CAR T-CELL THERAPIES
Scientific and Policy perspectives

WEBINAR
5 December 2017
16:00-17:30 CET

Viviana Galli
Coordinator, European Alliance for Responsible R&D and Affordable Medicines

Tuna Mutis, MD, PhD
VU University Medical Centre in Amsterdam

Anna Prokůpková
Policy & Project Officer, ECL

Théau Brigand
Advocacy Officer, Ligue Contre le Cancer, France
OUTLINE

16:00-16:15 INTRODUCTION OF THE TOPIC, SPEAKERS AND PARTICIPANTS
Viviana Galli

16:15-16:45 SCIENTIFIC ADVANCES AND RISKS OF CAR T-CELL THERAPIES & QA
Tuna Mutis, MD, PhD

16:45-17:15 CAR T-CELL THERAPIES FROM REGULATORY AND POLICY PERSPECTIVE & QA
Anna Prokůpková & Théau Brigand

17:15-17:30 CONCLUSIONS
Viviana Galli

It uses the body's own immune system to fight cancer.

1. remove immune cells called T cells from a patient's blood.
2. genetically alter the cells in a lab to contain certain proteins.
3. inject cells back into the patient.
4. Modified proteins help immune cells find and kill cancer cells.
CAR T-CELL THERAPIES
Scientific Advances and Risks

Tuna Mutis, MD, PhD
Department of Hematology, VU University Medical Centre Amsterdam
HOW OUR IMMUNE SYSTEM RECOGNIZE AND ELIMINATE TUMORS?

<table>
<thead>
<tr>
<th>B cell Immunity</th>
<th>T cell Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody (B cell receptor)</td>
<td>T cell receptor</td>
</tr>
<tr>
<td>B cells produce the antibody in a soluble form</td>
<td>T cell receptor is not soluble</td>
</tr>
</tbody>
</table>
HOW B CELL IMMUNITY WORKS?

- Tumor Cell antigens
- B cell
- Surface proteins
- A Small Tumor Specific peptide in HLA
- Tumor Cell antigens
ANTIBODIES GUIDE KILLER CELLS TO FIND AND KILL TUMORS
T CELLS SEEK TUMORS WITH THEIR RECEPTORS TO KILL THEM
HOW TO COMBINE THE BEST OF TWO SYSTEMS?
THE CART CELL CONCEPT

- HLA-peptide complex
- T cell Receptor
- Tumor-Specific Surface Antigen
- Antibody
- Chimeric Antigen Receptor (CAR)
HOW TO ENGINEER A CART CELL

Engineer the CAR DNA

Build CAR DNA in a carrier vector

Insert the vector in a “virus-producer cell” to incorporate the CAR DNA into a virus, which can infect a T cell but can not replicate itself (a modified retro- or lenti-virus)

Produce replication deficient virus with the CAR DNA

Infection of T cells

CAR DNA is built in the genome

and translated into CAR protein

CAR T cell

Car protein

Engineer the CAR DNA
Nomenclature: Targeted Surface molecule (eg: CD19, CD38, BCMA) + CART

Scientific papers also mention the type of stimulatory chain (eg: 28z or BBz)

Then

CD19-CART (-28z)

BCMA-CART (-BB1z)

NB: there are different antibodies with the same target specificity but with different potencies.

Thus the same name (eg: BCMA-CAR) may refer to different CART cells. Hence, the clinical efficacies may be different.

The same holds true for costimulatory domains (CD28z vs 41BB)
IMMUNOTHERAPY WITH CAR T CELLS
Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts J. Hartmann et al.
Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts J.Hartmann Et al.
Table 1 | CD19-specific-CAR T-cell therapy outcomes in patients with B-ALL

<table>
<thead>
<tr>
<th>Institution</th>
<th>CAR design</th>
<th>Patient population</th>
<th>Outcome</th>
<th>Toxicities</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC</td>
<td>CD28, CD3ζ</td>
<td>* n = 32 adults</td>
<td>91% CR</td>
<td>B-cell aplasia</td>
<td>NCT01044059</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* R/R B-ALL</td>
<td></td>
<td>CRS</td>
<td>[REF. 13]</td>
</tr>
<tr>
<td>UPenn/CHOP</td>
<td>4-1BB, CD3ζ</td>
<td>* n = 30 children and young adults, B-ALL</td>
<td>90% CR</td>
<td>B-cell aplasia</td>
<td>NCT01620495</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>CRS</td>
<td>[REF. 15]</td>
</tr>
<tr>
<td>NCI</td>
<td>CD28, CD3ζ</td>
<td>* n = 20 children and young adults, B-ALL</td>
<td>70% CR</td>
<td>B-cell aplasia</td>
<td>NCT01593696</td>
</tr>
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<td></td>
<td></td>
<td>CRS</td>
<td>[REF. 17]</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>4-1BB, CD3ζ</td>
<td>* n = 20 adults</td>
<td>84% CR</td>
<td>CRS</td>
<td>NCT01865617</td>
</tr>
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<td></td>
<td>[REF. 18]</td>
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</tbody>
</table>

Preconditioning chemotherapy was used in all the trials shown in this table. B-ALL, B-cell acute lymphoblastic leukaemia; chemo, chemotherapy; CHOP, Children’s Hospital of Philadelphia; CR, complete response; CRS, cytokine-release syndrome; Fred Hutchinson, Fred Hutchinson Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; R/R, relapsed and/or refractory; UPenn, The University of Pennsylvania.
1. The First ever FDA approval for a CAR-T cell therapy: Kymriah™ (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice (Novartis) 
Aug 30, 2017

Price tag: $475,000 per patient. "value-based" pricing (for those patients who go into remission within three months)

2. FDA also approves (CD19) CAR-T cell therapy, YESCARTA™, to treat adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy (Kite Pharma/Gilead) 
October 18, 2017

Price tag: $373,000 per patient.

3. FDA Grants BCMA CART-Cell Therapy Breakthrough Designation in Myeloma 
Nov 16, 2017
(Blue bird/Celgene)
<table>
<thead>
<tr>
<th>CART CELLS VS T CELLS</th>
<th>CART CELLS &amp; T CELLS VS ANTIBODIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANTAGES</td>
<td>ADVANTAGES</td>
</tr>
<tr>
<td>HLA non restricted: applicable to many patients</td>
<td>More potent, due to killer activity of T cells</td>
</tr>
<tr>
<td>No Tumor escape through HLA downregulation, blocked ag-processing</td>
<td>Tumor Escape via - Shedded (soluble) ags, - ag downregulation, - epitope mutation</td>
</tr>
<tr>
<td>Targeting non-peptide antigens possible</td>
<td>Should be relatively cheaper, but...</td>
</tr>
<tr>
<td>Better survival and persistence in the patient due to built-in costimulation</td>
<td></td>
</tr>
<tr>
<td>Better tumor targeting due to high affinity of antibodies and due to higher antigen load</td>
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CART CELL PROGRAM IN HEMATOLOGY

**Multiple Myeloma**
- **CD38-CART cells**
  - Preclinical-> clinical
- **BCMA-CART cells**
  - Clinical trial (2018)
- **Dual-CART cells**
  - Preclinical

**Acute Myeloid Leukemia**
- **CLEC12A-CART cells**
  - Preclinical
- **Dual-CART cells**
  - Preclinical

**Universal “Off the Shelf” CART cells**
- Preclinical
CAR T-CELL THERAPIES
Regulatory and Policy Perspectives

Anna Prokůpková & Théau Brigand
ECL Access to Medicines Task Force
### CAR T-CELL THERAPIES: A BRIEF HISTORY

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
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<tbody>
<tr>
<td>1993</td>
<td>First CAR T-cell developed by Dr. Zelig Eshhar</td>
</tr>
<tr>
<td>1996</td>
<td>The first CAR T-cell clinical trial began in 1996 in patients with ovarian cancer</td>
</tr>
<tr>
<td>2010-11</td>
<td>Phase 1 clinical trial of CAR T-cells in chronic lymphoid leukemia, two of the three patients achieved complete remission</td>
</tr>
<tr>
<td>2012</td>
<td>Emily Whitehead became the first paediatric patient to be treated with CAR T-cell therapy in acute lymphoblastic leukemia (ALL). Highly medialised, her remission helped re-energise a line of underestimated research</td>
</tr>
<tr>
<td>2017</td>
<td>The FDA approved the first CAR T-cell therapy, Kymriah®</td>
</tr>
<tr>
<td>2017</td>
<td>The FDA approved the second CAR T-cell therapy, Yescarta®</td>
</tr>
<tr>
<td>2018</td>
<td>The EMA to approve the first CAR T-cell therapy in Europe</td>
</tr>
</tbody>
</table>
CAR T-CELL, A NEW APPROACH TO TREATING CANCER

<table>
<thead>
<tr>
<th>Year</th>
<th>Publications</th>
<th>Patents</th>
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<tbody>
<tr>
<td>2007</td>
<td>1</td>
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<tr>
<td>2008</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>1</td>
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<td>2011</td>
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<td>2013</td>
<td>37</td>
<td>90</td>
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<tr>
<td>2014</td>
<td>65</td>
<td>106</td>
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<td>2015</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>231</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>365</td>
<td></td>
</tr>
</tbody>
</table>
EMA REGULATORY PROCEDURE FOR CAR T-CELL THERAPIES

- Orphan designation
- Paediatric Investigation Plan/PIP compliance check
- MA: Centralised Authorisation Procedure
- PRAC/CHMP/CAT scientific evaluation
- COMP orphan designation maintenance
- EC market approval
EMA PIPELINE

MA Application

<table>
<thead>
<tr>
<th>Submission date</th>
<th>Sponsor</th>
<th>Indication/Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 July 2017</td>
<td>Kite Pharma</td>
<td>Axicabtagene ciloleucel as a treatment for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL), and primary mediastinal B-cell lymphoma (PMBCL) who are ineligible for autologous stem cell transplant (ASCT)</td>
</tr>
<tr>
<td>6 November 2017</td>
<td>Novartis</td>
<td>CTL019 (tisagenlecleucel) application for the treatment of children and young adults with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) and for adult patients with r/r diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant (ASCT)</td>
</tr>
</tbody>
</table>

MA Timeline

- ATMPs – ca. 120 days (if no delay)
- Kite granted access to Priority Medicines (PRIME) regulatory support for development and accelerated review of new therapies to treat patients with a high unmet need
CLINICAL DATA

Novartis, Kymriah®

Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia (ALL) for patients aged from 3 to 25
n=63

- Phase II study,
- **82% of patients achieved complete remission**
- 48% experienced grade 3 or 4 cytokine release syndrome (CRS)

Relapsed/refractory diffuse large B-cell lymphoma (DLBCL), People > 18

- Phase II study, 81 infused patients
- At month 3, the complete remission rate was 32% and the PR rate 6%
- Among patients evaluable at 6 months, the CR rate was 30% and PR rate was 7%.
- CRS occurred in 58% of infused patients, with 15% grade 3 and 8% grade 4
Gilead/Kite, Yescarta®

Diffuse large B cell lymphoma (DLBCL) and other B Cell lymphomas

• 101 infused patients
• Complete response rate of 31% in 77 patients with DLBCL after 8.7 months of follow-up
• 51% of the patients, not just DLBCL, in complete remission
• 13% of patients experienced grade 3 or CRS and 31 percent experienced neurologic toxicities

Juno, JCAR017

Diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL) or transformed follicular lymphom

• Complete response rate of 73% in 15 DLBCL patients at three month
CAR T-CELL THERAPIES: PATIENT AND INVESTOR EXPECTATIONS

PATIENTS AND FAMILIES
• Hope for a cure
• Strong willingness to access

INVESTORS: A CAR T-CELL DEAL REVIEW
• 2012, 3 deals
• 2015, 35 deals
• Between 2012 and September 2016, the deals worth at least:
  • $2 billion in disclosed upfront payments
  • $4 billion in milestones, royalties...
• August 2017, Gilead's Kite Pharma acquisition for $11.9 billion
PRICING ISSUE

Highly personalised
+ Large health benefits
+ Difficult and supposedly expensive to produce
+ A response to an unmet medical need
  + Strong willingness to access
+ High investment return expectations
  = HIGH PRICES
HOW MUCH?

UK PREDICTIONS
National Institute for Health and Care Excellence (NICE) ran the numbers and found that CAR T-cell therapies could be worth up to $649,000, assuming that patients gain 10 QALYs over the current standard of care - NICE willing to pay up to $460,000 for this new technology.

U.S. PRICES

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>ALL</th>
<th>DLBCL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kymriah®</td>
<td>$475,000 + 1 month outcome based contracting</td>
<td>?</td>
<td>Novartis CEO Jimenez sees an opportunity for indication based pricing, based on the value it brings to the healthcare system</td>
</tr>
<tr>
<td>Yescarta®</td>
<td>XX</td>
<td>$373,000 without outcome based contracting</td>
<td>Gilead CEO Milligan finally said that they could be open to risk sharing agreements</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Might be two prices, one for ALL, a second for DLBCL</td>
</tr>
</tbody>
</table>
A clear lack of transparency

THE PUBLIC SECTOR ROLE IN FUNDING CAR T TECHNOLOGIES
- David Mitchell, Patients for Affordable Drugs, calculated that NIH poured $200 million into research that led to CAR T Therapy
- Only 20% of CAR T-cell trials are sponsored by pharmaceutical industry (Hartmann et al. *EMBO-Molecular Medicine*, 2017)
- Jimenez, Novartis, says that bringing Kymriah® to market cost more than $1 billion
- KEI notes that Kite reported spending $317 million in R&D from 2012 to June 30, 2017, and is selling the company for $11.9 billion

CAR T MANUFACTURING COSTS AND LACK OF TRANSPARENCY
- 2017, the French Health minister, Agnes Buzyn, explained that CAR-T Cells were going to be expensive because of manufacturing costs. Is that so?
  - 2015, Kite Chief Financial Officer Cynthia Butitta said that its financial models set a base case price at $150,000 per treatment

= CLEAR LACK OF TRANSPARENCY
WHAT’S NEXT?

Yescarta® and Kymriah® = first in class
  • Setting a benchmark
  • Pricing critical

The most advanced CAR T targets hematological malignancies, rare cancers
  • This space will soon be too crowded
  • And it will become more and more important to target solid tumors

78 clinical trials on solid tumors (Diane Singhroy, September 15th, 2017, Knowledge Ecology International https://www.keionline.org/23419/)
  • Lung, Breast, Ovarian, Multiple Myeloma etc.
CAR T-CELL THERAPIES
Scientific and Policy perspectives

THANK YOU FOR YOUR ATTENTION!