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Technical University Dresden

CEO Cellex and CMO GEMoaB (Dresden+Cologne)

February 10-12, 2020

CDDF Conference
Potential Conflicts of Interest

1. Positions and Ownership
   CMO GEMoaB GmbH and CEO Cellex GmbH
   Ownership GEMoaB and Cellex

2. Consultant
   Janssen

3. Stock
   BMS, Fresenius, Qiagen

4. Speaker
   -

5. Financial Support
   BMS (Celgene)

6. Any Other Relationship
   -
T cell receptor fusion construct

TIL
Tumor infiltration lymphocytes
CAR-T: Manufacturing of a Complex Cellular Product

- Patient infusion
- Centre-based Management
- Transport of Cryopreserved Final Product
- Transport of Starting Material
- CMO Manufacturing / QC Cryopreservation
- Allogeneic/autologous Apheresis
- Audit/Training Clinical Sites
- Transport of Starting Material

Cellex
CellCommunity
Autologous UniCAR02-T production cycle

Remove patient’s blood to isolate T lymphocytes

infusion of TM into patient

UniCAR T cells bind through TM to cancer cells and provoke their lysis

culturing of UniCAR T cells

infusion of UniCAR T cells into patient

ex vivo insertion of UniCAR gene

UniCAR T cell
UniCAR-T: TM-dependent activation and lysis

- Cancer cell
- Lysis of target cell
- Cancer specific targeting module
- Universal CAR
- Release of cytokines/cytotoxic molecules
General problems for all cellular therapies

• Setting up a reliable, consistent and scalable manufacturing system
• Automation needed
• Allogeneic products needed for immediate treatment
• Limited supply resources for goods
• Road blocks by multiple patents
• (Excessively) high pricing
• Regulatory hurdles
CAR-T Dosing and Scheduling

Screening
21d prior LEU

LEU
Salvage therapy

LD

CAR-T production/release/logistic

CAR-T Application

Active Drug

Dose-finding study using Bayesian Optimal Interval (BOIN) design for drug combination trials: BOIN-COMB (Lin and Yin, 2015)
Diffuse Large B-Cell-Lymphoma

CD19-CAR-T-Cells – Axicaptagen-Ciloleucel ('ZUMA-1')

(Locke et al, Lancet Oncol 20: 31, 2019)

119 patients with refractory/relapsed
DLBCL, PMBCL oder tFL
108 received Axi-Cel
101 with median Follow-up of 27 months

Lymphodepletion Fludarabin-Cyclophosphamide
Intervall apheresis – reinfusion: 17 days

Overall response rate 83 %
Complete remission 58 %
Remission ≥ 2 years 39 %

Grad 3/4-adverse events
‘CRS’ 11 % (start day 2 / Duration 8 days)
Neurotoxicity 32 % (start day 5 / Duration 17 days)

scFv (anti-CD19)

Hinge/Transmembrane

Signal 2: CD28

Signal 1: CD3ζ

scFv, single-chain variable fragment.
Diffuse Large B-Cell-Lymphoma

CD19-CAR-T-Cells – Axicaptagen-Ciloleucel (‘ZUMA-1‘)

(Locke et al, Lancet Oncol 20: 31, 2019)

Progression-free survival

Overall survival

(n=101)

Courtesy of U. Dührsen
Background – SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research)

- SCHOLAR-1, a retrospective, international, patient-level, multi-institution study and the largest reported analysis of outcomes in patients with refractory large B cell lymphoma, demonstrated that these patients have a very poor prognosis\(^1\)
  - \(N = 636\) (post-rituximab era, 2000-2017)
  - ORR = 26%
  - CR rate = 7%
  - Median OS = 6.3 mo
  - These results provided a benchmark for evaluation of new approaches

- Previous analyses of SCHOLAR-1 standardized to ZUMA-1 with ≥ 6 mo follow-up suggested the benefit of axi-cel in refractory large cell lymphoma\(^2\)

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CR, complete response; ORR, objective response rate; OS, overall survival.
Diffuse Large B-Cell-Lymphoma

CD19-CAR-T-Cells – Axicaptagen-Ciloleucel (‘ZUMA-1‘)

(Locke et al, Lancet Oncol 20: 31, 2019)

PFS and response rate

Response rate and cell dose

Courtesy of U. Dührsen
Diffuse Large B-Zell-Lymphoma

*CD19-CAR-T-Cells – Tisagen-Leclerucel ('JULIET')*


165 with refractory/relapsed DLBCL
111 received Tisa-Cel (Follow-up 14 months)
  93 with Follow-up ≥ 3 months

92 % Bridging therapies
93 % Lyphodepletion with Flu-Cy or Bendamustin
Intervall apheresis – reinfusion: 54 days

Response rate 52 %
Complete Remission 40 %
Remission ≥ 6 Months 33 %

Grad 3/4-adverse events
  'CRS' 22 % (start day 3 / duration 7 days)
  Neurotoxicity 12 % (start day 6 / duration 14 days)

Courtesy of U. Dührsen
Diffuse Large B-Zell-Lymphoma
CD19-CAR-T-Cells – Tisagen-Lecllucel (‘JULIET‘)

Progression-free survival

Overall survival

(n=40 / 111)

Courtesy of U. Dührsen
## Diffuse Large B-Zell-Lymphoma

**CD19-CAR-T-Cells – Tisagen-Leclercel (‘JULIET’)**


Refractory disease!

- Refractory to the last line of treatment

Molecular Subtype!

- Rearranged MYC plus BCL2, BCL6, or both

Tumor mass!

- $>100 \text{ ml}$

### Overall Response Rate

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Overall Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>52 (41–62)</td>
</tr>
<tr>
<td>Age</td>
<td>49 (37–61)</td>
</tr>
<tr>
<td>Sex</td>
<td>58 (39–74)</td>
</tr>
<tr>
<td>Age, Sex</td>
<td>59 (36–79)</td>
</tr>
<tr>
<td>Prior history of disease</td>
<td>40 (26–55)</td>
</tr>
<tr>
<td>IFI at enrollment</td>
<td>64 (49–78)</td>
</tr>
<tr>
<td>Prior histologically abnormal lines</td>
<td>56 (35–76)</td>
</tr>
<tr>
<td>Prior antineoplastic therapy</td>
<td>50 (38–62)</td>
</tr>
<tr>
<td>Molecule subtype</td>
<td>53 (38–68)</td>
</tr>
<tr>
<td>Molecular subtype</td>
<td>50 (35–65)</td>
</tr>
<tr>
<td>Molecular subtype</td>
<td>50 (38–62)</td>
</tr>
<tr>
<td>Molecular subtype</td>
<td>50 (38–62)</td>
</tr>
</tbody>
</table>

_Courtesy of U. Dührsen_
Children and Young Adults with B-Cell Lymphoblastic Leukemia

**CD19-CAR-T-Cells – Tisagen-Lecleucel**

107 Patients were screened
- 92 Were enrolled
  - 17 Were excluded
    - 7 Had tisagenlecleucel product-related issues
    - 7 Died
    - 3 Had adverse events
  - 75 Underwent infusion
    - 27 Discontinued
      - 11 Died
      - 9 Had lack of efficacy
      - 5 Underwent new therapy for ALL while in complete remission
      - 2 Withdrew or were withdrawn by guardian
  - 48 Remained in follow-up

**Event-free and Overall Survival**

<table>
<thead>
<tr>
<th>Months since Tisagenlecleucel Infusion</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>8</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>14</td>
<td>0.3</td>
</tr>
<tr>
<td>16</td>
<td>0.2</td>
</tr>
<tr>
<td>18</td>
<td>0.1</td>
</tr>
<tr>
<td>20</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Overall Survival**
- No. of Patients: 75
- No. of Events: 19
- Median Survival: 19.1 months (not reached)
- Rate at 6 Mo % (95% CI): 90 (81–95)
- 73 (60–82)

**Event-free Survival**
- No. of Patients: 75
- No. of Events: 27
- Median Survival: Not reached
- Rate at 6 Mo % (95% CI): 82 (60–82)

**No. at Risk**
- Overall survival: 75, 72, 64, 58, 55, 40, 30, 20, 12, 8, 2, 0
- Event-free survival: 75, 64, 51, 37, 33, 19, 13, 8, 3, 1, 0
Published Data from Phase I/II Clinical Studies Show Significant Treatment-Related Toxicities With CD19 CAR-T in NHL and ALL

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene ciloleucel</th>
<th>Tisagenlecleucel</th>
<th>JCAR017</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA 1 (adult, NHL)</td>
<td>CRS (≥ Gr 3) % 93 (11) %</td>
<td>Juliet (adult, NHL) 74 (24) %</td>
<td>ELIANA (pediatric, ALL) 77 (47) %</td>
</tr>
<tr>
<td>Juliet (adult, NHL)</td>
<td>NT (≥ Gr 3), % 67 (32) %</td>
<td></td>
<td>40 (13) %</td>
</tr>
<tr>
<td>ELIANA (pediatric, ALL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcend NHL 001 (adult, NHL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU (%)</td>
<td>NR</td>
<td>NR</td>
<td>47%</td>
</tr>
</tbody>
</table>

High rate and severity of **treatment-related toxicity** (on target/on tumor and on target/off tumor) observed in clinical trials of all CD19 CAR-T products.
Eliana trial: The probability of maintenance of **B-cell aplasia** at 6 months after infusion was 83% (95% CI, 69 to 91).

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1Neelapu SS et al. 2017, NEJM
2Schuster SJ et al. 2019, NEJM
3Maude SL et al. 2017, NEJM
Despite Advances in AE & Patient Management the Issue of Treatment-Related Toxicities With CAR-T Remains Unsolved – Real Life Data and Practice Guidelines

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene ciloleucel</th>
</tr>
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<tr>
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<tr>
<td>CRS (≥ Gr 3), %</td>
<td>93 (11) %</td>
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<tr>
<td>NT (≥ Gr 3), %</td>
<td>67 (32) %</td>
</tr>
<tr>
<td>ICU (%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

- Rate and severity of treatment-related toxicity is not improved through better treatment guidelines
- Intensive follow-up after administration of CD19 CAR-T for up to 6 weeks required
- ICU reservation is still required for all patients treated with CAR-T cells³


The Other Side of CAR T-Cell Therapy: Cytokine Release Syndrome, Neurologic Toxicity, and Financial Burden

“With more experience and collaboration, hopefully the toxicities and the costs will come down, increasing the availability of CAR T cells to patients in need”

Santomasso et al. 2019, American Society of Clinical Oncology Educational Book

“No impact of tocilizumab or corticosteroids on the expansion rate was observed. This work ... may be clinically impactful as future studies examine prophylactic interventions in patients at risk of higher grade cytokine release syndrome”

Stein et al. 2019, Pharmacometrics & Systems Pharmacology
Multiple Myeloma

**BCMA-CAR-T-Cells – bb2121**


36 patients with refractory/relapsed MM, ~7 line of therapies, 97% post-ASCT
33 received bb2121 (Follow-up 11 months)

Lymphodepletion Fludarabin-Cyclophosphamid
Phase II-cell dose: 150 - 450 x 10^6 CAR-T-Zellen

Overall response rate 85 %
Complete Remission 45 %
MRD-negative at CR/PR 100 %
Remission duration ≥ 12 months 42 %

Adverse events

<table>
<thead>
<tr>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS'</td>
<td>76 %</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>42 %</td>
</tr>
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</table>

scFv (anti-BCMA)

Hinge/Transmembrane

Signal 2: CD28
or CD137 (4-1BB)

Signal 1: CD3ζ

scFv, single-chain variable fragment.

Courtesy of U. Dührsen
Multiple Myeloma

BCMA-CAR-T-Cells – bb2121

Multiple Myeloma

**BCMA-CAR-T-Cells – bb2121**


Time to Recovery of Grade 3/4 Cytopenia

- **Neutropenia** (n=32/33), Median time to recovery: 1.3 wk (95% CI, 1.0–1.4); n=31 recovered by wk 4
- **Thrombocytopenia** (n=17/33), Median time to recovery: 2.0 wk (95% CI, 1.4–8.4); n=11 recovered by wk 4
**Immunotherapy with CAR-T is a new therapeutic venue in MM**

CAR-T cell therapy against multiple myeloma shows promising results in the eradication of the disease

<table>
<thead>
<tr>
<th>Product name</th>
<th>CART-BCMA</th>
<th>bb2121</th>
<th>LCAR-B3SM/Janssen</th>
<th>FCARB143</th>
<th>FCARB125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution</td>
<td>Upenn/Novartis</td>
<td>BlueBird/Celgene</td>
<td>Nanjing Legend Biotech</td>
<td>Juno/Fred Hutch</td>
<td>Juno/MSKCC</td>
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<tr>
<td>scFv derived from</td>
<td>Human library</td>
<td>Murine hybridoma</td>
<td>Murine hybridoma</td>
<td>Human library</td>
<td>Human library</td>
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<tr>
<td>Co-stimulatory domains</td>
<td>4-1BB</td>
<td>4-1BB</td>
<td>4-1BB</td>
<td>4-1BB</td>
<td>4-1BB</td>
</tr>
<tr>
<td>Elimination gene</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Gene transfer</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
<td>Retrovirus</td>
</tr>
<tr>
<td>Conditioning</td>
<td>None (cohort 1) &gt; Cy</td>
<td>Cy/Flu</td>
<td>Cy</td>
<td>---</td>
<td>Cy&gt;Cy/Flu</td>
</tr>
<tr>
<td>BCMA Ag required</td>
<td>No requirement</td>
<td>&gt;50%</td>
<td>„Clear expression“</td>
<td>---</td>
<td>&gt;1%</td>
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<tr>
<td>clinicaltrials.gov identification</td>
<td>NCT02546167</td>
<td>NCT02658929</td>
<td>NCT03090659</td>
<td>NCT03338972</td>
<td>NCT03070327</td>
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<tr>
<td>Median prior lines</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Efficacy</td>
<td>CR: 1 VGPR: 1 PR: 4 10 evaluable pts (cohort 3)</td>
<td>CR: 50% VGPR: 36% PR: 9% 11 pts MRD-22 pts</td>
<td>CR: 74% VGPR: 4% PR: 11% 39 pts MRD-57 pts</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
</tr>
</tbody>
</table>

However, there are still problems to face:

- Relapse has been observed as a common phenomenon after CAR immunotherapy treatment
- Cytokine release syndrome and suppression of hematopoiesis are well known toxicities

Data ASH 2018/19
Reasons for Disease Relapses

- Antigen loss
- Reduction of antigen expression
- Selection of cells being negative for target
- CAR-T exhaustion
- CAR-T loss
- PD1-L overexpression
- Other inhibitory signals
- Endogenous tumor cell factors (e.g. p53 loss)
- Inhibitory tumor milieu
- ....
Concept of Adapter CARs

Fig. 1 The schematic structure of a universal CAR system. The universal CAR (UniCAR) system splits the conventional CAR into two modules. The two modules are (1) the signaling module, which harbors a binding moiety to a specific epitope combined with the intracellular signaling domains via hinge and the transmembrane regions (TM) and (2) a switching module, which is a bispecific fusion molecule with one binding domain directed against a tumor-associated antigen (TAA) and an epitope specifically recognized by the signaling module.
TM-mediated cross-linkage of UniCAR-T

Homogenous distribution of UniCARs on engineered T cell in sleeping mode

Polarization of UniCARs upon TM-mediated cross-linkage to cancer cell
Fluorescein isothiocyanate (FITC)
Nuclear protein (5B9)=Our UniCAR adaptor
Transcription factor GCN4 (PNE)
<table>
<thead>
<tr>
<th>Company</th>
<th>Technology</th>
<th>Developmental stage</th>
<th>Platform limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMoAB</td>
<td>Chimeric receptor with CD3z, CD28 and anti-La scFv</td>
<td>Start of phase 1 Q1/2020</td>
<td>No obvious limitations</td>
</tr>
<tr>
<td></td>
<td>Switch: tagged humanized scFv or peptide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unum</td>
<td>Chimeric receptor with CD3z, 41BB and CD16 ECD</td>
<td>Phase I in NHL (rituximab), MM (SEA-BCMA), Her2+ solid tumors (trastuzumab)</td>
<td>Slow off switch due to long half-life of mAb, CD16 is cross-reactive with endogenous Abs</td>
</tr>
<tr>
<td></td>
<td>Switch: humanized/chimeric full-length mAb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miltenyi</td>
<td>Chimeric receptor with CD3z, 41BB and anti-biotin scFv</td>
<td>Pre-clinical</td>
<td>Slow off switch due to long half-life of mAb, cross-reactive, biotin is hapten and 10% of naïve humans have anti-biotin Abs</td>
</tr>
<tr>
<td></td>
<td>Switch: biotinylated full-length mAb</td>
<td></td>
<td></td>
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<tr>
<td>Endocyte/</td>
<td>Chimeric receptor with CD3z, CD28 and anti-FITC scFv</td>
<td>Pre-clinical, IND submission announced</td>
<td>FITC is a hapten (high immunogenicity risk)</td>
</tr>
<tr>
<td>Novartis</td>
<td>Switch: FITC-labeled folate</td>
<td></td>
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<tr>
<td>Calibr</td>
<td>Chimeric receptor with CD3z, 41BB and anti-GCN4 scFv</td>
<td>Pre-clinical, IND submission announced</td>
<td>GCN4 is yeast protein (high immunogenicity risk)</td>
</tr>
<tr>
<td></td>
<td>Switch: tagged humanized Fab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bellicum</td>
<td>Chimeric receptor with CD3z and anti-tumor scFv</td>
<td>Phase I in PSCA+ solid tumors</td>
<td>Only costimulatory signal can be turned off</td>
</tr>
<tr>
<td></td>
<td>Inducible 41BB costimulatory signal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xyphos</td>
<td>Chimeric receptor with CD3z, 41BB and mut. NKG2D</td>
<td>Pre-clinical, start of phase I planned for 2021 (rituximab &amp; trastuzumab)</td>
<td>Slow off switch due to long half-life of mAb, strong binding to effector cell poses safety risk</td>
</tr>
</tbody>
</table>
Recently Published PK Data on Rituximab Show an Increasing Serum Half-life per Treatment Cycle and a Very Long Elimination Half-Life of CD20-Bound Antibody

Repeated dosing significantly extends serum half-life (median ~ 6 weeks)

Pharmacokinetic of Rituximab is dependent on tumor mass: elimination half-life after 1st injection 2 – 100 days
Summary

• Highly efficient anti-tumor response of anti-CD19 CAR-T cells against ALL and NHL (anti-BCMA against myeloma)
• CAR-T cells are one of the first marketed cellular products
• Heterogenous landscape: Cell type, source, process, costimulation, switch mechanism etc.
• Major limitations are: Toxicities, resistance, production time, price, health care providers, and ...
• Next steps: Allogeneic products, switchable CARs, multitargeting, automation of production process
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