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A Phase I Trial of TB-403 in Relapsed Medulloblastoma, Neuroblastoma, Ewing Sarcoma, and Alveolar Rhabdomyosarcoma

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Conflict of Interest Statement

GSS serves on the scientific advisory boards for Y-mAbs Therapeutics, Illumina, and California Cryobank. JK serves on the scientific advisory board for Y-mAbs Therapeutics. RKJ serves as a consultant for Elpis, Innocoll, SPARC, SynDevRx and Twenty-eight-Sevan, owns equity in Accurius, Enlight and SynDevRx and serves on the Boards of Trustees of Tekla Healthcare Investors, Tekla Life Sciences Investors, Tekla Healthcare Opportunities Fund and Tekla World Healthcare Fund and received a grant from Boehringer-Ingelheim. DGD received consultant fees from Innocoll and has research grants from Bayer, Exelixis, BMS and Surface Oncology. ADD and LG are employees of Oncurious NV. The remaining authors have no further disclosures.

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Abstract

PURPOSE: Placental growth factor (PlGF) and its receptor neuropilin 1 (NRP-1) are elevated in malignant embryonal tumors and mediate tumor progression by promoting cell proliferation, survival, and metastasis. TB-403 is a blocking monoclonal antibody against PlGF that inhibits tumor growth and increases survival in orthotopic medulloblastoma (MB) models.

EXPERIMENTAL DESIGN: We conducted a phase 1, open-label, multicenter, dose-escalation study of TB-403 in pediatric subjects with relapsed or refractory cancers. The study involved 4 dose levels (20 mg/kg, 50 mg/kg, 100 mg/kg, 175 mg/kg) using a 3+3 dose-escalation scheme. Subjects received 2 doses of TB-403 (Days 1 and 15) per cycle. After cycle 1, temozolomide or etoposide could be added. The primary objective was to determine the maximum tolerated dose (MTD) of TB-403 monotherapy during a dose-limiting toxicity (DLT) assessment period. The secondary and exploratory objectives included efficacy, drug pharmacokinetics (PK) and detection of pharmacodynamic biomarkers.

RESULTS: Fifteen subjects were treated in 4 dose levels. All subjects received 2 doses of TB-403 in cycle 1. Five serious treatment emergent adverse events were reported in 3 subjects, but MTD was not reached. While no complete nor partial responses were observed, 7 of 11 relapsed MB subjects experienced stable disease, which persisted for more than 100 days in 4 out of 7 subjects.

CONCLUSIONS: TB-403 was safe and well tolerated at all dose levels. No MTD was reached. The results look encouraging and therefore warrant further evaluation of efficacy in pediatric subjects with MB.

Statement of translational relevance

Previous treatment strategies for medulloblastoma have shown moderate improvement in response. However, the long-term overall survival remains disappointing, and many survivors have profound long-term complications. Therefore, there is a tremendous need to develop novel, improved and safer therapeutic strategies for medulloblastoma. The critical tumor-stroma interactions mediated by the PlGF/NRP1 pathway make it an attractive target. We report a phase I, open-label, multicenter, dose-escalation study of the anti-PlGF antibody, TB-403, in pediatric subjects. TB403 treatment was well tolerated and induced stable disease in high risk, heavily pretreated relapsed medulloblastoma allowing for excellent quality of life. These findings indicate that treatment with TB-403 may represent a potentially transformative therapy for children with medulloblastoma and should be tested in larger studies.

Keywords

Pediatric Cancers; Medulloblastoma; Phase I; Placental Growth Factor (PlGF); Pharmacokinetics/pharmacodynamics

INTRODUCTION

Medulloblastoma (MB), neuroblastoma (NB), Ewing sarcoma (ES) and alveolar rhabdomyosarcoma (ARMS) are malignant embryonal tumors characterized by primitive histopathology, rapid growth, and aggressive behavior. MB, NB, ES and ARMS show expression of markers such as the surface antigen B7-H3[1]. Expression of placental growth factor (PIGF) is observed in multiple different tumor types[2], including primitive embryonal tumors[3].

Using a panel of MB cell lines and MB xenograft mouse models, we previously demonstrated that PlGF and its receptor NRP-1 are overexpressed in MB, are required for the growth and progression of MB, and that blockade of PlGF and NRP1 resulted in direct anti-tumor effects *in vivo*, including tumor regression, decreased spinal metastasis and increased survival[3]. PlGF is secreted by the cerebellar stroma via tumor-derived Sonic hedgehog (Shh) and acts through NRP1 but not its co-receptor, vascular endothelial growth factor receptor 1 (VEGFR-1) to promote tumor cell survival. This critical tumor-stroma interaction (mediated by Shh, PlGF and NRP1 across MB subtypes) provides a compelling rationale for targeting the PlGF/ NRP1 pathway in MB subjects[4]. In addition, due to shared similarities among primitive embryonal tumors, blockade of PlGF/ NRP1 pathway may potentially have anti-tumor effects in tumors with similar PlGF/ NRP1 expression (*e.g.*, NB, ES and ARMS).

TB-403 is a blocking monoclonal antibody (mAb) directed against PlGF[5]. In MB, PlGF seems to act as a tumor growth factor by activating the extracellular signal-regulated kinase (Erk) signaling pathway that promotes cell proliferation, cell survival and metastasis[3]. Pre-incubation with TB-403 completely abolished the NRP1 -driven effect on Erk-1/2 phosphorylation in a cell-based assay[3]. Moreover, TB-403 inhibited primary tumor growth and spinal metastasis in mice with orthotopically implanted MB tumors, and mice treated with TB-403 survived significantly longer than untreated animals[3]. TB-403 showed a favorable toxicology profile in pre-clinical studies; moreover, clinical studies conducted in healthy volunteers and adult subjects with advanced cancer indicated that TB-403 was well tolerated with minimal side effects[6,7]. The lack of suitable treatment alternatives for advanced primitive embryonal tumors and poor outcome at recurrence together with favorable safety profile makes TB-403 a promising novel approach for therapy. Based on these data, we designed and conducted a phase I clinical trial of TB-403 in pediatric subjects with relapsed or refractory primitive embryonal tumors.

METHODS

Study Design

This was a Phase 1, open-label, multicenter, dose-escalation study with TB-403 in pediatric subjects with relapsed or refractory MB, NB, ES or ARMS. Subjects were enrolled onto trial from August 2016 to March 2020. This trial was approved by the Western Institutional Review Board as well as by local Institutional Review Boards. Prior to study entry, written informed consent for study participation was obtained (subjects or legal representative). All methods were performed in accordance with the principles of the Declaration of Helsinki,

the International Council for Harmonization guideline for Good Clinical Practice, and all applicable local regulatory requirements. Institutional Review Board approval was obtained. ClinicalTrials.gov Identifiers: NCT02748135.

A schematic diagram of the overall study design is provided in Figure 1A and of the dose-escalation scheme in Figure 1B. The study had 4 cohorts (corresponding to dose levels 20, 50, 100 & 175mg/kg respectively) using a 3+3 dose-escalation scheme. TB-403 was administered via intravenous (IV) infusion over 60–90 minutes. Subjects with MB, NB, ES or ARMS were enrolled into the first 3 cohorts; Cohort 4 included only subjects with MB. Disease evaluations were performed at study entry, after Cycle 1 of TB-403 alone, and then every 8 to 12 weeks.

Subjects received up to 2 doses of TB-403 on Days 1 and 15 of each 28-day cycle. In the event of drug-related toxicity, a delay up to 28 days from last dose of TB-403 was allowed for resolution of the toxicity to ≤ Grade 2. Subjects who required a > 28-day dosing interval for resolution of a drug-related toxicity to ≤ Grade 2 were discontinued from the study treatment.

In Cycle 1, subjects received TB-403 as a single agent and the DLT assessment period was 28 days. At the completion of 3 subjects per dose level, a Data Safety Monitoring Board reviewed safety data prior to dose-escalation. At the end of the DLT assessment period (*i.e.*, Cycle 1), subjects in all cohorts who did not have a DLT were given the option to continue with TB-403 as a single agent at the same dose level they received during Cycle 1, or in combination with temozolomide or etoposide based on the investigator's judgment. When administered in combination with temozolomide or etoposide, the first dose of TB-403 was at 75% of the subject's current TB-403 dose; all subsequent doses of TB-403 were at the subject's current dose if combination therapy was well tolerated. Treatment was continued in Cohorts 1 to 3 until progressive disease, unacceptable toxicity, or withdrawal of consent. Subjects in Cohort 4 could receive up to a maximum of 5 cycles of TB-403, unless the subject had progressive disease, unacceptable toxicity, or withdrew consent.

Main inclusion criteria included: subjects had to have a histologically confirmed diagnosis of MB, NB, ES or ARMS that was refractory to, or relapsed after, standard-of-care therapy; > 6 months and < 18 years of age at the time of enrollment; and a Performance Status (Lansky or Karnofsky) score ≥ 40.

DLTs were defined as any Grade 3 or Grade 4 drug-related non-hematologic toxicity (with specific exclusions); any drug-related non-hematological toxicity that caused a delay of > 14 days between doses; drug-related Grade 4 anemia or thrombocytopenia; drug-related Grade 3 thrombocytopenia with clinically significant bleeding; drug-related Grade 4 neutropenia for > 7 days or febrile neutropenia; and drug-related myelosuppression that caused a delay of > 14 days between doses.

Study Objectives

The primary objective was to determine the MTD of TB-403 administered as a single agent during a DLT assessment period (1 cycle of therapy) in pediatric subjects with relapsed or refractory MB, NB, ES or ARMS.

The secondary objectives included evaluation of the PK, safety, and tolerability of TB-403 administered as a single agent or in combination with chemotherapy in pediatric subjects with relapsed or refractory MB, NB, ES or ARMS. The preliminary efficacy of TB-403 administered as a single agent or in combination with chemotherapy was evaluated in terms of best overall response and progression-free survival (PFS). For MB patients, the Investigators' assessment of response was complemented by Central Review, as per protocol.

Methodology PK Data

Serum samples were analyzed by electrochemiluminescence methodology at Charles River Laboratories Edinburgh Ltd. for the determination of TB-403 levels.

Methodology used in Optional Sub-Study to Assess Biomarkers

The optional sub-study included evaluation of plasma PlGF as a pharmacodynamic biomarker. Plasma aliquots were prepared after centrifugation from blood samples obtained and stored at <−78°C until collection of all samples. These samples were also used to measure circulating concentrations of pro-angiogenic and inflammatory biomarkers. The biomarkers evaluated included PlGF, vascular endothelial growth factor (VEGF), VEGF-C, VEGF-D, sVEGFR1, basic fibroblast growth factor (bFGF), and sTIE-2 (using a commercially available 7-plex Growth Factor array, MesoScale Discovery, Gaithersburg, MD); interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12 heterodimer p70 (using a 9-plex Inflammatory Factor array, MesoScale Discovery). The assay has a lower limit of quantification (ULOQ) of 0.77 pg/ml and an upper limit of quantification (ULOQ) of 2,402.65 pg/ml for PlGF. All samples were measured in duplicate on a commercially available MSD SECTOR Imager 2400 (MesoScale Discovery) in the Clinical Laboratory Improvement Amendments (CLIA) certified core of the Steele Laboratories at Massachusetts General Hospital, Boston, USA.

Statistical Analysis of Clinical Data

All analyses were done in the Full Analysis Set (FAS), defined as all subjects who received at least 1 dose of study drug. Descriptive statistics were presented by dose level and across dose levels. Descriptive summary statistics for continuous variables included mean, standard deviation (SD) and range, as applicable. Categorical data were expressed in count and percentage. Time to event data were summarized using Kaplan-Meier estimates, including the median.

Methodology Used to Assess PK and TB-403 Exposure Metrics for Each Cohort

Individual TB-403 PK parameter estimates as well as individual and summary exposure metrics were determined by Leiden Experts on Advanced PK and Pharmacodynamics.

A population PK model, developed using summary data in adults, and updated every time when data from 3 pediatric subjects were available, was used to describe the PK in this population, if needed based on allometric scaling. Additionally, individual parameter estimates were obtained using empirical Bayesian estimation. The influence of body size (i.e., weight, body mass index, body surface area or lean body mass) as well as age on clearance and volume was investigated. Simulations were performed based on the model to predict the anticipated plasma concentration time curve for the next Cohort.

Data availability statement.

The data generated in this study are available within the article and its supplementary data files. Raw data are available upon reasonable request to maintain patient confidentiality.

RESULTS

Subject demographics are shown in Table 1. Eighteen subjects were screened for entry in the study; 2 subjects were screen failures (Table S1). Of the remaining 16 subjects enrolled, 15 subjects were included in the FAS (3 subjects each in Cohort 1 [20 mg/kg], Cohort 2 [50 mg/kg] and Cohort 4 [175 mg/kg] and 6 subjects in Cohort 3 [100 mg/kg]). One of 16 subjects (enrolled in Cohort 4) did not receive study treatment and was discontinued from the study because of initiation of alternative cancer therapy. Two of the 15 subjects in the FAS discontinued the study; 1 in Cohort 1 due to disease progression and 1 in Cohort 2 due to other reasons (not specified). Thirteen of 15 subjects completed the study. Eleven of 15 subjects had MB as the primary tumor type and 2 subjects each had ES and ARMS.

Efficacy

Tumors were assessed by both the Investigator and by the Central Reading Center (CRC). Amongst the 11 subjects with MB, best overall response as assessed by the CRC was reported as stable disease in 7 subjects, and progressive disease in 4 subjects. Per protocol, response was only assessed by central review for MB subjects. PFS based on central review assessments showed a median PFS of 2.8 months (ranging from 0.0 to 8.0 months). Of note, subjects in Cohort 3 had a median PFS of 5.6 months (ranging from 0.0 to 8.0 months) (Table S2). Individual subject responses over time are shown in Figure 2. Of note, 4 MB subjects had prolonged stabilization of disease beyond 100 days.

Dose-Limiting Toxicities

Dose level 1 and 2 each enrolled 3 subjects without DLTs. In dose level 3, one of three subjects exhibited Grade 3 Dehydration, Diarrhea and Malabsorption DLTs and therefore an additional 3 subjects were enrolled and completed dose level 3. Dose level 4 only enrolled 3 subjects, all without additional DLTs. The dose level was not expanded to 6 subjects because the Sponsor decided to stop further development of the TB 403 project (Internal Company Decision). MTD was not reached in this study, the highest evaluated dose level of 175mg/kg was well tolerated.

Adverse Events (AEs)

All AEs summarized are treatment emergent AEs, defined as any AE that occurred after the first administration of TB-403, or any event that was present at Baseline and continued after the first administration of TB-403 but worsened in severity or became serious. In this study, relatedness to the study treatment was determined by the Investigator. All AEs that were at least possibly related to the study treatment were considered drug related. A total of 74 drug-related AEs were reported in 10 of 15 subjects across cohorts. No Grade 5 (fatal) AEs were reported during the study (Table 2). The most frequently reported drug-related AEs (≥2 subjects overall) were: Vomiting and White Blood Cell Count Decreased (3 subjects each), and Anemia, Decreased Appetite, Fatigue, Lymphocyte Count Decreased, Nausea, Neutrophil Count Decreased and Platelet Count Decreased (2 subjects each). Five serious AEs were reported in 3 / 15 subjects across cohorts (Table 3).

In Cohort 3, 1 subject had 3 serious AEs: Dehydration, Diarrhea and Malabsorption on Day 23 (7 days after Cycle 1, Day 15 dose of TB-403). The events were assessed as DLTs as they occurred during the DLT assessment period and were Grade 3 in severity (Table S3). All these events resolved after 15 days, and the subject was able to continue on study drug after a dose reduction.

Pharmacokinetics

A total of 139 observations from 15 subjects from this study were included in the population PK model; 3 non-zero pre-dose observations and 11 below of quantification values were excluded. TB-403 was detected in all samples following dose administration. TB-403 exposure and concentration at the end of infusion were found to increase dose-proportionally over the dose range of 20 to 175 mg/kg taking into account the body weight-based dosing ranging from a median of 399.59 mg/L to 5,575.60 mg/L for the first dose (Figure 3A, B).

Plasma Biomarkers

Pharmacodynamic plasma biomarker analysis showed that 4/6 patients had detectable levels in plasma; the levels of free PlGF levels were undetectable following treatment at all doses in all patients (Figure 3C). To confirm that the assay is measuring free (non-TB-403 bound) PlGF, a spiking experiment was performed by adding TB-403 in serial dilution to plasma samples from the subjects in this study as well as unrelated plasma samples. Measurements showed that samples treated with drug did not exhibit “binding” to PlGF as was seen in the untreated samples. These data confirm that the assay does not measure PlGF bound to TB-403. There were no apparent changes in other angiogenic (VEGF, VEGF-D) or inflammatory factors after TB-403.

DISCUSSION

Relapsed and refractory pediatric solid tumors are especially challenging once standard chemotherapy, radiation and surgery have failed. Currently, there are no curative treatments for relapsed MB and the 2-year survival rate following relapse is only 9%[8]. Additionally, for tumors such as ES and ARMS, survival after relapse is very poor with less than 20% or those who relapse within 2-years surviving[9,10]. Therefore, novel therapeutics are urgently

needed. Research in MB has identified multiple genomic subsets and potential targeted therapies[11–13]. Specific targeting of the Shh subgroup involves inhibition of the G protein-coupled receptor smoothened. In addition, targeting of the Notch signaling pathway by inhibiting the gamma-secretase, as well as epigenetic regulation through targeting of histone deacetylase pathways, are being examined in early phase trials[14].

PlGF expression was detected in the majority of human MBs independent of subtype, and high expression of its NRP1 was shown to correlate with poor overall survival[2]. Importantly, PlGF expression is low or undetectable in most healthy tissues but is upregulated under pathologic conditions, including some types of cancer[15–17]. So far, prior studies (Table S4) have not shown efficacy signals in adult colon, ovarian, brain, or liver cancers, even when used in combination with VEGF inhibitors. However, the feasibility and activity of PlGF blockade in MB patients has remained unknown.

Administration of TB-403 given as an IV infusion over 60 minutes every 14 days was well tolerated and found to be feasible in the outpatient setting. TB-403 was safe at the dose levels tested without significant toxicities, even in heavily pretreated relapsed subjects, and an MTD was not reached in this trial. Due to limitation of study drug supply, the final planned cohort only enrolled 3 patients, which was well tolerated. This cohort dose, 175 mg/kg/dose, is recommended for a phase II study with an initial confirmation safety cohort. Of note, subjects on this study were at home while on treatment, with few hospital admissions, which is critical for preserving the quality of life when additional time with family is often the goal of therapy.

TB-403 exposure and concentration increased dose-proportionally over the dose range of 20 to 175 mg/kg. The target of TB-403 in MB is PlGF, preventing it from activating the cancer cells through its receptor NRP-1. Pharmacodynamic biomarker studies confirmed a drop to undetectable levels for plasma PlGF at all TB-403 dose levels, indicating effective binding and clearing of the target in blood. Whether plasma PlGF is a potential biomarker of prognosis or response needs to be evaluated in larger studies. Exploratory analyses of plasma angiogenesis and inflammatory biomarkers did not reveal any other significant changes after TB-403 treatment, potentially due to the small number of patients. There are currently no data available on the passage of TB-403 over the BBB in humans. However, the preliminary evidence of response to treatment suggests adequate penetration through the tumor-blood brain barrier. Experimental data in mice suggested that enough TB-403 can reach the CNS and the tumor area to affect tumor growth[3].

While no best overall responses were observed, 7 of 11 subjects achieved stable disease in the MB cohort of subjects. Of these, 5 had the initial chemotherapy readded, and 2 had no additional agent. Thus, the disease stabilization may have been in part due to chemotherapy. All but one non-MB subject exhibited progressive disease suggesting that MB represents the most appropriate target population. In addition, over half of the MB subjects (4 of 7) who maintained stable disease, did so for more than 100 days. This provided disease control and prolonged quality of life in these pediatric subjects with relapsed MB after multiple prior lines of therapy and for whom limited options were available. These promising data, along with the favorable safety profile, warrant further evaluation of this drug in larger clinical

trials in MB subjects either alone or in combination with other therapies and potentially in earlier stages of therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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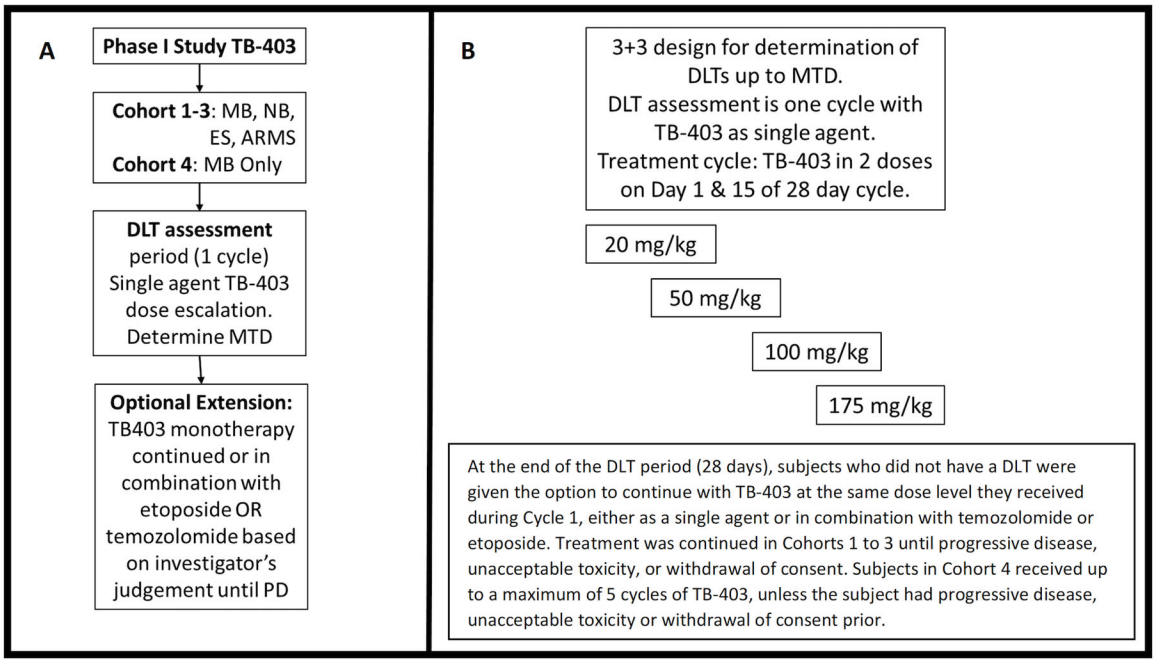

FIGURE 1. Design of phase I study of TB-403 in pediatric cancers.

(A) Study Design Diagram. **(B)** Dose-Escalation Schema 3+3 design for determination of DLT driven up to MTD or SMD (175 mg/kg). All indications: MB, NB, ES, ARMS (Cohorts 1–3); MB only (Cohort 4).

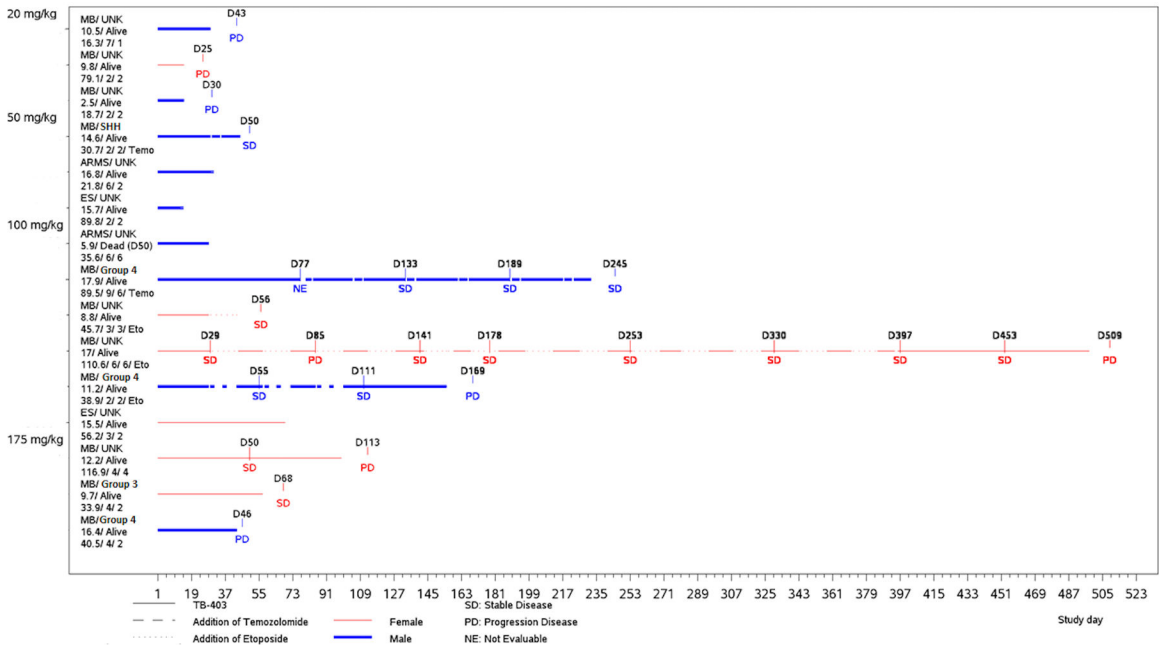

FIGURE 2.

Response over time, as assessed by Central Review, by subject.

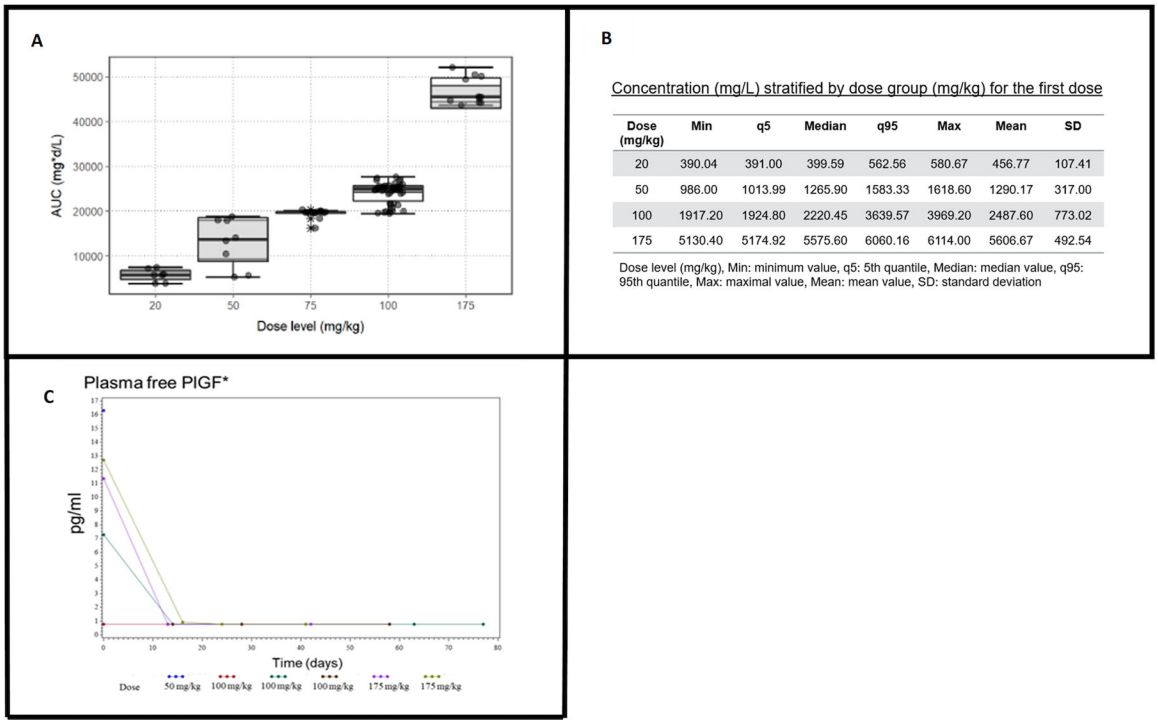

FIGURE 3. Pharmacokinetic/pharmacodynamics analyses of TB-403.

(A) Area under the Curve (AUC) of subjects at each dose level. **(B)** Minimum, Median and Mean dose concentrations at each dose level. **(C)** Plasma free PIGF levels detected over time.

Table 1.

Demographics and Other Baseline Characteristics (Full Analysis Set)

	All (N=15)	Cohort 1 TB-403 20 mg/kg (N=3)	Cohort 2 TB-403 50 mg/kg (N=3)	Cohort 3 TB-403 100 mg/kg (N=6)	Cohort 4 TB-403 175 mg/kg (N=3)
Gender, n (%)					
Male	9 (60.0)	2	3	3	1
Female	6 (40.0)	1	0	3	2
Race, n (%)					
White	13 (86.7)	2	3	5	3
Other	2 (13.3)	1	0	1	0
Age (years)					
Mean (SD)	12.30 (4.507)	7.60 (4.431)	15.70 (1.100)	12.72 (4.839)	12.77 (3.386)
Min, Max	2.5, 17.9	2.5, 10.5	14.6, 16.8	5.9, 17.9	9.7, 16.4
Time Since First Diagnosis (months)					
Mean (SD)	54.95 (33.586)	38.03 (35.585)	47.43 (36.959)	62.75 (30.479)	63.77 (46.133)
Min, Max	16.3, 116.9	16.3, 79.1	21.8, 89.8	35.6, 110.6	33.9, 116.9
Primary Tumor (Sub)Type, n (%)					
Medulloblastoma / Subtype	11 (73.3)	3	1	4	3
Group 1 (Sonic Hedgehog)	1	0	1	0	0
Group 2 (WNT)	0	0	0	0	0
Group 3	1	0	0	0	1
Group 4	3	0	0	2	1
Unknown	6	3	0	2	1
Neuroblastoma	0	0	0	0	0
Ewing Sarcoma	2 (13.3)	0	1	1	0
Alveolar Rhabdomyosarcoma	2 (13.3)	0	1	1	0
No. of previous therapy regimens					
2	5	2	2	1	0
3–4	5	0	0	2	3
6–9	5	1	1	3	0

[a]MB subjects only.

Table presents number and percentage of subjects, n (%) only for FAS (“All” column in the table).

Abbreviations: FAS=Full Analysis Set; MB=medulloblastoma; SD=standard deviation; WNT=wingless.

Table 2:

Overview of Treatment-Emergent Adverse Events (Full Analysis Set)

Category	All N=15		Cohort 1 TB-403 20mg/kg N=3		Cohort 2 TB-403 50mg/kg N=3		Cohort 3 TB-403 100mg/kg N=6		Cohort 4 TB-403 175mg/kg N=3	
	n (%)	E	n	E	n	E	n	E	n	E
Any TEAE	13 (86.7)	176	3	18	2	15	6	141	2	2
Drug-Related TEAE	10 (66.7)	74	3	10	1	3	6	61	0	0
Any Serious TEAE	3 (20.0)	5	0	0	1	1	2	4	0	0
Any TEAE Leading to Withdrawal from Study Treatment	0	0	0	0	0	0	0	0	0	0
TEAE Severity										
Grade 1	11 (73.3)	93	2	11	1	3	6	77	2	2
Grade 2	9 (60.0)	54	3	7	2	8	4	39	0	0
Grade 3	7 (46.7)	25	0	0	2	4	5	21	0	0
Grade 4	3 (20.0)	4	0	0	0	0	3	4	0	0
Grade 5	0	0	0	0	0	0	0	0	0	0

A TEAE is defined as any AE that occurred after the first administration of TB-403, or any event that was present at Baseline and continued after the first administration of TB-403 but worsened in severity or became serious.

Drug-related TEAEs is defined as those with relationship to study treatment as definitely, probably, or possibly related. Table presents number and percentage of subjects, n (%) only for FAS (“All” column in the table).

Abbreviations: AE=adverse event; E=total number of events reported; FAS=Full Analysis Set; N=number of subjects overall or in a dose cohort; n=number of subjects in each category; TEAE=treatment-emergent adverse event.

Table 3:

Drug-Related Treatment-Emergent Adverse Events by Preferred Term (≥2 subjects overall) (Full Analysis Set)

Preferred Term	All N=15		Cohort 1 TB-403 20mg/kg N=3		Cohort 2 TB-403 50mg/kg N=3		Cohort 3 TB-403 100mg/kg N=6		Cohort 4 TB-403 175mg/kg N=3	
	n (%)	E	n	E	n	E	n	E	n	E
Anemia	2 (13.3)	4	0	0	0	0	2	4	0	0
Decreased Appetite	2 (13.3)	2	1	1	0	0	1	1	0	0
Fatigue	2 (13.3)	2	0	0	0	0	2	2	0	0
Lymphocyte Count Decreased	2 (13.3)	9	0	0	0	0	2	9	0	0
Nausea	2 (13.3)	4	2	4	0	0	0	0	0	0
Neutrophil Count Decreased	2 (13.3)	4	0	0	1	1	1	3	0	0
Platelet Count Decreased	2 (13.3)	9	0	0	0	0	2	9	0	0
Vomiting	3 (20.0)	6	2	4	0	0	1	2	0	0
White Blood Cell Count Decreased	3 (20.0)	9	0	0	1	1	2	8	0	0

A TEAE is defined as any AE that occurred after the first administration of TB-403, or any event that was present at Baseline and continued after the first administration of TB-403 but worsened in severity or became serious.

If a subject had multiple events of the same severity, relationship, or outcome, they are counted only once in that severity, relationship, or outcome. However, subjects can be counted more than once overall.

Table presents number and percentage of subjects, n (%) only for FAS (“All” column in the table).

Drug-related TEAEs are defined as those with relationship to study treatment as definitely, probably, or possibly related.

Abbreviations: AE=adverse event; E=total number of events reported; FAS=Full Analysis Set; N=number of subjects overall or in a dose cohort; n=number of subjects in each category; TEAE=treatment-emergent adverse event.