Translating Breakthrough Science

Best in class treatments that restore the body’s ability to repair itself

R&D Day
New York, March 24th, 2016
Immuno-Oncology R&D Day

Michel Lussier, M.Sc. BME, MBA
Chairman
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In addition to historical facts or statements of current condition, this presentation contains forward-looking statements, including statements about the potential coverage of the US Patent No 9,181,527, the safety and efficacy of Celyad’s product candidates, the potential clinical and commercial potential of these product candidates, potential future product candidates and the timing of future clinical trials, which reflect our current expectations and projections about future events, and involve certain known and unknown risks, uncertainties and assumptions that could cause actual results or events to differ materially from those expressed or implied by the forward-looking statements.

In particular it should be noted that there are risks and uncertainties associated with strength of the Company’s intellectual property portfolio, including the US Patent No 9,181,527. Third parties may challenge the validity, enforceability, or scope of our patents, including the US Patent No 9,181,527, which may result in such patents being narrowed, invalidated, or held unenforceable. Furthermore, even if these patents are unchallenged, our patents may not adequately cover our products or prevent others from designing their products to avoid being covered by our claims.

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Purpose of today is to provide an update on...

1. Celyad progress
2. Vision & opportunity for immuno-oncology
3. The science behind NKR T-Cells (NKG2D)
4. NKR T-Cell unique profile & benefits
## Today’s agenda

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<th>Topic</th>
<th>Speaker</th>
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<td>Welcome and purpose of the day • Introduction of the speakers</td>
<td>Michel Lussier, M.Sc. BME, MBA Chairman, Celyad SA</td>
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<td>Celyad</td>
<td>• Strategic vision for Immuno-Oncology</td>
<td>Christian Homsy, MD, MBA CEO, Celyad SA</td>
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<td>Immunotherapy &amp; CAR-T</td>
<td>• Cancer Immunotherapy landscape • Adoptive therapy in liquid &amp; solid tumors</td>
<td>Jeffrey S. Weber, MD, PhD NYU Langone Medical Center</td>
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<td>Immunotherapy &amp; CAR-T</td>
<td>• Natural Killer Cells and NKG2D receptor • Physiology and ligand expression</td>
<td>Julie Y. Djeu, PhD Moffitt Cancer Center</td>
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<td>Natural Killer Receptor NKG2D</td>
<td>• NKR T-cells concept and technology • NKR-2 preclinical evidence</td>
<td>Charles Sentman, PhD Dartmouth College</td>
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**Break**
## Today’s agenda continued

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<td>Georges Rawadi, PhD, M.Sc. Celyad SA</td>
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<td>Celyad</td>
<td>• FTIH Phase I study</td>
<td>Sarah Nikiforow, MD, PhD Dana Farber Cancer Institute</td>
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<td>Immunotherapy &amp; CAR-T</td>
<td>• Liquid &amp; solid tumor development plan</td>
<td>Frederic Lehmann, MD Celyad SA</td>
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<td>• Portfolio and collaborations</td>
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<td>Immunotherapy &amp; CAR-T</td>
<td>• Q+A panel discussion</td>
<td>Debasish Roychowdhury, MD Board Member, Celyad SA</td>
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<td>Natural Killer Receptor NKG2D</td>
<td>• Celyad platform and opportunity</td>
<td>Debasish Roychowdhury, MD Board Member, Celyad SA</td>
</tr>
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<td></td>
<td>• Key insights from the program</td>
<td></td>
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Close
## Today’s guest experts

<table>
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<tr>
<th>Jeff S. Weber, MD, PhD</th>
<th>Charles Sentman, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deputy Director, Laura and Isaac Perlmutter Cancer Center, Co-director, Melanoma Program, NYU Langone Medical Center</td>
<td>Director, Center for Synthetic Immunity, The Geisel School of Medicine, Dartmouth College</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Julie Y. Djeu, PhD</th>
<th>Sarah Nikiforow, MD, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Center Director for Education and Training, Senior Member, Immunology Program, Garcia Endowed Chair in Cancer Leadership, Moffitt Cancer Center</td>
<td>Clinical Instructor, Stem Cell Transplantation Program, Cell Manipulation Facility, Dana Farber Cancer Institute</td>
</tr>
</tbody>
</table>
Positioned for success as a fully integrated biotech

- Differentiated best-in-class portfolio built on collaborations with premiere institutions
- Unprecedented results from our preclinical programs
- Diversified & robust pipeline to minimize risk
- Valuable & long-term patent estates
- Leveraging manufacturing expertise
- Global footprint
- Experienced management team focused on execution
Our Strong Collaborations: Breakthrough discoveries from premier institutions

Mayo Clinic collaboration led to novel cardiopoiesis platform

- Induces cardiac repair
- First Phase III program in ischemic heart failure
- Invented at Mayo Clinic, exclusively licensed to Celyad

Dartmouth collaboration led to novel NKR T-Cell platform

- T-cells engineered to express human Natural Killer Receptor NKG2D
- Phase I/IIa human trial ongoing
- Invented at Dartmouth College, exclusively licensed to Celyad
Our Opportunity: First time ever Class III ischemic heart failure patients experienced significant benefits with cell therapy

C-Cure® a first-in-class opportunity

IP
- Strong IP
- USPTO

Phase II
- Statistically Significant endpoints (1)
  1. Stronger
  2. Smaller
  3. Longer

Phase III
- CHART 1 complete
- Read out June '16
- CHART 2 FDA approved

Path to registration
- EMA Letter of Intent submitted

Who we are

Our focus is to translate breakthrough science into therapies that help restore the body’s ability to repair itself.

**CARDIOVASCULAR**

The cardiopoiesis cell platform
Unequalled Phase II data and currently in Phase III for ischemic heart failure.

**IMMUNO-ONCOLOGY**

A different approach combining Natural Killer Receptors with T-Cells called NKR-T cells. Our single NKR-T cell construct can target both solid and haematological tumors.

Strong Patent Family for CV & Oncology
Broad Product Portfolio
GMP production facilities

Seasoned leadership team with proven track records

Headquarters in Belgium, with subsidiary in the U.S.
What we deliver - Effectiveness

Unparalleled pre-clinical results: 100% tumor-free survival
- Survival >250 days in mice
- Well defined multiple mechanisms of action
- Long-term adaptive immune response
What we deliver - Breadth

**EFFECTIVENESS**

Unparalleled pre-clinical results: 100% tumor-free survival
- Survival >250 days in mice
- Well defined multiple mechanisms of action
- Long-term adaptive immune response

**BREADTH**

- Positive pre-clinical results in 5 different indications
- Ongoing Phase I study in MM and AML at DFCI
What we deliver - Safety

**EFFECTIVENESS**
- Unparalleled pre-clinical results: 100% tumor-free survival
  - Survival >250 days in mice
  - Well defined multiple mechanisms of action
  - Long-term adaptive immune response

**BREADTH**
- Positive pre-clinical results in 5 different indications
- Ongoing Phase I study in MM and AML at DFCI

**SAFETY**
- Remarkable safety profile
  - Low persistence of engineered T-cells shown
  - Selective targeting of tumor cells shown
  - Further safety profile being investigated in Phase I trial
Way forward for our immuno-oncology program

<table>
<thead>
<tr>
<th>2016 Q1</th>
<th>2016 Q2</th>
<th>2016 Q3</th>
<th>2016 Q4</th>
<th>2017</th>
</tr>
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<tbody>
<tr>
<td>MM &amp; AML Phase I</td>
<td></td>
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<tr>
<td>Results First 4 doses</td>
<td></td>
<td></td>
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<tr>
<td>Expand partnerships and collaborations</td>
<td></td>
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<tr>
<td>Solid tumors Phase I/II (NSCL, CRC, Ovarian, Bladder, Breast)</td>
<td></td>
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<tr>
<td>Allogeneic Platform</td>
<td></td>
<td></td>
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<tr>
<td>Other product candidates</td>
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</table>

Ambitious program, yet in line with capabilities and resources
A broad collaboration with world class research centers

Institut Curie

Broad scientific collaboration

- Inserm “Cancer and Immunity” Unit at the Institut Curie Paris, France
- Led by Sebastian Amigorena, PhD
- Objective is to further explore NKR T-Cells in solid tumors
- Adds expertise, research capability, and geographic reach to our immuno-oncology program

Dartmouth collaboration led to novel NKR T-Cell platform

- T-cells engineered to express human Natural Killer Receptor NKG2D
- Phase I/IIa human trial ongoing
- Invented at Dartmouth College, exclusively licensed to Celyad
Secured long-term and valuable patent estates

- **Three patent families** covering:
  - Autologous products
  - Pipeline
  - Allogeneic platform
- **Constructs** utilizing Natural Killer Receptor NKG2D
- **Three patents** issued by USPTO
- **Allogeneic Patent** - fundamental exclusivity for TCR deficient T-Cells
Translating Breakthrough Science: Celyad’s path to leadership in immuno-oncology

1. Deliver the current program
   - Establish proof of concept for NKR-2
   - Execute in MM & AML
   - Rapidly expand into solid tumors
   - Expand global reach

2. Build best in class portfolio
   - Advance B7H6 and NKp30
   - Transform cell manufacturing

3. Sustain leading position
   - Deliver allogeneic proof of concept
   - Investigate early stages of disease
   - Expand partnerships & collaborations
What makes us unique

**EFFECTIVENESS**

**Outperformed** other CAR-T pre-clinical results:
- 100% long-term tumor-free survival
- 100% survival on re-challenge

**BREADTH**

**One cell therapy** that can be applied broadly,
5 indications in pre-clinical in both liquid and solid tumors

**EXECUTION**

Rapid progress in Phase I study
Expertise in process development
Immuno-Oncology Therapy Area

Jeffrey S. Weber, MD, PhD
NYU Langone Medical Center
Celyad R&D Day
March 24, 2016
New York, NY

Jeffrey S Weber MD PhD
Laura and Isaac Perlmutter Cancer Center
NYU Langone Medical Center
Disclosures

• I consult for and have received less than $10,000 dollars per annum from BMS, Merck, Genentech, Astra Zeneca, GSK, Novartis, Nektar, Medivation, Celldex, Incyte and EMD Serono for membership on Advisory Boards
• I hold equity in Celldex, CytoMx and cCAM
• I am on scientific advisory boards for Lion Bioscience, Celldex, CytoMx, Incyte and cCAM
• I am not a member of any speaker’s bureau
• My institution, but not me personally received research support from BMS, Merck, GSK, Novartis and Astra Zeneca
• My laboratory receives research support from Mirati and Acetylon
Targeting the Immune System

Chen, D and Mellman, I 2013
Background: CAR T cells

- The initial design joined an antibody-derived scFv to the CD3z intracellular signaling domain of the T-cell receptor through hinge and trans-membrane domains
- CD3z signaling domain of the T-cell receptor, when engaged, will activate and induce proliferation of T cells but leads to anergy.
- The addition of a costimulatory domain in second-generation CARs improved replicative capacity and persistence of modified T cells
- Naive and memory T cells have significant replicative capacity and potential for long-term persistence
- CARs containing the 4-1BB costimulatory domain persist longer
- Retro- or lentiviral transduction approaches have the advantage of long-term gene expression but carry a risk of transformation
Schematic representation of the chimeric antigen receptor (CAR) structure.

CAR T development: academic-industry collaborations

- University of Pennsylvania with Novartis
- Baylor College of Medicine with Bluebird Bio and Celgene
- Memorial Sloan Kettering Cancer Center and the Fred Hutchinson Cancer Research Center with Juno Therapeutics
- National Cancer Institute with Kite Pharma
- Cellular Biomedicine Group with the Chinese PLA General Hospital
CD19 CAR T cells in CLL

- 45% ORR, no clear biomarkers associated with efficacy
- Long-term persistence of the genetically modified T cells with ongoing functional activity lasting beyond 3 years
- Patients with persistent CAR T cells develop B-cell aplasia and hypogammaglobulinemia, both “on-target” toxicity and a measure of persistence
- Ig replacement is absolutely required during prolonged CAR-mediated B cell aplasia.
- The most significant and unique toxicity from CAR T-cell therapy is cytokine release syndrome (CRS)
  - The hallmark is fevers that typically can exceed 40°C with associated myalgias, arthralgias, nausea, vomiting, and diarrhea.
  - IL-6 antibody reverses the CRS in all cases
CD19 CAR T cells in ALL

- Overall survival for adults with ALL is quite poor (30% to 40%)
- 83 relapsed pts treated, 70-90% CR rate with CAR T in 3 institutions; no GVHD observed; mostly pediatric patients
- Less persistence was seen compared to CLL treatment
- 6 month event free survival was 67% across studies
- Some B cell aplasia was seen
- Development of CRS seemed associated with benefit
- Relapsing patients still had CD19 expression on their cells, but most relapsers were CD19-
CD19 CAR T cells in non-Hodgkin’s lymphoma

- 39 patients reported from two institutions
- Response rate of approximately 67%
- Some responses were ongoing > 2 years
- Mostly DLBCL patients treated
- Two deaths at NCI, but lymphodepletion used
- Toxicity seen similar to that observed with CLL/ALL
Clinical efficacy of second generation CAR-T-cell therapy

<table>
<thead>
<tr>
<th>Disease and treating institute</th>
<th>Number of patients</th>
<th>Conditioning therapy</th>
<th>Infused CAR T-cell dose</th>
<th>Response rate</th>
<th>Survival outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>22</td>
<td>CY (1.5–3.0 g/m²)</td>
<td>1–3 × 10⁶/kg</td>
<td>NA</td>
<td>Median OS: 9 months</td>
</tr>
<tr>
<td>MSKCC</td>
<td>14 (3 = 11)</td>
<td>FLU (50 mg/m²) + CY (CY 500 mg/m² × 3 days) + 3: 1, corticosteroids, cyclophosphamide + desamethasone, cyclophosphamide + vincristine + doxorubicin</td>
<td>0.7–14.9 × 10⁶/kg</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>U Penn</td>
<td>5*</td>
<td>FLU (25 mg/m² × 3 days) + CY (200 mg/m² × 1 day)</td>
<td>1 or 3 × 10⁶/kg</td>
<td>NA</td>
<td>15 RFS: 7.8 months</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>7*</td>
<td>Lymphodepleting chemotherapy</td>
<td>2 × 10⁶/kg, 2 × 10⁶/kg, or 2 × 10⁷/kg</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CLL</td>
<td>10 (5 + 2*)</td>
<td>None: 4, CY-conditioning (1.5 or 3 g/m²), 4, BEAM conditioning + autologous SCT</td>
<td>0.4–1.0 × 10⁶/kg</td>
<td>10 10 10 20</td>
<td>NA</td>
</tr>
<tr>
<td>MSKCC</td>
<td>7*</td>
<td>PCRI + 6 cycles, CY (600 mg/m²)</td>
<td>3–30 × 10⁶/kg</td>
<td>57.2 14.3 42.9</td>
<td>NR NA</td>
</tr>
<tr>
<td>B-NHL</td>
<td>9*</td>
<td>FLU (25 mg/m² × 5 days) + CY (60 mg/kg × 2 days) + i.a. IL-2, following CAR-T cell infusion</td>
<td>3–3 × 10⁶/kg</td>
<td>100 0 100 0</td>
<td>NA</td>
</tr>
<tr>
<td>NCI</td>
<td>11*</td>
<td>FLU (25 mg/m² × 5 days) + CY (60 mg/kg × 2 days)</td>
<td>1–5 × 10⁶/kg</td>
<td>88.9 55.6 33.3</td>
<td>11.1</td>
</tr>
<tr>
<td>NCI</td>
<td>20</td>
<td>FLU (50 mg/m² × 3 days) + CY (300 mg/m² × 3 days)</td>
<td>1 × 10⁶/kg</td>
<td>66.7 11.1 55.6</td>
<td>0 NA</td>
</tr>
<tr>
<td>MSKCC</td>
<td>6*</td>
<td>BEAM conditioning + autologous SCT</td>
<td>5–10 × 10⁶/kg</td>
<td>100 0 0 0</td>
<td>NA</td>
</tr>
<tr>
<td>U Penn</td>
<td>8*</td>
<td>PCRI, CY, CY, CY + CY</td>
<td>3.7–8.9 × 10⁶/kg (median 5.8 × 10⁶/kg)</td>
<td>50 37.5 12.5</td>
<td>0 NA</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>9*</td>
<td>Lymphodepleting chemotherapy</td>
<td>2 × 10⁶/kg, 2 × 10⁶/kg, or 2 × 10⁷/kg</td>
<td>66.7 11.1 55.6</td>
<td>NA NA</td>
</tr>
</tbody>
</table>

*In published report, *a* reported as abstract, *doses unknown. PCRI is pentostatin 1 mg/m² day 1, cyclophosphamide 600 mg/m² day 1, rituximab 375 mg/m² day 1. Abbreviations: ALL, acute lymphoblastic leukemia; BEAM, BCNU (carmustine) + etoposide + cytarabine + melphalan; B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CR, complete response; CY, cyclophosphamide; CYVAD, cyclophosphamide + vincristine + doxorubicin + desamethasone; CY, cyclophosphamide + etoposide; CYVAD, cyclophosphamide + vincristine + doxorubicin + desamethasone; FD, Fred Hutchinson Cancer Research Center; i.a., intravenous; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; NA, not applicable; ORR, overall response rate; OS, overall survival; PR, partial response; RFS, relapse-free survival; SD, stable disease; U Penn, University of Pennsylvania; VP, etoposide.

What are the toxicities of CAR-T cells?

- Cytokine release syndrome (CRS) is an inflammatory process related to high levels of T-cell proliferation with resulting marked elevations in cytokine levels.
- CRS includes elevations in soluble interleukin-2 receptor alpha, IL-6, IL-10, and interferon-gamma.
- Hyperferritinemia (>10,000 ng/mL), hepatomegaly/ splenomegaly, and hypofibrinogenemia (>150 mg/dL) are also seen.
- High disease burden is associated with CRS.
- IL-6 antibody tocilizumab has been used to treat CRS successfully; IL-6 is not needed for CAR T efficacy in mice.
- Steroids are a second choice; they inhibit CAR efficacy.
What are the toxicities of CAR-T cells?

• B cell aplasia is a reliable PD marker of CAR T activity
• Delirium, dysphasia, akinetic mutism, and seizures are neurologic symptoms associated with CAR T therapy
• Although temporally related to the systemic CRS in first 5 days, they are not clearly correlated with the presence of CAR cells in the cerebrospinal fluid
• The neurologic symptoms do not appear to be modified by IL-6 antibody tocilizumab and resolve as the CRS resolves
What about CAR-T cells for solid tumors?
What about CAR-T cells for solid tumors?

- ERBB2 CAR T cells resulted in a fatal adverse event, felt due to low-level ERBB2 expression in healthy lung epithelial and cardiovascular cells.
- EGFRvIII and chondroitin sulfate proteoglycan-4 (CSPG4) felt to be good solid tumor targets.
- Mesothelin knock-outs survive normally – not essential molecule; expressed by 25-75% of epithelial malignancies, a good target.
- Interference from soluble mesothelin may occur, which in principle could occupy and block the scFv portion.
- At U Penn, 4 patients were treated with CAR T electroporated with the mRNA encoding for a second-generation mesothelin CAR; no RECIST responses.
- PD effects were seen with increased transient IL-12, IL6, G-CSF, MIP1β, MCP1, IL1RA, and RANTES in the serum.
- Treatment was well tolerated and trials continue to accrue.
What will CAR T cells be competing with?

- **Cell therapy**
  - BiTEs: Blinatumumab
  - Tumor Infiltrating Lymphocytes
  - Genetically modified TcR transduced peripheral blood T cells
- **Checkpoint Protein Inhibition**
  - CTLA-4: ipilimumab, tremelimumumab
  - PD-1: nivolumab, pembrolizumab
  - PD-L1: atezolizumab, avelomab, durvalomab
Structure of different types of T-cell-engaging antibodies

Bispecific T-cell engager (BiTE®)
- Single polypeptide chain

Dual affinity retargeting (DART)
- Two polypeptide chains
- Interchain disulfide bridge

Tetravalent tandem diabody (TandAb®)
- Single polypeptide chain
- Chain dimerization

Clinical efficacy of blinatumomab, a bispecific T cell engager

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
<th>Treatment schedule</th>
<th>Response rate</th>
<th>Relapse-free survival</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-positive ALL</td>
<td>20*</td>
<td>15 µg/m² per day continuous i.v. × 4 weeks every 6-week cycle</td>
<td>NA</td>
<td>80</td>
<td>61% at 33 months</td>
</tr>
<tr>
<td>ALL</td>
<td>36*</td>
<td>5 µg/m² and 15 µg/m² per day (week 1, and thereafter until 4 weeks, respectively)</td>
<td>NA</td>
<td>69</td>
<td>Median of 7.6 months</td>
</tr>
<tr>
<td>ALL</td>
<td>189*</td>
<td>9 µg and 28 µg per day (week 1, and thereafter, respectively) continuous i.v. × 4 weeks every 6-week cycle</td>
<td>NA</td>
<td>43</td>
<td>Median of 5.9 months</td>
</tr>
<tr>
<td>B-NHL (FL, MCL, DLBCL)</td>
<td>35*</td>
<td>60 µg/m² per day continuous i.v.</td>
<td>69</td>
<td>37</td>
<td>NA</td>
</tr>
<tr>
<td>DLBCL</td>
<td>21*</td>
<td>Cohort I and II: 9 µg, 28 µg, and 112 µg per day (week 1, week 2, and thereafter, respectively), cohort II: 112 µg per day × 8 weeks</td>
<td>43</td>
<td>19</td>
<td>NA</td>
</tr>
</tbody>
</table>

*In published report. †In reported abstract. Abbreviations: ALL, acute lymphocytic leukaemia; B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; DLBCL, diffuse large-B-cell lymphoma; FL, follicular lymphoma; i.v., intravenous; MCL, mantle-cell lymphoma; MRD, minimal residual disease; NR, not applicable or available; ORR, overall response rate; PR, partial response; SD, stable disease.


Adoptive Cell Therapy with TIL

Adoptive immunotherapy for cancer: harnessing the T cell response

Nature Reviews | Immunology
VOLUME 12 | APRIL 2012 | 269
How can TIL be grown for a phase III trial?

Somerville and Dudley Oncoimmunology 2012
**LN-144: PHASE 2 STUDY OVERVIEW**

- A Phase 2, Multicenter, Single-arm Study to Assess the Safety, Feasibility, and Efficacy of Cell Transfer Therapy Using Autologous Tumor Infiltrating Lymphocytes (LN-144) Followed by IL-2 for Treatment of Metastatic Melanoma

- 20 patients
  - Metastatic melanoma
  - Refractory to at least one systemic treatment

- Objectives:
  - Safety
  - Feasibility
  - Anti-tumor activity and other measures of efficacy
  - Immune correlates

- Treatment
  - Lymphodepletion
  - TIL infusion
  - IL-2
ACT with Genetically Modified Lymphocytes

Adoptive immunotherapy for cancer: harnessing the T cell response

Nicholas H. Kestin, Mark E. Dudley and Steven A. Rosenberg
Exploiting the curative potential of adoptive T-cell therapy for cancer: TIL recognizing neo-antigens
Checkpoint blockade is a major advance in cancer therapy

**Stimulatory and inhibitory responses mediated by immune checkpoints.**

Depicted are interactions between immune checkpoints and their ligands as well as their cellular effects. Stimulatory effects are depicted with green arrows, and inhibitory effects are depicted with red symbols. The effect of GITR ligation in NK cells is not yet fully understood. T REG: Regulatory T cell; DC: Dendritic cell; NK: Natural killer; MHC: Major histocompatibility complex; PD-1: Programmed death-1; KIR: Killer cell immunoglobulin like receptor; TCR: T-cell receptor; LAG-3: Lymphocyte activation gene-3; TIM-3: T-cell immunoglobulin and mucin protein-3; CTLA-4: Cytotoxic T lymphocyte associated antigen-4.
Overall Survival: First-line Nivolumab vs Chemotherapy

HR 0.42 (99.79% CI: 0.25–0.73; \( P < .001 \))

Patients who died, n/N
- Nivolumab: 50/210
- Dacarbazine: 96/208

Median OS mo (95% CI)
- Nivolumab: NR
- Dacarbazine: 10.8 (9.3–12.1)

1-yr OS 73%
1-yr OS 42%

Kaplan–Meier Curves for Overall Survival for Nivolumab in Squamous Cell Lung Cancer as Second Line Therapy


ORR 20% for nivolumab versus 9% for docetaxel
Response Characteristics and Changes in Tumor Burden in Patients with Hodgkin's Lymphoma Receiving Nivolumab

20/23 patients had ORR, and 3 with SD; 86% PFS rate at 24 weeks

How will CAR-T cells fit in in the new era of checkpoint blockade?

- New trials will add checkpoint blockade to CD19 CAR T therapy
- Future CD19 CAR T strategies will limit the persistence of the effectors, to avoid B cell aplasia, and checkpoint blockade may become a treatment for resistant patients or those who relapse
- For solid tumors, it seems unlikely that in the foreseeable future that CAR T cells will supplant checkpoint inhibition
- CAR T cells may be added to checkpoint inhibition, and will be part of a multi component therapy for solid tumors
What is the future for CAR-T cell strategies?

• In humanized mice bearing adenocarcinoma xenografts, CD4+ CAR T cells equipped with an ICOS signaling domain are superior, whereas 4-1BB domains are generally preferred in CD8+ T cells.
• Replicative capacity is the most important predictive biomarker of success.
• Isolate central memory or naive T cells from input lymphocytes obtained from whole blood. In contrast, use bulk T cells and then to culture the T cells under conditions that promote the maintenance of a less differentiated population of naive and central memory cells.
• Suicide constructs will enable attenuation of off-tumor toxicities with HSV-tk and iCaspace-9 inducible genes.
Strategies to improve chimeric antigen receptor (CAR) T-cell therapy.

Safety
- HSV thymidine kinase
- Inducible caspase 9
- Transient expression
- CCR
- iCAR
- Truncated EGFR

Persistence
- Selection of T-cell subsets for CAR transfer
- IL-15, IL-12 and other cytokines
- Select virus-specific T-cells for transduction
- Off-the-shelf CAR T-cell

Homing
- Chemokine receptors (CXCR2, CCR4, CCR2B)
- VEGFR2 CAR

Overcome immunesuppression
- Expression of survival genes such as Bel-X(L)
- Treg suppression
- CD25 expression upregulation
- IDO downregulation
- TRUCKs CAR (IL-12)
- Express dominant negative receptors (TGF-β)
- Switch receptor chimeras (PD1-CD28)
- Constitutive CD40L or 4-1BB

Combination therapies
- Checkpoint blockade (PD1, CTLA-4)
- GM-CSF neutralization
- Autologous transplantation
- Radiotherapy
- Chemotherapy


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Conclusions - CAR T cells

- CD19 CAR T cells have high response rates in various B cell malignancies and will likely show positive results in ongoing registration studies and be approved for those indications.
- They will reach widespread use, but the CRS toxicities will be challenging.
- The current strategy using CARs seems unlikely to have broad based success in solid tumors.
- Completely new approaches are needed to diminish the likelihood of off-target toxicities from CAR T cells in solid tumors.
- Complex multi part strategies will likely be needed to bind a CAR, then a second step to trigger it that will be more tumor-specific.
- Suicide CARs may also be useful.
- Masked antibodies that are only active within the tumor microenvironment are another potential advance.
Immuno-Oncology Therapy Area

Julie Y. Djeu, PhD
Moffitt Cancer Center
• High NK cell numbers are associated with a positive prognosis in cancer

• NK cells can spontaneously kill a wide spectrum of tumor cells and cells under stress by infection or DNA damage
NK cell receptors

E. Vivier et al., Nature Imm. Rev. 2012
# NK cell receptors and ligands

## Activating Receptor

<table>
<thead>
<tr>
<th>Receptor</th>
<th>CD#</th>
<th>Ligands shared by tumor cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>aKIR</td>
<td>CD156</td>
<td>HLA-A,B,C</td>
</tr>
<tr>
<td>NKG2C</td>
<td>CD159c</td>
<td>HLA-E</td>
</tr>
<tr>
<td>NKG2D</td>
<td>CD314</td>
<td>MICA/B, ULBP 1-6</td>
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<tr>
<td>FcγRIIIA</td>
<td>CD16</td>
<td>Fc – IgG-coated tumor cells</td>
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<tr>
<td>NKp46</td>
<td>CD335</td>
<td>Heparin Sulfate, unknown</td>
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<tr>
<td>NKp44</td>
<td>CD336</td>
<td>Heparin sulfate, unknown</td>
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<tr>
<td>NKp30</td>
<td>CD337</td>
<td>B7H6</td>
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<tr>
<td>DNAM1</td>
<td>CD226</td>
<td>PVR, PVRL2</td>
</tr>
</tbody>
</table>

## Difference from T cells

**T cell TCR**

antigen-specific, not shared
Mechanism of activating NK cell receptors

- KIR2DS
- KIR3DS
- NKG2C
- NKp44
- FcRγIII
- NKp46
- CD3γ
- CD3ζ
- Syk/Zap70
- TCR
- NKp30
- extracellular
- intracellular

MyVho θ A L 7 i A i h b

Djeu et al., Clinical Cancer Res. 2002
ERK and PI3K control lytic granule movement along the microtubules

Jiang et al., Nature Imm 2000
NK cell receptors

E. Vivier et al., Nature Imm. Rev. 2012
# NK cell receptors/ligands

<table>
<thead>
<tr>
<th>Inhibitory</th>
<th>Receptor</th>
<th>CD#</th>
<th>Ligand</th>
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<tr>
<td>iKIR</td>
<td>CD156</td>
<td>HLA-A,B,C</td>
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<tr>
<td>NKG2A</td>
<td>CD159a</td>
<td>HLA-E</td>
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<tr>
<td>TIGIT</td>
<td></td>
<td>PVR, PVRL2</td>
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<tr>
<td>Tactile</td>
<td>CD96</td>
<td>PVR</td>
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<tr>
<td>PD1</td>
<td>CD279</td>
<td>PDL1</td>
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<tr>
<td>LAG3</td>
<td>CD223</td>
<td>MHC-II</td>
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<tr>
<td>TIM3</td>
<td>CD366</td>
<td>galectin-9</td>
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</tr>
</tbody>
</table>
Mechanism of inhibitory NK cell receptor

Activating Receptor

extracellular

DAP10
DAP12
CD3ζ
FcεRγ

intracellular

ITIM

dephosphorylates

S. Donatelli et al. 2013
Balance of Activating and Inhibitory Receptors for NK cell function

Immune Escape Mechanisms

- Platelets
- Immunosuppressive factors
  - Adenosine
  - PGE2
  - TGFβ
  - IL10
- Ligand shedding
- Stromal/MDSC

TGFβ induces microRNA-183 to block DAP12 gene transcription and protein translation in NK cells

S. Donatelli et al., PNAS 2014
Djeu et al.
DAP12 is depleted in intratumoral NK cells in lung cancer

S. Donatelli et al., PNAS 2014
Djeu Lab
Antibody-based NK cell therapy

- **ADCC via CD16**
  - Rituximab (CD19)
  - Herceptin (Her2)

- **Checkpoint blockade**
  - KIR
  - NKG2A
  - PD1
  - LAG3
  - TIM3

- **Bispecific antibody - ScFv**
  - Anti-CD16 linked to
    - anti-CD19/CD30/EGFR/CD33,EPCAM
  - NKG2D linked to anti-CD3
  - Anti-B7H6 linked to anti-CD3

---

CAR-based NK therapy

- **TAA-CAR into NK cells**
  - CD19/CD20
  - mesothelin/HER2

- **NKR-CAR into T cells**
  - NKG2D
  - CD16
  - NKp46
  - NKp30
Immuno-Oncology Therapy Area

Charles Sentman, PhD
Dartmouth College
Charles Sentman, Ph.D.
Professor, Department of Microbiology & Immunology
Director, Center for Synthetic Immunity
The Geisel School of Medicine
Dartmouth College

Disclosures:
IP & patents on NK receptor based bi-specific proteins and chimeric antigen receptors (CARs).
Sponsored research support: Celdara Medical, Celyad.
Consulting: Celdara Medical, Celyad
These activities are managed in compliance with the polices of Dartmouth College.
NK cell receptor based CAR T cells mobilize the immune system to fight cancer

CAR: chimeric antigen receptor
NKG2D perfect candidate for CAR construct to treat multiple cancers

- NKG2D receptor is expressed on Natural Killer (NK) cells, T-Cells and macrophages
- It is an activating receptor that triggers cell killing activity
- Killing activity is dependent on the expression of NKG2D ligand at the surface of target cells
- Several NKG2D ligands can be expressed by cells during infection, tumorigenesis or DNA damage
- Numerous tumor types express NKG2D ligands: ovarian, prostate, lung, prostate, melanoma, leukemia, breast, colorectal cancers...

Human NKG2D ligands

- MIC molecules may be induced in association with DNA damage, cell stress, infection or malignant transformation
- System in which “self” alerts the immune system via upregulation of intrinsic NKG2D ligands
- Tumor cells may express one or more ligands
NKG2D ligand expression in tumor cells

**Ligands**

- MICA
- MICB
- ULBPs 1-6

---

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>(40, 43, 148-151)</td>
</tr>
<tr>
<td>Bladder</td>
<td>(152)</td>
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<tr>
<td>Breast</td>
<td>(40, 153-155)</td>
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<tr>
<td>Lung</td>
<td>(40, 156, 157)</td>
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<td>Hepatocellular</td>
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<td>Colon</td>
<td>(40, 41)</td>
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<td>Renal</td>
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<td>Prostate</td>
<td>(40, 161)</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>AML</td>
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<tr>
<td>CML</td>
<td>(39, 165, 166)</td>
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<tr>
<td>CLL</td>
<td>(167, 168)</td>
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<td>(169)</td>
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<td>Multiple Myeloma</td>
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<tr>
<td>Neuroblastoma</td>
<td>(104)</td>
</tr>
</tbody>
</table>

Spear et al., Cancer Immunity (2013)
CAR-NKG2D construct: NKR-2

- Expression of this receptor at the cell surface associates naturally with DAP10 and provides costimulation signaling.

- Vector: Moloney Murine Leukemia Virus (Mo-MuLV)-based oncoretroviral vector SFG-chNKG2D.

- Packaging cell line: PG13. Vector particles are pseudotyped with the Gibbon Ape Leukemia Virus (GAL-V) envelope glycoprotein.
NKR-2 T cells attack tumor cells

CAR- NKG2D T-Cells produce IFN-γ with NKG2D ligand-expressing tumor cells

CAR- NKG2D T-Cells kill NKG2D ligand-expressing tumor cells in a CAR-dependent manner
NKR-2 T cells recognize many tumor types

Pancreatic cancer

Breast cancer

NKR-2 T cells treatment regimen

NKR-2 T cells do not survive long in vivo

Spleen

Bone marrow

Peritoneal cavity

Spear and Sentman
Lymphodepletion is not required for NKR-2 T cell therapy

- *in vivo* studies were performed in suboptimal conditions of NKR-2 T cells
- Myeloma cancer model was used with or without lymphodepletion using Cyclophosphamide

---

Barber et al. Gene Therapy, 2011 18:509
NKR-2 T-cells induce long-term tumor free survival in animal models

Ovarian cancer model

100% animal survival

Healthy  Tumor-bearing

NKR-2 T cells induce durable anti-tumor immunity

Following CAR T-Cell therapy, long-term protection demonstrated against parental tumor, even if NKG2D ligand negative

Treatment with NKG2D CAR T-Cells led to long-term survival of mice injected with 5T33MM tumor cells (MM model)
Survivors were used to re-challenge

Survivors were either re-challenged with 5T33MM cells or with RMA cells a different tumor type; naive used as control
100% of animals re-challenged with the same tumor type survived

Host response to NKR-2 T cell therapy

Female B6 mice

Week 1 – 5
inject 5 x 10^6 T cells (i.p.)

d0- inject 2 x 10^6
ID8-GFP cells (ip)

\[ d+1, d+3, d+7- \]

examine host cell responses
NKR-2 T cells activate host immunity in TME

NKR-2 T cells deplete tumor Tregs

Peritoneal cells

Macrophage activation

Figure 1 | Colour wheel of macrophage activation.
NKR-2 T cells recruit macrophages to the tumor

NKR-2 T cells reduce myeloid suppression in the tumor

NKR-2 T cells inhibit the formation of new blood vessels
NKR-2 T cells alter the tumor microenvironment for long-term survival

1. CAR NKG2D T cells kill tumor cells

2. CAR NKG2D T cells activate & recruit anti-tumor immune cells

3. CAR NKG2D T cells induce protective immunity

- IFNγ
- GM-CSF
- Chemokines
- Perforin
Immuno-Oncology
Therapy Area

Georges Rawadi, PhD, MSc
VP Business Development
Celyad SA
Celyad’s competitive positioning in the CAR-T space

What is unique?

MULTIPLE
- Multiple cancer indications
  - hematological & solid
- Autologous and allogeneic approaches

BALANCED
- Well balanced portfolio
- NKR-2 & NKR-30 innovative chimeric T-cells
- B7-CAR-T classical chimeric T-cells

INTELECTUAL PROPERTY
- Three patent families covering autologous products, pipeline and allogeneic platform
Celyad’s competitive positioning in the CAR-T space
What makes NKR-2 lead candidate unique?

Classical CAR construct
- Uses scFv derived from Ab
- One CAR construct targets 1 tumor
- MOA: Direct killing
- 1st/2nd/3rd generation
- Mostly CD19 CAR-T
- Crowded IP

Celyad NKR-2 construct
- Uses NK cell receptors
- One CAR construct targets multiple ligands & tumors
- MOA: beyond direct Killing
- Use of the native sequence: natural co-signaling - DAP10
- Strong IP
Our Opportunity:
What would an ideal cell therapy need to be able to do?

- Selective targeting
- Ability to kill
- Shield against recurrence
- Cut off vital supply and disrupt TME
Our Solution: A weaponized NKR T-Cell that combines four proven mechanisms to help restore the body’s ability to repair itself

Selectively targets cancer cells via binding to 8 ligands of NKG2D present on multiple liquid & solid tumors

Promotes direct killing of cancer cells as NKG2D is an activating receptor

Promotes adoptive immunity through the induction of a specific cytokine profile

Cuts off blood supply by targeting the tumor neovasculature and attack Tregs & MDSCs

NKR-2 T cells
Well defined multiple mechanisms of action
### Celyad immuno-oncology pipeline

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-Clinical</th>
<th>Preclinical POC</th>
<th>Phase I/II</th>
<th>Phase II/III</th>
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<tbody>
<tr>
<td><em>Autologous NKR-2</em></td>
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<tr>
<td>Multiple Myeloma</td>
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<tr>
<td><em>Solid Tumors</em></td>
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<tr>
<td><em>New products and platform</em></td>
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<td></td>
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<tr>
<td>Allogeneic platform</td>
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<tr>
<td>NKR-30</td>
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- **Acute Myeloid Leukemia**
- **Solid Tumors**
- **B7CAR-T**
- **Allogeneic platform**
- **NKR-30**
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NKR-2 T cells
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Zhong et al. Cancer Res, 2005

NKR-2 CAR T cells
Control T cells
NKR-2 CAR T cells + Cy
NKR-2 CAR T cells

Ovarian cancer model
100% animal survival

Healthy Tumor-bearing
Celyad immuno-oncology pipeline

Autologous NKR-2

Multiple Myeloma
Acute Myeloid Leukemia
Solid Tumors
B7CAR-T

New products and platform

Allogeneic platform
NKR-30
Sarah Nikiforow, MD, PhD
Attending Physician
Dana-Farber Cancer Institute
Instructor in Stem Cell Transplantation
Assistant Medical Director – Cell Manipulation Core Facility
Harvard Medical School

Disclosures: None
Efforts to Optimally Harness Anti-tumor T-cell Immunity

- Bring targets and immune effectors physically together (blinotumumab)
- Stack the odds in our favor (CARS)
  - Genetically engineer a high % of T cells specific for tumor antigens
  - Set these T cells to react immediately and strongly
- Make the tumor targets more attractive
  - Load tumor antigens into dendritic cells
  - Attract dendritic cells to the tumor
  - Tumor vaccines
- Disable the brakes (checkpoint blockade)
Targeting NKG2D ligands – exploiting NK-cell recognition

- MIC molecules may be induced in association with DNA damage, cell stress, infection or malignant transformation.
- System in which “self” alerts the immune system via upregulation of intrinsic NKG2D ligands.
NKG2D Ligands in Cancer

- Multiple targets with expression across many tumors
- Targeted therapy may have broad applicability
- Potential to recognize solid and liquid tumors
- Low likelihood of “on target” off tumor effects as little expression on normal tissues

### Expression of NKG2D ligands on human tumor cells

<table>
<thead>
<tr>
<th>Tumor Type</th>
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</tr>
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<tbody>
<tr>
<td>Carcinoma</td>
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<td>Hepatocellular</td>
<td>(158)</td>
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<td>(104)</td>
</tr>
</tbody>
</table>

*Spear, Cancer Immunity. 2013*
Unmet Medical Need – Multiple Myeloma

**Then**

**Now**

PR post auto

---

Attal, NEJM. 1996

Ong, BMT. 2016
Unmet Medical Need – AML

Now +/- Transplant

Stelljes, JCO. 2014
CM-CS1/NKR-2 Design and Rationale

- Native TCR Complex
- Canonical CAR
- CM-CS1 CAR

---

Sadelain, Park ASH Educ Program, 2015
How it works for the patient – 8 days

1. T-CELL COLLECTION
2. T-CELL TRANSDUCTION
3. T-CELL ADOPTIVE TRANSFER
CM-CS1/NKR-2 T-cell GMP manufacturing at DFCI - Feasible

T-cell collection

Activation with IL-2 and soluble antiCD3-Ab

γ-retroviral transduction #1

γ-retroviral transduction #2

Grelex culture with IL-2

Release testing on CD8+ T cells

AML/MDS/MM Tumor cell

Native NKG2D

Mock processing #1

Mock processing #2

NKG2D CAR

Dap 10

CD3ζ

IV administration of autologous CM-CS1 T-cells

26.03.16 115
High-level transduction of T cells which is stable over time

<table>
<thead>
<tr>
<th>NKG2D expression on CD8+ T cells</th>
<th>Val #1 Healthy Donor</th>
<th>Val#2 Healthy Donor</th>
<th>Val #3 Healthy Donor</th>
<th>Val#4 AML</th>
<th>Val#5 AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector-driven NKG2D expression</td>
<td>41.9%</td>
<td>36.3%</td>
<td>49.3%</td>
<td>65.9%</td>
<td>23.6%</td>
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</table>

![Data chart showing NKG2D expression over time and conditions]
Consistent functional activity

<table>
<thead>
<tr>
<th>IFN-γ production (pg/ml)</th>
<th>Mock Transduced T Cells</th>
<th>NKG2D CM-CS1 T Cells</th>
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</thead>
<tbody>
<tr>
<td>CAR Cells Only</td>
<td>0,0</td>
<td>3,9</td>
</tr>
<tr>
<td>Murine Line - Ligand Neg</td>
<td>0,0</td>
<td>0,1</td>
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<tr>
<td>Murine Line - huMICA Pos</td>
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<td>723,9</td>
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<tr>
<td>huMyeloma Line</td>
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<td>4512,2</td>
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<tr>
<td>huPancreatic Tumor</td>
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<td>5596,2</td>
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</table>
Phase 1 Trial Eligibility

**Who is eligible:**
- Histologically confirmed AML, MDS-RAEB that is not in remission and for which there are no reasonable standard treatment options
- Relapsed or relapsed/refractory multiple myeloma with progressive disease

**Select exclusion criteria:**
- Chemotherapy or Radiotherapy in past 3 weeks
- Active Infections
- Active autoimmune disease
- CNS disease
- Prior allogeneic stem cell transplant, adoptive T-Cell therapy or gene therapy
Phase 1 Dose-Escalation 3+3 Design

- Per dose level, at least 1 patient with AML/MDS and 1 patient with myeloma must be represented.
- Ability to distinguish MTDs for individual diseases.
- Enrollment is staggered such that the 2nd patient on each dose level cannot be enrolled for 21 days after the 1st patient was treated with a 21 day wait between cohorts.
- No lymphodepleting chemotherapy
- 1 infusion

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>#Participants</th>
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<tr>
<td>1x10^8 cells</td>
<td>12-24</td>
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MTD:
- AML/MDS-RAEB: 6
- Multiple Myeloma: 6

Total: 24-36
Phase 1 Trial Objectives

Primary Objectives

• Safety
• Feasibility of intravenous administration of CM-CS1 T-Cells (at escalating doses)

Secondary Objectives

Clinical objectives
• To assess the progression-free survival (PFS)
• To assess the clinical anti-tumor effect by standard criteria for each tumor type

Correlative immunobiology objectives
Dose Limiting Toxicities (DLT)

 DLT refers to toxicities during treatment and within 30 days following dosing, that are new and at least possibly related to T cells. (CTCAE v4.0)

- Any Grade 3 or higher non-hematologic toxicity, not directly attributable to the underlying disease or progression of underlying disease, except: asymptomatic Grade 3 electrolytes, Grade 3 nausea, vomiting, or fatigue. except Grade 3 non-hematologic toxicities that can be controlled to Grade 1 or less within 72 hours with appropriate treatment

- Grade 2 or higher autoimmune toxicity, such as, but not restricted to interstitial pneumonitis, autoimmune colitis and thyroiditis. except Grade 2 or higher autoimmune toxicity that can be controlled to Grade 1 or less within 72 hours with appropriate treatment
Expected Toxicities from CM-CS1 T cells

- Transfusion/Hypersensitivity Reactions
- Cytokine Release Syndrome
- Neurologic Changes
- Management algorithms delineated

Potential Toxicities from CM-CS1

- Autoimmune Toxicities (Gastrointestinal and Pneumonitis)

Lee D., Blood. 2014

Celyad
Measures of Clinical Efficacy

AML/MDS:
- Peripheral blood profiles
- Bone marrow aspirate and biopsy (flow cytometry, cytogenetics and molecular studies)
- In patients with extramedullary disease: PET/CT

MM:
- Bone marrow aspirate and biopsy
- Serum and urine M-protein
- Serum free light chains
- PET/CT or MRI: Evaluation for measurable plasmacytomas

Patient

→

Progression-free survival
Immunologic Correlates

- Persistence and trafficking of NKG2D-CAR T-Cells
- Bioactivity of NKG2D-CAR T-Cells
- Impact on endogenous immune milieu responses against tumor
- NKG2D-ligand expression on tumor cells to assess for antigen-escape and ligand shedding

Gene therapy safety follow-up for 15 years from NKG2D-CAR T-cell infusion
CM-CS1/NKR-2 Phase I Trial Summary

- Combine multi-antigen NK-cell recognition with inducible T-cell activation
- Feasibility of manufacturing established and ongoing in patients
- Phase 1 dose-escalation study - safety and feasibility as primary endpoints
- Targeted patients: AML/MDS and MM without standard treatment options
- Escalation and accrual proceeding as planned with higher dose levels anticipated
- Robust immunologic correlates will inform future phases of trials and applicability in other malignancies
Immuno-Oncology Therapy Area

Frédéric Lehmann, MD
VP, Head of Oncology Franchise
Celyad SA
Celyad immuno-oncology pipeline

<table>
<thead>
<tr>
<th>Category</th>
<th>Discovery</th>
<th>Pre-Clinical</th>
<th>Preclinical POC</th>
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NKR-2 distinct target product profile in CAR-T space

Classical CAR-T
Graft-approach

- Direct killing activity
- Persistence of the CAR-T cells to impact the minimal residual disease

Innovative NKR-2
Targeted therapy-approach

- Mode of action beyond the direct killing activity
- Induce a long term memory immune response against tumor-specific antigens

Principles

- Lymphepletion
- Controlled safety profile
- Durabla adaptive immune response
- Tailored infusion program

Celyad
NKR-2 program in 2016 - projected milestones

**Phase I study expected outcome**
- MTD selection
- Signal /optimal biological active dose
- PK data

**Preclinical activities plan**
- Data generation to sustain unique mechanism of action
- Evaluate potential synergetic combination therapy
- Optimal T-cell subtypes composition
- Tumor NKG2D ligands expression for indication selection
Autologous NKR-2 clinical development plan projected milestones

HEMATOLOGICAL INDICATIONS

PHASE I
- Multiple Myeloma
- Acute Myeloid Leukemia

PHASE II (PoC)
- Multiple Myeloma
- Acute Myeloid Leukemia

SOLID CANCER INDICATIONS

PHASE I/II
- Ovarian Cancer
- Colo-Rectal Cancer
- Non Small Cell Lung Cancer*
- Bladder Cancer*
- Breast Cancer*
- Basket Trial

2015 | 2016 | 2017 | 2018 | 2019

* 2016- Tumor NKG2D ligands expression for indication selection
# Celyad immuno-oncology pipeline

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- Multiple Myeloma
- Acute Myeloid Leukemia
- Solid Tumors
- B7CAR-T
- Allogeneic platform
- NKR-30
Celyad portfolio: B7 CAR-T

- B7 CAR construct based on scFv for target recognition
- *In vitro* and *in vivo* preclinical POC
- Hematological & solid indications
- Strong IP

**B7 CAR-T cells**

**CAR B7H6 treats lymphoma**

![Graph showing percent survival over days for MockT cells and CAR B7H6 T cells]
Celyad portfolio: NKR-30

NKR-30 T cells

- NKp30 is another natural activating receptor that is expressed on NK cells
- In vitro preclinical PoC
- Hematological & solid indications
- Strong IP

CAR NKp30 kills tumor cells

Graph showing the percentage of specific lysis by CAR NKp30 against different cell lines.
Autologous B7 CAR-T and NKR-30 clinical development plan projected milestones

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**PHASE I/II**
- **Hematological indications**
- **Solid cancer indications**
Celyad’s competitive positioning in the CAR-T space
What makes our allogeneic platform unique?

• **First patent** relating to allogeneic human primary T-Cells engineered to be TCR-deficient and express any CAR
• The granted product claims are not limited to specific CARs or methods

• Genetic engineering method to inhibit the TCR expression by Celyad TCR-Inhibitory Molecules (i.e., TIMs)
Celyad’s competitive positioning in the CAR-T space
What makes our allogeneic platform unique?

Co-expression of NKR molecule and TCR Inhibitory Molecules (TIMs) from same retrovirus DNA

- Genetic engineering method to inhibit the TCR expression by Celyad TCR-Inhibitory Molecules (i.e., TIMs)
Allogeneic approach clinical development plan projected milestones

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Leveraging partnerships

Novel cardiopoiesis platform
Invented at Mayo Clinic, exclusively licensed to Celyad

Natural Killer Receptor based T cell platform
Invented at Dartmouth College, exclusively licensed to Celyad

Scientific Advisory Board

Broad scientific collaboration
Celyad’s 2016 priorities & projected milestones

- Finalize ongoing NKR-2 phase I study
- Initiate broad NKR-2 program in solid tumors (US & EU)
- Advance B7 CAR-T & allogeneic platform (*in vivo* PoC)
- Develop transformative cell manufacturing processes
- Expand academic research collaborations and strategic corporate partnerships
Positioned for success as a fully integrated biotech

- Differentiated best-in-class portfolio built on collaborations with premiere institutions
- Unprecedented results from our preclinical programs
- Diversified & robust pipeline to minimize risk
- Valuable & long-term patent estates
- Leveraging manufacturing expertise
- Global footprint
- Experienced management team focused on execution
Our Solution: A weaponized NKR T-Cell that combines four proven mechanisms to help restore the body’s ability to repair itself.

- Selectively targets cancer cells via binding to 8 ligands of NKG2D present on multiple liquid & solid tumors.
- Promotes direct killing of cancer cells as NKG2D is an activating receptor.
- Promotes adoptive immunity through the induction of a specific cytokine profile.
- Cuts off blood supply by targeting the tumor neovasculature and attack Tregs & MDSCs.

What we deliver

**EFFECTIVENESS**

- **Unparalleled pre-clinical results: 100% tumor-free survival**
  - Survival >250 days in mice
  - Well defined multiple mechanisms of action
  - Long-term adaptive immune response

**BREADTH**

- **Positive pre-clinical results in 5 different indications**
- **Ongoing Phase I study in MM and AML at DFCI**

**SAFETY**

- **Remarkable safety profile**
  - Low persistence of engineered T-cells shown
  - Selective targeting of tumor cells shown
  - Further safety profile being investigated in Phase I trial