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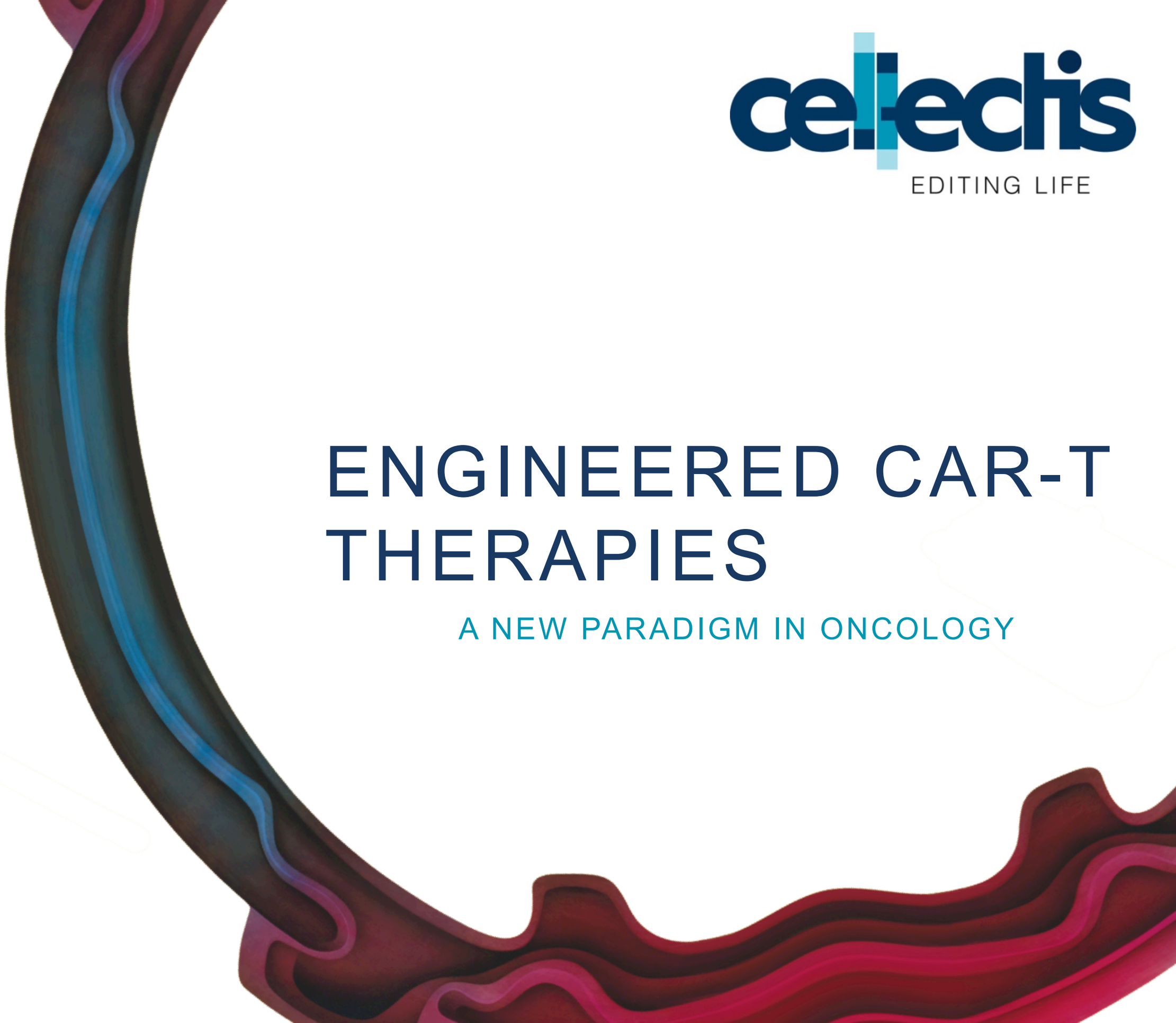
# ENGINEERED CAR-T THERAPIES

## A NEW PARADIGM IN ONCOLOGY



September 2017

# FORWARD-LOOKING STATEMENTS

THIS PRESENTATION CONTAINS "FORWARD-LOOKING" STATEMENTS THAT ARE BASED ON OUR MANAGEMENT'S CURRENT EXPECTATIONS AND ASSUMPTIONS AND ON INFORMATION CURRENTLY AVAILABLE TO MANAGEMENT.

FORWARD-LOOKING STATEMENTS INVOLVE KNOWN AND UNKNOWN RISKS, UNCERTAINTIES AND OTHER FACTORS THAT MAY CAUSE OUR ACTUAL RESULTS, PERFORMANCE OR ACHIEVEMENTS TO BE MATERIALLY DIFFERENT FROM ANY FUTURE RESULTS, PERFORMANCE OR ACHIEVEMENTS EXPRESSED OR IMPLIED BY THE FORWARD-LOOKING STATEMENTS.

THE RISKS AND UNCERTAINTIES INCLUDE, BUT ARE NOT LIMITED TO THE RISK THAT THE PRELIMINARY RESULTS FROM OUR PRODUCT CANDIDATES WILL NOT CONTINUE OR BE REPEATED, THE RISK OF NOT OBTAINING REGULATORY APPROVAL TO COMMENCE CLINICAL TRIALS ON THE UCART PRODUCT CANDIDATES, THE RISK THAT ANY ONE OR MORE OF OUR PRODUCT CANDIDATES WILL NOT BE SUCCESSFULLY DEVELOPED AND COMMERCIALIZED. FURTHER INFORMATION ON THE RISK FACTORS THAT MAY AFFECT COMPANY BUSINESS AND FINANCIAL PERFORMANCE, IS INCLUDED IN FILINGS CELLECTIS MAKES WITH THE SECURITY EXCHANGE COMMISSION FROM TIME TO TIME AND ITS FINANCIAL REPORTS.

EXCEPT AS REQUIRED BY LAW, WE ASSUME NO OBLIGATION TO UPDATE THESE FORWARD-LOOKING STATEMENTS PUBLICLY, OR TO UPDATE THE REASONS ACTUAL RESULTS COULD DIFFER MATERIALLY FROM THOSE ANTICIPATED IN THE FORWARD-LOOKING STATEMENTS, EVEN IF NEW INFORMATION BECOMES AVAILABLE IN THE FUTURE.

# *The Cellectis Group*

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- NASDAQ: CLLS
- ALTERNEXT: ALCLS
- 35.5M SHARES OUTSTANDING
- $272M IN CASH AS OF JUNE 30, 2017

- IMMUNO-ONCOLOGY / CAR T
- THERAPEUTIC GENE EDITING
- GENE THERAPY

80% ownership

calyxt

- NASDAQ: CLXT
- IPO JULY 2017
- $64M GROSS PROCEEDS
- 27.65M SHARES OUTSTANDING

- BASED IN MINNESOTA
- INNOVATIVE CROPS
- CONSUMER FOCUS
- NON-REGULATED PRODUCTS
- HIGH VALUE ASSET

*Gene editing is the link*

# CAR T 2.0

## *The Next Step in CAR T-Cell Treatment*

- **Allogeneic CAR T-cells**
  - ✓ Off-the-shelf pharmaceutical product
  - ✓ Not relying on patient's own T cells
  - ✓ Immediately ready to inject
  - ✓ Expanding patient access
  - ✓ Significantly lower cost
- **TALEN® Gene-Edited CAR T-cells**
  - ✓ Non-alloreactive
  - ✓ Compatibility with standard-of-care chemotherapies
  - ✓ Resistance to tumour inhibition (PD1, CTLA-4 knockout and more)
  - ✓ Reaching more targets/indications for CAR T-cells
- **Controllable CAR Activity / Persistence**
  - ✓ Mitigate risks of CAR T-cell-related toxicities
  - ✓ Possibility for a multiple dosing approach

# *UCART Pipeline*

## *Addressing a large spectrum*

| Program | Indication | Product development | Preclinical | Manufactu-ring | IND Filing* | Phase I | Phase II |
|---|---|---|---|---|---|---|---|
| UCART19** | ALL (PALL) | | | | | | |
| | ALL (CALM) | | | | | | |
| UCART123 | AML | | | | | ON HOLD | |
| | BPDCN | | | | | ON HOLD | |
| UCART22 | B-ALL | | | | | | |
| | B-NHL | | | | | | |
| UCARTCS1 | MULTIPLE MYELOMA | | | | | | |
| UCART38 | MULTIPLE MYELOMA | | | | | | |
| | T-CELL ALL | | | | | | |
| | NHL / MCL | | | | | | |

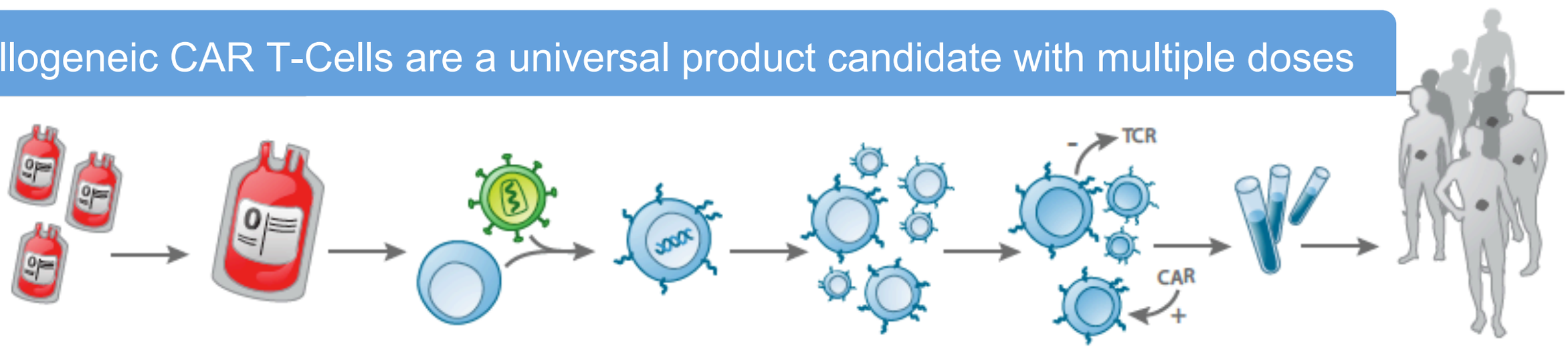
* or European equivalent

** UCART19 is exclusively licensed to Servier and under a joint clinical development program between Servier and Pfizer

# cGMP Manufacturing

## *Patient-Oriented Therapeutic Proposal*

Allogeneic CAR T-Cells are a universal product candidate with multiple doses




| Healthy Donor Leukopacks | From One Leukopack | Lentiviral Vector | Gene Editing TALEN® + Pulse Agile | Amplification x 100 | Filtration | Fill, Finish and Freeze | Stored/ Shipped to Hospitals |
|---|---|---|---|---|---|---|---|

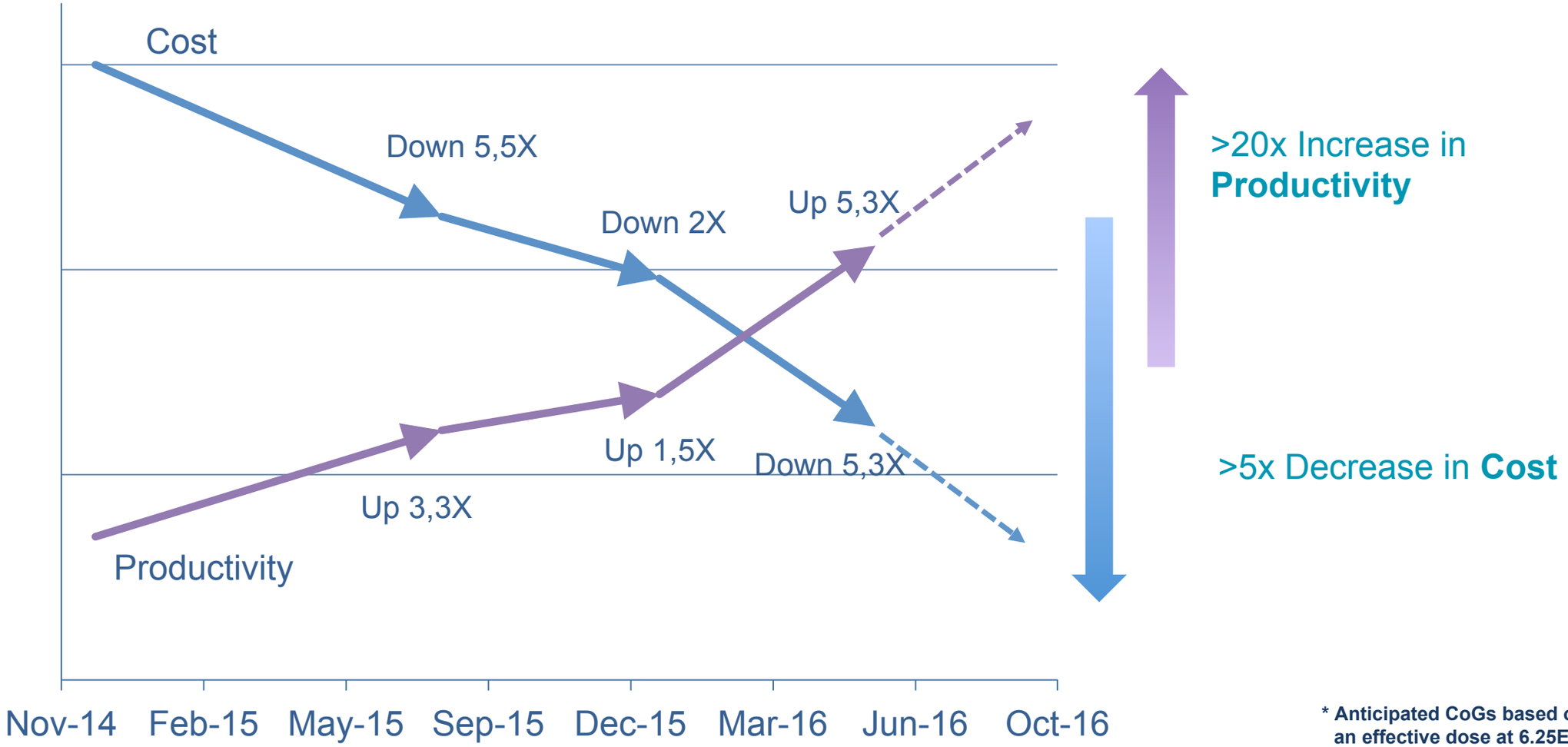
**One Leukopack can yield 100s of doses at a cost of goods of less than $4,000 per dose***

* **Anticipated CoGs based on current conditions and an effective dose at 6.25E5 UCART vialed cells/kg**

# *Entering Clinical Development*

## *Increasing Yields, Decreasing CoGs*

- Worldwide, immediate access to patients
- Since 2015, CoGs already decreased by 5x
- Productivity per manufacturing run increased by 20x




*** Anticipated CoGs based on current conditions and an effective dose at 6.25E5 UCART vialed cells/kg**

# *Unmet Medical Need*
## *in Clinical Oncology*

| US Estimate | Estimated New Cases in 2017 | Estimated Deaths in 2017 | Incidence | 5 Year Survival (2007-2013) |
|---|---|---|---|---|
| AML* | 21,380 | 10,590 | 4,2 per 100,000 | 26,9% |
| BPDCN | Estimated < 1% of all hematologic malignancies** | | 0,45 per 1,000,000*** | 38%*** |
| ALL* | 5,970 | 1,440 | 1,7 per 100,000 | 68,2% |
| CLL* | 20,110 | 4,660 | 4,7 per 100,000 | 83,2% |
| MYELOMA* | 30,280 | 12,590 | 6,6 per 100,000 | 49,6% |
| NON HODGKIN LYMPHOMA* | 72,240 | 20,140 | 19,5 per 100,000 | 71% |

* National Cancer Institute (NCI), https://seer.cancer.gov
** Riaz et al, 2014
*** Alsidawi et al, 2016

# AML Landscape

## *Area of high unmet need*

- Despite several late stage products in clinic, patients have minimal options
- Cytarabine, approved in 1969, is still the standard of care in AML today

| | Phase 3 | Filed | Approved / Mkt. |
|---|---|---|---|
| **Hypomethylating agents** | Otsuka / Celgene<br>• SGI-110 *(DNA methyl inhibitor)*<br>• CC-486 *(Oral Vidaza)* | | Jazz Pharmaceuticals<br>• Vyxeos *(Liposomal formulation)* |
| **Kinase inhibitors** | Daiichi-Sankyo<br>• Quizartinib *(FLT3 inhibitor)*<br>astellas<br>• Gilteritinib *(Kinase inhibitor)*<br>abbvie<br>• Venclexta *(Bcl-2 inhibitor)*<br>Boehringer Ingelheim<br>• Volasertib *(Plk1 inhibitor)* | | NOVARTIS<br>• Rydapt *(Kinase inhibitors)* |
| **Isocitrate dehydrogenase inhibitors** | | agios<br>• Ivosidenib *(IDH1 inhibitor)* | agios / Celgene<br>• Idhifa *(IDH2 inhibitor)* |
| **Antagonists** | Roche<br>• Idasanutlin *(MDM2 antagon.)* | | |
| **ADCs** | | | Pfizer<br>• Mylotarg *(Antibody drug conjugate)* |

Sources: Company reports and equity research

# *Leadership in Cell Therapy*
# *CAR T will be a cornerstone in AML*

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| | In vitro or Preclinical | Phase 1 or Phase 1/2 |
|---|---|---|
| AUTOLOGOUS CAR T CELLS | Anti-CD33 — Penn; Universitätsklinikum Carl Gustav Carus; Centre Léon Bérard<br>Anti-CD123 — Kite Pharma; City of Hope; BCM Baylor College of Medicine; University of Pennsylvania Abramson Cancer Center; Fondazione Tettamanti ONLUS; Intrexon; ZIOPHARM Oncology, Inc.; Shangdong University<br>Anti-CLL1 — BCM Baylor College of Medicine; Kite Pharma<br>Anti-CD33 & Anti-CD123 — Universitätsklinikum Carl Gustav Carus; gemoab Monoclonals GmbH<br>Anti-CD33 or Anti-CD123 — Università degli Studi di Milano Bicocca; Cancer Research UK<br>Anti-CD38 — Hiroshima University<br>Anti-CD44v6 — Molmed; Ospedale San Raffaele<br>Anti-FRB — Penn<br>Anti-HLA-A2 — The University of Texas MD Anderson Cancer Center | Anti-CD33 — Chinese PLA General Hospital; Intrexon; ZIOPHARM Oncology, Inc.<br>Anti-CD123 — Affiliated Hospital to Academy of Military Medical Sciences; City of Hope; Penn<br>Anti-NKG2D-L — Celyad<br>Anti-LewisY — Peter Mac Peter MacCallum Cancer Centre Victoria Australia |
| ALLOGENEIC CAR T CELLS | | Anti-CD123 — cellectis |
| AUTOLOGOUS CAR NK CELLS | Anti-CD123 — MHH Hannover Medical School | Anti-CD7 — PersonGen BioTherapeutics<br>Anti-CD33 — PersonGen BioTherapeutics |

# *UCART123 in AML and BPDCN – ON HOLD*
## *Entering Clinical Development*

*Acute Myeloid Leukemia (AML)*

- 21,380 new cases of AML were diagnosed in the US in 2017 with 10,590 deaths
- Five-year survival 27%; relapse rate 33-78%, depending on age and subtype
- Cellectis trial in the setting of relapsed/refractory AML and 1st line high risk AML
- Orphan Drug Designation potential

➢ ***AML Ph 1 dose escalation at Weill Cornell; First patient dosed in June 2017***

*Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)*

- Rare disease involving bone marrow, skin, lymph nodes with no standard of care
- In the US, a few hundred cases are diagnosed per year
- Classified under Myeloid Neoplasms and Acute Leukemia (WHO classification 2016)
- Orphan Drug Designation potential

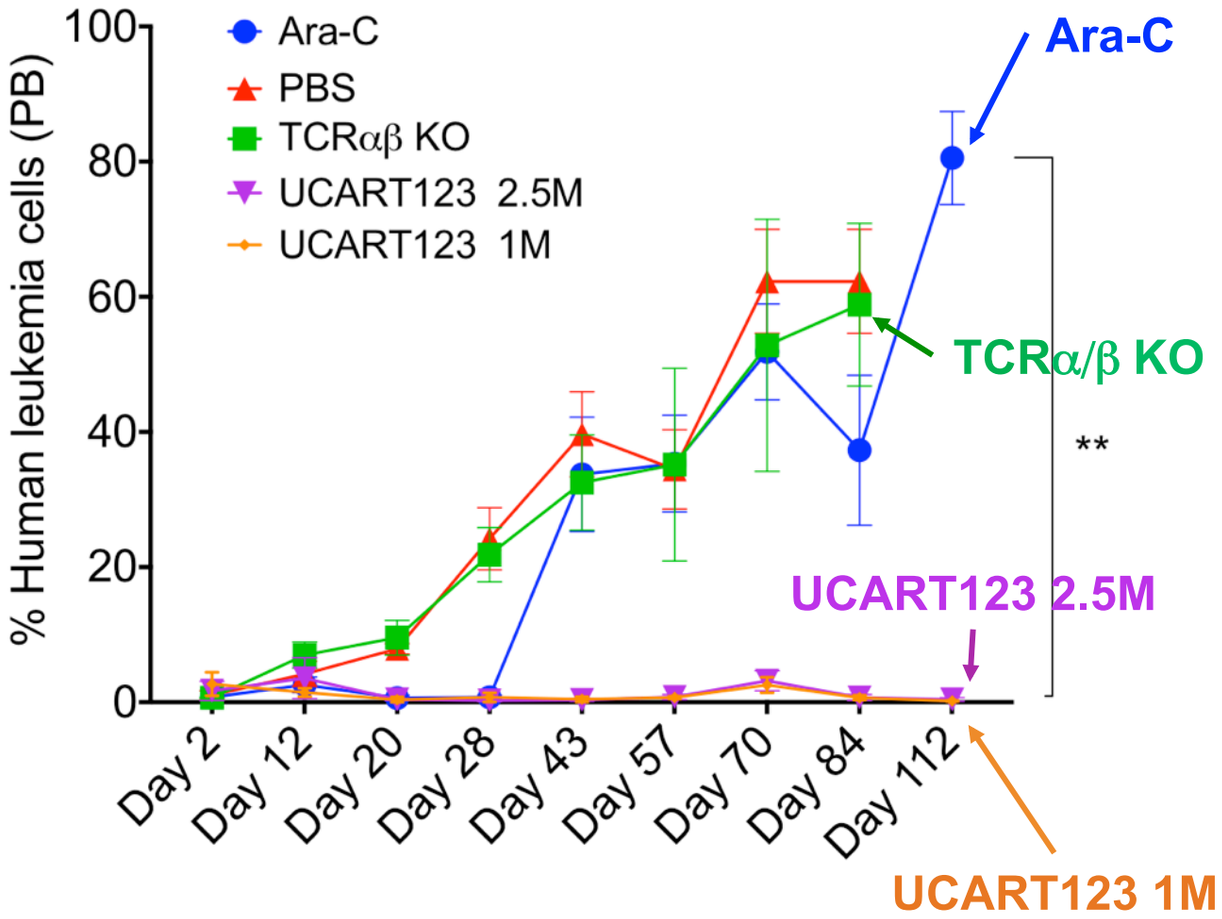
➢ ***BPDCN Ph 1 dose escalation at MD Anderson; First patient dosed in August 2017***

# *UCART123 in AML*

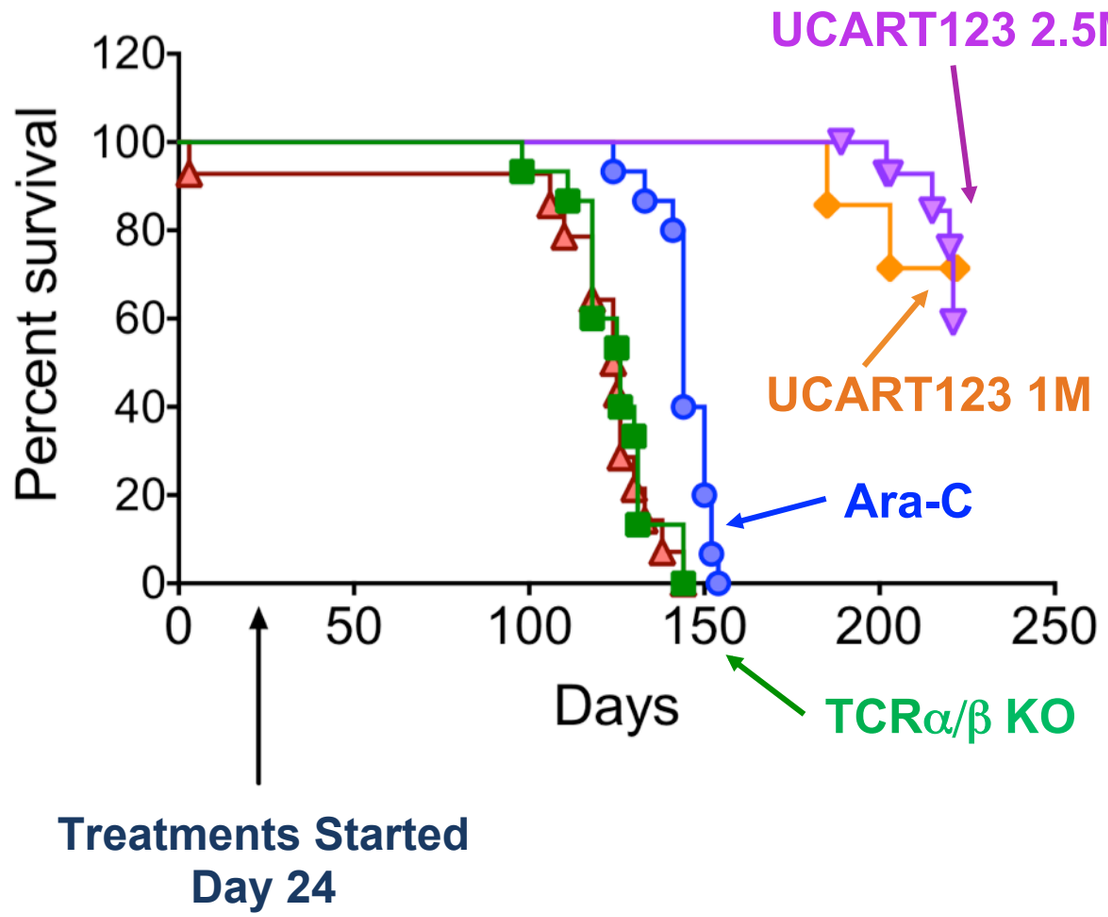
## *Encouraging Preclinical Efficacy Data at ASH 2016*

- UCART123 shows significant improvement compared to Cytarabine standard-of-care (Ara-C)

### Peripheral Blood Evaluation




### Overall Survival

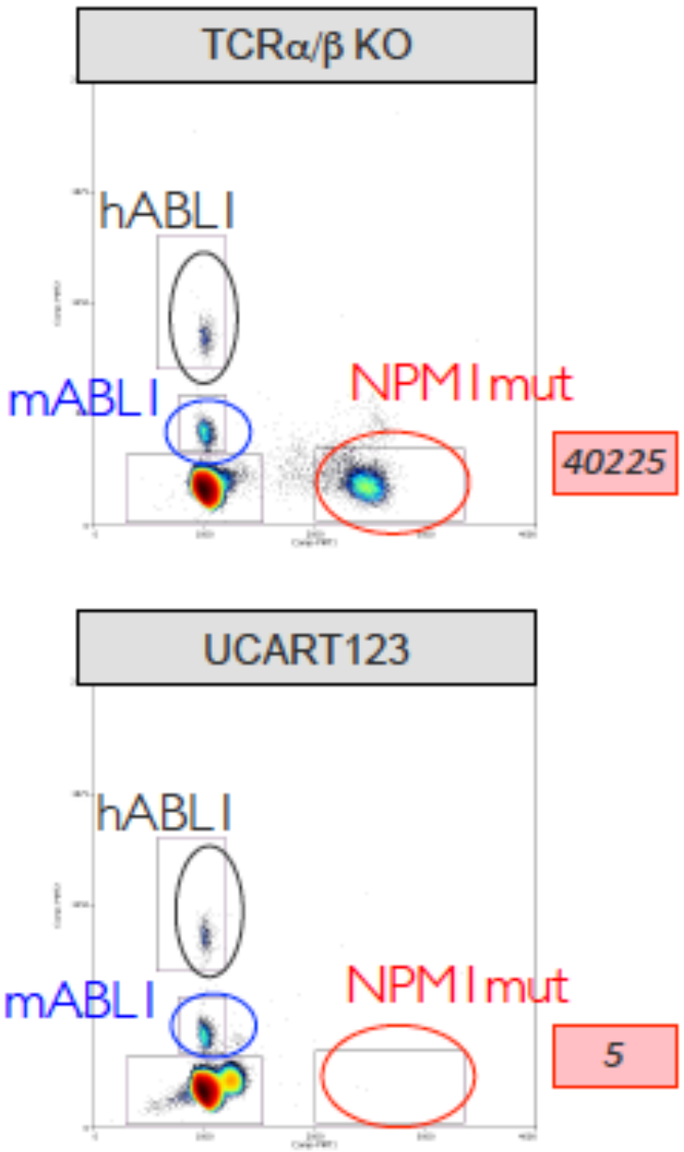


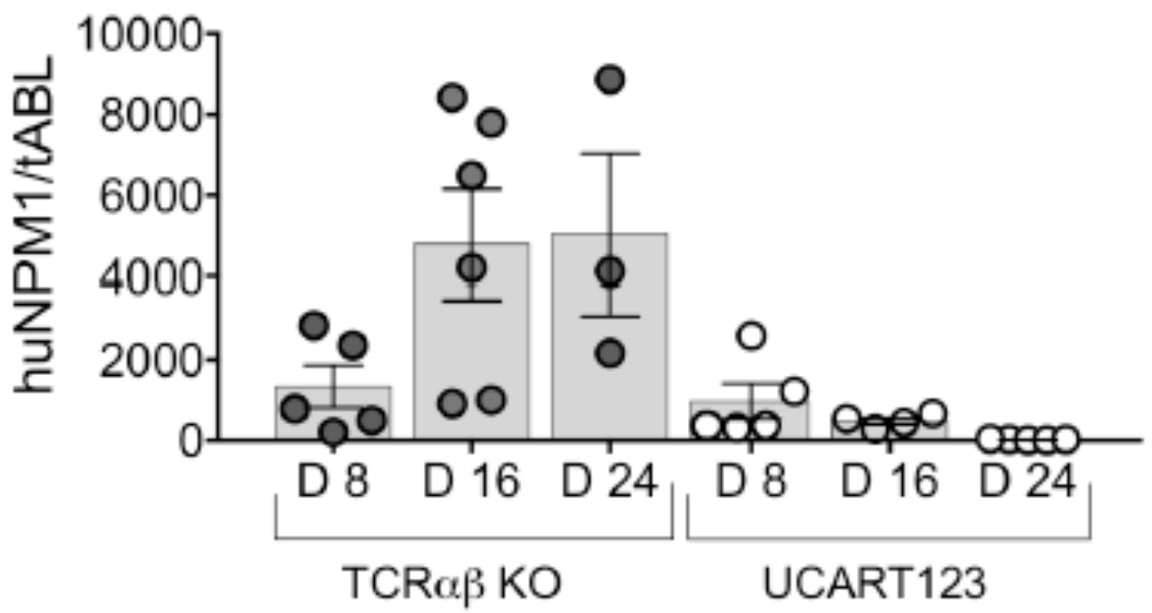

In collaboration with Dr. Monica Guzman, Cornell-Weill

# *UCART123 in AML*

## *Encouraging Preclinical Efficacy Data at ASH 2016*

- Animals treated with UCART123 achieve lasting molecular remission



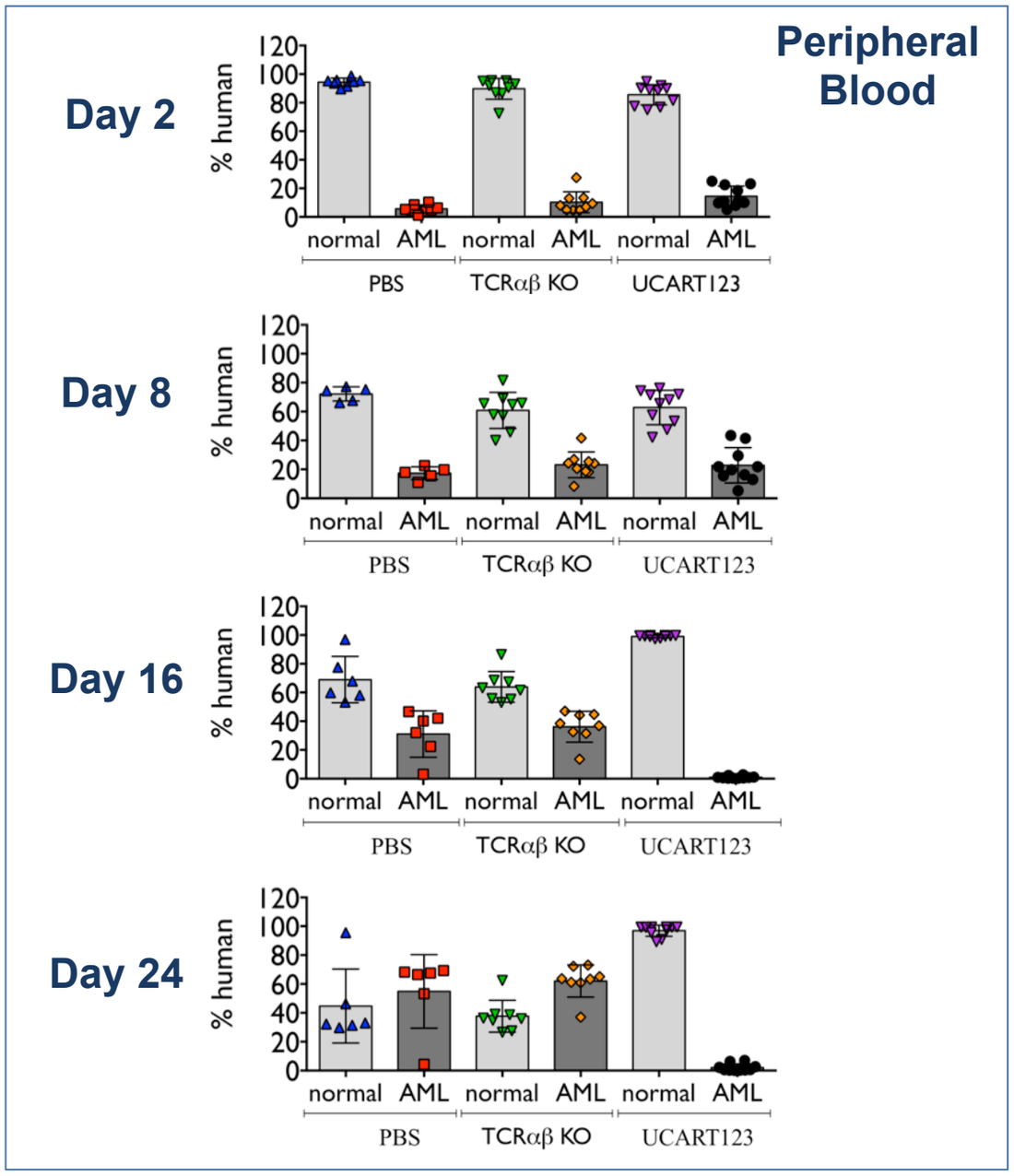



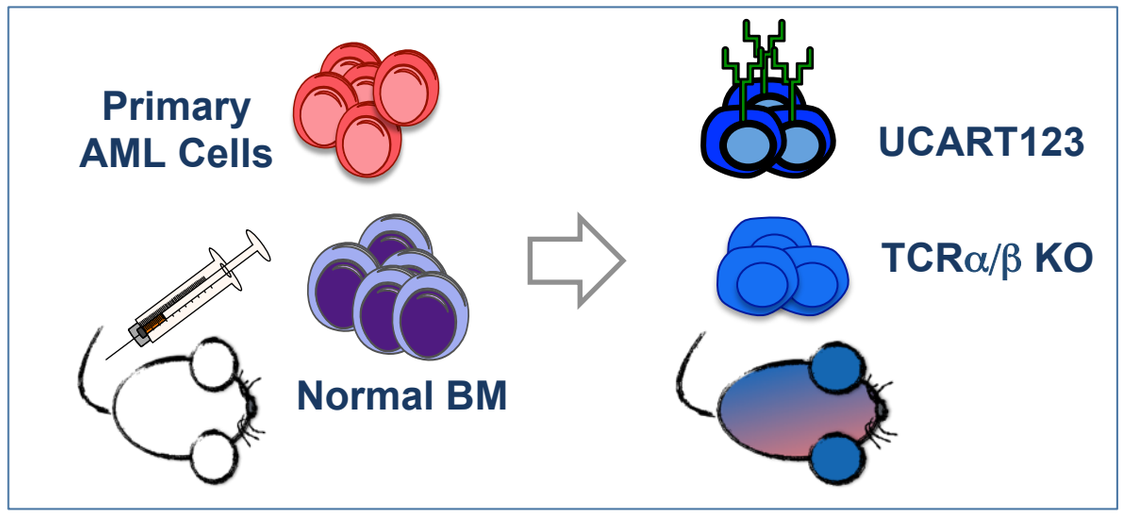

In collaboration with Dr. Monica Guzman, Cornell-Weill

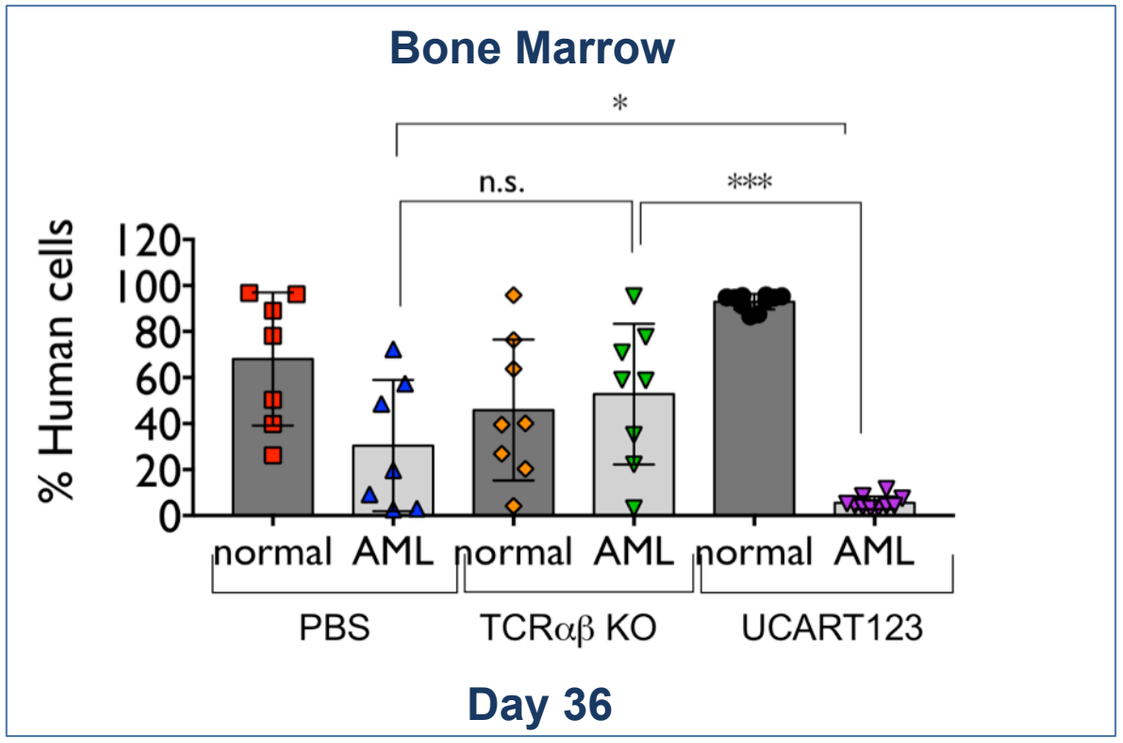
# *UCART123 in AML*

## *Encouraging Safety Profile*

- UCART123 preferentially eliminates AML cells over normal hematopoietic cells




In collaboration with Dr. Monica Guzman, Cornell-Weill

# *UCART123 in AML – ON HOLD*

## *Study Design*

**Dose Escalation Phase (R/R AML)**

| | |
|---|---|
| DL3 N=3 | $6.25x10^6$/kg |
| DL2 N=3 | $1.25x10^6$/kg |
| DL1 (start dose) N=3 | $6.25x10^5$/kg |
| DL-1 N=3 | $6.25x10^4$/kg |

**3 Patients Treated at the RP2D (Recommended Phase II Dose)**

**Total Dose Escalation N= 9-12 pts**

**Expansion Phase**

**RR AML N=18-37**

**Untreated AML ELN Adverse Genetic Group N=46-107**

**Total Phase I Expansion N=64-144**

In collaboration with Cornell-Weill

# UCART123 in BPDCN – ON HOLD

## Study Design

**Dose Escalation Phase (R/R BPDCN)**

| | |
|---|---|
| DL3 N=3 | $6.25x10^6$/kg |
| DL2 N=3 | $1.25x10^6$/kg |
| DL1 (start dose) N=3 | $6.25x10^5$/kg |
| DL-1 N=3 | $6.25x10^4$/kg |

**3 Patients Treated at the RP2D (Recommended Phase II Dose)**

**Total Dose Escalation N= 9-12 pts**

**Expansion Phase**

- RR BPDCN N=30
- Untreated BPDCN N=30

**Total Phase I Expansion N=60**

In collaboration with MD Anderson

# *UCART123 in AML and BPDCN*

## *Development plan*

**Preclinical Proof of Concept UCART123**
- *In vitro* and *in vivo* development finalized

completed November 2016 ☑

**Manufacturing UCART123**
- High yield, high potency cGMP batches

achieved November 2016 ☑

**IND for both indications**
- AML Cornell-Weill
- BPDCN MD Anderson

Cleared in February 2017 ☑

**Phase 1 – ON HOLD**
- First patient enrollment

Dosing started in Summer 2017 ☑

**Interim Data**
- Update on first AML patients

Expected in Q1 2018 ☐

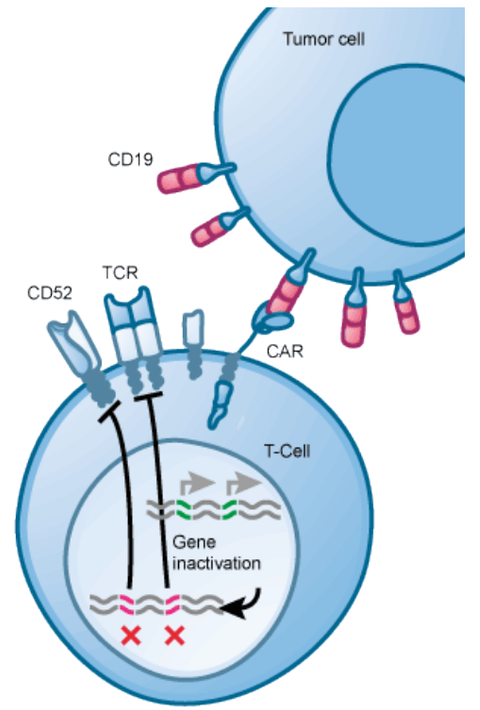
**Expansion Phase**
- Phase 1b in up to 200 first line AML and BPDCN patients

Expected in 2018 ☐

# *Entering Clinical Development*
## *UCART19 as Proof of Concept*

- Servier acquired exclusive rights to UCART19 from Cellectis in November 2015
- Joint clinical development program between Servier and Pfizer
- Servier has granted Pfizer exclusive rights to develop and commercialize UCART19 in the US

- Phase 1 Pediatric ALL (PALL) ongoing
  - Started June 2016 at University College London (UCL), UK
- Phase 1 Adult ALL (CALM) ongoing
  - Started July 2016 at King's College London (KCL), UK
- Servier and Pfizer received IND clearance in March 2017 to proceed in the U.S. with the clinical development of UCART19
  - CALM study will be expanded to include several centers in the U.S., including the MD Anderson Cancer Center in Houston (Texas)



# *Entering Clinical Development*
## *UCART19* Preliminary Data*

### *In Relapsed/Refractory ALL Patients*

Data Presented at the RAC meeting on December the 14th 2016

| Study | Age | Relevant Non-Hematologic AE | Status |
|---|---|---|---|
| Compassionate Use | 11 months** | •Grade 2 Skin GvHD | Alive, MRD-, 18+ Months |
| | 16 months*** | •Grade 1 Suspected Skin GvHD | Alive, MRD-, 12+ Months |
| | 44 years | •Grade 1 CRS | Died, Progressive Disease |
| PALL Study<br><br>(pediatric ALL patients) | 4.8 years | •Grade 3 CRS<br>•Grade 1 Suspected Skin GvHD<br>•Grade 1 Neurological | Alive, 6+ Months, Relapsed |
| | 2.7 years | •Grade 2 CRS<br>•Grade 1 Neurological | Alive, MRD-, 4+ Months |
| CALM Study<br><br>(adult ALL patients) | 42 years | •Grade 2 CRS | Alive, MRD-, 4+ Months |
| | 18 years | •Grade 4 CRS | Died, Cause Under Investigation |

* Exclusively licensed to Servier
** Qasim W et al., ASH 2015
***Qasim W et al., ASGCT 2016

# *UCART19 in ALL*
## *Development plan*

**Preclinical Proof of Concept UCART19**
- *In vitro* and *in vivo* development finalized

Completed 2014 ☑

**Manufacturing UCART19**
- High yield, high potency cGMP batches

achieved Nov 2015 ☑

**Successful Compassionate Use in Pediatric ALL**
- Two infants injected with UCART19
- Still in complete remission today

dosed in Jun and Dec 2015 ☑

**Phase 1**
- First patient enrollment

Dosing started in Jun 2016 ☑

**First Interim Data**
- Update on first seven patients with 100% ORR and 60% CR at 4+ months post injection

Presented at RAC in Dec 2016 ☑

**Second Interim Data**
- Update on Ph1 ALL trial ongoing in UK

Expected in Q4 2017 ☐

**Expansion Phase**
- Pfizer received IND clearance for adult ALL trial
- Ph1b expansion phase planned at U Penn and MD Anderson

Expected in 2018 ☐

# UCART22

## *Targeting ALL and other B-Cell Malignancies*

### Disease description

- Acute lymphoblastic leukemia (ALL) is a cancer of the white blood cells, characterized by the overproduction and accumulation of immature white blood cells (known as lymphoblasts).

### Rationale

- CD22 and CD19: same expression profile on various B-cell stages of development
- CD22 expression frequently maintained in CD19-negative blast cells in ALL [ref1]

### Target Antigen

- CD22, a single-family lectin, consists of 7 extracellular IgG-like domains and is expressed on the B-cell surface starting at the pre-B-cell stage, persists on mature B-cells, and is lost on plasma cells.

### Proof of concept

- Anti-CD22 monoclonal antibodies / immunotoxins (e.g. Inotuzumab ozogamicin)
- Autologous CAR-T in development (JCAR018)

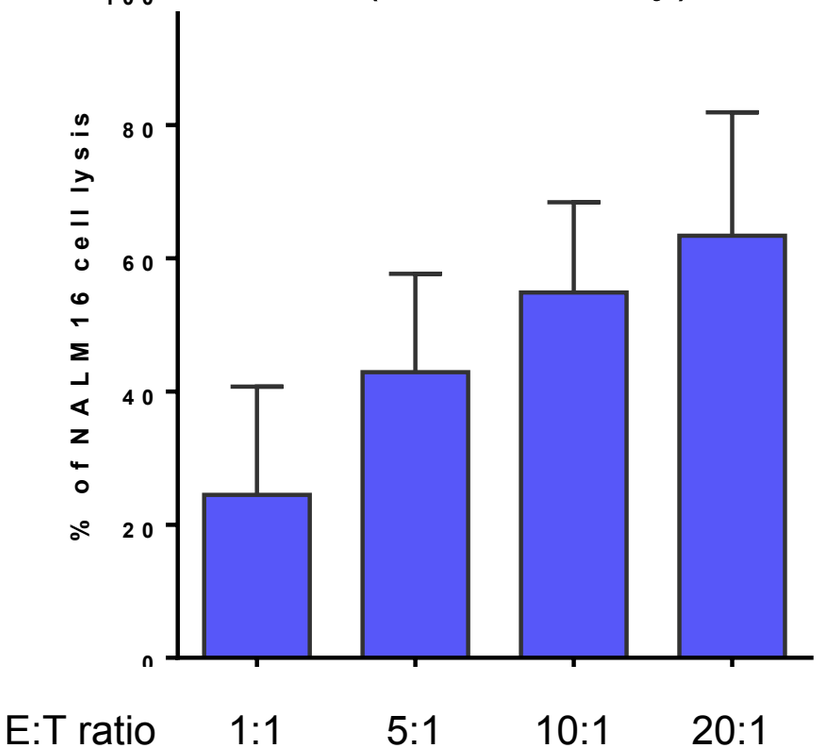
*Ref 1: Maude et al, Blood 2015 125:4017-4023.*

# *UCART22*

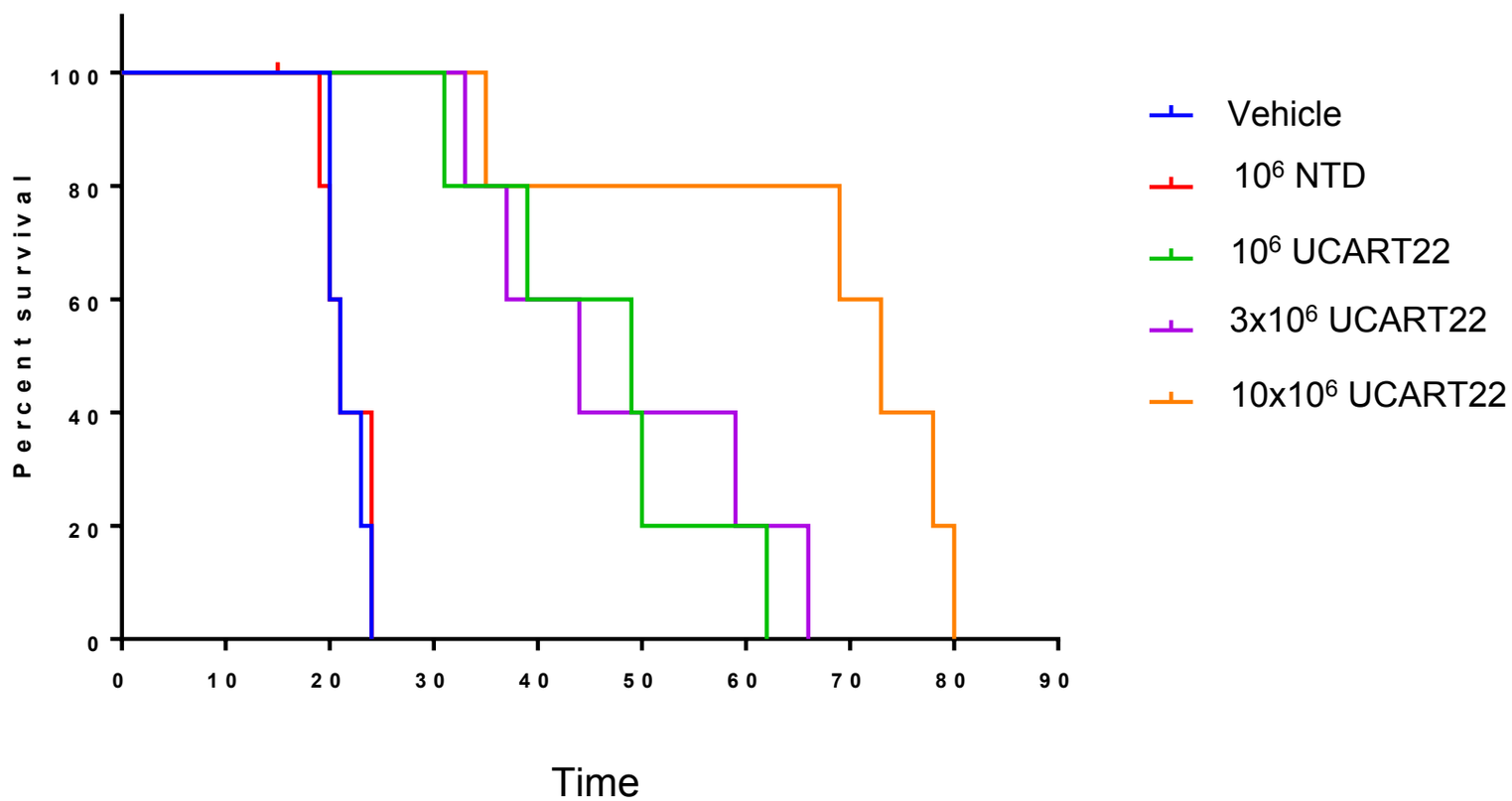
## *Anti-tumoral activity*

- CD22 CART cells are highly efficient at eradicating tumors *in vivo*
- Large Scale batches of UCART22 cells show comparable in vitro activity and increased mice survival

UCART22 large scale batches
(*In vitro* assay)




UCART22 treated mice survival



# *UCART22*

## *Development Plan*

**Proof of concept** — Q4 2016 ☑
- *In vitro* cytotoxic activity demonstrated in CD22+ cell lines
- Generation of anti-CD22 proprietary monoclonal antibodies (selection on going)

***In vivo* studies** — Q3 2017 ☑
- Preclinical studies ongoing in collaboration with MD Anderson Cancer Center

**Manufacturing** — Q4 2017 ☐
- Similar manufacturing process to UCART19

**IND filing** — Expected in 2018 ☐
- CD22 as another target for B-cell malignancies (e.g. ALL,CLL,NHL)
- Potential to use as alternative dosing regiment after CD19 ALL / CLL treatment relapse

# *UCARTCS1*

## *Targeting Multiple Myeloma*

### Disease Description

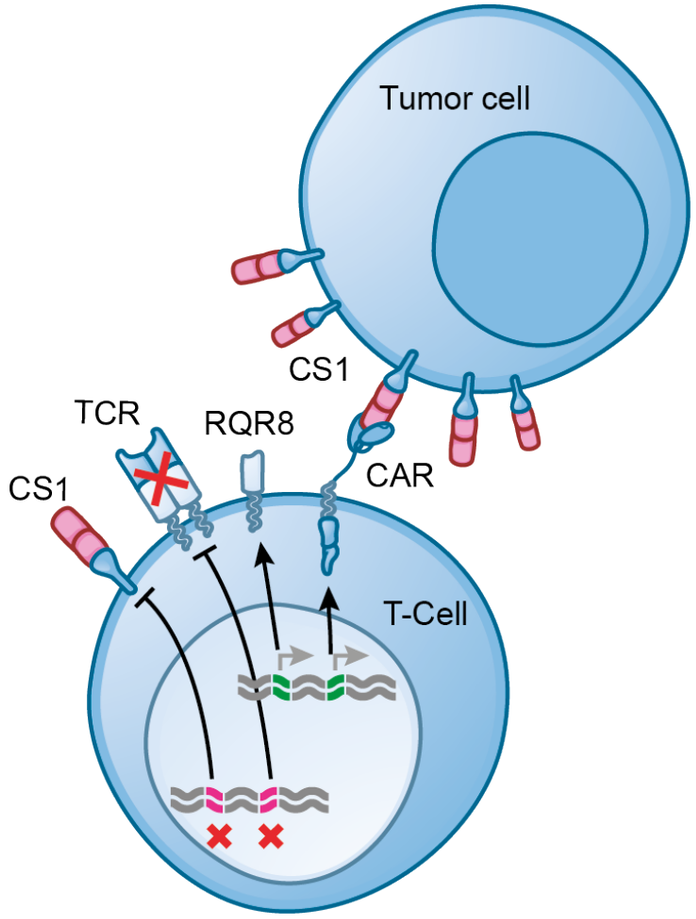
- Multiple myeloma (MM) is a hematologic malignancy characterized by proliferation of plasma cells
- In patients relapsing after prior therapy with immunomodulatory drugs (IMiDs) and bortezomib, the median overall survival rate is 9 months

### Target Antigen

- Elotuzumab (BMS/Abbvie) a monoclonal antibody targeting CS1 as proof of concept for target selection
- CS1 (CD319, SLAMF7) highly expressed on MM cells
- CS1 antigen not expressed on normal tissues or stem cells
- Low levels of expression on natural killer (NK) cells and a subset of T lymphocytes compared with malignant plasma cells

### UCARTCS1 Attributes

- Anti-CS1 CAR expression to redirect T-cells to tumor antigens
- Suicide gene for safety
- TCR disruption using TALEN®  to avoid GvHD
- CS1 is expressed on CD8+ T-cells; to facilitate CAR T-cell production, CS1 is disrupted using TALEN ® to prevent CAR T-cell cross reactivity

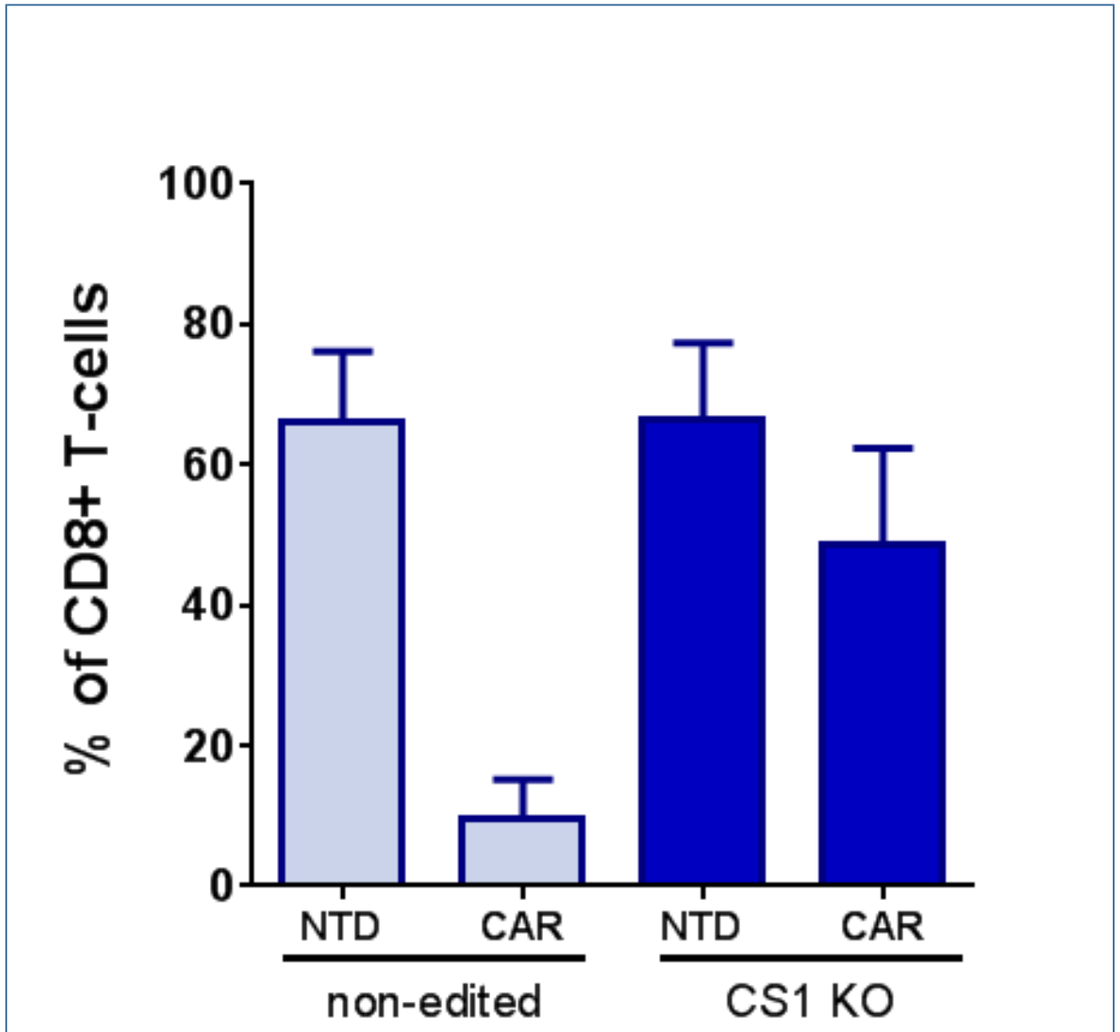


# *UCARTCS1*

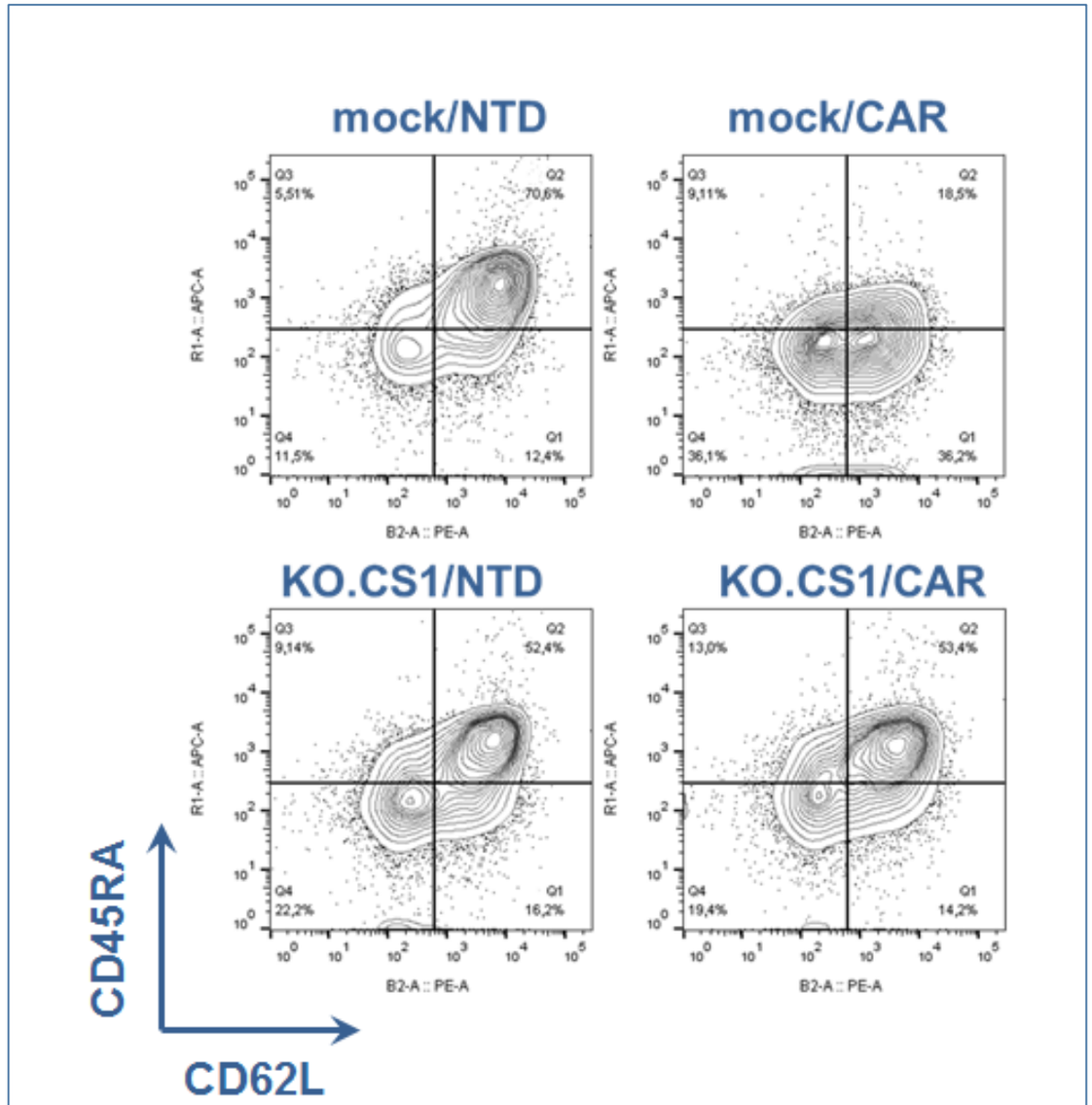
## *Phenotyping analysis*

**The inactivation of CS1 expression in T-cells leads to:**

- Increased yields of $CD8^+$ T-cells




- Prevention of the differentiation of CAR+ T-cells into memory cells

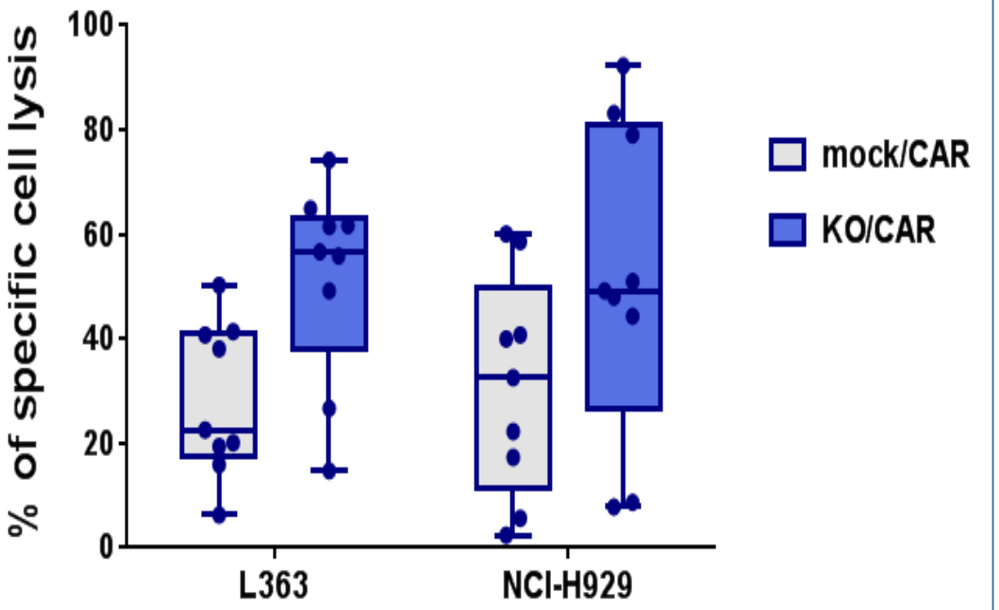


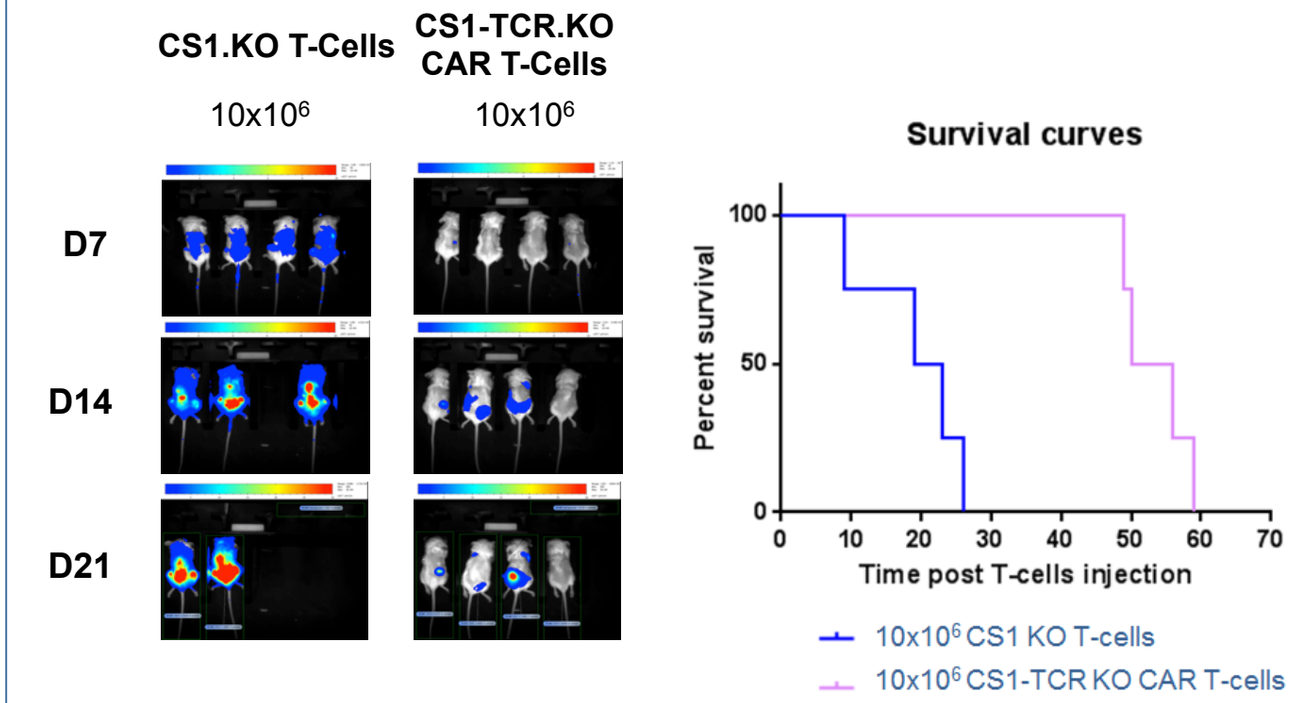
# *UCARTCS1*

## *Anti-tumoral activity*

**The inactivation of CS1 expression in T-cells also shows:**

- Higher *in vitro* anti-tumor activity when compared to mock transfected cells
- Significant *in vivo* anti-tumor activity




***In vitro***

***In vivo***

# *UCARTCS1*
## *Development Plan*

**Proof of Concept**
- Increased cytotoxic activity compared to non-edited T-cells

Completed in Q4 2016 ☑

***In vivo* studies**
- Preclinical studies ongoing in collaboration with MD Anderson Cancer Center (Dr. Jing Yang and Dr. Sattva Neelapu)

Ongoing ☑

**Manufacturing**
- Development of a modified GMP compatible manufacturing process (inversion of transduction/electroporation steps)

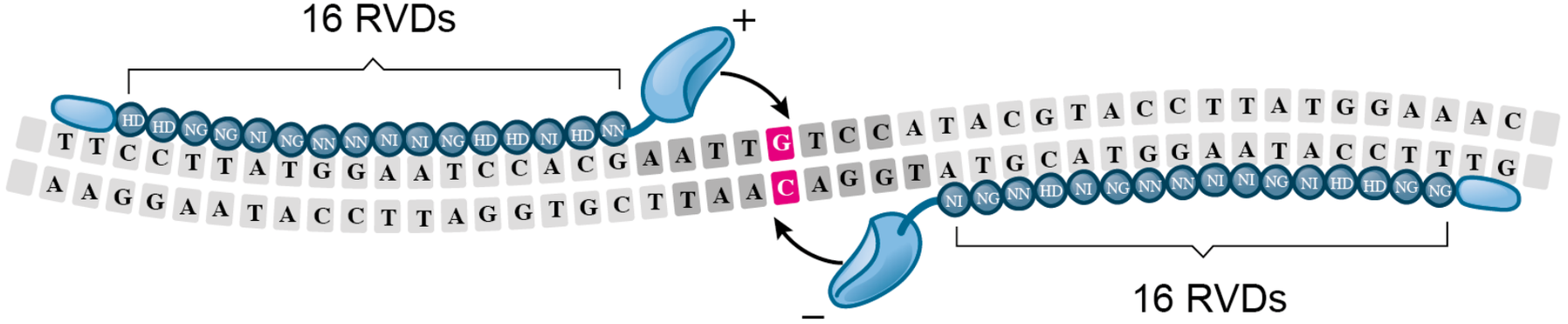
Expected in 2018 ☐

**IND Filing**

Expected in Q4 2018 ☐

# Controlled Gene Editing

## *Best-in-class technologies for therapeutic development*

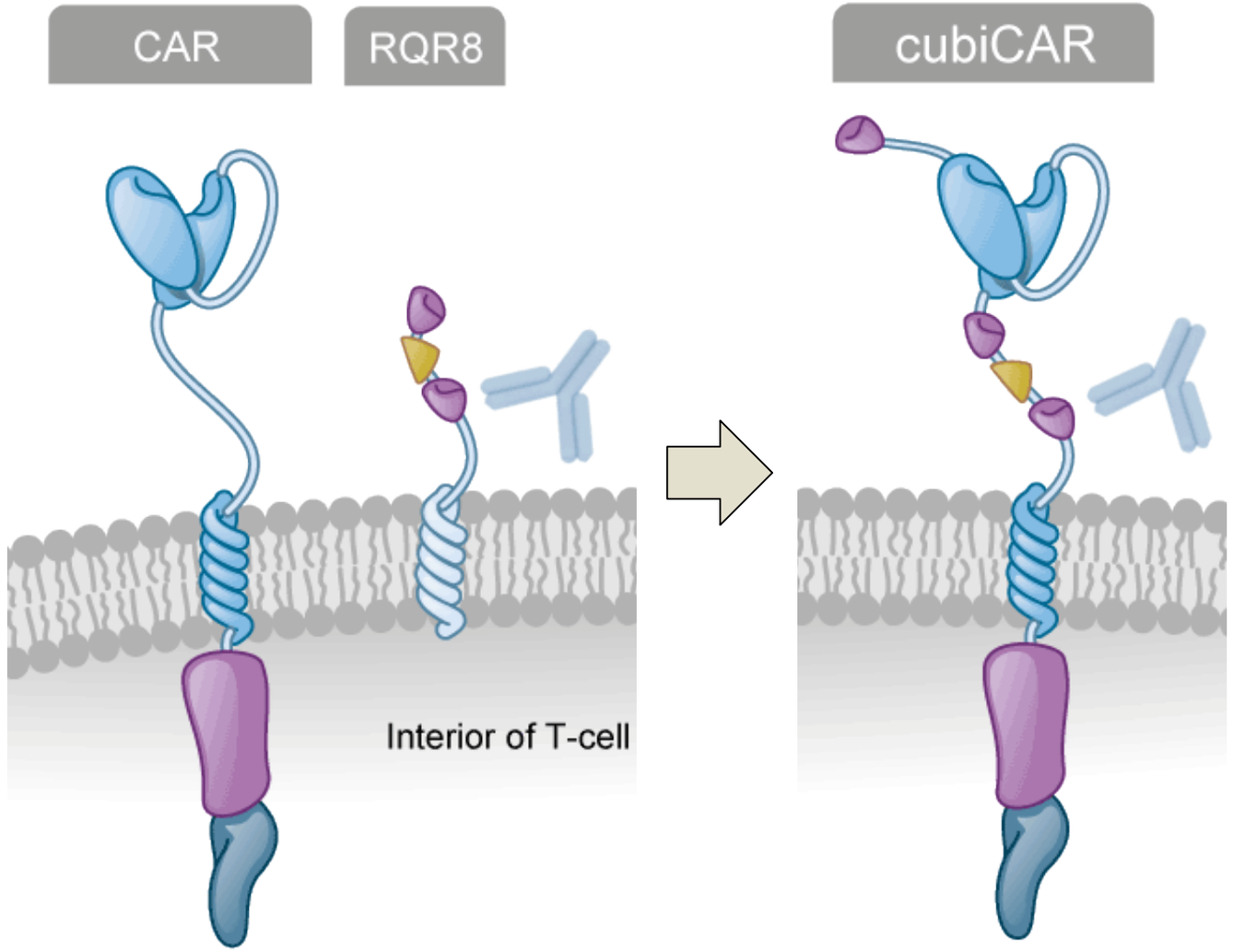




- Highly active: >80% knockout efficiency under GMP conditions
- Highly accurate: 6 base pair specific
- Low off target effect
- TALEN® discovered in 2010 but built on 17 years of experience in gene editing

# Controlling CAR T-Cell Persistence

## *A new generation of suicide switches*

- *Suicide switch is imbedded in the CAR molecule*
- *1:1 expression of CAR and suicide switch on cell surface*



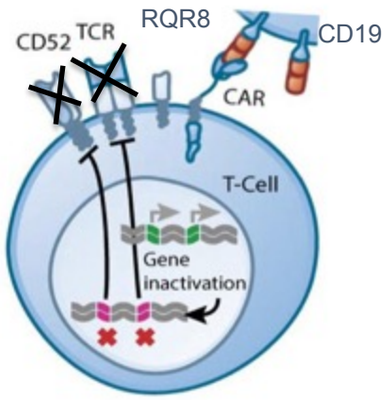

- ✓ Compact
- ✓ Specific cytotoxicity
- ✓ FDA-approved trigger molecule (Rituximab)

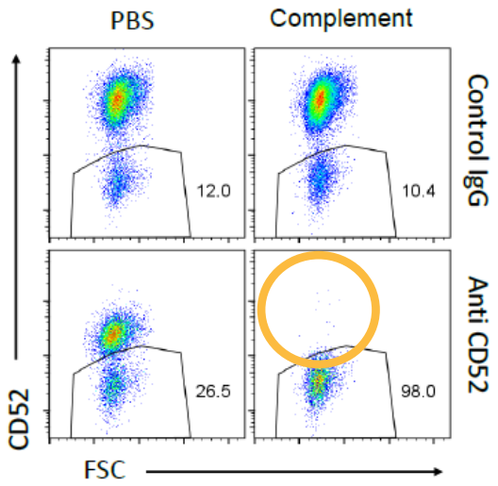
# *Disruptive innovation*

## *Building more powerful T-Cells*

## Mab-resistance

- **CD52 KO** for Alemtuzumab resistance



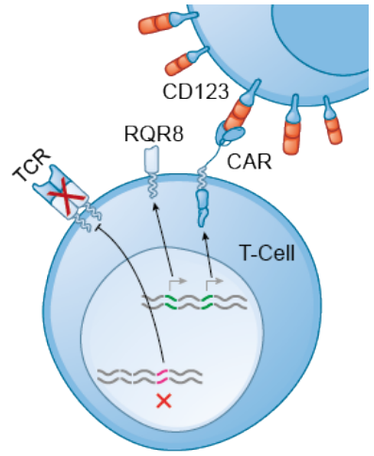




CD52-negative T-cells are resistant to Campath

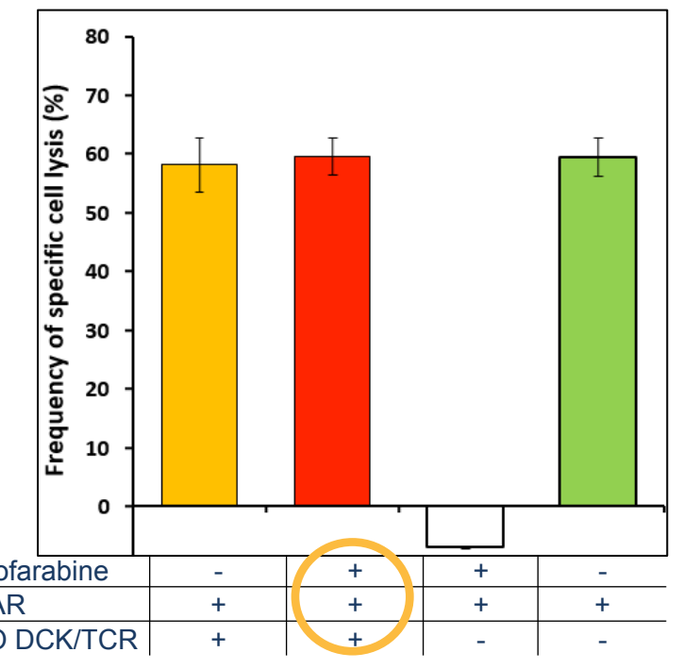
Poirot L *et al*. (2015) Cancer Res.

## Chemo-resistance

- **dCK KO** for Fludarabine and Clofarabine resistance

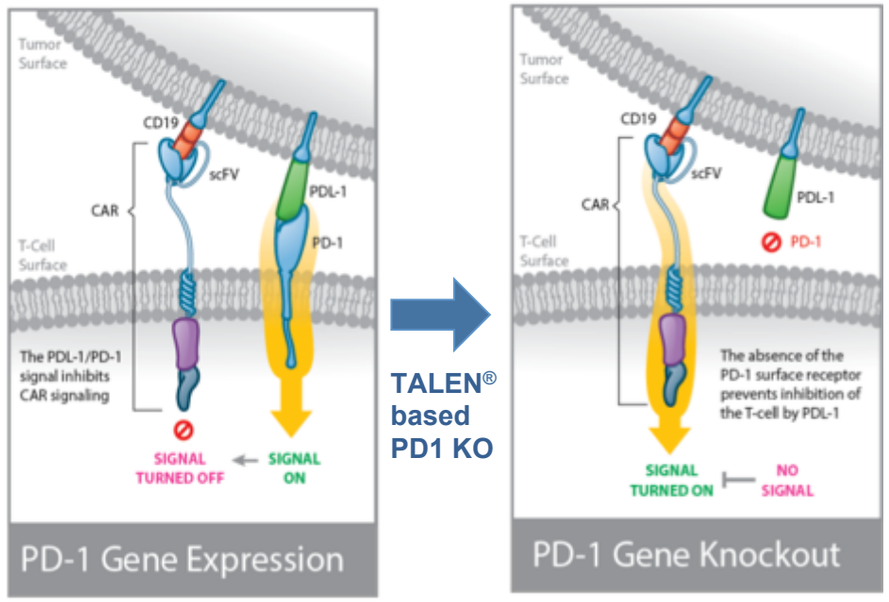


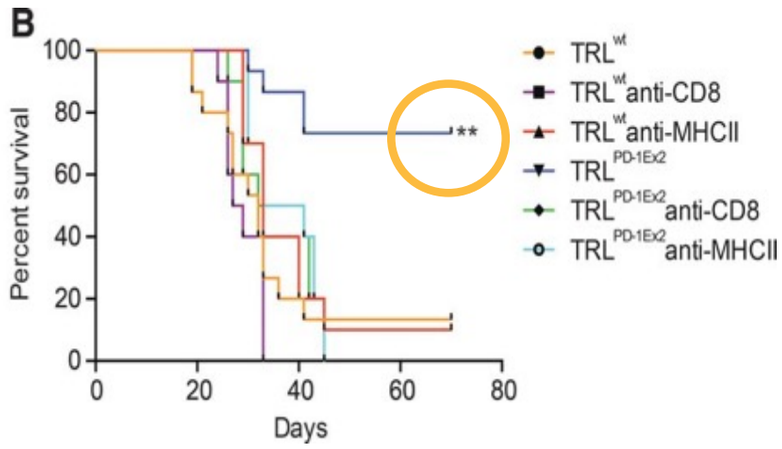

dCK-negative T-cells are resistant to Clofarabine




## PDL1-resistance

- **PD1 KO** to be insensitive to PD-L1 inhibition




PD1-negative T-cells have a higher efficacy on PD-L1 tumor

Menger L *et al.* (2016) Cancer Res.

# Strategic Partners

- Collaboration on up to 15 targets: 1st allogeneic BCMA CART
- 4 years exclusivity on CARTs in human oncology
- Up to $2.8B in total aggregated milestones
- Tiered Royalties on net sales

- Collaboration on up to 5 targets including UCART19
- UCART19 pediatric and adult trials ongoing in the UK
- Up to $974M in aggregate total milestones
- Tiered royalties on net sales

# World Class Clinical Centers

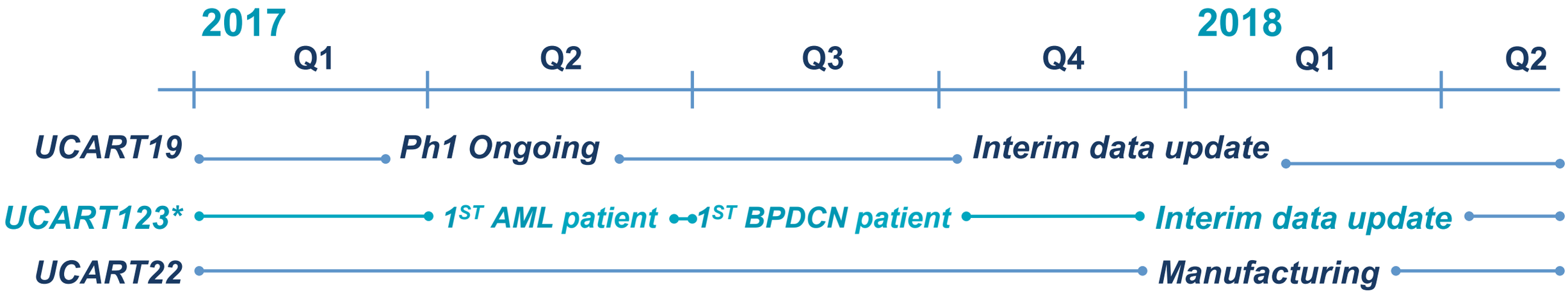
- Development of UCART123 for AML
- New York-Presbyterian Hospital was ranked in 2016 as New York's No. 1 hospital for the 16th year in a row, and No. 6 ranked hospital in all of the United States.

- Development of UCARTCS1 for Multiple Myeloma, UCART22 for ALL, UCART38 for T-Cell ALL and UCART123 for BPDCN
- MD Anderson is ranked the No. 1 hospital for cancer care in the nation by U.S. News & World Report's "Best Hospitals" survey

- Phase 1 clinical trial of Servier UCART19 in pediatric patients
- Great Ormond Street Hospital, London is ranked among the to best hospitals in the UK and top ranking in the world

- Phase 1 clinical trial of Servier UCART19 in adult patients
- King's is one of the world's most prestigious research universities, ranked 21st in the world in 2016/17

# Milestone Timeline




** UCART123 clinical studies suspended*

- **UCART19** in **ALL patients**
  – Ph1 clinical trials ongoing; interim data expected in Q4 2017

- **UCART123** in **AML and BPDCN patients**
  – Ph1 dose-escalation trial on hold; interim data expected in Q1 2018

- **UCART22**, **UCARTCS1** INDs will follow

- Strong partnerships with Servier and Pfizer producing additional CAR T programs

# THANK YOU

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