



# SINTOMA<sup>26</sup>

14 A 16 DE MAIO | HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA **soho**  
society of hematologic oncology

APOIO INSTITUCIONAL Faculdade **bp**

GERENCIAMENTO  
E PRODUÇÃO

**RV+**  
EVENTOS

# Secondary CNS Lymphoma: Diagnosis, Risk Stratification, and Modern Therapeutic Strategies

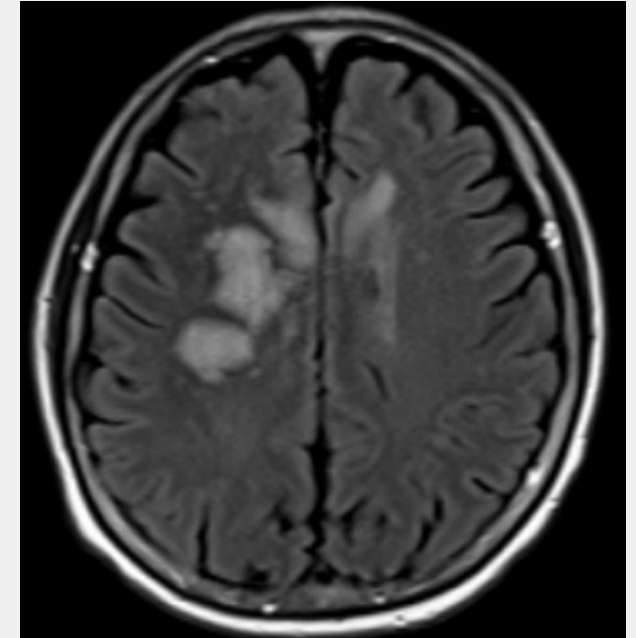
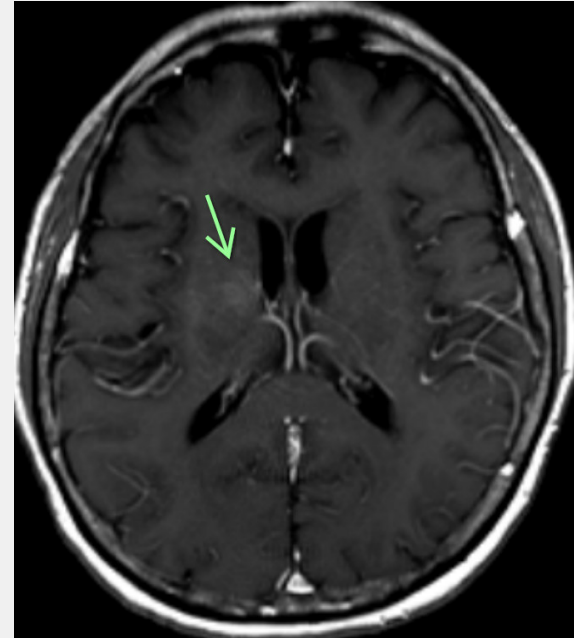
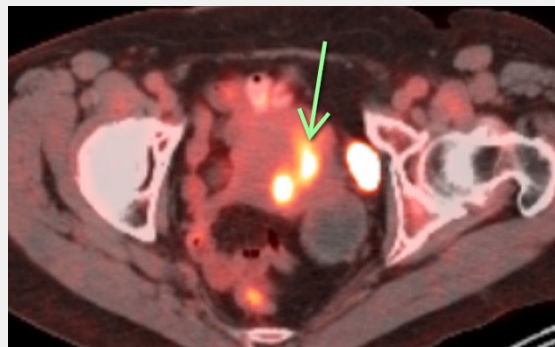
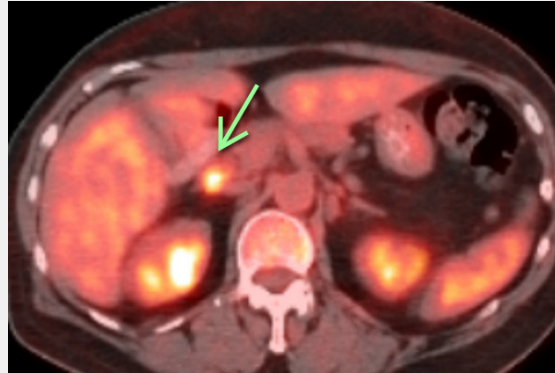
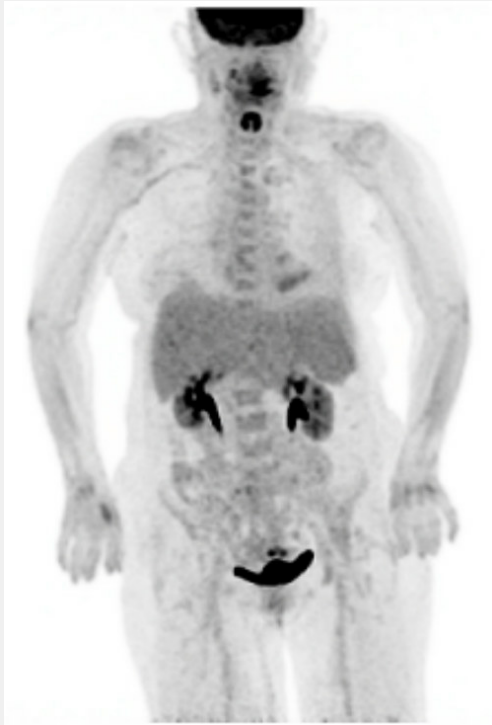
**Adam Olszewski**

Associate Professor of Medicine  
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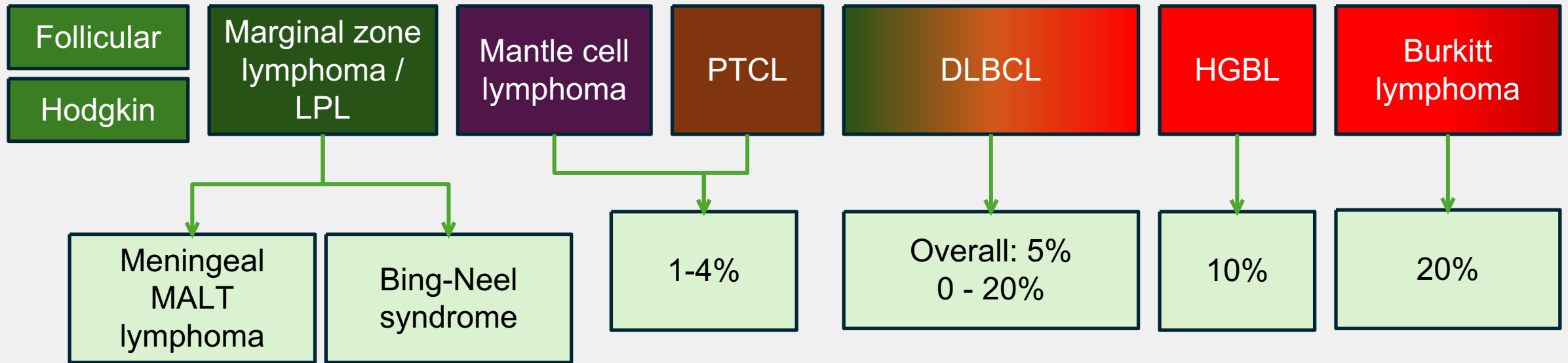
@lymphomatic



- 71 year-old healthy woman – abnormal mammogram in 12/2024: “0.8 cm mass at 2 o’clock”
- **Left breast, needle core biopsy: CD20-negative DIFFUSE LARGE B-CELL LYMPHOMA**, non-GCB: large cells (+) for CD19, BCL2, BCL6, MYC (60%), MUM1 (>30%), high Ki67 (>90% by MIB1), (-) EBER ish. FISH (-) for *IGH::BCL2*, *MYC*, *BCL6* rearrangements.
- **PETCT: no uptake in the breast.** 1 cm right cervical node; 1.6 cm portocaval lymph node (SUV=3.5); intense uptake in the spleen without foci, SUV=10; abnormal focal intense uptake in the uterus (SUV=10); **LDH - 537**
- Treated with **PolaRCHP x 4**

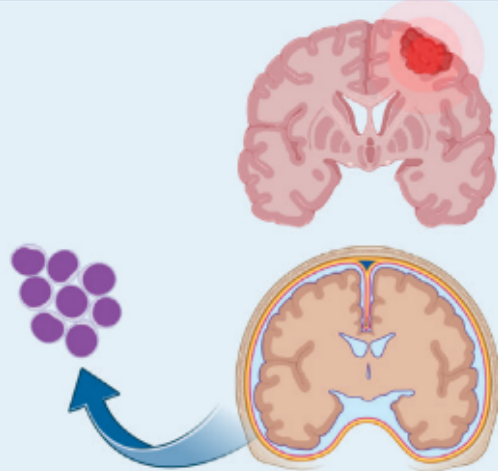


# Secondary CNS in different lymphomas



- Disease status
  - Newly diagnosed vs. relapsed
- Disease burden
  - CNS only vs. CNS + systemic
- CNS location
  - Parenchymal vs. leptomeningeal only

## Clinical presentation



- Cranial nerve deficits
- Visual symptoms (e.g. floaters, blurred vision, photophobia, and eye pain)
- Headache
- Mental status changes
- Focal weakness
- Sensory loss
- Radicular pain



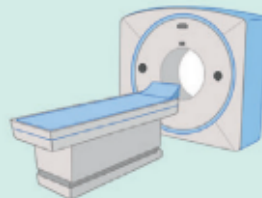
- Lymphadenopathy
- B symptoms
- Hepatomegaly
- Splenomegaly
- Elevated serum LDH

## Disease evaluation

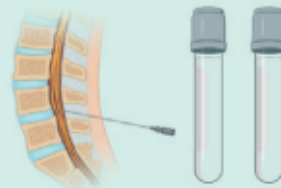
Brain MRI with contrast



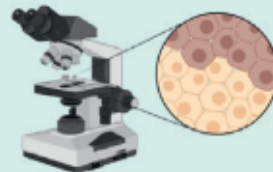
PET/CT



CSF analysis for cytology and flow cytometry



Tissue biopsy



Testicular ultrasound



Eye examination



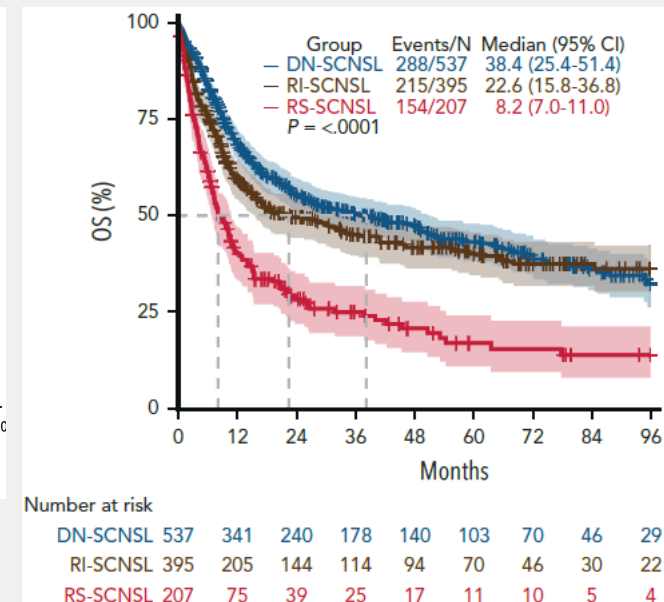
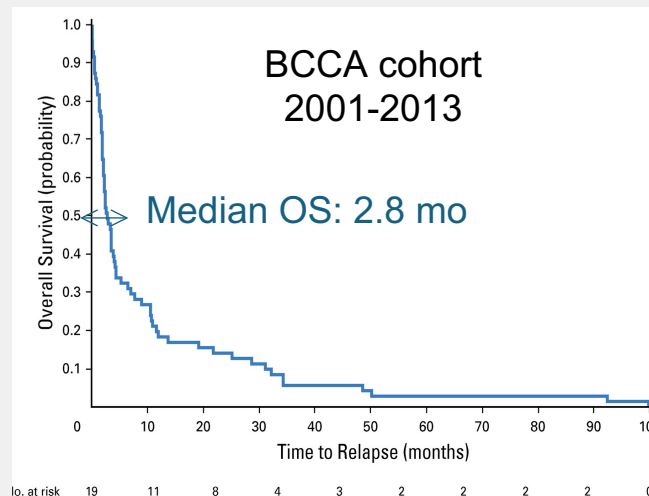
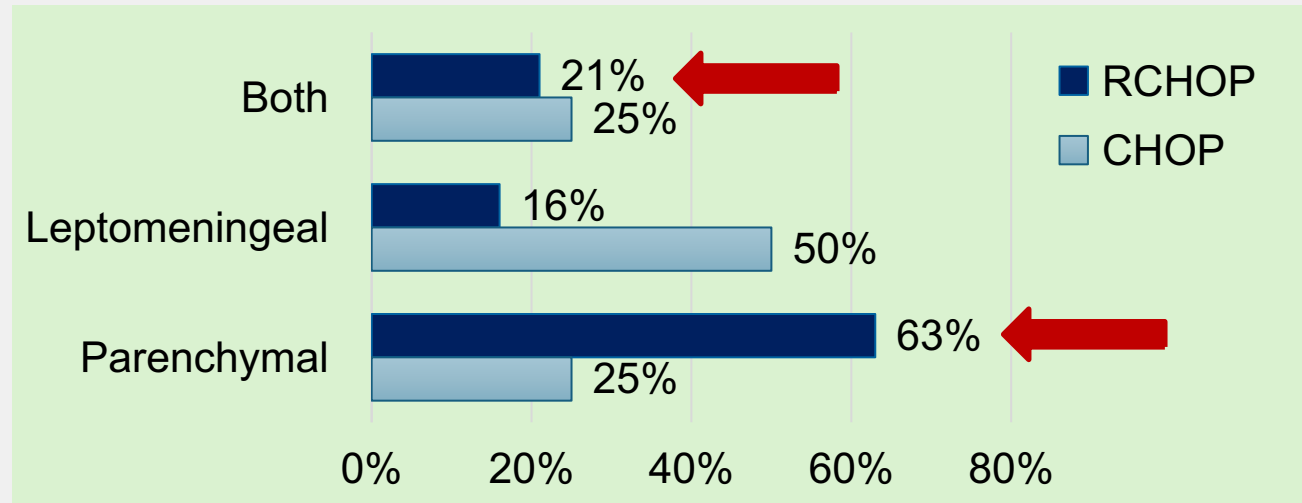
Consider Spine MRI with contrast



- Pain
- Weakness
- Spasticity
- Sensory loss
- Bowel/bladder dysfunction

# R-CHOP era: 5% CNS recurrence

Clinical trial	N	CNS relapse %
UK NCRI	984	21 (1.9%)
GOYA	1418	38 (2.6%)
R-MegaCHOEP	253	18 (7.1%)
PHOENIX	838	26 (3.1%)
CALGB 50303	524	18 (3.7%)
Outside of trials: <b>BCCA registry</b>	1732	84 (4.8%) • 44% concurrent systemic • 72% parenchymal

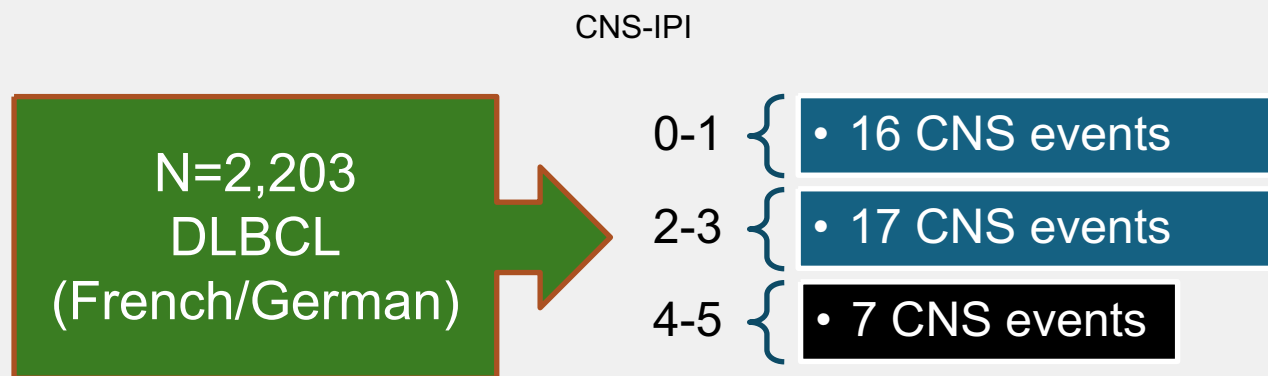
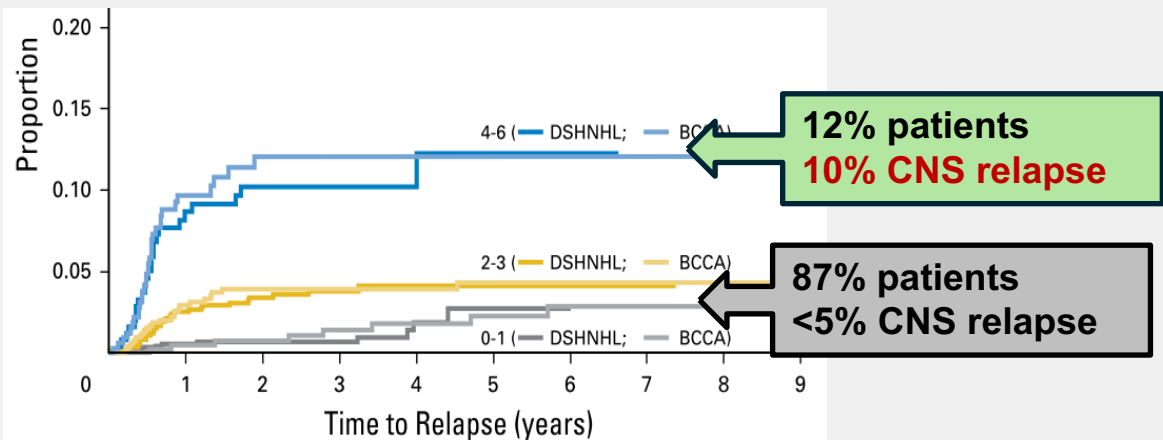
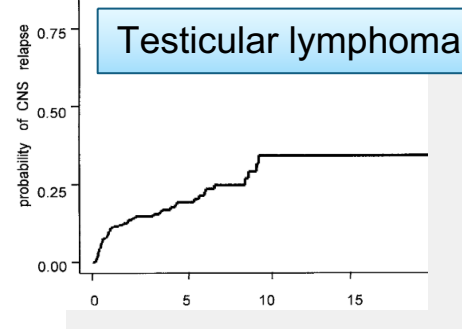
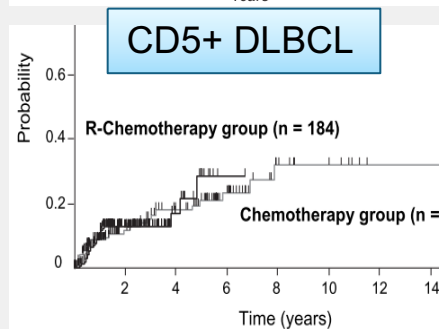
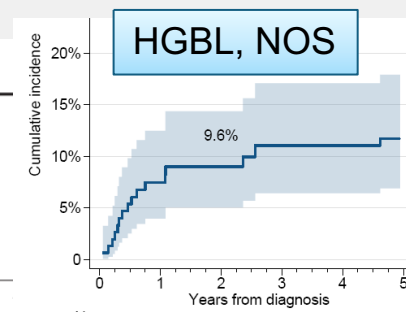
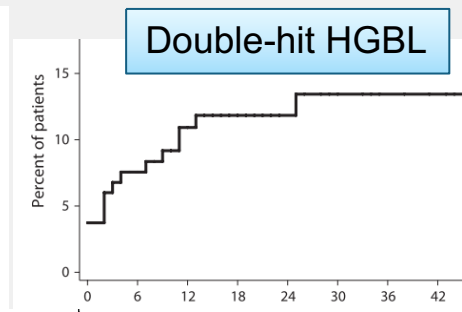
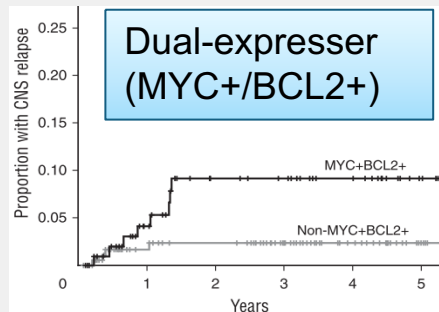


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 Kansara R, et al. Br J Haematol. 2017;179(3):508-510.  
 Cunningham D, et al. Lancet. 2013;381(9880):1817-26.  
 Younes A, et al. J Clin Oncol. 2019;37(15):1285-1295.  
 Chiappella A, et al. Lancet Oncol. 2017;18(8):1076-1088.  
 Vitolo U, et al. J Clin Oncol. 2017;35(31):3529-3537.  
 Bartlett NL, et al. J Clin Oncol. 2019;37(21):1790-1799.  
 Alderuccio et al., Blood 2026

# CNS-IPI: risk stratification – not that useful

- N=2,164 patients (80% DLBCL) from GNHL SG
- Validation: N=1597 patients from BCCA

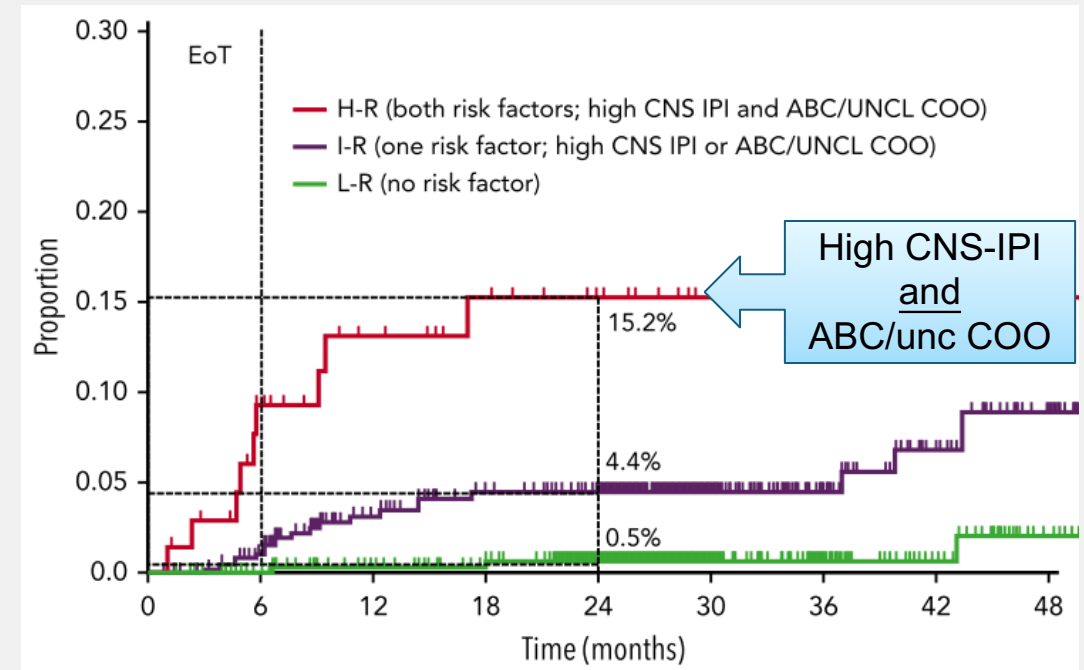
Factor	HR
Kidney or adrenal involvement	2.8
Age > 60	2.5
LDH > normal	2.4
ECOG PS > 1	2.2
Stage 3 or 4	2.0
Extranodal sites >1	1.0



# Molecular features: COO

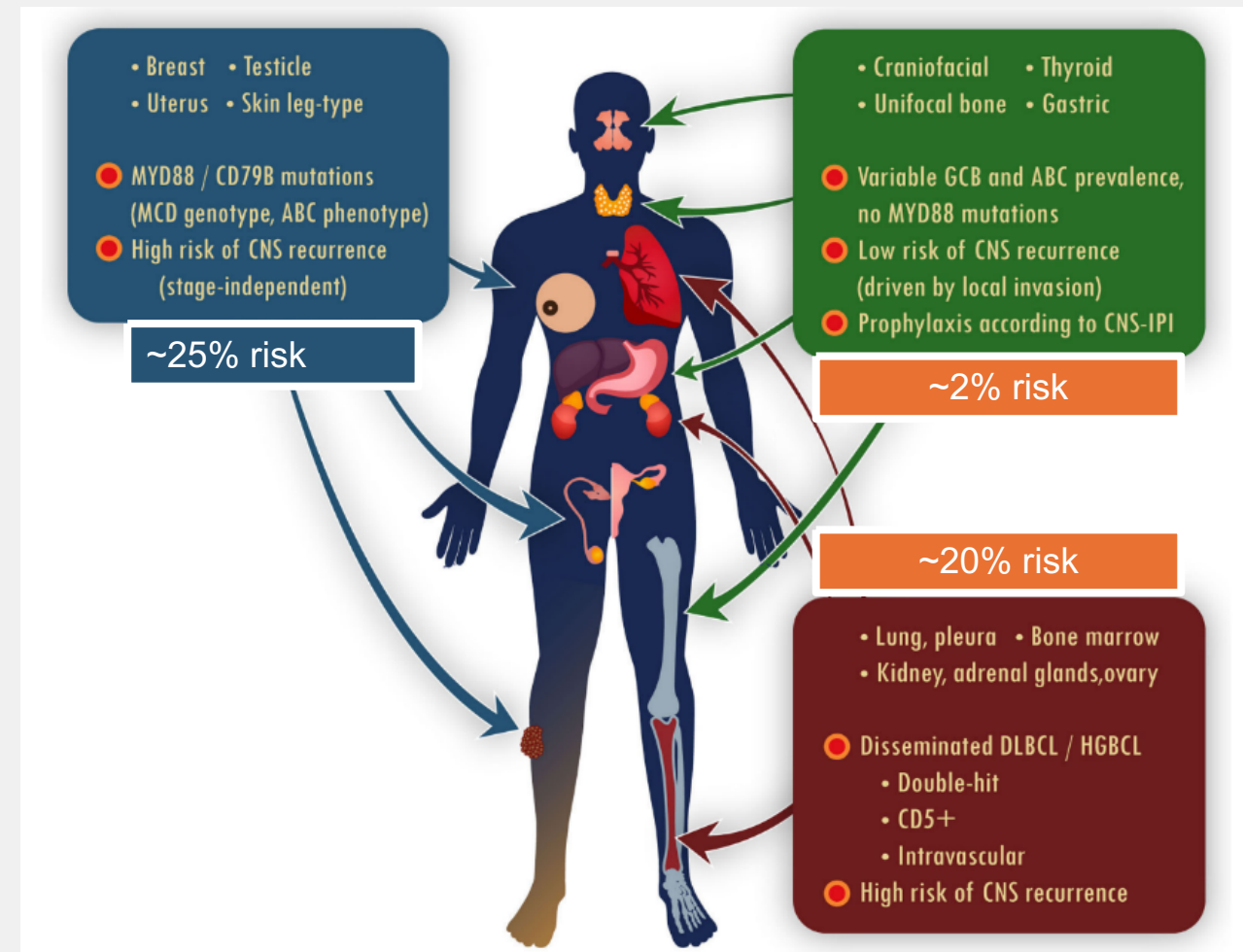
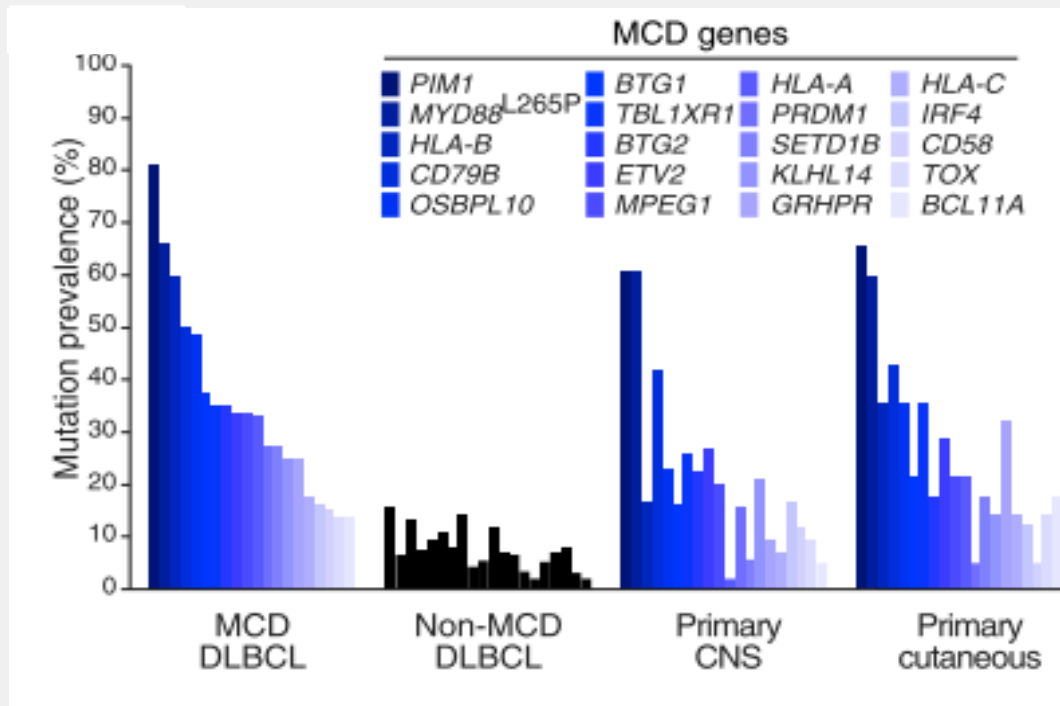
- GOYA trial
- N=1418 patients randomized to RCHOP vs GCHOP
- Genomic alterations in 18 patients with CNS recurrence (12 with NGS ):
  - **CDKN2A** deletion (67%)
  - **MYD88** mutation 42% with co-occurring **CD79B**

Factor	HR*	95% CI	P
CNS-IPI intermediate (vs low)	0.88	0.29-2.74	.8312
CNS-IPI high (vs low)	<b>3.97</b>	<b>1.28-12.33</b>	<b>.0172</b>
ABC COO (vs GCB)	<div style="background-color: #0056b3; color: yellow; padding: 5px; text-align: center;">                     Hans algorithm (GCG/non-GCG) does NOT discriminate                 </div>		4
Unclassified COO (vs GCB)			2



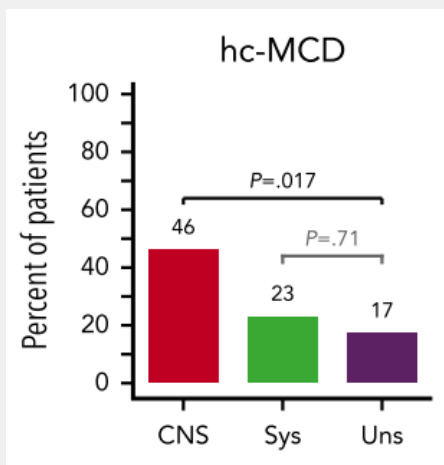
# Molecular features predict CNS recurrence

- PCNSL is similar to specific **extranodal ABC DLBCL**:
  - Testicular - Breast
  - Uterus
  - Cutaneous leg-type
- *MYD88/CD79B* mutation
- “Immune evasion”

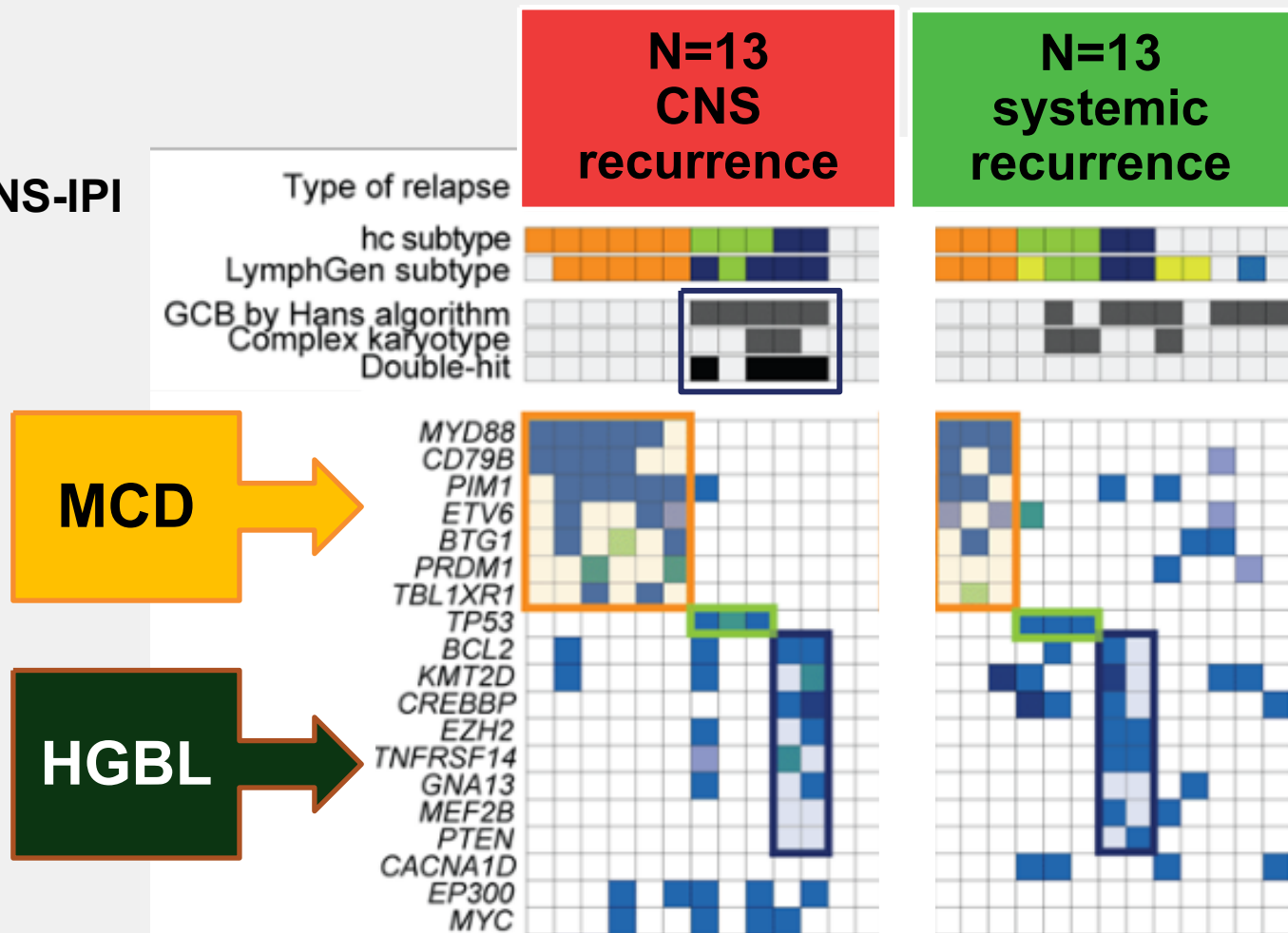


# MCD-DLBCL Is Only Half of the Story

- 26 DLBCL/HGBL relapsed tumors
- No significant clinical predictor of CNS vs. systemic recurrence
- 85% of CNS recurrences: **low/intermediate CNS-IPI**
- MCD subtype enriched in CNS recurrences
- But: **MCD only in half** of CNS relapses
- Other half: **GCB HGBL** (double-hit or *TP53*<sup>mut</sup>)

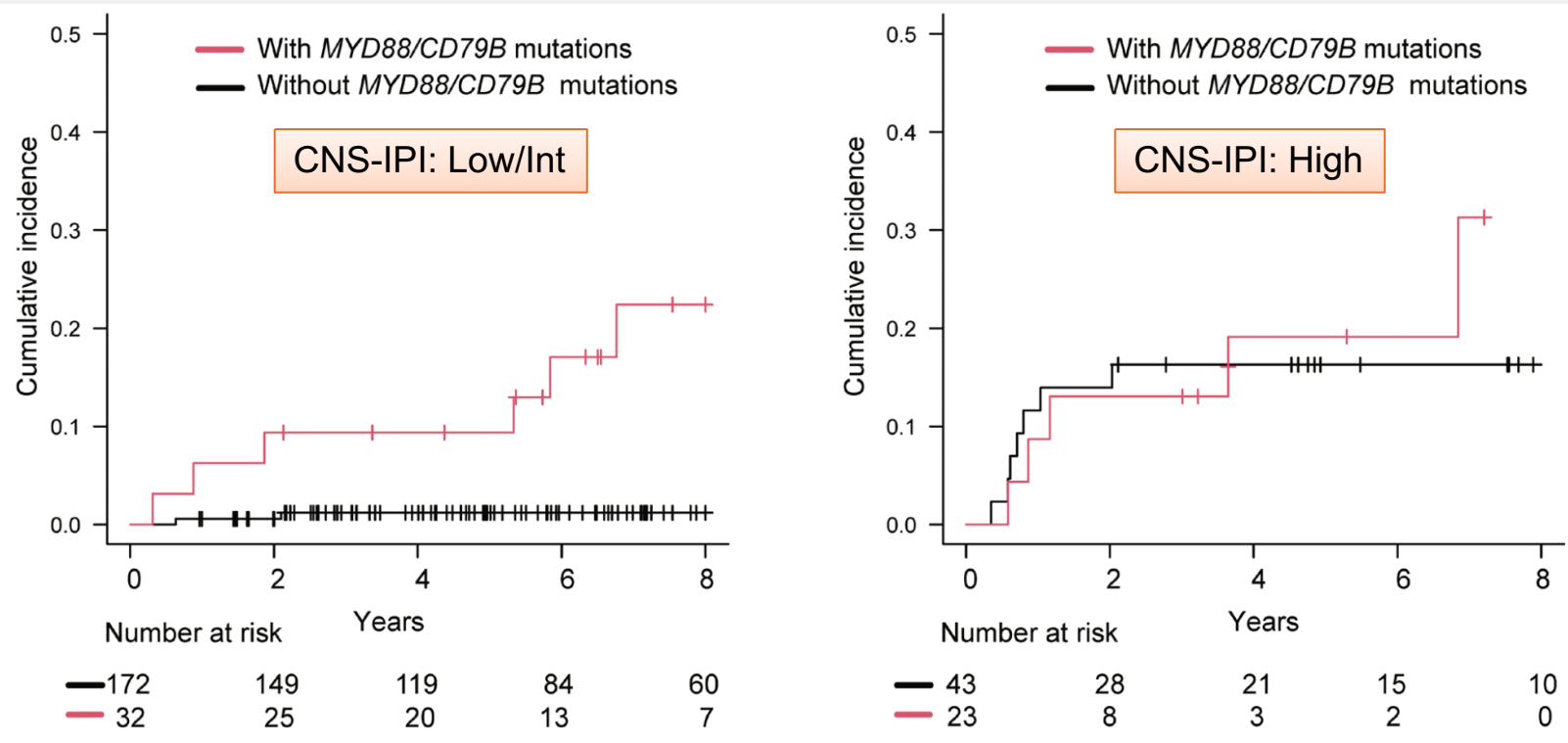


Unselected external DLBCL cohorts



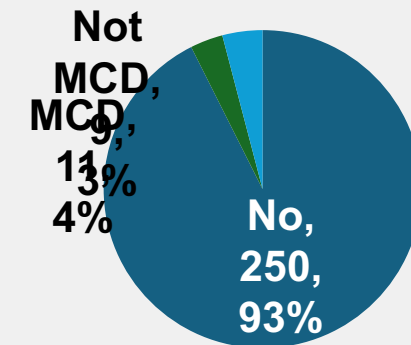
# Incidence of CNS relapse in MCD lymphoma

- N=270 patients with DLBCL
- All screened for *MYD88* L265P and *CD79B* Y196 mutations by PCR
- **20% (+)** for *MYD88+CD79B*



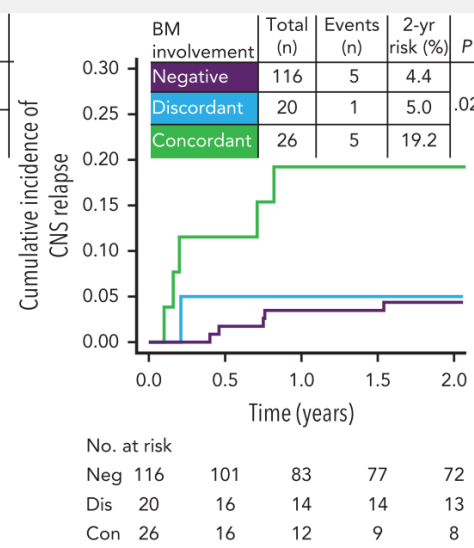
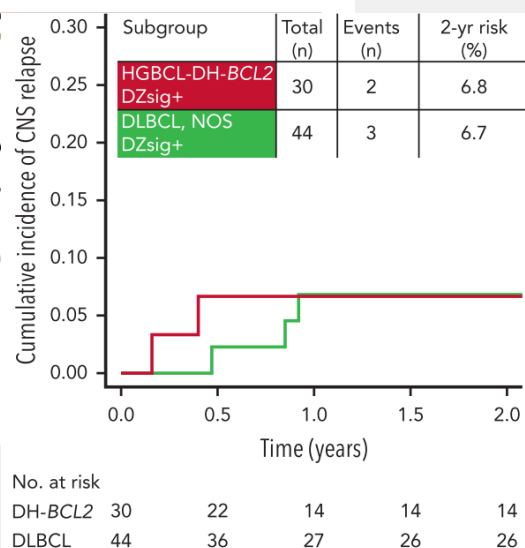
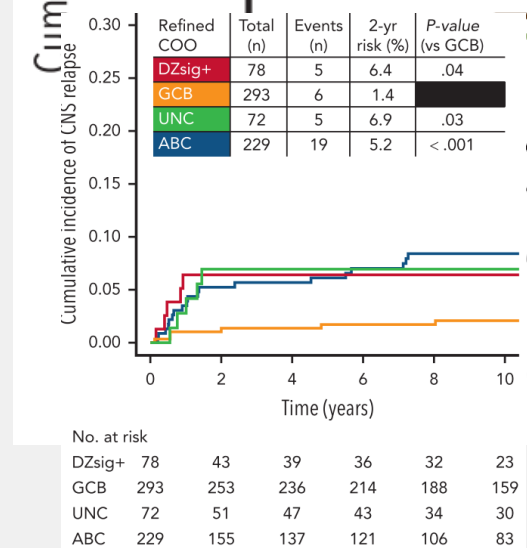
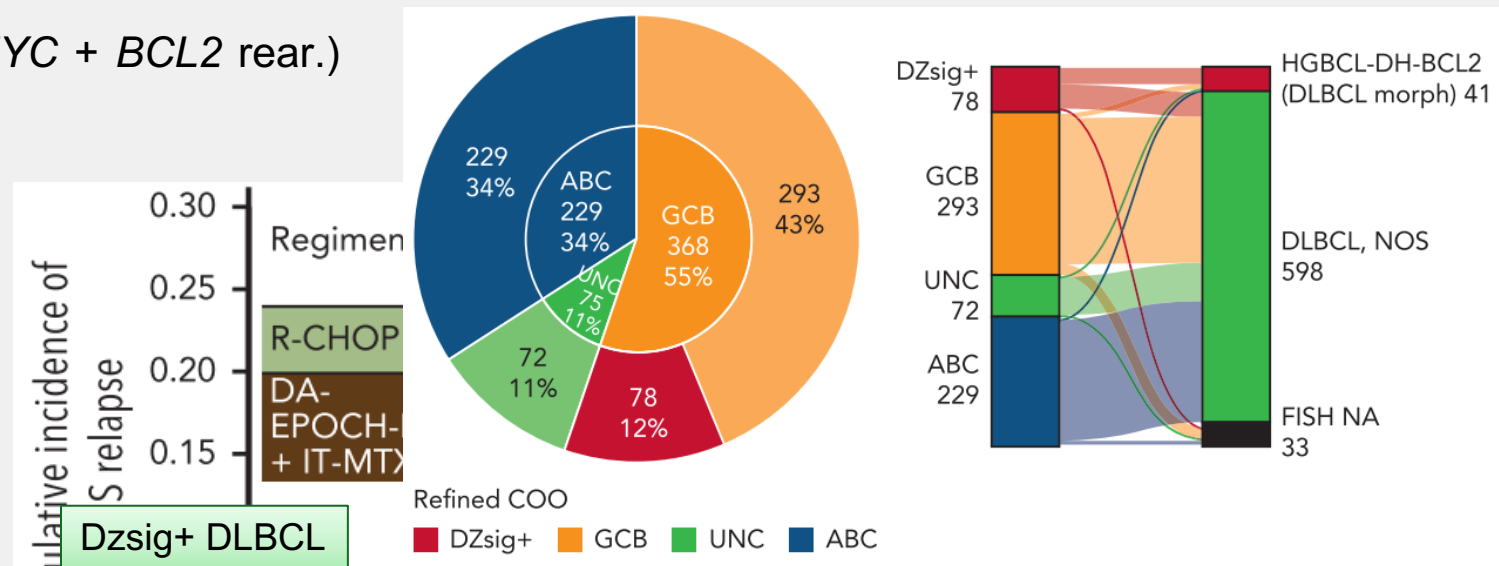
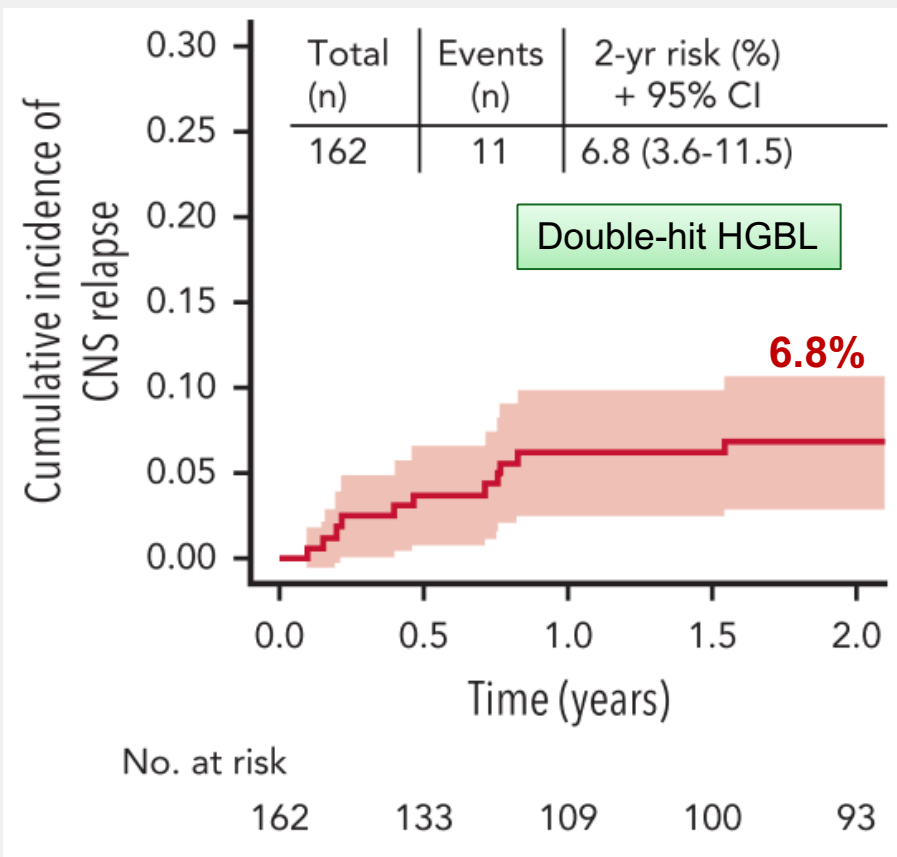
## CNS RELAPSE

■ No ■ Not MCD ■ MCD



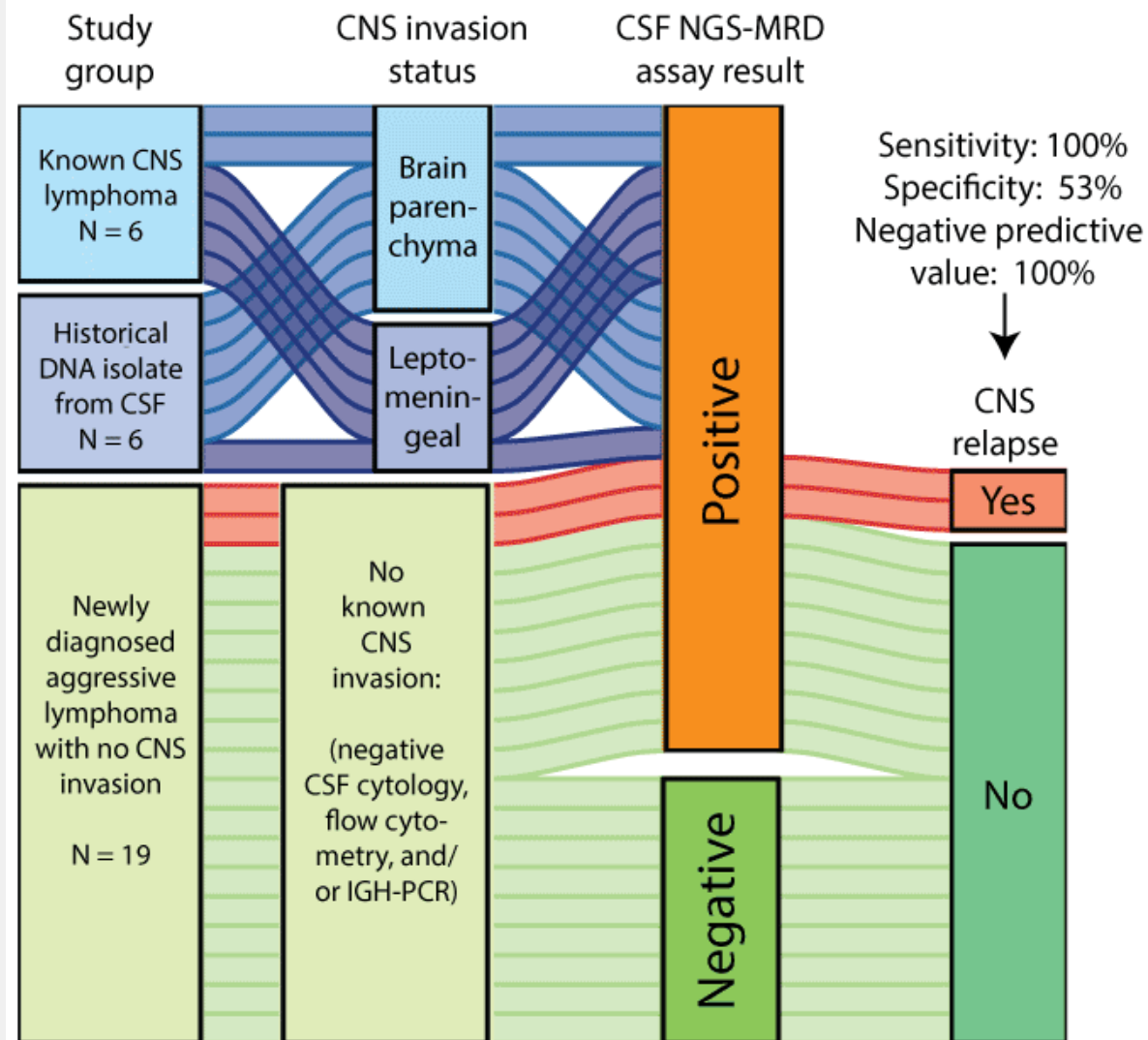
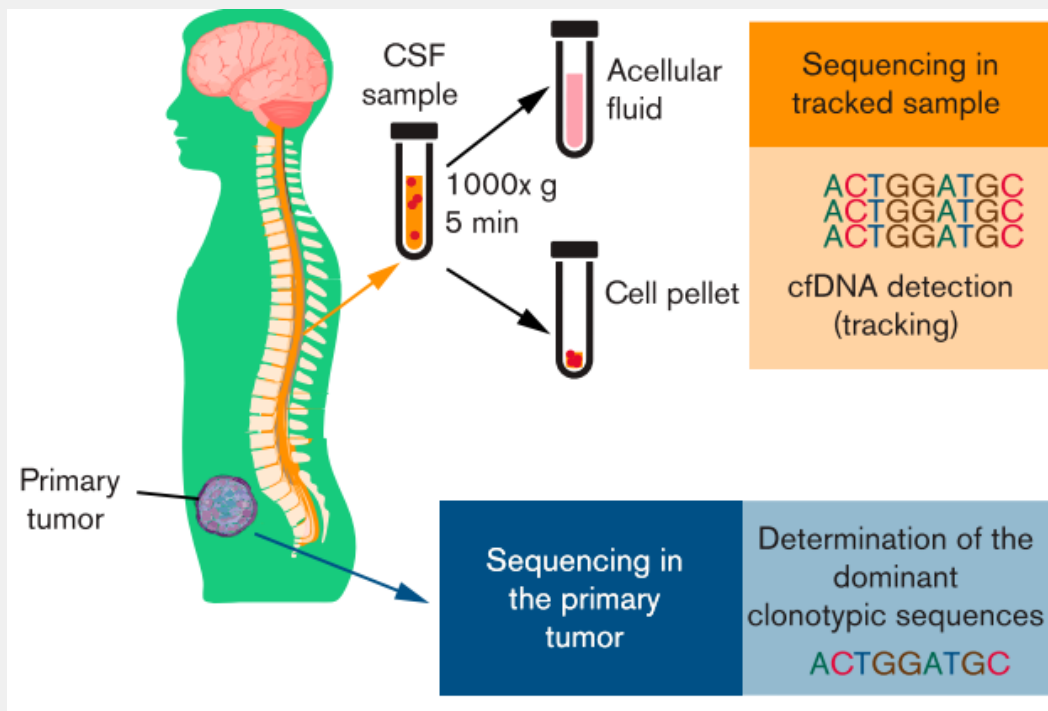
# Incidence of CNS relapse in DZSig+ lymphoma

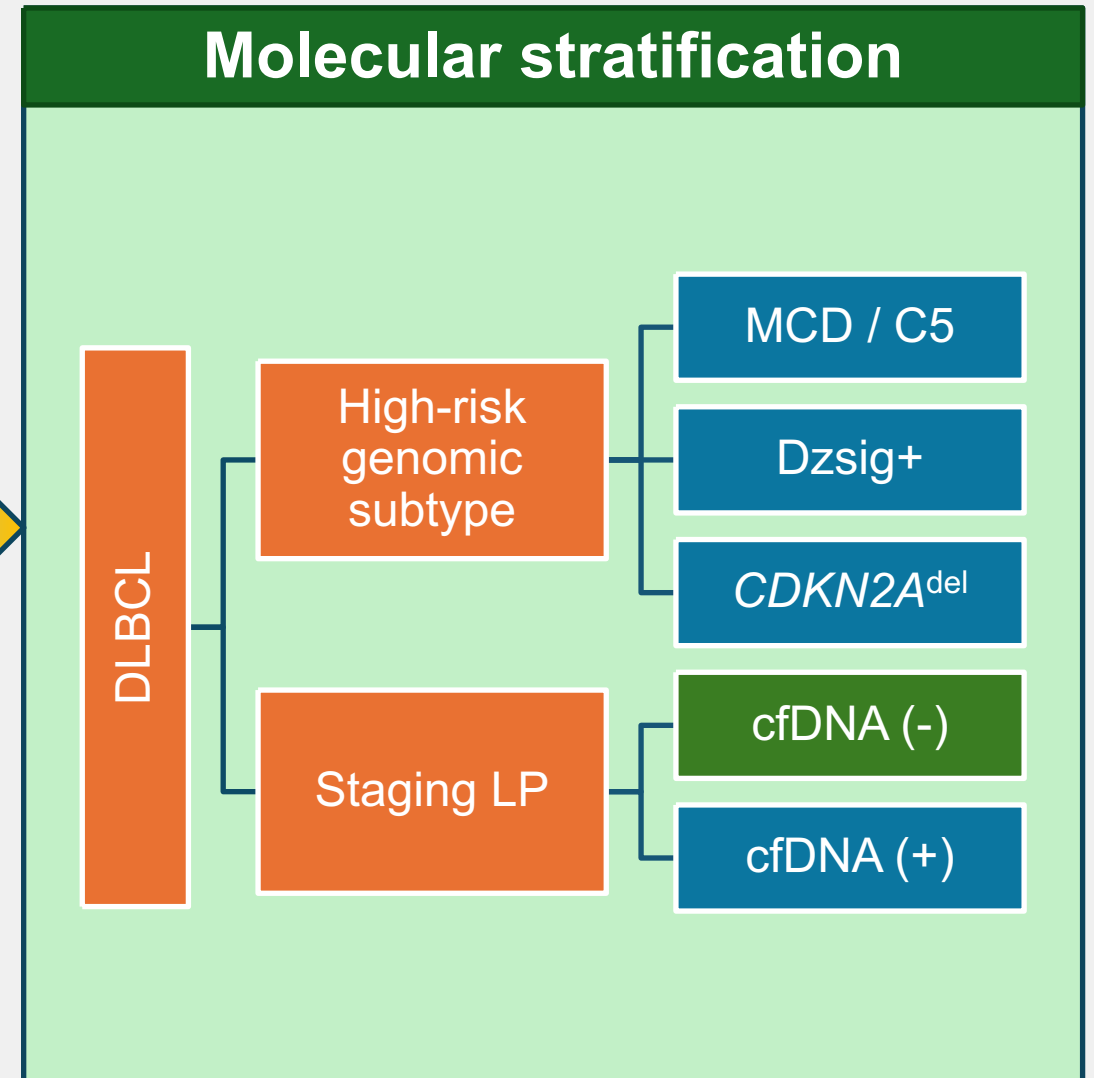
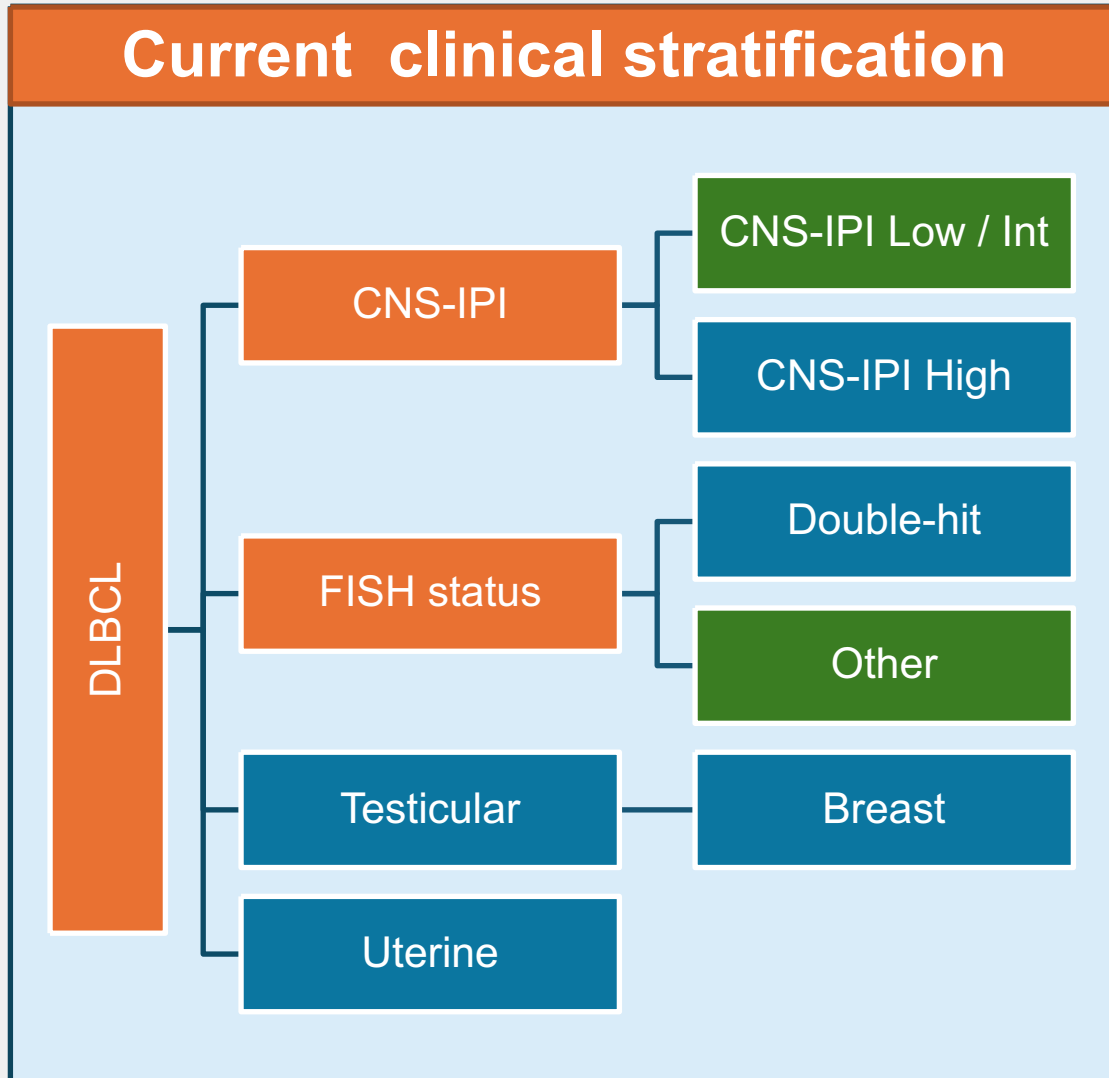
- Population-based screening for HGBL (*MYC* + *BCL2* rear.) or DZSig+ GEP



# ctDNA detection in CSF: staging or diagnosis?

- Adaptive ClonoSEQ assay
- 5 mL CSF from diagnostic LP
- High risk by:
  - High-risk histology
  - High-risk CNS-IPI
- All had negative CSF cytology ± flow cytometry ± IGH PCR





## Intrathecal

methotrexate

cytarabine

liposomal cytarabine

MTX + ARAC

## HDMTX ( $>3 \text{ g/m}^2$ )

Consolidation  
(2-3 cycles)

“Intercalated”  
(Day 15 R-CHOP)

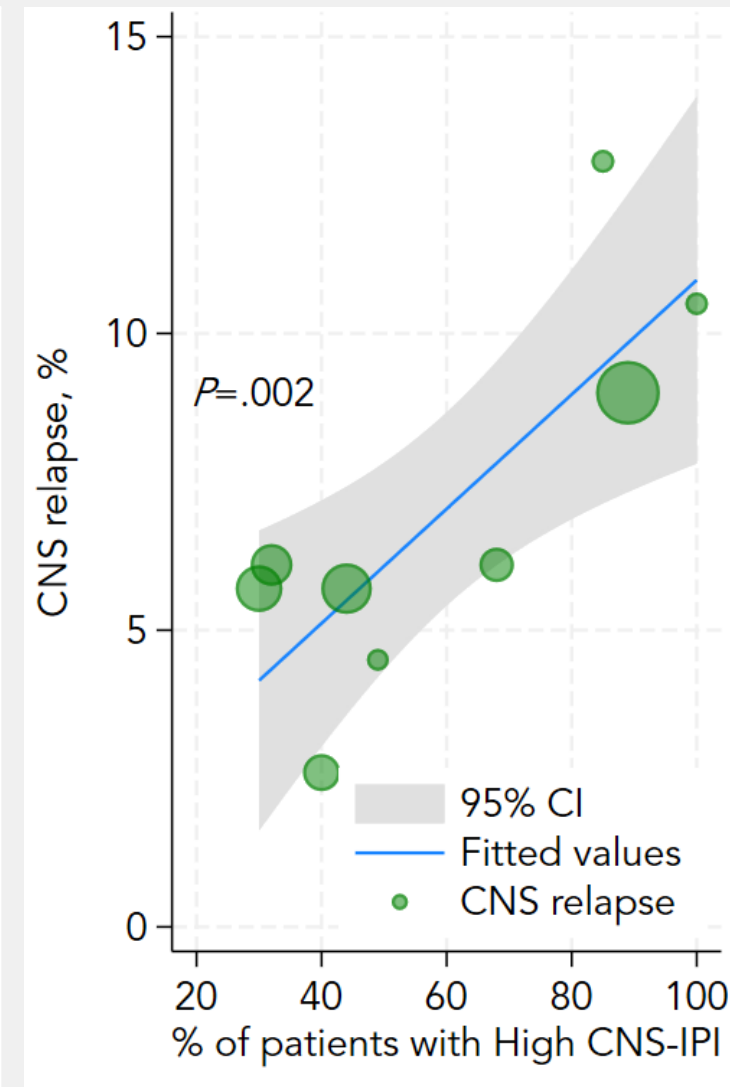
## Multiple CNS- penetrant drugs

CODOX-M/IVAC

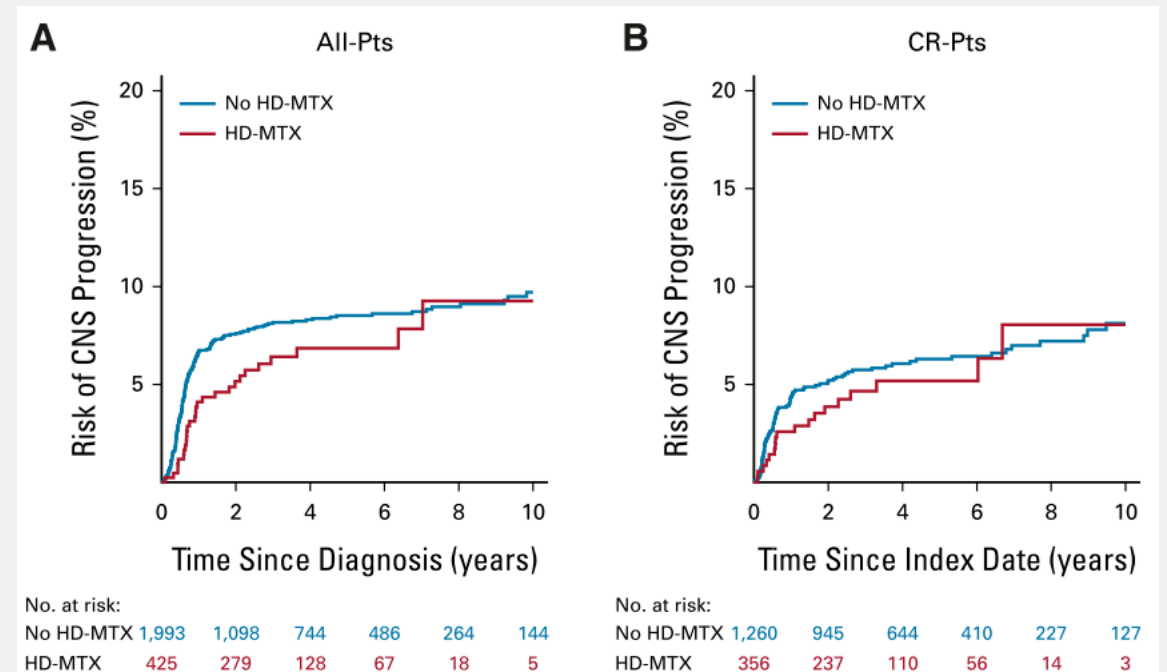
Intensified therapy:  
ICE, ASCT

# CNS prophylaxis: observational data

Study	Setting	CNS-IPI <sub>high</sub>	CNS relapse	Treatment results
Ferreri	N=200 Single center	49% "high risk"	4.5%	<b>Better</b> outcomes with prophylaxis: <b>12%</b> without • <b>2.4%</b> with prophylaxis, <b>0%</b> with HD-MTX
Cheah	N=217 Multicenter	100% "high risk"	10.5%	<b>Better</b> outcomes with prophylaxis: <b>18%</b> IT only • <b>6.9%</b> HDMTX, <b>2.3%</b> Dose-intensive chemo + HDMTX
Ong	N=226 Multicenter			<b>Better</b> outcomes with HDMTX: <b>15%</b> controls • <b>3.1%</b> HDMTX
Eyre	N=690 >70yo Multicenter	40%	2.6%	<b>No difference</b> with IT prophylaxis in CNS-IPI <sup>high</sup>
Bobillo	N=585 Single center	68%	6.1%	<b>Benefit</b> of prophylaxis early, but then lost at 3 years: • At 3 years: <b>3.8%</b> with and <b>7.5%</b> without prophylaxis
Orellana-Noia	N=1162 Multicenter	30%	5.7%	<b>No difference</b> between IT and HDMTX
Wilson	N=1384 Multicenter	44%	5.7%	<b>No difference</b> between intercalated vs consolidative HD-MTX
Puckrin	N=906 Multicenter	32%	6.1%	<b>No benefit</b> of intercalated HD-MTX in high-risk patients
Lewis	N=2300 Multicenter	89%	9%	<b>No benefit</b> of HD-MTX in high-risk patients



- N=2418 patients from 23 sites
  - CNS-IPI  $\geq 4$  (83%), or
  - HGBL, or breast/testicle
- RCHOP in 92%, HDMTX 18%
- **Only 51% underwent baseline staging**
- CNS recurrence:
  - **7.3%** for all patients
  - **5%** for those with CR at end of therapy
- 5-year risk of CNS recurrence for all:
  - **6.9% with HDMTX vs. 8.5%**
  - 1.6% absolute risk reduction
- For patients with CR (N=1,616):
  - **5.0% with HDMTX vs. 6.5%**
- No evidence of subgroup effect (CNS-IPI 5, 6, testicular/renal/adrenal)

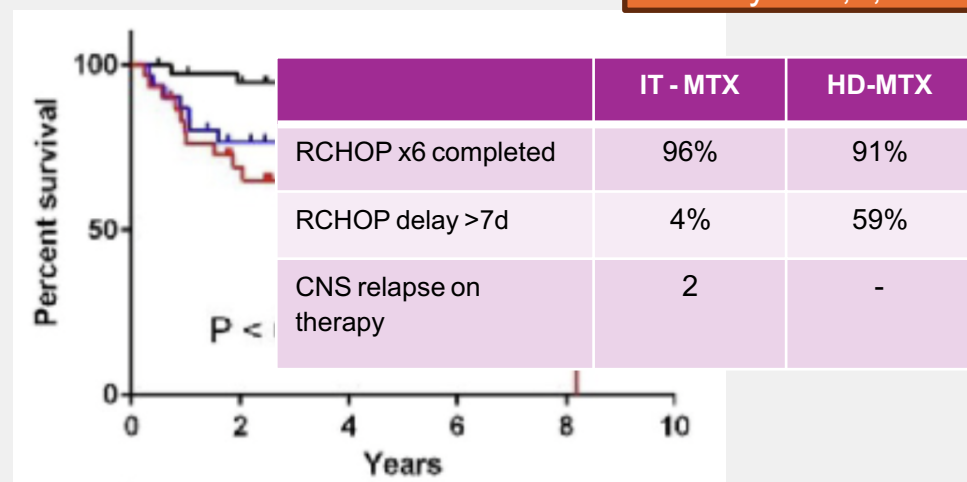
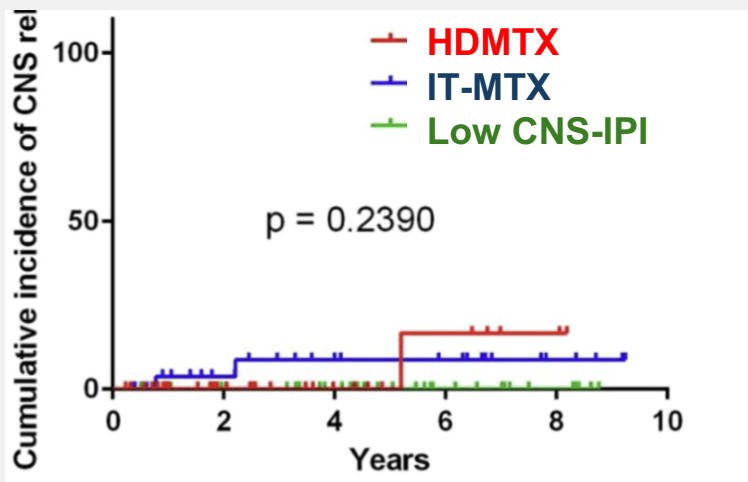


**Adjusted HR, 0.59**  
**[0.38 to 0.90]**  
P = .014

**Adjusted HR, 0.74**  
**[0.42 to 1.30]**  
P = .29

## Czech trial

- Intermediate or high CNS-IPI
- 2 doses of HDMTX 3g/m<sup>2</sup> vs 6xIT MTX 12mg
- N=60
  - HDMTX: ↑ neutropenia and infections
  - **HDMTX: worse OS!** (47% vs 72%)
  - HDMTX: 0% CNS relapse within 5 years
  - IT-MTX: 4% at 3 years

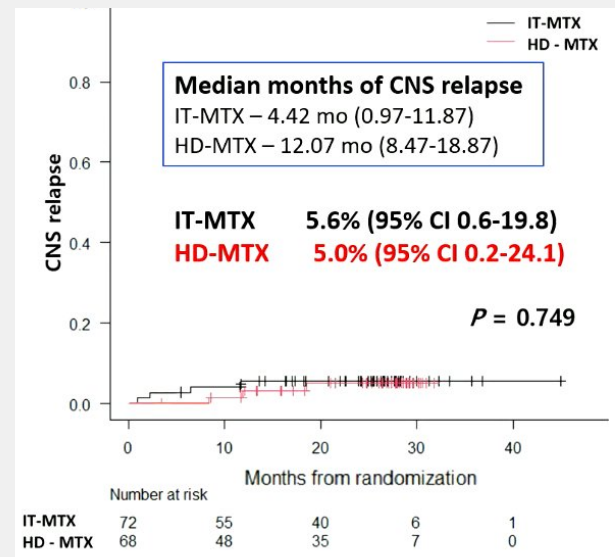


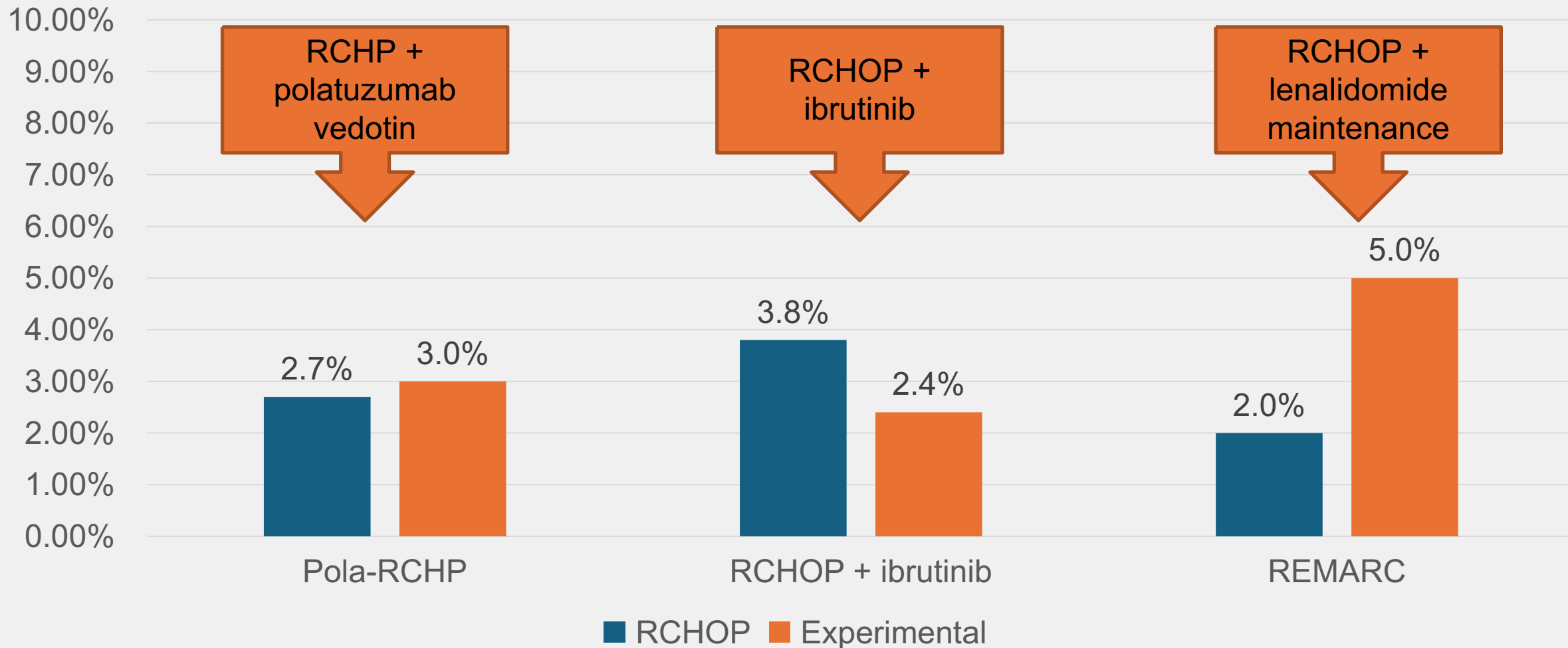
RCHOP +  
IT MTX on D3  
Cycle 2,3,4

RCHOP +  
HDMTX 3 g/m<sup>2</sup> on D14  
Cycle 2 & 6

## Korean trial

- N=142, DLBCL with:
  - IPI ≥ 4 or aaIPI ≥ 2 + LDH>ULN + ≥ 1 EN site
  - Epidural, testicle/breast, marrow, adrenal/kidney
- All patients had CSF analysis + IT MTX 15mg
- 2 excluded for (+) CSF





**NCCN** National Comprehensive Cancer Network®  
**NCCN Guidelines Version 3.2024**  
**Diffuse Large B-Cell Lymphoma**

**USEFUL IN SELECTED CASES:**

- **[Redacted]**
- **[Redacted]**
- HIV testing
- Hepatitis C testing
- Beta-2-microglobulin
- **[Redacted]**; see [BCEL-A 2 of 2](#)

Modality	UK	USA
Lumbar puncture	33%	15%
Imaging	8%	3%
Both	9%	3%
No record		28%
<b>None</b>	<b>50%</b>	<b>51%</b>

**PROGNOSTIC MODEL TO ASSESS THE RISK OF CNS DISEASE<sup>d</sup>**

- |                                       |                     |  |
|---------------------------------------|---------------------|--|
| • Age >60 years                       | • Low risk          | 0–1  |
| • Serum LDH > normal                  | • Intermediate-risk | 2–3  |
| • Performance status >1               | • High-risk         | 4–6 or kidney or adrenal gland involvement |
| • Stage III or IV                     |                     |  |
| • Extranodal involvement >1 site      |                     |  |
| • Kidney or adrenal gland involvement |                     |  |

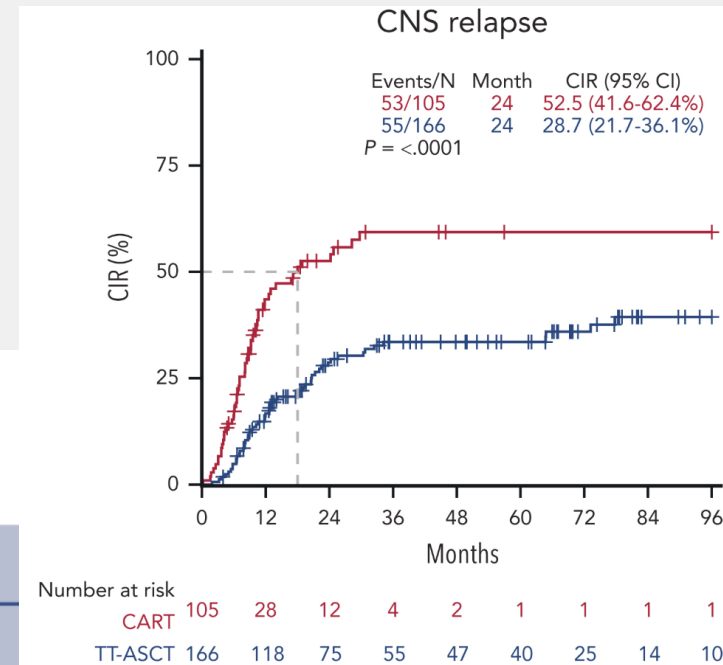
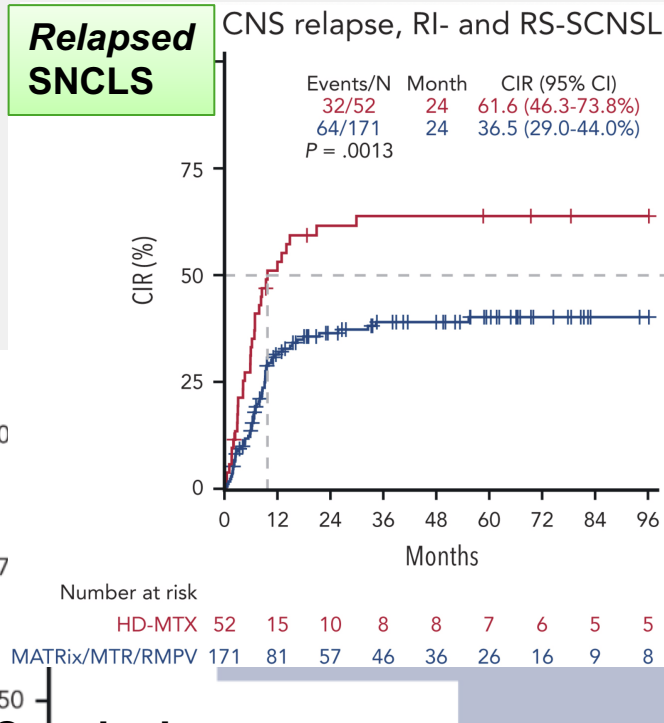
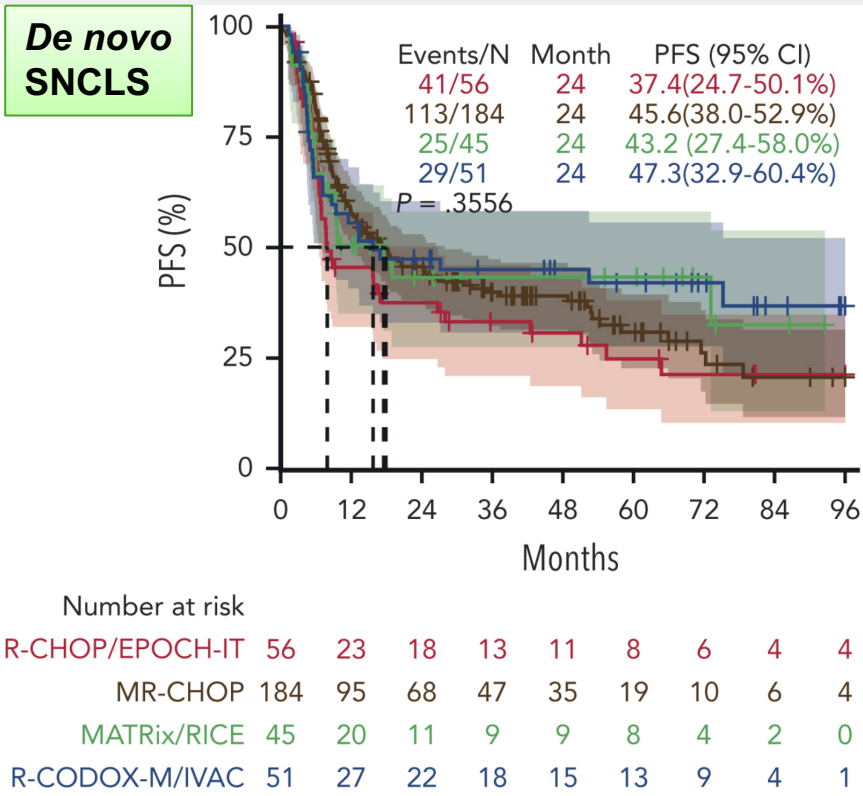
• Additional indications for CNS prophylaxis independent of CNS risk score

- ▶ Testicular lymphoma
- ▶ Primary cutaneous DLBCL, leg type
- ▶ Stage IE DLBCL of the breast
- ▶ Kidney or adrenal gland involvement

- Role of CNS prophylaxis remains controversial but can be considered in patients with high-risk factors based on the aforementioned criteria. If CNS prophylaxis is used, options include:
  - ▶ Systemic high-dose methotrexate (3–3.5 g/m<sup>2</sup> for 2–4 cycles) during or after the course of treatment<sup>e</sup> and/or
  - ▶ IT methotrexate and/or cytarabine (4–8 doses) during or after the course of treatment

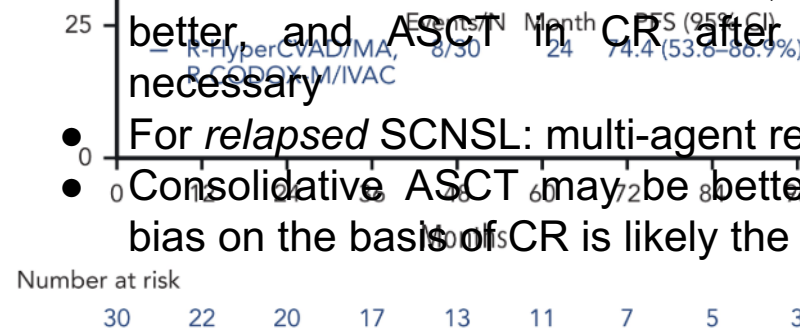
# sCNLS: treatments and outcomes

- N=1139 patients with:
  - *De novo* CNS involvement: 537
  - Relapsed SNCSL: 602
- DEL: 39%
- DHL: 16%



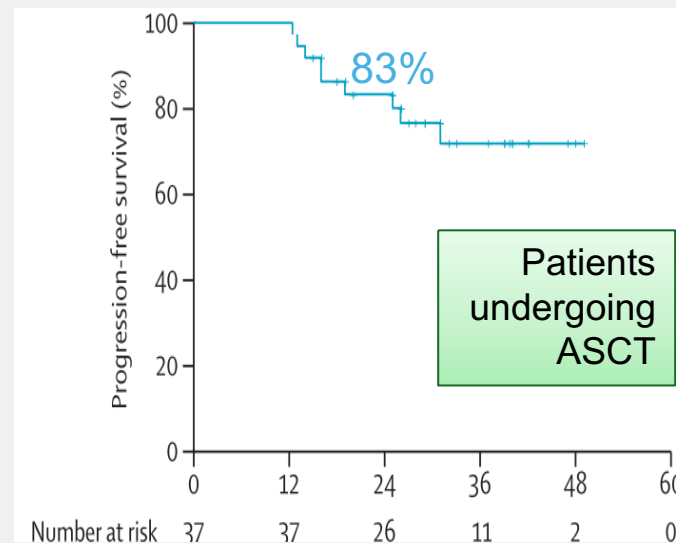
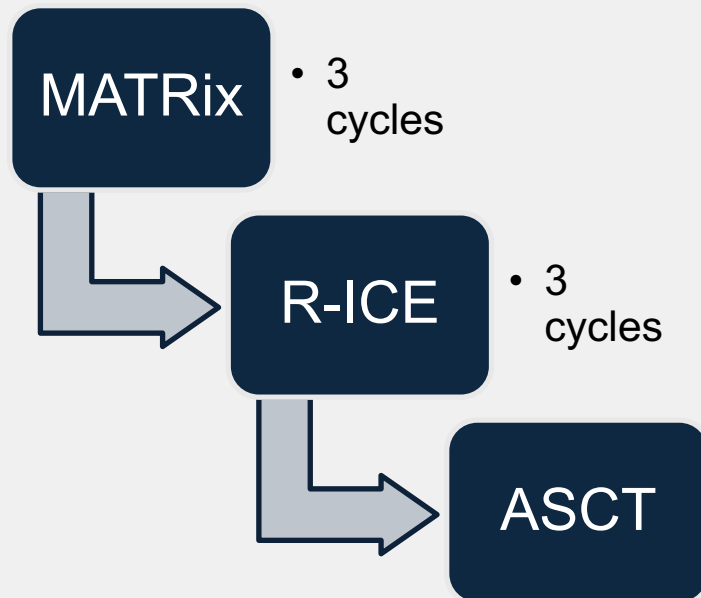
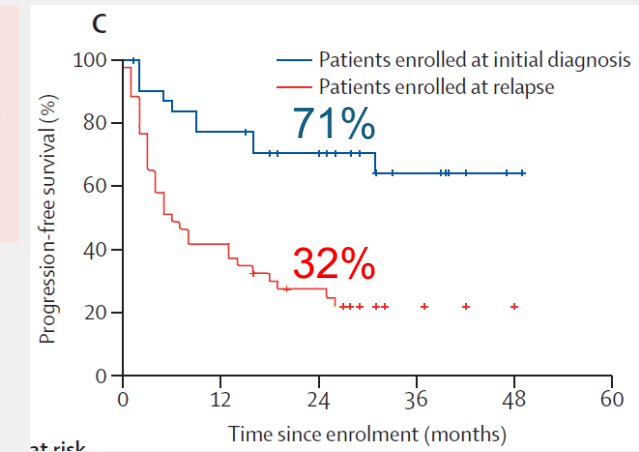
## Conclusions:

- For *de novo* CNS involvement, HDMTX-containing regimens are better, and ASCT in CR after R-CODOX-M/IVAC may not be necessary
- For *relapsed* SCNSL: multi-agent regimens are better than HDMTX
- Consolidative ASCT may be better than CAR T-cells, but selection bias on the basis of CR is likely the critical determinant.



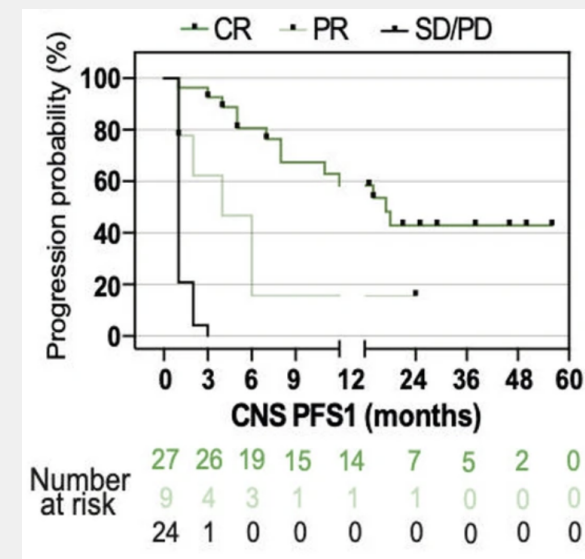
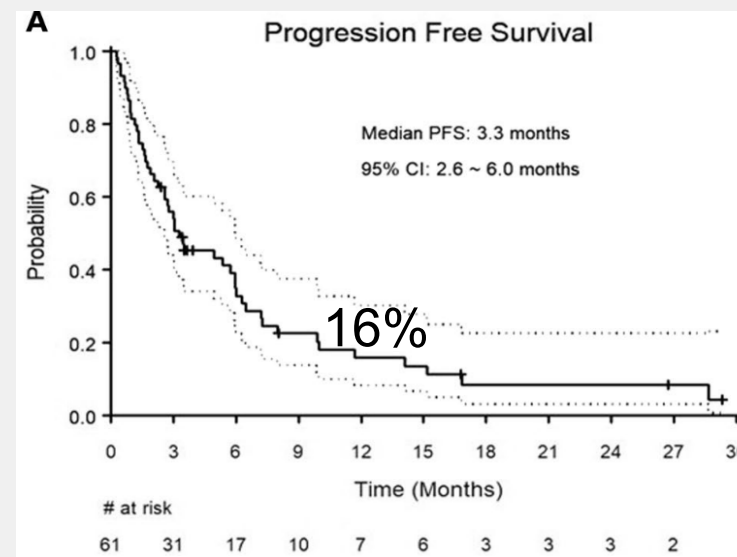
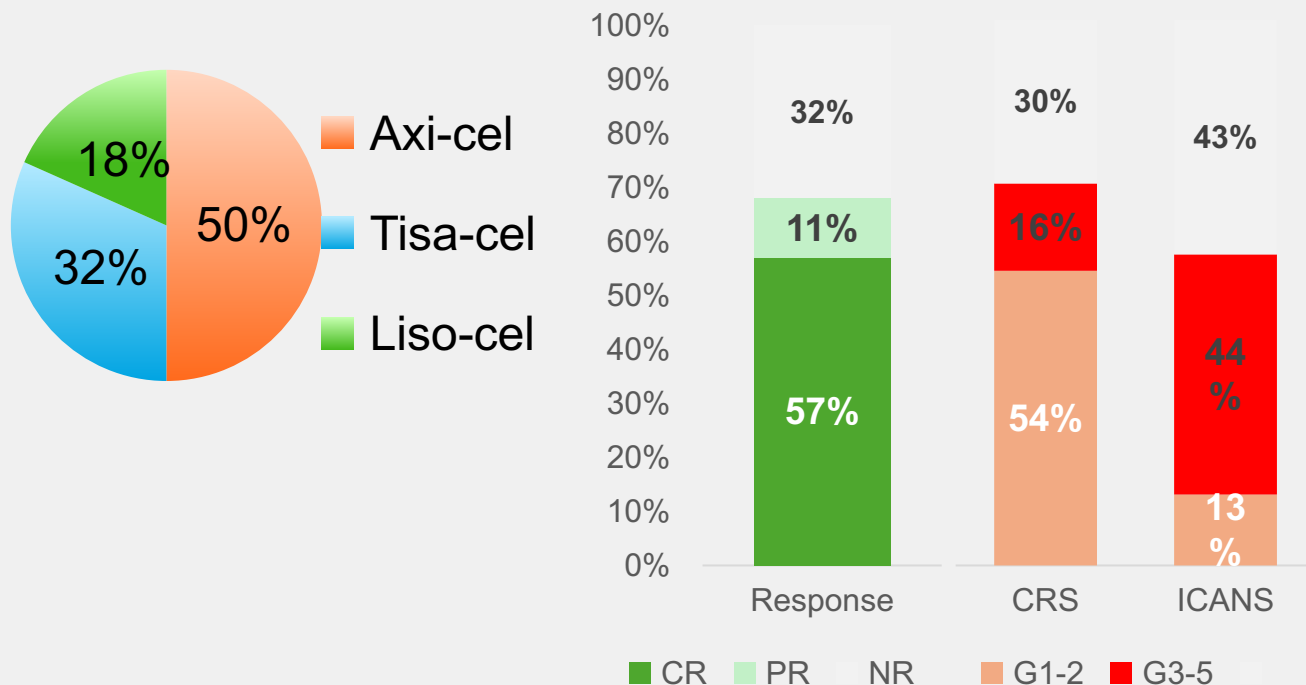
- Single-arm phase 2 trial
- N = 75
- Median age 58 (23-70)
- **43% primary CNS disease**
- 20% isolated CNS relapse
- 37% systemic relapse

	Whole series (n=75)	Relapse; isolated CNS disease (n=15)	Relapse; CNS-systemic disease (n=28)
Complete response	41 (55%)	7 (47%)	9 (32%)
Partial response	5 (7%)	0	3 (11%)
Objective response	46 (61%)	7 (47%)	12 (43%)



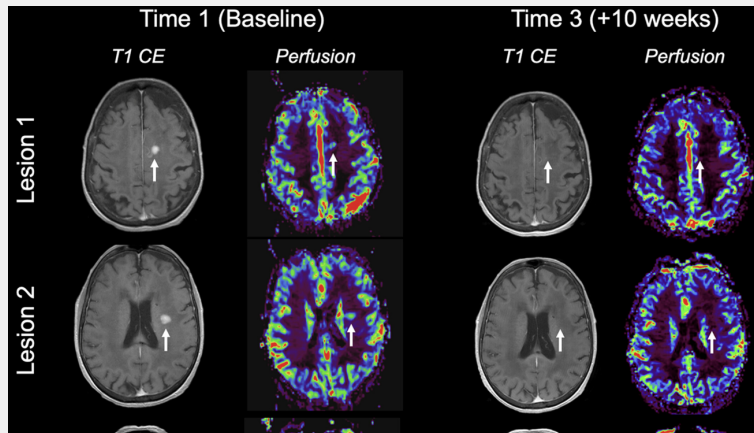
	Grade 1-2	Grade 3	Grade 4	Grade 5
Neutropenia	2 (3%)	5 (7%)	41 (55%)	0
Anaemia	8 (11%)	22 (29%)	4 (5%)	0
Thrombocytopenia	2 (3%)	1 (1%)	44 (59%)	0
Infections	17 (23%)	14 (19%)	8 (11%)	4 (5%)
Hepatotoxicity	8 (11%)	13 (17%)	0	0
Nephrotoxicity	7 (9%)	0	1 (1%)	0
Mucositis	8 (11%)	3 (4%)	1 (1%)	0
Nausea, vomiting, or diarrhoea	17 (23%)	3 (4%)	0	0
Central and peripheral neurotoxicity	10 (13%)	3 (4%)	0	0
Cardiotoxicity	2 (3%)	1 (1%)	0	0
Vascular events*	2 (3%)	1 (1%)	1 (1%)	0

- Multicenter US retrospective, N=61
- N=41 with concurrent systemic relapse
- 30% double-hit cytogenetics
- Median 3 prior lines of therapy (1-5)
- Median time from diagnosis 16 months (3-257)
- HD-MTX (41%), ASCT (23%)
- **CRS** in 70% (16% G3+), **ICANS** 57% (44% G3+)

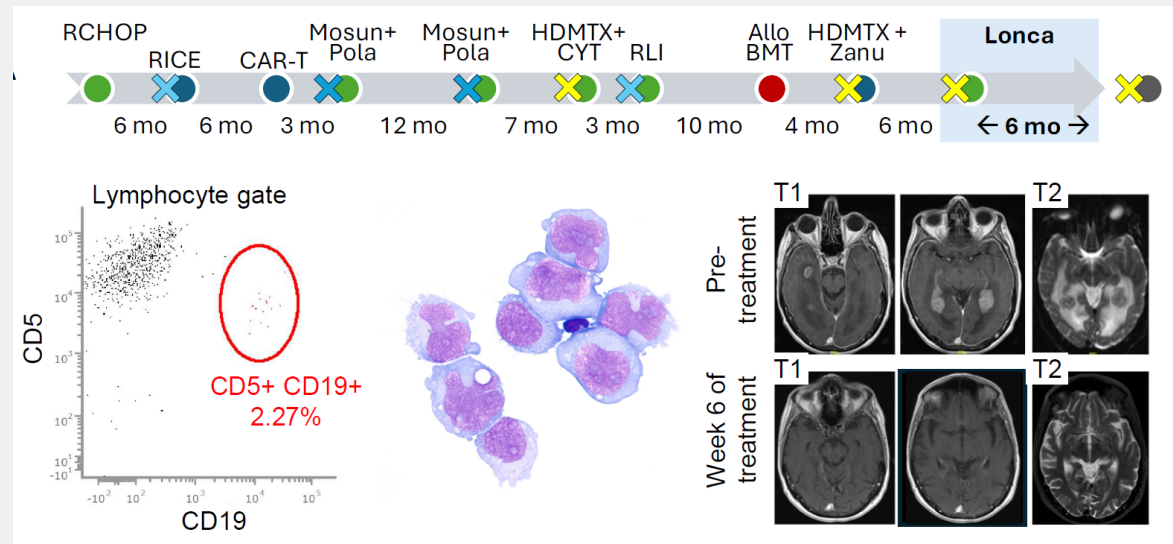


**Tafasitamab + Lenalidomide**

- 2 cases

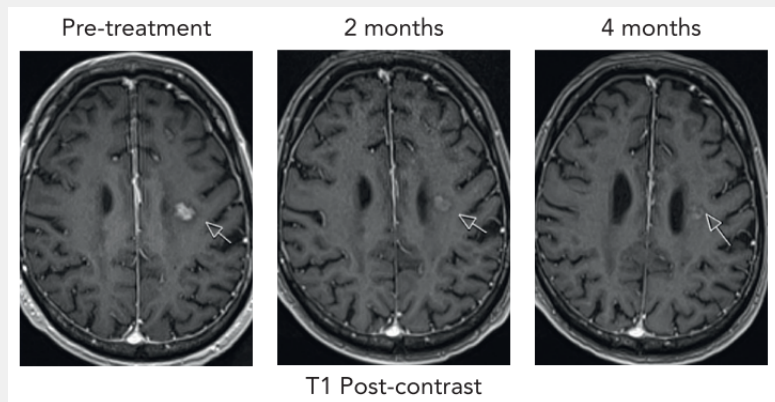


- **Loncastuximab tesirine**
- 3 cases, all with prior CAR T-cell exposure



**Glofitamab**

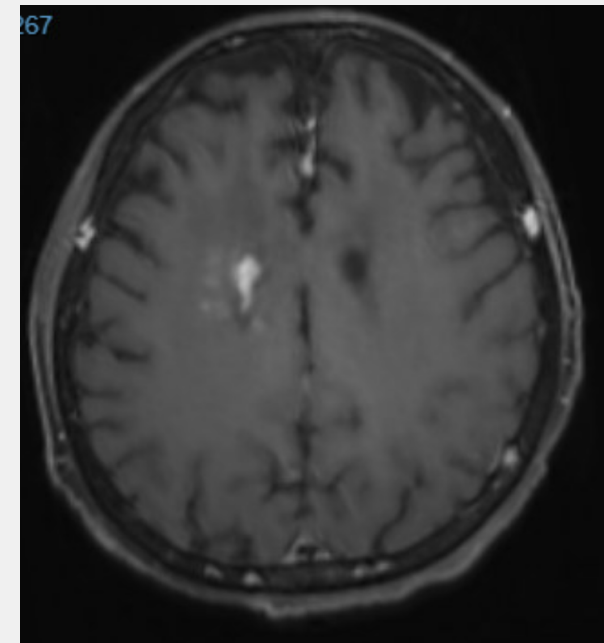
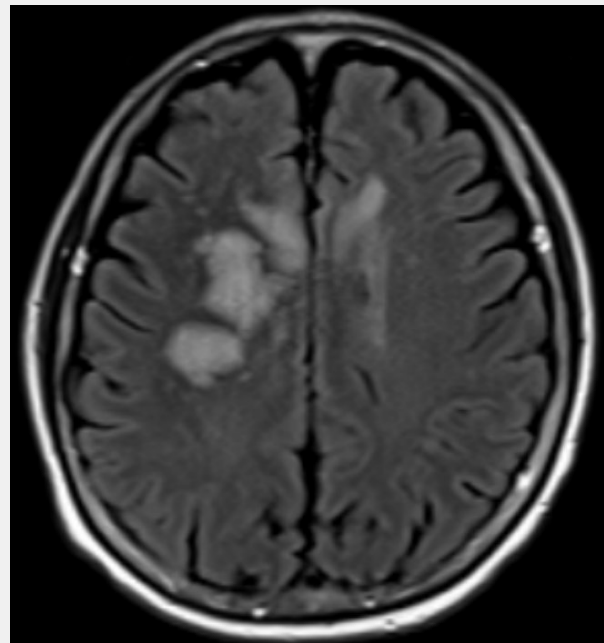
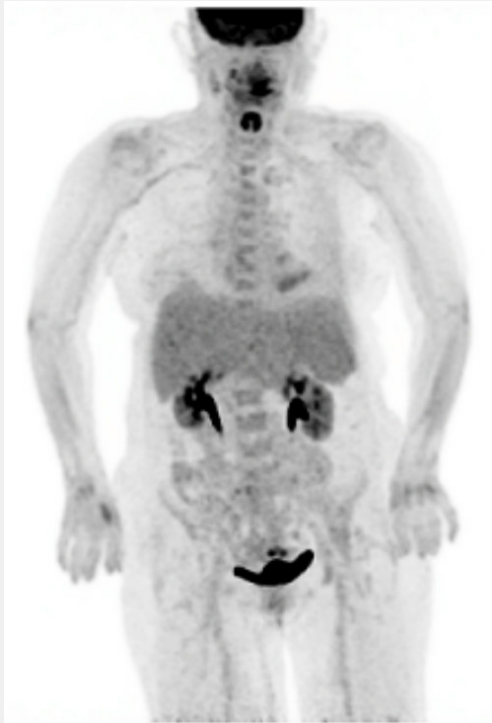
- 4 cases

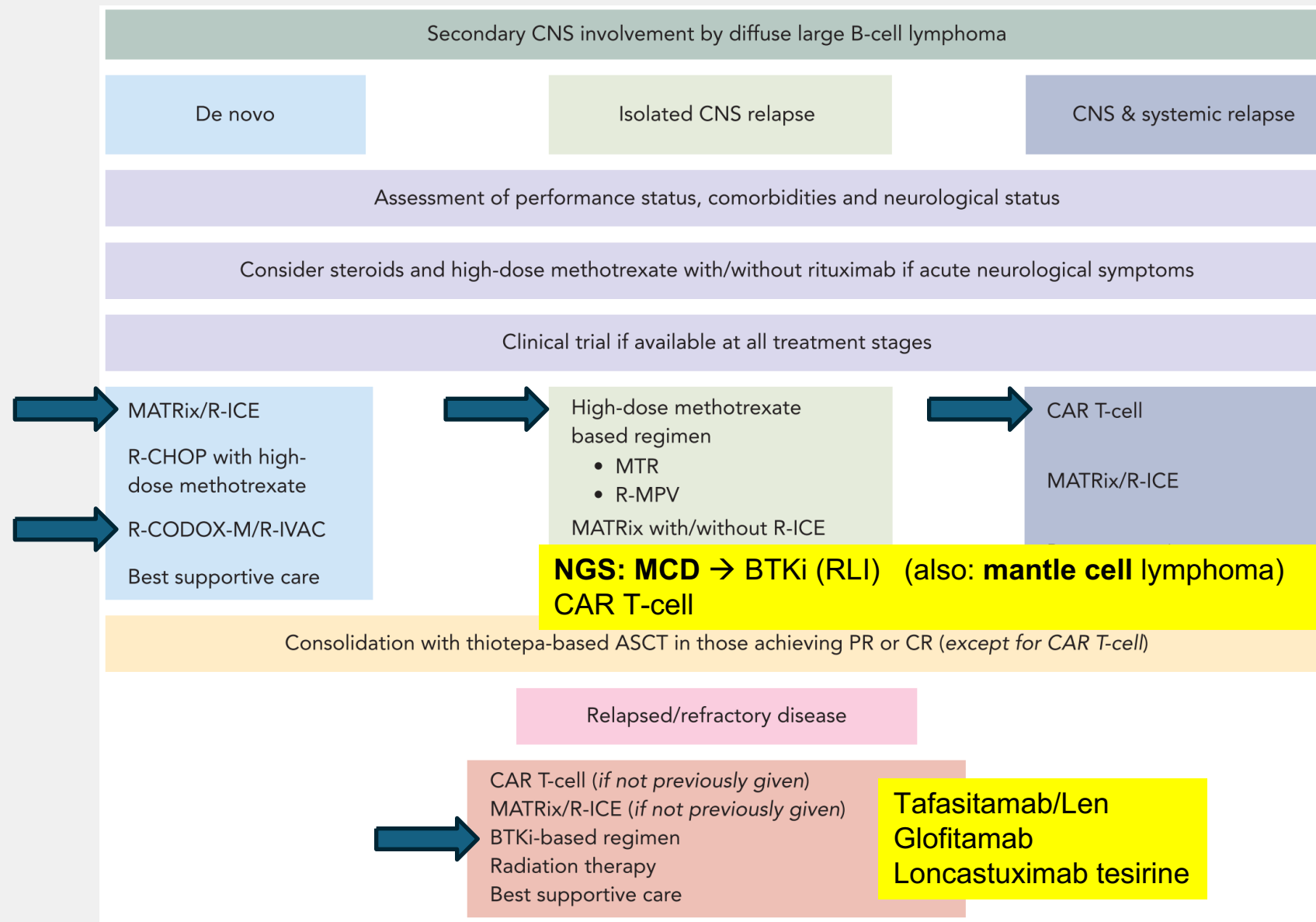


**Bispecific antibodies**

- 12 cases of DLBCL/PCNSL/HGBL/MCL/BL with CNS disease
- ORR 50%, CR in 25%
- 6-month PFS in CNS 65%

- 71 year-old healthy woman – abnormal mammogram in 12/2024: “0.8 cm mass at 2 o’clock”
- **Left breast, needle core biopsy: CD20-negative DIFFUSE LARGE B-CELL LYMPHOMA**, non-GCB: large cells (+) for CD19, BCL2, BCL6, MYC (60%), MUM1 (>30%), high Ki67 (>90% by MIB1), (-) EBER ish. FISH (-) for *IGH::BCL2*, *MYC*, *BCL6* rearrangements.
- **PETCT: no uptake in the breast.** 1 cm right cervical node; 1.6 cm portocaval lymph node (SUV=3.5); intense uptake in the spleen without foci, SUV=10; abnormal focal intense uptake in the uterus (SUV=10); **LDH - 537**
- **PolaRCHP x 4 → HDMTX x2 → SD → Acalabrutinib → SD → RT → Axi-cel → PR (?)**





**Thank you!**

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