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A Phase 1 Study of the c-Met Inhibitor, Tivantinib (ARQ197) in Children with Relapsed or Refractory Solid Tumors: A Children's Oncology Group Study Phase 1 and Pilot Consortium Trial (ADV1111)

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Abstract

Background—The c-Met receptor tyrosine kinase is dysregulated in many pediatric cancers. Tivantinib is an oral small molecule that inhibits the c-Met receptor tyrosine kinase. A phase I and pharmacokinetic (PK) trial evaluating tivantinib was conducted in children with relapsed/refractory solid tumors.

Methods—Oral tivantinib capsules were administered bid with food, continuously in 28-day cycles. Dose levels 170, 200 and 240 mg/m²/dose were evaluated using a rolling 6 design (Part A). In Part B, subjects received tivantinib powder sprinkled on food at the recommended phase 2 dose (RP2D) from Part A. PK, CYP2C19 genotyping, and baseline tumor tissue c-Met expression were analyzed.

Results—Thirty-six patients were enrolled: 20 in Part A, 6 to a PK expansion cohort, and 10 to Part B. Fifteen patients had primary CNS tumors and 21 had solid tumors. In Part A, there were no

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DLTs. One grade 4 intracranial hemorrhage occurred in a patient with a progressive brain tumor in the expanded PK cohort (240 mg/m²). PK analysis showed marked inter-patient variability (20-fold) in the C_{max} and AUC_{0–8h} across all dose levels. Sprinkling tivantinib powder over food did not alter exposure. Membranous and total c-Met expression was moderate (2), low (4), or not detected (26). Two patients had stable disease as best response.

Conclusions—The RP2D of tivantinib given with food in children with refractory solid tumors is 240 mg/m²/dose. PK of tivantinib in children demonstrated high variability. Objective responses were not observed in this phase I trial.

Keywords

c-Met; pediatric solid tumor; phase I; tivantinib

Introduction

Tivantinib is an oral small molecule that inhibits the c-Met receptor tyrosine kinase with an IC₅₀ of approximately 20 to 50 nM, in an ATP-independent fashion. (1–6) More recent publications suggest a c-Met independent mechanism of tumor cytotoxicity that involves anti-mitotic effects for tivantinib. (2–5)

Early adult phase 1 and 2 single agent tivantinib studies (ARQ 197–101, 103, 204, 205) evaluated doses extending up to 400 mg PO bid. A maximum tolerated dose (MTD) of 300 mg PO bid (approximately 170 mg/m²/dose) was established with the amorphous form adjusted to 360 mg PO bid (approximately 210 mg/m²/dose) for the currently available crystalline form. (6, 60–62) The early trials in adults demonstrated a favorable safety profile for tivantinib, with the most common adverse events in the first 175 patients treated being fatigue (42.9%), nausea (28.6%), vomiting (21.1%), anemia (18.3%), anorexia (16.0%), diarrhea (15.4%), pyrexia (12.0%), peripheral edema (11.4%), abdominal pain (10.3%), and back pain (10.9%). In addition, there were a total of 17 episodes (all grade 1) of sinus bradycardia reported in 6 of 175 (3.4%) patients. Serious adverse events were uncommon (17; 5.1%), and included 7 myelosuppression events in 5 patients and 5 gastrointestinal events in 2 patients. DLTs from single agent tivantinib included febrile neutropenia (2), thrombocytopenia (1), leukopenia (1), neutropenia (1), vomiting (1), dehydration (1), fatigue (1), mucosal inflammation (1), and palmar-plantar erythrodysesthesia syndrome (1). (7–10)

When considering the scope of pediatric and adolescent tumors affected by aberrant c-Met signaling, (11–41) as well as the encouraging preliminary results of studies using c-Met inhibition strategies, (7, 42–51) exploration of c-Met inhibition in pediatric patients has emerged as an important focus of clinical investigation.

We now report the results of a phase 1 trial of tivantinib in pediatric patients with relapsed or refractory solid tumors. Goals of this trial were to define a recommended dose for subsequent Phase 2 pediatric studies, describe the pharmacokinetics (PK) of tivantinib in pediatric patients when administered as either a solid or powder form with food, and to preliminarily investigate any impact of CYP2C19 genotype and c-Met tumor expression on PK or clinical parameters.

Materials and Methods

Patient eligibility

Eligible patients were > 12 months and ≤ 21 years of age with a histological diagnosis of cancer. Patients must have had either measurable or evaluable disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. Patients must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy and have undergone appropriate washout periods for biologic or short acting growth factors (7 days), long-acting growth factor (14 days), myelosuppressive chemotherapy (21 days), nitrosurea or immunotherapy (42 days), or monoclonal antibodies (3 half-lives). At least 14 days must have elapsed since local palliative XRT (small port) and at least 150 days must have elapsed if prior TBI, craniospinal XRT or ≥ 50% radiation of pelvis. At least 42 days must have elapsed if other substantial bone marrow radiation was given, and 84 days since stem cell infusion without TBI. Patients may not have received prior therapy with tivantinib.

Organ function requirements included adequate bone marrow function (absolute neutrophil count (ANC) ≥ 1000/mm³ and platelet count ≥ 100,000/mm³ (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment). Patients with known bone marrow involvement were eligible for study but were not evaluable for hematological toxicity provided they met these hematologic parameters with the exception of transfusion independence. In each cohort, at least 5 of every 6 patients with a solid tumor must have been evaluable for hematologic toxicity for the dose escalation part of the study. Adequate renal function (creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m² or predefined serum creatinine meeting age-appropriate levels), and adequate liver function defined as bilirubin (sum of conjugated + unconjugated) ≤ 1.5 times upper limit of normal (ULN) for age, SGPT (ALT) ≤ 110 U/L, serum albumin ≥ 2 g/dL, were required.

Exclusion criteria included pregnant or breast-feeding women, patients with active graft vs host disease, patients receiving corticosteroids who were not on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment, patients who were currently receiving another investigational drug or another anti-cancer agent or any of the following drugs: cyclosporine, tacrolimus or other agents to prevent graft vs host disease post bone marrow transplant, and CYP 2C19 substrates, inducers, or inhibitors for at least 24 hours prior to enrollment. Patients in Part A were required to be able to swallow capsules whole. Patients with an uncontrolled infection or who had received prior solid organ transplantation were excluded. In addition, patients with ≥ grade 2 sinus bradycardia or with a known history of ≥ grade 2 cardiac arrhythmia were not eligible.

All patients and/or their parents or legally authorized representatives signed a written informed consent. Assent, when appropriate, was obtained according to institutional guidelines. All participating institutions were required to have protocol IRB approval prior to patient enrollments.

Trial design

The primary objectives for this study were to estimate the maximum tolerated dose (MTD) and/or RP2D of tivantinib administered orally twice daily to children with refractory solid tumors; to define and describe the toxicities of tivantinib administered on this schedule, and to characterize the pharmacokinetics of tivantinib (capsule as well as powder formulation) in children with refractory cancer. Secondary aims were to preliminarily define the antitumor activity of tivantinib within the confines of a phase 1 study, to preliminarily investigate whether CYP2C19 polymorphisms impact pharmacokinetics or toxicity of tivantinib in pediatric subjects, and to preliminarily investigate whether tumor c-Met expression correlates with clinical response to tivantinib.

A rolling-six design was used for dose escalation, as previously described. (52) Dose levels 1 – 3 were 170 mg/m²/dose, 200 mg/m²/dose, and 240 mg/m²/dose, respectively. Patients in Part B of the study were treated at the MTD or RP2D found in Part A of this trial. Intra-patient dose escalation was not allowed.

Tivantinib (60 mg capsules) was supplied by Daiichi Sankyo and distributed by the NCI CTEP Pharmaceutical Management Branch under IND 112603. A dosing nomogram was used to prescribe dose based on body surface area (BSA) at each dose level. For Part A intact tivantinib capsules were administered with food, in part B the 60 mg capsules were opened and powder sprinkled on food.

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Non-hematological dose-limiting toxicity was defined as any grade 3 or 4 non-hematological toxicity attributable to the investigational agent with the specific exclusion of: grade 3 nausea and vomiting of < 3 days duration, grade 3 liver enzyme elevation (ALT, AST or GGT) that returns to levels that meet initial eligibility criteria or baseline within 7 days, grade 3 or 4 fever < 5 days duration, grade 3 infection < 5 days duration, grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation. Any grade 2 non-hematological toxicity that persisted for ≥ 7 days, and was considered sufficiently medically significant, or sufficiently intolerable by patients that it required treatment interruption, was considered a DLT. Hematological dose limiting toxicity was defined in patients evaluable for hematological toxicity as: grade 4 thrombocytopenia (platelet count < 25,000/mm³) or grade 4 neutropenia not due to malignant infiltration. Grade 4 fever of <5 days duration, with or without grade 1–3 neutropenia was not considered a DLT.

Supportive care, including appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care were used as necessary. Growth factors to support platelet or white cell number or function were not used. CYP2C19 substrates (omeprazole, esoprazole, lansoprazole, pantoprazole) or inducers (rifampin) were not permitted on study. CYP2C19 inhibitors (fluvoxamine or moclobemide) were avoided if possible. CYP3A4 inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), or voriconazole) or inducers (rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort) were not permitted on study.

Patient Monitoring

Clinical (history, physical exam and vital signs) and laboratory (complete blood counts with platelet and differential, electrolytes (including calcium, phosphorous and magnesium), creatinine, ALT, bilirubin) assessments were required at least weekly during cycle 1.

Albumin levels were monitored every cycle. A 12-lead EKG was obtained prior to therapy initiation and 2–3 hours after the first dose on day 1 of cycle 1 in all patients.

Pharmacokinetics

Blood samples (2–3 ml) were collected in pre-chilled polyethylene tubes containing potassium EDTA. After thorough mixing, plasma was separated by centrifugation (1500g, 10 min, 4°C) and transferred to a polypropylene cryogenic storage vial and stored frozen at –20°C. Blood samples were collected immediately before the initial dose of tivantinib on Day 1 of Cycle 1; at 1, 2, 4, 6 and 8–12 hours after the initial dose; and at the end of Cycle 1 prior to the morning dose on Day 1, Cycle 2. Plasma concentrations of tivantinib were measured by Covance Bioanalytical Services (Indianapolis, IN) using validated assays by HPLC with MS/MS detection in plasma samples. The lower limit of quantification and linear range were 20 ng/ml and 20 – 10,000 ng/ml, respectively. The precision defined as the percent relative standard deviation between the calculated and expected values and accuracy defined as the percent of the expected value were <5% and >94%, respectively, for the quality control and calibration curve standards. Pharmacokinetic parameters for tivantinib were calculated using standard non-compartmental methods with Phoenix WinNonlin 1.3 (Pharsight Corporation, Mountain View, CA). The apparent terminal elimination rate constants (k_z) were determined by linear least-squares regression through the 4 – 8 h plasma-concentration time points. The apparent elimination half-life ($t_{1/2}$) was calculated as $0.693/k_z$. Areas under the plasma concentration-time curves over the Pharmacokinetic study period (AUC_{0-8h}) were determined using the linear trapezoidal rule from time zero to time 8 h. Extrapolated areas under the plasma concentration-time curve through infinite time ($AUC_{8h-\infty}$) were calculated using the equation C_{8h}/k_z and added to AUC_{0-8h} to yield $AUC_{0-\infty}$. The clearance (CL) of tivantinib was calculated as dose/ $AUC_{0-\infty}$.

Pharmacogenomics

Consenting patients provided whole blood (5 ml) in EDTA tubes prior to treatment in an attempt to correlate three CYP2C19 polymorphisms of interest with pharmacokinetics, toxicity and response to protocol therapy. DNA was extracted by QIAamp DNA Blood Mini Kit (Qiagen) as per the manufacturer's instructions. Methods were validated with a panel of 60 Caucasian DNA samples from the Coriell Institute. Positive and negative controls were included for each analysis. The specific regions containing the CYP2C19 *2 (rs4244285), CYP2C19 *3 (rs4986893) and CYP2C19 *17 (rs12248560) polymorphisms were amplified and detected on a Bio-Rad CFX384 Real-Time PCR detection system. The real time PCR methods were validated against a standard PCR reaction with sequence detection of the polymorphisms. The CYP2C19 phenotype was defined using a published algorithm. (53)

Pharmacodynamics

Tissue from original diagnosis, relapse, and/or any subsequent resections or biopsies prior to treatment on this protocol were submitted to Affiliated Pathology Services for tumor membranous c-Met expression analysis (Ventana antibody, cat #790-4430). Tissue specimens (paraffin-embedded or fresh frozen tissue) were prioritized, but if a block was not available, then a minimum of 10 unstained slides were used for analyses. Scoring from 0–3 was provided for negative, weak, moderate or strong scoring respectively.

Criteria for assessment of response

Imaging studies to assess response were performed prior to the 2nd cycle, every other cycle twice, and then every 3rd cycle thereafter. Response assessments were based on revised RECIST criteria (version 1.1). (54) Standard RECIST definitions for the best response were incorporated, and any PR, CR or prolonged stable disease (greater than 6 months) required central radiology review.

Results

Patients

Thirty-six patients were enrolled with a median age of 11.5 years (range 3–21): 20 in Part A, 6 to a PK expansion cohort, and 10 to Part B. Patient characteristics are summarized in Table I. Fifteen patients had primary CNS tumors and 21 had solid tumors. All patients enrolled had at least one prior therapy including chemotherapy, radiation or both.

Toxicities

Twenty-six patients were evaluable for toxicity assessment. Ten patients (4 in Part A, 3 in the expanded PK cohort, and 3 in Part B) were not fully evaluable as they did not receive 80% of the prescribed study drug. None of the 10 toxicity inevaluable patients experienced a DLT. Likewise there were no DLTs in the 16 evaluable patients in Part A (0/5, 0/6 and 0/5 pts at dose levels 1–3, respectively). There was 1 grade 4 intracranial hemorrhage in a patient with a progressive brain tumor in the expanded PK cohort (240 mg/m²) (Table II). None dose-limiting grade 3 and 4 toxicities at least possibly attributable to tivantinib included rare grade 3 myelosuppression [lymphopenia (2), anemia (1)]. Grade 1 or 2 toxicities occurring in > 10% of evaluable patients included anemia (12), lymphopenia (8), leukopenia (5), neutropenia (5), fatigue (8), vomiting (5), nausea (5), hypoalbuminemia (4), and thrombocytopenia (3) (Table III).

Response

Of the 32 patients evaluable for response, two had stable disease as their best response, one with neuroblastoma (8 cycles) and 1 with medulloblastoma (15 cycles). Four patients were not evaluable for response due to withdrawal of consent during cycle 1 (1), refusal prior to end of cycle 1 (1), DLT (intracranial hemorrhage) prior to end of cycle 1 (1), and rapid early progressive disease (1). There were no objective responses to tivantinib therapy.

Pharmacokinetics and Pharmacogenetics

Thirty-five patients participated in the pharmacokinetics study; the results are summarized in Table IV, and a graph of AUC_{0-8h} vs BSA-adjusted dose is shown in Figure 1A. Peak plasma concentrations were achieved approximately 2 hrs (range, 1 – 8 hrs) after the oral dose. The apparent elimination half-life was evaluable in 29 of 35 patients and the median value was 2.7 hrs (range, 1.2 – 18.0 hrs). There was substantial inter-patient variability 20-fold) in the C_{max} and AUC_{0-8h} values across all dose levels. As a result, a dose-proportional increase in C_{max} and AUC_{0-8h} values was not observed (Table IV and Figure 1A). Since the apparent oral clearance could not be accurately calculated, the AUC_{0-8h} was normalized for the administered dose ($AUC_{0-8h}/Dose$) to assess factors that might contribute to the high inter-patient variability in pharmacokinetics. The similar median $AUC_{0-8h}/Dose$ values across dose levels (Table IV) were consistent with linear PKs for tivantinib. The median $AUC_{0-8h}/Dose$ values were also similar for females and males (22.1 vs 22.7), as well as for age ≤ 12 compared to age >12 years of age (24.3 vs 20.2). Finally, the powder formulation appeared to yield 43% higher median exposure compared with tivantinib than the capsule formulation, though such differences were not statistically significant ($p=0.11$) (Table IV).

Since tivantinib is metabolized by CYP2C19, which is known for genetic polymorphisms that can affect the pharmacokinetics of the drugs that are CYP2C19 substrates, we determined CYP2C19 genotypes for the three most common variants *2, *3 and *17) in 25 patients who enrolled in the optional pharmacogenomics study. The *2 and *3 variants result in reduced metabolism, while the *17 variant leads to increased metabolism. In this population, none of the patients had a *3 gene polymorphism. The distribution of the CYP2C19 genotypes was CYP2C19*1/*1 ($n=14$); CYP2C19 *2/*2 ($n=1$); CYP2C19*1/*2 ($n=4$), CYP2C19*1/*2/*17 ($n=1$); CYP2C19*1/*17 ($n=8$); CYP2C19*17/*17 ($n=2$). These genotypes comprised four phenotypes: poor metabolizer (PM, CYP2C19 *2/*2), intermediate metabolizer (IM, CYP2C19*1/*2 and CYP2C19*1/*2/*17), extensive metabolizer (EM, CYP2C19*1/*1) and ultra-rapid metabolizers (UM, CYP2C19*1/*17 and CYP2C19*17/*17) as shown in Table IV (53). Median (range) $AUC_{0-8h}/Dose$ were 285.5 for the PM ($n=1$), 40.5 (15.1–46.0) for IM ($n=5$), 23.4 (3.1–115.5) for EM ($n=14$), and 20.0 (2.8–128.5) for UM ($n=10$) (Figure 1B). Of note, high AUC_{0-8h} values were observed for three patients at the lower dose levels; 1 PM, 1 EM and 1 UM.

Tumor c-Met expression

Thirty-three patients had tissue available at enrollment and the required tissue sample for c-Met analysis was submitted for 32 of them. One site discovered, after enrollment, that tissue samples were not available, and could not submit. Membranous and total c-Met expression was high (0), moderate (2), low (4), or not detected (26). The two patients with stable disease had either low or undetectable c-Met expression.

Discussion

The *Met* oncogene was first identified in 1984 in a chemically transformed osteosarcoma cell line. (55) *Met* encodes for a membrane-spanning receptor tyrosine kinase which triggers multiple intracellular processes leading to proliferation, survival, motility, angiogenesis, and

invasion. (56, 57) The sole ligand for c-Met is hepatocyte growth factor (HGF), also called scatter factor. HGF and c-Met are widely expressed in mesenchymal and epithelial tissues in early development, and gene deletion results in lethal effects on embryogenesis. Expression in normal tissues persists even in adult life, as these genes are essential for survival and proliferation of epithelial cells participating in repair and regeneration. However, if this pathway becomes dysregulated, uncontrolled proliferation occurs and leads to a variety of malignancies, including both carcinomas and non-epithelial tumors. (56)

c-Met expression can be up-regulated in tumor cells by epigenetic factors such as growth factors secreted by tumors, activation of other oncogenes, and hypoxia, resulting in paracrine and/or autocrine loop formation. (58–60) Activating germline mutations have been reported in some tumors such as hereditary renal papillary carcinoma, (61) and somatic mutations have also been documented in childhood hepatocellular carcinoma. (62) While tumors with activating mutations may be predicted to be most sensitive to c-Met inhibition, antitumor activity in preclinical settings has been demonstrated in models without defined mutations. (57) The varied mechanisms of activation and lack of redundancy of this pathway, together with effects on tumor-associated angiogenesis, suggest that a mutation may not necessarily be required in order to observe clinical benefit. Importantly, c-Met/HGF dysregulation in common pediatric solid tumors has been well described, with evidence of both c-Met and HGF over-expression, associations with poorer outcome and/or higher tumor grade, and with demonstrable impact on downstream tumor signaling impacting chemoresistance, tumor growth, tumor invasiveness, and tumor angiogenesis (Table V). Targeting c-Met in pediatric solid tumors has therefore been of interest to the pediatric oncology community and the Children's Oncology Group (COG), with several studies to assess tolerance and benefit of known HGF/c-Met inhibitors being conducted. (63–65, NCT01606878, NCT01709435)

In this phase 1 clinical trial in children and adolescents with relapsed/refractory solid tumors, including CNS tumors, we demonstrated that tivantinib, either in tablet or powder form, is well tolerated in children when delivered with food. As seen in adult trials, adverse events reported in > 10% of patients included fatigue, nausea and vomiting, as well as hypoalbuminemia, and low-grade myelosuppression. Sinus bradycardia was not readily apparent in any patient treated on study. A single DLT was limited to intracranial (intratumoral) hemorrhage in a patient with a progressive brain tumor.

Across all dose levels, there was substantial inter-patient variability in the first dose $C_{\max}$ and AUC_{0-8h} . Given the large range in values and small number of patients treated at each dose level, a dose-dependent increase for $C_{\max}$ and AUC_{0-8h} was not clearly observed. While tivantinib is a CYP2C19 substrate, this variability could not be explained by metabolizer phenotype with the exception of a single patient with a poor metabolizer genotype (PM) treated at the 170 mg/m² dose level who had high $C_{\max}$ and AUC_{0-8h} values. These results are similar to the results observed in two adult Phase 1 studies from Japan where there was substantial overlap in pharmacokinetic parameters between the groups. (66, 67) Furthermore, tivantinib pharmacokinetics in children did not appear to be affected by age or sex. Finally, sprinkling tivantinib powder over food may increase exposure by only a small amount, and would provide a useful means of administering the drug to children who have difficulty swallowing.

Additional pharmacodynamic analyses in this trial demonstrated infrequent expression of c-Met on patient's tumor samples. However, it is possible that c-Met expression can be underestimated when tumor preparation and testing conditions are not optimized. Nonetheless, correlations of response with tumor c-Met expression were limited by poor response, infrequent expression, and limited patient numbers.

In conclusion, the RP2D of tivantinib capsules and powder in pediatric solid tumor patients is 240 mg/m²/dose given by mouth twice daily. While tivantinib was well tolerated, pharmacokinetic exposures demonstrated high variability, and single agent activity was not demonstrated in this phase 1 trial. The COG remains interested in pursuing HGF/c-Met inhibition strategies in select pediatric and adolescent solid tumors, with several c-Met targeting therapy trials ongoing. (NCT01606878, NCT01709435) Whether single agent activity of c-Met inhibitors or combination therapy proves beneficial in pediatric solid tumor patients remains to be determined.

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Abbreviations

ANC	Absolute Neutrophil Count
BSA	Body Surface Area
COG	Children's Oncology Group
DLT	Dose Limiting Toxicity
EM	Extensive Metabolizer
HGF	Hepatocyte Growth Factor
IM	Intermediate Metabolizer
MTD	Maximum Tolerated Dose
PK	Pharmacokinetic
PM	Poor Metabolizer
RP2D	Recommended Phase 2 Dose
TBI	Total Body Radiation
ULN	Upper Limit of Normal
UM	Ultra-rapid Metabolizer

XRT Radiation

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Figure 1.

(A) The exposure (AUC_{0-8h}) after the first dose of tivantinib for patients in Part A ($n=26$, intact capsules administered with food) is presented on left panel, and Part B ($n=9$, powder sprinkled on food) is presented in right panel. Due to the high variability in exposure and overlap in measured exposure among dose levels (170, 200 and 240 mg/m²/dose) the BSA corrected dose (mg/m²) was calculated by dividing the actual dose administered by the patient's BSA to demonstrate the relationship of exposure to actual dose delivered. Symbols represent CYP2C19 phenotype of each patient. (B) For each dose level, the dose normalized exposure ($AUC/dose$) is presented for each patient by CYP2C19 phenotype. The single

patient who was identified as a poor metabolizer (PM) received 170 mg/m² and had highest exposure (AUC/dose).

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Table 1

Patient Characteristics for eligible Patients (n=36)

Characteristic	Number (%)
Age (years)	
Median	11.5
Range	3 – 21
Sex	
Male	24 (66.7)
Female	12 (33.3)
Race	
White	24 (66.7)
Asian	1 (2.8)
American Indian or Alaska Native	0 (0)
Black or African American	9 (25.0)
Unknown	2 (5.6)
Ethnicity	
Non-Hispanic	30 (83.3)
Hispanic	5 (13.9)
Unknown	1 (2.8)
Diagnosis	
Central Nervous System Tumors	15
(Glioma (4); Medulloblastoma (4); ependymoma (2); anaplastic ependymoma (1) myxopapillary ependymoma (1); Atypical teritoid rhabdoid tumor (1); primitive neuroectodermal tumor (1))	
Sarcoma	14
(Ewing Sarcoma (4); Osteosarcoma (4); embryonal rhabdomyosarcoma (2); alveolar rhabdomyosarcoma (1); clear cell sarcoma of soft parts (1); synovial sarcoma (1); spindle cell sarcoma (1))	
Embryonal Tumors	6
(Wilms tumor (2); Neuroblastoma (2) ganglioneuroblastoma (1); hepatoblastoma (1))	
Carcinoma	1
Fibrolamellar Hepatocellular Carcinoma (1)	
Prior Therapy	
Chemotherapy Regimens	
N (%)	32 (88.9)
Median	2
Range	1 – 8
Radiation Regimens	
N (%)	30 (83.3)
Median	1

Characteristic	Number (%)
Range	1 – 3

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Table 2

Dose Limiting Toxicities (DLTs)

PART	Dose Level	# Entered	# Evaluable	# with DLT	DLT
A	170 mg/m ²	6	5	0	
	200 mg/m ²	7	6	0	
	240 mg/m ²	7	5	0	
A-PK	240 mg/m ²	6	3	1	Intracranial hemorrhage
B	240 mg/m ²	10	7	0	

Table 3

Non-Dose Limiting Toxicities in evaluable patients (n=26)

Grade	Cycle 1 (Total, 26 Cycles)								Cycle 2 to 15 (Total, 45 Cycles)							
	Hematologic Toxicities				Non-Hematologic Toxicities*				Hematologic Toxicities				Non-Hematologic Toxicities*			
	Maximum Grade of Toxicity				Maximum Grade of Toxicity				Maximum Grade of Toxicity				Maximum Grade of Toxicity			
	Gr.1	Gr.2	Gr.3	Gr.4	Gr.1	Gr.2	Gr.3	Gr.4	Gr.1	Gr.2	Gr.3	Gr.4	Gr.1	Gr.2	Gr.3	Gr.4
Toxicity Type																
Anemia	9	3	1										4			
Fatigue					5	3										
Hemoglobin increased												1				
Hypoalbuminemia					2	2										
Lymphocyte count decreased	3	5	2						2	2						
Lymphocyte count increased										1						
Nausea					4	1										
Neutrophil count decreased	3	2								2						
Platelet count decreased	3								2							
Vomiting					4	1										
White blood cell decreased	5	2							3							

* **Observed in more than 10 percent of evaluable patients (n=26).** Toxicities that occurred in more than as determined in the first cycle of protocol therapy and attribution is in 'PROBABLE'; or 'POSSIBLE', or 'DEFINITE'.

Table 4

Summary of Tivantinib Pharmacokinetic Parameters (median (range)) on Day 1, Cycle 1

Dose (mg/m ²)	Capsule			Powder
	170 (n=6)*	200 (n=7)*	240 (n=13)*	240 (n=9)*
T _{max} (h)	4.0 (2.0–8.0)	4.0 (1.0–8.0)	2.0 (1.0–8.0)	2.0 (1.0–6.0)
C _{max} (µg/ml)	0.88 (0.52–9.93)	2.18 (0.16–6.94)	1.30 (0.18 – 2.97)	1.53 (0.68–5.13)
Half-life (h)	2.3 (1.8–8.9)	3.6 (2.2–5.6)	3.0 (1.2–18.0)	2.7 (1.5–6.9)
AUC _{0–8h} (µg/ml × hr)	3.82 (2.14–51.4)	9.47 (0.57–30.8)	5.63 (0.75–16.1)	7.30 (3.44–23.4)
AUC _{0–8h} /Dose (× 10 ⁶)	21.1 (11.7–285)	26.3 (3.2–129)	20.2 (2.8–44.6)	25.4 (11.5–64.9)
CYP2C19 (PM/IM/EM/UM)	1/0/2/2	0/0/4/2	0/3/4/4	0/2/4/2

* Half-life- 170 (n=2); 200 (n=3); 240 (n=8); 240 (n=6). Genotype- 170 (n=5); 200 (n=6); 240 (n=11); 240 (n=8). Metabolizer phenotypes: PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; UM, ultra metabolizer.

Table 5

c-Met and HGF in select pediatric and adolescent solid tumors

	RMS	STS	OS	Medullo	HGG	NBL	WT	HBL	TRCC	Ref
c-Met expression	Y	Y	Y	Y	Y	Y	Y	Y	Y	15, 17, 18, 19, 20, 22–25, 27, 28, 29, 24, 35, 37, 38
HGF expression	Y	Y		Y	Y	Y	Y	Y		16, 23–25, 27–29, 34, 37, 38, 43, 44
c-Met and poor prognosis or grade	Y	Y		Y	Y					16–18, 23, 27, 29, 34
HGF and poor prognosis or grade	Y	Y		Y	Y					16, 23, 27, 29, 34
HGF/c-MET pathway	Ass. with PAX3-FKHR; Promotes chemo resistance		Oncogenic and activating of MAPK	Promotes chemo-resistance, invasiveness	Hypoxia induced, promotes cell migration, tumor growth, and tumor angiogenesis	Stimulates invasion	Ass. With tumor proliferation	Promotes chemo-resistance (+)	Translocation–upregulates c-Met via direct gene promoter binding	16, 17, 20, 21, 26–28,30–32, 36, 37, 39, 43, 44

RMS = rhabdomyosarcoma; STS = soft tissue sarcoma; OS= osteosarcoma; Medullo = Medulloblastoma; HGG = High Grade Glioma; NBL = neuroblastoma; WT = Wilms tumor; HBL = hepatoblastoma; TRCC = translocation renal cell carcinoma