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Clinical Cancer Research

A Phase I Dose-Escalation Study of Tivantinib (ARQ 197) in Adult Patients with Metastatic Solid Tumors

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Abstract

Background: Tivantinib, an oral, non-ATP competitive, selective c-MET inhibitor, exhibited antitumor activity in preclinical models. This open-label, phase I, dose-escalation study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of tivantinib in patients with advanced or metastatic solid tumors refractory to standard therapy.

Methods: Thirteen dose levels of tivantinib ranging from 10 to 360 mg twice a day were administered to patient cohorts in 21-day cycles (14 days on/7 days off); three active pharmaceutical ingredient forms of tivantinib (amorphous, crystalline A, and crystalline B) were also investigated. Treatment was continued until the occurrence of unacceptable toxicity, tumor progression, patient withdrawal, or death.

Results: A total of 79 patients with advanced solid tumors were enrolled. A maximum tolerated dose was not determined. Tivantinib was well tolerated, with mild to moderate toxicities. Two patients discontinued the study drug due to treatment-emergent adverse events. Dose-limiting grade of 3 or more toxicities including leukopenia, neutropenia, thrombocytopenia, vomiting, and dehydration, were observed in 2 patients treated with tivantinib 360 mg twice a day. The rate of absorption of tivantinib peaked approximately 2 to 4 hours after initial dosing, followed by a linear decrease in plasma concentrations. Increases in tivantinib exposure were not dose proportional. There was significant interpatient pharmacokinetic variability; however the clinical safety of tivantinib seemed unaffected. Three patients (3.8%) achieved a partial response and 40 patients (50.6%) maintained stable disease for a median of 19.9 weeks.

Conclusions: Tivantinib 360 mg twice a day was well tolerated in patients with refractory advanced solid tumors. The results of this trial warrant further clinical investigation. *Clin Cancer Res; 17(24); 7754–64. ©2011 AACR.*

Introduction

The receptor tyrosine kinase c-MET and its ligand hepatocyte growth factor (HGF), or scatter factor, play critical roles in cancer invasion and metastasis (1, 2). Stimulation of the HGF/c-MET signaling pathway leads to the activation of multiple intracellular effectors, such as the Src/FAK, Ras/Raf/MEK/ERK, phosphatidylinositol-3-kinase/Akt, and other key signaling pathways, resulting in increased cell survival, proliferation, growth, motility, and angiogenesis.

c-MET and HGF overexpression are found in multiple cancers and are associated with increased metastasis, cancer aggressiveness, and poor prognosis (3). Amplification of the *MET* gene has been reported in brain, colorectal, gastric, and non–small cell lung cancers, and is implicated in non–small cell lung cancer's resistance to epidermal growth factor receptor inhibitors (4–6). Activating *MET* gene mutations are also found in hereditary and up to 10% of sporadic papillary renal cell carcinomas as well as in gastric cancer (7, 8). In addition, HGF/c-MET signaling is indirectly implicated in tumor angiogenesis, as it stimulates the proliferation, survival, and migration of endothelial cells (9–11). c-MET activation increases proangiogenic factors, such as $VEGF_A$, VEGF receptor-2 (VEGFR2), and interleukin-8, and decreases the antiangiogenic factor thrombospondin-1.

In view of the diverse effects of HGF/c-MET signaling on cancer progression, inhibition of HGF/c-MET signaling is an attractive and rational anticancer strategy (12). A number of HGF- and c-MET–targeted therapeutics, including small-molecule inhibitors and monoclonal antibodies, have recently entered into clinical trials and are showing promising results (13–16).

Tivantinib (ArQule, Inc.; Daiichi Sankyo Co.) is a selective, orally administered, non-ATP competitive inhibitor of c-MET, with an inhibitory constant of 327 nmol/L.

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Translational Relevance

Inhibitors of the receptor tyrosine kinase c-MET and its ligand, hepatocyte growth factor (HGF), have shown activity in select cancer types. This article reports data from the first phase I, open-label clinical trial of tivantinib, a novel, selective, oral, non-ATP competitive inhibitor of c-MET.

Results of this trial show preliminary clinically relevant evidence of disease stabilization and changes in biomarker levels in response to tivantinib. These early clinical findings provide the basis for the recommended dose of tivantinib in future phase II/III trials, further research on the utility of HGF and VEGF as prognostic indicators, and the clinical development of tivantinib as a monotherapy in several advanced solid tumor types.

Tivantinib has been shown, in a large kinase panel screen to be 10 to 100 times more selective for c-MET than 230 other kinases tested. The agent has a novel binding mechanism of action that facilitates the stabilization of an inactive configuration of c-MET. Preclinical studies of tivantinib show *in vitro* and *in vivo* growth inhibition across a range of cancers, including breast, pancreatic, colon, and lung cancers (17–19).

This is a report of the first clinical evaluation of tivantinib in humans based on an open-label, phase I, dose-escalation study. The primary objectives of this study were to evaluate the safety and tolerability and define the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of tivantinib administered to patients with advanced or metastatic solid malignancies. Secondary objectives were to assess the preliminary antitumor activity of tivantinib in this patient population and to evaluate its pharmacokinetic and pharmacodynamic profile.

Patients and Methods

Patient selection

Eligible patients were required to be age $\geq$18 years with metastatic, solid tumors refractory to available therapy. In addition, patients were required to have: a Karnofsky performance status $\geq$70%; a life expectancy $\geq$12 weeks; the presence of clinically and/or radiologically assessable disease; and adequate bone marrow, liver, and renal function. In view of encouraging signals of activity seen during the course of the trial, the last cohort of patients included individuals with tumors likely to express c-MET including those with confirmed renal cell cancer (20–22). All patients gave written informed consent. Additional consent was obtained for biopsies and tumor samples. This study received institutional ethical approval and was conducted in accordance with the Declaration of Helsinki and good clinical practice. Patients were excluded if they had known untreated brain metastases, or were unable or unwilling to swallow capsules. Pregnant or lactating women were also excluded from the study. After observing episodes of bradycardia in other concomitant studies, the protocol was amended such that the last cohort excluded patients with known bradycardia (heart rate <60 beats per minute) or any kind of symptomatic arrhythmias.

Treatment plan

This was an open-label, single-arm, dose-escalation study of tivantinib. Tivantinib was administered orally, initially with intermittent dosing (twice a day, 2 weeks on, 1 week off) and later with continuous dosing. On the basis of the recommended phase II dose identified in a concomitant Phase I biomarker study (23), the current study was amended, and a final cohort of 360 mg twice a day was accrued. The study was conducted at 3 sites between January 31, 2006, and August 11, 2009 (24–26).

Three to 6 patients were enrolled in each dosing group. Each patient was treated with tivantinib and continued until the occurrence of unacceptable toxicity, tumor progression, patient withdrawal, or death. Thirteen dose levels were assessed (Table 1): tivantinib was administered in 21-day cycles (14 days on/7 days off treatment) at escalating twice a day doses in 14 cohorts (cohort 13 at 180 mg was never initiated due to a switch from the amorphous to crystalline preparation of tivantinib). Intrapatient escalation to a higher dose was allowed when such dose was deemed to be well tolerated. Cohorts 1 to 12 received an amorphous formulation of tivantinib; cohort 11 received either amorphous or a commercial crystalline formulation of the drug; cohort 14 received crystalline formulations. A conservative starting dose of 10 mg twice a day was chosen, which was predicted to be within the therapeutic range without being excessively toxic based on preclinical studies in dogs and assuming that oral bioavailability of tivantinib is similar in humans. Subsequent groups were treated according to a standard dose-escalation schema depending on the worst toxicity experienced by individuals enrolled at the prior dose level and the clinical significance of that toxicity. Toxicity was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0 (27, 28).

A DLT was defined as the occurrence of any of the following toxicities "possibly" or "probably" related to tivantinib within the first 21 days of treatment: grade 4 absolute neutrophil count or grade 3 thrombocytopenia in the presence of bleeding, adverse event grade $\geq$ 3 of any duration, and any other toxicity deemed by the investigators to represent a clinically significant hazard to the patient. Grade 3 or 4 diarrhea or nausea/vomiting was considered to be a DLT only if it occurred despite optimal medical management.

In the absence of any DLT within the first 21 days following commencement of treatment, dose escalation was used, and a group of 3 patients was enrolled at the next higher dose level. If a DLT was seen in one of the first 3 patients enrolled in a given group, at least 3 additional patients were enrolled at that dose level. If no DLT occurred

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Table 1. Treatment administration in each cohort

Cohort	Initial dose[a] (mg twice a day)	Planned number of patients	Actual number of patients	Formulation
1	10 (intermittent)	1[b,c]	1	Amorphous
2	20 (intermittent)	1[b,c]	1	Amorphous
3	30 (intermittent)	3–6	3	Amorphous
4	40 (intermittent)	3–6	4	Amorphous
5	50 (intermittent)	3–6	3	Amorphous
6	70 (intermittent)	3–6	5	Amorphous
7	90 (intermittent)	3–6	5	Amorphous
8	120 (intermittent)	3–6	7	Amorphous
9	150 (intermittent)	3–6	5	Amorphous
10	180 (intermittent)	3–6	3	Amorphous
11	120 (continuous)	3–6[d]	16	Amorphous
			5	Crystalline A
12	150 (continuous)	3–6	3	Amorphous[e]
13	180 (continuous)	3–6	0[f]	Amorphous
14	360 (continuous)[g]	3–6	2	Crystalline A
			16	Crystalline B

[a]Intrapatient dose escalation was allowed in the protocol. This table listed initial treatment doses.
[b]If a toxicity of grade $\geq$2 had occurred, additional 2 patients were to be enrolled.
[c]If a dose-limiting toxicity had been observed in a single-patient cohort, additional 5 patients were to be treated.
[d]If pharmacokinetics did not warrant additional dose escalation, additional patients may have been enrolled.
[e]Cohort 12 used amorphous formulation due to limited availability of low-dose capsules containing crystalline formulation.
[f]Cohort 13 was planned to enroll patients with an ARQ 197 dose of 180 mg twice a day (amorphous), but was never initiated because of the switch to the crystalline formulation.
[g]Originally, patients in Cohort 14 were to be treated with an ARQ 197 dose of 230 mg twice a day (continuous). Under protocol Amendment #4, patients were treated with an ARQ 197 dose of 360 mg twice a day (continuous).

in the additional patients, dose escalation continued to the next dose level. If a DLT occurred in 33% or more of patients in the initial or extended group, dose escalation was stopped, and the MTD for the schedule was considered to be exceeded. Therefore, the previous dose level was declared as the MTD. Two expanded cohorts of up to 20 patients, with twice a day dosing of 120 mg or 360 mg of tivantinib (amorphous and crystalline formulations), were included to obtain additional safety data.

Patient evaluation

Before study entry, all patients underwent physical examination, standard laboratory measurements, and computed tomography scans of the chest, abdomen, and pelvis. Tumor measurements were obtained every other cycle (every 6 weeks) for the first 4 cycles (the first 12 weeks on study), then every 3 cycles (every 9 weeks) for the remaining of the study. Tumor response and progression were evaluated using the international criteria proposed by Response Evaluation Criteria in Solid Tumors (RECIST 1.0; refs. 29, 30).

The duration of response was defined as the time from the initial measurement of complete response (CR) or partial response (PR), whichever was recorded first, to the first date that progressive disease (PD) or recurrent disease was objectively documented. The duration of stable disease (SD) was measured from the start of therapy until the criteria for progression were met. The same method of assessment and the same techniques were used to characterize each identified and reported lesion at baseline and during follow-up (30). Adverse events, serious adverse events (SAE), and all concomitant medications, procedures, and supportive therapies were also documented throughout the study. Laboratory abnormalities considered by the investigator to be clinically significant were reported as adverse events.

Pharmacokinetics

Blood samples (5-mL aliquots) for pharmacokinetic analysis were collected for cohorts 1 to 10 on days 1 and 14, and for cohorts 11 and 12 on days 1 and 21. On each of these days, blood samples were drawn at pretreatment, 0.5, 1, 2, 4, 8, 12, 24, and 48 hours after administration of the first tivantinib dose. In addition, for cohorts 11 and 12, blood samples were drawn predose and 2 hours after administration of tivantinib on day 14. For cohort 14, blood samples were drawn at pretreatment, 0.5, 1, 2, 4, and 8 hours on day 1 and 2 hours predose and 2 hours after tivantinib administration on day 21. Samples were collected in tubes containing K_2EDTA and centrifuged at 1,500 to 1,800 $\times$ *g* for 10 minutes at room temperature to separate the formed elements from plasma. Samples were transferred

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to polypropylene tubes and stored frozen at −60°C to −80°C until analysis.

The pharmacokinetic parameters measured included area under the plasma concentration–time curve for 0 to 24 hours (AUC_{0-24}), maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), and elimination half-life ($t_{1/2}$). These parameters were correlated with systemic toxicities associated with the administration of tivantinib and appropriate PD parameters. Tivantinib concentrations in plasma were determined using fully validated liquid chromatograph/tandem mass spectrometer methods, with a lower limit of quantification of 20 ng/mL. On the basis of quality control samples that were assayed along with the samples, the intraday and interday precision for tivantinib analyses ranged from a relative SD of 2.8% to 8.2%, and the accuracy ranged from 85.0% to 104.2%.

Plasma concentration–time data were analyzed by noncompartmental methods using the WinNonLin 4.0 program. The linear-logarithmic trapezoidal method was used to calculate AUC. Linear regression of the terminal slope of the logarithmic plasma concentration–time profile was used to calculate $t_{1/2}$.

Biomarker analysis

Exploratory plasma and tumor biomarker analyses were conducted in a subset of patients to determine the potential prognostic and predictive value of select biomarkers in patients treated with tivantinib. Baseline and posttreatment plasma samples collected for pharmacokinetic analysis were evaluated for HGF and VEGF levels using enzyme-linked immunosorbent assays. Archival formalin-fixed, paraffin-embedded tumor tissue samples were collected, when available, and subjected to immunohistochemical analysis to evaluate biomarkers of total c-MET, phosphorylated c-MET (p-MET), and phosphorylated FAK (p-FAK). Tumor tissue was scored by a clinical pathologist on a scale of 0 to 3+ for staining intensity and percentage of tumor area stained. The sample was considered positive if 10% or more of the tumor scored ≥2 in intensity; strongly positive if 50% or more of the tumor scored ≥2+ intensity. If less than 10% of the tumor stained or if the intensity was <2, the tumor was considered weakly positive.

Statistical analysis

A one-way ANOVA was used to evaluate the pharmacokinetic data. All continuous measurements were summarized by mean (or median for nonnormal data), SD, minimum, and maximum. Categorical data were summarized by frequency counts and percentages. Pharmacokinetic, safety, laboratory, and demographic data were all summarized by dosing cohort.

Results

Patient characteristics

A total of 79 patients, mostly heavily pretreated, were enrolled in this study and were evaluated for pharmacokinetic and safety analyses. Baseline characteristics are shown in Table 2. The most common primary tumor sites were the colon (12.6%) and kidney (12.6%). Five patients had clear cell carcinoma, 4 had nonspecified renal cancer, and one had papillary renal carcinoma.

Table 2. Patient demographics and disease characteristics at baseline

Characteristic	Total study population ($N = 79$)
Sex, *n*, %	
Male	45 (57.0)
Female	34 (43.0)
Median age, y (range)	61.2 (16.8–86.7)
Race/ethnicity, *n*, %	
White	65 (82.3)
Black	5 (6.3)
Asian	4 (5.1)
Hispanic	4 (5.1)
Other	1 (1.3)
Median time since cancer diagnosis, y (range)	3.6 (0.2–32.7)
Cancer stage at entry, *n*, %	
I	0 (0)
II	5 (6.3)
III	16 (20.3)
IV	56 (70.9)
Unknown	2 (2.5)
Cancer type, *n*, %	
Colon/rectum	11 (13.9)
Renal	10 (12.6)
Ovarian	6 (7.6)
Pancreas	6 (7.6)
Sarcoma	6 (7.6)
Thyroid	4 (5.1)
NSCLC	4 (5.1)
Urothelial tract/bladder	4 (5.1)
Prostate	3 (3.8)
Breast	2 (2.5)
Nasopharyngeal	2 (2.5)
Neuroendocrine	2 (2.5)
Head and Neck	2 (2.5)
Other	17 (21.5)
Karnofsky performance status, *n* (%)	
100	10 (12.7)
90	37 (46.8)
80	32 (40.5)
Median number of prior anticancer therapies (range)	9 (2–33)
Median number of prior anticancer systemic regimens	3 (0–12)

Dose modifications

The number of treatment months that patients received is presented in Table 3. The maximum duration of treatment received by any patient was 119 weeks. This patient

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Table 3. Number of ARQ 197 months administered in each dosing cohort

Pt #	Dose, mg twice a day	Tumor type	Best response	Time on study, wk
46	120	Adenoid cystic	SD	63
6	40–70	Angiomyolipoma	SD	35
36	180	Bladder carcinoma	SD	22
70	360	Bladder transitional cell carcinoma	SD	14
53	120	Endometrial adenoca (poorly differentiated)	SD	12
30	120	Liposarcoma	SD	41
43	150	Melanoma	SD	12
1	10–50	Neuroendocrine	PR	32
50	120	Neuroendocrine (high-grade, unknown primary)	SD	20
14	70	NSCLC	SD	17
5	30–50	NSCLC (adenocarcinoma)	SD	20
7	40–120	Pancreatic carcinoma	SD	102
52	120	Papillary adenoca of unknown primary	SD	39
26	120	Papillary thyroid carcinoma	SD	20
27	120–150	Papillary thyroid carcinoma	SD	119
38	180	Papillary thyroid carcinoma	SD	66
8	40–70	Prostate carcinoma	PR	29
44	150	Rectal carcinoma	SD	21
20	90–120	Renal Cell carcinoma	SD	36
28	120–150	Renal Cell carcinoma	SD	66
77	360	Renal Cell carcinoma	SD	12
65	120	Renal Clear Cell carcinoma	SD	28
73	360	Renal Clear Cell carcinoma	SD	30
34	150	Renal Clear Cell carcinoma	SD	21
32	150	Sarcoma	SD	47
45	150	Small cell undifferentiated carcinoma	SD	21
22	90–120	Testicular carcinoma	PR	66

originally received 120 mg of tivantinib twice a day, which was then escalated to 150 mg twice a day. Fifty-two patients (65.8%) received 3 months or less of treatment, whereas 27 patients (34.2%) received more than 3 months of treatment.

Eleven patients (13.9%) experienced dose escalations (10 of 11 patients) or reductions (1 of 11 patient, due to neutropenia). Ten patients (12.7%) had a temporary dose interruption due to an adverse event. These adverse events were deemed related to study treatment in 2 patients (one with drug-related bone marrow toxicity and fatigue, one with drug-related nausea/vomiting and dehydration).

DLTs, MTD, and safety profile

All of the 79 patients enrolled in this study received at least one dose of study treatment and were evaluable for safety analysis. Two patients experienced DLTs during the first month of treatment, which included leukopenia, neutropenia, thrombocytopenia, vomiting, and dehydration. Both of these patients received continuous dosing of tivantinib at 360 mg twice a day. No MTD was reached in this study given that less than 33% of patients experienced DLTs at any given dose. Thus, the recommended phase II dose was confirmed at 360 mg twice a day as per a concomitant phase I study that found this to be the MTD (23).

Treatment-emergent adverse events of any grade were reported in 78 patients (98.7%). These events were graded as severe (grade ≥ 3) in 40 patients (50.6%). Eight patients (10.1%) experienced at least one treatment-emergent adverse event leading to death. These events included disease progression in 5 patients, and pancytopenia/acute renal failure, cardiorespiratory arrest, and respiratory failure each in 1 patient. None of these events were deemed related to study treatment.

Drug-related adverse events of any grade were reported in 37 patients (46.8%; Table 4). The most commonly reported drug-related adverse events of any grade included fatigue, gastrointestinal (GI) disorders (nausea, vomiting, and diarrhea), and anemia. There was an apparent dose-related increase in the frequency of anemia, which was most pronounced at the tivantinib dose of 360 mg twice a day. However, there was no obvious dose-dependent change in the incidence of GI toxicity or fatigue. The most frequent grade III and IV adverse event was anemia, reported in 3 patients (Table 4). A total of 3 patients (3.8%) experienced at least one drug-related SAE, which included anemia, leukopenia, neutropenia, thrombocytopenia, nausea, vomiting, hepatic failure, and dehydration.

The majority of patients discontinued study medication due to either disease progression (47 patients; 59.5%) or

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Table 4. Incidence of ARQ 197-related adverse events in initial twice a day dosing cohorts[a]

	AEs occurring in ≥5% of all patients						
	Intermittent treatment				Continuous treatment		
System organ class preferred term	10–50 mg (*N* = 12)	70–90 mg (*N* = 10)	120 mg (*N* = 7)	150–180 mg (*N* = 8)	120–240 mg (*N* = 24)	360 mg (*N* = 18)	All patients (*N* = 79)
Blood and lymphatic system disorders							
Anaemia				1 (12.5%)	1 (4.2%)	4 (22.2%)	6 (7.6%)
Gastrointestinal disorders							
Nausea	2 (16.7%)	1 (10.0%)	1 (14.3%)	1 (12.5%)	3 (12.5%)	3 (16.7%)	11 (13.9%)
Vomiting		1 (10.0%)			3 (12.5%)	4 (22.2%)	8 (10.1%)
Diarrhoea	2 (16.7%)		1 (14.3%)	1 (12.5%)		1 (5.6%)	5 (6.3%)
General disorders and administration site conditions							
Fatigue	2 (16.7%)	2 (20.0%)	2 (28.6%)	2 (25.0%)	2 (8.3%)	1 (5.6%)	11 (13.9%)
	Grade 3/4 AEs occurring in all patients						
	Intermittent treatment				Continuous treatment		
Blood and lymphatic system disorders							
Anaemia				1 (12.5%)	1 (4.2%)	1 (5.6%)	3 (3.8%)
Neutropenia				1 (12.5%)		1 (5.6%)	2 (2.5%)
Leukopenia						1 (5.6%)	1 (1.3%)
Thrombocytopenia						1 (5.6%)	1 (1.3%)
Gastrointestinal disorders							
Nausea						1 (5.6%)	1 (1.3%)
Vomiting						1 (5.6%)	1 (1.3%)
General disorders and administration site conditions							
Asthenia						1 (5.6%)	1 (1.3%)
Fatigue			1 (14.3%)				1 (1.3%)
Hepatobiliary disorders							
Hepatic failure					1 (4.2%)		1 (1.3%)
Investigations							
AST increased						1 (5.6%)	1 (1.3%)
Blood ALP increased						1 (5.6%)	1 (1.3%)
Metabolism and nutrition disorders							
Dehydration						1 (5.6%)	1 (1.3%)
Hyperammonaemia					1 (4.2%)		1 (1.3%)
Hyponatraemia						1 (5.6%)	1 (1.3%)

[a]All values shown represent the number of AEs by severity, type, and dose.

symptomatic deterioration (15 patients; 19.0%). Only 2 patients (2.5%) discontinued tivantinib due to a treatment-emergent adverse event (one with grade 3 dyspnea, one with grade 3 deep vein thrombosis), which were not deemed related to study treatment.

Pharmacokinetics

Pharmacokinetic data were available for 77 patients. The plasma concentration–time profile of tivantinib was characterized by a moderate rate of absorption peaking approximately 2 to 4 hours after initial dosing. A linear decrease in plasma concentrations of tivantinib was generally observed approximately 4 hours after dosing.

The pharmacokinetic parameters of tivantinib are presented in Table 5. Considerable interpatient variability in the pharmacokinetics of tivantinib was observed. There was a substantial increase in tivantinib C_{max} and AUC values over the dosing period. However, tivantinib seemed to increase less than proportionally with increasing dose and exhibited variation in its accumulation, with mean $t_{1/2}$ values ranging from 1.5 to 2.7 hours (cycle 1, day 1). The mean plasma AUC_{0-8}, C_{max}, and t_{max} values for tivantinib 360 mg twice a day on day 1 of cycle 1 were 8,257 ng·h/mL, 1,459 ng/mL, and 3.1 hours, respectively.

To determine the impact of interpatient variability in the pharmacokinetics of tivantinib (given that patients with higher exposures might be at greater risk for an adverse event), the relationship between drug exposure and clinical safety was evaluated. Available data on tivantinib, although limited, suggest that there is no relationship between drug-related adverse events, dose, and extent of tivantinib exposure. Therefore, the interpatient variability in tivantinib

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Table 5. Plasma ARQ 197 pharmacokinetic parameters over the 21-day dosing period of cycle 1

Dose twice a day, mg	Formulation	$AUC_{(0-last)}$[c], ng h/mL		C_{max}, ng/mL		t_{max}, h		$t_{1/2}$, h	
		Day 1	Day 14/21[d]	Day 1	Day 14/21[d]	Day 1	Day 14/21[d]	Day 1	Day 14/21[d]
20[a]	Am	5,429 ($n = 1$)	16,802 ($n = 1$)	533 ($n = 1$)	1,970 ($n = 1$)	4.0 ($n = 1$)	1.0 ($n = 1$)	NA	NA
30[a]	Am	5,214 ± 2,494 ($n = 3$)	7,370± 6,366 ($n = 3$)	888 ± 195 ($n = 3$)	1,123 ± 711 ($n = 3$)	2.7 ± 1.2 ($n = 3$)	1.7 ± 0.6 ($n = 3$)	NA	4.3 ($n = 1$)
40[a]	Am	7,724 ± 5,628 ($n = 4$)	13,201 ± 10,634 ($n = 3$)	1,277 ± 655 ($n = 4$)	1,575 ± 1,006 ($n = 3$)	4.1 ± 5.3 ($n = 4$)	5.3 ± 5.8 ($n = 3$)	1.7 ($n = 1$)	NA
50[a]	Am	6,317 ± 4,877 ($n = 6$)	8,537 ± 7,247 ($n = 6$)	948 ± 574 ($n = 6$)	1,281 ± 912 ($n = 6$)	3.7 ± 4.2 ($n = 6$)	1.5 ± 0.5 ($n = 6$)	2.2 ± 0.5 ($n = 3$)	3.0 ± 1.1 ($n = 2$)
70[a]	Am	12,588 ± 10,912 ($n = 6$)	11,502 ± 8,353 ($n = 6$)	2,365 ± 2,046 ($n = 6$)	1,920 ± 993 ($n = 6$)	3.5 ± 4.3 ($n = 6$)	3.1 ± 4.4 ($n = 6$)	2.1 ± 0.12 ($n = 2$)	2.2 ± 0.3 ($n = 2$)
90[a]	Am	11,416 ± 5,965 ($n = 5$)	12,668 ± 10,318 ($n = 5$)	1,808 ± 386 ($n = 5$)	2,340 ± 1,097 ($n = 5$)	4.2 ± 2.5 ($n = 5$)	1.3 ± 0.7 ($n = 5$)	NA	3.3 ($n = 1$)
120[a]	Am	16,915 ± 11,330 ($n = 7$)	26,232 ± 24,610 ($n = 6$)	2,403 ± 1,037 ($n = 7$)	3,652 ± 2,709 ($n = 6$)	3.3 ± 2.4 ($n = 7$)	1.9 ± 1.2 ($n = 6$)	1.5 ($n = 1$)	2.6 ± 0.9 ($n = 2$)
120[b]	Am	10,469 ± 6,405 ($n = 16$)	13,297 ± 11,293 ($n = 14$)	1,812 ± 808 ($n = 16$)	2,051 ± 1,278 ($n = 14$)	2.7 ± 3.0 ($n = 16$)	2.1 ± 1.2 ($n = 14$)	2.7 ± 1.0 ($n = 9$)	2.7 ± 0.8 ($n = 6$)
120[b]	CA	12,538 ± 10,156 ($n = 4$)	24,609 ± 22,063 ($n = 3$)	1,736 ± 1,121 ($n = 4$)	2,758 ± 2,274 ($n = 3$)	3.0 ± 1.2 ($n = 4$)	3.3 ± 1.2 ($n = 3$)	2.5 ($n = 1$)	NA
150[a]	Am	11,503 ± 11,387 ($n = 5$)	7,665 ± 3,806 ($n = 4$)	1,716 ± 1,177 ($n = 5$)	1,724 ± 976 ($n = 4$)	2.2 ± 1.1 ($n = 5$)	1.5 ± 0.6 ($n = 7$)	NA	2.5 ± 0.4 ($n = 3$)
150[b]	Am	18,325 ± 13,538 ($n = 3$)	17,136 ± 12,858 ($n = 3$)	2,480 ± 1,264 ($n = 3$)	2,860 ± 1,165 ($n = 3$)	6.0 ± 5.3 ($n = 3$)	2.3 ± 1.5 ($n = 3$)	NA	3.6 ($n = 1$)
180[a]	Am	15,598 ± 12,203 ($n = 3$)	20,523 ± 21,548 ($n = 3$)	2,330 ± 1,050 ($n = 3$)	2,733 ± 1,857 ($n = 3$)	1.7 ± 0.6 ($n = 3$)	4.0 ± 3.5 ($n = 3$)	2.2 ($n = 1$)	1.9 ($n = 1$)
360[b]	CA	15,623 ± 3,338 ($n = 2$)	NA	2,595 ± 1,025 ($n = 2$)	NA	4.5 ± 4.9 ($n = 2$)	NA	NA	NA
360[b]	CB	8,257 ± 4,429 ($n = 15$)	NA	1,459 ± 740 ($n = 15$)	NA	3.1 ± 1.9 ($n = 15$)	NA	NA	NA

NOTE: Data are reported as mean ± SD

Am, amorphous; AUC, area under the curve; CA, crystalline A; CB, crystalline B; NA, value is not applicable or cannot be calculated.

[a]Intermittent dosing: 2 weeks on ARQ 197, 1 week off.

[b]Continuous dosing of ARQ 197.

[c]$AUC_{(0-last)} = AUC_{(0-24\ hr)}$ for all doses with the following exceptions: $AUC_{(0-last)} = AUC_{(0-12\ hr)}$ for the 360 mg twice a day CA dose, $AUC_{(0-last)} = AUC_{(0-8\ hr)}$ for the 360 mg twice a day CB dose.

[d]Pharmacokinetic parameters were measured on Day 14 for all doses with the following exceptions: 120 mg twice a day continuous doses (Day 21), 150 mg twice a day continuous dose (day 21).

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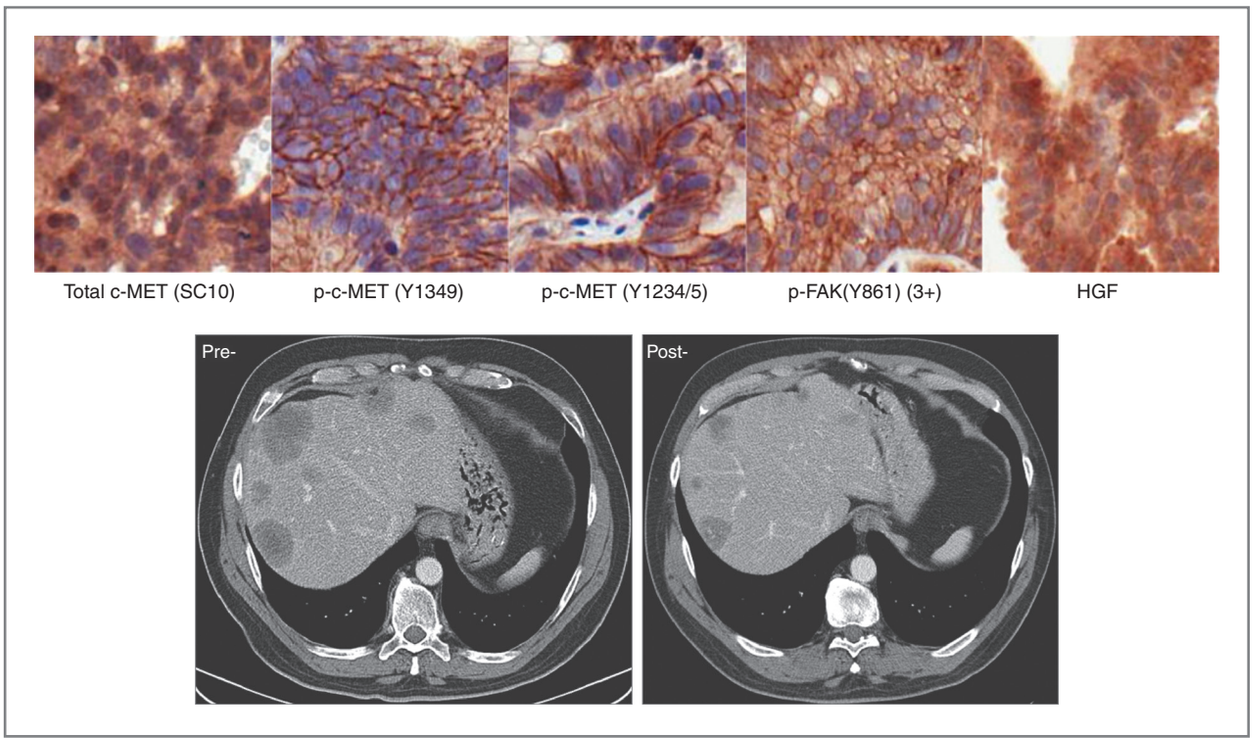

Figure 1. Baseline immunohistochemistry and CT scans of patient with metastatic prostate cancer in partial response (6 weeks on ARQ 197). The patient was diagnosed on April 2005, treated with radiotherapy in March 2006, treated with taxotere, estramustine (August 2005 to December 2005), LHRH, and casodex (August 2005 to March 2006), and progressed. The patient started ARQ 197 on May 16, 2006, at a dose of 80 mg daily, and was escalated to 100 mg/d for one cycle and subsequently to 140 mg/d.

pharmacokinetics is not believed to affect its clinical safety. There also seems to be no relationship between baseline demographic variables, such as age, gender, or body weight, and tivantinib exposure.

Response to therapy

In this study, 62 patients were evaluable for objective response. The best response observed in this study was PR in 3 patients (4.8%; Fig. 1). Sixteen patients (25%) stayed on study drug for more than 24 weeks, including 4 with renal cancer (2 each with clear cell renal carcinoma and unspecified renal cancer), 2 with papillary thyroid carcinoma, and the remaining 10 with different tumor types. The progression-free survival (PFS) rate for all 79 patients at 6 weeks was 77%, at 12 weeks was 52%, and at 21 weeks was 34%. The median PFS time was 85 days (12.1 weeks).

Biomarker analysis

Baseline and posttreatment plasma samples for 66 patients across all dosing cohorts were included in exploratory biomarker analysis of HGF and VEGF. Statistical analysis identified no significant difference between baseline and posttreatment levels of either HGF or VEGF. A comparison of biomarker levels in patients with PR/SD versus those with PD revealed that baseline levels of HGF were comparable between the PR/SD and PD groups (1,910 and 2,009 pg/mL, respectively), whereas posttreatment levels of HGF decreased in patients with PR/SD and increased in patients with PD (change from baseline: −295 and +328 pg/mL, respectively). The post-treatment difference in HGF levels between the PR/SD and PD groups did not reach statistical significance. For VEGF, baseline levels were higher in the PR/SD group than in the PD group (203 and 113 pg/mL, respectively), and posttreatment levels significantly increased in patients with PD but not in those with PR/SD (change from baseline: +169 and +0.5 pg/mL, respectively). The differences in baseline and post-treatment VEGF levels between the PR/SD and PD groups were not statistically significant.

Evaluable archival tumor tissue samples were obtained for 12 patients. All 12 samples were positive for total c-MET. Four were strongly positive ($\geq$2+ intensity and $\geq$50% of tumor area) whereas 3 samples were only weakly positive (intensity <2 or staining of <10% of the tumor area). Half of the samples were positive for p-MET, (3 were focal or weakly positive). Five of 12 samples were positive for p-FAK. All samples that were strongly positive for p-MET were also positive for p-FAK. Of the samples that were weakly positive for p-MET, one was negative and one was positive for p-FAK. No obvious association of p-MET or p-FAK staining with best clinical response was identified. A patient with prostate cancer showed high expressions of total c-MET, p-c-MET, p-FAK, and HGF at baseline, and obtained a radiographic partial remission (Fig. 1).

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Discussion

Results of this phase I study show that tivantinib is well tolerated in patients with advanced solid tumors when administered either continuously or for 14-days followed by a 7-day break. PK analysis in this study shows interpatient variability; this was further evaluated in subsequent studies where possible correlation with cytochrome CYP2C19 polymorphism was observed (23). Despite such variability in the pharmacokinetics of tivantinib, clinical safety does not seem to be affected. Tivantinib has preliminary antitumor activity, which is evident from observed PR in 3 patients and SD at 12 weeks in more than half of all patients included in the study.

The most common drug-related adverse events included fatigue, GI disorders, and anemia. The fatigue and GI disorders were generally mild to moderate in severity and unrelated to dose. However, there was an apparent dose-related increase in the frequency of anemia (grade I–III), especially at the tivantinib dose of 360 mg twice a day. Fatigue, nausea, vomiting, anemia, and diarrhea were the most frequently ($\geq$5%) reported drug-related adverse events. The most frequent grade III to IV adverse event was anemia, reported in 3 patients (Table 4). Drug-related SAEs occurred in only 3 patients (3.8%), highlighting the general safety of tivantinib. Two patients discontinued therapy due to adverse events, which were deemed to be unrelated to the study drug. Only 2 cases of DLTs were reported during the study, both at the 360-mg twice a day dose level. On the basis of these findings, the tivantinib 360-mg twice a day dose was recommended for further evaluation in phase II/III trials, consistent with findings in 3 other Phase I trials (23, 42, 43).

Pharmacokinetic analysis revealed that tivantinib has a moderate rate of absorption, followed by a linear decrease in plasma concentrations approximately 4 hours after dosing. Considerable interpatient variability in the pharmacokinetics of tivantinib was observed. Although there was a substantial increase in tivantinib exposure and maximum concentration over the dosing period, tivantinib seemed to increase less than proportionally with increasing dose and exhibited variation in its accumulation. Despite the observed interpatient variability in tivantinib pharmacokinetics, there seems to be no relationship between drug-related adverse events, dose, and extent of tivantinib exposure. There also seems to be no relationship between baseline demographic variables and tivantinib exposure.

Results from this phase I trial show that tivantinib has preliminary evidence of antitumor activity, mainly by inducing clinically relevant stabilization of disease as opposed to tumor regression. Results have also exhibited that tivantinib has activity in several different solid tumor types, with SD lasting a median of 19.9 weeks (3–119) occurring as the best response in 32 (51%) of evaluable patients. Confirmed PR was documented in 3 (4.8%) patients, one each with prostate cancer, neuroendocrine cancer, and testicular cancer.

Exploratory analyses were conducted in an attempt to identify prognostic and predictive biomarkers. Both HGF and VEGF have been shown to be prognostic indicators in several solid human tumors, and a number of receptor tyrosine kinase inhibitors affect plasma levels of VEGF. In our analyses, interesting trends were observed in posttreatment levels of HGF in patients with PR/SD versus PD. There was a decrease in HGF following tivantinib treatment in patients with PR/SD and an increase in patients with PD. However, the difference in posttreatment HGF levels between the PR/SD and PD groups was not statistically significant, perhaps due to small sample size. Therefore, the investigators believe that this study is insufficient to rule out the possibility that HGF or VEGF levels may change in response to tivantinib treatment. The results of this trial further showed the feasibility of detecting these tumor biomarkers from archival human tumors using immunohistochemistry. Further investigation of plasma and tissue biomarkers in larger numbers of patients may provide additional information regarding the prognostic and predictive utility of these markers.

Tivantinib was well tolerated and has exhibited antitumor effects in patients with advanced refractory solid tumors. The recommended dose of tivantinib for evaluation in phase II/III trials is 360 mg twice a day using a commercial crystalline formulation. The findings from this study suggest the potential utility of tivantinib as a monotherapy in several solid tumor types and warrant further clinical development of this compound (31–41).

Disclosure of Potential Conflicts of Interest

L.S. Rosen: other commercial research support, ArQule, Inc. R. Ganapathi: commercial research grant. F. Chai: employment, ArQule, Inc. (Director of Drug Safety); ownership interest, ArQule, Inc. stocks. R. E. Savage: employment (Director, Pre-Clinical development and clinical pharmacology); ownership interest, ArQule, Inc. stock options. C. Waghorne: employment, ArQule, Inc. (Lead Investigator). G. Abbadessa: employment, ArQule, Inc. (Senior Medical Director); ownership interest, ArQule, Inc. stock options. B. Schwartz: employment, ArQule, Inc. (Chief Medical Officer); ownership interest, ArQule, Inc. stocks. R. Dreicer: honoraria from speakers bureau, Centecor Ortho Biotech; consultant/advisory board, GTX, Sanofi Aventis, Novartis and Millenium.

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