ZIOPHARM Oncology

A Biopharmaceutical Company Focused on Controlled Immunotherapies and Point-of-Care Solutions

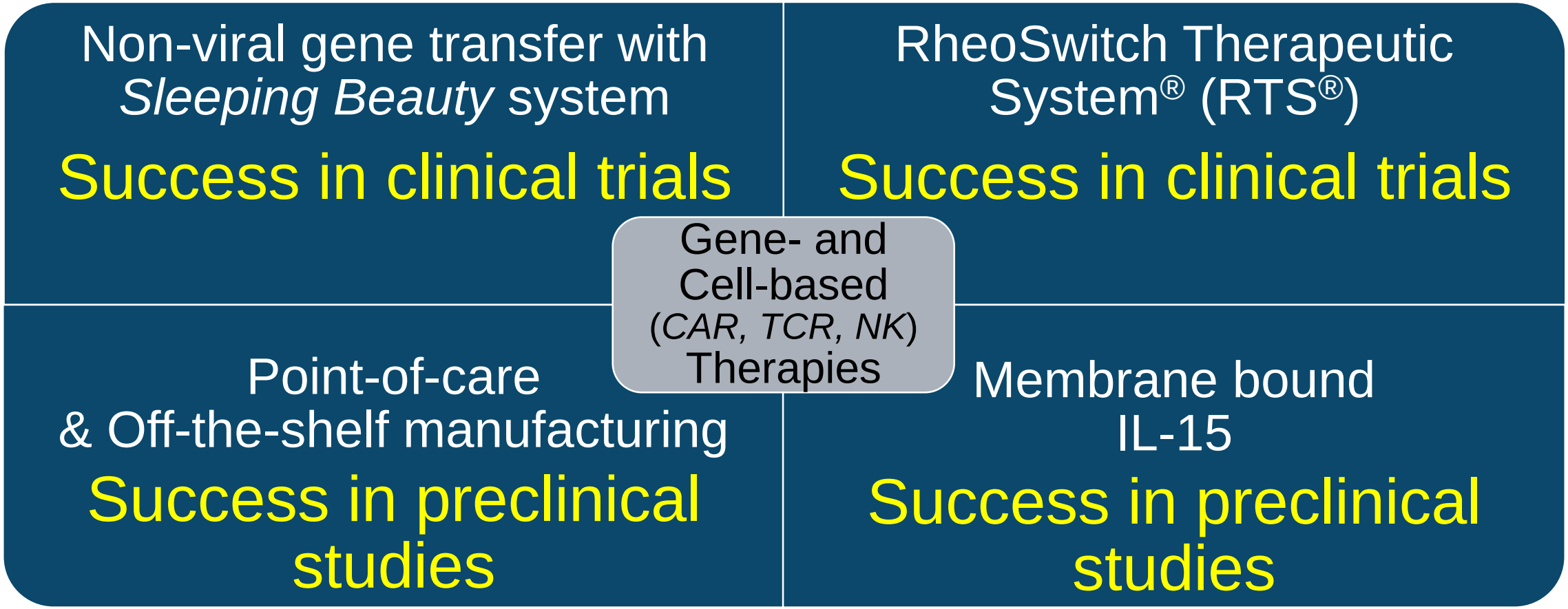
Second Quarter 2017 Company Update and Financial Results

July 31, 2017

Forward-Looking Statements

This presentation contains certain forward-looking information about ZIOPHARM Oncology, Inc. that is intended to be covered by the safe harbor for "forward-looking statements" provided by the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts, and in some cases can be identified by terms such as "may," "will," "could," "expects," "plans," "anticipates," and "believes." These statements include, but are not limited to, statements regarding the progress, timing and results of preclinical and clinical trials involving the Company's drug candidates, and the progress of the Company's research and development programs. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of the Company, that could cause actual results to differ materially from those expressed in, or implied by, the forward-looking statements. These risks and uncertainties include, but are not limited to: whether chimeric antigen receptor T cell (CAR^+ T) approaches, Ad-RTS-IL-12, TCR and NK cell-based therapies, or any of our other therapeutic candidates will advance further in the preclinical or clinical trials process and whether and when, if at all, they will receive final approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies and for which indications; whether chimeric antigen receptor T cell (CAR^+ T) approaches, Ad-RTS-IL-12, TCR and NK cell-based therapies, and our other therapeutic products will be successfully marketed if approved; the strength and enforceability of our intellectual property rights; competition from other pharmaceutical and biotechnology companies; and the other risk factors contained in our periodic and interim SEC reports filed from time to time with the Securities and Exchange Commission, including but not limited to, our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2017. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we do not undertake any obligation to revise and disseminate forward-looking statements to reflect events or circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.

What Has ZIOPHARM Accomplished to Succeed?



Progressing Point-of-Care With CD19-Specific CAR+ T cells

Implementing point-of-care (P-O-C)

1st generation complete

Survival rates doubled in comparison with historical controls for patients with NHL and ALL

Downloaded from http://www.jci.org on August 4, 2016. http://dx.doi.org/10.1172/JCI86721

The Journal of Clinical Investigation — CLINICAL MEDICINE

Phase I trials using *Sleeping Beauty* to generate CD19-specific CAR T cells

Partow Kebriaei,[1] Harjeet Singh,[2] M. Helen Huls,[2] Matthew J. Figliola,[2] Roland Bassett,[3] Simon Olivares,[2] Bipulendu Jena,[2] Margaret J. Dawson,[2] Pappanaicken R. Kumaresan,[2] Shihuang Su,[2] Sourindra Maiti,[2] Jianliang Dai,[2] Brandon Moriarity,[4] Marie-Andrée Forget,[1,5] Vladimir Senyukov,[1] Aaron Orozco,[1] Tingting Liu,[1] Jessica McCarty,[1] Rineka N. Jackson,[1] Judy S. Moyes,[1] Gabriela Rondon,[1] Muzaffar Qazilbash,[1] Stefan Ciurea,[1] Amin Alousi,[1] Yago Nieto,[1] Katy Rezvani,[1] David Marin,[1] Uday Popat,[1] Chitra Hosing,[1] Elizabeth J. Shpall,[1] Hagop Kantarjian,[1] Michael Keating,[1] William Wierda,[1] Kim Anh Do,[3] David A. Largaespada,[4] Dean A. Lee,[1,2] Perry B. Hackett,[4] Richard E. Champlin,[1] and Laurence J.N. Cooper[1,2]

[1]Department of Stem Cell Transplantation and Cellular Therapy, Division of Cancer Medicine, [2]Division of Pediatrics, and [3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA. [4]Center for Genome Engineering, The University of Minnesota, Minneapolis, Minnesota, USA. [5]Department of Melanoma and [6]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA. [7]The University of Texas Graduate School of Biomedical Sciences, Houston, Texas, USA.

BACKGROUND. T cells expressing antigen-specific chimeric antigen receptors (CARs) improve outcomes for CD19-expressing B cell malignancies. We evaluated a human application of T cells that were genetically modified using the *Sleeping Beauty* (SB) transposon/transposase system to express a CD19-specific CAR.

METHODS. T cells were genetically modified using DNA plasmids from the SB platform to stably express a second-generation CD19-specific CAR and selectively propagated ex vivo with activating and propagating cells (AaPCs) and cytokines. Twenty-six patients with advanced non-Hodgkin lymphoma and acute lymphoblastic leukemia safely underwent hematopoietic stem cell transplantation (HSCT) and infusion of CAR T cells as adjuvant therapy in the autologous (*n* = 7) or allogeneic settings (*n* = 19).

RESULTS. SB-mediated genetic transposition and stimulation resulted in 2,200- to 2,500-fold ex vivo expansion of genetically modified T cells, with 84% CAR expression, and without integration hotspots. Following autologous HSCT, the 30-month progression-free and overall survivals were 83% and 100%, respectively. After allogeneic HSCT, the respective 12-month rates were 53% and 63%. No acute or late toxicities and no exacerbation of graft-versus-host disease were observed. Despite a low antigen burden and unsupportive recipient cytokine environment, CAR T cells persisted for an average of 201 days for autologous recipients and 51 days for allogeneic recipients.

CONCLUSIONS. CD19-specific CAR T cells generated with SB and AaPC platforms were safe, and may provide additional cancer control as planned infusions after HSCT. These results support further clinical development of this nonviral gene therapy approach.

TRIAL REGISTRATION. Autologous, NCT00968760; allogeneic, NCT01497184; long-term follow-up, NCT01492036.

FUNDING. National Cancer Institute, private foundations, and institutional funds. Please see Acknowledgments for details.

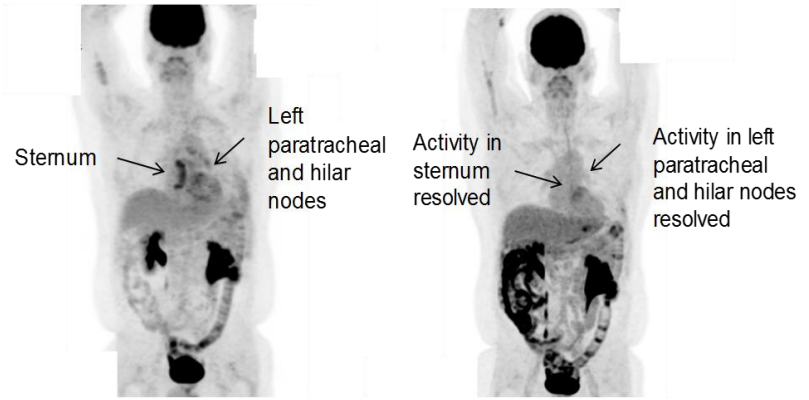
J Clin Invest. 2016 Sep 1;126(9):3363-76.

2nd generation ongoing

Shortening manufacturing process time from 4 weeks to ~2 weeks

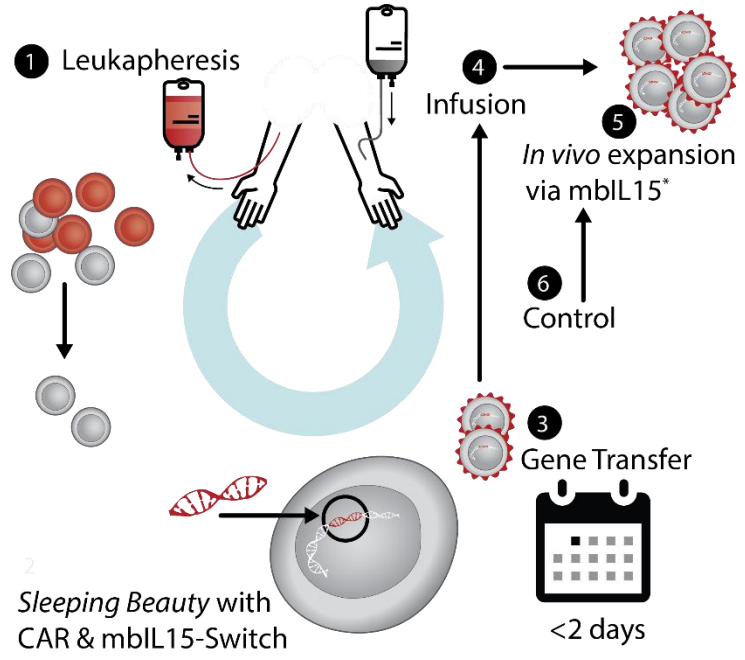
PET-CT Day -8: Extramedullary ALL

PET-CT Day 48: Extramedullary ALL resolved



Six-month CR (*e.g.*, 3-stim, 23-day manufacturing) with multiple-relapsed ALL after lymphodepleting chemotherapy

3rd generation ongoing: CAR+ mbIL15+Switch+ T cells in <2 days



*Membrane bound IL-15 (mbIL15)

Proc Natl Acad Sci U S A. 2016 Nov 29;113(48):E7788-E7797 & ASH 2016 Publication #2807

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CD19-Specific CAR+ T cells

Implementing point-of-care (P-O-C)

1st generation complete

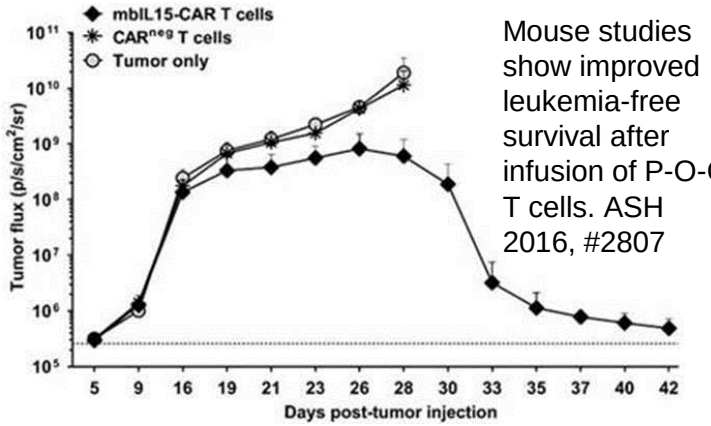
Update on long-term survivors and persistence of CAR+ T cells at upcoming meeting(s)

2nd generation ongoing

Update on patient responses and persistence of CAR+ T cells at upcoming meeting(s)

3rd generation ongoing: CAR+ mbIL15+Switch+ T cells in <2 days

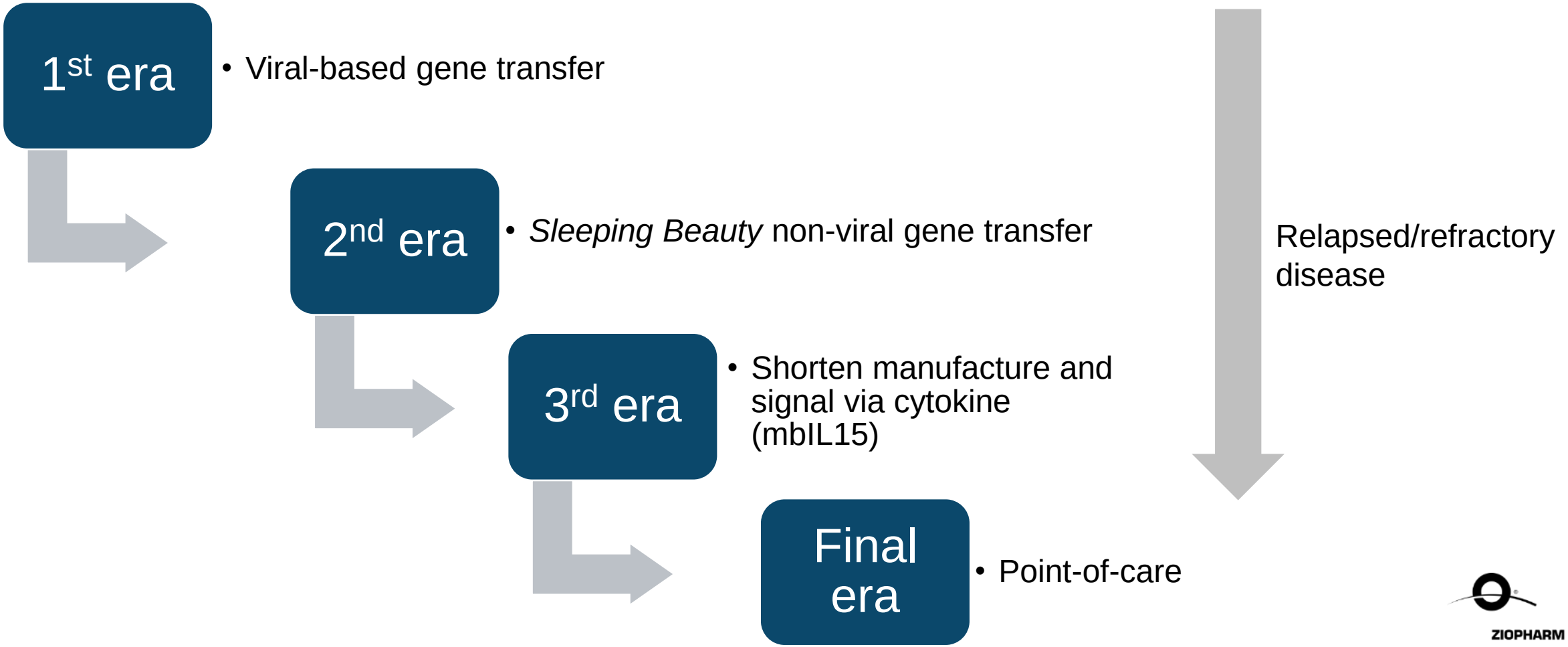
Progressing; data continues to be encouraging



Mouse studies show improved leukemia-free survival after infusion of P-O-C T cells. ASH 2016, #2807

CAR+ T cells for CD19+ Malignancies

Potential of very rapid manufacture under point-of-care (P-O-C)



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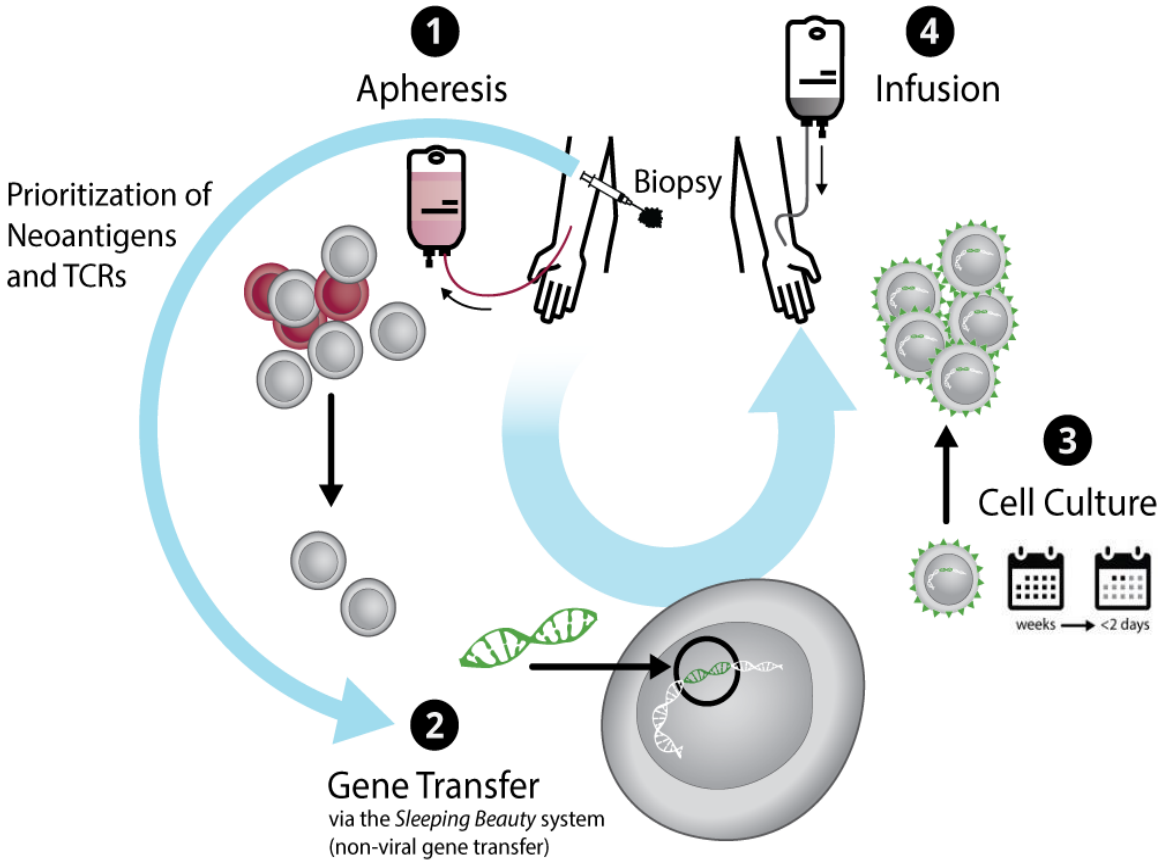
Targeting Neoantigens in Solid Tumors Using *Sleeping Beauty*



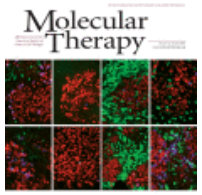
January 2017

ZIOPHARM and Intrexon Announce CRADA with National Cancer Institute (NCI) Utilizing *Sleeping Beauty* System to Generate T cells Targeting Neoantigens

June 2016

Stable, Nonviral Expression of Mutated Tumor Neoantigen-specific T-cell Receptors Using the *Sleeping Beauty* Transposon/Transposase System

Drew C Deniger[1], Anna Pasetto[1], Eric Tran[1], Maria R Parkhurst[1], Cyrille J Cohen[2], Paul F Robbins[1], Laurence JN Cooper[3,4] and Steven A Rosenberg[1]



January 2016

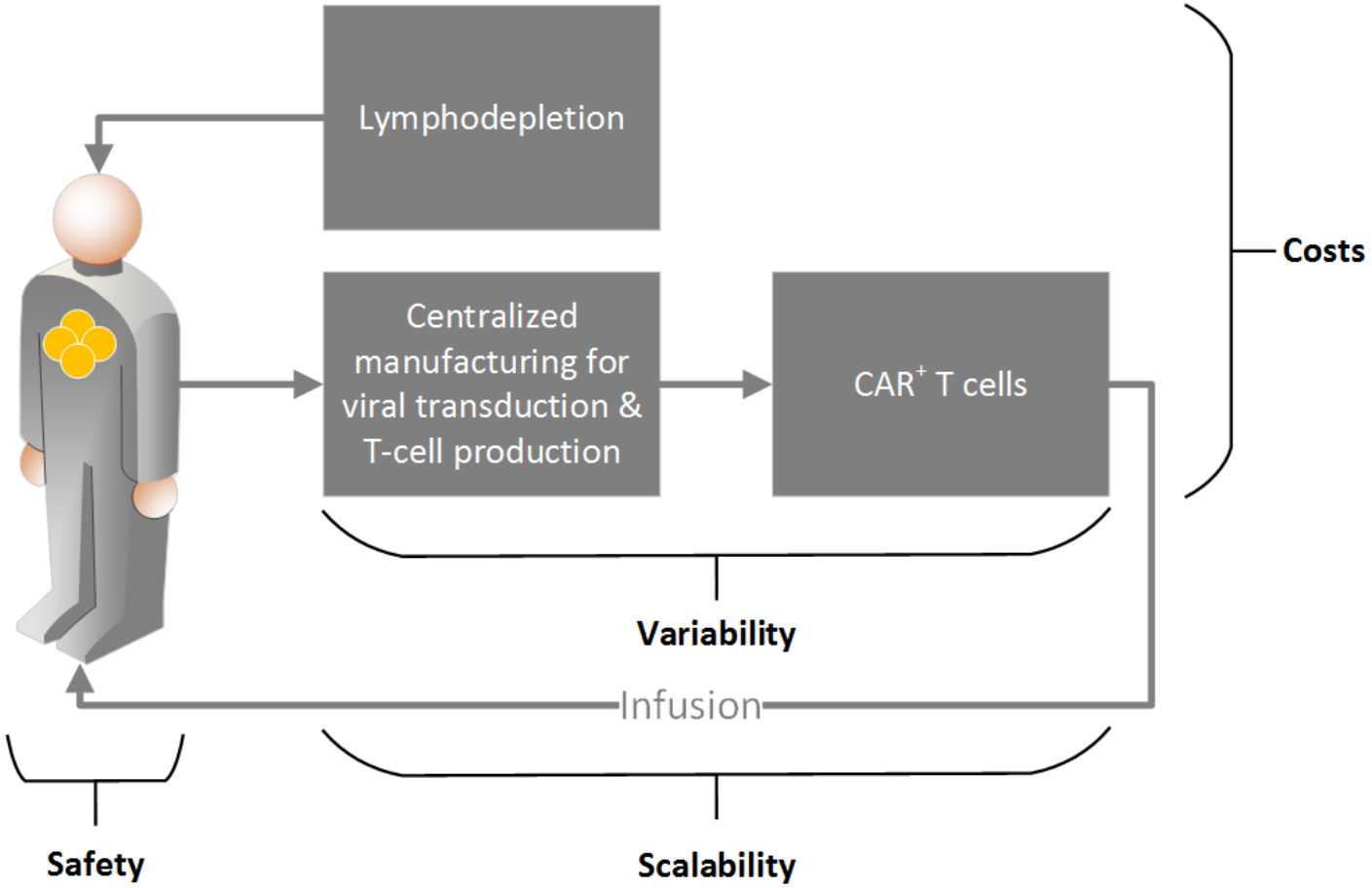
Prospects for gene-engineered T cell immunotherapy for solid cancers

Christopher A Klebanoff, Steven A Rosenberg & Nicholas P Restifo

Nat Med. 2016 Jan;22(1):26-36;
Mol Ther. 2016 Jun;24(6):1078-89.

Summary: Commercializing Genetically Modified T cells

Competitors



Point-of-care solutions

- Reduce concerns regarding heterogeneity to improve reliability and regulatory compliance
- Major reduction in costs
- Improve scalability to meet demands
- Rapidly deliver T-cell therapeutics, when the patient needs them rather than when they are available
- Improve safety enabling broad acceptance and delivery
- Avoid lymphodepletion
- Target solid tumors with TCR+ T cells

Building Upon Targets

AML

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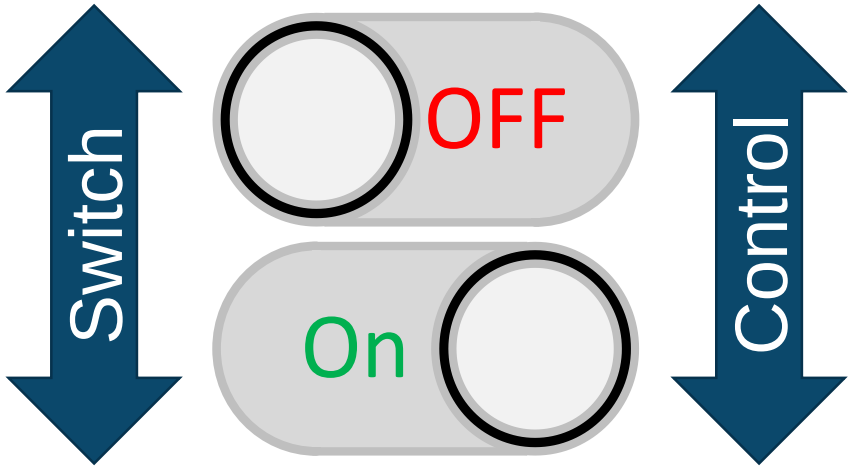
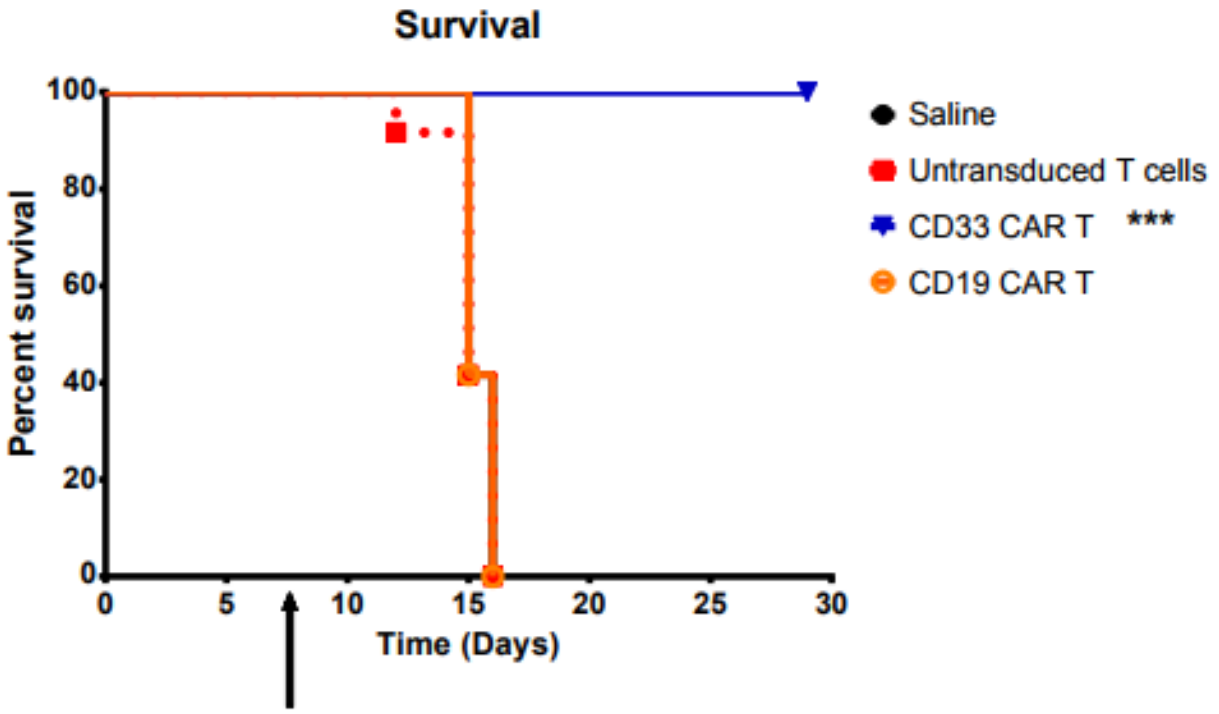
Targeting Unmet Needs in Acute Myeloid Leukemia (AML)

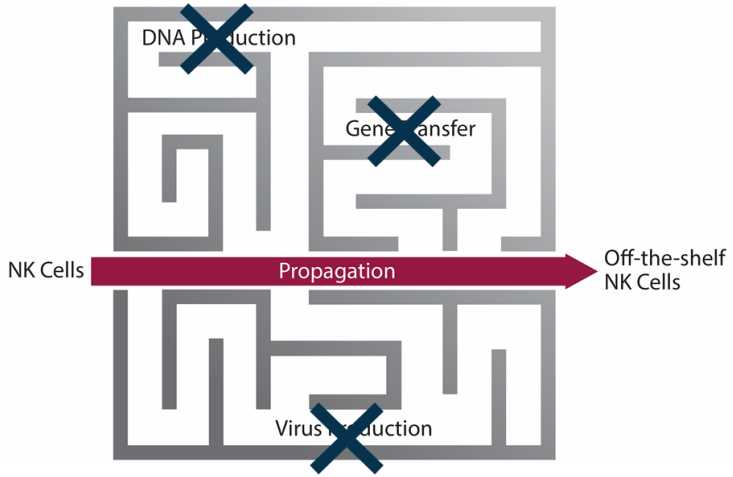


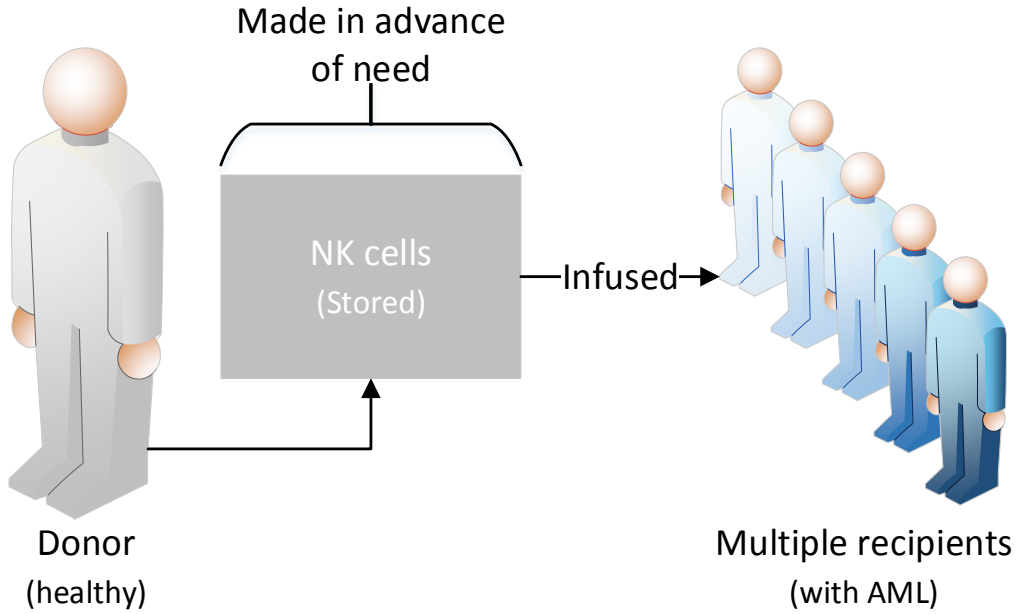
Control: CD33 CAR+ T program for Relapsed/Refractory AML

- Establish CD33 as a target for CAR+ T cells
- Employs lentivirus and kill switch technology
- Adult and pediatric relapsed/refractory AML
- Open Q3 2017



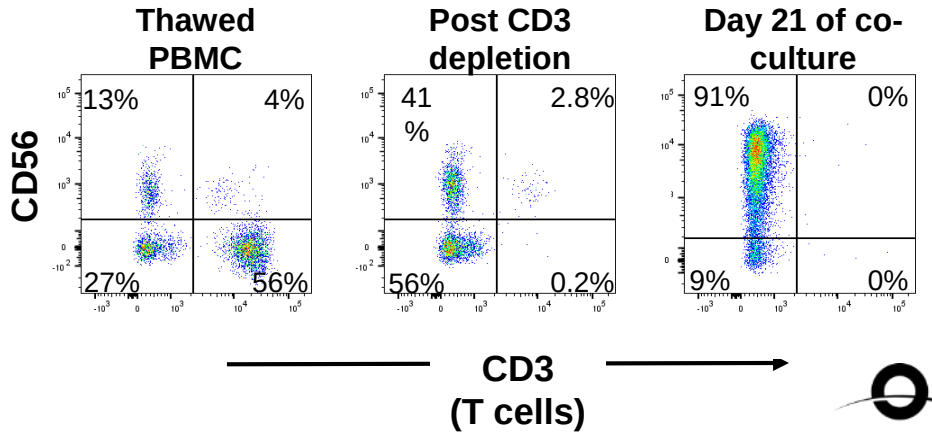
Targeting Unmet Needs in Acute Myeloid Leukemia (AML)





Cost: Off-the-shelf (O-T-S) primary NK cells for AML in elderly patients not eligible for standard intensive chemotherapy

- Establish NK as platform for O-T-S therapeutics
- NK cells lack TCR, thus well-suited for O-T-S therapy
- NK cells propagated on feeder cells expressing IL-21
- Open Q4 2017



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Advancing to Pivotal Trial

Ad-RTS-hIL-12 + Veledimex

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Multicenter Phase 1 Recurrent Glioblastoma (rGBM) Study Designed to Control IL-12 via RheoSwitch Therapeutic System® (RTS®) Gene Switch

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

CEDARS-SINAI

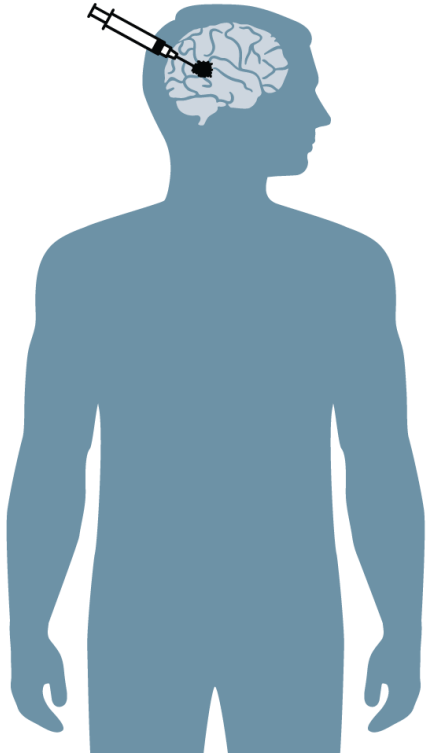
THE UNIVERSITY OF CHICAGO PRITZKER SCHOOL OF MEDICINE

UCSF

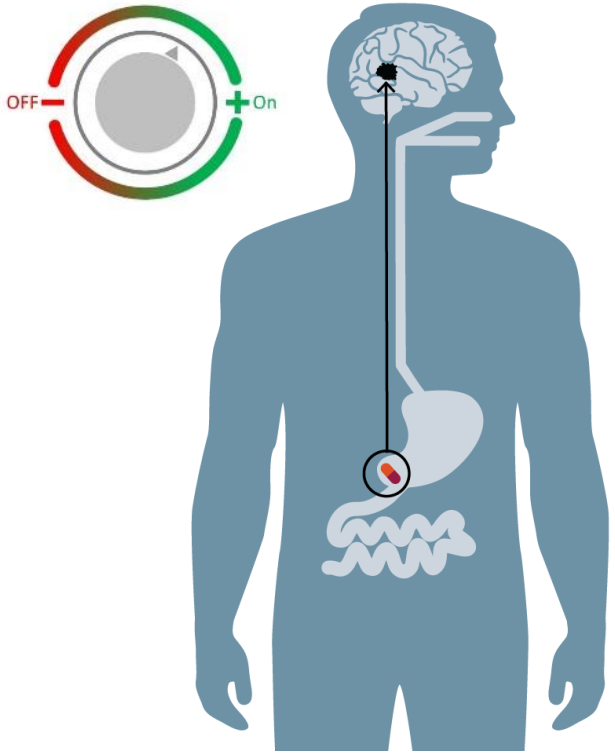
Northwestern Memorial Hospital

	Group 1: Ad 2X10^{11} vp			
	20 mg V Cohort (N=15)	30 mg Cohort (N=4)	40 mg Cohort (N=6)	Total (N=25)
Age in years Mean (Min, Max)	46 (26, 68)	60 (43, 74)	48 (36, 58)	49 (26, 74)
Recurrence (n) 1st 2nd 3rd or more	 4 5 6	 1 2 1	 2 2 2	 7 9 9
Prior Lines of Treatment (mean)	2.2	3.0	2.5	2.4
KPS at Screening ≥ 90 ≥ 70 and < 90	 9 6	 3 1	 2 4	 14 11
Veledimex Dosing Compliance	84%	63%	58%	73%

Intratumoral injection of Ad-RTS-hIL-12



14 days of veledimex taken by mouth



*As reported at ASCO 2017

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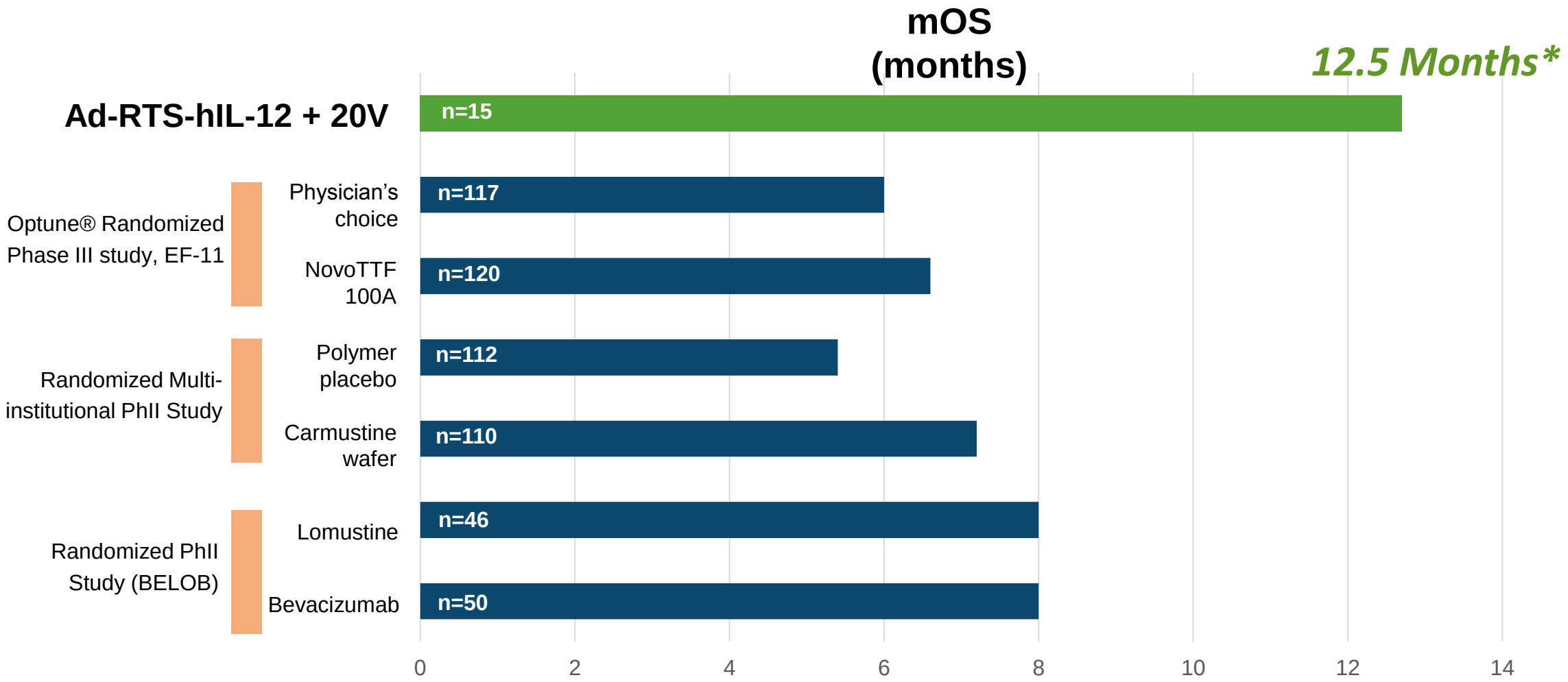
Compelling Interim Median Overall Survival (mOS) Relative to Historical Controls



* mOS is at 12.5 months with a mean follow up of 9.2 months; 6 of 15 subjects alive at 20 mg veledimex as of ASCO 2017

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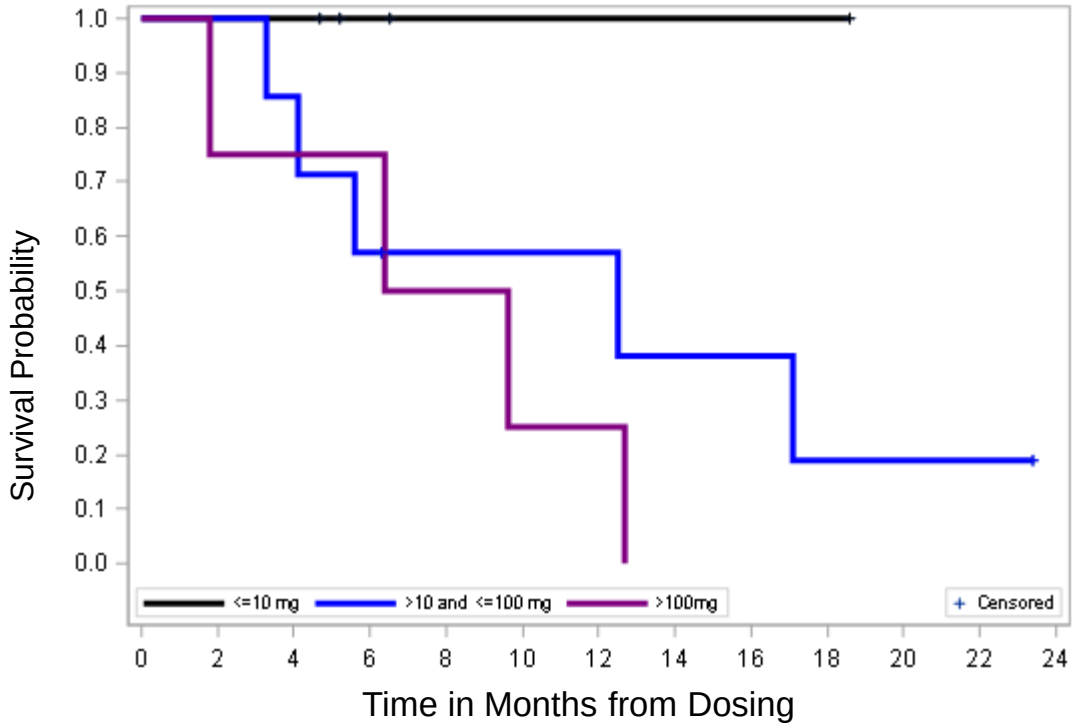
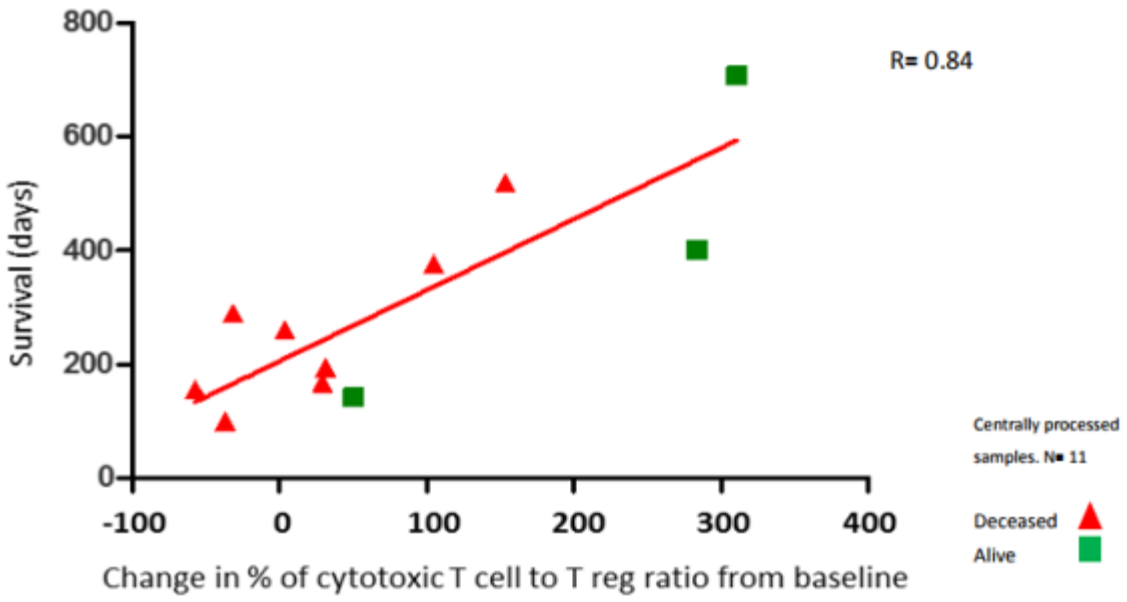
Correlation with Cellular Immune Activation and Concurrent Systemic Steroid Use

Dexamethasone Impact on Survival at 20 mg Veledimex



Peripheral Blood CD8+/FOXP3 Ratio at 14-28 Days After Viral Injection Suggests Correlation with Survival



Dexamethasone Use (Days 0-14)	Alive	Deceased	mOS	Lower bound	Upper bound
≤10 mg	4	0	Not reached	Not reached	Not reached
11-99 mg	2	5	12.5	3.3	Not reached
≥100 mg	0	4	8.0	1.8	12.7

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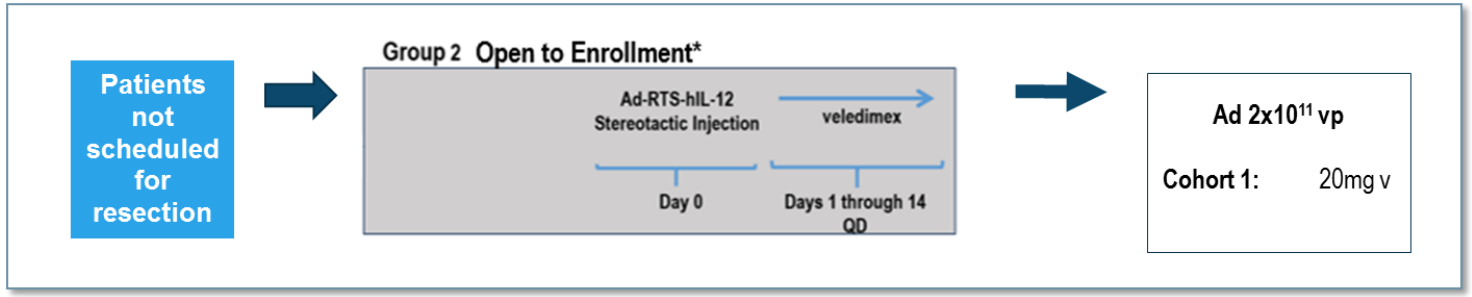
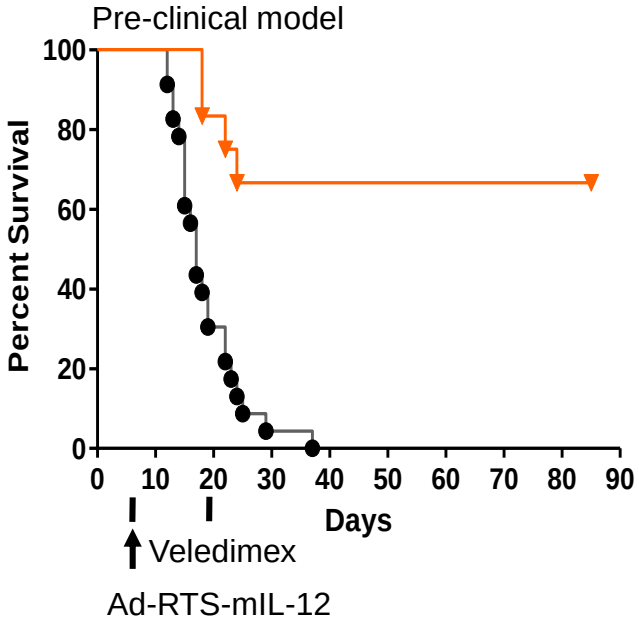
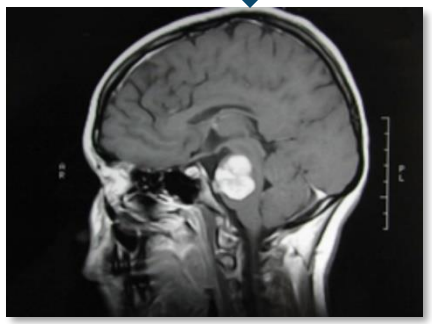
Enrollment in Stereotactic Arm Underway: Lead-in to Pediatric & Anti-PD-1 Studies



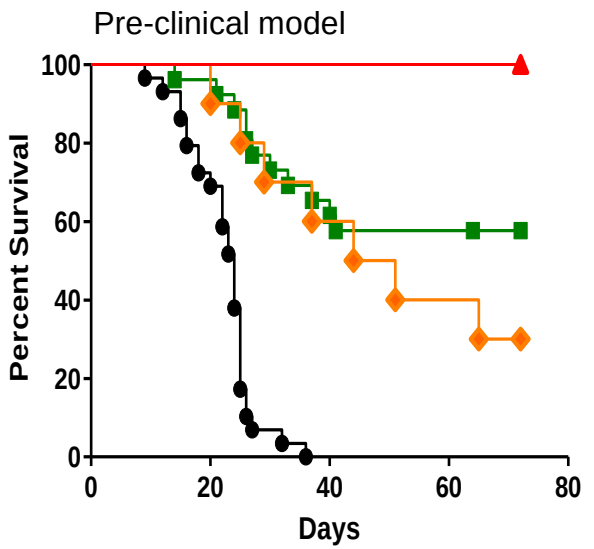
Pontine Glioma



e.g. for



Anti-PD-1 Combination



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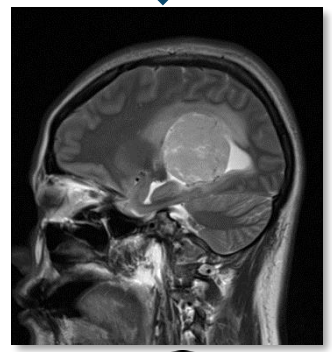

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Updated Phase 1 Results and Plans

Phase 1 results

RTS® gene switch

- Veledimex regulates IL-12 in a dose-related manner
- Strong correlation between veledimex, BBB penetration, IL-12 and IFN-γ

Safety

- Related AEs were tolerable, predictable, and rapidly reversed upon discontinuing veledimex
- No drug-related deaths

Efficacy

- Survival appears to correlate with cellular immune activation
- Low dose steroids improves survival benefit
- mOS at 20 mg of veledimex at 12.5 months* and continues to compare favorably to historical controls

Next steps

Clinical

- Updated data (clinical and non-clinical) at SNO 2017
- Enrolling stereotactic group; runway to pediatric monotherapy and combination therapy with anti-PD-1

Regulatory

- Assessing protocol design options for pivotal trial, including the potential for a single-arm study comparing Ad-RTS-hIL-12 + veledimex to historical controls in a subpopulation of patients with rGBM
- Details of pivotal trial after completion of discussions with clinical advisors and regulators

Strategic opportunity

- Evaluating partnership opportunities with goal of commercialization

*As reported at ASCO 2017

Financials and Summary

2017 Outlook

ZIOPHARM Oncology

Select Second Quarter 2017 Financial Results and Cash Outlook

- Basic and diluted net loss per share: $(0.13)
- General and Administrative Expense: $3.8M
- Research & Development Expense: $10.8M
- Shares outstanding: ~142M as of July 24, 2017
- Unrestricted Cash Resources: $97.2M
  - In addition, approximately $27.3M in cash on hand at MD Anderson Cancer Center for programs to be conducted at MD Anderson Cancer Center under the current Research and Development Agreement
- Capitalization
  - Cash runway into 4Q’18

Addressing Unmet Medical Needs

Target		Indication	Preclinical	Phase 1	Phase 2	Pivotal
Ad-RTS-hIL-12	Multicenter	GBM				
		GBM Stereotactic Treatment				
		Pediatric Brain Tumor				
		GBM & Checkpoint (anti-PD-1)				
		Combination with OTS NK cells				
CAR	CD19 2nd Gen. shortened manufacture	Leukemia/Lymphoma				**MDACC**
	CD19 3rd Gen CAR with mbIL15 (P-O-C)	Leukemia/Lymphoma				**MDACC**
	CD33	AML				**MDACC**
	Merck Target 1	Undisclosed				
	Merck Target 2	Undisclosed				
	P-O-C	Hematologic				
NK Cells	O-T-S primary NK Cells	AML				**MDACC**
	Generically engineered	TBD				
TCR	*Sleeping Beauty* neoantigen	TBD				**NCI**
	Sleeping Beauty neoantigen and cytokine	TBD				
Other	Regulatory T Cells	GvHD				
	Modified Bacteria (microbiome)	GvHD				

P-O-C = point-of-care
O-T-S = off-the-shelf

2H 2017 **2018**

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ZIOPHARM Competitive Advantages

- **Point-of-Care for CAR and TCR**
  - Clinically validated *Sleeping Beauty* platform has potential to allow <2 days manufacture for human application
  - Decrease cost and increase control of genetically modified T cells
- **RTS® Gene Switch**
  - First switch to demonstrate cytokine genetic control in the clinic
  - Ad-RTS-hIL-12 + veledimex proceeding to pivotal trial
  - Harness RTS® in T cells after infusion to customize mbIL15 expression using veledimex
- **Solid Tumors**
  - Target neoantigens via *Sleeping Beauty* platform
- **Off-the-Shelf**
  - Primary NK-cell platform

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