
500	1	56100	0.52	53886.08	0.79	9.28	10.60
	2	16800	1.00	21517.18	1.06	23.24	35.59
750	1	68700	0.50	60769.40	2.48	12.34	44.23
750	1	93700	0.53	118698.57	2.50	6.32	22.81
	2	117000	0.52	174238.48	2.77	4.30	17.22
1050	1	160000	0.50	171543.20	2.70	6.12	23.84

SUMMARY

- GGTI-2418 is well tolerated with the current daily time 5 every 21-day schedule, with nausea as the main adverse event
- Elevation in LFTs was identified as the dose limiting toxicity, with the LFTs returning to baseline upon discontinuation of GGTI-2418.
- GGTI-2418 plasma concentrations were dose proportional and far exceeded concentrations required for in-vitro inhibition of geranylgeryanlytransferase I.
- Durable stable disease was achieved in two colorectal cancer patients and one hepatocellular patient.
- The study is ongoing with expansion of cohort 8 (where DLT has been observed) to include 5 additional patients.