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Robert Jambou  
[jambour@od.nih.gov -- 301.435.8267].



# UCART Product Platform

David J.D. Sourdive Ph.D.

Executive Vice President Corporate Development & Manufacturing

# Collaborations

## Presentation

UCART Product Platform



UCART Pre-Clinical Development



UCART19 in ALL  
(#1610-1549)



MD Anderson  
~~Cancer~~ Network™

UCART123 in BPDCN  
(#1610-1547)



MD Anderson  
~~Cancer~~ Network™

UCART123 in AML  
(#1610-1548)



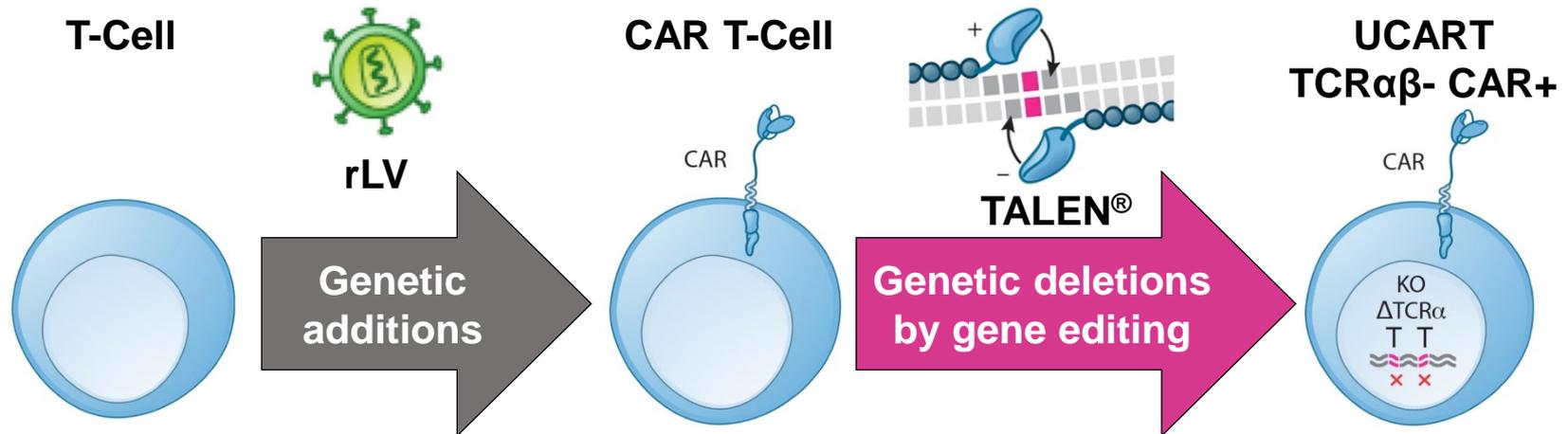
Weill Cornell  
Medicine

# Agenda

<b>Presentation</b>	<b>Presenter</b>
<b>UCART Product Platform</b>	<b>David Sourdive, PhD</b> <i>Collectis</i>
<b>UCART Pre-Clinical Development</b>	<b>Julianne Smith, PhD</b> <i>Collectis</i>
<b>UCART19 in ALL</b> <b>(#1610-1549)</b>	<b>Nitin Jain, MD</b> <i>MD Anderson Cancer Center</i>
<b>UCART123 in BPDCN</b> <b>(#1610-1547)</b>	<b>Naveen Pemmaraju, MD</b> <i>MD Anderson Cancer Center</i>
<b>UCART123 in AML</b> <b>(#1610-1548)</b>	<b>Gail Roboz, MD</b> <i>Weill Cornell</i>

# UCART Concept

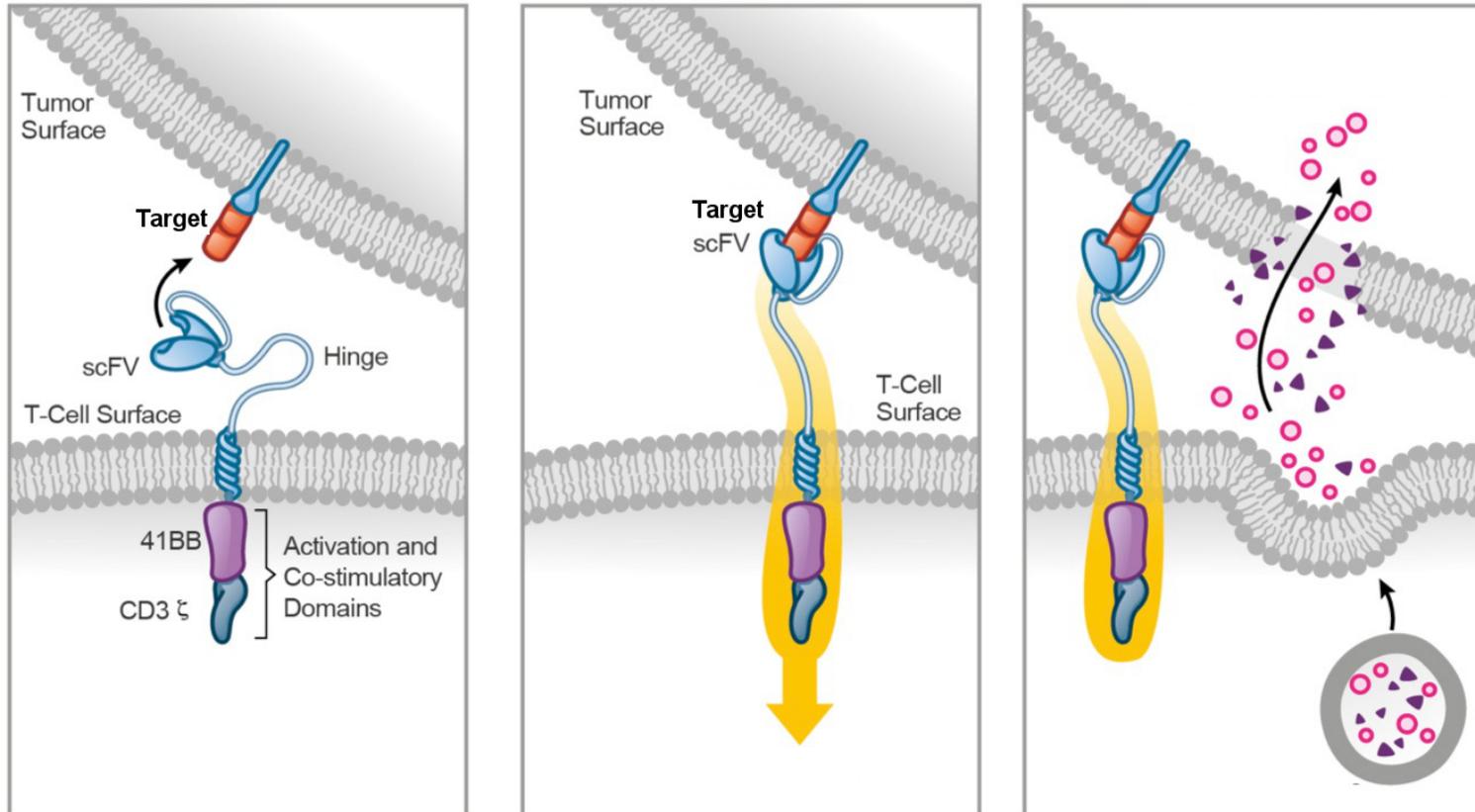
- Universal Chimeric Antigen Receptor T-cells products (UCARTs) are
  - ✓ “Off-the-shelf” allogeneic T-cells that are
  - ✓ Genetically engineered each
    1. To target a tumor-associated antigen and
    2. To carry specific additional features to make them suited for a particular clinical use



- As any “off-the-shelf” product, UCARTs are manufactured and controlled ahead of time
- UCARTs are stored as frozen vials, shipped to be readily available at the investigation sites, in defined dosage forms to be directly administered upon thawing

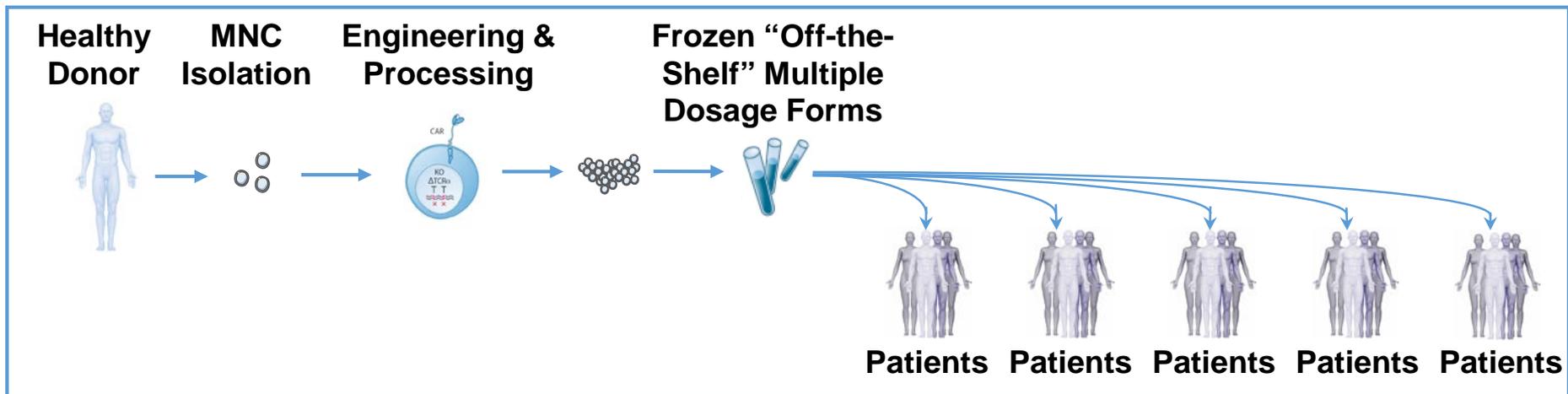
# UCART Concept

- UCARTs share some features with autologous CAR-T approaches
  - UCARTs carry chimeric antigen receptors that are ectopically expressed after vector-mediated transgenesis
  - UCARTs are an adoptive T-cell immunotherapy that relies on the capacity of T-cells to kill cancer cells that they recognize



# UCART Concept

- But they are a different concept. UCARTs are
  - Made from healthy donor T-cells, do not depend upon patient's lymphocytes
  - Not a bespoke production, manufactured ahead of time that could be deployed in a broad range of points of care and thus be made available to broad patient populations

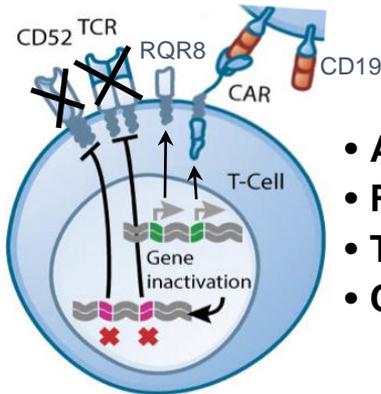


- In addition, through TALEN<sup>®</sup>-mediated gene editing, specific features are enabled such as
  - Loss of allo-reactivity to limit the risk of GvHD when using allogeneic T-cells<sup>1</sup>
  - Resistance to specific chemotherapies or antibody therapies or lymphodepleting agents<sup>2</sup>
  - resistance to checkpoint inhibition<sup>3</sup>
  - Capacity to target T-cell born targets without UCART-fratricide cell killing<sup>4</sup>

1. Poirot, L et al. 2012; 2. Valton, J. et al. 2015 ; Poirot, L et al 2012;  
3. Poirot et al. CGT conference, London 2015; 4. Galetto et al. ASH 2015

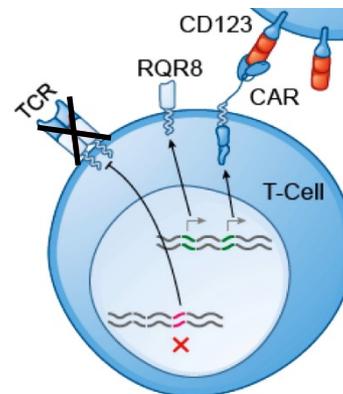
# UCART Products

## UCART19



- Anti-CD19 CAR
- RQR8+
- TCR $\alpha\beta$ - (TRAC knock-out)
- CD52- (CD52 knock-out)

## UCART123

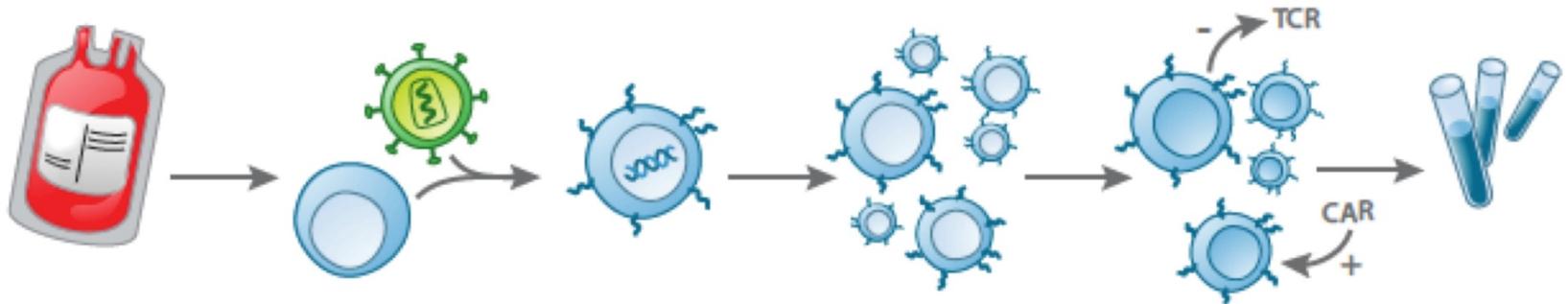


- Anti-CD123 CAR
- RQR8+
- TCR $\alpha\beta$ - (TRAC knock-out)

- Second Generation CARs
  - Murine scFv
  - Co-activation domains: 41BB and CD3 $\zeta$
- Common features
  - TCR $\alpha\beta$  elimination aims at making T-cells non-alloreactive, to limit the risk of GvHD
  - RQR8 addition provides a depletion mechanism, available in case of unmanageable safety issues
- For UCART19
  - CD52 elimination aims at making engineered T-cells resistant to anti-CD52 therapy

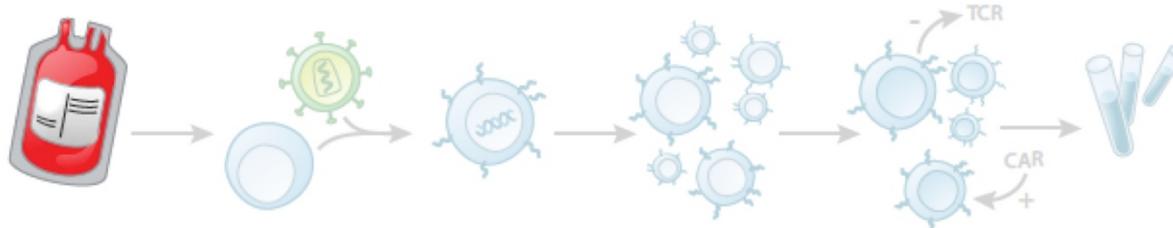
# UCART Platform

- UCARTs are designed and manufactured through a common platform that relies on defined unit operations and technologies combined into a single process



- The manufacturing runs per se take 19 days
- The main steps are
  - ✓ MNC thawing
  - ✓ T-cell activation
  - ✓ Transduction with a lentiviral vector
  - ✓ TALEN<sup>®</sup>-encoding mRNA electroporation for gene editing
  - ✓ Cell expansion
  - ✓ TCR negative T-cell purification
  - ✓ Fill & finish
- QC is applied to raw and starting material, in process controls, API and test product

# UCART Starting Material: Healthy Donor Cells



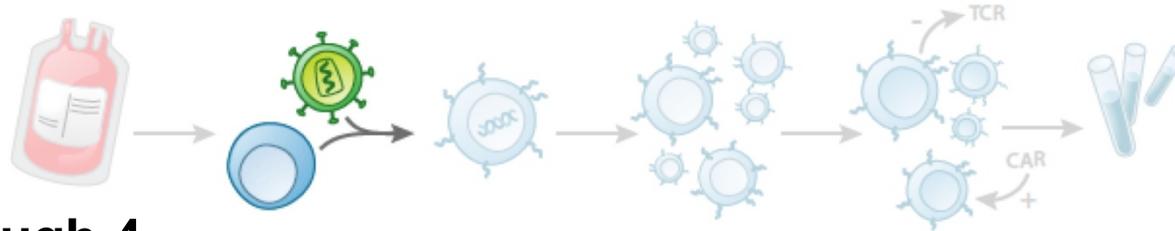
- MNCs are collected from healthy US donors in a FDA-licensed, California-State-licensed, AABB-accredited, CLIA-certified blood bank
- On-purpose lymphocytes apheresis (minimal yield:  $1.5 \times 10^9$  cells, typical yields  $>4 \times 10^9$  cells)
- Donors undergo selection, screening (<14 days prior to collection) and testing (on the day of collection)
- All testing performed as per EU/US directives or guidance on donation, procurement, testing, processing, preservation, storage and use of human cells (detailed in 21 CFR Parts 1270 and 1271 and the Guidance for industry: Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products, HCT/Ps)

✓ Age, BMI, medical history, interview, concomitant treatments, no pregnancy or breastfeeding, blood biological markers, CMP, pulse and blood pressure, CD3 CD4 CD8 levels, red blood cell antibody, HLA

✓ Absence of risk from infectious agents includes testing for evidence of, Toxoplasma, syphilis, CMV, Hepatitis A, B, C and E, HIV 1/2, HTLV-I/II, West Nile virus, Trypanosoma cruzi, Babesiosis and Kala Azar (visceral leishmaniasis), Sepsis and Malaria (if risk identified). It is also required that the donors have no known factors predisposing to infection with transmissible spongiform encephalopathies (TSE)

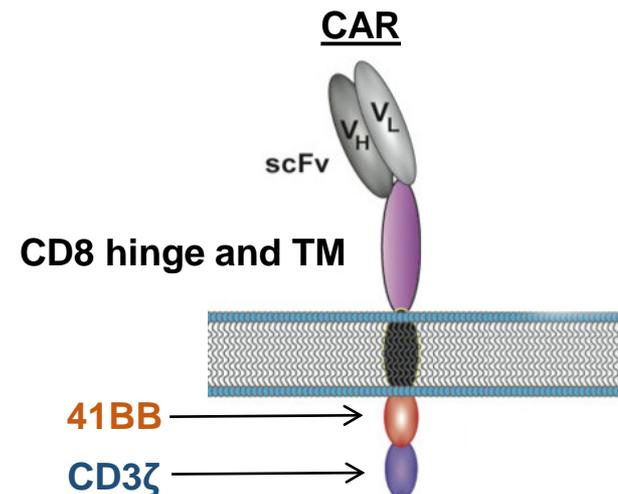
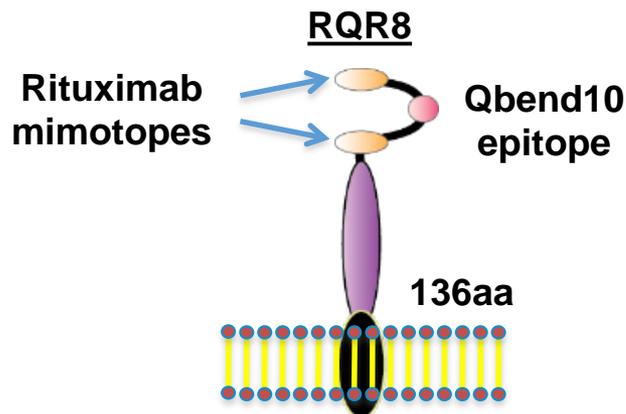
- One cGMP UCART manufacturing run starts with typically 1/5 to 1/3 of a collection

# First Engineering: Lentiviral Vector Transduction

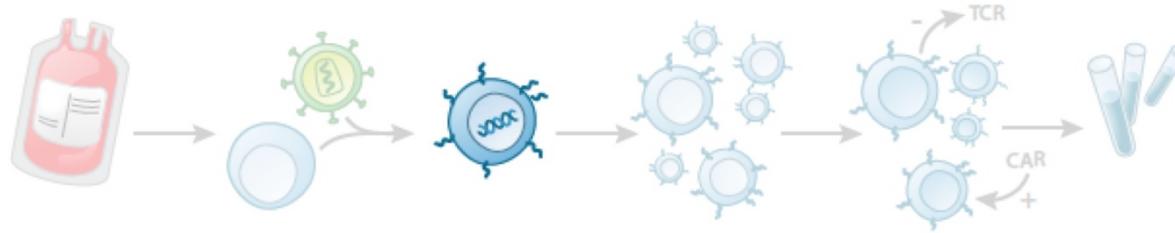


## • Day 1 through 4

- T-cell activation using antibody-coupled beads recognizing CD3/CD28
- Using a GMP-grade 3<sup>rd</sup> generation lentiviral vector, addition of one ORF coding for 2 separate proteins (T2A separated)
  - RQR8 depletion mechanism
  - A 41BB & CD3 $\zeta$  encompassing second generation CAR including a murine scFv



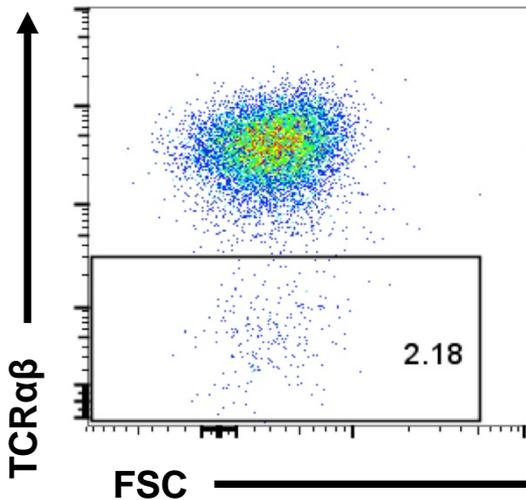
# Second Engineering: TALEN<sup>®</sup>-Mediated Gene Editing



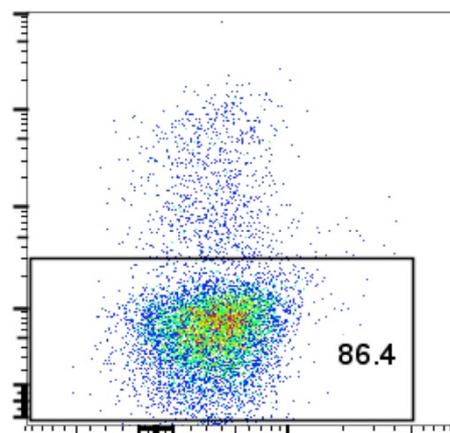
## • At Day 5

- GMP-grade TALEN<sup>®</sup>-encoding mRNAs are introduced into the cells by electroporation, leading to transient TALEN<sup>®</sup> expression
- The TALEN<sup>®</sup> used are designed to recognize and cleave DNA at precise residues in the TRAC (and CD52) gene(s) (Poirot et al 2012). TRAC (and CD52) gene knock-out result from non-homologous end-joining DNA repair of TALEN<sup>®</sup>-mediated targeted DNA double stranded break

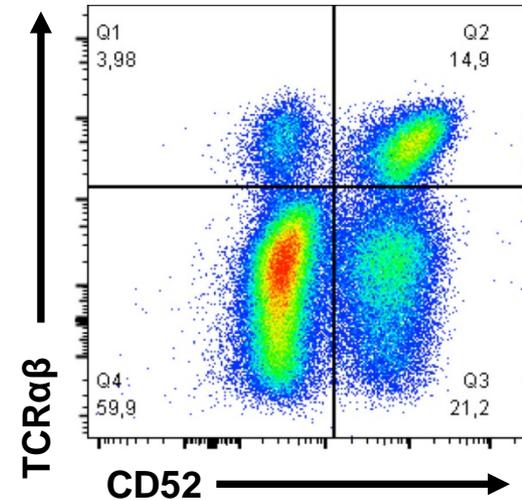
**No mRNA**



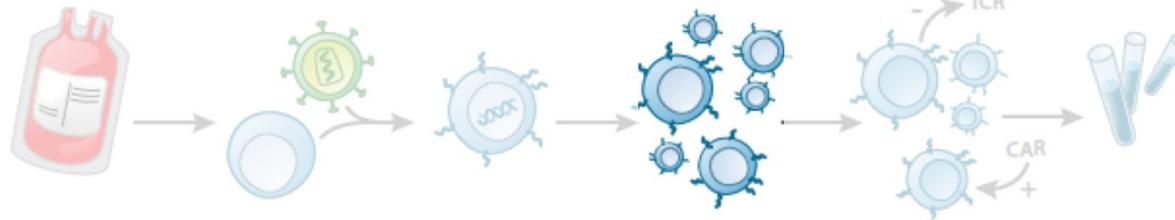
**TRAC TALEN<sup>®</sup> mRNA**



**TRAC & CD52 TALEN<sup>®</sup> mRNA**

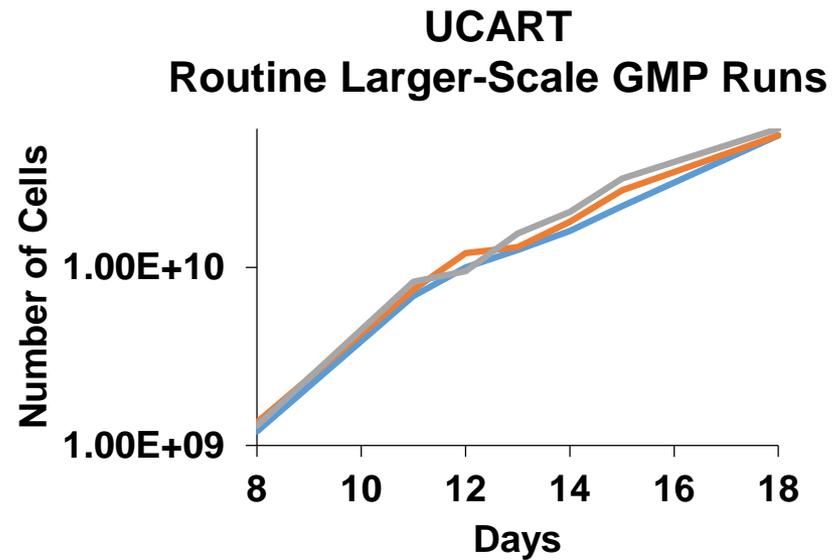
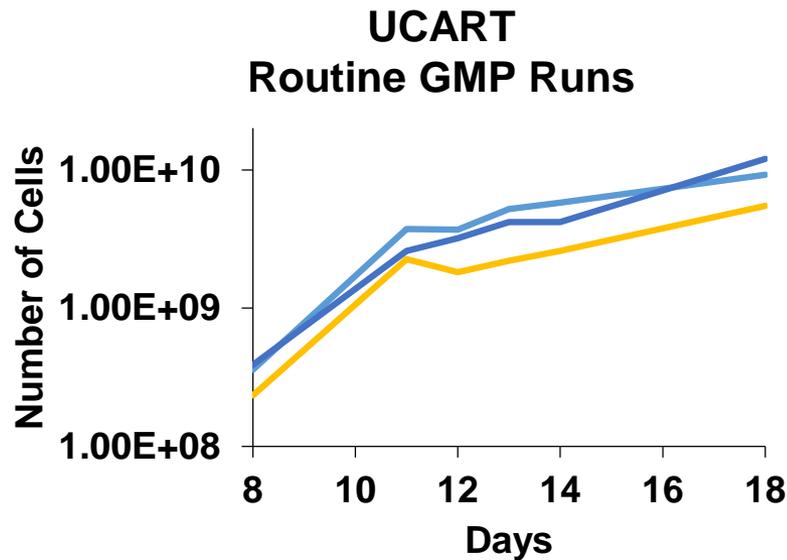


# Amplification

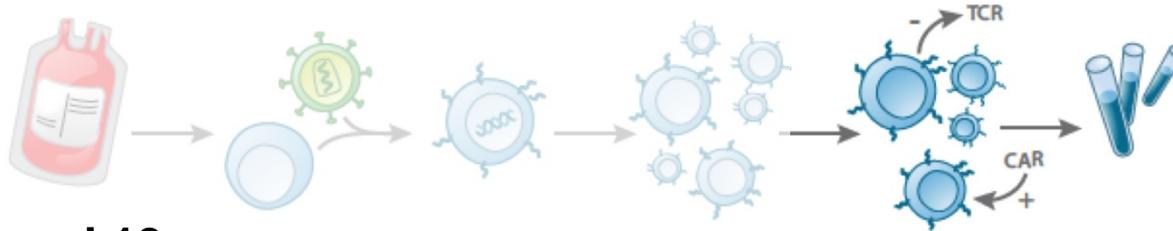


- **Over Days 6 through 17**

- Engineered cell expansion in controlled culture systems
- Potential multiple parallel wave bags

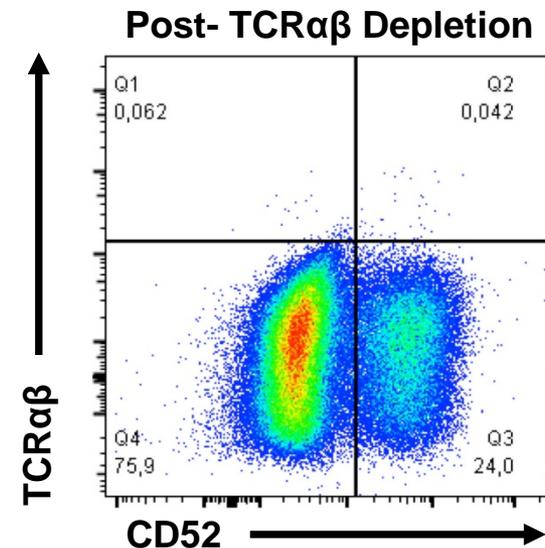
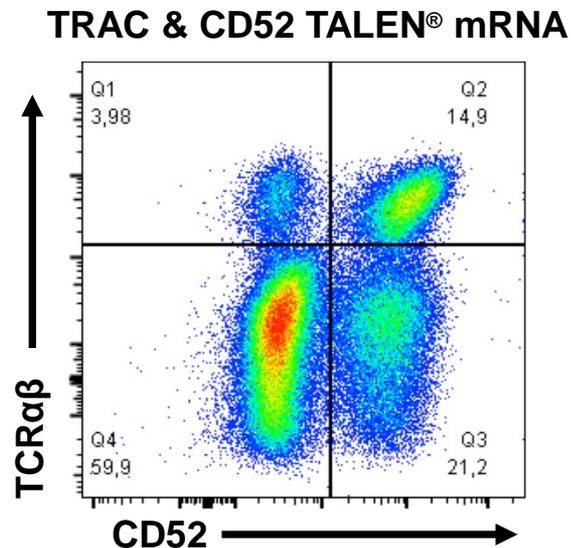


# Purification Fill & Finish



- **On Days 18 and 19**

- Purification of TCR $\alpha\beta$  negative cells by magnetic antibody-coupled bead separation (level is a release criterion)
- Fill & finish and controlled rate freezing
- Two or three dosage forms used for each product to cover the needs for dose escalation and potential de-escalation



# UCART QC Concept

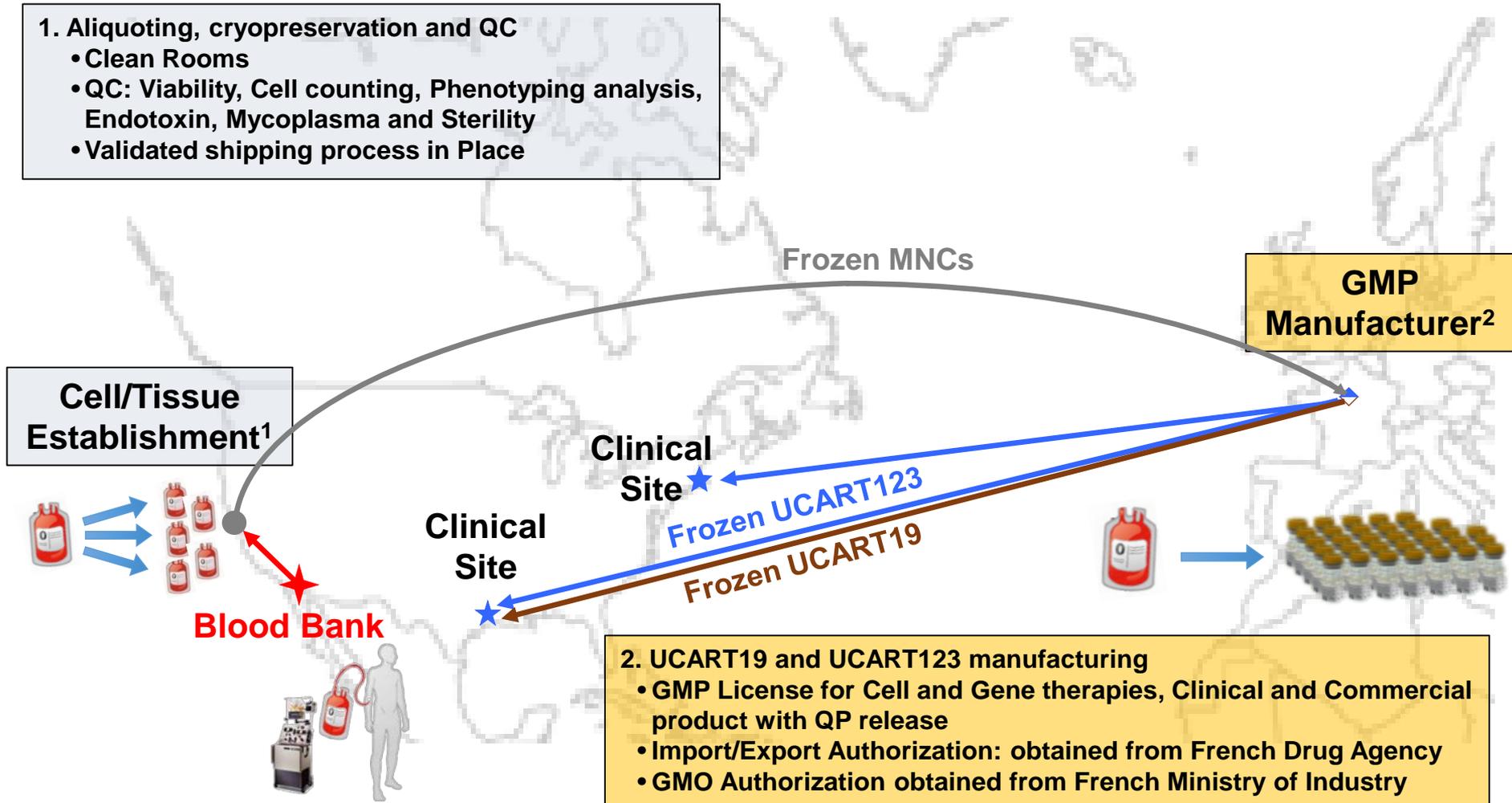
- Raw and starting material QC, closure integrity test
- In Process Controls on Cell counts, viability, Cells and Cells subpopulations characterization (flow cytometry)
- Final testing performed on API (Fresh) and Final Product (Post thawing DP)

<b>Identity, including</b>	• <b>Genetic signature (STR)</b>
<b>Purity, including</b>	• <b>≥97% TCRαβ negative cells</b>
<b>Safety, including</b>	<ul style="list-style-type: none"> <li>• <b>Sterility (USP [71], EuP 2.6.1 and JP XV 4.06), endotoxin, mycoplasma</b></li> <li>• <b>Replication Competent lentivirus (RCL)</b></li> <li>• <b>Viral testing</b></li> <li>• <b>Genetic stability (IL-2 independent proliferation, VCN, karyotype, off-target effect analysis)</b></li> </ul>
<b>Potency, including</b>	• <b>Functional response to target (cytokine, cell killing)</b>

# UCART Logistics

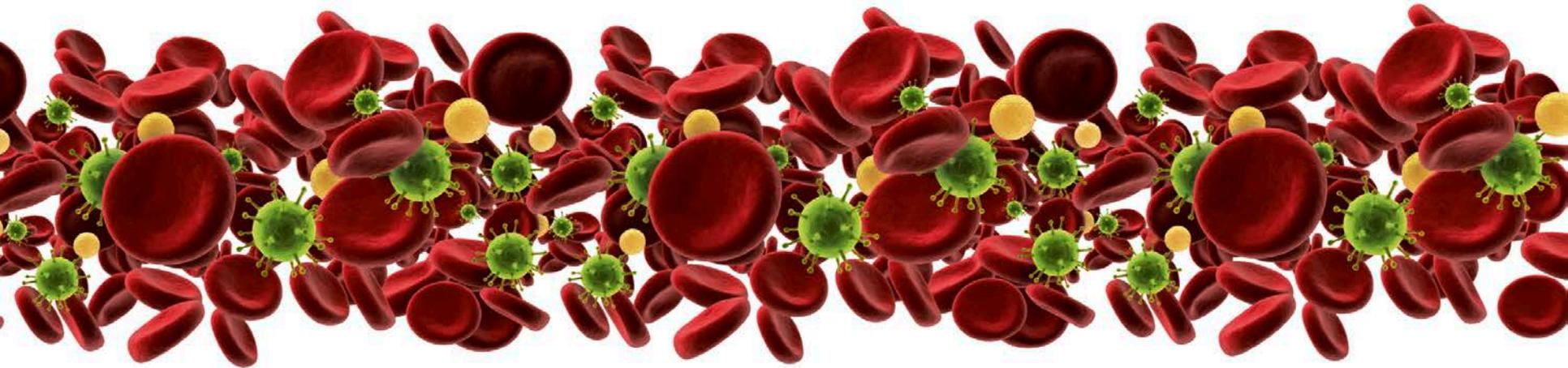
## 1. Aliquoting, cryopreservation and QC

- Clean Rooms
- QC: Viability, Cell counting, Phenotyping analysis, Endotoxin, Mycoplasma and Sterility
- Validated shipping process in Place



## 2. UCART19 and UCART123 manufacturing

- GMP License for Cell and Gene therapies, Clinical and Commercial product with QP release
- Import/Export Authorization: obtained from French Drug Agency
- GMO Authorization obtained from French Ministry of Industry



**THANK YOU**





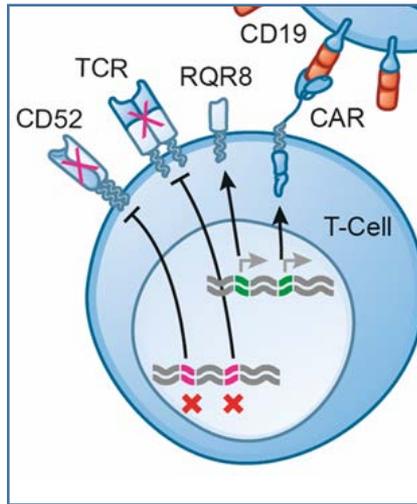
# **UCART Pre-Clinical Development**

Julianne Smith Ph.D.

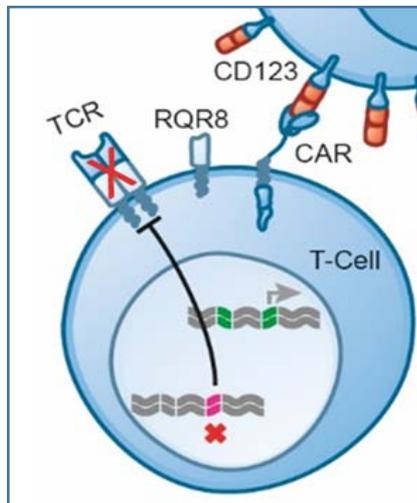
Vice President CAR-T Development

# UCART Non-Clinical Development

## UCART19



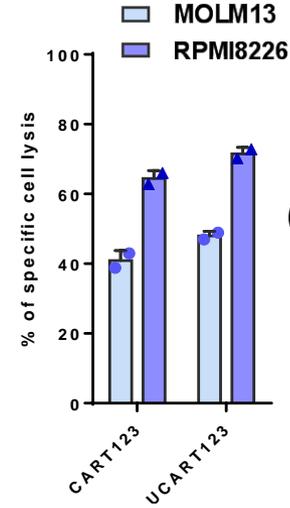
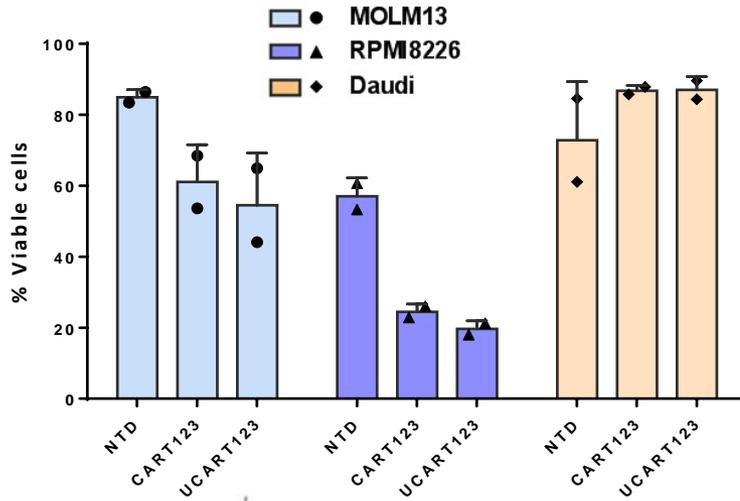
## UCART123



- CAR activity
  - Cytotoxicity, proliferation and cytokine *in vitro* assays
  - Anti-tumor studies in *in vivo* mouse model(s)
- CAR specificity
  - Potential off-target binding: Tissue cross reactivity
  - On-target / Off-tumor: UCART123
- RQR8 depletion mechanism
  - Rituxan-mediated depletion *in vitro* and *in vivo*
- TALEN<sup>®</sup>-mediated gene inactivation
  - Molecular characterization
  - Functional in *in vitro/in vivo* characterization
  - GvHD potential *in vivo*
- Genomic stability

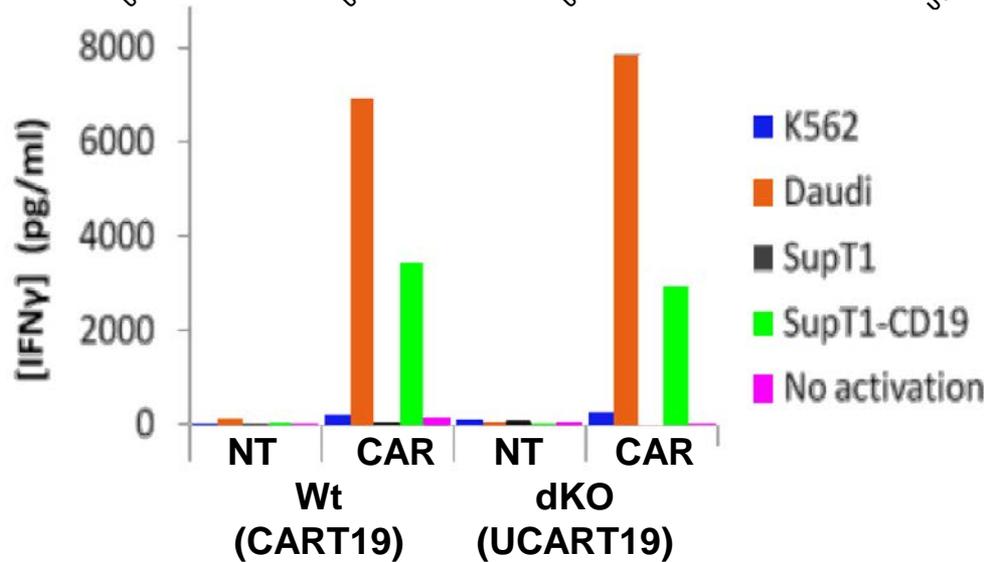
# UCART: Potent Antigen Driven In Vitro Activity

**CART123  
UCART123 (KO)**



**Cytotoxicity\***

**CART19  
UCART19 (dKO)**



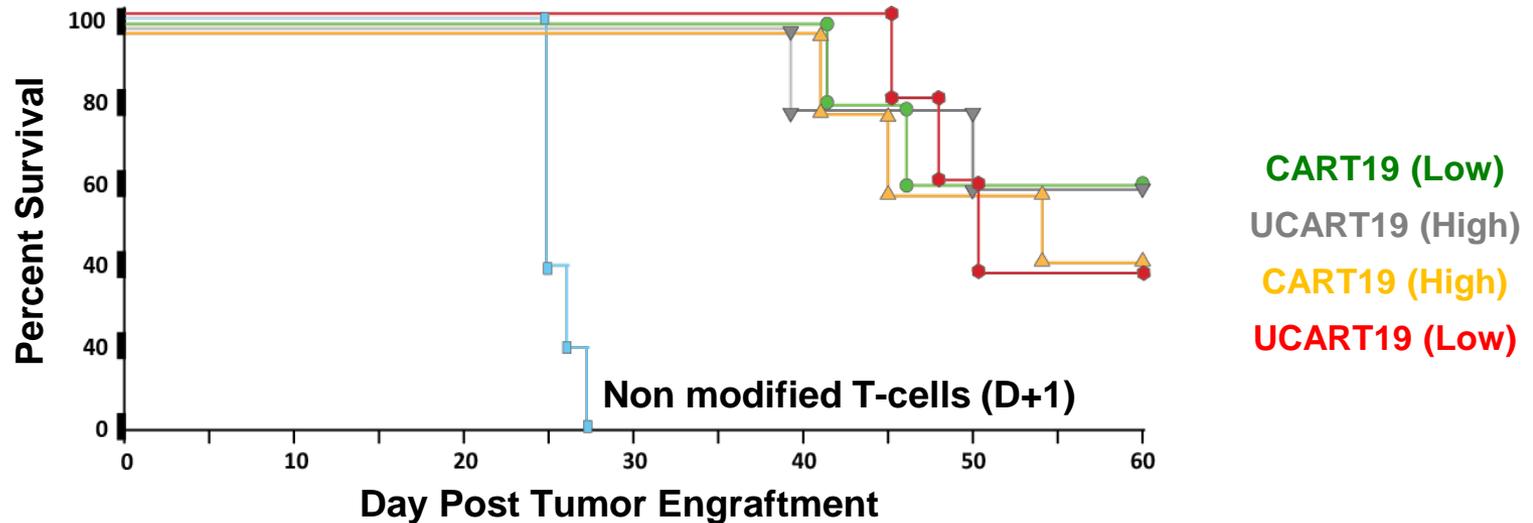
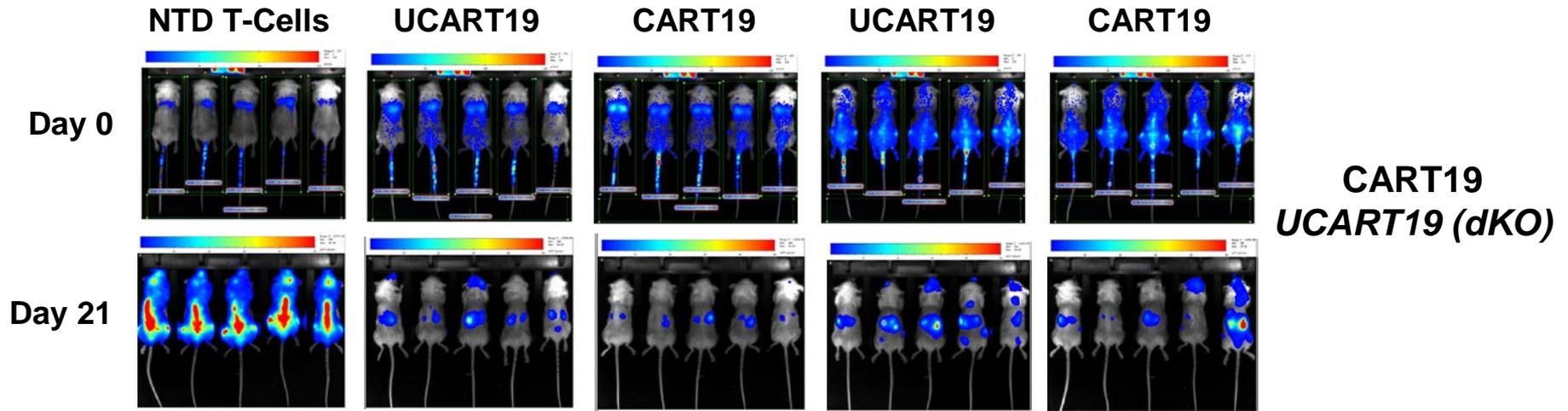
**IFN $\gamma$  Release\***

\*QC assay for GMP UCART19 and UCART123

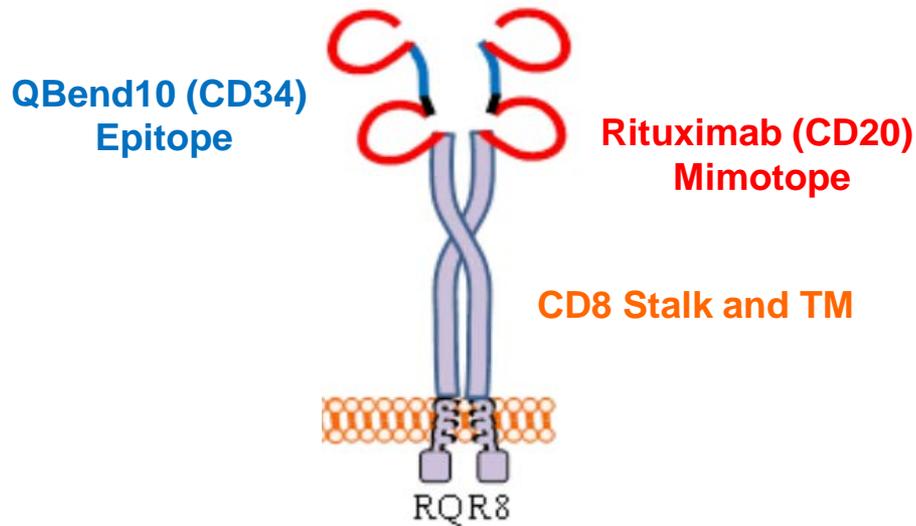
# UCART: Efficient In Vivo Anti-Tumor Activity

Low Tumor Burden (Daudi)

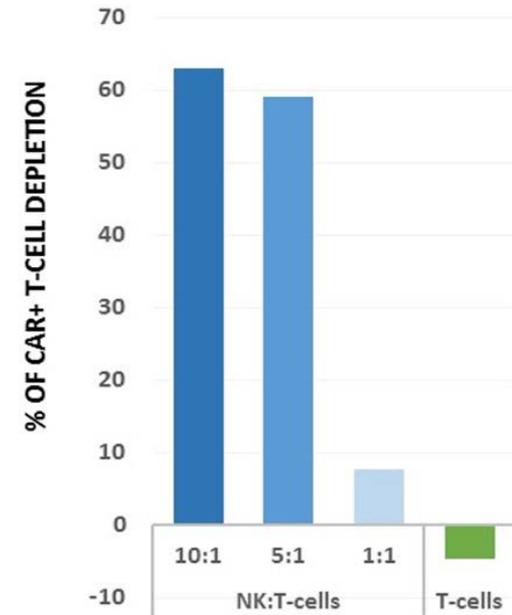
High Tumor Burden (Daudi)



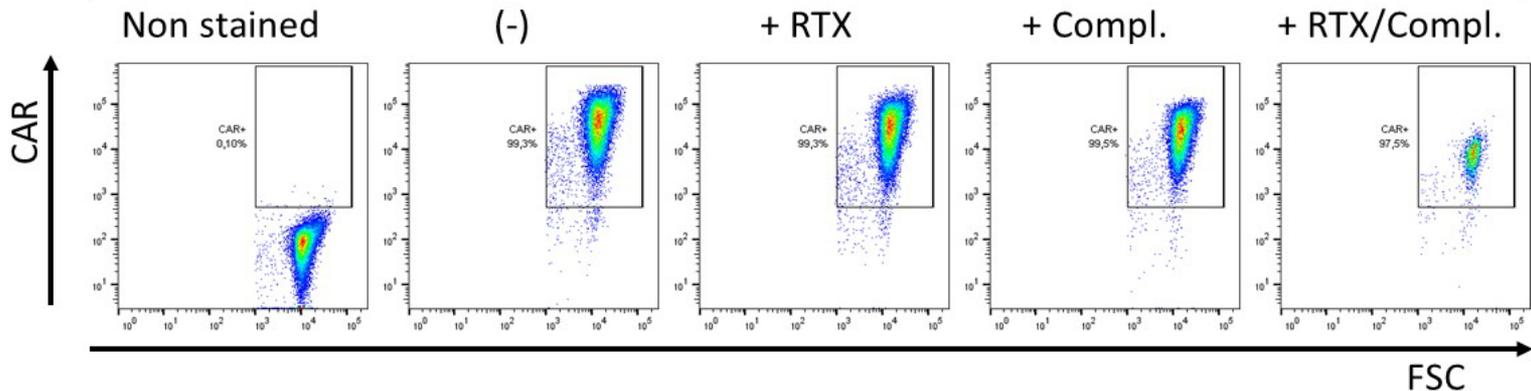
# Efficient Depletion of RQR8+ Cells by CDC and ADCC



## ADCC Assay

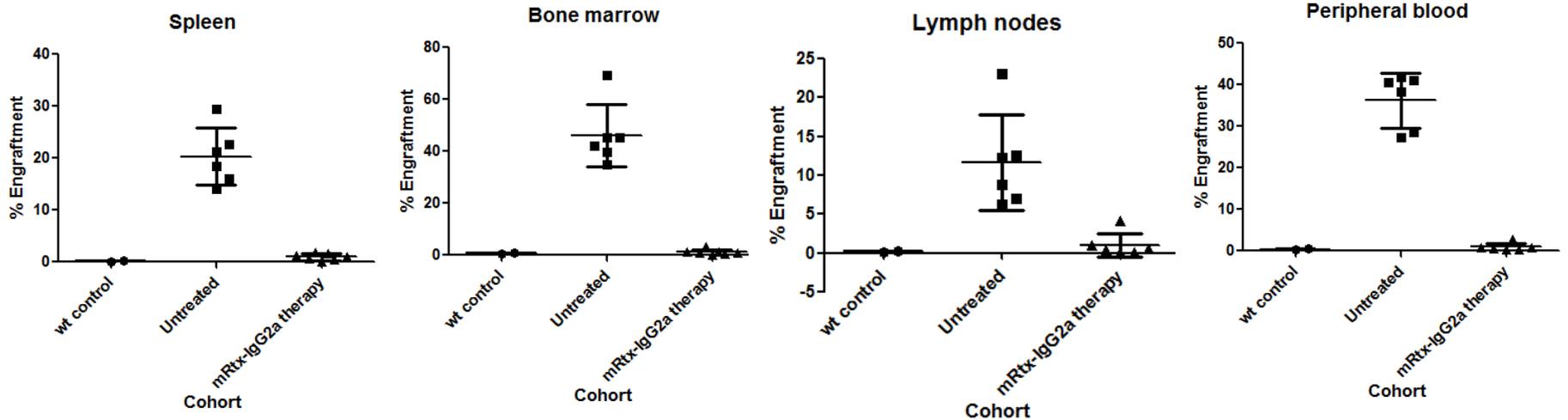
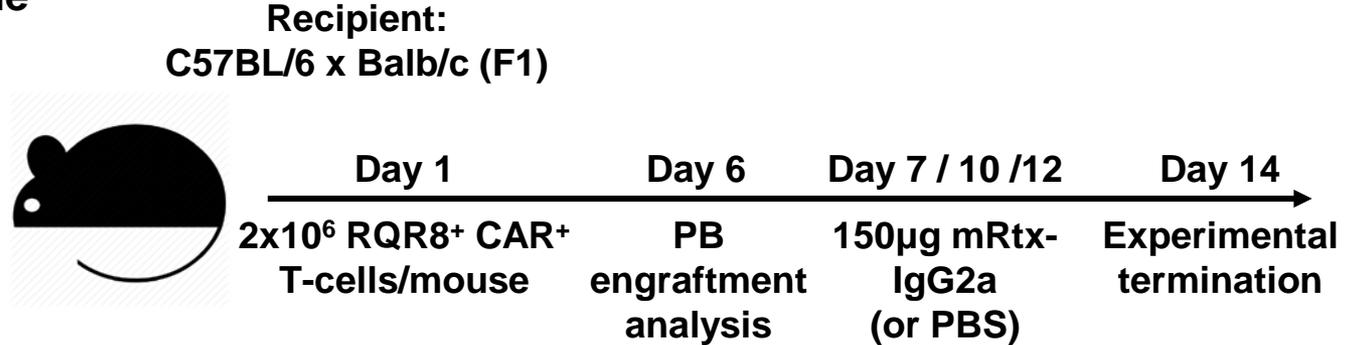
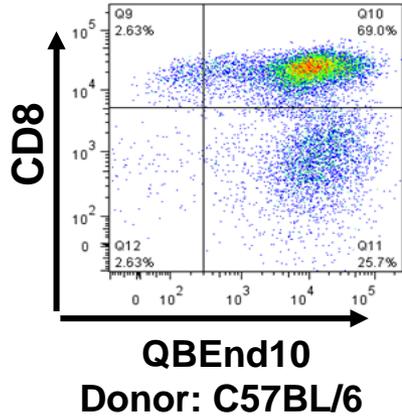


## CDC Assay

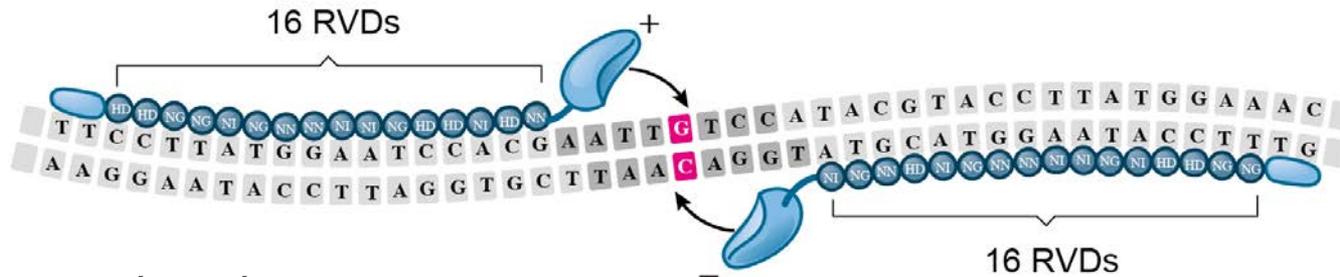


# Efficient Depletion of RQR8+ Cells In Vivo

## Infusion Sample Profile



# TALEN<sup>®</sup>: Gene Editing Tool



- Contains two domains
  - «Engineered» TAL effector DNA binding domain
  - Nuclease domain of *FokI* restriction enzyme
- Cleaves as a dimer – cleavage occurs within the 15 bp spacer sequence
- Each half TALEN<sup>®</sup> recognizes 17 bp

# TALEN<sup>®</sup>: Gene Editing Process

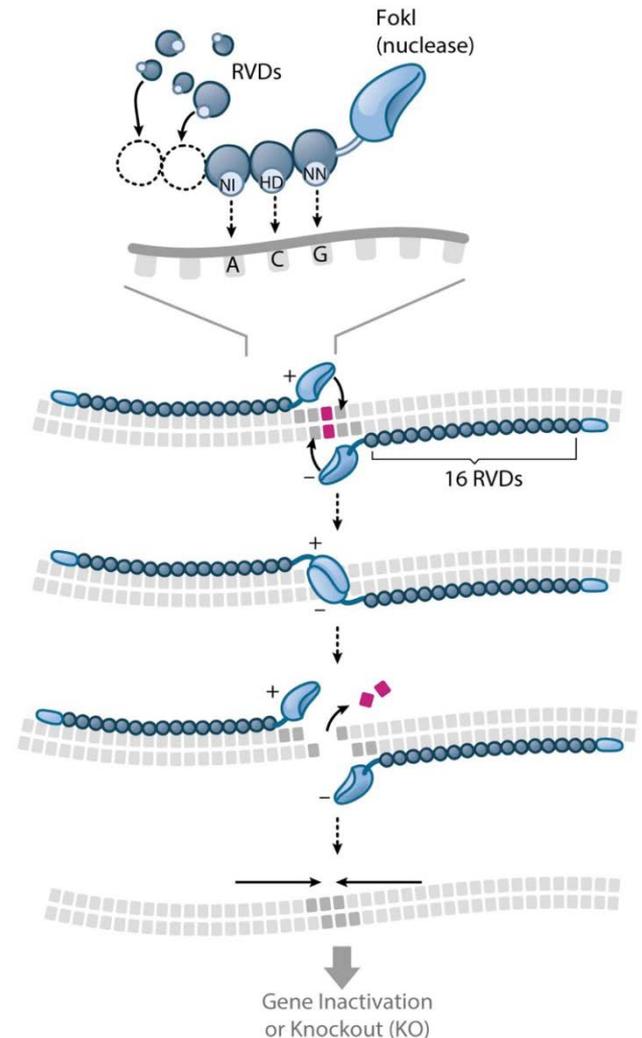
**TALEN<sup>®</sup> binds to its target sequence as a heterodimer, separated by a spacer region**

**Following binding, FokI nuclease heads clip the DNA at the target sequence**

**Cleavage generates DNA double-strand breaks that can be repaired by NHEJ**

**Addition or deletion of nucleotides can occur at the cleavage site**

**DNA ends are rejoined, resulting in a mutation that inactivates the target gene**



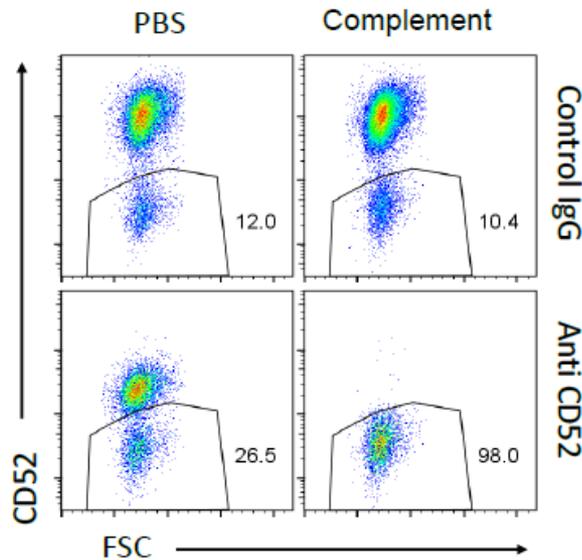
# Molecular and Functional Characterization of TALEN<sup>®</sup>-Mediated *CD52* / *TRAC* Gene Inactivation

## CD52 Gene Editing

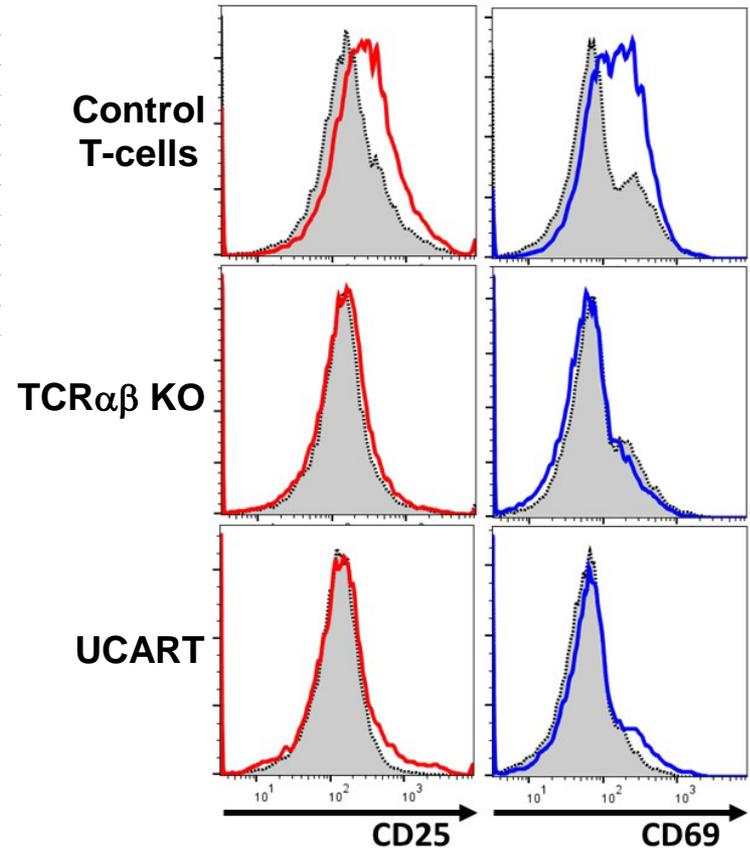
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```

## Molecular Characterization by NGS

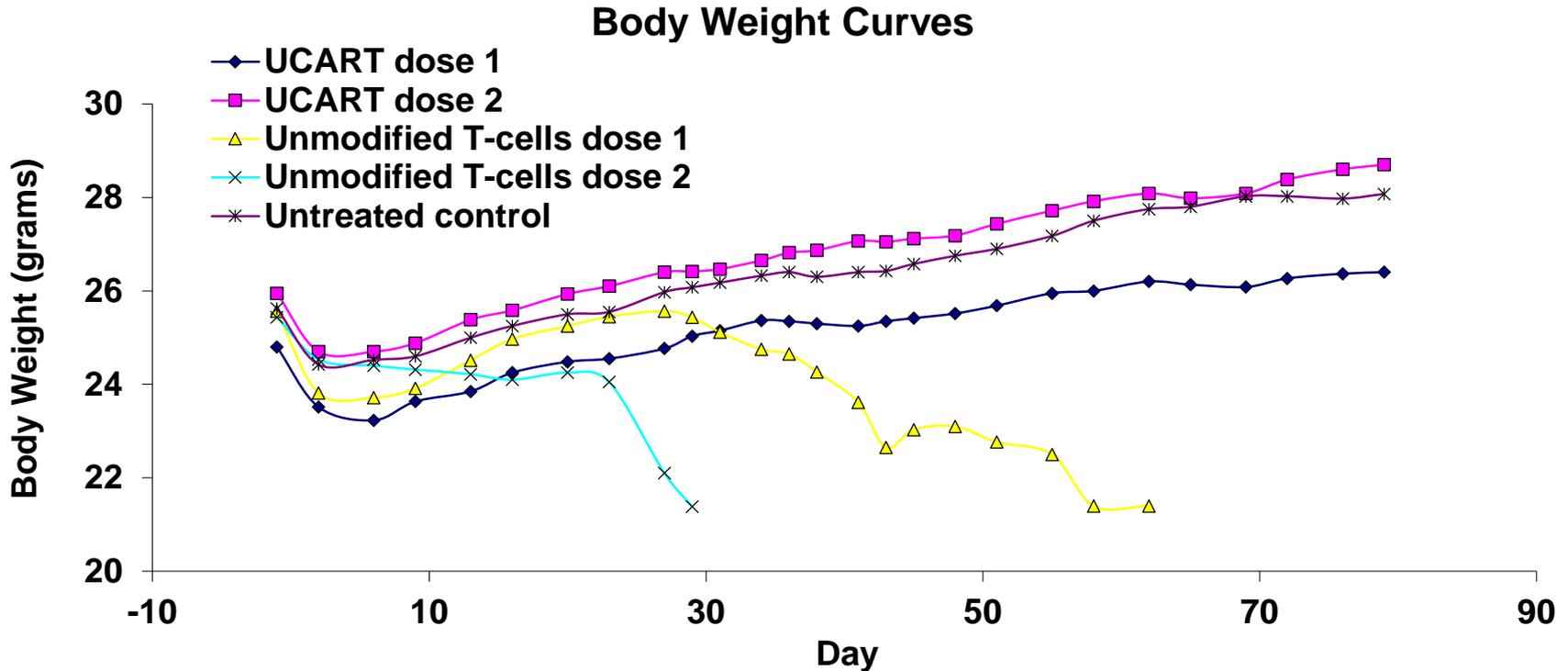


**CD52 negative cells are resistant to antibody mediated depletion**



Absence of activation markers on purified TCR negative cells following stimulation with PHA

# UCART Do Not Induce Xenogeneic-GvHD in an In Vivo Mouse Model



- Signs of GvHD development occur in all mice injected with unmodified T-cells (body weight loss, clinical and histopathological signs of GvHD)
- No GvHD related changes were seen in any UCART animal
- Similar results observed for UCART123 and UCART19

# UCART: Risk Analysis Related to Gene Editing

- **TALEN<sup>®</sup> mediated gene editing**

- Off-target cleavage and/or translocations leading to clonal expansion and eventual cellular transformation

- **Risk mitigation steps**

- Allogenic nature of UCART cells

- TALEN<sup>®</sup> targeting *TRAC* and *CD52* genes designed to minimize off-target cleavage (differ from other sites in the human genome by 3 or more nucleotides at either half site)

- Limited TALEN<sup>®</sup> expression within the cells (TALEN<sup>®</sup> introduced as mRNA)

- Presence of RQR8 depletion mechanism for UCART elimination

- Extensive monitoring of genomic integrity

# Monitoring Genomic Integrity of UCART

- **Off-target**

- NGS analysis of most likely *in silico* predicted off-target sites\*
- Genome wide unbiased analysis (Whole genome sequencing or GUIDE Seq)

- **Chromosome analysis**

- qPCR analysis for translocations
- Karyotype / FISH\*

- **Aberrant T-cell proliferation (IL2 independent proliferation assay\*)**

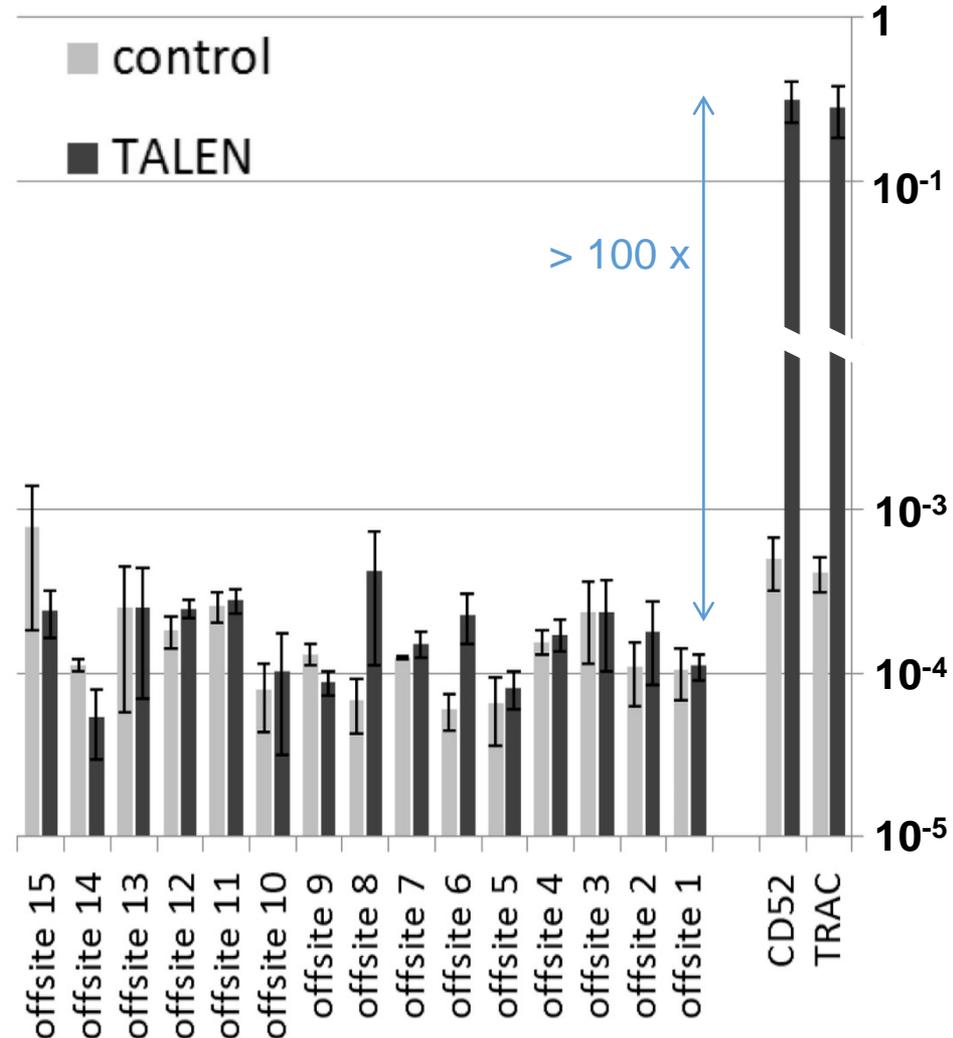
# Genomic Integrity of TALEN<sup>®</sup> Modified T-Cells

Potential offsite targets: close match sequences at hybrid sequences from mispairing of half nucleases

	LEFT HALF TARGET	SPACER	RIGHT HALF TARGET
TRAC	TTGTCCCACAGATATCC	agaaccctgaccctg-----	CCGTGTACCAGCTGAGA
CD52	TTCTCTACTCACCAT	cagcctcctggttat-----	GGTACAGGTAAGAGCAA
1	ttgtctc <b>CaccAgtaTA</b>	cgtattataccaaagtcaattctcg---	<b>TTtT</b> caggtaagTgcaa
2	t <b>CA</b> ctcttacctg <b>Gacc</b>	caacctttctgggagcactg-----	<b>CC</b> tacaggtaag <b>GgcCa</b>
3	tctcag <b>AtgAt</b> acac <b>CC</b>	acctcagcctcccaaagtgggg---	<b>Agt</b> acagg <b>CaT</b> gagc <b>Ca</b>
4	t <b>GAT</b> cccacaga <b>AatAc</b>	ttctgtggaatacagaa-----	<b>gCatTt</b> ctgtggga <b>TCa</b>
5	tt <b>CctctA</b> acctgta <b>TT</b>	ttgtcggctctctaaagtgtctca---	<b>gAtC</b> caggtaag <b>GT</b> caa
6	t <b>Agt</b> ccc <b>Cc</b> agatat <b>GA</b>	gtggccccaactttgaagg-----	<b>aA</b> gg <b>tTgGaT</b> gaggaa
7	ttgtc <b>AcacaTataCcG</b>	atggcaaagccaattttaaaa-----	<b>TgG</b> tat <b>Tt</b> gt <b>Tg</b> acaa
8	t <b>AA</b> ctcttacctgta <b>GT</b>	gtccactttaaacat-----	<b>AgatTt</b> ct <b>Ct</b> ggg <b>C</b> caa
9	tt <b>Act</b> cc <b>AactAacTat</b>	ccatgactgtccatt-----	ccgt <b>Tt</b> acc <b>G</b> gct <b>Taga</b>
10	t <b>Gg</b> ctc <b>At</b> acctgta <b>GT</b>	cacagctactcaag-----	<b>aGgA</b> tgag <b>GT</b> ggaggaa
11	ttgtctc <b>AtacAtgtGcA</b>	cctatgacttatgaataatc-----	atg <b>Ct</b> g <b>Tgt</b> agg <b>TggTa</b>
12	ttgtcccacaga <b>CatTc</b>	cctgggacaagctgggag-----	cc <b>AC</b> gta <b>Gc</b> agctg <b>Gga</b>
13	tc <b>AcaC</b> ctggtaca <b>TA</b> g	aaccocagccaaagacagagcacactca---	<b>GtgTtT</b> agtagg <b>Gggaa</b>
14	ttgtcccacag <b>CtaCcc</b>	atgtcagttatctccaactaacatttccaa---	<b>gAatCtTt</b> gt <b>A</b> ggacaa
15	tctca <b>ActgAA</b> aca <b>Agg</b>	caaatcccttccacctatgagcc-----	<b>TgtaA</b> ag <b>TC</b> aagagcaa

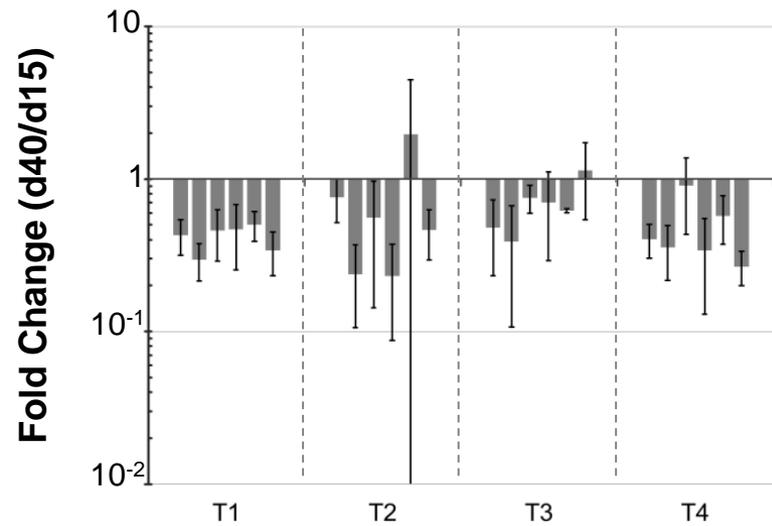
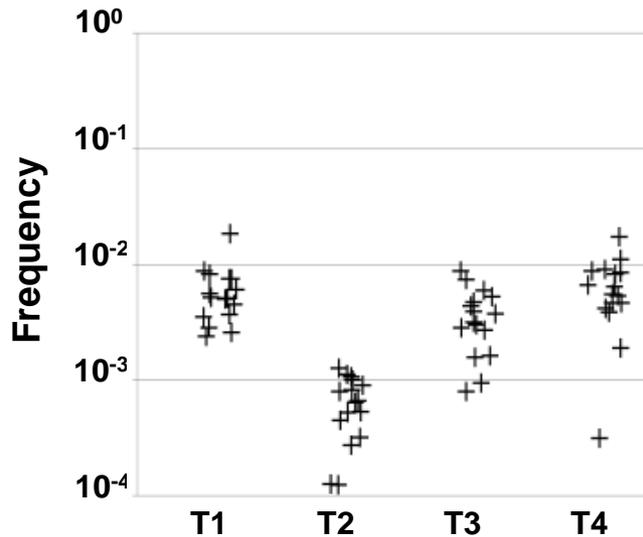
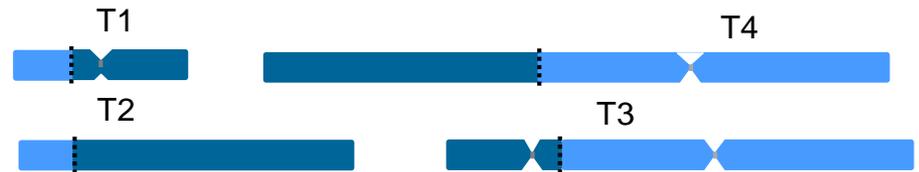
## TRAC/CD52 Off-Target

Poirot et al. (2015) Cancer Res. 75:3853



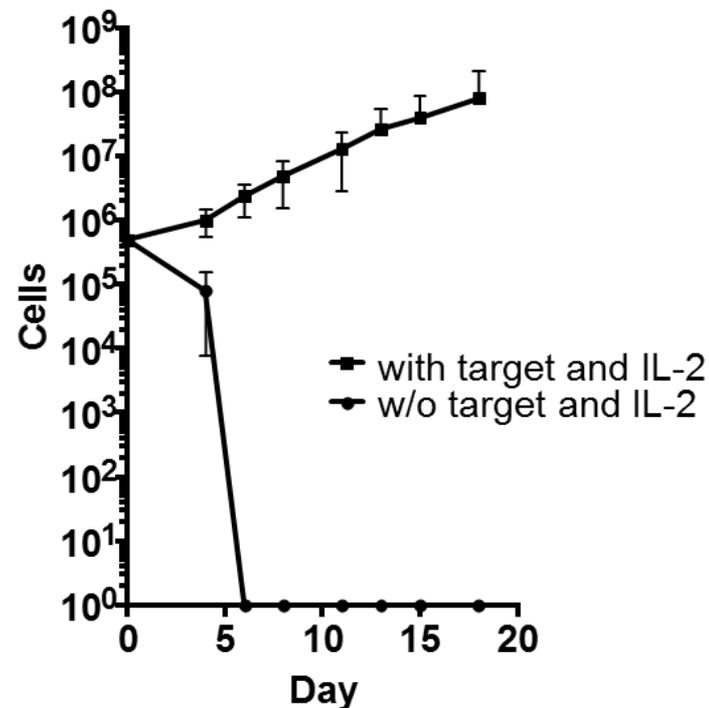
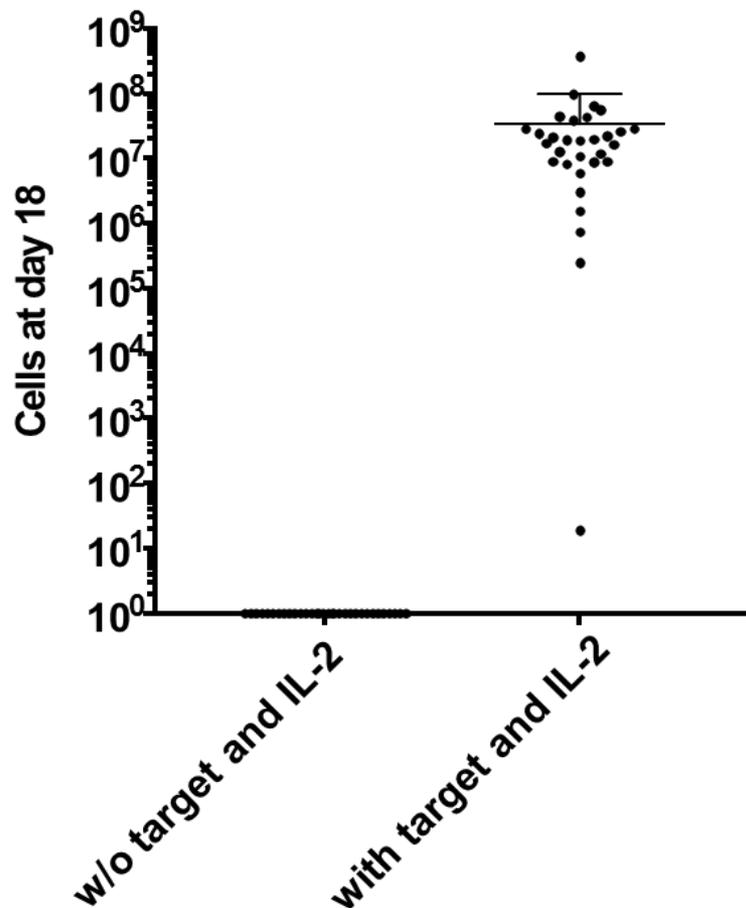
# Genomic Integrity of TALEN<sup>®</sup> Modified T-Cells

Detection of translocations by qPCR (*TRAC/CD52*)

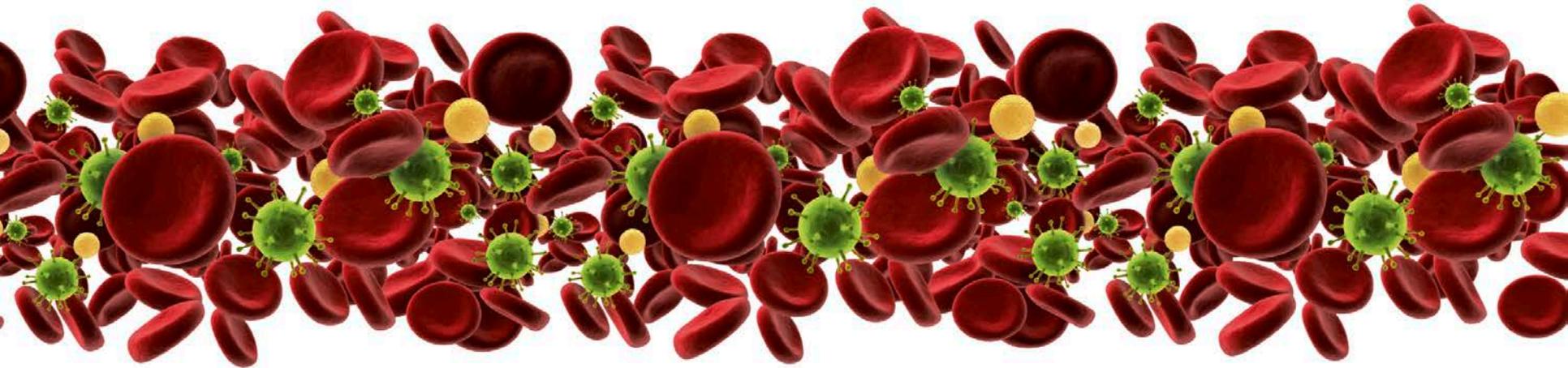


Translocations detectable at  $10^{-2}$ - $10^{-4}$  but no proliferative advantage

# Absence of IL-2 Independent Proliferation



- Analysis of over 30 UCART123 batches consistently shows no proliferation in absence of IL2
- Similar results observed for UCART19



**THANK YOU**



# UCART19 Clinical Program

**NIH #1610-1549**

**NCT #02746952**

***Presented by Nitin Jain, MD, MDACC Houston, USA***  
**RAC Meeting: December 14, 2016**



THE UNIVERSITY OF TEXAS  
**MD Anderson**  
~~Cancer Center~~

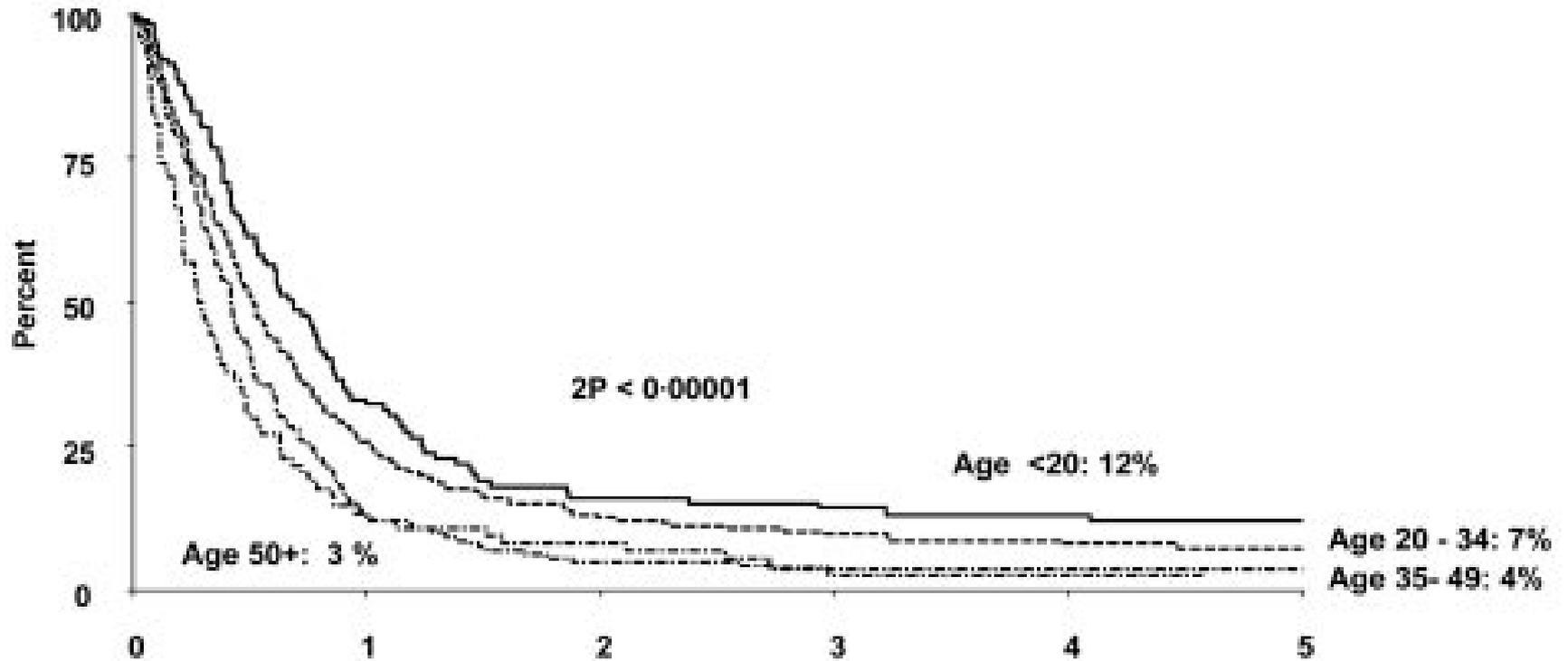
# UCART19 Clinical Program

A phase 1 dose-escalation study to evaluate the safety, expansion and persistence of a single dose of UCART19 administered intravenously in patients with relapsed or refractory CD19 positive

B-cell acute lymphoblastic leukemia (B-ALL):  
UCART19 in the treatment of Advanced Lymphoid Malignancies (**CALM**) Study

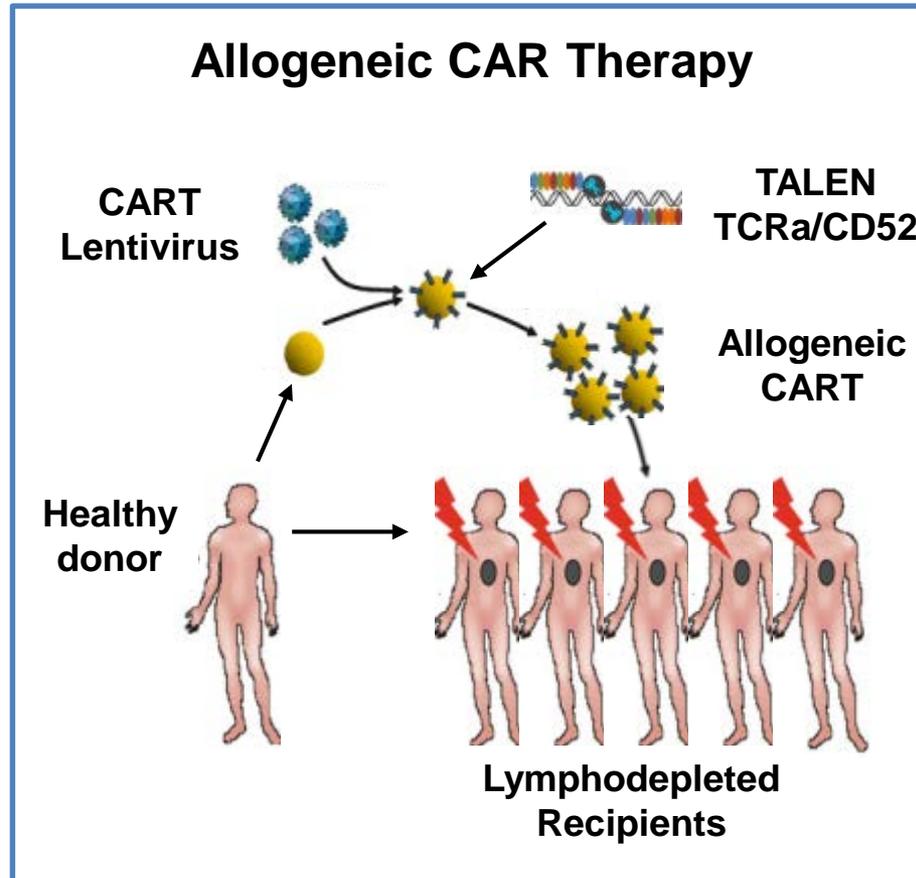
Followed by a Long-Term Follow-Up (**LTFU**) Study

# Poor Outcomes in Relapsed Adult ALL



At risk:	Time (years)					
	0	1	2	3	4	5
<20	117	35	17	14	11	10
20-34	236	57	27	19	13	8
35-49	182	23	8	5	4	3
50+	74	10	6	2	1	0

# Allogeneic CAR T Cell Program: Develop Advanced 'Off the Shelf' Cellular Therapy



# CALM Study

## Primary Objectives

- To evaluate the safety and tolerability of UCART19 and determine the maximal tolerated dose

## Secondary Objectives

- To assess the anti-leukemic activity
  - Rate of objective response at Day 28, Day 84 and overall response
  - Duration of response, time to response, disease-specific survival and progression-free survival
- An objective response is defined as
  - A morphologic complete response
  - Or a complete response with incomplete recovery of counts (based on National Comprehensive Cancer Network guidelines, 2015)
  - Or a molecular response (minimal residual disease MRD  $<10^{-4}$ )

## Exploratory Objectives

- ✓ Proportion of patients who underwent/planned allo-HSCT at Day 84
- ✓ Expansion, phenotype, trafficking and persistence of UCART19
- ✓ Cytokine and CRP levels
- ✓ Potential development of an anti-UCART19 immune response
- ✓ Immune cell depletion and reconstitution post lymphodepletion and UCART19
- ✓ Potential switch of CD19 expression on patient's leukemia cells
- ✓ Assessment of replication competent lentivirus (RCL)

### Optional collection of biological samples

- ✓ To collect blood and, if applicable, bone marrow samples for further analysis of safety and/or efficacy biomarkers in patients who consent (optional)

# CALM Study

## Methodology

- ✓ Phase I, dose escalation study, 4 pre-defined dose levels
- ✓ Patients with relapsed or refractory CD19+ B-ALL
- ✓ 3 countries planned: UK, US, FR
- ✓ 4 centers planned: 1 UK, 2 US, 1 FR
- ✓ International coordinator: Reuben Benjamin (King's College London, UK)
- ✓ Study duration: approximately 16 weeks
- ✓ Patients rolled-over to long-term follow-up study (15 years)

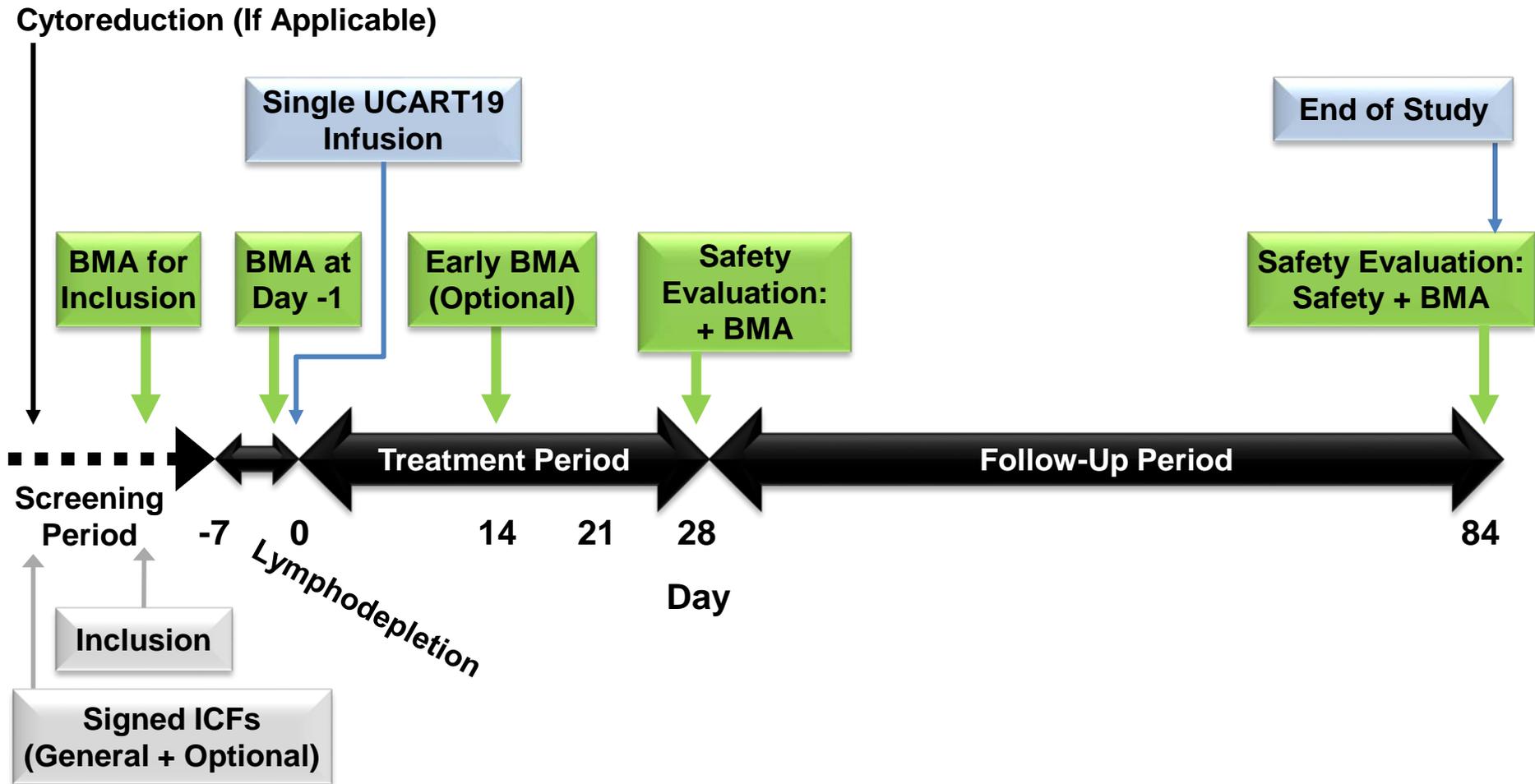
Review of safety data by DSMB (after Day 28 of each treated patient)

# CALM Study: Participating Centers



<b>Principal Investigator</b>	<b>Hospital/Institution</b>	<b>City, Country</b>
<b>Reuben Benjamin, MD</b>	<b>King's College London</b>	<b>London, UK</b>
<b>Nitin Jain, MD</b>	<b>MD Anderson Cancer Center</b>	<b>Houston, USA</b>
<b>Noelle Frey, MD</b>	<b>University of Pennsylvania</b>	<b>Philadelphia, USA</b>
<b>Mohamad Mohty, MD</b>	<b>Saint Antoine Hospital</b>	<b>Paris, France</b>

# CALM Study: Study Design



## Main Inclusion Criteria

- ✓ Age  $\geq 16$  years, relapsed or refractory CD19-positive B-ALL
  - Morphologically confirmed (more than 5% blasts)
  - Or presenting a quantifiable MRD load ( $1 \times 10^{-3}$  by multi-parameter flow cytometry and/or qPCR) at the end of the last induction treatment
  - Who have exhausted available therapeutic options
- ✓ Adequate organ functions including cardiac, renal and hepatic functions
- ✓ ECOG performance status 0-1

## Main Exclusion Criteria

- ✓ Prior gene-modified therapy
- ✓ Uncontrolled CNS leukemia
- ✓ Clinically active significant CNS dysfunction
- ✓ Clinically suspected extra-medullary involvement other than central nervous system (CNS)
- ✓ Previous severe neurological toxicity related to blinatumomab
- ✓ Rituximab and other anti-CD20 antibodies within 6 months prior to screening
- ✓ Presence of donor-specific anti-HLA antibodies
- ✓ Active acute or chronic Graft-vs-Host Disease (GvHD) requiring therapy
- ✓ Patients neither able nor willing to undergo a safety follow-up for 15 years

## Dose Escalation Procedure (mTPI Design)

- ✓ Determination of maximum tolerated dose (MTD), based on dose limiting toxicity (DLT) assessment
- ✓ Minimum of 3 patients per dose level
- ✓ Patients will be included by cohort of 2 to 4 according to a Bayesian design (mTPI design)
  - Target DLT rate = 30% and equivalent interval [25-35%]
  - At least 6 patients treated at MTD
- ✓ DLT observation period = 28 days post-UCART19 infusion
- ✓ Staggered enrollment to be set: 1<sup>st</sup> patient observed for 28 days then patients are enrolled with 2-week interval at each dose level

mTPI=modified Toxicity Probability Interval

# DLT Criteria

<b>Cytokine Release Syndrome*</b>	<ul style="list-style-type: none"> <li>• Grade <math>\geq 4</math></li> </ul>
<b>Tumor Lysis Syndrome</b>	<ul style="list-style-type: none"> <li>• Grade <math>\geq 4</math> that does not resolve within 7 days and with organ damage despite optimal treatment</li> </ul>
<b>GvHD**</b>	<ul style="list-style-type: none"> <li>• Acute GvHD <math>\geq</math> Grade 3 whatever the organ involved</li> </ul>
<b>Nervous System Disorders</b>	<ul style="list-style-type: none"> <li>• Grade 3 lasting more than 14 days</li> <li>• Grade <math>\geq 4</math></li> </ul>
<b>Electrolytes Abnormalities</b>	<ul style="list-style-type: none"> <li>• Grade <math>\geq 4</math> that does not resolve to CTCAE Grade <math>\leq 2</math> within 72 hours despite optimal treatment</li> </ul>
<b>Others</b>	<ul style="list-style-type: none"> <li>• Any event CTCAE <math>\geq 4</math> except alkaline phosphatase increase</li> <li>• <b>In the view of the Investigator and the DSMB, any other unacceptable toxicity</b></li> </ul>

\*CRS graded according to Lee et al. (2014)

\*\*The severity of GvHD will be assessed according to Glucksberg grading score

# Dose of UCART19: Flat Dosing Strategy



Dose Level	Flat Dose (Total UCART19)*	N of UCART19/kg Only Indicative
DL-1	$6 \times 10^5$	$1 \times 10^4/\text{kg}$
DL1 (Starting Dose)	$6 \times 10^6$	$1 \times 10^5/\text{kg}$
DL2	$6 \times 10^7$	$1 \times 10^6/\text{kg}$
DL3	$1.8 \times 10^8$	$3 \times 10^6/\text{kg}$

\*For an average weight of 60 kg

# UCART19 Program: Safety Mitigation Plan (1 of 3)



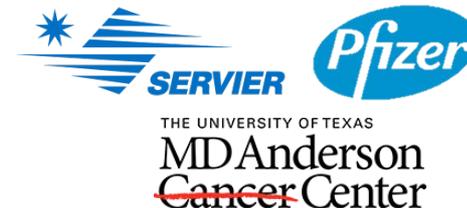
Risks	Risk Mitigation/Management
<b>Cytokine Release Syndrome (CRS)</b>	<ul style="list-style-type: none"> <li>• Treatment algorithm based on Lee (2014): Tocilizumab and corticosteroids as early as Grade 2</li> <li>• Targeted immunosuppressive agents and use of rituximab (suicide switch) in case of Grade 4 and no contraindication in addition to the above</li> </ul>
<b>Infusion-Related Reaction (IRR) other than CRS</b>	<ul style="list-style-type: none"> <li>• Patients with history of hypersensitivity or allergic reaction will be ineligible for the study</li> <li>• Prophylaxis with paracetamol, ranitidine and diphenhydramine</li> <li>• Close monitoring to detect IRR development</li> </ul>
<b>Tumor Lysis Syndrome (TLS)</b>	<ul style="list-style-type: none"> <li>• Frequent monitoring of electrolyte abnormality and renal function</li> <li>• Aggressive hydration, allopurinol and oral phosphate binders 24 hours before UCART19 administration</li> <li>• Early treatment with rasburicase as necessary</li> </ul>

# UCART19 Program: Safety Mitigation Plan (2 of 3)



Risks	Risk Mitigation/Management
<b>Neurological Toxicity</b>	<ul style="list-style-type: none"> <li>• Exclusion criteria for patients with uncontrolled CNS leukemia involvement and/or progressive neurological disease</li> <li>• Initiate tocilizumab (if associated to CRS) and corticosteroids as early as Grade 2</li> </ul>
<b>GvHD</b>	<ul style="list-style-type: none"> <li>• Topical therapies if GvHD limited to skin and &lt;50% of body area</li> <li>• Prednisolone therapy (<math>\geq 2</math> mg/kg/d or equivalent) if GvHD <math>\geq</math> Grade 2</li> <li>• Immunosuppressive agents in case of uncontrolled steroid-refractory GvHD</li> <li>• Addition of rituximab (suicide switch) to standard of care in case of intractable GvHD</li> <li>• Subsequent chemotherapy for transplant is expected to eliminate residual UCART19</li> </ul>
<b>B-cell Aplasia/Resultant Hypogammaglobulinemia</b>	<ul style="list-style-type: none"> <li>• Treatment by pooled IVIg in case of persistent B-cell depletion (as per institutional guidelines)</li> </ul>

# UCART19 Program: Safety Mitigation Plan (3 of 3)



Risks	Risk Mitigation/Management
<b>Infections</b>	<ul style="list-style-type: none"> <li>• Primary prophylaxis of viral, bacterial and fungal infections according to institutional guidelines</li> </ul>
<b>Genotoxicity/ Tumourigenicity</b>	<ul style="list-style-type: none"> <li>• Allogeneic feature</li> <li>• 3<sup>rd</sup> generation self inactivating non-replicative (SIN) lentiviral vector</li> <li>• Number of integration events per cell is monitored by real time qPCR (&lt;5 copies/cell)</li> <li>• mRNA-based TALEN<sup>®</sup> electroporation to abrogate risk of stable TALEN<sup>®</sup> expression</li> <li>• qPCR/high-throughput sequencing analysis to screen for translocation between cleavage sites</li> <li>• Karyotype / FISH analysis</li> <li>• Absence of IL-2 independent proliferation</li> <li>• Frequent CBC monitoring post-UCART19</li> <li>• Long-term follow-up for 15 years</li> </ul>

# Regulatory Status



Submission Status	Date
CALM study approved by MHRA (UK)	March 24, 2016
First Visit First Patient	August 17, 2016
Pre-IND meeting	October 18, 2016

# Preliminary Data: R/R ALL

Data as of December 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	4.8 years	• Grade 3 CRS • Grade 1 Suspected Skin GvHD • Grade 1 Neurological	Alive, 6+ Months, Relapsed
	2.7 years	• Grade 2 CRS • Grade 1 Neurological	Alive, MRD-, 4+ Months
CALM Study	42 years	• Grade 2 CRS	Alive, MRD-, 4+ Months
	18 years	• Grade 4 CRS	Died, Cause Under Investigation

\*Qasim W et al., ASH 2015

\*\*Qasim W et al., ASGCT 2016

**Long-Term Follow-Up study of patients who have previously been exposed to UCART19 (allogeneic engineered T-cells expressing a lentiviral-based anti-CD19 chimeric antigen receptor): LTFU Study**

# LTFU Study

## Primary Objectives

- ✓ To evaluate the long-term safety of patients with advanced lymphoid malignancies who have been previously administered with UCART19

## Secondary Objectives

- ✓ To assess the long-term anti leukemic activity of UCART19 (disease outcome, disease-free survival and overall survival)
- ✓ To assess the proportion of patients who underwent allogeneic hematopoietic stem cell transplantation
- ✓ To assess the time to transplant
- ✓ To monitor the long-term persistence of UCART19 in blood
- ✓ To monitor the absence of RCL in blood

# LTFU Study: Safety Reporting

## Safety Assessments

- Time-points: 3 months, 6 months, 12 months post last UCART19 infusion, then every 6 months up to year 3 included, then yearly up to 15 years
- At each visit, assessment of
  - CD19CAR vector copy number (by qPCR) (in blood)
  - Replication Competent Lentivirus testing (by qPCR) (in blood)
- All adverse events of special interest regardless of causality
  - New malignancy
  - New hematological disorder
  - Incidence/exacerbation of any autoimmune disorders
  - Incidence/exacerbation of neurologic disorder
  - B-cell aplasia and resultant hypogammaglobulinemia
- Any AE related to UCART19



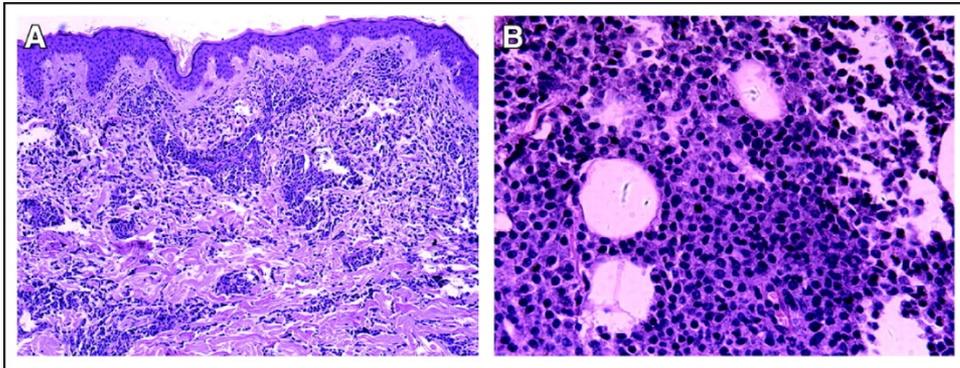
*Phase I, open label dose-escalation study to evaluate the safety, expansion, persistence and clinical activity of a single dose of UCART123 (allogeneic engineered T-cells expressing anti-CD123 chimeric antigen receptor), administered in patients with Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) (NIH #1610-1547)*

IRB Protocol # 2016-0840  
NIH OSP RAC Public Review  
December 13-15, 2016

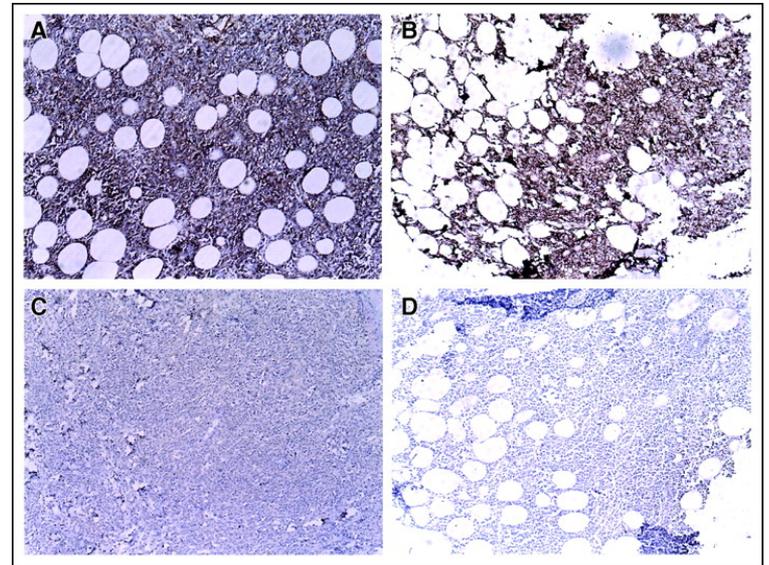
# Disease Background

- Blastic plasmacytoid dendritic cell neoplasm
  - BPDCN- previously NK cell leukemia/lymphoma- reclassified WHO 2008 (AML), WHO 2016 (Myeloid disorders- Acute Leukemia)
  - Little data on biology of BPDCN: No established standard of care
  - BPDCN usually involves skin, progresses to a terminal leukemic phase with bone marrow involvement and pancytopenia; lymph nodes and spleen may also be involved
  - Median age at presentation 60 to 70 years; 3:1 male predominance

# BPDCN: Clinical and Morphological Features



Jieping Chen et al. JCO 2011;29:e27-e29

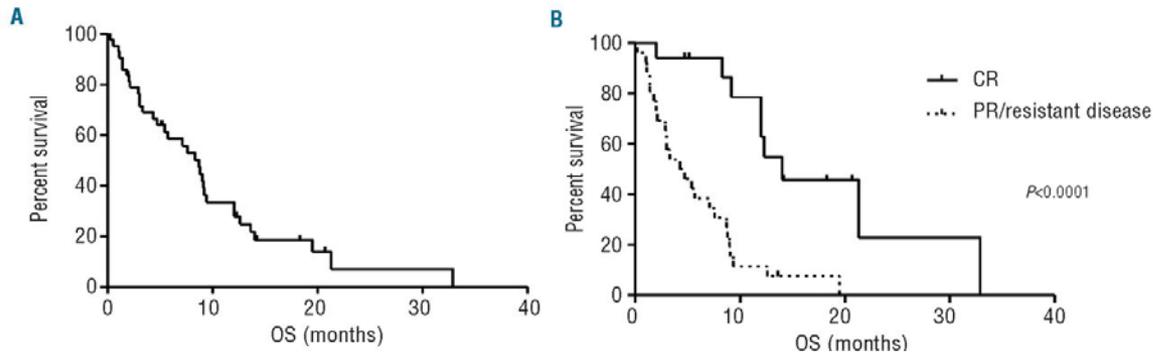


# Current Treatment and Outcome

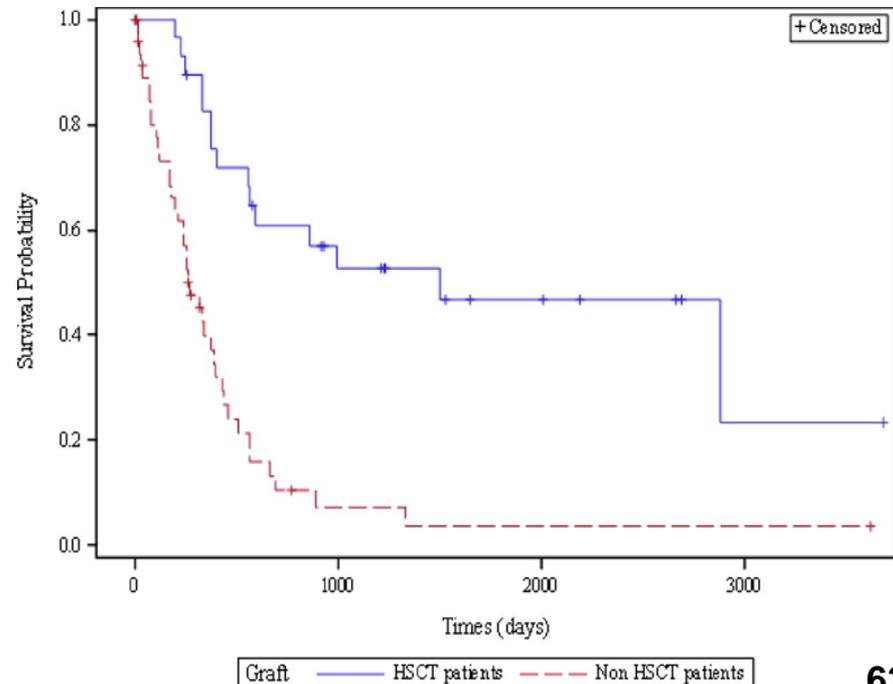
- No prospective randomized clinical study data, or prospective trial data, to define the optimal frontline therapy for BPDCN patients
- Response duration is typically brief
- Median survival from diagnosis has been reported to range from 9 to 12 months
- Second remissions with conventional chemotherapy are difficult to achieve
- Allo-HCT especially if offered in first remission, may result in longer remissions

# BPDCN Outcome According to Treatment

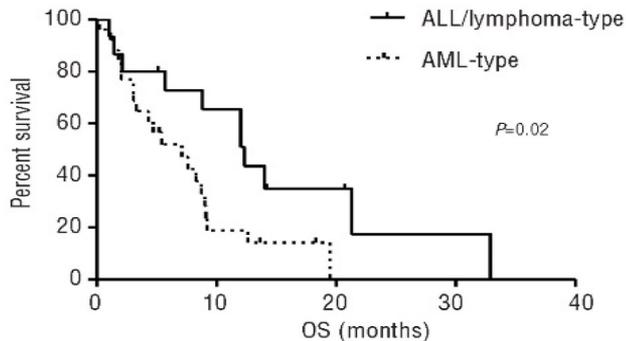
**(A) Overall Survival (OS) of the Whole Population (43 patients)<sup>1</sup>**



**Overall Survival of HSCT Patients and Non-HSCT Patients<sup>2</sup>**



**Overall Survival According to Types of Induction Therapy<sup>1</sup>**



1. Livio Pagano et al. Haematologica 2013;98:239-246

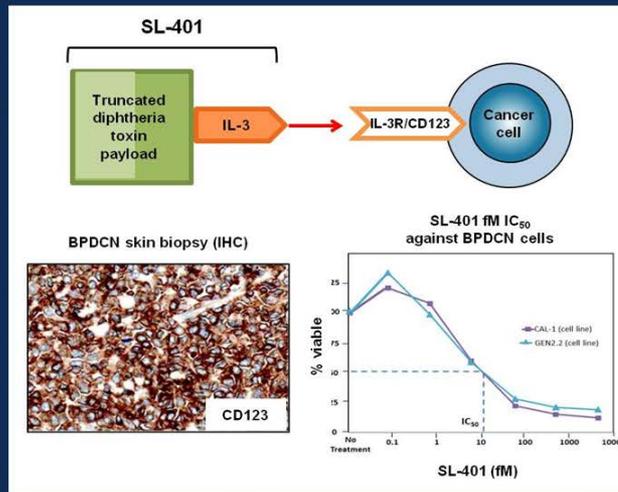
2. Eve Poret et al. Blood 2015;126:456

# CD123 as a Target

- CD123 surface receptor: Interleukin-3 receptor alpha chain (IL-3R $\alpha$ )
- CD123 constitutively expressed on normal, committed hematopoietic progenitor cells- Also expressed in a variety of hematological neoplasms, including AML, MDS, Hairy Cell Leukemia and BPDCN
- Majority of AML blasts express surface CD123, irrespective of AML subtype-CD123 expression at a higher density than observed in normal CD34+ cells
- High levels of CD123 expression on CD34+CD38- leukemic stem cells (LSCs), in contrast to minimal or absent expression on HSCs in normal bone marrow
- LSCs are resistant to conventional cytotoxic chemotherapy and are believed to be responsible for disease relapse and increased expression of CD123 on AML LSCs is associated with a poor prognosis

# SL-401: Novel Targeted Therapy Directed to the IL-3 Receptor (IL-3R / CD123)

- IL-3R $\alpha$  (CD123) overexpressed on BPDCN and many other hematologic cancers
- SL-401 is a targeted therapy directed to the IL-3R/CD123
- SL-401 is highly potent against BPDCN cells *in vitro* and *in vivo*
- Previous Phase 1 study, single cycle of SL-401:
  - Major responses in 7/9 patients (78%): 5 CR, 2 PR (Frankel. Blood, 2014)



## SL-401 Study Design and Eligibility Criteria (NCT02113982)

### Lead-in (Stage 1) - Completed

- BPDCN (n=9); R/R AML (n=14)
- SL-401 daily IV infusion for 5 days
- At 7, 9, 12, or 16  $\mu$ g/kg/day for 5 doses
- Repeated every 21 days



### Expansion (Stage 2) - Ongoing

- BPDCN (n=15; ongoing)
- SL-401 daily IV infusion for 5 days
- At recommended Stage 1 dose (12  $\mu$ g/kg/day) for 5 doses
- Repeated every 21 days

### Select inclusion criteria

- BPDCN: first-line or R/R (Stages 1 and 2)
- AML: R/R (Stage 1)
- Age  $\geq$  18; ECOG PS 0-2
- Adequate organ function including: LVEF  $\geq$  LLN, creatinine  $\leq$  1.5mg/dL, **albumin  $\geq$  3.2 g/dL**, bilirubin  $\leq$  1.5 mg/dL, AST/ALT  $\leq$  2.5x ULN

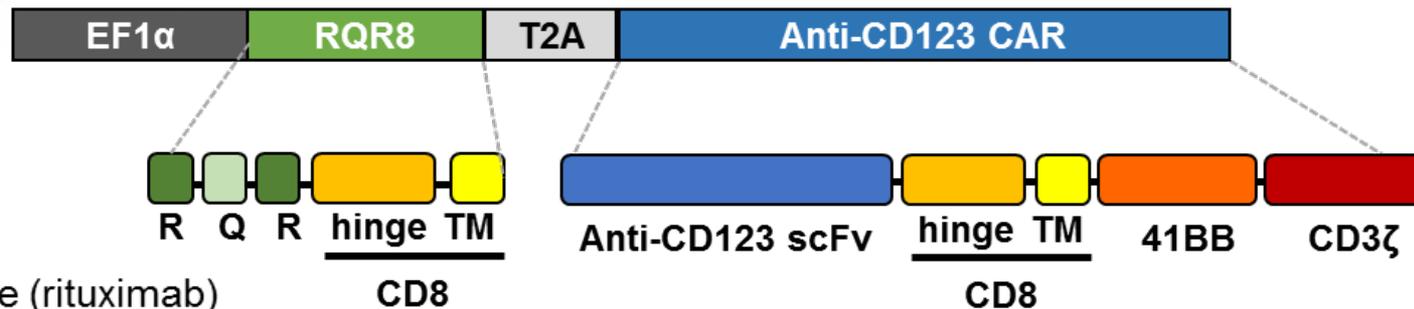
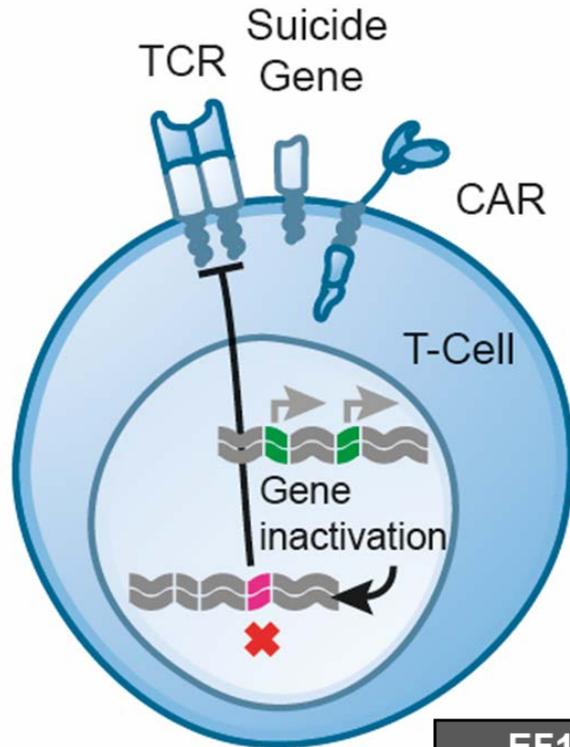
# Study Rationale

- Over-expression of CD123 in almost all patients with BPDCN
  - Rare hematologic malignancy with poor outcomes
- Lack of standard therapies available for treatment of this disease
- Novel methodology with which UCART123 is developed, unique compared to other CAR-T cell therapy designs
- Few available clinical trial therapies
- Urgent unmet medical need

# UCART123

## • UCART123 Attributes

- Anti-CD123 CAR expression to redirect T cells to tumor antigens
- Suicide gene (RQR8) for safety → Rituximab
- TCR disruption to avoid GvHD

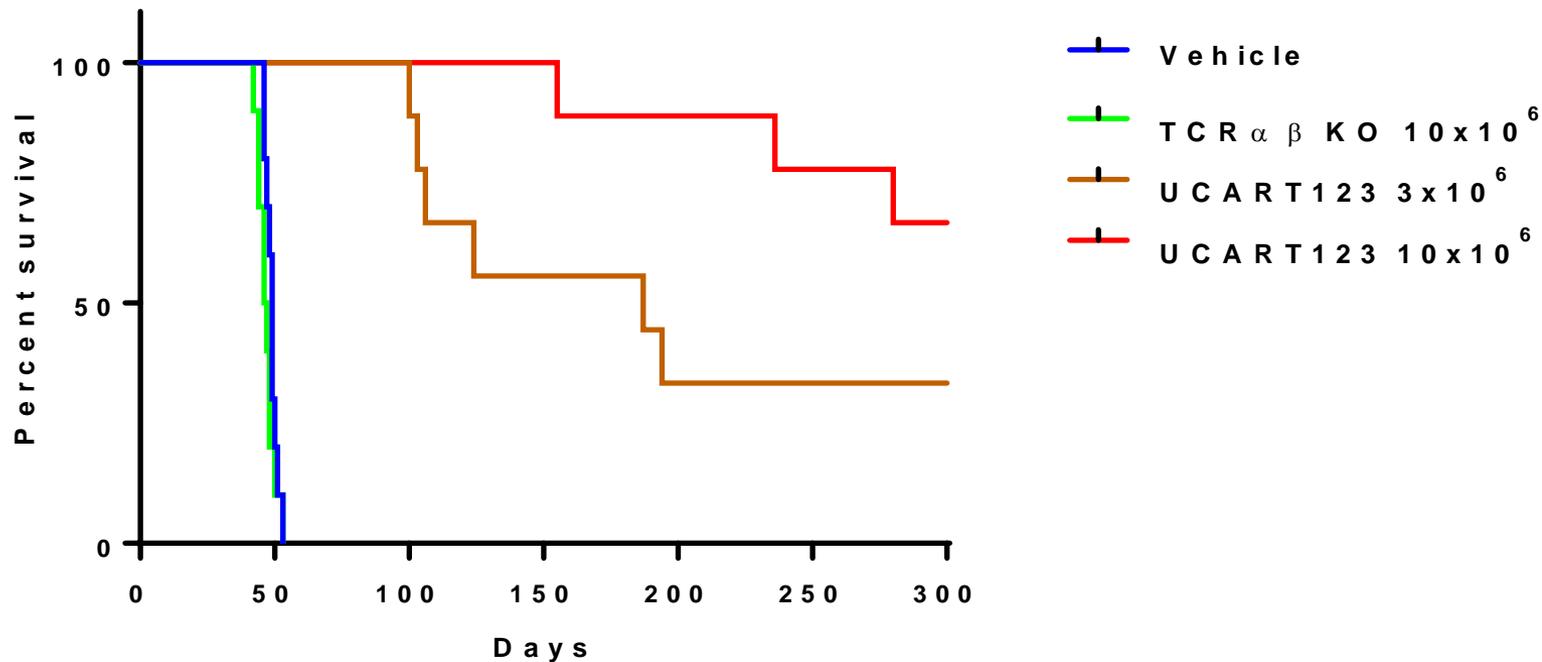


R=CD20 mimotope (rituximab)

Q= CD34 epitope (Qben10)

# Treatment with UCART123 Resulted in Significant Survival Advantages

Survival proportions: Survival of BPDCN mouse



- All mice in Vehicle and TCR $\alpha\beta$  KO groups died before Day 53
- 5 of 9 mice in UCART123 groups are alive until Day 299

# Study Objectives

- **Primary**

- To assess the safety and tolerability of UCART123 administered to patients with Blastic Plasmacytoid Dendritic Cell Neoplasm
- To determine the Recommended Phase 2 Dose of UCART123

- **Secondary**

- To assess the efficacy of UCART123 in Blastic Plasmacytoid Dendritic Cell Neoplasm patients as measured by OR rate, CR rate, Duration of Response, PFS and Overall Survival

# Exploratory Objectives

- Expansion, trafficking and persistence of UCART123 in blood, bone marrow and other sites of disease if applicable
- Cytokine and CRP levels after UCART123 infusion
- UCART123 immune response
- Potential relationship between baseline level of CD123 expression and clinical outcome
- Impact of UCART123 on LSCs, HSCs and progenitor cells
- To confirm the absence of replication competent lentivirus (RCL)

# UCART123\_02: Study Design

## Dose Escalation Phase (RR BPDCN)

DL3  
N=3

$6.25 \times 10^6 / \text{kg}$

DL2  
N=3

$1.25 \times 10^6 / \text{kg}$

DL1 (start dose)  
N=3

$6.25 \times 10^5 / \text{kg}$

DL-1  
N=3

$6.25 \times 10^4 / \text{kg}$

3 Patients Treated  
at the RP2D

## Expansion Phase

RR BPDCN  
N=30

Untreated BPDCN  
N=30

Total Dose Escalation N= 9-12 pts

Total Phase I Expansion N=60

# Inclusion Criteria: Dose-Escalation and Expansion

- Dose-Escalation

- Patients with a diagnosis BPDCN according to WHO classification confirmed by hematopathology
- Patients with histological and/or cytological evidence of BPDCN in the peripheral blood, bone marrow, spleen, lymph nodes, skin, and/or other sites that is persistent/recurrent following prior treatment for BPDCN
- Patients enrolled onto the dose finding phase of the study must have an available donor for a potential allogeneic bone marrow transplant (including matched related or unrelated donor, cord blood transplant, or haploidentical donor)
- Age >18 and <75 years

- Dose Expansion

- Age >18 years
- Patients with a diagnosis of BPDCN according to WHO classification (Arber et al., 2016)
- Patients either previously untreated or with persistent/recurrent disease following prior treatment for BPDCN
- For patients with persistent or recurrent disease
  - One or more prior salvage treatment for relapse or refractory disease
  - Patient may have undergone autologous or allogeneic stem cell transplantation

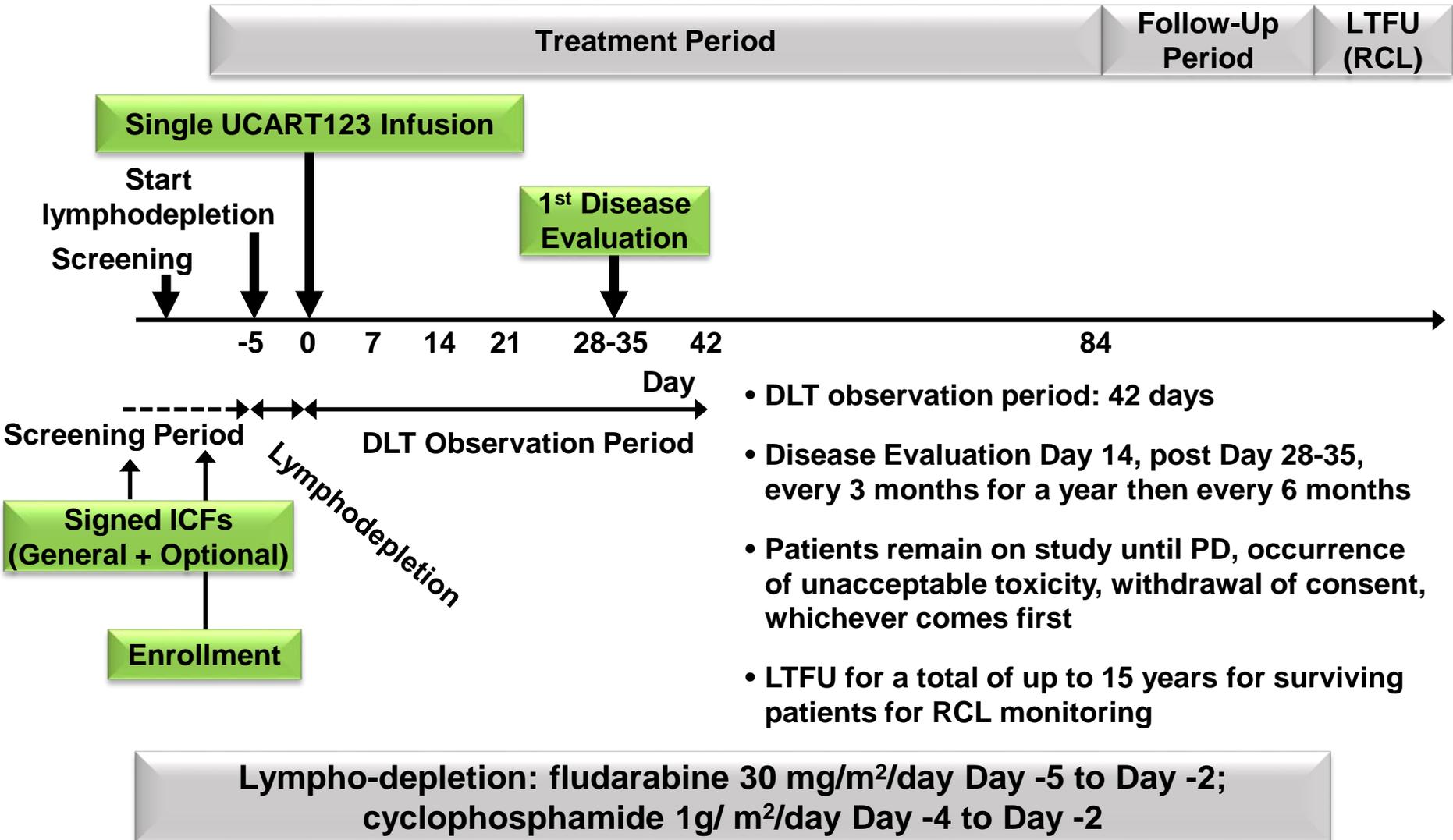
# Key Inclusion Criteria: All Patients

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1
- Adequate organ function
- Adequate contraception
- Patients who have undergone Hematopoietic Stem Cell Transplantation (HSCT) are eligible must be beyond 6 weeks from HSCT, off immunosuppression and without evidence of active Graft-vs-Host Disease at the time of study entry

# Key Exclusion Criteria

- Previous treatment with investigational gene therapy or chimeric antigen receptor therapy
- Active central nervous system leukemia involvement
- Presence of active and clinically relevant CNS disorder
- Use of rituximab and other anti CD20 antibodies known to have the same epitope as rituximab or anti CD20 for which the epitope is unknown within 3 months prior to screening
- Active treatment with steroids or other immunosuppressive agents that cannot be stopped
- Known infection with HIV or HTLV-1
- Presence of UCART123 donor-specific anti-HLA antibodies (DSA)

# Design



# Dose-Escalation Procedure

- 3 patients per cohort
- DLT observation period 42 days
- Patient enrollment timelines
- Dose Level 1: sequential enrollment
- Dose Levels 2 and 3: sequential and concurrent enrollment
- Dose escalation if 0/3 or 1/3 (33%) DLT at a dose level
- If DLT at any dose level in 2/3 patients: dose level immediately below to be expanded to 6 patients
- If at the lower dose 2/6 patients experience a DLT and no biological or clinical activity, the study will be stopped

# Dose Limiting Toxicities (DLTs)

- **Cytokine-Release Syndrome:** Grade 5; Grade 4 that does not resolve to Grade  $\leq 2$  within 72 hours; Grade 3 that does not resolve to Grade  $\leq 2$  within 2 weeks
- **Tumor Lysis Syndrome:** Grade  $\geq 4$  that does not resolve within 7 days and/or with organ damage despite optimal treatment
- **Acute Graft-vs-Host Disease:** Grade  $\geq 3$
- **Aplastic Bone Marrow:** Defined by marrow cellularity  $< 5\%$  in the absence of residual AML
- **Central Neurologic Toxicity:** Grade  $\geq 3$  lasting more than 2 weeks
- **Infusion-Related Reactions:** Grade 5
- **Capillary Leak Syndrome:** Grade  $\geq 3$  that does not resolve to Grade  $\leq 2$  within 72 hours
- **Any Clinically Significant Grade  $\geq 3$  Non-Hematological Toxicity:** Not attributable to another clearly identifiable cause and not recovering within 2 weeks
- **Any Other Unacceptable Toxicity:** Per investigator or DSMB

# RP2D Definition

- The dose level of UCART123 judged safe and with evidence of clinical activity (as measured by  $\geq 50\%$  reduction in BPDCN disease burden in any 1 of the 3 major compartments of disease involvement at baseline), will be expanded with three additional patients, in order to reach 6 patients to gain more information on safety and pharmacological activity of UCART123
- After 6 patients have been treated at a specific level, the confirmation of the recommended dose to be used at the expansion phase will be left to the decision of the Sponsor upon the recommendation of the DSMB

# Dose-Expansion Phase

- 30 patients relapsed/refractory
- 30 patients newly diagnosed
- Safety and efficacy
- Study will be stopped if non-hematological toxicities exceed 30% of patients and/or if there are other safety concerns expressed by the investigators and/or DSMB

# Risks

- Expected toxicities of BPDCN standard treatment
- Cytokine-Release Syndrome (CRS)
- Tumor Lysis Syndrome (TLS)
- Neurologic toxicities
- Off-target toxicity (HSCs, endothelial cells)
- Graft-vs-Host Disease (GvHD)
- Malignant transformation following lentiviral transduction

# RQR8 Activation

- In case of toxicity/adverse event attributable to UCART123, RQR8 suicide mechanism may be activated with Rituximab
- Events potentially triggering administration of Rituximab
  1. Acute Graft-vs-Host Disease of a Grade  $\geq 3$  refractory to steroids
  2. Any manifestation of genotoxicity or tumorigenicity, e.g. presence of a replication competent lentivirus
  3. Central neurologic toxicity of any grade, as determined by the investigator
  4. Absence of hematopoietic recovery by Day 56, without evidence of residual disease and allogeneic transplant not feasible due to clinical circumstances

# Safety

- Dose escalation phase conducted at one center with expertise in cellular therapy and BPCDN
- Other sites for expansion phase selected with specific expertise
- All sites to have dedicated team for this trial, including 24/7 on call experts in leukemia, transplant, ICU, neurology and infectious diseases
- AEs and toxicity NCI-CTCAE version V4.03
- Cytokine release syndrome Lee criteria (Lee et al., 2014)
- Tumor lysis syndrome Cairo and Bishop criteria (Cairo and Bishop, 2004)
- Acute Graft-vs-Host disease new consensus criteria (Harris et al., 2016)
- DSMB oversight

# Efficacy Assessments

Site of Disease	Assessment Tool	Criteria	Key Reference
<b>Primary</b>			
<b>Skin</b>	<b>mSWAT/biopsy</b>	<b>mSWAT calculation and pathology</b>	<b>Olsen, 2011</b>
<b>Bone Marrow (BM)</b>	<b>BM aspirate/biopsy, peripheral blood counts</b>	<b>AML</b>	<b>Cheson, 2003</b>
<b>Secondary</b>			
<b>Lymph nodes, viscera</b>	<b>CT or PET/CT</b>	<b>NHL</b>	<b>Cheson, 2014</b>

- **Tumor Assessment will be performed at the following timepoints**
  - During the screening period
  - Between Day 28 and Day 35 post infusion, in order to assess the clinical active dose of UCART123
  - Every 3 months for one year from Day 84
  - Every 6 months thereafter



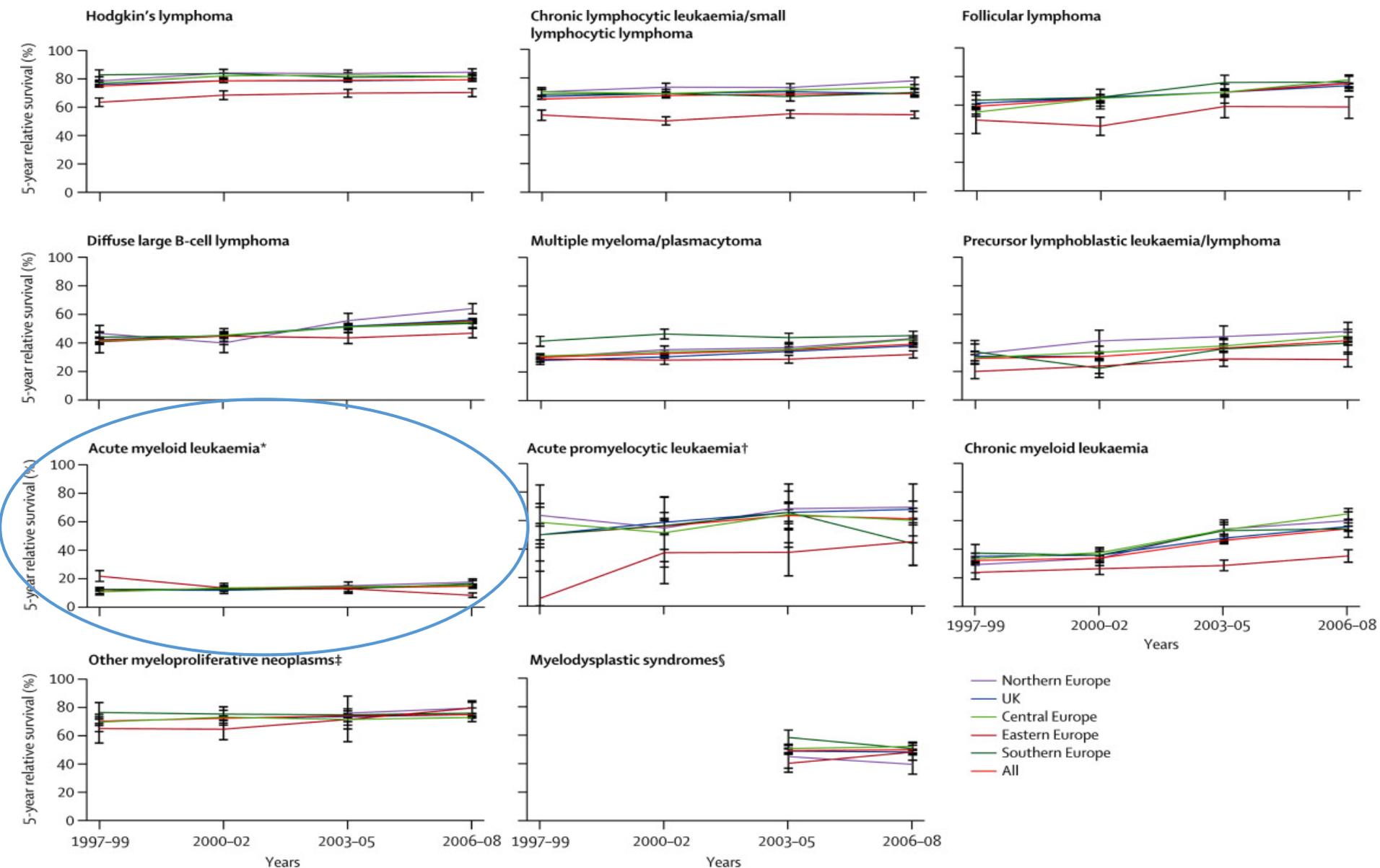
## **AML123:**

Phase I, open-label, dose-escalation, and expansion study to evaluate the safety, proliferation, persistence, and clinical activity of a single dose of UCART123 administered to patients with Relapsed/Refractory Acute Myeloid Leukemia (AML), and patients with newly diagnosed, high-risk AML  
**(NIH #1610-1548)**

NIH OSP RAC Public Review  
December 13-15, 2016

# Acute Myeloid Leukemia

- Most common acute leukemia in adults
- 2015  $\approx$  20,800 cases with 10,460 deaths
- Median age at diagnosis  $\approx$  70, but happens at all ages
- Associated with chemo +/- radiation exposure, antecedent hematologic disorders, environmental factors
- Progress severely lagging behind other hematologic malignancies, most young patients not cured, almost no older patients cured



Milena Sant , Pamela Minicozzi , Morgane Mounier , Lesley A Anderson , Hermann Brenner , Bernd Holleczeck , Rafael ... Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EURO CARE-5, a population-based study. *The Lancet Oncology*, Volume 15, Issue 9, 2014, 931 – 942.

[http://dx.doi.org/10.1016/S1470-2045\(14\)70282-7](http://dx.doi.org/10.1016/S1470-2045(14)70282-7)

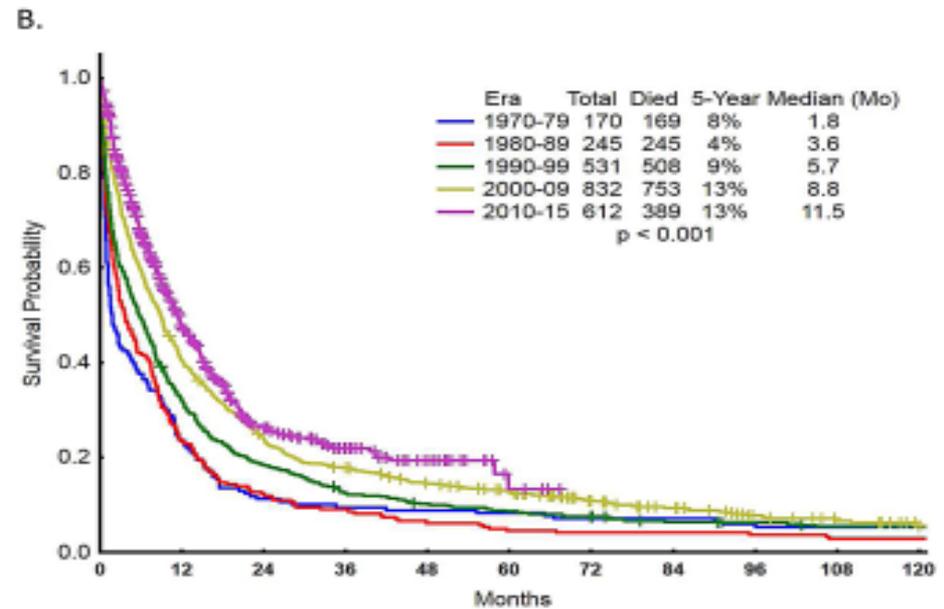
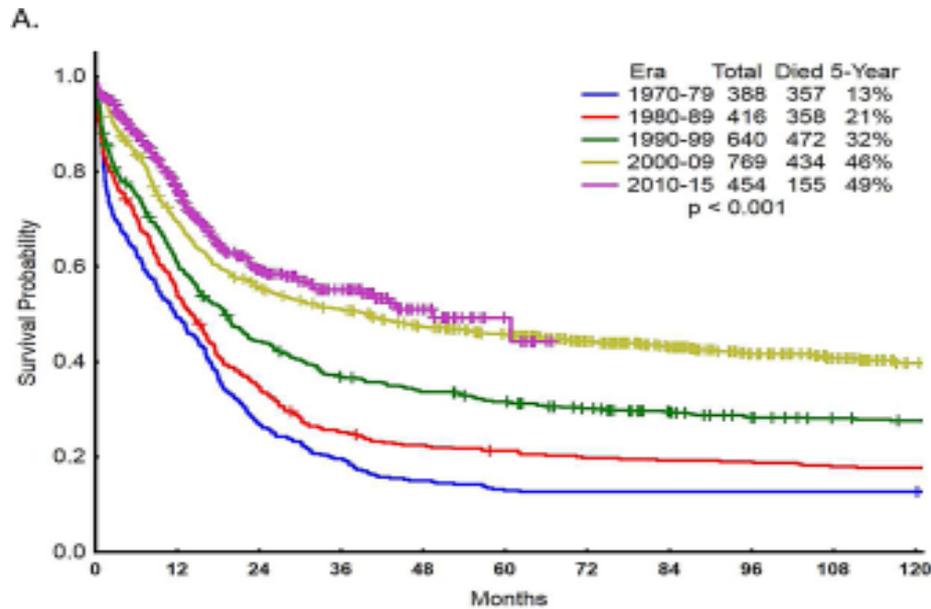
# Current Treatment Paradigm

- Newly diagnosed
  - Remission induction (anthracycline/cytarabine)
  - Consolidation
    - Cycles of chemotherapy
    - Auto or allo stem cell transplant
  - ? Maintenance
- Relapsed
  - Multi-agent chemotherapy
  - Clinical trials

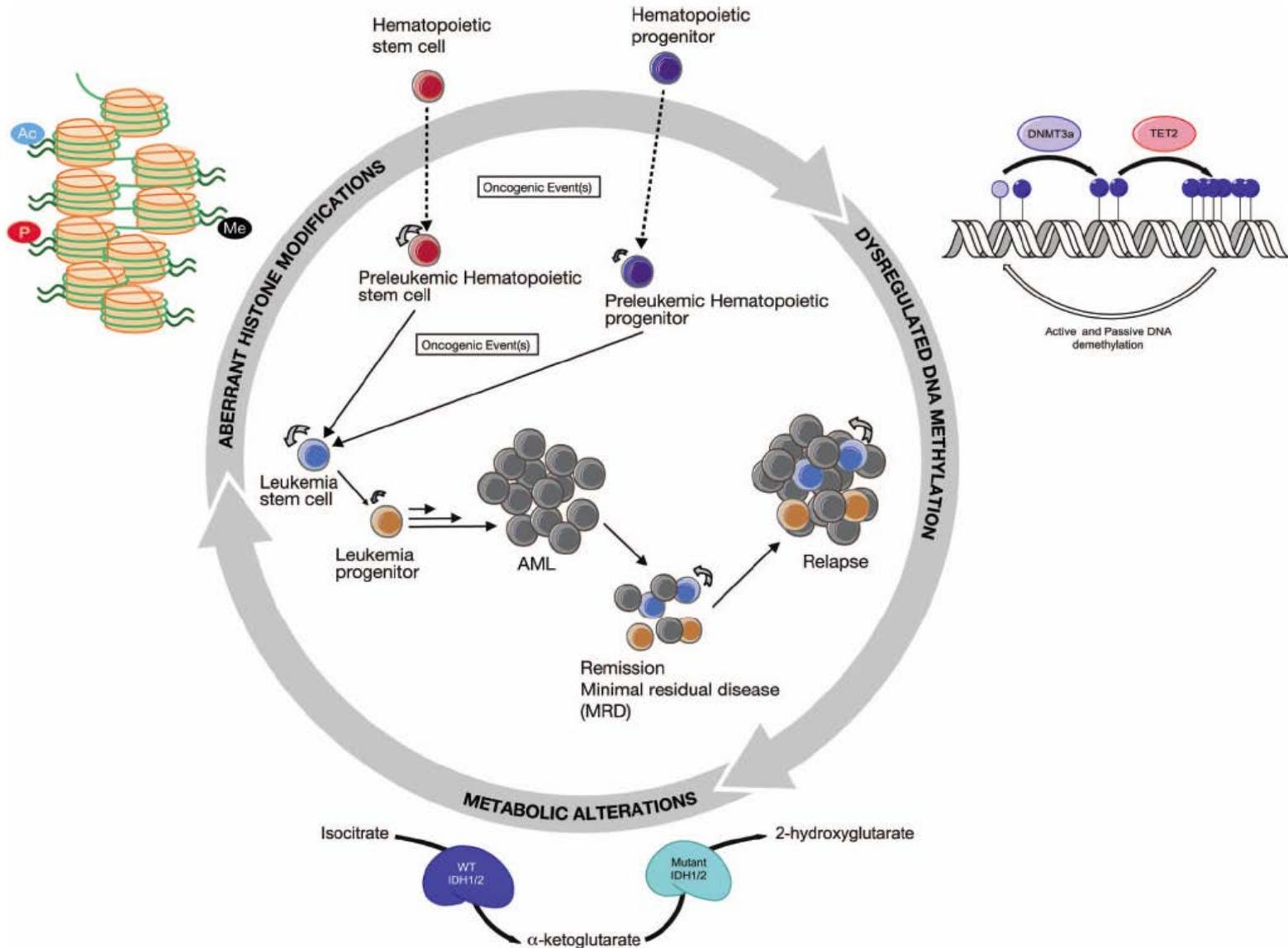
# The Bottom Line: Outcomes in Newly Diagnosed AML

- **Unselected <60 years:** CR 75%, 5-year OS 40-50% with anthracycline/cytarabine-based chemo
- **Not frail >60 years:** CR up to 50%, 5-year OS <20% with anthracycline/cytarabine-based chemo
- **Frail >60 years:** CR 15-30%, 5-year OS <10% with LDAC or hypomethylating agents

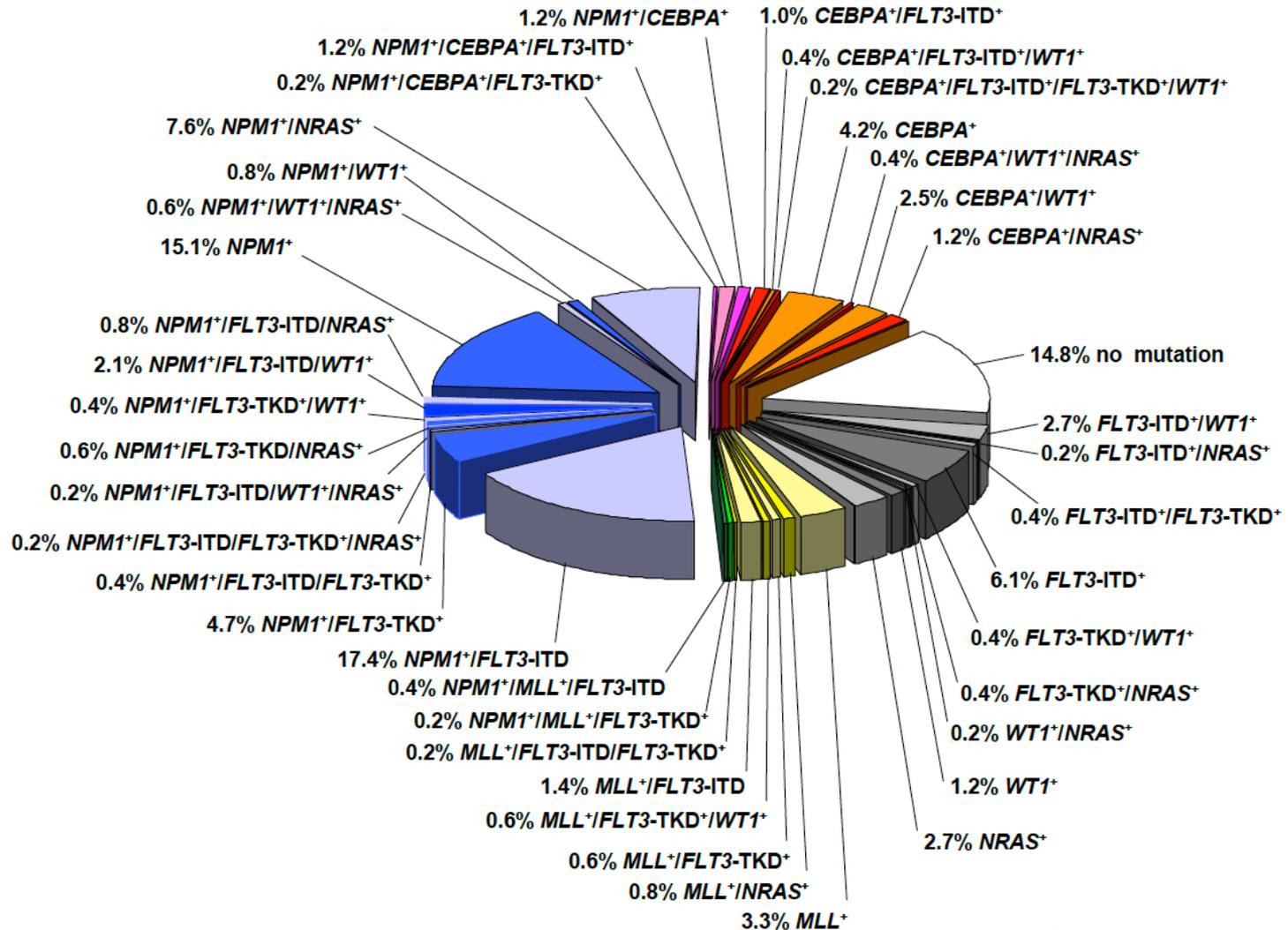
# Newly Diagnosed AML: Four Decades of Slow Progress



# The Biology of Leukemia (and This is the Simplified Version...)



# Molecular Heterogeneity of Cytogenetically Normal AML

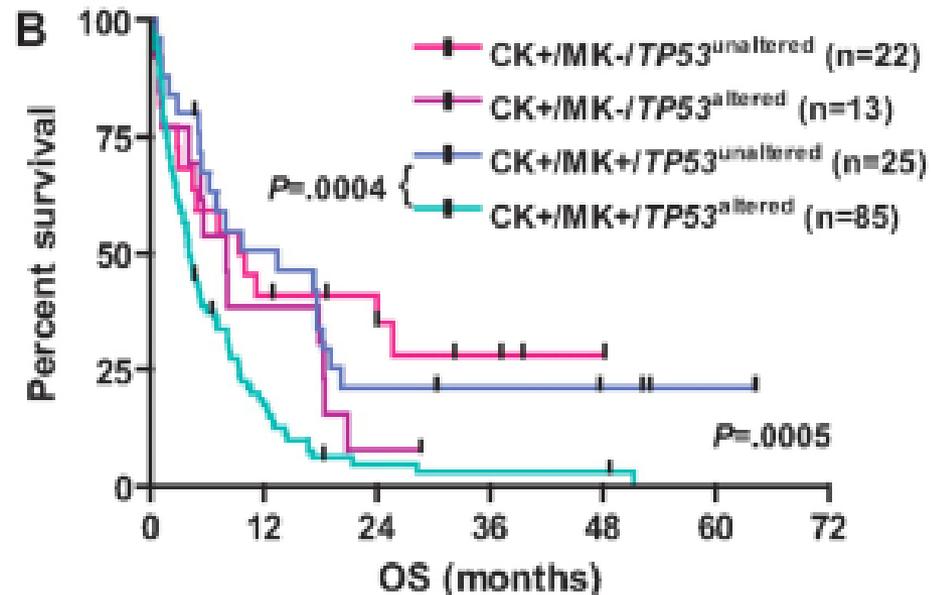
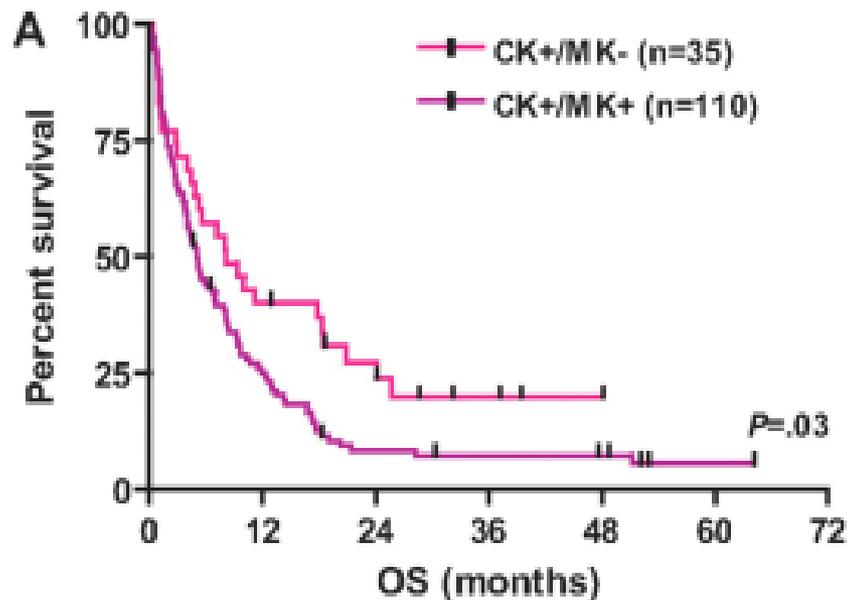


# 2017 European LeukemiaNet Guidelines

**Table 5. 2017 European LeukemiaNet risk stratification by genetics<sup>a</sup>**

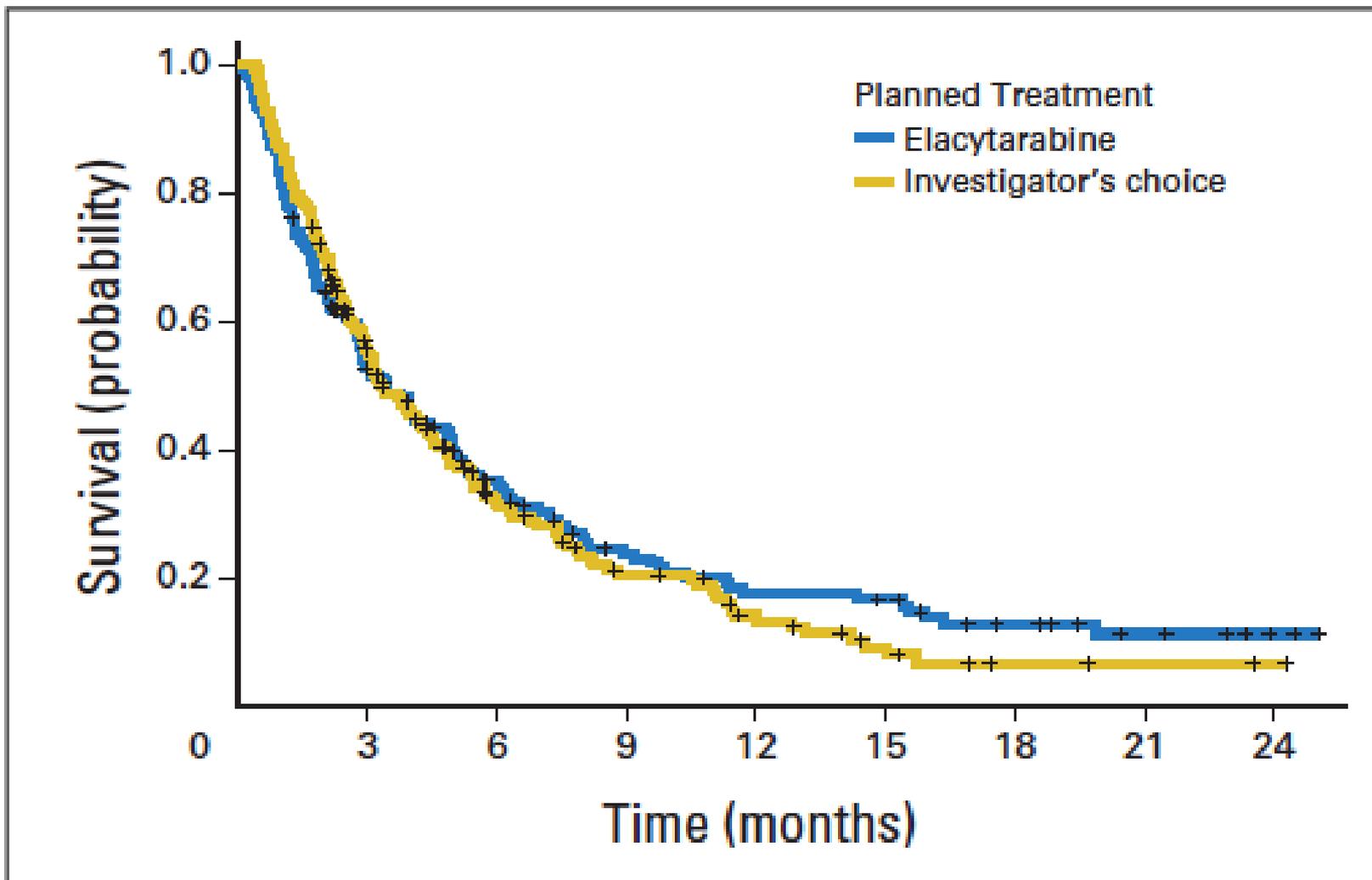
Risk Category <sup>b</sup>	Genetic Abnormality
<b>Favorable</b>	t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i> inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i> Mutated <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> <sup>low(c)</sup> Biallelic mutated <i>CEBPA</i>
<b>Intermediate</b>	Mutated <i>NPM1</i> and <i>FLT3-ITD</i> <sup>high(c)</sup> Wild type <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> <sup>low(c)</sup> (w/o adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i> <sup>d</sup> Cytogenetic abnormalities not classified as favorable or adverse
<b>Adverse</b>	t(6;9)(p23;q34.1); <i>DEK-NUP214</i> t(v;11q23.3); <i>KMT2A</i> rearranged t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i> inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2,MECOM(EVI1)</i> -5 or del(5q); -7; -17/abn(17p) Complex karyotype, <sup>e</sup> monosomal karyotype <sup>f</sup> Wild type <i>NPM1</i> and <i>FLT3-ITD</i> <sup>high(c)</sup> Mutated <i>RUNX1</i> <sup>g</sup> Mutated <i>ASXL1</i> <sup>g</sup> Mutated <i>TP53</i> <sup>h</sup>

# Acute Myeloid Leukemia Risk-Stratification- Complex Karyotype and TP53 Mutation



*TP53* is found in 8%–14% of AML

# Elacytarabine in Relapsed/Refractory AML – Roboz et al, JCO 2014



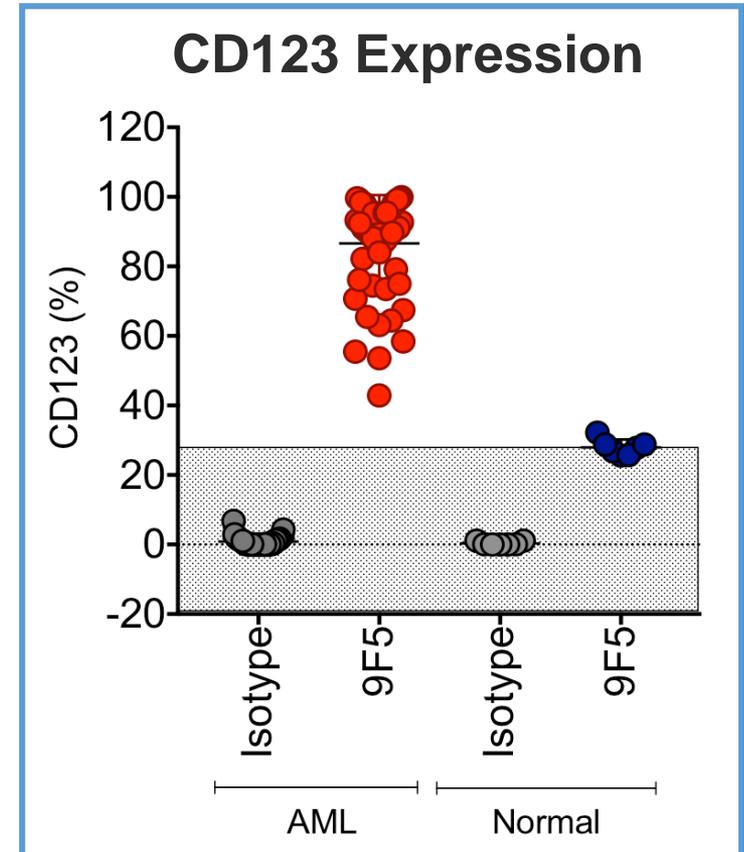
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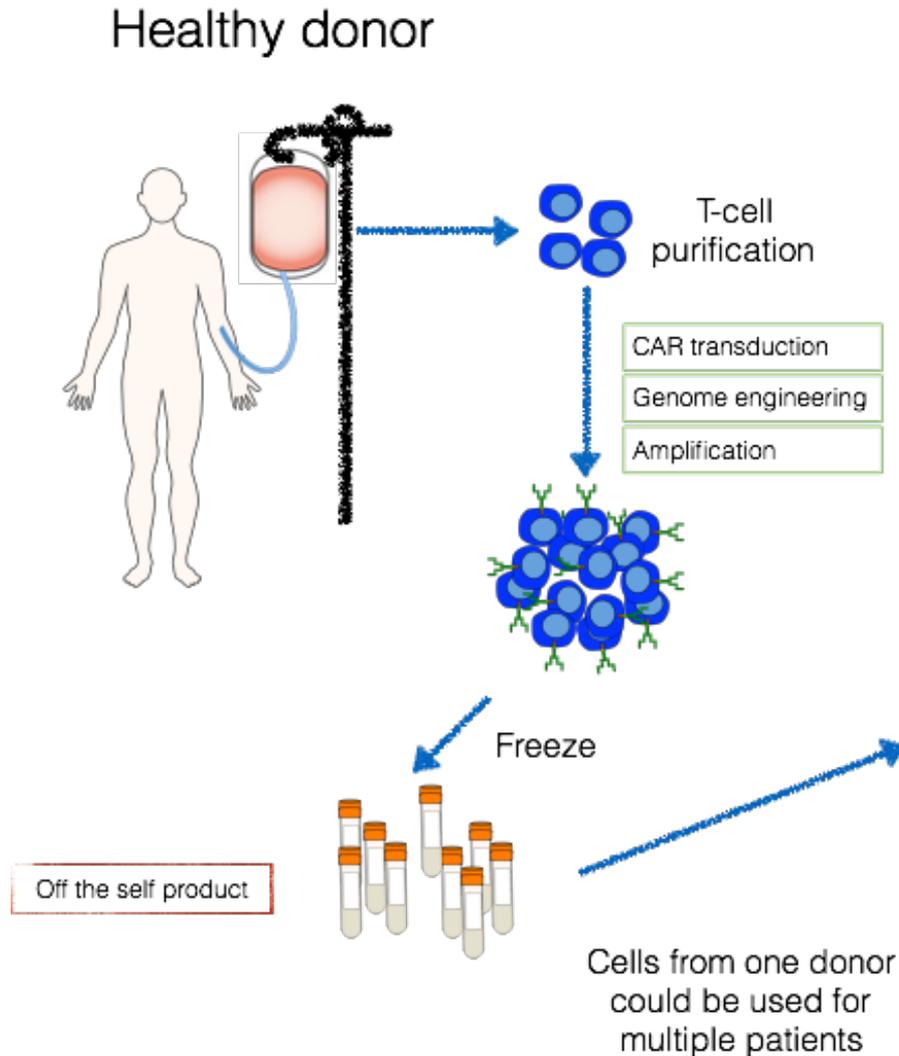
# CD123 as a Target in AML

- Almost universally expressed on AML blasts, irrespective of subtype
- Higher density than on normal CD34+ cells
- High levels on CD34+CD38- leukemic stem cells (LSCs)
- Minimal or absent expression on HSCs in normal bone marrow
- LSCs resistant to conventional cytotoxic chemotherapy and contribute to disease relapse
- Increased expression of CD123 on AML LSCs is associated with poor clinical outcomes

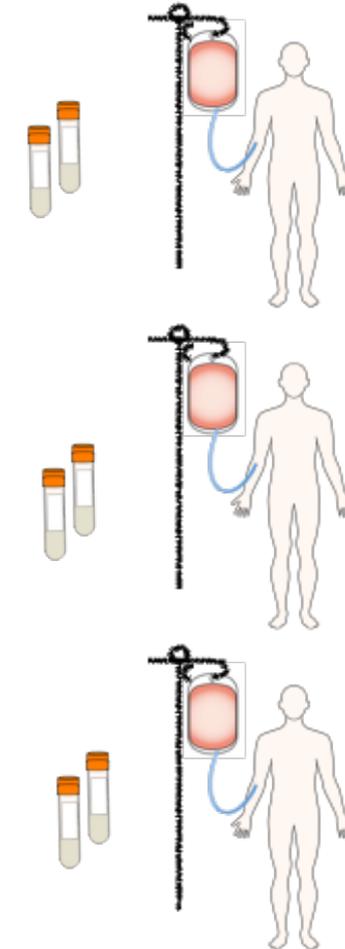


Cruz, N Abstract #1693

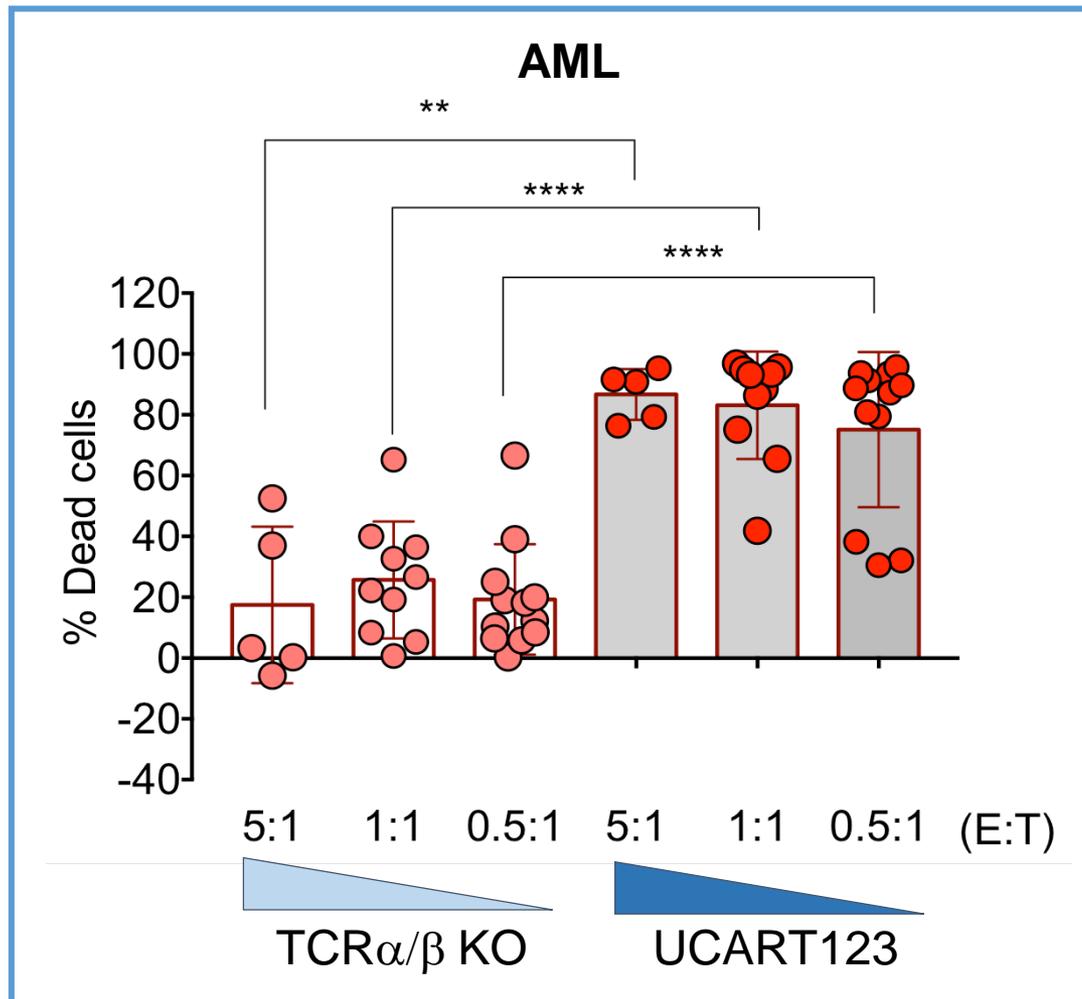
# Allogeneic CART Cell Process



## AML patients

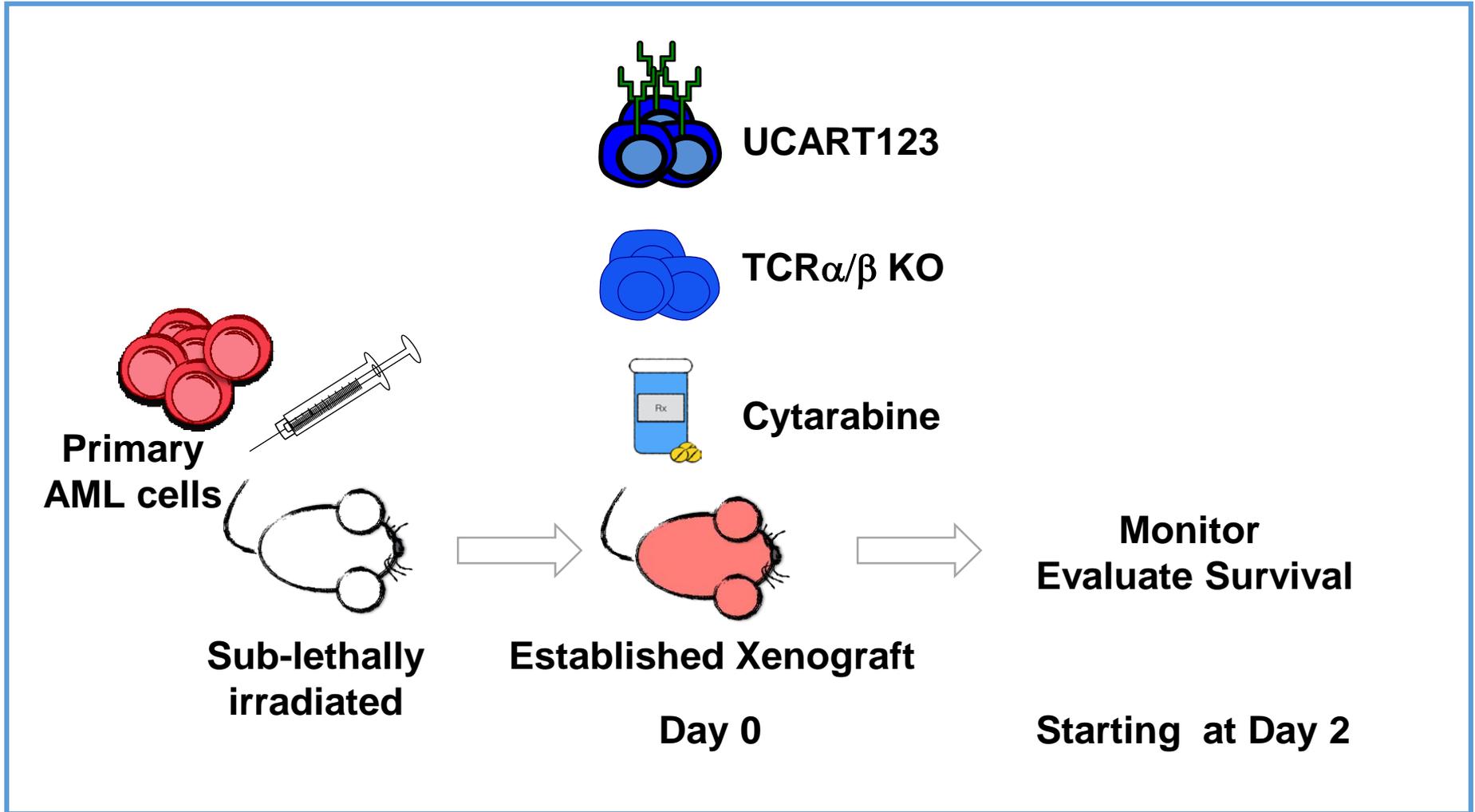


# UCART123 Demonstrate In Vitro Activity Against Primary AML Cells



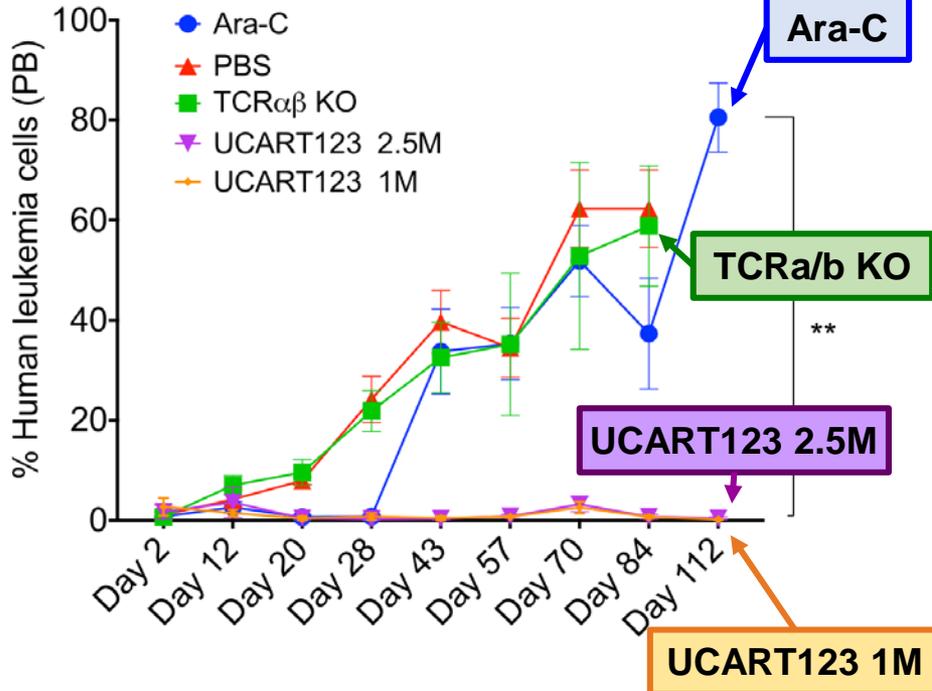
Each symbol represents a primary AML sample

# Patient Derived Xenografts (PDX) were Generated to Test In Vivo Activity of UCART123



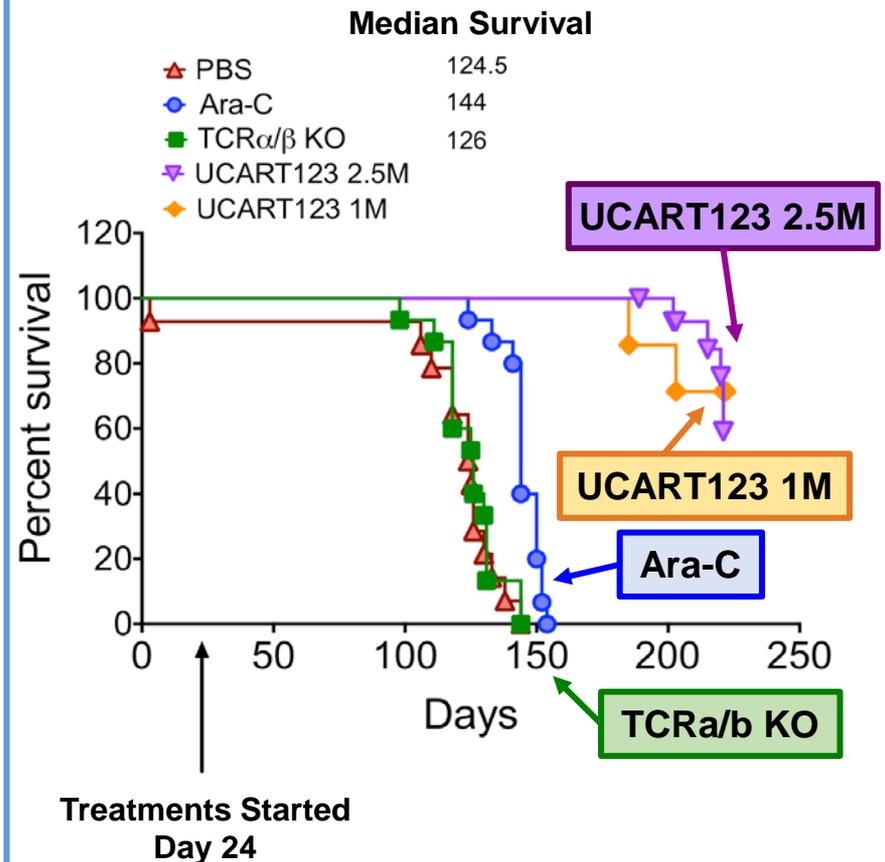
# UCART123 Cells Significantly Decrease Tumor Burden and Improve Overall Survival

## Peripheral Blood Evaluation



NPM1 mutant, FLT3-ITD+

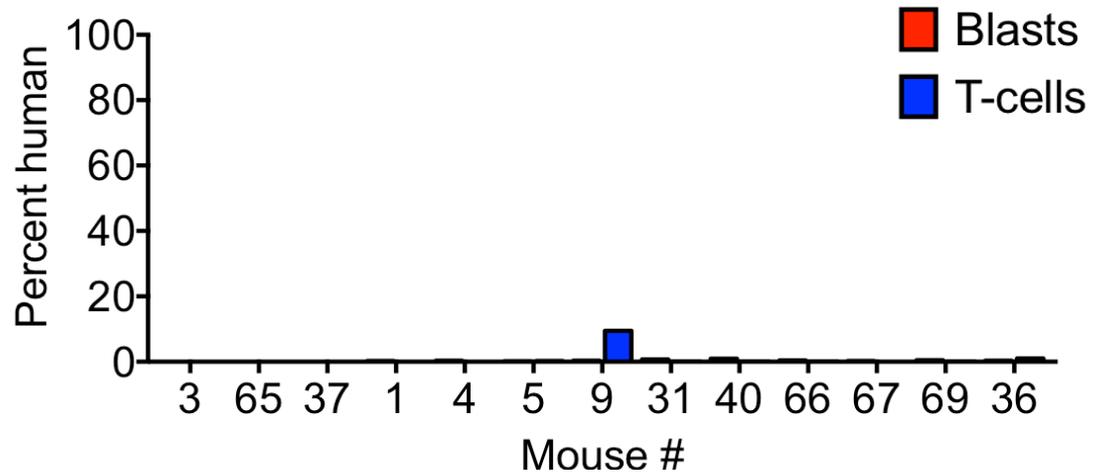
## Overall Survival



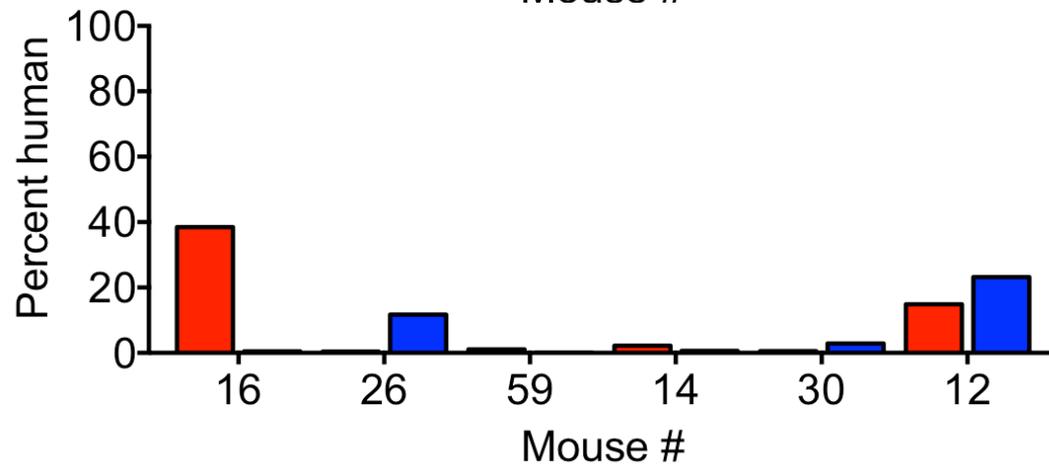
# The Majority of Mice were Disease Free

## Bone Marrow Day 221

**UCART123 2.5M**

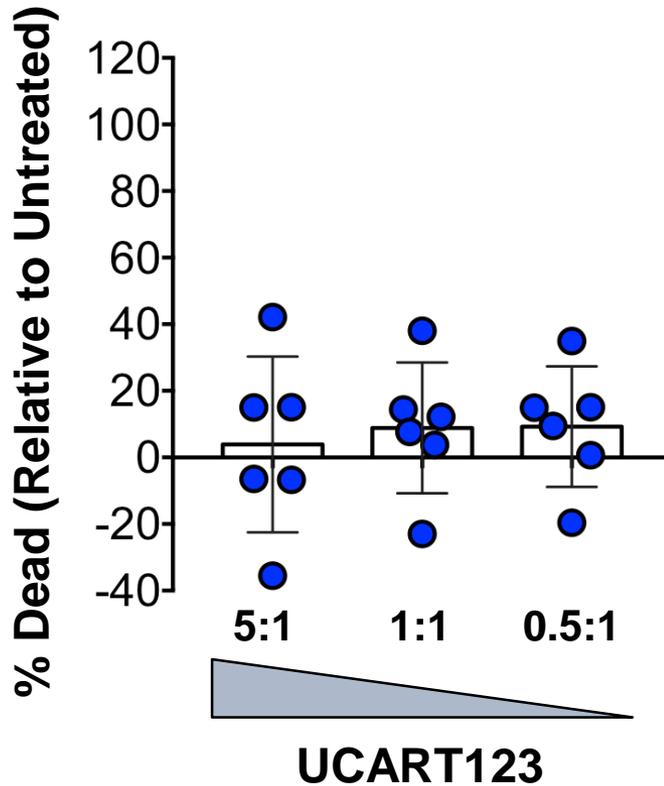


**UCART123 1M**

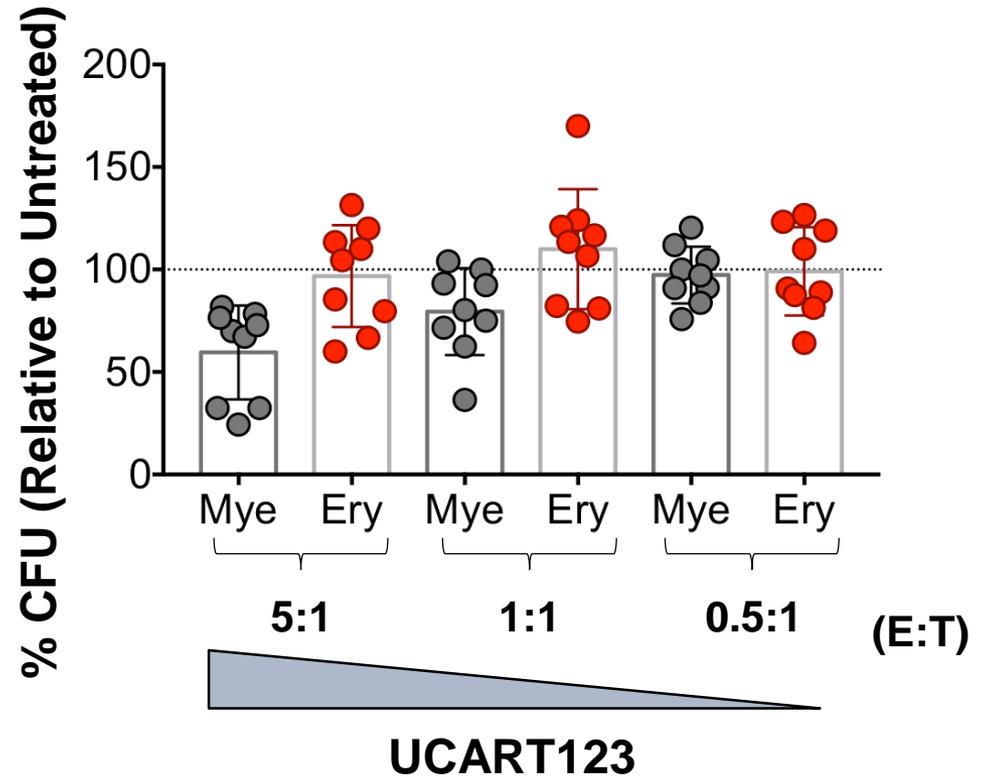


# UCART123 Has Minimal Toxicity Against Normal Hematopoietic Cells In Vitro

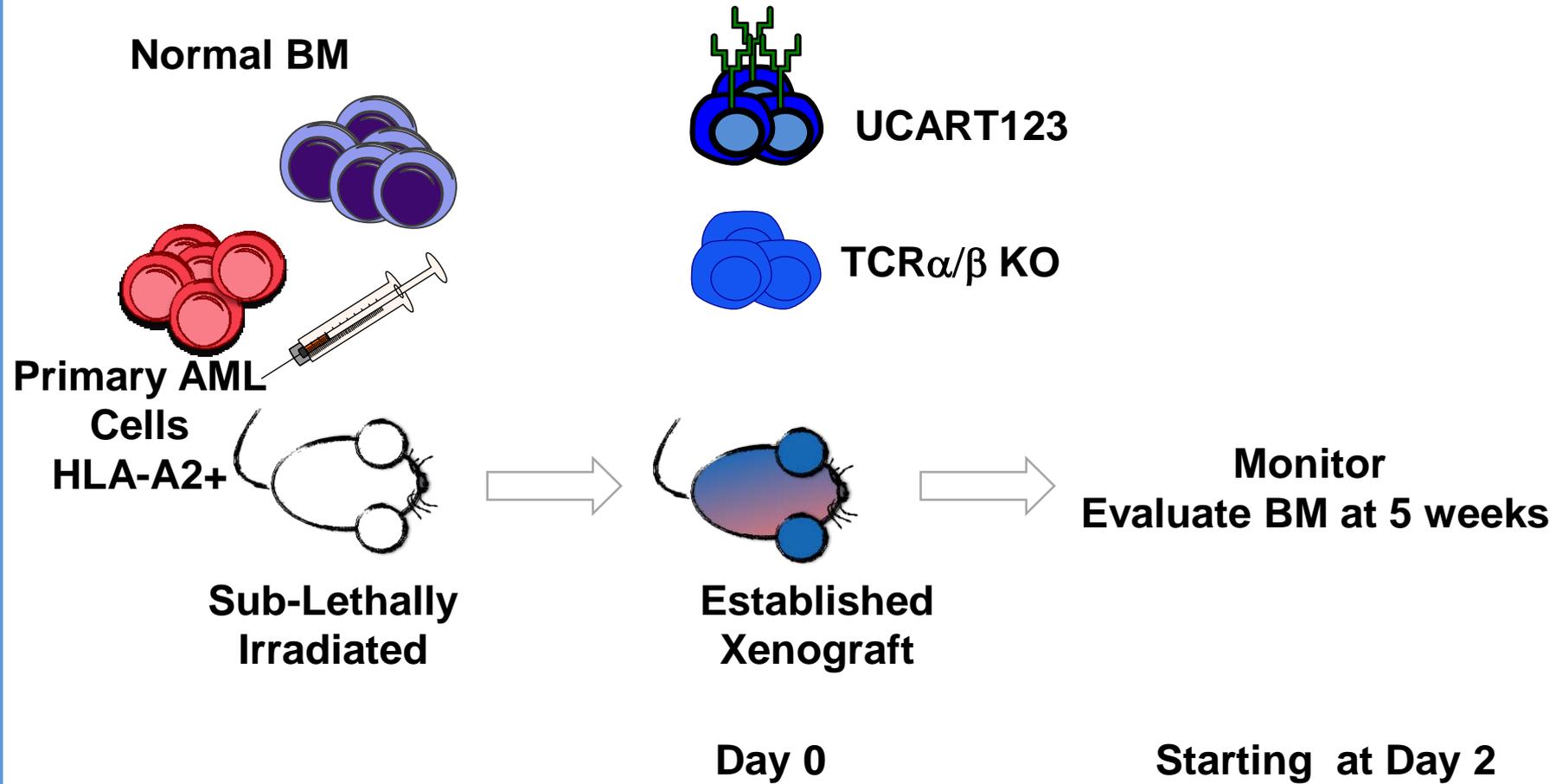
## Co-Cultured UCART123: Cord Blood



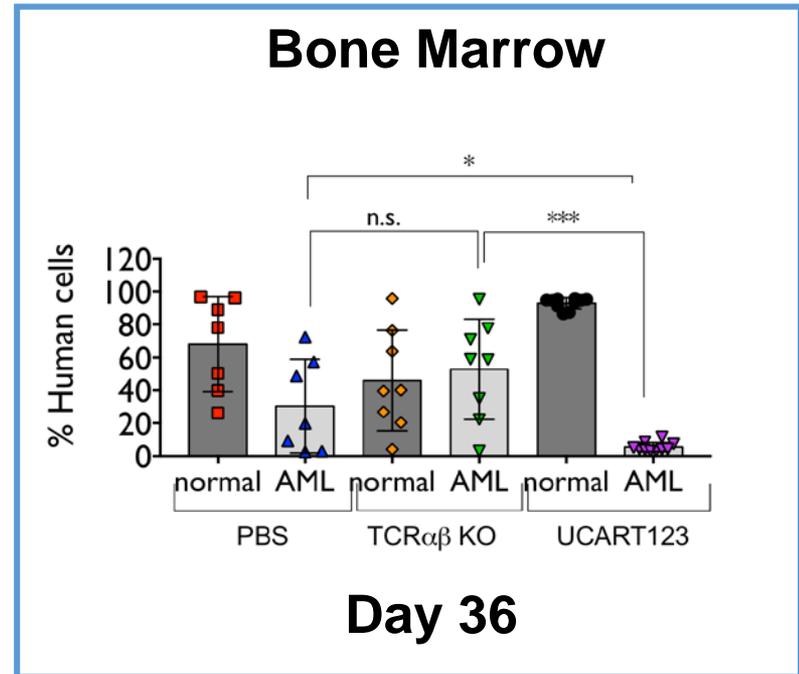
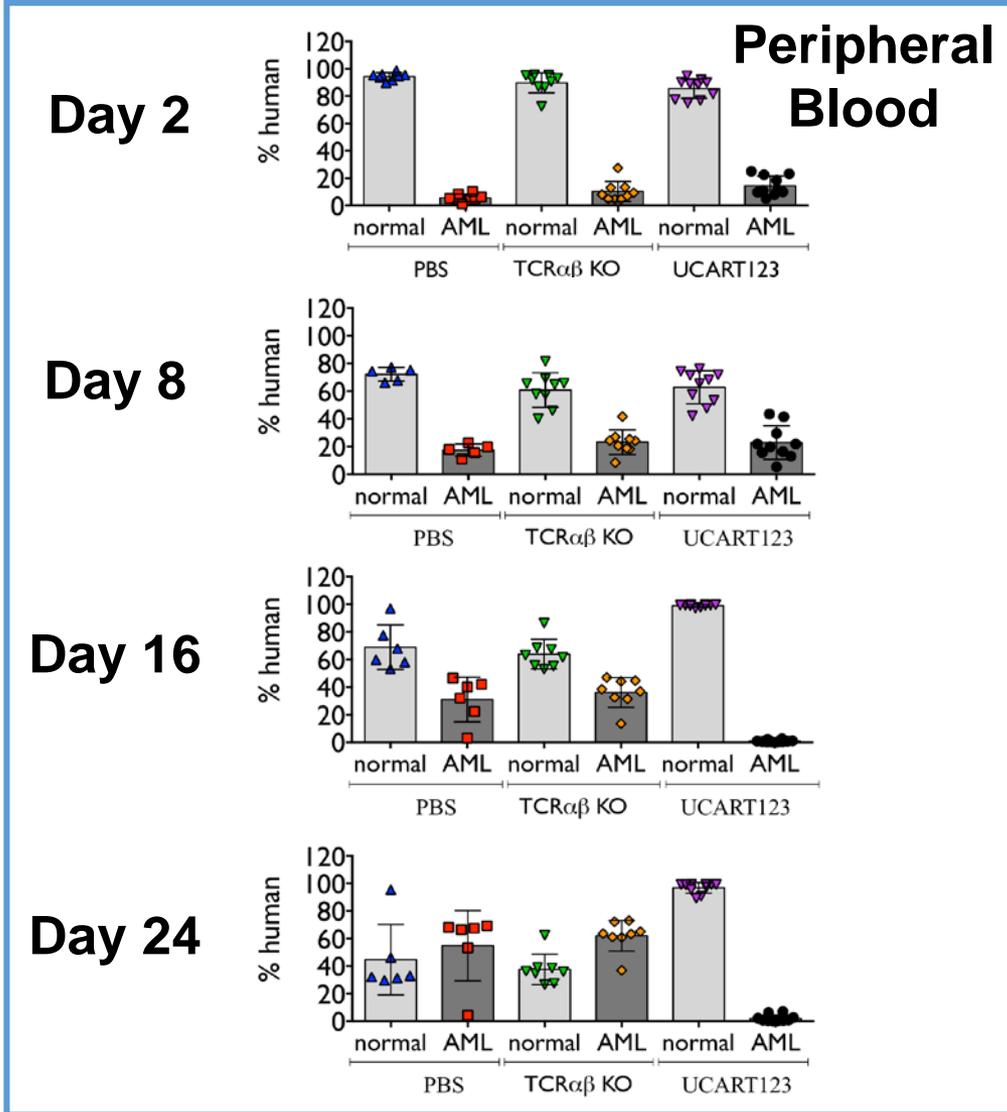
## Colony Forming Assays



# Competitive BM/AML Xenografts were Generated to Test In Vivo Selectivity of UCART123



# UCART123 Preferentially Eliminates AML Cells Over Normal Hematopoietic Cells



# Study Objectives

- **Primary Objectives**

- To assess the safety and tolerability of UCART123 in patients with relapsed/refractory AML
- To determine the Recommended Phase 2 Dose of UCART123

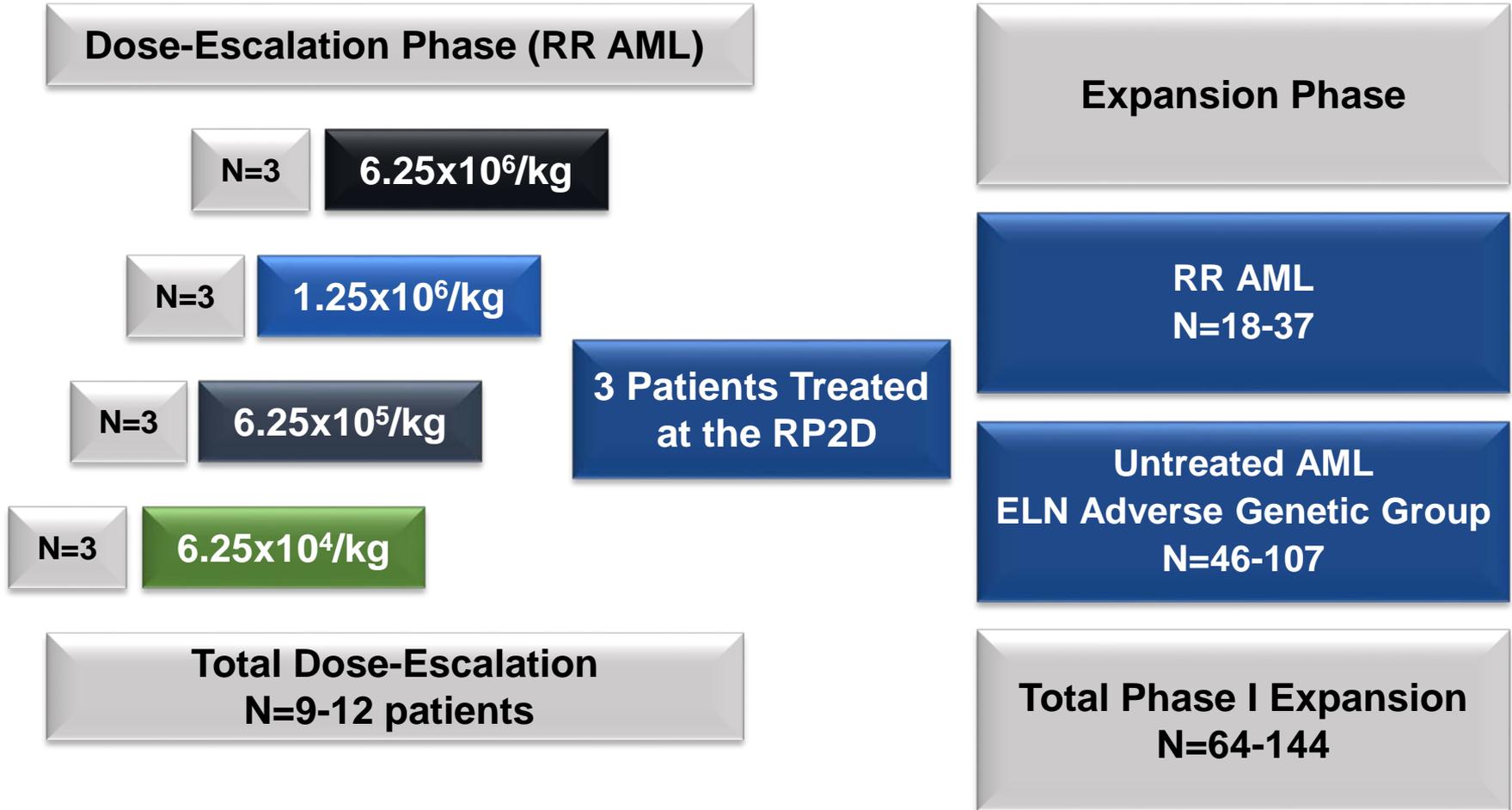
- **Secondary Objective**

- To assess the efficacy of UCART123 in relapsed or refractory AML patients and in newly diagnosed patients with high risk disease as measured by IWG response criteria (Cheson 2003)

# Exploratory Objectives

- Expansion, trafficking and persistence of UCART123 in blood and bone marrow
- Cytokine and CRP levels after UCART123 infusion
- UCART123 immune response
- Potential relationship between baseline CD123 expression and clinical outcome
- Impact of UCART123 on LSCs, HSCs and progenitor cells
- To confirm the absence of replication competent lentivirus (RCL)

# UCART123\_01: Study Design



# Inclusion Criteria: Dose-Escalation Phase

- Patients  $\geq 18$  and  $< 70$  years old with relapsed or primary refractory AML (WHO criteria)
- Must have an available donor for potential allogeneic HSCT (including matched related or unrelated donor, cord blood or haploidentical donor), in the event of persistent marrow aplasia without evidence of residual leukemia

# Inclusion Criteria: Dose-Expansion Phase

- **Relapsed/Refractory Cohort**

- Patients  $\geq 18$  and  $< 70$  years old with relapsed or primary refractory AML (WHO criteria)

- **Newly Diagnosed Cohort**

- Patients with newly diagnosed, untreated AML, ELN adverse risk

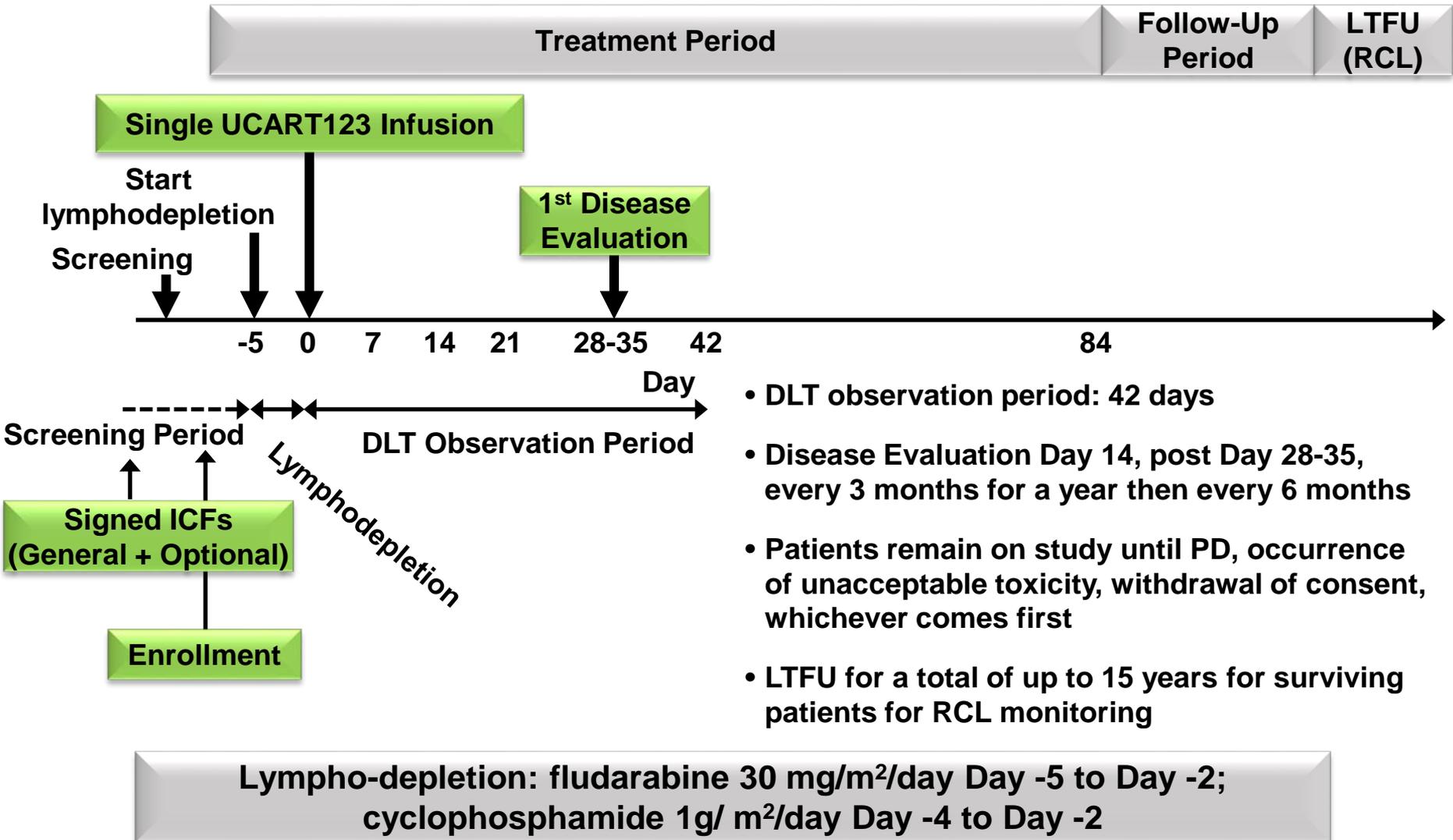
# Key Inclusion Criteria: All Patients

- CD123 expression by flow cytometry
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1
- Adequate organ function
- Adequate contraception
- Patients after hematopoietic stem cell transplantation (HSCT) if >6 weeks after HSCT, off immunosuppression and without evidence of active Graft-vs-Host Disease

# Key Exclusion Criteria

- Previous treatment with investigational gene therapy or chimeric antigen receptor therapy
- Acute Promyelocytic Leukemia
- Active central nervous system leukemia involvement
- Presence of active and clinically relevant CNS disorder
- Use of rituximab and other anti CD20 antibodies known to have the same epitope as rituximab or anti CD20 for which the epitope is unknown within 3 months prior to Screening
- Active treatment with steroids or other immunosuppressive agents that cannot be stopped
- Known infection with HIV or HTLV-1
- Presence of UCART123 donor-specific anti-HLA antibodies (DSA)

# Design



# Dose-Escalation Procedure

- 3 patients per cohort
- DLT observation period 42 days
- Patient enrollment timelines
- Dose Level 1: sequential enrollment
- Dose Levels 2 and 3: sequential and concurrent enrollment
- Dose escalation if 0/3 or 1/3 (33%) DLT at a dose level
- If DLT at any dose level in 2/3 patients: dose level immediately below to be expanded to 6 patients
- If at the lower dose 2/6 patients experience a DLT and no biological or clinical activity, the study will be stopped

## RP2D Definition

- The dose level of UCART123 judged safe and measured by reduction in bone marrow or peripheral blasts to  $\leq 50\%$  of baseline, or other evidence of clinical activity, will be expanded with three additional patients, in order to reach 6 patients to gain more information on safety and pharmacological activity of UCART123
- After 6 patients have been treated at a specific level, the confirmation of the recommended dose to be used at the expansion phase will be left to the decision of the Sponsor upon the recommendation of the DSMB

# Dose Limiting Toxicities (DLTs)

- **Cytokine-Release Syndrome:** Grade 5; Grade 4 that does not resolve to Grade  $\leq 2$  within 72 hours; Grade 3 that does not resolve to Grade  $\leq 2$  within 2 weeks
- **Tumor Lysis Syndrome:** Grade  $\geq 4$  that does not resolve within 7 days and/or with organ damage despite optimal treatment
- **Acute Graft-vs-Host Disease:** Grade  $\geq 3$
- **Aplastic Bone Marrow:** Defined by marrow cellularity  $< 5\%$  in the absence of residual AML
- **Central Neurologic Toxicity:** Grade  $\geq 3$  lasting more than 2 weeks
- **Infusion-Related Reactions:** Grade 5
- **Capillary Leak Syndrome:** Grade  $\geq 3$  that does not resolve to Grade  $\leq 2$  within 72 hours
- **Any Clinically Significant Grade  $\geq 3$  Non-Hematological Toxicity:** Not attributable to another clearly identifiable cause and not recovering within 2 weeks
- **Any Other Unacceptable Toxicity:** Per investigator or DSMB

# Dose Expansion Phase

- Up to 144 patients to be enrolled and treated at the dose of UCART123 judged safe by the DSMB and at which some evidence of biological and/or clinical activity was observed.
- **Cohort A:** patients  $\geq 18$  years old with relapsed or primary refractory
- **Cohort B:** patients with newly diagnosed, untreated AML with ELN adverse risk genetics
- Study will be stopped if non-hematological toxicities exceed 30% of patients and/or if there are other safety concerns expressed by the investigators and/or DSMB

# Risks

- Expected toxicities of AML standard treatment
- Cytokine-Release Syndrome (CRS)
- Tumor Lysis Syndrome (TLS)
- Neurologic toxicities
- Off-target toxicity (HSCs, endothelial cells)
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- Acute Graft-vs-Host disease new consensus criteria (Harris et al., 2016)
- DSMB oversight

# Efficacy Assessments

- Revised IWG-AML (Cheson 2003) to be used for assessment of disease response
- Bone marrow aspirate and biopsy
  - Screening
  - Day 14
  - Day 28-Day 35 post infusion
  - Every 3 months for one year from Day 84
  - Every 6 months for two years

*Thank you for  
your attention.*