Longitudinal circulating tumor DNA analysis for predicting response to osimertinib and disease progression in patients with EGFR-mutant non-small-cell lung cancer

Chul Kim1, Liqiang Xu2, Constanze M. Cultraro2, Trinh Hoc Tran Pham2, Ahmad Shafei2, Nitin Roper2, Mohammadhadi Bagheri3, John Beeler4, Gregory Jones4, Mark Raffeld1, Udayan Guha5
1Thoracic and GI Malignancies Branch, Laboratory of Pathology, Center for Cancer Research, NCI, NIH, Bethesda, MD
2Department of Imaging and Radiation Sciences, Clinical Center, NIH, Bethesda, MD and Inivata, Inc. Research Triangle Park, NC, USA
3Department of Imaging and Radiation Sciences, Clinical Center, NIH, Bethesda, MD and Inivata, Inc. Research Triangle Park, NC, USA
4*udyan.guha@nih.gov

Introduction

• Circulating tumor DNA (ctDNA) has emerged as a promising non-invasive tool to detect various mutations with molecular pathogenesis of a broad array of malignancies, including non-small-cell lung cancer (NSCLC) [1].

• Detection of sensitizing EGFR mutations as well as the resistant T790M mutation by plasma genotyping is being increasingly incorporated into routine clinical practice [2].

• Emerging evidence suggests that ctDNA may serve as a measure of tumor burden and could be used to monitor treatment response and tumor burden.

• Here, we aimed to assess whether longitudinal ctDNA monitoring could predict response to osimertinib, the 3rd generation TKI, and tumor burden in the setting of a prospective clinical trial of local ablative therapy (LAT) for oligoprogressive, EGFR-mutant NSCLC (NCT0279835).

Methods

• Schema of Clinical Trial

Volumetric measurement

• We identified all lesions for each patient at different time points. Then, in order to get an estimate of the total tumor burden in the body, we selected all other soft tissue lesions ≥10 mm in long axis diameter. All of these lesions were manually segmented and the volume was recorded.

Results

ctDNA testing

• 281 blood samples collected from 17 patients were analyzed by ddPCR.

• In 11 patients, an enhanced Tagged-Amplicon Sequencing NGS assay was performed on select 41 blood samples.

Baseline detection of ctDNA by ddPCR

• EGFR mutations (sensitizing and/or T790M) were detected in 15 (88%) of 17 patients at baseline.

• One patient (cohort 1) with overall metastatic tumor burden and another patient (cohort 3) with most tumor burden at baseline (both with no detectable ctDNA at baseline).

• Baseline EGFR mutation copy numbers were variable among patients. The copy numbers of EGFR sensitizing mutations ranged between 3-5599 copies/mL.

• Among 7 patients who had first progression, 6 (86%) patients had an increase in corresponding mutant EGFR allele in ctDNA 2-4 months before radiographic progression.

Dynamic ctDNA changes reflect treatment response and tumor burden

• For patients treated in cohort 1 and 2 (12%) achieved a partial response (PR) and 2 (12%) achieved stable disease or minor response as their best response.

• ctDNA decreased after initiation of osimertinib in these patients with 7 (50%) patients having no detectable ctDNA within 28 days. In those with ongoing PR (n=5) and pr Chung stable disease (n=1), ctDNA remains undetectable (n=5) or low (n=1).

Table 1. Patient characteristics (n=17)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Race</th>
<th>Gender</th>
<th>Tumor type</th>
<th>Exon L8585R/T790M</th>
<th>African American</th>
<th>Asian</th>
<th>African American</th>
<th>Asian</th>
<th>African American</th>
<th>Asian</th>
<th>African American</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Female</td>
<td>Lung cancer</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Male</td>
<td>Lung cancer</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Female</td>
<td>Lung cancer</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Male</td>
<td>Lung cancer</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Female</td>
<td>Lung cancer</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

Longitudinal quantitative assessment of plasma ctDNA is a relatively non-invasive tool to monitor the therapeutic response to treatment with EGFR-TKI and to enable early detection of resistance mechanisms for clinical decision making.

References