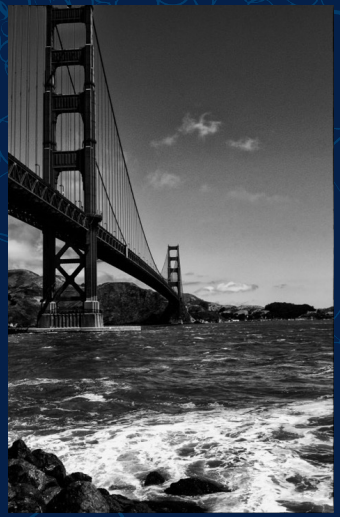
UCSF Helen Diller Family Comprehensive Cancer Center

CAR-T therapies: successes and challenges



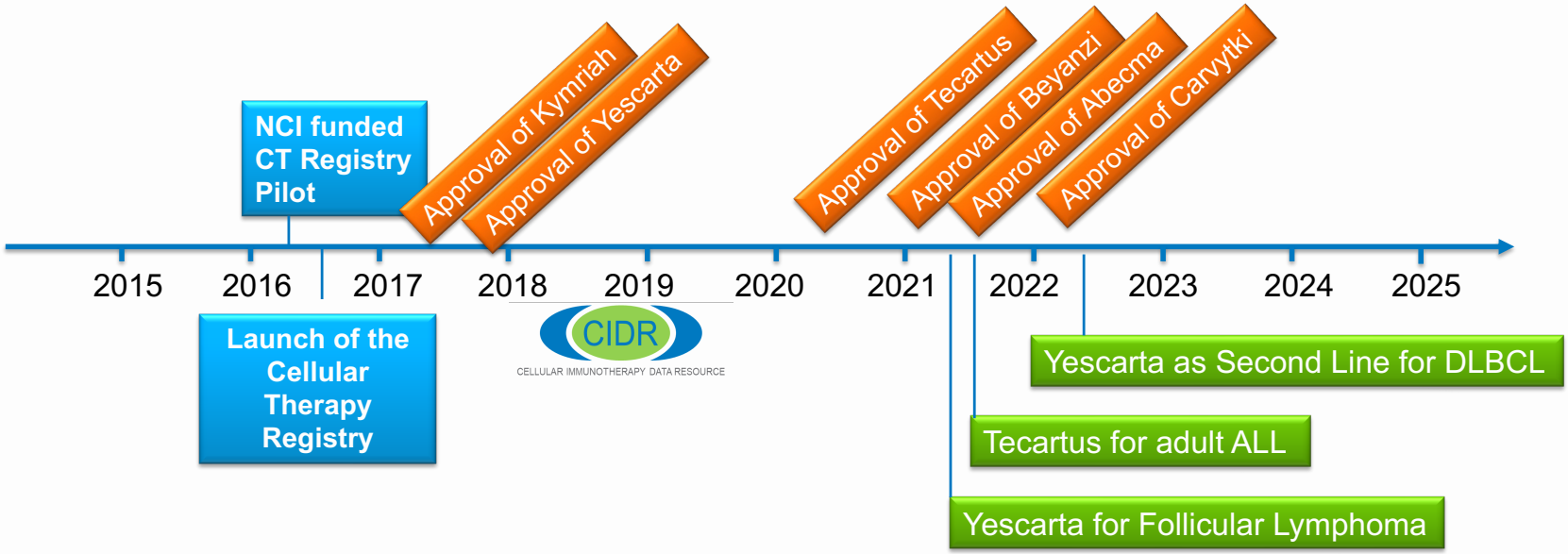
Krishna Komanduri, MD, FASTCT

Julius R. Krevans Distinguished Professor of Medicine

Chief, Division of Hematology/Oncology, UCSF Health

Physician-in-Chief, Helen Diller Family Comprehensive Cancer Center

The Development of the Registry Parallel to the Expansion of the Field of Cellular Immunotherapy

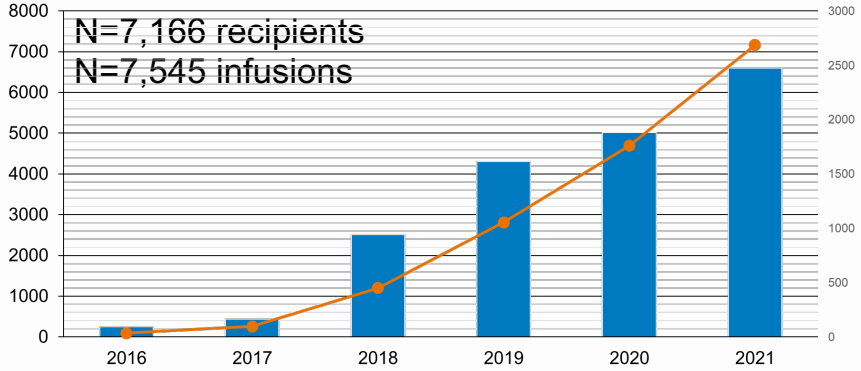


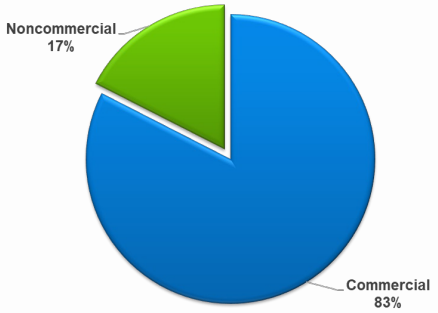
CELEBRATING 50 YEARS 1972-2022
CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

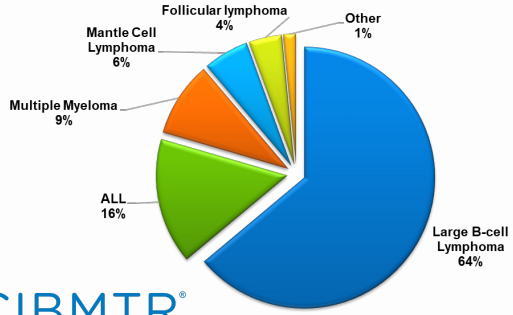
CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

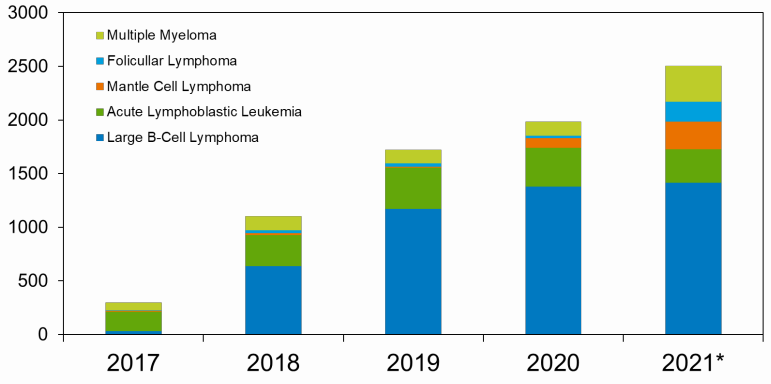
Cellular Immunotherapy Registry at a Glance

CELLULAR IMMUNOTHERAPY DATA RESOURCE









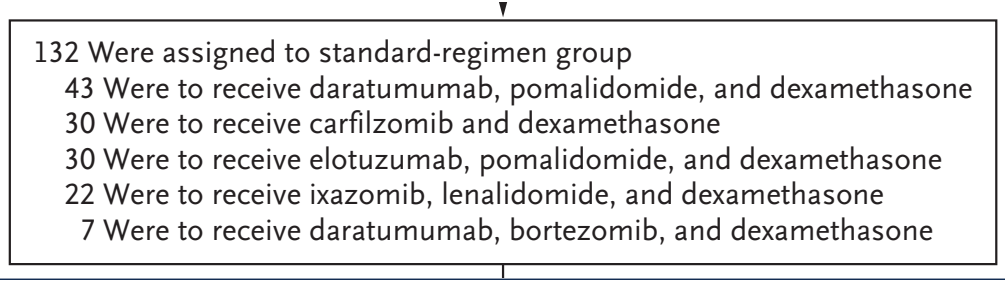
CELEBRATING 50 YEARS 1972-2022

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

CAR-T therapy in second line myeloma

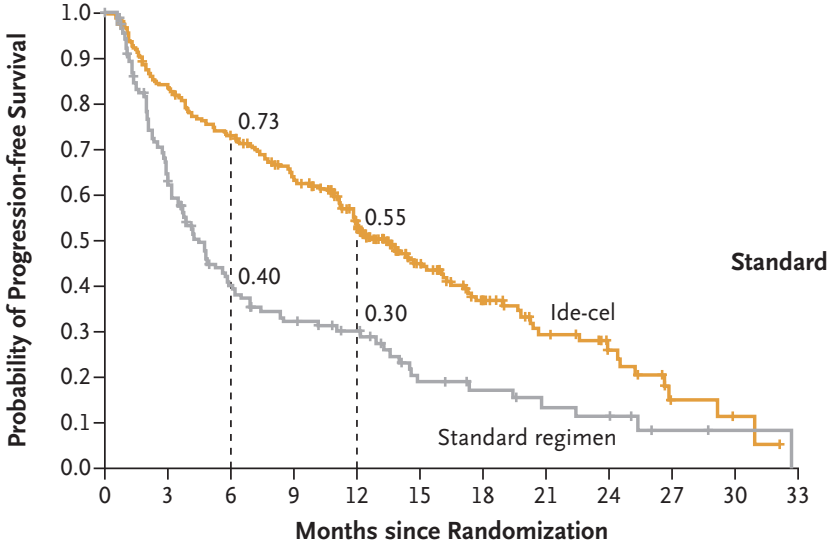
RCT of ide-cel vs. standard regimens in R/R myeloma

- Eligible patients had failed 2-4 prior therapies including daratumumab, an immunomodulatory agent and a proteasome inhibitor
- Documented disease progression within 60 days of the last cycle
- All patients had measurable disease and ECOG 0-1 performance status
- Median age 63 (range 30-83); 42-46% with high-risk cytogenetics
- ~85% had prior autologous SCT
- Ph3 RCT with 2:1 randomization to ide-cel vs. “standard regimens”



Rodriguez-Otero, *NEJM,* 2023

PFS of ide-cel vs. SOC regimens in R/R myeloma



No. at Risk												
Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimen	132	75	42	32	25	13	10	7	6	2	1	0

Median Progression-free Survival (95% CI)	*mo*
Ide-cel	13.3 (11.8–16.1)
Standard Regimen	4.4 (3.4–5.9)

Hazard ratio for disease progression or death, 0.49 (95% CI, 0.38–0.65)
P<0.001

Rodriguez-Otero, *NEJM,* 2023

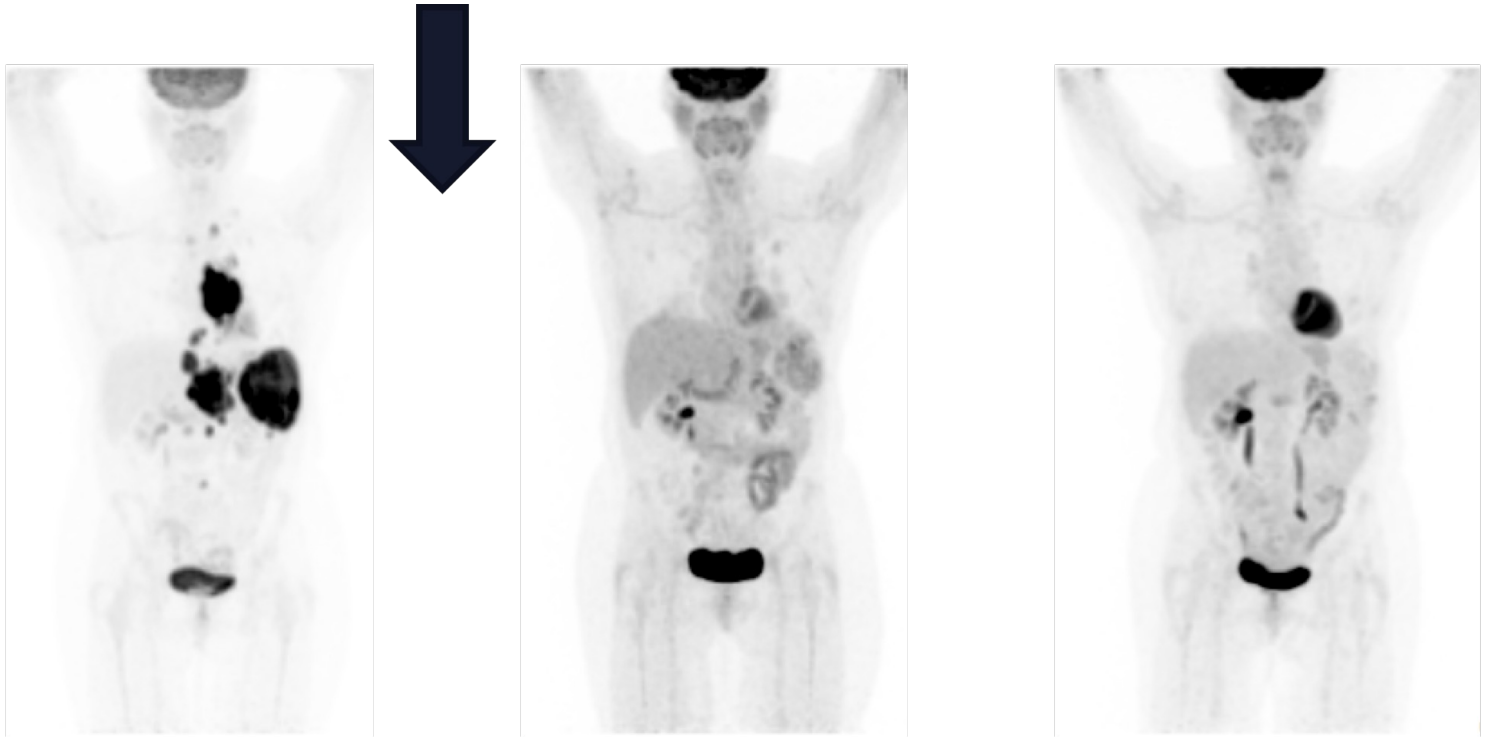
RCT of ide-cel vs. standard regimens in R/R myeloma

- Overall, ide-cel outperformed other SOC regimens in this population
- However, no plateau suggesting curative potential evident in PFS curves
- When progression did occur, BCMA (target) downregulation was NOT seen, in contrast to frequent target loss in CD19 CAR-T treatment failures

Rodriguez-Otero, *NEJM,* 2023

Updates: CAR-T therapies in NHL

CAR-T response to axi-cel after six prior lines of therapy



December 2015 February 2016 April 2016

Images by
Lazaros Lekakis, MD

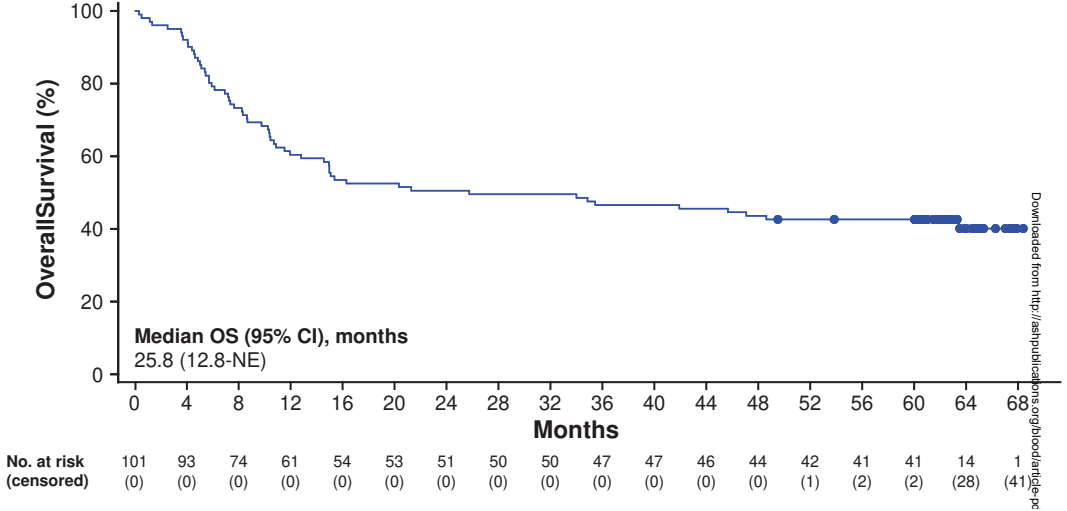
Neelapu, et al., long-term F/U of ZUMA-1 study in NHL

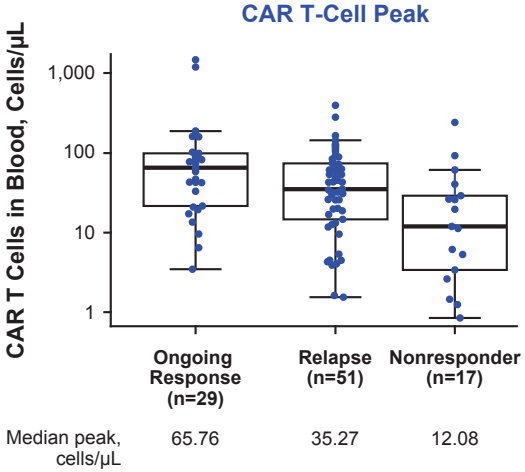
- Reported LTFU of patients treated with axi-cel for R/R LBCL (n=101)
- High-risk patients failing at least two prior lines of therapy, median age of 58
- Median F/U now 63 months
- Five-year OS 43%; PFS 32%
- Patients who had no defining events by 12 months had >90% OS at 5y
- Five deaths beyond year 3: one progressive disease and one secondary malignancy
- Secondary analyses reported positive association between early CAR-T expansion (peak numbers and AUC) and maintenance of long-term responses

Neelapu, et al., *Blood*, in press 2023

Is cell therapy standard of care for 2nd line DLBCL?

Neelapu, et al., long-term F/U of ZUMA-1 study in NHL





Neelapu, et al., *Blood*, in press 2023

UCSF Helen Diller Family Comprehensive Cancer Center

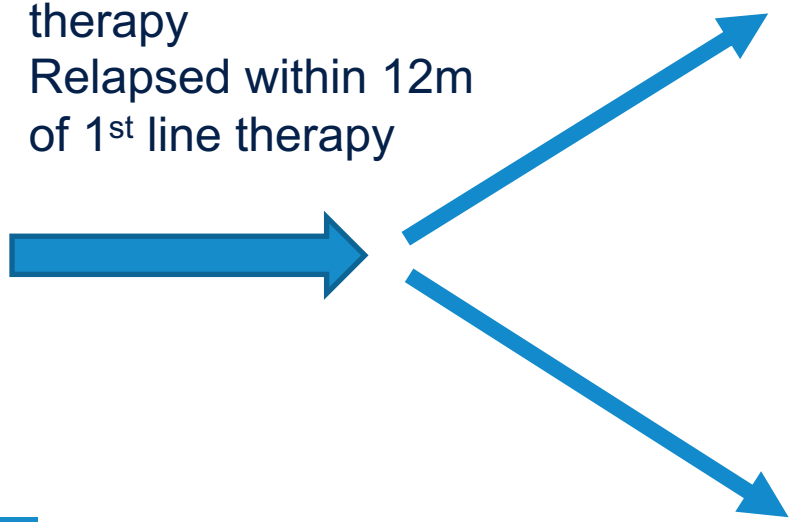
CD19 CAR T-cells in DLBCL: Earlier Lines

ZUMA-7
Axi-cel

BELINDA
Tisa-cel

TRANSFORM
Liso-cel

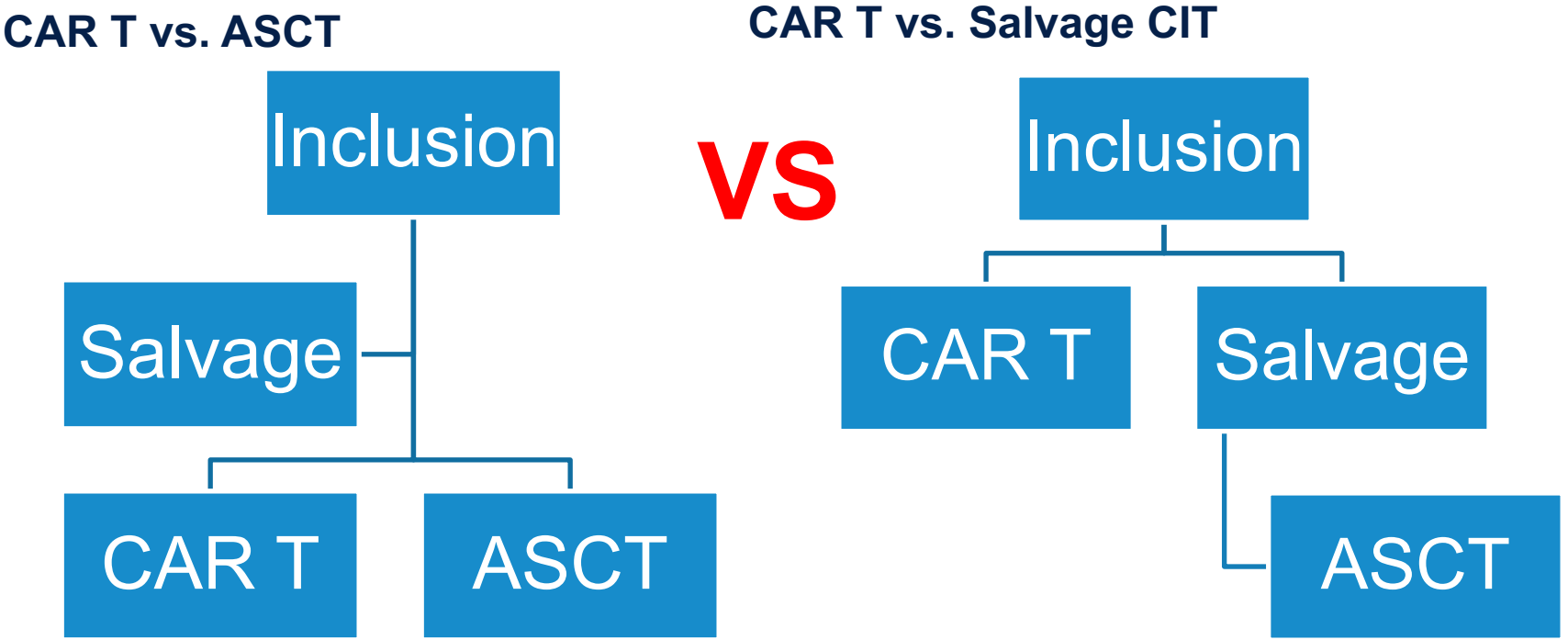
High Risk DLBCL:
- Refractory to 1st line therapy
- Relapsed within 12m of 1st line therapy



CAR T

Salvage /Auto

Which is the better study design?



Is CAR-T therapy the 2nd line DLBCL standard?

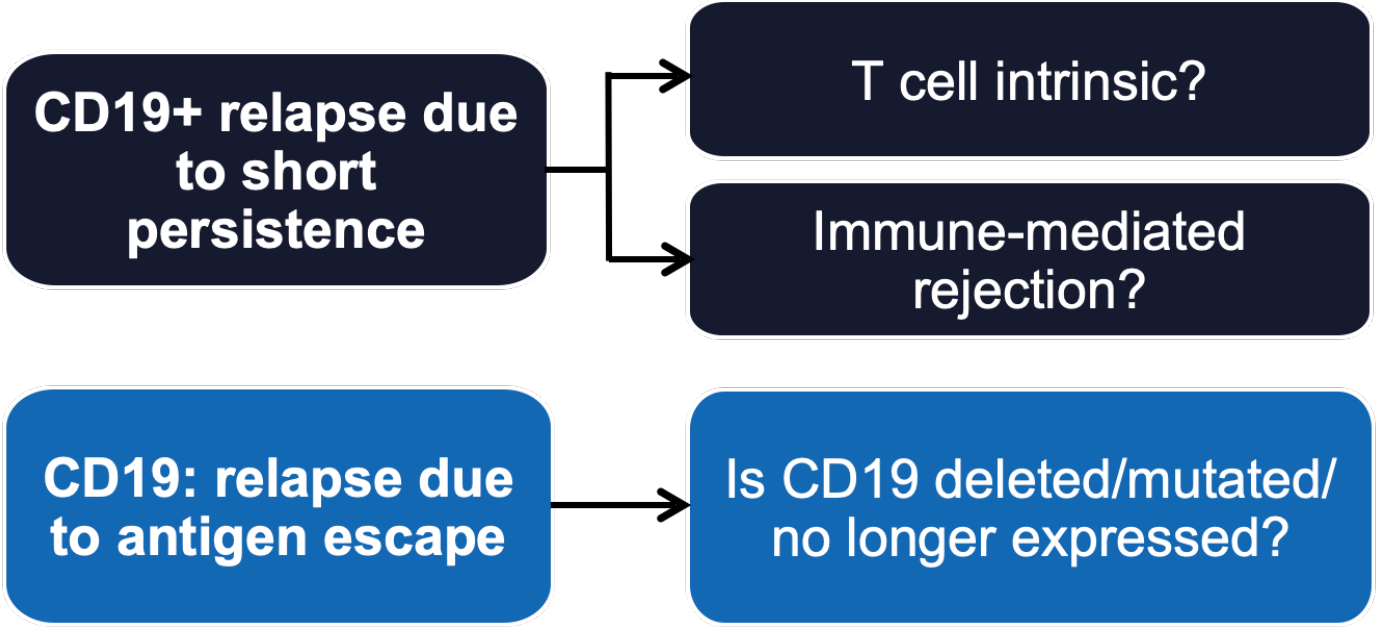
- Two of three RCTs favored CAR-T therapy in the second line setting (ZUMA-7 and TRANSFORM)
- RCTs demonstrated traditional salvage therapies are suboptimally effective (<40% achieved PR and had AutoSCT)
- Retrospective analyses suggest individuals who achieved a PR can do quite well with AutoSCT
- Key practical question is for someone responding to salvage, what to do? Many would still do a transplant for patients achieving a CR.
- All current data prone to selection bias
- Additional data (including from registries) needed
- Additional RCTs would be helpful (but are unlikely)

What about fourth line? First line?

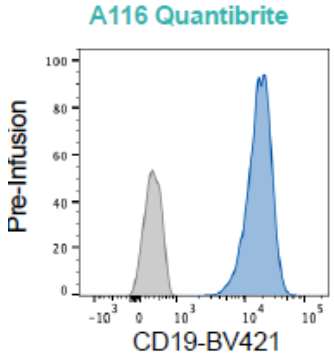
- We need better therapies following CAR-T failure
- Long-term results of all three commercial products suggest only 30-40% cure rates
- CAR-T trials (including CD19/22) demonstrate ≤30% ORR
- Second-line CAR-T therapies (following first failure) are needed
- First-line studies promising (ZUMA-12, Neelapu, *Nat Med* 2022) look very promising but additional data, RCTs needed.

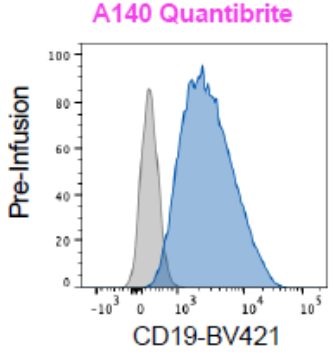
Can we predict cellular therapy failures?

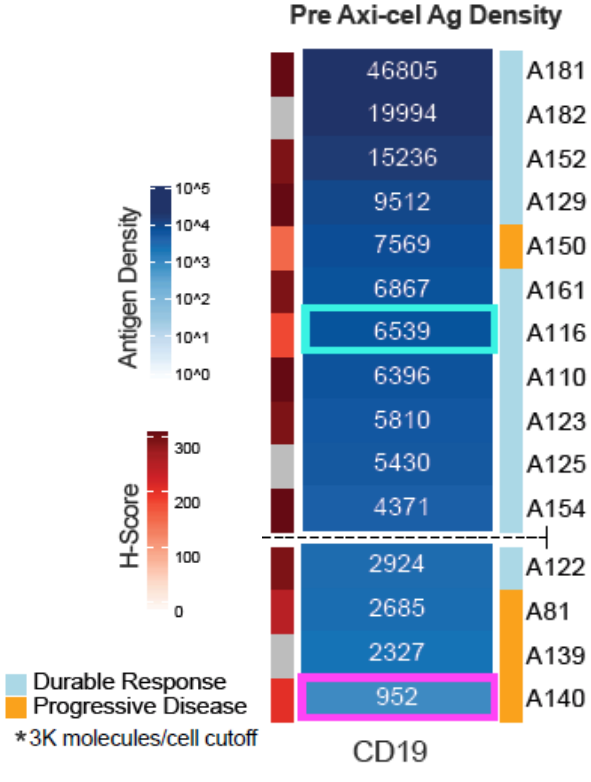
Mechanisms of relapse after CD19 CAR-T therapy



Pre-treatment quantitative flow (but not IHC) may identify patients at risk for treatment failure



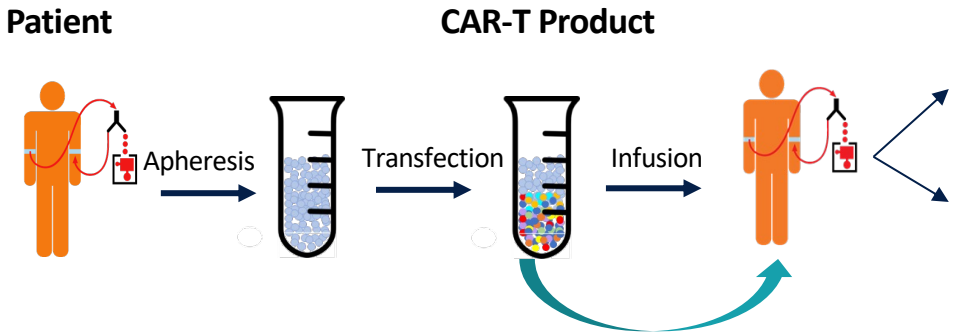


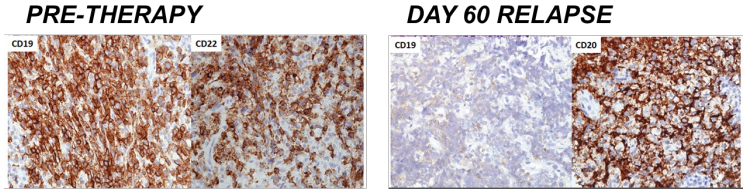


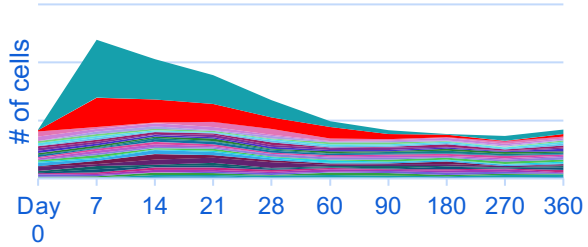
Spiegel, *Nat Medicine* 2021

Optimizing CAR-T Therapy: Model by Spiegel and Miklos

Tumor Biology:
- Tumor Antigen Density
- Tumor microenvironment





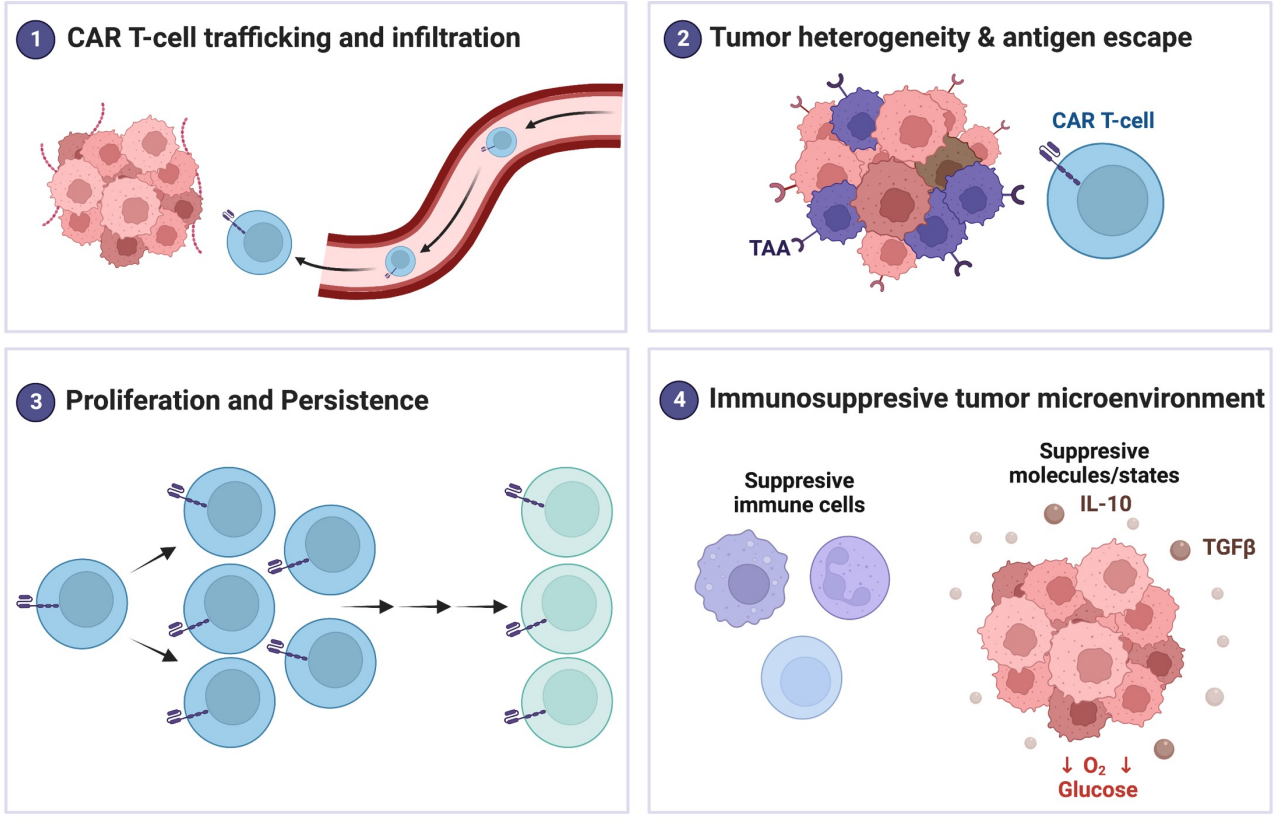


CAR-T Product Fitness:
- Patient T cell fitness
- CAR-T construct
- CAR-T manufacturing

CAR-T Pharmacokinetics and Pharmacodynamics
- Characterize which CAR-T localize to tumor
- Immune Phenotype of CAR-T blood expansion

from Spiegel and Komanduri, *Blood Feb 17, 2022*

Challenges for CAR-T cell efficacy/safety



adapted from slide by Julia Carnevale, MD, UCSF

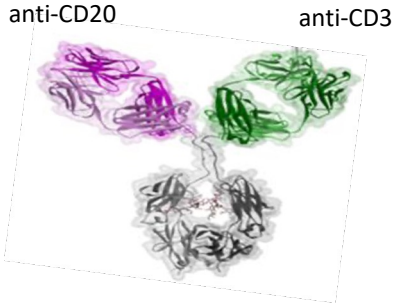
What developments will make a difference?

- Allogeneic CAR-T therapies are promising (limited data, and potential problems, including need for aggressive T cell depletion)
- Additional targets beyond those initially targeted (e.g., beyond CD19/BCMA) alone and bispecific/bicistronic therapies (e.g., CD20, CD22, CD19/20, CD19/22)
- NK cell therapies are exploding (including NK-CAR therapies) and appear promising, though with relatively limited data
- More therapies tested and approved for pediatric subjects (*just one to date)*
- Better pre-treatment predictors of treatment failure (e.g, antigen density) and measures of impending relapse (e.g, ctDNA) are needed.

What about relapses after CAR-T therapy?

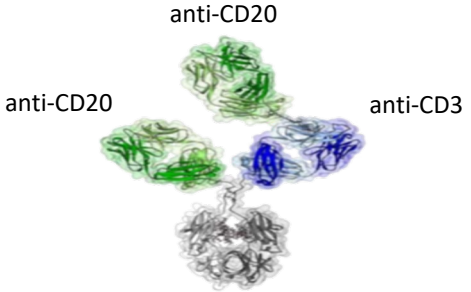
CD20xCD3 Bispecific antibodies

Mosunetuzumab



Tolerable safety profile may allow for outpatient administration without required monitoring

Glofitamab



Unique bivalent binding structure;
2:1 CD20:CD3 format engineered for high potency

Glofitamab in R/R DLBCL with ≥2 prior therapies: Ph2 expansion study

Heavily pre-treated, highly refractory population

n (%)*		N=154†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)

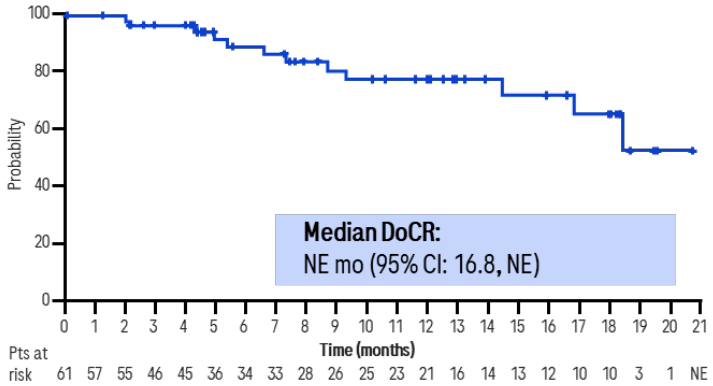
n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

- Clinical cut-off date: March 14, 2022; *unless otherwise specified; †safety-evaluable population (all treated patients); ‡ECOG PS 2, n=1 (0.6%); Ab, antibody; ASCT, autologous stem cell transplant; trFL, transformed follicular lymphoma.

Glofitamab monotherapy in 3L+ Large B-cell lymphoma
Phase 2 pivotal data

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)**
ORR*	**80 (51.6%)**
Median duration of follow-up, mos	12.6 (0-22 mos)
12-months DoR, % (95% CI)	**63.6 (51.1, 76.2)**
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**

Duration of complete response by IRC



Dickinson et al. ASCO 2022

UCSF Helen Diller Family Comprehensive Cancer Center

Glofitamab conclusions

- Glofitamab is the first T-cell-engaging bispecific monoclonal antibody to demonstrate clinically meaningful outcomes for patients with R/R DLBCL in a pivotal Phase II setting:
  - primary efficacy endpoint met; CR: 39.4% and ORR: 51.6% in heavily pre-treated, highly refractory patients with DLBCL after ≥2 prior lines
  - consistent CR rates in patients with prior CAR-T exposure; higher CR rate in relapsed patients versus refractory patients
  - CRs achieved early and durable even after fixed-duration treatment (max. 12 cycles)
  - glofitamab was well tolerated: low rate of treatment discontinuations; CRS was mostly low grade and during Cycle 1, with predictable time of onset; low rate of ICANS
- Glofitamab is a promising off-the-shelf treatment with a novel mode of action, *BUT…*
- Unclear how durable responses will be to bispecific antibody therapies, relative to CAR-T approaches
- How best to sequence therapies will be an increasing challenge, in lymphoma and myeloma

GemOx, gemcitabine plus oxaliplatin; ICANS, neurologic AEs potentially consistent with immune effector cell-associated neurotoxicity syndrome

CAR-T therapies: special problems

Transplantation and Cellular Therapy

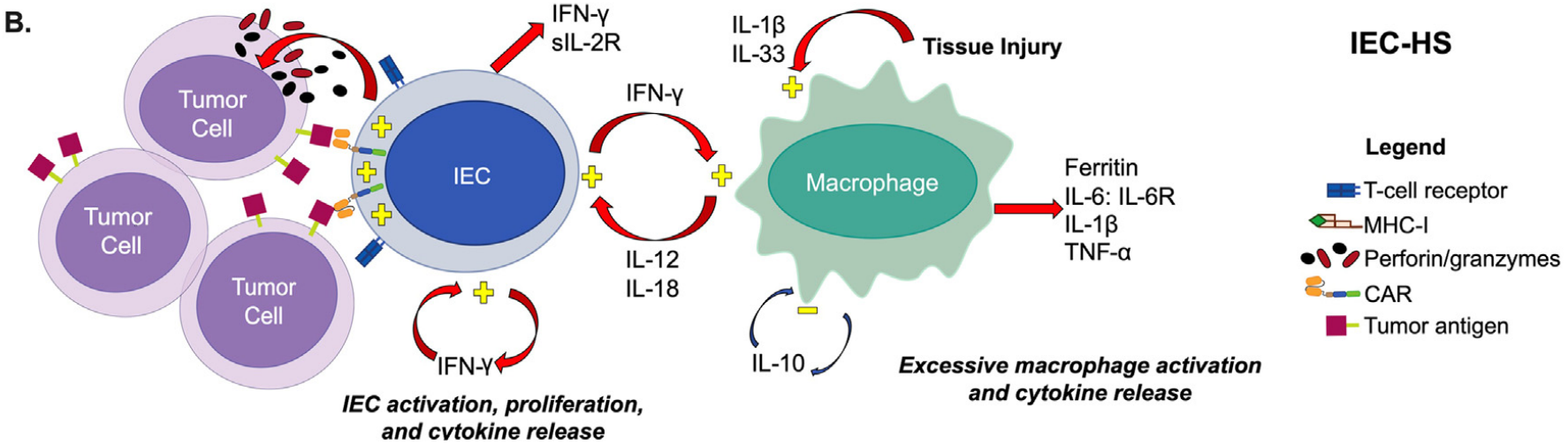
journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Cellular Therapy

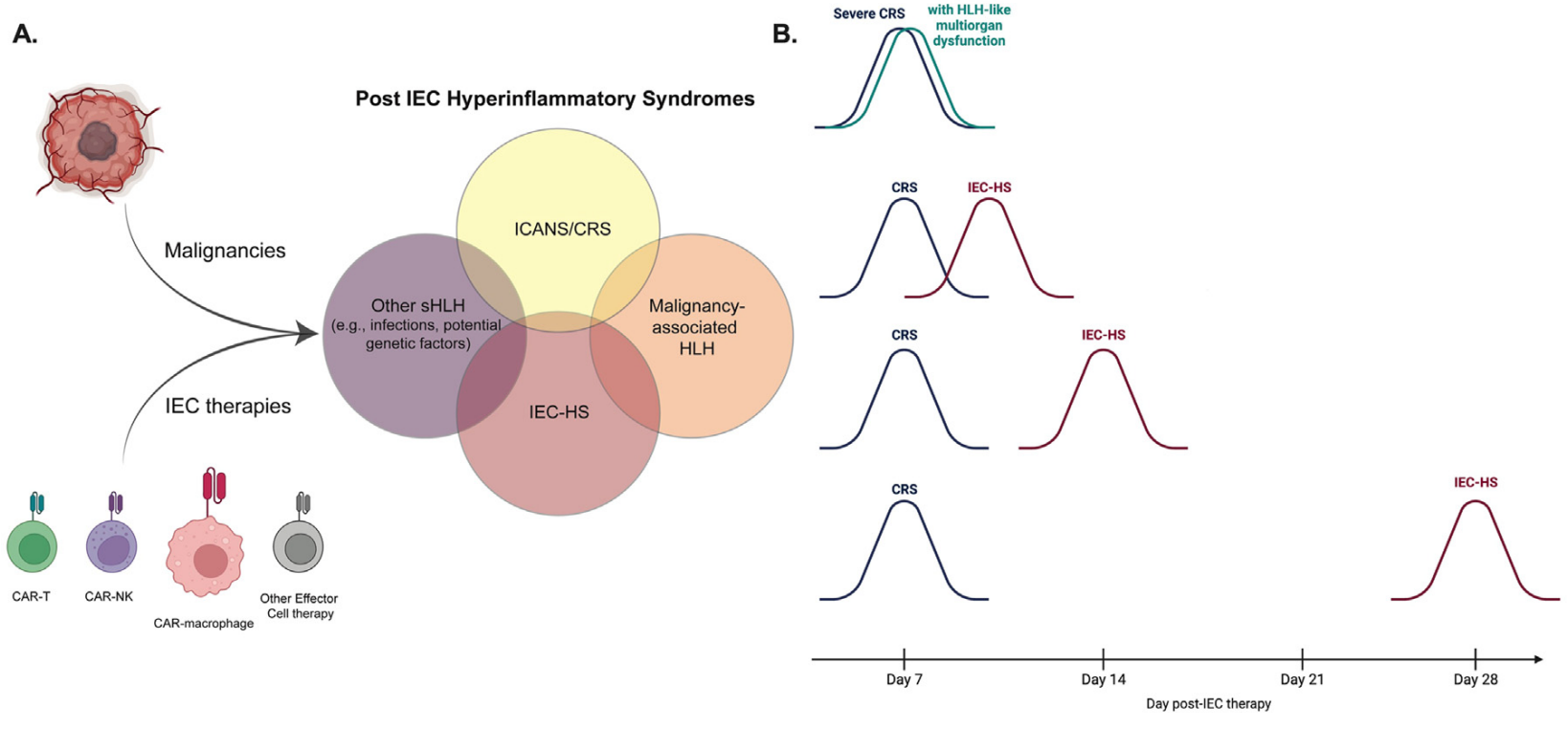
Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome

Melissa R. Hines[1], Tristan E. Knight[2], Kevin O. McNerney[3], Mark B. Leick[4], Tania Jain[5], Sairah Ahmed[6], Matthew J. Frigault[4], Joshua A. Hill[7], Michael D. Jain[8], William T. Johnson[9], Yi Lin[10], Kris M. Mahadeo[11], Gabriela M. Maron[12], Rebecca A. Marsh[13], Sattva S. Neelapu[6], Sarah Nikiforow[14], Amanda K. Ombrello[15], Nirav N. Shah[16], Aimee C. Talleur[17], David Turicek[18], Anant Vatsayan[19], Sandy W. Wong[20], Marcela V. Maus[4], Krishna V. Komanduri[20], Nancy Berliner[21], Jan-Inge Henter[22], Miguel-Angel Perales[23], Noelle V. Frey[24], David T. Teachey[25], Matthew J. Frank[26], Nirali N. Shah[18,*]



from Hines, Shah et al, TCT 2023

HLH syndromes after CAR-T therapy



from Hines, Shah et al, TCT 2023

IEC-HS: definition and diagnostic critera

Table 1
IEC-HS: Definition and Identification

Definition of IEC-HS	The development of a pathological and biochemical hyperinflammatory syndrome independent from CRS and ICANS that (1) manifests with features of macrophage activation/HLH, (2) is attributable to IEC therapy, and (3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis
Criteria for Identifying IEC-HS*	**Clinical/Laboratory Manifestations**
Most common manifestations†	Required: elevated ferritin (>2 × ULN or baseline (at time of infusion)) and/or rapidly rising (per clinical assessment)
	Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS-directed therapy‡
	Hepatic transaminase elevation§ (>5 × ULN (if baseline was normal) or >5 × baseline if baseline was abnormal)
	Hypofibrinogenemia (<150 mg/dL or <LLN)‖
	Hemophagocytosis in bone marrow or other tissue‖
	Cytopenias (new onset, worsening, or refractory¶)
Other manifestations that may be present	Lactate dehydrogenase elevations (>ULN)
	Other coagulation abnormalities (eg, elevated PT/PTT)
	Direct hyperbilirubinemia
	New-onset splenomegaly
	Fever (new# or persistent)‖
	Neurotoxicity
	Pulmonary manifestations (eg, hypoxia, pulmonary infiltrates, pulmonary edema)
	Renal insufficiency (new onset)
	Hypertriglyceridemia (fasting level, >265 mg/dL‖)

from Hines, Shah et al., TCT 2023

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Position Report

Paving the Road for Chimeric Antigen Receptor T Cells: American Society for Transplantation and Cellular Therapy 80/20 Task Force Consensus on Challenges and Solutions to Improving Efficiency of Clinical Center Certification and Maintenance of Operations for Commercially Approved Immune Effector Cell Therapies

Sarah Nikiforow[1,*], Matthew J. Frigault[2], Noelle V. Frey[3], Rebecca A. Gardner[4], Krishna V. Komanduri[5], Miguel-Angel Perales[6], Partow Kebriaei[7], Phyllis Irene Warkentin[8], Marcelo Pasquini[9], Joy Lynn Aho[10], Bruce L. Levine[11], Helen E. Heslop[12], Tracey L. Hlucky[13], Karen Habucky[14], Mecide Gharibo[15], Madan Jagasia[16], Frederick L. Locke[17,*]

Mission

- **Advocate** for standardization
- **Identify 80% common workflows** (contrasting **20% product-specific**)
- **Streamline** auditing and education
- **Leverage** existing entities

from Nikiforow, Locke et al, TCT 2023

The 80/20 Project: Challenges and Potential Solutions

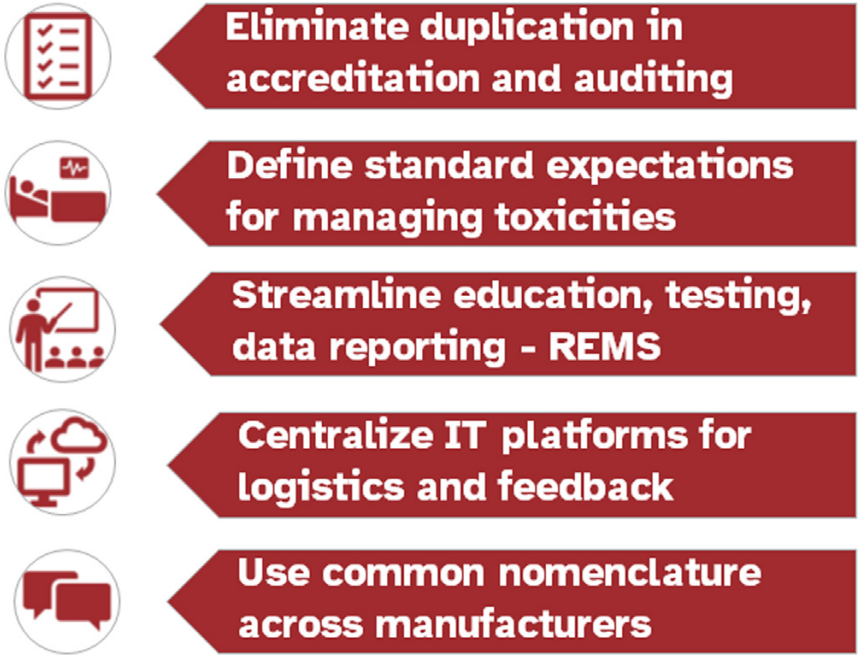


Figure 2. Potential solutions to challenges.

from Hines, Shah et al, TCT 2023

Streamlining CAR-T therapies: 80/20 Project Plans

Table 2
ASTCT 80/20 Task Force Stakeholder Recommendations for Immune Effector Cell Therapy Standardization

	ASTCT 80/20 Task Force and Stakeholder Goals	Strategies in Development	Potential Future Initiatives
1	Eliminate duplication in accreditation and auditing of clinical sites	• Risk-adapted or tiered algorithms to sponsor auditing, eg, using FACT accreditation • Existing accreditation entities with shared reports/findings, ie, FACT, NMDP, AABB	• Modularization of auditing for specific site or manufacturer needs • Hub-and-spoke model of quality programs/accreditation for smaller centers
2	Define standard and uniform safety guidelines for managing CAR-T cell therapy toxicities to potentially replace product-specific REMS programs	• Expert consensus guidelines exist on treatment management strategies, eg, NCCN	• Expert local and/or accrediting body-based treatment guidelines and oversight
3	Streamline education, testing and data reporting on CAR-T toxicities currently performed under REMS	• Commercial collaborations are considering a shared REMS program and/or centralized testing	• Centrally available education modules geared to individual roles within clinical sites • Agreement on common data points and central mechanism for reporting, ie, CIBMTR
4	Standardize IT platforms for enrollment, logistics of maintaining chain of identity/chain of custody across multiple transportation steps, and clinical site-manufacturer communication	• Limited number of portals using agreed-upon nomenclature, identifiers, and processes	• Limited number of portals using agreed-upon nomenclature, identifiers, and processes
5	Use of universal nomenclature, as much as possible, by cell therapy manufacturers	• ICCBBA/ISBT 128 labeling standards for apheresis and final manufactured products • Standards coordinating body initiatives	• Recognition of common workflows for apheresis collections, labels, and transportation documentation

from Nikiforow, Locke et al, TCT 2023

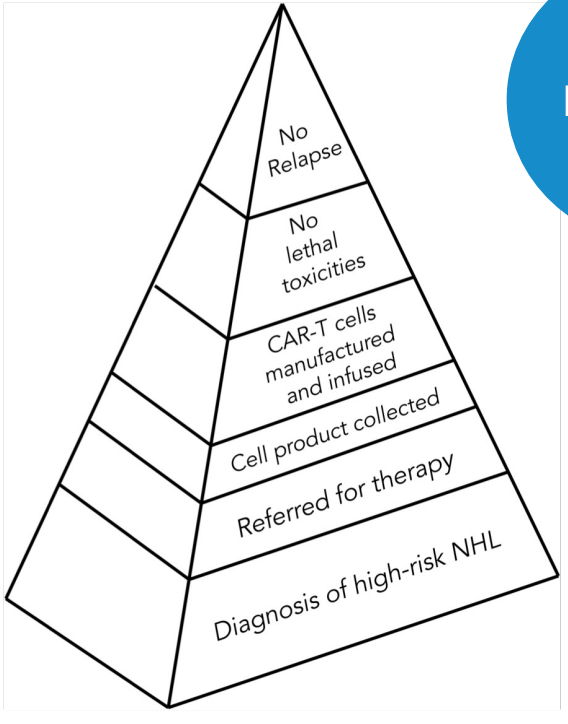
What about access and equity in CAR-T therapy?

- All approved CAR-T therapies, in aggregate, are underutilized
- Based on registry/public data, probably ≤30% of eligible 3L patients receive CAR-T therapy
- High cost, tertiary/quaternary therapies tend to maximize historical barriers to access (racial, socioeconomic, logistical)
- Early data suggest that African American patients are less likely to receive CAR-T therapy, and may have lower ORR, CR rates
- Unique access issues exist for pediatric patients, for whom fewer options exist

How can we improve access and equity in cellular therapy?

From diagnosis to cure

Better educate patients and referring physicians



Develop less costly therapies

Streamline and scale manufacturing

Measure and advocate for value

Komanduri, *J Clinical Oncology, 2021*

Acknowledgements

Slides: **Jay Spiegel (UM/Sylvester)**
Marcelo Pasquini (MCW/CIDR)
Miguel Perales (MSKCC)
Ginna Laport

Faculty, Staff and Patients at the University of Miami and UCSF