**RESULTS**

Archival formalin-fixed paraffin-embedded samples or baseline fresh-frozen tumor tissues were analyzed using a FoundationOne (n=1) and/or a Personalized Ancestry and Content Enriched (PACE) (n=2) panel. Analyses performed using samples pooled from both studies.

Analyses performed using tumor sequences from ctDNA (n=14 mIDH1 CC patients).

**DISCUSSION**

We report here for the first time the detection of mIDH1 in ctDNA from patients with cholangiocarcinoma.

**METHODS**

**Patients and samples.**

**Baseline mIDH1 detection in plasma is highly concordant with mIDH1 detection in tumor tissue.**

**ARCHIVAL**

- Somatic mutations in the isocitrate dehydrogenase 1 gene (IDH1) are detected in ~15% of hepatocellular carcinoma cases overall and up to ~25% of intrahepatic CC cases.

- The mutant IDH1 (mIDH1) enzyme has a gain-of-function activity, catalyzing the reduction of alpha-ketoglutarate to produce the mutagenic 2-hydroxyglutarate (2-HG), which leads to epigenetic dysregulation and block in cellular differentiation.

- Intrahepatic cholangiocarcinoma (CC) is a rare, poorly understood, and highly malignant cancer. Genetic characterization is critical for understanding disease biology and is essential for the development of targeted therapies.

- Plasma ctDNA was detected in 34 of 39 patients who had plasma samples collected immediately before treatment. The interval between tissue and blood collection was <30 days.

- Archival tumor tissue samples and plasma ctDNA samples without a baseline biopsy were excluded from this analysis.

- No significant correlation was found between baseline plasma mIDH1 VAF and tumor mIDH1 VAF (Spaenza et al., 2019) (Figure 3).

- Our results demonstrate the feasibility of detecting mIDH1 in plasma from patients with CC, with a 91.2% concordance rate with mIDH1 detection in tumor tissue.

- These results provide a rationale for exploring liquid biopsy-based genomic profiling as well as for disease monitoring upon treatment.

- Association of baseline circulating mIDH1 VAF with plasma 2-HG levels.

- A total of 33 patients with positive mIDH1 detection in ctDNA had matched plasma samples for 2-HG analysis.

- Spaenza’s rank correlation analysis demonstrated a significant correlation between both circulating biomarkers (Spaenza et al., 2019) (Figure 4).

- Our results demonstrate the feasibility of detecting mIDH1 in plasma from patients with CC, with a 91.2% concordance rate with mIDH1 detection in tumor tissue.

- These results provide a rationale for exploring liquid biopsy-based testing methods when the feasibility of repeated biopsies is an exhaustion limit. Further work is needed to identify actionable mutations through tissue-based panels, which can be a major challenge for trial participation.

**CONCLUSIONS**

- Table 1. Distribution of mIDH1-R132 alleles in tissue and plasma

<table>
<thead>
<tr>
<th>VAF (%)</th>
<th>IDH1-R132</th>
<th>Plasma (n=25)</th>
<th>Tumor (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>R132C</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>0</td>
<td>R132C</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>0</td>
<td>R132G</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>R132G</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**RESULTS**

- Baseline mIDH1 detection in plasma is concordant with mIDH1 detection in tumor tissue.

- mIDH1 detection in ctDNA was detected in 34 of 39 patients who had plasma samples collected immediately before treatment, demonstrating the feasibility of mIDH1 detection in plasma from patients with CC.

- Detection of mIDH1 in plasma ctDNA was concordant with IDH1 mutational status in tissue of 31 of 34 patients (91.2%), including 30 double positive and one double negative (Table 1). (Figure 2).

- Concordance: 91.2% (31/34) (positive-positive, negative-negative)

- Discordance: 8.8% (3/34), all three detected from tissue (NGS) but not plasma.

- Additional data points for patients with discordant mIDH1 detection between plasma and tissue can be found in Table 2. Failure to detect mIDH1 in ctDNA cannot be explained by low mIDH1 VAF in tissue or low tumor burden at baseline.

- Discordance: 8.8% (3/34), all three detected from tissue (NGS) but not plasma.

**BACKGROUND**

- The mutant IDH1 (mIDH1) enzyme has a gain-of-function activity, catalyzing the reduction of alpha-ketoglutarate to produce the mutagenic 2-hydroxyglutarate (2-HG), which leads to epigenetic dysregulation and block in cellular differentiation.

- Intrahepatic cholangiocarcinoma (CC) is a rare, poorly understood, and highly malignant cancer. Genetic characterization is critical for understanding disease biology and is essential for the development of targeted therapies.

**OBJECTIVES**

- To determine the feasibility of detecting mIDH1 in ctDNA from patients with mIDH1 CC enrolled in n=14 mIDH1 CC patients.

- To explore the concordance of mIDH1 detection in plasma ctDNA by digital PCR with that of tumor tissue using next-generation sequencing (NGS) assays.

- To determine the genetic characterization of tumors but also for monitoring tumor landscape in plasma appears similar to that of tissue, indicating that these fragments carry genetic and epigenetic alterations such as point mutations, copy number variations, and DNA-methylation patterns that reflect the biology of the original tumor.

- The evaluation of mIDH1 in ctDNA as emerging as a promising tool not only for the genetic characterization of tumors but also for monitoring tumor progression in a noninvasive manner.

- Previous work has demonstrated the feasibility of ctDNA detection in patients with liver cancer; however, including the liver in the landscape of plasma appears similar to that of tissue, indicating that liquid biopsies are a reliable approach for genetic profiling at baseline as well as for disease monitoring upon treatment.

**METHODS**

- Analyses performed using tumor sequences from ctDNA (n=14 mIDH1 CC patients).

- Plasma ctDNA was detected in 34 of 39 patients who had plasma samples collected immediately before treatment. The interval between tissue and blood collection was <30 days.

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