

HOW I TREAT HIGH-RISK EXTRANODAL DLBCL

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«High Risk» definition

**“conditions where R-CHOP is
unfeasible and/or associated with
substandard survival figures”**

Risk? What risk?

“High-risk” patient with DLBCL:

- Elderly
- Frail
- Comorbidities

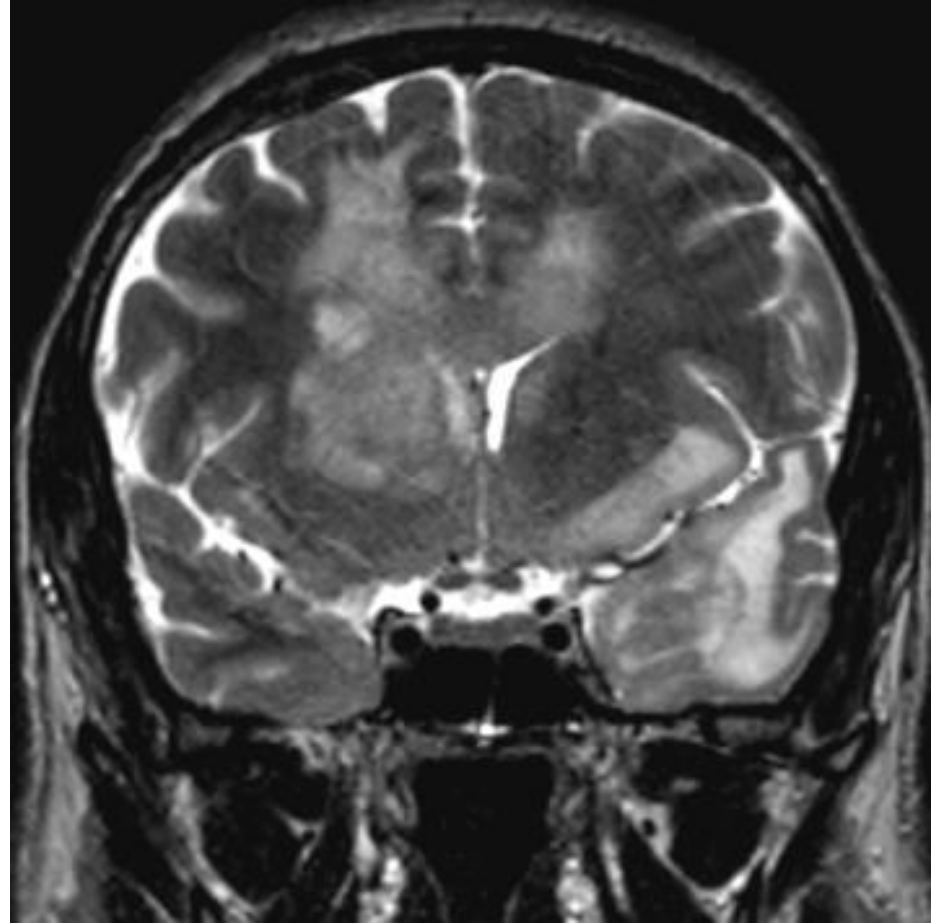
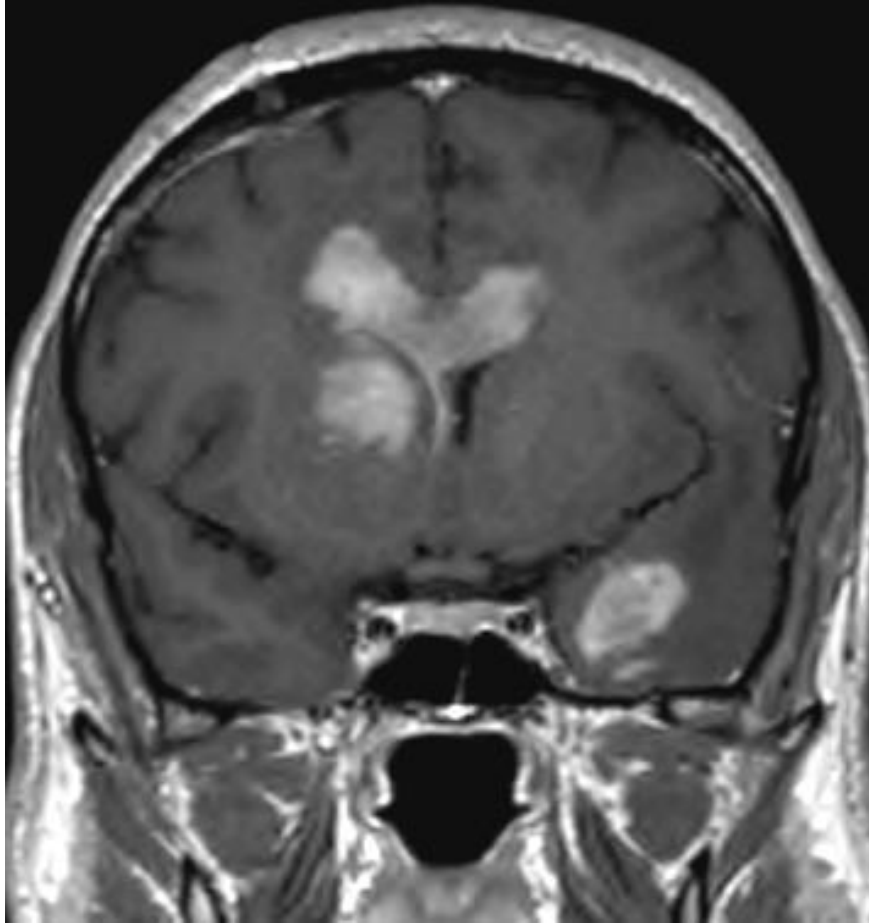
Patient with “high-risk” DLBCL:

- IPI score
- Cell of Origin
- Genetic abnormalities (double/triple hit)
- Primary refractory
- Relapses after ASCT
- Extranodal site untreatable with R-CHOP (CNS)
- Extranodal sites associated with increased risk of CNS relapse (PTL)
- Some of pts with extranodal DLBCL & poorer survival (PMLBCL)

Case 1: The Depressed Young Man with Seizures

- 41-year-old gentleman
- Acute prostatitis (2007)
- Two events of generalized seizures (2009)
- Bradypsychia; depression
- Emergency entry

Neuroimaging



Contrasted Whole-body CT scan and ^{18}F FDG-PET excluded extra-CNS disease

Symptomatic therapy: anticonvulsant and steroids (minimal disease regression)

Staging: NEGATIVE

Physical examination

Routine blood studies

Whole-brain MRI

Contrast total-body CT scan

Ophthalmologic evaluation (including slit-lamp examination)

Cerebrospinal-fluid cytology

Cerebrospinal-fluid biochemical examination

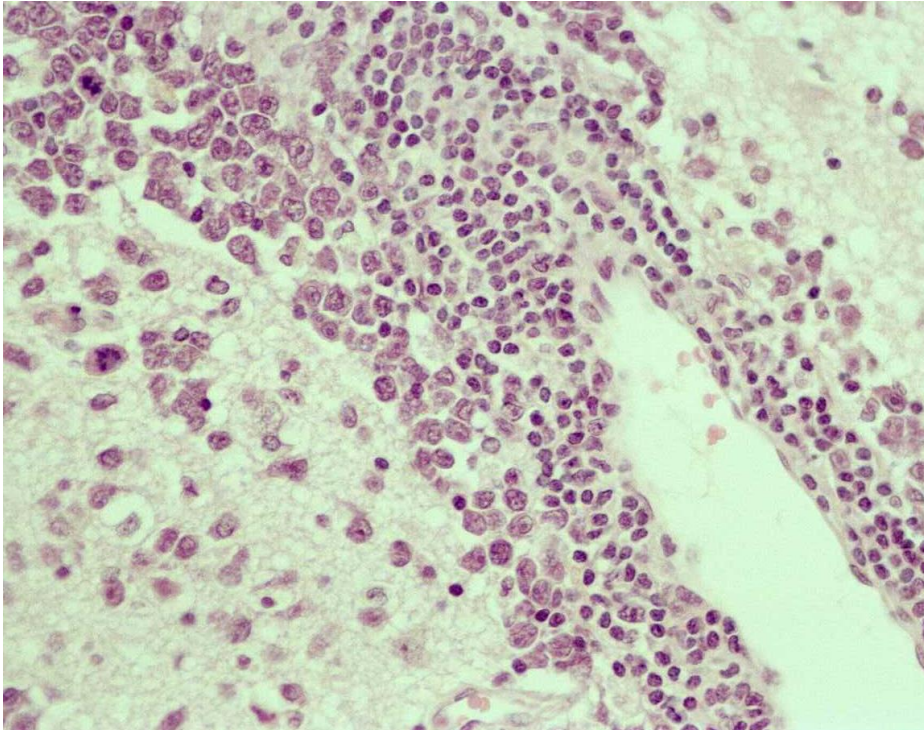
Bone-marrow biopsy

Testicular ultrasonography (older men)

FDG-PET (investigational role)

Suspicion of vitreal infiltration may require confirmation by vitrectomy

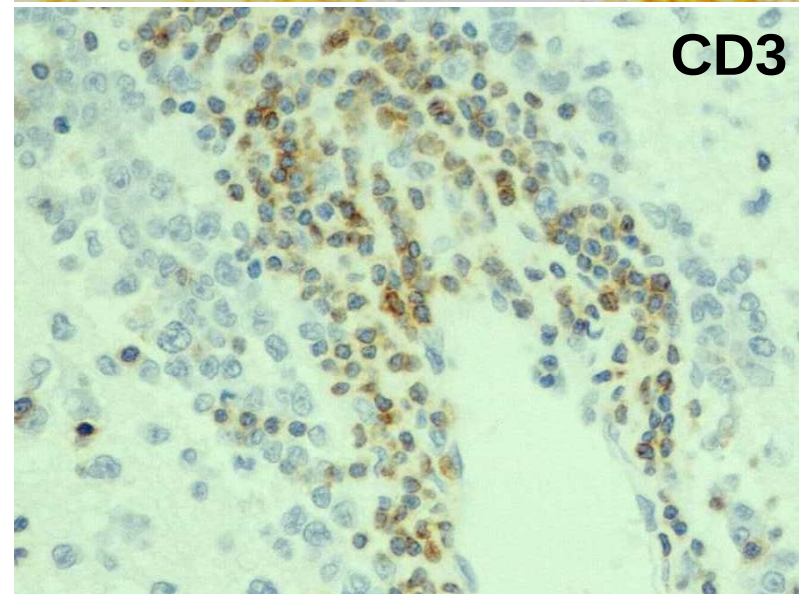
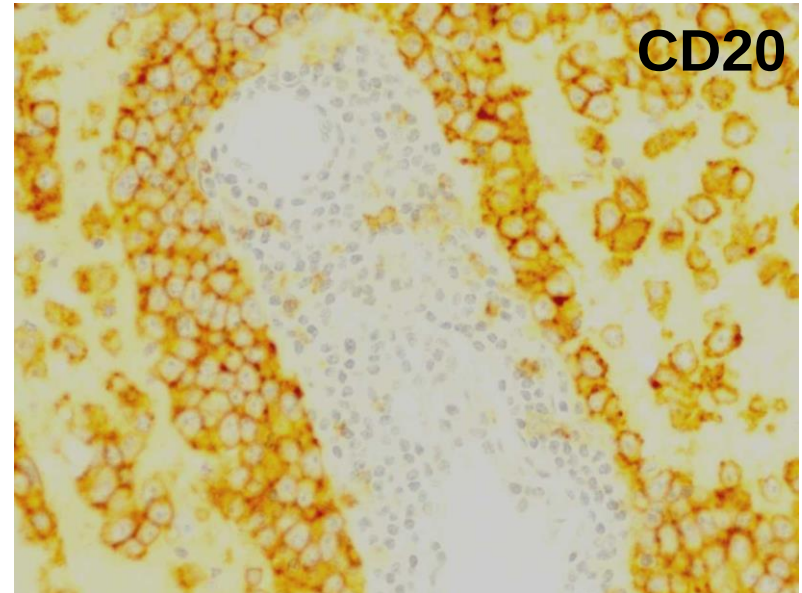
Histological Features



**Bcl-6 +
MUM-1 +
MIB-1: 70%**

**Bcl-2 +
CD10 -**

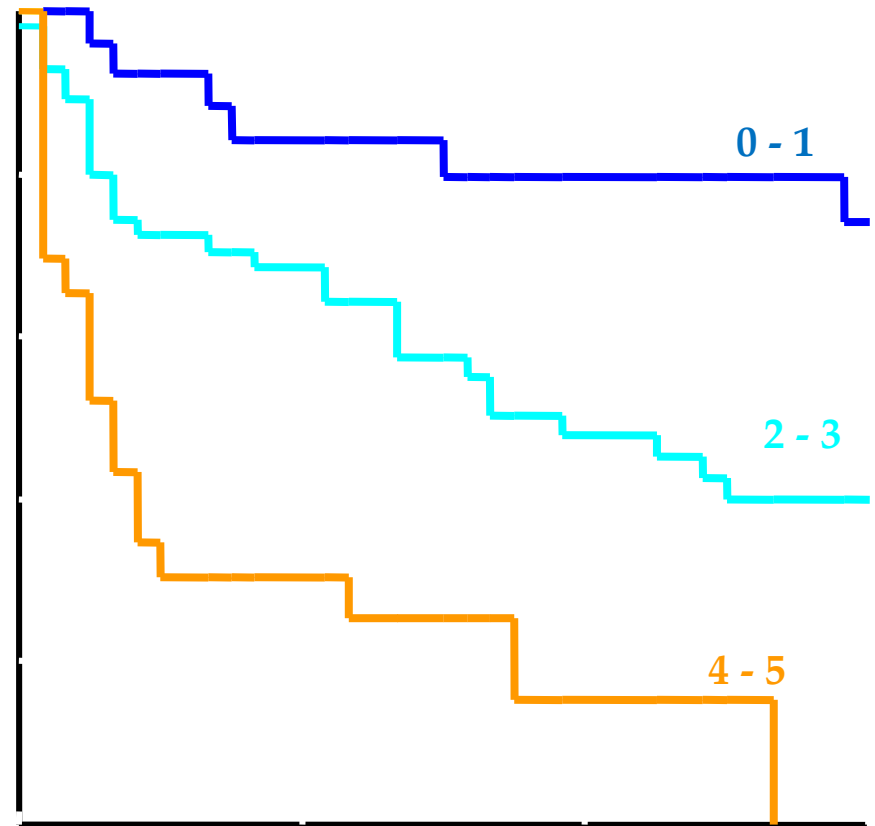
Diffuse large B-cell lymphoma



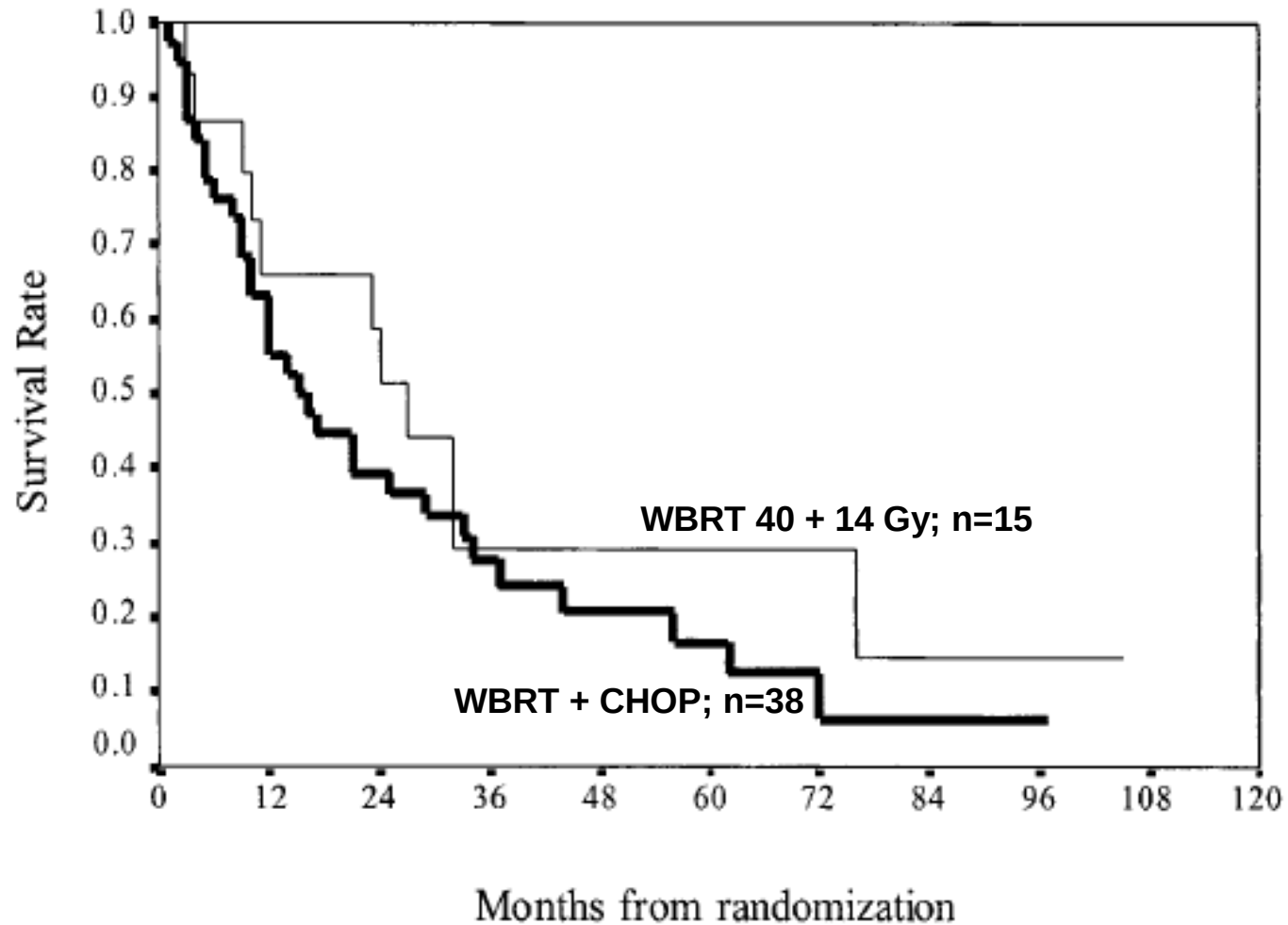
I.E.L.S.G. Prognostic Score

Variable	0	1
Age	≤ 60 ys.	> 60 ys.
ECOG-PS	0 - 1	2 - 4
LDH	normal	elevated
CSF protein	normal	elevated
Deep lesions	no	yes

2



CHOP regimen





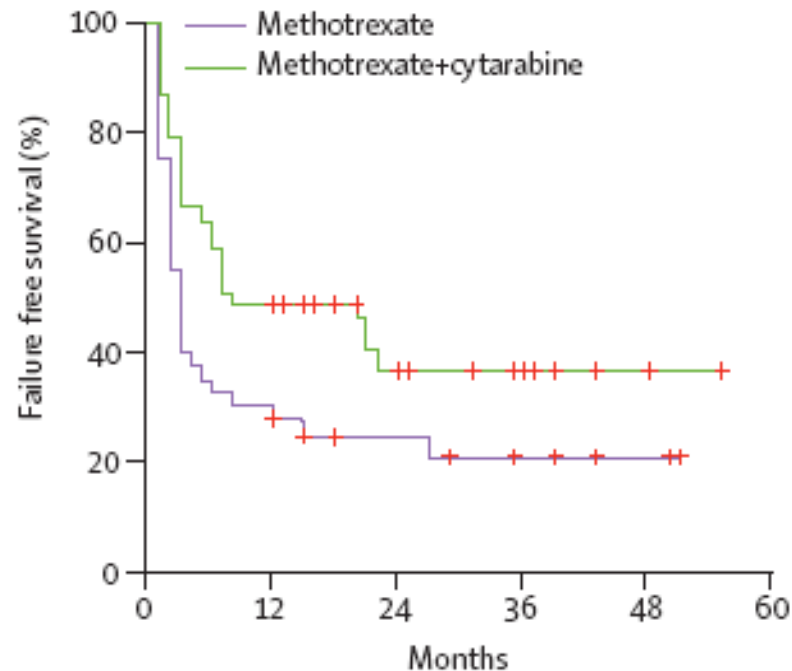
High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

Andrés J M Ferreri, Michele Reni, Marco Foppoli, Maurizio Martelli, Gerasimus A Pangalis, Maurizio Frezzato, Maria Giuseppina Cabras, Alberto Fabbri, Gaetano Corazzelli, Fiorella Ilariucci, Giuseppe Rossi, Riccardo Soffietti, Caterina Stelitano, Daniele Vallisa, Francesco Zaja, Lucía Zoppegno, Gian Marco Aondio, Giuseppe Avvisati, Monica Balzarotti, Alba A Brandes, José Fajardo, Henry Gomez, Attilio Guarini, Graziella Pinotti, Luigi Rigacci, Catrina Uhlmann, Piero Picozzi, Paolo Vezzulli, Maurizio Panzoni, Emanuela Zucca, Federico Caligaris Canto, Franco Cavalli, on behalf of the International Extranodal Lymphoma Study Group

Lancet 2009; 374: 1512-20

	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

	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



MTX + Alkylator + Rituximab

INDUCTION	CONSOLIDATION	N°	ORR	2-year PFS
Rituximab Methotrexate Procarbazine Vincristine ¹	low-dose WBRT	52	79%	57%
Rituximab Methotrexate Procarbazine Vincristine ²	TBC - ASCT	33 (≤ 65 ys)	94%	79%
Rituximab Methotrexate Temozolomide ³	Non-myeloablative HD-cytarabine HD-etoposide	44	77%	59%
Rituximab Methotrexate Temozolomide ⁴	Hyperfract WBRT + TMZ maintenance	53 (<60 yo: 62%)	57%	64%

¹Morris PG, et al. JCO 2013; ²Omuro A, et al. Blood 2015; ³Rubenstein JL, et al. JCO 2013; ⁴Glass J, et al. JCO 2016

The IELSG #32 trial

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



4 c. MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
every 3 weeks

4 c. rituximab 375 mg/m² d-5 & 0
MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
every 3 weeks

4 c. rituximab 375 mg/m² d-5 & 0
MTX 3.5 g/m² d.1
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Thiotepa 30 mg/m² d.4
every 3 weeks

Response assessment

CR – PR – SD



WBRT 36 Gy
± boost 9 Gy

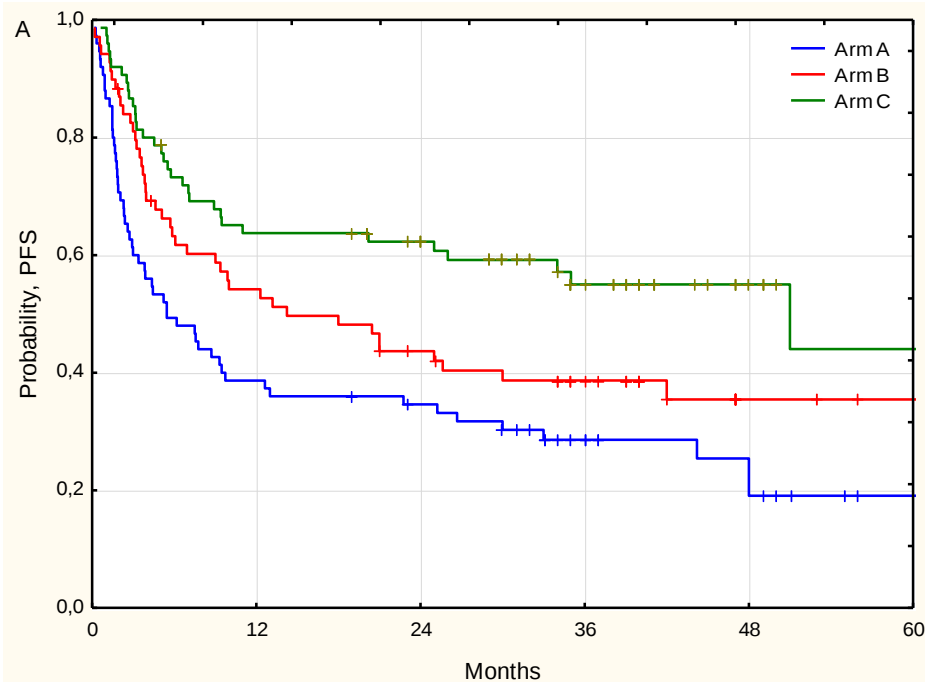
BCNU 400 mg/m² d.1
Thiotepa 5 mg/Kg x 2/d; d.2-3
+ APBSCT

PD – tox
↓ SC harvest

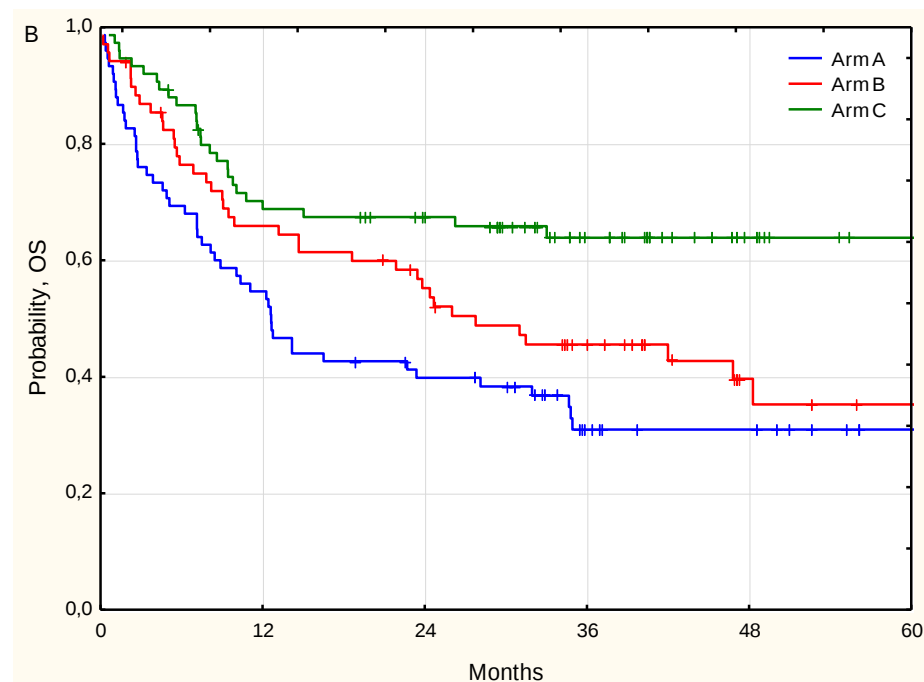
WBRT 40 Gy
± boost 9 Gy

MATRix: Efficacy

MEDIAN FOLLOW-UP: 40 MONTHS (24-76)

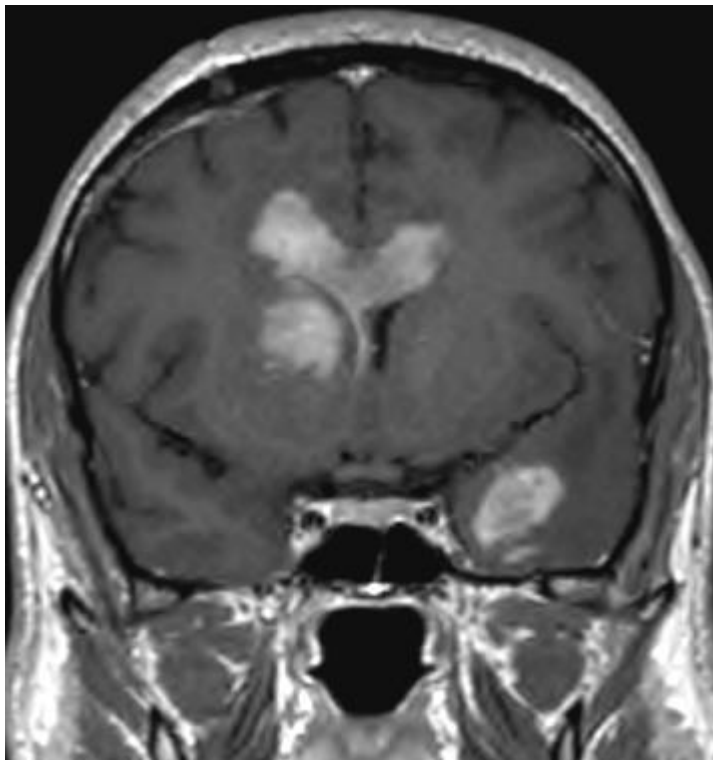


	HR	95%CI	p
A vs. B	0.68	0.45 - 1.02	0.06
A vs. C	0.66	0.53 - 0.81	0.0001
B vs. C	0.63	0.40 - 0.99	0.04

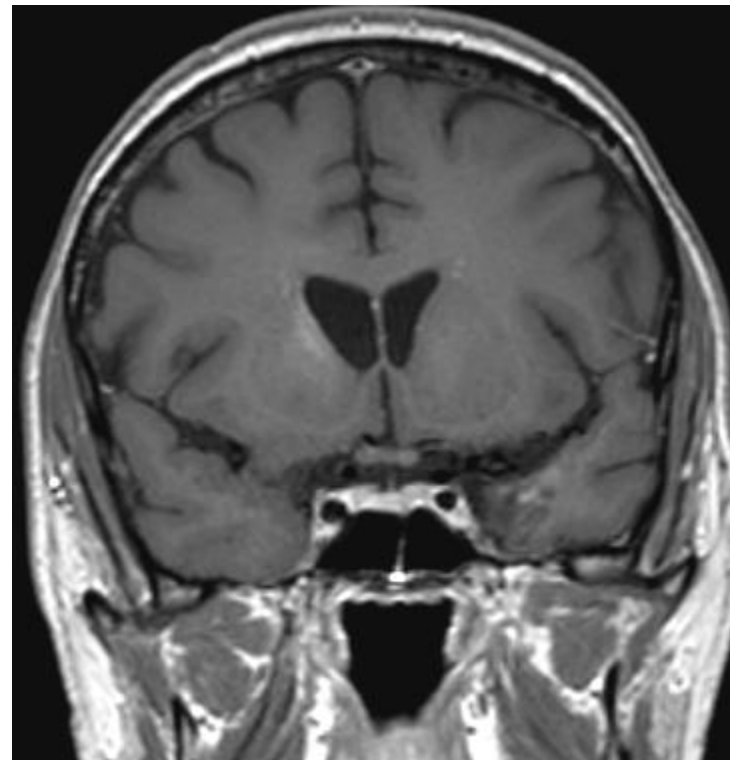


	HR	95%CI	p
A vs. B	0.73	0.48 - 1.11	0.14
A vs. C	0.65	0.52 - 0.83	0.0004
B vs. C	0.57	0.35 - 0.93	0.02

Case #1: Response to MATRix



Baseline



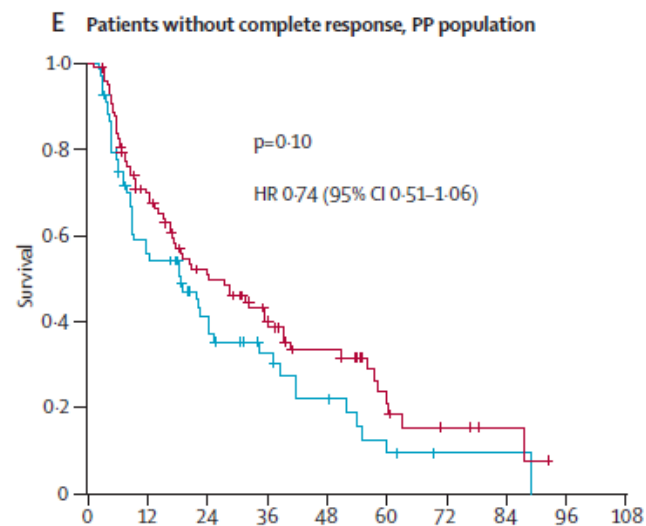
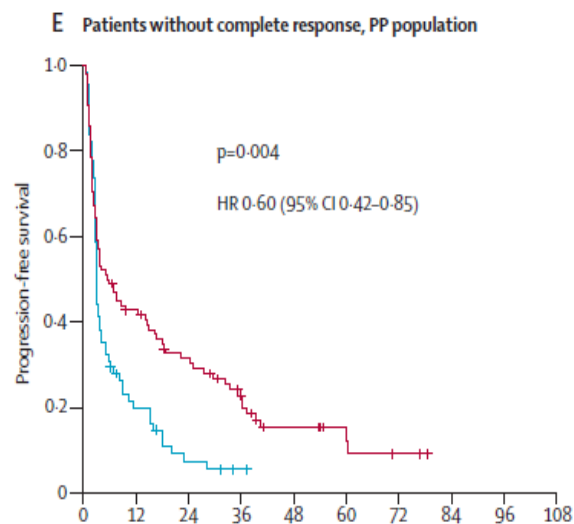
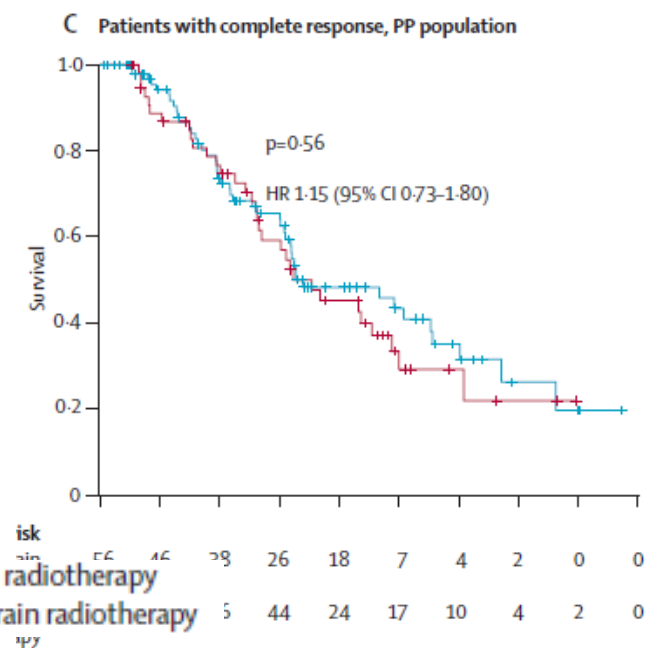
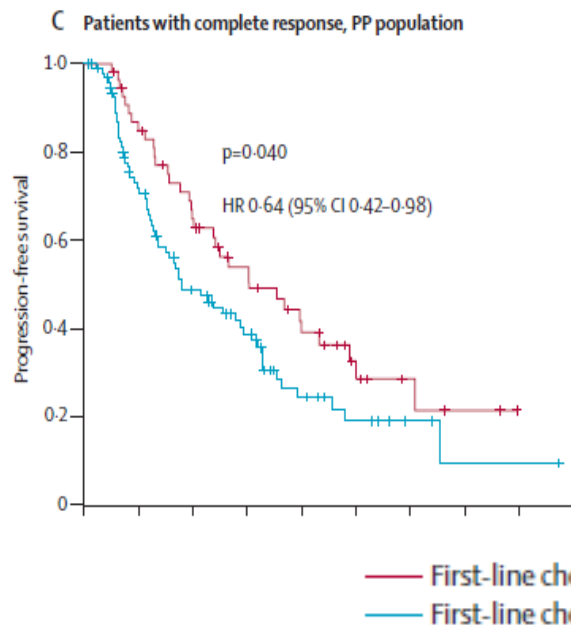
After 4 c. MATRix



Reducing Neurotoxicity Risk

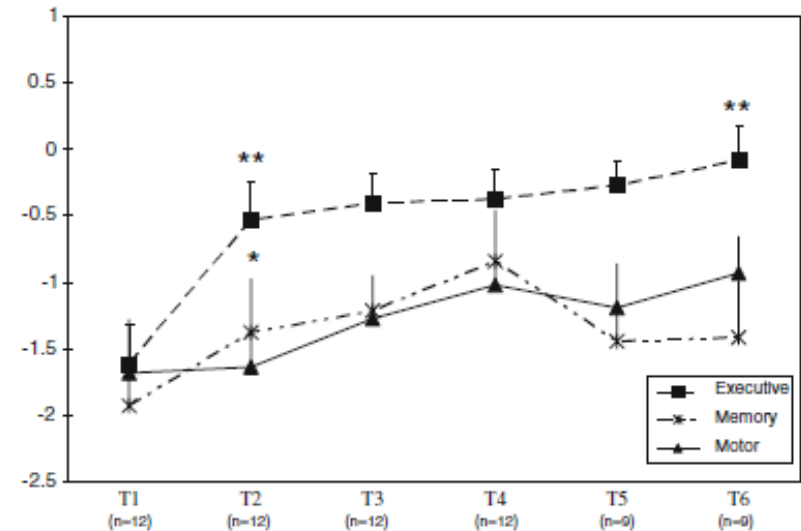
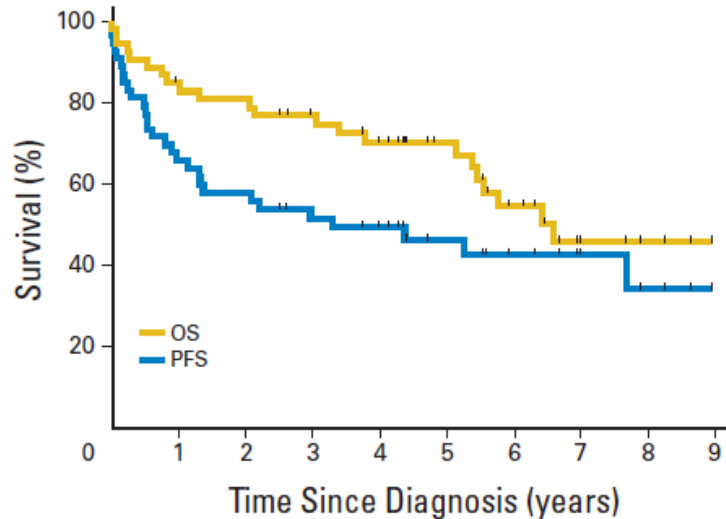
- ✓ To avoid consolidation RT (only CRs).
- ✓ To improve radiation parameters.
- ✓ To replace RT with other strategies.

G-PCNSL-SG-1 trial: results



Low-dose WBRT

C



No. at risk
PFS
OS

S T R A T I F Y	RPA Class	R A N D O M I Z E	Arm A (chemo only)							
			Arm A (chemo only)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)		Ara-C Cycle 1	Ara-C Cycle 2
	Class 1: age ≤ 50	↙ ↘								
	Class 2: age > 50 and KPS ≥ 70		Arm B (chemo + low-dose WBRT)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)	Low-Dose WBRT (13 fx)	Ara-C Cycle 1	Ara-C Cycle 2
	Class 3: age > 50 and KPS < 70									

RTOG
RADIATION THERAPY
ONCOLOGY GROUP

Consolidative HDC/ASCT

N°	Age m(r) PS m(r)	Induction	CRR (%)	Conditioning	ASCT (%)	F-up (mo)	2-yr PFS (%)	TRM (%)
25	51 (21-60) PS3-4: 32%	MVpBP +itx/araC	44	BEAM + RT	68	34	60	4
Colombat P, et al. BMT 2006								
28	53 (25-71) 70 (30-100)	MTX araC	18	BEAM	50	28	20	0
Abrey L, et al. JCO 2003								
11	52 (33-65) PS1: 91%	MTX araC	73	Bus, CTX VP16 ± RT	100	25	30	0
Yoon DH, et al. BMT 2011								
23	55 (18-70) 70 (30-100)	MTX	13	Thiotepa Busulfan	70	15	45	13
Montemurro M, et al. Ann Oncol 2007								
21	56 (34-69) PS>1: 70%	MTX ± others	24	Thiotepa Bus, CTX	100	60	72	14
Alimohamed N, et al. L&L 2012								
30	54 (27-64) 70 (30-100)	MTX araC, TTP	37	Thiotepa BCNU + RT	77	140	81	3
Kasenda B, et al. Ann Oncol 2012								
79	56 (51-62) 90 (70-90)	MTX araC, TTP	23	Thiotepa BCNU ± RT	92	57	75	5
Illerhaus G, et al. Lancet Haematol 2016								

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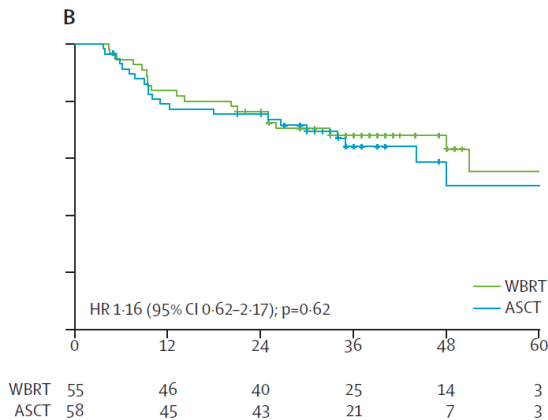
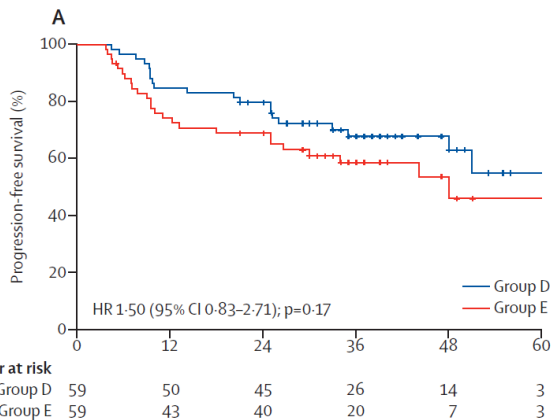
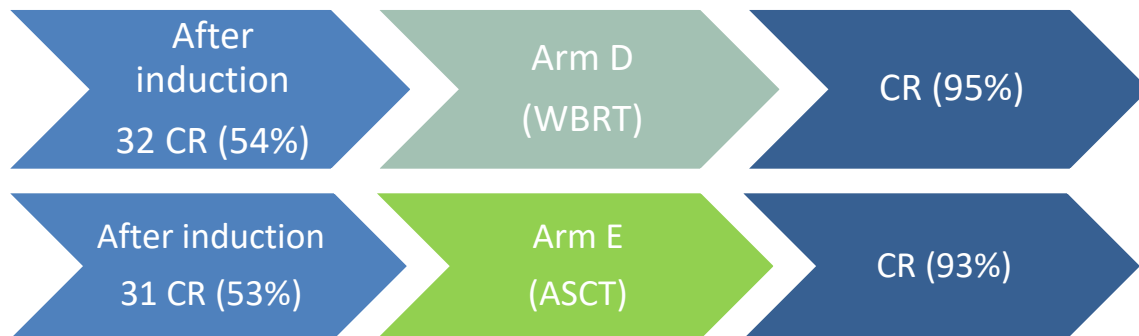
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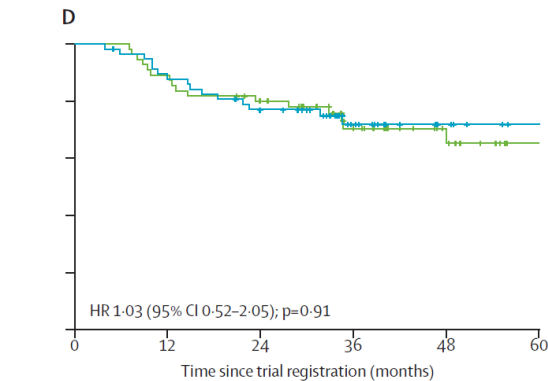
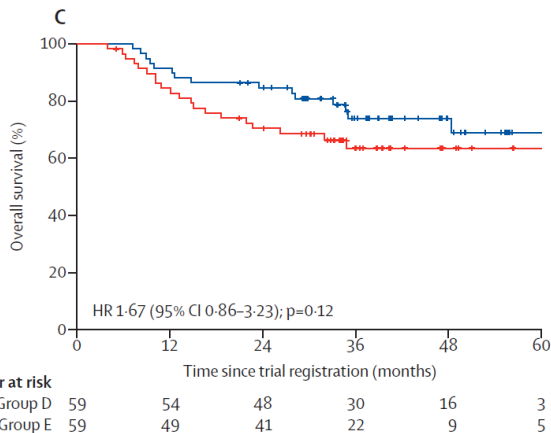
PD – tox
↓ SC harvest

WBRT 40 Gy
± boost 9 Gy

ACTIVITY AND EFFICACY

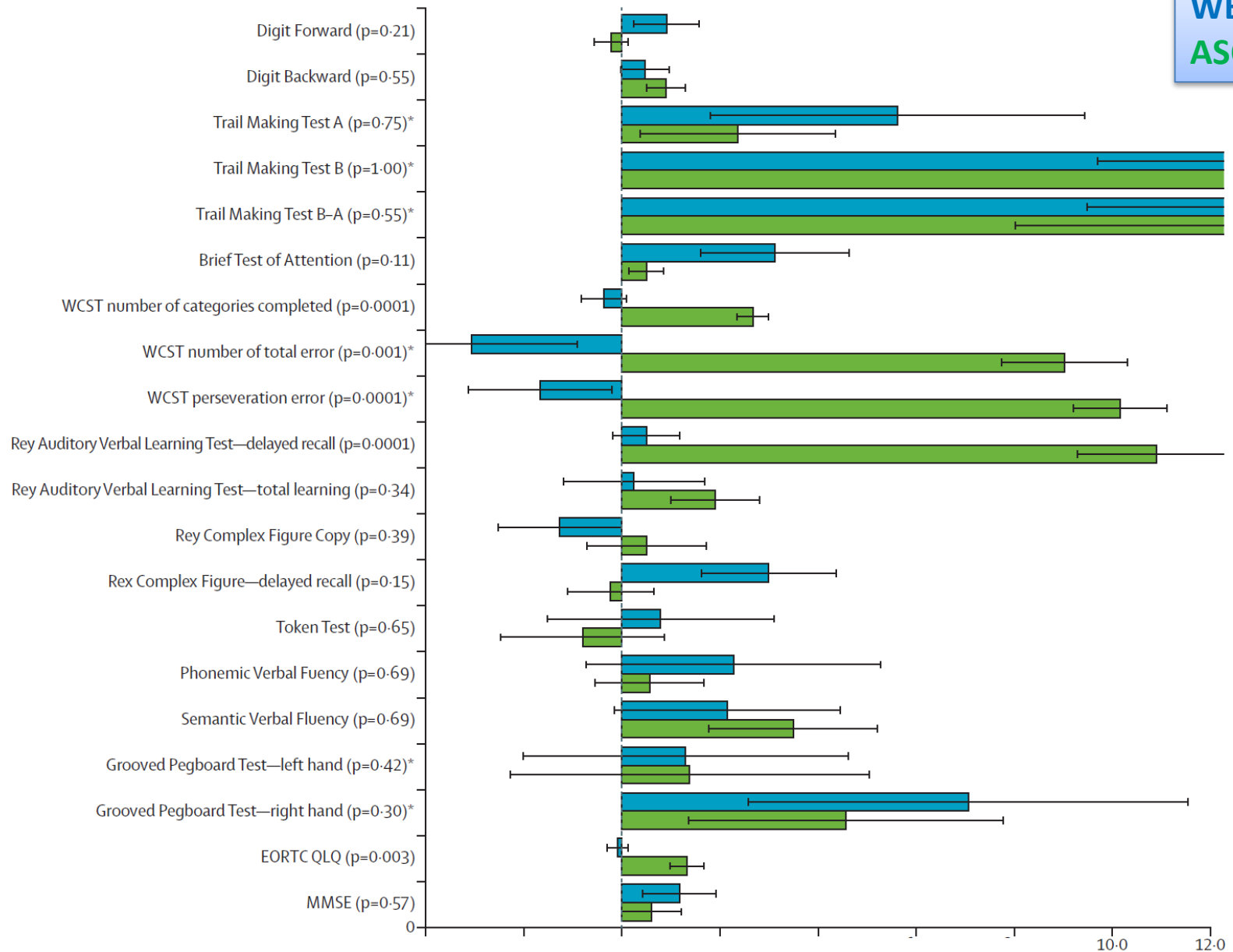


MEDIAN FOLLOW-UP: 40 MONTHS (24-76)



COGNITIVE FUNCTIONS AT 2 YEARS

WBRT
ASCT



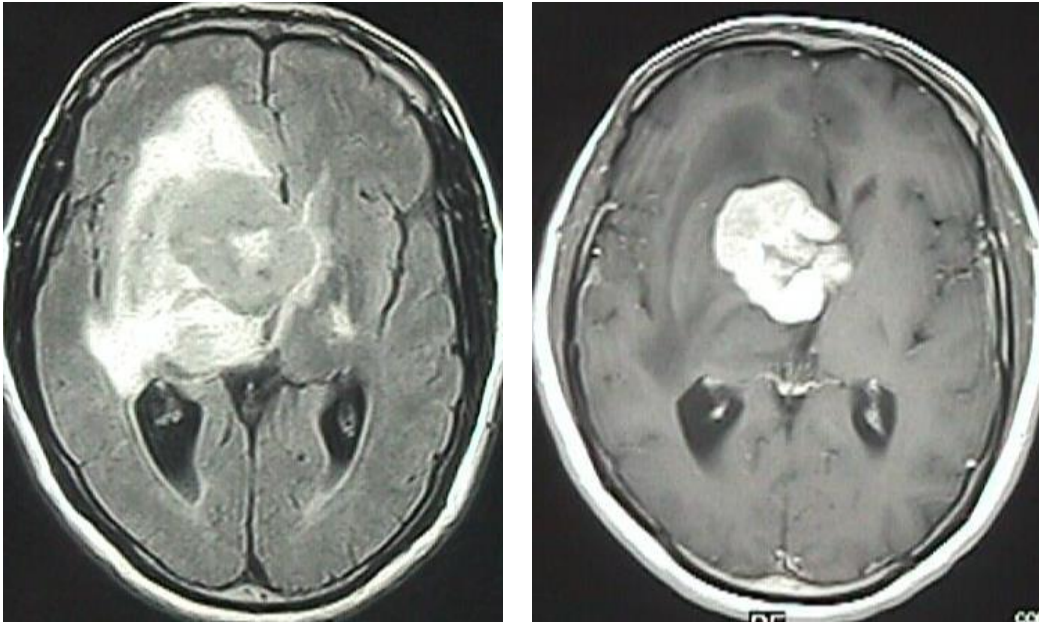
At 6 years



Case 2: The granddaddy who is going crazy fast

- 76-year-old gentelman
- Cured prostate cancer (68 yo)
- Arteria hypertension
- Progressive cognitive decline
- Prolonged hospitalization
- Emergency entry due to head trauma

Case #2: Imaging & Diagnosis



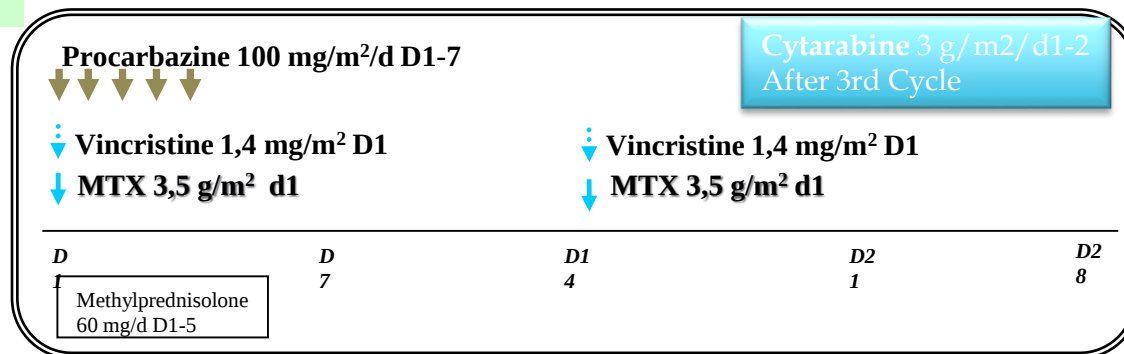
- Negative staging
- Unsuccessful steroid therapy
- Stereotactic biopsy: DLBCL

Elderly Pts: PHRC 2006 Trial

AGE $\geq$ 60 YEARS

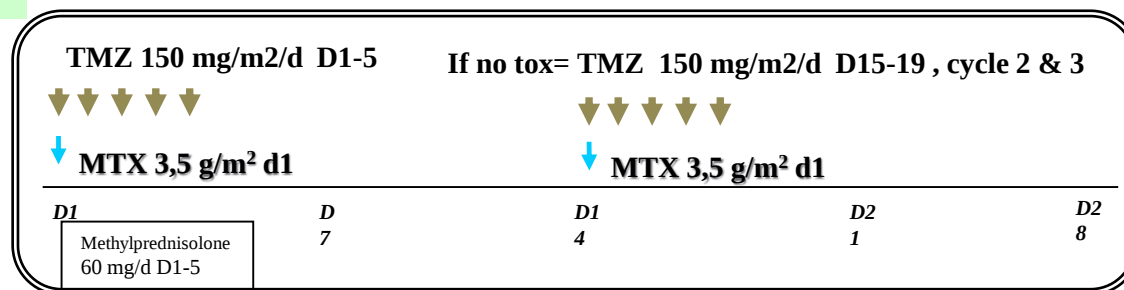
Arm A M-PVA

3 cycles/ 28 d



Arm B M-TMZ

3 cycles/28 d



Omuro A, et al. Lancet Haematol 2015

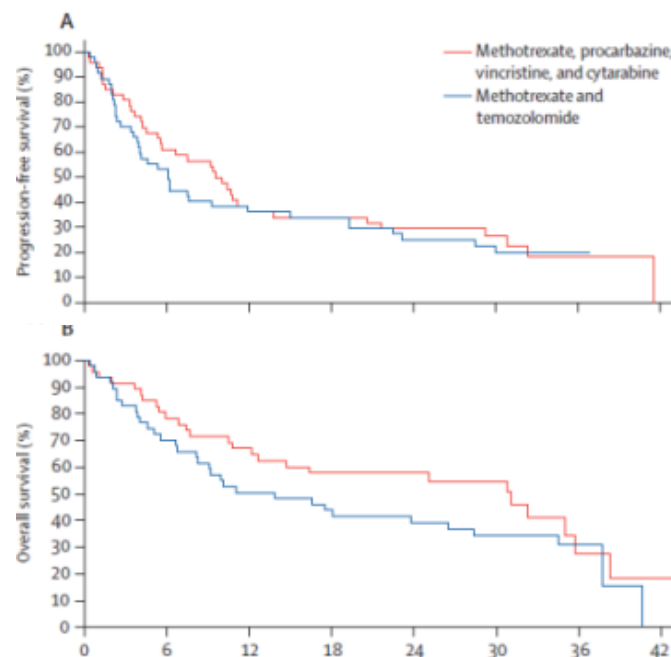


PHRC 2006 Trial

AGE ≥ 60 YEARS

	Methotrexate with temozolomide (n=48)	Methotrexate, procarbazine, vincristine, and cytarabine (n=47)
Grade 3 or 4 toxicities		
Non-haematological		
Liver dysfunction	21 (44%)	18 (38%)
Infection	6 (13%)	7 (15%)
Sepsis	3 (6%)	0
Renal	2 (4%)	3 (6%)
Cardiac	1 (2%)	0
Fatigue	1 (2%)	0
Peripheral neuropathy	0	1 (2%)
Venous thrombosis or pulmonary embolism	0	4 (9%)
Seizures	0	1 (2%)
Hypoglycaemia	0	1 (2%)
Hypophosphatemia	1 (2%)	1 (2%)
Hypokalaemia	4 (8%)	3 (6%)
Hyponatraemia	3 (6%)	3 (6%)
Hypernatraemia	0	1 (2%)
Haematological		
Leukopenia	6 (13%)	6 (13%)
Neutropenia	5 (10%)	4 (9%)
Anaemia	7 (15%)	5 (11%)
Thrombocytopenia	5 (10%)	6 (13%)
Lymphopenia	14 (29%)	14 (30%)
All grades 3 and 4 toxicities	34 (71%)	34 (72%)
Deaths due to toxicity*	5 (10%)	3 (6%)
Methotrexate dose reductions	12 (25%)	14 (30%)

	MPV-A (n= 47)	M-TMZ (n= 48)	<i>p</i>
CR	62%	45%	0.11
PR	20%	26%	
SD	2%	7%	
PD	16%	22%	
ORR	82%	71%	0.23

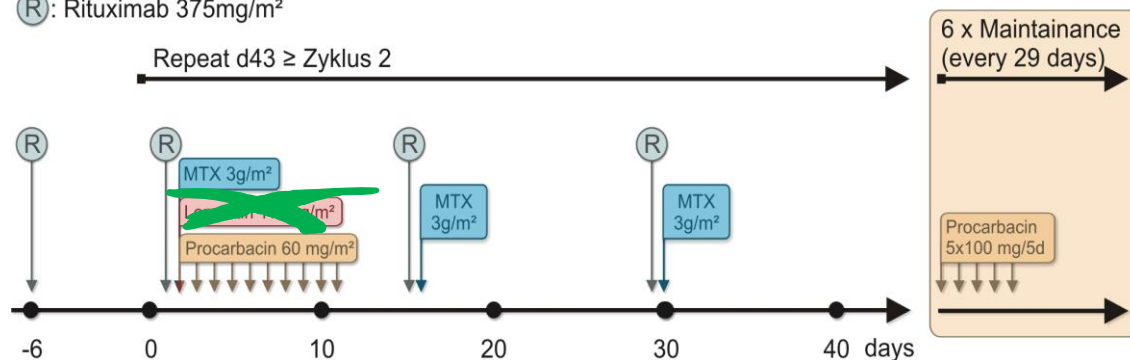


Elderly Patients: PRIMAIN Trial

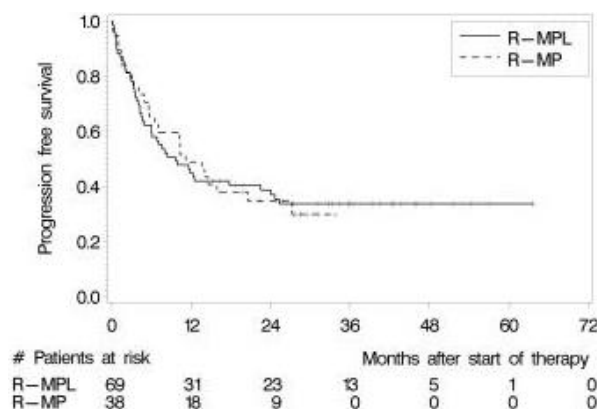
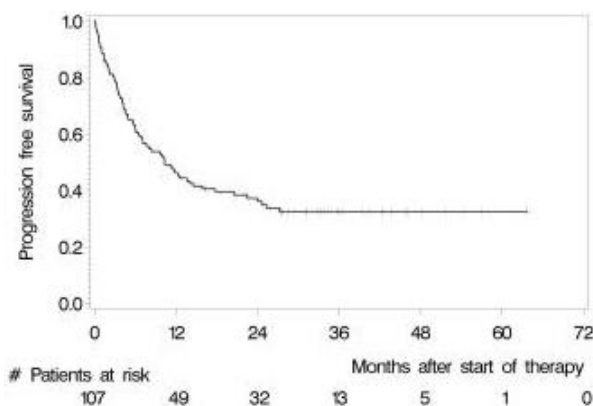
AGE > 65 YEARS

- Multicentre phase II trial (20 centres)
- N = 107

(R): Rituximab 375mg/m²



	R-MPL (N=69)	R-MP (N=38)	All (N=107)
CR	44%	40%	42%
PR	29%	37%	32%
SD	1%	0%	1%
PD	1%	3%	2%
NA	25%	21%	23%



Treatment

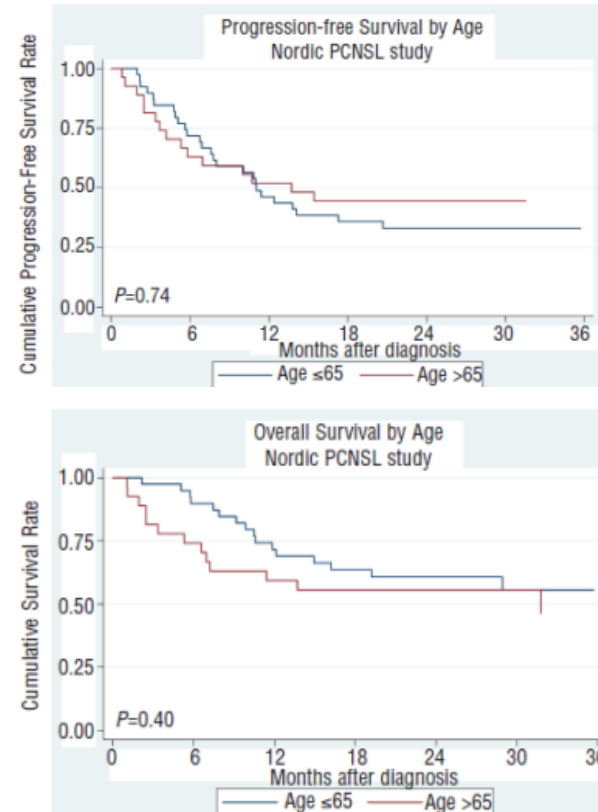
- Partial response after 2 courses of R-MPV
- Residual enhanced image after 4 c. of R-MPV
- Acceptable tolerability
- Patient wishes a therapy with curative intent
- Consolidation

Maintenance therapy

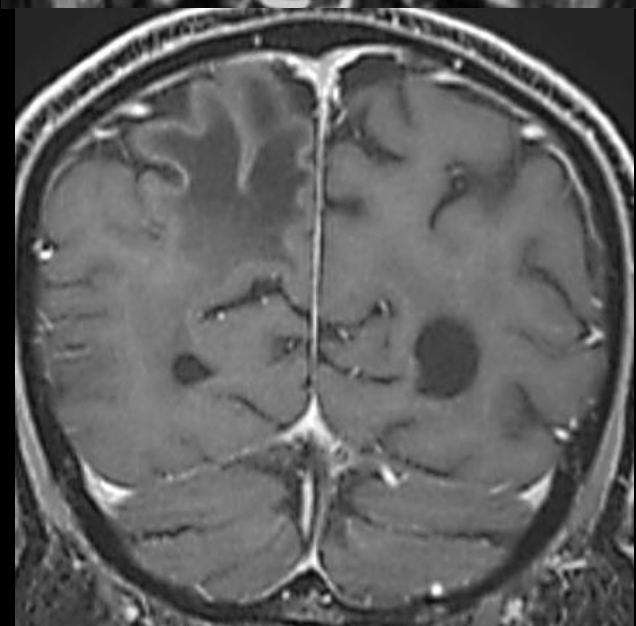
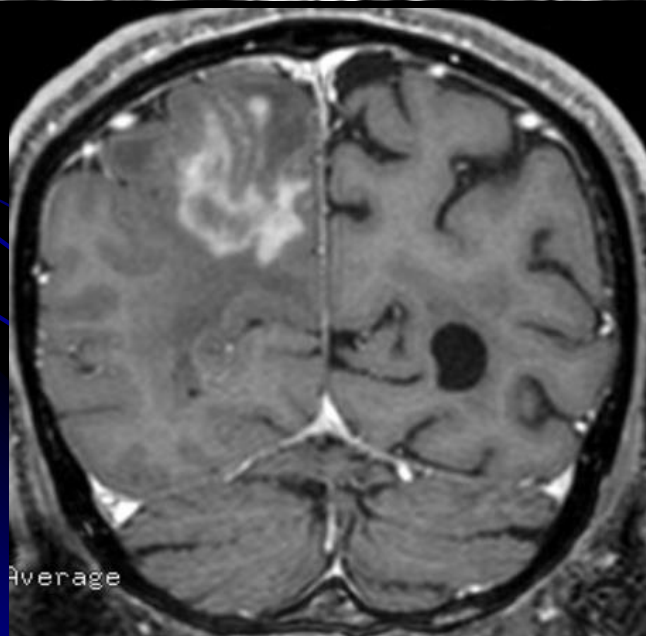
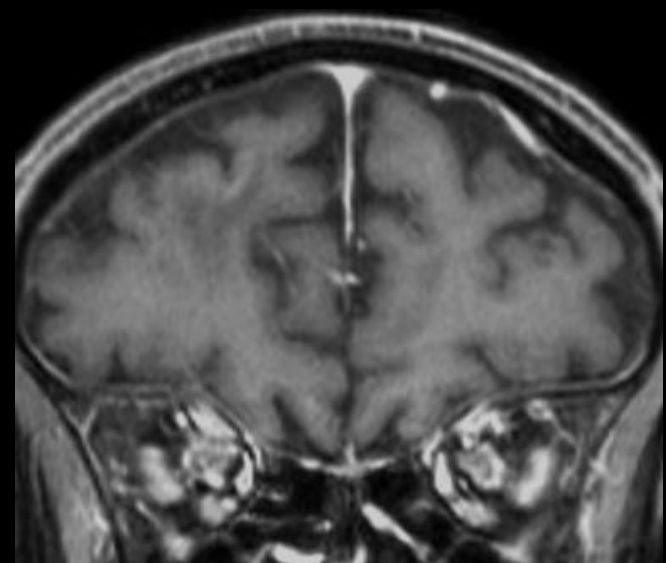
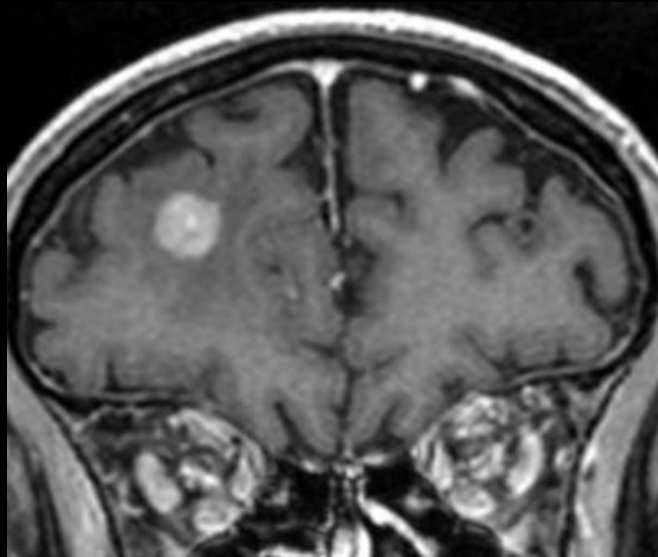
Nordic trial (Bonn Protocol plus:

- Rituximab
- IT Depocyte®
- Infusion time of MTX of 3 hours
- CTX - ITX replaced by TMZ in pts >65 yo
- Vincristine deleted in elderly pts
- **Maintenance TMZ in responding elderly pts)**

- 39 pts aged 18-65 ys
- 27 pts aged 66-75 ys



6 Months later



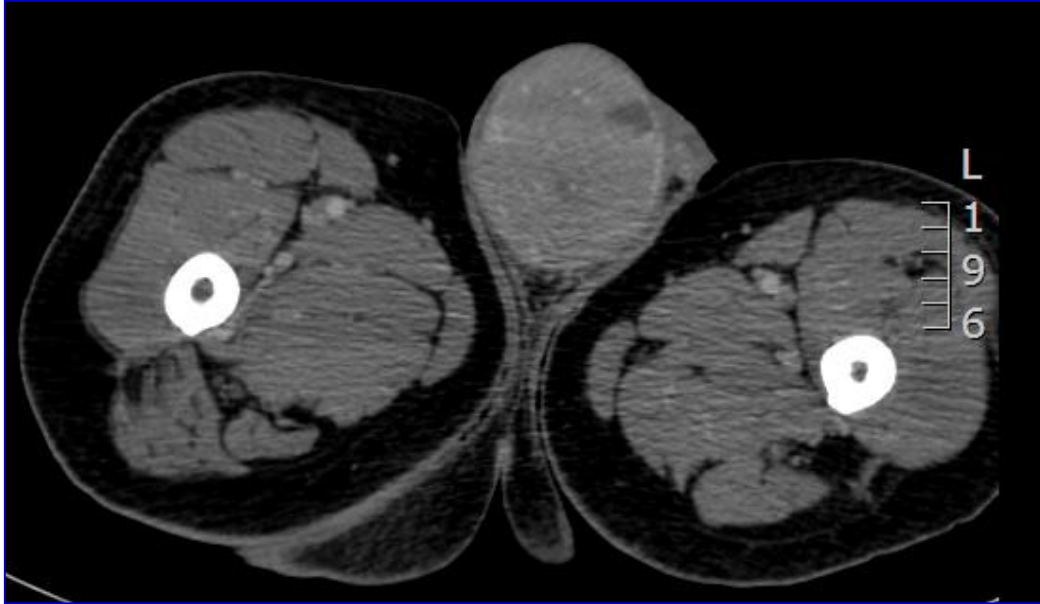
“High-risk” Extranodal DLBCL

- Areas adjacent to the CNS
 - epidural space
 - orbit
 - nasal cavity & paranasal sinuses
- Not explained by anatomical reasons
 - adrenal glands
 - kidney
 - testis
 - breast
- Only as part of advanced disease
 - Waldeyer's ring (nasopharynx)
 - ovary
 - bladder ?

Case #3: Presentation

- 67-year-old man
- Apparently healthy; smoker
- Right testis enlargement, no pain (2006)
- PE= right testis enlargement
- Lab= Mild anaemia
- Rx Tx and Abdominal ultrasound= neg

Case #3: Imaging



CT scan: negative

Eco: left testis negative

PET: negative

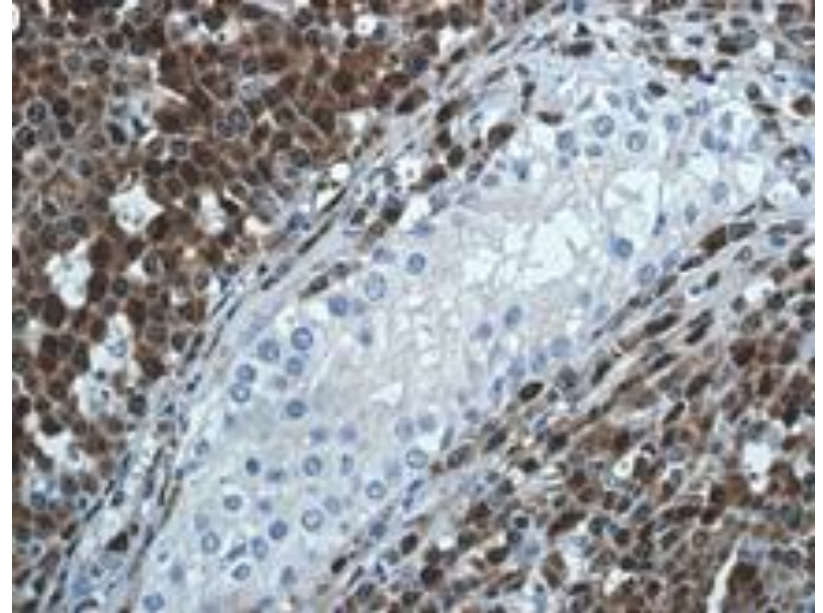
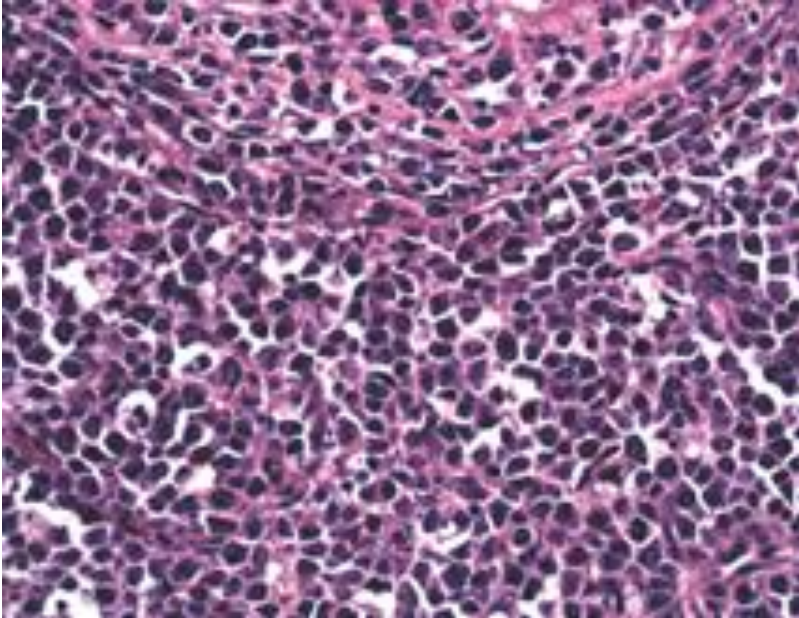
BMB: negative

Brain MRI: negative

CSF: negative

ORCHIECTOMY

Case #3: Diagnosis



CD20 +

CD10 –

Bcl-6 –

Bcl-2 +

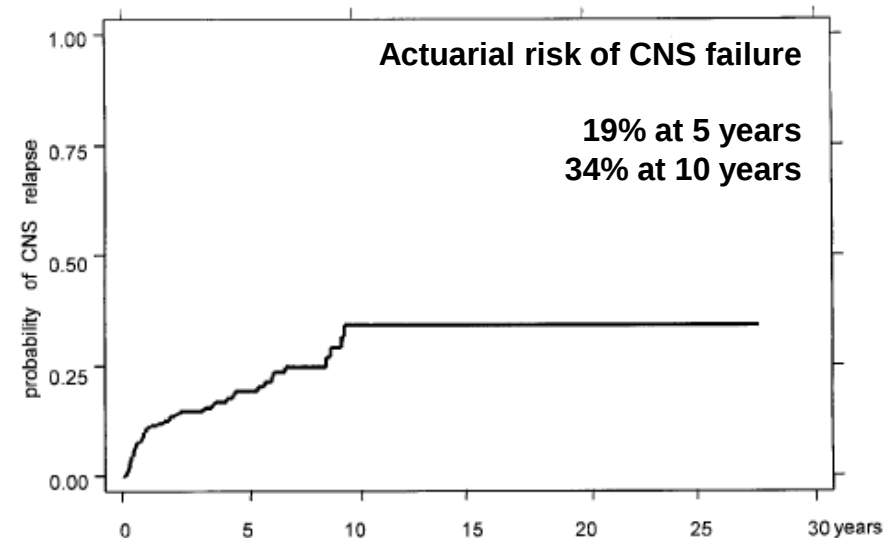
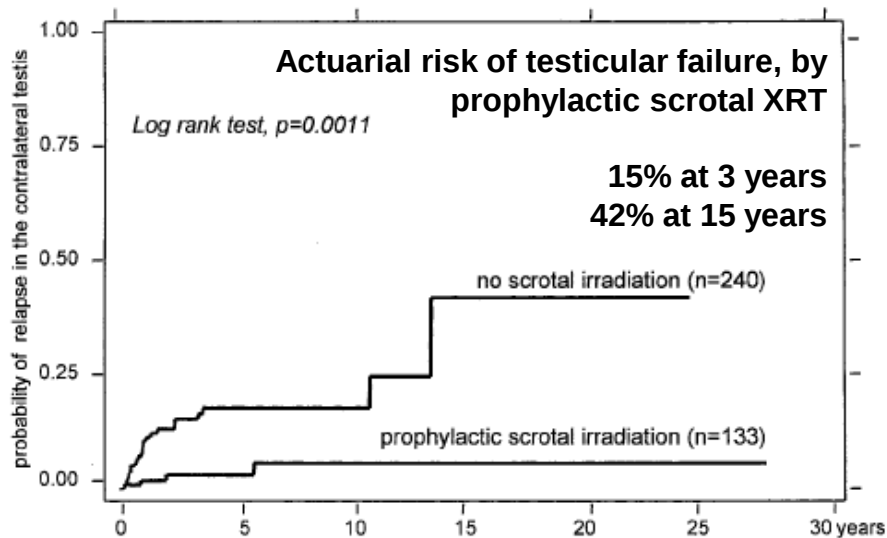
MUM1 +

Mib-1: 80%

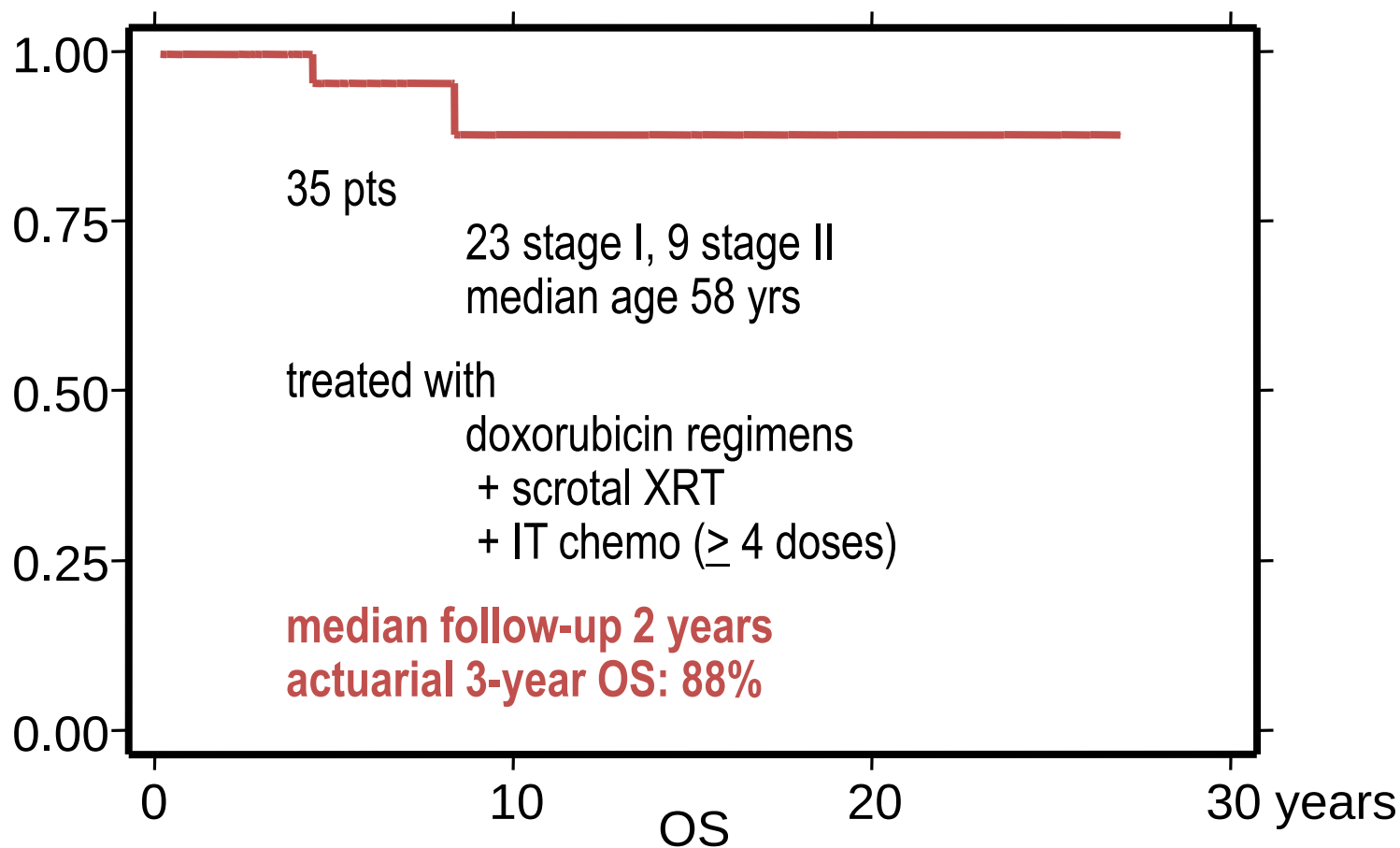
Diffuse large B-cell lymphoma

PTL: therapeutic challenges

- Poor prognosis even among pts with stage IEA disease
- High risk of extranodal relapses
- High risk of contralateral testicular failure
- High risk of CNS recurrence



PTL: pre-rituximab era

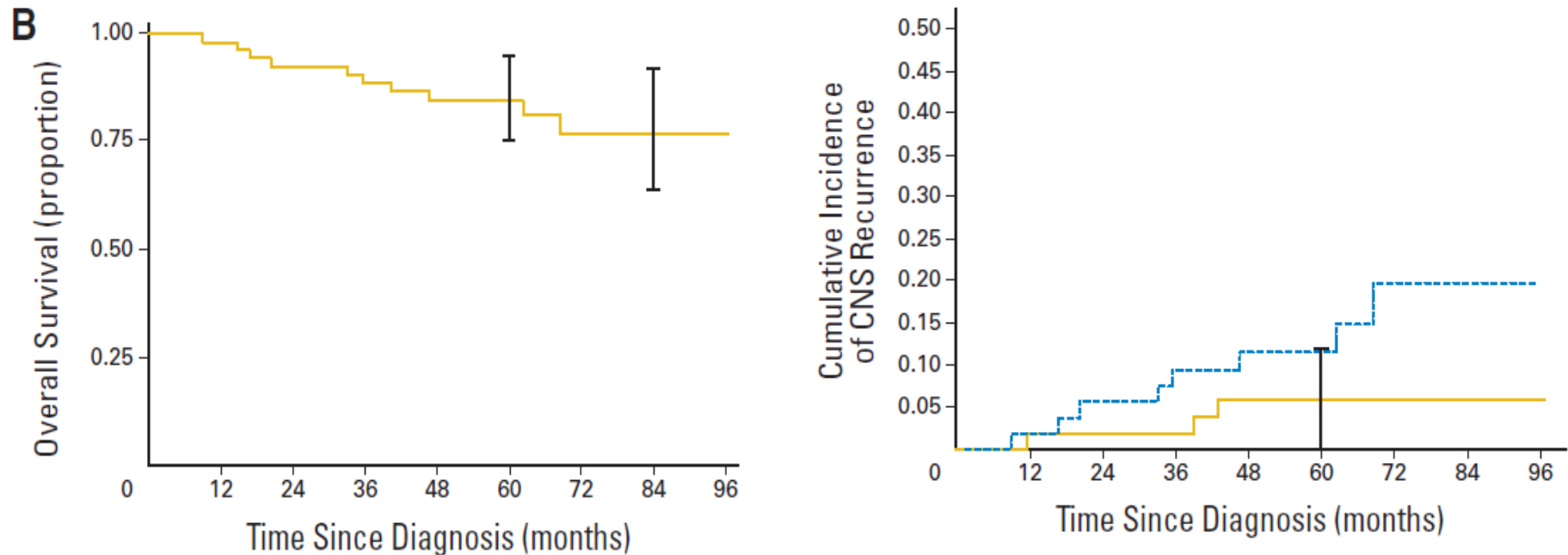


First-Line Treatment for Primary Testicular Diffuse Large B-Cell Lymphoma With Rituximab-CHOP, CNS Prophylaxis, and Contralateral Testis Irradiation: Final Results of an International Phase II Trial

Umberto Vitolo, Annalisa Chiappella, Andrés J.M. Ferreri, Maurizio Martelli, Ileana Baldi, Monica Balzarotti, Chiara Bottelli, Annarita Conconi, Henry Gomez, Armando Lopez-Guillermo, Giovanni Martinelli, Francesco Merli, Domenico Novero, Lorella Orsucci, Vincenzo Pavone, Umberto Ricardi, Sergio Storti, Mary K. Gospodarowicz, Franco Cavalli, Andreas H. Sarris, and Emanuele Zucca

Stage I	RCHOP × 3*	R E S T A G I N G	CR/PR	RCHOP × 3	Testicular RT [†]
			CR	RCHOP × 3	Testicular RT + IF-RT [†]
Stage II	RCHOP × 3*		PR	RCHOP × 5	Testicular RT + IF-RT [†]

IELSG #10 Trial: Results

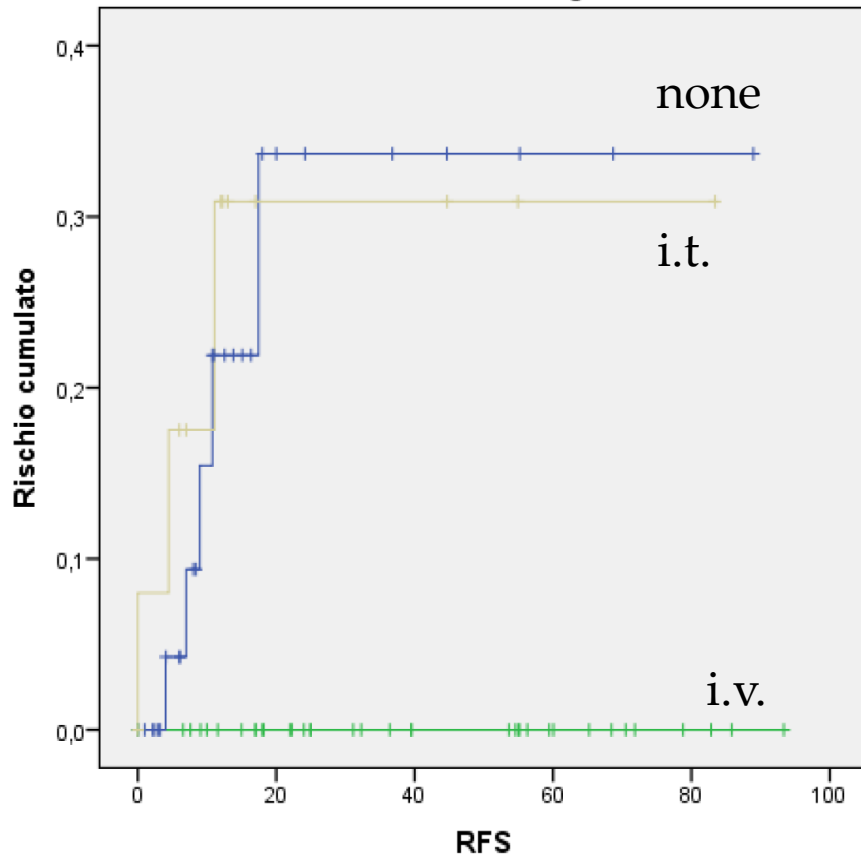


- This strategy is feasible and well tolerated
- Contralateral testis relapses have been eliminated (RT)
- CNS recurrence reduced but not eliminated
- New strategies to reduce CNS relapses

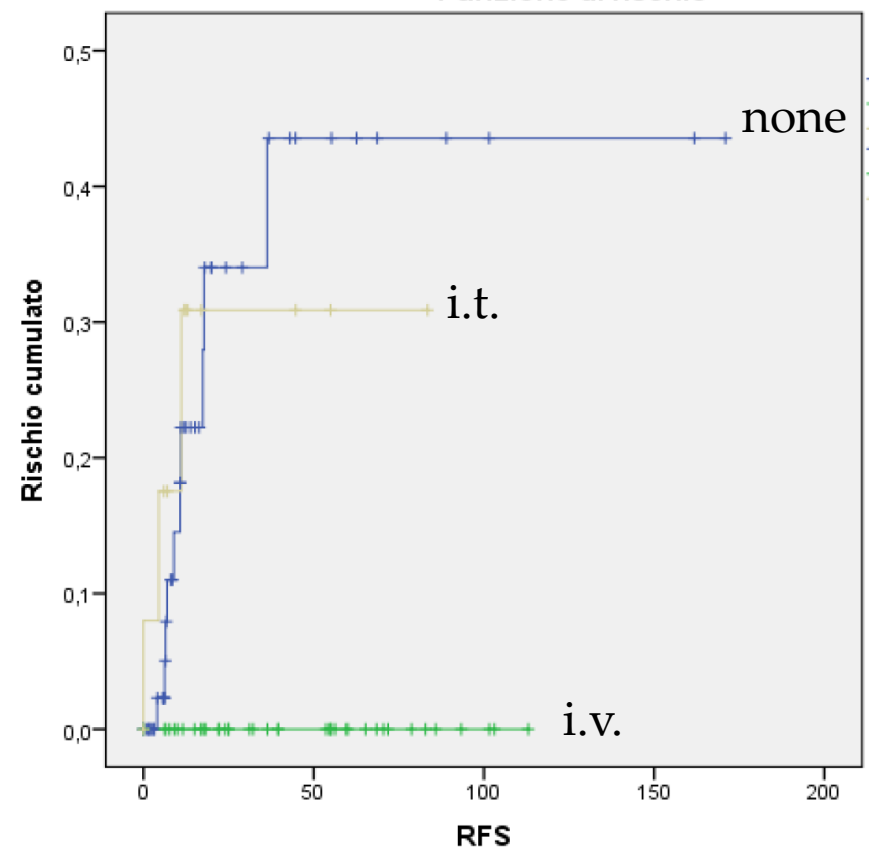
CNS Prophylaxis in the Rituximab Era

Reference	Study population (n)	Chemotherapy (median follow-up, months)	Patients with prophylaxis (n)	Prophylaxis type	HR-CNS control group (n)	CNS relapse rate (%)*	Risk definition and prophylaxis indications	Conclusion
Aviles <i>et al</i> (2013)	DLBCL (3258)	CHOP $\pm$ R (163)	1005	Varied	2-253 (CNS risk?)	5.9 vs. 5.9 ($P = \text{NS}$)	Physician's preference. LR-CNS patients included.	No benefit with prophylaxis
Krawczyk <i>et al</i> (2013)	HR-CNS aggressive NHL (79) [†]	Varied, including ASCT (28)	68	IT	None	0	Pre-rituximab risk factors	IT prophylaxis is encouraged
Murawski <i>et al</i> (2014)	Aggressive NHL with extranodal disease of craniofacial area (279) [†]	CHOP $\pm$ R (>36)	88	IT	191 (CNS risk?)	4.2 vs. 2.3 [‡] ($P = \text{NS}$)	LR-CNS patients included.	IT prophylaxis does not provide additional benefit
Wilson <i>et al</i> (2014)	Aggressive NHL with CSF assessment (326), including HIV+ patients and patients with CNS disease [†]	Varied $\pm$ R (47)	171	IT [§]	30 (CNS risk?)	5.3 vs. 7.2 [¶] ($P = \text{NS}$)	Not reported. LR-CNS patients included.	IT prophylaxis improves freedom from CNS relapse
Holte <i>et al</i> (2013)	Aggressive NHL with aaIPI: 2-3, aged $\leq$ 65 years (156) [†]	R-CHOEP (52)	156	HD-MTX + HD-araC $\pm$ IT	None	5.2**	High-risk extranodal sites not considered	Lower than expected CNS events
Guirguis <i>et al</i> (2012)	DLBCL (214)	R-CHOP (27)	27	HD-MTX and/or IT	None	3.7	Pre-rituximab risk factors. Imperfect compliance with guidelines	Only testicular lymphoma needs for prophylaxis
Abramson <i>et al</i> (2010)	DLBCL with HR-CNS (65)	CHOP $\pm$ R (33)	65	HD-MTX	None	3	Pre-rituximab risk factors	HD-MTX is safe and associated with a low risk of CNS recurrence
Present study	DLBCL treated with R-CHOP or similar (200)	R-CHOP (60)	40	HD-MTX $\pm$ IT	67	0 vs. 12 ^{††}	Pre-rituximab risk factors. LR-CNS patients were analysed separately.	IV prophylaxis reduces CNS relapses

Prophylaxis According to Risk Scores

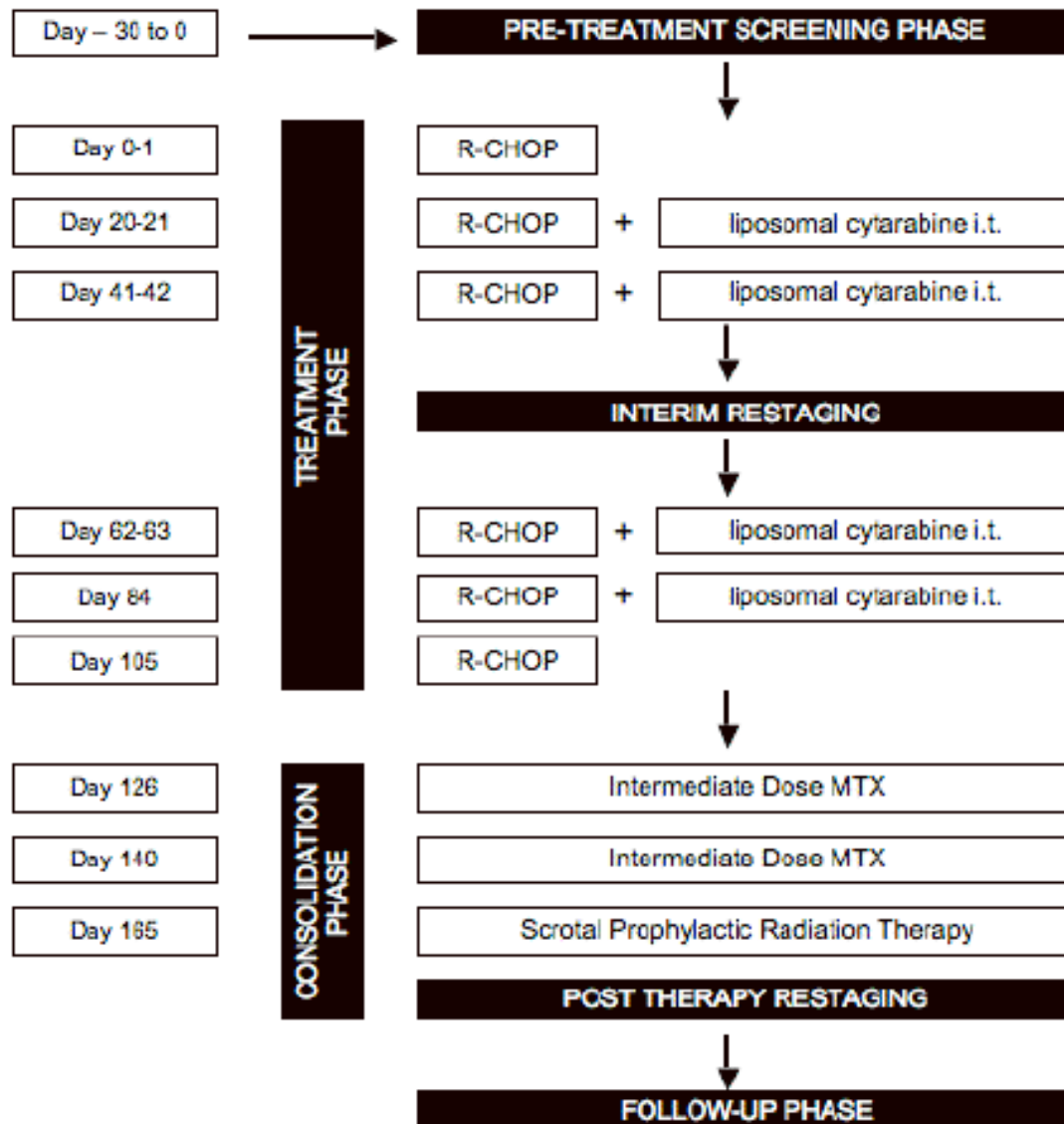


Schmitz N, et al. JCO 2016



Ferreri AJM, et al. ICML 2017

The IELSG #30 Trial



- ✓ Stage IE-IIIE DLBCL of testis
- ✓ Orchiectomy
- ✓ Age 18-80; PS <2
- ✓ HCV neg
- ✓ HBV neg or HBcAb +, HbsAg -, HBsAb+/- with HBV-DNA neg

R-CHOP21
 Day 0: Rituximab
 Day 1: CHOP21

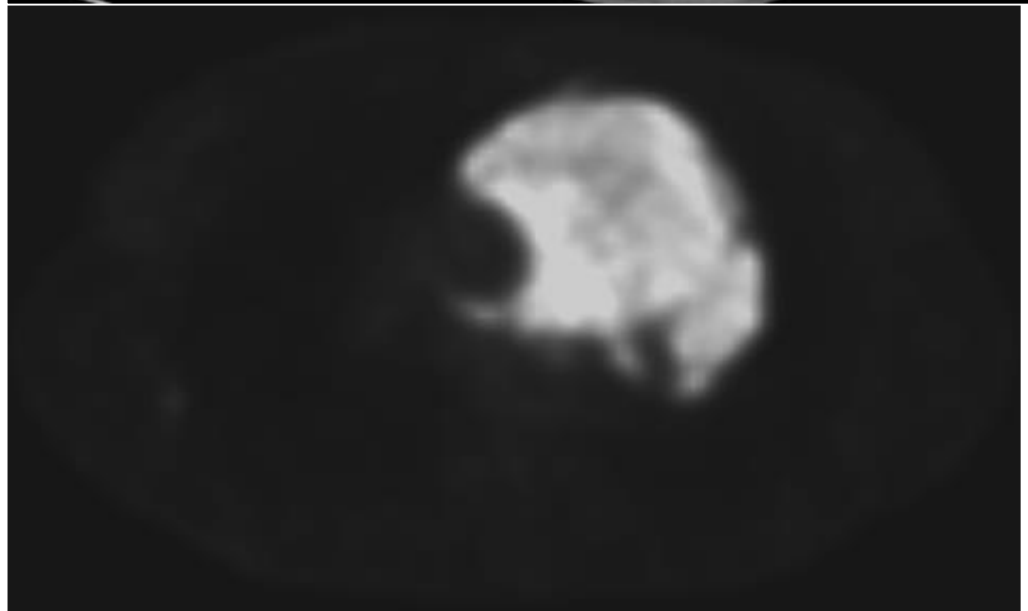
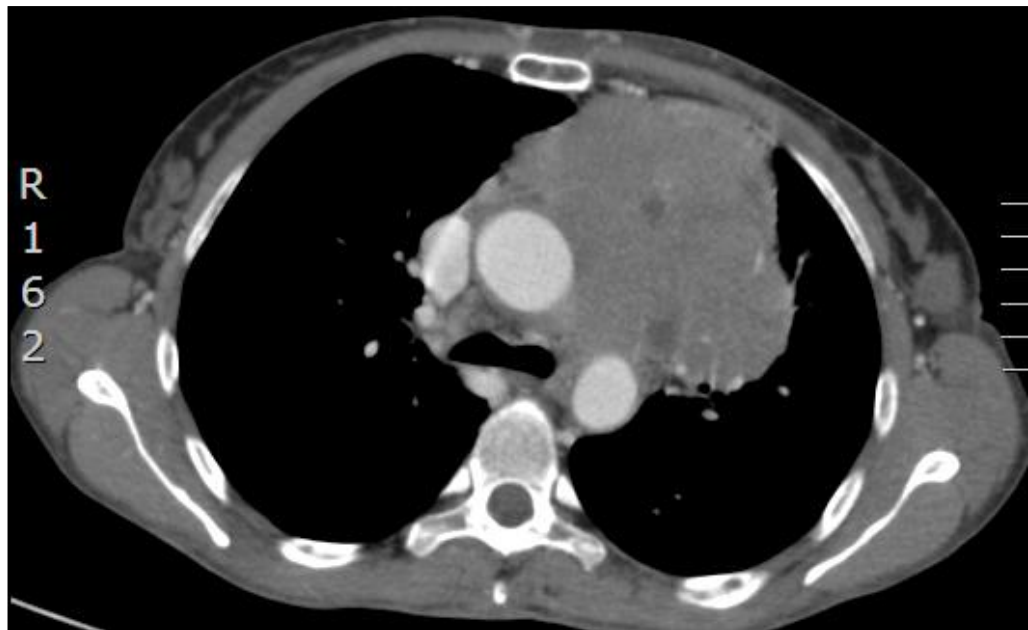
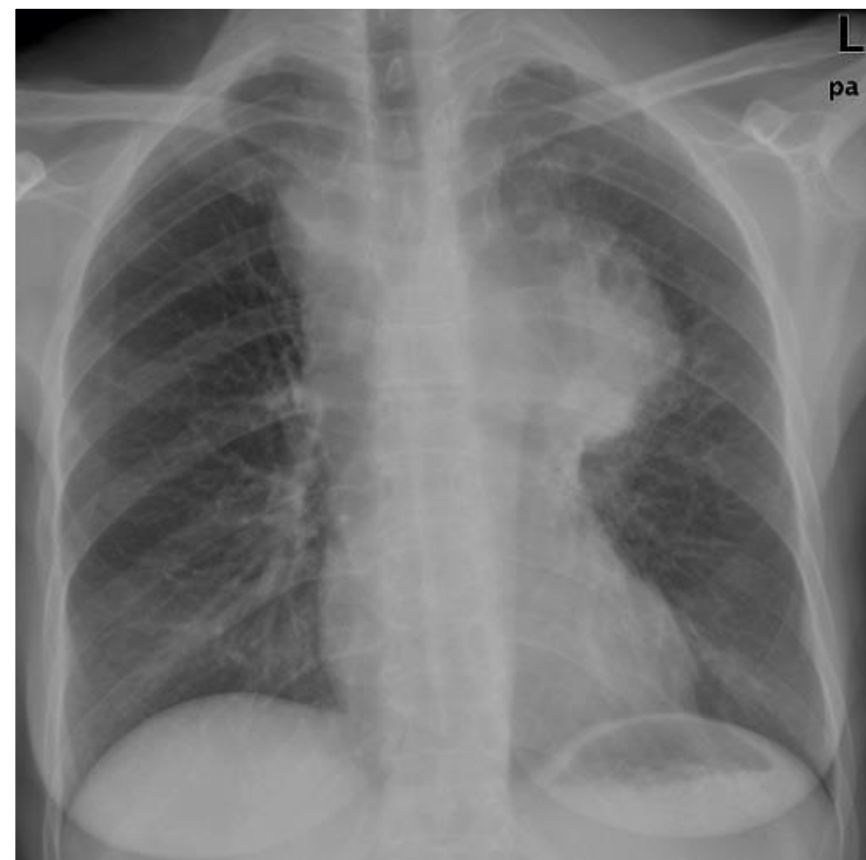
IT chemotherapy
 Day 0 of the II-III-IV-V courses R-CHOP21:
 Depocyte 50 mg IT

Methotrexate 1.5 g/mq
 Every 14 days

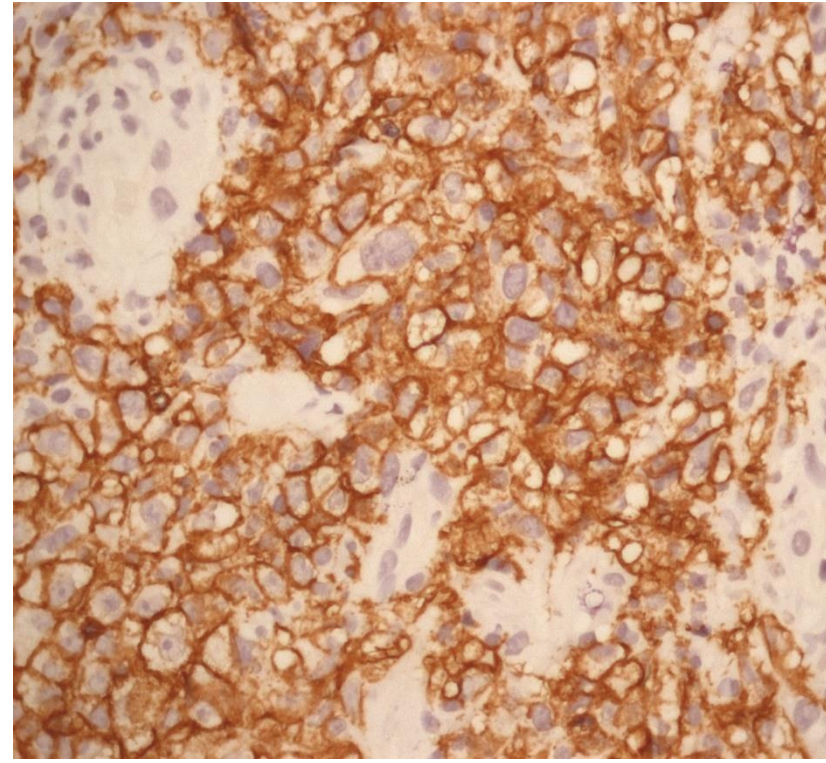
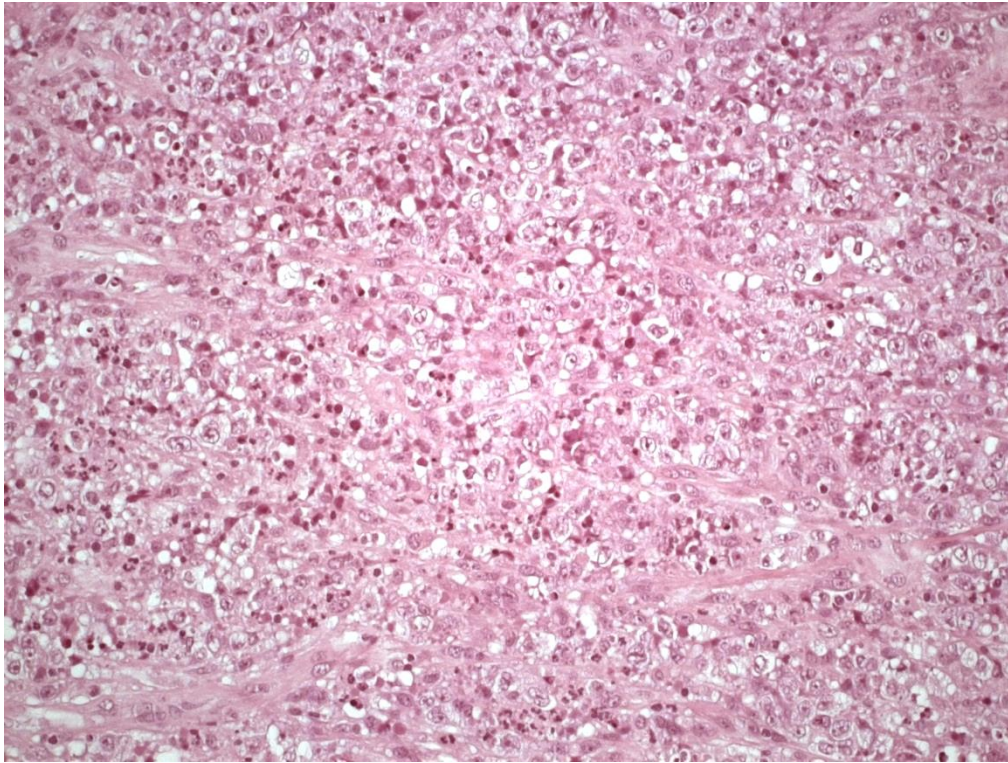
Case #4: Presentation

- 28-year-old woman
- Apparently healthy
- Dyspnoea in the last months of pregnancy (2006)
- Increased symptoms after childbirth
- Tachyarrhythmia, cervical oedema, lymphedema left arm and hand
- PE: left supraclavicular lymphadenopathies
- Lab: increased LDH serum level
- Rx Tx= mediastinal enlargement

Case #3: Imaging



Case #3: Histopathology

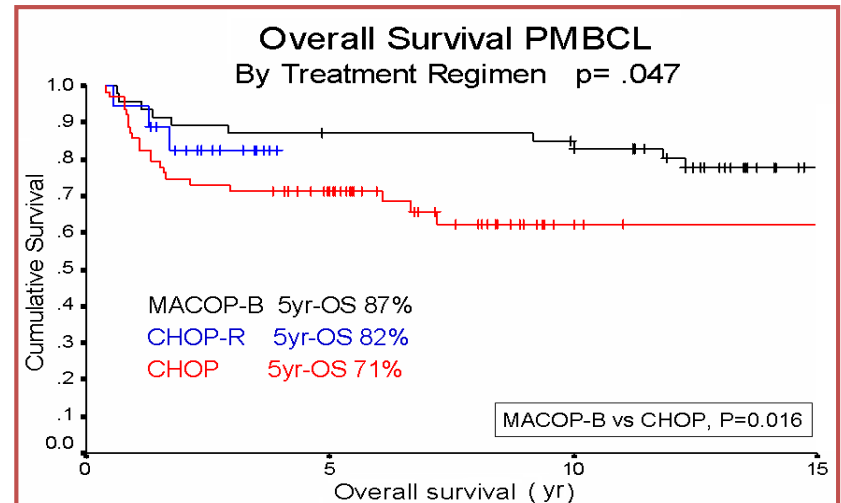
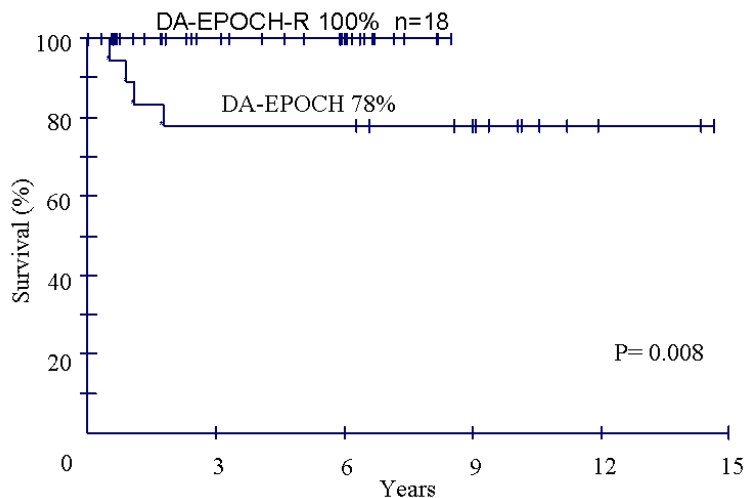
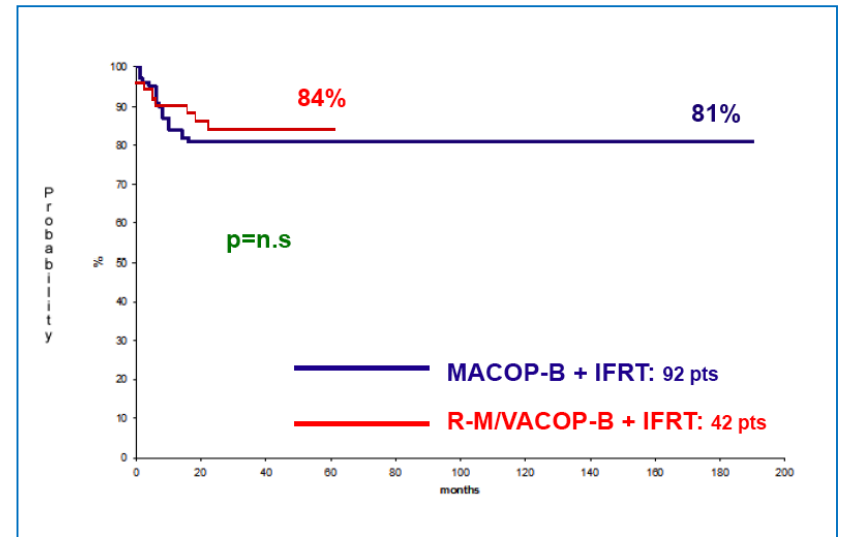
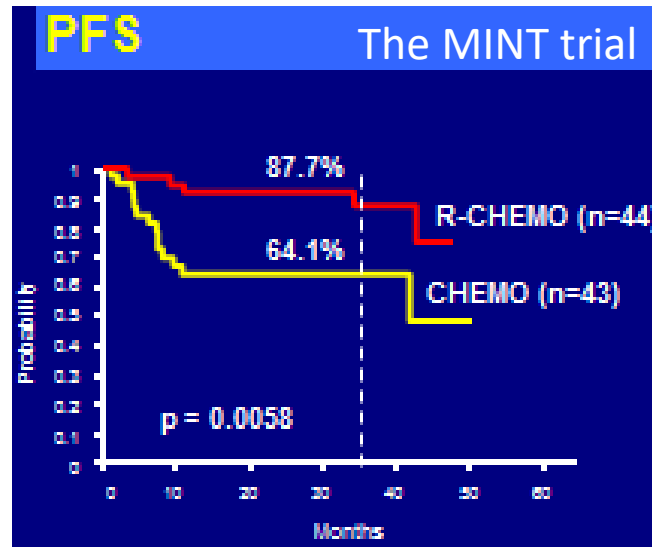


POS= CD20, PAX5, bcl-2, bcl-6, MUM1, BOB.1, Oct-2, CD30

NEG= CD3, CD4, CD8, CD10, CD15, CD68

Large B-cell lymphoma with sclerosis and necrosis - PML

Rituximab:

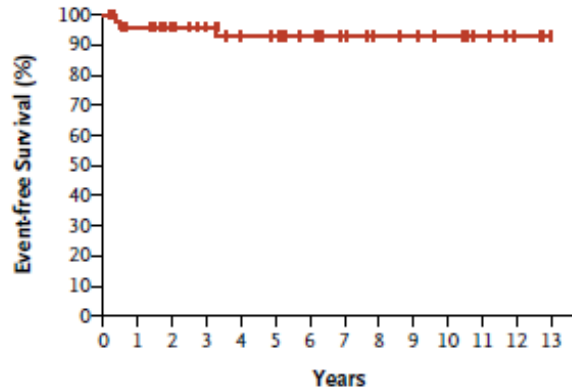


Status after chemotherapy

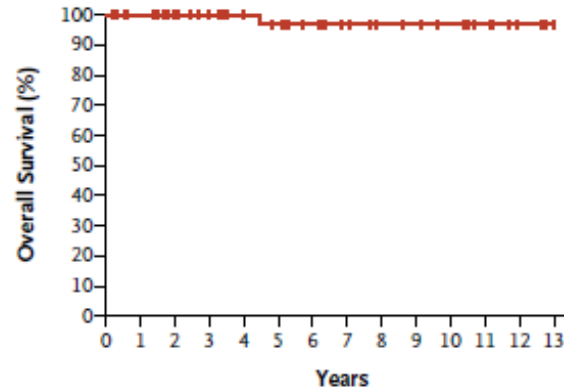
- Metabolic CR after 6 courses of R-CHOP
- Residual mass with extensive necrosis areas at CT scan
- Good tolerability
- Consolidation

R-CHOP vs. R-DA-EPOCH

A Event-free Survival (NCI Patients)

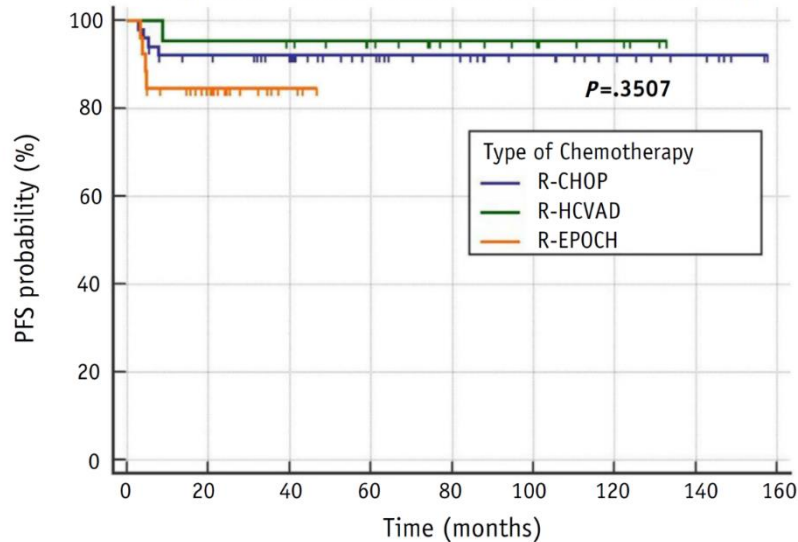


B Overall Survival (NCI Patients)



Dunleavy K et al NEJM 2013

Progression-Free Survival According to Chemotherapy



Treatment characteristics			
Characteristic	R-CHOP (n=50)	R-HCVAD (n=22)	R-EPOCH (n=25)
No. of cycles			
Median	6	6	6
Range	5-8	5-8	4-7
Radiation therapy			
Consolidative (presumed CR)	42 (84%)	17 (77.2%)	5 (20%)
Salvage	3 (6%)	1 (4.5%)	4 (16%)
No radiation	5 (10%)	4 (18.2%)	16 (64%)
Radiation dose			
Median, Gy	39.6	39.6	39.6
Range, Gy	30-45	16.2-45	30.6-43.2
Radiation technique			
3D	36 (80%)	16 (88.9%)	1 (11.1%)
IMRT	6 (13.3%)	1 (5.6%)	7 (77.8%)
Protons	3 (6.7%)	1 (5.6%)	1 (11.1%)

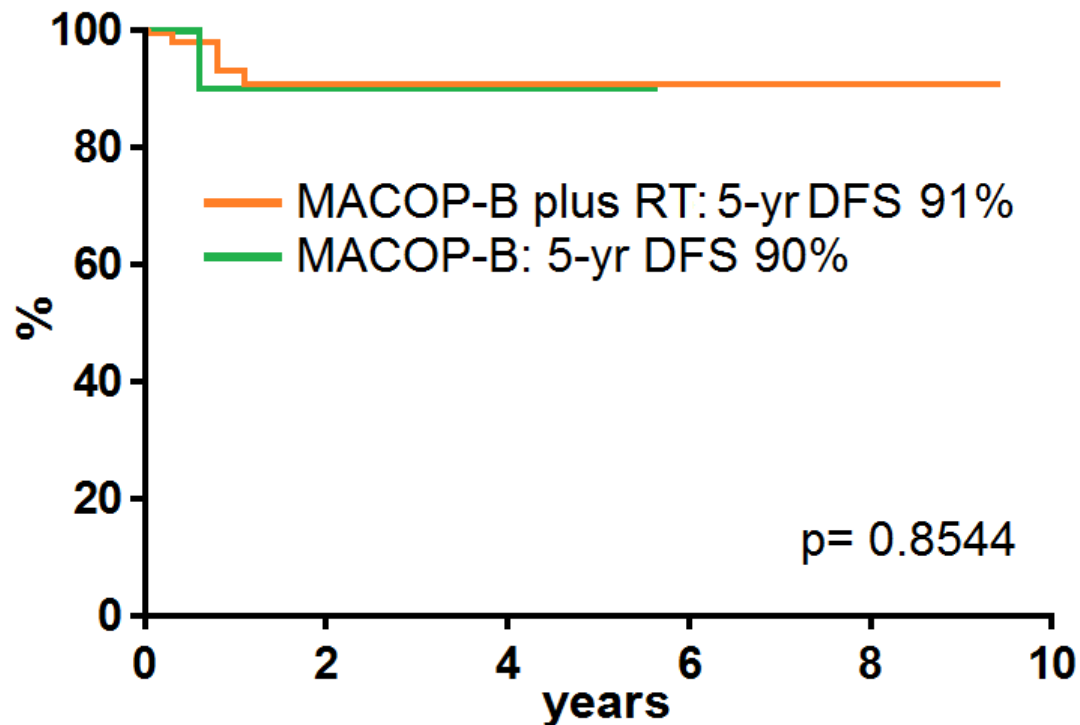
Pinnix CC et al. IJROBP 2015

PET-guided RT after R-MACOP-B in PMBCL

MACOP-B-R ± RT		
Response	N	%
CR	61/74	82.4
PR	5/74	6.8
PD	8/74	10.8

post-chemotherapy PET EVALUATION		
RESULT	N	%
PET- POSITIVE	51	68.9
PET-NEGATIVE	23	31.1

➡ RT



- *A PET-guided RT approach after MACOP-B plus rituximab may allow a patient tailored treatment*

The IELSG #37 trial

- Primary endpoint 3 yr PFS
- Expected PFS 85%
- Aim to exclude 10% reduction from omitting RT
- Require 376 randomised for 80% power, $p=0.05$
- Suggests 752 registered patients if 50% PET-ve

Registration
CT-PET 1

Standard therapy
R-Chemo x 6

CT-PET 2
central review

6 wks after R-Chemo

Positive

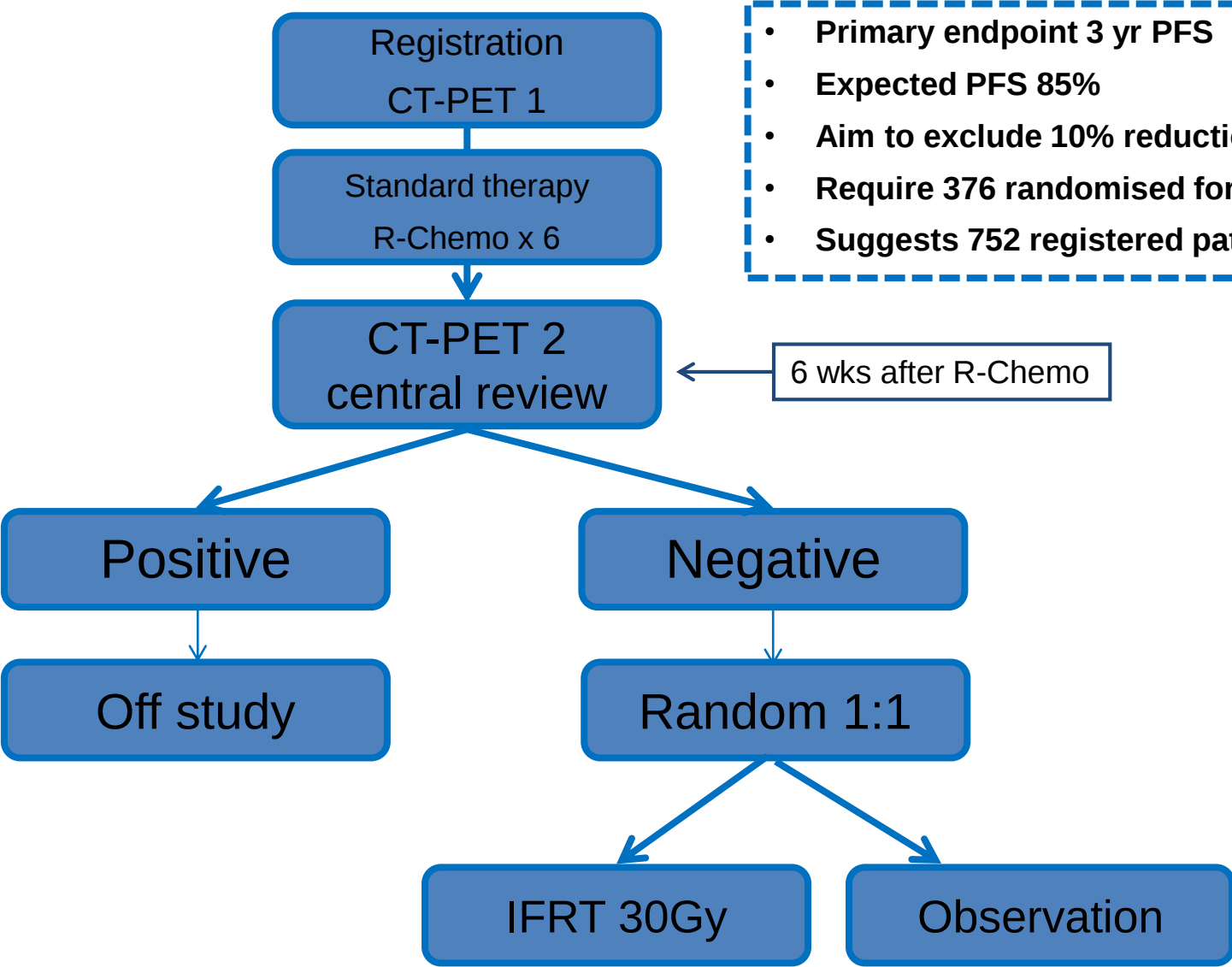
Off study

Negative

Random 1:1

IFRT 30Gy

Observation



Predicting role of PET: IELSG #26

125 PMLBL enrolled



Baseline PET

(within 14 days before R-Chemo)



Full course of chemotherapy:

R-CHOP 21 or R-CHOP 14 or
R-MACOP-B or R-VACOP-B

Suggested Interim PET →



Final PET

(3-4 weeks after R-Chemo)



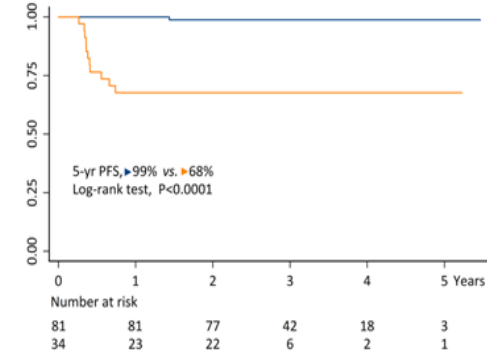
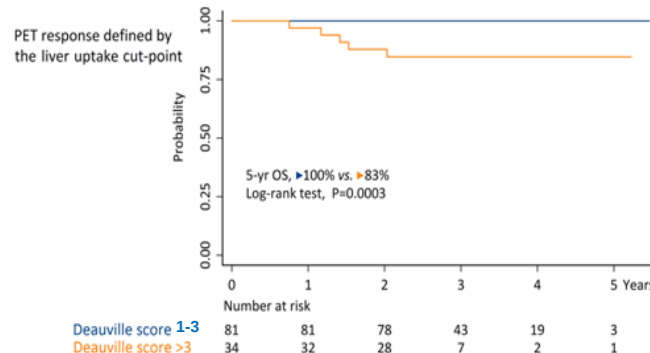
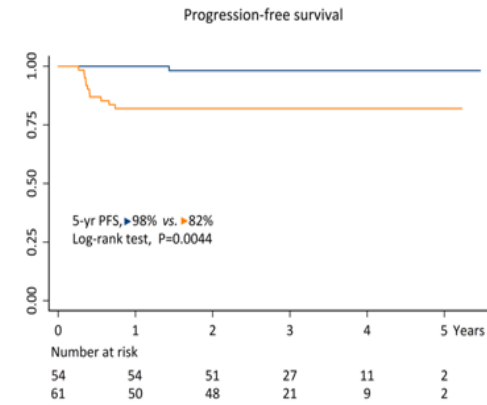
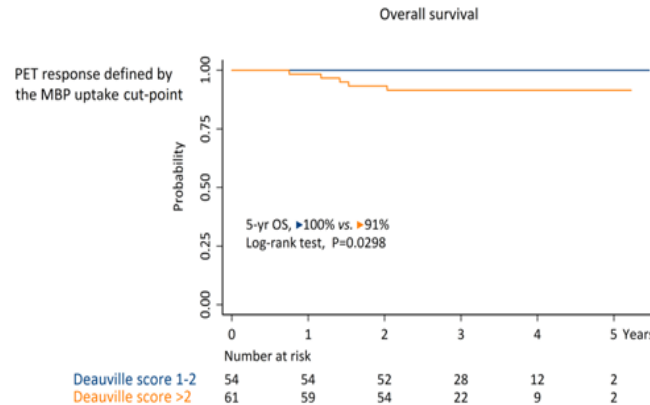
Consolidation RT

(local policy; n 112)



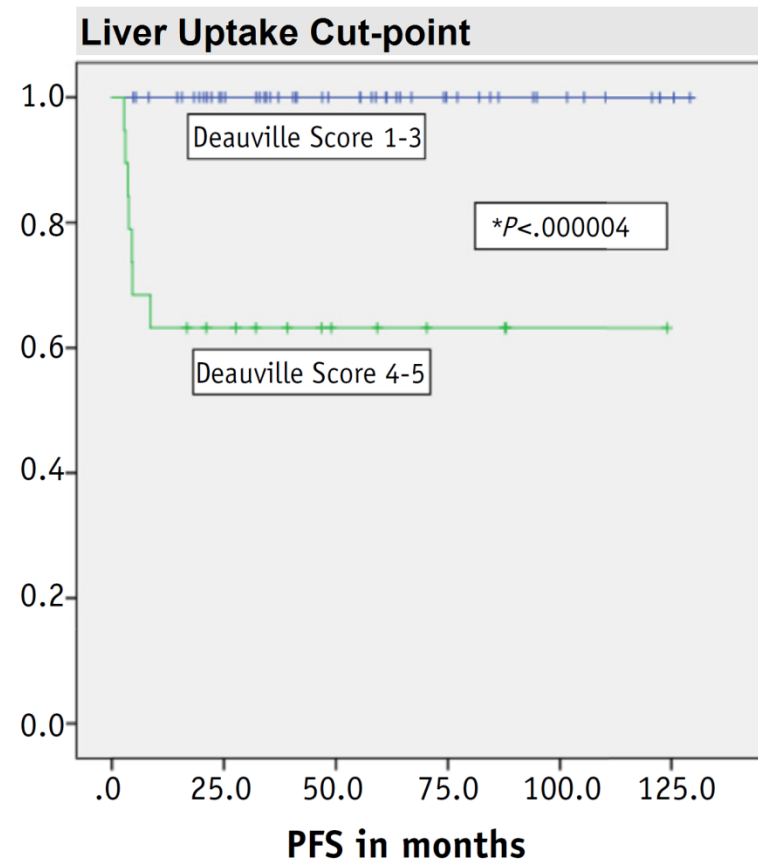
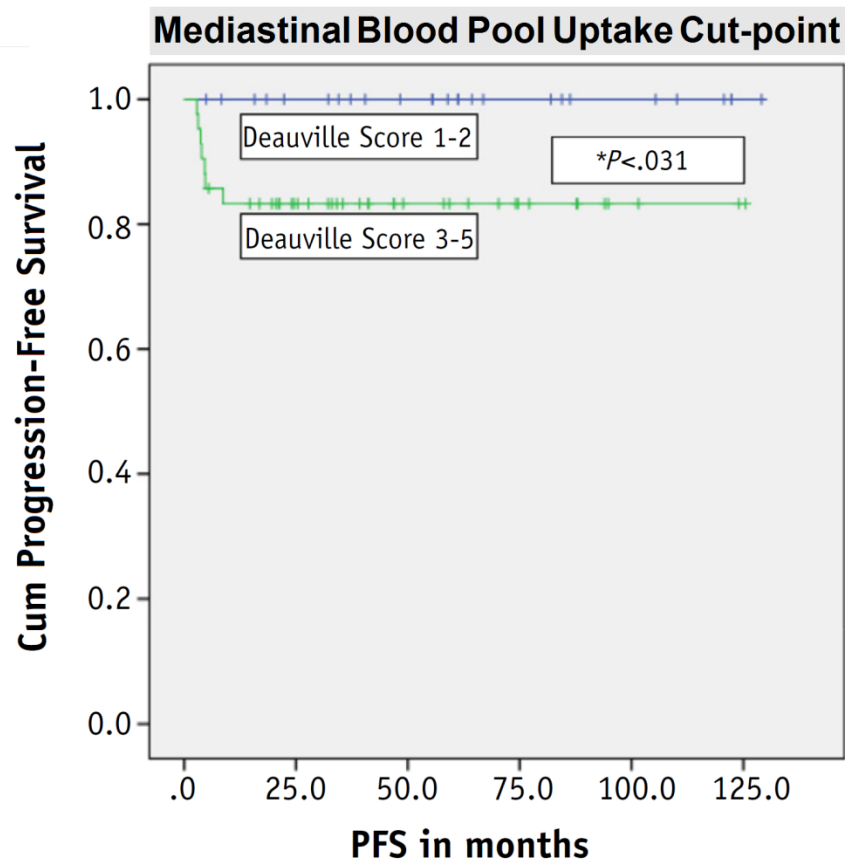
Post-RT PET (≥ 2 months) →

Follow-up

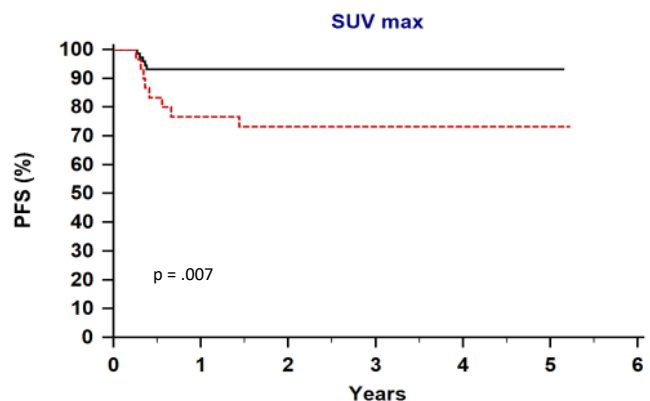
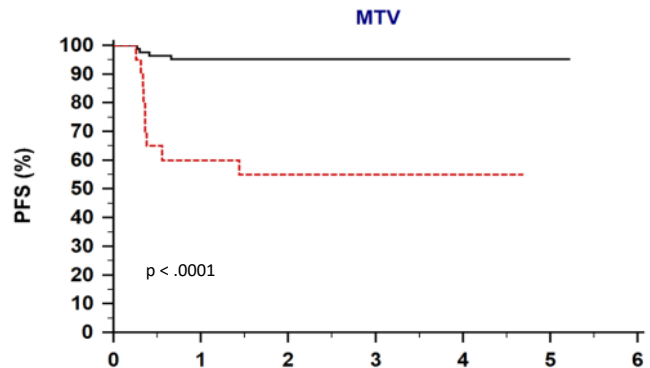
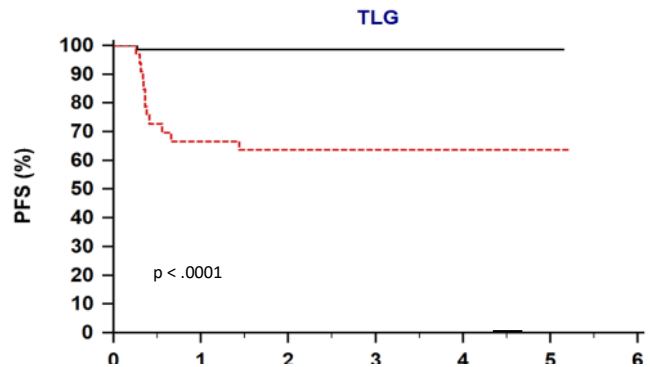


MDACC retrospective PMBCL series:

PFS according to the DS at the end of immunochemotherapy



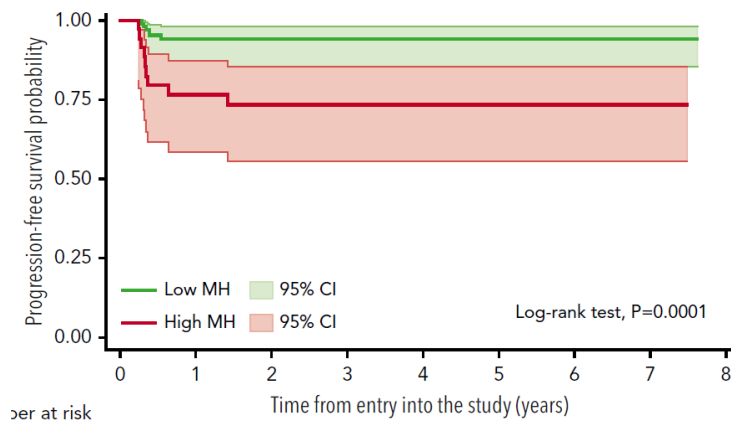
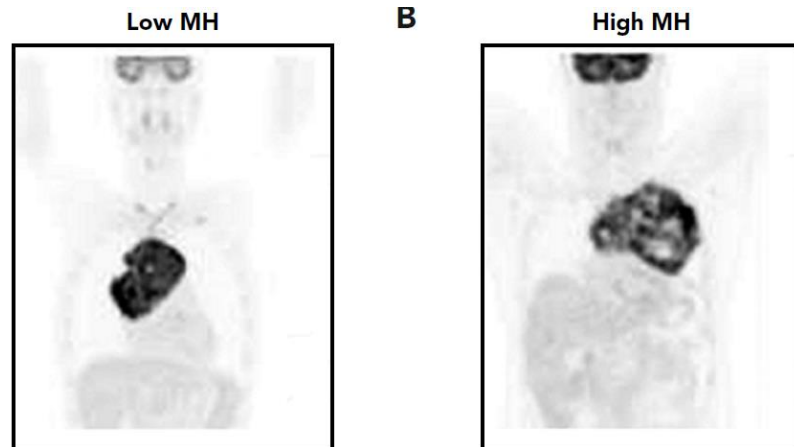
Prognostic value of baseline functional ^{18}F FDG parameters in PMBCL



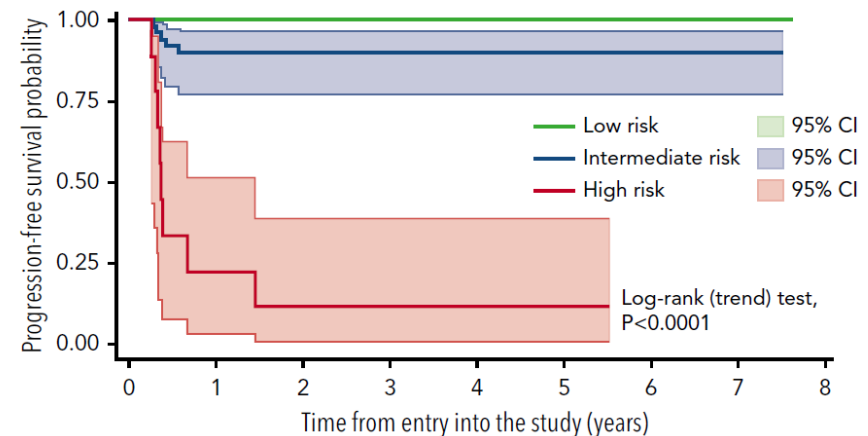
total lesion glycolysis (TLG)
metabolic tumor volume (MTV)
maximum standardized uptake value (SUVmax)

Parameter	HR	95% CI	P
Multivariate analysis of OS (103 subjects, 6 deaths)			
MTV (increments of 10^2 ml)	0.96	0.66-1.40	.833
TLG (increments of 10^3)	1.49	1.18-1.89	.001
Multivariate analysis of PFS (103 subjects, 13 events)			
Bulky disease (<10 cm vs ≥ 10 cm)	1.73	0.31-9.52	.526
MTV (increments of 10^2 mL)	1.03	0.80-1.33	.812
TLG (increments of 10^3 mL)	1.36	1.16-1.58	<.001

Prognostic value of baseline functional ^{18}F FDG parameters in PMBCL



Risk	MH	TLG
Low	Low	Low
Intermediate	Low	High
	High	Low
High	High	High



Number at risk	45	45	45	40	39	28	10	4	0
Low risk	45	44	44	41	41	27	13	3	0
Intermediate risk	9	2	1	1	1	1	0	0	0
High risk									

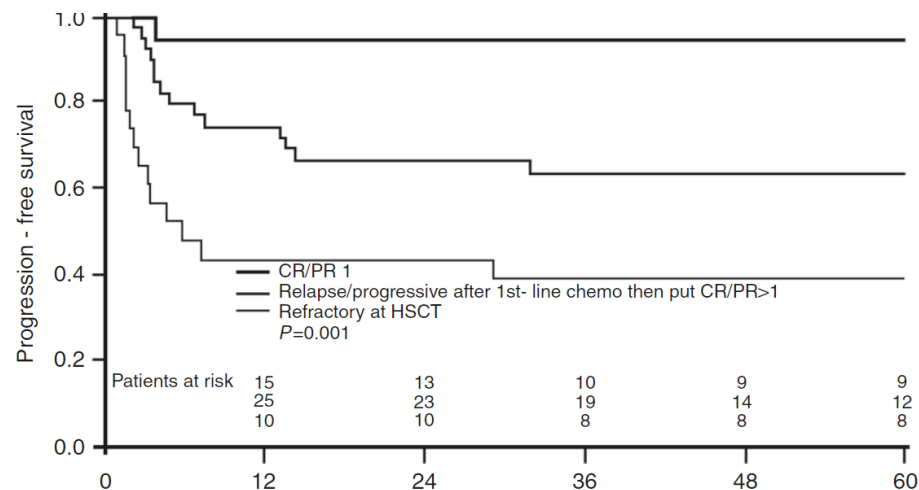
metabolic heterogeneity (MH)
total lesion glycolysis (TLG)

ASCT for Pts with High-Risk PMLBCL



86 pts in 22 centers in 12 years!!!

	Cases available	Entire cohort <i>N</i> = 86 ^a	CR/PR 1 <i>N</i> = 16 (19%)	CR/PR>1 <i>N</i> = 44 (52%)	Refractory <i>N</i> = 24 (28%)	<i>p</i> -Value
Transplant period						
2000–2005	86	24 (28%)	4 (25%)	14 (32%)	6 (25%)	0.732
2006–2012		62 (72%)	12 (75%)	30 (68%)	18 (45%)	
Male gender	86	42 (49%)	7 (41%)	22 (50%)	11 (46%)	0.7672
Age at autoSCT, years [median (range/IQR)]	86	35 (20–69)	30 (22–62)	36 (20–69)	32 (19–67)	0.8928
Disease stage III–IV at diagnosis [<i>n</i> , (%)] ^b	82	33 (40%)	7 (44%)	16 (37%)	8 (38%)	0.8979
B-symptoms at diagnosis [<i>n</i> , (%)] ^b	80	35 (44%)	5 (38%)	15 (36%)	14 (61%)	0.1359
Size of mediastinal mass at diagnosis (cm) [<i>n</i> , (%)] ^b						
<5 cm	74	5 (7%)	0	5 (13%)	0	0.0689
5–10 cm		22 (30%)	4 (31%)	14 (36%)	3 (14%)	
>10 cm		47 (63%)	9 (69%)	20 (51%)	18 (86%)	
Size of mediastinal mass at autoSCT (cm) [<i>n</i> , (%)] ^b						
No mass	69	14 (20%)	4 (36%)	10 (27%)	0	<0.001
<5 cm		31 (45%)	5 (45%)	22 (59%)	3 (16%)	
5–10 cm		13 (19%)	1 (9%)	3 (8%)	9 (47%)	
>10 cm		7 (11%)	0	1 (3%)	6 (32%)	
Unmeasured		4 (6%)	1 (9%)	1 (3%)	1 (5%)	
Number of previous chemotherapy regimens before SCT [median (range)]	82	2 (1–4)	2 (1–2)	2 (2–3)	2 (2–4)	<0.0001
Number of previous chemotherapy lines before SCT ^c						
1	81	16 (20%)	16 (100%)	0	0	<0.0001
2		55 (68%)	0	40 (95%)	15 (65%)	
≥3		10 (12%)	0	2 (5%)	8 (35%)	
Rituximab-based therapy prior autoSCT [<i>n</i> , (%)] ^b	85	73 (85%)	14 (87%)	38 (86%)	20 (83%)	0.9176
Pre-SCT radiotherapy	86	28 (30%)	2 (13%)	16 (36%)	8 (33%)	0.2049
Interval diagnosis—autoSCT in months [median (IQR)]	86	12 (8–18)	6 (6–10)	16 (11–22)	10 (8–13)	0.0832
Poor performance score at HCT ^d	78	24 (31%)	2 (14%)	9 (23%)	12 (57%)	0.01213
High-dose regimen						
BEAM	84	63 (75%)	11 (69%)	34 (77%)	16 (67%)	0.5468
Other		23 (27%)	5 (31%)	10 (23%)	8 (33%)	
Follow-up of alive patients in months [median (IQR)]	62	60 (32–90)	64 (30–74)	49 (28–91)	72 (50–109)	0.728

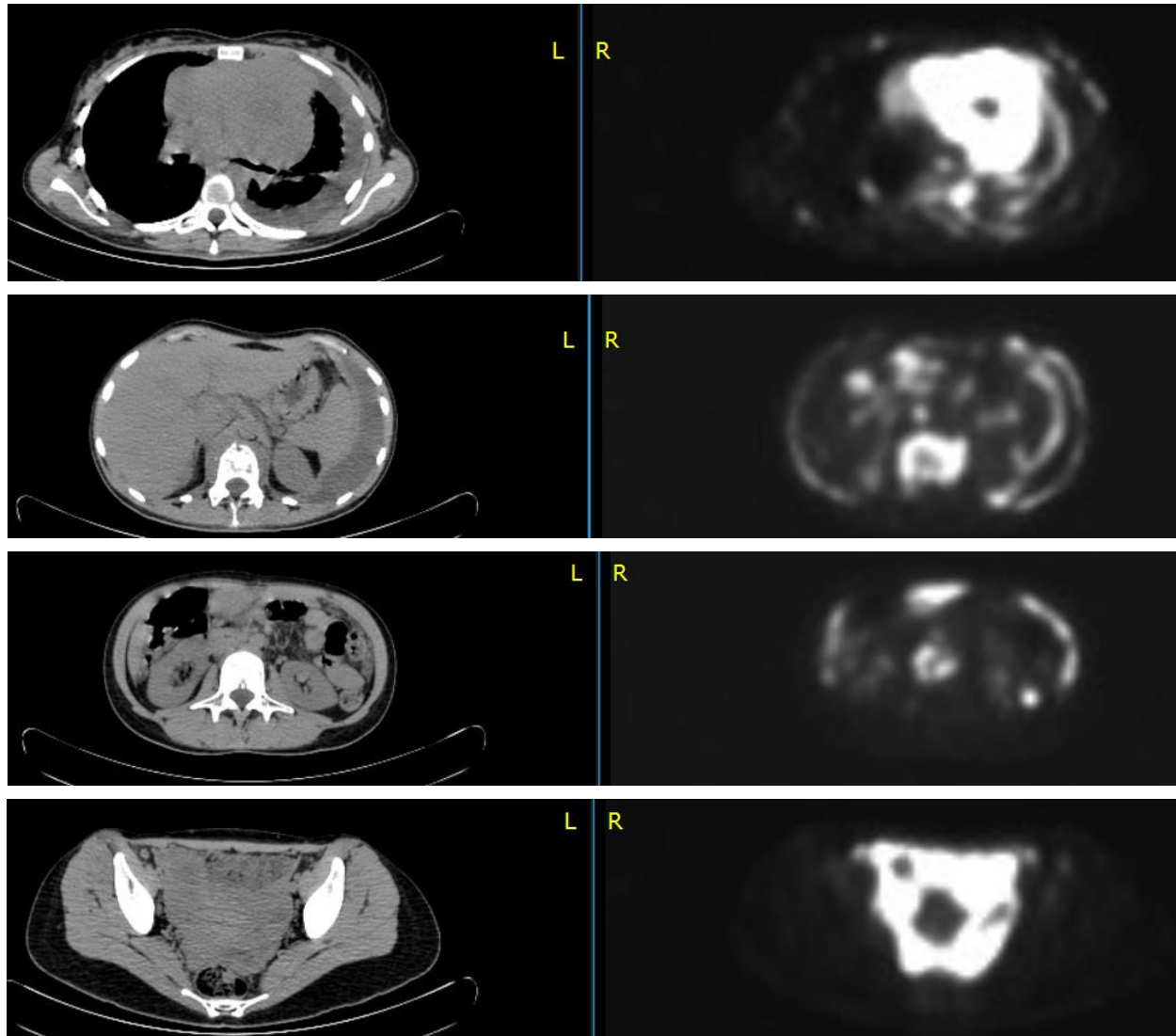


Avivi, et al. BMT 2018

Case #5: Presentation

- 39-year-old woman
- Coeliac disease, atopic dermatitis
- Dyspnoea and low back pain in the last two months (2016)
- PE: Lymphedema left arm, clinical signs of pleural effusion and multiple breast nodules
- Lab: increased LDH serum level
- Rx Tx= mediastinal enlargement

Case #5: Imaging & Diagnosis

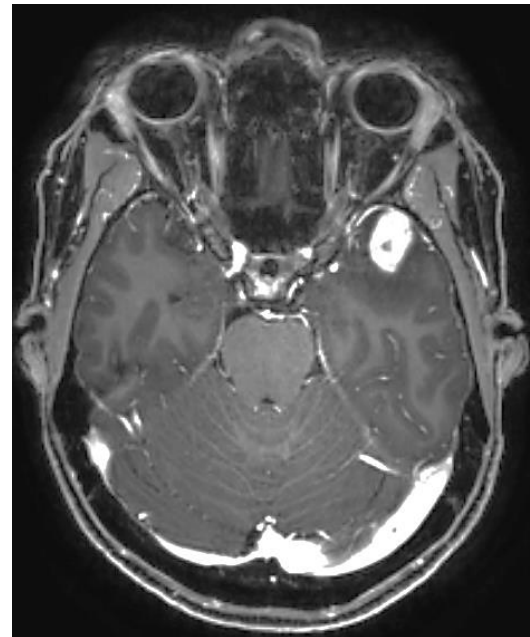
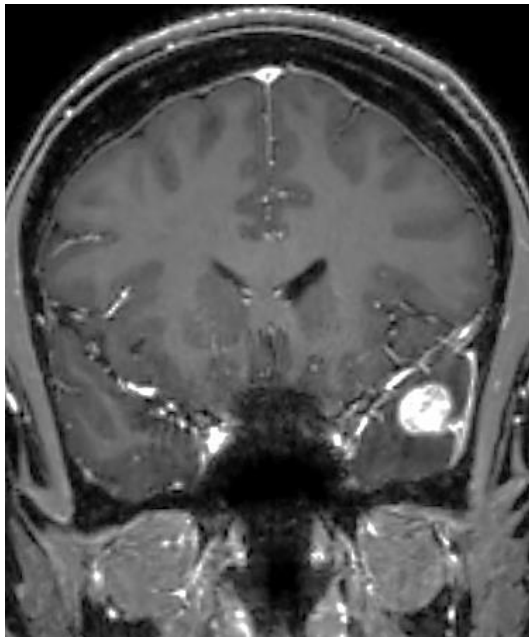


Biopsy: PMLBCL

Case #5: Treatment

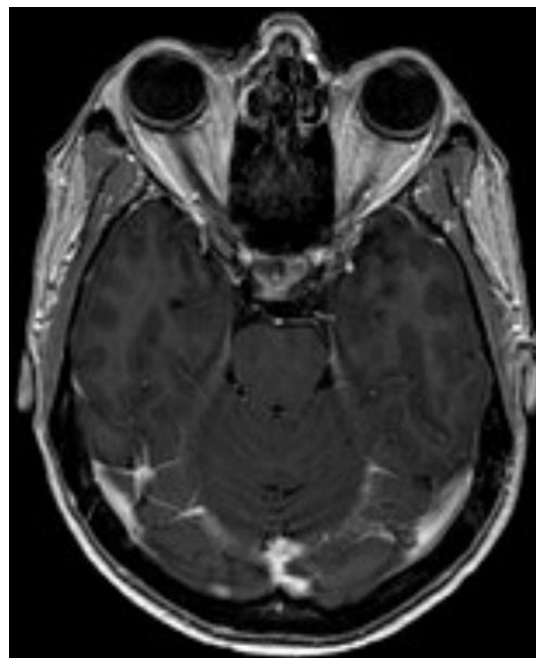
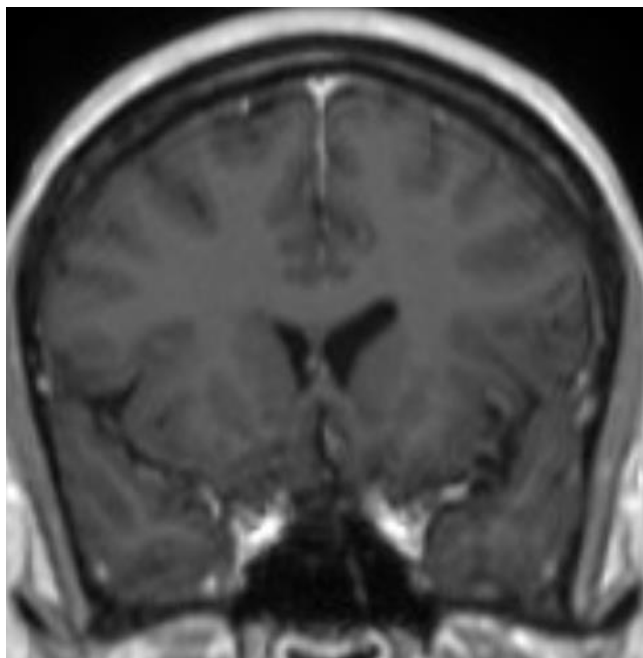
R-CHOP x 6c + intrathecal liposomal cytarabine + HD-MTX x 3c

- PET after R-CHOP + IT chemo: residual DS-4 mediastinal lesion
- Mediastinal irradiation 40 Gy
- Generalized seizures



Case #5: Salvage Therapy

MATRix x 3 c $\Rightarrow$ R-ICE x 3 c $\Rightarrow$ BCNU-Thiotepa/ASCT



Alive and NED at 1 year from ASCT

Take Home Messages

- Investigation of extranodal lymphomas at different sites may provide opportunities to learn more about the host factors and mechanisms involved in the lymphoma development
- This may lead to a better characterization of high-risk subgroups and improvements in the clinical management
- Specific situations (e.g. DLBCL at immuno-privileged sites) may require specific management strategies
- Please, do not forget CNS prophylaxis.