Intra-patient genomic heterogeneity of single circulating tumor cells (CTCs) associated to phenotypic CTC heterogeneity in metastatic castrate resistant prostate cancer (mCRPC)

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Table 3. CTCs/patient

<table>
<thead>
<tr>
<th>Sample</th>
<th>AR</th>
<th>PSMA</th>
<th>RB loss</th>
<th>ATM loss</th>
<th>IAP loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.M.</td>
<td>Yes</td>
<td>No</td>
<td>RB</td>
<td>ATM</td>
<td>IAP</td>
</tr>
<tr>
<td>Z, Schreiber</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2. Patient demographics

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.25%</td>
</tr>
<tr>
<td>Sex</td>
<td>50%</td>
</tr>
<tr>
<td>Race</td>
<td>50%</td>
</tr>
</tbody>
</table>

Analysis of somatic genomic alterations in primary tumors is often used to define mutational status and guide therapeutic decisions. Selective pressures can lead to clonal selection and tumor evolution resulting in intra-tumor clonal heterogeneity. Circulating tumor cells (CTCs) in mCRPC pts have demonstrated phenotypic heterogeneity in size, shape, cytokeratin (CK) and androgen receptor (AR) expression, which can be associated with resistance to androgen receptor signaling targeted therapies (ARs) [1,2]. To understand if there is an underlying genomic heterogeneity leading to phenotypic heterogeneity, we performed NGS whole genome copy number variation (CNV) analysis at the single CTC level in the context of patients progressing in mCRPC and baseline to change in therapy. We assessed the CTCs for driver somatic alterations, phenotypic features, phenotypic heterogeneity and subsequent therapeutic resistance.

Table 1. Description of the CTC morphological and molecular features analyzed during the EpCt analysis (right).

Method

CTC Genotype to Phenotype Correlation

Figure 6. CTC Genotype to Phenotype Correlation

Conclusions

- CTCs from progressing mCRPC patients can harbor multiple genomic alterations per cell
- CTC alterations were strongly associated with CTC phenotypic features, but not with CTC/mL count
- Intra-patient CTC clonal heterogeneity is higher in patients who went on to resist therapy with multiple subclonal drivers of therapeutic resistance
- DNA repair genes BRCA & ATM were often found to be deleted in patients resisting therapy, identifying potentially actionable non-point mutation based alterations
- Single CTC sequencing through a liquid biopsy provides a platform for assessing selection and evolution of clonal subtypes through therapeutic monitoring
- Utilization of single CTC genomic data and genomic heterogeneity to associate to clinical endpoint will require prospective validation

References