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# A phase 1 trial utilizing a pharmacokinetic endpoint to determine the optimal dose of ramucirumab in children and adolescents with relapsed or refractory solid tumors, including central nervous system tumors

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## Abstract

**Background:** Ramucirumab is a monoclonal antibody that binds the extracellular domain of vascular endothelial growth factor receptor (VEGFR-2) and prevents binding of VEGF ligands. Based on population pharmacokinetic (PK) analysis and correlation with efficacy in adults, a target steady state trough concentration ( $C_{ss,min}$ )  $\geq 50$   $\mu\text{g/mL}$  was established.

**Procedures:** This phase 1 trial (ADVL1416) used a rolling six design and a PK primary endpoint to define the recommended phase 2 dose (RP2D) of ramucirumab in children with recurrent/refractory solid tumors. Two dose levels (DL) were planned (DL1: 8 mg/kg, DL2: 12 mg/kg administered intravenously [IV] every 2 weeks). Toxicity during the initial 6 weeks was used to assess maximum tolerated dose (MTD). Cycle 1 Day 42 trough ( $C_{min}$ )  $\geq 50$   $\mu\text{g/mL}$  was the target concentration for the PK endpoint. At the RP2D, cohorts for PK expansion and children with central nervous tumors were planned.

**Results:** Twenty-nine patients were enrolled; 28 were eligible; median age [range] = 13.5 [1-21] years; 22 were evaluable for the PK endpoint. Dose-limiting proteinuria occurred at both DLs; however, the MTD was not exceeded. At DL2 (12 mg/kg), the median Day 42  $C_{min}$  (n = 16) was 87.8  $\mu\text{g/mL}$ ; 15 of 16 patients achieved a  $C_{min} \geq 50$   $\mu\text{g/mL}$ .

**Conclusion:** Ramucirumab was well tolerated in children and adolescents with solid tumors. The RP2D for ramucirumab was 12 mg/kg IV every 2 weeks. This trial demonstrates the feasibility of incorporating a primary PK endpoint to determine dose escalation and the RP2D in children. Studies of ramucirumab in children with selected solid tumors are ongoing.

**Keywords:** anti-angiogenesis; pediatric cancer; pharmacokinetics; ramucirumab.

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