Primary Central Nervous System Lymphoma: The Past, Present and Future

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03/07/2026

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Disclosures

- Advisory Board Participation - AstraZeneca

Epidemiology

- Rare extranodal non-Hodgkin lymphoma confined to brain, spinal cord, leptomeninges, or vitreoretinal space.
- Annual incidence: 0.4 per 100,000 (increases to 4 per 100,000 in patients >70 years).
- Predominantly diffuse large B-cell lymphoma, activated B-cell subtype.
- 5-year survival: 30-40% despite treatment advances.
- 33-60% of patients relapse after initial therapy.

Biology

- Genetic alterations and the local microenvironment are thought to collectively contribute to the pathophysiology of PCNSL.
- Mutations in MYD88, CD79B, MYC, PAX5 and CDKN2A are frequently observed.
- PCNSLs also exhibit frequent focal deletions of 6p21-22, encompassing the human leukocyte antigen (HLA) locus, as a potential mechanism of immune evasion.
- Reduced cerebrospinal fluid (CSF) glucose levels as well as T-cell exhaustion have been linked to microenvironment changes.

Zhang et. al. Blood. 2024
Batchelor TT. Hematology Am Soc Hematol Educ Program. 2016

Work up

MRI Findings

Solitary or multiple, homogenous enhancing lesions with marked restriction in water diffusion.

Often T1-hypointense and T2-isointense to hypointense, surrounded by low edema.

Biopsy of Lesion

CSF Analysis

Eye and Testicular Exam

If symptomatic Initiate steroids

Proceed with treatment

Treatment

The Past – Historical Evolution

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- Pre-Methotrexate (MTX) Era:
  - CHOP regimen ineffective - CHOP has poor CNS penetration of doxorubicin and cyclophosphamide because of their high molecular weight
  - Whole-brain radiotherapy (WBRT, 40-45 Gy) alone: Median survival 12-18 months
  - WBRT + CHOP: no survival improvement over WBRT alone
  - MTX with CHOP or WBRT combination deemed to be too toxic, no better

- The Methotrexate Revolution:
  - HD-MTX established as backbone therapy in 1990s-2000s, 74% response rate at dose of 8 gm/m^2
  - Dose ≥3 g/m^2 required to achieve cytotoxic CSF levels

Schultz et al. RTOG 88-06. J Clin Oncol. 1996
Glass et al. J Neurooncol 1996
Mead et al. Cancer 2000
Batchelor TT et al. JCO. 2003
Thiel et al. G-PCNSL-SG-1. Lancet Oncol. 2010

The Present

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- MTX remains the backbone of first line management
- Usual approach includes induction followed by consolidation +/- maintenance
- Common Induction regimens currently used in practice are:
  - **RTOG 0227 (R-MTX-Temozolomide)**
  - **MATRix/IELSG32 (methotrexate, cytarabine, thiotepa, and rituximab)**
  - RTOG 9310 (rituximab, methotrexate, procarbazine, vincristine and cytarabine)
- Consolidation options include thiotepa based Autologous stem cell transplant (ASCT), WBRT and Cytarabine +/- Etoposide (EA)

Which Induction to Consider?

RTOG 0227 vs MATRix

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Phase II Study	Phase II Study
Induction Rituximab 375 mg/m2 and MTX 3.5 g/m2 for 5 cycles TMZ was administered on weeks 4 and 8 at 200 mg/m2	**Induction** Group A: MTX 3·5 g/m2 plus Ara-C 2 g/m2 twice daily Group B: Group A + two doses of rituximab 375 mg/m2 Group C: Group B + thiotepa 30 mg/m2 on 4 cycles every 3 weeks.
Consolidation WBRT 36 Gy. TMZ 200 mg/m2 daily for 5 days was administered for 10 cycles.	**Randomization** Patients with responsive or stable disease after the induction were randomized between whole-brain radiotherapy and autologous stem cell transplantation.
End Points Overall Survival, Progression-free survival, neurologic toxicities	**End Points** Overall Survival vs RTOG 9310 (2-yr 64%)

Glass J. et. al. J Clin Oncol. 2016
Ferrari AJM et. al. Lancet Hematology. 2016

RTOG 0227 vs MATRix – Responses

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Characteristic	RTOG 0227	MATRix		
		G-A	G-B	G-C
Total Patients	53	74	75	78
Completed Treatment	85%		84%	
ORR	85%	53%	74%	87%
CR	51%	23%	30%	49%
PD	6%	29%	16%	8%
PFS	63.6% (2 yr)	20%	29%	52%
OS	80.8% (2 yr)	21%	37%	56%
Deaths	0	9%	4%	4%

RTOG 0227 vs MATRix – Toxicity (G3/G4)

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Characteristic	RTOG 0227	MATRix		
Heme Toxicities	14%	~51%	~55%	~67%
Neurotoxicity*	7%	~2%	~2%	~3%
Memory Assessment				
MMSE score decrease**	3	n/a	n/a	n/a

*RTOG 0227, Brain, hearing loss, leukoencephalopathy
**One patient at each assessment interval

RTOG 9310

- 102 patients included who received 5 cycles of HD-MTX (2.5 g/m2) in conjunction with intrathecal methotrexate, vincristine, and oral procarbazine were followed by whole-brain radiotherapy and cytarabine for consolidation.
- The overall survival and progression-free survival were 36.9 and 24.0 months, respectively.
- A total of 58% of patients experienced complete response, with an additional 36% of patients experiencing partial responses, prior to delivery of whole-brain radiotherapy.

DeAngelis LM et. al. J Clin Oncol. 2002

RTOG 9310

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- Older age and intervention with whole-brain radiotherapy, even at a lower dose of 36 Gy (decreased from the original 45 Gy dose in this trial), did not prevent treatment-related deleterious neurotoxicity.
- Approximately 24% of patients treated with combined chemoradiotherapy for diffuse large B-cell lymphoma of the CNS developed serious neurotoxicity, which increased over time.
- This trial also established role of WBRT as consolidation albeit with toxicity.

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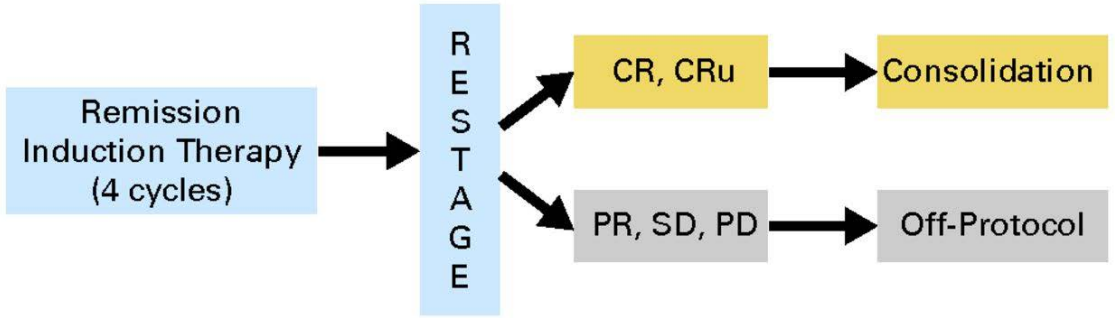
Established Induction but what about Consolidation?

1. Chemo
2. WBRT
3. ASCT

CALGB 50202 – EA Consolidation



Remission Induction Therapy: MT-R (14-day cycle)	
Day 1	Methotrexate 8 grams/m² IV over 4 hrs
Day 2	Leucovorin 100 mg/m² every 6 hrs, until methotrexate < 0.05 mM
Day 3	Rituximab 375 mg/m² IV cycles 1 through 6
Day 7-11	Temozolomide 150 mg/m² 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/m² IV over 2 hrs every 12 hrs × 8 doses

End Points

Complete Response Rate and PFS

Results

47 patients included

CR rates were **66%**

2-year PFS was **57%**, median follow-up of 4.9 years

The 2-year time PFS who completed consolidation was **77%**

Toxicity

55% of patients experienced grade 4 neutropenia, and 50% of patients experienced grade 4 thrombocytopenia

1 death was reported who received EA

Rubenstein JL et. al. J Clin Oncol. 2013

Chemo

VS

ASCT

Alliance 51101– EA vs ASCT

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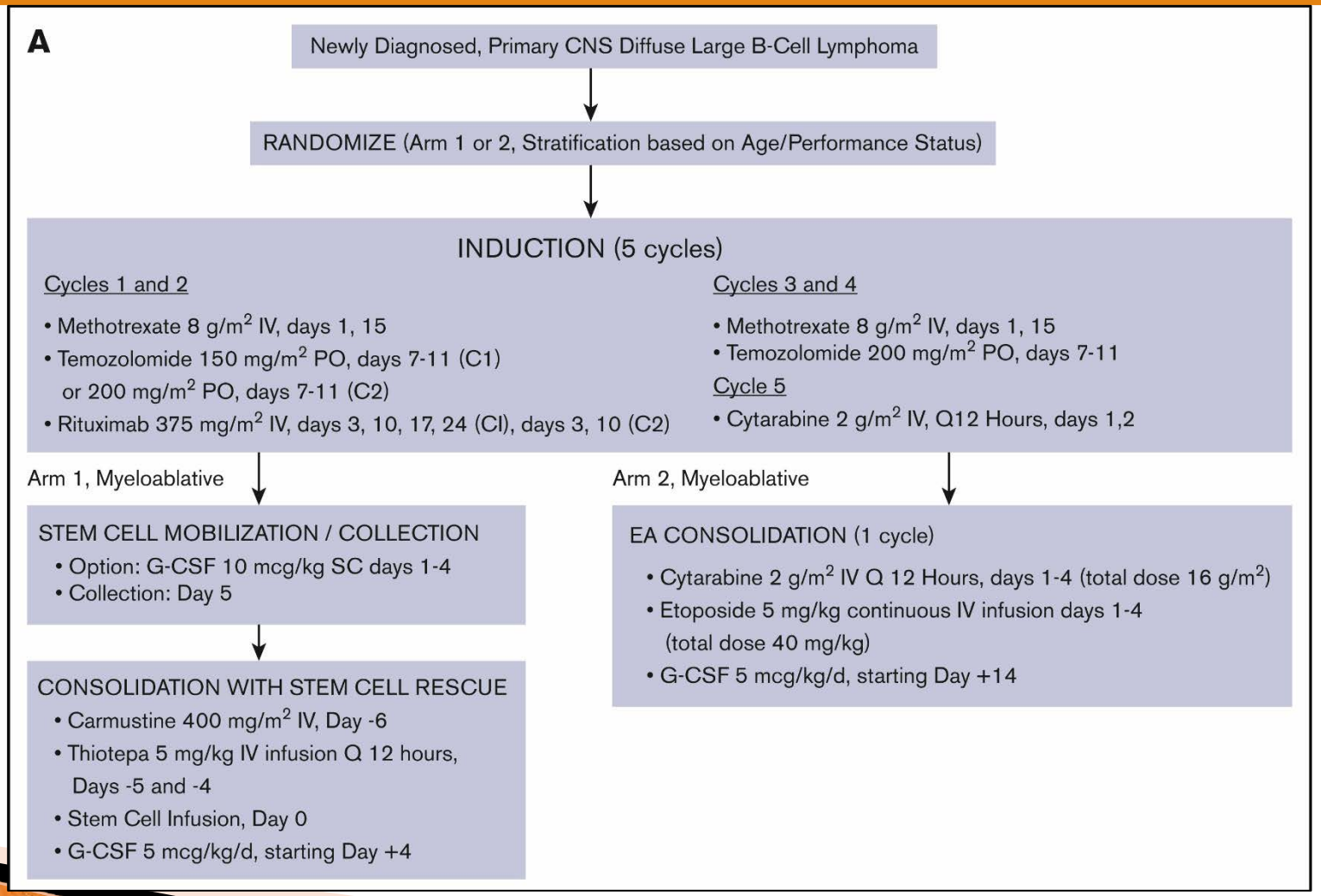
Phase II



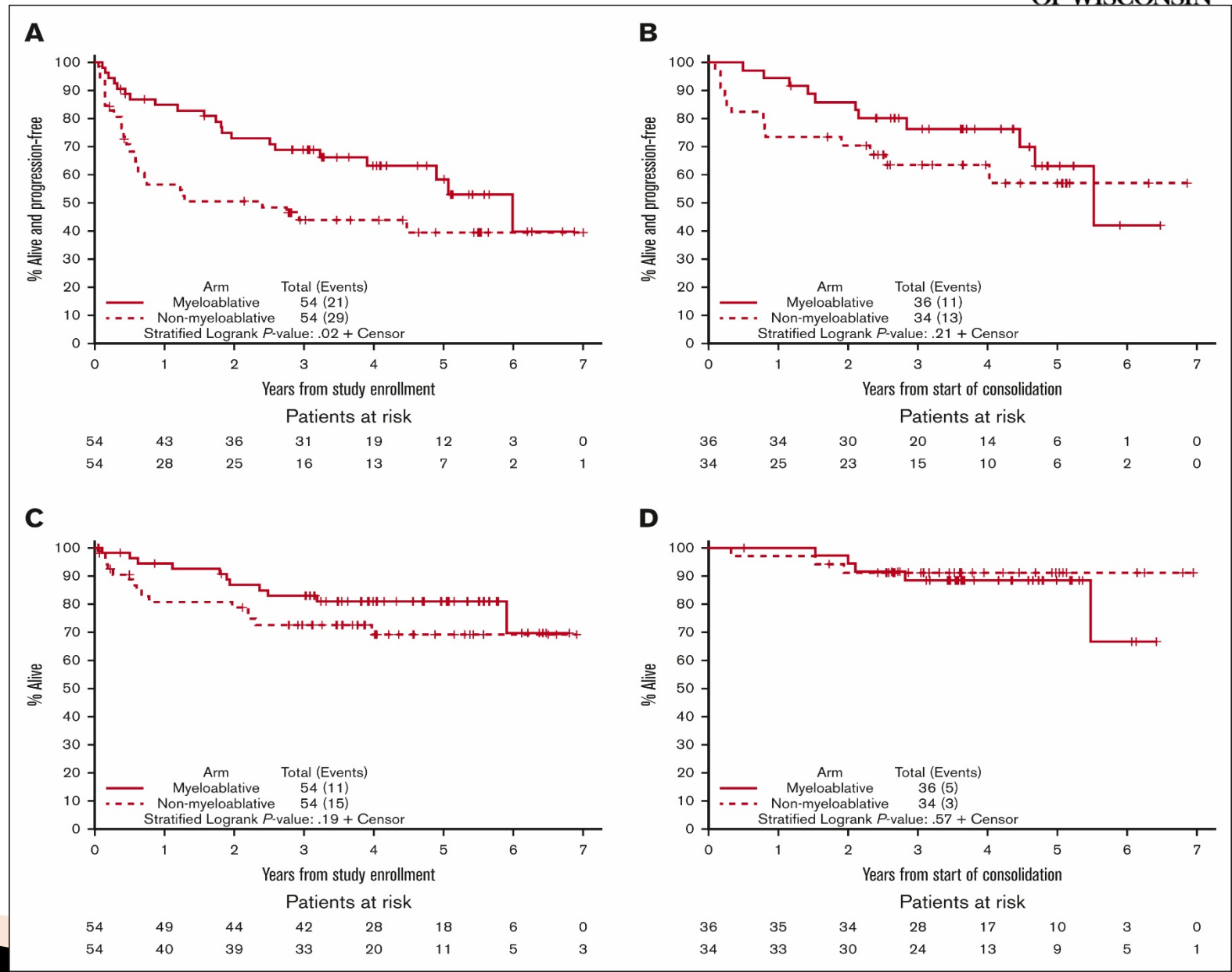
Batchelor TT et. al. Blood Adv. 2024

Alliance 51101 – EA vs ASCT

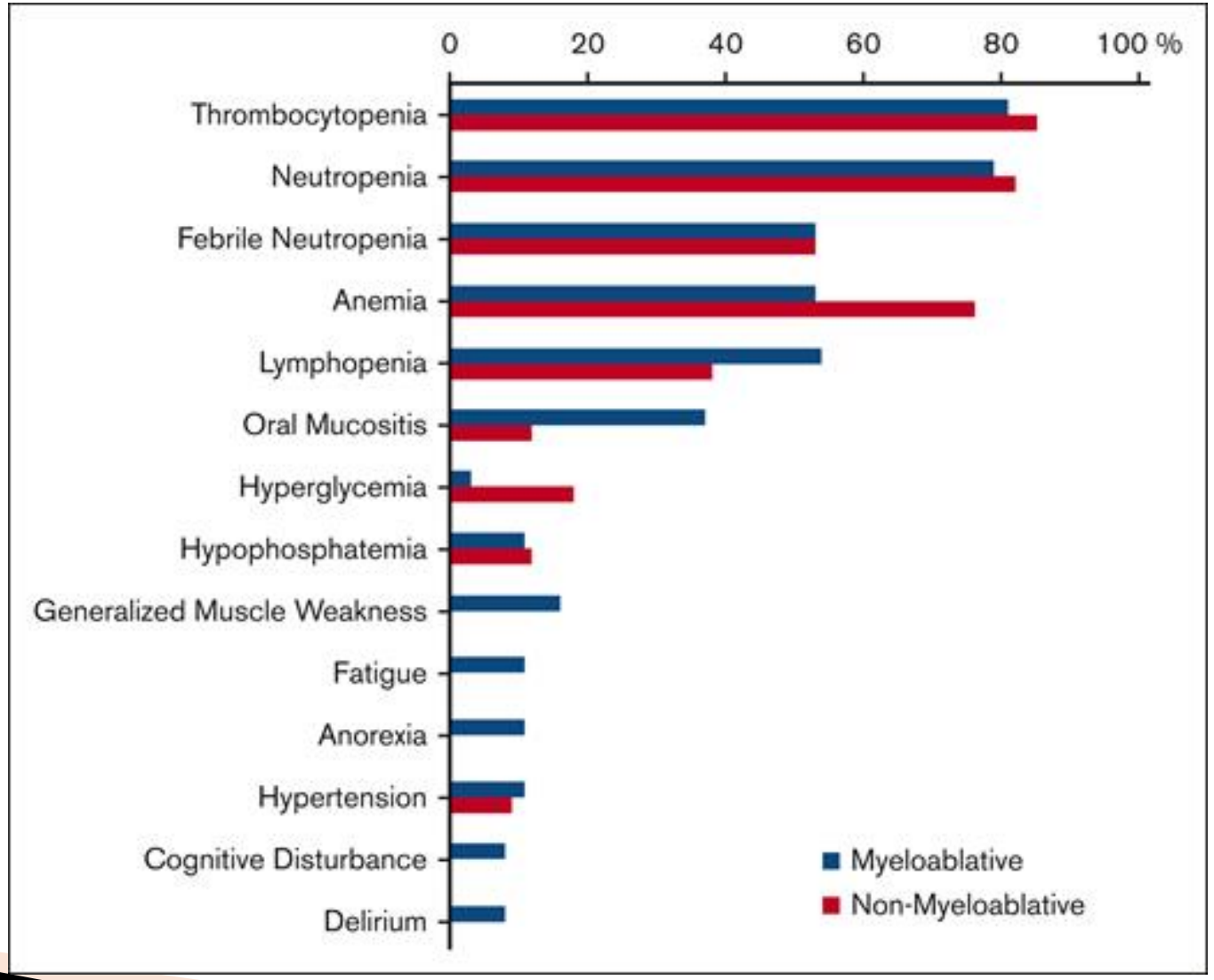
- N = 113, Auto = 57, EA = 56
- Completed induction: Auto – 45; EA – 40
- Among the 108 eligible patients who started induction therapy, 85 (79%) completed all 5 cycles.
- At completion of induction therapy, 72% ORR with 50 CR. 16 had progressive disease (PD).

Alliance 51101 – EA vs ASCT

Characteristic	MAC	Non-MAC
Enrollment		
PFS 2-yrs	73%	51%
OS 2-yrs	87%	78%
Consolidation		
PFS 2-yrs	85%	72%
OS 2-yrs	87%	78%



Alliance 51101– EA vs ASCT



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WBRT

VS

ASCT

PRECIS Trial – WBRT vs ASCT

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Phase II Study, <60 years, 140 patients

Induction

Two 28-day cycles of R-MBVP (rituximab 375 mg/m2, MTX 3 g/m2, Etoposide 100 mg/m2, BCNU 100 mg/m2, prednisone 60 mg/m2/d) followed by two 21-day cycles of R-AraC (rituximab 375 mg/m2, cytarabine 3 g/m2/day).

Randomization

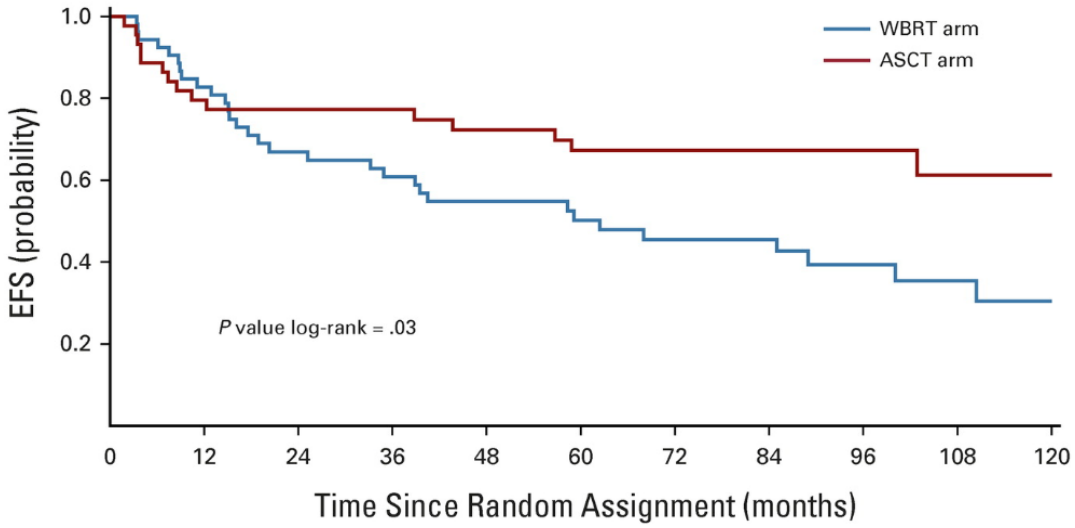
WBRT vs ASCT

End Points

PFS and Cognitive decline

Results

63% vs 87%



The difference between the WBRT and the ASCT group was statistically significant for the Mattis Dementia Rating Scale test (P = .004).

Houillier C et al. J Clin Oncol. 2022

Established Induction but what about Consolidation?

~~1. Chemo~~

~~2. WBRT~~

3. ASCT

Is there anything we can do to further improve the above?

Thiotepa-Based Conditioning

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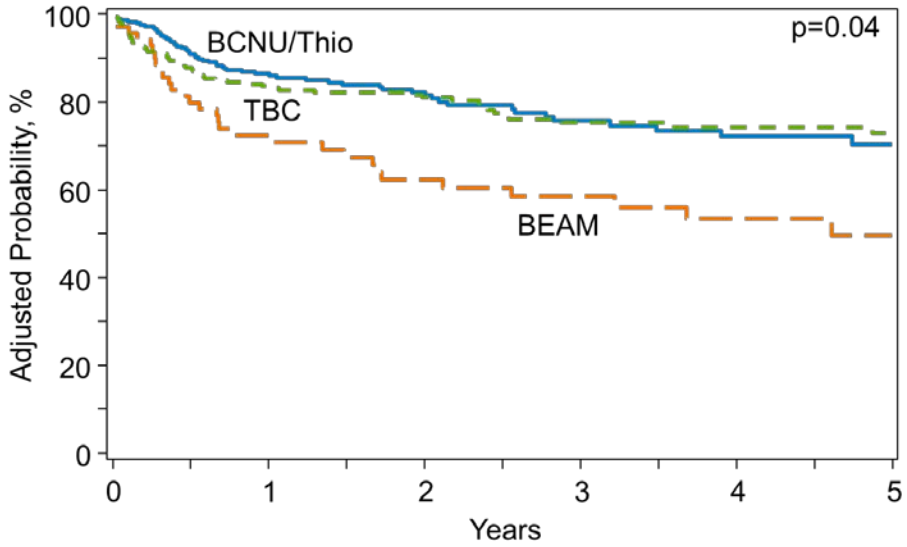
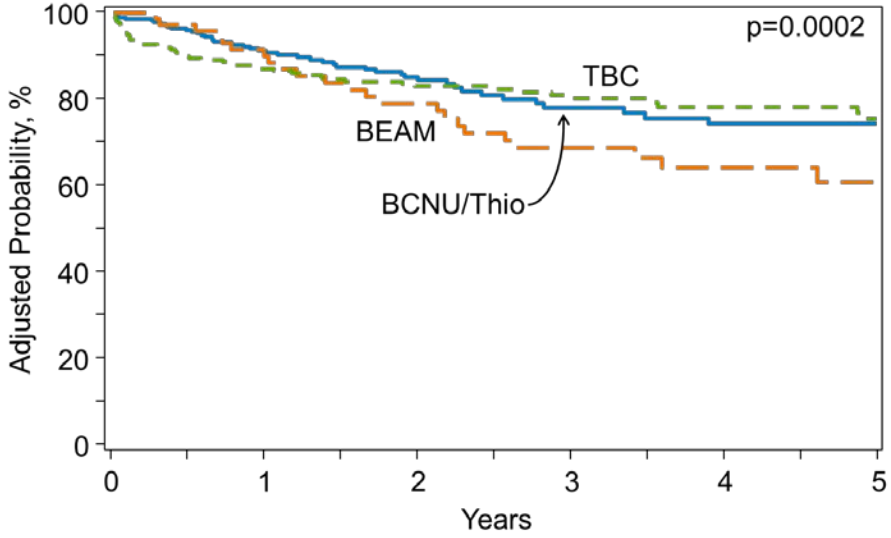
Progression-Free Survival



Overall Survival



	TBC	TT-BCNU	BEAM	P-value
Adjusted PFS				
3-year	75 (69-81%)	76 (70-82%)	58 (46-70%)	0.03
Adjusted OS				
3-year	81 (75-86%)	78 (72-85%)	69 (58-80%)	0.17

Scordo M. JAMA Oncol. Jul 2021

Age Not a Barrier: MARTA Study

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- Prospective study enrolled PCNSL patients > 65 years of age. Conditioning with R/Bu/Thiotepa
- 52 patients enrolled, mean age 72 (range 65-80) years
- Median follow-up of 23 months
- 2-year PFS and OS rates were 71.7% (95% CI 53.4-83.8%) and 80.8% (95% CI 63.8-90.3%), respectively. Transplant related mortality; N=1

Our Experience with RTOG 0227

- 29 patients received induction regimen consisting of R (dose between 375- 500 mg/m^2) and 3.5 g/m^2 of MTX with leucovorin on weeks 1, 3, 5, 7 and 9 along with TMZ 200 mg/m^2 daily for 5 days on weeks 4 and 8, followed by consolidation with either WBRT/TMZ or ASCT.

- Median age 62. On average, patients received 4 cycles of MTX and 8 cycles of TMZ.

- 18 (62%) pts received WBRT/TMZ consolidation, while 11 (38%) received ASCT consolidation.

Ahmed R and Fenske TS. Blood. Nov 2023

Our Experience with RTOG 0227

Characteristic	N (%)		
Total Patients	29		
ORR	27 (93.1)		
CR	8 (27.5)		
PD	1 (3.5)		
TRM	0		
Median Follow Up	36 months		
Survival	Overall	ASCT	WBRT
PFS (2-yr)	83%	87%	81%
OS (2-yr)	96%	100%	94%
PD Post Consolidation	5	1	4

Relapsed Disease

- NCCN Recommended Approaches:
  - For patients with prior response ≥12 months:
    - Re-treat with HD-MTX ± rituximab
    - Consider HDC-ASCT if eligible and not previously done

- Other Recommended Options:
  - Ibrutinib
  - Lenalidomide ± rituximab
  - Pomalidomide
  - Temozolomide
  - Pemetrexed
  - Zanubrutinib ± high-dose cytarabine
  - Nivolumab

Relapsed Disease

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Authors	Treatment	PCNSL Patients	ORR (%)	CR (%)	PFS (m)	OS (m)
Grommes et al	Ibrutinib (560 – 840 mg daily)	13	77	38	4.6	15
Grommes et al	Ibrutinib Phase II (560 – 840 mg daily)	31	74	39	4.5	25.4
Lin et al	Zanu (160 BID) + Ara-C (3.0 g/m^2)	34	64.7	47.1	4.5	18
Ghesquieres et al	Lenalidomide (25 mg) + Rituxan (375 mg/m^2)	50	32	29	7.8	17.7
Perez et al	Ibrutinib + Lenalidomide + Rituximab	5	80	40	5.5	80%
Nayak et al	Axi-cel	13/18	94	67	14.3	26.4

Grommes et al., Cancer Dis. 2017
Grommes et al., Clin Cancer Res. 2024
Lin Z et al. Acta Haematol. 2024
Ghesquieres H et al. Ann Oncol. 2019
Perez AP et al. Blood. 2023
Nayak L et al. JCO. 2024

Axi-cel for relapsed/refractory PCNSL and SCNSL

Characteristic	Patients
ORR	17/18 (94%)
CR	12/18 (67%)
Median Followup	24.2-months
Median DOR	13.4 months
PD	9 (50%)
CRS	16/18 (89%); No Grade 3
ICANS	8/18 (44%); 28% G3+
Seizure	1/18 (6%)

The Future – Emerging Therapies

- Combination of current approved therapies
  - R-MPV + lenalidomide or ibrutinib
  - Lenalidomide 15 mg + ibrutinib 560 mg

- Novel Targeted Therapies in Development:
  - Pirtobrutinib (non-covalent BTKi) for patients progressing on covalent BTKis
  - Bispecific antibodies (Epcoritamab, glofitamab) + BTKi
  - Immunotherapy – Nivolumab + Len

The Future Direction

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- Biomarker driven approaches with circulating tumor DNA in CSF as response marker and molecular profiling to guide targeted therapy selection
- Integration of targeted therapies (BTKis, IMiDs) into first-line treatment
- Novel immunotherapies (PDL-1, bispecific antibodies)
- Continued clinical trial enrollment to define optimal treatment sequences and identify patients who benefit most from specific therapies

Takeaway Points

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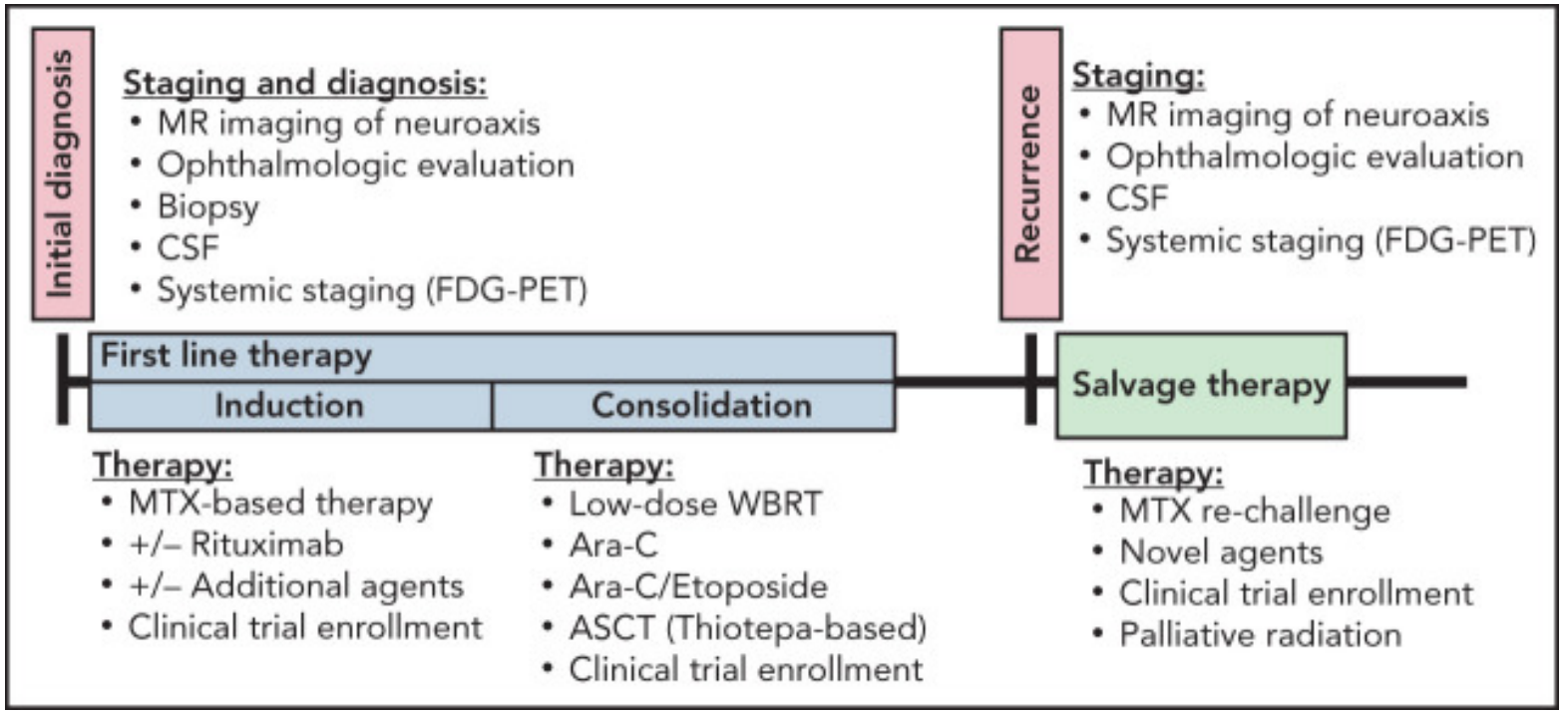
- In PCNSL patients responding to methotrexate-based induction treatments, consolidation with autologous HCT is standard-of-care
- Thiotepa-based conditioning is important in auto transplant package
- In select patients, radiation treatment is reasonable but does carry risk of neurocognitive decline, would consider adding TMZ maintenance
- In early relapsed setting consider early CAR-T with promising early results

Summary of Current Landscape



Schaff LR, Grommes C. Blood. 2022

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Thank you!