Impact of mismatch repair deficiency in the systemic treatment of colorectal cancer

Lars Henrik Jensen, Ph.D., Department of Oncology, Vejle Hospital
Lars.henrik.jensen@rsyd.dk
RESULTS – CRC RECURRENCE BY STAGE

Multivariable HR=0.22; 95% CI 0.02–0.78; 
$P=0.014$

Multivariable HR=0.54; 95% CI 0.15–1.34; 
$P=0.21$

Mutations per tumor

Mutations per tumor

Mismatch-repair proficient colon cancers

Mismatch-repair deficient colon cancers

Hypothesis

• Mutations have been shown to encode proteins that can be recognized and targeted by the immune system

• Average tumor has dozens of somatic mutations; Mismatch repair deficient tumors harbor thousands of mutations

• Immune augmentation with PD-1 blockade may be highly effective in mismatch repair deficient tumors

Mismatch Repair Deficiency

**Microsatellite instability** in tumor cells is due to deficient DNA mismatch repair:

- **germline** (Lynch syndrome) and/or **sporadic** mutations (MLH1, MSH2, MSH6, PMS2, EpCAM)
- **epigenetic silencing** (MLH1 hypermethylation)
## Study Design

<table>
<thead>
<tr>
<th>Colorectal Cancers</th>
<th>Non-Colorectal Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A</strong></td>
<td><strong>Cohort B</strong></td>
</tr>
<tr>
<td>Deficient in</td>
<td>Proficient in</td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td>Mismatch Repair</td>
</tr>
<tr>
<td>(n=25)</td>
<td>(n=25)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort C</strong></td>
<td></td>
</tr>
<tr>
<td>Deficient in</td>
<td></td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td></td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
</tr>
</tbody>
</table>

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate

<table>
<thead>
<tr>
<th></th>
<th>MMR-deficient CRC</th>
<th>MMR-proficient CRC</th>
<th>MMR-deficient non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>20</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td><strong>Objective Response Rate</strong></td>
<td>55%</td>
<td>0%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Disease Control Rate</strong></td>
<td>90%</td>
<td>16%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Target Lesions: CRC Cohorts

MMR-proficient CRC
MMR-deficient CRC

% Change from Baseline SLD

Survival Curves (October 2015)

Overall Survival

Progression-Free Survival

Study Treatment

**Pembrolizumab Arm**
- Pembrolizumab 200 mg IV Q3W

**Standard of Care Arm**
- Investigator's choice of one of the following Q2W:
  - mFOLFOX6
  - mFOLFOX6 + bevacizumab
  - mFOLFOX6 + cetuximab
  - FOLFIRI
  - FOLFIRI + bevacizumab
  - FOLFIRI + cetuximab
Keynote 177

- First-line treatment
- Immunohistochemistry or DNA MSI
- Essential to identify patients at the MDT conference
- Herlev
- Odense
- Vejle
Take home

• Immunotherapy - a revolution for the one in twenty patients with metastastic dMMR colorectal cancer
• Be aware of both sporadic cases and Lynch Syndrome patients – the possibility of trials
• Pathologists identifies the patients
• MDT conferences
Future perspective (hope)

Combination immunotherapy

Control

Checkpoint blockade

Standard therapy