STRATEGIES FOR THE TREATMENT OF SECONDARY CNS LYMPHOMAS

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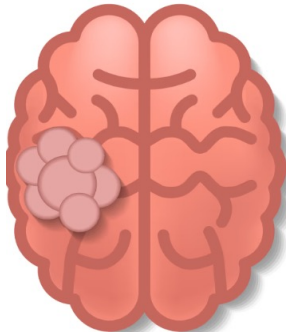
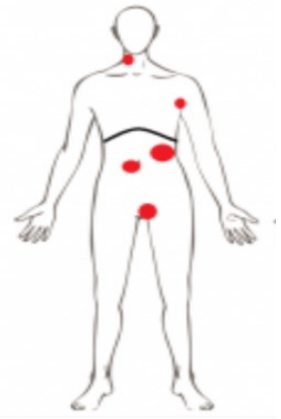
DISCLOSURES

- Consulting: Kite/Gilead, Novartis, BMS, GenMab, Genentech, AstraZeneca, Autolus, Allogene
- Research support: Genmab, Janssen
- Independent review committee: Atara/Pierre Fabre

CLINICAL PRESENTATIONS OF SECONDARY CNS LYMPHOMAS

SCNS De novo

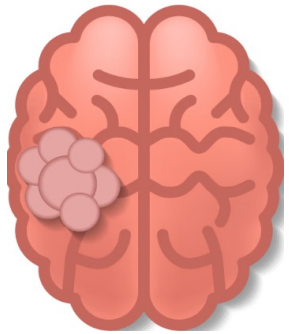




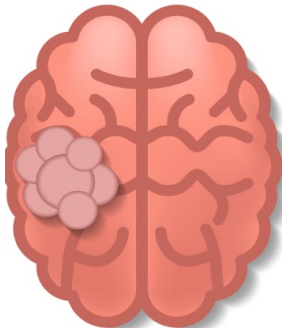
Histology
Aggressive B-cell lymphomas
Burkitt's lymphoma
Mantle cel lymphomas
Indolent lymphomas
T-cell lymphomas

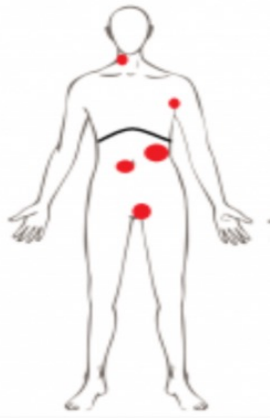
SCNS Relapse

Isolated relapse

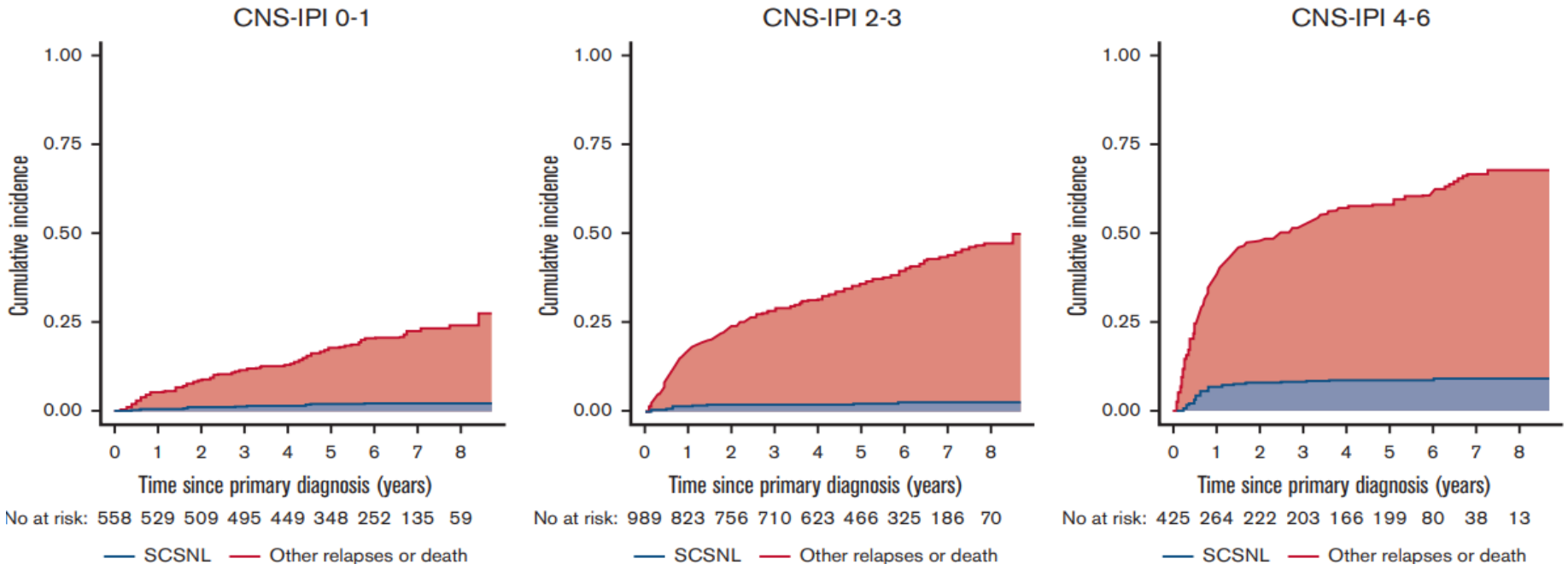


Concurrent CNS/Systemic





SCNS LYMPHOMAS: INCIDENCE



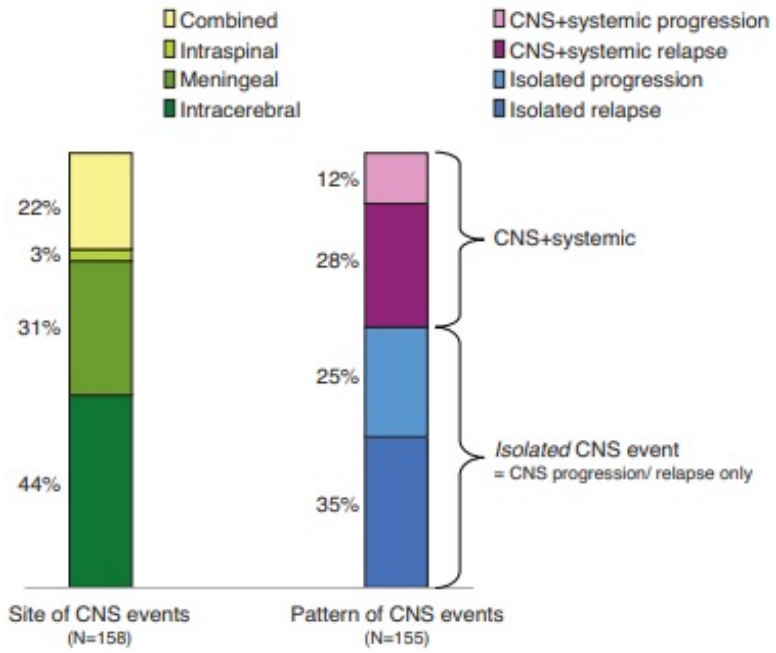
N= 1972

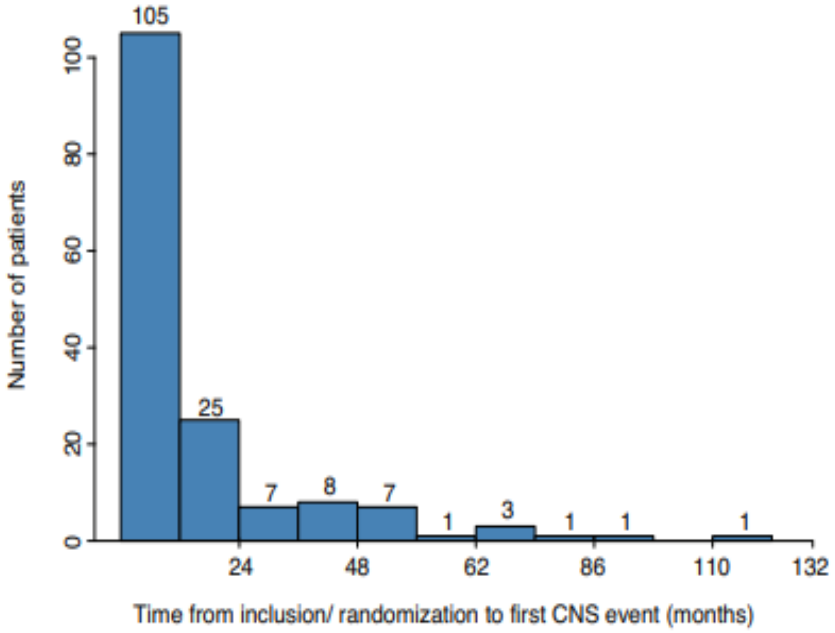
Median time Dx DLBCL to SCNSL: 8.4 months

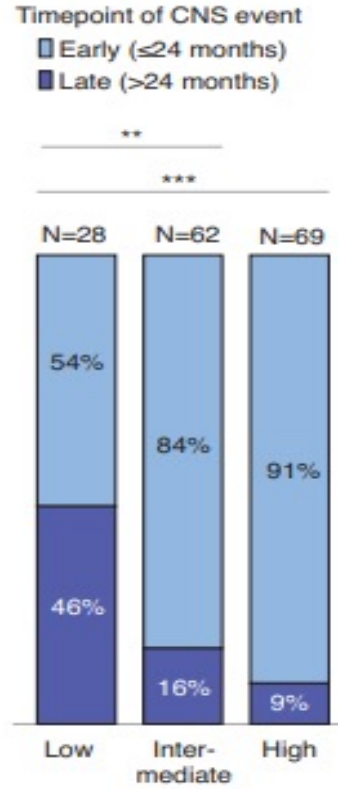
Incidence: 1-y= 2.2%; 2-y= 2.9%

Tolley et al. Blood Adv 2025

SCNS LYMPHOMAS: LYSA AND GLA/DSHNHL, EVALUATION OF PROSPECTIVE TRIALS





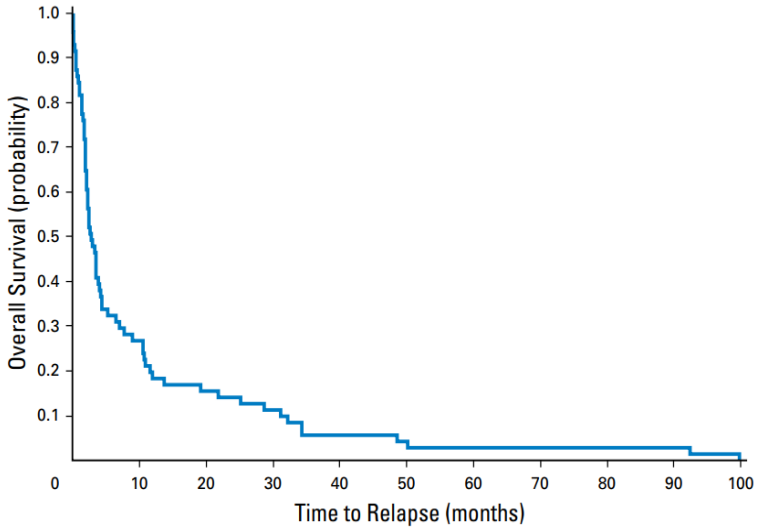


Parenchymal>LMN>combined. Isolated 60%, systemic/CNS= 40%
Early: most within a year, particularly for high risk CNS-IPI score

Frontzek et al. Leukemia 2024

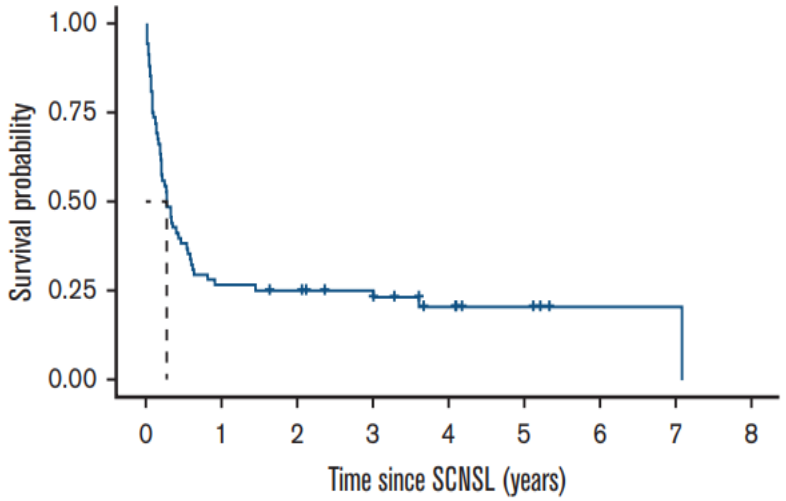
SCNS: PROGNOSIS IS POOR

German/British Columbia



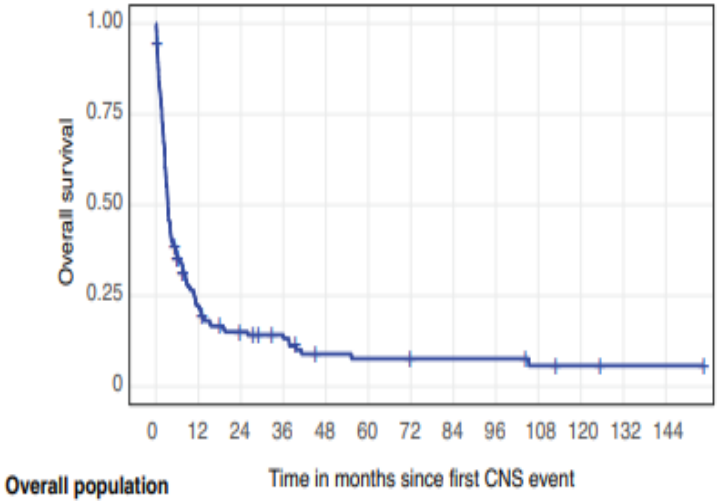
Median OS: 3.5 months

Danish/LYFO



Median OS: 3.2 months

LYSA/GLA (German)



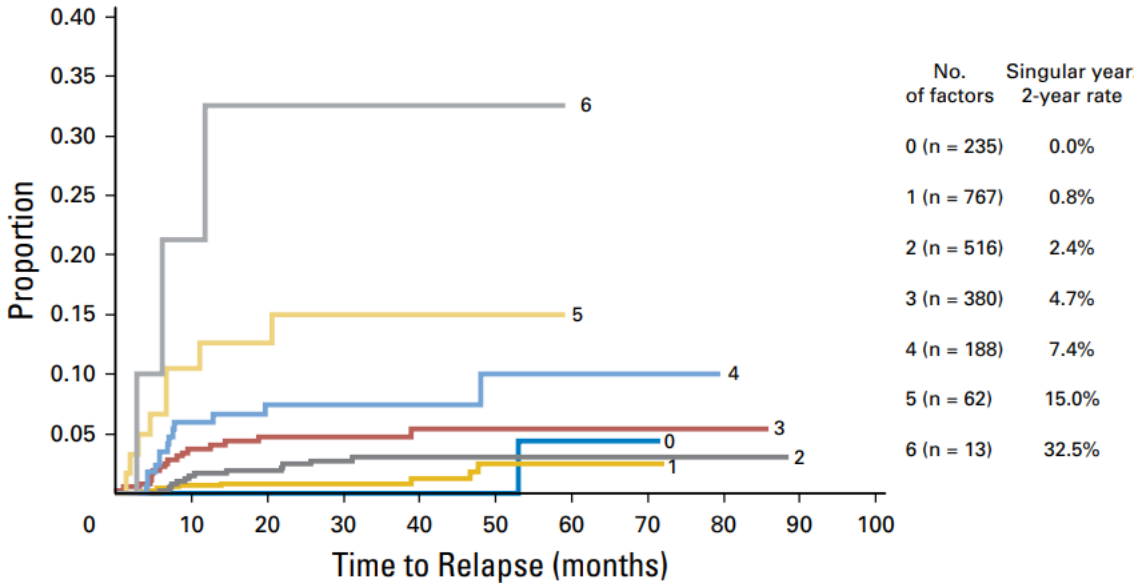
Median OS: 3.4 months

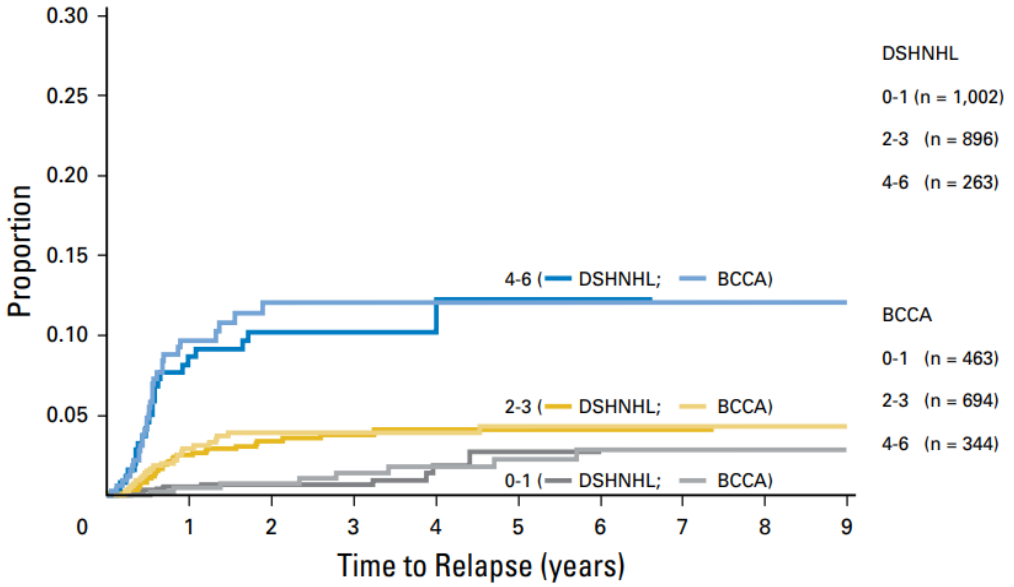
Schmitz N et Al. J Clin Oncol 2016,Tolley et al. Blood Adv 2025, Frontzek et al. Leukemia 2024

SCNS: RISK STRATIFICATION (CNS-IPI SCORE)

Factor	Hazard Ratio	95% CI	*P*
Kidney and/or adrenal glands involved	2.8	1.3 to 5.8	.006
Age > 60 years	2.5	1.3 to 4.5	.001
LDH > normal	2.4	1.3 to 4.5	.005
ECOG PS > 1	2.2	1.3 to 3.9	.006
Stage III/IV disease	2.0	1.0 to 3.8	.039
Extranodal involvement > 1	1.0	0.5 to 1.8	.935

CNS IPI: risk of relapse
Score 0 – 1: 0.6%
Score 2 – 3: 3.4%
Score 4 – 6 : 10.2%





Schmitz N et Al. J Clin Oncol 2016

CNS-IPI SCORE CONSISTENT ACROSS SERIES: 2-YEAR CNS RELAPSE

	No patients	All pts with DLBCL 2-year CNS rate of relapse	Low risk (0–1 factors)	Intermediate risk (2–3 factors)	High risk (4–6 factors) 2-year
DSHNHL*[1]	2164‡	4%	0·6%	3·4%	10·2%
BC Cancer*[1]	1597	4%	0·8%	3·9%	12%
Multi-centre[2]	1532	4% (3-year)	0·4% (3-year)	3% (3-year)	11% (3-year)
GOYA[3]	1418	2·8%	0·8%	1·9%	8·9%
UK NCRI[4]	1080	1·9% (All)	0%	2·2%	5·2%

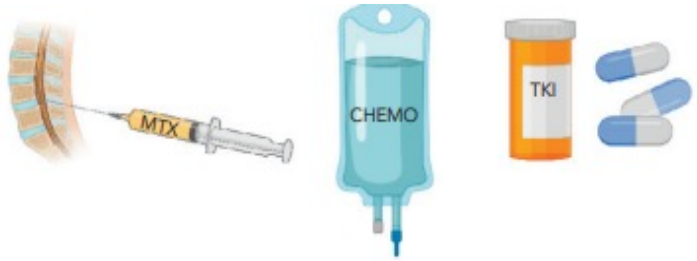
Eyre T et Al. Lancet Oncol 2022

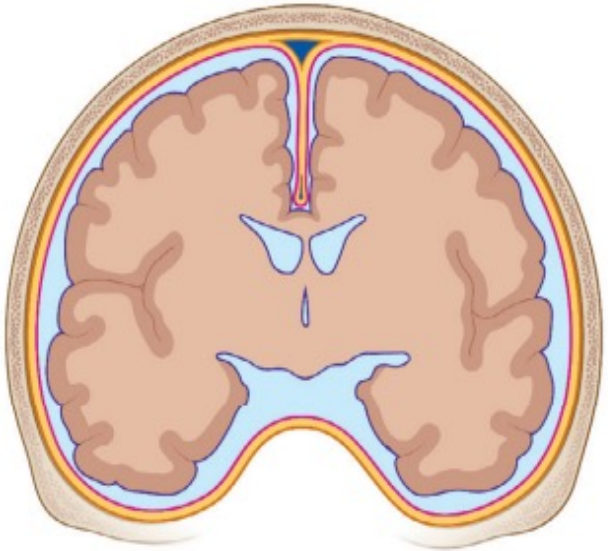
BIOMARKERS ARE ALSO ASSOCIATED WITH CNS RELAPSE SIK

Biomarkers	Frequency	Incidence CNS relapse	
MYC^{+} *BCL2*$^{+}$ double hit[8]	~5–10%	13–50%	Exclusively GCB; estimates highly variable depending on selection criteria
ABC DLBCL[3, 9]	30–40%	7–9%	..
MYC^{+} *BCL2*$^{+}$ dual expressers[9]	~30%	All 9·3% CNS-IPI high 22·7% CNS-IPI intermediate 11%	Two-thirds are ABC subtype
MCD DLBCL subtype[10]	~15%	38% (overall risk)	No large-scale studies
CD5^{+} DLBCL[11]	5–10%	12·7%	No large-scale studies

Eyre T et Al. Lancet Oncol 2022

DOES CNS PROPHYLAXIS WORK? YES





CNS-directed prophylaxis

Cheah et al (N=217)
High risk/multiple EN
LDH, B sx

	Relapse risk	
None	18%	(p= 0.006)
HD-MTX	6.9%	
HD-MTX + IT	2.3%	

Ong et al (N= 226)
CNS-IPI ≥4, HR-EN

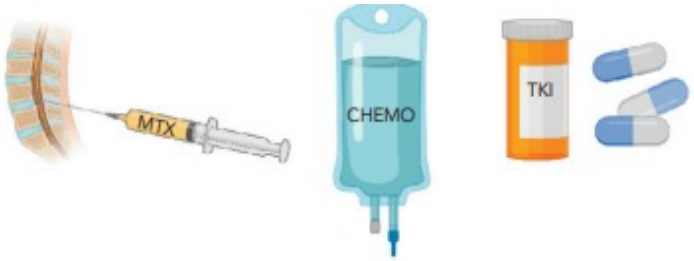
	Relapse risk	
No HD-MTX	14.6%	(p= 0.046)
HD-MTX	3.1%	

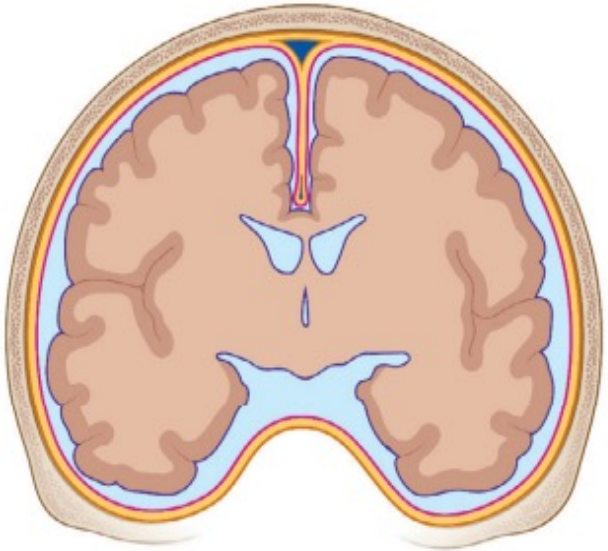
Ferreri et al (N= 200)
HR-EN, stage IV
LDH

	Relapse risk	
None or IT	12 %	(p= 0.046)
HD-MTX	0%	

Chea CY et Al. Br J Cancer 2014, Ong SY. Blood Cancer J 2021, Ferreri A et Al. Br J Haematol 2015

DOES CNS PROPHYLAXIS WORK? NO





CNS-directed prophylaxis

Bobillo et al (N=585)
HR-EN, DHL
CNS-IPI ≥ 4

	Relapse risk	
None	7.5%	(HR .76[0.35-.1,5])
IT-MTX	5.5%	
HD-MTX	5%	

Relapse reduction at 1-y but not a 5-y

Puckrin et al (N= 906)
CNS-IPI ≥4, DHL,HR-EN
>1 EN, PS> 1, LDH

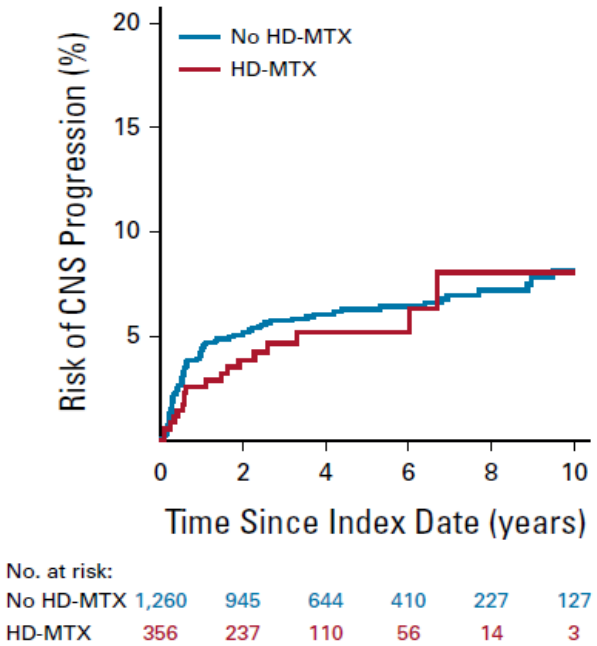
	Relapse risk	
No HD-MTX	12.2%	(p= NS)
HD-MTX	11.2.%	

Lewis et al (N= 2418)
CNS IPI ≥4, HR-EN, DHL
Testicular/breast

	Relapse risk	
None	9.1%	(p= 0.43)
HD-MTX+/- IT	8.4%	

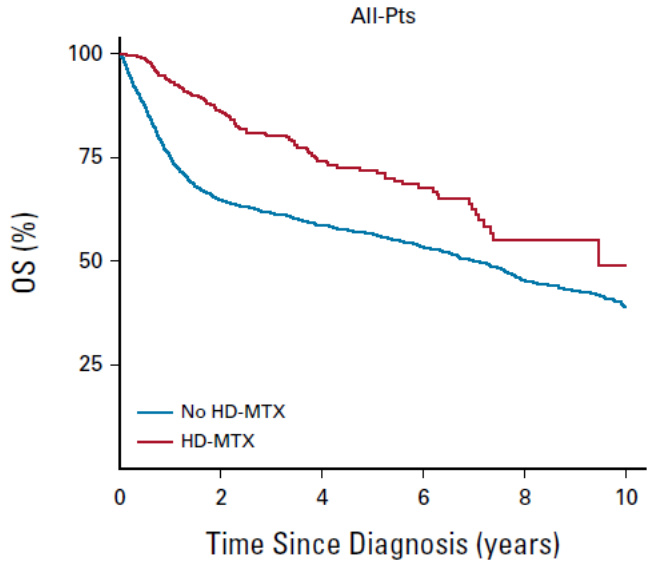
Bobillo S et Al. Blood Cancer J 2021 , Puckrin et Al. Am J Hematol 2021, Lewis K et Al. J Clin Oncol 2022

HD METHOTREXATE AS CNS PROPHYLAXIS FOR HR AGGRESSIVE LYMPHOMAS (N= 2418 PTS)



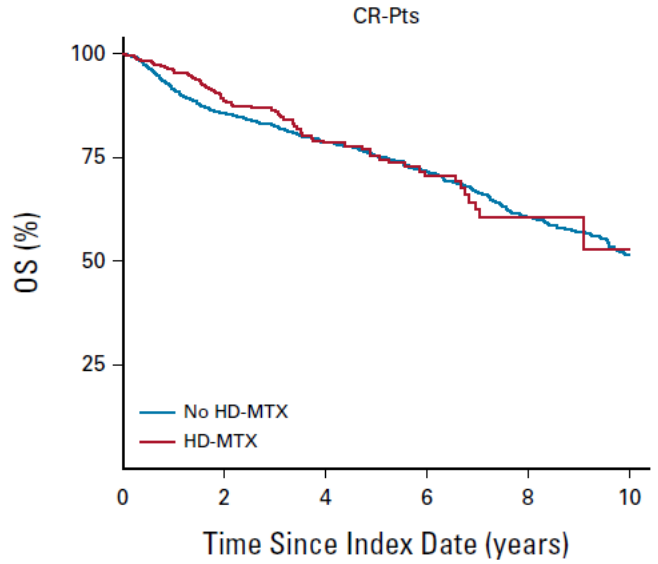
No. at risk:

No HD-MTX	1,260	945	644	410	227	127
HD-MTX	356	237	110	56	14	3



No. at risk:

No HD-MTX	1,993	1,224	841	554	311	180
HD-MTX	425	307	146	79	22	7



No. at risk:

No HD-MTX	1,260	1,001	697	451	257	149
HD-MTX	356	255	124	64	16	4

No differences between intercalated or EOT HD MTX, <3gm2 vs ≥ 3gm2
Systemic disease control seems important

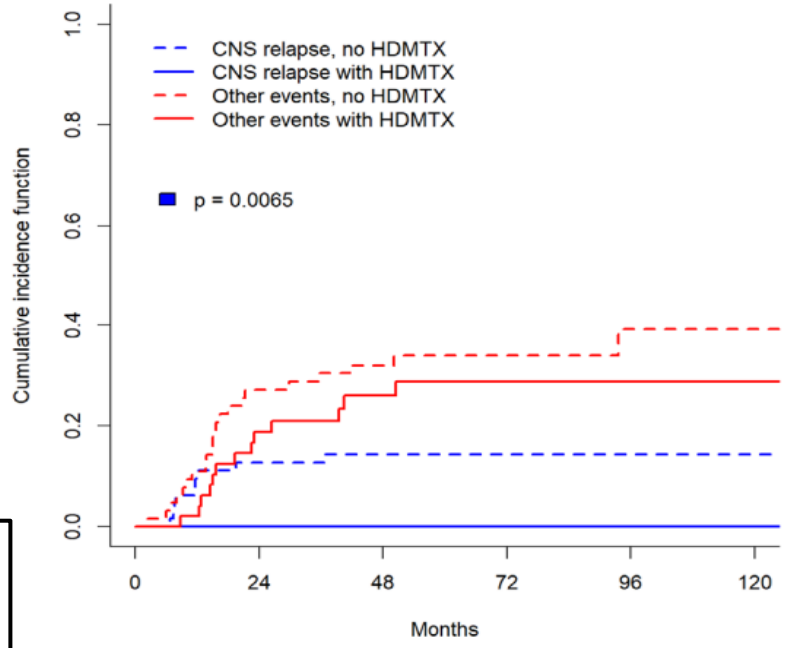
Lewis K et Al. J Clin Oncol 2022

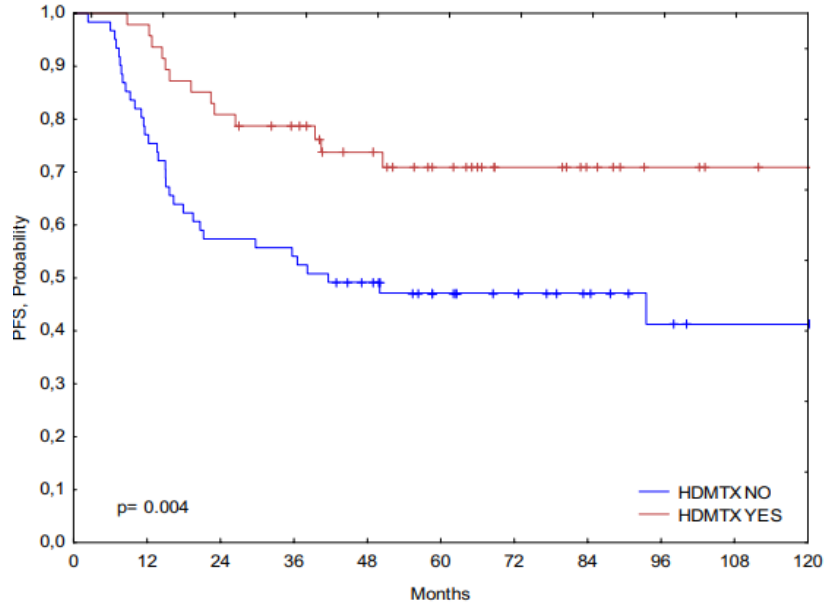
3 HR HD MTX INFUSION IMPROVES PFS AND REDUCES CNS RELAPSE

N= 336
High CNS risk (N= 108)
- CNS IPI ≥4
- EN ≥3
- 1 HR EN (breast, testicular, kidney)

HD MTX 3g/m2 (2-4 cycles) EOT

	Relapse risk
HD MTX	14%
No HD MTX	0%





Ferreri A et Al. Am J Hematol 2026

Guilherme Perini, MD
@GuiperiniMD

𝕏.com

The history of CNS prophylaxis remains open?

> **Mostafa Faisal** @MostafaFaisal14 · 3d
> Three-Hour Infusion of Methotrexate at 3 g/m2 With or Without Intrathecal Chemotherapy Significantly Reduces CNS Relapses and Improves Survival in Patients With Large B-Cell Lymphomas at Increased CNS Risk
> onlinelibrary.wiley.com/doi/abs/10.100...

6:24 AM · 3/17/26 · **3.7K** Views

1 2 12 14

Toby Eyre @tobyeyre82 · 3d
wait for EHA26.....

3 21 1.8K

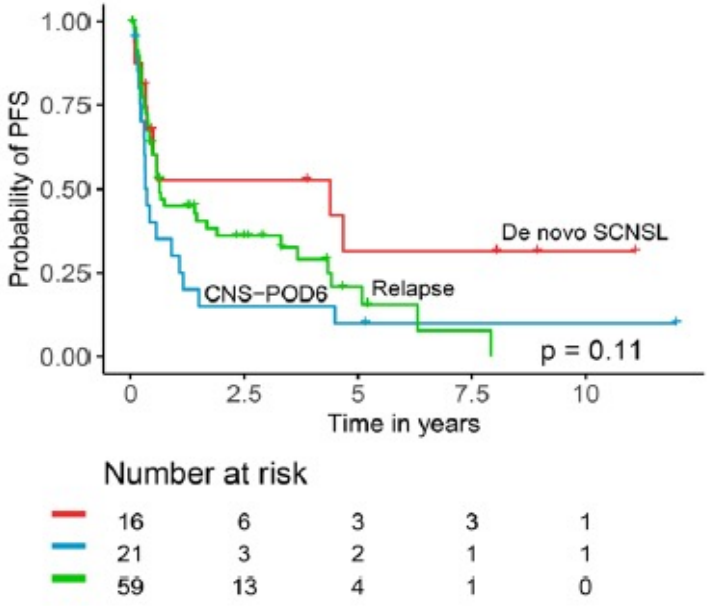
APPROACH TO MANAGEMENT

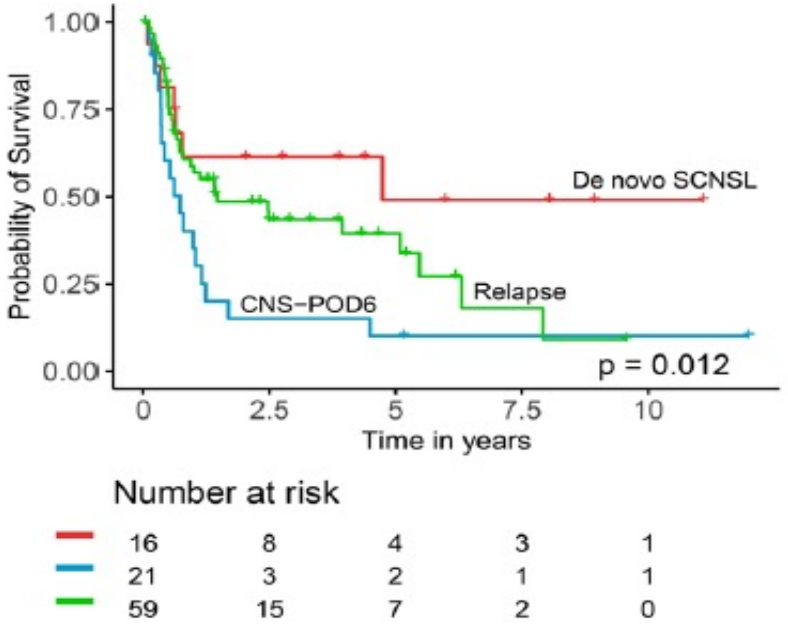
SCNS HETEROGENEITY IMPACTS MANAGEMENT

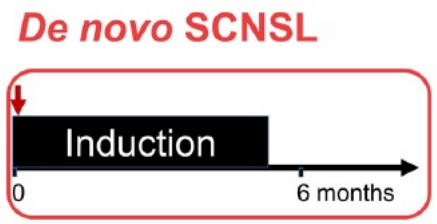
Type of SCNS	Temporal	Clinical factors	Biology/Molecular
Leptomeningeal	De novo	Age	ABC vs GCB
Parenchymal	During systemic Rx	Performance status	MYC rearrangements
Parenchymal/LMN	Post CNS prophylaxis	Stage	C5, MCD
Spine	Post systemic CR	Availability of novel therapies	
Vitreoretinal			
Concurrent w/ systemic			

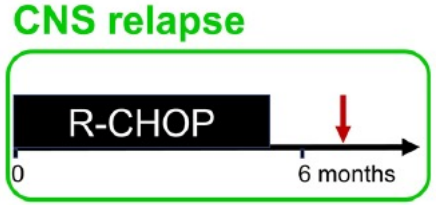
They can overlap!

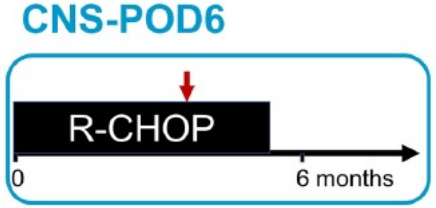
TIMING OF SECONDARY CNS LYMPHOMA SEEMS IMPORTANT







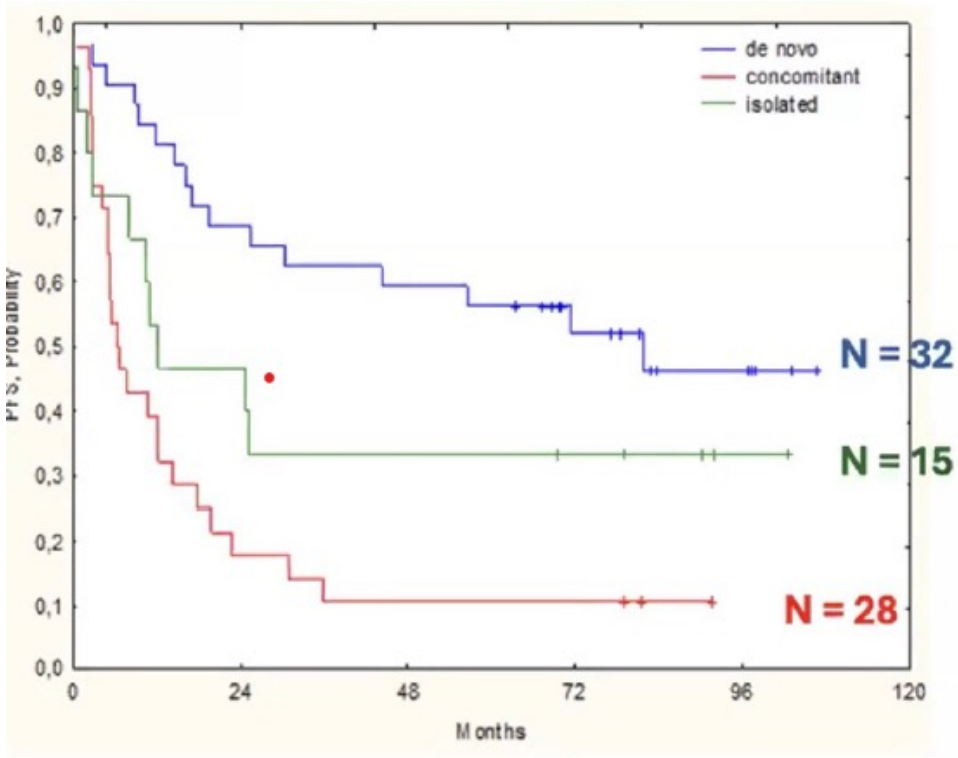




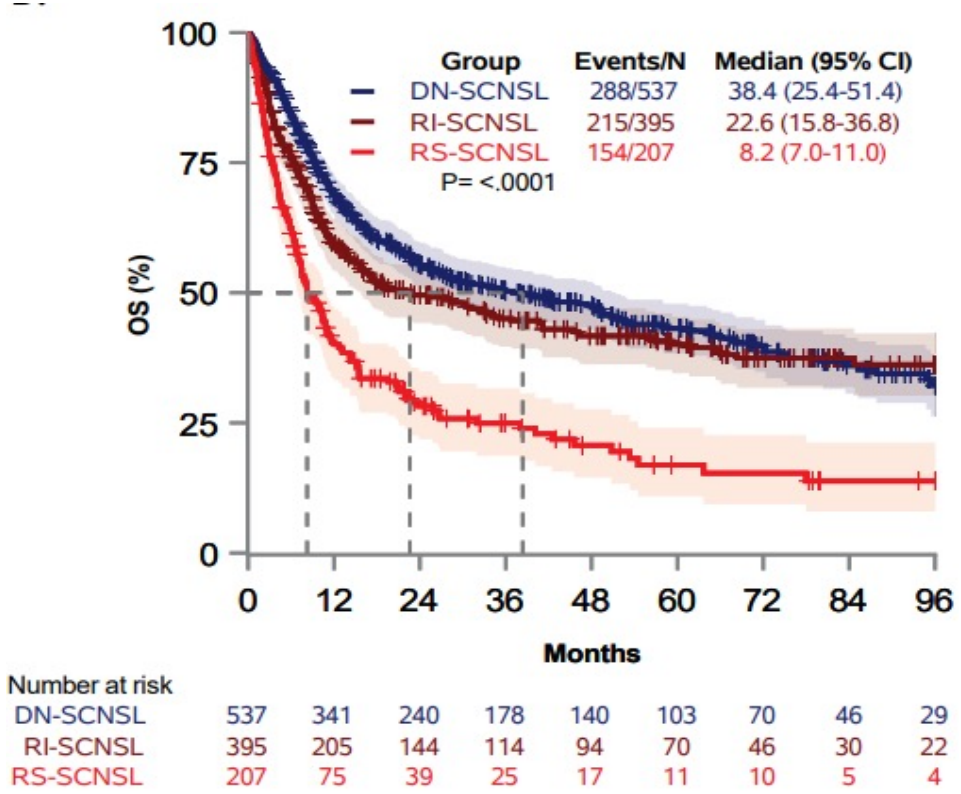
Treiber H et Al. Hemasphere 2023

POOR PROGNOSIS FOR CONCURRENT SYSTEMIC/CNS RELAPSES VS DE NOVO AND ISOLATED RELAPSES

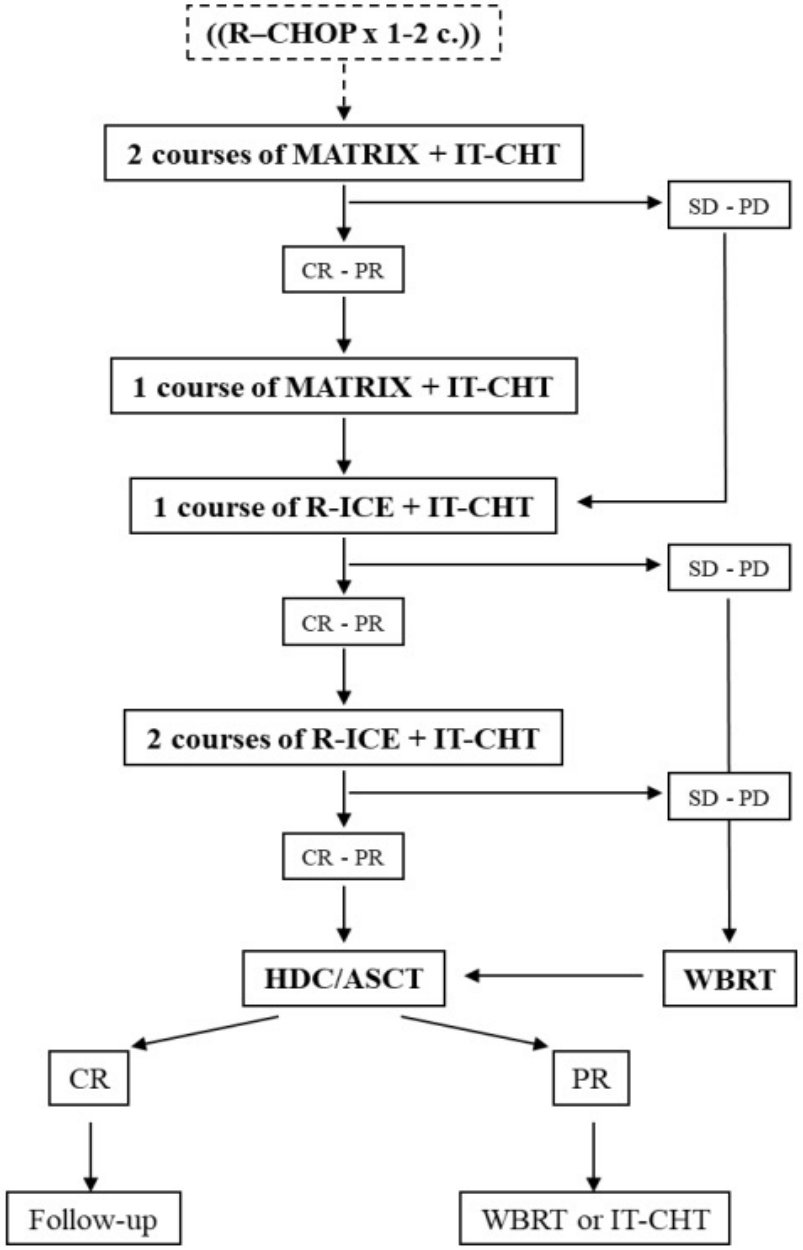
MARIETTA/IESLG42



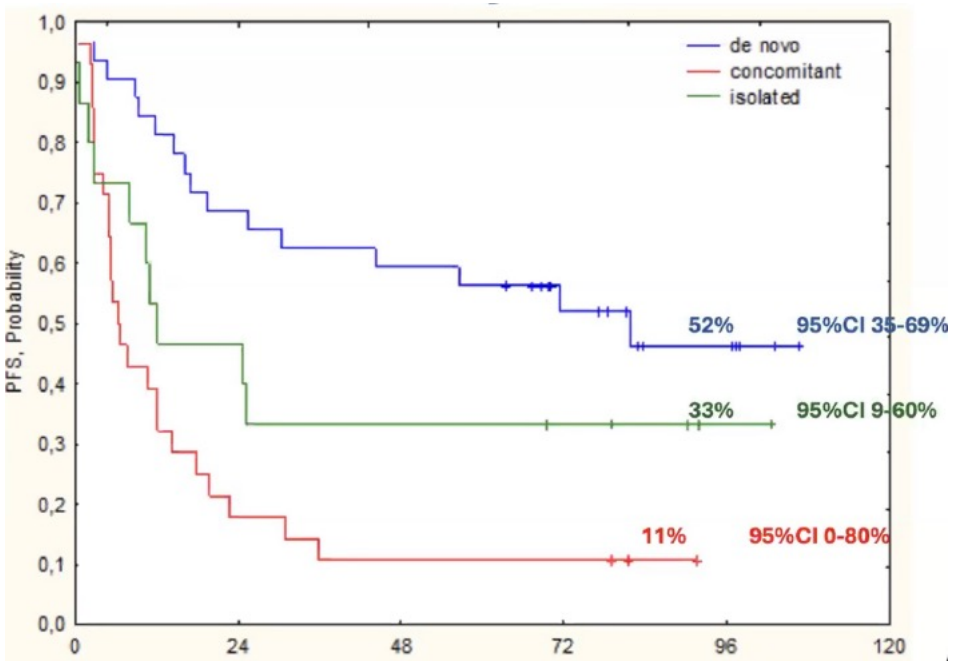
MULTICENTER UK/US/CAN



Cwynarski et Al. ICML 2025, Alderuccio JP, Baggio D et Al. Blood 2026



MARIETTA/IELSG42 TRIAL 7-YEAR OS FOLLOW UP



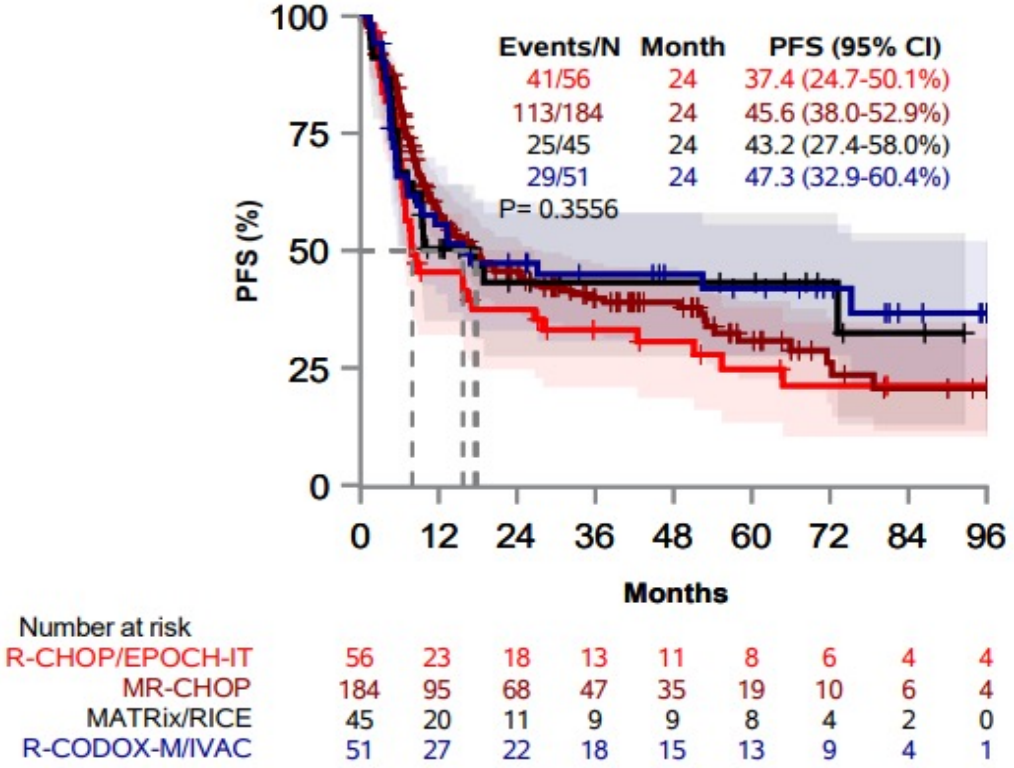
TRM: 5%
Sepsis most common
Dose reductions
- MATRiX: 28 – 35%
- R-ICE: 11 – 19%

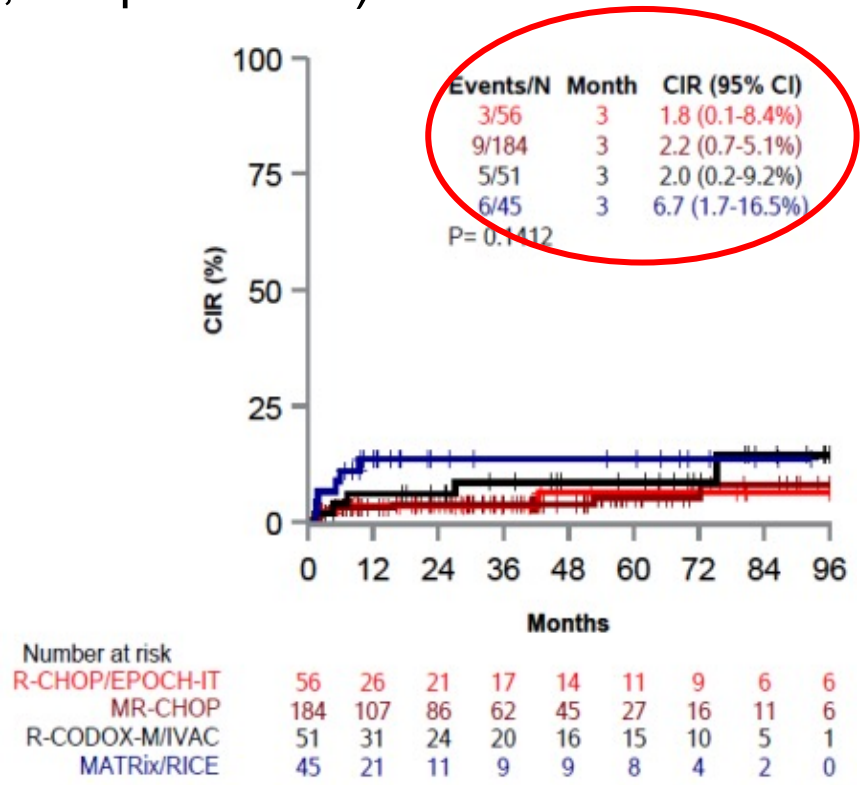
Cwynarski et Al. ICML 2025, Ferreri et Al. Lancet Haematol 2021

BEST STRATEGY FOR DE NOVO CNS/SYSTEMIC LBCL: CONSIDER TREATMENT RELATED DEATHS

MULTICENTER UK/US/CAN

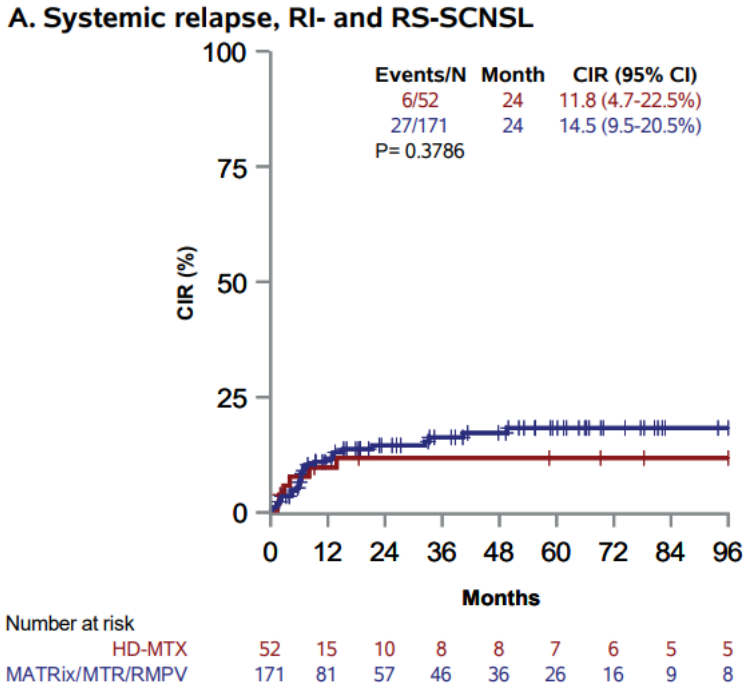
N= 1139 (De Novo:537, relapsed: 602)

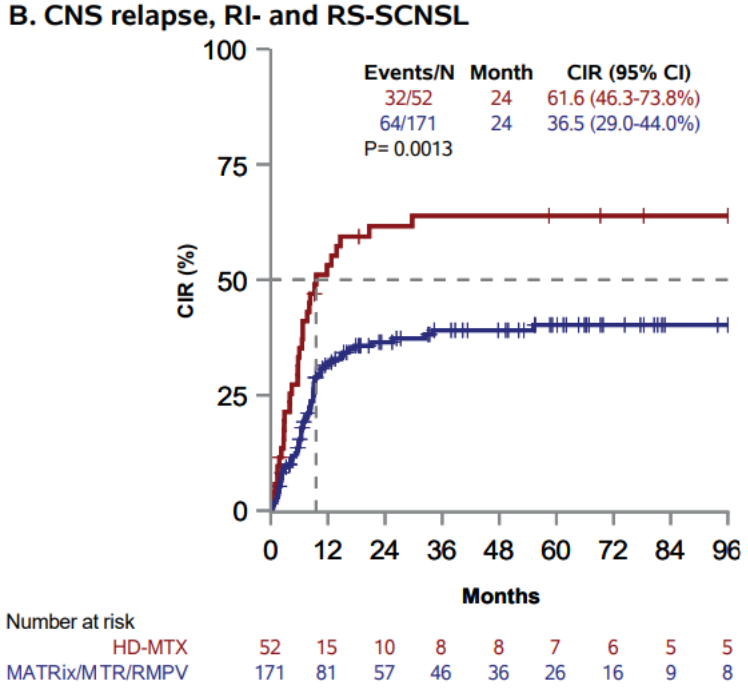




Alderuccio JP, Baggio D et Al. Blood 2026

COMBINATION THERAPY SEEMS TO BE BETTER STRATEGY THAN SINGLE HD-MTX IN SCNS RELAPSES

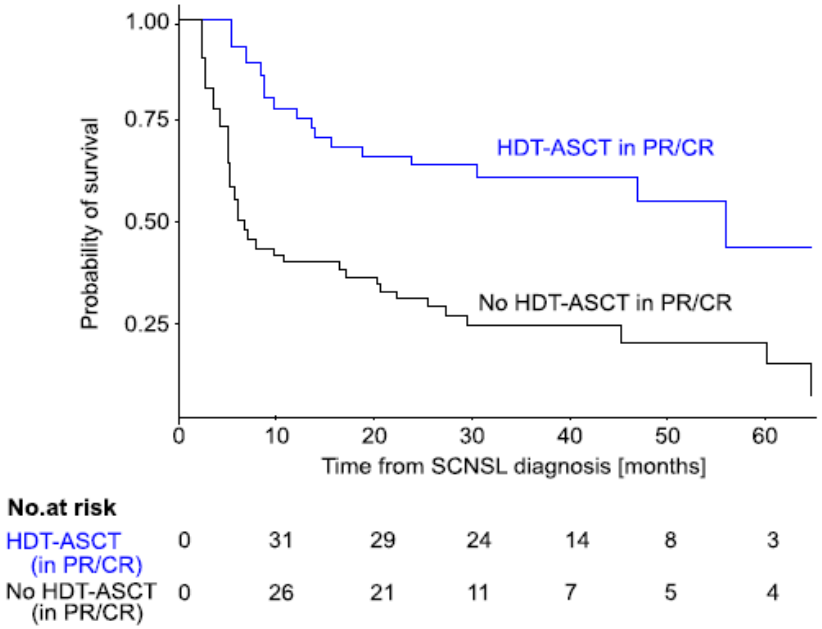




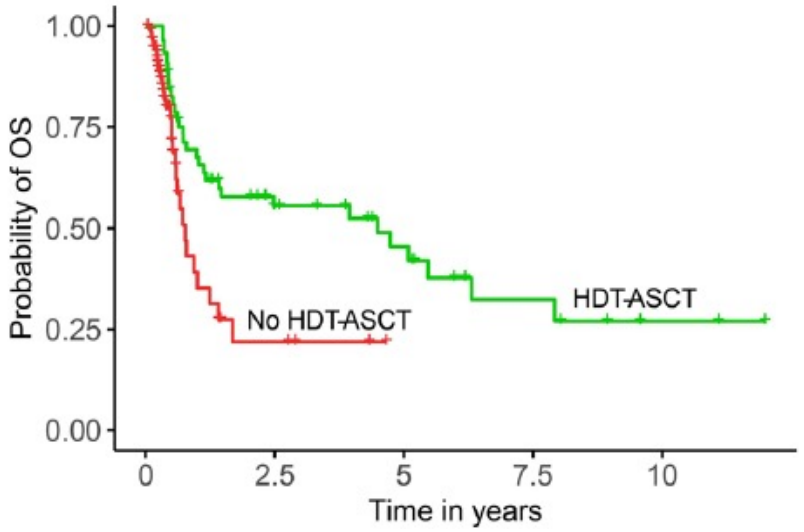
Alderuccio JP, Baggio D et Al. Blood 2026

IS AUTOLOGOUS HCT NEEDED FOR ALL SCNS LYMPHOMAS?

MULTICENTER GER/SWIS/ISR/AUS



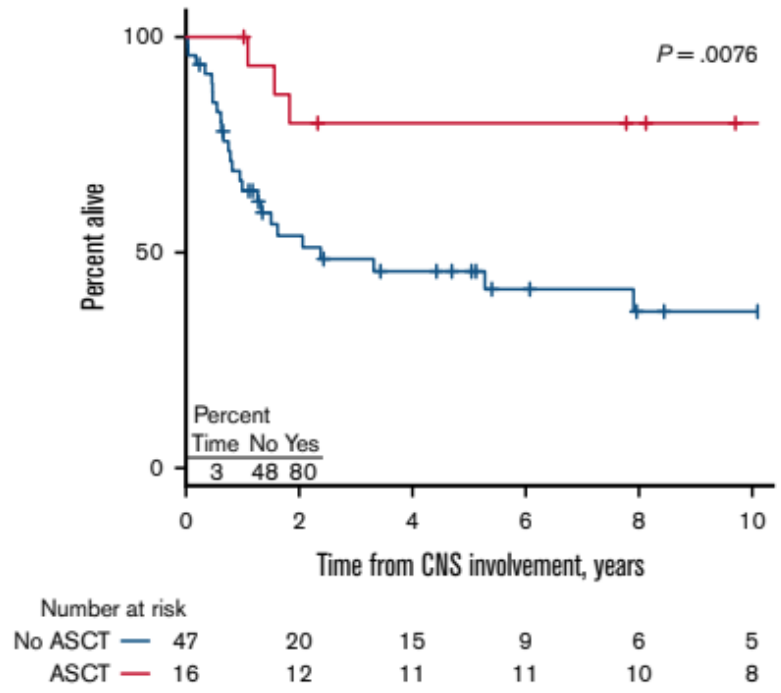
MULTICENTER Germany

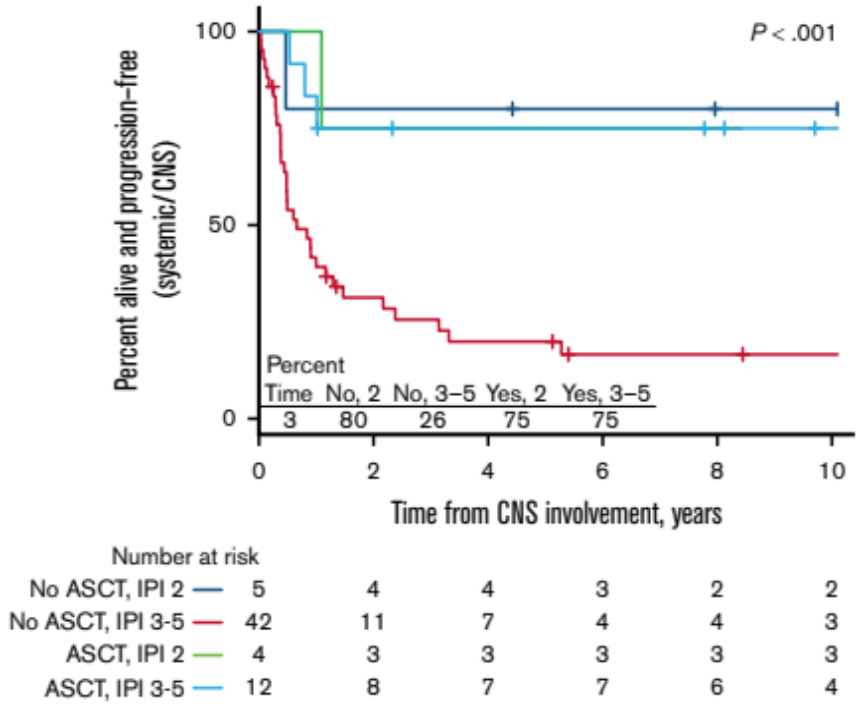


Habringer S et Al. Eur J Cancer 2023, Treiber H et Al. Hemasphere 2024

AUTOLOGOUS HCT FOR DE NOVO CNS/SYSTEMIC LYMPHOMAS

MGH/DFCI Experience

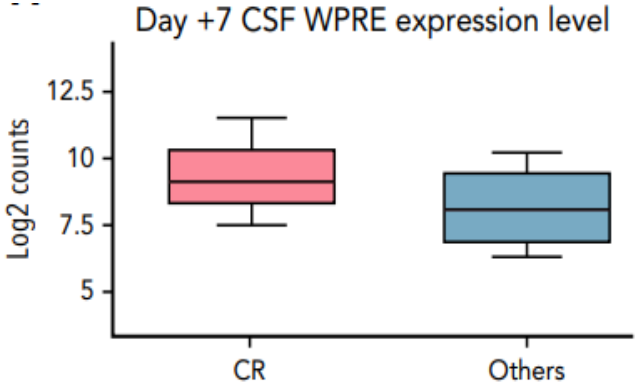


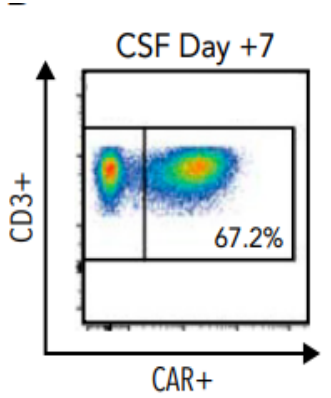


Haydu JE et Al. Blood Adv 2026

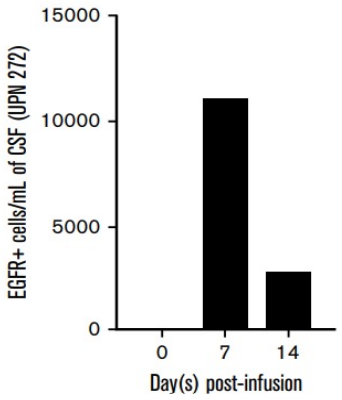
IS CAR-T EFFECTIVE IN CNS LYMPHOMAS?

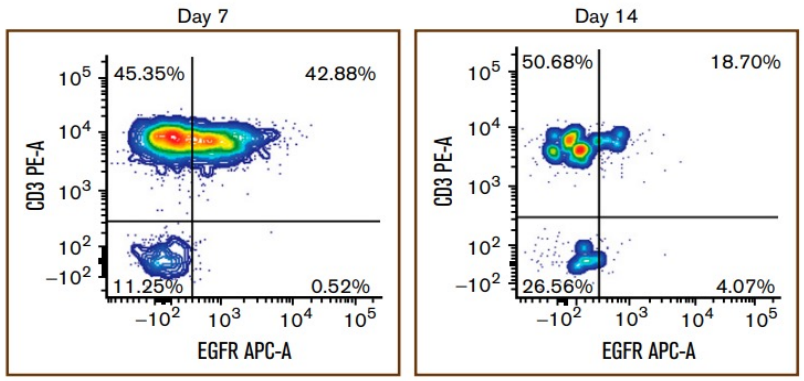
N= 12 PCNSL and SCNSL
Tisagenlecleucel
ORR: 58% (25% in remission at last F/U)





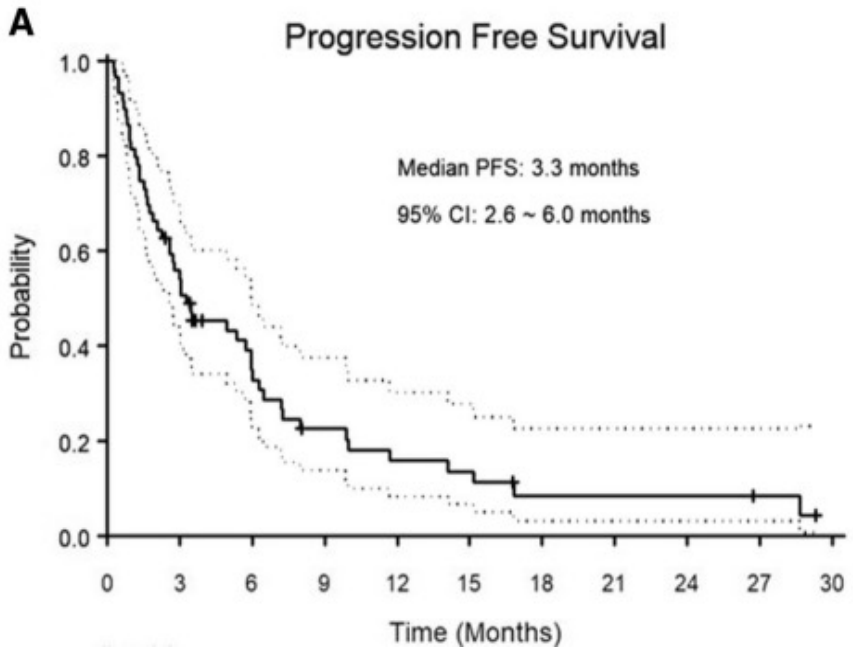
N= 5 PCNSL
EGFR+ CD19 CAR-T (liso-cel)
CR 3/5 (1/5 still in remission > 1y)

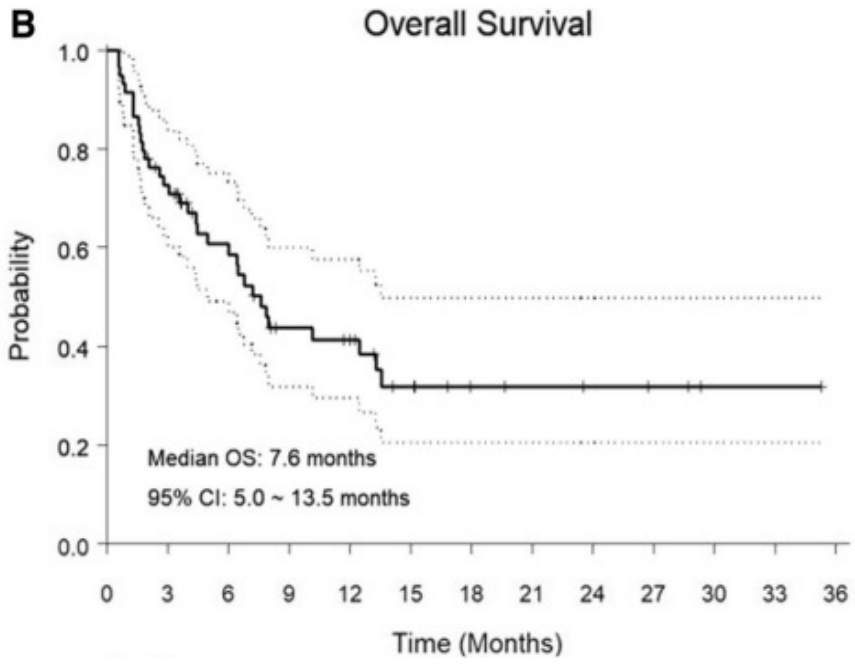




Frigault et Al. Blood 2022, Siddiqi T et Al. Blood Adv 2021

CAN CAR-T CURE SCNS LYMPHOMAS?



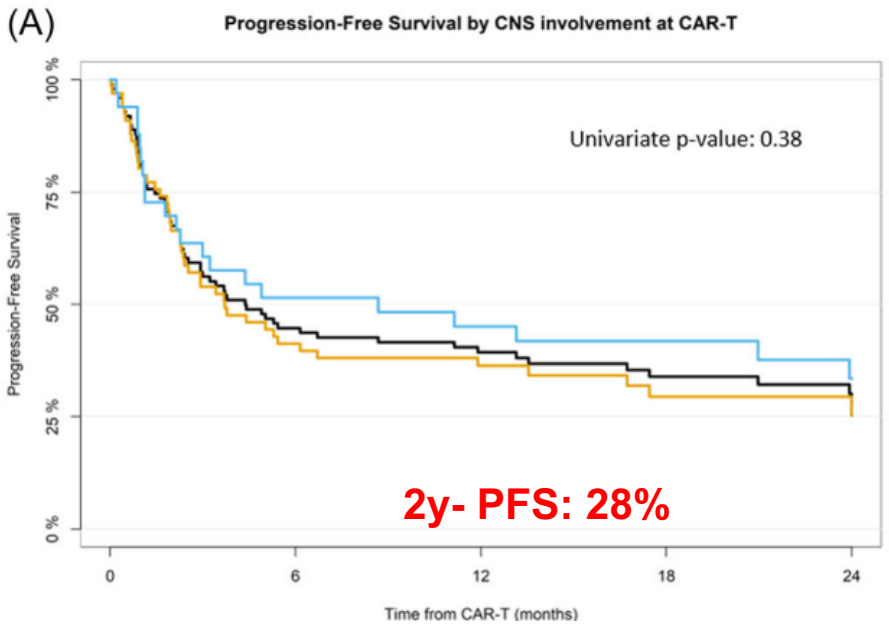


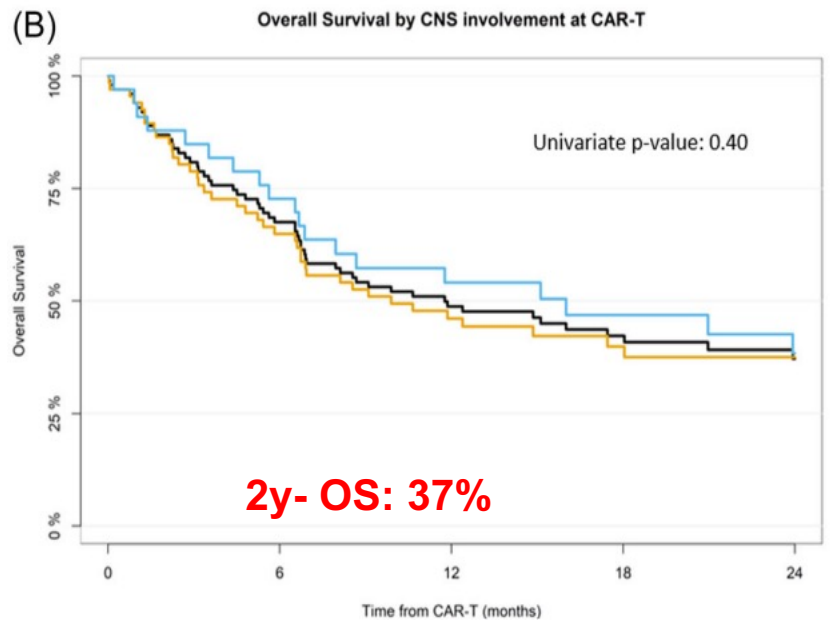
N= 61
Median age: 56 (18 – 82)
Parenchymal: 42%
LMN: 48%, Both: 10%

Median lines: 3 (1 – 5)→ Too late?
Prior HD MTX: 41%→ Too sick?
Tisa-cel: 31%→ Ideal CAR-T?

Epperla N et Al J Hem Oncol 2023

CAR-T FOR CNS LYMPHOMAS: EBMT/GO CART COALITION





N=108 (84 SCNSL)
Median age: 62 (23 – 80)
Parenchymal: 68%
LMN: 26%, Both: 10%

> 3 prior LOT: 58%
Prior HD MTX: 77%
Axi-Cel: 59% Tisa-cel: 38%, Liso-Cel: 2%
CRS: 84%, ICANS 42%
2 deaths from ICANS (1 without active CNS)

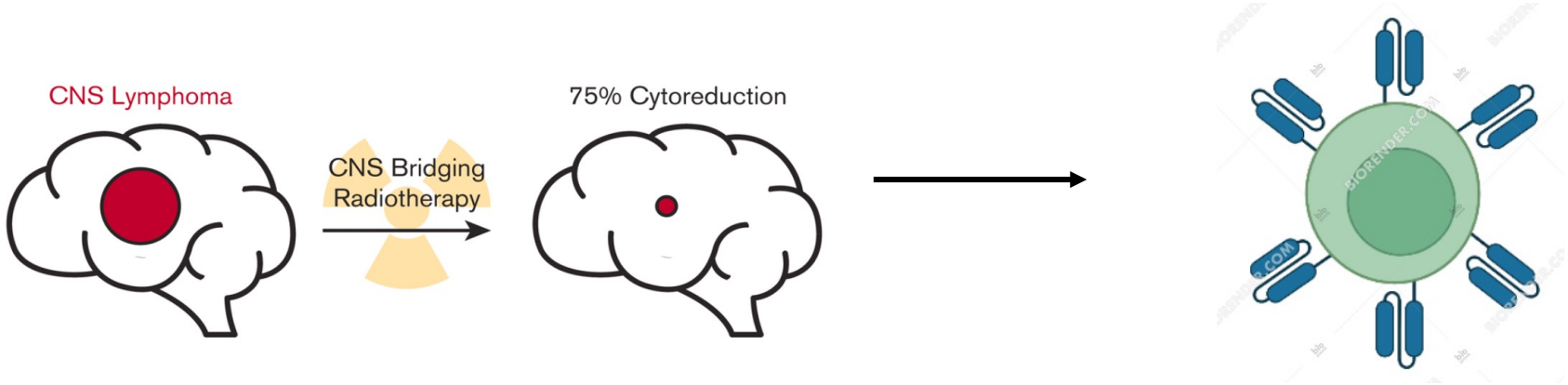
Saiddy et Al. Hemasphere 2025

PROPSPECTIVE STUDIES OF CAR-T IN CNS LYMPHOMA

- **Axi-cel (CD19)**
  - N= 18 pts (SCNSL=4, PCNSL= 13)
  - ORR: 89% CR: 67%
  - CRS: 89%(G≥3 0)
  - PFS: 14.3 months
  - ICANS: 44% (G≥3 28%)
  - CAR-T expansion in CSF
- **Zamto-Cel (CD20/CD19)**
  - N= 16 treated (SCNSL= 5)
  - ORR: 85.7% CR: 64%
  - CRS: 43.7% G≥3 0
  - ICANS: 25% G≥3 0

Nayak L et Al. ASCO 2024, Johnston P et Al. ICML 2025

CAN BRIDGING XRT IMPROVE OUTCOMES WITH CAR-T IN CNS LYMPHOMAS?

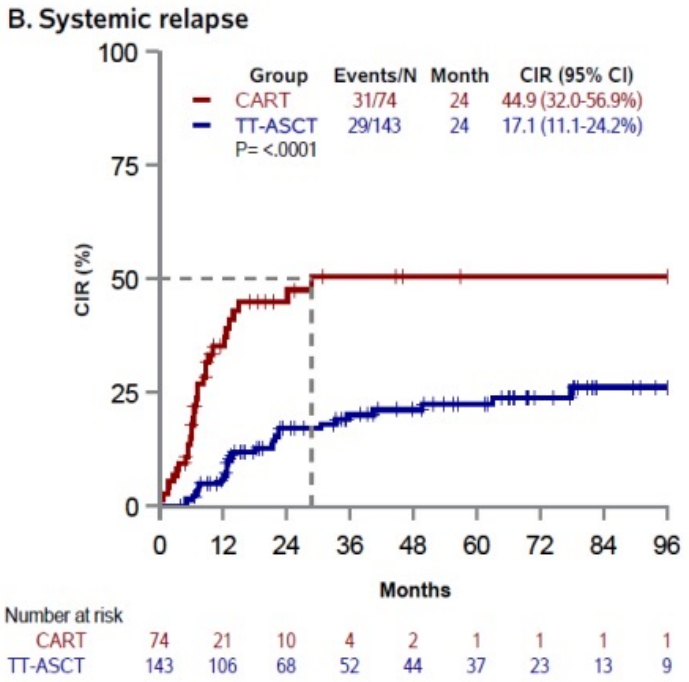


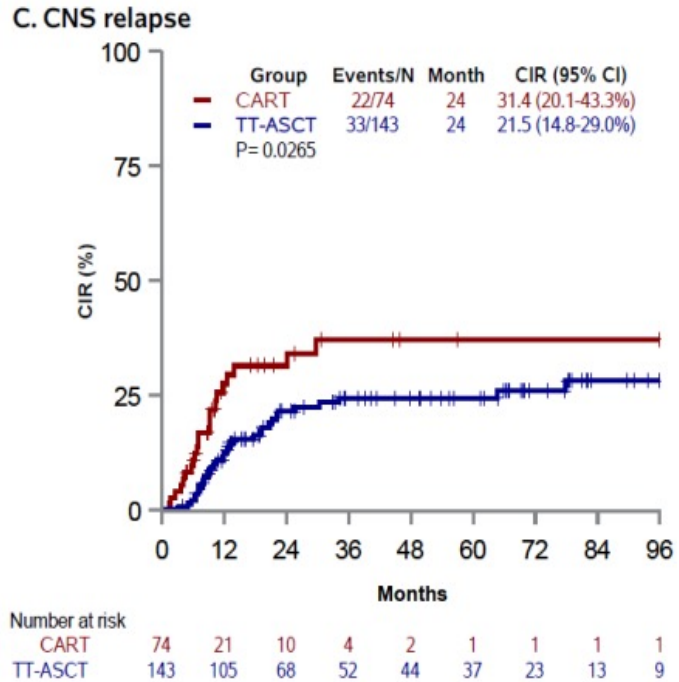
N= 12 pts (1 PCNS, 11 SCNSL)
Median XRT dose: 22 Gy in 10 fractions
Best CNS response after CAR-T
PR=1, **CR=8**, PD=3

Deaths: 3 (2 of PD)
CRS all grades (G≥3): 75% (8%)
ICANS all grades (G≥3): 42% (25%)

Cederquist G et Al. Blood Adv 2024

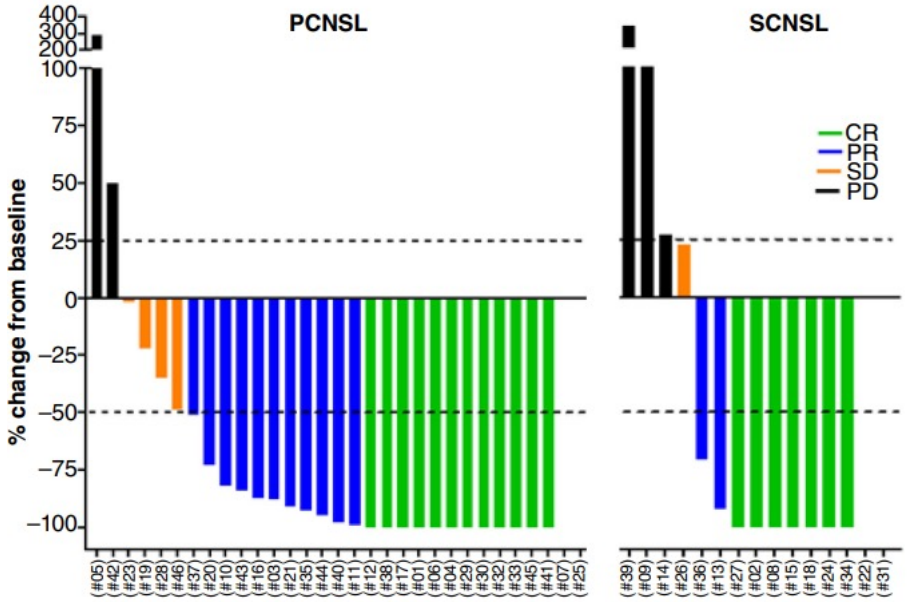
CAR-T OR AUTO-HCT FOR RELAPSED SCNS LYMPHOMAS?

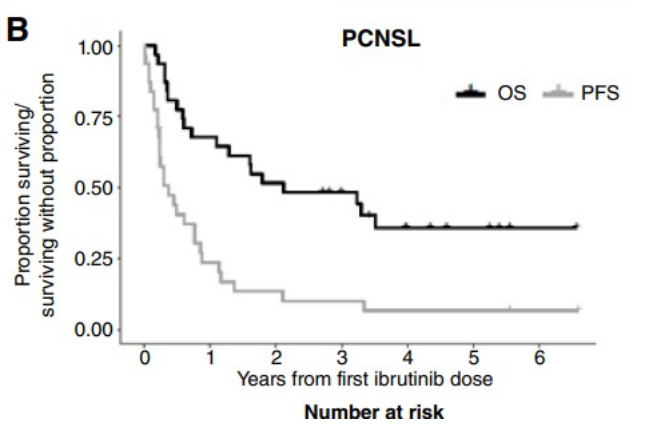


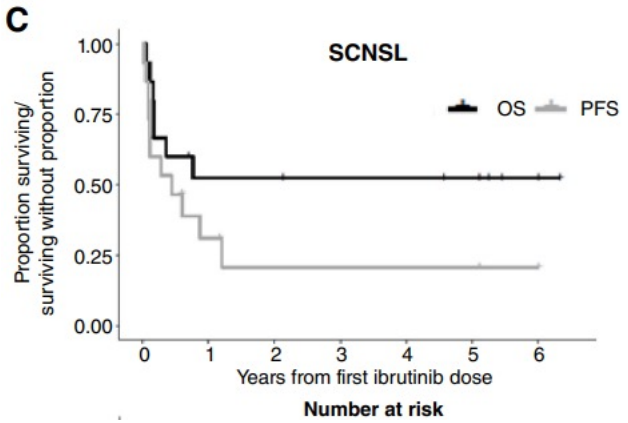


Alderuccio JP, Baggio D et Al. Blood 2026

BTK INHIBITION IN CNS LYMPHOMAS: IBRUITINIB







Grommes C et Al. Clin Can Res 2024

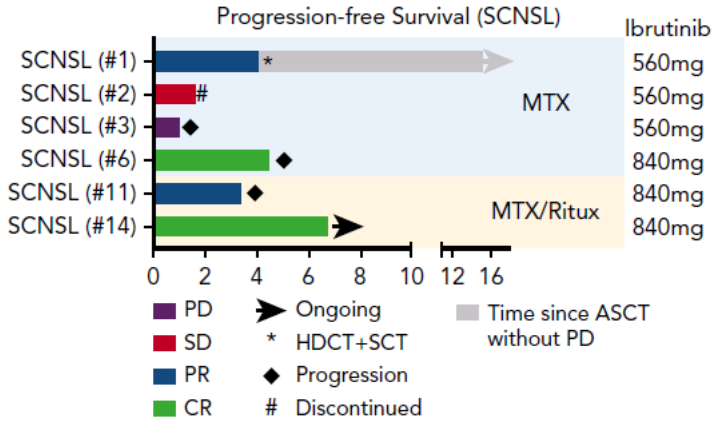
EFFICACY OF NOVEL AGENTS

	N pts	ORR/CR	PFS	OS
Ibrutinib	52	61%/23%	4.8 months	19.1 months
Tirabrutinib	44	64%	2.9 months	NR
TEDDI-R	28	96%/71%	15.3 months	NR
Ibrutinib+ Len+R	25	80%/42%	4.3 months	NR
Ibrutinib-Nivolumab	18	78%/50%	6.5 months	21.5 month

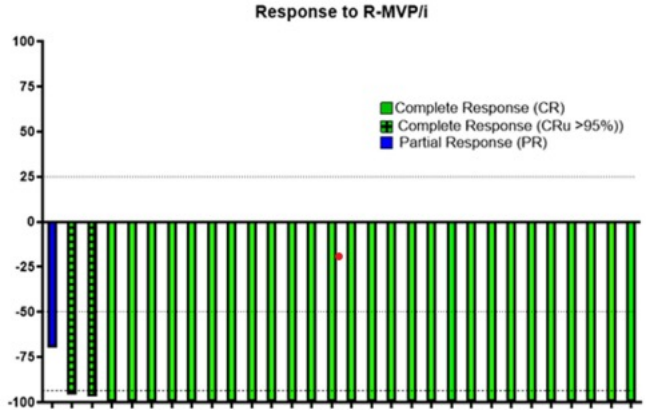
Soussain C et Al. Eur J Cancer 2019, Narita Y et Al. Neuro Oncol 2021, Simard J et Al. ASH 2023, Schaff L et Al. Neuro Oncol 2025, Chihara et Al. Blood Adv 2025

BTKI COMBINATION FOR CNS LYMPHOMAS

- **Ibrutinib + HD MTX + Rituximab**
  - 15 pts (9 PCNSL, 6 SCNCL)
  - 9 with recurrent disease
  - Prior HD-MTX (100%)
  - Refractory HD-MTX (25%)
  - ORR= 80% ,CR= 55%



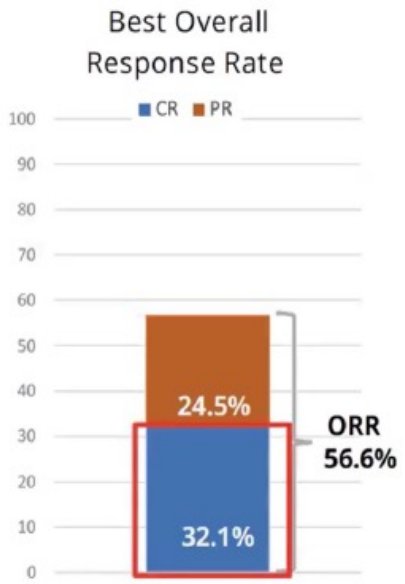
- **Ibrutinib MVP-R for PCNSL**
  - 30 patients
  - ORR= 100%, CR: 90%
  - 2- PFS: 80%

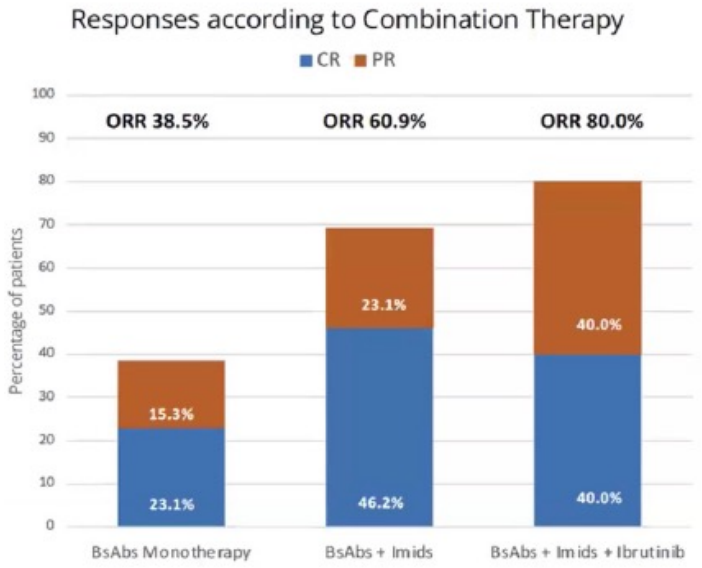


Schaff L et al. Neuro Oncol 2026

BISPECIFIC ANTIBODIES FOR SCNS LYMPHOMAS

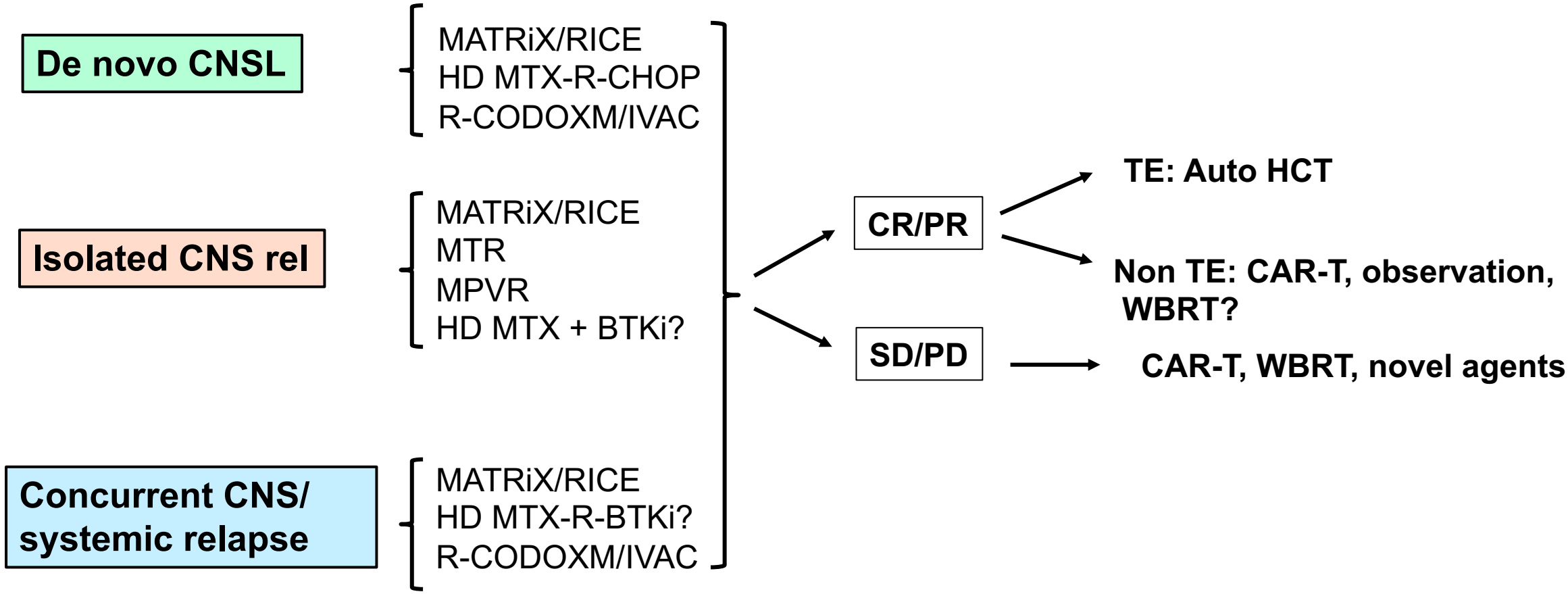
Multicenter France and Belgium sites
N= 53 pts
49 SCNSL
Epcoritamab: 34
Glofitamab: 19





Gilbert A et Al. ASH 2025

SCNS LYMPHOMAS: TREATMENT APPROACH



CONCLUSIONS

- The prognosis of secondary CNS lymphomas is poor. It remains a treatment challenge
- Although CNS prophylaxis remains controversial, it is still a good strategy.
- HD-MTX combination therapy is more effective.
- Consolidation with thiotepa based auto-HCT if disease if eligible and induction response

