



UNC Lineberger Cancer Network

RESEARCH TO PRACTICE 


July 27, 2022

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OUR PRESENTER



**Christopher Dittus,
DO, MPH**

Dr. Dittus specializes in diagnosing and managing all types of lymphoma, including B-cell non-Hodgkin lymphoma (NHL), T-cell NHL, and Hodgkin lymphoma.

Dr. Dittus is also a clinical researcher specializing in investigator-initiated clinical trials aimed at rare and underserved lymphomas. He serves as the AIDS Malignancy consortium (AMC) site PI at UNC.

He headed south to North Carolina to take his current faculty position at UNC Chapel Hill. He has been here for over four years and enjoys spending time outdoors with his wife, children, and dog, Charlie.

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Primary central nervous system lymphoma is a disease in which malignant cancer cells form in the lymph tissue of the brain and/or spinal cord.

True **A**

False **B**

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Primary central nervous system lymphoma is a disease in which malignant cancer cells form in the lymph tissue of the brain and/or spinal cord.

True **A**

False **B**

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Primary CNS Lymphoma Management in North Carolina: Updates for 2022

Christopher Dittus, DO, MPH
Associate Professor of Medicine
University of North Carolina at Chapel Hill
July 27, 2022



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Outline

- Case Presentation
- Background
- Diagnosis & Workup
- Treatment



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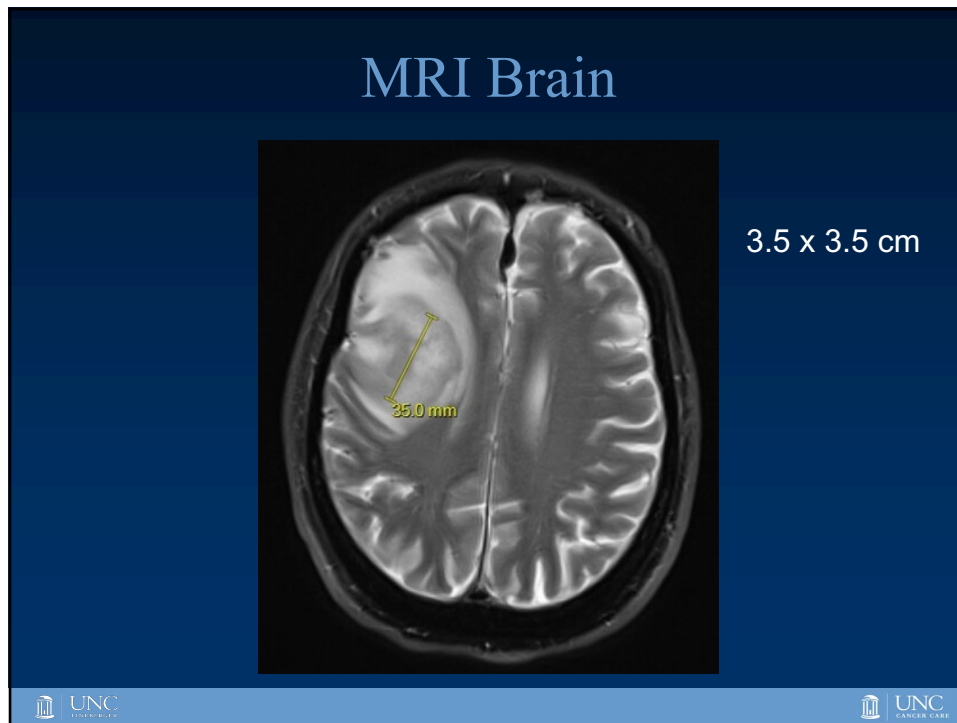
Case Presentation

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PCNSL Case

- 72y M with h/o HTN presents with confusion and left-sided weakness.
- ECOG: 2
- Decreased motor function in RUE/RLE
- Normal CBC, CMP, LDH; HIV/HBV neg
- Brain imaging obtained for further evaluation

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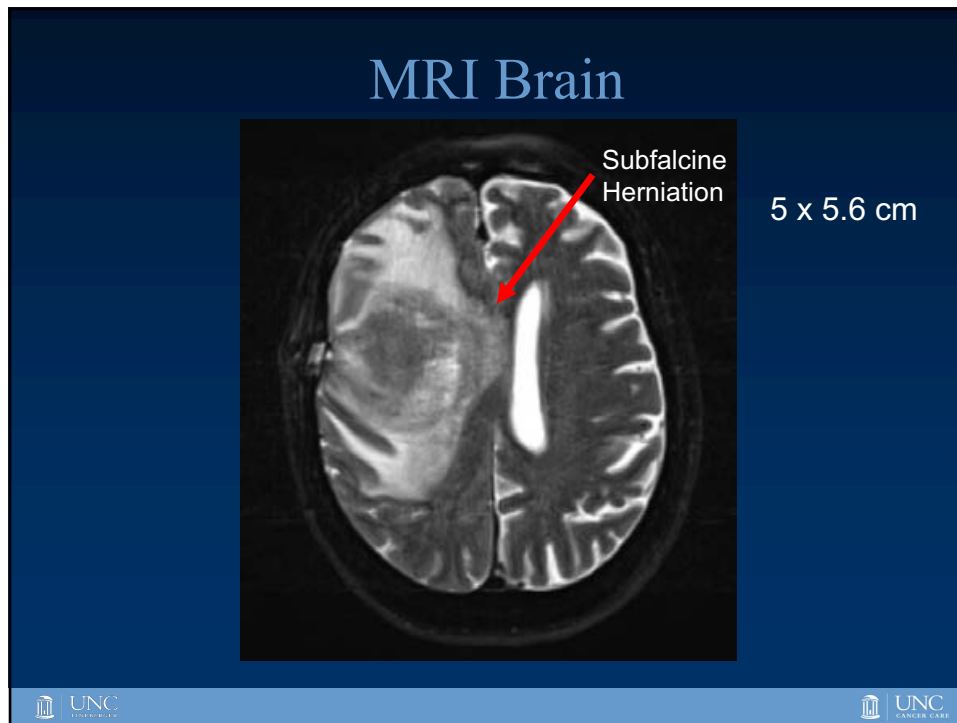
15

PCNSL Case

- Had right frontal lobe brain biopsy: DLBCL
- The patient was discharged after biopsy.
- Presented to hematology clinic and was obtunded.
- Admitted to Neuro ICU and found to have subfalcine herniation.
- New ECOG PS: 4

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Further Workup

- Patient started on Dexamethasone
- Evaluation for systemic disease:
 - PET-CT negative
- CSF: not obtained due to herniation
- Slit Lamp Exam: negative
- Plan to start chemotherapy once workup complete

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What is Lymphoma?

Adaptive Immune System:

- B Cells (Humoral immunity)
- T Cells (Cell-mediated immunity)

Lymphoma = Cancer of *mature* B-cells and T-cells

Often in Lymph Nodes

Extranodal=disease outside the lymph nodes

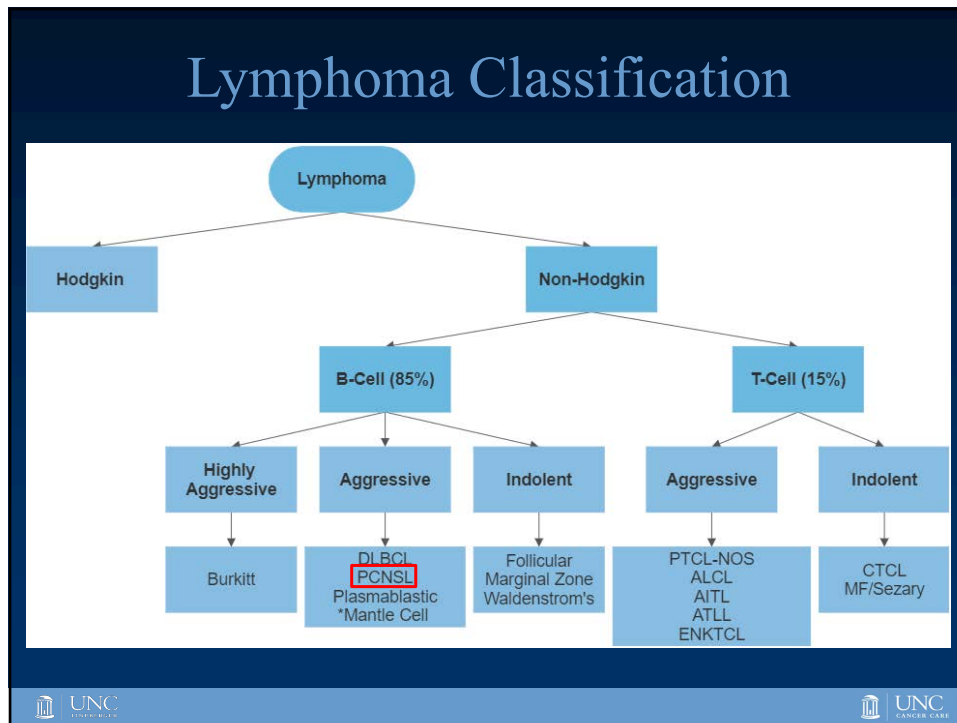
T Cells
Account for approximately 80 percent of circulating lymphocytes; are of three major types

- Cytotoxic T Cells**
Attack foreign cells or body cells infected by viruses, commonly by direct contact; are the primary cells involved in the production of cell-mediated immunity (cellular immunity)
- Helper T Cells**
Stimulate the activation and function of both T cells and B cells
- Suppressor T Cells**
Inhibit the activation and function of both T cells and B cells; the interplay between suppressor T cells and helper T cells helps establish and control the sensitivity of the immune response

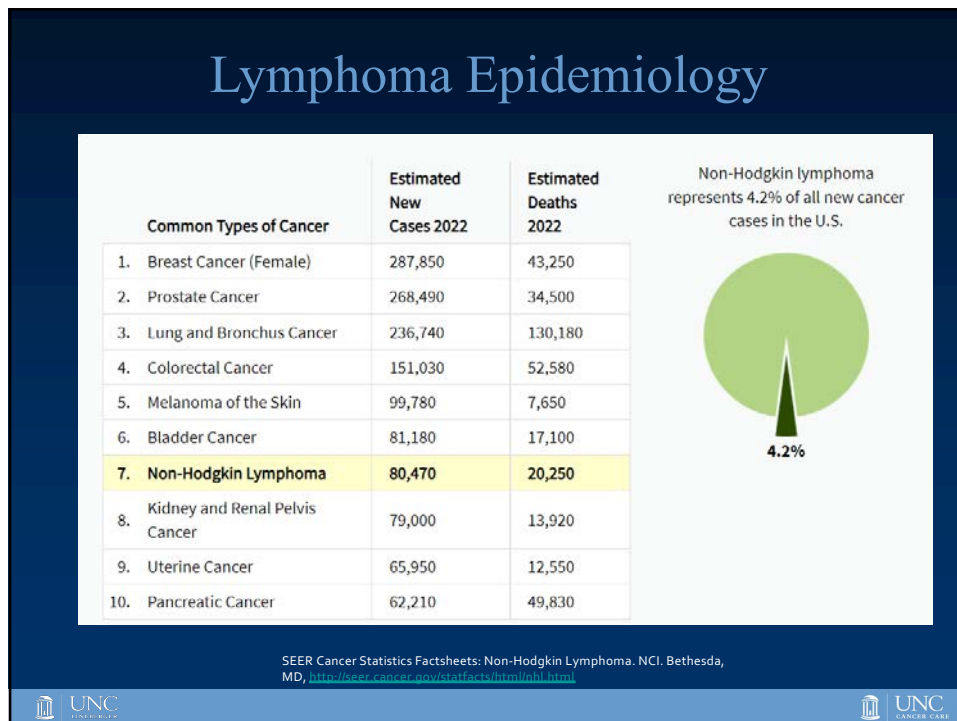
B Cells
Account for 10-15 percent of circulating lymphocytes

Plasma Cells
When stimulated can differentiate into plasma cells, which produce and secrete antibodies; are said to be responsible for antibody-mediated immunity (humoral immunity) because antibodies circulate widely in body fluids

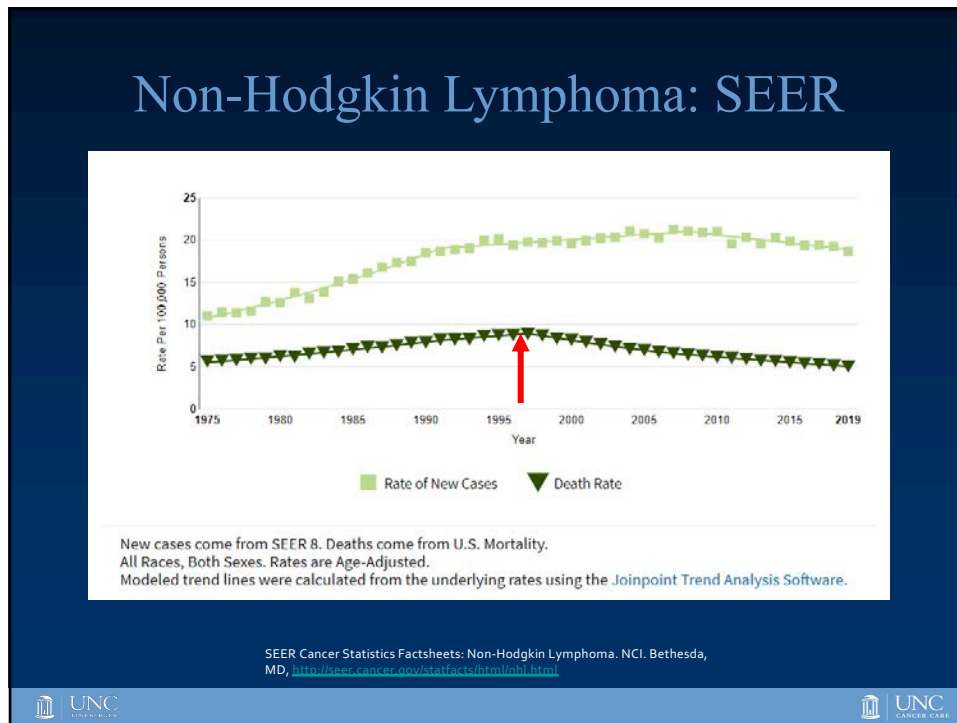
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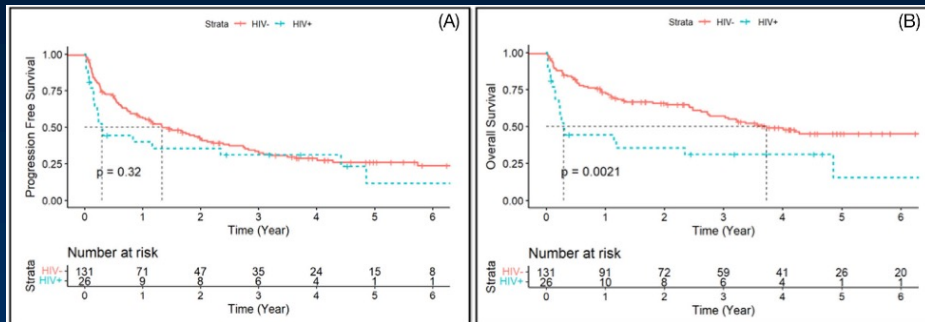
PCNSL Background

- Aggressive lymphoma
- Rare disease:
 - 3-4% of CNS cancer
 - Incidence: 0.3 cases/100,000 pop
 - **1100 cases/year** in US
- Median Age: 66 (immunocompetent)
- Increasing in pts >60 yrs
- Decreasing in HIV+
- HIV+ has worse survival

Teras, Ca Cancer J Clin, 2016

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PCNSL: HIV vs non-HIV



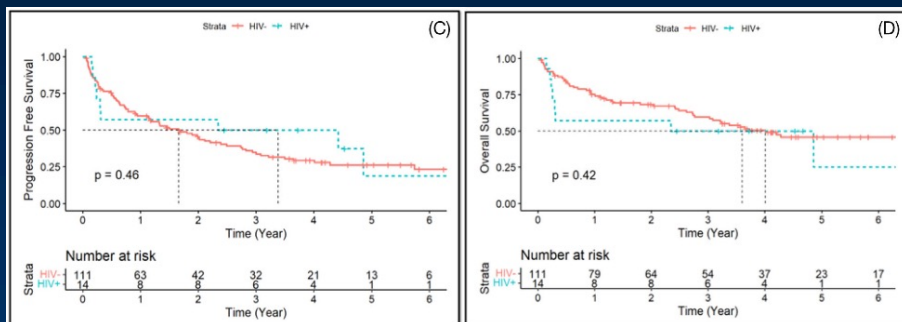
N=158 total (26 with HIV)
 3 Centers: UNC, Emory, Vanderbilt
 Dates: 2004-2020
 DLBCL histology (no secondary CNS included)

Dittus, eJHaem, 2022



25

PCNSL: HIV vs non-HIV (MTX-only)



MVA: Age, HIV and HD MTX
 all significant for OS

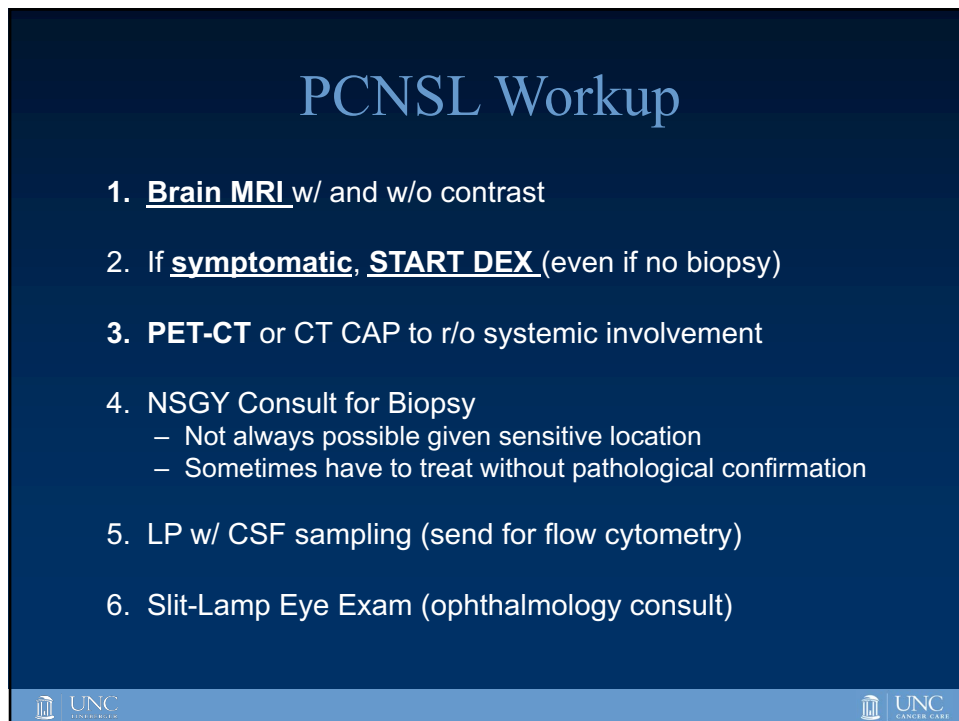
Dittus, eJHaem, 2022



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Prognostic Score: IELSG

General Index	Parameter	Remarks
1	Age > 60y	None
1	PS 2-4	ECOG Performance Score
1	Serum LDH elevated	above upper normal
1	Cerebrospinal fluid protein elevated	above upper normal
1	Deep structures involved	basal ganglia, corpus callosum, brain stem, or cerebellum
5	Maximum Score	NOT evaluated for HIV+

# of Risk Factors - General index	Risk Group
0 - 1	1 = low
2 - 3	2 = intermediate
4 - 5	3 = high

2-year Survival

Low: 80%

Int: 48%

High: 15%

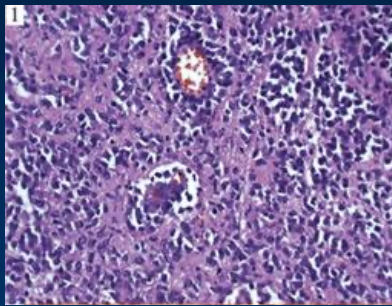
Ferrerri, JCO, 2003

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Diagnosis

Morphology:

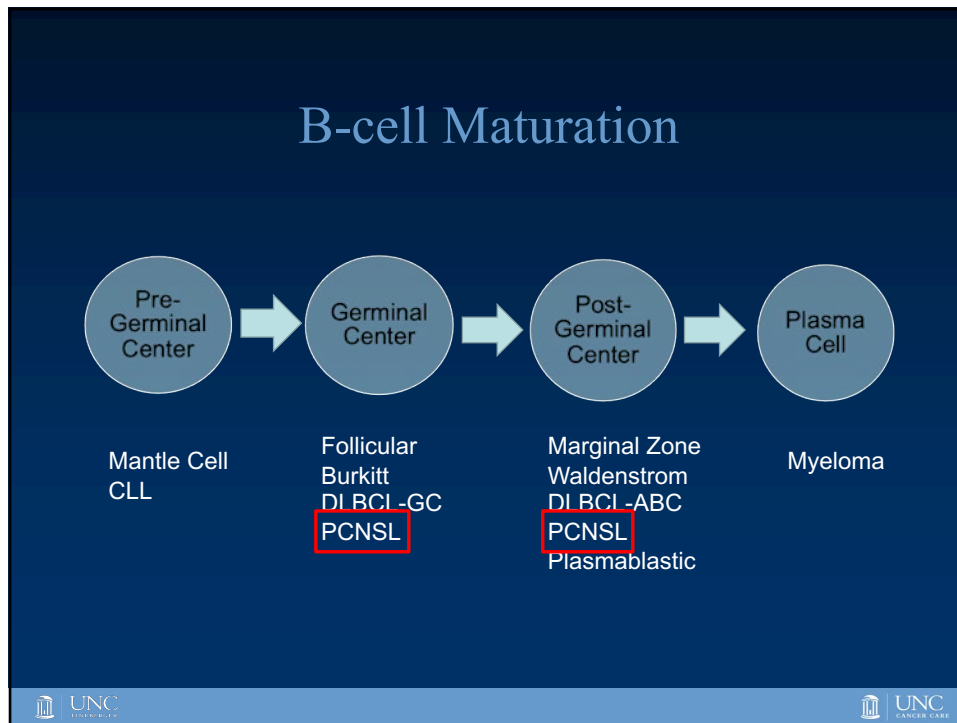
- Atypical cells w/ medium to large centroblasts or immunoblasts.



Flow/IHC:

- B-cell Markers: CD19, CD20, PAX5
- CD10 < 10%
- BCL6 (70%); MUM1 (90%)
- BCL2/MYC+: 82%

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Ann Arbor/Lugano Staging

Revised staging system for primary nodal lymphomas (Lugano classification)

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Extent of disease is determined by positron emission tomography/computed tomography (PET/CT) for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

* Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Lymph node regions used to determine stage in lymphoma. UptoDate

Cheson et al, JCO, 2014

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PCNSL Response Criteria

Table 4. Response Criteria for Primary Central Nervous System Lymphoma

Response	Brain Imaging	Corticosteroid Dose	Eye Examination	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	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			

Abbreviations: CR, complete response; CRu, unconfirmed complete response; RPE, retinal pigment epithelium; PR, partial response; PD, progressive disease.

Abrey, JCO, 2005

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The patient had a brain mass, but no systemic involvement. What stage is the patient's PCNSL?

- Stage I
- Stage IE
- Stage IIE
- Stage IV

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Treatment of PCNSL

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Approach to PCNSL Treatment

- Initiate Dexamethasone
 - Often requires a slow taper over 1-2 months
 - Improves ECOG PS
- Methotrexate-based Induction:
 - **R-MPV** (Rituximab, Methotrexate, Procarbazine, Vincristine)
 - **MATRIx** (Methotrexate, Cytarabine, Thiotepa, Rituximab)
- Consolidation:
 - Autologous SCT (BCNU/TT vs. TBC)
 - Reduced dose WBRT (23.4Gy)
 - Clinical Trial

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Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Jeffrey J. Raizer, David Schiff, Barbara Grant, Sean Grimm, Rose K. Lai, Anne S. Reiner, Kathy Panageas, Sasan Karimi, Richard Curry, Gaurav Shah, Lauren E. Abrey, Lisa M. DeAngelis, and Antonio Omuro

R-MPV Approach:

- R-MPV q14d x5 → MRI
- MRI=PR: R-MPV x2 (7 total)
- MRI=CR:
 - rdWBRT + Cytarabine
 - AutoSCT

N=52

-mAge: 60 (30-79)

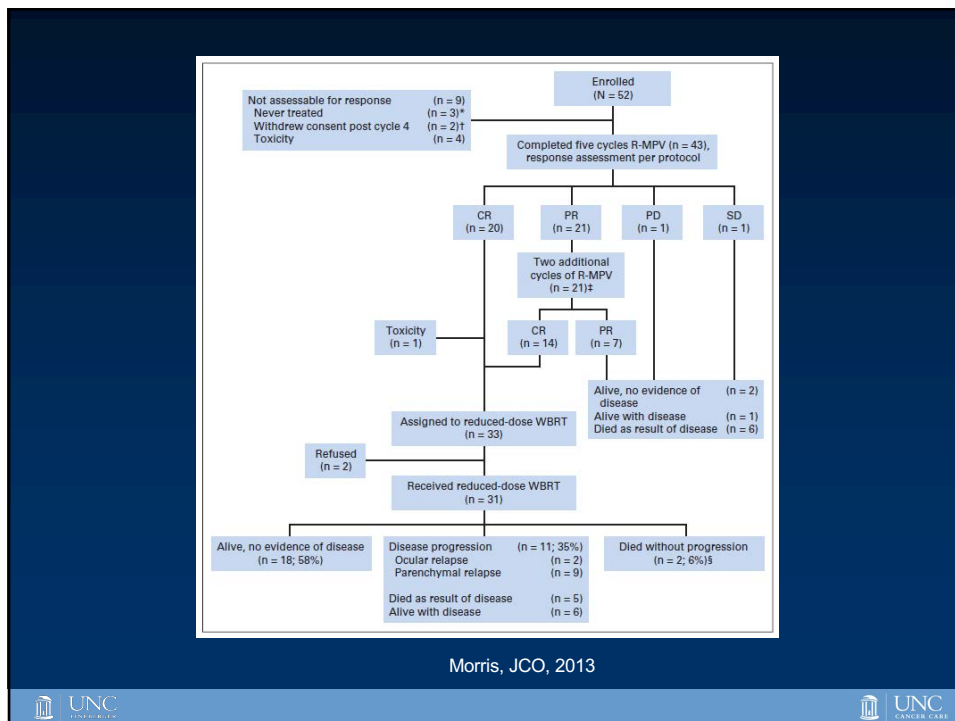
-R-MPV x5-7 then rdWBRT

(23.4Gy if in CR)

-Consolidation with cytarabine

Morris, JCO, 2013

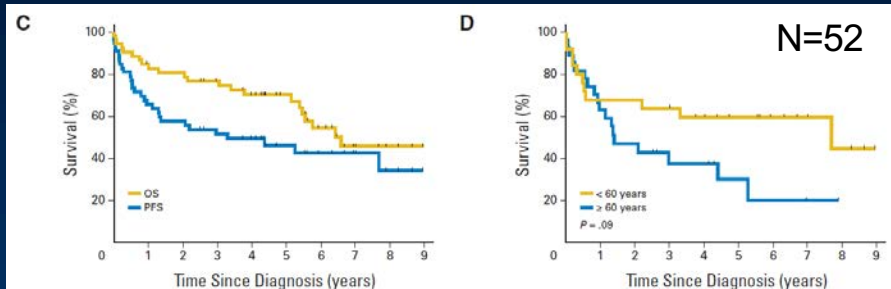
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Morris, JCO, 2013

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Survival in the Whole Cohort



2-year PFS: 57%
 2-year OS: 81%
 5-year OS: 70%

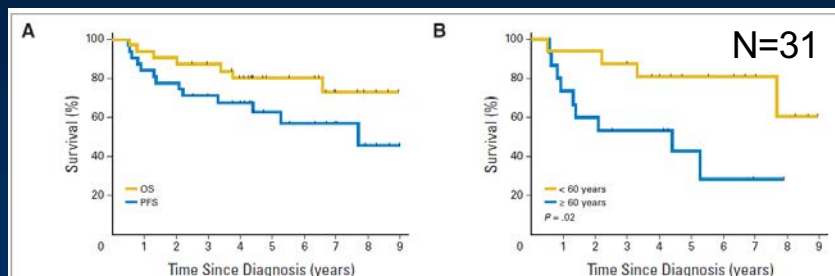
2-year PFS <60: 64%
 2-year PFS ≥60: 47%

Morris, JCO, 2013



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Survival in Patients with a CR and rdWBRT



2-year PFS: 77%
 2-year OS: 90%
 5-year OS: 80%

2-year PFS <60: 94%
 2-year PFS ≥60: 60%

Morris, JCO, 2013



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R-MPV with AutoSCT Consolidation

R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma

Antonio Omuro,¹ Denise D. Correa,¹ Lisa M. DeAngelis,¹ Craig H. Moskowitz,² Matthew J. Matasar,² Thomas J. Kaley,¹ Igor T. Gavrilovic,¹ Craig Nolan,¹ Elena Pentsova,¹ Christian C. Grommes,¹ Katherine S. Panageas,³ Raymond E. Baser,³ Geraldine Faivre,¹ Lauren E. Abrey,¹ and Craig S. Sauter²

Table 1. Patient characteristics (N = 32)

Characteristic	Value
Median age (range)	57 (23-67)
Age < 60	21 (66%)
Age < 50	11 (34%)
Median KPS (range)	80 (40-100)
KPS < 70	6 (19%)
KPS < 50	1 (3%)

TBC:
 -Thiotepa 250 mg/m² IV on D -9, -8, and -7
 -Busulfan 3.2 mg/kg IV on D -6, -5, and -4
 -Cyclophosphamide 60 mg/kg IV on D -3 and -2

Omuro, Blood, 2015

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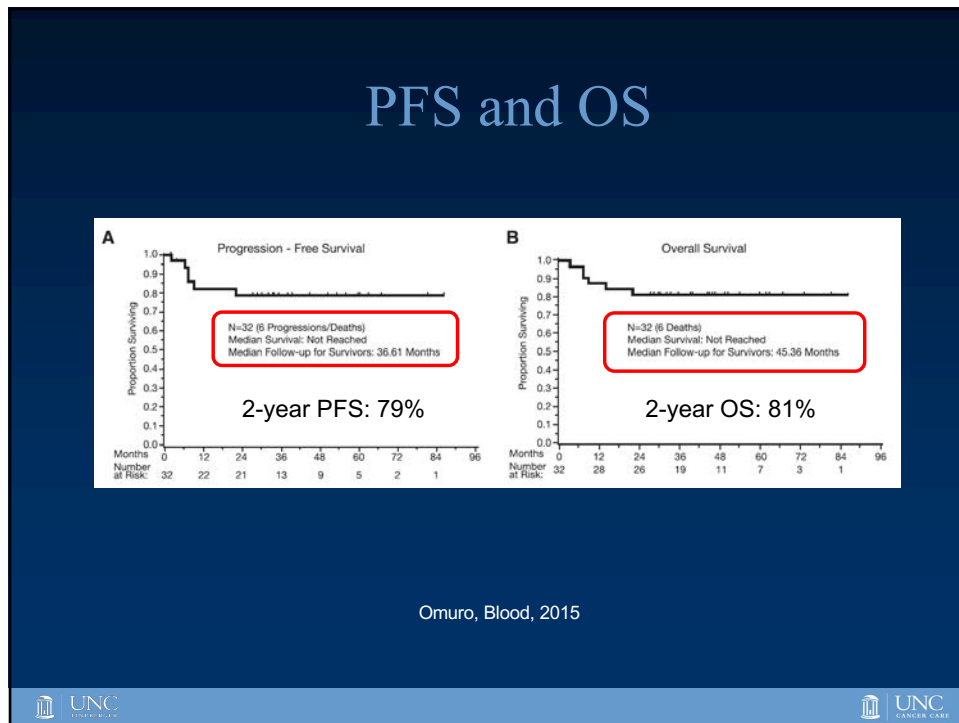
Response Rate

Table 3. Response status after R-MPV and following transplant

	CR/CRu	PR	SD	PD
Response after 5 R-MPV cycles (N = 32)	14 (44%)	16 (50%)	1* (3%)	1 (3%)
Best response to R-MPV induction chemotherapy (5 or 7 cycles) (N = 32)	21 (66%)	9 (28%)	1* (3%)	1 (3%)
Pretransplant response status in the transplanted patients (N = 26)	18 (69%)	7 (27%)	1* (4%)	0 (0)
Best response after transplant (N = 26)	21 (81%)	3 (11%)	1* (4%)	1 (4%)

Omuro, Blood, 2015

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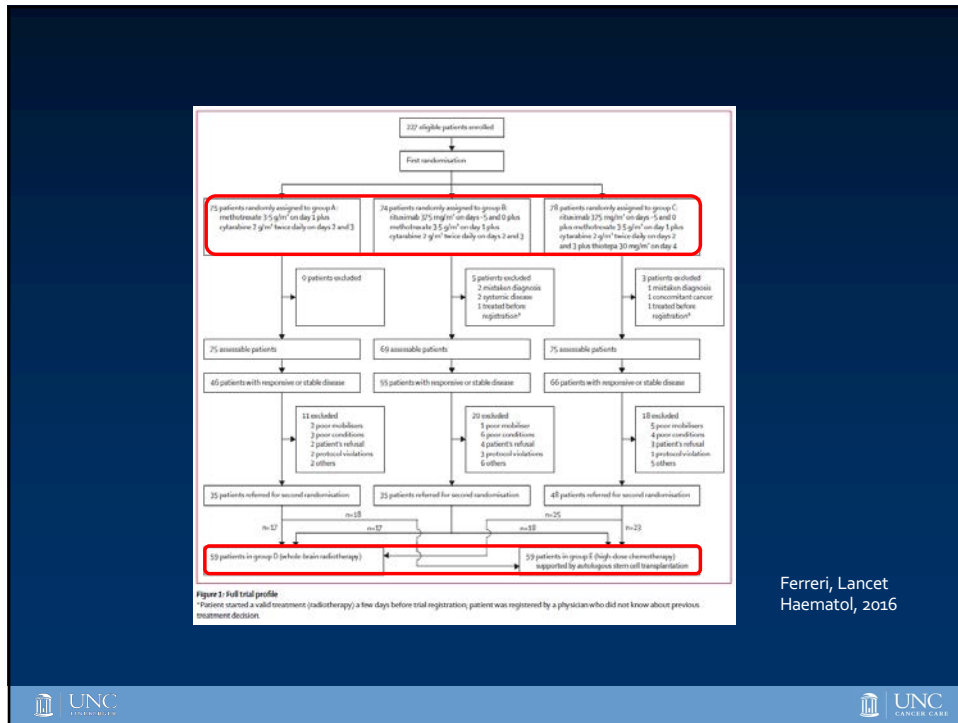
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Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial

Rand. Ph 2
 -N=227
 -HIV-neg
 -Age: 18-72

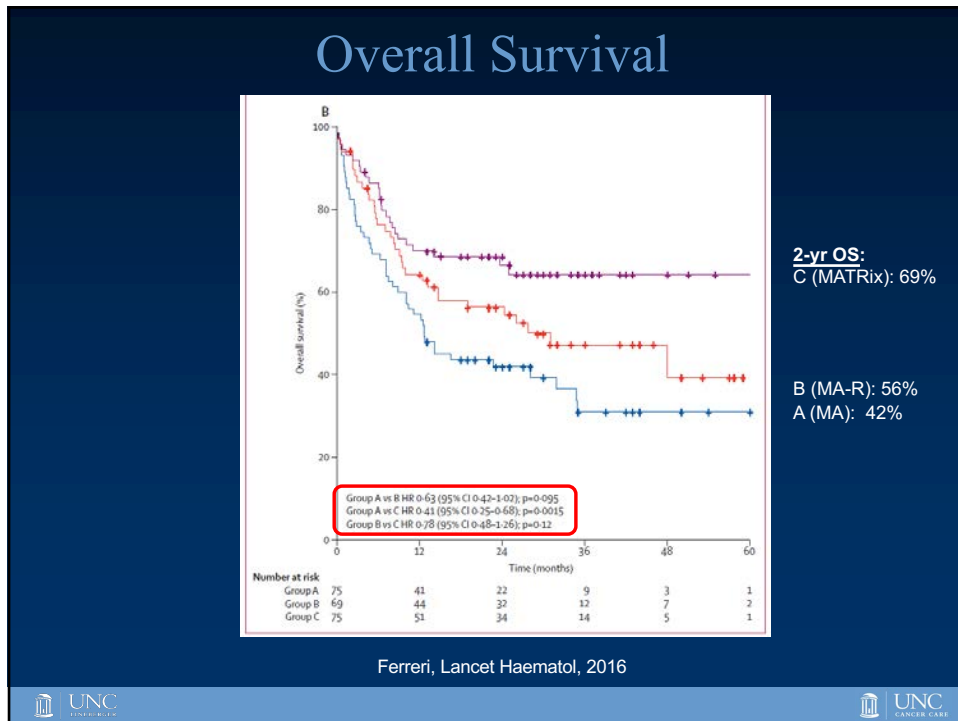
Ferreri, Lancet Haematol, 2016

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Ferreri, Lancet Haematol, 2016

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Our patient should receive a high-dose methotrexate-based induction regimen.



True
 False

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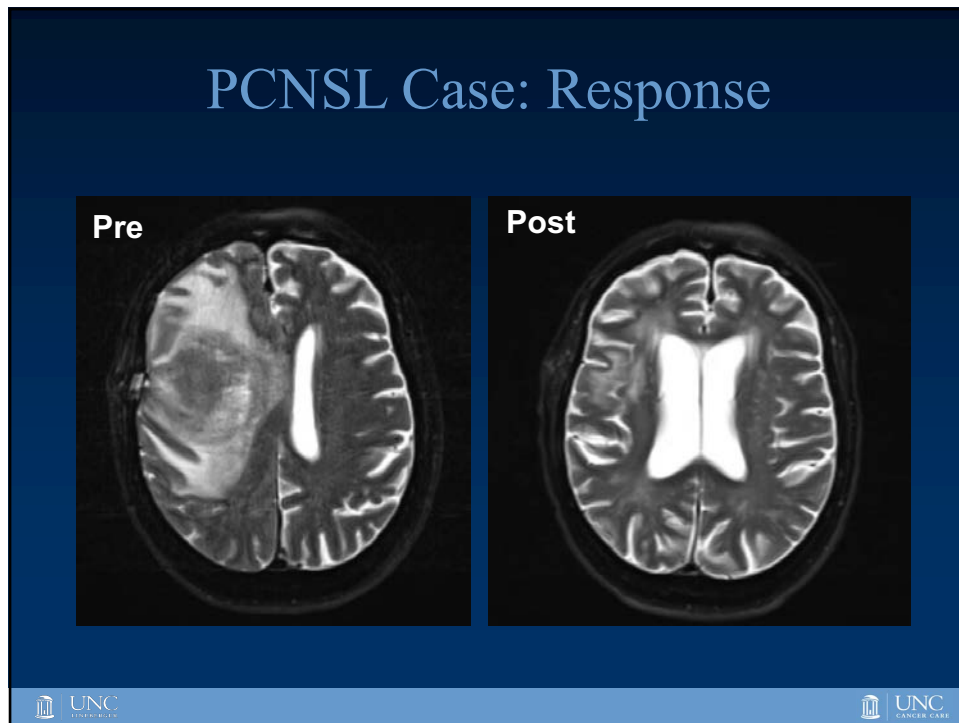
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PCNSL Case

- Pt started on R-MPV chemotherapy
- He completed 5 cycles of R-MPV and had a Complete Response on MRI
- ECOG PS improved to a 2

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Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial



N=118

- Rand. to WBRT (36Gy) or AutoSCT
- Age: 18-70

AutoSCT:

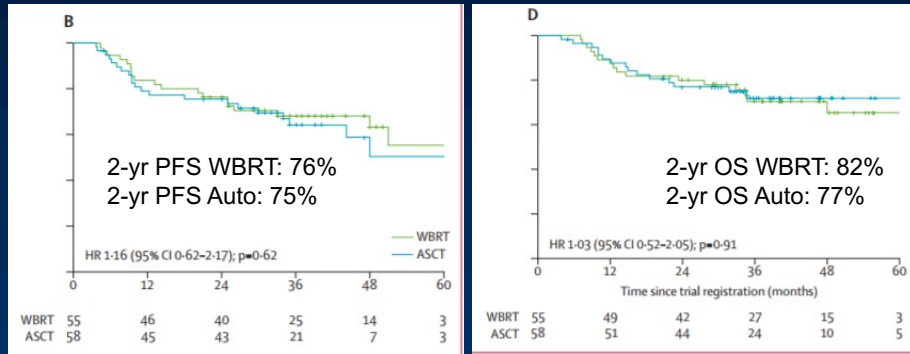
- Carmustine 400 mg/m² on day -6
- Thiotepa 5 mg/kg every 12 h on D -5 and -4

Ferrari, Lancet Haematol, 2017

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WBRT vs. ASCT: No Survival Difference

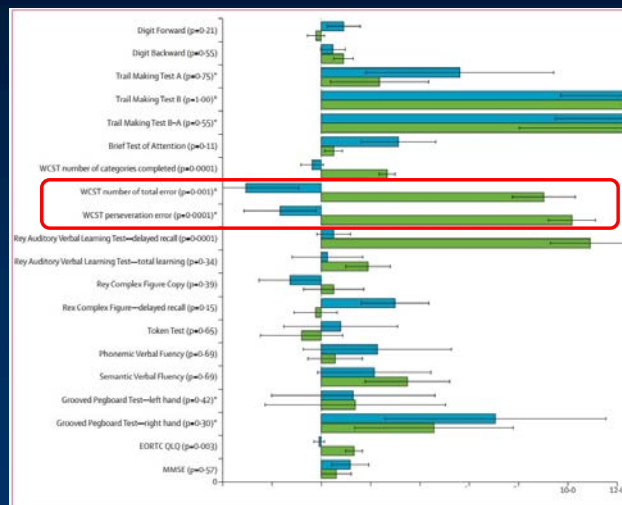


Ferrari, Lancet Haematol, 2017

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Neurotoxicity at 2 Years

Wisconsin Card Sorting Test:
-Working memory
-Hard to interpret
-Longer Follow-up



Ferrari, Lancet Haematol, 2017

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TITLE: A Phase 1B Trial of Nivolumab Consolidation Following Completion of High-Dose Methotrexate Containing Induction Chemotherapy in Older (≥ 65) Patients with Primary CNS Lymphoma

- Background: Nivolumab had a 78% ORR in 7 of 8 pts w/ R/R PCNSL (Gavrilenko, ASH, 2020)
- Primary Site: Levine Cancer Institute
- PI: Steven Park
- N =20 patients
- Avoids WBRT consolidation in older patients (who are highest risk for cognitive dysfunction)
- UNC: 4 patients enrolled

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Study Schema

```

    graph LR
      A["• Histological or cytological confirmation of PCNSL  
• Age ≥ 65 years  
• Received ≥ 2 cycles of HD-MTXa containing induction chemotherapy without evidence of PD  
• Measurable disease at pre-induction assessment"] --> B[Screening]
      B --> C[Enrollment]
      C --> D[Consolidation Nivolumab x 6 cycles]
      D --> E["Follow-up :  
• MRI of Brain per follow-up scheduleb until PD or start of subsequent anti-cancer therapy"]
    
```

^a HD-MTX= high-dose methotrexate
^b MRI Brain 8 weeks after last dose of nivolumab (± 2 weeks) then every 4 months (± 2 weeks) x 1 year, every 6 months (± 2 weeks) x 1 year; then at the frequency as determined by the investigator

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Pt is now in a CR after induction therapy. What would be the best consolidation treatment for our frail 72 yo patient?



- Allogeneic stem cell transplant
- Autologous stem cell transplant
- Full dose WBRT
- Clinical trial evaluating Nivolumab in patients >65 yo

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PCNSL Case

- The patient is 72 yrs old with a poor PS at diagnosis.
- His PS improved with induction therapy, but he is still frail.
- Options for consolidation included:
 - Reduced dose WBRT
 - Clinical trial for elderly patients with PCNSL
- Patient decided to proceed with LCI Clinical Trial evaluating Nivolumab consolidation.

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What about Relapsed PCNSL?

- **Re-treat with HD-MTX** (if initial response >12mo)
- **Ibrutinib** (N=52)*
 - DC: 70%; ORR: 52%; CR: 19%
 - PFS: 4.8mo; OS: 19.2mo
- **Lenalidomide/Ritux** (N=50)**
 - x8C; if response, x12C maintenance
 - ORR: 39%; CR: 30%
 - OS: 15.3mo; PFS: 8.1mo

*Soussain, European J Ca, 2019

**Ghesquieres, Ann, 2019



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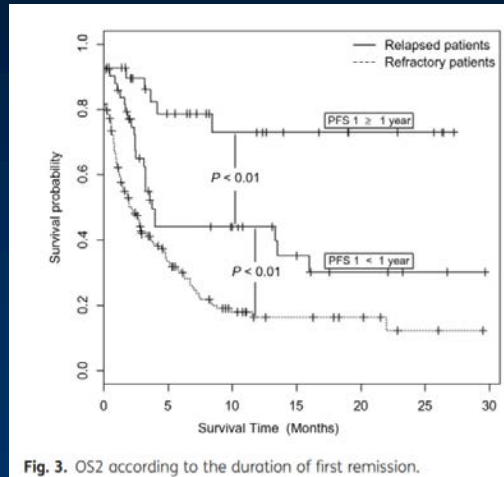
Relapsed PCNSL

- **PD-1 Inhibition**
 - Nivolumab:
 - Nayak et al (2017): 5 pts, ORR 100%
 - Gavrilenko et al (2020): 8 pts, ORR 78%
 - Pembrolizumab:
 - Hoang-Xuan et al (2020): 50 pts, ORR 26%
- **CD19 CAR-T Cell Therapy**
 - Siddiqi et al (2021): 5 pts, CR 60%
 - Frigault et al (2022): 12 pts, CR 50%
 - Low grade ICANS 41.6%; Gr 3 in 1 pt
 - CRS: 58.3% (Gr 1 only)
 - LCCC 1813 (CD19 CAR-T trial at UNC)




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Poor outcomes for early relapses



Langner-Lemerrier, Neuro-Onc, 2016

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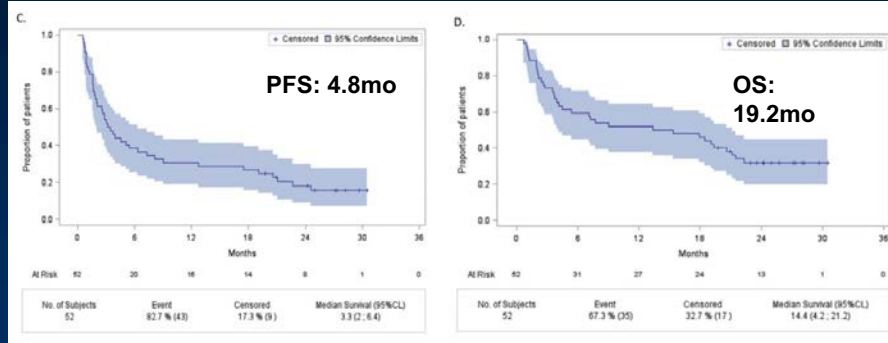
Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II ‘proof-of-concept’ *i* LOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network 

	52	44
N	52	44
Sex ratio M:F	6:7	5:6
Median age	67.5 (range, 47–82)	70 (range, 52–81)
≥ 60	35 (67%)	33 (75%)
PS		
0–1	35 (67%)	33 (77%)
2	17 (33%)	11 (23%)
Number of previous lines of treatment		
1	19 (36.5%)	18 (41%)
2	19 (36.5%)	15 (34%)
3	9 (17%)	6 (14%)
4	5 (10%)	5 (11%)
Previous ASCT	7	4
Previous WBRT	11	1

Soussain, European J Ca, 2019

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Survival with Ibrutinib



ORR: 52%
 CR: 19%
 2 w/ Pulm
 Aspergillosis

Soussain, European J Ca, 2019

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LCCC1841: A Pilot Study Evaluating Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas

- N=16 patients
- Up to 50% SCNSL
- Acalabrutinib 100mg BID
- Aspergillosis ppx: Isavuconazole 200mg daily (after loading dose)
 - Moderate CYP3A4 Inhibitor
- Open at Wake Forest; will open at Moffitt Cancer Center

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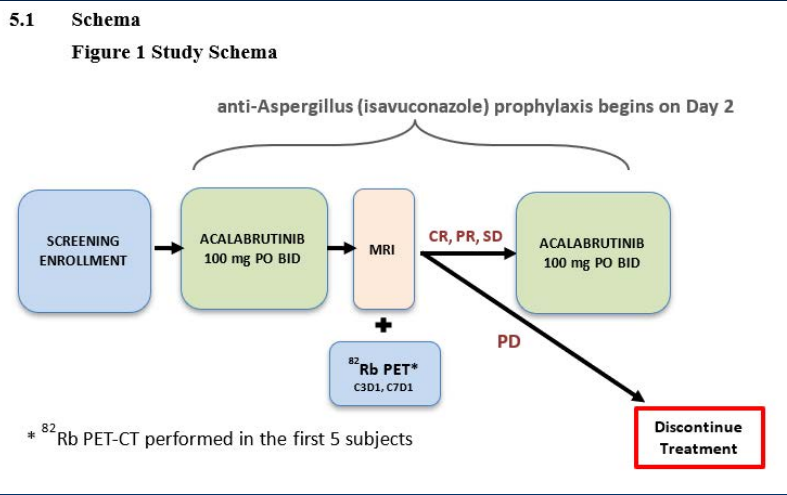
LCCC1841: A Pilot Study Evaluating Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas

- Primary Objectives
 - Determine overall response rate (ORR)
- Secondary Objectives
 - Toxicity, CR rate, PFS, OS
- Exploratory Objectives
 - ⁸²Rb PET efficacy for response assessment
 - Assess pharmacokinetic parameters (plasma and CSF)
 - MYD88 and CXCR4 mutational status and response
 - Evaluate mental status and cognitive function



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LCCC1841: A Pilot Study Evaluating Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas



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Our patient is still in a CR, but if he relapses within 1 year, what would be his best treatment option (not CAR-T eligible)?

- None, he should go on hospice
- Re-treat with HD-MTX
- BTK Inhibitor
- Full dose WBRT



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Clinical Trials at UNC

- Frontline Consolidation:
 - LCI Trial: A Phase 1B Trial Nivolumab Consolidation Following Completion of High-Dose Methotrexate Containing Induction Chemotherapy in Older (≥ 65) Patients With Primary CNS Lymphoma
- Relapsed:
 - LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas
 - LCCC1813: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects With Relapsed/Refractory B-cell Lymphoma

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