19TH ULTMANN

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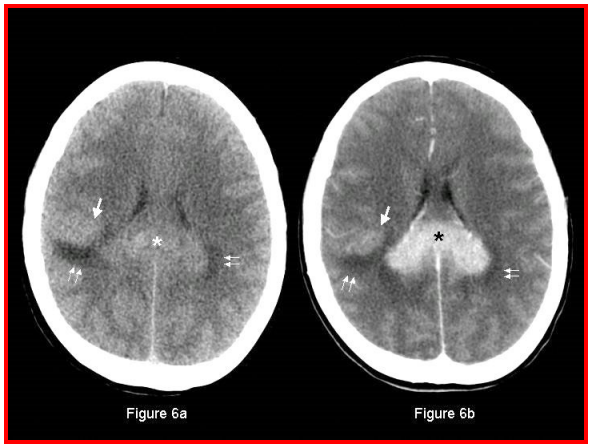
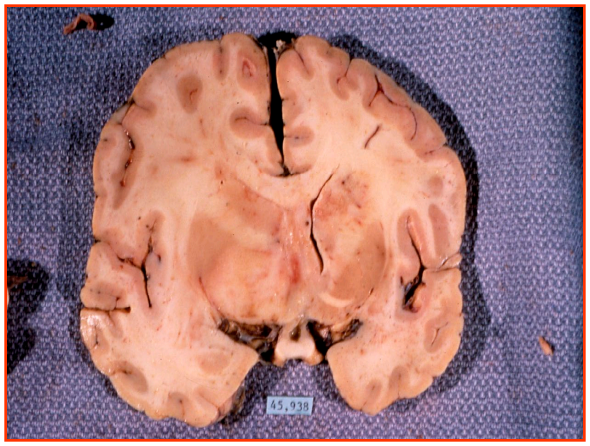
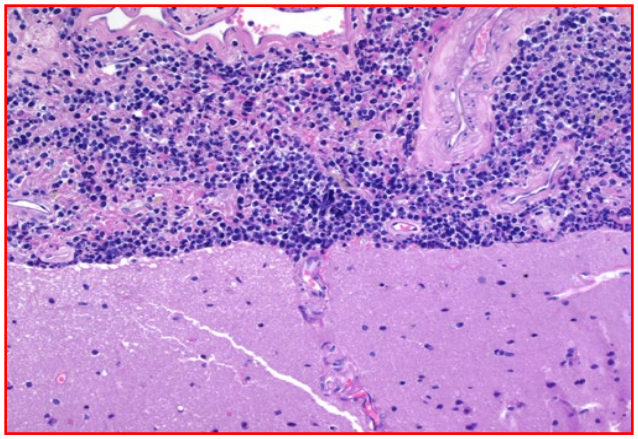
THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES







Primary CNS Lymphoma – Focus on Consolidation

Tracy Batchelor, M.D.
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Ultmann Chicago Lymphoma Symposium
April 30, 2022

Disclosures

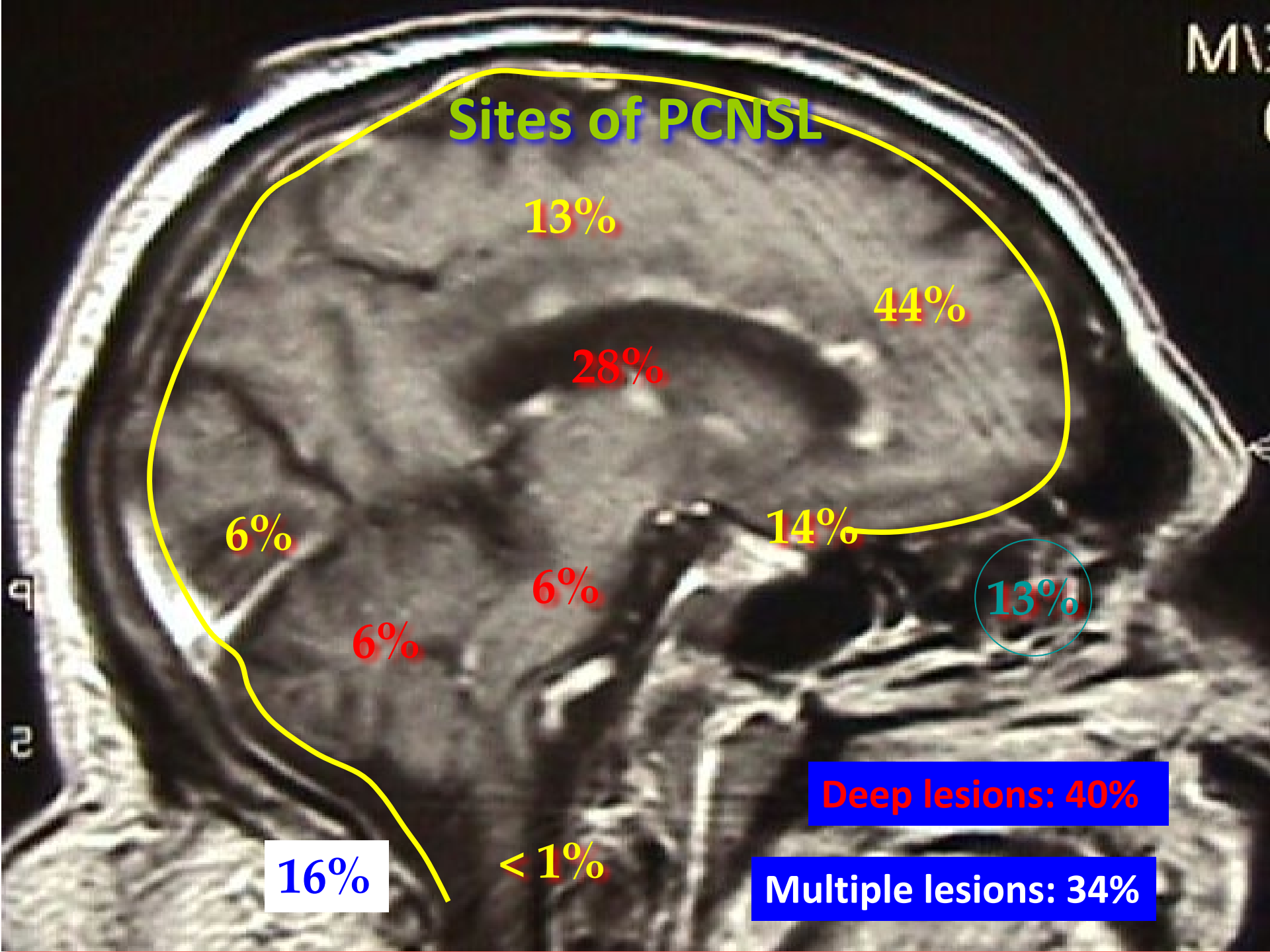
- Tracy Batchelor, MD is the principal investigator for Ono Pharmaceuticals.

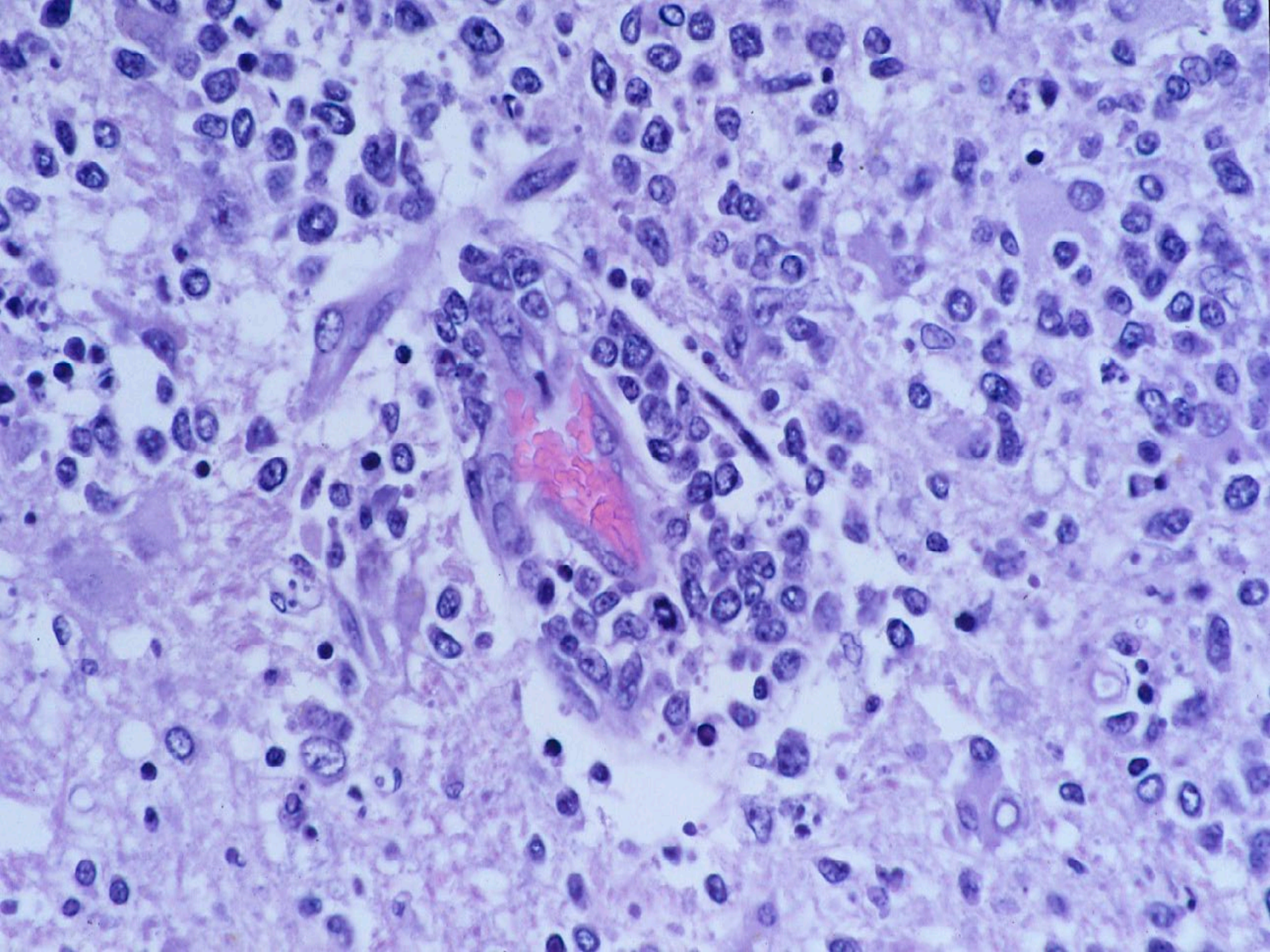
- Dr. Batchelor will discuss the unapproved/investigational Clinical trials of investigational new agents in primary CNS lymphoma.

Case Definition

Primary diffuse large B-cell lymphoma of the CNS (WHO) - Lymphoma confined to the craniospinal axis without evidence of systemic involvement (Brain > Eye > Leptomeninges > Spinal Cord)

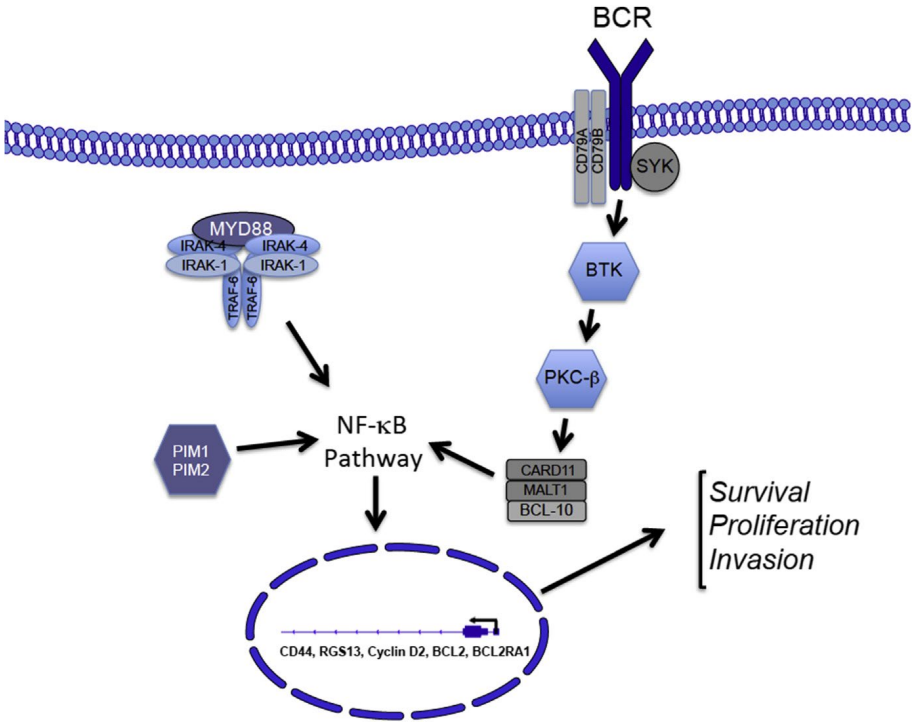
Batchelor and DeAngelis, *Lymphoma and Leukemia of the Nervous System*, 2nd ed, New York; Springer, 2012


Sites of PCNSL
13%
44%
28%
6%
14%
6%
6%
13%
16%
< 1%
Deep lesions: 40%
Multiple lesions: 34%



Pathology and Biology

- Primary DLBCL of the CNS (> 90% of all CNS lymphomas)
- "Non-GCB" (95%)
  - Accounting for inferior prognosis?
- High frequency of genetic alterations leading to aberrant activation of NF-κβ signaling pathways



Camilleri-Broet S, et al *Blood* 2006; Carnevale J, et al *Hematol Oncol Clin N Am* 2016

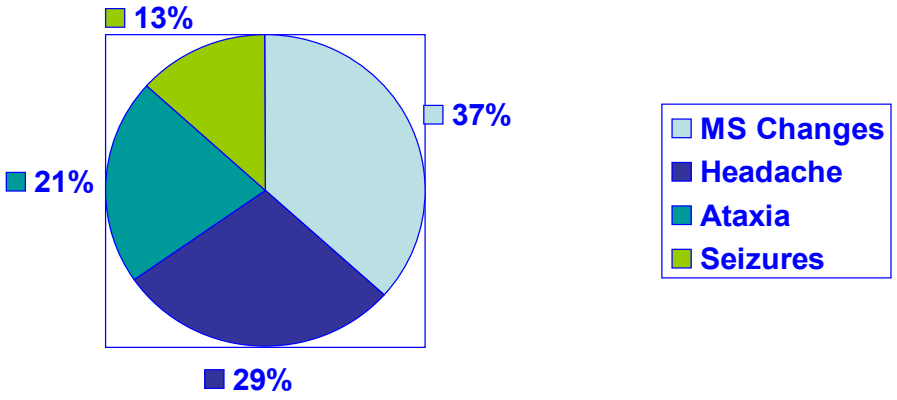
Epidemiology

- ***Central Brain Tumor Registry of the United States (CBTRUS)***
  - Primary CNS Lymphoma
    - 1,630 cases of PCNSL diagnosed each year in the United States from 2013-2017
    - Incidence increased ~3-fold from 1973-1984 but recent SEER data suggests plateau of incidence
    - **33% 5-year survival; 25.6% 10-year survival**

Source: CBTRUS (2019). CBTRUS Statistical Report. www.cbtrus.org

Clinical Features

- **Demographics**
  - Median Age = **67**
  - Gender: Male/Female = **1.35/1**
- **Symptoms**
  - Average Symptoms Duration = **2.77** months



Batchelor and DeAngelis, *Lymphoma and Leukemia of the Nervous System*, New York; Springer, 2012

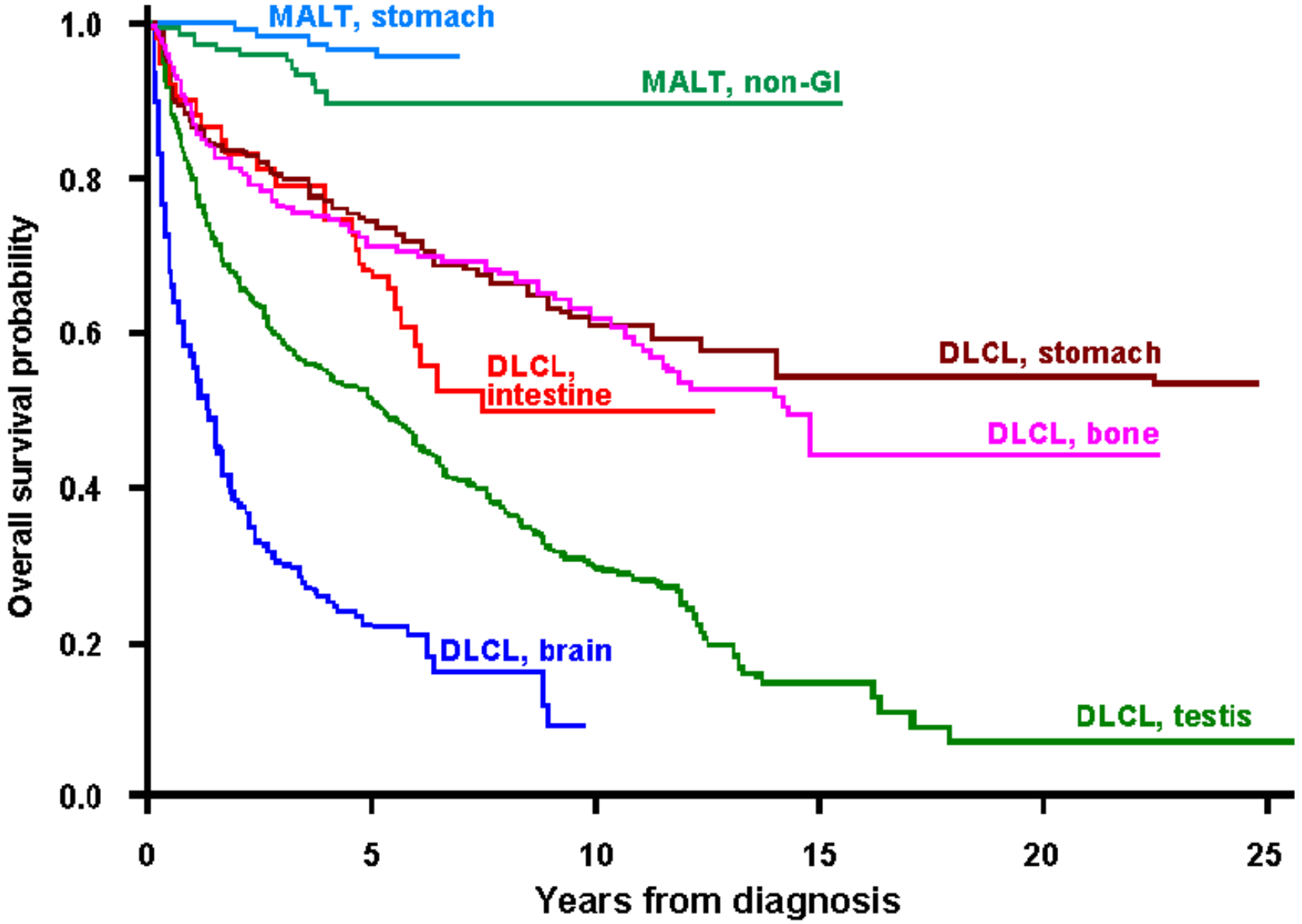
Diagnosis

Baseline Evaluation
"IPCG Criteria"

- **Clinical Evaluation**
  - Complete medical, neurological examination (lymphatic chain, testes)
  - Cognitive examination (IPCG battery)
  - Determination of prognostic factors (age, PS)
- **Laboratory Evaluation**
  - HIV, lactate dehydrogenase, creatinine clearance
- **Extent of Disease Evaluation**
  - ***Brain- Contrast-enhanced cranial MRI***
  - ***CSF- Cytology, flow cytometry, IgH PCR*** *(MYD88, IL-10)*
  - ***Eye- inclusive of slit lamp evaluation*** *(MYD88, IL-10)*
  - ***Body- FDG-PET or CT/PET of chest/abdomen/pelvis; BM aspiration/biopsy; Testicular US in older men***

Abrey et al, *J Clin Oncol* 2005

Prognosis



Database of the International Extranodal Lymphoma Study Group

Treatment

Response Assessment

IPCG Consensus Guidelines

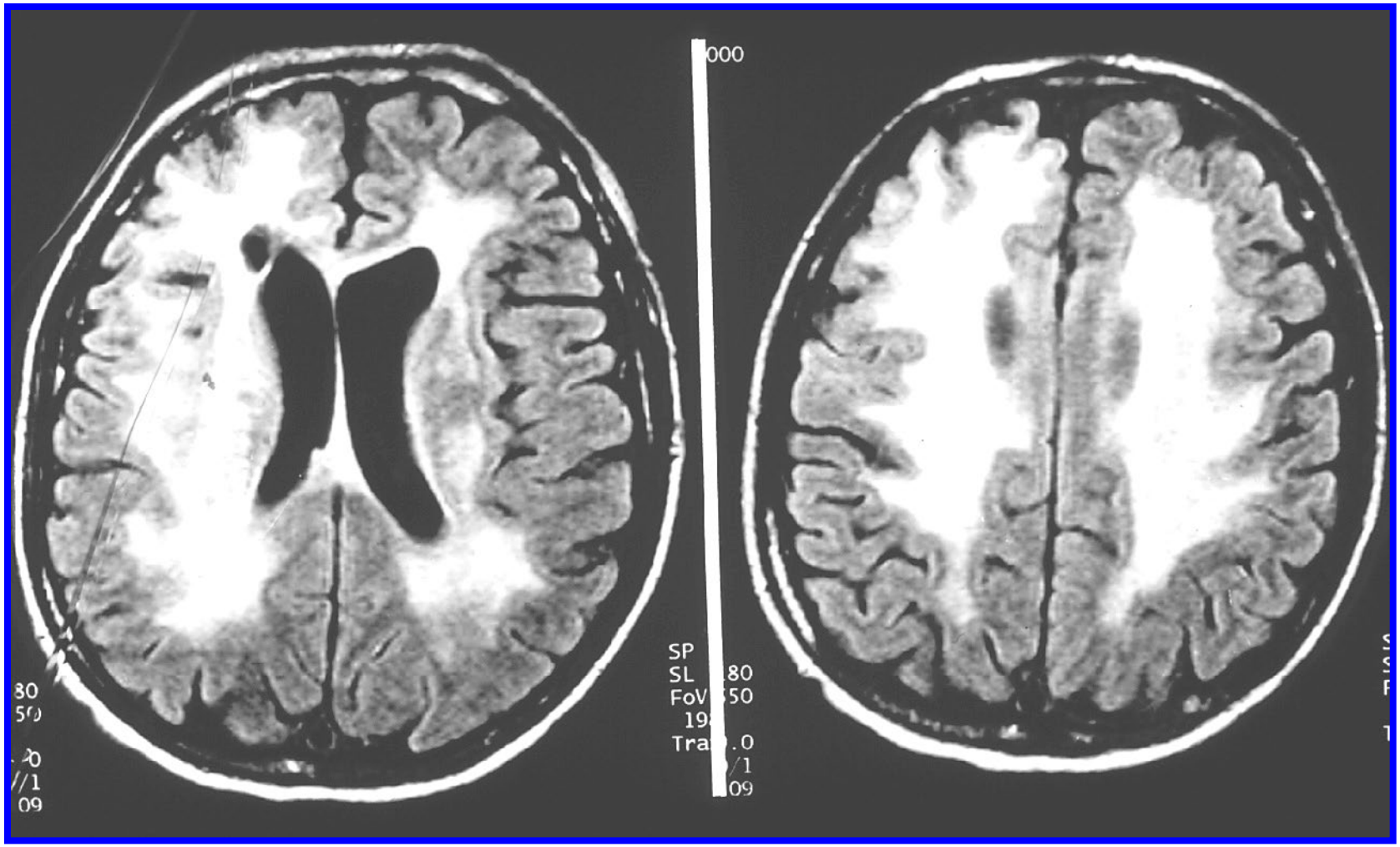
Table 2. International PCNSL Collaborative Group Guidelines for Response Assessment for Clinical Trials[a]

Response	Brain Imaging	Corticosteroid Dose	Eye Examination Results	CSF Cytology Results
Complete	No enhancing disease	None	Normal	Negative
Unconfirmed complete	No enhancing disease	Any	Normal	Negative
	Minimal enhancing disease	Any	Minor RPE abnormality	Negative
Partial	50% Decrease in enhancement	NA	Minor RPE abnormality or normal	Negative
	No enhancing disease	NA	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
Progressive disease	25% Increase in enhancement	NA	Recurrent or new disease	Recurrent or positive
	Any new site of disease			
Stable disease	All scenarios not covered by responses above			

Abbreviations: CSF, cerebrospinal fluid; NA, not applicable; PCNSL, primary central nervous system lymphoma; RPE, retinal pigment epithelium.
[a]Adapted from the article by Abrey et al.[5]

Abrey et al *J Clin Oncol* 2005

Neurotoxicity



Increased T2/FLAIR subcortical white matter signal abnormality associated with diffuse cerebral atrophy and ventricular enlargement

Neurotoxicity

- **Risk Factors**
  - Age > 60, WBRT or WBRT + Chemotherapy
- **Clinical Features**
  - Four domains most sensitive to disease and treatment
    - ***Attention***
    - ***Executive Functions***
    - ***Memory***
    - ***Psychomotor Speed***
  - With neuropsychological testing is detected in ~100% of PCNSL patients > 60 and in 63% < 60
  - IPCG Cognitive Battery has been developed for incorporation into prospective clinical trials
  - ***Neurocognitive endpoints are critical outcomes…***

Correa D, et al. *Ann Oncol* 2007

Current Induction Treatments (Randomized Trials)

Study	Sample Size	Regimen	CR + CR_U	Consolidation per protocol
J Clin Oncol 2019; 37: 823	140 (18-60)	R-MBVP	**43%**	**69%**
Lancet Haematol 2016; 3: e217	227 (<70)	MATRIX	**49%**	**61%**
Lancet Oncol 2019; 20: 216	200 (18-70)	MBVP, R-MBVP f/b Ara-C	**49%**	-
Lancet 2009; 374: 1512	79 (18-75)	MTX + Ara-C MTX	**46%** **18%**	-
Lancet 2010; 11: 1036	551 (>/= 18)	MTX +/- IFOX	**35%**	-
Lancet Haematol 2015; 2: e251	98 (>/= 60)	MT MPVA	**45%** **62%**	-
ASCO 2021	110 (18-75)	MTR	**49%**	**64%**

Why does induction fail?

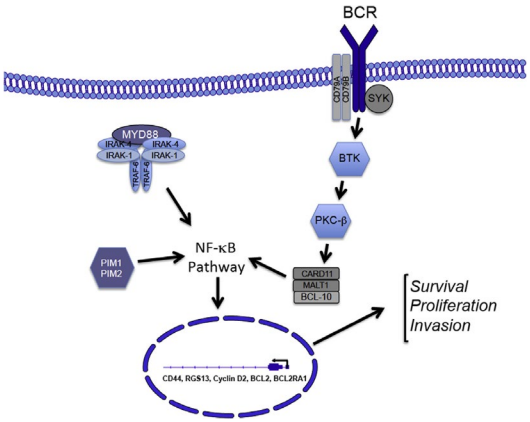
- Non-GCB
- 20-30% refractory
- Insensitivity of MRI to define CR
  - ? Clonotypic DNA in CSF (*Blood Adv* 2021)
- Blood brain barrier
- Lack of anthracycline

Consolidation

Consolidation Options

- Whole brain radiation therapy
  - **Standard Dose (30-36, 45 Gy to whole brain)**
  - **Reduced Dose (23 Gy to whole brain)**
- High-dose chemotherapy / autotransplant
  - **Thiotepa/Carmustine**
  - **Thiotepa/Busulfan/Cyclophosphamide**
  - BEAM
- Chemotherapy
  - **Cytarabine**
  - **Etoposide/Cytarabine**
  - Methotrexate
- Other
  - Lenalidomide

Dose-Adapted TEDDI-R (Induction/Consolidation)



- Temozolomide, Etoposide, Doxorubicin, Dexamethasone, Ibrutinib
- N = 18 PCNSL patients
- 94% tumor reduction with ibrutinib alone
- 86% entered CR with DA-TEDDI-R
- Incomplete responses occurred in patients with CD79b mutations
- Aspergillosis observed – linked to BTK-dependent fungal immunity in a murine model

Lionakis MS, et al Cancer Cell 2017

Whole Brain Radiation Therapy

High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

Eckhard Thiel, Agnieszka Korfel*, Peter Martus, Lothar Kanz, Frank Griesinger, Michael Rauch, Alexander Röth, Bernd Hertenstein, Theda von Toll, Thomas Hundsberger, Hans-Günther Mergenthaler, Malte Leithäuser, Tobias Birnbaum, Lars Fischer, Kristoph Jahnke, Ulrich Herrlinger, Ludwig Plasswilm, Thomas Nägele, Torsten Pietsch, Michael Bamberg, Michael Weller*

Lancet Oncol 2010; 11: 1036–47
Published Online
October 21, 2010
DOI:10.1016/S1470-2045(10)70229-1

Summary

Background High-dose methotrexate is the standard of care for patients with newly diagnosed primary CNS lymphoma. The role of whole brain radiotherapy is controversial because delayed neurotoxicity limits its acceptance as a standard of care. We aimed to investigate whether first-line chemotherapy based on high-dose methotrexate was non-inferior to the same chemotherapy regimen followed by whole brain radiotherapy for overall survival.

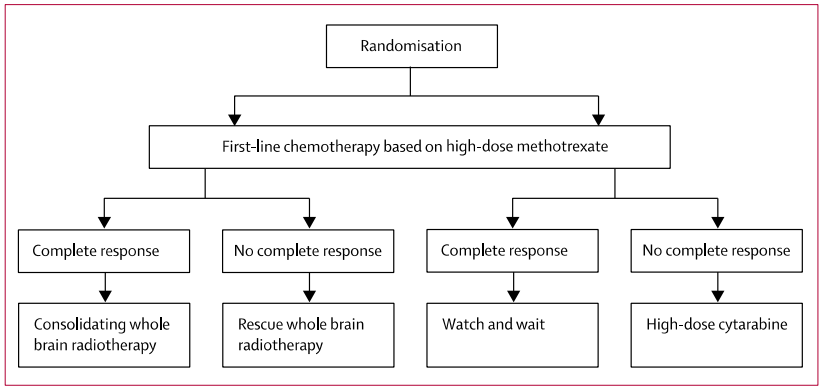


Figure 1: Trial design

Thiel, et al *Lancet Oncol* 2010

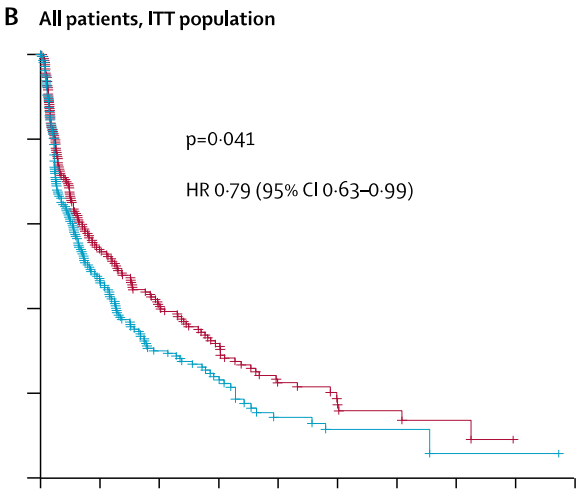
2000-2009, 75 centers in Germany
551 patients randomized, 318 treated PP
Chemo alone versus Chemo + WBRT

Chemotherapy
2000-2006: MTX 4 g/m^2 Q14D
2006-2009: MTX 4 g/m^2 Q14D
+ IFX 1.5 g/m^2 days 1-3 Q14D
WBRT
1.5 Gy X 30 fractions = 45 Gy

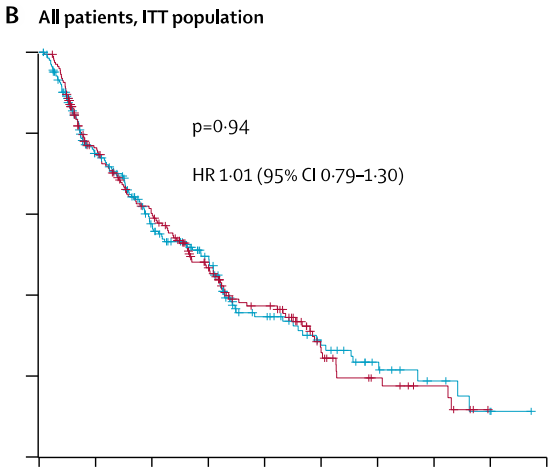
PP: No difference in PFS or OS between 2 groups

ITT: PFS superior in WBRT group but no difference in OS between 2 groups

Progression-Free Survival



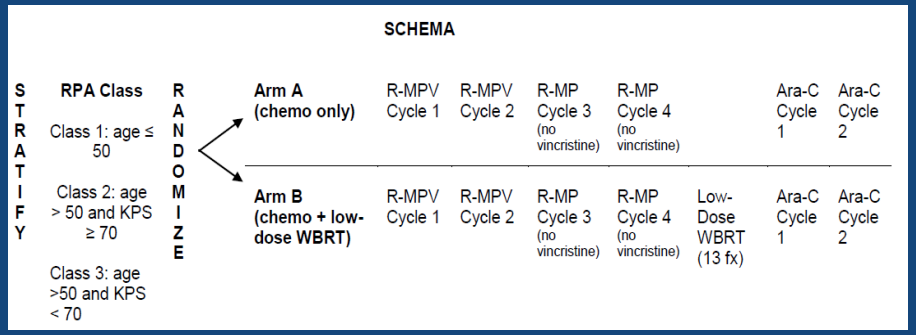
Overall Survival



Thiel, et al *Lancet Oncol* 2010

“Lower Dose” Whole Brain Radiation Therapy

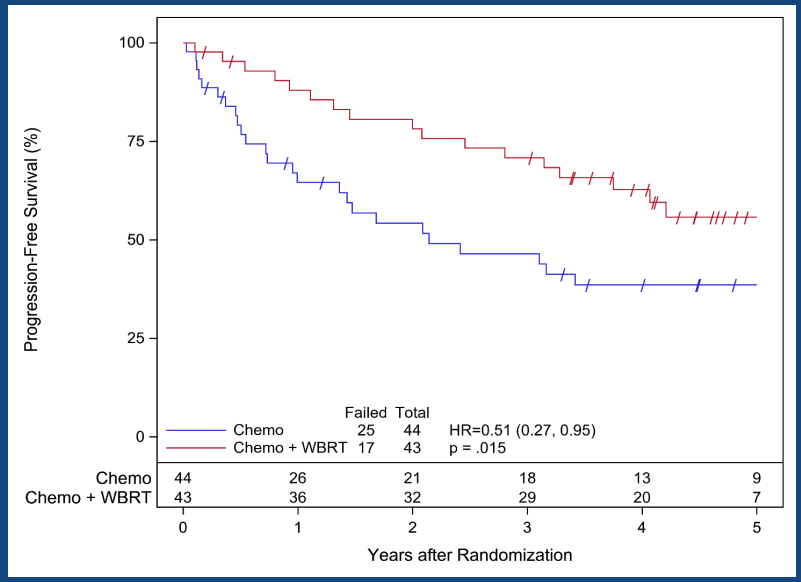
RTOG 1114



- N = 87 randomized patients evaluable
- Primary Endpoint = Progression-Free Survival
- Secondary Endpoints = Overall Radiographic Response, Overall Survival, QOL, Toxicities (Neurotoxicity)

Overall Radiographic Response

- Chemotherapy Arm = 83%
- Chemoradiation Arm = 81%



Progression Free Survival at 2 Years

- Chemotherapy Arm = 54%
- Chemoradiation Arm = 78%

High dose chemotherapy and autologous stem cell transplant

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

Strata: IELSG score

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
ev. 3 wks

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
ev. 3 wks

Response assessment

CR – PR - SD

PD – toxicity
Poor mobilizers

Strata: previous arm
& OR (CR vs. PR/SD)

R

WBRT 40 Gy
± boost 9 Gy

WBRT 36 Gy
± boost 9 Gy

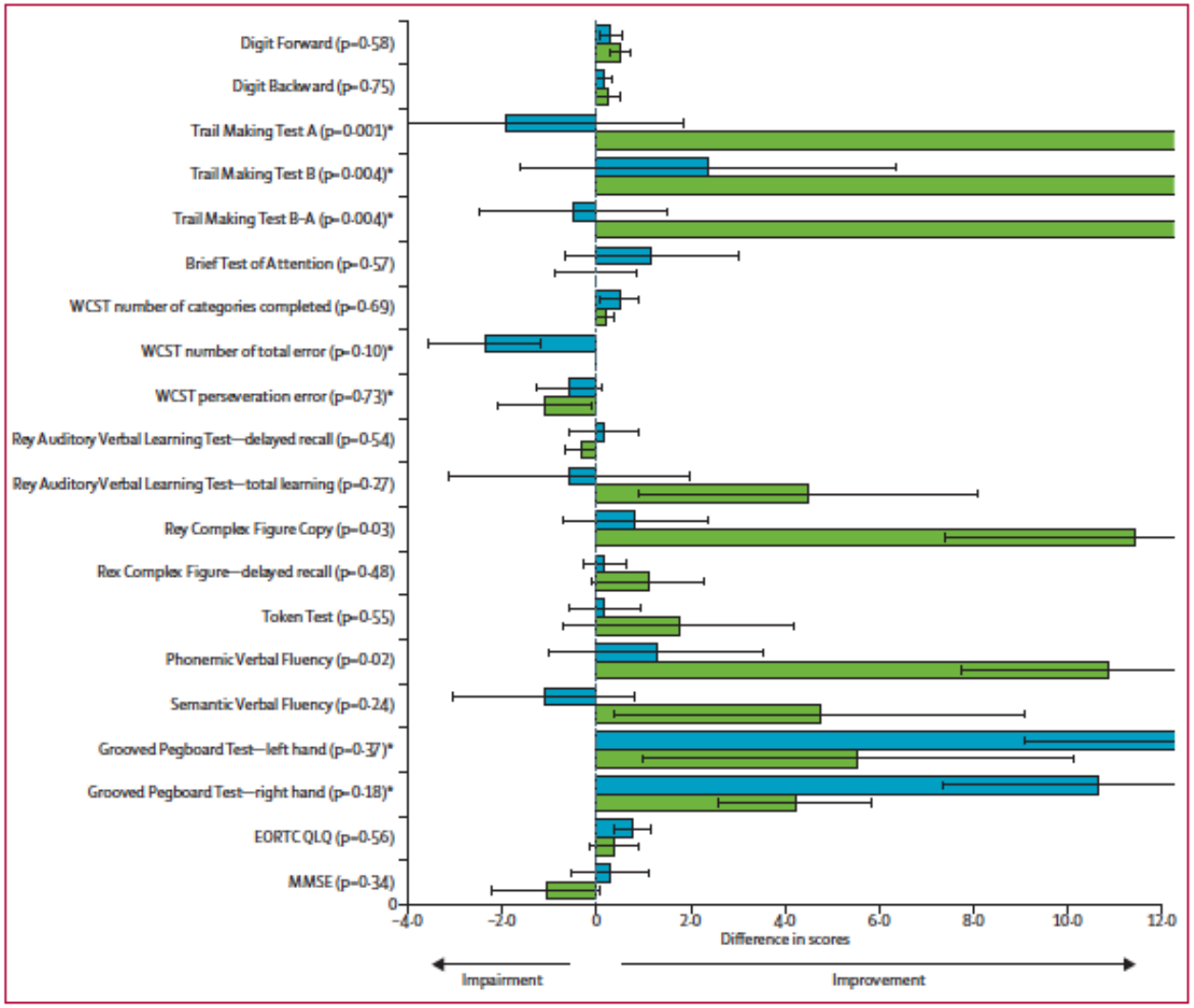
BCNU 400 mg/m² d.1
Thiotepa 5 mg/Kg x 2/d; d.2-3
+ APBSCT

IELSG32 Results of RCT2 (Consolidation)

- Consolidation with WBRT versus HDT-ASCT
  - 118 with (CR, PR, SD) after induction were randomized to WBRT (59) or HDT-ASCT (59)
  - Both WBRT and HDT-ASCT arms achieved their PFS2 endpoints
    - ITT PFS2 = 80% for WBRT, 69% for HDT/ASCT (NS)
    - Per protocol PFS2 = 76% for WBRT, 75% for HDT/ASCT
  - 57/113 (50%) had serial cognitive and QOL assessments

Ferreri AJ, et al Lancet Haematol 2017

IELSG32-RCT2 Results



Ferreri AJ, et al Lancet Haematol 2017

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 Comillon, 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

abstract

PURPOSE To determine the efficacy and toxicity of chemoimmunotherapy followed by either whole-brain radiotherapy (WBRT) or intensive chemotherapy and autologous stem-cell transplantation (ASCT) as a first-line treatment of primary CNS lymphoma (PCNSL).

PATIENTS AND METHODS Immunocompetent patients (18 to 60 years of age) with untreated PCNSL were randomly assigned to receive WBRT or ASCT as consolidation treatment after induction chemotherapy consisting of two cycles of R-MBVP (rituximab 375 mg/m^2 day (D) 1, methotrexate 3 g/m^2 D1; D15, VP16 100 mg/m^2 D2, BCNU 100 mg/m^2 D3, prednisone 60 mg/kg/d D1-D5) followed by two cycles of R-AraC (rituximab 375 mg/m^2 D1, cytarabine 3 g/m^2 D1 to D2). Intensive chemotherapy consisted of thiotepa (250 mg/m^2/d D9; D8; D7), busulfan (8 mg/kg D6 through D4), and cyclophosphamide (60 mg/kg/d D3; D2). WBRT delivered 40 Gy (2 Gy/fraction). The primary end point was 2-year progression-free survival. Cognitive outcome was the main secondary end point. Analysis was intention to treat in a noncomparative phase II trial.

RESULTS Between October 2008 and February 2014, 140 patients were recruited from 23 French centers. Both WBRT and ASCT met the predetermined threshold (among the first 38 patients in each group, at least 24 patients were alive and disease free at 2 years). The 2-year progression-free survival rates were 63% (95% CI, 49% to 81%) and 87% (95% CI, 77% to 98%) in the WBRT and ASCT arms, respectively. Toxicity deaths were recorded in one and five patients after WBRT and ASCT, respectively. Cognitive impairment was observed after WBRT, whereas cognitive functions were preserved or improved after ASCT.

CONCLUSION WBRT and ASCT are effective consolidation treatments for patients with PCNSL who are 60 years of age and younger. The efficacy end points tended to favor the ASCT arm. The specific risk of each procedure should be considered.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

PRECIS Study

- **Randomized, intergroup, phase 2 trial**
  - 140 newly diagnosed primary CNS DLBCL
- **WBRT versus HDT/ASCT (TBC) consolidation**
  - Induction
    - 2 cycles of R-MBVP (rituximab, methotrexate, BCNU, VP16)
    - 2 cycles of R-Ara-C
- **Primary Endpoint**
  - *2-Year Progression Free Survival*
    - ***63% for WBRT and 87% for HDT/ASCT (pre-defined thresholds reached for each arm)***
- **Secondary Endpoints**
  - *Cognitive*
    - ***Cognitive impairments noted after WBRT, Cognitive improvements after HDT/ASCT***
- **ASH 2021: Long-term follow-up results (Median 8 years)**
  - Superior EFS, RFS in HDT/ASCT arm, no difference in OS
  - Severe neurotoxicity (cognitive, balance/gait) in 50% of WBRT cohort including 6 ischemic strokes
  - Minimal to no neurotoxicity in HDT/ASCT cohort

Houillier C, et al J Clin Oncol 2019; Houillier C, et al ASH 2021

2021 ASCO ANNUAL MEETING

#7506: MYELOABLATIVE VERSUS NON-MYELOABLATIVE CONSOLIDATION FOR PRIMARY CNS LYMPHOMA

CALGB 51101 – ALLIANCE RANDOMIZED PHASE 2 STUDY

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network
a National Cancer Institute program

Tracy T. Batchelor, Sharmila Giri, Amy S. Ruppert, Nancy L. Bartlett, Eric D. Hsi, Bruce D. Cheson, Lakshmi Nayak John P. Leonard, James L. Rubenstein

Federally Funded Research™

51101 Schema

Newly Diagnosed, Primary CNS Diffuse Large B-cell Lymphoma

↓

RANDOMIZE (Arm 1 or Arm 2, Stratify on Age/Performance Status)

↓

INDUCTION (5 Cycles)

Cycles 1 and 2

- Methotrexate 8 g/m^2 IV, Days 1, 15
- Temozolomide 150 mg/m^2 PO, Days 7-11 (C1)
  or 200 mg/m^2 PO, Days 7-11 (C2)
- Rituximab 350 mg/m^2 IV, Days 3, 10, 17, 24 (C1)
  or Days 3, 10 (C2)

Cycles 3 and 4

- Methotrexate 8 g/m^2 IV, Days 1, 15
- Temozolomide 200 mg/m2 PO, Days 7-11

Cycle 5

- Cytarabine 2 g/m^2 IV, Q12 Hours, Days 1, 2

Arm 1: Myeloablative ↓

STEM CELL MOBILIZATION / COLLECTION

- Option: G-CSF 10mcg/kg SC Days 1-4
- Collection: Day 5

CONSOLIDATION / STEM CELL RESCUE

- Carmustine 400 mg/m^2 IV, Day -6
- Thiotepa 5 mg/kg IV, Q12 Hours Days -5, -4
- Stem Cell Infusion Day 0
- G-CSF 5 mcg/kg/day SC Days +4 until ANC > 1500 mcg

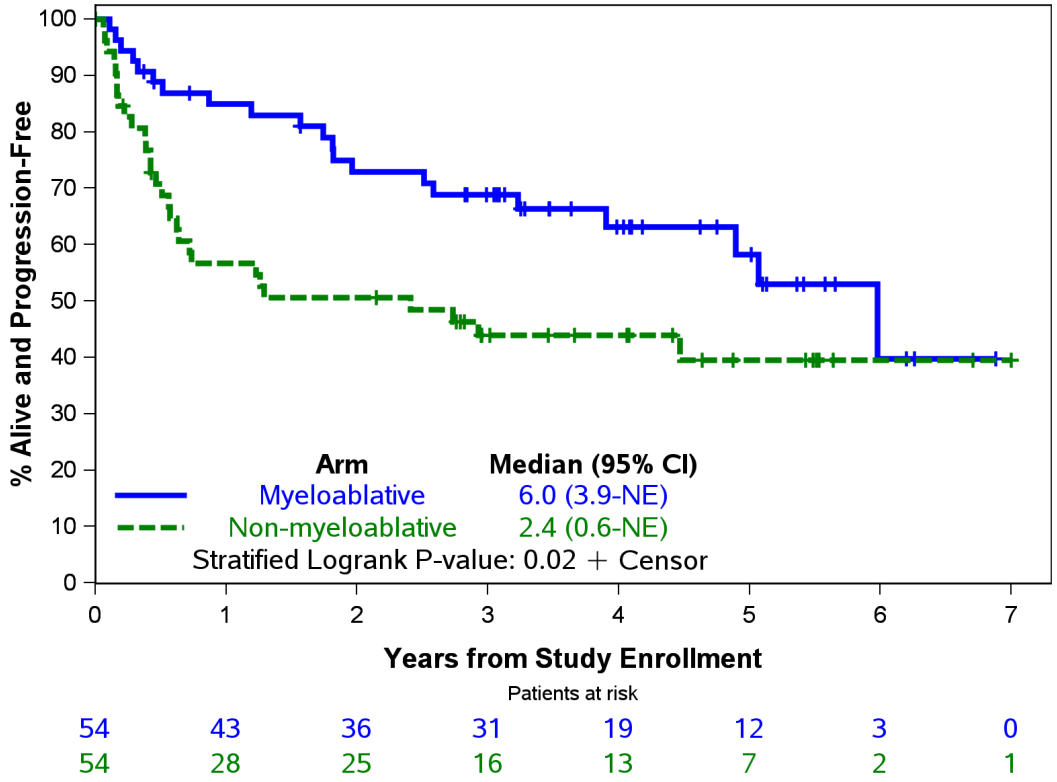
Arm 2: Non-Myeloablative ↓

CONSOLIDATION (1 cycle)

- Cytarabine 2 g/m2 IV, Q12 Hours, Days 1, 2
- Etoposide 5 mg/kg IV, over 12 Hours, Q12 Hours x 8 doses, Days 1-4

Primary Endpoint: Progression-free Survival

Modified Intent-to-Treat Population



- Median follow-up: 3.8 years
- PFS at 2 years
  - Myeloablative: 73% (59-83%)
  - Non-myeloablative: 51% (36-63%)
- However, early separation in curves when all subjects were receiving the same induction therapy

Summary

- Uncommon subtype of lymphomas (90% DLBCL, 95% ABC)
- Suboptimal results with methotrexate-based chemotherapy induction (MTR, MATRix, R-MPV, MBVP)
- Optimal consolidation therapy after CR not clearly defined (HDT/ASCT, WBRT, Chemotherapy)
- Elderly
  - WBRT = high risk of neurotoxicity
  - Higher risk of HDT/ASCT
  - Maintenance therapy?
    - Lenalidomide
    - Methotrexate

BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S HOSPITAL

Thank You

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL