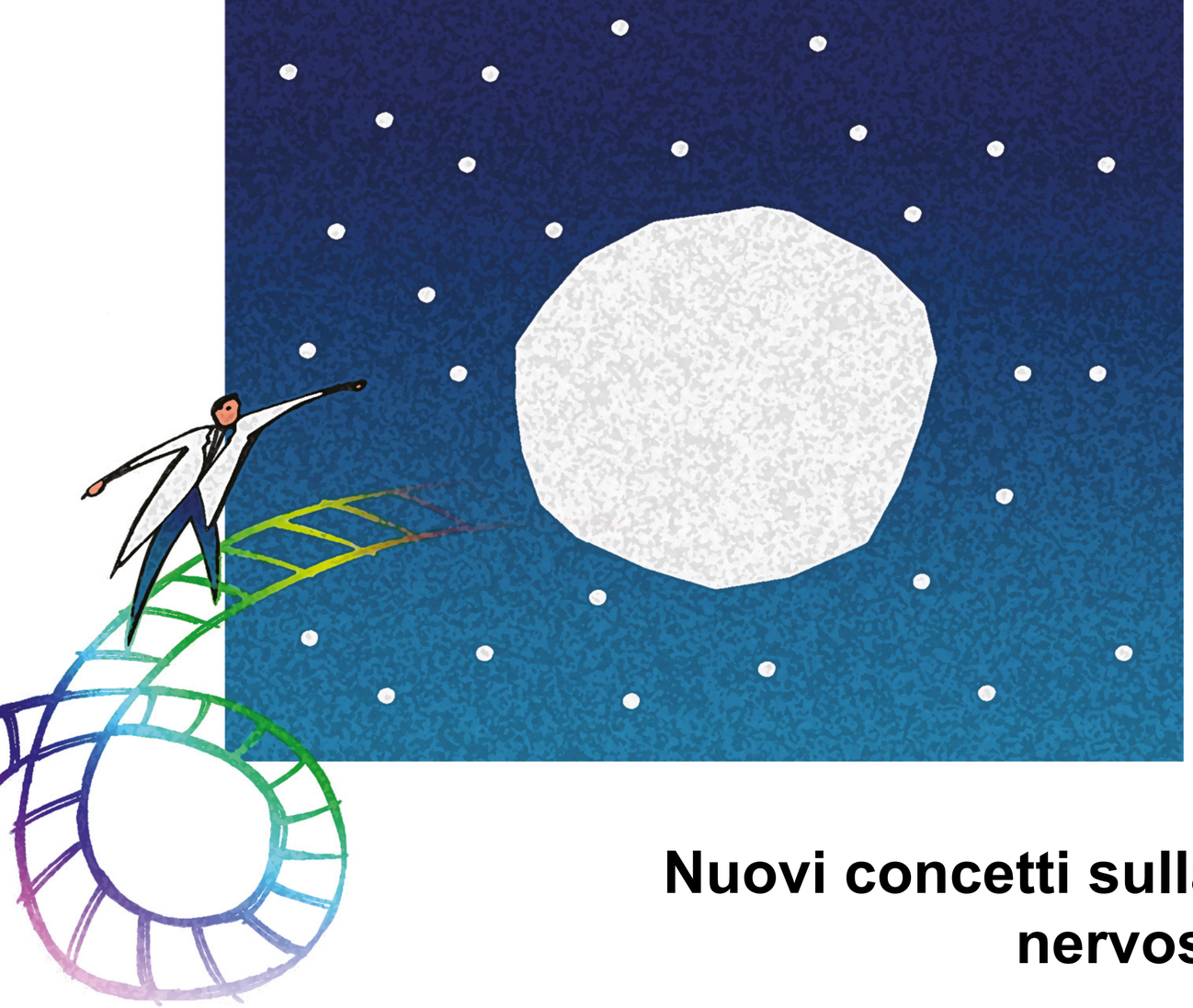

The young side of
LYMPHOMA

gli under 40 a confronto

Milano, 14-15 aprile 2023

Nuovi concetti sulla profilassi del sistema nervoso centrale

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Ematologia
ASST Spedali Civili di Brescia

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Disclosures of Chiara Pagani

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sandoz			x				

BACKGROUND

- CNS relapses of DLBCL: relatively rare but often devastating
  estimates incidence: about 5% of DLBCL

- Most occur during or closely following frontline immunochemotherapy (median time 6-8 months)

- Secondary CNS lymphomas have poor outcomes

Wilson MR et al. Hematology Am Soc Hematol Educ Program. 2022

- Identify patients at highest risk of CNS relapse
  - Clinical risk factor
  - Biological risk factor

- How to manage patients at high risk of CNS dissemination

- Treatment of patients with CNS involvement

- Future perspectives
  - Improve baseline screening
  - Novel therapies

CASE REPORT 1

February 2018

HISTORY-PRESENTATION

34-year-old pregnant women (29 week), no comorbidities ECOG 0

Physical examination: unilateral breast mass in progressive growth, no B symptoms
Laboratory test: normal LDH

HISTOLOGY

Breast biopsy: Diffuse large B cell Lymphoma
IHC: Ki67 80%, Myc>40%, Bcl2 80%, Bcl6+, CD10+, MUM1+
FISH: *BCL6* rearranged, *MYC* and *BCL2* negative
Bone marrow biopsy: pathological lymphocyte infiltrate (7%)

IMAGING

Whole body MRI: breast mass, liver node, increased nodes above diaphragm, focal vertebral lesion (C2)

DLBCL "double expressor" non GCB (Hans algorithm)
Stage IVA (breast, bone marrow, bone, liver)
IPI: 2/5
CNS IPI: 2/6

March 2018

1° course R-CHOP 20 March spontaneous delivery

CASE REPORT 1

Does this patient have risk factors for CNS recurrence?

IDENTIFY PATIENTS AT HIGHEST RISK OF CNS RELAPSE

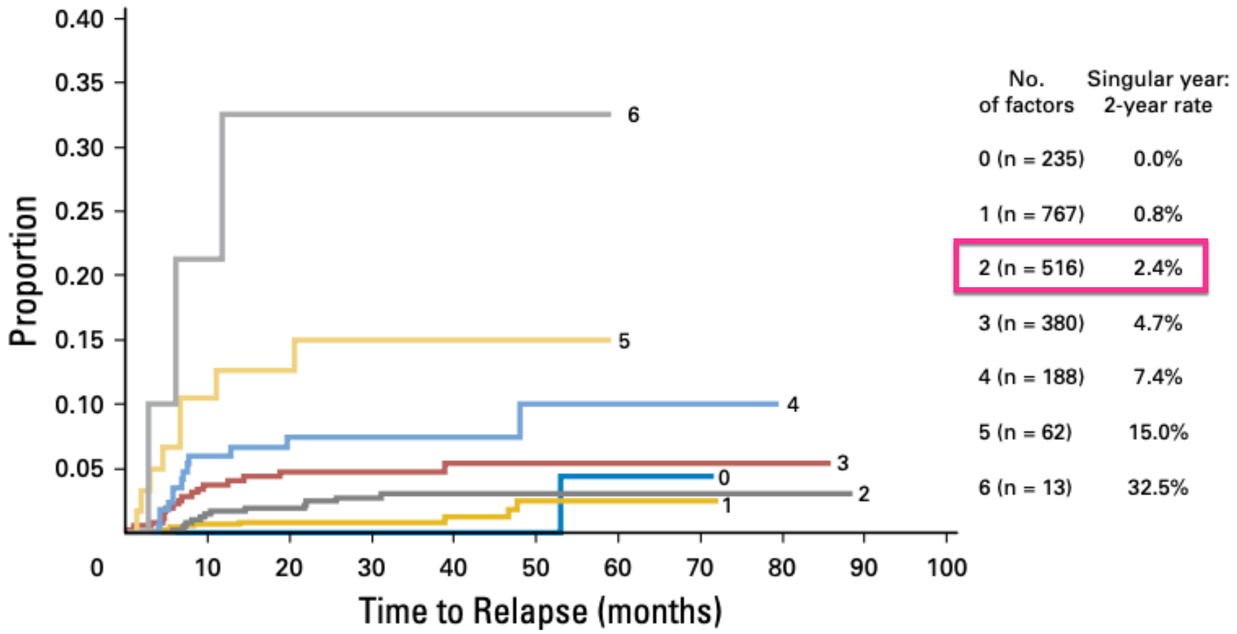
Guideline	Patient selection	Method for CNS prophylaxis suggested
British Society for Haematology (2021)[8]	*Offer to:* • High (4–6) CNS-IPI • ≥3 EN sites • High-risk EN site involvement—testicular, renal/adrenal, intravascular *Consider in:* • Breast involvement • Uterine involvement	• HD-MTX (≥3g/m^2 for 2-3 cycles) as early as possible as part of first-line therapy without compromising dose and time intensity of R-CHOP-like treatment • IT prophylaxis not recommended if HD-MTX successfully delivered • Consider IT as well as systemic prophylaxis in testicular DLBCL
NCCN (2022)[48]	*Consider in:* • High (4–6) CNS-IPI • Double/triple-hit HGBL • High-risk EN site involvement—testicular, breast, primary cutaneous, renal/adrenal	• HD-MTX (3-3.5g/m^2 for 2-4 cycles) during or after the course of treatment and/or • IT methotrexate and/or cytarabine (4-8 doses) during or after the course of treatment
ESMO (2018)[49]	*Consider in:* • High IPI • High-risk EN site involvement—testicular, renal/adrenal, breast, bone marrow, bone	• HD-MTX is "an option . . . even though the level of supporting evidence is low" • "Little or no role" for IT therapy

ESMO, European Society for Medical Oncology; HGBL, high-grade B-cell lymphoma; NCCN, National Comprehensive Cancer Network.

Wilson et al. Hematology Am Soc Hematol Educ Program. 2022
McKay et al. BJH 2020
NCCP B-Cell Lymphoma Version 3 2022
Tilly el al. Ann Oncol 2015

CLINICAL FACTORS

CNS International Prognostic Index (CNS-IPI)

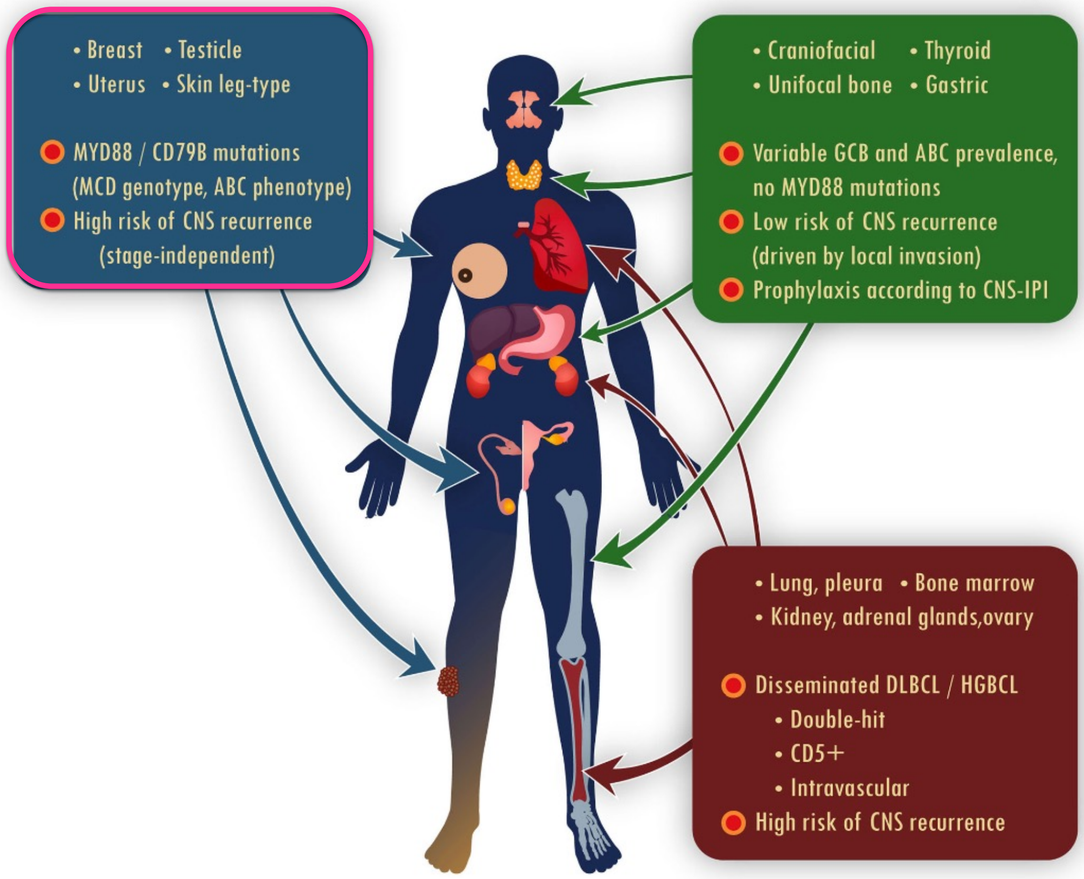


No. of factors	Singular year: 2-year rate
0 (n = 235)	0.0%
1 (n = 767)	0.8%
2 (n = 516)	2.4%
3 (n = 380)	4.7%
4 (n = 188)	7.4%
5 (n = 62)	15.0%
6 (n = 13)	32.5%

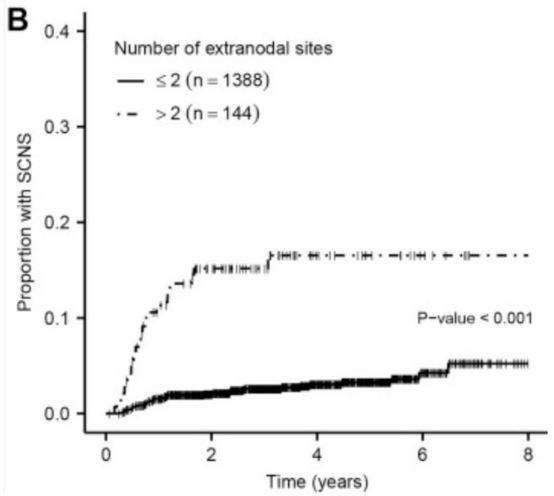
CNS IPI score (1 post per risk factor)
Age>60 years
LDH> upper limit normal
ECOG Performance status>1
Stage III/IV disease
Extranodal involvement ≥ 2 sites
Kidney and/or adrenal involvement

Schmitz N et al. J Clin Oncol. 2016
Eyre TA et al. Lancet Oncol 2022

CLINICAL FACTORS



Anatomical site	Number of assessed patients (ref)	Cumulative risk of CNS relapse	Treatment (Induction + Prophylaxis)
Renal/adrenal gland	55 (DLBCL) (23)	35%	R-CHOP (46%)/CHOP-like (54%); IT (14%)
Testis	371 (DLBCL) (24)	34%	Anthracyclines-based chemo; IT (18% of pts)
	73 (DLBCL) (26)	25%	R-CHOP + variable prophylaxis (6 HD-MTX; 2 HD-MTX + IT)
Breast	204 (DLBCL) (25)	5%	Anthracycline-based chemo + IFRT; IT (4%)
	84 (51 high grade) (27)	14%	Variable Treatment w/o prophylaxis
	75 (DLBCL) (28)	20%	Chemo with Rtx (in 69%) + IT (in 8%)
Paranasal sinus	44 (37 DLBCL) (17)	11%	Anthracycline-based chemo; IT (89%)
	40 (DLBCL) (29)	1.5%	R-CHOP + IT proph (in 30% of pt)
Orbit	143 (not specified) (30)	5%	Not specified
Spine/epidural soft tissue	48 (28 Intermediate; 12 High Grade) (31)	8%	Anthracycline-based chemo; IT (19% of pts; none of those who relapsed)



3-year cumulative incidence of SCNS

extranodal sites >2: 15.2%

≤2: 2.6%

Ollila T et al, Curr Treat Options in Oncol 2018
Calimeri T et al, Ann Lymphoma 2019
El-Galaly T et al, Eur J Cancer 2017

BIOLOGICAL FACTORS

MYC and *BCL2* translocations-overexpression

- "Double-triple hit lymphomas": historically associated with high CNS risk (5-20%)
  - early stage: low rate of CNS events
  - selection bias and non uniform application of *FISH*
  - risk may be rated to high risk clinical features

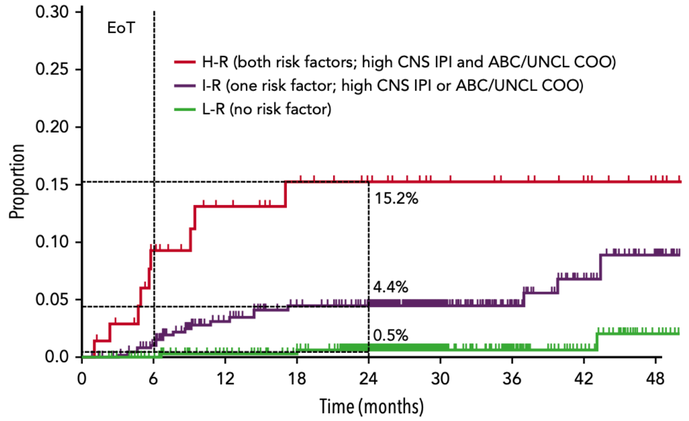
- "Double expressor" lymphomas: most ABC

Cell of Origin (COO)

- Activated B-cell phenotype (determined by GEP): independent risk factor for CNS relapse—> CNS Relapse risk: 7-9%

- GOYA *post-hoc* analysis: ABC (GEP)+CNS IPI

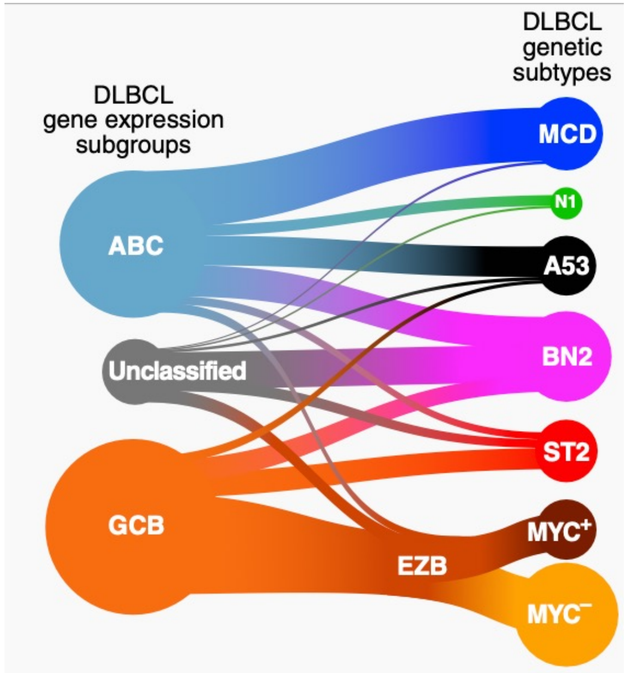
CNS relapse risk 15%
(8% of study population)



Savage KJ et al. Blood 2016
Torka P et al. Blood Adv 2022
Klanova M et al. Blood 2019

BIOLOGICAL FACTORS

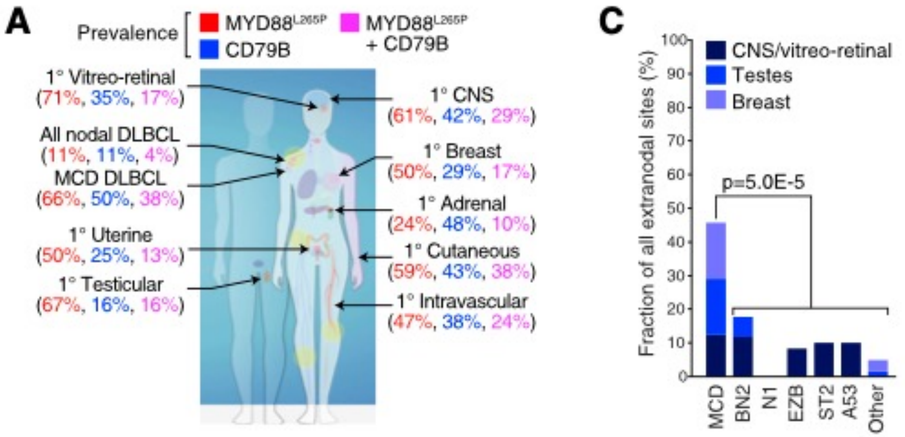
New taxonomy of DLBCL



Multiplatform analyses encompassing point mutations, structural variants and copy-number alterations identify new molecular subgroup:

MCD and C5 clusters

- almost exclusively ABC subtypes
- high frequency of *MYD88*, *CD79*, *PIM1*, and *ETV6* mutations
- genetic features overlap with those observed in primary extranodal lymphomas of immune-privileged sites (e.g. CNS, testes, breast, vitreo-retina)
- elevated CNS risk (38% vs 8%)
- present in almost 50% of CNS relapses



Schmitz R et al. NEJM 2018
Chapuy B et al. Nat Medicine 2018
Wright GW et al. Cancer Cell 2020
Ollila T et al. Blood 2021

CASE REPORT 1

Does this patient have risk factors for CNS recurrence?

*9,7%

*7-9%

DLBCL "double expressor" non GCB (Hans algorithm)
Stage IVA (breast, bone marrow, bone, liver)
IPI: 2/5
CNS IPI: 2/6

*15-20%

*2,4%

>2 extranodal sites: 15%*

* Cumulative risk of CNS relapse

HOW TO MANAGE PATIENTS AT HIGH RISK OF CNS DISSEMINATION

Optimize baseline screening

- Watch out for symptoms

Table 4 Most common neurological symptoms at CNS dissemination in DLBCL

Symptoms	Incidence
Cranial nerve palsy	30%
Intracranial hypertension (nausea, vomiting)	4–10%
Mental status changes	20–30%
Gait/balance disturbance	10%
Peripheral sensory/motor symptoms	25%
Headaches	20–50%
Visual symptoms (uveitis, floaters or campimeter deficits)	5–10%
Seizures, brain stem or cerebellum symptoms	5%
Focal CNS deficits	50%
No symptoms	<5%

- Consider baseline CNS assessment (CSF study, MRI brain +/- spine)

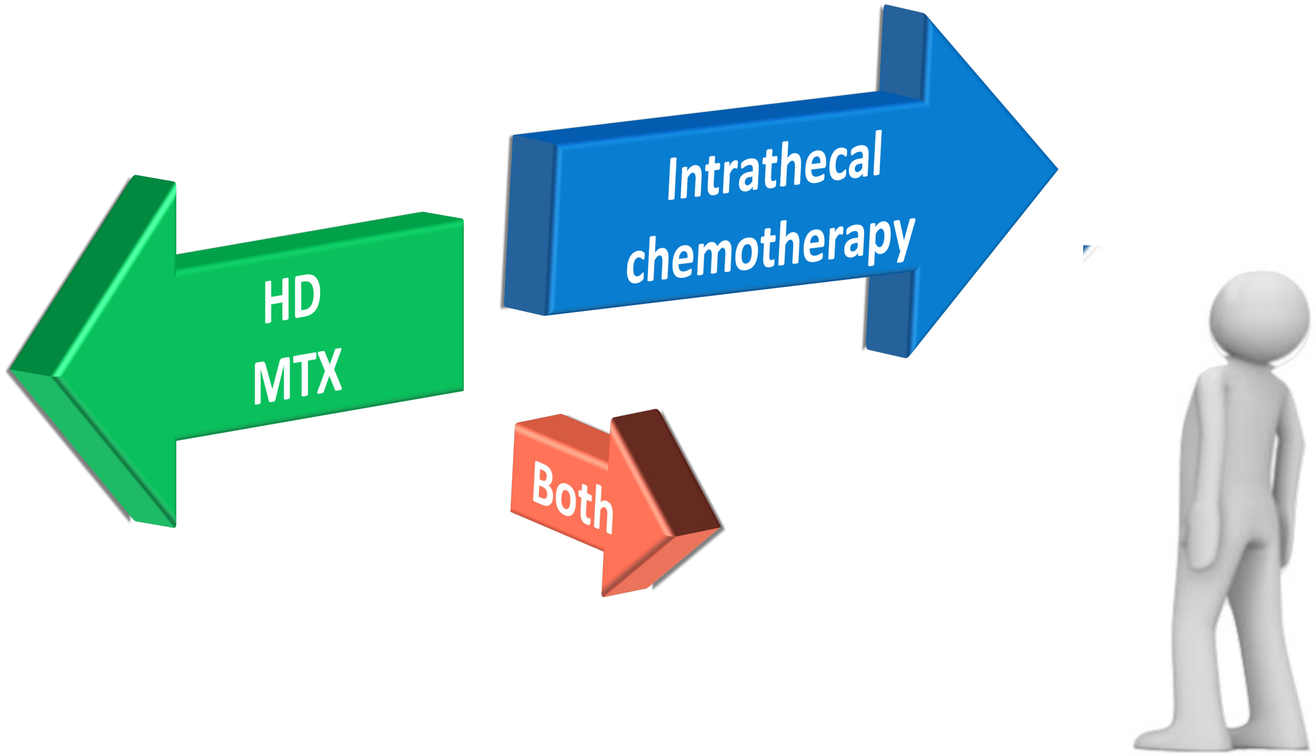
CSF studies

- Cytology (high specific, limited sensitivity)
- Flow citometry
- Increased soluble CD19 protein
- ctDNA
- *MYD88* and *ASXL2* mutations

Bobillo S et al. Haematologica 2023
Calimeri T et al, Ann Lymphoma 2019

HOW TO MANAGE PATIENTS AT HIGH RISK OF CNS DISSEMINATION

Strategies for prophylaxis of CNS



INTRATHECAL CHEMOTHERAPY (IT)

- Large systematic review (>7000 patients):
  - Most of CNS relapses are parenchymal
  - NO benefit of stand-alone IT prophylaxis

- exception: testicular DLBCL
  IELSG-10 and IELSG-30 study

↓

No CNS relapses with 6RCHOP-2HD-MTX-IT liposomal cytarabine and contralateral RTT (54 pts)

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

Bobillo S et al. Haematologica 2023
Eyre T et al. Haematologica 2020

HIGH-DOSE METHOTREXATE (HD-MTX)

HD-MTX (≥3g/m^2)

- several large retrospective studies have failed to demonstrate a reduction in CNS relapse or superiority over IT

- No consensus on the optimal dose or timing of HD-MTX

Intercalated vs end of treatment HD-MTX (i-MTX vs EOT-MTX):

- increased toxicity and risk of RCHOP delay (19,3%) with i-MTX
- No differences in CNS relapses (3y CNS relapse 9,1%)

Wilson et al. Blood 2022

Study (year)	n	Design	Risk factors	Systemic treatment	CNS Prophylaxis	CNS relapse	Comments
Lewis et al[32] (2022)	2300	Multicenter, retrospective	CNS-IPI ≥4 Testicular, breast involvement DHL	R-CHOP (94%) R-EPOCH (6%)	1. HD-MTX (18%) 2. No HD-MTX (82%)	1. 9.2% (5y) 2. 8.1% (5y)	No benefit HD-MTX
Wilson et al[33] (2022)	1384	Multicenter, retrospective	High-risk EN sites CNS-IPI ≥4 ≥2 EN and LDH ↑	R-CHOP	1. HD-MTX (all, intercalated, or EOT)	1. 5.7% (3y) 2. 5.8% (3y)	No difference between EOT and intercalated HD-MTX
Orellana-Noia et al[34] (2022)	1030	Multicenter, retrospective	Not described	R-CHOP (48%) R-EPOCH (45%) Other (7%)	1. HD-MTX (20%) 2. IT (77%)	1. 6.8% 2. 5.4%	No benefit HD-MTX vs IT
Puckrin et al[35] (2021)	326	Multicenter, retrospective	CNS-IPI ≥4 Testicular DHL LDH ↑ + ECOG >1 + >1 EN	R-CHOP (85%) Intensive chemo-therapy (15%)	1. HD-MTX (35%) 2. No HD-MTX (65%)	1. 12.2% 2. 11.2%	No benefit HD-MTX
Bobillo et al[36] (2021)	585	Single-center, retrospective	CNS-IPI ≥4 High-risk EN sites DHL	R-CHOP (68%) R-EPOCH (15%) Other (17%)	1. HD-MTX (7%) 2. IT MTX (43%) 3. None (50%)	1. 7.5% (5y) 2. 5.5% (3y) 3. 5%	No benefit (IT or HD-MTX)
Ong et al[37] (2021)	226	Multicenter, retrospective	High-risk EN sites CNS-IPI ≥4	R-CHOP	1. HD-MTX (29%) 2. No HD-MTX (71%)	1. 3.1% (3y, isolated) 2. 14.6% (3y, isolated)	HD-MTX signifi-cantly reduced risk of isolated CNS relapse
Wilson et al[38] (2020)	334	Multicenter, retrospective	CNS-IPI ≥4 High-risk EN sites ≥2 EN sites and LDH ↑	R-CHOP	1. HD-MTX (all, intercalated, or EOT)	1. 6.8% (3y) 2. 4.7% (3y)	No difference between EOT and intercalated HD-MTX
Lee et al[39] (2019)	130	Single-center, retrospective	CNS-IPI ≥4 High-risk EN sites ≥2 EN and LDH ↑	R-CHOP	1. HD-MTX (49%) 2. None (51%)	1. 6.9% (2y) 2. 8.1% (2y)	No benefit HD-MTX
Goldschmidt et al[40] (2019)	480	Multicenter, retrospective	High-risk EN sites Stage IV, LDH ↑, ≥1 EN	CHOP +/−R (80%)	1. HD-MTX (27%) 2. None (73%)	1. 6.9% 2. 6.3%	No benefit HD-MTX

Wilson et al. Hematology Am Soc Hematol Educ Program. 2022
Bobillo S et al. Haematologica 2023

CASE REPORT 1

34-year-old women

DLBCL "double expressor" non GCB (Hans algorithm)
Stage IVA (breast, bone marrow, bone, liver)
IPI: 2/5
CNS IPI: 2/6

What therapy would you suggest to this patient?
Would you recommend CNS prophylaxis?

1. R-CHOP without CNS prophylaxis
2. R-CHOP with CNS prophylaxis
3. Intensified chemotherapy with CNS prophylaxis

CASE REPORT 1

34-year-old women

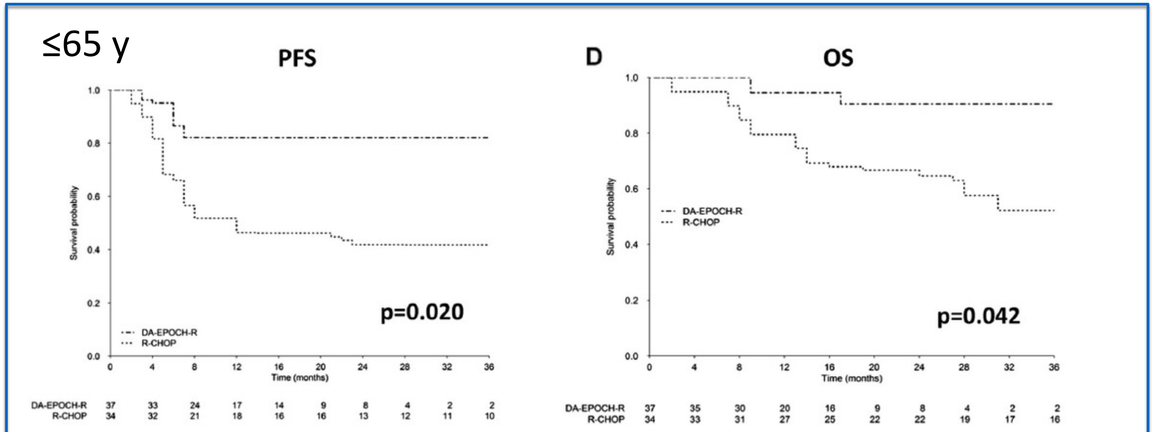
DLBCL "double expressor" non GCB (Hans algorithm)
Stage IVA (breast, bone marrow, bone, liver)
IPI: 2/5
CNS IPI: 2/6

TREATMENT

R-DAEPOCH + IT MTX Prophylaxis

Dose-adjusted EPOCH plus rituximab improves the clinical outcome of young patients affected by double expressor diffuse large B-cell lymphoma

A. Dodero[1] · A. Guidetti[1,2] · A. Tucci[3] · F. Barretta[4] · M. Novo[5] · L. Devizzi[1] · A. Re[3] · A. Passi[3] · A. Pellegrinelli[6] · G. Pruneri[2,6] · R. Miceli[4] · A. Testi[6] · M. Pennisi[1] · M. C. Di Chio[1] · P. Matteucci[1] · C. Carniti[1] · F. Facchetti[7] · G. Rossi[3] · P. Corradini[1,2]



Dodero et al Leukemia 2019

CASE REPORT 1

TREATMENT

April 2018

1° RDAEPOCH level 0 + 1° IT MTX
2° RDAEPOCH level 0 + 2° IT MTX
3° RDAEPOCH level 1 + 3° IT MTX

4° RDAEPOCH level 2 + 4° IT MTX
5° RDAEPOCH level 1 + 5° IT MTX
6° IT MTX

Restaging
PET: negative
Whole body MRI: complete remission

August 2018

Restaging (PET, TC, BM biopsy): COMPLETE METABOLIC RESPONSE

April 2019

Back pain, paresthesias —> *Whole spine and brain MRI*: bone lesions (D2, D4, L4, L5, ribs), radiculitis of the cauda and lumbar nerve roots

-> CFS exam: T reactive lymphocytes
-> bone biopsy: Diffuse large B cell Lymphoma
WB PET-TC: diffuse bone lesions and pathological tissue from right iliac region to medullary canal, solid intramedullary tissue between D12 and L5

CNS and systemic RELAPSE of DLBCL

CASE REPORT 1

3 MATRix-3 RICE-ASCT (“MARIETTA”)

May 2019

1° MATRix + IT MTX arac
2° MATRix + IT MTX arac

Whole spine and brain MRI- WB TC: PR

3° MATRix + IT MTX arac

Leukapheresis

1° RICE + IT MTX arac
2° RICE + IT MTX arac

Evaluation for CAR-T therapy:
Not elegible

BONE PROGRESSION

2RMEGA CHOP —> responsive

ASCT—> ALLOGENEIC sibling SCT

SPLENIC-EPATIC PROGRESSION

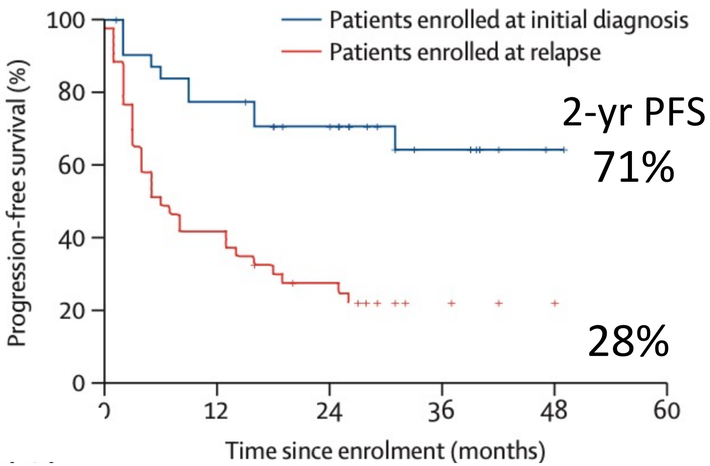
August 2020

DEATH FOR LYMPHOMA PROGRESSION

TREATMENT OF PATIENTS WITH CNS INVOLVEMENT

Prospective Study: MARIETTA n=75 -> HSCT=37

Ferreri AJM et al. Lancet Haematol 2021

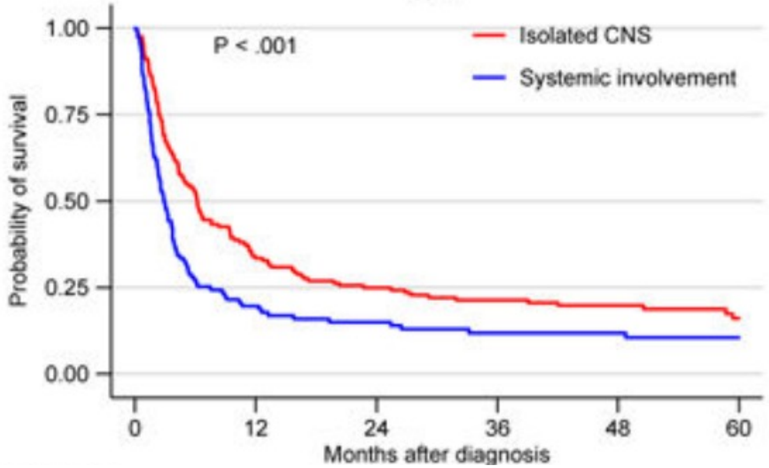


2-yr PFS
71%

28%

Retrospective study SCNSL n=291 -> HSCT=25

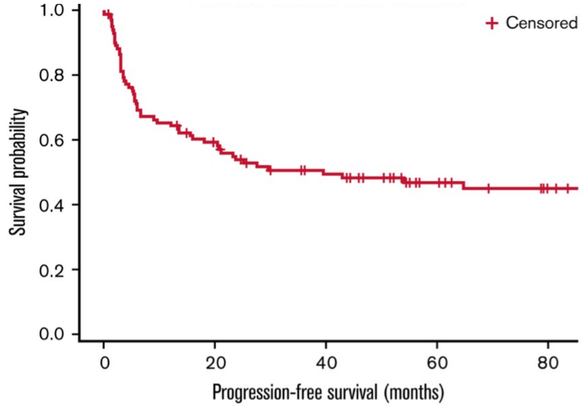
El-Galaly TC et al. Eur J Cancer 2018



2-yr OS
All: 20%
25 HSCT: 68%

Retrospective study SCNSL HSCT n=102

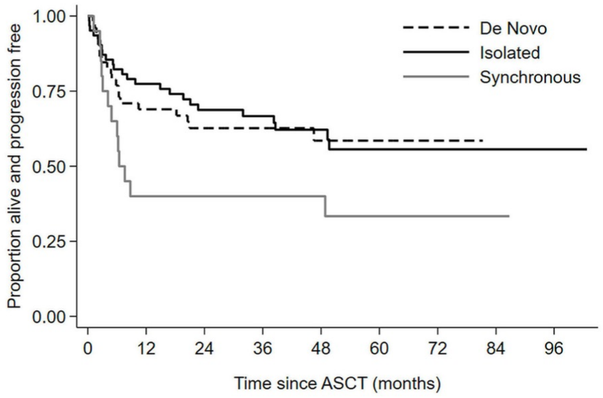
Akin S et al. Blood Adv 2022



4-yr PFS 48%
4-yr OS 57%

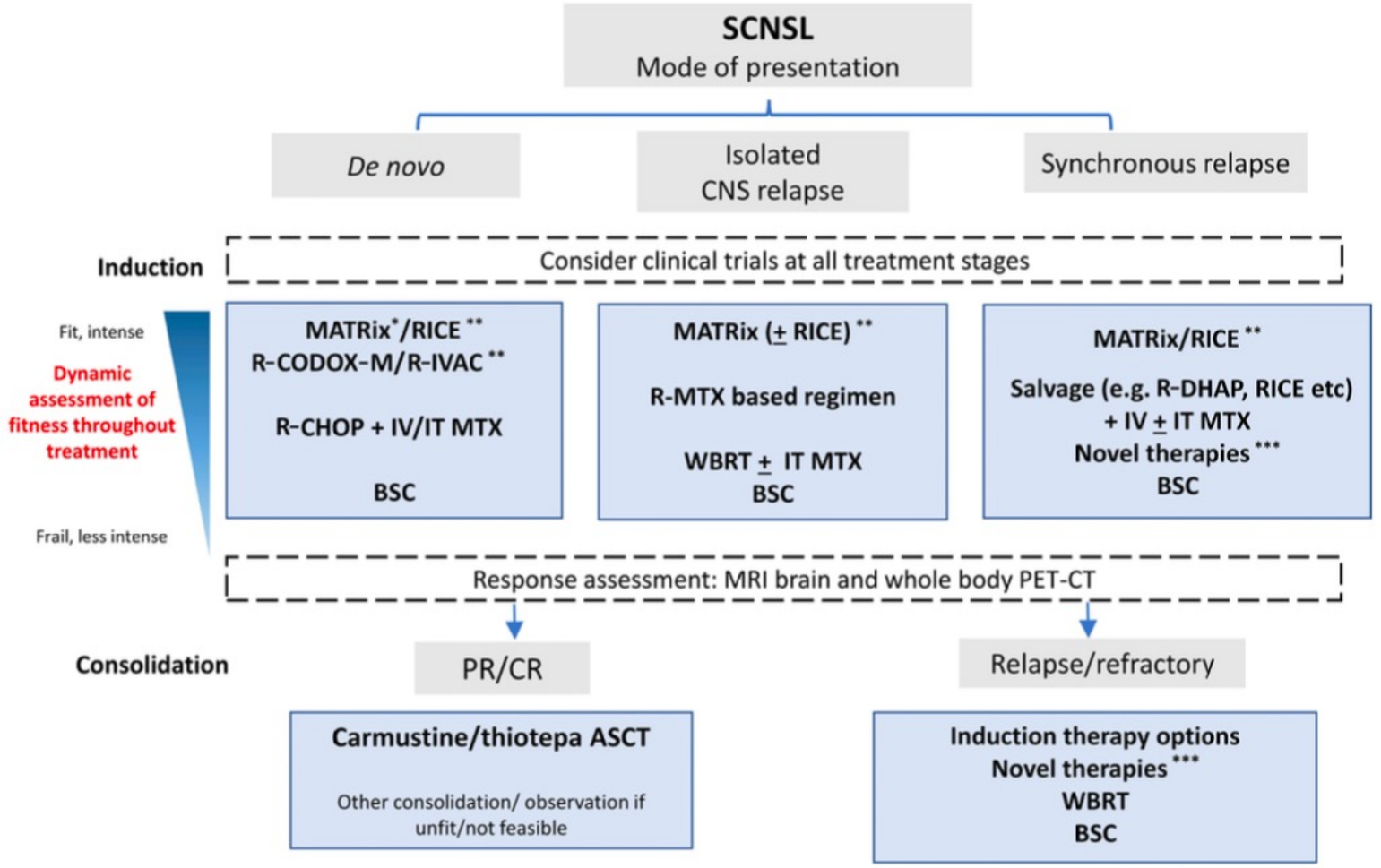
Retrospective study SCNSL HSCT n=134

Khwaja J et al Haematologica 2023



3-yr PFS 72%
3-yr OS 61%

TREATMENT OF PATIENTS WITH CNS INVOLVEMENT



Bobillo S et al. Haematologica 2023

CASE REPORT 2

February 2020

HISTORY-PRESENTATION

75-year-old women

Medical history: 2011 Lymphoplasmacytic lymphoma (LPL) treated with 4 FCR courses (stop for cytopenias)

Physical examination-clinic: polistational adenopathies, pleural effusion, edema

Laboratory test: elevated LDH

ECOG 2

Simplified GA: unfit

HISTOLOGY

Lymphnode biopsy: Diffuse large B cell Lymphoma

IHC: Ki67 90%, Myc 50%, Bcl2 100%, Bcl6+, CD10-, MUM1+

FISH: *BCL6, BCL2* and *MYC* not rearranged

Bone marrow: pathological small-medium size lymphocyte infiltrate (15%), mutation of *MYD88 L265P*

IMAGING

WB PET-TC: pathological uptake of diffuse increased lymphnodes, uterus, tibia, bones

CNS exam: B clonal lymphocytes CD19+CD20+CD5-CD38-sIgk, large lymphocytes (30 cells/mcl)

Whole spine-brain MRI: cauda equina thickening

Secondary CNS lymphoma
DLBCL "Double expressor" non GCB (Hans algorithm)
Stage IVA (bone marrow, bone, uterus, CNS)
IPI: 5/5

CASE REPORT 2

75-year-old women
Unfit

Secondary CNS lymphoma
DLBCL "Double expressor" non GCB (Hans algorithm)
Stage IVA (bone marrow, bone, uterus, CNS)
IPI: 5/5

What therapy would you suggest to this patient?

1. Best supportive care
2. R-CHOP (reduced dose) + IV/IT MTX
3. MATRix/R-ICE

CASE REPORT 2

TREATMENT

Proposed therapy: 6 R-CHOP21 + IT MTX-Cytarabine

February 2020

1° course R-CHOP 100% (VCR 50%) + tibial RTT 8Gy

9/3/2020

2° course R-CHOP 100% (VCR 50%) + 1° IT MTX Cytarabine (4 cells/mcl)
2° IT MTX Cytarabine (negative IF e cytology)

16/4/2020

→ CVC-related polymicrobial sepsis, enteritis, herpetic mucositis

3° course R-CHOP 75%
3° IT MTX Cytarabine (negative IF e cytology)
4° IT MTX Cytarabine (negative IF e cytology)

28/5/2020

→ Neutropenic fever - FUO

4° course R-miniCHOP + 5° IT MTX Cytarabine (negative)

Restaging after 4 courses
TC: CR
BOM: negative

→ Persistent neutropenia and thrombocytopenia

16/7/2020

4 rituximab (21d) + 4 IT MTX Cytarabine

CASE REPORT 2

September 2020

Restaging at the end of treatment

WB TC-PET: inguinal increased nodes and pulmonary nodules with increased uptake

Whole spine MRI: negative

Lymph node biopsy: Diffuse large B cell Lymphoma

Systemic relapse of DLBCL
Stage IVA (lung, lymphnodes)
IPI: 3/5

CASE REPORT 2

TREATMENT

Proposed therapy: Loncastuximab tesirine-ibrutinib
(Phase 1/2 Open-Label Study ADCT-402-103)

L= Loncastuximab-tesirine: 60 µg/kg IV Q3W × 2 ->QW4 x10
I= Ibrutinib: 560 mg/day po continuous beginning C1D1

November 2020

- C1 L-I → thrombocytopenia grade II
- C2 L-I → atrial fibrillation grade II

Restaging
WB TC-PET: PR

- C3 L-I
- C4 L-I

WB TC-PET: improved PR

- C5 L-I
- C6 L-I → neutropenia and thrombocytopenia grade III → stop Ibrutinib -> ↓ 420 mg

WB TC-PET: improved PR

- C7 L-I
- C8 L-I → neutropenia grade III + erythema grade III → stop Ibrutinib -> ↓ 280 mg
- C9 L-I

WB TC-PET: CR

- C10 L-I
- C11-13 I → relapsing erythema grade III → October 2021 → stop Ibrutinib

WB TC-PET: CR

February 2023 → Persistent CR

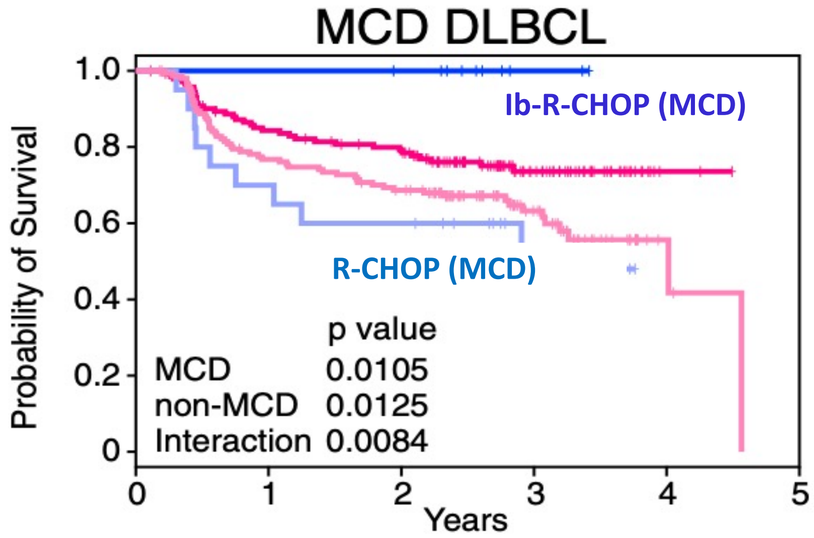
FUTURE PERSPECTIVES: Novel therapies

Ibrutinib

	Patients	Treatment	Response	Median Follow up	Outcome (median)
1	29 PCNSL R/R 15 SCNSL R/R	Ibr	ORR 31/40 (78%) 17/40 (42%) CR	22 m	PFS 4 m OS 19,5 m
2	9 PCNSL R/R 6 SCNSL (3 de novo)	Ibr-R-MTX	ORR 12/15 (80%) 8/15 CR (53%) 4/15 PR (27%)	19,7 m	PFS 9,2 m OS n.r
3	13 PCNSL R/R 5 PCNSL de novo	Ibr-DA-TEDDI-R	17/18 reduction 15/18 (83%) PR*	15,5 m	PFS 15,5 m (R/R) OS n.r.

* 39% aspergillosis, ^ 3 pts stop for AE

Ongonig study with acalabrutinib and durvalumab (NCT04462328)



Wilson WH et al. Cancer Cell 2021

1. Grommes C et al. Blood 2018
2. Grommes C et al. Blood 2019
3. Lionakis et al. Cancer Cell 2017

m: months, Ibr: ibrutinib, R/R: refractory/relapsed, len: lenalidomide, pom: pomalidomide, DMZ: desametazone, PVRL: primary vitro retinal lymphoma

FUTURE PERSPECTIVES: Novel therapies

Immunomodulatory agents

	Patients	Treatment	Response	Median Follow up	Outcome (median)
1	25 PCNSL or PVRL R/R	pom-DMZ	ORR 12/25 (48%) 8/25 (32%) CR/CRu 4/25 (16%) PR	16,5 m	PFS 5 m
2	34 PCNSL R/R 11 PVRL R/R (+5 early death/PD)	len-RTX	ORR 16/45 (36%) 13/45 (29%) CR 3/45 (7%) PR	19,2 m	PFS 8 m OS 18 m
3	6 PCNSL R/R 8 SCNSL R/R	HD MTX/RTT + len-RTX	ORR 64% (4 sustained response>18 m)	12,5 m	PFS 6 m

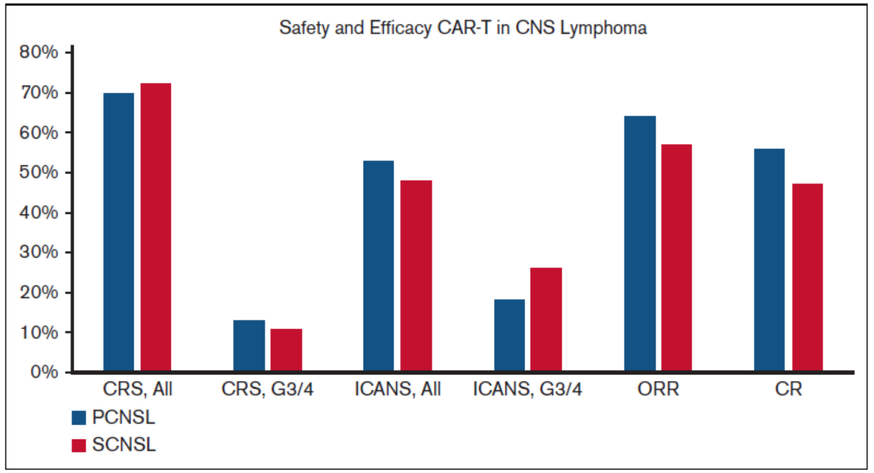
R2CHOP (136 patients): 2y CNS relapse 0,7% (11)

1. Tun HW et al. Blood 2018
2. Ghesquieres H et al. Ann of Oncol 2019
3. Rubensteins JL et al. Blood Adv 2019

CAR-T

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

	Median follow up	Ongoing response
PCNSL: 30 pts	12,2 m	37%
SCNSL: 98 pts	10 m	46%



Cook M et al. Blood adv 2023

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FUTURE PERSPECTIVES: Improve baseline screening

- **ctDNA**

  - 136 patients (92 CNSL): ctDNA detectable in 100% of CFS and 78% of plasma samples
  - Pretreatment plasma ctDNA is related to outcome

  Mutter J et al JCO 2022

  - 19 patients 6 isolated CNSL, 1 SCNSL, 12 systemic lymphomas (SL)
    - ctDNA found only in all CNSL-SCNSL
    - ctDNA detected in CSF before CNS relapse in 2 patients

  Bobillo S et al.Haematologica 2021

- **Clonotypic DNA-NGS MRD**

  - 13 CNSL -> detected in 100% of CSF samples
  - 22 DLBCL HR -> 8 (36%) detectable clonotypic DNA (ClDNA) in CSF: 2 relapsed in CNS

  12 months CNS relapse risk 29% in clDNA+ vs 0% in clDNA-

  Olszewski A et al. Blood Adv 2021

- ***MYD88 L265P* mutation**

  - 73 PCNSL de novo or R/R: Mut *MYD88* in 88% of PCNSL biopsies- 82% concordance in paired tissue-CSF samples
    -> combined analysis of *MYD88* and IL-10: sensibility 94% and specificity 98% in distinguishing PCNSL
  - *MYD88* mutations identified in 70% of primary testicular lymphomas

  Ferreri AJM et al BJH 2021

CONCLUSIONS

- Try to optimize baseline screening (MRI-CSF) to identify very high risk patients

- To date, there is an absence of robust prospective data informing risk estimation and the definitive benefit of prophylactic strategies
  - in high-risk patients consider HD-MTX (at EOT)
  - IT therapy + HD-MTX in Testicular DLBCL

- Future direction:
  - expand ultrasensitive technology to detect occult CNS involvement at presentation (ctDNA, *MYD88* mutation)
  - biological agents active against B lymphomas with good CNS bioavailability could improve front-line treatment effectiveness and reduce CNS dissemination