IMMUNOTHERAPY FOR LOWER GASTROINTESTINAL CANCERS

Dr Elizabeth Smyth
Cambridge University Hospitals NHS Foundation Trust

ESMO Colorectal Cancer Preceptorship Valencia 2019
DISCLOSURES

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

- Immunotherapy primer
- Colorectal cancer
- Anal 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 LANDSCAPE

In CRC high mutation burden = IO efficacy

Immune checkpoint blockade efficacy

MSI-H

POLE mut

Low mutation burden
COLORECTAL CANCER AND IMMUNOTHERAPY

MMRd vs MMRp tumours

From an immunotherapy perspective there are two CRC categories

1. **Mismatch repair deficient (MMRd)** – 2-5% of Stage IV cancers, more common in Stage II>III
2. **Mismatch repair proficient (MMRp)** - majority of Stage IV cancers

Mismatch repair status can be assessed using:

- **Protein immunohistochemistry for MMR proteins** (MLH1, MSH2, MSH6 and PMS2)
- **PCR** to detect high levels of microsatellites in DNA (microsatellite instability, **MSI**)
- Next generation sequencing

>80% of MMRd tumours are sporadic (methylation of MLH1), however as 15-20% may be germline (Lynch syndrome) genetics referral should be considered in MMRd patients.
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
- Mismatch repair proficiency
- ER
- Neoprotein-MHC class I
- CD8+ T cells
- Anti-PD-1 Antibody
- PD-L1
- Anti-PD-L1 Antibody

Baretti et al, Pharmacol Ther. 2018
PEMBROLIZUMAB IN MMRD AND MMRP 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>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, %</td>
<td>57</td>
</tr>
<tr>
<td>Response, %</td>
<td></td>
</tr>
<tr>
<td>▪ CR</td>
<td>11</td>
</tr>
<tr>
<td>▪ PR</td>
<td>46</td>
</tr>
<tr>
<td>▪ SD</td>
<td>32</td>
</tr>
<tr>
<td>▪ PD</td>
<td>4</td>
</tr>
<tr>
<td>▪ Not evaluable</td>
<td>7</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>NR</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>NR</td>
</tr>
</tbody>
</table>

Le DT, et al. ASCO 2016. Abstract 103
Le DT et al, NEJM 2015
Deep and sustained responses in MMRd patients treated with pembrolizumab

May 2017 – FDA licensed pembrolizumab in previously treated MMRD colorectal cancer
PEMBROLIZUMAB IN MMRD/MMRP CRC
KEYNOTE 164

Responses observed in all lines of therapy

ORR 32%
Benefits of anti-PD-1 therapy are sustained in MMRd CRC
76% alive at one year follow up
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
Benefits of nivolumab in MMRD CRC very similar to those observed for pembrolizumab

ORR 34%
Anti-PD1 therapy is a good choice for MMRd patients regardless of family history, BRAF status or PD-L1 expression.
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)

48% progression free and 74% alive at 1 year

August 2017 – FDA licensed nivolumab in MMRD colon cancers
No responding patient relapsed during follow up.
LICENSING STATUS OF ANTI-PD-1 THERAPIES

- Neither pembrolizumab nor nivolumab is licensed by EMA for treatment of MMRd colorectal cancer
- Randomised data are awaited
NIVOLUMAB + IPILIMUNAB FOR MMRD-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, DOR, PFS, OS, and safety

Overman et al, JCO 2018
NIVOLUMAB + IPILIMUMAB FOR MSI-CRC

Investigator assessed response

ORR to combination therapy appears greater than nivolumab alone (no formal comparison planned)

Andre et al, ASCO GI 2018
Overman et al, Journal of Clinical Oncology 2018
**NIVOLUMAB + IPILIMUMAB FOR MSI-CRC**

Progression free and overall survival

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab + ipilimumab&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Nivolumab + ipilimumab&lt;sup&gt;a,d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-month rate (95% CI), %</td>
<td>76 (67.0, 82.7)</td>
<td>87 (80.0, 92.2)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>71 (61.4, 78.7)</td>
<td>85 (77.0, 90.2)</td>
</tr>
</tbody>
</table>

Combination nivolumab/ipilimumab results in 71% 12 month progression free survival and 85% one year overall survival
### NIVOLUMAB + IPILIMUMAB FOR MSI-CRC

**Safety data**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Nivolumab + ipilimumab N = 119</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>87 (73)</td>
</tr>
<tr>
<td>Any serious TRAE</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Any TRAE leading to discontinuation</td>
<td>15 (13)(a)</td>
</tr>
</tbody>
</table>

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

- **Diarrhea**: 26 (22) | 2 (2)
- **Fatigue**: 21 (18) | 2 (2)
- **Pruritus**: 20 (17) | 2 (2)
- **Pyrexia**: 18 (15) | 0
- **Increased AST**: 17 (14) | 9 (8)
- **Hypothyroidism**: 16 (13) | 1 (1)
- **Nausea**: 15 (13) | 1 (1)
- **Increased ALT**: 14 (12) | 8 (7)
- **Rash**: 13 (11) | 2 (2)
- **Hyperthyroidism**: 13 (11) | 0

**Toxicity with combination ipilimumab plus nivolumab**

10% patients discontinued treatment

André et al, ASCO GI 2018

Overman et al, Journal of Clinical Oncology 2018
MOVING IMMUNOTHERAPY INTO EARLIER LINES
CHECKMATE 142 1L cohort

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory

Previously treated

NIVO3 Q2W

NIVO3 + IPI1 Q3W
(4 doses and then NIVO3 Q2W)

Previously treated

1L

NIVO3 Q2W + IPI1 Q6W

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

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

Lenz et al, ESMO 2018
NIVOLUMAB AND IPILIMUMAB IN 1L
CHECKMATE 142 1L cohort

ORR 60%

ORR not compromised by low dose ipilimumab

Lenz et al, ESMO 2018
NIVOLUMAB AND IPILIMUMAB IN 1L
CHECKMATE 142 1L cohort

<table>
<thead>
<tr>
<th>PFS*</th>
<th>NIVO3 (Q2W) + IPI1 (Q6W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 45</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (14.1–NE)</td>
</tr>
<tr>
<td>9-mo rate (95% CI), %</td>
<td>77 (62.0–87.2)</td>
</tr>
<tr>
<td>12-mo rate (95% CI), %</td>
<td>77 (62.0–87.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS*</th>
<th>NIVO3 (Q2W) + IPI1 (Q6W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 45</td>
<td></td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NE)</td>
</tr>
<tr>
<td>9-mo rate (95% CI), %</td>
<td>89 (74.9–95.1)</td>
</tr>
<tr>
<td>12-mo rate (95% CI), %</td>
<td>83 (67.6–91.7)</td>
</tr>
</tbody>
</table>

Lenz et al, ESMO 2018
TOXICITY IS IMPROVED WITH LOW DOSE IPILIMUMAB

<table>
<thead>
<tr>
<th></th>
<th>Nivo + q3wk ipi</th>
<th>Nivo + q6wk ipi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 TRAE</td>
<td>32%</td>
<td>16%</td>
</tr>
<tr>
<td>Serious TRAE</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>10%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Nivolumab plus low dose ipilimumab is a safe and effective choice for MMRd CRC (not yet licensed)

Lenz et al, ESMO 2018
NEOADJUVANT IMMUNOTHERAPY FOR MMRD CRC

Neoadjuvant nivolumab plus ipilimumab: NICHE study

*MMR protein staining for MLH1, PMS2, MSH2, MSH6

Chalabi et al, ESMO 2018
NEoadjuvant nivolumab plus ipilimumab

No residual tumour in MMRd patients treated with nivolumab plus ipilimumab
NEOADJUVANT IMMUNOTHERAPY FOR MMRD CRC

Neoadjuvant nivolumab plus ipilimumab

<table>
<thead>
<tr>
<th></th>
<th>dMMR (n=7)</th>
<th>pMMR (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-yr (range)</td>
<td>60.9 (41 - 75)</td>
<td>63.1 (44 - 73)</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>4 (57%)</td>
<td>5 (62%)</td>
</tr>
<tr>
<td>CEA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>≥5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Clinical disease stage – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>3 (43%)</td>
<td>5 (62%)</td>
</tr>
<tr>
<td>III</td>
<td>4 (57%)</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>right</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Lynch syndrome – no. (%)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>TMB* – median (range)</td>
<td>1795 (1324 - 4458)</td>
<td>103 (68 - 269)</td>
</tr>
</tbody>
</table>

No/minimal effect of MMRp patients treated with nivolumab plus ipilimumab

Chalabi et al, ESMO 2018

<table>
<thead>
<tr>
<th>pMMR (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment clinical stage</td>
</tr>
<tr>
<td>cT3N1a</td>
</tr>
<tr>
<td>cT3N0</td>
</tr>
<tr>
<td>cT2N0</td>
</tr>
<tr>
<td>cT2N0</td>
</tr>
<tr>
<td>cT3N1b</td>
</tr>
<tr>
<td>cT3N1b</td>
</tr>
<tr>
<td>cT3N0</td>
</tr>
<tr>
<td>cT2N0</td>
</tr>
</tbody>
</table>
NEOADJUVANT IMMUNOTHERAPY FOR MMRD CRC

Neoadjuvant nivolumab plus ipilimumab

Neither pre-treatment CD3 infiltrate nor immune gene signature were predictive of response to nivo/ipi
BIOMARKERS IN MMRD CRC

Does tumour mutation burden matter?

High TMB was associated with higher change of radiological response, and improved PFS and OS
Caveat – small dataset (n=22), targeted panel to assess TMB

Shrock et al, Annals Oncol 2019
BIOMARKERS IN MMRD CRC

Markers of resistance and secondary targets

- Recurrent mutations and LOH in antigen presenting machinery (HLA, B2M) in MSI tumours
- JAK1/2 mutations
- High incidence of TRK, ALK, ROS fusions – consider referring for screening for clinical trials
- Synthetic lethality with Werner helicase inhibition

Grasso et al, Cancer Discovery 2018
Shin et al, Cancer Discover 2016
Pietrantonio et al, JCNI 2017
Bass, Nature 2109
Conclusions

- Anti-PD-1 is a standard of care for MMRD CRC associated with high response rates and durable benefit
- European license awaited pending randomised data
- Dual immunotherapy blockade will become standard, low dose ipilimumab appears safe and tolerable
- Moving immune checkpoint blockade to earlier lines of therapy is an exciting prospect
IMMUNOTHERAPY FOR MMRP CRC
# 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>Topialan et al</td>
<td>Refractory CRC Nivolumab</td>
<td>19</td>
<td>0%</td>
</tr>
</tbody>
</table>

COLORECTAL CANCER MOLECULAR AND IMMUNE LANDSCAPE

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI Immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

- MSI, CIMP high, hypermutation
- SCNA high
- Mixed MSI status, SCNA low, CIMP low
- SCNA high

- BRAF mutations
- KRAS mutations

- Immune infiltration and activation
- WNT and MYC activation
- Metabolic deregulation
- Stromal infiltration, TGFβ activation, angiogenesis

- Worse survival after relapse
- Worse relapse-free and overall survival

---

**Genomic**
- MSI
  - Mutation count
  - Methylation

**Epigenomic**
- CIN
  - Copy number

**Transcriptomic pathways**
- CMS1
  - 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
- CMS2
  - Highly immunogenic
  - Adapted immune system
- CMS3
  - Poorly immunogenic
  - Inflamed (immune-tolerant)
- CMS4

**Stroma-immune microenvironment**

---

Gunney et al, Nat Med. 2015 Nov;21(11):1350-6
CMS2, WNT ACTIVATION AND IMMUNE EVASION

Most current WNT inhibitors are upstream of APC mutation.

High beta-catenin expression results in low CD3 and CD8 infiltrate.

WNT signalling via APC mutation is fundamental in CRC.

Targeting WNT is challenging! Most inhibitors are upstream of APC; exception porcupine inhibitors.

Grasso et al., Cancer Discovery 2018
CRC TCGA, Nature 2012
Graveley et al, Nat Med. 2015 Nov;21(11):1350-6
In preclinical models, inhibition of MEK signalling leads to ↑ CD8 T cell infiltration and MHC1 expression. Combination of MEKi and anti-PD-L1 showed synergy.
TARGETING MAPK AND IMMUNE IN CRC
Cobemetanib plus atezolizumab in mCRC

Early results were positive

<table>
<thead>
<tr>
<th>BOR (n = 84)a</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>SD</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>DCR</td>
<td>26 (31%)</td>
</tr>
<tr>
<td>PD</td>
<td>51 (61%)</td>
</tr>
</tbody>
</table>

Best response
- Partial response
- Stable disease
- Progressive disease

MSI statusb,c
- S MSS
- L MSI-low
- H MSI-high

Bendell et al, ASCO GI 2018
TARGETING MAPK AND IMMUNE IN CRC
Cobemetanib plus atezolizumab in mCRC: IMBLAZE

ORR <3% in all arms
No difference in PFS or OS
Outcome not different in RAS mt patients

Future questions
Scheduling of MEKi – effect on T-cells
MEK signatures
Novel IO combinations

Bendell et al, Lancet Oncol 2019
Role for CXCR3

- KRAS mutation decreases IRF2 expression
- Decreased IRF2 leads to increased CXCL3 expression
- CXCL3 acts on CXCR2 on MDSC to attract to TME
- MDSC causes immunosuppression

- In mouse models, inhibition of CXCR2 leads to increased sensitivity to immunotherapy

Liao et al, Cancer Cell 2019
TARGETING TGF-B IN CMS 4 CRC

CMS4 Mesenchymal
23%

SCNA high

Stromal infiltration, TGFβ activation, angiogenesis

Worse relapse-free and overall survival

1 CRC responder: MSS, CMS4, KRAS mutant and PD-L1+, high signature for complement cascade and MDSC

Ongoing clinical trial in CMS4 CRC

M7824 Bifunctional fusion protein targeting PD-L1 and TGF-β

Lan et al, Sci Trans Med 2018
Kopetz et al, ASCO GI 2018
TGF-B INDUCTION BY RADIOTHERAPY AS TARGET FOR IMMUNOTHERAPY COMBINATIONS
RADIOTHERAPY DOSE AND IMMUNE RESPONSE

BEST RT DOSE QUESTION

Vanpouille-Box et al, Nature Comm 2017,
ANGIOGENESIS AS A MECHANISM OF IMMUNE EXCLUSION

MODUL BRAFwt cohort

Patients screened (n=824)

Patients enrolled (n=696)

BRAFwt/BRAF status unknown patients enrolled into Induction Treatment Population in Cohort 2 (n=634)

BRAF\textsuperscript{mut} patients enrolled into Induction Treatment Population in Cohort 1 (n=62; 9%)\textsuperscript{a}

Not randomized into Maintenance Treatment Population (n=189; 30%)\textsuperscript{b}

Randomized into Maintenance Treatment in Cohort 2 (n=445)

2:1 ratio

FP + bevacizumab + atezolizumab (n=297)

FP + bevacizumab (n=148)

Grothey et al, ESMO 2018
ANGIOGENESIS AS A MECHANISM OF IMMUNE EXCLUSION

MODUL results: no benefit to addition of anti-PD-L1 to FP-bev in MSS
ANGIOGENESIS AS A MECHANISM OF IMMUNE EXCLUSION

Anti-angiogenic TKI +IO in other cancers

Breaking news
ASCO 2019
Fukuoka et al abstract 2552
Regorafenib + nivolumab
MSS CRC cohort 29% ORR

Endometrial
BRINGING THE T CELLS TO THE TUMOUR: CEA BISPECIFIC

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

ORR 6%

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

ORR 18%
CCTG CO.26 Study Schema:

**Randomize**

- Patients with advanced CRC refractory to all available therapy
- Stratify:
  - ECOG
  - Side of tumor

**2:1**

- Durvalumab: 1500 mg IV q 28 days
- Tremelimumab: 75 mg IV q 28 days, cycles 1-4
- Best Supportive Care
- Primary endpoint:
  - OS
- Secondary endpoints:
  - PFS
  - Safety and toxicity
  - ORR
- Tertiary endpoints:
  - QoL
  - Correlative studies

Sample Size: 180

---

**Concerns**

1. Extra interventions in experimental arm
2. High alpha 0.1 risks false positive
3. No PFS correlate for OS benefit
4. No responses in experimental arm

---

**Results: overall survival**

- Median BSC = 4.1 months; 90% CI (3.3-6.0)
- Median Durval+Trem = 6.6 months; 90% CI (6.0-7.4)
- Stratified Hazard Ratio = 0.72; 90% CI (0.54-0.97); p=0.07
- Unadjusted HR = 0.70; 90% CI (0.53-0.92); p=0.03

---

**Results: progression-free survival**

- Median BSC = 1.9 months; 90% CI (1.8-1.9)
- Median Durval+Trem = 1.8 months; 90% CI (1.8-1.9)
- Stratified Hazard Ratio = 1.01; 90% CI (0.76-1.34); p=0.97
• Multiple mechanisms lead to immune evasion in MMRp CRC including WNT, MAPK, and TGFβ signalling

• WNT signalling is difficult to target due to upstream site of APC mutation, downstream inhibitors are required

• Targeting MAPK signalling has not been successful in increasing sensitivity to immunotherapy

• Targeting TGFβ shows promise in early phase trials for CMS4 patients

• CEA bispecific antibody plus immunotherapy also shows early evidence of activity
II. ANAL CANCER
RATIONALE FOR IMMUNOTHERAPY IN ANAL CANCER

90% HPV positive

Normal epithelium → AIN → AIN1 → AIN3 → ASCC

- HPV infection → E6/E7 → TP53 downregulation → pRB downregulation
- High immunogenicity: CD8+, PD1+, PD-L1, FOXP3+, Casp8
- Low immunogenicity: CD8+, PD1+, PD-L1, FOXP3+, Casp8

Cancer cell, CD8+ T cell, Dendritic cell, Treg, PD1+ T cell, Myeloid cells

Martin et al, Biochimica et Biophysica Acta 2017
NIVOLUMAB IN ANAL CANCER
First evidence of efficacy of anti-PD1 in anal cancer

PD-L1 unselected
ORR 24%

Median PFS 4.1 months
Median OS 11.5 months

Increased ORR in high CD8 and PDL1
Small numbers”
All patients were PD-L1 positive (74% of screened)
Mostly pretreated
ORR 17% (4/24 SCC patients)

Median PFS 3.5 months (95% CI 1.7–7.3 months)
Median OS 9.3 months (95% CI, 5.9 months to not reached)

Ott et al, Annals Oncol 2017
ANAL CANCER BIOMARKERS

HPV ctDNA as a prognostic and response metric

HPV ctDNA after chemotherapy is prognostic

HPV ctDNA under anti-PD-1 therapy
ANAL CANCER AND IMMUNOTHERAPY

Summary

- Anal carcinoma is a virally driven, immunogenic tumour
- Preliminary results in previously treated patients are encouraging
- Randomised data and integration into earlier lines of therapy are awaited