CAR-T Therapy: The Past, The Present, and The Future

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WVU Medicine
Mary Babb Randolph Cancer Center
Objectives

- Review indications for FDA approved CAR-T therapy
- Become familiar with the CAR-T engineering process and administration processes
- Analyze clinical data for CAR-T therapy
- Outline place in therapy of CAR-T
- Create plans for the management of CAR-T toxicities
Emily Whitehead

NO ONE FIGHTS ALONE.
Breakthrough of the Year

Cancer Immunotherapy

T cells on the attack
CAR T-Cell Therapy: ASCO’s Advance of the Year
Chimeric Antigen Receptotor T-Cells (CAR-T)

- Chimeric Antigen Receptor (CAR): fusion protein containing T-cell signaling domains and an antigen recognition moiety

- CAR-T therapy modifies a patient’s own immune system (T cells) to fight cancer.
Engineering CAR-T

4-1BB:
- Enhances early expansion and long-term persistence in vitro
- Induces central memory T-cell differentiation for enduring protection and immnosurveillance in vitro
- Metabolic profile supports gradual sustained expansion (oxidative metabolism)

CD28/4-1BB:
- The impact of 4-1BB/CD28 combined costimulatory domains on expansion, persistence, and central memory is being investigated\(^1\)

This information is based on animal model data. No head-to-head comparisons of the clinical efficacy of these costimulatory domains have been conducted.

### Commercially Available Products

<table>
<thead>
<tr>
<th>Tisagenlecleucel (Kymriah®)</th>
<th>Axicabtagene Ciloleucel (Yescarta®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treatment of relapsed or refractory large B-cell lymphoma in adults (after ≥2 lines of systemic therapy)</td>
<td>• Treatment of relapsed or refractory large B-cell lymphoma in adults (after 2 or more lines of systemic therapy)</td>
</tr>
<tr>
<td>• Treatment of B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in patients up to 25 years of age.</td>
<td>• Anticipation of B-cell ALL indication</td>
</tr>
<tr>
<td>• 4-1BB/CD3-ζ costimulatory domain</td>
<td>• CD28/CD3-ζ costimulatory domain</td>
</tr>
<tr>
<td>• Novartis Pharmaceuticals Corp.</td>
<td>• Kite Pharma, Inc</td>
</tr>
</tbody>
</table>
Patient Eligibility

- FDA labeled indication for use
- Adequate performance status
- Absence of active infection
  - Influenza testing
- Sufficient organ function
  - Kidney, liver, heart, lung
Bridging to CAR-T

• May be necessary to control disease burden during manufacturing process
Lymphodepletion

Purpose:
- Depletion of endogenous lymphocytes with low-dose chemotherapy
- Enhance proliferation of infused CAR-T

Regimens:
- Fludarabine 25-30 mg/m²/day x 3-4 doses
  Cyclophosphamide 250-500 mg/m²/day x 2-3 doses
- Bendamustine 90 mg/m² x 2 days
- No lymphodepletion
CAR-T Infusion

- Cryopreservation of CAR-T product
- Currently no standard dose (may depend on indication)
  - $2 \times 10^5$ – $6 \times 10^8$ cells/kg
- Single vs multiple infusion bags
Toxicities

- CRS: Cytokine release syndrome
- CRES: CAR-T related encephalopathy syndrome
- TLS: Tumor lysis syndrome
- B-cell aplasia
- Infection

CRS: Cytokine release syndrome
CRES: CAR-T related encephalopathy syndrome
TLS: Tumor lysis syndrome
Cytokine Release Syndrome (CRS)

- Well-documented entity with CAR-T
- Usually reversible, but potentially life-threatening
- Related to T-cell expansion
- May correlate with efficacy

**Symptoms:**
- Fever
- Malaise
- Myalgias
- Hypotension
- Shock
- End organ damage
- Coagulopathy
## CRS Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Constitutional symptoms (ie. fever)</td>
</tr>
<tr>
<td>2</td>
<td>Hypotension responsive to fluids or low dose vasopressors FiO₂ &lt;40% Grade 2 organ toxicity</td>
</tr>
<tr>
<td>3</td>
<td>Hypotension requiring high dose vasopressors FiO₂ ≥ 40% and/or requiring BiPAP Grade 3 organ toxicity, Grade 3-4 transaminitis</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening hypotension Ventilator support Grade 4 organ toxicity</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Lee DW et al. Blood. 2014;124(2):188-95
# CRS Management

| Grade 1           | - Vigilant supportive care  
<table>
<thead>
<tr>
<th></th>
<th>- Treat fever and pain</th>
</tr>
</thead>
</table>
| Grade 2           | - Tocilizumab 8 mg/kg (max 800 mg) for hypotension refractory to fluid resuscitation  
|                  | - +/- vasopressors         
|                  | - Methylprednisolone 2 mg/kg if no clinical improvement after 12-18 hours of tocilizumab |
| Grade 3           | - Tocilizumab +/- methylprednisolone per Grade 2  
|                  | - Consider repeat tocilizumab dose  
|                  | - Consider siltuximab 11 mg/kg IV  |
| Grade 4           | - Tocilizumab + high-dose steroids + siltuximab + vasopressors |

Lee DW et al. Blood. 2014;124(2):188-95
Tocilizumab and CRS

- IL-6 receptor antagonist
- FDA approved for CAR-T induced CRS

Lee C et al. Blood. 2017;130(suppl 1) [abstract 2553].
Schuster SJ et al. Blood. 2017;130(suppl 1) [abstract 577].
Data on file, Novartis Pharmaceuticals Corp.
CRES: CARTOX-10 Assessment

**Orientation:** 5 points
- Year, month, city, hospital, President

**Identification:** 3 points
- Name 3 separate objects

**Writing:** 1 point
- Ability to write a standard sentence

**Counting:** 1 point
- Count backwards from 100 by ten
CRES Management

Grade 1-2
• Vigilant supportive care
• Consider tocilizumab if associated with CRS

Grade 3
• Transfer to ICU

Grade 4
• Consider corticosteroids for severe neurotoxicity not associated with CRS
REVIEW OF CLINICAL DATA
<table>
<thead>
<tr>
<th>Disease</th>
<th>Response Rate</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell acute lymphoblastic leukemia (in adults)</td>
<td>83–93</td>
<td>High initial remission rates; unresolved issue is whether CAR T-cell therapy is definitive therapy or should be followed by allogeneic hematopoietic stem-cell therapy</td>
<td>Park et al., Davila et al., Turtle et al.</td>
</tr>
<tr>
<td>B-cell acute lymphoblastic leukemia (in children)</td>
<td>68–90</td>
<td>Approximately 25% of patients reported to have a relapse with CD19-negative or CD19-low leukemia; CD22 CAR T cells may improve survival among some patients with CD19 relapses</td>
<td>Maude et al., Maude et al., Fry et al., Lee et al.</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>57–71</td>
<td>Relapse is rare in patients who have a complete response; ibrutinib appears to increase response rates</td>
<td>Porter et al., Turtle et al.</td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>64–86</td>
<td>Approximately 40–50% of patients reported to have a durable complete response</td>
<td>Turtle et al., Kochenderfer et al., Schuster et al., Neelapu et al.</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>71</td>
<td>At a median follow-up of 28.6 mo, the response was maintained in 89% of patients who had a response</td>
<td>Schuster et al.</td>
</tr>
<tr>
<td>Transformed follicular lymphoma</td>
<td>70–83</td>
<td>A total of 3 of 3 patients with transformed follicular lymphoma had a complete response</td>
<td>Turtle et al., Schuster et al., Neelapu et al.</td>
</tr>
<tr>
<td>Refractory multiple myeloma</td>
<td>25–100</td>
<td>B-cell maturation antigen CAR T cells; stringent complete response in approximately 25% of patients</td>
<td>Ali et al., Fan et al., Berdeja et al.</td>
</tr>
<tr>
<td><strong>Solid tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>ND</td>
<td>In case report from phase 2 study, complete response on magnetic resonance imaging after intravenous and cerebrospinal fluid administration of CAR T cells; response lasted 7.5 mo</td>
<td>Brown et al.</td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>17</td>
<td>In one patient with liver metastasis, CAR T-cell treatment produced a complete metabolic response in the liver but was ineffective against the primary pancreatic tumor</td>
<td>Beatty et al.</td>
</tr>
</tbody>
</table>
Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

ELIANA

Design
- Global, single arm, open-label, multicenter
- Phase II

Patients
- n=75 infused; 92 enrolled
- Median age (range): 11 years (3-23)
- Median prior therapies: 3 (46% had prior allogeneic HSCT)
- Median marrow blast percentage: 74%

Endpoints
- Primary: Overall remission rate
- Secondary: CR/Cri with MRD negativity; Duration or remission, EFS, OS

Response
- Overall remission rate (CR/Cri): 81% (median follow up 13.7 months)
- 60% achieved CR; 21% achieved Cri
- Engineered T-Cells detected up to 20 months out

<table>
<thead>
<tr>
<th>Event</th>
<th>≤8 Wk after Infusion (N = 75)</th>
<th>&gt;8 Wk to 1 Yr after Infusion (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 number of patients (percent)</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any grade 3 or 4 adverse event</td>
<td>19 (25)</td>
<td>33 (44)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>16 (21)</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (9)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Decrease in lymphocyte count</td>
<td>5 (7)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>5 (7)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Increase in blood bilirubin</td>
<td>8 (11)</td>
<td>---</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Decrease in neutrophil count</td>
<td>1 (1)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Decrease in white-cell count</td>
<td>---</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>3 (4)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Decrease in appetite</td>
<td>6 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>5 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6 (8)</td>
<td>---</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (1)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>4 (5)</td>
<td>---</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase</td>
<td>4 (5)</td>
<td>---</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>4 (5)</td>
<td>---</td>
</tr>
</tbody>
</table>
FDA Approval Brings 1st Gene Therapy to the United States
ZUMA 3

**Design**
- Multicenter, single arm, open-label
- Phase I/II
- R/R B-Cell ALL

**Patients**
- n=24
- **18 years and older**

**Endpoints**
- Primary: Overall complete remission rate
- Secondary: DOR, RFS, OS, MRD negative remission rates, Allo HSCT rate,

**Response**
- 17/24 patients (71%) with complete tumor remission (CR)
- 100% of responders were MRD negative

Shah B, et al. ASH 2017;Abstract 888
ZUMA 3

Response
- 17/24 patients (71%) with complete tumor remission (CR)
- 100% of responders were MRD negative

Adverse Events
- 8/29 (28%) Grade 3 or higher CRS
- 18/29 (52%) with neurological toxicity
- Two patients died – CVA (unrelated), fatal CRS

Shah B, et al. ASH 2017;Abstract 888
ZUMA 3

• In the subset of patients previously treated with Blinatumomab, 5/8 (63%) achieved CR/Cri and all 5 patients had MRD negative remissions
• KTE-C19 was also manufactured successfully in all patients
• Important to note that prior therapy directed against CD19 did not affect the manufacturing of the product

Shah B, et al. ASH 2017;Abstract 888
ZUMA 4

- Phase I/II
  - Actively recruiting
- Evaluating KTE-C19 (Yescarta) in pediatric and adolescent patients (age 2-21) with r/r B-Cell ALL
- Reported data on 4 treated patients:
  - All 4 patients MRD negative at 5 months
  - No dose limiting toxicity

Lee D.W., Ann Oncol 2017;28(suppl 5):v355-v371
# Adult ALL

<table>
<thead>
<tr>
<th></th>
<th>Blincyto</th>
<th>Inotuzumab</th>
<th>19-28Z CAR</th>
<th>19-41BB CAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>III</td>
<td>III</td>
<td>I/II</td>
<td>II</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>≥ 18</td>
<td>≥ 18</td>
<td>≥ 18</td>
<td>≤ 21</td>
</tr>
<tr>
<td>No. enrolled</td>
<td>271</td>
<td>141</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>No. evaluable</td>
<td>267</td>
<td>109</td>
<td>53</td>
<td>75</td>
</tr>
<tr>
<td>Follow-up (m)</td>
<td>11.7</td>
<td>NA</td>
<td>29</td>
<td>13.1</td>
</tr>
<tr>
<td>CR%</td>
<td>44</td>
<td>80.7</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>OS (m)</td>
<td>7.7</td>
<td>7.7</td>
<td>12.9</td>
<td>NR</td>
</tr>
<tr>
<td>CRS % (≥ grade 3)</td>
<td>4.9</td>
<td>NA</td>
<td>26</td>
<td>47</td>
</tr>
<tr>
<td>Neurotoxicity %</td>
<td>11</td>
<td>12</td>
<td>31</td>
<td>32</td>
</tr>
</tbody>
</table>
SCHOLAR-1

- Retrospective review of 636 patient with refractory NHL
  - Stable/progressive disease as best response to chemotherapy or relapse within 12 months of Auto-SCT
- ORR 26% with CR rate of only 7%
  - Lowest rates in patients with high IPI score or primary refractory disease
- Median OS 6.3 months
- 1 yr and 2 yr survival rates 28% and 20% respectively
Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma

Frederick L. Locke,1,8 Sattva S. Neelapu,2,8 Nancy L. Bartlett,3 Tanya Siddiqi,4 Julio C. Chavez,5 Chitra M. Hosing,6 Armin Ghabadi,3 Lihua E. Budde,4 Adrian Bot,7 John M. Rossi,7 Yizhou Jiang,7 Allen X. Xue,7 Meg Elias,7 Jeff Aycock,7 Jeff Wiezorek,7 and William Y. Go7

1Department of Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL 33612, USA; 2Division of Cancer Medicine, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; 3Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO 63110, USA; 4Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA 91010, USA; 5Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL 33612, USA; 6Division of Cancer Medicine, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; 7Kite Pharma, Santa Monica, CA 90404, USA
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

ZUMA – Phase 2

Design

• Global, multicenter, single arm, open-label
• Phase II
• r/r Diffuse Large B-Cell Lymphoma. Primary Mediastinal Lymphoma, or transformed Follicular Lymphoma

Patients

• n=101 (received infusion) and included in modified intention-to-treat analysis
• At least 2 lines of therapy; progressive/stable disease to most recent therapy or relapse within 12 months of Auto-SCT
• Median age: 58 (range 23-76)
• 85% with stage III/IV disease
• 77% resistant to second line or later therapies; 69% received at least 3 lines
• 21% of patients had prior auto-SCT

Endpoints

• Primary: Overall Response Rate (CR + PR)
• Secondary: DOR, PFS, OS, Safety, Biomarker assessment

ZUMA 1 – Phase 2

A. Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>ORR (N=77)</th>
<th>SD (N=77)</th>
<th>PD (N=77)</th>
<th>NE (N=77)</th>
<th>ORR (N=24)</th>
<th>SD (N=24)</th>
<th>PD (N=24)</th>
<th>NE (N=24)</th>
<th>ORR (N=101)</th>
<th>SD (N=101)</th>
<th>PD (N=101)</th>
<th>NE (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>32 (25%)</td>
<td>12 (9%)</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
<td>83 (17%)</td>
<td>8 (2%)</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
<td>82 (28%)</td>
<td>11 (11%)</td>
<td>5 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>PMBCL or TFL</td>
<td>12 (3%)</td>
<td></td>
<td></td>
<td></td>
<td>71 (17%)</td>
<td></td>
<td></td>
<td></td>
<td>54 (55%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend:
- Complete response
- Partial response
- Stable disease
- Disease progression
- Could not be evaluated

ZUMA 1 – Phase 2

C Overall Survival

Overall Survival (%)

No. at Risk

108 105 102 101 98 91 84 82 78 74 72 66 63 51 40 30 23 16 11 8 4 3 3 3 2 1 0

Months

Median (95% CI)

mo
NR (12.0–NE)

# ZUMA 1 – Phase 2

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 1 or 2</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurologic event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>65 (64)</td>
<td>37 (37)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>34 (34)</td>
<td>13 (13)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>29 (29)</td>
<td>20 (20)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Tremor</td>
<td>29 (29)</td>
<td>28 (28)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>18 (18)</td>
<td>11 (11)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Sornolence</td>
<td>15 (15)</td>
<td>8 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Agitation</td>
<td>9 (9)</td>
<td>5 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>7 (7)</td>
<td>6 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mental-status change</td>
<td>6 (6)</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Cytokine release syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>94 (93)</td>
<td>81 (80)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>77 (76)</td>
<td>66 (65)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>41 (41)</td>
<td>32 (32)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>22 (22)</td>
<td>13 (13)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>21 (21)</td>
<td>20 (20)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chills</td>
<td>20 (20)</td>
<td>20 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>8 (8)</td>
<td>8 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>
Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

KYMRIAH

- Single center (U Penn) case series
- Evaluating CD19+ DLBCL/FL patients with no curative options, limited options, and partial/no response to most recent therapy
- Objectives: Overall Response Rate at 3 months
  - Secondary: PFS, DOR, Estimated OS
- 23 DLBCL patients enrolled, 14 received therapy
- Response: 50% had noted response.
  - 6/14 had complete response by 6 months (sustained)

JULIET

Design

- Global, multicenter, single arm, open-label
- Phase II
- r/r Diffuse Large B-Cell Lymphoma (including transformed FL)

Patients

- n=81 (evaluated); 99 patients infused (18 outside US, not part of primary analysis)
- At least 2 lines of therapy and ineligible for/failed Auto-SCT
- Median age: 56 (23 patients > 65)
- 77% with stage III/IV disease
- Median lines of therapy: 3
- 47% of patients had prior auto-SCT

Endpoints

- Primary: Best Overall Response Rate
- Secondary: DOR, OS, Safety
JULIET

- Study Schema

Screening
Apheresis and Cryopreservation

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Bridging Chemotherapy

Enrollment

CTL019 Manufacturing

Restaging Lymphodepletion

CTL019 Infusion

Safety and Efficacy Follow-Up

Imaging at months 1, 3, 6, 9, 12...

WVUMedicine

JULIET

- Efficacy
  - ORR: 53%; CR 39.5%
  - Median DOR: Not reached; 6 mo relapse free rate 73.5%
  - Median OS: Not reached; 6 mo survival rate 64.5%
JULIET

- Safety
  - CRS: Grade 3 – 15%; Grade 4 – 8%
    - 15% received Tocilizumab; 11% received steroids
  - Neurologic events: Grade 3 – 8%; Grade 4 – 4%
  - No deaths from CRS of neurologic event

The first FDA-approved CAR-T cell therapy now has 2 indications

**KYMRIAH**
(tisagenlecleucel) Suspension for IV infusion

**NOW APPROVED in adults with relapsed/refractory DLBCL**
Acute Lymphoblastic Leukemia

- Currently only Kymriah (CTL-019) has approval for ALL
  - B-Cell ALL in second or later relapse in patients up to 25 years old
THERAPEUTIC ROLE for CAR-T

Diffuse Large B-Cell Lymphoma

• Both products (Kymriah and Yescarta) currently have indications in r/r Large Cell Lymphoma
  • At least two lines of therapy
  • Previously failed or not candidate for Auto-SCT
• Zuma 7 could answer question about efficacy vs Auto-SCT after first relapse
Obstacles and Limitations

• Manufacturing turnaround time
• Cost
• Lack of payment model
• Authorization
CAR-T in Multiple Myeloma

CAR-BCMA

- CD28/CD3ζ, γ-retroviral vector
- n=16,
- number of prior regimens (median): 9.5
- 63% refractory to last treatment regimen
- ORR=81%, CR+VGPR=63%

Brudno et al. JCO 2018
CARs in the Future

- Availability in numerous malignancies
- “Off the shelf” CAR-T
- Precise dosing (patient specific preferred)
- On/Off switch
Future Directions

**Multiple Myeloma**
- CRB-401: multicenter, phase 1
- Bb2121 targeting anti-B-cell maturation antigen (BCMA)
- Number of prior regimens (median): 8
- ORR = 95.5%, sCR/CR = 50%
- Median duration of response = 10.8 months

**Acute Myeloid Leukemia**

**Follicular Lymphoma**
- JULIET, ZUMA
Future Directions

Breast cancer
- Targets: CEA, mesothelin
- NCT02792114

Pancreatic cancer
- Anti-mesothelin
- NCT02930993
Capabilities at WVU

- Kymriah product
  - Both indications
- First patient received cell infusion in September 2018 for DLBCL indication
Conclusions

• CAR-T available in specialized centers
• Novel treatment demonstrates significant clinical response
• Definitive place in therapy to be determined
• CAR-T technology is continuing to evolve
• Expansion of CAR-T into various malignancies
THANK YOU
QUESTIONS?