Primary CNS Lymphoma

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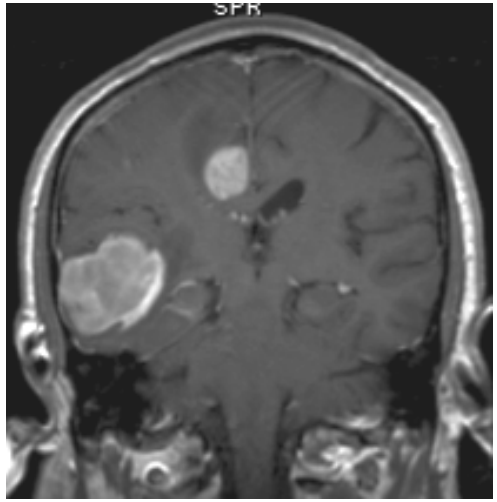
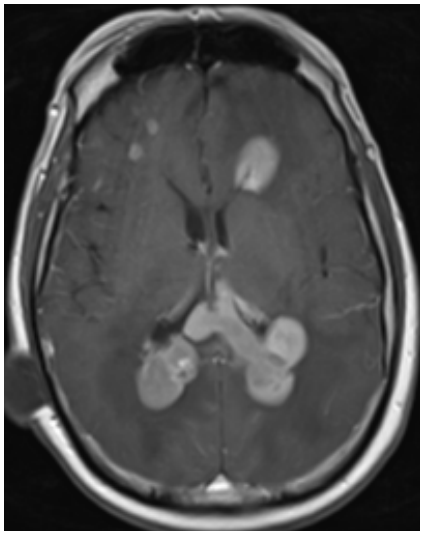
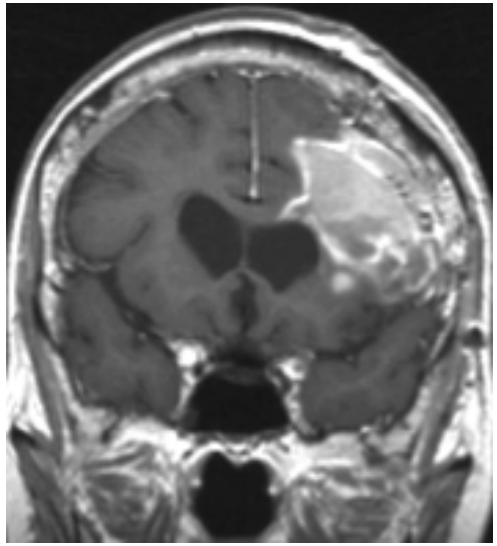
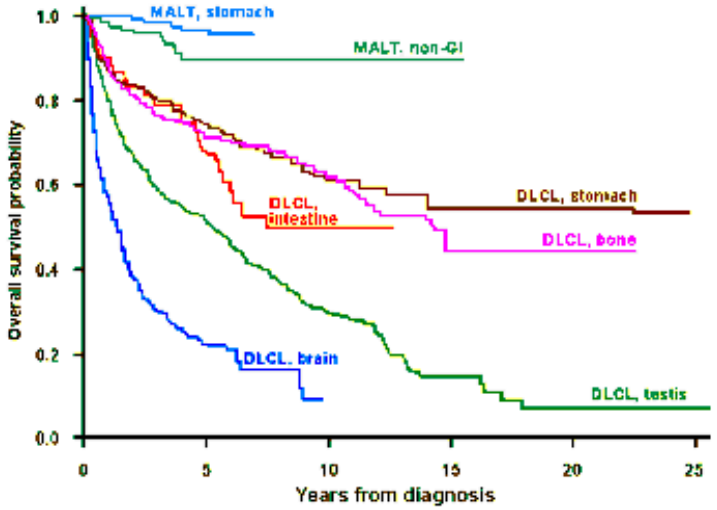
Management difficulties

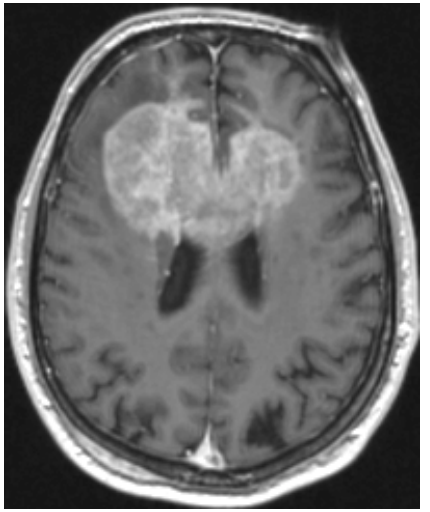


- High proportion of elderly pts
- Poor PS at presentation
- Biopsy not performed
- Palliative treatment
- Therapeutic consensus is lacking
- A few centers with adequate expertise
- Many pts can not be referred to other centers









Early Diagnosis is the Best Therapy

- Several patients receive steoids for months before biopsy:
  - Confounding effect on neuroimaging
  - Delayed and unsuitable biopsy (52% inter-observer variability)
  - Diabetes and other metabolic disorders
  - Immunodepression (severe infections)
  - Half of cases of early PD are related to interruptions due to toxicity

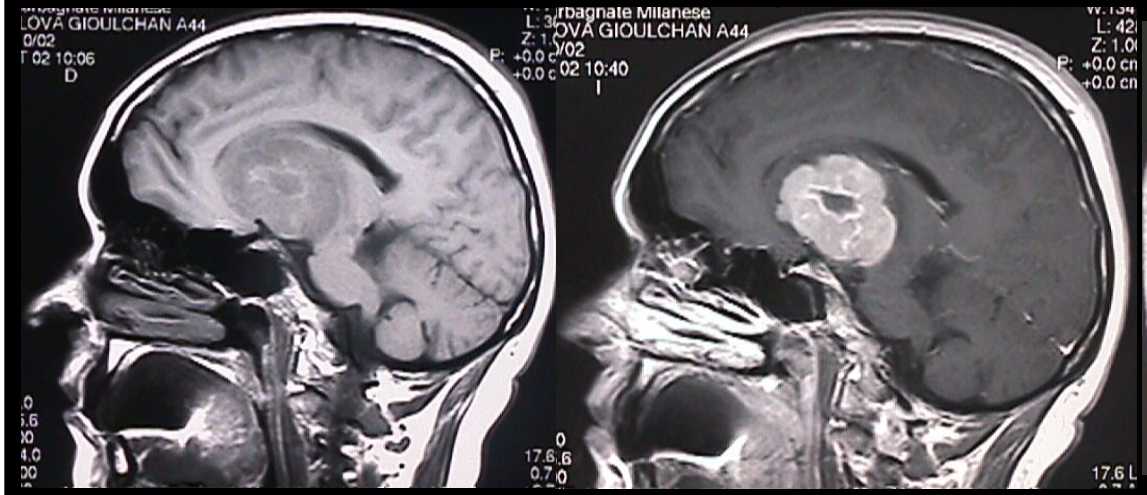
- CNS tissues exposed to lymphoma infiltration by months:
  - Tissue damage results in poor PS and disabling symptoms
  - Loss of autonomy and poor treatment tolerability
  - CR and cure do not result in neurological and PS improvement
  - Therapeutic interruptions due to poor, irreversible conditions
  - Negative effects on trials accrual

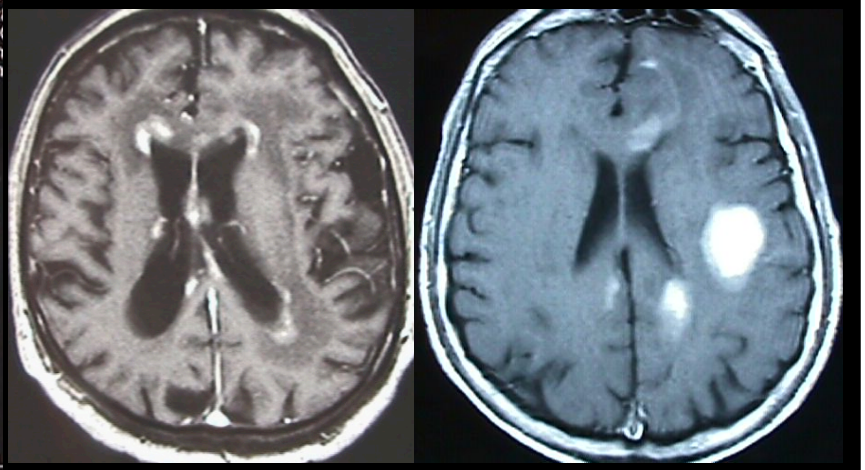
PCNSL suspicion

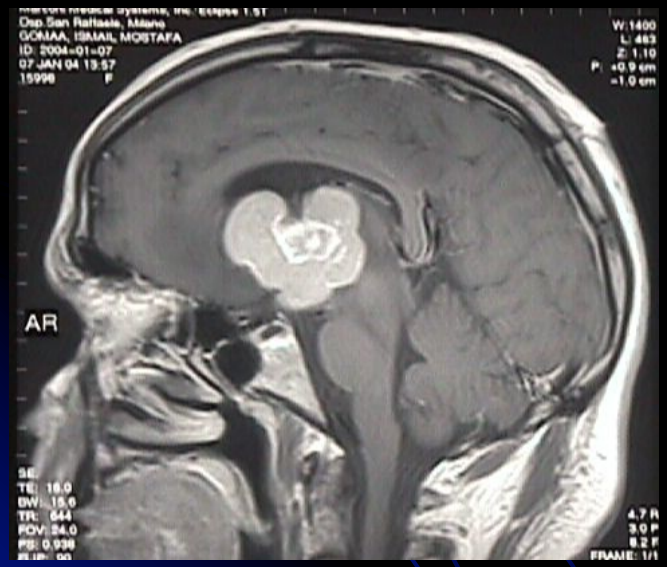
Current strategy= low diagnosis sensitivity

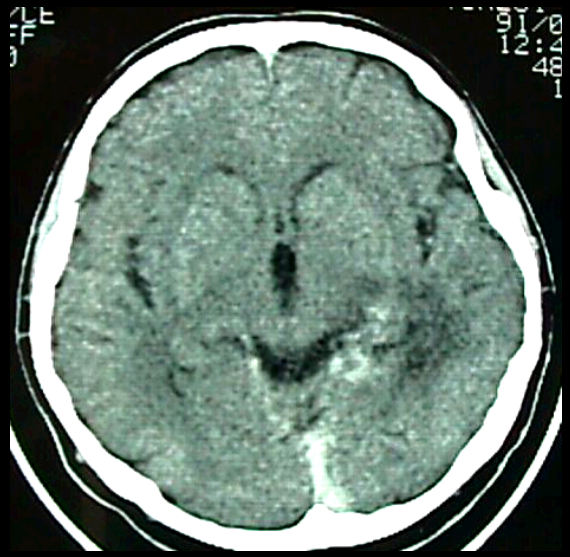
- **Neuroimaging: T1, T2, flair, DWI, enhancement, spectroscopy**
- **Site: corpus callosum , basal ganglia, periventricular areas, …**
- **Response to steroids**

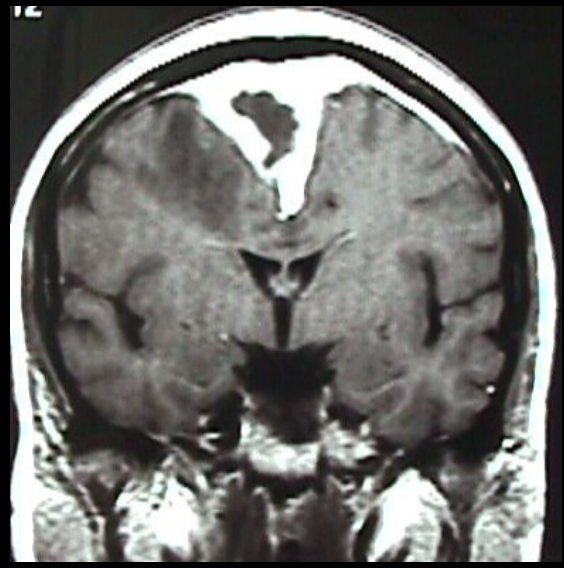
Neuroimaging

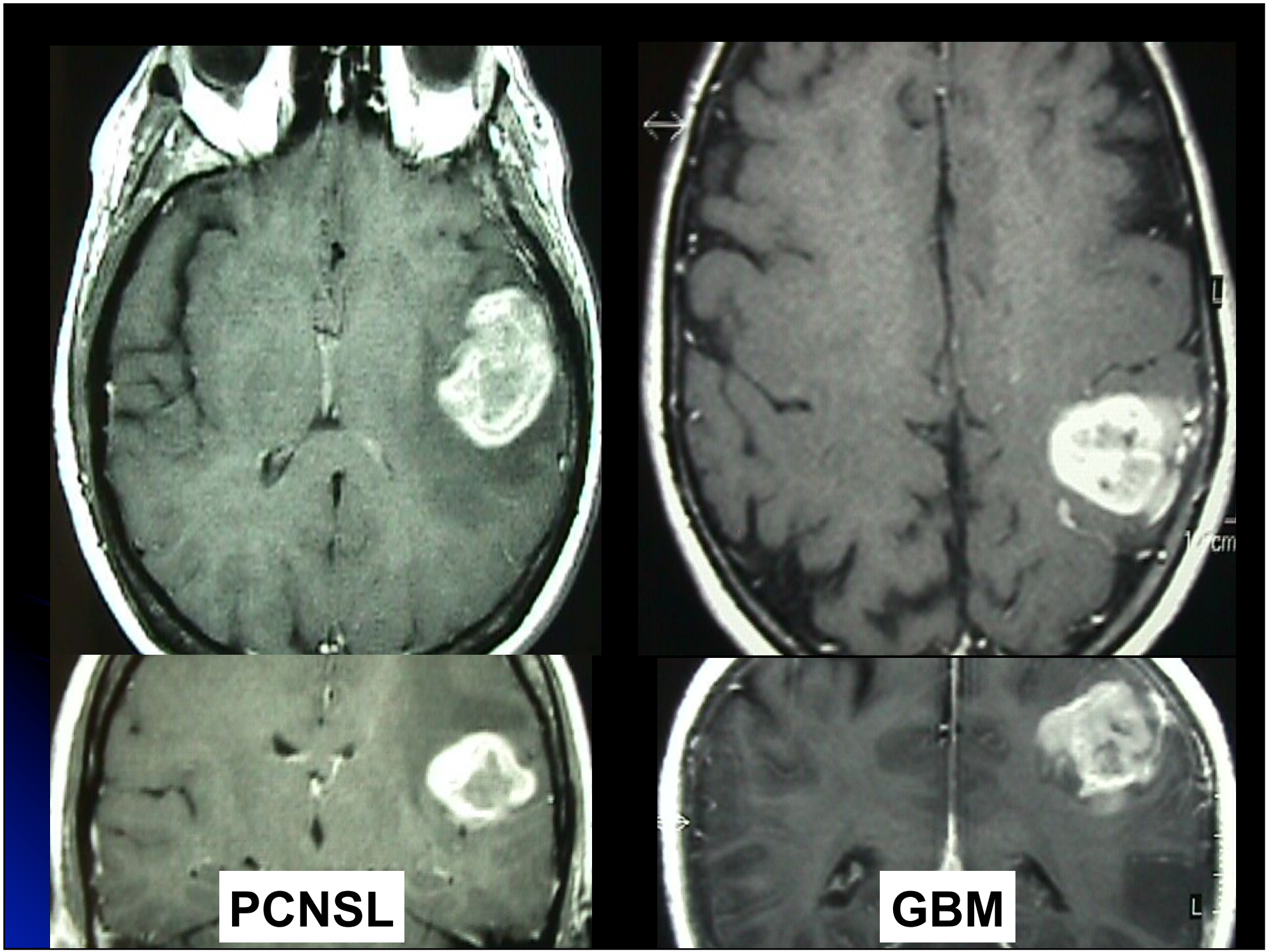




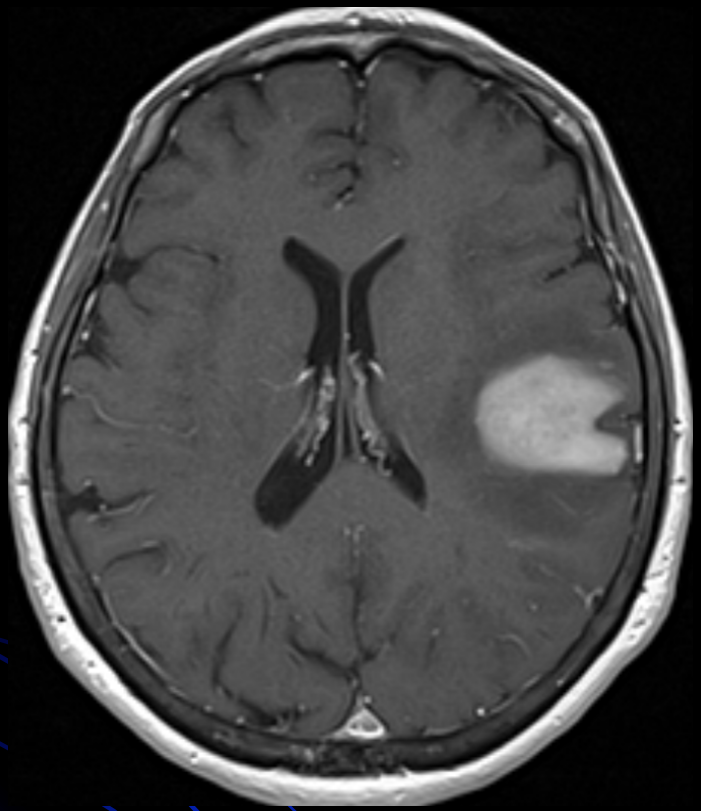






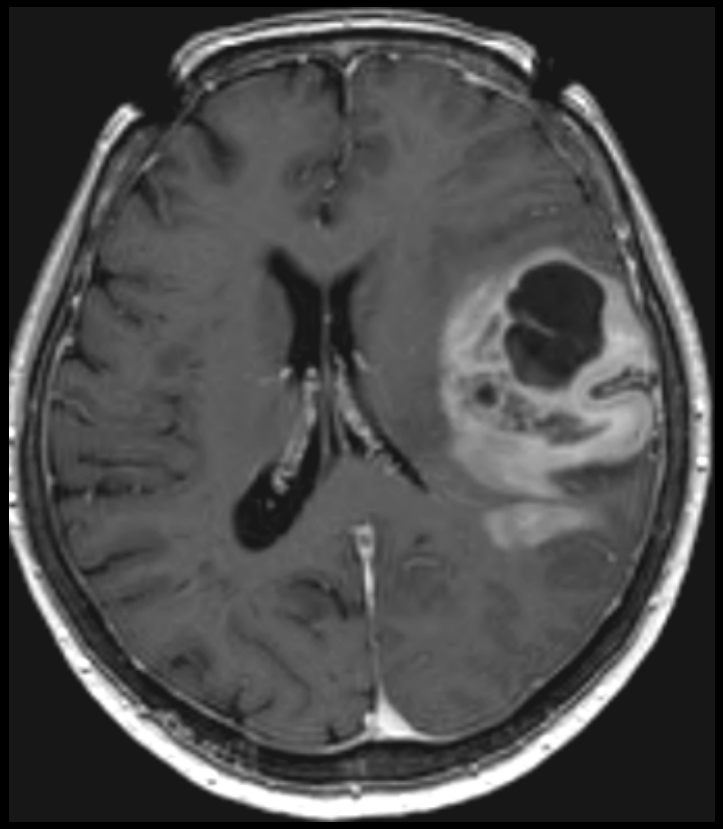

PCNSL
GBM

Response to Steroids



Lymphoma

Bp: no tumor



Response to steroids

Bp: Glioblastoma multiforme

Response to Corticosteroids

Is a "vanishing tumor" always a lymphoma?

Abstract—The authors report clinical and radiologic characteristics and ultimate diagnosis in 12 patients with a regressing cerebral mass lesion. Primary CNS lymphoma (PCNL) was found in only half of the patients with such a lesion. In patients showing a complete resolution of the enhancing lesion the probability of finding a PCNL is smaller and survival is longer.

NEUROLOGY 2002;59:762–764

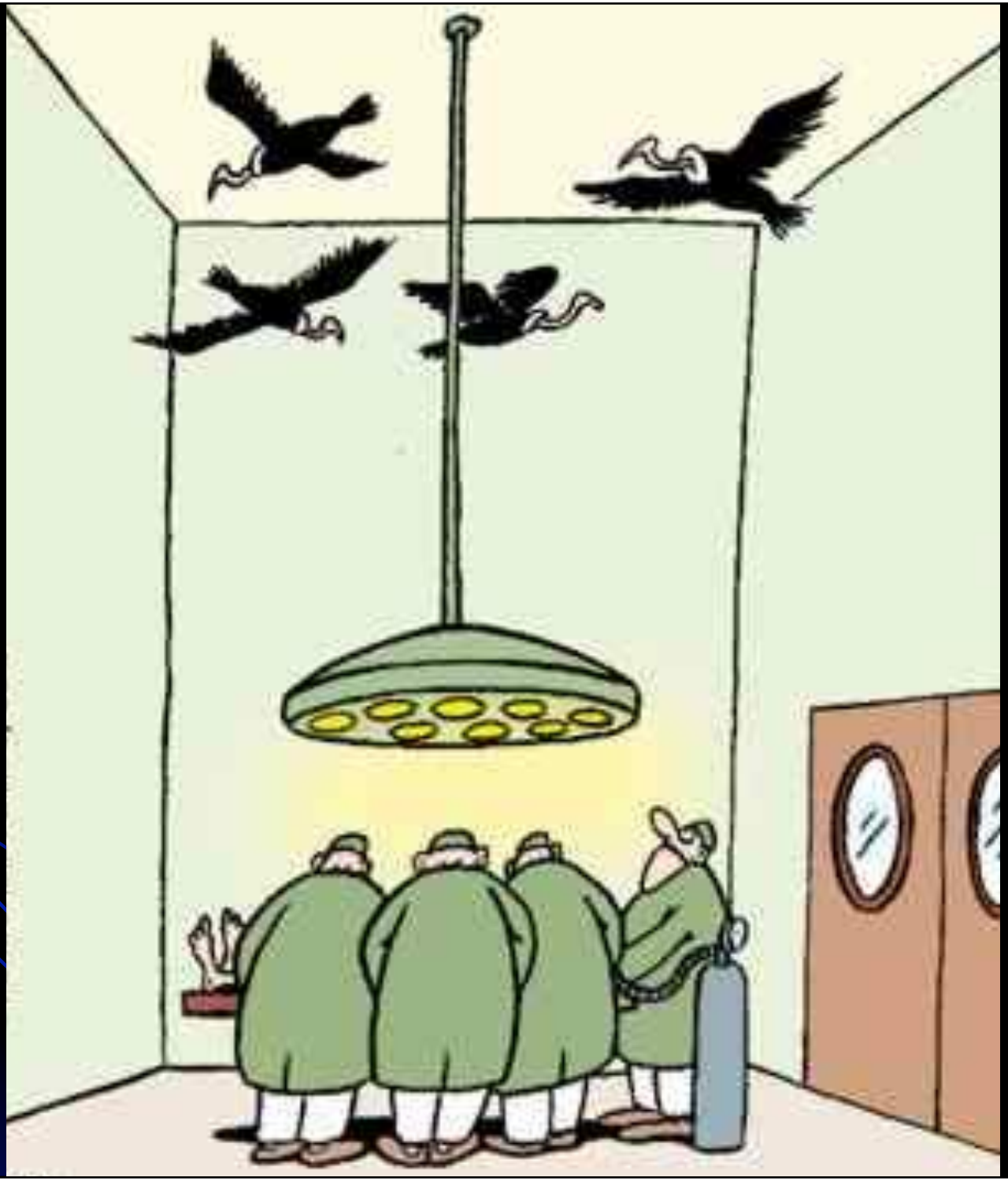
J.E.C. Bromberg, MD; M.D. Siemers, MD; and M.J.B. Taphoorn, MD

- Multiple sclerosis
- Acute disseminated encephalomyelitis
- Cerebral infarction
- Neurosarcoidosis
- Germinoma
- Renal cell carcinoma metastases
- Prolactinoma
- Hemangioma

Early Reliable Suspicion

- ✓ Reliable molecular and biological parameters that can be easily incorporated in routine practice.
- ✓ Some chemokines (CXCL13) can be used as diagnostic & prognostic tools.
- ✓ IL-10 concentration in the CSF is a useful diagnostic and prognostic biomarker.
- ✓ Some miRNA (21, 19b, 92a) are expressed in the CSF of PCNSL patients, with a diagnosis sensitivy and specificity >95%
- ✓ Recurrent mutations of *CD79B* (83%) and *MYD88* (76%) in tissue samples.
- ✓ *MYD88* mutations can be detected in the vitreous and plasma (CSF?).
- ✓ The combined use of ADC, CSF CXCL13, and IL-10 results in increased diagnostic performance in CNSL.

Rubenstein J, et al. Blood 2013; Fisher L, et al. CCR 2009;
Nguyen-Them L, et al. EJH 2016; Baraniskin A, et al. Blood 2011; Bonzheim I, et al. Blood 2015;
Fontanilles et al. ASH 2015; Nakamura T, et al. Neuropathol Appl Neurobiol 2016; Mabray MC, et al. AJNR 2016



Modern Approach

Age & PS

Comorbidity

Prognostic score

Histotype (DLBCL)

Induction

Response

Quality response

INDUCTION

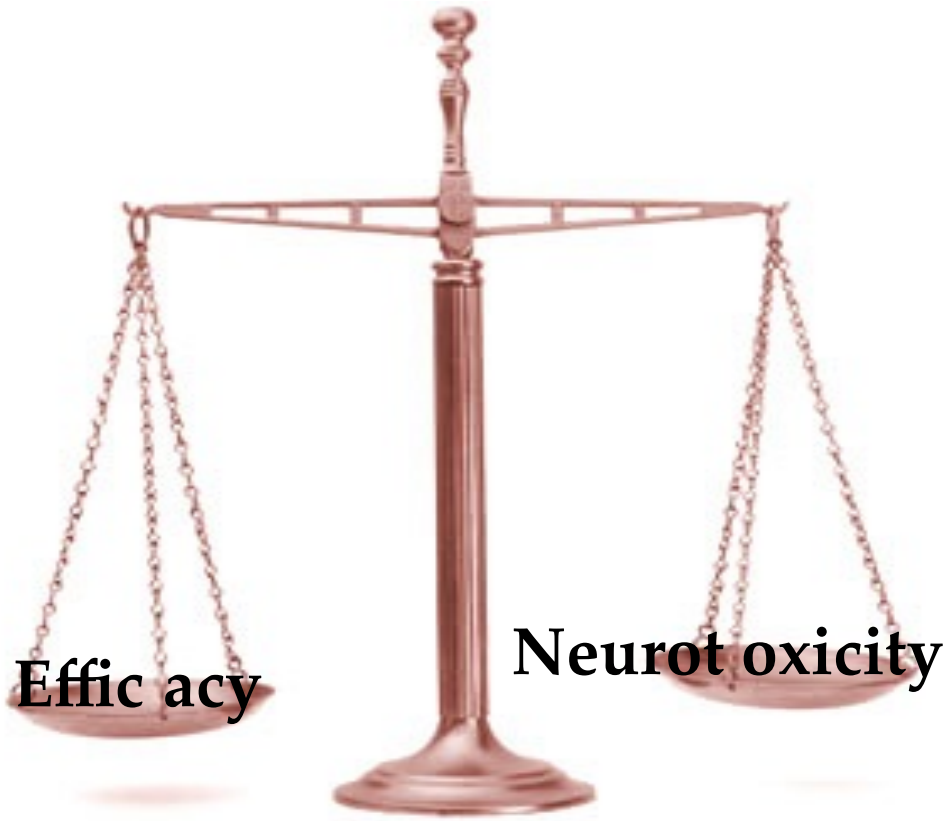
- HD-MTX poly
- WBRT
- Others

CONSOLIDATION

- Observation
- WBRT
- HDC/ASCT
- Non-myeloablative
- Maintenance

Updated from Ferreri AJM, ASCO 2012

Therapeutic Dilemma



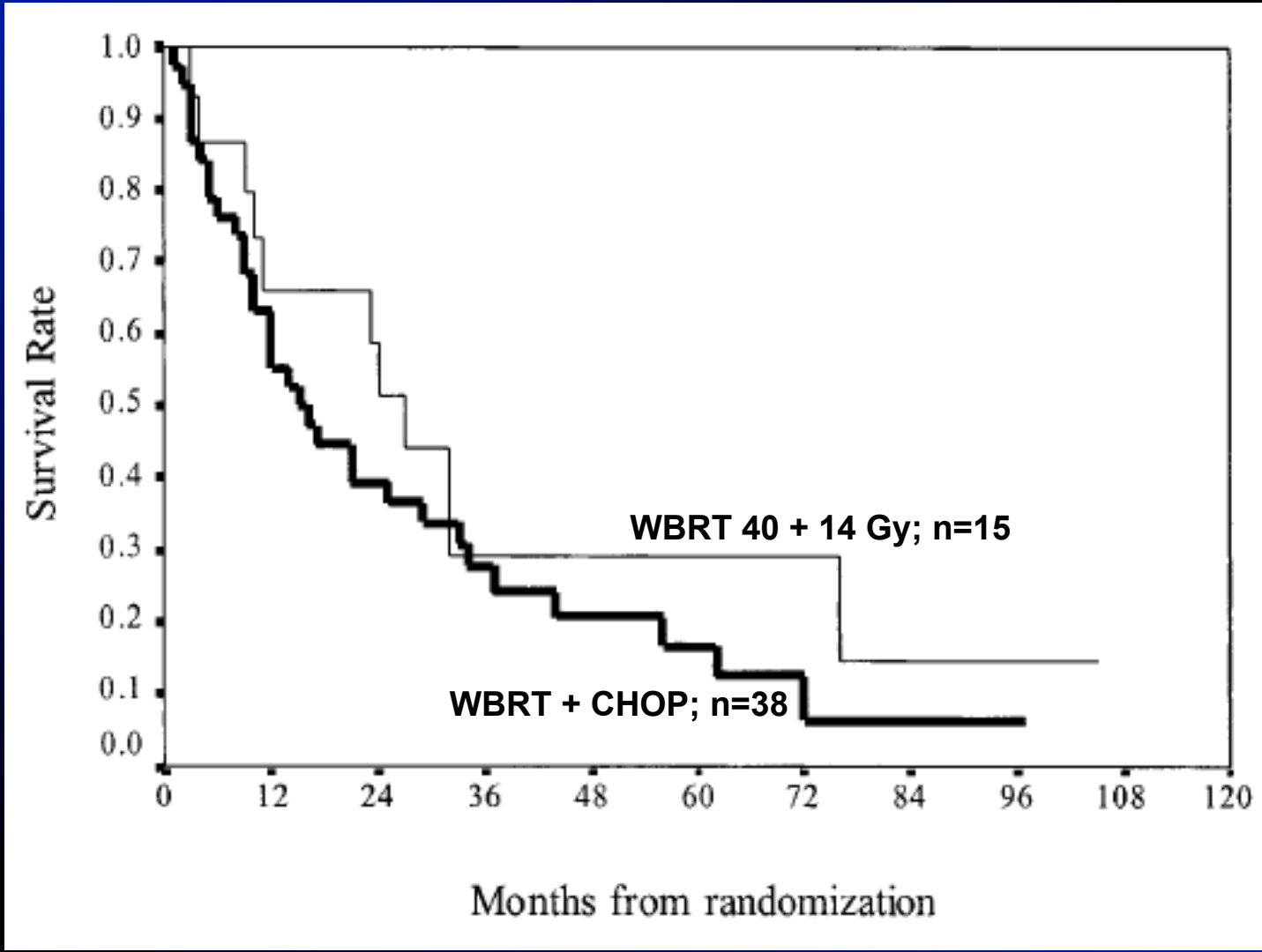
the dilemma posed by PCNSL treatment is the choice between strategies designed to intensify therapy to improve cure rate and treatment de-escalation strategies to avoid neurotoxicity.

Chemotherapy

Its efficacy is limited by several factors including the biology and microenvironment of this malignancy, which is "protected" by the BBB.

BBB penetration	Doses	CNS availability	Examples
Good	conventional	good	steroids, alkylating ag.
Low to moderate	high	good	MTX, araC
Poor	conventional (-limiting tox)	low	anthracyclines, vinca-alkaloids

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	≥ 3 g/m^2

CNS availability

≥ 1 g/m^2	tumoricidal levels in the brain
≥ 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

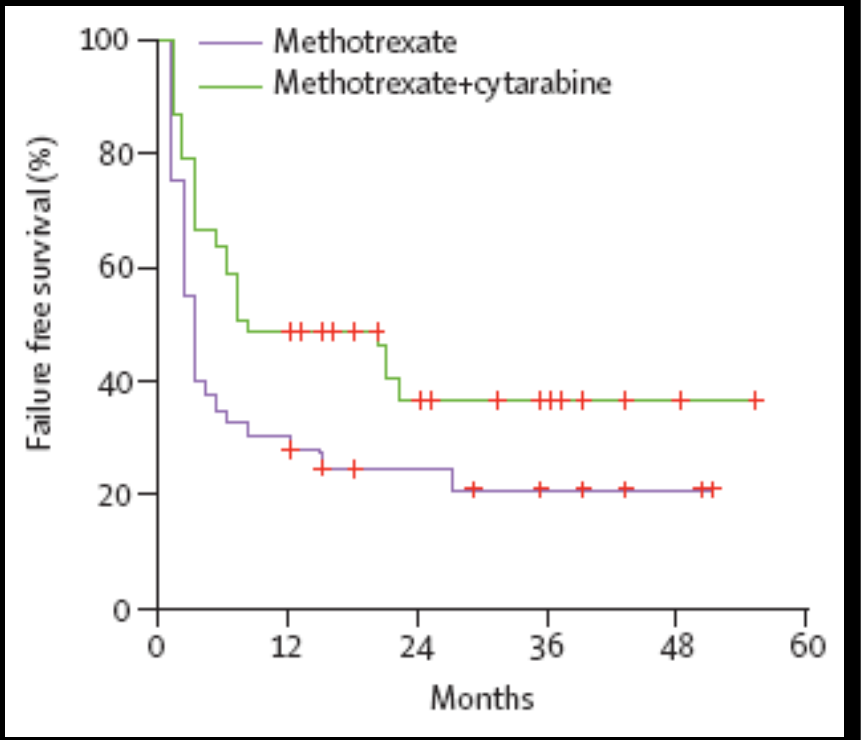
High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

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, Ma[illegible] Franco Cavalli, on behalf of the International Extranodal Lymphoma Study Grou[illegible]

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

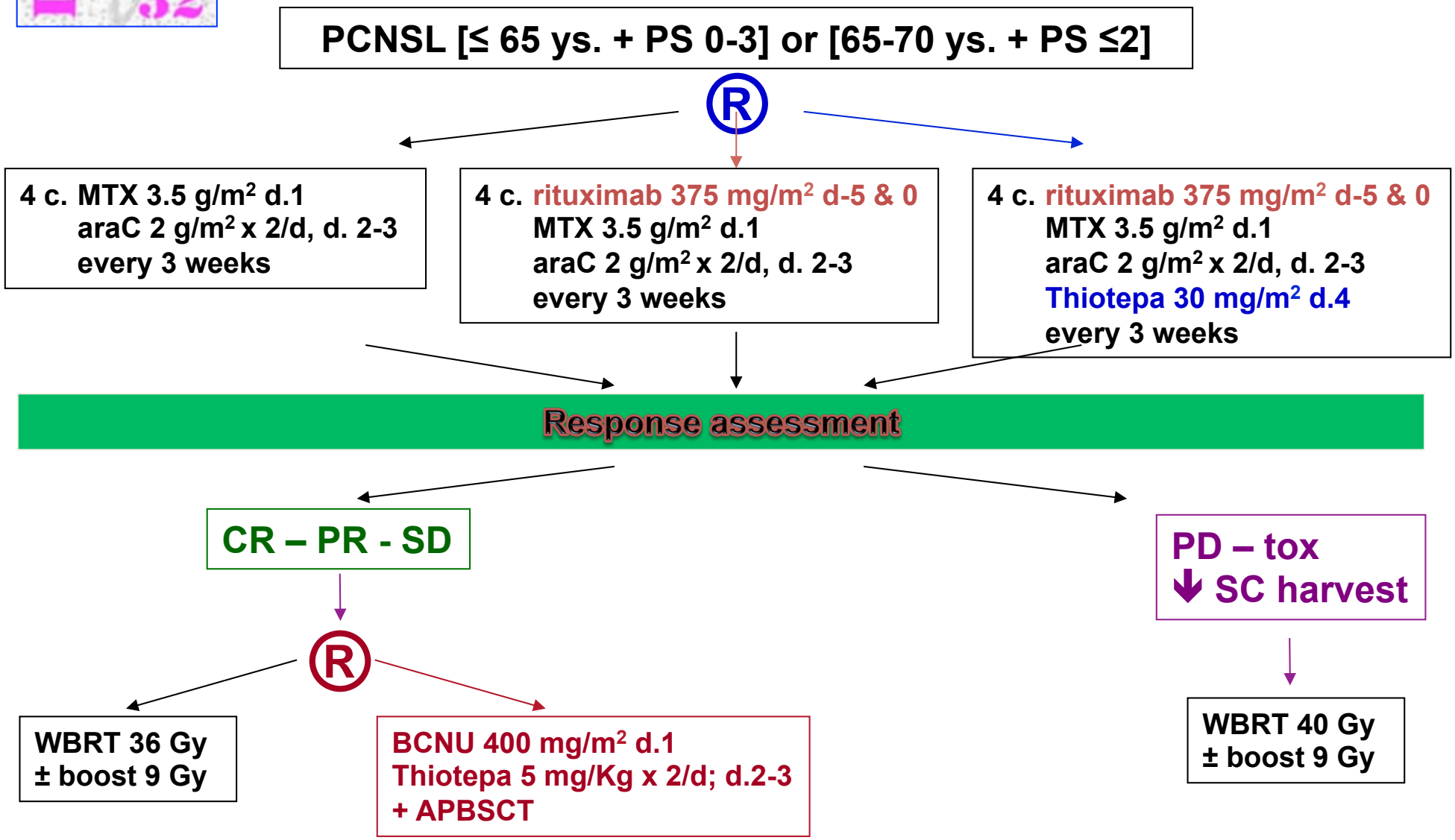


MTX + Alkylator + Rituximab

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%

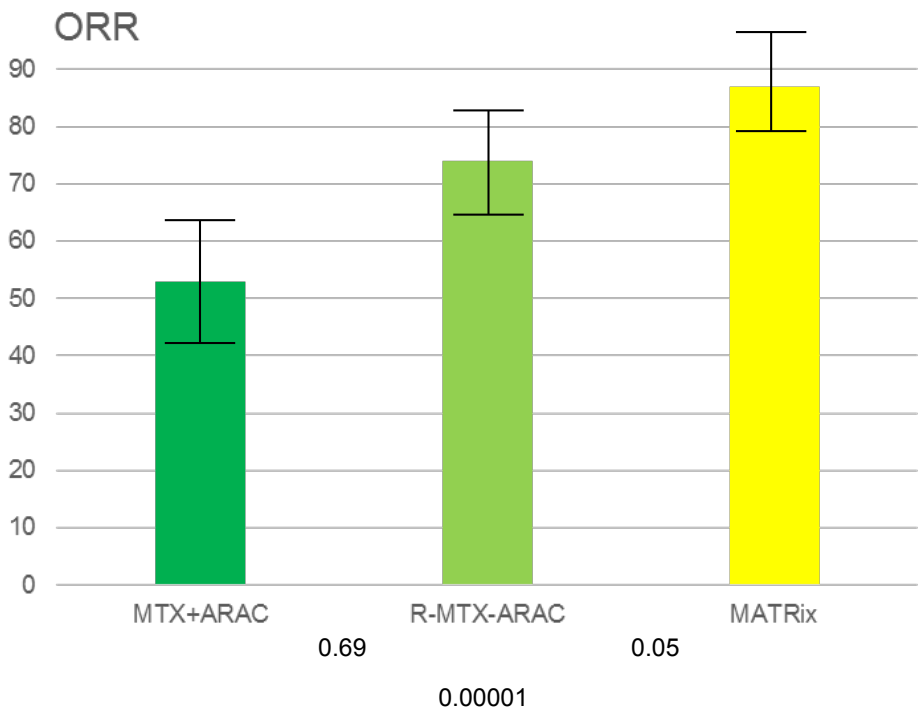
[1]Morris PG, et al. JCO 2013; [2]Omuro A, et al. Blood 2015; [3]Rubenstein JL, et al. JCO 2013; [4]Glass J, et al. JCO 2016

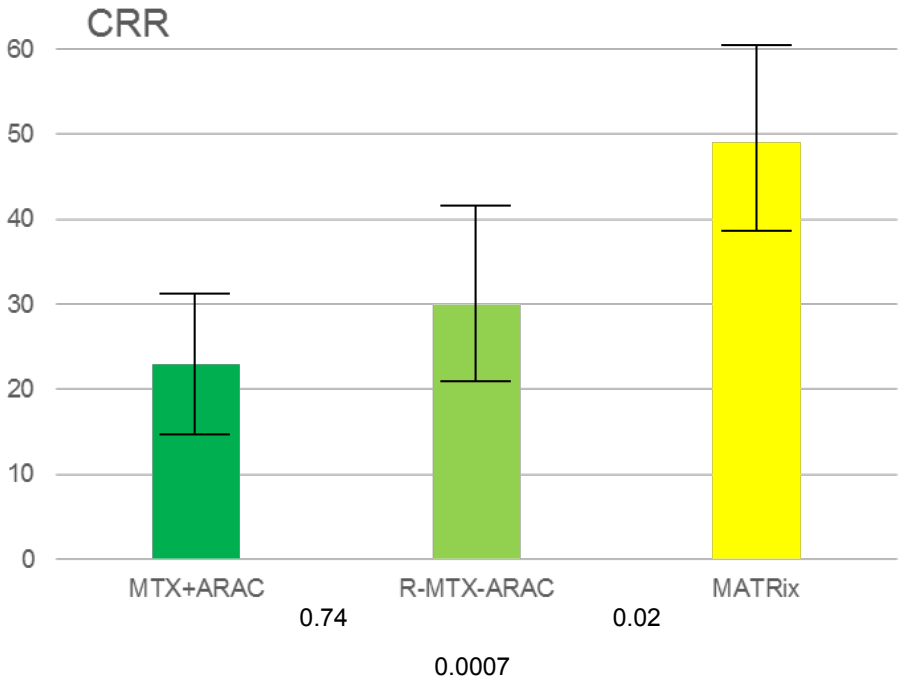
The IELSG #32 trial



Ferreri AJM, et al. 13-ICML, Lugano 2015

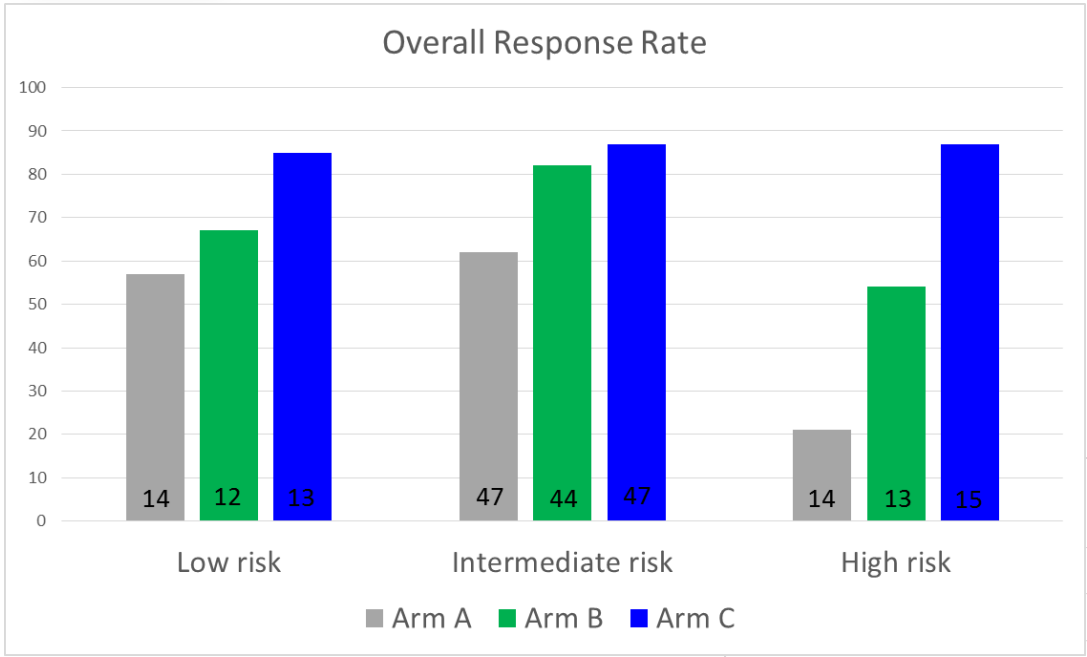
Arms Activity

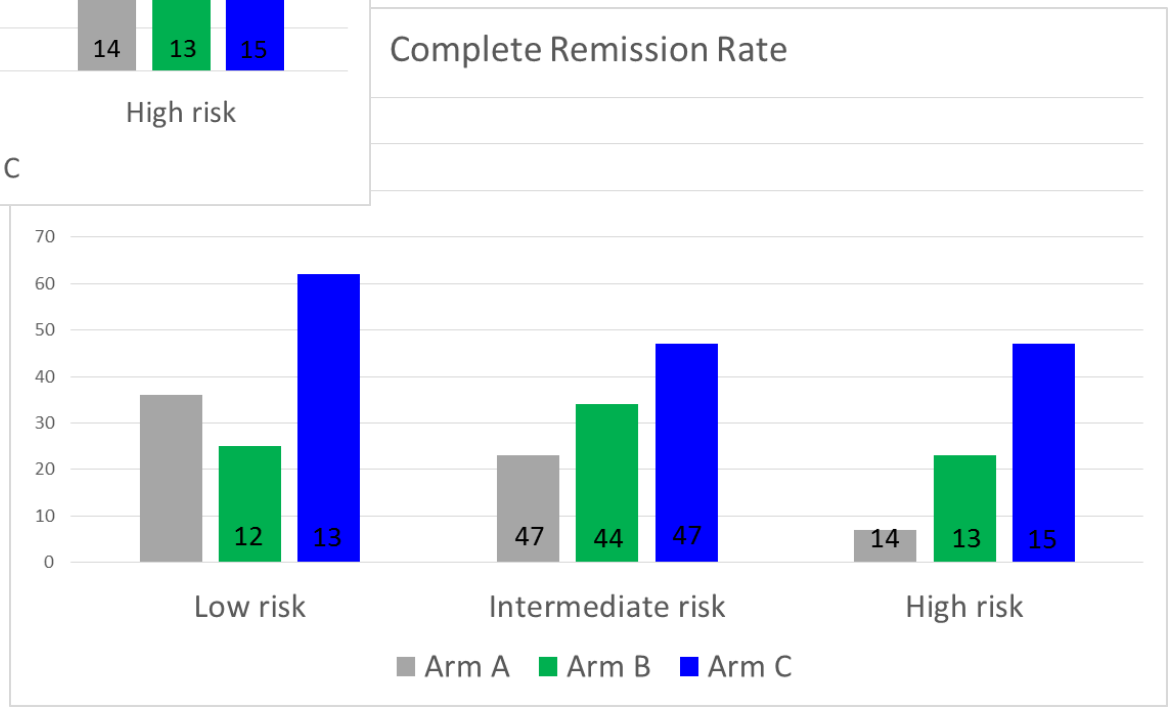




Ferreri AJM, *et al*. Lancet Haematol 2016

Activity: Arm and IELSG risk

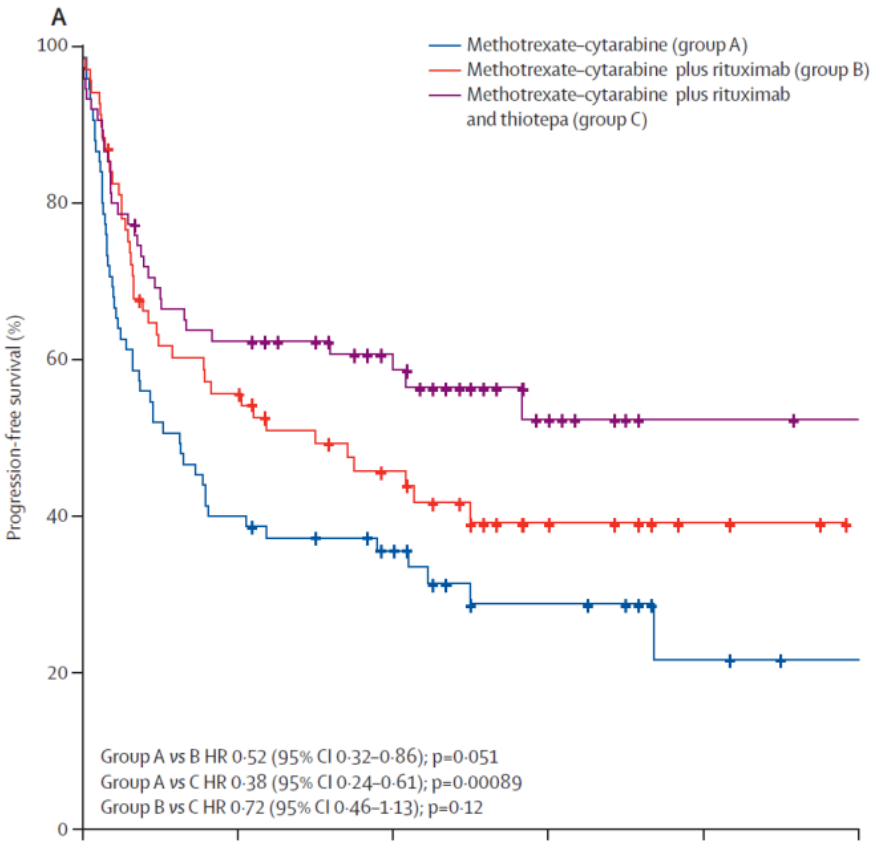


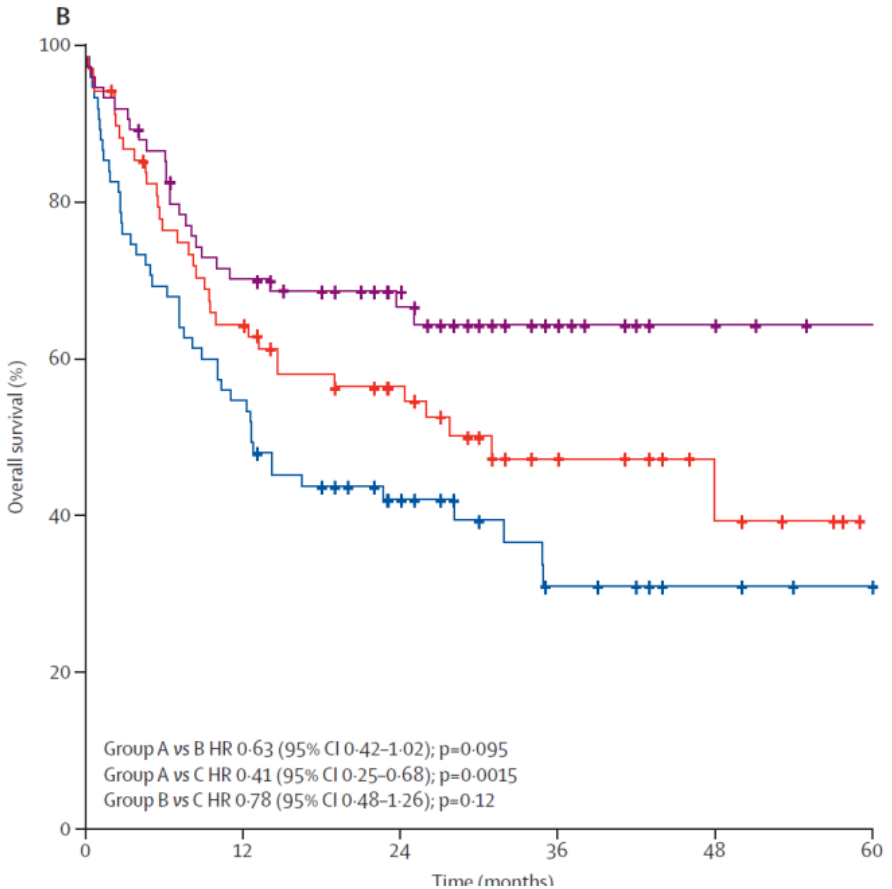


Logit	CR	OR
IELSG risk score	0,13	0,09
Arm	0,0004	0,000004

PFS and OS

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





Ferreri AJM, *et al*. Lancet Haematol 2016

Chemotherapy: Elderly Patients

- ✓ HD-MTX improved outcome in selected pts (biased results).

Table 3. Reported studies focused on elderly patients with PCNSL

Ref.	N	Median age, y (range)	MTX, g/m²	Other drugs	IT	WBRT	PFS, mo
43	23	68 (60-79)	3	Te	No	No	8
66	10	73 (66-75)	8	—	No	No	18
	22	70 (54-89)	3.5	O, P	Yes	No	NR
79	12	67 (60-72)	3.5	O, P	Yes	Yes	NR
93	13	76 (54-89)	1-3.5	A, O, P, T	Yes	No	NR
94	50	72 (60-81)	1	CN, P, S	Yes	No	7
95	30	70 (57-79)	3	CN, P	No	No	6
96	17	67 (58-78)	1	MCN, P, S	Yes	No	20

The age upper limit to define elderly pts remains uncertain.

Ferreri AJM. Blood 2011

AGE ≥ 60 YEARS

Elderly Pts: PHRC 2006 Trial

Arm A M-PVA

3 cycles/ 28 d

Procarbazine 100 mg/m²/d
D1-7

Vincristine 1,4 mg/m² D1
MTX 3,5 g/m² d1

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

Vincristine 1,4 mg/m² D1
MTX 3,5 g/m² d1

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

Methylprednisolone
60 mg/d 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*

Methylprednisolone
60 mg/d D1-5

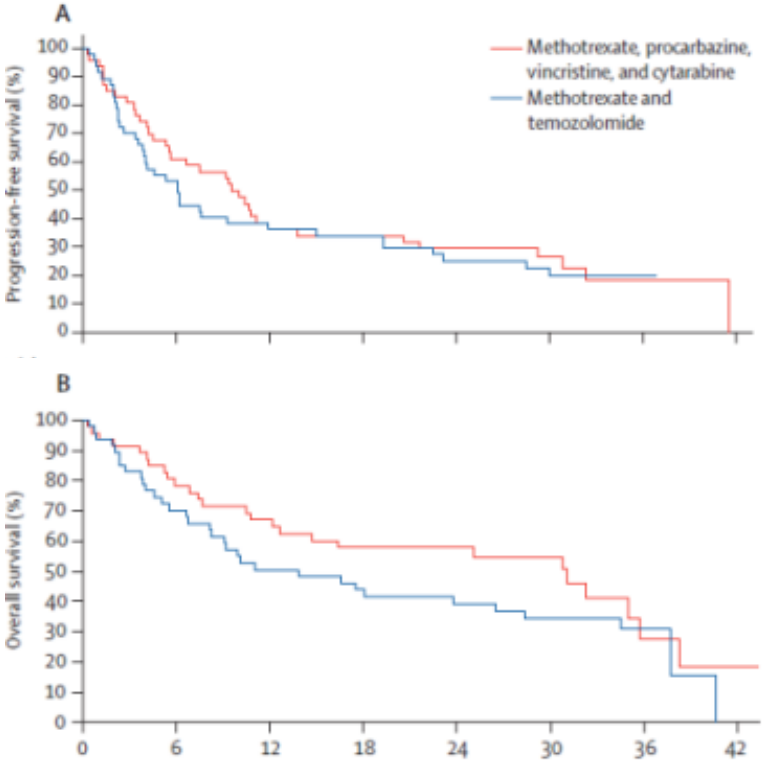
Omuro A, *et al.* Lancet Haematol 2015

AGE ≥ 60 YEARS

PHRC 2006 Trial

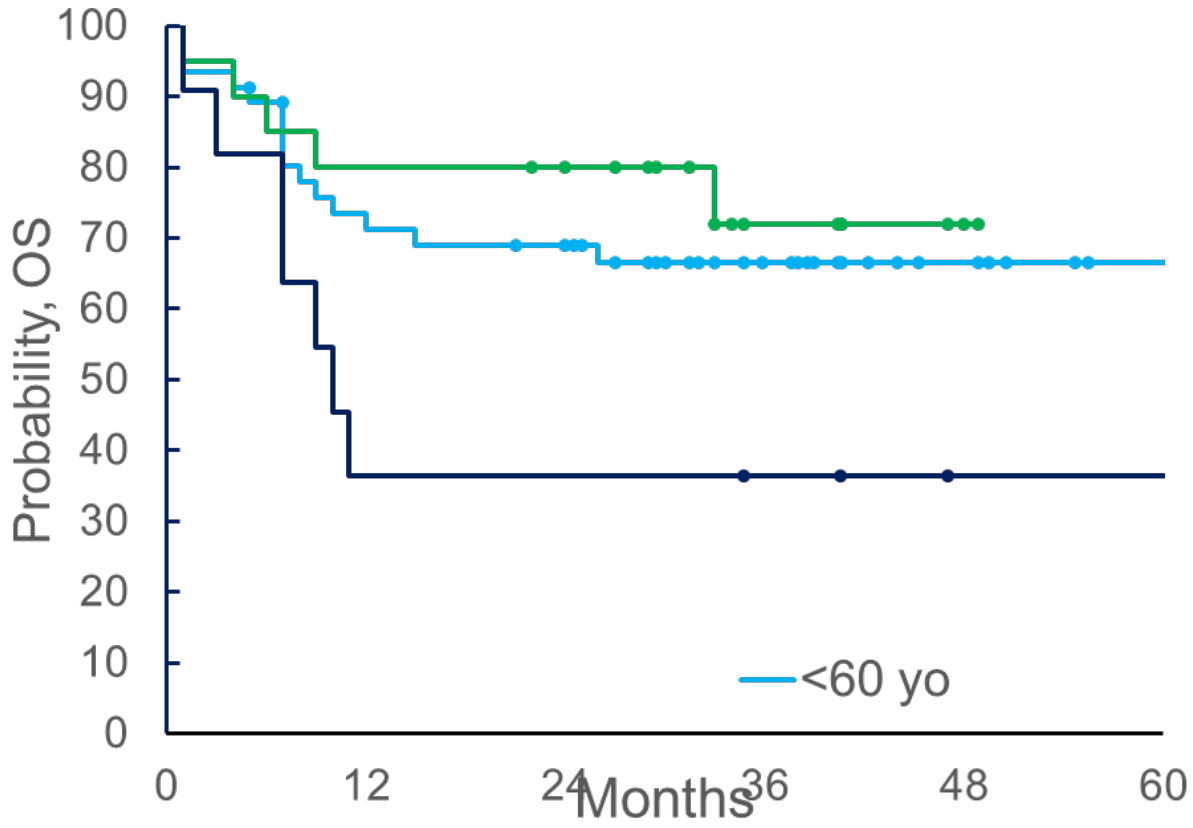
	Methotrexate with temozolomide (n=48)	Methotrexate, procarbazine, vincristine, and cytarabine (n=47)
Grade 3 or 4 toxicities		
Non-haematological		
Liver dysfunction	21 (44%)	18 (38%)
Infection	6 (13%)	7 (15%)
Sepsis	3 (6%)	0
Renal	2 (4%)	3 (6%)
Cardiac	1 (2%)	0
Fatigue	1 (2%)	0
Peripheral neuropathy	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**



Omuro A, *et al.* Lancet Haematol 2015

Age effect on MATRix

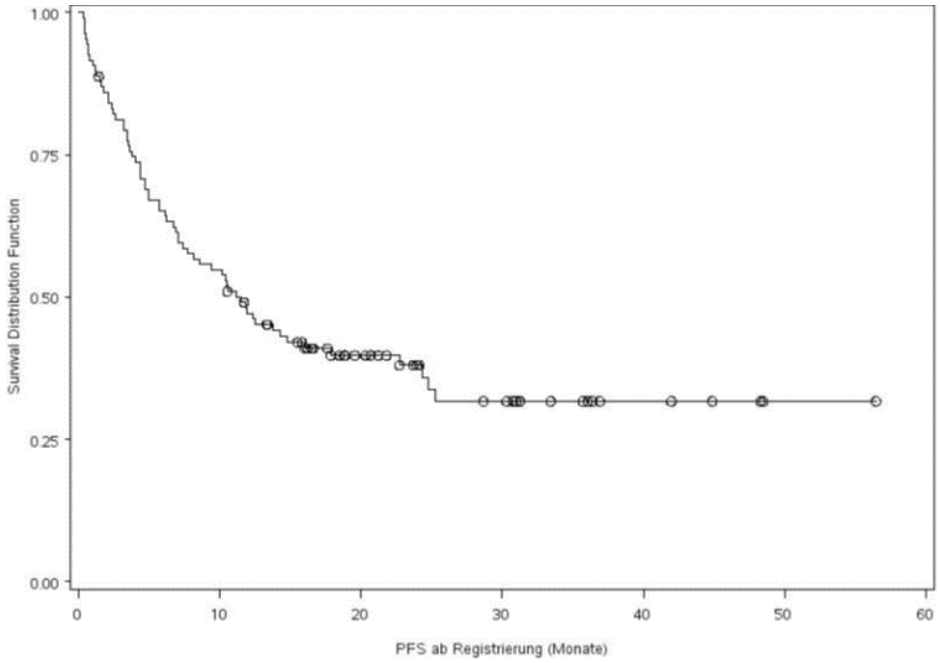


AGE ≥ 65 YEARS

Elderly pts: PRIMAIN Trial (n= 108)

Primary chemoimmunotherapy (PRIMAIN regimen, 2 courses; every 35 days)			
Rituximab	375 mg/m^2	standard infusion	days -5, 0, 15 & 30
Methotrexate	3 g/m^2	0.5 g/m^2 in 15 min. + 2.5 g/m^2 in 3-hr inf.	days 1, 15 & 30
Procarbazine	60 mg/m^2/d	oral	days 1 to 10
Procarbazine maintenance (6 courses; every 4 weeks)			
Procarbazine	100 mg/d	oral	days 1 to 5

Best response	Values
CR	46 (42.6%)
PR	34 (31.5%)
PD	12 (11.1%)
SD	1 (0.9%)
Missing	15 (13.9%)



Kindly provided by G. Illerhaus and B. Kasenda

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 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

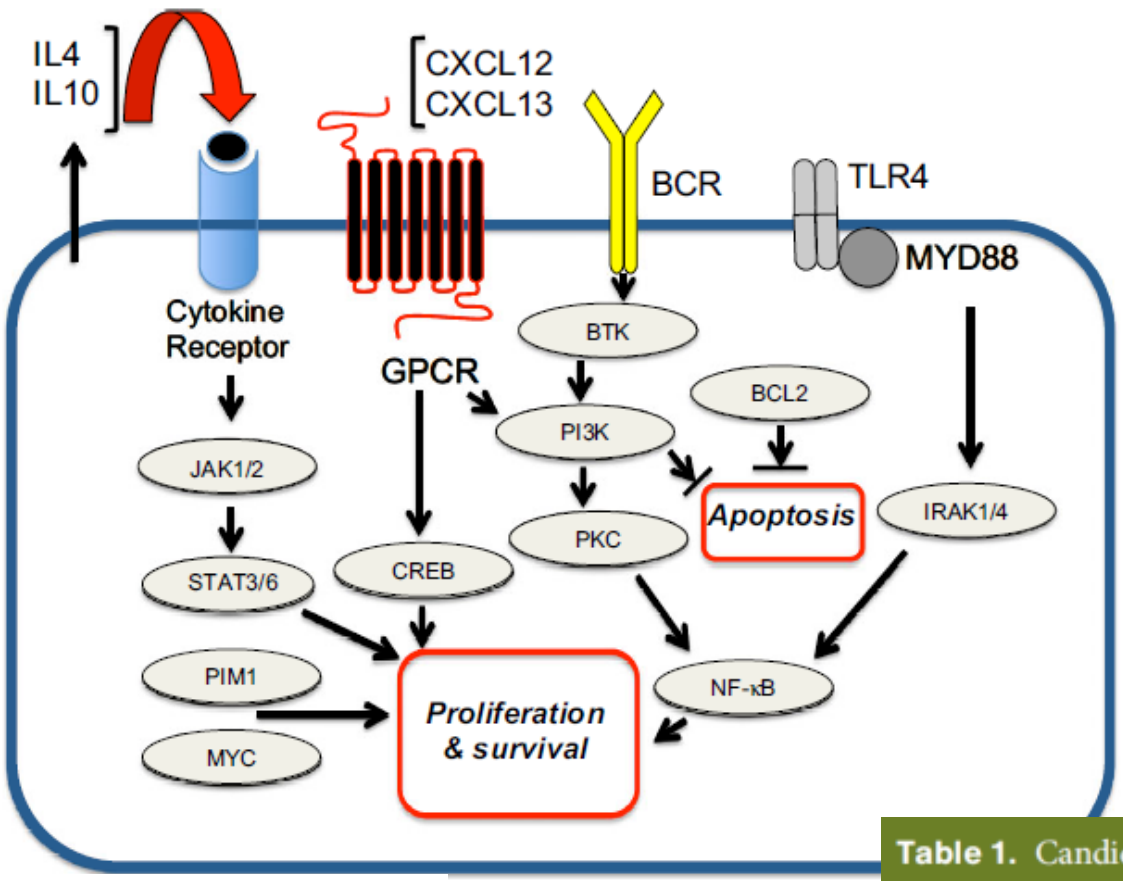
High-dose Ifosfamide

	R-IE (n= 22)	VIA (n= 16)	ICE (n= 17)	ICED (n=25)	De-VIC
Line	Salvage	Salvage	Salvage	Salvage	First
ITX (g/m^2/d)x[days]	2 x [3]	1 x [5]	5 x [1]	1.5 x [5]	1,5 x [3]
Other drugs	R, VP16	araC; VP16	CBDCA; VP16	CBDCA; VP16	CBDCA; VP16
Previous chemo	MA	CHOD, MA	MA	M	-
Pre-irradiated pts	55%	100%	NR	27%	-
Median age	60 (39-72)	54 (31-69)	62 (28-84)	58 (20-73)	61 (19-79)
Refractory (mPFS)	50% (8 mo)	6% (19 mo)	24% (12 mo)	36% (12 mo)	0
Dose reduction	0%	NR	24%	NR	NR
NF (TRM)	14% (5%)	50% (0%)	53% (6%)	NR (8%)	10% (0%)
ASCT	20%	0%	35%	52%	NA
CRR	27%	37%	76% (ASCT)	48%	62% (2c.)
mPFS	4.0 mo	4.5 mo	2.6 mo	11 mo	37 mo
mOS	6.0 mo	6.0	7.3 mo	27 mo	48 mo

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

Salvage Single-Agent in Trials

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%
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 Raizer JJ, et al. Cancer 2012	11	55%	6	63%	50%	13%
Temsirolimus Korfel A, et al. JCO 2016	37	54%	2	20%	22%	14%



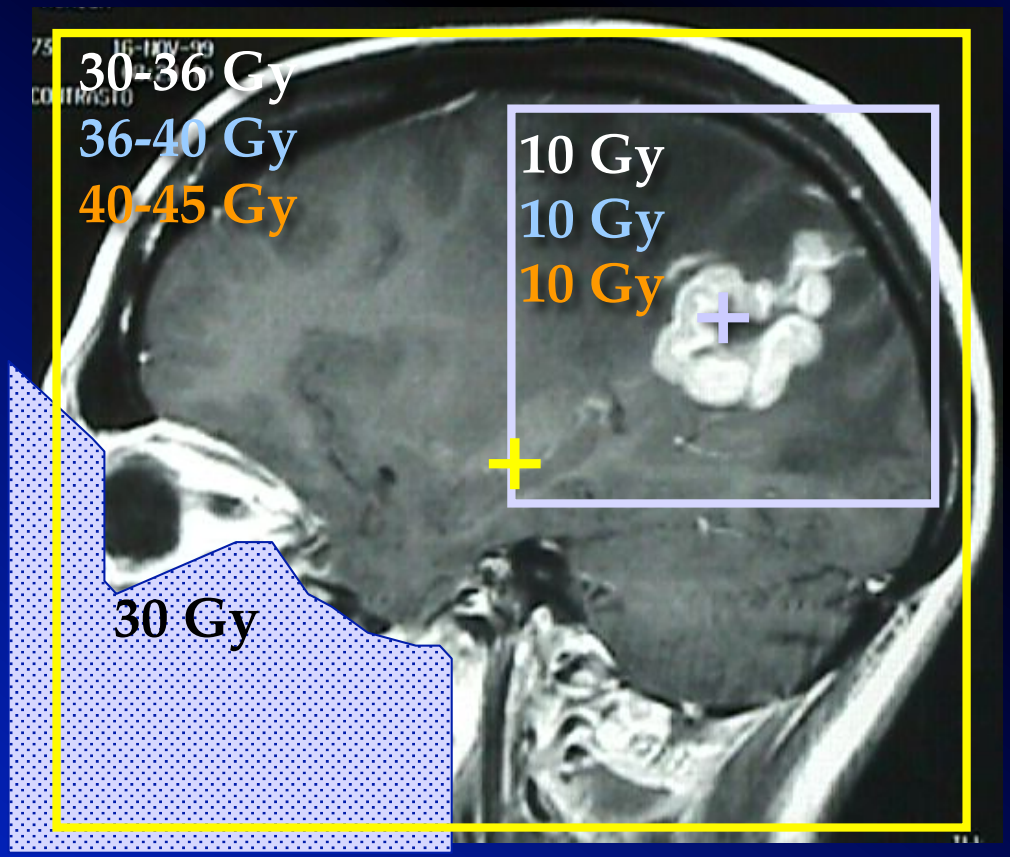
Chia-Ching W, et al. BJH 2014

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

Radiation Field and Doses



RESPONSE

COMPLETE REMISSION

PARTIAL RESPONSE

PROGRESSIVE DISEASE

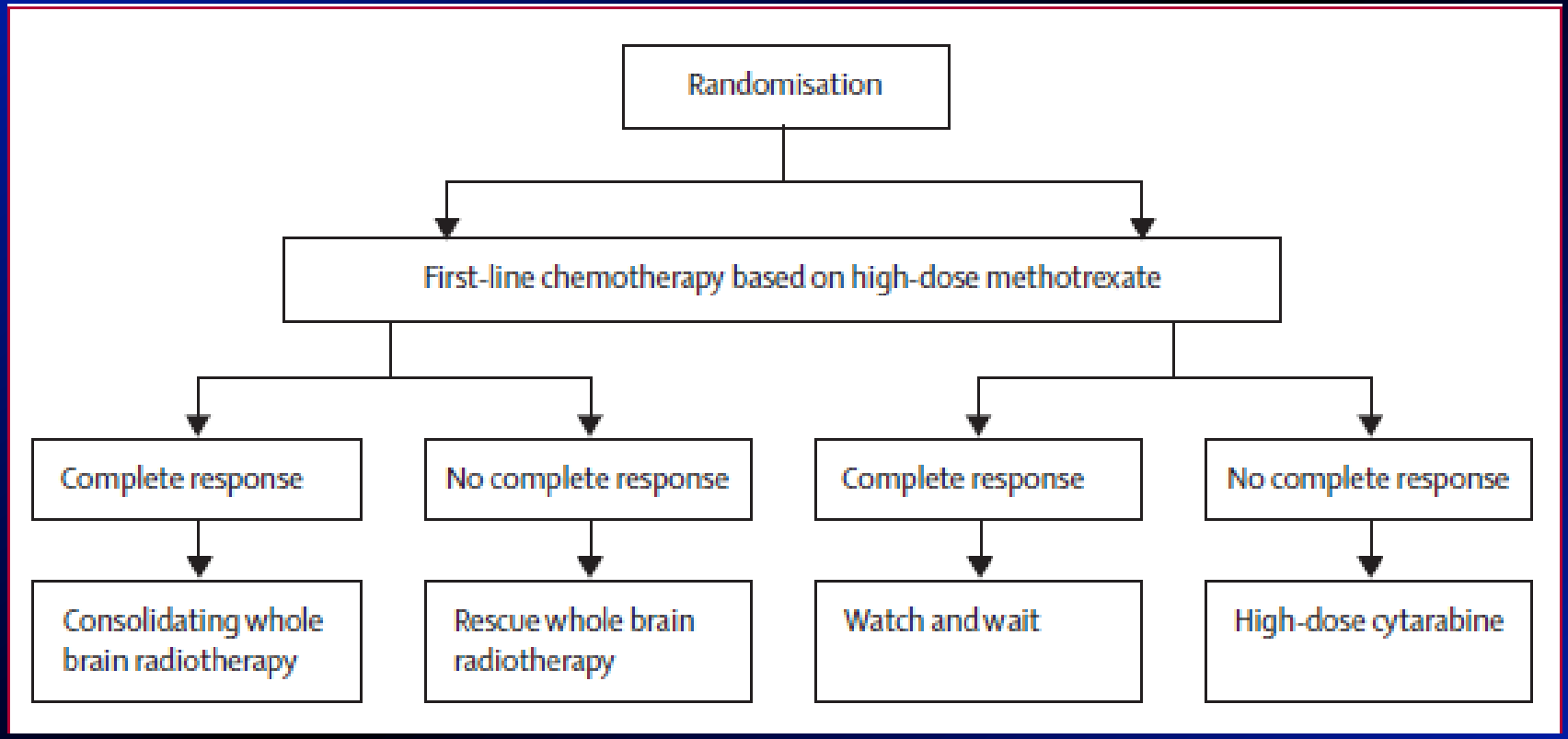
Reducing Neurotoxicity Risk

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

Ferreri AJM, et al. Blood 2011

Consolidation RT withdrawal?

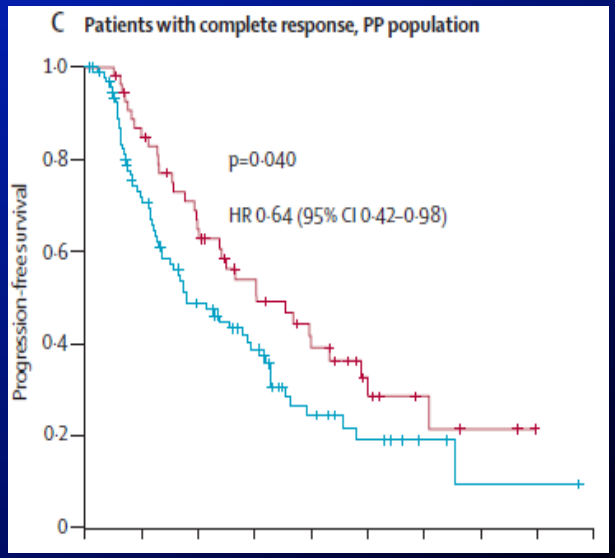
G-PCNSL-SG-1 trial

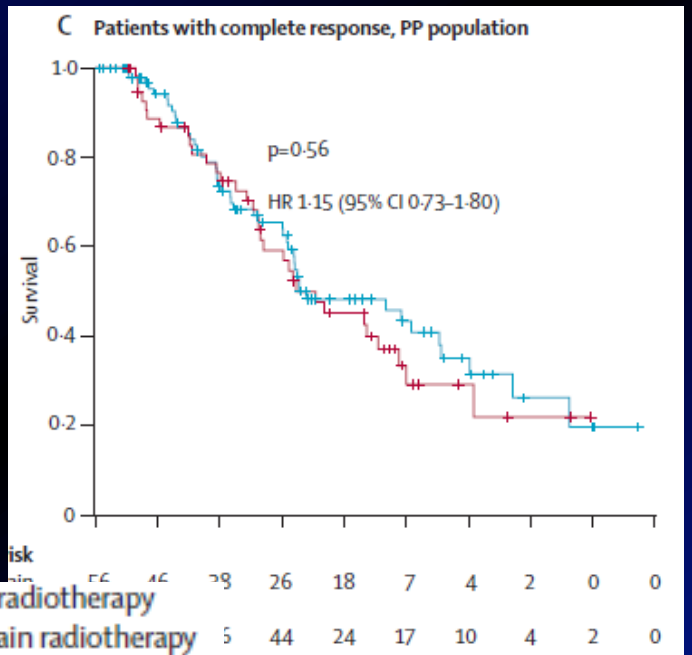


551 pts with newly diagnosed PCNSL were enrolled from 75 German Centers and treated between 2000 and 2009

Thiel E, et al. Lancet Oncol 2011

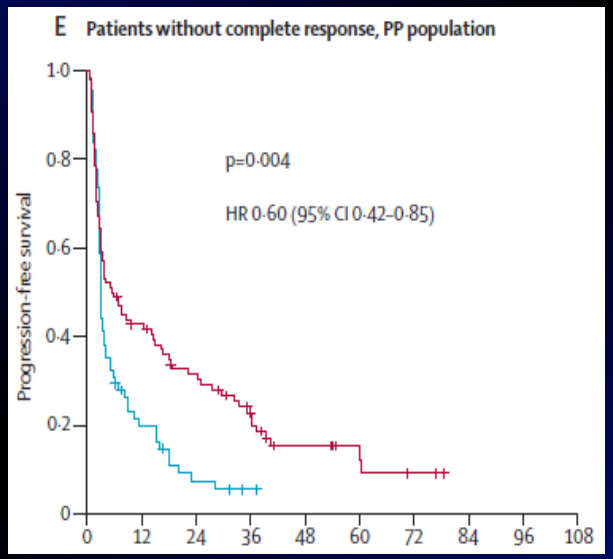
G-PCNSL-SG-1 trial: results

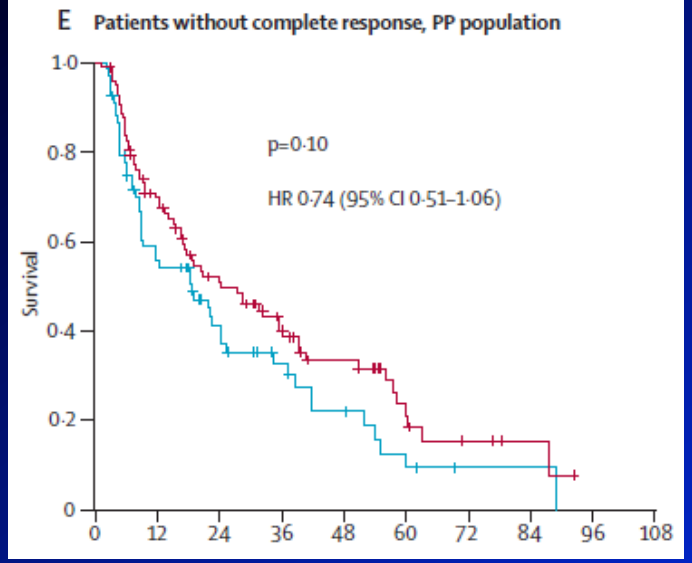




First-line chemotherapy with whole brain radiotherapy

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;

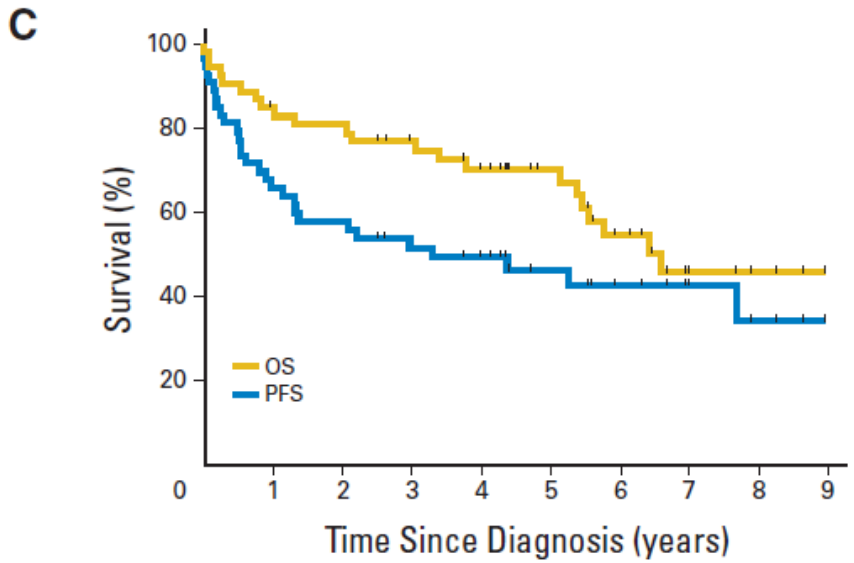
> “The trial was inconclusive, but the authors proceeded with further analyses...”

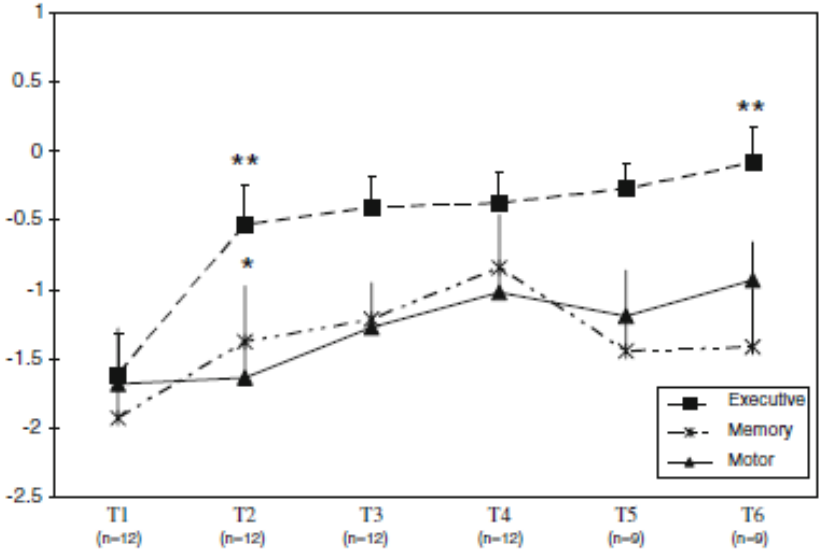
Practice point

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





STRATIFY

RPA Class

Class 1: age ≤ 50

Class 2: age > 50 and KPS ≥ 70

Class 3: age >50 and KPS < 70

RANDOMIZE

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
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

RTOG® RADIATION THERAPY ONCOLOGY GROUP

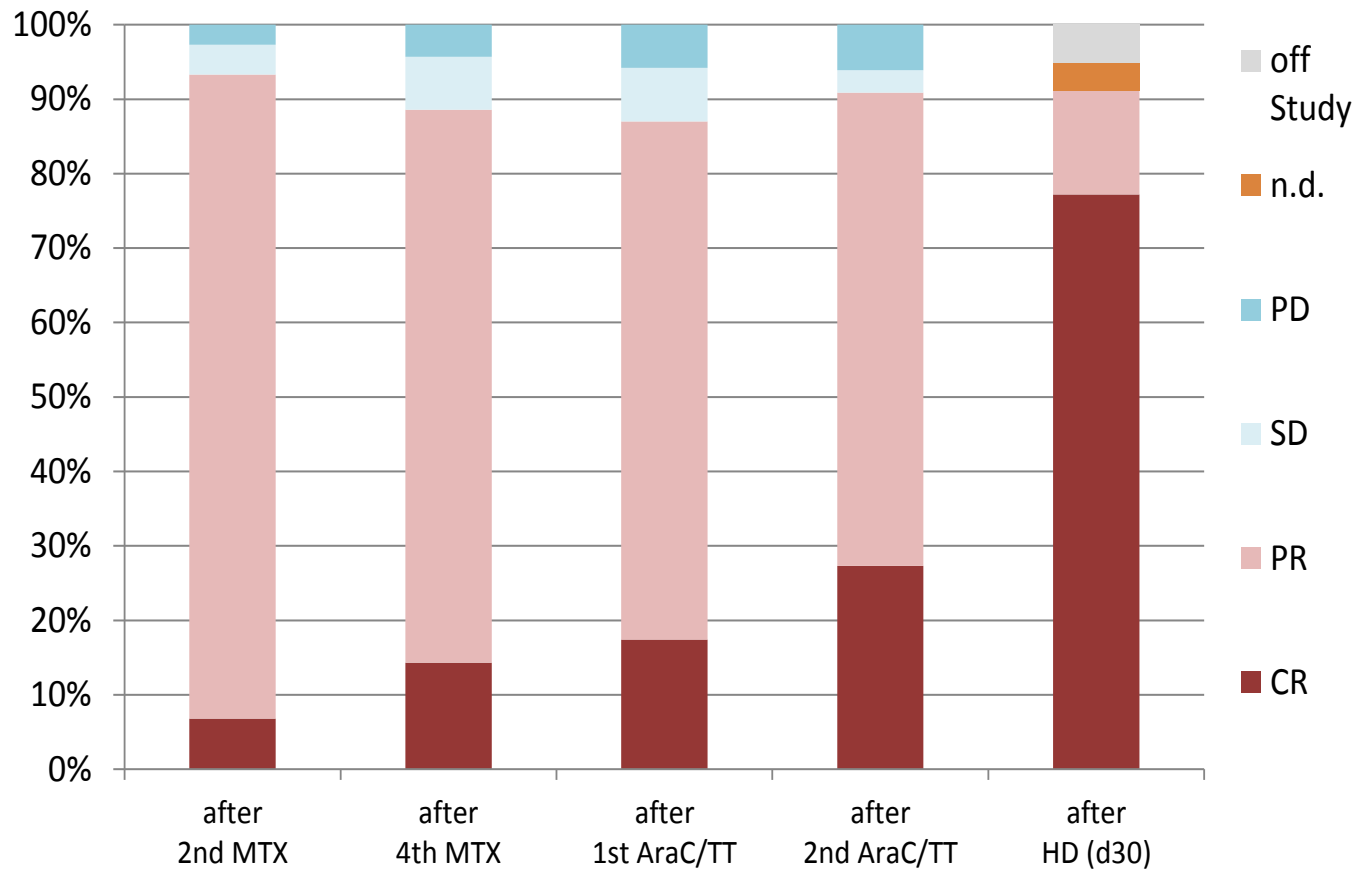
Morris PG, *et al.* JCO 2013; Correa DD, *et al.* JNO 2009; Kim BH, et al. Cancer Res Treat. 2014

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	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	
13	54 (38-67) 90 (30-100)	MTX araC, TTP	54	Thiotepa BCNU ± RT	85	72	77	0
							Kasenda B, et al. Ann Oncol 2012	

Activity of HDC/ASCT

(central neuroradiological review)



Kindly provided by G. Illerhaus, Stuttgart, Germany

ASCT vs. Alternatives

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

IELSG32 and PRECIS trials

	IELSG32	PRECIS
Background	Same rationale	Same rationale
Primary endpoint	2-year PFS	2-year PFS
Upper age limit	70 yo	60 yo
Induction regimen	MTX-araC ± rituximab ± thiotepa	R-MBVP-AraC
WBRT dose	Response-tailored	40 Gy
Conditioning regimen	BCNU-thiotepa	thiotepa-busulfan-cyclophospamide
Randomization	after confirmation of response to induction	at registration

Attention: results interpretation should take into account these relevant differences

Ferreri AJM & Illerhaus G. Blood 2016

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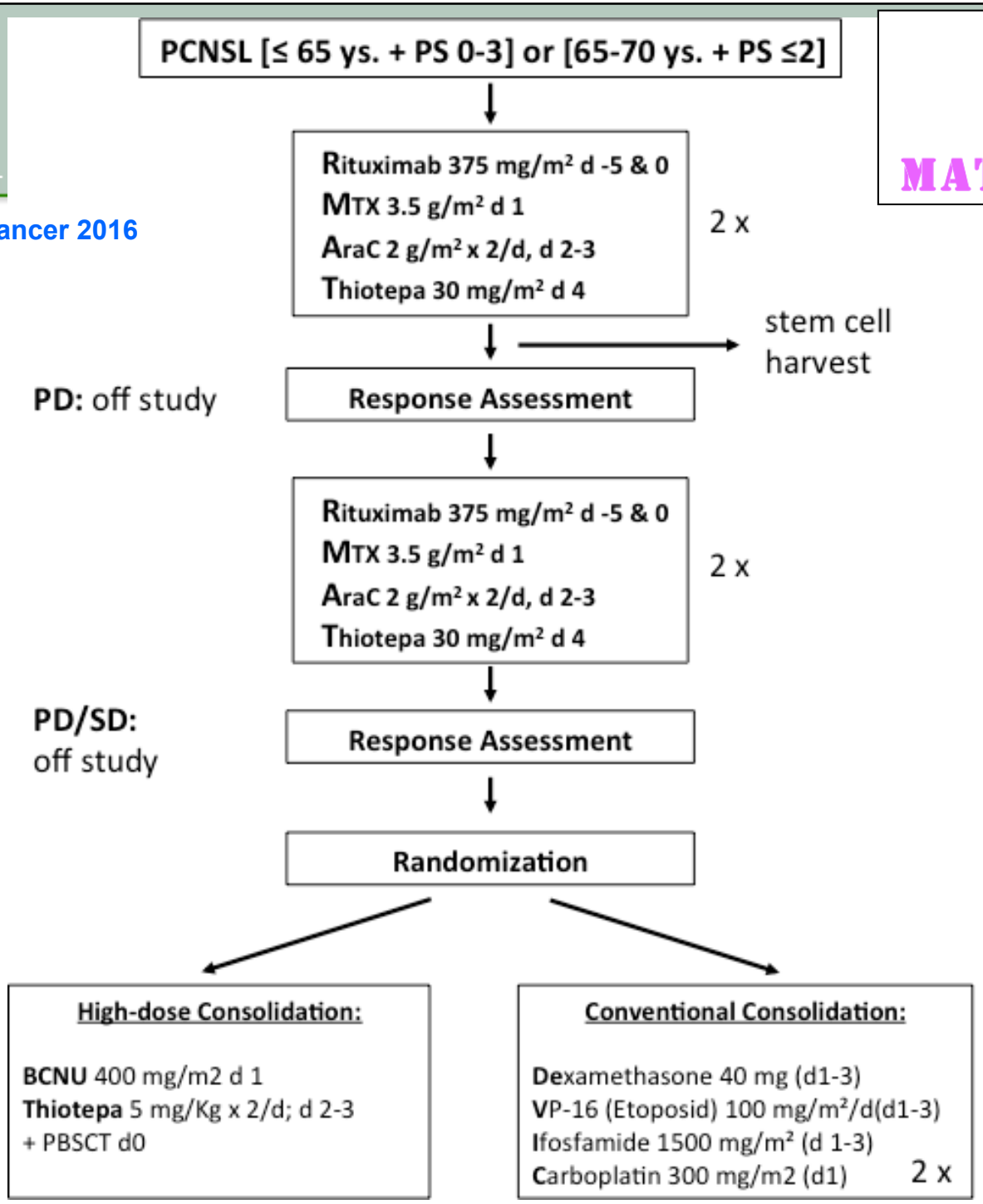
MATRIX / IELSG 43

Schorb E, *et al.* BMC Cancer 2016



Non-Myeloablative Chemo

Alliance/CALGB 50202 trial

44 pts
(age: 12-76)

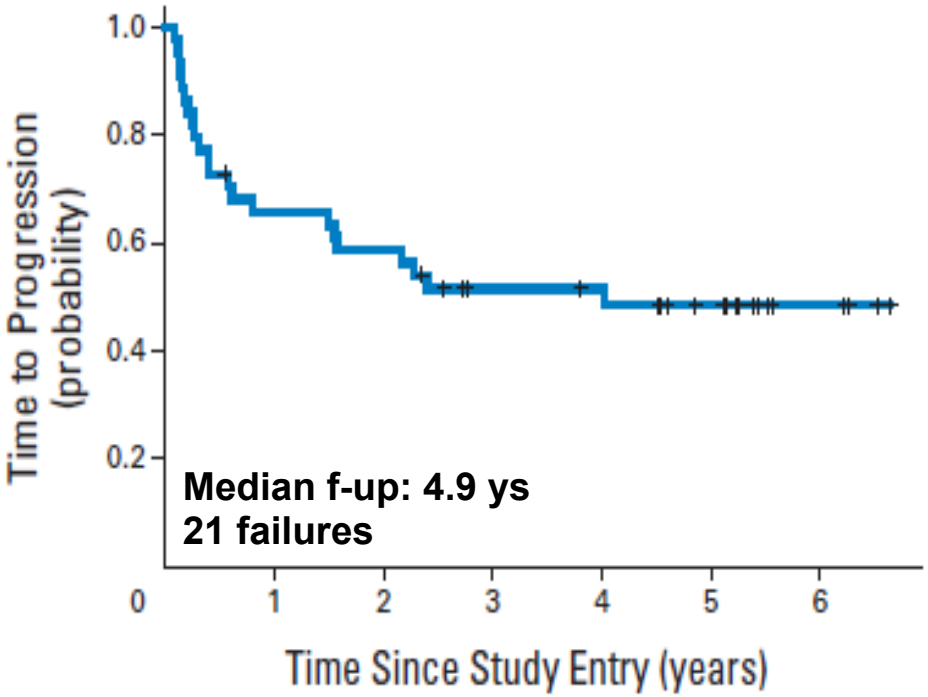
MTX (8)
Rituximab
TMZ x 8 c.

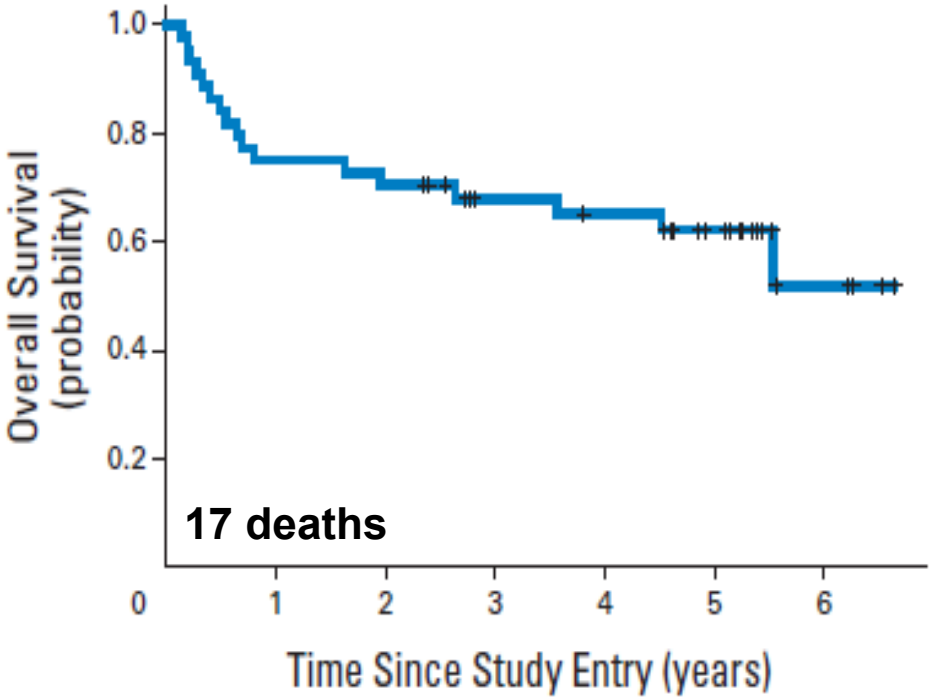
CR (66%)

TRM (sepsis) 2%

araC (8)
96-hr VP16

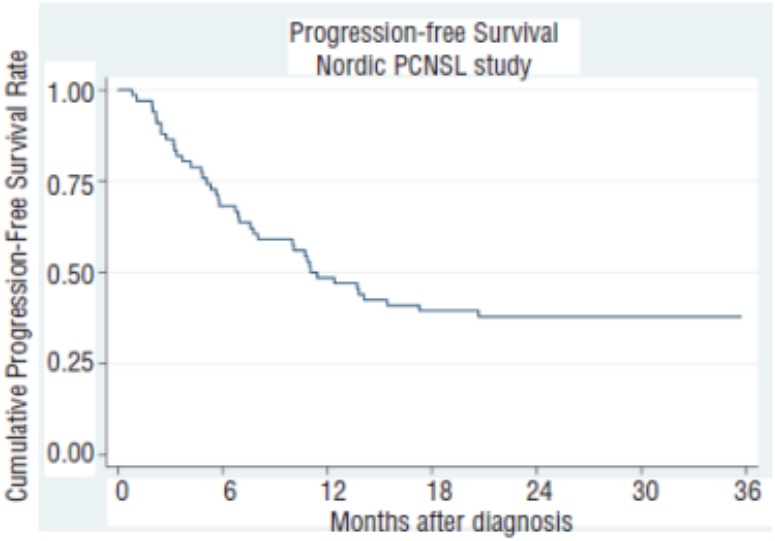
No neurotox

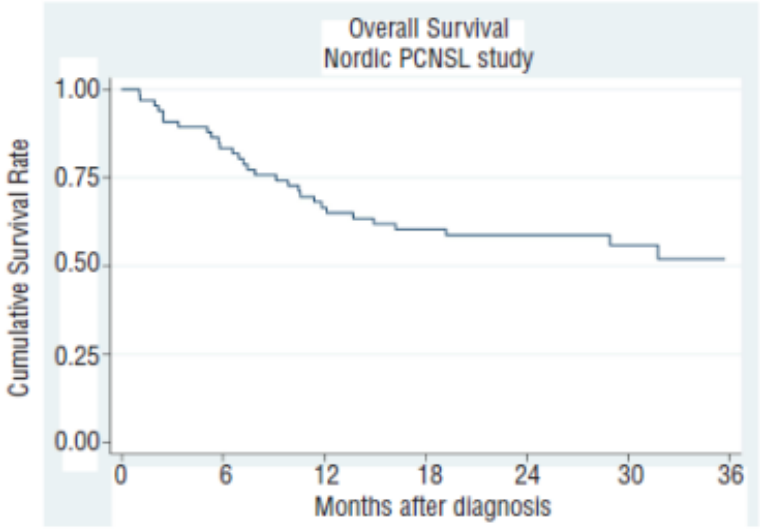


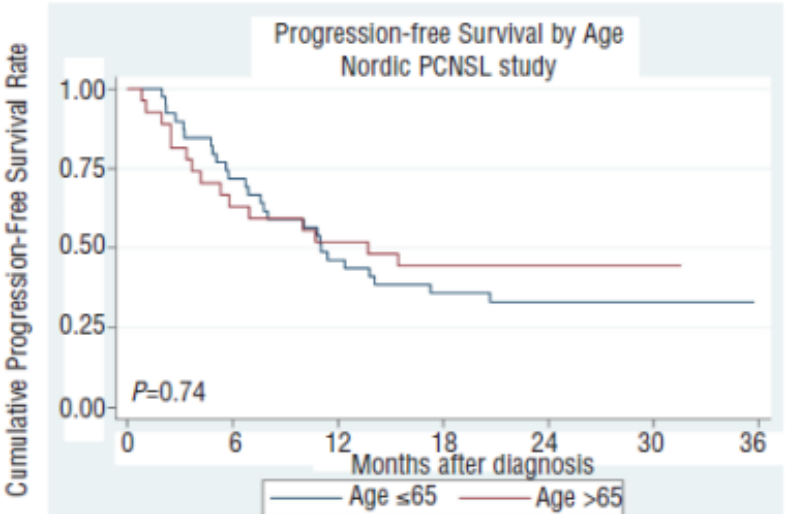


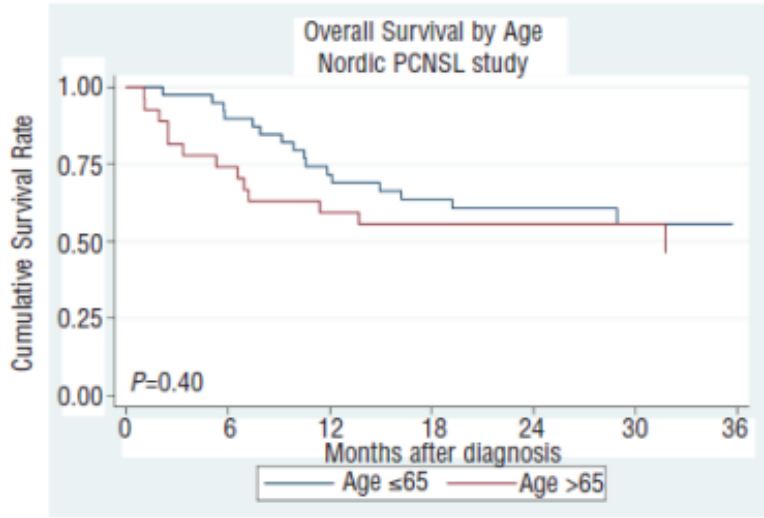
Rubenstein J, et al. JCO 2013

Nordic Trial: TMZ maintenance









Pulczynski EJ, et al. Haematologica 2015

Lenalidomide Maintenance

- Lenalidomide has shown activity as single agent or in combination in ABC-DLBCL
- It was associated with significantly improved PFS and acceptable toxicity in pts with relapsed DLBCL

Ferreri AJM, et al. ASH 2015

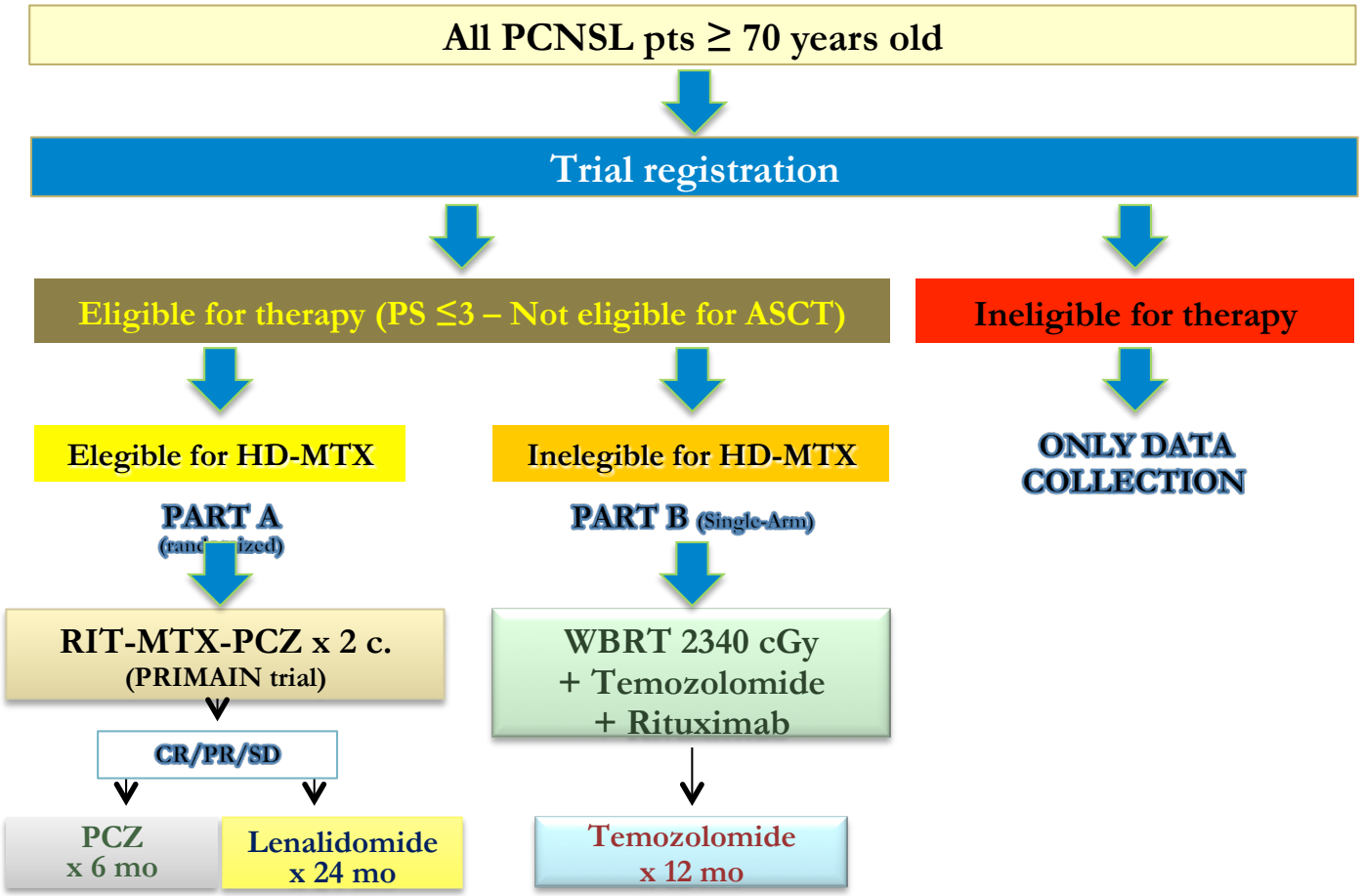
- Lenalidomide was associated with long-lasting remission in 2 out of 6 highly pretreated pts with recurrent PCNSL, and was well tolerated in elderly pts. Related phase II trial.

Houillier C, et al. Neurology 2015

- Lenalidomide (5-10 mg) maintenance after salvage therapy was associated with durable response in 5/10 pts with rrPCNSL. Good lenalidomide penetration in ventricular CSF 2-15h after dosing at 20 mg.

Rubenstein JL et al. 13-ICML, 2015

FIORELLA Trial: Design



Strategies for Future Studies

- To potentiate early diagnosis
- To identify new active drugs
- To amply our biological and molecular knowledge
- To establish reliable prognostic factors & potential targets
- To enhance drug bioavailability
- To improve radiation therapy
- To reduce neurotoxicity and improve patients' QoL
- To improve international cooperation

International Collaborative Group Against Primary CNS Lymphomas

To the Editor: Current therapeutic knowledge in primary CNS lymphoma (PCNSL) has come from nonrandomized phase II trials, meta-analyses of published series, and large, retrospective, multicenter series. Despite the fact that literature on PCNSL has been increasing, several fundamental therapeutic questions remain unanswered. The evaluation of new first-line chemotherapy combinations in nonrandomized phase II trials, even in large series with adequate follow-up, has produced some therapeutic progress, but the 5-year progression-free survival for patients with PCNSL remains approximately 25%.[1] In a recent editorial written by Dr H.A. Fine in the *Journal of Clinical Oncology*,[2] several important issues with respect to PCNSL research and treatment were enumerated. In this editorial, Dr Fine concluded that further single-arm phase II trials will not add significant, new information and that it is time to proceed with cooperative group, multi-institutional randomized trials to address the most pressing clinical questions in PCNSL. To date, only one randomized trial for patients with PCNSL has been published.[3] Some authorities contend that the rarity of PCNSL is a major obstacle for the development and execution of randomized trials. However, over the past 3 years, more than 850 patients with newly diagnosed PCNSL

representation including laboratory investigators, pathologists, oncologists, radiation oncologists, neurologists, hematologists, and biostatisticans. An international, multidisciplinary collaborative group is an ideal setting in which to address some of the fundamental clinical and biologic research questions for PCNSL. In the years ahead, it is hoped that the International PCNSL Collaborative Group established under the sponsorship of the IELSG will assume a prominent role in such investigations.

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JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Ten Years of International Primary CNS Lymphoma Collaborative Group Studies

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked

To the Editor: Ten years ago, we announced in *Journal of Clinical Oncology* the formation of a multidisciplinary scientific group focused on primary CNS lymphomas (PCNSL) called the International PCNSL Collaborative Group (IPCG).[1] Since then, more than 100 researchers and clinicians working on PCNSL from 19 countries have been actively involved in this group, established under the sponsorship of the International Extranodal Lymphoma Study Group with conference grant support from the National Cancer Institute (Grant No. R13CA124293). Since 2003, this multidisciplinary group has met annually or biannually, in Europe or the United States, and meetings

Ferreri AJM, *et al.* JCO 2003; Ferreri AJM, *et al.* JCO 2013

Trend in Survival

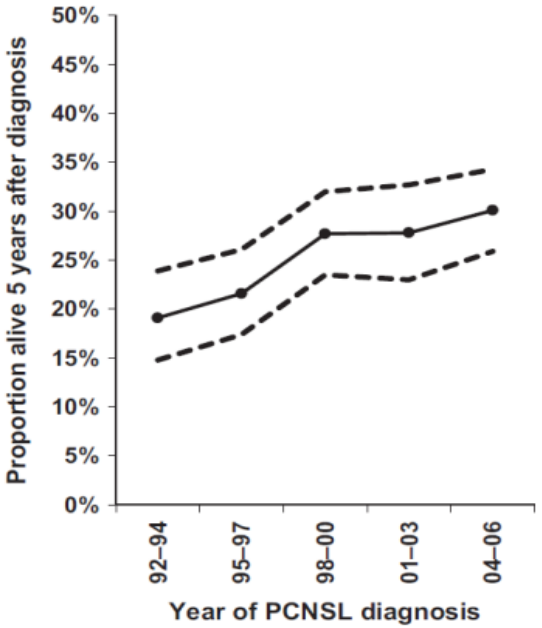
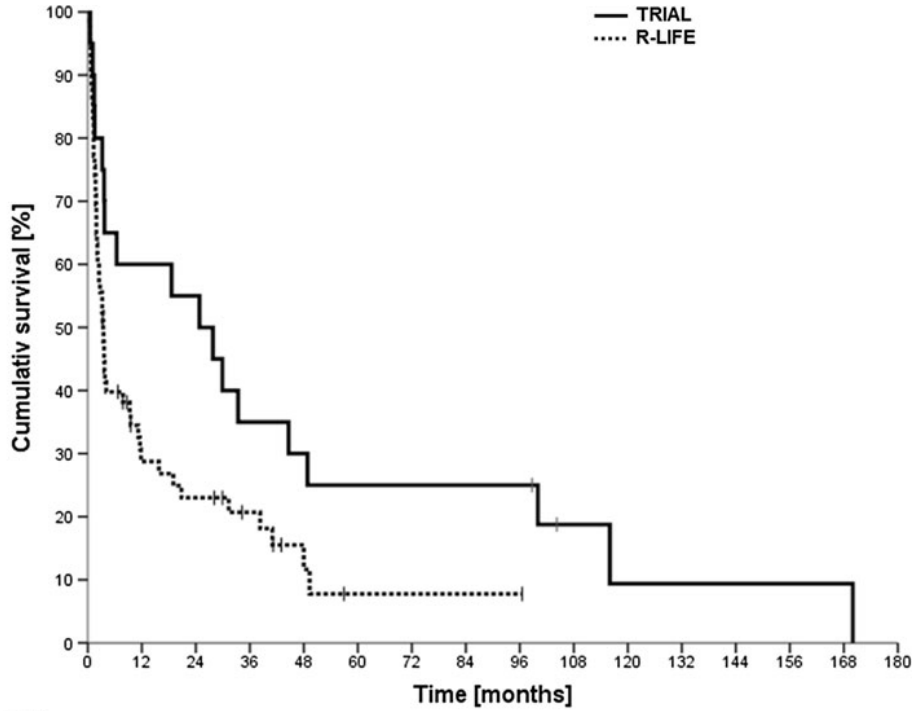


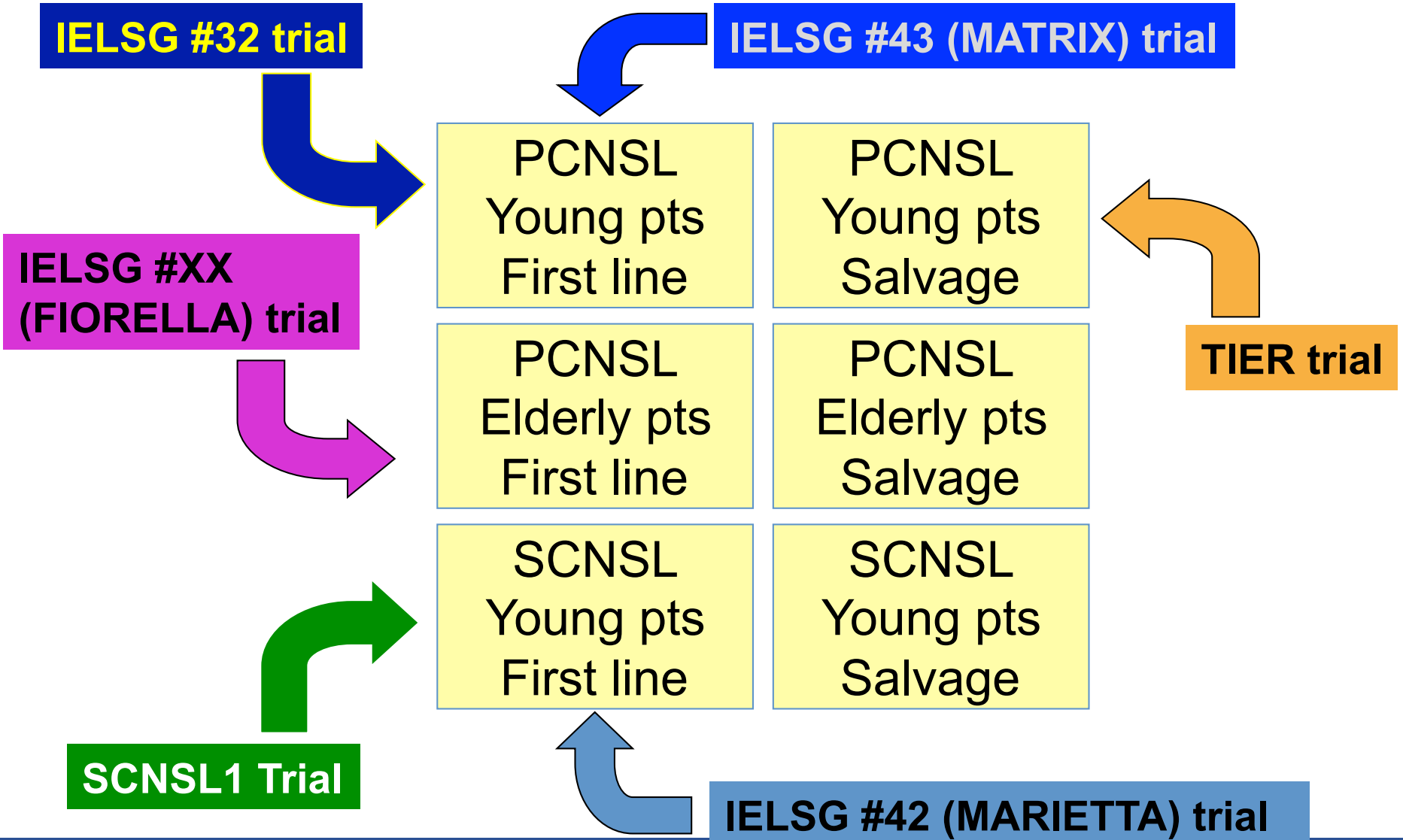
Fig 3. Age-standardized 5-year survival estimates for HIV-uninfected PCNSLs by 3-year categories of calendar year of diagnosis in 10 SEER registries during 1992-2005. Points represent estimates and dashed lines represent 95% confidence intervals.



Shields MS, *et al.* BJH 2016

Zeremski V, *et al.* Ann Hematol 2016

European PCNSL Collaborative Group



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- Colleagues, data managers and friends of the Fondazione Italiana Linfomi (FIL)
- Colleagues and friends of the European PCNSL Collaborative Group (EPCG)
- Colleagues and friends of the International PCNSL Collaborative Group (IPCG)
- Unit of Lymphoid Malignancies of the San Raffaele Scientific Institute, Milano