IMMUNOTHERAPY FOR GASTROINTESTINAL CANCERS

Dr Elizabeth Smyth
Royal Marsden Hospital

ESMO Colorectal Cancer Preceptorship Valencia 2018
DISCLOSURES

Honoraria for advisory role
Servier, Celgene, BMS, Five Prime Therapeutics, Gritstone Oncology
OUTLINE

- Immunotherapy primer
- Colorectal cancer
- Hepatocellular Cancer
- Gastroesophageal Cancer
Antigen presenting
Can cytotoxic T-cells be generated?

T-cell trafficking
Can the T-cells get to the tumour?

Peptide-MHC recognition
Can the T-cells see the tumour?

PD-L1 on tumour/inhibitory cytokines
Can the T-cells be deactivated?
Anti-CTLA4 antibodies (ipilimumab, tremilimumab) block a negative regulatory signal during T-cell priming.

Anti-PD-1 antibodies (pembrolizumab, nivolumab) block the negative regulatory signal of PD-1 which is expressed on T-cells during long term antigen exposure.
I. COLORECTAL CANCER
# Colorectal Cancer Molecular and Immune Landscape

**CMS1: MSI Immune**
- 14%
- MSI, CIMP high, hypermutation
- Immune infiltration and activation
- Worse survival after relapse

**CMS2: Canonical**
- 37%
- SCNA high
- WNT and MYC activation
- Worse relapse-free and overall survival

**CMS3: Metabolic**
- 13%
- Mixed MSI status, SCNA low, CIMP low
- Metabolic deregulation

**CMS4: Mesenchymal**
- 23%
- SCNA high
- Stromal infiltration, TGFβ activation, angiogenesis

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**Genomic**
- MSI
- CIN

**Epigenomic**
- Mutation count
- Promoters

**Transcriptomic Pathways**
- Immune activation
  - Jak-Stat activation
  - Caspases
  - DNA damage repair
  - Glutaminolysis
- Lipidogenesis
- Cell cycle
- WNT targets
- MYC activation
- EGFR or SRC activation
- VEGF or VEGFR activation
- Integrins activation
- TGFβ activation
- Mesenchymal transition
- Complement activation
- Immunosuppression

**Stroma-Immune Microenvironment**
- Highly immunogenic
- Poorly immunogenic
- Inflamed (immune-tolerant)

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**Figure: CMS Classification**

- CMS1
  - T cell clonal expansion
  - CD8+ T cell infiltration
  - Inflamed stroma

- CMS2
  - T cell infiltration
  - CD8+ T cell activation
  - Immunogenic

- CMS3
  - Lyric cell infiltration
  - T cell activation
  - Activated stroma

- CMS4
  - NK cell infiltration
  - Immune evasion
  - Tumor-associated macrophages

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Gunney et al. Nat Med. 2015 Nov;21(11):1350-6
MISMATCH REPAIR DEFICIENCY AND THE IMMUNE SYSTEM

1. Insertion mutation in coding microsatellites leading to frameshift mutation

2. Translation of frameshift peptides

3. Processing and presentation of frameshift peptides

Mismatch repair deficiency across 12,019 tumours.

Mismatch repair deficiency across 12,019 tumours.

Mismatch repair deficiency across 12,019 tumours.
PEMBROLIZUMAB IN CRC

- MMRP or MMRD (loss of MLH1, MSH2, MSH6 or PMS2, or MSI in ≥ 2 loci)
- ≥ 2 prior cancer therapy regimens
- ECOG PS ≤ 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MMRD CRC (n = 28)</th>
<th>MMRP CRC (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, %</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Response, %</td>
<td></td>
<td></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>Not evaluable</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>NR</td>
<td>2.3</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>NR</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Le DT, et al. ASCO 2016. Abstract 103
Le DT et al, NEJM 2015
May 2017 – FDA licensed pembrolizumab in previously treated MMRD colorectal cancer
NIVOLUMAB FOR MMRD-CRC
CHECKMATE-142

- Histologically confirmed metastatic or recurrent CRC
- dMMR/MSI-H per local laboratory
- ≥ 1 prior line of therapy

Primary endpoint:
- ORR per investigator assessment

Other key endpoints:
- ORR per BICR, DCR, DOR, PFS, OS, and safety

Nivolumab 3 mg/kg Q2W
## NIVOLUMAB FOR MMRD-CRC
### CHECKMATE-142

<table>
<thead>
<tr>
<th></th>
<th>All patients N = 74</th>
<th>Group A&lt;sup&gt;a&lt;/sup&gt; n = 53</th>
<th>Group B&lt;sup&gt;b&lt;/sup&gt; n = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>52.5 (26–79)</td>
<td>53.0 (26–79)</td>
<td>52.0 (27–77)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>44 (59)</td>
<td>30 (57)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32 (43)</td>
<td>21 (40)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>1</td>
<td>41 (55)</td>
<td>31 (58)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Disease stage at diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–III</td>
<td>41 (55)</td>
<td>31 (58)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>IV</td>
<td>33 (45)</td>
<td>22 (42)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Mutation status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF/KRAS wild type</td>
<td>29 (39)</td>
<td>21 (40)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>BRAF mutated</td>
<td>12 (16)</td>
<td>6 (11)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>KRAS mutated</td>
<td>27 (36)</td>
<td>22 (42)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (8)</td>
<td>4 (8)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Clinical history of Lynch syndrome, n (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (38)</td>
<td>20 (38)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>No</td>
<td>27 (36)</td>
<td>15 (28)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Unknown</td>
<td>19 (26)</td>
<td>18 (34)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Overman et al, ASCO GI 2018
NIVOLUMAB FOR MMRD-CRC
CHECKMATE-142

Overman et al, ASCO GI 2018
NIVOLUMAB FOR MMRD-CRC
CHECKMATE-142

Median PFS 6.6 months
Median PFS 4.2m (A) vs NR(B)

Median OS not reached
12 month OS 68% (A) vs 81%(B)

August 2017 – FDA licensed nivolumab in MMRD colon cancers
NIVOLUMAB + IPILIMUMAB FOR MSI-CRC
CHECKMATE-142

Phase 2 Nonrandomized Study

- Histologically confirmed metastatic or recurrent CRC
- dMMR/MSI-H per local laboratory
- ≥ 1 prior line of therapy

Combination cohort

Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W
(4 doses and then nivolumab 3 mg/kg Q2W)

Monotherapy cohort

Nivolumab 3 mg/kg Q2W

Primary endpoint:
- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
- ORR per BICR, DCR,b DOR, PFS, OS, and safety

Andre et al, ASCO GI 2018
NIVOLUMAB + IPILIMUMAB FOR MSI-CRC

Investigator assessed response

Andre et al, ASCO GI 2018
NIVOLUMAB + IPILIMUMAB FOR MSI-CRC

Response across molecular subsets

<table>
<thead>
<tr>
<th>Tumor PD-L1 expression, n (%)</th>
<th>Nivolumab + ipilimumab (N = 119)*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR</td>
<td>DCRb</td>
</tr>
<tr>
<td>≥ 1%</td>
<td>26</td>
<td>14 (54)</td>
<td>20 (77)</td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>65</td>
<td>34 (52)</td>
<td>51 (78)</td>
</tr>
<tr>
<td>BRAF/KRAS mutation status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>31</td>
<td>17 (55)</td>
<td>24 (77)</td>
</tr>
<tr>
<td>BRAF mutant</td>
<td>29</td>
<td>16 (55)</td>
<td>23 (79)</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>44</td>
<td>25 (57)</td>
<td>37 (84)</td>
</tr>
<tr>
<td>Clinical history of Lynch syndrome, n (%)c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>25 (71)</td>
<td>30 (86)</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>15 (48)</td>
<td>25 (81)</td>
</tr>
</tbody>
</table>

Responses equivalent across RAS mutant and WT groups

ORR Lynch>non-Lynch MMRD

Andre et al, ASCO GI 2018
NIVOLUMAB + IPILIMUMAB FOR MSI-CRC
Progression free and overall survival

<table>
<thead>
<tr>
<th>Nivolumab + ipilimumab</th>
<th>Nivolumab + ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-month rate (95% CI), %</td>
<td>76 (67.0, 82.7)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>71 (61.4, 78.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nivolumab + ipilimumab</th>
<th>Nivolumab + ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-month rate (95% CI), %</td>
<td>87 (80.0, 92.2)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>85 (77.0, 90.2)</td>
</tr>
</tbody>
</table>
# NIVOLUMAB + IPILIMUMAB FOR MSI-CRC

## Safety data

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Nivolumab + ipilimumab N = 119</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
<td></td>
</tr>
<tr>
<td>Any TRAE</td>
<td>87 (73)</td>
<td>38 (32)</td>
<td></td>
</tr>
<tr>
<td>Any serious TRAE</td>
<td>27 (23)</td>
<td>24 (20)</td>
<td></td>
</tr>
<tr>
<td>Any TRAE leading to discontinuation</td>
<td>15 (13)%</td>
<td>12 (10)</td>
<td></td>
</tr>
</tbody>
</table>

**TRAEs reported in > 10% of patients**

<table>
<thead>
<tr>
<th>TRAE</th>
<th>Any grade</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>26 (22)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (18)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20 (17)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>17 (14)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16 (13)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (13)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>14 (12)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Rash</td>
<td>13 (11)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>13 (11)</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity with combination ipilimumab plus nivolumab

10% patients discontinued treatment

Andre et al, ASCO GI 2018
MMRD PREDICTS RESPONSE TO IMMUNOTHERAPY IN MANY CANCERS

ORR = 53% across all MMRd cancers

Dung T. Le et al. Science 2017;357:409-413
# Checkpoint Immune Blockade Is Ineffective in MSS CRC

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>N</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le et al</td>
<td>MSS CRC Pembrolizumab</td>
<td>18</td>
<td>0%</td>
</tr>
<tr>
<td>Overman et al</td>
<td>MSS CRC Nivolumab + ipilimumab</td>
<td>20</td>
<td>5%</td>
</tr>
<tr>
<td>Chung et al</td>
<td>Refractory CRC Tremelimumab</td>
<td>49</td>
<td>2%</td>
</tr>
<tr>
<td>Topalian et al</td>
<td>Refractory CRC Nivolumab</td>
<td>19</td>
<td>0%</td>
</tr>
</tbody>
</table>

**MEK INHIBITION + IMMUNE CHECKPOINT BLOCKADE IN CRC**

COBIMETINIB + ATEZOLIZUMAB IN MCRC

BOR (n = 84)a | n (%)  
---|---
ORR | 7 (8%)  
CR | 0  
PR | 7 (8%)  
SD | 19 (23%)  
DCR | 26 (31%)  
PD | 51 (61%)  

- 7 patients (8% [95% CI: 3, 16]) experienced PR (confirmed per RECIST v1.1)
  - 4 patients had MSS and 1 patient had MSI-low mCRC; the remaining 2 had unknown MSI statusb
- The DCR was 31% (DCR defined as PR + SD ≥ 6 weeks)

Bendell et al, ASCO GI 2018
Responses equivalent across KRAS mutant and WT groups
**COBIMETINIB + ATEZOLIZUMAB IN MCRC**

**Phase III COTEZO trial – cobimetinib/atezolizumab vs regorafenib vs atezolizumab**

<table>
<thead>
<tr>
<th>Patients</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (95% CI)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td></td>
<td>6-mo</td>
<td>6-mo</td>
</tr>
<tr>
<td></td>
<td>12-mo</td>
<td>12-mo</td>
</tr>
<tr>
<td>All (n = 84)</td>
<td>1.9 mo (1.8, 2.3)</td>
<td>9.8 mo (6.2, 14.1)</td>
</tr>
<tr>
<td>MSS (n = 42)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.5 mo (1.8, 3.7)</td>
<td>13.0 mo (6.0, 25.8)</td>
</tr>
<tr>
<td>KRAS mutant (n = 57)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.0 mo (1.8, 2.3)</td>
<td>9.5 mo (6.0, 17.6)</td>
</tr>
<tr>
<td>KRAS wild type (n = 25)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.8 mo (1.8, 2.6)</td>
<td>10.0 mo (4.9, 17.1)</td>
</tr>
</tbody>
</table>

**Notes:**
- <sup>a</sup> MSS: Mutually Exclusive Systematic Genotyping
- <sup>b</sup> KRAS: Kirsten Human Retinoblastoma Sarcoma

**Summary:**
Cobimetinib/atezolizumab showed promising results compared to regorafenib and atezolizumab in the COTEZO trial.
CEA BISPESIFIC ANTIBODY

- Binds simultaneously with 1 arm to CD3 on T cells and with 2 arms to CEA on tumor cells
- Flexible 2-to-1 format enables high-avidity binding and selective killing of high CEA-expressing tumor cells
- Longer half-life compared with other TCB formats
- Silent Fc results in reduced risk of FcγR-related cytokine release/IRRs

- Simultaneous binding of TCB to tumor (CEA) and T cells (CD3)
- Killing of tumor cells independent of pre-existing immunity
- T-cell proliferation at site of activation

- PD-L1 is upregulated upon IFNγ secretion, providing rationale for combining CEA-TCB with atezolizumab

Tabernero et al, ASCO 2017
## CEA-TCB & ATEZOLIZUMAB IN MCRC

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Study 1: CEA-TCB monotherapy</th>
<th>Study 2: CEA-TCB + aezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 31, 60-600 mg</td>
<td>n = 25, 5-160 mg</td>
</tr>
<tr>
<td>Median age, years</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>19 (61%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>ECOG PS 0 / 1, n (%)</td>
<td>19 (61%) / 12 (39%)</td>
<td>13 (52%) / 12 (48%)</td>
</tr>
<tr>
<td>MSS / MSI / Unknownª</td>
<td>28 (90%) / 0 / 3 (10%)</td>
<td>23 (92%) / 2 (8%) / 0</td>
</tr>
<tr>
<td>Metastatic sites, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>21 (68%)</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Liver</td>
<td>26 (84%)</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis</td>
<td>7 (23%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>1-2 organs involved</td>
<td>6 (19%)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>≥ 3 organs involved</td>
<td>25 (81%)</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Prior adjuvant therapy, n (%)</td>
<td>12 (39%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>No. of prior regimens (metastatic), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (26%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>19 (61%)</td>
<td>17 (68%)</td>
</tr>
</tbody>
</table>

Tabernero et al, ASCO 2017
CEA-TCB & ATEZOLIZUMAB IN MCRC

Study 1: CEA-TCB monotherapy
n = 31, 60-600 mg

Study 2: CEA-TCB + atezolizumab
n = 25, 5-160 mg

<table>
<thead>
<tr>
<th>Confirmed best overall response (RECIST v1.1), n (%)</th>
<th>Study 1: CEA-TCB monotherapy</th>
<th>Study 2: CEA-TCB + atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 31, 60-600 mg MSS, n = 28 (90%)b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (6%)</td>
<td>3 (12%)d</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (39%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Disease control</td>
<td>14 (45%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>n = 25, 5-160 mg MSS, n = 23 (92%)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
<td>2 (18%)d</td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td>7 (64%)</td>
</tr>
<tr>
<td>Disease control</td>
<td></td>
<td>9 (82%)</td>
</tr>
<tr>
<td>n = 11, 80 or 160 mga MSS, n = 11 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tabernero et al, ASCO 2017
COLORECTAL CANCER IMMUNOTHERAPY CONCLUSIONS

MSI CRC
1-2% patients. Test!
PD-1 ORR 40%+
Combination IO ↑ efficacy

MSS CRC
Mostly immune evasive
Combinations are the future
II. HEPATOCELLULAR CANCER
TREMELIMUMAB

Proof of concept for IO in HCC

- Chronic hepatitis C
- Child-Pugh class A or B (43%) HCC
- Previously treated with sorafenib (24%)

- 3/17 evaluable patients had PR (3.6, 9.2, and 15.8 m)

- Grade 3+ increased AST (45%) – transient

- Statistically significant decrease in viral load

## Nivolumab in 2nd Line HCC (CHECKMATE-040)

<table>
<thead>
<tr>
<th>Without viral hepatitis</th>
<th>Dose escalation (n=48)</th>
<th>Dose expansion (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3+3 design</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>n=6</td>
<td>0.1 mg/kg (n=1)</td>
<td>Sorafenib untreated or intolerant (n=56)</td>
</tr>
<tr>
<td></td>
<td>0.3 mg/kg (n=3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 mg/kg (n=3)</td>
<td>Sorafenib progressor (n=57)</td>
</tr>
<tr>
<td></td>
<td>3.0 mg/kg (n=3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/kg (n=13)</td>
<td></td>
</tr>
<tr>
<td>n=9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=10</td>
<td>0.3 mg/kg (n=3)</td>
<td>HCV infected (n=50)</td>
</tr>
<tr>
<td></td>
<td>1.0 mg/kg (n=4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 mg/kg (n=3)</td>
<td></td>
</tr>
<tr>
<td>n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=13</td>
<td>0.3 mg/kg (n=3)</td>
<td>HBV infected (n=51)</td>
</tr>
<tr>
<td></td>
<td>1.0 mg/kg (n=3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 mg/kg (n=4)</td>
<td></td>
</tr>
</tbody>
</table>

## NIVOLUMAB IN 2\textsuperscript{ND} LINE HCC (CHECKMATE-040)

Radiological response rates

<table>
<thead>
<tr>
<th></th>
<th>Uninfected non-PD (n = 56)</th>
<th>Uninfected Progressor (n = 57)</th>
<th>HCV (n = 50)</th>
<th>HBV (n = 51)</th>
<th>All (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, %</strong></td>
<td>23</td>
<td>21</td>
<td>20</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>▪ <strong>CR</strong></td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>▪ <strong>PR</strong></td>
<td>23</td>
<td>18</td>
<td>20</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>▪ <strong>SD</strong></td>
<td>52</td>
<td>40</td>
<td>46</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>▪ <strong>PD</strong></td>
<td>23</td>
<td>32</td>
<td>28</td>
<td>45</td>
<td>32</td>
</tr>
</tbody>
</table>

NIVOLUMAB IN 2ND LINE HCC CHECKMATE-040

Median OS NR
Median OS 13.2m
Median OS NR
Median OS NR

Nivolumab licensed in sorafenib treated HCC September 2017

NIVOLUMAB IN HCC
Responses by PD-L1 expression

<table>
<thead>
<tr>
<th>PD-L1:</th>
<th>&lt; 1%</th>
<th>≥ 1%</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 &lt; 1%</td>
<td>4/26 (15.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 ≥ 1%</td>
<td>2/9 (22.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1:</th>
<th>&lt; 1%</th>
<th>≥ 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 &lt; 1%</td>
<td>17/99 (17.2)</td>
<td></td>
</tr>
<tr>
<td>PD-L1 ≥ 1%</td>
<td>8/25 (32.0)</td>
<td></td>
</tr>
</tbody>
</table>

Slide adapted from clinicalcareoptions.com
Pembrolizumab in HCC

Study Design
- Key eligibility criteria
  - ≥18y
  - Pathologically confirmed HCC
  - Progression on or intolerance to sorafenib treatment
  - Child Pugh class A
  - ECOG PS 0-1
  - BCLC Stage C or B disease
  - Predicted life expectancy >3 mo

Pembrolizumab
200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent, or investigator decision

Survival follow-up

Response
- Response assessed Q3W
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability

<table>
<thead>
<tr>
<th>Response</th>
<th>Total N=104</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+PR)</td>
<td>17 (16.3)</td>
<td>9.8 - 24.9</td>
</tr>
<tr>
<td>Disease control (CR+PR+SD)</td>
<td>64 (61.5)</td>
<td>51.5 - 70.9</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (1.0)</td>
<td>0.0 - 5.2</td>
</tr>
<tr>
<td>PR</td>
<td>16 (15.4)</td>
<td>9.1 - 23.8</td>
</tr>
<tr>
<td>SD</td>
<td>47 (45.2)</td>
<td>35.4 - 55.3</td>
</tr>
<tr>
<td>PD</td>
<td>34 (32.7)</td>
<td>23.8 - 42.6</td>
</tr>
<tr>
<td>No Assessment</td>
<td>6 (5.8)</td>
<td>2.1 - 12.1</td>
</tr>
</tbody>
</table>

Percent change from baseline

All
Uninfected
HCV
HBV
Zhu et al, ASCO GI 2018
TREMELIMUMAB + RFA OR TACE IN HCC

Proof of concept for combination with local therapy

V. GASTROESOPHAGEAL ADENOCARCINOMA
NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER

ATTRACTION-02

Key eligibility criteria:
- Unresectable advanced or recurrent gastric or gastroesophageal junction cancer
- Refractory to/intolerant of ≥2 standard therapy regimens
- ECOG PS of 0 or 1

**ECOG 0 vs. 1**
- 29% vs. 71%

**Site of disease**
- Gastric vs. other
  - 82% vs. 18%

**Prior regimens**
- 2 vs. 3 vs. ≥4
  - 20% vs. 40% vs. 40%

Primary endpoint:
- OS

Secondary endpoints:
- Efficacy (PFS, BOR, ORR, TTR, DOR, DCR)
- Safety

Exploratory endpoint:
- Efficacy by tumor PD-L1 expression

Kang et al, Lancet 2017
ATTRACTION-02

Response rates and duration

ORR 12%

Responses seen in PD-L1 positive and negative patients

Median time to response was 1.6m (1.4-7.0m)

Responses also seen as late at 7 months

Boku et al, ESMO 2017
**ATTRACTION-02**

Updated overall survival results

Kang et al, Lancet 2017
14% tested population were PD-L1 positive

PD-L1 antibody 28-8 pharmDx assay

PD-L1 positivity was defined as staining in 1% or more of tumour cells.

Kang et al, Lancet 2017
Primary endpoints: ORR, safety; secondary endpoints: DoR, PFS, OS
**KEYNOTE-059**

Study design

PTS with recurrent or metastatic gastric or GEJ; ECOG PS 0/1; no prior PD-1/PD-L1

Cohort 1
≥ 2 prior lines chemotherapy

Pembrolizumab
200 mg Q3W

Treatment until PD, 24m, intolerable toxicity, or withdrawal of consent.

<table>
<thead>
<tr>
<th>Keynote -059 patient characteristics (N = 259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
</tr>
<tr>
<td>US vs. East Asia vs. Other</td>
</tr>
<tr>
<td>ECOG PS</td>
</tr>
<tr>
<td>0 vs. 1</td>
</tr>
<tr>
<td>Tumour site (%)</td>
</tr>
<tr>
<td>Gastric vs. GOJ</td>
</tr>
<tr>
<td>Prior therapies</td>
</tr>
<tr>
<td>2 vs. 3 vs. ≥4</td>
</tr>
</tbody>
</table>
PEMBROLIZUMAB IN CHEMOREFRACTORY GC
KEYNOTE-059

**Majority of responses are early**

Median duration of response:
- All patients: 8.4m
- PD-L1 positive: 16.3m
- PD-L1 negative: 6.9m

**Change From BL (%)**

- PD-L1 positive
- PD-L1 negative
- PD-L1 expression unknown

*Included pts with measurable disease at BL and ≥ 1 post-BL assessment (n = 223).

**ORR 11.6%**

**Treatment Exposure and Duration of Response**

**Confirmed Responders (n = 30)**

- CR
- PR
- PD
- Death

**Responses in PDL1 positive and negative patients**

**RECIST response rates are modest**

(identical to nivolumab in ATTRACTION-02)

Fuchs et al, JAMA Oncology 2018
## KEYNOTE-059

**ORR according to PD-L1 status and line of Tx**

<table>
<thead>
<tr>
<th>PD-L1 status</th>
<th>Line of Treatment</th>
<th>PD-L1 and 3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (n = 148)</td>
<td>3rd (n = 134)</td>
<td>Positive (n = 75)</td>
</tr>
<tr>
<td>15.5 (10.1-22.4)</td>
<td>≥ 4th (n = 125)</td>
<td>Negative (n = 58)</td>
</tr>
<tr>
<td>Negative (n = 109)</td>
<td>Positive (n = 75)</td>
<td>22.7 (13.8-33.8)</td>
</tr>
<tr>
<td>6.4 (2.6-12.8)</td>
<td>Negative (n = 58)</td>
<td>8.6 (2.9-19.0)</td>
</tr>
</tbody>
</table>

Response rates ↑ PD-L1 positive vs. PD-L1 negative (15.5% vs 6.4% )
Pembrolizumab may be more effective in earlier lines of treatment
Combination PD-L1 positive and earlier line of treatment (3rd) ORR 23%

**PD-L1 assay is 22C3 antibody using CPS score.**
CPS score = (number positive cells (IC, tumour)/tumour cells) x 100
PD-L1 positive if ≥1%

Fuchs et al, JAMA Oncol 2018
NIVOLUMAB AND PEMBROLIZUMAB IN CHEMOREFRACTORY GASTROESOPHAGEAL CANCER

**ATTRACTION-02**

**CHECKMATE 032**

- nivolumab arm
  - ORR 12%
  - ORR 19% vs 12% PD-L1+ vs -

**KEYNOTE 059 cohort 1**

- Median OS (m)
  - PD-L1 positive: 5.6
  - PD-L1 negative: 5.8
  - PD-L1 expression unknown: 4.6

**ORR**

- PD-L1 positive: 11.6%
- PD-L1 negative: 15.5% vs 6.4% PD-L1+ vs -

**Median OS (m)**

- PD-L1 positive: 5.26
- PD-L1 negative: 5.22
- PD-L1 expression unknown: 6.05

**Change From BR (%)**

- PD-L1 positive
- PD-L1 negative
- PD-L1 expression unknown
PEMBROLIZUMAB IN TREATMENT NAÏVE GC

Pts with recurrent or metastatic gastric or GEJ adenocarcinoma; ECOG PS 0/1;
Cohort 3 Treatment naïve PD-L1+
Pembrolizumab 200 mg Q3W
Treatment until PD, 24m, intolerable toxicity, or withdrawal of consent.

ORR 26%

Wainberg et al, ESMO 2017.
NEGATIVE TRIALS OF PD-1/L1 INHIBITORS IN GC

Maintenance ipilimumab vs. BSC

3rd line avelumab vs BSC/chemotherapy

KEYNOTE-061

ORR to ipilimumab 1.8%
Results consistent with those previously observed for tremilimumab in phase II trial

Press release Nov 28th trial negative for OS
Full results awaited
Effect of PD-L1 vs PD-1 or control arm

Press release December negative for OS
HR = 0.82, 95% CI= 0.66−1.03; P = .042 [one-sided] in PD-L1 +

Conclusions
Single agent anti-CTLA-4 inhibition ineffective in unselected gastric cancer
Single agent anti-PD-1 /anti-PD-L1 vs chemo – is there a subgroup which benefits?

COMBINATION S: ANTI-CTLA4 + ANTI-PD-1
CHECKMATE-032

Western patients with advanced/metastatic EG cancer with progression on ≥1 prior chemotherapy
N = 160

Nivolumab 3 mg/kg IV Q2W (NIVO 3)
Median (range) follow-up, mo:
28 (17 to 35)

Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W* (NIVO 1 + IPI 3)
24 (21 to 33)

Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W* (NIVO 3 + IPI 1)
22 (19 to 25)

CHECKMATE-032 Patient Characteristics

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>Gastric vs. GOJ</th>
<th>37% vs. 63%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior regimens</td>
<td>≤1 vs. 2 vs. 3 vs. ≥4</td>
<td>20% vs. 34% vs. 27% vs. 18%</td>
</tr>
</tbody>
</table>

CHECKMATE-032
Radiological responses by treatment arm

**NIVO 3**
PD-L1–evaluable patients, 38 of 53

- ORR 12%
- PD-L1 positive ORR 19%
- PD-L1 negative ORR 12%

**NIVO 1 + IPI 3**
PD-L1–evaluable patients, 38 of 42

- ORR 24%
- PD-L1 positive ORR 40%
- PD-L1 negative ORR 22%

**NIVO 3 + IPI 1**
PD-L1–evaluable patients, 34 of 41

- ORR 8%
- PD-L1 positive ORR 23%
- PD-L1 negative ORR 0%

CHECKMATE-032
Radiological responses by treatment arm

| Patients, n (%) | NIVO 3  
|----------------|--------|
| NIVO 3  
| n = 59 | Any grade | Grade 3/4 |
| Any TRAE | 41 (69) | 10 (17) |
| Serious TRAEs | 6 (10) | 3 (5) |
| TRAEs leading to treatment discontinuation | 2 (3) | 2 (3) |

| Overall survival | 12-month OS rate, % | NIVO 3  
|------------------|----------------------|
| NIVO 3  
| NIVO 1 + IPI3  
| NIVO 3 + IPI 1 |
| NIVO 3 | 62 (34, 74) | 39 | 25 |
| NIVO 1 + IPI3 | 60 (32, 72) | 35 | 28 |
| NIVO 3 + IPI 1 | 48 (30, 66) | 24 | 12 |

COMBINATION CHEMOTHERAPY PLUS ANTI-PD-1

KEYNOTE-059

Pts with recurrent or metastatic gastric or GEJ adenocarcinoma; ECOG PS 0/1; HER2/neu negative*; no prior PD-1/PD-L1 tx)

Cohort 2
Treatment naive

Pembrolizumab 200 mg Q3W + Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2 Q3W or Capecitabine 1000 mg/m^2 BID Q3W

Treatment until PD, 24m, intolerable toxicity, or withdrawal of consent.

<table>
<thead>
<tr>
<th>ORR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>60%</td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>69%</td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>38%</td>
</tr>
</tbody>
</table>

Wainberg et al, ESMO 2017.
COMBINATION CHEMOTHERAPY PLUS ANTI-PD-1

KEYNOTE-059

Pts with recurrent or metastatic gastric or GEJ adenocarcinoma; ECOG PS 0/1; HER2/neu negative*; no prior PD-1/PD-L1 tx)

Cohort 2
Treatment naive

Pembrolizumab 200 mg Q3W + Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m² Q3W or Capecitabine 1000 mg/m² BID Q3W

Treatment until PD, 24m, intolerable toxicity, or withdrawal of consent.

*patients withdrew for chemotherapy related toxicity

Wainberg et al, ESMO 2017.
**IMMUNE ENVIRONMENT IN A HETEROGENEOUS DISEASE**

- **Subtype characteristics**
  - CIN
    - $ERBB2$ amplification
    - $VEGFA$ amplification
    - $TP53$ mutation
  - EBV
    - EBV-CIMP
    - $PIK3CA$ mutation
    - $PD-L1/2$ overexpression
  - MSI
    - Hypermutation
    - Gastric-CIMP
    - $MLH1$ silencing
  - GS
    - Diffuse histology
    - $CDH1$, $RHOA$ mutations
    - $CLDN18-APC$ fusions

- **Immune characteristics**
  - Copy number changes:
    - Low immune score
    - Low IFNγ signature
  - Rare in metastatic patients
    - PD-L1:
      - tumour ++
      - TILs +++
      - High IFNγ signature
  - Rare in metastatic patients
    - PD-L1:
      - tumour ++
      - TILs ++
      - High IFNγ signature
  - Genomically bland
    - Diffuse type rarely PD-L1+
    - Subsets may have TIL

---

Oesophageal TCGA Nature 541, 169–175 (12 January 2017)
Derks et al, Oncotarget. 2016 May 31;7(22):32925-32
Böger et al, Oncotarget. 2016 Apr 26; 7(17):
MSI-H GASTRIC CANCER IMMUNE ENVIRONMENT

<table>
<thead>
<tr>
<th>Subtype</th>
<th>MSI-H</th>
<th>MSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor purity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p16 loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mut.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2 loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6 loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1 silencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH1 high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CROMOS silencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKCSA mut.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MSI-H 4% of advanced GC

<table>
<thead>
<tr>
<th>KEYNOTE-059</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR %</td>
<td>MSI-H (n = 7)</td>
<td>MSS (n = 167)</td>
</tr>
<tr>
<td>ORR</td>
<td>57.1</td>
<td>9.0</td>
</tr>
<tr>
<td>CR</td>
<td>14.3</td>
<td>2.4</td>
</tr>
<tr>
<td>PR</td>
<td>42.9</td>
<td>6.6</td>
</tr>
<tr>
<td>DCR</td>
<td>71.4</td>
<td>22.2</td>
</tr>
</tbody>
</table>

Survival from surgery according to MSI status in MAGIC

MSI-H vs non-MSI HR: 0.35 surgery alone
HR: 2.22 chemo/surgery (P = .04)

Fuchs et al, JAMA Oncology 2018
CIN-GC characterised by high somatic copy number alterations (SCNA)

Copy number alterations associated with low immune gene expression

↑CNA associated with ↓benefit from IO in melanoma

CIN GASTROESOPHAGEAL CANCER IMMUNE ENVIRONMENT

In TGCA dataset
CIN tumours have lowest INFγ signature

GC-CIN tumours have the lowest proportion of T-cell inflamed tumours

Specific mutations associated with inflamed subtype: PIK3CA, ATM, RHOA and CDH1

Amplifications associated with immune ignorance: ERBB2, MYC, VEGFA

Maron et al, ASCO SITC 2017
CIN GASTROESOPHAGEAL CANCER IMMUNE ENVIRONMENT

3 oesophageal adenocarcinoma genomic signatures identified using whole exome NGS

Mutagenic subtype associated with ↑ neoantigen and ↑ immune infiltrates

Oesophageal TCGA Nature 541, 169–175 (12 January 2017)
IMMUNOTHERAPY FOR GASTROESOPHAGEAL CANCER
CONCLUSIONS

Anti-PD-1 therapy is a new standard for patients with chemorefractory gastroesophageal cancer
  - Single agent activity is modest
  - MSI-H, rare but sensitive to IO. All patients should be tested.
  - PD-L1 enriches for response but lacks true predictive value

Combinations (chemotherapy, immunotherapy) increase efficacy
  - Subtype biology and interaction with immune system key to designing effective personalised immunotherapy combinations.
THANK YOU
elizabeth.smyth2@nhs.net