Pioneering innovative therapies for patients with life-threatening diseases

Research & Development Day
March 18, 2019
New York City
## Today’s Agenda – Building a Disruptive Pipeline in CAR-T Cell Therapy

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Continuing the Advancement of CAR-T Therapies

**Today**
- Accelerate the clinical development program for CYAD-01 for the treatment of r/r AML and focus on path to commercialization

**Tomorrow**
- Leverage our innovative allogeneic approaches including TIM for CYAD-101, novel shRNA platform for CYAD-200 series and broad allogeneic IP to become a leading player in the field

**Beyond**
- “Crack the code” in solid tumors with an NKG2D-based CAR-T therapy through well-established and novel combination regimens to pursue multiple indications
2018 – A Year in Review

**January 2018**
- First patient in THINK trial treated with drug product from amended manufacturing process

**April 2018**
- Haematologica publishes case report of complete response in r/r AML patient from THINK Phase 1 trial

**May 2018**
- Initiation of Phase 1 SHRINK trial evaluating CYAD-01 concurrent with FOLFOX chemotherapy

**October 2018**
- Exclusive agreement for Horizon Discovery’s shRNA platform for the development of next-generation allogeneic CAR-T therapies
- Initiation of Phase 1 DEPLETHINK trial evaluating CYAD-01 following treatment with CyFlu preconditioning in patients with r/r AML

**November 2018**
- Initiation of Phase 1 alloSHRINK trial evaluating non-gene edited allogeneic CAR-T, CYAD-101, in patients with mCRC

**December 2018**
- Interim results from Phase 1 THINK trial in r/r AML patients presented at ASH 60th Annual Meeting

AML: Acute myeloid leukemia; CyFlu: cyclophosphamide and fludarabine; FOLFOX: leucovorin, fluorouracil, and oxaliplatin; mCRC: Metastatic colorectal cancer; r/r: relapsed/refractory.
Established Expertise in Cell Therapies Manufacturing

- 15 years expertise in cell therapy
- Over 350 patients treated in our cardiology and oncology trials from cells manufactured in our facility in Mont-Saint-Guibert
- Proprietary manufacturing facility to independently improve and optimize our streamlined process to successfully produce engineered cell therapies
- Seamless and efficient reproduction of materials to advance our pipeline from preclinical stage through clinical evaluation to commercialization
Capabilities Support Clinical Development and Future Product Launch

- Over 30 people in Production, Logistics, Facility, QA and QC departments to support four - six patient products per week
- 1,100 sq. meter facility in Mont-Saint-Guibert is equipped to supply all of Celyad’s expected clinical trials as well as support over 1,000 patients (annually) treated with CYAD-01 if approved
  - Two independent (flow and HVAC) GMP zones with multiple cleanrooms allowing 24/7 production
  - QC lab with release capabilities for viral vectors and CAR-T products
  - Logistic area (200 m²) with storage capacity and global supply capability of cryopreserved drug products
Leading Manufacturing Capabilities with Two Production Areas

- Two production areas allow for continuous cell manufacturing with no downtime for routine maintenance
- Scaling of our production accordingly depending on our needs
- Advancing in parallel both R&D efforts and clinical-stage product production
Turning Research Process into Commercially Viable Manufacturing Process

**Process Development**
- Cryopreservation
- Mitigate patient variability in a fixed production process
- On site reconstitution in a closed system

**Logistics & Supply Chain**
- Supply of apheresis within 48 hours including shipping from the U.S. to Belgium
- Personalized global supply of Frozen Drug Product
- Critical raw materials supply management (e.g. viral vector)

**Quality Assurance**
- “Real-time” release
- Multiple personalized product management
- GMP certifications – Manufacturing Authorization for investigational Cell and Gene Therapy Products (1)
- Human cells and tissues establishment license for T-cells procurement (1)
- Biosafety license for viral vector manipulation (1)
- Stability of cryopreserved product of nine months

**Regulatory**
- Advanced therapy medicinal products (ATMPs) expertise in European Union, United Kingdom and the United States

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(1) Regulated by European authorities.
Rapidly Scaling Production to Meet Current and Future Clinical Needs

Over 600 billion cells produced in 2018

94% manufacturing success rate in 2018 vs. 75% in 2017

Streamlined centralized logistics to supply both U.S. and EU

33 Patients treated in 2018 vs. 16 in 2017 and 8 in 2016

Cryopreserved products
**Advancing Clinical Pipeline**

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<tr>
<th>Product</th>
<th>Target</th>
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**Definitions:**
- **AML:** Acute myeloid leukemia
- **mCRC:** Metastatic colorectal cancer
- **MDS:** Myelodysplastic syndrome
- **r/r:** relapse/refractory
- **CyFlu:** cyclophosphamide and fludarabine
- **FOLFOX:** leucovorin, fluorouracil, and oxaliplatin
Recent Updates to Current Trials in r/r AML/MDS

THINK – Schedule Optimization Cohorts

- Cohorts will assess a more frequent dosing schedule of CYAD-01 including six injections of CYAD-01 without preconditioning over two cycles
- Preliminary data from Cohort 10 are expected in second quarter 2019
- Recent addition of Cohort 11 will evaluate six injections of CYAD-01 without preconditioning (first cycle evaluating three injections of $3 \times 10^9$ cells per injection followed by a consolidation cycle)
- Initial data from Cohort 11 are anticipated for year-end 2019

DEPLETHINK

- Dose escalation trial evaluating a single injection of CYAD-01 following treatment with the preconditioning regimen of CyFlu
- Preliminary data from initial dose-levels evaluated shows regimen is well-tolerated, with no DLTs observed to date
- Recent trial amendments include fourth cohort ($1 \times 10^9$ cells of CYAD-01) and potential for expanded Phase 2 segment
- Interim data from first two cohorts are expected in mid-2019 with full data from dose escalation segment expected by year-end 2019
## r/r AML/MDS Program – Summary of Ongoing Studies

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<td>Allogeneic</td>
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<td>1x10^9 / 3x10^9</td>
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<td>6 (^{(2)})</td>
<td>1 (^{(3)})</td>
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<td>Data / Next milestone(s)</td>
<td>40% CR</td>
<td>Q2:2019 / YE:2019</td>
<td>mid-2019</td>
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(1) In dose levels 2 and 3, patients presenting no signs of progression are eligible to receive a second cycle of three CYAD-01 injections without preconditioning for a total of six injections.
(2) First three injections of CYAD-01 separated by one-week intervals, while the second cycle of three injections of CYAD-01 separated by two-week intervals.
(3) Patients presenting no signs of progression are eligible to receive a second cycle of three CYAD-01 injections without preconditioning.

CR: Complete response including either marrow complete response (mCR), complete remission with partial hematologic recovery (CRh) or complete remission with incomplete marrow recovery (CRi).
### Solid Tumor Program – Summary of Ongoing Studies in mCRC

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<th>THINK CyFlu</th>
<th>SHRINK</th>
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<th>THINK CyFlu</th>
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<th>alloSHRINK</th>
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<th>SHRINK</th>
<th>alloSHRINK</th>
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<td>27% SD in mCRC</td>
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(1) In dose levels 2 and 3, patients presenting no signs of progression are eligible to receive a second cycle of three CYAD-01 injections without preconditioning for a total of six injections.

SD: Stable disease.
Building a CAR-T Pipeline Through shRNA
Developing a Next-Generation, Non-Gene Edited Platform for CAR-T

- Exclusive agreement with Horizon Discovery Group for the use of its shRNA technology to generate next-generation, non-gene edited allogeneic platform for CAR-T therapies
  - Collaboration includes use of shRNA technology for additional targets as well
- shRNA platform provides flexibility to potentially combine with a broad array of CARs
- Establish a single vector approach to generate allogeneic CAR-T cells which builds upon Celyad's "All-in-One Vector" approach
- TCR knockout using shRNA compares favorably to gene editing methods to inhibit TCR expression

(1) Preliminary data, abstract P220 SITC 2018 Generating allogeneic CAR T cells without gene editing
SMARTvector technology mimics endogenous mature microRNA

- Based on miR-196a-2 scaffold with patented optimization
- Processed efficiently from a Pol II promoter allowing co-expression of a reporter (Figure 1)
- Maintains good functionality from the active strand while minimizing passenger strand activity (Figure 2)
- Developed after extensive analyses of multiple endogenous microRNA scaffolds (Figure 2)

Versatility of shRNA Platform Offers Broad Approach to CAR-T Development

Dharmacon’s SMARTvector shRNA Platform Yields Multiple Candidates

**CYAD-02**
- Utilizing shRNA to target NKG2D ligands MICA/MICB creates next-generation, NKG2D-based, autologous CAR-T candidate
- Current data suggest potential broader applicability of targeting MICA/MICB in all CAR-T therapies

**CYAD-200 Series**
- Targeting CD3ζ to knockdown the TCR/CD3 complex to deliver novel, non-gene edited allogeneic CAR-T candidates

**Future Candidates**
- Research ongoing to investigate additional undisclosed targets to pair with CARs to develop novel cell therapies, in particular for the treatment of solid tumors
CYAD-02 – Next Generation NKG2D CAR-T
NKG2D-based CAR-T Presents Key Differentiation

Hexamer arrangement:
two co-stimulatory domains
to one activatory domain

4xDAP-10 : 2xNKG2D.CD3 ζ

Low immunogenicity

Full length, human NKG2D receptor with minimal engineering involving the intracellular fusion with CD3ζ

Target binding affinity in the range of a TCR-peptide suggesting natural receptor

Natural receptor configuration
on the cell surface

Spontaneous association with endogenous DAP10 protein

Generic targeting of broad solid and liquid malignancies

NKG2D binds eight target ligands

Avoidance of clonal selection and escape

Multiple antigen binding
NKG2D Ligands are Expressed Transiently on Human T cells Leading to Fratricide which is Overcome by Antibody Blockade

Can we permanently modulate the expression of NKG2D ligands in T cells?
Cell Line Screening Identified Multiple shRNAs Targeting NKG2D Ligands MICA/B
Incorporating shRNA-14 into the Construct Improves the Proliferative Potential of CYAD-01

NKG2D Constructs

**CYAD-01**

- LTR → NKG2D CAR → LTR

**CYAD-02**

- LTR → NKG2D CAR → 2A → tCD19 Marker → LTR

1. Expression of shRNA-12 or shRNA-14
2. Truncated CD19 transgene serves as positive selection

**Improved Proliferation in Absence of Antibody Blockade**
Robust Increase in Persistence from CYAD-01 Construct Plus shRNA-14

Frequency of Animals with Detectable NKG2D CAR-T Cells
Increased Expansion and Persistence of Cells With Next-Generation, NKG2D-based CAR-T, CYAD-02

Combining CYAD-01 with shRNA-14 and continued process improvement leads to development of CYAD-02

NSG Mice with Established AML Tumor
CYAD-02 Exhibits Improved Anti-tumor Activity in Established AML Model

Seven Day AML (THP-1) Model

CYAD-02 demonstrates improved survival at dose level where CYAD-01 has minimal activity (three doses of $3 \times 10^6$ cells)
No Overt Disturbance of the Transcriptome Through shRNA Expression

**CYAD-02 vs CYAD-01 Volcano Plots**

- **CD4**
  - MICB

- **CD8**
  - MICB
Summary and Next Steps for CYAD-02

- Single shRNA is able to modulate the expression of MICA/B which translates to encouraging increase in \textit{in vivo} engraftment and anti-tumor activity
- Generate additional preclinical proof-of-concept data for program throughout 2019
- Submission of investigational new drug (IND) application in first half 2020
Multiple Targets to Generate Allogeneic T-cells

**TCR complex is responsible for Graft-versus-Host Disease (GvHD)**

As such, elimination of the TCR complex is necessary for creating allogeneic CAR-T therapies

**TCRα (TRAC) is a common target for gene edited approaches**

Knockdown of specific CD3 components (i.e. CD3ε) could also lead to loss of the TCR at cell surface

**CD3ζ is the rate-limiting factor to the TCR complex moving to the cell surface and an attractive target**
Initial Screening of shRNA Targeting CD3 in Jurkat T-cells

Specificity of Targeting Individual CD3 Components

Reduction of T-Cell Response Through shRNA

shRNA targeting CD3ζ is more effective in blunting T-cell responsiveness
Comparison of shRNA vs. Gene Editing

- To compare in preclinical models the ability of shRNA to modulate the expression levels of the TCR complex from the cell surface of T-cells with that of gene editing technology, we developed a CRISPR control knockout of the CD3ζ to mimic our shRNA approach.

- Both approaches used an eight-day process from activation to TCR-positive depletion and harvest:
  - shRNA approach also included retroviral transduction, positive purification of cells using a truncated CD19 receptor (similar to our CYAD-101 approach) as well as cell expansion.
  - CRISPR control included nucleofection of CRISPR-CD3ζ and cell expansion.
shRNA vs. CRISPR: Equivalent Knockdown of TCR

Cell Surface TCR Complex
- CD4
- CD8

Intensity of TCRα/β

TCR Stimulation Assay

- OKT3 (ng/ml)
- CD25 MFI
- IFN-γ (ng/ml)
- CTR (tCD19)
- shRNA CD3ζ
- CRISPR CD3ζ

shRNA targeting CD3ζ reduces TCR expression and cytokine response
**In Vivo** Protection of GvHD by shRNA targeting CD3ζ

**Survival**

**Persistence**

**Mean Weight**

1) **Controlled GvHD within the persistence window of allo-CAR despite T cell expansion**

2) **Persistence of T cells with shRNA superior to gene editing technologies**

3) **No evidence of major weight loss – a typical characteristic of GvHD induction**

**Mann-Whitney U-Test** p-value of 0.0017; **** Mann-Whitney U-Test p-value of <0.0001.
Summary of shRNA Platform Benefits

- Differentiated methodology to knockout the TCR complex in allogeneic CAR-T therapies compared to gene editing techniques.

- Ability to knockdown the majority but not all of the TCR complex versus gene edited approaches allows for increased persistence of shRNA-based T cells and positions the technology as a potential "game-changer" in the field of allogeneic CAR-T for the treatment of cancer.

- Streamlined broad implementation to develop CAR-T candidates thanks to the "plug & play" nature within Celyad’s “All-in-One Vector” approach.

CYAD-200 Series of Allogeneic CAR-Ts
Trio of Disruptive, First-in-Class, Non-Gene Edited Allogeneic CARs

**BCMA CAR-T for multiple myeloma**
- Evaluate shRNA approach with validated target
- Potential best-in-class allogeneic approach given increased persistence vs. gene edited candidates
- Expected to enter the clinic by mid-2020

**CD19 CAR-T for B-cell malignancies**
- Despite multiple marketed products for the treatment of B-cell malignancies, many patients fail to receive treatment given manufacturing challenges
- Expected to enter the clinic by late 2020

**Dual specific NKG2D x Undisclosed CAR-T**
- Currently evaluating multiple CARs / targets to pair with NKG2D receptor
- Expected to enter the clinic by early 2021
Anti-tumor Activity of BCMA-CAR.shRNA CD3z in Preclinical Model

**KMS.11 Multiple Myeloma Model**

**BCMA-CAR.shRNA CD3z demonstrates tumor control as early as one week after single injection of 10 x 10^6 CAR T cells without any signs of toxicity**
CYAD-200 Series of CAR-T Candidates is Strategically Positioned to Leapfrog the Competition in Allogeneic CAR-T Development

- shRNA platform provides us with a next-generation, potential best-in-class allogeneic approach to CAR-T development
  - Single step gene engineering combining inhibition of TCR complex and CAR transduction
  - Persistence of CAR-T cells significantly longer than gene edited approaches
  - Highly competitive turn around time in development due to no DNA editing
  - Significant cost of goods benefits using a single vector platform

- Initial proprietary CYAD-200 series candidates include:
  - CYAD-211 (BCMA), CYAD-221 (CD19) and CYAD-231 (NKG2D x Undisclosed)

- Goal is to initiate several Phase 1 trials to evaluate the CYAD-200 series

- Importantly, the shRNA platform complements our strong intellectual property of six U.S. patents related to allogeneic T-cell technology and producing TCR deficient cells expressing a CAR construct
“All-in-One Vector” Approach
“All-in-One Vector” Approach Provides Flexibility and Versatility to Design Novel CAR-T Therapies

- Ability to include several T cell engineering steps in one single step
- Efficiencies across all segments of R&D as well as cell manufacturing
- Leverages experience and expertise gained to date from lead candidates CYAD-01 and CYAD-101, while considering the company’s future CAR-T pipeline including allogeneic shRNA-based CAR-T candidates
Final Remarks and Q&A
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AML: Acute myeloid leukemia; mCRC: Metastatic colorectal cancer; MDS: Myelodysplastic syndrome; MM: Multiple myeloma; r/r: relapse/refractory. CyFlu: cyclophosphamide and fludarabine; FOLFOX: leucovorin, fluorouracil, and oxaliplatin.
Upcoming Milestones

**Second Quarter 2019**
- Updated data from dose level 3 and initial data from Cohort 10 of THINK trial evaluating CYAD-01 without preconditioning in r/r AML
- Preliminary data from first two cohorts of dose-escalation DEPLETHINK trial evaluating CYAD-01 following preconditioning in r/r AML
- Updated data from THINK CyFlu and SHRINK trials evaluating CYAD-01 in mCRC

**Second Half 2019**
- Additional data from Cohort 11 of THINK trial as well as full data from DEPLETHINK trial
- Preliminary data from alloSHRINK trial evaluating allogeneic CYAD-101 with FOLFOX chemotherapy in mCRC
- Initiation of Phase 2 clinical trial evaluating CYAD-01 in r/r AML

**First Half 2020**
- Submission of IND for next-generation NKG2D CAR-T CYAD-02
- Submission of IND for first-in-class shRNA allogeneic BCMA CAR-T, CYAD-211, for the treatment of patients with multiple myeloma
Continuing the Advancement of CAR-T Therapies

Today

- Accelerate the clinical development program for CYAD-01 for the treatment of r/r AML and focus on path to commercialization

Tomorrow

- Leverage our innovative allogeneic approaches including TIM for CYAD-101, novel shRNA platform for CYAD-200 series and broad allogeneic IP to become a leading player in the field

Beyond

- “Crack the code” in solid tumors with an NKG2D-based CAR-T therapy through well-established and novel combination regimens to pursue multiple indications
Thank you