

Le cure palliative precoci in EMATO-ONCOLOGIA: la nuova risposta ai bisogni di pazienti e caregivers

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 **fondazione GIMEMA onlus**
per la promozione e lo sviluppo della ricerca scientifica
sulle malattie ematologiche. **FRANCO MANDELLI**

Si ringrazia per il supporto



SIE
Società Italiana
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Con il patrocinio di

LE CURE PALLIATIVE PRECOCI IN
EMATO-ONCOLOGIA:
la nuova risposta ai bisogni di pazienti e caregivers

19 maggio 2023

Roma, Hotel Donna Camilla Savelli



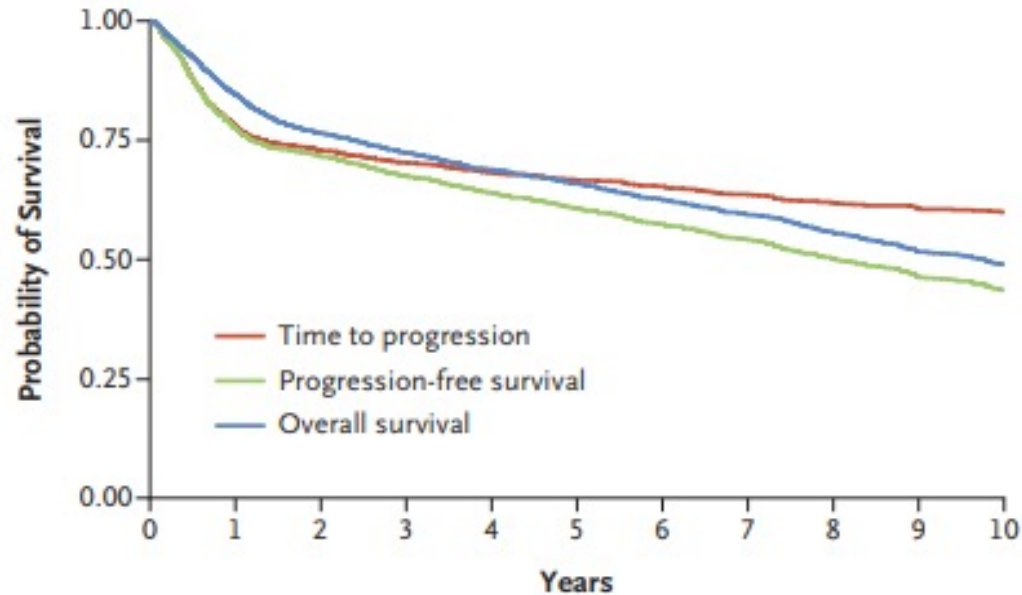
Disclosures of Alice Di Rocco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche			X		X		
Janssen			X				
Takeda			X			X	
Incyte			X				
Novartis					X		
Kite-Gilead			X		X	X	
Eli-Lilly					X		
Abbvie			X				



Relapsed/refractory DLBCL: the size of the issue

Outcomes of Patients with DLBCL



**35-40% failures after
R-CHOP first line therapy**

No. at Risk

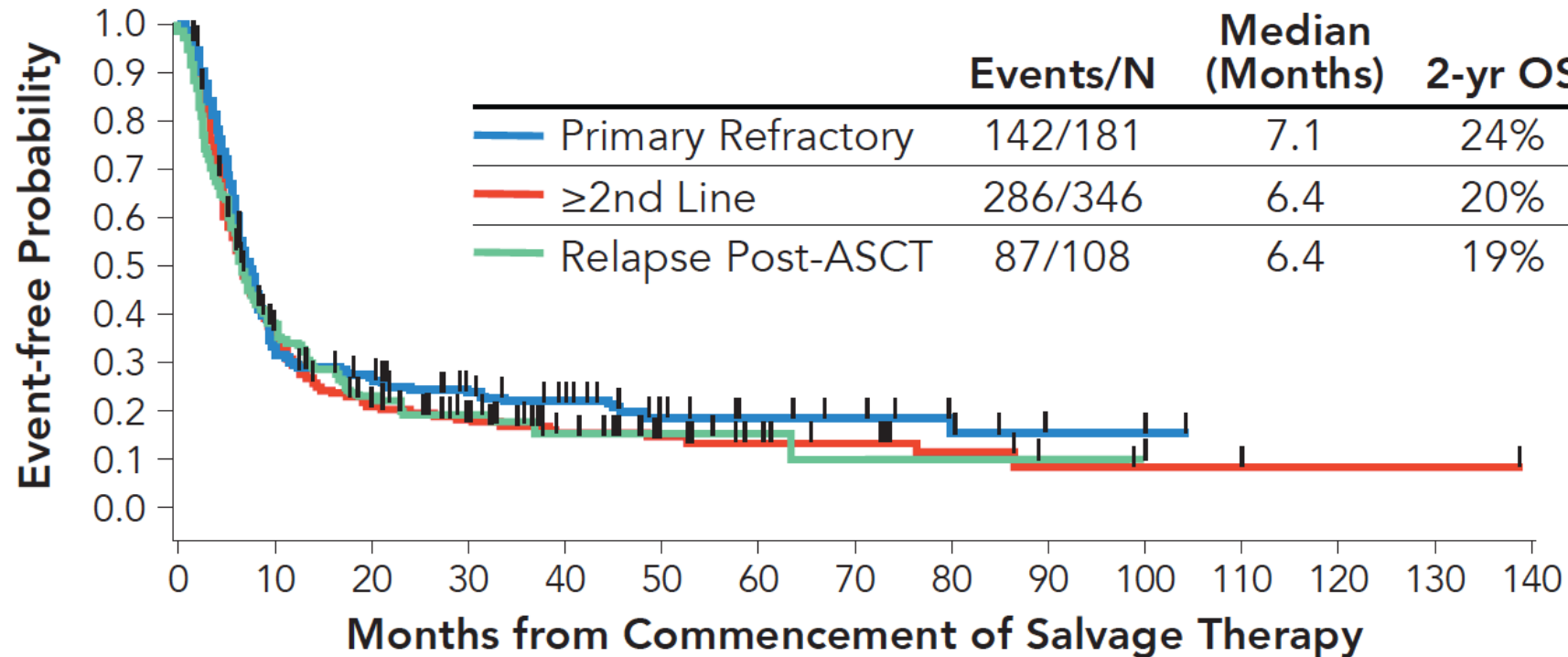
Time to progression	3082	2133	1775	1446	1236	1048	830	700	585	468	391
Progression-free survival	3082	2132	1774	1445	1235	1047	829	699	584	467	390
Overall survival	3082	2336	1900	1558	1338	1140	911	767	647	519	437

What outcome can we expect in relapsed/refractory DLBCL?

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,¹ Sattva S. Neelapu,² Umar Farooq,³ Eric Van Den Neste,⁴ John Kuruvilla,¹ Jason Westin,² Brian K. Link,³ Annette Hay,¹ James R. Cerhan,⁵ Liting Zhu,¹ Sami Boussetta,⁴ Lei Feng,² Matthew J. Maurer,⁵ Lynn Navale,⁶ Jeff Wiezorek,⁶ William Y. Go,⁶ and Christian Gisselbrecht⁴



ORR= 26%
CR-rate= 7%

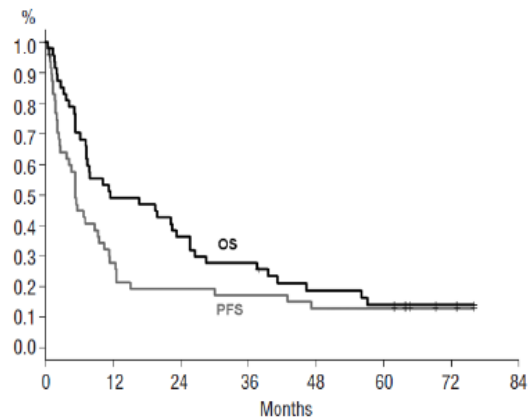
**Median OS
6.3 months**

RR-DLBCL is an unmet clinical need : low activity of standard salvage therapy

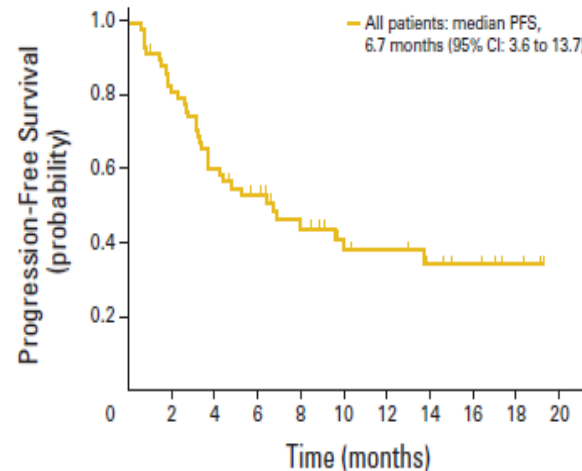
Unsatisfactory outcome among patients non-eligible to ASCT

REGIMEN	N	Median age	ORR%	CR %	PFS	Reference
R-GEMOX	32	65	78	50	Median 9 mo	Corazzelli G, Cancer Oncol 2009
R-Bendamustine	55	76	50	28	Median 8.8 mo	Arcari A, Leuk Lymphoma 2015
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Oncol 2012
Lenalidomide	49	65	35	12	Median 4 mo	Wiernik PH, JCO 2008

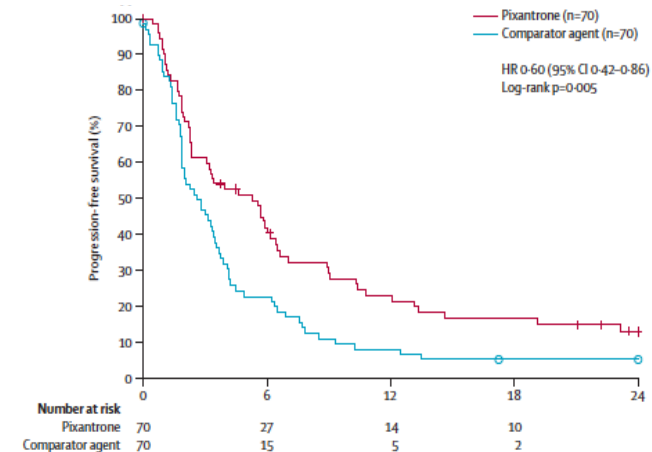
R-GemOx



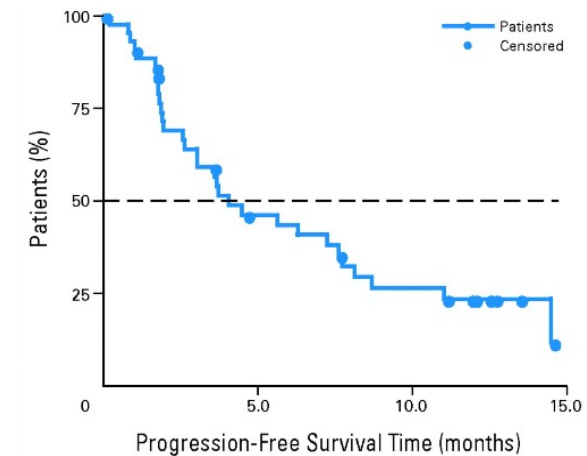
R-bendamustine



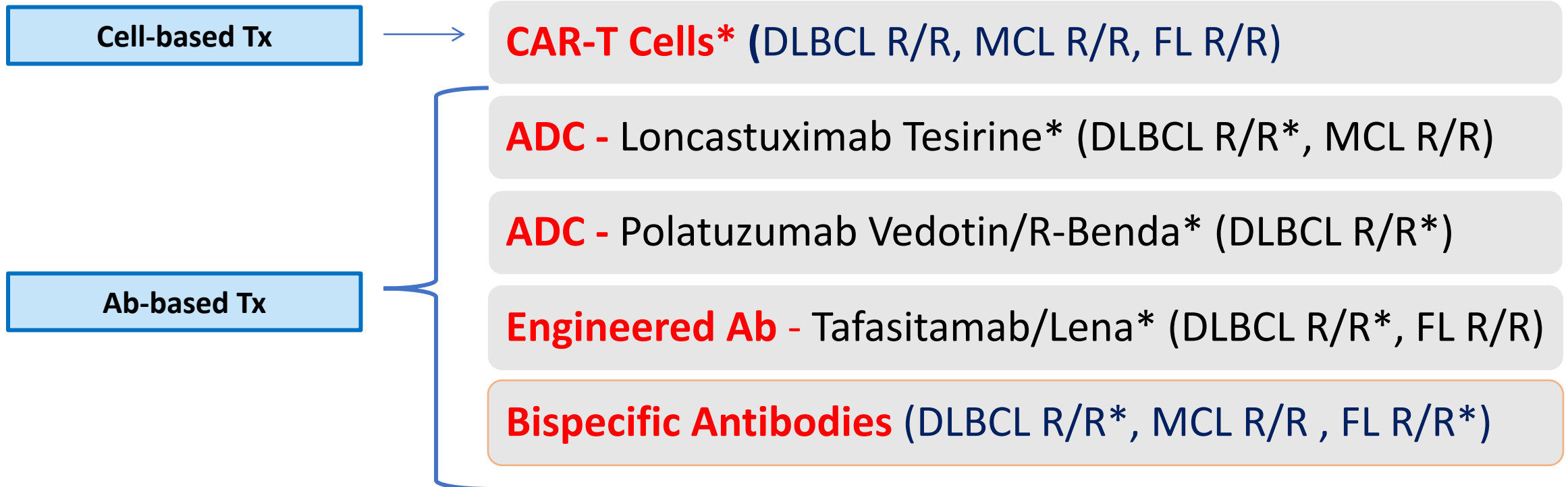
Pixantrone



Lenalidomide

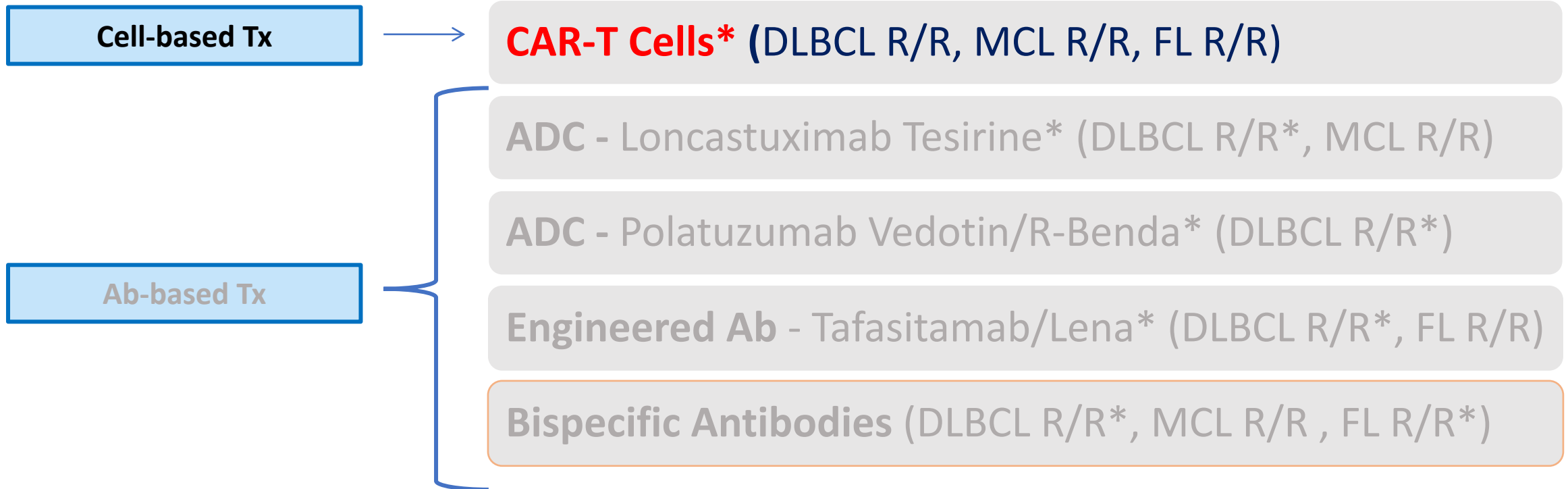


Emerging therapies for R/R B-NHL: a busy space



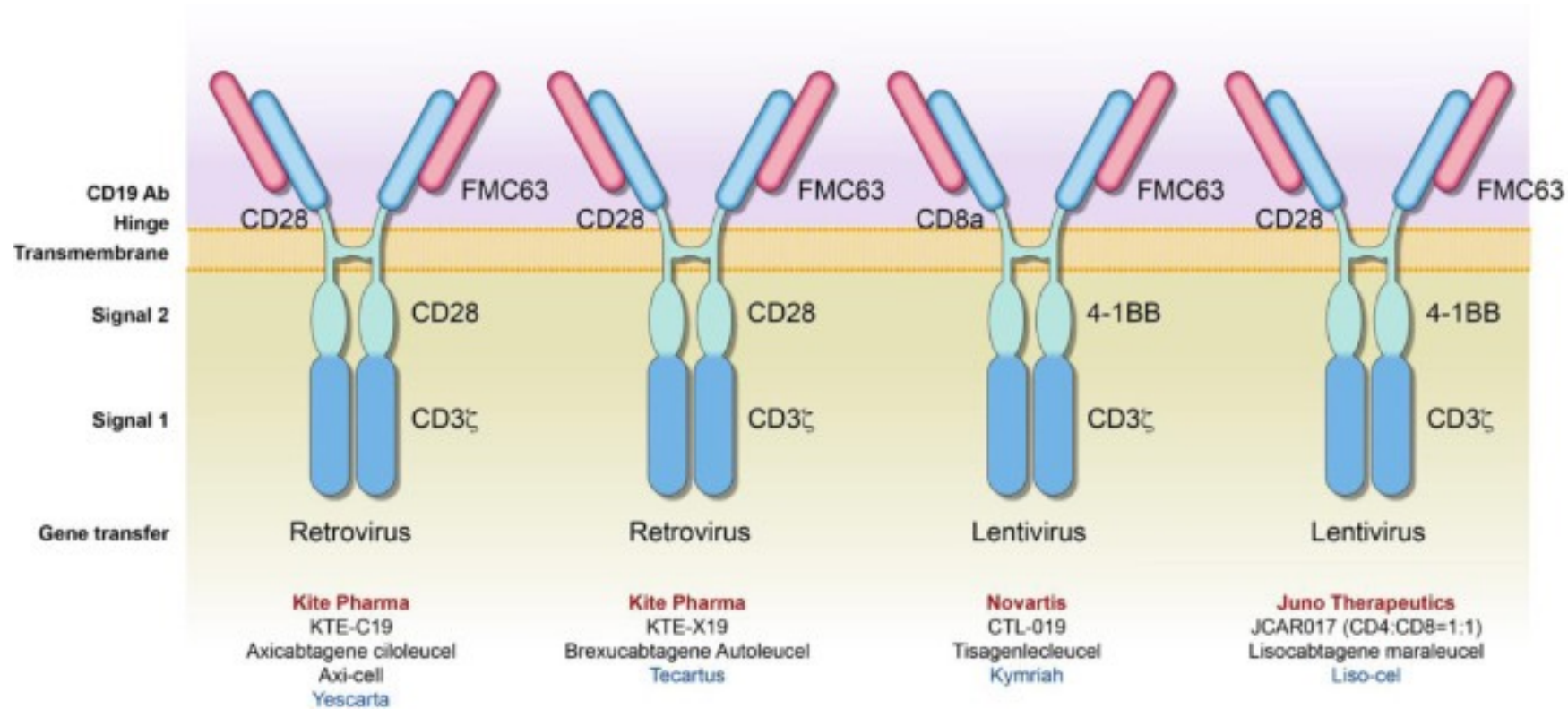
* FDA/EMA approved

Emerging therapies for R/R B-NHL: a busy space



* FDA/EMA approved

CAR T-cells anti CD 19



Leucemia Acuta
Linfoblastica B

-3 linea

Linfomi B aggressivi

-3 linea
-2 linea

Linfoma mantellare

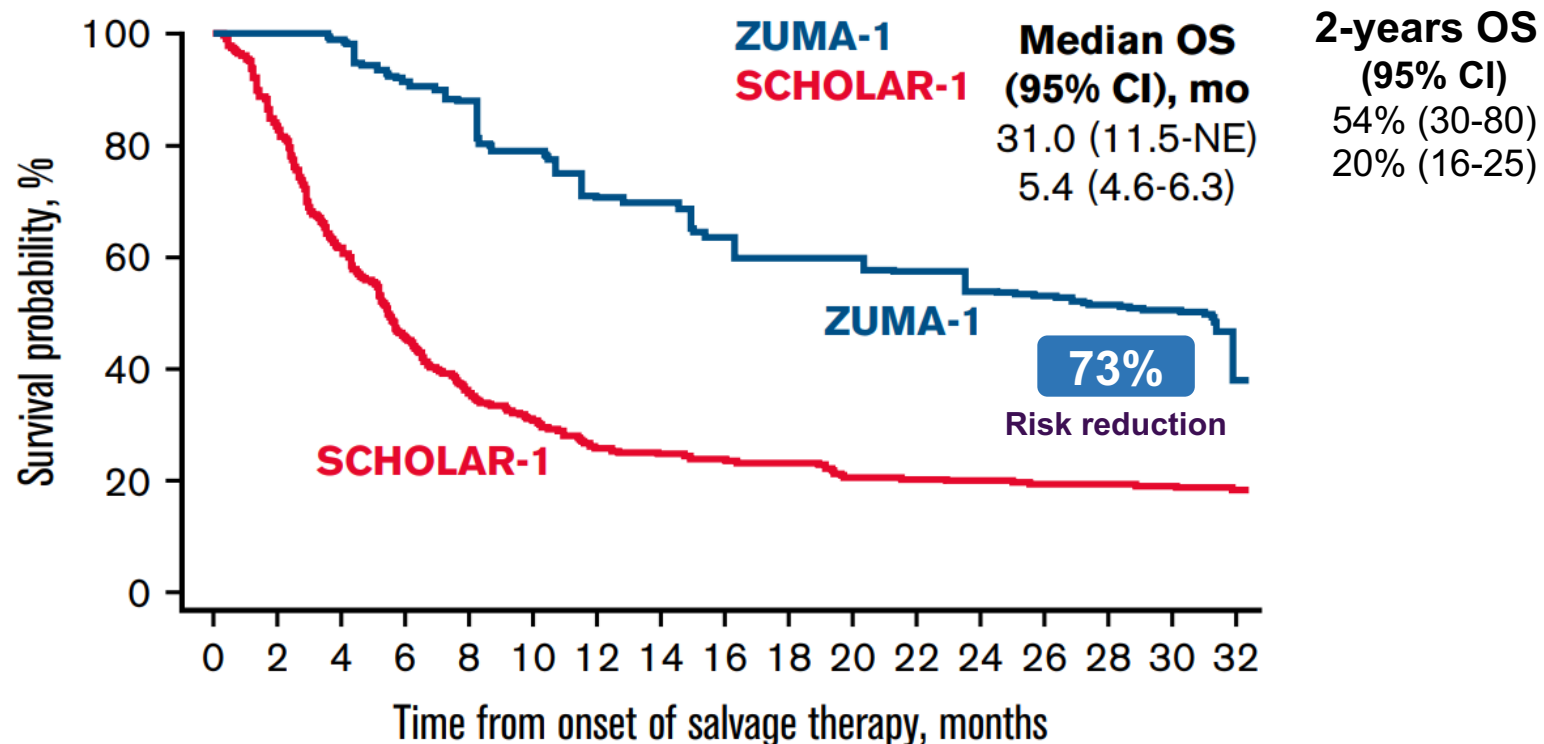
-3 linea

Linfoma follicolare

-3 linea
-4 linea

How has CAR-T therapy improved survival for patients with R/R-DLBCL

Retrospective and comparative analysis of confounder-adjusted OS between ZUMA1 (axi-cel) vs SCHOLAR-1 (SOC)



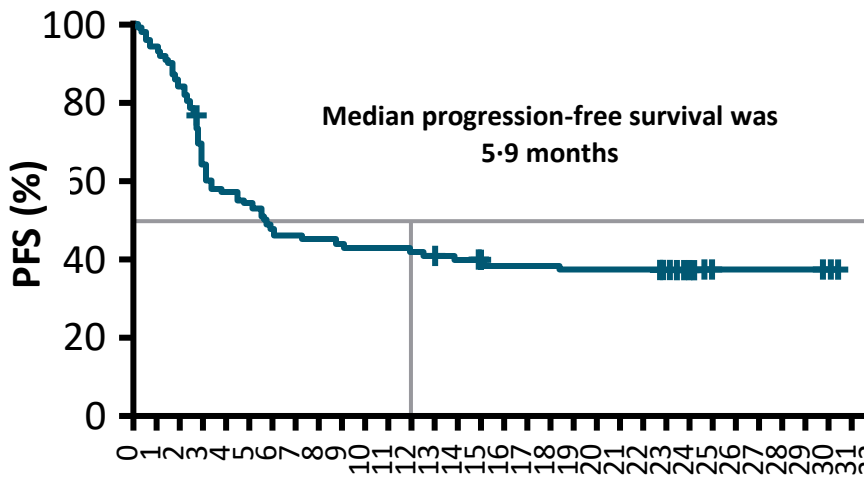
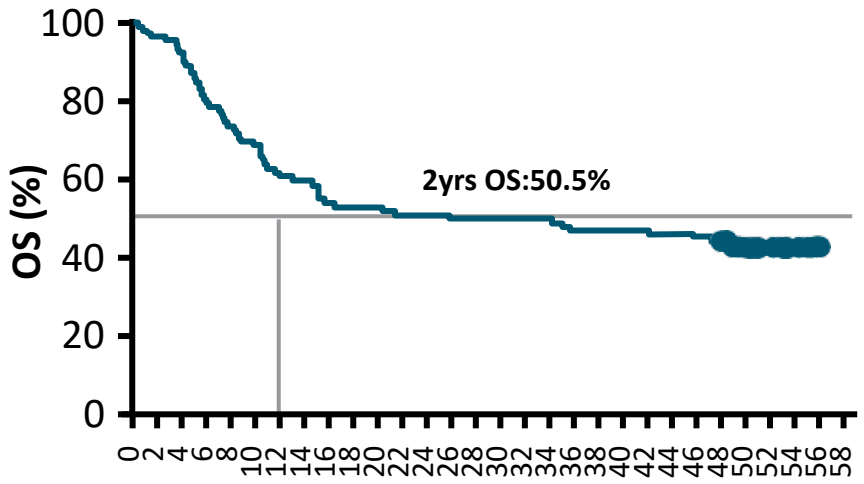
- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

- N = 108
- ORR = 82%; CR rate = 54%
- Median OS = >18 months

Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL

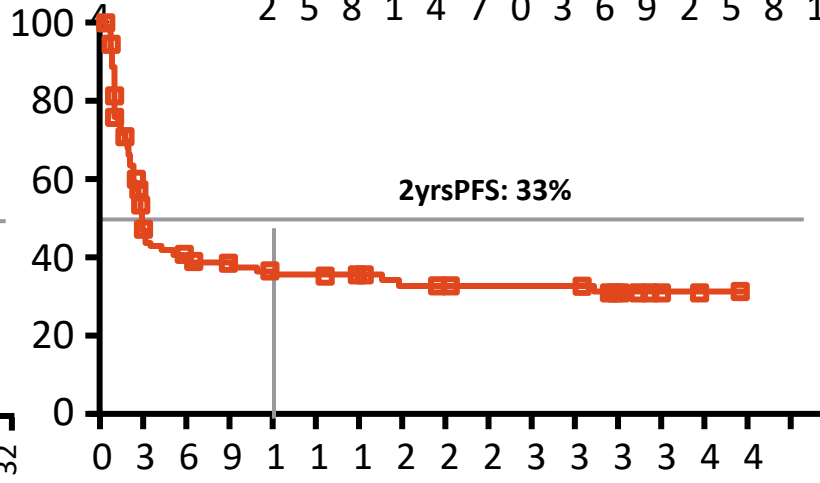
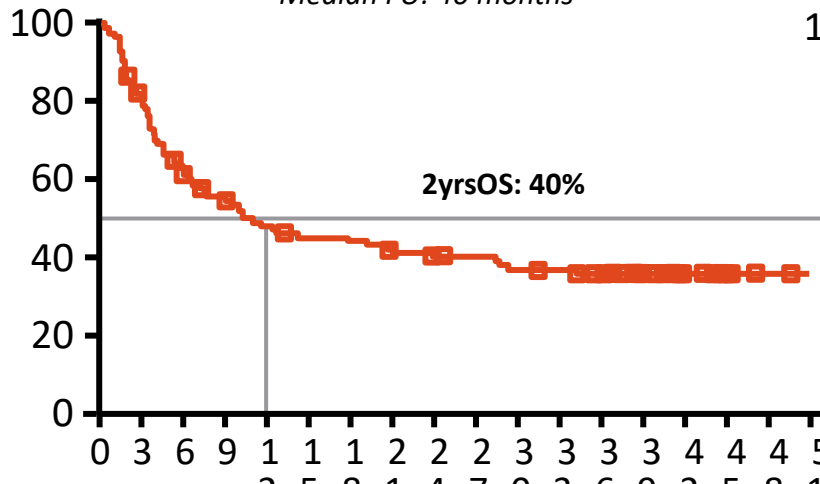
ZUMA-1
Axicabtagene Ciloleucel

Median FU: 27.1 months



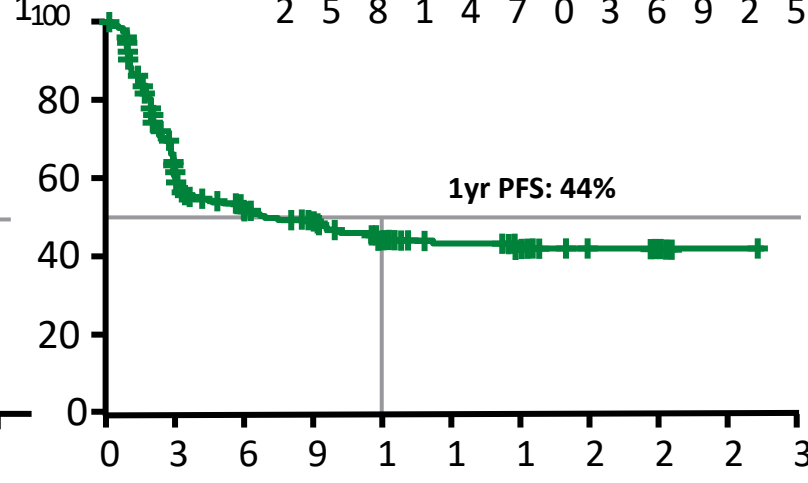
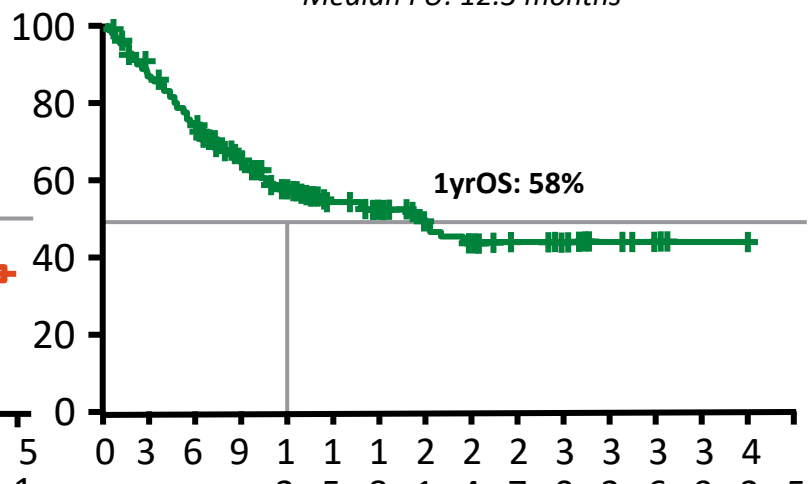
JULIET
Tisagenlecleucel

Median FU: 40 months



TRANSCEND NHL 001
Lisocabtagene Maraleucel

Median FU: 12.3 months

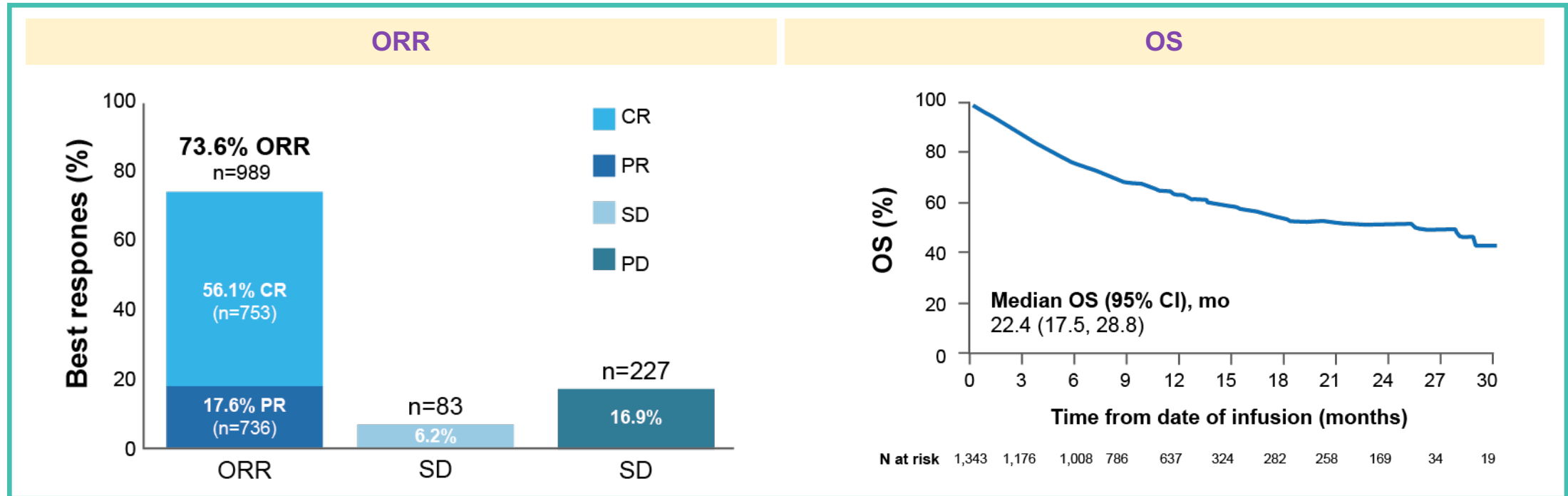


Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

Real-world outcomes for patients treated with Axi-cel in the US

CIBMTR registry: 79 centers analysis from October 2017 to August 2020 (N= 1343)

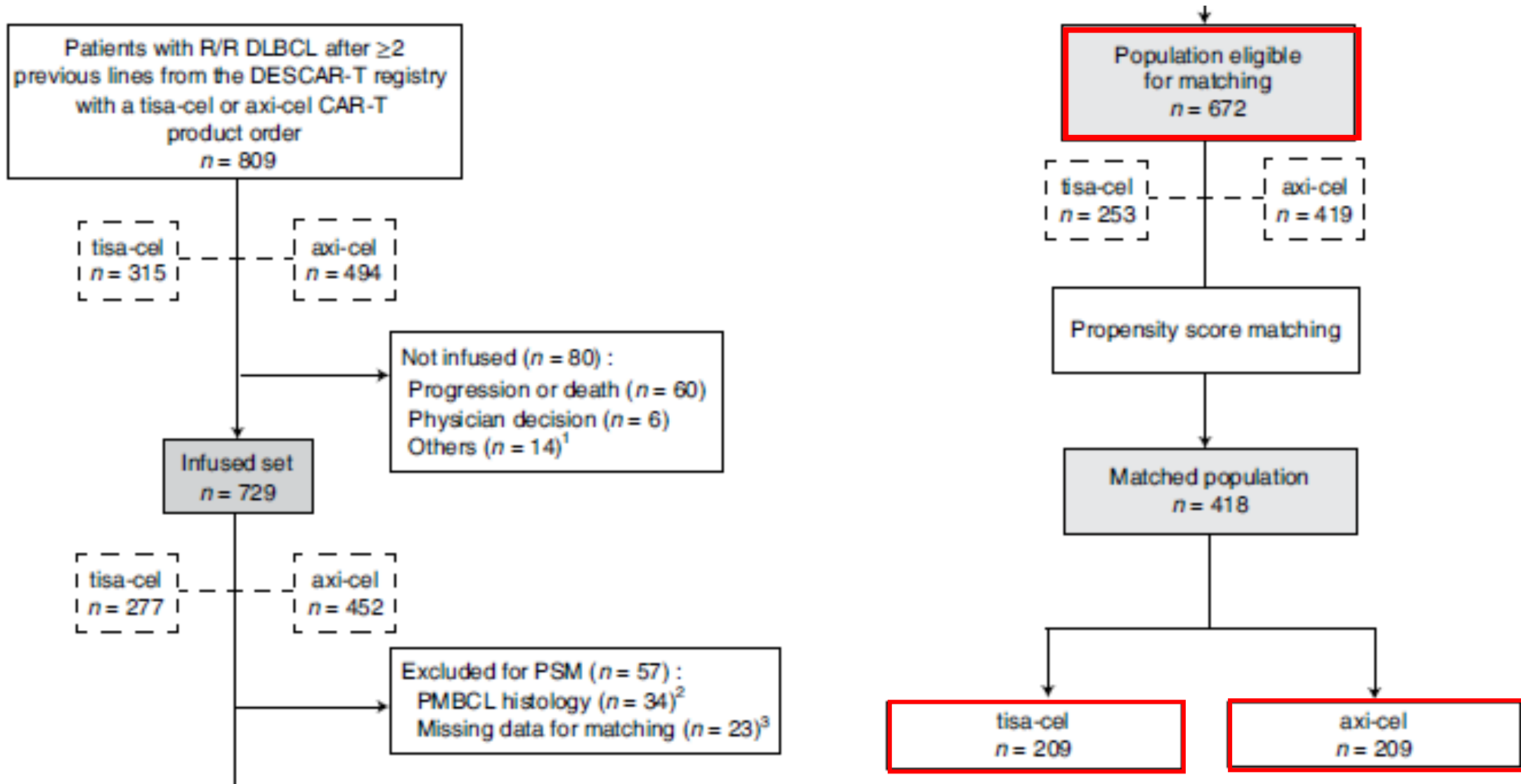
682 patients (51%) had ECOG ≥ 2 and/or comorbidities that would have made them ineligible for ZUMA-1 trial



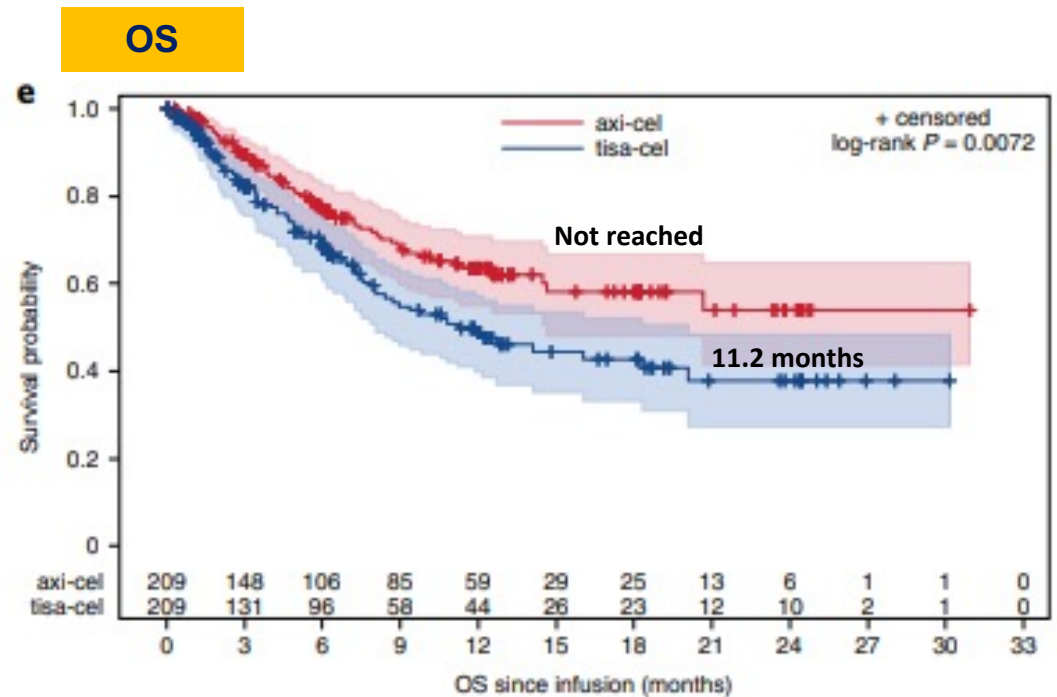
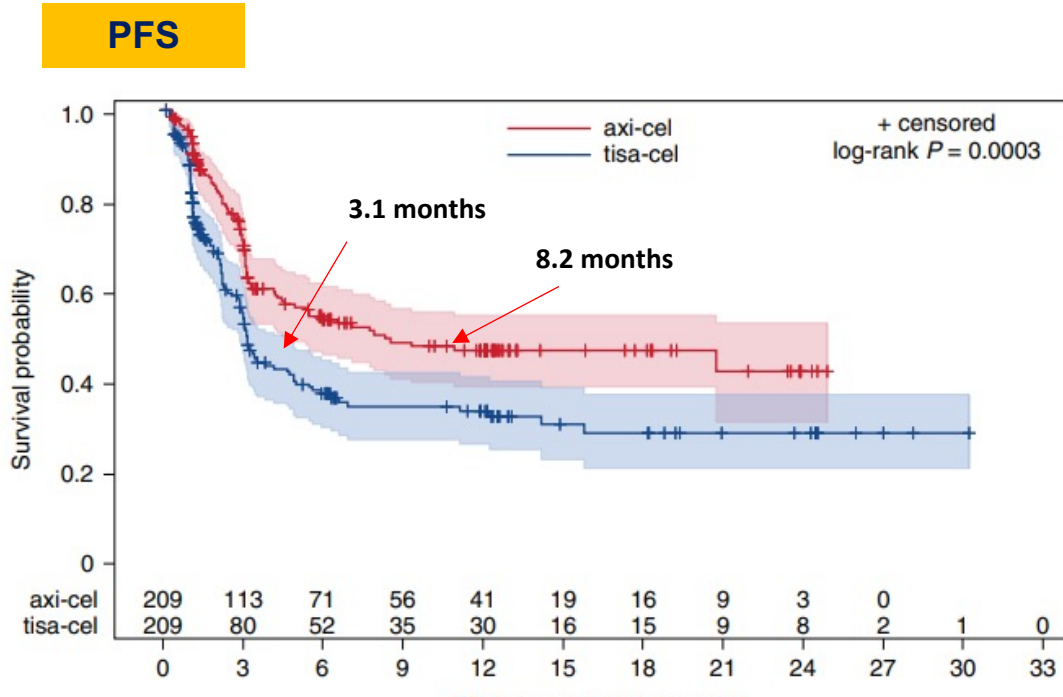
• CRS Grade ≥ 3 = 3.8% and ICANS ≥ 3 = 25%

- **Age ≥ 65 years did not have an impact on survival** (HR 1.05, 95% CI, 0.88-1.26), although it was associated with CRS (OR 1.42, 95% CI, 1.03-1.96) and ICANS (OR 1.78, 95% CI, 1.39-2.28)
- **ECOG significantly impacted all efficacy outcomes**

Real-world outcomes for patients treated with CAR T-cell therapy in France



Real-world outcomes for patients treated with CAR T-cell therapy in France



Median FU: 13 months

Table 3 | Toxicity after CAR T infusion according to CAR T product in the PSM cohorts

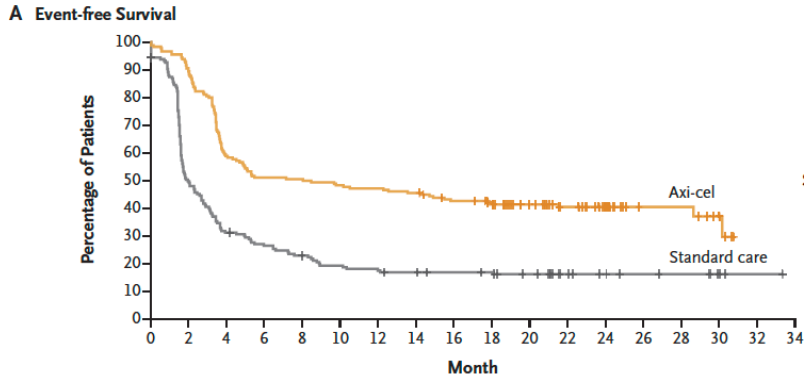
	axi-cel		tisa-cel		<i>P</i>
	<i>n</i> = 209		<i>n</i> = 209		
CRS of any grade	180	(86.1%)	158	(75.6%)	0.006
Grade 1-2	169	(80.9%)	139	(66.5%)	<0.001
Grade ≥3	11	(5.3%)	19	(9.1%)	0.130
ICANS of any grade	102	(48.8%)	46	(22.0%)	<0.001
Grade 1-2	73	(34.9%)	40	(19.1%)	<0.001
Grade ≥3	29	(13.9%)	6	(2.9%)	<0.001
Cytopenia of any grade at M1	135	(64.6%)	82	(39.2%)	<0.001

Randomized Phase 3 Trials CART-cells vs ASCT 2L RR-DLBCL

ZUMA-7

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

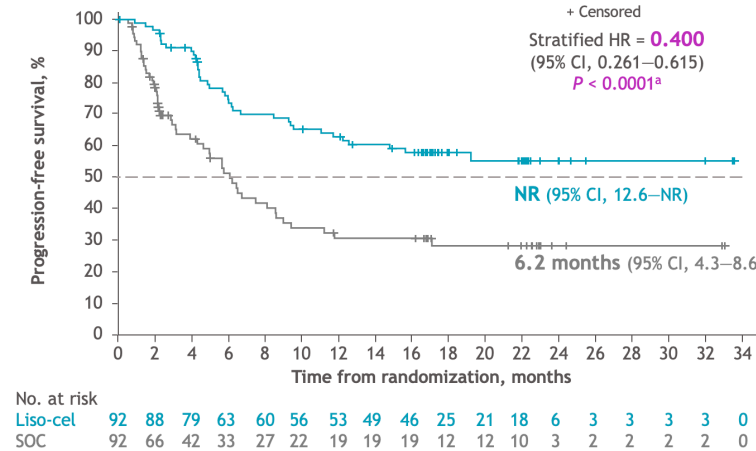
F.L. Locke, NEJM, 386:640, 2022



Transform

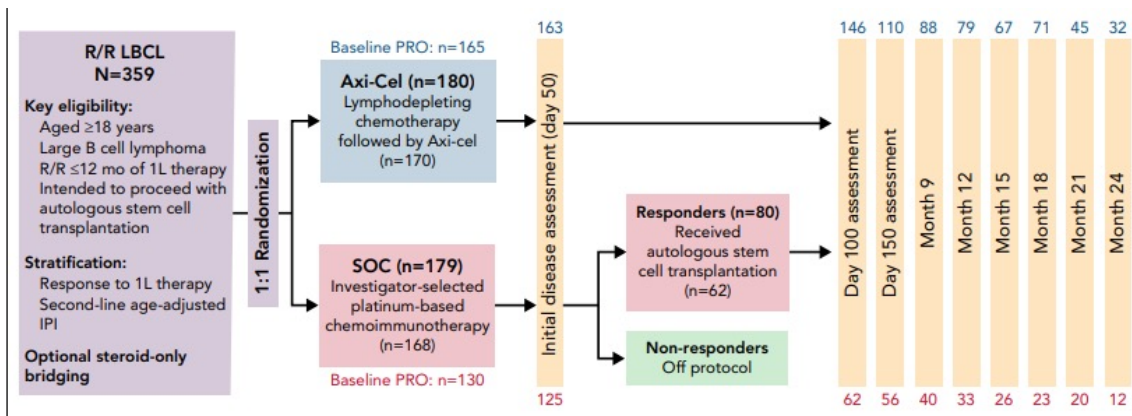
Liso-Cel as second line therapy for LBCL

Kamdar, Lancet, 399:2294, 2022



18-month PFS rate	
Liso-cel	SOC
58.2%	28.8%
(95% CI, 47.7–68.7)	(95% CI, 17.7–40.0)
Median follow-up: 17.5 months	

QoL in CAR-T trials



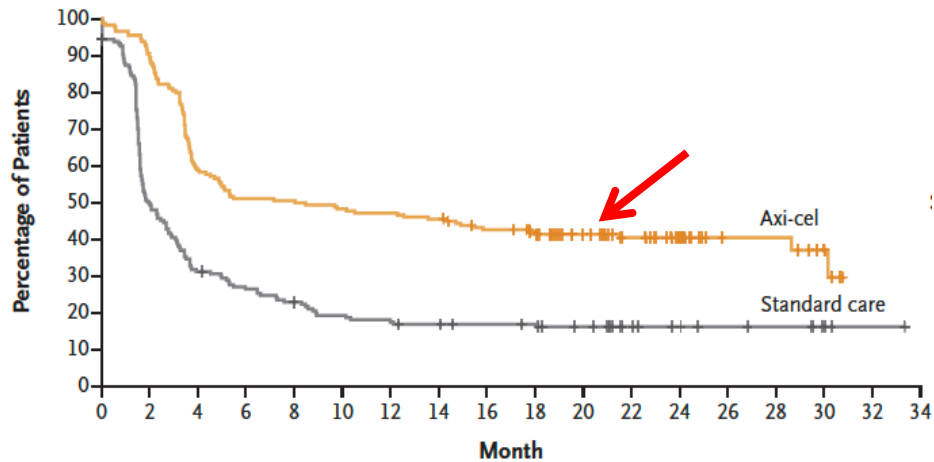
Treatment with axi-cel resulted in clinically meaningful and statistically significant improvements in quality of life and an earlier return to baseline functioning compared with salvage chemotherapy followed by ASCT.

Preliminary results from the TRANSFORM study reported favorable improvement in most PROs with liso-cel compared with salvage chemotherapy followed by ASCT

Diminishing Role of ASCT: CORAL study

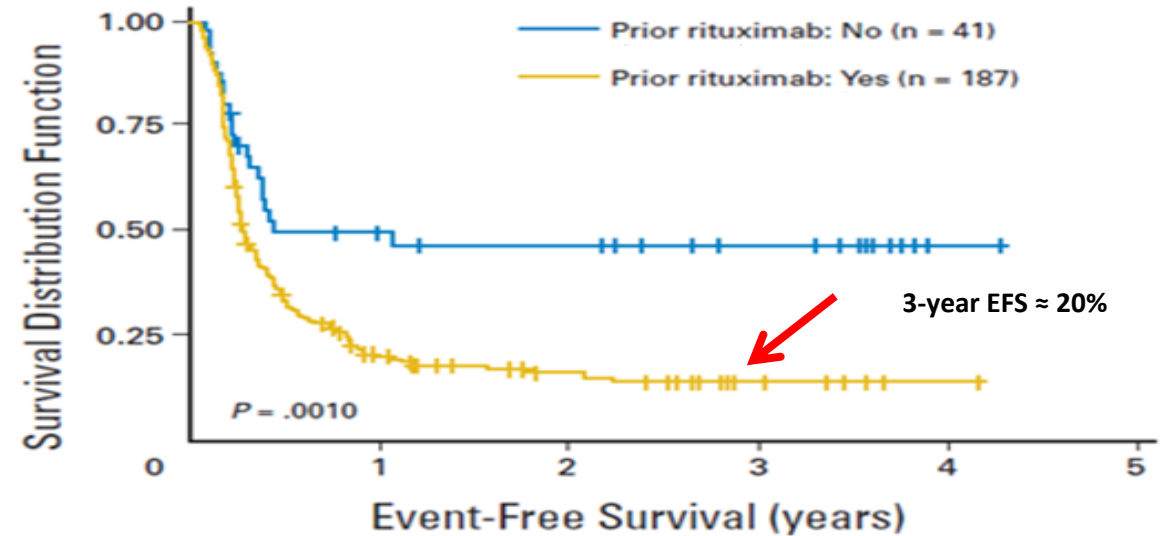
Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

A Event-free Survival



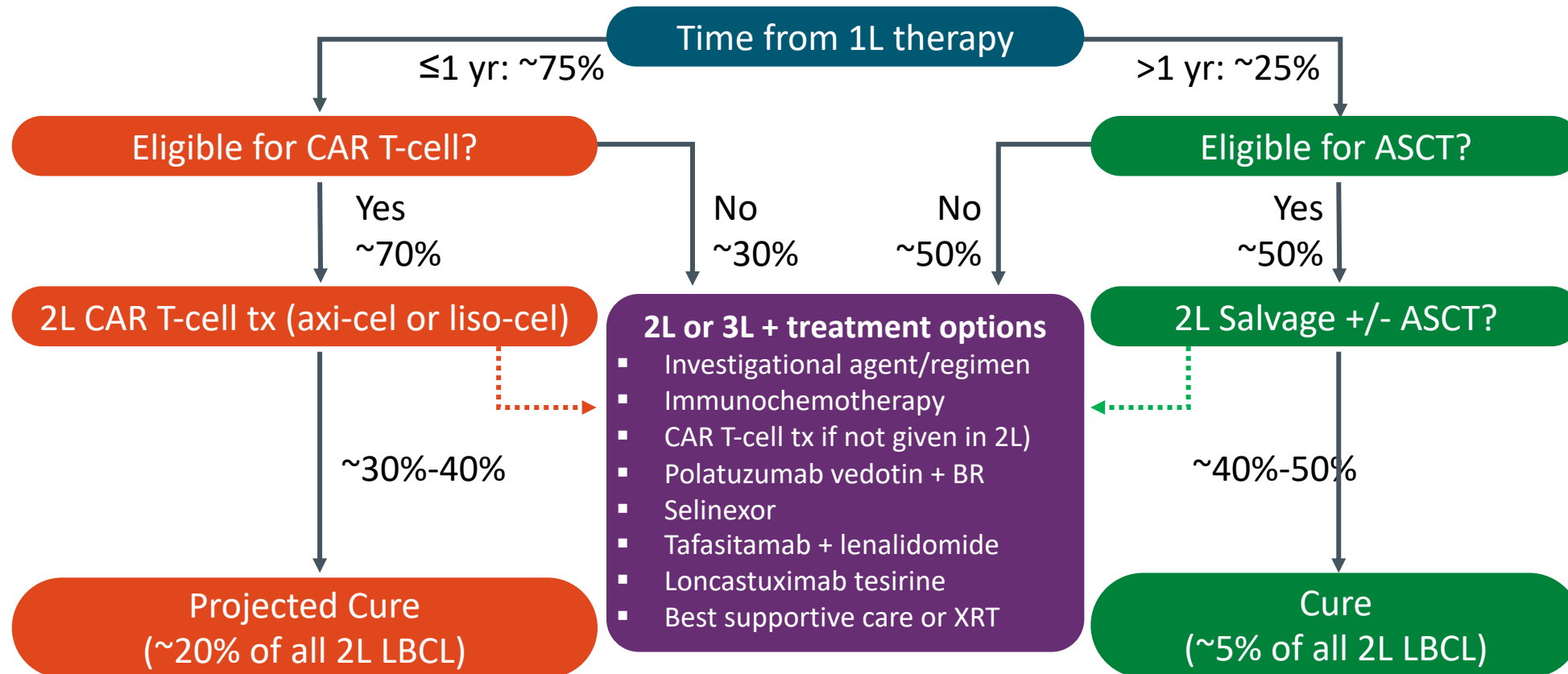
No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6		
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

EFS for rituximab treatment + relapse <12 months after diagnosis



CD19-Targeted CAR T-Cell Therapy Has Dichotomized the Management of R/R DLBCL

Algorithm for Second-line Therapy of LBCL



Take Home messages

- Relapsed/refractory DLBCL (RR-DLBCL) treated with **standard CHT-ASCT** have a poor survival
- New emerging therapy are changing the management of R/R DLBCL
- CAR T therapy in lymphoma appears to lead to long lasting remissions especially for patients with Complete Remission
- CAR-T in second line is superior to SOC in R/R DLBCL
- PROs from ZUMA7 and TRANSFORM demonstrated that CAR-T therapy is better tolerated than SOC

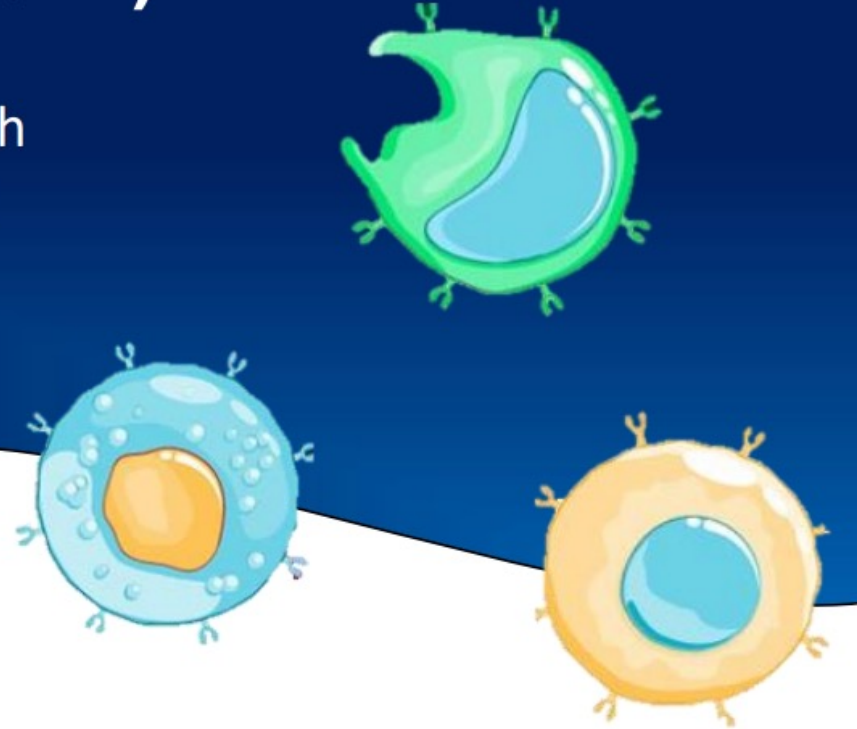
How do we translate the improved efficacy and tolerability in clinical trials to benefiting patients with relapsed or refractory large B-cell lymphoma in the real world?



fondazione GIMEMA ^{onlus}
per la promozione e lo sviluppo della ricerca scientifica
sulle malattie ematologiche. FRANCO MANDELLI

GIMEMA CAR-T Quality of Life (QoL)

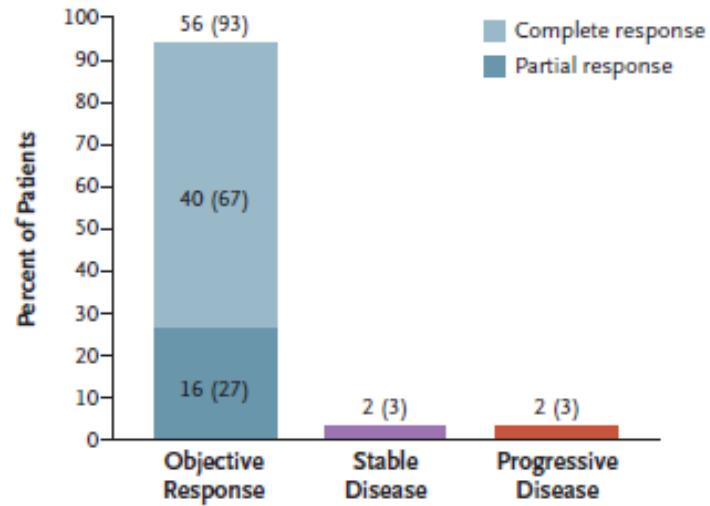
Health-Related Quality of Life Outcomes in Patients with
Aggressive B-Cell Lymphomas treated with CAR-T Cell
Therapy in Real Life:
A Multicenter Prospective Observational Study



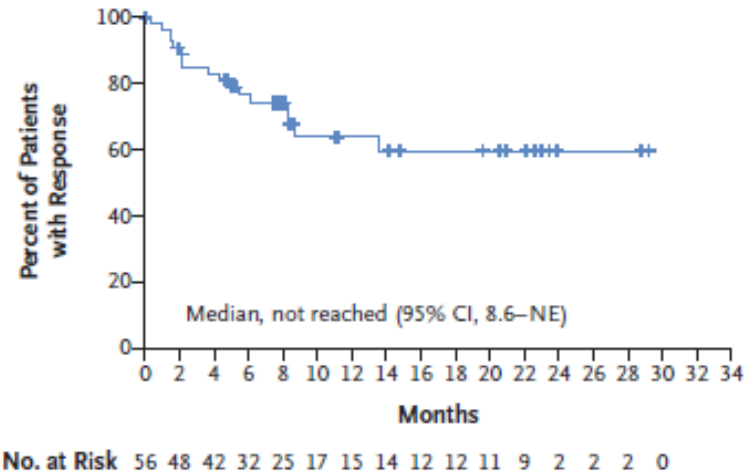
...Recruiting...

R/R MCL Brexucabtagene autoleucel ZUMA 2: phase 2 study

A Best Response



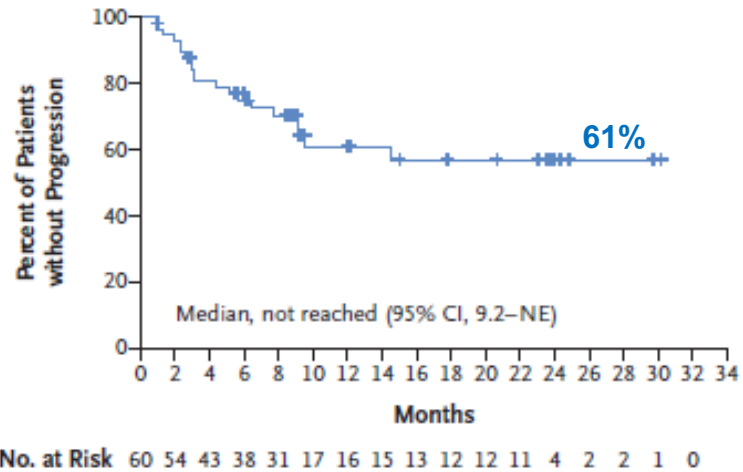
B Duration of Response



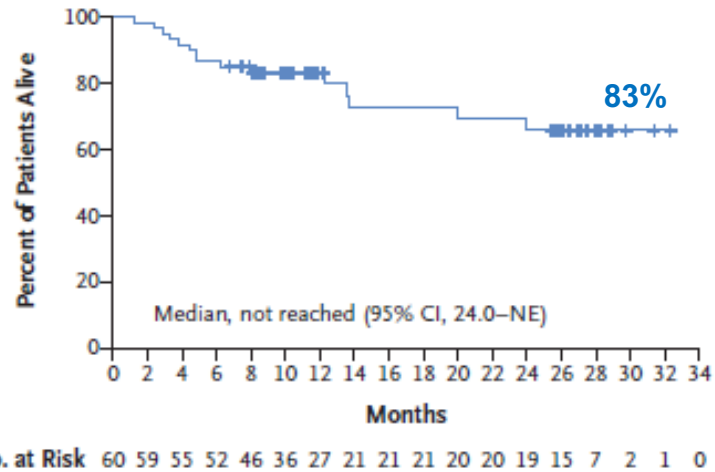
Median follow up:
12.3 months

74 patients enrolled

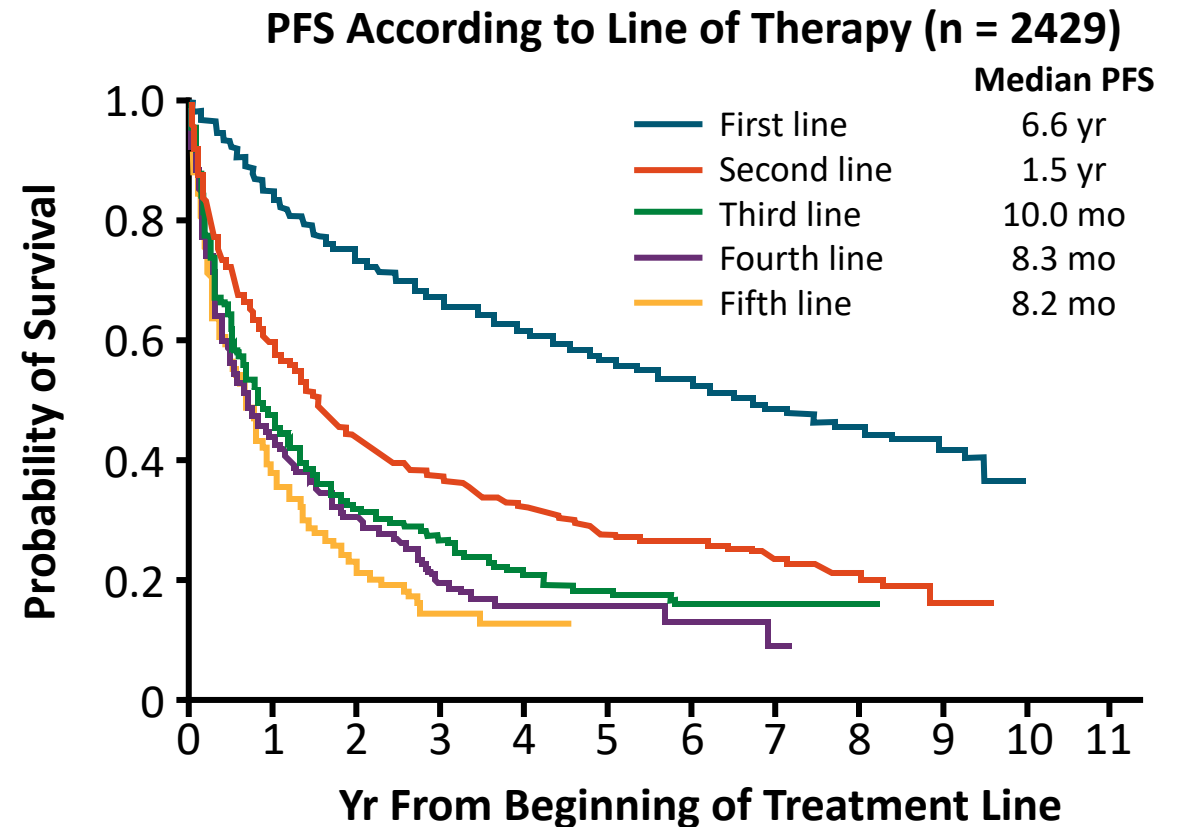
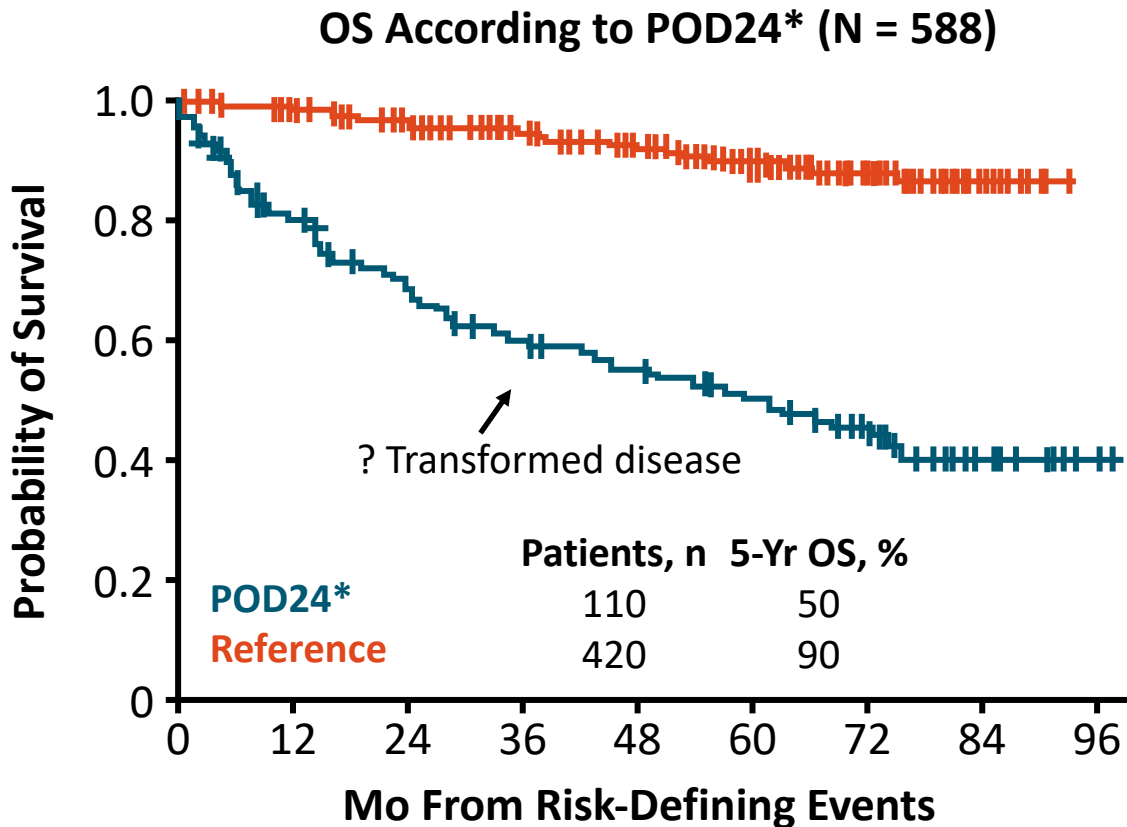
C Progression-free Survival



D Overall Survival

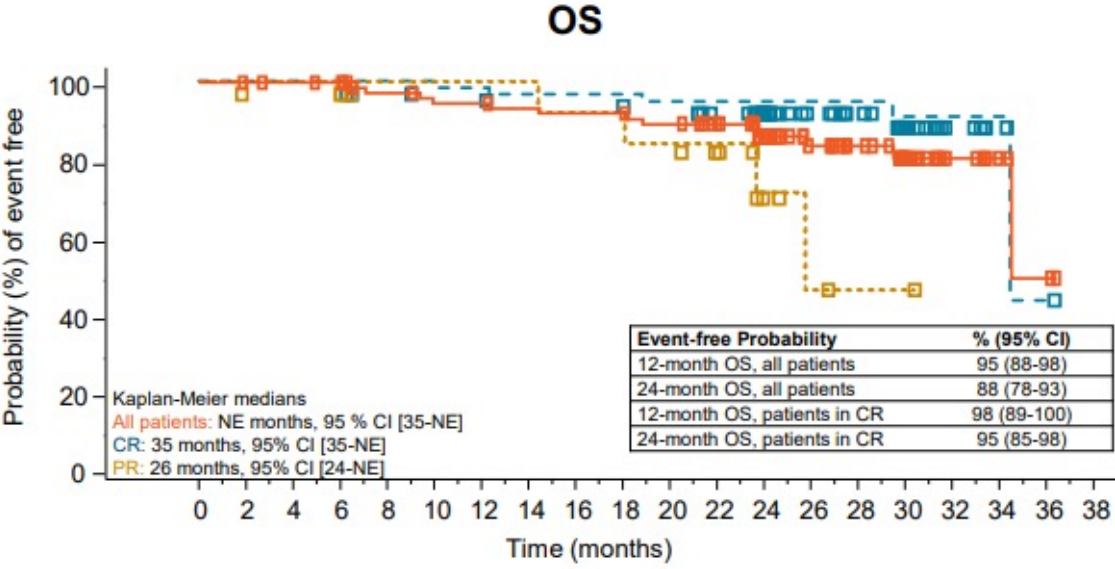
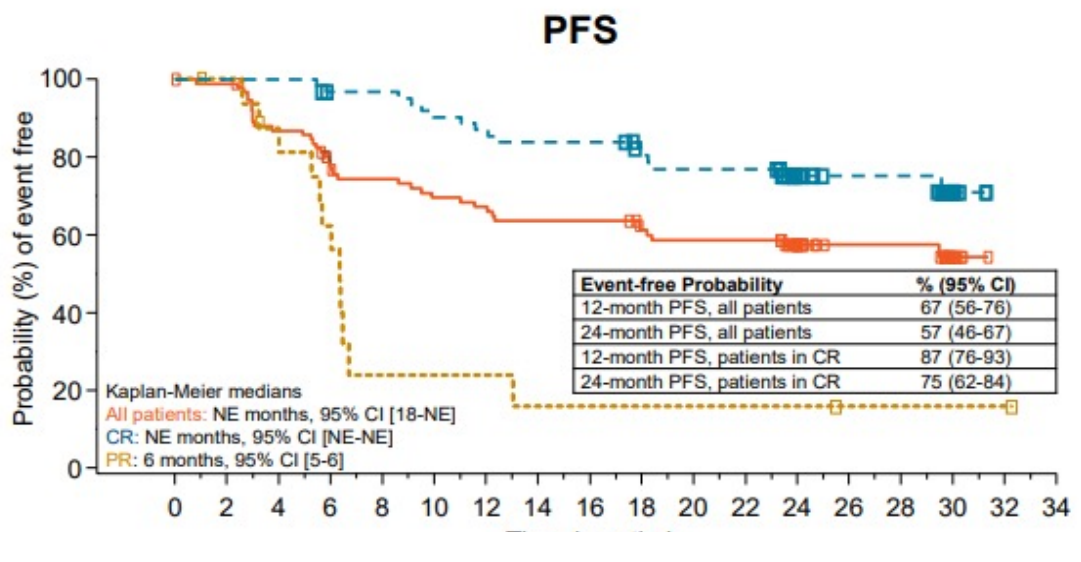


FL R/R: Outcomes According to POD24 and Line of Therapy



*POD24: relapse within 24 mo after initial therapy. Given figure is of patients treated with 1L R-CHOP. Similar results found for independent validation set and for 1L R-CVP/R-fludarabine in exploratory analyses.

Long-Term Clinical Outcomes and Correlative Efficacy Analyses in Patients with Relapsed/Refractory Follicular Lymphoma Treated with Tisagenlecleucel in the ELARA Trial



- ✓ 97 pts
- ✓ median age 57 (49-64)
- ✓ median no previous tx : 4 (3-13)
- ✓ POD 24 : 61/97 (62%)

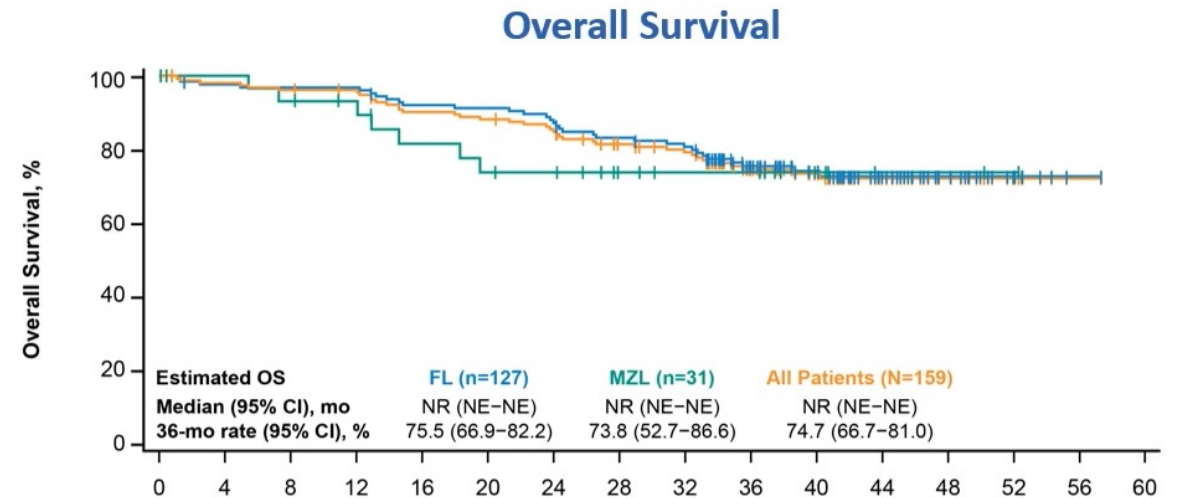
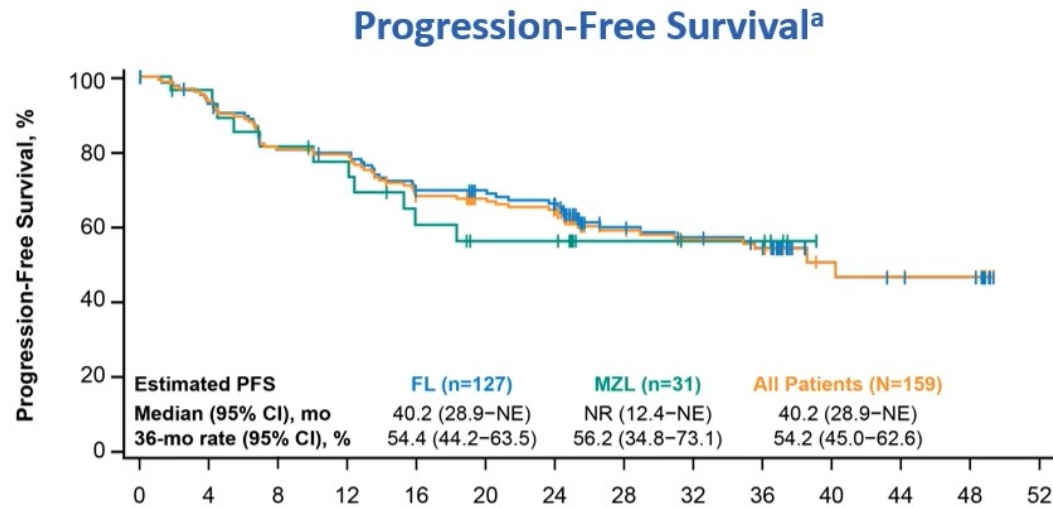
Selected Adverse Events Anytime Post Infusion	Safety Analysis Set ^a (N=97)	
	All Grade, n (%)	Grade ≥3, n (%)
Number of patients with at least 1 AE	73 (75)	45 (46)
CRS ^{b,c}	47 (49)	0
Hematological disorders including cytopenias	45 (46)	43 (44)
Neutropenia	23 (24)	23 (24)
Anemia	13 (13)	7 (7)
Thrombocytopenia	6 (6)	5 (5)
Infections	16 (17)	9 (9)
Hypogammaglobulinemia	11 (11)	1 (1)
Serious neurological adverse events	8 (8)	2 (2)
ICANS	4 (4)	1 (1)

Fowler N, Nature M 2022; Dreyling M et al. ASH 2022. Abstr 608

3-Year Follow-up Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL)

N= 159 iNHL

- Median Follow up was **40.5 months** (range 8.3-57.4)
- RESULTS: in FL ORR was 94% (79% of CR rate); in MZL ORR was 77% (65% CR rate)



- In FL, patients with POD24 had a PFS similar to that of the overall population
- In MZL survival outcomes improved with a longer follow up, with a median PFS not yet reached
- Longer Follow up is needed to determine whether the emergence of plateau in lymphoma-specific PFS will be maintained

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