CAR-T:

una continua
innovazione
nel mondo
- **"Linfoma"**

Roma, 4 Aprile 2024
NH Vittorio Veneto

Il linfoma follicolare. Seconda e terza linea

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Ematologia e Terapie Cellulari

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OSPEDALE POLICLINICO SAN MARTINO
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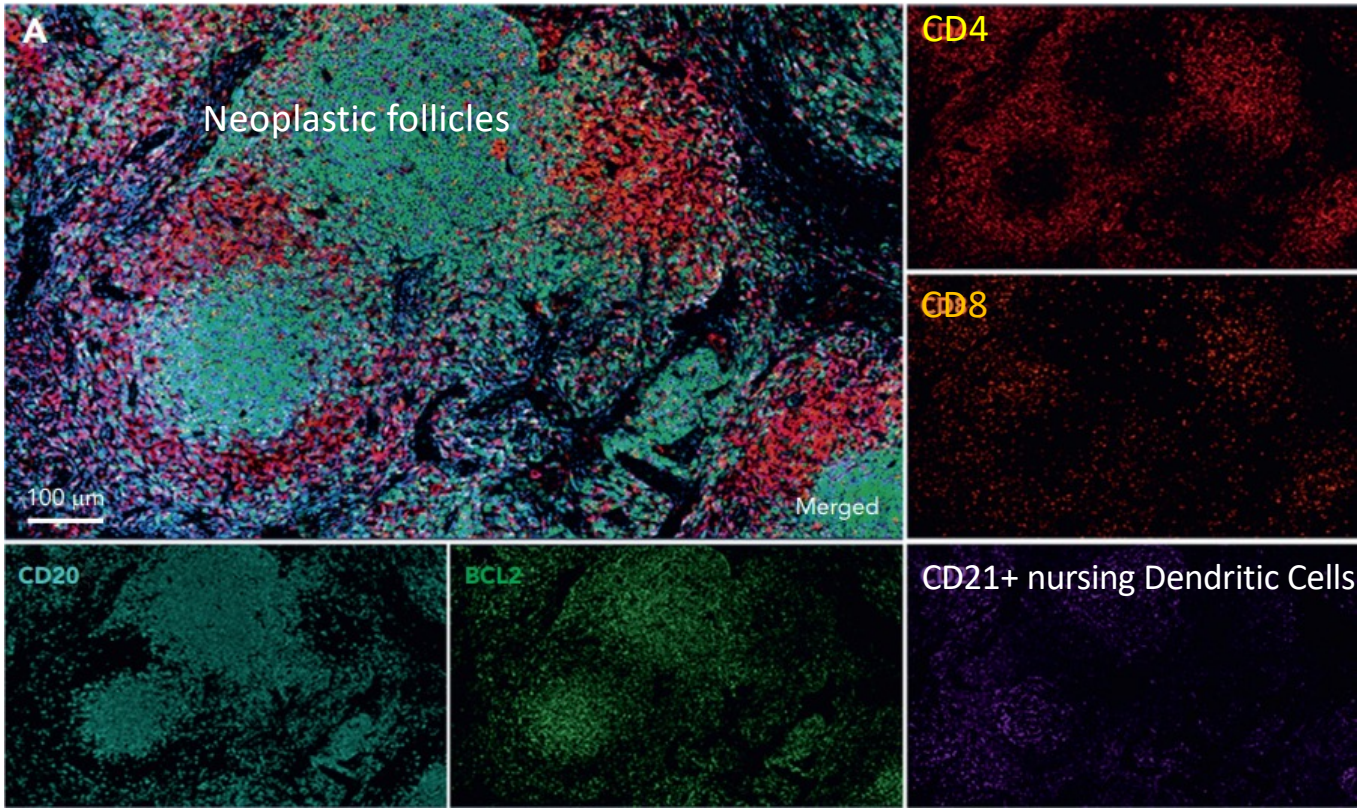
Istituto di Ricovero e Cura a Carattere Scientifico

Confluenza di interessi:

Vertex (DMC), BMS (DMC), Vifor (DMC), Sanofi, Regeneron, Novartis, Gilead, Menarini

Follicular Lymphoma – a complex tumor microenvironment



Multiplex Immunohistochemistry

Neoplastic follicles

CD21+ nursing Dendritic Cells

Inter - Intrafollicular CD4+ T cells

Peripheral, spared CD8+ T cells

Laurent et al. *Blood* 143.12 (2024): 1080-1090.

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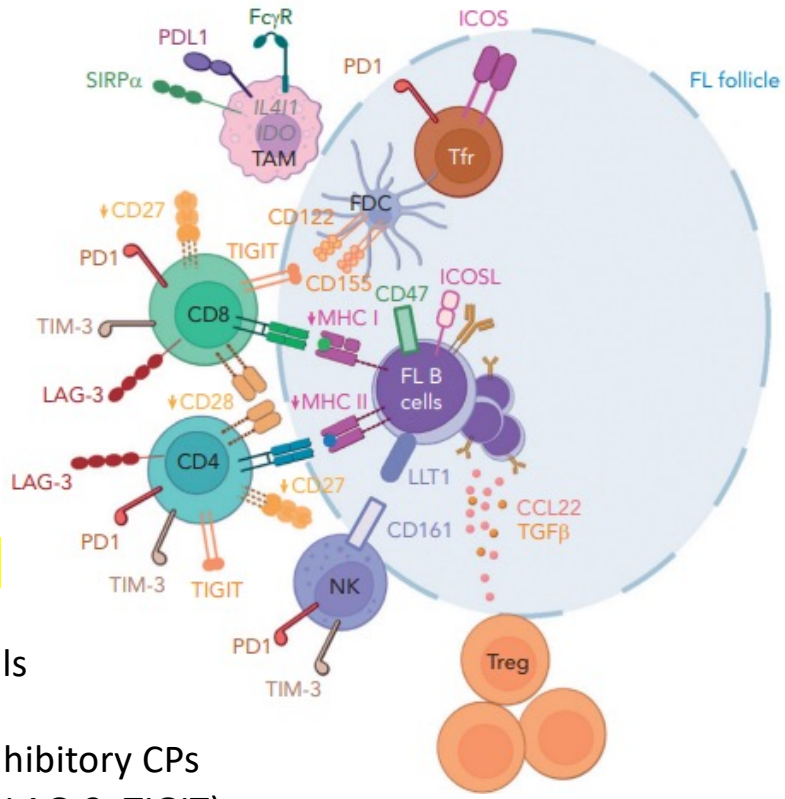


1) Exhausted

CD4+/CD8+

Effector T cells

-

Expressing inhibitory CPs

(PD1, TIM-3, LAG-3, TIGIT)

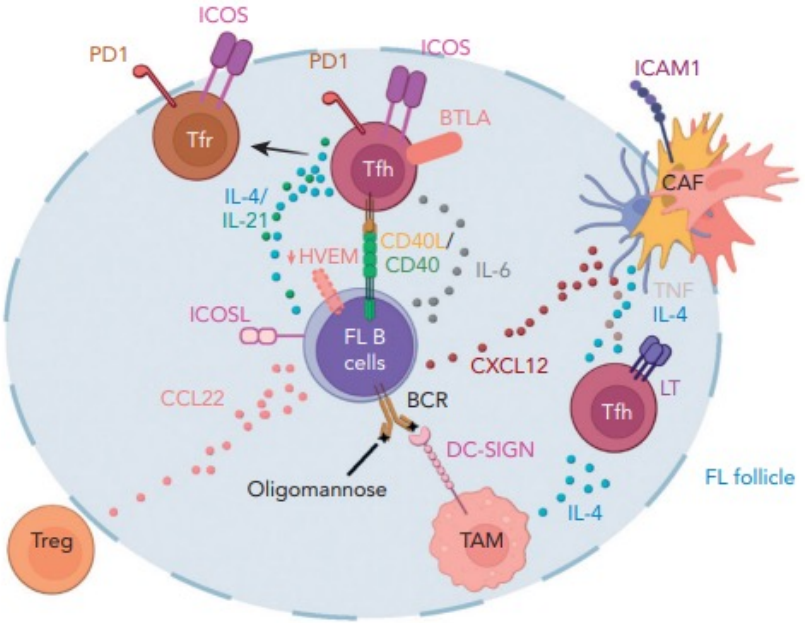
CD4 and CD8 effectors cells blocked in their anti-tumor action

Laurent et al. *Blood* 143.12 (2024): 1080-1090.

2) Survival promoting T Follicular helper

(TFh) via IL-4, IL-21 and CD40L

Follicular T cells that support follicle tumor cell survival



3) Activating

Tumor Associated Macrophages (TAMs)

Trigger BCR signaling via DC-SIGN

Macrophage cells that activate tumor cells through BCR

Beyond the first line:
several classes of agents, opportunities for synergy

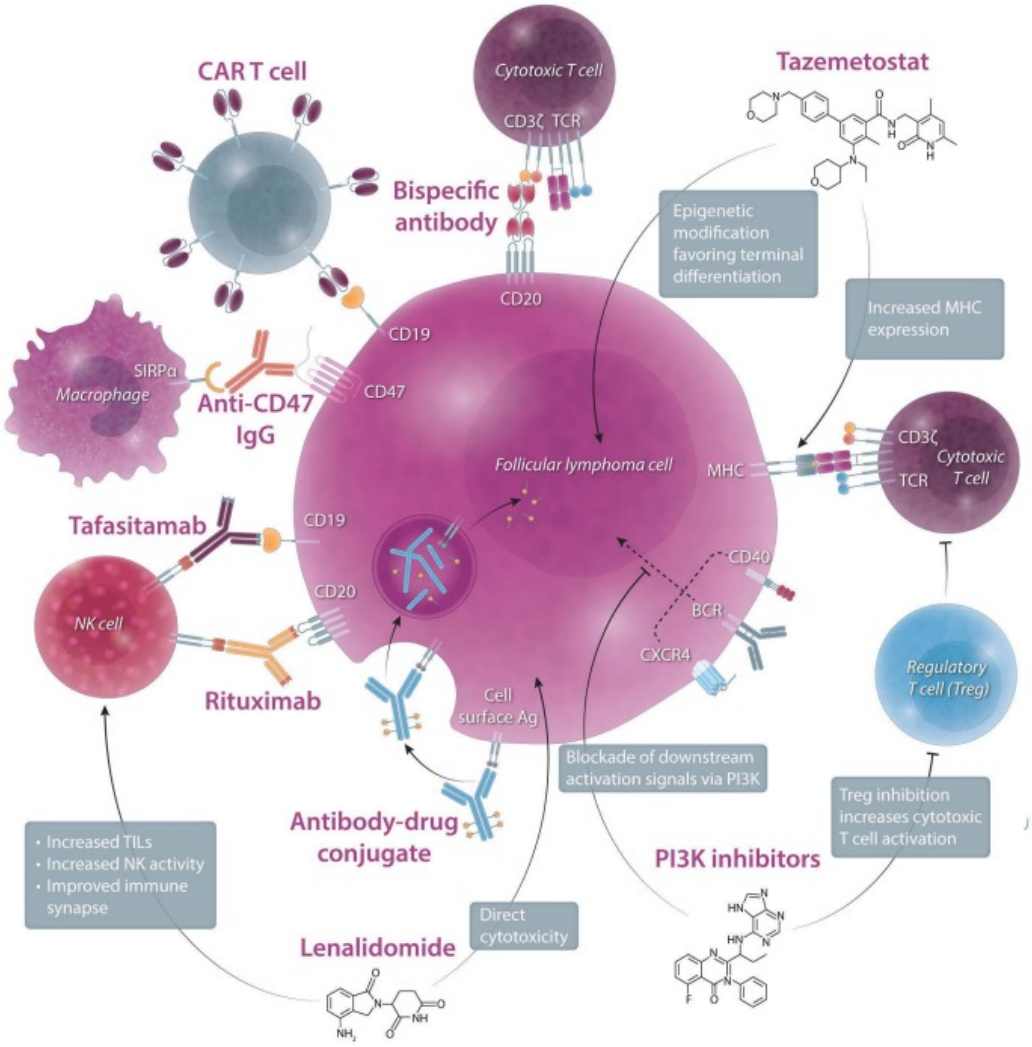
Immunomodulatory drugs (IMIDs – lenalidomide)

PI3K inhibitors (idelasilib)

Novel Monoclonal Antibodies (es anti CD19, CD 20)

Bispecific Antibodies

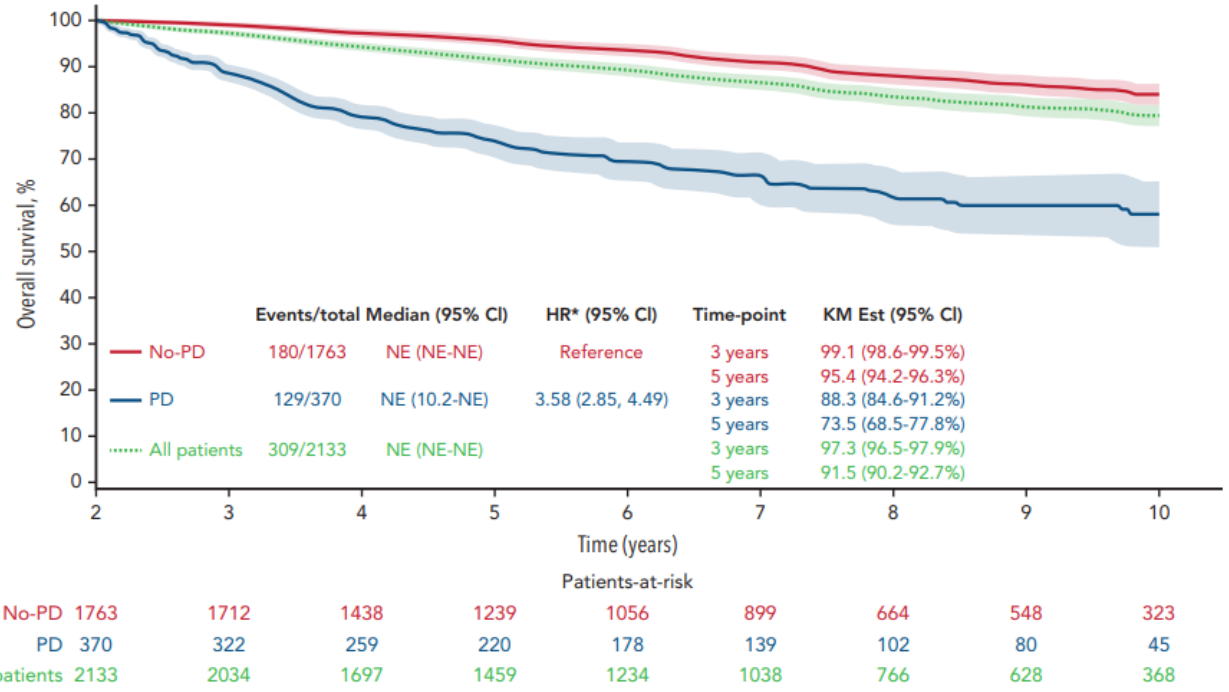
CAR-T cells



Qualls et al. *Haematologica* 107.1 (2022): 19.

Prognostic determinants at first progression following ICT: POD24

*POD24: **recurrence or progression of disease within 24 months of front-line treatment***



Landmark analysis: OS in pts alive 24 months following trial registration

Casulo et al. *Blood* 139.11 (2022): 1684-1693.

Determinants of POD24

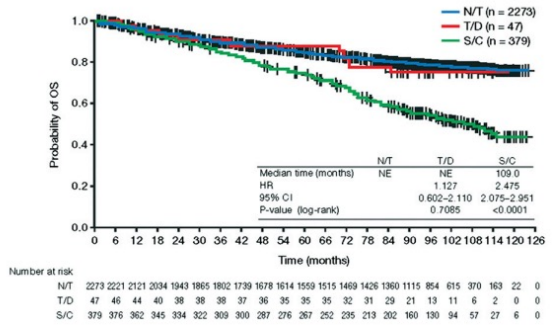
Patient factors

- gender: male
- PS: ECOG ≥2

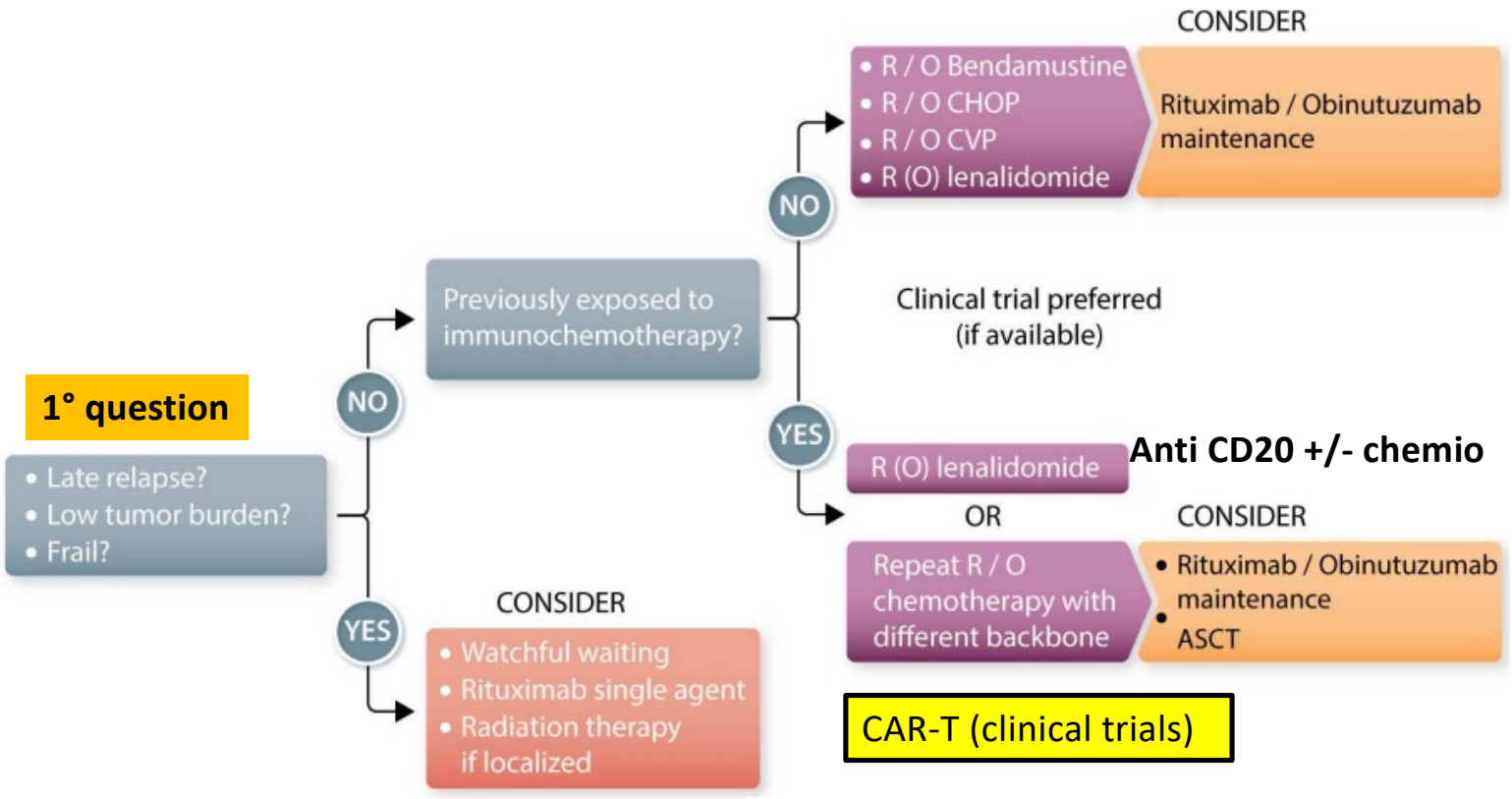
Disease factors

- High beta2 microglobulin
- High Risk FLIPI

*consider aggressive transformation
- Frequent: >20% cases of POD24
- Impacts survival
→ **Rule out histological transformation**



Second Line – First progression



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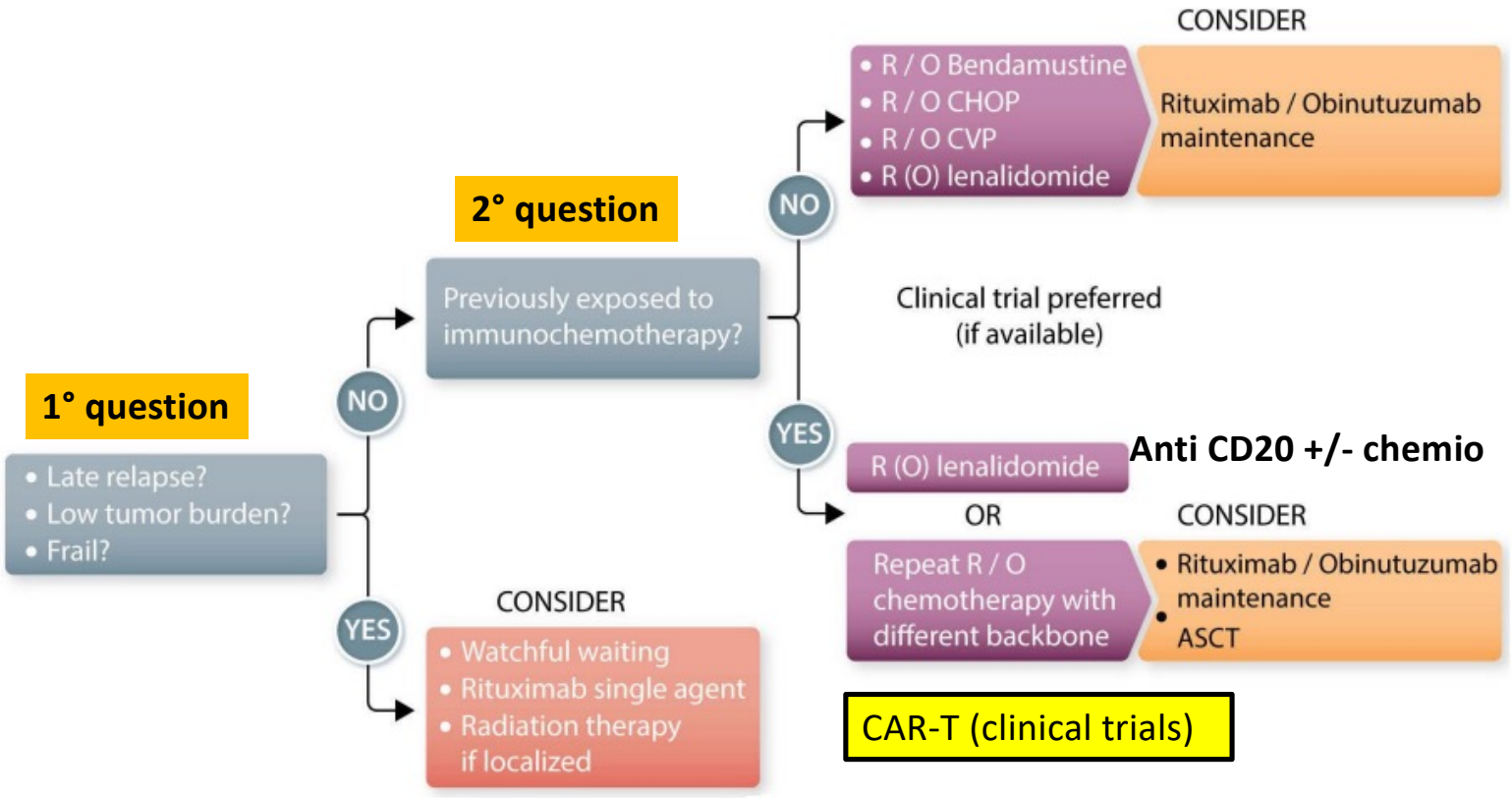

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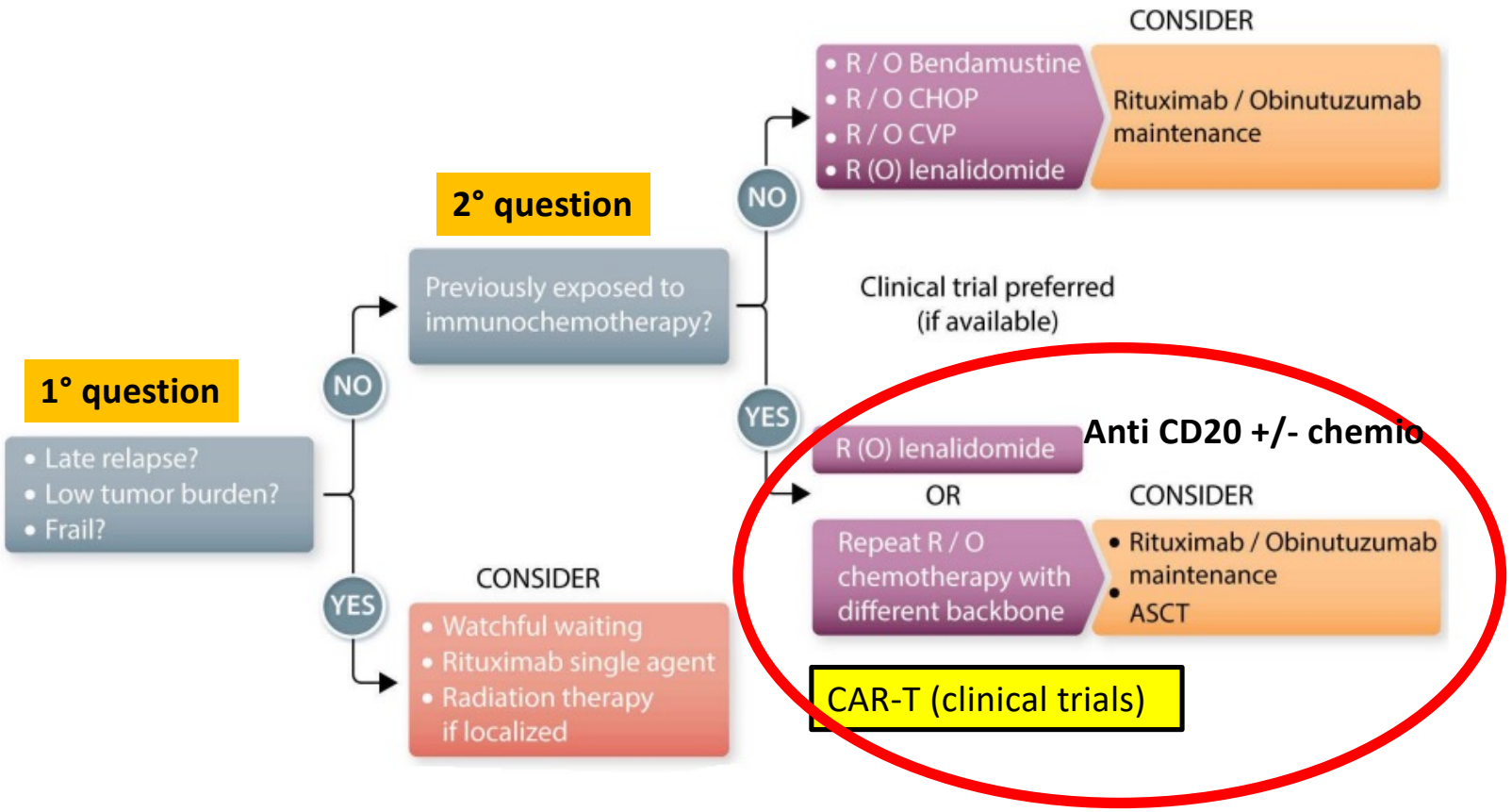
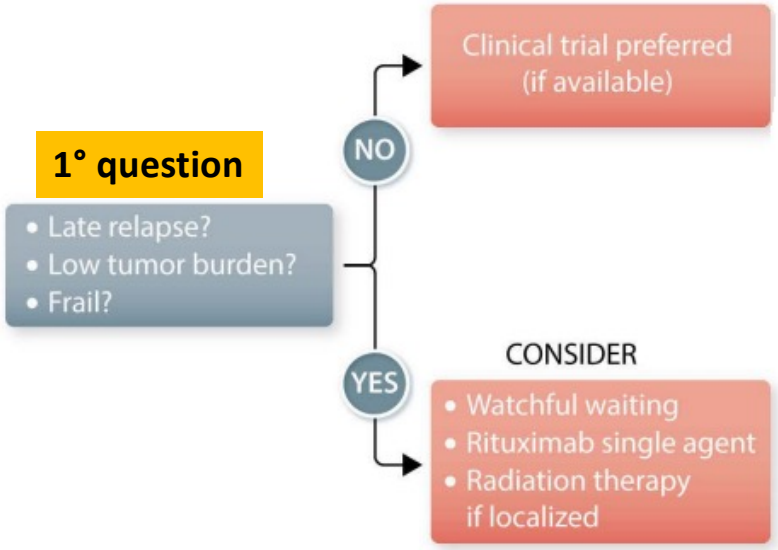


Adapted from Qualls et al. *Haematologica* 107.1 (2022): 19.

Third Line – Subsequent progressions



CAR-T (tisagenlecleucel; axicabtagene ciloleucel)

Chemo + anti-CD20
R2
PI3K inhibitor
Radioimmunotherapy

Consider ASCT (?)

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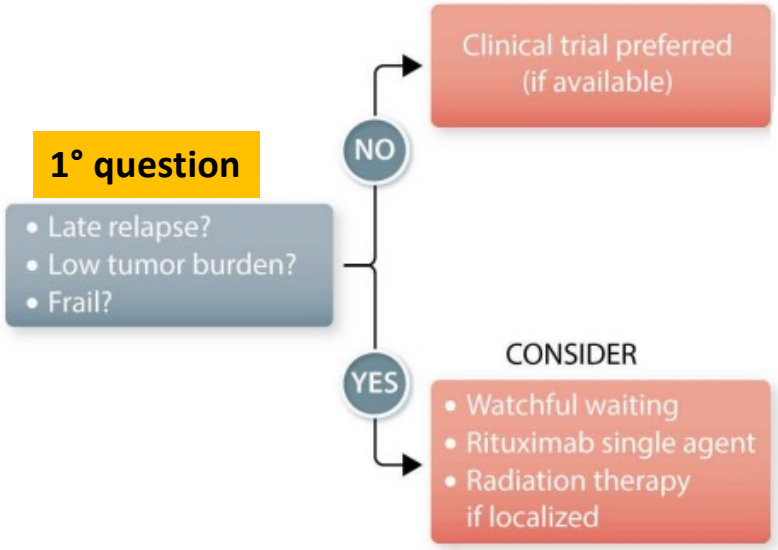

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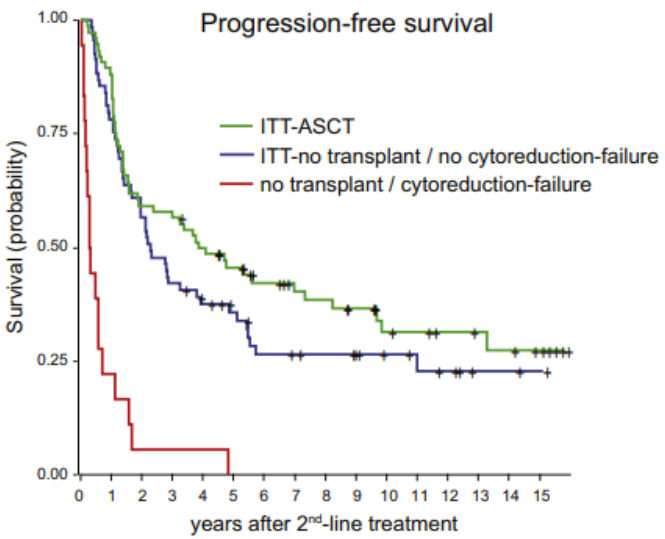
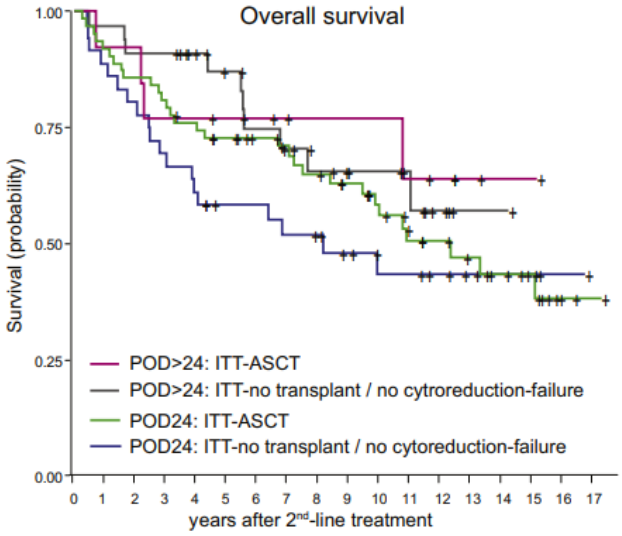
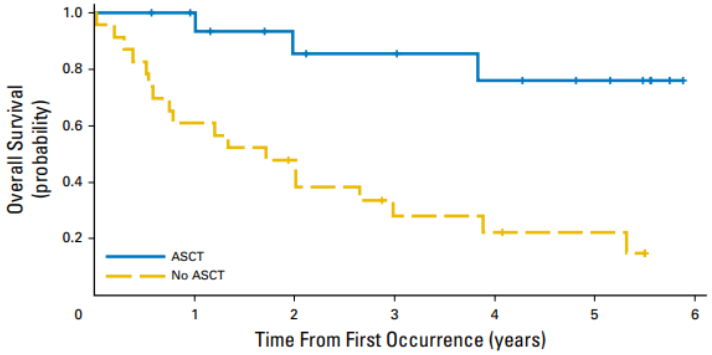
Consolidation with ASCT in R/R FL







FL: ASCT improves PFS vs responding, not transplanted

POD24: ASCT improves OS vs responding, not transplanted

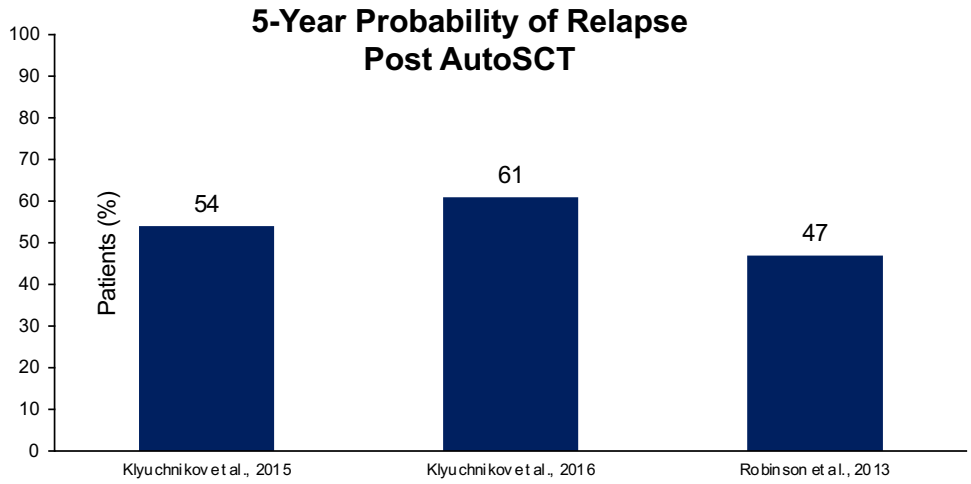
Transformed FL: ASCT improves OS vs not transplanted (not reached, not referred)

- ASCT improves PFS in R/R FL
- ASCT improves PFS & OS in HR patients (POD24; Transformed FL)

Jurinovic et al. Biology of Blood and Marrow Transplantation 24.6 (2018): 1172-1179.
Sarkozy et al. *Journal of Clinical Oncology* 34.22 (2016): 2575-2582.

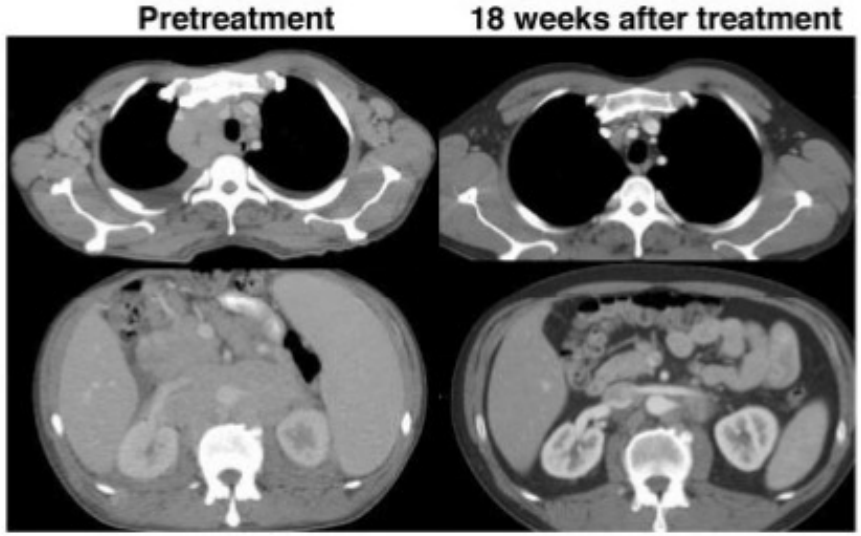
Progression: an Unmet Need despite ASCT – long term follow up

- most patients undergoing autoSCT as a consolidation strategy eventually relapse and most experience short- and long-term complications.
- **Work in progress**: novel treatments (CAR-T): efficacy despite active disease at treatment, with prolonged duration of response

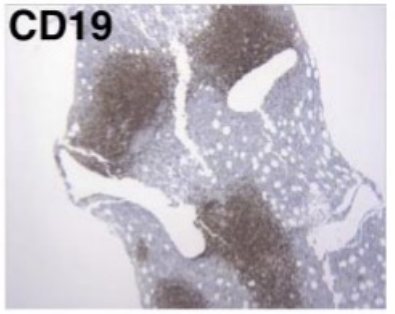


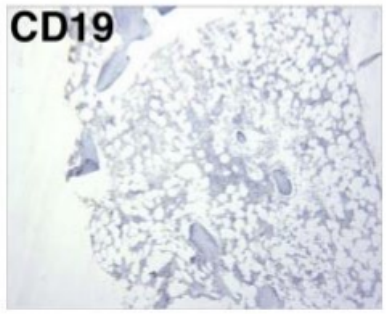
CAR-T experiences

Kochenderfer et al. 2010 NIH - NCT00924326 Trial
First report of B-cell lymphoma eradication
with anti-CD19 CAR-T cells

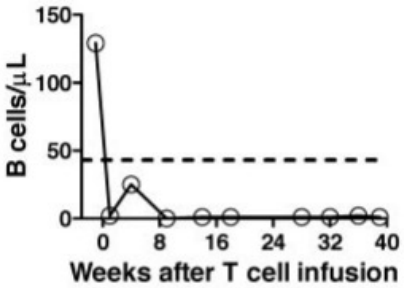


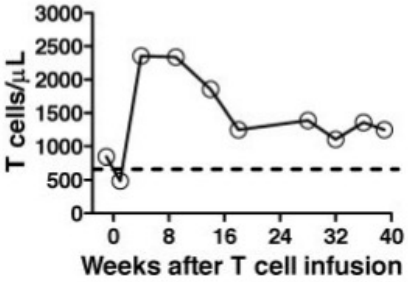
FMC63-28Z autologous CAR-T





BM CD19+ (malignant and normal):
pre vs 36-weeks post CAR-T





Kochenderfer et al. Blood. 116.20 (2010): 4099-4102.

Schuster et al. 2017 UPENN – NCT02030834 Trial
First evidence of efficacy with CTL019 for NHLs

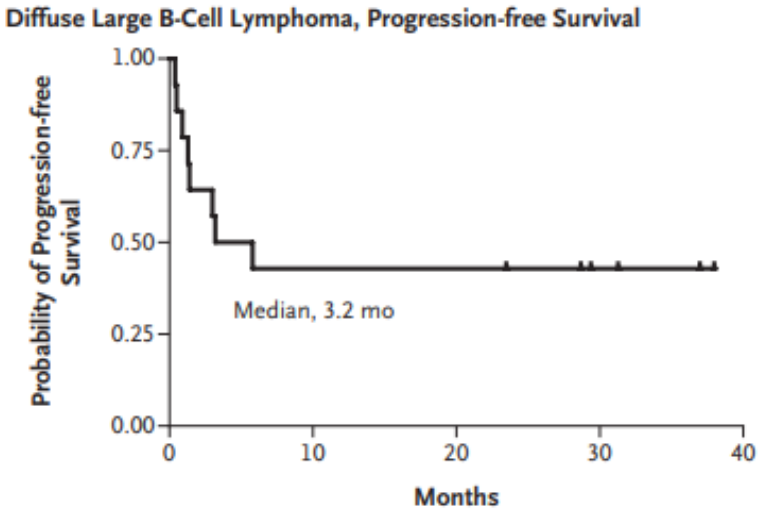
28 Adult Patients with B-cell lymphoma

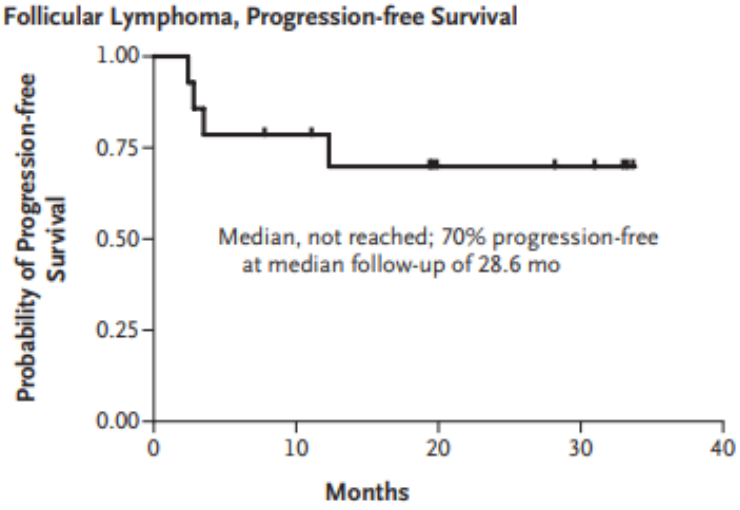
- 14 DLBCL→ CR 6/14 (43%)
- 14 FL → CR 10/14 (71%)

Follicular Lymphoma (N=14)	
Double Refractory, n(%)	**8 (57)%**
Previous lines, median (range)	**5 (2-10)**
Previous SCT, n(%)	**4 (28%)**

UPENN CTL019
FMC63-41BBZ autologous CAR-T

Schuster et al. NEJM. 377.26 (2017): 2545-2554.





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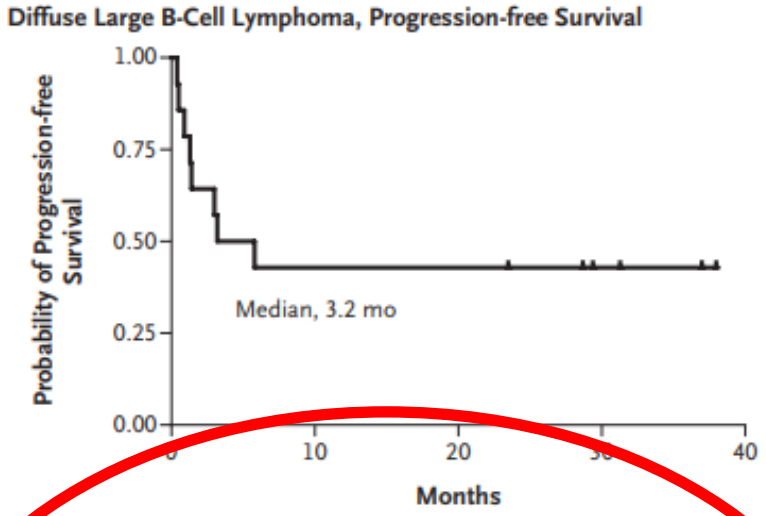
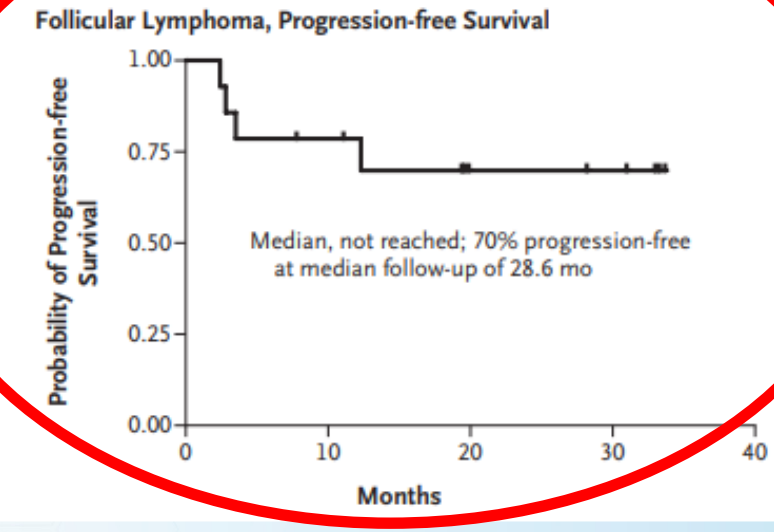
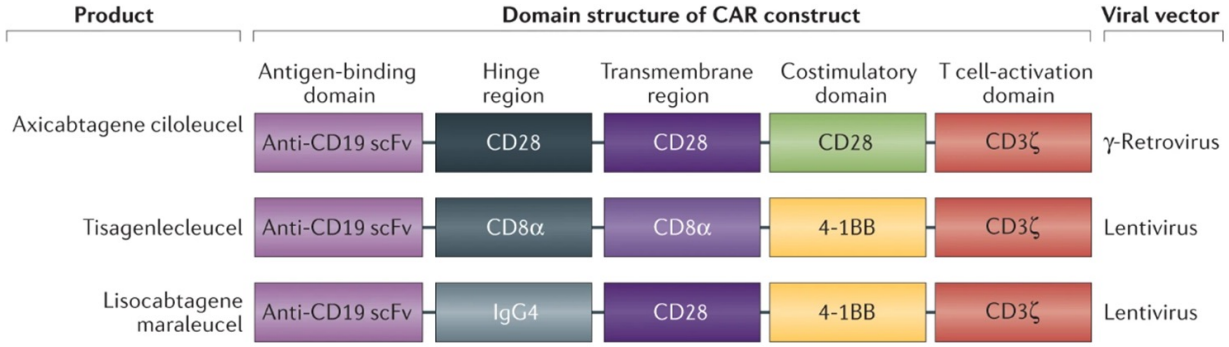




Selected CAR-T trials including Follicular Lymphoma

Product	Trial	Phase	Prior lines of therapy	Key Exclusion Criteria
Tisagenlecleucel	**ELARA** NCT03568461	II	≥2	- Transformed FL - Gr.3B FL
Axicabtagene ciloleucel	**ZUMA-5** NCT03105336	II	≥2	- Transformed FL - Gr.3B FL
Lisocabtagene maraleucel	**TRANSCEND FL** NCT04245839	II	≥2*	- Transformed FL - Gr.3B FL

*High-Risk cohort with **Liso-cel** as 2nd line therapy



Second generation CAR-T

- anti-CD19
- single costim. (CD28 or 4-1BB)
- autologus

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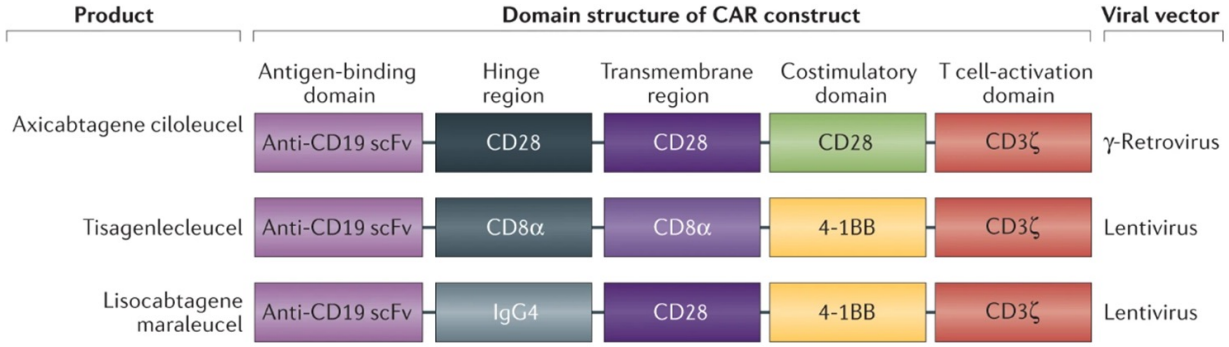

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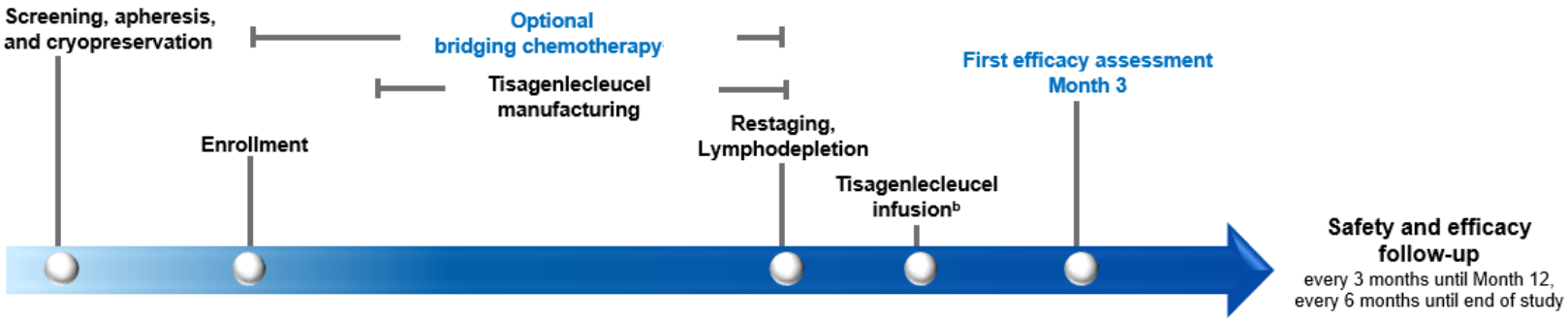
ELARA: Efficacy and Safety of Tisagenlecleucel in Adult Patients With Refractory or Relapsed Follicular Lymphoma



Study design: multicenter, single-arm, open-label**, Phase II** study of a single infusion of tisagenlecleucel in adult patients with r/r FL (NCT03568461). 97 patients

Key eligibility criteria	Study treatment	End points
• ≥18 years of age • FL grade 1, 2, or 3A • **Relapsed/refractory disease** • 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

ELARA: Study Population and Primary End Point Results

	Infused Patients (N=97)
Median age (range), y	57.0 (29-73)
≥65 y, %	24.7
ECOG PS prior to infusion, %	
0	56.7
1	39.2
2	4.1
Stage at study entry III-IV, %	85.6
FLIPI ≥3, %	59.8
Median no. of prior therapies (range)	**4 (2-13)**
≥3, %	**76.3**
POD24 from first anti-CD20 mAb containing therapy,[a] %	62.9
Refractory to last line of therapy,[b] %	**78.4**
Prior autologous HSCT, %	**36.1**
Refractory to ≥2 regimens, %	71.1
Prior therapy, %	
Anti-CD20 mAb and alkylating agents[c]	100
PI3K inhibitors	20.6
Lenalidomide and rituximab	16.5

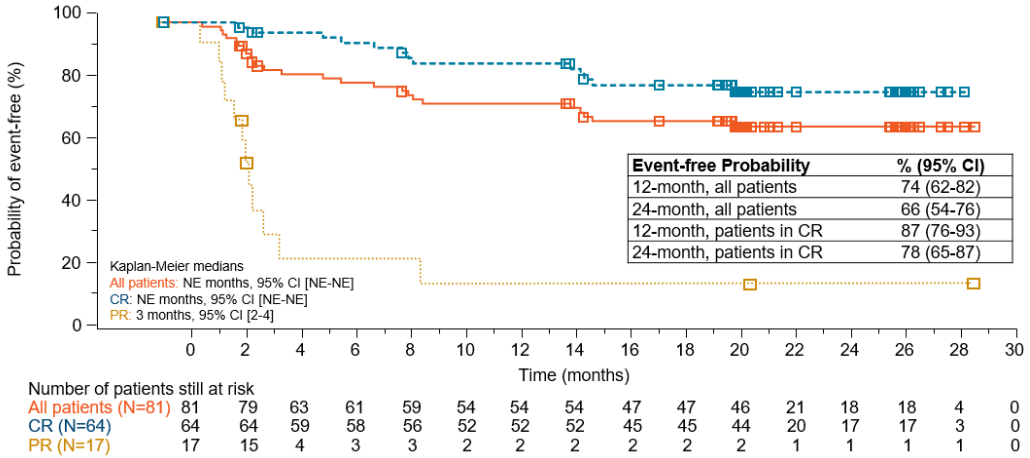
Primary End Point	Secondary End Points
• Complete response rate	• ORR • DOR, PFS, OS • Safety, cellular kinetics

Endpoint in Efficacy Analysis Set (IRC Assessment)	% (95% CI) N=94
CRR	**68 (58-77)**
ORR	**86 (78-92)**

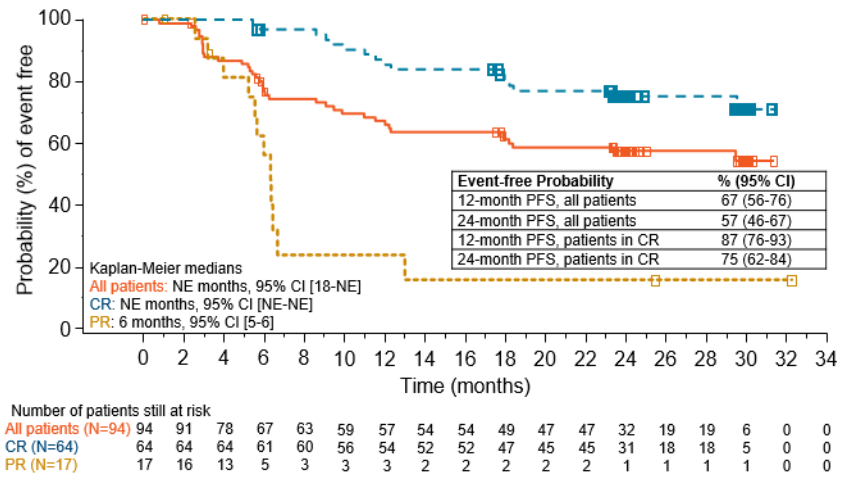
Baseline Disease Characteristic	All Patients n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume	20 (21)	40 (19-64)	75 (51-91)
Bulky disease	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

RED = all patients

Duration Of Response

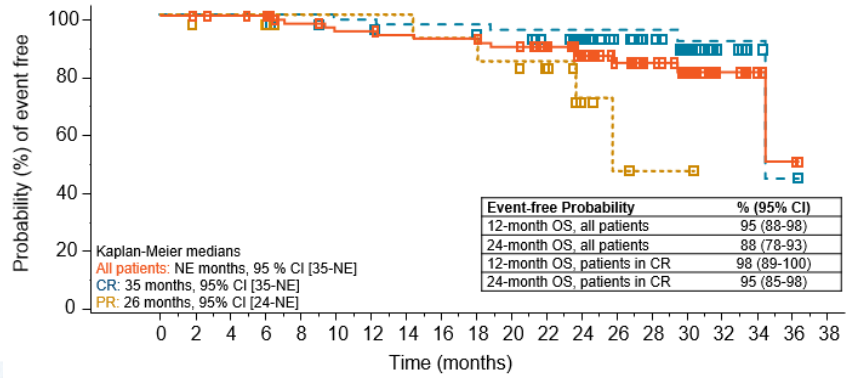


Progression Free Survival



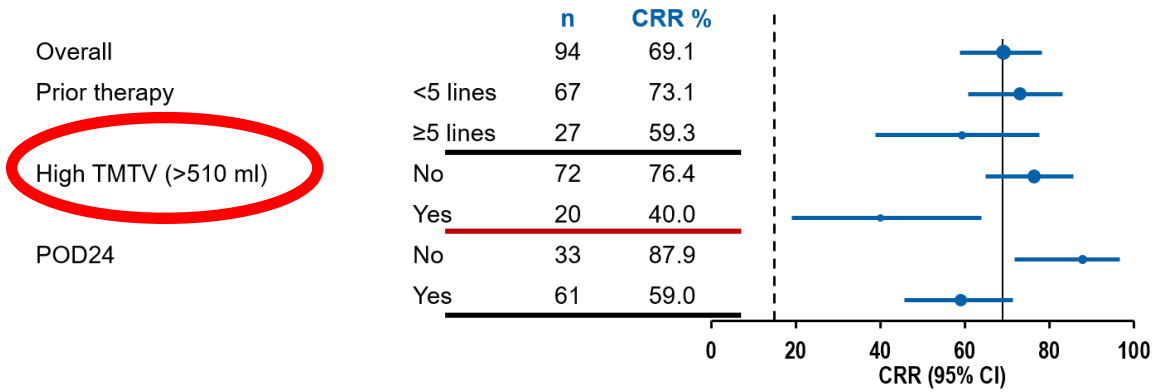
Secondary End Point	29 Months Median Follow-Up Analysis
Duration Of response, median	Not reached
Progression Free Survival, median	Not reached
Overall Survival, median	Not reached

Overall Survival

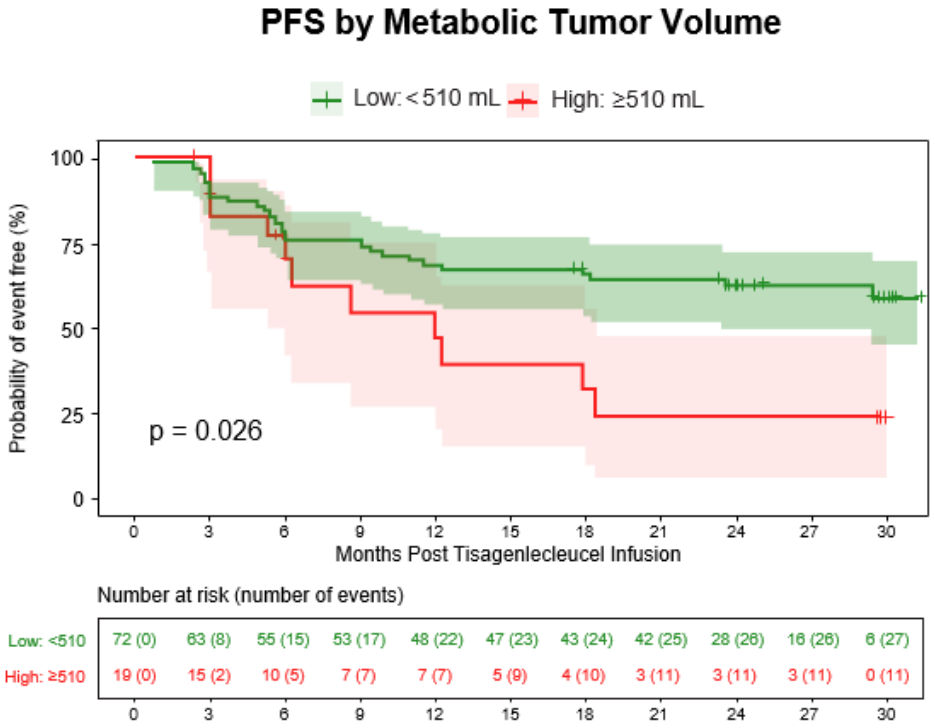


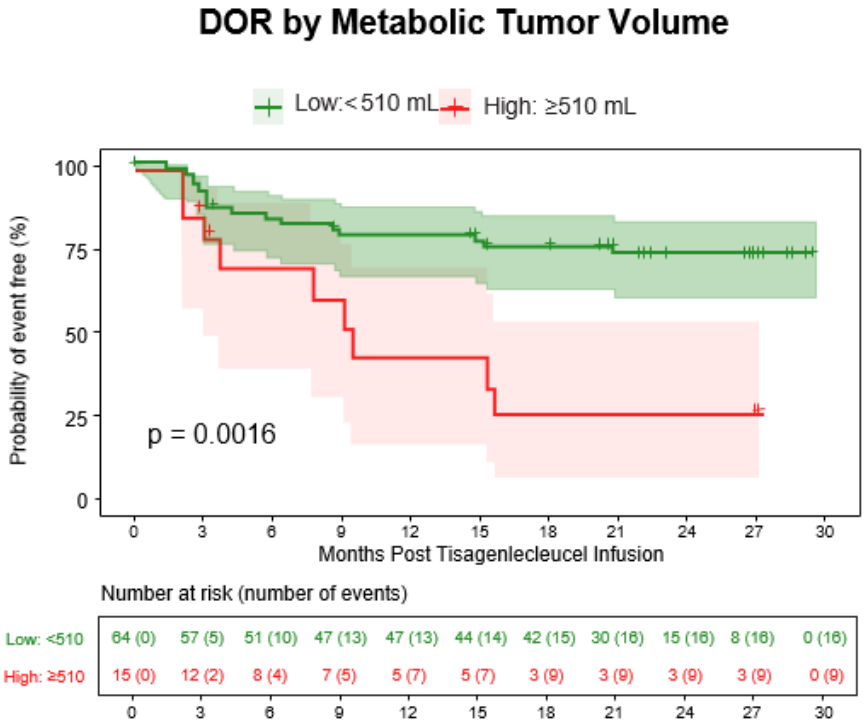
ELARA: Efficacy Subanalysis according to 9 High-Risk Subgroups: metabolic tumor volume (=> 510 ml)

High-Risk Group	Patients (N=94), %
≥5 lines of prior therapy	28.7
High FLIPI score at study entry	60.6
Prior HSCT therapy	37.2
POD24	64.9
Bulky disease at baseline (GELF criteria)	64.9
LDH prior to infusion > ULN	31.9
CRP prior to infusion > ULN	51.1
Double refractory	69.1
High TMTV >510 ml at baseline	21.3



ELARA: higher (=>510 ml) Metabolic Tumor Volume associated with shorter PFS and DOR



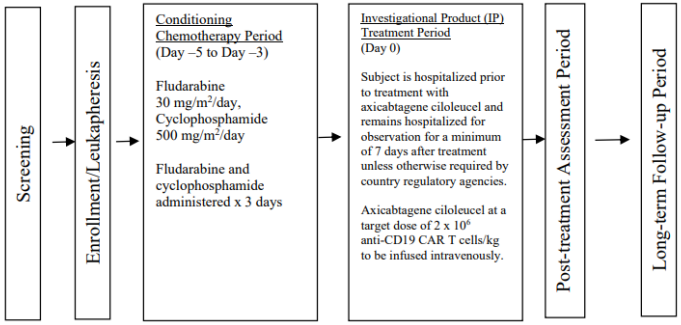


ELARA: Adverse Events of Special Interest

Selected Adverse Events Anytime Post Infusion	Safety Analysis Set (N=97)	
	All Grade, n (%)	Grade ≥3, n (%)
Number of patients with at least 1 AE	73 (75)	45 (46)
CRS (Lee Scale)	47 (49)	0
Hematalogical 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)
Encephalopathy	3 (3)	1 (1)
Dyskinesia	1 (1)	0
Muscular weakness	1 (1)	0
Tremor	1 (1)	0

ZUMA-5: Axicabtagene ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Bridging therapy administered per investigator discretion

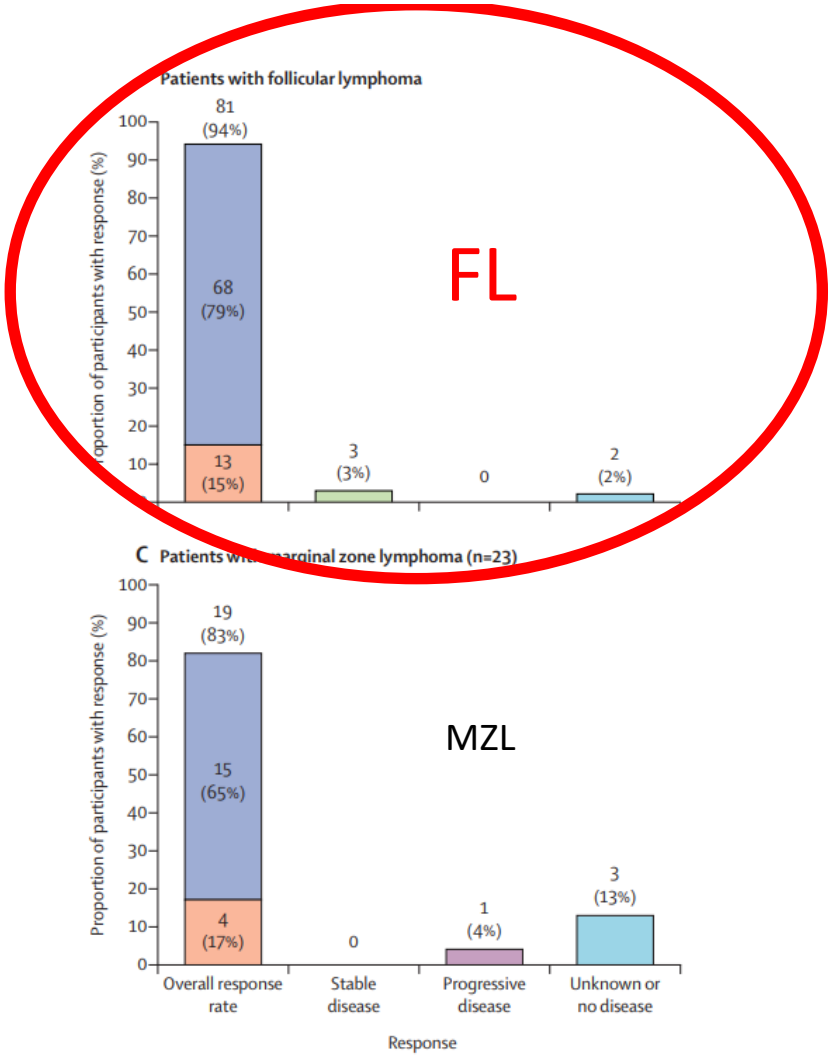


Study design: multicenter, single-arm, open-label, Phase II study of a single infusion of Axicabtagene ciloleucel in adult patients with r/r indolent lymphoma (NCT03105336)

Key eligibility criteria	Study treatment	End points
• ≥18 years of age • FL grade 1, 2, or 3A (FL cohort) • **progressed after at least 2 lines of treatment with combination chemoimmunotherapy** • No evidence of histological transformation/FL3B (FL cohort) • No ASCT within 6 weeks of planned leukapheresis or allogeneic HSCT • No requirement for urgent therapy due to ongoing or impending oncologic emergency	Axicabtagene ciloleucel dose (single IV infusion) was **2 × 10^6 CAR-T cells per kg**	**Primary: ORR (CR+PR)** **Key Secondary:** DOR, PFS, OS, incidence of AEs

ZUMA-5: Study Population and Primary End Point Results

Characteristic	FL (n = 127)	MZL (n = 31)	All patients (N = 159)*
Age, median (range), y	60 (34-79)	64 (43-77)	60 (34-79)
≥65 y, n (%)	40 (31)	14 (45)	54 (34)
Male sex, n (%)	75 (59)	15 (48)	90 (57)
FL histological category, n (%)			
Grade 1	34 (27)	—	—
Grade 2	63 (50)	—	—
Grade 3a	30 (24)	—	—
MZL histological category, n (%)			
Nodal	—	10 (32)	—
Extranodal	—	21 (68)	—
ECOG PS of 1, n (%)	48 (38)	16 (52)	65 (41)
Stage III-IV disease, n (%)	109 (86)	29 (94)	139 (87)
High-risk FLIPI (≥3), n (%)	56 (44)	—	—
High tumor bulk (GELF criteria), n (%)†	65 (51)	16 (52)	82 (52)
SPD, median (range), mm^2	2604.15 (289.2-34 675.0)	1746.45 (306.5-7 471.8)	2449.50 (289.2-34 675.0)
TMTV, median (range), mL	438.50 (11.21-5 576.58)	368.83 (5.15-3 239.43)	420.33 (5.15-5 576.58)
Number of prior therapies, median (range)‡	3 (1-10)	3 (2-8)	3 (1-10)
R/R subgroup, n (%)			
Refractory to last prior therapy	87 (69)	25 (81)	113 (71)
Double refractory to prior anti-CD20 mAb and alkylating agent	56 (44)	13 (42)	70 (44)
POD24 from initiating first anti-CD20 mAb–containing therapy§	70 (56)	18 (60)	89 (57)

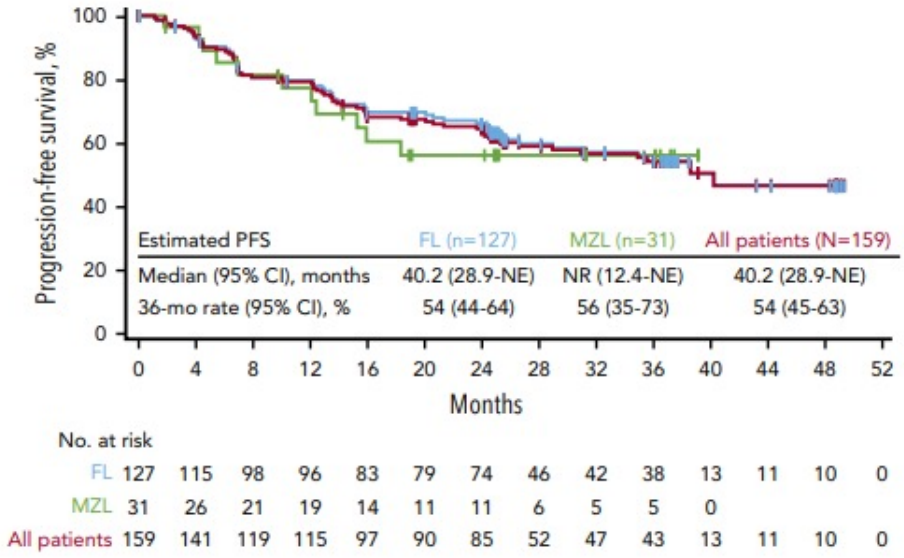


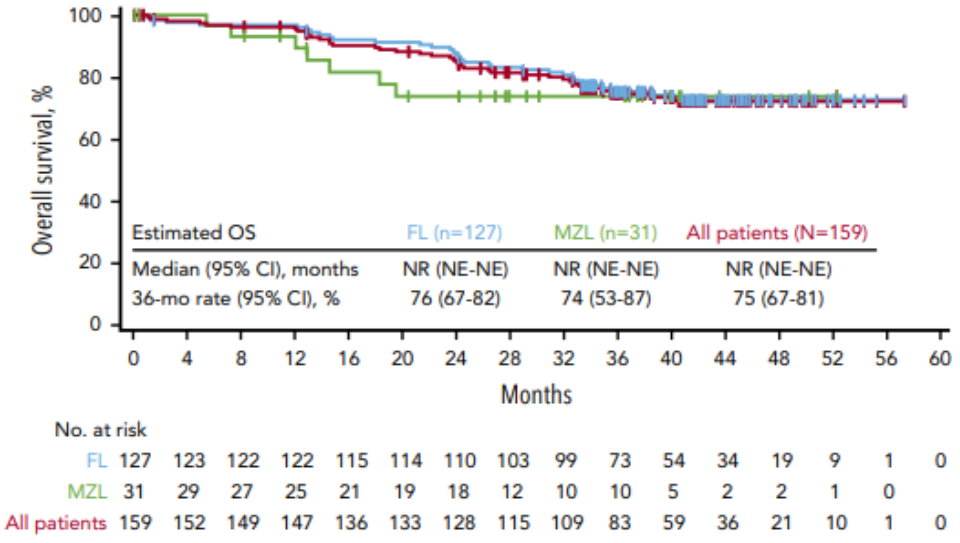
Neelapu et al. *Blood* 143.6 (2024): 496-506.
Jacobson et al. The lancet oncology 23.1 (2022): 91-103.

Primary EP: ORR as assessed by an IRRC

ZUMA-5: Updated, Three-Year Follow-Up Survival Analysis

Progression Free Survival FL = light blue **Overall Survival**





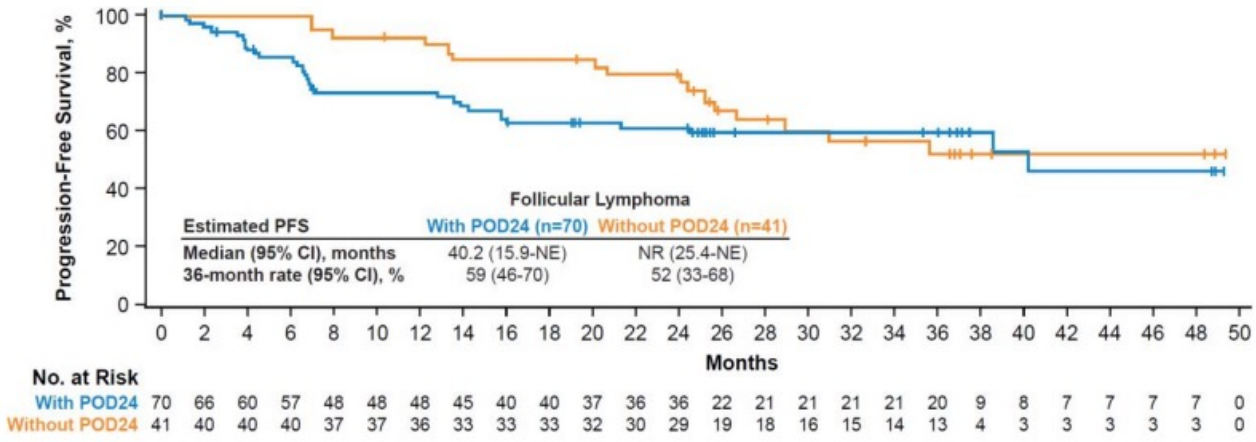
FL: Median PFS (95% CI), months: 40.2 (28.9-NE)

FL: Median OS (95% CI), months: NR (NE-NE)

Neelapu et al. *Blood* 143.6 (2024): 496-506.

ZUMA-5: Efficacy Analysis according to High-Risk Subgroups

Progression Free Survival, according to POD24

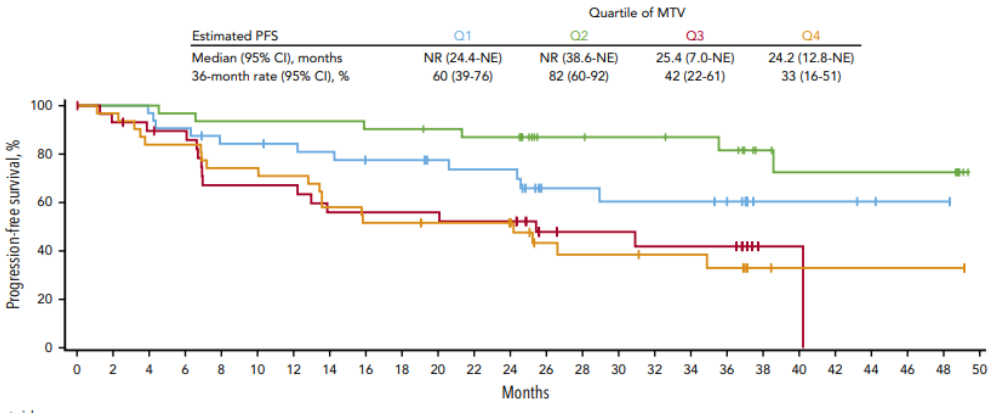


- 36 month PFS, POD24 : 59%
- 36 month PFS, w/o POD24 : 52%

Neelapu et al. *Blood* 143.6 (2024): 496-506.

ZUMA-5: Efficacy Analysis according to High-Risk Subgroups

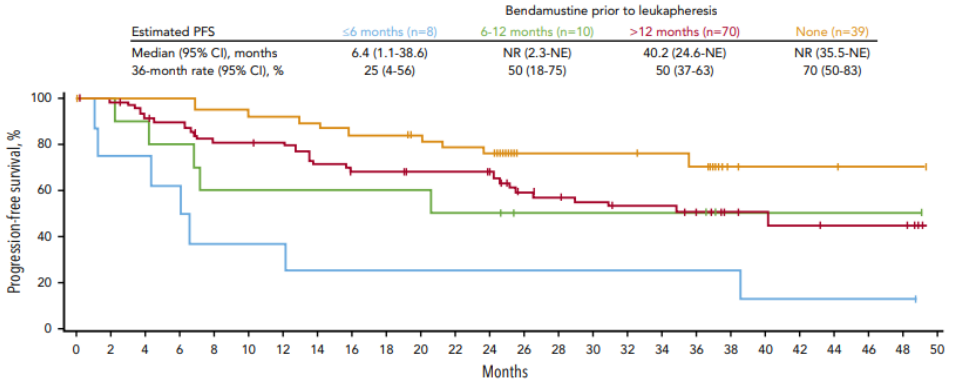
Progression Free Survival, according to
Metabolic Tumor Volume (*quartiles*)



Metabolic Tumor Volume, median, mL: 438.5

- 36-month PFS, below the median: 71.2%
- 36-month PFS, above the median: 37.3%
- No association with ORR and CR

Progression Free Survival, according to Benda prior to LA



Bendamustine prior to Leukapheresis: 88/128 (68%)

- Higher CR rate and 36 month duration of response in pts not exposed to Bendamustine

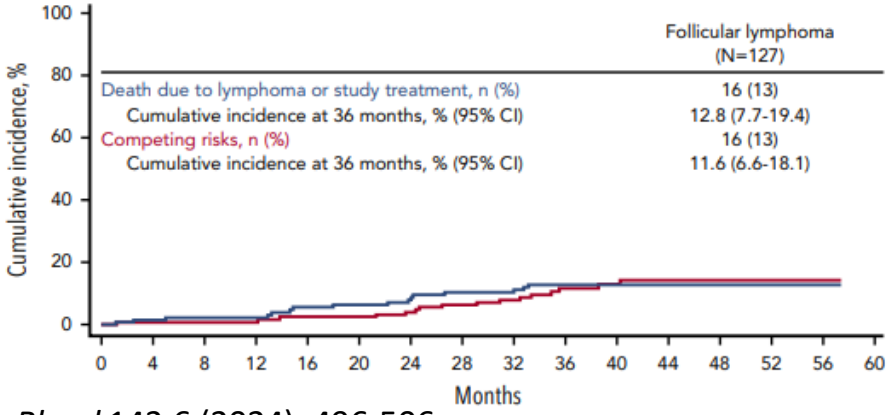
BUT

- **Small subgroup numbers prevent further analysis**
- **Higher prevalence of high-risk features in the Benda group**

Neelapu et al. *Blood* 143.6 (2024): 496-506.

ZUMA-5: Adverse Events of Special Interest, FL cohort

Selected Adverse Events Anytime Post Infusion	FL, Safety Analysis Set (N=124)	
	All Grade, n (%)	Grade ≥3, n (%)
CRS	97 (78)	8 (6)
Neutropenia	79 (64)	75 (60)
Anemia	44 (35)	29 (23)
Thrombocytopenia	44 (35)	29 (23)
Neurological adverse events	70 (56)	19 (15)
Encephalopathy	24 (19)	10 (8)
Confusional state	28 (23)	6 (5)
Tremor	36 (29)	1 (1)

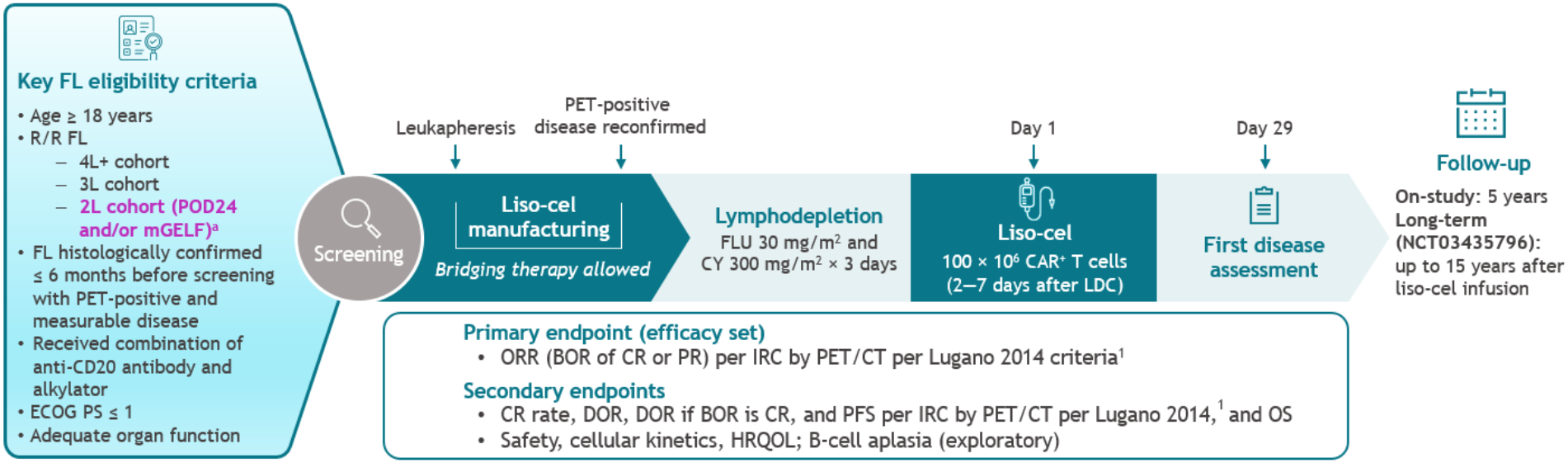


36-month CI of death due to FL or study-treatment, % (95% CI):
12.8 (7.7-19.4)

Among 16 related events:
- 9 PD
- 3 AEs
- 4 unknown

Neelapu et al. *Blood* 143.6 (2024): 496-506.

TRANSCEND FL: Efficacy and Safety of JCAR017 in Adult Subjects With Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma



ClinicalTrials.gov identifier: NCT04245839

3L+ cohort (Leukapheresis, N = 114; Infused, N = 107)

2L cohort (Leukapheresis, N = 25; Infused, N = 23)

[a]POD24: progression within 24 months of diagnosis after treatment with an anti-CD20 antibody and an alkylating agent within the first 6 months of initial FL diagnosis.

Patients who did not meet criteria of POD24 had to meet at least 1 criterion of the mGELF criteria **(symptoms attributable to FL; threatened end-organ function, or cytopenia secondary to lymphoma or bulky disease [single mass > 7 cm, or 3 or more masses > 3 cm]; splenomegaly; or steady progression over at least 6 months)**

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TRANSCEND FL: Patient demographics and baseline characteristics

	2L FL (n = 23)	3L+ FL (n = 107)
Median (range) age, y	53 (34–69)	62 (23–80)
Male, n (%)	17 (74)	66 (62)
FL grade 1 or 2 / 3a at screening,[a] n (%)	17 (74) / 6 (26)	81 (76) / 25 (23)
Ann Arbor stage at screening, n (%)		
Stage I/II	6 (26)	12 (11)
Stage III/IV	17 (74)	95 (89)
FL International Prognostic Index at screening, n (%)		
Low risk (0–1) / intermediate risk (2)	11 (48) / 4 (17)	12 (11) / 34 (32)
High risk (3–5)	8 (35)	61 (57)
LDH > ULN before lymphodepletion, n (%)	6 (26)	47 (44)
Met mGELF criteria at most recent relapse, n (%)	16 (70)	57 (53)
Symptoms attributable to FL	6 (26)	13 (12)
Threatened end-organ function/cytopenia secondary to lymphoma/bulky disease	7 (30)	24 (22)
Splenomegaly	0	4 (4)
Steady progression over at least 6 months	3 (13)	16 (15)
Median (range) prior lines of systemic therapy	1 (1–1)	3 (2–10)
Prior HSCT, n (%)	0	33 (31)
Received prior rituximab and lenalidomide, n (%)	0	23 (21)
Refractory to last systemic therapy,[b] n (%)	15 (65)	72 (67)
Double refractory (anti-CD20 and alkylator),[c] n (%)	11 (48)	69 (64)
POD24 from initial immunochemotherapy, n (%)	15 (65)	58 (54)
POD24 from diagnosis, n (%)	12 (52)	46 (43)
Received bridging therapy, n (%)	5 (22)	44 (41)

Similar characteristics (POD 24) but less high risks, less LDH and less chemo in 2L

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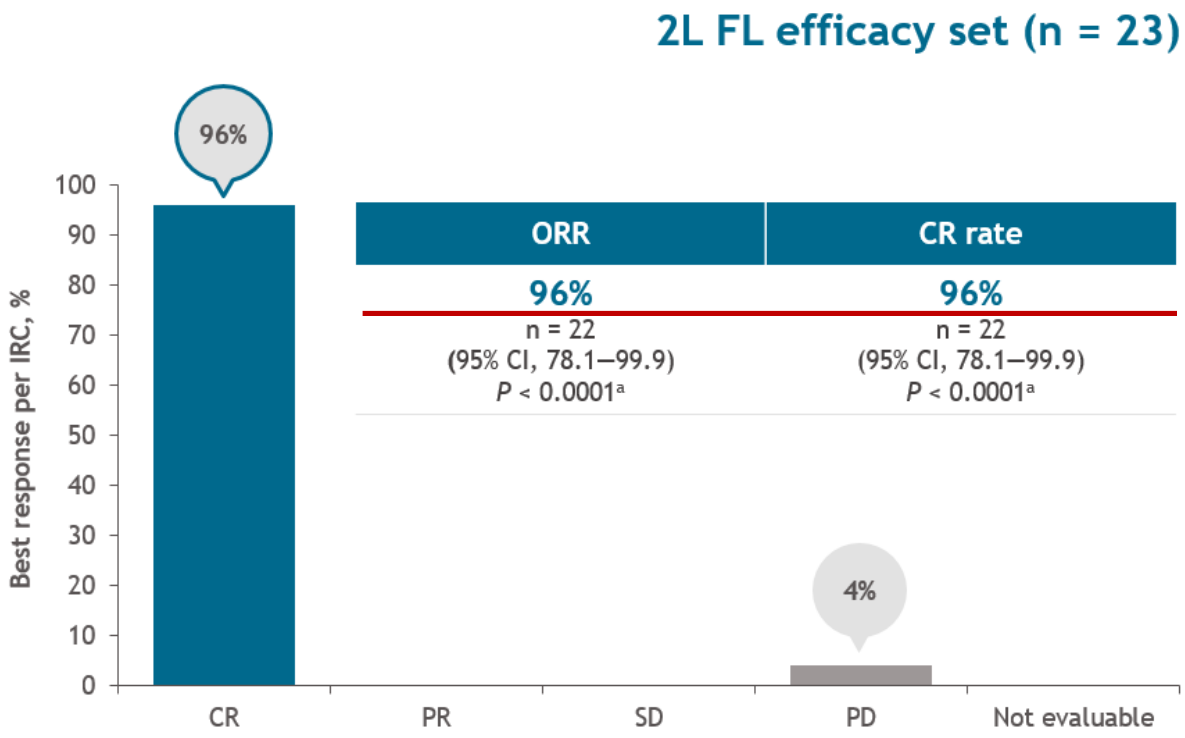
TRANSCEND FL: Primary End Point Results, 2L and 3L+ cohorts



3L FL

ORR was 96%, with all responders achieving CR

In patients with 3L+ FL

- ORR = 97%
- CR rate = 94%

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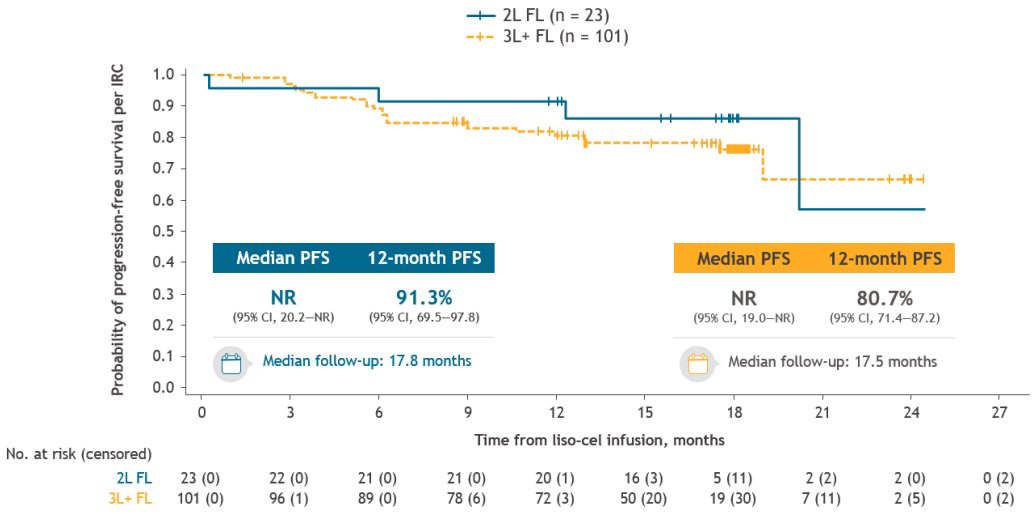
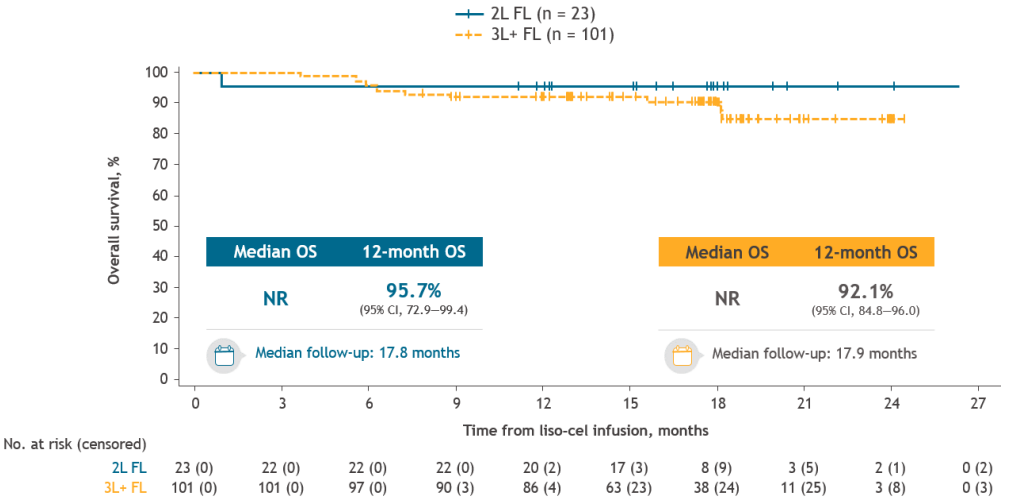
TRANSCEND FL: Survival Analysis, 2L and 3L+ cohorts

2L = blue

Progression Free Survival



Overall Survival



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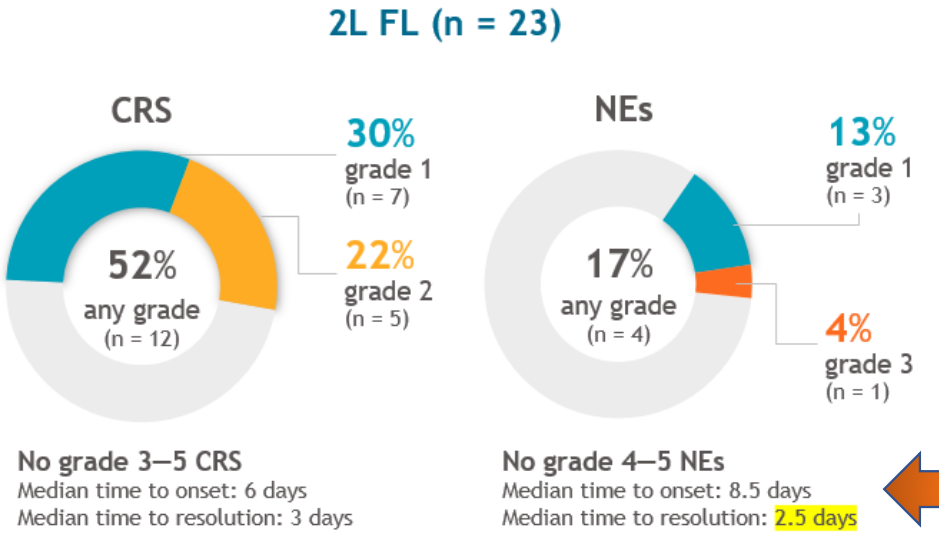
TRANSCEND FL: Adverse Events of Special Interest, 2L and 3L+ cohorts



CRS and NEs incidence	3L+ cohort	
	All Grade	Grade ≥3
CRS	59%	1%
Median time to CRS resolution: 4 days		
Neurological adverse events	15%	2%
Median time to resolution: 4.5 days		

CRS and ICANS, 2L & 3L+ with Liso-cel

Low rate of Gr.3-4 CRS and NEs

2L vs 3L+: possible impact on NEs duration and subsequent need of mitigation strategies (steroids; tocilizumab)

2L NE (gr. 3) = 1 case, duration 2 days

13% vs 31% received tocilizumab and/or corticosteroids to manage CRS/NEs

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REAL LIFE early experiences with CAR-T cells for Follicular Lymphoma

Ysebaert et al. Axi-cel / Tisa-cel for R/R FL, French DESCART ASH 2023	
Patients, n (Tisa-cel; Axi-cel)	70 (62; 8)
Median Age	62y
POD24 after 1st CT, %	62.8
Previous ASCT, %	44.3
Previous lines, median (range)	3 (2-9)
ORR, %	97.5
CR, %	87.5
CRS Gr.≥3	1.4
ICANS Gr.≥3	4.3
6-month estimated PFS	71.8 (56.6-82.4)
6-month estimated OS	97.4 (83.2-99.6)
Median FU	7.3 months

JACOBSON et al. Axi-cel for R/R FL, US ASCO 2023	
Patients, n	230
Median Age	62y
Chemo-resistant, %	66
ZUMA-5 ineligible, %	40
Previous lines, median (range)	4 (1-13)
ORR, % (95% CI)	93 (88-97)
CR, % (95% CI)	84 (77-89)
CRS Gr.≥3, % (95% CI)	2 (0-6)
ICANS Gr.≥3, % (95% CI)	13 (8-19)
6-month estimated PFS	88 (81-92)
6-month estimated OS	96 (91-98)
Median FU	6.2 months

Comparative effectiveness of ZUMA-5 (axi-cel) vs SCHOLAR-5 external control in relapsed/refractory follicular lymphoma

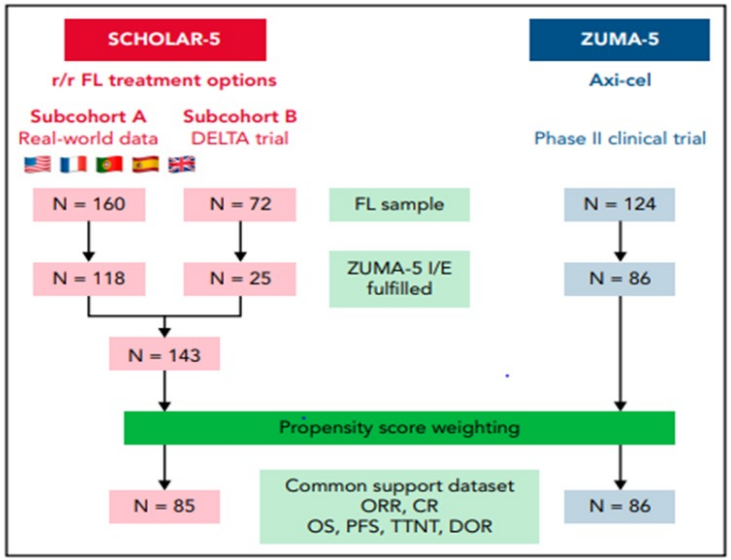
Paola Ghione,[1,2,*] M. Lia Palomba,[2,*] Anik R. Patel,[3] Sabela Bobillo,[4] Kevin Deighton,[5] Caron A. Jacobson,[6] Myrna Nahas,[3] Anthony J. Hatswell,[5] A. Scott Jung,[3] Steve Kanters,[7] Julia Thornton Snider,[3] Sattva S. Neelapu,[8] Maria Teresa Ribeiro,[9] M. Alan Brookhart,[10,11] Herve Ghesquieres,[12] John Radford,[13] and John G. Gribben[14]

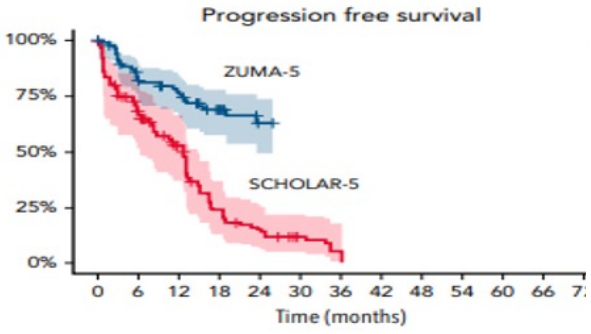
blood Regular Article

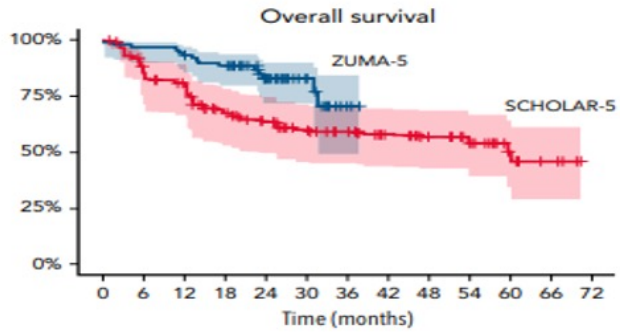
Inclusion criteria, external control

- diagnosed r/r FL
- 3 or more lines of therapy, on or after 23 July 2014

	SCHOLAR-5 (n = 85)*	ZUMA-5 (n = 86)	Treatment effect
Response outcomes	**Responders (%)**	**Responders (%)**	**Odds ratio (95% CI)**
ORR	42 (49.9%)	81 (94.2%)	OR: 16.2 (5.6, 46.9)
CR	25 (29.9%)*	68 (79.1%)†	OR: 8.9 (4.3, 18.3)





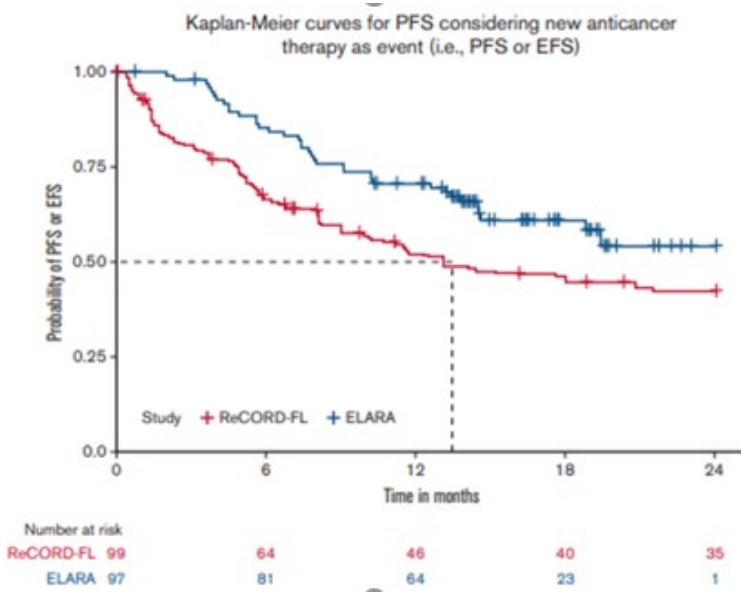


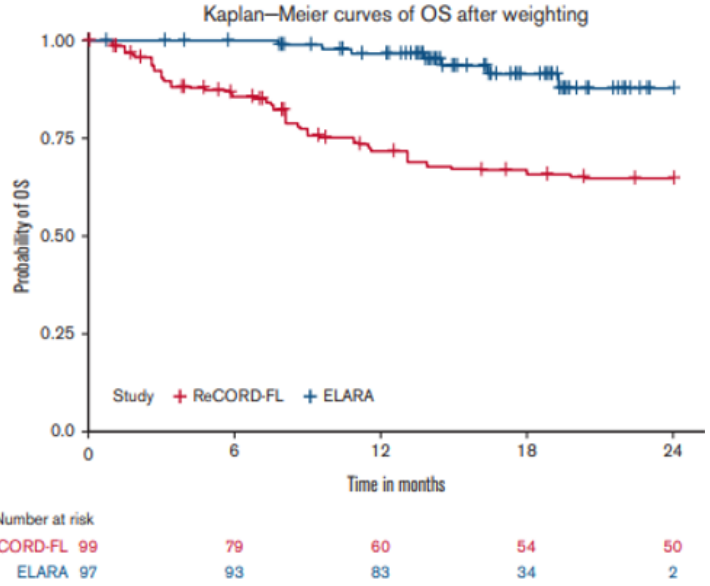
Efficacy comparison of tisagenlecleucel vs usual care in patients with relapsed or refractory follicular lymphoma

blood advances

Gilles Salles,[1] Stephen J. Schuster,[2] Martin Dreyling,[3] Luca Fischer,[3] John Kuruvilla,[4] Piers E. M. Patten,[5,6] Bastian von Tresckow,[7,8] Sonali M. Smith,[9] Ana Jiménez-Ubieto,[10] Keith L. Davis,[11] Carla Anjos,[12] Jufen Chu,[12] Jie Zhang,[12] Chiara Lobetti Bodoni,[12] Catherine Thieblemont,[13] Nathan H. Fowler,[14] Michael Dickinson,[15] Joaquin Martínez-López,[10] Yucai Wang,[16] and Brian K. Link[17]

Usual Care data obtained from ReCORD-FL, a global retrospective cohort study of clinical outcomes in patients who met the ELARA trial's eligibility criteria.





PFS, 12-month
Tisa: 70.5% (61.4%-79.7%)
UC: 51.9% (40.6%-63.3%)
HR: 0.60 (0.34-0.86)

OS, 12-month
Tisa: 96.6% (92.9%-100%)
UC: 71.7% (61.2%-82.2%)
HR: 0.20 (0.02-0.38)

Conclusions - Discussion

- How to treat
  - Who to treat with CAR-T
  - When to use CAR-T
  - Predictive characteristics
- Referral
  - Out patients setting ?
- Availability
- Risk-cost/benefit ratio
- Cost effectiveness
- New products (CAR-NK ?)

Thank you for your kind attention

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico