Das primäre ZNS-Lymphom

Fortbildungsreihe Medizinische Onkologie
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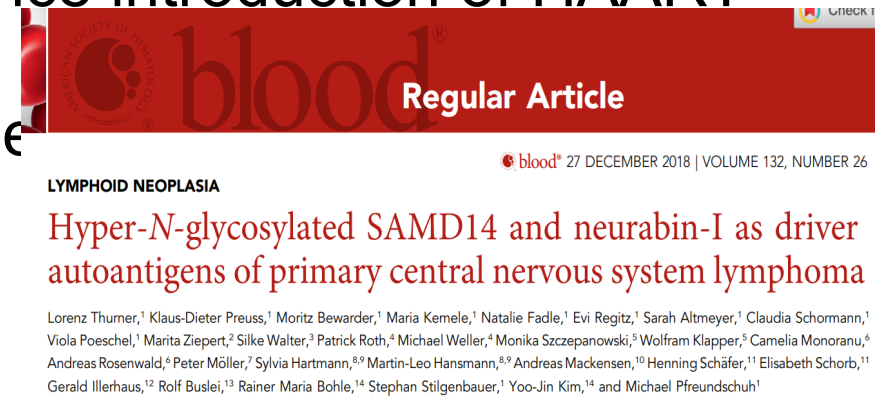
Patrick Roth
Klinik für Neurologie und Hirntumorzentrum
UniversitätsSpital Zürich

Primary CNS lymphoma

- Lymphoma with exclusive manifestation in the CNS
- Median age: ~ 60 years
- Incidence: approximately 0.5/100.000
  → increasing for unkown reasons
- Particular situation: HIV-associated CNS lymphomas
  → incidence decreasing since introduction of HAART
- Unclear pathogenesis => spe

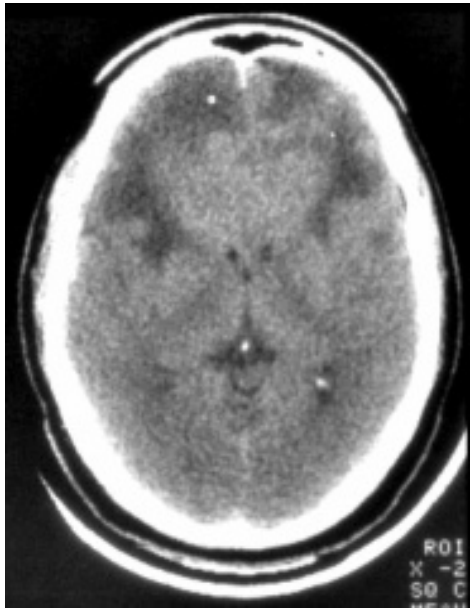


Clincal presentation

- Personality changes
- Symptoms associated with increased intracranial pressure
- Motor and sensory deficits
- Cranial nerve palsies
- Seizures (rare)
- Cerebellar symptoms

Imaging: CT

- Iso- or hyperdense mass
- Multiple lesions in about 30-40% of all patients



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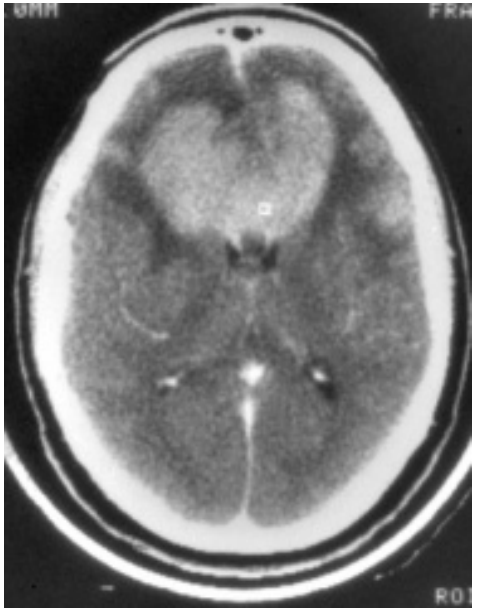
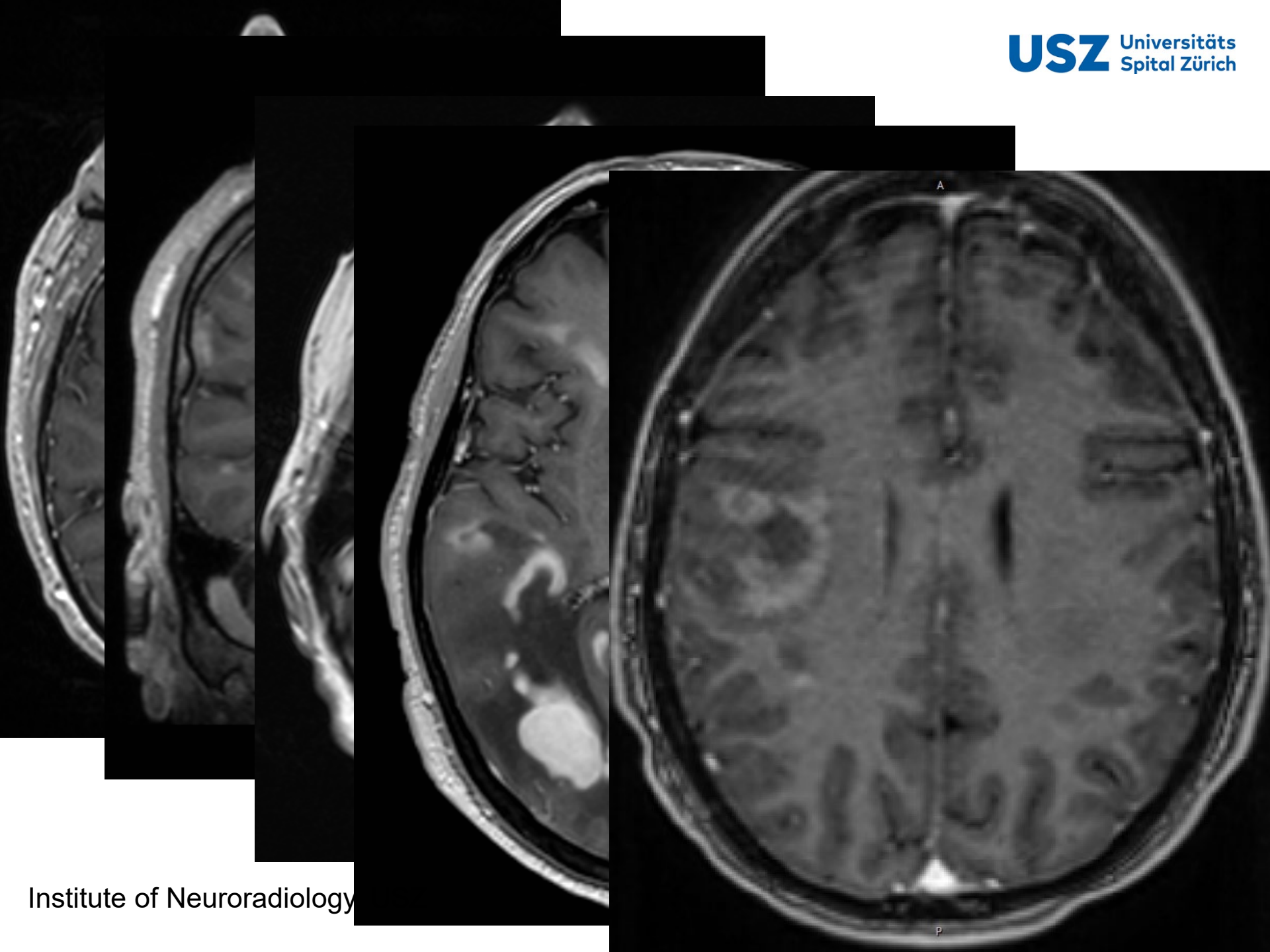


contrast



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Institute of Neuroradiology

How to confirm the diagnosis?

- Lumbar puncture: dissemination in the CSF in 20-30% of the patients with newly diagnosed PCNSL

  → Confirmation of a malignant B cell clone (FACS) or clonal IgH rearrangement using PCR

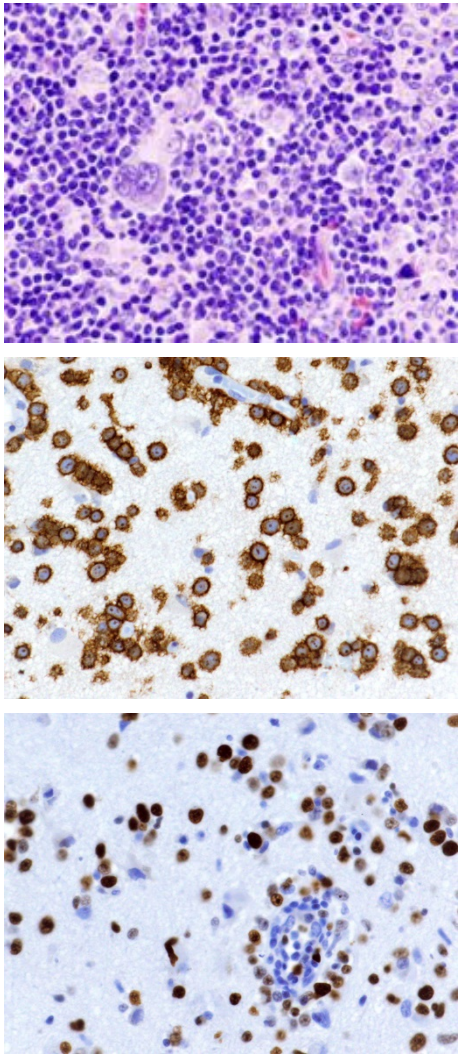
- Stereotactic biopsy: do not administer steroids before!
- Tumor resection does not affect survival (really…?)

Staging:

- Slit lamp examination (ocular involvement in 10-15%)
- (PET)-CT scan chest and abdomen, bone marrow biopsy
- HIV testing

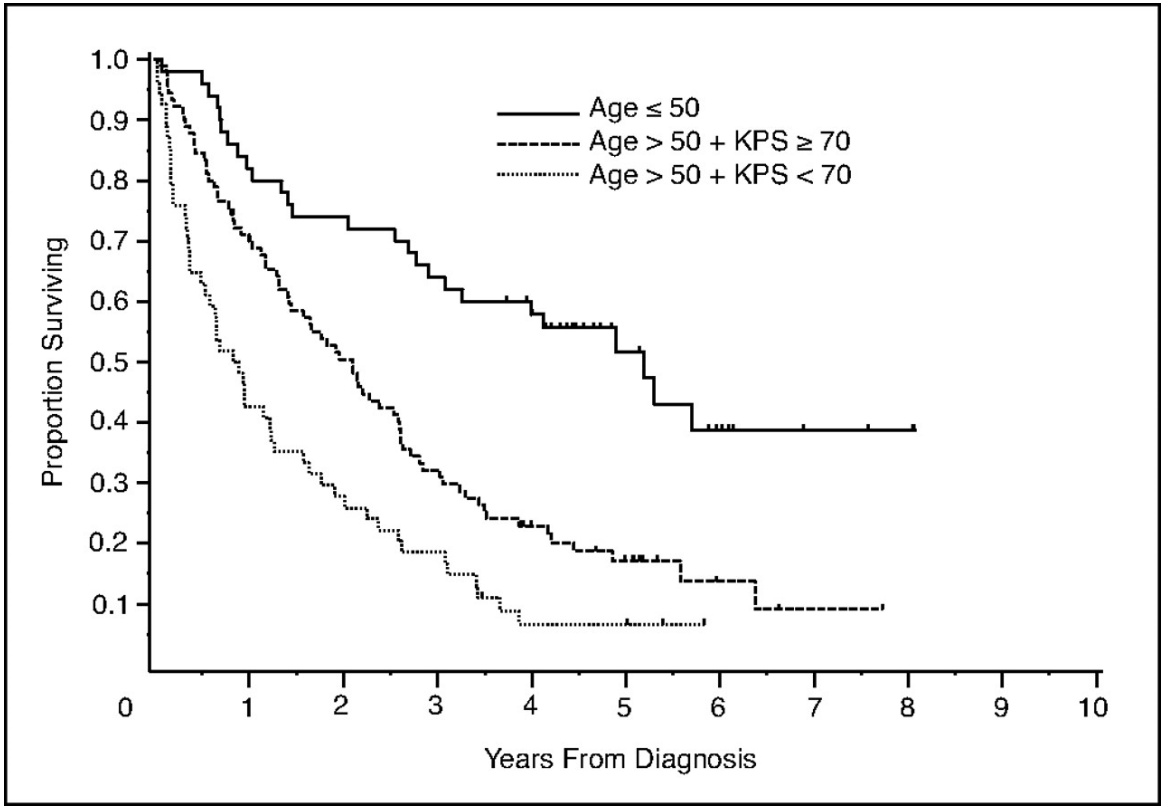
Histology

- Diffuse large B cell lymphoma (98%)
- CD20^{+}
- High proliferation index (>50% Ki-67^{+})



Prognosis

- Survival without treatment: weeks / few months
- Age and performance status are the most important prognostic factors



Abrey et al. J Clin Oncol 2006

No role for resection – for 4 decades

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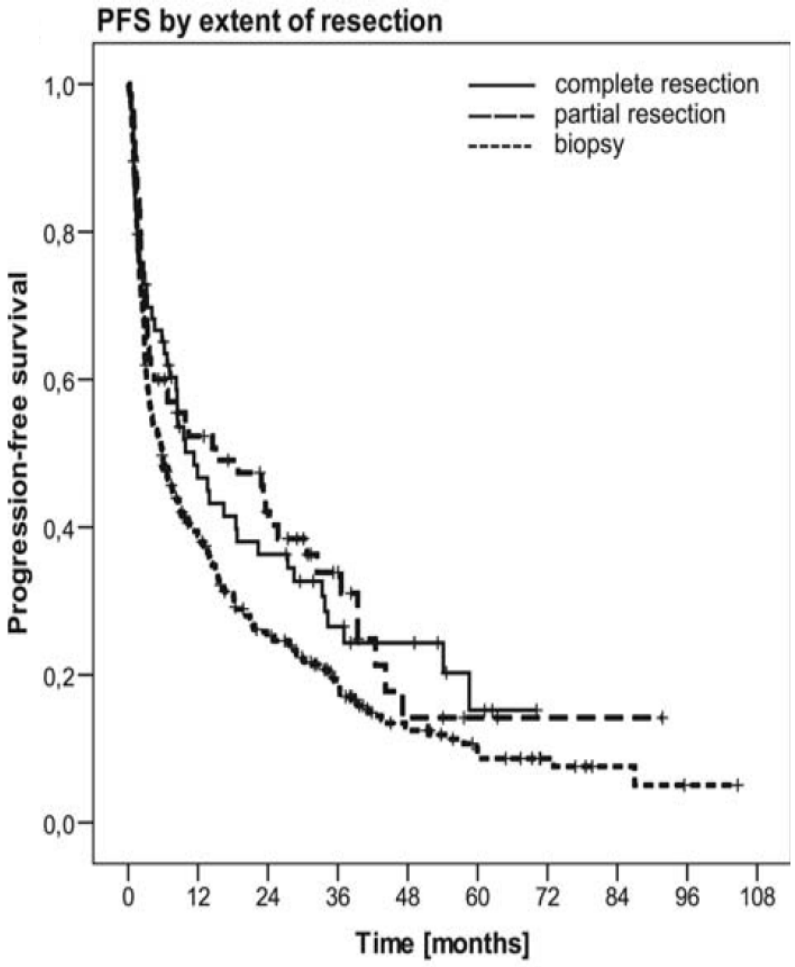
PRIMARY MALIGNANT LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM

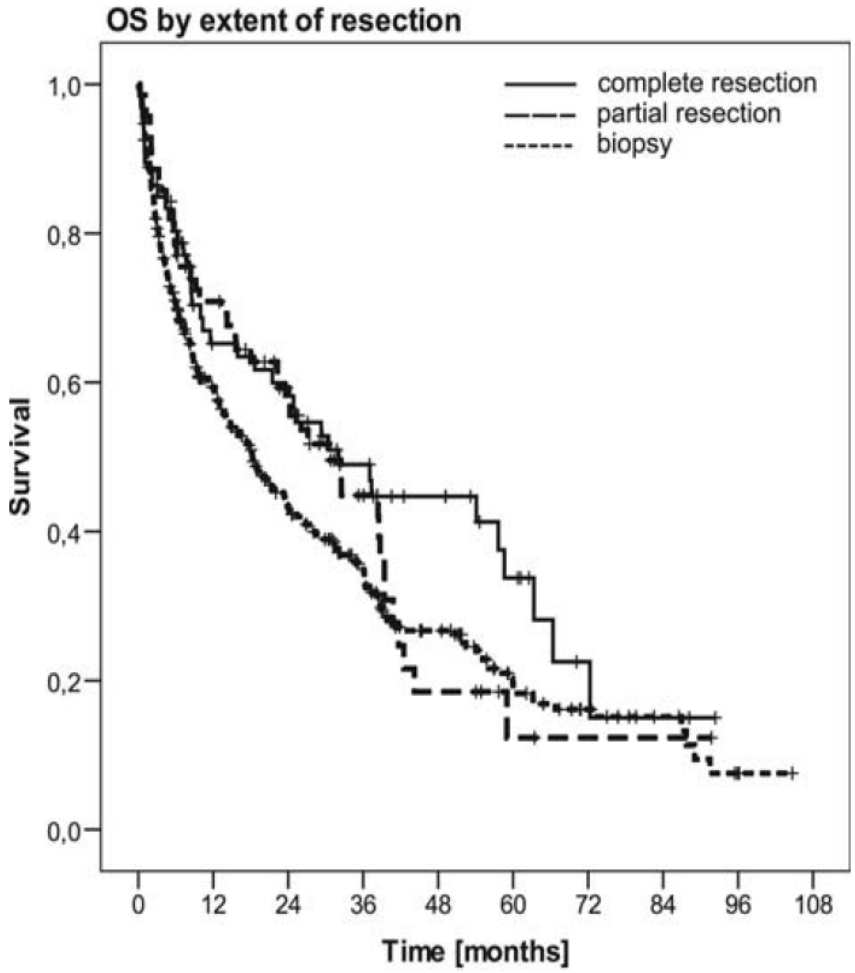
JAMES M. HENRY, MAJ, MC, USA, REID R. HEFFNER, JR, MD,
SAMUEL H. DILLARD, MAJ, MC, USA, KENNETH M. EARLE, MD,*
AND RICHARD L. DAVIS, MD†

Eighty-three cases of primary malignant lymphomas of the central nervous system (CNS) from the files of the AFIP were studied according to various clinical and pathologic parameters. The histologic patterns observed are analogous to those seen in the spectrum of malignant lymphomas arising in the reticuloendothelial system of other organs. The authors favor the diagnosis of primary malignant lymphoma of the CNS rather than that of "reticulum cell sarcoma" or "microgliomatosis" used in the past. Lesions are frequently multifocal, and surgery, other than for diagnostic biopsy, is not usually beneficial. The clinical course can be significantly prolonged by radiation therapy.

Cancer **34:1293–1302, 1974.**

Resection – may be considered…





Weller et al., Neuro Oncol 2012

Treatment of PCNSL over time

- **WBRT (>40 Gy)**
  - Median OS 12 months, <5% 5-year survival (Nelson et al., 1992)
- **High-dose methotrexate (HD-MTX)**: most active drug
  - Median survival approximately 25 months
  - ~25% surviving 5 years or more (Herrlinger et al., 2005)
- **HD-MTX + intrathecal MTX + WBRT**
  - Median OS 42 months
  - 25% 5-year survival (Abrey et al., 1998, DeAngelis et al., 2002)
  - **BUT**: up to 60% of all patients (and virtually all elderly patients) suffer from severe **neurotoxicity** (Abrey et al., 1998; Harder et al., 2004)

How to improve induction and consolidation therapy and avoid neurotoxicity?

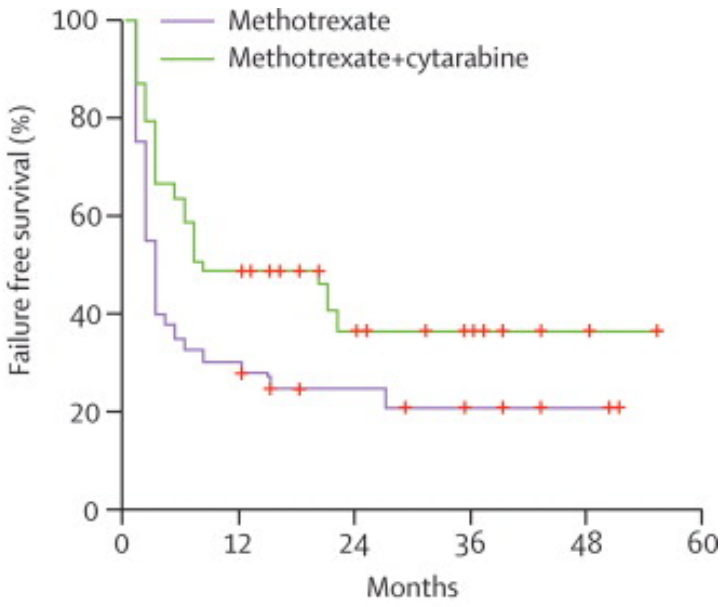
IELSG-20: MTX vs. MTX/Ara-C

- Randomized phase II trial, 24 centers, 6 countries
- 79 patients, age 18-75 Jahre
- 4 cycles of MTX, 3.5 g/m^2 alone **OR** MTX plus 4x Ara-C, 2 g/m^2 d2+3, every 3 weeks, followed by WBRT
- CR rate after MTX-based therapy:
  18% (MTX) versus 46% (MTX + Ara-C)
- Hematological toxicity more frequent and severe with combination

Ferreri et al., Lancet 2009

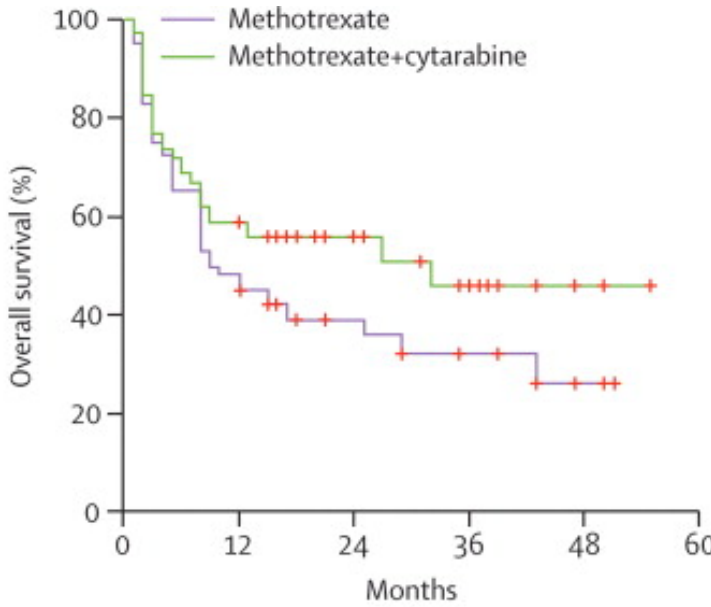
IELSG-20: MTX vs. MTX/Ara-C

PFS



Number at risk				
Methotrexate	11	7	4	2
Methotrexate+cytarabine	19	9	6	2

OS



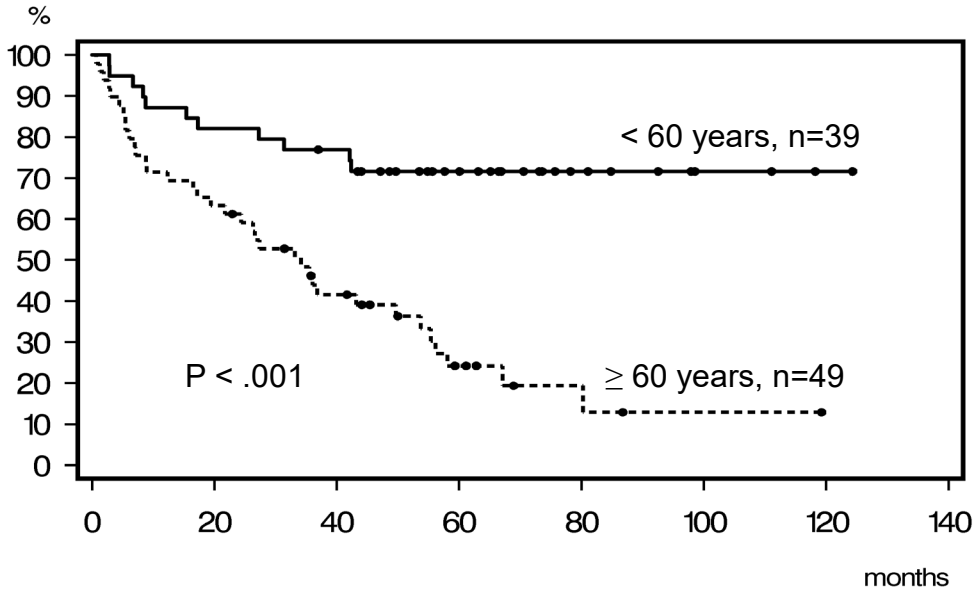
Number at risk				
Methotrexate	19	12	7	3
Methotrexate+cytarabine	22	13	7	3

3 year survival rate 32% versus 46% (p = 0.07)

Ferreri et al., Lancet 2009

Bonn protocol - polychemotherapy

- 88 patients
- Systemic therapy (HD-MTX, Ara-C, vinca-alkaloids, ifosfamide, cyclophosphamide) + intraventricular chemotherapy (MTX, prednisolone, Ara-C)
- 60% CR, median OS 55 months

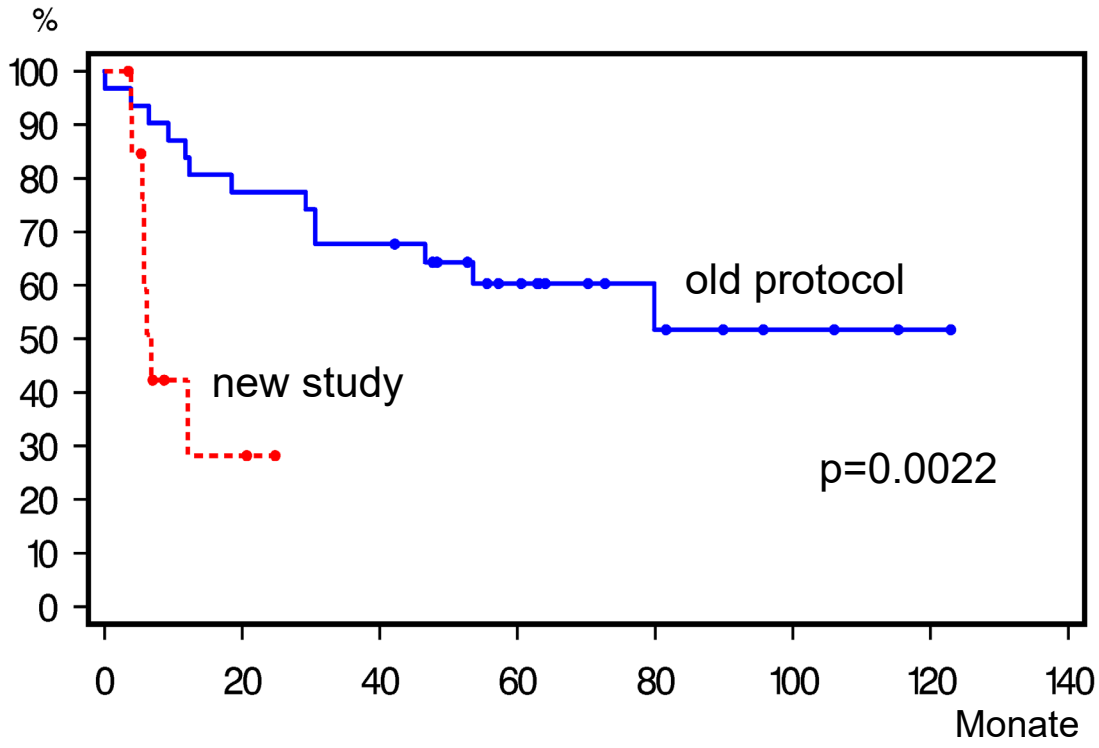


9% dying from toxicity
23% reservoir infection

Pels et al., J Clin Oncol 2003

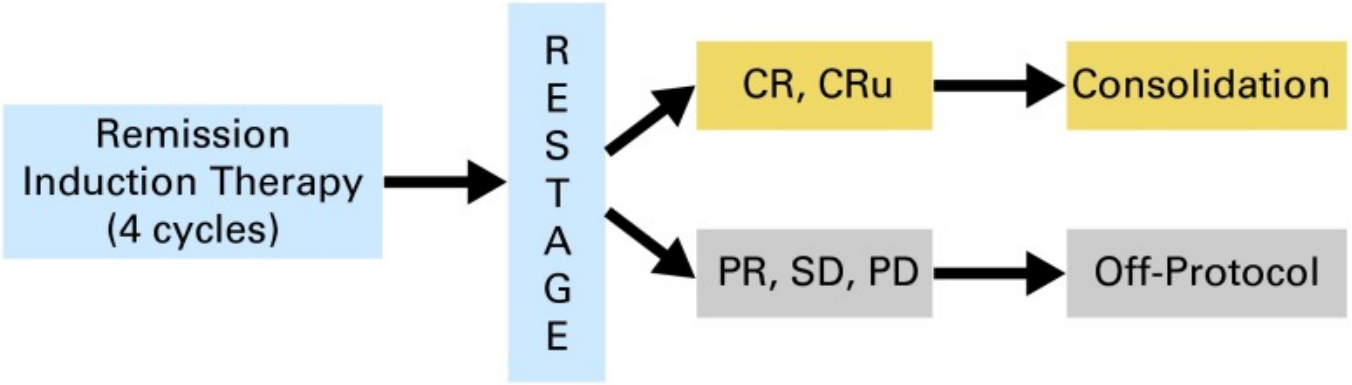
Bonn protocol 2

- No intrathecal chemotherapy (n=18):
- CR rate reduced compared to previous study (53%)
- PFS shorter



Pels et al., J Neurooncol 2009

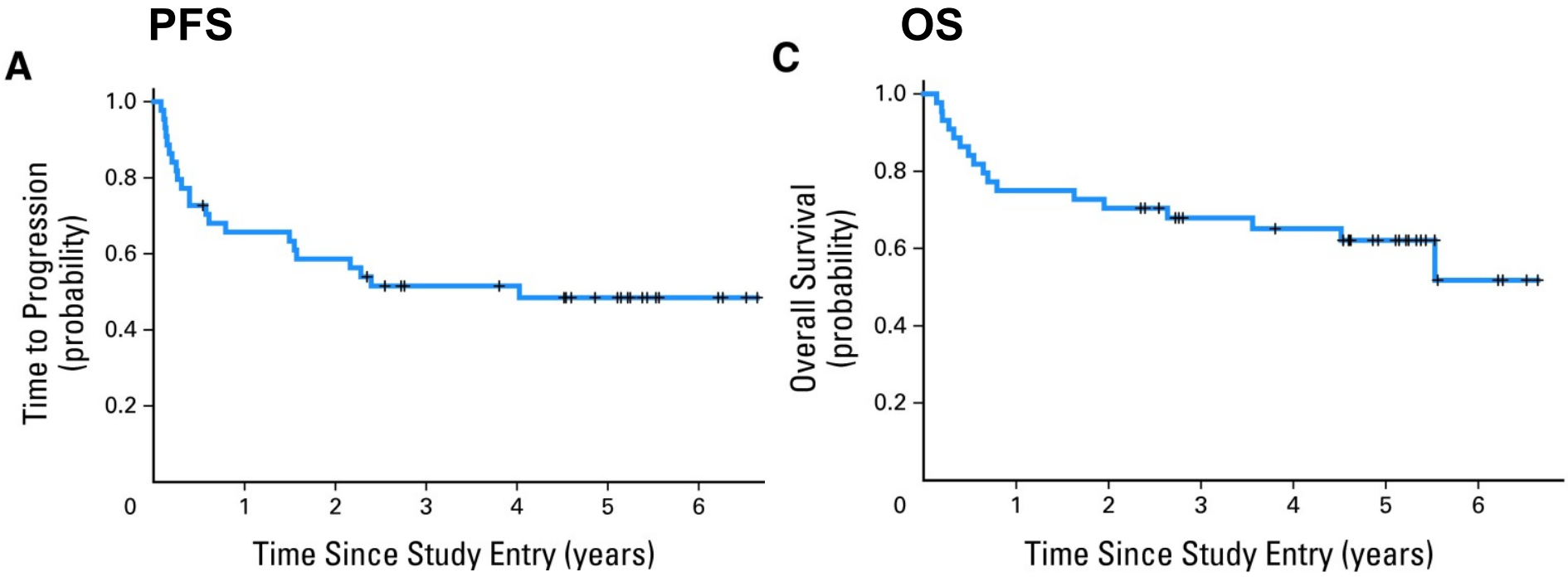
CALGB 50202
intensive chemotherapy + rituximab



Remission Induction Therapy: MT-R (14-day cycle)	
Day 1	Methotrexate 8 grams/m^2 IV over 4 hrs
Day 2	Leucovorin 100 mg/m^2 every 6 hrs, until methotrexate < 0.05 mM
Day 3	Rituximab 375 mg/m^2 IV cycles 1 through 6
Day 7-11	Temozolomide 150 mg/m^2 PO (odd cycles only)
Consolidation Therapy: EA	
Day 1-4	Etoposide 40 mg/kg continuous IV over 96 hrs
Day 1-4	Cytarabine 2 gm/m^2 IV over 2 hrs every 12 hrs × 8 doses

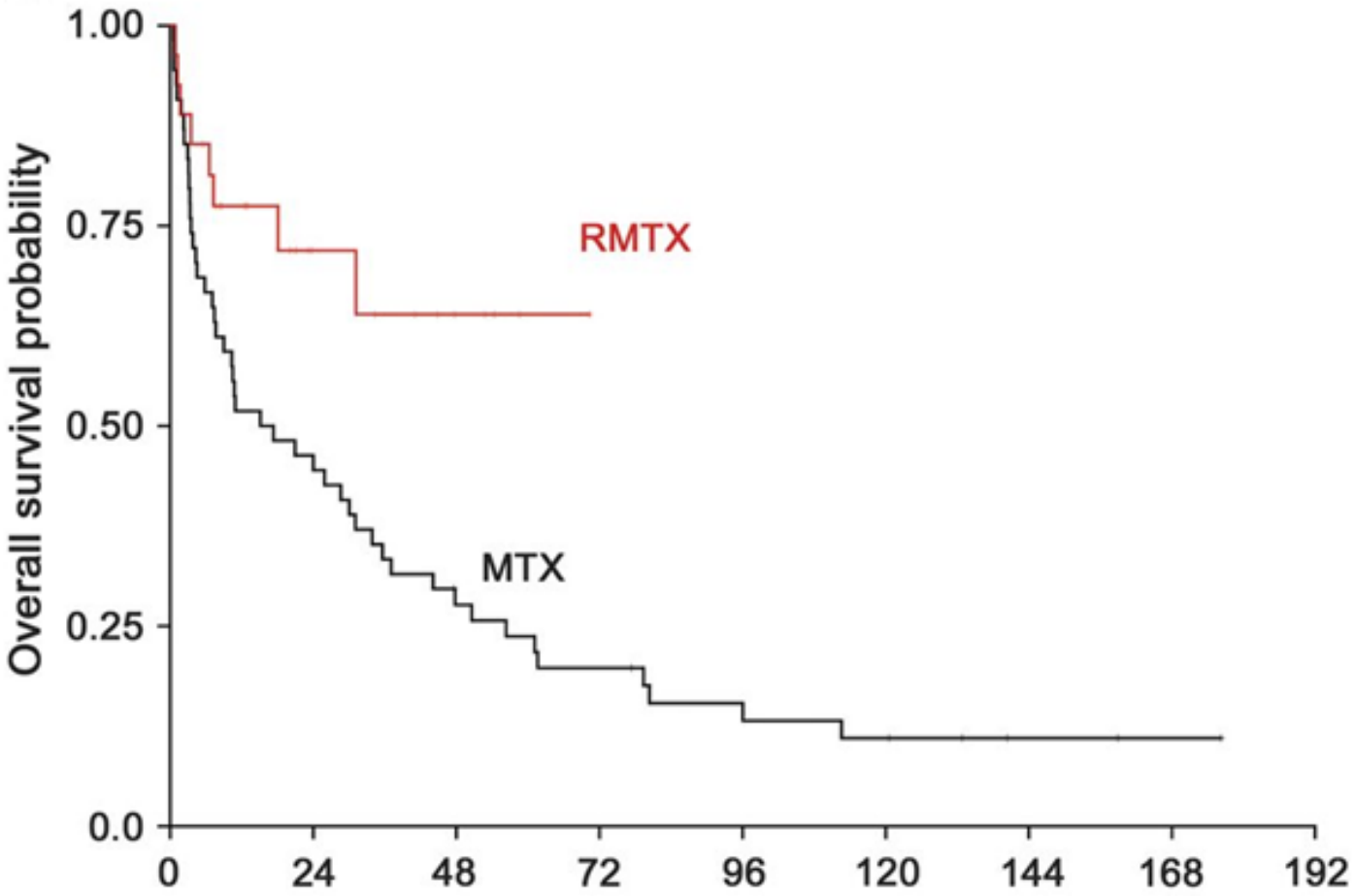
Rubenstein et al., J Clin Oncol 2013

CALGB 50202
intensive chemotherapy + rituximab



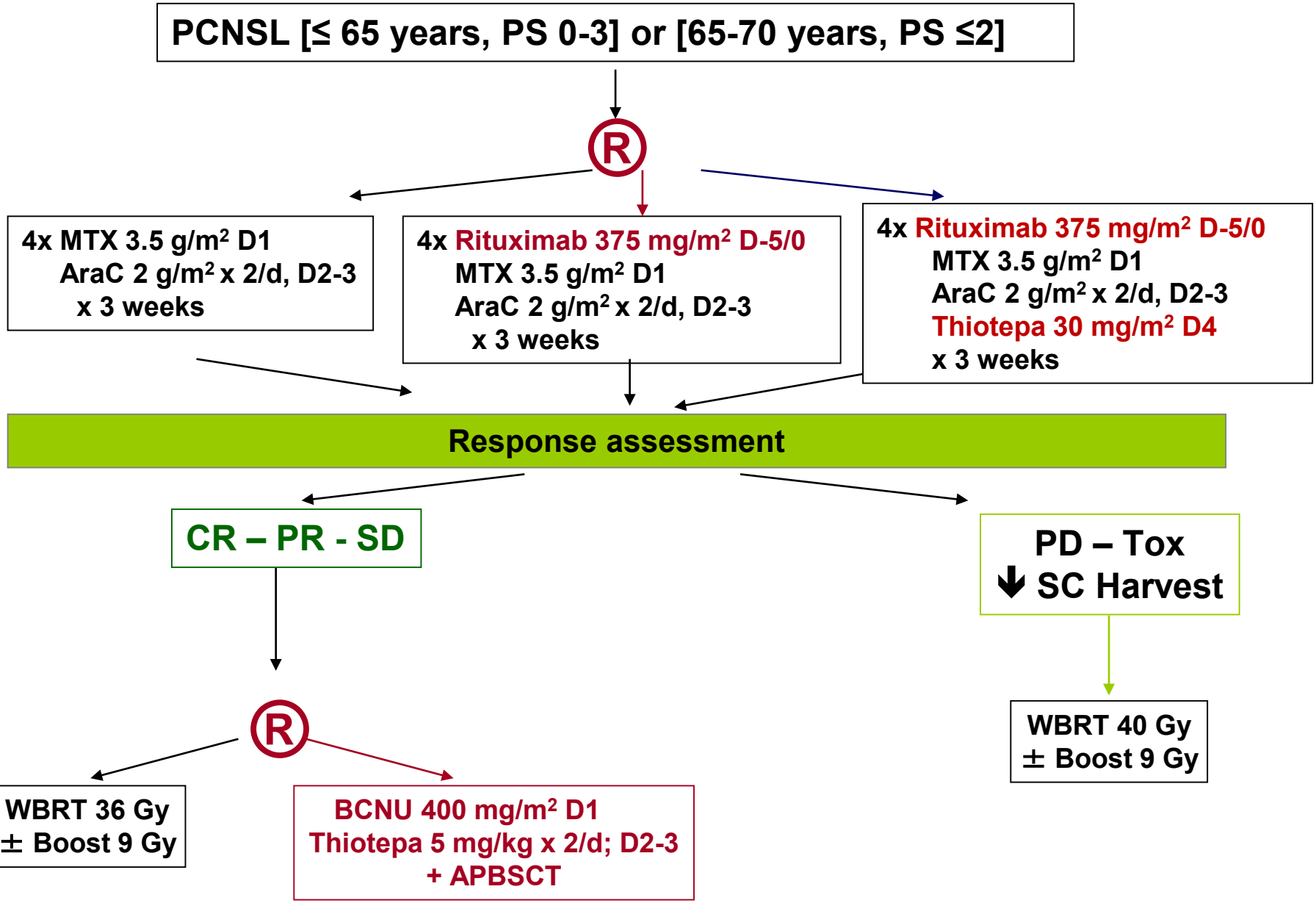
Rubenstein et al., J Clin Oncol 2013

What is the role for rituximab in PCNSL?



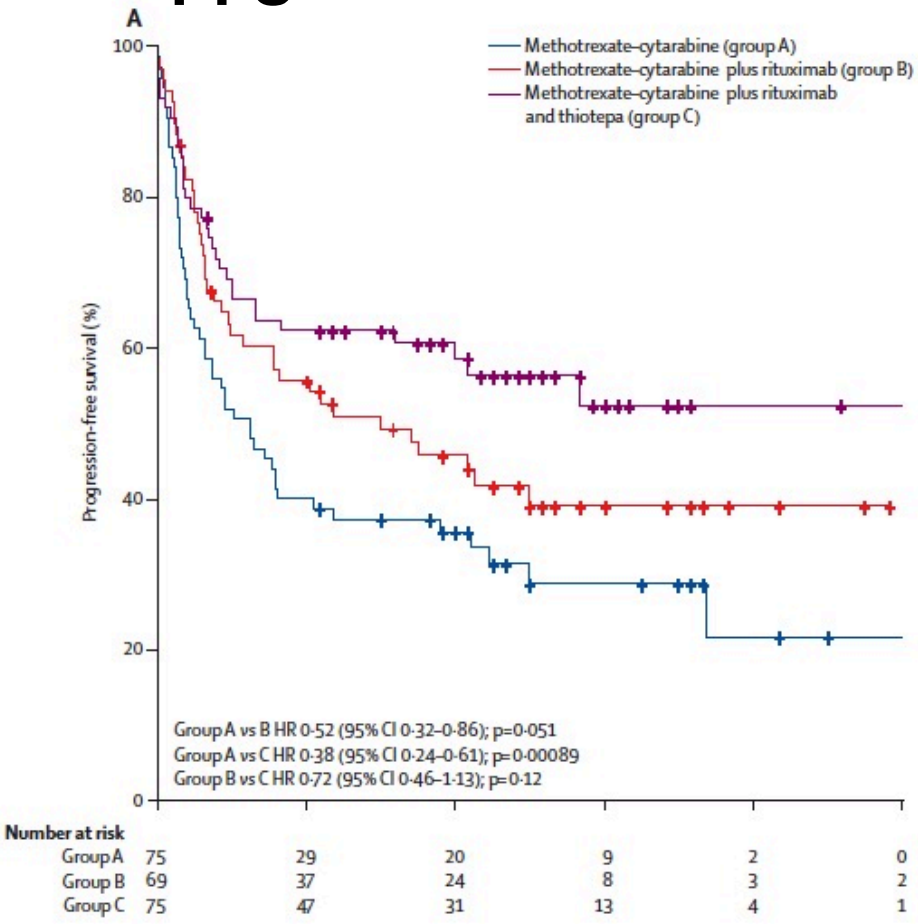
Holdhoff et al., Neurology 2014

IELSG-32 trial



IELSG-32 trial

PFS



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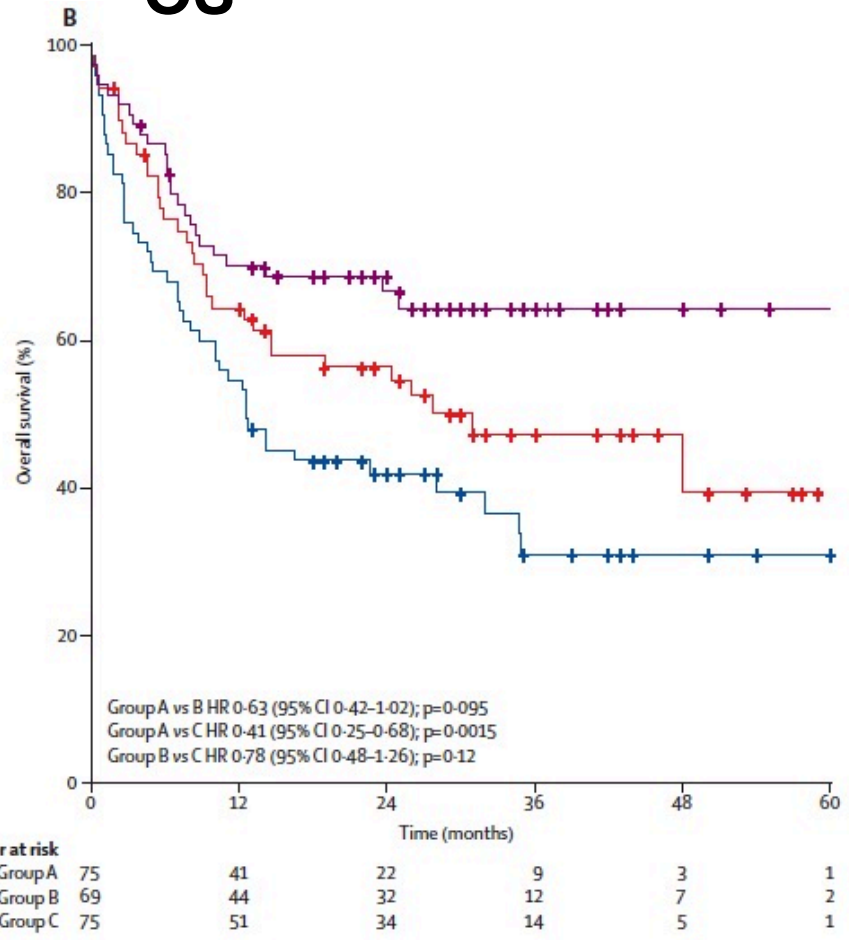
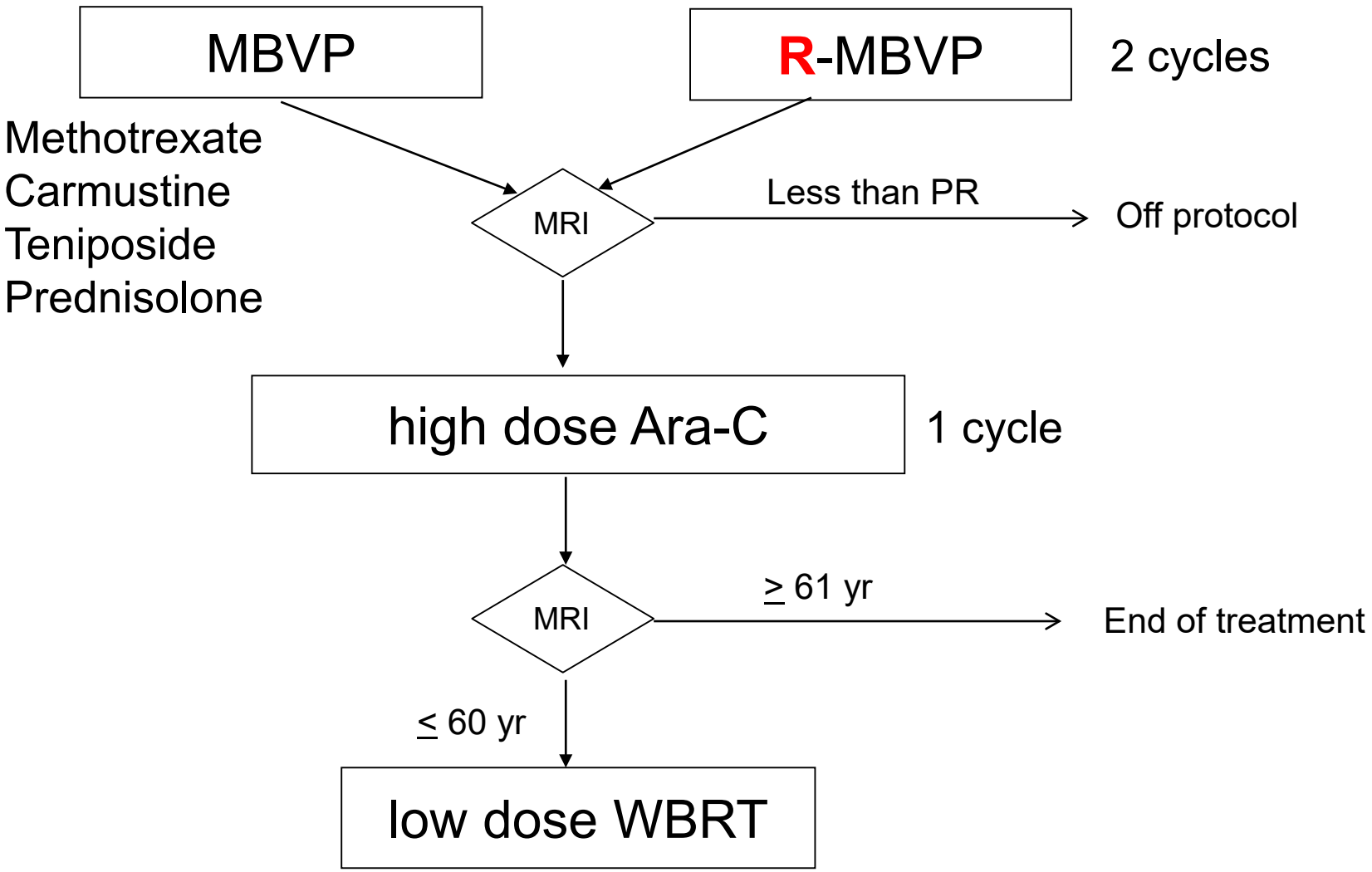


Ferreri et al., Lancet Haematol 2016

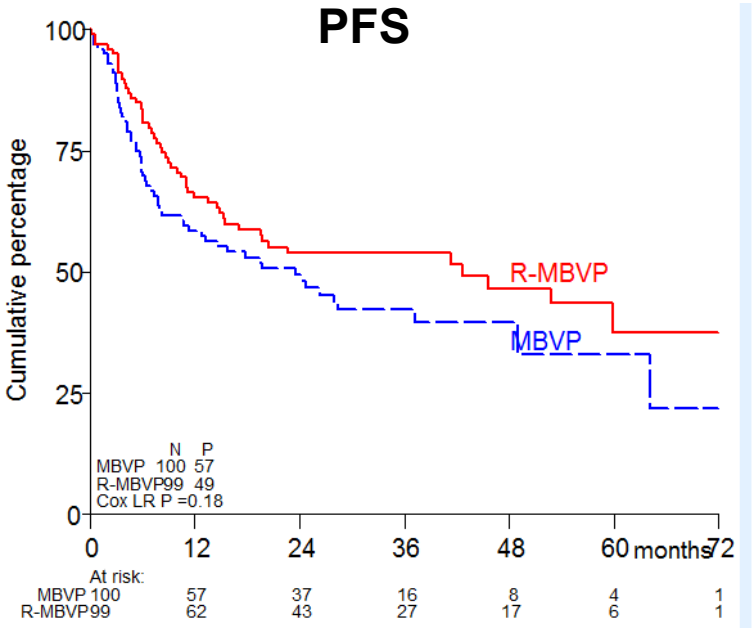
HOVON 105/ALLG NHL 24 trial

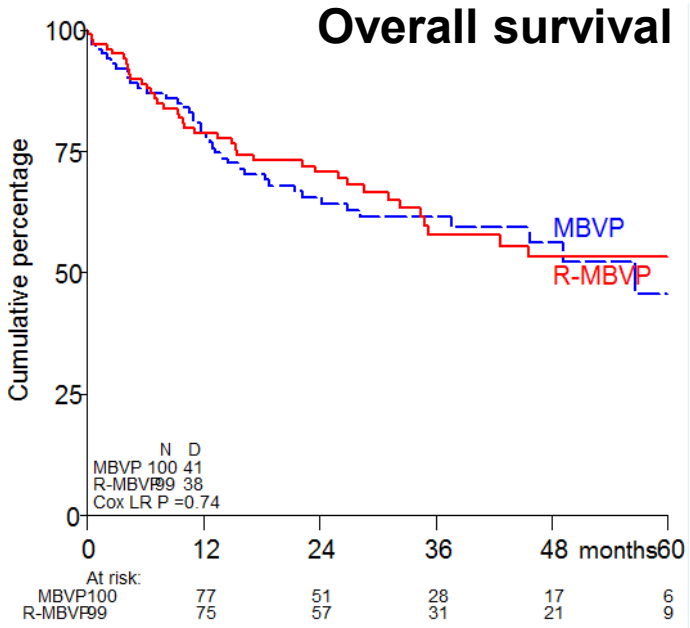


Bromberg et al., Lancet Oncol 2019

Response to treatment / survival

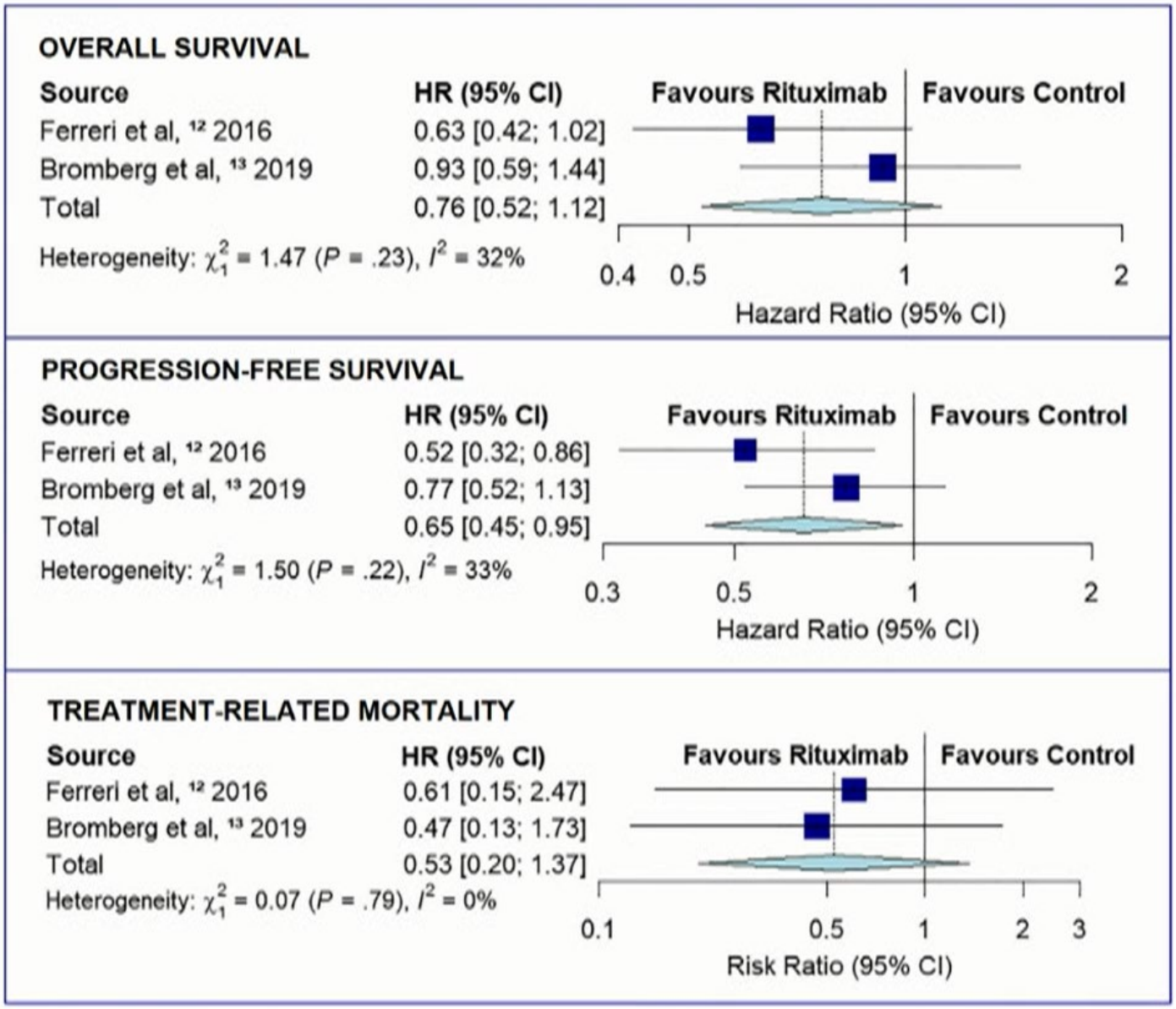
	MBVP (n=100)	R-MBVP (n=99)
After (R-)MBVP		
CR/CRu	36%	30%
PR	50%	56%
ORR	86%	86%





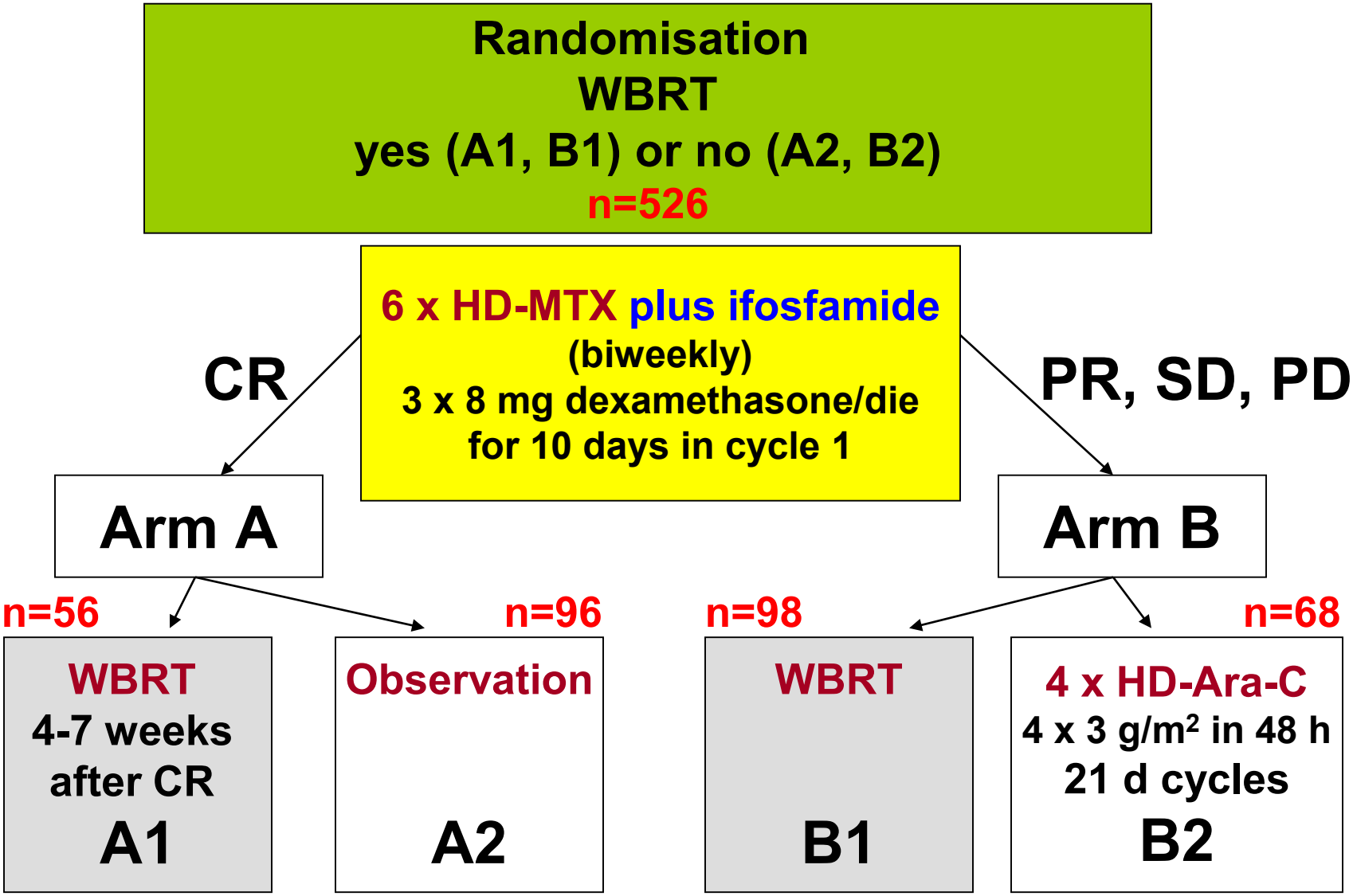
Bromberg et al., Lancet Oncol 2019

Rituximab in PCNSL



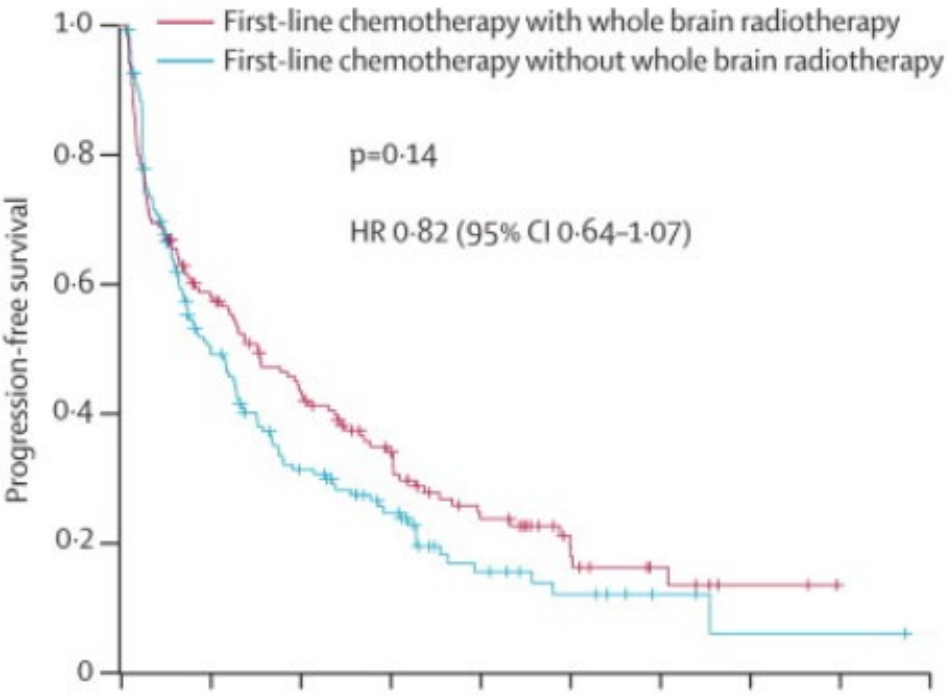
Schmitt et al., Hematol Oncol 2019

The G-PCNSL-SG1 trial



The G-PCNSL-SG1 trial

PFS



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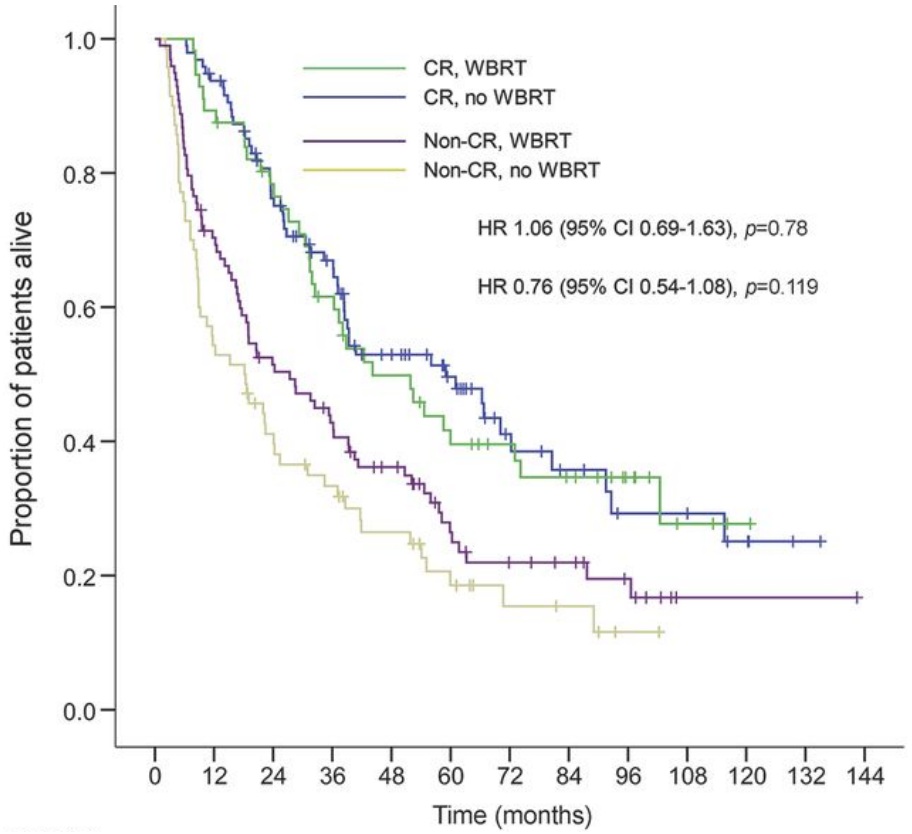


→ early WBRT does not prolong overall survival

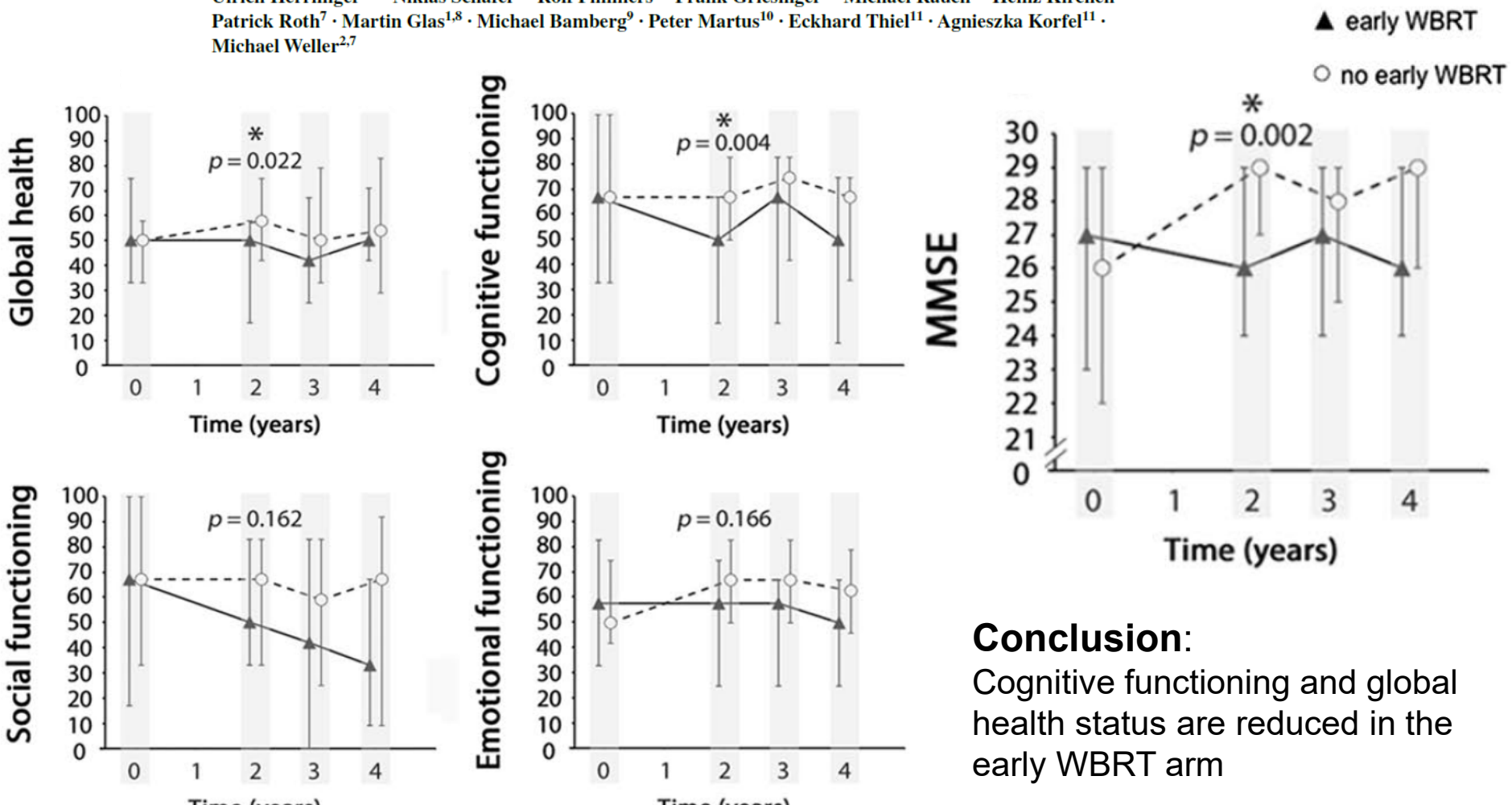
Thiel et al., Lancet Oncol 2009
Korfel et al. Neurology 2015

J Cancer Res Clin Oncol
DOI 10.1007/s00432-017-2423-5

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Early whole brain radiotherapy in primary CNS lymphoma: negative impact on quality of life in the randomized G-PCNSL-SG1 trial

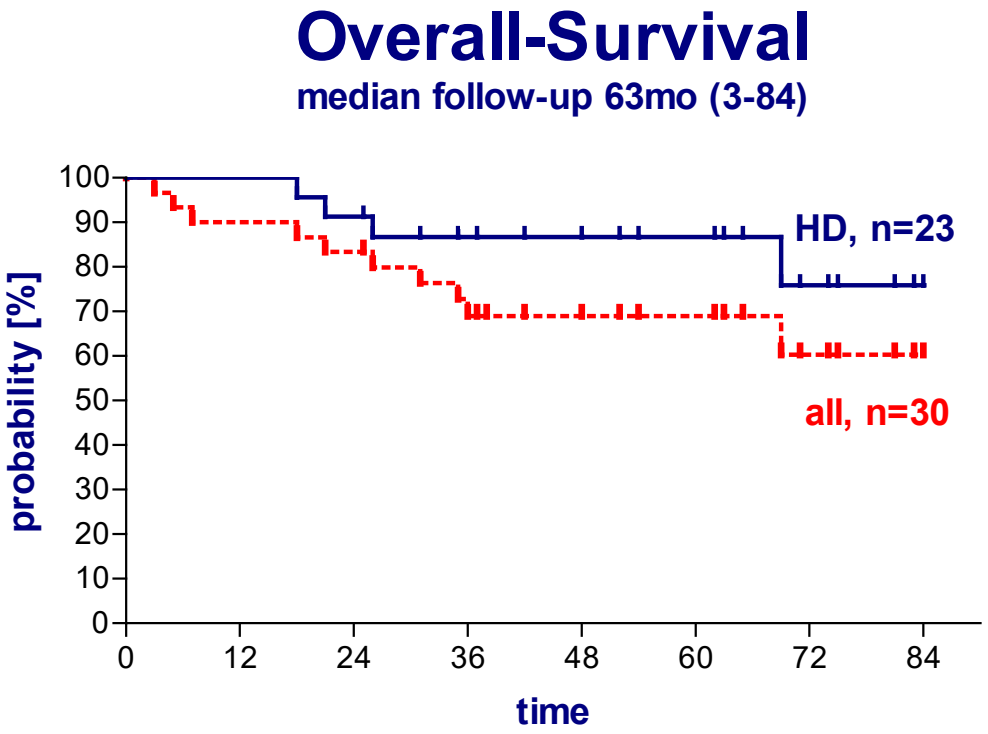
Ulrich Herrlinger[1,2] · Niklas Schäfer[1] · Rolf Fimmers[3] · Frank Griesinger[4] · Michael Rauch[5] · Heinz Kirchen[6] · Patrick Roth[7] · Martin Glas[1,8] · Michael Bamberg[9] · Peter Martus[10] · Eckhard Thiel[11] · Agnieszka Korfel[11] · Michael Weller[2,7]



Conclusion:
Cognitive functioning and global health status are reduced in the early WBRT arm

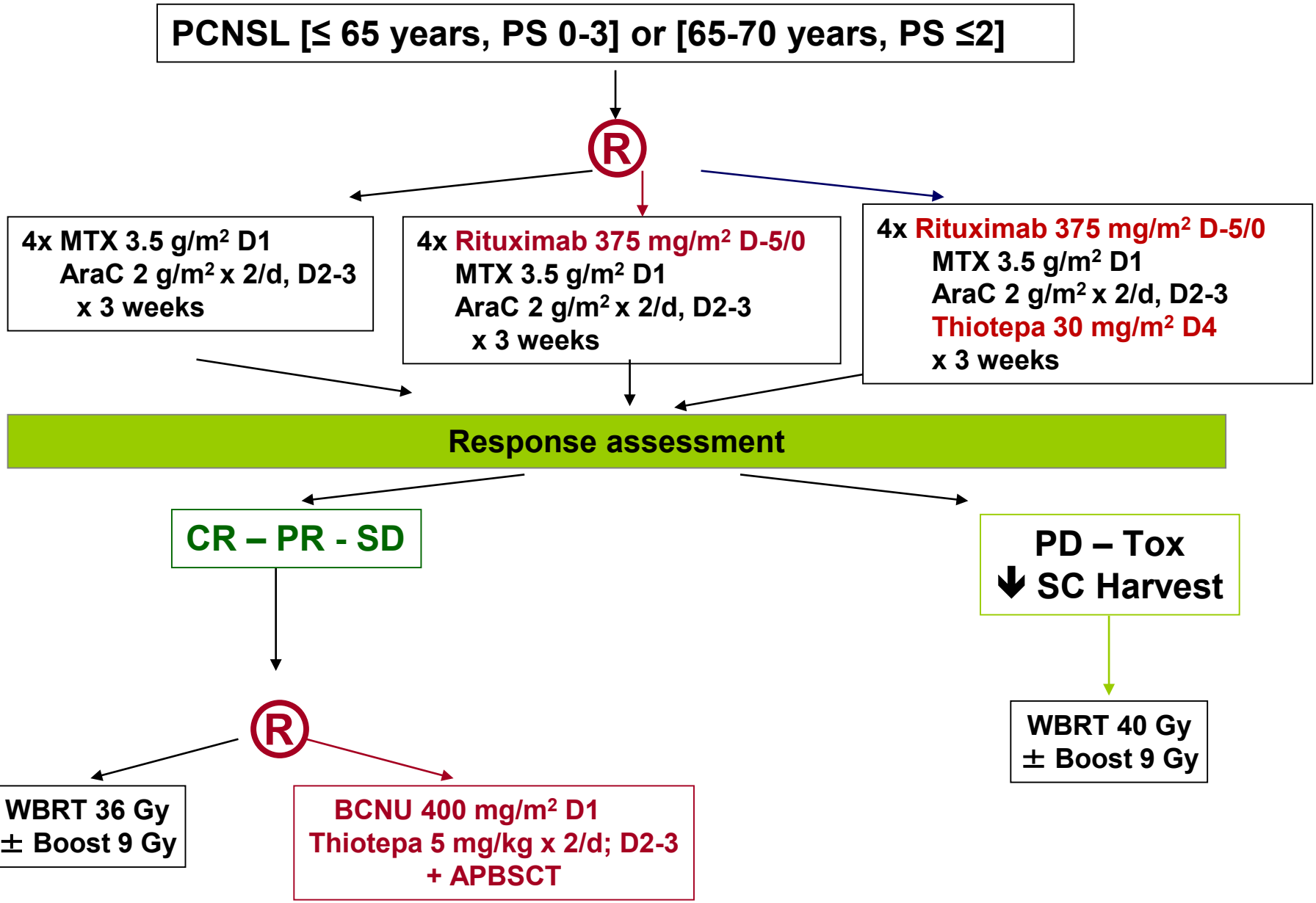
High-dose chemotherapy with autologous stem cell support

- High-dose chemotherapy followed by autologous stem cell transplantation
- Only patients younger than 60 years



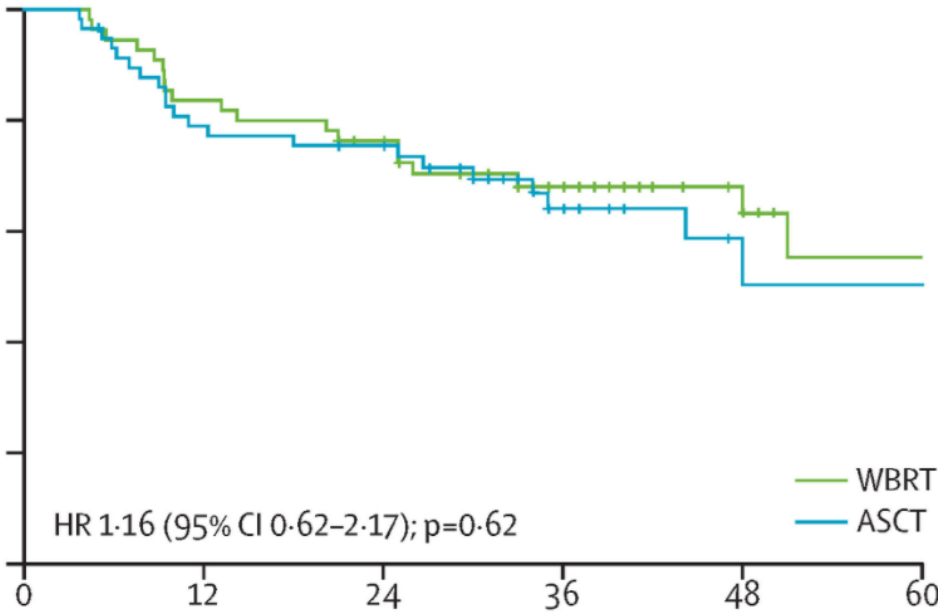
Illerhaus et al., J Clin Oncol 2006

IELSG-32 trial: 2nd randomization

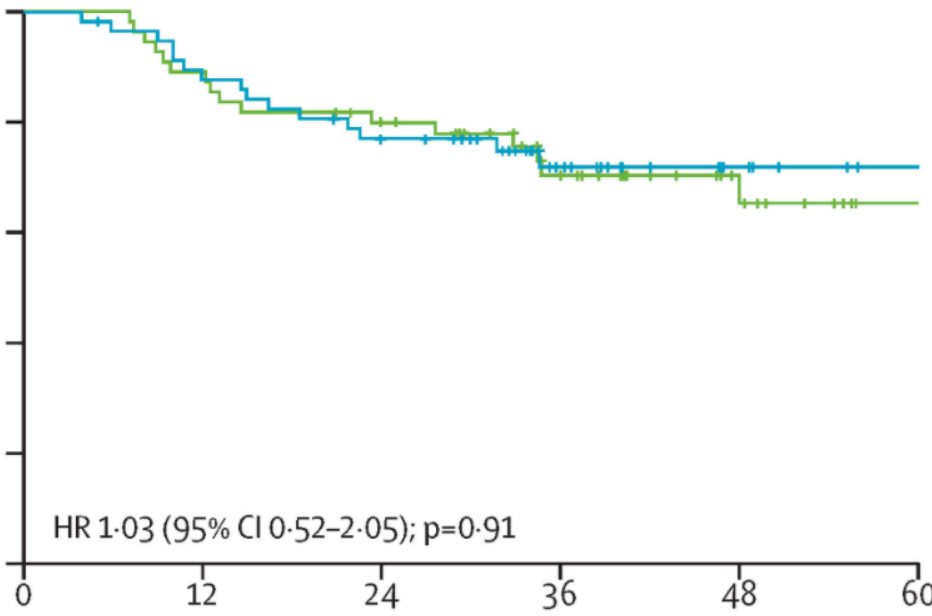


IELSG-32 trial: 2nd randomization

Progression-free survival



Overall survival



Ferreri et al., Lancet Hematol 2017

PRECIS study: WBRT vs. ASCT

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- 140 patients with newly diagnosed PCNSL
- Induction chemotherapy: R-MBVP, followed by R-AraC

original report

Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study

Caroline Houillier, MD[1]; Luc Taillandier, PhD[2]; Sylvain Dureau, PharmD[3]; Thierry Lamy, MD, PhD[4]; Mouna Laadhari, MD[3]; Olivier Chinot, MD, PhD[5]; Cecile Moluçon-Chabrot, MD[6]; Pierre Soubeyran, MD, PhD[7]; Remy Gressin, MD[8]; Sylvain Choquet, MD[1]; Gandhi Damaj, MD, PhD[9]; Antoine Thyss, MD[10]; Julie Abraham, MD[11]; Vincent Delwail, MD[12]; Emmanuel Gyan, MD, PhD[13]; Laurence Sanhes, MD[14]; Jérôme Cornillon, MD, PhD[15]; Reda Garidi, MD[16]; Alain Delmer, MD, PhD[17]; Marie-Laure Tanguy, PharmD[13]; Ahmad Al Jijakli, MD[18]; Pierre Morel, MD[19]; Pascal Bourquard, MD[20]; Marie-Pierre Moles, MD[21]; Adrien Chauchet, MD[22]; Thomas Gastinne, MD[23]; Jean-Marc Constans, MD, PhD[9]; Adriana Langer, MD[3]; Antoine Martin, MD, PhD[24]; Patricia Moisson, MD[3]; Lucette Lacomblez, PhD[1]; Nadine Martin-Duverneuil, MD[1]; Daniel Delgadillo, PhD[1]; Isabelle Turbiez, HDR[3]; Loïc Feuvret, MD[1]; Nathalie Cassoux, MD, PhD[3]; Valérie Touitou, MD, PhD[1]; Damien Ricard, MD, PhD[25]; Khê Hoang-Xuan, MD, PhD[1]; and Carole Soussain, MD, PhD[3] on behalf of the Intergroupe GOELAMS–ANOCEF and the LOC Network for CNS Lymphoma

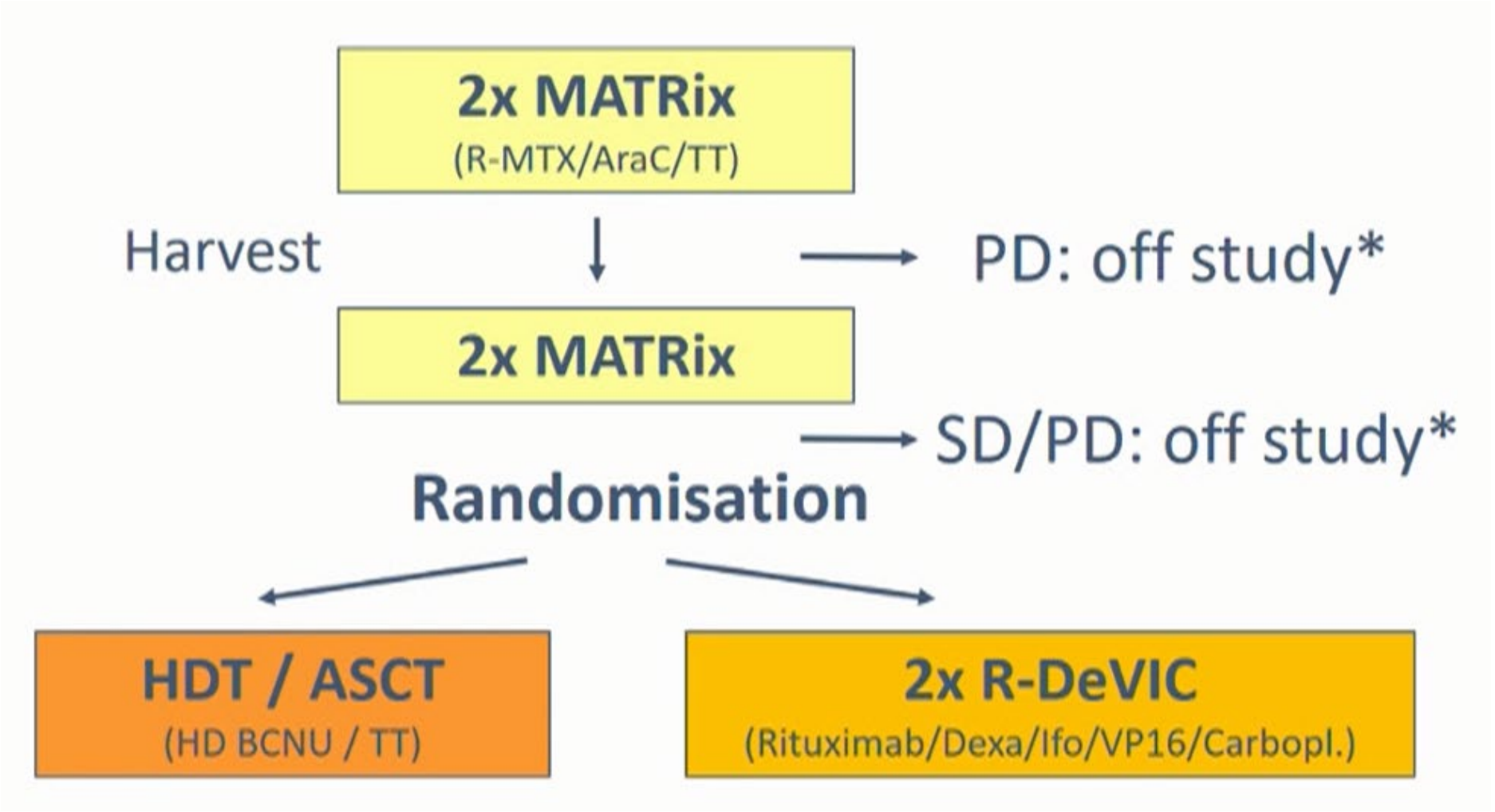
Randomization:

- Thiotepa, busulfan, cyclophosphamide → ASCT
- WBRT (40 Gy)

- 2-year PFS rates: WBRT: 63%; ASCT: 87%
- Cognitive impairment was observed after WBRT but not after ASCT

Houillier et al., J Clin Oncol 2019

IELSG-43 trial



High-dose chemotherapy and autologous stem cell transplant
or
consolidating conventional chemotherapy

Treatment at recurrence

- **No standard of care**

  Individual decision based on previous treatment, response to initial therapy, performance status, age….

- **Available options**

  HD-MTX re-challenge

  Other chemotherapeutic drugs (topotecan, temozolomide…)

  High-dose chemotherapy + stem cell transplantation

  WBRT

Elderly PCNSL patients: a particular challenge

- Median age of PCNSL patients: ~ 60 years
- Definition of “elderly“ is imprecise:
  - ≥ 60 years?
  - ≥ 65 years?
  - ≥ 70 years?

Neue Zürcher Zeitung

Die älteste Schweizerin ist 112 Jahre alt geworden – nun ist sie gestorben

Alice Schaufelberger wurde vor dem Ersten Weltkrieg geboren. Kürzlich ist sie in einem Zürcher Altersheim für immer eingeschlafen.

Dorothee Vögeli, Pauline Voss
28.11.2020, 11.13 Uhr

Hören Merken Drucken Teilen

- Therapeutic relevance: age is an inclusion criterion in many trials
- (Neuro)toxicity is a particular concern in the elderly

Elderly PCNSL patients in G-PCNSL-SG1

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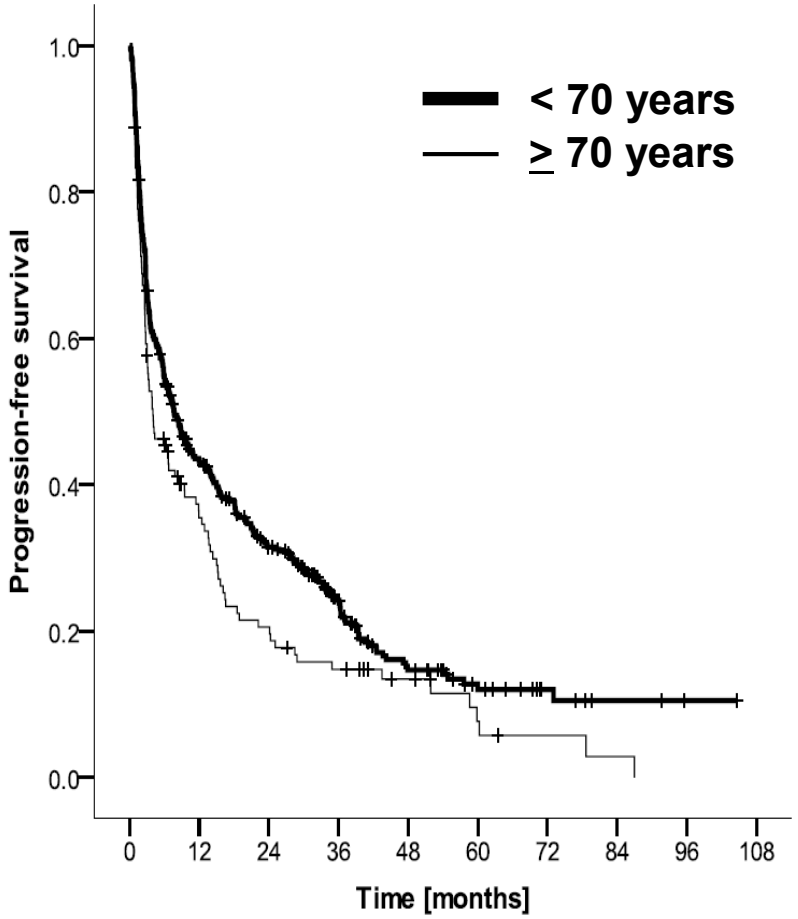
n=526

PFS



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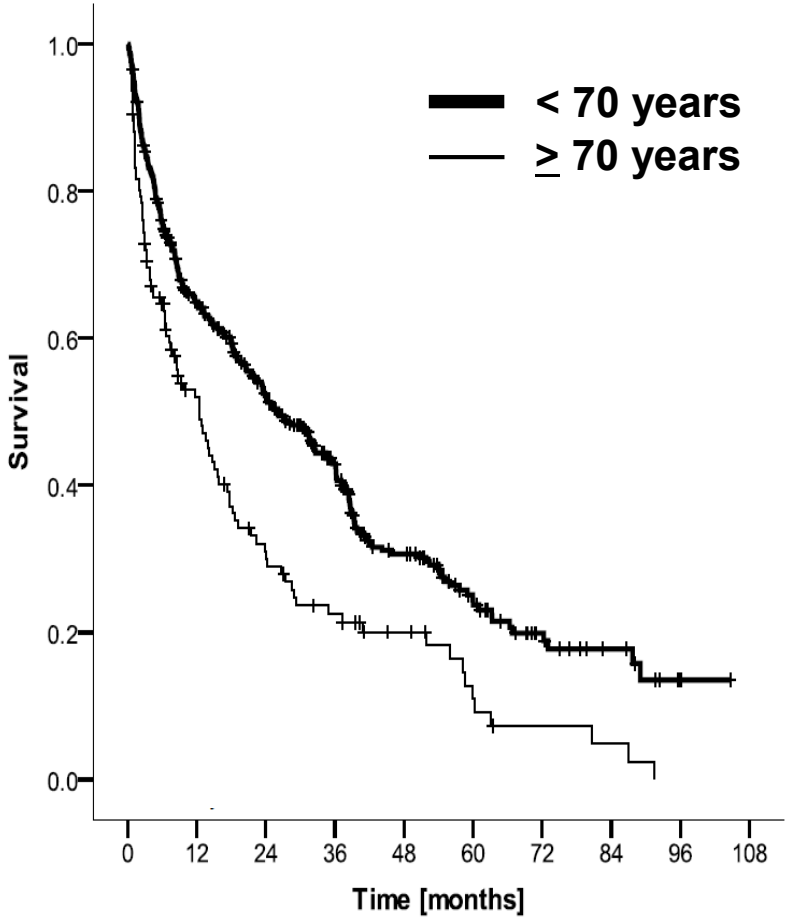


Roth et al., Neurology 2012

Elderly PCNSL patients in G-PCNSL-SG1

	PFS (months)	OS (months)
No-CR patients		
≥ 70 years	3.2	17.3
< 70 years	3.5	22.3
CR patients		
≥ 70 years	16.1	26.7
< 70 years	35.0	44.2

=> Relapses occur earlier in elderly patients

Roth et al., Neurology 2012

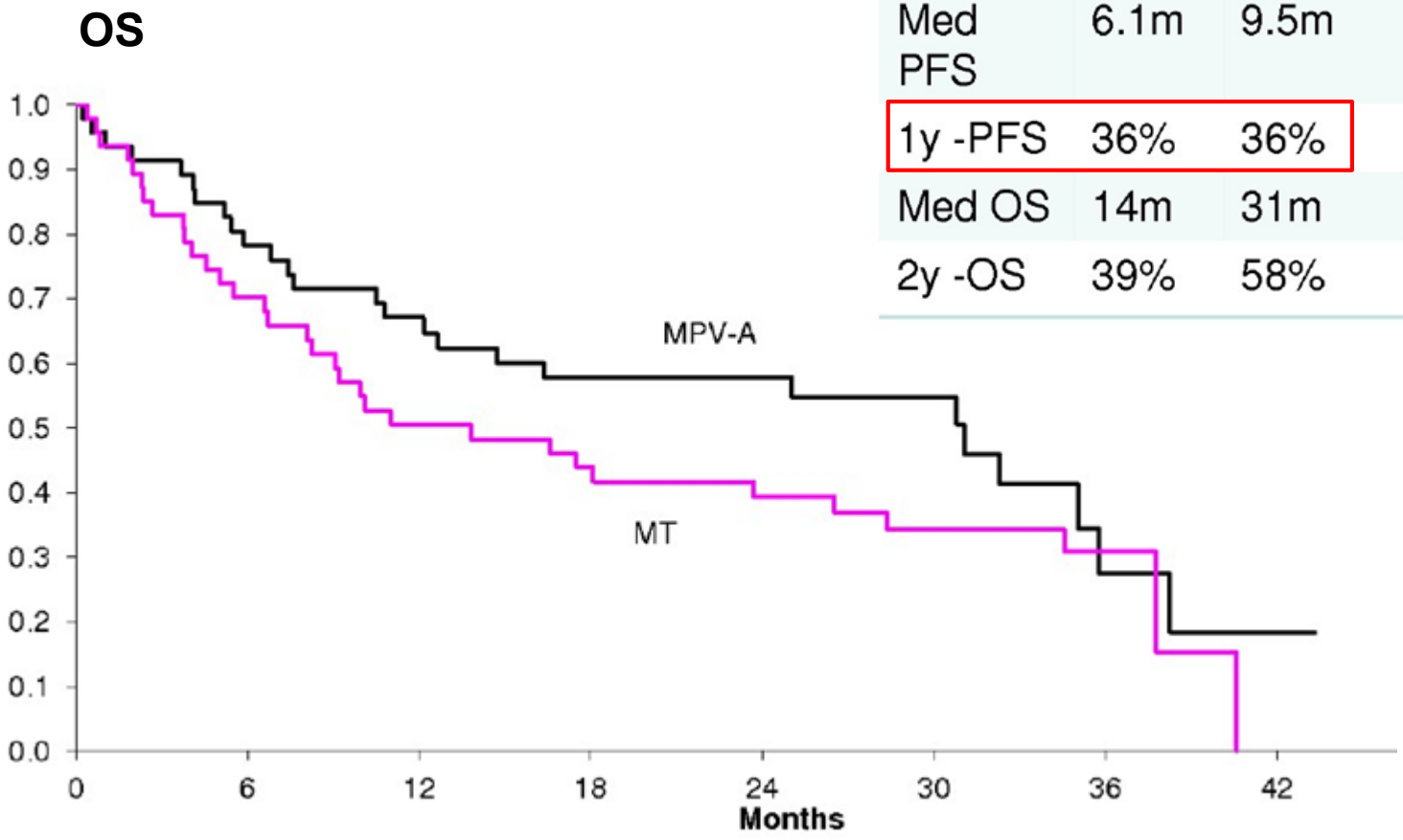
MTX/TMZ vs. MPV-A in elderly patients

- Randomized phase II trial
- 95 patients, median age 72 years (60–85)
- Treatment arms:
  - MTX 3.5 g/m^2 + Temozolomide
  - MTX 3.5 g/m^2 + Procarbazine, Vincristine, AraC
- Primary einpoint: PFS at 1 year (PFS-1)
- Toxicity (Grad 3/4): no difference
- CR rate: 45% (MT) vs. 62% (MPV-A)

Omuro et al., Lancet Hematol 2015

MTX/TMZ vs. MPV-A in elderly patients

	MT	MPV-A	Pvalue
Med PFS	6.1m	9.5m	0.6
1y -PFS	36%	36%	
Med OS	14m	31m	0.2
2y -OS	39%	58%	



Omuro et al., Lancet Hematol 2015

MTX-based therapy in elderly patients

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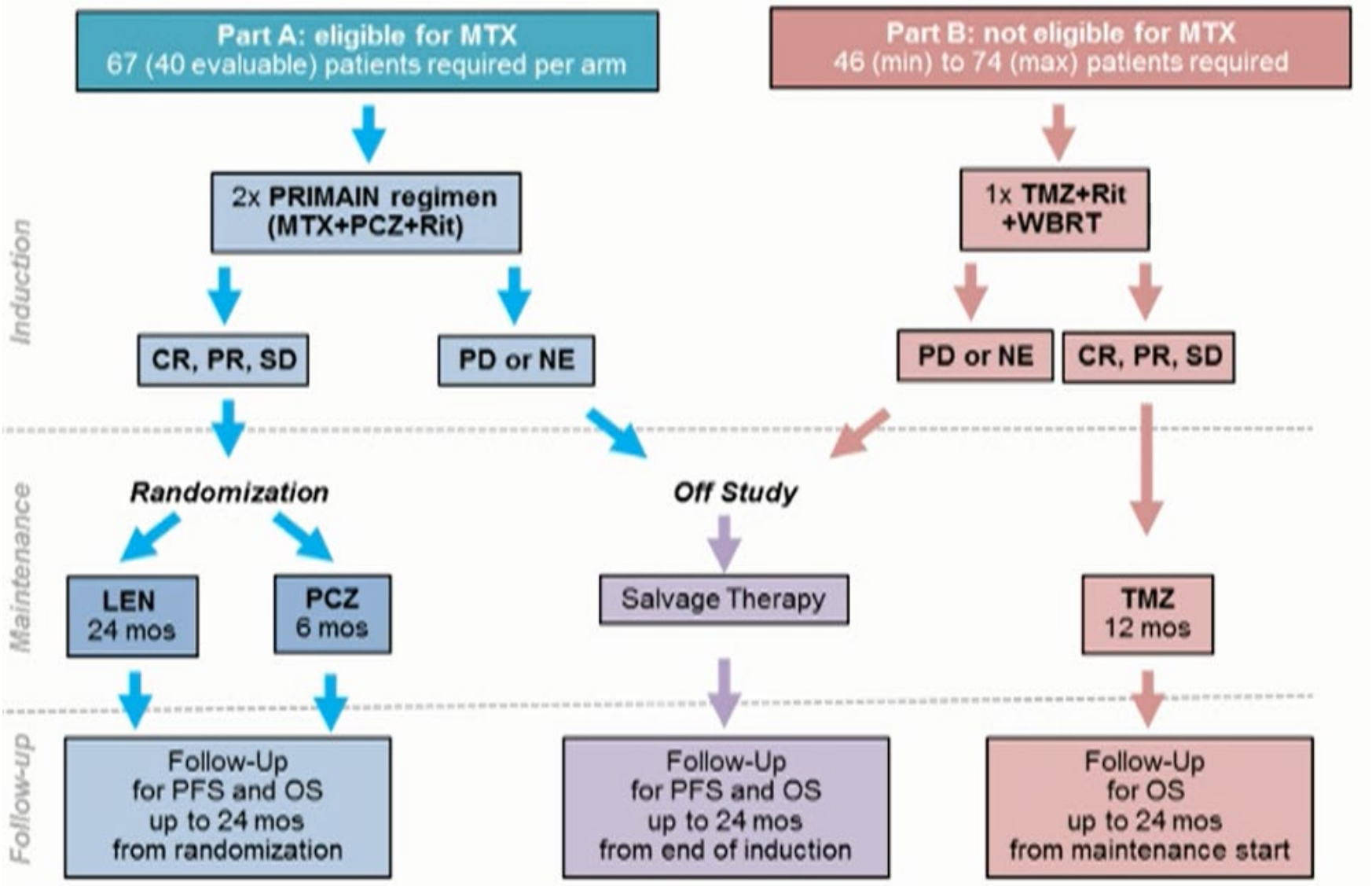
Prospectively collected study data

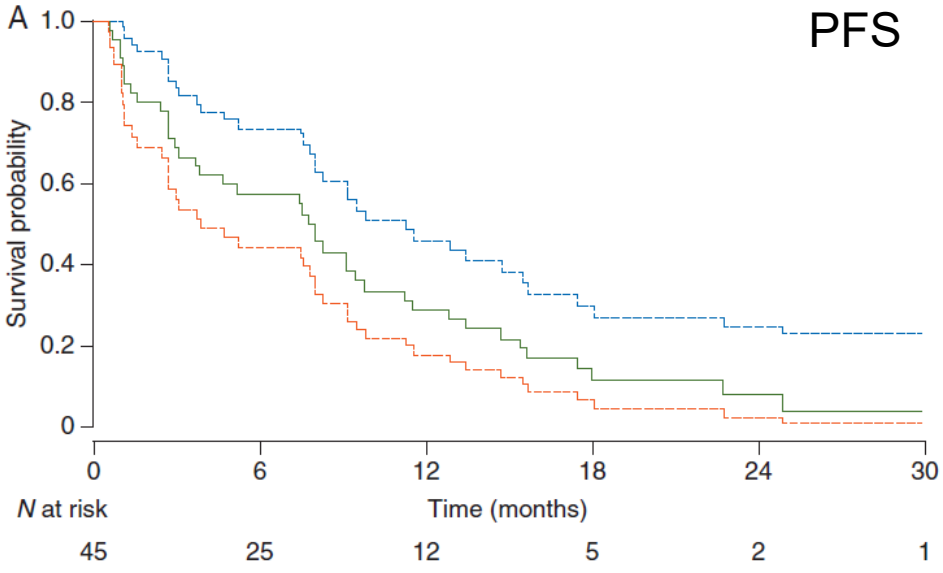
First author	n	age	Treatment	CR	PR	PFS	OS
Omuro	23	68	MTX, Temozolomide	55%	0%	8	35
Hoang-Xuan	50	72	MTX, CCNU, PCZ, Prednisolone. MTX and AraC i.th.	42%	6 %	10.6	14.3
Illerhaus	30	70	MTX, CCNU, Procarbazine	44%	26%	5.9	15.4
Fritsch	28	76	MTX, CCNU, PCZ, Rituximab	64%	18%	16	17.5
Roth	126	73	MTX, ifosfamide, +/- WBRT	30%	14%	4.0	12.5
Omuro	95	73	MTX, PCZ, VCR, AraC MTX, TMZ	62% 45%	26% 20%	9.5 6.1	31 14
Fritsch	107	73	MTX, PCZ, Rituximab (+ Lomustine)	42%	32%	10.3	20.7

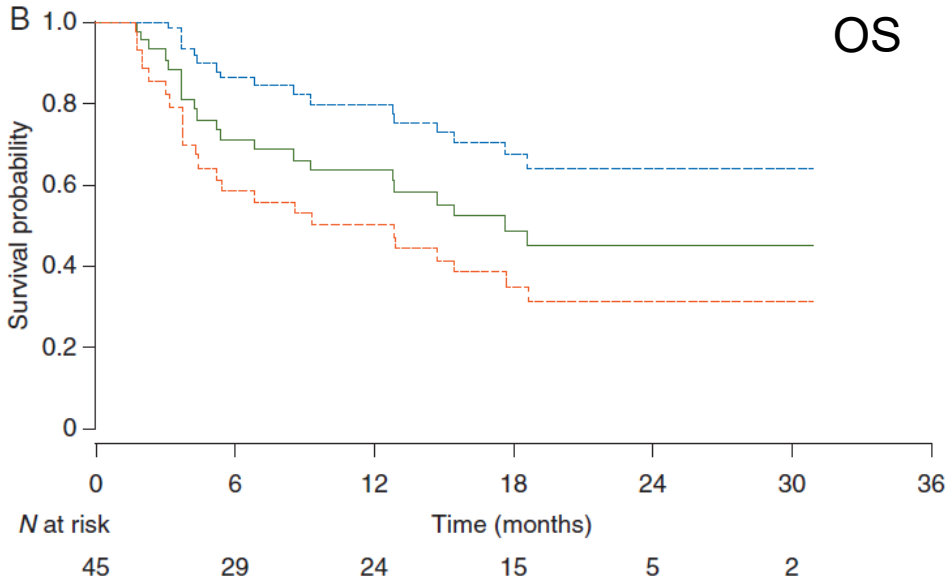
FIORELLA trial in elderly PCNSL patients



Novel agents: lenalidomide

- Lenalidomide + rituximab (8 cycles), followed by lenalidomide maintenance therapy (up to 12 cycles)
- Relapsed/recurrent PCNSL / PIOL: 50 patients, 45 assessable
- Median age: 69 years
- CR rate: 29%
- mPFS: 7.8 months, mOS: 17.7 months





Ghesquieres et al. Ann Oncol 2019

Novel agents: Ibrutinib

- Bruton tyrosine kinase (BTK) inhibitor

  → BTK links the B-cell antigen receptor (BCR) and Toll-like receptors with the NF-κB pathway

- Monotreatment or in combination with other drugs
- Aspergillosis observed as a particular side effect
- 52 patients with relapsed/refractory PCNSL / PIOL
- CR rate: 19%, PR rate 33%
- Median PFS: 4.8 months; median OS 19.2 months
- Ibrutinib detectable in the cerebrospinal fluid

Soussain et al., Eur J Cancer 2019

Novel agents: Ibrutinib

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First published November 18, 2016, DOI: https://doi.org/10.1212/WNL.0000000000003420

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Inhibition of B Cell Receptor Signaling by Ibrutinib in Primary CNS Lymphoma

Michail S. Lionakis,[1,7] Kieron Dunleavy,[2,7] Mark Roschewski,[2] Brigitte C. Widemann,[3] John A. Butman,[4] Roland Schmitz,[2] Yandan Yang,[2] Diane E. Cole,[3] Christopher Melani,[2] Christine S. Higham,[3] Jigar V. Desai,[2] Michele Ceribelli,[5] Lu Chen,[5] Craig J. Thomas,[2,5] Richard F. Little,[6] Juan Gea-Banacloche,[3] Sucharita Bhaumik,[3] Maryalice Stetler-Stevenson,[3] Stefania Pittaluga,[3] Elaine S. Jaffe,[3] John Heiss,[3] Nicole Lucas,[2] Seth M. Steinberg,[3] Louis M. Staudt,[2,8,*] and Wyndham H. Wilson[2,8,*]

[1]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases
[2]Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute
[3]Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute
[4]Radiology and Imaging Sciences, Clinical Center
National Institutes of Health, Bethesda, MD 20892, USA
[5]Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Gaithersburg, MD 20850, USA
[6]Cancer Therapy Evaluation Program, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
[7]These authors contributed equally
[8]Lead Contact
*Correspondence: lstaudt@mail.nih.gov (L.M.S.), wilsonw@mail.nih.gov (W.H.W.)
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Novel agents: PD-1 inhibitors

PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma

Lakshmi Nayak,[1,2] Fabio M. Iwamoto,[3] Ann LaCasce,[1,2] Srinivasan Mukundan,[1,2] Margaretha G. M. Roemer,[1] Bjoern Chapuy,[1] Philippe Armand,[1,2] Scott J. Rodig,[1,2] and Margaret A. Shipp[1,2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; and [3]New York Presbyterian Hospital, New York, NY

Key Points

- Genetic analysis reveals frequent 9p24.1/PD-L1/PD-L2 copy-number alterations and increased expression of the PD-1 ligands in PCNSL and PTL.
- PD-1 blockade with nivolumab demonstrated activity in patients with relapsed/refractory PCNSL and PTL.

Primary central nervous system (CNS) lymphoma (PCNSL) and primary testicular lymphoma (PTL) are rare extranodal large B-cell lymphomas with similar genetic signatures. There are no standard-of-care treatment options for patients with relapsed and refractory PCNSL and PTL, and the overall prognosis is poor. PCNSLs and PTLs exhibit frequent 9p24.1 copy-number alterations and infrequent translocations of 9p24.1 and associated increased expression of the programmed cell death protein 1 (PD-1) ligands, PD-L1 and PD-L2. The activity of PD-1 blockade in other lymphomas with 9p24.1 alterations prompted us to test the efficacy of the anti–PD1 antibody, nivolumab, in 4 patients with relapsed/refractory PCNSL and 1 patient with CNS relapse of PTL. All 5 patients had clinical and radiographic responses to PD-1 blockade, and 3 patients remain progression-free at 13^+ to 17^+ months. Our data suggest that nivolumab is active in relapsed/refractory PCNSL and PTL and support further investigation of PD-1 blockade in these diseases. (*Blood*. 2017;129(23):3071-3073)

blood

Summary & take home messages

- Cure is probably restricted to younger patients
- Standard of care is only poorly defined
  → further trials are urgently needed
- HD-MTX as the therapeutic backbone / rituximab increasingly used
- WBRT should be avoided in the first-line setting
- Open questions:
  - Role for new drugs, e.g. immune checkpoint inhibitors, lenalidomide, ibrutinib…?
  - Optimal treatment for elderly/frail patients?

patrick.roth@usz.ch