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Current
Opinions,
Advances,
Controversies in
HEmatology in
Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | 14 aprile 2025 | Grand Hotel Salerno

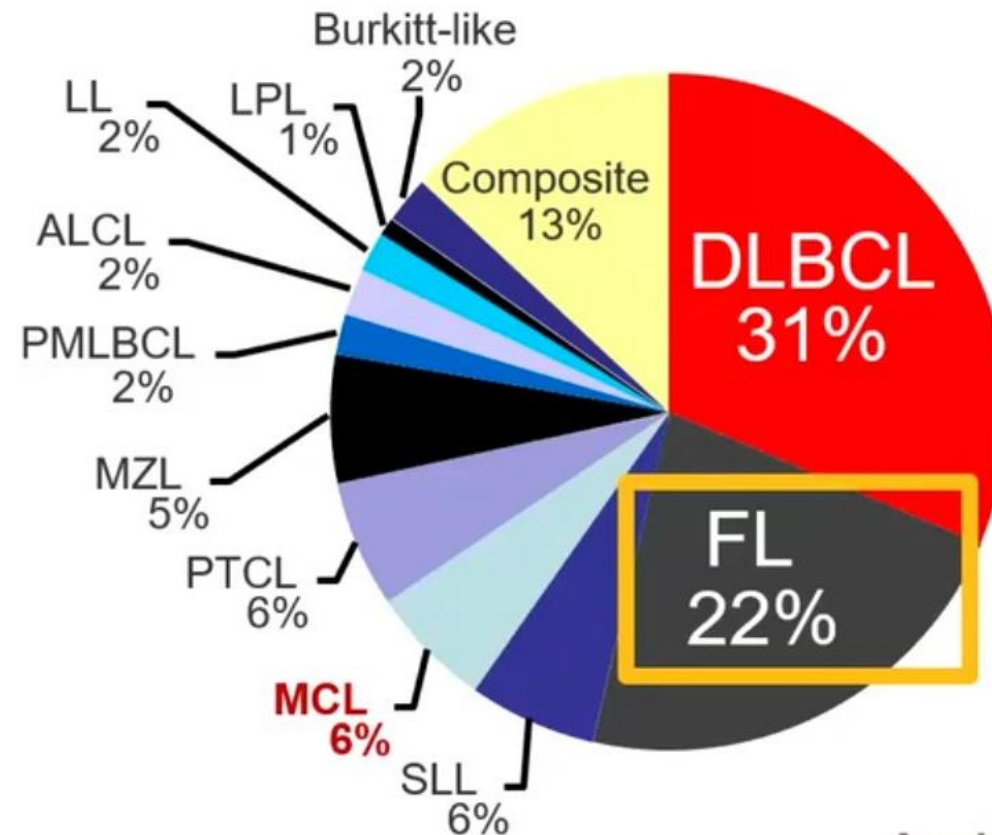
SESSION V: CONTROVERSIES IN R/R FL CAR-T cell before new drugs: Yes

*Dott. Ferdinando Frigeri
UOC Ematologia
AORN «Sant'Anna e San Sebastiano»
Caserta*

Disclosures of Ferdinando Frigeri

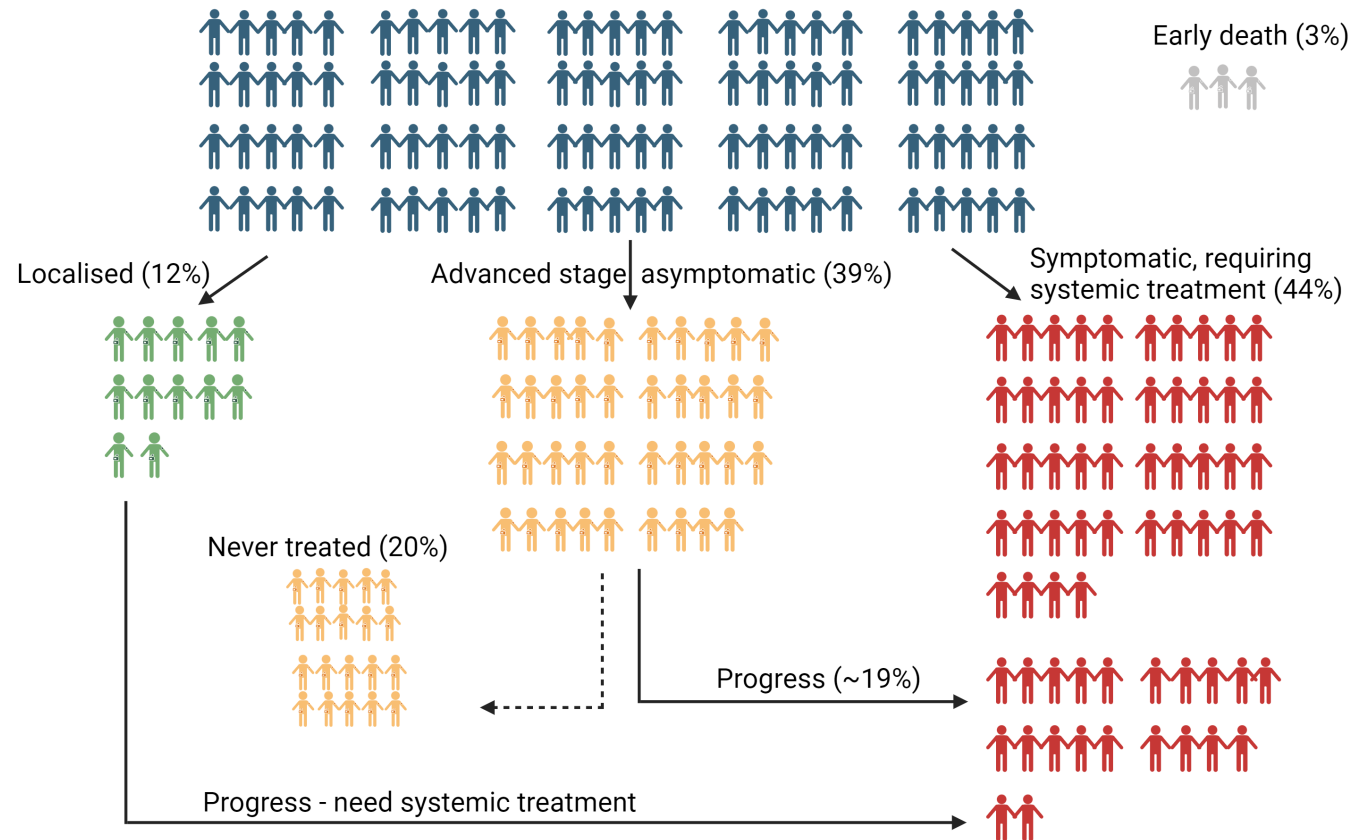
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
CELGENE					X	X	
JANSSEN-CILAG					X	X	
BMS					X	X	
GSK					X	X	
ABBVIE					X	X	
RECORDATI - EUSAPHARMA					X	X	
NOVARTIS					X	X	
ASTRAZENECA					X	X	
SOBI					X	X	
INCYTE					X	X	
GILEAD					X	X	
ELI LILLY					X		
TEVA - GENTILI					X	X	

Non-Hodgkin Lymphomas



Armitage JCO 2018

A Roadmap for Follicular Lymphoma



Trotman & Falconer. Hematology Am Soc Hematol Educ Program 2024

FL: Current first line therapy



ANNALS OF
ONCOLOGY
driving innovation in oncology

2020

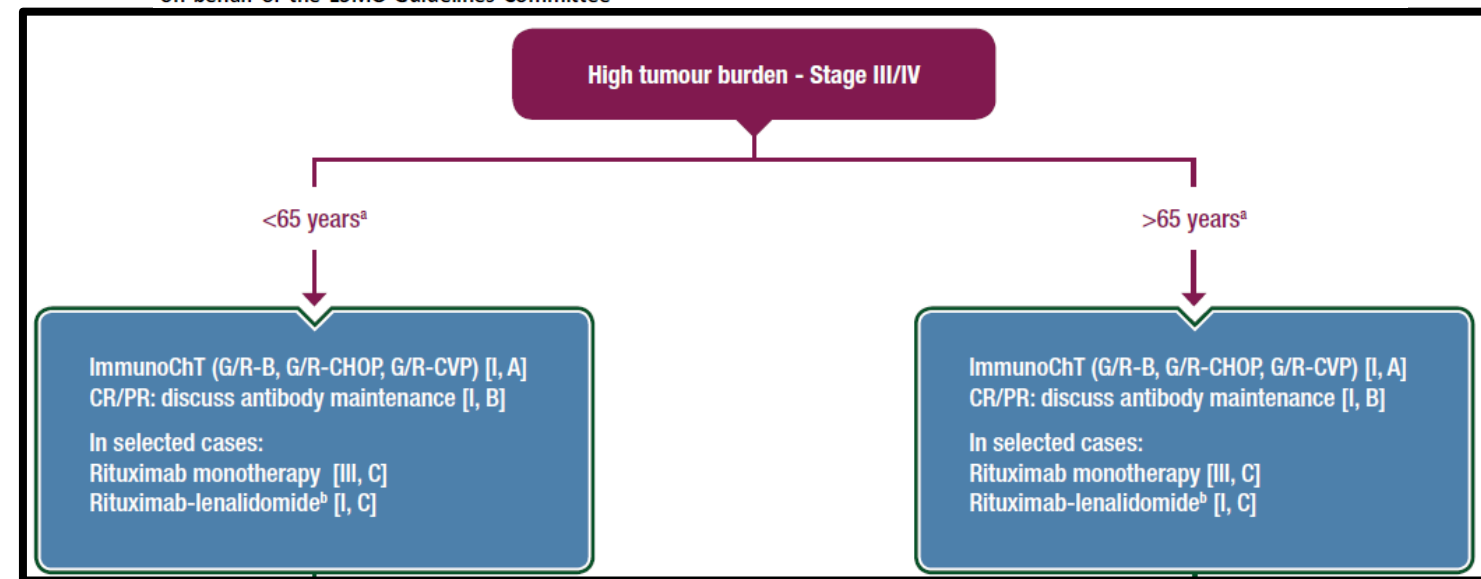
SPECIAL ARTICLE

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up^{†☆}

M. Dreyling¹, M. Ghielmini², S. Rule³, G. Salles^{4,5}, M. Ladetto⁶, S. H. Tonino⁷, K. Herfarth⁸, J. F. Seymour⁹ & M. Jerkeman¹⁰, on behalf of the ESMO Guidelines Committee^{*}

Immuno-chemo + maintenance

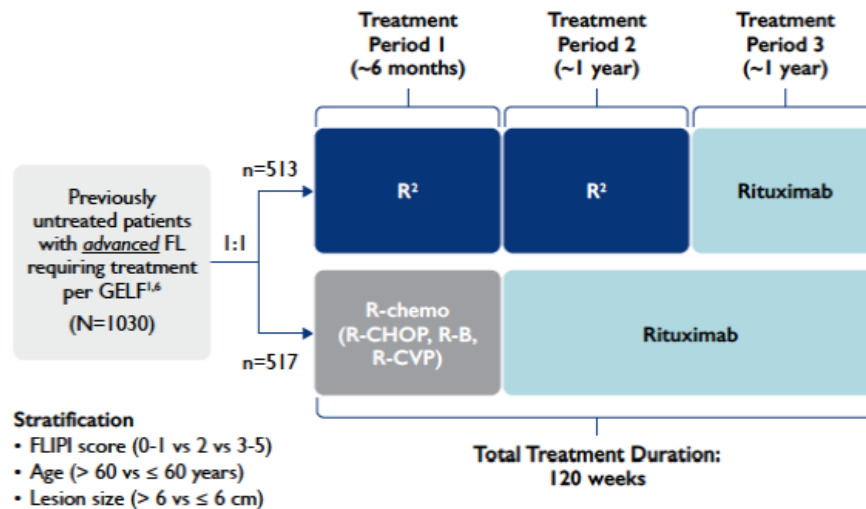
R/O CVP maintenance R/O
CHOP
BENDA



FL: Current chemo-free first line therapy (not in Italy)

Six-Year Results from the Phase 3 RELEVANCE Study: Similar Outcomes for Previously Untreated FL Receiving Lenalidomide Plus Rituximab (R²) versus R-Chemotherapy Followed by R Maintenance

Figure 1. RELEVANCE Study Design



- More patients died from lymphoma in R² arm
- No difference in transformation rate

Figure 3: Progression-Free Survival by IRC, FDA Censoring Rules

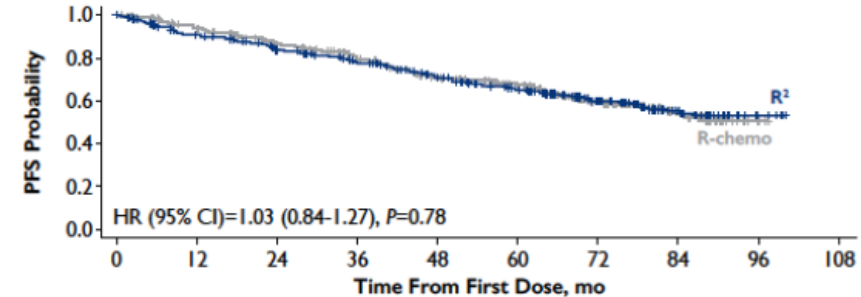
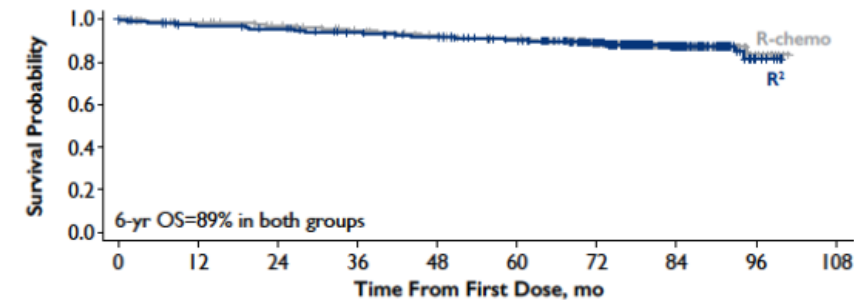
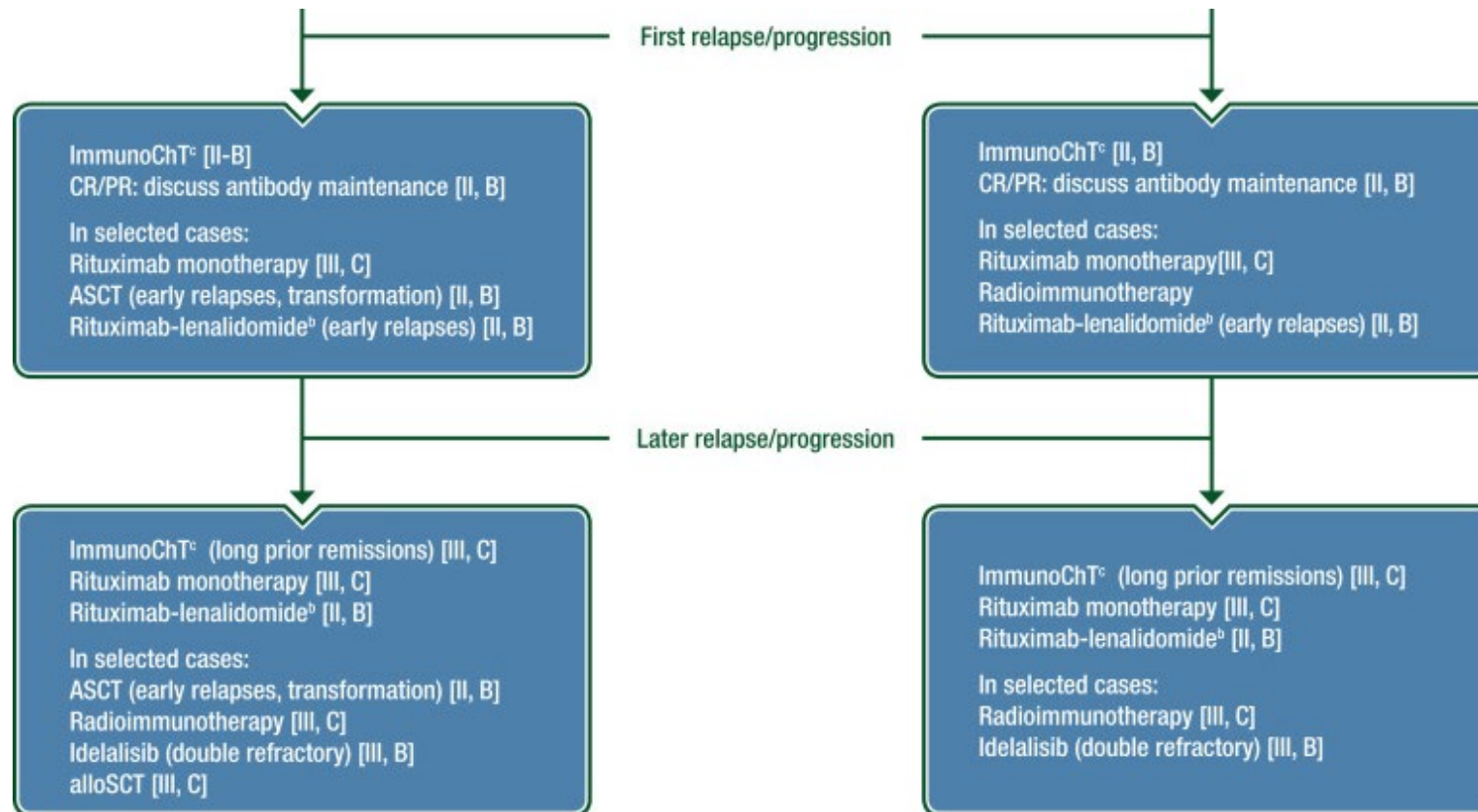


Figure 6: Overall Survival



Morschhauser F, et al JCO 2022

ESMO/EHA treatment algorithm (2021) for R/R FL with high tumor burden



Dreyling M et al, Ann of Oncology 2020

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Treatment patterns and outcomes in FL with POD24

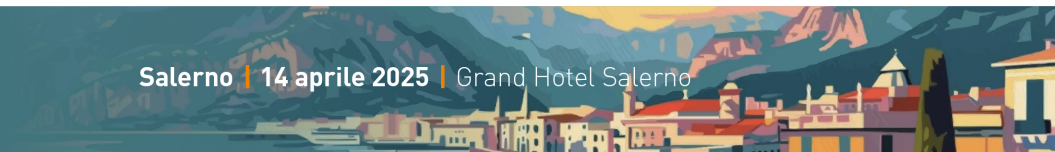
Day JR, et al. *Blood Adv.* 2025 Mar 11;9(5):1013-1023

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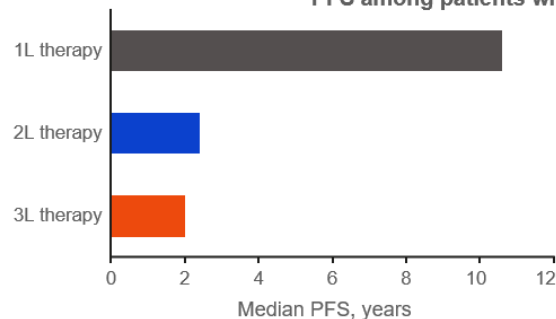
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R/R FL: Outcome by line of therapy

PFS among patients with FL by line of therapy³

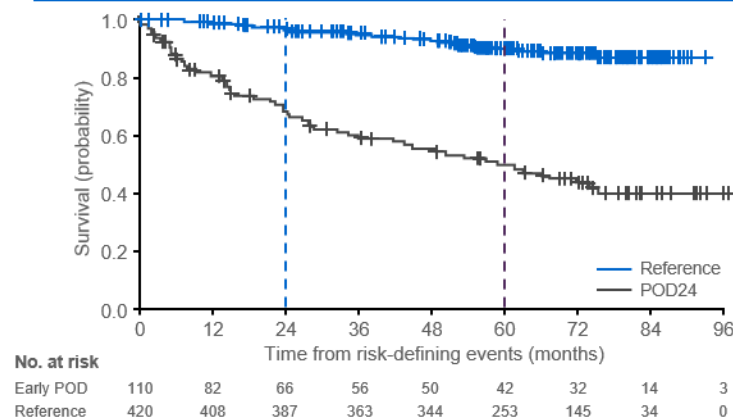


Line of therapy	n	Median PFS, years	5-year PFS
1L	348	10.6	61%
2L	111	2.4	35%
3L	41	2.0	23%

first line; 2L, second line; 3L, third line, FL, follicular lymphoma; PFS, progression-free survival.

1. Teras LR, et al. CA Cancer J Clin 2016;66:443–59;
2. Freedman A & Jacobsen E. Am J Hematol 2019;95:316–27;
3. Rivas-Delgado A, et al. Br J Haematol 2019;184:753–59.

OS by POD24 status (National LymphoCare Study database)*³



	POD24 (n=110)	Reference (n=420)
2-year OS, % (95% CI)	68 (58.2–76.3)	97 (94.6–98.1)
5-year OS, % (95% CI)	50 (39.4–59.2)	90 (86.2–92.4)

Median follow-up: 7 years

*Analysis of 530 patients with previously untreated FL who received R-CHOP.
CI, confidence interval; FL, follicular lymphoma; OS, overall survival; POD, progression of disease; POD24, progression of disease within 24 months; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone.

1. Bachy E, et al. Blood Adv 2021;5:1729–32;
2. Seymour JF, et al. Haematologica 2019;104:1202–8;
3. Casulo C, et al. J Clin Oncol 2015;33(23):2516–22.

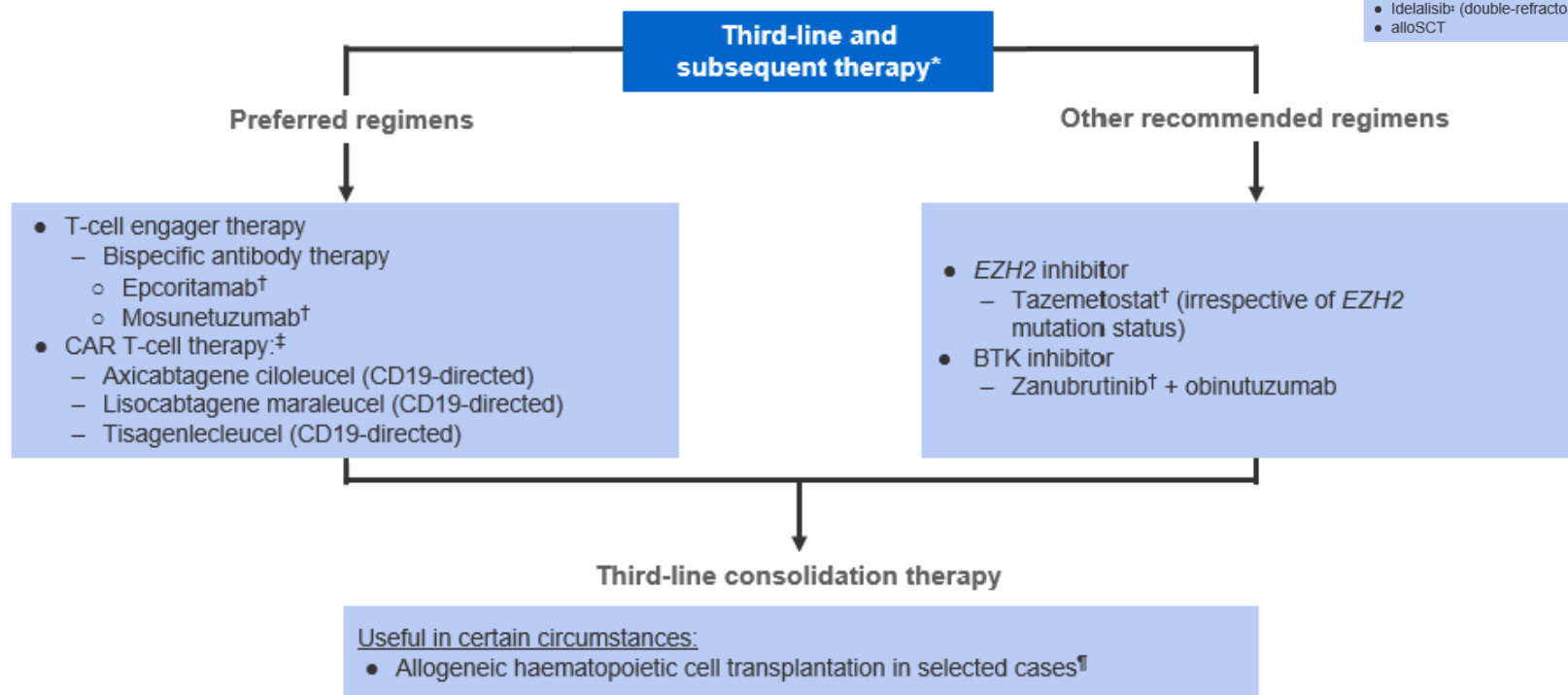
- After the second line of therapy, PFS is significantly lower
- Role of POD24

Historical outcomes in FCL: Third line and Beyond

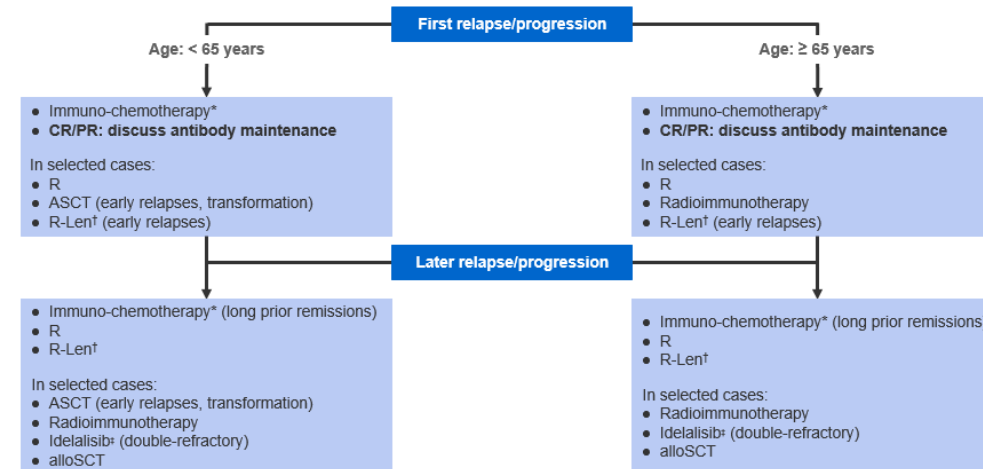


FL: Current ≥3L therapy

NCCN Guidelines for 3L+ R/R FL (V2.2024)



Recommended treatment algorithm for R/R FL with high tumor burden

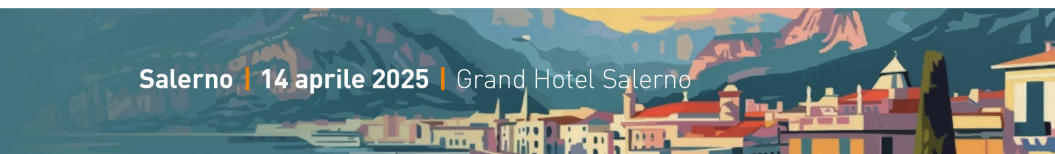


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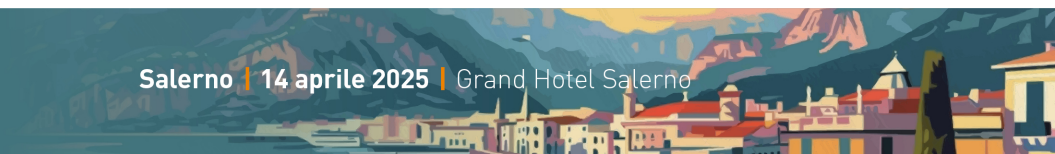


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Bispecific Antibodies and CAR T Cells



T-Cells redirecting strategies in FL ($\geq 3L$)

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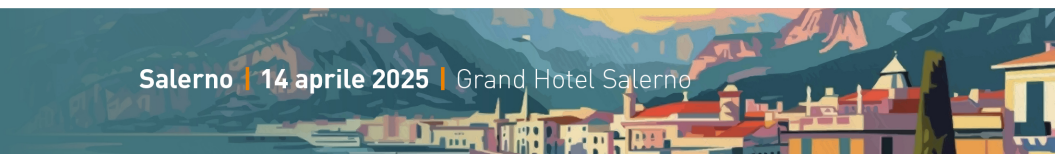


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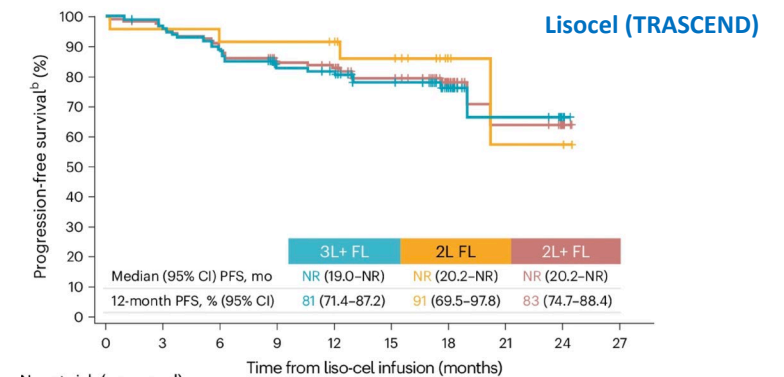
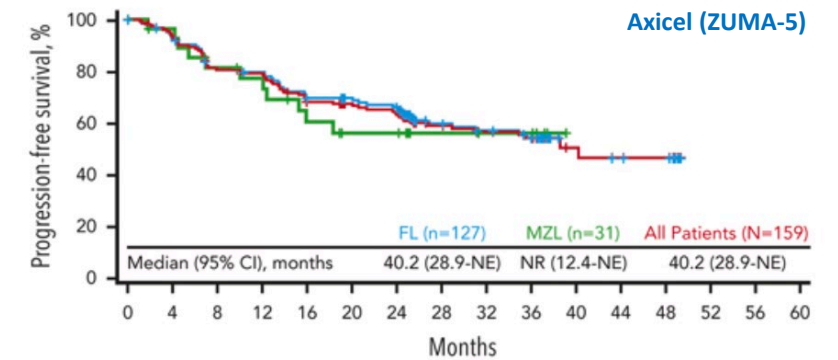
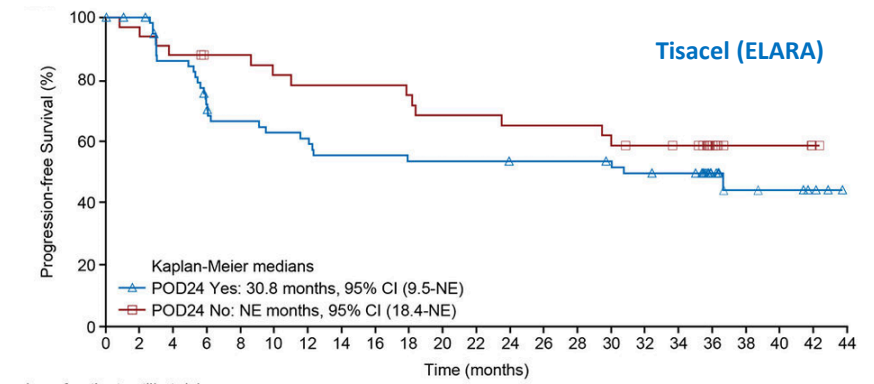
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864. 5-Year Follow-up Analysis from ZUMA-5: A Phase 2 Trial of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. *Neelapu S.S. et al.* Oral presentation.



CAR-T cells Outcomes in RR-FL ($\geq 3L$)



CAR-T and BsAbs in $\geq 3L$ FL

	CAR-Ts			BsAbs		
	Axi-cel	Tisa-cel	Liso-cel	Mosunetuzumab	Epcoritamab	Odronextamab
Main characteristics						
References	(25-27)	(28, 29)	(30)	(46-48)	(49)	(50)
Primary end point	ORR	CRR	ORR	CRR	ORR	ORR
Route	IV	IV	IV	IV	SC	IV
Duration	Single	Single	Single	Fixed	Indefinite	Indefinite
Apheresis, N	127	98	114	—	—	—
Treated, N	124	97	107	90	128	128
Median age, y*	60 (53-67)	57 (49-64)	62 (23-80)	60 (53-67)	65 (39-84)	61 (22-84)
Male, n (%)	73 (59%)	64 (66%)	66 (62%)	55 (61%)	79 (62%)	53%
POD24, n (%)†	68 (56%)	61 (63%)	58 (54%)	47 (52%)	42%	49%
Stage III-IV, n (%)	106 (85%)	83 (86%)	95 (89%)	69 (77%)	85%	85%
High-risk FLIPI (≥ 3), n (%)	54 (44%)	58 (60%)	61 (57%)	40 (44%)	61%	58%
Prior HCT, %	24%	36%	31%	21%	19%	31%
Prior lines, median	3	4	3	3	3	3
Bridging, n (%)	4 (3%)	44 (45%)	44 (41%)	—	—	—
FU, months	53.7	28.9	17.6	37.4	17.7	22.4

Iacoboni G and Morschhauser F, Blood 2025

CAR-T and BsAbs in $\geq 3L$ FL

Iacoboni G and Morschhauser F, Blood 2025

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T-Cells redirecting strategies & POD24 ($\geq 3L$)

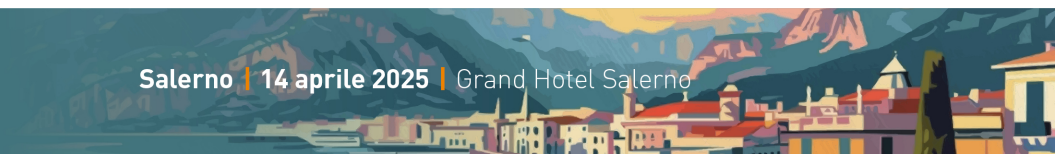
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T-Cells redirecting strategies in FL ($\geq 3L$)

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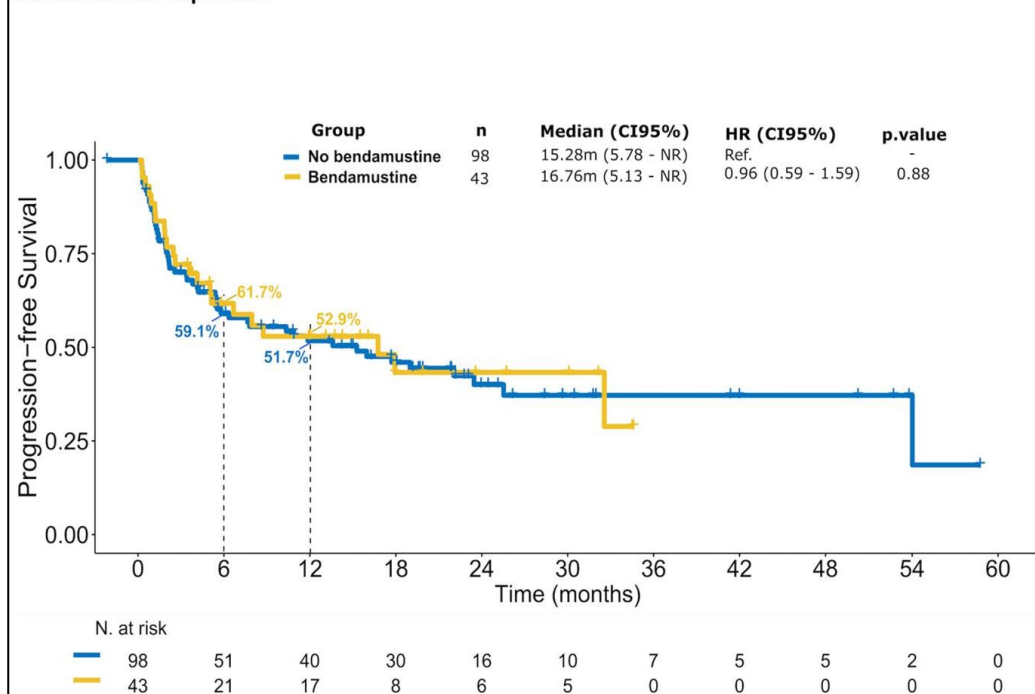


T-Cells redirecting strategies in B-Cell NHL

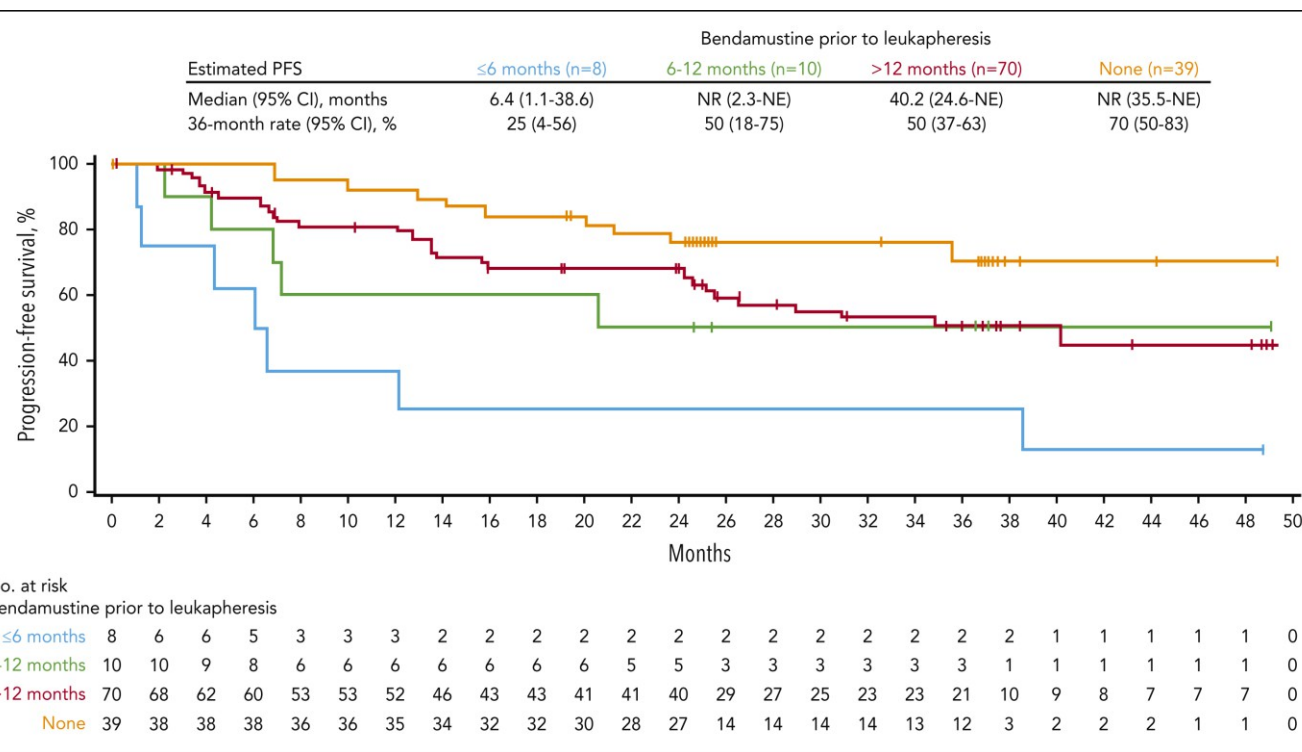


The bendamustine story...

Figure.- Progression-free survival after bispecific antibody treatment according to previous bendamustine exposure.



Iacoboni et al. Blood (2023) 142 (Supplement 1): 310.



Neelapu et al, DOI: 10.1182/blood.2023021243

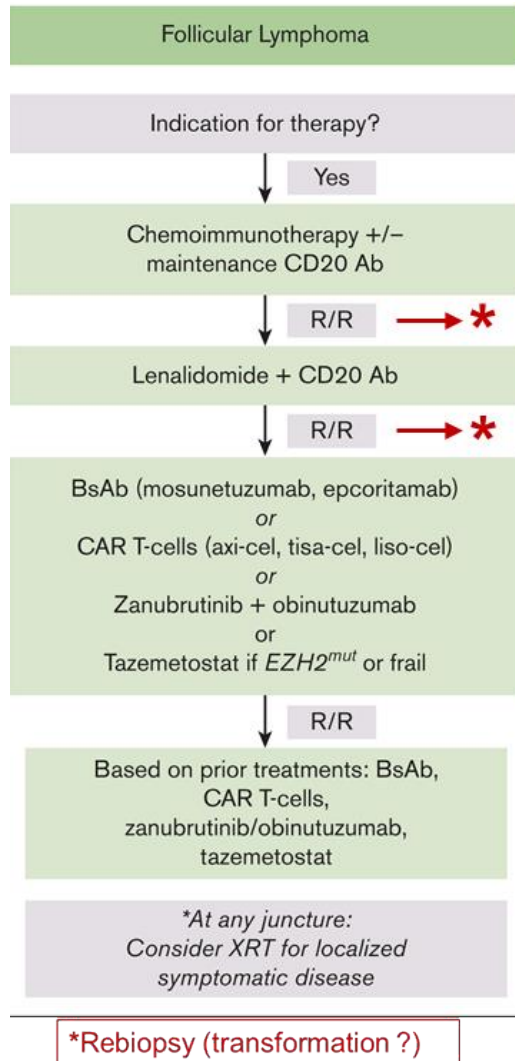
Current treatment algorithm in FL



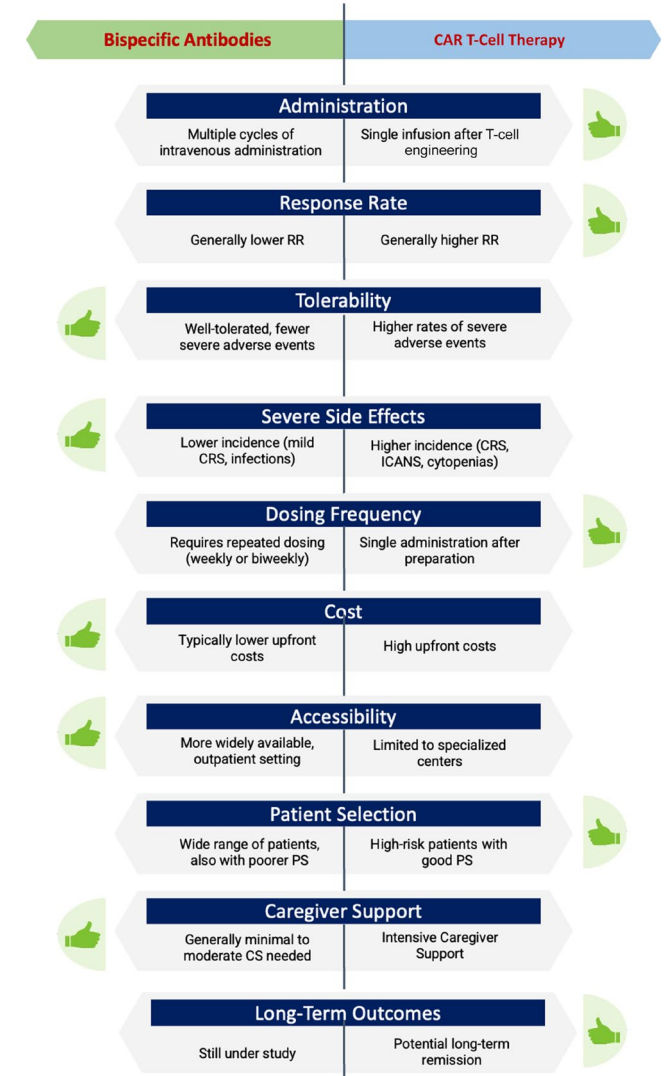
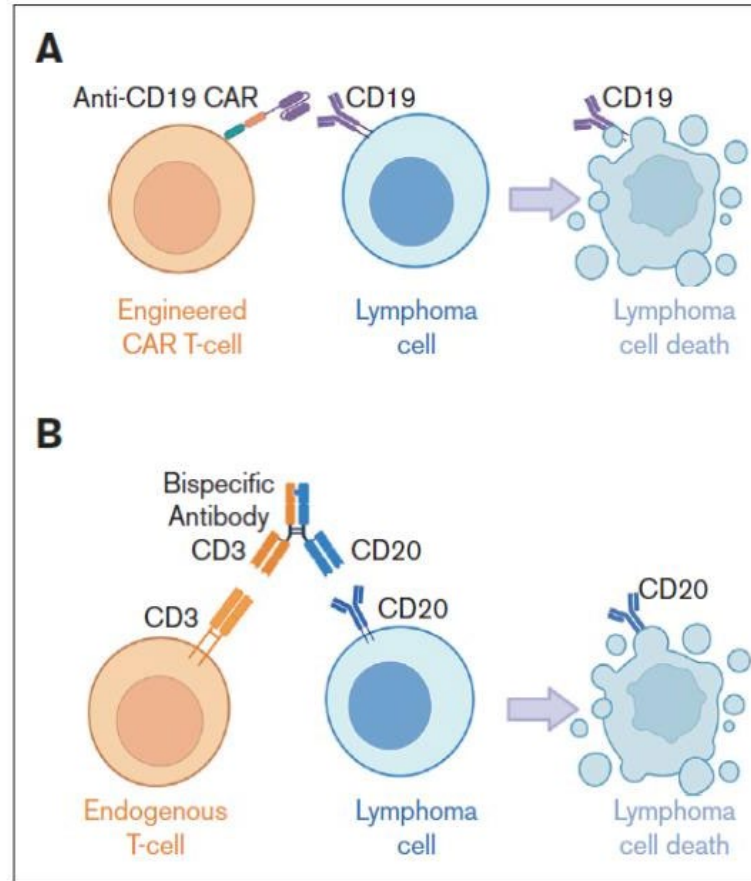
POD24: CAR-T and BsAbs efficacy



Treatment of Follicular Lymphoma



Treatment strategies in RR-FCL: an overview



Haydu JE, Abramson JS. Blood Adv. 2024 Sep 10;8(17):4700-4710

Morabito F et al, Eu J Hematol 2025

Take home messages

- CAR-T therapy offers potential curative benefits with a single infusion, but adverse events (CRS, ICANS, and cytopenias) require specialized management and patient monitoring
- BsAbs provide a more tolerable treatment option counterbalancing by lower response rates and frequent dosing requirements
- CAR-T therapy seem to bypass POD24 status
- There are existing data on BsAbs efficacy after CAR-T, but not vice versa
- A comparative analysis is crucial for informed decision-making by clinicians, patients, and healthcare providers
- *T-cell engagers alone or in combination bring the goal of FL cure closer*

