Primary and Secondary CNS Lymphomas

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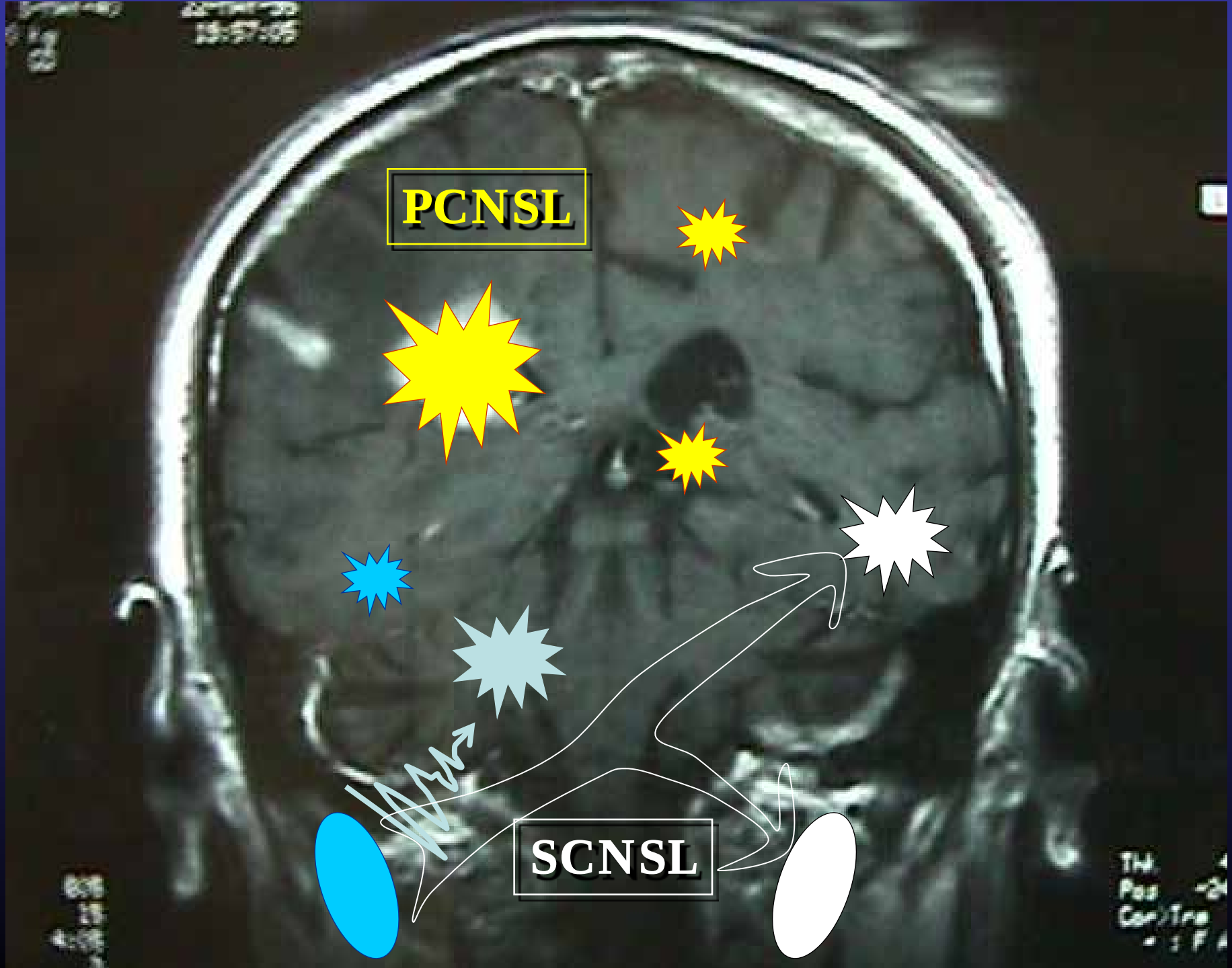
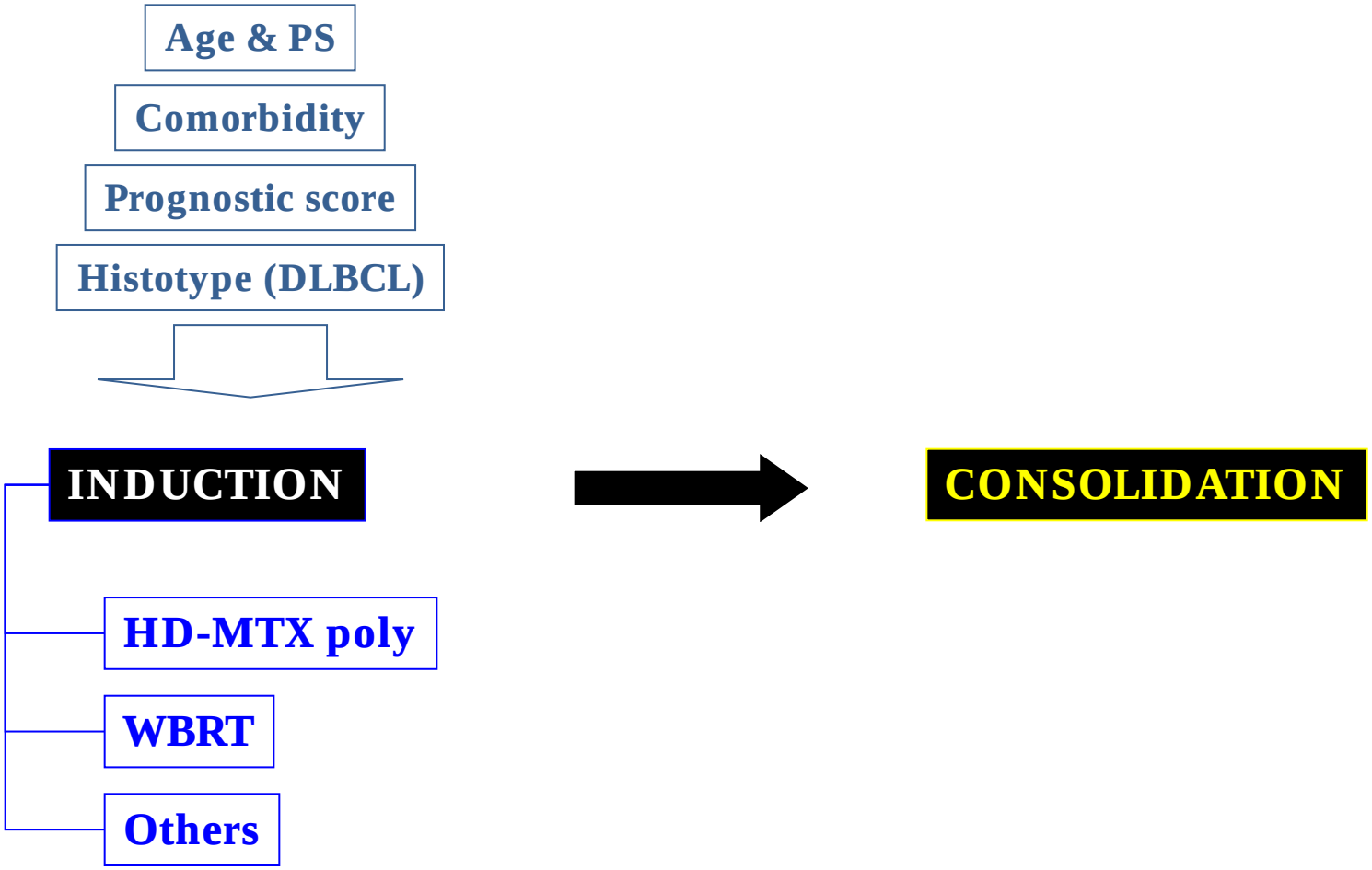

PCNSL
SCNSL

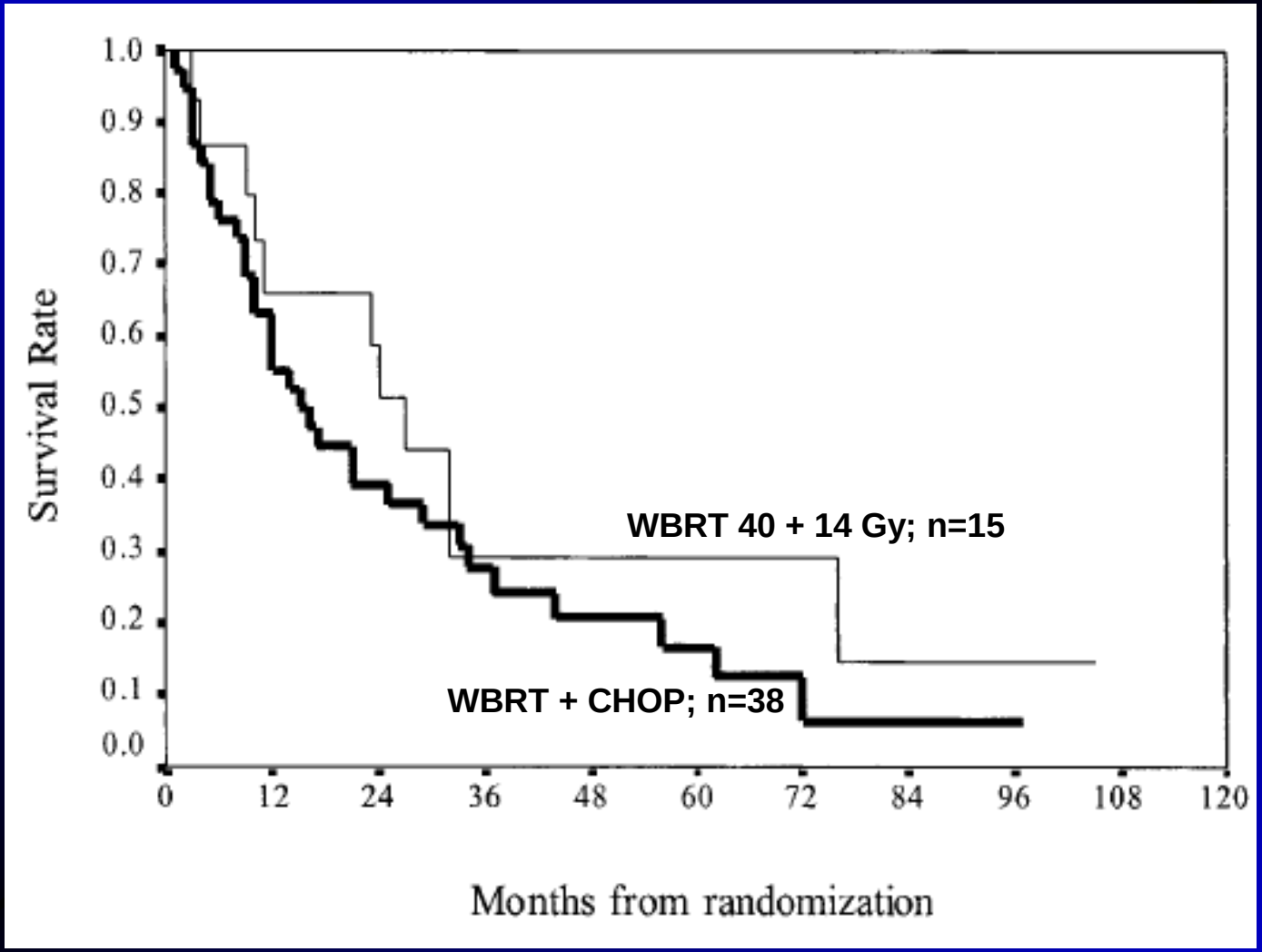
PCNSL vs. SCNSL

	PCNSL	SCNSL
Median age	65	Variable
PS	poor	good
Time to diagnosis	months	weeks
Steroids	Long-term	Less common
Need for biopsy	Near always	Less common
Histotype	DLBCL	HA-NHL
Meningeal involv.	16%	35%
Ocular involv.	10%	<1%
Systemic disease	0%	35%
Systemic relapse	7%	50%

Modern Approach



CHOP regimen



Mead GM, et al. Cancer 2000

HD-MTX

Pharmacokinetics Triphasic plasmatic clearance

Good BBB penetration at HD

Schedule

Infusion duration 3 hours

Infusion timing every 2 wks = 3 wks

Dose $\geq$ 3 g/m^2

CNS availability

$\geq$ 1 g/m^2 tumoricidal levels in the brain

$\geq$ 3 g/m^2 tumoricidal levels in the CSF

24-hr inf. ~~tumoricidal levels in the CSF~~

Tolerability

8 g/m^2 45% dose reductions

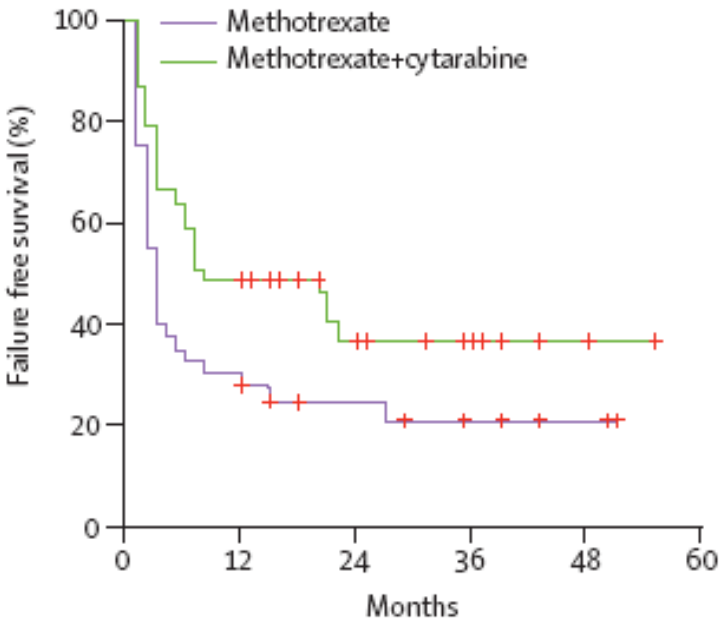
3.5 g/m^2 good compromise

Ferreri AJM. Blood 2011

IELSG #20 trial: MTX + ARAC

	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



Median f-up: 30 months

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%

[1]Morris PG, et al. JCO 2013; [2]Omuro A, et al. Blood 2015; [3]Rubenstein JL, et al. JCO 2013

The IELSG #32 trial

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

R

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
araC 2 g/m² x 2/d, d. 2-3
Thiotepa 30 mg/m² d.4
every 3 weeks

Response assessment

CR – PR - SD

R

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
ê SC harvest

WBRT 40 Gy
± boost 9 Gy

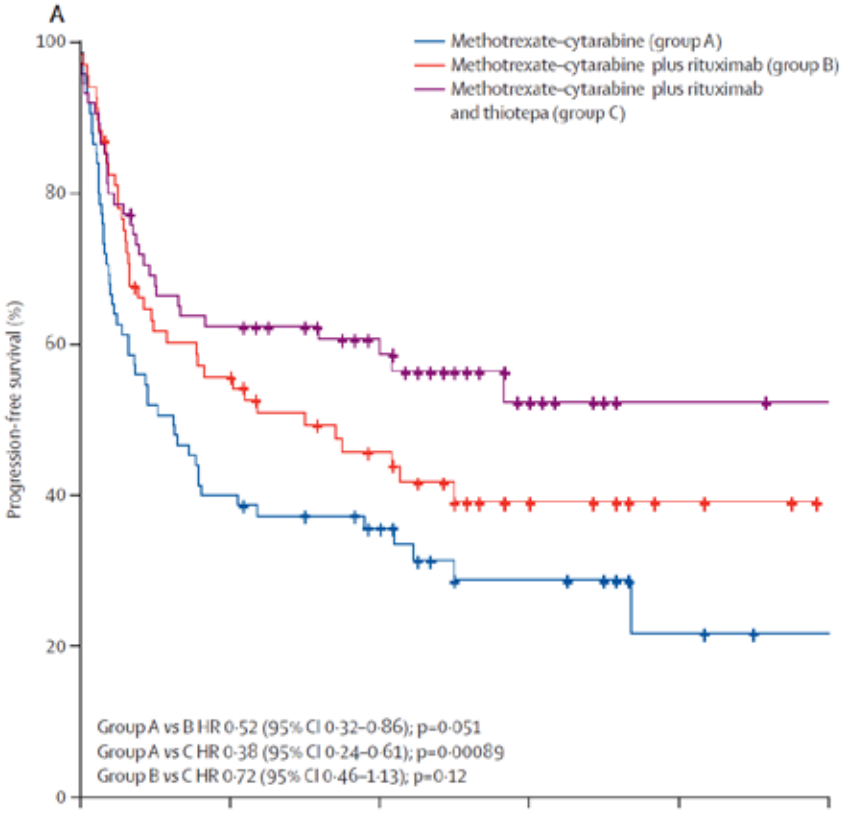
Arms Activity

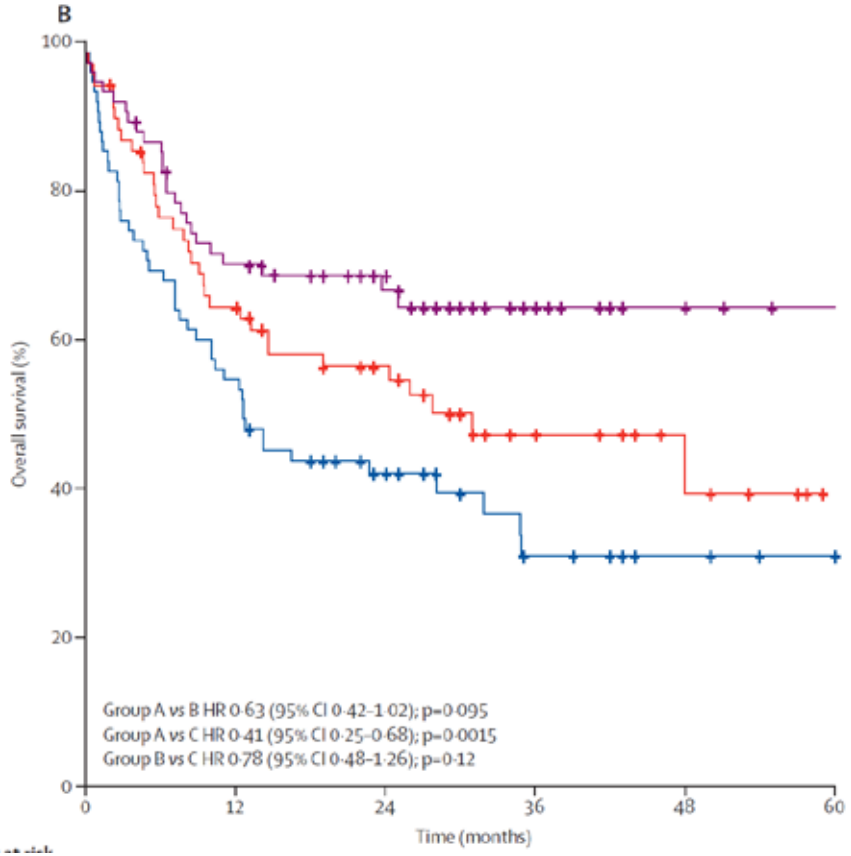
	Methotrexate–cytarabine (group A; n=75)	Methotrexate–cytarabine plus rituximab (group B; n=69)	Methotrexate–cytarabine plus rituximab and thiotepa (group C; n=75)	HR (95% CI) for group A *vs* group B	p value	HR (95% CI) for group A *vs* group C	p value	HR (95% CI) for group B *vs* group C	p value
Complete 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 [A:q1]
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 [A:q1]	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%)	..	..	..	..	..	..

Ferreri AJM, et al. Lancet Haematol 2016

PFS and OS

median follow-up: 30 months (12-66)





Ferreri AJM, et al. Lancet Haematol 2016

Elderly Pts: PHRC 2006 Trial

Arm A M-PVA

3 cycles/ 28 d

Procarbazine 100 mg/m²/d D1-7

Cytarabine 3 g / m2 / d1-2
After 3rd Cycle

Vincristine 1,4 mg/m² D1

MTX 3,5 g/m² d1

Vincristine 1,4 mg/m² D1

MTX 3,5 g/m² d1

D1 *D7* *D14* *D21* *D28*

Méthylprednisolone
60 mg/j en in D1-5

Arm B M-TMZ

3 cycles/28 d

TMZ 150 mg/m2/d D1-5

MTX 3,5 g/m² d1

If no tox= TMZ 150 mg/m2/d D15-19 , cycle 2 & 3

MTX 3,5 g/m² d1

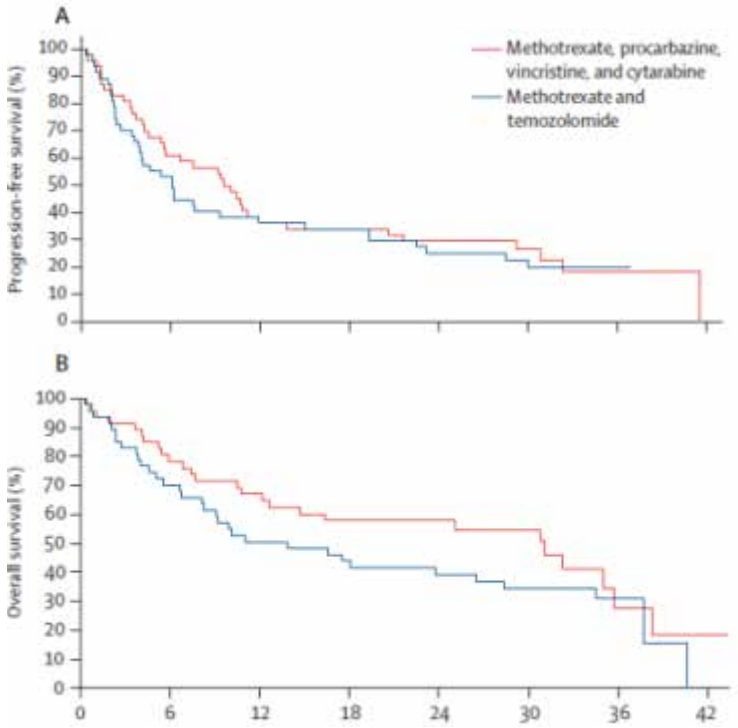
D1 *D7* *D14* *D21* *D28*

Méthylprednisolone
60 mg/d en in D1-5

PHRC 2006 Trial

	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)	*p*
CR	**62%**	**45%**	**0.11**
PR	20%	26%	
SD	2%	7%	
PD	16%	22%	
ORR	82%	71%	**0.23**



Sanctuaries

- CSF and eyes (intrathecal and intravitreal chemo).
- IT/IV chemo efficacy has not been prospectively confirmed. Most trials do not include IT/IV drug delivery.
- IT is associated with additional risk of infective complications, neurotoxicity and chemical meningitis.
- HD-MTX (³ 3 g/m^2) treats adequately meninges.
- IVi: is active, but toxic (visual acuity deterioration in 27%).
- Impact on OS???

Ferreri AJM, et al. Neurology 2002
Ferreri AJM, et al. J Clin Oncol 2003
Pels H, et al. J Clin Oncol 2003
Weigel R, et al. Clin Neurol Neurosurg 2004
Batchelor T, et al. Clin Cancer Res 2003
Smith JR, et al. Ophthalmology 2002

Molecular components of oncogenic survival signalling in PCNSL

Chia-Ching W, et al. BJH 2014

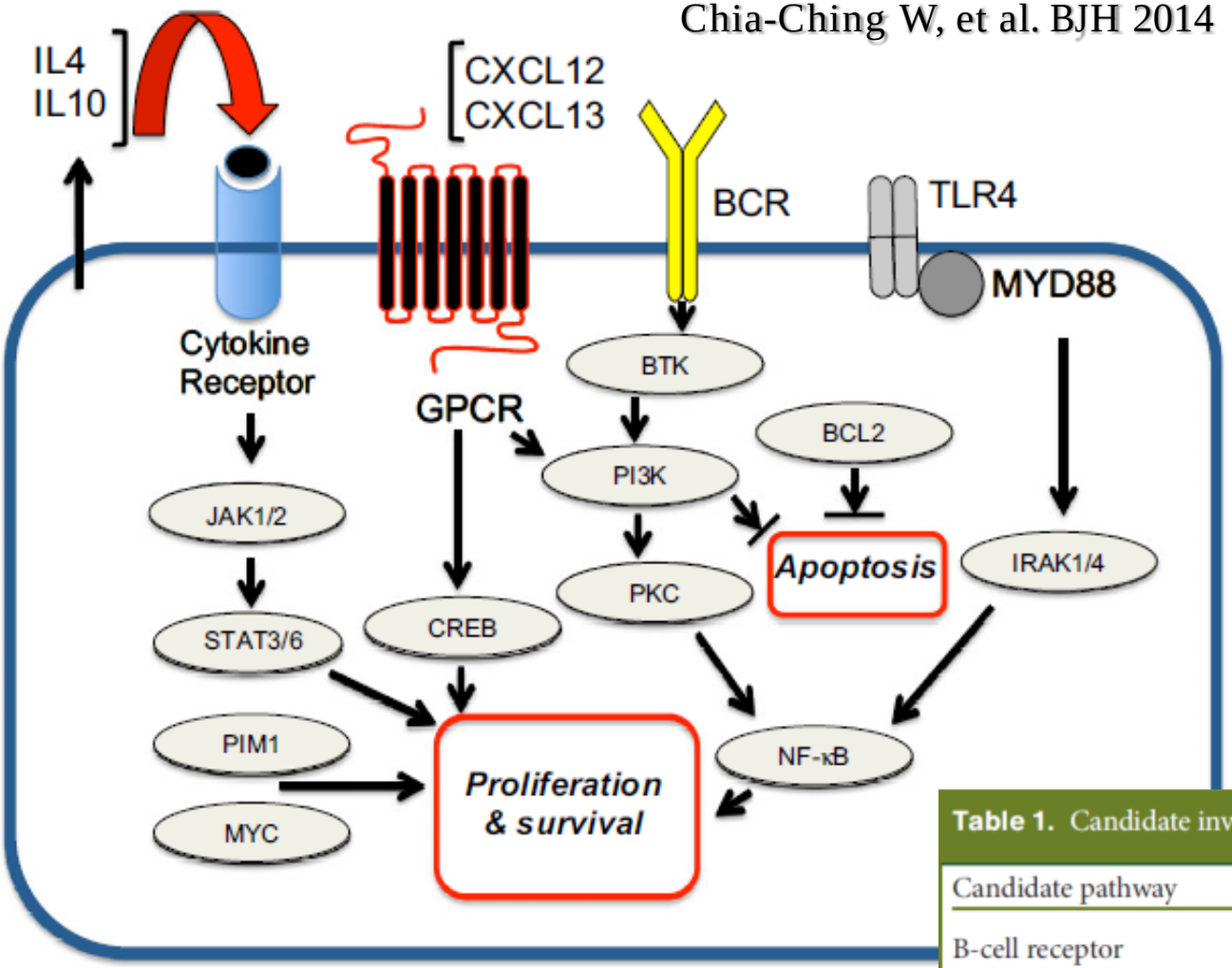
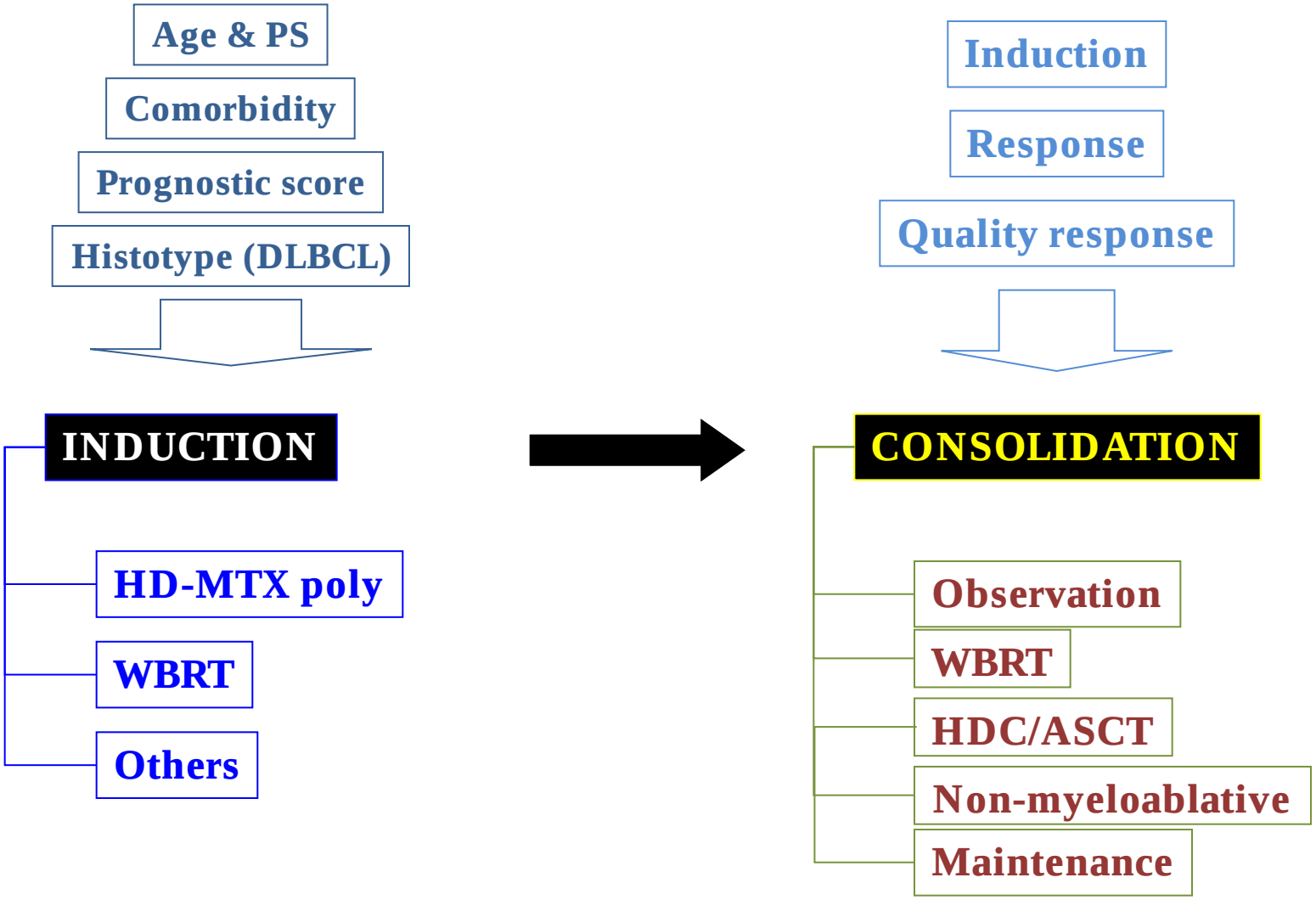


Table 1. Candidate investigational agents in CNS lymphoma

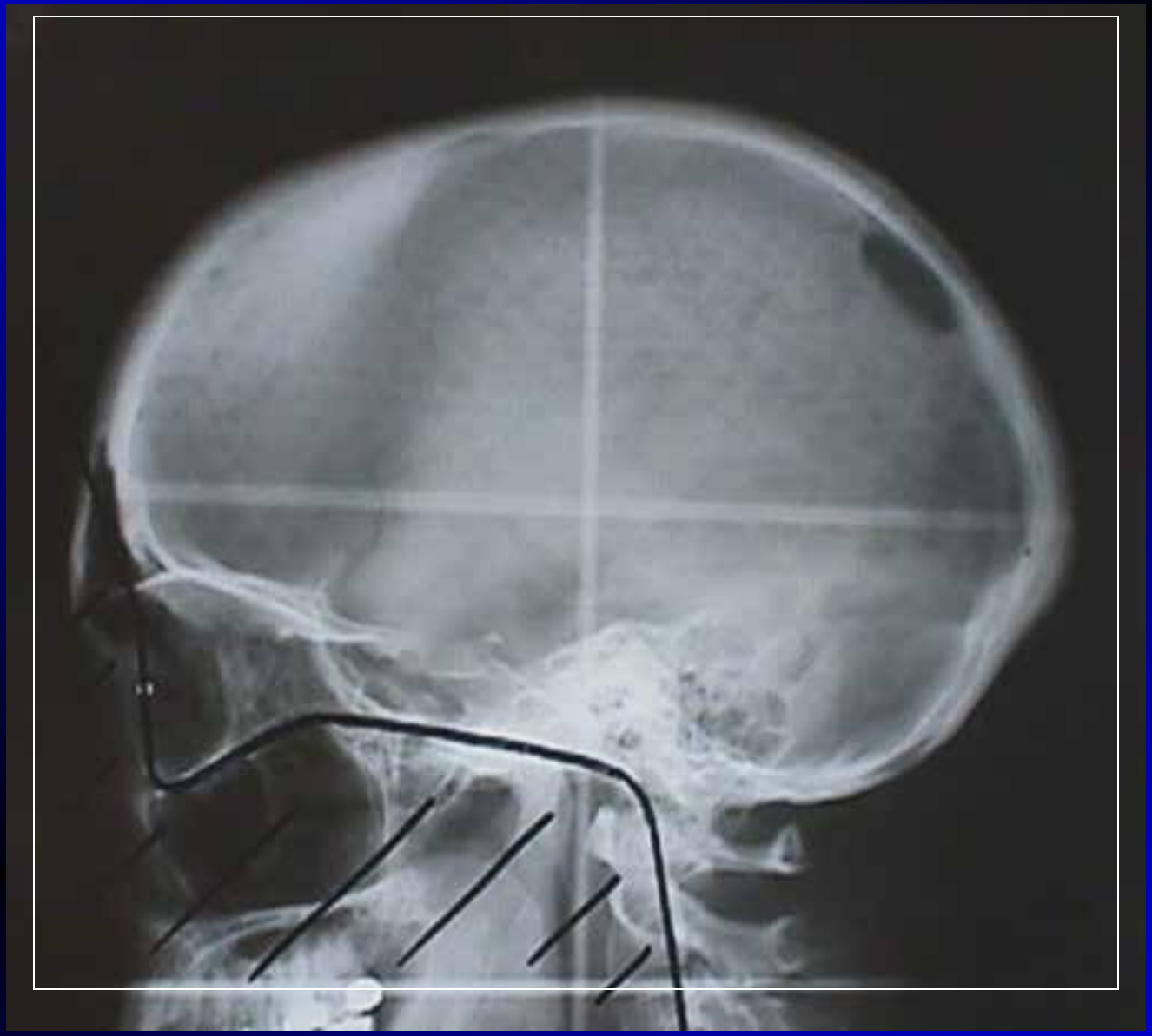
Candidate pathway	Investigational agent
B-cell receptor	Ibrutinib, fostamatinib, BKM120, GA101
JAK/STAT	Ruxolitinib
IRF4/MUM1	Lenalidomide, pomalidomide
BCL-6	RI-BPI
NFkB	MALT1 inhibitors
CXCL12, CXCL13	Plerixafor (AMD3100), BKM120, GA101
PIM kinases	SGI-1776
Mtor	Temsirolimus, everolimus

Ponzoni M, et al. Ann Oncol 2014

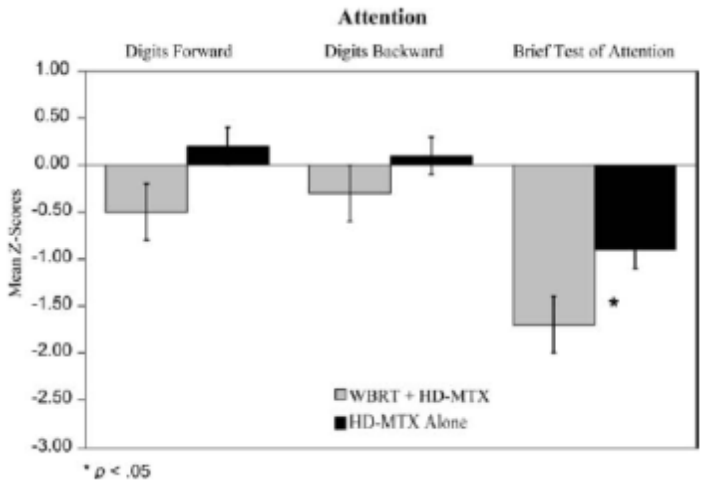
Modern Approach

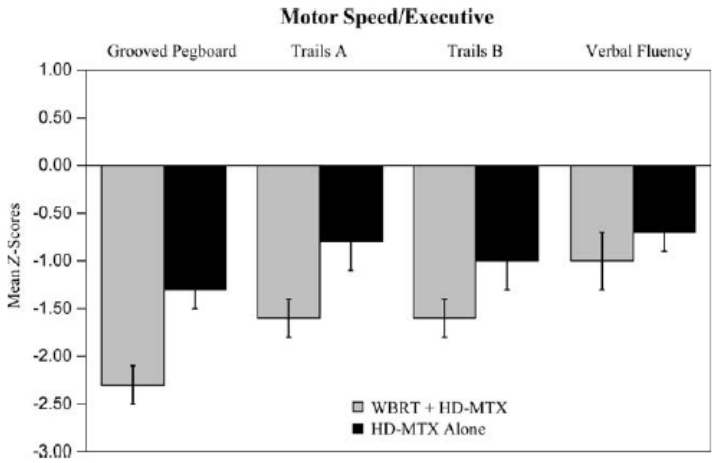


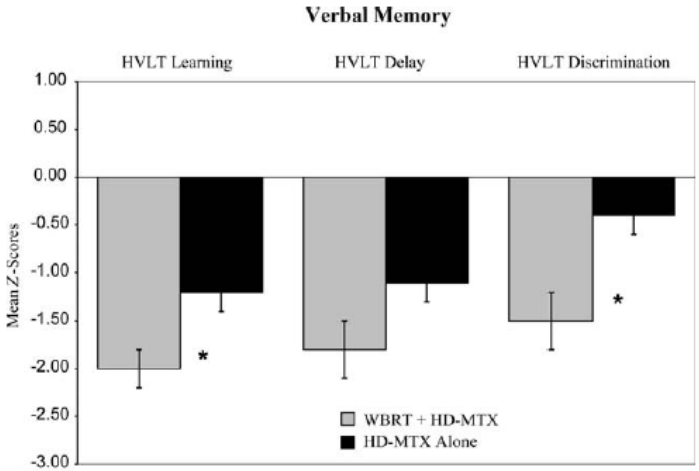
Radiation Field



Neurotoxicity





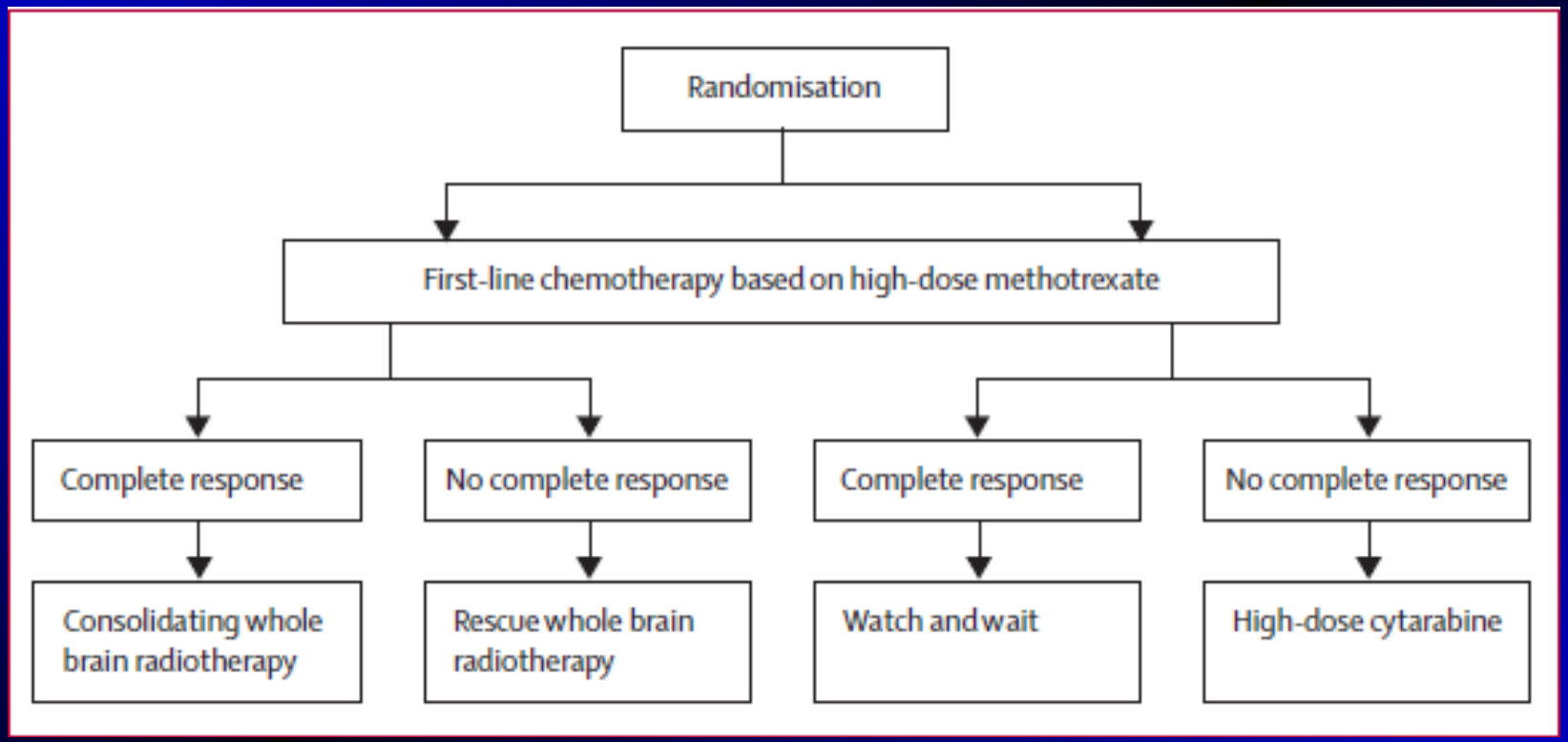


Deficits interfere with QoL

>50% were not working due to illness

Consolidation RT withdrawal?

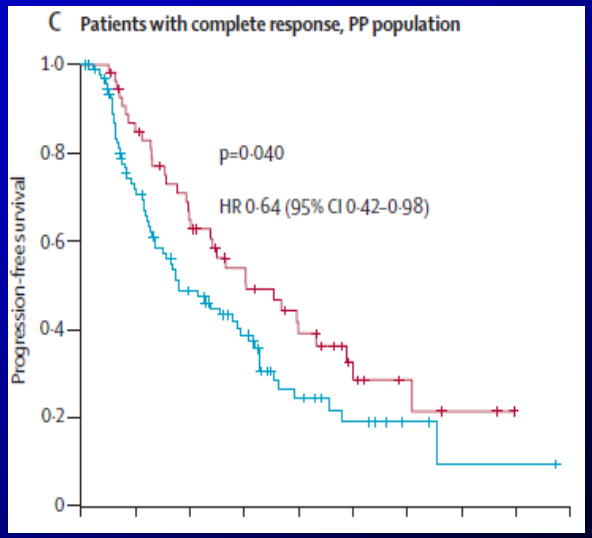
G-PCNSL-SG-1 trial

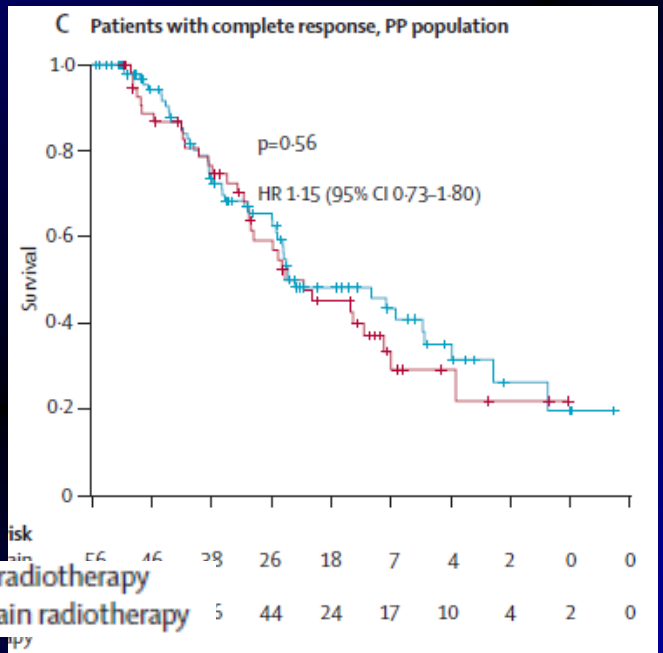


551 pts with newly diagnosed PCNSL were enrolled from 75 German Centers and treated between 2000 and 2009

Thiel E, et al. Lancet Oncol 2011

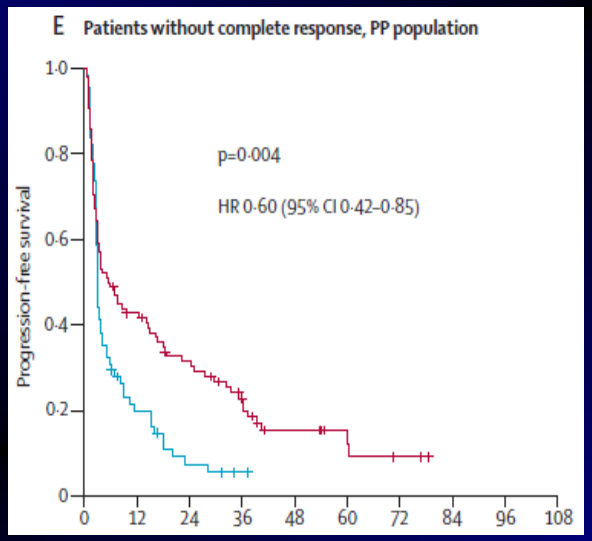
G-PCNSL-SG-1 trial: results

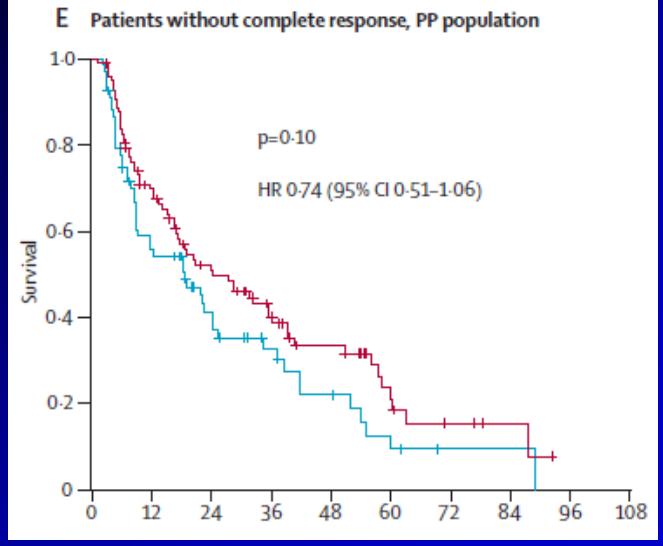




First-line chemotherapy with whole brain radiotherapy

First-line chemotherapy without whole brain radiotherapy





RADIOTHERAPY

Has the role of WBRT in primary CNS lymphoma been settled?

Lisa M. DeAngelis

The use of whole-brain radiation therapy (WBRT) in the treatment of primary central nervous system lymphoma is controversial. A recent randomized study addressing the use of this therapy was flawed and questions remain about the use of WBRT in these patients.

DeAngelis, L. M. *Nat. Rev. Clin. Oncol.* **8**, 196–198 (2011); published online 8 February 2011;

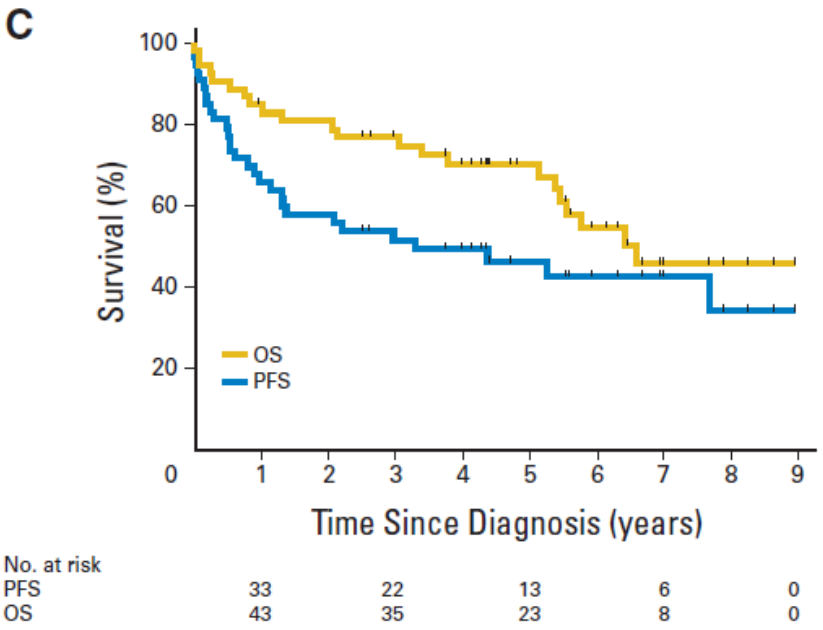
> "The trial was inconclusive, but the authors proceeded with further analyses..."

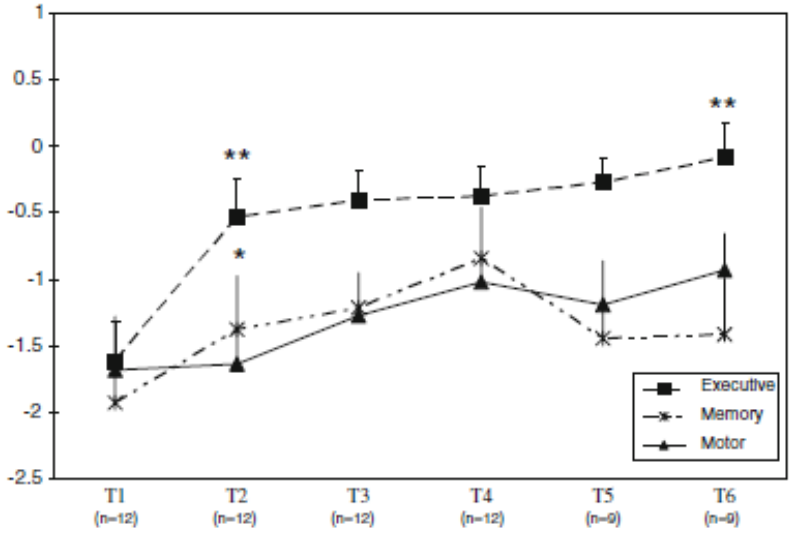
Practice point

Further study is necessary to clarify the true role of whole-brain radiation therapy for patients with primary central nervous system lymphoma.

answers to these thorny questions. Two large European studies are randomizing patients to high-dose chemotherapy with autologous stem-cell transplant versus WBRT after induction chemotherapy. Although these European studies are necessarily limited to younger patients because of the transplant option, I do not think that either patients or physicians should hesitate to be randomized to a regimen that incorporates WBRT on the basis of this recently published *Lancet Oncology* article.[4]

Low-dose WBRT





High-dose Chemo + ASCT

Rationale — **Higher doses to cross the BBB.**
… to achieve therapeutic concentrations in "sanctuaries".
… to overcome drug resistance.

Concerns — **Feasible only in fit and young patients.**

Facts — **Encouraging results both as upfront & salvage treatment.**
Excellent neurotolerability when RT is avoided.
High activity in pts with residual disease after induction.

Consolidative HDC/ASCT

N °	Age m(r) PS m(r)	Induction	CRR (%)	Conditioning	ASCT (%)	F-up (mo)	2-yr EFS (%)	TRM (%)
25	51 (21-60) PS3-4: 32%	MVpBP +itx/araC	44	BEAM + RT	68	34	60 Colombat P, et al. BMT 2006	4
28	53 (25-71) 70 (30-100)	MTX araC	18	BEAM	50	28	20 Abrey L, et al. JCO 2003	0
11	52 (33-65) PS1: 91%	MTX araC	73	Bus, CTX VP16 ± RT	100	25	30 Yoon DH, et al. BMT 2011	0
23	55 (18-70) 70 (30-100)	MTX	13	Thiotepa Busulfan	70	15	45 Montemurro M, et al. Ann Oncol 2007	13
21	56 (34-69) PS>1: 70%	MTX ± others	24	Thiotepa Bus, CTX	100	60	72 Alimohamed N, et al. L&L 2012	14
30	54 (27-64) 70 (30-100)	MTX araC, TTP	37	Thiotepa BCNU + RT	77	140	81 Kasenda B, et al. Ann Oncol 2012	3
13	54 (38-67) 90 (30-100)	MTX araC, TTP	54	Thiotepa BCNU ± RT	85	72	77 Kasenda B, et al. Ann Oncol 2012	0

Non-Myeloablative Chemo

Alliance/CALGB 50202 trial

44 pts
(age: 12-76)

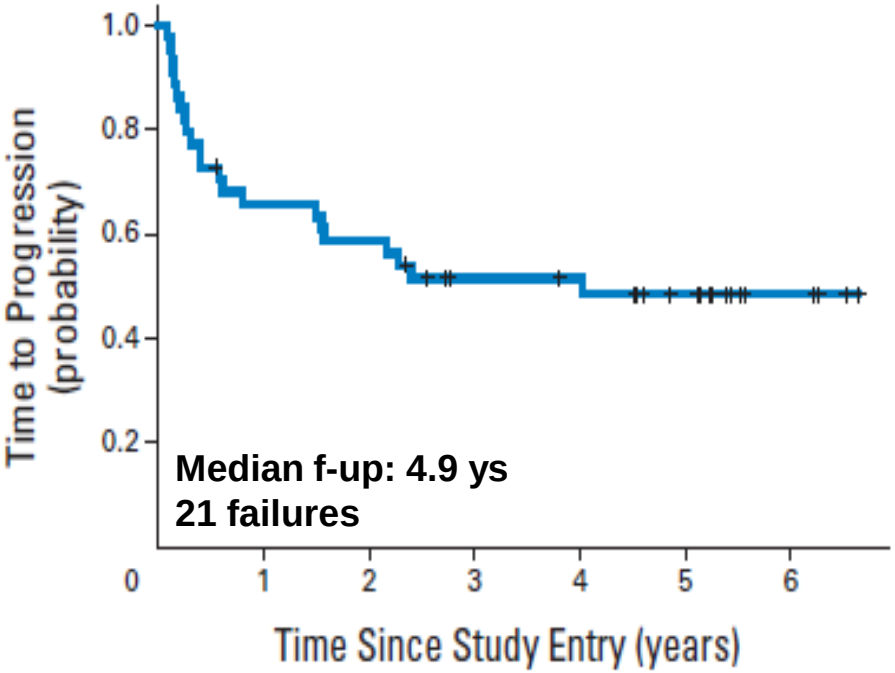
MTX (8)
Rituximab
TMZ x 8 c.

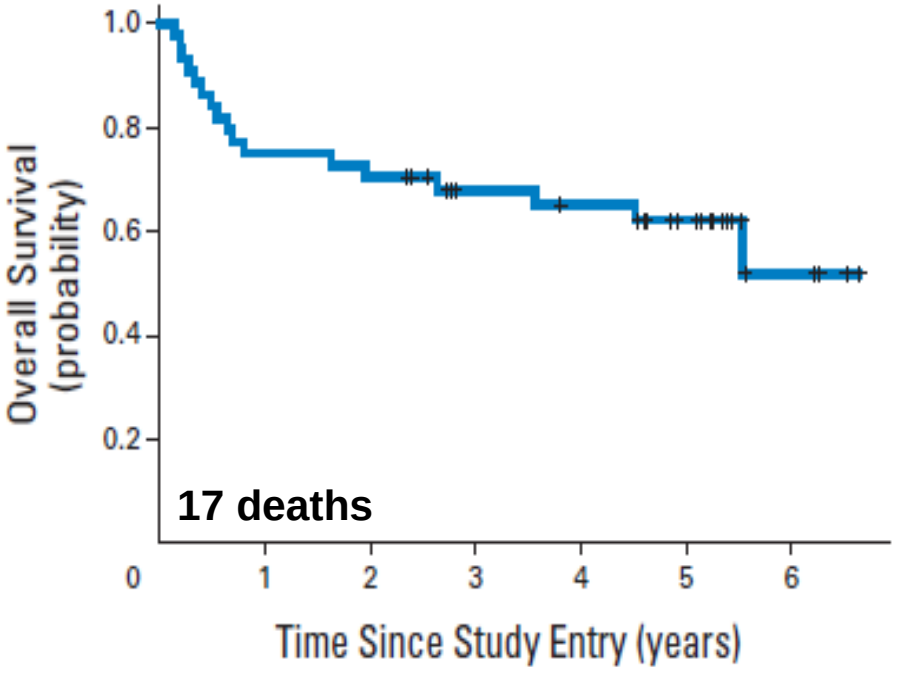
CR (66%)

TRM (sepsis) 2%

araC (8)
96-hr VP16

No neurotox

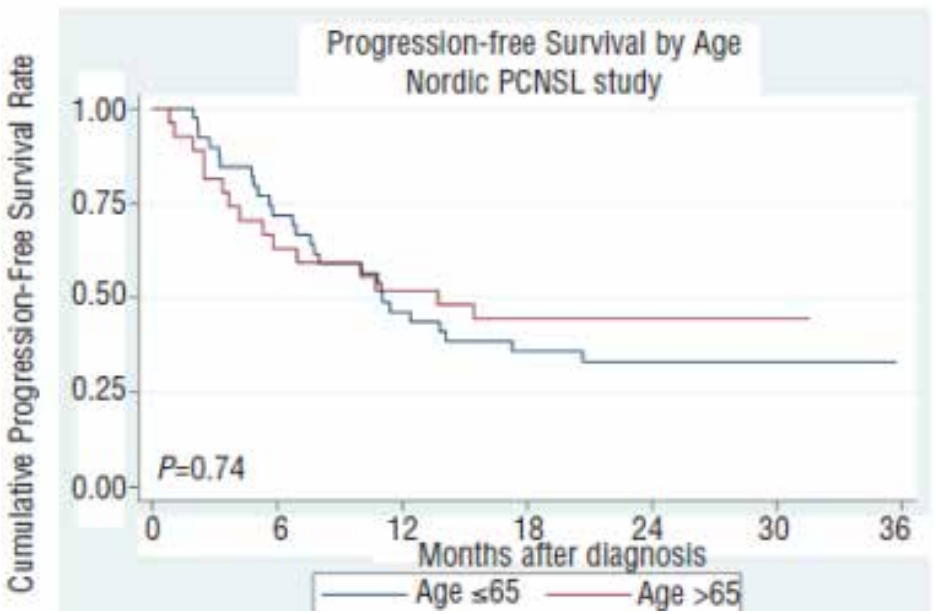


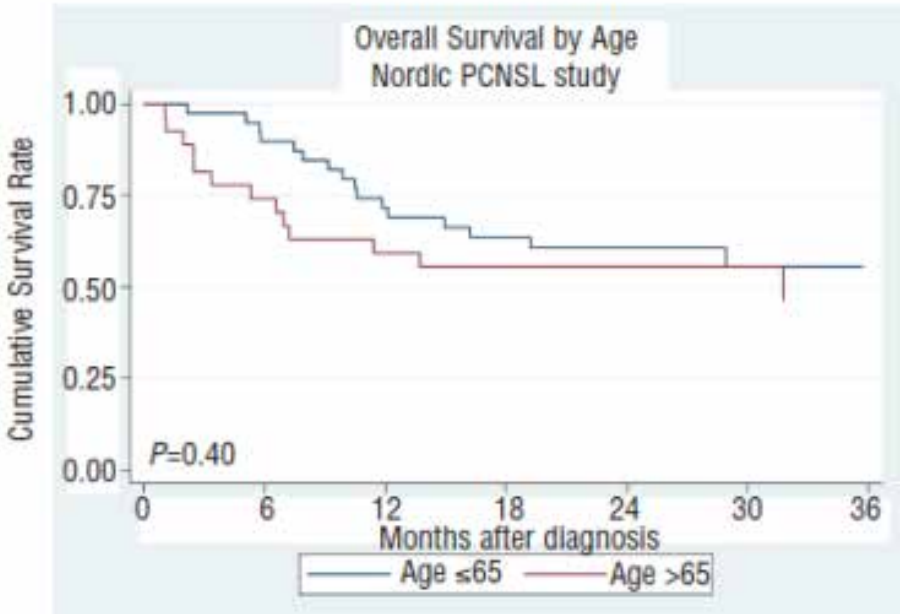


ASCT vs. Alternatives

IELSG32:	WBRT vs. ASCT
PRECIS:	WBRT vs. ASCT
IELSG43 (MATRix):	ASCT vs. NMC
ALLIANCE:	ASCT vs. NMC

Nordic Trial: TMZ maintenance





Secondary CNS Lymphoma

- **Rare**
- **Early**
- **Fatal**
- **Preventable**

CNS recurrence

CNS recurrence	
indolent lymphomas	<3%
MCL	4% - 13%
DLBCL & PTCL	5%
highly aggressive lymphomas	19% - 78%

4-yr CNS relapse risk (all NHL)	17%
1-yr CNS relapse risk (DLBCL)	5%
1-yr CNS risk (DLBCL w/ HD-MTX + it cht)	<2%

van Besien K, et al. Blood 1998; Zinzani PL, et al. Leuk Lymphoma 1999

CNS recurrence

Median NHL diagnosis - CNS recurrence	3-6 m (0-44)
MCL	17 m (6-96)
CNS relapses occuring in the first year	96%
MCL	35%
one-yr SAR	25%
median SAR	3 - 5 m

Isolated CNS recurrence	1 - 5%
Concurrent CNS and systemic recurrences	20 - 35%
CNS relapse à systemic progression	30 - 50%
MCL (CNS + systemic)	> 90%

Levitt, Cancer 1980; Litam, Blood 1979; Bollen, Arch Neurol 1997;
Hollender, Ann Oncol 2002; van Besien, Blood 1998; Haioun, Ann Oncol 2000

Risk of prophylaxis

WBRT	**Leucoencephalopathy** **Myelotoxicity**
Intrathecal chemotherapy	**Chemical meningitis** **Leucoencephalopathy** **Headache, Hemorrhage**
Intraventricular chemo (Ommaya)	**Septic complications**
Intravenous high-dose chemo	**Leucoencephalopathy** **Myelotoxicity** **Nephrotoxicity** **Hepatotoxicity**

Risk Factors

- **Hystotype**
  - **Burkitt, lymphoblastic lymphoma**
- **Extranodal organs**
  - **testis, breast, ovary, paranasal s., skin, soft tissue, BM**
- **Regions near to the h**
  - **oral ca** **salivary glands, orbita**
- **Others (DLBCL)**
  - **H** **sites >1, B symptoms, c-myc**

UNCONFIRMED DATA

SCORES= LOW SENSITIVITY

Feugier P et al. Ann Oncol 2004
Avilés A e al. Oncology 2005
Boehme V et al Ann Oncol 2007

Laskin JJ et al. Leuk Lymphoma 2005
Zucca E et al. J Clin Oncol 2003
Savage K et al JCO 2009

“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 ?**

Ferreri AJM. Lancet Oncol 2014

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 *et al* (2013)	DLBCL (3258)	CHOP ± R (163)	1005	Varied	2·253 (CNS risk?)	5·9 vs. 5·9 (P = NS)	Physician's preference. LR-CNS patients included.	No benefit with prophylaxis
Krawczyk *et al* (2013)	HR-CNS aggressive NHL (79)†	Varied, including ASCT (28)	68	IT	None	0	Pre-rituximab risk factors	IT prophylaxis is encouraged
Murawski *et al* (2014)	Aggressive NHL with extranodal disease of craniofacial area (279)†	CHOP ± R (>36)	88	IT	191 (CNS risk?)	4·2 vs. 2·3‡ (P = NS)	LR-CNS patients included.	IT prophylaxis does not provide additional benefit
Wilson *et al* (2014)	Aggressive NHL with CSF assessment (326), including HIV+ patients and patients with CNS disease†	Varied ± R (47)	171	IT§	30 (CNS risk?)	5·3 vs. 7·2¶ (P = NS)	Not reported. LR-CNS patients included.	IT prophylaxis improves freedom from CNS relapse
Holte *et al* (2013)	Aggressive NHL with aaIPI: 2–3, aged ≤ 65 years (156)†	R-CHOEP (52)	156	HD-MTX + HD-araC ± IT	None	5·2**	High-risk extranodal sites not considered	Lower than expected CNS events
Guirguis *et al* (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 *et al* (2010)	DLBCL with HR-CNS (65)	CHOP ± 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 ± IT	67	0 vs. 12††	Pre-rituximab risk factors. LR-CNS patients were analysed separately.	IV prophylaxis reduces CNS relapses

Ferreri AJ, *et al*. BJH 2015

bjh research paper

Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era

LR	Low risk	no CNS prophylaxis	89
HR	High risk	no CNS prophylaxis	65
HR-Pro	High risk	CNS prophylaxis	40

- INVOLVEMENT of: testis, spine, base of skull, kidney, breast
- IPI score ≥2 (including E >1, stage III-IV and high serum LDH level).

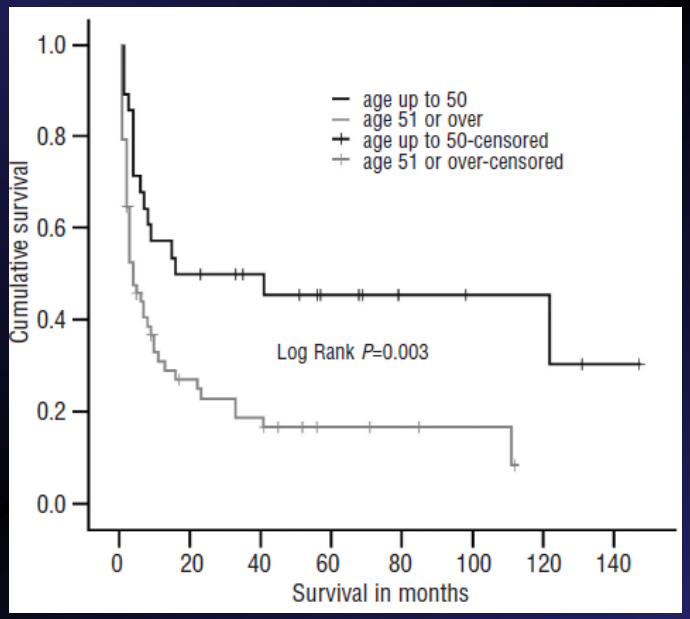
3-4 c. MTX 3 g/mq ev ± liposomial ARAC it	33 (82%)
Intrathecal MTX + araC + steroid alone	7 (18%)

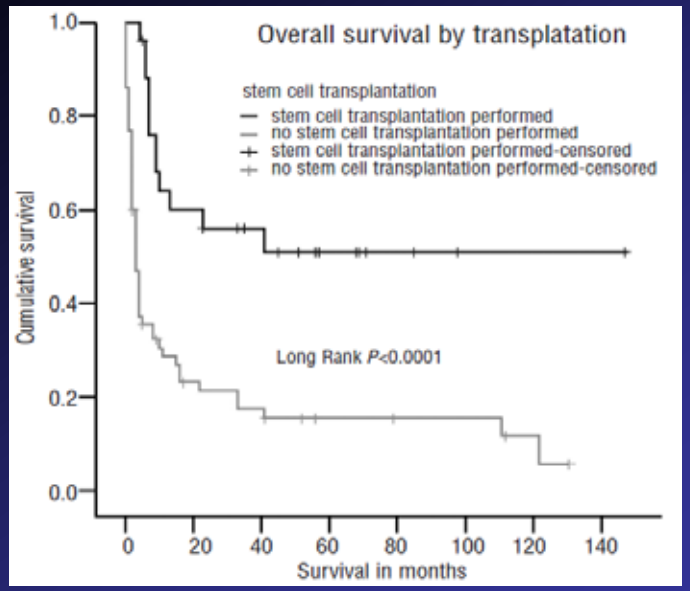
	LW (93)	HR (67)	HR Pro (40)
CNS relapses	1 (1%)	8 (12%)	1 (3%)
I.V. prophylaxis (n=33)	-	-	0 (0%)
I.T. prophylaxis (n= 7)	-	-	1 (14%)

Ferreri AJ, *et al*. BJH 2015

CNS Recurrence in the Rituximab era

Treatment	N. of patients (%)
Systemic chemotherapy	73 (79%)
MTX+araC combinations	18 (25%)
MTX + ifosfamide	13 (18%)
MTX + other	14 (19%)
Bonn combination	3 (4%)
MTX monotherapy	6 (8%)
Any including HD-MTX	54 (74%)
HD-araC + other	12 (16%)
Any including HD-araC	30 (41%)
Other (no HD-MTX or ara-C)	7 (9%)
Intravenous rituximab	
Yes	23 (25%)
No	53 (58%)
Not reported	16 (17%)
Radiotherapy	22 (24%)
Cranial radiotherapy only	1 10 (11%)
Cranial radiotherapy + chemotherapy	7 (8%)
Brain + spinal cord	3 (3%)
Focal other	2 (2%)
Intrathecal/intraventricular	56 (60%)
MTX	25
Ara-C, native or sustained release	6
MTX + ara-C	25
None	34
Not reported	2
Myeloablative treatment	28 (30%)
Chemotherapy	24 (26%)
BCNU/TT	10
BEAM/BEAC	3
Busulfan and cyclophosphamide	3
Other	8
Total body irradiation	4 (4%)
Transplantation	
Yes	27 (29%)
No	65 (71%)
No treatment	4 (4%)





Bromberg J, et al. Haematol 2013

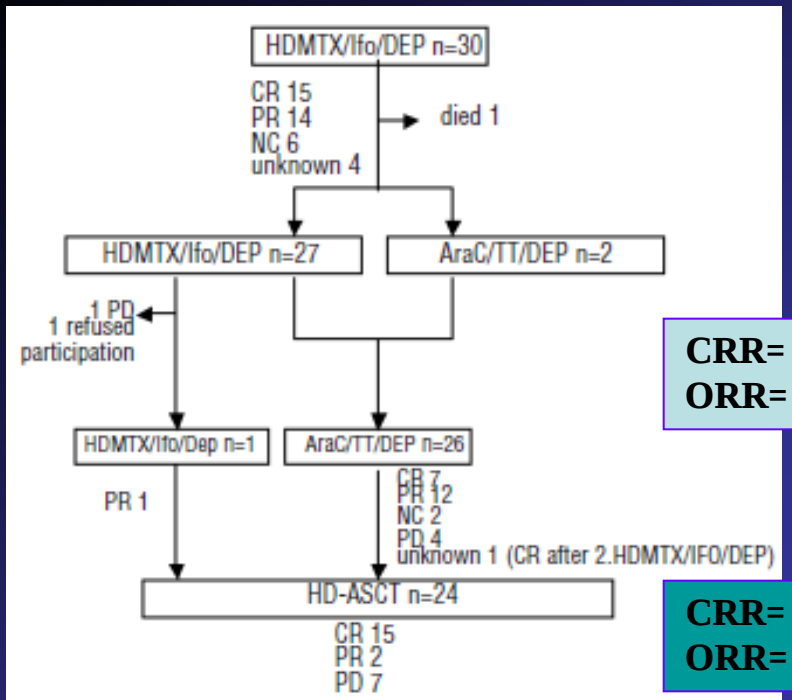
Phase II study of central nervous system (CNS)-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation for CNS relapse of aggressive lymphomas

Agnieszka Korfel,[1] Thomas Elter,[2] Eckhard Thiel,[1] Matthias Hänel,[3] Robert Möhle,[4] Roland Schroers,[5] Marcel Reiser,[2] Martin Dreyling,[6] Jan Eucker,[1] Christian Scholz,[1] Bernd Metzner,[7] Alexander Röth,[8] Josef Birkmann,[9] Uwe Schlegel,[10] Peter Martus,[11,12] Gerard Illerhaus,[13] and Lars Fischer[1]

haematologica | 2013; 98(3)

Characteristic	N	(%)
Age (years): median/range	58/29-65	
Sex: male/female	15/15	50/50
ECOG performance status:		
0-1	18	60
2	12	40
Diffuse large B-cell lymphoma	27	90
Peripheral T-cell lymphoma, unspecified	3	10
LDH elevation at relapse		
No	17	57
Yes	10	33
Unknown	3	10
Localization of CNS relapse		
Brain parenchyma only	17	57
Meninges only	7	23
Both	6	20
Systemic disease at time of CNS relapse:		
Present/absent	6/24	30/70
Symptoms (>20% of patients)		
Personality changes	7	23
Cranial nerves	9	30
Focal deficits	17	57
Headache	16	53

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



CRR= 23%
ORR= 67%

CRR= 50%
ORR= 57%

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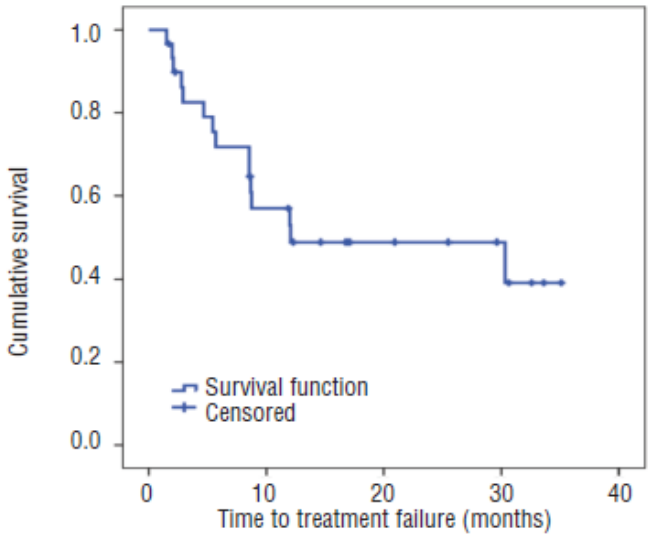
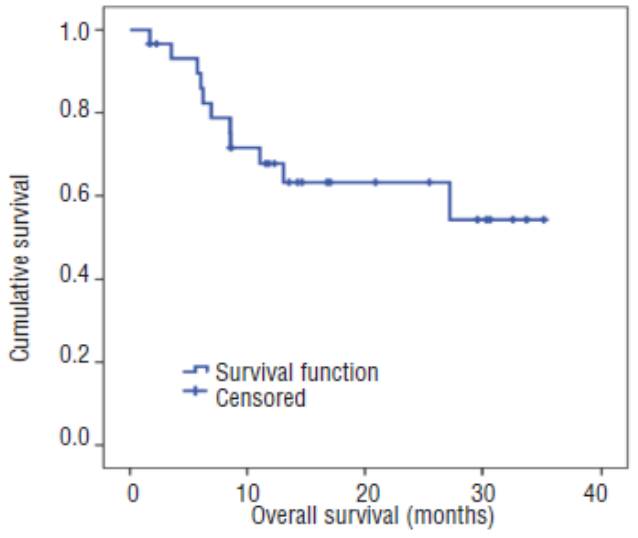
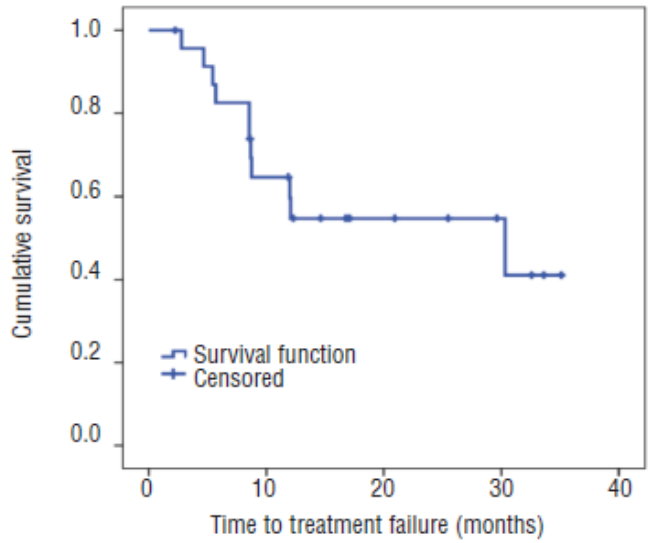
haematologica | 2013; 98(3)

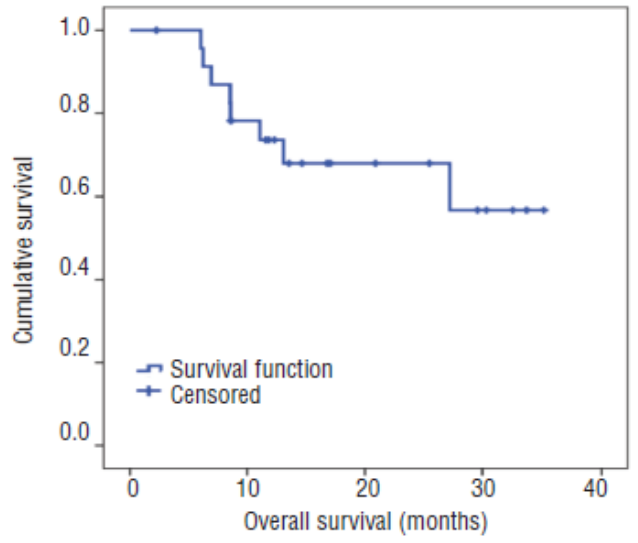
Whole series

Transplanted









Hovon 80 study with HD-ASCT in SCNSL

- N=36, med. age 57 (23-65)
- 3xR-DHAP-MTX
  - (Cisplatin, AraC 2x2g/m2 d2, MTX 3g/m2 d 15, rituximab IT)

  followed by HD-ASCT (BuCy)
- 15 (42%) completed treatment
- RR 53% (CR 28%)
- median PFS 6 mo, median OS 7 mo

Doorduijn et al, 2012

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High Doses of Antimetabolites Followed by High-Dose Sequential Chemoimmunotherapy and Autologous Stem-Cell Transplantation in Patients With Systemic B-Cell Lymphoma and Secondary CNS Involvement: Final Results of a Multicenter Phase II Trial

Andrés J.M. Ferreri, Giovanni Donadoni, Maria Giuseppina Cabras, Caterina Patti, Michael Mian, Renato Zambello, Corrado Tarella, Massimo Di Nicola, Alfonso M. D'Arco, Gianluca Doa, Marta Bruno-Ventre, Andrea Assanelli, Marco Foppoli, Giovanni Citterio, Alessandro Fanni, Antonino Mulè, Federico Caligaris-Cappio, and Fabio Ciceri

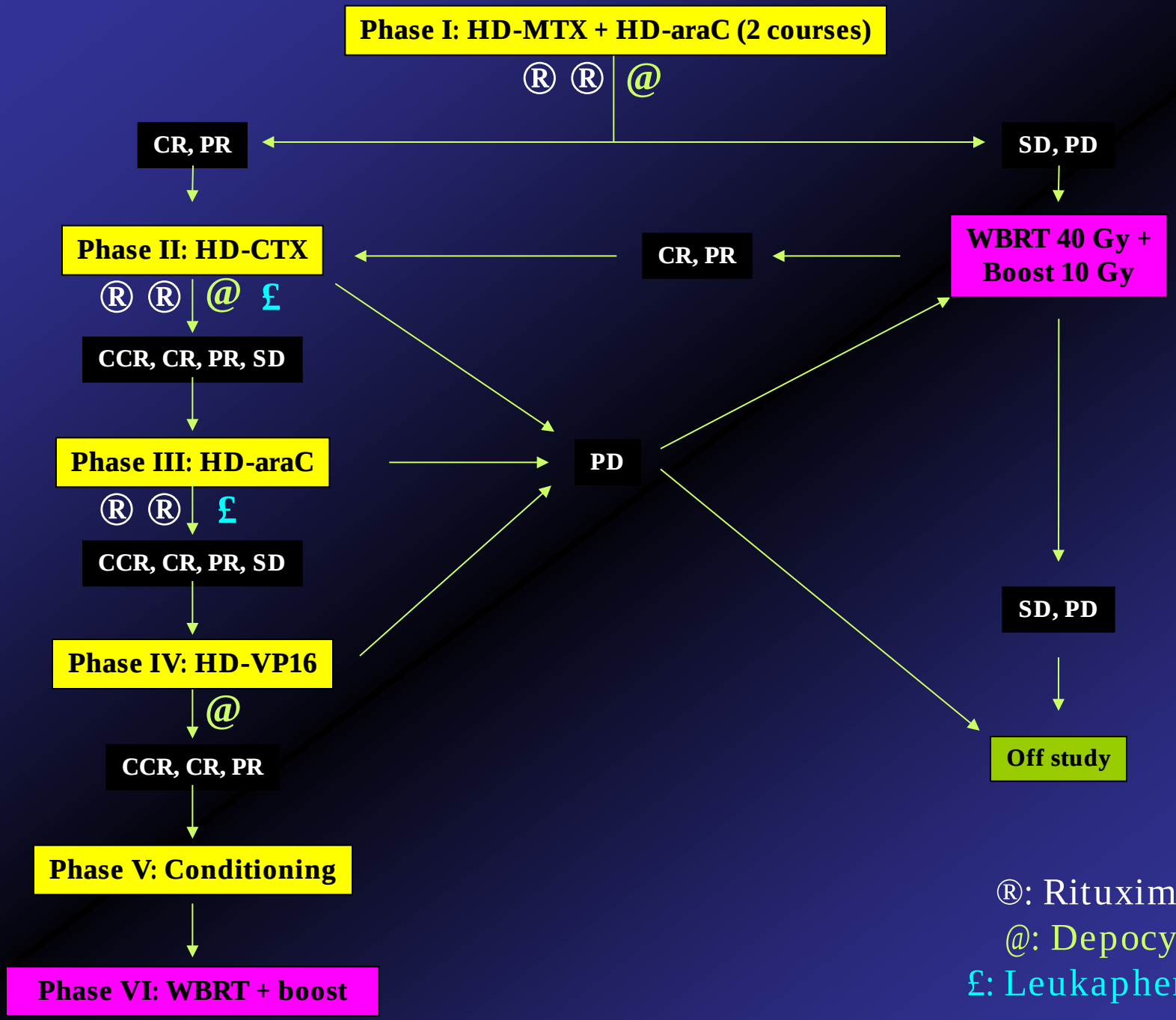
See accompanying editorial on page 3851

DLBCL, FL G3 or blastoid MCL

CNS involvement

Age 18 - 70 years

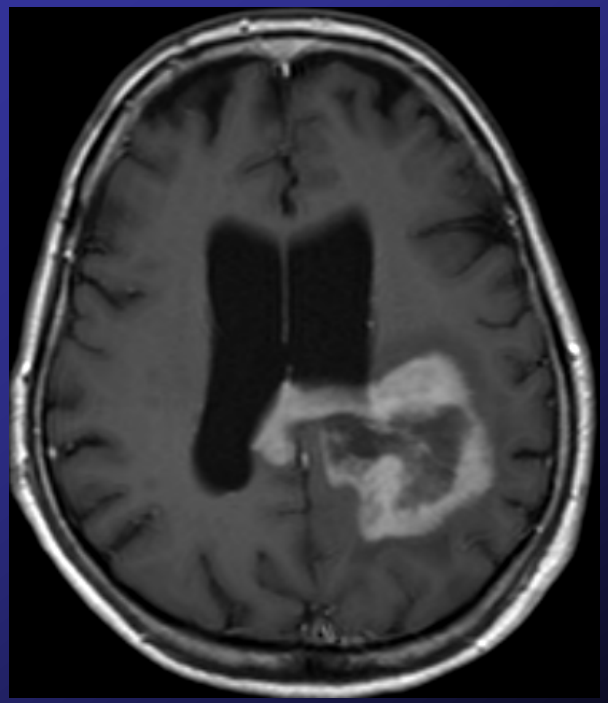
ECOG PS 0 – 3

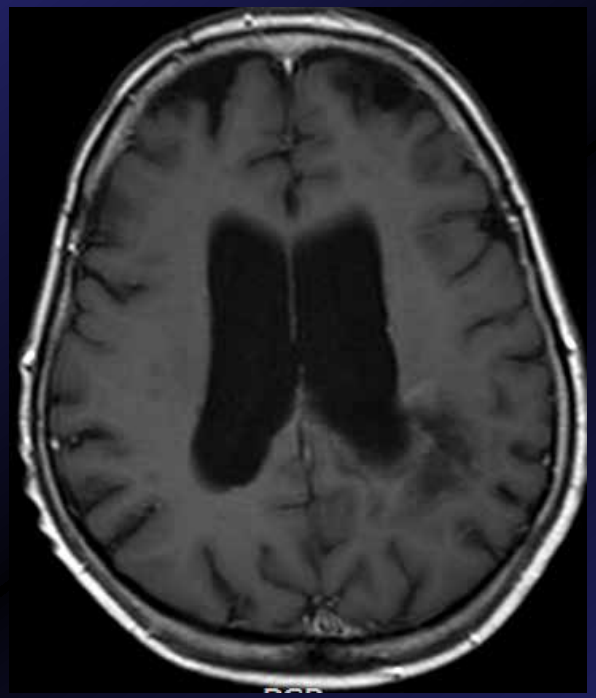

Phase I: HD-MTX + HD-araC (2 courses)
® ® @
CR, PR
SD, PD
Phase II: HD-CTX
® ® @ £
CR, PR
WBRT 40 Gy + Boost 10 Gy
CCR, CR, PR, SD
Phase III: HD-araC
® ® £
PD
CCR, CR, PR, SD
SD, PD
Phase IV: HD-VP16
@
CCR, CR, PR
Off study
Phase V: Conditioning
Phase VI: WBRT + boost
®: Rituximab
@: Depocyte
£: Leukapheresis

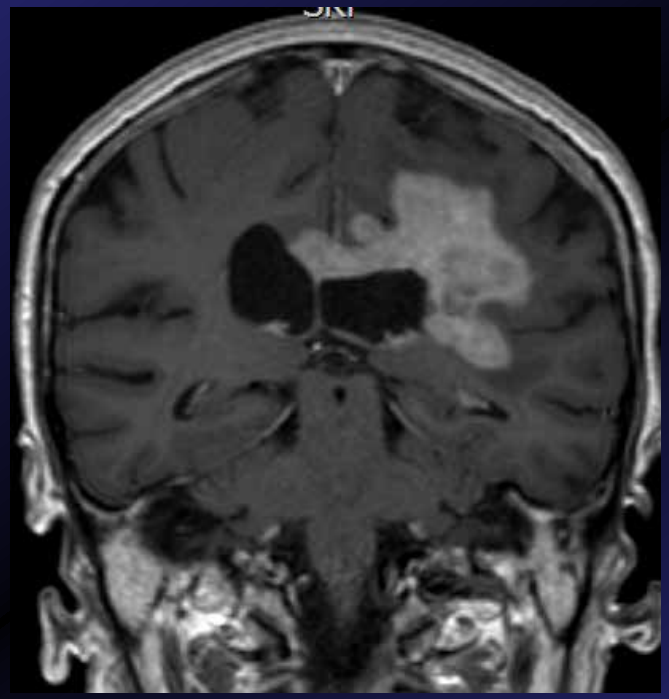
SCNSL1: Toxicity & Activity

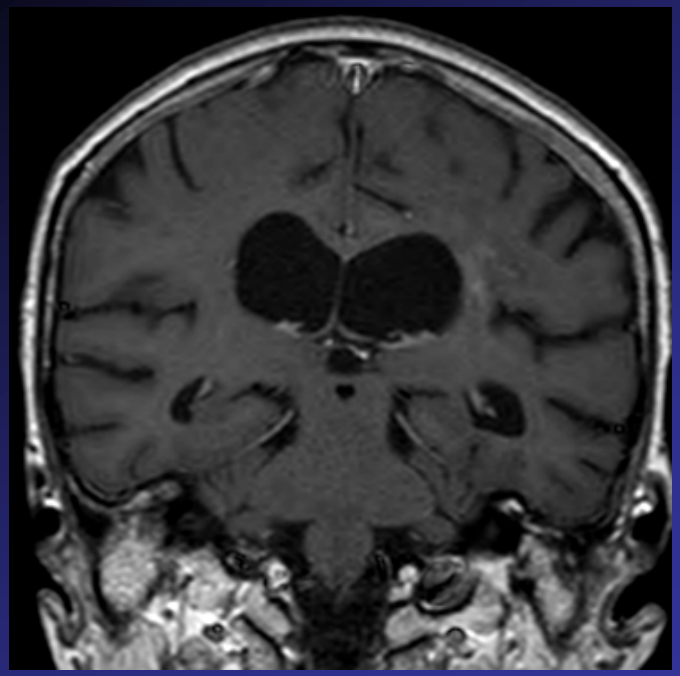
Toxicity	Induction Phase	High-Dose Cyclophosphamide	High-Dose Cytarabine
Assessable patients†	38	28	26
Planned courses	76	28	26
Delivered courses	71 (93)	27 (96)	25 (96)
Neutropenia			
Grade 3	1 (1)	2 (7)	0 (0)
Grade 4	55 (77)	18 (67)	20 (80)
Thrombocytopenia			
Grade 3	4 (6)	0 (0)	0 (0)
Grade 4‡	44 (62)	16 (59)	18 (72)
Anemia			
Grade 3	15 (21)	8 (30)	4 (16)
Grade 4	4 (6)	2 (7)	2 (8)
Febrile neutropenia/infection			
Grade 3	9 (13)	11 (41)	6 (24)
Grade 4	2 (3)	1 (4)	1 (4)
Hepatotoxicity			
Grade 3	6 (8)	3 (11)	3 (12)
Grade 4	2 (3)	0 (0)	0 (0)
Grade 3 nephrotoxicity	2 (3)	0 (0)	0 (0)
GI/mucositis			
Grade 3	1 (1)	1 (4)	1 (4)
Grade 4	1 (1)	0 (0)	0 (0)
Grade 3 hyperglycemia	1 (1)	0 (0)	2 (8)
Grade 3 neurotoxicity	2 (3)	0 (0)	0 (0)
Dose reduction > 25%	3 (4)	0 (0)	0 (0)
Interruption as a result of toxicity§	1 (3)	0 (0)	0 (0)
Toxic deaths§‖	3 (8)	1 (4)	0 (0)

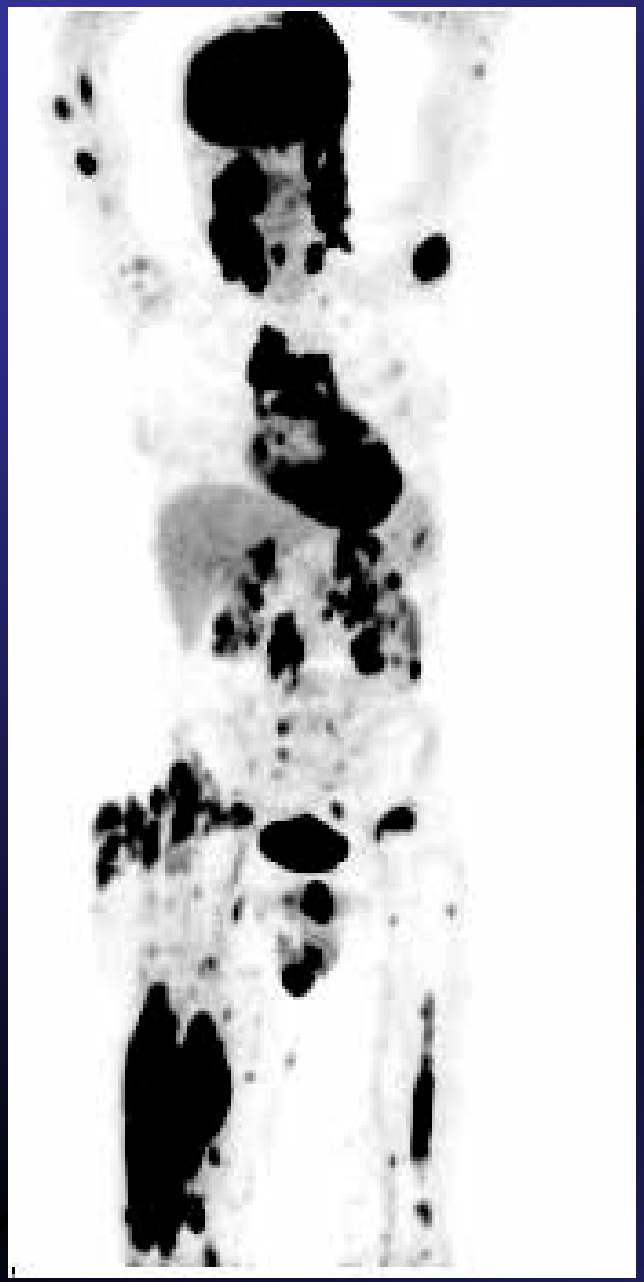
Response and Site	Induction	Intensification	Consolidation	Whole Cohort*
Complete response				
CNS	10 of 38 (26)	23 of 28 (82)	20 of 20 (100)	24 of 38 (63)
Extra-CNS	8 of 23 (35)	16 of 18 (89)	14 of 14 (100)	17 of 23 (74)
Both	9 of 38 (24)	23 of 28 (82)	20 of 20 (100)	24 of 38 (63)
Partial response				
CNS	18 of 38 (47)	1 of 28 (4)	0 of 20 (0)	0 of 38 (0)
Extra-CNS	8 of 23 (35)	1 of 18 (6)	0 of 14 (0)	0 of 23 (0)
Both	19 of 38 (50)	1 of 28 (4)	0 of 20 (0)	0 of 38 (0)
Overall response				
CNS	28 of 38 (74)	24 of 28 (86)	20 of 20 (100)	24 of 38 (63)
Extra-CNS	16 of 23 (70)	17 of 18 (94)	14 of 14 (100)	17 of 23 (74)
Both	28 of 38 (74)	24 of 28 (86)	20 of 20 (100)	24 of 38 (63)

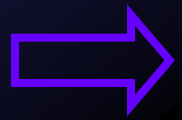


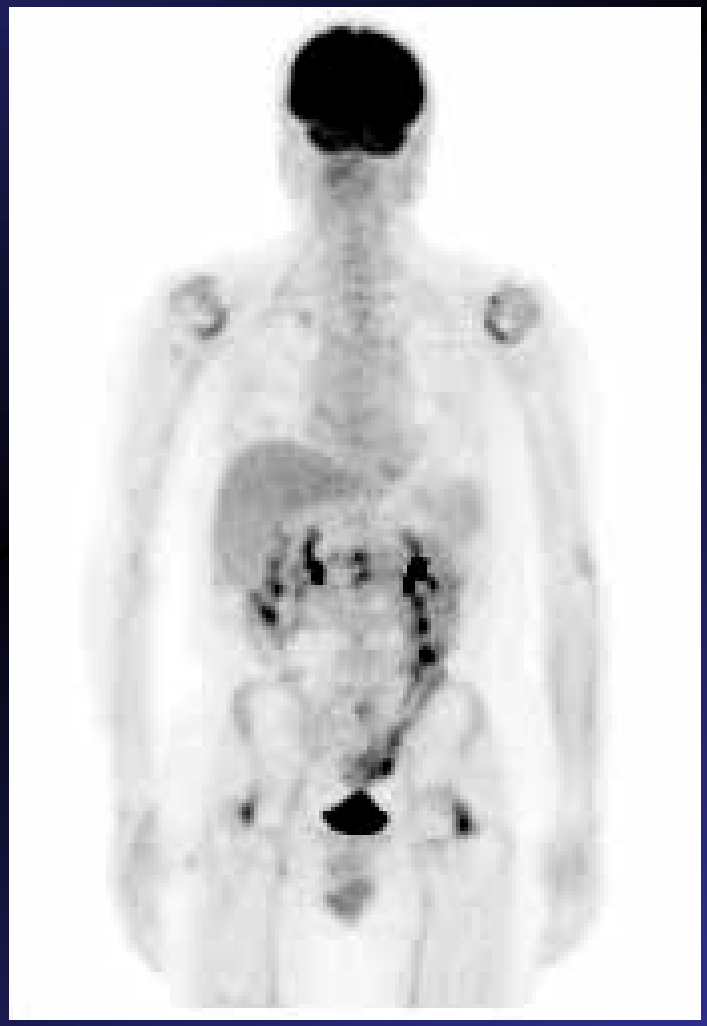






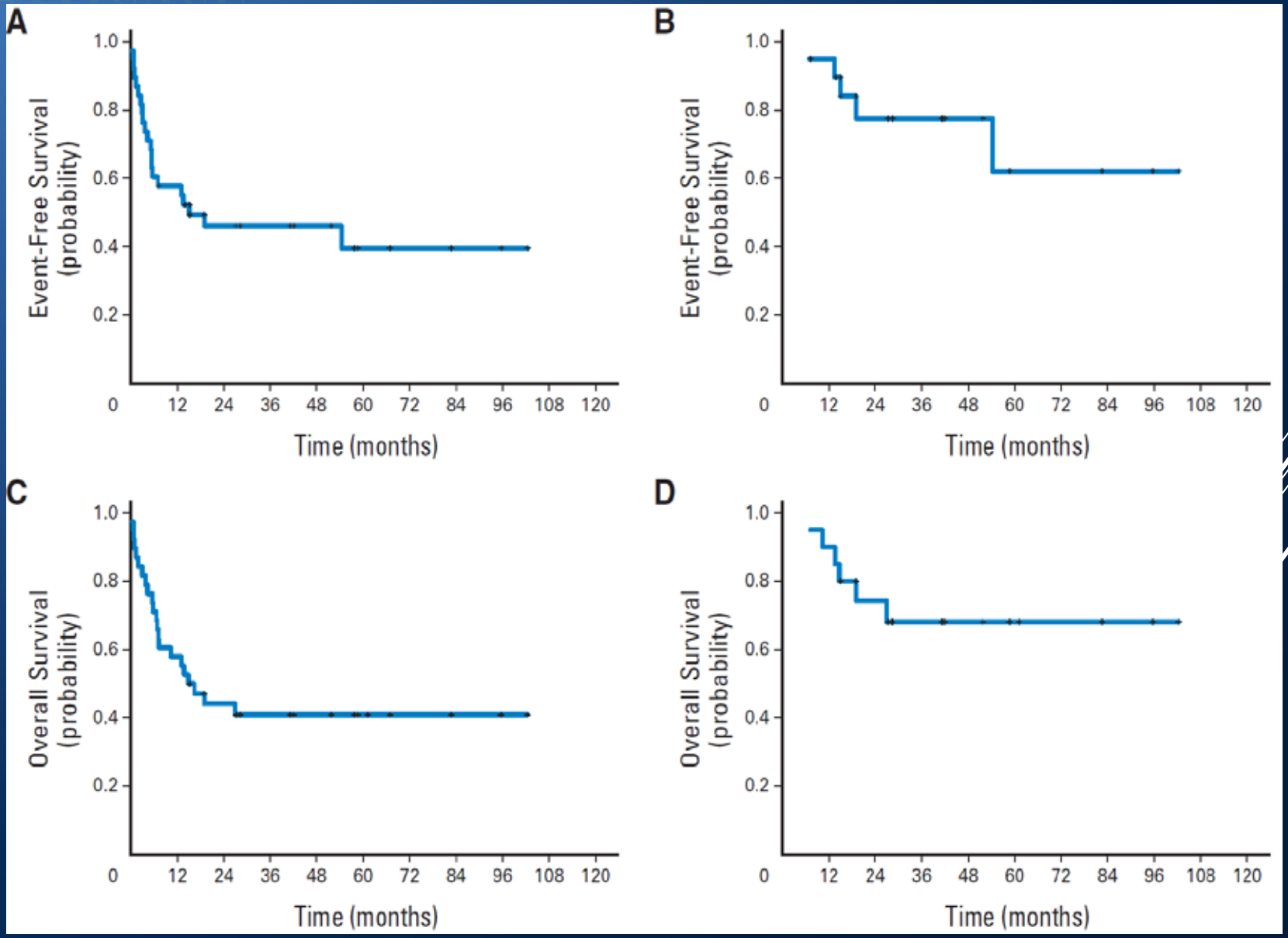






Efficacy

Median follow-up: 48 months



IELSG #42 (MARIETTA) TRIAL

((R–CHOP x 1-2 c.))

R – HD-MTX – HD-araC + it CHT

R – HD-MTX – HD-araC + it CHT

R – HD-MTX – HD-araC + it CHT

R – HD-ITX – VP16 - CBDCA + it CHT

R – HD-ITX – VP16 - CBDCA + it CHT

R – HD-ITX – VP16 - CBDCA + it CHT

HDC/ASCT

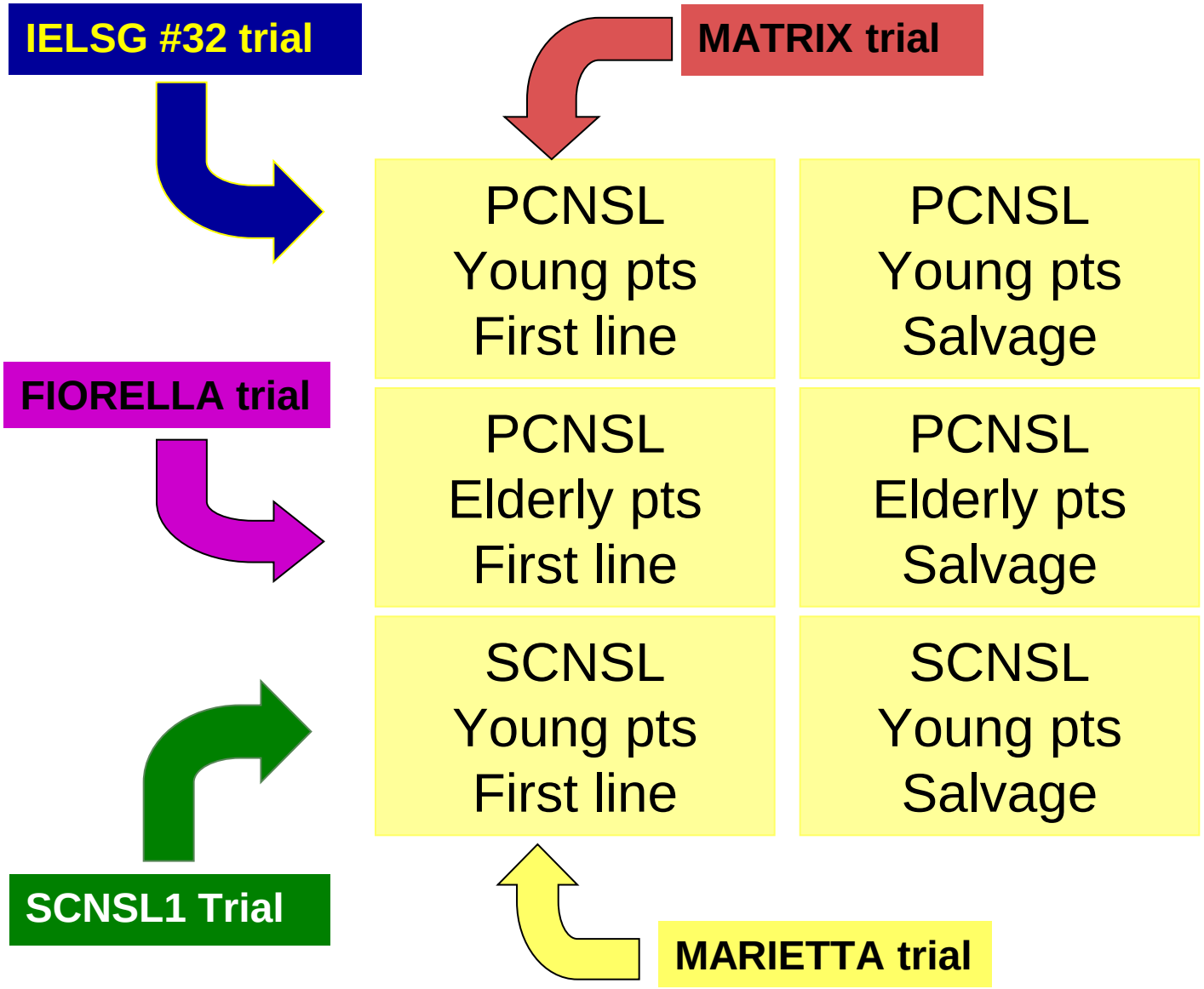
CR

< CR

Follow-up

WBRT or it CHT

EPCG trials


IELSG #32 trial
MATRIX trial
PCNSL
Young pts
First line
PCNSL
Young pts
Salvage
FIORELLA trial
PCNSL
Elderly pts
First line
PCNSL
Elderly pts
Salvage
SCNSL
Young pts
First line
SCNSL
Young pts
Salvage
SCNSL1 Trial
MARIETTA trial