IMMUNOTHERAPY: Using the Body To Fight Cancer

Adrian Ochsenbein
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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
  - Beyond Immune Checkpoint Blockade
Milestones of Immuno-Oncology

1860
First Tumor-Immunotherapy using bacteria (Wilhelm Busch)

1890s
Vaccination with bacteria extracts; William Coley (Coley-Toxin)

1900
“Magic bullets“ recognize tumor cells (Paul Ehrlich)

1957
Tumor Immunosurveillance Hypothesis (F. Burnet Thomas)

1969
First allogeneic stem cell transplantation in leukemia in Seattle (Edward D. Thomas)
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**: First adoptive T-cell Immunotherapy
- **2000**: Approval of IFN-α as adjuvant therapy of melanoma
- **2000**: Approval of Rituximab for the therapy of B-Zell-lymphoma
- **2011**: Approval of Immunotherapy for prostate cancer (Sipuleucel-T)
- **2011**: Approval of the first Checkpoint Inhibitory molecule Ipilimumab for the treatment of metastatic melanoma
- **1970**: Discovery of Dendritic cells
- **1980**: First tumor-specific monoclonal antibody
- **2000**: Approval of IL-2 therapy for metastatic RCC and melanoma (US)

**Checkpoint Inhibitory Molecules**
CinicalTrial.gov: 1740 immunotherapy trials
Overview

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  - Immune Checkpoint Blockade
    - Blocking B7/CTLA-4 Interaction
    - Blocking PD1/PD-L1 Interaction
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>Type</th>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>congenital:</td>
<td>X-linked agamaglobulinemia</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>ataxia telangiectasia</td>
<td>12-15%</td>
</tr>
<tr>
<td>acquired:</td>
<td>bone marrow transplantation</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>heart-lung transplantation</td>
<td>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

B7
CD28

activation

anergy deletion
Anti-tumoral immune response

Ochsenbein AF et al. Cancer Gene Ther 2003
Cancer Immunoediting

Schreiber RD et al. Science 2011
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
**Immune checkpoints: T cell exhaustion**

- naive T-cell
- effector T-cell
- memory T-cell

**Effector-function**

- Apoptosis

- **antigen**
  - is eliminated
  - persists

- «exhausted» T-cell

- PD-1
- TIM-3
- LAG-3

...and many more

Adrian Ochsenbein
Exhaustion of cancer-specific T cells

Exhausted gene set enrichment in Melan-A-specific T cells from TILN

Blood

Melan-A

TILN

Isotype

KLRG-1

2B4

PD-1

TIM-3

CD160

LAG-3

CTLA-4

Baitsch L, J Clin Invest 2011
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>Tecemotide 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>Blagenpumatumcel-L 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>MAGE A3 vaccine 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

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

**Randomisation (2:1)**
- 13 IM injections of MAGE-A3 CI
- 13 IM injections of placebo

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

**p** \(= 0.7379\)
- HR 1.02 (95% CI 0.89, 1.18)

**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

**Median FU 38.8 months**

*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 CR+PR</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

GMK Vaccine

observation

% overall survival

years

HR 1.57  p=0.03

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

BCG+Placebo

BCG+Canvaxin

% overall survival

month

HR 1.26  p=0.04

Eggermont AM, ASCO 2010

Morton DL, ASCO 2007
**Dendritic cell - based Immunizations**

- **metastatic castration-refractory prostate cancer** (n=512)
- **sipuleucel-T** *(3 infusions every 2 wks)*
- **placebo**

**primary endpoint: OS**
**2:1 randomisation**

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) takes in the antigen and becomes activated.
2. APC processes the antigen.

**In the patient**

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

3-4 Days
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.
Adoptive T cell Therapy

1. Harvest PBMCs by apheresis
2. Excise tumor mass
3. T cell activation
4. Transduction
5. TIL cell isolation
6. TIL cell expansion
7. Infusion
8. CAR T cells
9. CAR T cells
10. TCR T cells
11. Lymphodepleted cancer patient
12. Host condition chemotherapy
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
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

Dudley et al. Science 2002
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<sub>SCM</sub>**
  - CD45RA<sup>+</sup>
  - CD62L<sup>+</sup>
  - CCR7<sup>+</sup>
  - CD95<sup>+</sup>

- **T<sub>CN</sub>**
  - CD45RA<sup>-</sup>
  - CD62L<sup>-</sup>
  - CCR7<sup>+</sup>
  - CD95<sup>+</sup>

- **T<sub>EM</sub>**
  - CD45RA<sup>-</sup>
  - CD62L<sup>-</sup>
  - CCR7<sup>-</sup>
  - CD95<sup>+</sup>

**APC**

**TN**

- IL-7 + IL-15

- IL-2

**Therapeutic efficacy**
- Self renewal
- Survival
- GVHD

**Senescence**
- Differentiation
- Effector function

**Short-lived T<sub>EF</sub>F**
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 (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable disease</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mixed response</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Minor response</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Category</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</td>
<td>most tumors</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
# 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>
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</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>Melanoma</td>
<td>MART-1</td>
<td>16</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Gp100</td>
<td></td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>CEA</td>
<td>3</td>
<td>33%</td>
<td>Parkhurst, 2011</td>
</tr>
<tr>
<td>Different tumors</td>
<td>NY-ESO-1</td>
<td>17</td>
<td>53%</td>
<td>Robbins, 2011</td>
</tr>
<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></td>
<td></td>
<td></td>
</tr>
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</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
- T cells from peripheral blood or tumor
- Co-culture T cells
- Some mutations are presented by APC in the context of autologous MHC
- Select using activation marker
- Expand and treat or isolate TCR for insertion into autologous lymphocytes

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)

Tran E et al. NEJM 2016
loss of HLA-C*08:02
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
- + 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

Lymphoma
Breast cancer
Colon cancer
Head/Neck cancer

Blocking pathways

C1q

Immune cell

FcR

Iölsiche 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% compete remissions

*Topp MS. Lancet Oncology. 2015*
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 1861 839 370 254 192 170 120 26 15 5 0

Schadendorf, ESMO 2013
Leben gerettet durch Immuntherapie

Anton Howald (69), Patient Universitätsklinik für Medizinische Onkologie
Lungenmetastasen vor Therapie (Dezember 2011) keine Lungenmetastasen nach Immuntherapie (seit März 2012)
PD-1 signalling

immature DC

mature DC

lymph node

Ochsenbein AF et al. Cancer Gene Ther 2003
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

**Renal cell carcinoma**
median OS: >22 month

**Melanoma**
Median OS: 16.8 month

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Overall survival (%) month after treatment start

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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

R

Nivolumab 3mg/kg q 2wk

Docetaxel 75mg/m2 q3wk

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

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

1:1

Pembrolizumab 200mg q 3wk

Platinum-based standard

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

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

- Very promising
  - Bladder cancer
  - HeadNeck Carcinoma

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 ≤ 500nM binding affinity to HLA alleles

Cut off: 178 mutations
HR 0.19, p=0.004
n=17

p=0.002
n=17

Rizvi NA, Science 2015
Side effects of Immune checkpoint Modulation
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)

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

**Endocrine**
- Signs and symptoms such as:
  - Fatigue
  - Headache
  - Mental status changes
  - Abnormal thyroid function tests and/or serum chemistries

**Skin**
- Symptoms such as:
  - Pruritus
  - Rash

Other adverse reactions including ocular manifestations
Ipilimumab adverse events

![Graph showing the severity of symptoms over duration weeks for different adverse events.](image)

- **Exanthema, pruritus**: 40%
- **Diarrhea, colitis**: 33%
- **Liver**: 4%
- **Hypophysitis**: 5%
Immune checkpoint blockade of PD-1/PD-L1 pathway

ORR: approximate objective response rate
Combination of immune-checkpoint inhibition

<table>
<thead>
<tr>
<th>1. Immune checkpoint inhibitor</th>
<th>2. Immune checkpoint inhibitor</th>
<th>phase</th>
<th>Tumor types</th>
<th>Trial Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-LAG-3</td>
<td>Anti-PD1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAG525</td>
<td>PDR001</td>
<td>1/2</td>
<td>Advanced cancer</td>
<td>NCT02460224</td>
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<tr>
<td>BMS-986016</td>
<td>Nivolumab</td>
<td>1</td>
<td>Advanced solid tumors</td>
<td>NCT01968109</td>
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<tr>
<td>Anti-TIM3</td>
<td>Anti-PD1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBG453</td>
<td>PDR001</td>
<td>1/2</td>
<td>Advanced cancer</td>
<td>NCT02608268</td>
</tr>
</tbody>
</table>
Talimogene laherparepvec (T-VEC)

1. Inside a healthy cell, the virus is unable to replicate, leaving the cell unharmed.

2. Inside a cancer cell, the virus replicates and secretes GM-CSF until the cell lyases, releasing more viruses, GM-CSF, and antigens.

3. GM-CSF attracts dendritic cells to the site, which process and present the antigens to T cells. The T cells are now "programmed" to identify and destroy cancer cells throughout the body.

T cells destroy cancer cells throughout the body, including those not directly injected with the virus.
Talimogene laherparepvec (T-VEC)

stage III or IV Melanoma (N=437)
* suitable for direct or ultrasound-guided injection

2:1

R

T-VEC i.t. day 1, 14

GM-CSF s.c. day 1-14

ORR 26.4%

Andtbacka R., JCO 2015
Indoleamine 2,3 dioxygenase (IDO) inhibition

Indoleamine 2,3 dioxygenase

Tryptophan $\rightarrow$ Kynurenin

EPACADOSTAT

Abstract 3003: Perez et al.

Epacadostat plus nivolumab in patients with advanced solid tumors: Preliminary phase I/II results of ECHO-204

<table>
<thead>
<tr>
<th>Disease</th>
<th>Overall Response Rate (CR/PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
</tr>
<tr>
<td>Treatment-naïve Melanoma</td>
<td>62.5% (25/40)</td>
</tr>
<tr>
<td>SCCHN (&lt; 2 prior treatment)</td>
<td>25.8% (8/31)</td>
</tr>
<tr>
<td>Ovarian Ca (prev treated)</td>
<td>14% (4/29)</td>
</tr>
<tr>
<td>CRC (prev treated)*</td>
<td>3.8% (1/26)</td>
</tr>
</tbody>
</table>

- Response **durability** seen across tumor subtypes
Adenosine receptor (A2A) inhibition

Safety and clinical activity of adenosine A2a receptor (A2aR) antagonist, CPI-444, in anti-PD1/PDL1 treatment-refractory renal cell (RCC) and non-small cell lung cancer (NSCLC) patients

Abstract 3004: Fong et al.
Personalized immunotherapy

- Immune
- Elimination
- Equilibrium
- Escape

Regulation
- Checkpointblockade
- Regulatory cytokines
- Tregs, MDSC

Exclusion
- Radiation
- Oncolytic viruses
- BiTe

Ignorance

Editing
- Generate new effectors
  - ACT
  - Vaccination

Universitätsklinik für Medizinische Onkologie, Inselspital Bern
Adrian Ochsenbein
Cancer Immunotherapy 2017

Operation

Strahlentherapie

Immunonkologie

? 

Chemo- & zielgerichtete Therapien