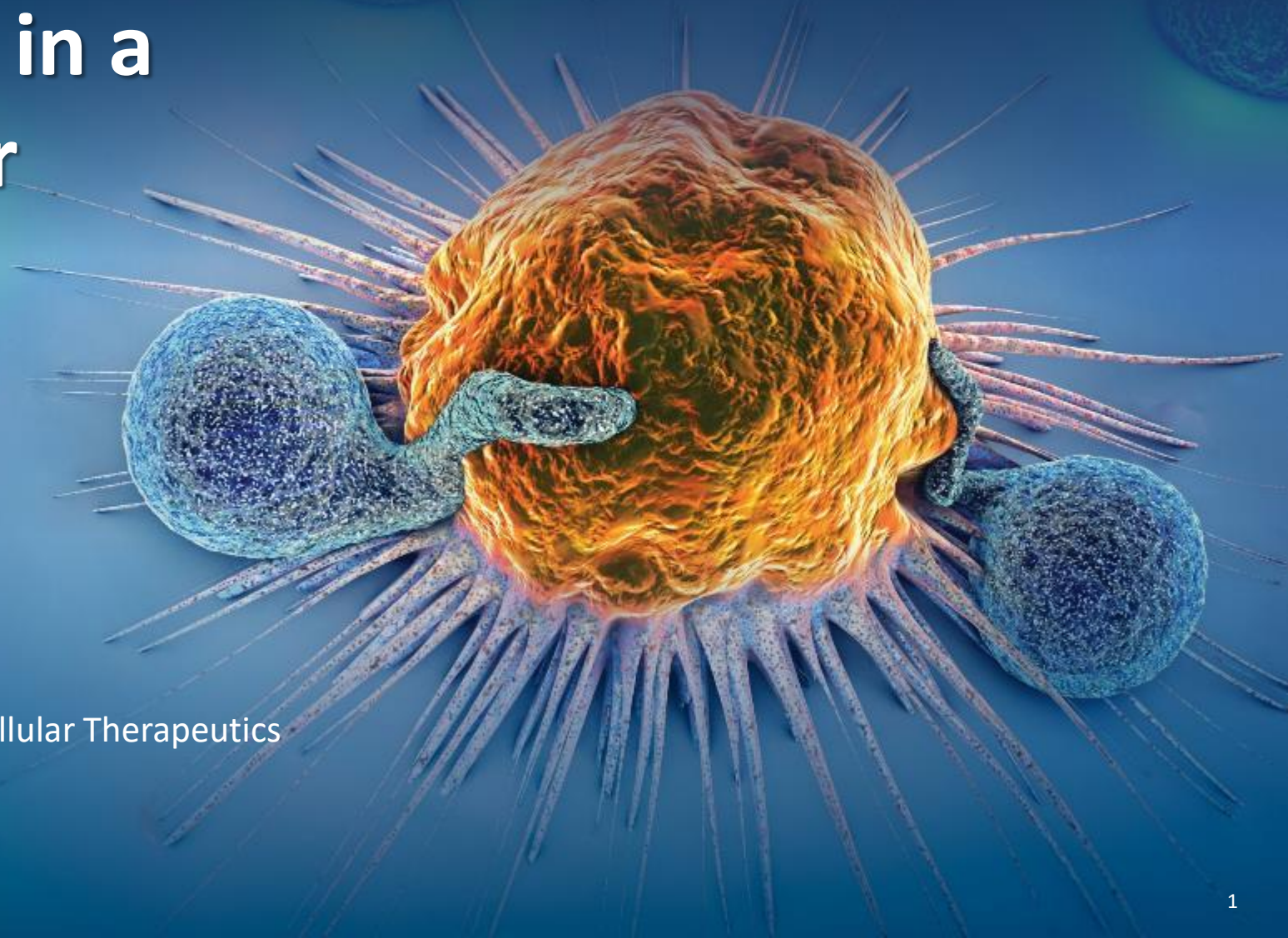
THE UNIVERSITY OF KANSAS
CANCER CENTER

NCI Designated Comprehensive Cancer Center

CAR-T: Continuation in a Revolution of Cancer Therapeutics



Joseph McGuirk, DO, FACP

Professor of Medicine

Schutte-Speas Professor of Hematology-Oncology

Medical Director, BMT and Cellular Therapeutics

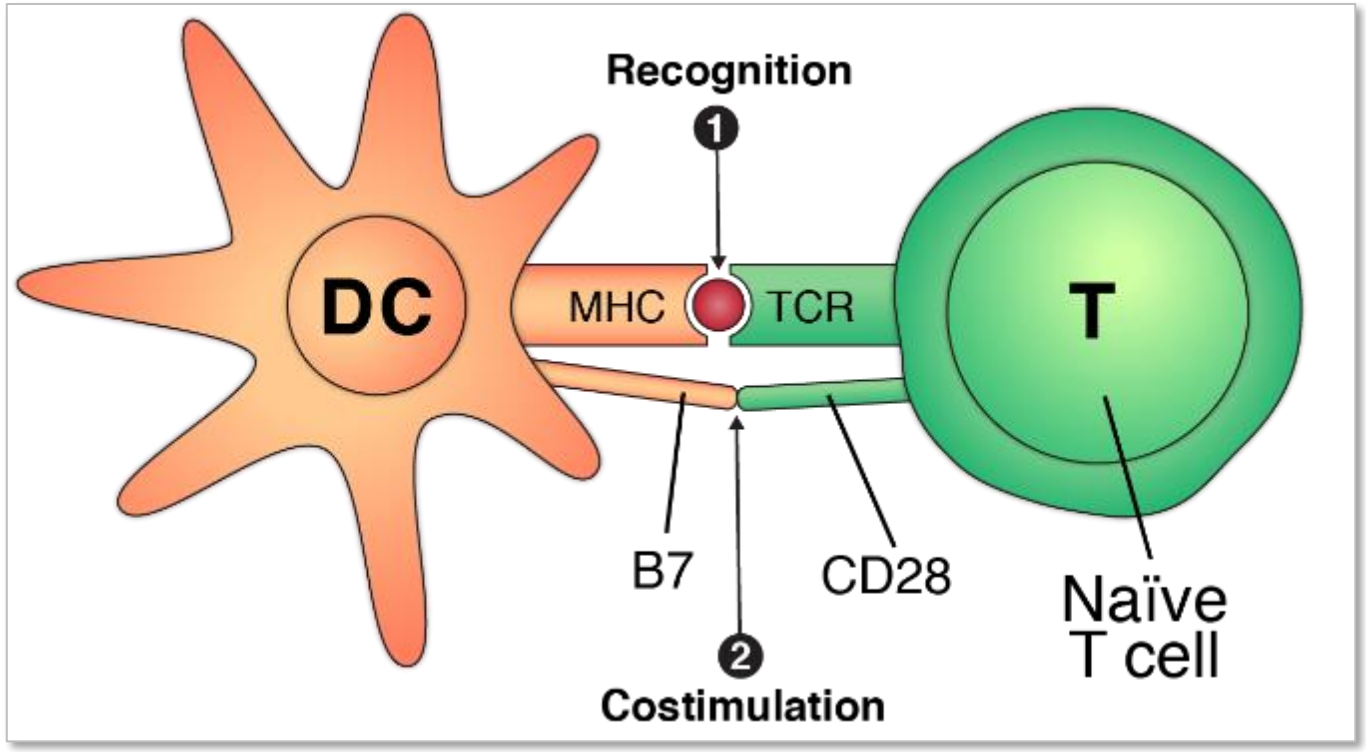
Division Director, Hematologic Malignancies and Cellular Therapeutics

Disclosures

- Kite
- AlloVir
- Novartis
- Nektar
- BMS
- Envision
- Caribou
- Sana
- Legend Biotech
- CRISPR

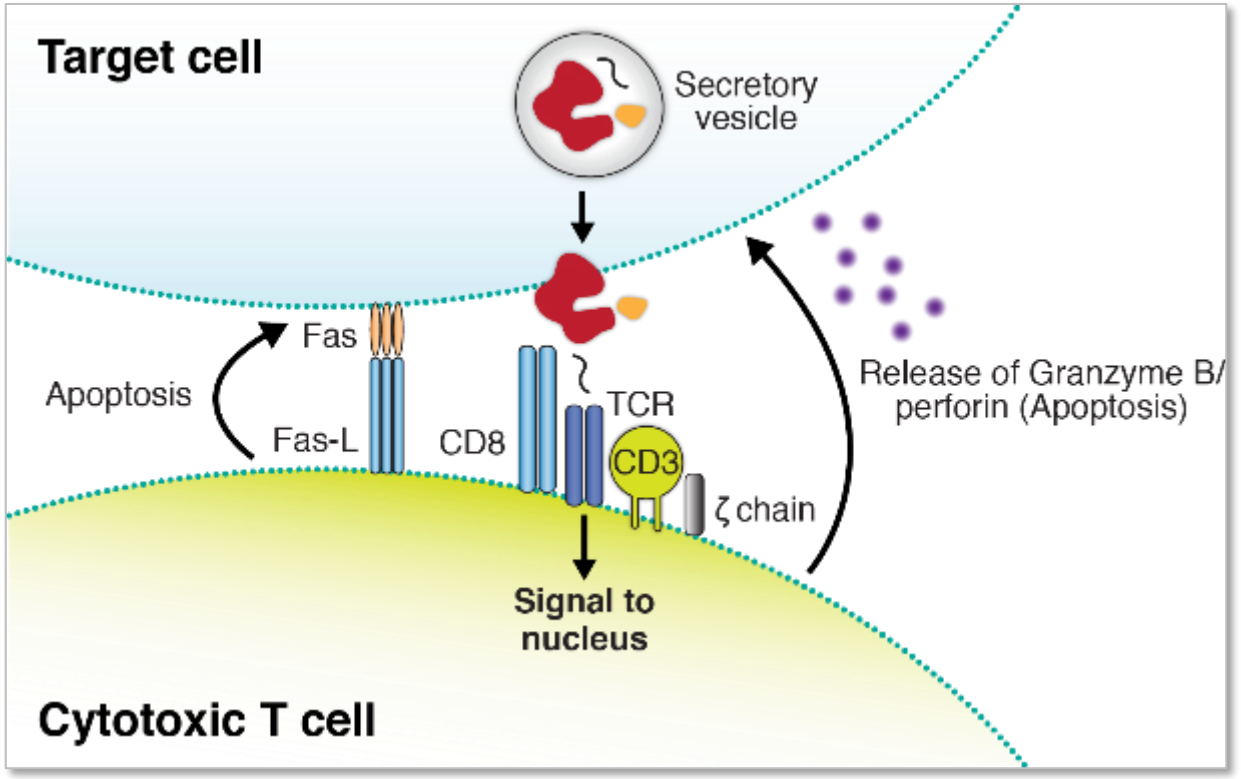
T Cell Activation

- Signal 1: Recognition: TCR binds to MHC (or HLA):antigen
- Signal 2: Co-stimulation: CD28 binds to its ligand on APC

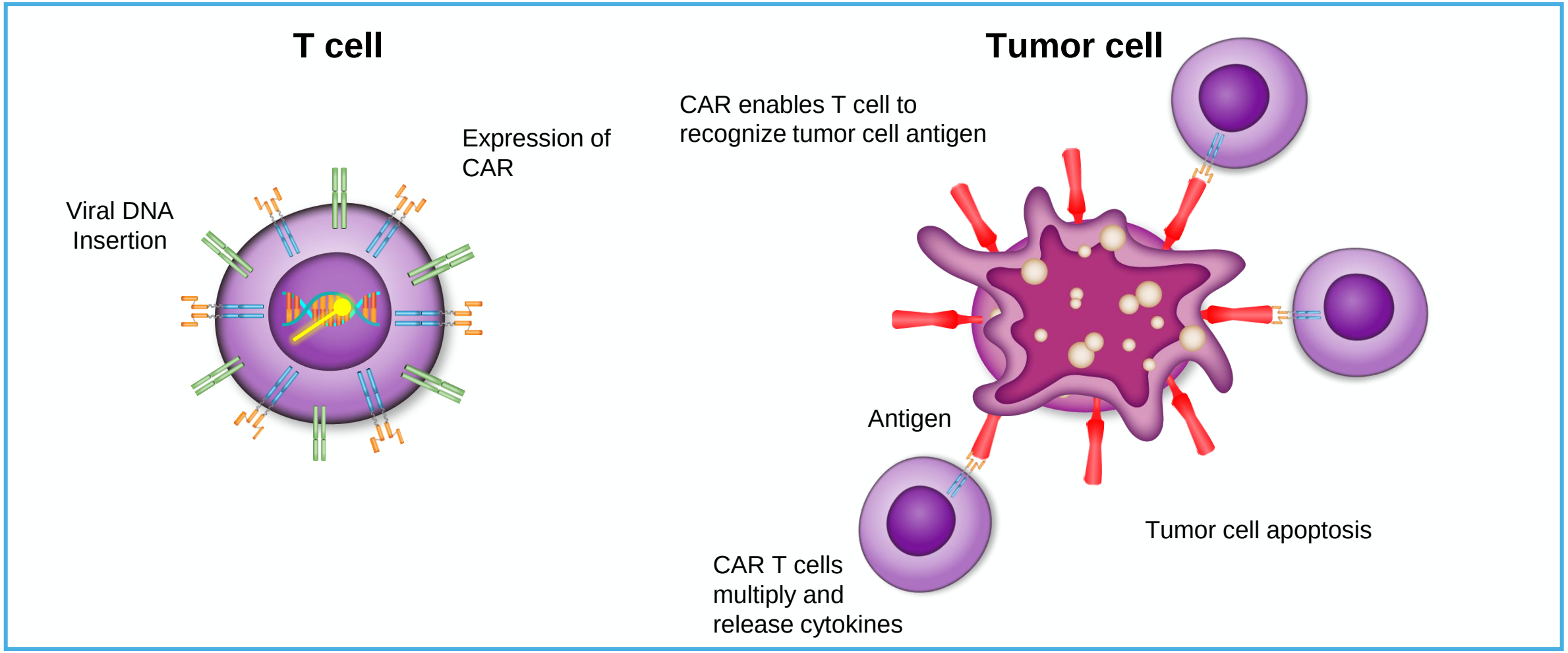


Activated T Cells: Effector CD8 CTLs

- **CTLs induce apoptosis through multiple mechanisms, including:**
  - Release of cytotoxic granules containing perforin and granzyme B
  - Surface receptor engagement such as Fas/FasL

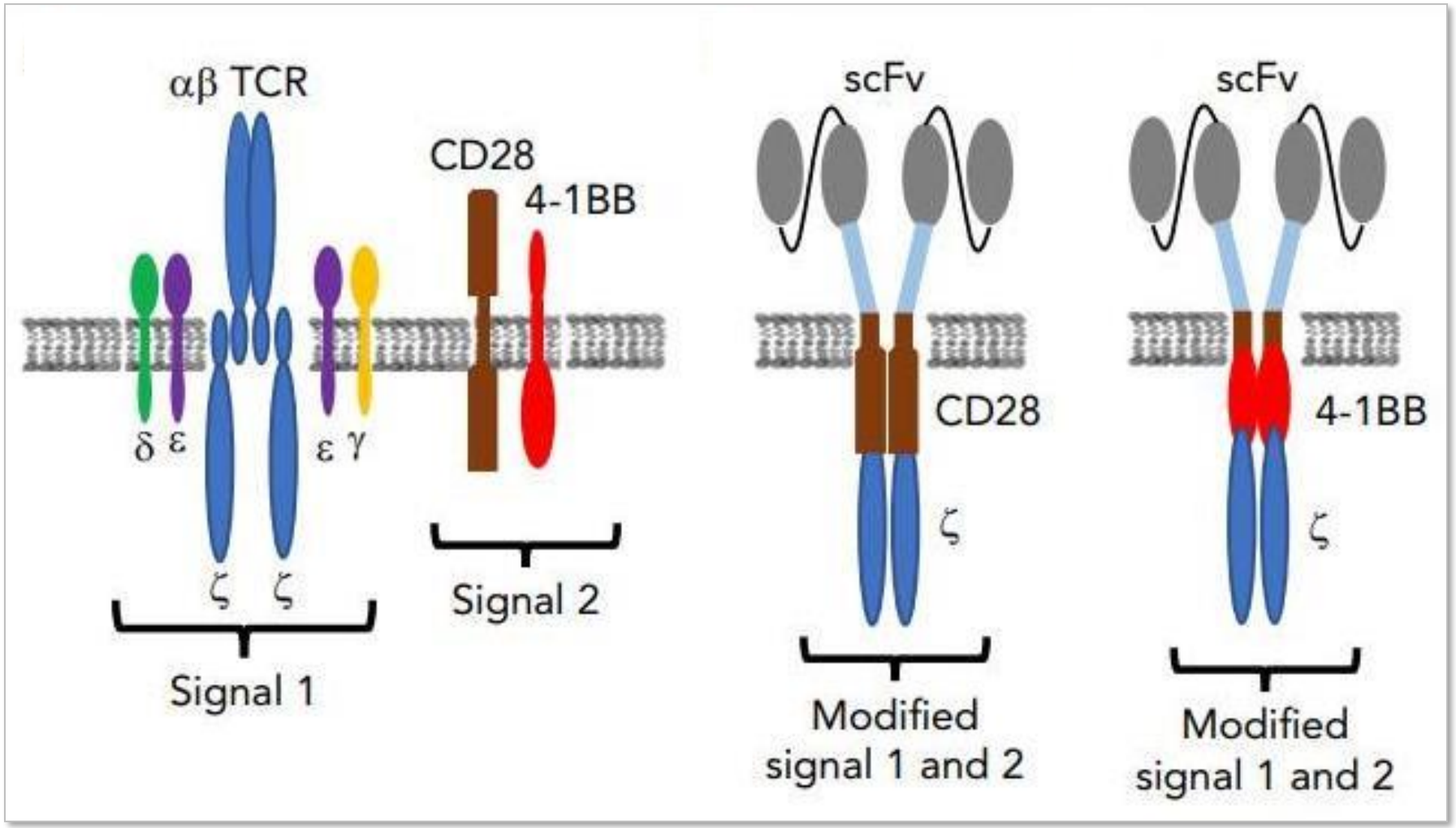


CAR T Cells: Mechanism of Action

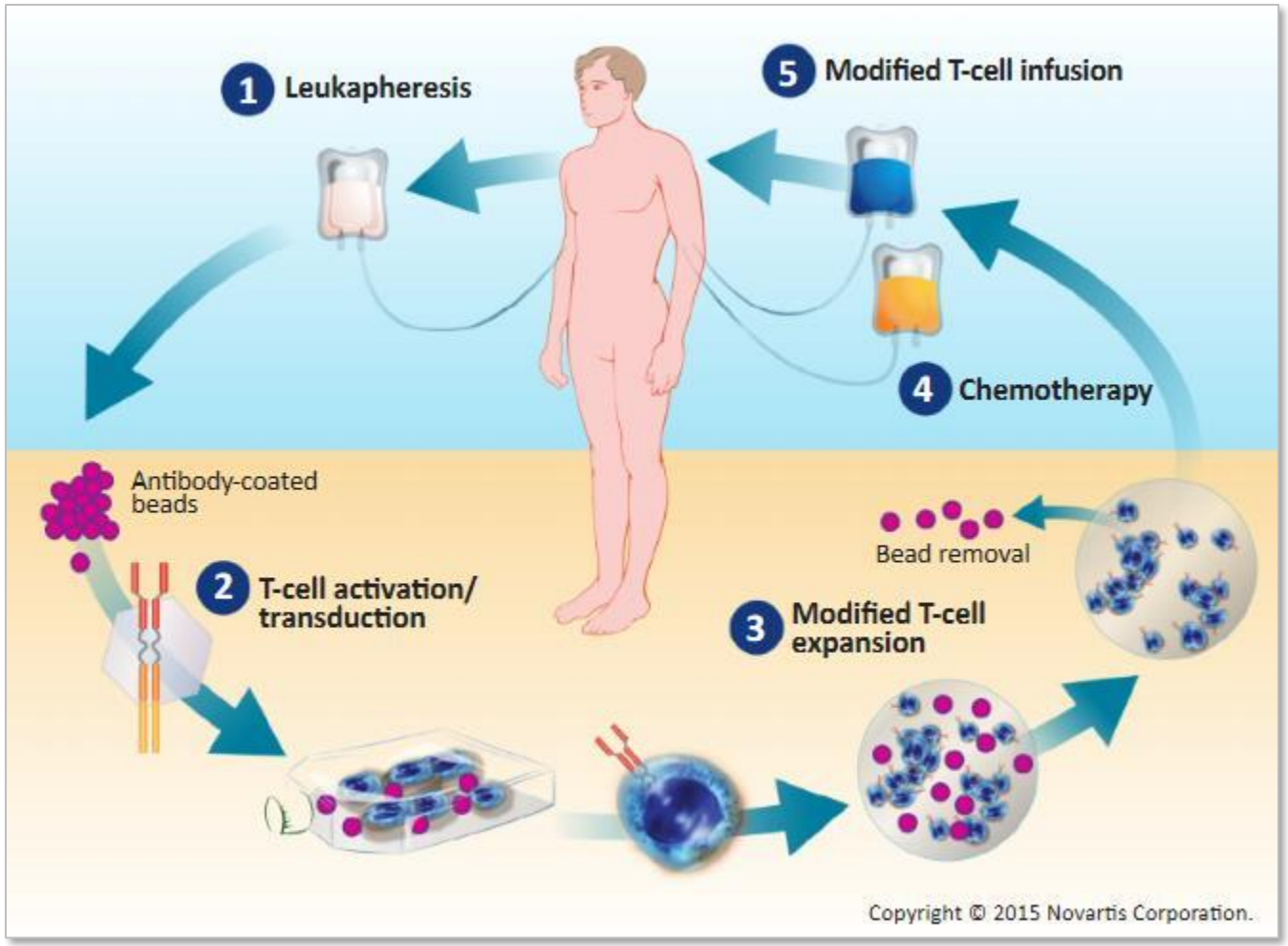


CAR T WORKING GROUP

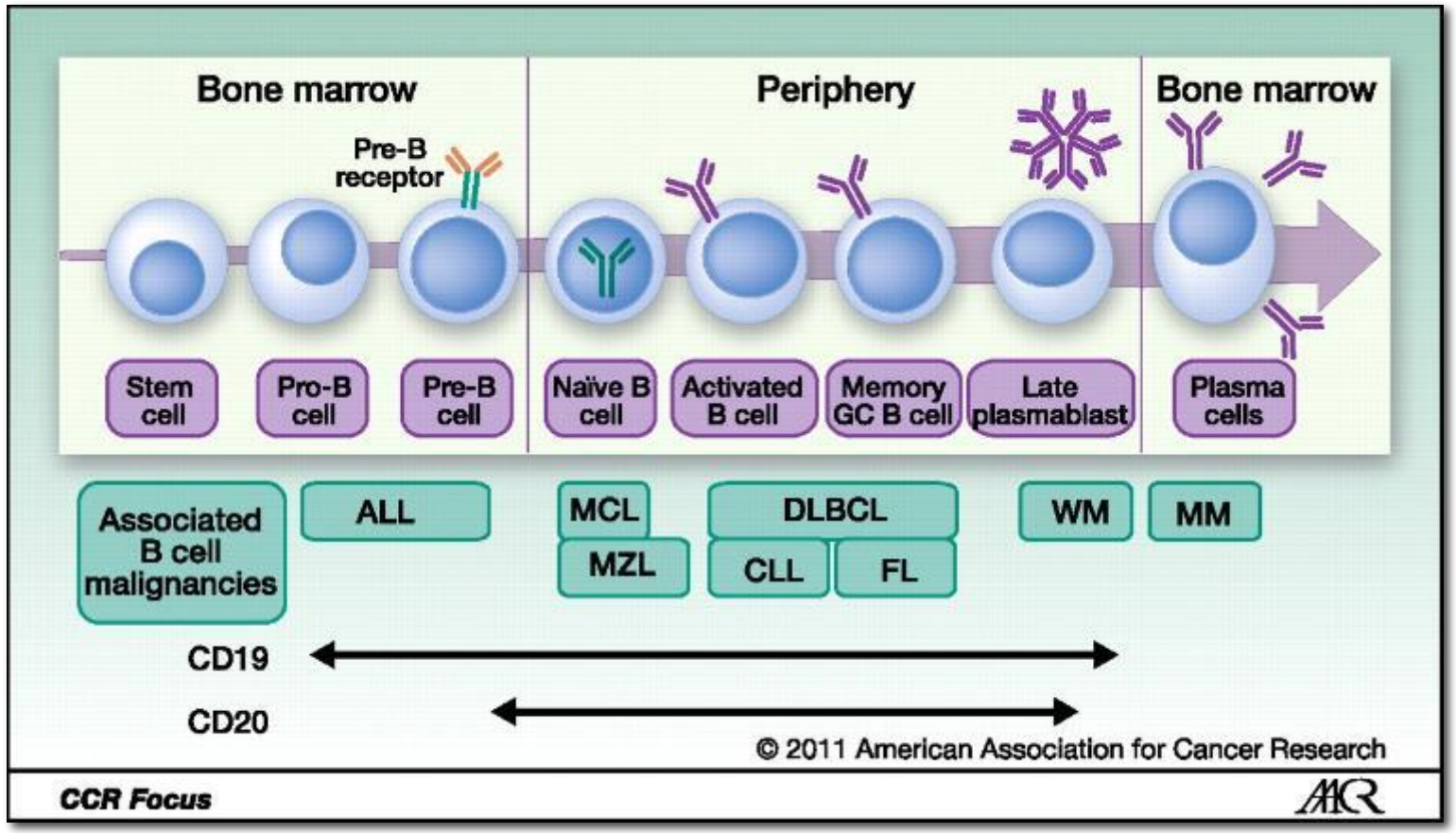
Chimeric Antigen Receptors



T-Cell Therapies- KU CAR HUB Team

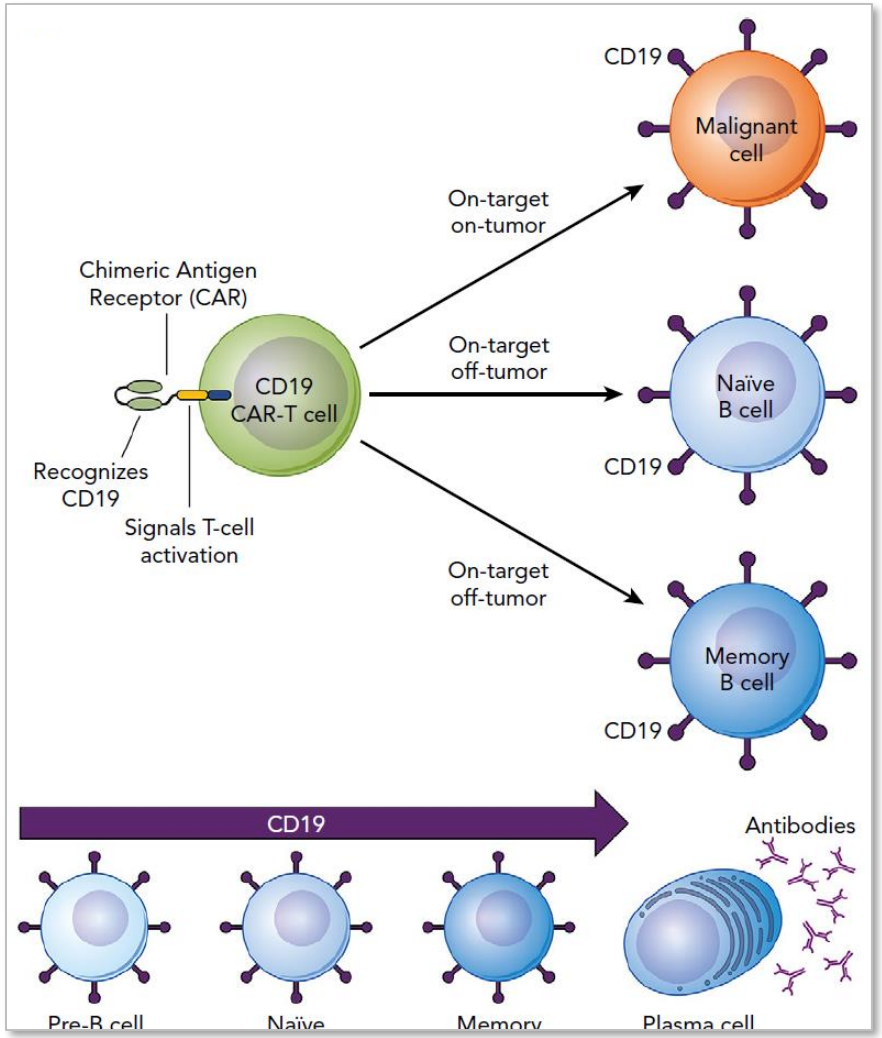


Rationale for CD19 as a CAR T-Cell Therapy Target



- CD19 is expressed on precursor and mature B-cells
- Not expressed on BM stem cells or other tissues
- Present on a wide range of B-cell malignancies

On-target, off-tumor side-effects of CD19-targeted CAR T-cell therapy

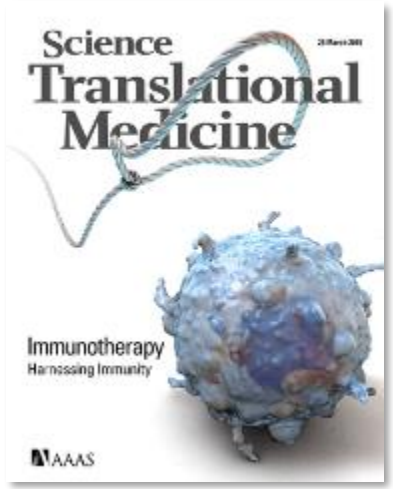


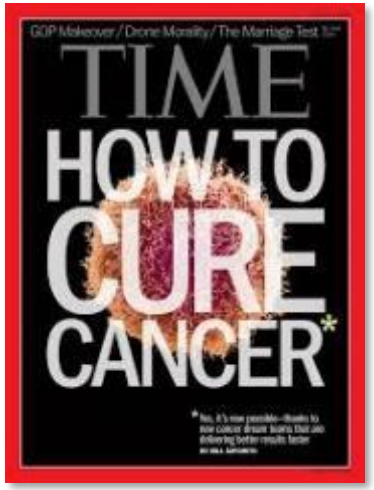
J Hill and S. Seo. Blood (2020) 136 (8): 925–935

The Revolution of Immunotherapy

ASCO Cancer.Net

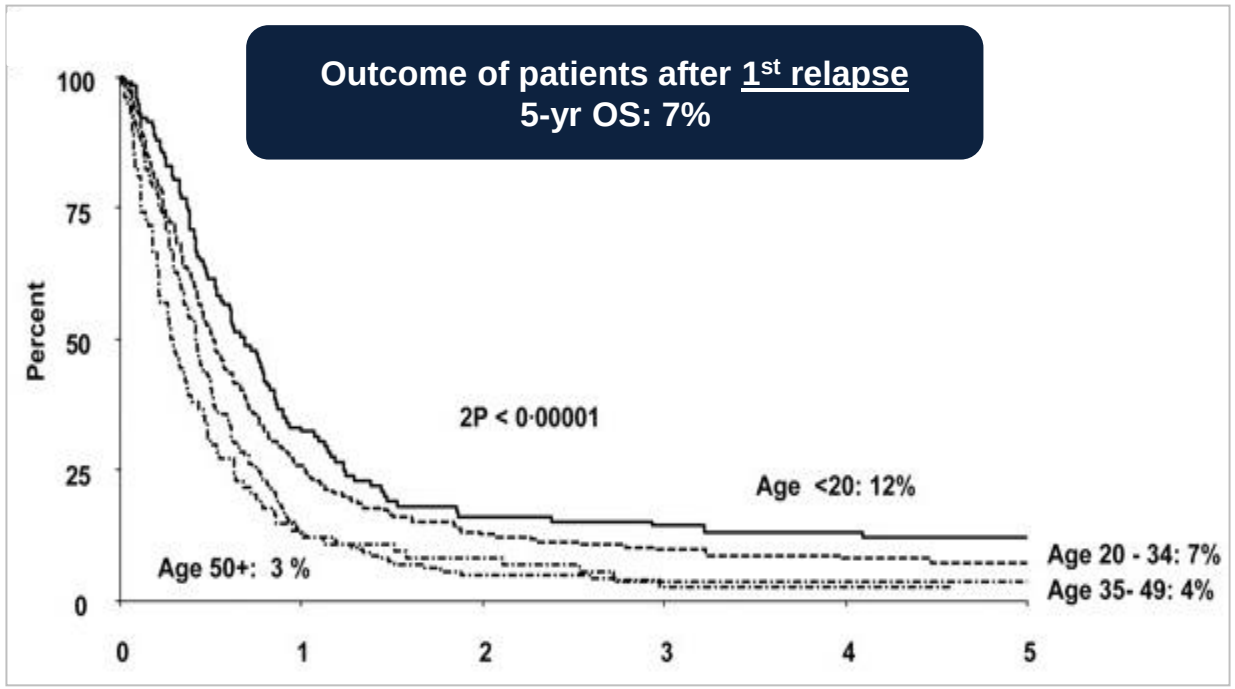
CAR T-Cell Immunotherapy: The 2018 Advance of the Year





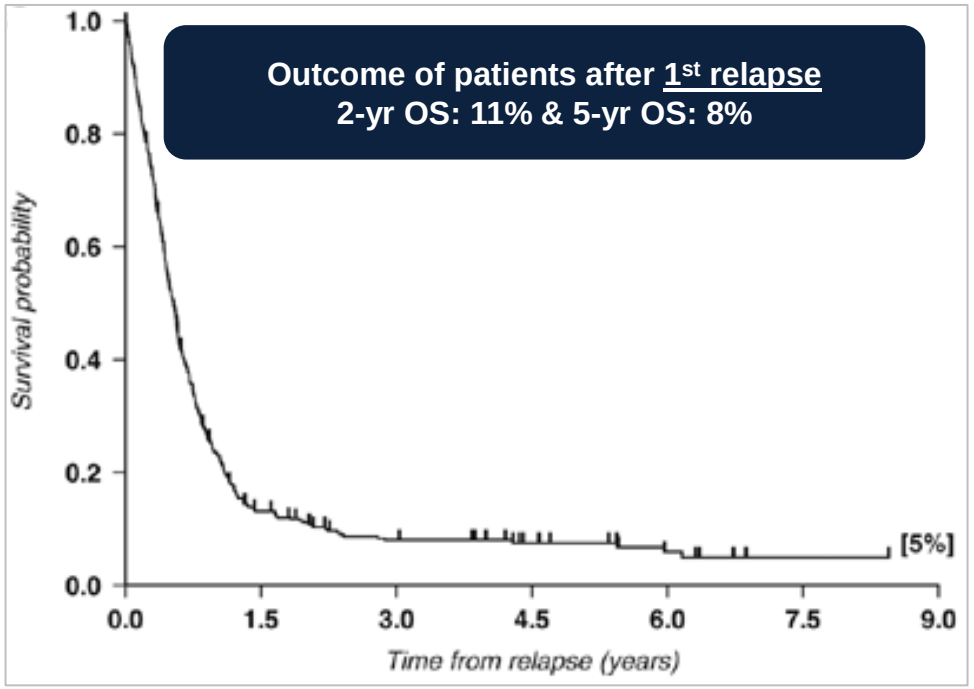
Poor Prognosis of Relapsed ALL in Adults

MRC UKALL2/ ECOG2993 Study (n=609)



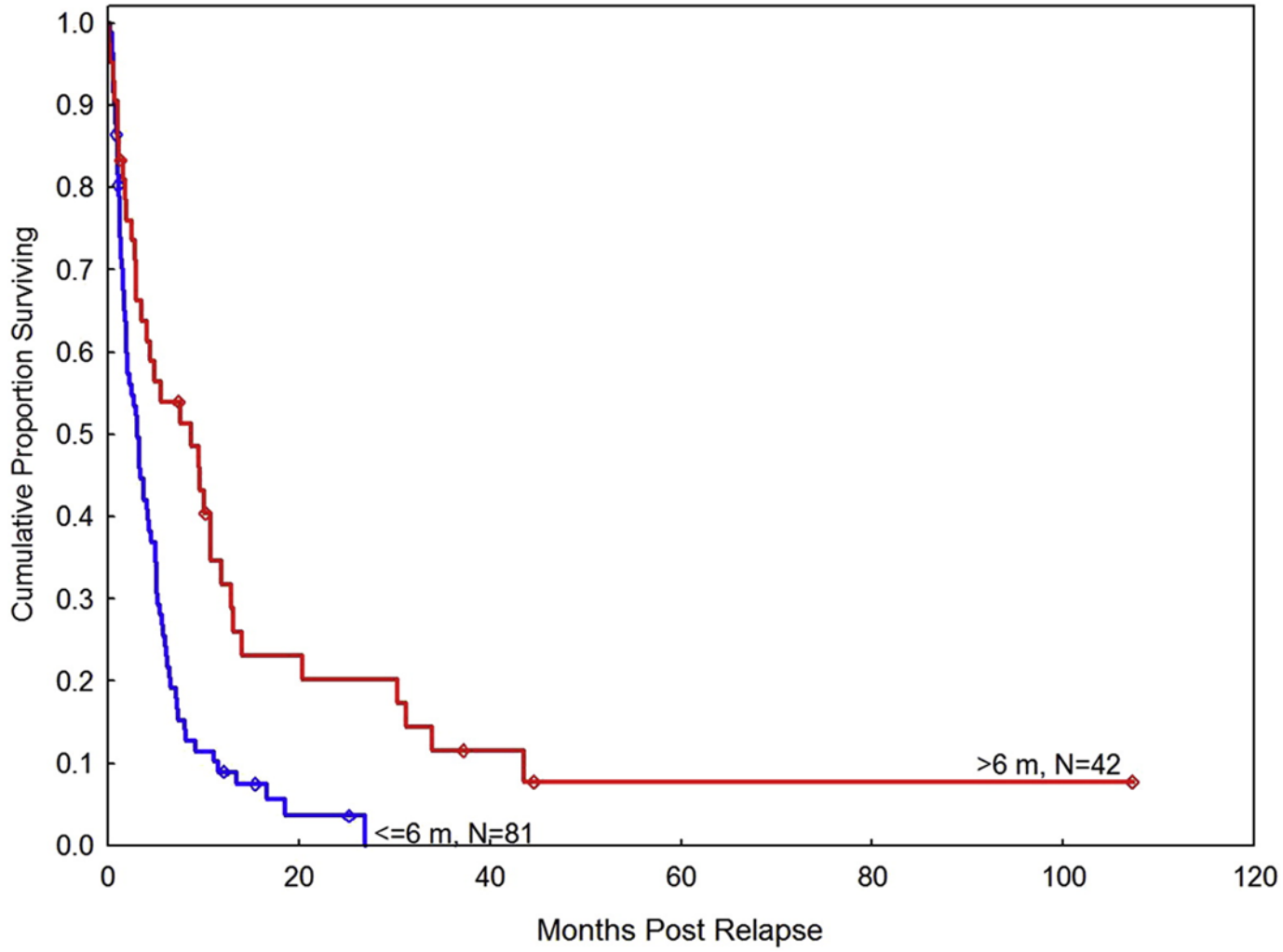
Fielding A, et al. Blood 2007;109(3):944-950

LALA-94 Study (n=421)



Tavernier E, et al. Leukemia 2007;21:1907-1914

Outcomes for Adults with Relapsed ALL after Allogeneic SCT



Poon, et al. BBMT 2013;19, 1064

Survival Rates

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

N=75 Median F/U= 31.1 months Allo-SCT= 61%		
CR	61/75	81%
RFS	6 months	80%
	12 months	59%
EFS	6 months	73%
	12 months	50%
OS	6 months	90%
	12 months	76%

Maude SL, et al. N Engl J Med. 2018 Feb 1;378(5):439-448.

Long-Term Follow-up of CD19 CAR Therapy in Adult Acute Lymphoblastic Leukemia

N= 53 Median F/U= 29 months Allo-SCT= 36%	
CR	44 (83%)
Median EFS	6.1 months
Median OS	12.9 months

Park JH et al. N Engl J Med. 2018 Feb 1;378(5):449-459.

Brexucabtagene Zuma-3 Adult Acute Lymphoblastic Leukemia

N= 116 Median F/U= 16.4 months Allo-SCT= 45%	
CR	71%
Median DOR	12.8 months
Median OS	18.2 months

Shad, BD, et al. The Lancet

FDA Approval

Emily is now 8 years cancer free after successful CAR T cell therapy treating her leukemia

emilywhiteheadfoundation.org


AACI

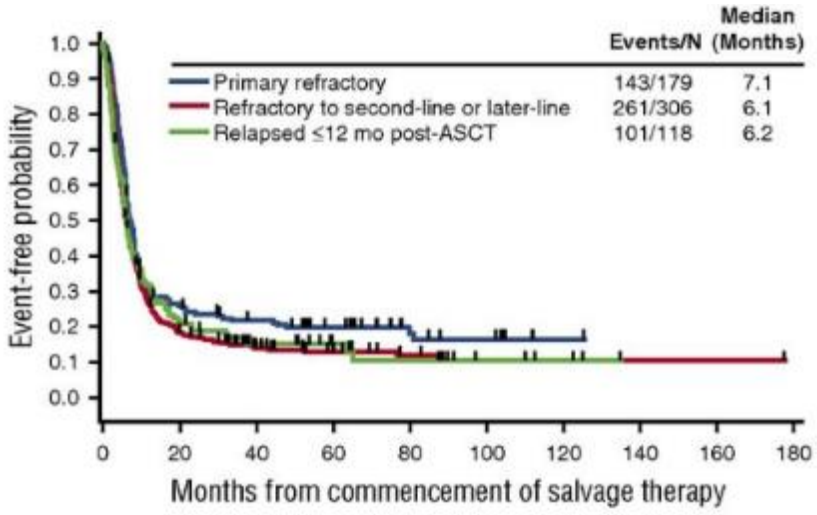
SCHOLAR-1: The First and Largest Patient-Level Meta-Analysis of Chemorefractory DLBCL

SCHOLAR-1: is a retrospective analysis of 636 patients with refractory DLBCL

Integrated data from:

- **Two large phase 3 studies**
  - LYSARC-CORAL
  - Canadian Cancer Trials Group-LY.12
- **Two observational cohorts**
  - MD Anderson Cancer Center
  - Mayo Clinic/University of Iowa

Median OS was 6.3 months (95% CI, 5.9-7.0)



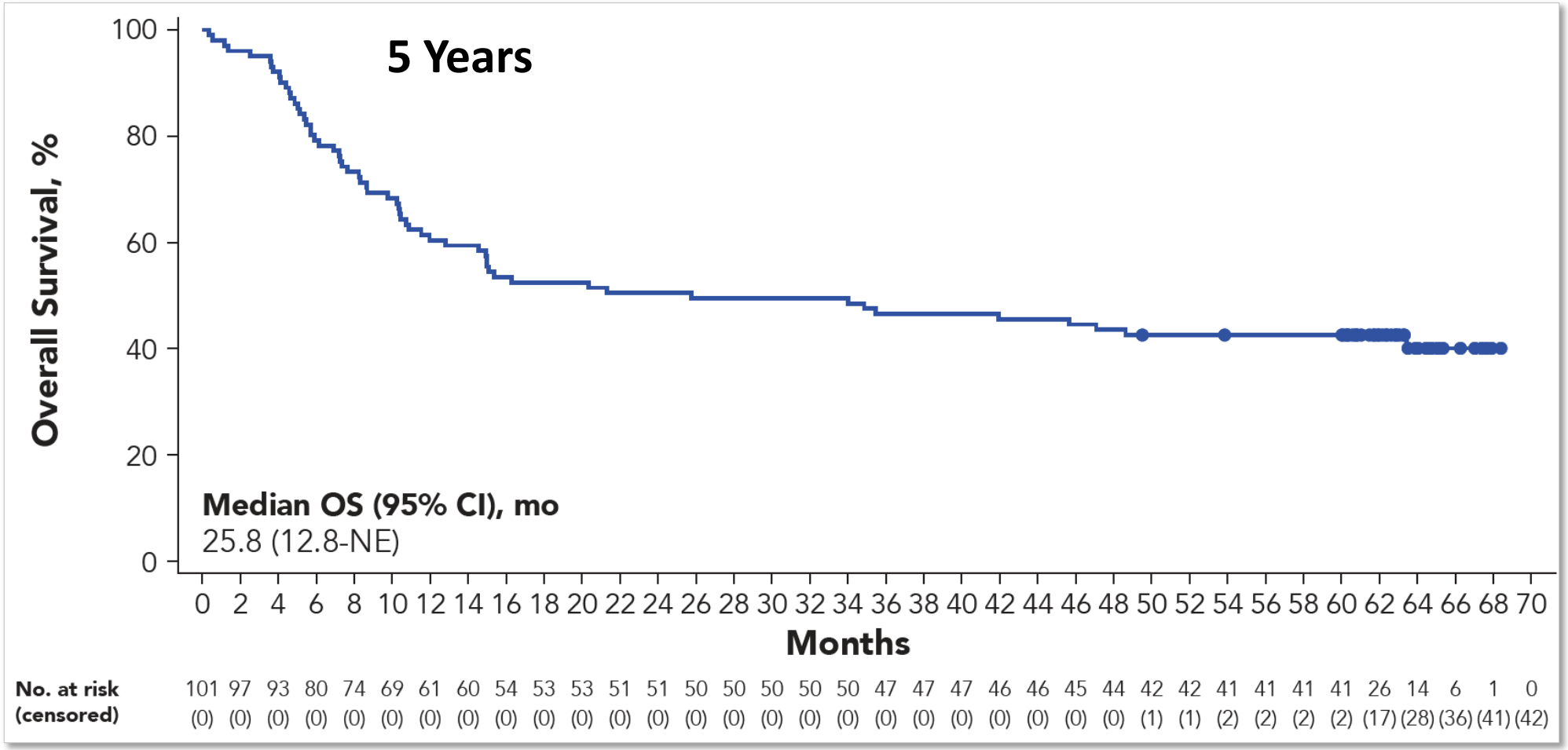
The pooled CR was 7%

Multicenter CD19 CAR T-cell Trials in Aggressive NHL

Study / Sponsor	ZUMA1 / Kite	JULIET / Novartis	TRANSCEND / Juno
Reference	Neelapu et al, NEJM 2017	Schuster, McGuirk, et al, NEJM 2018	Abramson et al, ASH 2019
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	0.6-6 x 10^8	0.5-1.5 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL/PMBCL/TFL/FL Gr 3B
Treated/Enrolled	101/111 (91%)	111/165 (67%)	268/342 (78%)
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	21%	49%	34%
Bridging therapy	0%	92%	59%
Median Time from apheresis to CAR T	17 days (to CAR T delivery)	54 days (to CAR T infusion)	24 days (“optimized subset”)
ORR / CR (%)	83 / 58	52 / 40	73 / 53

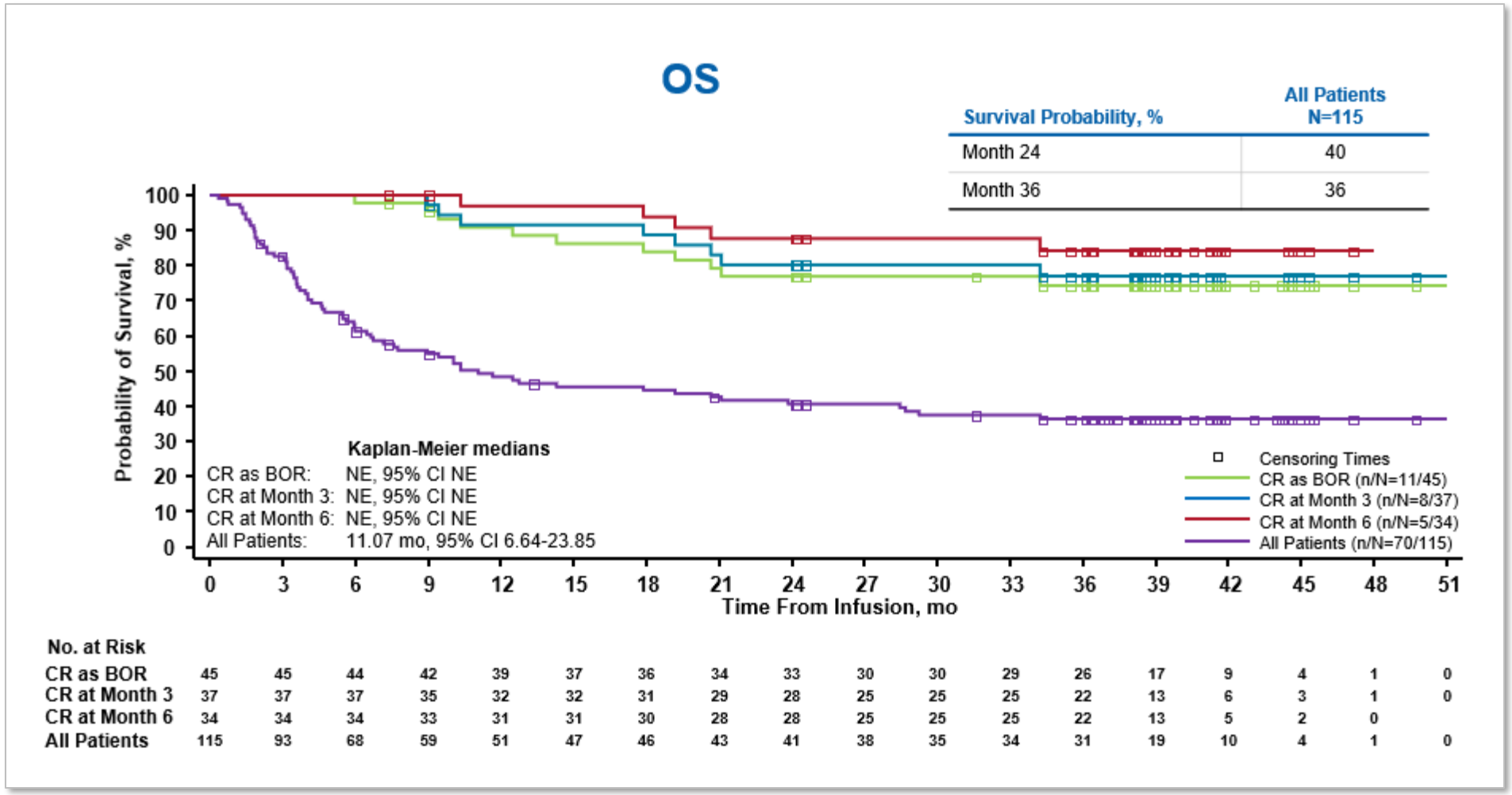
FDA Approved | FDA Approved | FDA Approved

ZUMA-1 (Axicabtagene): Overall Survival



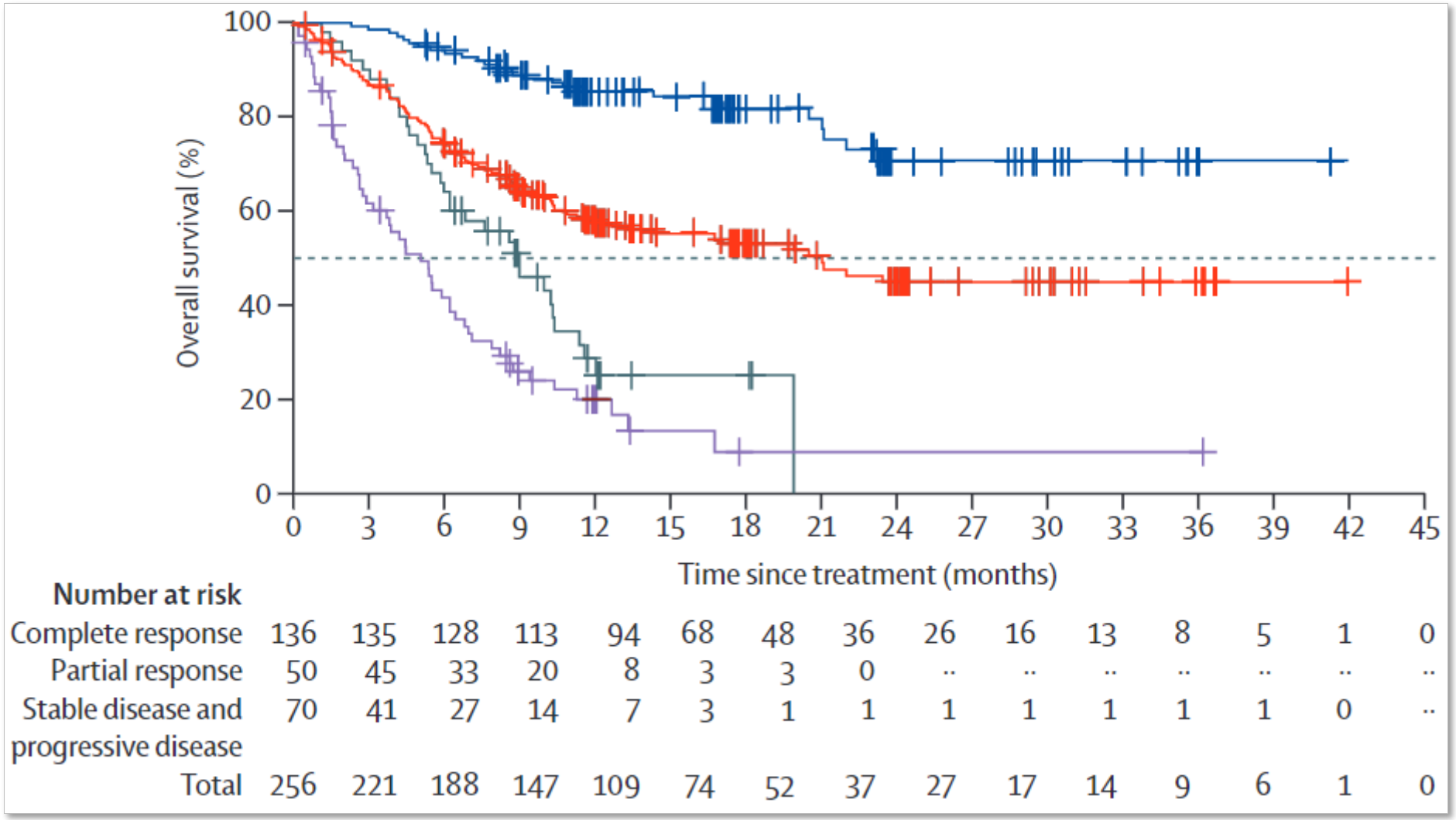
Jacobson CA, et al. ASH 2021, Abstract 1764

JULIET (Tisagenlecleucel): Overall Survival



Juliet 40-Month ASH 2020

TRANSCEND (Lisocabtagene): Overall Survival



Number at risk															
Complete response	136	135	128	113	94	68	48	36	26	16	13	8	5	1	0
Partial response	50	45	33	20	8	3	3	0	..	..	..	..	..	..	..
Stable disease and progressive disease	70	41	27	14	7	3	1	1	1	1	1	1	1	0	..
Total	256	221	188	147	109	74	52	37	27	17	14	9	6	1	0

Abramson, J; et al, The Lancet, Vol 396, Sept 19, 2020

Real-world efficacy and safety outcomes with axi-cel in patients with r/r large B-cell lymphoma comparable to the ZUMA-1 clinical trial

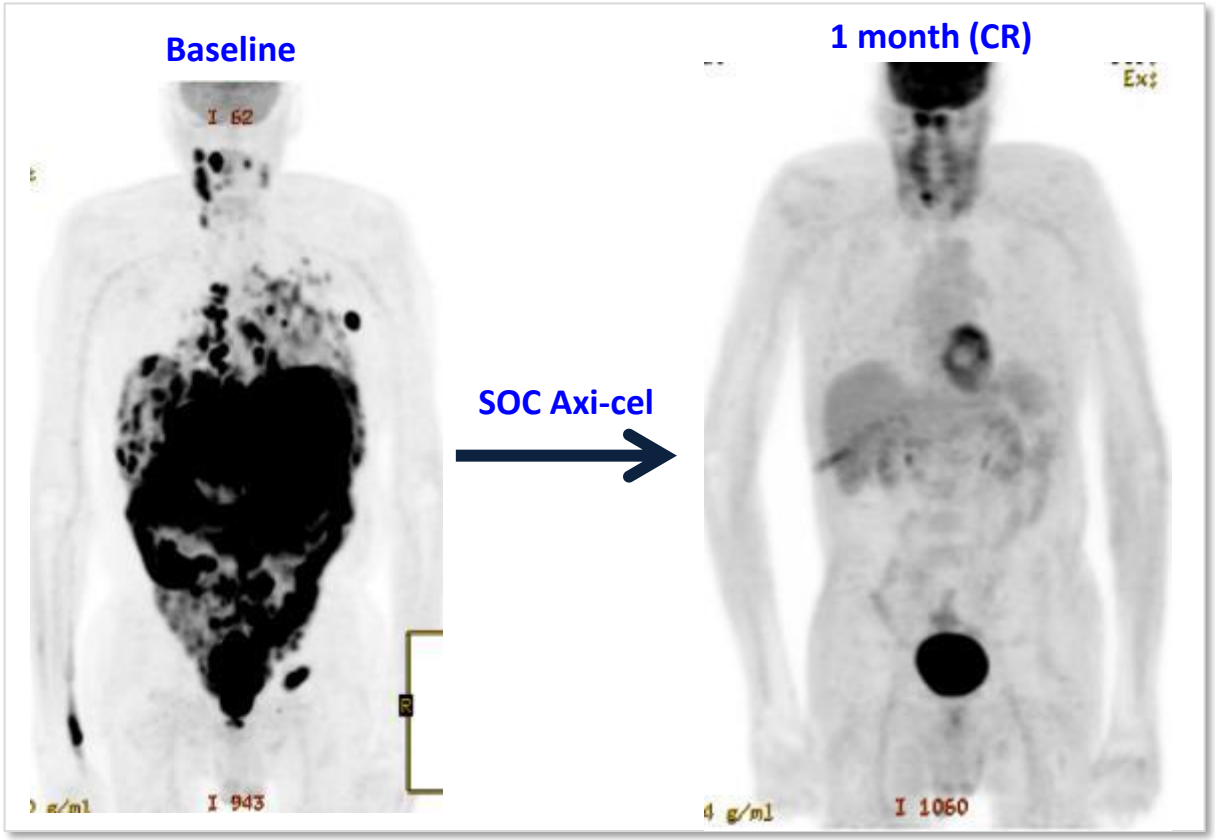
68 yo M with DLBCL-GCB

Prior therapies – 7

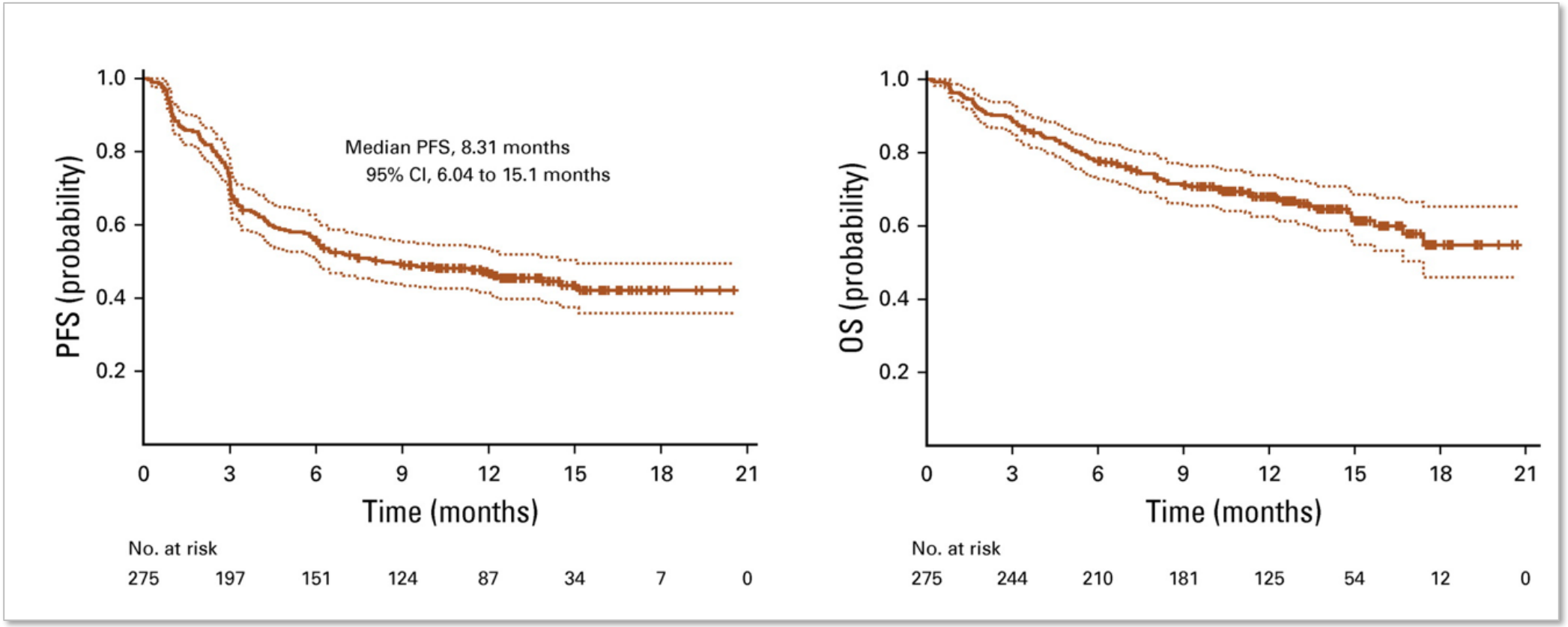
- R-CHOP
- ICE → Zevalin
- R-ESHAP
- R-Hypercytoxan
- Gemcitabine
- Bendamustine
- R-Hypercytoxan

Co-morbidities

- ECOG PS 3
- EF – 45%
- Pulmonary embolism
- GI bleed
- Obstructive jaundice → Biliary catheter



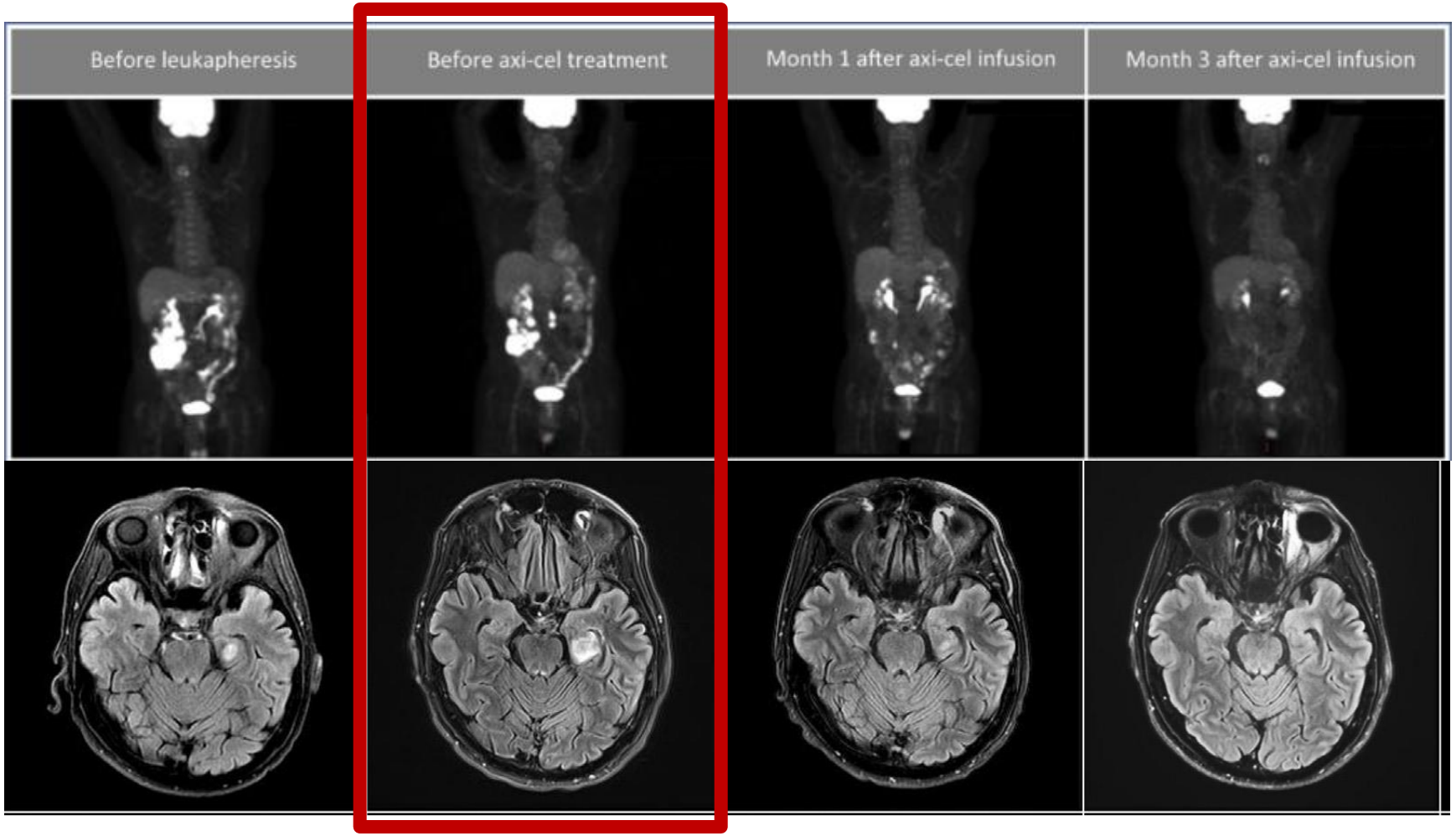
Axicabtagene Ciloleucel CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Large B-cell Lymphoma: Real World Experience



Loretta J. Nastoupil, Joseph McGuirk, et al. J Clin Oncol. 2020 May 13

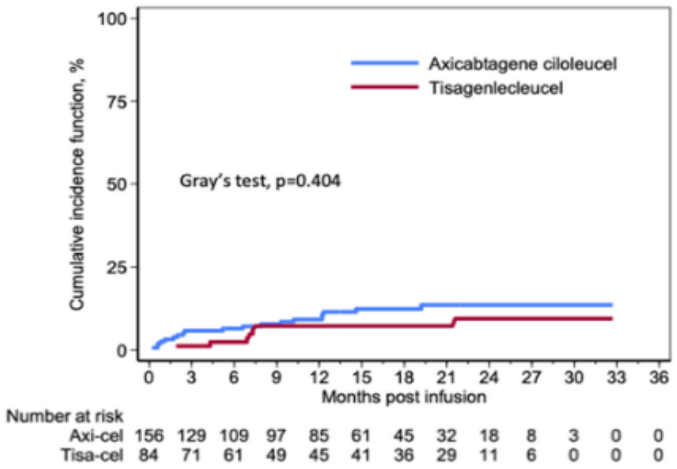
Response Post Axi-Cel Infusion

- **Complete response**
  - By day 30 for CNS disease
  - By 3 months for systemic disease
- **He remains in CR 1 year post infusion**

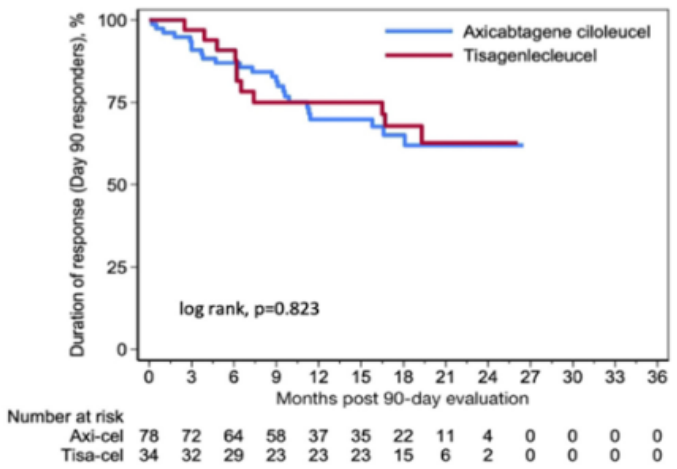


Patterns of Use, Outcomes, and Resource Utilization Among Recipients of Commercial Axicabtagene Ciloleucel and Tisagenleucleuceleucel for Relapsed/Refractory Aggressive B-Cell Lymphomas

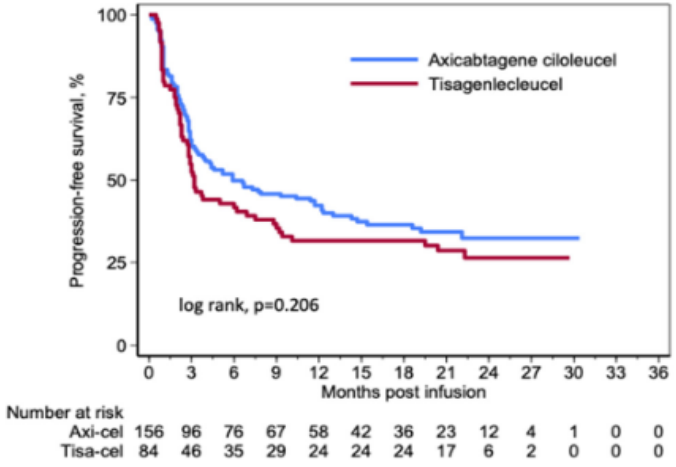
NRM



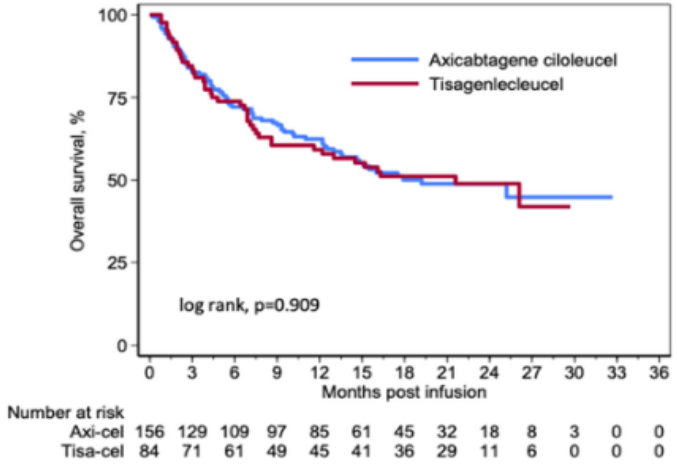
DOR d-90



PFS

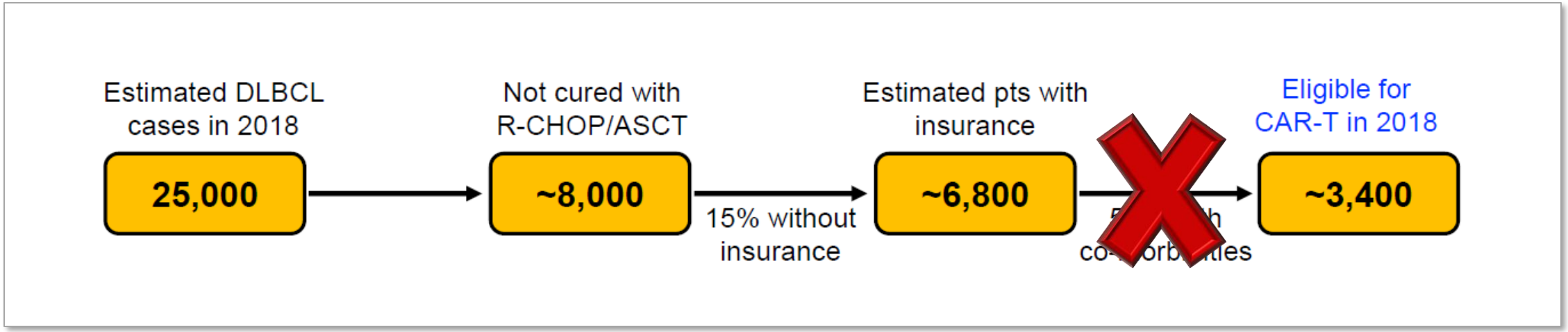


OS



Riedell, P., McGuirk, J. et al. In Press TCT

Real-World CAR T Adoption has been slow in US

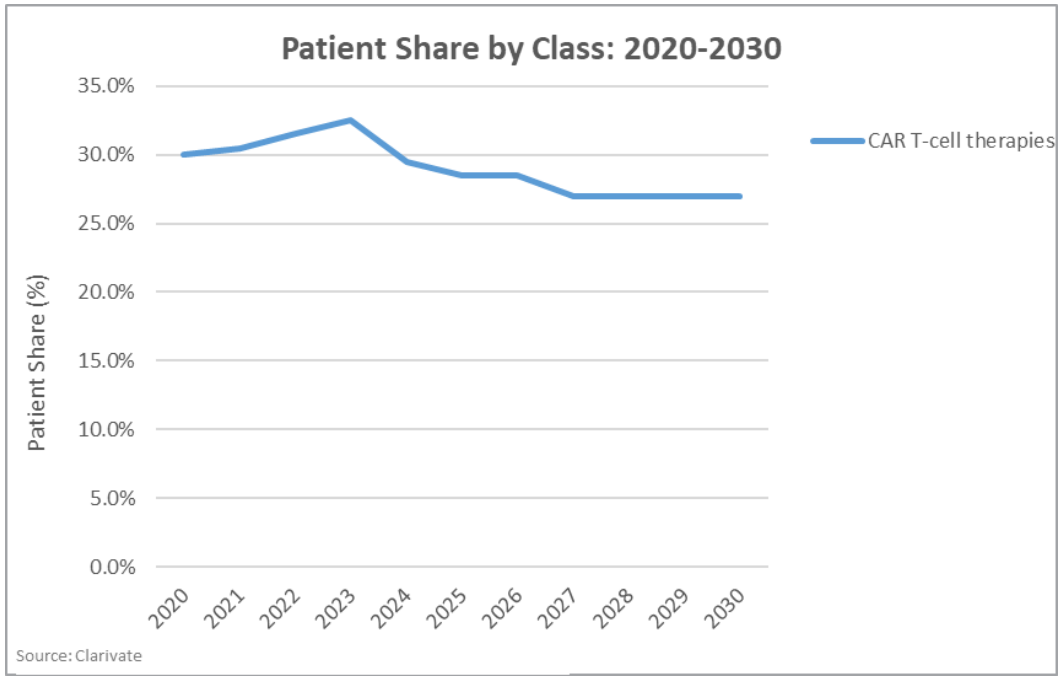


Number of patients treated with axi-cel in 2018 ~700

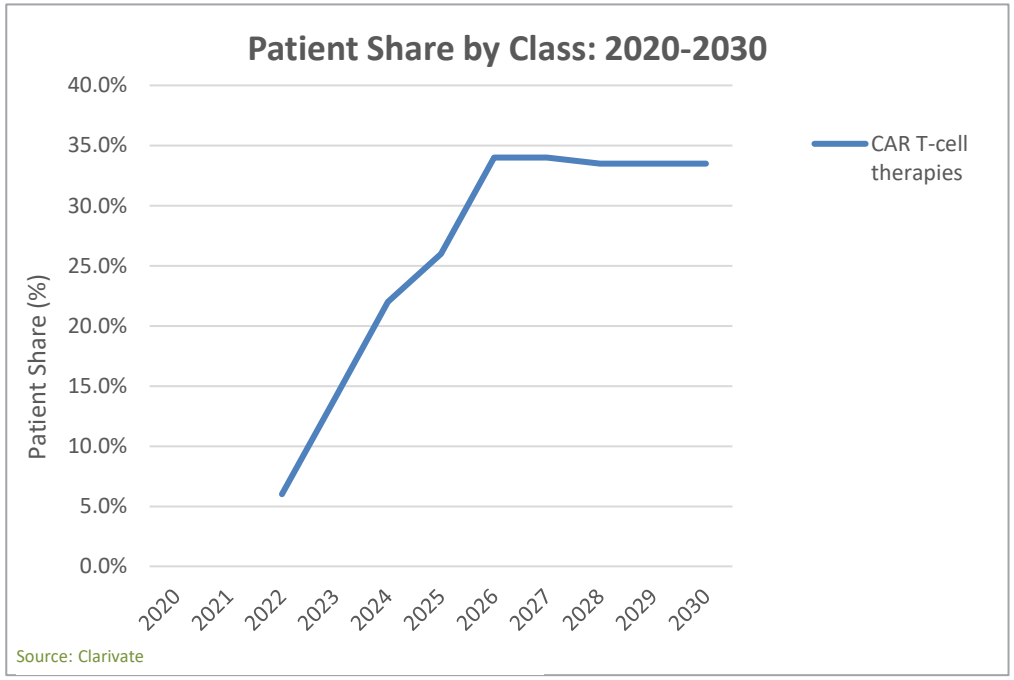
Jacobson, et al. 2019 ASH Abstracts 4107

Access Barriers to Autologous CAR T therapies

3L DLBCL - United States

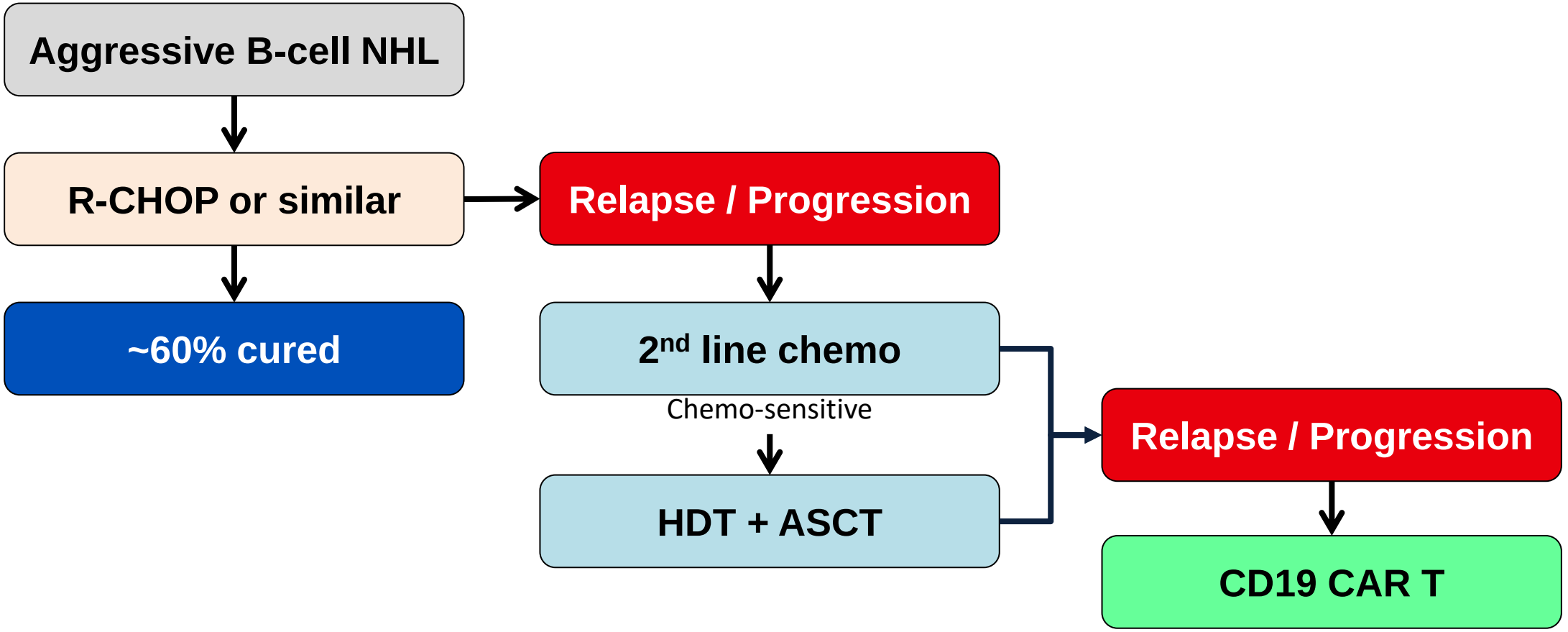


2L DLBCL – United States



Source: Clarivate Analytics

CD19 CAR T in NHL: Current Management of DLBCL



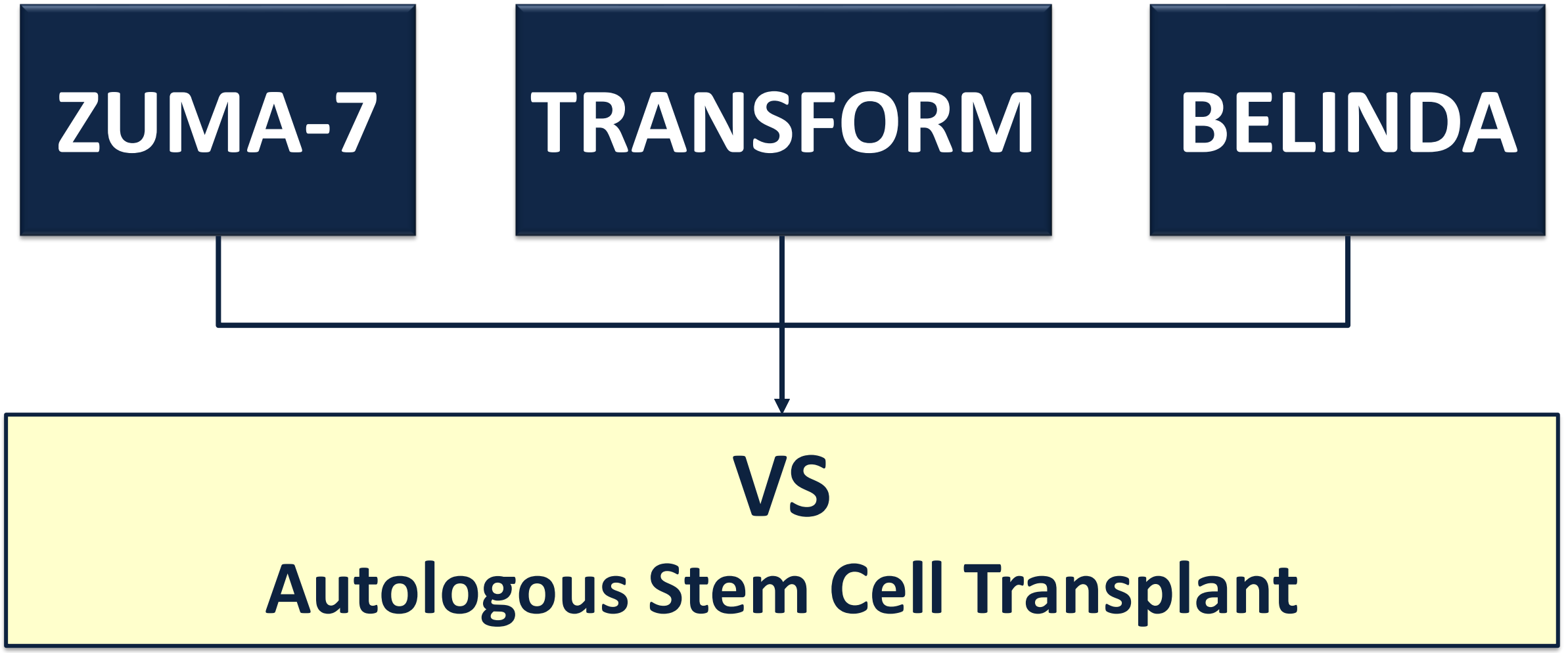
Future Directions:

CD19 CAR T in high-risk aggressive B-cell NHL

Randomized trials of CD19 CAR T vs. ASCT

CD19 CAR T in high-risk iNHL, MCL;
Off the shelf CAR Ts
Exploiting Mechanisms of Resistance

Global Randomized CAR T Studies in R/R DLBCL



CD19-Directed CAR-T Cell Therapy Versus Standard of Care in 2L

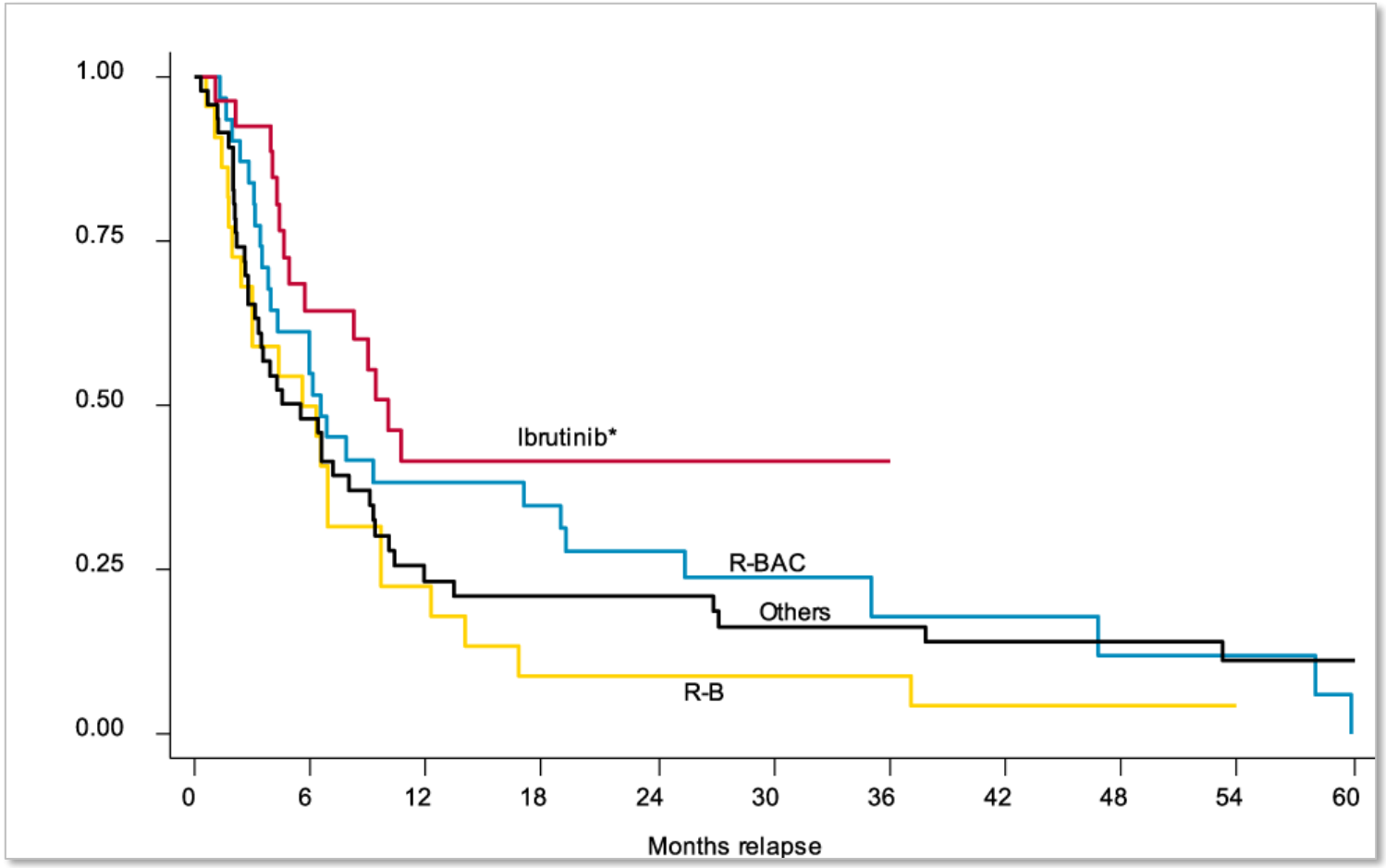
	Lisocabtagene Maraleucel (Breyanzi®)		Axicabtagene Ciloleucel (Yescarta®)		Tisagenlecleucel (Kymriah®)	
Trial	PHASE 3 TRANSFORM		PHASE 3 ZUMA-7		PHASE 3 BELINDA	
Median Follow-up (months)	6.2		24.9		10	
Bridging Therapy	Yes		Yes Optional Steroid-Only Bridging (No Chemotherapy)		Yes Bridging chemotherapy as needed	
Crossover Allowed	Yes		No		Yes, if no response at week 12	
Treatment Arm	Liso-cel (n=92)	SOC (n=92)	Axi-cel (n=180)	SOC (n=179)	Tisa-cel (n=162)	SOC (n=160)
EFS Definition	Time from randomization to death from any cause, PD, failure to achieve CR or PR, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first		EFS: time from randomization to the earliest date of disease progression per Lugano Classification, new lymphoma therapy, or death from any cause		Time from the date of randomization to the date of the first documented disease progression or stable disease at or after the week 12 (+/- 1 week) assessment	
Median EFS (months; 95% CI)	10.1 (6.1-NR)	2.3 (2.2-4.3)	8.3 (4.5-15.8)	2.0 (1.6-2.8)	3.0 (2.9-4.2)	3.0 (3.0-3.5)
HR (95% CI); P-value	0.349 (0.229-0.530); P<0.0001		0.398 (0.308-0.514); P<0.0001		1.07 (0.82-1.40); P=0.69)	

FDA Approved

FDA Approved

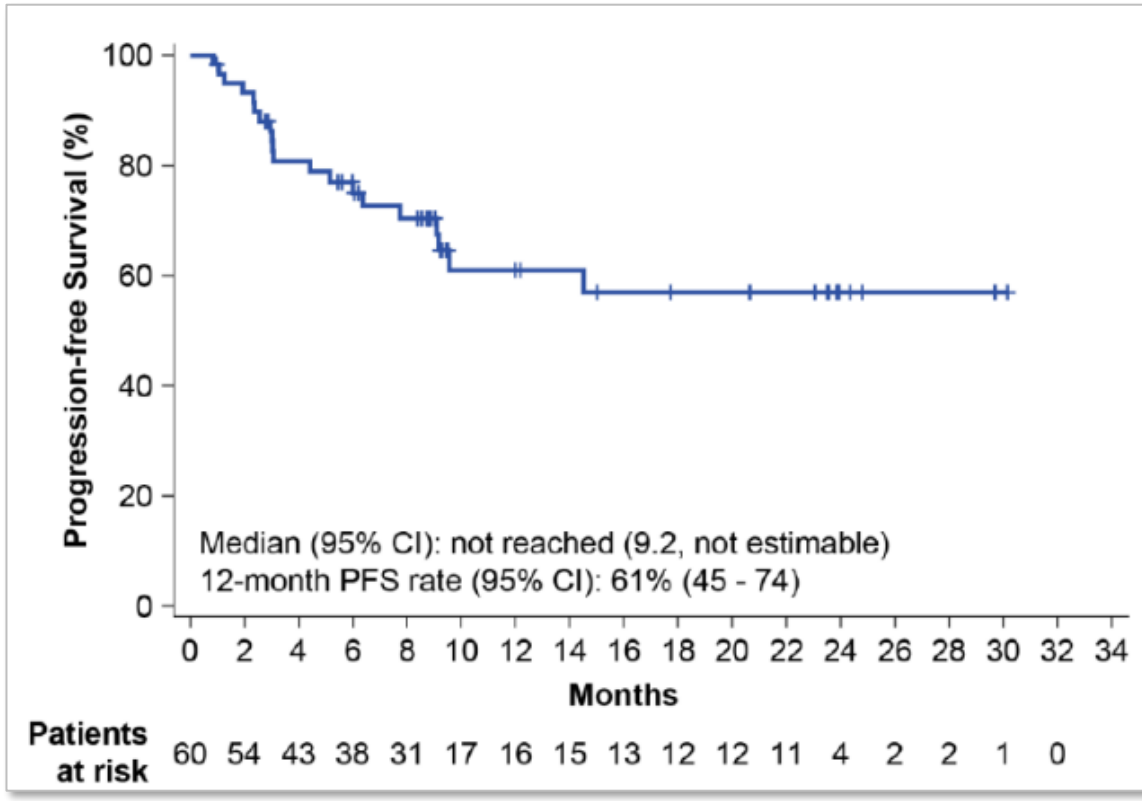
R/R Mantle Cell Lymphoma in younger patients

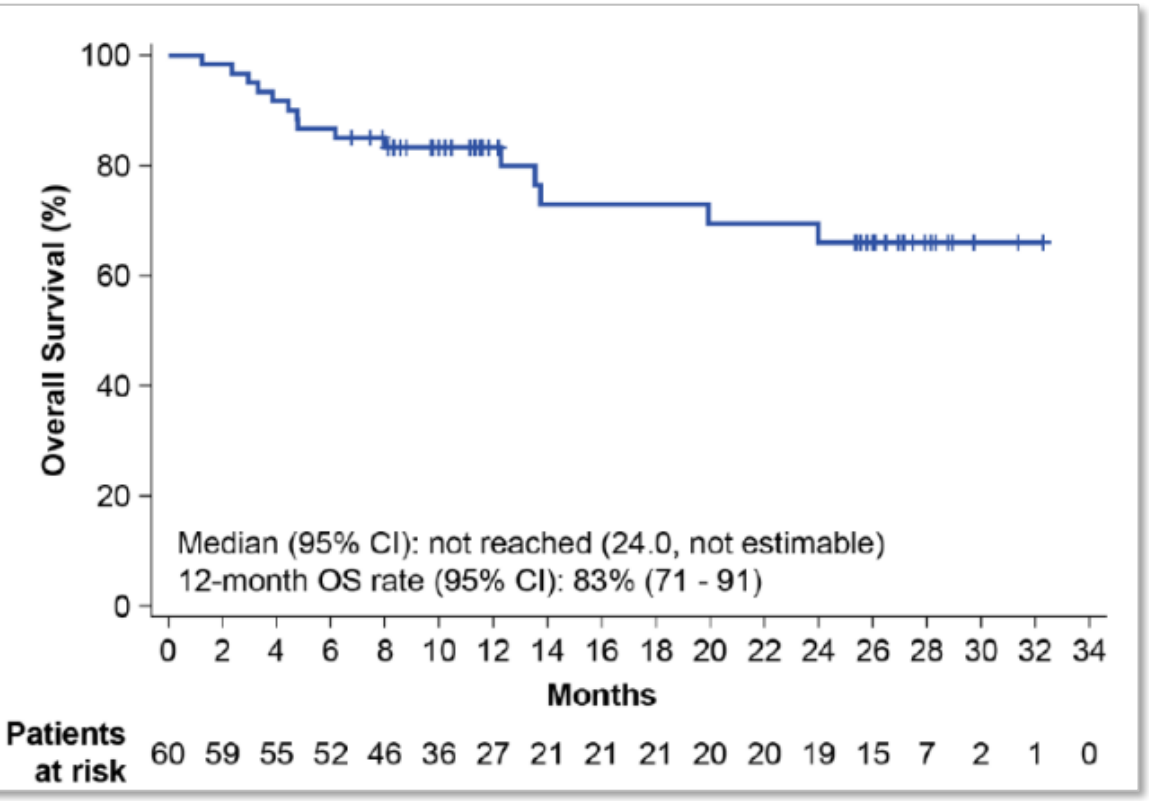
OS for patients with early progression of Disease



ZUMA 2 (Brexucabtagene): CAR-T Mantle Cell Lymphoma

Median PFS and median OS were not reached after a median follow-up of 12.3 months



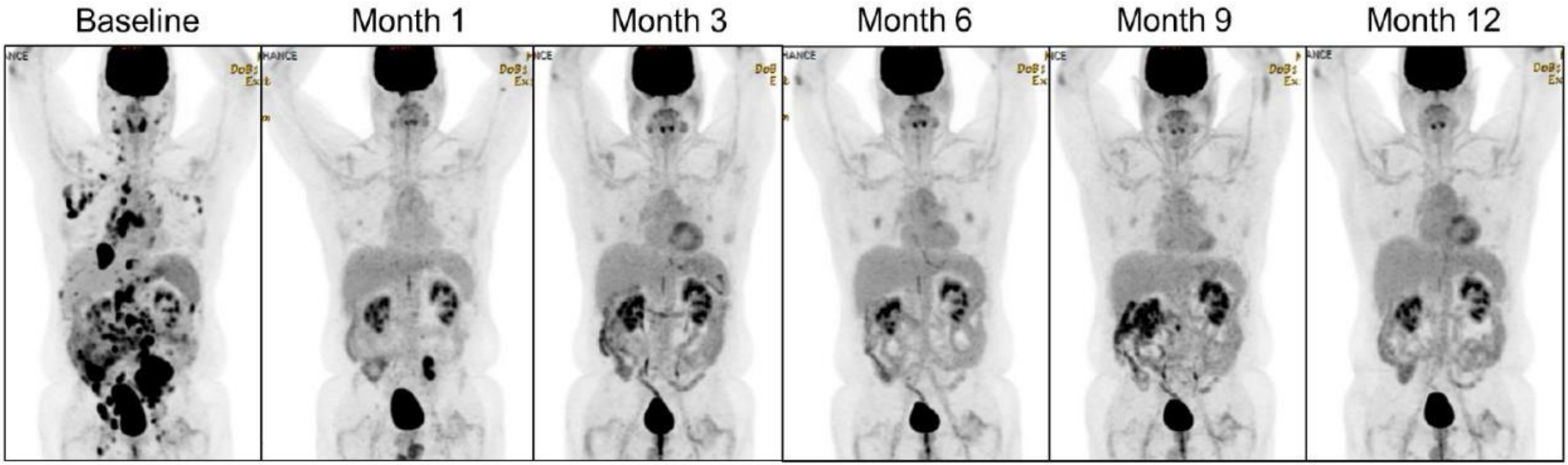


FDA Approved

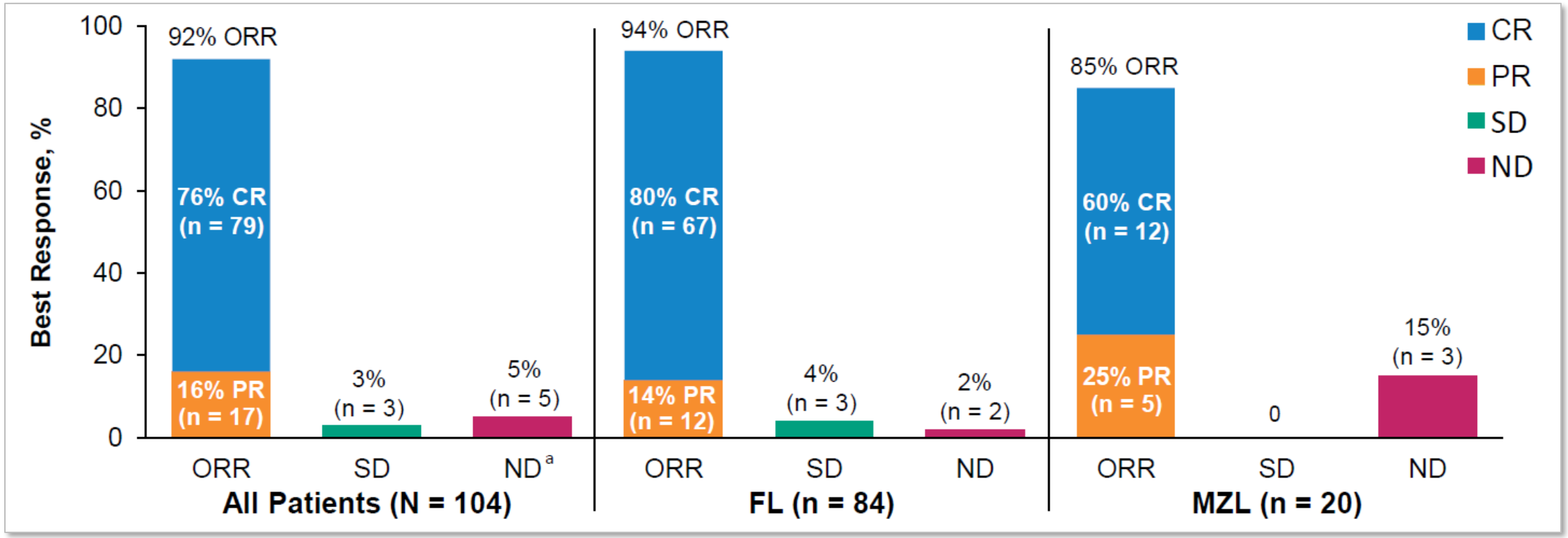
ML Wang, et al, NEJM, April 2, 2020

Representative PET Scans of Complete Response

- 50-year-old male patient with 3 prior therapies who presented with multi-compartmental MCL
- With KTE-X19, he achieved PR at month 1 and CR at month 3 and remains in remission 18 months

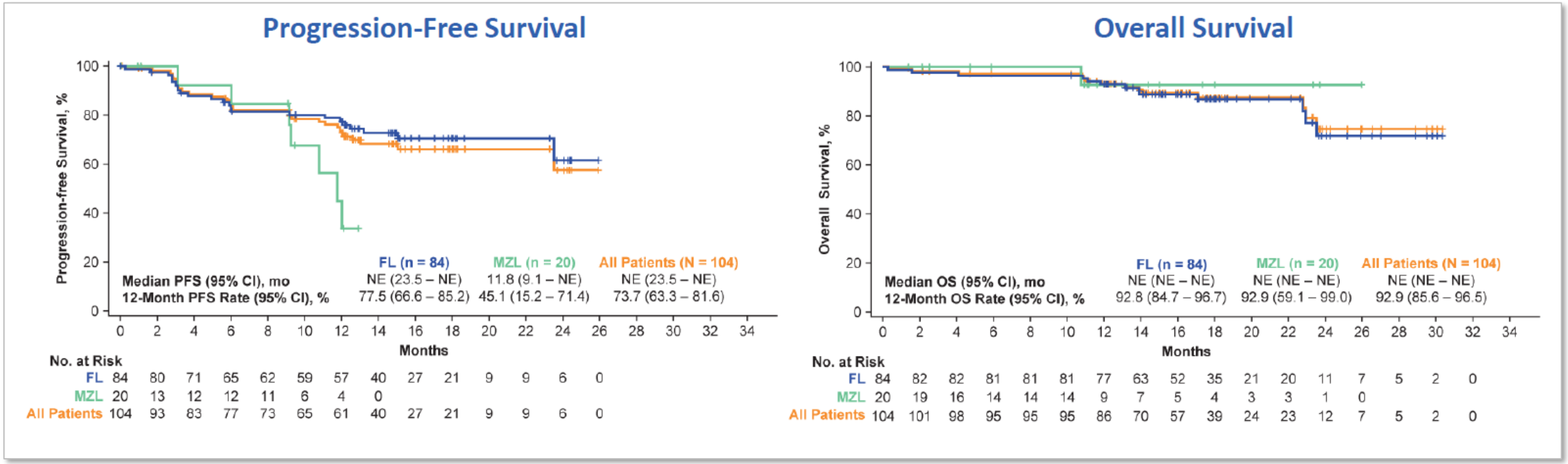


ZUMA 5: Follicular Lymphoma R/R



Jacobson, et. al.; The Lancet, Vol 23, January 2022

ZUMA 5: Progression-Free Survival and Overall Survival



FDA Approved

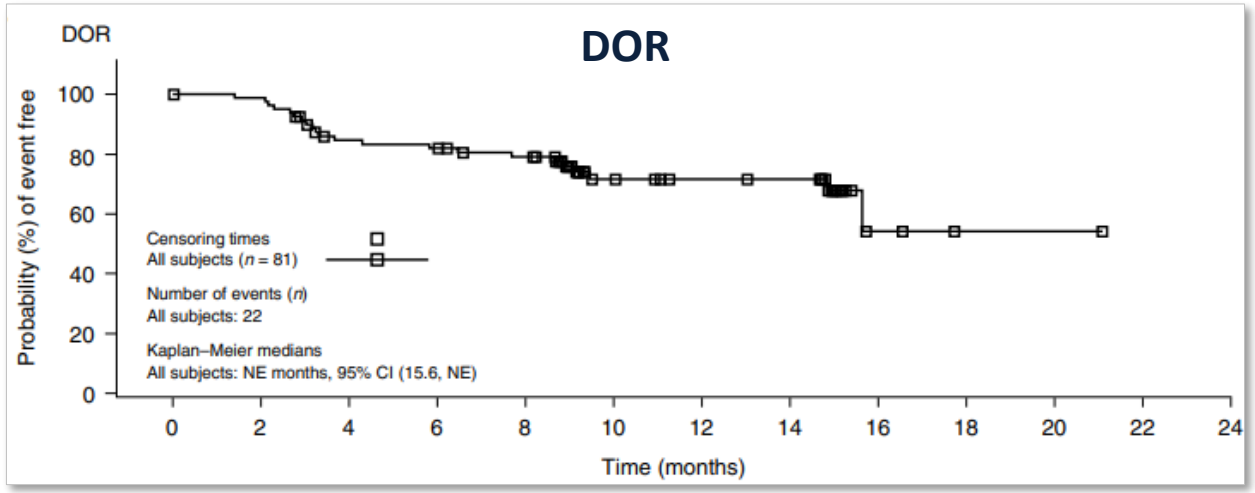
Jacobson, et. al.; The Lancet, Vol 23, January 2022

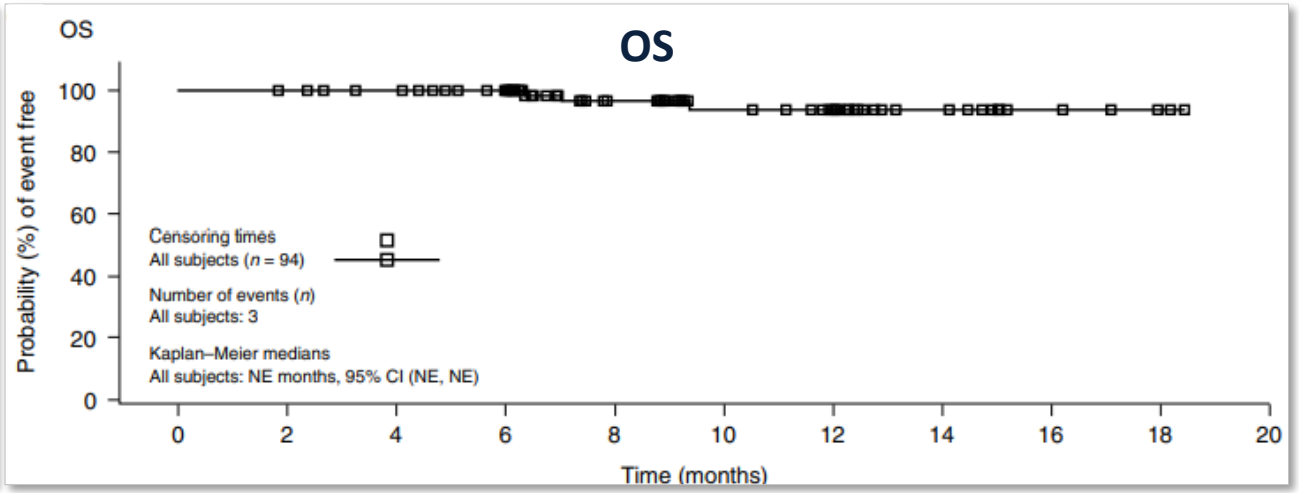
ELARA (Tisagenlecleucel): Overall Response and Complete Response Rate

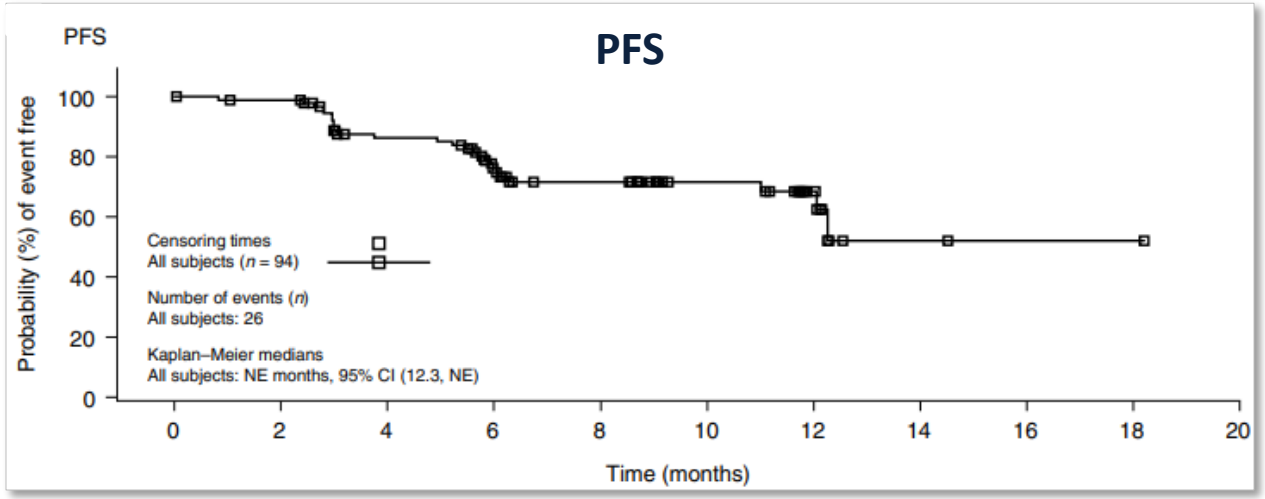
Response Rate, %	Patients Evaluable for Efficacy[a] (n=52)
CR	65.4[a]
PR	17.3
ORR (CR + PR)	82.7

Fowler, McGuirk, et al; Nature Medicine (2022) 28, 325-332

ELARA







FDA Approved

Fowler, McGuirk, et al; Nature Medicine (2022) 28, 325-332

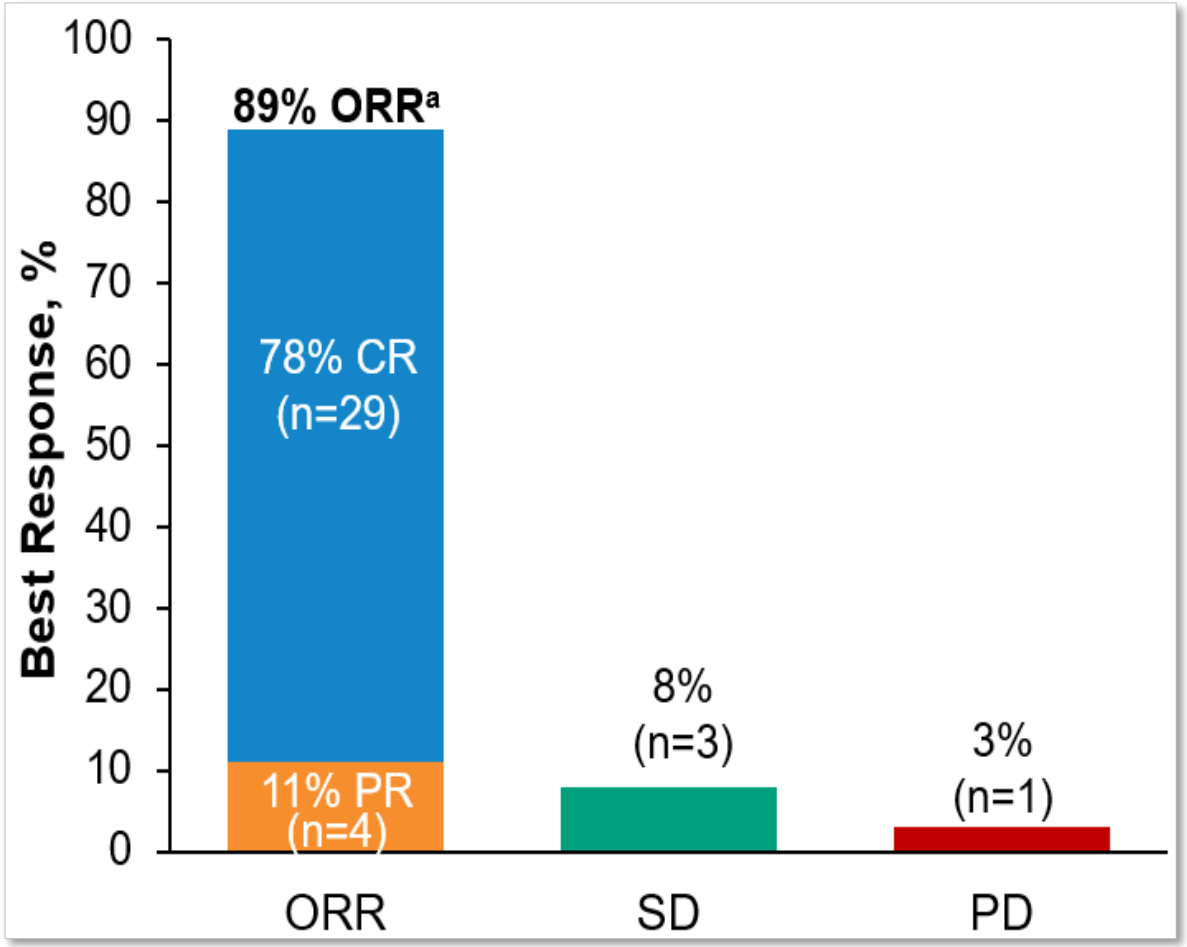
ZUMA 12: Newly Dx HR DLBCL

High-Risk LBCL
- High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations, or
- LBCL with IPI score ≥ 3 any time before enrollment

Systemic Therapy
- 2 Cycles of an anti-CD20 mAb + anthracycline-containing regimen

Dynamic Risk Assessment
- Positive interim PET (DS 4 or 5)

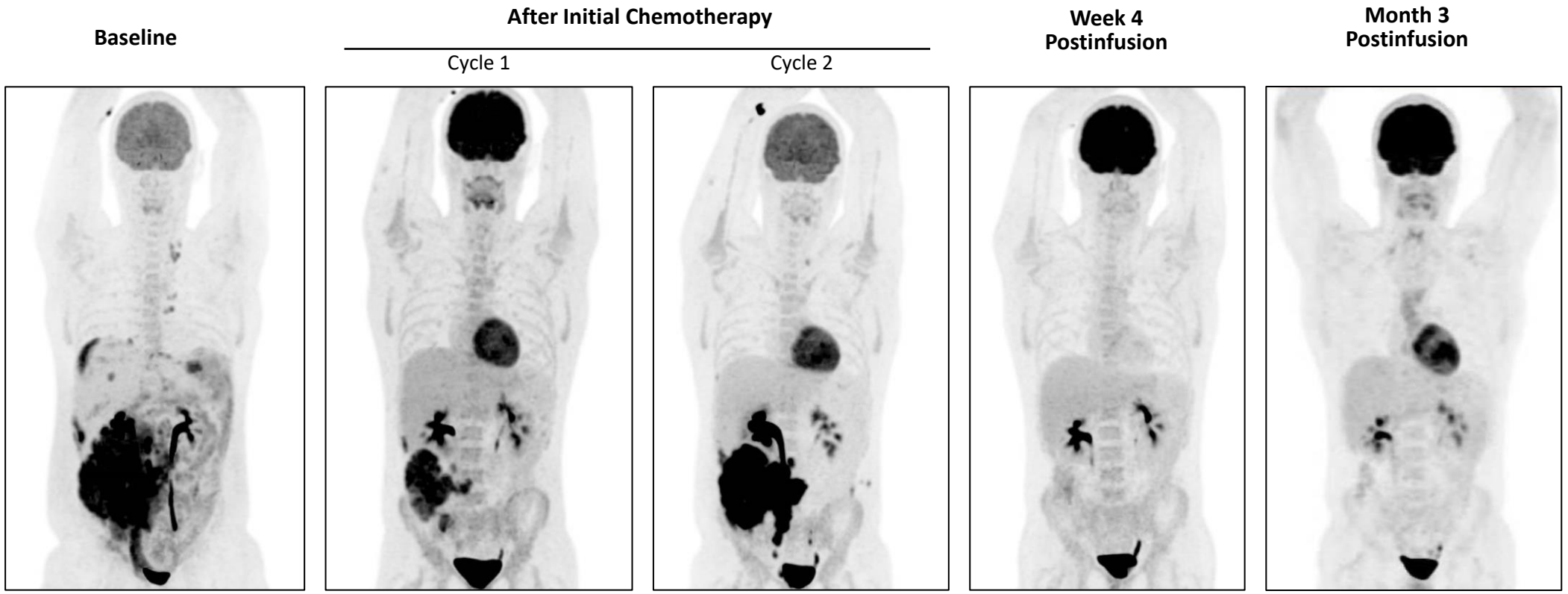
Additional Key Inclusion Criteria
- Age ≥ 18 years
- ECOG 0 – 1



Neelapu, et. al.; ASH 2021; Abstract 739

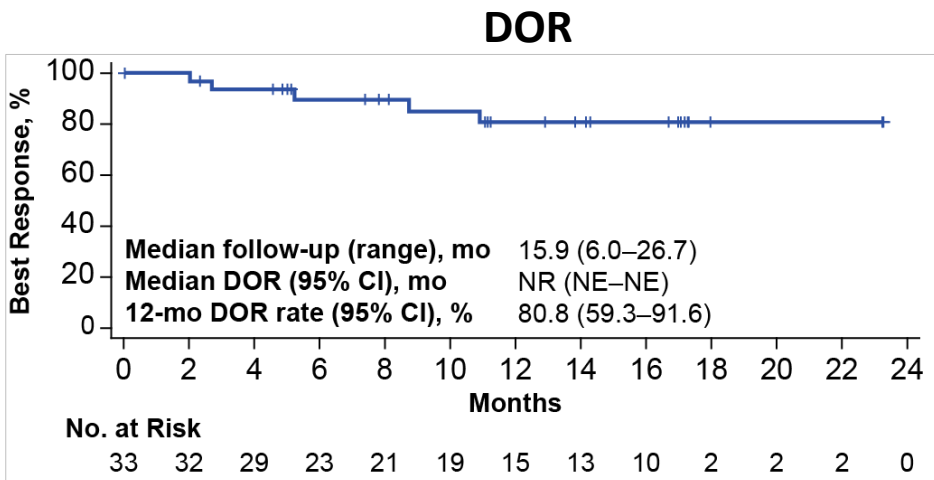
Representative Images of a Complete Response

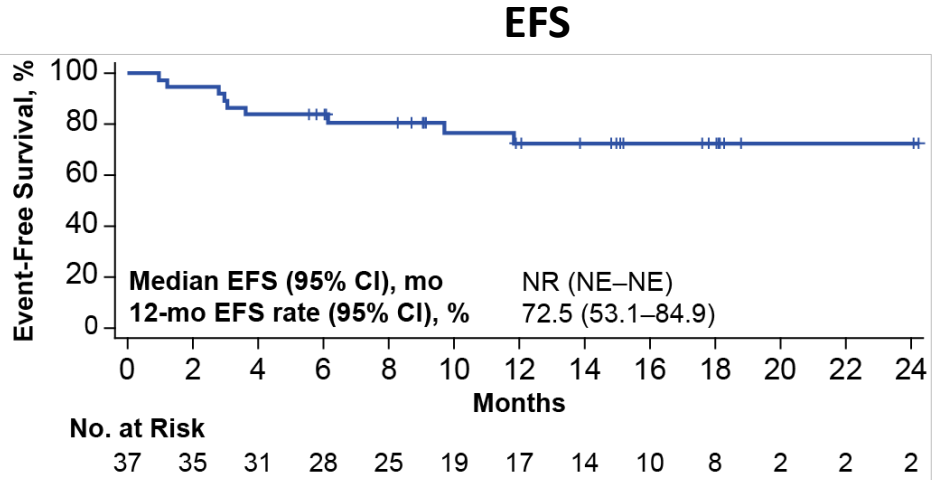
- 23-year-old male with HGBL-NOS per investigator (MYC rearrangement), IPI 3, and tumor burden (SPD) 7424 mm2
- After axi-cel infusion, he achieved a CR at Month 3 and remains in response 7 months later

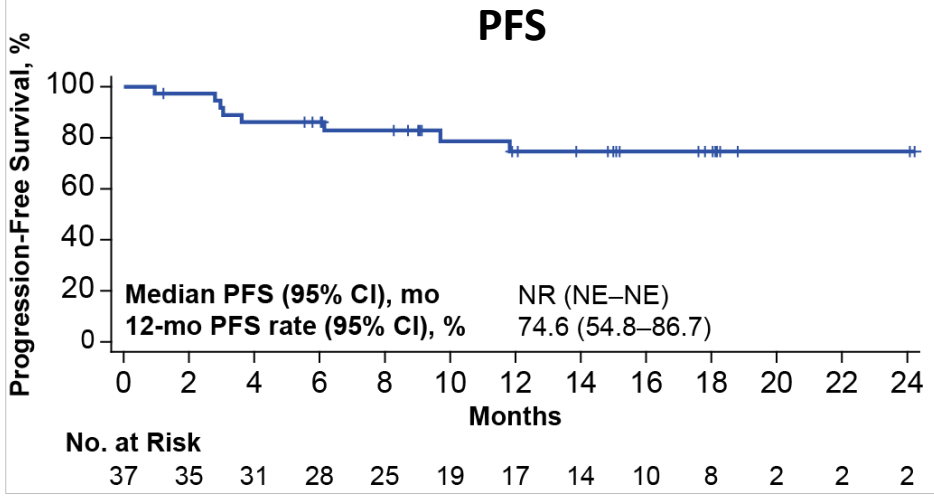


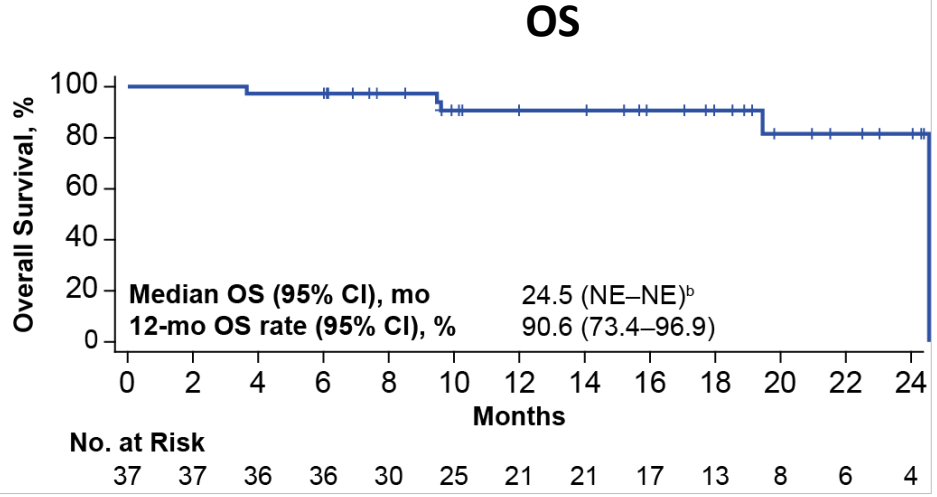
Neelapu, et. al.; ASH 2021; Abstract 739

Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival

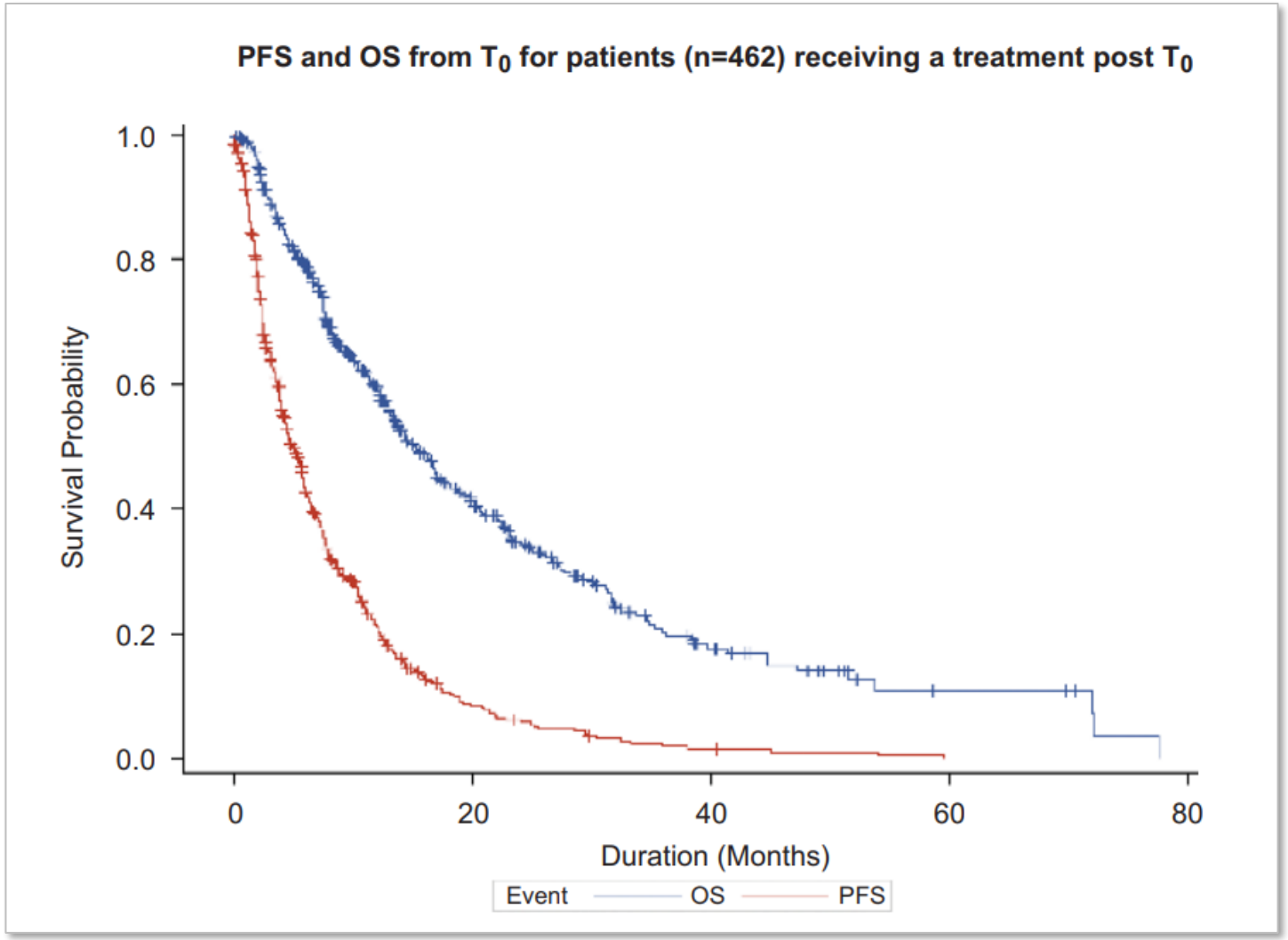






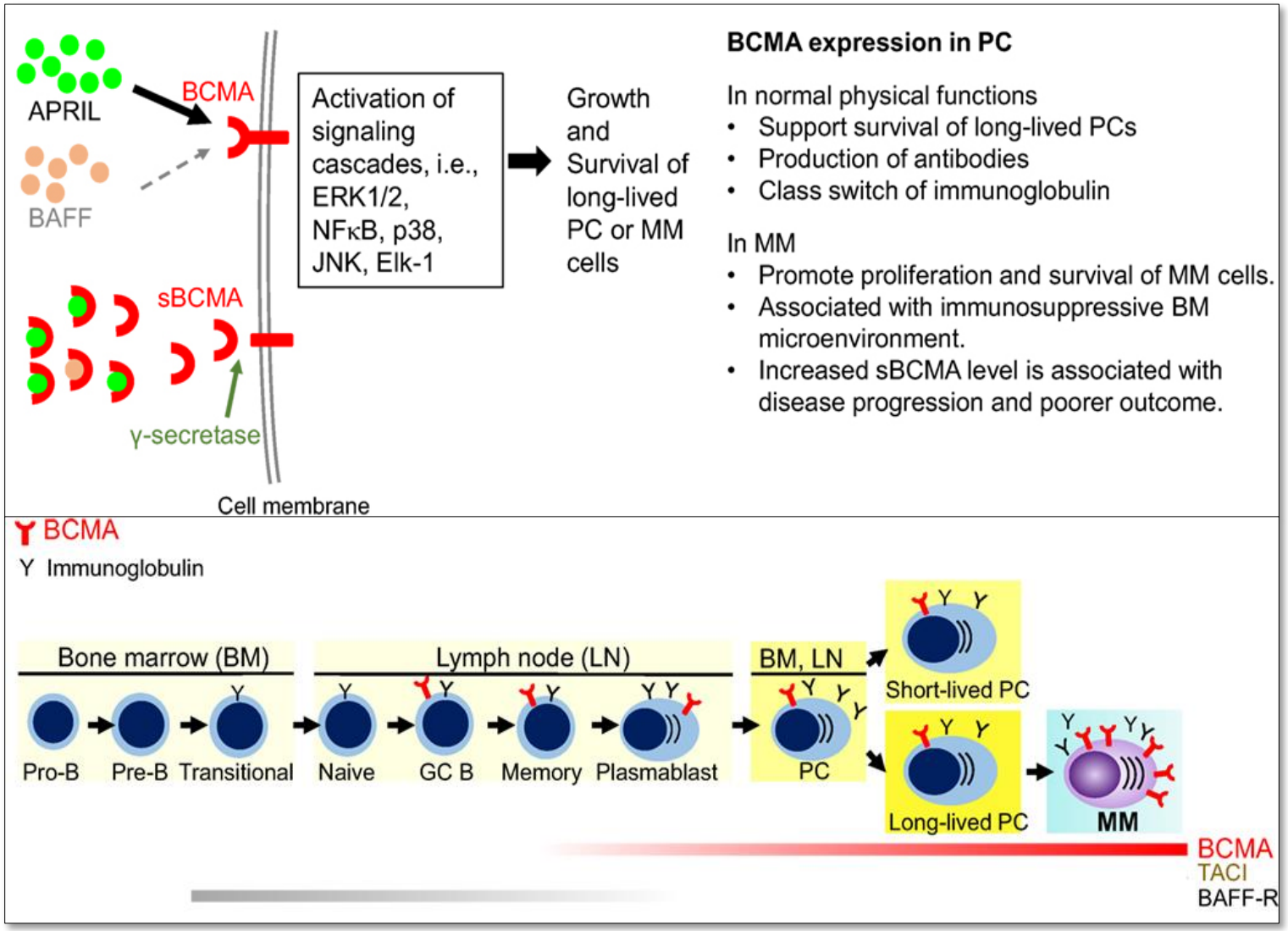


Myeloma Survival Rates



Kumar SK, et al. Leukemia (2017) 31, 2443–2448

BCMA Target



Cho S-F et al, Frontiers in Immunology, 2018

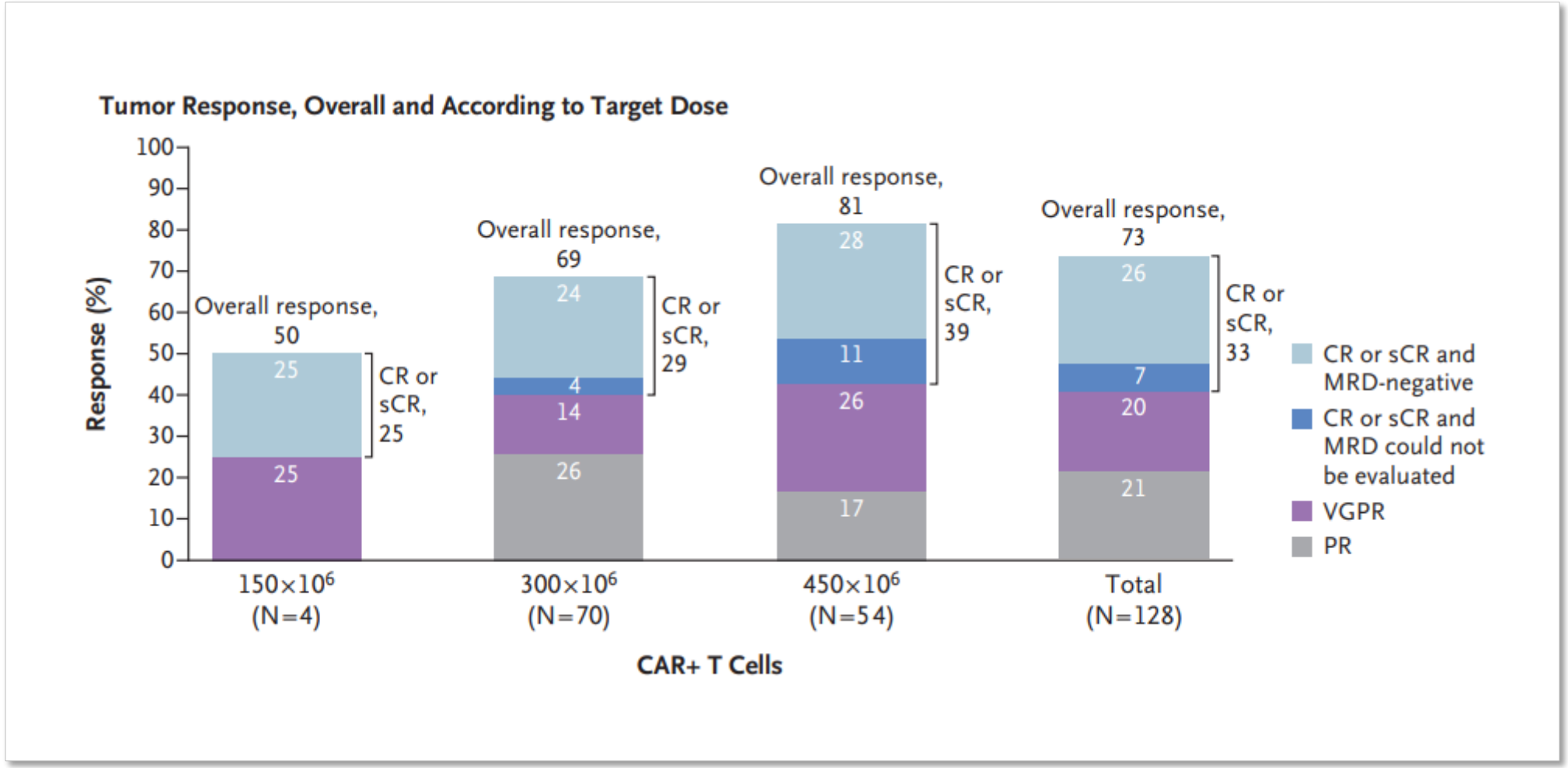
Idecabtagene Vicleucel in Relapsed & Refractory Multiple Myeloma

- **Relapsed after at least three previous regimens**
  - Proteasome inhibitor
  - Immunomodulatory agent
  - Anti-CD38 antibody
- **Primary end point was an overall response (partial response or better)**
- **Secondary end point was complete response or better**

Results	
Median follow-up	13.3 months
ORR	73%
CR	33%
Median PFS	8.8 months

Munshi, N et al. NEJM 384;8, February 25, 2021

Idecabtagene Vicleucel in Relapsed & Refractory Multiple Myeloma



FDA Approved

Munshi, N et al. NEJM 384;8, February 25, 2021

Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up

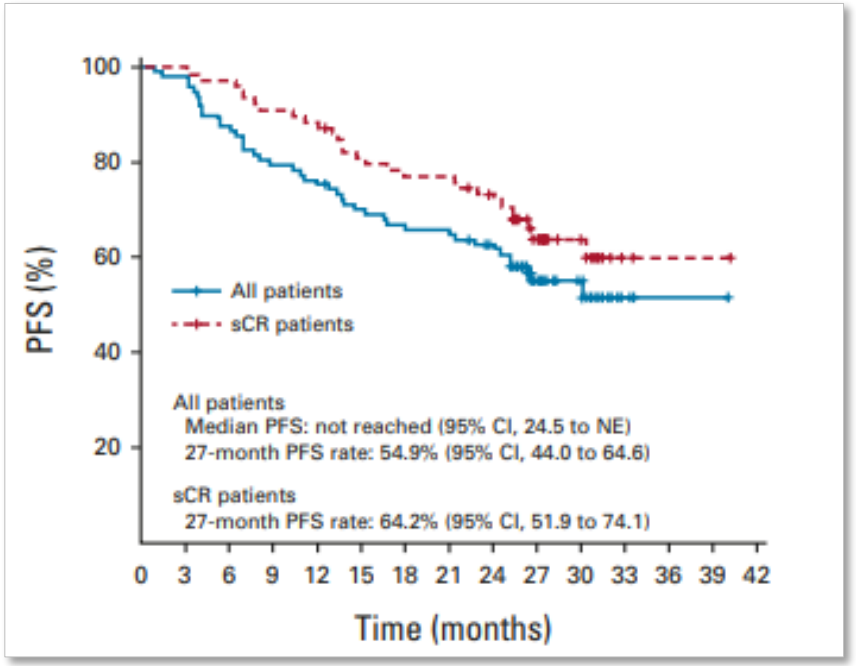
- MFU = 27.7 months
- ≥ 3 prior lines of therapy or:
  - double refractory to a proteasome inhibitor & immunomodulatory drug
  - prior proteasome inhibitor, immunomodulatory drug, & anti-CD38 therapy
- ORR = 97.9%
- sCR = 82.5%
- Median duration of response was not estimable
- Median PFS was not reached
- PFS = 54.9%
- OS = 70.4%
- ORR high across all subgroups
- Duration of response, PFS and/or OS were shorter in patients with:
  - high-risk cytogenetics
  - ISS Stage III
  - High tumor burden
  - Plasmacytomas

Martin, T, et al. JCO, July 2022

Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up

Variable	Total (N = 97)
Overall response	
Patients with a response, No.[b]	95
Rate, % (95% CI)	97.9 (92.7 to 99.7)
Best overall response rate, % (95% CI)	
sCR	82.5 (73.4 to 89.4)
MRD-negative sCR[c]	44.3 (34.2 to 54.8)
CR	0 (NE to NE)
VGPR	12.4 (6.6 to 20.6)
PR	3.1 (0.6 to 8.8)
Minimal response	0 (NE to NE)
SD	0 (NE to NE)
PD	1.0 (0 to 5.6)
Not evaluable	1.0 (0 to 5.6)

Variable	Total (N = 97)
Median duration of response, months (95% CI)	NE (23.3 to NE)
Median time to first response, months (range)	1.0 (0.9 to 10.7)
Median time to best response, months (range)	2.6 (0.9 to 17.8)
Median time to CR or better, months (range)	2.9 (0.9 to 17.8)
MRD negativity, No. (%)	
No. of patients evaluable for MRD at 10^{-5}	61
Rate, No. (%)	56 (91.8)
No. of patients evaluable for MRD at 10^{-6}	52
Rate, No. (%)	39 (75.0)



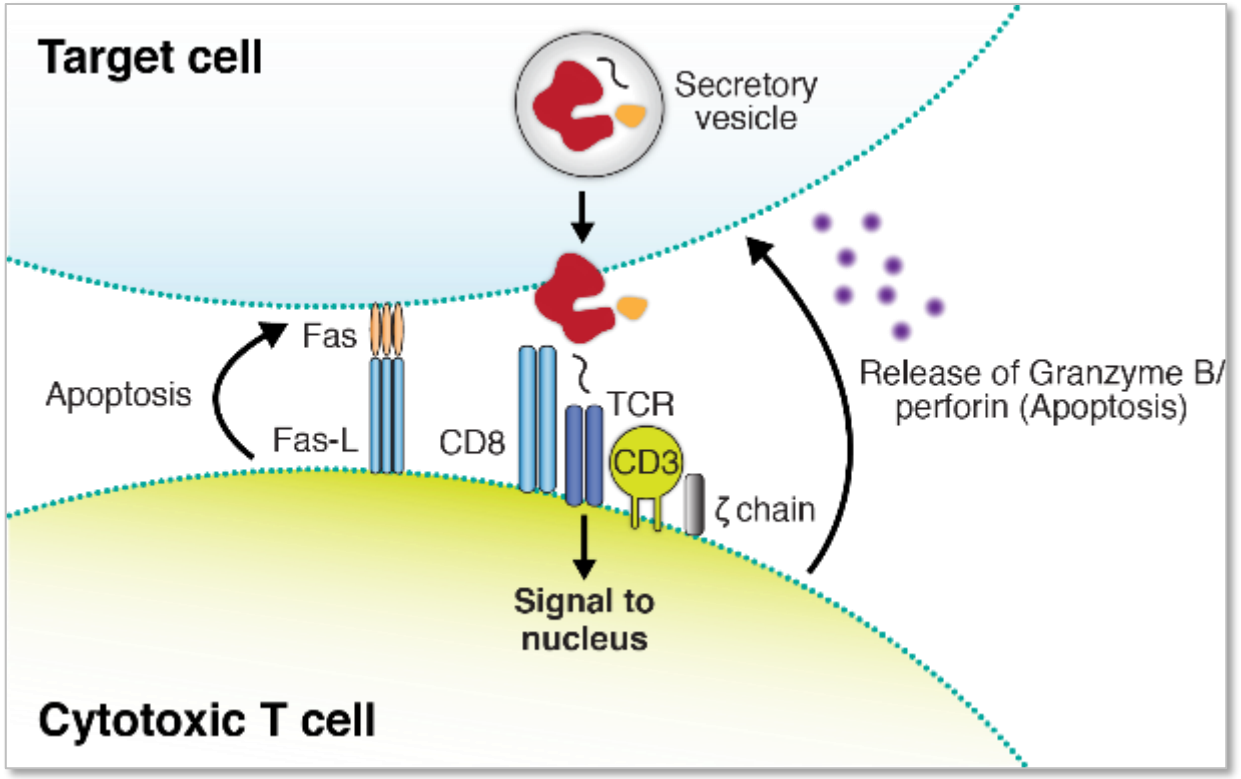
Martin, T, et al. JCO, July 2022

Problems

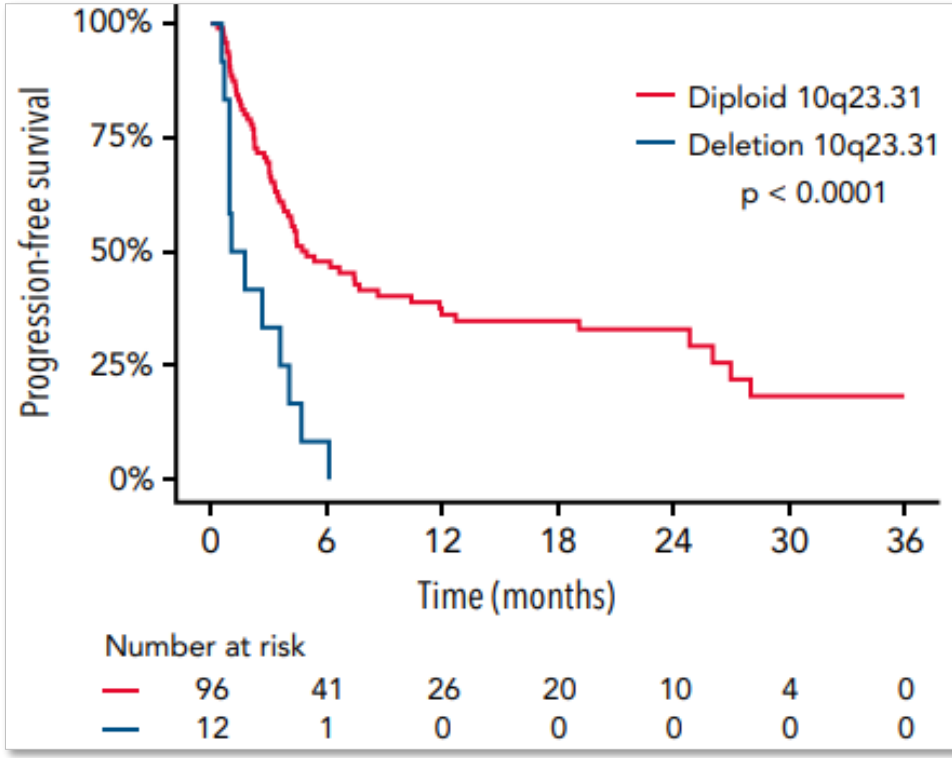
- **ACCESS**
  - Production Capabilities (lack of clinical window for leukapheresis)
  - Long manufacturing times
  - Need for bridging therapy
- **Lack of Response/Relapse**
  - Suboptimal construct/T-Cell exhaustion
  - Antigen loss
  - Fas Receptor Loss

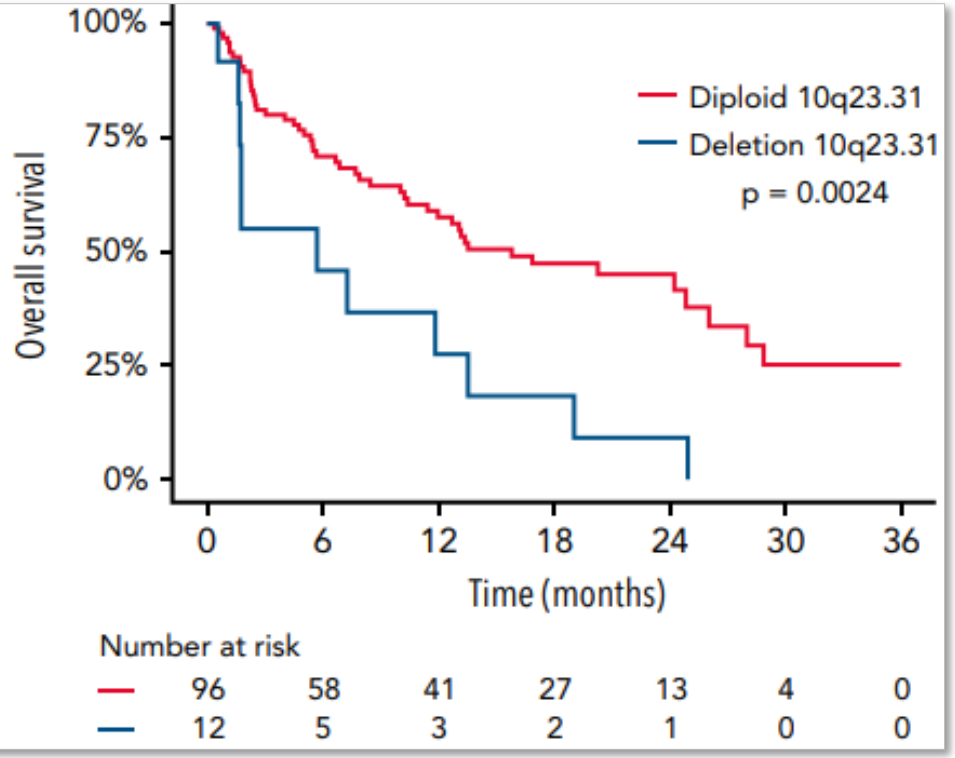
Activated T Cells: Effector CD8 CTLs

- **CTLs induce apoptosis through multiple mechanisms, including:**
  - Release of cytotoxic granules containing perforin and granzyme B
  - Surface receptor engagement such as Fas/FasL



Risk assessment with low-pass whole-genome sequencing of cell-free DNA before CD19 CAR T-cell therapy for large B-cell lymphoma





Cherng, H. et al., Blood, Vol 140, August 2022

Rationale for Allogeneic CAR T-Cell Therapy

- Potential to improve efficacy as the T-cell fitness is expected to be better than autologous products and ability to select specific t-cell subsets
- Consistent product quality
- No wait period as they are off the shelf
- Precise placement of the gene construct in the genome
- Long-term risk of insertional mutagenesis unlikely
- **Problem! Rejection or GVHD**

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

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

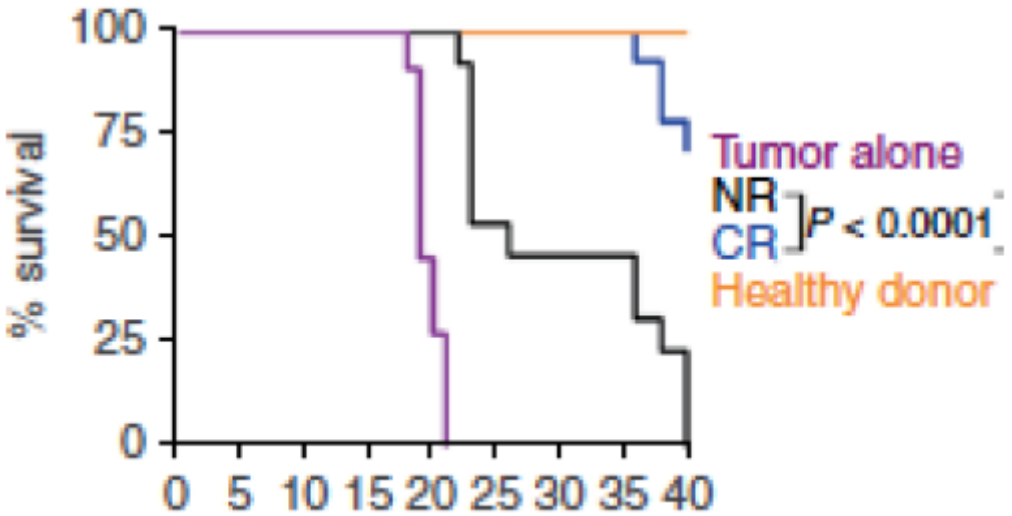
Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia

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

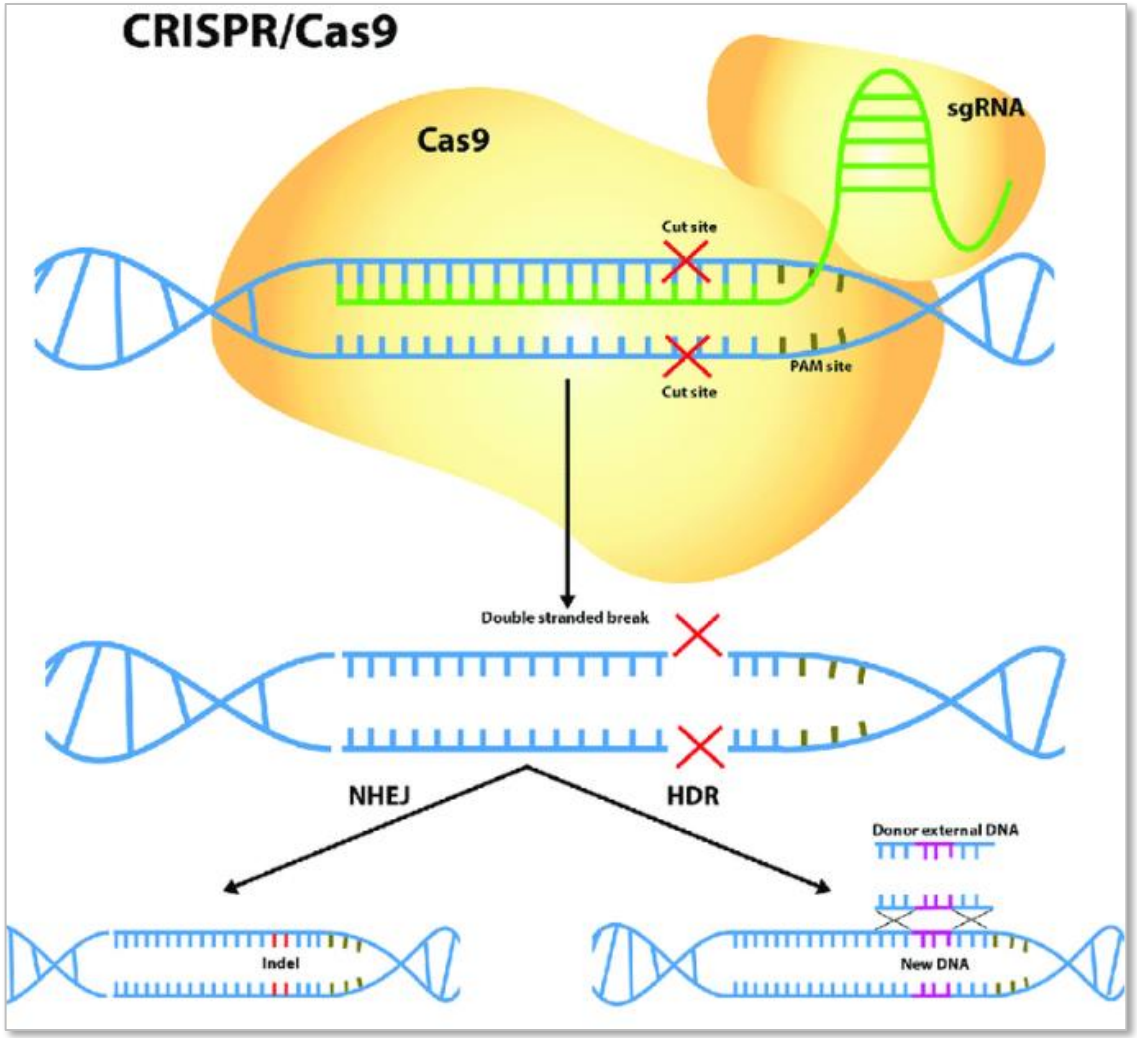
- Rationale for allogeneic CAR or banking T cells when healthy

- 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



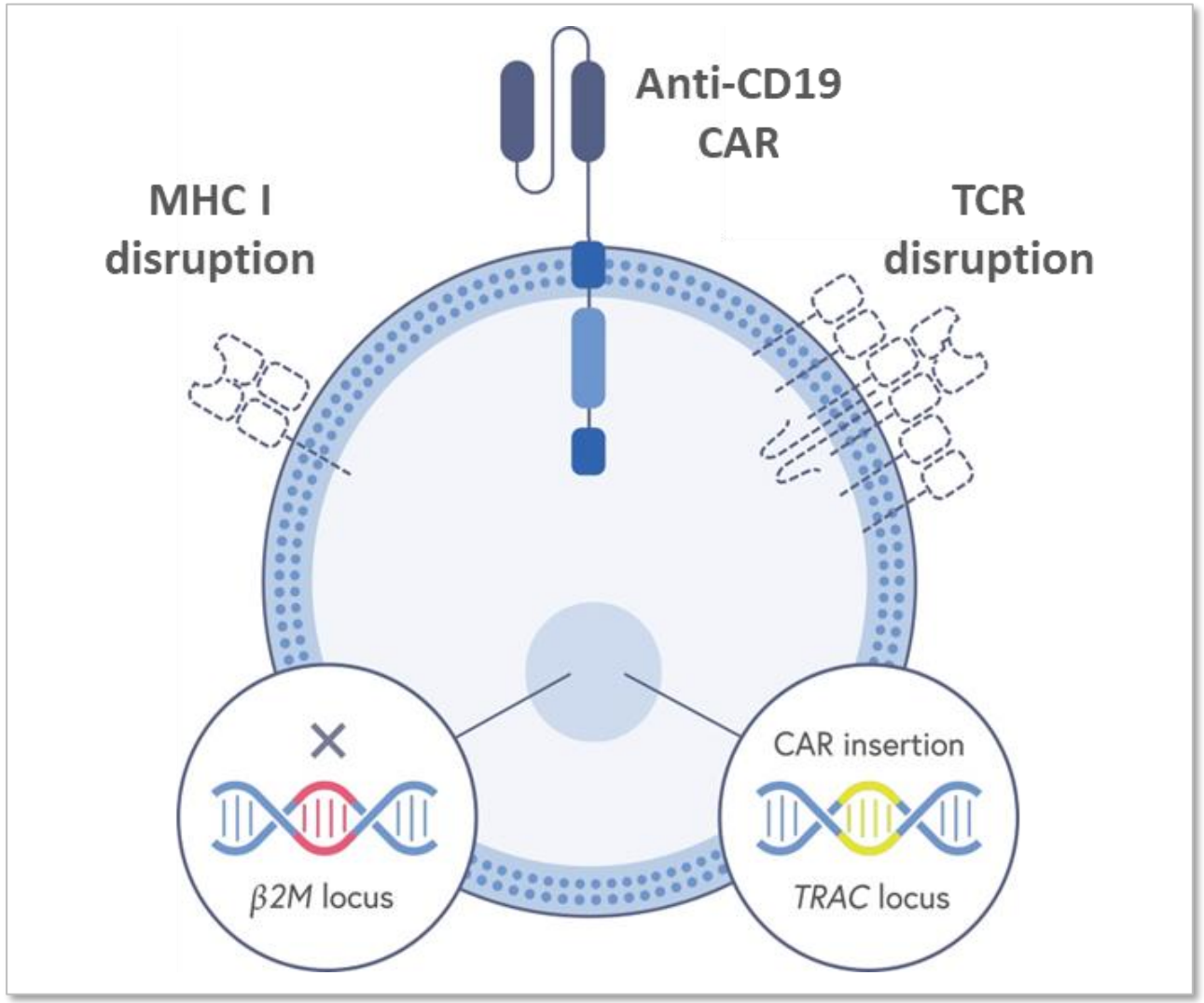
Precise Gene Editing-CRISPR

Precise and Simple Gene Editing



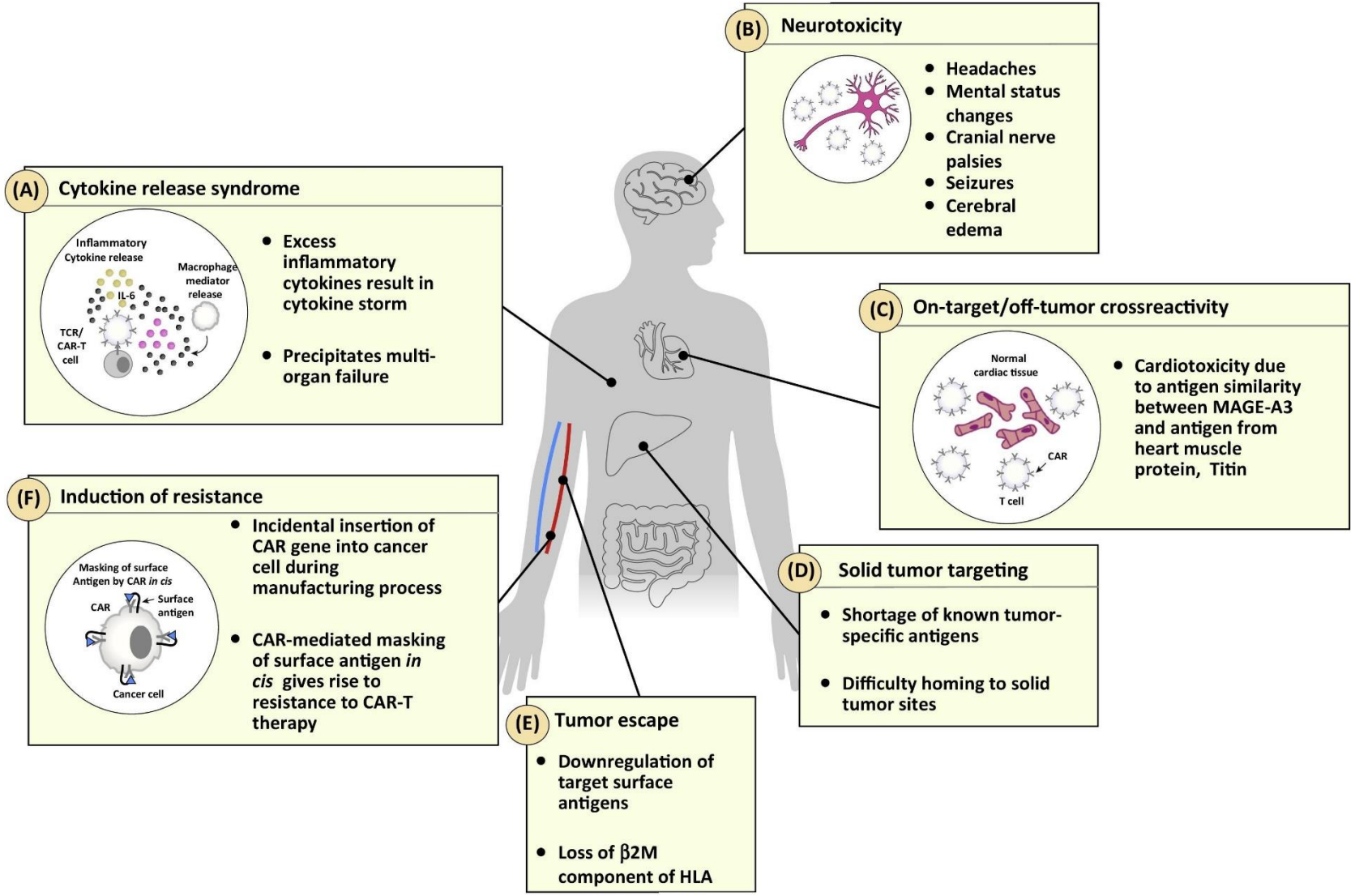
Potential Applications

Gene-Edited Allogeneic Anti-CD19 CAR-T: Mitigating Rejection and GVHD

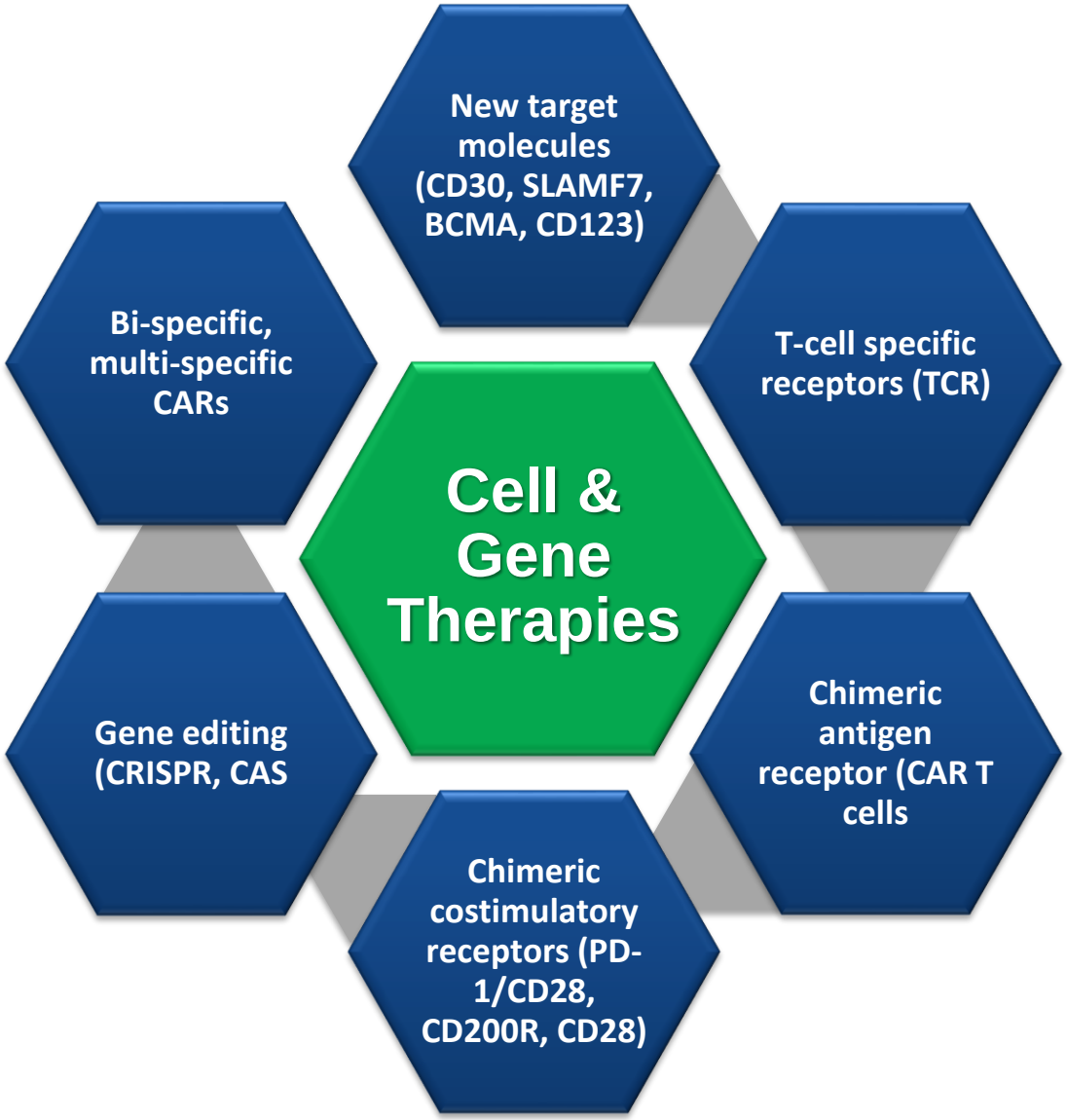


McGuirk ASCO 2021, June 4-8, 2021

CAR-T Toxicities



Continued Advances



Cell Therapy Clinical Trials at KUCC

Post – Transplant	Lymphoma	Leukemia	Multiple Myeloma	Solid Tumor
Active 1	Active 5	Active 7	Active 5	Active 4
Startup 2	Startup 4	Startup 2	Startup 3	Startup 2

**Does not include Biomarker, EAP, MAP, LTFU protocols, CAR-T Ancillary Studies*

Pipeline

- Multiple Myeloma
- Lymphoma
- Leukemia Ovarian Fallopian Peritoneal
- Glioblastoma
- Pancreatic
- Dual Target CAR
- CAR-T combination therapy
- Advanced Solid Tumors
- Allogeneic Leukemia
- Allogeneic Lymphoma
- Allogeneic Multiple Myeloma
- Sickle Cell
- NK Cell

University of Kansas Cancer Center Current State

- **NCI Comprehensive Cancer Center Designation**
- **Cambridge Tower expansion (3 floors)**
- **Expand Cellular Therapeutics program**
  - Including solid tumors
- **Increase the availability of clinical trials and increase clinical research trials accruals**
- **Development of novel clinical laboratory research**
- **Collaboration with NCI & CMH on Tri-Specific LAR CD19, 20, 22**


Where cancer meets its match.
THE UNIVERSITY OF KANSAS
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