Cell Therapy

Dr. Ronan Foley
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Cell Therapy

- Ronan Foley
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Disclosures - Foley

- **Advisory Boards**: Celgene, Janssen, TEVA
- **Lectures**: Celgene, Amgen, Janssen
- **Funding**: nil
Key Themes for Cell Therapy - Future

Immunotherapy is evolving rapidly with remarkable results

Novel technologies and combinations are in early phase studies

Creating capacity and timely delivery of products are critical immediate goals
Cancer Immunotherapy: treatment that uses the body’s immune system to fight cancer.

- Monoclonal Antibodies
- Checkpoint Inhibitors
- Adoptive Cell Transfer
- Dendritic Cell Therapy
- CARS
- Cytokines
- Cancer Vaccines
One Major Issue For All Cell Therapy:

**patient cells have to be individually collected/processed**
Novel Manufacturing Platforms

- **Automation**: product consistency, yield and reproducibility

- **Decentralized Manufacturing**: treatment site and reduced turnaround times, cost of shipping and delivery processes, increased capacity

- **Allogeneic CAR-T cells**: immediate availability, supply chain, validate lack of GVHD

- **Non viral approaches**: DNA plasmids electroporation vs viral
Clinical development of CAR T cells

Hartmann et al. (2017), EMBO Molecular Medicine
Clinical development of CAR T cells

Hartmann et al. (2017), EMBO Molecular Medicine
Clinical development of CAR T cells

Hartmann et al. (2017), EMBO Molecular Medicine
Update of CARTITUDE-1: A phase 1b/2 study of JNJ-4528, a B-cell maturation antigen (BCMA)-directed CAR-T cell therapy, in relapsed/refractory multiple myeloma

Jesus G. Berdeja,1 Deepu Madduri,2 Saad Z. Usmani,3 Indrajeet Singh,4 Enrique Zudaire,4 Tzu-Min Yeh,5 Alicia J. Allred,4 Yunsi Olyslager,6 Arnob Banerjee,4 Jenna D. Goldberg,5 Jordan M. Schecter,5 Dong Geng,7 Xiaoling Wu,7 Marlene J. Carrasco-Alfonso,7 Syed Rizvi,7 Frank Fan,8 Andrzej Jakubowiak,9 Sundar Jagannath2

1Sarah Cannon Research Institute, Nashville, TN, USA; 2Mount Sinai Medical Center, New York, NY, USA; 3Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; 4Janssen R&D, Spring House, PA, USA; 5Janssen R&D, Raritan, NJ, USA; 6Janssen R&D, Beerse, Belgium; 7Legend Biotech USA Inc., Piscataway, NJ, USA; 8Nanjing Legend Biotech, Nanjing, China; 9University of Chicago, Chicago, IL, USA
**JNJ-4528: BCMA-targeted CAR-T Cell Therapy**

- **JNJ-68284528 (JNJ-4528)** is a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy
  - Contains a CD3ζ signaling domain and 4-1BB costimulatory domain
  - 2 BCMA-targeting single chain antibody designed to confer avidity
  - Identical to the CAR construct used in the LEGEND-2 study

- **Deep and durable responses observed in patients with R/R MM**
  - LEGEND-2 (N = 57): mPFS of 20 mo and mOS of 36 mo at median 25-mo follow-up\(^1\)
    - CRS events were mostly grade 1 – 2; one grade 1 neurotoxic event

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\(^1\)Wang et al. Blood 2019;134(Suppl_1):579 (oral presentation); BCMA—B-cell maturation antigen; CRS—cytokine release syndrome; mPFS—median progression-free survival; MM—multiple myeloma; mOS—median overall survival; ORR—overall response rate; R/R—relapsed/refractory; VH—variable domain on a heavy chain
# CARTITUDE-1: Safety

## CAR-T-associated AEs, n (%)

<table>
<thead>
<tr>
<th></th>
<th>All Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome (CRS)(^a)</td>
<td>27 (93)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Neurotoxicity consistent with ICANS(^b)</td>
<td>3 (10)(^c)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

### Timing and management of CRS

- Median time to onset of CRS = 7 days (2 – 12)
- Median duration of CRS = 4 days (2 – 64)
- 23 (79%) patients were given tocilizumab
- 6 (21%) patients each were given anakinra or corticosteroids

## AE (≥25% All Grade), n (%)

<table>
<thead>
<tr>
<th></th>
<th>All Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29 (100)</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25 (86)</td>
<td>20 (69)</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (76)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>20 (69)</td>
<td>19 (66)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>15 (52)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>9 (31)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>9 (31)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (35)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (28)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Graded according to Lee et al. *Blood* 2014;124:188.  \(^b\) Graded using Common Terminology Criteria for Adverse Events, v.5.0. \(^c\) One event of facial nerve disorder not included as it is not consistent with ICANS. AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ICANS=immune effector cell-associated neurotoxicity syndrome; SOC=systom organ class.
CARTITUDE-1: Overall Response Rate

ORR$^a = 100\%$ ($N = 29$)

- 25 of 29 (86%) patients achieved sCR
- ORR and depth of response were independent of BCMA expression on myeloma cells at baseline
- Median time to first response = 1 mo (1 – 3)
- Median time to CR = 3 mo (1 – 13)

$^a$PR or better; Independent Review Committee-assessed. $^b$No patient had complete response, stable disease, or progressive disease as best response. CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

56th ASCO Annual Meeting 2020, Berdeja et al. Abstract #8505
CARTITUDE-1: Minimal Residual Disease

- 26 patients had baseline and at least one post-baseline bone marrow sample available for MRD assessment by NGS (clonoSeq)
- Majority of patients continue to show MRD-negative responses beyond day 28
- Of 16 patients in CR who were evaluable for MRD assessment at the time CR* was adjudicated:
  - 81% (n=13) MRD negative at $10^{-5}$ or $10^{-6}$
  - 69% (n=11) MRD negative at $10^{-6}$

<table>
<thead>
<tr>
<th>Patient</th>
<th>D28</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 001</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Patient 002</td>
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<td>✔️</td>
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<td>✔️</td>
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<td>Patient 004</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>Patient 005</td>
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<td>✔️</td>
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<tr>
<td>Patient 006</td>
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<td>✔️</td>
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<td>Patient 007</td>
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<td>Patient 008</td>
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<td>Patient 026</td>
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<tr>
<td>Patient 028</td>
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<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Patient 029</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Patient 030</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Sample not collected or calibration failure
- MRD positive at $10^{-4}$
- MRD negative at $10^{-4}$ and indeterminate at $10^{-5}$ and $10^{-6}$
- MRD negative at $10^{-5}$ and indeterminate or positive (*) at $10^{-6}$
- MRD negative at $10^{-6}$

*suspected CR, 3 month window of confirmed CR / sCR; D-day; MRD=minimal residual disease; NGS=next generation sequencing
CARTITUDE-1: Conclusions

- **JNJ-4528 has a safety profile consistent with LEGEND-2**
  - CRS events were mostly grade 1 – 2 with median time of onset of 7 days, suggesting that outpatient dosing is feasible
  - Neurotoxicity (ICANS) was infrequently observed in the context of CRS and generally low-grade with one grade 3 event
  - Most grade 3–4 cytopenias were resolved after 60 days; low incidence of infectious complications

- **Early, deep, and durable responses were observed in heavily-pretreated patients**
  - 100% ORR with 86% sCR and 97% ≥VGPR at median 11.5-mo follow-up
  - Median time to first response = 1 mo (1 – 3); median time to CR = 3 mo (1 – 13)
  - Of the 16 patients in CR evaluable for MRD assessment, 13 were MRD neg at 10⁻⁵ or better and 11 at 10⁻⁶
  - 9-mo PFS was 86% (95% CI, 67 – 95)

- **JNJ-4528 has received Breakthrough Therapy Designation; Phase 2 portion of the study is fully enrolled, and phase 2 and 3 studies⁴ have been initiated**
ABSTRACT 122

Safety of Lisocabtagene Maraleucel Given With Durvalumab in Patients With Relapsed/Refractory Aggressive B-Cell Non-Hodgkin Lymphoma: First Results From the PLATFORM Study

Tanya Siddiqi,1 Jeremy S. Abramson,2 Hun Ju Lee,3 Stephen Schuster,4 Jens Hasskarl,5 Sandrine Monthéard,5 Justine Dell’Aringa,6 Ethan Thompson,6 Revathi Ananthakrishnan,7 Matthew Lunning8

1City of Hope National Medical Center, Duarte, California, USA; 2Massachusetts General Hospital, Boston, Massachusetts, USA; 3The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; 4Abramson Cancer Center, Philadelphia, Pennsylvania, USA; 5Celgene International, Boudry, Switzerland; 6Juno Therapeutics, a Celgene Company, Seattle, Washington, USA; 7Celgene, Summit, New Jersey, USA; 8University of Nebraska Medical Center, Omaha, Nebraska, USA

This study was funded by Celgene

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CAR T Cell Therapy and Checkpoint Inhibition

• Immune system modifiers may further enhance the response and response durability of anti-CD19 CAR T cell therapy

  – Checkpoint inhibition following CAR T cell therapy has therapeutic potential by reversing T-cell exhaustion and reducing the influence of the tumor microenvironment, thereby supporting optimal antitumor activity of T cells

• We evaluated the PD-L1 inhibitor durvalumab in combination with liso-cel in patients with R/R B-cell NHL

CAR, chimeric antigen receptor; NHL, non-Hodgkin lymphoma; PD-L1, programmed cell death ligand 1; R/R, relapsed/refractory.

**PLATFORM – Phase 1, Arm A**

**Key Eligibility**
- Age ≥18 years
- Aggressive NHL (DLBCL NOS, de novo and transformed indolent NHL, DHL/THL, FL3B, EBV-positive DLBCL, PMBCL) – PET-positive
- Relapsed or refractory ≥2 prior lines, including anthracycline/anti-CD20
- ECOG ≤1
- Post allo-HSCT if >90 days of leukapheresis
- No prior treatment with anti-PD1 or -PD-L1
- No active CNS disease
- Adequate organ function

**Endpoints**
- **Primary Endpoints**
  - Incidence of dose-limiting toxicities (DLTs)
  - **DLT period:** from first dose of liso-cel until 28 days after first infusion of durvalumab
- **Secondary Endpoints**
  - Incidence of adverse events
  - Overall response rate, duration of response, PFS, OS, EFS
  - Pharmacokinetics

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**On-study: 24 months**
- Long-term: up to 15 years after liso-cel treatment

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**Data cutoff: April 2019**

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*Monthly until D180 in case of non-CR at D85.
CNS, central nervous system; CY, cyclophosphamide; D, day; DHL/THL, double/triple-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FL3B, follicular lymphoma grade 3B; FLU, fludarabine; HSCT, hematopoietic stem cell transplant; NHL, non-hodgkin lymphoma; NOS, not otherwise specified; OS, overall survival; PD1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PET, positron emission tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03310619. Accessed May 14, 2019.
## Treatment-Emergent AEs of Special Interest

**In All Patients Who Received Durvalumab**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Cohort 1A</th>
<th>Cohort 1B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=14</td>
<td>n=8</td>
<td>n=6</td>
</tr>
<tr>
<td><strong>Cytokine release syndrome, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>3 (21)</td>
<td>0</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time to first onset, median (range) days</td>
<td>4 (3–7)</td>
<td>0</td>
<td>4 (3–7)</td>
</tr>
<tr>
<td>Duration, median (range) days</td>
<td>4 (4–4)</td>
<td>0</td>
<td>4 (4–4)</td>
</tr>
<tr>
<td><strong>Neurological events, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>2 (14)</td>
<td>1 (12.5)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (7)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Time to first onset, median (range) days</td>
<td>11.5 (8–15)</td>
<td>15 (15–15)</td>
<td>8 (8–8)</td>
</tr>
<tr>
<td>Duration, median (range) days</td>
<td>6.5 (5–8)</td>
<td>8 (8–8)</td>
<td>5 (5–5)</td>
</tr>
<tr>
<td>Tocilizumab use, n (%)</td>
<td>2 (14)</td>
<td>0</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Corticosteroid use, n (%)</td>
<td>1 (7)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td><strong>Infections grade ≥3, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (21)</td>
<td>1 (12.5)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Prolonged cytopenia grade ≥3,a n (%)</td>
<td>5 (36)</td>
<td>3 (37.5)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2 (14)</td>
<td>1 (12.5)</td>
<td>1 (17)</td>
</tr>
</tbody>
</table>

No grade 5 AEs of special interest occurred.

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aLaboratory results of hemoglobin, neutrophils, and platelets at Day 29.
Best Overall Response Rate
In All Patients Who Received Durvalumab

<table>
<thead>
<tr>
<th>Best ORR (%)</th>
<th>Total</th>
<th>Cohort 1A</th>
<th>Cohort 1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>92.9% (95% CI, 66.1–99.8) n=13/14</td>
<td>87.5% (95% CI, 47.4–99.7) n=7/8</td>
<td>100% (95% CI, 66.1–99.8) n=6/6</td>
</tr>
<tr>
<td>PR</td>
<td>79% n=11</td>
<td>75% n=6</td>
<td>83% n=5</td>
</tr>
<tr>
<td>SD</td>
<td>14% n=2</td>
<td>12.5% n=1</td>
<td>17% n=1</td>
</tr>
</tbody>
</table>

Median (range) follow-up, months
Total: 3 (1–12)
Cohort 1A: 6.2 (3–12)
Cohort 1B: 2.7 (1–6)

CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease.

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**Duration of Response**
In All Patients Who Received Durvalumab

Median follow-up 3 months (range, 1–12)

**Response per investigator**
- CR: Complete response
- PR: Partial response
- SD: Stable disease
- NE: Not evaluated
- PD: Progressive disease
- †: Death
- X: Durvalumab exposure

**Cohort 1A**
- **Evaluable Patients (N=14)**
  - 79% (11/14) of patients achieved CR
  - 64% (9/14) of patients achieved CR at first response assessment
  - 82% (9/11) of patients with CR at any time remained in CR at last follow-up
  - 4/5 in CR past 6 months remained in CR at 9 months, including 3 patients in CR past 12 months
  - 2 patients converted from PR to CR

**Cohort 1B**

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Effect of Durvalumab on liso-cel Pharmacokinetics

Median time to CAR T cell peak expansion ($T_{\text{max}}$)
11 days (range, 11–15)

- Cohort 1A (n=8)
- Cohort 1B (n=6)

<table>
<thead>
<tr>
<th></th>
<th>Median $C_{\text{max}}$ (cells/µL)</th>
<th>AUC$_{\text{c}-25}$ (day cells/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1A (n=8)</td>
<td>29.7 (10.4–59.3)</td>
<td>219.7 (125.6–444.4)</td>
</tr>
<tr>
<td>Cohort 1B (n=6)</td>
<td>55.1 (27.5–89.1)</td>
<td>578.9 (312.4–668.1)</td>
</tr>
</tbody>
</table>

CAR T cell numbers and persistence trended higher in patients receiving combination therapy compared with patients who received liso-cel monotherapy in TRANSCEND NHL 001.
‘Off-the-shelf’ allogeneic CAR T cells development and challenges

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Autologous CAR T cells</th>
<th>Allogeneic CAR T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin of the donor</td>
<td>Patient</td>
<td>Healthy donor</td>
</tr>
<tr>
<td>Production and manufacturing process</td>
<td>Complex logistics; delay from leukapheresis to CAR-T cell administration; variations of T-cell characteristics according to the patient’s immune characteristics and influence of previous treatments</td>
<td>Scaled-up industrialized process in which a high number of CAR T cells can be produced and cryopreserved from a single donor; batches immediately available for patient treatment; possible standardization of T cell characteristics</td>
</tr>
<tr>
<td>Clinical indications</td>
<td>Haematological malignancies (demonstrated activity); solid tumours</td>
<td>Haematological malignancies (ongoing trials); solid tumours</td>
</tr>
<tr>
<td>Main issues/risks</td>
<td>Cytokine release syndrome; CAR-related gene modifications; potential long-term side effects (B cell aplasia for anti-CD19 CAR T cells)</td>
<td>Cytokine release syndrome; CAR and/or gene editing-related gene modifications; GVHD; rejection of allogeneic cells; toxicity in the case of intense lymphodepletion</td>
</tr>
<tr>
<td>Persistence</td>
<td>Intermediate to long (months to years)</td>
<td>Short to intermediate (weeks to months)</td>
</tr>
<tr>
<td>Redosing</td>
<td>Limited by the number of cells</td>
<td>Not limited by the number of cells but risk of alloimmunization</td>
</tr>
<tr>
<td>Cost</td>
<td>Currently high (may decrease in the future)</td>
<td>Expected to be moderate</td>
</tr>
</tbody>
</table>

CAR, chimeric antigen receptor; GVHD, graft versus host disease.

• Depil et al. (2020), Nature Reviews|Drug Discovery
Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors

NK Cells

- Innate immune system
- CD56+CD3-
- Differentiate in the BM
- No antigen priming
- Primarily in blood
- No/low risk of GVHD
- Recognition takes place through complex array of receptors

T Cells

- Adaptive immune system
- CD3+CD4+ or CD3+CD8+
- Differentiate in the thymus
- Antigen priming required
- Antigen specific
- Allogeneic T cells induce GVHD
- Recognize targets through TCR rearrangement

Liu et al. (2020), NEJM
Rezvani “CAR NK Cell Therapy” at ISCT 2020
Advantages of NK cells over T cells for CAR therapy

**CAR-T**
- Autologous Product
  - Production time
  - Cost
  - 1 patient, 1 product
- If allogeneic: GVHD Risk
- Toxicity: cytokine release syndrome; neurotoxicity (50% need ICU care)
- CAR-mediated killing

**CD19 CAR-NK**
- Allogeneic Product
  - “Off the shelf”
  - Potential low cost
  - 1 cord, > 100 doses
- Low/absent GVHD
- CAR + NK Receptor mediated

Slide from Dr. Katy Rezvani presentation “CAR NK Cell Therapy” at ISCT 2020
Dasatinib acts as an on/off switch for CAR T cells

- Mestermann et al. (2019), Science Translational Medicine
A highly soluble sleeping beauty transposase improves control of gene insertion

- Querques et al. (2019), Nature Biotechnology
CRISPR-engineered T cells in patients with refractory cancer

CRISPR-Cas9 engineering of T cells in cancer patients. T cells (center) were isolated from the blood of a patient with cancer. CRISPR-Cas9 ribonuclear protein complexes loaded with three sgRNAs were electroporated into the normal T cells, resulting in gene editing of the TRAC, TRBC1, TRBC2, and PDCD1 (encoding PD-1) loci.

The cells were then transduced with a lentiviral vector to express a TCR specific for the cancer-testis antigens NY-ESO-1 and LAGE-1 (right). The engineered T cells were then returned to the patient by intravenous infusion, and patients were monitored to determine safety and feasibility.

PAM, protospacer adjacent motif.

• Stadtmauer et al. (2020)
Engineered T Cell Therapy and HPV-Associated Epithelial Cancer

**Engineered T Cell Therapy**

- T cells gene-engineered with an antigen receptor
  - Chimeric antigen receptor (CAR)
  - T cell receptor (TCR)
- Success in B cell malignancies
- Encouraging results in melanoma and synovial cell sarcoma
- Need for research in epithelial cancers

**HPV-Associated Epithelial Cancer**

- Difficult to treat
- Attractive therapeutic targets
  - E6 and E7 oncoproteins
  - Defined, constitutively expressed, foreign antigens

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CAR, chimeric antigen receptor; HPV, human papillomavirus; TCR, T cell receptor.

**Trial Design and Treatment Schema**

**Trial Design**
- First-in-human, Phase I, 3+3 dose escalation
- E7 TCR gene engineered T cells (E7 TCR-T cells)
- Metastatic HPV-16+ cancer, HLA-A*02:01 allele
- Any prior treatment, including checkpoint
- Dose levels
  - DL1: $1 \times 10^9$ E7 TCR-T cells
  - DL2: $10 \times 10^9$ E7 TCR-T cells
  - DL3: $100 \times 10^9$ E7 TCR-T cells

**Treatment Schema**
- Fludarabine $25 \text{ mg/m}^2$
- E7 TCR-T cells
- Cyclophosphamide 30 or 60 mg/Kg
- Aldesleukin 720,000 IU/KG

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DL, dose level; HLA-A, human leukocyte antigen; HPV, human papillomavirus; TCR, T cell receptor.

Patient 12

- 40-year-old female with cervical cancer
- 7 prior systemic agents
- Prior atezolizumab (PD-L1 blockade)
- Soft tissue, retroperitoneal, and rectal metastases
- 8-month response

PD-L1, programmed death ligand-1.

Persistence of Engineered T Cells in Blood

PD-1, programmed death receptor-1; TCR, T cell receptor.

Summary and Authors’ Conclusions

Summary

- Responses in 6/12 patients with highly refractory disease
- Responses in 4/8 patients previously treated with PD-1-based therapy
- Durable, complete regression of one or more tumors in most responding patients
- Treatment resistance appears driven by tumor-intrinsic immune-related gene defects

Authors’ Conclusions

- Robust regression of epithelial cancer following engineered T cell therapy
- Tumor-intrinsic defects in antigen processing and presentation appear to be important in the highly advanced cancer setting
Somatic cells (e.g. skin fibroblasts)

Donor/patient

iPS cells

Differentiation

Adipocytes
Blood cells
Neural cells
Skin cells
Pancreatic cells

Reprogramming factors (Oct4, Sox2, c-Myc, KIF4)

iPSC Reprogramming
Making NK Cells And T Cells From iPSCs
Modification Of iPSCs To Change Their Immune Properties

Our Advantage? We can readily modify these cells Add factors/remove factors, etc.
Summary

- Immunotherapy is rapidly changing the landscape of cancer therapy
- Cell-based therapies are emerging in the clinic
- Efforts to scale-up and create capacity with autologous and “off the shelf” products are in progress
- Modifications of current successful approaches for “greater efficacy” have created a new modality of cancer therapy