INTERNATIONAL PALERMO WORKSHOP ON:
INNOVATIVE THERAPIES FOR LYMPHOID MALIGNANCIES

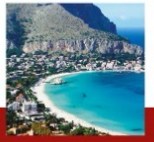
Palermo March 18, 2023
Hotel Federico II Central Palace

Central nervous system Lymphoma: novel approaches?

Teresa Calimeri

Disclosures of Teresa Calimeri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen-Cilag			X				
Sandoz							X



Oncologic Paradigm: Early Diagnosis is the best treatment

Early diagnosis → early institution of treatment → neurological recovery

- ♂ 68 y
- Neurological symptoms onset: December 2020
  Biopsy not performed, steroids start

- Diagnostic brain biopsy: February 14, 2022
- Treatment Start: March 2, 2022
- Outcome: death on March 14, 2022 because of infectious complication

PCNSL Diagnosis

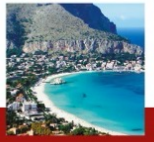
Brain Biopsy Weaknesses

The success of stereotactic biopsy, while the histologic gold standard, depends on accessible lesions, and it is sometimes unfeasible when lesions lie close to or within critical brain structures.

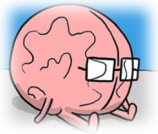
- *up to a 7% risk of hemorrhage/complications (especially in elderly or frail persons).*
- *up to a 35% risk of failure to achieve a definitive histologic diagnosis*

Indication to brain biopsy should be supported by robust suspicion and performed by an expert neurosurgeon

Illerhaus G. and Batchelor T. Blood 2011
Josephson SA et al. J Neurosurg. 2007

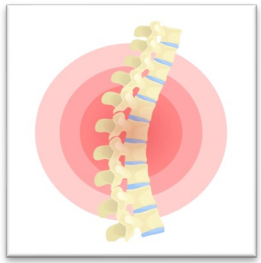


PCNSL Diagnosis



Diagnostic Procedures on other CNS Components

Other diagnostic procedures have low-yield & may delay diagnosis and treatment



CSF cytopathologic analysis

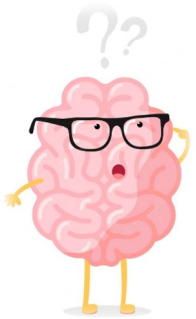
Vitreous aspirate analysis

Examination can only provide definitive info in the presence of leptomeningeal or ocular dissemination and is <50% sensitive for the diagnosis of PCNSL in this setting

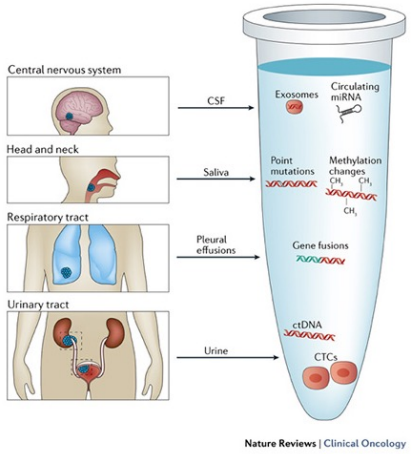
Illerhaus G. and Batchelor T. Blood 2011
Chamberlain MC. Et al. 2000

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?



Liquid Biopsy

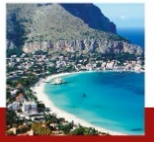


- **Samples**: Blood, CSF and vitreous humor
- **Techniques**: next generation sequencing, ELISA, ddPCR …
- **Biomarkers:** chemokine, genomic fragment (cfDNA, microRNA), transmembrane receptors …

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]

Baraniskin A. and Roland Schroers R. Cancers 2021



Cell free circulating tumor DNA in blood samples

	Methods	Samples type	N of samples	sensitivity	specificity	Notes
Fontanilles M. et al. Oncotarget 2017	NGS	Tissue and plasma ctDNA	25	32%	100%	Detection of mutations in ctDNA was independent from the clinical or tumor characteristics
Yoon SE et al. Cancer Res Treat. 2022	Targeted deep sequencing of 54 genes	Plasma ctDNA	41	27%	-	Detection of ctDNA was not related to the concentration of cell-free DNA or tumor volume
Montesinos-Rongen et al. J Mol Diagn 2020	NGS/ddPCR - CD79B and MYD88 hot spot mutations	Frozen tissue and plasma	27	4%	-	The extensive control analyses suggest that low-level CD79B and MYD88 mutations might exist in cfDNA in healthy individuals
Hattori S. et al. Cancer Science 2017	droplet digital PCR (ddPCR) and targeted deep sequencing (TDS)	Paired tumor-derived DNA and cell-free DNA	14	57% ddPCR 0% TDS	-	The mutations disappeared after chemotherapy, remaining undetectable in all patients. MYD88 L265P mutation in cell-free DNA could be used as non-invasive diagnostics, but may not be applicable for monitoring minimal residual diseases in PCNSL.

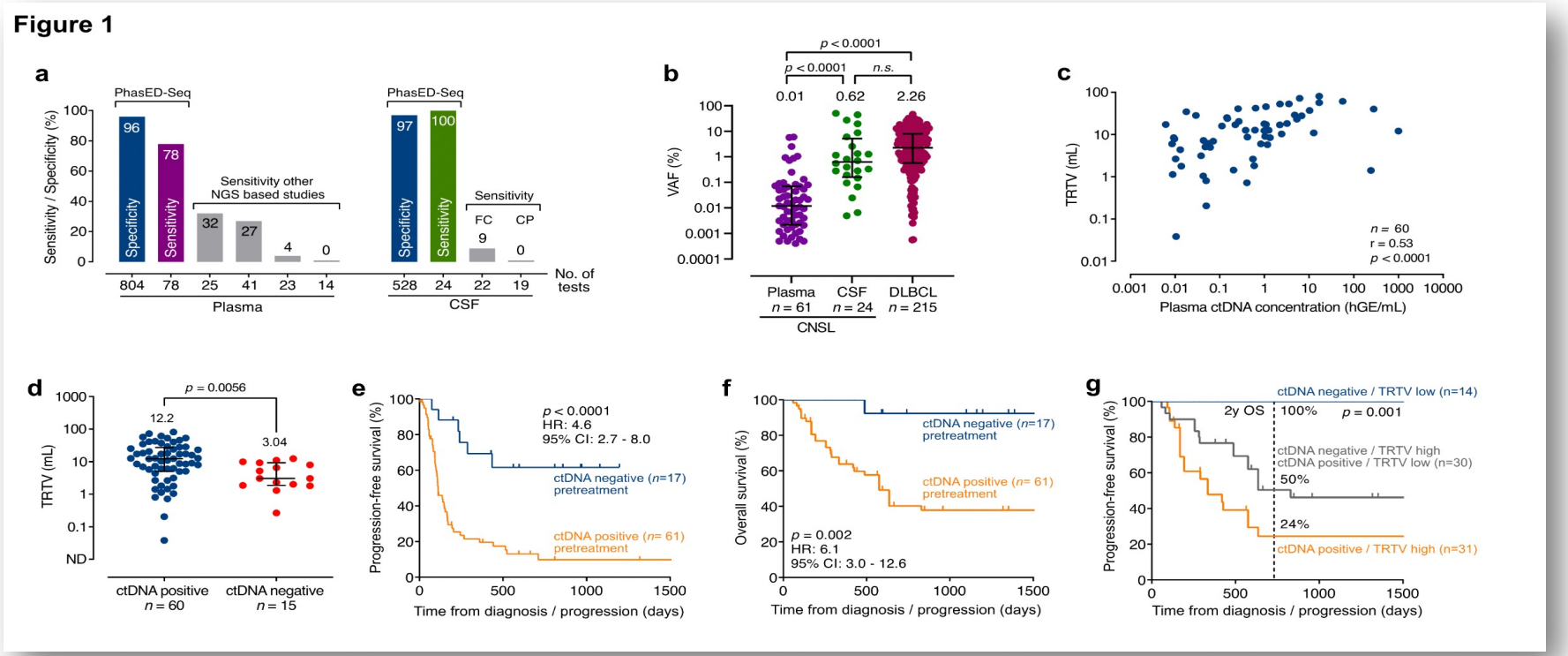
Cell free circulating tumor DNA in cerebrospinal fluid

Table 1. Patients' characteristics and tumor mutations at the time of enrolment and outcome.

ID	Age	Histol	Dx	Disease status	Systemic inv	CNS inv	CNS (FC/C)	Tumor seq	Tumor mutations	VAF tumor	VAF CSF	VAF plasma	Outcome
CNS lymphoma													
NHL1	59	DLBCL	PCNSL	New dx	No	P	-/-	–	*MYD88* L265P	–	48%	N	CR
NHL2	60	DLBCL	SCNSL	Relapse	No	P, LM	+/-	WES	*CD79B* Y197D	17%	9%	–	CR
									MYD88 L265P	22%	25%	–	
									FOXO1 D69A	13%	–	–	
									TMSB4A Q24P	54%	20%	–	
NHL3	53	DLBCL	SCNSL	Relapse	No	P, LM	+/+	Panel	*B2M* M1T	41%	N	N	PD, died
									BCOR N145S	68%	52%	N	
									CREBBP R1664C	21%	N	N	
NHL4	75	WM	SCNSL	Relapse	No	LM	+/+	–	*MYD88* L265P	–	33%	N	CR
NHL5	58	DLBCL	SCNSL	Relapse	No	P, LM	+/+	–	*MYD88* L265P	86%	29%	5%	CR, CNS relapse
NHL6	73	MCL	SCNSL	Relapse	No	LM	+/+	Panel	*ATM* H2872L	31%	34%	2%	PD, died
									MEF2B K23R	90%	95%	4%	

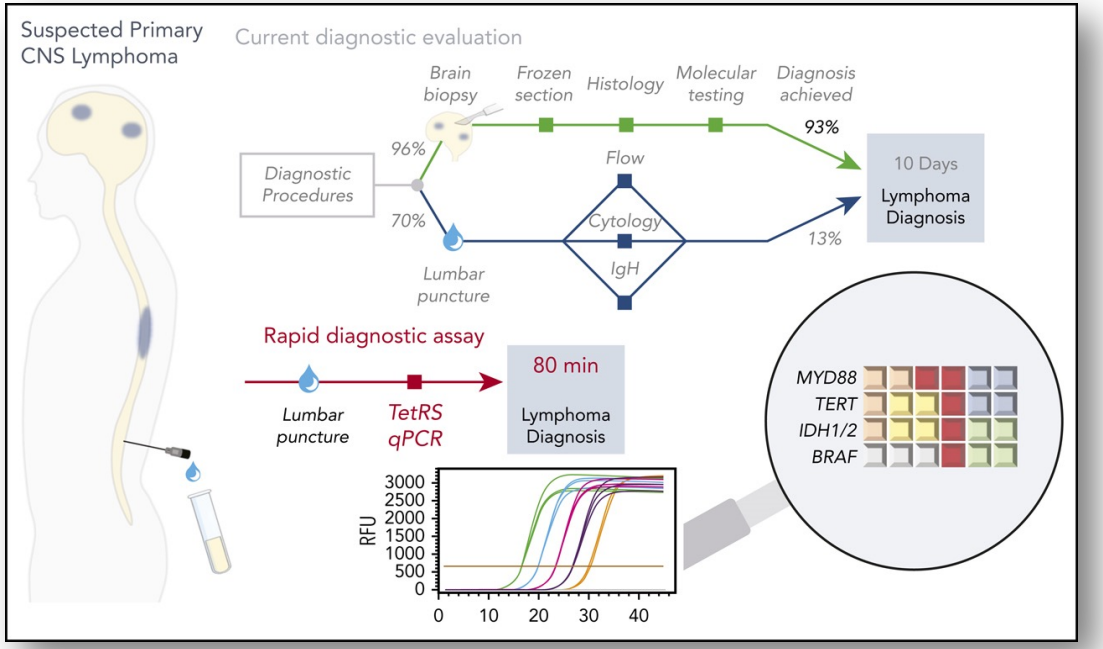
Bobillo S. et al. Haematologica 2021

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



Using a machine learning classifier to 207 specimens from an independent validation cohort of CNSL and Non-CNSL patients showed high specificity (100%) and positive predictive value (100%) for non-invasive diagnosis of CNSL, with a sensitivity of 57% for CSF and 21% for plasma, suggesting that a significant subset of CNSL patients might be able to forego invasive surgical biopsies

A rapid genotyping panel for detection of primary central nervous system lymphoma



qPCR-based assays for detecting of hotspot mutations found in PCNSL and glioma

Gupta M. et al. Blood 2021

C

Final histologic diagnosis: hematologic malignancy

TetRS Result: MYD88 L265P mt	+	-	
+	34	0	*Sensitivity: 57.6% (44.1 – 70.4%)*
-	25	27	*Specificity: 100% (87.2 – 100%)*

86 archived clinical specimens

B

Malignancy present

TetRS Result: Any variant detected	+	–	
+	73	0	*Sensitivity: 65.8% (56.2 – 74.5%)*
–	38	21	*Specificity: 100% (83.9 – 100%)*

Prospectively collected liquid biopsies from 32 pts

VOLUME 23 · NUMBER 22 · AUGUST 1 2005

JOURNAL OF CLINICAL ONCOLOGY

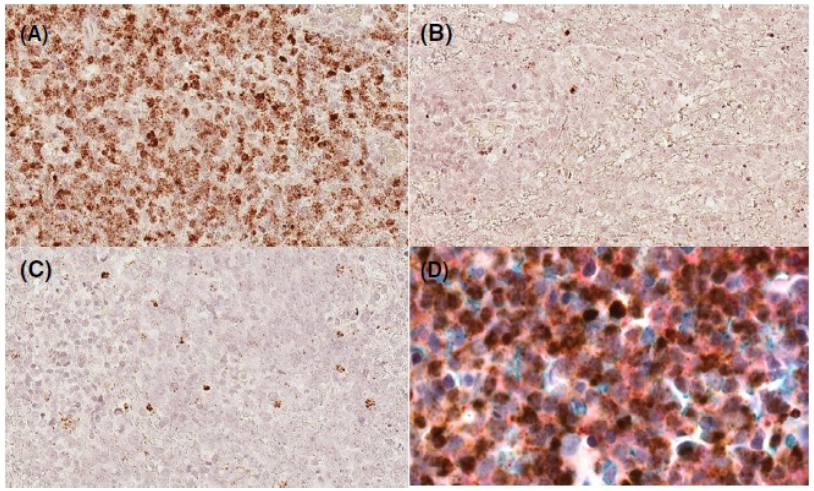
ORIGINAL REPORT

Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma

Lauren E. Abrey, Tracy T. Batchelor, Andrés J.M. Ferreri, Mary Gospodarowicz, Elisa J. Pulczynski, Emanuele Zucca, Justine R. Smith, Agnieszka Korfel, Carole Soussain, Lisa M. DeAngelis, Edward A. Neuwelt, Brian Patrick O'Neill, Eckhard Thiel, Tamara Shenkier, Fransesc Graus, Martin van den Bent, John F. Seymour, Philip Poortmans, James O. Armitage, and Franco Cavalli

What Changed since 2005?

Biomarkers

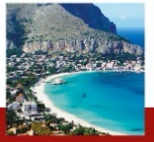


Variable, *n* (%)	*MYD88* L265P (*n* = 36)			IL-6 level (*n* = 33)			IL-10 level (*n* = 32)		
	WT	MUT	*P*	Low	High	*P*	Low	High	*P*
Negative CSF cytology	9 (29)	22 (71)		9 (33)	19 (67)		4 (14)	24 (86)	
Positive CSF cytology	1 (20)	4 (80)	1·00	0 (0)	5 (100)	0·29	0 (0)	4 (100)	1·00
Normal CSF protein level	5 (26)	14 (74)		5 (28)	13 (72)		3 (18)	14 (82)	
High CSF protein level	5 (29)	12 (71)	1·00	4 (27)	11 (73)	1·00	1 (7)	14 (93)	0·60
Single lesions	4 (29)	10 (71)		3 (23)	10 (77)		2 (17)	10 (83)	
Multiple lesions	6 (27)	16 (73)	1·00	6 (30)	14 (70)	0·71	2 (10)	18 (90)	0·62
Peripheral lesions	5 (50)	5 (50)		1 (11)	8 (89)		1 (11)	8 (89)	
Deep lesions	5 (19)	21 (81)	0·11	8 (33)	16 (67)	0·38	3 (13)	20 (87)	1·00
Tumour size ≤27 mm*	5 (31)	11 (69)		5 (31)	11 (69)		2 (13)	13 (87)	
Tumour size >27 mm*	3 (19)	13 (81)	0·68	3 (21)	11 (79)	0·69	2 (14)	12 (86)	1·00

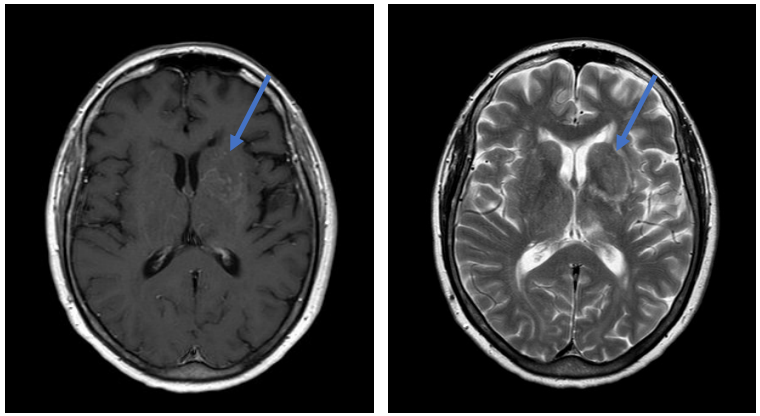
Variable	PCNSL (*n* = 36)	Neurological controls (*n* = 106)	*P**	Systemic DLBCL (*n* = 44)	*P*†
MYD88 L265P mutation, *n* (%)	26 (72)	1/86 (1)‡	<0·00001	1 (2)§	<0·00001
IL-6 level, pg/ml, median (IQR)	4·6 (0–91)	2·3 (0–5·7)	0·007	0 (0–0·6)	0·0003
High IL-6 levels >2·5 pg/ml, *n/N* (%)	24/33 (73)	38/79 (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

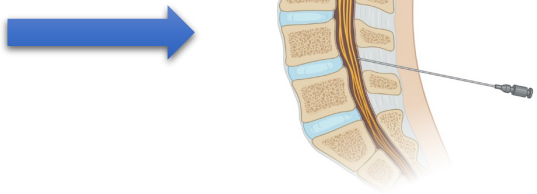


Oncologic Paradigm: Early Diagnosis is the best treatment

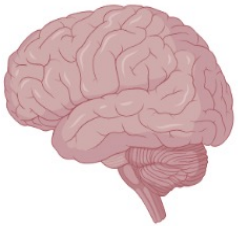


T1-Gd

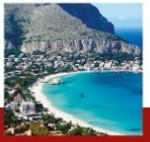
T2



MYD88: p.Leu265Pro (c.794T>C)



Histopathological diagnosis

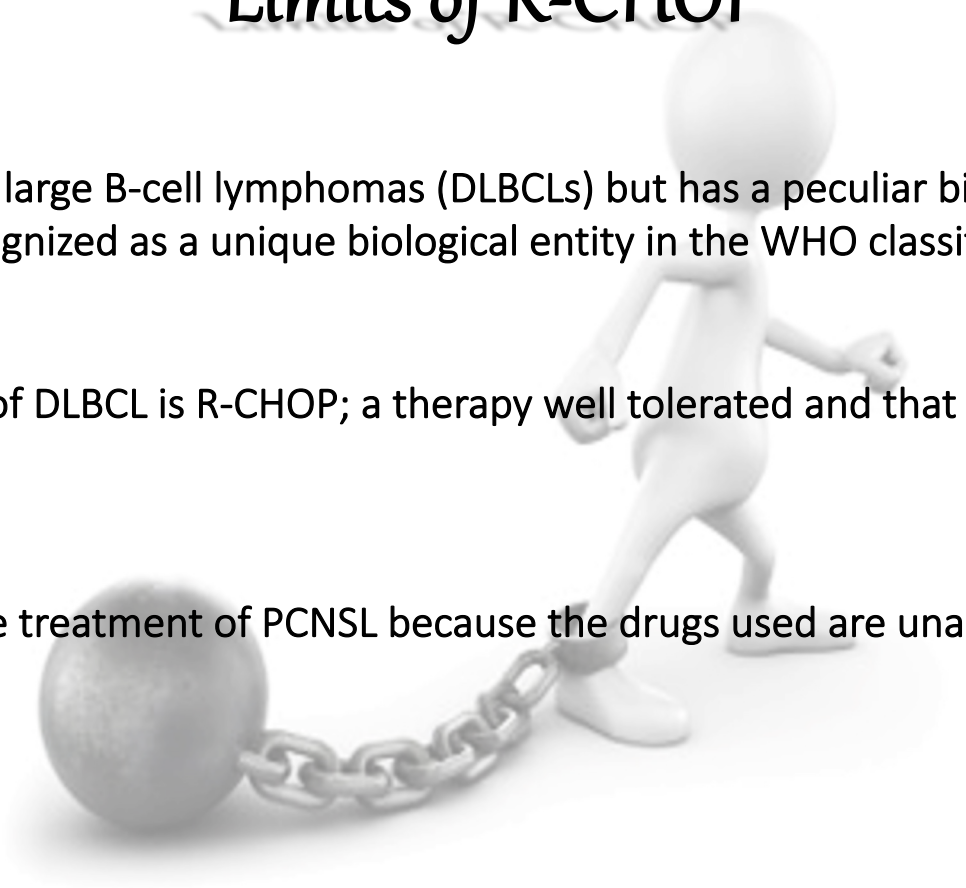


Limits of R-CHOP

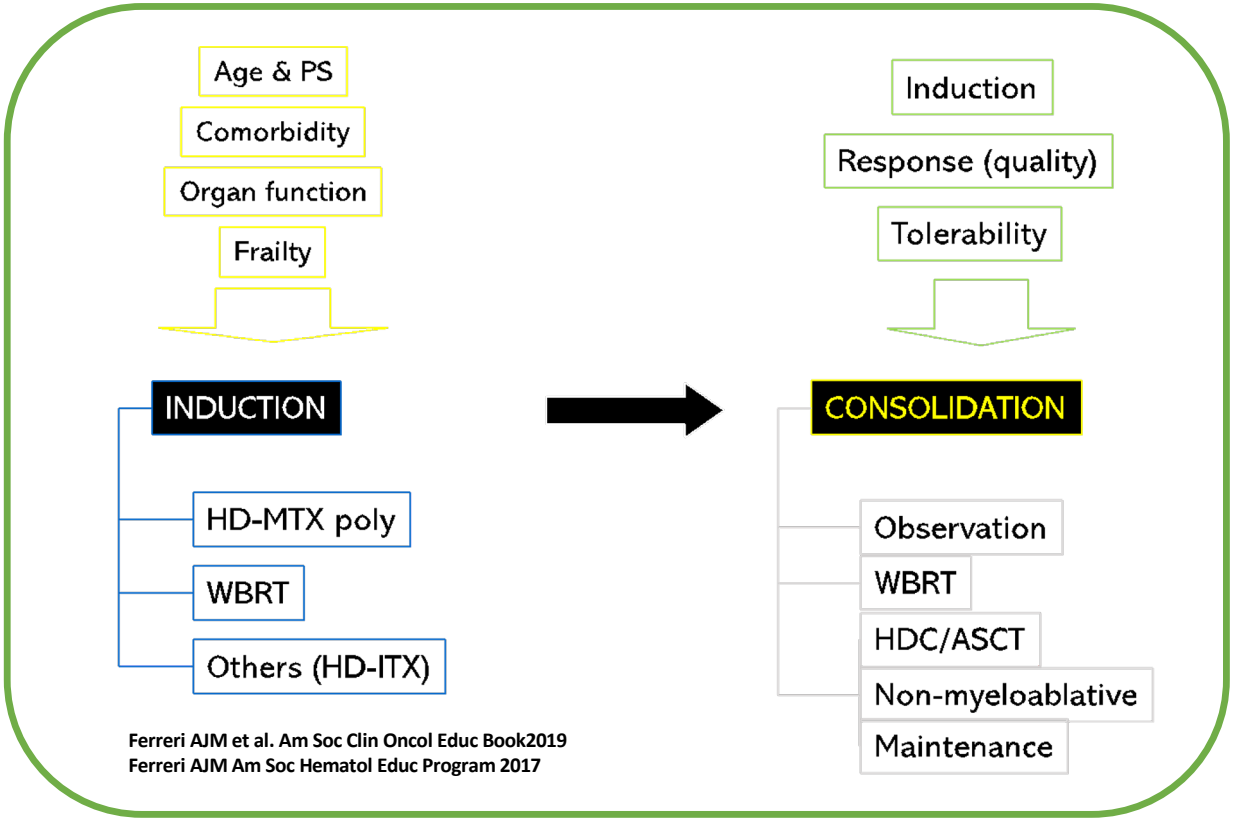
PCNSL belongs to diffuse large B-cell lymphomas (DLBCLs) but has a peculiar biological and molecular behavior so that it is recognized as a unique biological entity in the WHO classification of hematopoietic and lymphoid tumors

The standard treatment of DLBCL is R-CHOP; a therapy well tolerated and that does not require hospitalization.

R-CHOP is not used in the treatment of PCNSL because the drugs used are unable to cross the blood-brain barrier (BBB).



Background: Modern Approach



Ferreri AJM et al. Am Soc Clin Oncol Educ Book2019
Ferreri AJM Am Soc Hematol Educ Program 2017

Limitations in Induction Paradigms

- No reliable selection method for the best post-induction strategy.
- No universally accepted duration and frequency of induction therapy (inter-trial heterogeneity).
- No head-to-head comparison among the induction HD-MTX combinations.

IELSG 32

PCNSL [≤ 65 ys. + PS 0-3] or [65-70 ys. + PS ≤2]

R

4 c. MTX 3.5 g/m^2 d.1
araC 2 g/m^2 x 2/d, d. 2-3
every 3 weeks

4 c. rituximab 375 mg/m^2 d-5 & 0
MTX 3.5 g/m^2 d.1
araC 2 g/m^2 x 2/d, d. 2-3
every 3 weeks

4 c. rituximab 375 mg/m^2 d-5 & 0
MTX 3.5 g/m^2 d.1
araC 2 g/m^2 x 2/d, d. 2-3
Thiotepa 30 mg/m^2 d.4
every 3 weeks

Response assessment

CR – PR - SD

R

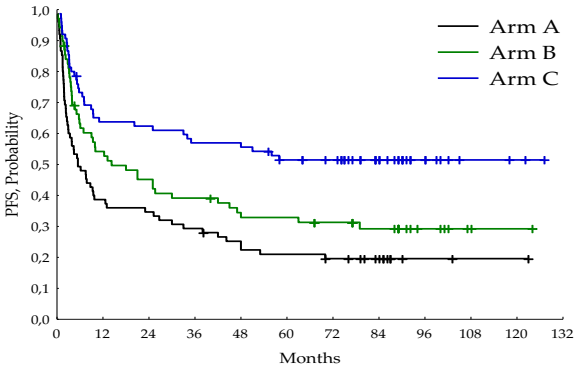
WBRT 36 Gy
± boost 9 Gy

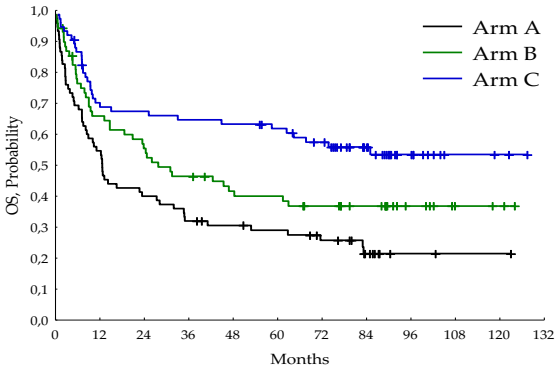
BCNU 400 mg/m^2 d.1
Thiotepa 5 mg/Kg x 2/d; d.2-3
+ APBSCT

PD – tox
↓ SC harvest

WBRT 40 Gy
± boost 9 Gy

MEDIAN FOLLOW-UP: 88 MONTHS (IQR 77-99)

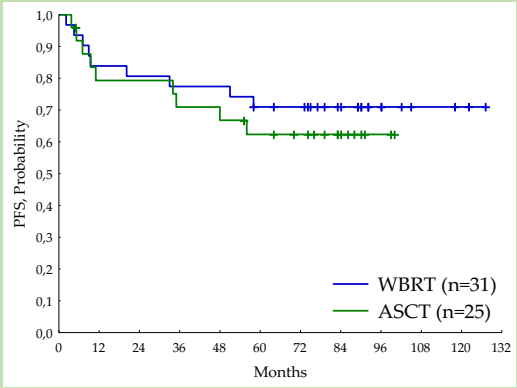


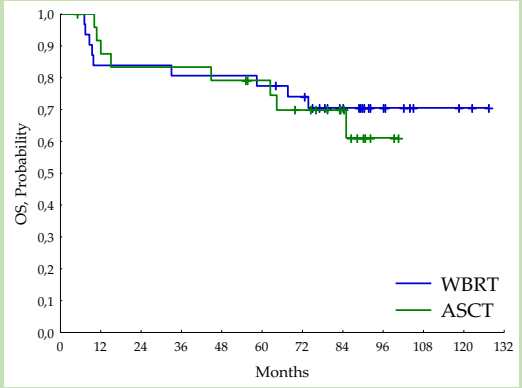


As main findings, MATRix was associated with excellent long-lasting outcome, with a 7-year OS of 21%, 37%, and 56% respectively for arms A, B, and C.

IELSG32

Patients treated with MATRix + consolidation had a 7-year OS of 70%, without a difference between WBRT and BCNU-TT conditioned ASCT

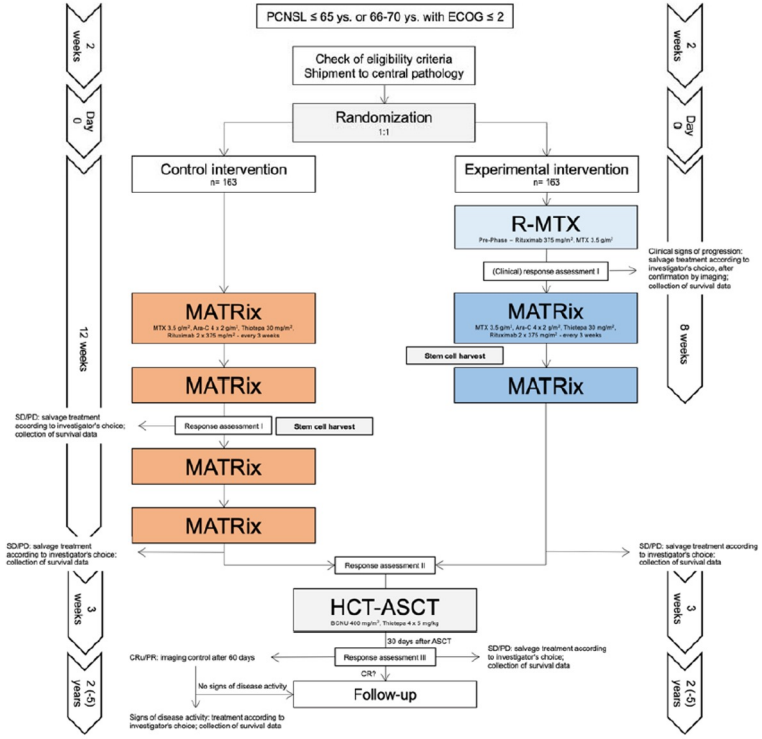




Ferreri AJM et al. Leukemia 2022

OptiMATe Traial

Trial design



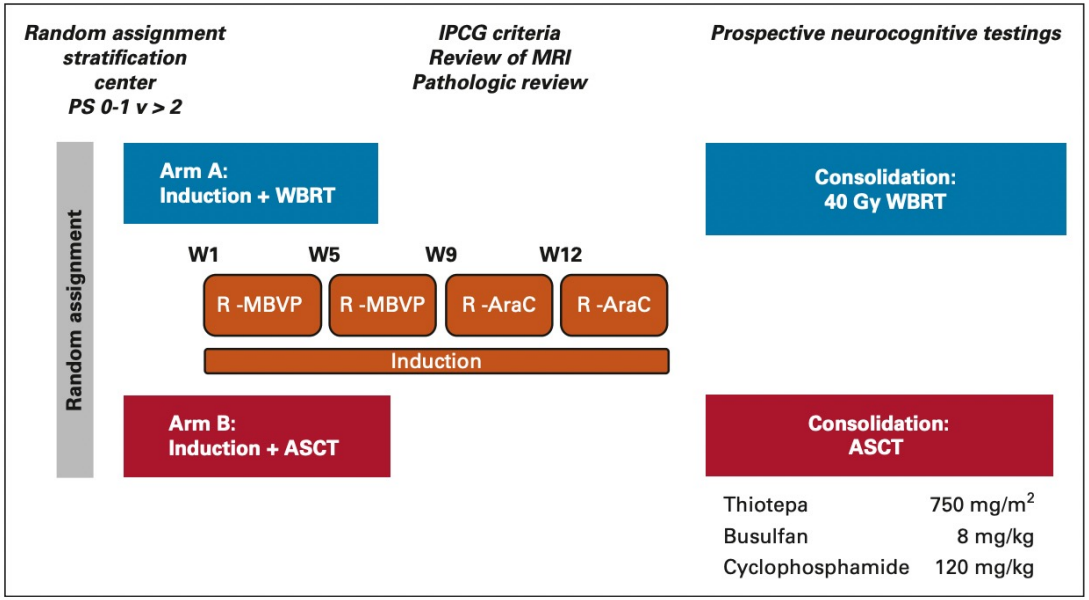
- **Randomized Phase III trial, with two parallel arms**
- **Investigator initiated**
- **Multicentric international: Germany, Austria, United Kingdom, Italy**
- **326 patients to be randomized**

PRECIS Trial (NON comparative study): 18 to 60 years old

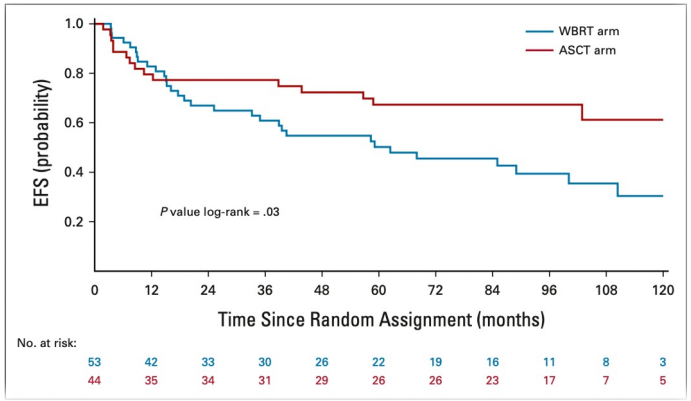
Induction: 2 cycles of R-MBVP (rituximab/HD-MTX/etoposide/carmustine/prednisone) followed by 2 cycles of Rituximab/AraC

Consolidation

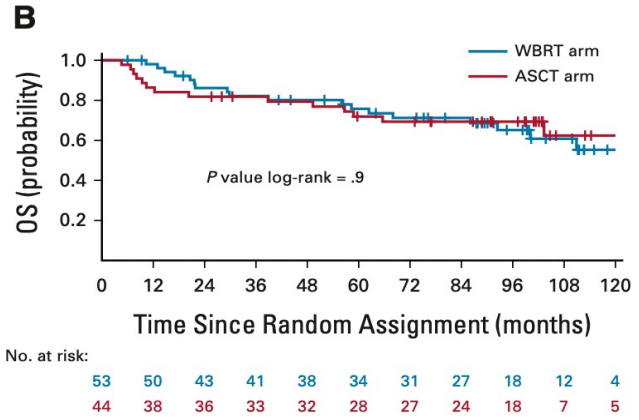
- WBRT (40 Gy; 2 Gy/fraction)
- Thiotepa, busulfan, and cyclophosphamide conditioned ASCT



Houillier C et al. J Clin Oncol. 2022



8-Years EFS: 67% ASCT and 39% in WBRT



8-Years OS: 69% ASCT and 65% in WBRT

PRECIS

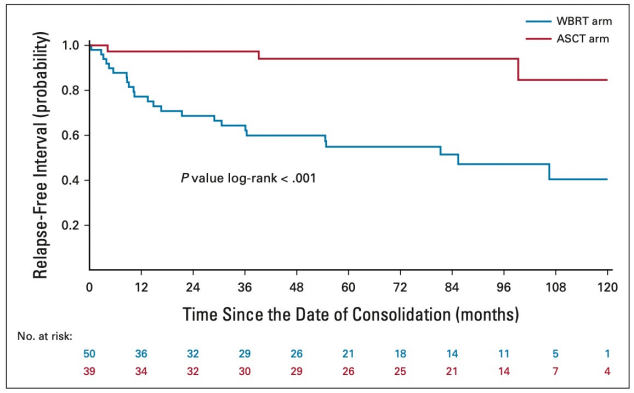


FIG A4. Relapse-free interval from consolidation. ASCT, autologous stem-cell transplantation; WBRT, whole-brain radiotherapy.

The risk of relapse was significantly lower after ASCT (24 WBRT vs 3 after ASCT; HR 0.13; P=.001

Houillier C et al. J Clin Oncol. 2022

NO RT

the long-term analysis of the PRECIS trial confirms that conventional 40 Gy WBRT should be avoided in first-line treatment because of its neurotoxicity and suboptimal efficacy in reducing relapses and favors ASCT consolidation in first-line treatment for a better disease control.

Study is still limited by the **small number of patients in the per-protocol population because of the failure of the induction chemotherapy**, which definitively needs to be improved

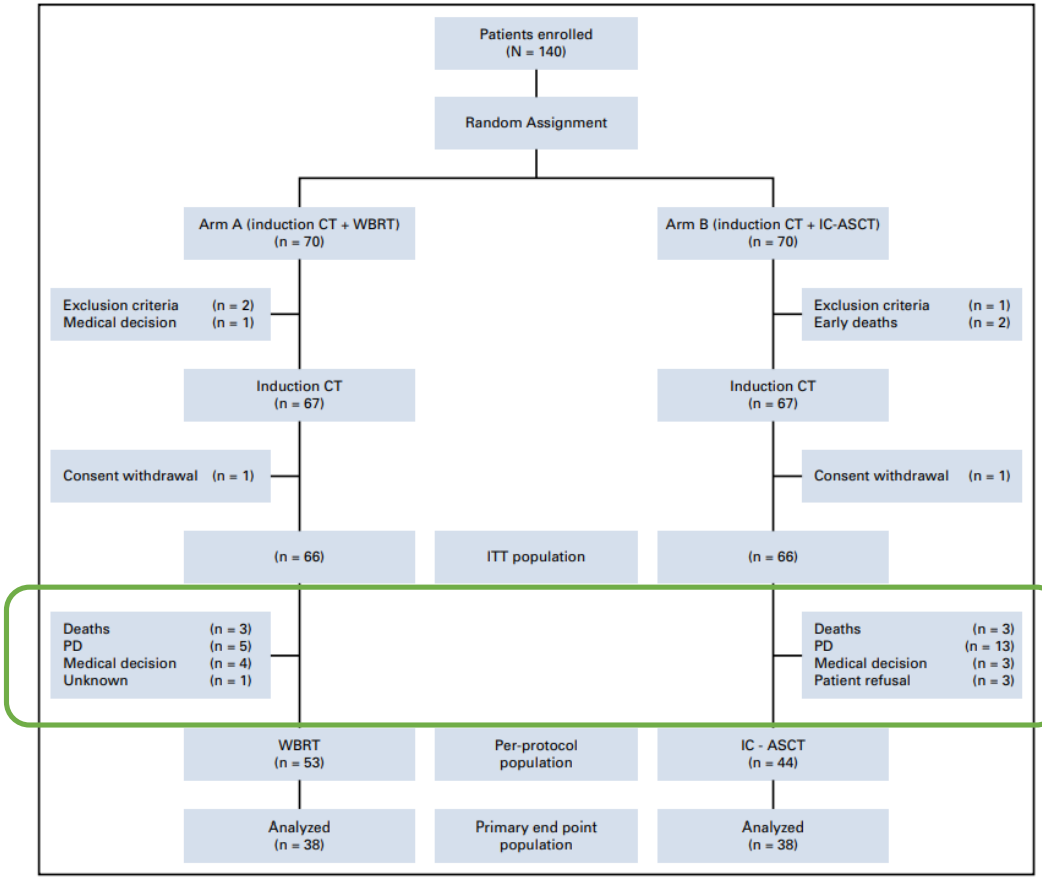
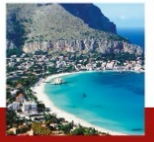
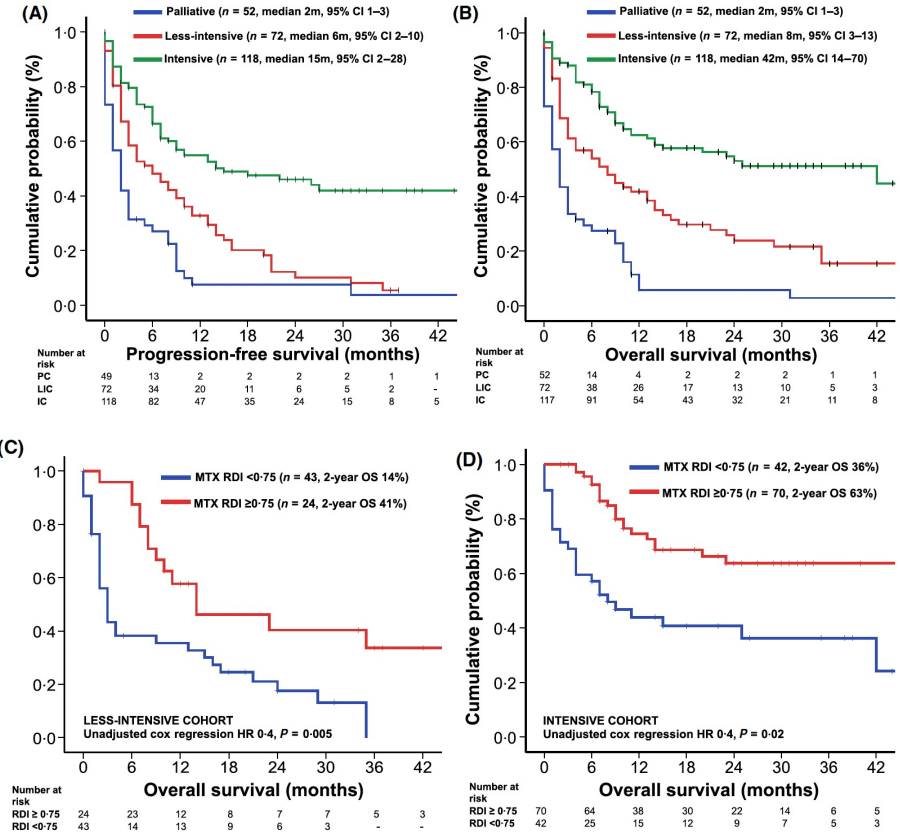


FIG 1. CONSORT diagram. CT, chemotherapy; IC-ASCT, intensive chemotherapy–autologous stem-cell transplantation; ITT, intention-to-treat; PD, progressive disease; WBRT, whole-brain radiotherapy.

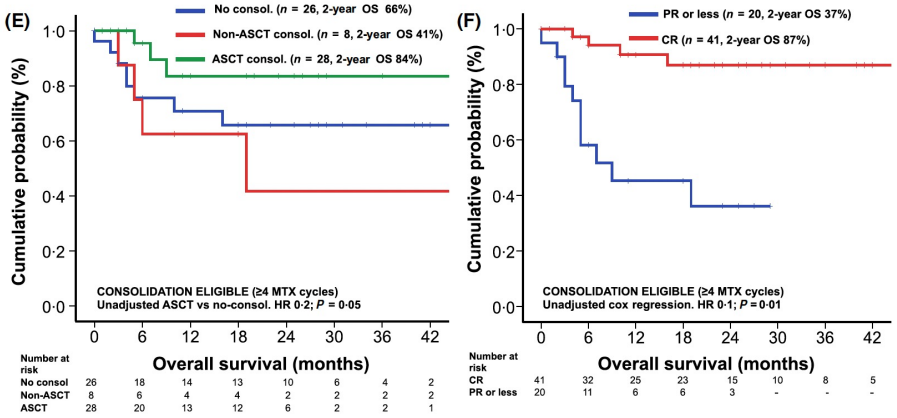




Routine clinical practice in the UK

244 consecutive patients ≥65 years with PCNSL diagnosed 2012–2017 from 14 UK centres

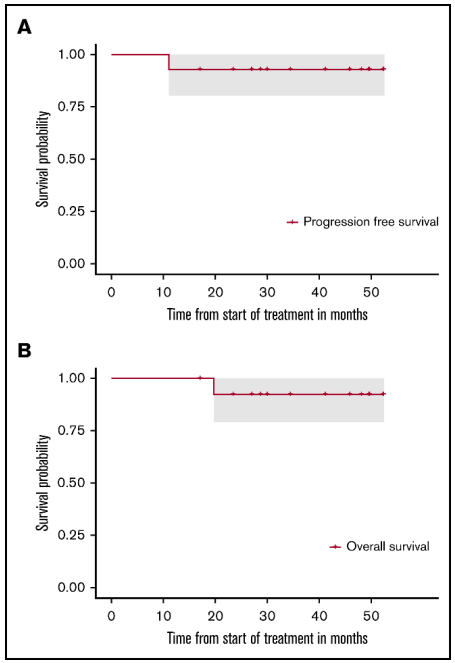
'palliative' (n = 52)
'less intensive: MTX rituximab alkylators' (n = 74)
'intensive: MTX/cytarabine combinations' (n = 118)



Martinez-Calle N et al. *BJH* 2020

Schorb et al. Blood Adv 2020

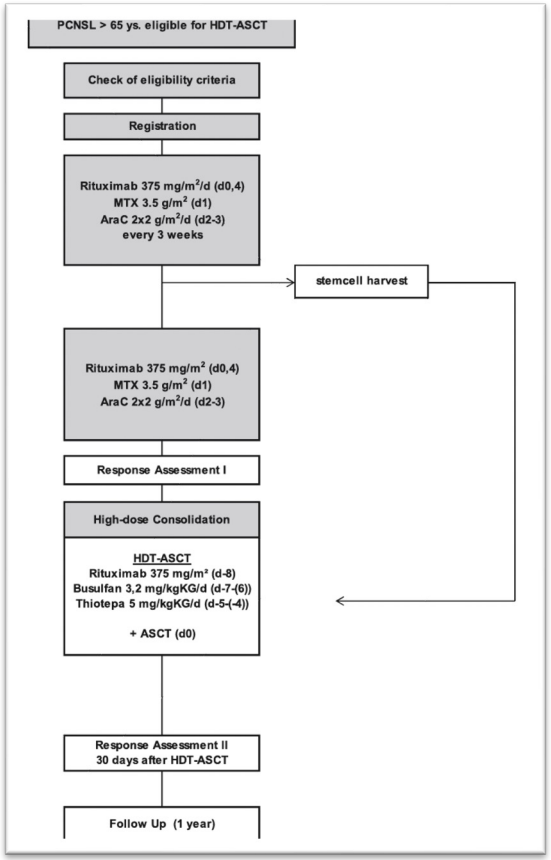
MARITA Trial



HDC-ASCT seems to be a safe and effective therapeutic option for selected elderly patients

2-year PFS 92.9%

MARTA Trial



Elderly and ASCT

	PFS	OS
12 months	57,7	63,1
24 months	54,8 71,1 - ASCT	60,5 80,8 - ASCT
Median	41.1 mo	41.1 mo

Schorb et al. ASH 2022

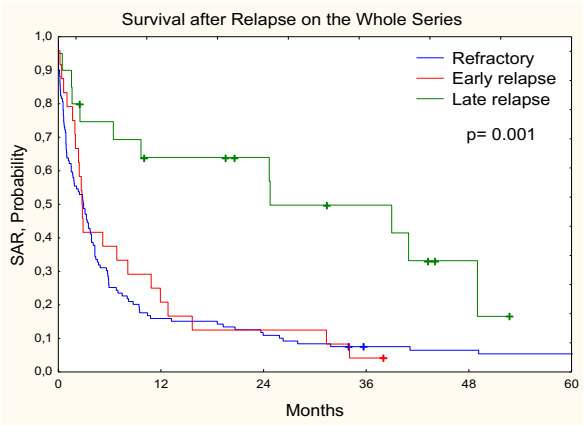
TREATMENT OF PATIENTS WITH rrPCNSL ENROLLED IN THE RANDOMIZED TRIALS OF THE IELSG

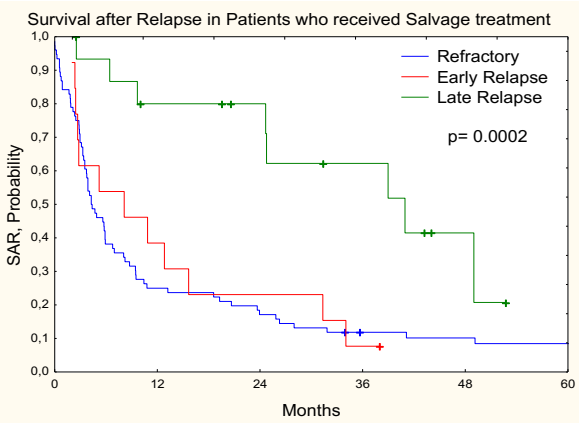
At a median follow-up from relapse/PD of 40 (range 3-118) months

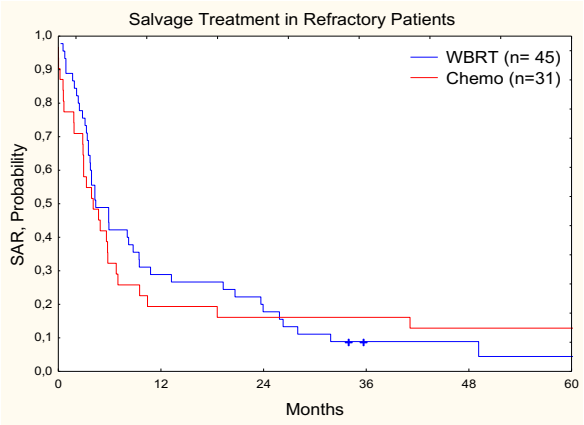
Alive and disease free	16 (10%)
Dead	148 (90%)
• Lymphoma	137 (84%)
• Infectious complications during treatment	6 (4%)
• Thromboembolic events	2 (1%)
• Unknown	2 (1%)

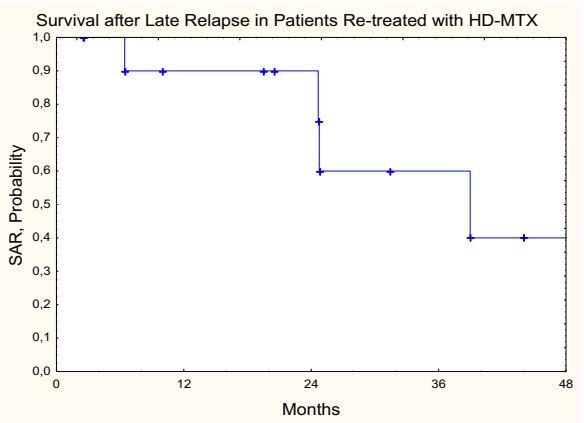
Multivariable analysis showed that ECOG PS 0-1, LR and HD-MTX retreatment were independently associated with better SAR and that outcome was not affected by age, gender, first-line induction and consolidation, and considered trial.

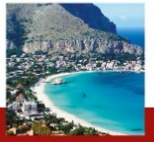
Ferreri AJM et al. ASH 2021 – Abstract #1417



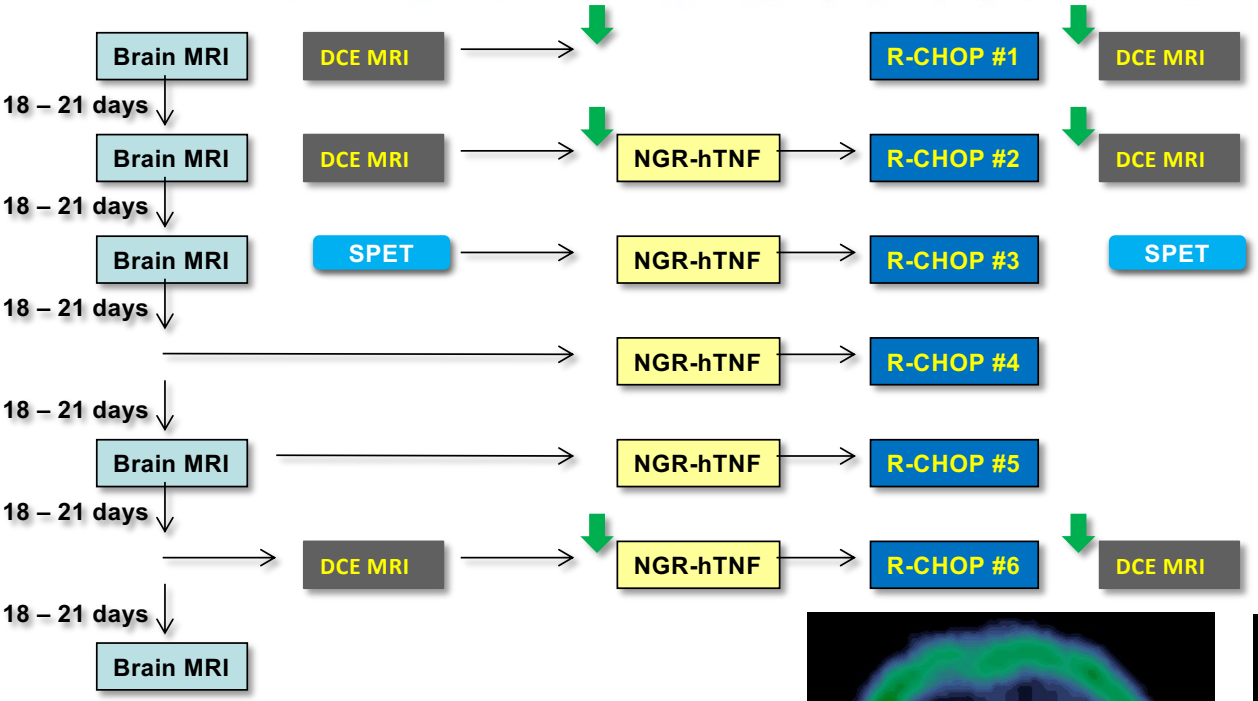


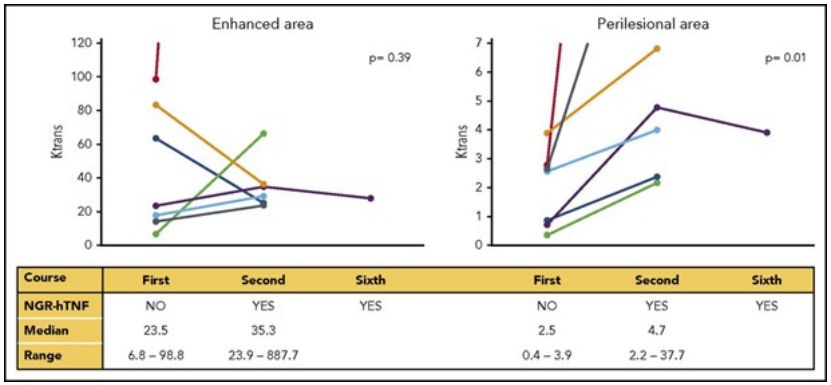






International Palermo Workshop on: Innovative Therapies for Lymphoid Malignancies

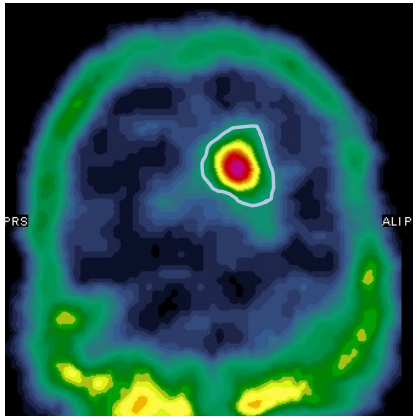


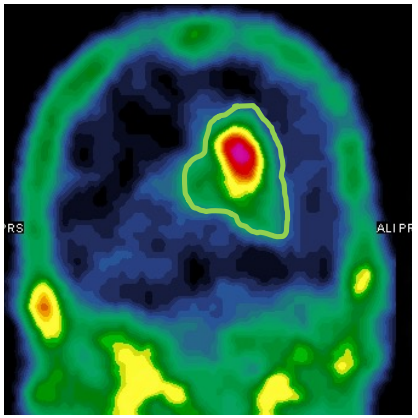


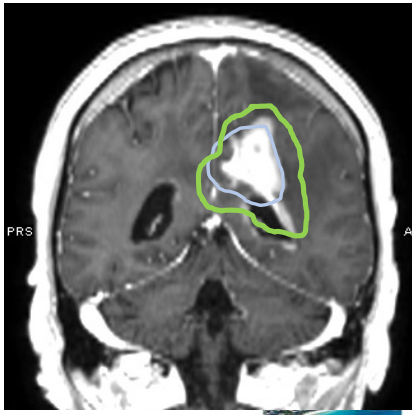
Course	First	Second	Sixth	First	Second	Sixth
NGR-hTNF	NO	YES	YES	NO	YES	YES
Median	23.5	35.3		2.5	4.7	
Range	6.8 – 98.8	23.9 – 887.7		0.4 – 3.9	2.2 – 37.7	

Ferreri AJM et al Blood 2019 and Blood Adv 2020

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







ReWIP: aim of the study

Better outcomes in patients aged < 60 years with systemic DLBCL treated with IBR plus R-CHOP [1]

Permeabilizing effect on blood-brain barrier to cytostatics in pre-clinical models [2]

R-CHOP combined with NGR-hTNF obtained high ORR in rrPCNSL [3]

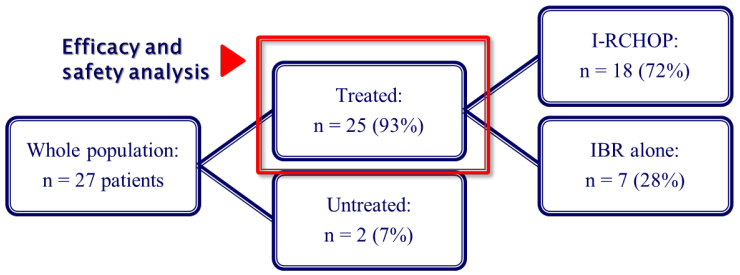
IBR was combined with R-CHOP or "CHOP-like" (I-RCHOP) regimen, based on safety data from systemic DLBCL[1]

Multicentric nationwide retrospective study to evalutate safety and feasibility of IBR alone or within I-RCHOP in a "real life" setting of rrPCNSL

[1] Younes A et al. JCO, 2019;
[2] Meeks C et al. Neuro Oncol, 2019;
[3] Ferreri AJM et al. Blood, 2019

From January 2020 to June 2022:

27 patients from 15 Italian centers have been included

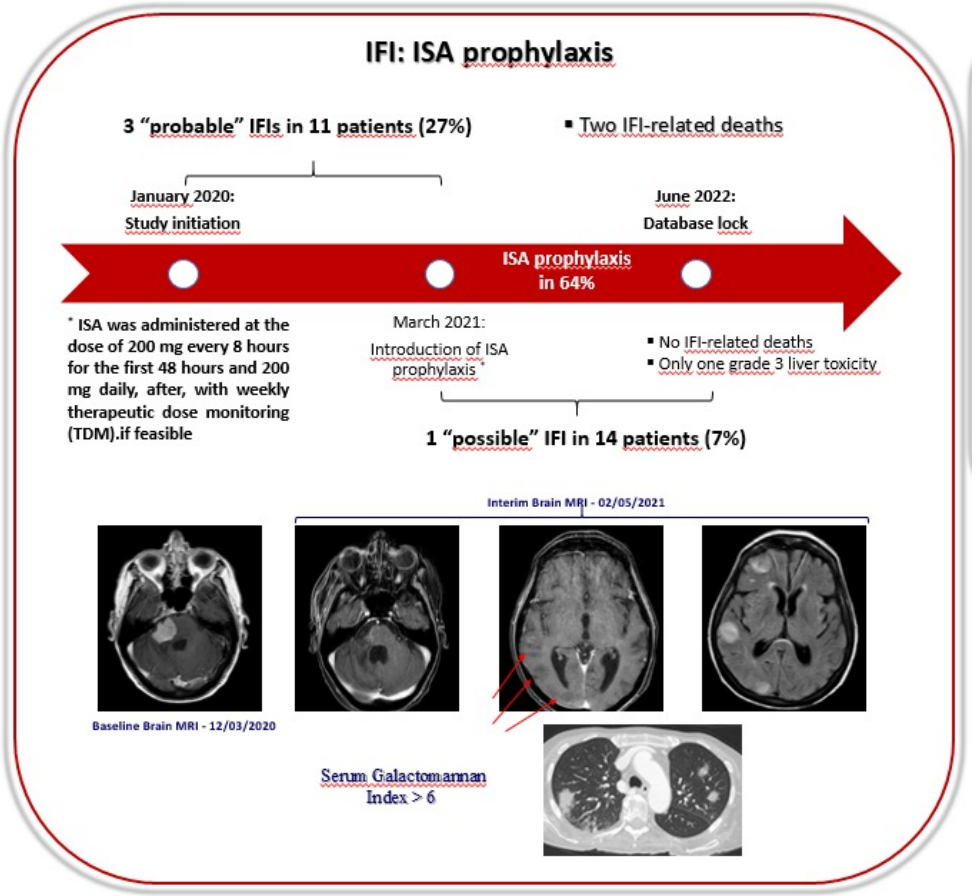


Calimeri T. et al ASH 2022

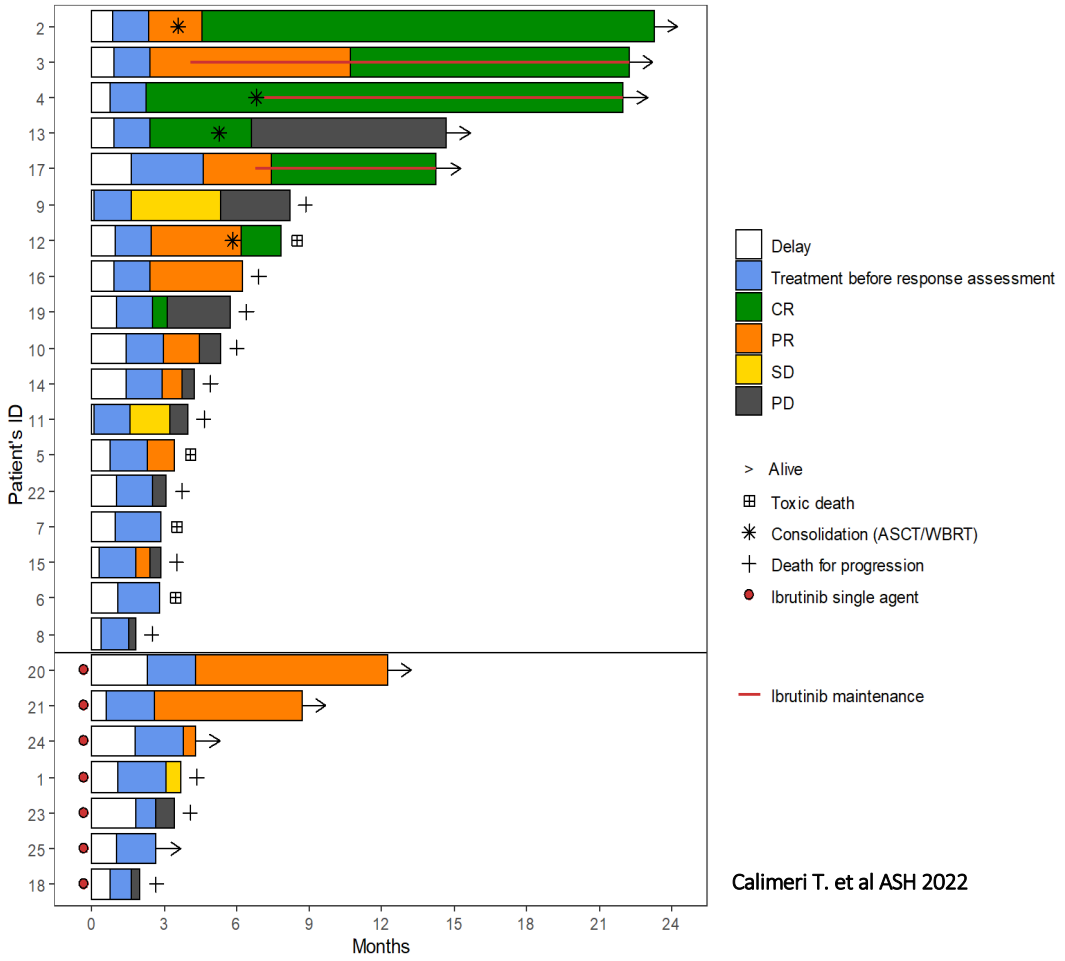
Disease response (IPCG 2005 criteria)*	Treated patients n=25 (100%)
Overall Response Rate ORR)	**15 (60%)**
Complete Response (CR)	7 (28%)
Partial Response (PR)	8 (32%)
Stable Disease (SD)	3 (12%)
Progressive disease (PD)	4 (16%)
Not evaluable	3 (12%)

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 T. et al ASH 2022



Calimeri T. et al ASH 2022

9 patients alive:

- 7 in confirmed disease response
- 1 in clinical response
- 1 alive after relapse

16 patients dead:

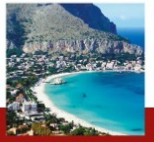
- 12 PD
- 4 toxic deaths

Five progression-free at ≥12 months: **4 treated with I-RCHOP and underwent consolidation and/or IBR maintenance**

PCNSL patients often excluded form registrational CART cell studies (although 7 patients with secondary CNS involvement were included in 1 registrational trial – TRANSCEND NHL 001 - Abramson JS et al. Lancet 2020).

Challenges:

- Higher risk of ICANS? (potential off-tumor target expressing CD19 brain mural pericytes)
- Unclear if CAR T cells undergo peripheral expansion without the antigenic stimulation of systemic lymphoma
- Enough traffic of expanded CART through the BBD?



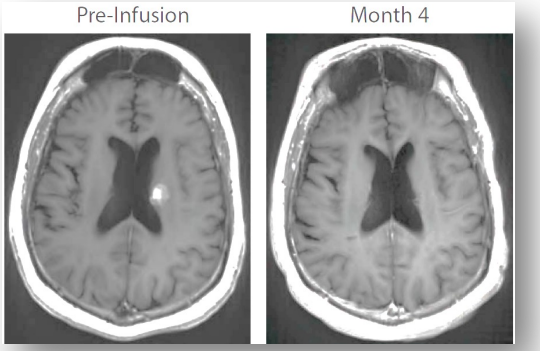
Anti-CD19 CAR-T (Tisa)

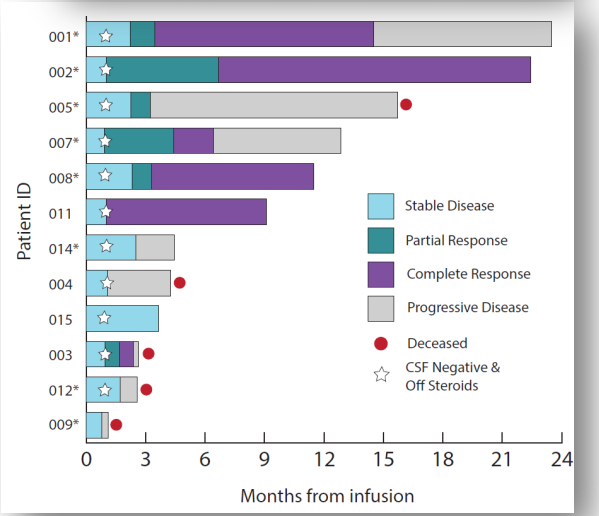
At a median time of 12 months,
6 pts achieved a CR, maintained in 3,
with low grade CRS and ICANS

Median age (range) – yr	63, (34-81)
Male:Female	7:5
Infused/Enrolled	12/13
ECOG performance status – no %	
• 0-1	7/12
• 2+	5/12
Disease location	
• Parenchymal	11/12
• Leptomeningeal enhancement/CSF+	2/12
Cell of origin	
• Germinal center B-cell type	1/12
• Non-germinal center B-cell type	11/12
Median no. of previous lines of anti-neoplastic therapy, (range)	4, (2-9)
Prior methotrexate-based regimen	
• Yes	12/12
• No	0/12
Prior thiotepa based ASCT	
• Yes	3/12
• No	9/12
BTKi refractory	
• Yes	12/12
• No	0/12
IMiD refractory$	
• Yes	4/12
• No	8/12
TEDDI-R refractory	
• **Yes**	6/12
• **No**	6/12
Prior radiotherapy	
• Yes	4/12
• No	8/12
Bridging therapy (including high dose steroids)	
• Yes	12/12
• No	0/12
Median Vein-to-Vein Time (days)	33, (27-37)

Frigault M, et al. Blood 2022

Cytokine release syndrome (CRS)$	
• Any CRS	7/12
• Grade 1	7/12
• Grade 2	-
• Grade 3	-
• Grade 4	-
Required tocilizumab	-
Median onset of CRS (day post infusion)	4
Median duration of CRS (day post infusion)	2
Immune Cell Associated Neurotoxicity Syndrome (ICANS)$	
• Any ICANS	6/12
• Grade 1	3/12
• Grade 2	2/12
• Grade 3	1/12
• Grade 4	-
Required corticosteroids	
• At time of infusion for disease control*	4/12
• Additional provided for ICANS following infusion	6/12
Median onset (day post infusion)	5
Median duration (day post infusion)	3



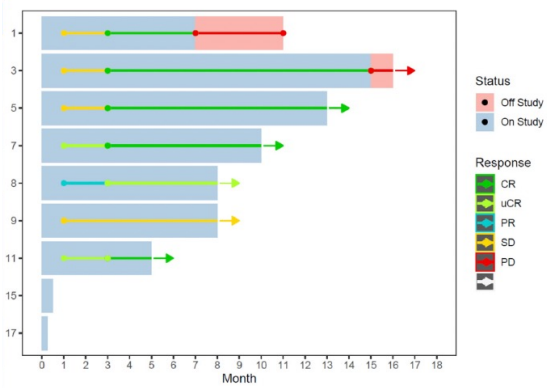


Caron A. Jacobson et al. (ASH 2022)

Pilot Study of Axi-cel for the treatment of RR PCNSL (cohort 1) and SCNCL (cohort 2). 9 pts apheresed. Stable steroid doses allowed but tapered to 2 mg qd by day 0 → 2 pts were on steroids at the time of infusion.

- 8 pts (89%) experienced CRS of any grade. 4 pts (44%) experienced ICANS of any grade. No pts had G4 ICANS
- ORR 86% with all 6 responders achieving a CR by 3m (CR rate 86%). The one non-responder has stable disease (SD) through 6m of follow-up. Two of the responders have progressed, at 6 and 15m.
- Median DOR 11.3 mo and median PFS 11.5 mo
- PK similar to that observed in ZUMA-1
- While blood CAR-Ts exhibited a prominent proliferation gene expression signature (analyzed by single cell GSEA), CSF CAR-Ts, obtained on the same days as those from the blood, exhibited strong enrichment for interferon-pathway associated genes (5)

Figure 1. Swimmer Plot of Response to Axi-cel Over Time



CR: complete response; uCR: unconfirmed complete response; PR: partial response; SD: stable disease (SD); PD: progressive disease

Anti-CD19 CAR-T (LOC Experience)

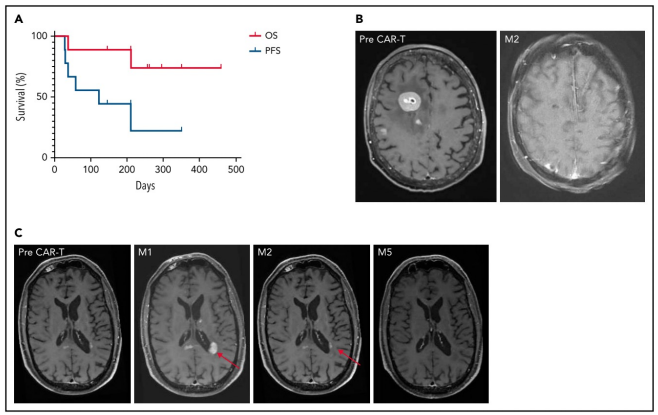
Cohort of rrPCNSL treated with CAR T-cells within the French national expert network for oculo-cerebral lymphomas (LOC).

Between May 2020 and March 2021 9 patients treated with anti-CD19 CAR T-cells:

7 tisa-cel and 2 axi-cel.

- 7 pts/9 experienced any grade CRS (including 1 G3 CRS).
- ICANS of any grade occurred in 5 patients, including 1 G3 after tisa-cel and 1 G4 after axi-cel.

- Median follow up 8.5 months:
- Best response to CAR T-cells was PR in 1 of 9 (tisa-cel) and CR in 5 of 9 patients (2 axi-cel, 3 tisa-cel).
- Median PFS was 122 days, increasing to 210 days for responders.



Alcantara M, et al. Blood 2022

Claire Roddie et al. (EHA 2022) – CAROUSEL trial of AUTO1, a CD19 CAR with a fast off-rate CD19 binding domain, designed to reduce immune toxicity and improve engraftment, in RR PCNSL.

- Testing both IV and Intraventricular route.
- Anti-PD1 incorporated in conditioning too prevent PD-1 mediated CAR silencing in the PCNSL microenvironment
- 6 pts
- 2 grade 3 ICANS reported
- Engraftment evaluable in 4 pts after 1 month both in blood and CSF

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Immunotherapy Using **CAR T**-cells to Target CD19 for Relapsed/Refractory CD19+ Primary **CNS Lymphoma**	• Primary **CNS Lymphoma**	• Biological: CD19**CAR T**-cells	• University College London Hospital London, United Kingdom

ClinicalTrials.gov Identifier: NCT04443829

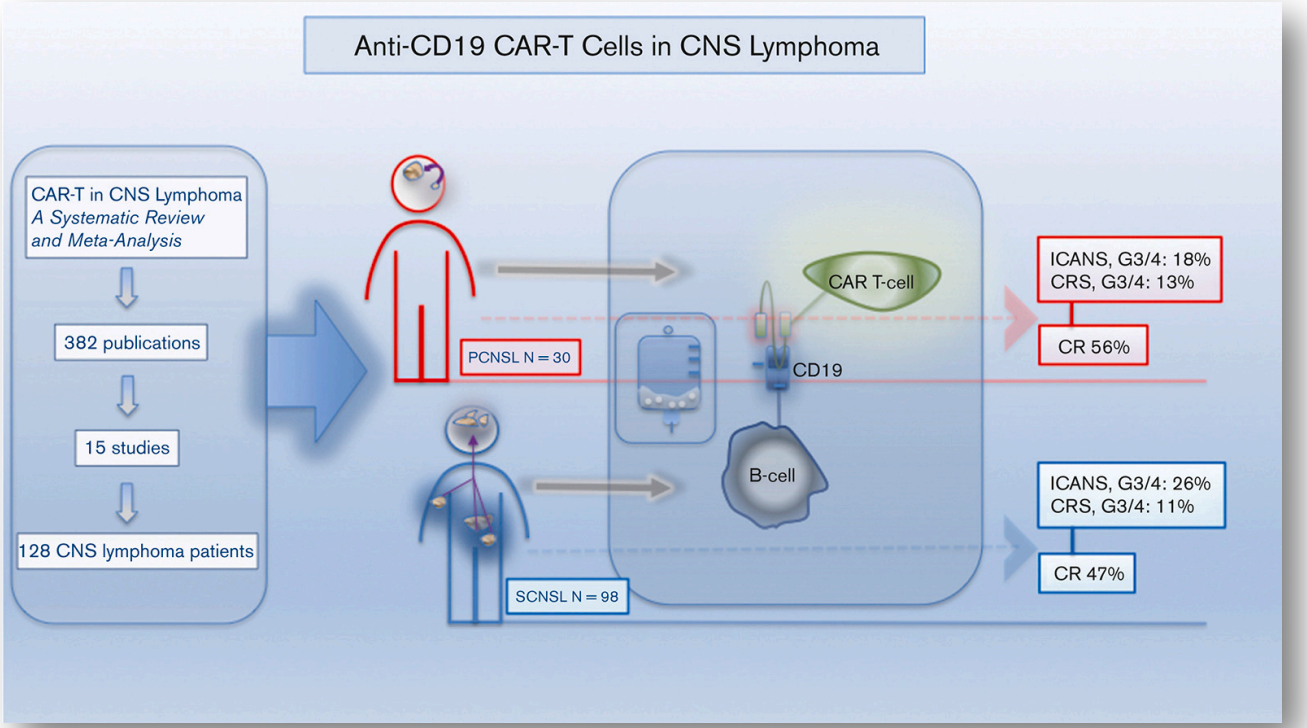
Tanya Siddiqui et al. (Blood Adv 2021)

Subgroup of patients with PCNSL (n=5), treated at City of Hope (COH) on the ongoing phase 1 clinical trial (NCT02153580).

- All patients developed grade ≥ 1 CRS and NT post–CD19CAR T-cell infusion, with highest-grade CRS of 2 and highest grade NT of 3.
- At initial disease response evaluation on day 28 post-infusion, 3 of 5 (60%; 90% confidence interval, 19-92%) patients seemed to achieve CR, based on imaging; 2 patients had stable disease.
- Blood collected from 4 of 5 patients during the 28 days post- infusion demonstrated CAR T-cell expansion by flow cytometry and qPCR, as well as the absence of CD19+ B cells or systemic lymphoma. CSF collected from 1 patient showed CAR T cells by flow cytometry, demonstrating that IV-delivered CAR T cells could traffic to the CSF, despite the absence of systemic lymphoma.
- Reversible and tolerable grade < 3 NT suggests that targeting of pericytes was probably not a major issue here

2	☐	Recruiting	Intracerebroventricular Administration of CD19-**CAR T** Cells (CD19**CAR**-CD28-CD3zeta-EGFRt-expressing Tcm-enriched **T**-lymphocytes) for the Treatment of Primary **Central Nervous System Lymphoma**	• **Central Nervous System Lymphoma**	• Procedure: Aspiration • Procedure: Biospecimen Collection • Procedure: Catheterization • (and 8 more...)	• City of Hope Medical Center Duarte, California, United States

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



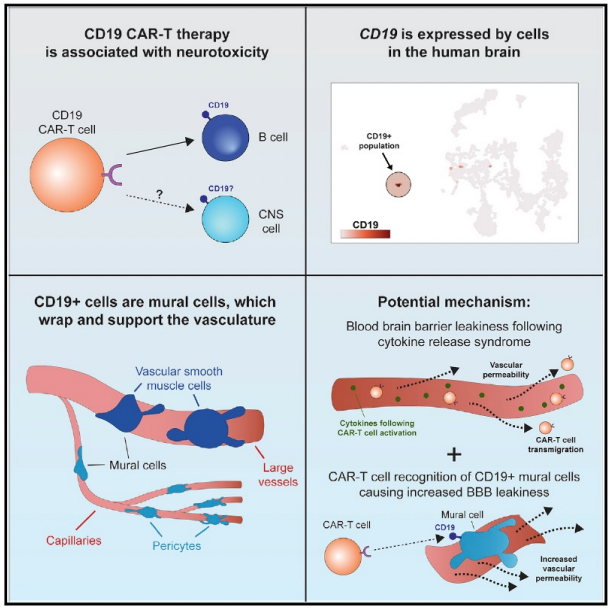
Of the patients with PCNSL, 56% achieved a complete remission (CR) with 37% remaining in remission at 6 months. Similarly, 47% of patients with SCNSL had a CR, with 37% in remission at 6 months

Cell

Article

Single-Cell Analyses Identify Brain Mural Cells Expressing CD19 as Potential Off-Tumor Targets for CAR-T Immunotherapies

Graphical Abstract



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Kevin R. Parker, Denis Migliorini, Eric Perkey, ..., Howard Y. Chang, Avery D. Posey, Jr., Ansuman T. Satpathy

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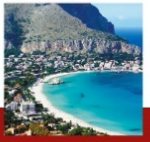
In Brief

Single-cell RNA sequencing analysis shows that CD19, primarily considered as a B cell-specific surface antigen, is expressed in human brain mural cells that are critical for blood-brain-barrier integrity, suggesting that this cell population may contribute to the neurotoxicity of CD19-directed immunotherapy including CAR-T.

Highlights

- Single-cell RNA-seq reveals *CD19* expression in human brain mural cells
- Mural cells line blood vessels and maintain blood-brain barrier integrity
- Brain mural cell *CD19* expression is present across brain regions and human age
- Targeting CD19^{+} mural cells may contribute to neurotoxicity of CAR-T therapy

CellPress



Received: 15 December 2022 | Accepted: 9 January 2023
DOI: 10.1111/bjh.18660

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BRITISH JOURNAL OF HAEMATOLOGY

LETTER TO THE EDITOR

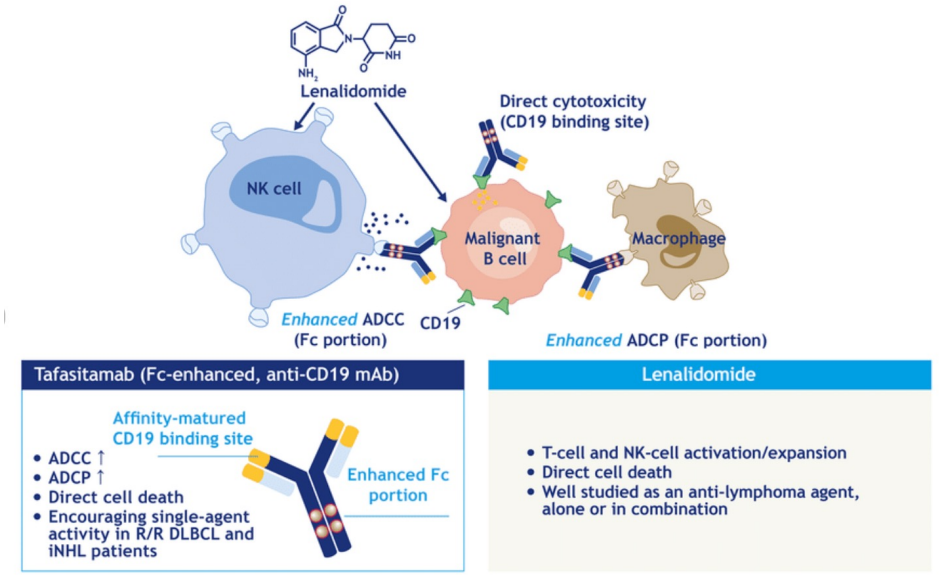
Tafasitamab at the blood–brain barrier

Rationale:

Tafasitamab in rrCNSL with potential to modulate BBB integrity by perturbation of CD19 expressed by mural cells, but without concomitant CRS, given that tafasitamab does not recruit the cytotoxic payload of T cells

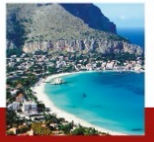
Phase II L-MIND study (NCT02399085): synergistic efficacy in RR aggressive NHL

- ORR 60%
- CR 4%
- favourable toxicity profile compared to CAR-T: no neurotoxicity



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; DLBCL, diffuse large B-cell lymphoma; iNHL, indolent non-Hodgkin's lymphoma; mAb, monoclonal antibody; NK, natural killer; R/R, relapsed/refractory.

Combination mechanism of action of tafasitamab and lenalidomide. 41



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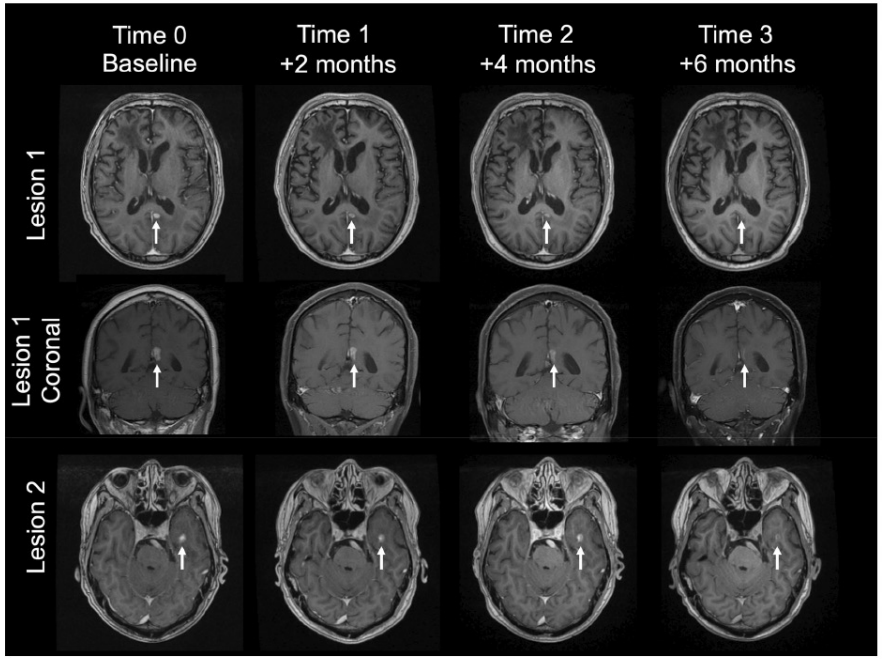

FIGURE 1 Regression of two lesions of highly refractory secondary central nervous system (CNS) lymphoma with tafasitamab plus lenalidomide. Axial spoiled gradient recalled echo (SPGR) and coronal spin-echo T1 post-contrast sequences are shown for Lesion 1 at the margin of the splenium of the corpus callosum with the left posterior cingulate cortex. Lesion 2 in the left anterior temporal lobe, shown on axial SPGR T1 post-contrast sequence, demonstrates similar time-dependent response to treatment. No perfusion imaging was obtained in this patient. A complete radiographic response on magnetic resonance imaging persists at 22 months since initial treatment with tafasitamab plus lenalidomide, markedly exceeding prior response durations with autologous stem cell transplant and lenalidomide maintenance, ibrutinib and combination ibrutinib plus lenalidomide.

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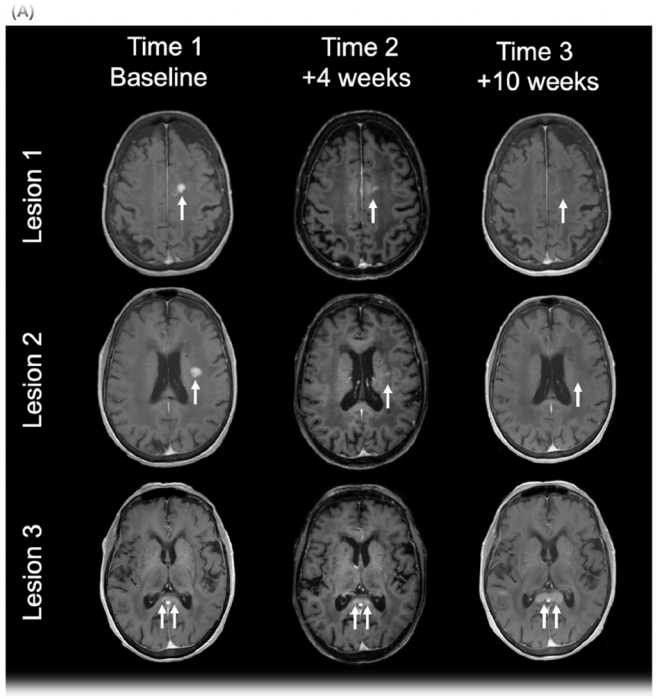
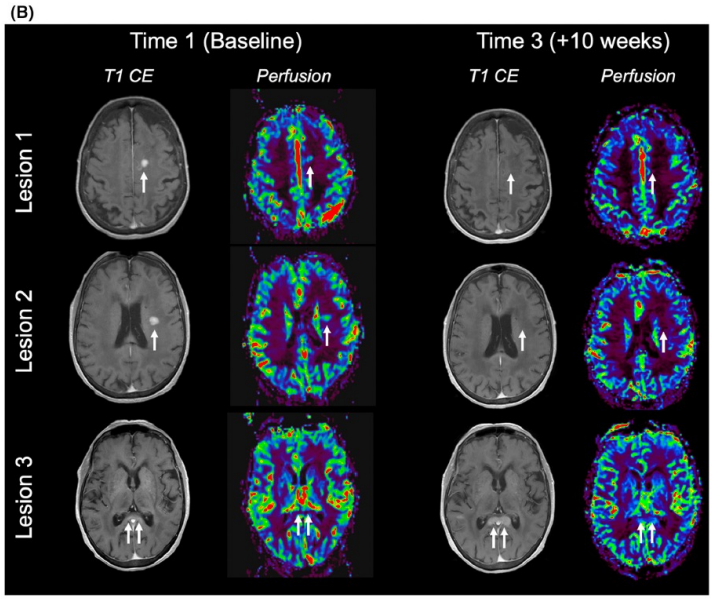
Tafasitamab at the blood–brain barrier





In this case, MRI perfusion-weighted imaging13 was also performed and demonstrated elevated vascular perfusion solely in the two responding lesions.

Ongoing trial on Tafasitamab in CNSL

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	**Tafasitamab** Plus Lenalidomide in Relapsed **CNS Lymphoma**	• **CNS Lymphoma** • Primary **Central Nervous System Lymphoma** • Secondary **Central Nervous System Lymphoma**	• Drug: **Tafasitamab** • Drug: Lenalidomide	• University of California, San Francisco San Francisco, California, United States
2	☐	Not yet recruiting	Methotrexate, **Tafasitamab**, Lenalidomide and Rituximab in Patients With PCNSL	• Non-Hodgkin **Lymphoma**	• Drug: **Tafasitamab** • Drug: Lenalidomide • Drug: Rituximab • Drug: Methotrexate	• University of Cologne Cologne, Germany

Journal Pre-proof

Molecular and clinical diversity in primary central nervous system lymphoma

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OCCAM'S RAZOR

"WHEN FACED WITH TWO POSSIBLE EXPLANATIONS, THE SIMPLER OF THE TWO IS THE ONE MOST LIKELY TO BE TRUE."

ARTICLE

https://doi.org/10.1038/s41467-022-30050-y OPEN

Check for updates

The genomic and transcriptional landscape of primary central nervous system lymphoma

Acknowledgements

Patients and Their Families

<u>Lymphoma Unit</u>
Andrés J.M. Ferreri
Fabrizio Marino
Elena Flospergher
Federico Erbella
Marco Foppoli
Piera Angelillo
Carolina Steidl
Paolo Fiore
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<u>Ophthalmology Unit</u>
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<u>Hematology & TMO Unit</u>
Fabio Ciceri &
All colleagues

<u>Neuroradiology Unit</u>
Andrea Falini
Nicoletta Anzalone
Paolo Vezzulli
Claudia Godi

<u>Pathology Unit</u>
Maurilio Ponzoni
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