Chimeric Antigen Receptor (CAR)-T cells

David Lebwohl, MD, Sr. VP and Global Program Head, CART Novartis London, UK
November 15, 2016
Disclaimer

• This presentation contains information about investigational compounds that have not been approved in any country or region of the world.

• Efficacy and safety have not been established.

• The information presented should not be construed as recommendations for use.
Cell & gene therapies are a new pillar of the life science industry

Cell & Gene Therapies

Cell & Gene Transfer

• Cell therapy: transfer cells with relevant function into patient

• Gene therapy: transfer of genetic material into appropriate cells of the body

Biologics

Protein engineering

Small Molecules

Chemical engineering

Collaboration with University of Pennsylvania

Cell therapy research collaboration

Collaboration on study of chimeric antigen receptor (CAR) technology for cancer treatment; exclusive worldwide license to CARs developed through the collaboration

Design of CD19-targeted CTL019

- FDA granted “breakthrough therapy” designation to CTL019, the anti-CD19 CAR T-cell therapy developed at the University of Pennsylvania (July 2014)

- CTL019 CAR consists of T-cell activation domains coupled to an anti-CD19 single-chain variable fragment¹⁻³

CD19: An ideal target for CAR T-cells

• CD19 is a cell surface protein whose expression is restricted to B cells and B cell precursors\(^1\)
  – Importantly, CD19 is not expressed on hematopoietic stem cells\(^1\)
• CD19 is expressed by most B-cell malignancies\(^1\)
  – CLL, B-ALL, DLBCL, FL, MCL\(^1\)

Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity\(^1,2\)

CTL019 therapy takes advantage of the cytotoxic potential of T cells, thereby killing tumor cells in an antigen-dependent manner\(^1,3\)

Persistent CTL019 cells consist of both effector (cytotoxic) and central memory T cells\(^3\)

---

CTL019 is designed to hunt and destroy CD19-positive B-cell cancers in patients.

1. Leukapheresis
2. T-cell activation/transduction
3. Modified T-cell expansion
4. Chemotherapy
5. Modified T-cell infusion

a. Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.
# CD19-targeted CAR therapies under investigation

<table>
<thead>
<tr>
<th>Academic Group</th>
<th>Company (Drug)</th>
<th>Costimulatory Domain</th>
<th>Vector Delivery</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPenn</td>
<td>Novartis (CTL019)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>ALL, CLL, DLBCL, FL</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Juno (JCAR 015)</td>
<td>CD28</td>
<td>Retroviral</td>
<td>ALL, CLL, various B-cell malignancies</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>Juno (JCAR 017)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td></td>
</tr>
<tr>
<td>NCI (NIH)</td>
<td>Kite Pharma (KTE-C19)</td>
<td>CD28</td>
<td>Retroviral</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Baylor</td>
<td>Bluebird/Celgene</td>
<td>CD28</td>
<td>Retroviral</td>
<td>ALL, CLL</td>
</tr>
<tr>
<td>MDACC</td>
<td>Ziopharm/Intrexon</td>
<td>CD28 $\rightarrow$ 4-1BB</td>
<td>Transposon/transposase</td>
<td>Adjuvant, pre/post transplant</td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>Cellectis/Pfizer (UCART19)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>ALL, CLL, AML, MM</td>
</tr>
<tr>
<td>Baylor</td>
<td>Bellicum (BPX-401)</td>
<td>MyD88 + CD40</td>
<td>Retroviral</td>
<td>Various</td>
</tr>
<tr>
<td>Dartmouth</td>
<td>Cardio3</td>
<td>DAP-10 transmembrane</td>
<td>Retroviral</td>
<td>AML, MDS, MM</td>
</tr>
</tbody>
</table>
CAR T cell Therapy – Leukemia as a Model

Shannon Maude MD PhD
Center for Childhood Cancer Research
Children’s Hospital of Philadelphia
University of Pennsylvania Perelman School of Medicine

ASGCT, May 7, 2016
CTLO19 experience in ALL

Pediatric ALL phase 1/2a study (N = 59):

Population
- 2\textsuperscript{nd} or greater relapse or refractory
- 2/3 relapsed post SCT

Outcomes
- 55/59 (93\%) in complete remission at 1 month
- 18 patients in remission ≥1 year, 13 without further therapy
- Median follow-up 12 months, range 1-43 months
- 20 relapses, 7 CD19(+) and 13 CD19(-)
- 6 patients proceeded to SCT, 1 to DLI

Grupp et al. ASH 2015
Disease Burden and Response

Patient population
- ≥ 2\textsuperscript{nd} relapse or refractory
- Majority refractory to multiple prior therapies

* <0.01% MRD by flow cytometry
** \( \frac{1}{3} \) CD19+, \( \frac{2}{3} \) CD19-MRD- by 3 months without further therapy

Abbreviations: CR, complete response, MRD, minimal residual disease; NR, no response
Most patients treated POST allo

- 39 patients post-allo SCT
- T cells collected from patient
  - No evidence of GVHD
  - 6 months post-SCT
- Median donor chimerism 100%
- No GVHD to date

Abbreviations: GVHD, graft-versus-host disease; SCT, stem cell transplant
Toxicity

• **Cytokine Release Syndrome (CRS)**
  – Correlates with T cell proliferation and efficacy
  – Severity related to disease burden
  – Observed in 88%; 27% required hemodynamic and/or respiratory support
  – Reversed with novel approach – cytokine blockade

• **Neurotoxicity**
  – Seen in several CD19 immunotherapy trials: NCI, CHOP/UPenn, MSKCC, Blinatumomab
  – In our experience - generally untreated, fully resolves

• **Chronic B cell aplasia requiring Ig replacement**
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
Severe CRS management

• Supportive Care
  – Vasopressors
  – O2, CPAP, ventilation
  – Blood products (FFP, cryo)

• Lympholytics
  – Steroids tried with some effect but potential to reduce efficacy

• Cytokine-directed therapy
  – IL-6 noted to be very elevated
  – Anti-IL-6 therapy highly effective with no apparent effect on efficacy

Grupp et al. NEJM 2013
Disease Burden Correlates with CRS Severity

Maude et al. ASPHO/EHA 2015
Novel approaches in patients with aggressive lymphomas: Chimeric antigen receptor modified T cell and other CD19-directed T cell therapies

Stephen J. Schuster, M.D.
Director, Lymphoma Program and Lymphoma Translational Research Abramson Cancer Center
Robert and Margarita Louis-Dreyfus Associate Professor of CLL & Lymphoma Perelman School of Medicine, University of Pennsylvania

EBMT 2016
Study Design: CTL019 T Cells in NHL

Enrollment started Feb 2014

Key eligibility criteria
- Adult histologically proven CD19+ relapsed or refractory DLBCL, FL or MCL
- Measurable disease
- ECOG PS 0 or 1

Primary Objectives: ORR at 3 months; determine response rate by lymphoma histology
Secondary endpoints: Determine CTL019 cell manufacturing feasibility; safety; best response; PFS; in vivo expansion of CTL019 cells

Single IV dose of CTL019 cells, 1 - 4 days after lymphodepletion chemotherapy

Initial tumor response assessed 3 months after infusion using IWG response criteria
Patient allocation

Patients enrolled (n = 43)
- DLBCL (n = 26)
- FL (n = 14)
- MCL (n = 3)

CTL019 not infused (n = 13)
- Progressive disease (n = 4)
- Production failure (n = 6)
- Withdrew consent (n = 3)

Received 1 – 5 E+08 CTL019 (n = 30)
- DLBCL (n = 15)
- FL (n = 13)
- MCL (n = 2)

EBMT 2016
## Results: Diffuse Large B Cell Lymphoma

### DLBCL: Patient Characteristics (n = 26 enrolled)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>54.5 years (range 25 - 77)</td>
</tr>
<tr>
<td>Sex</td>
<td>18 (69%) men</td>
</tr>
<tr>
<td>Median prior therapies</td>
<td>3 (range 1 - 8)</td>
</tr>
<tr>
<td>Prior stem cell transplant</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Stage III – IV (enrollment)</td>
<td>19 (73%)</td>
</tr>
<tr>
<td>Increased LDH (enrollment)</td>
<td>20 (77%)</td>
</tr>
<tr>
<td>&gt; 1 extranodal site (enrollment)</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Median ECOG PS (enrollment)</td>
<td>1 (range 0 - 1)</td>
</tr>
</tbody>
</table>

**Lymphodepleting therapy (n = 15)**

- 2 EPOCH (w/o vincristine); 7 hyperfractionated cyclophosphamide (1.8 gm/m²); 2 bendamustine (180 mg/m²); 2 cyclophosphamide (1 gm/m²);
- 1 XRT (4000 cGy) + cyclophosphamide (750 mg/m²);
- 1 infusional etoposide + bolus cyclophosphamide ("EPOCH" dosing)

EBMT 2016
**Response: Diffuse Large B Cell Lymphoma**

<table>
<thead>
<tr>
<th>DLBCL: ORR at 3 months 47% (N = 15)</th>
<th>DLBCL: Best Response Rate 47% (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CR: 3</td>
<td>- CR: 6</td>
</tr>
<tr>
<td>- PR: 4</td>
<td>- PR: 1</td>
</tr>
<tr>
<td>- PD: 8</td>
<td>- PD: 8</td>
</tr>
</tbody>
</table>

- 3 patients with PRs by CT criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months had PD at 6 months

EBMT 2016
Duration of Response: DLBCL

Response Duration: Diffuse Large B-cell Lymphoma

EBMT 2016
### Adverse Events at least possibly related: ≥ Grade 3 (N=30)

<table>
<thead>
<tr>
<th>AE</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>Total ≥ G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Alk. phos. increased</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Agitation</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Delirium</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>CRS</td>
<td>2</td>
<td>2</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>3</td>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>10</td>
<td>8</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>7</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>2</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
Acknowledgements

Lymphoma Program
• Jakub Svoboda, Sunita Dwivedy Nasta, David L. Porter, Elise A. Chong, Daniel J. Landsburg, Anthony R. Mato, Lauren Strelec, Mariusz A. Wasik

Translational Research Program
• Carl H. June, Bruce L. Levine, Simon F. Lacey, Jan J. Melenhorst, Anne Chew, Katherine T. Marcucci, Zhaohui Zheng

Novartis

Our patients and their families
Adverse Events and Management
CRS across different B-Cell malignancies

- CRS is observed in NHL and ALL patients treated with CTL0191-3
- CRS for a patient with ALL and NHL typically occurs 1-14 days after CAR T-cell therapy infusion1,4,5,6
- Severe CRS manifests earlier at approximately 1-3 days after infusion, compared with >3 days for non-severe cases in patients with ALL4
- Severity and incidence CRS varies with disease setting
  - Pediatric ALL: 35-45% Grade 3/4 CRS (no Grade 5 CRS)
  - Adult NHL: 16% Grade 3/4 CRS (no Grade 5 CRS)
  - Adult ALL: 85% Grade 3,4 or 5 CRS (3 cases with Grade 5 CRS)
  - Dose and schedule in r/r adult ALL is under investigation

Summary of Novartis sponsored trials with CTL019

- In 2015, Novartis initiated phase 2 studies in both pediatric ALL and adult diffuse large B-cell lymphoma patients
  - Novartis CTL019 paediatric ALL program granted Breakthrough Therapy Designation by US FDA (April 2016) & designated as a Priority Medicine (PRIME) by EMA (June 2016)

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Sponsor</th>
<th>Patient Population</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02435849</td>
<td>Novartis</td>
<td>Pediatric patients with relapsed and refractory B-cell ALL</td>
<td>2</td>
<td>Enrolled</td>
</tr>
<tr>
<td>(ELIANA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02445248</td>
<td>Novartis</td>
<td>Adult patients with diffuse large B-cell lymphoma</td>
<td>2</td>
<td>Enrolled</td>
</tr>
<tr>
<td>(JULIET)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
We are pursuing personalized cellular immunotherapy with a portfolio of CARTs

CART therapy pipeline

– Exploratory CTL019 in clinical trials for adult ALL and CLL

– Exploratory CART trials in multiple myeloma (BCMA target)

– Multiple CART programs are in discovery and pre-clinical research, and exploratory clinical trials, for both heme and solid tumors

CTL019 is an investigational therapy. Efficacy and safety have not been established. There is no guarantee CTL019 will become commercially available.
Lessons learned along the way (1/3)

Need for harmonization across the globe

• Our goal is to conduct global development programs to address serious conditions with unmet medical need
  – Endorse efforts for regulatory convergence where ultimately a single MAA dossier will meet registration requirements across regions
  – Great need for uniform manufacturing & quality standards
  – Need for exceptional release process in clinical setting
Lessons learned along the way (2/3)

Need for harmonization across EU

• Clinical Trial Application review and approval process under existing Directive 2001/20/EC can be complex & time consuming for gene therapy products
  – Due to need for individual MS review & approval
  – Difficult to enable efficient start to multi-center, multi-national clinical trials

• Welcome the implementation of the Clinical Trials Regulation (EU No 536/2014) provided
  – Adequate resources and qualified ATMP reviewers onboard to assure timely & efficient review without unwarranted administrative clock stops due to resource limitations
Lessons learned along the way (3/3)

Need for harmonization across EU

• Similar need for harmonized centralized Environmental Risk Assessment for ATMPs that are considered GMOs
  – National requirements differ across MS again making efficient initiation of clinical trials difficult

• Manufacturing licenses for product manipulations also have different requirements across MS
Looking toward the future

• Manufacturing changes will be frequent and mechanisms should be in place to permit rapid review, approval and implementation of such changes that enhance consistent product yield and quality

• Current health economic systems are
  – Not set up to deliver such complex therapies
  – Apt to undervalue ATMPs, reducing incentives to develop them
  – Not set up to properly fund ATMPs, thus limiting access

• Encourage continued support for parallel Scientific Advice to assure HTA input at early stages of clinical development program to help de-risk these uncertainties
CTL019 and CAR T-Cell therapy outlook

• Clinical data to date shows that CAR T-cell therapy leads to a high rate of complete and durable remission in patients with r/r B-cell ALL and DLBCL

• CRS is a class effect observed with all CD19-directed CAR-T therapies, and can generally be managed with supportive care with or without anti-cytokine therapy (including tocilizumab)

• Pivotal studies of CTL019 in pediatric ALL and lymphomas are ongoing
  - First BLA submission in 1Q2017

CTL019 is an investigational therapy. Efficacy and safety have not been established. There is no guarantee CTL019 will become commercially available.
Questions