Detection and clearance of RET variants in plasma cell free DNA (cfDNA) from patients treated with LOXO-292


Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Massachusetts General Hospital Cancer Center, Boston, MA; Sinai-Cannon Research Institute/Tennece Oncology, Nashville, TN; Texas A&M Cancer Institute, Cleveland Clinic, Cleveland, OH; Stanford Medicine, MD; Guangzhou Institute, Tsinghua University; Sunnybrook NCI Centre, Singapour University School of Medicine, Seui, Republic of Korea; The University of Chicago, Chicago, IL.

Abstract 9048

Background

LOXO-292 is a novel, highly selective, small molecule inhibitor of RET tumor type and starting dose were not major determinants of the magnitude of cfDNA response (Serial plasma genotyping warrants continued study as an early indicator of disease.

The expected sensitivity of cfDNA analysis was studied in pretreatment plasma samples from 62 patients with RET alterations detected by tumor genotyping.

Blood samples were collected in Cell-Free DNA BCT® 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 hours.

Gene alterations were assessed in RET and 12 other cancer-related genes, by next-generation sequencing (NGS) of cfDNA (Guardant360 assay; Guardant Health).

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

Methods

This phase I, open-label, dose-escalation, bio/pharmacokinetic study in patients with RET-altered tumors is designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of orally administered LOXO-292.

The primary objective is to determine the maximum tolerated dose (MTD) of LOXO-292 and/or the recommended dose for further study.

One exploratory objectives is to assess the association between monitoring of RET gene alterations in plasma cfDNA.

Blood samples were collected in Cell-Free DNA BCT® 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 hours.

Gene alterations were assessed in RET and 12 other cancer-related genes, by next-generation sequencing (NGS) of cfDNA (Guardant360 assay; Guardant Health).

Results

As of April 2, 2018, 82 patients had been enrolled to 1 of 8 dose levels [20mg QD, 20mg BID, 40mg BID, 60mg BID]; see also abstract 102, ASCO 2018). 3

Of the remaining 34, 21 had RET fusions and 13 had RET mutations detected in pretreatment cfDNA:

– In 15 (14.4%) of 34 samples, the variant became undetectable at C1D15 (clearance);
– In 27 (79%) of 34 samples, the AF decreased by at least 50% ; the median decrease was 96% ;
– Tumor type and drug dose were not major determinants of the magnitude of cfDNA response (Figures 4 & 5).

Comparison of imaging- and cfDNA-based tumor changes

Changes in tumor burden as measured by imaging (RECIST) and cfDNA analysis were compared for 27 patients for whom both measures were available.

cfDNA analysis identified a subset of cases with radiographic stable disease but molecular evidence of a treatment effect (Figures 4, 6, 9).

The 3 cases with a RECIST partial response and a limited cfDNA response at C1D15 had a <90% AF decrease after long follow-up.

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 dose, tumor types and RET alterations.

NGS of plasma cfDNA can detect early signs of treatment response, though tumor genotyping remains critical if the initial plasma NGS is negative.

Serial plasma genotyping warrants continued study as an early pharmacodynamic marker for novel targeted therapies.

References


Correspondence

Address correspondence to Geoffrey R. Oxnard, MD, Dana-Farber Cancer Institute, 44 Binney Street, Bldg. 10, Room 10.206, Boston, MA 02215, USA. E-mail: Geoffrey.Oxnard@dfci.harvard.edu

Figure 1. Antitumor activity in RET altered cancers

Figure 2. Analysis cohort

Figure 3. Plasma detection analysis

Table 1. RET alterations

Table 1. Gene fusions

Figure 4. Plasma response analysis by tumor type

Figure 5. Plasma response analysis: by starting dose

Figure 6. Imaging (RECIST) vs cfDNA

Figure 7. Maximum change in tumor size (%)

Figure 8. Changes in A F

Figure 9. Comparison of RECIST and cfDNA (Nguyen et al., ASCO 2018).