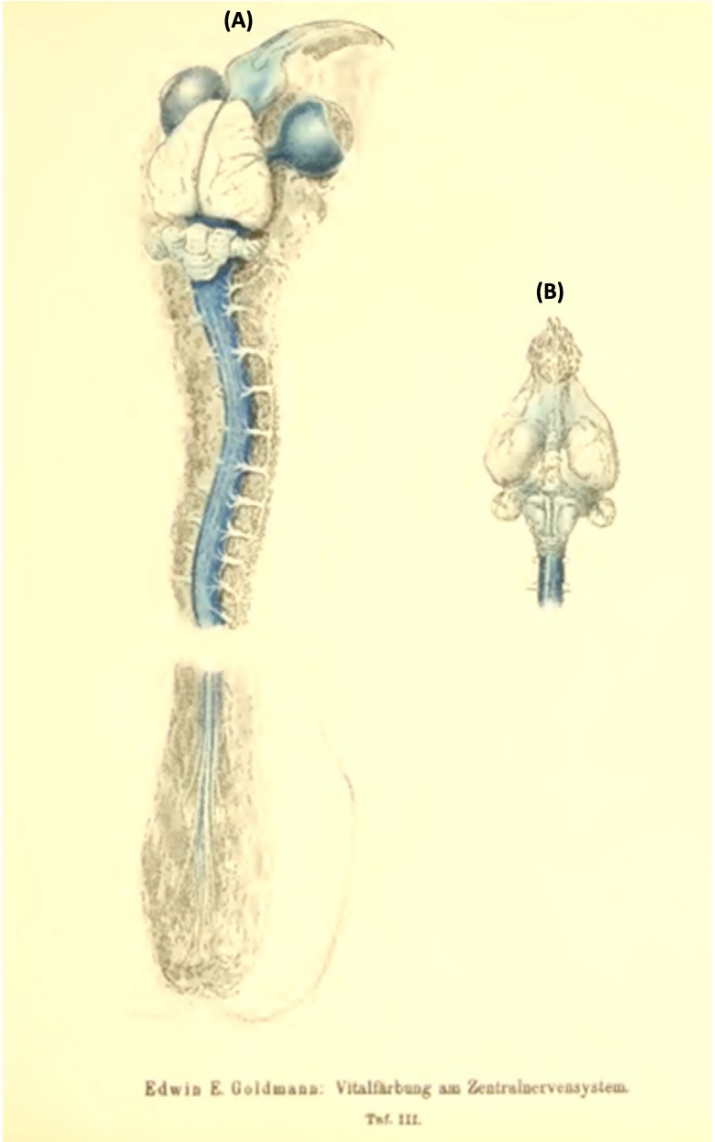
Diagnosis, prophylaxis and treatment of (secondary) CNS lymphoma

Elisa Lucchini - Trieste

The Blood-Brain-Barrier



Wislocki GB 1920; Contrib. Embryol. Carnegie Inst 11, 45-60

Bentivoglio M. Trends in neurosciences, 2014

The Blood-Brain-Barrier

The term BBB is used to describe the unique characteristics of the blood vessels that vascularize the CNS:

- expression of tight junctions
- absence of fenestrations
- active transport mechanisms

It plays a critical role in protecting the brain parenchyma from blood-born agents, drugs and other exogenous compounds.

Various efflux transporters are present (eg: MDR1, P-gp, BCRP) and also drug-metabolzing enzymes (CYP3A4).

→ Obstacle to the entry of drugs

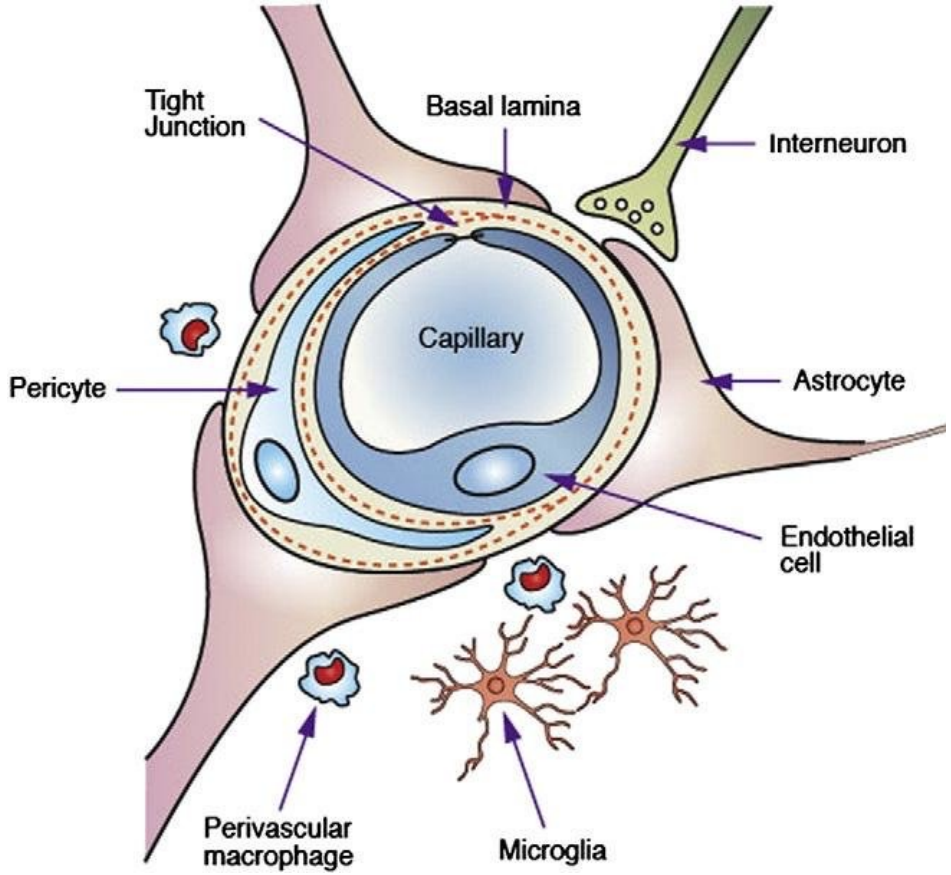


Image: Parashar AK et al. Curr Res Pharmaceutical sciences. 2012

Kadry H et al. Fluids Barriers CNS. 2020; Profaci CP et al. Journal of Experimental Medicine. 2020

Secondary CNS involvement

Risk of CNS involvement in patients with DLBCL: 5%, but up to 15% for high-risk patients/histotypes

Poor outcome of secondary CNS involvement: median OS 6-12 months

Secondary CNS - DLBCL may involve the brain, meninges, cranial nerves, eyes and/or spinal cord.

- Parenchymal involvement: 70%
- Leptomeningeal involvement 20%
- Parenchymal + leptomeningeal: 10%

40% de novo disease; 60% at relapse

Always perform CT/PET to stage systemic disease + testicular ultrasound + ocular assessment (vitreo-retinal involvement)

CNS involvement by DLBCL

- **Diagnosis**
- **Prophylaxis**
- **Treatment**

Diagnosis

- Stereotactic brain biopsy: is the **gold standard** for the diagnosis of CNS involvement by lymphoma.
- CSF analysis: low sensitivity, but highly specific if malignant cells are detected.
- MRI imaging: homogeneous contrast enhancement, without central necrosis, marked peritumoral edema and T2 hyperintensity are characteristic features of lymphoma, but are not pathognomonic, and the specificity for lymphoma is low.

Corticosteroid therapy should not be administered before having a diagnosis due to the risk of inconclusive biopsy and «ghost/vanishing» lesions.

Futhermore, timing of corticosteroid tapering is not defined.

Scheichel et al. 2022

Diagnosis - biopsy

Clinical utility of brain biopsy for presumed CNS relapse of systemic lymphoma

Desmond A. Brown, MD, PhD,[1] Anshit Goyal, MBBS, MS,[1] Kent R. Richter, BS,[2]

60 patients with a history of systemic lymphoid malignancy, who underwent initial treatment and remission with a subsequent appearance of a MRI lesion suspected for secondary CNS relapse.

All underwent stereotactic brain biopsy.

65% had an initial diagnosis of **DLBCL**.
Median time between diagnosis and CNS relapse: 45.5 months

- 97.2% of brain biopsies showed DLBCL relapse.
- One new diagnosis: brain astrocytoma

Among patients with an initial diagnosis of «other» lymphoma, 0% showed the initial histology.

Brown DA et al. J Neurosurg 2022.136:30-39

Diagnosis - biopsy

→ Among patients with a previous diagnosis of DLBCL, the decision to perform a stereotactic biopsy should be weighed against treatment delay and procedural complications[1].

	Frameless	Frame-based [2,3]
Diagnostic yeld	86,6-100%	84-100%
Hemorrhage	0-17,8%	0-14,2%
Morbidity	1,3-21,4%	3,8-27,8%
Mortality	0-3,6%	0-3,9%

- Hemorrhage risk is higher for PCNSL compared to other brain tumors
- Postoperative CT-scan recommended

1.Brown DA et al. J Neurosurg 2022.136:30-39; 2.Dhawan et al. 2019; 3.Peciu-Florianu et al. 2021

Diagnosis - biopsy

When to perform stereotactic biopsy in case of suspected CNS relapse?

Concurrent CNS and systemic lymphoma

Biopsy of a systemic-site alone if MRI findings are consistent with lymphoma

Isolated CNS involvement

Biopsy can be omitted if early relapse (< 2 years) and characteristic brain MRI features

Biopsy recommended if late relapse (>2 years from diagnosis)

Bobillo et al. Haematologica 2023

Diagnosis – CSF analysis

«Collection of up to 30 mL of CSF is well tolerated and safe when atraumatic puncture needles are used»

Biochemistry:

- Increased protein concentration = BBB disruption → parenchymal lesions
- Decreased glucose concentration → CSF or meningeal infiltration

Citology: sensitivity 2-32% (need for large CSF volumes)

Flow cytometry: positive in leptomeningeal involvement; requires high amount of cells

Molecular testing and cytokine levels

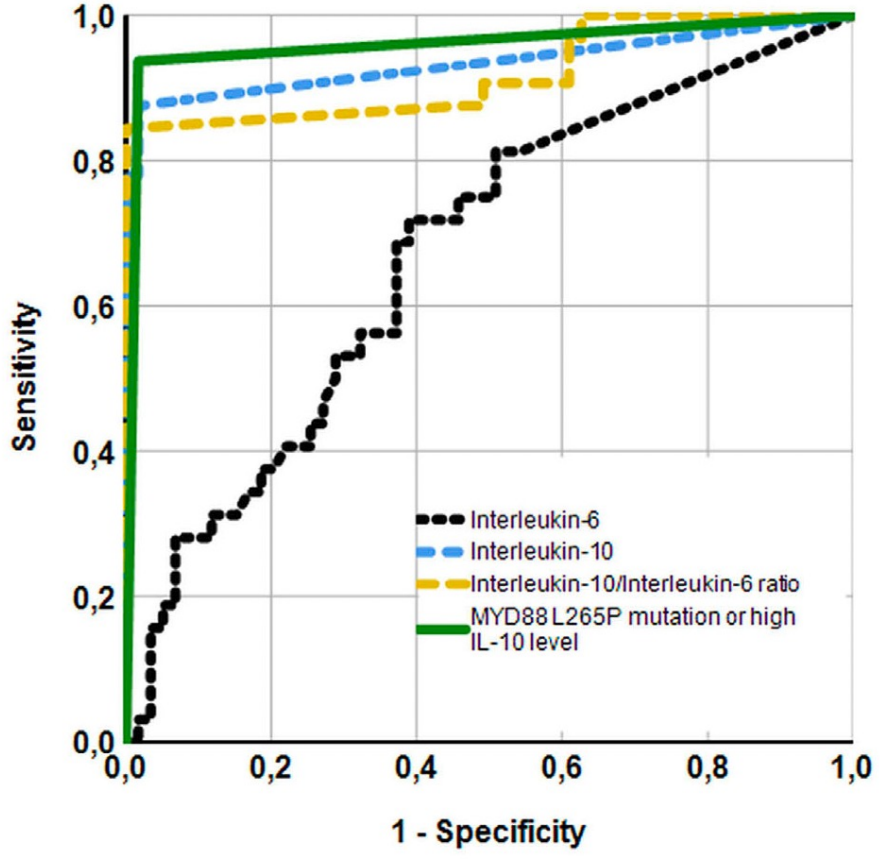
Nguyen-Them et al, 2020; Ahle et al. 2017

Diagnosis – CSF analysis

bjh research paper

MYD88 L265P mutation and interleukin-10 detection in cerebrospinal fluid are highly specific discriminating markers in patients with primary central nervous system lymphoma: results from a prospective study

- Presence of MYD88 L265P mutation in CSF of 72% of PCNSL
- High IL-10 CSF levels in 88% of PCNSL
- IL-6 CSF levels high in PCNSL, but also in patients with neurological diseases and systemic-only DLBCL
- Concordance between MYD88 mut and IL-10 levels in CSF and tissue biopsy



Presence of MYD88 L265P mutation and elevated IL-10 exhibit a very high sensitivity and specificity in detecting PCNSL both at diagnosis and at relapse.

	Sensitivity	Specificity	AUC
Interleukin-6	72%	52%	0·66 (0·55 - 0·78)
→ Interleukin-10	88%	99%	0·94 (0·86 - 1·00)
IL-10/IL-6 ratio	85%	99%	0·92 (0·84 - 0·99)
→ *MYD88* mutational status & IL-10	94%	98%	0·96 (0·91 - 1·00)

Ferreri AJM et al. BJH 2021.

Diagnosis – CSF analysis

Combining *MYD88* L265P mutation detection and clonality determination on CSF cellular and cell-free DNA improves diagnosis of primary CNS lymphoma

Bravetti C et al. BJH 2022.

Cell free circulating tumor DNA in cerebrospinal fluid detects and monitors central nervous system involvement of B-cell lymphomas

Bobillo S et al. Haematologica 2021.

Rapid tumor DNA analysis of cerebrospinal fluid accelerates treatment of central nervous system lymphoma

Gupta M et al. Blood 2024.

Entirely noninvasive outcome prediction in central nervous system lymphomas using circulating tumor DNA

Heger JM et al Blood 2024

Caso clinico

F, 71 aa

Gen-24: deficit facciale dx + ipostenia arti inferiori.
Mingazzini II pos a sinistra; ROT assenti agli arti inferiori; ipopallestesia arto inf sin; ipocinesia emirima orale destra

RMN encefalo: enhancement bilaterale del pacchetto acustico, del nervo facciale, dei glossofaringei e del IV nc a sinistra. Tessuto solido con enhancement a livello del cavo di Meckel di sinistra e formazione nodulare di circa 5 mm adesa al tentorio a sinistra a livello dell'angolo ponto-cerebellare.

Valutazione neurochirurgica: non eseguibile biopsia.

Valutazione liquor:

- Chimico-fisico: proteine 85.5 mg/dL
- Citologico: tappeto di emazie; alcune cellule linfoidi mononucleate
- **IF**: 30 linfociti/uL, di cui il 2% di dimensioni medio-grandi CD19+CD20+CD5-CD10+ clonali kappa
- **MYD88 L265P**: positiva
- **Dosaggio IL-10**: 10.6 pg/mL

Caso clinico

- PET/TC: focale iperaccumulo sul versante basale mediale del polo temporale sinistro in verosimile corrispondenza del cavo di Meckel (SUV 17); focali ipercaptazioni a carico di radici nervose a livello C1-C2 a destra (SUV 4,6), L3-L4 a sinistra (SUV 7,3)
- BOM: negativa.

Terapia eseguita:
4 x MATRIX dal 09/02/24 al 05/05/24 → RC
ASCT (condizionamento carmustina+tiotepa) il 20/06/24

Eseguite 7 rachicentesi diagnostiche e medicate (MTX, ARA-C, MP), negative

Rivalutazione a +3 mesi da ASCT:

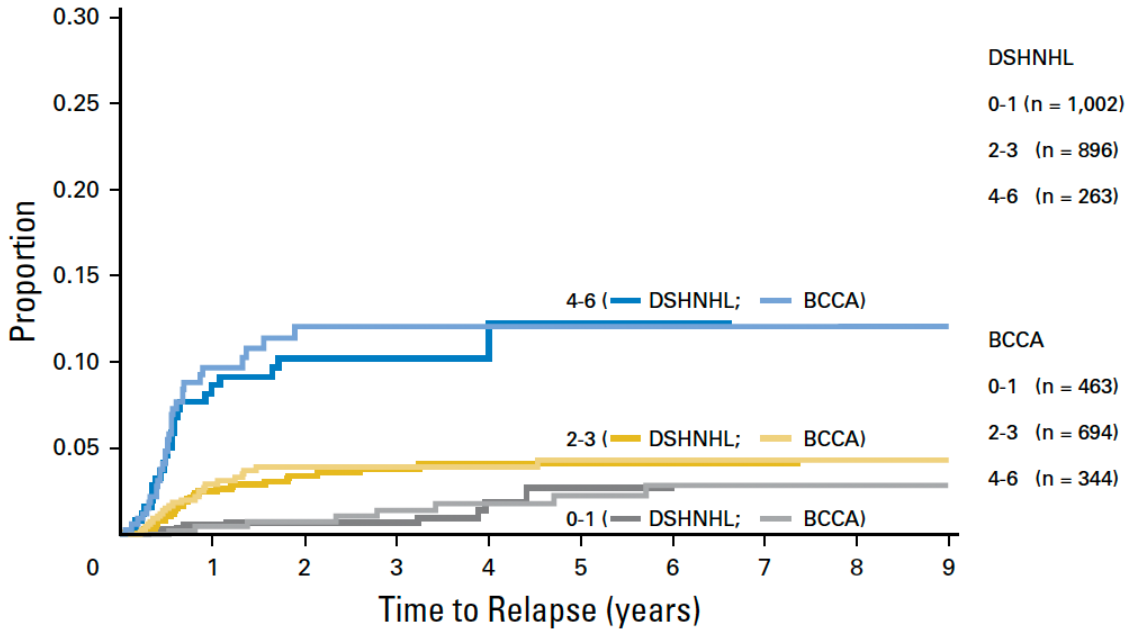
- PET/TC: risposta metabolica completa. Scomparsa del focale iperaccumulo al polo temporale sinistro in corrispondenza del cavo di Meckel. Scomparsi gli accumuli descritti in precedenza a livello delle radici nervose C1-C2 a destra e L3-L4 a sinistra.
- RMN encefalo: invariata per dimensioni (5-6 mm) formazione nodulare all'angolo ponto-cerebellare di sinistra a impianto durale.

CNS involvement by DLBCL

- Diagnosis
- **Prophylaxis**
- Treatment

Identification of high-risk patients

CNS-IPI[1]



Age > 60 years	Stage III/IV
LDH > ULN	Extranodal disease > 1
ECOG PS > 1	**Kidney/adrenal glands**

Risk:

- 0-1 Low
- 2-3 intermediate
- **4-6 High: 10.2% rate of CNS relapse**

Limitations:

- Underestimates the risk of CNS recurrence in certain extranodal lymphomas: **primary testicular (10-yrs CNS relapse: 10-25%),** primary breast[2,3]
- Involvement of ≥ 3 extranodal sites by CT/PET confers a high risk of CNS-relapse (15.2% at 3 years)[4]
- Does not include biological risk factors

1.Schmitz N et al JCO 2016

2.Kridel R et al. BJH 2017. 3. Hosein PJ et al. BJH 2014. 4.El-GalalyTC et al. Eur J Can 2017

Identification of high-risk patients

Biological risk-factors

1. Double-hit lymphoma and high-grade lymphoma: CNS recurrence of 5-20%[1]

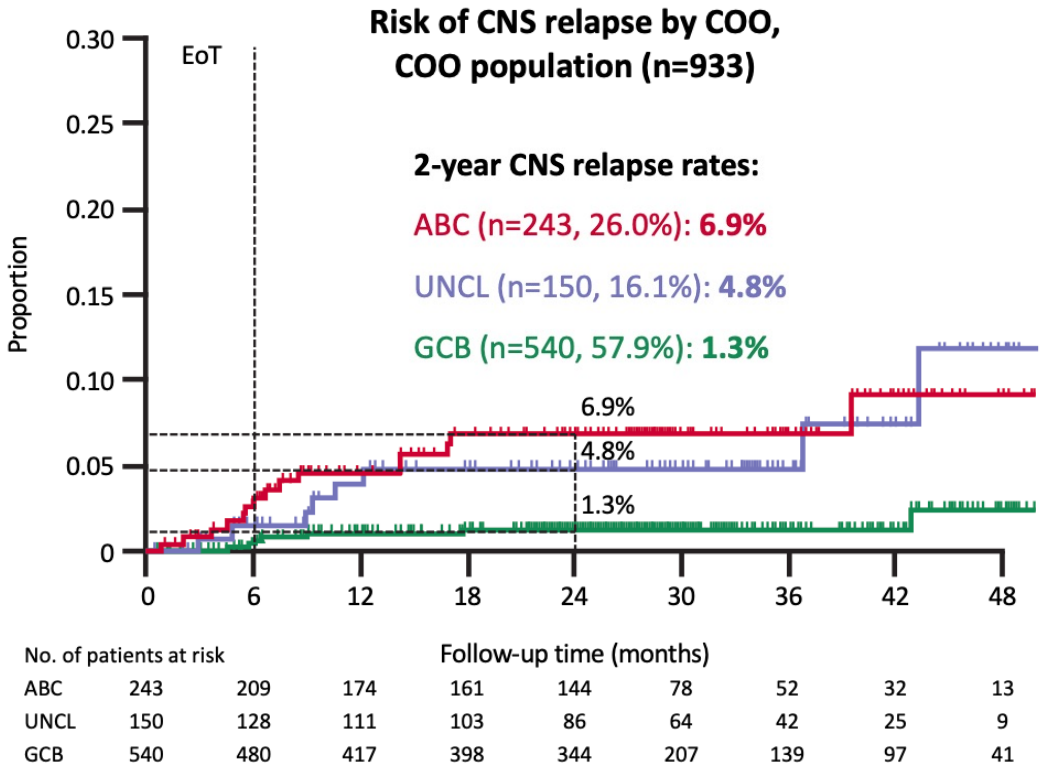
2. ABC-phenotype by GEP: 7-9% CNS relapse[2]

1. Savage KJ et al Blood 2016 2.Klanova M et al. ICML 2017

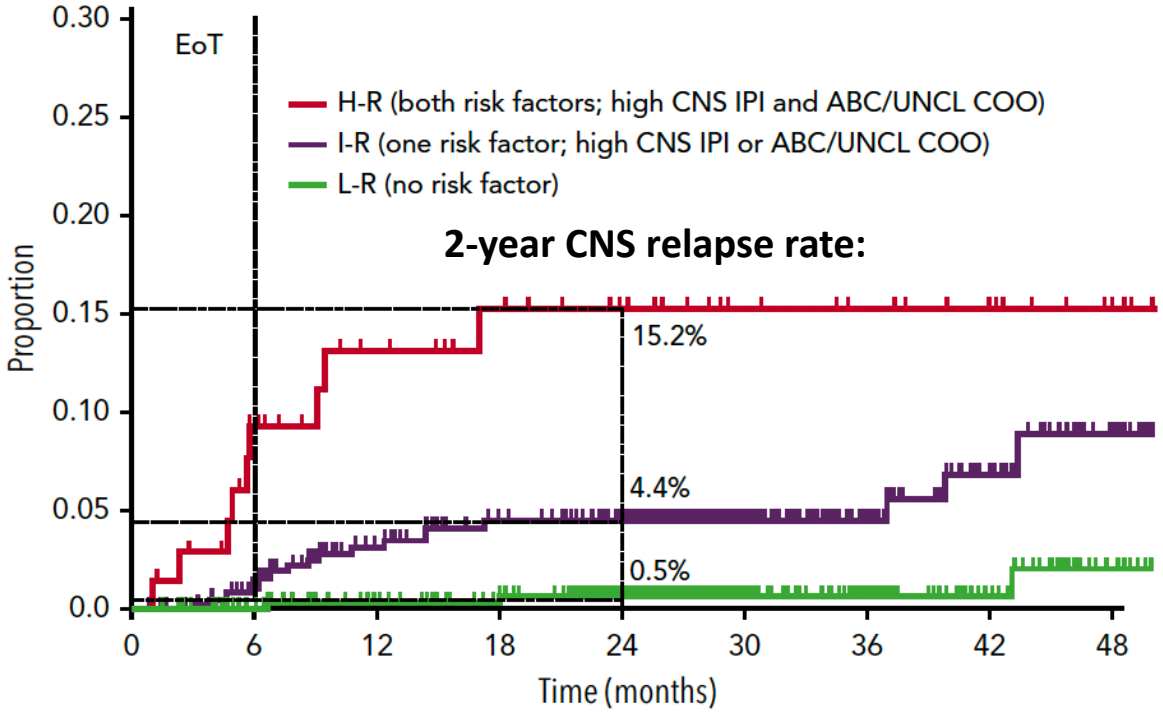
Identification of high-risk patients

ABC-phenotype by GEP: 7-9% CNS relapse

Risk for CNS relapse: COO analysis from the GOYA study



Risk for CNS relapse: CNS-IPI + COO (CNS-IPI-C)



Klanova M et al. ICML 2017

Klanova M et al. Blood 2019

Identification of high-risk patients

Biological risk-factors

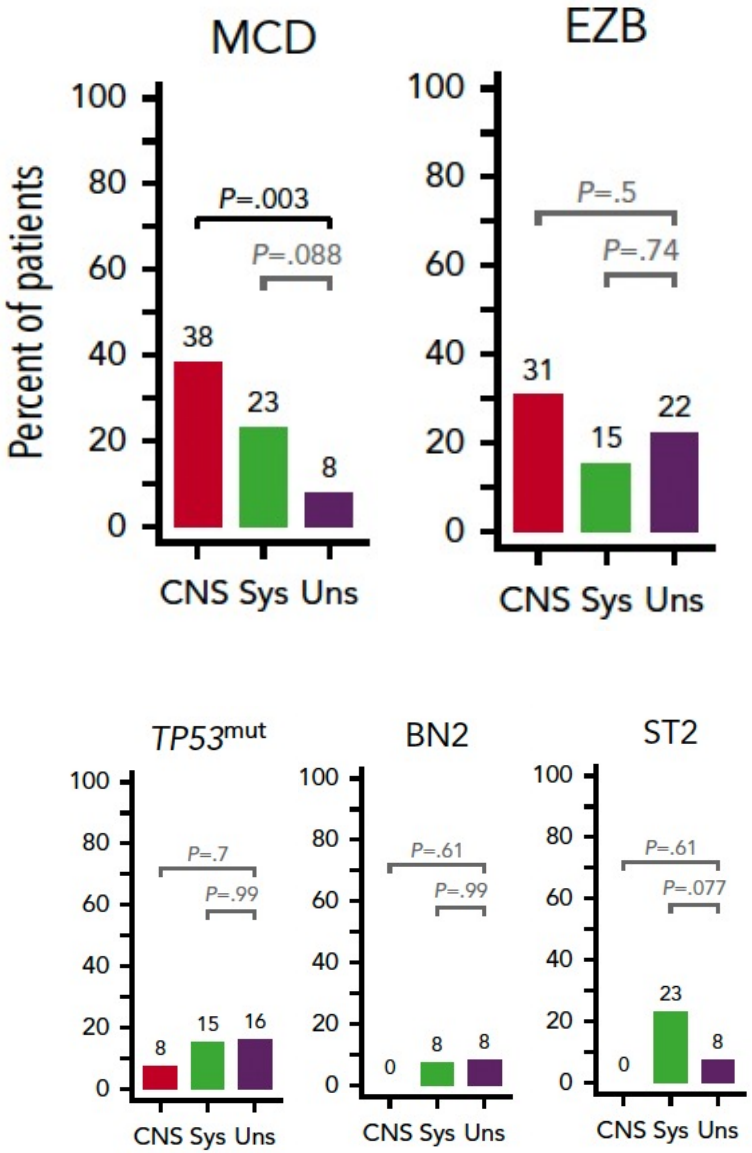
1. Double-hit lymphoma and high-grade lymphoma: CNS recurrence of 5-20%[1]

2. ABC-phenotype by GEP: 7-9% CNS relapse[2]

3. Double expressor not associated to an increased risk of CNS relapse[1,2]

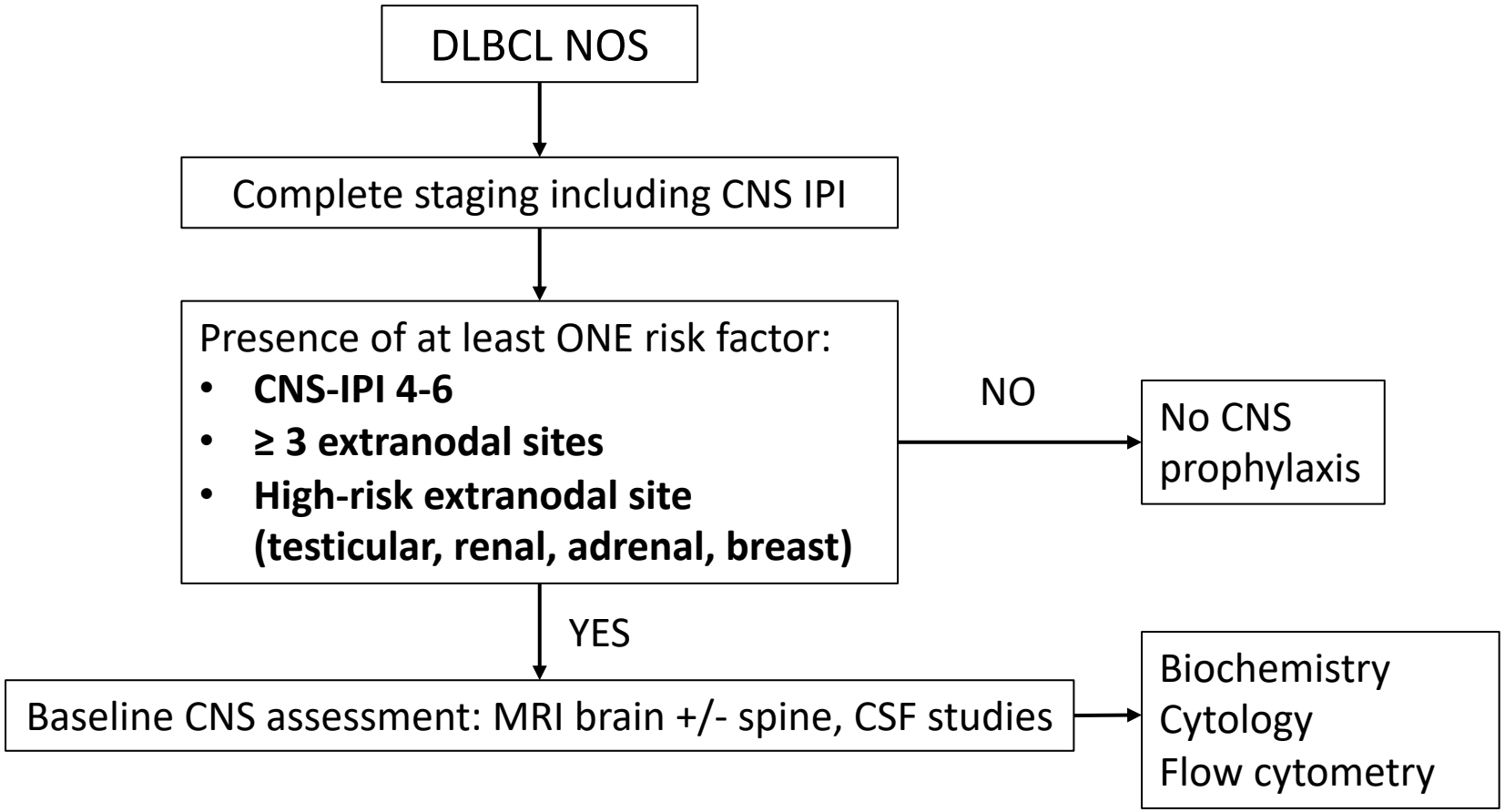
4. CD5 positivity is associated with an increased risk of CNS relapse[3]

5. MCD-subtype DLBCL is associated with increased risk of CNS involvement[4]



1. Savage KJ et al Blood 2016 2.Klanova M et al. ICML 2017. 3. Xu-Monette et al. Oncotarget 2015 4.Ollila TA et al. Blood 2021

Identification of high-risk patients



Adapted from Bobillo S et al Heamtologica 2023

Prophylaxis

IT prophylaxis: MTX +/- Cytarabine + steroids x 4 doses ⟶ no apparent benefit

1

Study (year)	Study design	N	Patients	Treatment	IT MTX prophylaxis	Time to CNS relapse	CNS relapse risk
Boehme V *et al.* (2009)[90]	*Post-hoc* analysis RICOVER-60	1,217	61-80 yr "aggressive"	CHOP *vs.* R-CHOP	57%	8 mth	6.9% *vs.* 4.1% (2 yr) No benefit in the rituximab group
Tai WM *et al.* (2011)[91]	Retrospective	499	≥18 yr (R)-CHOP	18%*	6%* (2 yr)	6.7 mth	No benefit
Villa D *et al.* (2011)[92]	Retrospective	435	>16 yr, III-IV or testicular	(R)-CHOP	4%*	6.7 mth	6.4% (R-CHOP) No benefit
Schmitz N *et al.* (2012)[93]	*Post-hoc* analysis MinT trial and others	2,210	18-60 yr	CHOP *vs.* R-CHOP	NR	7 mth	2.3% (2 yr) No benefit in the rituximab group
Kumar A *et al.* (2012)[94]	Prospective NCCN database	989	≥18 yr	R-CHOP	11% (72% IT)	12.8 mth	2% (2.5 yr) 5.4% with prophylaxis *vs.* 1.4% without prophylaxis No benefit
Gleeson M *et al.* (2017)[95]	*Post-hoc* analysis UK NCRI trials	984	≥18 yr, II-IV or I Bulky	R-CHOP 14 *vs.* R-CHOP 21	18%	8 mth	1.9% (6 yr) No benefit No benefit by CNS-IPI
Klanova M *et al.* (2019)[25]	*Post-hoc* analysis GOYA	1,418	≥18 yr	R-CHOP *vs.* G-CHOP	10%	8.5 mth	2.5% (2 yr) No benefit No benefit by CNS-IPI
Eyre T *et al.* (2019)[35]	Retrospective	690	>70 yr	R-CHOP	14%	9.4 mth	3.1% (3 yr) No benefit

Studies with > 400 pts evaluating the use of IT prophylaxis.

R-CHOP chemothrapy

Retrospective/post-hoc

In DLBCL, recurrences less frequently interest leptomeninges[2]

1.Bobillo et al. Haematologica 2023

2. Ghose et al. Lymph Myel Leuk. 2015

Prophylaxis

IT prophylaxis: a role in primary testicular lymphoma

IELSG10 study[1]:

53 patients

R-CHOP + contralateral testicular irradiation + 4 x IT-MTX

5-years cumulative risk of CNS relapse: 6%.

IELSG37 study[2]:

54 patients

R-CHOP + contralateral testicular irradiation + 4 x IT lyposomal cytarabine + 2xHD-MTX (1.5 g/mq)

No CNS relapses after a median follow-up of 6 years.

1.Vitolo U et al. JCO 2011. 2. Conconi A et al. Blood Advances 2024

Prophylaxis – High-dose Methotrexate

70-80% of DLBCL recurrences affect the parenchyma.
Optimal MTX AUC for primary CNS is obtained with 3 g/mq in 4-6h

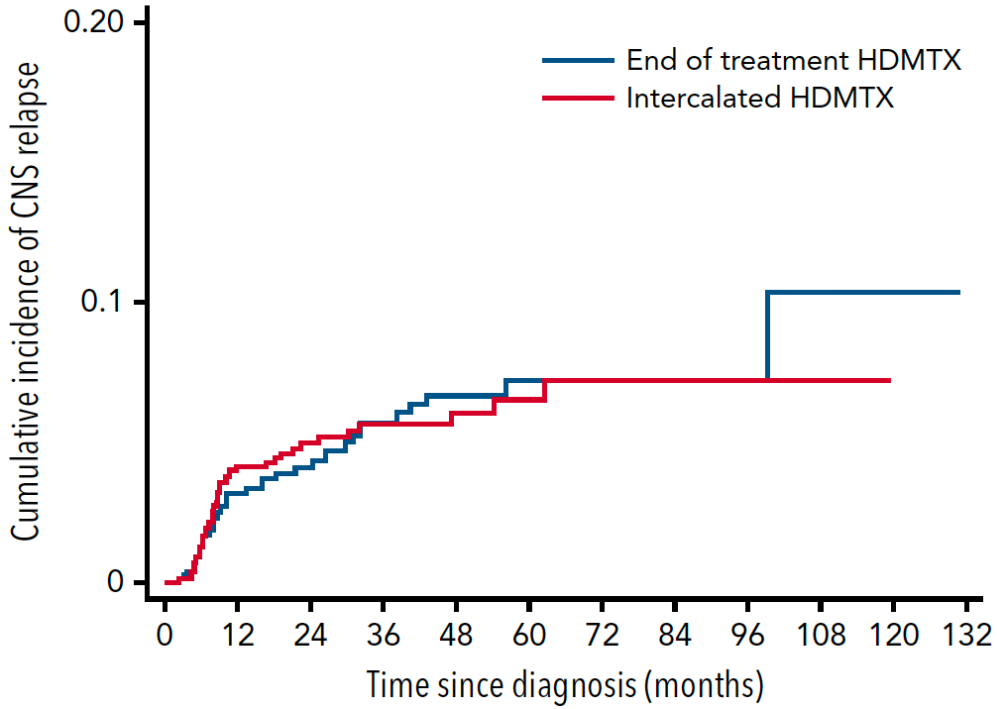
Timing of high-dose CNS prophylaxis in DLBCL: international analysis of 1384 patients

R-CHOP + intercalated-HD-MTX (749) vs EOT-HD-MTX (635)

Rate of CNS relapse: 5.7% vs 5.8%

Concurrent IT prophylaxis not associated with a reduction in CNS relapse

R-CHOP delays of ≥7 days increased with i-HD-MTX (19.6%)



Wilson R et al. Blood 2022

Prophylaxis

Efficacy of intravenous high-dose methotrexate in preventing relapse to the central nervous system in R-CHOP(-like)-treated, high-risk, diffuse large B-cell lymphoma patients and its effect on mortality: a systematic review and meta-analysis

7 Observational studies with 1661 patients.
No randomized-controlled trials identified.

DLBCL patients at high-risk of CNS relapse

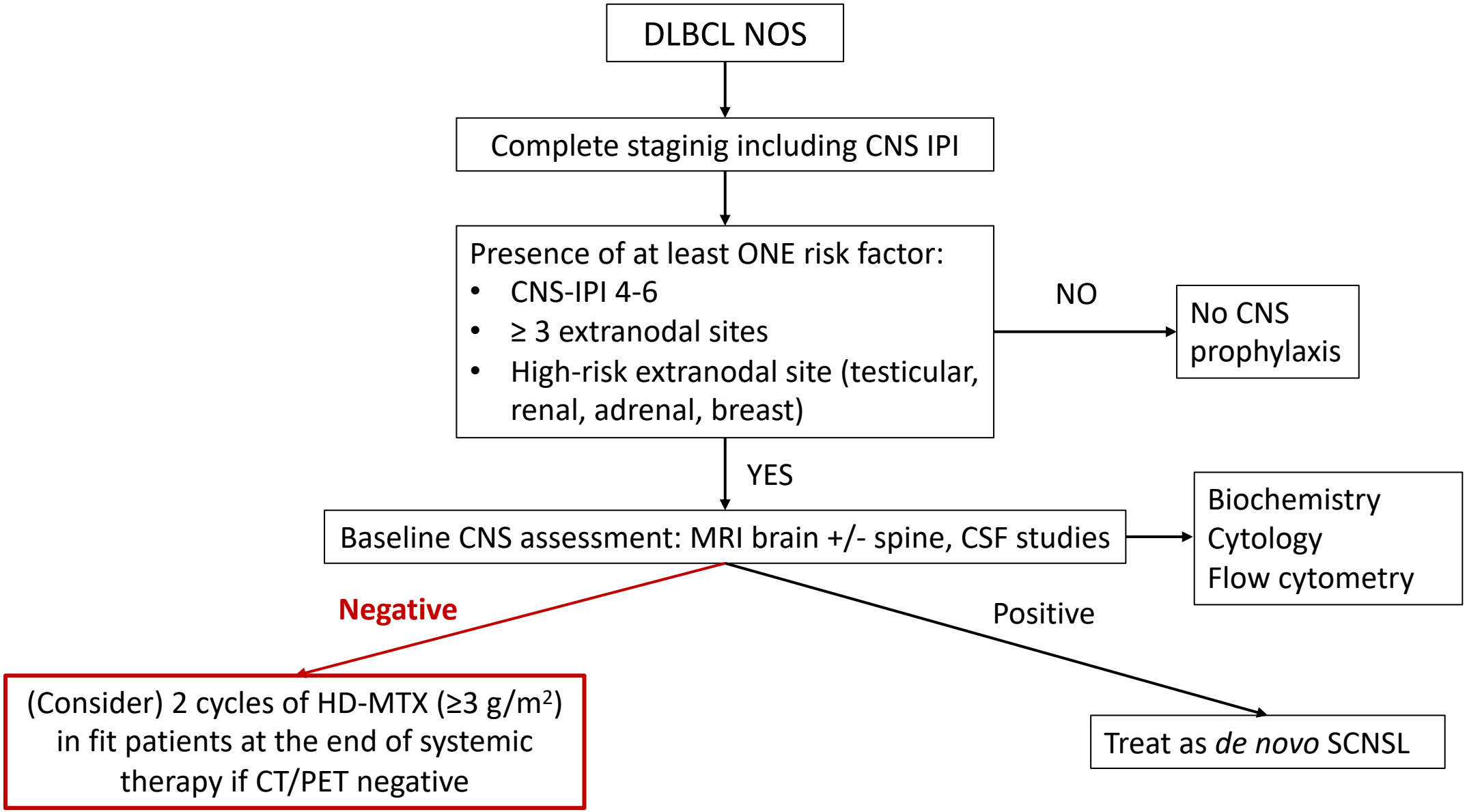
Treated with R-CHOP who receive HD-MTX (452)
Vs patients who received IT prophylaxis alone or none (1209)

- Non-significant relative risk of CNS relapse of 0.54 for patients receiving HD-MTX (8.4% vs 10.3%)
- Non-significant relative risk of death of 0.70 for patients receiving HD-MTX (28.2% vs 39.7%)

«HD-MTX only slightly reduces the risk of CNS-relapse and confers no survival benefit»

Tolley ER et al. Haematologica 2024.

Prophylaxis



Adapted from Bobillo S et al Heamtologica 2023

Incorporating new drugs into first-line treatment

Lenalidomide:

- **R2-CHOP**[1] – Phase II: 5% CNS relapse in high-risk patients
- **REMARC study**[2]**:** Lenalidomide maintenance not associated with lower incidence of CNS relapse
- **Randomized trials (ROBUST, ECOG-ACRIN)**[3,4]**:** not reported**.**

Ibrutinib – PHOENIX[5]

- CNS relapse: 2.4% vs 3.8%

Polatuzumab Vedotin – POLARIX trial[6]

- CNS recurrence: 3% vs 2.7%

1. Ayed AO et al. Blood Cancer J 2018. Bernard S et al. Blood Adv 2021. 3. Nowakowski GS et al. JCO 2021. 4. Nowakowski GS et al. JCO 2021. 5.Younes A et al. JCO 2019. 6.Tilly H et al. NEJM2022

CNS involvement by DLBCL

- Diagnosis
- Prophylaxis
- **Treatment**

Treatment

- Lack of randomized trials
- No international guidelines
- Treatment recommendations based on phase II studies and retrospective series

Bobillo S et al Heamtologica 2023

Treatment: *de novo* SCNSL

MARIETTA trial[1]:
3xMATRIX + 3xR-ICE + Carmustine-Thiotepa ASCT in FIT patients age 18-70 years.
32 patients
- ORR 75% - CR 55%
- 2-yrs PFS: 71%

SCNSL 1 study[2]:
HD-MTX + ARA-C followed by R-HDS + Carmustine-Thiotepa ASCT in FIT patients age 18-70 years.
14 patients with treatment-naive DLBCL
- CR 71%
- 2-yrs EFS: 48%

R-CODOX-M/R-IVAC[3]:
10 with treatment-naive SCNSL
- 2-yrs PFS: 70%

1.Ferreri AJM et al. Lancet Hematol 2021; 2.Ferreri et al. JCO 2015. 3.McMillan AK et al. Ann Oncol 2020

Treatment: *relapsed* SCNSL

Isolated.

MARIETTA[1]: considering MATRIX alone (ORR 67% after 2 cycles of MATRIX)

HD-MTX/ARA-C/Rituximab (for patients > 70 yrs)

Concomitant.

MARIETTA[1]: ORR 46%; 2-yrs PFS 14%; better outcomes for those who undergo ASCT.

Unfit/Elderly.

- HD-MTX + Rituximab
- HD-MTX+Rituximab+Temozolomide
- Rituximab+Temozolomide+WBRT.

1.Ferreri AJM et al. Lancet Hematol 2021

Ibrutinib monoterapy R/R PCNSL

Prospective, multicenter phase II study
R/R PCNSL or primary vitreoretinal lymphoma (PVRL)

Treatment: ibrutinib 560 mg/day
44 patients, median age 70 yrs; 30 PCNSL, 14 PVRL

Response:
- ORR at 2 months: 62%
- CR 19%

Reasons for Ibrutinib discontinuation:
- PD: 31 pts
- Non-PD: 11 pts
  - Toxicity (6)
  - Medical decision (5)

Median FUP: 66 months
10 pts alive, 5 in CR

All patients:
- Median OS: 20 months (7-29)
- Median PFS: 4.8 months (3-13)

Better outcome for patients with PVRL:
- Median OS: 69 months
- Median PFS: 24 months

Soussain C et al. Eur J Cancer, 2019; Soussain C et al. Eur J Cancer, 2023

Lenalidomide + Rituximab R/R PCNSL

Prospective, multicenter phase II study
R/R PCNSL or primary vitreoretinal lymphoma (PVRL)

Treatment:
Induction (8 cycles):
- Lenalidomide 20 mg/day C1, then 25 mg/day, days 1-21 every 28
- Rituximab 375 mg/mq D1

Maintenance:
- Lenalidomide 10 mg/day days 1-21 for max 12 cycles

45 patients, median age 69 yrs (46-86); 11 PVRL

ORR at the end of induction: 32%

Best response: ORR 65%, 35% CRs

Treatment interruption during induction:
- PD n=23/45 (51%)
- Toxicity n=2
- Other reasons n=2

5 patients completed the maintenance phase, 4 being in CR.

Median FUP: 19.2 months
Median OS: 17.7 months
Median PFS: 7.8 months (9.2 months for responders)

Ghesquieres H et al. Ann Oncol. 2019

Treatment

Toxicity and efficacy of CAR T-cell therapy in primary and secondary CNS lymphoma: a meta-analysis of 128 patients

15 studies: 8 prospective and 7 retrospective

	PCNSL n=30	SCNSL n=98
Median age	56yrs (44.5-67)	50yrs (38-58)
CAR: • Axi-cel (CD28) • Tisa-cel (4-1BB) • Other	 2 (6.7) 19 (63.3) 9 (30)	 50 (51) 12 (12) 36 (37)
Bridging therapy • Yes • No • NR	 24 (80) 2 (7) 4 (13)	 30 (30.6) 7 (7) 61 (62.4)

	PCNSL n=30	SCNSL n=98
ICANS • All grade • Grade 3-4	 53% 18%	 48% 26%
CRS • All grade • Grade 3-4	 70% 13%	 72% 11%
CR ORR	56% 64%	47% 57%
CR at 6 months	37%	37%
Median DOR months	8.9 (5.8-9.3)	4.6 (2.8-16)

CD28 costimulatory: higher CRs; higher rates of ICANS and CRS

Heterogeneity in bridging therapy

No major differences in toxicity incidence and severity when compared to systemic DLBCL

1.Cook MR et al. Blood Advances 2023

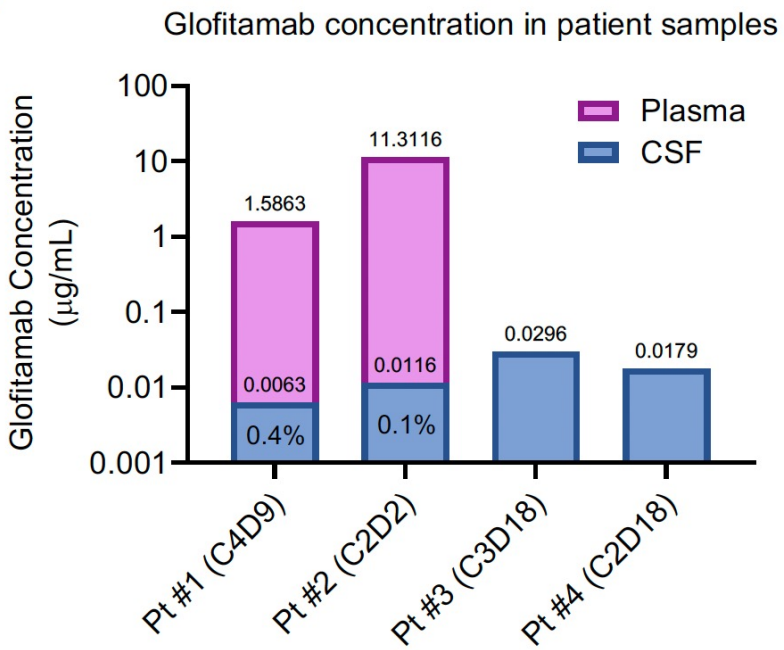
Treatment

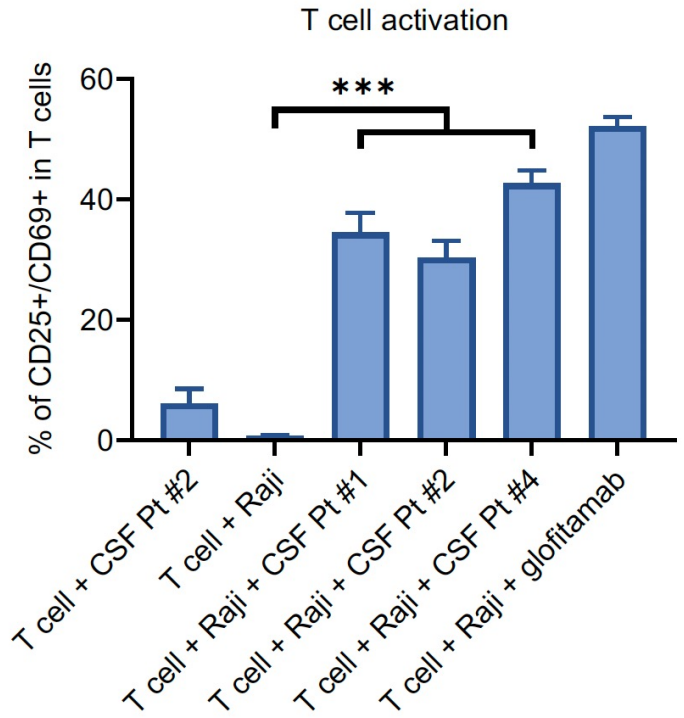
Glofitamab stimulates immune cell infiltration of CNS tumors and induces clinical responses in secondary CNS lymphoma

blood

4 patients with CD20+DLBCL with secondary CNS involvement treated with Glofitamab

On-treatment CSF samples analyzed by ELISA-assay; Glofitamab detected in all 4 samples, at a sufficient concentration to induce T-cell activation.
Increased number of CSF leukocytes after the first glofitamab dose





Godfrey JK et al. Blood 2024

Treatment

Tafasitamab

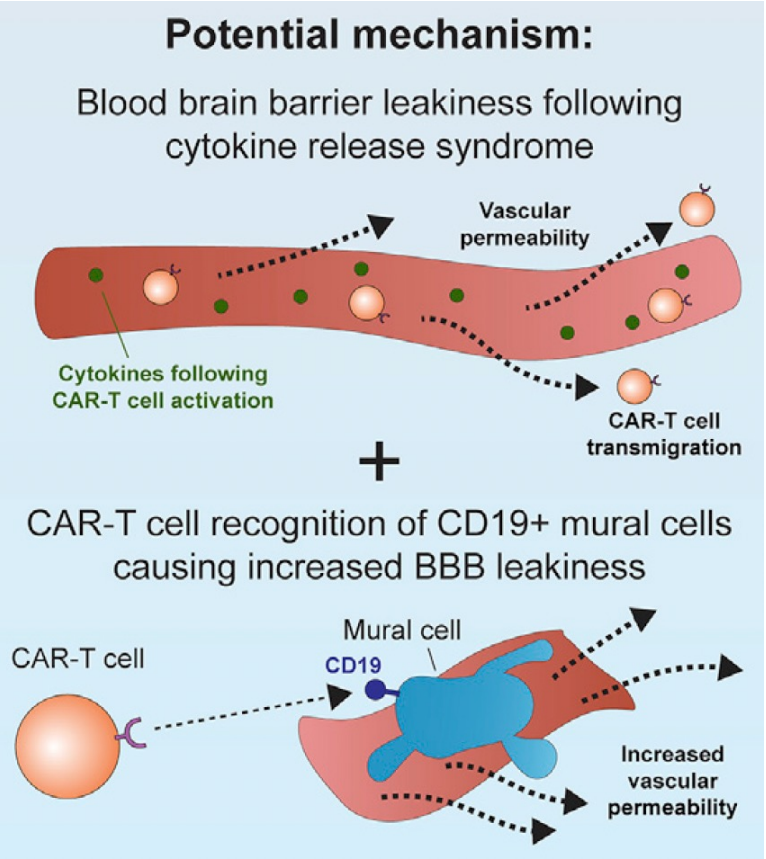
CD19 is expressed in human brain mural cells (critical for BBB integrity). This cell population may contribute to the neurotoxicity of CD-19 directed CAR-T[1]

Tafasitamab can modulate BBB integrity by perturbation of CD19, without CRS

[2]Two patients, 1 relapsed SCNSL and 1 relapsed PCNSL

Treated with Tafa-Lena (both patients relapsed during Lena).

No neurotoxicity
1 CR and 1 PR



Phase I/II trial: NCT05351593 → **Tafasitamab Plus Lenalidomide in Relapsed CNS Lymphoma**

1. Parker KT et al. Cell. 2020; 2.Rauschecker AM et al. BJH 2023

Treatment

R-CHOP preceded by blood-brain barrier permeabilization with engineered tumor necrosis factor-α in primary CNS lymphoma

TNFalfa coupled with NGR, a peptide targeting CD13+ vessels induces endothelial permeabilization → break BBB →improves penetration and activity of R-CHOP in R/R PCNSL.

12 pts
Treatment: 1xR-CHOP + 5xR-CHOP preceded by NGR-hTNF iv.

All brain biopsies CD13+
BBB permeability increased after NGR-hTNF infusion, especially in the perilesional areas.

8CRs and 1 PR

Ferreri AJM et al. Blood 2019

Treatment

Article

Blood–Brain Barrier Disruption (BBBD)-Based Immunochemotherapy for Primary Central Nervous System Lymphoma (PCNSL), Early Results of a Phase II Study

BBB disruption through intra-arterial infusion of hypertonic mannitol (25%)

Prospective phase II study, newly diagnosed PCNSL 18-70 years old

Treatment:

- One cycle MATRix
- BBBD treatment every 3 weeks for up to 6 cycles
- ASCT consolidation

Chemotherapy Agent	Dose	Route	Day of Cycle
Rituximab	375 mg/m^2	intravenous	0
Methotrexate	2500 mg/m^2	intra-arterial	1–2
Carboplatin	200 mg/m^2	intra-arterial	1–2
Dexamethasone	6 mg × 4–6	peroral	2–10
Cytarabine	40 mg	intrathecal	14
Cyclophosphamide	330 mg/m^2	intravenous	1–2
Etoposide	200 mg/m^2	intravenous	1–2

[a] BBBD = blood–brain barrier disruption.

25 patients.

- Before ASCT: CR 88%, PR 8%
- 2-years PFS: 70%.

Adverse events of interest:

- Occult focal ischemic lesions caused by catheterization in 5 patients (20%)
- Thromboembolic events in 24%

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