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

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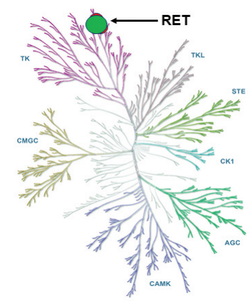
Background

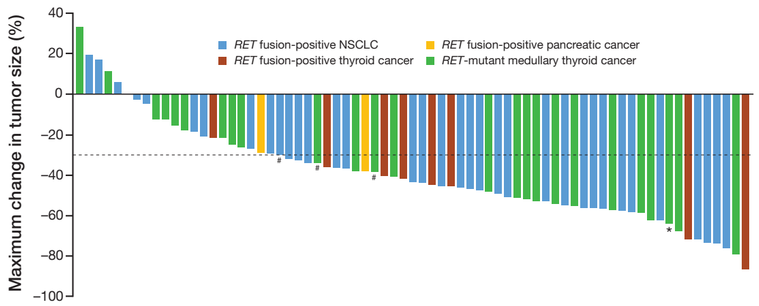
- *RET* fusions and RET-activating point mutations are primary oncogenic drivers that show predominantly mutual exclusivity with driver alterations in other oncogenes:[1-13]
  - Activating point mutations have been detected in ~65% of sporadic medullary thyroid carcinomas (MTC), and in >90% of hereditary 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.[14]
- 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]

Figure 1. Antitumor activity in *RET*-altered cancers in the LIBRETTO-001 study

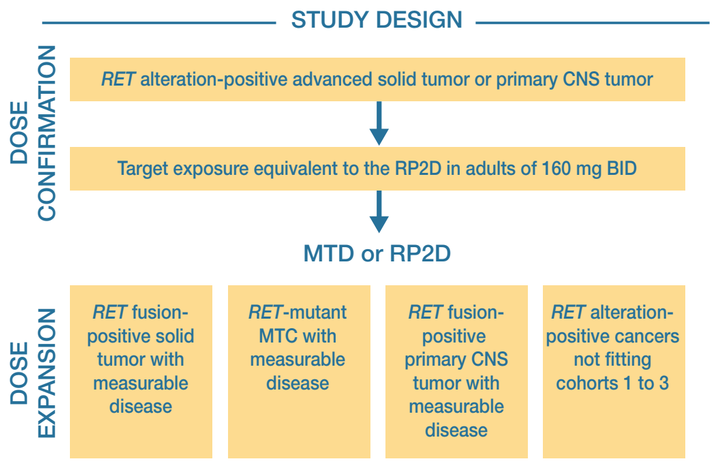


Patients shown were enrolled as of April 2, 2018 with a data cutoff July 19, 2018.
Note: 7 patients not displayed; 4 due to treatment discontinuation prior to first post-baseline response assessment, 3 due to nonmeasurable disease at baseline (2 stable disease, and 1 complete response). *Complete response; #Unconfirmed response awaiting confirmatory response assessment. NSCLC, non-small cell lung cancer.

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 CNS tumors harboring activating *RET* alterations (NCT03899792; **Figure 2**). LOXO-292, as a liquid suspension or capsule formulation, will be administered orally twice daily (BID) until progressive disease, unacceptable toxicity, or other reason for treatment discontinuation.

Figure 2. Study design schema



BID, twice daily; CNS, central nervous system; MTC, medullary thyroid cancer; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

Phase 1/2 study objectives

PHASE 1

Primary objective

Safety, including dose limiting toxicities (DLTs)

Secondary objectives

- Pharmacokinetic properties
- Maximum tolerated dose and/or the appropriate dose for further clinical investigation
- Antitumor activity
- Changes from baseline in pain and health related quality of life (HRQoL) measures

Exploratory objective

Potential biomarkers of response and resistance to LOXO-292

PHASE 2

Primary objective

Objective response rate (ORR) determined by an Independent Review Committee (IRC) based on Response Evaluation Criteria in Solid Tumors version 1.1 or Response Assessment in Neuro-Oncology criteria

Secondary objectives

- ORR (treating investigator)
- Duration of response (DOR) in patients with best overall response of a complete response or partial response (IRC and treating investigator)
- Progression-free survival (PFS) (IRC and treating investigator)
- Overall survival (OS)
- Clinical benefit rate (IRC and treating investigator)
- Safety profile and tolerability
- Pharmacokinetic properties
- Concordance rate of a prior molecular profiling that detected a *RET* alteration in the patient's tumor tissue with diagnostic tests being evaluated by the sponsor
- Post-operative staging and surgical margin status
- Putative pretreatment surgical plan and the actual post-treatment approach

Exploratory objectives

- Relationship between pharmacokinetics and drug effects
- Changes in serum carcinoembryonic antigen and calcitonin levels for patients with MTC and thyroglobulin for patients with *RET* fusion-positive thyroid cancer
- Changes in pain and HRQoL measures
- *RET* fusions and mutations in tumor biopsies and circulating tumor (ct)DNA
- Concurrently activated oncogenic pathways in pre-treatment tumor biopsies
- Changes in tumor molecular status in tumor biopsies and ctDNA obtained during treatment and after progression on LOXO-292

Key inclusion criteria

- Patients 6 months–21 years of age with a locally advanced relapsed 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.

Key exclusion criteria

- Major surgery within the 14 days before C1D1.
- Cardiovascular disease within the 6 months prior to C1D1.
- Active uncontrolled systemic bacterial, viral, or fungal infection.
- Clinically significant active malabsorption syndrome.
- Pregnancy or lactation.
- Uncontrolled symptomatic hyper/hypothyroidism, or hyper/hypocalcemia.

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.

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