Original Article

Tivantinib (ARQ 197), a Selective Inhibitor of MET, in Patients With Microphthalmia Transcription Factor–Associated Tumors

Results of a Multicenter Phase 2 Trial

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BACKGROUND: Microphthalmia transcription factor (MITF)-associated (MiT) tumors are a family of rare malignancies, including alveolar soft part sarcoma (ASPS), clear cell sarcoma (CCS), and translocation-associated renal cell carcinoma (tRCC) that have dysregulated expression of oncogenic MITF family proteins. The MET receptor tyrosine kinase gene is transcriptionally activated by MITF family proteins, making MET a potential therapeutic target for MiT tumors. This study assessed the activity of tivantinib (ARQ 197), a selective MET inhibitor, in patients with MiT-associated tumors. **METHODS:** This multicenter, single-arm, phase 2 trial enrolled patients with advanced MiT tumors. Patients initially received tivantinib 120 mg orally twice daily, then 360 mg twice daily per protocol amendment. The primary endpoint was overall response rate. Secondary endpoints included safety, progression-free survival, pharmacokinetics, and correlative studies. **RESULTS:** A total of 47 patients (median age, 25 years; range, 11-73 years) with ASPS (n = 27), CCS (n = 11), tRCC (n = 6), or other tumor types (n = 3) were enrolled. Common grade 3/4 drug-related adverse events included anemia (4%) and neutropenia (4%). Three patients (6.4%) experienced 4 treatment-related serious adverse events (grade 3 febrile neutropenia, thrombocytopenia, and deep vein thrombosis, and grade 4 thrombocytopenia). Best response was partial response in 1 CCS patient (2%) and stable disease in 28 patients (60%). Median progression-free survival was 3.6 months (overall), 5.5 months (ASPS), and 1.9 months (CCS and tRCC). Baseline MET expression was strongly or focally positive in tumor samples from 14 of 19 patients (74%). **CONCLUSIONS:** Tivantinib was safe and tolerable in patients with MiT tumors, but antitumor activity was modest. ***Cancer* 2012;118:5894-902.** © *2012 American Cancer Society.*

KEYWORDS: tivantinib, ARQ 197, proto-oncogene proteins c-met/*antagonists and inhibitors, microphthalmia-associated transcription factor, clear cell sarcoma, alveolar soft part sarcoma, renal cell carcinoma, pediatric, protein kinase inhibitors/pharmacokinetics.

The microphthalmia transcription factor (MITF)-associated (MiT) tumors are a family of rare malignancies including alveolar soft part sarcoma (ASPS), clear cell sarcoma (CCS), and translocation-associated renal cell carcinoma (tRCC).[1] MiT tumors are morphologically and clinically distinct, yet share certain clinical features such as a disproportionate incidence among younger individuals and a strong propensity to metastasize.[1] These tumors are also highly refractory to conventional chemotherapy and radiation[1] and have been the subject of very few reported prospective studies.

MiT tumors are biologically linked by dysregulated expression of a family of homologous transcription factors including E-box binding transcription factors TFE3, TFEB, TFEC, and MITF[2] that regulate development of cell lineages such as melanocytes and osteoclasts.[3-5] Gene knockout experiments have demonstrated partial functional redundancy for MITF family members and have implicated them in the transcriptional regulation of key genes involved in cell proliferation and survival, including *B cell lymphoma 2* (*BCL2*), *MET*, and $p21^{CIP}$.[6-8]

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The *MITF* gene is amplified in 20% of malignant melanomas and is aberrantly expressed in CCS secondary to overexpression of the *EWSR1-ATF1* (Ewing sarcoma breakpoint region 1–activating transcription factor 1) fusion gene product.[9,10] Likewise, translocation of MITF family genes *TFE3* and *TFEB* to heterologous promoters characteristically leads to overexpression of the TFE3 and TFEB transcriptional activators in ASPS, tRCC, and certain malignant perivascular epithelioid cell tumors (known as "PEComa").[11-16] Modulation of the DNA-binding activity of MITF family members has demonstrated a requirement for their transcriptional activator functions in oncogenesis, suggesting that MITF family regulatory pathways may be attractive targets for development of therapeutic agents to treat MiT tumors.[10]

Potentially, one could directly inhibit these transcription factors using small interfering RNA (siRNA) or agents that disrupt specific protein–DNA interactions. An alternative therapeutic approach may be to inhibit critical downstream targets that are regulated by MITF family proteins. One such potential target is the MET receptor tyrosine kinase, the expression of which is up-regulated by MITF and TFEB.[17] Amplification or activation of MET has been implicated in several human cancers, including non–small cell lung cancer, hepatocellular carcinoma, and colorectal cancer.[18-24] Likewise, MET activity has been shown to be essential for proliferation and survival of CCS and tRCC cell lines in studies using specific inhibitors of MET signaling, including antibodies to hepatocyte growth factor, and siRNA or small-molecule tyrosine kinase inhibitors of MET.[7,17,25,26] These studies provide a strong rationale for specifically targeting MET in patients with MiT tumors.

Tivantinib (ARQ 197) is a selective, oral, non–adenosine triphosphate-competitive, small-molecule inhibitor of MET that has demonstrated antitumor activity in a wide range of human tumor cell lines and in xenograft models of human lung, prostate, colon, pancreas, and breast cancer.[27] Phase 1 studies have shown that single-agent tivantinib is well tolerated at doses up to 360 mg twice daily (BID) without dose-limiting toxicity.[28] Here, we report a phase 2, multicenter, single-arm study assessing the safety and efficacy of tivantinib monotherapy in adolescent and adult patients with metastatic or surgically unresectable MiT tumors, including ASPS, CCS, and tRCC.

MATERIALS AND METHODS

Patients

Patients ($\geq$13 years of age) with metastatic and/or surgically unresectable ASPS, CCS, or tRCC who were either newly diagnosed with metastatic disease or had received any number of previous therapies were eligible. Key inclusion criteria included measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0,[29] Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, hepatic, and renal function. Patients who had received chemotherapy, radiotherapy, or investigational drug therapy within 4 weeks before the first dose of tivantinib, or who had significant gastrointestinal disorders that could interfere with absorption of an oral agent, baseline bradycardia, or history of arrhythmia were excluded. Patients with brain metastases were also excluded unless the metastases had been stable for at least 3 months and the patient had no ongoing neurologic symptoms.

This study was approved by the institutional review boards of the participating institutions and was conducted according to institutional and federal guidelines and registered with ClinicalTrials.gov (trial number NCT00557609). Written informed consent was obtained from all patients or legal parent/guardian if under the age of 18 years.

Study Design

This was a multicenter, single-arm, phase 2 study. The primary endpoint was overall response rate in the intent-to-treat (ITT) population. Secondary endpoints included progression-free survival (PFS), 6- and 12-month overall survival (OS), pharmacodynamic (PD) assessments, and pharmacokinetic (PK) profiling of tivantinib in patients $\leq$20 years of age.

Treatment

Patients were initially treated with tivantinib 120 mg BID in a fasting state, in 28-day cycles with no planned breaks between cycles. During the course of this study, data from a concurrent phase 1 study established the recommended phase 2 dose of tivantinib at 360 mg BID.[28] Accordingly, this study was amended to permit dose escalation to 360 mg BID for patients who had begun treatment at 120 mg BID, and all newly enrolled participants from that point forward began tivantinib dosing at 360 mg BID.

Dose delays up to 14 days were permitted for patients experiencing tivantinib-related toxicity. Dose delays longer than 14 days resulted in patient withdrawal from the treatment phase of the study; however, the patient had the option to continue on the study to receive all follow-up evaluations if no other study discontinuation criterion was met. If dose reductions occurred, all subsequent cycles were administered at the modified dose

unless further dose reduction was required. A maximum of 2 dose reductions was permitted per patient.

Assessments

Tumor evaluations according to RECIST version 1.0 were performed at baseline and every 8 weeks thereafter until treatment was halted because of disease progression, unacceptable toxicity, or other reason. Adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Optional blood samples for PK analysis in patients ≤20 years of age were collected before the first dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 26, and 48 hours after the morning dose on days 1 and 22 during the first treatment cycle. Tivantinib was assayed using a validated high-performance liquid chromatography with tandem mass spectrometric detection method, and PK parameters were calculated using WinNonlin version 5.2 (Pharsight, St. Louis Mo).

Immunohistochemistry was used to assess baseline tumor total MET expression in archival tumor samples using anti-total c-MET (SP44) monoclonal antibody (Spring Bioscience, Pleasanton, Calif). Slides were scored by a board-certified pathologist using a digital imaging system (Aperio Technologies, Vista, Calif). Staining intensity was scored on a scale of 0, 1+, 2+, or 3+ and was used to rank tumor MET expression as positive (≥2+ in ≥50% of tumor cells), focally positive (≥2+ in ≥10% but <50% of tumor cells), weakly positive (1+ in ≥10% of tumor cells), or negative (0 or any score in <10% of tumor cells).

Statistical Methods

The sample size, calculated using a Simon optimal 2-stage method,[30] was powered at 90% to detect a significant difference between an assumed tivantinib response rate of 11% and a fixed no-effect response rate of 1%, with a 1-sided type 1 error rate of 5% ($\alpha = .05$). After patients discontinued tivantinib treatment, follow-up assessments of OS were performed every 3 months. In the original protocol of this 2-stage study, enrollment of 23 patients was planned for stage 1, with an expansion of 22 additional patients in stage 2 if more than 1 RECIST response was observed in stage 1. After the protocol was amended to dose all patients with the higher dose of tivantinib (360 mg BID), the statistical design was amended to a planned enrollment of 26 patients in stage 1 (23 of whom were evaluable), with the possible addition of 18 patients in stage 2 (16 of whom were evaluable), if at least 1 response was observed in stage 1.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Patients (N = 47)
Median age, years (range)	25 (11-73)
Sex, n (%)	
Male	16 (34)
Female	31 (66)
Race, n (%)	
American Indian or Alaska Native	1 (2)
Asian	6 (13)
Black or African American	7 (15)
White	29 (62)
Other[a]	4 (9)
ECOG performance status, n (%)	
0	27 (57)
1	20 (43)
Histologic classification, n (%)	
Alveolar soft part sarcoma	27 (57)
Clear cell carcinoma	11 (23)
Translocation-associated renal cell carcinoma	6 (13)
Other[b]	3 (6)
Median number of previous surgery (range)	3 (0-19)
Median number of previous radiotherapy (range)	1 (0-7)
Median lines of systemic or other local[c] treatment (range)	1 (0-8)

ECOG indicates Eastern Cooperative Oncology Group.
[a] Other races included Hispanic (n = 2), Hispanic or Latino (n = 1), and White and Asian (n = 1).
[b] Other tumor types included papillary renal cell carcinoma, Wilms' tumor, and high-grade clear cell renal cell carcinoma (n = 1 for each), which were initially diagnosed as tRCC.
[c] Excluding surgery and radiotherapy.

RESULTS

Patient Demographics and Baseline Characteristics

Forty-seven patients with ASPS (n = 27), CCS (n = 11), tRCC (n = 6), or other histologies (n = 3) were enrolled at 9 study centers in the United States, Canada, and the United Kingdom from November 15, 2007, to December 23, 2009 (Table 1). Median age was 25 years (range, 11-73 years), which is consistent with the characteristically young age of occurrence for these tumor types. One heavily pretreated 11-year-old patient with ASPS was approved for enrollment despite not meeting the inclusion criteria of age ≥13 years and presence of measurable disease, because the patient had excellent performance status, high levels of tumor MET expression, and limited treatment options. Three patients originally enrolled with a diagnosis of tRCC were reclassified after central pathology review as having papillary RCC, Wilms' tumor, or high-grade clear cell RCC. Although ineligible, these patients were included in the ITT population. Patients enrolled under the original protocol (n = 26) received tivantinib at an initial dose of 120 mg BID. After the protocol

amendment was approved, a subgroup of these patients (n = 8) had dose escalation to 360 mg BID and all newly enrolled patients (n = 21) received study treatment at an initial dose of 360 mg BID. Median duration of exposure to tivantinib in this study was 4 months (range, 0 to 30 months).

Safety

The majority of patients (92%) experienced at least 1 treatment-emergent adverse event (TEAE) and 17% of patients experienced at least 1 grade 3 or 4 TEAE considered possibly or probably related to study drug by the investigators (Table 2). The 3 most common nonhematologic drug-related TEAEs were fatigue (49%), nausea (43%), and vomiting (28%). The 3 most common hematologic drug-related TEAEs were anemia (17%), neutropenia (13%) and leukopenia (13%). Seven patients (15%) experienced severe (grade 3 or 4) hematologic drug-related TEAEs, and no patients experienced drug-related fatal (grade 5) TEAEs.

Fourteen patients (30%) experienced serious adverse events (SAEs) from any cause, whereas 3 patients (6%) experienced 4 drug-related SAEs (grade 3 febrile neutropenia, thrombocytopenia, and deep vein thrombosis, and grade 4 thrombocytopenia); all were receiving tivantinib 360 mg BID when drug-related SAEs occurred. All drug-related SAEs resolved, although the grade 3 deep vein thrombosis resolved with sequelae.

Two patients (4%) experienced drug-related TEAEs that led to treatment discontinuation (grade 4 thrombocytopenia in 1 patient, and grade 2 diarrhea, fatigue, headache, and cough in 1 patient). Two deaths were reported within 30 days of last administration of tivantinib, both as a result of disease progression.

Table 2. Most Common (≥5%) Drug-Related TEAEs

Adverse Event	Patients, n (%) (N = 47)	
	All Grades	Grade 3 and 4[a]
Any drug-related TEAE	43 (92)	8 (17)
Hematologic		
Anemia	8 (17)	2 (4)
Leukopenia	6 (13)	1 (2)
Neutropenia	6 (13)	2 (4)
Lymphopenia	4 (9)	1 (2)
Thrombocytopenia	3 (6)	1 (2)
Nonhematologic		
Fatigue	23 (49)	0
Nausea	20 (43)	0
Vomiting	13 (28)	0
Sinus bradycardia	8 (17)	0
Diarrhea	7 (15)	0
Headache	6 (13)	0
Cough	5 (11)	0
ALT increase	4 (9)	0
Anorexia	4 (9)	0
AST increase	4 (9)	0
Rash	4 (9)	0
Dyspnea	3 (6)	0
Insomnia	3 (6)	0
Pyrexia	3 (6)	0
Retching	3 (6)	0

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.
[a] Additional drug-related grade 3 or 4 TEAEs included amenorrhea, epigastric discomfort, febrile neutropenia, hypophosphatemia, and deep vein thrombosis (n = 1 for each).

Efficacy Analyses

At the final analysis with a median follow-up time of 12 months, all 47 patients had discontinued the study, most commonly because of disease progression (38 patients [81%]). One patient (2%) with CCS had a confirmed partial response (PR) that was first detected after 4 cycles of tivantinib 120 mg BID. At the time of progression, after 10 cycles of tivantinib, the patient's dose was increased to 360 mg BID with no evidence of additional clinical benefit. Stable disease (SD) was observed in 27 patients (57%) (median duration, 4 months; range, 1-30 months; Table 3). Subgroup analysis indicated that disease control rates (PR plus SD) in the ASPS, CCS, and tRCC cohorts were 78%, 36%, and 50%, respectively. Median PFS in the ITT population was 4 months (Figure 1a). Median PFS was 6 months in the ASPS cohort and 2 months in both the CCS and tRCC cohorts (Figure 1b).

Table 3. Tumor Responses by Tumor Histology

Best Response, n (%)	ASPS (n = 27)	CCS (n = 11)	tRCC (n = 6)	Other[a] (n = 3)	Overall (N = 47)
Partial response (PR)		1 (9)			1 (2.1)
Stable disease (SD)	21 (78)	3 (27)	3 (50)		27 (57)
Progressive disease	5 (19)	6 (55)	3 (50)	3 (100)	17 (36)
Not evaluable[a]	1 (4)	1 (9)			2 (4)
Disease control rate (PR + SD)	21 (78)	4 (36)	3 (50)		28 (60)

ASPS indicates alveolar soft part sarcoma; CCS, clear cell sarcoma; tRCC, translocation-associated renal cell carcinoma.
[a] Patients who were not evaluable discontinued treatment because of adverse events before having at least 1 posttreatment tumor measurement.

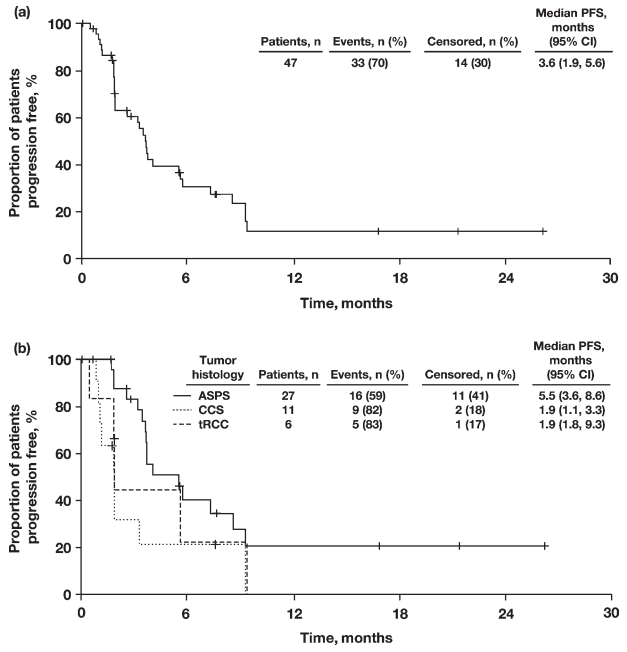

Figure 1. Kaplan-Meier plots of progression-free survival (PFS) (a) in the intent-to-treat (ITT) population and (b) by tumor type. Abbreviations: ASPS, alveolar soft part sarcoma; CCS, clear cell sarcoma; CI, confidence interval; NA, not applicable; OS, overall survival; tRCC, translocation-associated renal cell carcinoma.

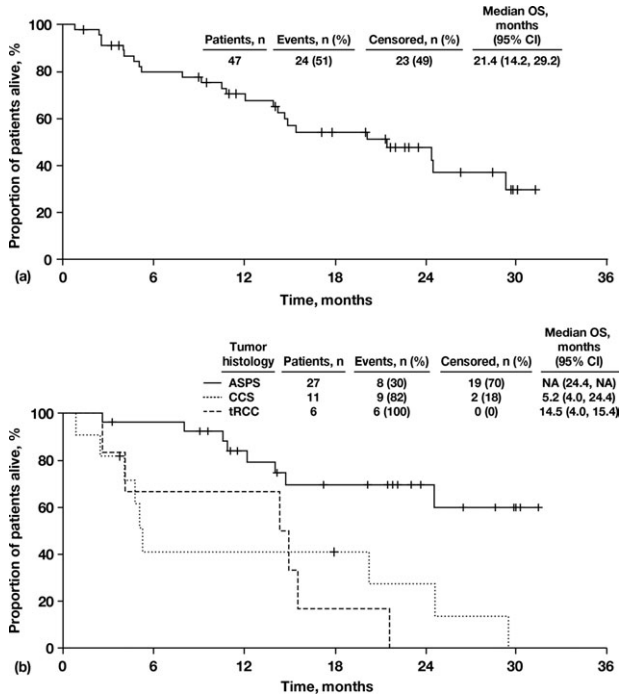

Figure 2. Kaplan-Meier plots of overall survival (OS) (a) in the intent-to-treat (ITT) population and (b) by tumor type. Abbreviations: ASPS, alveolar soft part sarcoma; CCS, clear cell sarcoma; CI, confidence interval; NA, not applicable; tRCC, translocation-associated renal cell carcinoma.

No significant relationships were observed between outcomes and dose of tivantinib, although this study was neither designed nor powered to identify such differences.

Overall Survival

Median OS in the ITT population was 21 months (Figure 2a), and Kaplan-Meier estimates of 6-month, 1-year, and 2-year OS were 80%, 70%, and 48%, respectively (Table 4). Median OS was not reached in the ASPS cohort, was 5 months in the CCS cohort, and was 15 months in the tRCC cohort (Figure 2b).

Exploratory Analysis

An exploratory analysis compared the median duration of patients' most recent previous systemic therapy with the median duration of tivantinib treatment in the current study. Overall, 18 patients who were evaluable in the current study also received at least 1 previous systemic therapy for which response data were available for analysis (Table 5). In patients with ASPS (n = 13), median duration of treatment with tivantinib was 6 months (range, 2-30 months) compared with 3 months (range, 1-36 months) for previous systemic therapy ($P = .25$).

Pharmacokinetics

Blood samples for PK analysis were collected from 8 patients with median age of 18 years (range, 14 to 21 years). Mean concentration–time profiles of plasma tivantinib after single-dose (day 1) and multiple-dose (day 22) administration at either 120 mg BID (n = 6) or 360 mg BID (n = 2) demonstrated mean peak plasma levels at 2 hours after dose (Figure 3). No apparent tivantinib accumulation was observed between days 1 and 22 in the 120-mg BID cohort; small sample size precluded conclusive results for the 360-mg BID cohort. Mean total exposure (area under the curve from time 0 to the last measurable concentration [AUC_{last}] and area under the curve from time 0 to 12 hours after the start of drug administration [$AUC_{0\text{-}12}$]) in the tivantinib 120-mg BID cohort increased slightly (8.8% and 3.5%, respectively) between day 1 and day 22 (Table 6). Accumulation ratios near 1.0 for AUC_{last} (1.1), $AUC_{0\text{-}12}$ (1.1), and C_{max} (1.2) suggested that there was no plasma accumulation of tivantinib with multiple drug dosing.

Correlative Immunohistochemistry

Archival tumor samples from 19 patients were evaluated by immunohistochemistry for total MET protein expression. Overall, tumors from 10 patients (53%) were

Table 4. Overall Survival by Tumor Histology

Survival, % (95% CI)	ASPS (n = 27)	CCS (n = 11)	tRCC (n = 6)	Other[a] (n = 3)	Overall (N = 47)
6 mo	96 (77, 100)	41 (13, 68)	67 (20, 90)	100 (100, 100)	80 (65, 89)
1 y	84 (63, 94)	41 (13, 68)	67 (20, 90)	50 (1, 91)	70 (55, 82)
2 y	70 (46, 84)	27 (5, 57)	0	50 (1, 91)	48 (31, 63)

ASPS indicates alveolar soft part sarcoma; CCS, clear cell sarcoma; CI, confidence interval; tRCC, translocation-associated renal cell carcinoma.
[a] Other tumor types included papillary renal cell carcinoma, Wilms tumor, and high-grade clear cell renal cell carcinoma (n = 1 for each).

Table 5. Duration of Last Systemic Therapy and Tivantinib Therapy by Tumor Histology

Median Treatment Duration, mo (Range)	ASPS (n = 13)	CCS (n = 4)	tRCC (n = 1)	Overall (N = 18)
Tivantinib therapy in this study	6 (2-30)	3 (1-4)	6	4 (1-30)
Most recent previous systemic therapy	3 (1-36)	4 (3-26)	2	3 (1-33)

ASPS indicates alveolar soft part sarcoma; CCS, clear cell sarcoma; tRCC, translocation-associated renal cell carcinoma.

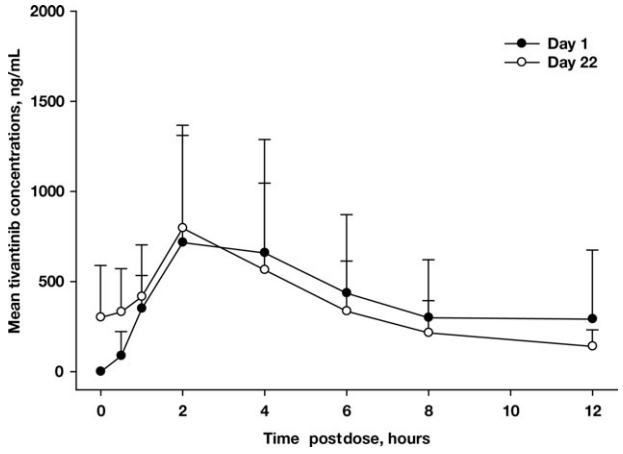

Figure 3. Mean concentration–time profiles of plasma tivantinib after single-dose (day 1) and multiple-dose (day 22) administration at either 120 mg twice daily (n = 6) or 360 mg twice daily.

positive, 4 (21%) were focally positive, 3 (16%) were weakly positive, and 2 (11%) were negative (Figure 4). By tumor type, 86% of RCC (6 of 7 cases), 14% of ASPS (1 of 7 cases), and 60% of CCS (3 of 5 cases) were positive for total MET protein expression. There were no obvious correlations between total MET protein expression levels in archival tumor samples and best response, change in tumor burden, or treatment duration. The tumor sample from the patient with CCS who had a PR was negative for MET protein expression.

DISCUSSION

MiT tumors are typically refractory to current chemotherapy and few treatment alternatives are currently in clinical development. Activation of MET by MiT proteins suggests a potential therapeutic strategy and provided the rationale for investigating tivantinib in this setting.

In the current study, 57% of patients had stable disease for at least 4 months, including the majority of patients with ASPS, and 1 patient with CCS had a PR. Median OS for the ITT population was 21 months but was not reached for the subgroup of patients with ASPS at a median follow-up of 12 months. By comparison, a retrospective analysis of outcomes for patients with ASPS (n = 15) who were receiving conventional treatment reported a median survival of 48 months and a 5-year OS rate of 48%.[31] In the current study, there was a 3-month increase in the median duration of therapy with tivantinib compared with the median duration of previous systemic therapy in patients with ASPS; however, it is unclear whether this difference was an effect of treatment or of the indolent nature of the disease.[32] Outcomes for patients with CCS in the current study did not differ substantially from those of a retrospective analysis of patients treated with systemic chemotherapy that reported a PR in 1 of 24 patients and SD in 9 patients, with a median PFS of 2.8 months.[33] However, these comparisons to observational historical data outside of a clinical trial must be interpreted with caution.

The PK parameters indicated no apparent tivantinib accumulation in plasma after multiple dose administrations of tivantinib 120 mg (crystalline A formulation); however, interpretation of these results is limited by the small sample size and high interpatient variability. Likewise, PK data for tivantinib 360 mg, the established BID dose,[28] were not conclusive because of small sample size. This study represents the first available PK data for younger cancer patients treated with tivantinib, including 4 patients $\leq$17 years of age.

Table 6. Pharmacokinetic Parameters of Tivantinib

Pharmacokinetic Parameter	Tivantinib Dose Cohort			
	120 mg BID		360 mg BID	
	Day 1	Day 22	Day 1	Day 22
AUC_{last}, ng·h/mL	(n = 6)	(n = 5)	(n = 2)	(n = 1)
Mean (SD)	4448 (3965)	4842 (3226)	8367 (7322)	1814
Geometric mean (CV%)	3032 (128)	3909 (89)	6573 (136)	1814
$AUC_{0\text{-}12}$, ng·h/mL	(n = 6)	(n = 5)	(n = 2)	(n = 1)
Mean (SD)	4807 (4345)	4976 (3311)	8480 (7482)	1916
Geometric mean (CV%)	3222 (132)	4017 (89)	6627 (138)	1916
C_{max}, ng/mL	(n = 6)	(n = 5)	(n = 2)	(n = 1)
Mean (SD)	788 (616)	920 (555)	1251 (607)	421
Geometric mean (CV%)	616 (88)	793 (66)	1175 (54)	421
$t_{1/2}$, h	(n = 3)	(n = 3)	(n = 1)	(n = 1)
Median (range)	2.5 (2.5, 2.9)	3.5 (3.2, 3.6)	3.0	4.3

$AUC_{0\text{-}12}$ indicates area under the plasma concentration–time curve from 0 to 12 hours; AUC_{last}, area under the plasma concentration–time curve from time 0 to time of last measureable concentration; BID, twice daily; C_{max}, maximum (peak) plasma concentration; CV%, coefficient of variation; SD, standard deviation; $t_{1/2}$, elimination half-life.

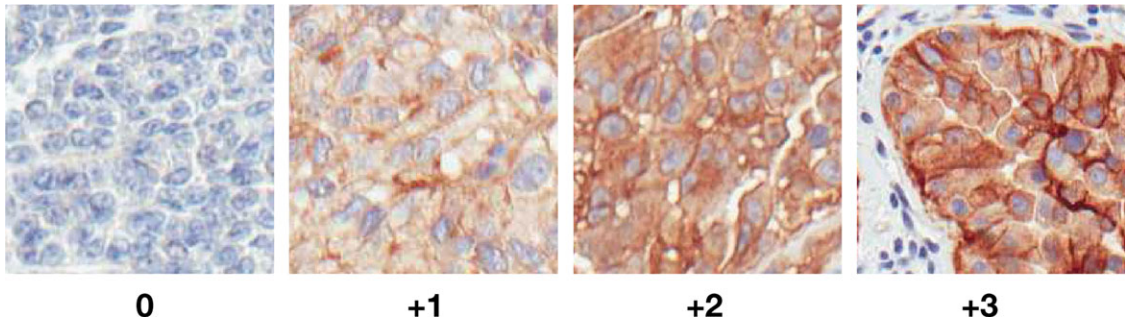

Figure 4. Total MET protein expression evaluated by immunohistochemical analysis of archival tumor samples. Staining patterns are shown for MET ranging from negative (0) to strong positive (+3).

Compelling laboratory evidence links MET activity to the neoplastic transformation and maintenance of MiT tumors, and it is unclear why the antitumor activity observed with tivantinib in this study was low. Baseline expression of total MET in archival tumor samples was strongly positive or focally positive in the majority of patients tested; however, there was no obvious correlation between MET expression in archival tumor samples and tivantinib clinical activity. One possible explanation is that MET may play a greater role in cell culture and xenograft systems, perhaps through the ex vivo selection process, and may play a less critical role in human tumors. Alternatively, MET inhibition may confer primarily tumor growth inhibition rather than tumor regression; therefore, it would be difficult to demonstrate clinical benefit in a nonrandomized study. On the other hand, MET activity in tumor tissue may have been incompletely inhibited by tivantinib treatment; unfortunately, paired tumor biopsies and PD studies to assess MET pathway suppression were not performed because most patients had metastases that are difficult to biopsy, primarily lung metastases. Finally, although MiT family members can induce expression of MET in preclinical models, other key factors also likely drive tumor proliferation and survival, such as the epidermal growth factor receptor (EGFR) family member HER3, which is commonly activated in CCS and may contribute to tumorigenesis and resistance to MET inhibitors.[34-36]

Several groups have recently reported responses in MiT tumors treated with multitargeted kinase inhibitors that block vascular endothelial growth factor receptor 2 (VEGFR2). Decreases in tumor dimensions and/or density were reported in ASPS and CCS treated with sunitinib[37-40] or cediranib.[41] Moreover, minor responses have been reported in a patient with ASPS treated with bevacizumab,[42] and both sunitinib and sorafenib have been reported to have activity in patients with tRCC.[43,44] These reports may provide a rationale for future studies

exploring MET inhibitors in combination with EGFR and/or VEGFR pathway antagonists for the treatment of MiT tumors. The combination of tivantinib with EGFR inhibitors has already shown promising clinical activity in phase 1 and 2 trials in patients with non–small cell lung cancer and colorectal cancer.[45-47] As our understanding of the interplay among these pathways increases, it may also be possible to identify subgroups of patients with MiT tumors that are more likely to benefit from specific combinations of selectively targeted anticancer therapies.

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CONFLICT OF INTEREST DISCLOSURE

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