



# Incontro sui PSDTA del gruppo linfomi Rete Oncologica Piemonte e Valle d'Aosta



TORINO  
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AULA LENTI  
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## Linfoma Cerebrale

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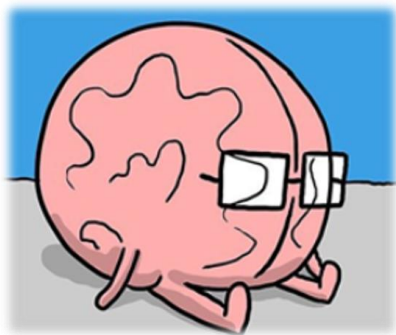


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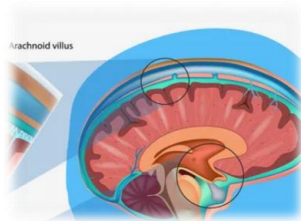


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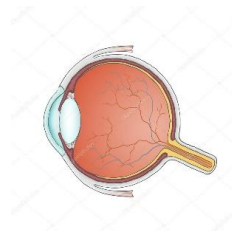
# Primary Central Nervous System Lymphoma (PCNSL)



Brain Parenchima  
(100%)



Leptomeninges  
CSF (~15%)



Eyes  
(15-25%)



Spinal cord  
(<1%)

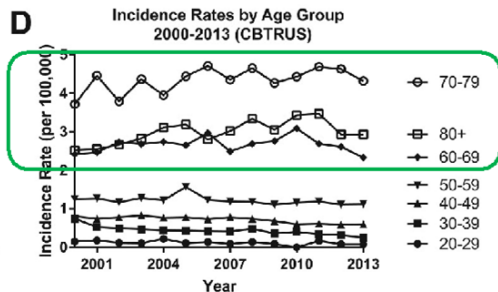
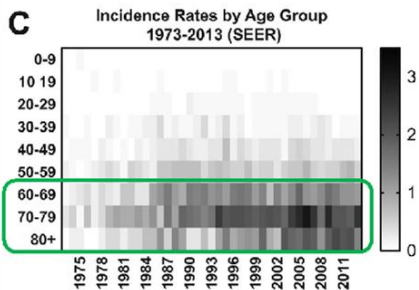
1-2% of brain tumors

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



**Table 1** Basic patient characteristics

	SEER 1973–2013	CBTRUS 2000–2013
	Patients	Patients
	N (%)	N (%)
<b>All Patients</b>	6765 (100)	19027 (100)
<b>Age at Diagnosis, y</b>		
0–9	27 (0.4)	52 (0.3)
10–19	76 (1.1)	137 (0.7)
20–29	172 (2.5)	484 (2.5)
30–39	401 (5.9)	1233 (6.5)
40–49	695 (10.3)	2181 (11.5)
50–59	1136 (16.8)	3190 (16.8)
60–69	1745 (25.8)	4617 (24.3)
70–79	1761 (26)	4903 (25.8)
80+	752 (11.1)	2230 (11.7)
<b>Sex</b>		
Male	3583 (53)	10112 (53.1)
Female	3182 (47)	8915 (46.9)

The median age of presentation has generally been reported at around 60 years although recent real-world data suggests this may be higher

**Table 1** Main patient characteristics at diagnosis

	Median (range) or n/N (%)
<b>No.</b>	1,002
<b>Age, y</b>	68 (18–91) ←
18–60	285/1,002 (28)
60–70	290/1,002 (29)
70–80	307/1,002 (31)
80–90	116/1,002 (12)
>90 y	4/1,002 (0.4)
<b>Sex ratio, M/F</b>	1.1

# PCNSL Epidemiology

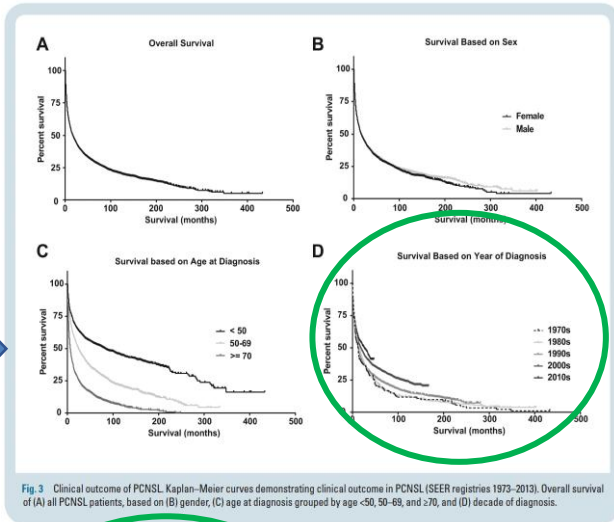
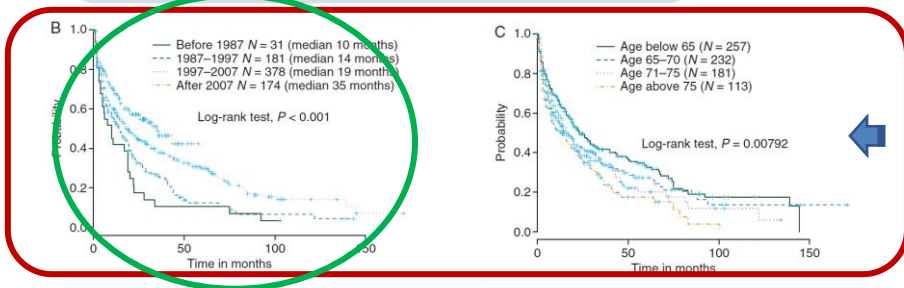


Fig 3 Clinical outcome of PCNSL Kaplan-Meier curves demonstrating clinical outcome in PCNSL (SEER registries 1973–2013). Overall survival of (A) all PCNSL patients, based on (B) gender, (C) age at diagnosis grouped by age <50, 50–69, and ≥70, and (D) decade of diagnosis.

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

## Gestione PCNSL: multidisciplinare

Neurologo-neuro-oncologo

Neurochirurgo

Neuroradiologo

Oculista

Medico Nucleare

Patologo

Ematologo

Radioterapisti

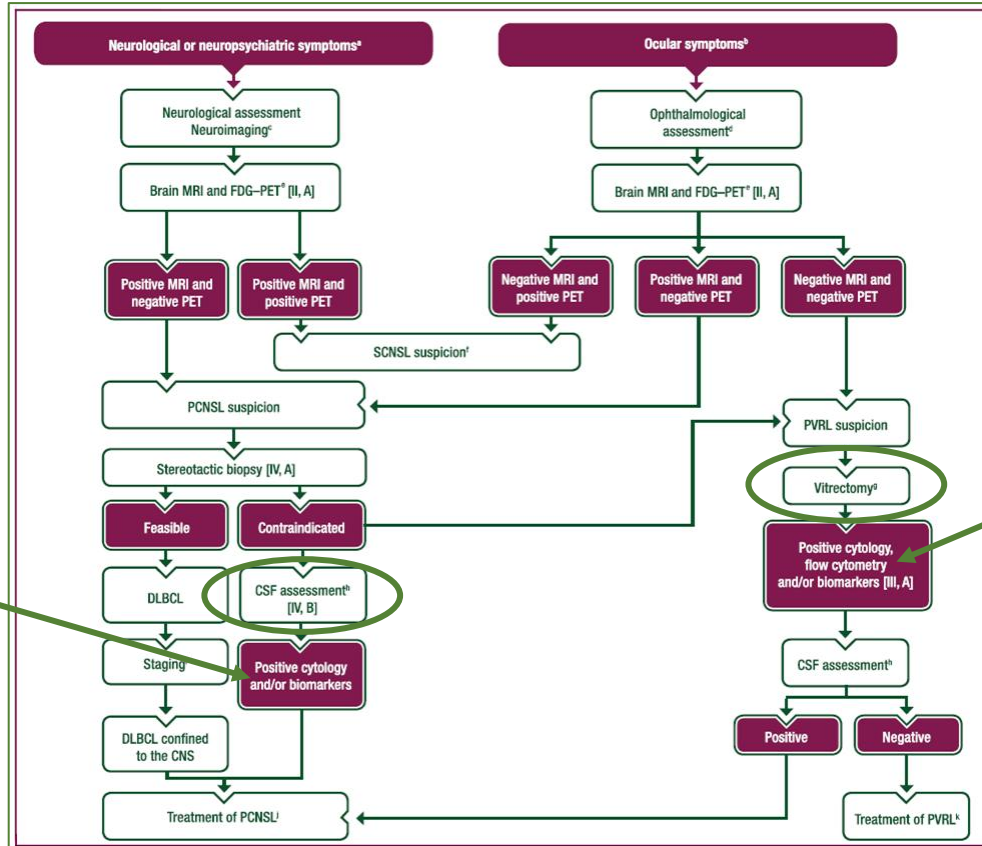
Psicologi

Fisiatri/Fisioterapisti

## Esami per diagnosi e stadiazione da PSDTA

- ❖ Biopsia diagnostica stereotassica
- ❖ RM encefalo (+ RM colonna se sintomi)
- ❖ rachicentesi consigliata (se fattibile) (con ricerca MYD88 se disponibile)
- ❖ visita oculistica con lampada a fessura
- ❖ ecografia testicolare se uomo > 60 anni

# Diagnostic algorithm for PCNSL in immunocompetent patients



Ferreri et al. Ann Oncol. 2024



SPECIAL ARTICLE

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

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

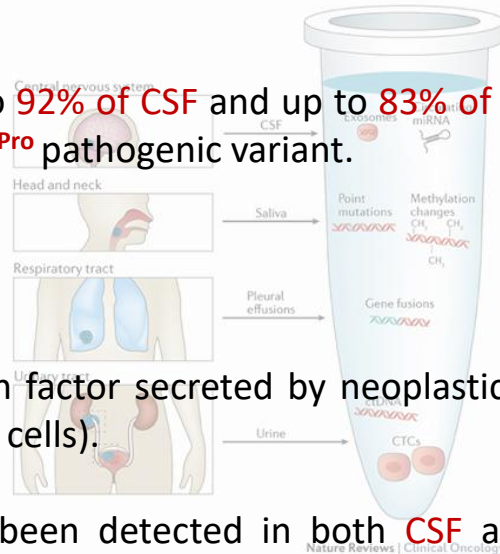
Volume 35 – Issue 6 – 2024



### **MYD88 L265P pathogenic variant:**

✓ *MYD88* is the most commonly mutated gene in PCNSL and other lymphomas of the immune-privileged sites.

✓ It has been found that up to **92% of CSF** and up to **83% of ocular fluids** from patients with PCNSL carry the ***MYD88 p.Leu265Pro*** pathogenic variant.



### **IL-10 levels:**

✓ IL-10 is an autocrine growth factor secreted by neoplastic large B lymphocytes (receptor expressed by PCNSL neoplastic cells).

✓ **High levels** of IL-10 have been detected in both **CSF** and **ocular fluids**, and they are statistically significantly higher in patients with PCNSL than in non-neoplastic controls.

**Table 2.** Overview of the novel diagnostic approaches.

Biomarker/Method.	Number of Patients	Body Fluid	Sensitivity (%)	Specificity (%)	References
FLC concentrations/ratios	21	CSF	52.3	-	Schroers et al. [16]
IL-10 (cut-off 9.5 pg/mL)	66	CSF	71	100	Sasayama et al. [17]
IL-10 (cut-off 4 pg/mL)	119	CSF	88.6	88.9	Nguyen-Them et al. [18]
IL-10 (cut-off 8.2 pg/mL)	102	CSF	95.5	96.1	Song et al. [19]
IL-10 (cut-off 8.3 pg/mL)	108	CSF	59	98	Shao et al. [20]
IL-10/IL-6 ratio (cut-off 1.6 pg/mL)	108	CSF	66	91	Shao et al. [20]
IL-10/IL-6 ratio (cut-off 0,72 pg/mL)	102	CSF	95.5	100	Song et al. [19]
IgH gene rearrangement	32	CSF	54	97	Eckstein et al. [21]
CXCL13	220	CSF	69.9	92.7	Rubenstein et al. [22]
Combination of CXCL13 and IL-10	77	CSF	76.7	90.9	Mabray et al. [23]
MYD88	225	CSF	72	-	Ferreri et al. [24]
Combination of MYD88 and IL-10	225	CSF	94	98	Ferreri et al. [24]
MYD88	90	vitreous	69	100	Bonzheim et al. [25]
microRNA (miR-21, -19b, and -92)	53	CSF	95.7	96.7	Baraniskin et al. [26]
microRNA (miR-21, -19b, and -92)	53	CSF	63.3	80.7	Zajdel et al. [27]
Combination of RNU2-1f and miR-21	119	CSF	91.7	95.7	Baraniskin et al. [28]
miR-222	150	serum	80	82	Thapa et al. [29]

Several independent studies have shown that *MYD88*<sup>p.Leu265Pro</sup> and IL-10 concentrations can distinguish PCNSL with high sensitivity and specificity from other neurological (neoplastic and non-neoplastic) disorders

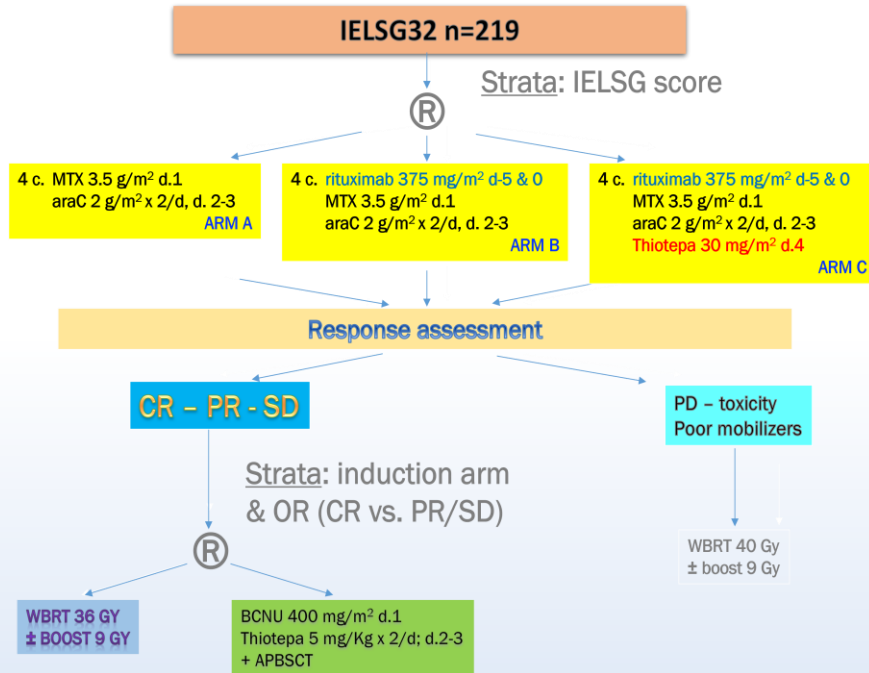
Baraniskin A. and Roland Schroers R.  
Cancers 2021

	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%	0.95 (0.91 - 1.00)

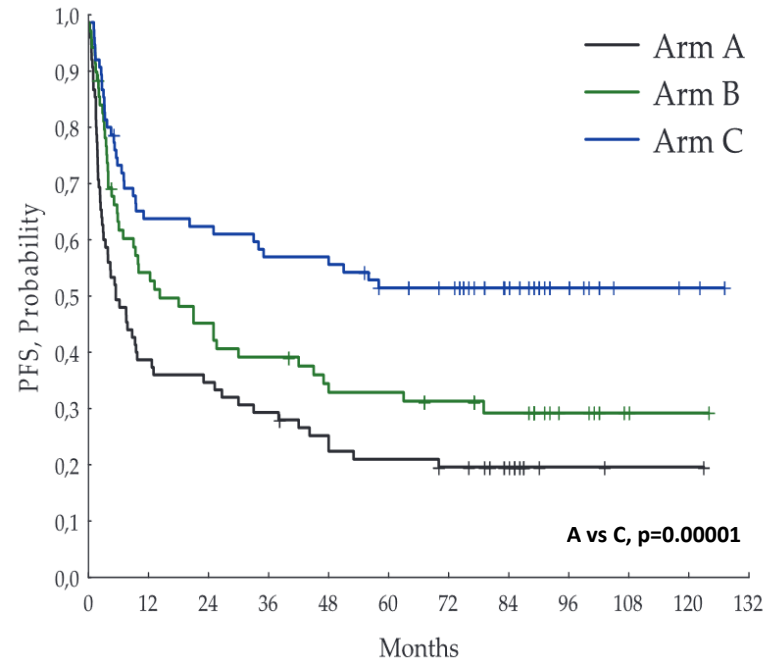
Ferreri A.J.M. et al. British Journal of Haematology 2021

# IELSG32: Addition of (cytarabine) thiotepa and rituximab (MATRix) induction is associated with improved outcome

**Eligibility:**  
**< 65 yrs & PS  $\leq$  3 OR < 70 yrs & PS  $\leq$  2**



Median follow up: 88 months (IQR 77-99)



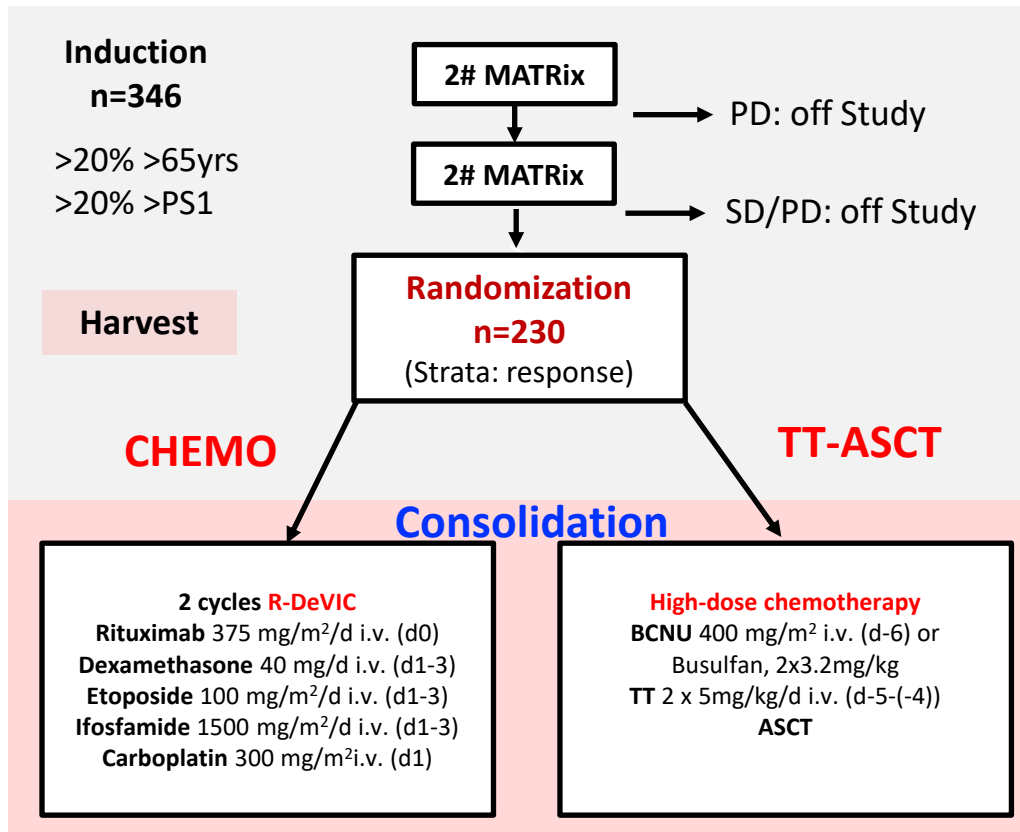
# Terapia di I linea PSDTA

Pazienti FIT < 70 anni:

1) MATRIX (R-HDMTX + R-HDARAC + Thiotepa) x 4 cicli + consolidamento con ASCT (condizionamento TT-BCNU) o RT (nei pz poor mobilizers o se tossicità durante induzione) (23,4 Gy se risposta completa dopo MATRIX, 30-36 Gy se risposta parziale ed eventuali 45 Gy su residuo) (whole brain + prime 2 vertebre cervicali + 2/3 posteriori dell'orbita)

2) Inserimento in protocolli clinici

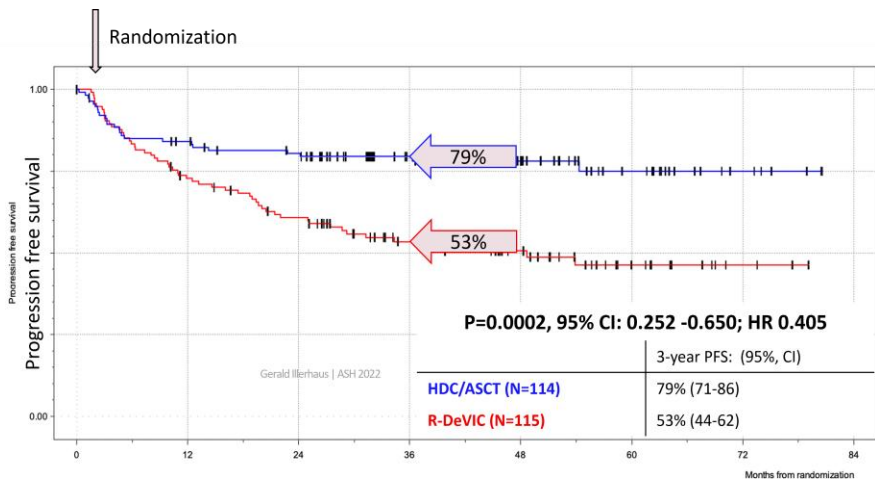
# Optimal Consolidation? MATRix/IELSG43 <70yrs



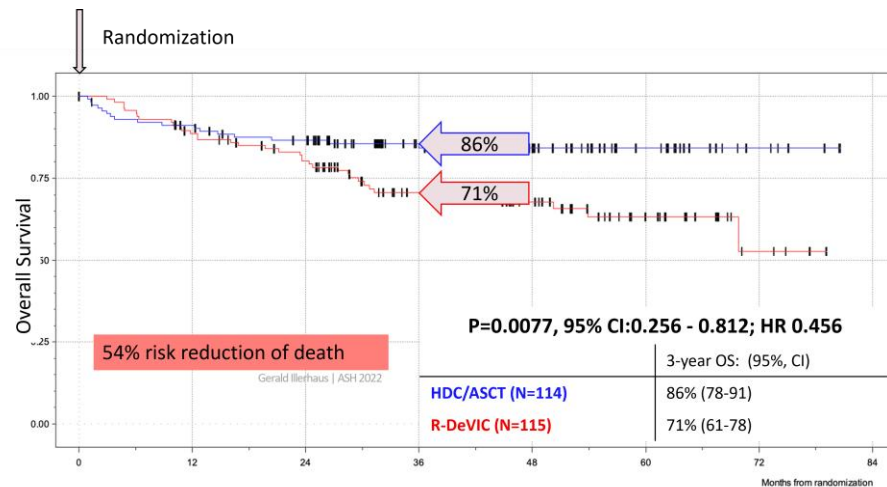
Median follow-up: 45 months (0.2-86)

# Superior PFS and OS (ITT) after BCNU-TT ASCT Despite Similar Response Rates

## Progression Free Survival



## Overall Survival



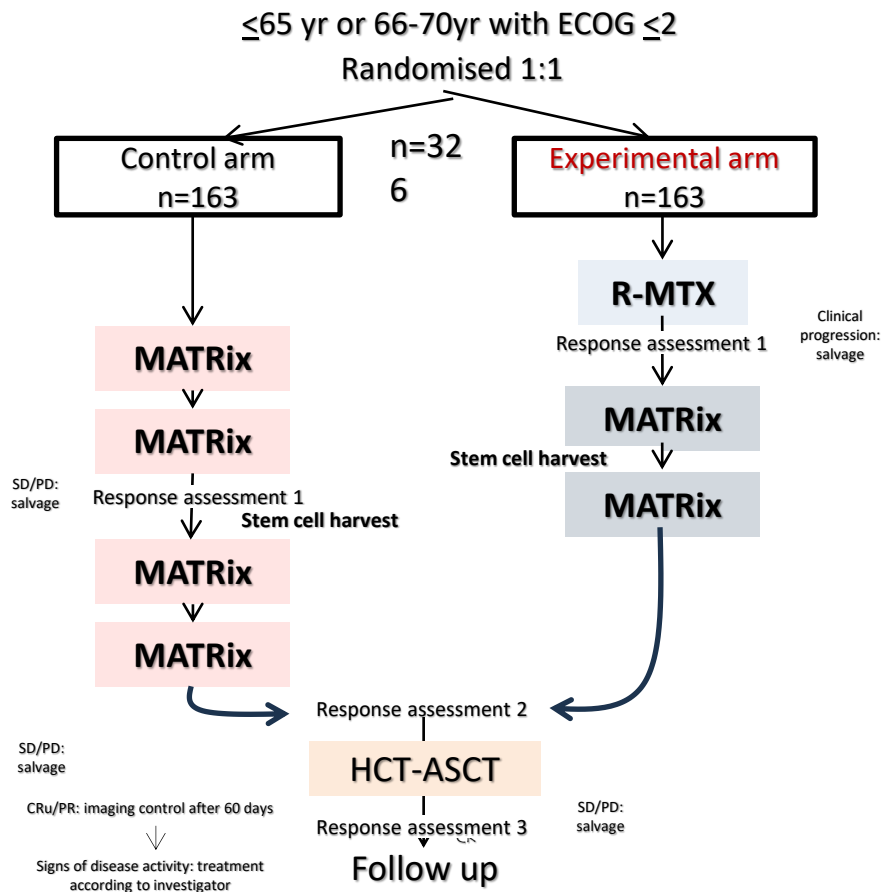
# OptiMATE

## Optimizing MATRix as induction in newly diagnosed PCNSL:

Randomized phase III trial  
De-escalated induction treatment

Multicentre international trial:  
Germany, Austria, Italy, UK

**Primary Objective:** 2yr EFS (superiority)



# Terapia di I linea PSDTA

Pazienti FIT > 70 anni:

1) R-Metotrexate ad alte dosi (1.5-3 g/mq in base a fitness e funzionalità renale) + AraC o + vincristina/procarbazine (MPV) x 4 cicli + eventuale mantenimento con alchilanti orali (temozolamide o procarbazine) + se localizzazione meningea e MTX < 3 g/mq eseguire MTX-AraC IT, nei casi di RC o RP possibile consolidamento con RT 23,4 Gy

2) Inserimento in protocolli clinici

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

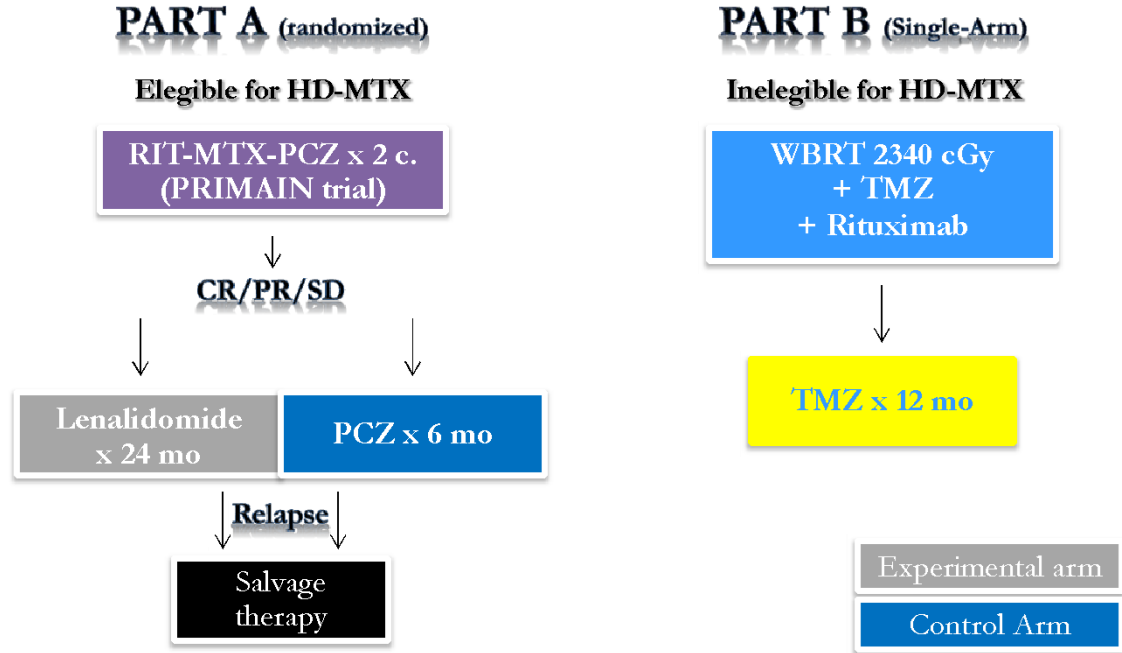
Author	Type	N	Median Age (Range)	Induction	Consolidation	Maintenance	CR % I/M or C 1	PFS OS mo	Toxic Deaths %
Hoang-Xuan 2003 [9]	Phase II	50	72 (60-81)	HD-MTX IV + IT, IT ARAC, CCNU, PCB	None	HD-MTX IV + IT, IT ARAC, CCNU, PCB	42	7 14.3	4
Omuro 2007 [53]	Retrospective	23	68 (60-79)	HD-MTX, TMZ	None	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
			72 (60-84)	HD-MTX, PCB, VCR, ARAC			53	9.5 31	
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 1<sup>st</sup> line treatment, elderly patients are more often untreated or less vigorously treated than younger patients.

Morales-Martinez A. et al Cancers 2021

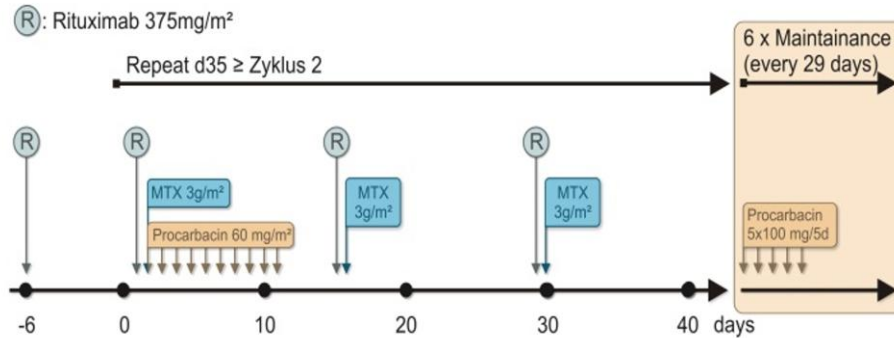
# FIGRELLA Trial

PCNSL age  $\geq 70$  yo  
ECOG-PS  $\leq 3$

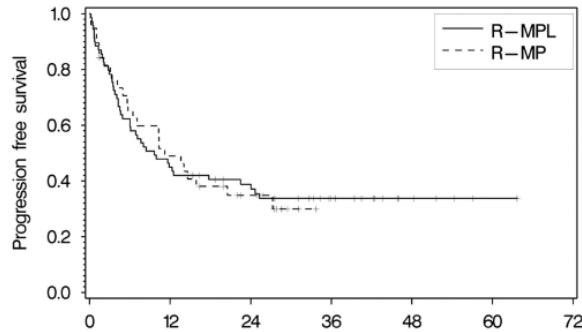


# Alternative treatment options for 'older (non-ASCT) patients'

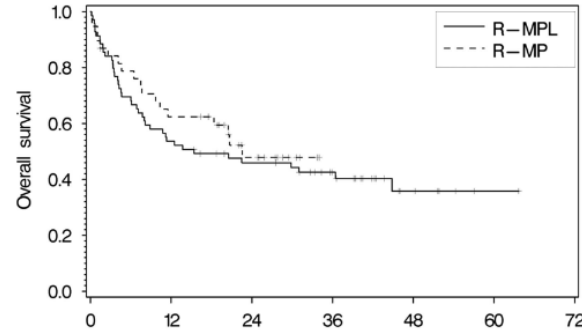
## PRIMAIN approach: R-MTX-Procarbazine and Procarbazine maintenance



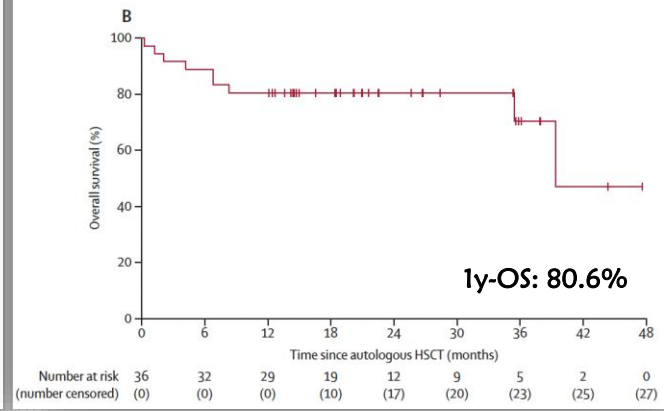
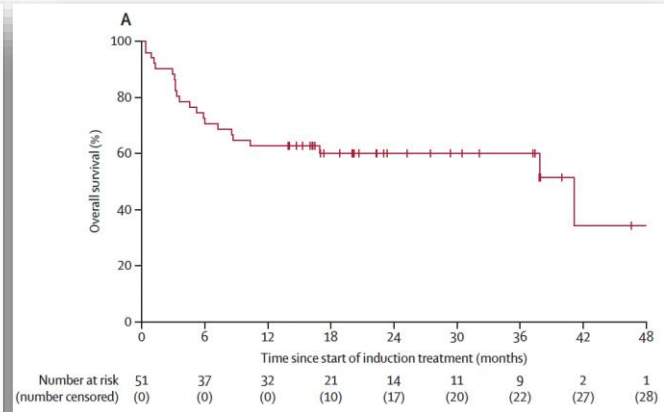
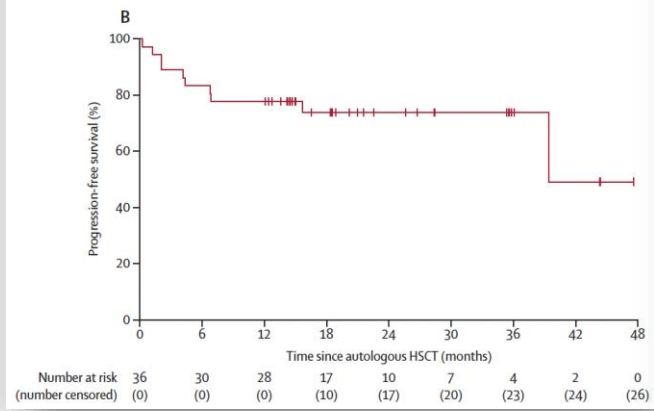
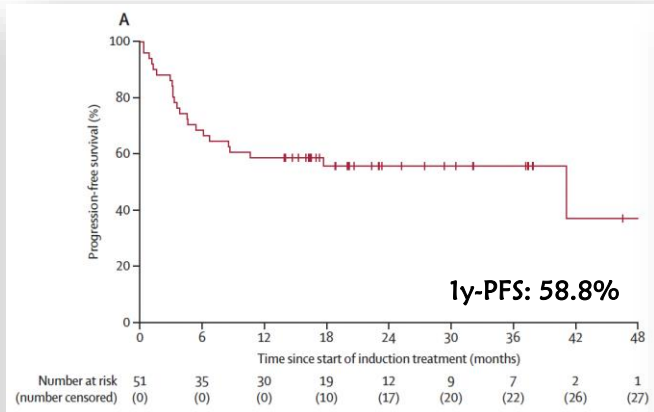
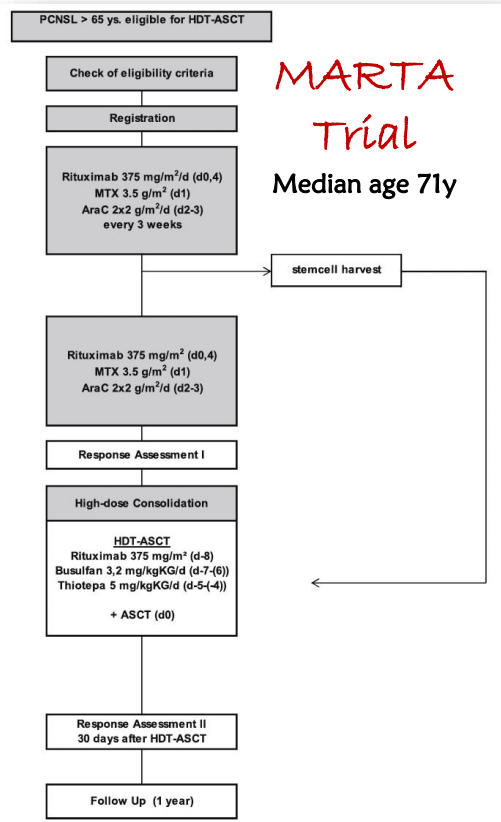
Median age 75yr (65-83)



# Patients at risk	Months after start of therapy						
	0	12	24	36	48	60	72
R-MPL	69	31	23	13	5	1	0
R-MP	38	18	9	0	0	0	0



# Patients at risk	Months after start of therapy						
	0	12	24	36	48	60	72
R-MPL	69	37	28	19	6	1	0
R-MP	38	23	11	0	0	0	0



# Stratification of 'Elderly'

Eligible for intensive combination  
immune chemotherapy

Ineligible for HDT-ASCT, but  
eligible for HD-MTX

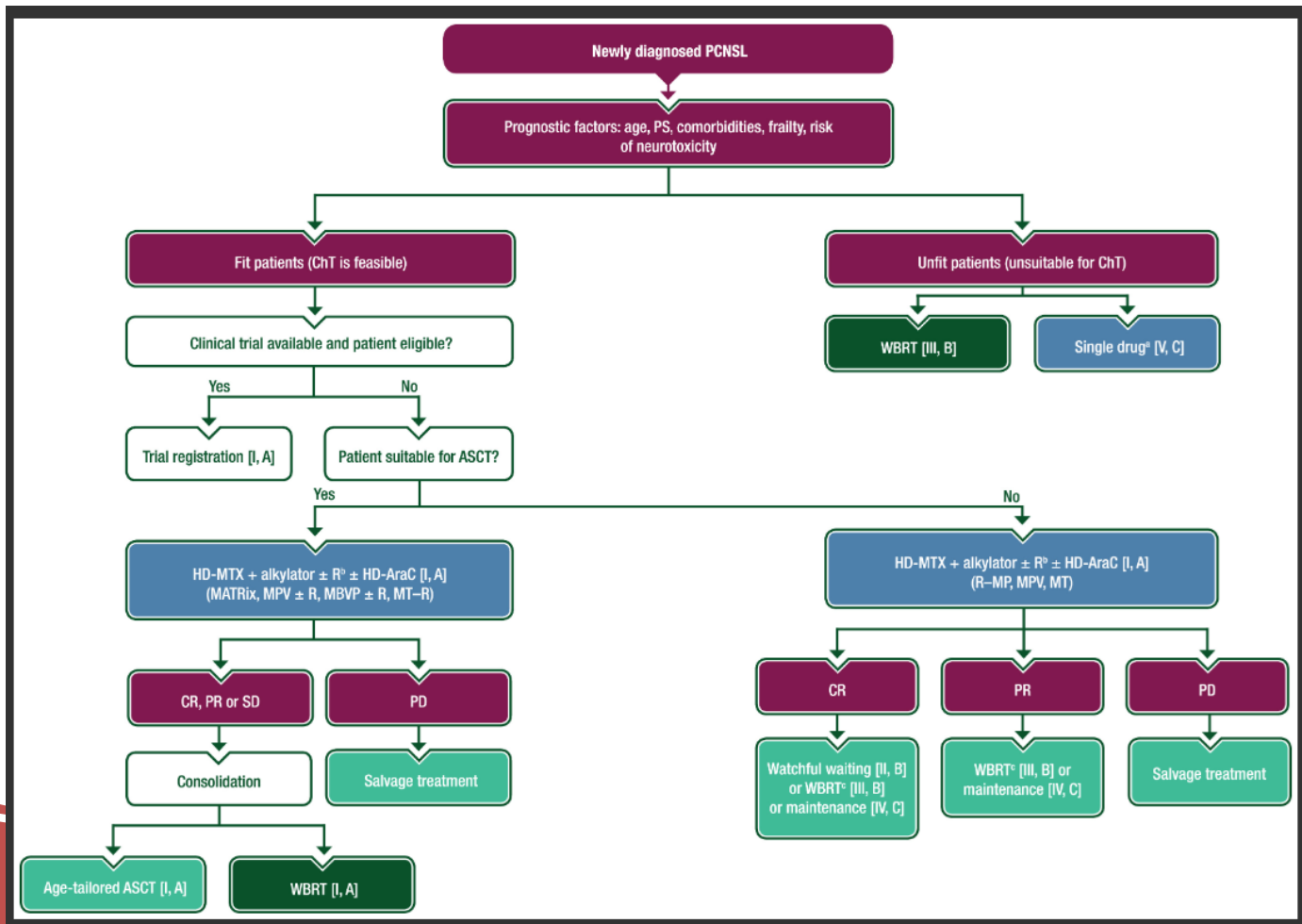
**Chronological age, on its own, should not be a barrier for delivery of HD-MTX**

- GFR > 50 ml/min
- Adequate bone marrow reserve
- Preserved cardiac function (ventricular ejection fraction  $\geq 45\%$ , no recent acute coronary artery disease or uncontrolled arrhythmias)
- Pre-morbid PS

(a minority of patients)

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

Longitudinal stratification



# Terapia di I linea PSDTA

## Pazienti UNFIT:

- 1) R-Metotrexate (1.5 g/mq) ogni 15 gg +/- vincristina +/- procarbazine (MPV) + consolidamento con WBRT (se < 60 anni) o mantenimento con alchilanti orali (temozolamide o procarbazine) + se localizzazione meningea MTX-AraC IT
- 2) Inserimento in protocolli clinici

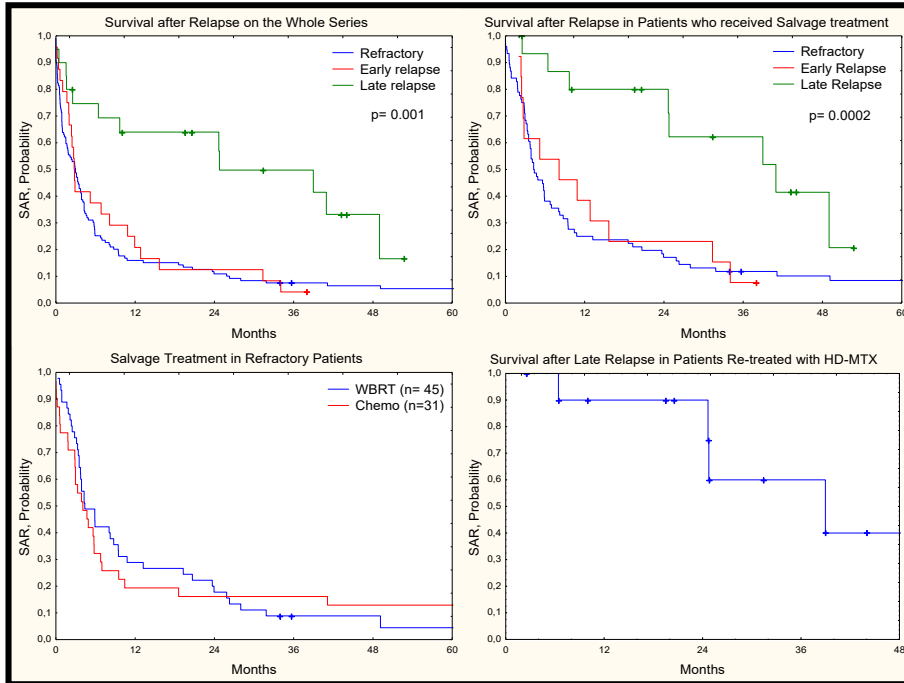
## Pazienti FRAIL:

- 1) WBRT (24-36 Gy + boost 45 Gy su residuo) o palliazione
- 2) se localizzazione meningea: MTX-AraC IT
- 3) se localizzazione oculare: trattamento intravitreale con Rituximab o MTX
- 4) inserimento in protocolli clinici

# Unfavourable Prognosis of rrPCNSL

## TREATMENT OF PATIENTS ENROLLED IN THE RANDOMIZED TRIALS OF THE IELSG

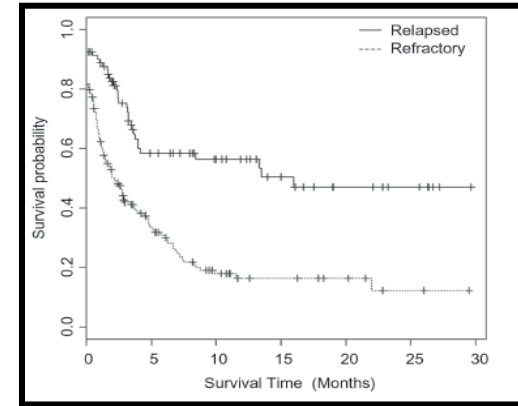
*Ferreri et al. ASH (2021) – Abstract #1417*



The prognosis is disastrous, especially in refractory/early relapse pts median overall survival of 3.5-6 months

French LOC network National Registry  
Median OS 3.5 months

*Langner-Lemerrier et al. Neuro Oncol (2016)*



## Terapia di II linea PSDTA

Pazienti FIT eleggibili a terapia ad alte dosi:

- se recidiva > 24 mesi dopo HD-MTX: considerare retreatment con HD-MTX
- se recidiva < 24 mesi: R-ICE, R-chemio + ASCT (se non eseguito precedentemente; condizionamento TT-BCNU)

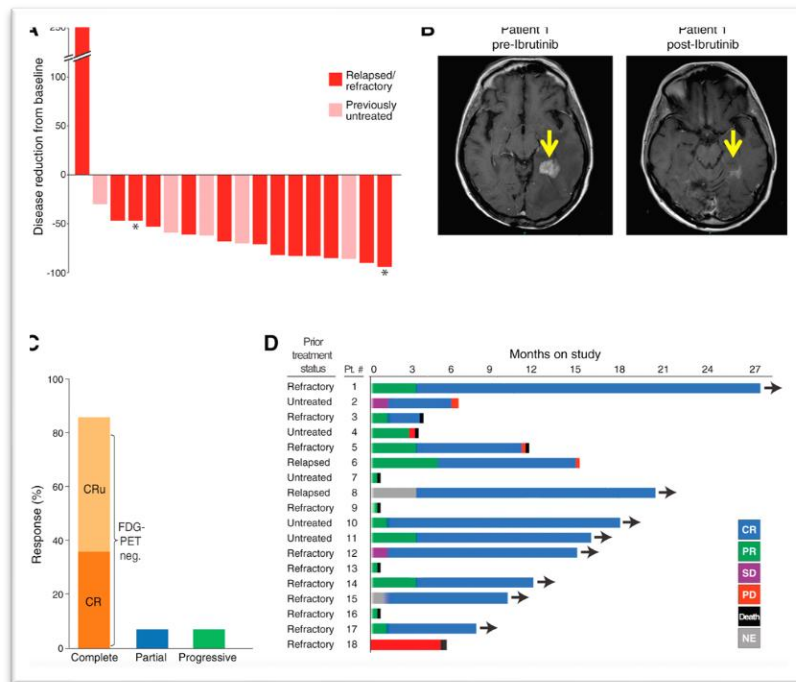
Pazienti non eleggibili a terapia ad alte dosi:

- ibrutinib (uso compassionevole)
- lenalidomide L.648
- WBRT
- Palliazione (temozolamide, altro procarbazine, steroidi)
- Inserimento in protocolli clinici

# Ibrutinib in rrCNSL

Median PFS from 4.5 months (mono)  
to 15.3 months (combo)

Lionakis MS Cancer Cell. 2017



# Lenalidomide Maintenance

- Lenalidomide has shown activity as single agent or in combination in ABC-DLBCL

- Lenalidomide was associated with significantly improved PFS and acceptable toxicity in pts with relapsed DLBCL

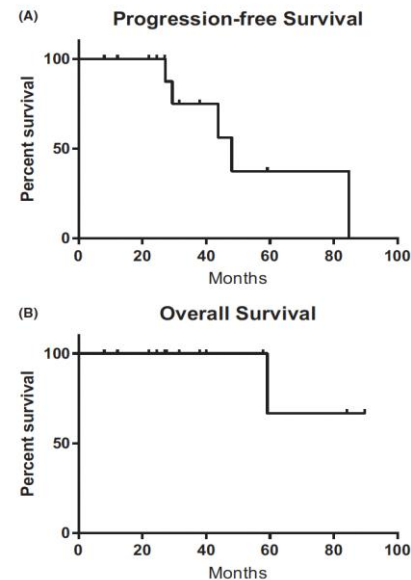
Ferreri AJM, et al. ASH 2015

- 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 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 2019*

# Vitreoretinal Lymphoma



Perspective



**Unmet Clinical Need:**  
Standard Treatment



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

Table 4. Characteristics and therapeutic results of retrospective and prospective studies of first-line treatment of PVRL

Reference	Type of study/time period	n	Median age (range), y	Type of treatment	Survival	CNS events
9	International multicenter retrospective study 1977-2005	83	63 (24-85)	Local (IVT MTX or ORT): n = 23 Systemic + local*: n = 53	Median PFS = 29.6 mo Median OS = 58 mo Median follow-up of surviving patients = 32 mo No difference among treatment groups	CNS relapse in 29 patients (35%) No difference among treatment groups
50	European multicenter retrospective study 1991-2012	78	58 (39-86)	Local (IVT MTX ± rituximab or ORT): n = 31 Extensive: n = 21 Local and extensive†: n = 23	PFS: NA 5-y OS = 68% when no CNS relapse occurred 5-y OS = 35% when CNS relapse occurred	Median CNS-free survival = 47 mo No difference between treatment groups
51	Retrospective single-center study 2004-2016	10	59 (48-71)	Local (IVT MTX): n = 3 Local + IV MTX-based: n = 7	Median PFS not reached in the local + IV treatment group NA in the local treatment group P = .032	NA
52	Retrospective single-center study 1990-2018	32‡	67 (36-84)	Local (IVT MTX ± rituximab or ORT): n = 17 IV‡: n = 7 Local + IV: n = 8	PFS = NA FFS: Local = 1.8 y IV = 3.2 y Local + IV = NR P = .002	Median CNS-free survival = NR CNS relapse = 37% with a median follow-up = 2.8 y
53	Retrospective single-center study 2007-NA	11	66 (48-72)	Local + IV RMPV + 36 Gy binocular + HD cytarabine	Median PFS = 3.8 y	4-y cumulative incidence of CNS progression = 58%
54	Retrospective single-center study 2007-2009	5	65 (43-72)	Local (IVT MTX or ORT) + IV RMPV + rdWBRT	5 patients alive in CR with a median follow-up = 32 mo	NA
55	Retrospective single-center study 2001-2011	26	67 (36-85)	Local IVT MTX or IVT rituximab: n = 15 Local + systemic IV HD MTX or IT MTX: n = 11	NA	Median follow-up = 44 mo CNS relapse: Local treatment = 73% Local + IV or IT = 40% (ns) Median time to CNS relapse:

Intravitreal injection of methotrexate or rituximab or local radiotherapy is 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

Table 4. (continued)

Reference	Type of study/time period	n	Median age (range), y	Type of treatment	Survival	CNS events
82	Retrospective single-center study 2005-2018	12	64 (38-81)	Local (bilateral ORT) + MPV ± rituximab: n = 10 Bilateral ORT: n = 1 IVT MTX: n = 1	5-y PFS = 62% 5-y OS = 71%	5-y cumulative incidence of CNS progression = 37.5%
56	Prospective single-center cohort study 2007-2013	10	68 (46-78)	Local (IVT MTX) followed by IV HD MTX	NA	2-y CNS-free survival = 58%
57	Prospective single-center study 2008-2015	11	63 (43-72)	Local (IVT MTX) + systemic IV RMPV + rdWBRT   + IV HD cytarabine	4-y PFS = 73% 4-y OS = 89%	Median follow-up = 40 mo 4-y cumulative incidence of CNS progression = 10%
8	Retrospective multicenter study 2011-2018	59	70 (39-88)	Systemic IV HD MTX-based chemotherapy: n = 51 Local (IVT MTX or ORT) + systemic IV HD MTX: n = 8	Median PFS = 18 mo Median OS = 75 mo	Median follow-up = 61 mo Median CNS-free survival = 73 mo

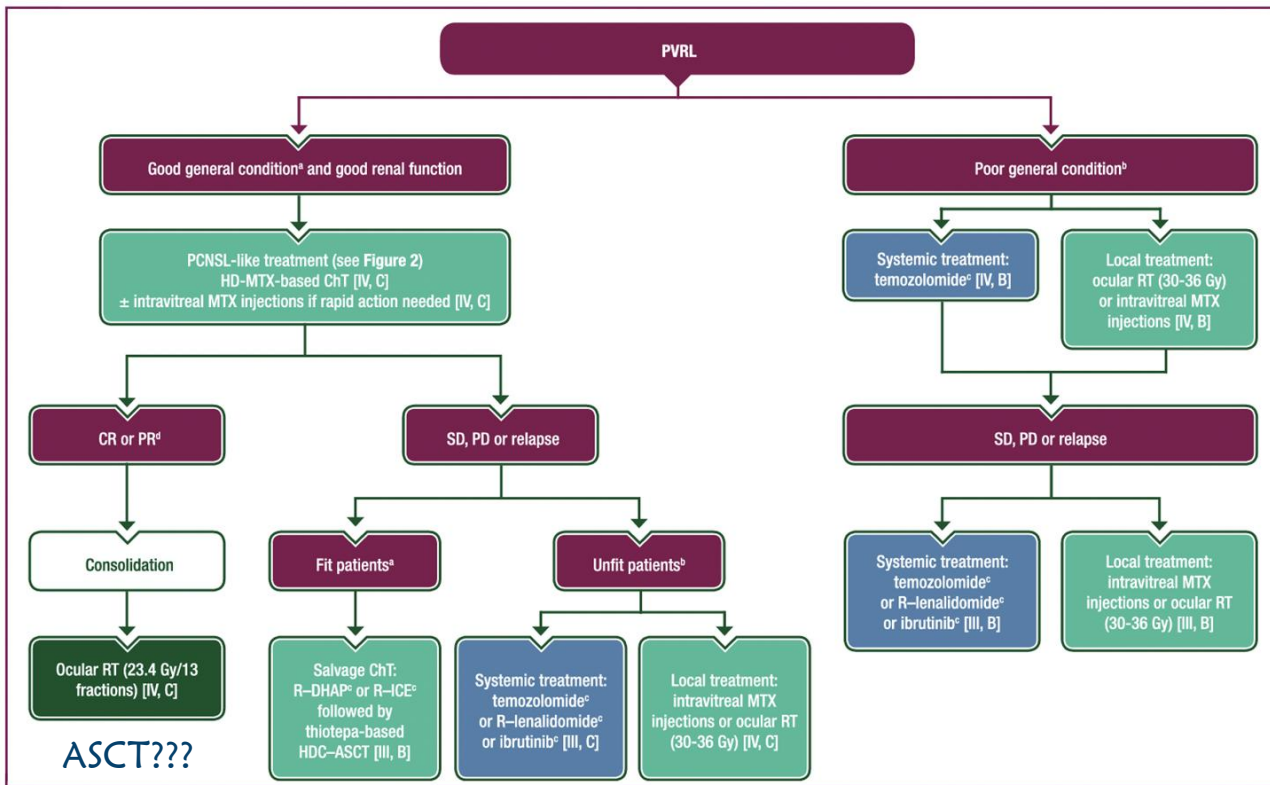
*Very low level of evidence*

Small and heterogeneous series

Varied treatment

Several years of collection

Biased analysis



# PVRL: treatment

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

Figure 3. Treatment algorithm for PVRL.

ASCT, autologous stem cell transplantation; CR, complete response; HD-MTX, high-dose methotrexate; MTX, methotrexate; PCNSL, primary CNS lymphoma; PR, partial response; R-DHAP, rituximab-dexamethasone-cytarabine-cisplatin; R-ICE, rituximab-ifosfamide-carboplatin-etoposide; SD, stable disease

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