Targeted Immunotherapy with CAR T cells for Acute Lymphoblastic Leukemia

Shannon Maude, MD PhD
Cancer Immunotherapy Program
Children’s Hospital of Philadelphia
The University of Pennsylvania School of Medicine
Children’s of Alabama Pediatric Cancer and Blood Disorders Symposium
November 16, 2018
Disclosures

• Consultancy – Novartis: advisory boards, clinical trial development

• CTL019 (now known as Kymriah, tisagenlecleucel) licensed by Novartis
• CTL119 (investigational product) licensed by Novartis
Objectives

• Describe CAR design and mechanism of action
• Discuss toxicity management
• Summarize data from phase 1/2 trials of CD19-directed CAR T cells for ALL
• Discuss mechanisms of relapse
• Discuss next-generation approaches, including combinations
Outline

• CAR design and mechanism of action
  • Toxicity
  • Results of phase 1/2 trials of CD19-directed CAR T cells for ALL
  • Mechanisms of relapse
  • Next-generation approaches
CAR links extracellular antibody to intracellular T cell signaling domains

- scFv binds antigen ➔ engages CAR ➔ cytotoxic response – killing antigen-expressing cell

Selecting a target antigen:

- Ideally, universally expressed on tumor cells and not expressed on normal cells, but RARE
- Close to ideal – CD19 as example:
  - Expressed on most B cell malignancies
  - Expression restricted to B cells
CAR T cell Engineering

- T cells collected from patient
- Lentiviral vector introduces gene encoding CAR
- CAR links extracellular antibody to intracellular T cell signaling domains
- T cells expanded ex vivo
- Reinfused → come in contact with antigen → engage CAR → cytotoxic response and in vivo proliferation
- Persistent CART19 (CTL019) cells may allow long-term disease control
**In vivo Proliferation**

- In circulation, supraphysiologic in vivo proliferation can be seen
- Proliferation required for efficacy
BM MRD testing

Day -1

RESULTS

Day 28

RESULTS

MRD assessment after CD19-directed therapy challenging
Outline

- CAR design and mechanism of action
- Toxicity
- Results of phase 1/2 trials of CD19-directed CAR T cells for ALL
- Mechanisms of relapse
- Next-generation approaches
Cytokine Release Syndrome

CRS is related to T cell expansion and is likely necessary for efficacy

- Symptoms typically occur 1-14 days after CTL019 cell infusion in ALL

- Severity scales with disease burden
Example of severe CRS

21 year old male with 2nd relapse of ALL

- BM with >90% blasts
- CTL019 infusion – 1st split dose
- CTL019 infusion – 2nd split dose
- Fever
- Confusion with high fevers
- Hypotension
- Received tocilizumab

Day: -1 0 +1 +2 +3 +4 +5
Prodromal syndrome: low-grade fevers, fatigue, anorexia (hours to days)

Management: Observation, rule out infection (surveillance cultures); antibiotics per local guidelines (febrile neutropenia); symptomatic support

First-Line Management:
- Oxygen, fluids, low-dose vasopressor support, antipyretics; monitor/manage complications of TLS

Further symptom progression:
- High fevers, hypoxia, mild hypotension
- Hemodynamic instability despite IV fluids and moderate- to “high-dose” vasopressor support OR
- Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow oxygen OR
- Rapid clinical deterioration

Second-Line Management:
- Tocilizumab: IV infusion over 1 hour (patient weight < 30 kg: 12 mg/kg IV; patient weight ≥ 30 kg: 8 mg/kg IV [maximum dose 800 mg])
- Hemodynamic and respiratory support

Pretreatment:
- Acetaminophen/paracetamol and diphenhydramine/H1 antihistamine
- Prophylaxis for complications of tumor lysis syndrome (TLS) as appropriate

CTL019 Infusion

☞ Treat symptomatically

⁹⁹See definition of “high-dose” vasopressors.
### CRS Management Algorithm

#### Pretreatment
- Acetaminophen/paracetamol and diphenhydramine/H1 antihistamine
- Prophylaxis for complications of tumor lysis syndrome (TLS) as appropriate

---

#### CTL019 Infusion

---

#### Symptom progression:
- High fevers, hypoxia, mild hypotension

**First-Line Management:** Oxygen, fluids, low-dose vasopressor support, antipyretics; monitor/manage complications of TLS

---

#### Further symptom progression
- Hemodynamic instability
- Worsening hypoxia
- Rapid clinical deterioration

**Second-Line Management:**
- Tocilizumab: IV infusion over 1 hour (patient weight < 30 kg: 12 mg/kg IV; patient weight ≥ 30 kg: 8 mg/kg IV [maximum dose 800 mg])
- Hemodynamic and respiratory support

---

#### Progression of CRS:
- Vascular leak starting 2-5 days after fever onset leading to hypotension and fluid overload
- Fluids (limited), oxygen

---

#### Unstable hypotension, not immediately responsive to fluids:
- Start low-dose pressors, consider toci

---

*a* See definition of “high-dose” vasopressors.
Further symptom progression

- Hemodynamic instability despite IV fluids and moderate- to “high-dose”\textsuperscript{a} vasopressor support OR
- Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation OR
- Rapid clinical deterioration

\textbf{Second-Line Management}

- Tocilizumab: IV infusion over 1 hour (patient weight < 30 kg: 12 mg/kg IV; patient weight ≥ 30 kg: 8 mg/kg IV [maximum dose 800 mg])
- Hemodynamic and respiratory support

\textsuperscript{a} See definition of “high-dose” vasopressors.
Lack of clinical improvement while awaiting tocilizumab response

Third-Line Management

- Consider other diagnosis causing clinical deterioration (ie, sepsis, adrenal insufficiency)
- If no improvement with first dose of tocilizumab within 12 to 18 hours, consider steroids (plan rapid taper after hemodynamic normalization): 2 mg/kg methyl-prednisolone as an initial dose, then 2 mg/kg per day; as steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement
- If no response to steroids within 24 hours, consider second dose of tocilizumab (dose as above)

Hemodynamic and respiratory support

Transient or insufficient response to toci (12-18h):
- Unable to wean pressors
  - Steroids

 permanent (24h):
- Pressors + fever
- Second toci

Still no improvement (24h):
- Unable to wean pressors
- Second toci
Toxicity

- **Cytokine Release Syndrome (CRS)**
  - Correlates with T cell proliferation and efficacy
  - Severity related to disease burden
  - Reversed with anti-IL6 therapy
  - Severe CRS mirrors HLH/MAS

- **Neurotoxicity**
  - Seen in several CD19 immunotherapy trials: CAR T cells (NCI, CHOP/UPENN, MSKCC, Seattle) and Blinatumomab
  - In our experience - generally untreated, fully resolves

- **Chronic B cell aplasia requiring IgG replacement**

- **Prolonged cytopenias**
  - Risk correlates with prior therapy and cytopenias pre-infusion
CRS symptoms:

- Systemic inflammatory response with vascular leak, hypotension, respiratory and renal insufficiency
- HSM, Transaminitis, Hyperbilirubinemia
- **Coagulopathy**
  - Marked by low fibrinogen
- Extraordinarily high ferritin levels
  - 16,000 to 415,000 ng/ml
- Mitigated with cytokine blockade
  - IL-6R blocking agent tocilizumab

CRS mirrors HLH/MAS

Requires close monitoring and cryo replacement
Toxicity

- Cytokine Release Syndrome (CRS)
  - Correlates with T cell proliferation and efficacy
  - Severity related to disease burden
  - Reversed with anti-IL6 therapy
  - Severe CRS mirrors HLH/MAS

- Neurotoxicity
  - Seen in several CD19 immunotherapy trials: CAR T cells (NCI, CHOP/UPENN, MSKCC, Seattle) and Blinatumomab
  - In our experience - generally untreated, fully resolves

- Chronic B cell aplasia requiring IgG replacement

- Prolonged cytopenias
  - Risk correlates with prior therapy and cytopenias pre-infusion
Neurotoxicity

• **Symptoms**
  – Confusion/delirium
  – Expressive aphasia
  – Global encephalopathy
  – Tremor
  – Seizure

• **Management**
  – Supportive care/seizure management
  – Steroids?

• **Pathophysiology**
  – Cytokine-mediated?
CRS severity linked to neurotoxicity

Neurotoxicity analyzed in cohort of 51 children and young adults (age 4-22y) treated with CTL019 on pediatric trial

Incidence: 23/51 (45%)

Common neurotoxicities:
- Encephalopathy
- Seizure
- Aphasia

Occurrence of neurotoxicity correlated with grade of CRS

Cytokines elevated in neurotoxicity

Serum cytokines measured over first month after infusion

IL-2, IL-15, sIL-4R, and HGF elevated in patients who developed neurotoxicity compared to those who did not

Potential mechanisms:
- Endothelial activation: HGF
- NK cells: IL-2, IL-15

Toxicity

• Cytokine Release Syndrome (CRS)
  – Correlates with T cell proliferation and efficacy
  – Severity related to disease burden
  – Reversed with anti-IL6 therapy
  – Severe CRS mirrors HLH/MAS

• Neurotoxicity
  – Seen in several CD19 immunotherapy trials: CAR T cells (NCI, CHOP/UPENN, MSKCC, Seattle) and Blinatumomab
  – In our experience - generally untreated, fully resolves

• Chronic B cell aplasia requiring IgG replacement

• Prolonged cytopenias
  – Risk correlates with prior therapy and cytopenias pre-infusion
Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Any Grade (N=75)</th>
<th>Grade 3 (N=75)</th>
<th>Grade 4 (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event of special interest</td>
<td>67 (89)</td>
<td>26 (35)</td>
<td>30 (40)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>58 (77)</td>
<td>16 (21)</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>30 (40)</td>
<td>10 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>32 (43)</td>
<td>16 (21)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>26 (35)</td>
<td>24 (32)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cytopenia not resolved by day 28</td>
<td>28 (37)</td>
<td>12 (16)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>
Outline

• CAR design and mechanism of action
• Toxicity
• Results of phase 1/2 trials of CD19-directed CAR T cells for ALL
• Mechanisms of relapse
• Next-generation approaches
# Phase 1/2a Trial of CTL019 in Pediatric ALL

## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>11 (1.7,24)</td>
</tr>
<tr>
<td>Post Allogeneic Transplant</td>
<td>39 (65%)</td>
</tr>
<tr>
<td>Baseline ALL burden</td>
<td></td>
</tr>
<tr>
<td>&gt;5% Blasts</td>
<td>32 (53%)</td>
</tr>
<tr>
<td>0.01-5% Blasts</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>&lt;0.01% Blasts</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>CNS status at infusion</td>
<td></td>
</tr>
<tr>
<td>CNS1</td>
<td>54 (90%)</td>
</tr>
<tr>
<td>CNS2</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>CNS3 at infusion; within 12 months</td>
<td>2 (3%); 16 (27%)</td>
</tr>
</tbody>
</table>
CTL019 Outcomes

CR: 56/60 (93%)

RFS:
12 mo – 60% (48, 75)
24 mo – 53% (39, 70)

7 pts proceeded to SCT, 1 to DLI – 2 relapses after SCT

Median f/u: 15 mo (1-48 mo)

Maude et al., ASCO 2016
ELIANA Phase 2 Trial of CTL019

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

CRs with CD19 CARs

NCI CD19-28 CAR

- 31/51 (60.8%) CR, 28 MRD-in children and young adults with R/R B-ALL
- Median Leukemia-free survival 18 mo in 28 MRD-CR
- 21/28 receiving subsequent SCT

Lee D et al. ASH 2016
CRs with CD19 CARs

FHCRC CD19-4-1BB CAR

- 40/43 93% MRD- CR in children and young adults with R/R B-ALL
- 12mo EFS 50.8% (95% CI, 36.9-69.9%)
- 11 underwent HSCT

<table>
<thead>
<tr>
<th></th>
<th>Patients (N = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>11 (3-23)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>43 (57)</td>
</tr>
<tr>
<td>Prior stem cell transplant, n (%)</td>
<td>46 (61)</td>
</tr>
<tr>
<td>Previous line of therapies, median (range), n</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>Disease status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Chemo-refractory or relapsed</td>
<td>69 (92)</td>
</tr>
<tr>
<td>Morphologic blast count in bone marrow, median (range), %</td>
<td>74 (5-99)</td>
</tr>
<tr>
<td>CNS status classification, n (%)*</td>
<td></td>
</tr>
<tr>
<td>CNS-1</td>
<td>63 (84)</td>
</tr>
<tr>
<td>CNS-2</td>
<td>10 (13)</td>
</tr>
<tr>
<td>CNS-3</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
</tr>
<tr>
<td>High-risk genomic lesions, n (%)†</td>
<td>28 (37)</td>
</tr>
<tr>
<td>Down syndrome, n (%)</td>
<td>6 (8)</td>
</tr>
</tbody>
</table>

CNS, central nervous system.
* The most current assessment on or prior to the date of enrollment. † BCR-ABL1, MLL rearrangement, hypoploidy, lesions associated with BCR-ABL1-like gene signature, or complex karyotype (≥5 unrelated abnormalities).
Primary Endpoint: 61/75 CR/CRi (81%)

RFS: 80% (95% CI, 65 to 89) at 6 mo
59% (95% CI, 41 to 73) at 12 mo
First US FDA approval of a CAR T cell therapy

After unanimous recommendation of Oncologic Drugs Advisory Committee

The FDA approved the first CAR T cell therapy, Kymriah™ for children and young adults up to age 25 with B-ALL that is refractory or in second or greater relapse
Outline

• CAR design and mechanism of action
• Toxicity
• Results of phase 1/2 trials of CD19-directed CAR T cells for ALL
• Mechanisms of relapse
• Next-generation approaches
Mechanisms of Relapse

CD19+ relapse - due to short persistence
  o T cell intrinsic?
  o Immune-mediated rejection?

CD19- relapse - due to antigen escape
  o Is CD19 deleted/mutated/no longer expressed?
Comparing CARs

CAR design important for persistence and sustained efficacy

scFv

CD28

CD3z

retrovirus

MSKCC

CD28

CD3z

retrovirus

NCI

4-1BB

CD3z

lentivirus

Penn/CHOP

Persistence Variables

– CAR design
  • CD28 domain associated with more rapid early proliferation and more rapid loss (by 2 months in most cases)
  • 4-1BB domain associated with somewhat slower initial proliferation and prolonged persistence (years)

– T cell repertoire
  • Naïve and central memory T cells persist longer
  • Manufacture process may contribute or may be T cell intrinsic

– Immune-mediated rejection
  • Anti-murine, anti-CAR
Pediatric phase 1 trial of CTL019 (CHP959):

- 93% CR
- 22% early B cell recovery (<6 months)
- 15% CD19+ relapse

CR: complete remission
NR: no response
BMT: bone marrow transplant; DLI: donor lymphocyte infusion

Maude et al, ASCO 2016
CD19+ relapse - due to short persistence
  o T cell intrinsic?
  o Immune-mediated rejection?

CD19- relapse - due to antigen escape
  o Is CD19 deleted/mutated/no longer expressed?
Frameshift mutations → Protein truncated shortly after mutation point

In frame mutation (substitutions, insertions of aa)

Exons 2 and 4 seem to be hot-spots
1nt in/del: frameshift → truncated protein
Most are de novo in relapse sample

ESCAPING

CTL019

SPLICING
Exon 2
Exon 5-6
Partial exon 3

RESISTANT TO CTL019
(in vitro killing assay, Ruella & Gill)

MUTATIONS

Elena Sotillo-Peneiro, David Barrett, Cancer Discov 2015
Outline

• CAR design and mechanism of action
• Toxicity
• Results of phase 1/2 trials of CD19-directed CAR T cells for ALL
• Mechanisms of relapse
• Next-generation approaches
Hypotheses:

• Immune-mediated rejection
  – CD19 scFv domains of murine origin – possible anti-murine immunogenicity
  – Humanized CART19 (CTL119) Pediatric Phase 1 Clinical Trial (NCT02374333) for patients previously treated with CAR T cells

• T cell exhaustion
  – Immune checkpoints may play a role
  – Combination with PD-1 checkpoint blockade may improve persistence
Humanized CART19 (CTL119)

- Most scFv domains of murine origin
- Possible anti-murine immune-mediated rejection
Pediatric Phase 1 Clinical Trial

• Eligibility
  – Relapsed/Refractory CD19+ B-ALL and B cell lymphoma
  – Previously treated with CAR T cell therapy and:
    • partial response or no response to CAR T cell therapy
    • relapsed after CAR T cell therapy
    • demonstrated B cell recovery suggesting loss of CAR T cells
  – Not previously treated with CAR T cell therapy
## Phase 1 Trial of CTL119

### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Allogeneic Transplant</td>
<td>22  (58%)</td>
</tr>
<tr>
<td>B-ALL</td>
<td>37  (97%)</td>
</tr>
<tr>
<td>Primary Refractory</td>
<td>4   (11%)</td>
</tr>
<tr>
<td>1(^{st}) Relapse</td>
<td>8   (22%)</td>
</tr>
<tr>
<td>2(^{nd}) or greater Relapse</td>
<td>25  (68%)</td>
</tr>
<tr>
<td>B Lymphoblastic Lymphoma</td>
<td>1   (3%)</td>
</tr>
<tr>
<td>CNS Relapse</td>
<td>7   (19%)</td>
</tr>
<tr>
<td>Extramedullary Relapse</td>
<td>6   (16%)</td>
</tr>
<tr>
<td>Pre-infusion BM burden</td>
<td></td>
</tr>
<tr>
<td>&gt;5% Blasts</td>
<td>12  (32%)</td>
</tr>
<tr>
<td>0.01-5% Blasts</td>
<td>8   (21%)</td>
</tr>
<tr>
<td>&lt;0.01% Blasts</td>
<td>18  (47%)</td>
</tr>
</tbody>
</table>

Maude, et al., ASH 2017
Humanized CART19 (CTL119) – Relapse-free survival

Retreatment cohort: 12/16 CR (75%); 9/16 CR with B cell aplasia (56%)

CAR-naïve cohort: 22/22 CR (100%)

Retreatment RFS

- 6-mo RFS: 67% (28,88)
- 12-mo RFS: 56% (20,80)
- Median f/u: 13 mo

CAR-Naive RFS

- 6-mo RFS: 86% (63,95)
- 12-mo RFS: 82% (58,93)
- Median f/u: 14 mo

Maude et al., ASH 2017
Poor CAR T cell Persistence

Hypotheses:

• Immune-mediated rejection
  – CD19 scFv domains of murine origin – possible anti-murine immunogenicity
  – Humanized CART19 (CTL119) Pediatric Phase 1 Clinical Trial (NCT02374333) for patients previously treated with CAR T cells

• T cell exhaustion
  – Immune checkpoints may play a role
  – Combination with PD-1 checkpoint blockade may improve persistence

Proposal:

– Patients with poor persistence eligible to receive repeat infusion
– Trial pembrolizumab in retreatment with 2° poor persistence
Humanized CART19 (CTL119) Study Schema

Relapsed/Refractory ALL

Enrollment

- CTL119 manufacturing

Chemotherapy* → Lymphodepletion**

Baseline Assessment (BM/LP) – Day -1

Option for reinfusion

Response Assessment (BM/LP) – Day 28

Follow-up Assessment (BM/LP) – Month 3/6/9/12

Monitor for MRD, B cell aplasia, and CTL019 persistence

Pembrolizumab† for poor persistence in retreatment

†after recovery from CRS, no earlier than day 14

*SOC chemotherapy at treating physician’s discretion
**Recommended LD chemo – flu/cy 55/60 received LD chemo
Pembrolizumab for poor persistence

Maude et al., ASCO 2017
Pembrolizumab for poor persistence

Comparison of huCART19 infusions with or without pembro

Maude et al., ASCO 2017
Summary

• Pediatric Phase 1 trial of CTL019 in relapsed/refractory ALL
  – 93% CR, 12-mo RFS 60%
  – Long-term remissions (1-4 years) without further therapy
• Control of CNS disease
  – Sustained CNS remissions in patients with h/o CNS involvement
• Early B cell recovery (< 6 months) associated with higher risk of relapse
  – Reinfusion can prolong B cell aplasia in some patients
• Humanized CTL119 can induce remissions
  – 56% (9/16) CR in retreatment, including patients with no response to murine CAR
  – 100% (22/22) CR in CAR-naïve patients
• Immunogenicity may contribute to poor persistence
What’s next for CAR T cells in ALL?

Expanding the role of CTL019

• Moving into upfront therapy for VHR subsets at high risk of relapse
• Phase 2 trial in pediatric NHL
• Phase 3 trial in adult B-ALL
• Planning trials in other VHR populations
  – DS-ALL in first relapse
  – Hypodiploid B-ALL
  – B-ALL with t(17;19)

Overcoming relapse

• Due to short persistence – humanized anti-CD19 CAR
• Due to antigen escape – alternative targets: anti-CD22 CAR
AALL1721 Trial Design

**de novo NCI HR B-ALL**

- **HR Induction**
  - MRD ≥1%
  - Leukapheresis

- **HR Consolidation**
  - MRD ≥0.01%
  - Continue protocol
  - Chemotherapy
  - Proceed to CTL019 infusion when available

- **Screen and Enroll**
  - CTL019 Manufacture
  - Infusion

- Pi: Maude

*The world’s childhood cancer experts*
### Cancer Immunotherapy Program

**CHOP Cell Therapy Infusions (Infusions to date >250)**

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Sponsor</th>
<th>Status</th>
<th>Start Year</th>
<th>Disease</th>
<th>PI</th>
<th>Total # Enrolled</th>
<th>Total # Infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHP959</td>
<td>Penn/NVS</td>
<td>Complete</td>
<td>2012</td>
<td>ALL</td>
<td>Grupp</td>
<td>74</td>
<td>62</td>
</tr>
<tr>
<td>NY-ESO 1 TCR</td>
<td>Adaptimmune</td>
<td>Complete</td>
<td>2012</td>
<td>Sarcoma</td>
<td>Grupp</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Humanized anti-CD19 CAR</td>
<td>Penn</td>
<td>Open</td>
<td>2014</td>
<td>ALL</td>
<td>Maude</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>Pediatric (US) Multisite Trial</td>
<td>Novartis</td>
<td>Complete</td>
<td>2014</td>
<td>ALL</td>
<td>Grupp</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Global FDA Registration Trial</td>
<td>Novartis</td>
<td>Complete</td>
<td>2015</td>
<td>ALL</td>
<td>Grupp</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>RNA anti-CD19 CAR</td>
<td>Penn</td>
<td>Open</td>
<td>2015</td>
<td>Hodgkins</td>
<td>Rheingold</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CD22</td>
<td>Penn</td>
<td>Open</td>
<td>2016</td>
<td>ALL</td>
<td>Grupp</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Early Toci</td>
<td>Penn</td>
<td>Open</td>
<td>2016</td>
<td>ALL</td>
<td>Grupp</td>
<td>75</td>
<td>63</td>
</tr>
<tr>
<td>NVS LTFU</td>
<td>Novartis</td>
<td>Open</td>
<td>2015</td>
<td>ALL</td>
<td>Grupp</td>
<td>50+</td>
<td>N/A</td>
</tr>
<tr>
<td>KTE-C19-104/ZUMA</td>
<td>Kite</td>
<td>Pending</td>
<td>2017</td>
<td>ALL</td>
<td>Grupp</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### FDA Approved

<table>
<thead>
<tr>
<th>FDA Approved</th>
<th>Start Year</th>
<th>Disease</th>
<th>Total # Infused</th>
<th>Patients in Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisagenlecleucel</td>
<td>2017</td>
<td>ALL</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>
## CHOP Cell Therapy Trial Pipeline

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Status</th>
<th>Start Yr</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humanized (CTL119) ph 2</td>
<td>Opening soon</td>
<td>Q3 2018</td>
<td>ALL</td>
</tr>
<tr>
<td>Up front ALL pilot</td>
<td>Written/approved</td>
<td>Q4 2018</td>
<td>Early, VHR ALL</td>
</tr>
<tr>
<td>Down Syndrome (BMT replacement)</td>
<td>Late development</td>
<td>Q4 2018</td>
<td>ALL</td>
</tr>
<tr>
<td>UHR 1st remission</td>
<td>Late development</td>
<td>Q4 2018</td>
<td>ALL (17;19, hypodiploid plus CNS 1st relapse)</td>
</tr>
<tr>
<td>CD22 CAR</td>
<td>Written Pending vector</td>
<td>Q3 2018</td>
<td>ALL CD19 escape</td>
</tr>
<tr>
<td>CD123 CAR</td>
<td>Pending vector</td>
<td>Q4 2018</td>
<td>AML</td>
</tr>
<tr>
<td>CD33 CAR</td>
<td>Pending vector</td>
<td>Q1 2019</td>
<td>AML</td>
</tr>
<tr>
<td>Upcoming</td>
<td>Eureka, Juno, Cellectis CD19 &amp; CD123 off the shelf</td>
<td>Over next 6-18 mo</td>
<td>ALL, AML</td>
</tr>
</tbody>
</table>
Determinants of response

• T cell intrinsic
  o T cell repertoire
• Leukemia/tumor intrinsic
  o Checkpoint pathways

Determinants of relapse

• Relapse due to short persistence
  o Immune rejection
• Relapse due to antigen escape
  o Are CD19 escape variants present at baseline?

Toxicity Correlates

• Genetic predisposition
• Early prediction models
Patients and Families

CHOP Cancer Immunotherapy Program
Stephan Grupp
Shannon Maude
Amanda DiNofigia
Sue Rheingold
Colleen Callahan
Diane Baniewicz
Christine Strait
Christina Fasano
Lauren Vernau
Beth McBride
Dana Haagen

Grupp Lab
David Barrett
David Teachey
Alix Seif
Shannon Maude
Hamid Bassiri
Ted Hoffman
Jessica Perazzelli

CHOP Nursing

CHOP CRSO Office

CHOP Stem Cell Lab
Yongping Wang

U Penn Biostatistics
Pamela Shaw

ACC CCI
Carl June
Anne Chew
Michael Milone
Yangbing Zhao
John Scholler
Regina Young
Katie Marcucci

U Penn Clinical
David Porter
Noelle Frey

CVPF
Bruce Levine
Don Siegel
Andrew Fesnak

TCSL
Simon Lacey
Jos Melenhorst
Jeff Finklestein
Frazana Nazimuddin
Vanessa Gonzalez

Adaptive TcR
David Lebwohl
Tetiana Taran
Patricia Wood

St. Baldrick’s Foundation
Conquer Childhood Cancers

The Leukemia & Lymphoma Society
Fighting Blood Cancers

The Children’s Hospital of Philadelphia
Hope lives here.