Reduced PD-1/PD-L1 expression in KRAS-mutant versus wild-type Microsatellite-Instability-High (MSI-H) Colorectal Cancer (CRC) and association of Wnt pathway corepressor TLE-3.

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Methods
The study included 55 MSI-H (including 20 confirmed Lynch syndrome cases), 9 MSI-low (MSI-L) and 2 cases of microsatellite-stable (MSS) cases that were profiled at Caris Life Sciences (Phoenix, AZ) using immunohistochemistry (IHC) and sequencing (NextGen and Sanger). MSI status was determined using a combination of IHC (MLH1, MSH2, MSH6) and MIA (Microsatellite Instability Analysis) fragment analysis. MIA included fluorescently-labeled primers for co-amplification of seven markers including microsatellite (MS)-locus pentanucleotide repeats and one mononucleotide marker. MSI was defined as more than 2/10 MS-locus repeats were identical between the tumor and adjacent normal tissue. Other specific tests were performed per physician request. Biomarker results were statistically analyzed using Fisher’s exact test. The associations were statistically analyzed by two-tailed Fisher Exact tests.

Conclusions
• Out of the 55 MSI-H patients, 20 had confirmed Lynch syndrome, while the other 35 carried the MSI-H phenotype as tested by IHC and MIA, but no further testing on sporadic or germline status.
• Compared with the complete cohort of MSI-H CRC patients, those with confirmed Lynch syndrome are younger in age and more likely to be male.
• Patient age and gender are not significantly different in P+ and P- MSI-H patients.

Table 1: Patient characteristics among PD-1/PD-L1+ (P+) and negative (P-) MSI colorectal tumors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Average age</th>
<th>Age range</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>P+ MSI-H Cohort</td>
<td>11</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>P+</td>
<td>12</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>P+</td>
<td>13</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>P- MSI-H Cohort</td>
<td>11</td>
<td>40</td>
<td>36</td>
</tr>
</tbody>
</table>

Star: significant differences by Fisher-Exact test

References

Figure 1: Tumor sites

Figure 2: PD-1/PD-L1 expression frequency in MSI-H CRC

Figure 3: Sporadic MSI-H CRC (BRAF V600E) H&E (a: 40x) and PD-1 staining on TIL (b: 40x, TIL count/HPF=5)

Figure 4: Mutation frequencies observed in MSI-H CRC cohort.