Chimeric Antigen Receptor - CAR T cell therapy

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T cells are immune system cells that normally fight infection

- Each T cell recognizes a specific target
- T cells multiply and activate for a fight when they encounter their target
- Cancers are able to evade patients’ T cells
What are CAR T cells?

- Autologous Cellular Immunotherapy
- T cells removed and engineered to express a chimeric antigen receptor (CAR)
- Reprogrammed T cells recognize cancer cell targets
- CD19 targeted CARs are furthest in development
Single centers focused early CD19 CAR T cell development for the treatment of Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Center</th>
<th>n</th>
<th>Co-stim domain</th>
<th>Vector</th>
<th>Conditioning Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI ¹</td>
<td>21 peds</td>
<td>CD28</td>
<td>retro-virus</td>
<td>Flu/CY</td>
</tr>
<tr>
<td>UPENN ²</td>
<td>25 peds</td>
<td>4-1BB</td>
<td>lenti-virus</td>
<td>various</td>
</tr>
<tr>
<td></td>
<td>5 adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSKCC ³</td>
<td>16 adults</td>
<td>CD28</td>
<td>retro-virus</td>
<td>CY</td>
</tr>
<tr>
<td>FHCRC ⁴</td>
<td>30 adults</td>
<td>4-1BB</td>
<td>lenti-virus</td>
<td>Flu/CY vs CY</td>
</tr>
</tbody>
</table>

CAR T cell engineering schema and manufacturing process
CD19 CAR T cell therapy causes two major categories of toxicities

- **Cytokine Release Syndrome**
  - Associated with adoptive cell therapies that activate lymphocytes.
  - Results from the release of cytokines from targeted cells and activated immune effector cells recruited to the tumor area.

- **Neurologic events**
  - Wide ranging from tremor to transient aphasia and seizures. There have been cases of death due to cerebral edema. However, these are generally reversible.
  - Etiology is unknown, however CAR T cells and elevated cytokines can be found in the CSF.
## Cytokine Release Syndrome (CRS)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, hypoxemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Elevated D-dimer, hypofibrinogenemia ± bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, hyperbilirubinemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dyemetria, altered gait, seizures</td>
</tr>
</tbody>
</table>
Cytokine Release Syndrome grading and treatment recommendations

**GRADING ASSESSMENT**

**Grade 1 CRS**
- Fever, constitutional symptoms

**Grade 2 CRS**
- Hypotension: responds to fluids or one low dose pressor
- Hypoxia: responds to <40% O2
- Organ toxicity: grade 2

**Grade 3 CRS**
- Hypotension: requires multiple pressors or high dose pressors
- Hypoxia: requires ≥ 40% O2
- Organ toxicity: grade 3, grade 4 transaminitis

**Grade 4 CRS**
- Mechanical ventilation
- Organ toxicity: grade 4, excluding transaminitis

**TREATMENT**

- Vigilant supportive care
  - Assess for infection
  (Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)

- Extensive co-morbidities or older age?
  - Yes
    - Vigilant supportive care
      (Monitor cardiac and other organ function closely)
      - Tocilizumab
      ± corticosteroids

  - No
    - Vigilant supportive care
Estimated timeline of toxicities after CD19 CAR T cell therapy
<table>
<thead>
<tr>
<th>Company</th>
<th>Indication</th>
<th>Population</th>
<th>Expected FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kite</td>
<td>r/r DLBCL</td>
<td>Adults</td>
<td>2Q17</td>
</tr>
<tr>
<td>Kite</td>
<td>r/r ALL</td>
<td>Adults</td>
<td>1Q18</td>
</tr>
<tr>
<td>Kite</td>
<td>r/r MCL</td>
<td>Adults</td>
<td>2Q18</td>
</tr>
<tr>
<td>Novartis</td>
<td>r/r ALL</td>
<td>Pediatrics/AYA</td>
<td>3Q17</td>
</tr>
</tbody>
</table>

CD19 CARs are likely to land FDA approval in 2017-18
Collaborative Immune Cell Therapy (ICE-T) Team

- Conducts daily inpatient and outpatient rounds and is the service of record during hospitalization
  - One Moffitt faculty physician at all times (7 days a week)
  - Advanced practice professional(s) responsible for orders, presenting on rounds and provide first response
  - First call medical coverage at night by a nocturnist
  - Outpatient treatment center and inpatient nursing
  - Nurse transplant coordinators
  - Trial coordinators
  - Cell therapy facility
Axicabtagene Ciloleucel (KTE-C19) is a centrally manufactured CD3/CD28 based CAR T cell therapy

Upon recognition of CD19, KTE-C19 is designed to:

- Target
- Activate
- Proliferate
- Systematically kill target cells throughout the body
There is a substantial unmet need for patients with Diffuse Large B cell Lymphoma (DLBCL).

DLBCL is the most common subtype of NHL.

**Outcomes in chemorefractory DLBCL are poor**
- ORR: 26%, CR: 8%
- Median OS 6.6 months

ZUMA-1: first multicenter trial of CD19 CAR T therapy in aggressive NHL
Phase 1 of ZUMA-1: ongoing CRs in 43% at 12+ months
**Eligibility criteria**

- Aggressive NHL: DLBCL, PMBCL, TFL
- Chemotherapy-refractory disease: no response to last chemotherapy or relapse ≤12 mo ASCT

**Pre-specified interim efficacy analysis**

- Phase 2 cohort 1 (n=50 with ≥3mo follow-up)

**Primary endpoint**

- Phase 2: ORR

**Key secondary endpoints**

- DOR, OS, Safety, Levels of CAR T and Cytokines
Zuma-1 KTE-C19 Treatment Schema

*KTE-C19 treatment consists of conditioning chemotherapy of 500 mg/m² cyclophosphamide and 30 mg/m² fludarabine on Day −5, Day −4, Day −3 followed by a target of \(2 \times 10^6\) CAR T cells/kg (minimum \(1 \times 10^6\) CAR T cells/kg) on Day 0.
22 sites enrolled; 99% manufacturing success rate
91% of enrolled patients dosed

Enrolled & Leukapheresed (n=111)

Conditioning
Cy 500 mg/m^2
Flu 30mg/m^2 × 3 days

KTE-C19
2 × 10^6 /kg (n=101)

No bridging therapy allowed

Not treated:
- n=5 SAE
- n=1 Product unavailable
- n=2 Non-measurable disease

- n=2 SAE

1 month follow-up (n=93 DLBCL, TFL, PMBCL)
≥3 month follow-up (n=51 DLBCL*, n=11 TFL/PMBCL)

*Pre-specified interim analysis; data cutoff: Aug 24, 2016

Neelapu & Locke, et al., ASH 2016, #LBA6
### ZUMA-1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DLBCL (n=73)</th>
<th>TFL/PMBCL (n=20)</th>
<th>All Patients (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>59 (25-76)</td>
<td>58 (28-76)</td>
<td>59 (25-76)</td>
</tr>
<tr>
<td>Age ≥60 years, n (%)</td>
<td>36 (49)</td>
<td>9 (45)</td>
<td>45 (48)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>47 (64)</td>
<td>15 (75)</td>
<td>62 (67)</td>
</tr>
<tr>
<td>ECOG performance status 1, n (%)</td>
<td>48 (66)</td>
<td>8 (40)</td>
<td>56 (60)</td>
</tr>
<tr>
<td>Median number of prior therapies (#)</td>
<td>3 (1-7)</td>
<td>4 (2-12)</td>
<td>3 (1-12)</td>
</tr>
<tr>
<td>IPI 3-4, n (%)</td>
<td>32 (44)</td>
<td>9 (45)</td>
<td>41 (44)</td>
</tr>
<tr>
<td>Disease stage III/IV, n (%)</td>
<td>64 (88)</td>
<td>15 (75)</td>
<td>79 (85)</td>
</tr>
<tr>
<td>Refractory subgroup, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to 2\textsuperscript{nd} or later-line therapy</td>
<td>56 (77)</td>
<td>16 (80)</td>
<td>72 (77)</td>
</tr>
<tr>
<td>Relapse post-ASCT</td>
<td>15 (21)</td>
<td>4 (20)</td>
<td>19 (20)</td>
</tr>
</tbody>
</table>

*2 patients had primary refractory status

Neelapu & Locke, et al., ASH 2016, #LBA6
KTE-C19 Therapy Induces Rapid Response

Patient Response at the 1 Month Follow-up

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>73</td>
<td>68%</td>
<td>33%</td>
</tr>
<tr>
<td>PMBCL/TFL</td>
<td>20</td>
<td>80%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>93</strong></td>
<td><strong>71%</strong></td>
<td><strong>38%</strong></td>
</tr>
</tbody>
</table>

- Follow up ongoing
- Does not include responses after 1 month

Positive ZUMA-1 Pivotal Trial Data in Aggressive Non-Hodgkin Lymphoma (NHL)

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1 Phase 1(^1) (n=7)</th>
<th>ZUMA-1 Phase 2(^2) (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR (%)</td>
<td>ORR (%)</td>
</tr>
<tr>
<td></td>
<td>CR (%)</td>
<td>CR (%)</td>
</tr>
<tr>
<td>ORR</td>
<td>71</td>
<td>79</td>
</tr>
<tr>
<td>Month 3</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Months 6, 9, and 12</td>
<td>43</td>
<td>Pending</td>
</tr>
</tbody>
</table>

Met Primary Endpoint of Objective Response Rate (p < 0.0001) at Interim Analysis vs. historical refractory DLBCL (ORR 26%, CR 8%)

1. Locke F et al Mol Ther 2017
### Consistent Treatment Effect Across Key Covariates

<table>
<thead>
<tr>
<th>Refractory Subgroup</th>
<th>Overall (N=93)</th>
<th>Refractory to ≥2 line therapy (n=72)</th>
<th>Relapse post ASCT (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Stage</td>
<td></td>
<td>I-II (n=13)</td>
<td>III-IV (n=79)</td>
</tr>
<tr>
<td>IPI Risk Score</td>
<td></td>
<td>1-2 (n=49)</td>
<td>3-4 (n=41)</td>
</tr>
<tr>
<td>CD19 H-Score*</td>
<td></td>
<td>≤150 (n=23)</td>
<td>&gt;150 (n=53)</td>
</tr>
<tr>
<td>CD4/CD8 Ratio</td>
<td></td>
<td>&gt;1 (N=42)</td>
<td>≤1 (n=45)</td>
</tr>
<tr>
<td>Steroid Use</td>
<td></td>
<td>Yes (n=21)</td>
<td>No (n=72)</td>
</tr>
<tr>
<td>Tocilizumab Use</td>
<td></td>
<td>Yes (n=35)</td>
<td>No (n=58)</td>
</tr>
</tbody>
</table>

*CD-19 H Score definition: (3 x % of 3+intensity) + (2 x % of 2+ intensity) + (% of 1+ intensity), giving a range of 0 to 300.
Ongoing 9+ mo Durable CR in Refractory DLBCL

- 62-yo M with DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-lenalidomide
- No response to last 3 lines of therapy

Baseline Day 90

Neelapu & Locke, et al., ASH 2016, #LBA6
## Summary of Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Cohort 1 (n=73)</th>
<th>Cohort 2 (n=20)</th>
<th>Total (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade $\geq$3 adverse event</td>
<td>68 (93)</td>
<td>18 (90)</td>
<td>86 (92)</td>
</tr>
<tr>
<td>Grade $\geq$3 cytokine release syndrome</td>
<td>10 (14)</td>
<td>2 (10)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Grade $\geq$3 neurologic events (NE)</td>
<td>18 (25)</td>
<td>9 (45)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Fatal events excluding PD</td>
<td>1 (1)</td>
<td>2 (10)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>2 of 3 KTE-C19-related</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CRS and NE were generally reversible
  - All CRS events resolved except 1 cardiac arrest
  - 3 NEs ongoing at data-cut (Gr 1 memory impairment, Gr 1 tremor, Gr 2 tremor)
  - 38% received tocilizumab, 17% received corticosteroids, 17% received both

- No cases of cerebral edema
- Grade 5 events occurred in 3 patients (3%)
  - KTE-C19-related: HLH and cardiac arrest in the setting of CRS
  - KTE-C19-unrelated: pulmonary embolism

HLH = hemophagocytic lymphohistiocytosis

Neelapu & Locke, et al., ASH 2016, #LBA6
CAR T Cell Expansion is Associated with Ongoing CR and Grade ≥3 NE, but not CRS

- Peak CAR T cell expansion between 7-14 days
- Wilcoxon rank-sum test used to calculate P values

Ongoing CR at Month 3
- *P = 0.004

Neurologic Events
- *P-value = 0.02

CRS
- *P-value = 0.7
p-values were adjusted by stepdown Bonferroni method. AUC was over 0-28 days (n=62 patients).
Zuma-1 Conclusions

• ZUMA-1 met primary endpoint with 76% ORR and 47% CR (p<0.0001) at the pre-specified interim analysis
  - 6-fold higher CR rate compared with historical outcomes

• First pivotal, multicenter study of anti-CD19 CAR T cells in refractory aggressive NHL

• AE management effectively implemented across 22 sites, most with no prior CAR T therapy experience
  - Grade 5 adverse event rate was 3%
  - Grade ≥3 CRS (13%) and neurologic events (29%)
Expected CD19 CAR T cell
Indications and Delivery

- Relapsed or refractory DLBCL
- Relapsed or refractory ALL
- Care delivery will likely be restricted to specialized hematology centers:
  - Have active transplant programs
  - Participated in the CAR-T development phase
- CAR T production plants are available to meet demand
Summary

- CD19 CAR T cells are autologous cellular immunotherapy for patients with B cell malignancies
- Associated with CRS and Neurologic events
- Optimal care of CAR T cell patients requires a collaborative effort between physicians, nurses, and others
- FDA approval for CAR T cells is expected in 2017
- Interim results against aggressive lymphomas demonstrate a significant improvement over the standard of care
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- Research Data Specialists
- Social Workers
- Pharmacists
- Patient Service Representatives