Phase I study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma.


Abstract

BACKGROUND.: Sonidegib (LDE225) is a potent, selective Hedgehog (Hh) inhibitor of SMOOTHENED. This study explored the safety and pharmacokinetics (PK) of sonidegib in children with relapsed/recurrent tumors followed by a phase II trial in pediatric and adult patients with relapsed medulloblastoma (MB) to assess tumor response.

METHODS.: Pediatric patients aged ≥1-<18 years were included according to a Bayesian design starting at 372mg/m2 of continuous once daily oral sonidegib. Tumor samples were analyzed for Hh pathway activation using a validated 5-gene Hh signature assay. In phase II, pediatric patients were treated at the recommended phase II dose (RP2D) while adults received 800mg daily.

RESULTS.: Sixteen adult (16 MB) and 60 pediatric (39 MB, 21 other) patients with an age range of 2-17 years were enrolled. The RP2D of sonidegib in pediatric patients was established at 680mg/m2 once daily. The phase II study was closed prematurely. The 5-gene Hh signature assay showed that the 4 complete responders (2 pediatric and 2 adult) and 1 partial responder (adult), all had Hh-activated tumors, while 5 patients with activated Hh had either stable disease (n=3) or progressive disease (n=2). No patients with Hh-negative signatures (n=50) responded. The safety profile for pediatric patients was generally consistent with the one established for adult patients; however, growth plate changes were observed in pre-pubertal pediatric patients'.

CONCLUSIONS.: Sonidegib was well tolerated and the RP2D in pediatric patients was 680mg/m2 once daily. Five of the 10 MB patients with activated Hh pathway demonstrated complete or partial responses.

KEYWORDS: Medulloblastoma; PTCH; SMO; clinical trial; sonic hedgehog

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