Current and Emerging Role of Immune Checkpoint Inhibitors in the Management of mCRC

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MD Anderson Cancer Center
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Reimbursement and regulatory issues aside, for a patient with minimally symptomatic, MSI-high mCRC with modest tumor burden, in which line of therapy would you like to use an anti-PD-1/PD-L1 antibody?

First line
- Nivolumab/ipilimumab: 14
- Pembrolizumab: 9

Second line
- Nivolumab: 1

For a younger, otherwise healthy patient with MSI-high mCRC for whom you are planning to administer immune checkpoint inhibitor therapy, in general which agent or regimen would you most likely recommend?

- Nivolumab/ipilimumab: 14
- Pembrolizumab: 8
- Nivolumab: 1

A 65-ya patient with right-sided, MSI-high, pan-RAS WT, BRAF WT mCRC who receives FOLFOX/bev then FOLFIRI/bev is now experiencing progression. What would be your most likely third-line treatment?

- Nivolumab/ipilimumab: 11
- Pembrolizumab: 9
- Nivolumab: 2
- Panitumumab + irinotecan: 1

**Immune checkpoint inhibitors**

**MSI-high disease**
- Sequencing and selection of treatment
- Autoimmune toxicity
- Treatment discontinuation

**Microsatellite-stable disease**
- Regorafenib/nivolumab
Immune checkpoint inhibitors

MSI-high disease
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Immune checkpoint inhibitors

**MSI-high disease**
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**Microsatellite-stable disease**
- Regorafenib/nivolumab

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A 65- yo patient with right-sided, MSS mCRC with a RAS mutation who receives FOLFOX/bev then FOLFIRI/bev is now experiencing progression (PS 0). What would be your most likely treatment?

- Regorafenib
- Regorafenib or TAS-102 — coin flip
- TAS-102
- FOLFOXIRI

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To approximately how many patients with metastatic colorectal or gastric cancer have you administered regorafenib in combination with nivolumab either on or off protocol?

- 23 patients treated by 9 clinical investigators

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Have you or would you use regorafenib in combination with nivolumab for a patient with metastatic colorectal or gastric cancer?

- I have
- I have not but would for the right patient
- I have not and would not

---

Have you observed any objective responses after administering regorafenib in combination with nivolumab for patients with metastatic colorectal or gastric cancer?

- Yes
- No
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## Disclosures

<table>
<thead>
<tr>
<th>Consulting Agreements</th>
<th>Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, CatalYm, Gritstone Oncology, Promega Corporation, Roche Laboratories Inc</th>
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<tr>
<td>Contracted Research</td>
<td>Apexigen, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Merck, Nouscom, Roche Laboratories Inc.</td>
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</tbody>
</table>
dMMR or MSI-H CRC: Frameshift Neoantigens

dMMR Testing

- **MLH1** and **PMS2/1**
- **MSH2** and **MSH6**

Small IDLs (1-2 nucleotides)

**Immunohistochemistry**
Complete loss of expression in one of the MMR proteins = MSI-high

**Polymerase Chain Reaction**
Panel of 5 or more microsatellites with allelic shift in 2 (>30%) or more markers = MSI-high

**Next-generation Sequencing**

Latham + Stadler et al. JCO 2018
TCGA Analysis: 39 cancer types; 11,139 tumors

TOP 15

- Uterine Endometrial Carcinoma
- Colon Adenocarcinoma
- Stomach Adenocarcinoma
- Rectal Adenocarcinoma
- Adrenocortical Carcinoma
- Uterine Carcinosarcoma
- Cervical
- Wilms Tumor
- Mesothelioma
- Esophageal Carcinoma
- Breast Carcinoma
- Renal Clear Cell
- Ovarian
- Cholangiocarcinoma
- Thymoma

Bonneville et al., JCO PO 2017
dMMR and Pembrolizumab

Le et al. NEJM 2015; Le et al. Science 2017; Marabelle JCO 2019; Le ASCO 2018 a3514

ORR 53%
Keynote 16

ORR 34%
Keynote 158

ORR 32%
Keynote 164 cohort B

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The NEW ENGLAND JOURNAL of MEDICINE

% Change from Baseline SLD

MMR-proficient CRC
MMR-deficient CRC
dMMR and Nivolumab, Nivolumab/Ipilimumab

Nivolumab and Ipilimumab

ORR 55%

Checkmate 142

Nivolumab

ORR 31%

Checkmate 142

Overman Lancet Onc 2017; Overman JCO 2018
Efficacy for NI Refractory vs Frontline Cohorts

Refractory (n=119)
Frontline (n=45)

Progression-free Survival

Frontline
Refractory

Overall Survival

Frontline
Refractory

Overman JCO 2018, Heinz-Lenz ESMO 2018 and GI ASCO 2020
NICHE Clinical Trial

- Ipilimumab 1mg/kg Day 1
- Nivolumab 3mg/kg Day 1 + 15

- Median duration from first tx to surgery 32 days (IQR: 28-35)

<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>

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<th>Pre-treatment clinical stage</th>
<th>Pathological stage at resection</th>
<th>Residual vital tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT3N1a</td>
<td>ypT3N2</td>
<td>85 %</td>
</tr>
<tr>
<td>cT3N0</td>
<td>ypT3N0</td>
<td>90 %</td>
</tr>
<tr>
<td>cT2N0</td>
<td>ypT3N1</td>
<td>90 %</td>
</tr>
<tr>
<td>cT3N1b</td>
<td>ypT3N1</td>
<td>90 %</td>
</tr>
<tr>
<td>cT3N1b</td>
<td>ypT3N2</td>
<td>95 %</td>
</tr>
<tr>
<td>cT3N0</td>
<td>ypT3N0</td>
<td>100 %</td>
</tr>
<tr>
<td>cT2N0</td>
<td>ypT2N0</td>
<td>100 %</td>
</tr>
</tbody>
</table>
non-CRC dMMR

Nivolumab

Pembrolizumab

Lee et al Science 2017, Pembrolizumab FDA label; Azad + Overman JCO 2019
Frontline Metastatic

NRG-GI004/SWOG-1610
MSI-high mCRC

PI: Michael Overman and Caio Max S. Rocha Lima

N=315

mFOLFOX6/Bevacizumab

Atezolizumab

mFOLFOX6/Bevacizumab + Atezolizumab

KEYNOTE 177
MSI-high mCRC

PI: Luis Diaz

N=270

mFOLFOX6/Bevacizumab

Pembrolizumab

Enrollment Completed 2/2018

Stage III Adjuvant

Alliance 021502 (ATOMIC)
Resected MSI-H Stage III

PI: Frank Sinicrope

N=700

mFOLFOX6 + Atezolizumab (12 cycles)
then Atezolizumab x 6 months

mFOLFOX6 (12 cycles)

POLEM
Resected MSI-H or POLE Stage III post adjuvant tx

PI: Tony Dhillon

N=402

Avelumab x 6 months

observation
Novel Phase IIs

N=40
High risk locally advanced dMMR resectable or unresectable tumor
PI: Michael Overman

NCT04082572
Pembrolizumab x 6m → Resection
Primary endpoint: Path CR

N=48
MSI-H ctDNA+ post curative surgery/adjuvant tx
PI: Yelena Janjigian

NCT03832569
R
Placebo
Pembrolizumab x 12m
Primary endpoint: ctDNA clearance at 12m
Are There Response Predictors?

Cohen et al. 2019 Jama Onc, Mandal et al. 2019 Science

Table. Misdiagnosis of Microsatellite Instability and Mismatch Repair-Deficient Tumors by Local Assessment

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Local Assessment</th>
<th>Central Review</th>
<th>Best Response Under Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IHC</td>
<td>PCR</td>
<td>IHC</td>
</tr>
<tr>
<td>Patients included in immunotherapy trials (n = 38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>pMMR</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>115</td>
<td>NE</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>181</td>
<td>dMMR</td>
<td>NE</td>
<td>pMMR</td>
</tr>
<tr>
<td>Retrospective historical cohort (n = 93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>pMMR</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>41</td>
<td>NE</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>42</td>
<td>NE</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>43</td>
<td>NE</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>46</td>
<td>NE</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>56</td>
<td>NE</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>64</td>
<td>pMMR</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>94</td>
<td>pMMR</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
<tr>
<td>106</td>
<td>NE</td>
<td>MSI</td>
<td>pMMR</td>
</tr>
</tbody>
</table>

Cohen et al. 2019 Jama Onc, Mandal et al. 2019 Science

Graphs and diagrams illustrating Tumor PD-L1 Expression, BRAF Mutation Status, and Clinical History of Lynch Syndrome.
Negative anti-PD1/PDL1 trials in MSS CRC

CHECKMATE 142 (MSS CRC)

<table>
<thead>
<tr>
<th></th>
<th>Nivo 1/ Ipi 3 (n = 10)</th>
<th>Nivo 3/ Ipi 1 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>2.28 (0.62, 4.40)</td>
<td>1.31 (0.89, 1.71)</td>
</tr>
</tbody>
</table>

KEYNOTE-028 (PDL-1+ CRC)

The only MSI-high pt was the one responder.

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab + Cobimetinib</th>
<th>Atezolizumab + Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>1 (10)</td>
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</table>

Bendell et al. GI ESMO 2018, Grothey ESMO 2018, O’Neil et al. ESMO 2015
High TMB as a Marker for Response in MSS CRC?

**CO.26 Durvalumab/Tremelimumab in MSS CRC**

GuardantOMNI cfDNA panel: 500 genes, 2.1MB

- 42% of patients had TMB > 20
- This is usually the range for MSI-H CRC
- *This is one of the most heavily pre-treated cohorts to date*

**TAPUR: Pembrolizumab in high TMB (≥9) CRC**

<table>
<thead>
<tr>
<th>Number of pts</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, yrs</td>
<td>59 (34-79)</td>
</tr>
<tr>
<td>≥3 Prior systemic regimens, %</td>
<td>78</td>
</tr>
<tr>
<td>DC rate, % (OR or SD16+) (90% CI)</td>
<td>28 (16, 45)</td>
</tr>
<tr>
<td>OR rate, % (95%)</td>
<td>4 (0, 19)</td>
</tr>
<tr>
<td>Median PFS, wks (95% CI)</td>
<td>9.3 (7.3, 16.1)</td>
</tr>
<tr>
<td>1 year OS, % (95% CI)</td>
<td>45.6 (22.2, 66.3)</td>
</tr>
</tbody>
</table>

HTMB ranged from 9 to 54 Muts/Mb

FoundationOne data

Fabrizio J of Gastro Onc 2018; Chen ASCO 2019; Meriri et al. GI ASCO 2020 a133
Regorafenib and Nivolumab

Regorafenib 80mg/d 21on/7off
Nivolumab 3mg/kd q2wks

Fukuoka et al. a2522 ASCO 2019
# Treatment-Related Adverse Events for N/I

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Frontline (N=45)</th>
<th>Refractory (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>35 (78)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Any serious TRAE</td>
<td>6 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Any TRAE leading to discontinuation</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRAEs reported in &gt;10% of patients</th>
<th>Frontline</th>
<th>Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>11 (24)</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8 (18)</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7 (16)</td>
<td>21 (18)</td>
</tr>
<tr>
<td>Anthralgia</td>
<td>6 (13)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>5 (11)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (11)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (11)</td>
<td>26 (22)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;10%</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Overman JCO 2018, Heinz-Lenz ESMO 2018