Therapeutic biomarker differences between MSI-H and MSS colorectal cancers

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Abstract #3597

Background: Approximately 15% of colorectal cancers (CRC) display high level of microsatellite instability (MSI-H) due to either hereditary predisposition (Lynch syndrome, LS) or somatic hypermethylation of MLH1. They carry a significantly different prognosis and responses to treatments compared with microsatellite stable (MSS) or low microsatellite instability (MSi-L) CRC. We investigated therapeutically important biomarkers, which may underlie different treatment options for CRC.

Methods: Sixty-four MSI-H (including 20 confirmed LS cases), 9 MSI-L and 558 MSS cases were profiled at Caris Life Sciences (Phoenix, AZ) using immunohistochemistry and sequencing (NextGen and Sanger).

Results: Conclusions: There were significantly different prognosis and responses to treatments compared with microsatellite stable (MSS) or low microsatellite instability (MSI-L) CRC. We found significantly different expression profiles of genes such as Thymidylate Synthase (TS), PTEN, STK11, FBXW7, HNF1A, BRCA1/2, and BRCA2 in MSI-H compared with MSS and MSI-L CRCs.

Conclusions: The MSI-H CRC tumors (Lynch status unknown) (N=40) carry high mutations per case, which may be due to lower average age of Lynch syndrome patients.

Results

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Total N</th>
<th>Average Age</th>
<th>Male Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cohort</td>
<td>649</td>
<td>59 yrs</td>
</tr>
<tr>
<td>MSI-H cohort</td>
<td>64</td>
<td>59 yrs</td>
</tr>
<tr>
<td>BRCA-mutated MSI-H cohort</td>
<td>17</td>
<td>73 yrs</td>
</tr>
<tr>
<td>BRCA-wildtype MSI-H cohort</td>
<td>23</td>
<td>66 yrs</td>
</tr>
<tr>
<td>MSI-L cohort</td>
<td>19</td>
<td>67 yrs</td>
</tr>
<tr>
<td>MSI-Negative cohort</td>
<td>557</td>
<td>59 yrs</td>
</tr>
</tbody>
</table>

• Consistent with previous studies, in our cohort, MSI-H patients with sporadic CRC are older in age and are more likely to be female.

• On the other hand, patients with Lynch syndrome are significantly younger in age and are more likely to be male.

• In general, patients with MSI-H phenotype have similar ages and gender distribution as those that are MSI-L.

Figure 1: Sporadic MSI-H CRC (BRCA-V600E) with a poor differentiation and a high number of mitotic figures (A), due to the loss of MYH-1 (B) and its interacting partner PM25 (C).

Figure 2: Biomarker features in molecular subgroups of CRC tumors:

• High expression of TS in both sporadic MSI-H and Lynch tumors suggests lack of benefit from fluorouracil in sporadic CRC patients, very similar to that seen in patients with Lynch syndrome. In CRC patients who are MSI-negative, TS expression is significantly lower, rendering clinical benefit seen in majority of CRC patients.

• Homologous Recombination Deficiency is higher in MSI-H patients, supporting DDX11L3 inhibitors as promising agents that could be used in patients with MSI-H CRC.

• As shown by mutations in PTEN, STK13 and FBW7, PIK3CA/Akt/mTOR pathway activation is high in sporadic MSI-H CRC but low in Lynch tumors and MSI-L tumors, supporting therapeutic opportunities for sporadic MSI-H CRC.

References