GIORNATE EMATOLOGICHE VICENTINE

XI edizione

9-10 Ottobre 2025
Palazzo Bonin Longare - Vicenza

I linfomi primitivi cerebrali: quali novità nel 2025

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Disclosures of Paolo Fiore

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lor

Primary Central Nervous System Lymphoma (PCNSL)

Brain Parenchima
(100%)

Leptomeninges
CSF (~15%)

Eyes
(15-25%)

Spinal cord
(<1%)

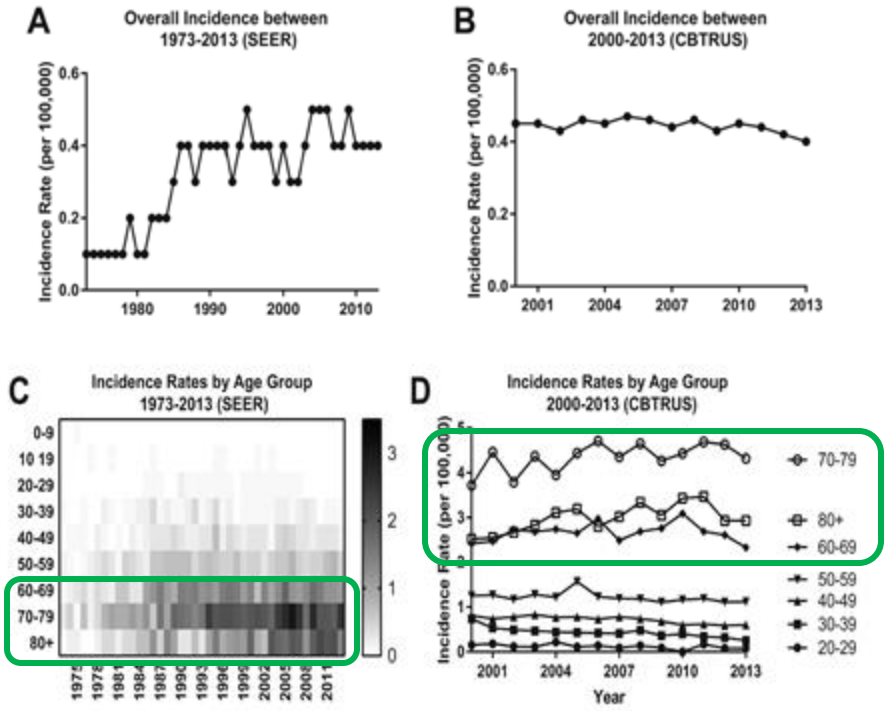
1-2% of brain tumors
4-6% of Extranodal Non-Hodgkin Lymphoma (NHL)
PCNSL incidence varies globally, with 0.3 to 0.6 cases per 100,000 individuals reported in population-based studies

PCNSL is a rare sub-type of non-Hodgkin lymphoma. It is a diffuse large B-cell type (DLBCL), involving the brain, leptomeninges, eyes, or spinal cord, without involvement of other organs at initial diagnosis and with anecdotal cases of systemic dissemination at relapse

PCNSL Epidemiology

Incidence 0.47/100 000 person-years

Median age at diagnosis: 68 y



The incidence of PCNSL differed greatly between age groups.

Mendez JS et al. Neuro Oncol. 2018

PCNSL Epidemiology

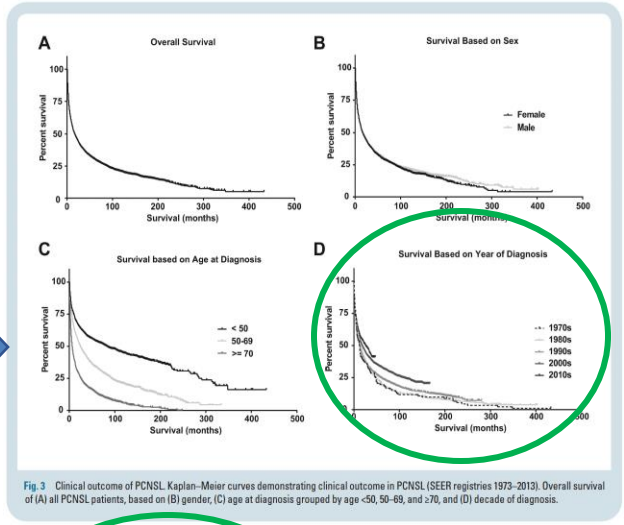
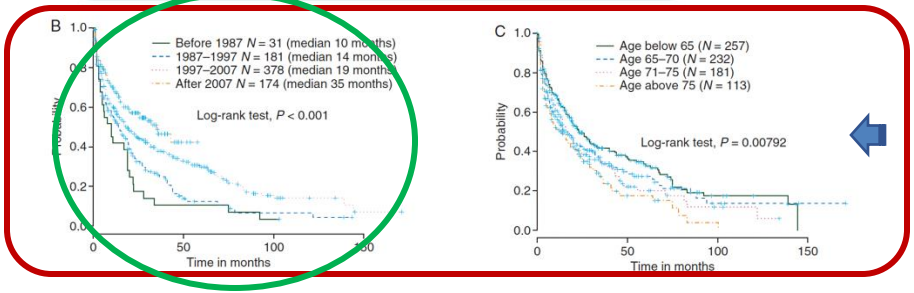


Fig. 3 Clinical outcome of PCNSL. Kaplan–Meier curves demonstrating clinical outcome in PCNSL (SEER registries 1973–2013). Overall survival of (A) all PCNSL patients, based on (B) gender, (C) age at diagnosis grouped by age <50, 50–69, and ≥70, and (D) decade of diagnosis.

Table 2 Median overall survival

Median Overall Survival Based on Age, mo				
Time of Diagnosis	**<50 y**	**50–69 y**	**≥70 y**	**All Patients**
1970s	35.5	8	6	12.5
1980s	19.5	18	8.5	14
1990s	23	18	6	13
2000s	134	25	6	18
2010s	NR	35	7	26
1973–2013	83	25	6	17

NR, not reached.

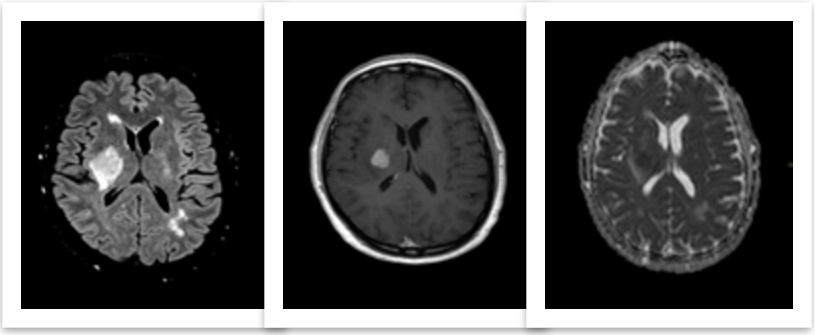


Outcome increased over time and by age groups
(with the Elderly left behind)

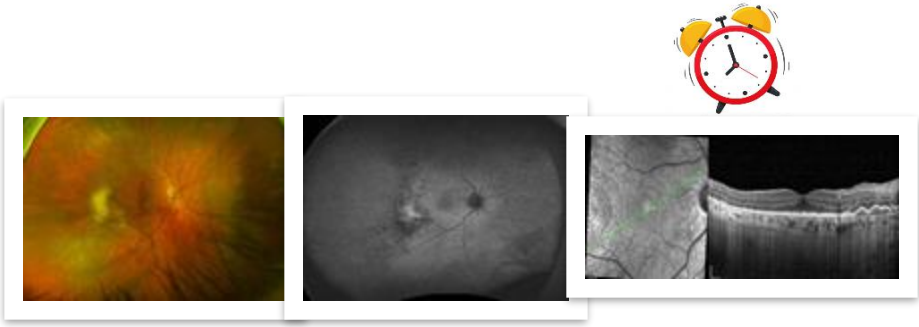
Mendez JS et al. Neuro Oncol. 2018
Kasenda B et al. Ann Oncol 2015

Oncologic Paradigm: Early Diagnosis is the best treatment

- The successful treatment (and the subsequent neurological recovery) of PCNSL, a rapidly progressing tumour, depends on early diagnosis
- A histological diagnosis of a tumor specimen obtained by stereotactic biopsy is required to validate a suspicion raised by brain MRI
- Cerebrospinal fluid (CSF) or vitreous humour might aid in providing a cytological diagnosis



Images courtesy of Prof. Nicoletta Anzalone, IRCCS San Raffaele Scientific Institute, Milan, Italy



Images courtesy of Prof. Elisabetta Miserocchi, IRCCS San Raffaele Scientific Institute, Milan, Italy

PCNSL - Diagnosis

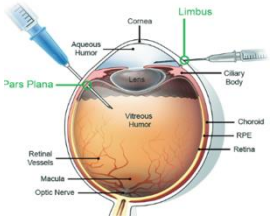
Current strategy = ***low*** diagnostic sensitivity

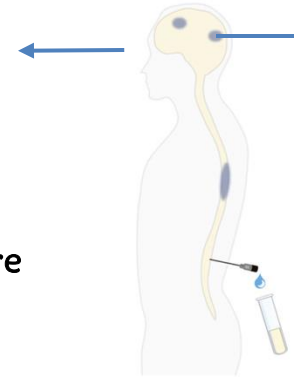
- **Neuroimaging**: T1, T2, flair, DWI, enhancement, spectroscopy
- Site: corpus callosum, basal ganglia, periventricular areas...
- **Response to steroids**

Ferreri AJM et al. ESMO-EHA CPG 2024
Ann. Oncol. 2024 & Hemasphere 2024

PCNSL - Diagnosis

Vitreous aspirate



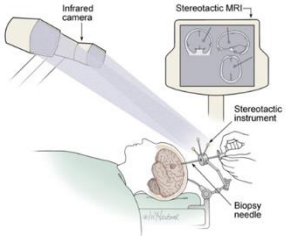


Lumbar puncture

Low sensitivity (<50%)
Small number of tumor cells in these CNS compartments
Definitive diagnosis possible only if disease dissemination

Illerhaus G. and Batchelor T. Blood 2011
Chamberlain MC. Et al. 2000

Stereotactic Brain Biopsy



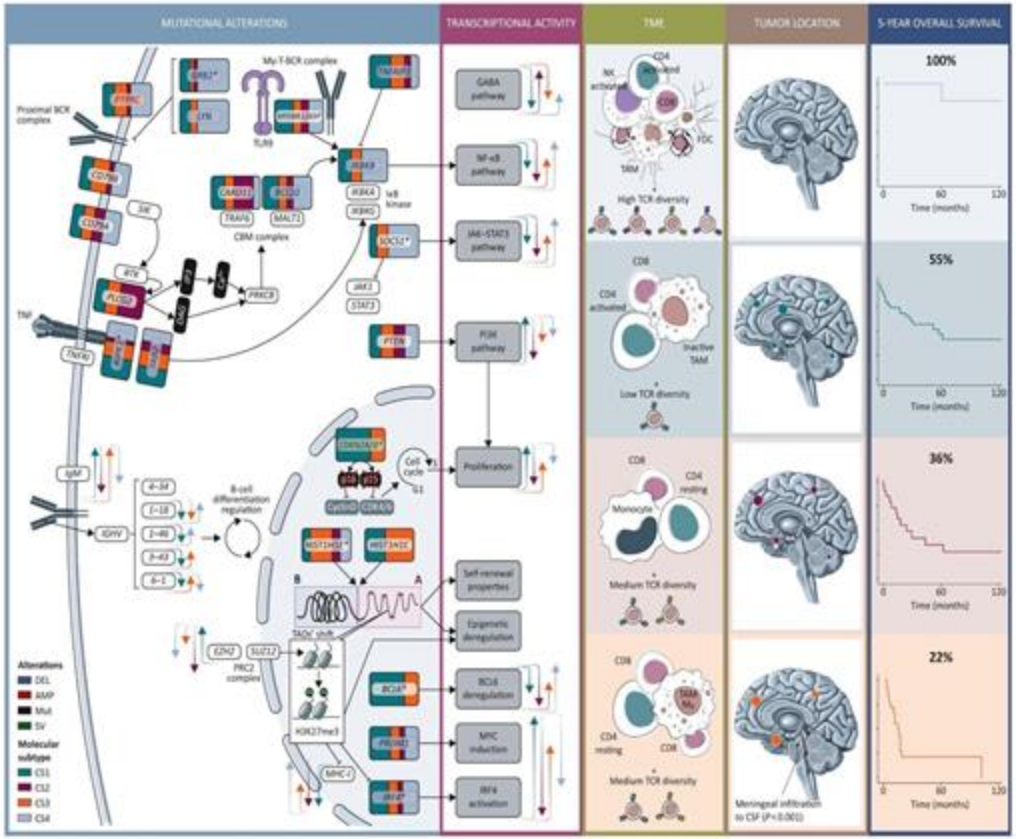
Gold standard approach
Caveats:
Risk of morbidity/death
Geographical misses
Vanishing tumours
due to:
Deep lesions
Fragile patients
Prior corticosteroid exposure

PCNSL Diagnosis: limits

Based on this background, the development of alternative strategies to stereotactic biopsy in order to improve early diagnosis of PCNSL could be really beneficial and desirable

How can we improve diagnostic sensitivity and specificity?

Understanding molecular biology of PCNSL



- PCNSL displays **perturbation of pathways** related to:
  - signalling of **B-cell receptor** (BCR),
  - **toll-like receptor** (TLR) and
  - **NF-κB**, as well as
  - terminal B-cell differentiations, deregulation of the cell cycle, immune escape, and protection from apoptosis

Diagnostic potential: co-occurring mutations in **CD79B** and **MYD88** (L265P), have been identified in 70%-89% of PCNSL

Therapeutic approach: BTK-i; anti-PD1

Hernández-Verdin, Ann. of onco. 2022

PCNSL Diagnosis: what's new
Liquid Biopsy

- **Samples:** Blood, CSF and vitreous humor
- **Techniques:** next generation sequencing, ELISA, ddPCR …
- **Biomarkers:** chemokine, genomic fragment (cfDNA, microRNA), transmembrane receptors

PCNSL Diagnosis: what's new
PAMINA study

MYD88 L265P mutation and **IL-10 level** in CSF in:
- **63 PCNSL** (36 newly diagnosed, 27 relapsed) and
- **162 controls** (118 CNS disorders, 44 extra-CNS lymphomas).

Mut-MYD88 was detected in 15/17 (88%) PCNSL biopsies, with an 82% concordance in paired tissue-CSF samples.

In CSF, **mut-MYD88** and high **IL-10** levels were detected in:
- **72% and 88% of newly diagnosed PCNSL**
- **1% of controls.**

Combined analysis of MYD88 and IL-10 exhibits a:
- **sensitivity of 94%** and
- **specificity of 98%**

to distinguish PCNSL.

Variable	PCNSL (*n* = 36)	Neurological controls (*n* = 106)	*P**	Systemic DLBCL (*n* = 44)	*P*†
MYD88 L265P mutation, *n* (%)	26 (72)	1/86 (1)‡	<0·00001	1 (2)§	<0·00001
IL-6 level, pg/ml, median (IQR)	4·6 (0–91)	2·3 (0–5·7)	0·007	0 (0–0·6)	0·0003
High IL-6 levels >2·5 pg/ml, *n/N* (%)	24/33 (73)	38/79 (48)	0·02	6 (14)	<0·00001
IL-10 level, pg/ml, median (IQR)	69·5 (0–200)	0 (0–0)	<0·00001	0 (0–0)	<0·00001
High IL-10 levels >2 pg/ml, *n/N* (%)	28/32 (88)	1/79 (1)¶	<0·00001	1 (2)**	<0·00001
At least one between *MYD88* mut and high IL-10, *n/N* (%)	30/32 (94)	1/59 (2)	<0·00001	2 (4)	<0·00001

	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)

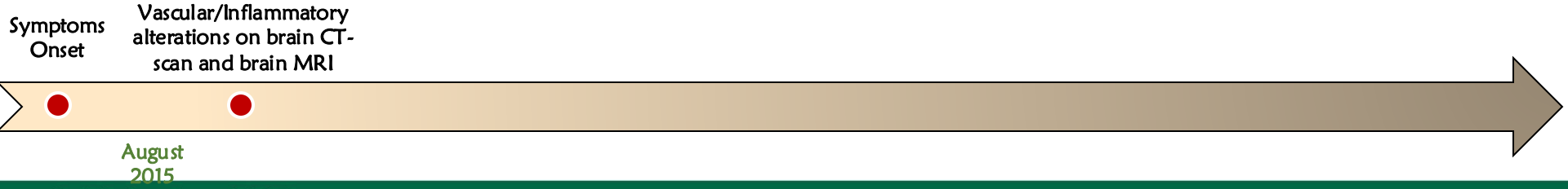
Ferreri AJM, et al. BJH 2021

Clinical Case: Unfeasible brain biopsy - The Frail Old Man

August 2015:

A 79-year-old Caucasian male was admitted in the hospital due to an acute onset of dizziness, nausea, and vomiting.

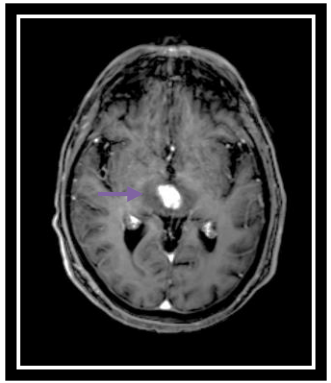
A brain CT-scan and a subsequent brain MRI showed a pattern of right frontal ischemia and vestibular neuronitis (images not available)

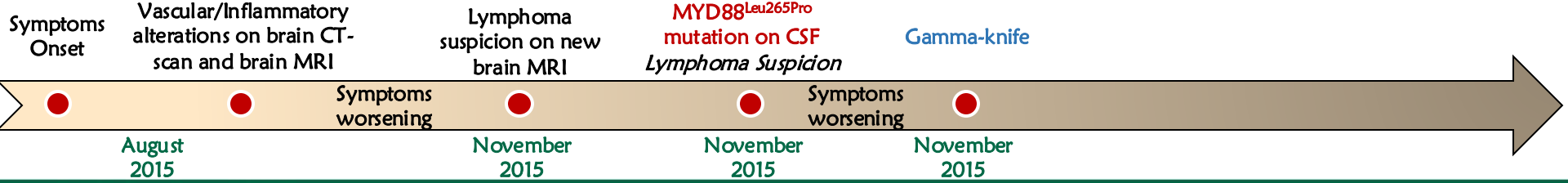


Clinical Case: Unfeasible brain biopsy - The Frail Old Man

November 2015: After 3 months, the patient developed diplopia and equilibrium disorders and was referred to our Center. A new brain MRI showed a mass forming enhancing lesion at the level of the third ventricle.

A stereotactic brain biopsy was proposed, but patient refused due to the risk of morbidity and mortality.
A **lumbar puncture**, while negative for cancer cells, revealed the presence of the **MYD88^{L265P} mutation** in the cerebrospinal fluid.





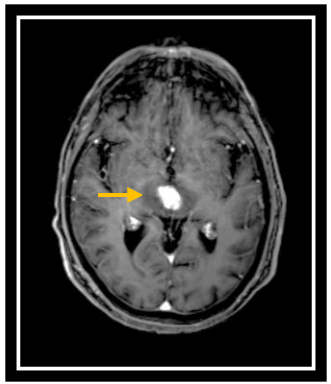
Clinical Case: Unfeasible brain biopsy - The Frail Old Man

Post-treatment MRI showed complete remission of the mesencephalic lesion (yellow arrow) but revealed the onset of a right peri-trigonal lesion (green arrow).

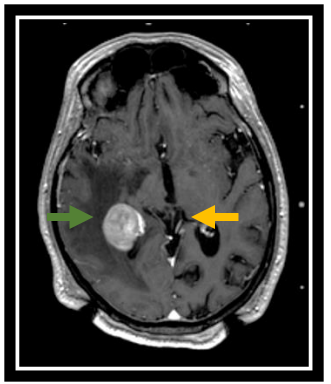
Diagnostic Delay – 6 months

Died in 1.5 months

August 2015



January/February 2016



Symptoms Onset — August 2015

Vascular/Inflammatory alterations on brain CT-scan and brain MRI

Symptoms worsening — August 2015

Lymphoma suspicion on new brain MRI — November 2015

MYD88^{Leu265Pro} mutation on CSF *Lymphoma Suspicion* — November 2015

Symptoms worsening — November 2015

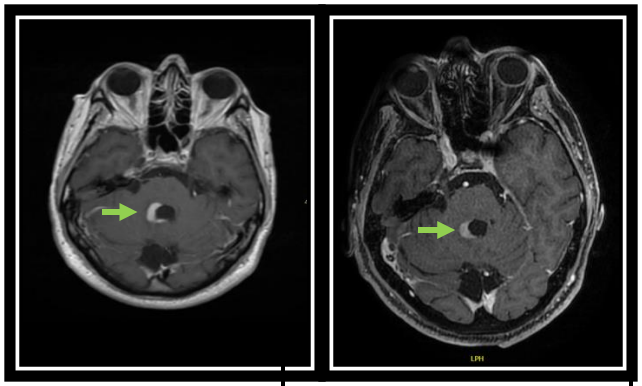
Gamma-knife — November 2015

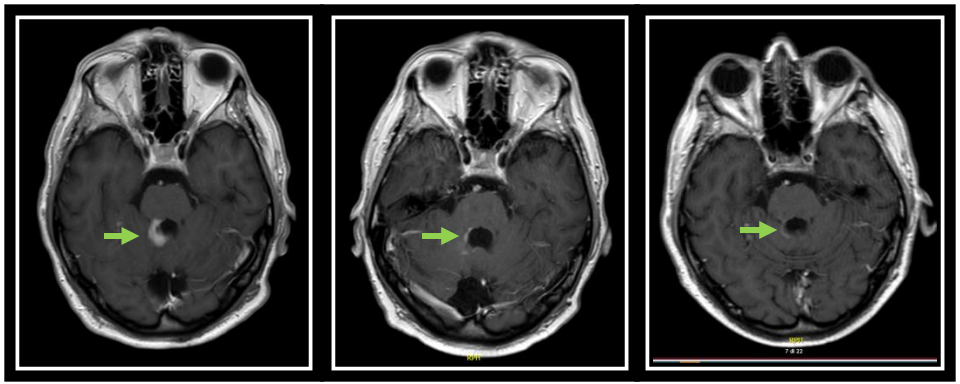
Brain Biopsy: DLBCL harboring MYD88^{Leu265Pro} *Lymphoma Diagnosis* — January/February 2016

Chemo — March 2016

Clinical Case: Unfeasible brain biopsy – Deep lesion

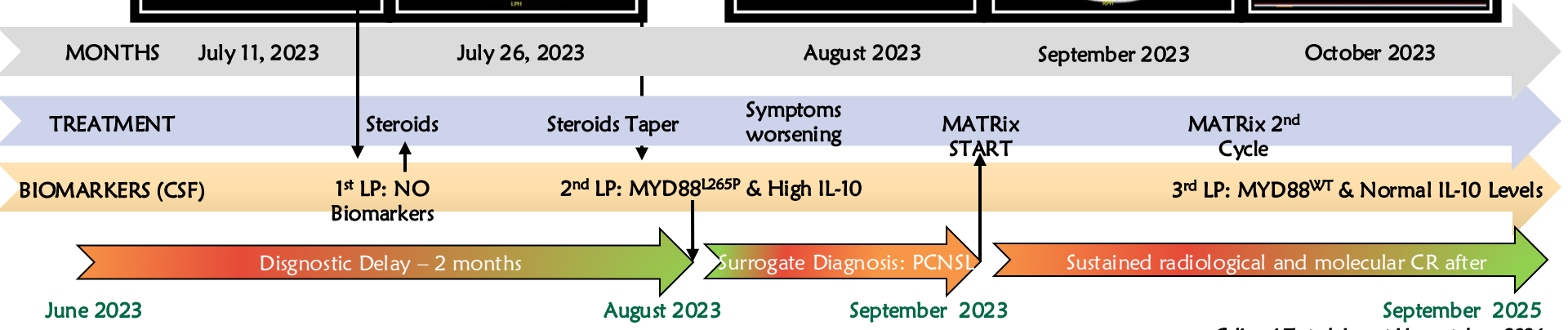
June 2023: A 62-year-old Caucasian male reported hearing loss, postural instability, intermittent diplopia, and impaired speech.





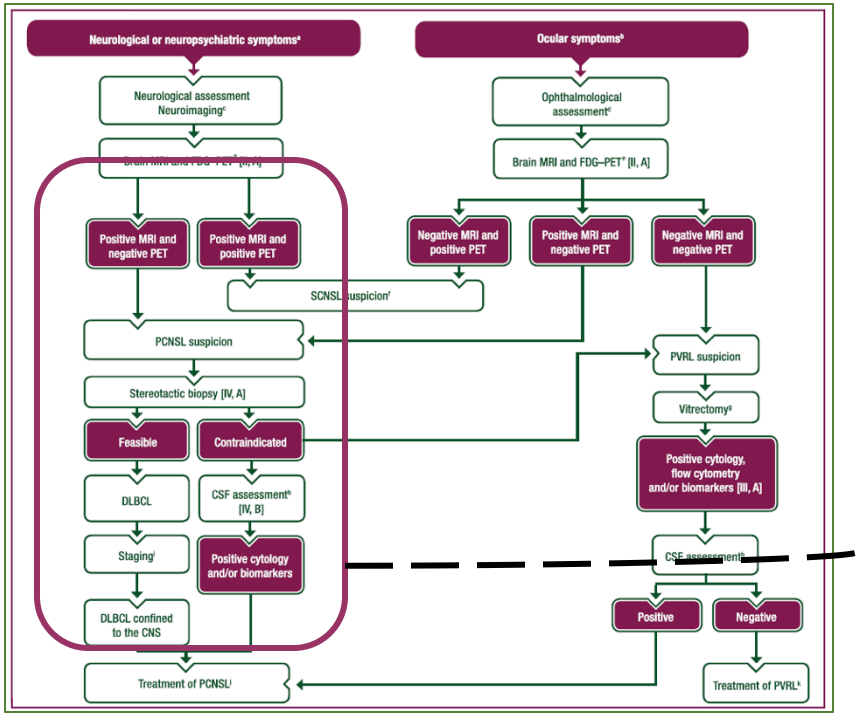
MRI after 1st Cycle

Interim MRI



Calimeri T et al. Lancet Haematology 2024

Diagnostic algorithm for PCNSL in immunocompetent patients

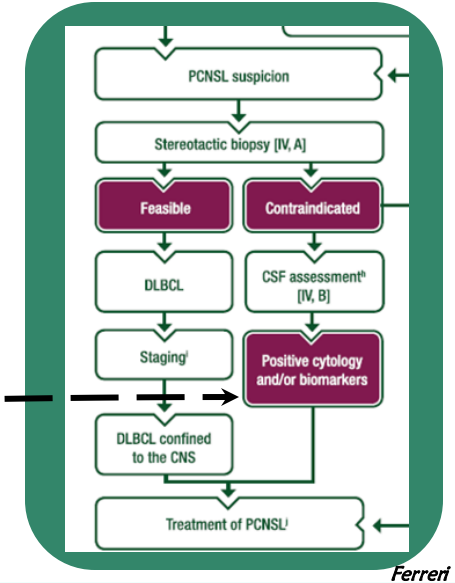


ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
EHA EUROPEAN HEMATOLOGY ASSOCIATION
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Primary central nervous system lymphomas: EHA–ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

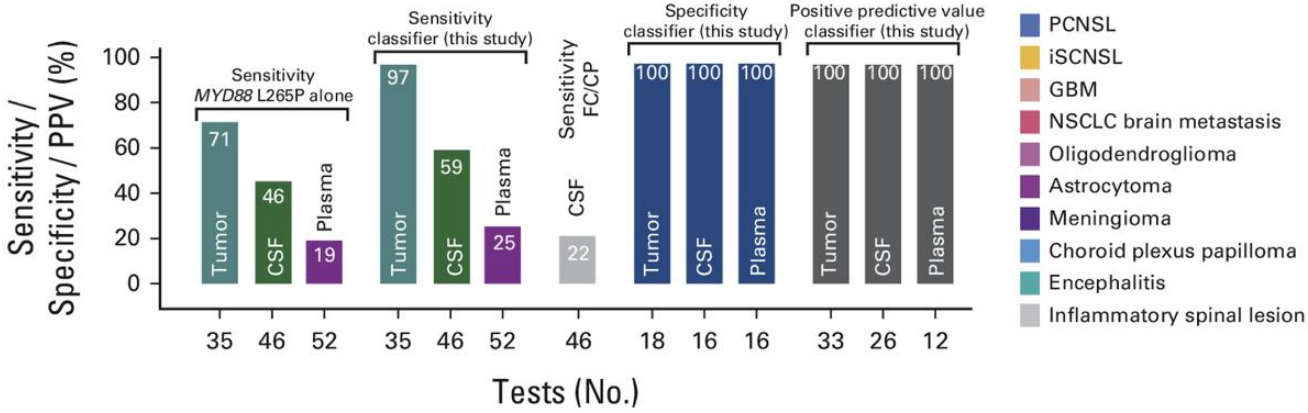
A. J. M. Ferreri[1,2†], G. Illerhaus[3†], J. K. Doorduijn[4†], D. P. Auer[5,6], J. E. C. Bromberg[7], T. Calimeri[3], K. Cwynarski[8], C. P. Fox[9], K. Hoang-Xuan[10], D. Malaise[11,12], M. Ponzoni[1,2,13], E. Schorb[14], C. Soussain[15,16], L. Specht[17], E. Zucca[18,19,20], C. Buske[21], M. Jerkeman[22] & M. Dreyling[23], on behalf of the EHA and ESMO Guidelines Committees*



Ferreri et al. Ann Oncol. 2024

PCNSL Diagnosis: what's next
Liquid Biopsy

Ultrasensitive targeted high-throughput sequencing technologies to explore the role of ctDNA



ctDNA:

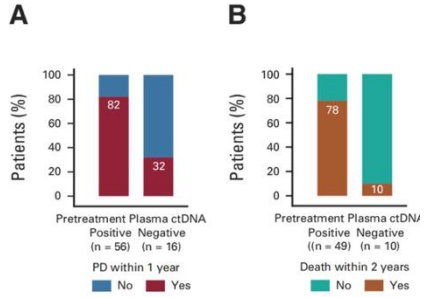
- Specificity 100%
- Positive predictive value (100%)
- Sensitivity of 57% for CSF and 21% for plasma

→

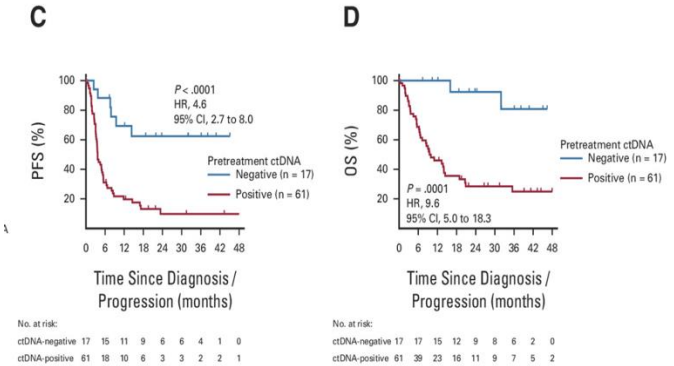
A significant subset of CNSL patients might be able to forego invasive surgical biopsies

Mutter JA. et al. JCO 2022

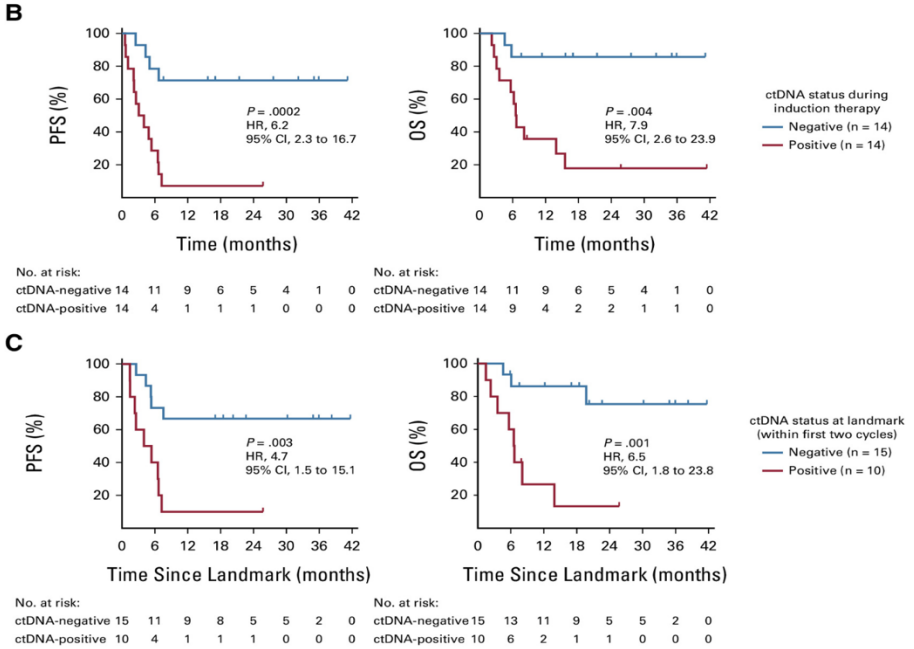
PCNSL Diagnosis: what's next
Liquid Biopsy



Prognostic value of ctDNA in **pretreatment** plasma samples



Prognostic value of ctDNA in plasma samples **during treatment**



Mutter JA. et al. JCO 2022

PCNSL Diagnosis: what's next
Liquid Biopsy

Ion Ampliseq Liverpool Lymphoid Network Panel

Ion AmpliSeq Panel Design

DNA PANEL (60 genes)

Essential Exons (36)

- *BCL6*
- *BIRC3*
- *BRAF*
- *BTK*
- *CARD11*
- *CCND1*
- *CCND3*
- *CD79B*
- *CXCR4*
- *DNMT3A*
- *EP300*
- *ETV6*
- *EZH2*
- *FAS*
- *FBXW7*
- *FOXO1*
- *HRAS*
- *IDH2*
- *IRF4*
- *KRAS*
- *MAP2K1*
- *MYD88*
- *NOTCH1*
- *NOTCH2*
- *NRAS*
- *PLCG2*
- *POT1*
- *RHOA*
- *RPS15*
- *SF3B1*
- *SMARCA4*
- *STAT3*
- *STAT5B*
- *STAT6*
- *TNFRSF14*
- *XPO1*

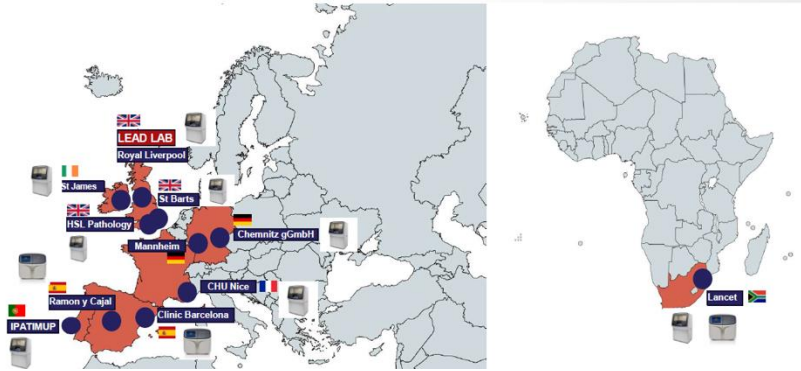
Full Coding Sequence (24)

- *ARID1A*
- *ATM*
- *B2M*
- *BCL2*
- *CDKN2A*
- *CREBBP*
- *DIS3*
- *GNA13*
- *ID3*
- *KMT2D*
- *MEF2B*
- *MYC*
- *NFKBIE*
- *PAX5*
- *PIM1*
- *PRDM1*
- *PTEN*
- *SAMHD1*
- *SGK1*
- *SOCS1*
- *TENT5C*
- *TET2*
- *TNFAIP3*
- *TP53*

Liverpool Lymphoid Network – Participant sites 2023

ThermoFisher SCIENTIFIC

11 clinical research laboratories



PCNSL – Prognostic scores

To predict outcome and better stratify patients in clinical trials, two scoring systems have been proposed

IELSG Score

Ferreri A.J. *et al*. JCO 2003

Table 5. The International Extranodal Lymphoma Study Group (IELSG) prognostic score for PCNSL

Variable	Favourable feature (value '0')	Unfavourable feature (value '1')
Age (years)	<60	>60
ECOG PS score	0–1	>1
Lactate dehydrogenase serum level	Normal	Elevated
Cerebrospinal fluid protein level	Normal	Elevated
Involvement of deep regions of the CNS[a]	No	Yes

IELSG score 0–1, low risk; 2–3, intermediate risk; 4–5, high risk.
PCNSL, primary central nervous system lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system.
Reprinted from [12] with permission. @2003 American Society of Clinical Oncology. All rights reserved.
[a]Deep regions include the corpus callosum, basal ganglia, brain stem and cerebellum.

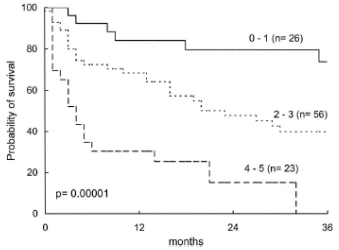


Fig 1. Survival curves for patients grouped according to the proposed prognostic score: patients with 0 to 1 (solid line), 2 to 3 (dotted line), or 4 to 5 (dashed line) unfavorable features. Analysis was performed on the 105 assessable cases in which complete data from all 5 variables were available.

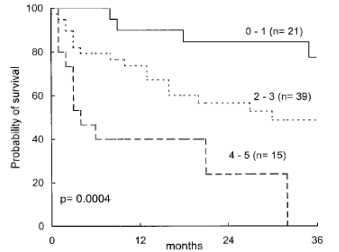


Fig 2. Survival curves for patients grouped according to the proposed prognostic score: patients with 0 to 1 (solid line), 2 to 3 (dotted line), or 4 to 5 (dashed line) unfavorable features. Analysis was performed on the subgroup of 75 assessable patients treated with high-dose methotrexate-based chemotherapy ± radiotherapy.

MSKCC Score

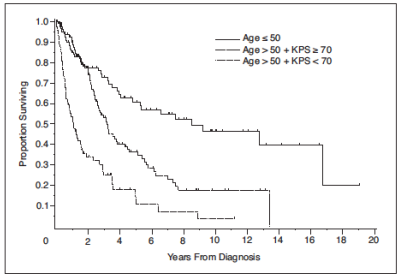


Fig 1. Kaplan-Meier curve showing overall survival of the 282 Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) primary CNS lymphoma patients stratified by recursive partitioning analysis classification. Age younger than 50, class 1; age older than 50 and Karnofsky performance score (KPS) higher than 70, class 2; age older than 50 and KPS less than 70, class 3.

Abrey L.E. *et al*. JCO 2006

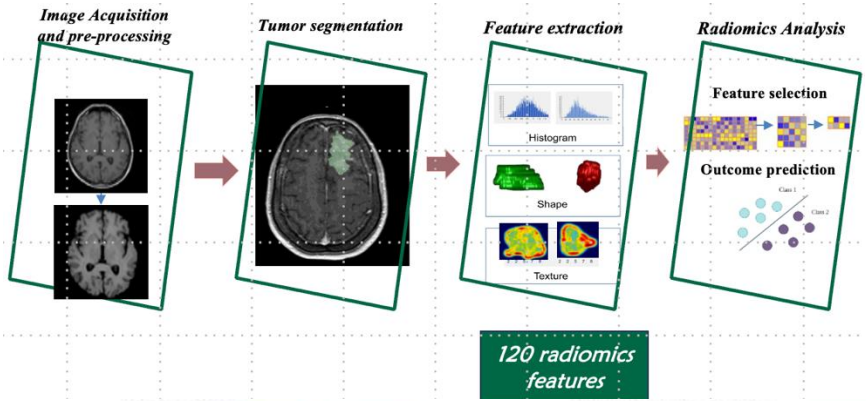
PCNSL – Prognostic scores: what's new
Radiomics

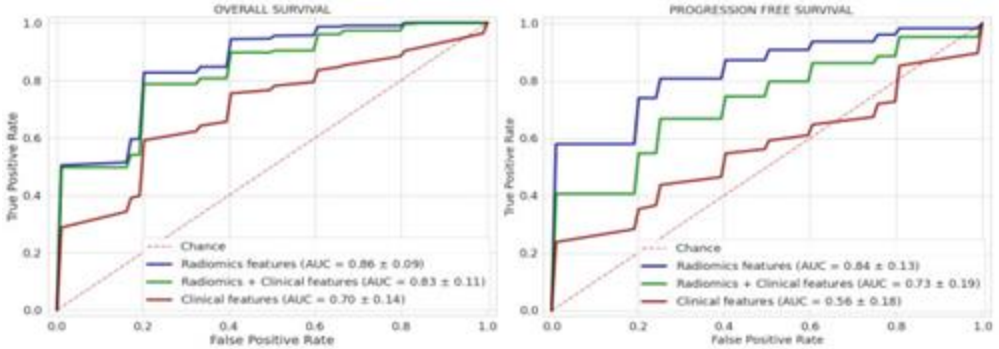
Machine learning-based approach for predicting 1-y OS and PFS in PCNSL.

80 patients were enrolled→ 23 pts, with complete MRI series, selected.

AUC showed that radiomics-based prediction overcame prediction based on clinical prognostic factors with an improvement of:
- 23% for OS,
- 50% for PFS.

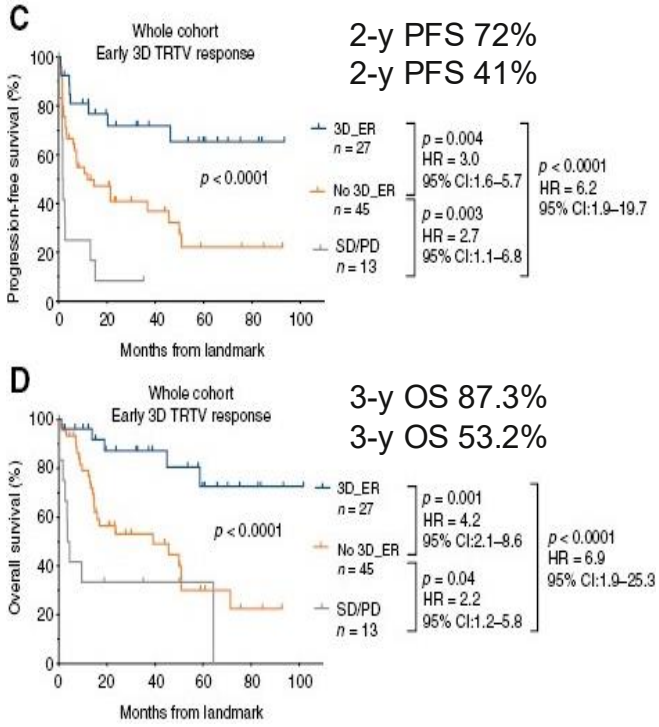
Radiomics features extracted from MR images can improve prognosis stratification of PCNSL patients.

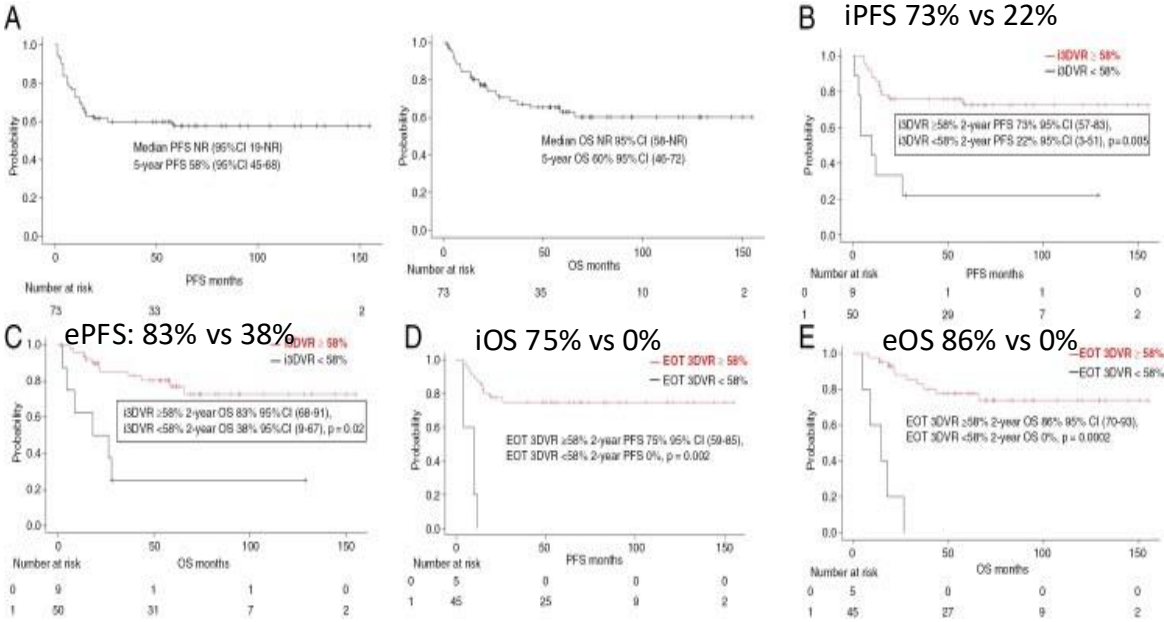




Destito et al. Bioing 2023

PCNSL – Prognostic scores: what's new
Radiomics





Lauer et al. Neuro Oncol. 2024
O'Shaughnessy et al Neurooncol Adv. 2025

PCNSL – Treatment

The treatment of newly diagnosed PCNSL is now typically approached in a sequential manner, which has led to improvements in outcomes.

Induction (Immuno)-Chemotherapy
has the goal of achieving an objective response on imaging studies

Consolidation Therapy
has the objective to eliminate any remaining visible or residual molecular lymphoma

PCNSL – Treatment

Randomized trials using up front Consolidation Strategy in PCNSL

WBRT vs ASCT

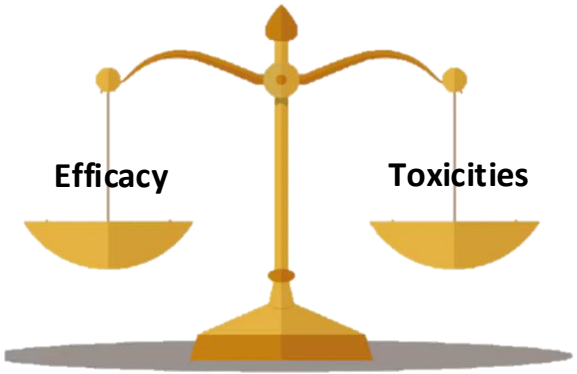
IELSG 32

PRECIS

ASCT vs Chemo

IELSG43

CALGB [Alliance] 51101

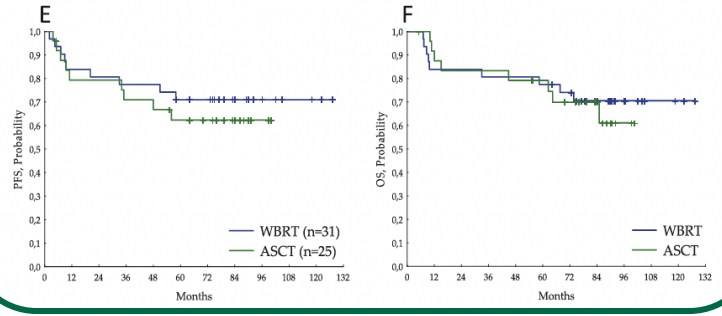


PCNSL Treatment: Randomized Trials

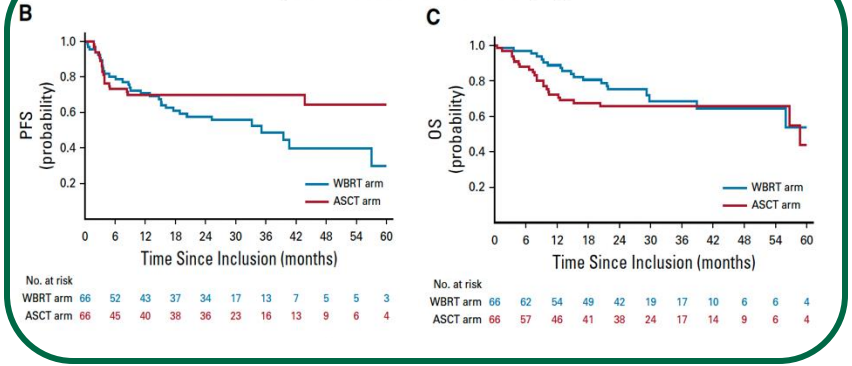
Sequential **induction and consolidation** regimens achieve a **cure** in approximately **50% of patients.**

15-25% refractory to HD-MTX
25-50% relapse after

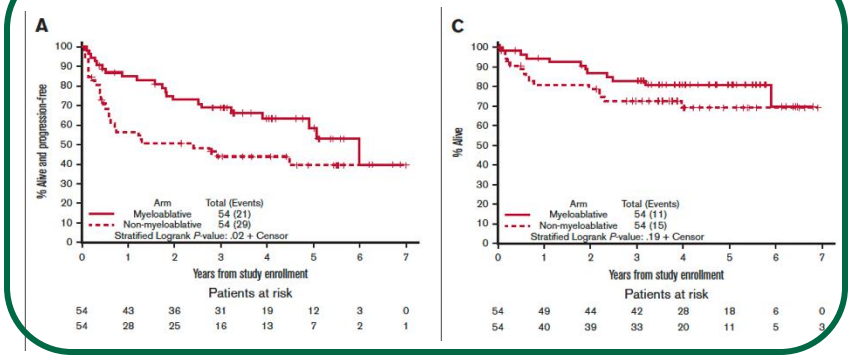
IELSG32 - Ferreri AJM et al. Leukemia 2022



PRECIS - Houillier C et al. JCO 2022



Alliance/CALGB 51101 – Batchelor TT et al. Blood Adv. 2024



PCNSL Treatment: what's new

Low-Dose WBRT

Randomized Phase 2 study
(NRG [RTOG] 1114)

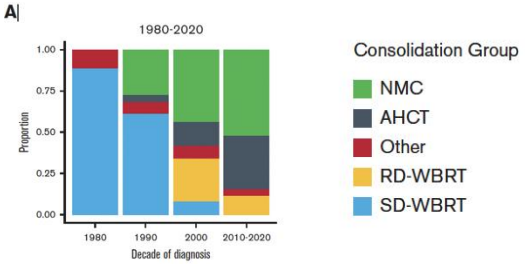
lower dose of consolidative **WBRT (23.4 Gy)** after R-MPV-A to mitigate the risk of NT.

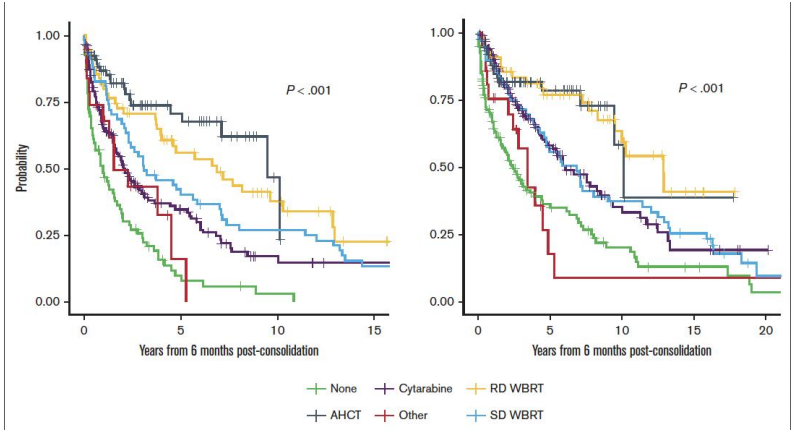
Median follow-up of 55 months
median ITT PFS: 25 m (chemo arm)
NR in the chemoRT arm
(p = 0.015).

2-year PFS: 54% (chemo) *vs.* **78% (chemoRT).** Salvage radiotherapy has been given to 11 patients in the chemo arm.

As per investigator's assessment, NT rates were not statistically signifcantly increased, with further neuropsychological testing and neuroimaging analyses ongoing

Omuro et al. JCO 2020

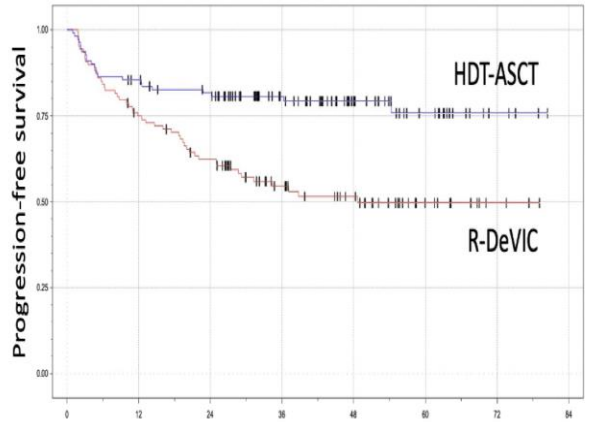


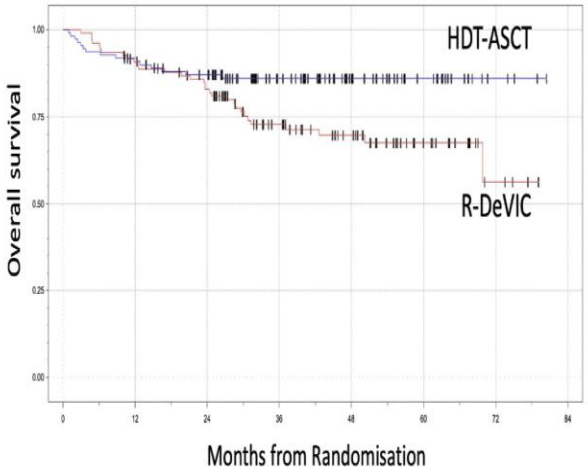


Tringale KM et al. Blood Advances 2024

PCNSL Treatment: what's new

IELSG43





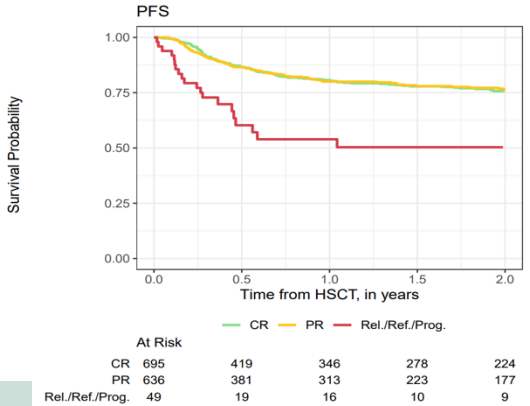
IELSG43 – Illerhaus G et al. ICML 2023

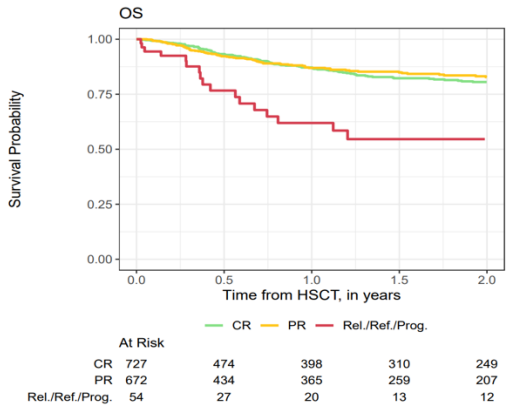
PCNSL Treatment: what's new

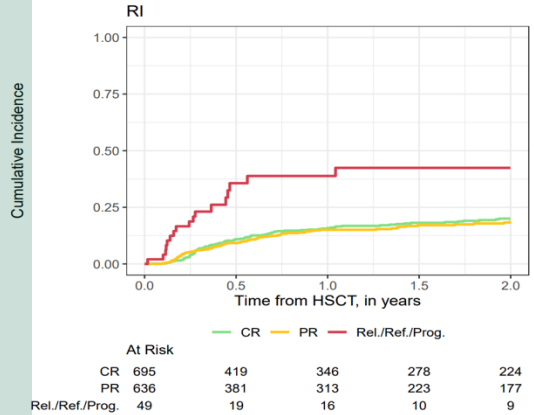
EBMT registry: **1545 pts**
Outcome by Disease Status

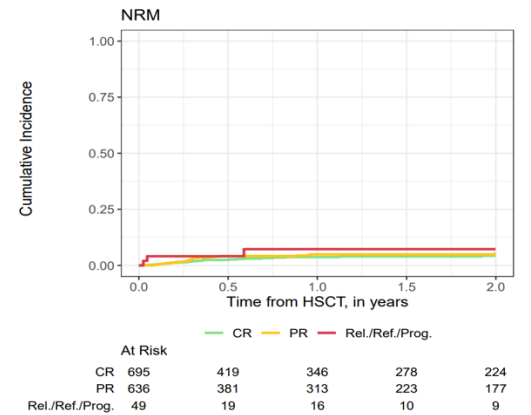
No significant difference in PFS and OS between CR and PR
@ASCT time: **2-year PFS of 76%**

PD @ASCT time exhibited worse outcomes: **2-year PFS of 50%**







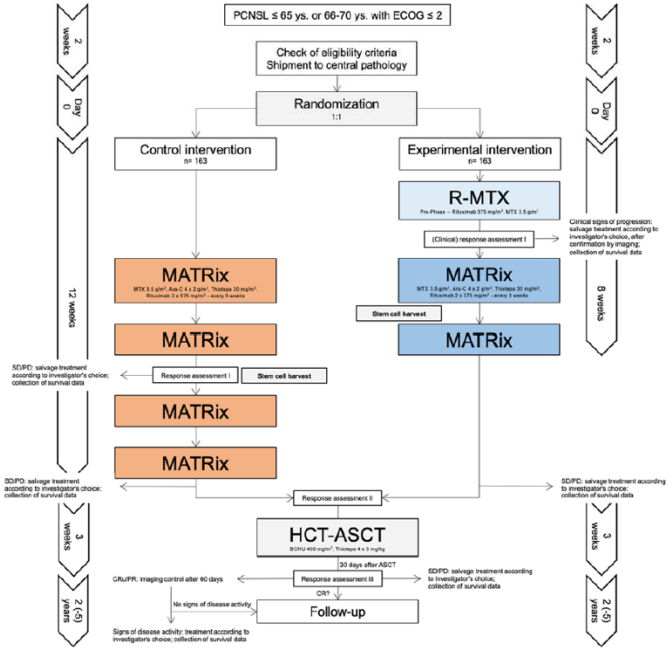


Calimeri et al. ICML 2025

PCNSL Treatment: what's next

OptiMATe Trial

Trial design



- Randomized Phase III trial, with two parallel arms
- Investigator initiated
- Multicentric international: Germany, Austria, United Kingdom, Italy
- 326 patients to be randomized

PCNSL –Elderly

Table 1. Main studies evaluating chemotherapy alone dedicated to newly diagnosed PCNSL in the elderly.

Author	Type	N	Median Age (Range)	Induction	Consolidation	Maintenance	CR % I/M or C [1]	PFS OS mo	Toxic Deaths %
Hoang-Xuan 2003 [9]	Phase II	50	72 (60–81)	HD-MTX IV + IT, IT ARAC, CCNU, PCB	None	HD-MTX IV + IT, IT ARAC, CCNU, PCB	42	7 14.3	4
Omuro 2007 [53]	Retrospective	23	68 (60–79)	HD-MTX, TMZ	None	HD-MTX, TMZ	30/61	8 35	4
Zhu 2009 [54]	Retrospective	31	74 (70–85)	HD-MTX	None	HD-MTX	60	7.1 37	0
Illerhaus 2009 [55]	Phase II	30	70 (57–79)	HD-MTX, CCNU, PCB	None	None	44.4	5.9 15.4	6
Fritsch 2011 [56]	Phase II	28	75 (65–83)	HD-MTX, RTX, PCB, CCNU	None	None	64	16 18	7
Roth 2012 [8]	Retrospective	66	≥70 (NR)	HD-MTX based CT	None	None	64	13.9 26.7	9
					WBRT		75	24.1 29.3	
Olivier 2014 [57]	Phase I	35	65 (61–70)	MTX, VIND, IDA	None	None	17	13 19	8.5
Omuro 2015 [22]	Phase II randomized	48	73 (60–85)	HD-MTX, TMZ	None	None	38	6 14	10
		47	72 (60–84)	HD-MTX, PCB, VCR, ARAC	None		53	9.5 31	6
Pulczynski 2015 [58] [2]	Phase II	27	70 (66–75)	RTX, HD-MTX, TMZ, IFOS, IV + IT ARAC, VIND	None	TMZ	69/58	14 NA	15
Schorb 2017 [59]	Retrospective	15	70 (66–75)	HD-MTX based CT	HDC-ASCT (BCNU-TT, Bu-TT + Cy, TT)	None	27/73	NA NA	4
Fritsch 2017 [60]	Phase II	107	73 (66–85)	HD-MTX, RTX, PCB + CCNU	None	PCB	35.5	10.3 20.7	8
Houillier 2017 [11]	Retrospective	90	68 (60–87)	RTX, HD-MTX, PCB, VCR	3 cycles ARAC	None	55	10 28.1	6
Faivre 2019 [61]	Retrospective	10	67 (61–76)	MTX, PCB, VCR ± RTX	None	TMZ [6]	60/80	57 63	0
Vu 2019 [62]	Retrospective	13	77 (70–86)	MTX, RTX ± TMZ	None	LNL (NR)	85	29.4 31.6	0
Schorb 2020 [24]	Pilot trial	14	74 (69–79)	RTX, HD-MTX, ARAC	HDC-ASCT (Bu-TT)	None	29/85	NA NA	0

In 1st line treatment, elderly patients are more often untreated or less vigorously treated than younger patients.

	Young	Old
CRR	50–70%	30-60%

PFS after CR: 28-35 mo vs. 8-16 mo

Morales-Martinez A. et al Cancers 2021

PCNSL – Elderly stratification

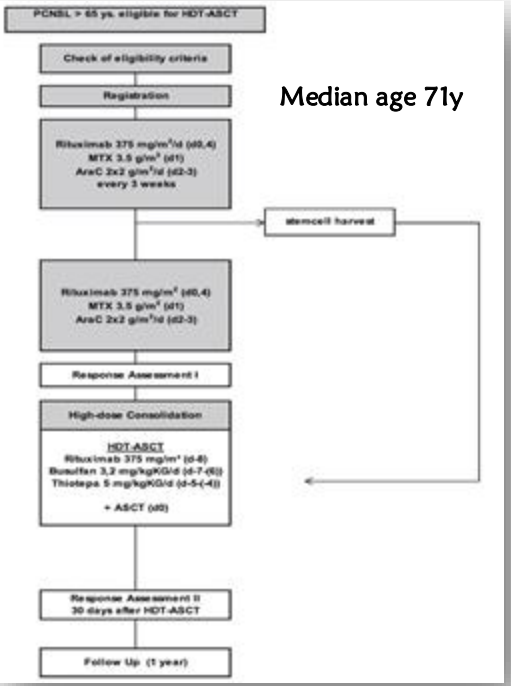
Chronological age, on its own, should not be a barrier for delivery of HD-MTX

- GFR>50 ml/min
- Adequate bone marrow reserve
- Preserved cardiac function
- Pre-morbid PS

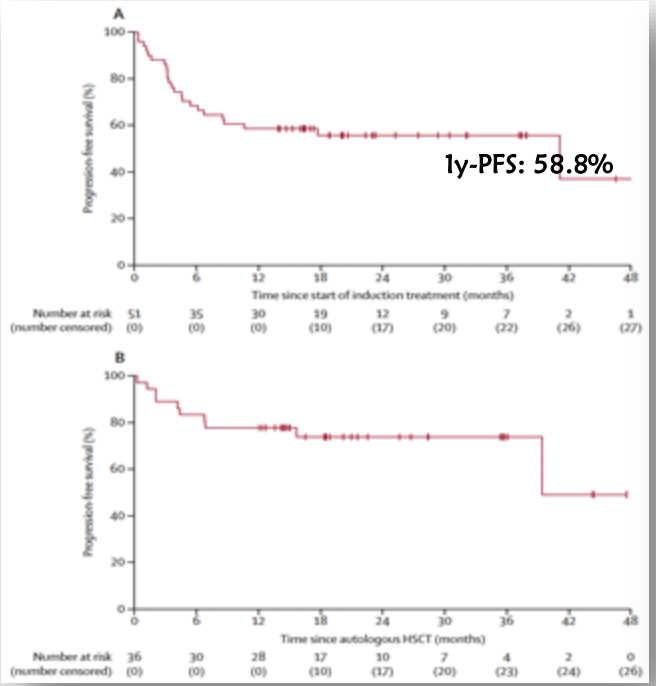
Eligible for intensive combination immuno-chemotherapy incorporating HDT-ASCT	Ineligible for HDT-ASCT, but eligible for HD-MTX-based immuno-chemotherapy	Ineligible for HD-MTX-based therapy: palliative treatment (a minority of patients)

Martinez-Calle N et al. Annals of Lymphoma 2021
Calimeri T et al .ESMO Open 2021

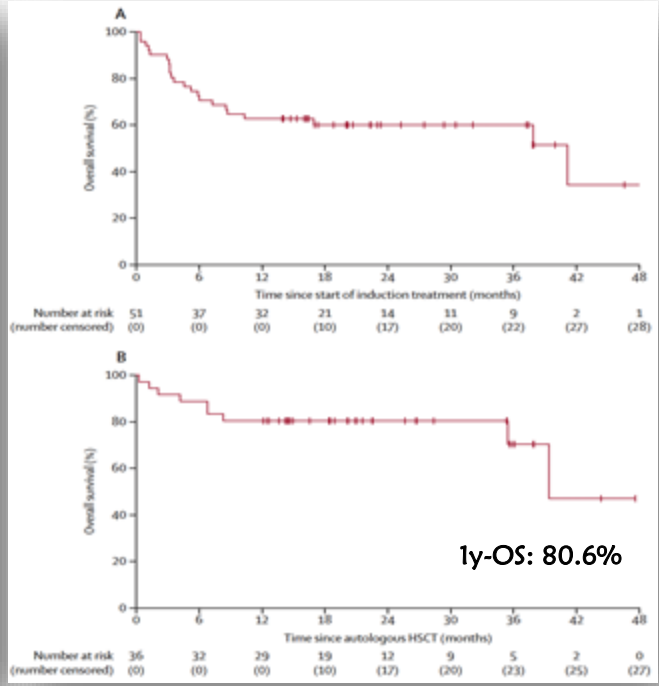
PCNSL – Elderly: what's new
MARTA trial



Median age 71y



1y-PFS: 58.8%



1y-OS: 80.6%

Schorb et al. BMC Cancer 2019

Schorb et al. Lancet Haematology 2024

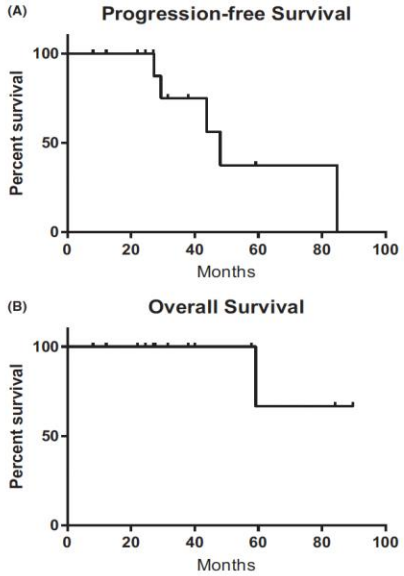
PCNSL – Elderly: what's new
Lenalidomide maintenance

- Lenalidomide was associated with long-lasting remission in 2 out of 6 highly pretreated pts with recurrent PCNSL and was well tolerated in elderly pts. Related phase II trial.

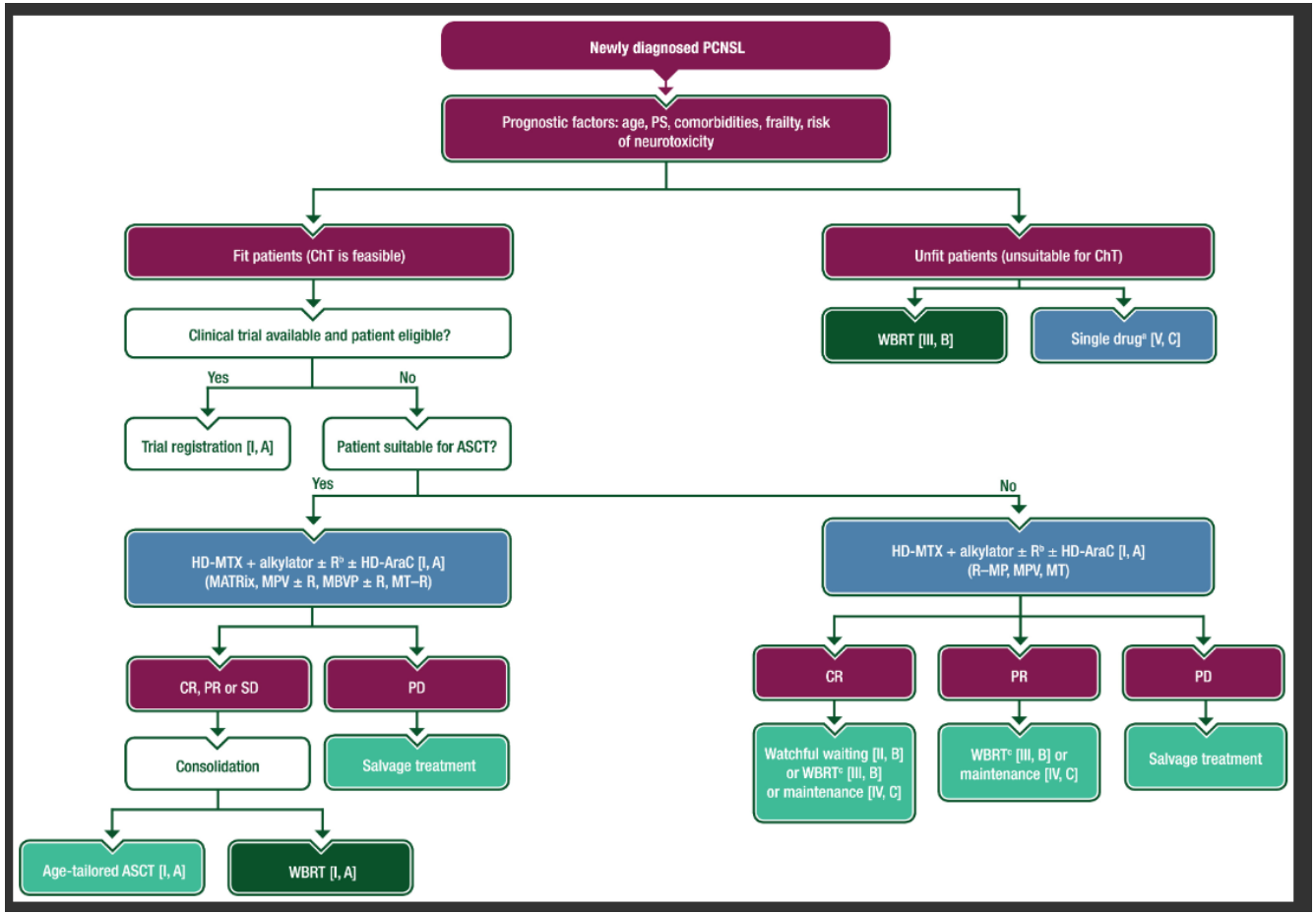
Houillier C, et al. Neurology 2015

- Lenalidomide (5-10 mg) maintenance was associated with durable response in 5/10 pts with rrPCNSL treated with after salvage therapy. Good lenalidomide penetration in ventricular CSF 2-15h after dosing at 20 mg.

Rubenstein JL et al. 13-ICML, 2015



Vu K et al. BJH 20219



Ferreri et al. Ann Oncol. 2024

PCNSL – Relapse/Refractory disease

- 15-25% non responder to first line induction HD-MTX based
- 25-50% relapse after consolidation

Prognosis: OS 2 months

unmet clinical need

PCNSL – Relapse/Refractory disease: ongoing trial

Table 2. Selected ongoing and currently recruiting clinical trials in relapsed/refractory primary central nervous system lymphoma

Study	Drug	Estimated enrolment	Primary endpoint	Preliminary data
NCT05209620 Phase II	Orelabrutinib + Pemetrexed	30	Objective response rate	
NCT04899427 Phase II	Orelabrutinib + Sintilimab or Tislelizumab	32	ORR after 4 cycles	ORR 61%, estimated 1-year PFS 67.7%
NCT04548648 Phase II	Acalabrutinib	16	ORR after 2 months on treatment	
NCT02315326 Phase I/II	Ibrutinib + HD-MTX or HD-MTX and Rituximab	109	MTD of Ibrutinib in combination with HD-MTX alone and Ibrutinib in combination with HD-MTX and Rituximab	ORR 80%, G3 neutropenia = 7%, G3 lung infection = 13%
NCT03770416Phase II	Nivolumab + Ibrutinib	40	ORR after 24 weeks on treatment	
NCT05117814Phase II	Zanubrutinib	20	ORR	
NCT05681195	Zanubrutinib + Pemetrexed	15	ORR	
NCT04947319 Phase II	Tirabrutinib	112	ORR, tirabrutinib dose estimate, incidence of AEs	
NCT04446962 Phase Ib/II	Lenalidomide + Ibrutinib + R-MPV	128	DLTs, CRR	
NCT04443829 Phase I	CD19 CAR-T cell	12	Toxicity (*n* of G3-5 AEs) and feasibility of manufacturing (*n* of products manufactured)	Five patients infused; G1 and G2 CRS reported in one and three patients, respectively; any grade ICANS reported in two patients
NCT04608487 Phase I	Axi-cel	18	Number of treatment-related AEs	Best ORR 78%, uCR/CR 67%; median DoR 11.3 mo; no cases of G4 ICANS
NCT03277729 Phase I/II	CD20 CAR-T cell	50	DLTs	
NCT03581942 Phase Ib/II	Copanlisib + Ibrutinib	45	ORR (phase II)	ORR 67%
NCT05131022 Phase Ia/Ib	NX-5948 (BTK Degrader)	130	Number of DLTs, MTD (phase Ia) ORR (phase Ib)	
NCT04830137 Phase Ia/Ib	NX-2127 (BTK Degrader)	160	Number of DLTs, MTD (phase Ia) ORR (phase Ib)	
NCT03328078 Phase I	Emavusertib	221	Number of DLTs, MTD, RP2D (Part A) CRR, ORR (Part B)	
NCT04401774 Phae II	Nivolumab maintenance (in patients with persistent ctDNA in the CSF)	25	Toxicity, cfDNA conversion rate in CSF	

Calimeri et. Al, Curr. Op. Onco 2023

PCNSL – Rel/Ref disease: Lenalidomide

Phase	Dose (mg/d)	N°	ORR	Median TTP (months)	Toxicity / Notes
Retro	25 mg (21 / 28 d)	6 rrPCNSL	3 / 6	NR	Expected
I	± Rituximab (MTD)	6 rrPCNSL 8 rrSCNSL	64%	7	Responses in brain, CSF & IOL
II	+ Rituximab (I: 20-25 mg) (M: 10 mg)	45 rrPCNSL rrPVRL	36%	7.8 4 PCNSL 9 PVRL	60% interruptons x PD/tox 42% dose reductions 11% completed treatment

Houllier et al. Neurology 2015;
Rubenstein et al. Blood Adv 2018;
Ghesquieres et al. Ann Oncol 2019

PCNSL – Rel/Ref disease: BTKi

Study	Dose (mg/d)	N°	ORR	CRR	Median TTP (months)	Tox
LYSA	560	29 rPCNSL 14 rVRL	70%	23%	4.8	5% ASP 10% Hemorr
MSKCC	560 840	13 rPCNSL 7 SCNSL	77%	38%	4.6	5% ASP
NCI	TEDDI 560 - 840	13 rPCNSL 5 PCNSL	94%	11%	15.3	39% ASP
MSKCC	R-MTX		80%		9.2	0% ASP
PROSPECT	**Tirabrutinib 480 mg**	**48**	**66.7%**	**43.8%**	**6.0**	

Soussain C et al. EJC 2019 - NCT02542514
Grommes C et al. Cancer Disc 2017 - NCT02315326
Lionakis et al. Cancer Cell 2017
Grommes C et al. Blood 2019
Nayak L et al. JCO 2025

PCNSL – Rel/Ref disease: what's new

R2 plus Ibrutinib

Trial	Pts # Age (range)	ORR	CR	PR	mPFS / mOS (months)	1y PFS / OS	Note
Houllier et al. Neurology 2021	14 63	9/14 (57%) m time to BR 2.5 months	4 (28%)	4 (28%)	-	-	Consolidation: 3 ASCT, 1 WBRT, 1 CART Tox 1 ASP, 3 disc
Perez et al. ASH 2023 (retro)	10 (5 PCNSL) 71 (57-85)	8/10 (80%) m time to BR 1.5 months	4/10 (40%)	4/10 (40%)	-	PCNSL 60% / 80%	-
Schaff et al. Neuro Oncol 2025	25 67 (41–85)	20/25 (80%) m time to BR 2 months	-	-	4.3 / NR	PFS 37%	Tox No ASP or G5

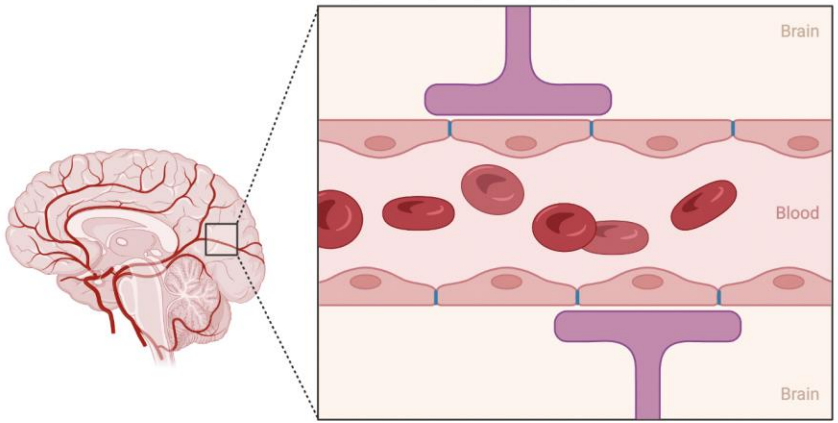
Nivolumab + Ibrutinib

Chihara et al. Blood Adv 2025	18 (16 PCNSL) 63 (43-88)	78%	50%	-	6.5 / 21	42%/ 63%	2 discont (fatigue)

Barriers of the CNS

Chemo efficacy is limited by several factors including the biology and microenvironment of this malignancy, which is “protected” by the BBB

The Blood Brain Barrier (BBB)

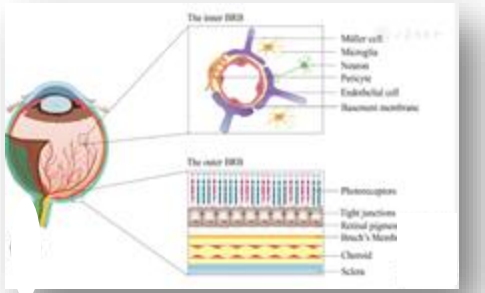


The core anatomical element of the BBB is the cerebral blood vessel formed by endothelial cells (ECs)

The BBB is a multicellular vascular structure that separates the CNS from the peripheral blood circulation

Obermeier B, Daneman R, Ransohoff RM. Nat Med. 2013

The Blood-Retinal Barrier



PCNSL – Rel/Ref disease: *INGIRID trial*

NGR-hTNF can locally enhance vascular permeability.

INGRID trial: **R-CHOP preceded by low doses of NGR-hTNF.**

28 enrolled patients

ORR - CR - PR	21 (75%) 11 (39%) 10 (36%)	95% CI: 64-86% 95% CI: 21-57%
PD	7 (25%)	

- 17/21 responder received consolidation (ASCT, WBRT, and/or lenalidomide maintenance).
- Response lasted more than 6 months in all complete responder (median 10 m; range 6-19).
- At a median follow-up of 52 months (ranfe 45-58), five pts remain relapse-free and six are alive.

PCNSL – Rel/Ref disease: what's new
ReWIP trial

25 enrolled patients
18 (72%) R-CHOP + Ibr; 7 (28%) Ibr monotherapy

Disease response (IPCG 2005 criteria)*	Treated patients n=25 (100%)
Overall Response Rate ORR)	**15 (60%)**
Complete Response (CR)	7 (28%)
Partial Response (PR)	8 (32%)
Stable Disease (SD)	3 (12%)
Progressive disease (PD)	4 (16%)
Not evaluable	3 (12%)

* International PCNSL Collaborative Group 2005 criteria

Study	N° of patients	Treatment	ORR %	CR %	PR %
Soussain et al. [1]	38	IBR monotherapy	37%	21%	16 %
Grommes et al.[2]	15	IBR-Rituximab-HDMTX	80%	53%	27%
Lionakis et al.[3]	18	Da-TEDDi-R	94 %	67%	23%

Treatment group	N° of patients	ORR %	CR %	PR %
I-RCHOP	18	67%	39%	28%
IBR single agent	7	43%	0%	43%

Responders:

- 40% addressed to consolidation and/or maintenance
- 40% progressed after initial disease response → all treated with I-RCHOP (median 3 cycles)

Calimeri et al, ASH 2022

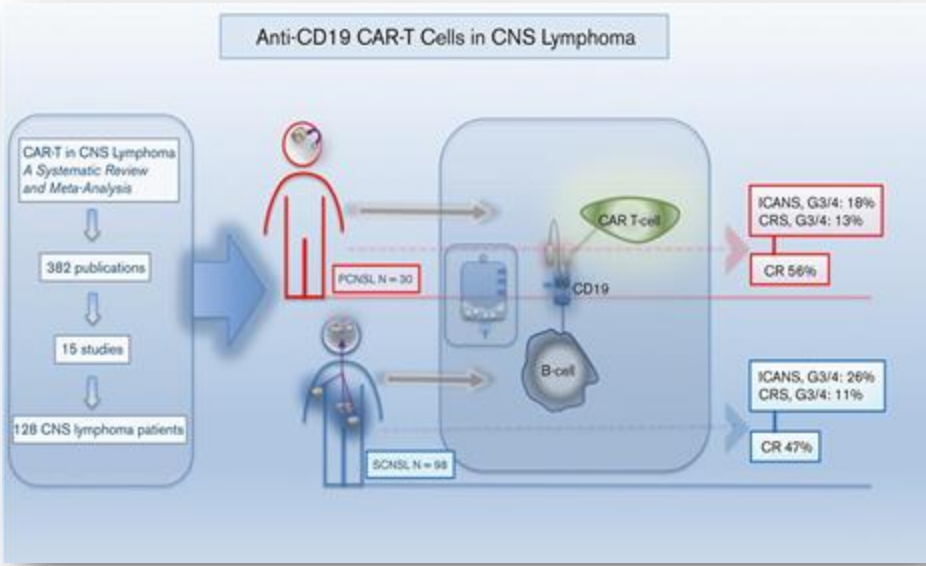
PCNSL – Rel/Ref disease: what's new
CAR-T cell

PCNSL patients often excluded form registrational CART cell studies
Challenges:

- Higher risk of ICANS?
- Less CAR T cells peripheral expansion?
- Enough traffic of expanded CART through the BBD?

In a **large meta-analysis** (15 trials encompassing 128 patients with CNSL were included) of CNS lymphomas, **toxicity of anti-CD19–CAR T-cell therapy was similar to that of registrational studies in systemic LBCL** with no increased signal of neurotoxicity observed

Cook et al. Blood Adv. 2023



Of the patients with PCNSL, 56% achieved a complete remission (CR) with 37% remaining in remission at 6 months. Similarly, 47% of patients with SCNSL had a CR, with 37% in remission at 6 months

PCNSL – Rel/Ref disease: what's new

CAR-T cell

Trial	Pts #	ORR	CR	other	mPFS / mOS (months)	1y PFS / OS	Note
Siddiqi et al.	5	3 (60%)	3 (60%)	SD 2 (40%)	ICANS G3: 1	-	phase I, novel CAR construct
Frigault et al. Blood 2022	12	7 (58%)	6 (50%)	PR 1 (8%)	ICANS G3: 1	25%	All tisa-cell
Alcantara et al. Blood 2022	9	6 (66%)	5 (55%)	PR 1 (11%)	CRS G3: 1 ICANS G3: 2	6-m: 44% / 89%	axi-cel: 2 tisa-cel: 7
Choquet et al. Hamatol. 2024	25	20 (80%)	16 (64%)	PR 4 (16%) PD 5 (20%)	CRS: 23 ICANS: 17 (68%) G3: 5	46% / 55%	axi-cel: 9 tisa-cel: 16
Mercadal et al. Haematol. 2025	24	14 (61%) at d100	11 (48%)	PR 3 (13%)	CRS 16, no G3 ICANS: 8, G3: 2	2-y: 28% / 50%	axi-cel: 3 tisa-cel: 21

PCNSL – Rel/Ref disease: what's new *CAR-T cell*

Real life LOC experience

CAR-T cells from the third line

- 27 patients (ASCT in 14/27) had LK,
- 25 received CAR T-cells (tisa-cel: *N* = 16, axi-cel: *N* = 9)

All but one received a bridging therapy

mFU after LK **20.8 months**

Efficacy

- **CR in 16 (64%), PR in 4 (16%), PD in 5 (20%)**
- **1-y PFS 43%**
- **1-y RFS 79%** for pts in CR/PR at infusion
- mOS 21.2 months

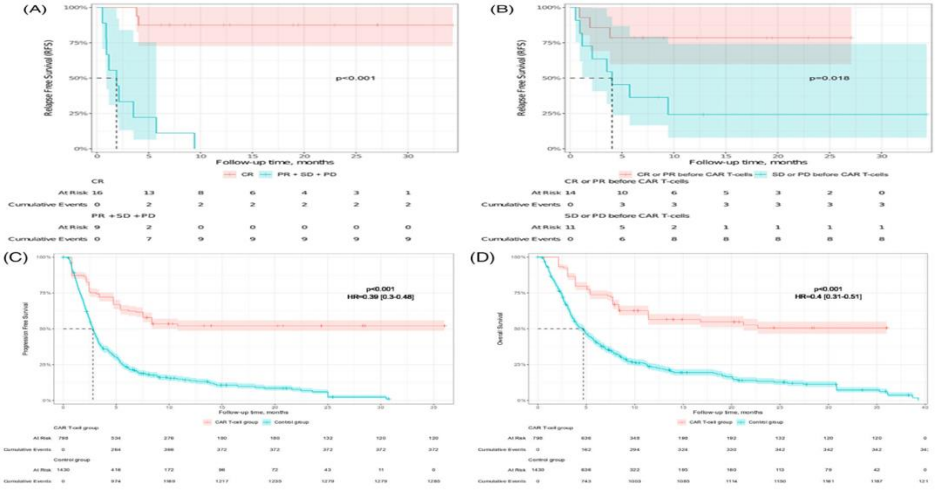
Toxcity

- CRS occured in 23 pts
- ICANS occured in 17 (68%), 5 were grade ≥3

Historicall control group (*N* = 247)

- mPFS: 3 months
- mOS: 4.7 months

Response	CR	PR	PD
At 1 month	8 (32%)	11 (44%)	6 (24%)[a]
At 3 months	14 (56%)	3 (12%)	8 (32%)
Best response	16 (64%)	4 (16%)	5 (20%)[a]
Best response in each CNS compartment			
Brain	12 (60%)	4 (20%)	4 (20%)
CSF	7 (87%)	0	1 (13%)
Eye	2 (67%)	0	1 (33%)
Best response according to the type of CAR T-cells			
Axi-cel	8 (89%)	1 (11%)	0 (0%)
Tisa-cel	8 (50%)	3 (19%)	5 (31%)
Best response according to the disease status at CAR T-cell injection			
CR or PR	12 (86%)	1 (7%)	1 (7%)
SD or PD	4 (36%)	3 (27%)	4 (36%)



Choquet et al. Hematology 2024

PCNSL – Rel/Ref disease: what's new *CAR-T cell*

CIBMTR registry analysis

- 23 patients

Only 5 (21%) received a bridging therapy

mFU after infusion **26 months**

Efficacy

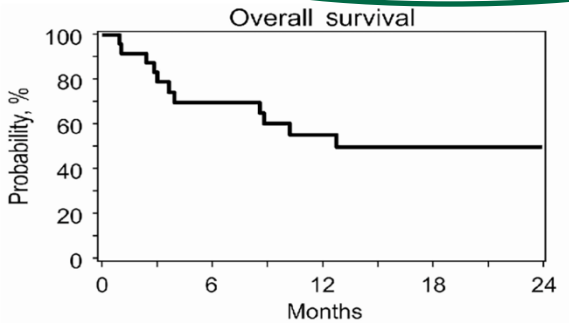
- ORR 14 (61%)
- **CR in 11 (48%), PR in 3 (13%), PD in 5 (20%)**
- 1y PFS 48% > **2y PFS 28%**
- 1y OS 55% > **2y OS 50%**
- **Relapse/PD 72%**

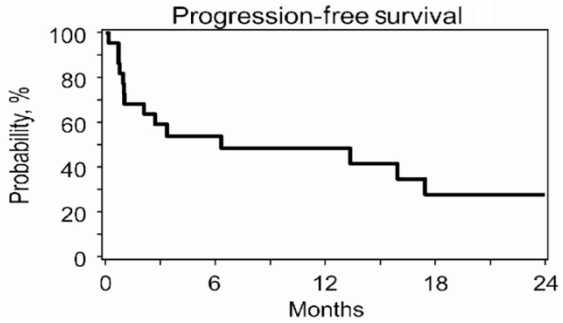
Toxcity

- CRS occured in 16 pts, no G≥3
- ICANS occured in 5, 2 were grade ≥3

Baseline characteristics	Patients N=24
N of centers	12
Age at CAR T infusion in years, median (min-max)	57 (25-81)
Age at CAR T infusion in years, N (%)	
18-64	18 (75)
≥65	6 (25)
Male sex, N (%)	16 (67)
Recipient race, N (%)	
White	20 (83)
African-American	1 (4)
Asian	0 (<1)
Not reported	3 (13)
Recipient ethnicity, N (%)	
Hispanic or Latino	2 (8)
Non-Hispanic or non-Latino	17 (71)
Unknown/not reported	5 (21)
Karnofsky performance score prior to CAR T, N (%)	
90-100	11 (46)
<90	10 (42)
Not reported	3 (13)
HCT-CI, N (%)	
≥3	5 (21)
Site of CNS involvement, N (%)	
Parenchymal involvement	12 (50)
CSF/leptomeningeal involvement	1 (4)
Parenchymal and CSF/leptomeningeal involvement	3 (13)
Not reported	8 (33)
Disease status prior to CAR T infusion (%)	
Complete remission	3 (13)
Not complete remission/active disease	21 (88)

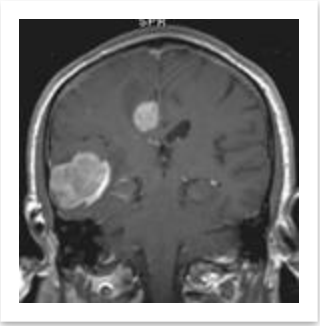
Baseline characteristics	Patients N=24
Primary refractory disease, N (%)	
No	7 (29)
Yes	9 (38)
Not reported	8 (33)
Elevated LDH prior to infusion, N (%)	
No	2 (8)
Yes	0 (<1)
Not reported	22 (92)
Bridging therapy, N (%)	
Yes	5 (21)
Single agent chemotherapy	3 (13)
Monoclonal antibodies	1 (4)
BTKi/IMID	1 (4)
No	15 (63)
Not reported	4 (17)
N of lines of prior therapies, median (min-max)	4 (1-10)
Time from initial diagnosis to CAR T in months, median (min-max)	36 (10-120)
Types of prior HCT, N (%)	
Prior auto-HCT	12 (50)
CAR T product, N (%)	
Tisagenlecleucel	21 (88)
Axicabtagene ciloleucel	3 (13)
Year of CAR T, N (%)	
2019	6 (25)
2020	10 (42)
2021	7 (29)
2022	1 (4)

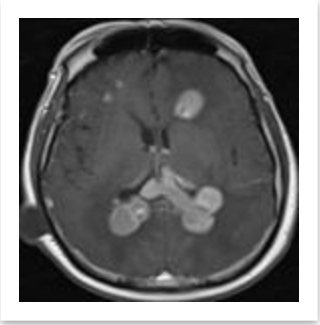




Mercadal et al. Haematologica 2025

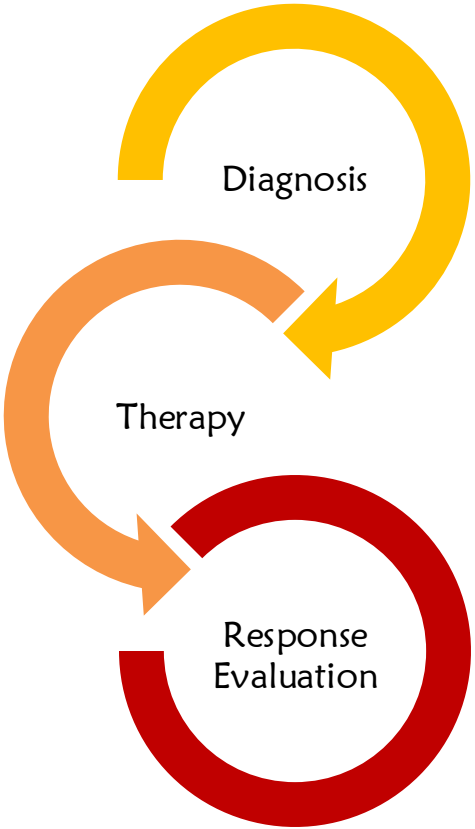
PCNSL Conclusions

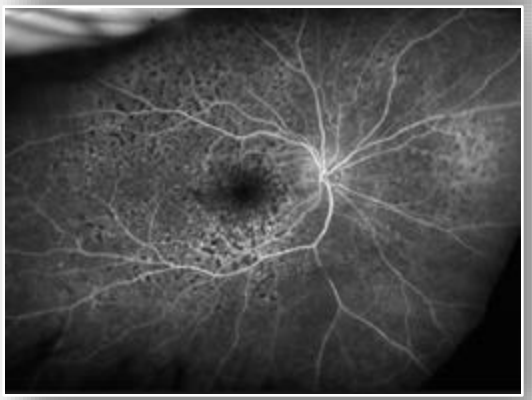




- Early diagnosis is the best treatment: time is brain!
- Treatment based on DUAL strategy: HD-MTX (rapid infusion!) based induction and TT based HDC-ASCT consolidation
- Important unmet medical need: rel/ref disease (BTKi, CART), elderly (personalized strategy)
- In the near future, more sensitive and promising tools will hopefully be implemented and harmonised in the diagnostic, response, and disease monitoring work flows

Primary Vitreoretinal Lymphoma



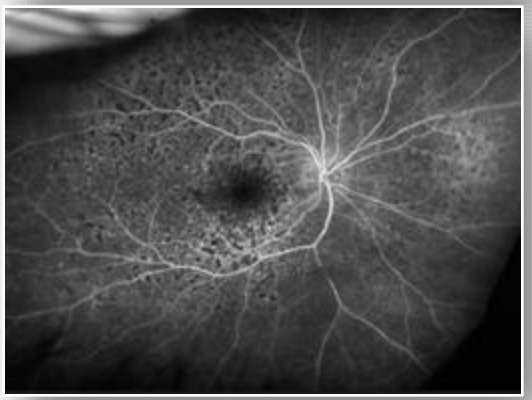


Images courtesy of PROF. Elisabetta Miserocchi
(Ophthalmology Unit,
IRCCS San Raffaele Scientific Institute, Milan, Italy)

PVRL Diagnosis

Gold standard:
cytological *identification of lymphomatous cells in the eye*

Because of the difficulties of sampling, the ***sensitivity*** *of cytology alone in diagnosing PVRL* ***is low (45% to 60%)****.*



Images courtesy of PROF. Elisabetta Miserocchi
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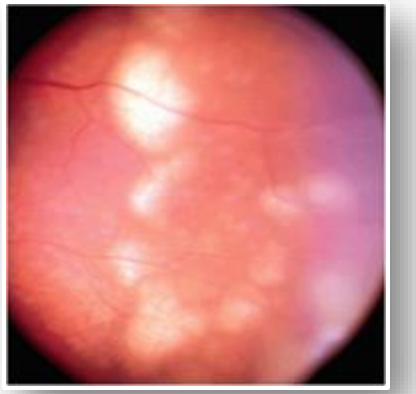
PVRL Diagnosis: what's new

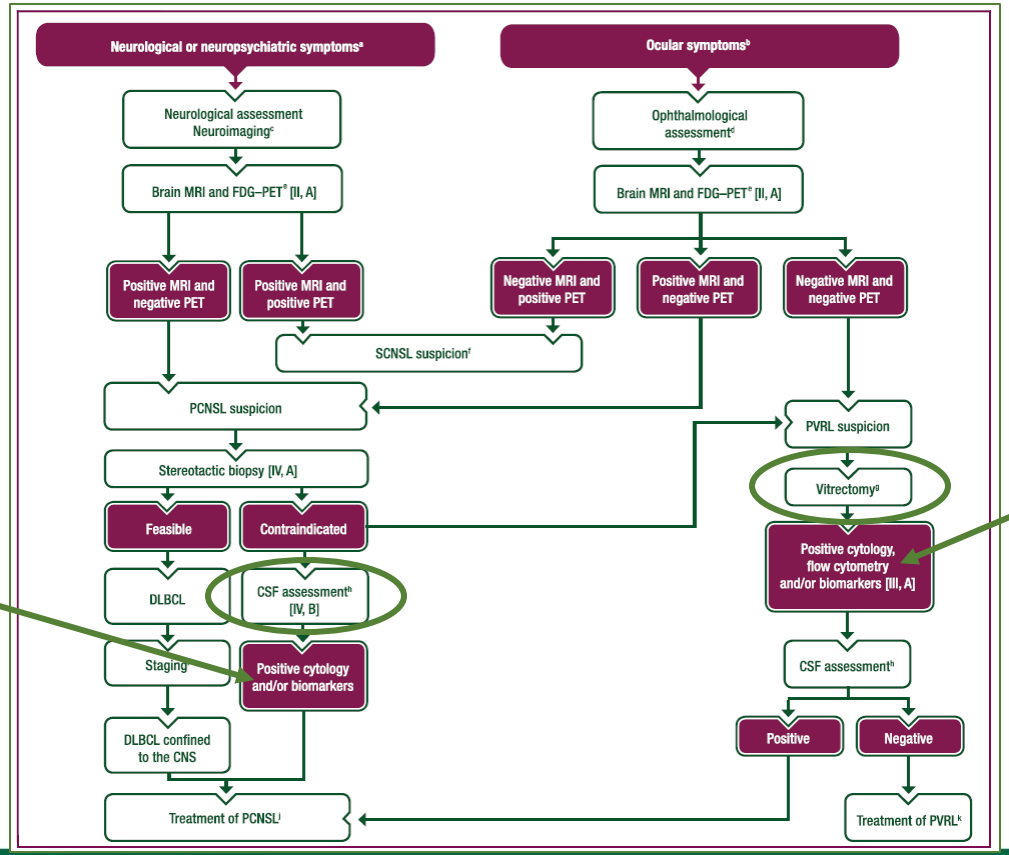


Images courtesy of DR. Giulio Modorati (Ophthalmology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy)

- Validated biomarkers in CSF samples (**i.e., $MYD88^{L265P}$ and high IL-10 levels**) may support a diagnosis of PCNSL in patients where brain biopsy is contraindicated [IV, B]

- **$MYD88^{L265P}$ mutation and IL-10 levels** may be assessed in the vitreous and aqueous humours as indicators of ocular lymphoma [III, A]

PVRL Diagnosis: what's new



Ferreri et al. Ann Oncol. 2024

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE · EHA EUROPEAN HEMATOLOGY ASSOCIATION · ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Primary central nervous system lymphomas: EHA–ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

A. J. M. Ferreri[1,2†], G. Illerhaus[3†], J. K. Doorduijn[4†], D. P. Auer[5,6], J. E. C. Bromberg[7], T. Calimeri[8], K. Cwynarski[9], C. P. Fox[9], K. Hoang-Xuan[10], D. Malaise[11,12], M. Ponzoni[1,2,13], E. Schorb[14], C. Soussain[15,16], L. Specht[17], E. Zucca[18,19,20], C. Buske[21], M. Jerkeman[22] & M. Dreyling[23], on behalf of the EHA and ESMO Guidelines Committees*

Volume 35 - Issue 6 - 2024

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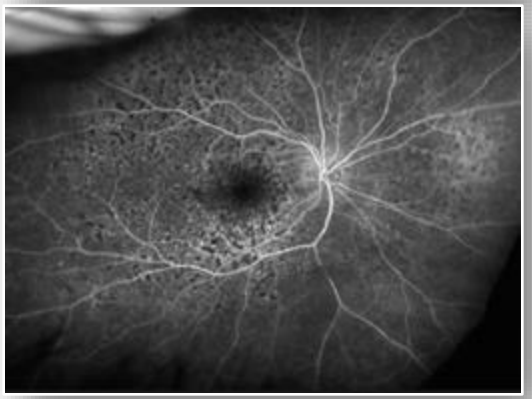
PVRL Treatment

Therapy

Unmet Clinical Need:
Standard Treatment



Images courtesy of PROF. Elisabetta Miserocchi
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PVRL Treatment

The goals of the treatment of PVRL are to control intraocular disease and to prevent CNS dissemination

Local therapies

(e.g. using intravitreal (IVT), MTX or RTX, and/or
binocular external beam radiation)

Systemic chemotherapy

IVT or RTare effective at clearing tumor cells within the eyes but does not prevent CNS relapse.

Systemic treatment based on high-dose methotrexate chemotherapy, with or without local treatment, might reduce this risk.

Soussain C et al. Blood. 2021

Primary Vitreoretinal Lymphoma: what's new

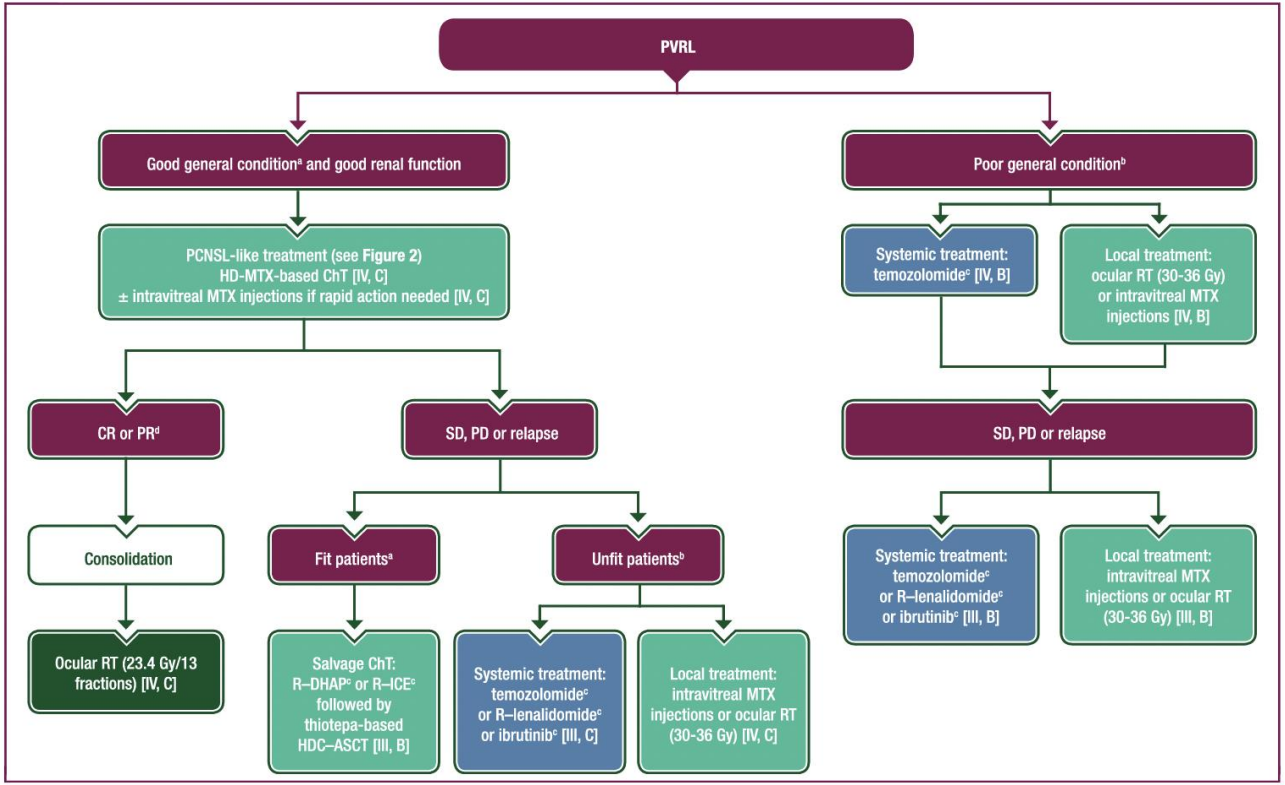

Figure 3. Treatment algorithm for PVRL.

The 2024 ESMO guidelines for PVRL provide recommendations with evidence levels IV-C or III-B

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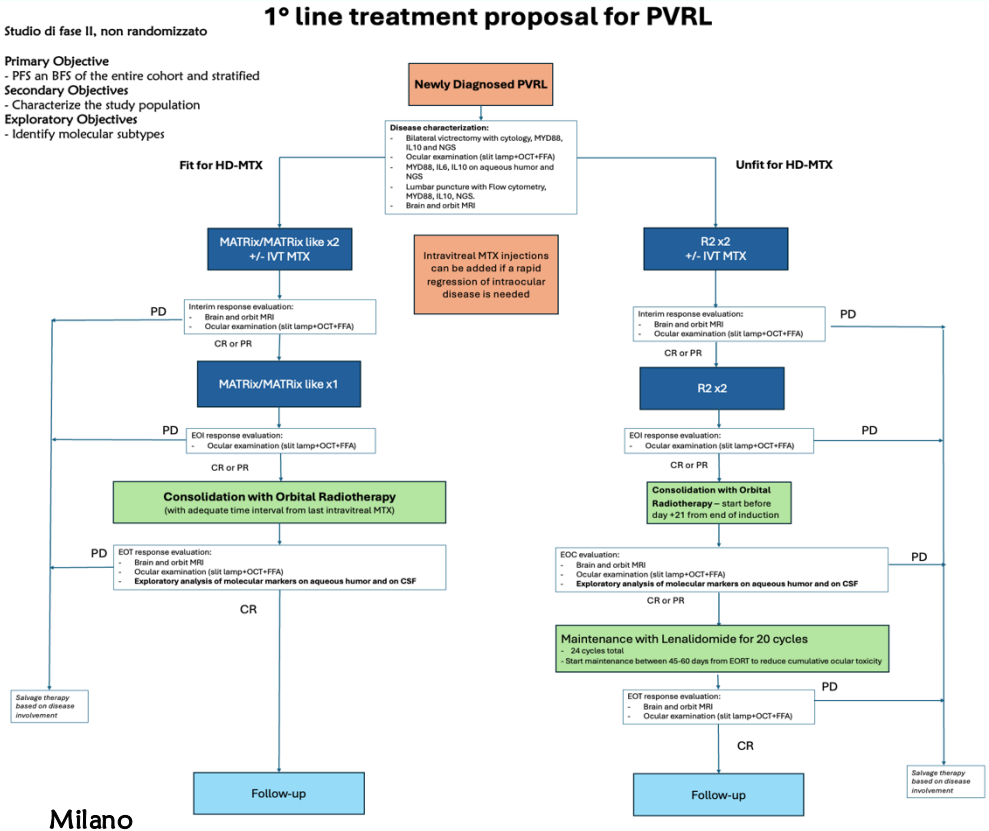
PVRL Conclusions

- PVRL is rare disease and much of the current state of knowledge is actually inferred from the investigation of more frequent PCNSL
- International and multidisciplinary efforts are needed in order to contribute to solve the pressing dilemma of *who is who* in PVRL
- Systemic treatment is required to reduce the risk of brain relapse



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SSD di Immunologia Oculare dell'AUSL-IRCCS di Reggio Emilia.

Acknowledgments

Lymphoma Unit OSR

Andrés J.M. Ferreri

Teresa Calimeri

Piera Angelillo

Giulio Cassanello

Federico Erbella

Elena Flospergher

Fabrizio Marino

Luca Saliani

Giuseppina D'Elia

Vincenzo Mercurio

& UL Trial Office

UOETMO

Fabio Ciceri

Andrea Assanelli

Massimo Bernardi

MT Lupo Stanghellini

Sarah Marktel

All Phycian and Residents

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UMG Catanzaro (IT)

KIT (Karlsruhe, DE)

Maria Francesca Spadea

Paolo Zaffino

POLIMI (Milano)

Elena De Momi

UNICAL (Cosenza)

Francesco Calimeri

Aldo Marzullo

Thank you

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