VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

Terapie innovative (anticorpi bi-specifici e CAR-T) nei linfomi follicolari e diffusi a grandi cellule: il futuro della immunoterapia

Beatrice Casadei

IRCSS, AOU di Bologna

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Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene-BMS						X	
Kite-Gilead					X	X	X
Novartis					X	X	
Takeda						X	
Roche			X		X	X	
Janssen						X	
Lilly					x		
Abbvie					x		
BeOne					x		
MSD					x		

Agenda:

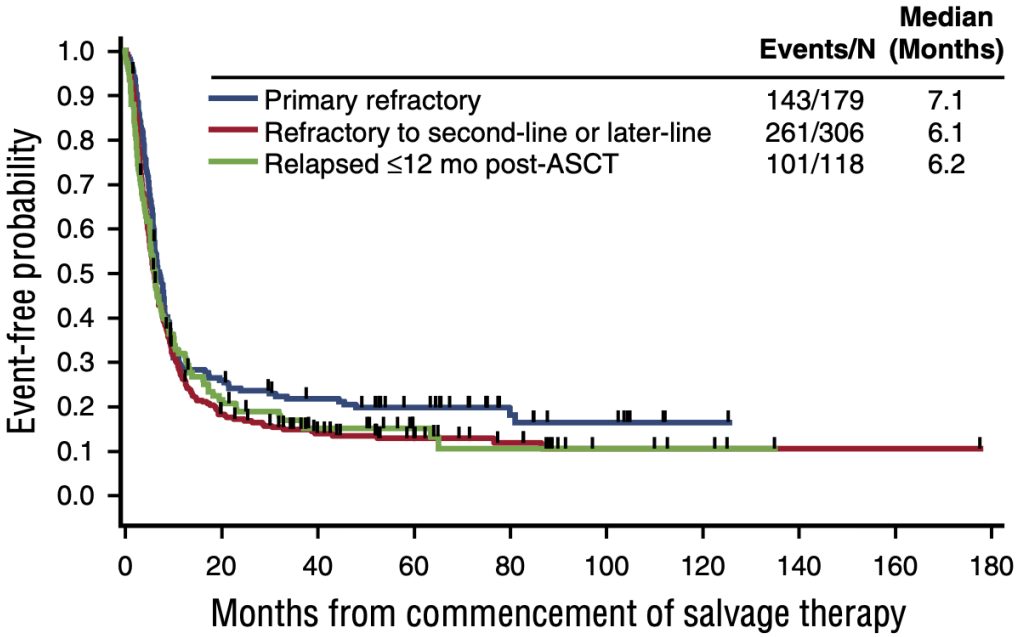
- Introduction on CAR T-cells in LBCL and FL
- DLBCL:
  - Introduction
  - CAR T-cell therapy: Results from clinical trial
  - BsAbs: Results from clinical trial
  - Conclusions

- Introduction on CAR T-cells in LBCL
- FL:
  - Introduction
  - CAR T-cell therapy: Results from clnical trial
  - Conclusions

Introduction: Second Generation anti CD19 CAR T-cell Therapy

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene Maraleucel
Construct	CD19 scFV-**CD28**-CD3z	CD19 scFV-**41BB**-CD3z	CD19 scFV-**41BB**-CD3z
Source	Fresh unsorted PBMCs	Cryopreserved unsorted PBMCs	Fresh sorted PBMCs
Viral Vector	Gamma retrovirus	Lentivurs	Lentivirus
AIFA approval status	1. Adult patients with **LBCL** (DLBCL NOS, HGBCL**)** refractory to or relapsed within 12 months of first-line chemoimmunotherapy (**2 Line**) 2. Adult patients with r/r **LBCL** (DLBCL NOS, HGBCL, tFL/tMZL or PMBCL) after **≥ 2 lines** of systemic therapy 3. Adult patients with r/r **FL after ≥ 3** lines of systemic therapy	1. Adult patients with r/r **LBLC** (DLBCL NOS, HGBCL or tFL/tMZL) after **≥2 lines** of systemic therapy 2. Adult patients with **r/r FL after ≥ 2** lines of systemic therapy 3. Paediatric and young patients ≤25 years of age with B-cell ALL that is refractory, relapsed post-transplant or in second or later relapse	1. Adult patients with **LBCL** (DLBCL NOS, HGBCL, FL gr3B and PMBCL) refractory to or relapsed within 12 months of first-line chemoimmunotherapy **(2 Line)** 2. Adult patients with **r/r LBCL** (DLBCL NOS, HGBCL, FL grade 3B, tFL/tMZL or PMBCL) after **≥2 lines** of systemic therapy

Outcomes in RR LBCL Before CAR T-cell Therapy and BsAbs

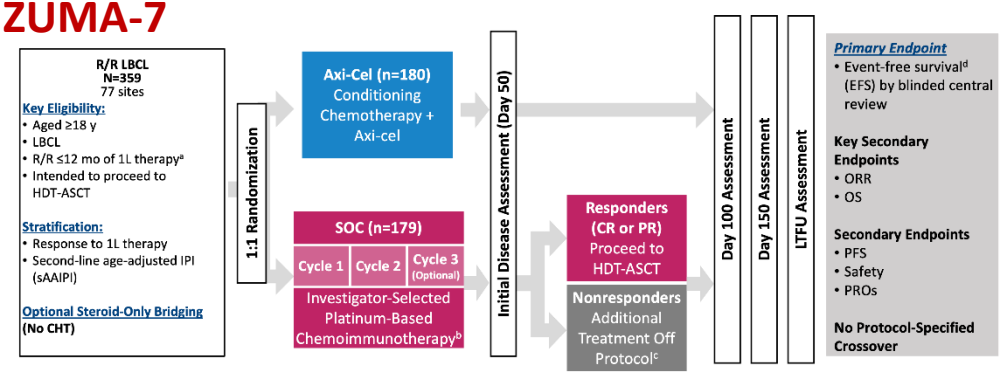


Refractory: progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or relapsed at ≤ 12 months from autologous stem cell transplantation.

Crump M et al, Blood 2017

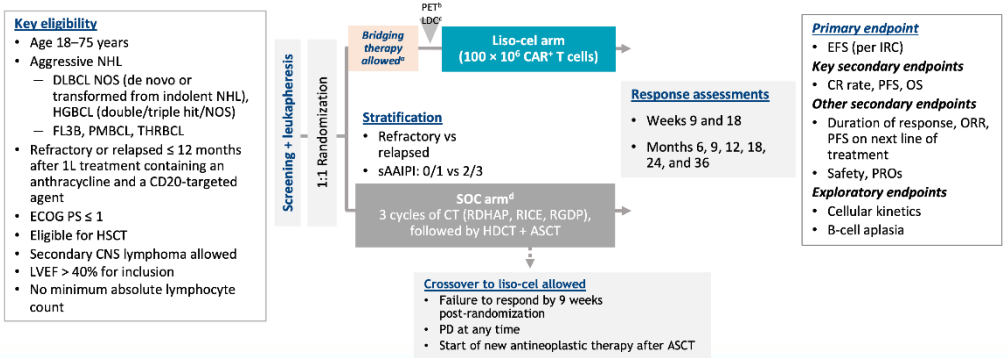
ZUMA-7 and Transform: Ph 3 clinical trial of CAR-T vs SoC

ZUMA-7



- 359 pts enrolled
- 74% primary refractory
- median age 59 (21-81)
- DLBCL NOS 69% (GCB 58%)
- HGBCL (including rearrang of *MYC* + *BCL2* or *BCL6* or both): 17%
- tFL 13%
- CD19+ status on IHC: 77%

TRANSFORM

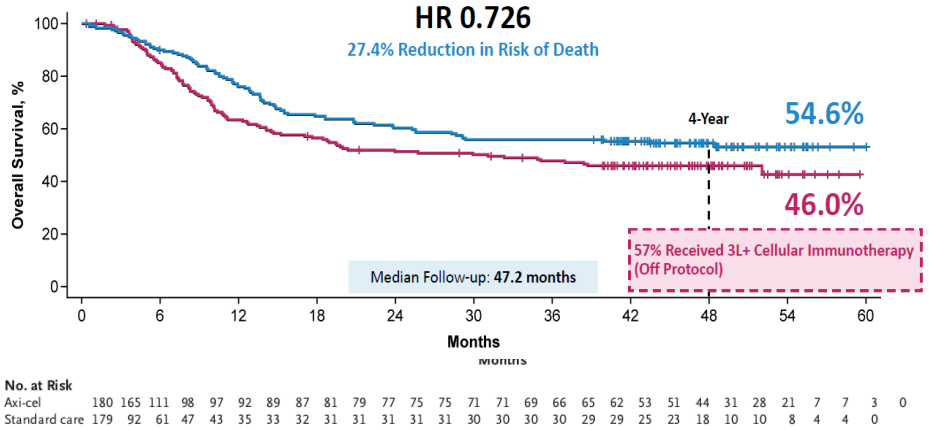


- 184 pts
- 73% primary refractory
- median age 60 (20-74)
- DLBCL NOS 56%
- HGBCL (including rearrang of *MYC* + *BCL2* or *BCL6* or both): 23%
- Transformed from INHL 8%
- PMBCL 10%

Westin JR et al, New Eng J Med 2023; Locke FL et al, New Engl J Med 2022

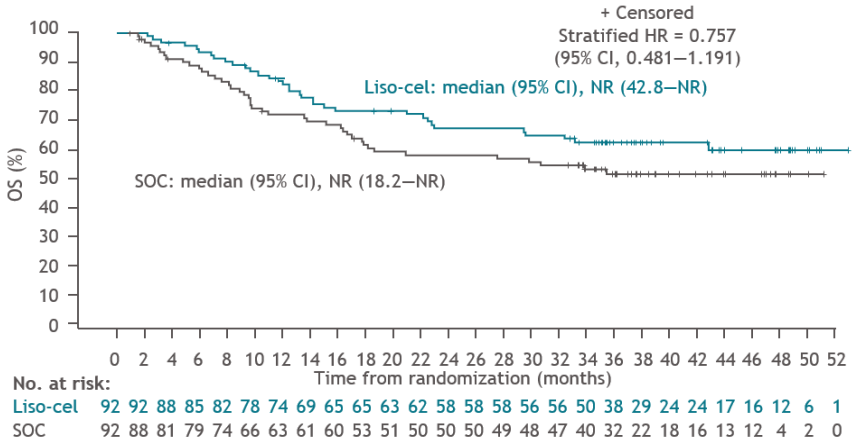
CAR T-cell in 2L has Improved Outcomes over SOC in Refractory LBCL

OS-Axicel (median f-up 47.2 mo)



Response n (%)	Axicel (n=180)	SoC (n=179)	p
ORR	150 (83)	90 (50)	<0.0001
CR	117 (65)	58 (32)	
Survival, mo			**HR**
Median PFS	**14.7**	**3.7**	**0.49**
Median OS	NR	31.1	0.73

OS-Lisocel (median f-up 33.9 mo)

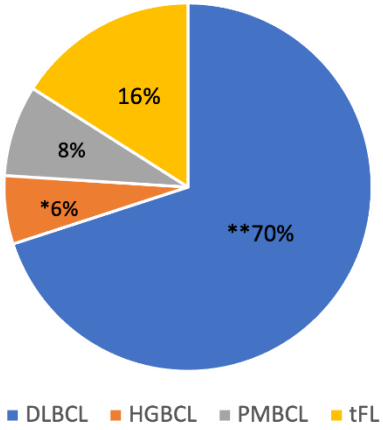


Response n (%)	Lisocel (n=92)	SoC (n=92)	p
ORR	80 (87)	45 (49)	<0.0001
CR	68 (74)	40 (43)	
Survival, mo			**HR**
Median PFS	NR	6.2 mo	0.4
Median OS	NR	29.9 mo	0.72

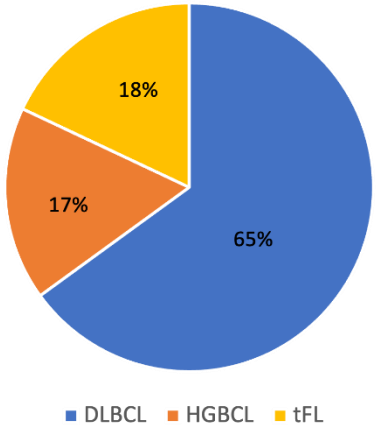
Westin JR et al, New Eng J Med 2023; Locke FL et al, New Engl J Med 2022; Abramson JS et al, Blood 2023; Kamdar M et al, JCO 2025

CAR T-cell In 3° or Later Line of LBCL: Different Products for Different Trials

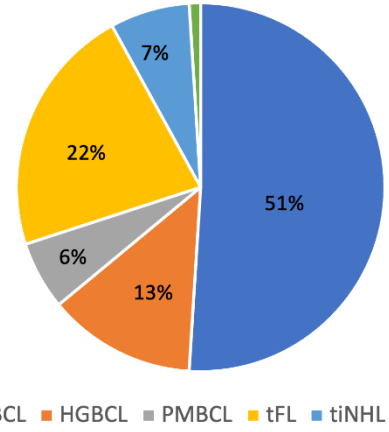
ZUMA-1 (n=101)



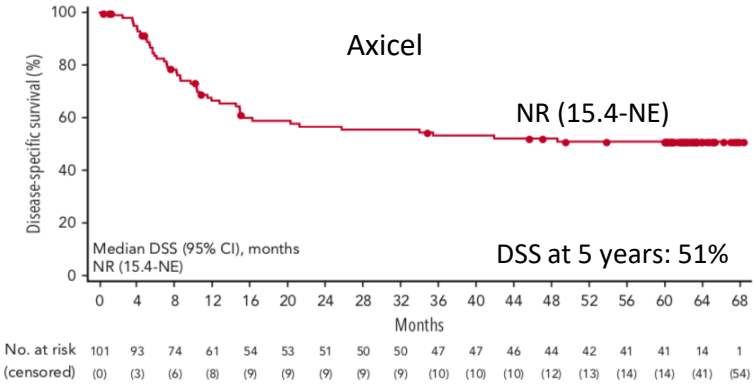
JULIET (n=115)

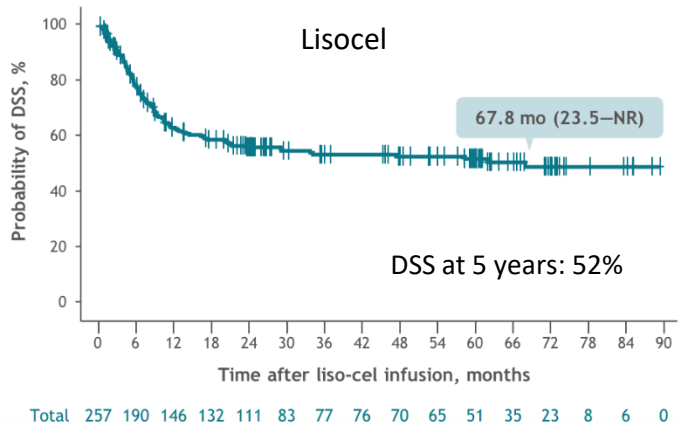


TRANSCEND NHL 001 (n=270)



CAR T-Cell In 3° or Later Line: almost 40% of LBCLs are Potentially Cured





	Axi-cel	Tisa-cel	Liso-cel
Pivotal trial	ZUMA-1	Juliet	Transform
Most mature follow up (m)	63.1	40.3	24
Median duration of response (m)	11.1	NE	23.1
ORR/CR (%)	83/58	52/39	73/53
Median PFS (m)	5.9	2.9	6.8
PFS, 24 m (%)	36	33*	40.6
Median OS (m)	25.8	11.1	27.3
OS, 24 m (%)	50.5	40*	50.5

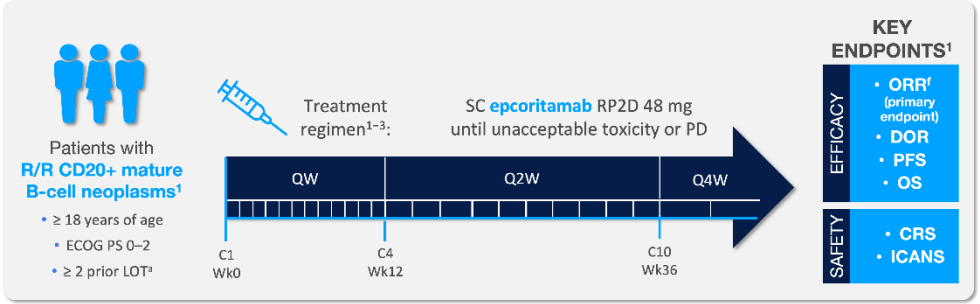
Neelapu SS, et al. Blood 2023; Schuster SJ, et al. Lancet Oncol 2021; Abramson JS, et al. Blood 2024.

Introduction: BsAbs Products and Approvals

	Glofitamab	Epcoritamab	Mosunetuzumab
Construct	CD20xCD3	CD20xCD3	CD20xCD3
CD20:CD3 ratio	2:1	1:1	1:1
Administration	EV, 12 cycles (21 days)	SC, until PD or severe toxicity (28days cycle)	EV, 17 cycles (21 days)
AIFA approval status	1. Adult patients with **DLBCL NOS** after **≥ 2 lines** of systemic therapy 2. Plus Gemox in Adult patients with **DLBCL RR** to a previous systemic therapy and not elegible to ASCT (COOMING SOON in **2L**)	1. Adult patients with **DLBCL NOS** after **≥ 2 lines** of systemic therapy 2. Adult patients with **r/r FL after ≥ 2** lines of systemic therapy	1. Adult patients with **r/r FL after ≥ 2** lines of systemic therapy

Epcoritamab and Glofitamab: Ph 2 clinical trial of BsAbs in LBCL

Epcoritamab



- 157 pts enrolled
- Median age 64 (20-83)
- DLBCL NOS 88%
- tINHL 25.5%
- HGBCL 5.7, DH/TH: 8.3%
- PMBCL 2.5%; FL gr3B: 3.2%
- 61% Primary Refractory
- Median n Lines: 3 (2-11)
- Prior CART 38.9% (75% refractory to CART)

Glofitamab

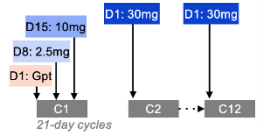
Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline

Glofitamab IV administration

Fixed-duration treatment
- Max. 12 cycles (8.3 months)

CRS mitigation:
- Obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Endpoints

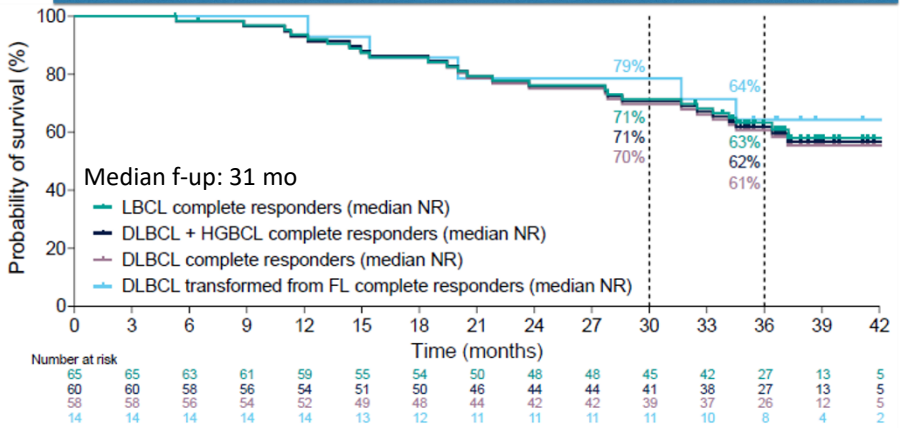
Primary: CR (best response) rate by IRC*
Key secondary: ORR rate,† DoR, DoCR,† PFS, and OS

- 154 pts enrolled
- Median age 66 (21-90)
- DLBCL NOS 71%
- tFL18%
- High grade (including DHL) 7%
- PMBCL 4%
- 58% Primary Refractory
- Median n Lines: 3 (2-7)
- Prior CART 33% (90% refractory to CART)

Dickinson MJ, et al. New Engl J Med 2022 ; Thieblemont C et al. Leukemia 2024

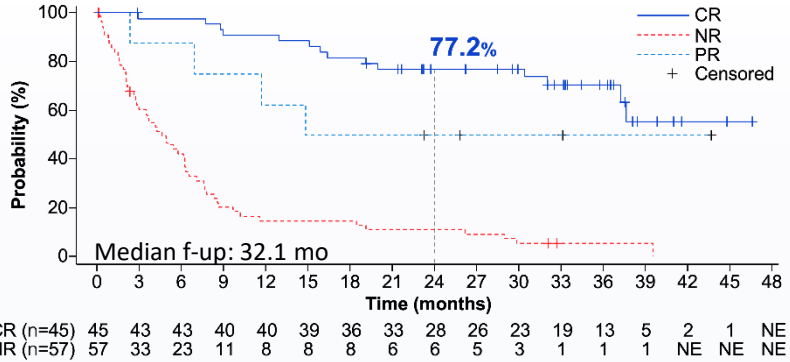
BsAbs Modified Outcomes of Very High Risk Patients

OS with Epco for CR pts



Response n (%)	Epco (157)
ORR	59%
CR	41%
Median DoR	20.8 mo (13-32)
Median time to CR	2.6 mo (1.2-23-2)
Survival, mo	
Median PFS	**4.4**
Median PFS in CR pts	**37.3**
Median OS	18.5

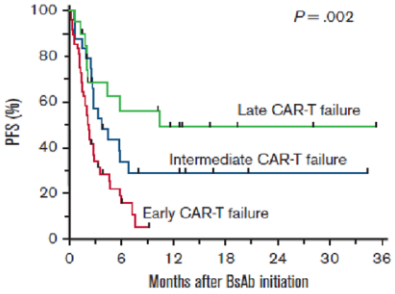
OS with Glofi for CR pts



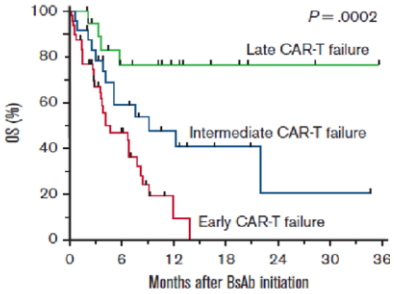
Response n (%)	Glofit (155)
ORR	52%
CR	40%
Median DoR	18.4 mo (13.7-NR)
Median time to CR	41 days
Survival, mo	
Median PFS	**4.9**
Median PFS in CR pts	**NR**
Median OS	11.5

Dickinson M, et al. ASH 2024; oral presentation (abstract #865 ; Vose JM et al. ASH 2024; Dec 2024; P4480, San Diego, Virtual

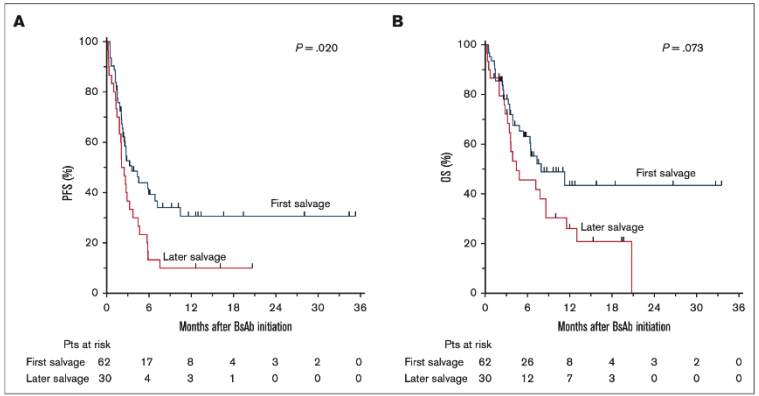
Does Prior CAR T-Cell Treatment Have an Impact on BsAb Efficacy?



Pts at risk							
Early CAR-T failure	48	5	0	0	0	0	0
Intermediate CAR-T failure	24	7	5	2	1	1	0
Late CAR-T failure	20	9	6	3	2	1	0



Pts at risk							
Early CAR-T failure	48	15	1	0	0	0	0
Intermediate CAR-T failure	24	12	7	3	1	1	0
Late CAR-T failure	20	11	7	4	2	1	0



Pts at risk							
First salvage	62	17	8	4	3	2	0
Later salvage	30	4	3	1	0	0	0

Pts at risk							
First salvage	62	26	8	4	3	2	0
Later salvage	30	12	7	3	0	0	0

Shumilov E, et al. Blood Adv 2025; Brooks TR et al, Blood 2025.

BsAbs in 2L: Glofit+Gemox (STARGLO ph 3 trial)

Patients R/R DLBCL (N=274)
- R/R DLBCL NOS after ≥1 prior systemic therapy
- Patients with one prior line must be transplant ineligible
- ECOG PS 0–2

Stratification factors
- Relapsed vs refractory disease‡
- 1 vs ≥2 prior lines of therapy

R 2:1

Glofit-GemOx (n=183)
Glofitamab plus gemcitabine and oxaliplatin*
Step-up dosing in Cycle 1,
30mg administered on Day 1 from Cycle 2 onwards

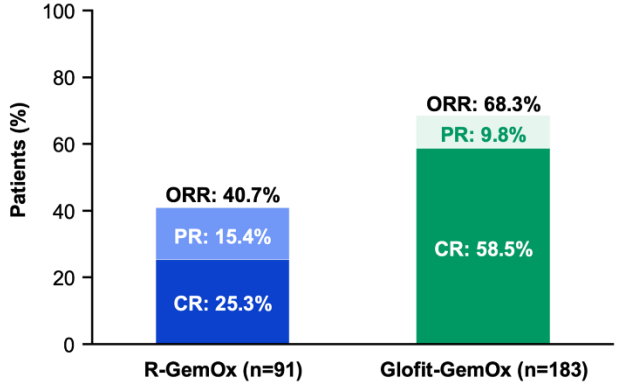
Glofitamab
30mg administered on Day 1 of each cycle

Cycles 9–12

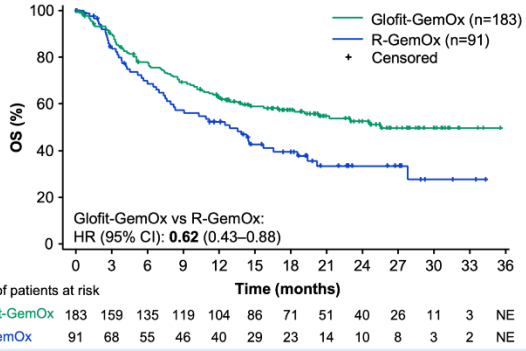
Cycles 1–8
(21-day cycles)

R-GemOx (n=91)
Rituximab† plus gemcitabine and oxaliplatin
Administered on Day 1 of each cycle

Response rates at the updated analysis



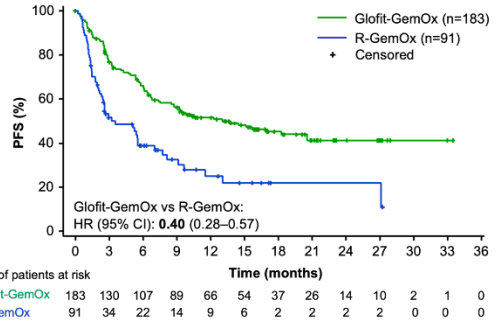
Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

- Statistically significant and clinically meaningful **OS benefit for Glofit-GemOx** versus R-GemOx

Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 9.6 months)		
PFS, median (95% CI); months	3.3 (2.5–5.6)	12.1 (6.8–18.3)
HR (95% CI)	**0.37** (0.25–0.55)	
p-value*†	<0.000001	
Updated analysis (median follow-up: 16.1 months)		
PFS, median (95% CI); months	3.6 (2.5–7.1)	13.8 (8.7–20.5)
HR (95% CI)	**0.40** (0.28–0.57)	
p-value*†	<0.0001	
12-month PFS, % (95% CI)	25.2 (13.6–36.9)	51.7 (44.0–59.4)

Statistically significant and clinically meaningful PFS benefit for Glofit-GemOx versus R-GemOx

Abramson J. et al, *Lancet*. 2024

Conclusions and Next Steps of CART and BsAbs in LBCL

FRONT LINE

CAR-T in very HR patients??

Tafa+Lena (FrontMind)

Golca (Golseek-1)

RCHOP +

Acala (ESCALADE)

Epco (EPCORE-DLBCL)

Odro (Olympia 3)

R-Pola-CHP +

Glofit (SKY-Glo)

R-Pola +

Glofit (ph2)

≥ 2 LINE

CHT: Gemox R-DHAP

EPCO +

ADC: Lonca

Small Molec Golca Lena Ibr + Len

CPi: Atezo englumafusp

ADC: Pola Lonca

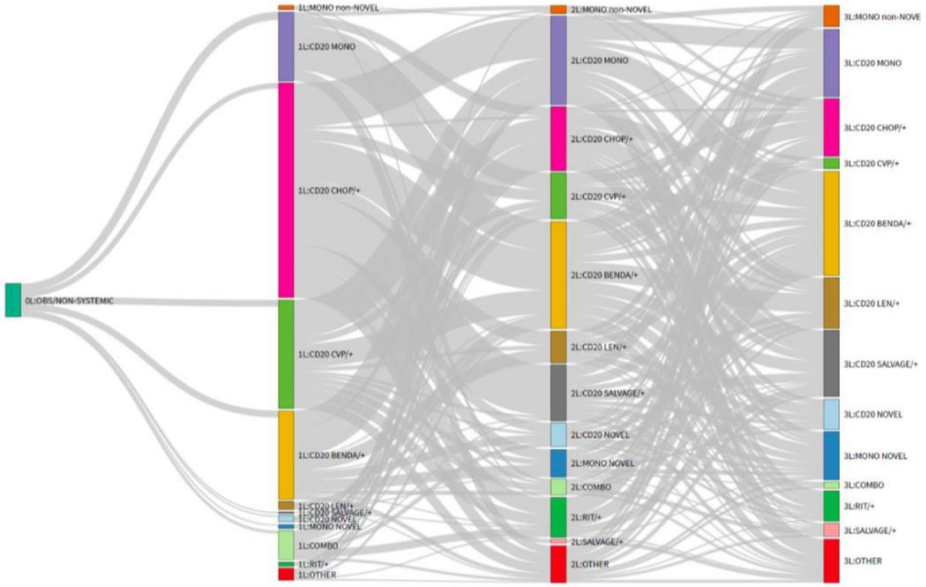
GLOFIT +

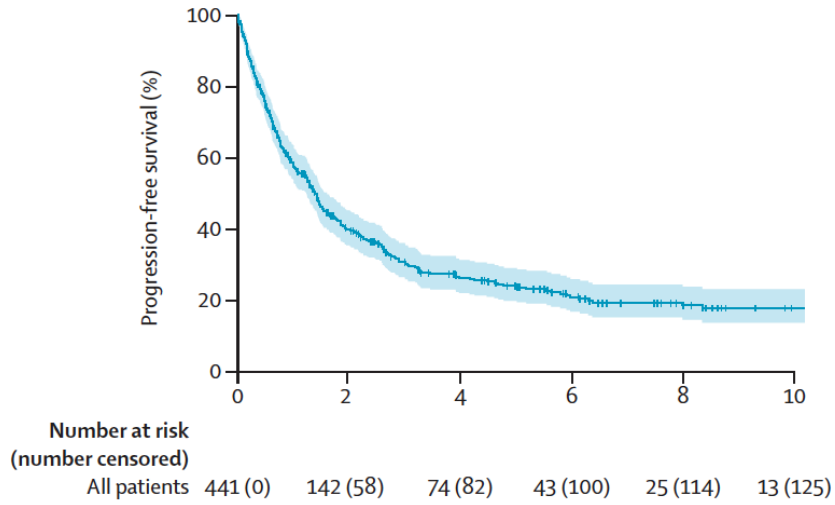
Small Molec: Golca

Chemo: R-ICE

CART Bicistrionic + "New" BsAbs

Outcomes in RR FL Before CAR T-cell Therapy and BsAbs





High response rates (ORR: 70%, CR 47%) but of short duration
Inferior outcome in patients with high FLIPI, refractory to alkylator and POD24

Casulo C. et al ,Lancet Haematol 2022

RR FL and Second Generation anti CD19 CAR T-cell Therapy

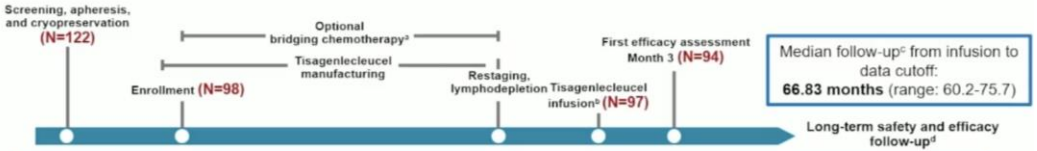
Agent and trial	Ph	Pts n	POD24 %	Prior tx median	BT %	V2Vt, days	ORR/CR^ %	Median f-up, mo	PFS, %	OS, %	CRS (any/ gr ≥3) %	ICANS (any/ gr ≥3) %
Tisa-cel (ELARA)[1,2,3]	II	97	63	4 (2-13)	45	46*	86 / 68	66.8	60mo: 46% (57)	60mo: 74.1%	48/0	4/1
Axi-cel (ZUMA-5)[4,5]	II	124	56	3 (2-4)	4	40	90 / 75	64.6	60mo: 49.8	60mo: 69%	97/8	56/15
Liso-cel[6,7] (TRANSCEND -FL)	I/II	101 (3L) 23 (2L)	55	3 (2-10)	38	49	97 / 94	36	36mo: 68	36mo: 86	58/1	15/2

*median time from enrollment to infusion. ^consistent response rates were seen also in those patients with high-risk characteristics

1. Dreyling M. et al. Blood 2024. 2. Fowler N.H. et al, Nature Med 2022, 3. Schuster S. et al. ASH 2025; 4 Jacobson A.C. et al, Lancet Oncol 2022; 5 Neelapu S. et al. JCO 2025; 6. Morschauser F et al. Nature 2024 . 7. Nastoupil L. et al. ASH 2024

RR FL and Second Generation anti CD19 CAR T-cell Therapy

ELARA (Tisacel)

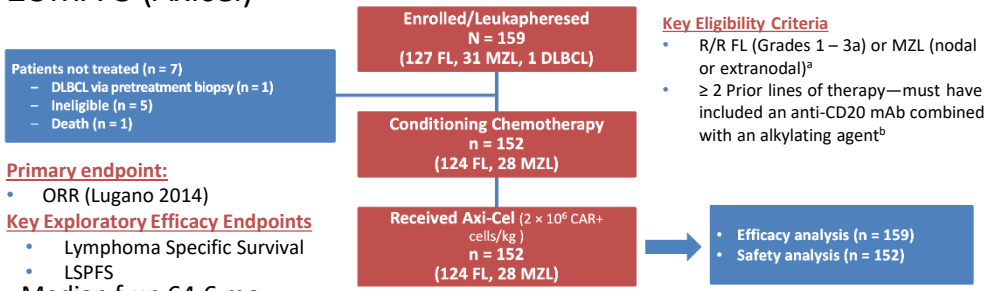


Key eligibility criteria	Study treatment	End points
• ≥18 years of age • FL grade 1, 2, or 3A • Relapsed/refractory disease[e] • No evidence of histological transformation/FL3B • No prior anti-CD19 therapy or allogeneic HSCT	Tisagenlecleucel dose range (single IV infusion) was 0.6-6×10[8] CAR-positive viable T cells	**Primary:** CRR by IRC **Secondary:** ORR, DOR, PFS, OS, safety, cellular kinetics

- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion
- Cellular kinetics were determined by measurement of transgene levels by qPCR

	Infused set (N = 97) n (%)
Median age (range), years	57.0 (29-73)
ECOG PS ≥1 prior to infusion	42 (43)
Stage at study entry III-IV	83 (86)
Bone marrow involvement	37 (38)
Bulky disease[a]	63 (65)
FLIPI high at study entry (≥3)	58 (60)
Median no. of prior therapies (range)	4 (2-13)
POD24[b]	61 (63)
Refractory disease to last line of therapy	76 (78)
Refractory to ≥2 regimens	69 (71)
Double refractory: anti-CD20 mAb + alkylating agent	66 (68)
Refractory to PI3K inhibitors	14 (14)
Prior autologous HSCT	35 (36)

ZUMA-5 (Axicel)



Key Eligibility Criteria

- R/R FL (Grades 1 – 3a) or MZL (nodal or extranodal)[a]
- ≥ 2 Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary endpoint:

- ORR (Lugano 2014)

Key Exploratory Efficacy Endpoints

- Lymphoma Specific Survival
- LSPFS

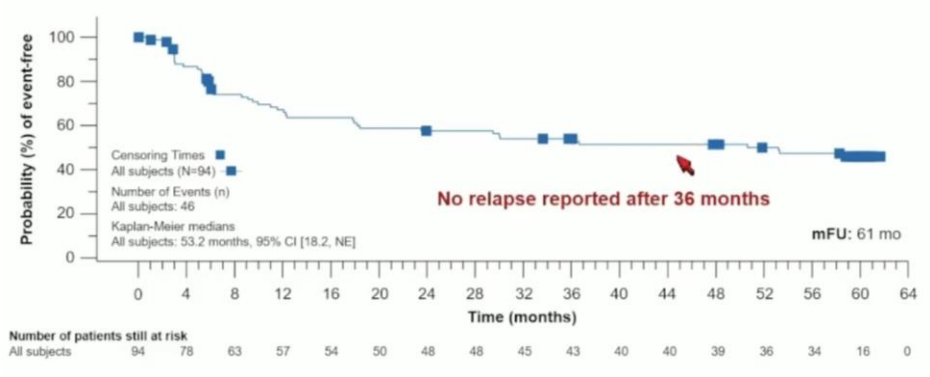
Median f-up 64.6 mo

Characteristics	FL Pts, 124 (n)
Median age, years (range)	60 (53-67)
ECOG 1, %	37
Ann Arbor stage III-IV, %	85
FLIPI ≥ 3, %	44
Median line of prior tx, n (range) ≥ 3 previuos lines of tx, %	3 (2-4) 63
Refractory to last previous therapy, %	68
Positive CD19 status,%	90
POD24, %	55

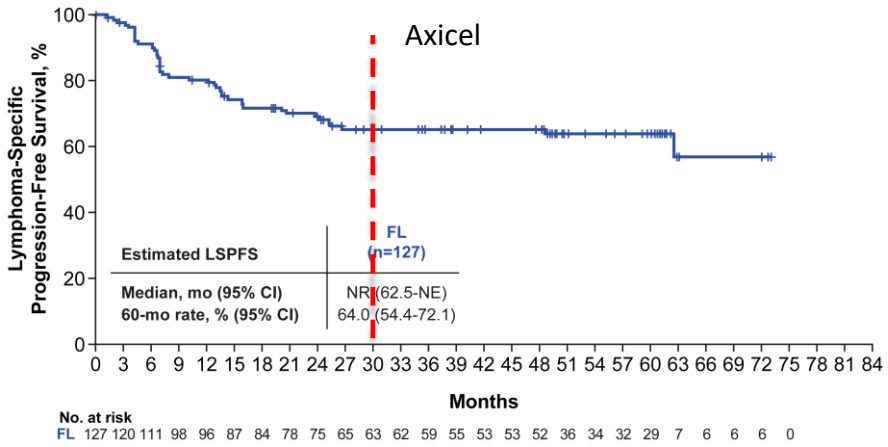
Dreyling M. et al. Blood 2024. Fowler N.H. et al, Nature Med 2022; Jacobson A.C. et al, Lancet Oncol 2022; 5 Neelapu S. et al. JCO 2025

CAR T-cell Can be a Cure for RR FL?

Tisacel



Axicel



Agent and trial	Ph	Pts n	POD24 %	Prior tx median	BT %	V2Vt, days	ORR/CR^ %	Median f-up, mo	PFS, %	OS, %	CRS (any/ gr ≥3) %	ICANS (any/ gr ≥3) %
Tisa-cel (ELARA)[1,2,3]	II	97	63	4 (2-13)	45	46*	86 / 68	53	60mo: 46% (57)	60mo: 74.1%	48/0	4/1
Axi-cel (ZUMA-5)[4,5]	II	124	56	3 (2-4)	4	40	90 / 75	64.6	60mo: 49.8	60mo: 69%	97/8	56/15

Neelapu SS, ASH 2024 abs#864 Schuster S. et al, ASH 2025 abs#468; Thieblemont C et al. Blood. 2024; Jacobson CA, et al. Lancet Oncol. 2022

BsAbs CD20xCD23 in Monotherapy Developed in FL 3L+

Monotherapy CD20xCD3												
Agent and trial	**Ph**	**Administration**	**Pts n**	**POD24 %**	**Prior tx median n**	**ORR (CR), %**	**Follow-up median, mo**	**PFS median, mo**	**OS median, mo**	**CRS (any/ gr ≥3), %**	**ICANS (any/gr≥3), %**	**Infections gr ≥3, %**
Mosunetuzumab (GO29781)[1,2]	II	EV, fixed duration	90	52	3 (2-4)	78 (60)	49.4	24	NR	44/2	5/0	16
Odronextamab (ELM-2)[3,4]	II	EV, Until PD	128	48	3 (2-13)	82 (73)	22.4	20.7	NR	57/1	1/0	32
Epcoritamab[5] (EPCORE-NHL)	I/II	SC, Until PD	214	42	3 (2-4)	82 (62.5)	36	15.4	NR	59/2	6/2	19
Glofitamab[6,7]	I	EV, Fixed duration	53	36	3 (1-12)	81 (70)	NA	NA	NA	67/5	NA	NA

1. Budde L.E., et al. Lancet Oncol 2022. 2. Sehn LH et al, Blood 2025. 3 Kim T.M., et al. Blood 2022. 4 Kim TM. Annals Oncol. 2024; 5. Linton KM, et al Lancet Hematol 2024. 6. Morschhauser F. et al, Blood 2022. 8.Hutchings M. et al, J Clin Oncol 2021*

BsAbs CD20xCD23 in Monotherapy Developed in FL 3L+

Mosu

Pivotal, single-arm, multicenter, Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

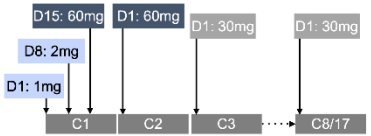
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Primary endpoint: CR by independent review committe (IRC)*
- Secondary endpoints: investigator assessed, ORR, DoR, PFS, OS, TTNT, safety
- **Median follow-up: 37.4 mo**

Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles
- Corticosteroid premedication ev 1 h before each mosu dose at cycle 1 and 2, optional from cycle 3
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



* Response assessed using the International Harmonization Project (Cheson 2007)

Characteristics	Pts, 90 (n)
Median age, years (range)	60 (29-90)
Male, %	61
ECOG 0, %	59
Anna Arbor stage III-IV, %	77
Median line of prior tx, n (range)	3 (2-4)
Refractory to last prior therapy, %	69
POD24, %	52
FLIPI ≥ 2; %	70
Previous CAR T-cell tx, %	3

Epco

TRIAL DESIGN: PIVOTAL EPCORE™ NHL-1 STUDY

Dose expansion

Key inclusion criteria[a]:

- R/R CD20[a] mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide
- FDG-avid disease by PET/CT
- Prior CAR T allowed

Data cutoff: April 21, 2023
Median follow-up: 17.4 mo

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
Treatment until PD[e] or unacceptable toxicity
R/R FL grade 1–3A expansion cohort, N=128

SC injections in minutes

QW | Q2W | Q4W

C1 2 3 4 5 6 7 8 9 10
Wk 0 4 8 12 16 20 24 28 32 36

- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** MRD[d], DOR, TTR, PFS, OS, CR rate, and safety/tolerability

C1 optimization

CRS prophylaxis with dexamethasone 15 mg

C1D22
First full dose: 48 mg

C1D15
SUD 3: 3 mg

C1D8
SUD 2: 0.8 mg

C1D1
SUD 1: 0.16 mg

Recommendations for adequate hydration

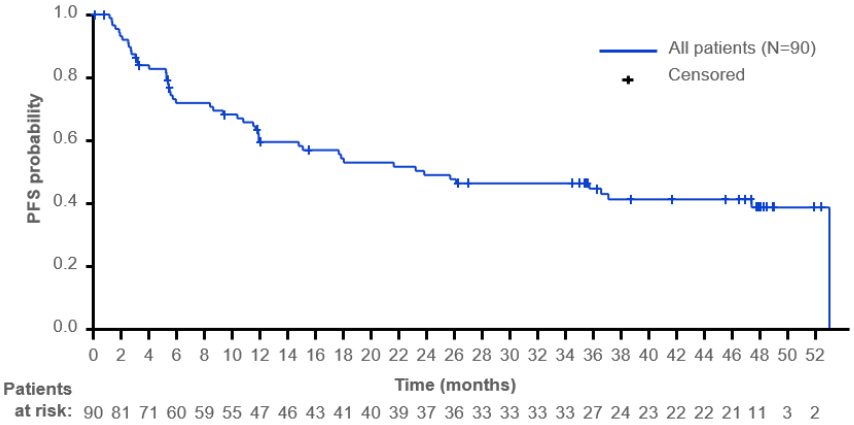
- Hospitalization not mandated in this setting
- **Primary objective:** Assess impact on risk and severity of CRS

Characteristics	Pivotal Cohort (n 128)	Cycle 1 Optimisation Cohort (n 86)
Median age, years (range)	65 (55-72)	64 (55-71)
Male, %	62	57
ECOG 0, %	55	60
Anna Arbor stage III-IV, %	85	79
Median line of prior tx, n (range)	3 (2-4)	2 (2-3)
Double refractory disease, %	70	63
Refractory to last prior therapy, %	69	57
POD24, %	42	42
FLIPI ≥ 2; %	85	77
Previous CAR T-cell tx, %	5	7

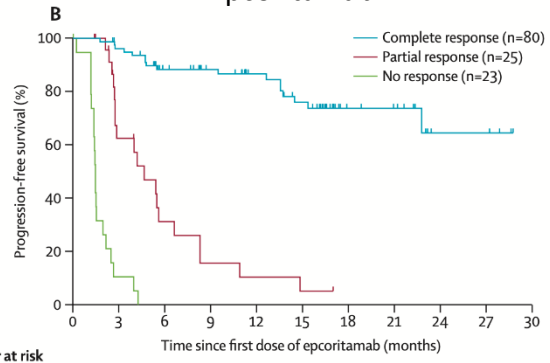
Budde L.E., et al. Lancet Oncol 2022. Sehn LH et al, Blood 2025. Linton KM, et al Lancet Hematol 2024

BsAbs as single Agent in RR FL Show High Efficacy

Mosunetuzumab



Epcoritamab

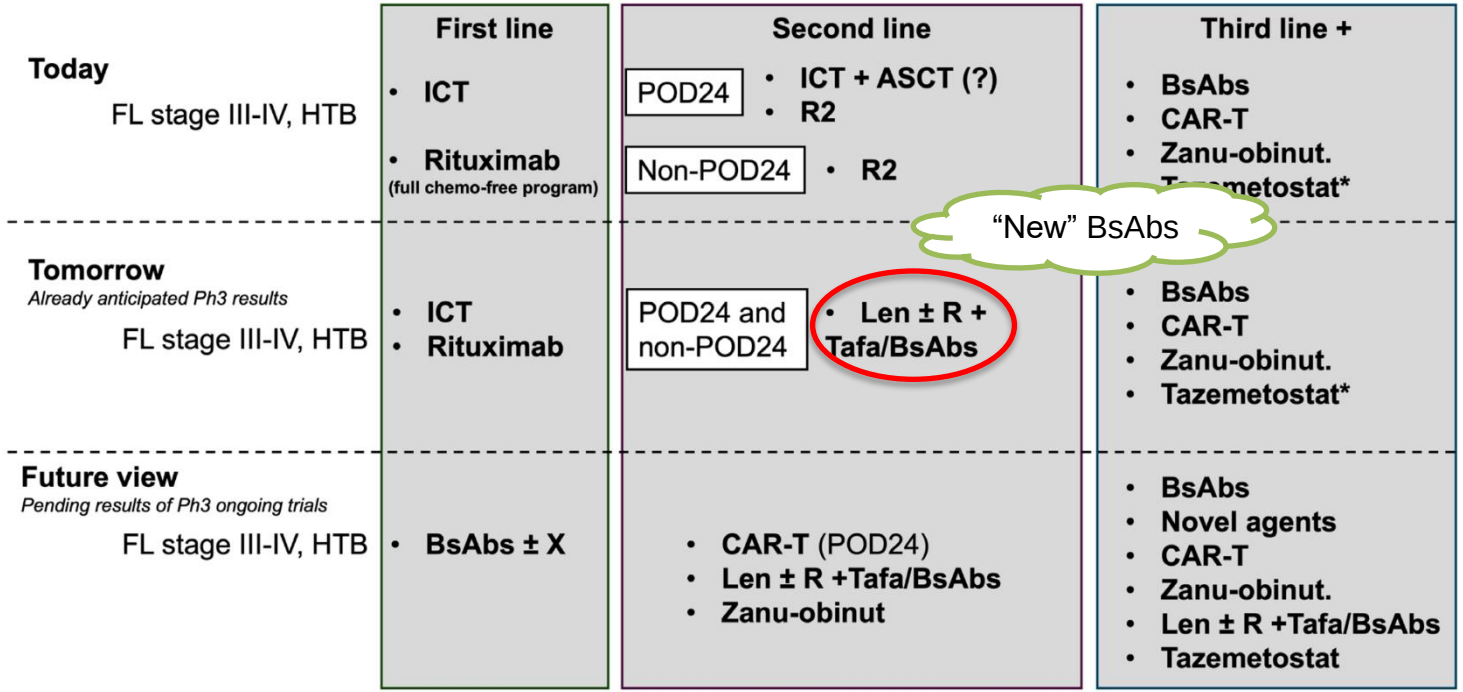


Number at risk number censored)											
Complete response	80	75	61	54	41	34	14	12	4	4	0
	(0)	(2)	(10)	(17)	(29)	(31)	(50)	(52)	(59)	(59)	(63)
Partial response	25	13	6	3	2	1	0	0	0	0	0
	(0)	(4)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(6)
No response	23	2	0	0	0	0	0	0	0	0	0
	(0)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

Agent and trial	Ph	Administration	Pts n	POD24 %	Prior tx media n	ORR (CR), %	Follow-up median, mo	PFS median, mo	OS median, mo	CRS (any/ gr ≥3), %	ICANS (any/gr≥3), %	Infections gr ≥3, %
Mosunetuzumab (GO29781)[1,2]	II	EV, fixed duration	90	52	3 (2-4)	78 (60)	49.4	24	NR	44/2	5/0	16
Epcoritamab[5] (EPCORE-NHL)	I/II	SC, Until PD	214	42	3 (2-4)	82 (62.5)	36	15.4	NR	59/2	6/2	19

Budde L.E., et al. Lancet Oncol 2022. Sehn LH et al, Blood 2025. Linton KM, et al Lancet Hematol 2024

Conclusions and Next Steps of CART and BsAbs in FL



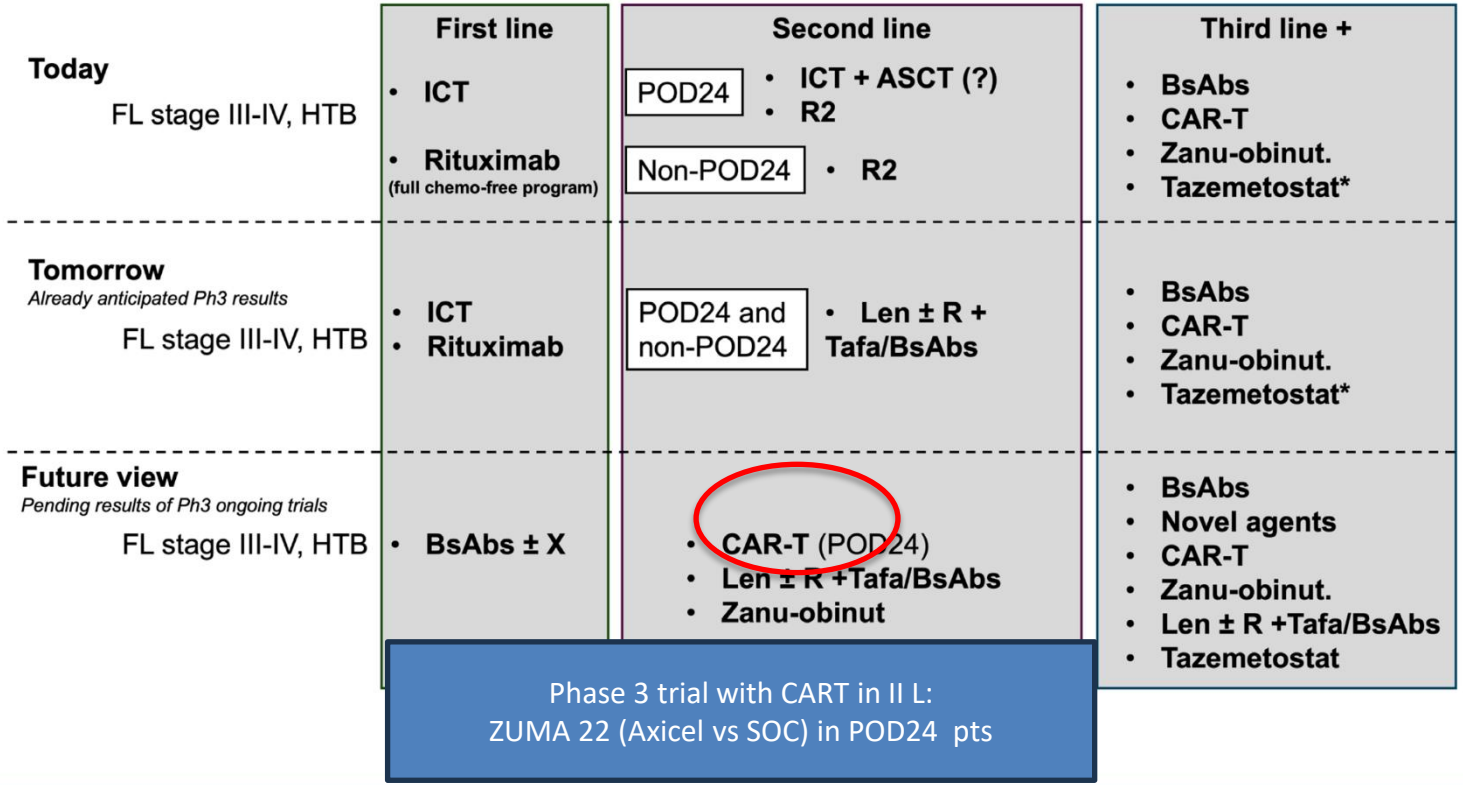
2L Ongoing Ph 3 Trial with BsAbs and Lena as Backbone

CAR T-cell therapies		anti-CD20xCD3 bsAbs			anti-CD19	Other targeted therapies	
ZUMA-22[1]	TRANSFORM FL[2]	EPCORE® FL-1[3]	Celestimo[4]	OLYMPIA-5[5]	inMIND[6]	SYMPHONY-1[7]	MAHOGANY[8]
axi-cel	liso-cel	epcoritamab + R[2]	mosunetuzumab + len	odronextamab + len	tafasitamab + R[2]	tazemetostat + R[2]	zanubrutinib + R/O
						vs	vs
Comparator: R-chemo or R[2]							
Primary Endpoint(s): PFS	PFS					PFS	PFS

Data from Ph 2 Trial:
Epcore NHL2 – Arm 2 (Falchi L et al Blood 25)
Phase 1b CO41942 (Morschhauser et al, ASH 2021)

Adapted from: 1. NCT05371093. 2. NCT06515990. 3. NCT05409066. 4. NCT04712097. 5. NCT06149286. 6. NCT04080052. 7. NCT04224493. 8. NCT05100862.

Conclusions and Next Steps of CART and BsAbs in FL



Conclusions and Next Steps of CART and BsAbs in FL

	First line	Second line	Third line +
Today FL stage III-IV, HTB	• **ICT** • **Rituximab** (full chemo-free program)	POD24: • **ICT + ASCT (?)** • **R2** Non-POD24: • **R2**	• **BsAbs** • **CAR-T** • **Zanu-obinut.** • **Tazemetostat***
Tomorrow *Already anticipated Ph3 results* FL stage III-IV, HTB	• **ICT** • **Rituximab**	POD24 and non-POD24: • **Len ± R + Tafa/BsAbs**	• **BsAbs** • **CAR-T** • **Zanu-obinut.** • **Tazemetostat***
Future view *Pending results of Ph3 ongoing trials* FL stage III-IV, HTB	• **BsAbs ± X**	• **CAR-T** (POD24) • **Len ± R +Tafa/BsAbs** • **Zanu-obinut**	• **BsAbs** • **Novel agents** • **CAR-T** • **Zanu-obinut.** • **Len ± R +Tafa/BsAbs** • **Tazemetostat**

Selected Ph 3 Study Design in 1L FL

anti-CD20xCD3 bsAbs				anti-CD19xCD3 bsAb
EPCORE FL-2[1]	**OLYMPIA-1[2*]**	**OLYMPIA-2[3*]**	**MorningLyte[4]**	**SOUNDTRACK-F1[5]**
Induction:  **Epcor + R²**	 **Odron monotherapy**	 **Odron + CHOP/CVP**	 **Mosun + Len**	 **AZD0486 + R**
Maintenance:  ± epcor maintenance	 + odron maintenance	 ± odron maintenance	 + mosun maintenance	 + R maintenance
vs	vs	vs	vs	vs
Induction: • R/G-CHOP • R/G-Benda • R²	• R-CHOP/CVP • R-Benda	• R-CHOP	• R/G-CHOP • R/G-Benda	• R-CHOP/CVP • R/Benda
Maintenance:  + R maintenance	 + R maintenance	 + R maintenance	 + R maintenance	 + R maintenance (with R-CHOP/CVP only)
Primary Endpoint(s): CR30, PFS	CR30	CR30	PFS	PFS

Adapted from: 1. NCT06191744. 2. NCT06091254. 3. NCT06097364. 4. NCT06284122. 5. NCT06549595

IRCCS Azienda Ospedaliero-Universitaria di Bologna
Dipartimento di Scienze Mediche e Chirurgiche – Università di Bologna

Istituto di Ematologia "Lorenzo e Ariosto Seràgnoli"
Diagnosi e terapie dei linfomi e delle sindromi linfoproliferative croniche
Prof Pier Luigi Zlnzani

Gianmarco Bagnato
Alessandro Broccoli
Matteo Carella
Beatrice Casadei
Simona Citro
Flvaia D'Aniello
Alessandro Desiderio
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