L’approccio terapeutico ai linfomi primitivi del SNC

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Disclosures: ALESSANDRO BROCCOLI

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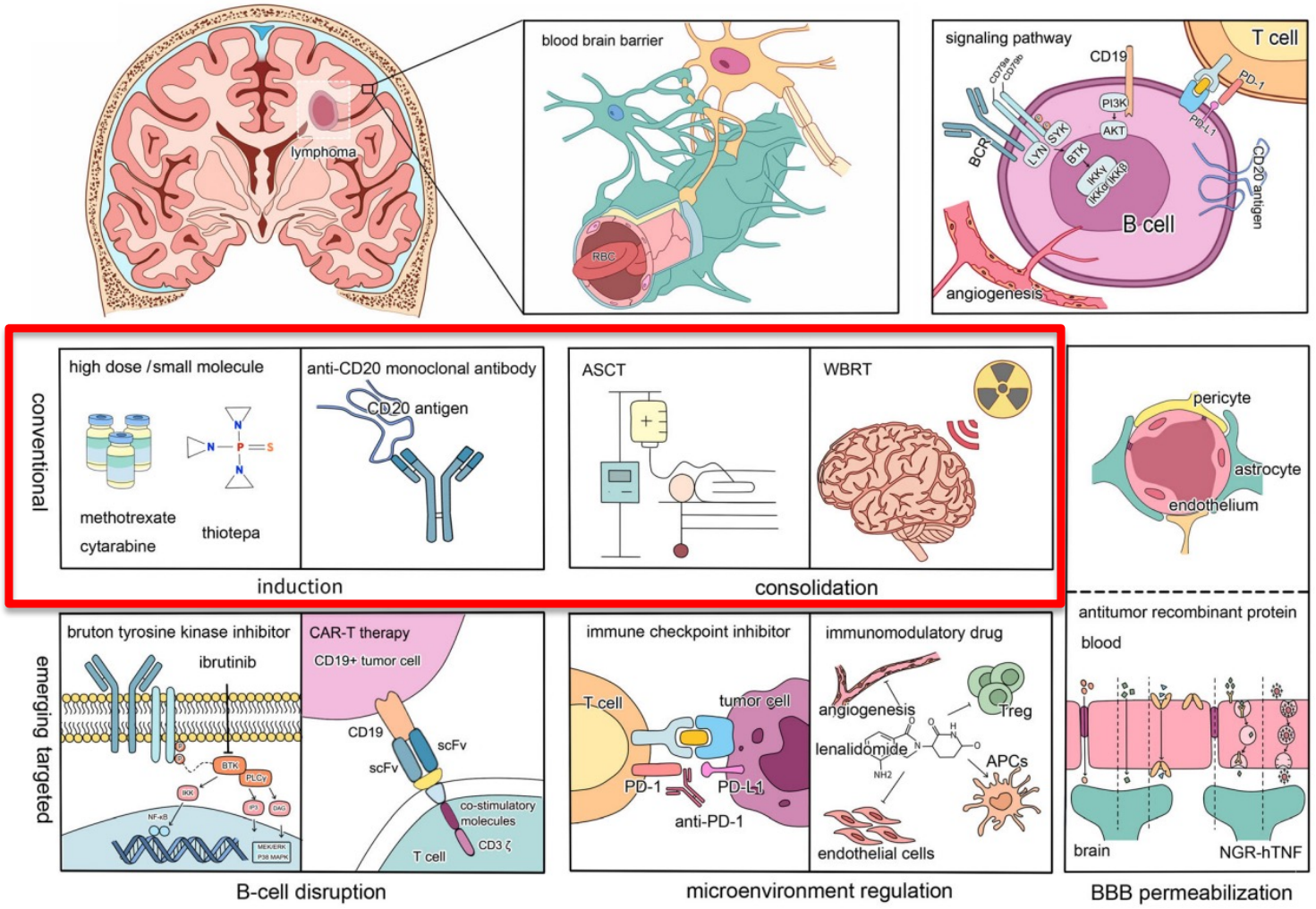
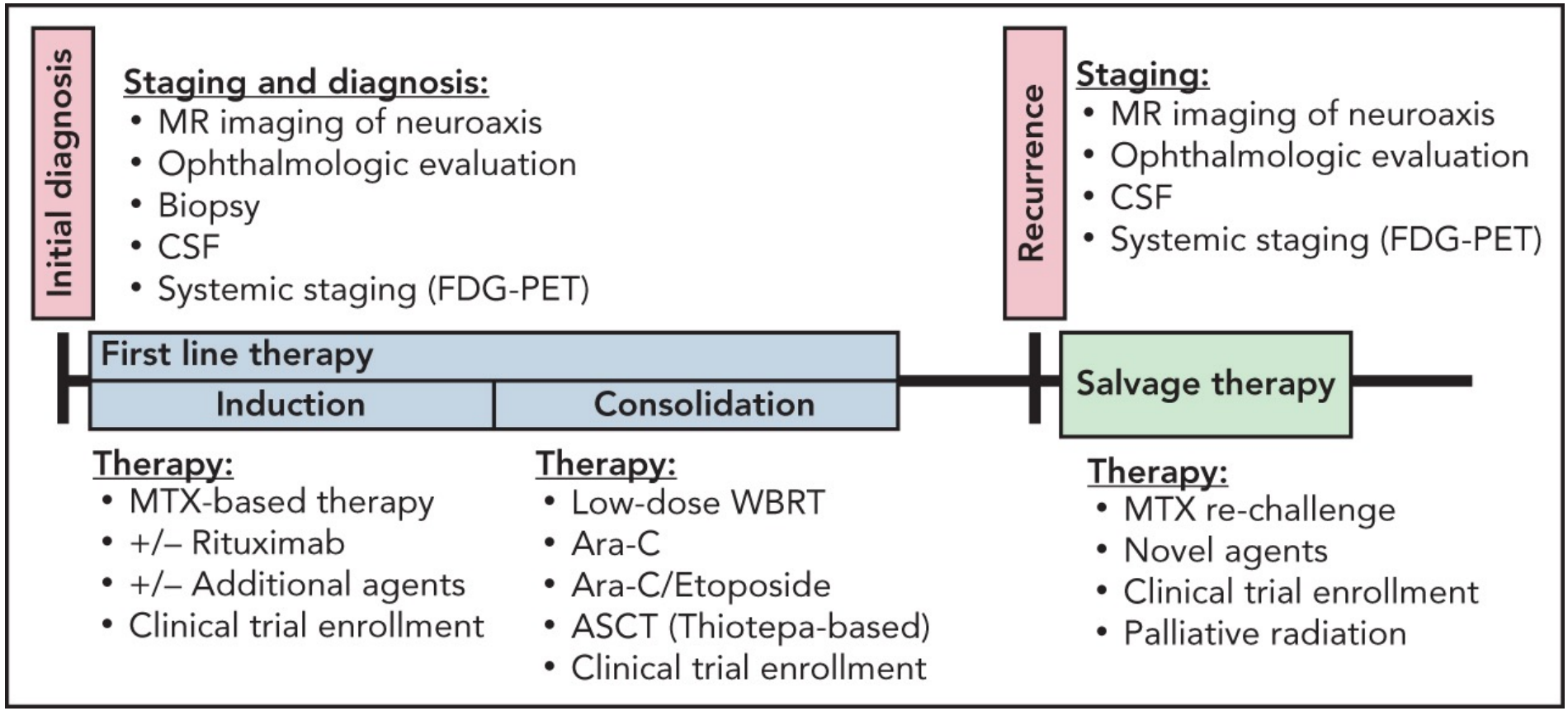


Yuan Y. *Biomarker Res*, 2021; 9: 32

Percorso di trattamento del linfoma primitivo del sistema nervoso centrale



Schaff LR. *Blood*, 2022;140: 971-979

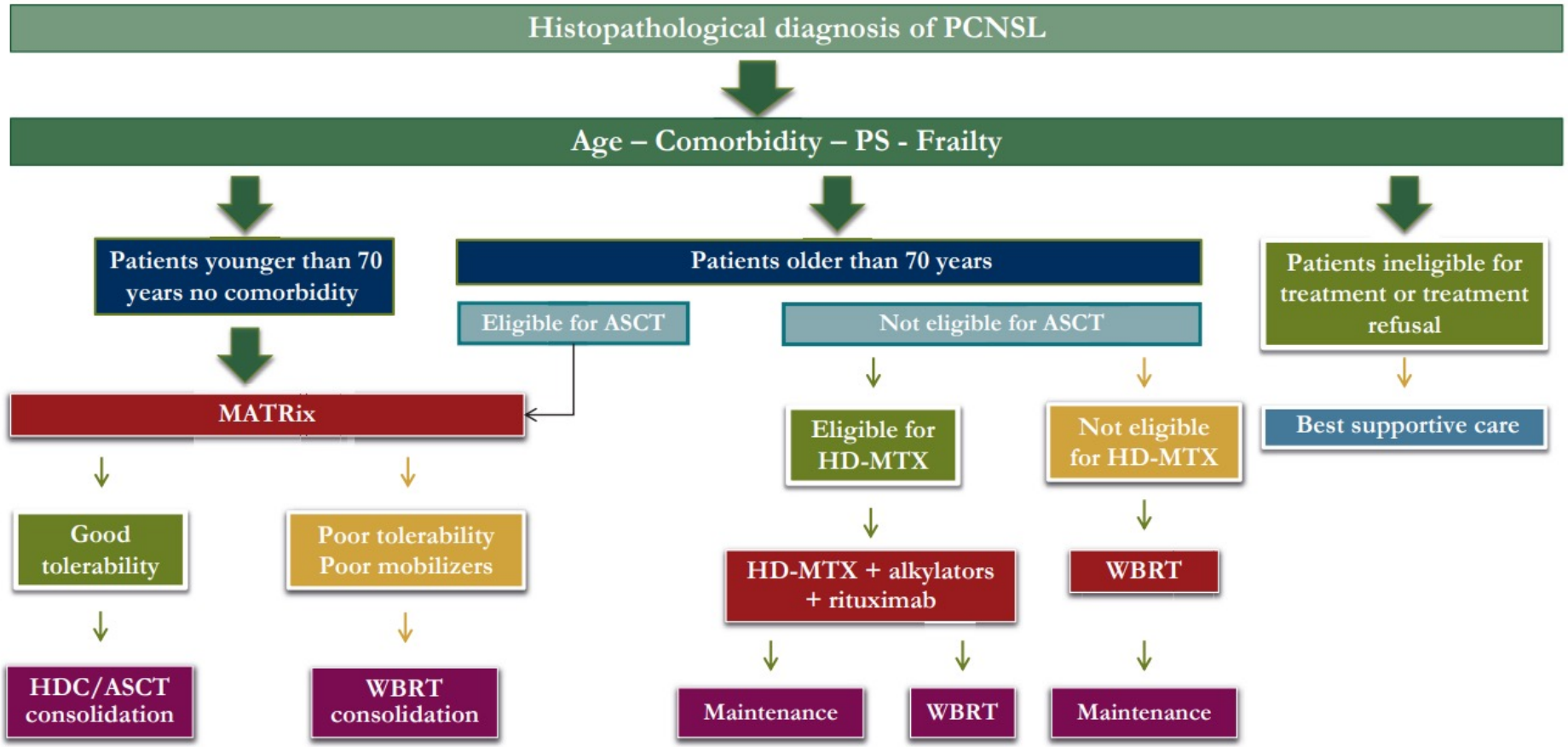
Farmaci antiblastici e barriera emato-encefalica

	Preferred regimens	Agent [a]	MW (Da)	Route	Protein binding (%)	CSF (brain)/blood (%)
Induction	R+MTX(8) R+MTX(8)+ TMZ R+M(3.5)VP(+WBRT in con.) R+MTX(3.5)+TMZ(+WBRT in con.)	MTX(M)	454	iv	46.5-54	2-20
		rituximab(R)	143857	iv	NA	0.1
		temozolomide (TMZ)	194	oral	15	20-30
		procarbazine(P)	221	oral	NA	NA
		vincristine(V)	824	iv	75	undetected
Consolidation	ASCT with condition regimen BCNU+T TBC HD-AraC(±VP16)	thiotepa(T)	189	iv	NA	95-100
		carmustine (BCNU)	214	iv	80	20-30
		Busulfan(B)	246	iv	32	95
		cyclophosphamide(C)	261	iv	20	50
		etoposide (VP16)	589	iv	97	0.5-5
		cytarabine (AraC)	243	iv	13	6-22
Refractory/ Relapse	Retreat with HD-MTX ±R +R+ibrutinib Ibrutinib TMZ Lenalidomide or others	ibrutinib	440	oral	irreversible	1-20(28.7[c])
		lenalidomide	259	oral	30	11[p]-20
		topotecan	421	iv/oral	35	13-68
		cisplatin	300	iv	90	50
		pemetrexed	427	iv	81	<5
		pomalidomide	273	oral	12-44	17-19

Abbreviations: *a* associated conditions collected from the public data sources of drugbank (https://www.drugbank.ca/drugs); *c* corrected for protein binding; *con* consolidation; *CSF* cerebrospinal fluid; *iv* intravenous; *MTX* methotrexate (g/m^2); *MV* molecular weight; *NA* not available; *NCCN* national comprehensive cancer network; *p* nonhuman primates

Yuan Y. *Biomarker Res*, 2021; 9: 32

Come operare la scelta terapeutica



Calimeri T. *ESMO Open*, 2021; 6: 100213

Studi randomizzati per induzione e consolidamento

	Year	N	Age (y)	Regimens (Arms)			Outcome		
							ORR/CR	PFS	OS
Induction	**2000**	53	NA	WBRT(40)	WBRT(40)+CHOP		18% vs 46%	NA	NA
	2009	79	18-70	MTX(3.5)	MTX(3.5)+AraC(2)		40% vs 69%	NA	NA
	2015	95	≥60	MTX(3.5)+TMZ(150)	MTX(3.5)+Pro(100) +V(1.4) +AraC(3)		71% vs 82%	6.1m vs 9.5m	NA
	2016	219	18-70	MTX(3.5)+AraC(2)	MTX(3.5)+AraC(2)+R(375)	MTX(3.5)+AraC(2) +R(375) +T(30) (MATRix)	53% vs 74% vs 87%	42% vs 56% vs 69%	NA
	2018	49	14-69	MTX(3.5)+ AraC(1.0)	F(100)+Ten(60)+DXM(40)		40% vs 33%	NA	NA
	2019	199	18-70	MTX(3.0) +BCNU(100) +Ten(100) +Pred(60)	R(375, weekly)+MTX(3.0) +BCNU(100) +Ten(100) +Pred(60)		86% vs 86%	(≤60 y) 26.3m vs 59.9m (>60 y) 19.6m vs 14.6m	(≤60 y) 56.7m vs not reached (>60 y) 49.2m vs 34.9m
Consolidation	**2010**	318	55-69	w/w	WBRT(45)		NA	11.9m vs 18.3m	37.1m vs 32.4m
	2017	118	18-70	WBRT	ASCT		95% vs 93%	NA	NA
	2017	318	55-69	w/w	WBRT(45)		Reduced QoL and lower value of MMSE in WBRT arm		
	2019	140	18-60	WBRT	ASCT		NA	63% vs 87%	Cognitive impairment after WBRT

Abbreviations: *A* cytarabine (g/m^2); *BCNU* carmustine (mg/m^2); *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone;*CR* complete remission; *DXM* dexamethasone (mg); *EFS* event-free survival; *I* ifosfamide (g/m^2); *F* fotemustine (mg/m^2); *M* methotrexate (g/m^2); *MMSE* Mini Mental State Examinations; *NA* not available; *NCR* no complete remission; *ND* newly diagnosed; *ORR* overall response rate; *OS* overall survival; *PCNSL* primary central nervous system lymphoma; *PFS* progression-free survival; *PR* partial remission; *Pred* prednisone (mg/m^2); *Pro* procarbazine (mg/m^2); *QoL* quality of life; *R* rituximab (mg/m^2); *T* thiotepa (mg/m^2); *Ten* teniposide (mg/m^2); *TMZ* temozolomide (mg/m^2); *WBRT/RT* whole brain radiotherapy (Gy); *w/w* wait and watch; *V* vincristine (mg/m^2); *VP16* etoposide (mg/m^2)

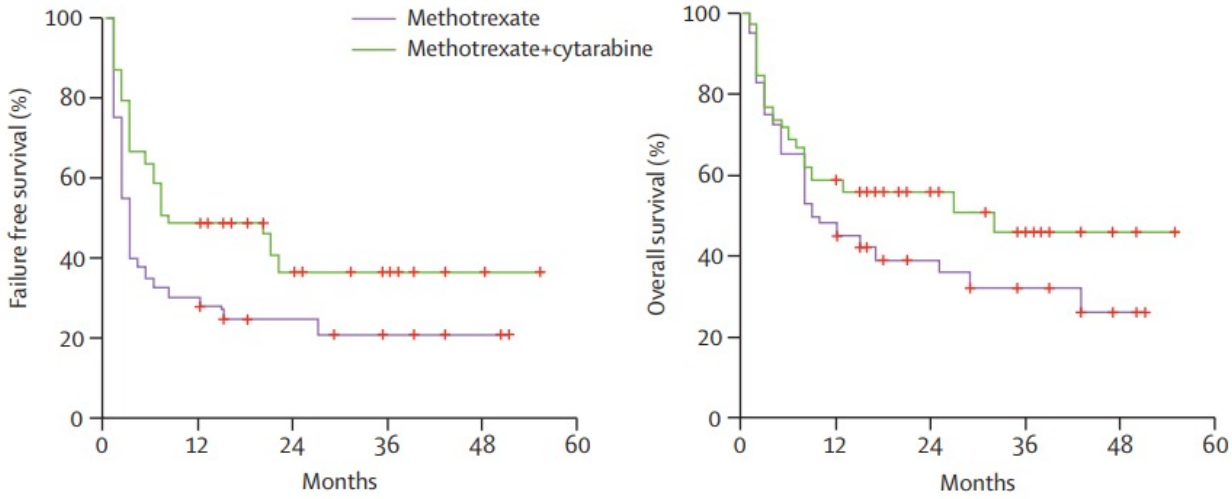
Yuan Y. *Biomarker Res*, 2021; 9: 32

High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

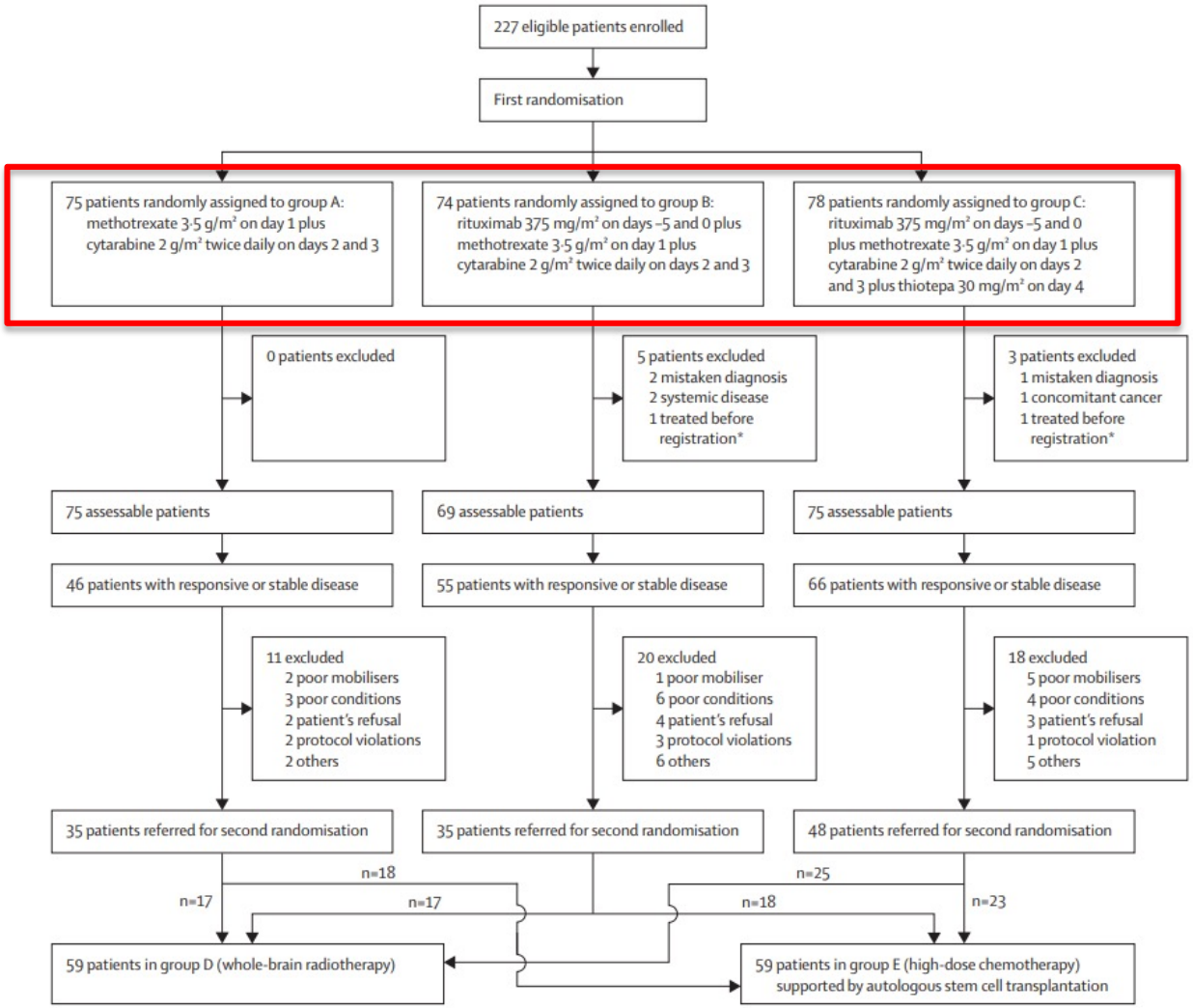
	Methotrexate (n=40)	Methotrexate+cytarabine (n=39)	p value
Toxic deaths	1 (3%)	3 (8%)	0·35
Neutropenia	6 (15%)	35 (90%)	0·00001
Thrombocytopenia	3 (8%)	36 (92%)	0·00001
Anaemia	4 (10%)	18 (46%)	0·00001
Infective complications	1 (3%)	9 (23%)	0·0002
Hepatotoxicity	1 (3%)	4 (10%)	0·05
Nephrotoxicity	2 (5%)	1 (3%)	0·31
GI/mucositis	2 (5%)	1 (3%)	0·31
Cardiotoxicity	1 (3%)	1 (3%)	0·87
Neurotoxicity	0	1 (3%)	0·29
Coagulation/DVT	4 (10%)	1 (3%)	0·002

The worst toxicity per organ, per patient was considered for analyses. GI=gastrointestinal. DVT=deep venous thrombosis.

	Methotrexate (n=40)	Methotrexate+cytarabine (n=39)	p value
Complete remission	7 (18%)	18 (46%)	0·006
Partial response	9 (23%)	9 (23%)	..
Overall response	16 (40%)	27 (69%)	0·009
Stable disease	1 (3%)	2 (5%)	..
Progressive disease	22 (55%)	7 (18%)	..
Toxic deaths	1 (3%)	3 (8%)	0·35
CRR/IELSG score			
Low risk	5/12 (42%)	5/10 (50%)	..
Intermediate risk	2/24 (8%)	11/24 (46%)	..
High risk	0/4 (0%)	2/5 (40%)	..
ORR/IELSG score			
Low risk	8/12 (67%)	10/10 (100%)	..
Intermediate risk	7/24 (29%)	15/24 (63%)	..
High risk	1/4 (25%)	2/5 (40%)	..
3-year FFS (SE)			
Low risk	33% (13)	70% (14)	..
Intermediate risk	14% (8)	32% (11)	..
High risk	11% (10)	20% (17)	..



Ferreri AJM. *Lancet*, 2009; 374: 1512-1520



Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial

Braccio A: metotrexato + citarabina
Braccio B: rituximab + metotrexato + citarabina
Braccio C: rituximab + metotrexato + citarabina + tiotepa

Ferreri AJM. *Lancet Haematol*, 2016; 3: e217-e227

Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial

	Methotrexate–cytarabine (group A; n=75)	Methotrexate–cytarabine plus rituximab (group B; n=69)	Methotrexate–cytarabine plus rituximab and thiotepa (group C; n=75)	HR (95% CI) for group A *vs* group B	p value	HR (95% CI) for group A *vs* group C	p value	HR (95% CI) for group B *vs* group C	p value
Complete remission	17 (23%; 95% CI 14–31)	21 (30%; 95% CI 21–42)	37 (49%; 95% CI 38–60)	0·74 (0·43–1·29)	0·29	0·46 (0·28–0·74)	0·0007	0·61 (0·40–0·94)	0·020
Partial response	23 (31%)	30 (43%)	28 (37%)	..	..	..	..	..	..
Overall response*	40 (53%; 95% CI 42–64)	51 (74%; 95% CI 64–84)	65 (87%; 95% CI 80–94)	0·69 (0·54–0·88)	0·010	0·61 (0·49–0·77)	0·00001	0·89 (0·76–1·03)	0·053
Stable disease	6 (8%)	4 (6%)	1 (1%)	..	..	..	..	..	..
Progressive disease	22 (29%)	11 (16%)	6 (8%)	..	..	..	..	..	..
Deaths due to toxicity	7 (9%)	3 (4%)	3 (4%)	..	..	..	..	..	..

HR=hazard ratio. *Overall response=complete response and partial response.

Ferreri AJM. *Lancet Haematol*, 2016; 3: e217-e227

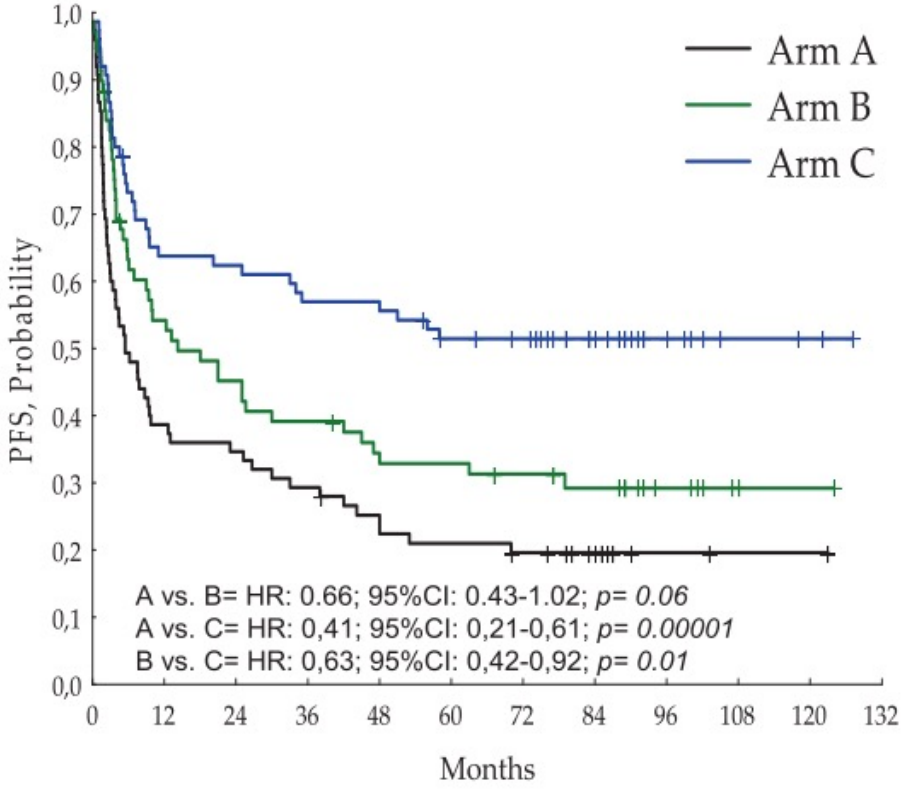
Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial

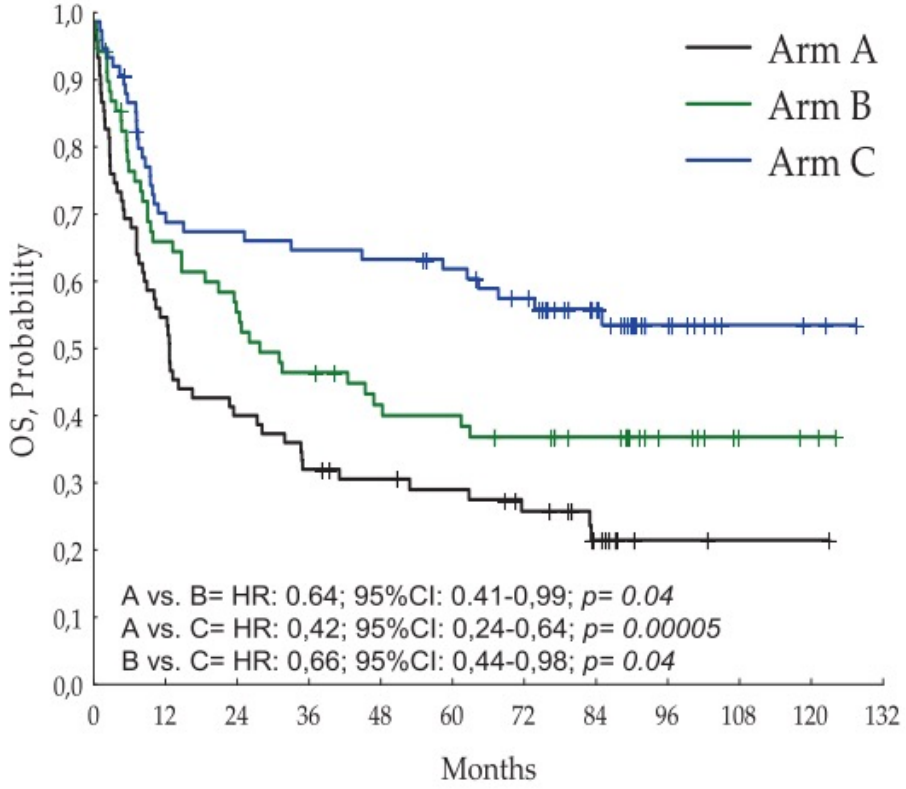
	Total	Arm A ($n=75$)	Arm B ($n=69$)	Arm C ($n=75$)	WBRT ($n=70$)	ASCT ($n=60$)	Others ($n=74$)
Toxic deaths (1st line)	15	7 (9%)	3 (4%)	3 (4%)	0 (0%)	2 (2%)	-
Progressive disease	66	26 (35%)	18 (26%)	13 (17%)	4 (4%)	2 (2%)	3 (4%)
Relapse after response	51	19 (25%)	17 (25%)	15 (20%)	22 (31%)	19 (32%)	10 (14%)
Salvage therapy	75	30 (40%)	22 (32%)	23 (31%)	15 (21%)	18 (30%)	42 (57%)
Second tumors	8	1/38 (3%)	2/47 (4%)	5/59 (8%)	5/67 (7%)	3 (5%)	0 (0%)
Deaths during/after salvage	7	4 (13%)	0 (0%)	3 (13%)	2 (13%)	2 (11%)	3 (4%)
Deaths of lymphoma	96	43 (57%)	32 (46%)	21 (28%)	19 (27%)	16 (27%)	61 (82%)
Deaths in relapse-free patients	14	2/17 (12%)	6/28 (21%)	6/42 (14%)	9/44 (20%)	3/37 (8%)	2/6 (33%)

Braccio A: metotrexato + citarabina
Braccio B: rituximab + metotrexato + citarabina
Braccio C: rituximab + metotrexato + citarabina + tiotepa

Ferreri AJM. *Leukemia*, 2022; 36: 1870-1878

Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial





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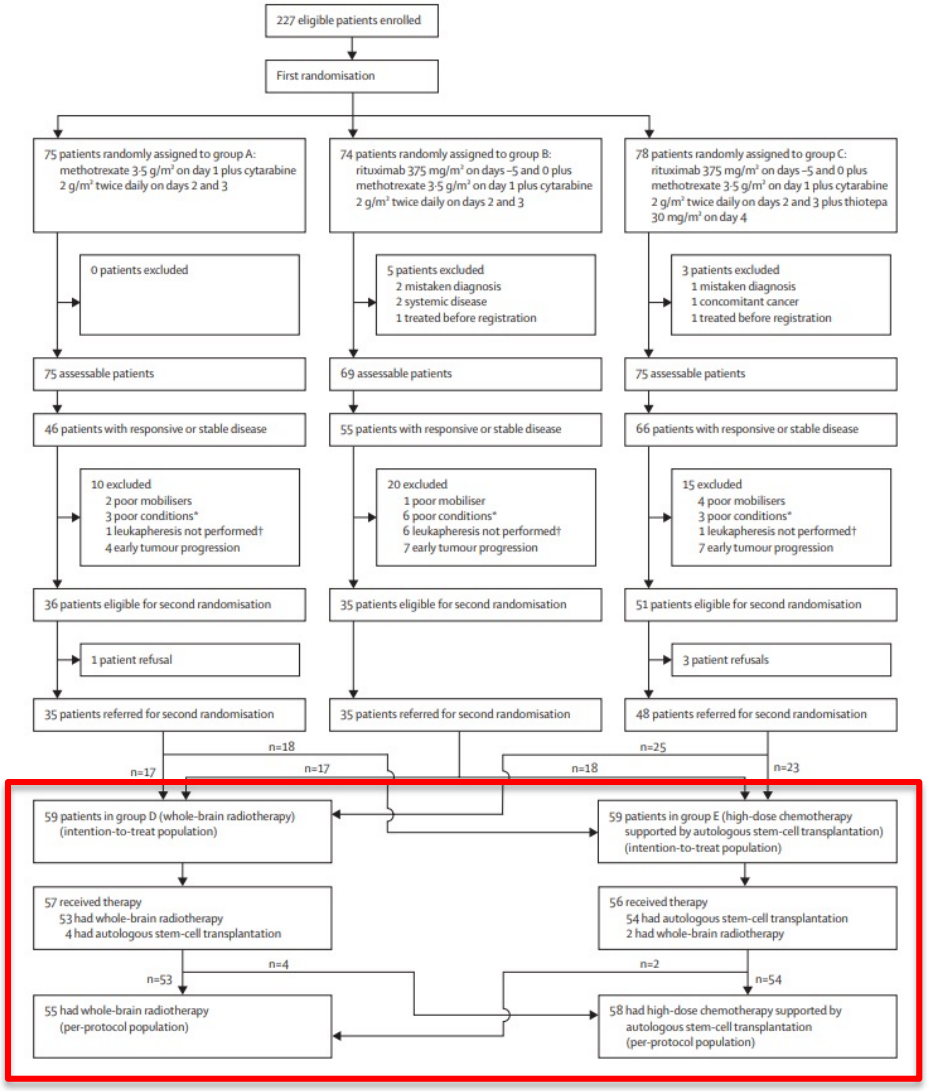
Ferreri AJM. *Leukemia*, 2022; 36: 1870-1878

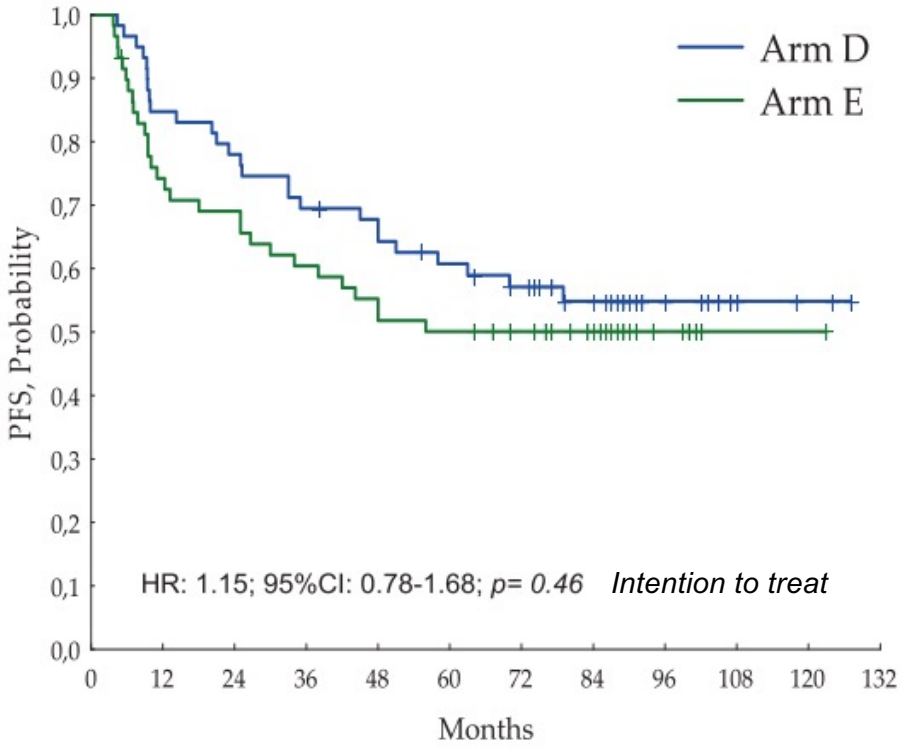


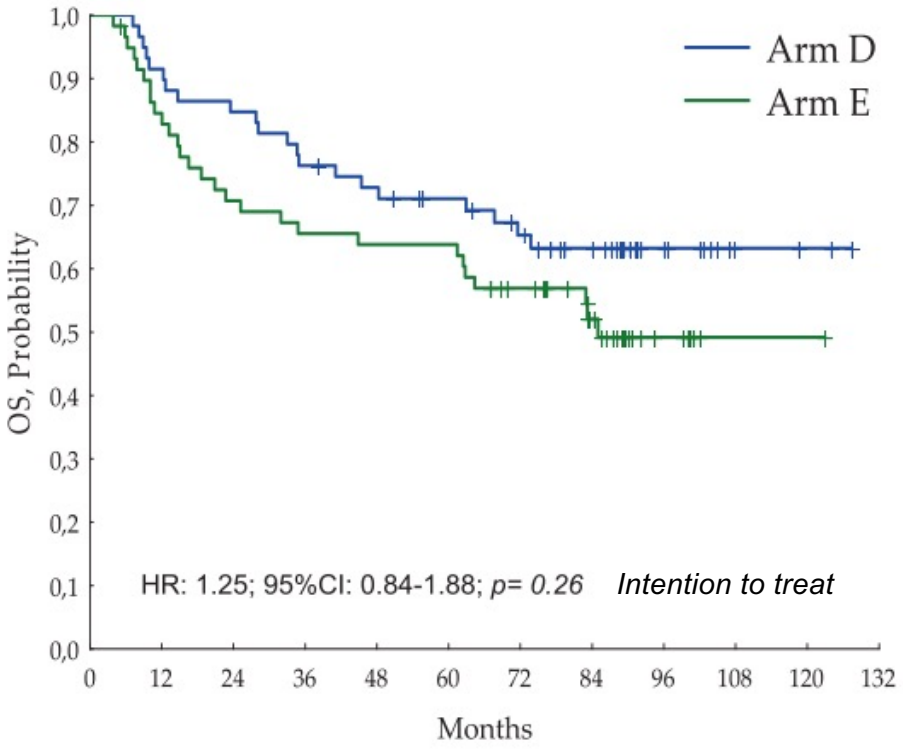
Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial

Braccio D: radioterapia panencefalica
Braccio E: terapia ad alte dosi (BCNU + tiotepa) + trapianto autologo

Ferreri AJM. *Lancet Haematol*, 2017; 4: e510-e523

Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial





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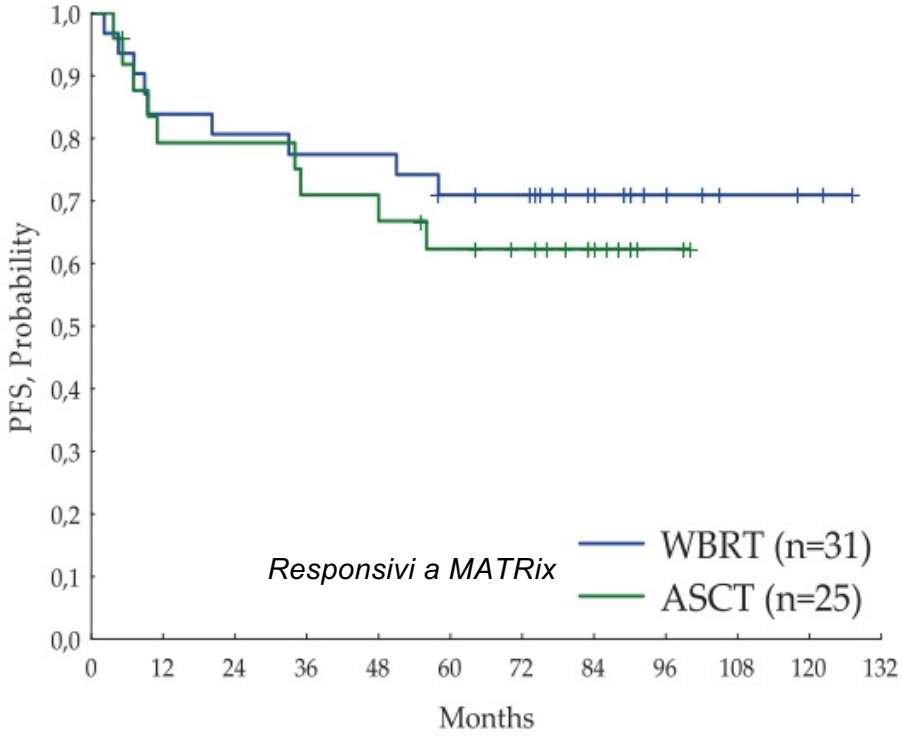
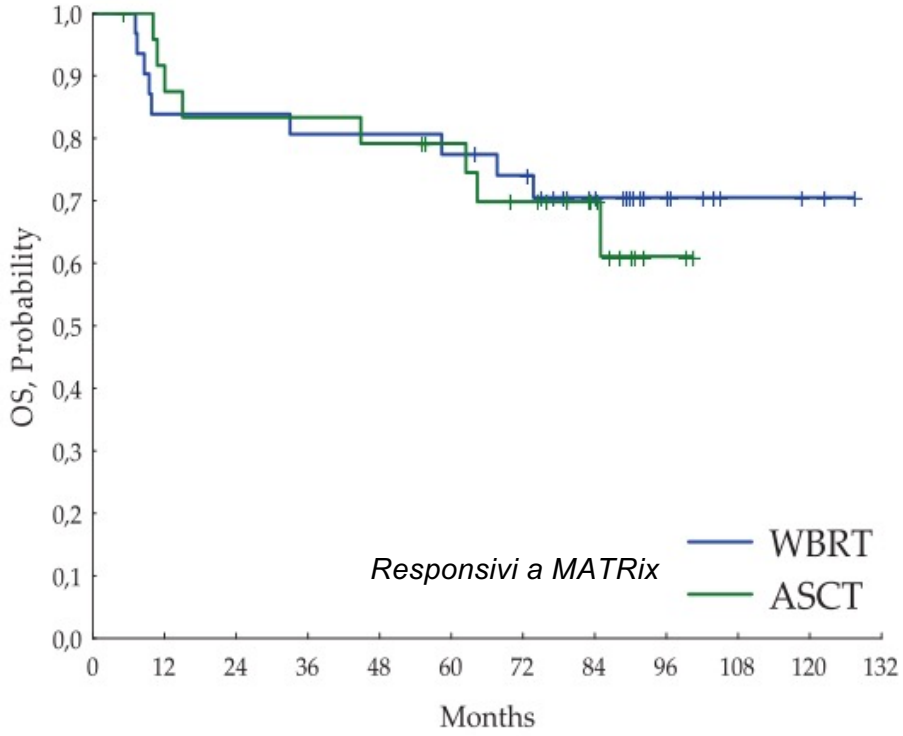
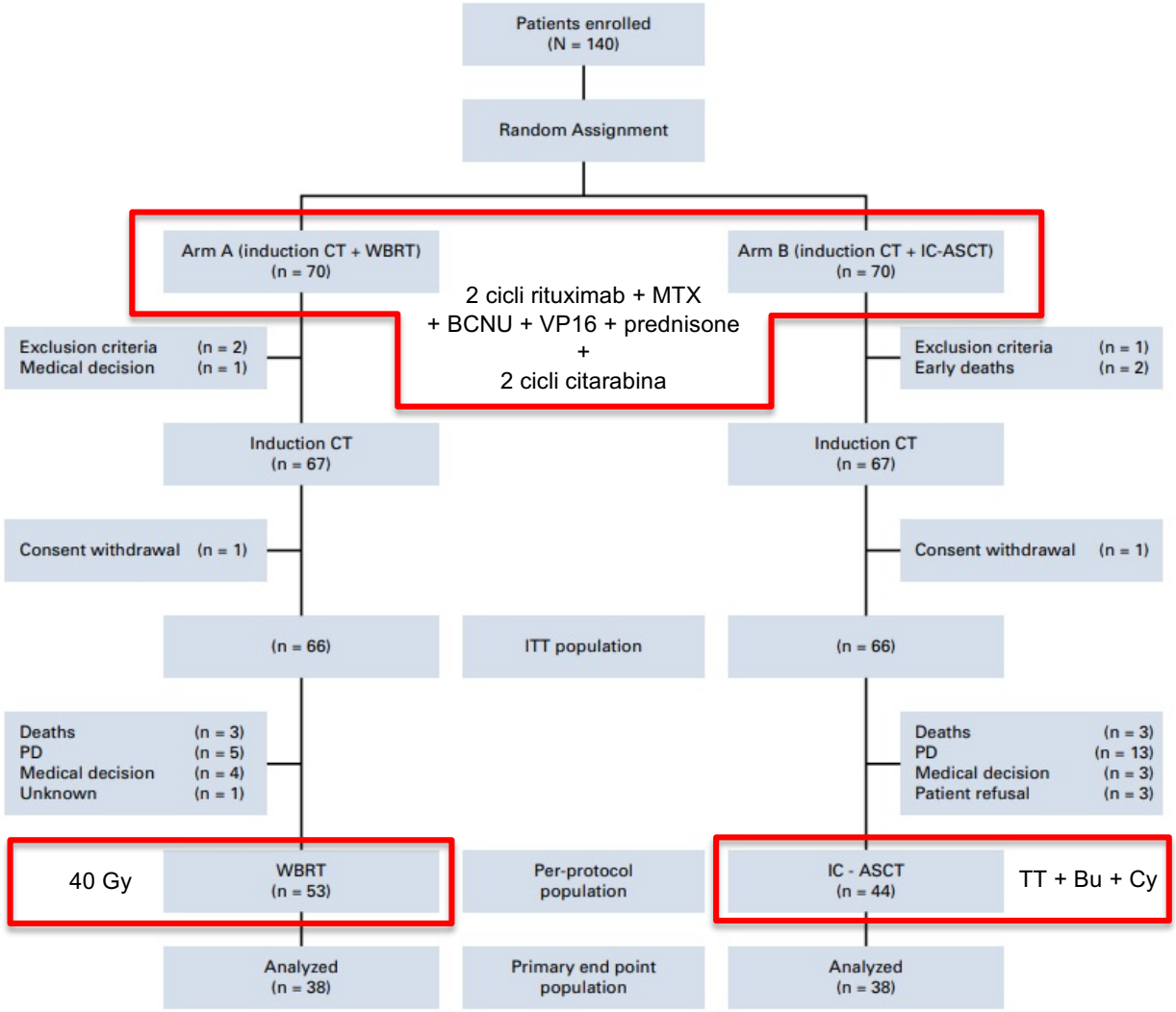




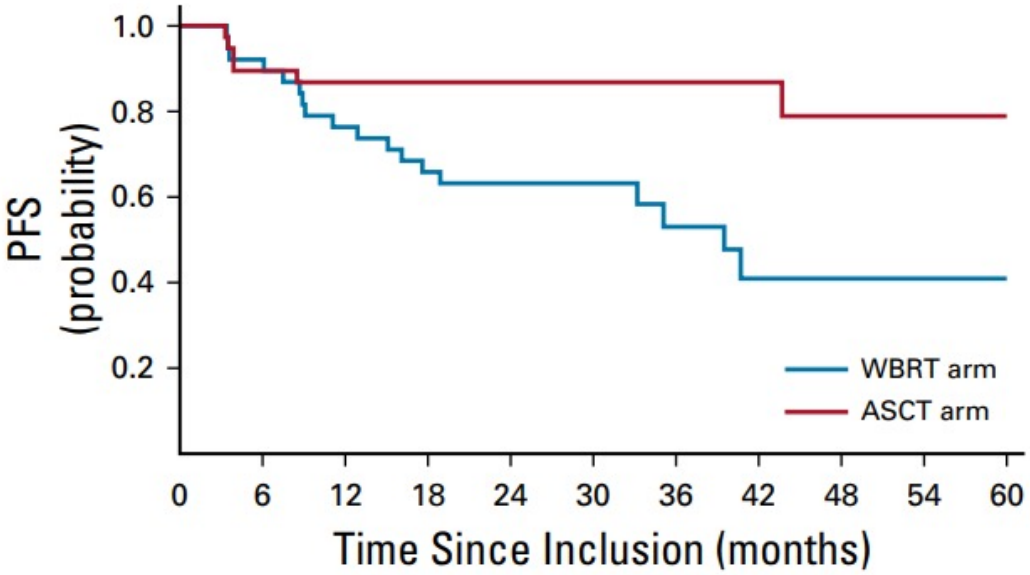
Ferreri AJM. *Leukemia*, 2022; 36: 1870-1878

Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study

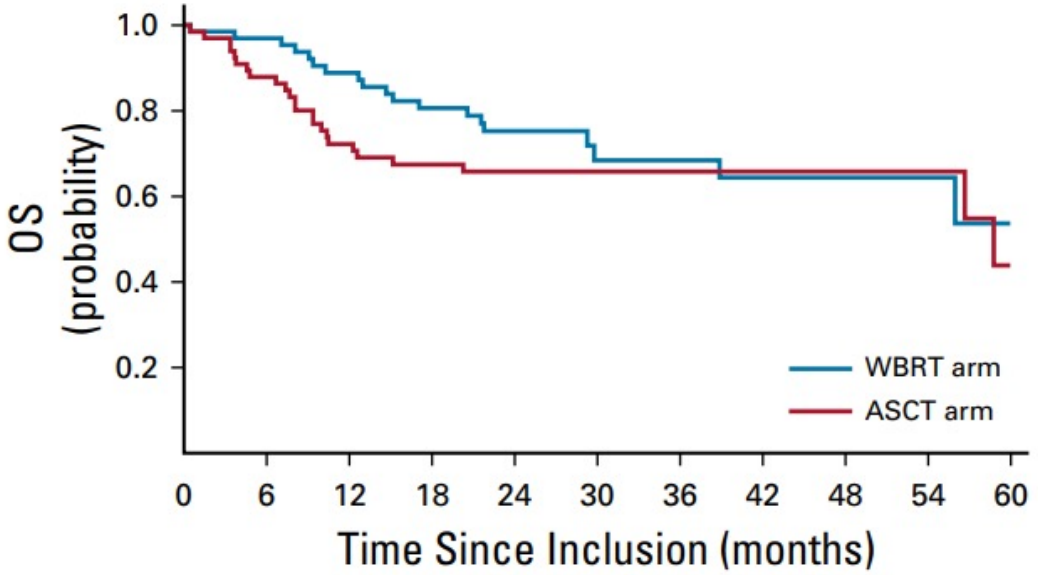


Houillier C. *J Clin Oncol*, 2019; 37: 823-833

Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study



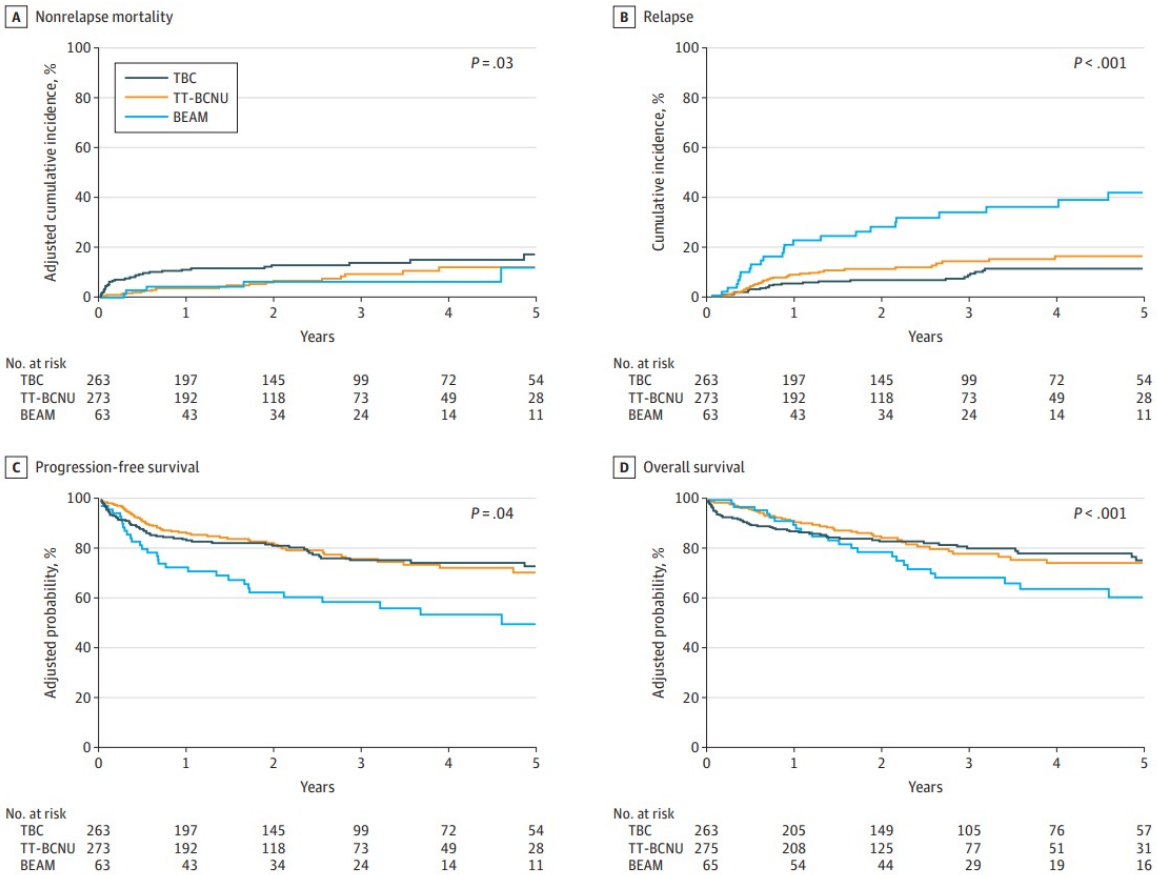
No. at risk											
WBRT arm	38	35	29	25	24	13	10	6	4	4	3
ASCT arm	38	34	31	31	30	20	14	11	8	5	3



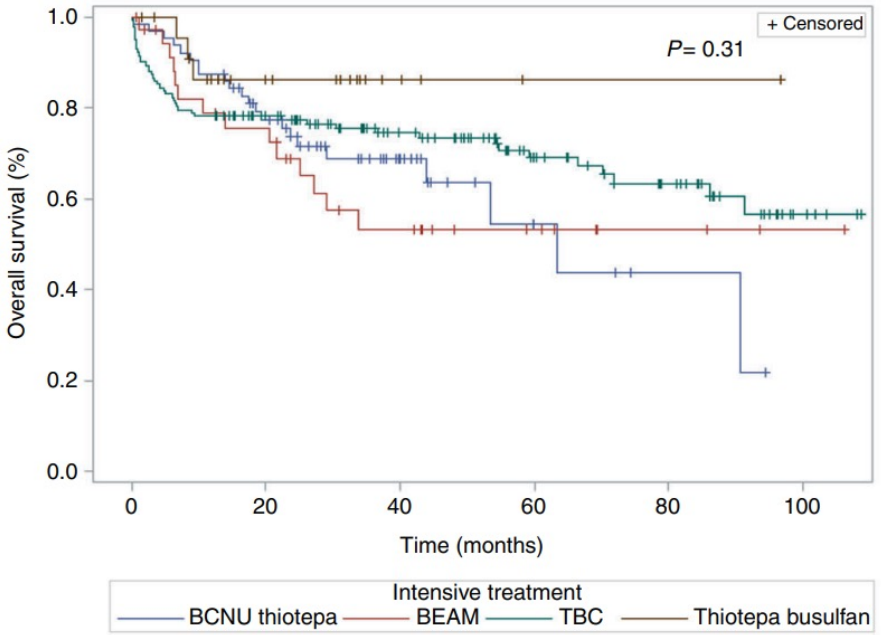
No. at risk											
WBRT arm	66	62	54	49	42	19	17	10	6	6	4
ASCT arm	66	57	46	41	38	24	17	14	9	6	4

Houillier C. *J Clin Oncol*, 2019; 37: 823-833

Confronto tra diversi regimi di condizionamento

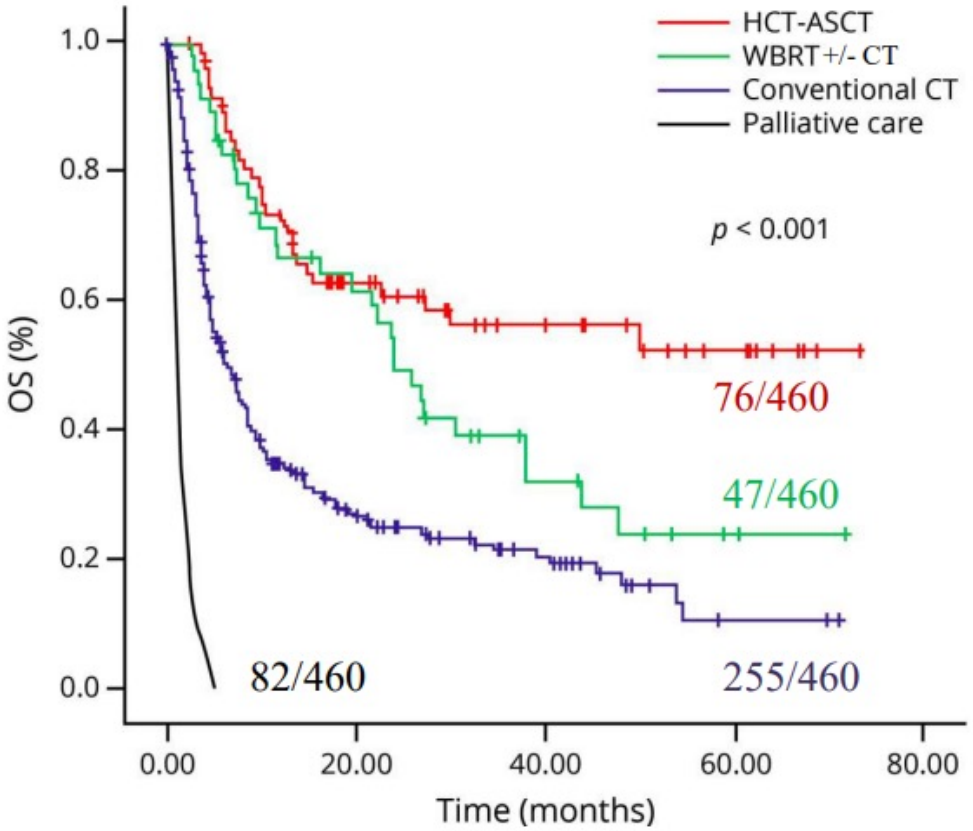


BEAM indicates carmustine, etoposide, cytarabine, melphalan; TBC, thiotepa, busulfan, cyclophosphamide; TT-BCNU, thiotepa, carmustine.



Scordo C. *JAMA Oncol*, 2021; 7: 993-1003 — Schenone L. *Bone Marrow Transplant*, 2022; 57: 966-974

Prognosi della malattia in ricaduta in funzione del salvataggio



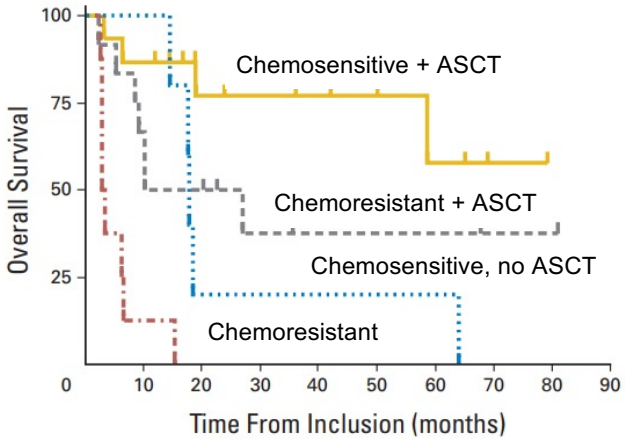
Whole population: 460 pz
- 3-y OS = 25 %
- Median = 6.7 months

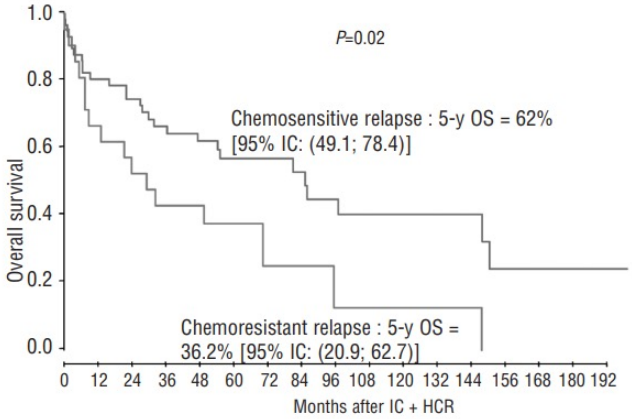
After ASCT:
- 3-y OS = 57%
- Median OS = NR

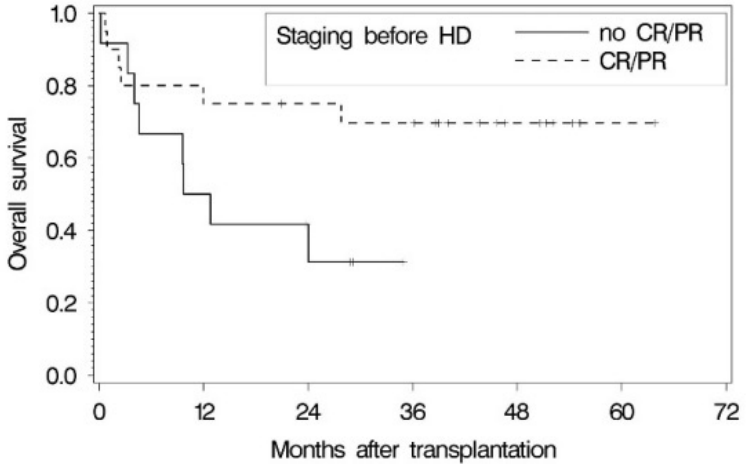
Houillier C. *Neurology*, 2020; 94: e1027-e1039

Terapia convenzionale alla ricaduta

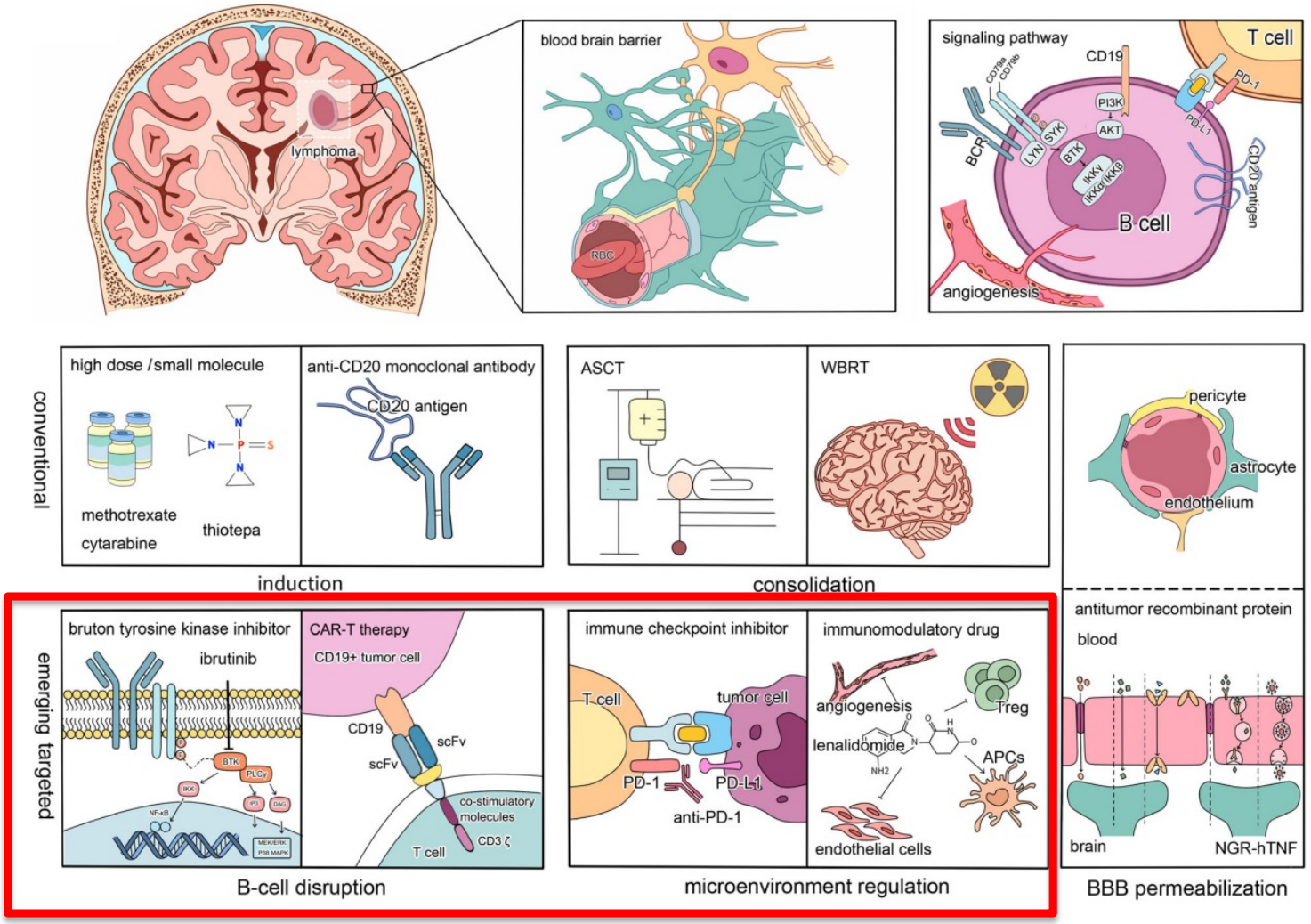
WBRT	ORR: 74 %; Median OS = 11 months
Re-HD MTX	In selected cases with long lasting CR1 with previous course of MTX
HD Ara-C or Ifosfamide based Chemo (e.g R-DHAP, R-ICE)	**ORR: 60-80 %,**
but short duration of response if no further consolidation ASCT	







Soussain C. *J Clin Oncol*, 2008; 26: 2512-2518 — Soussain C. *Haematologica*, 2012; 97: 1751-1756 — Kasenda B. *Leukemia*, 2017: 31: 2623-2629



Yuan Y. *Biomarker Res*, 2021; 9: 32

Agenti attivi nella malattia in ricaduta

	Study	Agents	Patients, n	ORR* (%)	Median PFS, mo	Median OS, mo
	Fischer et al, 2006	Topotecan	27	9/27 (33)	2	8.4
	Reni et al, 2007	Temozolomide	36	11/36 (31)	2.8	3.9
	Soussain et al, 2008	CYVE+ASCT	43	20/40 (50)	11.6	18.3
	Batchelor et al, 2011	Rituximab	12	5/12 (42)	1.9 (57 d)	20.9
	Raizer et al, 2012	Pemetrexed	11	6/11 (55)	5.7	10.1
	Rubenstein et al, 2013	IT rituximab+IT MTX	14	6/14 (43)	1.2	NR
	Nayak et al, 2013	Rituximab+TMZ+pred	16	5/14 (36)	1.6 (7 wk)	NR
	Korfel et al, 2016	Temsirolimus	37	20/37 (54)	2.1	3.7
BTKi	Grommes et al, 2017	Ibrutinib	13	10/13 (77)	4.6	15
BTKi	Grommes et al, 2019	Ibrutinib/MTX/rituximab	15	8/15 (80)	9.2	NR
BTKi	Soussain et al, 2019	Ibrutinib	52	27/52 (52)	4.8	19.2
IMiDs	Ghesquieres et al, 2019	Lenalidomide/rituximab	45	28/45 (62)	7.8	17.7
IMiDs	Tun et al, 2018	Pomalidomide	25	12/25 (48)	5.3	NR
IMiDs	Rubenstein et al, 2018	Lenalidomide	13	8/13 (62)	NR	NR

CYVE, cytarabine + etoposide; NR, not reached; pred, methylprednisone; TMZ, temozolomide.
*Partial response/complete response.

Schaff LR. *Blood*, 2022;140: 971-979

Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' *i*LOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network

	Enrolled	Evaluable for response
N	52	44
Sex ratio M:F	**6:7**	**5:6**
Median age	**67.5 (range, 47–82)**	**70 (range, 52–81)**
≥ 60	**35 (67%)**	**33 (75%)**
PS		
0–1	**35 (67%)**	**33 (77%)**
2	**17 (33%)**	**11 (23%)**
Number of previous lines of treatment		
1	**19 (36.5%)**	**18 (41%)**
2	**19 (36.5%)**	**15 (34%)**
3	**9 (17%)**	**6 (14%)**
4	**5 (10%)**	**5 (11%)**
Previous ASCT	7	4
Previous WBRT	11	1
Status from previous treatment		
Relapse	**38 (73%)**	**31 (70%)**
Refractory	**14 (27%)**	**13 (30%)**
Disease assessment at the time of inclusion in the study		
Brain parenchyma/spinal cord	**38**	**30**
With IO	4	4
With CSF	2	1
With IO + CSF	1	1
Intraocular	**14**	**14**
With CSF	2	2
Corticosteroids during cycle 1	**19**	**14**

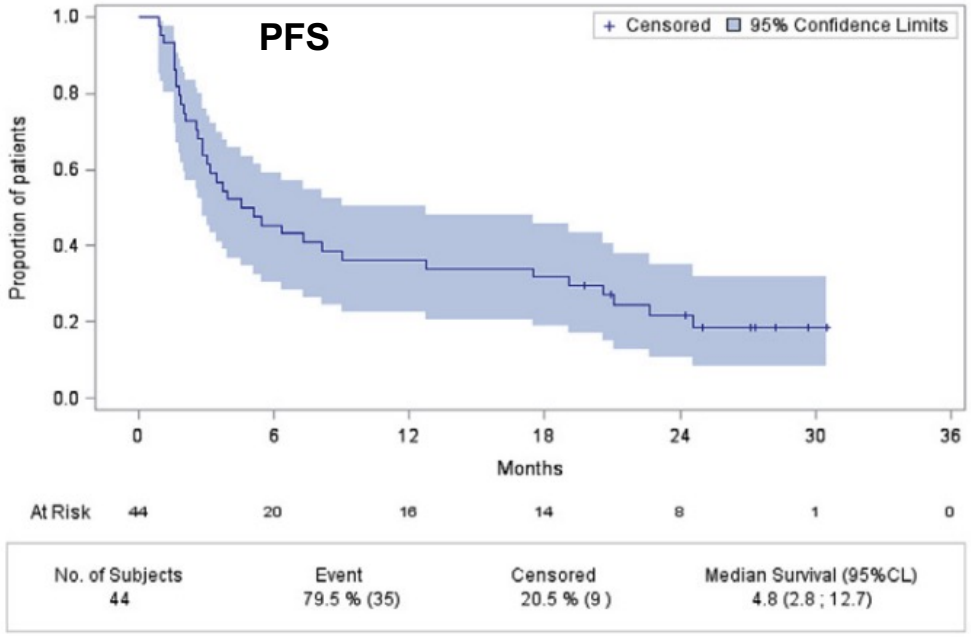
ITT population, intention-to-treat population; PS, performance status; IO, intraocular; CSF, cerebrospinal fluid; ASCT, autologous stem cell transplantation; WBRT, whole-brain radiotherapy.

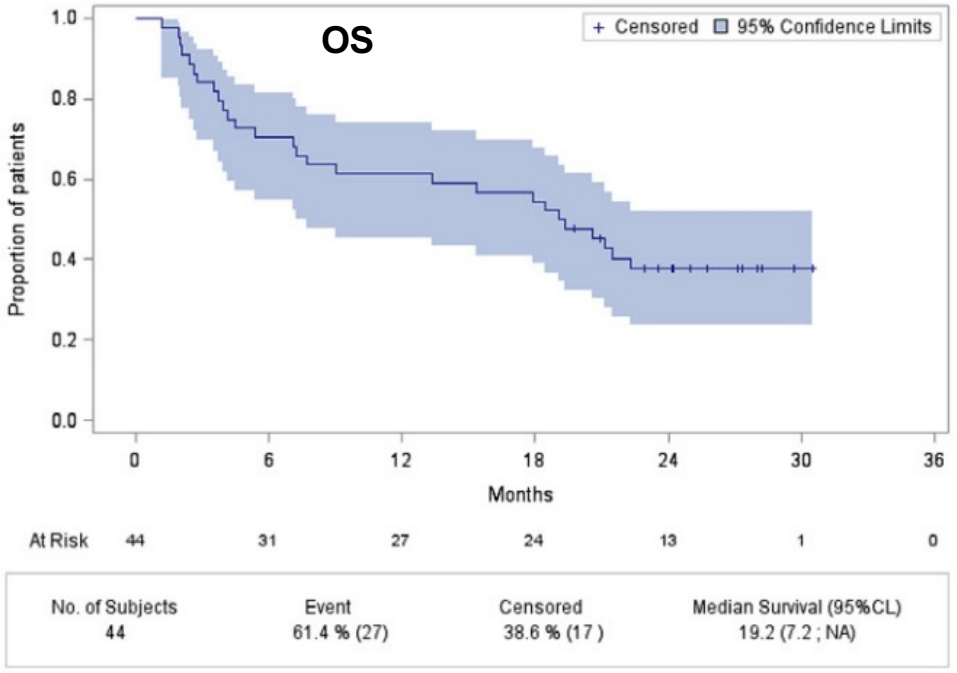
Therapeutic response	Cycle 4	Cycle 6	Cycle 9	Cycle 12
CR + uCR	9	11	13	11
PR	8	1	0	0
ORR	**39%**	**27%**	**29%**	**25%**
SD	0	2	1	1
DC	**39%**	**32%**	**32%**	**27%**
PD	8	2	3	0
Not reaching the time point	19	28	27	32

CR, complete response; uCR, unconfirmed complete response; PR, partial response; SD, stable disease; DC, disease control; PD, progressive disease

Soussain C. *Eur J Cancer*, 2019;117: 121-130

Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' *i*LOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network

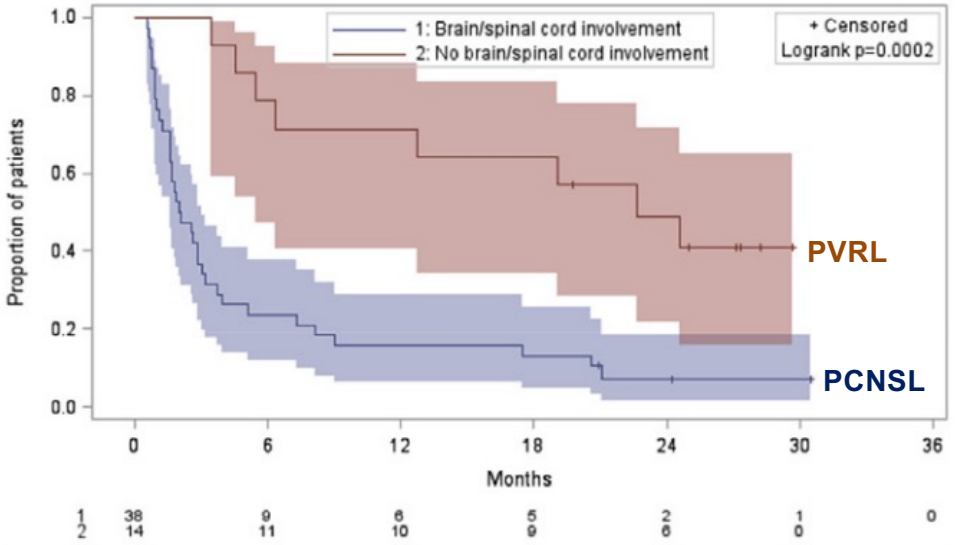




Soussain C. *Eur J Cancer*, 2019;117: 121-130

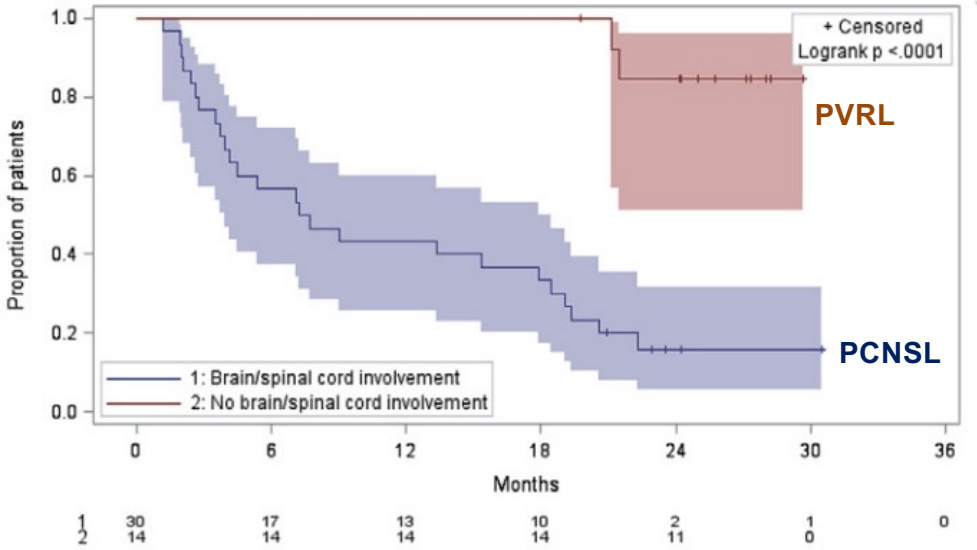
Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' *i*LOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network

PFS



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Brain/spinal cord involvement	38	92.1 % (35)	7.9 % (3)	2.1 (1.6 ; 3)
No brain/spinal cord involvement	14	57.1 % (8)	42.9 % (6)	22.7 (5.5 ; NA)

OS



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Brain/spinal cord involvement	30	83.3 % (25)	16.7 % (5)	7.5 (3.9 ; 18.4)
No brain/spinal cord involvement	14	14.3 % (2)	85.7 % (12)	Not reached

Soussain C. *Eur J Cancer*, 2019;117: 121-130

	All $n = 45$	
Clinical characteristics	*n*	%
Age, years		
Median (range)	69 (46–86)	
Sex		
Male	16	36
Female	29	64
ECOG, PS		
0–1	20	51
2–4	19	49
NE	6	
Localization at inclusion		
Brain	34	76
Brain alone	23	
Brain+eye	6	
Brain+CSF	5	
Eye	11	24
Eye alone	9	
Eye+CSF	2	
Histology subtypes		
DLBCL	45	100
Previous treatment		
Number of previous treatments		
Median	1 (1–4)	
1	23	51
2	14	31
3	5	11
4	3	7
HDT+ASCT	9	20
Radiotherapy	5	11
Rituximab	30	67
First-line therapy		
MPVA protocol	30	67
MBVP protocol	6	13
HD MTX-containing treatment	9	20
Type of disease at inclusion		
Relapse	38	84
Refractory	7	16
Corticosteroids during cycle 1 of R^2	29	64

Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)

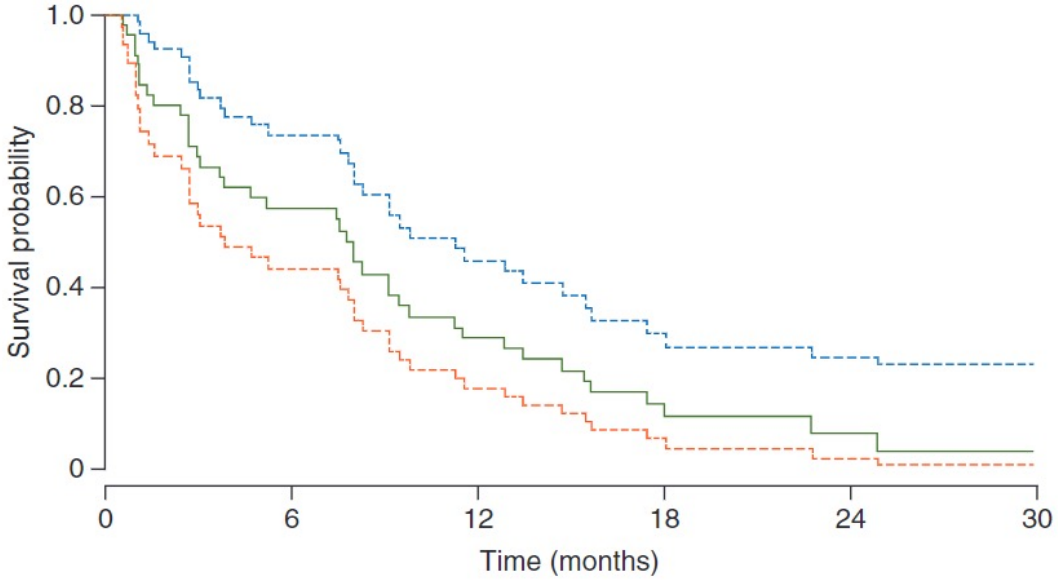
- **8 cicli di induzione**: rituximab + lenalidomide (20 mg/die al 1° ciclo; 25 mg/die dal 2°)
- **12 cicli di mantenimento**: lenalidomide (10 mg/die)

Response	Patients *n*	CR+uCR *n* (%)	PR *n* (%)	SD *n* (%)	PD *n* (%)	NE *n* (%)
After C1	45	9 (20)	19 (42)	2 (5)	10 (22)	5 (11)
After C4	28	16 (36)	5 (11)	3 (7)	3 (7)	1 (2)
After C8	23	13 (29)	3 (7)	1 (2)	6 (13)	–

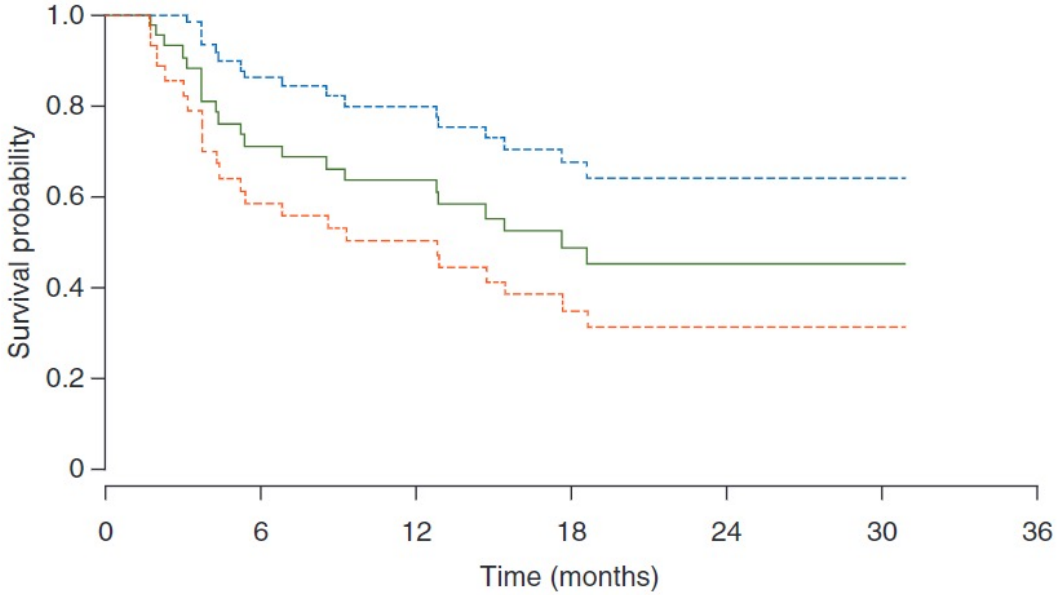
Ghesquieres H. *Ann Oncol*, 2019;117: 121-130

Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)

PFS



OS



Ghesquieres H. *Ann Oncol*, 2019;117: 121-130

CLINICAL/SCIENTIFIC NOTE

Rituximab-Lenalidomide-Ibrutinib Combination for Relapsed/Refractory Primary CNS Lymphoma

N = 14 R/R PCNSL (11 pts refractory to last treatment)

Response in 8 patients: 4 CR and 4 PR

Median time to response = 2.5 months

- Consolidation in 3: 2 WBRT ; 1 ASCT
- Bridge to CART-cell in one patient

1-y OS = 53%

Houillier C. *Neurology*, 2021;97: 628-631

CD19-directed CAR T-cell therapy for treatment of primary CNS lymphoma

Patient UPN	Age, y	Disease location (size at study entry)	KPS at study entry	Prior lines of therapy, n	Bridging therapy	Cell dose, M	CRS max grade	Symptoms (NT max grade)*	Intervention for CRS/NT	Best Response	Duration of response, d	Current status
286	53	Left temporal lobe (0.6 cm)	90	3	High-dose methotrexate-based chemotherapy	200	2	Headache (3), agitation (1), restlessness (1)	Toci and Dex	CR	273	Progressed/alive
310†	53	Posterior corpus callosum (1.6 cm)	80	6	Pomalidomide	115‡	1	Headache (2), dizziness (2), memory impairment (1)	None	SD	13	Off protocol therapy/ alive, on maintenance pomalidomide
272	47	Right temporal lobe (3 cm), left temporal lobe (1.5 cm), and right basal ganglia (3 cm)	70	12	Brain radiation; steroids	200	1	Tremor (1), dysarthria (1), hallucinations (1)	None	SD	32	Progressed/lost to follow-up
346	49	Right temporal lobe (0.9 cm)	90	2	None	600	2	Concentration impairment (1), dysphasia (1)	Toci and Dex	CR	520§	CR/alive
475	42	Left basal ganglia (0.5 cm)	90	5	Brain radiation; steroids	600	1	Seizure (1), dizziness (1)	None	CR	43	Off protocol therapy/ alive, on maintenance lenalidomide

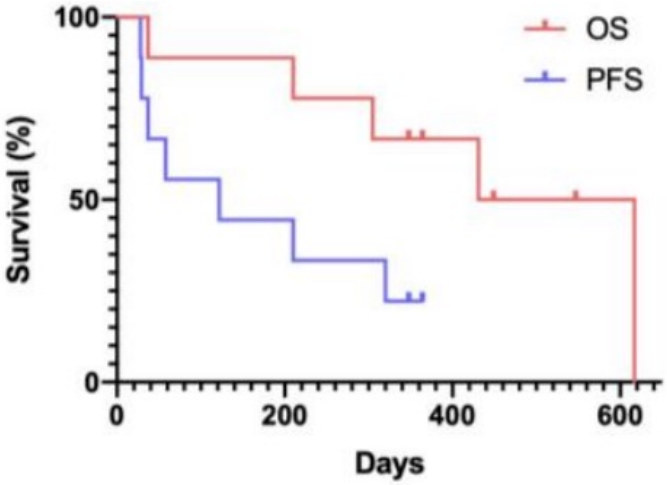
Dex, dexamethasone; KPS, Karnofsky Performance Status; max, maximum; NA, not applicable; SD, stable disease; Toci, tocilizumab; UPN, unique patient number.
*Highest grade possibly, probably, or definitely related to T-cell infusion. Symptoms experienced by UPN 346 were probably related to T-cell infusion, whereas all other symptoms were possibly related.
†The patient declined all research studies on the trial after receiving CD19CAR T cells and received pomalidomide at day 28, which took them off protocol therapy.
‡The manufactured dose for UPN 310 was 115M.
§Most recent disease assessment based on clinical assessment.

Siddiqi T. *Blood Adv*, 2021;5: 4059-4063

CAR T-cell therapy in primary central nervous system lymphoma: the clinical experience of the French LOC network

	LCP N = 9
Age, median (min – max)	**67 (48 – 75)**
male	3 (33%)
ECOG médian (min – max)	**1 (0 – 4)**
N (median) previous line (min – max)	**3 (2 – 5)**
Previous MTX HD	9 (100%)
Previous ASCT	**7 (78%)**
Previous WBRT	1 (eye)
Bridge therapy	**8 (89%)**
PD at time of CART-cells infusion	**4 (44%)**
T-cell depletion : FC	9 (100%)
Tisa-cel	7 (78%)
Axi-cel	2 (22%)

	LCP; N = 9
Response at M1	
ORR	6 (67%)
CR	3 (33%)
PD	2 (22%)
Response at M3	
ORR	6 (67%)
CR	5 (56%)
PD	2 (22%)
Best response	
CR	**5 (56%)**
PR	**1 (11%)**

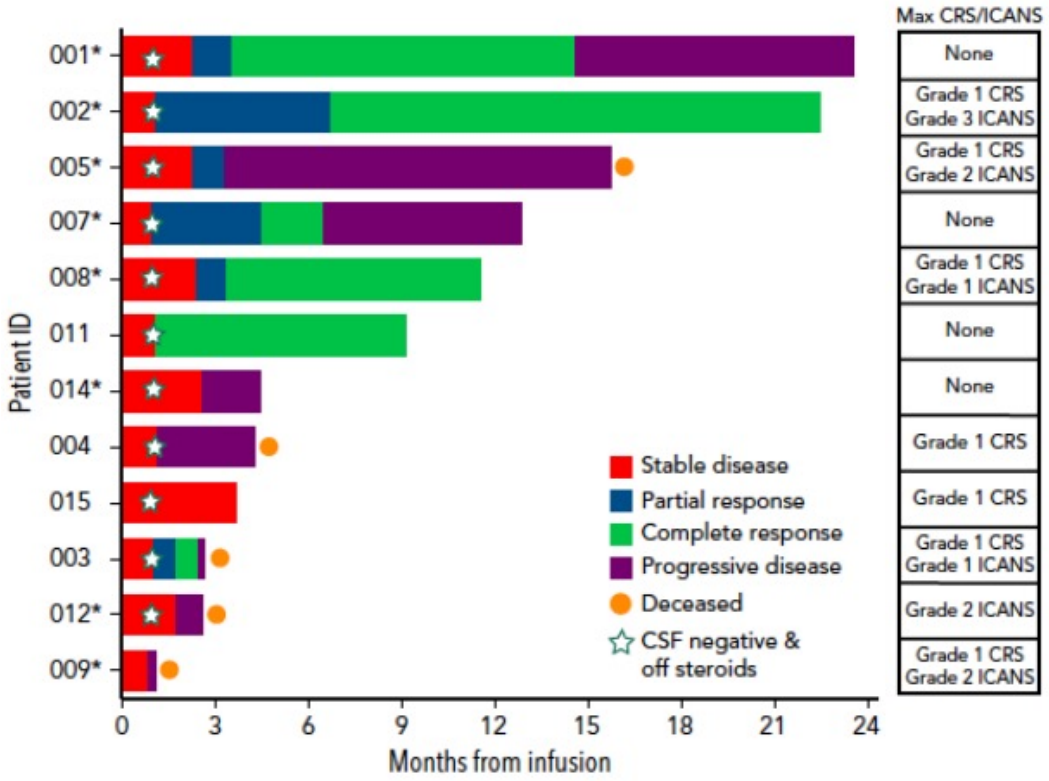


1-year OS: 67%
Median OS: 17 months
1-year PFS: 22%
Median DOR: 10 months

Alcantara M. *Blood*, 2022;139: 792-796

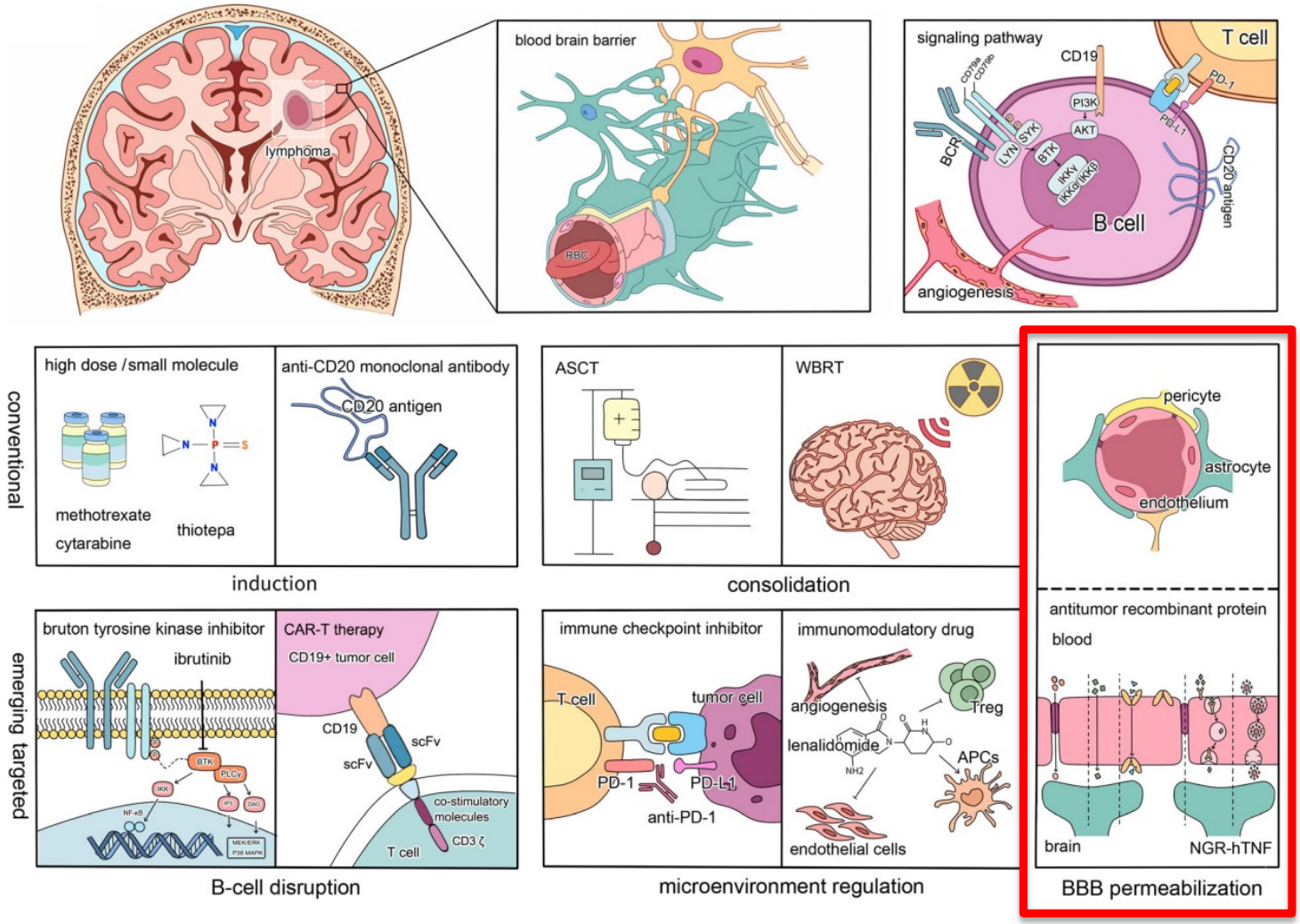
Characteristics	Patients (n = 12)
Median age (range), y	63 (34-81)
Male:female	7:5
Infused/enrolled	12/13
ECOG performance status, no. %	
0-1	7/12
2+	5/12
Disease location	
Parenchymal	11/12
Leptomeningeal enhancement/CSF+	2/12
Cell of origin	
Germinal center B-cell type	1/12
Nongerminal center B-cell type	11/12
Median no. of previous lines of antineoplastic 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

Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial



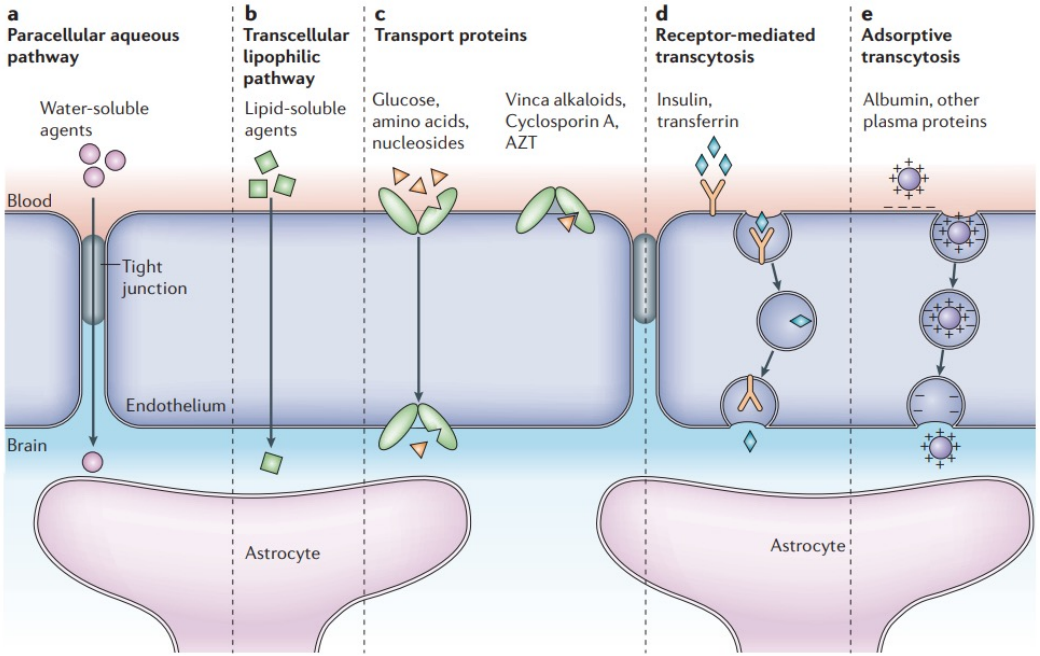
ORR: 7/12 (58%)
CR: 6/12 (50%)

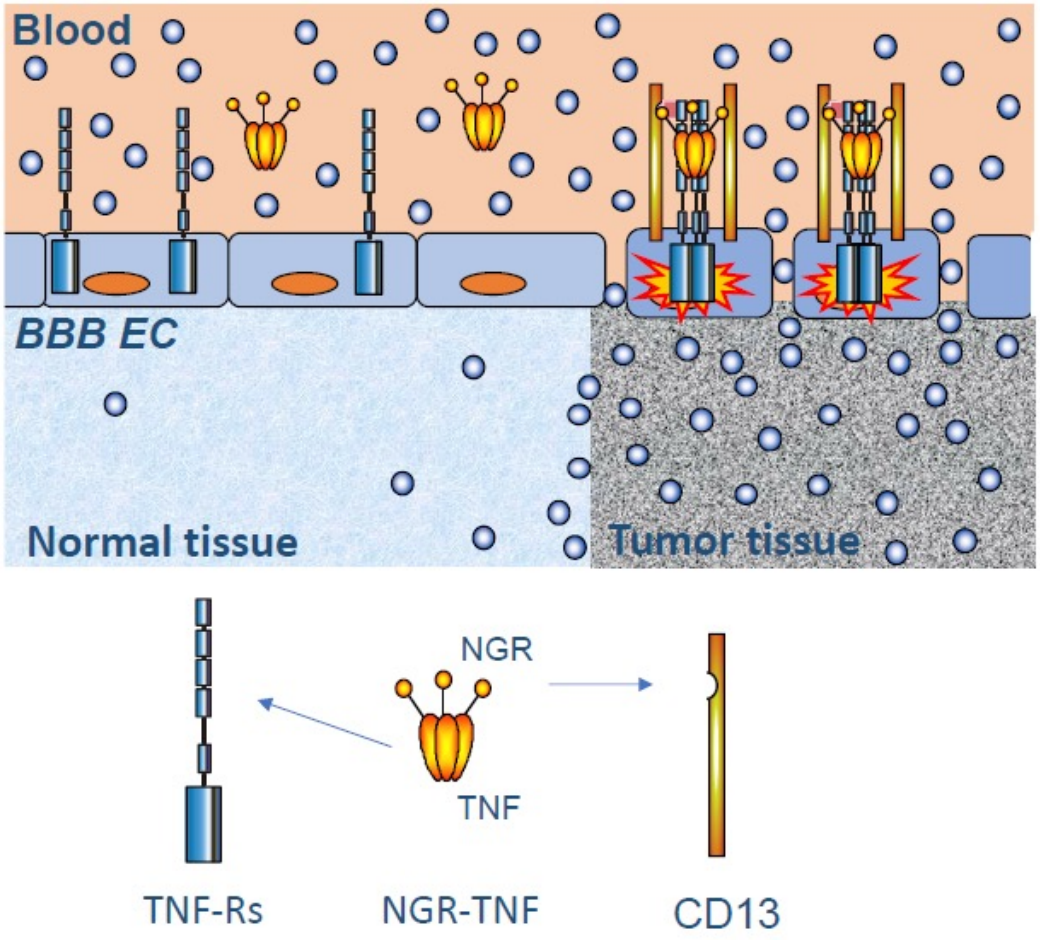
Frigault MJ. *Blood*, 2022;139: 2306-2315



Yuan Y. *Biomarker Res*, 2021; 9: 32

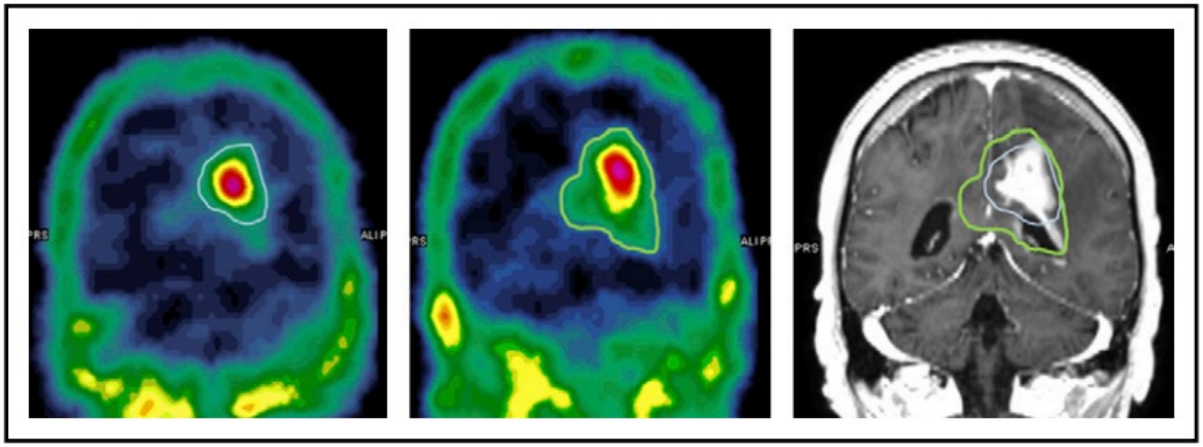
Permeabilizzazione della barriera emato-encefalica





Abbott NJ. *Nat Rev Neurosci*, 2006;7: 41-53

Marcucci F. *Cancers (Basel)*, 2021;13: 2391



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

Drug concentrations	Without NGR-hTNF*	After NGR-hTNF†	*P*
Plasma			
Doxorubicin, ng/mL	29.6 ± 7.4	26.0 ± 6.7	.43
Cyclophosphamide, mg/L	26.3 ± 7.7	27.8 ± 7.9	.17
Rituximab, ng/mL	45.4 ± 17.0	69.1 ± 13.4	.04
CSF			
Doxorubicin, ng/mL	<2.5 (all samples)	<2.5 (all samples)	
Cyclophosphamide, mg/L	14.1 ± 3.5	15.5 ± 4.8	.27
Rituximab, ng/mL	<1.0 (all samples)	<1.0 (all samples)	
CSF/plasma ratio‡			
Cyclophosphamide, %	60 ± 20	62 ± 19	.73

*Samples collected after the first course of treatment (ie, after R-CHOP without NGR-hTNF).

†Samples collected after the second course of treatment (ie, after NGR-hTNF followed by R-CHOP).

‡The ratio was not estimated for doxorubicin and rituximab because CSF concentrations resulted below the lower limit of quantification.

Ferreri AJM. *Blood*, 2019; 134: 252-262 — Ferreri AJM. *Blood Adv*, 2020; 4: 3648-3658

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

Response to NGR-hTNF/R-CHOP	Consolidation	Response to consolidation	Treatment failure	TTTF, mo*	Status	Survival, mo
PD	None	—	Yes	4	DoD	5
CR	Lenalidomide	CR	Yes	11	DoD	11
PD	None	—	Yes	4	DoD	14
CR	WBRT > lenalidomide	CR	Yes	6	DoD	18
PD	None	—	Yes	4	DoD	6
CR	WBRT > lenalidomide	CR	Yes	9	DoD	22
CR	ASCT > WBRT	CR	Yes	6	Alive	31
CR	ASCT > lenalidomide	CR	Yes	17	Alive	30
CR	ASCT	CR	Yes	9	DoD	11
PR	WBRT	CR	No	10	DUC	10
CR	ASCT	CR	Yes	6	DoD	7
CR	ASCT	CR	No	25	Alive	25
PD	None	—	Yes	1	DoD	2
PD	None	—	Yes	1	DoD	2
CR	None	—	Yes	13	DoD	19
PR	WBRT	CR	Yes	10	DoD	11
PR	WBRT	PR	Yes	5	DoD	7
PR	WBRT	PR	Yes	5	DoD	7
PR	None	—	Yes	5	DoD	6
PD	None	—	Yes	0	DoD	1
PR	None	—	Yes	5	DoD	7
PR	None	—	Yes	6	DoD	9
PR	WBRT	PR	Yes	7	DoD	8
CR	ASCT	CR	No	17	Alive	17
PD	None	—	Yes	1	DoD	3
PR	WBRT	PR	Yes	3	DoD	6
CR	ASCT	CR	No	14	Alive	14
PR	WBRT	CR	No	14	Alive	14

28 pazienti arruolati e valutabili

- 21 pazienti in risposta (75%)
  - 11 risposte complete (39%)
  - 10 risposte parziali (36%)
- 17 pazienti consolidati
  - 10 con radioterapia
  - 7 con trapianto autologo
- 16 ricadute/progressioni

Ferreri AJM. *Blood*, 2019; 134: 252-262 — Ferreri AJM. *Blood Adv*, 2020; 4: 3648-3658

Take home messages

- La terapia di prima linea del paziente con linfoma primitivo del sistema nervoso centrale deve auspicabilmente prevedere una fase di induzione e una fase di consolidamento.
- Il consolidamento con autotrapianto è la prima scelta nel caso di pazienti giovani e in grado di tollerare un condizionamento mieloablativo.
- La radioterapia *whole brain* è da prendere in considerazione nei pazienti non candidabili ad una chemioterapia ad alte dosi.
- L'utilizzo di farmaci che oltrepassano la barriera ematoencefalica è essenziale sia nella fase di induzione (metotrexato, citarabina, tiotepa), sia nel consolidamento (tiotepa).
- L'approccio alla malattia in ricaduta può prevedere il riutilizzo dei farmaci utilizzati nella prima linea e, quando possibile, ancora una volta un consolidamento (autotrapianto, radioterapia panencefalica).
- Tra i nuovi agenti attivi nella malattia in ricaduta, spiccano gli inibitori di BTK (ibrutinib) e gli IMiDs (lenalidomide). Sono in corso studi che ne valutano la combinazione.
- La terapia con cellule CART è efficace nella malattia in ricaduta, i risultati sono preliminari.
- Possono essere percorribili strategie mirate all'aumento della permeabilità della barriera ematoencefalica, favorenti la diffusione di chemioterapici non altrimenti attivi sul tessuto cerebrale.