Developments in Immune Checkpoint Inhibition

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Disclosure

In Compliance with UEMS/EACCME Guidelines

Role as advisor for:
Astra Zeneca, BMS, Boehringer Ingelheim, MSD, Pfizer, Roche, Takeda
Neoantigens can be targeted by the immune system

CANCER CELL

Gene Mutations

Neu-Antigens

HLA

T CELL

TCR
Activation of T cells requires two signals
CD28 induces direct effect on transcription factors
Targeting CD28 for therapy

TAB08: Phase I stopped
→ life-threatening cytokine storm and multi-organ failure in six volunteers treated with the antibody (0.1 mg/kg TGN1412)

T cells undergo three phases after antigen stimulation

Nature Reviews Immunology 12, 749-761 (November 2012)
Fine-tuning of the immune response

Inhibition

Stimulation
Fine-tuning of the immune response
CD40/CD40L

Expression of CD40L
- T cells

Expression of CD40
- DC cells
- B cells
- Macrophages
- Tumor cells

FUNCTION
- Maturation of dendritic cells
- Activation/differentiation of T Cells

CD40/CD40L

FUNCTION on B cells
- Activation
  - immunoglobulin switching
  - antibody secretion
- Rescue from apoptosis
- Development of germinal centres
- Survival of memory B cells
Treatments targeting CD40/CD40L
Targeting CD40/CD40L

NCT01103635 I Melanoma
NCT02304393 I Solid tumors
NCT02482168 I NSCLC, melanoma, urothelial cancer, HNSCC
NCT03165994 II Esophageal and gastroesophageal tumors
NCT02706353 I/II Melanoma with pembrolizumab.
NCT03123783 I/II Melanoma, NSCLC with nivolumab
NCT02379741 I Solid Tumors
NCT02829099 I Solid Tumors
NCT02829099 I Solid Tumors
NCT02829099 I Solid Tumors and lymphomas with pembrolizumab
NCT02304393 I Solid Tumors
NCT02588443 I Pancreatic cancer with Nab-paclitaxel and gemcitabine
NCT02760797 I Solid Tumors with Emactuzumab
NCT02665416 I Solid Tumors
OX40/OX40L, expression

OX40
- Following antigen stimulation on activated naïve CD4 and CD8 T cells

OX40L
- Following antigen stimulation on APCs \(\rightarrow\) extent of T cell priming
- Following recognition of antigen on T cells \(\rightarrow\) T cell-T cell interactions

OX40/OX40L determines the size of effector and memory T cell pools

OX40/OX40L

Function
• Regulatory T cells → inhibition by downregulation of CTLA4 and FoxP3
Rational for targeting OX40/OX40L

- T Cell Agonists
  - αOX40
  - α4-1BB
  - αGITR
  - rIL-2
- Immunization
- Chemotherapy
- Radiation Therapy
- Tumor Antigens
- Tumor-Reactive Effector T Cells
- Checkpoint Blockade
  - αPD-1/αPD-L1
  - αCTLA-4
  - αTIM3
  - αLAG3
  - αBTLA
- Regulatory T Cells
- Treg Antagonism
  - αCTLA-4
  - αOX40
- Tumor
Targeting OX40/OX40L

NCT01644968 | Solid tumors
NCT02410512 | Solid tumors with atezolizumab
NCT02315066 | Melanoma
NCT02221960 | Solid tumors
NCT02705482 | Solid tumors
NCT02923349 | Solid tumors
NCT02528357 | Solid tumors
Function of CD137: CD137L

On T cells increasing:
- proliferation, resistance to apoptosis, IFNγ secretion
  → increase in tumor-selective cytolytic T-cell activity

On T reg:
- Reduction of T regs infiltration

On DC
- Enhancing co-stimulation

On NK
- Enhanced ADCC (antibody-dependent cell-mediated cytotoxicity)
Clinical trials with Abs targeting CD137: the experience with Urelumab

Phase I, NCT00309023:
- low grade fatigue
- grade 2+ neutropenia, leukopenia, thrombocytopenia, increased in AST and ALT

Phase II NCT00612664:
- terminated due to high incidence of Grade IV, potentially fatal, hepatitis

<table>
<thead>
<tr>
<th>Ab</th>
<th>Trial number</th>
<th>Combination</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Urelmab</td>
<td>NCT01471210</td>
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<td>solid tumors and NHL</td>
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<tr>
<td>Urelmab</td>
<td>NCT02110082</td>
<td>Cetuximab</td>
<td>CRC and HN cancer</td>
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<td>Urelmab</td>
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<td>Rituximab</td>
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<td>Urelmab</td>
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<td>PF-05082566</td>
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<td>solid tumors</td>
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<td>NHL</td>
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Fine-tuning of the immune response
Co-inhibitory molecules
Co-inhibitory molecules

Co-inhibitory molecules
Co-inhibitory molecules
LAG3: binds to MHC II

Expression

- On exhausted T cells
- On TIL
- On T regs
- On NK
LAG3: binds to MHC II

**Function**

- Confers a Treg function on CD4 naïve T cells
- Negatively regulates
  - T-cell activation
  - Proliferation
  - Homeostatic expansion

Adapted from Nature Reviews Immunology 15; 2015: 45-56
Soluble LAG3: is an immunoadjuvant

Adapted from Nature Reviews Immunology 15; 2015: 45-56
Targeting LAG3

NCT01968109, Melanoma: in combination with nivolumab, ORR 16%, DCR 45%

- Responses are related to LAG3 expression?
- What about the soluble form?

CA224-220:
An Investigational Immuno-therapy Study to Assess the Safety, Tolerability and Effectiveness of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors
Fine-tuning of the immune response
Tumor-extrinsic acquired resistance: TIM-3 up-regulation (NSCLC)

Preclinical model

S. Koyama et al; Nature Communications 2016
Targeting TIM3

NCT02608268, I/II: Advanced Malignancies

NCT02503774, I: Solid tumors
CD73

Activation
- A2aR Blockade (T_{eff} and APCs)
- CTLA-4 Blockade
- Vaccines

Cellular Breakdown
- Chemotherapy
- ATP Release
- TAA Release
- Hypoxia
  - HIF1-α → CD39 → CD73

Effectors Phase
- A2aR Blockade (T_{eff}, NKs, MDSC, TAMS, T_{REG})
- PD-1 Blockade
- PD-L1 Blockade
- Adoptive T-cell Therapy

RD Leone, Computational and Structural Biotechnology Journal, 2015
Targeting CD73 and A2aR

Targeting CD73: NCT02503774 | Solid tumors

Targeting A2aR: NCT02655822 | Solid tumors DCR 42%
# Targeting TIGIT

<table>
<thead>
<tr>
<th>Company</th>
<th>mAb</th>
<th>IgG Isotype and Fc effector functions</th>
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<tbody>
<tr>
<td>Genentech</td>
<td>MTIG7192</td>
<td>IgG1</td>
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<td>Merck Sharp &amp; Dohme</td>
<td>MK-7684</td>
<td>IgG1</td>
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<td>Bristol-Myers Squibb</td>
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<td>OMP-313M32</td>
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<td>Arcus</td>
<td>AB-154</td>
<td>IgG4 S228P</td>
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<td>Potenza</td>
<td>ASP8374</td>
<td>IgG1mut, FcγR null</td>
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- NCT03119428 | I Solid tumors
- NCT03563716 | I-II NSCLC, with Atezolizumab
- NCT03628677 | I Solid tumors
Available and upcoming

Antigen-Presenting Cell

- PD-L1
- CD80
- ICOSLG
- B7-H3/B7-H4
- VISTA
- B7-H6
- B7-H7
- HVEM
- Gal-9
- MHC class I or II
  - CD137L
  - OX40L
  - CD70
  - CD40
  - GITRL
  - CD155
  - CD112
  - CD200
  - CD48
  - Adenosine

T-Cell

- PD-1
- CD28
- CTLA-4
- ICOS
- ?
- ?
- NKp30
- TMIGD2
- BTLA
- LIGHT
- TIM-3
- KIR
- KIR3DL2
- TCR
- LAG-3
- CD137
- OX40
- CD27
- CD40L
- GITR
- CD96
- CD226
- TIGIT
- CD112R
- CD200R
- 2B4
- A2aR

Cytokines
- TGFβ, IL-1, IL-6, IL-10, IL-12, IL-18

Key
- Target = Available
- Target = Upcoming

Adapted with modification from:
P.D. Rentier, Nat. Rev. Dis. 4, 351 (2013)
Thank you for your attention!
## Anti PD1/PD1: which IgG?

<table>
<thead>
<tr>
<th>Target</th>
<th>Company</th>
<th>mAb</th>
<th>Clinical stages</th>
<th>IgG isotype or mutant with effector function nullified</th>
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<tbody>
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<td>PD-1</td>
<td>Bristol-Myers Squibb</td>
<td>Nivolumab</td>
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<td>Merck</td>
<td>Pembrolizumab</td>
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<td>Regeneron/Sanofi</td>
<td>Cemiplimab</td>
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<td>BeiGene</td>
<td>Tislelizumab</td>
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