Protocol Title: Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, & Other Tumors with RET Activation (LIBRETTO-001)

Target Population: RET Fusion + Solid Tumors, Medullary Thyroid Cancer, or other tumors with RET Activation

Summary: This is a Phase 1/2, open-label, first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of LOXO-292 administered to patients with advanced solid tumors, including RET fusion + solid tumors, medullary thyroid cancer and other tumors with RET activation.

Key Inclusion Criteria for Phase 1:
• Patients with a locally advanced or metastatic solid tumor who:
  o Have progressed on or are intolerant to standard therapy or
  o No standard therapy exists, or not candidates for or would be unlikely to tolerate standard therapy or
  o Decline standard therapy
• Prior MKIs with anti-RET activity are allowed.
  o However, prior treatment with a selective RET inhibitor(s) is prohibited.
• Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumor type.
• ECOG score of 0, 1, or 2 with no sudden deterioration 2 weeks prior to the first dose of study treatment.
• Adequate hematologic, hepatic and renal function.
• Life expectancy of at least 3 months.

Key Inclusion Criteria for Phase 2 – Same as Phase 1 with the following modifications:
• Cohorts 1 & 3 must have received prior standard therapy appropriate for their tumor type and stage of disease or would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy.
• Cohorts 1-4: enrollment will be restricted to patients with evidence of a RET gene alteration in tumor.
  o However, a positive germline DNA test for a RET gene mutation is acceptable in the absence of tumor tissue testing for patients with MTC.
• Cohorts 1-4: at least one measurable lesion as defined by RECIST 1.1 and not previously irradiated.
• Cohort 4: radiographic PD within the previous 14 months.
• Note: Patients otherwise eligible for Cohort 4 who do not demonstrate radiographic PD within the previous 14 months may be enrolled to Cohort 5 if approved by the Sponsor.
• Cohort 5:
  o Cohorts 1-4 without measurable disease;
  o MTC not meeting the requirements for Cohorts 3 or 4 (a known RET mutation is NOT required)
  o MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior Sponsor approval
  o cfDNA positive for a RET gene alteration not known to be present in a tumor sample.

Key Exclusion Criteria:
• Phase 2 Cohorts 1-4: an additional known oncogenic driver.
• Prior treatment with a selective RET inhibitor.
• Symptomatic primary CNS tumor, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Patients are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of LOXO-292.

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For additional information: https://clinicaltrials.gov/ct2/show/NCT03157128

IRB #: 2018.211