Multiple Myeloma Immunotherapy Updates

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What is Immunotherapy?

• Using the immune system to help fight myeloma.

• The immune system is 2 parts
  – Humoral immunity mediated by antibodies
  – Cellular immunity mediated by cytotoxic lymphocytes and natural killer cells.
Antibodies Mediated Immunotherapy

• Using genetically engineered antibodies to bind to the myeloma cells and kills them.

• Either by bringing on
  – Proteins that kills the myeloma cells (complement)
  – Cells that kills the myeloma cells like cytotoxic lymphocytes or natural killer cells.
MAb-Based Targeting of Myeloma

**Antibody-dependent cellular cytotoxicity (ADCC)**

- Effector cells: MM
- ADCC

- Lucatumumab or dacetuzumab (CD40)
- Elotuzumab (SLAM 7)
- Daratumumab (CD38)
- MOR208 (HM1.24)

**Complement-dependent cytotoxicity (CDC)**

- CDC
- MM
- Daratumumab (CD38)

- C1q

**Apoptosis/growth arrest via targeting signaling pathways**

- Lorvotuzumab mertansine (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

Targets on the Myeloma Cell Surface

SLAMF7  CD38
Daratumumab Efficacy in Combined Analysis

- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

N = 148

ORR = 31%

- 3% CR or better
- 10% VGPR or better
- 18% PR
- 2% VGPR
- 1% CR
- 1% sCR

16 mg/kg
Responders (Median ~7.4 months)

MR/SD: 3.2 (2.8-3.7) months

PD (median ~0.9 months)

Patients progression-free and alive, %

Patients at risk

Responders 46 46 41 35 27 14 13 5 3 3 0
MR/SD 77 45 21 13 3 2 1 0 0 0 0
PD/NE 25 0 0 0 0 0 0 0 0 0 0
For the combined analysis, median OS = 19.9 months
1-year overall survival rate = 69% (95% CI, 60.4-75.6)
Elotuzumab (HuLuc63) is an IV humanized monoclonal antibody targeting human SLAMF7, a cell surface glycoprotein.

Elotuzumab is an IV humanized monoclonal antibody targeting human SLAMF7

- Elotuzumab may not work on its own.
- Original study with elo only in 35 pts, doses ranging from 0.5-20 mg/kg every two weeks demonstrated no responses but stable disease in 27% of pts.
- However combined with revlimid and dex in relapsed pts, response rate was 82% (expected would be about 60%).
ELOQUENT-2: Elotuzumab With Lenalidomide/Dexamethasone R/R MM

- Randomized, open-label, multicenter phase III trial

  Elotuzumab 10 mg/kg IV QW cycles 1, 2 then Q2W +
  Lenalidomide 25 mg PO D1-21 +
  Dexamethasone 40 mg PO QW
  (n = 321)

  Pts with relapsed MM and 1-3 prior treatments
  (N = 646)

  Lenalidomide 25 mg PO D1-21 +
  Dexamethasone 40 mg PO QW
  (n = 325)

  28-day cycles

  Until Progression or unacceptable toxicity

- Primary endpoints: Progression Free time (PFS), Overall Response
- Secondary endpoints: Overall Survival, safety, health-related Quality of Life

### ELOQUENT-2 Results

<table>
<thead>
<tr>
<th></th>
<th>E-Rd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>19.4</td>
<td>14.9</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>79</td>
<td>66</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>≥VGPR, %</td>
<td>33</td>
<td>28</td>
<td></td>
<td></td>
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<tr>
<td>AEs, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 cardiac failure</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 acute renal failure</td>
<td>4</td>
<td>4</td>
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</table>

No benefit observed in patients who were previously exposed to immunomodulatory agent.

Patients with Del17p, 1q21 amplifications and t(4;14) faired as well as standard risk.
Cellular Mediated Immunotherapy

• Off the shelf: not custom made to attack myeloma but turns on the immune system to recognize myeloma cells and destroy it. The classic drugs are call checkpoint inhibitors.

• Custom made patients T cells to recognize myeloma cells and kill it. The porotype called CAR-T cells.
The old: Lenalidomide enhances checkpoint blockade and induces the destruction of myeloma cells by cytotoxic lymphocytes.

The new: Anti PDL-1 and anti PD-1. First in class is the drug Pembrolizumab. Not approved yet in myeloma abut many clinical trials are ongoing and some has shown great efficacy with other drugs such as Lenalidomide.
CAR – T Immune Therapy
**Chimeric antigen receptors (CARs) help T-cells recognize and destroy cancer cells**

T cells are white blood cells that attack and kill viruses and cancer cells.

**Chimeric antigen receptors (CARs) help T-cells recognize and destroy cancer cells**

1. T cells are collected from the patient. A machine removes the desired cells from the blood, then returns the rest back to the patient.
2. A modified virus (blue) is used to transfer DNA to the patient’s T cells so they will produce CAR proteins.
3. CARs have two ends: a binding site (blue) specific to the tumor cells, and a signaling engine that activates the T cell to kill the tumor it binds to.
4. Once designed, millions of engineered CAR T cells are grown in the laboratory.
5. The expanded population of CAR T cells is infused into the patient through a standard blood transfusion.
CAR-BCMA T Cells in Myeloma: Background

- T cells can be genetically modified to express chimeric antigen receptors (CARs) specific for malignancy-associated antigens.
- B-cell maturation antigen (BCMA) is expressed by normal and malignant plasma cells.
  - BCMA is a potential target for CAR T-cell therapy for MM.
- The patient’s own T-cells were stimulated, transduced with CAR-BCMA retroviruses, and cultured for 9 days before infusion.
- Study presented ASH 2015 evaluated CAR-BCMA T cell infusion for treatment of advanced MM.

CAR-BCMA T Cells in Myeloma: Study Design

- First-in-human phase I trial
  - Pts with advanced relapsed/ refractory MM
  - More than 3 prior lines of therapy;
  - BCMA expression on myeloma cells
  - 12 patients enrolled

**Study Design**

**Cyclophosphamide 300 mg/m²**
**Fludarabine 30 mg/m²**
QD for 3 days

**CAR-BCMA T cells**
Single infusion

*Dose escalation of CAR+ T cells/kg

- 0.3 x 10^6
- 1.0 x 10^6
- 3.0 x 10^6
- 9.0 x 10^6

CAR-BCMA T Cells in Myeloma: Response to therapy

<table>
<thead>
<tr>
<th>Response to Therapy</th>
<th>Number of Patients (total 12 treated)</th>
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<tbody>
<tr>
<td>Stringent complete response(sCR)</td>
<td>1</td>
</tr>
<tr>
<td>Very good partial response VGPR</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8</td>
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Conclusions:

• Immunotherapy has come a long way.
• Treatment with monoclonal antibodies has resulted in remarkable results.
• Checkpoint inhibitors are showing great promise and may lead to the eradication of residual myeloma.
• Engineered T cells are very promising.
Cellular Immunotherapy Against CD19 for Myeloma

September 22, 2016

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1. Novel agents and autoSCT extend survival but progression is common
2. T and NK cells from myeloma patients can kill autologous myeloma cells ex vivo
3. Allogeneic SCT may “cure” myeloma by a T-cell mediated 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 myeloma effect without the GVHD.

“Novel agents” (-imid’s, proteasome inhibitors)

The CTL019 therapeutic approach involves the adoptive transfer of autologous T cells that have been genetically modified to express anti-CD19 CARs into patients.

1. **Leukapheresis:** patient’s T cells are harvested

2. T cells are activated and genetically transduced ex vivo with a construct encoding the anti-CD19 CAR

3. **CTL019 cells undergo ex vivo expansion** on antibody-coated magnetic beads

4. **Chemotherapy:** patient receives a preparative lymphodepleting regimen before T-cell infusion

5. **CTL019 cells are reinfused** into the patient

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

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
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
  – many durable CRs > 3 years
  – Relapses do occur: CD19 negative or loss of CAR T cells

• 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, Ferritin
    • responds to steroids \(\rightarrow\) but lose CAR T cells
    • tocilizumab (anti-IL6 receptor mAb) can abrogate CRS

93% CR rate for r/r ALL after CTL019

- 59 r/r pediatric ALL pts: 55 in CR at 1 mo (93%) median f/u 12 mo
- 6 went to subsequent transplant, 1 to DLI
- 6 mo RFS: 76% (95%ci 65-89%) 12 mo RFS: 55% (95%ci 42-73%)
- No relapses past 1 year
- 18 patients in remission beyond 1 year, 13 without further therapy

>200 patients with CLL, ALL, NHL, MM have received CTL019
CD19: An ideal B-cell cancer target, but myeloma?

- 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
- CD19 is not expressed on the majority of malignant plasm cells

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

- CD19+ myeloma stem cells?
- CD19+ phenotypic transition states?
  - drug-resistant
  - clonogenic
- Dominant population CD19-dim?

• 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?
In our retrospective analysis of second salvage ASCT for r/r MM
56% R/R (≥PR)
No remission inversions
Clinical trial design

- 10-patient pilot study
- CTL019 + high-dose melphalan + ASCT
- Key inclusion/exclusion criteria
  - Prior ASCT with <1y response duration
  - Interim salvage therapy allowed
- Primary endpoints
- Secondary endpoints
  - CTL019 expansion, persistence, and in vivo activity (B cell aplasia)
  - Duration/depth of response (compared to prior ASCT)
  - Assessment of CD19 expression and association with response.

1-5 x 10^7 CAR+ cells on day 12-14
melphalan 140-200 mg/m^2

Defines a high-risk population.
Provides patient-specific control.

Safety (cytokine release syndrome)
Feasibility (manufacturing)
Safety and feasibility

• No significant toxicity attributable to CTL019
  – Transient hypogammaglobulinemia
  – One episode of grade 1 cytokine release syndrome (fever only)
  – ASCT toxicities have been as expected
    • 2 episodes of uncomplicated bacteremia
    • no ICU care required
    • no readmission for transplant-related complications

• Manufacturing feasibility
  – One manufacturing failure
  – One product release deviation (borderline transduction efficiency, dose achieved)
Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt 02413-01

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
99.95% CD19 negative malignant plasma cells

Progression by IMWG Criteria

Transplant Day

IgA (mg/dl)

Progression
by IMWG
Criteria

Mel 200
ASCT #1

Mel 140
ASCT #2

CART19
Day 129

448

99.95% CD19 negative malignant plasma cells
Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt 02413-01

Clinical sCR
MRD neg (flow/deep sequencing)
2 Days before ASCT more than 95% involvement by multiple myeloma vs Day 100 1 to 2% overall cellularity and no plasma cells on hematoxylin and eosin staining and CD138 immunostaining

Response persisted for 15 mos where her initial remission showed signs of progression in 3 months and lasted 6 months.

CTL019 persisted in her for only 100 days

Garfall et al, NEJM September 10 2015
Patient #5: Response

The graph illustrates the response of Patient #5 over time, focusing on IgA and M-spike levels. Key events and treatments are marked on the timeline:

- **Day 0**: ASCT #1
- **Day 137**: ASCT #1
- **Day 0**: ASCT #2
- **Day 132**: ASCT #2
- **Day 0**: CTL019 first undetectable

Treatments and interventions include:

- **RVD**: Remdesivir/Verdinib/Dexamethasone
- **CDE**: Carfilzomib/Dexamethasone/Encorafenib
- **MEL200**: Melphalan 200 mg
- **VDAC**: VDAC (Antibody)
- **MEL140**: Melphalan 140 mg
- **CD38 Ab**: CD38 Antibody
- **CTL019**: CTL019

The graph shows how these treatments affected IgA and M-spike levels over time, with notable declines and increases at specific intervals.
Why did this lead to clinical benefit in a subset of patients?

- Our hypothesis was that a combination of chemotherapy and myeloma stem cell or chemotherapy resistant clone directed therapy would result in improved duration and depth of remission in myeloma.

- Correlative studies are still pending including searching for clonogenic myeloma stem cells

- Further experience with other study designs and targets will provide much need information.
Potential Strategies to Improve CTL019 in MM

• Treat patients earlier in the natural history of the disease
  – First line of therapy
  – Prior to the development of more resistant CD19 neg clones

• Maximize persistence of CTL019
  – 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
• The age of (cellular) immunotherapy for myeloma is upon us
Plasma cells develop from B-cells

- 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
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
BCMA-specific CAR in rel/ref MM

- At 3 lower dose levels: mild fevers, cytopenias, 1 CRS (VGPR)
- At highest dose level:
  - Pt 10: relapsed 3 mos. post-auto, 90% MM cells pre-tx → ongoing sCR at 14 weeks
    - Severe CRS, prolonged pancytopenia
    - Myositis/elevated CPK, AKI
  - Pt 11: 5 priors, 80% MM cells pre-tx → ongoing PR at 6 weeks, BM neg.
    - Severe CRS, delirium, coagulopathy
- Responses associated with CAR-T expansion, CRS, and IL-6 levels
- soluble BCMA levels decreased in responding patients

Ali et al, ASH 2015, LBA #1
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