Background

LOXO-292 is a novel, highly selective, small molecule inhibitor of RET currently in clinical development for patients with advanced cancers harboring oncogenic RET gene alterations, such as RET fusions (non-small cell lung cancer, papillary and other thyroid cancers, other solid tumors) – Activating RET mutations (medullary thyroid cancer)

LIBRETTO-601 is a phase I/II clinical trial evaluating the safety and efficacy of LOXO-292 in patients with RET altered cancers. Best tumor response for the first 82 patients enrolled to 1 dose level

We studied the mutational status of RET variant allele frequencies (AF) in plasma cfDNA of patients receiving LOXO-292 therapy.

Methods

This phase 1/2, open-label, dose-escalation, first-in-human study (NCT03157128) aims to evaluate the safety, tolerability, pharmacokinetics and preliminary antitumor activity of orally administered LOXO-292.

The primary objective of phase 1 is to determine the maximum tolerated dose of LOXO-292 and the recommended phase 2 dose.

One exploratory objective is the assessment and monitoring of RET gene alterations in plasma cfDNA.

Blood samples were collected in Cell-Free DNA Kit* blood collection tubes (Streck) prior to treatment, after 15 days of treatment (cycle 1; day 15; C1D15), and at each restaging, and shipped to a central laboratory for plasma isolation within 72 h.

Gene alterations were assessed in RET and 72 other cancer-related genes, by next-generation sequencing (NGS) of cfDNA (GuardianTM assay; Guardian Health)

Results

As of April 2, 2018, 82 patients had been enrolled to 1 of 8 dose levels (20–120 mg QD-24h in 6:1 RRD; Figure 2).

Table 1. RET alterations

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<th>Mutation</th>
<th>AF (%)</th>
<th>NGS, C1D15</th>
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Plasma response analysis

Plasma response was studied in pretreatment plasma samples from 72 patients with RET alterations detected by tumor genotyping (Figure 3).

- In 34 (81%) of 42 samples, the AF decreased by at least 50%
- In 21 (50% ) of 42 samples, the variant became undetectable at C1D15 (clearance)
- Mutations were detected in 18 patients with thyroid cancer and 5 with thyroid cancer and 1 lymphoproliferative disorder
- The expected RET alteration was not found in 23 plasma samples: 3 had no somatic mutations of any type; 2 of these samples had >5 ng DNA input (below the minimum required for the assay)

Plasma detection analysis

- Of the remaining 42, 27 had RET fusions and 15 had RET mutations detected in pretreatment cfDNA
- In 34 (81%) of 42, the variant became undetectable at C1D15 (clearance)
- In 34 (81%) of 42, the AF decreased by at least 50%
- The median AF decrease at C1D15 was 99%

Comparison of imaging- and cfDNA-based tumor changes

- Changes in tumor burden as measured by RECIST and cfDNA analysis were compared for 36 patients where both measures were available

- cfDNA analysis identified a subset of cases with radiographic stable disease harboring molecular evidence of a treatment effect (Figure 4).

Conclusions

- The rapid clearance of RET variants from plasma cfDNA on LOXO-292 treatment supports the clinical activity of this agent across a range of doses, tumor types and RET alterations.

- NGS of plasma cfDNA can detect a range of targetable RET variants, though tumor genotyping remains critical if the initial plasma NGS is negative.

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References

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