cellectis

EDITING LIFE

ENGINEERED CAR-T THERAPIES

A NEW PARADIGM IN ONCOLOGY

November 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.

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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

80% ownership

- NASDAQ: CLLS
- ALTERNEXT: ALCLS
- 35.5M SHARES OUTSTANDING
- $304M IN CASH AS OF SEPTEMBER 30, 2017

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

- 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						
	BPDCN						
UCART22	B-ALL						
	B-NHL						
UCARTCS1	MULTIPLE MYELOMA						
UCART38	MULTIPLE MYELOMA						
	T-CELL ALL						
	NHL / MCL						

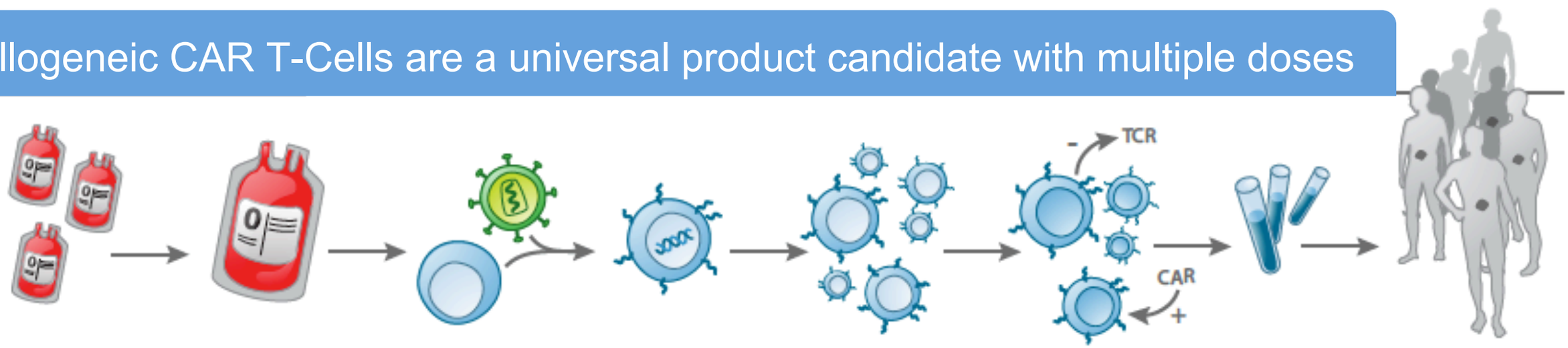
* or European equivalent

** 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

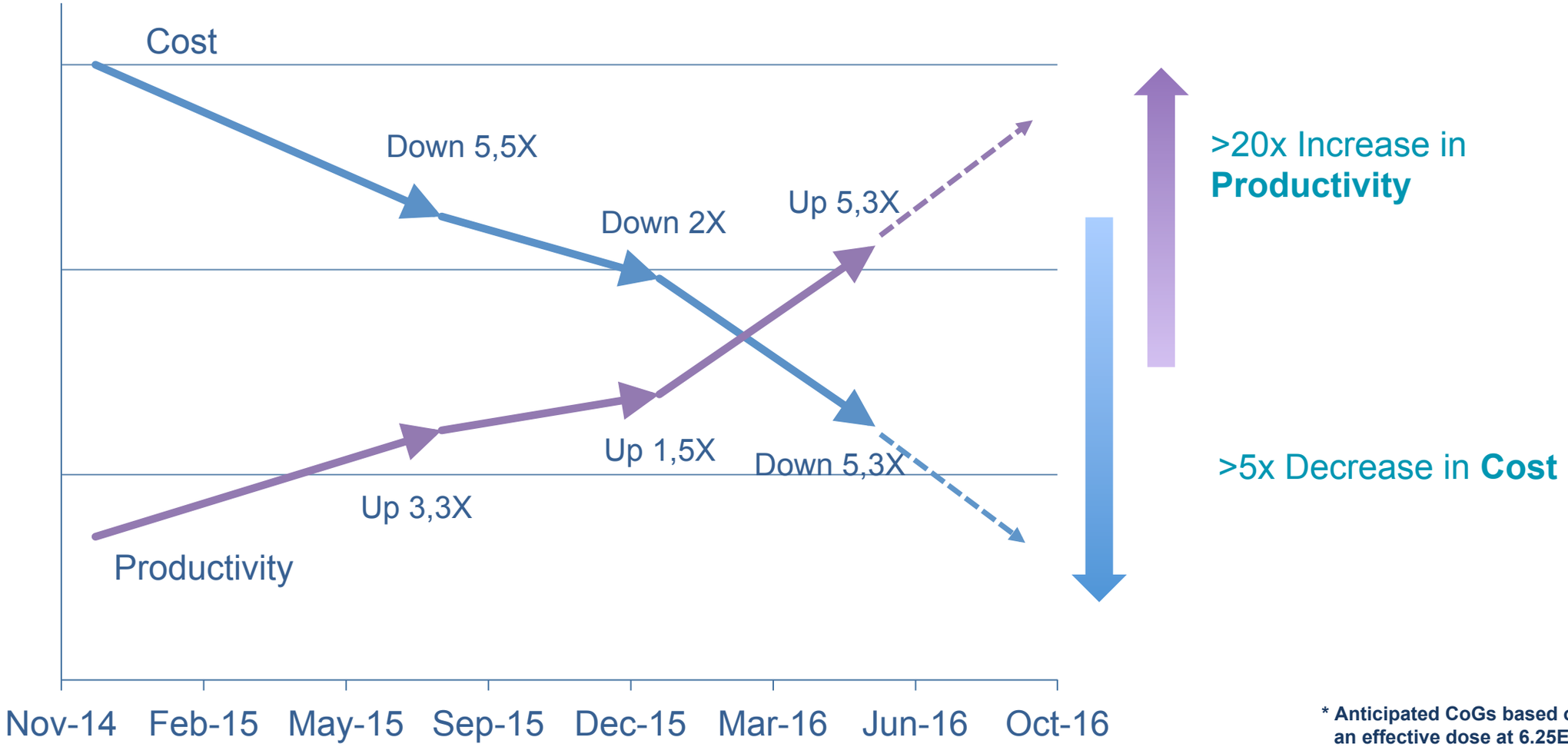
One Leukopack can yield 100s of doses at a cost of goods of less than $4,000 per dose*

* **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 • SGI-110 *(DNA methyl inhibitor)* • CC-486 *(Oral Vidaza)*		Jazz Pharmaceuticals • Vyxeos *(Liposomal formulation)*
Kinase inhibitors	Daiichi-Sankyo • Quizartinib *(FLT3 inhibitor)* astellas • Gilteritinib *(Kinase inhibitor)* abbvie • Venclexta *(Bcl-2 inhibitor)* Boehringer Ingelheim • Volasertib *(Plk1 inhibitor)*		NOVARTIS • Rydapt *(Kinase inhibitors)*
Isocitrate dehydrogenase inhibitors		agios • Ivosidenib *(IDH1 inhibitor)*	agios / Celgene • Idhifa *(IDH2 inhibitor)*
Antagonists	Roche • Idasanutlin *(MDM2 antagon.)*		
ADCs			Pfizer • 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 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 Anti-CLL1 — BCM Baylor College of Medicine; Kite Pharma Anti-CD33 & Anti-CD123 — Universitätsklinikum Carl Gustav Carus; gemoab Monoclonals GmbH Anti-CD33 or Anti-CD123 — Università degli Studi di Milano Bicocca; Cancer Research UK Anti-CD38 — Hiroshima University Anti-CD44v6 — Molmed; Ospedale San Raffaele Anti-FRB — Penn Anti-HLA-A2 — The University of Texas MD Anderson Cancer Center	Anti-CD33 — Chinese PLA General Hospital; Intrexon; ZIOPHARM Oncology, Inc. Anti-CD123 — Affiliated Hospital to Academy of Military Medical Sciences; City of Hope; Penn Anti-NKG2D-L — Celyad 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 Anti-CD33 — PersonGen BioTherapeutics

UCART123 in AML and BPDCN
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

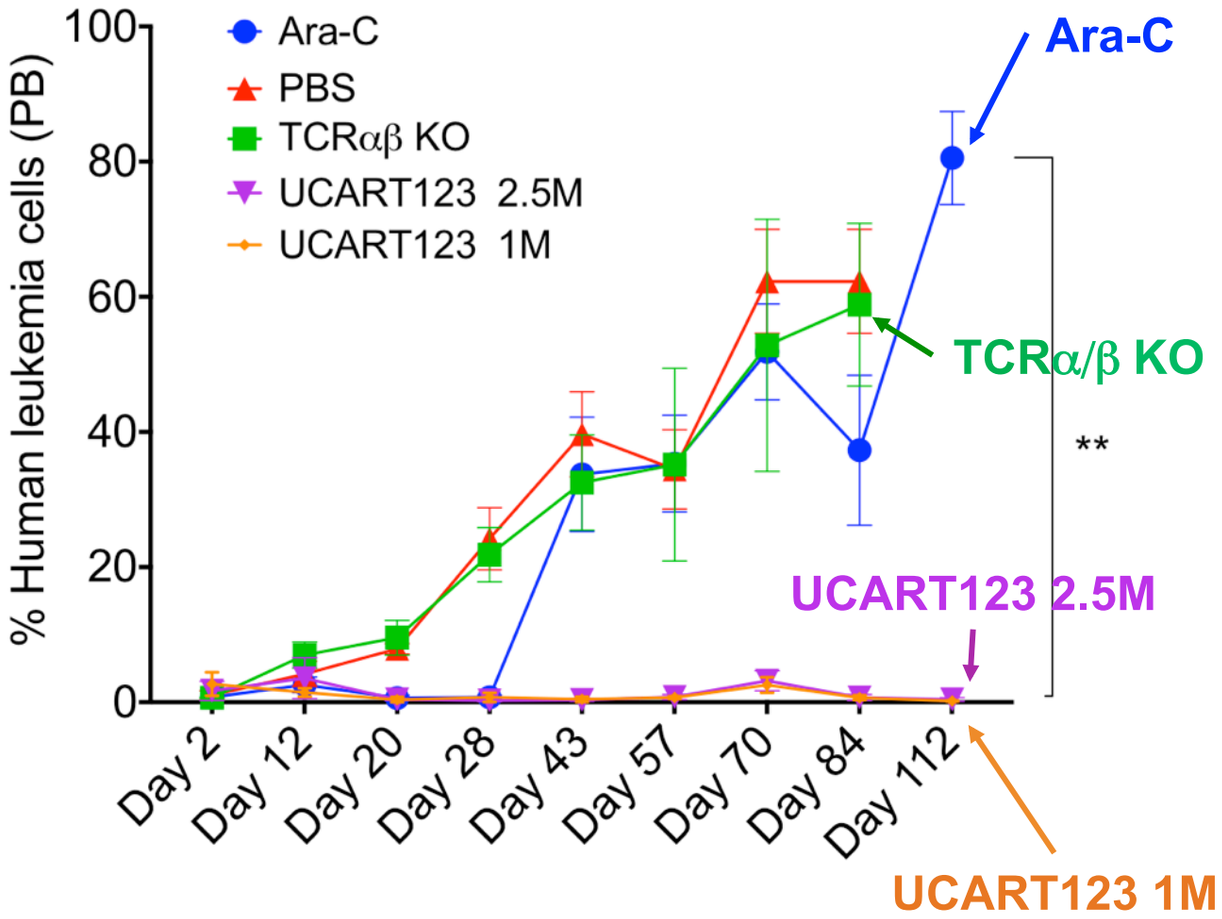
➢ ***BPDCN Ph 1 dose escalation at MD Anderson; First patient dosed in August 2017***

UCART123 in AML

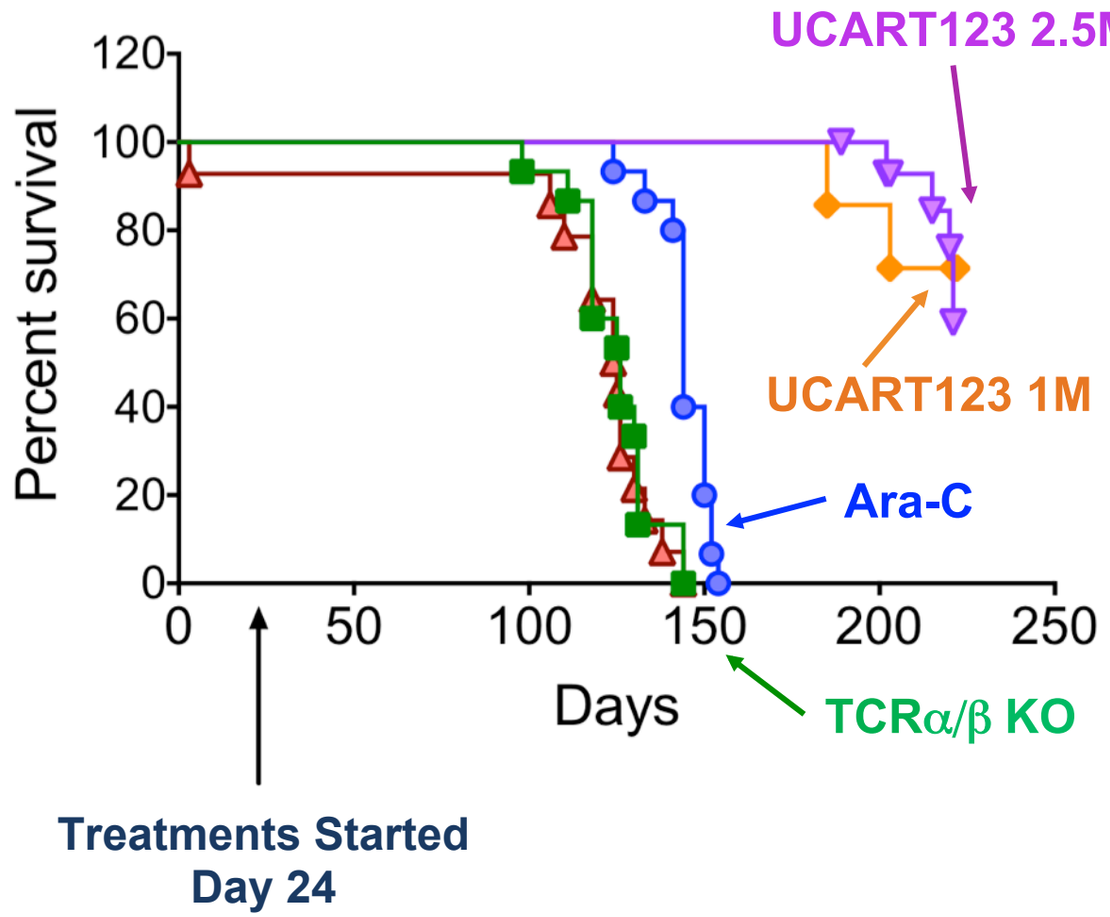
Encouraging Preclinical Efficacy Data at ASH 2016

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

Peripheral Blood Evaluation



Overall Survival

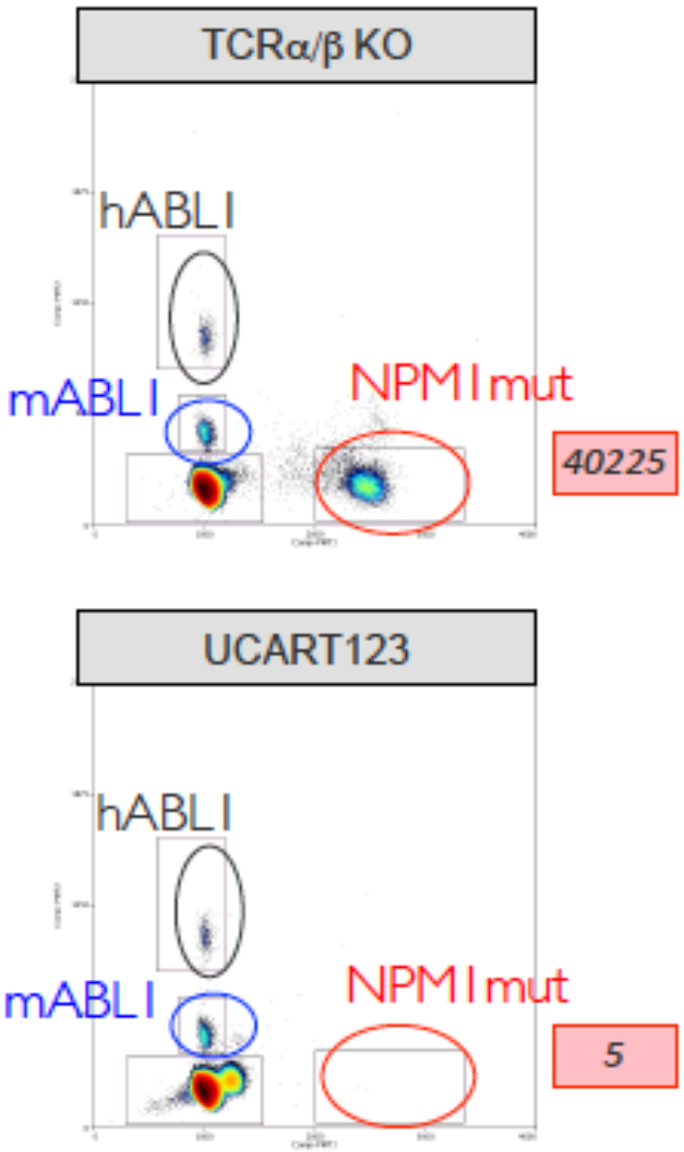


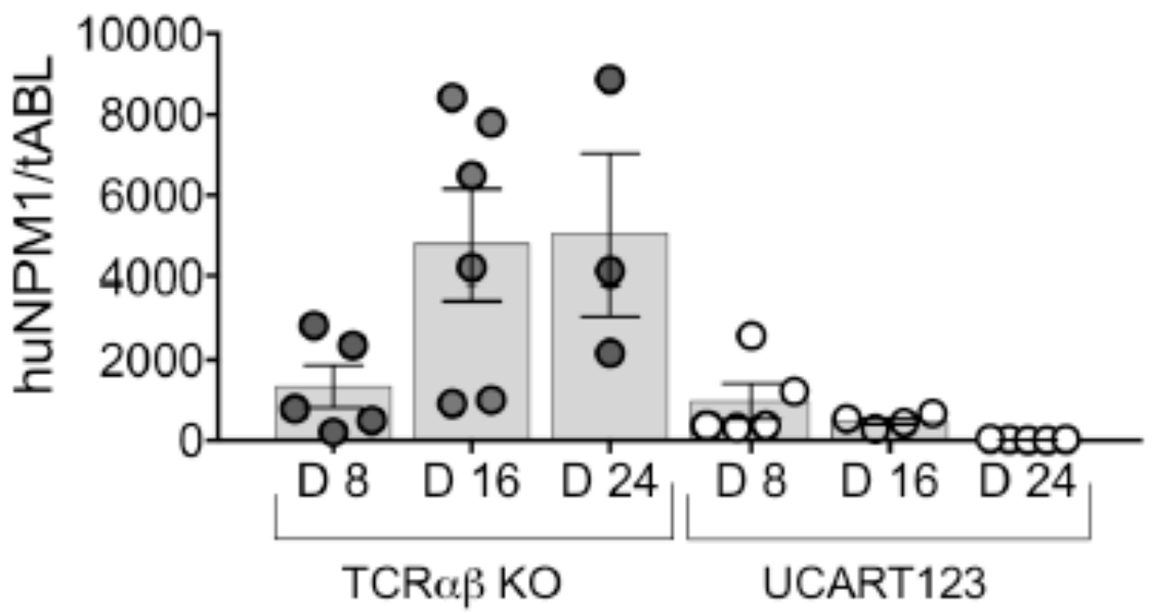
In collaboration with Dr. Monica Guzman, Cornell-Weill

UCART123 in AML

Encouraging Preclinical Efficacy Data at ASH 2016

- Animals treated with UCART123 achieve lasting molecular remission



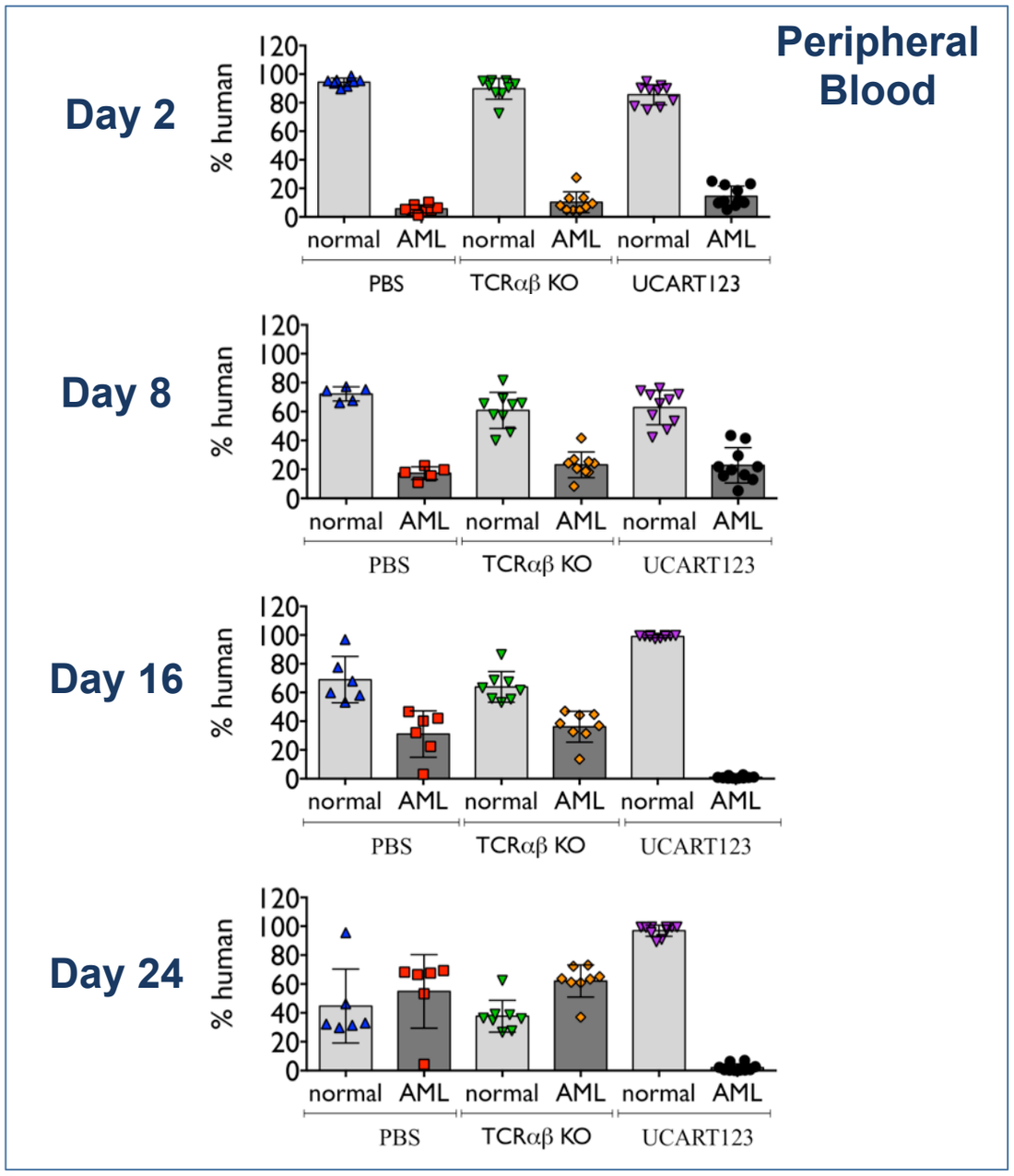


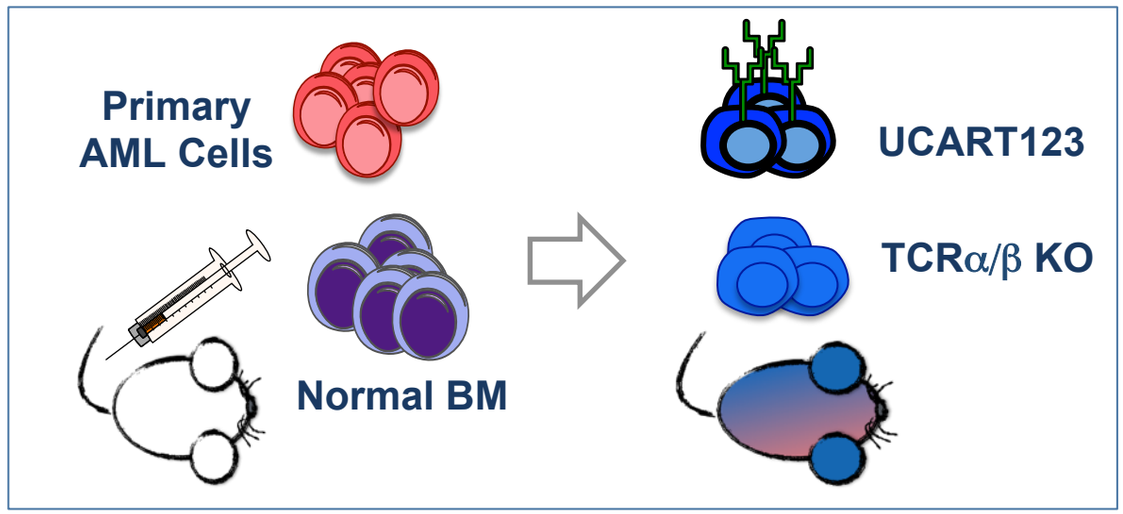
In collaboration with Dr. Monica Guzman, Cornell-Weill

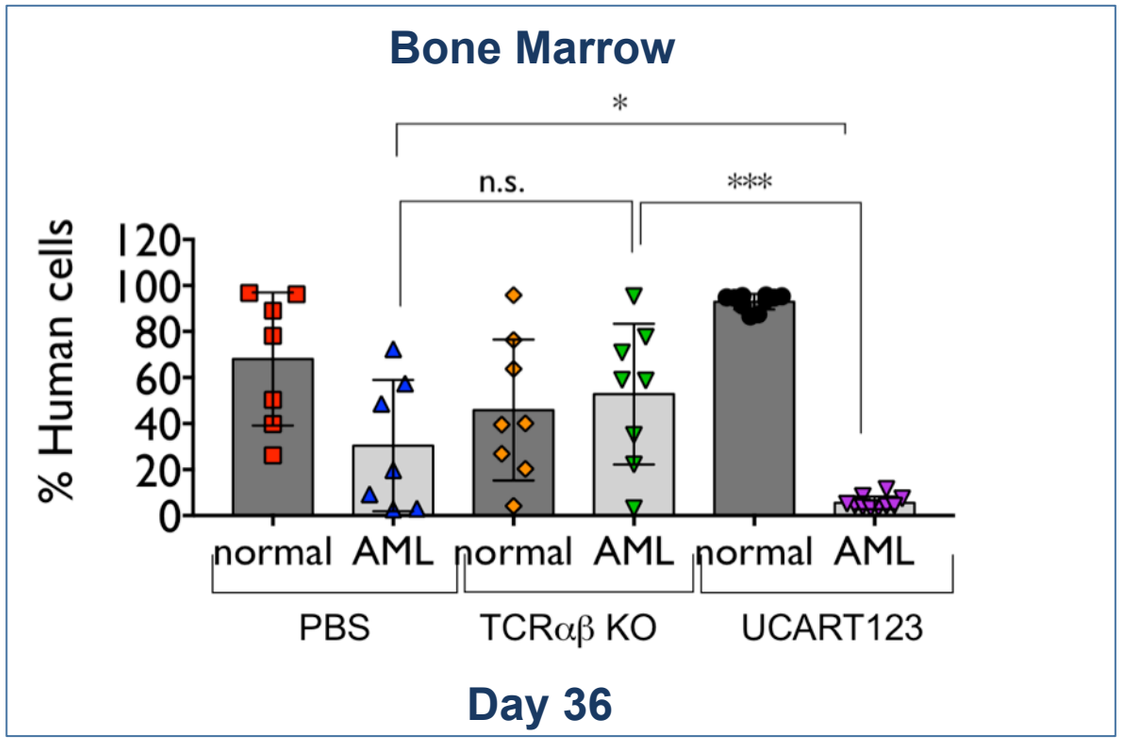
UCART123 in AML

Encouraging Safety Profile

- UCART123 preferentially eliminates AML cells over normal hematopoietic cells







In collaboration with Dr. Monica Guzman, Cornell-Weill

UCART123 in AML

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

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
- First patient enrollment

Dosing started in Summer 2017 ☑

Interim Data
- Update on first AML patients

Expected in Q1 2018 ☐

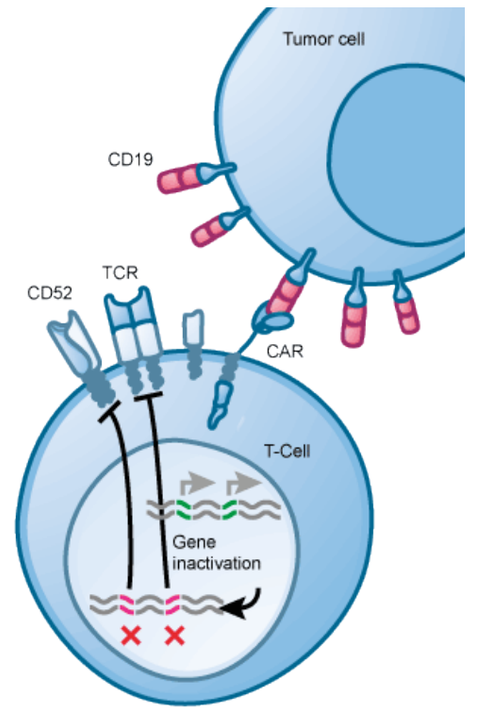
Expansion Phase
- Phase 1b in up to 200 first line AML and BPDCN patients

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* ASH Abstract in Adult ALL Patients

887 Preliminary Results of UCART19, an Allogeneic Anti-CD19 CAR T-Cell Product, in a First-in-Human Trial (CALM) in Adult Patients with CD19+ Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia
Program: Oral and Poster Abstracts
Type: Oral
Session: 612. Acute Lymphoblastic Leukemia: Clinical Studies: Immune-based therapies and rare subgroups
Monday, December 11, 2017: 7:15 PM
Bldg C, Lvl 3, Georgia BR 1-3 (Georgia World Congress Center)

Charlotte Graham, MRCP, BSc, MBBS1,2*, Deborah Yallop, MBBS FRCP FRCPath PhD1*, Agnieszka Jozwik2*, Piers Patten, BSc, MRCP, MRCPath, PhD1,2, Alan Dunlop1*, Rose Ellard1*, Orla Stewart1*, Victoria Potter1*, Victoria Metaxa1*, Shireen Kassam1*, Farzin Farzaneh, PhD3*, Stephen Devereux, FRCP, FRCPath, PhD1, Antonio Pagliuca, MD1, Amina Zinai, MD4*, Florence Binlich, MD4*, Sandra Dupouy, Pharm.D, Ph.D4*, Anne Philippe4*, Svetlana Balandraud, MD4*, Frédéric Dubois4*, Cyril Konto, MD5*, Premal Patel, MD, PhD, BSPharm5*, Ghulam J Mufti, DM, FRCP, FRCPath3,6* and Reuben Benjamin1,2*

1King's College Hospital NHS Foundation Trust, London, United Kingdom
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3Haematology Department, King's College London, London, United Kingdom
4Institut de Recherches Internationales Servier, Suresnes, France
5Pfizer, San Francisco
6Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, United Kingdom

Background
UCART19 is a genetically modified T-cell product manufactured from non-HLA matched healthy donor cells. Lentiviral-transduced CAR T-cells express (1) an anti-CD19 CAR (anti-CD19 scFv- 41BB- CD3ζ) and (2) an RQR8 "safety switch" that is intended to allow targeted elimination of RQR8+ cells by rituximab. UCART19 has been additionally modified to disrupt the T-cell receptor alpha constant (TRAC) and CD52 genes. The preliminary results of this "off-the-shelf" allogeneic CAR T-cell therapy in a phase I, dose-escalation trial of UCART19 in CD19+ R/R B-ALL adult patients (pts) are described.

Methods
The primary objective of this study is to determine the maximum tolerated dose of UCART19 by investigating up to four dose levels (DL) in separate sequential cohorts. Adult pts (age ≥16 years) with CD19+ R/R B-ALL who have exhausted available treatment options are eligible. Disease burden must be quantifiable morphologically or with a minimal residual disease (MRD) load ≥1x10-3 at the end of the last anti-leukemic treatment. The lymphodepletion regimen combines cyclophosphamide and fludarabine, with or without alemtuzumab (FC or FCA). A single dose of UCART19 is administered on Day 0, and pts are closely monitored for safety and anti-leukemic activity until the end of study, 3 months after UCART19 administration. Pts are then rolled-over into a 15-years long-term follow-up study. The dose escalation follows a modified Toxicity Probability Interval (mTPI) design based on the occurrence of dose-limiting toxicity (DLT) assessed at the end of the 28-day evaluation period post UCART19 (D28).

Results
As of 24 June 2017, the 2 first cohorts (3 pts each) who received the first DL (DL1=6x106 total CAR+ cells) have been completed. Median age was 22.5 years (range 18-42). Pts received 1 to 5 previous lines of treatment with 5 out of 6 pts having undergone an allogeneic stem cell transplant (allo-SCT). Four of them had relapsed within 4-6 months post-transplant. Prior to UCART19 infusion, 4 pts had low disease burden (<5% leukemic blasts in bone marrow (BM)) and 2 pts had high disease burden (69 and 100% blasts respectively). All pts received lymphodepletion with FCA.

All pts experienced cytokine release syndrome (CRS): 1 G1, 4 G2 and 1 G4. CRS G1 and G2 were manageable by supportive care ± tocilizumab. CRS G4, assessed as a DLT, occurred in the context of neutropenic sepsis, and was considered to be a contributory factor in the patient's death from multiple organ failure at D15. Time to onset of first CRS symptoms ranged between D5 and D10. CRS correlated with serum cytokine increase (IL-6; IL-10 and INFγ) and UCART19 expansion in the blood**. One patient was reported to have probable skin GvHD G1. Only G1 neurotoxic events were observed in 1 patient.** Asymptomatic viral reactivations (CMV and/or adenovirus) were seen in 3 pts and resolved with antiviral therapy. Among the 6 pts, 4 achieved a CRi with MRD negativity at D28 (MRD-ve, defined as a tumor burden <0.01% assessed by flow cytometry and/or qPCR), 1 was refractory to treatment at D28 and 1 died at D15.

All 4 pts achieving MRD-ve remission underwent a subsequent allo-SCT, 3 of them within 3 months of UCART19 infusion and 1 following retreatment with FC lymphodepletion and the same dose of UCART19, this patient having relapsed with CD19+ disease 2 months post initial UCART19 infusion. Post allo-SCT, 1 patient relapsed at 100 days with CD19+ disease, 1 died from infection and 2 remain in complete remission. Three pts remain alive at 2.4, 5.3 and 10.2 months respectively post UCART19 treatment.

UCART19 (both cells and transgene levels) peaked between D12 and D17 in blood (flow cytometry and qPCR, respectively). UCART19 was detectable in blood from D10 to D28 (up to D42 in 1 patient) and in BM aspirates performed at D14 and D28. **In-vivo cell expansion in BM occurred in all but the refractory patient.**

Conclusion
Preliminary results of this first-in-human trial of UCART19 treatment in a high risk R/R B-ALL adult population revealed no unexpected toxicities. Asymptomatic lymphodepletion-related viral reactivations and a probable skin GvHD G1 were encountered. **CRi with MRD-ve was achieved in 4 out of 5 pts who reached D28.** The 2 first cohorts treated at DL1 have been completed and DL2 will now be investigated on which further results may be presented. The study is active in the UK and will be expanded to other EU countries and the US (NCT 02746952).

Entering Clinical Development

UCART19* ASH Abstract in Pediatric ALL Patients

1271 Preliminary Results of UCART19, an Allogeneic Anti-CD19 CAR T-Cell Product in a First-in-Human Trial (PALL) in Pediatric Patients with CD19+ Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia
Program: Oral and Poster Abstracts
Session: 612. Acute Lymphoblastic Leukemia: Clinical Studies: Poster I

Saturday, December 9, 2017, 5:30 PM-7:30 PM
Bldg A, Lvl 1, Hall A2 (Georgia World Congress Center)

Waseem Qasim, MD, PhD1*, Oana Ciocarlie1*, Stuart Adams, PHD1*, Sarah Inglott1*, Claire Murphy1*, Christine Rivat1*, Gary Wright1*, Giovanna Lucchini, MD2*, Juliana Silva, MD2*, Kanchan Rao2*, Amina Zinaï, MD3*, Florence Binlich, MD3*, Sandra Dupouy, Pharm.D, Ph.D3*, Jeanne Pauly, PharmD3*, Svetlana Balandraud, MD3*, Frédéric Dubois3*, Cyril Konto, MD4*, Premal Patel, MD, PhD, BSPharm4*, Robert Chiesa1*, Sujith Samarasinghe5*, Havinder Hara1*, Alayna Boyle1*, Jan Chu1*, Danielle Pinner1*, Persis J Amrolia2*, Ajay Vora, MD6, Anupama Rao1*, Philip Ancliffe, MD1* and Paul Veys, MD1*
1Bone Marrow Transplantation Department, Great Ormond Street hospital NHS trust, London, United Kingdom
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3Institut de Recherches Internationales Servier, Suresnes, France
4Pfizer, San Francisco
5Haematology Department, Great Ormond Street hospital NHS trust, London, United Kingdom
6Haematology, Great Ormond Street Hospital, London, United Kingdom

Background
UCART19 is a genetically modified T-cell product manufactured from non-HLA matched healthy donor cells and aims to provide a ready to use, off-the-shelf allogeneic engineered CAR T-cell product. Lentiviral-transduced CAR T-cells express (1) an anti-CD19 CAR (anti-CD19 scFv- 41BB- CD3ζ), and (2) an RQR8 "safety switch" that is intended to allow targeted elimination of RQR8+ cells by rituximab. UCART19 has been additionally modified to disrupt the T-cell receptor alpha constant (TRAC) and CD52 genes. **We previously reported the success of this approach in two infants treated under compassionate use who achieved molecular remissions ahead of allogeneic transplantation and remain in remission with follow-up for 18 and 24 months.** Here we describe preliminary results of a Phase 1 trial of UCART19 in pediatric patients (pts) with high risk relapsed refractory (R/R) CD19+ B-ALL and no therapeutic options.

Methods
This study evaluates the safety and tolerability of a fixed dose (2x107 total cells or 1.1 to 2.3x106 cells/kg) of UCART19 and its ability to achieve molecular remission at day (D) 28 to enable allogeneic stem cell transplantation (allo-SCT). Up to 10 subjects with R/R B-ALL aged between 6 months and < 18 years, with morphologically confirmed CD19+ B-ALL or an MRD load ≥ 1x10-3 are eligible. The lymphodepletion regimen combines cyclophosphamide and fludarabine with or without alemtuzumab (FC or FCA). UCART19 is administered thereafter (Day 0) as a single dose infusion. If the patient achieves molecular remission, allo-SCT is scheduled within 6 to 12 weeks (wks) after infusion, and trial period continues for a further 12 months before entry into a long-term follow-up study.

Results
As of 24 June 2017, 5 children (3 males and 2 females), including two infant leukaemias, aged between 8 months and 16.4 years had been enrolled and treated. Four pts had received 3 or more previous lines of treatment and 2 had undergone a previous allo-SCT**. All patients were unsuitable for or had failed generation of an autologous CAR T-cell product.** All had received debulking chemotherapy and/or inotuzumab ozogamicin therapy before UCART19. All pts received lymphodepletion with FCA. No immediate infusion related reaction (IRR) related to UCART19 were reported. **All pts experienced reversible cytokine release syndrome (CRS) (1 grade (G) 1, 3 G2, 1 G3)**, with one child requiring 2 doses of tocilizumab. Time to onset of first CRS symptoms was between D4 and D8. Two pts presented mild neurological symptoms that recovered (within 1 to 3 days) without treatment. **Acute skin GvHD G1 was reported in two pts (one with biopsy confirmation) and both recovered with topical steroids**. Four children experienced viral complications (CMV, ADV, BK, metapneumovirus) related to lymphodepletion, and all experienced neutropenia, which was prolonged in 2/5 pts. **By D28-42, 5/5 pts had achieved complete remission with incomplete blood count recovery albeit with hypoplastic marrows (all patients were MRD negative by flow cytometry or qPCR). UCART19 were detectable from D7 to at least D28 in all subjects by qPCR and/or flow cytometry and by molecular signatures of T-cell donor chimerism. All proceeded to conditioned allo-SCT between 7 to 9 weeks after UCART19 infusion, with no gene-modified cells detectable thereafter.** Two children relapsed 3 months after transplantation (one CD19- and one CD19+) and died 7 and 8 months after UCART19 infusion respectively. One subject died in remission from transplant related complications including thrombotic microangiopathy and BK haemorrhagic cystitis and nephritis. **Two subjects remain in molecular remission 2 and 2.5 months post-transplant.**

Conclusion
Preliminary results of this first-in-human trial of UCART19 treatment in a high risk R/R B-ALL pediatric population revealed no unexpected toxicities. GvHD seen in 2 patients was mild and self-limiting. Lymphodepletion-related viral complications and persisting neutropenia were encountered**. All five treated subjects were rendered either flow or PCR MRD negative enabling allogeneic transplantation to proceed.** The trial is ongoing in the UK and further data may be presented (NCT02808442) .

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

To be presented at ASH 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)

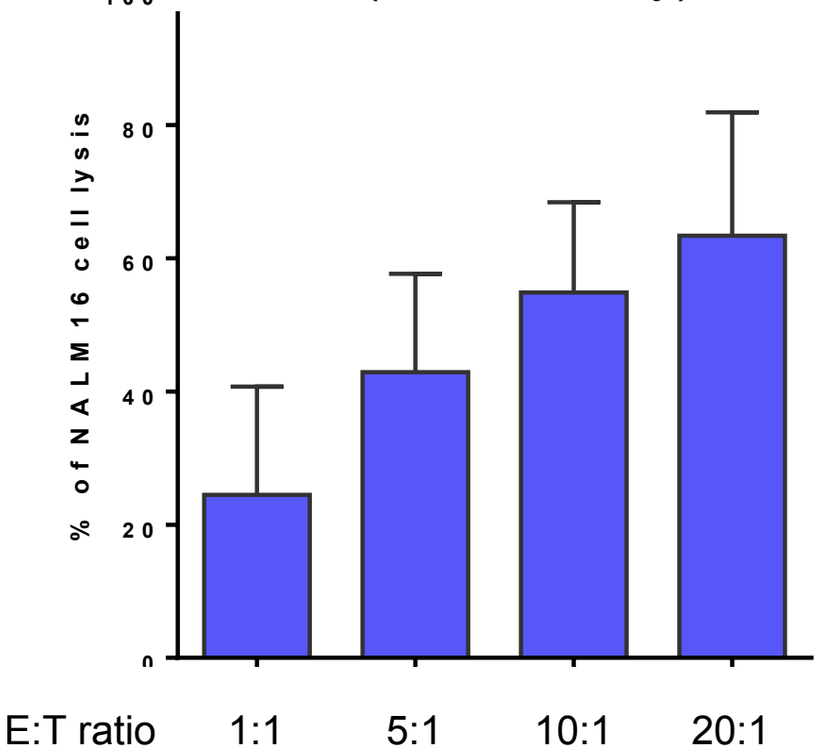
Ref 1: Maude et al, Blood 2015 125:4017-4023.

UCART22

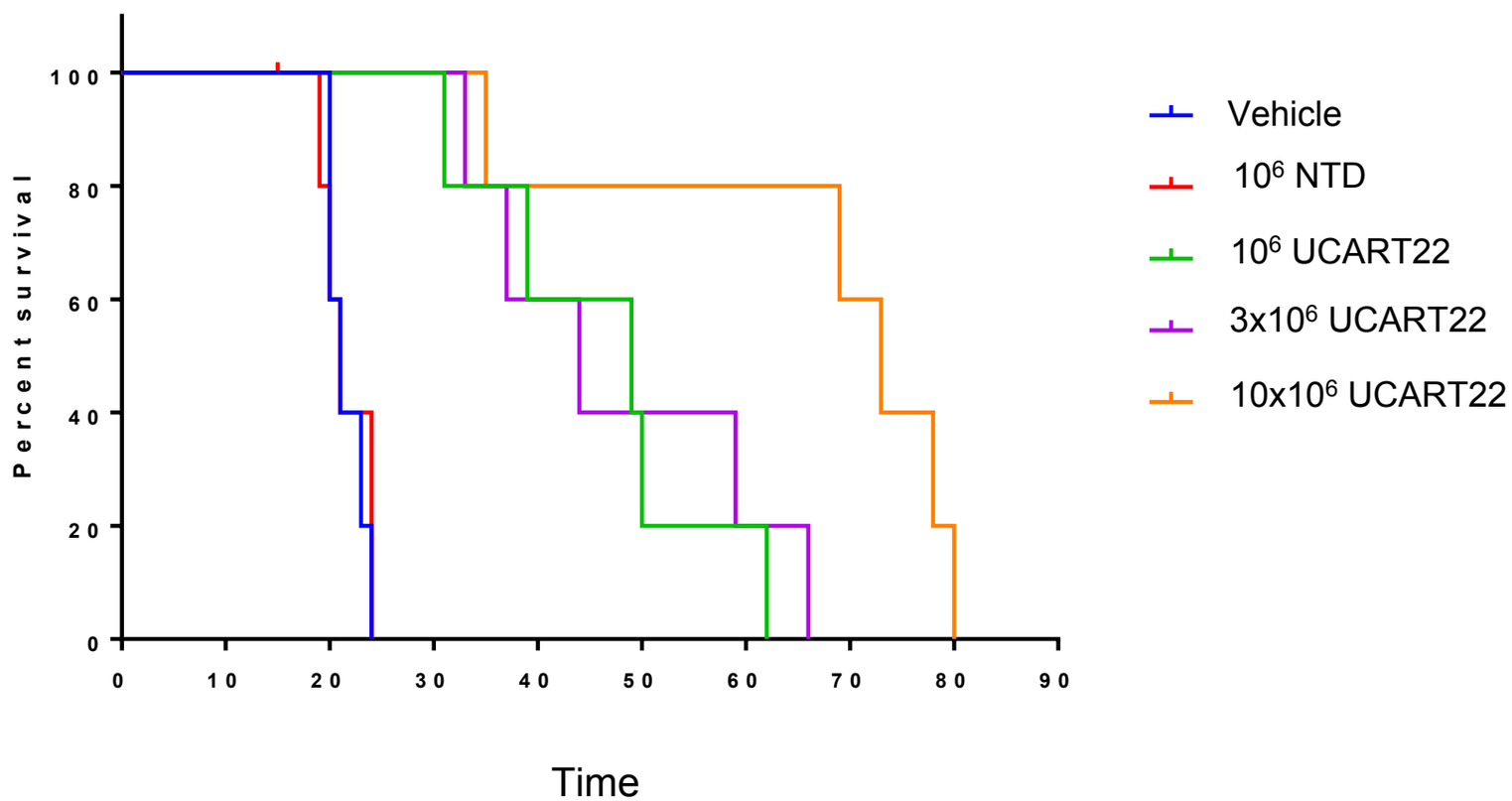
Anti-tumoral activity

- 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

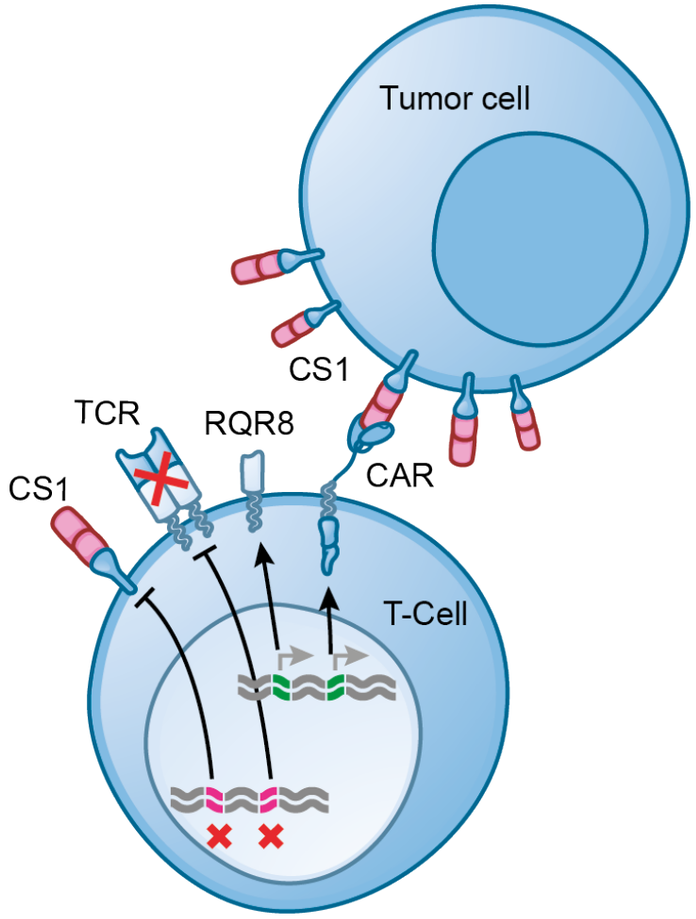
- Multiple myeloma (MM) is a hematologic malignancy characterized by proliferation of plasma cells
- In patients relapsing after prior therapy with immunomodulatory drugs (IMiDs) and bortezomib, the median overall survival rate is 9 months

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

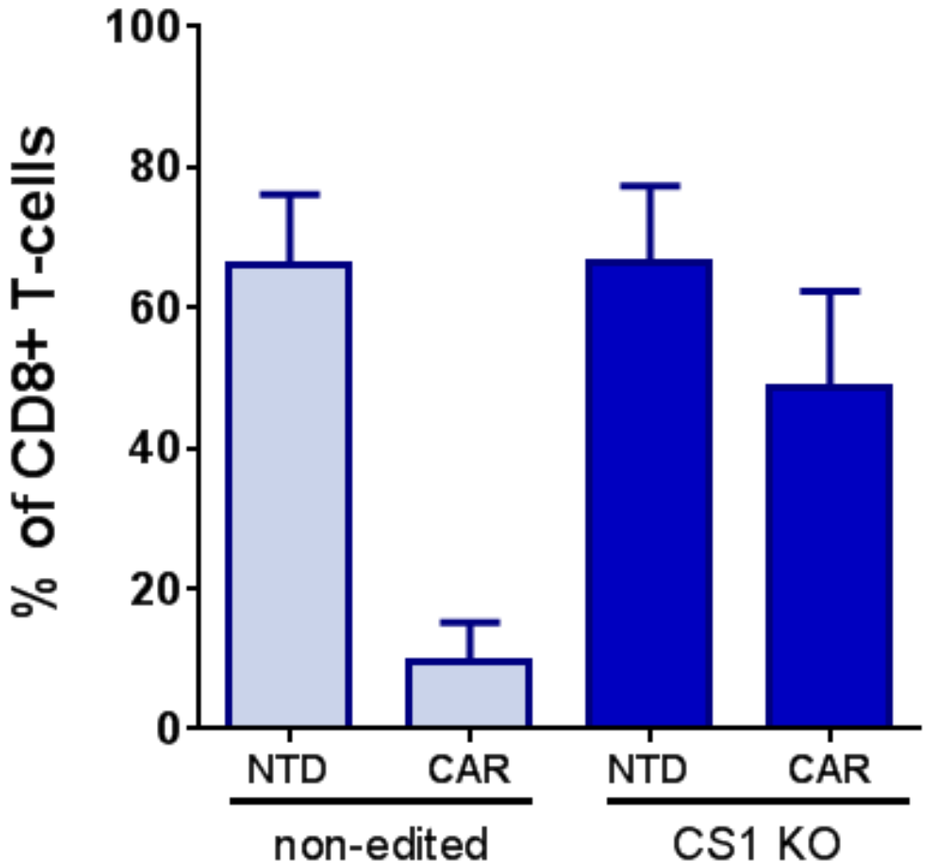


UCARTCS1

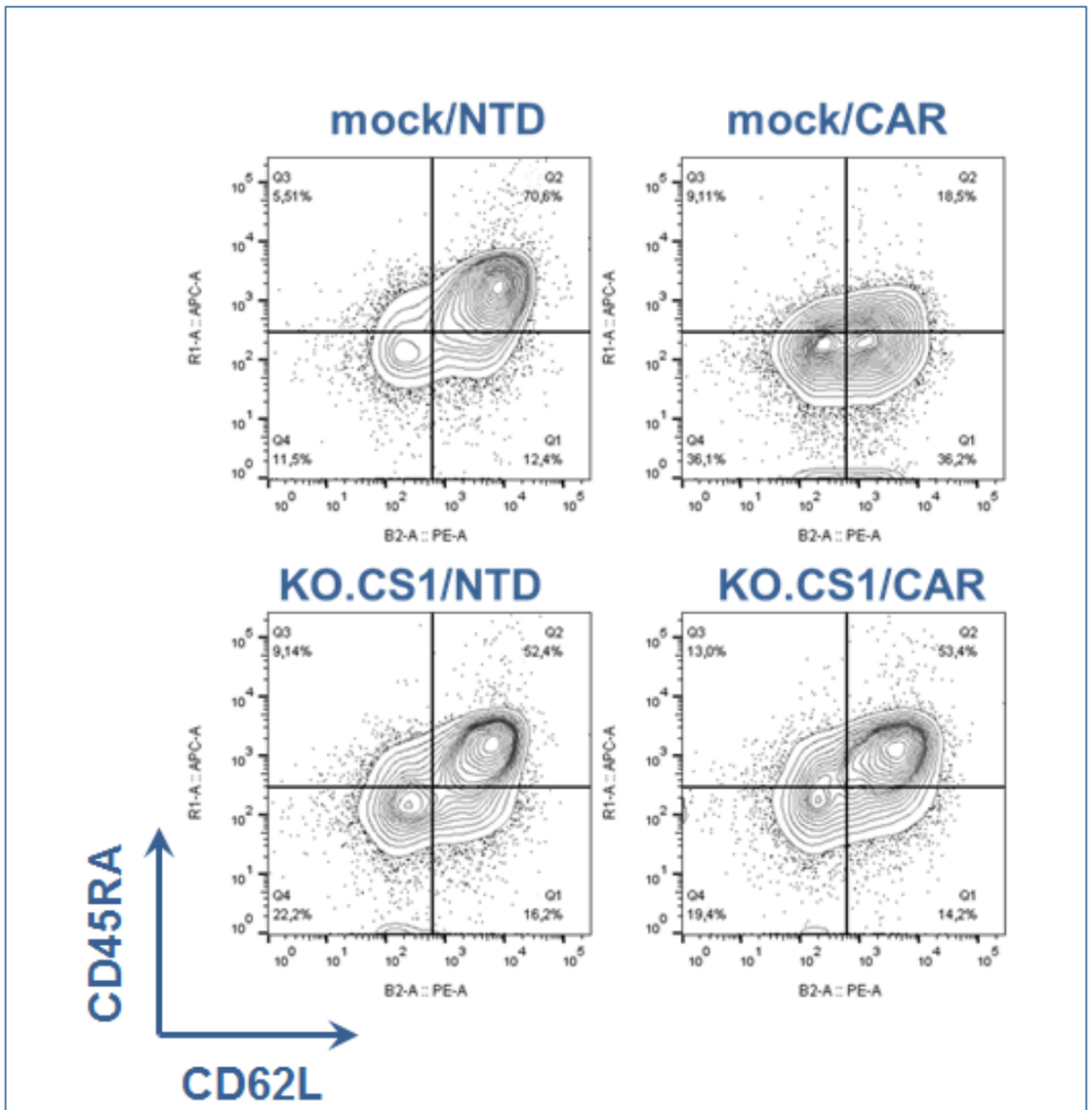
Phenotyping analysis

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

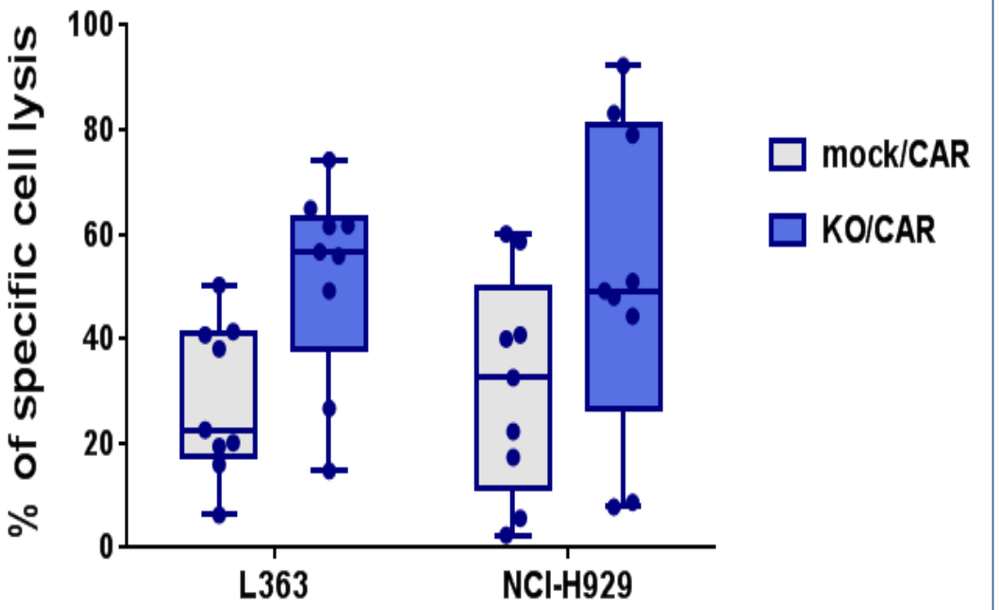


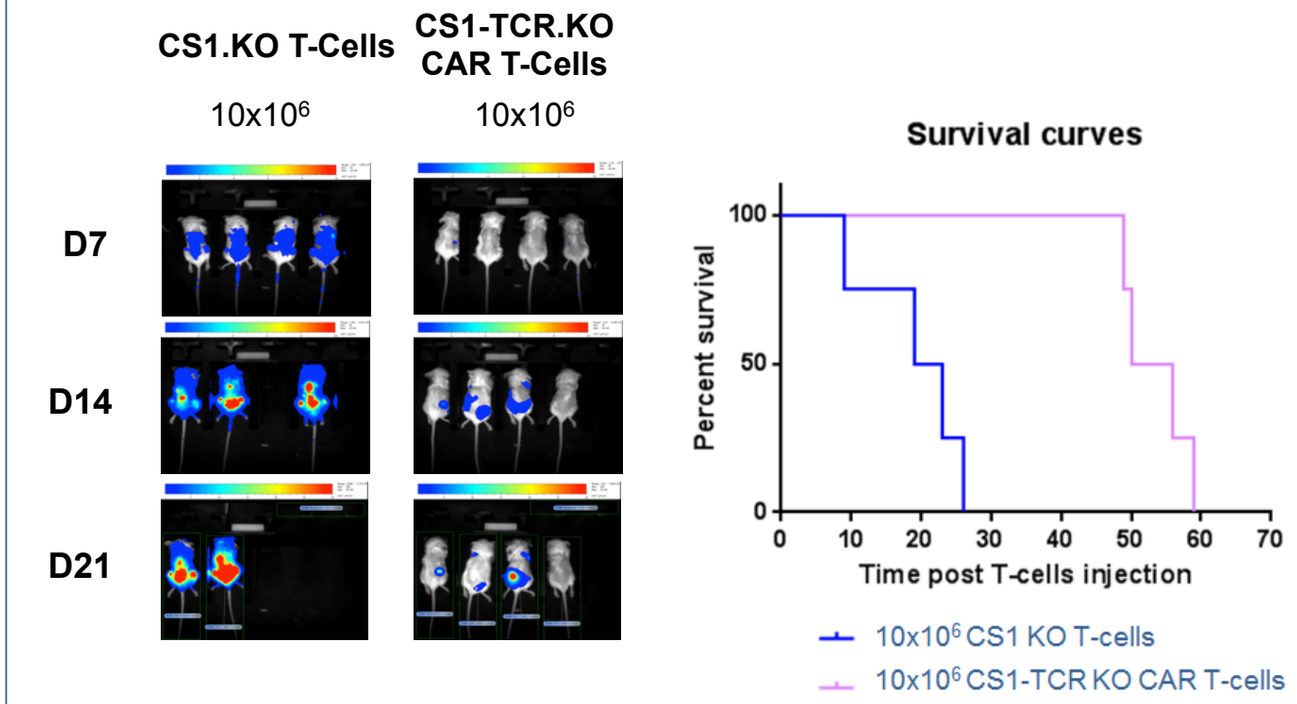
UCARTCS1

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)

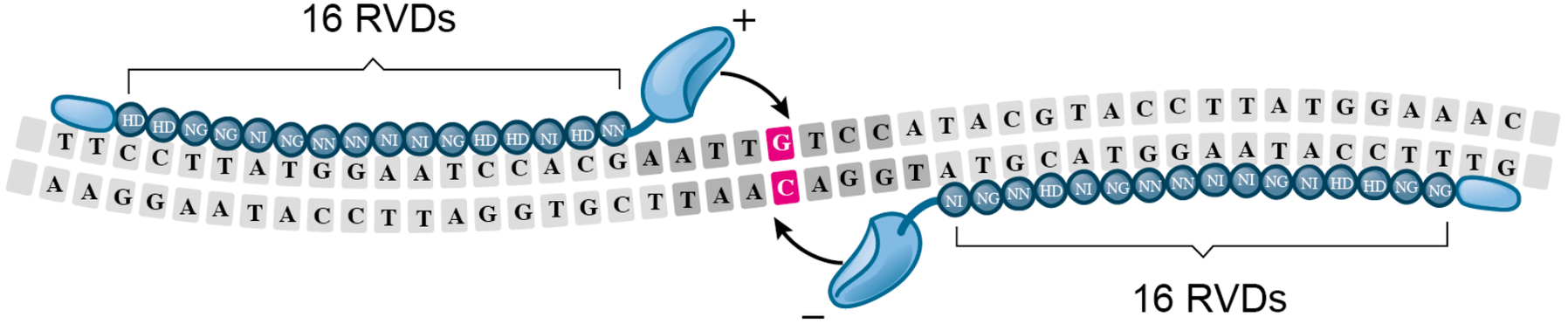
Expected in 2018 ☐

IND Filing

Expected in Q4 2018 ☐

Controlled Gene Editing

Best-in-class technologies for therapeutic development

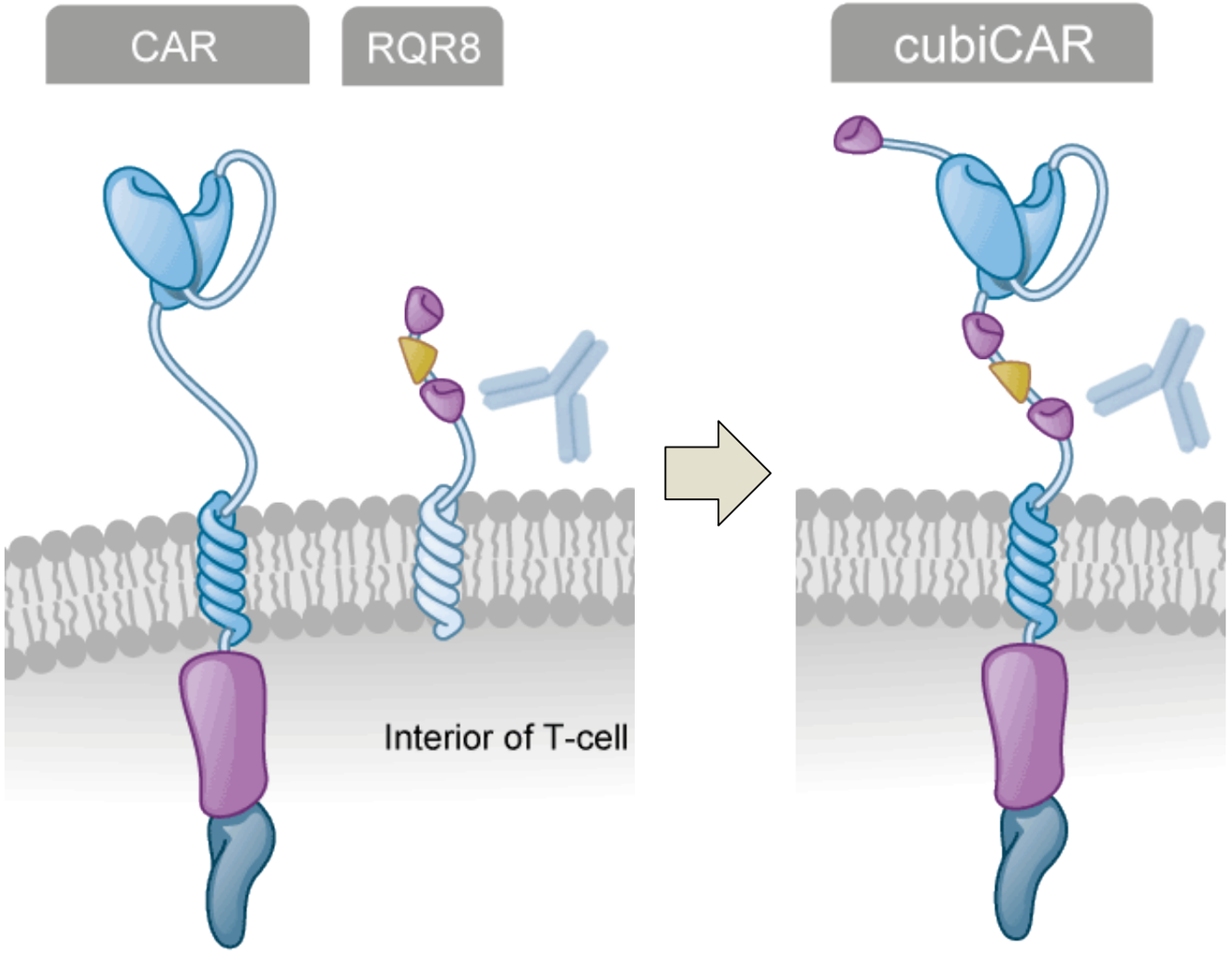


- Highly active: >80% knockout efficiency under GMP conditions
- Highly accurate: 6 base pair specific
- Low off target effect
- TALEN® discovered in 2010 but built on 17 years of experience in gene editing

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*



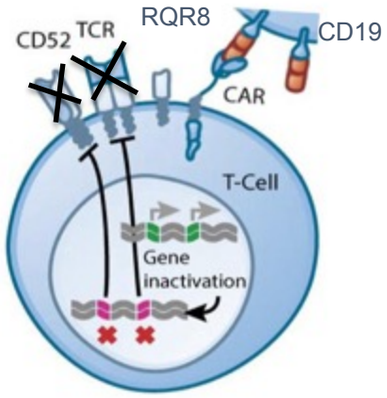
- ✓ Compact
- ✓ Specific cytotoxicity
- ✓ FDA-approved trigger molecule (Rituximab)

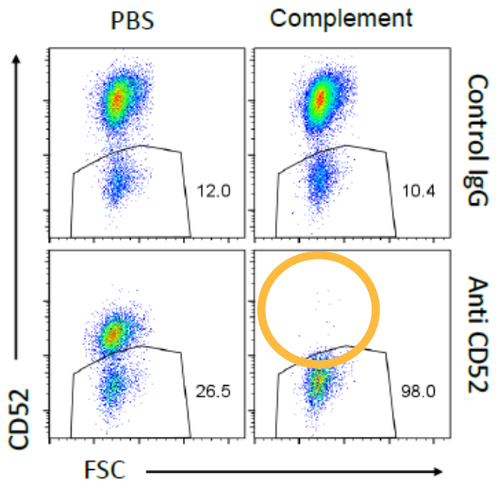
Disruptive innovation

Building more powerful T-Cells

Mab-resistance

- **CD52 KO** for Alemtuzumab resistance



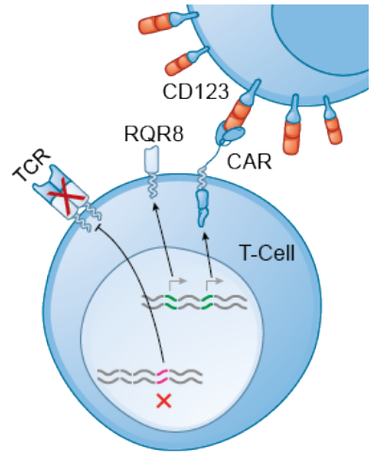


CD52-negative T-cells are resistant to Campath

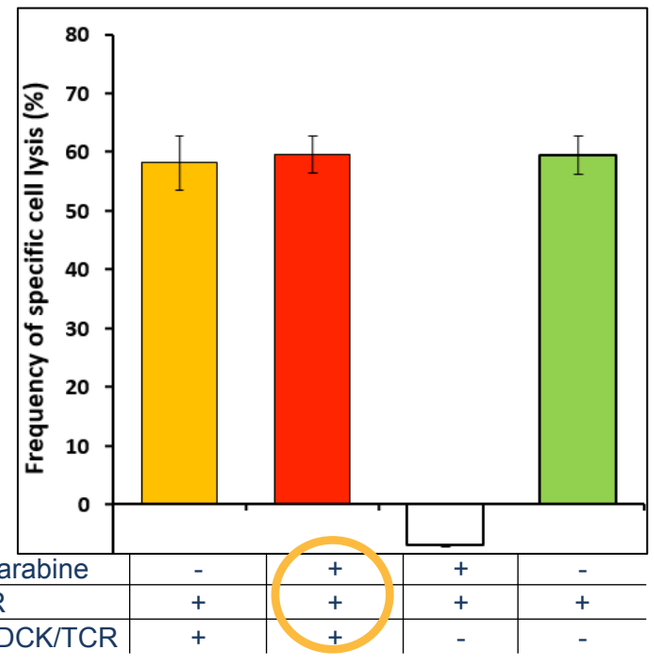
Poirot L *et al*. (2015) Cancer Res.

Chemo-resistance

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

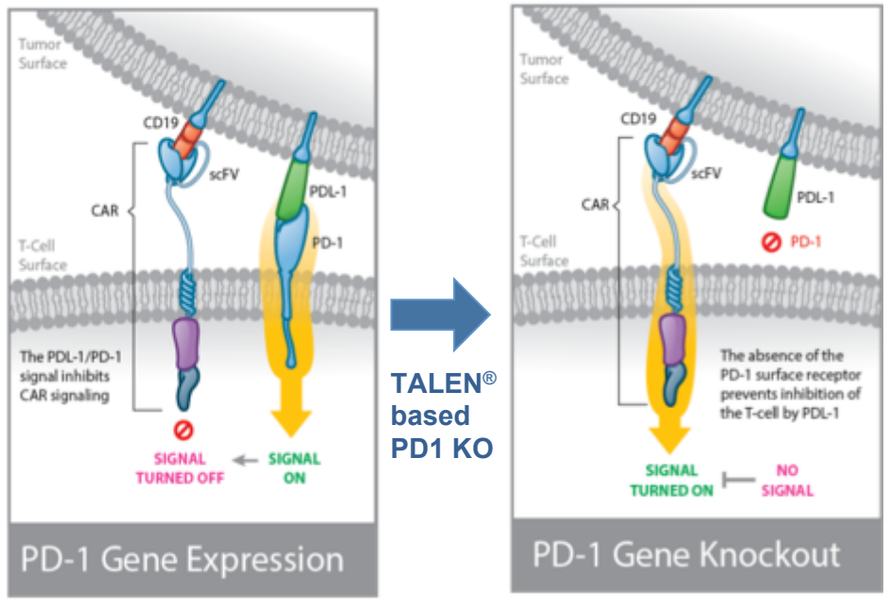


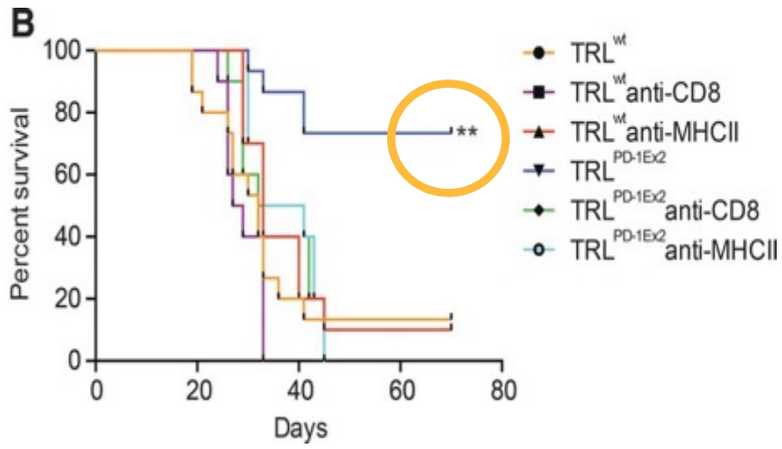
dCK-negative T-cells are resistant to Clofarabine



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

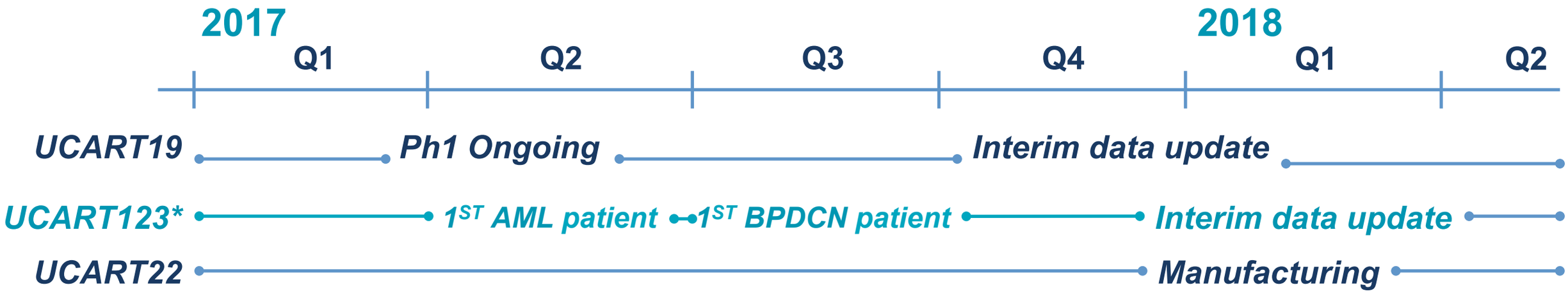
- Development of UCART123 for AML
- New York-Presbyterian Hospital was ranked in 2016 as New York's No. 1 hospital for the 16th year in a row, and No. 6 ranked hospital in all of the United States.

- 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 to be presented at ASH 2017

- **UCART123** in **AML and BPDCN patients**
  – Ph1 clinical trials on-going

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

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

THANK YOU

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