Cellular Therapies in Leukemias

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Dana-Farber Cancer Institute

Disclosures

- Advisory board participation: Abbvie, Lumanity, Enos

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Outline

- Recap: current treatment landscape
- Recap: treatment landscape of the near-future
- Emerging real-world evidence of cell therapy
- Updates in CAR-T toxicity

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Recap – current treatment landscape

Indication	Reference	Intervention	OS	CR	Composite remission*	MRD-neg	CRS ≥Gr 3	Neurotoxicity ≥Gr 3
R/R B-ALL	*Kantarjian, NEJM 2017* Phase 3 TOWER	Blinatumomab	7.7mo	34%	44%	76%	4.9%	9.4%
		Chemotherapy	4.0mo	16%	25%	48%	0%	8.3%
B-ALL in MRD+ CR	*Gökbuget, Blood 2018* Phase 2	Blinatumomab	36.5mo	N/A		78% after cycle 1	1.7% all w/in cycle 1	13%
R/R B-ALL (≤25 years, ≥2 relapses)	*Maude, NEJM 2018* *Laetsch, JCO 2022* Phase 2 ELIANA	Tisagenlecluecel (41BB co-stim)	76% @12mo 63% @36mo	60% @3mo	82% @3mo	100%	46% w/in 8 wks	13% w/in 8 wks
R/R B-ALL (≥18 years)	*Shah, Lancet 2021* Phase 2 ZUMA-3	Brexucabtagene autoleucel (CD28 co-stim)	18.2mo	56%	71%	97%	24%	26% 18% grade 5

*CR+CRi+CRh for *Kantarjian, NEJM 2017*. CR+CRi for all other studies

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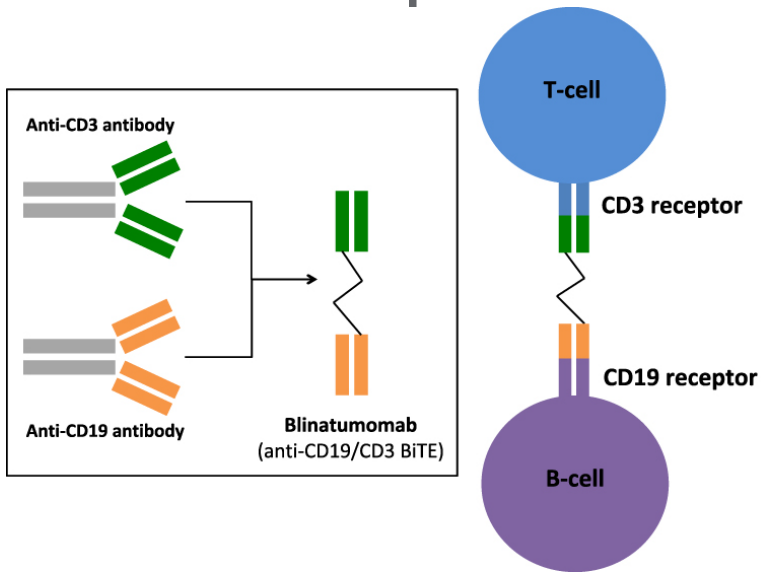

Sigmund et al, Blood and Lymph Cancer, 2020

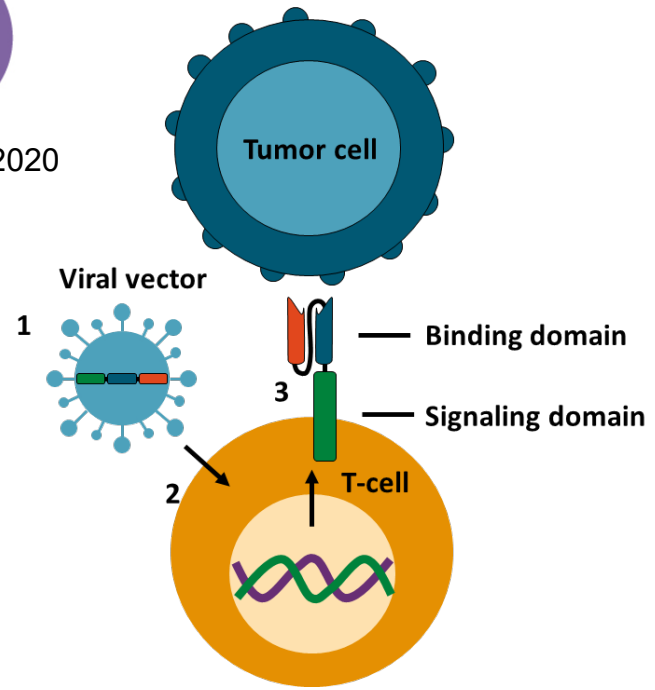

Image credit: clinicaloptions.com

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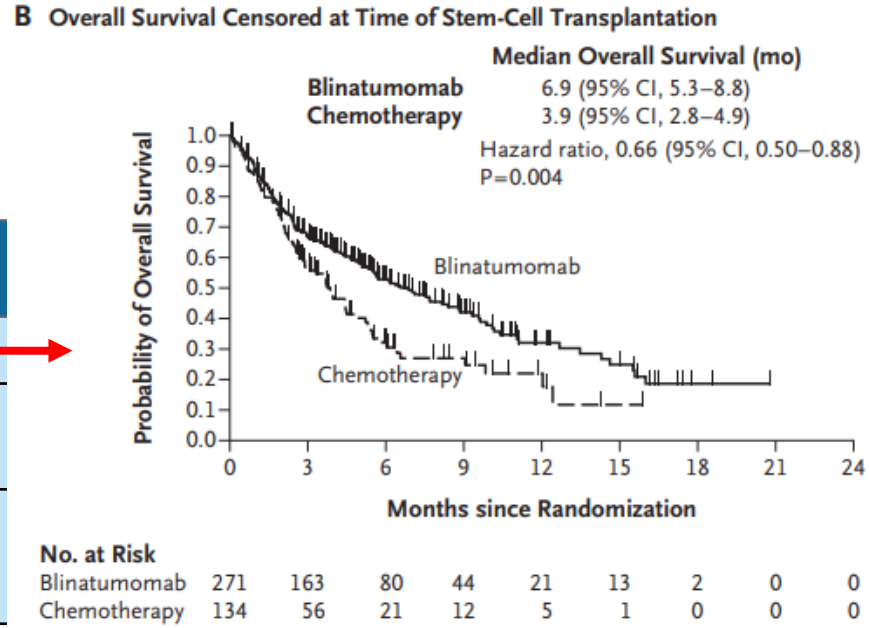

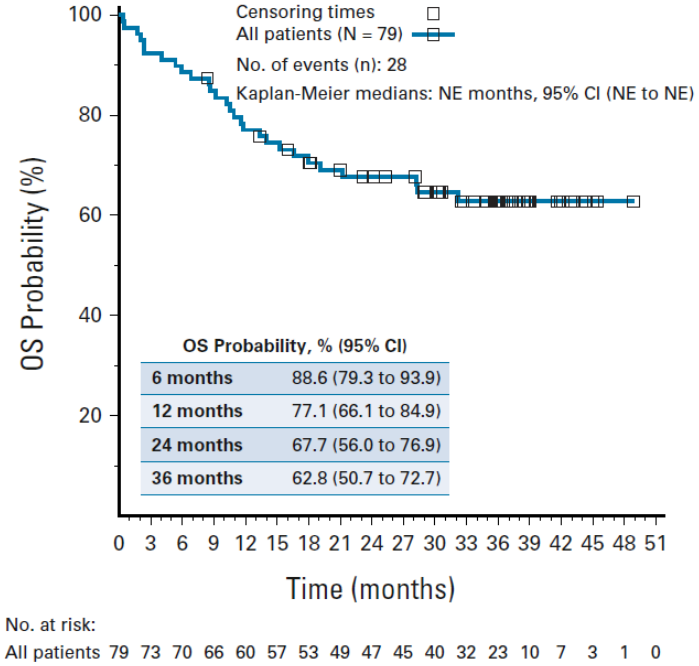

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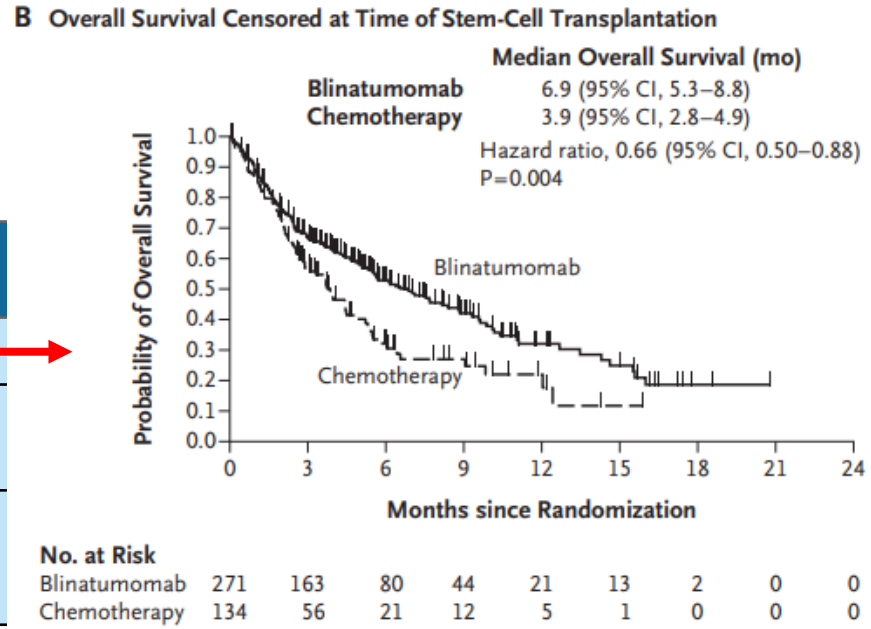

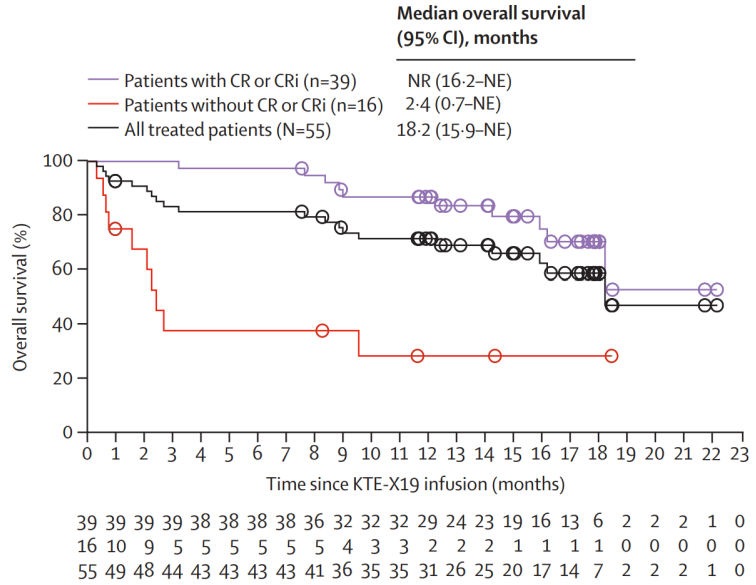

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Blinatumomab: ↓ toxicity, long-term survival dependent on HCT
CAR-T: ↑ toxicity, long-term survival without HCT unclear

3-year update of ZUMA-3 (brexucabtagene autoleucel)

OS			
Overall	26.0mo	**Patients in CR**	38.9mo
Age <26 (n=12)	28.6mo	**Age ≥26 (n=43)**	34.1mo
1 prior tx (n=10)	NR	**2 prior tx (n=45)**	25.6mo
Prior blina (n=25)	14.2mo	**No prior blina (n=20)**	NR
Subsequent HCT (n=10)	NR	**No HCT (n=29)**	38.9mo
CR/CRi			
Overall	71%	**CR**	56%
Age <26 (n=12)	67%	**Age ≥26 (n=43)**	72%
1 prior tx (n=10)	90%	**1 prior tx (n=10)**	67%
Prior blina (n=25)	60%	**Prior blina (n=25)**	80%
Grade ≥3 TRAEs			
1 prior tx (n=10)	90%	**1 prior tx (n=10)**	89%
Prior blina (n=25)	80%	**Prior blina (n=25)**	97%

Shah, Hemasphere. 2023 Aug; 7(Suppl): e54499e3.

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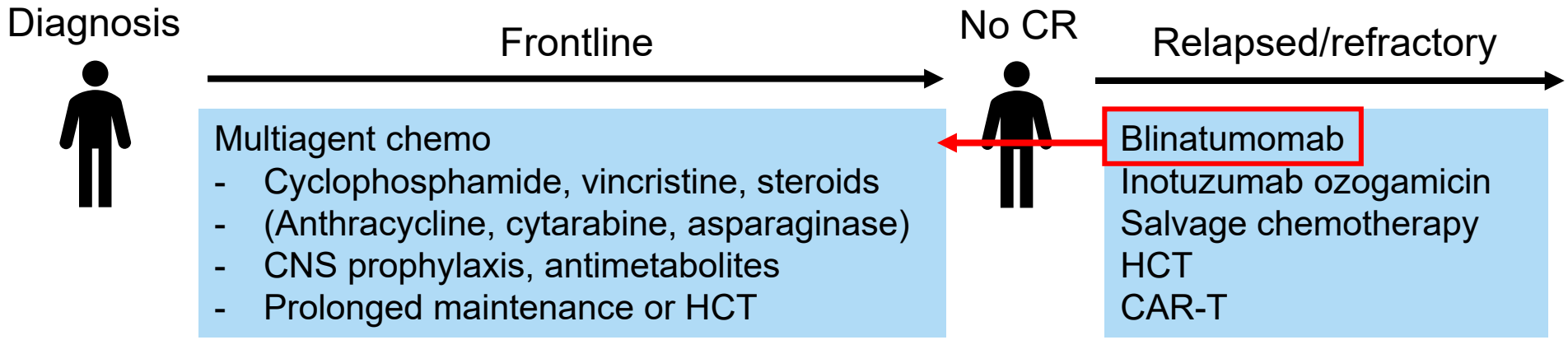
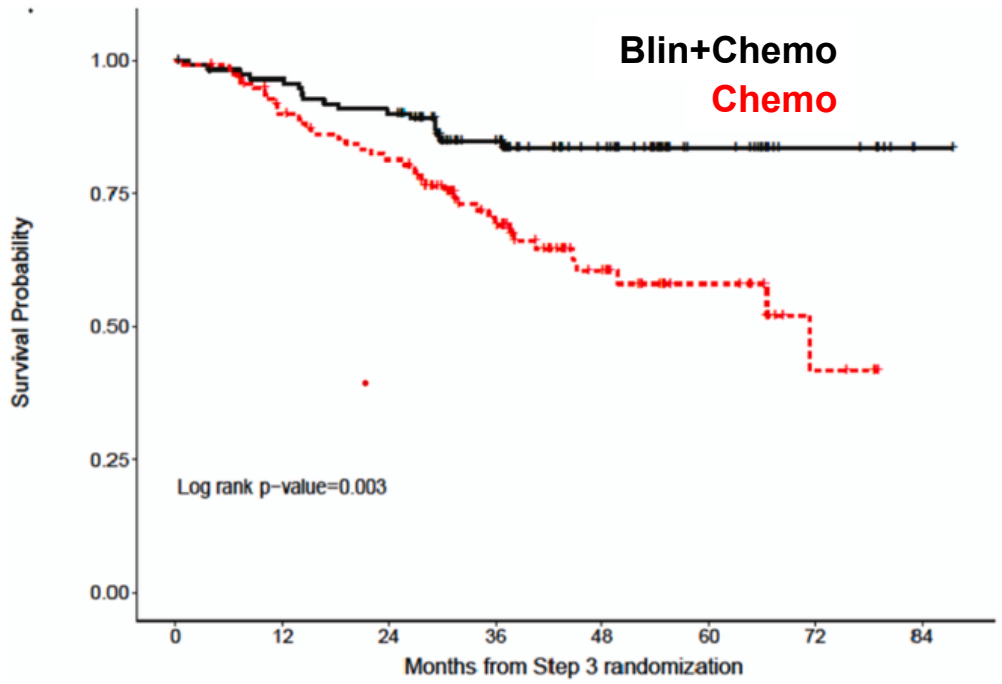
Ph-neg ALL – current treatment landscape

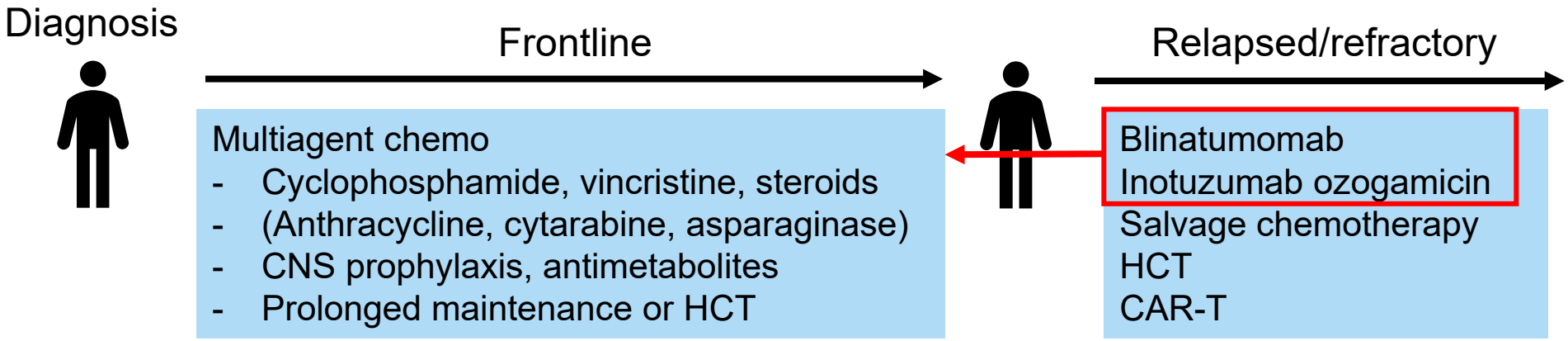




Ph-neg ALL – ECOG-ACRIN E1910

- N=224 pts already in MRD-negative (<0.01%) CR/CRi after induction
- Age 30-70 (median 51)
- Randomized to consolidation with chemo or blinatumomab

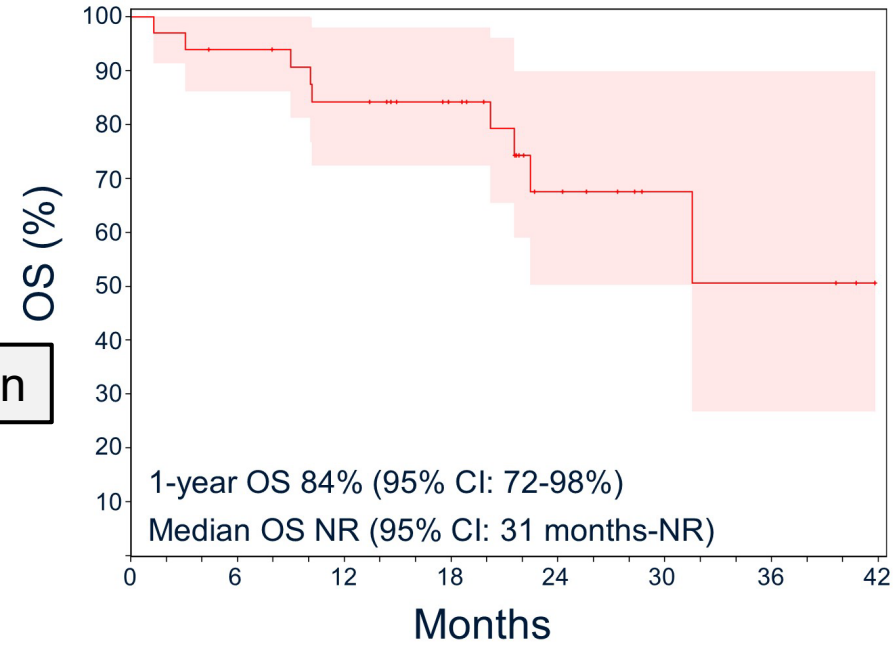
Ph-neg ALL – current treatment landscape



Inotuzumab induction

↓

Blinatumomab consolidation



Ph-neg ALL – Alliance A041703

- Newly-diagnosed, Ph-neg, CD22+, B-ALL
- Age ≥ 60, ECOG 0-1
- No plan for HCT
- No active CNS or testicular leukemia

Ph-neg ALL – current treatment landscape

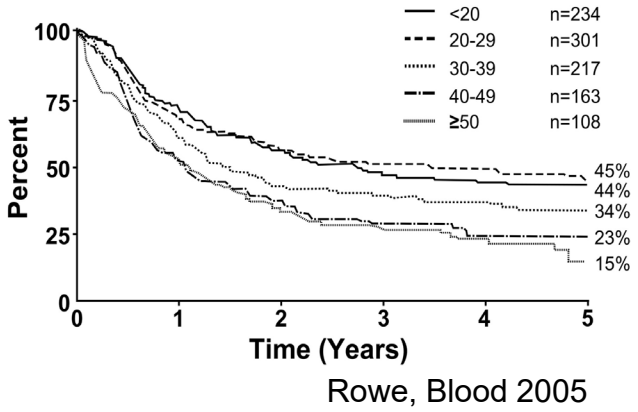
Diagnosis

Frontline

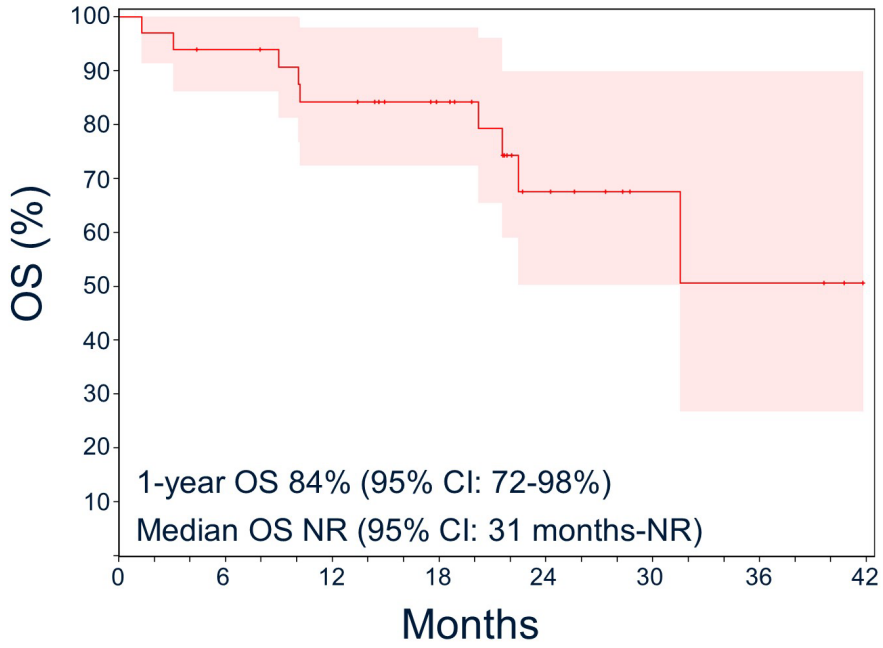
Multiagent chemo
- Cyclophosphamide, vincristine, steroids
- (Anthracycline, cytarabine, asparaginase)
- CNS prophylaxis, antimetabolites
- Prolonged maintenance or HCT

Relapsed/refractory

Blinatumomab
Inotuzumab ozogamicin
Salvage chemotherapy
HCT
CAR-T



Rowe, Blood 2005



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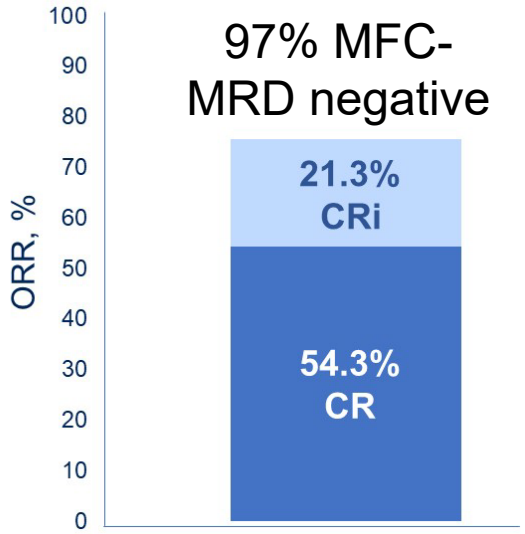


Obecabtagene-autoleucel (FELIX study)

- CD19-directed, second-generation CAR
- CD3-ζ and 4-1BB costimulatory domain (same as tisa-cel)
- Uses a scFv with a faster off-rate -> decreased toxicity profile
- Split-dosing schedule based on initial disease burden

94% of infused patients received both obe-cel infusions

CRS, cytokine release syndrome; cy, cyclophosphamide; flu, fludarabine; ICANS, immune effector cell associated neurotoxicity syndrome

Future CAR-T cell therapy for B-ALL

Intervention	OS	CR	CR + CRi	MRD-neg	CRS	ICANS
Tisagenlecluecel (≤25 years, ≥2 relapses)	76% @12mo 63% @36 mo	60% @3mo	82% @3mo	100%	Gr ≥3: 46% Any grade: 77%	Gr ≥3: 13% Any grade: 40%
Brexucabtagene autoleucel (≥18 years)	18.2mo	56%	71%	97%	Gr ≥3: 24% Any grade: 89%	Gr ≥3: 26% Any grade: 60% Grade 5: 18% (n=2 CAR-T related)
Obecabtagene autoleucel (≥18 years)	61% @9.5mo	54.3%	76%	97%	**BM blasts ≤20%**	
					Gr ≥3: 2.7% Any grade: 65%	Gr ≥3: 2.7% Any grade: 14%
					BM blasts >20%	
					Gr ≥3: 3.5% Any grade: 83%	Gr ≥3: 10.5% Any grade: 33%

ASH 2023 update of FELIX (obecabtagene autoleucel)

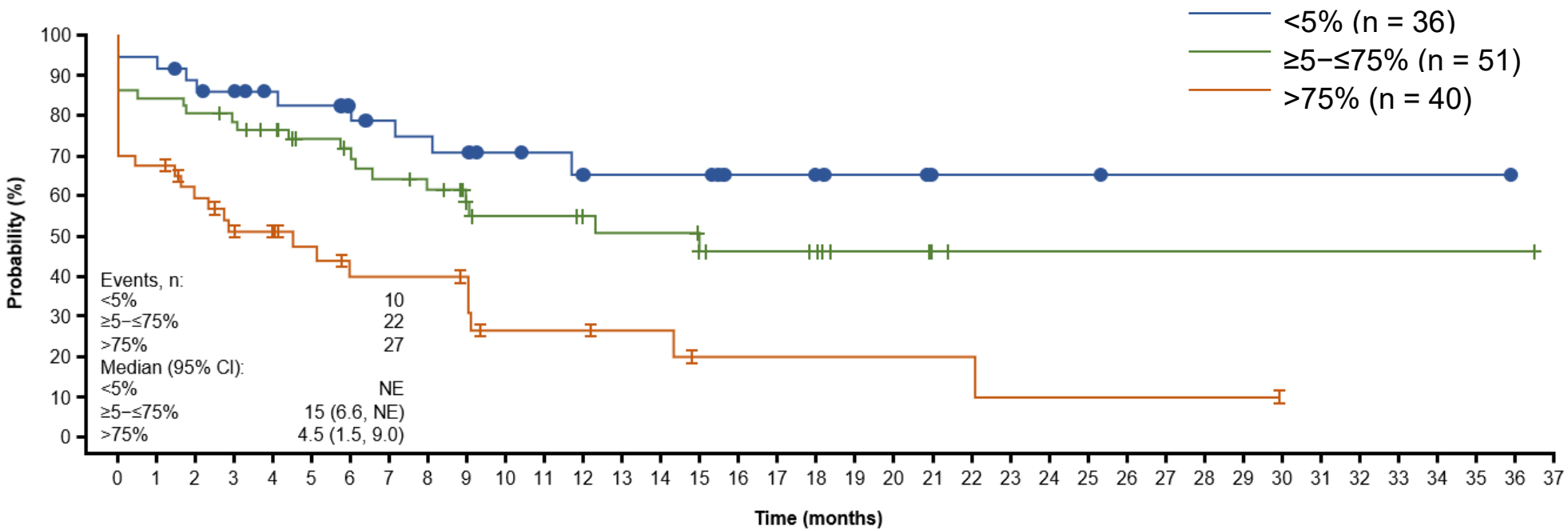
We present results from the FELIX Phase Ib/II study as a pooled analysis of all patients treated to date with obe-cel, including patients with low leukemic burden* at treatment

Cohort A
≥5% BM blasts at screening

Cohort B
MRD-positive at screening

Cohort C
Isolated EMD at screening

Key eligibility
- R/R adult B-ALL
- Age ≥18 years



Data censoring at non-protocol tx including HCT (only 17% received HCT)

↓ leukemic burden at lymphodepletion ↑ improved EFS

*Defined as morphological remission per investigator assessment (<5% BM blasts without EMD) as measured at screening and lymphodepletion

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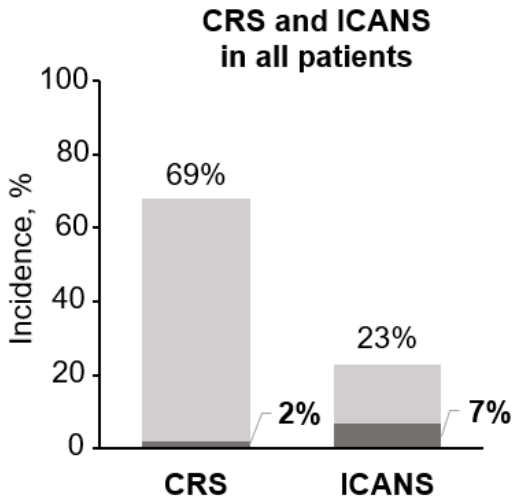

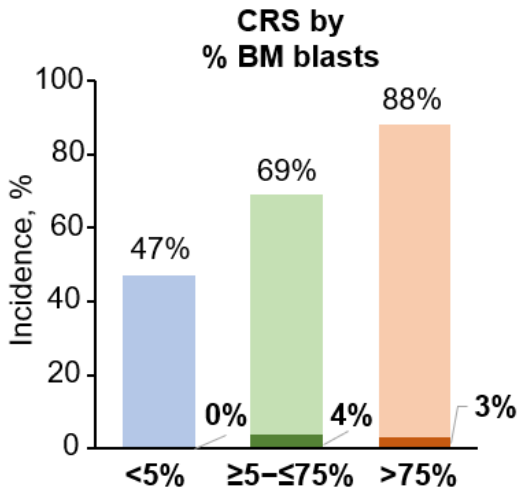

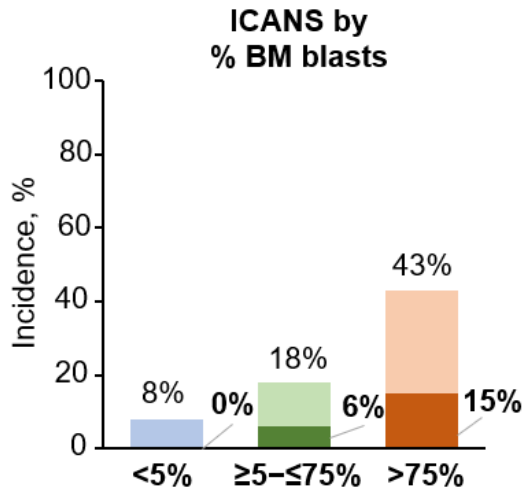

Light colors = grade ≤2
Dark colors = grade ≥3

BM blasts % at lymphodepletion

<u>Overall</u>:
2% gr ≥3 CRS
7% gr ≥3 ICANS

↓ leukemic burden ↓ lower toxicity

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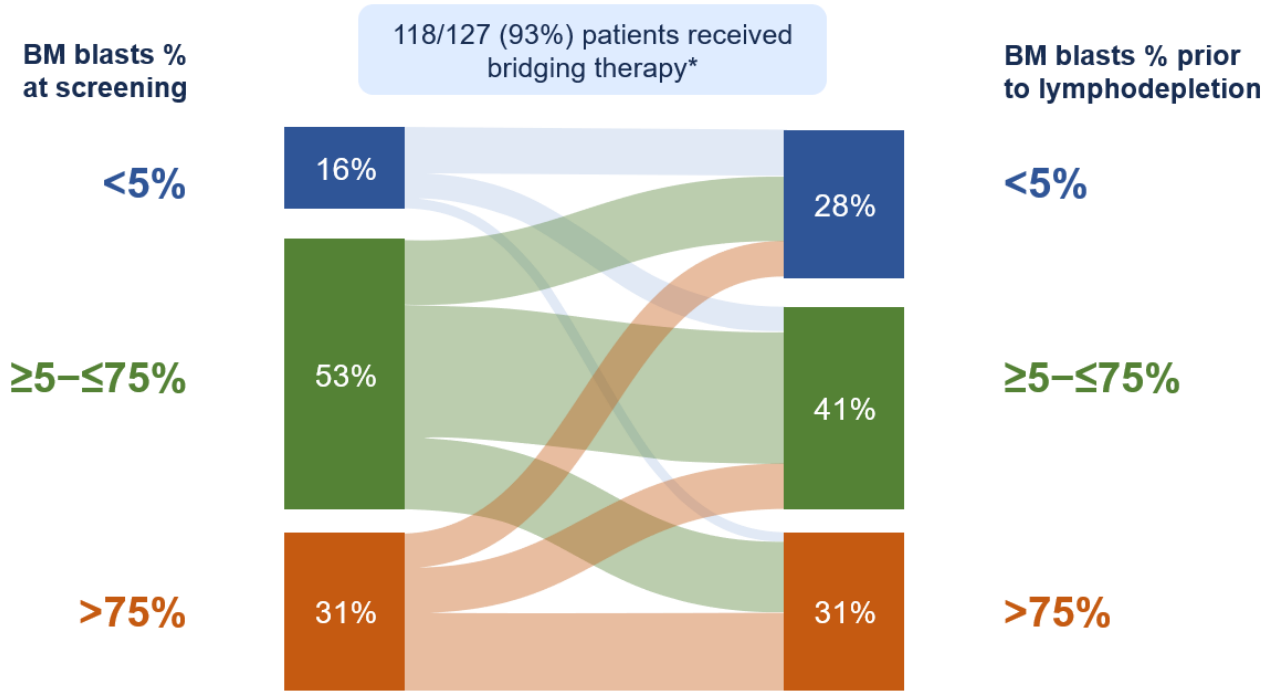
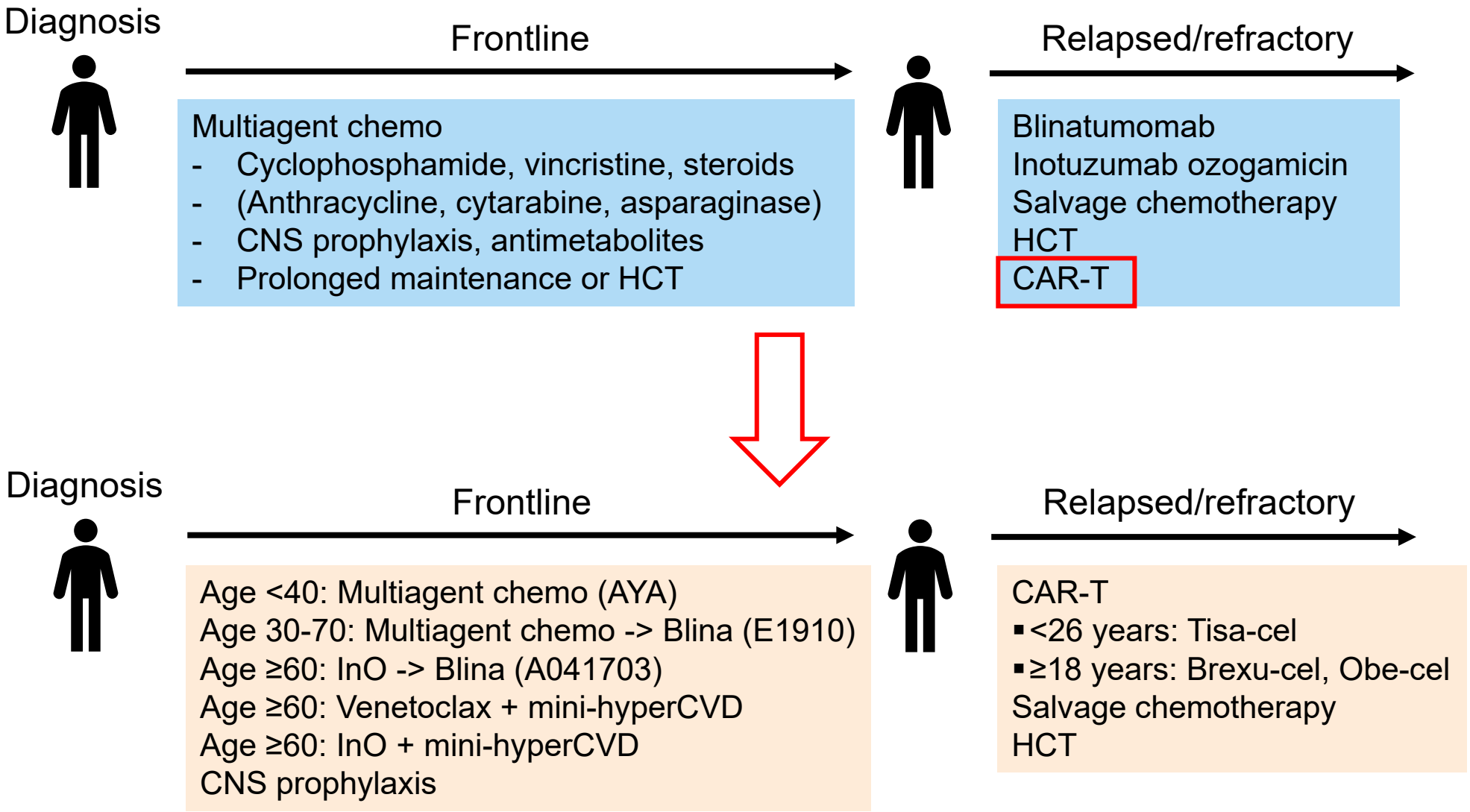


Leukemic burden at screening ≠ Leukemic burden at lymphodepletion

Ph-neg ALL – future treatment landscape?



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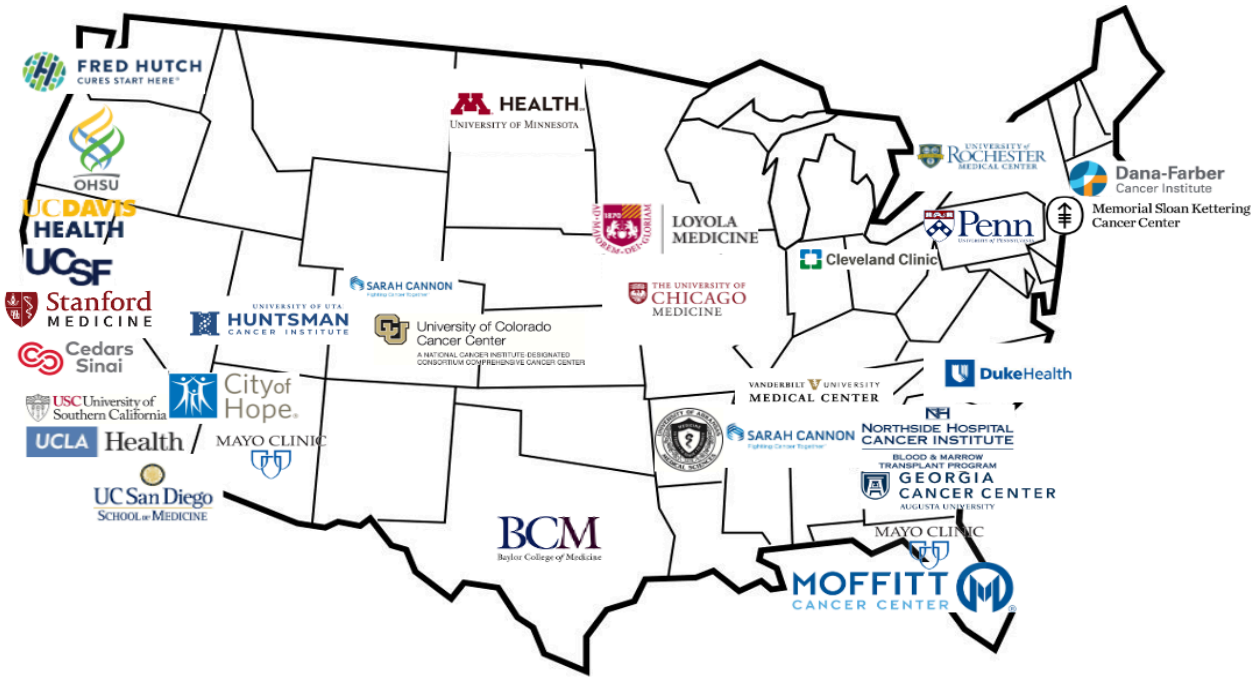
RWE of brexucabtagene autoleucel

ASH Abstract #1029 (Evandro Bezerra, OSU)

- CIBMTR registry study
- 2021-2023, 6.1 month median follow-up
- N=150
- 90% would have been ineligible for ZUMA-3
  - Blasts <5% prior to infusion (43%)
  - Plt <50 (33%)
  - Mod-sev pulmonary disease (32%)
  - CV, cerebrovascular disease (17%)

ASH Abstract #1030 (Greg Roloff, U Chicago)

- ROCCA study (N=30 centers)
- 2021-2023, minimum 3 months of follow-up
- N=224 apheresed, 205 infused, 189 included for analysis



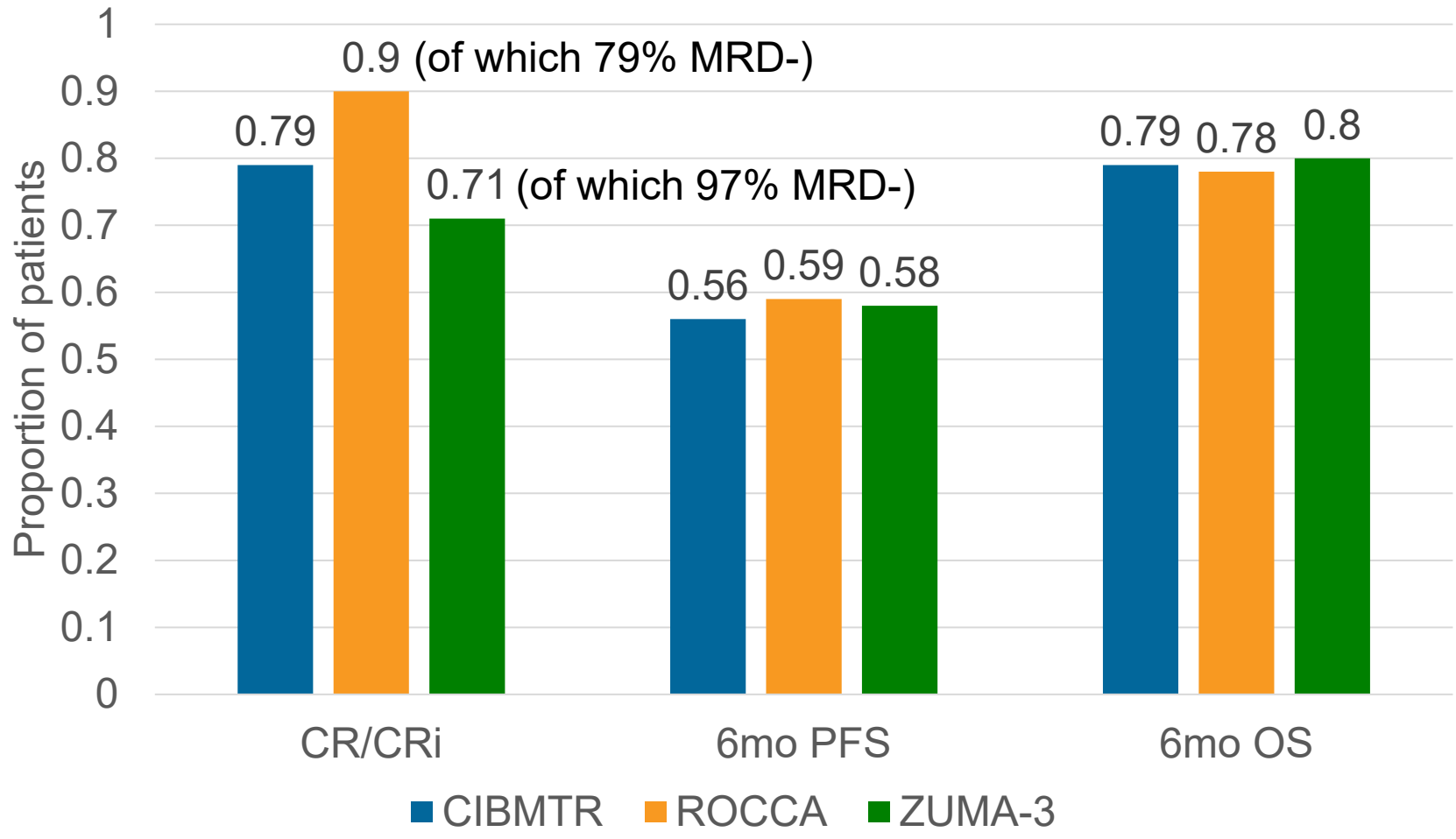
RWE of brexucabtagene autoleuce – pt characteristics

Characteristic	CIBMTR (N=150)	ROCCA (N=189)	ZUMA-3 (N=55)
Median age (range), years	42.9 (19.4-79.4)	46 (18-81)	40 (28-52)
≥26 years / ≥60 years, n (%)	139 (93) / 28 (19)		
Race/ethnicity			
Non-Hispanic White, n (%)	78 (52)	81 (43)	37 (67)
Non-Hispanic Black, n (%)	16 (11)		1 (2)
Non-Hispanic Asian, n (%)	9 (6)		3 (5)
Hispanic, n (%)	40 (27)	58 (30)	11 (20)
Not reported, n (%)	7 (5)		
Cytogenetic risk score of poor at diagnosis	84 (56)		
Median number of prior lines of therapy, no. (range)	4 (1-13)	4 (2-12)	2 (2-3)
Prior blinatumomab, n (%)	77 (51)	112 (59)	25 (45%)
Prior inotuzumab, n (%)	61 (41)	91 (48)	12 (22%)
Prior alloSCT, n (%)	52 (35)	77 (41)	23 (42%)

RWE of brexucabtagene autoleucel – dz characteristics

Characteristics	CIBMTR (N=150)	ROCCA (N=189)	ZUMA-3 (N=55)
Extramedullary disease prior to infusion, n (%)	32 (21)	43 (23)	6 (11)
CNS involvement prior to infusion, n (%)	14 (9)	35 (19)	5 (9)
MRD status prior to…	**Infusion**	**Apheresis**	
CR/CRi, MRD-	36 (24)	28 (15)	
CR/CRi, MRD+ / unknown	18 (20)	51 (27)	
Not in CR/CRi	96 (64)	95 (50)	
% BM blasts prior to…	**Infusion**		**Infusion**
≥0 to <5, n (%)	65 (43)		5 (9)
≥5 to ≤25, n (%)	14 (9)		10 (18)
>25, n (%)	21 (14)		40 (73)
Not reported	50 (33)		
Received bridging therapy, n (%)	61 (41)		
ZUMA-3 ineligible, n (%)	135 (90)		

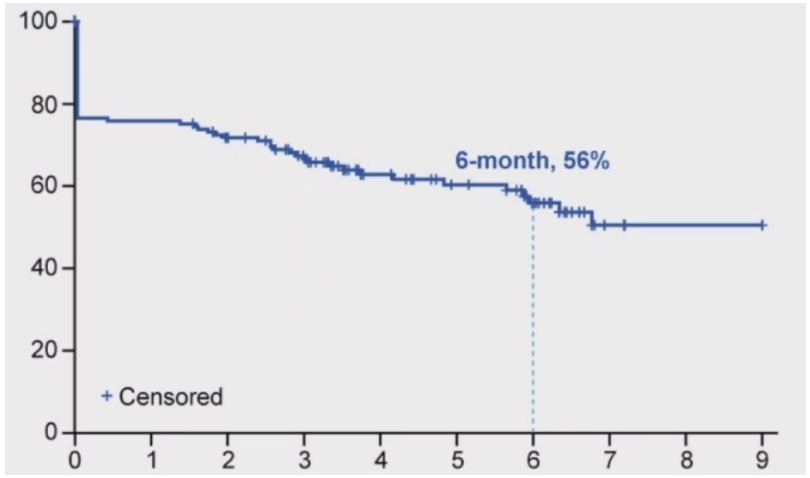
RWE of brexucabtagene autoleucel - response

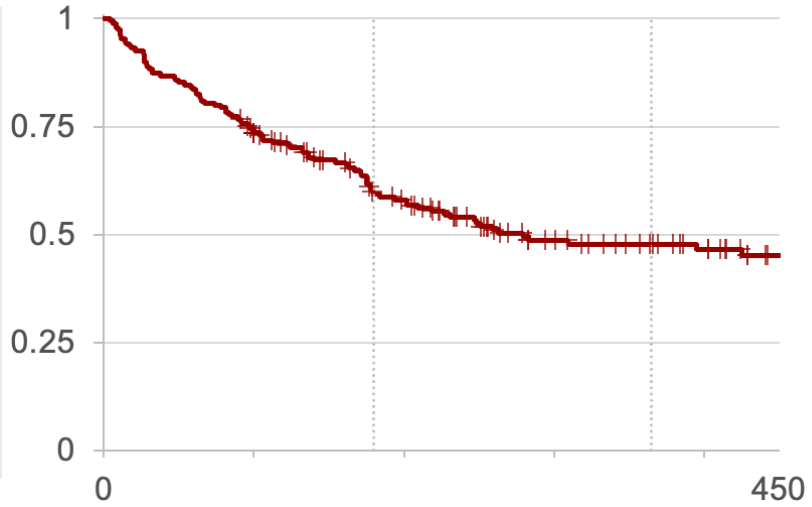


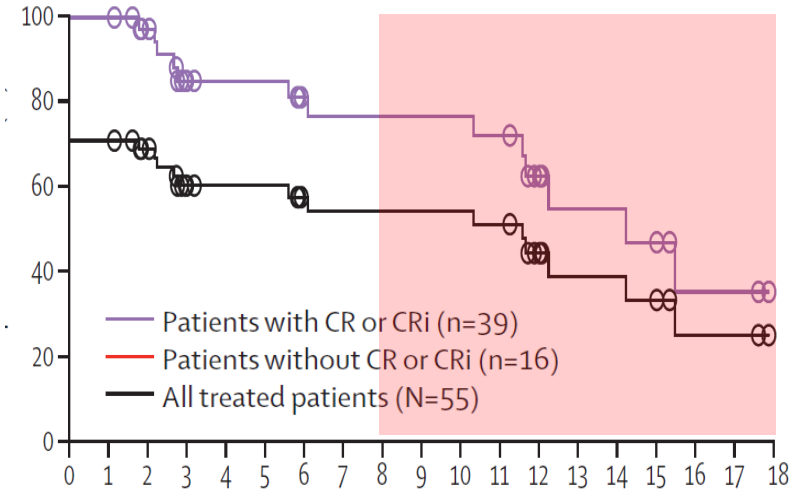
RWE of brexucabtagene autoleucel - survival

CIBMTR | **ROCCA** | **ZUMA-3**

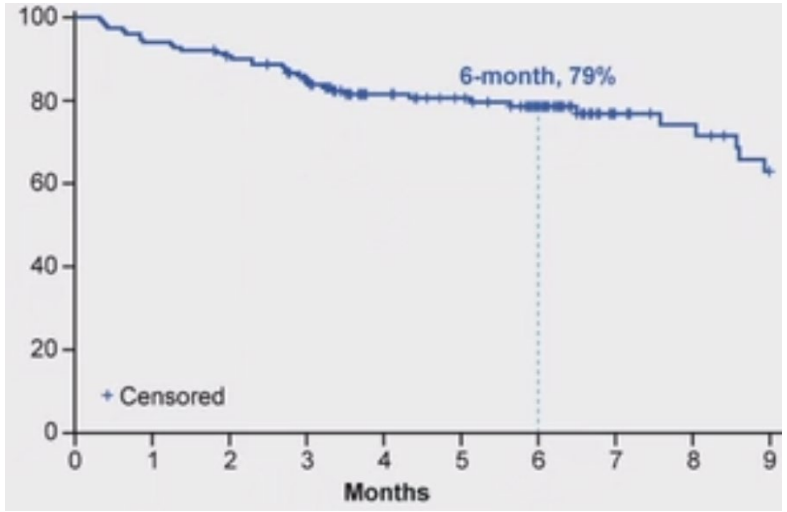
PFS

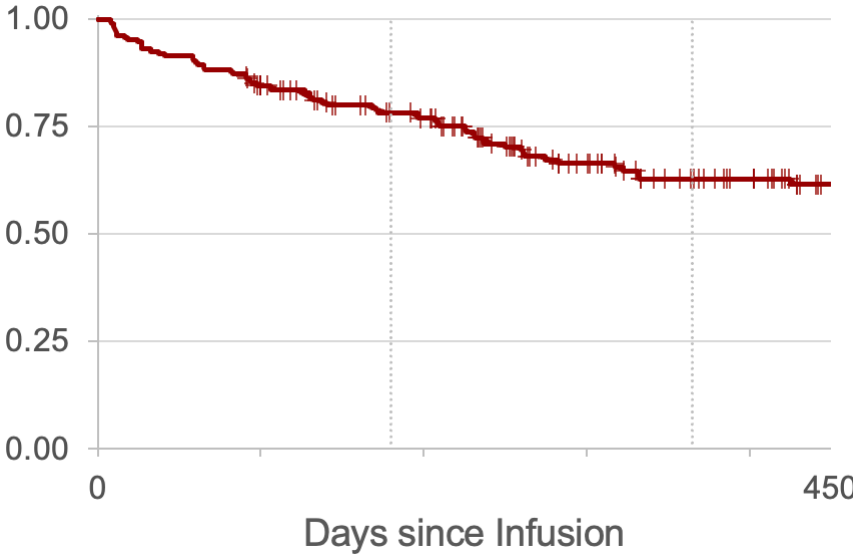


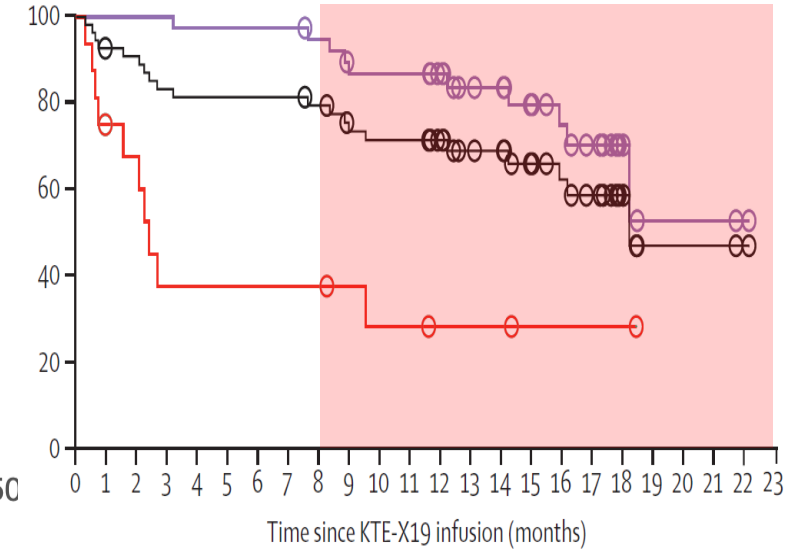




OS

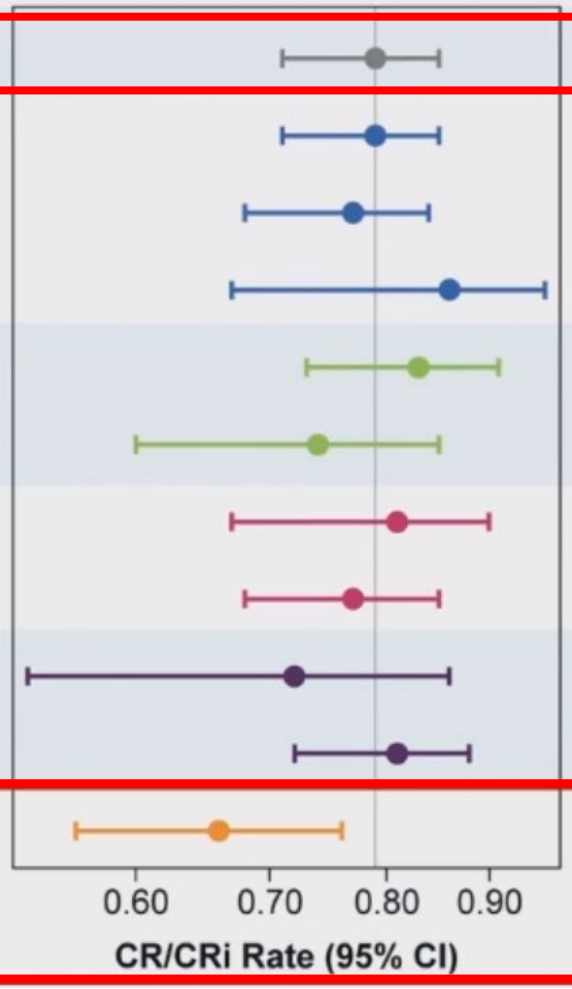




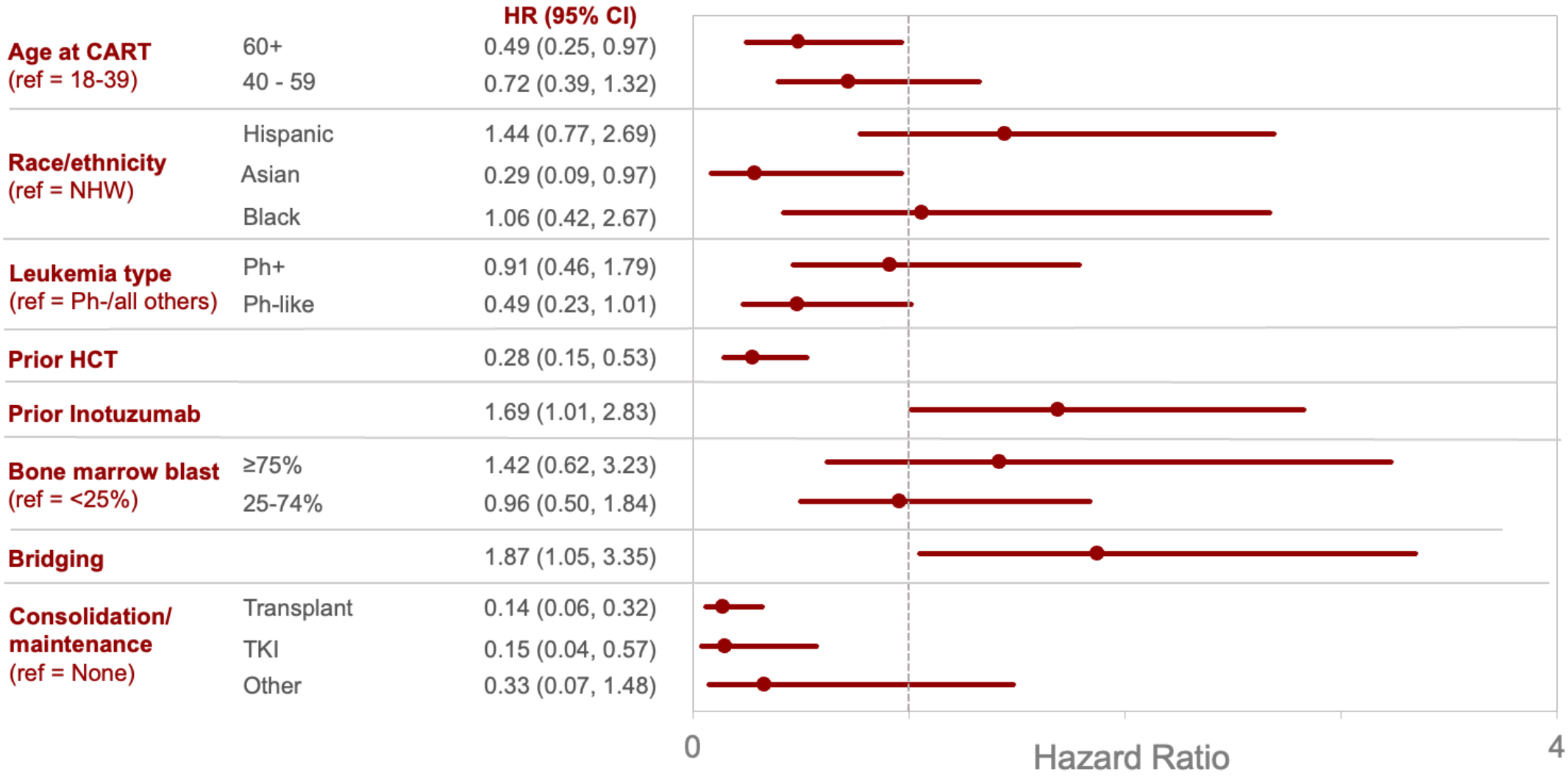


RWE of brexucabtagene autoleucel – CIBMTR

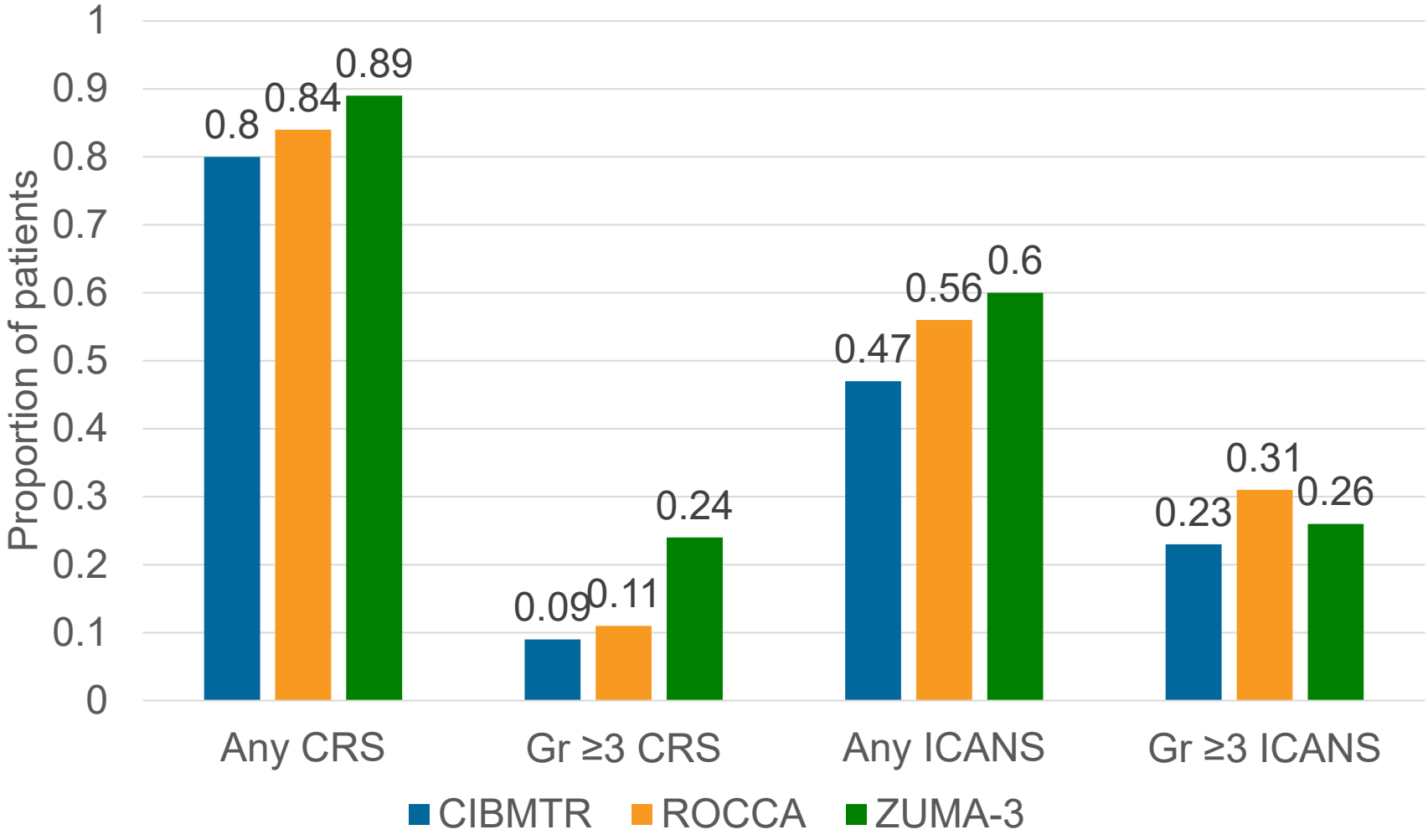
		No. of Patients with CR or CRi/Total No.[a]	CR/CRi Rate (95% CI)
Overall (N=150)		117/149	0.79 (0.71-0.85)
Age[b]	≥26 Years (n=139)	109/138	0.79 (0.71-0.85)
	<60 Years (n=122)	93/121	0.77 (0.68-0.84)
	≥60 Years (n=28)	24/28	0.86 (0.67-0.96)
Prior Blinatumomab	Yes (n=77)	64/77	0.83 (0.73-0.91)
	No (n=55)	40/54	0.74 (0.60-0.85)
Prior AlloSCT	Yes (n=52)	42/52	0.81 (0.67-0.90)
	No (n=98)	75/97	0.77 (0.68-0.85)
Extramedullary Disease	Yes (n=32)	23/32	0.72 (0.53-0.86)
	No (n=101)	82/101	0.81 (0.72-0.88)
Not in CR/CRi Prior to Infusion (n=96)		63/95	0.66 (0.56-0.76)



RWE of brexucabtagene autoleucel – ROCCA

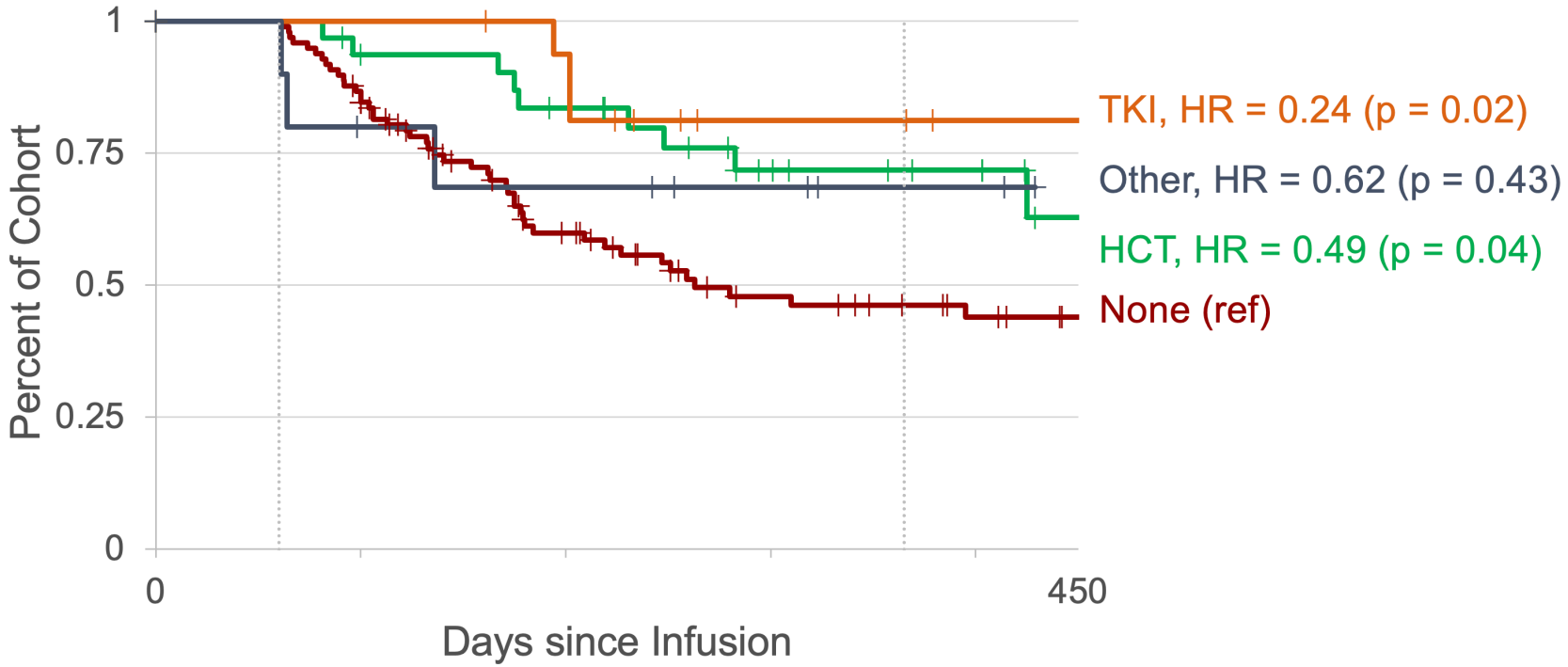


RWE of brexucabtagene autoleucel - toxicity



What about post-CAR-T tx? - ROCCA

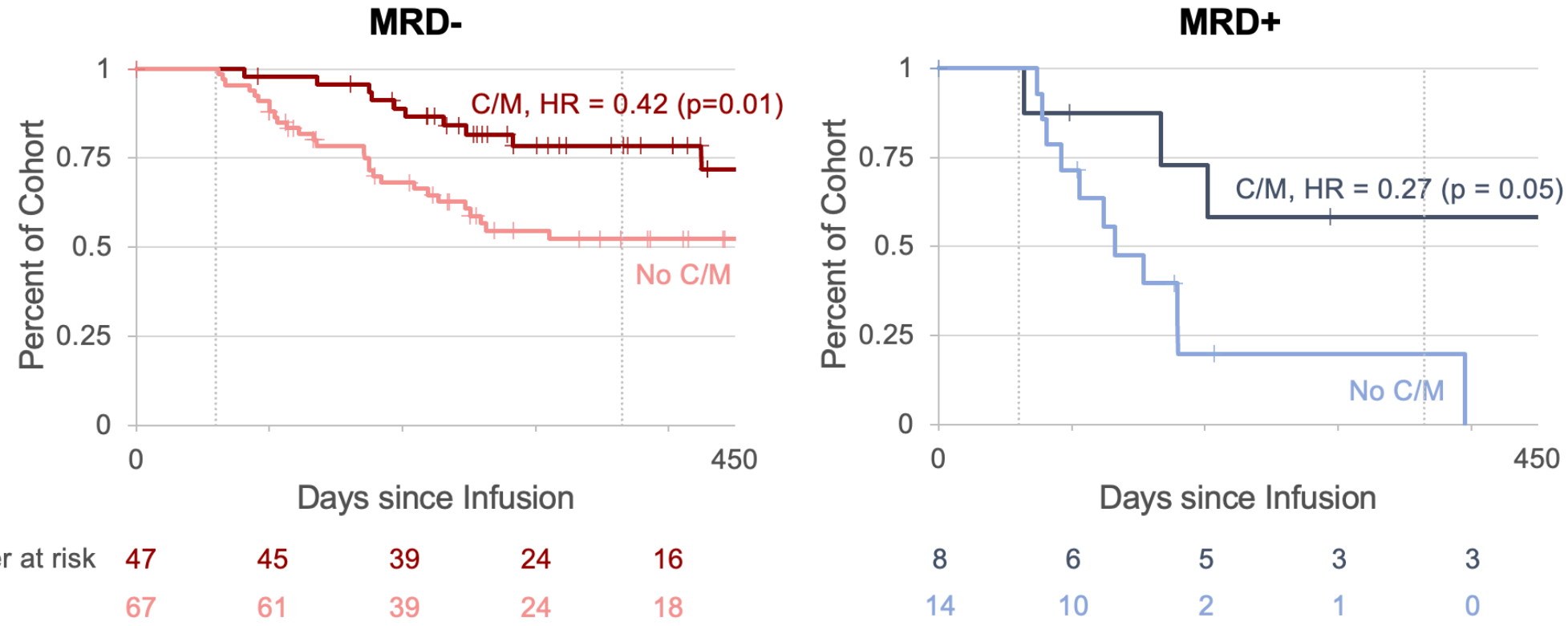
Ph+ / Ph-neg / Ph-like (%) **29 / 53 / 18**



Number at risk					
	17	17	15	9	7
	10	7	6	4	2
	32	29	24	15	11
	98	84	46	28	20

What about post-CAR-T tx? - ROCCA

Ph+ / Ph-neg / Ph-like (%) **29 / 53 / 18**

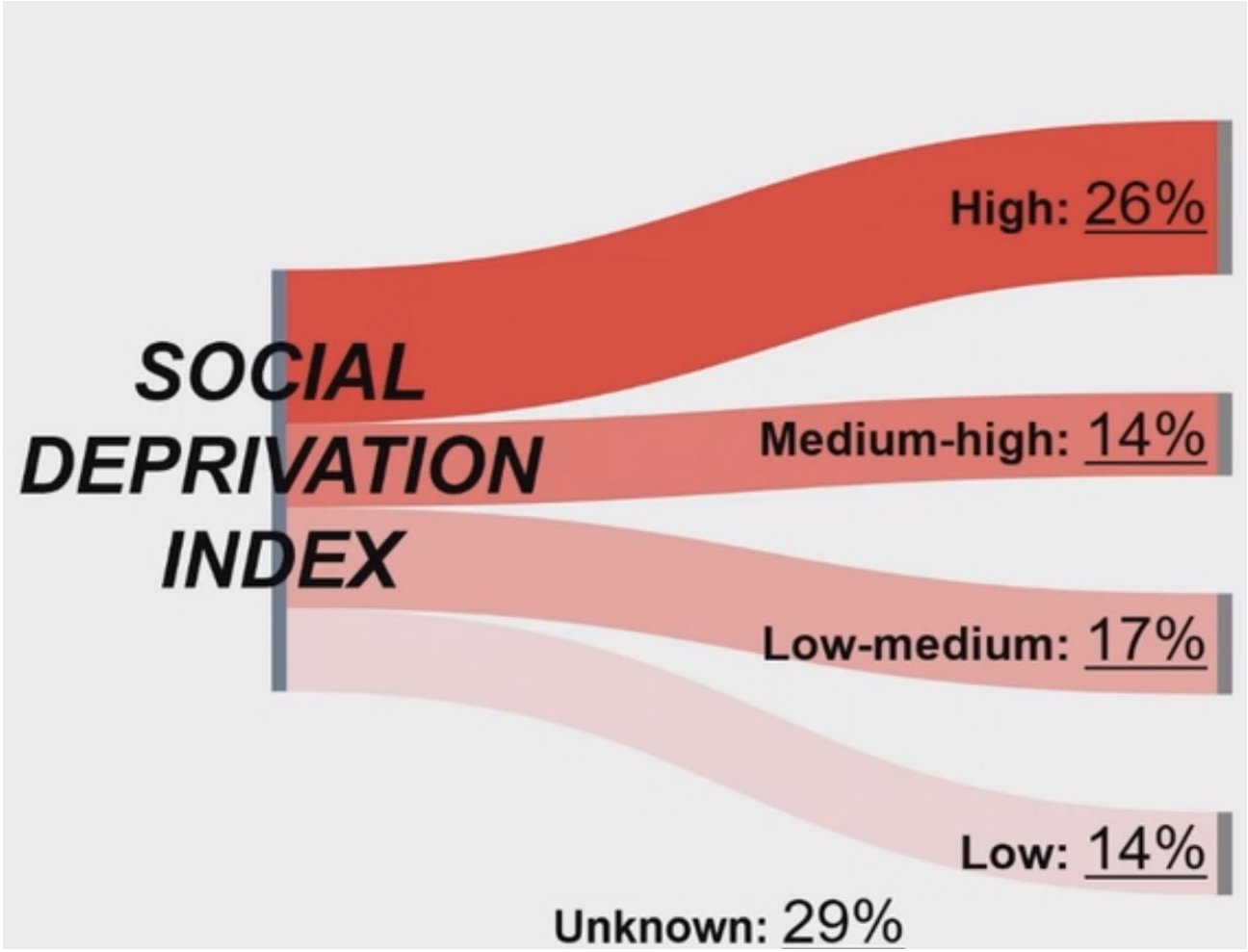


Number at risk					
	47	45	39	24	16
	67	61	39	24	18
	8	6	5	3	3
	14	10	2	1	0

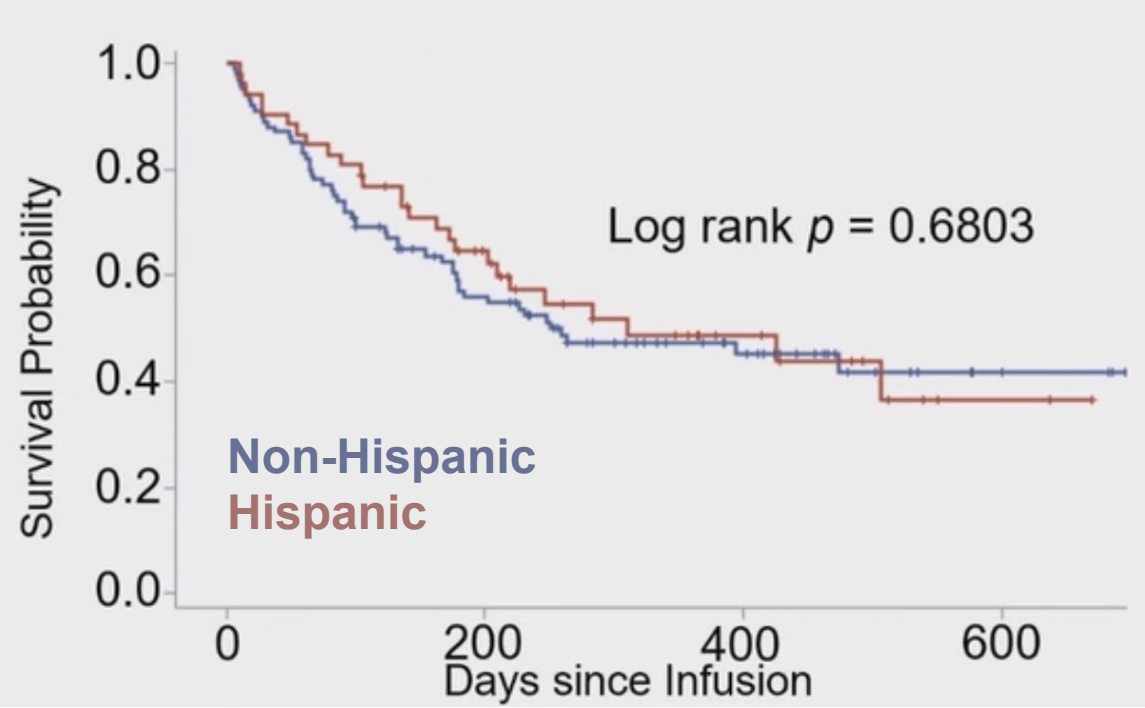
C/M = Consolidation/Maintenance

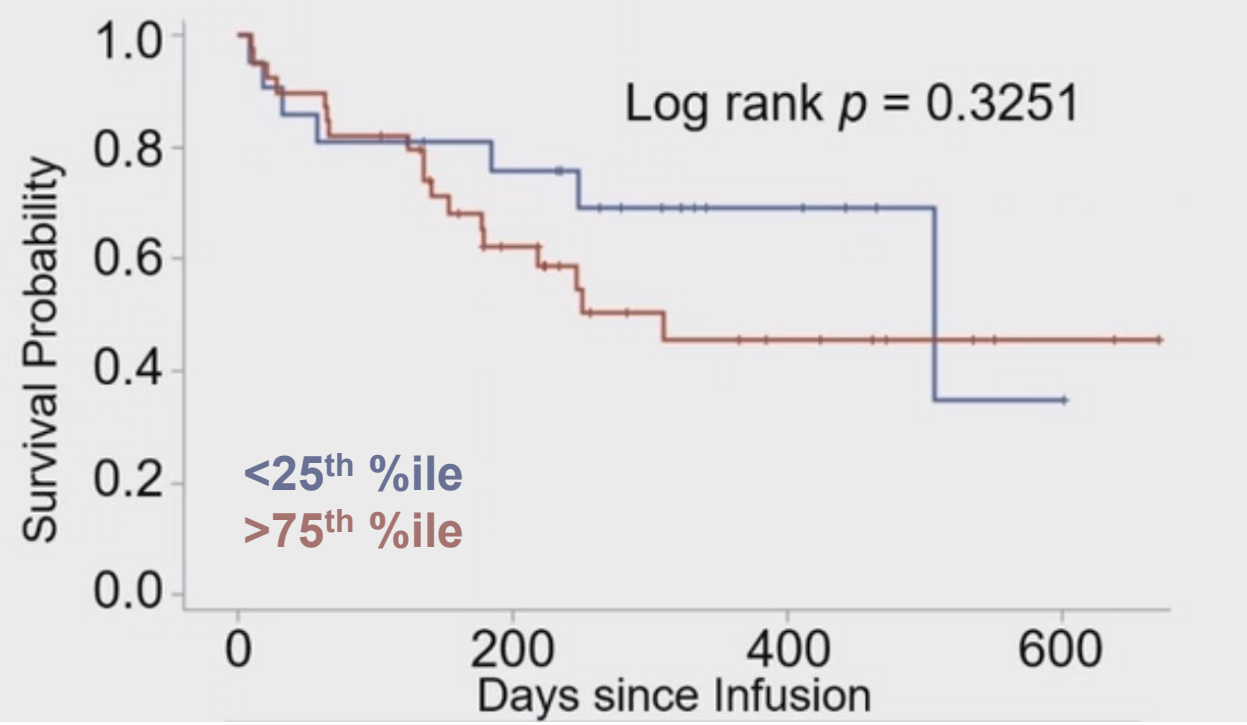
What about social determinants of health? - ROCCA

- Poverty
- <12 years education
- Single parent household
- Rented housing
- Overcrowded housing
- Housing without car
- Non-employed adults

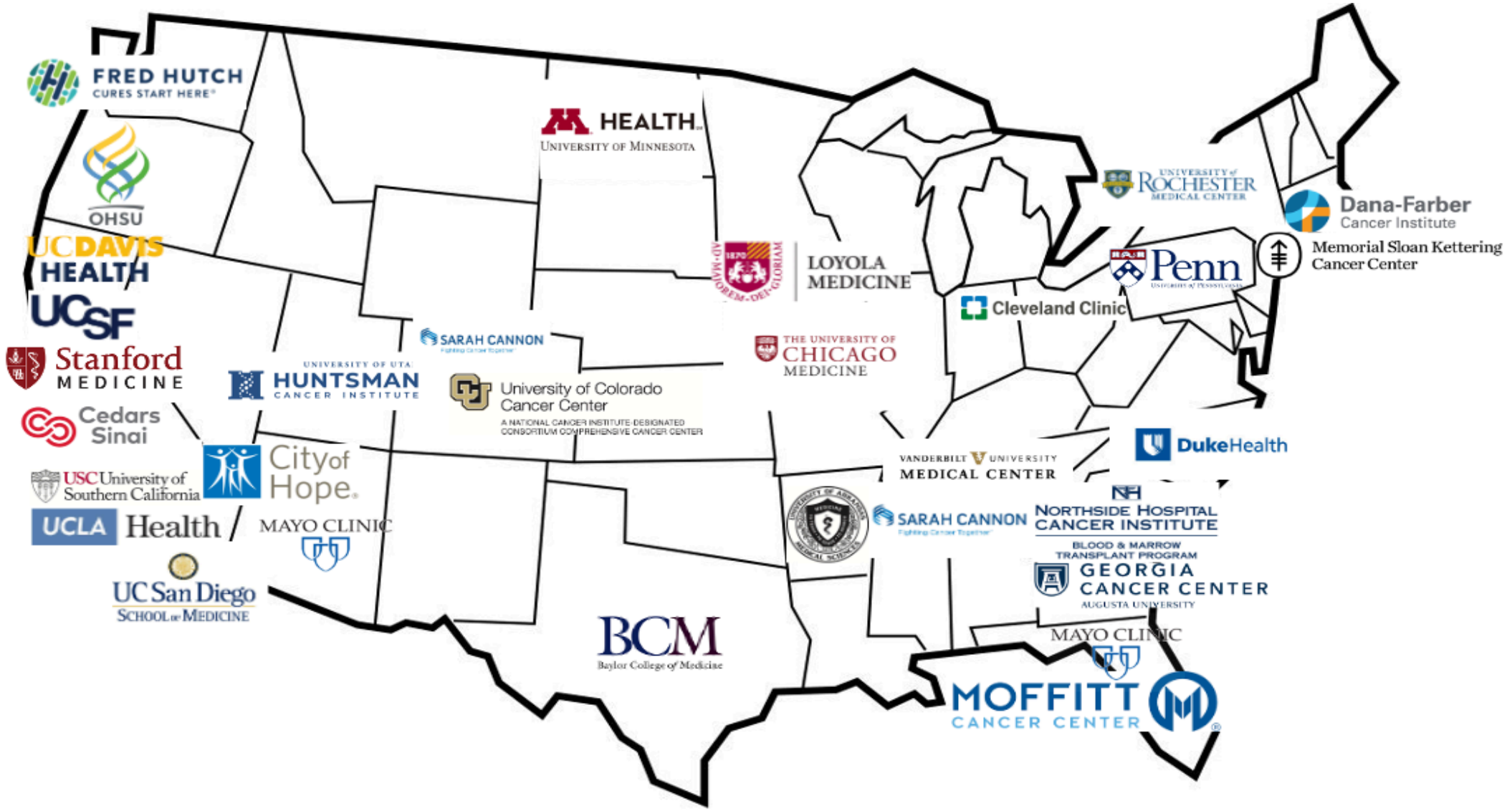


What about social determinants of health? - ROCCA





Could CAR-T overcome historical disparities in ALL?



How “Real-World” is this? Needs community sites such as CONCERT Network

Outline

- Recap: current treatment landscape
- Recap: treatment landscape of the near-future
- Emerging real-world evidence of cell therapy
- Updates in CAR-T toxicity

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Secondary malignancies following CAR-T

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES | NOVEMBER 28, 2023

CAR+ T-Cell Lymphoma Post Ciltacabtagene Autoleucel Therapy for Relapsed Refractory Multiple Myeloma

Simon J. Harrison, Tamia Nguyen, Marzia Rahman, Jeremy Er, Jessica Li, Katherine Li, Nikoletta Lendvai, Jordan M. Schecter, Arnob Banerjee, Tito Roccia, Brad Foulk, Junchen Gu, Hao Zhao, Denis Smirnov, Ana Slaughter, Carolina Lonardi, Erin Lee, Loreta Marquez, Shirin Jadidi, Octavio Costa Filho, Nitin Patel, Dong Geng, Nicole M Haynes, Hannah Kelly, Stephen Lade, Sean Grimmond, Piers Blombery

Blood (2023) 142 (Supplement 1): 6939.

https://doi.org/10.1182/blood-2023-178806

CARTITUDE-4

- BCMA-directed ciltacabtagene autoleucel vs. physician's choice for len-refractory MM
  - 1 patient developed CAR+ TCL post cilta-cel

EHA/EMBT consensus grading for IEC-Hematotoxicity

- Immune cell associated hematotoxicity **(ICAHT)**
- Per expert panel
  - Focus is on duration and severity of neutropenia given clinical relevance
  - Early ICAHT: ≤30 days after infusion, Late ICAHT: >30 days after infusion

Table 1. ICAHT grading

Grading	1	2	3	4
Early ICAHT (day 0-30)				
ANC ≤500/μL	<7 d	7-13 d	≥14 d	Never above 500/μL
ANC ≤100/μL	—	—	≥7 d	≥14 d
Late ICAHT (after day +30)*				
ANC	≤1500/μL	≤1000/μL	≤500/μL	≤100/μL

*Measured ≥2 time points, or nontransient neutropenia.

Rejeski et al., Blood 2023

Identifying patients at high risk for prolonged neutropenia (HEMATOTOX score)

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

Features	0 Point	1 Point	2 Points
Platelet count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute neutrophil count (ANC)	> 1200/µl	≤ 1200/µl	-
Hemoglobin	> 9.0 g/dl	≤ 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	≥ 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 High: ≥2			

Low risk (HT 0-1)

High risk (HT 2-7)

Risk profile

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

Rejeski et al., Blood 2023

FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

Share | Post | Linkedin | Email | Print

November 28, 2023

Summary of the Issue

The Food and Drug Administration (FDA) has received reports of T-cell malignancies, including chimeric antigen receptor CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T cell immunotherapies. Reports were received from clinical trials and/or postmarketing adverse event (AE) data sources.

FDA has determined that the risk of T-cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies. T-cell malignancies have occurred in patients treated with several products in the class. Currently approved products in this class (listed alphabetically by trade name) include the following:

- Abecma (idecabtagene vicleucel)
- Breyanzi (lisocabtagene maraleucel)
- Carvykti (ciltacabtagene autoleucel)
- Kymriah (tisagenlecleucel)
- Tecartus (brexucabtagene autoleucel)
- Yescarta (axicabtagene ciloleucel)

"Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T cell malignancy with serious outcomes, including hospitalization and death, and is evaluating the need for regulatory action."

Innovative Cancer Treatment May Sometimes Cause Cancer, F.D.A. Says

By Gina Kolata

Nov. 28, 2023

The New York Times

Secondary malignancies following CAR-T

FDA Adverse Event Reporting System (FAERS)

Therapy	Company	Indications	Total Reported Cases	Serious Cases	Deaths Reported	Reported T-Cell Lymphoma Cases
Kymriah	Novartis	Large B-cell lymphoma, follicular lymphoma and acute lymphoblastic leukemia	2,470	2,303	662	7
Yescarta	Gilead	Large B-cell lymphoma and follicular lymphoma	3,729	3,551	746	3
Carvykti	J&J and Legend	Multiple myeloma	408	251	28	1
Breyanzi	Bristol Myers Squibb	Large B-cell lymphoma	202	172	38	1
Abecma	Bristol Myers Squibb	Multiple myeloma	528	454	60	0
Tecartus	Gilead	Mantle cell lymphoma and acute lymphoblastic leukemia	609	570	136	0
						Total: 12

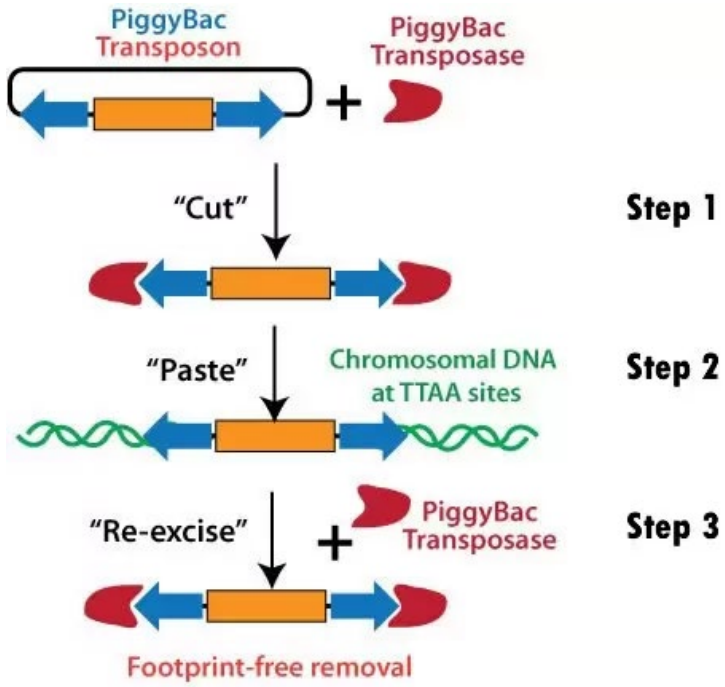
Voluntary reporting system (~35,000 pts have received CAR-T in the U.S.)

Liu, FiercePharma 2023

Secondary malignancies following CAR-T

Potential mechanisms

Very high insertion copy numbers using a transposon system for CAR gene delivery



BioCat.com, accessed Jan 29, 2024

CD-19-targeting CAR-T using *piggyBac* transposon system, for DLBCL

- Para-aortic node remained PET-avid → ↑size over 12 months after CAR-T infusion → biopsied, showing malignant CAR-T cells
- Malignant CAR-T cells:
  - Did not expand in response to CD19 (in contrast with peripheral blood CAR-T cells)
  - Had higher levels of CAR compared to peripheral blood CAR-T cells, but tonic signaling was not seen
  - Did not contain transgene insertion into typical oncogenes
  - Acquired *PIGA* mutation and widespread CNV (gain of 1q, 4q, 5, 6, 10q, 11q, 17q; loss of 4q and 17p)
- Transgene promoter activity increased transcription of surrounding genes
  - *FYN*: proximal component of TCR-mediated T-cell activation, previously associated with adult T-cell leuk/lymph

Micklethwaite, Blood 2021

Secondary malignancies following CAR-T

Potential mechanisms

Retroactive activation of oncogenes

BCMA-targeting CAR-T for R/R MM

- Achieved stringent complete response
- 5 months post-infusion: rapidly growing facial plaque → biopsy showed atypical T cells
- PET showed b/l FDG-avid cervical LAD → biopsy showed CAR+
- *Mut-TET2* and *JAK3* detected in CAR-T cells
  - Clonal *TET2*-mut, not due to CAR insertion
  - *JAK3*-mut found in germline
- CAR inserted primarily into 3'UTR of *PBX2* (91.1% VAF), significance unclear

Harrison, Blood (2023) 142 (Supplement 1): 6939.

Secondary malignancies following CAR-T

Potential mechanisms

Retroactive activation of oncogenes

CD19-targeting axicabtagene ciloleucel for grey zone lymphoma (features of DLBCL and cHL)

- Achieved complete metabolic remission except for RLL lesion → biopsied + 3 LNs removed → revealed NSCLC + 1 LN with PTCL (NSCLC not involved)
- *JAK3* VUS (VAF 11%) identified
- The PTCL was negative for CAR transgene
- TCRG clonotype abundance was assessed
  - Pre-LD blood (D -5): 0.01%
  - D14 post-CAR-T blood: 0%
  - 1mo NSCLC tissue: 1%
  - PTCL tissue: 20%
- Did CART manufacturing or post-CAR-T inflammation (possibly 2/2 NSCLC tumor immune reaction) contribute to activation of the PTCL clone?

<u>Retrospective study</u>

- N=449 receiving commercial CART for NHL, MM, and ALL (1/2018-11/2023 at Upenn)
  - 16/449 (3.6%) developed second primary malignancy
  - 5-year predicted incidence of 17.0%
  - Hematologic cancers in 5/449 (1.1%) patients
    - 2 MDS, 1ML, 1 smoldering MM, 1 TCL

Ghilardi, Nature Med 2024

Secondary malignancies following CAR-T

Table 1: Suggested discussion framework regarding SPMs following CAR T therapy

Discussion point	Supporting evidence
The benefits of CAR T therapy generally outweigh the risks	• CAR T therapy has been shown to extend PFS, OS, and QOL compared to traditional therapies in several cancers. • CAR T therapy offers a "one-and-done" treatment for patients with the potential for rapid and durable remissions.
A causal association is possible but many confounders exist	• Many other factors, including prior alkylating chemotherapy and immortal time bias, need to be examined carefully. • The presence of neoplastic CAR-positive T cells does not itself prove that the CAR "caused" the malignancy.
Patients' active cancers are often a bigger threat than a hypothetical cancer years later	• Even in patients who develop SPMs, their original malignancy can remain a cause of death. • T-cell malignancies are heterogenous, and some (e.g., T-LGL) may have excellent prognoses even if they occur.
Abbreviations: CAR T, chimeric antigen receptor T-cell therapy; OS, overall survival; PFS, progression-free survival; QOL, quality of life; SPM, second primary malignancy; T-LGL, T-cell large granular lymphocytic leukemia.	

Banerjee,Blood Adv 2024

Thank you

DFCI Adult Leukemia Program

- Daniel DeAngelo, MD, PhD
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- Virginia Volpe, MD
- Andy Lane, MD, PhD
- Coleman Lindsley, MD, PhD
- Anthony Letai, MD, PhD
- Rahul Vedula, MD
- Chris Reilly, MD
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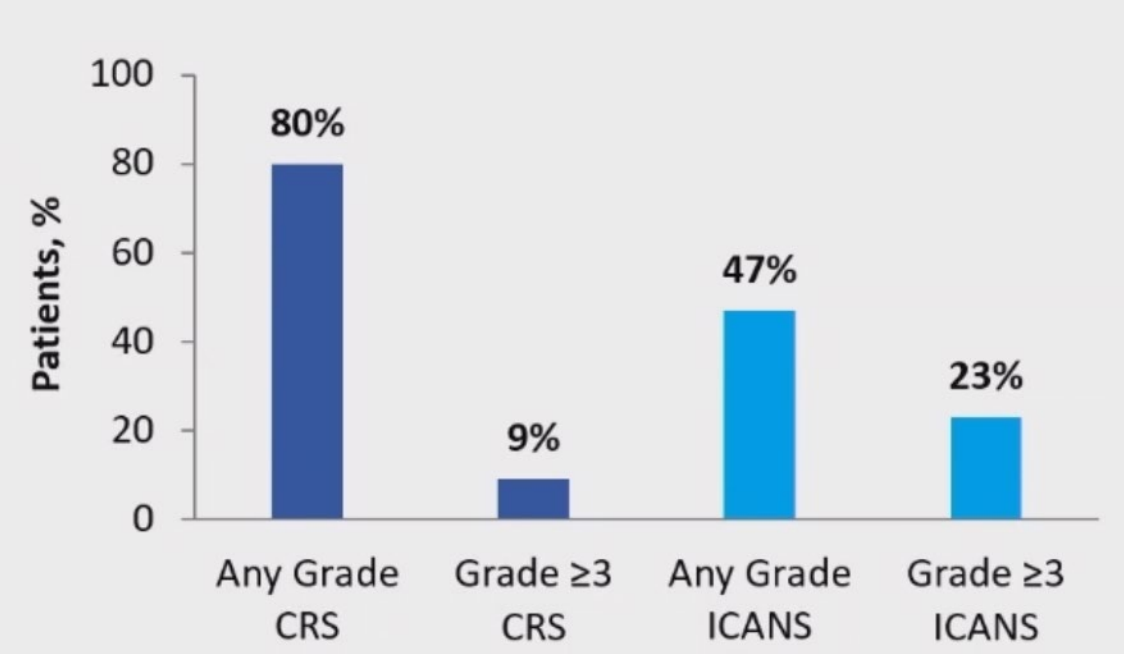
- Shai Shimony, MD
- Ilene Galinsky, NP
- Mary Gerard, PA-C
- Theresa Nguyen, NP
- Ryan Osborn, PA-C
- Donna Neuberg, ScD
- Yiwen Liu, MS
- Robert Soiffer, MD

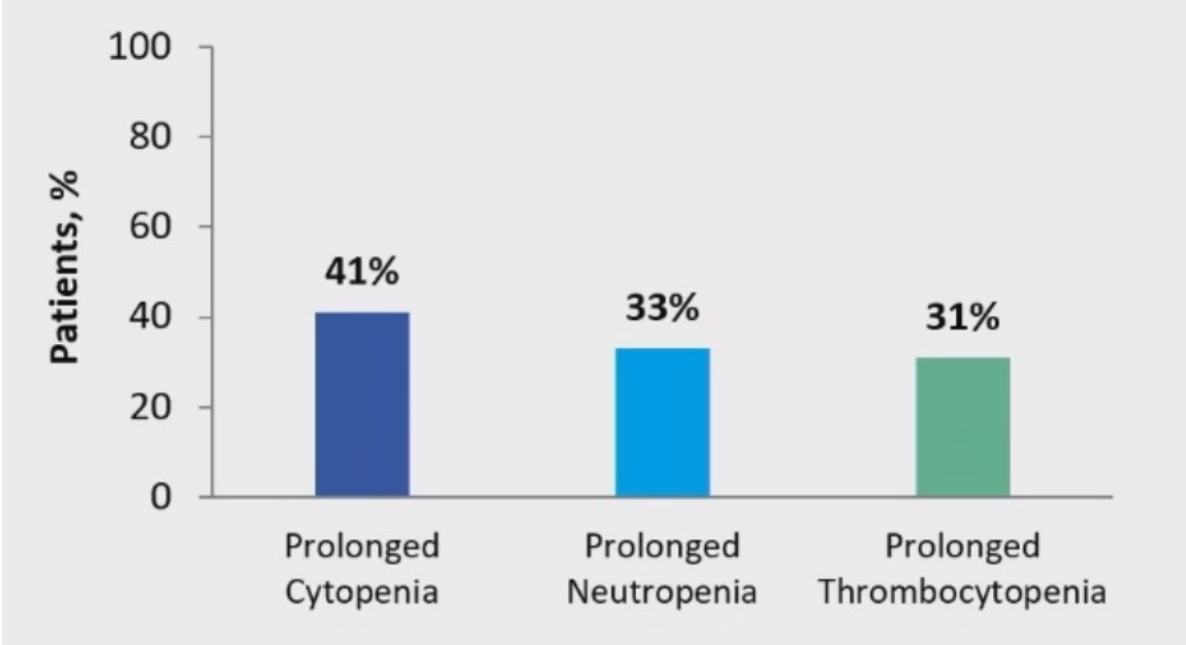
RWE of brexucabtagene autoleucel – CIBMTR

CRS and ICANS



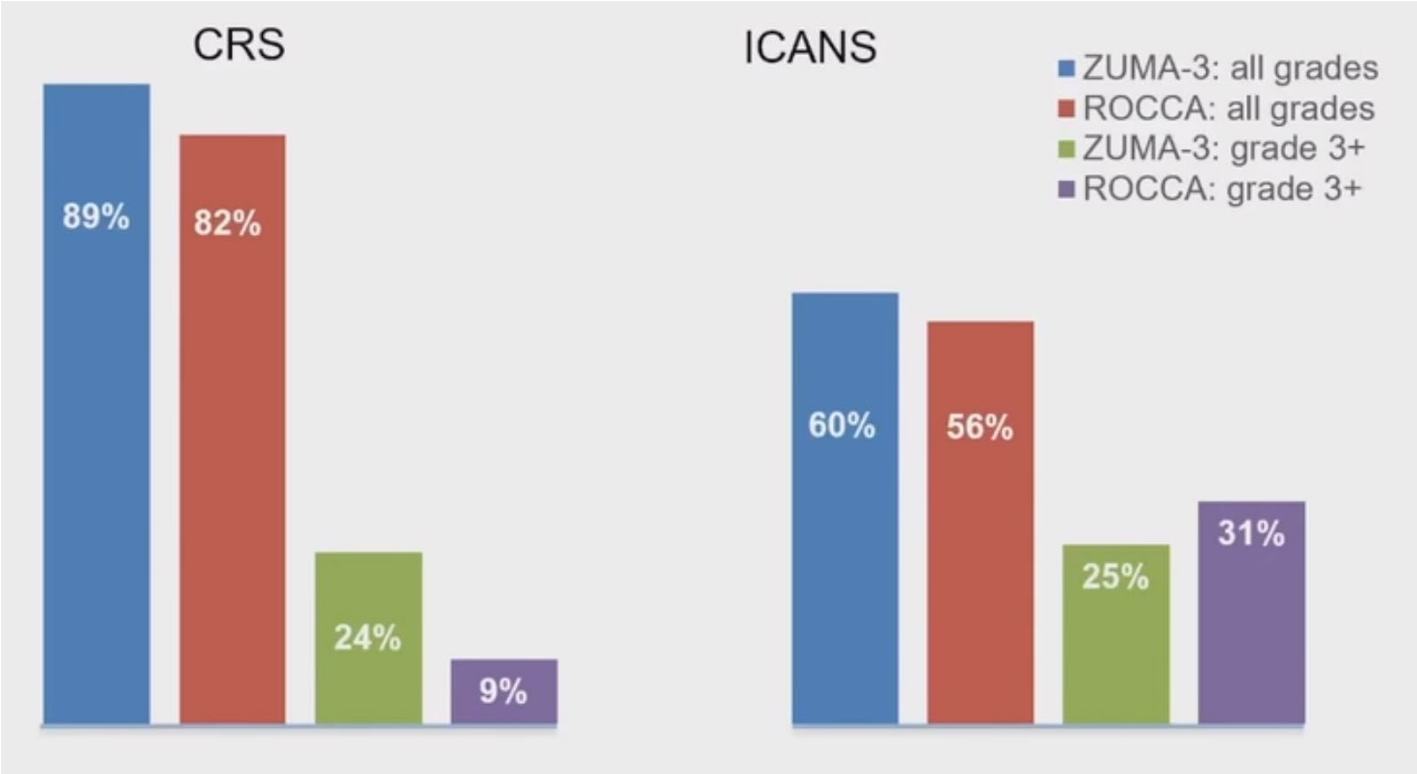
Median time to onset: 6-8 days
Median duration: 6 days
15% of patients with 0-<5% blasts had Gr ≥3 ICANS

Prolonged Gr 4 cytopenias ≥ 30 days from infusion



RWE of brexucabtagene autoleucel

ASH Abstract #522 (Noam Kopmar) - Toxicity



<u>OR for severe toxicity for blasts ≥5% blasts at time of apheresis</u>

Gr ≥3 CRS: OR 2.35, p=0.17

Gr ≥3 ICANS: OR 2.63, p=0.008

<u>HR for death given severe toxicity</u>

Gr ≥3 CRS: HR 2.38, p=0.05

Gr ≥3 ICANS: HR 1.11, p=0.74