CAR-T in Community Oncology Practice

Houston Holmes MD MBA FACP
Texas Oncology PA
Baylor/Charles A Sammons Cancer Center
Dallas, TX
The patient was a 7-year-old girl with a second recurrence of ALL diagnosed 2 years earlier. A remission with a negative test for minimal residual disease had been achieved, then she had a relapse 17 months after the original diagnosis.

She had a second remission after reinduction chemotherapy, but the cancer recurred 4 months later. She did not have a response to further intensive chemotherapy, including clofarabine, etoposide, and cyclophosphamide.
Peripheral-blood mononuclear cells (PBMCs) were collected by means of apheresis before administration of the intensive chemotherapy, with the anticipation that there might be an insufficient number of circulating T cells available for cell manufacturing after such intensive treatment.

The patient received an infusion of CTL019 cells that had been expanded with anti-CD3 and anti-CD28 antibodies and lentivirally transduced to express the **anti-CD19 chimeric antigen receptor**; the total dose was 10E8 CD3+ cells per kilogram (1.2×10E7 CTL019 cells per kilogram), given over a period of 3 consecutive days.
She did not receive lymphocyte-depleting chemotherapy before treatment with the CTL019 infusions, with the most recent cytotoxic therapy having been given 6 weeks before CTL019 infusion.

No immediate infusion-related toxic effects were noted, but she was hospitalized for low-grade fevers that progressed to high fevers by day 4. On day 5, she was transferred to the pediatric intensive care unit.

This was followed by rapid progression to respiratory and cardiovascular compromise requiring mechanical ventilation and blood-pressure support.
Clinical Responses to CTL019 Infusion in Two Children with Relapsed, Chemotherapy-Refractory Acute Lymphoblastic Leukemia (ALL).

Chimeric Antigen Receptor T-cell Therapy Headlines

CAR T-Cell Immunotherapy Named Advance of the Year in Annual ASCO Report

Immunotherapy: Tisagenlecleucel — the first approved CAR T-cell therapy: implications for payers and policy makers

‘A new frontier:’ US FDA approves Novartis’ $475,000 CAR-T cell cancer therapy
Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity
(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

Department of Chemical Immunology. The Weizmann Institute of Science. Rehovot 76100, Israel

Communicated by Michael Sela, July 13, 1989 (received for review June 18, 1989)
TcR constant domain fused to the antibody’s variable domains...

endowed the T cells with a non-MHC-restricted response...

chimeric receptor provides the T cell with an antibody-like specificity and is able to effectively transmit the signal for t-cell activation and execution of effector function...
T cells from any individual...

This approach can be exploited...to direct cytotoxic T lymphocytes to kill tumor...

Pave the way for an approach for the design at will of TcRs of any desired specificity, provided that such specificity can be predefined by a mAb. Our ability to combine antibody specificity with T-cell-mediated target cell lysis may have clinical potential: it enables the construction of chimeric TcR genes using the V regions of antibodies directed at desired antigens on a given target cell. These chimeric genes, once produced, are non-MHC-restricted and universal in the sense that a given set of chimeric genes could then be transfected into T cells from any individual. Upon returning the cells to their donors, they should manifest the specificity of the cTcR by proliferating and mediating specific effector function (cytolysis, production of lymphokines, help, or suppression) when encountering their target cells. This approach can be exploited, for example, to direct cytotoxic T lymphocytes to kill tumor or virally infected cells. Construction of cTcRs with anti-tumor specificity will enable testing of the feasibility of this approach in combating human tumors.
General structure of CAR

Chimeric antigen receptors


Original Article: Brief Report

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachevy, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

N Engl J Med
Volume 368(16):1509-1518
April 18, 2013
Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

CTL019 cells expanded in the peripheral blood and bone marrow to levels that were more than 1000 times as high as the original engraftment levels.

Severe cytokine-release syndrome developed. A single course of anticytokine therapy, consisting of etanercept and tocilizumab, was given on day 7, with rapid clinical effects: within hours, defervescence occurred, and the patient was weaned from vasoactive medications and ventilatory support as the clinical and radiologic manifestations of the acute respiratory distress syndrome resolved.

Approximately 1 month after infusion, morphologic remission of leukemia (minimal residual disease, <0.01%) was achieved.

Remission has been sustained.
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

Shannon L. Maude, M.D., Ph.D., Theodore W. Laetsch, M.D., Jochen Buechner, M.D., Ph.D., Susana Rives, M.D., Ph.D., Michael Boyer, M.D., Henrique Bittencourt, M.D., Ph.D., Peter Bader, M.D., Michael R. Verneris, M.D., Heather E. Stefanski, M.D., Ph.D., Gary D. Myers, M.D., Muna Qayed, M.D., Barbara De Moerloose, M.D., Ph.D., Hidefumi Hiramatsu, M.D., Ph.D., Krysta Schlis, M.D., Kara L. Davis, D.O., Paul L. Martin, M.D., Ph.D., Eneida R. Nemecek, M.D., Gregory A. Yanik, M.D., Christina Peters, M.D., Andre Baruchel, M.D., Nicolas Boissel, M.D., Ph.D., Francoise Mechinaud, M.D., Adriana Balduzzi, M.D., Joerg Krueger, M.D., Carl H. June, M.D., Bruce L. Levine, Ph.D., Patricia Wood, M.D., Ph.D., Tetiana Taran, M.D., Mimi Leung, M.P.H., Karen T. Mueller, Pharm.D., Yiyun Zhang, Ph.D., Kapildeb Sen, Ph.D., David Lebwohl, M.D., Michael A. Pulsipher, M.D., and Stephan A. Grupp, M.D., Ph.D.
25-center, global study of tisagenlecleucel in pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL. The primary endpoint was the overall remission rate.

75 patients received an infusion of tisagenlecleucel, with a median time from enrollment to infusion of 45 days.

- median age of 11 years (range, 3 to 23)
- median of 3 previous therapies (range, 1 to 8)
- median marrow blast percentage of 74% (range, 5 to 99)
- 46 patients (61%) had undergone previous allogeneic hematopoietic stem-cell transplantation

The overall remission rate was 81%. 60% had complete remission and 21% had complete remission with incomplete hematologic recovery. All patients who had a best overall response of complete remission with or without complete hematologic recovery were negative for minimal residual disease; 95% (58 of 61) of these patients were negative by day 28.

- relapse-free survival among patients with a response to treatment was 80% at 6 months and 59% at 12 months

- overall survival among the 75 patients who received tisagenlecleucel was 90% at 6 months and 76% at 12 months after infusion

- median duration of persistence of tisagenlecleucel in blood was 168 days (range, 20 to 617 days; 60 patients)

Duration of Remission, Event-free Survival, and Overall Survival.

Adverse events of special interest included:

- cytokine release syndrome
- neurologic events
- cytopenias not resolved by day 28
- infections
- tumor lysis syndrome

67 of 75 patients (89%) had an adverse event of special interest within 8 weeks after infusion.
Cytokine Release Syndrome

- occurred in 58 of 75 patients (77%)
- the median time to onset was 3 days (range, 1 to 22)
- median duration was 8 days (range, 1 to 36)

35 of 75 patients (47%) were admitted to the intensive care unit (ICU) for CRS

- median stay of 7 days (range, 1 to 34)
- 25% treated with high-dose vasopressors
- 44% received oxygen supplementation
- 13% received mechanical ventilation
- 9% underwent dialysis
- 37% received tocilizumab

Neurologic events occurred in 30 of 75 patients (40%) within 8 weeks after infusion. Ten patients (13%) had grade 3 neurologic events; no grade 4 events reported.

The most common neurologic events of any grade were:

- encephalopathy (11%)
- confusional state (9%)
- delirium (9%)
- tremor (8%)
- agitation (7%)
- somnolence (7%)
- 1 patient had a seizure (grade 3)

Among grade 3 neurologic episodes that resolved, 50% resolved within 10 days, and 75% resolved within 18 days. Neurologic events were managed with supportive care after ruling out other potential causes of the symptoms.

Conclusions

• In this global study of CAR T-cell therapy, a single infusion of tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects.
Original Article

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma


N Engl J Med
Volume 377(26):2531-2544
December 28, 2017
ZUMA-1

101 patients received axi-cel, median age 58, range 23-76

- diffuse large B-cell lymphoma n=77
- primary mediastinal B-cell lymphoma n=8
- transformed follicular lymphoma n=16

Patients had refractory disease which was defined as progressive or stable disease as the best response to the most recent chemotherapy regimen or disease progression or relapse within 12 months after autologous stem-cell transplantation

- 77% had disease that was resistant to second-line or later therapies
- 21% had disease relapse after transplantation
- 69% had received at least three previous therapies
- 26% had a history of primary refractory disease

101 patients received axi-cel

- objective response rate 82%
- complete response rate 54%
- median time to response 1.0 month (range, 0.8 to 6.0)
- median duration of response 8.1 months
- progression-free survival 49% at 6 months, 44% at 12 months
- overall survival 78% at 6 months, 59% at 12 months, and 52% at 18 months

Of the patients who did not have a complete response at the time of the first tumor assessment (1 month after the infusion of axi-cel), 23 patients (11 of 35 with a partial response and 12 of 25 with stable disease) subsequently had a complete response in the absence of additional therapies as late as 15 months after treatment.

Kaplan–Meier Estimates of the Duration of Response, Progression-free Survival, and Overall Survival.
Objective Response Rate among the 101 Treated Patients.

### A Objective Response Rate

<table>
<thead>
<tr>
<th>Best Response (%)</th>
<th>ORR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>ORR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>ORR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>32</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>28</td>
<td>11</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
</tr>
</tbody>
</table>

### B Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients Who Could be Evaluated</th>
<th>No. of Patients with Event</th>
<th>Objective Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>101</td>
<td>83</td>
<td>0.82 (0.73–0.89)</td>
</tr>
<tr>
<td>Refractory subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to second-line therapy</td>
<td>78</td>
<td>65</td>
<td>0.83 (0.73–0.91)</td>
</tr>
<tr>
<td>Relapse after ASCT</td>
<td>21</td>
<td>16</td>
<td>0.76 (0.53–0.92)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>77</td>
<td>61</td>
<td>0.79 (0.68–0.88)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>24</td>
<td>22</td>
<td>0.92 (0.73–0.99)</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>15</td>
<td>13</td>
<td>0.87 (0.60–0.98)</td>
</tr>
<tr>
<td>III or IV</td>
<td>86</td>
<td>70</td>
<td>0.81 (0.72–0.89)</td>
</tr>
<tr>
<td>IPI risk score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>53</td>
<td>46</td>
<td>0.87 (0.75–0.95)</td>
</tr>
<tr>
<td>3 or 4</td>
<td>48</td>
<td>37</td>
<td>0.77 (0.69–0.88)</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>56</td>
<td>0.80 (0.69–0.89)</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>27</td>
<td>0.87 (0.70–0.96)</td>
</tr>
<tr>
<td>Bulky disease (≥10 cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>12</td>
<td>0.71 (0.44–0.90)</td>
</tr>
<tr>
<td>No</td>
<td>84</td>
<td>71</td>
<td>0.85 (0.75–0.91)</td>
</tr>
<tr>
<td>Treatment history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary refractory disease</td>
<td>26</td>
<td>23</td>
<td>0.88 (0.70–0.98)</td>
</tr>
<tr>
<td>Refractory to two consecutive lines</td>
<td>54</td>
<td>42</td>
<td>0.78 (0.64–0.88)</td>
</tr>
<tr>
<td>CD19 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>74</td>
<td>63</td>
<td>0.83 (0.75–0.92)</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>6</td>
<td>0.75 (0.35–0.97)</td>
</tr>
<tr>
<td>CD19 histologic score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤150</td>
<td>26</td>
<td>22</td>
<td>0.85 (0.65–0.96)</td>
</tr>
<tr>
<td>&gt;150</td>
<td>56</td>
<td>47</td>
<td>0.84 (0.72–0.92)</td>
</tr>
<tr>
<td>Cell of origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germinal center B-cell-like subtype</td>
<td>49</td>
<td>43</td>
<td>0.88 (0.75–0.95)</td>
</tr>
<tr>
<td>Activated B-cell-like subtype</td>
<td>17</td>
<td>13</td>
<td>0.76 (0.50–0.93)</td>
</tr>
<tr>
<td>CD4:CD8 ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>47</td>
<td>41</td>
<td>0.87 (0.74–0.95)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>52</td>
<td>40</td>
<td>0.77 (0.63–0.87)</td>
</tr>
<tr>
<td>Tocilizumab use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>36</td>
<td>0.84 (0.69–0.93)</td>
</tr>
<tr>
<td>No</td>
<td>58</td>
<td>47</td>
<td>0.81 (0.69–0.90)</td>
</tr>
<tr>
<td>Glucocorticoid use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>21</td>
<td>0.78 (0.58–0.91)</td>
</tr>
<tr>
<td>No</td>
<td>74</td>
<td>62</td>
<td>0.84 (0.73–0.95)</td>
</tr>
</tbody>
</table>
All 101 patients who had received axi-cel had adverse events, grade 3 or higher in 95%.

The most common adverse events of grade 3 or higher were neutropenia (in 78%), anemia (in 43%), and thrombocytopenia (in 38%).

43% of patients received tocilizumab and 27% received glucocorticoids for the management of the cytokine release syndrome, neurologic events, or both, with no apparent effect on overall or ongoing response rates.
The cytokine release syndrome occurred in 94 patients (93%) 
- 9% of grade 3 and 3% of grade 4, most commonly fever, hypoxia, hypotension  
- Vasopressors were used in 17% of the patients.  
- Median time after infusion until the onset of CRS was 2 days (range, 1 to 12)  
- Median time until resolution was 8 days

Neurologic events occurred in 65 patients (64%);  
- 28% were grade 3 or higher, most commonly encephalopathy, confusion, aphasia  
- median onset of neurologic events occurred on day 5 (range, 1 to 17)  
- median resolution on day 17
Conclusions

- In this multicenter study, patients with refractory large B-cell lymphoma who received CAR T-cell therapy with axi-cel had high levels of durable response, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events.
JCAR017 is a CD19-directed 4-1BB CAR T cell product administered in a defined composition at a precise dose of CD8 and CD4 CAR T cells.

69 DLBCL NOS (de novo or transformed from indolent lymphoma, PMBCL, FL grade 3B) patients were treated.

No acute infusional toxicity occurred, and the majority of patients, 64% (44/69), had no CRS or NT, suggesting outpatient delivery of JCAR017 may be feasible. No patients had Gr 3 CRS and only one (1%, 1/69) had Gr 4 CRS and required ICU care. Of the 20% of patients with NT, 6% (4/69) had Gr 1-2 and 14% (10/69) had Gr 3-4; 2 (3%) had seizure.

All CRS and NT events resolved except one case of Gr 1 tremor, which was ongoing at the time of data cutoff. Overall, <20% required anti-cytokine therapy (tocilizumab alone 1 (1%), dexamethasone alone 6 (9%), and both 6 (9%)) and only one required any vasopressor support.
Three-step approach to the assessment and management of acute toxicities associated with chimeric antigen receptor (CAR)-T-cell therapy

Step 1
- CRS
  - Fever
  - Hypotension
  - Hypoxia
  - Organ toxicity
    - Cardiac
    - Respiratory
    - Gastrointestinal
    - Hepatic
    - Renal
    - Dermatological
    - Coagulopathy

- CRES
  - CARTOX-10
    - Orientation/alertness
    - Name objects
    - Writing
    - Counting
  - Seizures
    - Convulsive
    - Non-convulsive
  - Increased ICP
    - CSF opening pressure
    - Papilloedema
    - Cerebral oedema
  - Motor weakness

- HLH/MAS
  - Ferritin level
  - Hepatic toxicity
  - Renal toxicity
  - Pulmonary toxicity
  - Haemophagocytosis

Step 2
- Grade CRS
- Grade CRES
- Grade organ toxicity as per CTCAE

Step 3
- Manage according to grade of CRS
- Manage according to grade of CRES
- Manage HLH/MAS as per algorithm

Treatment algorithm for management of CRS based on the revised CRS grading system.

**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**

- **Extensive co-morbidities or older age?**
  - Yes
    - **Vigilant supportive care**
    - + Tocilizumab
    - ± corticosteroids
  - No
    - **Vigilant supportive care**
    - - Assess for infection
      - (Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)


©2014 by American Society of Hematology
CAR T-cell therapy program

- PBMC collection--apheresis
- Pharmacy
- Toxicity management
- Nursing services
- FACT/CIBMTR accreditation/REMS
- Social work
- Consultant support-- Critical care, Neurology, ID, Cardiology, ED
Kymriah $475,000     Yescarta $373,000

1. All major payers have approved coverage for CAR-T therapy.
2. Cost for CAR-T therapy very high, so major payers are accessing Transplant Network agreements for this treatment (Optum, Aetna Institutes of Excellence, CIGNA LifeSource, etc).
3. Most manufacturer protocols are for CAR-T cells to be reinfused in a hospital transplant setting, so for now the billing and collections risk is on the hospital, not the physician. With experience and more data, the therapy could be given in the outpatient setting, which would transfer the cell acquisition, billing and collection to the physician practice.
4. Insurers are not agreeing to mark-up on the cost of CAR-T, so expect for this to be a pass-through or cost plus a nominal fee for “shipping and handling”.

- Chris Henderson, Exec Dir Payer and Public Health Relations, Texas Oncology
Clinical case study

Ex vivo cell processing

T cells are transduced with an expression vector containing a gene encoding the CAR construct

CAR T cells are grown in culture (closed system)

Patient’s T cells are collected by leukapheresis

Patient receives chemotherapy

Patient receives infusion of CAR T cells

Modified conditioning regimens
- Optimize CAR-T-cell efficacy
- Minimize toxicity

Addition of pharmacological agents following cell infusion
- Checkpoint inhibition with PD-1 or PD-L1 inhibitors
- Ibrutinib
- Infusion of immunostimulatory cytokines, such as IL-15

Modifications in CAR design
- Less immunogenic scFv
- Evaluation of different co-stimulatory domains (CD28, 4-1BB, ICOS, OX40)
- Optimize structure of hinge region
- Expand repertoire of CAR target antigens (e.g., CD20, CD22, CD30, and κ-light chain)

Improvements in vector design
- Incorporation of suicide genes to enhance safety
- Gene-editing technologies to increase efficacy and decrease toxicity (CRISPR/Cas9)

Changes in cell-culture methods
- Production of a cell product with a defined CD4⁺:CD8⁺ T-cell ratio
- Generation of less-differentiated central memory T-cell subsets
CAR T CELLS IN MULTIPLE MYELOMA

Jesús G. Berdeja, M.D.
Director of Multiple Myeloma Research
Sarah Cannon Research Institute
Tennessee Oncology
Improving Survival in MM

Adapted from Kumar SK et al. Leukemia. 2014;28:1122.
Despite Progress in Multiple Myeloma
There Remains a Need for New Therapies

Analysis of Real-World Data on Overall Survival in Multiple Myeloma Patients With ≥3 Prior Lines of Therapy Including a Proteasome Inhibitor (PI) and an Immunomodulatory Drug (IMiD), or Double Refractory to a PI and an IMiD.

“Although newer PIs and IMiDs, such as carfilzomib and pomalidomide, have been introduced into the treatment regimen, our study of real-world data from electronic medical records of two independent U.S. databases suggests that median OS durations remain poor (approximately 8 months) in patients with MM who are heavily pretreated, those refractory to a PI and an IMiD, or both.”

Current U.S. Standard of Care in 4\textsuperscript{th} Line MM

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Pomalyst and dex. (Pomalyst Product Monograph)</th>
<th>Daratumamab (Lancet 2016, Lonial, S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Tx</td>
<td>5 (2-14)</td>
<td>5 (2-14)</td>
</tr>
<tr>
<td>CR Rate (%)</td>
<td>&lt;1%</td>
<td>~3%</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>23.5%</td>
<td>29%</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>3.6 months</td>
<td>3.7 months</td>
</tr>
</tbody>
</table>

Current U.S. Standards of Care For Multiple Myeloma

4\textsuperscript{th} Line of Therapy
CAR T Cells against CD19 for Multiple Myeloma.
CASE Report

“A patient with refractory multiple myeloma received an infusion of CTL019 cells, a cellular therapy consisting of autologous T cells transduced with an anti-CD19 chimeric antigen receptor, after myeloablative chemotherapy (melphalan, 140 mg per square meter of body-surface area) and autologous stem-cell transplantation.

Four years earlier, autologous transplantation with a higher melphalan dose (200 mg per square meter) had induced only a partial, transient response. Autologous transplantation followed by treatment with CTL019 cells led to a complete response with no evidence of progression and no measurable serum or urine monoclonal protein at the most recent evaluation, 12 months after treatment. This response was achieved despite the absence of CD19 expression in 99.95% of the patient's neoplastic plasma cells.”

Rationale for CTL019 in Multiple Myeloma

- **CTL019**: Anti-CD19 CAR T cells (lentiviral gene transfer, CD3zeta/4-1BB signaling domains) with clinical activity in advanced CLL, ALL, and NHL.
- Dominant population of myeloma plasma cells is CD19-negative in nearly all cases.
- Minor CD19+ components of the myeloma clone can be identified in patients.
- CD19+ subsets may have cancer stem cell properties.
- **Hypothesis**: CTL019 would prolong response to standard therapy by depleting a minor CD19+ population of MM cells with cancer stem cell properties.
### Study Design and Patient Characteristics

**Eligibility Criteria**
- Multiple Myeloma
- Progression within one year of prior ASCT
- Age < 70
- Fit for 2nd ASCT

**Primary Endpoints**
- Safety (CRS, neurotoxicity)
- Feasibility (manufacturing success)

**Secondary Endpoints**
- CTL019 engraftment and B cell aplasia
- Day 42 and day 100 response
- Progression-free survival (vs. last ASCT)
- Correlation of response to CD19 expression

<table>
<thead>
<tr>
<th>ID</th>
<th>Age/Sex</th>
<th>TTP1 (days)</th>
<th>Prior Tx</th>
<th>Baseline Prognostic Features</th>
<th>Mel. Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48F</td>
<td>181</td>
<td>10</td>
<td>Complex karyotype, t(4;14), del17p, +1q21</td>
<td>140</td>
</tr>
<tr>
<td>2</td>
<td>58M</td>
<td>341</td>
<td>7</td>
<td>Complex karyotype, BRAFV600E</td>
<td>200</td>
</tr>
<tr>
<td>3</td>
<td>65F</td>
<td>210</td>
<td>3</td>
<td>Plasma cell leukemia</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>64F</td>
<td>127</td>
<td>7</td>
<td>t(4;14), +1q, &lt;PR to induction</td>
<td>140</td>
</tr>
<tr>
<td>5</td>
<td>53M</td>
<td>100</td>
<td>2</td>
<td>BRAF V600E mutation</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>62F</td>
<td>342</td>
<td>6</td>
<td>Not available</td>
<td>140</td>
</tr>
<tr>
<td>7</td>
<td>57F</td>
<td>334</td>
<td>4</td>
<td>t(4;14), +1q</td>
<td>200</td>
</tr>
<tr>
<td>8</td>
<td>62M</td>
<td>266</td>
<td>4</td>
<td>t(4;14), +1q</td>
<td>140</td>
</tr>
<tr>
<td>9</td>
<td>68F</td>
<td>249</td>
<td>10</td>
<td>del(17p), +1q</td>
<td>140</td>
</tr>
<tr>
<td>10</td>
<td>59M</td>
<td>325</td>
<td>6</td>
<td>Not available</td>
<td>200</td>
</tr>
</tbody>
</table>

Penn Medicine
Clinical Responses

- 2/10 subjects had substantially longer progression-free survival after ASCT + CTL019 compared to prior ASCT.
- Compares favorably with historical cohort of 18 salvage transplants in “modern era,” where no subjects exhibited longer PFS compared to prior ASCT.
BCMA – A Promising Target in Multiple Myeloma

- BCMA is member of the TNF receptor superfamily
  - Receptor for BAFF and APRIL
  - Promotes plasma cell pathogenesis
  - Expressed nearly universally on multiple myeloma cells
  - Expression largely restricted to plasma cells and some mature B cells

Multiple myeloma cells expressing BCMA
(brown color = BCMA protein)
### BCMA-Directed CAR T Cells in Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>NCI (NOVARTIS)</th>
<th>PENN BLUEBIRD</th>
<th>BB2121 BLUEBIRD</th>
<th>LCAR-B38M LEGEND</th>
<th>MCARH171 MSK/JUNO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TARGET</strong></td>
<td>BCMA</td>
<td>BCMA</td>
<td>BCMA</td>
<td>BCMA (2 epitopes)</td>
<td>BCMA</td>
</tr>
<tr>
<td>Ag-binding domain</td>
<td>scFv (M)</td>
<td>scFv (H)</td>
<td>scFv (M)</td>
<td>2-VHH (H)</td>
<td>scFv (H)</td>
</tr>
<tr>
<td><strong>VECTOR</strong></td>
<td>Y-Retroviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
</tr>
<tr>
<td># Cell Doses</td>
<td>1</td>
<td>1 (10/30/60)</td>
<td>1</td>
<td>1 (20/30/50)</td>
<td>1</td>
</tr>
<tr>
<td>Lymphodepletion</td>
<td>Flu/Cy</td>
<td>+/- Cy</td>
<td>Flu/Cy</td>
<td>*Flu/Cy</td>
<td>Flu/Cy</td>
</tr>
<tr>
<td>Indication</td>
<td>R/R</td>
<td>R/R</td>
<td>R/R</td>
<td>R/R</td>
<td>R/R</td>
</tr>
<tr>
<td>BCMA High Required</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

## BCMA-Directed CAR T Cells in Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>NCI (NOVARTIS)</th>
<th>PENN BLUEBIRD</th>
<th>BB2121 BLUEBIRD</th>
<th>LCAR-B38M LEGEND</th>
<th>MCARH171 MSK/JUNO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>26 (16*)</td>
<td>24 (19*)</td>
<td>21 (18*)</td>
<td>35 (30*)</td>
<td>6</td>
</tr>
<tr>
<td># Prior Tx</td>
<td>10</td>
<td>7</td>
<td>7</td>
<td>3-4</td>
<td>7.5</td>
</tr>
<tr>
<td>CART Dose</td>
<td>9x10^6/kg</td>
<td>1-5x10^8</td>
<td>150-800 x10^6</td>
<td>Varied</td>
<td>?</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>81%*</td>
<td>53%*</td>
<td>94%*</td>
<td>100%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>18%</td>
<td></td>
<td>56%</td>
<td>63% (sCR)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>CRS (All Grades)</strong></td>
<td>81%</td>
<td>83%</td>
<td>71%</td>
<td>83%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>CRS (Gr 3/4)</strong></td>
<td>37%</td>
<td>33%</td>
<td>10%</td>
<td>5.7%</td>
<td>None</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>19%</td>
<td>25%</td>
<td>24%</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Responses at therapeutic CAR T Dose Levels

CRB-401 Study Design and Status

Expansion Cohort Initiated in August 2017

- 12 additional patients have been collected and dosed in the Expansion Cohort as of 02 Nov 2017

3 + 3 Dose Escalation of CAR+ T Cells

- 50 x 10^6
- 150 x 10^6
- 450 x 10^6
- 800 x 10^6
- 1200 x 10^6 (*dose cohort no longer planned)

Leukapheresis

Screening

bb2121 manufacturing

Manufacturing (10 days) + release

bb2121 infusion

1st Response Assessment (Wk 4)

Sample collections for T cell expansion & cytokines

Day 0

- Flu 30 mg/m^2
- Cy 300 mg/m^2

Days -5,-4,-3

BM BX (Wk 2)

BM BX (Wk 4)

Study Status (Escalation Phase)

- Cells Collected N=24
- Clinical deterioration prior to infusion n=3
- Dosed N=21
- Evaluable for Response N=21

Manufacturing success rate of 100%
Baseline Demographics, Clinical Characteristics and Treatment History from Dose Escalation

21 patients have received bb2121 as of the data cut-off of October 2, 2017. Median follow-up is 35 weeks (min, max: 6.6, 69)

### Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Dosed Patients (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median (min, max)</td>
<td>58 (37, 74)</td>
</tr>
<tr>
<td>Male</td>
<td>n (%)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>Median (min, max)</td>
<td>4 (1.3, 15.8)</td>
</tr>
<tr>
<td>ECOG PS$^1$</td>
<td>n (%)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>ISS$^2$ stage</td>
<td>n (%)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>High-risk cytogenetics</td>
<td>n (%)</td>
<td>9 (43)</td>
</tr>
</tbody>
</table>

$^1$ECOG, Eastern Cooperative Oncology Groups Performance Status

$^2$ISS, International Staging System

### MM Treatment History

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Dosed Patients (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior lines of therapy</td>
<td>Median (range)</td>
<td>7 (3, 14)</td>
</tr>
<tr>
<td>Prior autologous SCT$^3$</td>
<td>n (%)</td>
<td>21 (100)</td>
</tr>
<tr>
<td>Prior Therapies</td>
<td>Exposed, n (%)</td>
<td>Refractory, n (%)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>21 (100)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>19 (91)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>21 (100)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>19 (91)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>15 (71)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Cumulative Exposure</td>
<td>Exposed, n (%)</td>
<td>Refractory, n (%)</td>
</tr>
<tr>
<td>Bort / Len</td>
<td>21 (100)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Bort / Len / Car</td>
<td>19 (91)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Bort / Len / Pom</td>
<td>19 (91)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Bort / Len / Car / Pom</td>
<td>18 (86)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Bort / Len / Car / Pom / Dara</td>
<td>15 (71)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

$^3$SCT, Stem Cell Transplant
• No dose-limiting toxicities (DLTs) observed in dose escalation.

Cytopenias mostly related to Cy/Flu lymphodepletion – Recovery to Grade < 3 cytopenias by Month 2 following infusion:

- ANC ≥1000/mm$^3$ – 70% of patients
- PLT ≥75/mm$^3$ – 75% of patients

• 5 deaths – 3 due to disease progression at 50×10$^6$ dose – 2 in patients treated at active doses in CR at the time of death (cardiac arrest, MDS following discontinuation)

• 14 patients experienced 1 or more SAEs – CRS* Grade 1-2 that required hospitalization per protocol (N=4) – Pyrexia (N=2)

---

#### Dose Escalation Patients (N = 21)$^1$

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Overall n (%)</th>
<th>Grade 3 or higher n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>15 (71)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Neurotoxicity$^2$</td>
<td>5 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18 (86)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (52)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (67)</td>
<td>12 (57)</td>
</tr>
</tbody>
</table>

$^1$Data cut-off of October 2, 2017
$^2$Neurotoxicity includes the preferred terms: depressed level of consciousness, confusional state, bradyphrenia, somnolence

*CRS uniformly graded according to Lee et al., Blood 2014;124:188-195
Robust bb2121 CAR+ T Cell Expansion with Persistence > 6 months

Vector Copies in CD3-enriched Peripheral Blood by Individual Patients

Median (Q1, Q3) Vector Copies in CD3-enriched Peripheral Blood by Dose Cohorts

- bb2121 persistence in 6 patients at 6 months and 1 patient at 12 months
- Peak bb2121 CAR+ T cell expansion higher at active dose levels

LLOQ = lower limit of quantitation
High Frequency of Deep and Durable Tumor Response in Active Dose Cohorts (150 – 800 × 10^6 CAR+ T Cells)

- 17/18 (94%) ORR, 10/18 (56%) CR at active doses
- 9/10 evaluable patients MRD negative
- Durable ongoing responses over 1 year
- Responses continue to improve as late as month 15 (VGPR to CR)
- Median PFS not reached in active dose cohorts
- 4 patients progressed
- Median follow up 40 weeks

* High Tumor Burden (>50% Bone Marrow Involvement)
### Legend LCAR-B38M patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>r/r MM patient, total number enrolled</td>
<td>35</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>55 (43-72)</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>19(54)</td>
</tr>
<tr>
<td>Number of prior lines of therapy, n(%)</td>
<td>14 (40)/ 16 (46)/ 5 (14)</td>
</tr>
<tr>
<td>3/4/≥5</td>
<td></td>
</tr>
<tr>
<td>Refractory subgroup, n(%)</td>
<td>35(100)</td>
</tr>
<tr>
<td>Refractory to ≥ 2nd line therapy</td>
<td></td>
</tr>
</tbody>
</table>

Zhang et al, EHA 2017
Safety: Major adverse events is cytokine release syndrome

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Patients (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS (All Grade)</td>
<td>29 (83%)</td>
</tr>
<tr>
<td>CRS Grade ≥3</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatal events excluding disease progression</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Zhang et al, EHA 2017
Efficacy follow-up of LCAR-B38M CAR-T cells

Patients Treated Before April 5, 2017

<table>
<thead>
<tr>
<th>Best Efficacy</th>
<th>Total</th>
<th>PR</th>
<th>VGPR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>100%</td>
<td>6.7%</td>
<td>30%</td>
<td>63.3%</td>
</tr>
<tr>
<td>30*</td>
<td>2</td>
<td>9</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

- 30 of 35 Patients evaluable for response
- 3 Patients have relapsed
- LCAR-B38M cells are undetectable in PB beyond 4 months post-infusion
- 5 Patients in sCR beyond 12 mos

Zhang et al, EHA 2017
Future Directions in Myeloma

● Race to FDA Approval
  ○ Global Pivotal Trial (KarMMa) is open for enrollment
    ■ bb2121 dose range: $150\text{ - }300 \times 10^6$ CAR+ T cells
  ○ Legend in partnership with Janssen soon to start pivotal trial of LCAR-B38M
  ○ Others not far behind

● Some of the New and Improved CARs in Clinical Trials
  ○ Bluebird has started trial with CRB-402/bb21217 - confer memory t cell phenotype
  ○ Autolus has a CAR that expresses the ligand APRIL and thus able to bind to both BCMA and TACI
  ○ Poseida has a CAR that uses centyrin molecule to bind BCMA and a nonviral method of encoding CAR (piggyBac™)
Future Directions

- **Improving Efficacy**
  - Understand mechanisms of resistance
  - Identify correlates to response & long-term survival
  - Next-generation or “armored” CAR T cells
  - Combination with immune checkpoint blockade

- **Improving Safety**
  - Identify correlates to predict and reduce rates of CRS & NTX
  - Safety switches to induce suicide or eliminate CAR T

- **Improving Access**
  - Allogeneic off-the-shelf CAR T
  - CAR T therapy for other stages of disease, new disease targets
  - Reducing cost of therapy
  - Providing therapy beyond the transplant centers
THANK YOU