Manipulating the immune system in GI cancer

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Brussels

ESMO-Asia, Singapore, December 21, 2015
Disclosures

- iTeos Therapeutics: co–founder and consultant
- Amgen: consultant
Pembrolizumab in treatment-refractory progressive metastatic CRC (anti-PD-1 IgG4)

P = 0.03 by log-rank test

Mismatch repair-deficient
Mismatch repair-proficient

No. at Risk
Mismatch repair-deficient 11 9 7 5 1 1 0
Mismatch repair-proficient 21 12 5 1 1 0

Le et al. - 2015 - NEJM
Antigens recognized by CD8 T cells on the surface of tumor cells

Cytolytic T lymphocytes (CTL) recognize on the surface of target cells **peptides** presented by **HLA class I** molecules (HLA-A, B, C).
Five classes of tumor antigens recognized by CD8 T cells:

<table>
<thead>
<tr>
<th>Antigen class</th>
<th>Advantages</th>
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<tr>
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<td>tumor-specific</td>
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Coulie, Van den Eynde, van der Bruggen, Boon - 2014 - Nat Rev Cancer
Classes of tumor antigens recognized by CD8 T cells

- ‘mutated’ antigens (neoepitopes)
- MAGE-type antigens
- viral antigens
- differentiation antigens (melanoma, B cells)
- overexpressed antigens

Genetic process:
- Mutation
- Tumor-specific gene expression
- Oncogenic virus
- Tissue-specific gene expression
- Gene overexpression

- Tumor cells
- Normal cells

- All normal cells
- Other normal cells
- Spermatocytes spermatogonia trophoblast
- All normal cells
- Melanocytes
- Other normal cells
- All normal cells
Only *some* tumor antigens recognized by T cells are tumor-specific.

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*Coulie, Van dan Eynde, van der Bruggen, Boon - 2014 - Nat Rev Cancer*
Cancer immunotherapy: 3 main modalities

- Therapeutic vaccine
- Adoptive transfer of anti-tumor T lymphocytes
- Immunostimulating antibodies (anti-CTLA4, anti-PD1)

In patients: weak «spontaneous» activity of anti-tumor T lymphocytes
Two signals required for T cell priming

T lymphocyte (naive) → Lymph node → Tumor

TCR + CD28

- proliferation
- differentiation

Lymph node

Tumor
CTLA-4 surface expression 4-48h following T-cell activation
CTLA-4 is a physiological brake during T-cell activation

Affinity of CTLA-4 for B7: 30-fold higher than that of CD28

TCR

B7

CD28

Affinity of CTLA-4-4 for B7: 30-fold higher than that of CD28

T lymphocyte

‘naive’

professional antigen-presenting cell
(dendritic cell)

TCR

B7

CD28

CTLA-4

CD28

‘antigen experienced’

target cell
(tumor cell)
**Immunostimulatory activity of anti-CTLA-4 antibodies**

Anti-CTLA-4 antibody that blocks the binding to B7 (ipilimumab)

1. **T lymphocyte**
   - TCR
   - CD28
   - 'naive'

2. **Professional antigen-presenting cell** (dendritic cell)
   - TCR
   - CD28
   - B7
   - antigen
   - ++
   - +
   - +++

3. **Target cell** (tumor cell)
   - TCR
   - CD28
   - B7
   - antigen
   - +
   - ++

4. **'Antigen experienced'**
   - TCR
   - CD28
   - B7
   - antigen
   - ++
PD-1 expressed on activated effector T-cells

T lymphocyte (naive) → Priming (first activation) → Effector function (subsequent activations)

professional antigen-presenting cell (dendritic cell) vs target cell (tumor cell)

TCR + B7

CD28

CTLA-4

PD-1

++

+++:

+:

-:

++:

++:

‘naive’ vs ‘antigen experienced’
PD-1 dampens T cell activation

T lymphocyte

'naive'

professional antigen-presenting cell (dendritic cell)

CD28

TCR

B7

antigen

++

+++ +

CD28

CTLA-4

target cell (tumor cell)

PD-L1

PD-1

TCR

antigen

++

++

Dampens T cell activation
**PD-1 dampens T cell activation**

- Anti-PD1 (or anti-PDL1) antibody that blocks the PD1/PDL1 interaction
  - Anti-PD1: nivolumab, pembrolizumab
  - Anti-PDL1: BMS-936559

**Diagram Description**

- **T lymphocyte**
  - TCR
  - CD28
  - 'naive'

- **Professional antigen-presenting cell (dendritic cell)**
  - TCR
  - CD28
  - B7
  - Antigen
  - '++'
  - '+++'

- **Target cell (tumor cell)**
  - TCR
  - CD28
  - CTLA-4
  - PD-1
  - Antigen
  - PD-L1
  - '++'
  - '+'

- **Antigen Exposed T Cell**
  - TCR
  - Antigen
  - CD28
  - '++'
  - '+'

- **Regulatory Factors**
  - PD-1 dampens T cell activation
  - Anti-PD1 (or anti-PDL1) antibodies block PD1/PDL1 interaction

- **Antigen Exposed T Cell:**
  - Anti-PD1 or anti-PDL1 antibodies
  - BMS-936559

Clinical success of immunotherapy in metastatic melanoma: 23% patients are still alive 5 years after ipilimumab (anti-CTLA4)

- long-term responses in a fraction of patients
- autoimmune toxicity, particularly with combos (anti-CTL4 + anti-PD1)

### Initial results with immunostimulatory antibodies in GI tumors

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<tr>
<th>Antigen</th>
<th>Antibody</th>
<th>Refractory Tumor Type</th>
<th>Patients</th>
<th>RR</th>
<th>References</th>
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<tr>
<td>CTLA-4</td>
<td>Tremelimumab</td>
<td>refractory CRC</td>
<td>49</td>
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One patient with a complete response, ongoing at 3 years: MSI-H

Lipson et al - 2013 - Clin Cancer Res
Pembrolizumab in treatment-refractory progressive metastatic cancer (anti-PD-1 IgG4)
Pembrolizumab in treatment-refractory progressive metastatic CRC (anti-PD-1 IgG4)

P = 0.03 by log-rank test

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Antigens resulting from mutations (single nucleotide variations)

Non-Synonymous mutations per tumor (median ± one quartile)

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<tr>
<th>Mutagens</th>
<th>Adult solid tumor</th>
<th>Liquid</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal (MSI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (SCLC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (NSCLC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal (ESCC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal (MSS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and Neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal (EAC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial (endometrioid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian (high-grade serous)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prostate</td>
<td></td>
<td></td>
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<tr>
<td>Hepatocellular</td>
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<td></td>
<td></td>
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<tr>
<td>Glioblastoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Endometrial (serous)</td>
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<tr>
<td>Lung (never smoked NSCLC)</td>
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<tr>
<td>Chronic lymphocytic leukemia</td>
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<tr>
<td>Acute myeloid leukemia</td>
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<tr>
<td>Medulloblastoma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdoid</td>
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adapted from Vogelstein et al. 2013 Science 339:1546
Mutational landscape of melanomas according to clinical benefit from ipilimumab treatment

Snyder et al. 2014 NEJM

**Discovery Set**
- Long-term benefit
- Minimal or no benefit

**Validation Set**
- Long-term benefit
- Minimal or no benefit

P = 0.009 by Mann–Whitney test

P = 0.01 by Mann–Whitney test
Nonsynonymous mutation burden in NSCLC treated with anti-PD1

**Discovery Cohort**

- Durable Clinical Benefit (n=7)
- No Durable Benefit (n=9)

Mann-Whitney $P = 0.02$

**Validation Cohort**

- Durable Clinical Benefit (n=7)
- No Durable Benefit (n=8)

Mann-Whitney $P = 0.04$

Rizvi et al. 2014 Science
Immunotherapy for GI tumors: towards improvements

1. Combinations of several immunostimulatory antibodies
   probl: autoimmune toxicity!

2. Understanding and counteracting tumor resistance
   blocking local immunosuppression + immunostimulatory antibodies
   - IDO inhibitor
   - Treg inhibitor
   - Microbiota
   - ...

3. Trigger anti-tumor immune responses in « cold » tumors (non-MSI)
   - vaccines + immunostimulatory antibodies
     - individual mutated antigens (long peptides, RNA, viral vectors, ...)
     - MAGE-type antigens
     - viral antigens
   - chemo ± radiotherapy + immunostimulatory antibodies
CD28

B7

HLA + peptide

T lymphocyte

CTLA-4

CD28

TCR

signal 1

PD-1

costimulatory receptor

inhibitory receptors

B7-2

B7-1

HLA + peptide

PD-L1

PD-L2

antigen presenting cell
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IDO1 protein expression (IHC) in human tumors (mAb 4.16H1)

(IDO: indoleamine dioxygenase)

Theate et al - 2015 - Cancer Immunol Res
Cervical carcinoma

IDO1 protein expression (IHC) in human tumors (mAb 4.16H1)

Gastric carcinoma
Anti-tumor vaccine (P1A)

P815B

P815B-IDO clone 7

control

+ 1-methyl-L-tryptophan in the drinking water (20mg/day)

Mean tumor volume (mm³ ± SEM)

P815B-IDO clone 7

+ 1-methyl-L-tryptophan

P815B clone 1

Uyttenhove et al, 2003, Nat Med, 9, 1269-74
Colon carcinoma model CT26

subcutaneous inoculation (5 x 10^5 cells)
oral treatment with IDO inhibitor MMG-0358 (1mM in the drinking water)
starting day 3 (palpable tumor)
Colon carcinoma model CT26

subcutaneous inoculation (5 x 10^5 cells)
oral treatment with IDO inhibitor MMG-0358 (1mM in the drinking water) starting day 3 (palpable tumor)

![Graph showing tumor volume over time for different treatments: control, IDO inhibitor, anti-CTLA4, and anti-CTLA4 + IDO inhibitor. The graph includes data points for days 0 to 40.]
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Catherine Uyttenhove  
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