Early plasma circulating tumor DNA (ctDNA) changes predict response to first-line pembrolizumab +/- chemotherapy in non-small cell lung cancer (NSCLC)

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Introduction
The PD-1 inhibitor pembrolizumab represents an important component of frontline treatment of metastatic non-small cell lung cancer (NSCLC) patients, either as monotherapy or in combination with platinum doublet chemotherapy [1-2]. Current biomarkers are insufficiently to optimally guide decision-making for individual patients with PD-L1 expression and tumor mutational burden (TMB), limited in their ability to distinguish between patients who will benefit from immune checkpoint inhibitors (ICIs). Detection of plasma circulating tumor DNA (ctDNA) is an emerging tool that may permit real-time assessment of response to ICIs.

In this study we hypothesized that early changes in plasma ctDNA changes by next generation sequencing (NGS) would enable early detection of response to frontline pembrolizumab +/- chemotherapy in treatment naïve NSCLC patients prior to radiological assessment.

Methods
Patients with advanced NSCLC who received first-line treatment with pembrolizumab alone or in combination with platinum doublet chemotherapy at the Dana-Farber Cancer Institute, and had consented to a prospective research study (NCT03749066), were enrolled in this study.

Blood samples were collected from each lung cancer patient on the first day of pembrolizumab administration (day 1) and at each subsequent cycle prior to therapy administration. All plasma extraction, 2q of plasma were stored at -80°C according to validated specifications and shipped to the Inivata Clinical Laboratory Improvement Amendments-accredited laboratory (Research Triangle Park, NC) for InivacuffPrep CDNA analysis [3]. For longitudinal monitoring and assessment of changes in ctDNA, if more than one mutation was identified in a baseline sample, the mutation with the highest allelic fraction was used to track ctDNA levels over time compared to baseline.

Distribution of baseline mutations detected by plasma NGS

Results

Clinical outcomes to pembrolizumab +/-chemotherapy according to early ctDNA change

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>PR/CR</th>
<th>N=11</th>
<th>SD</th>
<th>N=11</th>
<th>PD</th>
<th>N=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) -90 (-100 to -94.7)</td>
<td>35 (-100 to 100)</td>
<td></td>
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<tr>
<td>PFS ≥6 months</td>
<td>N=18</td>
<td>PFS ≥6 months</td>
<td>N=11</td>
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<tr>
<td>Median (range) -86 (-57.2 to -94.7)</td>
<td>35 (-100 to 100)</td>
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<td>P = 0.008</td>
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Conclusions

The amplicon-based plasma NGS platform, InivacuffPrep, demonstrated the ability to detect early quantitative changes across a wide range of variants in samples from patients with advanced NSCLC treated with first-line immunotherapy.

- Rapid decreases and clearance of ctDNA in advance of radiological and clinical assessment correlated with clinical benefit, while increasing ctDNA was a harbinger of progressive disease.
- These results suggest a potential role for longitudinal plasma NGS analysis as a new efficacy metric to rapidly assess response or resistance to pembrolizumab +/- chemotherapy.

References