PRECISION BIOSCIENCES

Dedicated to Improving Life.

ASH 2019 Investigator Update

December 9, 2019
Orlando, FL

Overcome cancer.
Cure genetic disease.
Feed the planet.

Forward Looking Statements

This presentation (together with any other statements or information that we may make in connection herewith) may contain forward-looking statements. All statements other than statements of present and historical facts contained in this prospectus, including without limitation, statements regarding our future results of operations and financial position, business strategy and approach, including related results, prospective products, planned preclinical or greenhouse studies and clinical or field trials, regulatory approvals, research and development costs, the status and results of our preclinical and clinical studies, expected release of interim data, planned explorations following completion of initial clinical studies, capabilities of our manufacturing facility, management's expectations regarding near-term value catalysts, expectations for data to be presented at the ASH annual meeting, and timing, expected results and likelihood of success, as well as plans and objectives of management for future operations, may be forward-looking statements. Without limiting the foregoing, the words "anticipate," "believe," "could," "expect," "should," "plan," "intend," "estimate," "target," "may," "will," "would," "potential," the negative thereof and similar words and expressions are intended to identify forward-looking statements. These forward-looking statements reflect various assumptions of Precision's management that may or may not prove to be correct. No forward-looking statement is a guarantee of future results, performance, or achievements, and one should avoid placing undue reliance on such statements.

Forward-looking statements are based on our management's beliefs and assumptions and on information currently available to us. Such statements are subject to a number of known and unknown risks, uncertainties and assumptions, and actual results may differ materially from those expressed or implied in the forward-looking statements due to various factors, including, but not limited to, our ability to become profitable; our ability to procure sufficient funding; our limited operating history; our ability to identify, develop and commercialize our product candidates; our dependence on our ARCUS technology; the initiation, cost, timing, progress and results of research and development activities, preclinical or greenhouse studies and clinical or field trials; our or our collaborators' ability to identify, develop and commercialize product candidates; our or our collaborators' ability to advance product candidates into, and successfully complete, clinical or field trials; our or our collaborators' ability to obtain and maintain regulatory approval of future product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate; the regulatory landscape that will apply to our and our collaborators' development of product candidates; our ability to achieve our anticipated operating efficiencies as we commence manufacturing operations at our new facility; our ability to obtain and maintain intellectual property protection for our technology and any of our product candidates; the potential for off-target editing or other adverse events, undesirable side effects or unexpected characteristics associated with any of our product candidates; the success of our existing collaboration agreements; our ability to enter into new collaboration arrangements; public perception about genome editing technology and its applications; competition in the genome editing, biopharmaceutical, biotechnology and agricultural biotechnology fields; potential manufacturing problems associated with any of our product candidates; potential liability lawsuits and penalties related to our technology, our product candidates and our current and future relationships with third parties; and other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2019 filed with the SEC on November 12, 2019, as such factors may be updated from time to time in our other filings with the SEC, which are accessible on the SEC's website at www.sec.gov.

All forward-looking statements speak only as of the date of this presentation, and except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. This presentation may also contain estimates, projections, and/or other information regarding our industry, our business and the markets for certain of our product candidates, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, clinical trials, studies and similar data prepared by market research firms and other third parties, from industry, medical and general publications, and from government data and similar sources. Information that is based on estimates, forecasts, projections, market research, or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information.

Agenda

Welcome	**Nick Riddle, MD, PhD,** VP Financial Strategy & IR **Matt Kane,** CEO and co-founder
Review of PBCAR0191 Interim Phase 1 Data	**Chris Heery, MD,** Chief Medical Officer
Opportunities Offered by Allogeneic Cell Therapy	**Sattva Neelapu, MD,** MD Anderson Cancer Center
Guest Speaker Panel discussion and Q&A	**Chris Heery, MD,** Chief Medical Officer **Sattva Neelapu, MD,** MD Anderson Cancer Center **Bijal Shah, MD,** Moffitt Cancer Center **Marco Davila, MD, PhD,** Moffitt Cancer Center
Closing remarks	**Matt Kane,** CEO and co-founder

Welcome

Matt Kane, CEO & co-founder

Dedicated To Improving Life

Overcome Cancer.

Cure Genetic Disease.

Feed the Planet.

Delivering on the Promise of Genome Editing to Address Core Challenges of Human Health

Proprietary **ARCUS genome editing platform** *built for translation with full freedom to operate*

Scaled and cell phenotype-optimized **allogeneic CAR T platform** *in the clinic for R/R NHL and ALL. IND accepted for second program*

World class team of Precisioneers that includes the **pioneers** *in genome editing*

Industry leading ***in vivo*** **gene correction platform** *first to publish in non-human primates*

Wholly integrated **food editing platform** *focused on human wellness and food security*

Multiple Key Milestones Delivered Since IPO

- ✓ Dosed first patients in Phase 1/2a trial with PBCAR0191
- ✓ Opened Manufacturing Center for Advanced Therapeutics (MCAT), first US in-house cGMP facility for production of genome edited allogeneic CAR T cell therapies
- ✓ IND accepted for second CAR T program PBCAR20A
- ✓ Built out senior leadership team and Board
- ✓ Presented first validating clinical data from PBCAR0191 Phase 1 trial at ASH 2019 Annual Meeting

Unique Features of Precision's Allogeneic CAR T Platform Require Proprietary Technology and Know-How

Starting material	Significant focus on best donor cells	Proprietary markers and selection criteria
ARCUS editing	Gentle, single-step genome editing avoids off-targeting and preserves T cell phenotype	Product of 15+ years of research & IP at Precision
CAR insertion	CAR directly into TCR locus every time – consistent expression in therapeutic product	Issued Precision IP
Construct	Proprietary N6 co-stimulatory domain – maintains T cell phenotype	Precision IP patent pending
Length of process	Short, 10-day manufacturing	Optimizes expansile phenotype
Quality	Consistent batch-to-batch performance (yield, quality, purity)	Proprietary platform, product of >2.5 years development and scaling
Product supply	Supply chain controlled end-to-end. Uninterrupted supply to patients	

Precision's Off-the-shelf CAR T Immunotherapy Pipeline

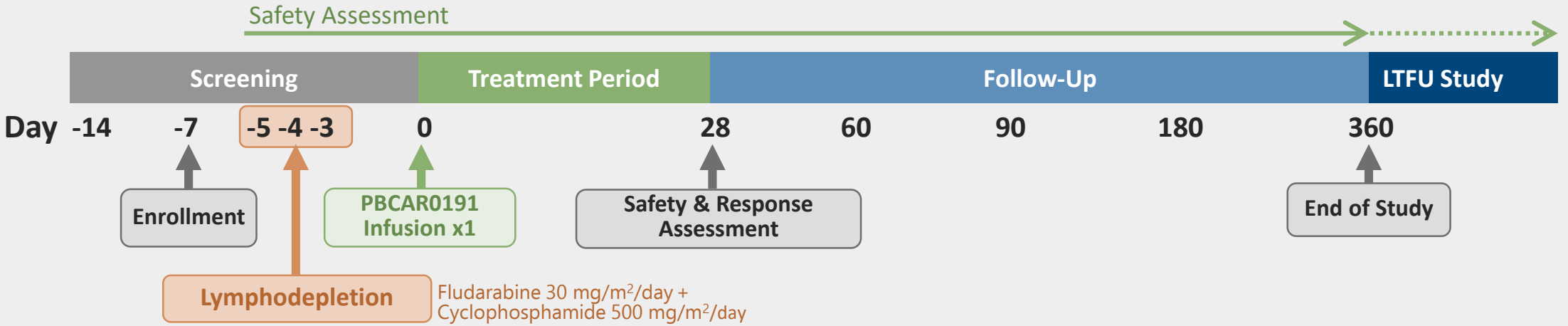
Product Candidates	Program Area	Discovery	Pre-clinical	Clinical	Rights
PBCAR0191 (CD19)	NHL and ALL - Ph1/2a initiated Q2 2019, Initial Data at ASH 2019				
PBCAR20A (CD20)	NHL, CLL, SLL - IND accepted, Ph1/2a start by early Q1 2020				
PBCAR269A (BCMA)	MM - IND 2020				

Review of PBCAR0191 Interim Phase 1 Data

Chris Heery, MD, Chief Medical Officer

PBCAR0191 Study Design

- Phase 1/2a: Open-label, Single Dose, First-in-Human, 3+3 Dose Escalation Phase 1 → Dose Expansion Phase 2a
- Cohort A: B-ALL and Cohort N: NHL – each cohort evaluated independently
- No DLTs at DL1 in cohort N, allows both cohorts to move to DL2



Eligibility

- Adult patients with R/R B-NHL or R/R B-ALL

Clinical Sites

- Moffitt (Bijal Shah / Mike Jain)
- City of Hope (Anthony Stein / Alex Herrera)
- Dana Farber (Caron Jacobson / Dan DeAngelo)
- MD Anderson (Nitin Jain / Sattva Neelapu)

Objectives

- Primary: safety and tolerability
- Secondary: anti-tumor activity
- Exploratory: expansion, trafficking, and persistence

Dose Escalation (standard 3+3)

- DL1 = 3.0 x 10^5 cells/kg
- DL2 = 1.0 x 10^6 cells/kg
- DL3 = 3.0 x 10^6 cells/kg

Recap of ASH Abstract - Initial Clinical Data Supporting Safety and Clinical Activity of PBCAR0191 at Dose Level 1

Abstract dataset

- 3 patients treated at DL1 (3 x 10^5 cells/kg)
- Advanced NHL (1 patient MCL, 2 patients DLBCL)
- August 1st, 2019 data cutoff date
- Single infusion of PBCAR0191
- Mild lymphodepletion regime (flu/cy only)

Key findings

1. ***Safety***
   - No serious adverse events or DLTs observed over median 60 days follow up
2. ***Clinical activity***
   - Objective tumor responses (Lugano criteria) in 2 of 3 patients – at day 14 and day 28 respectively
   - Third patient (progressed after Yescarta® treatment) had evidence of anti-tumor activity at data cutoff
3. ***Cell expansion***
   - Preliminary evidence of CAR T cell expansion

Data provided first clinical validation of allogeneic CAR T anti-tumor activity in the absence of biologic lymphodepletion

Demographics Consistent With Heavily Pretreated NHL & B-ALL Populations

		NHL Dose Level 1 3×10^5 cells/kg (n=3)	NHL Dose Level 2 1×10^6 cells/kg (n=3)	B-ALL Dose Level 2 1×10^6 cells/kg (n=3)	Total (n=9)
Age, years	*Mean (min, max)*	54 (34, 64)	74 (71, 77)	56 (48, 72)	**61 (34, 77)**
Sex, n(%)	*Female*	1 (33%)	0	1 (33%)	**2 (22%)**
Race, n(%)	*Asian*	0	1 (33%)	1 (33%)	**2 (22%)**
	White	3 (100%)	2 (67%)	2 (67%)	**7 (78%)**
Weight at screen (kg)	*Mean (min, max)*	88 (82, 92)	83 (63, 106)	88 (45.4, 111)	**87 (45, 111)**
Prior # of Lines of Therapy	*Median (range)*	4 (4, 5)	2 (1, 3)	4 (3, 5)	**4 (1, 5)**
Response to prior line of therapy					
Refractory		2 (66%)	1 (33%)	3 (100%)	6 (66%)
Relapsed		1 (33%)	2 (66%)	0	3 (33%)

15 subjects were screened starting on March 25, 2019
9 were dosed at two dose levels, among NHL and B-ALL subjects

Adverse Events in NHL Cohort - Early Data Compare Favorably to Autologous CAR T Experience

System Organ Class *Preferred Term, n(%)*	NHL Dose Level 1 3 x 10^5 cells/kg (n=3)	NHL Dose Level 2 1 x 10^6 cells/kg (n=3)	NHL Overall (n=6)
Grade 3 or Higher Treatment Emergent Adverse Events			
Hematologic			
Neutropenia	1 (33%)	1 (33%)	2 (33%)
Lymphocyte count decreased	1 (33%)	2 (67%)	3 (50%)
Neutrophil count decreased	1 (33%)	2 (67%)	3 (50%)
White blood cell count decreased	1 (33%)	2 (67%)	3 (50%)
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain	1 (33%)	0 (0%)	1 (17%)
Vascular disorders			
Hypertension	1 (33%)	0 (0%)	1 (17%)
Adverse Events of Special Interest (Max Grade)			
CRS (Cytokine Release Syndrome) – Max Grade 2	1 (33%)	0	1 (17%)
CRS – Max Grade 1	0 (0%)	1 (33%)	1 (17%)
ICANS (Immune Effector Cell Associated Neurotoxicity) – Max Grade 2	0 (0%)	0 (0%)	0 (0%)
GvHD (Graft Versus Host Disease)	0 (0%)	0 (0%)	0 (0%)

Adverse Events in B-ALL Cohort - Early Data Compare Favorably to Autologous CAR T Experience

System Organ Class *Preferred Term, n(%)*	B-ALL Dose Level 2 1 x 10^6 cells/kg (n=3)	B-ALL Overall (n=3)
Grade 3 or Higher Treatment Emergent Adverse Events		
Hematologic		
Hemoglobin decreased (anemia)	2 (67%)	2 (67%)
Lymphocyte count decreased	3 (100%)	3 (100%)
Neutrophil count decreased	2 (67%)	2 (67%)
Platelet count decreased	3 (100%)	3 (100%)
White blood cell count decreased	3 (100%)	3 (100%)
Febrile neutropenia	1 (33%)	1 (33%)
Gastrointestinal disorders		
Dysphagia	1 (33%)	1 (33%)
Metabolism and nutrition disorders		
Hyperglycemia	1 (33%)	1 (33%)
Hypophosphatemia	1 (33%)	1 (33%)
Nervous system disorders		
Facial nerve disorder	1 (33%)	1 (33%)
Headache	1 (33%)	1 (33%)
Vascular disorders		
Hypertension	1 (33%)	1 (33%)
Adverse Events of Special Interest (Max Grade)		
CRS (Cytokine Release Syndrome) – Max Grade 1	1 (33%)	1 (33%)
ICANS (Immune Effector Cell Associated Neurotoxicity) – Max Grade 2	1 (33%)	1 (33%)
GvHD (Graft Versus Host Disease)	0 (0%)	0 (0%)

Lymphodepletion-Related Adverse Events Consistent With Flu/Cy Regime

Both NHL and B-ALL Cohorts, n(%)	Maximum Grade in Distinct Patients (n=9)		
	Grade 3	Grade 4	Total
WBC decrease	-	3 (33%)	3 (33%)
Platelet decrease	-	2 (22%)	2 (22%)
Neutrophil decrease	-	2 (22%)	2 (22%)
Lymphocyte (ALC) decrease	2 (22%)	3 (33%)	5 (56%)
Hyperglycemia	1 (11%)	-	1 (11%)
Infection	0	0	0

Mild lymphodepletion approach so far sparing patients potentially severe AEs (e.g. infections) associated with biologic agents

Summary of Individual Subjects' Clinical Activity and Mechanistic Support

	Patient ID	Best Overall Response	Best Response Day ≥28	Progression Free Survival (Days)**	CRS or ICANS? (Mechanistic Demonstration of Cell Expansion)	External PCR Expansion (Study Days +)#	Internal Flow Expansion (Study Days +)##
Dose Level 1 NHL	1-NHL-DL1	**Partial Response Day 28**	**Partial Response**	60	None	**Positive (Day 3)**	Negative##
	2-NHL-DL1	**Complete Response Day 14**	Progressive Disease	N/A	None	**Positive (Day 1)**	Negative##
	3-NHL-DL1	**Partial Response Day 60**	**Partial Response**	180*	CRS Grade 2	Negative#	Negative##
Dose Level 2 NHL	4-NHL-DL2	**Partial Response Day 28***	**Partial Response**	60*	None	**Positive (Day 1-21)**	**Positive (Day 1-60)**
	5-NHL-DL2	**Partial Response Day 14**	Progressive Disease	N/A	Hypotension Grade 1; No Fever; ASCTC Gr = Not CRS	**Positive (Day 1-10)**	**Positive (Day 1)**
	6-NHL-DL2	**Complete Response Day 28***	**Complete Response***	28+*	CRS Grade 1*	**<LLQ; Detectable (Day 7)**	**Positive (Days 1-3)**
Dose Level 2 B-ALL	7-ALL-DL2	Progressive Disease	Progressive Disease	N/A	None	Negative#	**Positive (Day 7)**
	8-ALL-DL2	Progressive Disease*	Progressive Disease*	N/A	None*	Negative#	Negative##
	9-ALL-DL2	**Complete Response Day 28***	**Complete Response***	28+*	CRS Grade 1; ICANS Grade 2*	**<LLQ; Detectable (Day 1, 3, 10, 14)#**	**Positive (Day 28)**

* Denotes any data acquired after November 4th data cut and prior to December 2nd

** Progression free survival is estimated at the time of study visit

qPCR performed on DNA extracted from isolated PBMC. Note: extremely low PBMC isolation in 6-NHL-DL2, 7-ALL-DL2, 8-ALL-DL2, and 9-ALL-DL2 yielded low DNA quantities, making interpretation of these results difficult. They are shown for completeness

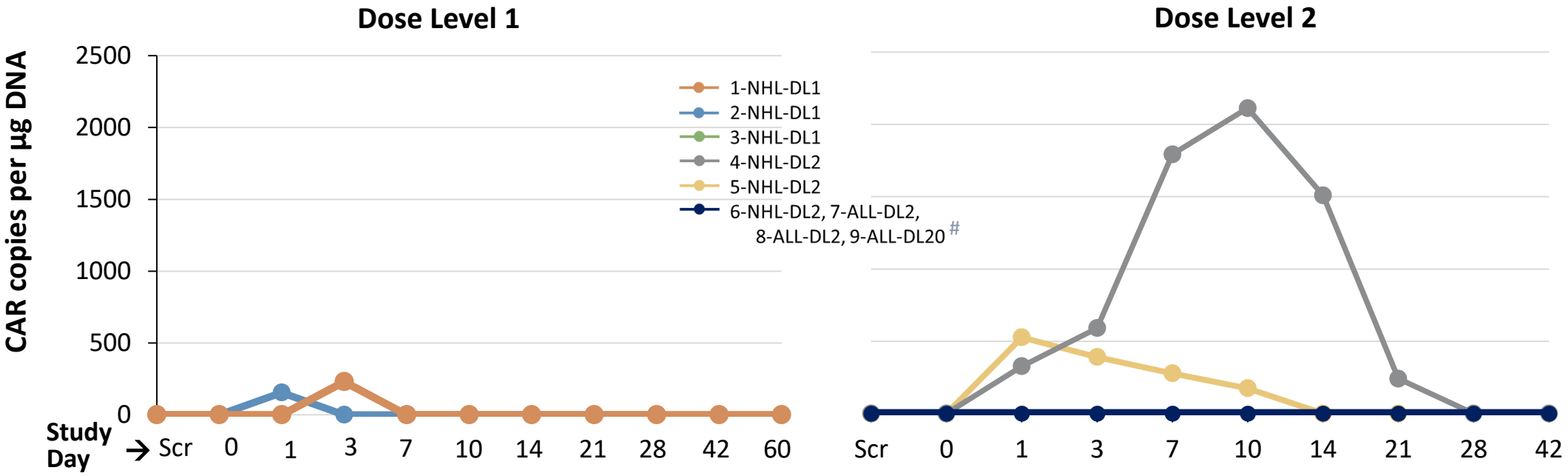
Lower limit for CAR+ cells was set as 0.03% of lymphocytes. All positive have ≥0.03%, with highest detected at 0.43%

Total of 7 of 9 (78%) Patients Experienced Objective Evidence of Tumor Shrinkage at any Timepoint

n(%)		NHL Dose Level 1 3×10^5 cells/kg (n=3)	NHL Dose Level 2 1×10^6 cells/kg (n=3)	NHL Total (n=6)	B-ALL Dose Level 2 1×10^6 cells/kg (n=3)
Best Response	*Complete*	1 (33%)	1 (33%)	2 (33%)	1 (33%)
	Partial	2 (66%)	2 (66%)	4 (66%)	0
	Progressive Disease	0	0	0	2 (66%)
Response at Day ≥28		2 (66%)	2 (66%)	4 (66%)	1 (33%)
Progressive Disease Day <28		1 (33%)	1 (33%)	2 (33%)	2 (66%)

5 of 9 (56%) patients experienced objective responses at or beyond day 28

Quantitative PCR Suggests Higher Peak Expansion and Greater Persistence at Dose Level 2

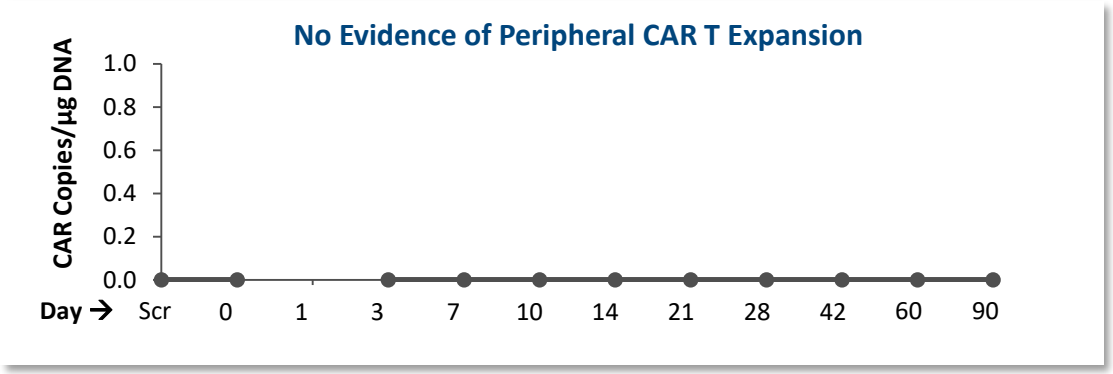


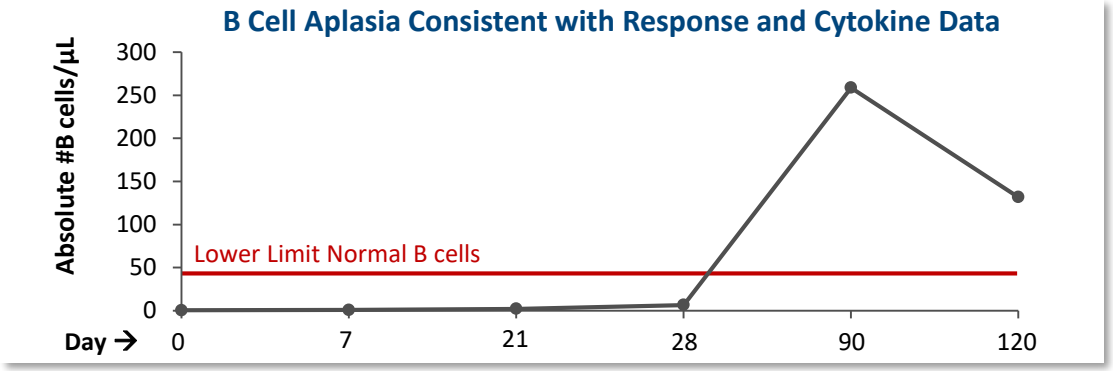
	PCR Expansion	Latest Persistence	Flow Expansion	Latest Persistence
NHL DL1 (n = 3)	2/3 (66%)	Day 3	0/3 (0%)	--
NHL DL2 (n = 3)	3/3 (100%)	Day 21	3/3 (100%)	Day 60
ALL DL2 (n =3)	1/3 (33%)	Day 14	2/3 (66%)	Day 28

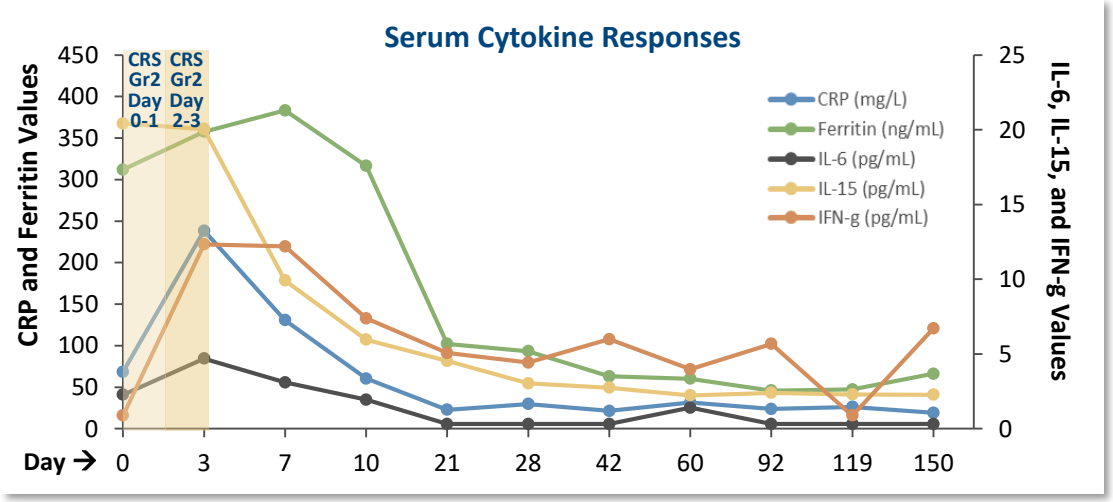
- Early evidence of dose-dependent increases in cell expansion and persistence
- Persistence to 28 and 60 days, respectively, suggests rejection is not necessarily an early event
- Evaluation in larger numbers of patients at Dose Level 3 may provide additional insight

qPCR performed on DNA extracted from isolated PBMC. Note: extremely low PBMC isolation in 6-NHL-DL2, 7-ALL-DL2, 8-ALL-DL2, and 9-ALL-DL2 yielded low DNA quantities, making interpretation of these results difficult. They are shown for completeness

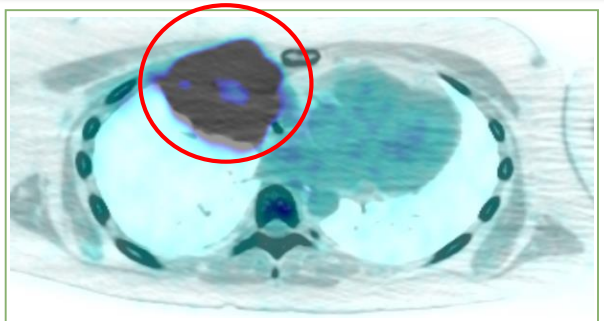
Case Study: Patient 3-NHL-DL1 – PR to 6 Months, Prior Relapse with Yescarta



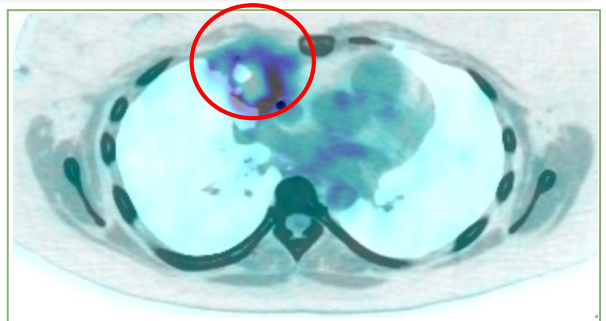




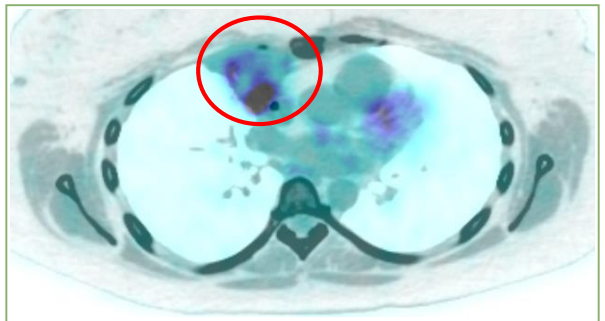
- 34 yo female diagnosed with DLBCL in Feb 2016
- Previously treated with 4 prior regimens, including an autologous stem cell transplant and auto-CAR T targeting CD19
- Partial response until 6 months
- Cytokine data (IFN-gamma; IL-6, CRP, Ferritin) and immediate pain at tumor site after infusion supports T cell expansion
- B-cell aplasia followed by repletion first observed at day 90



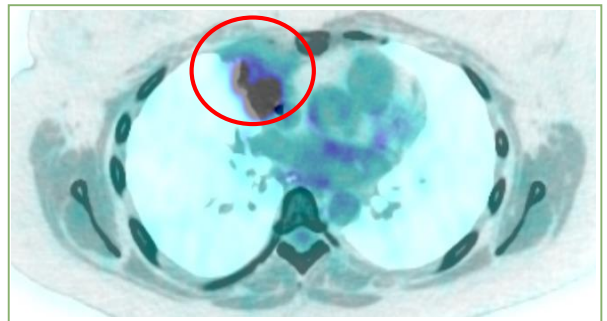
Baseline PET Avid Mediastinal Mass (SPPD = 42.9)



Day 28 PET Avid Mediastinal Mass (SPPD = 23.5) **STABLE DISEASE**

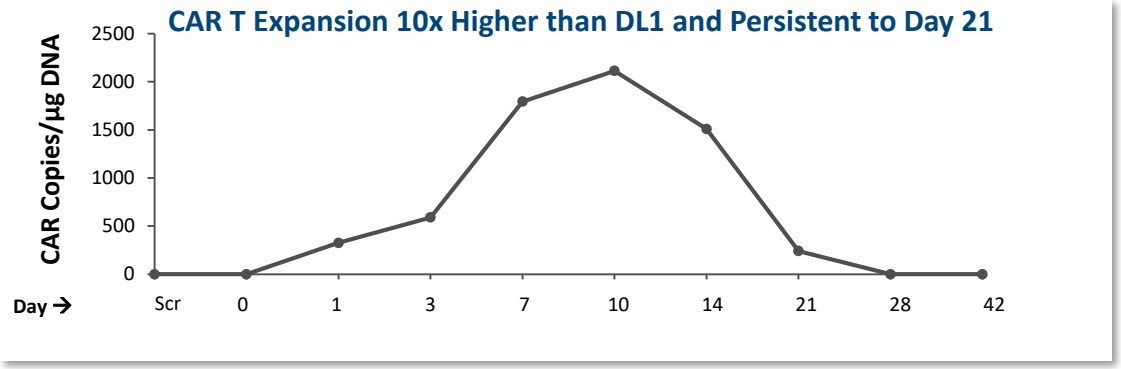


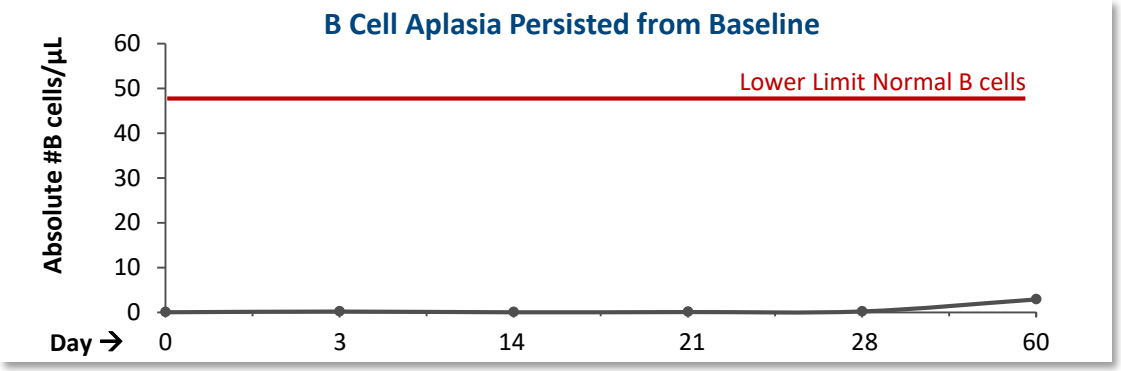
2 Month PET Avid Mediastinal Mass (SPPD = 16.2) **PARTIAL RESPONSE**

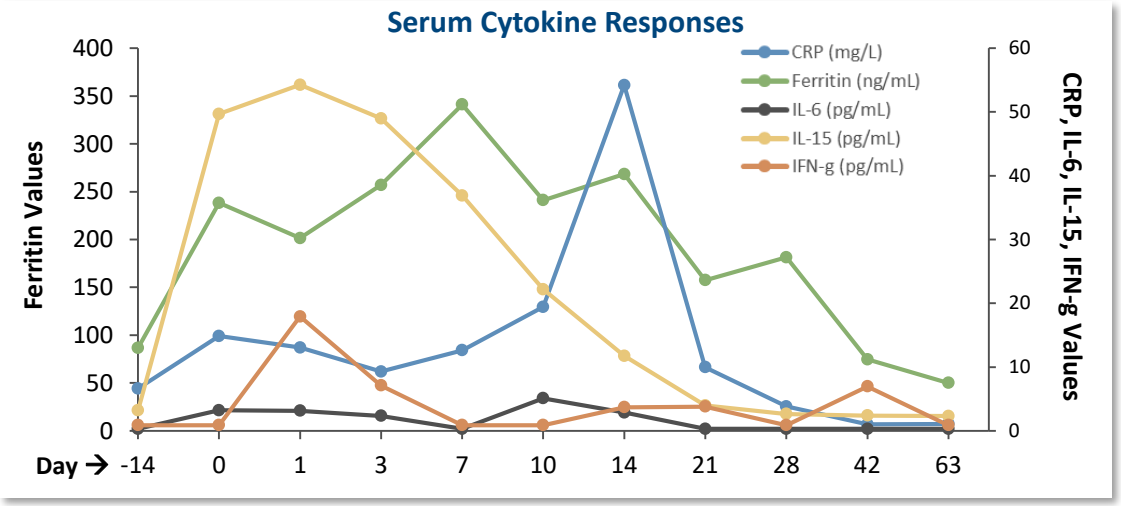


3 Month PET Avid Mediastinal Mass (SPPD = 8.2) **ONGOING PARTIAL RESPONSE**

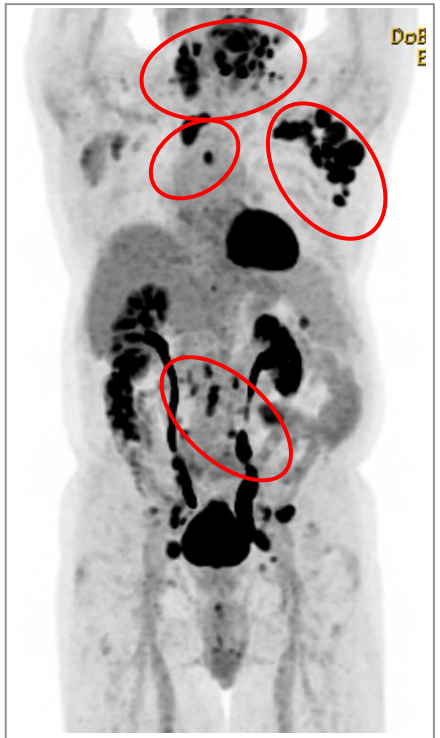
Case Study: Patient 4-NHL-DL2 – Notable CAR T Cell Expansion



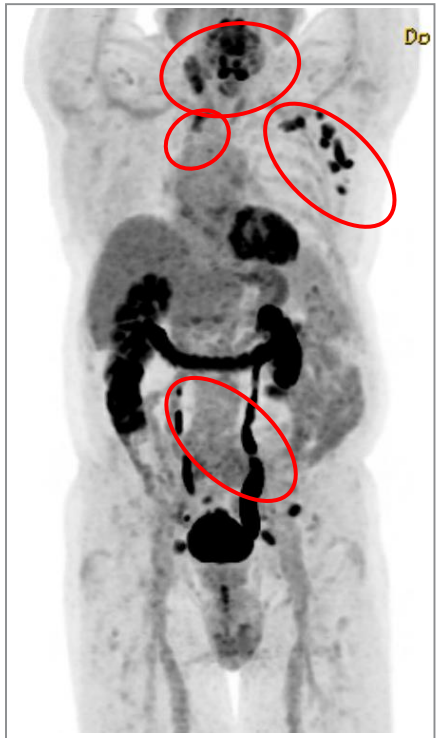




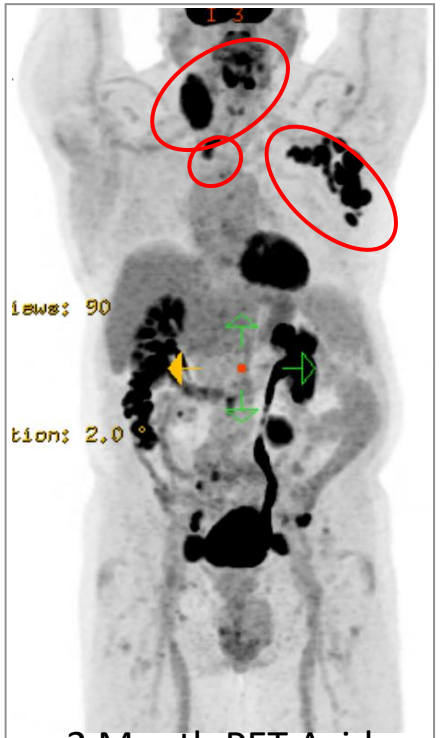
- 71 yo male, diagnosed Feb 2018 with MCL
- Previously treated with 3 prior lines (lenalidomide+rituximab, bendamustine+ rituximab, acalibrutinib)
- Partial response Day 28 with peak CAR T expansion 10x highest observed at DL1 and persistence at day 21 by PCR assay, day 60 persistence by flow cytometry
- Large tumor burden at baseline. Tumor regrowth at day 60



Baseline PET Avid Lesions
SPPD = 3,692



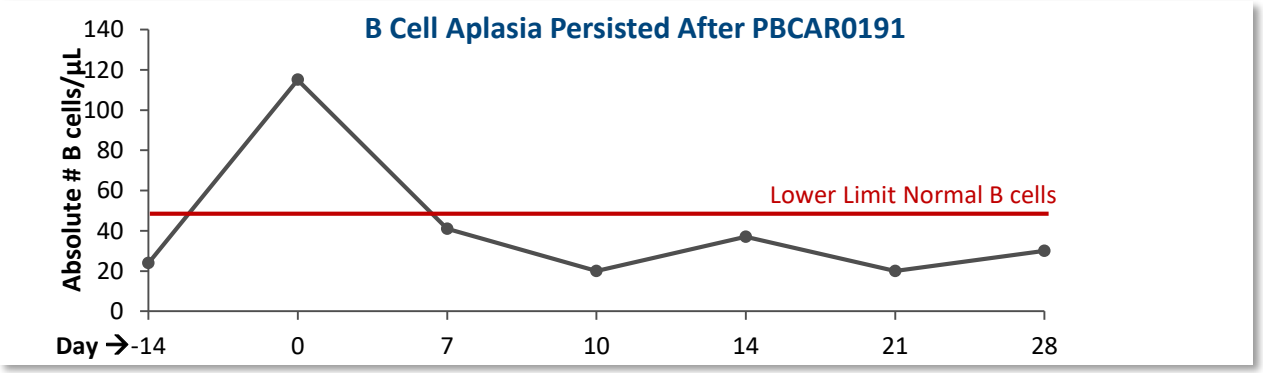
Day 28 PET Avid Lesions SPPD = 1,700
PARTIAL RESPONSE

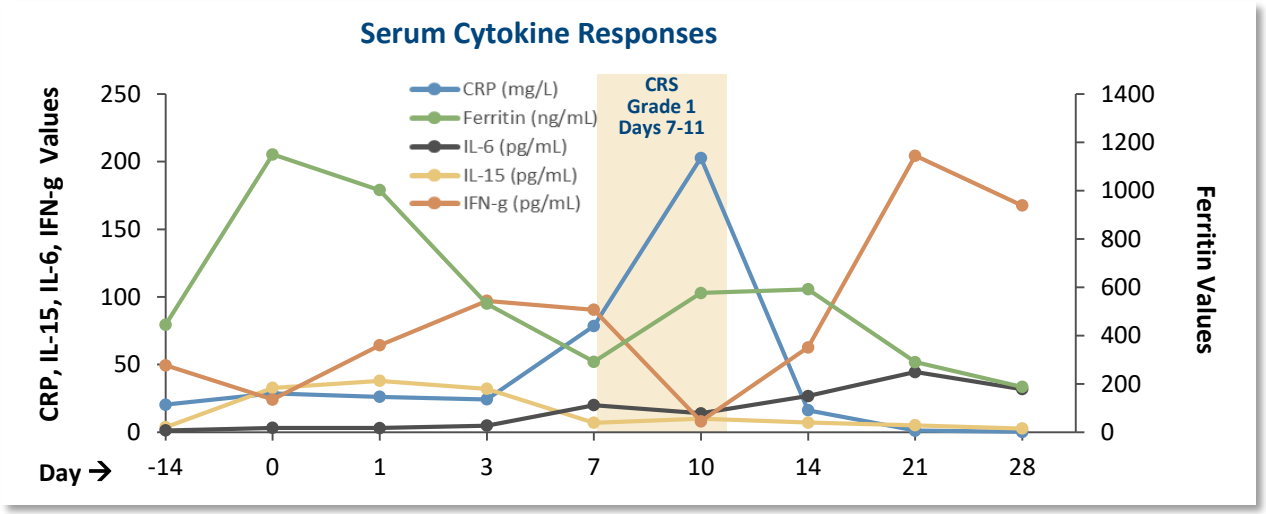


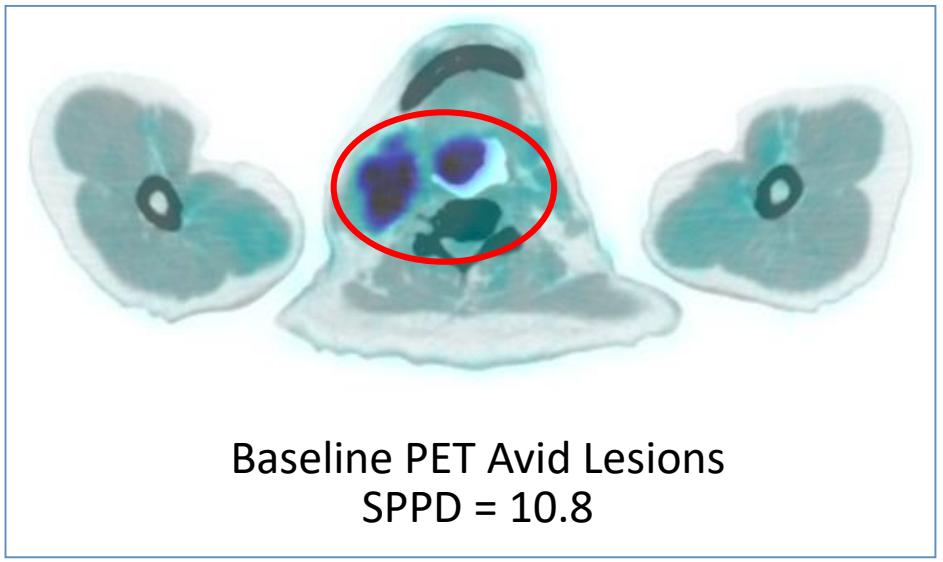
2 Month PET Avid Lesions SPPD = 1,700
PROGRESSIVE DISEASE

Case Study: Patient 6-NHL-DL2 – Ongoing CR at Day 28+

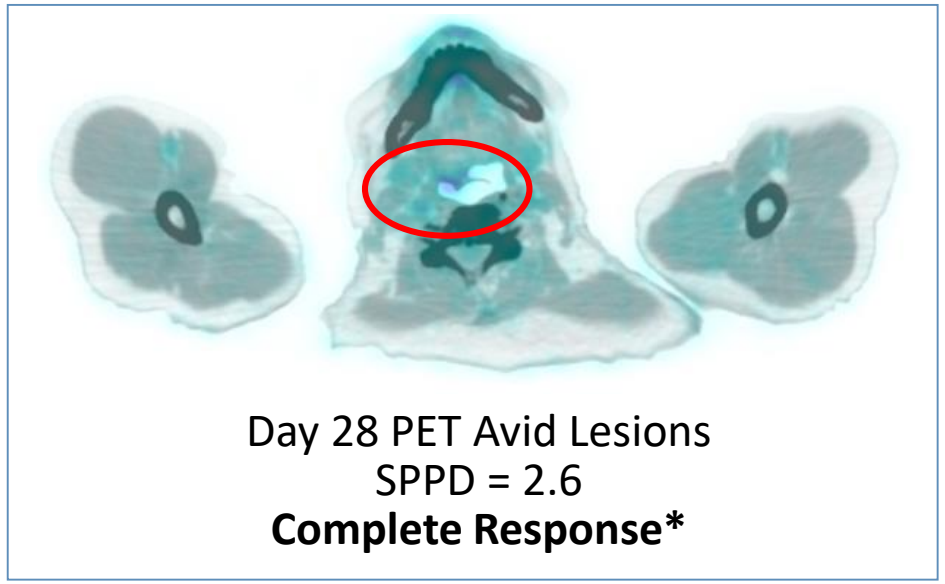
- 77 year old male diagnosed with Mantle Cell Lymphoma 2017
- 2 prior lines of therapy
- Complete Response (Lugano) at day 28 visit with Clonoseq MRD negative
- B cell aplasia induced after cell infusion, detectable cell expansion (limited by low PBMC isolation), and CRS associated with expected cytokine profiles (IFN-gamma rise early then CRP rise)







Baseline PET Avid Lesions
SPPD = 10.8

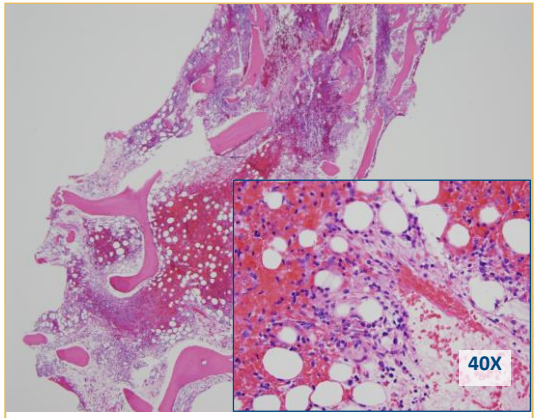


Day 28 PET Avid Lesions
SPPD = 2.6
Complete Response*

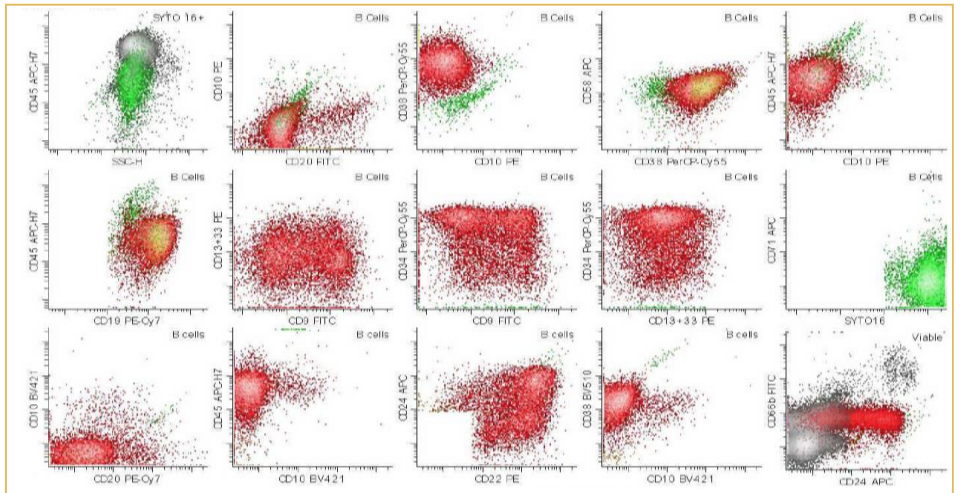
*Peripheral Blood Clonoseq MRD negative

Case Study: Patient 9-ALL-DL2 – Ongoing CR in B-ALL at Day 28+

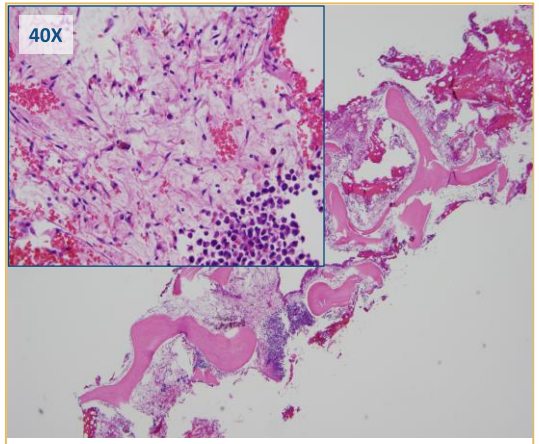
- 48 year old female, diagnosed with B-ALL April 2018
- Previously treated with 5 lines of therapy including 2 allogeneic stem cell transplants
- Baseline – 19.8% blasts
- Day 28 bone marrow – No blasts present. Acellular marrow. MRD negative by flow cytometry
- CRi – counts not recovered (day 30)
- PCR limited by low PBMC isolation; Flow demonstrates CAR T in peripheral blood at day 28
- Presence of CRS and ICANS also demonstrate expansion



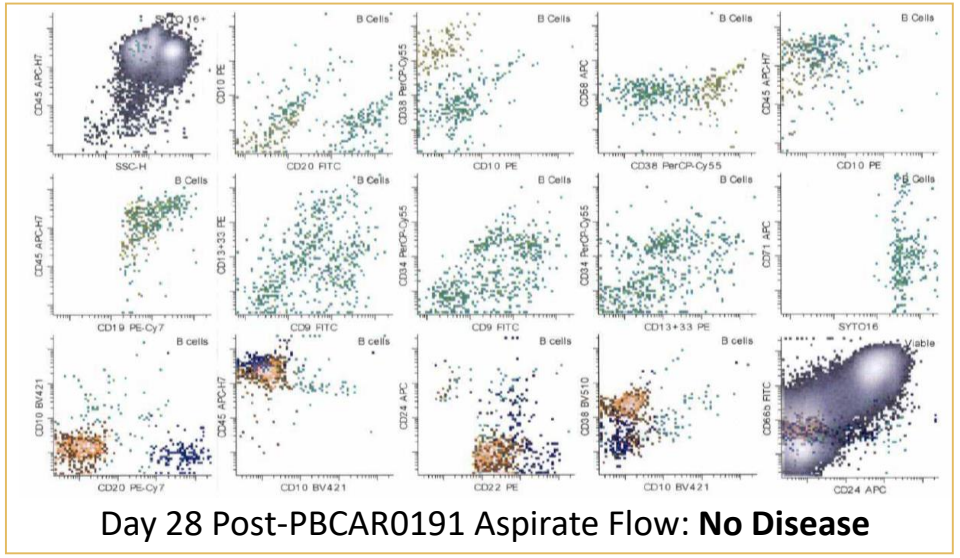
Bone Marrow Pre-PBCAR0191: Relapsed B-ALL



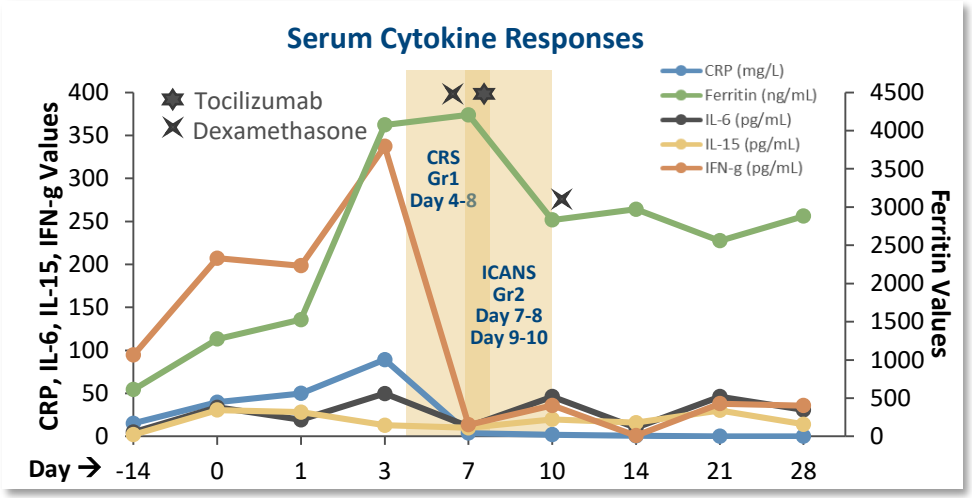
Pre-PBCAR0191 Aspirate Flow: B-ALL Blasts



Bone Marrow Day 28 PBCAR0191: **No B-ALL**



Day 28 Post-PBCAR0191 Aspirate Flow: **No Disease**



Encouraging Early Data with Potentially Best-In-Class Allogeneic CD19 CAR T

- First-in-human study of PBCAR0191: adverse event profile is acceptable and may compare favorably with approved autologous products
- No Maximum Tolerated Dose has yet been identified
- Objective evidence of cell-mediated anti-tumor effect has been observed at DL1 and DL2
- Dose dependent demonstration of mechanism of action
- To the best of our knowledge, this is the first time, using an allogeneic CAR T product and non-biologic lymphodepletion, that a clinical study has shown:
  - Anti-tumor activity and cell expansion
  - No evidence of GvHD, DLTs, or > Grade 2 CRS
  - Objective response after progression from an autologous CAR T product

DL3 dosing underway – data expected in Q1 2020

Early Activity and Safety Open Up Multiple Avenues for Product Optimization and Utilization

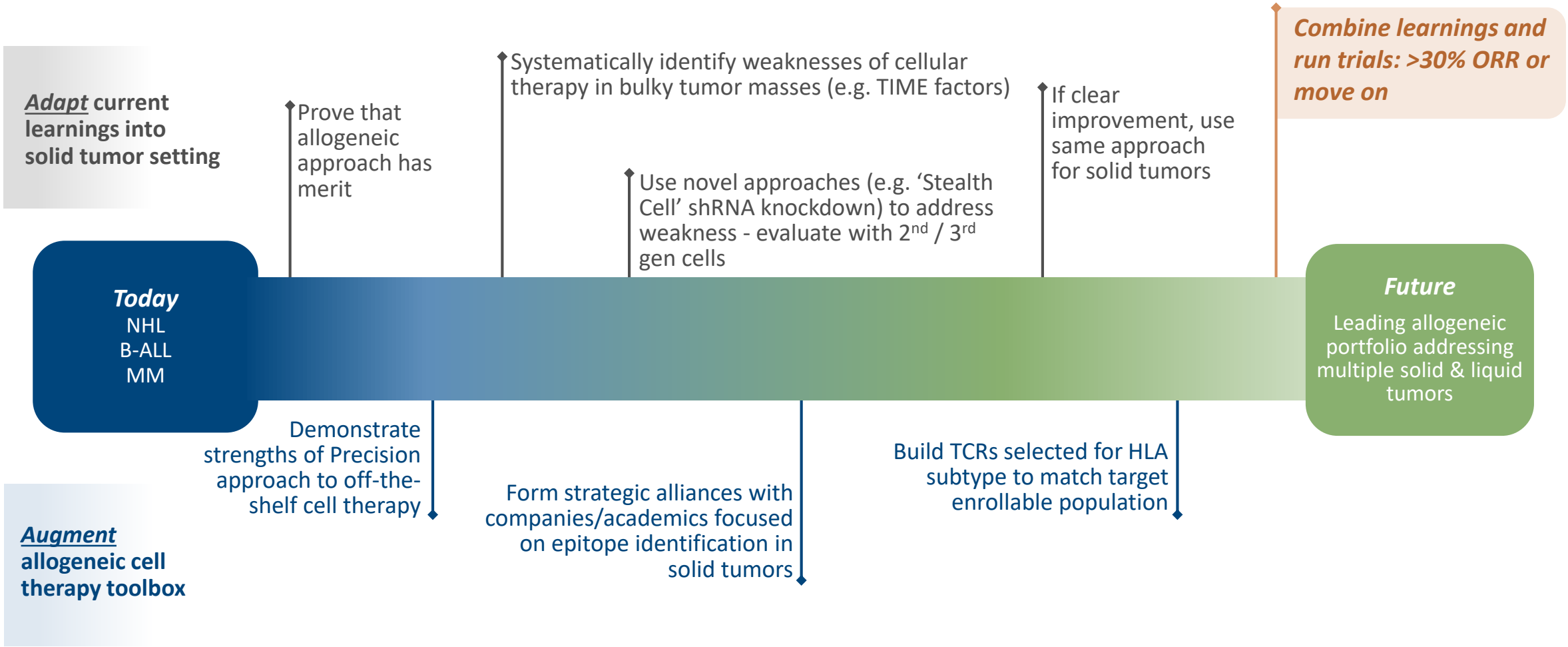
1. ***Safety profile may support increased upper end of dosing***
   - Reported data today are at DL1 (3 x 10^5 cells/kg) and DL2 (1 x 10^6 cells/kg); currently dosing at DL3 (3 x 10^6 cells/kg)
   - If AE trend continues, could enable doses above DL3 if desired

2. ***Mild lymphodepletion expands potential patient access scenarios***
   - Data clearly demonstrate cell killing occurs without a harsh biologic LD agent
   - Suggests significant flexibility to 'fine tune' LD for different dosing strategies
   - Creates long-term potential opportunities to treat in outpatient and/or non-ICU settings

3. ***Possibility for repeat dosing – facilitating 'biologic-like' use***
   - Combination of activity, safety and availability opens door to repeat administration
   - Dosing and timing tailored to individual patient disease

4. ***Potential combinations further expand possible utilization***
   - CAR T combos (e.g. CD19/CD20) to circumvent antigen escape
   - CAR T plus other agents could also be explored

Pathway to Solid Tumors - Expanding the Reach of Precision's Allogeneic CAR T



Opportunities Offered by Allogeneic Cell Therapy

Sattva Neelapu, MD, MD Anderson

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Opportunities Offered by Allogeneic Cell Therapy

Sattva S. Neelapu, M.D.
Professor and Deputy Chair
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas, USA

Disclosures

- Research support from Kite/Gilead, Merck, BMS, Cellectis, Poseida, Karus, Acerta, and Unum Therapeutics
- Advisory Board Member / Consultant for Kite/Gilead, Merck, Celgene, Novartis, Unum Therapeutics, Pfizer, Precision Biosciences, Cell Medica, Allogene, Incyte, Calibr, and Legend Biotech
- I will discuss investigational use of CAR T-cell therapy

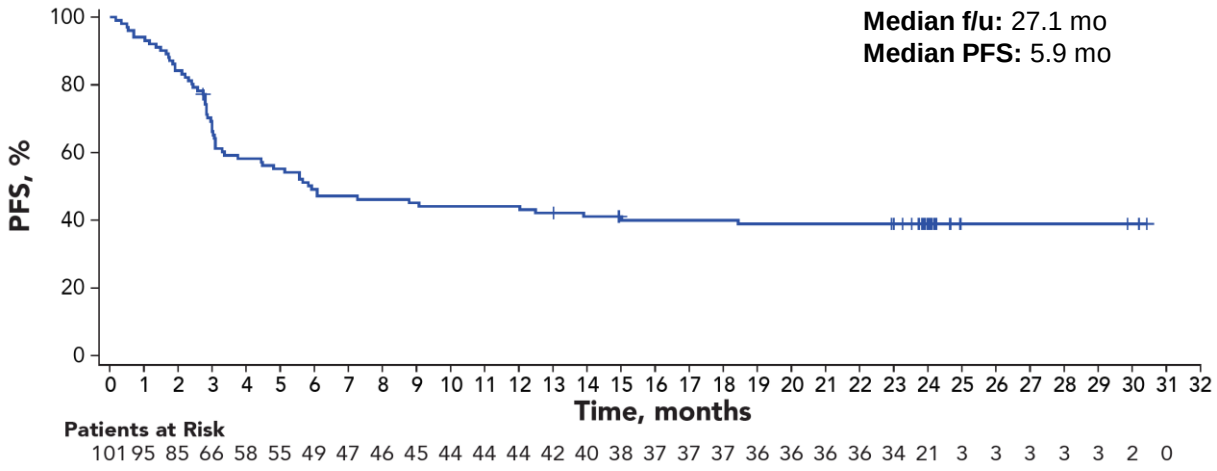
Outline

- Is there sufficient rationale to develop allogeneic cell therapy?
- Is allogeneic cell therapy likely to be successful?

Durable responses with autologous CAR-T in r/r large B-cell lymphoma

ZUMA-1: PFS with axi-cel

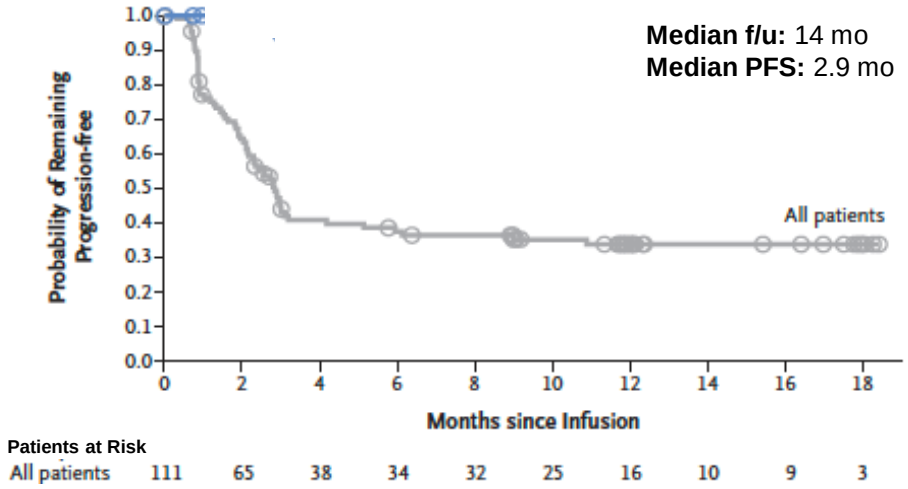
39% progression-free at 27.1 mo



Neelapu et al. *N Eng J Med* 2017
Locke et al. *Lancet Oncol* 2019

JULIET: PFS with tisagenlecleucel

34% progression-free at 14 mo#

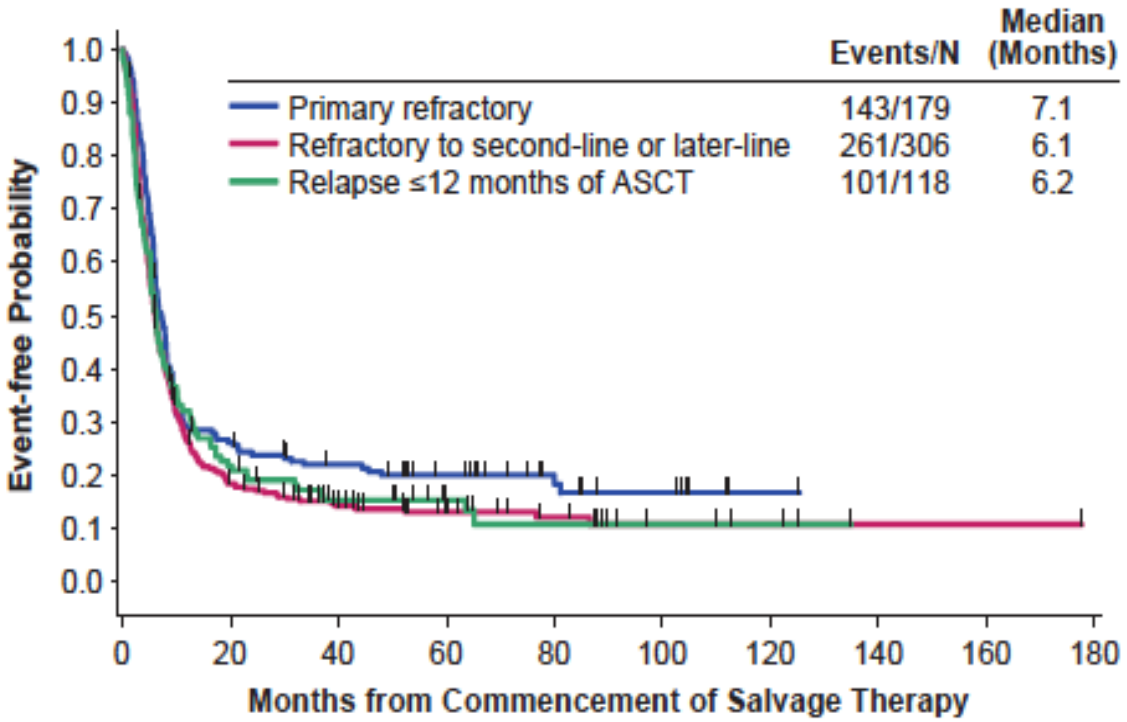


#Calculated value from publication

Schuster et al. *N Eng J Med* 2019

Major improvement with autologous CAR-T in r/r DLBCL vs. historical

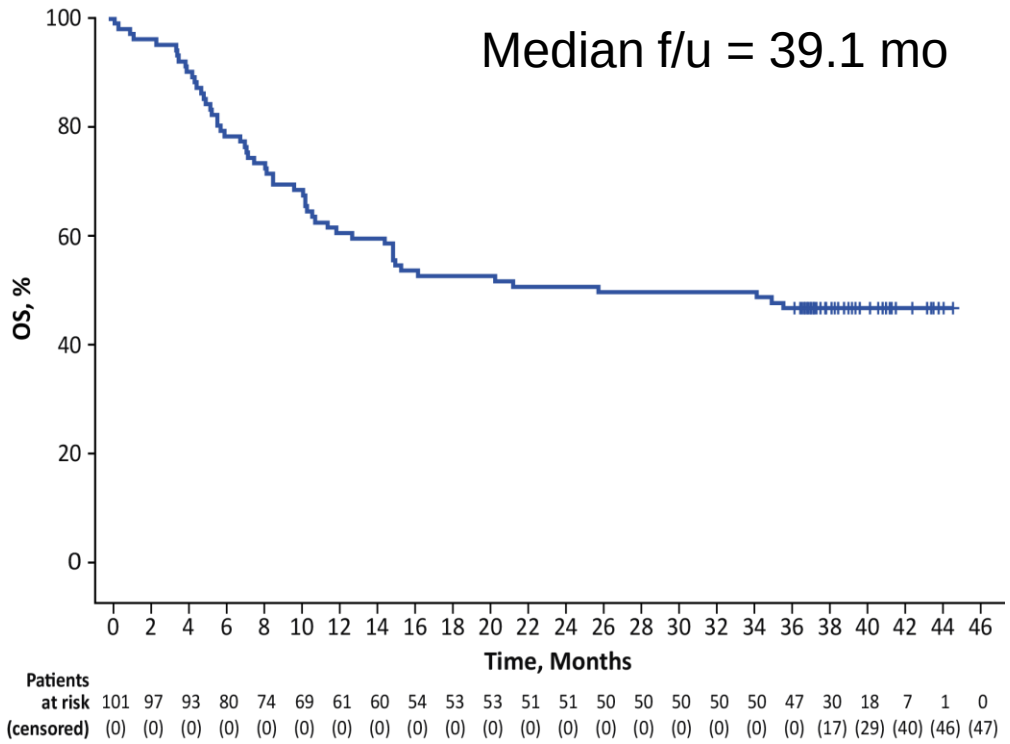
Overall survival: SCHOLAR-1



- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

Crump, Neelapu et al. *Blood* 2017

Overall survival: ZUMA1



- N = 108
- ORR = 83%; CR rate = 58%
- Median OS = 25.8 months

Neelapu, Locke et al. *N Eng J Med* 2017
Neelapu et al. *ASH* 2019

Experience with axi-cel in the standard of care setting

Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real World Experience

N = 274

Loretta J. Nastoupil, Michael D. Jain, Jay Y. Spiegel, Armin Ghobadi, Yi Lin, Saurabh Dahiya, Matthew A. Lunning, Lazaros J. Lekakis, Patrick M. Reagan, Olalekan O. Oluwole, Joseph P. McGuirk, Abhinav Deol, Alison R. Sehgal, Andre Goy, Brian T. Hill, Charalambos Andreadis, Javier Munoz, Jason R. Westin, Julio C. Chavez, Amanda F Cashen, Nora N Bennani, Aaron P. Rapoport, Julie M. Vose, David B. Miklos, Sattva S. Neelapu, and Frederick L. Locke

Blood 2018 132:91; doi: https://doi.org/10.1182/blood-2018-99-114152

Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance and Toxicity

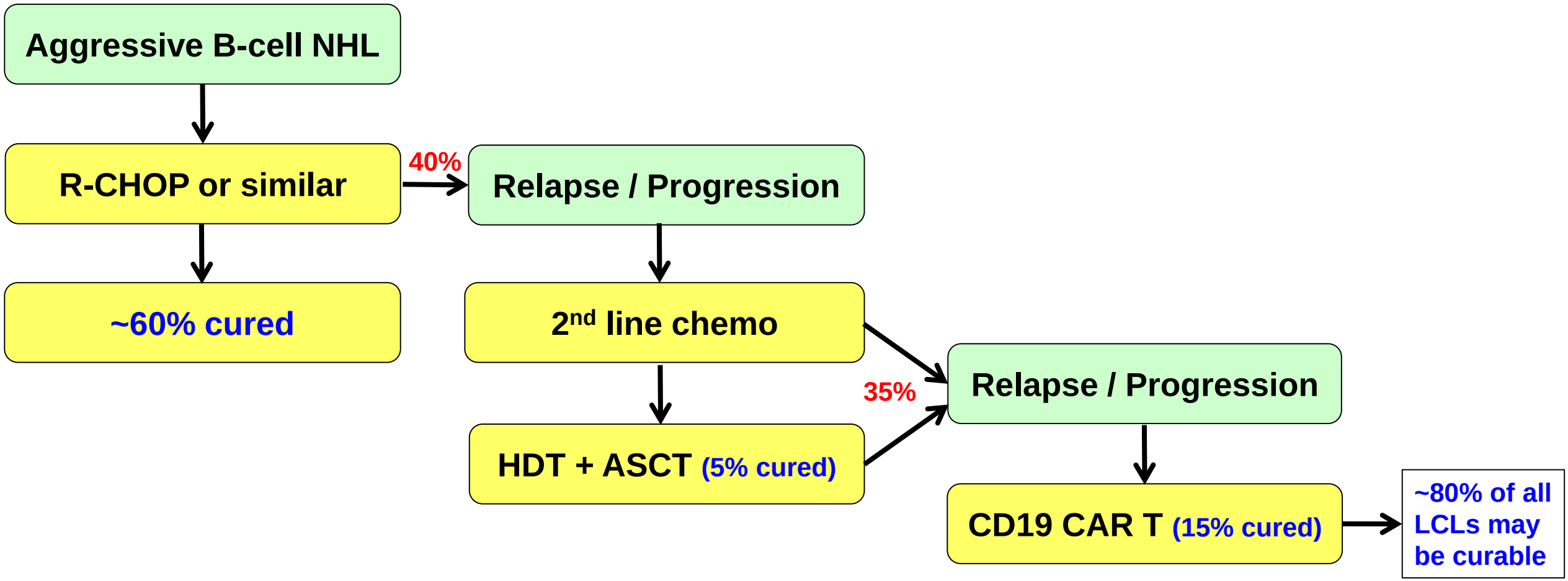
N = 104

Caron A. Jacobson, Bradley Hunter, Philippe Armand, Yusuke Kamihara, Jerome Ritz, Scott J Rodig, Kyle Wright, Mikel Lipschitz, Robert A. Redd, Marcela V. Maus, Yi-Bin Chen, Jeremy S. Abramson, Justin Kline, Jonathon B. Cohen, Joseph Maakaron, Samantha Jaglowski, Stephen D. Smith, David G. Maloney, Ajay K. Gopal, Matthew J. Frigault, and Utkarsh H. Acharya

Blood 2018 132:92; doi: https://doi.org/10.1182/blood-2018-99-117199

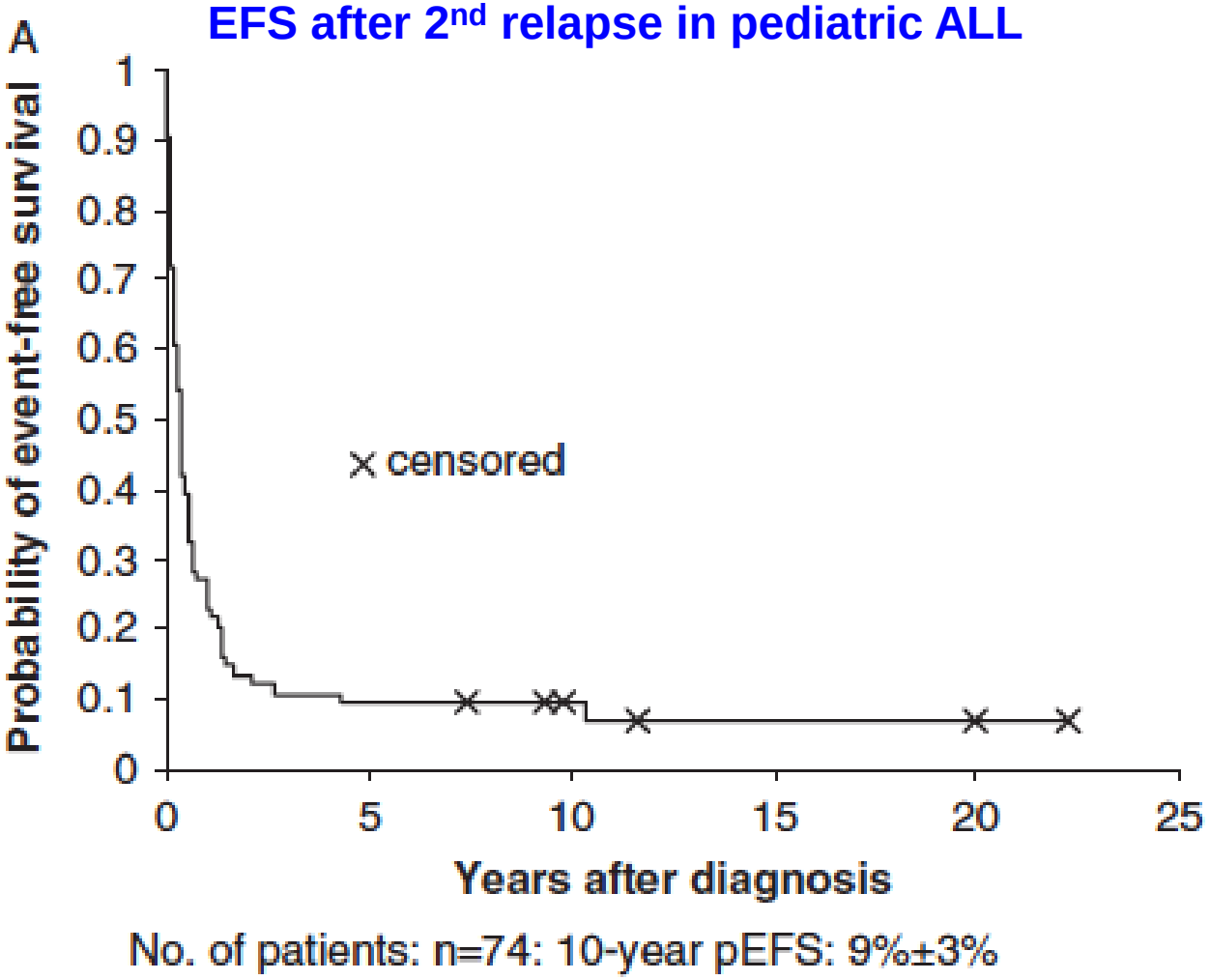
- ORR and CR rates and safety comparable to ZUMA-1
- ~40% of patients would not have been eligible for ZUMA-1

CD19 CAR T in NHL: Beginning of a paradigm shift



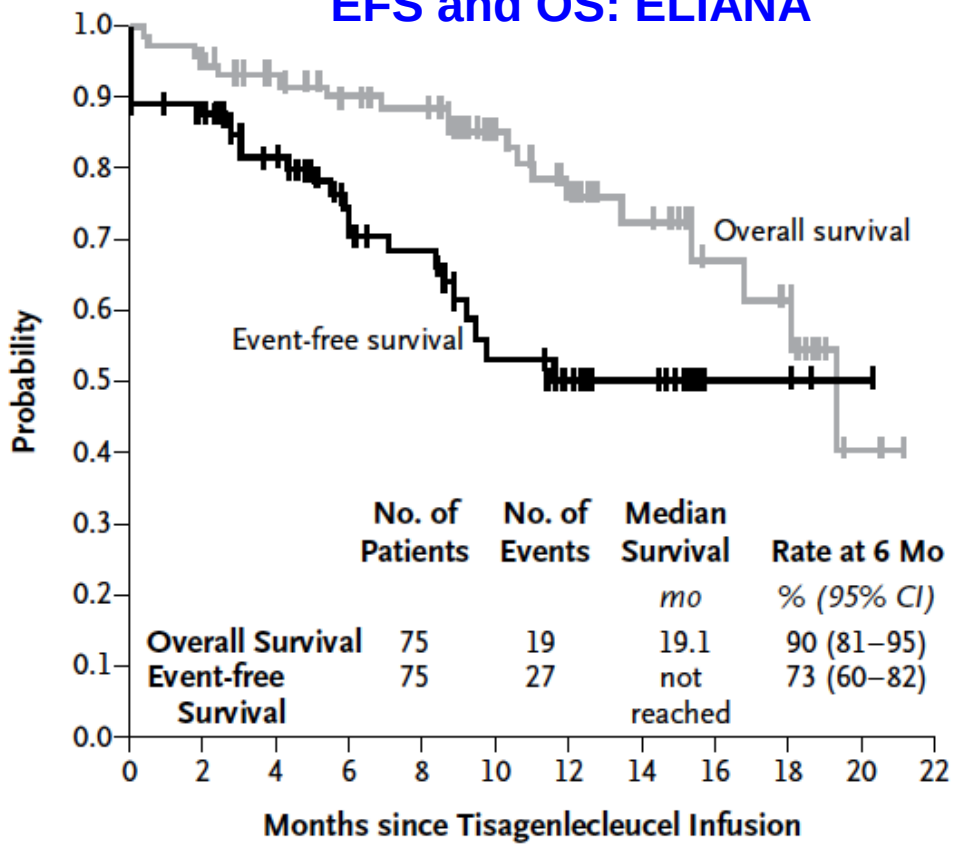
Major improvement with autologous CAR-T in r/r pediatric ALL vs. historical

EFS after 2nd relapse in pediatric ALL



Reismuller et al, J Pediatr Hematol Oncol 2013

EFS and OS: ELIANA

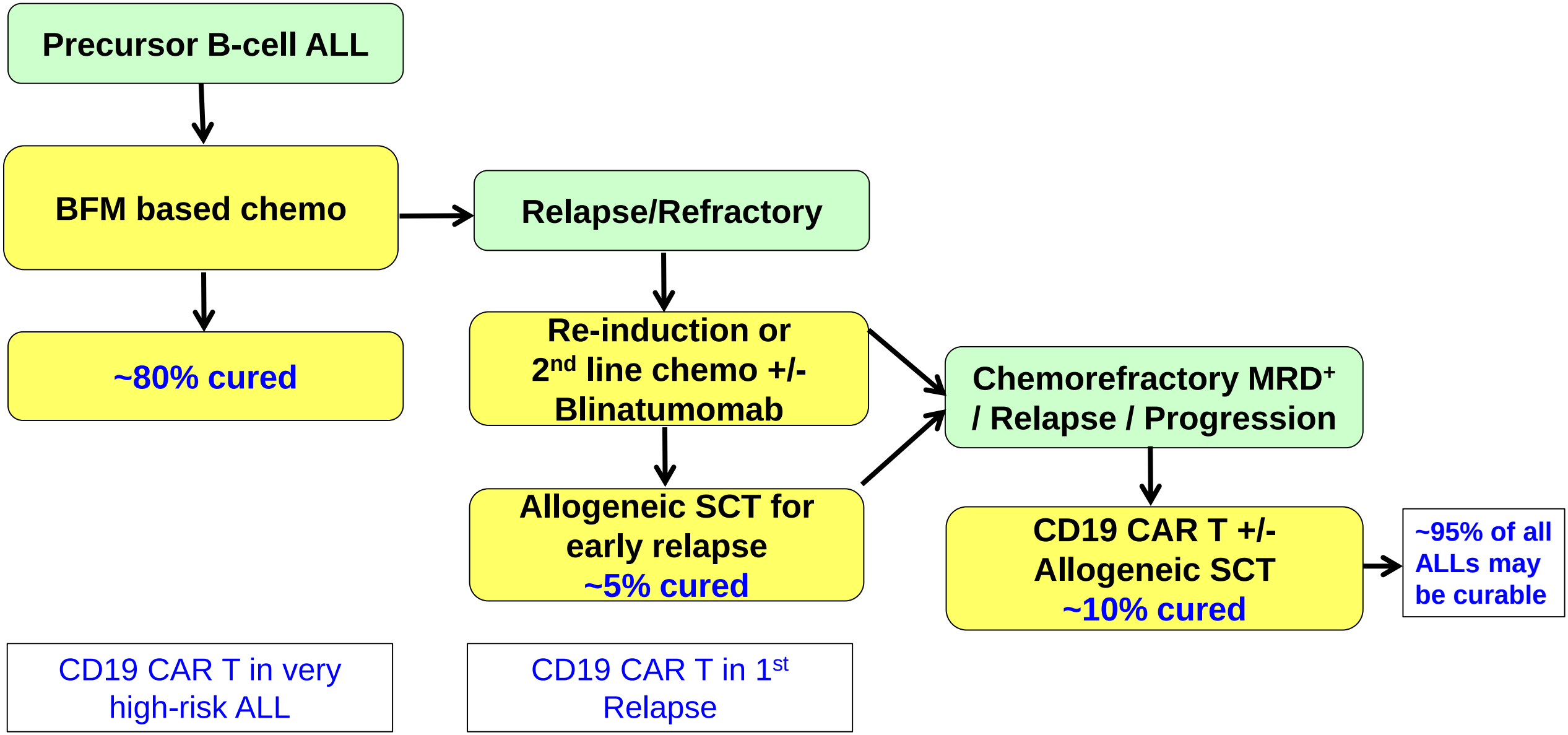


	No. of Patients	No. of Events	Median Survival (mo)	Rate at 6 Mo % (95% CI)
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

No. at Risk												
Overall survival	75	72	64	58	55	40	30	20	12	8	2	0
Event-free survival	75	64	51	37	33	19	13	8	3	3	1	0

Maude et al, N Eng J Med 2018

CD19 CAR T in pediatric ALL: Beginning of a paradigm shift

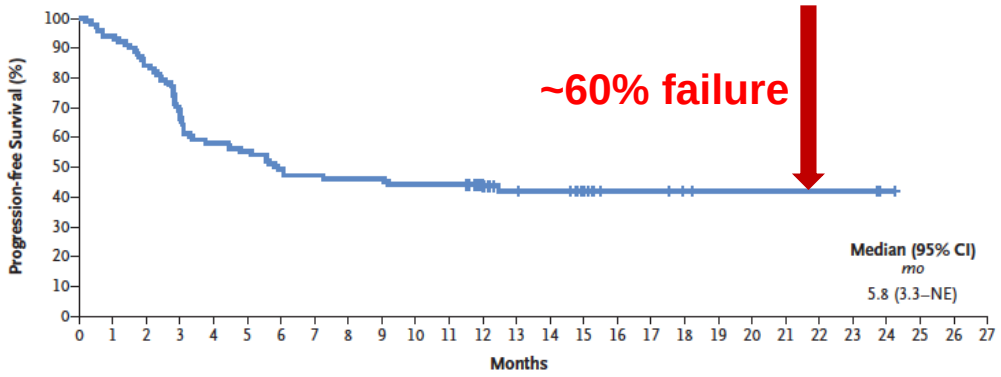


10-33% of eligible patients may not get autologous CARs

Study / Sponsor	ZUMA1 / Kite	JULIET / Novartis	TRANSCEND / Juno
Reference	Neelapu et al. NEJM 2017 Locke et al. Lancet Oncol 2019	Schuster et al. NEJM 2019	Abramson et al. ASCO 2018
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	94%	99%
Treated/Enrolled	109/120 (90%)	111/165 (67%)	114/134 (85%)

- In the SOC setting 9-11% of DLBCL patients did not get CAR-T after apheresis – Nastoupil et al, ASH 2018; Jacobson et al, ASH 2018
- In addition ~5% of patients referred do not even get the apheresis

Patterns of failure in DLBCL after axi-cel



Axi-cel CD19 CAR T therapy

~20%

Primary resistance

1 mo

~80%

Responders

~60%

CRs

~20%

PRs

Durable CRs

~40%

Early relapse

~10%
2-6 mo

Late relapse

~10%
> 6 mo

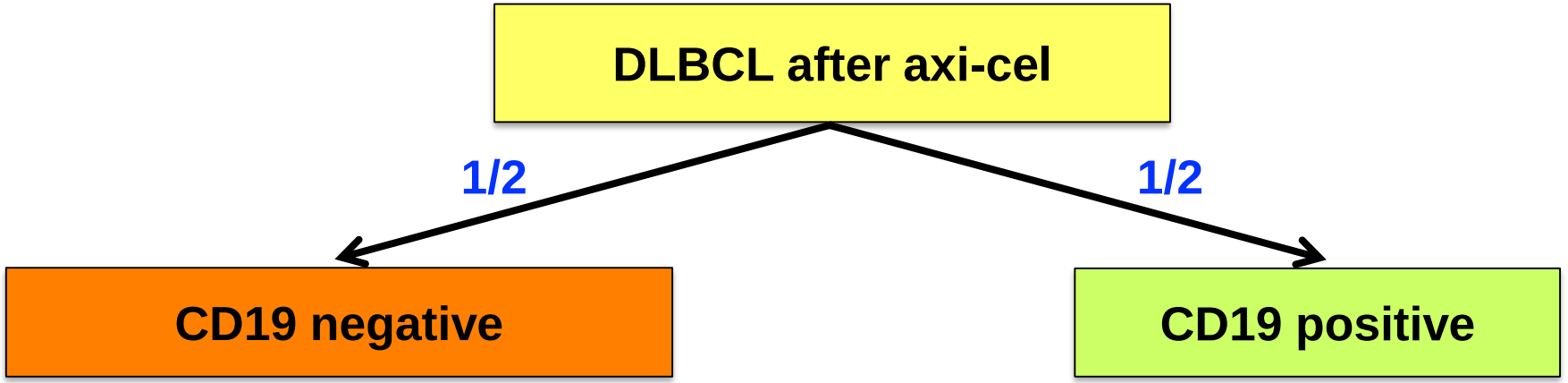
Early relapse

~20%
1-2 mo

Neelapu et al. *N Eng J Med* 2017

- All numbers are rounded off

Mechanisms of anti-CD19 CAR T resistance



- **Antigen escape**
  - CD19 alternative splicing
  - CD19 mutation
- **Impaired T-cell fitness**
  - Apheresis product
  - CAR T product
  - Host environment
  - Tumor microenvironment

T-cell intrinsic fitness in apheresis product may affect CAR T efficacy

nature medicine

LETTERS

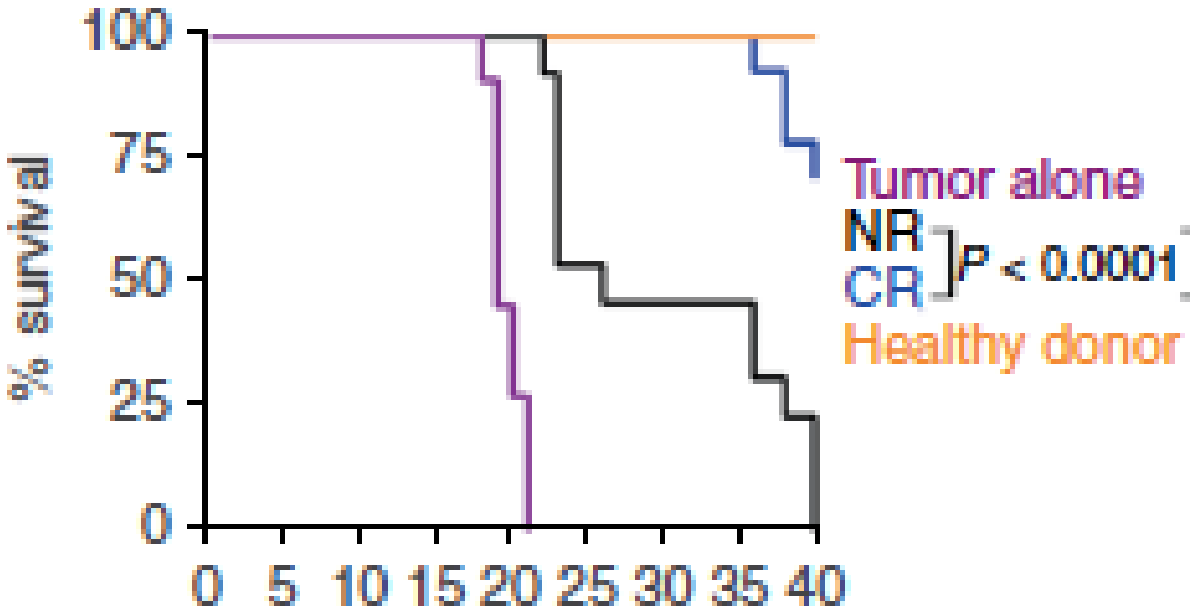
https://doi.org/10.1038/s41591-018-0010-1

Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia

Joseph A. Fraietta[1,2,3], Simon F. Lacey[1,2,3,9], Elena J. Orlando[4,9], Iulian Pruteanu-Malinici[4], Mercy Gohil[2], Stefan Lundh[2], Alina C. Boesteanu[2], Yan Wang[2], Roddy S. O'Connor[2], Wei-Ting Hwang[5], Edward Pequignot[2], David E. Ambrose[2], Changfeng Zhang[2], Nicholas Wilcox[2], Felipe Bedoya[2], Corin Dorfmeier[2], Fang Chen[2], Lifeng Tian[2], Harit Parakandi[2], Minnal Gupta[2], Regina M. Young[2], F. Brad Johnson[1], Irina Kulikovskaya[2], Li Liu[2], Jun Xu[2], Sadik H. Kassim[4], Megan M. Davis[1,2], Bruce L. Levine[1,2], Noelle V. Frey[2,6], Donald L. Siegel[1,2,7], Alexander C. Huang[3,8], E. John Wherry[3,8], Hans Bitter[4], Jennifer L. Brogdon[4], David L. Porter[1,6], Carl H. June[1,2,3] and J. Joseph Melenhorst[1,2,3]*

Fraietta et al, *Nat Med* Apr 2018

- Increased frequency of $CD27^+CD45RO^-$ $CD8^+$ T cells before CAR T generation associated with durable remission in CLL
- $CD27^+PD\text{-}1^-CD8^+$ CAR T cells associated with response



- Rationale for allogeneic CAR or banking T cells when healthy

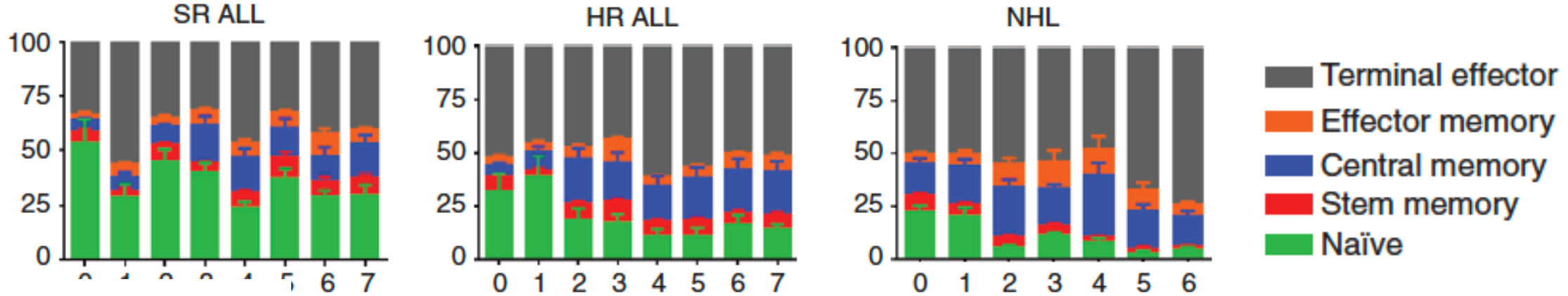
T-cell maturation and function affected by chemotherapy

Naïve T-cell Deficits at Diagnosis and after Chemotherapy Impair Cell Therapy Potential in Pediatric Cancers

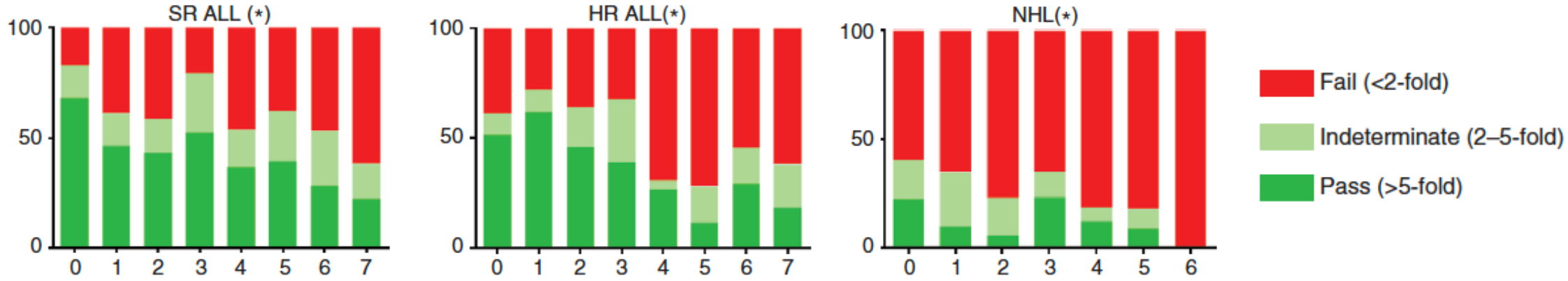
Rajat K. Das, Lauren Vernau, Stephan A. Grupp, et al.

Cancer Discov Published OnlineFirst January 10, 2019.

T-cell phenotype



T-cell proliferation

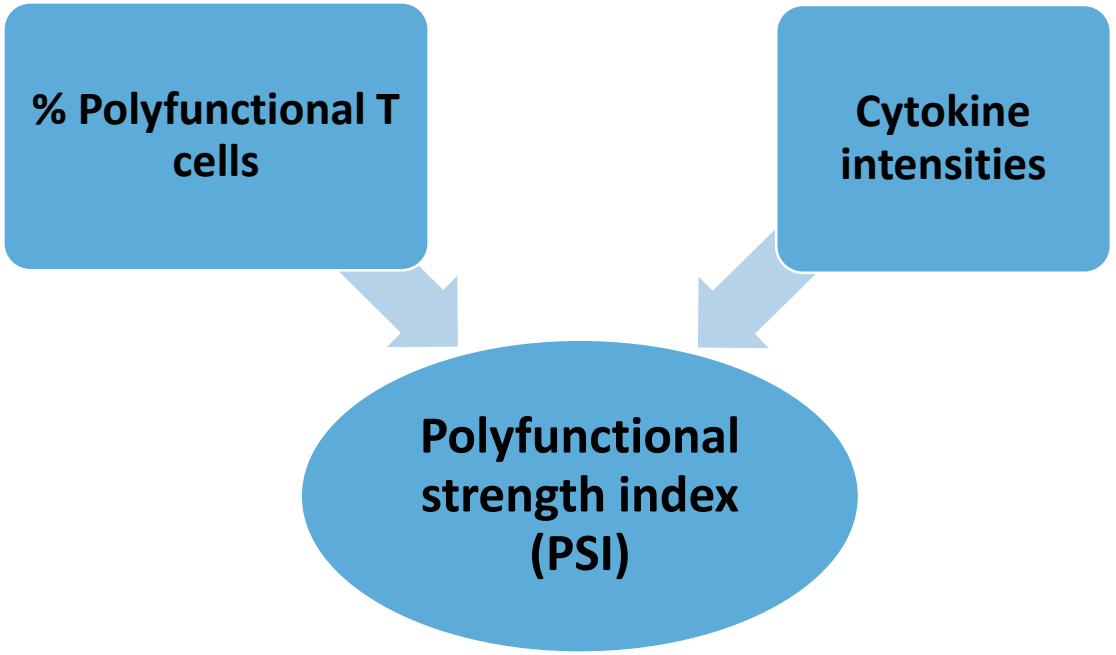


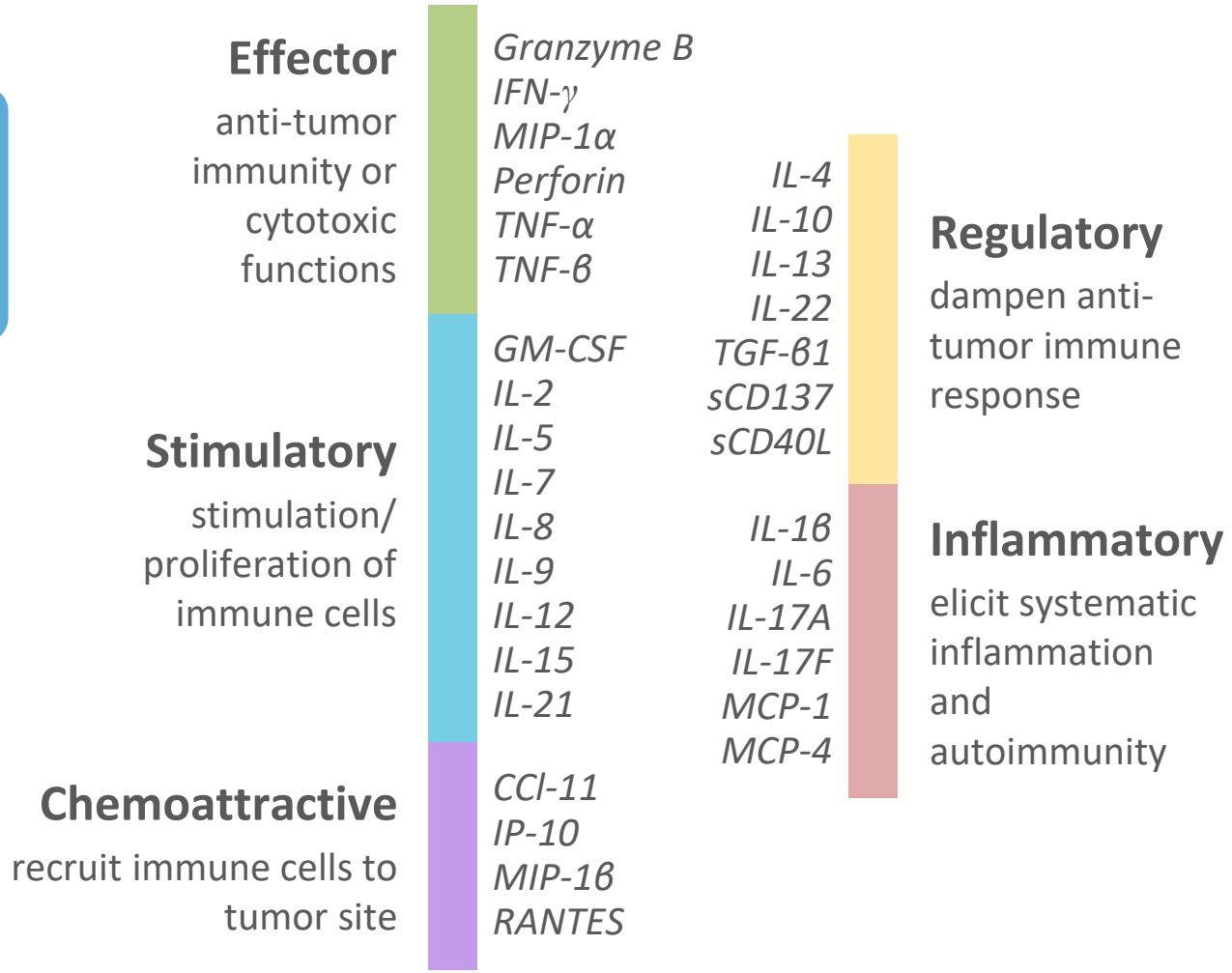
ZUMA-1: CAR T-cell fitness by prior lines of therapy

# Prior Lines	Quartile (# Subjects)	Doubling Time	Median CAR $AUC_{D_{y}0\text{-}28}$	%ORR (n, %)	%Ongoing @12Mth (n, %)
Healthy Donor	n=152	1.34	-	-	
≤2 Lines	Q1 (n=31)	1.42	469.3	28 (90%)	12 (39%)
3 Lines	Q2 (n=29)	1.51	476.6	28 (97%)	10 (34%)
4 Lines	Q3(n=28)	1.7	491.4	23 (82%)	13 (46%)
≥5 Lines	Q4 (n=12)	1.68	211.0	5 (42%)	3 (25%)

- Rationale for allogeneic CAR T

Quantification of 32-plex CAR T cell polyfunctionality using IsoPlexis Platform and Polyfunctional Strength Index (PSI)



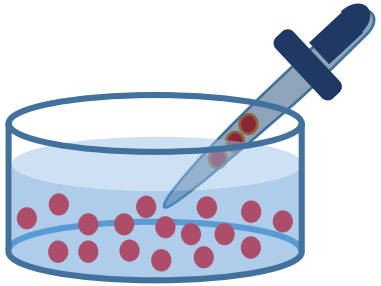


IsoPlexis IsoCode Technology and Ma et al 2013

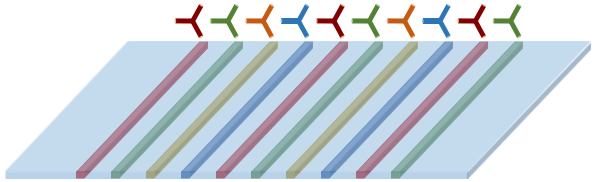
Rossi et al. *Blood* 2018;132:804-814

Analysis of pre-Infusion CAR T cell polyfunctionality on the IsoPlexis Single-Cell, High-Multiplexing ELISA System

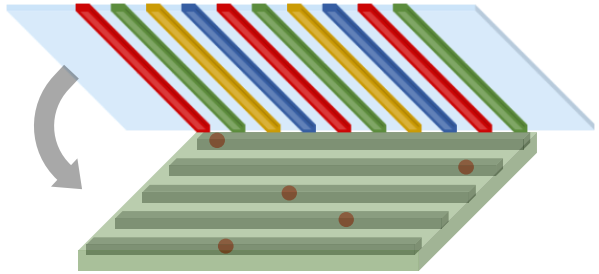
CAR T cells, versus CD19



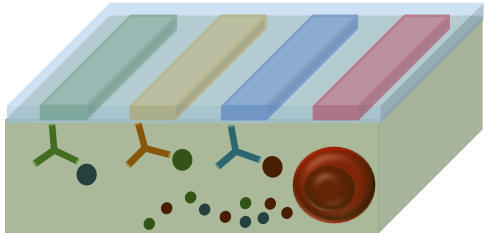
Single-cell antibody barcode cytokine panel



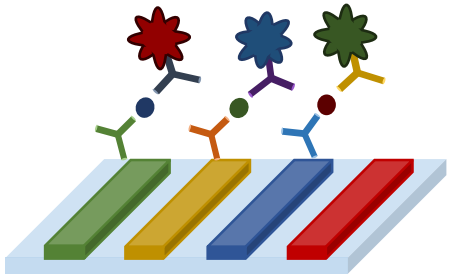
Antibodies “barcode” each single-cell chamber



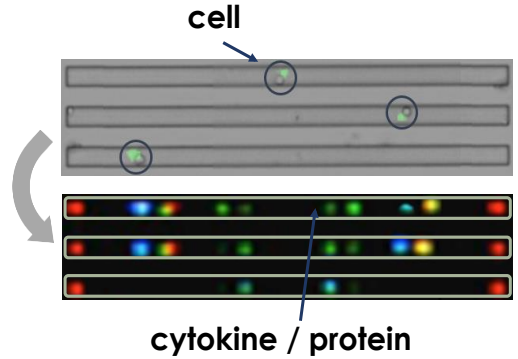
32 cytokines captured, per CAR T cell



ELISA steps allow cytokine monitoring

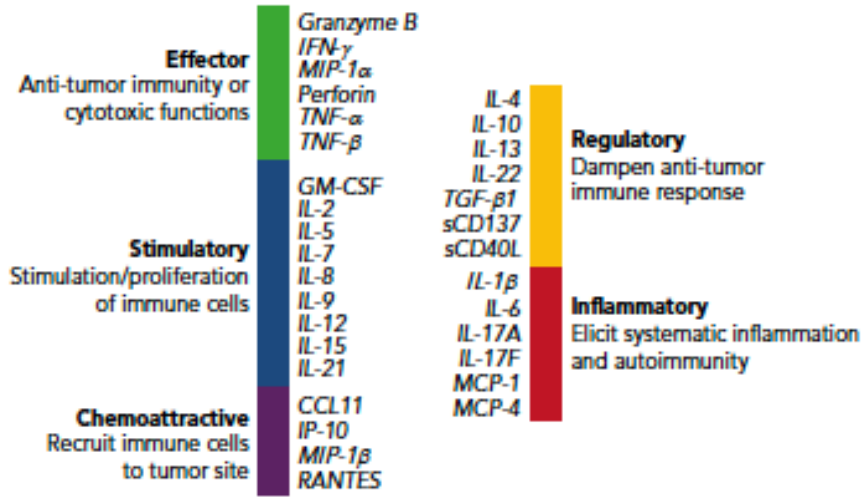


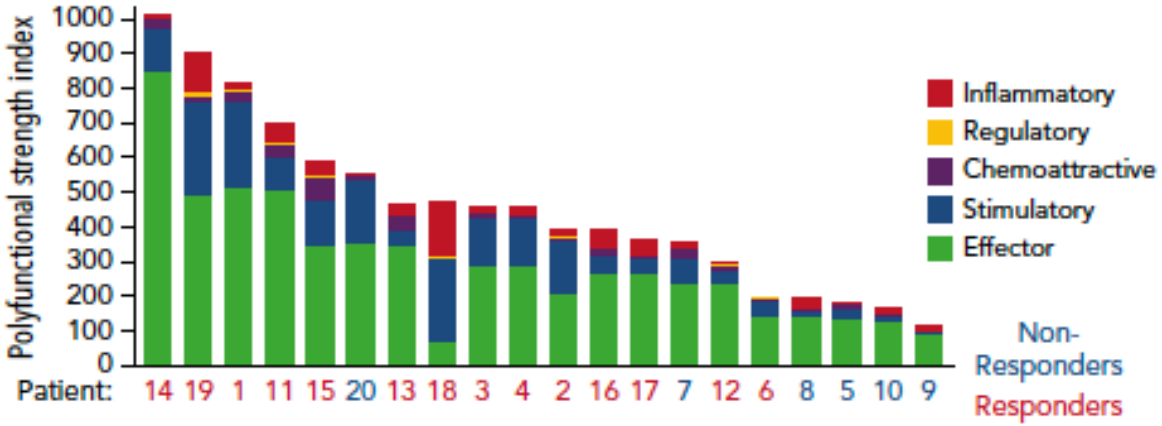
Each “barcoded cytokine readout” per cell x 1000s of patient cells

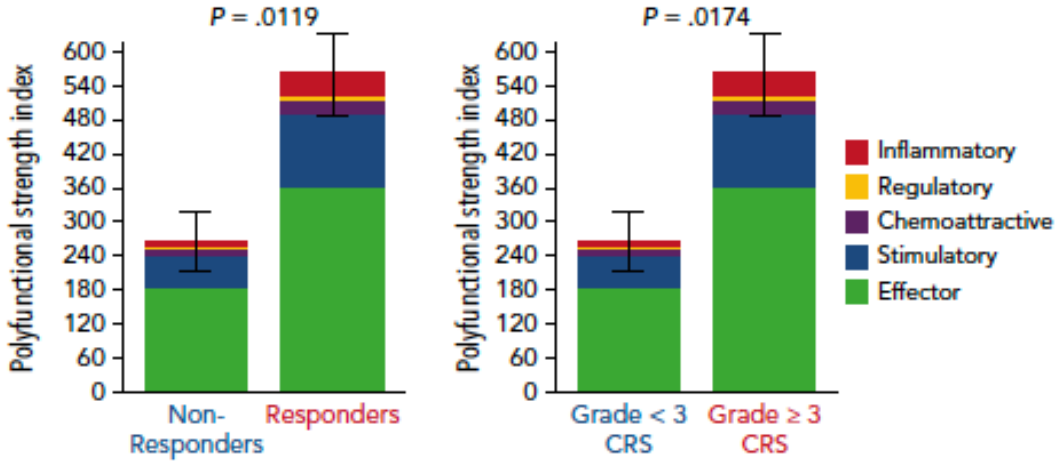


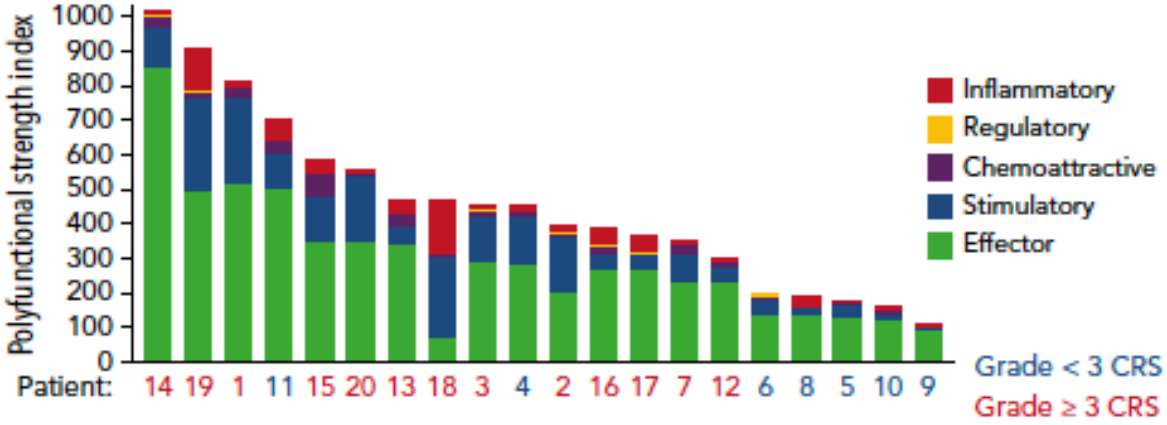
Rossi et al. *Blood* 2018;132:804-814

Autologous CAR-T products are heterogeneous: Impact on safety and efficacy



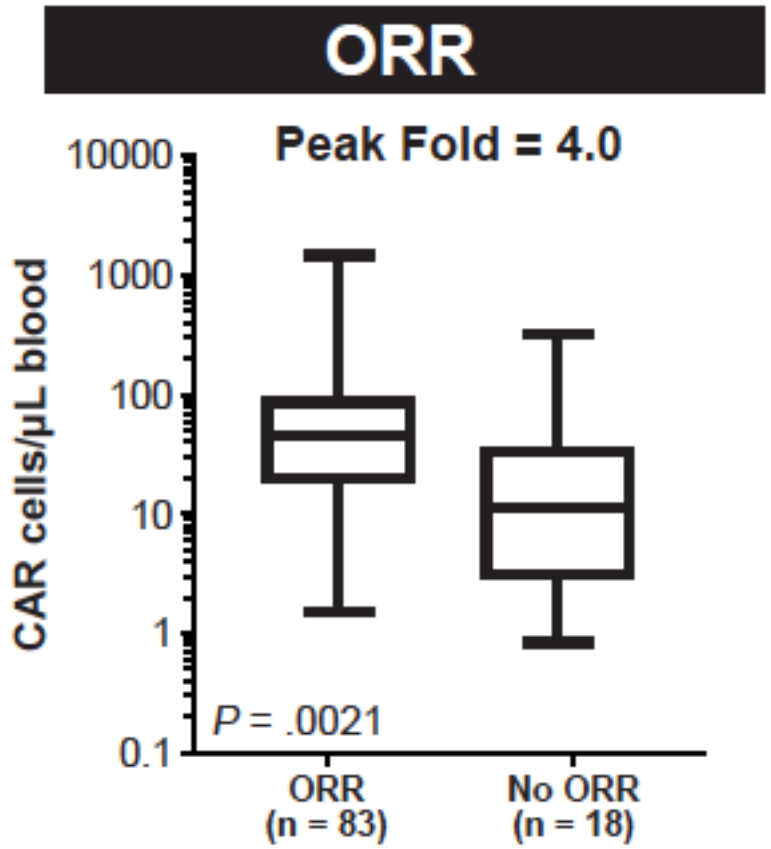


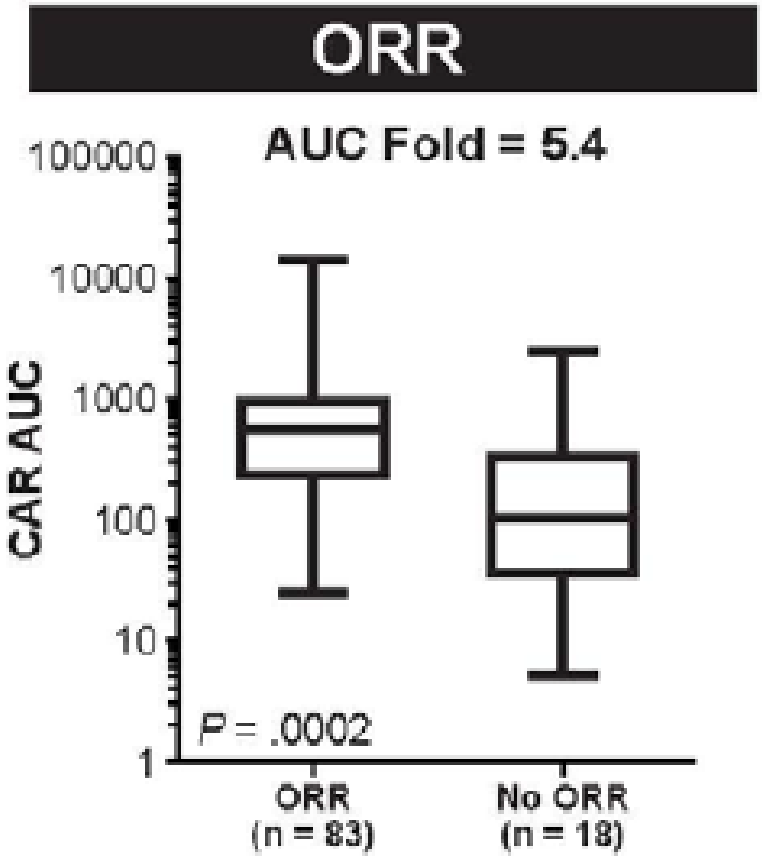




Rossi et al. *Blood* 2018;132:804-814

ZUMA-1: Wide range of peak and AUC levels of autologous CAR-T post-infusion

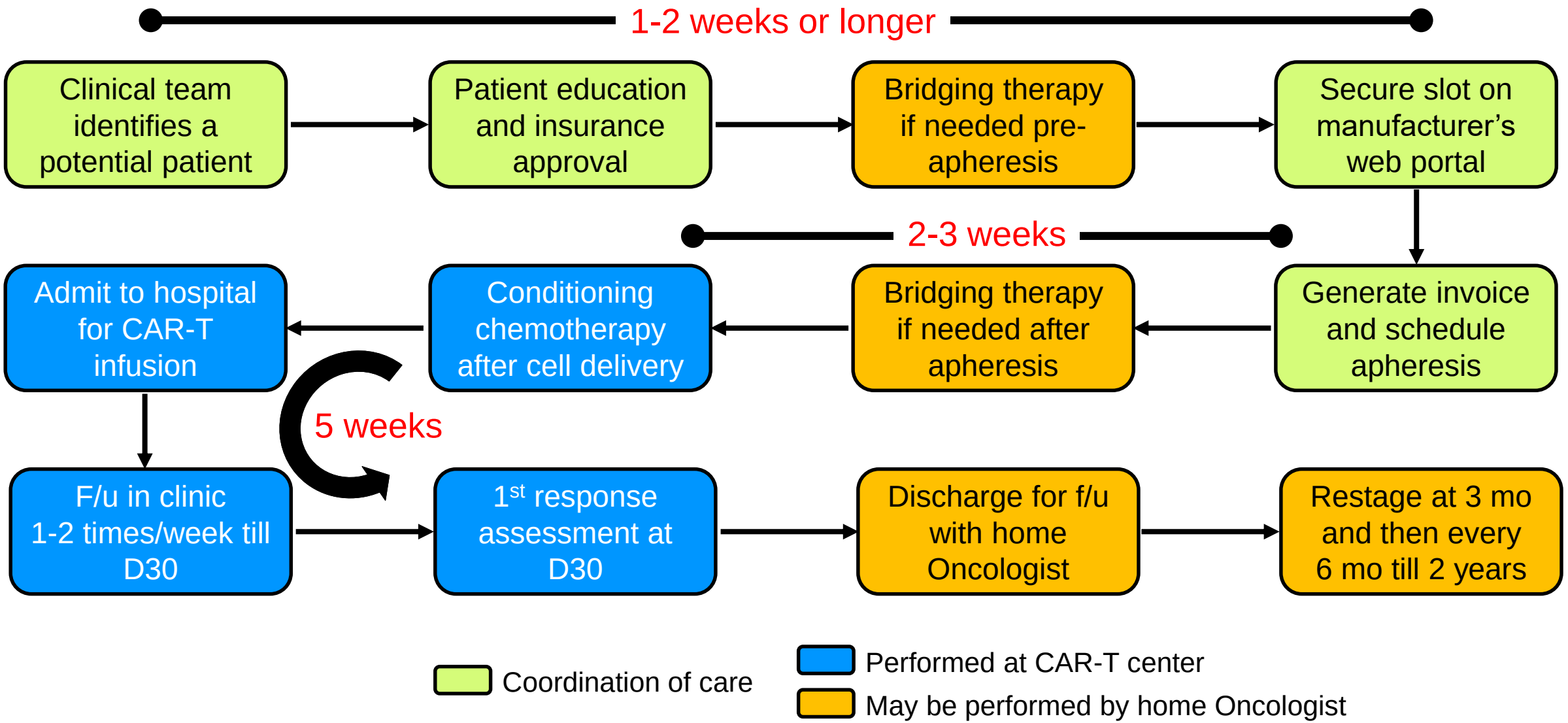




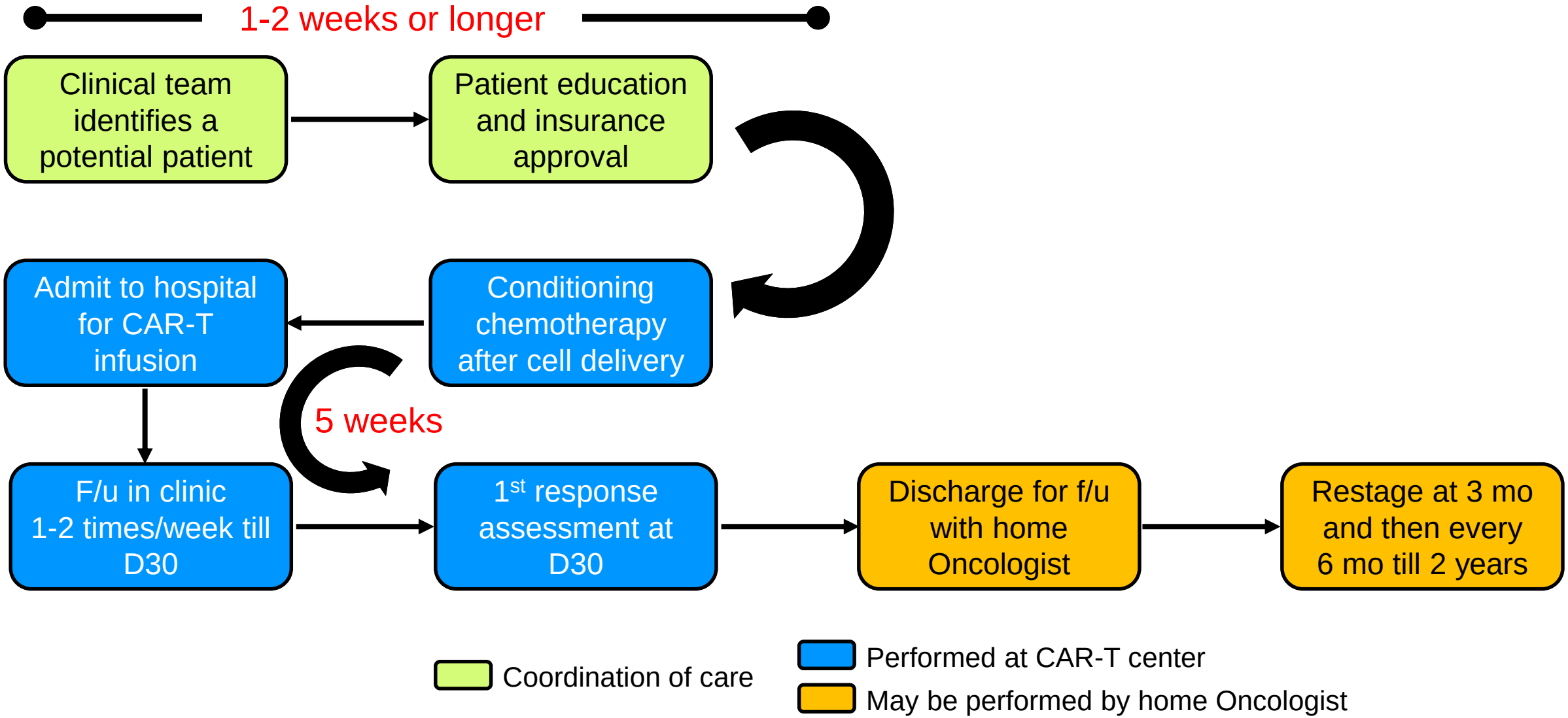
- Unique pharmacokinetics compared with traditional therapeutic agents
- Up to 4-log difference in peak levels and AUC across patients

Neelapu et al. *N Eng J Med* 2017

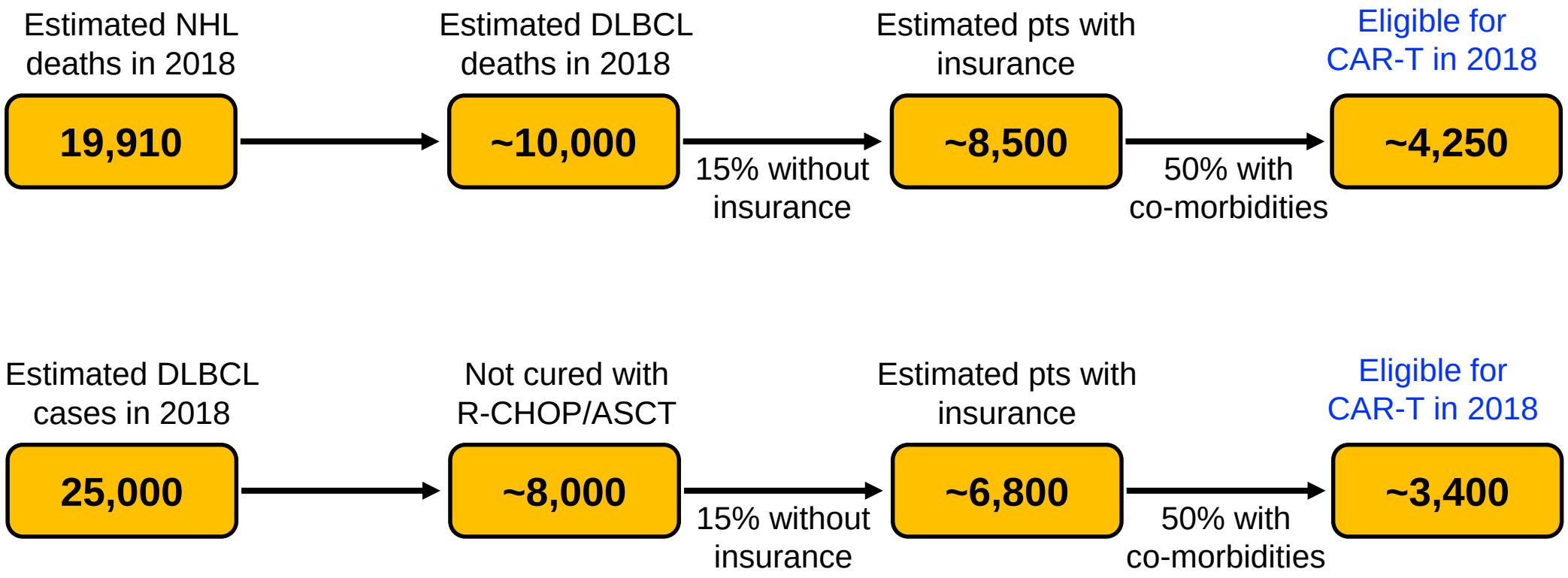
Patient journey in the US with autologous CARs



Expected patient journey in the US with allogeneic CARs



Real-World CAR T Adoption has been slow in US



- **Number of patients treated with axi-cel in 2018 as per Kite/Gilead: ~700**

Reasons for slow CAR T Adoption in US ???

- Authorized centers for Yescarta: started with 16 → currently 80 centers
- Slow roll-out at new centers because of required training of staff and FACT accreditation
- Access to care: Not all patients can travel to authorized centers
- Physician awareness: In an online survey by Medscape between Dec 22, 2017 to Dec 17, 2018, ~60% of community oncologists lacked foundational knowledge of CAR construct and FDA-approved indication for axi-cel (Willis et al, *EHA* 2019)
- Reimbursement issues
  - ✓ Significant delays in pre-approvals from insurers
  - ✓ Major delay in reimbursement decision from CMS for Medicare and Medicaid pts
  - ✓ Hospitals are concerned about financial impact as the reimbursement from CMS does not cover the cost of care or the cost of the CAR-T product
  - ✓ Cost, cost, cost!!!

Referral patterns for CAR-T in US

- Established patients at CAR-T centers are considered for CAR-T as soon as they fail 2nd line therapy
- Patients from non-CAR-T centers are frequently referred after 3 or more lines of therapy, which is not optimal
  - ✓ T-cell fitness may be affected with additional lines of therapy
  - ✓ Tend to have bulkier disease
  - ✓ Frequently cytopenic at the time of referral to CAR-T centers, which delays apheresis
  - ✓ May have more toxicities with CAR-T
  - ✓ Efficacy may also be lower

Challenges with autologous CARs in commercial setting

- About 5% of patients expire prior to apheresis because of delays in insurance approvals
- About 10% of patients expire after apheresis because of rapid disease progression, infection or other complications, or manufacturing failure (1%)
- Some patients have out-of-specification products because of low cell dose, low viability, or either low or high IFN-γ release
  - ✓ Need a trial to allow patients to be treated with out-of-spec products
  - ✓ This is only available at a handful of centers and thus poses a challenge for patient access
- Rapid and reliable turnaround time is essential for optimal patient outcomes
- Patient access
- Cost!!!

Rationale for allogeneic CAR T-cell therapy: Summary

- Potential to improve efficacy as the T-cell fitness is expected to be better than autologous products
- Consistent product quality
- No wait period as they are off-the-shelf
- Potential to lower the cost of CAR T-cell therapy
- Possibly wider access at non-transplant centers
- Long-term B-cell aplasia and hypogammaglobulinemia unlikely
- Long-term risk of insertional mutagenesis unlikely

Outline

- Is there sufficient rationale to develop allogeneic cell therapy?
- Is allogeneic cell therapy likely to be successful?

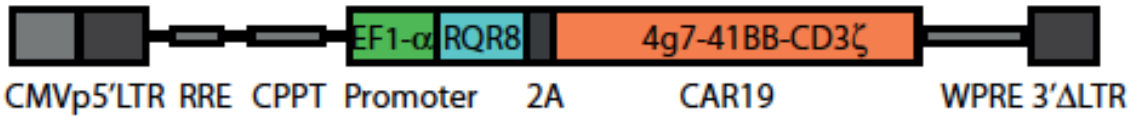
Challenges for allogeneic CAR T-cell therapy

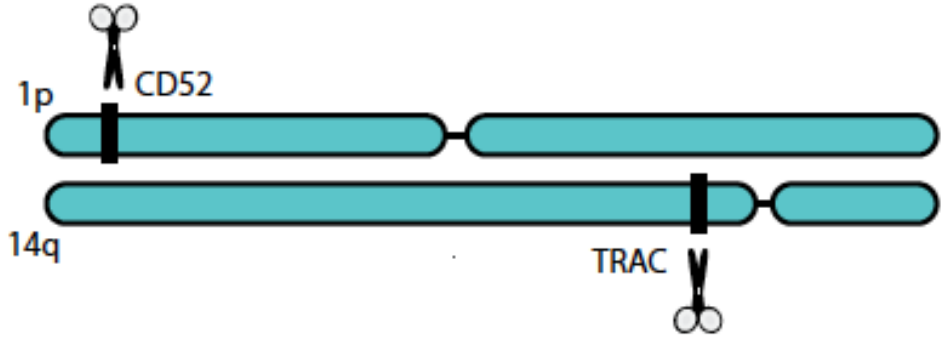
- GVHD
- Graft rejection / persistence

Short-term efficacy of allogeneic CAR-T comparable to autologous CAR-T in ALL

Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells

Waseem Qasim,[1,2]* Hong Zhan,[1] Sujith Samarasinghe,[2] Stuart Adams,[2] Persis Amrolia,[1,2] Sian Stafford,[1] Katie Butler,[1] Christine Rivat,[1] Gary Wright,[2] Kathy Somana,[2] Sara Ghorashian,[1] Danielle Pinner,[2] Gul Ahsan,[2] Kimberly Gilmour,[2] Giovanna Lucchini,[2] Sarah Inglott,[2] William Mifsud,[2] Robert Chiesa,[2] Karl S. Peggs,[3] Lucas Chan,[4] Farzin Farzaneh,[4] Adrian J. Thrasher,[1] Ajay Vora,[5] Martin Pule,[3] Paul Veys[1]





Disrupt TRAC (loss of TCR$\alpha\beta$) to prevent GVHD

Qasim et al. *Sci Transl Med* 2017

PALL Study in pediatric ALL

- 5 children treated
- 5/5 CRi → alloHSCT → 2 alive in CR, 2 relapse, 1 death in CR
- Persistence for up to 3 months

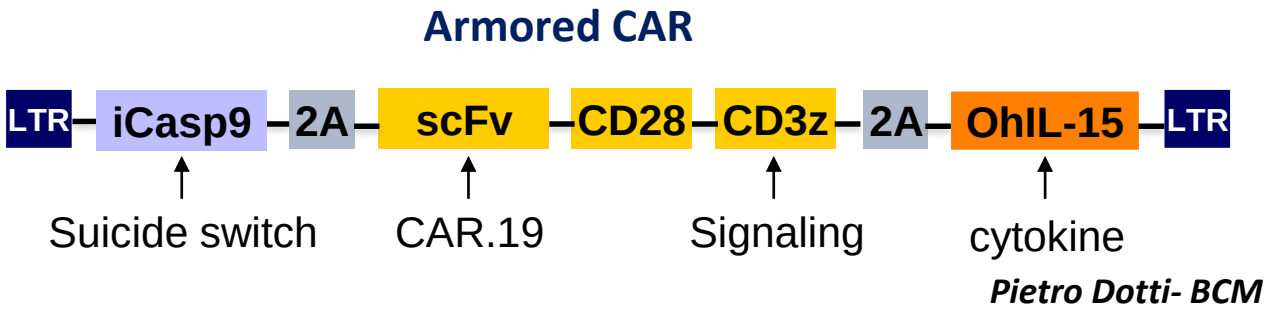
Qasim et al. *ASH 2017*, Abstract 1271

CALM study in adult ALL

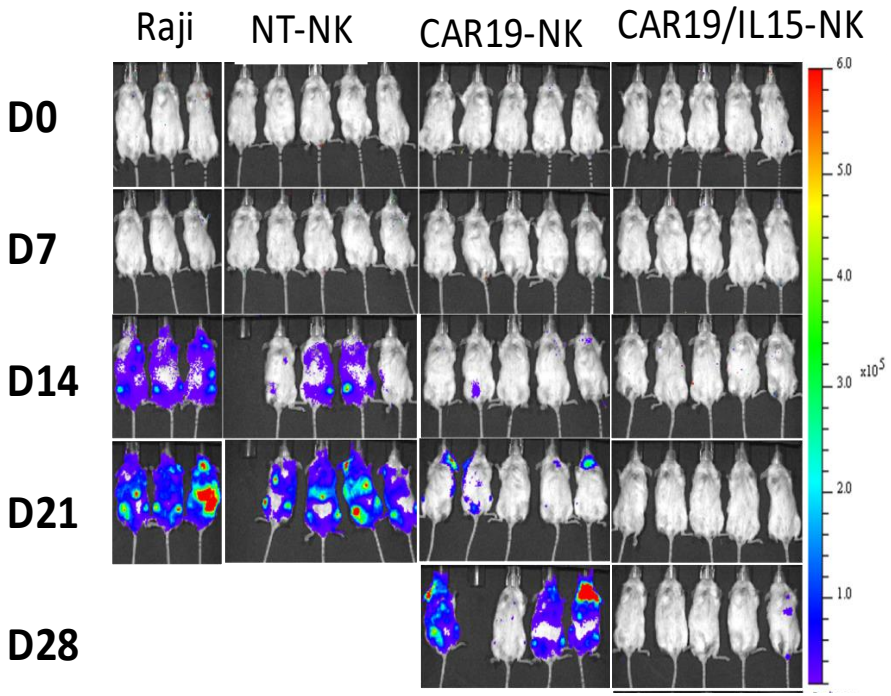
- 6 adults treated
- 4/6 CRi → alloHSCT → 2 alive in CR, 1 relapse, 1 death in CR

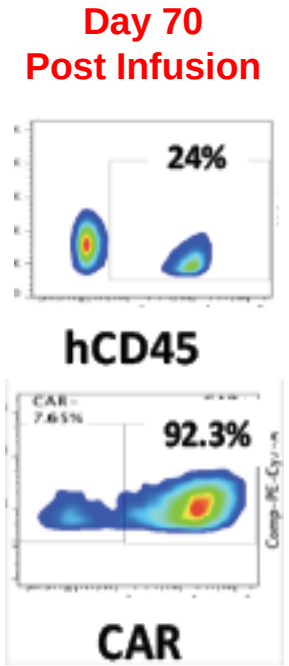
Graham et al. *ASH 2017*, Abstract 887

Allogeneic CAR-NK cell therapy



Pietro Dotti- BCM





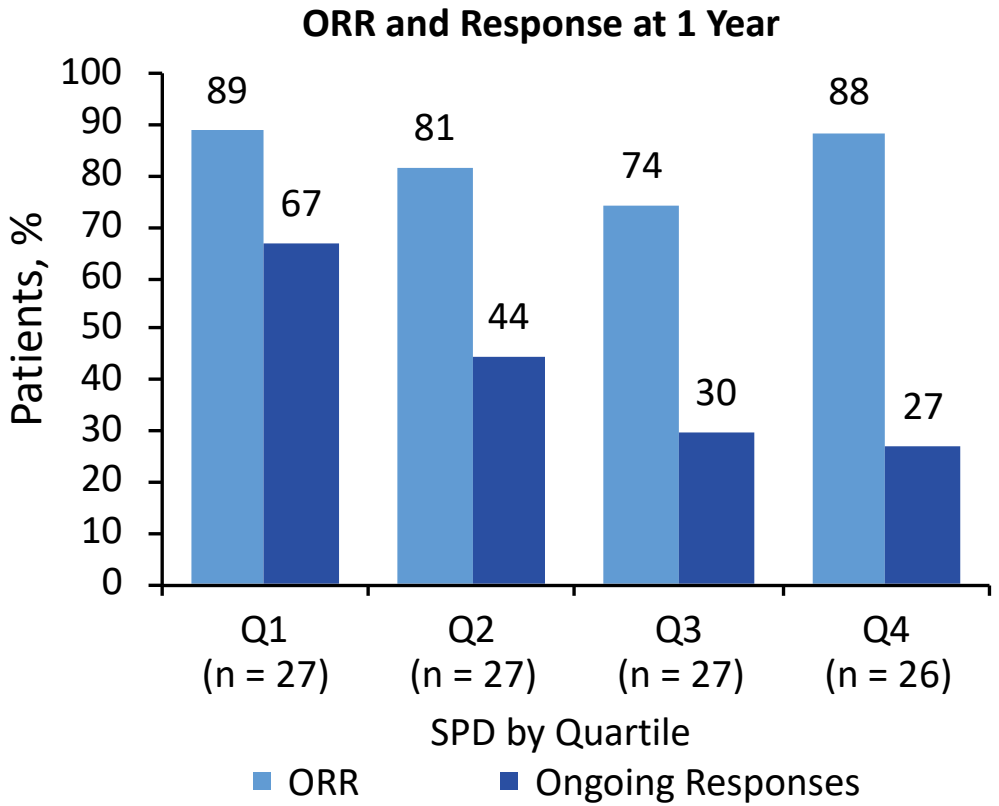
- No risk of GVHD with allogeneic NK cells
- > 100 doses of CAR-NK from one cord unit
- More homogeneous product
- First-in-human phase I/II trial of CAR-NK cells at MDACC in NHL, CLL, and ALL
- Dose escalation: 1 x 10^5/kg; 1 x 10^6/kg; 1 x 10^7/kg
- Cy-Flu conditioning chemotherapy

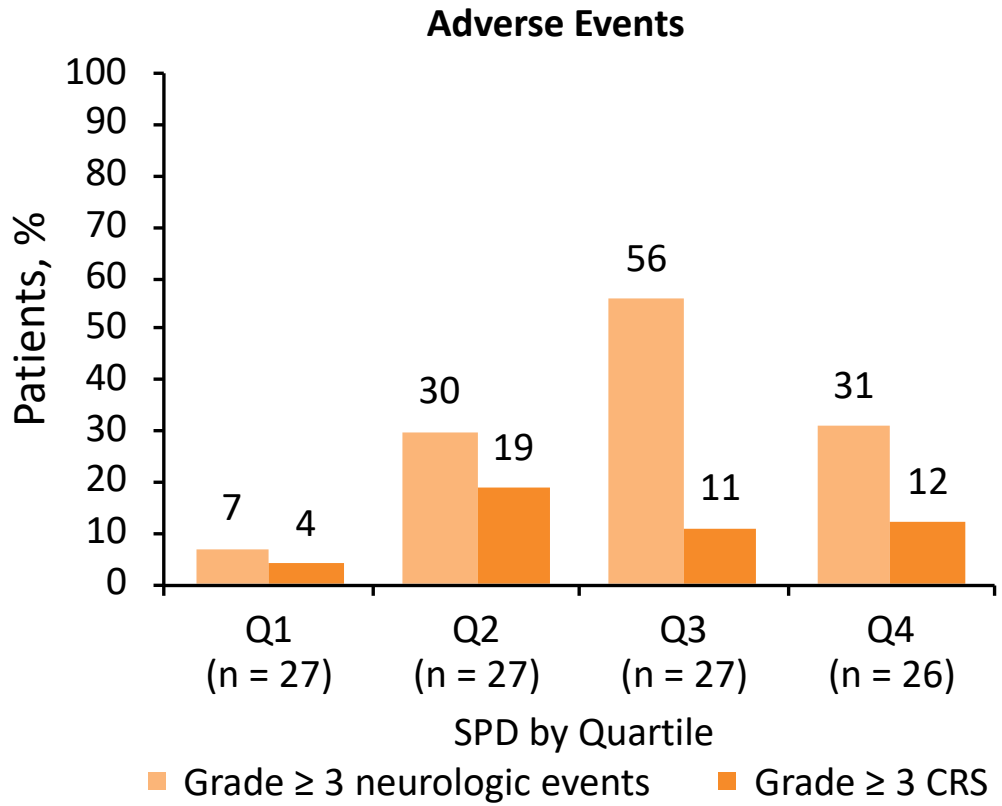
- **7/9 CRs in DLBCL, FL, CLL, Richter's**
- **No CRS or ICANS**

Liu et al. *Leukemia* 2018

Provided by Katy Rezvani, MDACC

ZUMA-1: Outcomes better with lower tumor burden in r/r DLBCL after axi-cel





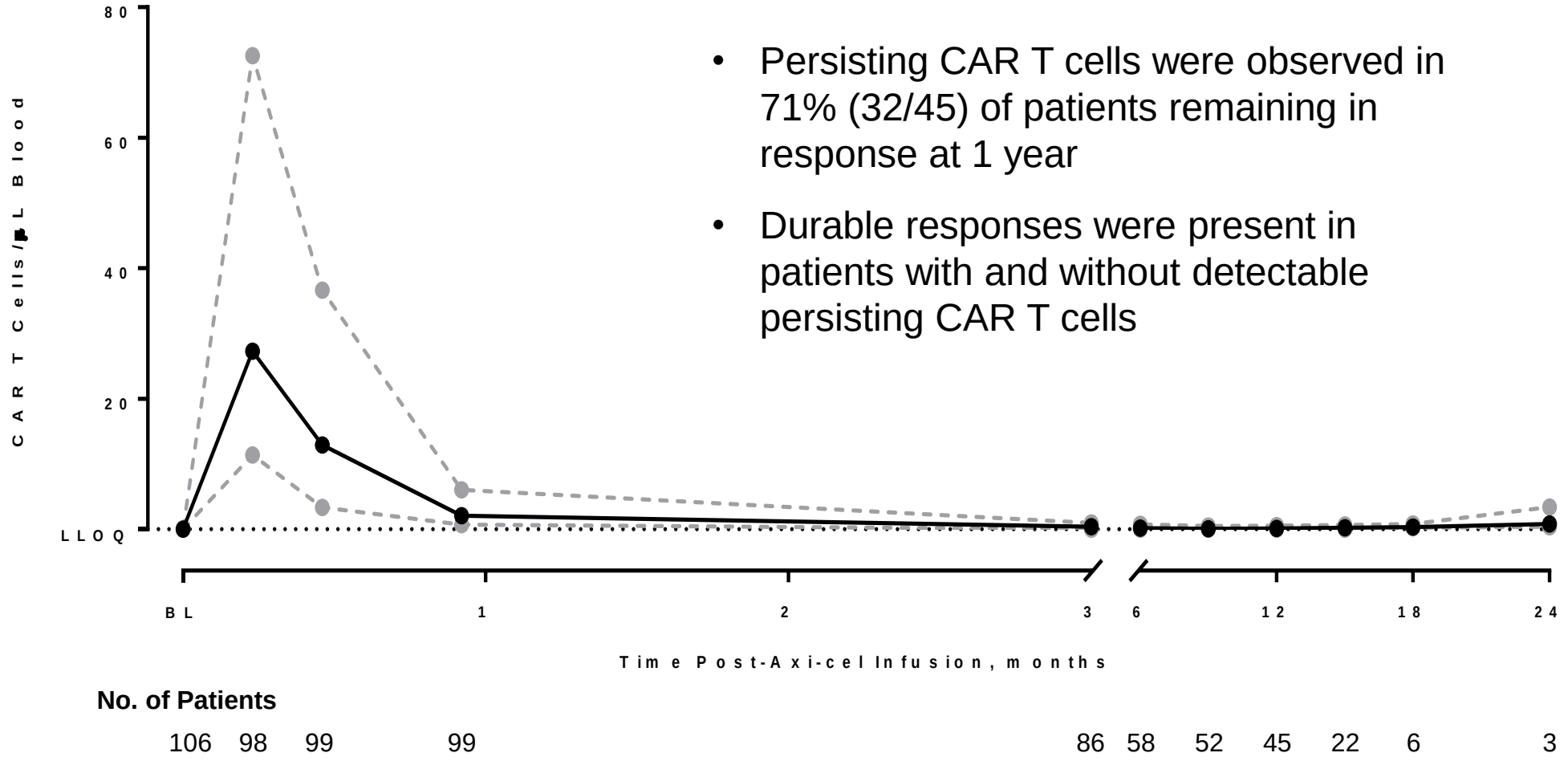
- **Shortening wait times with allogeneic CARs would allow treating patients with lower tumor burden**

Neelapu et al. SOHO 2018

Long-term persistence of CAR T cells may not be needed to achieve cures in NHL

- R-CHOP chemotherapy does not persist long-term but cures ~60% of DLBCL patients
- If every cancer cell in the body is eliminated within the first 1-3 months, long-term persistence of CAR T cells is not needed!
- ***Need to cure the cancer only once!***
- Short- to intermediate-term persistence is likely sufficient

ZUMA1: ~30% of patients in remission at 1 year did not have detectable CAR T cells

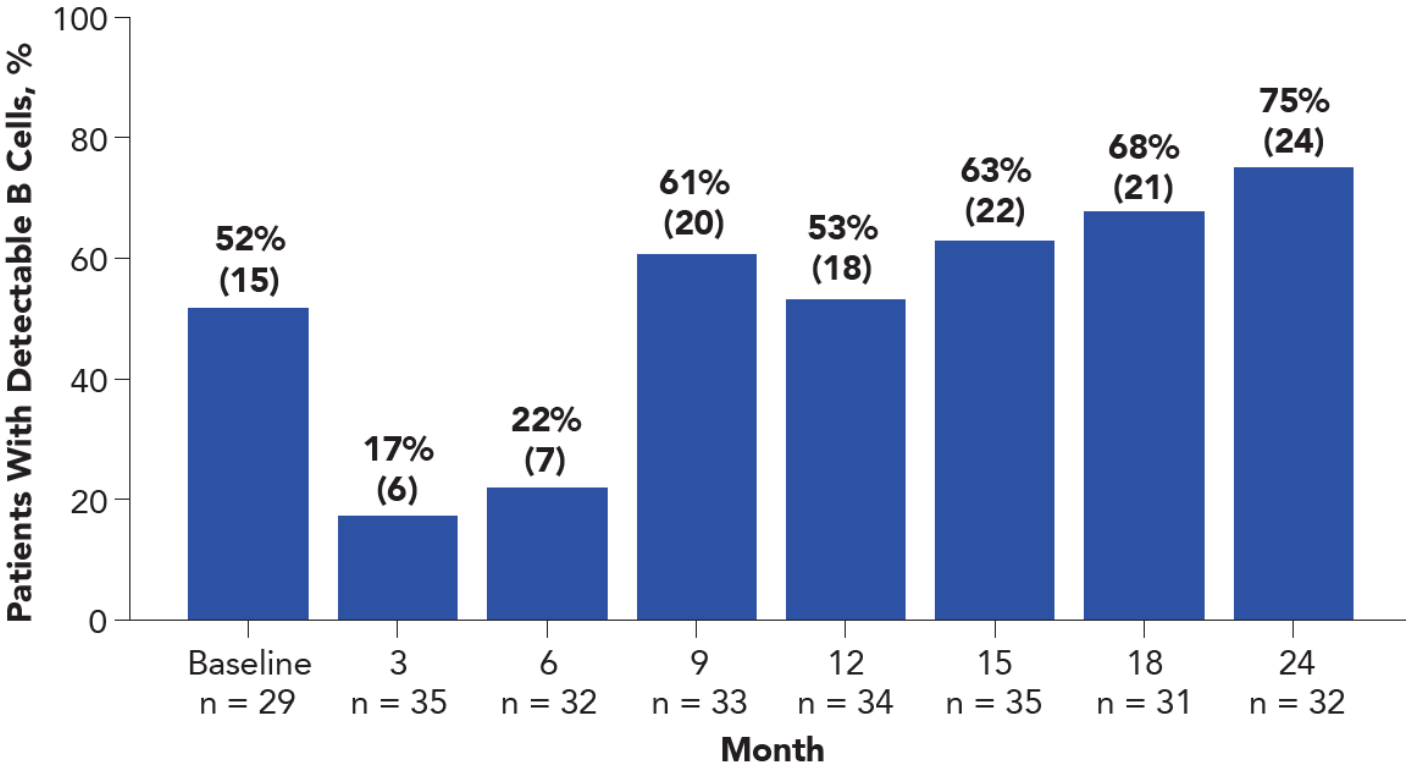


- Persisting CAR T cells were observed in 71% (32/45) of patients remaining in response at 1 year
- Durable responses were present in patients with and without detectable persisting CAR T cells

BL, baseline; LLOQ, lower level of quantification.
Solid line indicates median. Dashed lines indicate Q1 and Q3.

Neelapu et al. ASH 2017

ZUMA1: 75% of patients in remission at 2 years had detectable B cells

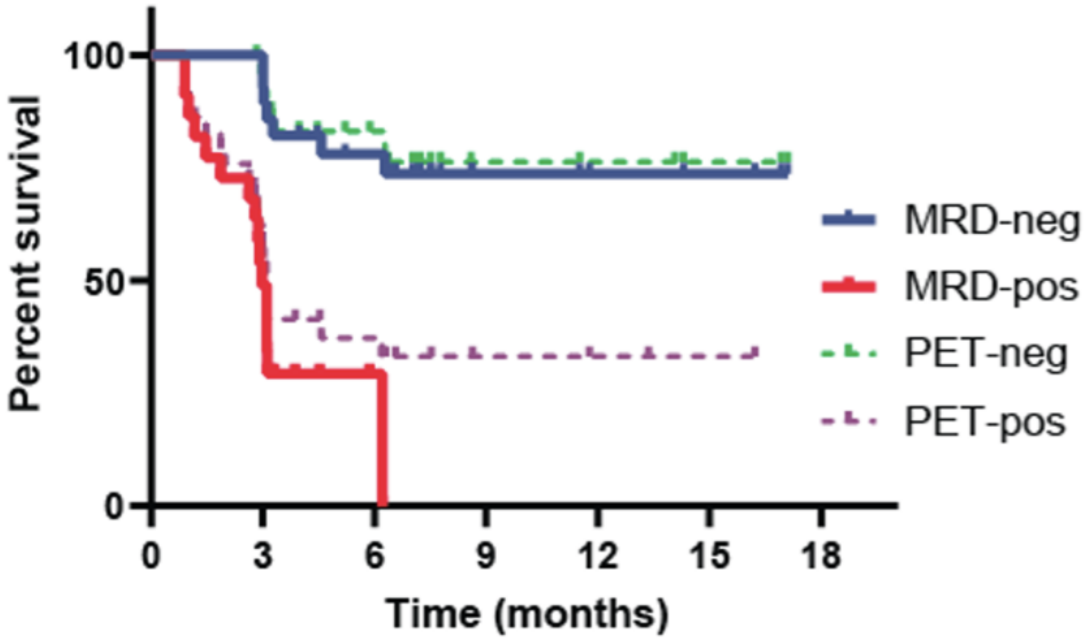


- 75% of patients (24/32) with ongoing responses had detectable B cells 2 years after axi-cel infusion
- Throughout the course of the study, 31% of patients received intravenous immunoglobulins

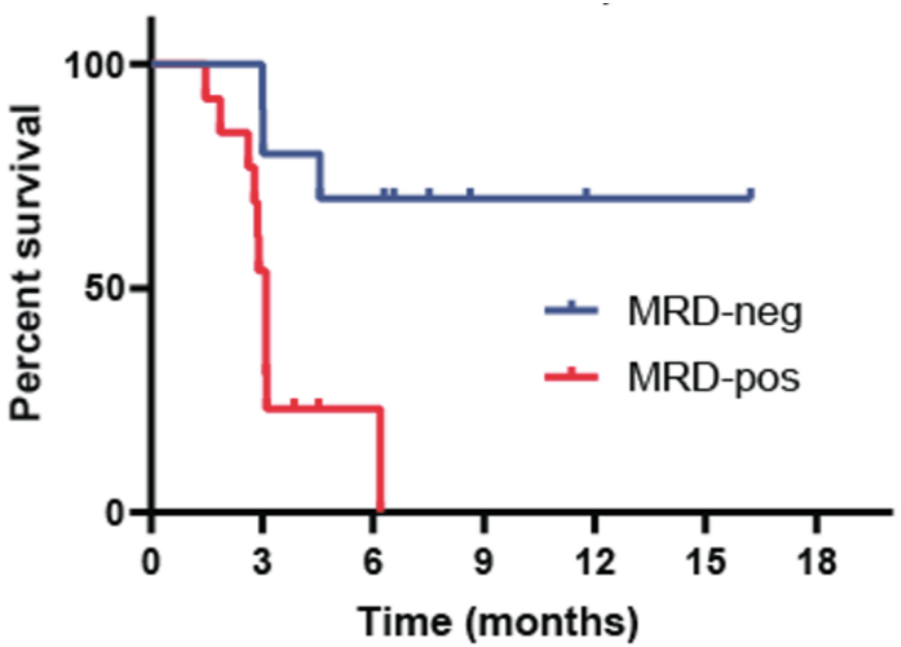
Locke et al Neelapu, *Lancet Oncol* 2019

MDR negativity at day 28 strongly associated with durability in DLBCL after axi-cel

PFS by Day 28 MRD or Day 28 PET



PFS by Day 28 MRD in patients with PR/SD by D28 PET



Frank et al, *ASH* 2019, Abstract 884

Is allogeneic CAR T-cell therapy likely to be successful?

Summary

- Short-term efficacy in ALL with allogeneic CAR T is comparable to autologous CAR T
- Data from autologous CD19 CAR T in DLBCL suggests that cures are likely occurring within 1-3 months and long-term persistence of CAR T cells may not be needed to maintain durability
- Potential to improve efficacy with allogeneic CARs as the T-cell fitness is expected to be better than autologous products
- Shortening wait times with allogeneic CARs would allow treating patients with lower tumor burden and may improve efficacy

Guest Speaker Panel Discussion and Q&A

Guest Speaker Panel Discussion Participants

Sattva Neelapu, MD

MD Anderson
Cancer Center

Bijal Shah, MD

Moffitt
Cancer Center

Marco Davila, MD, PhD

Moffitt
Cancer Center

Closing Remarks

Matt Kane, CEO & co-founder

ASH Highlights – Emerging Leadership in Allogeneic CAR T

- Differentiated approach to allogeneic CAR T made possible by unique ARCUS genome editing technology. Approach protected by substantial know-how and investment
- Initial validating first-in-man data for PBCAR0191 presented at ASH
  - Clear objective tumor responses demonstrated at first two, relatively low, dose levels. Safety profile so far compares favorably to autologous CAR T
  - Early evidence of dose-dependent mechanism of action, to be further explored
- Evidence that by focusing on cell quality and consistency, allogeneic CAR T can be efficacious in true "off-the-shelf" setting – without harsh biologic lymphodepletion. **First time this has ever been shown**
- Data de-risk rest of Precision CAR T portfolio, which is moving forward rapidly
- Clear path to further optimization of approach, and potential expansion into solid tumors

Multiple Key Milestones Achieved – Strong Momentum into 2020

- ✓ Initial Public Offering (Ticker: DTIL) - Q2 2019
- ✓ Clinical dosing of allogeneic CD19 CAR T - Q2 2019
- ✓ Open cGMP manufacturing facility: CAR T, mRNA, AAV – Q3 2019
- ✓ IND acceptance and ODD for wholly owned CD20 CAR T
- ✓ Interim data from Ph1/2a CD19 CAR T – ASH 2019
- CD19 CAR T Dose Level 3 Data - Q1 2020
- IND for wholly-owned BCMA CAR T - 2020

Cash Runway Takes Us Into 2021

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