Cellular Immunotherapy for B-cell Malignancies

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Manifestations of WM Disease

- ↓Hb, ↓PLT, ↓WBC

- Bone Marrow

- Adenopathy, splenomegaly, ≤20% at diagnosis; 50-60% at relapse.

- Hepcidin, ↓Fe Anemia

- Hyperviscosity Syndrome:
  - Epistaxis, Headaches
  - Impaired vision
  - >6,000 mg/dL or >4.0 CP

- IgM Neuropathy (22%)
- Cryoglobulinemia (10%)
- Cold Agglutinemia (5%)


Presented By Steven Treon at 2016 ASCO Annual Meeting
Multiple Myeloma and Lymphoma are Characterized by Significant Immune Dysfunction

Lymphoma and myeloma may be promoted by:
• Compromised immune function\(^1-6\)
  – Abnormal cytokine profiles
  – Defective T cell activation due to increased expression of PD-1 and TGFbeta
  – Down regulation of NKG2D
• Decreased immune surveillance\(^1,2,6\)
  – Impaired APCs
• Aberrant stromal cell support\(^3,7\)
  – Myeloid-derived suppressor cells

Alterations in cytokines (eg, increased IL-6, decreased IL-2, decreased IFN-\(\gamma\)), myeloid-derived suppressor cells and growth factors\(^1-4,7,8\)

IFN, interferon; IL, interleukin; NK, natural killer; PD, programmed death.

Immunologic Approaches to Overcome Self Tolerance in Lymphoma

Checkpoints Inhibition Therapies

Cytokine Therapy
- IL-2, IFN
- IL-7, IL-15, IL-21

Therapeutic Vaccines
- Dendritic cell vaccines
- DNA, RNA, Engineered tumor cells

ACT Therapies

TILs

CAR T cells

TCR T Cells

Monoclonal Antibodies (Rituxan Dara/ELO/) +

Antibody-drug conjugates (Gentuzumab ozogamicin)

Chemotherapy + IMIDs

Treg MDSC

# Common rituximab based regimens for primary therapy of WM

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>VGPR/CR</th>
<th>TTP (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab x 4</td>
<td>25-30%</td>
<td>0-5%</td>
<td>13</td>
</tr>
<tr>
<td>Rituximab x 8</td>
<td>40-45%</td>
<td>5-10%</td>
<td>16-22</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide CDR</td>
<td>70-80%</td>
<td>20-25%</td>
<td>30-36</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogues FR</td>
<td>70-90%</td>
<td>20-30%</td>
<td>36-62</td>
</tr>
<tr>
<td>Rituximab/Proteasome Inhibitor BDR, VR</td>
<td>70-90%</td>
<td>20-40%</td>
<td>&gt;42-52</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>90%</td>
<td>30-40%</td>
<td>69</td>
</tr>
</tbody>
</table>

Rationale for Cellular Immunotherapy in Lymphoma

1. Novel agents and autoSCT extend survival but progression is common

2. T and NK cells from lymphoma and myeloma patients can kill autologous myeloma cells ex vivo

3. Allogeneic SCT may “cure” lymphoma and myeloma by a T-cell graft vs tumor effect
   - high morbidity and mortality
   - usually associated with GVHD

4. Perhaps if we could engineer our own immune cells to specifically attack myeloma we would get the good graft vs lymphoma effect without the GVHD.

Adoptive T cell therapy (three major approaches)

- June et al Sci Trans Med 2015
Anatomy of a CAR (Gill and June, CCR 2015)

Ectodomain (antigen recognition)
- Light (or heavy) chain: Derived from an scFv of known specificity
- Heavy (or light) chain
- Hinge region: Derived from CD8 or IgG4

Lipid bilayer

Transmembrane domain
- Derived from the transmembrane domain of CD8 or CD28

Endodomain (stimulation)
- Co-stimulatory molecule(s): None, one, or more of: CD27, CD28, ICOS, 4-1BB, OX40
- Stimulatory molecule: CD3 ζ chain or FcRy chain
CD19 Expression: Normal B Cells and Related B Cell Malignancy

Bone Marrow

Pluripotent Stem Cell  Lymphoid Stem Cell  Pre-B Cell  B Cell  Activated B Cell  Plasma Cell

Lymph Node

Germinal Center

Antigen Expression: CD19  CD19  CD19  CD19  CD20  CD20

Precursor B Cell Acute Leukemias  Non Hodgkin & Hodgkin Lymphomas; Chronic Lymphocytic Leukemia, WM  Myeloma
2nd Generation CAR for B Cell Malignancy:

Autologous T Cells Transduced w/ Anti-CD19 Receptor Spliced to CD3 zeta and 4-1BB Signaling Domains

Lentiviral vector to deliver construct

CD3-ζ and 4-1BB signaling domains augments proliferation and survival

Anti-CD3/anti-CD28 mab coated bead stimulation (artificial DC)

CARs directed against CD19 have been tested in CLL and ALL
Targeting myeloma with Receptor Modified T cells (CARs)

- CARs combine an Ag recognition domain of antibody with intracellular signaling domain into single chimeric protein.
- Gene transfer (lentivirus vector) to stably express CAR on T cells confers novel Ag specificity.
Overview of activated/engineered T cell therapy

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

*Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

Courtesy of D. Porter
### Published Outcomes with Anti CD 19 CAR T cell Therapy

<table>
<thead>
<tr>
<th>Ref</th>
<th>Program/CAR</th>
<th>Population</th>
<th>Response</th>
<th>CRS</th>
<th>Neuro Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al. NEJM 2014</td>
<td>PENN 4-1BB</td>
<td>N=30 (ALL) 25Peds&amp;5Adults</td>
<td>CR=90%</td>
<td>100% CRS 27% Severe</td>
<td>43%</td>
</tr>
<tr>
<td>Davila et al. SciTrMed 2014</td>
<td>MSK CD28</td>
<td>N=16 (ALL) Adults</td>
<td>CR=88%</td>
<td>43% Severe</td>
<td>25% Gr3-4</td>
</tr>
<tr>
<td>Lee et al. Lancet 2015</td>
<td>NCI CD28</td>
<td>N=21 (ALL) Peds&amp;AYA</td>
<td>CR=67% Intent to Treat</td>
<td>76% CRS 28% Severe</td>
<td>29%</td>
</tr>
<tr>
<td>Turtle et al. JCI 2016</td>
<td>Seattle 4-1BB</td>
<td>N=30 (ALL) (Adults)</td>
<td>CR=93%</td>
<td>83% CRS</td>
<td>50% Severe</td>
</tr>
</tbody>
</table>

Presented By Noelle Frey at 2016 ASCO Annual Meeting
CTL019 (tisagenleuclucel-T): ALL Patient #1

April 2012

CHP #100

Grupp et al NEJM 2013

May 2016

Presented By Carl June at 2016 ASCO Annual Meeting
CD19-targeted CAR T cells for B cell malignancies

- Results published from 8 trials
  - 27 ongoing/planned trials at 10 centers
  - autologous and allogeneic T cells
- Responses seen in heavily-pretreated CLL, ALL, and B-cell NHL
  - ORR 40-50% in CLL, 80% in ALL
  - some durable CRs > 3 years
- Toxicities:
  - tumor lysis syndrome
  - B cell aplasia / hypogammaglobulinemia
  - Cytokine release syndrome
    - persistent high fevers, rigors, myalgias, hypotension, hypoxia, neurologic dysfunction, HLH/macrophage activation syndrome
    - very high IL6, also IFN-gamma, TNF
    - responds to steroids → but lose CAR T cells
    - tocilizumab (anti-IL6 receptor mAb) can abrogate CRS

## CTL019 Phase I Trial for r/r CLL: 5 yr follow up

Summary of patient baseline characteristics

N = 14 patients, protocol 04409 (NCT01029366)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statistics, N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
</tr>
<tr>
<td>Age at infusion in years</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.9 (8.1)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>66 (51-78)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (85%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Number of prior therapies</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.3 (2.8)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>5 (1-11)</td>
</tr>
<tr>
<td>P53 or 17p deletion</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>IGHV mutation</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

- Overall response rate: 57%
- CR 4/14 (28%)
- PR 4/14 (28%)
- NR 6/14 (43%)

Protocol Schema

CD19+ Lymphoma
- Eligibility determination
- Enrollment

Apheresis
- Baseline immune assays

Restaging and Lymphodepleting chemotherapy
- CT scans
- Bone marrow
- Physician’s choice
- Ends 1 – 4 days before CTL019 infusion

CTL019 Infusion, Monitoring and Response Assessments

CTL019 infusion
- Clinical evaluation; immune/CTL019 assays

Day -1
Day 0
Month +1
Month +2 and +3 evaluations
Quarterly f/u x 2 years
Long-term f/u x 15 years

Adverse event monitoring

30 Nov 2015
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 1.0 - 5.0E+08 CTL019 (n = 30)
- DLBCL (n = 15)
- FL (n = 13)
- MCL (n = 2)

30 Nov 2015
## 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)
Response Rates: 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

30 Nov 2015
Results: Diffuse Large B Cell Lymphoma

![Graph showing DLBCL: PFS (months)]

**ID**
- 13413-01: 5.00E+08, 28.30%, +10
- 13413-02: 5.00E+08, 29.30%, +7
- 13413-05: 5.00E+08, 5.30%, +7
- 13413-06: 5.00E+08, 6.90%, +7
- 13413-09: 5.00E+08, 3.90%, +7
- 13413-10: 5.00E+08, 43.10%, +14
- 13413-12: 5.00E+08, 4.10%, +2
- 13413-16: 5.00E+08, 2.50%, +7
- 13413-17: 5.00E+08, 12.20%, +7
- 13413-21: 5.00E+08, 5.70%, +7
- 13413-22: 5.00E+08, 16.50%, +10
- 13413-23: 5.00E+08, 17.80%, +10
- 13413-28: 1.93E+08, 4.10%, +10
- 13413-36: 5.00E+08, 0.10%, +7
- 13413-39: 5.00E+08, 1.80%, +1

**Ongoing clinical responses**
- PR
- CR
- PD

**Days to progressive disease**
- +10
- +7
- +14
- +2
- +7
- +7
- +7
- +10
- +10
- +10
- +7
- +1

†Deceased

28 Feb 2016
“Double Hit” Diffuse Large B Cell Lymphoma: 13413-12

07/11/2014

CTL019: 07/22/2014

08/19/2014
## FL: Patient Characteristics (n = 14 enrolled)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>59 years (range 43 - 72)</td>
</tr>
<tr>
<td>Sex</td>
<td>6 (43%) men</td>
</tr>
<tr>
<td>Median prior therapies</td>
<td>5 (range 2 - 10)</td>
</tr>
<tr>
<td>• Prior transplant %</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>• Prior R-CHOP/R-EPOCH</td>
<td>12 (86%)</td>
</tr>
<tr>
<td>• Prior R-bendamustine</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>• Prior idelalisib</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>Stage III – IV (enrollment)</td>
<td>13 (93%)</td>
</tr>
<tr>
<td>Increased LDH (enrollment)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>&gt; 1 extranodal site (enrollment)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Median ECOG PS (enrollment)</td>
<td>0 (range 0 – 1)</td>
</tr>
</tbody>
</table>
# Response Rates: Follicular Lymphoma

<table>
<thead>
<tr>
<th>FL: ORR at 3 Months 77% (N = 13)</th>
<th>FL: Best Response Rate 77% (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CR: 6</td>
<td>- CR: 9</td>
</tr>
<tr>
<td>- PR: 4</td>
<td>- PR: 1</td>
</tr>
<tr>
<td>- PD: 3</td>
<td>- PD: 3</td>
</tr>
</tbody>
</table>

- 3 patients with PRs by CT/MR criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months who remained in PR at 6 and 9 months had PD at approximately 12 months
Results: Follicular Lymphoma

FL: PFS (months)

<table>
<thead>
<tr>
<th>ID</th>
<th>Total CTL019 Dose</th>
<th>Peak %CD3+CAR19</th>
<th>Peak Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>13413-04</td>
<td>3.76E+08</td>
<td>0.70%</td>
<td>+7</td>
</tr>
<tr>
<td>13413-07</td>
<td>5.00E+08</td>
<td>3.00%</td>
<td>+10</td>
</tr>
<tr>
<td>13413-11</td>
<td>5.00E+08</td>
<td>38.20%</td>
<td>+7</td>
</tr>
<tr>
<td>13413-13</td>
<td>5.00E+08</td>
<td>3.20%</td>
<td>+7</td>
</tr>
<tr>
<td>13413-15</td>
<td>5.00E+08</td>
<td>40.50%</td>
<td>+7</td>
</tr>
<tr>
<td>13413-19</td>
<td>1.79E+08</td>
<td>1.00%</td>
<td>+7</td>
</tr>
<tr>
<td>13413-24</td>
<td>5.00E+08</td>
<td>8.40%</td>
<td>+10</td>
</tr>
<tr>
<td>13413-31</td>
<td>2.84E+08</td>
<td>3.50%</td>
<td>+10</td>
</tr>
<tr>
<td>13413-32</td>
<td>1.95E+08</td>
<td>5.10%</td>
<td>+10</td>
</tr>
<tr>
<td>13413-33</td>
<td>5.00E+08</td>
<td>23.60%</td>
<td>+10</td>
</tr>
<tr>
<td>13413-34</td>
<td>3.62E+08</td>
<td>40.00%</td>
<td>+14</td>
</tr>
<tr>
<td>13413-37</td>
<td>5.00E+08</td>
<td>41.90%</td>
<td>+7</td>
</tr>
<tr>
<td>13413-38</td>
<td>5.00E+08</td>
<td>26.20%</td>
<td>+7</td>
</tr>
</tbody>
</table>

- PR: Partial Response
- PD: Progressive Disease
- †: Deceased

Ongoing complete response
Days to progressive disease

28 Feb 2016
## Adverse Events at Least Possibly Related: ≥ Grade 3

<table>
<thead>
<tr>
<th>AE</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>Total ≥ G3</th>
<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>
<td>Headache</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Alk. phos. increased</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Hypoxia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
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<td></td>
<td>1</td>
<td>Hypertension</td>
<td>1</td>
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<td></td>
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</tr>
<tr>
<td>Agitation</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Hypotension</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Delirium</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td>Hypocalcemia</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>Encephalitis</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Hyponatremia</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>
<td>Hypophosphatemia</td>
<td>3</td>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Insomnia</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Laryngeal edema</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Anemia</td>
<td>5</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Lymphopenia</td>
<td>10</td>
<td>8</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Neutropenia</td>
<td>7</td>
<td>7</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td>Thrombocytopenia</td>
<td>4</td>
<td>2</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>Weight loss</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
CD19: An ideal B-cell cancer target, but…

- CD19 is expressed on the surface of most B cell malignancies
- Antibodies against CD19 inhibit growth of tumor cells
- CD19 expression is restricted to B cells and their precursors
- CD19 is not expressed on pluripotent bone marrow stem cells
- On target expected SE is B cell aplasia

Rationale for anti-CD19 therapy in multiple myeloma

- **Myeloma Plasma Cells (CD19-)**
  - CD19+ Myeloma PC subset
  - Clonotypic B cells (CD19+)

- **Dominant**
  - Responsible for clinical complications

- **Minor subsets**
  - Uncertain clinical relevance
Rationale for anti-CD19 therapy in multiple myeloma

CD19+ myeloma stem cells?
Rationale for anti-CD19 therapy in multiple myeloma

- CD19+ myeloma stem cells?
- CD19+ phenotypic transition states?
  - drug-resistant
  - clonogenic
Rationale for anti-CD19 therapy in multiple myeloma

- Might CART19 be useful in multiple myeloma, even though it is “CD19-negative?”
  - CART19 recognizes <100 molecules of CD19
  - A pool of CD19+ otherwise resistant cells?
- How can we give CART19 so that we could test to see if it worked by any of these mechanisms?
Pilot Study of CART19 in Multiple Myeloma

In our retrospective analysis of second salvage ASCT for r/r MM
56% R/R (&gt;PR)
No remission inversions
Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt -01

48 y/o F
IgA kappa
TTP 6 mo after ASCT #1
10 prior lines of therapy over 5 years
Lenalidomide, pomalidomide,
Bortezomib, carfilzomib, MEL 200 SCT,
Vorinostat, elotuzumab, cyclophosphamide
Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt 02413-01

Progression by IMWG Criteria

CD19 negative PCs
Clinical CR
MRD neg (flow/deep sequencing)
Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt 02413-01

Garfall et al, NEJM September 10 2015
Response summary

- 1/10 progression free, 6/10 alive
- 3/9 with longer response than prior ASCT (lower melphalan dose)
- Mean TTP2/TTP1 = 0.96
- Historical cohort of 2nd ASCT at Penn (1st ASCT since 2008, alive 30d post-ASCT, and no subsequent allo-SCT) (N=18)
  - Mean TTP2/TTP1 = 0.32 (p=0.003)
  - No patients with TTP2>TTP1
Plasma cells lose expression of typical lineage-specific markers of mature B cells like CD19 and CD20.

B-cell maturation antigen (BCMA) expression is up-regulated during normal B cell differentiation into plasma cells.
**Study design/schema**

Adam Cohen, PI (PENN)
Mike Malone, Scientific Advisor
Bruce Levine, Cell Manufacturing
J. Joseph Melenhorst Correlative labs
Simon Lacey, Correlative Labs
Gabrela Plesa, Protocol Officer

Patients may receive therapy during manufacturing to maintain disease control.

After first 28 days, follow-up is q4 wks up to 6 mos., then q3 mos. up to 2 years.

***Pre-tx = pre-treatment, 3 to 7 days before CAR T cell infusion***
Subject 1

- 66M, IgG kappa MM dx’d April 2006
  - 11 prior lines, progressing on last therapy
  - Pre-treatment bone marrow bx: 70% MM cells
    - FISH: gain CCND1, del17p, loss of MAF (16q)
    - NGS: mutations in NRAS, TP53, TP53
CART-BCMA Cells for Multiple Myeloma

Subject 1

- $2 \times 10^8$ CART-BCMA cells
  - no lymphodepletion
- Grade 3 CRS $\rightarrow$ responded to tocilizumab
- Robust CART-BCMA expansion and persistence

Pre-tx

Day 7

PB CART cells

CAR qPCR

CD8

BCMA-CAR

Car +

0.1

34.7

Copies/μg DNA

Days post CAR infusion
CART-BCMA Cells for Multiple Myeloma

Subject 1
- Day 28 marrow: negative by IHC and flow
- Ongoing VGPR
### BCMA-specific CAR in rel/ref MM

<table>
<thead>
<tr>
<th>Pt</th>
<th>Myeloma Type</th>
<th>CAR-BCMA Dose (T cells/kg)</th>
<th>Response</th>
<th>Response Duration, Wks</th>
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<td>1</td>
<td>κ light chain only</td>
<td>$0.3 \times 10^6$</td>
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<tr>
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<tr>
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<td>PR</td>
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<tr>
<td>12</td>
<td>IgA λ</td>
<td>$3.0 \times 10^6$</td>
<td>SD</td>
<td>2</td>
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</table>
Potential Strategies to Improve CAR T Therapy in Lymphoma

- Treat patients earlier in the natural history of the disease
  - First line of therapy
  - Prior to the development of more resistant clones

- Maximize persistence of CAR T cells
  - Better lymphodepleting conditioning
  - Dose intensity
  - Serial infusions

- Engineer the CARs for greater potency
- Potentiate with such agents as PD-1 inhibitors
- Cocktails of CARs with multiple targets
Multiple other CARs, TCRs, BiTEs for Lymphoma

- **CTL019+ASCT** high RR, remission inversions
  - Garfall et al, NEJM 2015

- **BCMA-CAR**
  - Chekmasova et al, ASH 2015

- **SLAMF7/CS1-CAR**
  - Chu et al, Clin Can Res 2014
  - Danhof, ASH 2015; Galetto, ASH 2015

- **NY-ESO1 TCR Transgenic + ASCT**
  - High RR, some durable

- **BCMA BiTE**
  - Hipp, ASH 2015

- **CD38 BiTE**
  - Moore, ASH 2015
**Conclusions: Lymphoma Immunotherapy**

- Successful immunotherapy for lymphoma started with rituxan, lenalidomide and pomalidomide.

- Check-point Inhibitors (ant-PD-1) in combination with IMIDs are active in RR lymphoma and myeloma.

- Multiple promising targets doe CARs, TCRs and MoAbs:

  - Functional CAR T cells and TCR engineered T cells can be generated from Lymphoma patients.

  - CAR T and TCR T and NK cells have in vitro and in vivo activity against Lymphoma.

- The age of immunotherapy for B-cell malignancies is upon us.
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TOO NUMEROUS TO PUT ON SLIDE

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