



The young side of **LYMPHOMA**


gli under 40 a confronto

Pescara, Auditorium Petruzzi
11-12 ottobre 2024

DLBCL R/R: ruolo delle CART in 2^a linea

Filippo BAGNOLI, MD

Hematology Unit,
Humanitas Research Hospital
Humanitas University



Disclosures of Filippo Bagnoli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead							X (travel support)
Eli Lilly					x		
Astra Zeneca							X (travel support)

CLINICAL CASE

Mario

57yo, M

Hx:
-HTN

November/2023

DLBCL, non-GCB, double-expressor
St. IV, IPI 3

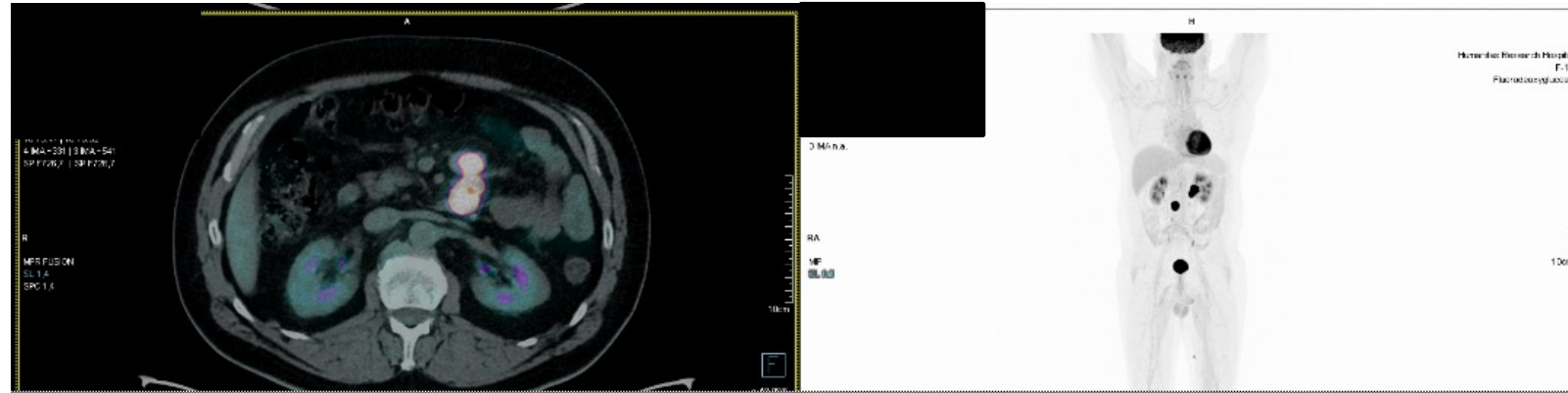
1L: R-CHOP (Dec/2023 – May/2024)

-interimTC: PR

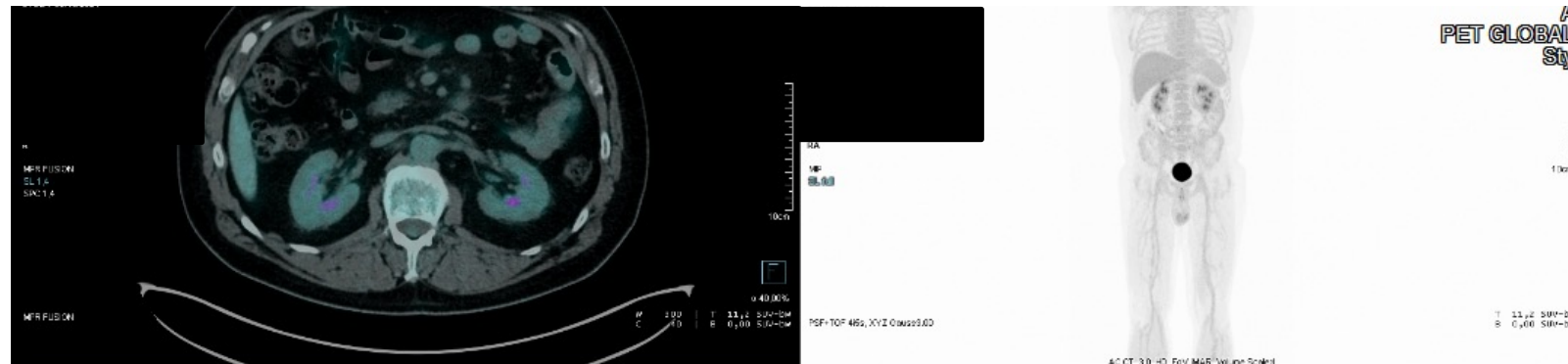
-EoT: PD

Referral

July/2024 – Apheresis
Bridge PolaV-BR



August/2024 – LDT -> Axi-cel reinfusion



AIFA-APPROVED CAR-T for 2L LBCL_AxiCel



Diagnosis

DLBCL & HGBCL

PMBCL
Richter's S.

Previous Tx

1L (including anti-CD20 + anthracycline)
EITHER REFRACTORY
OR RELAPSE <12 MONTHS SINCE EoT

Disease characteristics

Active CNS-involvement

IF PREVIOUS CNS+ -> NEGATIVE: MRI (x2), CSF (x2), CLINICAL DEFICIT

Patient characteristics

AGE 18-75 yo
ECOG ≤ 1
CrCl ≥ 60 mL/min
AST/ALT ≤ 2,5 ULN & bilirubin < 1.5 mg/dL (<3 if Gilbert)
LVEFs ≥ 50%
SpO2 > 92% in room air

ANC < 1'000/mm³
PLT < 75'000/mm³
Hb < 8 g/dL
DVT/PE < 6 months
SEIZURES < 3 months
AUTOIMMUNE DISEASE Tx in < 24 months
ACUTE CORONARY SYNROME < 12 months

THE BEGINNING OF IT ALL

Table 1. MORTALITY FOLLOWING S-180 IMPLANTATION.

		Days between B.C.G. infection and tumour inoculation					
Controls ..		1	7	14	19	25	67
68/79† ..		13/15	3/12	0/12	9/30	0/8	0/9

† mortality/number per group.

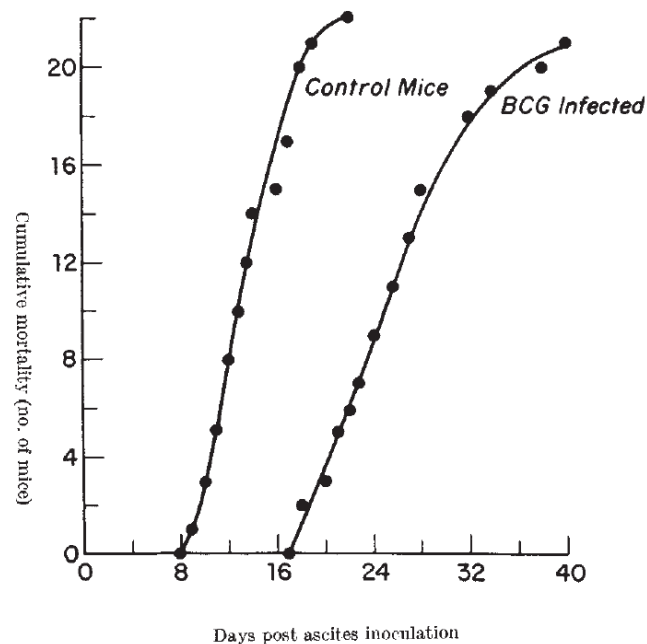


Fig. 1.

GENE TRANSFER INTO HUMANS — IMMUNOTHERAPY OF PATIENTS WITH ADVANCED MELANOMA, USING TUMOR-INFILTRATING LYMPHOCYTES MODIFIED BY RETROVIRAL GENE TRANSDUCTION

STEVEN A. ROSENBERG, M.D., PH.D., PAUL AEBERSOLD, PH.D., KENNETH CORNETTA, M.D., ATTAN KASID, PH.D., RICHARD A. MORGAN, PH.D., ROBERT MOEN, M.D., EVELYN M. KARSON, PH.D., M.D., MICHAEL T. LOTZE, M.D., JAMES C. YANG, M.D., SUZANNE L. TOPALIAN, M.D., MARIA J. MERINO, M.D., KENNETH CULVER, M.D., A. DUSTY MILLER, PH.D., R. MICHAEL BLAESE, M.D., AND W. FRENCH ANDERSON, M.D.

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

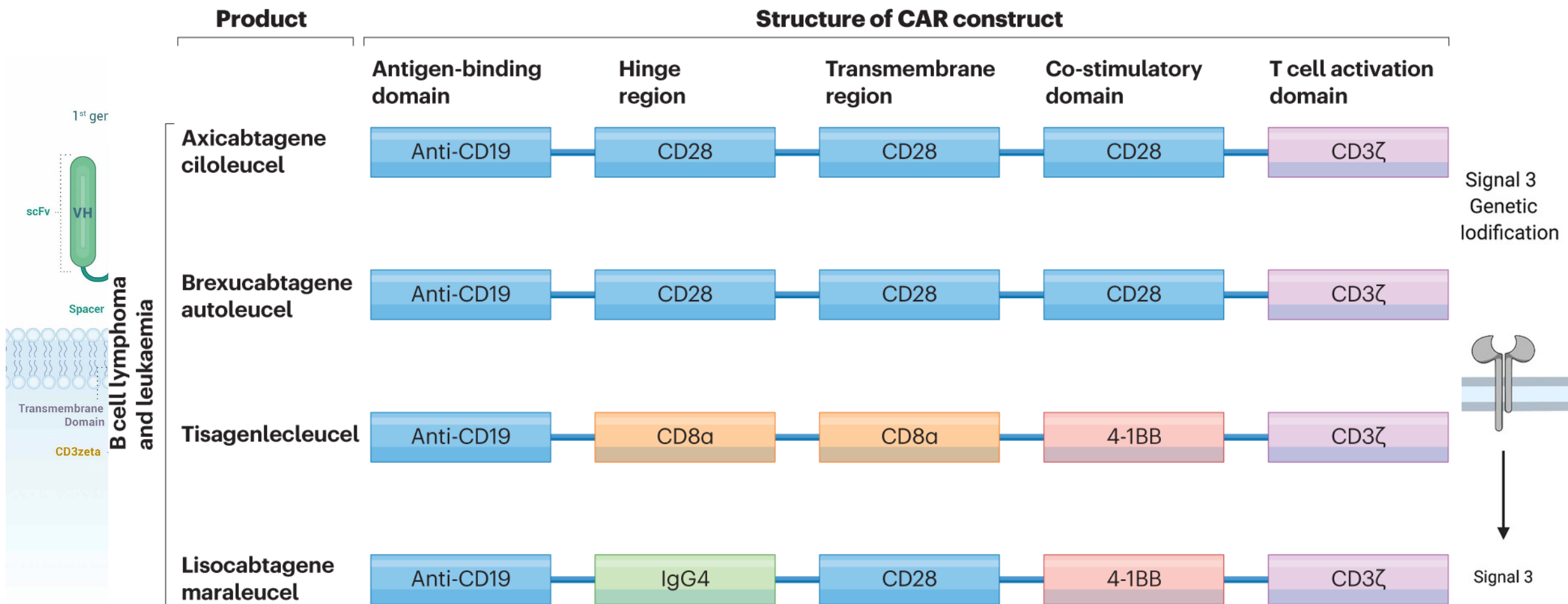
(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

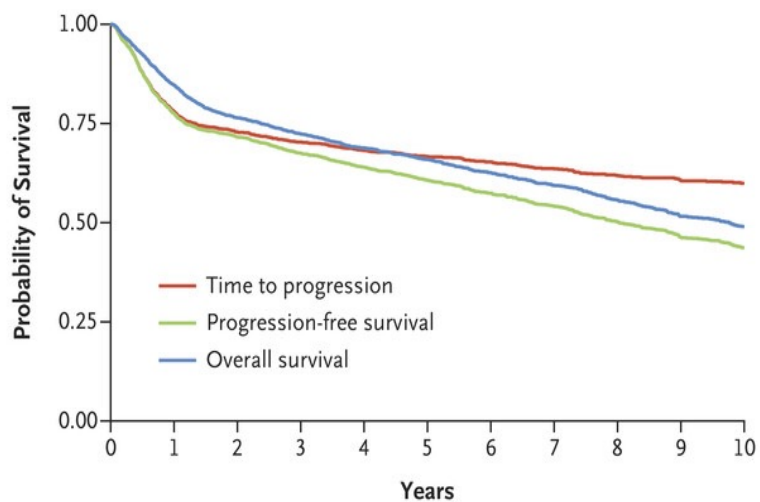
Communicated by Michael Sela, July 13, 1989 (received for review June 18, 1989)

THE FOLLOWING STEPS

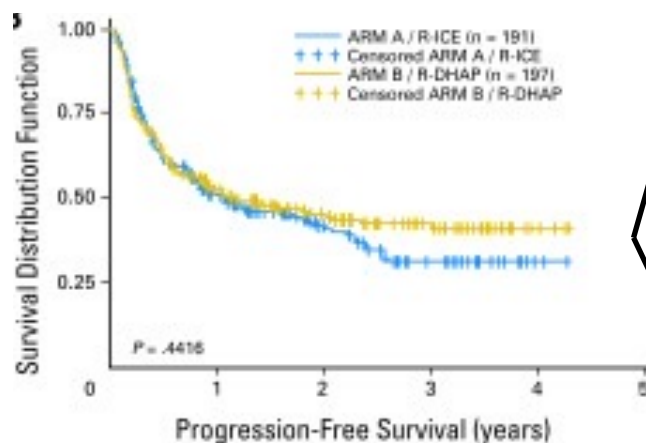


Cappell KM, Kochenderfer JN. Nat Rev Clin Onc 2023

THE UNMET NEED

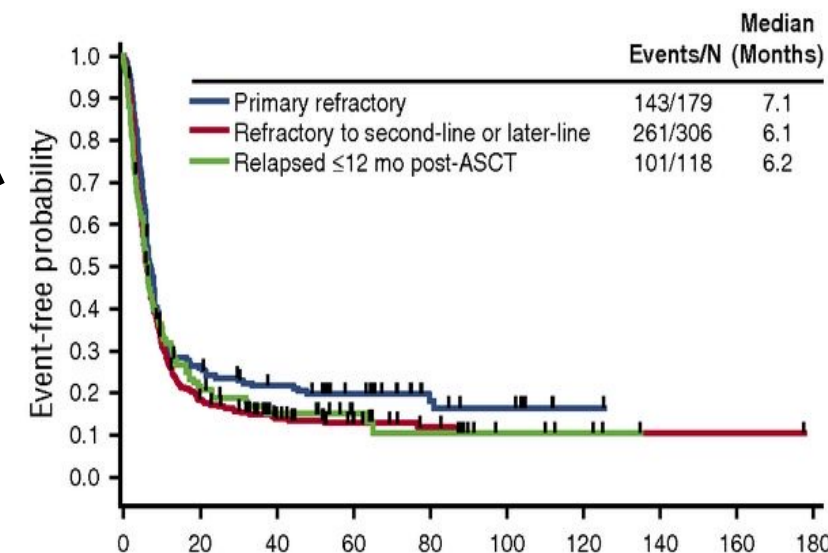
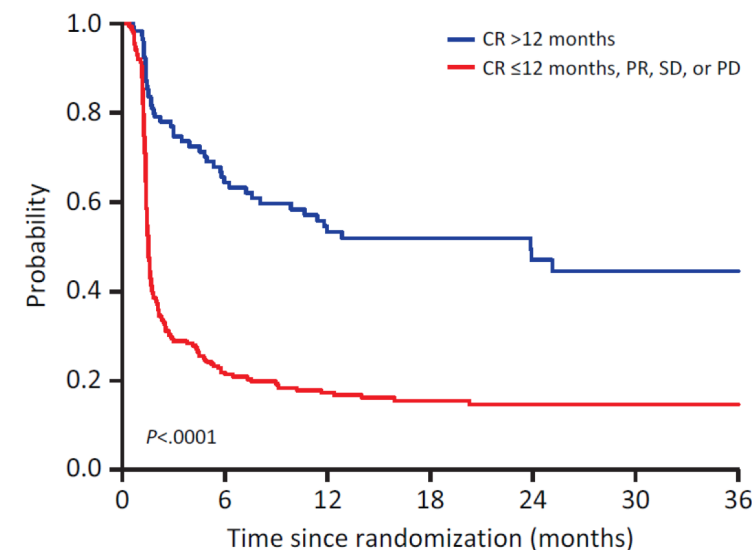


R-CHOP 1L
(...same with PolaV-R-CHP?)



PLATINUM-BASED
SALVAGE
&
BEAM/ASCT
CONSOLIDATION

Gisselbrecht C, JCO. 2010; 28(27): 4184–4190



van Imhoff GW, JCO 2017;35(5):544-551.
Crump M, Blood 2017; 130(16): 1800–1808

CART 2L. STUDY DESIGN OF 3 RCTs

KEY ELIGIBILITY CRITERIA:

Patients ≥18 yr
 LBCL *FL,3b* *PMBCL*
 ECOG PS 0-1,
 R/R disease ≤12 mo since 1L EoT
 HDT-ASCT ELIGIBILITY
 GOOD ORGAN FUNCTION
2° CNS INVOLVEMENT ALLOWED

Stratified by:
 -1L refractory vs relapsed

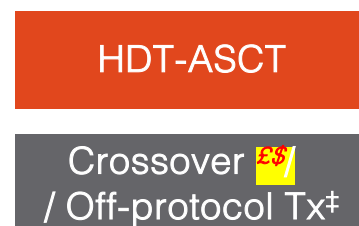
-2L aalPI
 -Region

SCREENING
 LEUKAPHERESIS
 RANDOMIZATION 1:1

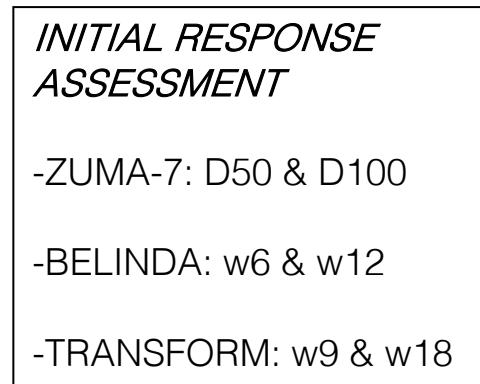


*SoC included R-GDP, R-DHAP, R-ICE
 (and also R-ESHAP in ZUMA-7)

CR/PR
 No
 CR/PR



‡ Over 50% received subsequent CART



£ = BELINDA
 \$ = TRANSFORM

#Bridging:
 -ZUMA-7: optional, only corticosteroids allowed (no CIT)
 -BELINDA: CIT allowed
 -TRANSFORM: CIT allowed

*LDT differs according to specific CAR T product

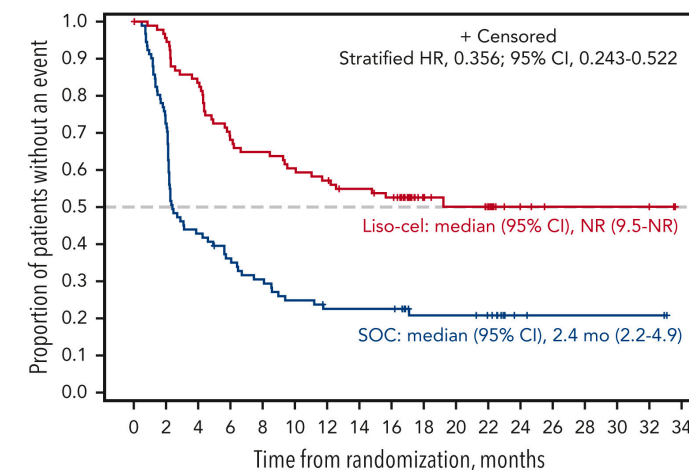
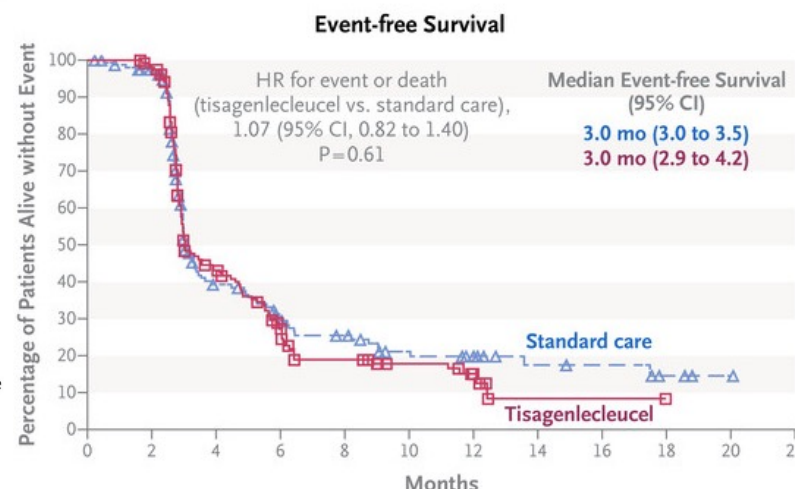
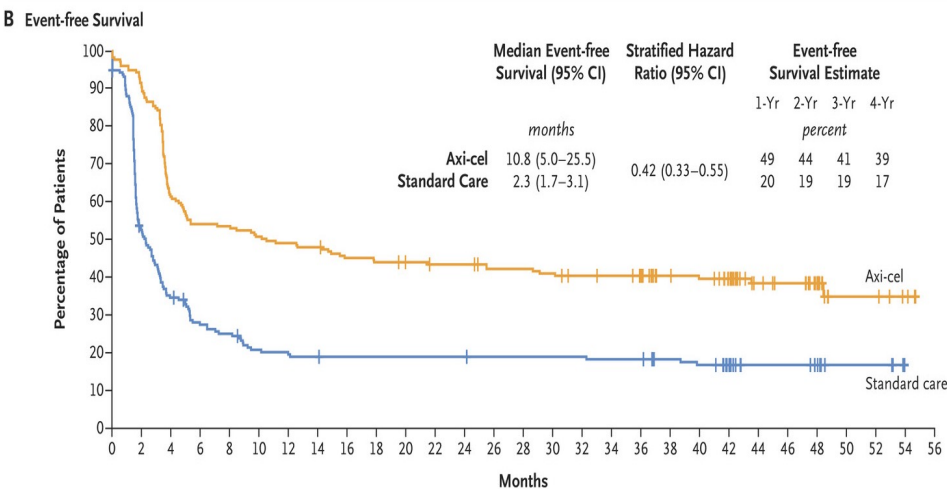
PRIMARY ENDPOINT: EFS
 ...Different definitions in each trial

CAR-T 2L Ph.3 TRIALS_EFS

ZUMA-7
Axi-cel

BELINDA
Tisa-cel

TRANSFORM
Liso-cel



No. at Risk

Axi-cel	180	165	111	98	97	92	89	87	81	79	77	75	75	71	71	69	66	65	62	53	51	44	31	28	21	7	7	3	0
Standard care	179	92	61	47	43	35	33	32	31	31	31	31	31	30	30	30	30	29	29	25	23	18	10	10	8	4	4	0	0

No. at risk

SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	2	0
Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0

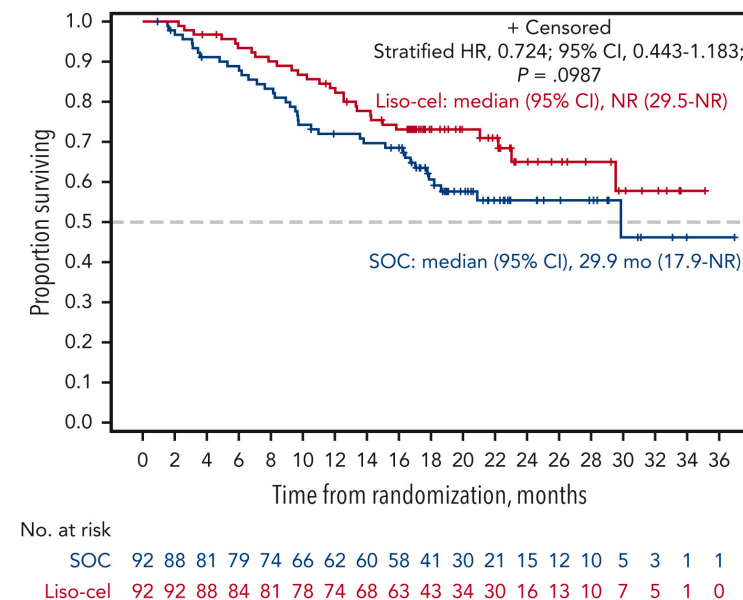
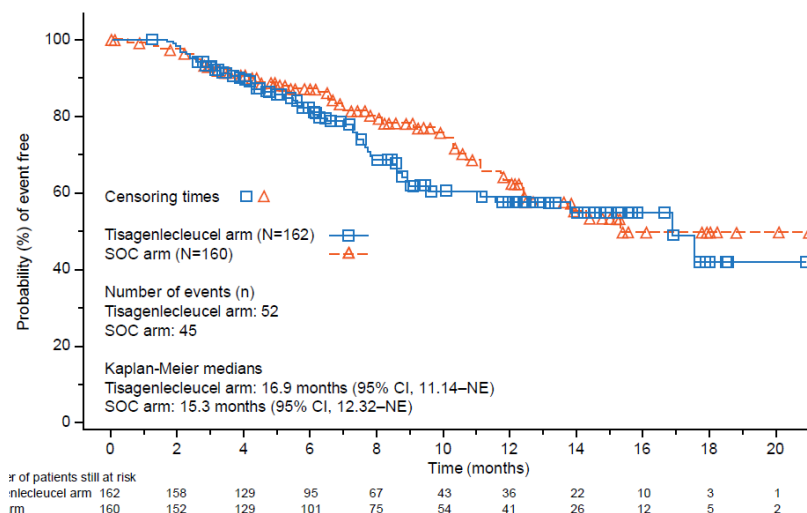
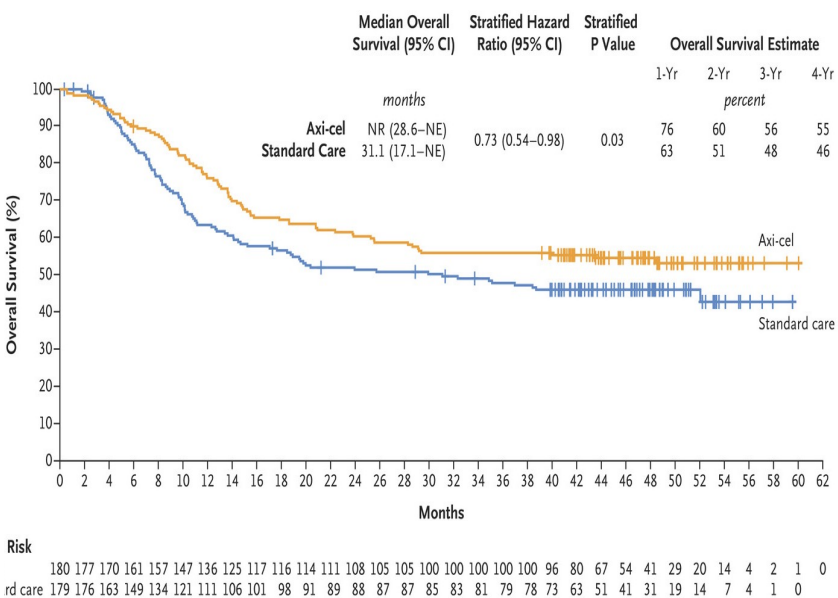
EFS-event	ZUMA-7	BELINDA	TRANSFORM
PD	x	X (@/after w12)	x
<PR as best	by w21 (D150)	X (@/after w12)	by w9
DEATH	x	x	x
New treatment	x	@/after w12	x

CAR-T 2L Ph.3 TRIALS_OS

ZUMA-7
Axi-cel

BELINDA
Tisa-cel

TRANSFORM
Liso-cel



CAR-T 2L Ph.3 TRIALS_SAFETY AND AEs

	ZUMA-7		Belinda		Transform	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
CRS, any grade (%)	92	—	61	—	49	—
CRS, grade ≥ 3 (%)	6	—	5	—	1	—
Neurologic toxicity, any grade (%)	60	—	10	—	12	—
Neurologic toxicity, grade ≥ 3 (%)	21	—	2	—	4	—
Tocilizumab use (%)	65	—	32	—	24	—
Corticosteroid usage for toxicity management (%)	24	—	10	—	17	—
Anemia, grade ≥ 3 (%)	30	39	33	58	49	49
Thrombocytopenia, grade ≥ 3 (%)	15	57	32	48	49	64
Neutropenia, grade ≥ 3 (%)	69	41	40	39	80	51
Febrile neutropenia, grade ≥ 3 (%)	2	27	13	25	15	24
Fatigue, any grade (%)	42	52	24	31	39	38
Nausea, any grade (%)	41	69	41	49	53	57

CAR-T 2L Ph.3 TRIALS_ WHAT DID DRIVE THE DIFFERENCE?

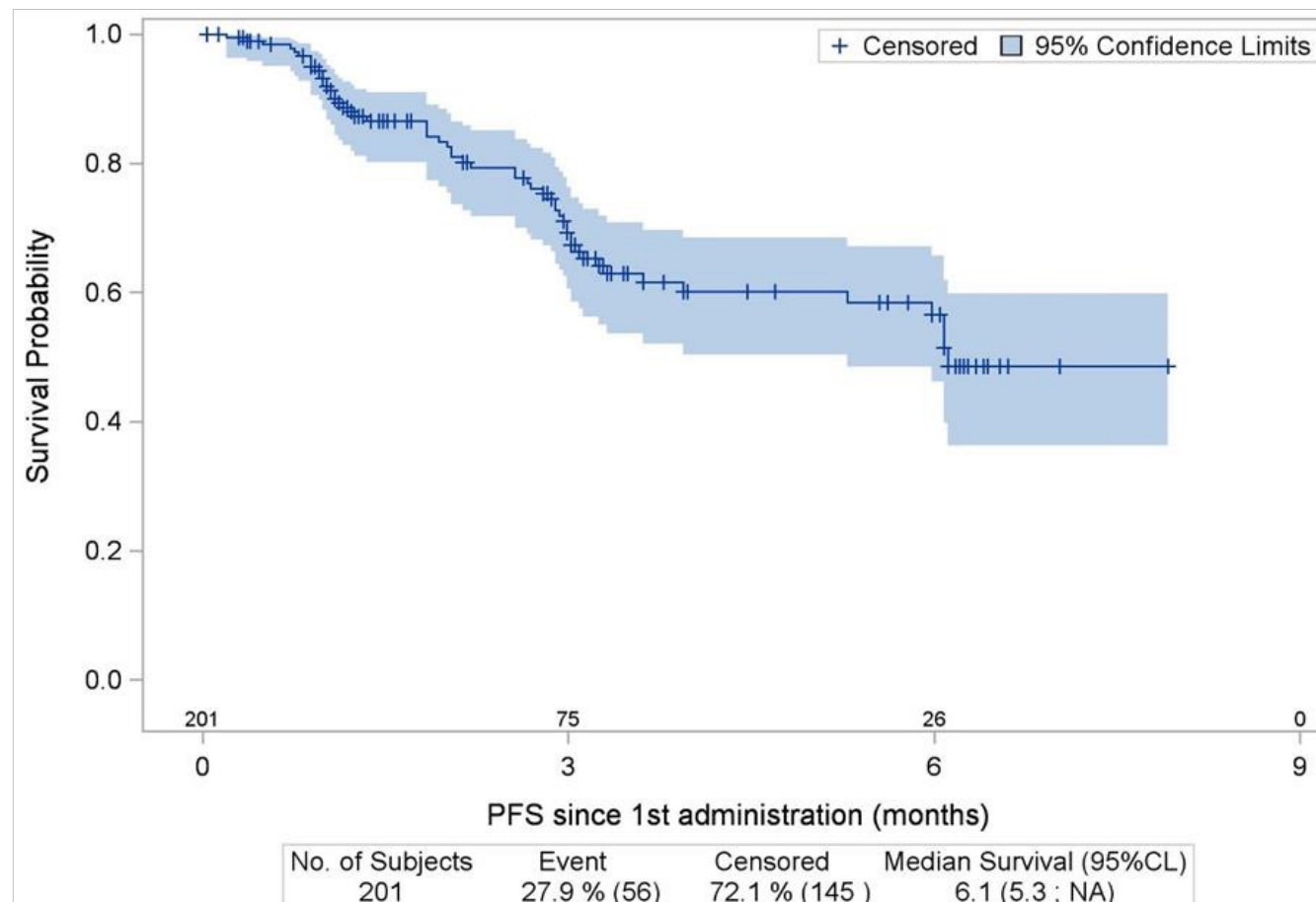
- study design
 - EFS survival definition
 - Bridging therapy usage & biased pt populations
- CAR T cell products
- Other factors (LDT? Vein-to-vein time?)
 - HUGE Vein-to-Vein time in BELINDA (+23 days vs ZUMA-7; +16 vs TRANSFORM)
- a combination of factors

THE PRODUCTS

	[KTE-C19] Axicabtagene Ciloleucel	[CTL-019] Tisagen- lecleucel	[JCAR-017] Lisocabtagene Maraleucel	[KTE-X19] Brexucabtagene Autoleucel
Construct	Anti-CD19-CD28-CD28- CD28 -CD3z	Anti-CD19-CD8a-CD8a- 41BB -CD3z	Anti-CD19-IgG4-CD28- 41BB -CD3z	Anti-CD19-CD28-CD28- CD28 -CD3z
Transduction	Viral - retrovirus	Viral - lentivirus	Viral - lentivirus	Viral - lentivirus
Dose	2 x 10 ⁶ / kg (max 2 x 10 ⁸)	0.6 to 6.0 x 10 ⁸	1 x 10 ⁸	2 x 10 ⁶ / kg (max 2 x 10 ⁸)
LDT (mg/m ²)	Flu/Cy 30/ 500 x 3 days	Flu/Cy 25/250 x 3 days, or Benda 90 x 2 days	Flu/Cy 30/ 300 x 3 days	Flu/Cy 30/ 500 x 3 days

CAR-T 2L_FRENCH REAL-LIFE

PFS since CAR-T infusion



CAR-T 2L Ph.3 TRIALS_UNANSWERED QUESTIONS

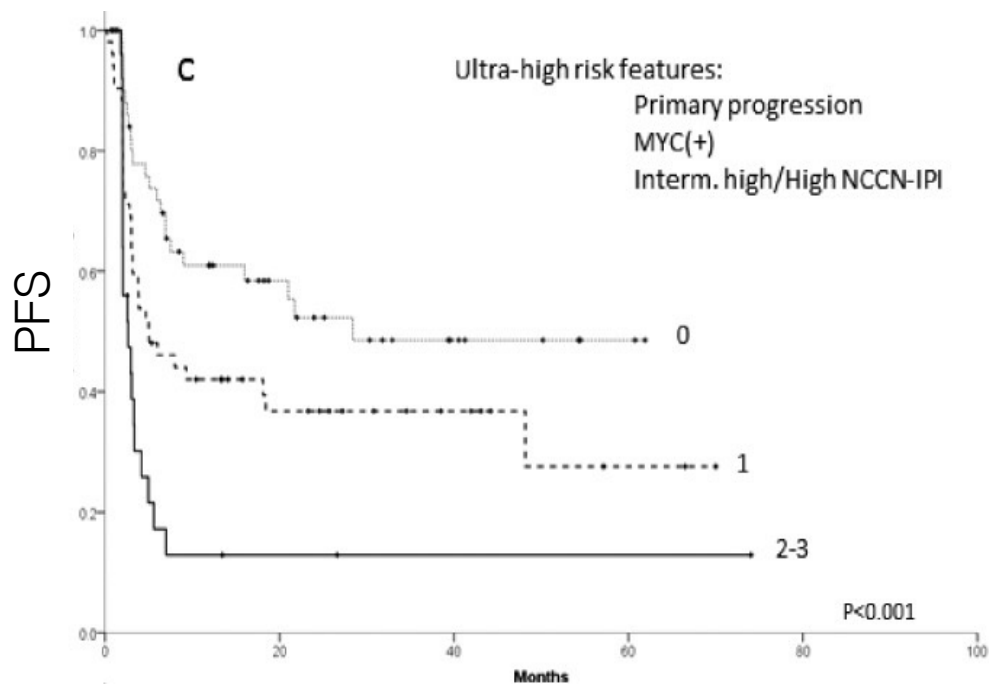
Where to expect the highest benefit compared to CIT/ASCT?

Where to expect the lowest benefit compared to CIT/ASCT?

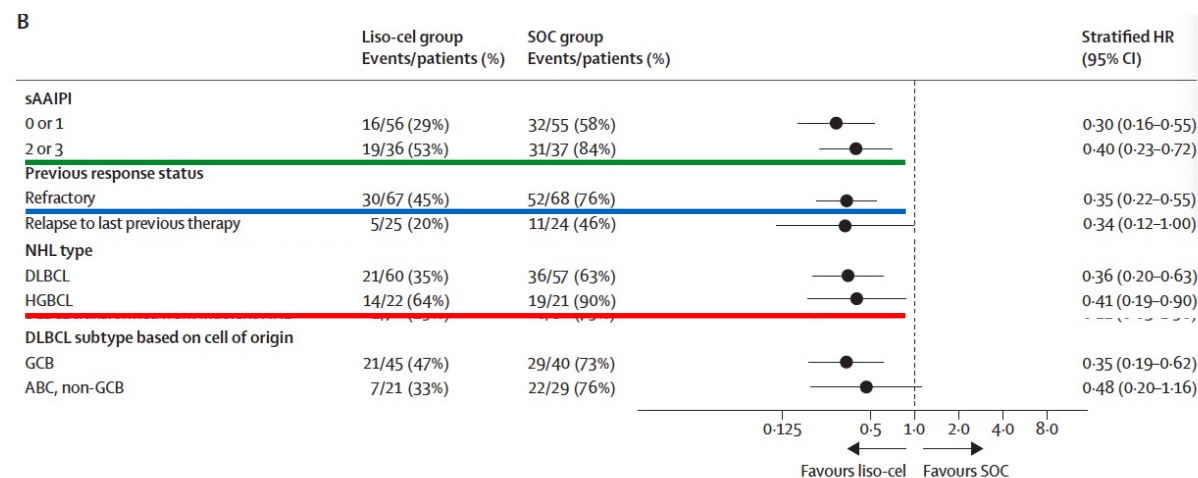
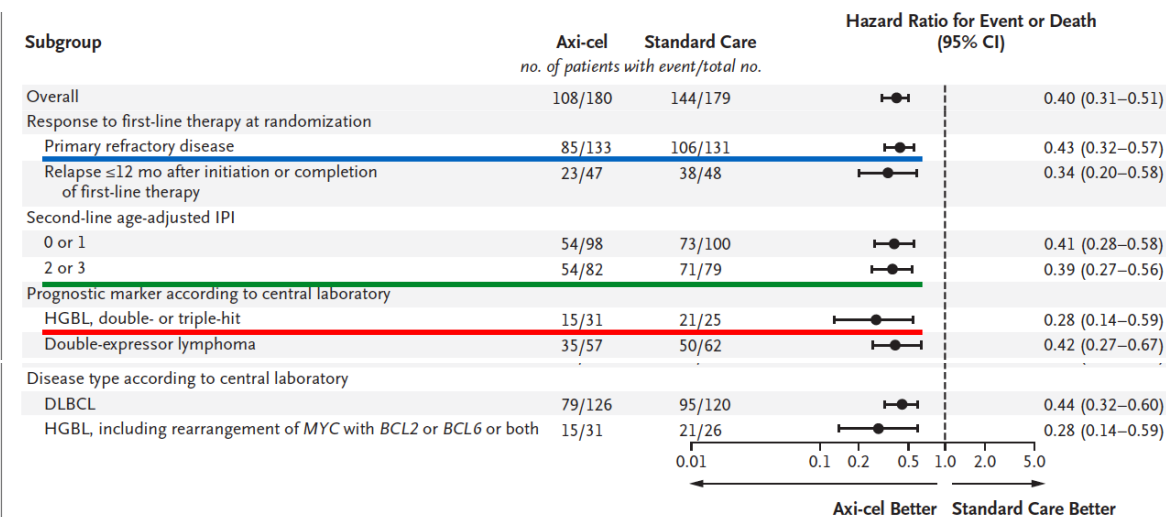
-Are CART superior to AutoHSCT even for chemosensitive relapse?

i.e. For patient achieving PR/CR after bridge, what is the optimal treatment?

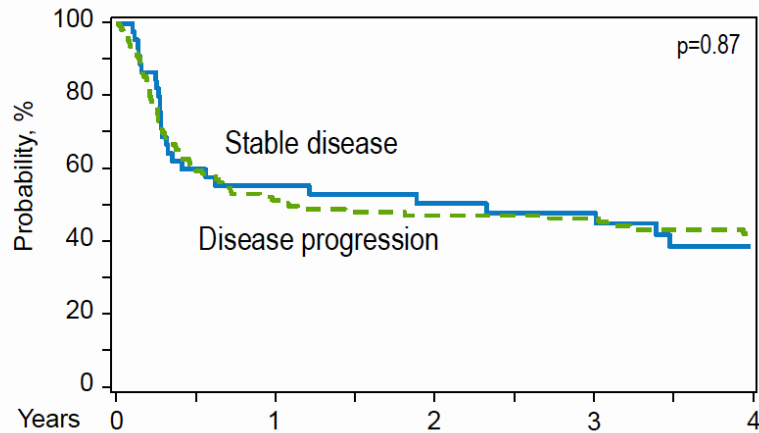
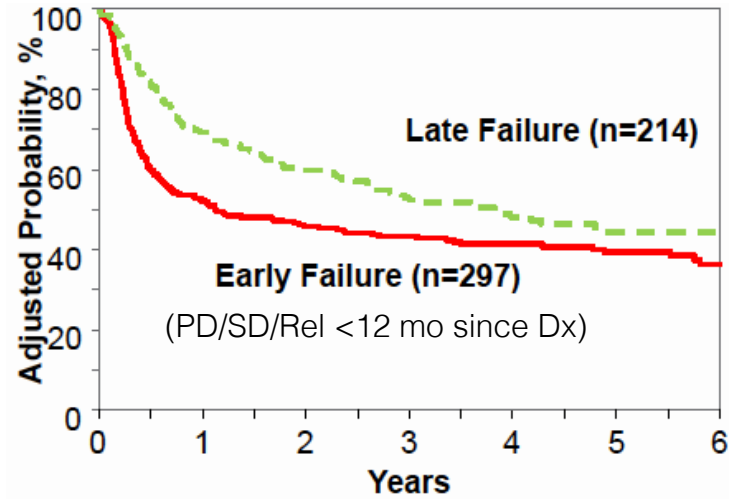
2L ASCT OUTCOME IN HIGH-RISK EARLY FAILURE (<12m since Dx)



FEATURE	HR (PFS)	p value
1° progressive (vs early relapse)	2.46	0.01
NCCN-IPI inter-high/high (vs low)	3.16	0.04
MYC-R (vs no MYC-R)	3.52	0.002

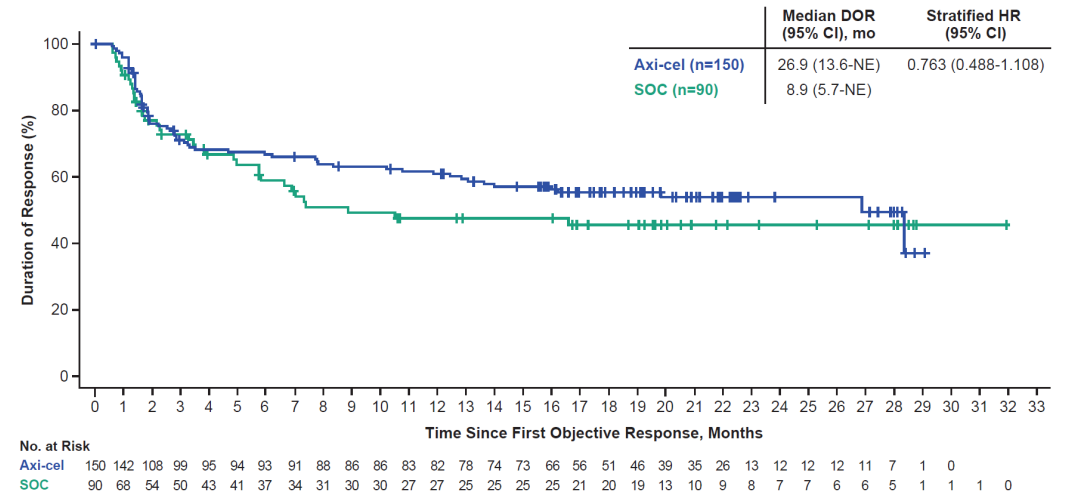


2L ASCT OUTCOME FOR CHEMOSENSITIVE SALVAGE



# at Risk	0	1	2	3	4
Stable Disease	45	24	22	18	12
Disease Prog.	124	64	55	51	37

ZUMA-7 DoR



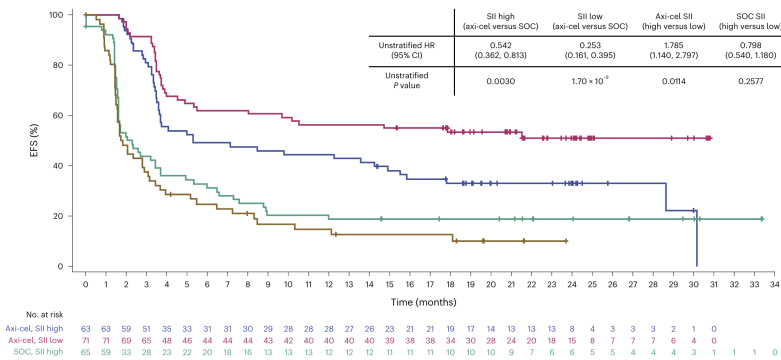
2L CART PREDICTORS

IMMUNOSUPPRESSIVE
TME

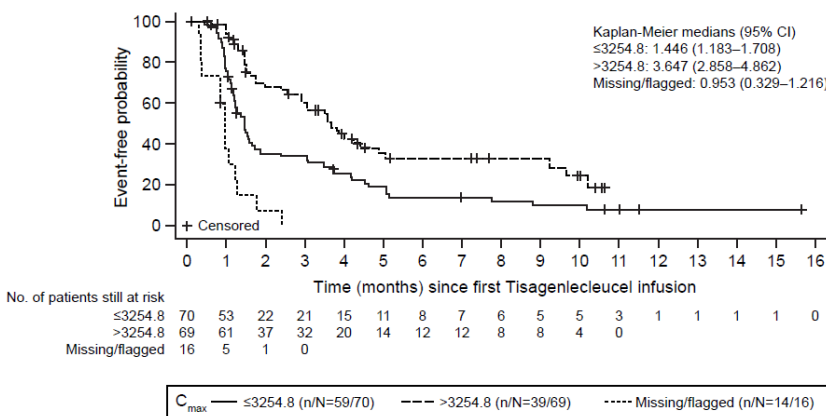
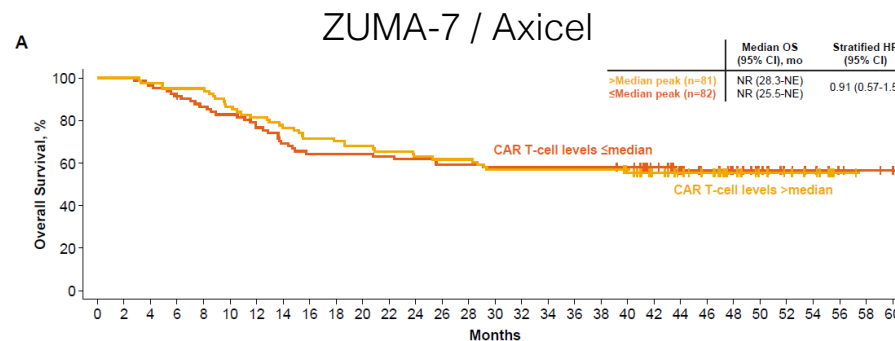
CAR PEAK

Dz STATUS @INFUSION

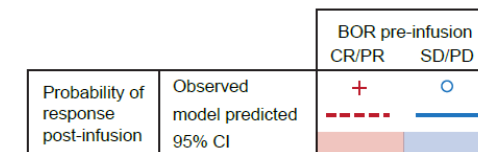
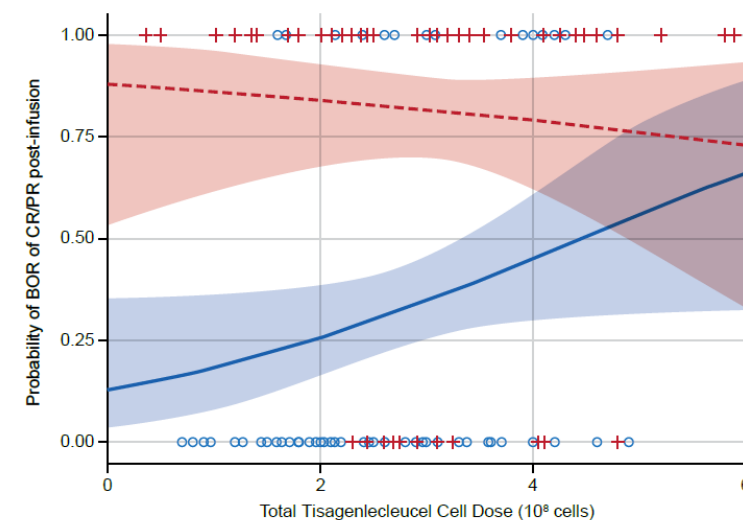
EFS by median of SII and by axi-cel and SOC arms



ZUMA-7 / Axicel



BELINDA / Tisacel



BELINDA / Tisacel

2L CART PREDICTORS (2)

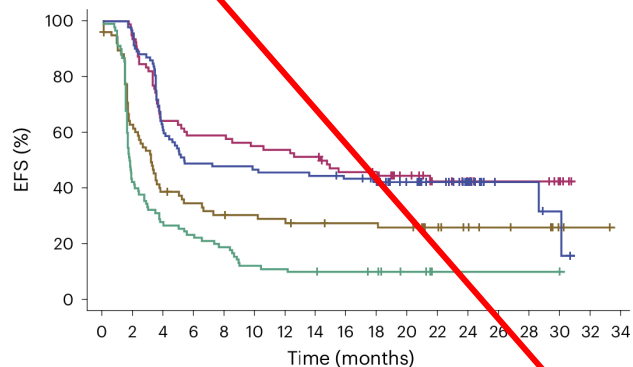
LDH

CT scan SPD

MTV

b

	LDH elevated (axi-cel versus SOC)	LDH normal (axi-cel versus SOC)	Axi-cel LDH (elevated versus normal)	SOC LDH (elevated versus normal)
Unstratified HR (95% CI)	0.321 (0.228, 0.459)	0.496 (0.333, 0.739)	1.108 (0.745, 1.648)	1.556 (1.102, 2.195)
Unstratified P value	2.50×10^{-10}	0.0006	0.6132	0.0119

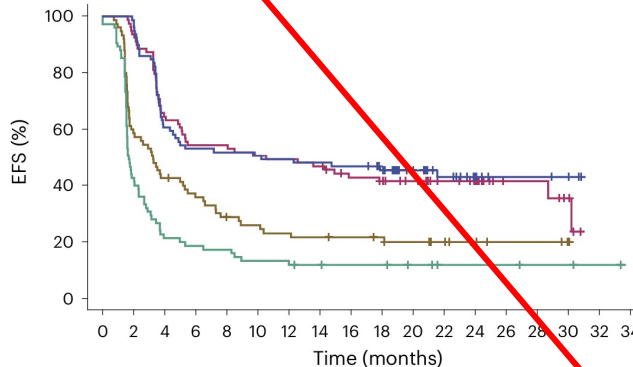


No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Axi-cel, LDH elevated	92	88	55	45	44	43	42	41	39	35	26	21	12	4	4	4	2	0
Axi-cel, LDH normal	78	73	50	46	46	43	42	40	34	31	25	18	14	8	8	4	1	0
SOC, LDH elevated	90	38	24	20	17	11	10	9	8	7	4	1	1	1	1	1	1	0
SOC, LDH normal	78	46	29	25	21	21	19	18	17	17	16	11	8	6	5	2	1	0

ZUMA-7 / Axicel

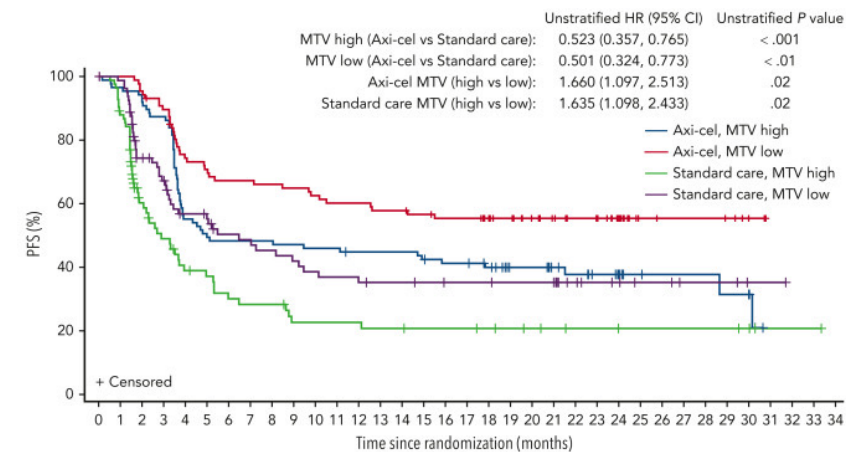
a

	SPD high (axi-cel versus SOC)	SPD low (axi-cel versus SOC)	Axi-cel SPD (high versus low)	SOC SPD (high versus low)
Unstratified HR (95% CI)	0.291 (0.198, 0.430)	0.484 (0.329, 0.712)	0.930 (0.617, 1.400)	1.516 (1.065, 2.159)
Unstratified P value	4.74×10^{-10}	0.0002	0.7265	0.0210



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Axi-cel, SPD high	79	78	48	42	41	40	39	38	37	33	22	17	8	5	5	2	0	0
Axi-cel, SPD low	79	74	51	43	43	40	39	37	31	29	25	20	17	7	7	4	0	0
SOC, SPD high	75	32	16	14	13	10	9	8	7	7	5	3	3	2	2	1	0	0
SOC, SPD low	75	44	32	26	20	18	16	15	14	13	11	8	5	3	3	1	0	0

ZUMA-7 / Axicel



ZUMA-7 / Axicel

Prof. Armando SANTORO

*Clinical Trial
Data Manager*

Medici in formazione specialistica

Prof. Carmelo CARLO-STELLA

Dott.ssa Monica BALZAROTTI
Dott. Massimo MAGAGNOLI
Dott.ssa Rita MAZZA
Dott.ssa Francesca RICCI

Elisa Carra
Francesca Stante
Laura Rossi
Giulia Tavanti
Laura Paladini

Alessandro Buizza
Jacopo Calabrese De Feo
Davide Chizzoniti
Alessandra Crespi
Maria Di Matteo
Ivan Ferrari
Giulia Figini
Arianna Giacomel
Antonio Imparato
Ciro Improta
Luca Lanino
Chiara Pinton
Flavio Pistolese
Filippo Viviani
Cristina Zucchinetti

Any questions?

filippo.bagnoli@cancercenter.humanitas.it

 @Filippo_Bagnoli

