19TH ULTMANN

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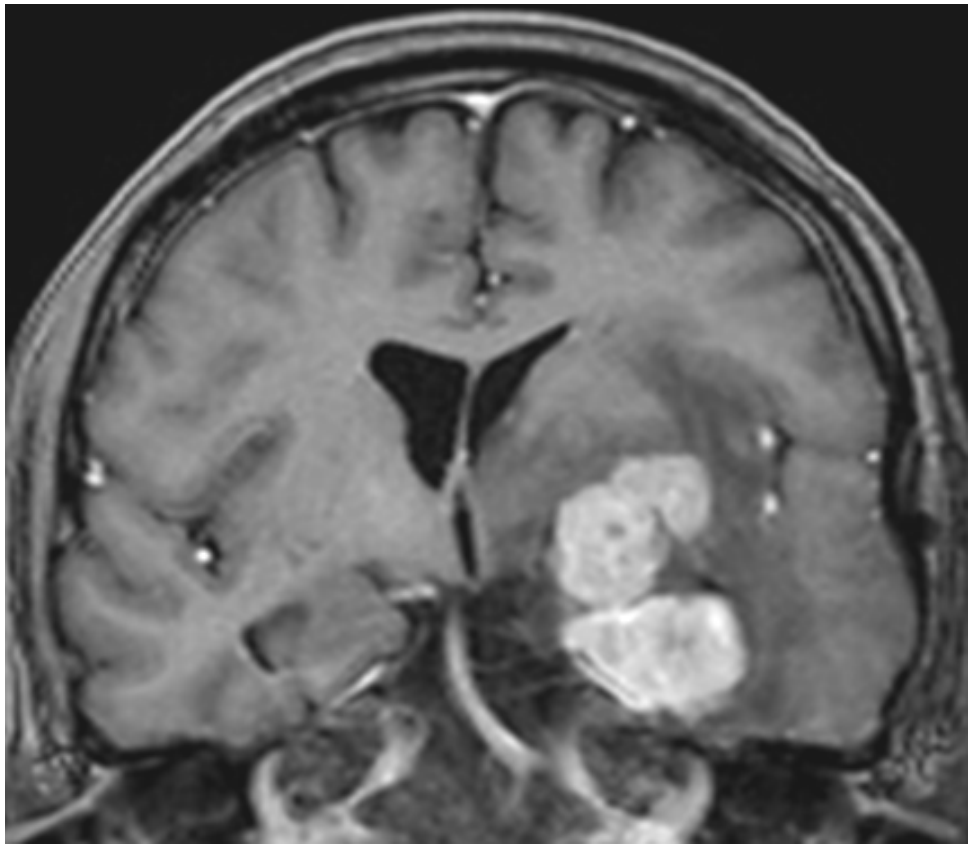
Disclosures

Speaker fee	Adienne
Research grants	BMS, Beigene, Pharmacyclics, Hutchison Medipharma, Amgen, Genmab, ADC Therapeutics, Gilead, Novartis, Pfizer
Advisory boards	Gilead, Novartis, Juno, PletixaPharm
Inventor of patents	NGR-hTNF/RCHOP in relapsed or refractory PCNSL; SNGR-hTNF in brain tumours.

Case #1: Primary Refractory PCNSL

- 39-year-old gentleman
- Apparently healthy; smoker
- 2018= PCNSL
- MATRix 2 courses => PD

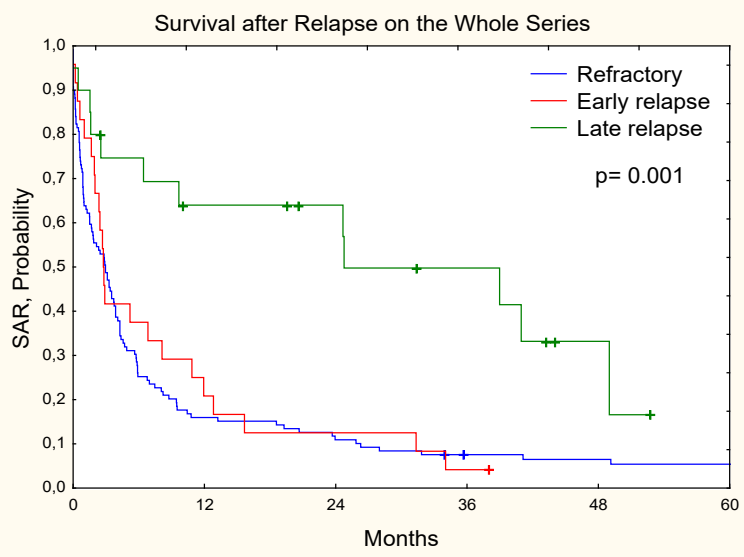


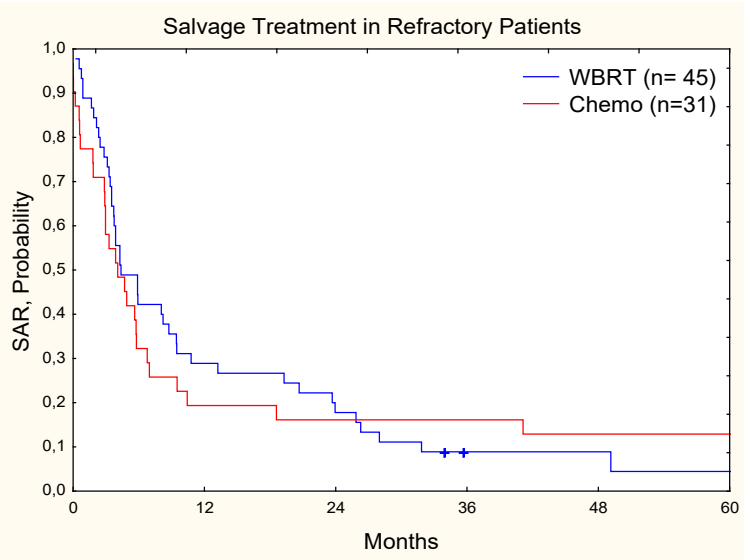
Prognosis of Refractory PCNSL IELSG Randomized Trials

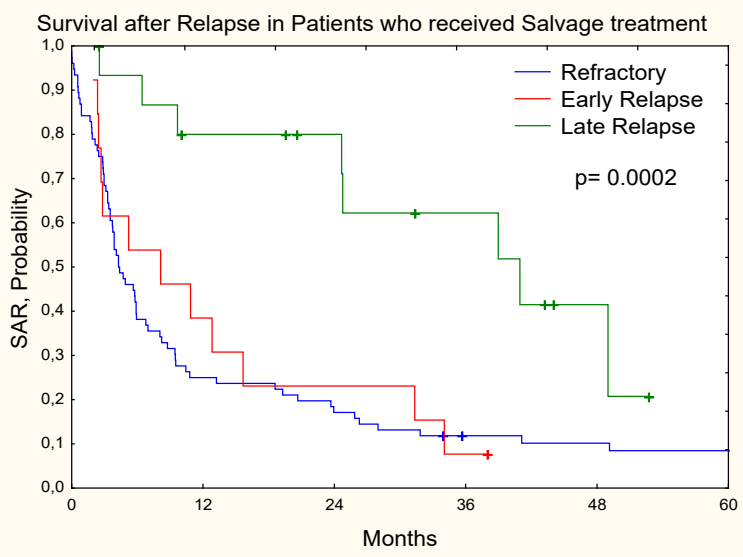
Mortality of rrPCNSL is ≈90%

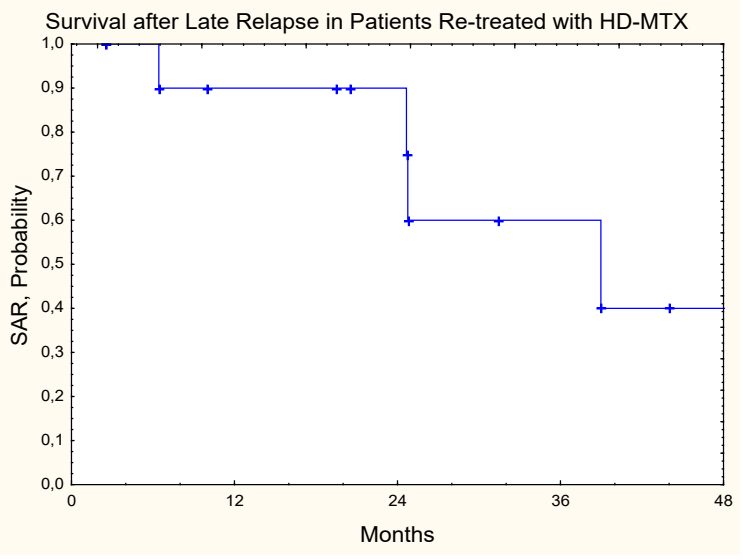
1/3 are not candidates for salvage.

Efficacy of salvage therapy appears to be independent of the 1L.









Ferreri AJM, et al. ASH 2021

Audience response question:
Which is the best induction for RR/PCNSL?

1- High-dose-ifosfamide-based chemotherapy

2- Temozolomide

3- Temsirolimus

4- Lenalidomide

5- Ibrutinib

6- Enrollment in a prospective trial

7- Too complex! Let me see in pubmed

High-dose-Ifosfamide-based Salvage Therapy

	R-IE (n= 22)	VIA (n= 16)	ICE (n= 17)	ICED (n=25)
Line	Salvage	Salvage	Salvage	Salvage
Schedule (g/m²/d)x[days]	2 x [3]	1 x [5]	5 x [1]	1.5 x [5]
Other drugs	VP16, Rituximab	ARAC; VP16	CBDCA; VP16	CBDCA; VP16
Previous chemotherapy	MTX-ARAC	CHOD, MA	MTX-ARAC	MTX
Pre-irradiated pts	55%	100%	NR	27%
Median age	60 (39-72)	54 (31-69)	62 (28-84)	58 (20-73)
Refractory disease (median TTP)	50% (8 mo)	6% (19 mo)	24% (12 mo)	36% (12 mo)
Dose reduction	0%	NR	24%	NR
Febrile neutropenia (TRM)	14% (5%)	50% (0%)	53% (6%)	NR (8%)
ASCT	20%	0%	35%	52%
CRR	27%	37%	76% (ASCT)	48%
mPFS	4.0 mo	4.5 mo	2.6 mo	11 mo
mOS	6.0 mo	6.0	7.3 mo	27 mo

Mappa, HemOnc 2013; Arellano-Rodrigo, EJH 2003; Choquet, Abs #3664; Motomura, L&L 2011; Choi, IJH 2013

Single-Drug Therapy for Relapsed PCNSL

Regimen	N	ORR	m TTP	G3-4 N	G3-4 T	TD
Rituximab Batchelor T, et al. Neurology 2011	12	42%	8	0%	0%	0%
Temozolomide Reni M, et al. Br J Cancer 2007	36	31%	7+	6%	3%	0%
Temozolomide + Rituximab Enting RH, et al. Neurology 2004	15	53%	14	20%	27%	0%
Temozolomide + Rituximab Wong ET, et al. Cancer 2004	7	100%	6			0%
Topotecan Voloschin A, et al. JNO 2008	15	40%	3	73%	20%	0%
Topotecan Fischer L, et al. Ann Oncol 2006	27	33%	9	25%	11%	13%
Pemetrexed Altman JK, et al. ASCO 2008	8	50%	5+	63%	50%	13%
Temsirolimus Kiewe P, et al. Lugano 2013	28	63%	2	20%	24%	4%

Lenalidomide

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

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

Ibrutinib

Study	Dose (mg/d)	N°	ORR	CRR	Median TTP (months)	Tox
LYSA	560	29 rPCNSL 14 rVRL	70%	23%	4.8	5% ASP 10% Hemorr
MSKCC	560 - 840	13 rPCNSL 7 SCNSL	77%	38%	4.6	5% ASP
NCI	TEDDI 560 - 840	13 rPCNSL 5 PCNSL	94%	11%	15.3	39% ASP
MSKCC	R-MTX		80%		9.2	0% ASP (discontinued schedule?)
LOC	560 + R^2	14 rrPCNSL	57%	29%	1-yr PFS: 40%	7% ASP Tox discontinuation 21%

Meaningful concentrations in the CSF
Activity no related to gene mutations

Soussain C et al. EJC 2019; Grommes C et al. Cancer Disc 2017;
Lionakis et al. Cancer Cell 2017; Grommes C et al. Blood 2019
Houillier C et al. Neurology 2021

Tirabrutinib: a Good Option

- Highly selective BTK inhibitor. Oral route. Good CNS availability.
- 44 pts rrPCNSL in a phase I-II trial
- No DLT. MTD not reached at 480 mg/d.
- Grade ≥3 AEs in 48% of pts (neutropenia 9%)
- 1 case of grade 5 PJP
- ORR: 64%; CRR= 34% - no related to gene mutations.
- Median PFS= 2.9 months

Narita Y et al. Neuro-Oncol 2021

Immune Evasion and PCNSL

	DLBCL		PTL	EBV⁻ PCNSL	PMBL
	All	ABC-type			
Genomic instability					
CDKN2A^{loss}	24% (43/180)[a]	35% (19/55)[a]	88% (44/50)[c]	71% (15/21)[k]	0% (0/11)
bi-alleic	19% (8/43)[a]	26% (5/19)[a]	77% (34/44)	73% (11/15)	0% (0/11)
CNAs of additional p53/cell cycle components	multiple[a,b]	multiple[a,b]	no	rare[d]	no
Total CNAs	high	high	high	high	low
Oncogenic TLR and BCR Signaling					
MYD88^{L265P}	12% (6/49)[e]	29% (45/155)[f]	78% (38/49)[g]	60% (33/55)[l]	NA
NFKBIZ^{gain}	9% (16/180)[a]	20% (11/55)[a]	42% (21/50)[h]	45% (28/62)[m]	0% (0/11)
NFKBIZ^{gain} and/or *MYD88*^{L265P}	NA	NA	92% (45/49)	83% (44/53)[n]	NA
CD79B^{Y196mut}					
Total	16% (8/49)[e]	23% (35/155)[f]	49% (22/45)[i]	38% (19/50)[o]	NA
Concurrent with *MYD88*^{L265P}	38% (3/8)[e]	43% (15/35)[f]	91% (20/22)	89% (17/19)	NA
PD-1 Ligand Deregulation					
9p24.1/*PD-L1*^{gain} and/or *PD-L2*^{gain}	6% (11/180)[a]	7% (4/55)[a]	54% (26/50)[h]	52% (33/63)[p]	55% (6/11)
PD-L1 or *PDL-2* translocation	NA	NA	4% (2/50)[j]	6% (4/66)[q]	20% (25/125)[r]

Frequent copy number gains at chromosome 9p24.1, which includes the PD-L1/PD-L2 locus and chromosomal translocation involving the PD-L1 and PD-L2 locus in PCNSL samples

Chapuy B et al. Blood 2016

Immune Checkpoint Inhibitors

Table 1. Patient characteristics and responses to nivolumab

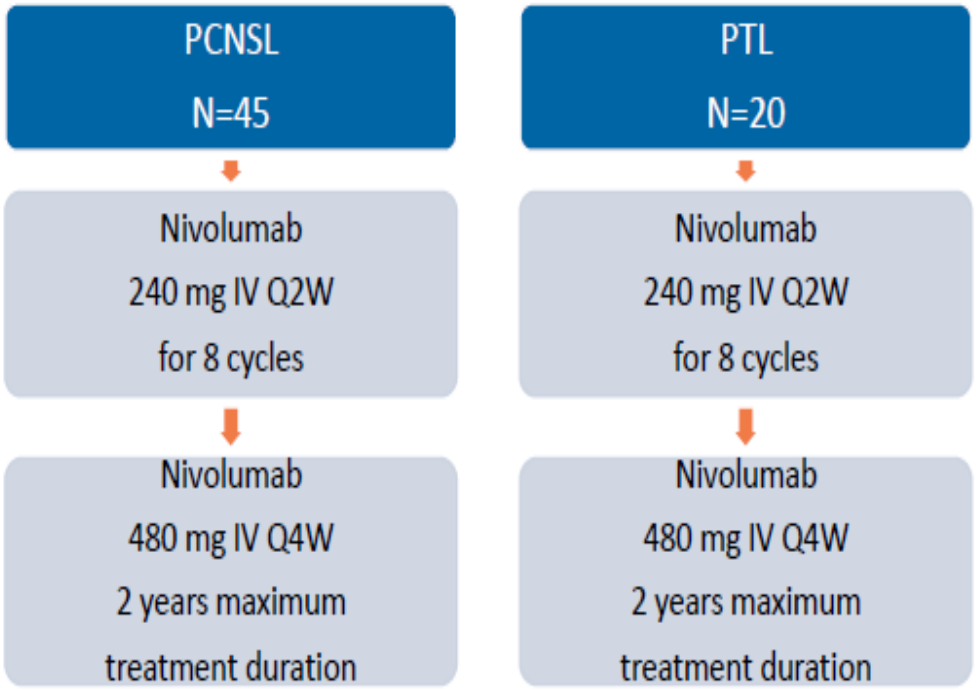
	Patient				
	1	2	3	4	5
Disease	Primary refractory PCNSL	Recurrent PCNSL	Recurrent PCNSL	Recurrent PCNSL	CNS recurrence of PTL
Symptoms at current presentation, KPS (%)	Subtle visual field deficit and cognitive changes; 70	Cognitive changes; 80	Nausea, vomiting, ataxia; 50	Asymptomatic; 80	Aphasia, impaired level of consciousness (LOC); 40
Radiographic response	Complete response	Complete response*	Partial response	Complete response	Complete response†
Neurologic/clinical response, KPS (%)	Resolution of visual field deficit and cognitive changes; 90	Resolution of cognitive changes; 80	Resolution of nausea, vomiting and ataxia; 70	Stable (asymptomatic); 80	Resolution of aphasia and impaired LOC; 80
Progression-free survival (mo)	13+	17	17+	14	14+

*The patient was subsequently unable to get gadolinium contrast due to renal insufficiency. The radiographic complete response reflects complete resolution of the nonenhancing T2 signal change in the area of prior involvement.

†The patient's parenchymal and leptomeningeal disease completely responded to nivolumab therapy; persistent intraocular disease was treated with ocular radiation.

Nayak L et al. Blood 2017

Immune Checkpoint Inhibitors - Ongoing Trials



NCT02857426

Acsé trial Pembrolizumab for rrPCNSL

Preliminary results (n=50):

ORR: 26%

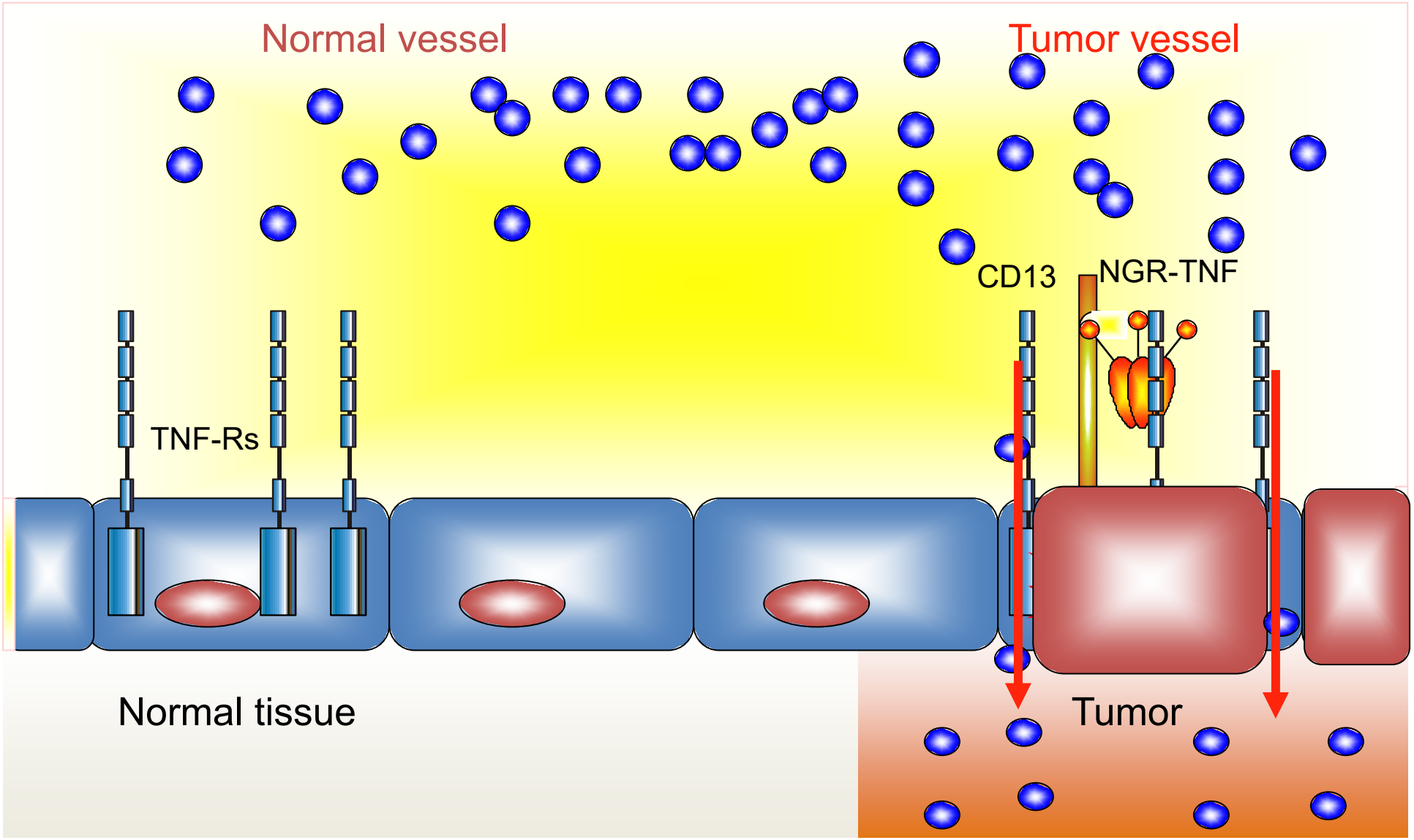
mPFS: 2,6 months

Phase II, single Institution trial

(Medical University of Vienna)

NCT02779101

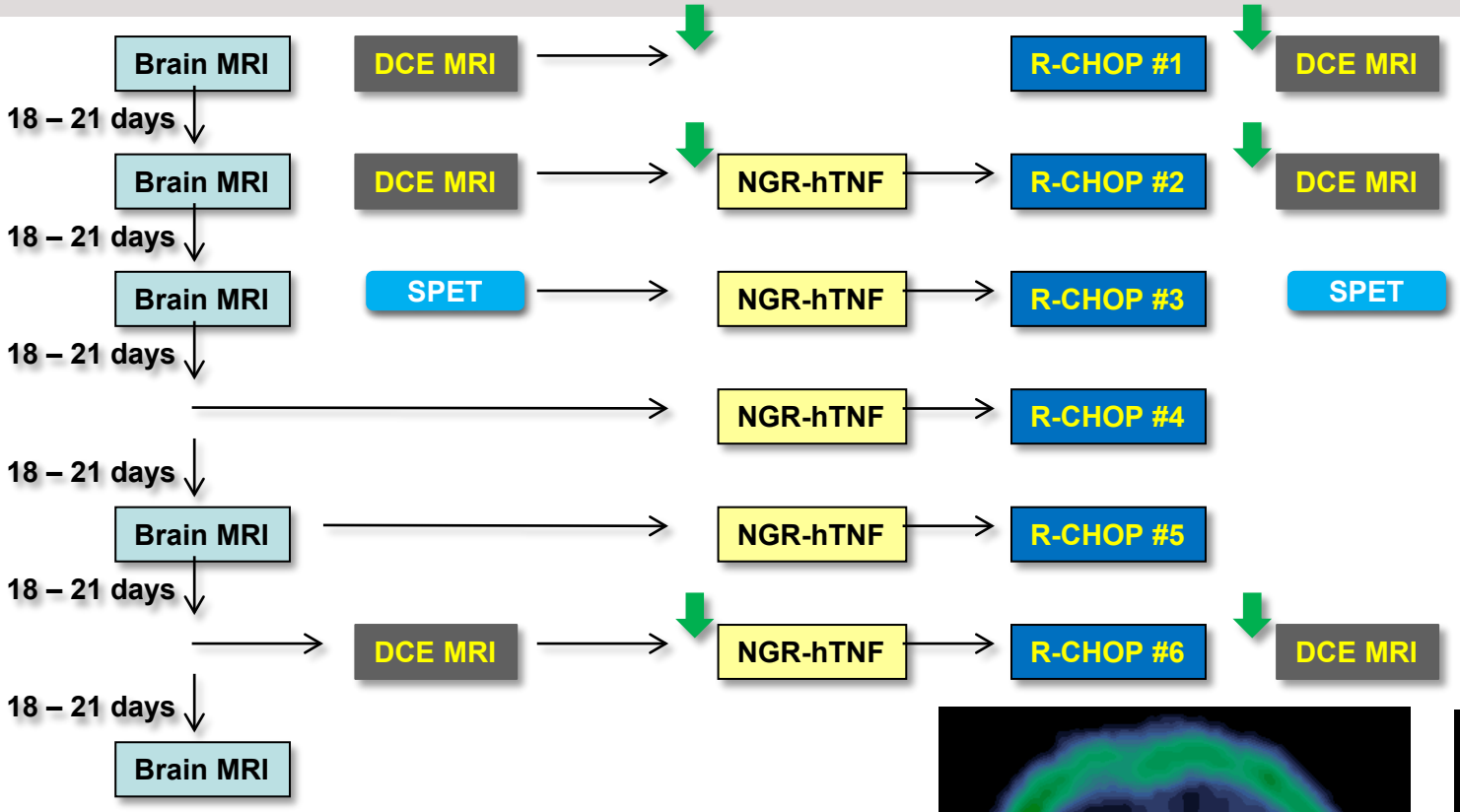
INGRID Trial: *Rationale*

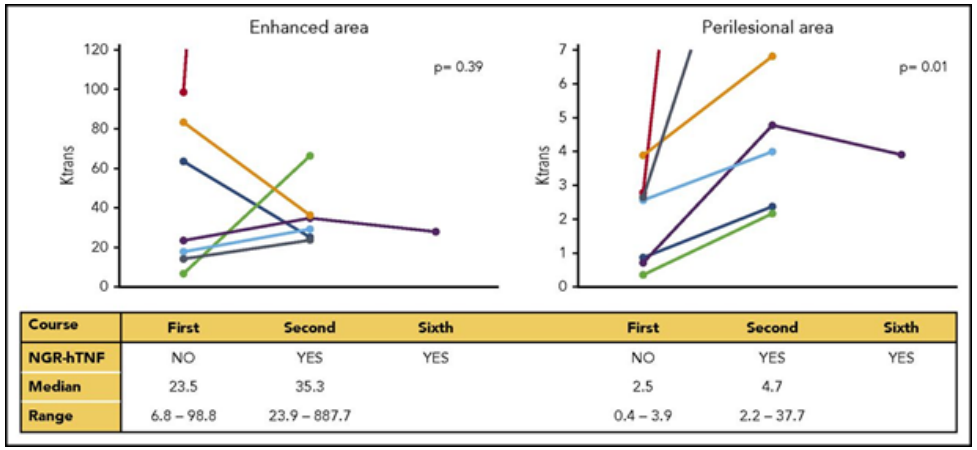


Corti A, et al
Nature Biotechnol 2000
J Clin Invest 2002

Ferreri AJM, et al. Blood 2019

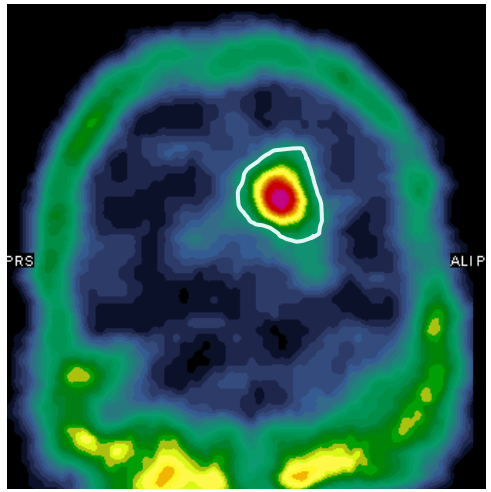
INGRID Trial: Design and Results

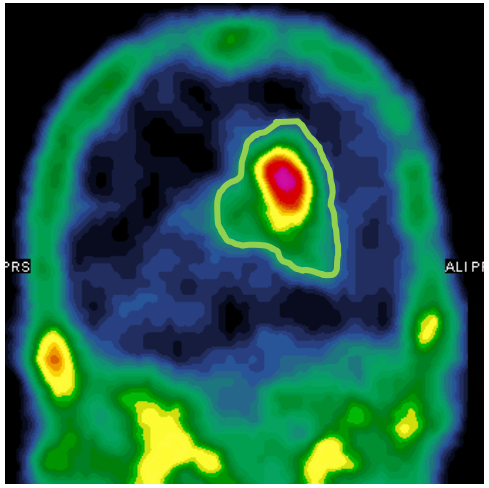


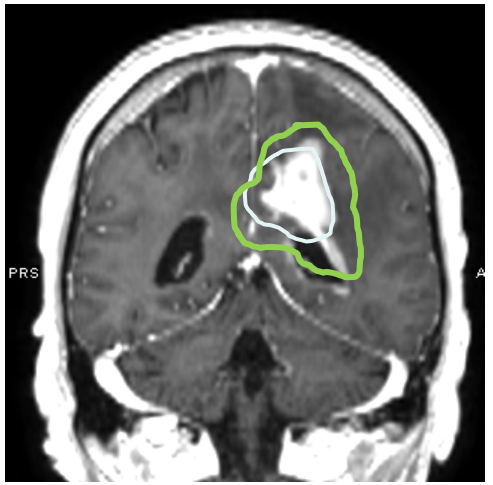


Course	First	Second	Sixth	First	Second	Sixth
NGR-hTNF	NO	YES	YES	NO	YES	YES
Median	23.5	35.3		2.5	4.7	
Range	6.8 – 98.8	23.9 – 887.7		0.4 – 3.9	2.2 – 37.7	

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

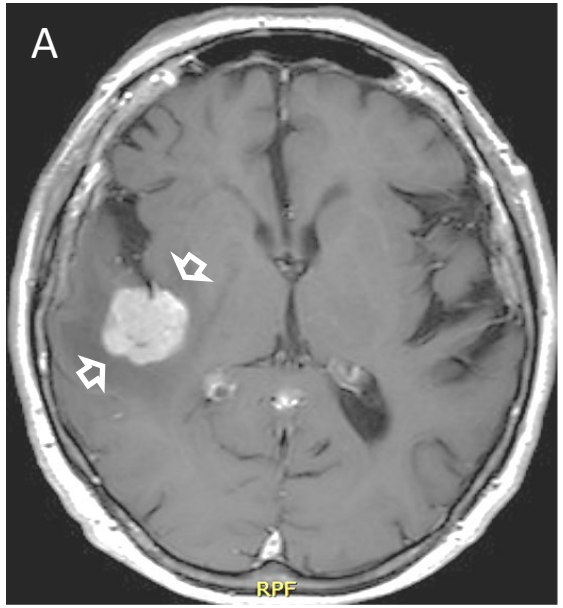


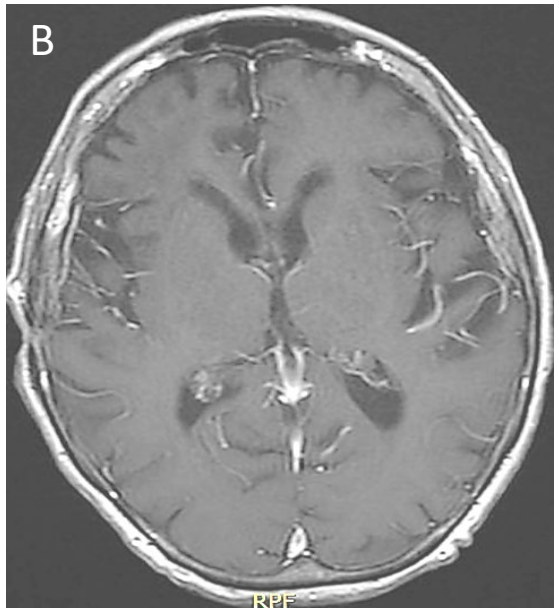


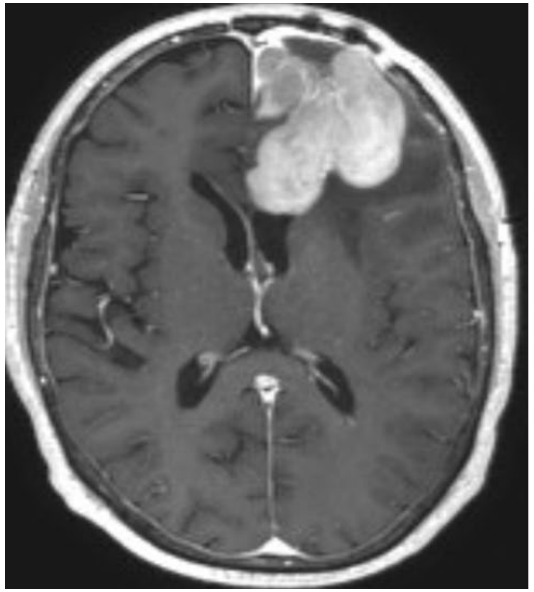


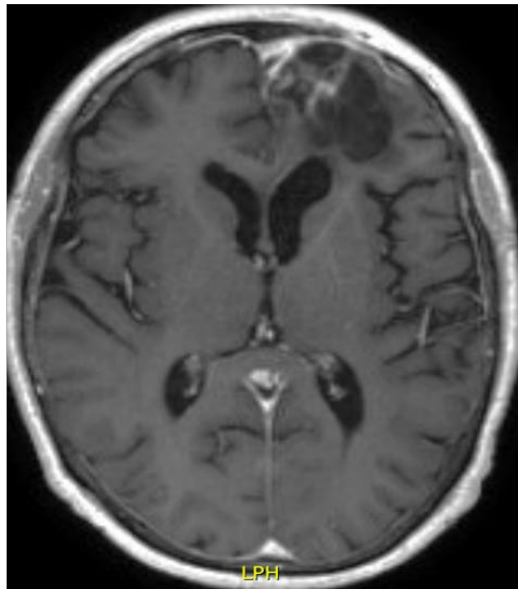
OSPEDALE SAN RAFFAELE
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Ferreri AJM, et al. Blood 2019


A
RPF


B
RPF

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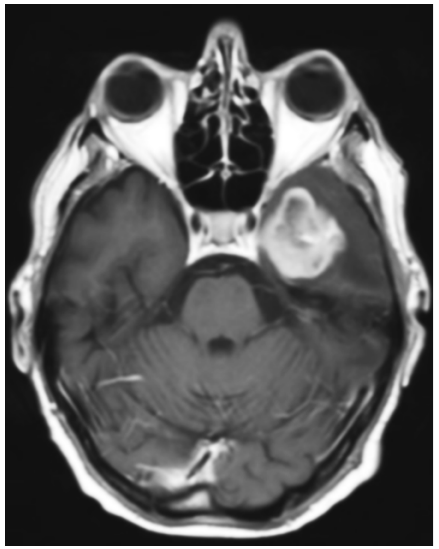
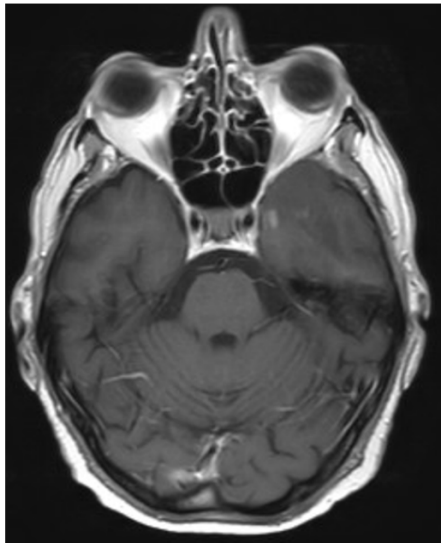
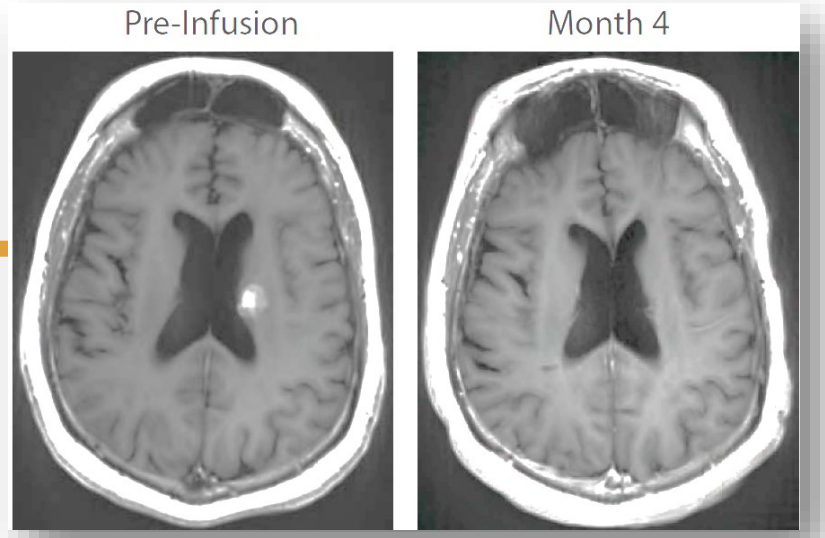


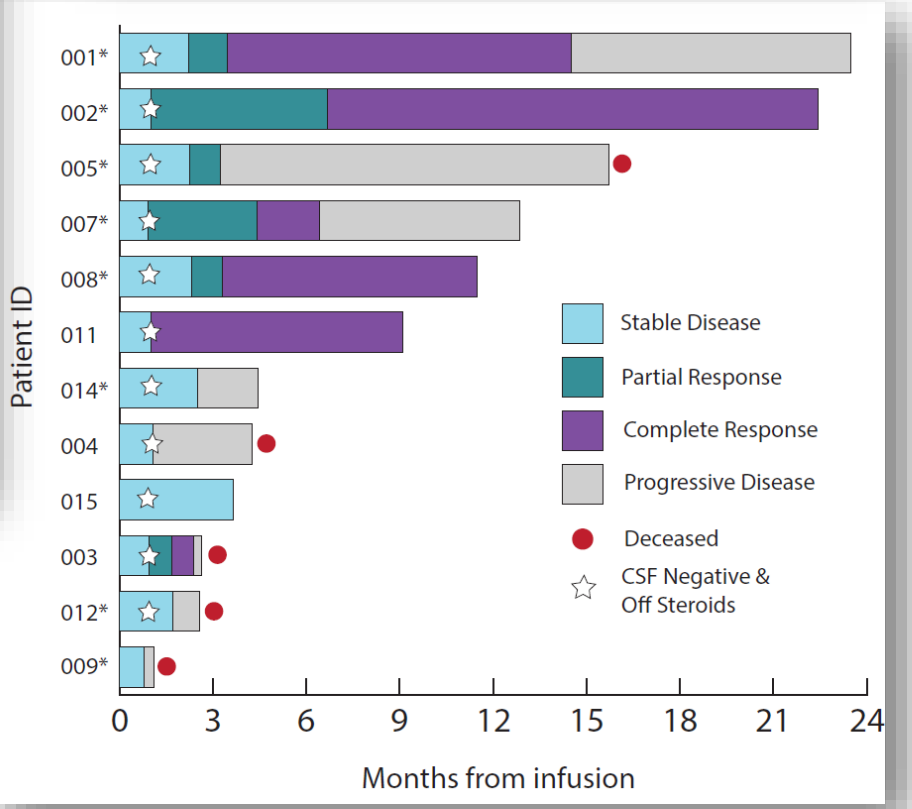


Anti-CD19 CAR-T

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)

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





Frigault M, et al. Blood 2022

Audience response question:
Which is the best induction for RR/PCNSL?

1- High-dose-ifosfamide-based chemotherapy

2- Temozolomide

3- Temsirolimus

4- Lenalidomide

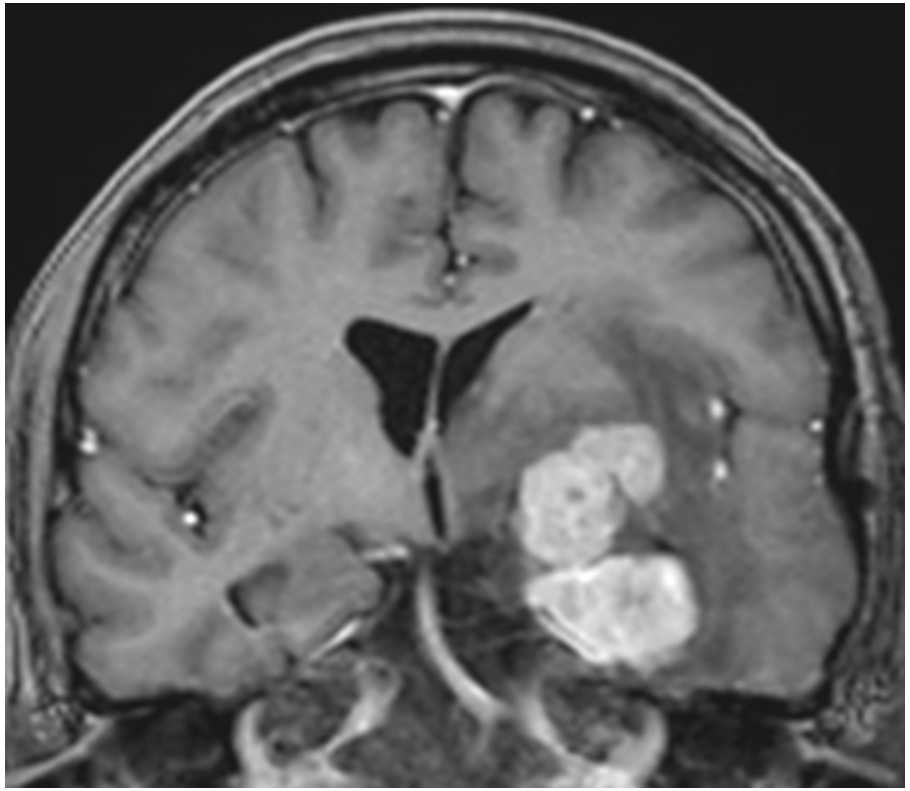
5- Ibrutinib

6- Enrollment in a prospective trial

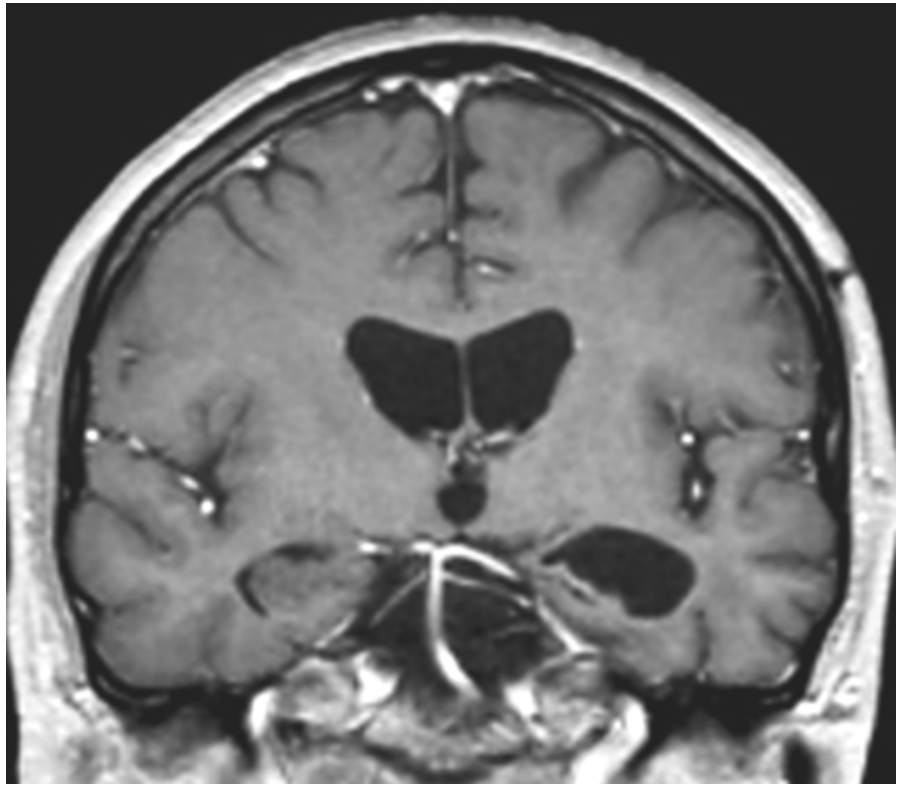
7- Too complex! Let me see in pubmed

Answer: **Enrollment in a Prospective Trial**

Case #1: Response after INGRID trial



Baseline

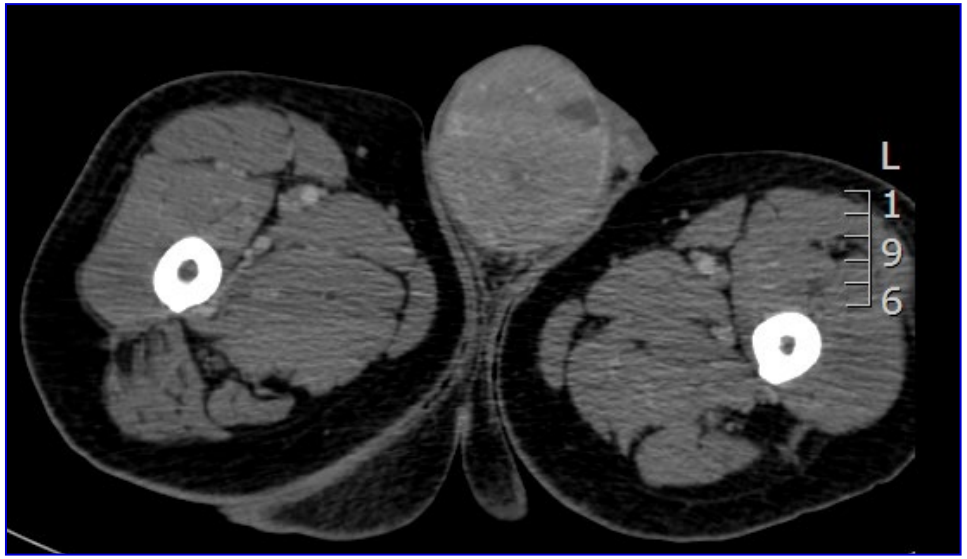


After 4 c. of NGR-TNF / R-CHOP

Consolidation with HDC-ASCT
Relapse-free at 40 months

Case #2: Rising from the testicles to the brain

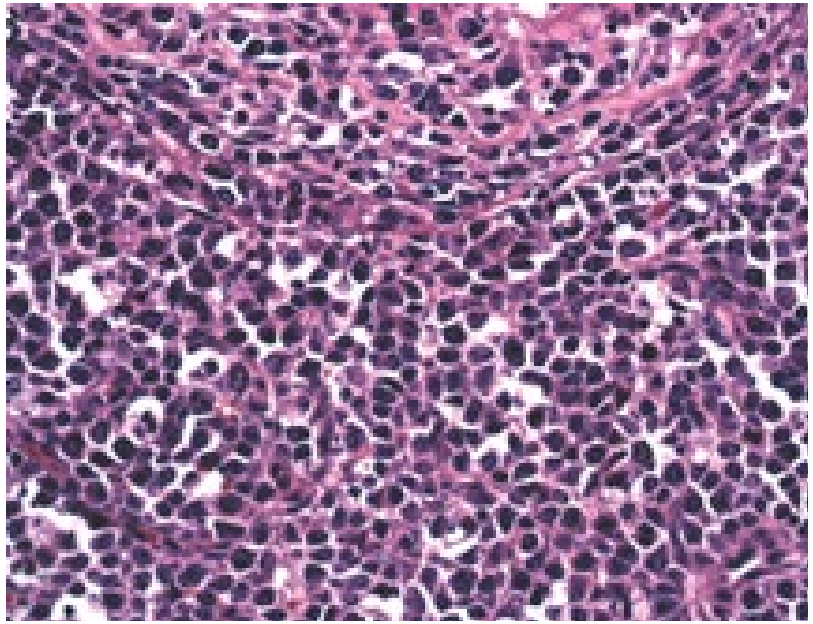
- 67-year-old man
- Apparently healthy; smoker
- Right testis enlargement, no pain (2006) =>

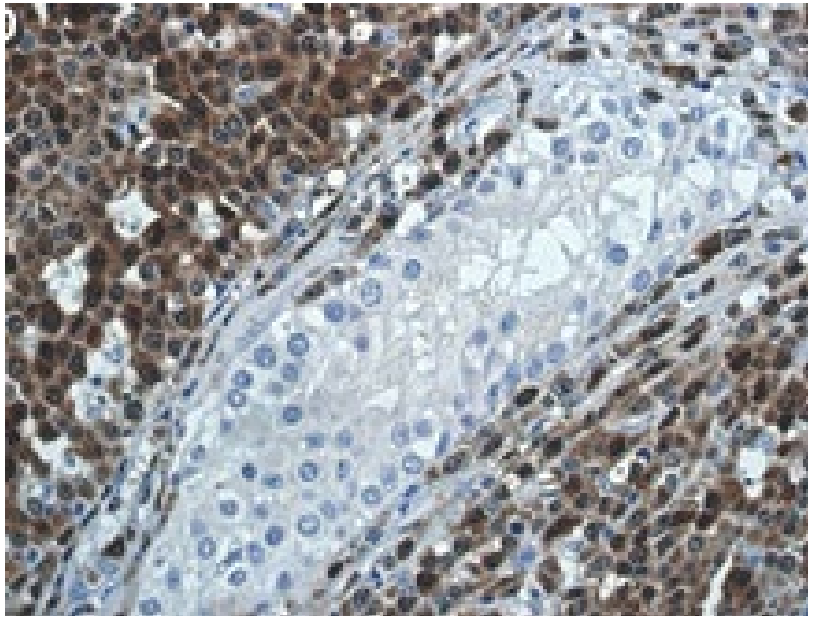


- Rx Tx and Abdominal ultrasound= neg

- Orchidectomy

Case #2: Diagnosis





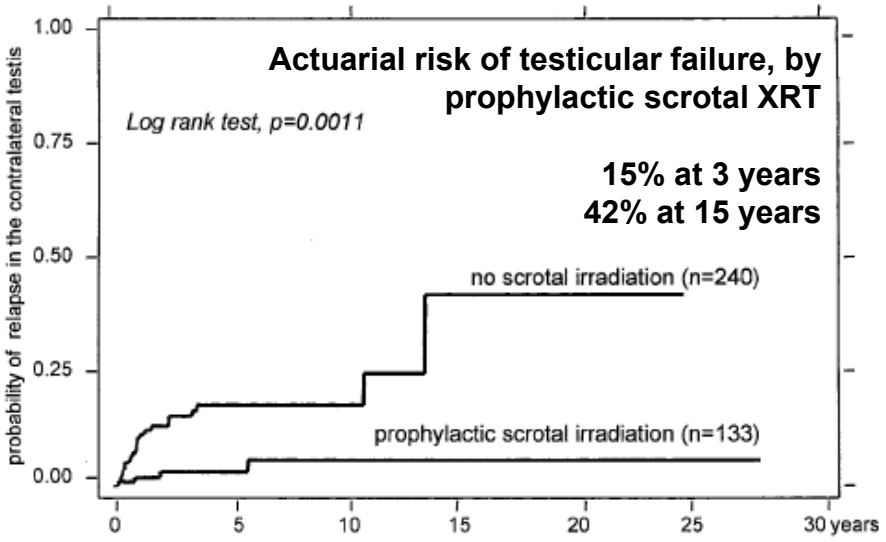
CD20 + CD10 – Bcl-6 - Bcl-2 +

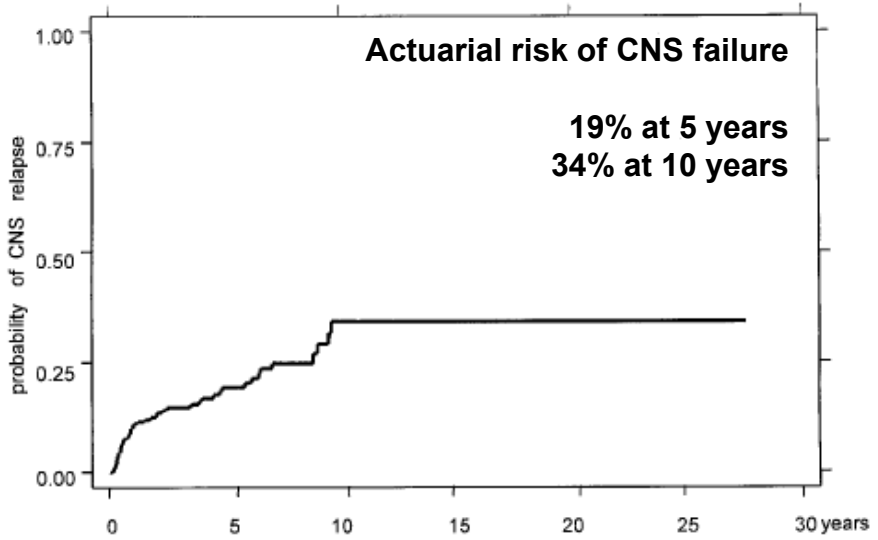
MUM1 + Mib-1: 80%

Diffuse large B-cell lymphoma

Case #2: Treatment

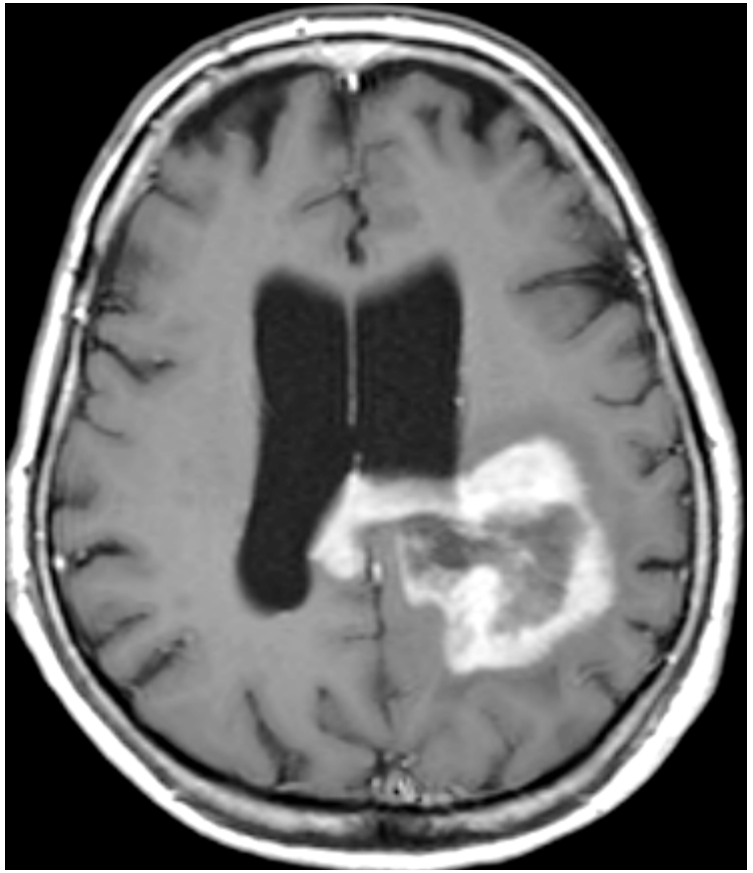
- 6 courses of R-CHOP
- Contralateral testis irradiation
- 4 doses of intrathecal chemotherapy

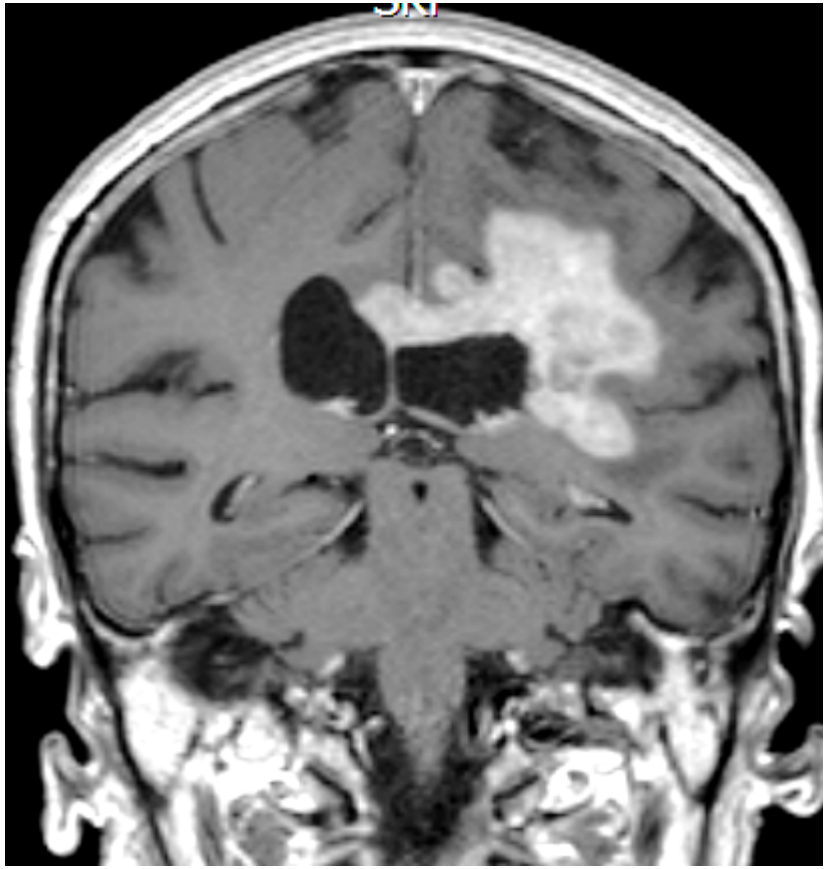




Zucca et al. JCO 2003

Case #2: Brain relapse (8 months later)





ARS question #2:
Which is your therapeutic choice for SCNSL patients?

1- WBRT

2- PCNSL-like approach (HD-MTX + WBRT/ASCT)

3- HD-ARAC or HD-IFO polychemo => ASCT

4- CNS-directed & systemic-directed chemo => ASCT

5- Too complex! Headache is killing me

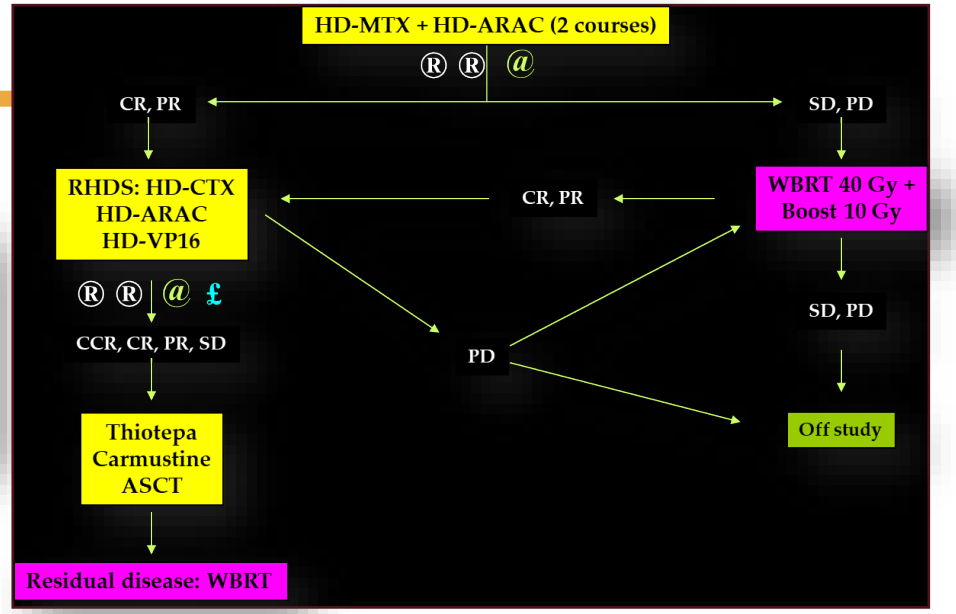
Answer:

SCNSL: Phase II Trials and Routine Practice

Protocol	Dose	Route of administration	Time
HDMTX/IFO/DEP			
Methotrexate	4g/m²[a]	4 hours i.v.	day 1
Ifosfamide	2g/m²	3 hours i.v.	Days 3-5
Liposomal cytarabine	50 mg	intrathecally	Day 6
Dexamethasone	2x4 mg	orally	Days 6-10
Folinic acide	30mg/m²	every 6h i.v.[b]	Day 2[c]
Mesna	20% of ifosfamide dose	i.v.[d]	Days 3-5
To repeat			Day 22
HDAraC/TT/DEP			
Cytarabine	3g/m²	3 hours i.v.	Days 1-2
Thiotepa	40 mg/m²	1 hour i.v.	Day 2
Liposomal cytarabine	50 mg	intrathecally	Day 3
Dexamethasone	2x4 mg	orally	Days 3-7
To repeat			Day 22
HD-ASCT			
Carmustin	400 mg/m²	2 hours i.v.	Day -5
Thiotepa	2x5 mg/kg	2 hours i.v.	Days -4 and -3
Etoposide	150 mg/m²	2 hours i.v.	Days -5 to -3
Autologous stem cell transplantation			Day 0

3xR-DHAP-MTX
- (Cisplatin, AraC 2x2g/m2 d2, MTX 3g/m2 d 15, rituximab IT)

followed by HD-ASCT (BuCy)



	Type	N°	Upper age	ECOG PS	DLBCL	TRM	Median f-up (months)	CRR (%)	EFS	OS
Routine[1]	R	92	23-88	~	76%	15-32	51	36	NR	1-y: 35%
German[2]	P	30	65	≤2	90%	3	21	50	2-y: 44%	2-y: 63%
HOVON[3]	P	36	65	≤2	100%	14	20	28	1-y: 21%	1-y: 22%
SCNSL1[4]	P	38	70	≤3	84%	11	48	63	2-y: 73%	2-y: 83%

MATRix–RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial

Andrés J M Ferreri, Jeanette K Doorduijn, Alessandro Re, Maria Giuseppina Cabras, Jeffery Smith, Fiorella Ilariucci, Mario Luppi, Teresa Calimeri, Chiara Cattaneo, Jahanzaib Khwaja, Barbara Botto, Claudia Cellini, Luca Nassi, Kim Linton, Pam McKay, Jacopo Olivieri, Caterina Patti, Francesca Re, Alessandro Fanni, Vikram Singh, Jacoline E C Bromberg, Kelly Cozens, Elisabetta Gastaldi, Massimo Bernardi, Nicola Cascavilla, Andrew Davies, Christopher P Fox, Maurizio Frezzato, Wendy Osborne, Anna Marina Liberati, Urban Novak, Renato Zambello, Emanuele Zucca, Kate Cwynarski, for the International Extranodal Lymphoma Study Group (IELSG)

Lancet Haematol 2021; 8: e110–21

See Comment page e96

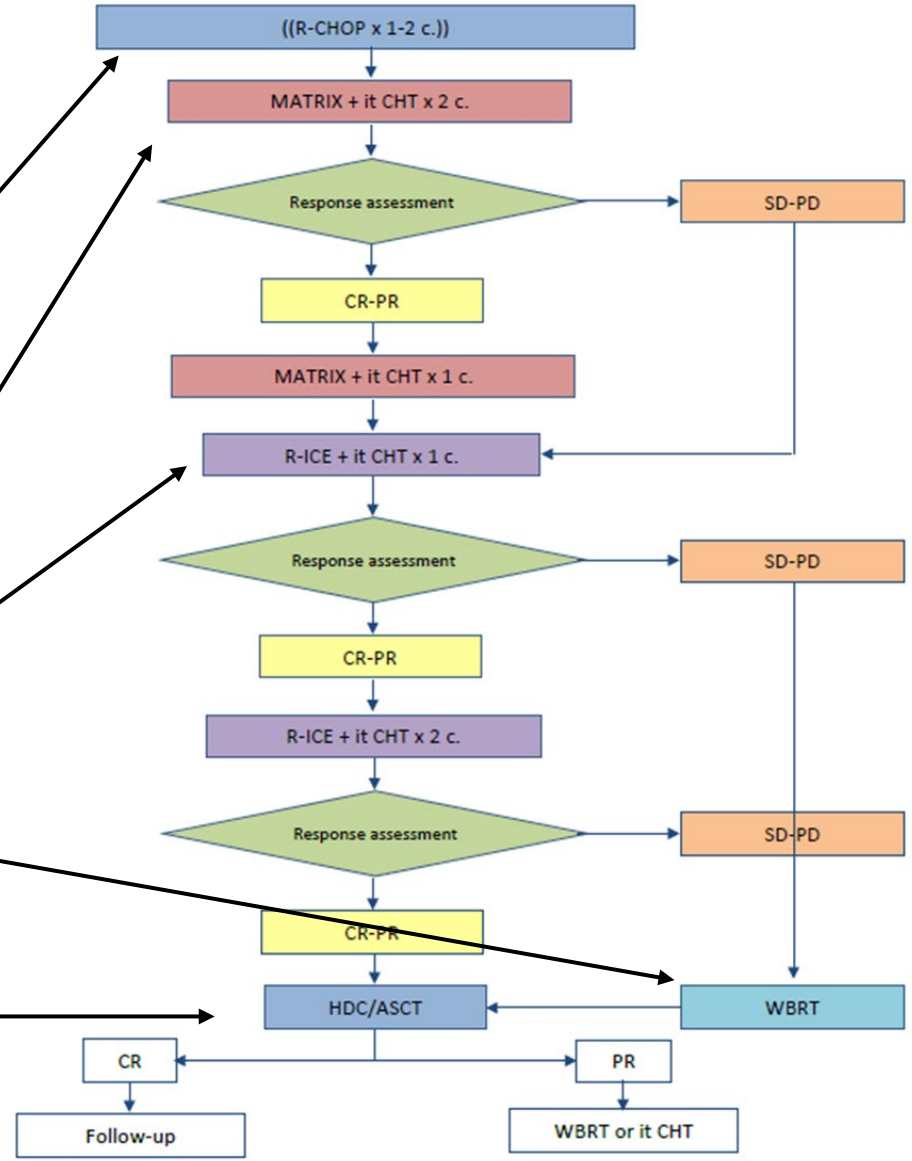
Summary

Background Secondary CNS lymphoma is a rare but potentially lethal event in patients with diffuse large B-cell lymphoma. We aimed to assess the activity and safety of an intensive, CNS-directed chemoimmunotherapy consolidated by autologous haematopoietic stem-cell transplantation (HSCT) in patients with secondary CNS lymphoma.

MARIETTA: Trial Design

Rationale: Dose intensity; active drugs with good CNS bioavailability.

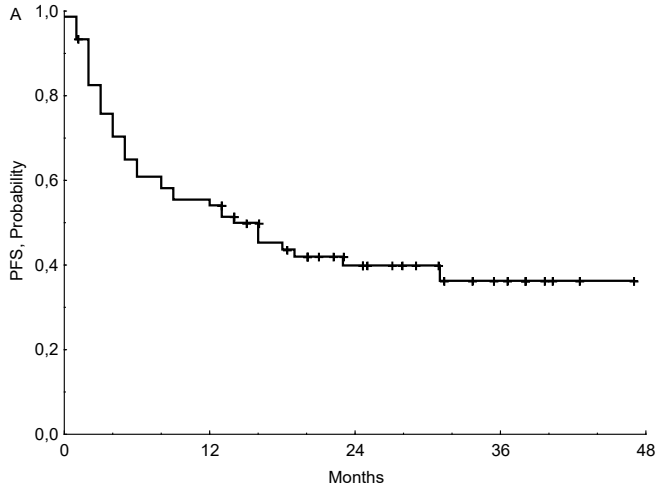
- To start with R-CHOP in the case of life-threatening systemic disease.
- Positive experiences on PCNSL with HD-MTX, HD-ARAC and thiotepa (MATRIX).
- R-ICE is standard in pts with rrDLBCL, and active in rrPCNSL.
- To deliver WBRT in pts with PD during induction and pts with residual CNS disease after ASCT.
- BCNU/thiotepa is safe and active in PCNSL pts.

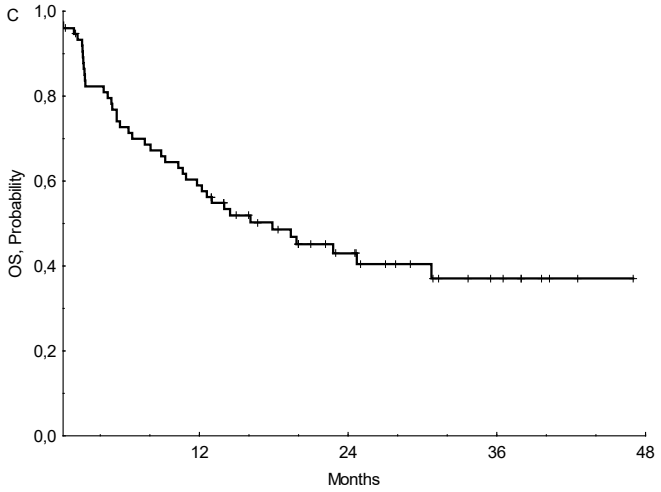


Ferreri et al. Lancet 2009; Gisselbrecht et al. JCO 2010; Kasenda et al. Ann Oncol 2012; Mappa et al. HemOnc 2012; Ferreri et al. Lancet Haematol 2016; Ferreri et al. Lancet Haematol 2017; Schorb et al. Br J Haematol 2020

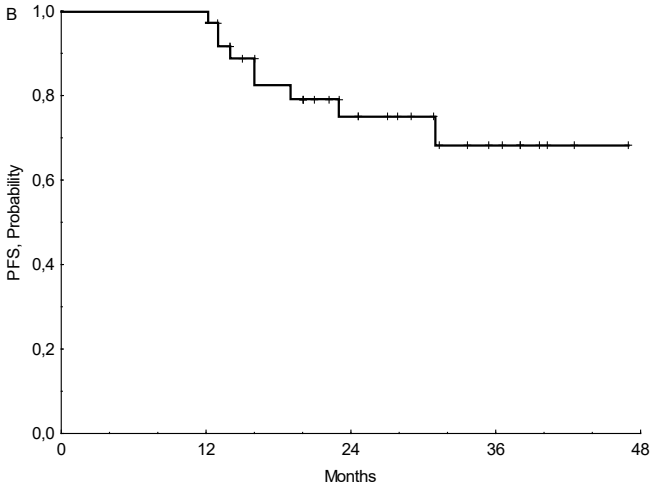
MARIETTA: Efficacy

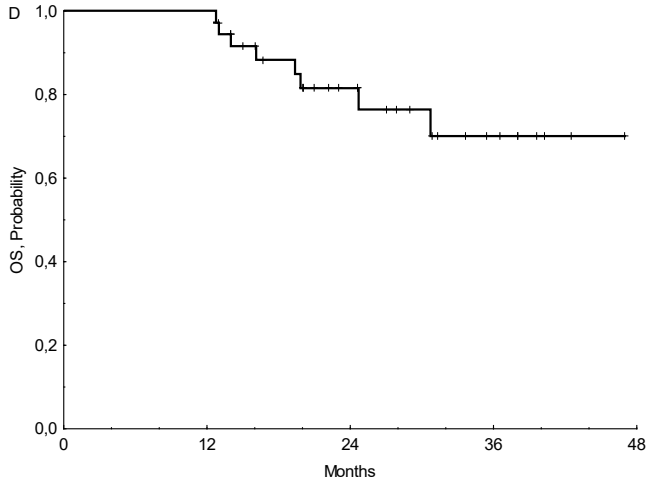
Whole series



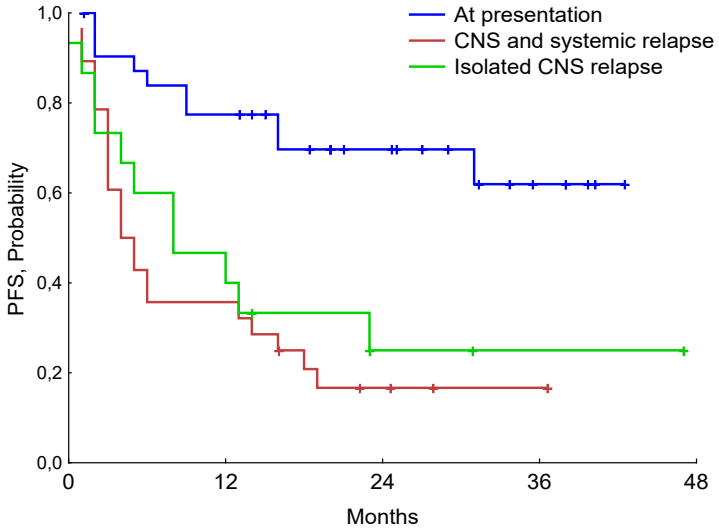


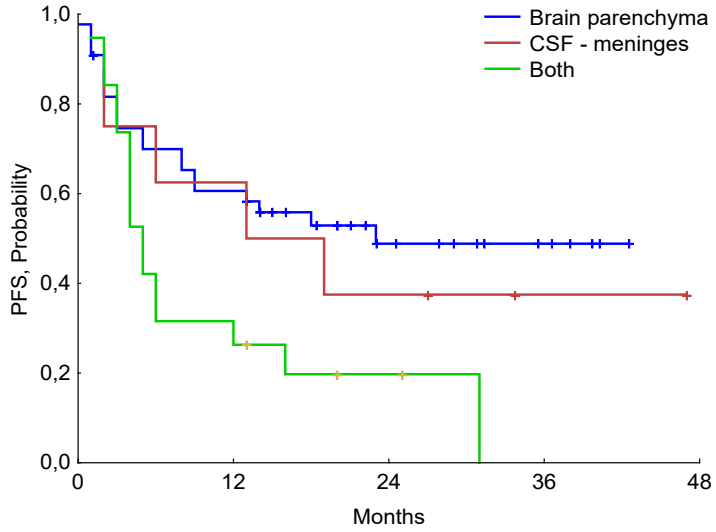
Transplanted patients

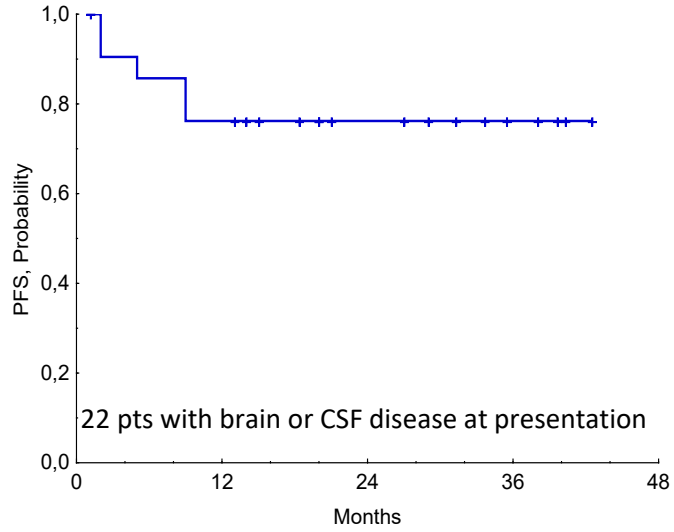




MARIETTA: Subgroup Analyses

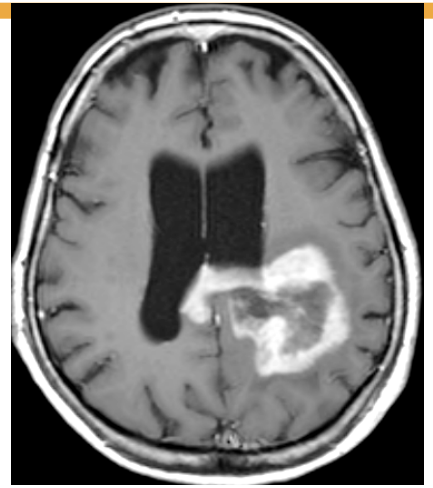


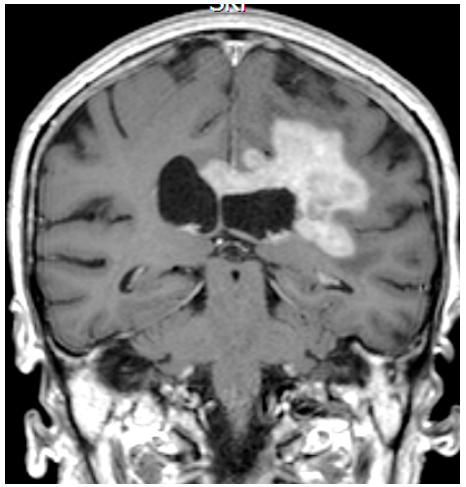




Variable	Subgroups	Assessed patients	1-year PFS	HR (95%IC)	p value
IPI	score 0 - 2	32	45 ± 8%	1	
	score 3 - 5	43	35 ± 8%	1.92 (0.35 – 2.31)	0.66
CNS disease	At presentation	32	77 ± 7%	1	
	Isolated relapse	15	47 ±13%	3.11 (1.25 – 7.71)	0.014
	Concomitant relapse	28	36 ± 9%	3.09 (1.44 – 6.61)	0.003
CNS site	Brain parenchyma	44	61 ± 7%	1	
	CSF/meninges	8	62 ±17%	0.57 (0.21 – 1.61)	0.293
	Both brain and CSF	19	32 ±11%	1.91 (0.91 – 3.97)	0.083

Case #2: Response and follow-up



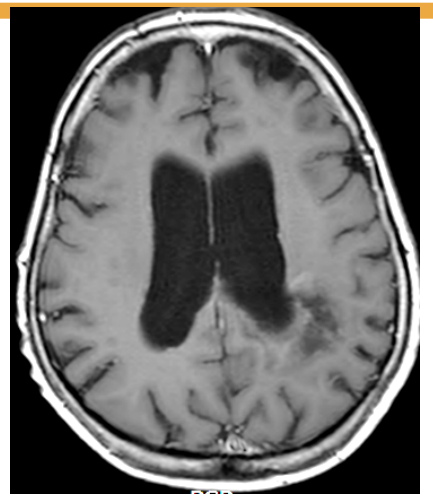


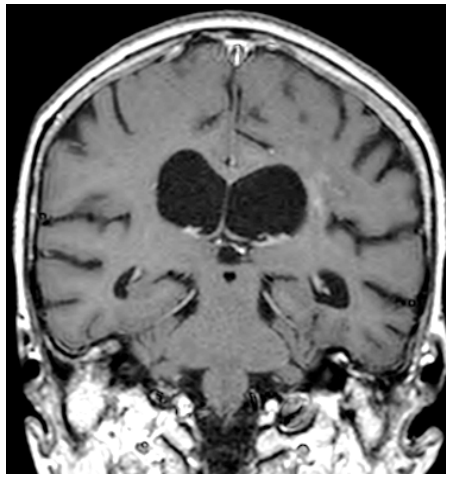
At relapse

Enrollment in the SCNSL1 trial

- 2 courses of MTX-ARAC-Rituximab =>
- R-HDS chemotherapy
- Carmustine-thiotepa ASCT

Alive and NED at 6 years of follow-up





After 2 c. of MTX-ARAC

ARS question #2:
Which is your therapeutic choice for SCNSL patients?

1- WBRT

2- PCNSL-like approach (HD-MTX + WBRT/ASCT)

3- HD-ARAC or HD-IFO polychemo => ASCT

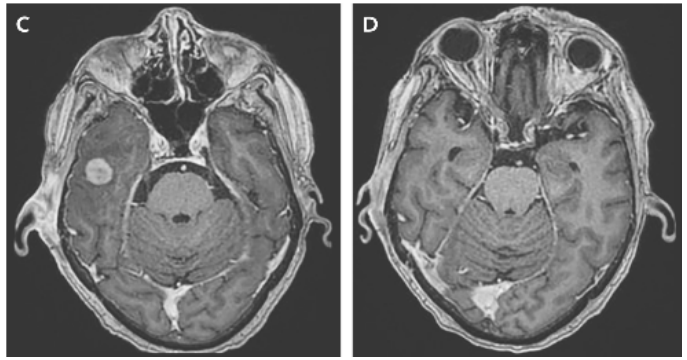
4- CNS-directed & systemic-directed chemo => ASCT

5- Too complex! Headache is killing me

Answer: **CNS & systemic chemo => ASCT**

Which Option When SCNSL Recurs?

- 2/3 of treatment failures are due to early progression (primary refractory)
- 1/3 of treatment failures occurs after one year of follow-up
- Progression/relapse usually occurs in the CNS (+ systemic in half of patients)
- Progression/relapse is followed by dead within 1-2 months
- Most patients are not suitable for salvage polychemotherapy
- Single drugs were inefficient
- CAR-T



Ferreri AJM, et al. Lancet Haematol 2021

Abramson JS, et al. NEJM 2017

Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma

Matthew J. Frigault,[1,2] Jorg Dietrich,[1,3] Maria Martinez-Lage,[4] Mark Leick,[1] Bryan D. Choi,[1,5] Zachariah DeFilipp,[1,2] Yi-Bin Chen,[1,2] Jeremy Abramson,[1,6] Jennifer Crombie,[7] Philippe Armand,[7] Lakshmi Nayak,[7] Chris Panzini,[1] Lauren S. Riley,[1] Kathleen Gallagher,[1] and Marcela V. Maus[1,2]

[1]Cellular Immunotherapy Program, Massachusetts General Hospital Cancer Center, [2]Blood and Marrow Transplant Program, Massachusetts General Hospital, [3]Division of Neuro-Oncology, Department of Neurology, Massachusetts General Hospital Cancer Center, [4]Department of Pathology, Massachusetts General Hospital, [5]Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, and [6]Center for Lymphoma, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; and [7]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Eight patients (median age 50 years; range 17-79)

The median number of prior therapies was 5 (range, 3-6); Two patients had systemic disease

All patients were receiving CNS-directed therapy until lymphodepletion.

Half pts received concomitant ibrutinib (nonresponsive patients)

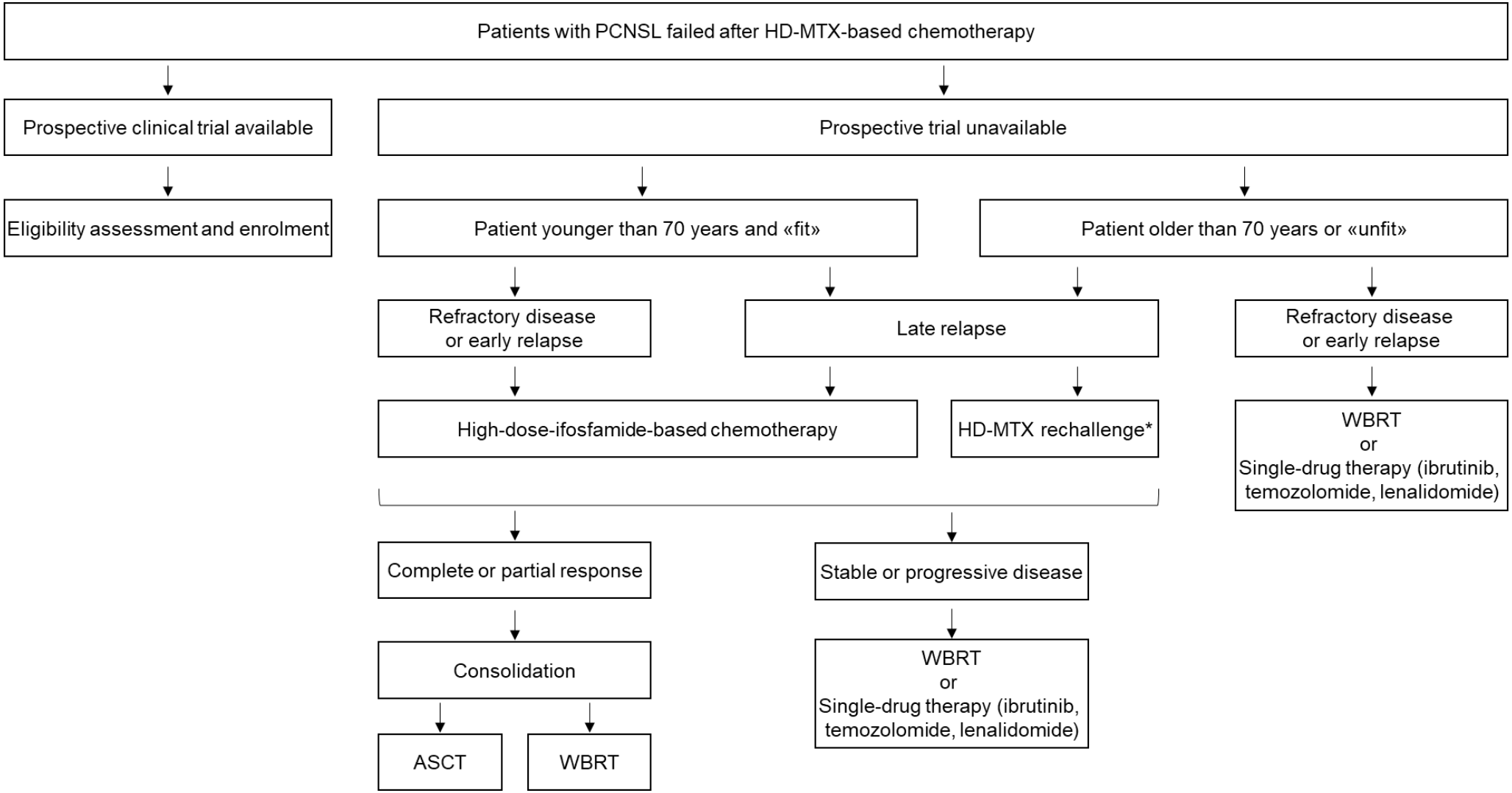
Grade-1 neurotoxicity in 2 pts; grade-1 CRS in all cases

No patient required tocilizumab or steroids for toxicity.

2 CR 2 PR

Short follow-up

rrPCNSL: Take Home Messages



rrSCNSL: Take Home Messages