Incontri Bresciani di Radioterapia Oncologica

HODGKIN AND NON HODGKIN LYMPHOMAS: A NEW ROLE FOR RADIATION THERAPY

Extranodal NHL: the Case of CNS The role of Chemotherapy

Dott.ssa Tucci

S.C. Ematologia

Spedali Civili di Brescia

Brescia, 14 maggio 2010

Trials and tribulations in PCNSL

- Uncommon extranodal B cell lymphoma
- Poor drug penetration into the CNS
- Elderly age of the majority of patients

SM Ansell and SV Rajkumar, Nature Reviews Clinical Oncology, 2010; 7: 125

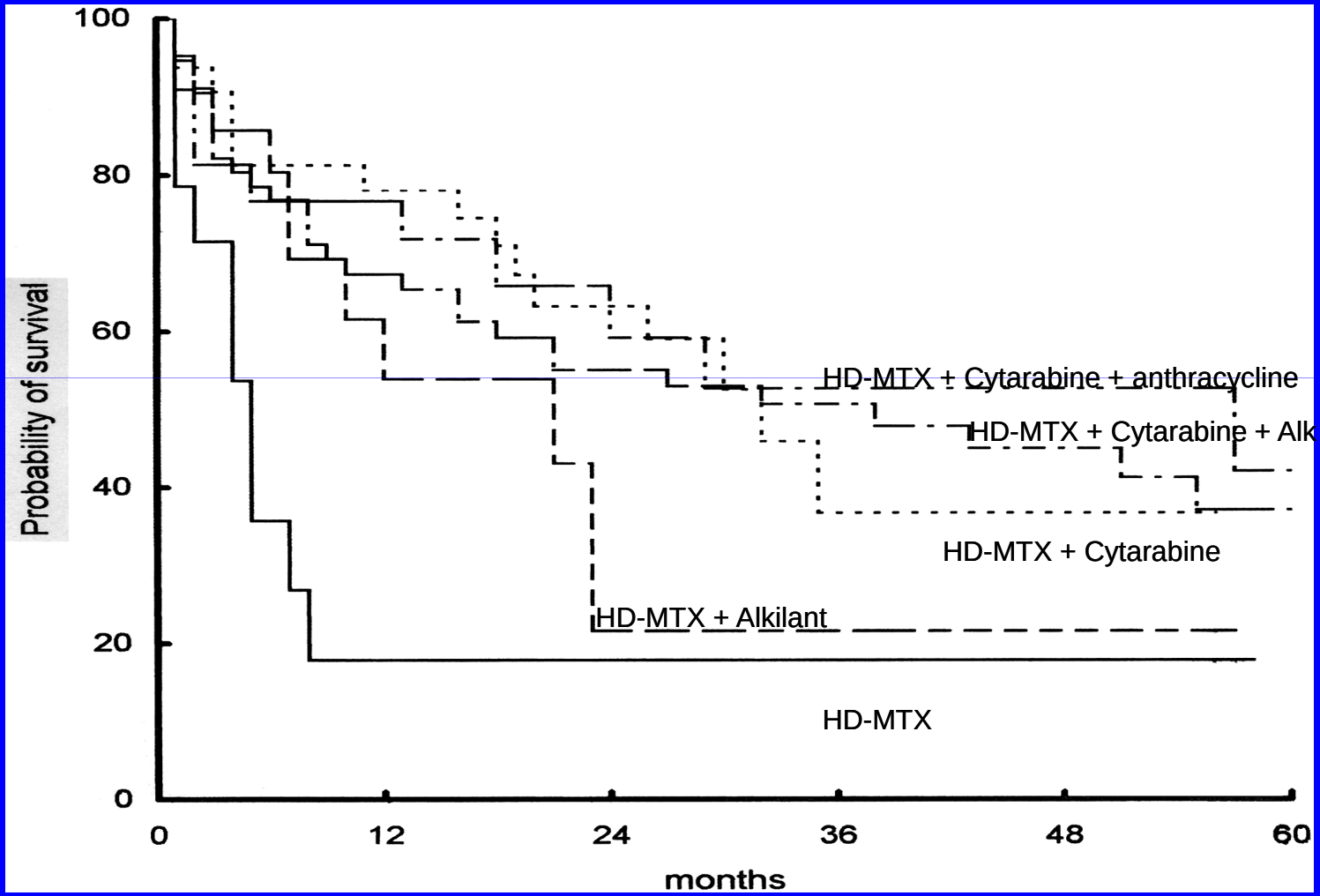
A multicenter study of treatment of PCNSL

RT	RT→CHT	CHT	CHT→RT
98	36 (9 HD-MTX)	32 (25 HD-MTX)	197 (135 HD-MTX)
2y OS	25 ± 4	35 ± 8	34 ± 10	45 ± 3

P=0.01

Ferreri AJM et al, Neurology 2002;58:1513

A multicenter study of treatment of PCNSL



Ferreri AJM et al, Neurology 2002;58:1513

Randomized phase II trial on primary chemotherapy with high-dose methotrexate, alone or associated with high-dose cytarabine, followed by response- and age-tailored radiotherapy for immunocompetent patients with newly diagnosed primary central nervous system lymphoma

Andrès J M Ferreri et al., Lancet 2009, 374*: 1512-20*

PCNSL age 18-75

R

4 c. MTX 3.5 g/m² d.1
every 3 weeks

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

Two courses

Response assessment

CR – PR - SD

Two courses

PR

CR

SD - PD

PD

WBRT 36 Gy
± boost 9 Gy

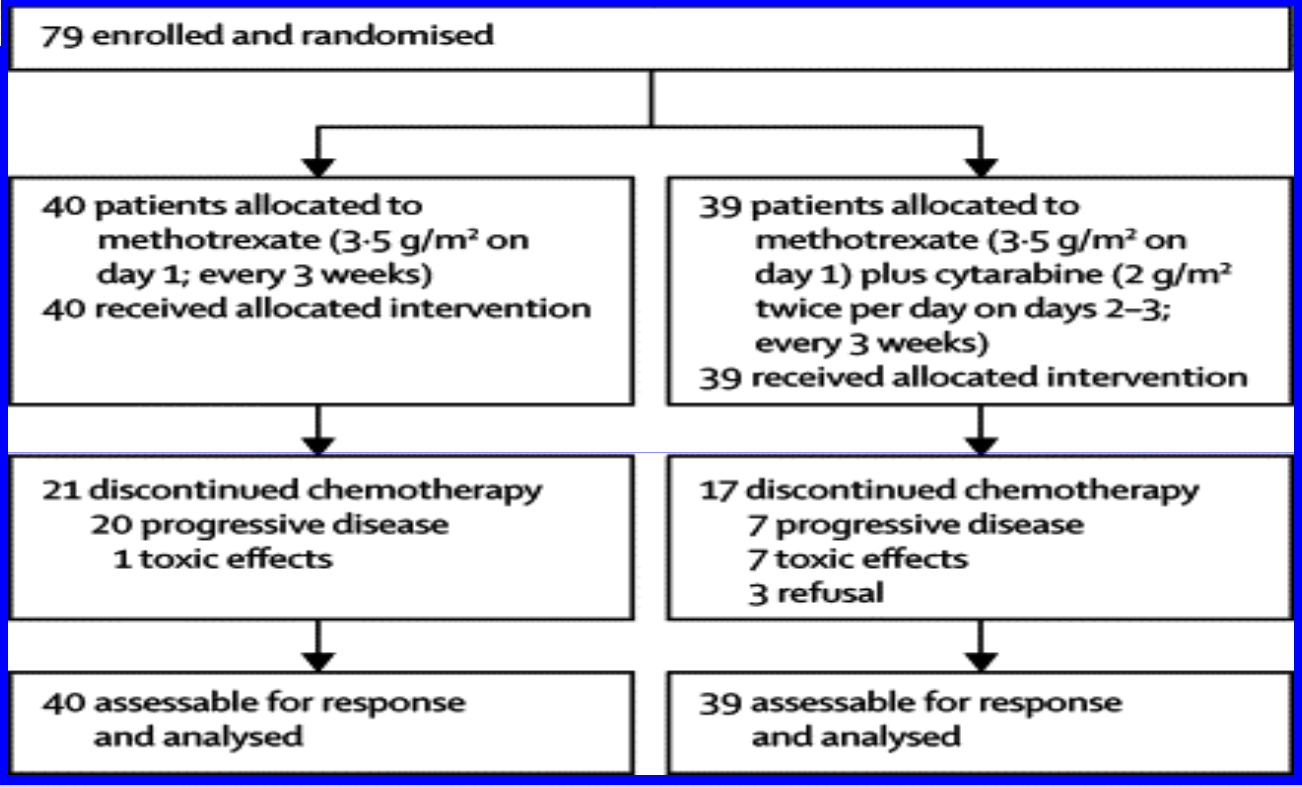
WBRT 36 Gy*

Off study
Salvage
therapy

* At the discretion of the participant center in patients older than 60 years

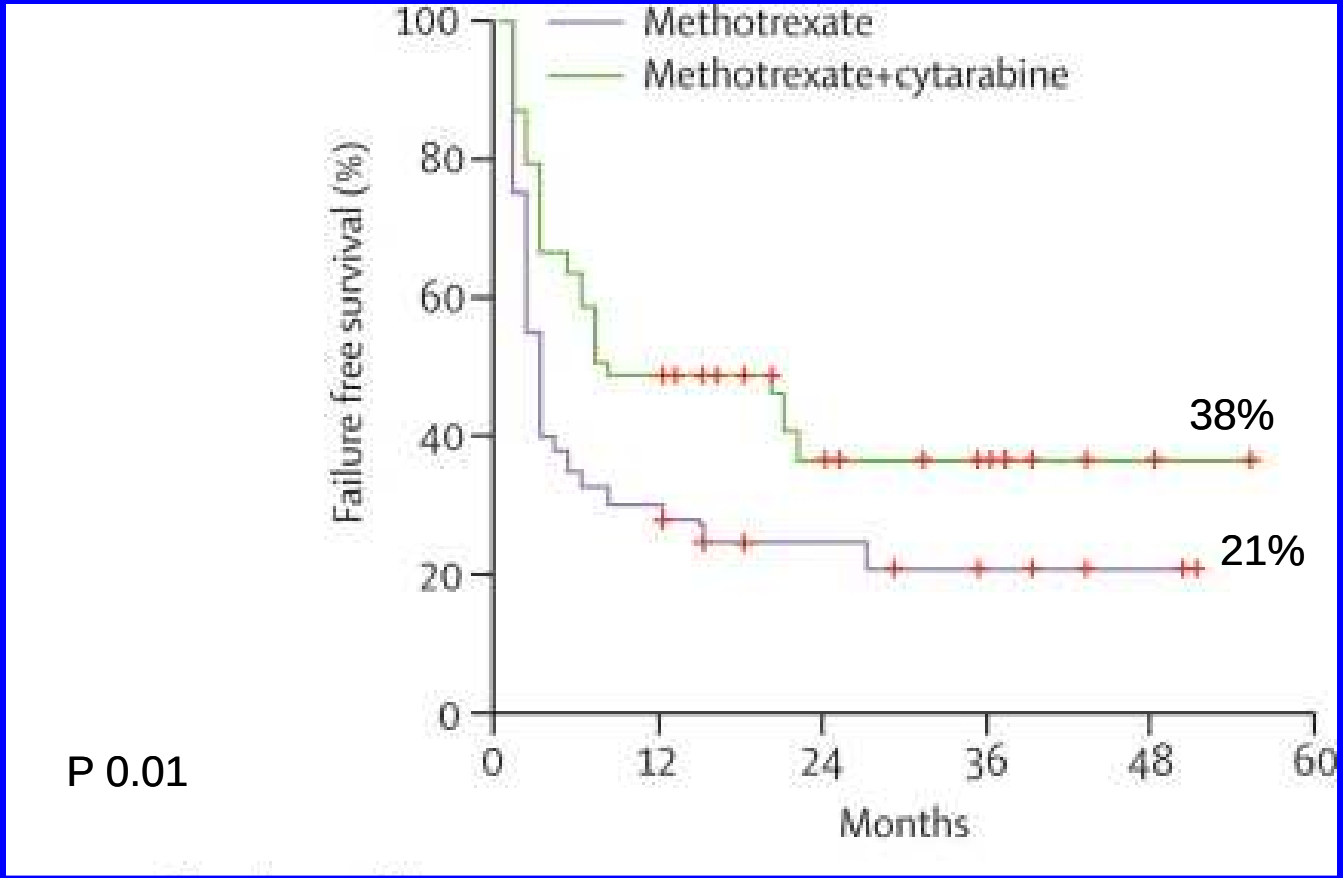
Ferreri et al, Lancet 2009;374:1512

Results



	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

FFS



P 0.01

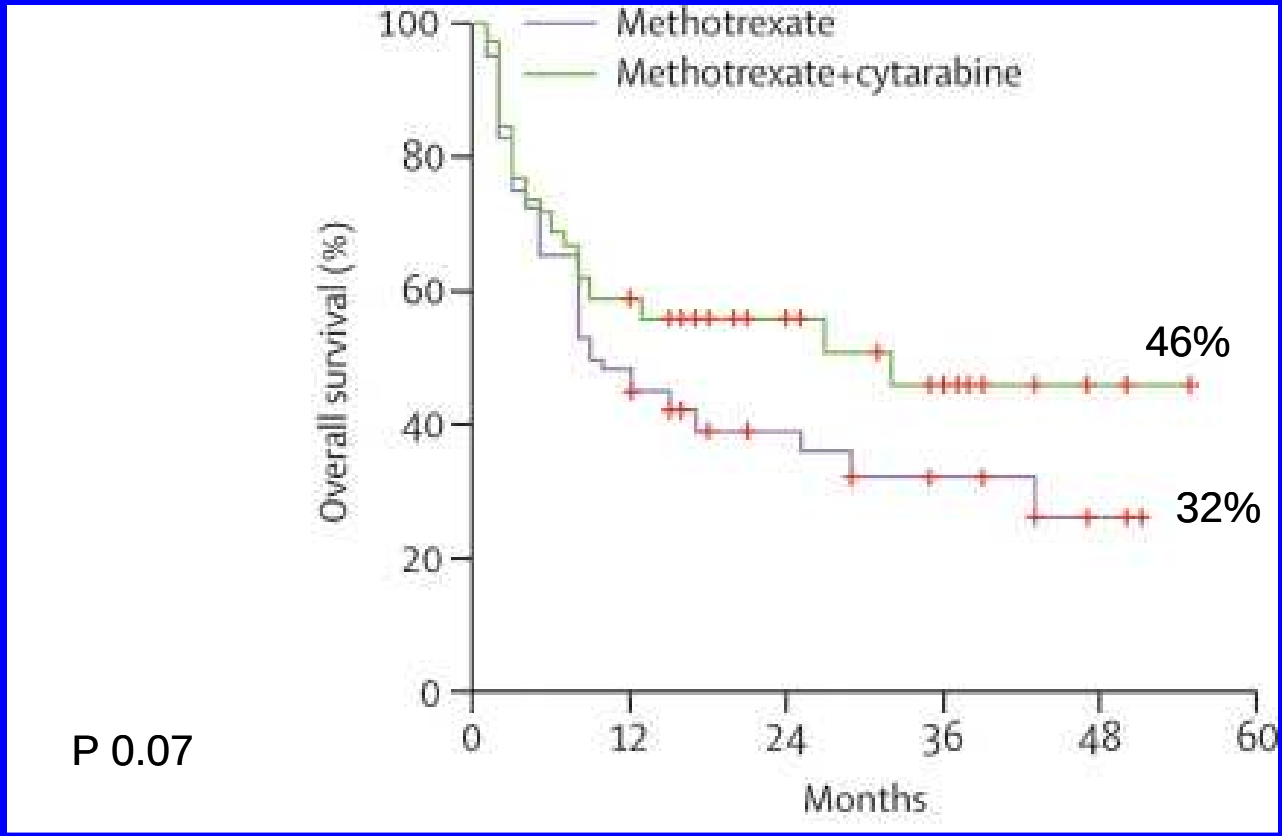
Ferreri et al, Lancet 2009;374:1512

Grade 3–4 toxic effects per treatment group

	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

Ferreri et al, Lancet 2009;374:1512

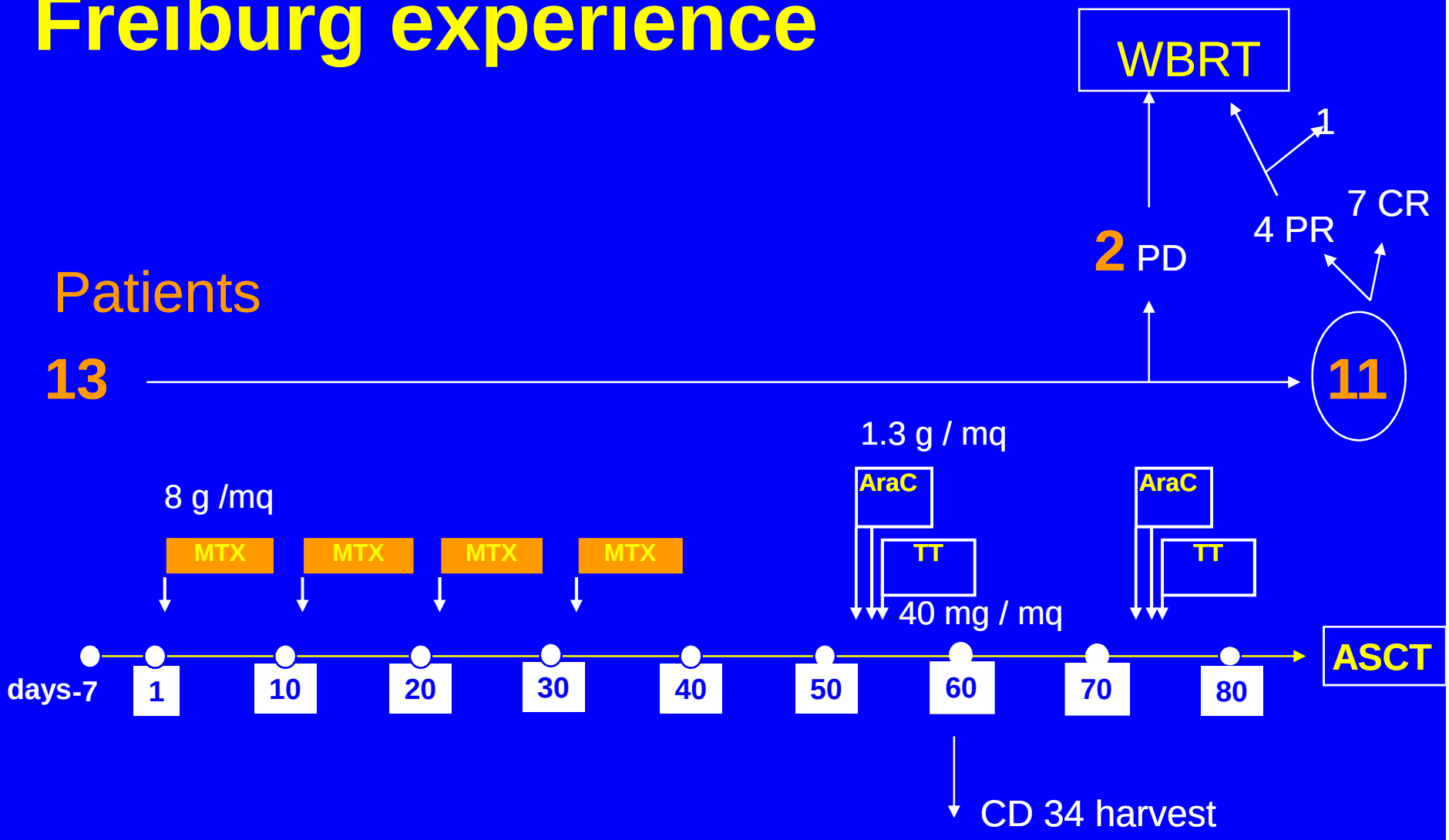
OS



P 0.07

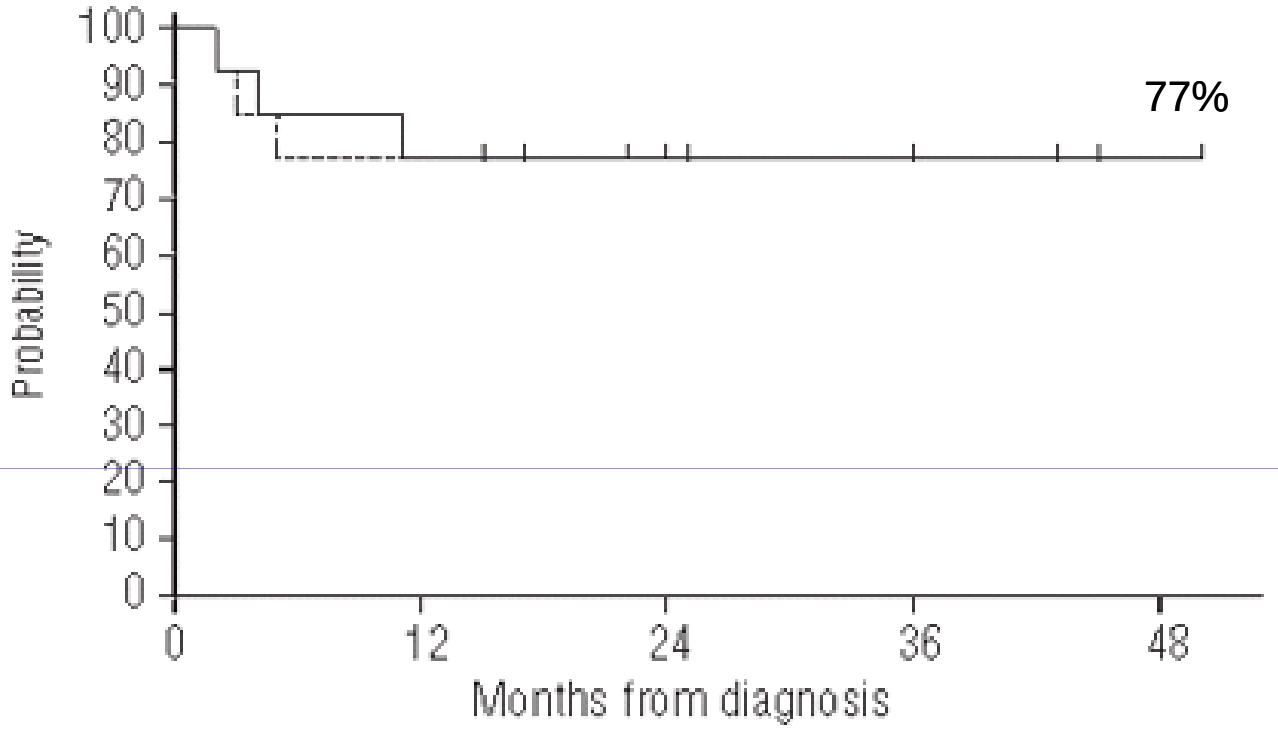
Ferreri et al, Lancet 2009;374:1512

Freiburg experience



Illerhaus et al , Haematologica. 2008 Jan;93(1):147-8

Freiburg experience



Median follow up of 25 months

Figure 1. Kaplan-Meier plot: disease-free survival (- -) and overall survival (–) from time of initial diagnosis of all patients.

Illerhaus et al , Haematologica. 2008 Jan;93(1):147-8

ASCT as first-line treatment in PCNSL

Authors	Induction treatment	Conditioning	2yrs OS	WBRT
Abrey et al. JCO 2003	HD-MTX	BEAM	55%	Only refractory
Cheng et al. BMT 2003	HD-MTX	Thiotepa Bus CTX	50%	Only refractory
Brevet et al. EJH 2005	MVPB	BEAM	50%	30 Gy +10boost
Illerhaus et al. JCO 2006	HD-MTX	BCNU Thiotepa	69%	Hyper fractionated
Colombat et al. BMT 2006	MVPB	BEAM	64%	30 Gy +10boost
Montemurro et al Ann Oncol 2007	HD-MTX	Thiotepa Bus	61%	Only PR

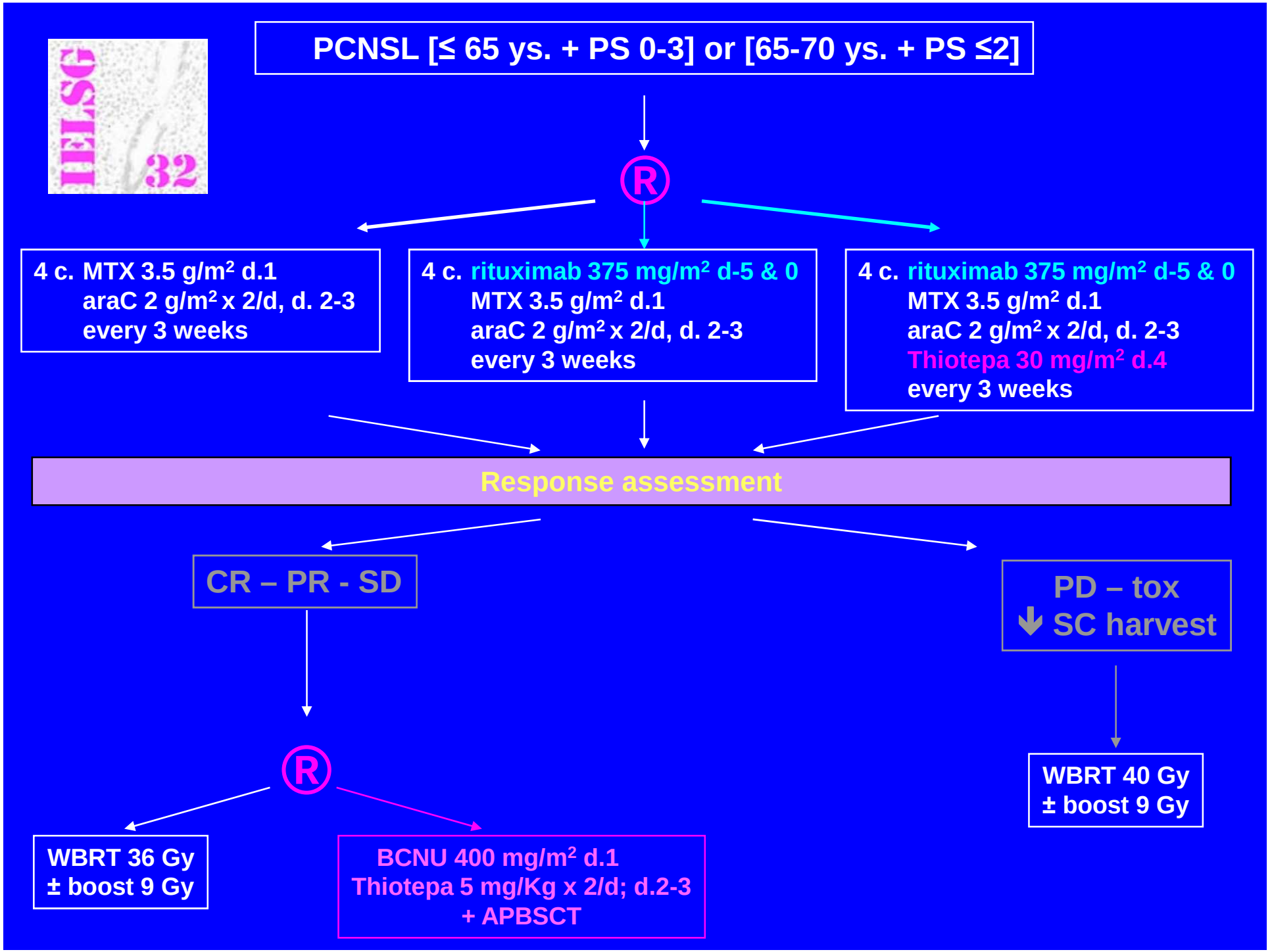
A multicenter study of treatment of PCNSL

	All Patients (N=57)		Patients < 60 Chemo / WBRT* (n=19)		Patients ≥ 60 Chemo / WBRT (n=12)		Chemo Alone (n=26)	
Outcome	No.	%	No.	%	No.	%	No.	%
Median Survival (months)	51		NR		29		29	
PFS, months	129		NR		NR		7	
Relapse	25	44	7	27	3	25	15	58
Neurotoxicity	17	30	5	26	9	75	3*	
Alive	17	30	13	68	0		4	15

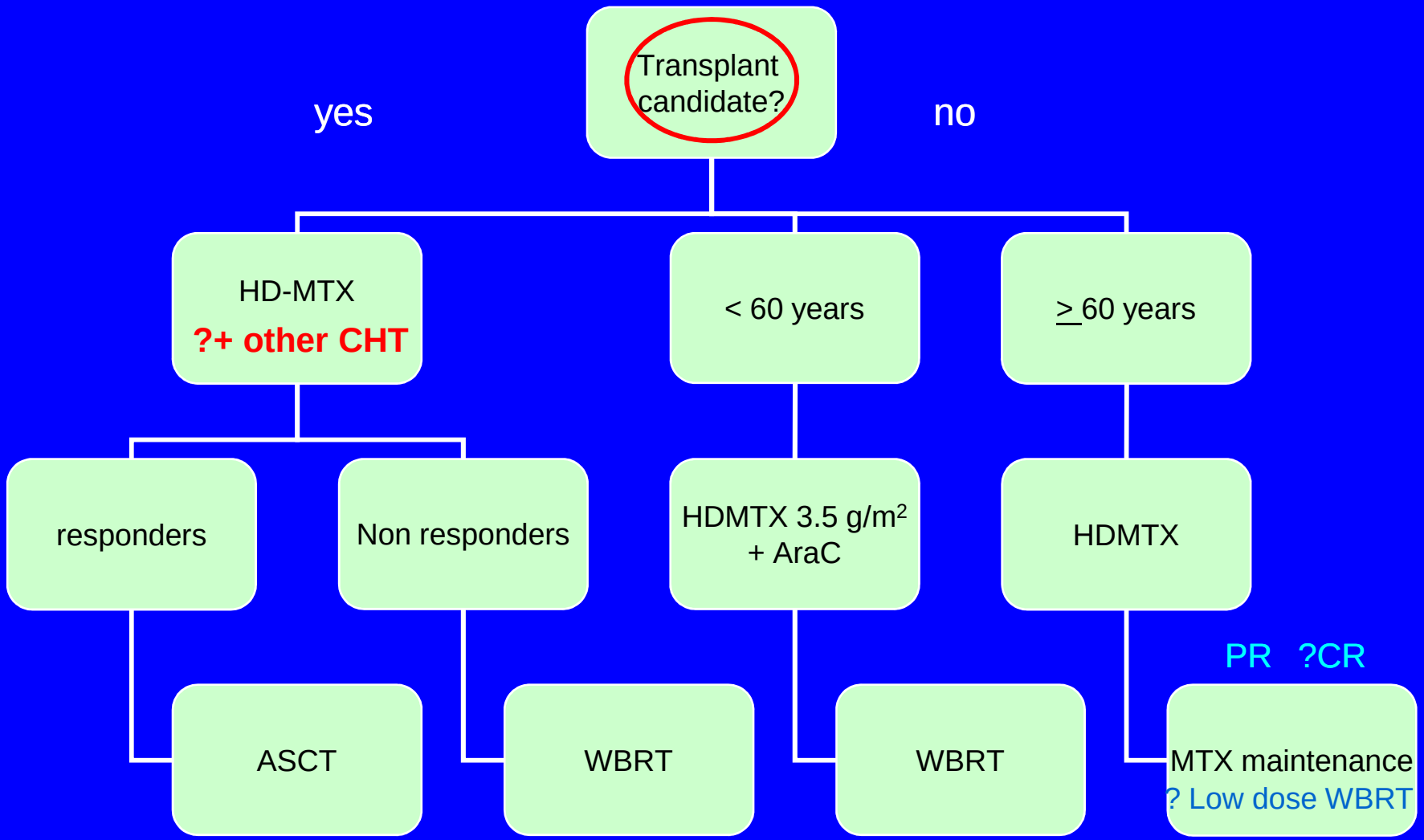
*45 Gy
** 2 pts developed neurotoxicity only after receiving WBRT for recurrent PCNSL

Gavrilovic et al, JCO 2006; 24:1470

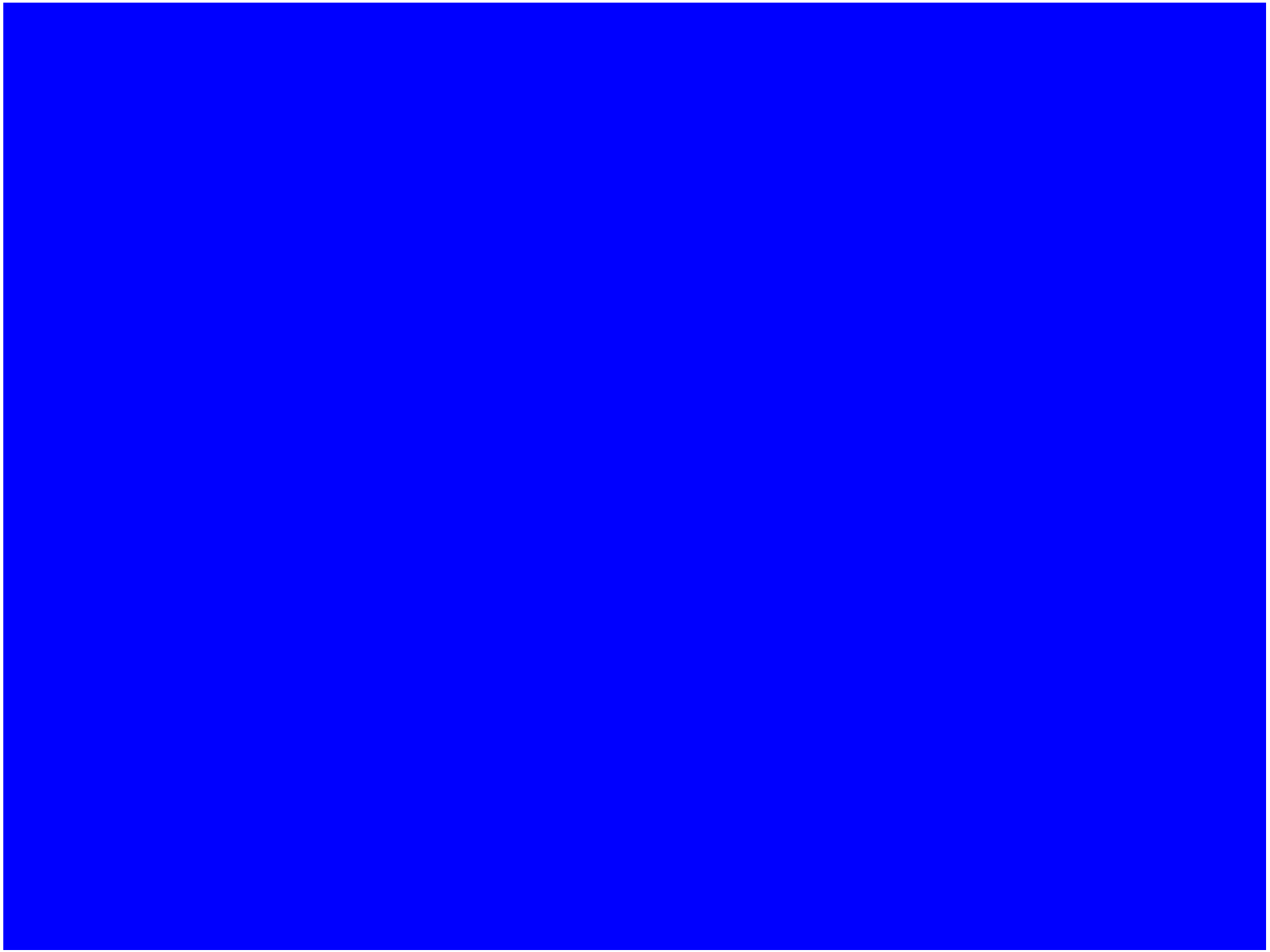
RANDOMIZED PHASE II TRIAL
on primary chemotherapy with HD-MTX + HD-araC
with or without THIOTEPA,
and with or without RITUXIMAB,
followed by BRAIN IRRADIATION versus
HIGH-DOSE CHEMOTHERAPY supported by ASCT
for IMMUNOCOMPETENT PATIENTS
with NEWLY DIAGNOSED PCNSL


IELSG 32
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
PD – tox
SC harvest
R
WBRT 40 Gy
± boost 9 Gy
WBRT 36 Gy
± boost 9 Gy
BCNU 400 mg/m² d.1
Thiotepa 5 mg/Kg x 2/d; d.2-3
+ APBSCT

Approach to the treatment of PCNSL



SM Ansell and SV Rajkumar, Nature Reviews Clinical Oncology, 2010; 7: 125



IPCG NEUROPSYCHOLOGICAL TESTS (MODIFIED FROM REF 34)

Cognitive domain	Test	References
Attention/executive funtions	Digit forward Digit backward	WAIS III
	Trail Making Test Brief Test of Attention WCST – Brief form	Reitan 1958 Schretlen 1997 Nelson 1976
Memory	Hopkins Verbal Learning-Revised Rey Auditory Verbal Learning Test Rey complex figure delayed	Brandt 1991 Rey, 1964 Taylor, 1959 Rey 1968
Language	Token Test Phonetic Verbal Fluency Semantic Verbal Fluency	De Renzi, Vignolo 1962; Spinnler e Tognoni 1987 Novelli 1986
Pre-morbid IQ estimation	NART Barona index	Nelson 1982 Barona 1984; 1996
Quality of Life	EORTC- QLQ	Fayers 1998
	BCM 20	Osoba 1996
Motor	Grooved pegboard Test	Heaton et al., 1991

Aims of the study

- Primary objective at first randomisation
  - To compare different CHT combinations

    Endpoint: CR rate after CHT

- Primary objective at second randomisation
  - To compare two different consolidation strategies (WBRT vs ASCT)

    Primary endpoint: 2 years PFS

    Secondary endpoints. OS, meningeal relapse rate and late neurotoxicity

IPCG RESPONSE CRITERIA[32]

Abrey et al. JCO 2005

	Brain Imaging	Steroid Dose	Eye Exam	CSF Cytology
CR	No contrast enhancement	None	Normal	Negative
Cru	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion Any new site of disease: CNS or systemic	Irrelevant	Recurrent or new ocular disease	Recurrent or positive

Study chairmen	**Andrés J. M. Ferreri** Unit of Lymphoid Malignancies, Department of Oncology San Raffaele H Scientific Institute, Milan, Italy **Gerald Illerhaus** Department of Hematology and Oncology University Medical Center Freiburg, Freiburg, Germany
Co-chairmen	Michele Reni, Milan, Italy Juergen Finke, Freiburg, Germany Emanuele Zucca, Franco Cavalli, Bellinzona, Switzerland
Data management	Elena Porro, Cristina Morinini IELSG Studies Coordination IOSI, Ospedale San Giovanni CH 6500 Bellinzona, Phone 0041 91 8119040 Fax 0041 91 8119182 E-mail ielsg@ticino.com
Radiology Review	Andrea Falini Department of Neuroradiology San Raffaele H Scientific Institute, Milan, Italy
Neuropsychologist	Monica Falautano Psychology Unit Department of Neurology San Raffaele H Scientific Institute, Milan, Italy
Statistician	Valter Torri Istituto di Ricerche Farmacologiche Mario Negri Milan, Italy

IELSG score

- Age (≤60 *vs* > 60 years)
- ECOG PS (0 to 1 *vs* 2 to 4)
- LDH serum level (normal *vs* elevated)
- Protein CSF concentration (normal *vs* elevated)
- Involvement of the deep structures of the brain (no *vs* yes)

0-1 low
2-3 intermediate
4-5 high

Ferreri et al, JCO, 2003

Why MTX + Ara-C?

IELSG 20 trial

Why MTX + araC + rituximab?

R-MPV study Abrey et al.JCO 2007

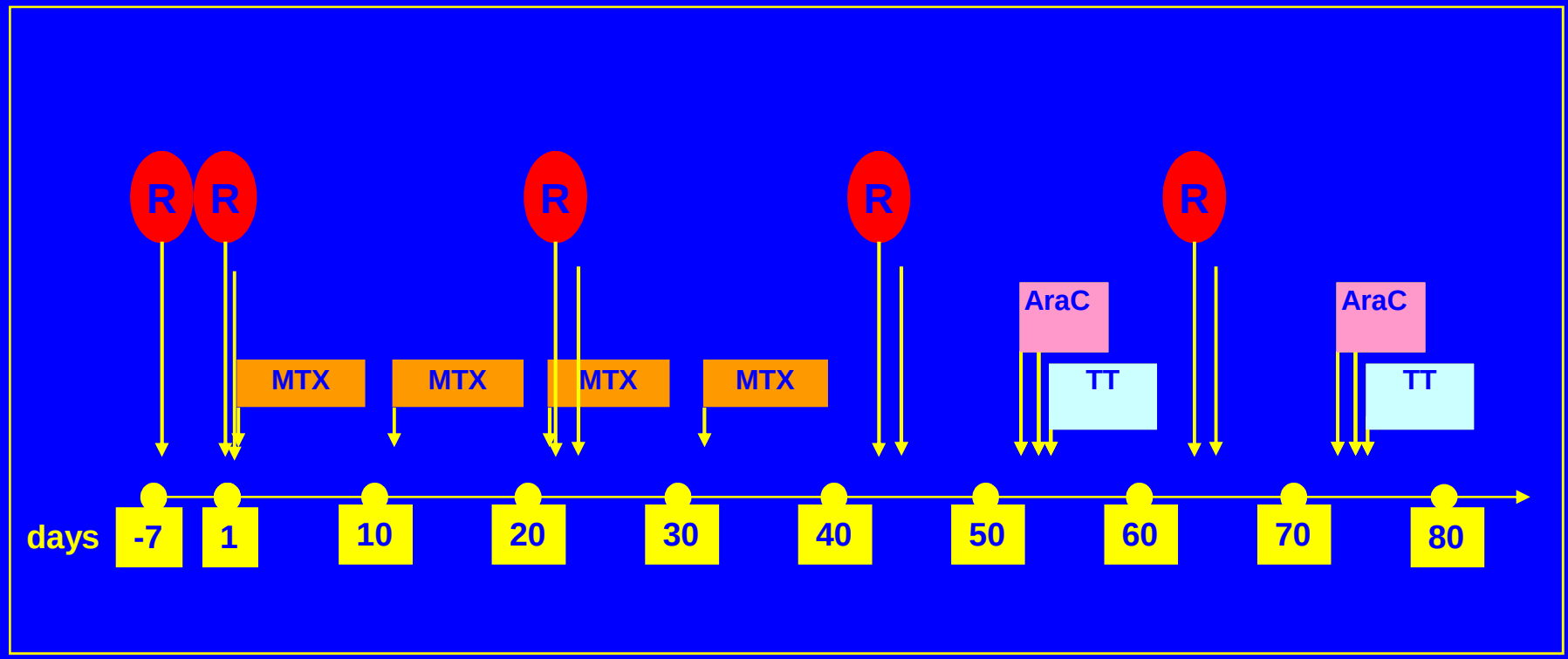
Why MTX + araC + rituximab + TTP?

MATILDE study and Freiburg experience

Why ASCT vs WBRT

Freiburg experience

Freiburg experience



Illerhaus et al, Haematologica 2008; 93: 147

IELSG 32

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