The differential response to immune checkpoint inhibitors (ICIs) according to mismatch repair alterations in gastrointestinal (GI) non-colorectal cancers (non-CRCs) and the impact of dual vs. monotherapy ICIs on survival in GI (CRC and non-CRC) cancers.

**Introduction**

Here, we expanded our analysis and included gastrointestinal (GI) non-CRCs and explored the impact of dual vs. monotherapy ICIs on mOS in GI (CRC and non-CRC) cancers.

**Material and Methods**

- Specimens were profiled by next-generation sequencing (592, NextSeq; WES, WTS NovaSeq) (Carcis Life Sciences, Phoenix, AZ).
- MMR/microsatellite instability (MSI) status was determined by immunohistochemistry (IHC) of MMR protein.
- Real world OS was extracted from insurance claims and calculated using Kaplan-Meier estimates for molecularly defined cohorts from first treatment with ICIs (Nivolumab, Ipilimumab, Ipi; or Pembrolizumab, Pembro) to last contact.
- Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons (q < 0.05).

**Results**

- The GI non-CRC cohort (N=19,767) included cancers of the esophagus, stomach, gastroesophageal junction, pancreas, bile duct and small bowel with 97 (0.49%) patients having MutS co-loss, and 494 (4.03%) patients having MutL co-loss.
- MutS co-loss was associated with increased KRAS (45.4% vs 25.2%, q<0.01), CDKN2A (29.2% vs 9.0%), GNAS (27.8% vs 7.8%) and SMAD4 (17.5% vs 5.9%) mutations compared to MutL co-loss.
- Independent of treatment, MutS co-loss (N=74) had improved mOS compared to MutL co-loss.
- In ICI-treated GI (CRC and non-CRC) patients with MutL co-loss, there was a trend for better survival with ipi/nivo compared to pembro. Our data suggest that the MutS vs. MutL status may guide the choice of ICIs regimen (Dual vs. Monotherapy) but more data are needed.

**Conclusion**

- In ICI-treated GI non-CRCs, the mOS was longer in MutS co-loss compared to MutL co-loss.
- In ICI-treated GI CRC and non-CRC patients with MutL co-loss, there was a trend for better survival with ipi/nivo compared to pembro.

**Table 1: Prevalence of MutS and MutL in non-CRC GI cancers**

<table>
<thead>
<tr>
<th>MutL co-loss</th>
<th>MutS co-loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>pos</td>
<td>neg</td>
</tr>
<tr>
<td>pos</td>
<td>80</td>
</tr>
<tr>
<td>neg</td>
<td>9</td>
</tr>
</tbody>
</table>

**Figure 1: Prevalence of MutS and MutL in non-CRC GI cancers**

**Figure 2: Molecular features in MutS and MutL non-CRC cancers**

**Figure 3: Median Overall survival (collection to last contact)**

**Figure 4: Median Overall survival (ICIs treatment to last contact)**

**Figure 5: mOS in GI (CRC and non-CRC) MutL (Ipi/Nivo vs Pembro)**

**Figure 6: mOS in GI (CRC and non-CRC) MutS (Ipi/Nivo vs Pembro)**