How to Improve the Results with IO Agents in MSI GI Cancer?

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Disclosures Information

Consulting or Advisory Role and/or Honoraria: Astra-Zeneca, Amgen, BMS, Chugai, MSD Oncology, HalioDx, Roche/Ventana, Sanofi, Sevier, Yakult
#### Emidemiology of MSI/dMMR GI Cancer

<table>
<thead>
<tr>
<th>Primary</th>
<th>Locally non M+</th>
<th>M+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colo-Rectal/Small Intestine</td>
<td>10-20%</td>
<td>4-5%</td>
</tr>
<tr>
<td>Oeso-Gastric ADK</td>
<td>8-24%</td>
<td>3-6%</td>
</tr>
<tr>
<td>Chlangiocarcinoma</td>
<td>4-5%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1-2%</td>
<td>≤ 1%</td>
</tr>
<tr>
<td>Hepatocarcinoma</td>
<td>1-2%</td>
<td>≤ 1%</td>
</tr>
<tr>
<td>Anus</td>
<td>Unknown but &lt; 1%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Colle R et al; Bull du cancer 2018
Anti-Tumour Immunity Across Different Stages of MSI CRC

- Most of dMMR/MSI tumours are highly infiltrated with cytotoxic T cells

**STAGE 2**
- Infiltration with activated cytotoxic T-cell L (CD8+/Th1) = effective anti-tumor immunity
- Good prognosis for MSI

**STAGE 3**
- Positive effect of cytotoxic T-cell L predominant
- Expression of immune-checkpoints counterbalances the effects of cytotoxic T-cell in some patients who then progress to stage 4
- Overall prognosis unclear

**STAGE 4**
- Concomitant and specific overexpression of multiple immune checkpoints (e.g. CTLA-4, PD-1, LAG-3) and immune-inhibitory molecules (e.g. IDO) attenuate anti-tumoural immunity
- Prognosis worse compared to MSS

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Potential of Immune Checkpoint Inhibitors in MSI mCRC

Investigation of checkpoint inhibitors as novel agents in Cancer treatment

- Dendritic cell
  - MHC II
  - TCR
  - B7
  - Tremelimumab
  - Ipilimumab

- T cell
  - CTLA-4

- Tumor cell
  - MHC II
  - TCR
  - PD-1
  - PD-L1
  - Pembrolizumab
  - Nivolumab
  - TSR-042
  - Atezolizumab
  - Durvalumab
  - Avelumab
### Pembrolizumab: NCT01876511
Summary of Clinical Activity¹⁻²

#### Best Radiographic Response¹⁻²

<table>
<thead>
<tr>
<th>Response</th>
<th>dMMR CRC</th>
<th>pMMR CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>57 (39–73)</td>
<td>0 (0–13)</td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
<td>89 (73–96)</td>
<td>16 (6–35)</td>
</tr>
<tr>
<td>CR, %</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>PR, %</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>SD*, %</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>PD, %</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>NE, %</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>PFS, mo</td>
<td>NR</td>
<td>2.3</td>
</tr>
<tr>
<td>OS, mo</td>
<td>NR</td>
<td>5.98</td>
</tr>
</tbody>
</table>

Réponse au Pembrolizumab pour non mCRC MSI-H/dMMR

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Patients (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>18 (21%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>28 (33%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (23%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Objective response rate 95% CI</td>
<td>53% 42% to 64%</td>
</tr>
<tr>
<td>Disease control rate 95% CI</td>
<td>77% 66% to 85%</td>
</tr>
<tr>
<td>Median progression-free survival time 95% CI</td>
<td>NR 14.8 months to NR</td>
</tr>
<tr>
<td>2-year progression-free survival rate 95% CI</td>
<td>53% 42% to 68%</td>
</tr>
<tr>
<td>Median overall survival time 95% CI</td>
<td>NR NR to NR</td>
</tr>
<tr>
<td>2-year overall survival rate 95% CI</td>
<td>64% 53% to 78%</td>
</tr>
</tbody>
</table>

11 patients on CR and stopped pembrolizumab at 2 years
Without any progression after (median time after stopping: 8.3 months)

Le DT, Science 2017
ORR (Checkmate 142) mCRC after ≥ 2 lines of chemo ± targeted therapy (76%)

Disease Control Rate (Same Follow up):
85% with nivo + ipi and 69% with nivo monotherapy

1 Overman M, Lancet Oncol 2017; 2 Overman M, J Clin Oncol. 2018; 3 André T, ASCO GI 2018
Progression-Free and Overall Survival (Checkmate 142)

Median follow-up was 13.4 (range, 9–25) months

1 Overman M, Lancet Oncol 2017; 2 Overman M, J Clin Oncol. 2018; 3 André T, ASCO GI 2018
The true problem is not how to improve the results with IO agents in MSI GI Cancer but to have access to IO for these patients (labelling only in US and Switzerland)

- Why EMA ask phase III for labelling in Europe?
- How many time patients will wait to treat?
- We have to improve results but the first step is to increase the number of patients with MSI GI cancer treated with IO Agents
Challenge # 1:

MSI/dMMR diagnostic without mis-diagnosed
## Determining MMR/MSI Status

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Measurement and Classification</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMR protein deficiency</strong></td>
<td>- Antibodies to detect MLH1, MSH2, MSH6, and PMS2 proteins; visual scoring</td>
<td>• Guideline-recommended; complementary to PCR</td>
</tr>
<tr>
<td>(IHC)(^1,2)</td>
<td>- dMMR defined as loss of any protein by IHC</td>
<td>• IHC used to screen for Lynch Syndrome</td>
</tr>
<tr>
<td><strong>Microsatellite instability</strong></td>
<td>• 2 reference panels:</td>
<td>• Guideline-recommended</td>
</tr>
<tr>
<td>(PCR)(^1,3,4)</td>
<td>- Bethesda: BAT25 and BAT26 (mononucleotide); D5S346, D2S123, D17S250 (dinucleotide)</td>
<td>• Performed on tumoral DNA compared to germline DNA; normal tissue not needed</td>
</tr>
<tr>
<td></td>
<td>- Promega: BAT25, BAT26, NR21, NR24, NR-27 (mononucleotide)</td>
<td>• &gt;93% concordance between PCR and IHC methods (Colo-rectal cancer)</td>
</tr>
<tr>
<td></td>
<td>• MSI-H defined as &gt;30% of markers with instability</td>
<td></td>
</tr>
<tr>
<td><strong>Genomic sequencing</strong></td>
<td>• Assesses MSI phenotype and/or mutational load</td>
<td>• Currently in development</td>
</tr>
<tr>
<td>(NGS)(^5,6)</td>
<td>• MSI threshold determined by number of markers analyzed</td>
<td>• Potential to offer one-step sequencing for other common mutations (ie, BRAF and RAS)</td>
</tr>
</tbody>
</table>

MMR Immunohistochemistry

Concurrent loss  Isolated loss
HMLH1 -/PMS2-  HMLH1 +/PMS2-
MSH2-/MSH6-  MSH2+/MSH6-

- 4-antibodies screening approach
- or 2-antibody panel including only PMS2 and MSH6
- But the interpretation can be challenging for PMS2 and MSH6 and may fail to detect MMR deficiency if only two antibodies

4-stain method recommended for optimal dMMR screening detection

Shia et al Am J; Surg Pathol 2009; Pearlman R; Modern Pathology 2018
ESMO Recommendations on MSI testing

- Immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 first action to assess MSI/dMMR
- In case of doubt of IHC, confirmatory molecular analysis is mandatory by PCR
- Next-generation sequencing, coupling MSI and TMB analysis, may represent a decisive tool for selecting patients for immunotherapy, for common or rare cancers not in the spectrum of Lynch syndrome.

Luchini C, Annals Oncol 2019
**All cancer: n=11348**
Metastatic for vast majority

- MSI: 3%
  - (30% are TB Low, 26% PDL1+)
- High TB: 7.7%
- PDL1 +: 24.4%

**Colorectal Cancer n=1395**
Metastatic for vast majority

- MSI: 5.7%= 80 pts
  - (only 5% TB Low (4/80), 29% PDL1+ (23/80))
- High TB: 6.7% = 93 pts
- PDL1 +: 7.2% = 100 pts

**Comparaison NGS MSI vs PCR MSI**
Sensitivity: 95.8%
Specificity: 99.4%

**TMB High if ≥ 17 mutations/megabase**

**MSI = hypermutated (High TMB)**
Beyond MSI CRC, there are "ultra-mutated" tumors, which correspond to POLE-mutated CCRs and all are not MSI/dMMR.

*Vanderwalde et al., Cancer Med 2018*
MSI/dMMR diagnosed: Not simple in Pancreatic adenoC

• Incidence: between 1 and 2%

• Frequently associated with specific histological features (medullary carcinoma, acinar cell carcinoma, intraductal papillary mucinous neoplasms)

• IHC with 4 anti-bodies is the best screening method!

• False negative case by PCR is frequent (< 50% concordance between PCR and IHC methods)

• Futur for screening is NGS: not sure it’s work for MSI for pancreatic cancer

Lupinacci R et al, Gastroenterology2018; Lipinacci R, Surgical Oncology 2019
MSS cancers mis-diagnosed as MSI/dMMR
no consensus for inclusion in clinical trials

CheckMate-142:
- 19% of discrepancies between centralized (PCR on metastasis biopsy) and local analysis (primary tumor or metastasis by IHC or PCR)
- Amongst these patients: 50% of immediate progression disease

Misdiagnosis of MSI: a cause of immediate progression under ICKi;
- Cohort of Saint-Antoine hospital, Paris, France (Jan 2015 - Dec 2016)
- 38 patients locally diagnosed (center we refer the patient for inclusion in IO studies) with MSI or dMMR mCRC
- 5/38 patients with immediate disease progression under ICKi
- 3/5 patients were both MSS (PCR) and pMMR (IHC)

Kopetz, J Clin Oncol 35, 2017 (suppl; abstr 3548)
Cohen R, JAMA Oncol 2018
How many MSS mCRC patients were included in ICKi trials dedicated to MSI?

- No central confirmation of the MSI/dMMR status prior to inclusion in the CheckMate-142, KEYNOTE-164 trials and others

→ how much MSI misdiagnosis is responsible for primary resistance?

nivolumab

pembrolizumab

Overman et al., Lancet Oncol 2017; Diaz et al., J Clin Oncol 35, 2017 (suppl; abstr 3071)
Challenge # 2:

What is the best regimen?
When we will treat: First line or if refractory to standard therapy?

In refractory tumor
- Anti-PD1\(^1\) (30-50\% ORR in refractory tumor)
- Anti-PDL1\(^2\) (21\% ORR on in refractory tumor)
- Anti-PD1 and anti-CTL4\(^3\) (55-60\% ORR)
- Other Immuno-oncology?

In first line
- Pembrolizumab (Keynote 177): waiting results
- Anti-PD1 and anti-CTL4\(^4\) (60\% RP)
- Combined with chemo?

ORR (Checkmate 142) mCRC after ≥ 2 lines of chemo ± targeted therapy (76%)

Disease Control Rate (Same Follow up):
80% with nivo + ipi and 69% with nivo monotherapy

1 Overman M, Lancet Oncol 2017; 2 Overman M, J Clin Oncol. 2018; 3 André T, ASCO GI 2018
## Checkmate 142: ORR in first line in MSI mCRC

<table>
<thead>
<tr>
<th>Overall Response Rate, n (%)</th>
<th>NIVO3 (Q2W) + IPI1 (Q6W)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 45</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>27 (60)</td>
</tr>
<tr>
<td></td>
<td>[44.3–74.3]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best response, n (%)*</th>
<th>NIVO3 (Q2W) + IPI1 (Q6W)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 45</td>
</tr>
<tr>
<td>CR</td>
<td>3 (7)</td>
</tr>
<tr>
<td>PR</td>
<td>24 (53)</td>
</tr>
<tr>
<td>SD</td>
<td>11 (24)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Non done</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Control Rate , n (%)</th>
<th>NIVO3 (Q2W) + IPI1 (Q6W)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 45</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>38 (84)</td>
</tr>
<tr>
<td></td>
<td>[70.5–93.5]</td>
</tr>
</tbody>
</table>

Challenge # 3:
To deal with the patient in clinical practice

• How long of treatment: one year, two year ? more?
• What interval between infusions?
• When monotherapy (pembrolizumab or nivolumab) and when combination of nivolumab + ipilimumab?
• What is indication for surgery
  – In case of partial response (residual mass) ?
  – When ?

• In case of progressive disease: What will do ?
Challenge # 4: Labelling in Europe and Asia of pembrolizumab and/or nivolumab ± ipilimumab in MSI mCRC and other metastatic GI cancer

• For treating patients MSI mCCR only possible in clinical trials in Europe and other part of the world: Unbelievable situation!
Patients
• MSI-high or dMMR mCRC
• No prior therapy
• Measurable disease per RECIST v1.1
• ECOG PS 0 or 1

Pembrolizumab 200 mg IV Q3W

Investigator-Choice Chemotherapy

Crossover Eligible

Pembrolizumab 200 mg IV Q3W

Primary end point: PFS per RECIST 1.1 by central imaging vendor

Inclusion closed Q1 2018

• Open label, N = 307 included and inclusion closed. Curative resection permitted on study
Phase 3b Randomized Clinical Trial of NIVO Alone, NIVO + IPI, or an Investigator’s Choice Chemotherapy For MSI-H/dMMR mCRC

**Inclusion criteria**
- Recurrent or metastatic CRC
- MSI-H/dMMR by local testing
- ECOG 0 and 1

**Arm A:** Nivolumab monotherapy
**Arm B:** Nivolumab plus ipilimumab
**Arm C:** Investigator’s choice chemotherapy

Randomization (N = 494*)

Follow-up

- Treat until progression or toxicity
- Participants in Arm C would be allowed to receive nivolumab plus ipilimumab if they progress

**Primary endpoint**
- PFS per BICR

**Key Secondary endpoints**
- PFS, ORR, DCR per investigator assessment
- ORR, DCR per BICR
- OS, TTR, DOR
**Challenge # 5:**
Try to understand Primary Resistance

- Misdiagnose MSI/dMMR (What is standard for agency ?)
- Pseudoprogession++++
- Deficiency of antigen presentation: Beta 2 microglobuline mutation some MSI mCRC; Mutation of JAK1/2
- Evaluation of Immunoscore and Immunune Check Point expression to use other IO (anti-Lag3, IDO inhibitors……..)
- Exome sequencing if resistance to find genes fusion for targeted therapy ?
- Microbiote ?

Jass, Histopathology 2007; Llosa et al., Cancer Discov 2015; Klooor et al., Int J Cancer 2010
Llosa et al., Cancer Discov 2015; Clendenning, Fam Cancer 2018
Syn et al., Lancet Oncol 2017; Routy et al., Science 2018; Guinney et al., Nature Med 2015
Challenge # 6: Neo-adjuvant Treatment

• Proof of concept
• Better that neo-adjuvant or adjuvant chemotherapy?
• Rate of complete histological response?
• The dream: avoid surgery!
Neoadjuvant Ipilimumab plus Nivolumab in Early Stage Colon Cancer

- first results of the NICHE study

**dMMR (n=7)**

<table>
<thead>
<tr>
<th>Age-yr (range)</th>
<th>60.9 (41 - 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex – no. (%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>CEA</td>
<td>\n</td>
</tr>
<tr>
<td>≥5</td>
<td>1</td>
</tr>
<tr>
<td>Clinical disease stage – no. (%)</td>
<td>\n</td>
</tr>
<tr>
<td>III</td>
<td>4 (57%)</td>
</tr>
</tbody>
</table>

**dMMR (n=7)**

<table>
<thead>
<tr>
<th>Pre-treatment clinical stage</th>
<th>Pathological stage at resection</th>
<th>Residual vital tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT2N2a</td>
<td>ypT0N0</td>
<td>0 %</td>
</tr>
<tr>
<td>cT2N0</td>
<td>ypT0N0</td>
<td>0 %</td>
</tr>
<tr>
<td>cT2N0</td>
<td>ypT0N0</td>
<td>0 %</td>
</tr>
<tr>
<td>cT3N0</td>
<td>ypT0N0</td>
<td>0 %</td>
</tr>
<tr>
<td>cT3N2a</td>
<td>ypT1N0</td>
<td>1 %</td>
</tr>
<tr>
<td>cT4aN2a</td>
<td>ypT2N0</td>
<td>2 %</td>
</tr>
<tr>
<td>cT4aN1a</td>
<td>ypT3N1</td>
<td>2 %</td>
</tr>
</tbody>
</table>
Peri-operative nivolumab and ipilimumab with post-operative nivolumab alone in localized MSI/dMMR oeso-gastric adenocarcinoma:
An open-label GERCOR phase II study (PI: T André)
EudraCT Number: 2018-004712-22
Thanks for your attention