A phase 1 study of LOXO-292, a highly selective RET inhibitor, in pediatric patients with RET-altered cancers

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Background

- RET fusions and RET-activating point mutations are primary oncogenic drivers that show predominant mutational exclusivity with driver alterations in other oncogenes.1-13
- Activating point mutations have been detected in ~65% of sporadic medullary thyroid carcinomas (MTC), and in ~80% of hereditary MTC.
- RET fusions have been reported in 10-20% of sporadic papillary thyroid carcinomas, approximately 2% of non-small cell lung cancers, and at a lower frequency (<1%) in other tumor types, including breast, colorectal and pancreatic cancers.
- Children and adolescents with papillary thyroid cancer and MEN 2B medullary thyroid cancer are more likely to harbor RET fusions than older patients with those malignancies.
- In infants and young children, RET fusions have been predominantly reported in patients with various sarcoma subtypes.
- No agents are currently approved by the U.S. Food and Drug Administration for treatment of adult or pediatric patients with RET-altered cancers.

LOXO-292

- LOXO-292 is a novel, highly selective, small molecule inhibitor of RET currently in clinical development for patients with advanced cancers harboring oncogenic RET alterations.14
- LOXO-292 has nanomolar potency against activating RET alterations in RET fusion- or point mutation-positive (including the gatekeeper residue) preclinical cell-based cancer models.15
- LOXO-292 is clinically active in patients with RET-altered solid tumors, including those that have metastasized to the central nervous system (CNS) (Figure 1).13, 15-17

Methods

- LIBRETTO-121 is an ongoing, multicenter, phase 1/2 dose-confirmation study of LOXO-292 in pediatric patients 6 months–21 years of age with advanced solid or fusion-positive thyroid cancer
- Recruitment start date: February 12, 2019.

Key inclusion criteria

- Patients 6 months–21 years of age with a locally advanced resected solid or primary CNS tumor and no available therapeutic options.
- Activating RET gene alterations identified in the tumor and/or blood.
- Neurologically stable patients with primary CNS tumors and without a steroid dose increase within the 7 days prior to cycle 1 day 1 (C1D1).
- Histologic verification of malignancy at original diagnosis or relapse.
- Imaging study within the 28 days of C1D1.
- Measurable or evaluable disease.
- Karnofsky or Lansky score of ≥50.
- Full recovery from prior chemotherapy (CTCAE v5.0 grade ≤2) and/or systemic therapy including tyrosine kinase inhibitors.
- Availability of a formalin-fixed paraffin-embedded, fresh frozen, or fresh tumor sample.
- Adequate organ function.

Statistical considerations

- In the dose-escalation phase, the observed DLT rate will be calculated with a 2-sided 95% exact binomial confidence interval (CI).
- The estimate of the ORR will be accompanied by 1- and 2-sided CIs with various coverage probabilities (e.g., 80%, 95%).
- DOR, PFS and OS will be summarized descriptively using the Kaplan-Meier method with 95% CIs calculated using Greenwood’s formula.
- Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up.
- Event-free rates at selected time points and corresponding 95% CIs will be estimated using the Kaplan-Meier method.
- Greenwood’s formula will be used to calculate the standard errors of the Kaplan-Meier estimate, and upper and lower limits of the 95% CI.

Current status

- Recruitment start date: February 12, 2019.
- Dose confirmation following a rolling 6 design is ongoing.

References


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