T cell Therapies for Cancer

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The George Washington University
Disclosures

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Co-Founder: Mana Therapeutics and Catamaran Bio

Board of Directors: Cabaletta Bio

Stock/ownership: Repertoire Immune Medicines and Neximmune Therapeutics
Blood drawn contains different kinds of killer cells called “T cells”

Some T cells have the potential to recognize and kill cancer

These cancer-killing T cells are enriched or modified in the lab

Cancer-killing cells infused back into patient
Advantages of T-cell therapies

- sequentially kill a multiplicity of target cells
- recruit additional components of the immune system
- migrate through microvascular walls, extravasate and penetrate the core of solid tumors (e.g. EBV lymphomas)
T cell mediated killing of its target cell

CD8+ T cell
- Perforin
- Granzymes

Class I MHC molecule

Cancer cell (target cell)

Released CD8+ T cell

Pore

Dying Cancer cell
Antigen Targets and T cell effectors

**CAR-T cells**
- CAR Construct
  - Costim - TCR - Fv
- Single surface antigen target
  - Gene modified cells

**TCR transduced T cells**
- TCR construct
  - Single peptide target
  - HLA restriction
- Gene modified

**Donor Lymphocyte Infusions (TILs)**
- Unselected alloreacting or anergic T cells

**Multiantigen-specific T cells**
- Multiple peptides
  - No HLA restriction

**Ex-vivo expansion**

**TCR transduced T cells**
- Single peptide target
  - HLA restriction
  - Gene modified

**Other ?**
- CD19
- CD22

**Tumor-associated antigens**
- Survivin, PRAME, MAGE, NY-ESO1, WT1

**EBV antigens:**
- LMP1/LMP2

**Surface Present Ag**
- MHC

**Alloantigens TAAs/self Ags**
1. DLI and TILs
DLI FOR POST SCT RELAPSE MOST EFFECTIVE WITH CHEMOTHERAPY

Prolonged survival after DLI / 2nd SCT

2815 RIC allo SCT (1999-2008)
263 relapse CR after relapse 32%

DLI or SCT (7.6%) +/- Chemo


Best results for DLI after CR induction

LFS after complete remission

P<0.0001

RI + Consol+ DLI

RI+ DLI

Yan et al. Journal of Hematology & Oncology (2016) 9:87
Establish and Screen TIL cultures for Tumor Reactivity

Expansion of Tumor Reactive Specific TIL

Liver Tumor Resection

Adoptive Transfer of Tumor Reactive Specific TIL

Adoptive Immunotherapy for Metastatic Melanoma
Rapid Tumor Response after TIL Transfer Therapy: Cutaneous Melanoma
Adoptive TIL Transfer Therapy for Metastatic Cutaneous Melanoma: Surgery Branch/NIH

<table>
<thead>
<tr>
<th>$n$</th>
<th>PR (%)</th>
<th>CR (%)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>194</td>
<td>62 (32%)</td>
<td>44 (23%)</td>
<td>106 (55%)</td>
</tr>
</tbody>
</table>

- *J Clin Oncol.* 2005 Apr 1;23(10):2346-57
- *J Clin Oncol.* 2016 Jul 10;34(20):2389-97
Survival of Metastatic Melanoma Patients After TIL Therapy
Adoptive TIL Transfer for Additional Metastatic Solid Tumors

**Cervical Cancer**
3/9 responses (1 CR) - NCI

**Cholangiocarcinoma**
Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer.

**Colorectal Cancer**
T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer.
Evidence of efficacy
- Documented PR and CR rates with long durations
- Patients with prior immunotherapy
- Patients with brain metastases
- Patients with advanced, high bulk disease

One treatment
- No ancillary therapies needed after TIL and IL-2

TIL can now be successfully prepared from > 90% of melanoma patients (NCI, Moffitt)

Response rates reproduced at multiple sites and in multiple countries

Opportunity for combination with checkpoint inhibitors
TIL CHALLENGES

- Requires GMP manufacturing facility
- Special skills required for manufacture
- Production is expensive (labor, cytokines, plasticware)
- Length of time from tumor resection to treatment
  - Some patients may progress in the interim
- Preconditioning with cy/flu required → TOXICITY
- High dose IL-2 used
  - Inpatient treatment to monitor toxicities
  - Centers need to be comfortable administering high dose IL-2
  - IL-2 is expensive

Optimizing Antigen-specific T cells

2. Targeting EBV+ Lymphomas
Types of EBV Latency

**Type 3**
- Post transplant lymphoproliferative Disease
- Lymphoblastoid cell lines

**Type 2**
- NHL and HL
- Nasopharyngeal carcinoma

**Type 1**
- Burkitt’s lymphoma

**EBNA-1**
**LMP 1**
**LMP 2**

**EBNA-3a**
**EBNA-3b**
**EBNA-3c**

**LP**
EBV-specific T cells for PTLD

- Use of EBV-CTL post HSCT is highly successful
  
  *(Rooney and Heslop, Blood 2010 / Doubrovina and O’Reilly, Blood 2012)*

  155 patients

  6.5% GVHD

  ≈91% success (durable)

  14 failures - 1 death from PTLD

  1.2% CRS

  *(Heslop and Bollard, Blood 2016)*
Rationale of Immunotherapy for Lymphoma....Beyond PTLD

• Significant failure rate of therapy for advanced stage or recurrent disease
• Long-term side effects of chemotherapy and radiation
• EBV antigens expressed by 20-40% of lymphomas are potential targets for T cell immunotherapy
Types of EBV Latency

**Type 3**
- Post transplant lymphoproliferative Disease
- Lymphoblastoid cell lines

**Type 2**
- NHL and HL
- NPC

**Type 1**
- Burkitt’s lymphoma
Making LMP1 and LMP2 Immunodominant Antigens

Bollard et al, JIT 2004

 Straathof et al J Immunol 2005

adherent PBMC

rAd5f35dLMP1-I-LMP2
or Ad5f35LMP2

EBV-infected B cells

PBMC moDC

IL15 IL2 IL2

LMP-specific CTL

GMCSF IL4
IL1b IL6
TNFα PGE2
Clinical Responses Post LMP T cells in Patients with Active Disease and Adjuvant Rx

12/21 CR - 50% Disease Free Survival at 2 Years

27/28 CR as Adjuvant Therapy 90% DFS at 2 years

Bollard et al, JCO 2014
Conclusions – LMP1/2 T Cells

• No toxicity
• Accumulation of LMP-T at disease sites
• Anti-tumor effects seen (13/21 patients PR/CR) (*Bollard et al, JCO 2014*)

Next....

→ LMP T cells post allo BMT (*McLaughlin et al, Blood 2018*)

→ TGFβ resistant LMP-T (*Bollard et al, JCO 2018*)
Antigen specific T cells

3: Making T cells “Off the Shelf”
Making T cell Therapies “Off the Shelf”

Utilizing a third party EBV/LMP T cell bank can bypass the need for an available donor, and eliminates the wait for T cell production.
# Third-Party EBV-directed T cells Support Safety

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>n</th>
<th>SAEs</th>
<th>Clinical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haque, 2007</td>
<td>EBV post SOT / BMT</td>
<td>33</td>
<td>None</td>
<td>14 patients achieved CR, 3 PR (52%)</td>
</tr>
<tr>
<td>Barker, 2010;</td>
<td>EBV</td>
<td>5</td>
<td>None</td>
<td>4 patients achieved CR (3-5 VST doses)</td>
</tr>
<tr>
<td>Doubrovinova, 2012</td>
<td>EBV</td>
<td>1</td>
<td>None</td>
<td>CR (2 VST doses)</td>
</tr>
<tr>
<td>Uhlin, 2010</td>
<td>EBV</td>
<td>1</td>
<td>None</td>
<td>CR (2 VST doses)</td>
</tr>
<tr>
<td>Leen, 2013</td>
<td>CMV, EBV, Adv</td>
<td>50</td>
<td>8 cases GvHD after VST (2 de novo)</td>
<td>74% CR/PR (69% for EBV n=9)</td>
</tr>
<tr>
<td>Tzannou, 2017</td>
<td>EBV, BKV, CMV, Ad, HHV6</td>
<td>38</td>
<td>2 cases denovo GVHD (grade I)</td>
<td>92% CR/PR (100% for EBV n=2).</td>
</tr>
<tr>
<td>Prockop, JCI, 2020</td>
<td>EBV post SOT/BMT</td>
<td>46</td>
<td>None</td>
<td>65% CR/PR (BMT) 54% CR/PR (SOT)</td>
</tr>
</tbody>
</table>
CNS Disease Successfully Treated with 3rd party EBV-directed T cells

87% CR/PR after SOT or BMT (MSKCC, BCM, CNMC)

Prockop et al, JCI 2020
Bollard et al, ASHI 2017 Keller et al, ESID 2017

Pakakasama S et al, Transplantation. 2004
Third party VSTs provide rescue therapy

Pre-VST therapy (following steroids, XRT rituxan)

2 months post VST dose 2

1 month post VST dose 1

Mike Keller, unpublished
4. Antigen specific T cells - Targeting tumor associated antigens (TAA)
# Targeting TAAs in Heme Malignancies– The Shortlist

<table>
<thead>
<tr>
<th>Protein</th>
<th>AML</th>
<th>CML</th>
<th>ALL</th>
<th>CLL</th>
<th>HL</th>
<th>NHL</th>
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<tbody>
<tr>
<td>WT1</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Proteinase 3</td>
<td>+</td>
<td>+</td>
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<tr>
<td>PRAME</td>
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<td>RHAMM</td>
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<td>MPP11</td>
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<tr>
<td>HAGE</td>
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<tr>
<td>BCR/ABL</td>
<td>+</td>
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<td>NY ESO 1</td>
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<td>BMI-1</td>
<td>+</td>
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<tr>
<td>Telomerase</td>
<td>+</td>
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<tr>
<td>Fibromodulin</td>
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<td>Syntaxin</td>
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<td>SSX</td>
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<td>+</td>
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<tr>
<td>Survivin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Goswami et al, Leukemia 2014
Rooney et al, Imm Rev 2014
Use of Donor-derived WT-1 specific T cells for Acute Leukemia

- 11 patients infused with HLA-A*0201-restricted WT1-specific donor-derived CD8+ T cell clones.
- No attributed toxicities/GVHD.
- 2 clinical responses
- 3 patients at high risk for relapse remain in CR.
- CTLs generated in the presence of IL-21 remained detectable long-term

Studies using WT1 specific T cells generated using overlapping peptides ongoing at MSKCC

(Koehne and O’Reilly)

Chapuis and Greenberg Sci Trans Med 2013
Clinical Use of Multi TAA T cells for Cancer

TAA-T for AML after Allogeneic SCT – Phase I study

TAA: WT1 NyESO PRAME Survivin  
Dose escalation $5 \times 10^6 \rightarrow 1 \times 10^7 \rightarrow 2 \times 10^7 /m^2$

27 enrolled

20 treated

13 HIGH RISK for relapse ADJUVANT
3  CR2/3
3  FLT3-ITD
3  MDS tAML
2  MLL-r
1  Ph+
1  DNMT3a

8  CCR
4  Relapsed

7 RELAPSE /ACTIVE DISEASE POST SCT >d30
5  30-70% blasts in BM
2  extramedullary relapse

1  CR
1  PR
4  NR
1  NE

Lulla et al, TCT meeting 2019 and Blood 2020
Use of TAA-T cells in Myeloma

Lulla et al, STM 2020
Prolonged Disease Stabilization in Patients with Solid Tumors post TAA-T

No SAEs attributable to Rx
No CRS

Hont et al
JCO 2019
Summary- Use of TAA-T as Treatment for Relapsed Cancers

• TAA-T cells can be generated from healthy donors for clinical use (> 90% success rate)
• TAA-T cells are safe for patients with relapsed hematopoietic malignancies (lymphoma, AML, myeloma) after chemotherapy/autologous BMT and post allo HSCT
• Early evidence of efficacy?
5. abTCR transduced T cells
HIGH AFFINITY WT1 TCR TRANSDUCED T CELLS
TO PREVENT POST SCT RELAPSE

12 AML  HLA A2  (10 proven WT1 +)  RISK: 6 adverse, 4 intermediate, 2 favorable
At transplant 8 CR 4 detectable disease
Days between SCT and T cell infusion 47-175 median 100d
1-4 infusions of WT1 high affinity TCR transfected into donor EBV specific CD8+ T cells

Study group
12 AML
100% RFA at 44 mo

Comparative untreated group
88 AML
54% RFS

P = 0.002

Long-term persistence of functional WT1 TCR T cells

Published clinical TCR-T therapy for solid tumors and Myeloma.

<table>
<thead>
<tr>
<th>Target</th>
<th>Disease</th>
<th>Vector</th>
<th>Pretreatment</th>
<th>#patients</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>MART-1</td>
<td>Melanoma</td>
<td>Retrovirus</td>
<td>Chemotherapy</td>
<td>20</td>
<td>30% objective antitumor response</td>
</tr>
<tr>
<td>Gp100</td>
<td>Melanoma</td>
<td>Retrovirus</td>
<td>Chemotherapy</td>
<td>16</td>
<td>19% objective antitumor response</td>
</tr>
<tr>
<td>CEA</td>
<td>Colorectal</td>
<td>Retrovirus</td>
<td>Chemotherapy</td>
<td>3</td>
<td>1 objective response</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>Melanoma/sarcoma</td>
<td>Retrovirus</td>
<td>Chemotherapy</td>
<td>17</td>
<td>2 CR; 1 PR</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>MM</td>
<td>Lentivirus</td>
<td>Chemotherapy</td>
<td>20</td>
<td>80% maintained remissions post ASCT</td>
</tr>
<tr>
<td>MAGE A3</td>
<td>Melanoma</td>
<td>Retrovirus</td>
<td>Chemo/RT/Surgery</td>
<td>9</td>
<td>4 PR (4-12+mths), 1 CR (15+mths)</td>
</tr>
<tr>
<td>MAGE A3</td>
<td>Sarcoma</td>
<td>Retrovirus</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>MAGE A3</td>
<td>Esophageal</td>
<td>Retrovirus</td>
<td>Surgery; radiotherapy; chemotherapy</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>MAGE A3</td>
<td>Melanoma/MM</td>
<td>Lentivirus</td>
<td>CY</td>
<td>2</td>
<td>2 died of cardiac toxicities (titin)</td>
</tr>
<tr>
<td>MAGE A4</td>
<td>Esophageal</td>
<td>Retrovirus</td>
<td>Surgery; radiotherapy; chemotherapy</td>
<td>10</td>
<td>7/10 tumor progression</td>
</tr>
</tbody>
</table>

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma


1Siteman Cancer Center and Departments of Medicine and Pathology and Immunology, Washington University School of Medicine, St. Louis, MO; 2Abramson Cancer Center, Department of Medicine, and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; 3The Greenebaum Cancer Center, University of Maryland, Baltimore, MD; 4Adaptimmune Ltd, Philadelphia and Abingdon, United Kingdom; and 5Immunocore Ltd, Abingdon, United Kingdom
Chimeric Antigen Receptor (CAR) T cells

4: CD19 CAR T cells
Designing a Chimeric Antigen Receptor antibody

scFv hinge co-stim \(\zeta\) 

SIGNAL 2 co-stimulatory molecule 

TCR zeta chain SIGNAL 1
Redirecting the Specificity of T Cells

• Different transduction systems to get CARs into T cells:
  → Retroviral transduction
  → Lentiviral transduction
  versus
  → non viral transduction (Sleeping Beauty)

Courtesy of David Porter- U Penn
Original CD19 CARs

**MSKCC**
- **CD28z CAR**

**Juno**
- **MSKCC**

**Axicabtagene Ciloleucel**
- **Kite/Gilead (NCI)**

**Bluebird Bio**
- **Baylor**

**SJRH-4**
- **4-1BB CAR**

**Lisocabtagene Maraleucel**
- **Juno (FHCRC)**

**Novartis**
- Tisagenlecleucel
- **CHOP + UPenn**

*Courtesy of M Sadelain MSKCC*
### Three Major anti-CD19 CAR T-cell Products for Aggressive B-cell NHL

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene Ciloleucel (KITE)</th>
<th>Tisagenlecleucel (Novartis)</th>
<th>Lisocabtagene Maraleucel (Juno)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Construct</strong></td>
<td>antiCD19-<strong>CD28</strong>-CD3z</td>
<td>antiCD19-<strong>41BB</strong>-CD3z</td>
<td>antiCD19-<strong>41BB</strong>-CD3z</td>
</tr>
<tr>
<td><strong>Vector</strong></td>
<td>Retrovirus</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td><strong>T-cell manufacturing</strong></td>
<td>Bulk</td>
<td>Bulk</td>
<td>Defined doses CD4, CD8</td>
</tr>
</tbody>
</table>
| **Dose**            | $2 \times 10^6$/kg (max $2 \times 10^8$) | $0.6$ to $6.0 \times 10^8$   | DL1: $0.5 \times 10^7$  
DL2: $1.0 \times 10^8$  
DL3: $1.5 \times 10^8$   |
| **Bridging therapy** | None allowed in pivotal trial but often used in standard practice | 93%                          | 72%                            |
| **Lymphodepletion**  | Flu/Cy 500/30 x 3d              | Flu/Cy 250/25 x 3d, or Benda | Flu/Cy 300/30 x 3d              |
| **Approval status**  | FDA/EMA approved for DLBCL, high grade B-cell lymphoma, transformed FL, PMBCL | FDA/EMA approved for pediatric B-ALL, DLBCL, high grade B-cell lymphoma, transformed FL | Not yet FDA/EMA approved |
## Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Phase 1 and 2 (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>58 (23–76)</td>
</tr>
<tr>
<td>Age ≥ 65 years, n (%)</td>
<td>27 (25)</td>
</tr>
<tr>
<td>Disease stage III/IV, n (%)</td>
<td>90 (83)</td>
</tr>
<tr>
<td>IPI risk score 3 or 4, n (%)</td>
<td>48 (44)</td>
</tr>
<tr>
<td>≥ 3 prior therapies, n (%)</td>
<td>76 (70)</td>
</tr>
<tr>
<td>Refractory to 2nd- or later-line therapy, n (%)</td>
<td>80 (74)</td>
</tr>
<tr>
<td>Best response as PD to last prior therapy, n (%)</td>
<td>70 (65)</td>
</tr>
<tr>
<td>Relapse post ASCT, n (%)</td>
<td>25 (23)</td>
</tr>
</tbody>
</table>

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**ORR**: (n=101): 83% [74% by IRC]  
**CR**: 58% [54% by IRC]

**JULIET: PFS and OS of patients with R/R DLBCL receiving tisagenlecleucel (CD19-CAR.41BB)**

**Characteristics** | **Patients (N = 111)**
---|---
Median age (range), years | 56 (22–76)
Double-/triple-hit lymphoma, % | 27
Number of prior lines of therapy, % | 
  2 | 44
  3 | 31
  4–6 | 21
Refractory to last therapy, % | 55
Prior ASCT, % | 49


**ORR: 52%**

**CRR: 40%**
TRANSCEND-NHL-001 trial: liso-cel in multiply R/R aggressive B-NHL (CD19.CAR.41BB - CD4/CD8)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>63 (18–86)</td>
</tr>
<tr>
<td>Double- / triple-hit lymphoma, n (%)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>CNS involvement, n (%)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Median prior lines, n (range)</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Chemo-refractory, n (range)</td>
<td>181 (67)</td>
</tr>
<tr>
<td>Prior HSCT, n (%)</td>
<td>94 (35)</td>
</tr>
</tbody>
</table>

**Best response**

<table>
<thead>
<tr>
<th>Best response</th>
<th>Patients (N = 256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best ORR, %</td>
<td>73</td>
</tr>
<tr>
<td>Best CR, %</td>
<td>53</td>
</tr>
<tr>
<td>12-month duration of response, %</td>
<td>55</td>
</tr>
</tbody>
</table>


ORR: 73%
CRR: 53%

PFS median follow-up (95% CI), months: 12.3 (12.0–17.5)

2 yr PFS approx 45% (70% if in CR)

OS median follow-up (95% CI), months: 17.6 (13.5–18.0)
Notable CAR-T Toxicities

• Cytokine Release Syndrome (CRS)
• Neurological toxicity
  – CAR T-cell associated Encephalopathy Syndrome (CRES)
  – Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)
• Prolonged cytopenias
• B-cell aplasia
• Hypogammaglobulinaemia
• Toxicities are usually manageable and reversible
Toxicity of 3 Major CAR T-cell Products for relapsed/refractory DLBCL

<table>
<thead>
<tr>
<th>Construct</th>
<th>Axicabtagene Ciloleucel</th>
<th>Tisagenlecleucel</th>
<th>Lisocabtagene Maraleucel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>101</td>
<td>111</td>
<td>269</td>
</tr>
<tr>
<td>Any CRS Median time to onset</td>
<td>93% 2 days</td>
<td>58% 3 days</td>
<td>42% 5 days</td>
</tr>
<tr>
<td>≥ Gr 3 CRS†</td>
<td>11%</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>Any neurotoxicity</td>
<td>64%</td>
<td>21%</td>
<td>30%</td>
</tr>
<tr>
<td>≥ Gr 3 neurotoxicity</td>
<td>32%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>43%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Steroid use</td>
<td>27%</td>
<td>11%</td>
<td>21%</td>
</tr>
</tbody>
</table>

* Caveats in cross trial comparisons: Different eligibility criteria, phase of study, dose levels
†CRS toxicity grading scales differ across studies. Axi-Cel and Liso-cel used Lee criteria. Tisa-cel used Penn criteria
ZUMA-2: Brexucabtagene autoleucel (KTE-X19) in relapsed/refractory mantle cell lymphoma

- **KTE-X19 approved by FDA.** ASCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; CR, complete remission; CRS, cytokine release syndrome; NE, not estimatable; NR, not reached; NT, neurological toxicity; mORR, overall response rate; PD, progressive disease; PR, partial response; PFS, progression-free survival; SD, stable disease.

Current Challenges and Opportunities

- Understand and overcome mechanisms of resistance
- Understand sequencing and combining of novel agents pre CAR, at bridging, and post CAR
- Move CAR T-cells earlier in the course of disease
- Expand indications
- Further understand mechanisms of toxicities and develop prophylactic strategies
- Develop new CAR T-cell constructs including off the shelf products
BCMA-CAR T cells for Myeloma

B-cell maturation antigen (BCMA)-directed CAR T cells have shown promising efficacy and safety profiles in various phase I/II clinical trials.

CR rates range from <10- 30%

However, almost all treated patients continue to relapse

A BCMA-directed product for the treatment of multiple myeloma may be approved in 2021
## Published Clinical Results: CAR-T Cells in AML

<table>
<thead>
<tr>
<th>CAR Target</th>
<th>Cytotoxicity</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD123</td>
<td>Long term hematopoiesis</td>
<td>Potent in vitro activity In vivo studies No clinical trials results</td>
</tr>
<tr>
<td></td>
<td>High rates of CRS</td>
<td></td>
</tr>
<tr>
<td>CD33</td>
<td>Lung and GI Hematopoietic toxicity</td>
<td>“potent but transient”</td>
</tr>
<tr>
<td>Lewis-Y Antigen</td>
<td>GI Toxicity</td>
<td>Transient – all pts relapsed</td>
</tr>
<tr>
<td></td>
<td>High rates of CRS</td>
<td></td>
</tr>
<tr>
<td>NKG2D</td>
<td>No toxicity</td>
<td>No response</td>
</tr>
</tbody>
</table>

**Other Targets Under Investigation:**
CD33, CD38, CD56, CD117, CD123, CD34 or Muc1 *
Current clinical target of CAR-T therapy in solid tumor

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumor</th>
<th>Target</th>
<th>CAR Design</th>
<th>Phase</th>
<th>Best Response Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al¹⁶</td>
<td>Glioblastoma</td>
<td>IL-13Ra2</td>
<td>CD3ζ</td>
<td>I</td>
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</tr>
<tr>
<td>Louis et al²⁷</td>
<td>Neuroblastoma</td>
<td>GD2</td>
<td>CD3ζ</td>
<td>I</td>
<td>CR, 27%; 19 patients*</td>
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<tr>
<td>Park et al²⁸</td>
<td>Neuroblastoma</td>
<td>CD171</td>
<td>CD3ζ</td>
<td>I</td>
<td>PD</td>
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<tr>
<td>Feng et al²⁹</td>
<td>Non–small cell lung cancer</td>
<td>EGFR</td>
<td>4-1BB/CD3ζ</td>
<td>I</td>
<td>PR, 18%; SD, 45%; 11 patients</td>
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<tr>
<td>Beatty et al¹⁷</td>
<td>Mesothelioma/pancreatic cancer</td>
<td>Mesothelin</td>
<td>4-1BB/CD3ζ</td>
<td>I</td>
<td>PR, 50%; 2 patients</td>
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<tr>
<td>Junghans et al³⁰</td>
<td>Prostate cancer</td>
<td>PSA</td>
<td>CD3ζ</td>
<td>I</td>
<td>PR, 40%; 5 patients</td>
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<tr>
<td>Lamers et al³¹</td>
<td>Renal cell carcinoma</td>
<td>CAIX</td>
<td>FcRγ</td>
<td>I</td>
<td>PD</td>
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<tr>
<td>Kershaw et al³²</td>
<td>Ovarian cancer</td>
<td>Folate receptor α</td>
<td>FcRγ</td>
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<td>PD</td>
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<tr>
<td>Ahmed et al³³</td>
<td>Sarcoma</td>
<td>HER2</td>
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<td>SD, 24%; 17 patients</td>
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<td>Colorectal cancer</td>
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<tr>
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<tr>
<td></td>
<td>Mesothelioma</td>
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<td>NCT02107963</td>
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<td>OX40/CD28/CD3ζ</td>
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</tr>
</tbody>
</table>

*Patients underwent craniotomy before CAR therapy.
**Patients with NED before CAR therapy were not included in denominator of responders.

Abbreviations: CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CR, complete response; EGFRIII, EGFR variant III; FcR, fragment crystallizable receptor; GD2, disialoganglioside GD2; IL-13Ra2, interleukin-13 receptor α2; MUC-16, mucin 16; N/A, not applicable; NED, no evidence of disease; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SD, stable disease.
CAR Therapy in the USA 2014 to present:

Summary

Large trials with long follow up confirm ability of CD19-directed CAR T cells to induce CRs

Partnerships with industry and licensure now broaden applicability

But still no major “home run” beyond CD19-CAR
Overall Summary

• CD19 CAR-T cells highly effective in R/R - B cell NHL and Acute lymphoblastic leukemia
• CD19-negative escape is a mechanism of relapse
• Other CAR targets are available (with advantages and disadvantages) - still in early stages of development
• Combinatorial targeting could reduce antigen-negative escape and improvement of T cell based therapies overall?

→ improve outcome with a combination approach (SCT, checkpoint blockade, vaccines, multi tumor antigen specific T cells, oncolytic viruses, nanoparticles, etc etc etc)?
Cell Therapy for Cancer – The Vision

Potential for Combination Therapies

Chemotherapy
Small molecules
Checkpoint inhibitors
Antibodies
Surgery

DC Vaccines
Ag-T Cells
CAR-Ts
NK Cells
TCR-T cells

Disease Burden

Minimal Residual Disease

Cure

Sources: Autologous/Allogeneic
Acknowledgements

Cameron Turtle
David Maloney
Jim Kochenderfer
Carlos Ramos
Helen Heslop
Clio Rooney
George Carrum

David Porter
Stephen Schuster
Craig Sauter
Renier Brentjens
Susan Prockop

Michael T. Lotze
Jeremy Abramson

Amy Hont, Holly Meany
Patrick Hanley, Keri Toner, Mike Keller