

**Phase 1/2 study of elraglusib (9-ING-41), a small molecule selective glycogen synthase kinase-3 beta (GSK-3 $\beta$ ) inhibitor, alone or with irinotecan, temozolomide/irinotecan or cyclophosphamide/topotecan in pediatric patients with refractory malignancies: Interim results.**

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**Background:** GSK-3 $\beta$  overexpression is associated with aggressive malignancies, treatment resistance and poor prognosis. The GSK-3 $\beta$  inhibitor Elraglusib induces apoptosis via NF $\kappa$ B and p53 pathways and has potent anti-fibrotic and immunomodulatory activity. Adult studies of elraglusib demonstrate clinical activity in pancreatic cancer, melanoma, lymphoma and sarcoma as a single agent or in combination with cytotoxic chemotherapy. Elraglusib is active in *in vivo* models of neuroblastoma (NBL) and malignant glioma. This first-in-pediatrics study (NCT04239092) is evaluating the safety, pharmacokinetics (PK), and efficacy of elraglusib monotherapy and in combination with chemotherapy in patients with refractory malignancies. **Methods:** Elraglusib is given intravenously (IV) twice-weekly at 3 dose levels (DL) (9.3, 12.4 and 15 mg/kg) as a single agent or in combination with irinotecan, cyclophosphamide/topotecan or temozolomide/irinotecan in 21-day cycles. A cohort of pts with refractory NBL will be treated at the recommended phase 2 dose (RP2D) of elraglusib with temozolomide/irinotecan. **Results:** As of January 2022, 23 pts (n = 7 female, median age 14.2 years) have received at least one dose of elraglusib. Tumor types: 5 NBL, 3 diffuse midline glioma (DMG), 3 osteosarcoma (OS), 3 ependymoma (EP), 2 alveolar rhabdomyosarcoma (aRMS), 1 angiosarcoma (AS), 1 Ewing sarcoma (ES), 1 glioblastoma (GBM), 1 hepatoblastoma (HB), 1 embryonal CNS tumor NOS, 1 NUT midline carcinoma, 1 pineoblastoma (PB). Median time from diagnosis is 26 months (range: 6.7 – 156.3) and median number of lines of prior systemic therapy is 2 (range 0-14). Two DLs of single agent (6 pts) have been completed (9.3 and 12.4 mg/kg) without elraglusib-attributable severe adverse events (SAEs). Of the 15 patients on the combination arm with irinotecan or cyclophosphamide/topotecan, a single adverse event (Grade 4 hypotension/infusion reaction) was reported. Grade 1/2 elraglusib attributable-AEs include: transient visual change (n = 10), nausea (n = 7), vomiting (n = 6), fatigue (n = 2), hypotension (n = 2) and infusion reaction (n = 1). One pt with recurrent ES had a radiographic and pathologic CR after 3 cycles of elraglusib/cyclophosphamide/topotecan. 6 pts (26.1%) had SD (2 NBL, 1 aRMS, 1 EP, 1 OS, 1 GBM). 8 pts (35%) remained on study treatment  $\geq$  3 months (2 NBL, 2 EP, 1 OS, 1 aRMS, 1 ES, 1 PB). Median treatment duration was 40 days (range 1 - 126). 4 pts remain on therapy. **Conclusions:** Elraglusib is well tolerated as a single agent and with several chemotherapy regimens in this heavily pretreated pediatric population with refractory cancers. It has encouraging antitumor activity, with 1 CR in a patient with recurrent ES. Enrollment is ongoing; a RPD2 has not been reached. Clinical trial information: NCT04239092. Research Sponsor: Actuate Therapeutics, Inc.