ABSTRACT

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

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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.

PATIENTS AND METHODS: 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.

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