IMMUNOTHERAPY: Using the Body To Fight Cancer

Adrian Ochsenbein
Universitätsklinik für Medizinische Onkologie, Bern
Overview

- Milestones in Immuno-Oncology
- Immunosurveillance of Cancer
- Immunotherapy
  - Antigen-specific Immunotherapy
    - Active Immunotherapy
    - Passive Immunotherapy
  - Immune Checkpoint Blockade
    - Blocking B7/CTLA-4 Interaction
    - Blocking PD1/PD-L1 Interaction
Milestones of Immuno-Oncology

First Tumor-Immunotherapy using bacteria (Wilhelm Busch)

1860

Vaccination with bacteria extracts; William Coley (Coley-Toxin)

1890s

“Magic bullets“ recognize tumor cells (Paul Ehrlich)

1900

Tumor Immunosurveillance Hypothesis (F. Burnet Thomas)

1957

First allogeneic stem cell transplantation in leukemia in Seattle (Edward D. Thomas)

1969
Milestones of Immuno-Oncology

- **1970**: Immune system induces spontaneous regression of melanoma
- **1980**: Cloning of first Tumor-antigen (MAGE-1)
- **1990**: Approval of BCG (Bacillus Calmette-Guérin) for bladder cancer
- **1990**: Approval of IFN-α as adjuvant therapy of melanoma
- **2000**: Approval of Rituximab for the therapy of B-Zell-lymphoma
- **2011**: Approval of the first Checkpoint Inhibitory molecule Ipilimumab for the treatment of metastatic melanoma
- **2011**: Approval of Immunotherapy for prostate cancer (Sipuleucel-T)

**Discovery of Checkpoint Inhibitory Molecules**

- **1970**: Discovery of Dendritic cells
- **1980**: First tumor-specific monoclonal antibody
- **1980**: First adoptive T-cell Immunotherapy
- **2000**: Discovery of Checkpoint Inhibitory Molecules
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Immunosurveillance Hypothesis

- 1909  „… the immune system recognizes and eliminates developing tumors…“
  Paul Ehrlich

- 1957  „… the primary function of cellular immunity is in fact not to promote allograft rejection but rather to protect from neoplastic disease, thereby maintaining tissue homeostasis in complex multicellular organisms.“
  Lewis Thomas

„It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence.“
  Sir Macfarlane Burnet

- 1964  „In large, long-lived animals, like most of the warm-blooded vertebrates, inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step towards malignancy. It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially dangerous mutant cells and it is postulated that this mechanism is of immunological character.“
  Sir Macfarlane Burnet
Immunosurveillance of lymphohematopoietic tumors

Higher incidence of lymphomas in patients with congenital or acquired immunodeficiency

→ *Immunodeficiency-associated lymphoproliferative disorders (IALD)*

- extranodal sites
- rapid progression
- diffuse large cell histology
- association with EBV

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>congenital: X-linked agamaglobulinemia, ataxia telangiectasia</td>
<td>0.7%</td>
</tr>
<tr>
<td>acquired: bone marrow transplantation, heart-lung transplantation</td>
<td>0.5% 10%</td>
</tr>
</tbody>
</table>
Spontaneous tumors in immunodeficient mice

RAG2-/-: no B and no T cells
STAT1-/-: defect in IFNγ signaling

Shankaran V, Nature 2001
Successful immunosurveillance in humans?

Ovarian cancer St. III, IV

Zhang et al. NEJM 2003
Immune responses against cancer

- **Innate immunity**
  - Natural killer cells (NK-Zellen)
  - complement
  - macrophages

- **Aquired immunity**
  - antibodies
  - helper cells (CD4+ T-cells)
  - Cytotoxic T-cells (CD8+ T-cells)
Induction of a tumor-specific CTL response

ICAM-1
LFA-1
LFA-3
CD40-CD40L
CD27-CD70
IL-2

Signal 1 + Signal 2

Signal 1

activation

anergy deletion
Anti-tumoral immune response

immature DC

mature DC

immature

mature

tumor

lymph node

CD4

CD8

CD4

B

Anti-tumoral immune response

Ochsenbein AF et al. Cancer Gene Ther 2003
Ignorance

Ochsenbein AF et al. Nature 2001
T cell exhaustion in viral infections

- non-cytopathic virus (LCMV, HBV, HIV) persist in the host in the presence of T cells
- cytotoxic T cells lose effector function
- cytotoxic T cells induce the disease → immunopathology

Virgin HW, Cell 2009
Molecular Mechanisms of T cell exhaustion

Werry EJ, Immunity 2007
Immune checkpoints: T cell Exhaustion

Highly polyfunctional memory CD8\(^+\) T cell

<table>
<thead>
<tr>
<th>IFN-(\gamma)</th>
<th>TNF</th>
<th>CTL</th>
<th>IL-2</th>
<th>Proliferative potential</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>++</td>
<td>++/−</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>++</td>
<td>+</td>
<td>+</td>
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<td>+/−</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+++</td>
</tr>
</tbody>
</table>

Naive CD8\(^+\) T cell

Acute infection
Antigen cleared

Effector CD8\(^+\) T cell

Antigen + costimulation
+ high inflammation

Chronic infection
Antigen persists

PD-1
LAG-3
CD244 (2B4)
CD160 (and so on)

Inflammation

Viral load and/or duration
CD4\(^+\) T cell help

Werry EJ, Nature Immunology 2011
Molecular Mechanisms of T cell exhaustion
Exhaustion of cancer-specific T cells

Baitsch L, J Clin Invest 2011
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Cancer immunotherapy

**Active Immunization**
- Inactivated tumor cells
- Tumor antigens, peptides
- Dendritic cells
- DNA vaccination
- Viral vectors

**Passive Immunization**
- Infusion of autologous T cells
- DLI of allogenic T cells after bone marrow transplantation
- Infusion of monoclonal antibodies

**Immune Modulation**
- Checkpoint Inhibitors
- IDO
- Depletion of Tregs, MDSCs
Vaccination

- Inactivated tumor cells
- Tumor antigens, peptides
- Dendritic cells
- DNA vaccinations
- Viral vectors
Peptide-based Immunizations
Adjuvants!

The immunologists dirty little secret


• enhance immunogenicity
• depot effect

- Aluminium salts
- Tensoactive compouds (Saponin)
- Microorganism-derived adjuvants (LPS, CpG)
- Emulsions (Freund‘s, Montanide)
- Cytokines (GM-CSF)
Shrinkage of melanoma metastasis after peptide immunisation

4 cm mass prior to vaccination

70% regression 4 months post-vaccine
# Phase II/III studies with active vaccination (NSCLC)

<table>
<thead>
<tr>
<th>Investigational agent</th>
<th>Study</th>
<th>n</th>
<th>Patients</th>
<th>Primary Endpoint</th>
<th>Treatment-group</th>
<th>Control</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tecemotide</strong>&lt;br&gt;peptide vaccine, which targets the exposed core peptide of MUC-1</td>
<td>II</td>
<td>171</td>
<td>IIIB or IV, SD or OR after 1. L chemotherapy</td>
<td>OS</td>
<td>17.2 m</td>
<td>13 m</td>
<td>ns</td>
<td>Butts 2011</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>1513</td>
<td>IIIA, SD or OR after 1. L chemoradiotherapy</td>
<td>OS</td>
<td>25.6 m</td>
<td>22.3 m</td>
<td>ns</td>
<td>Butts 2014</td>
</tr>
<tr>
<td><strong>Blagenpumatumcel-L</strong>&lt;br&gt;allogeneic tumor cell vaccine</td>
<td>II</td>
<td>75</td>
<td>II, IIIA, IIIB and IV; after chemotherapy</td>
<td>OS</td>
<td>Dose related improvement in OS</td>
<td>NA</td>
<td></td>
<td>Nemunaitis 2006</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>532</td>
<td>IIIA, IIIB, and IV SD or OR after 1. L chemotherapy</td>
<td>OS</td>
<td>20.3</td>
<td>17.8</td>
<td>ns</td>
<td>Giaccone 2013</td>
</tr>
<tr>
<td><strong>MAGE A3 vaccine</strong>&lt;br&gt;protein-based vaccine</td>
<td>II</td>
<td>182</td>
<td>IB/II MAGE-A3 expressing tumors</td>
<td>DFI</td>
<td>HR 0.74</td>
<td></td>
<td>ns</td>
<td>Vansteenkiste 2007</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>2312</td>
<td>IB/II and IIIA MAGE-A3 expressing tumors</td>
<td>DFI</td>
<td>60.9</td>
<td>57.9</td>
<td>ns</td>
<td>Vansteenkiste 2015</td>
</tr>
</tbody>
</table>
MAGRIT, phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer vaccine

**Background:**
- **NSCLC St IB, II, IIIA**
- Completely resected tumour
- MAGE-A3-positive
- PS 0–2 (n=2,272)

**Study Design:**
- **Randomization (R):**
  - 2:1
  - 13 IM injections of MAGE-A3 CI
  - 13 IM injections of placebo

**Outcome:**
- **DFS:**
  - **MAGE-A3 CI (597 events):** Median: 60.5 (95% CI 57.2, –)
  - **Placebo (298 events):** Median: 57.9 (95% CI 55.7, –)

**Significance:**
- p* = 0.7379
- HR 1.02 (95% CI 0.89, 1.18)
- Median FU 38.8 months

**Number at risk:**
- **MAGE-A3 CI:** 1,515, 1,257, 1,115, 1,013, 887, 656, 476, 339, 220, 127, 19, 2
- **Placebo:** 757, 639, 562, 514, 448, 328, 253, 180, 114, 62, 6, 0

Vansteenkiste. Ann Oncol 2014; 25 (suppl 4)
Dendritic cell immunization

- Professional antigen presenting cells
- Express co-stimulatory molecules that activate T cells
- Mature DCs migrate to the lymph node after injection
# Immunotherapy: Dendritic cell Immunization

<table>
<thead>
<tr>
<th>Tumor (Stage IV)</th>
<th>antigen</th>
<th>DC</th>
<th>immune Response</th>
<th>clinical response</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>melanoma</td>
<td>MAGE-3 peptide</td>
<td>Mo-DC</td>
<td>8/8</td>
<td>0/8</td>
<td>Schuler et al. J Immun 2000</td>
</tr>
<tr>
<td>melanoma</td>
<td>4 peptides</td>
<td>CD34 derived</td>
<td>16/18</td>
<td>7/17</td>
<td>Banchereau et al. Cancer Res. 2001</td>
</tr>
</tbody>
</table>
Negative Phase III trials
(significantly negative!)

EORTC 18961 (Melanoma Stage II)
- Ganglioside / Carrier / Adjuvants

MMAIT-III (Melanoma Stage III)
- allogeneic irradiated melanoma cells

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Eggermont AM, ASCO 2010

Morton DL, ASCO 2007
Dendritic cell - based Immunizations

metastatic castration-refractory prostate cancer (n=512)

primary endpoint: OS
2:1 randomisation

sipuleucel-T
(3 infusions every 2 wks)

placebo

HR: 0.78, p=0.03
Median survival:
- sipuleucel T 25.8 mts
- control 21.7 mts

Kantoff PW, NEJM 2010
Sipuleucel-T immunization in prostate cancer

During manufacturing

1. Inactive antigen presenting cell (APC)
2. APC takes in the antigen, becomes activated.
3. APC processes the antigen.

In the patient

4. APC is fully activated.
5. APC seeks out and alerts T-cells.
6. T-cells attack prostate cancer cells.
Sipuleucel-T immunization in prostate cancer

3-4 Days
Immune responses Sipuleucel-T

Immune responses:
A) antibodies
   PA2024: 66.2% in sipuleucel-T treated patients
            2.9% in controls
   PAP:    28.5% in sipuleucel-T treated patients
            1.4% in controls
  → correlation with survival

B) T cell responses
   PA2024: 73.0% in sipuleucel-T treated patients
            12.1% in controls
   PAP:    27.3% in sipuleucel-T treated patients
            8.0% in controls
  → no correlation with survival
Dendritic cell Immunization current phase III trails

- NCT00045968; Northwest Therapeutics: RCT to test DCVax®-L in patients with newly diagnosed GBM in addition to standard radiochemotherapy

- NCT01582672; ADAPT trial, Argos Therapeutics: RCT to test autologous dendritic cell immunotherapy plus standard treatment (Sunitinib) in advanced renal cell carcinoma

1. Vaccination of subjects with resected tumors and thus lower tumor burden
2. Vaccination in combination with other therapy
3. Loading DCs with autologous tumor preparations.
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Adoptive T cell Therapy
ACT using tumor infiltrating lymphocytes (TIL)
Adoptive T cell therapy: TIL

1. Isolation of tumor from different tumor sites
2. Cultivation *in vitro* for 24-56 days
3. Expansion of T cells 300-45x10^6 fold
4. Infusion of 3-75x10^10 cells

Objective regression:
- 9/15 pts not treated with IL-2 (60%)
- 2/5 pts with previous IL-2 treatment (40%)

*Rosenberg SA et al. NEJM 1988*
Autologous T cell therapy after lymphodepletion

1. lymphodepletion: Fludarabin + Endoxan
2. adoptive transfer of lymphocytes
3. IL-2 i.v.

*Dudley et al. Science 2002*
Autologous T cell therapy after lymphodepletion

- 13 patients with metastatic melanoma
- 6 (46%) PR (sustained)
- Autoimmunity: vitiligo, uveitis
Long term survival of patients with metastatic melanoma treated with TILs

cyclophosphamide 60 mg/kg/d (2 days)
fludarabine 25 mg/m2/d (5 days)

Rosenberg SA, Clin Cancer Res. 2011
Factors associated with clinical response

Independent of prior treatment:
- IL-2
- Chemotherapy
- BRAF/MEK inhibitors
- αCTLA4
- αPD1

Dependent on T cell differentiation:

Rosenberg SA, Clin Cancer Res. 2011
Differentiation of T cells

- $T_{SCM}$: CD45RA$^+$, CD62L$^+$, CCR7$^+$, CD95$^+$
- $T_{CM}$: CD45RA$^-$, CD62L$^+$, CCR7$^+$, CD95$^+$
- $T_{EM}$: CD45RA$^-$, CD62L$^-$, CCR7$^-$, CD95$^+$

Therapeutic efficacy
Self renewal
Survival
GVHD

Senescence
Differentiation
Effector function

Short-lived T Eff
In vitro stimulation of TILs

Stimulation with the **target antigen**

**T cell clones**
- Selection of one single CD8+ T cell
- Expansion to $10^{11}$

**T cell lines**
- Enrichment of a polyclonal antigen-specific T cell population
- Contains CD8+ and CD4+ T cells
ACT using MART1-specific T cell clones

Clinical Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Stable disease</td>
<td>5</td>
<td>(2-21month)</td>
</tr>
<tr>
<td>Mixed response</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Minor response</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Yee C et al. JEM 2000
Yee C et al. PNAS 2002
# Classification of tumor antigens

<table>
<thead>
<tr>
<th>Antigen Type</th>
<th>Specificity</th>
<th>Tolerance</th>
<th>Avidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutational antigens</td>
<td>patient, tumor</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Viral antigens</td>
<td>tumor</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Cancer-testis antigens</td>
<td>various tumors</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Differentiation antigens</td>
<td>tissue of origin</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Overexpressed gene products (oncogens)</td>
<td>most tumors</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

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Universitätsklinik für Medizinische Onkologie, Inselspital Bern
Adrian Ochsenbein
# ACT trials using TCR T cells

<table>
<thead>
<tr>
<th>Cancer Histology</th>
<th>Target</th>
<th>Patients</th>
<th>CR + PR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>MART-1</td>
<td>15</td>
<td>13%</td>
<td>Morgan, 2006</td>
</tr>
<tr>
<td>Melanoma</td>
<td>MART-1</td>
<td>20</td>
<td>30%</td>
<td>Johnson, 2009</td>
</tr>
<tr>
<td></td>
<td>Gp100</td>
<td>16</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>CEA</td>
<td>3</td>
<td>33%</td>
<td>Parkhurst, 2011</td>
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<tr>
<td>Different tumors</td>
<td>NY-ESO-1</td>
<td>17</td>
<td>53%</td>
<td>Robbins, 2011</td>
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<tr>
<td>Melanoma</td>
<td>MAGE-A3</td>
<td>9</td>
<td>56%</td>
<td>Radvanyi, 2013</td>
</tr>
<tr>
<td>Melanoma</td>
<td>MAGE-A3</td>
<td>2</td>
<td>0%</td>
<td>Linette, 2013</td>
</tr>
<tr>
<td>Myeloma</td>
<td>MAGE-A3</td>
<td>2</td>
<td>0%</td>
<td></td>
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</tbody>
</table>
### On-target, off-tumor toxicity

<table>
<thead>
<tr>
<th>Target Antigen</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MART-1, gp100</td>
<td>skin, eyes, and ears</td>
</tr>
<tr>
<td>carbonic anhydrase 9</td>
<td>liver toxicity</td>
</tr>
<tr>
<td>CEA</td>
<td>severe colitis, hemorrhage</td>
</tr>
<tr>
<td>MAGE-A3</td>
<td>brain toxicity due to cross-reactivity with MAGE-A12</td>
</tr>
<tr>
<td>ERBB2</td>
<td>death due to pulmonary toxicity</td>
</tr>
<tr>
<td></td>
<td>fatal cardiogenic shock due to recognition of titin (high affinity TCR)</td>
</tr>
</tbody>
</table>
Selection of target antigens for ACT

Antigens expressed on cancers that are non-essential human tissues
CD19, CD20, CD22, CD23, CD30, CD133, ROR-1

Private tumor antigens
«neo-antigens»
Mutational rate of tumors

Alexandrov LB, Nature 2013
Generation of neo-epitope specific T cells

- Tumor sample
- Extract DNA from normal and malignant tissue
- Exome sequencing to identify cancer mutations
- Some mutations are presented by APC in the context of autologous MHC
- T cells from peripheral blood or tumor
- Co-culture T cells
- Select using activation marker
- 41BB or OX40
- Expand and treat or isolate TCR for insertion into autologous lymphocytes

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Infusion of $1.48 \times 10^{11}$ tumor-infiltrating lymphocytes, which consisted of approximately 75% KRAS G12D-specific CD8$^+$ T cells ($1.11 \times 10^{11}$ cells)
loss of HLA-C*08:02

Tran E et al. NEJM 2016
Chimeric Antigen Receptor (CAR) T cells

Riether C. Swiss Medical Weekly 2013
Chimeric Antigen Receptor (CAR) T cells
Adoptive T cell therapy with Chimeric Antigen Receptors (CAR)

$V_H, V_L$ CD19

hinge 4-1BB CD3ζ

Porter DL. NEJM. 2010
Update results with CD19 CAR-T cells 
ASCO 2016

<table>
<thead>
<tr>
<th>Disease</th>
<th>patients</th>
<th>CR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>&gt; 100</td>
<td>80-90</td>
</tr>
<tr>
<td>CLL</td>
<td>&gt; 100</td>
<td>40-60</td>
</tr>
<tr>
<td>NHL</td>
<td>&gt; 40</td>
<td>~ 30%</td>
</tr>
</tbody>
</table>
GD2-specific CAR T cells in neuroblastoma

CR in 3/11 patients

Pule MA. Nature Medicine 2008
Louis CU, Blood 2011
Summary: adoptive T cell therapy

**Stimulation of TIL with antigen**
- + targeted to tumor antigen
- - massive expansion
- - low affinity TCR

**TIL**
- + polyspecific
- + antigen not characterized
- - massive expansion
- - low affinity TCR

**TCR T cells**
- + less expansion needed
- + surface and internal antigens
- + driver antigens?
- + high affinity TCR
- - off-tumor toxicity
- - dependent on MHC-I

**CAR T cells**
- + less expansion needed
- + not dependent on MHC-I
- - only surface antigens
- - selection of antigens (solid tumors)
Monoclonal Antibodies

**Immune effects**

**Immune cell**

**Lymphoma**

**Breast cancer**

**Colon cancer**

**Head/Neck cancer**

**Blocking pathways**

- lösliche Liganden
- membranständige Rezeptoren
- Komplement-Komponente C1q
- Fc-γ Rezeptor
Novel antibody formats: bispecific antibodies

- Phase II trial in refractory B precursor ALL
- 189 patients
- 41% complete remissions

Topp MS. Lancet Oncology. 2015
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    - Blocking PD1/PD-L1 Interaction
    - Other pathways
Immunecheckpoint Modulation
Immunecheckpoint Modulation
CTLA-4 Blockade
Long-term survival ("cure?") of patients with metastatic melanoma

- Survival of 1861 patients treated with (Yervoy®)

Patients at risk
Ipilimumab 1.861 839 370 254 192 170 120 26 15 5 0

Schadendorf, ESMO 2013
PD-1 signalling

Immature DC

Mature DC

Lymph node

anti-PD-1/PD-L1

Anti-CTLA-4
Blocking the PD-1 / PD-L1 Interaction
### PD-1 targeting antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Kd Binding Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Optivo)</td>
<td>Human IgG4</td>
<td>3 nM</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Humanized IgG4 kappa</td>
<td>28 pM</td>
</tr>
</tbody>
</table>

### PD-L1 targeting antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Kd Binding Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab, MPDL3280A</td>
<td>ADCC reduced, engineered IgG1</td>
<td>NA</td>
</tr>
<tr>
<td>Durvalumab, MEDI4736</td>
<td>ADCC reduced, engineered IgG1 kappa</td>
<td>NA</td>
</tr>
<tr>
<td>Avelumab, MSB0010718C</td>
<td>fully human IgG1</td>
<td>NA</td>
</tr>
</tbody>
</table>
Clinical activity in different tumor entities

- **NSCLC**
  - Median OS: 9.9 month
  - 42% survival at 6 months
  - 24% survival at 12 months

- **Melanoma**
  - Median OS: 16.8 month
  - 62% survival at 18 months
  - 43% survival at 24 months

- **Renal cell carcinoma**
  - Median OS: >22 month
  - 70% survival at 6 months
  - 50% survival at 12 months

Nivolumab first line in metastatic melanoma

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer (CheckMate 017)

- **NSCLC St IIIB, IV, squamous cell**
  1. Prior chemotherapy
  PS 0–1
  (n=272)

  **1:1**

  - **Nivolumab 3mg/kg q 2wk**
  - **Docetaxel 75mg/m2 q3wk**

**Graph:**
- **Median Overall Survival**
  - Nivolumab (N=135): mo (95% CI) 9.2 (7.3–13.3)
  - Docetaxel (N=137): 6.0 (5.1–7.3)
- **1-Yr Overall Survival**
  - % of patients (95% CI)
  - Nivolumab: 42 (34–50)
  - Docetaxel: 24 (17–31)
- **No. of Deaths**
  - Nivolumab: 86
  - Docetaxel: 113

**Hazard ratio for death:** 0.59 (0.44–0.79)
P < 0.001

**Adrian Ochsenbein**

**Bramer J, NEJM 2015**
Pembrolizumab versus Chemotherapy for PD-L1-positive Non-Small Cell Lung Cancer (Keynote 024)

**Patient Characteristics**
- NSCLC St IIIB, IV
- PD-L1 expression > 50%
- PS 0–1
(n=305)

**Randomization**
1:1

**Treatments**
- Pembrolizumab 200mg q 3wk
- Platinum-based standard

**Outcomes**
- Progression-free Survival
- Overall Survival

**Key Results**
- Hazard ratio for disease progression or death, 0.50 (95% CI, 0.37–0.68)
  - P<0.001
- Hazard ratio for death, 0.60 (95% CI, 0.41–0.89)
  - P=0.005

**References**
Reck M, NEJM 2016
Nivolumab in refractory Hodgkin’s disease

Nivolumab in refractory Hodgkin’s disease

Individual Patient Data (N=23)

- ASCT failure and brentuximab failure
- No ASCT and brentuximab failure
- No brentuximab

PD1/ PD-L1 efficacious in all tumors?

- Very efficacious
  - Melanoma
  - Lung cancer
  - Hodgkin’s lymphoma
  - Renal cell carcinoma

- Very promising
  - Bladder cancer
  - HeadNeck Carcinoma

- Less promising (with the exception of subgroups)
  - Breast cancer
  - Colon cancer
  - Prostatic cancer

Efficacious not in all, but in many different tumors
Mutational Rate and Clinical Response

Alexandrov LB, Nature 2013
High mutational burden predicts response to pembrolizumab in NSCLC

Predicted neo-epitopes:
Mutant nanomers with \( \leq 500\text{nM} \) binding affinity to HLA alleles

Cut off: 178 mutations
HR 0.19, \( p = 0.004 \)

n = 17

p = 0.002

Rizvi NA, Science 2015
anti-CTLA-4 blockade: anti-tumor immunity, autoimmunity

The good news....

The bad news....

Skin
 Colon
 Colon CD3
 Liver
Ipilimumab adverse events

Gastrointestinal
Signs and symptoms such as:
- Diarrhoea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

Liver
Signs such as:
- Abnormal liver function tests (e.g. AST, ALT or total bilirubin)

Skin
Symptoms such as:
- Pruritus
- Rash

Neurologic
Symptoms such as:
- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

Endocrine
Signs and symptoms such as:
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

Other adverse reactions
including ocular manifestations
Ipilimumab adverse events

**Determine Severity of Enterocolitis**

**Moderate**
- 4 to 6 stools/day over baseline
- Abdominal pain
- Blood or mucus in stool

**Management**
- Omit YERVOY
  - Symptomatic treatment (e.g., loperamide, fluid replacement) and close monitoring while etiology is investigated

**Follow-Up**
- Symptoms Improved to Mild Severity or Resolved
  - Resume YERVOY at the next scheduled dose
  - Doses omitted due to an adverse reaction must not be replaced
  - Start corticosteroids (e.g., prednisone 1 mg/kg orally once daily or equivalent)
  - Continue steroids until improvement to mild severity or resolution; taper steroids as medically appropriate
  - **IF SYMPTOMS WORSEN TO SEVERE, SEE BELOW**

- Symptoms Ongoing >1 Week*
- Continue steroids until improvement to mild severity or resolution; taper steroids as medically appropriate

**Severe or Life-threatening**
- > 7 stools/day over baseline
- Peritoneal signs consistent with bowel perforation
- Ileus
- Fever

**Permanently Discontinue YERVOY**
- Rule out bowel perforation; if bowel perforation is present, do not administer corticosteroids
- Consider endoscopic evaluation
- Administer high-dose intravenous corticosteroid (e.g., methylprednisolone 2 mg/kg/day or equivalent)

**Symptoms Resolved**
- Continue steroids until improvement to mild and taper steroids over 1 month

**Patient Should Do Not Respond Within 5-7 Days**
- Patient should be continually evaluated for evidence of gastrointestinal perforation or peritonitis
- Consider repeat endoscopy
- Consider alternative immunosuppressive therapy unless contraindicated (e.g., a single dose of infliximab 5 mg/kg)

* The recommendations below should also be considered if mild symptoms recur or persist for 5-7 days after initiation of symptomatic treatment
Ipilimumab adverse events

- Diarrhea, colitis: 33%
- Exanthema, pruritus: 40%
- Hypophysitis: 5%
- Liver: 4%
Personalized immunotherapy

- Immune
- Elimination ➔ Equilibrium ➔ Escape

**Ignorance**
- Checkpoint blockade
- Regulatory cytokines
- Tregs, MDSC

**Exclusion**
- Radiation
- Oncolytic viruses
- BiTe

**Editing**
- Generate new effectors
  - ACT
  - Vaccination

**Regulation**
Cancer Immunotherapy 2017