Primary CNS Lymphoma: What is the optimal treatment?

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Disclosures

- Consulting/Advisory Role: Roche, Takeda, Celgene, Atara, Gilead, KITE, Janssen, Incyte, Abbvie
- Speakers' Bureau: Roche, Takeda, KITE, Gilead,
- Conferences/Travel support: Roche, Takeda, KITE, Janssen

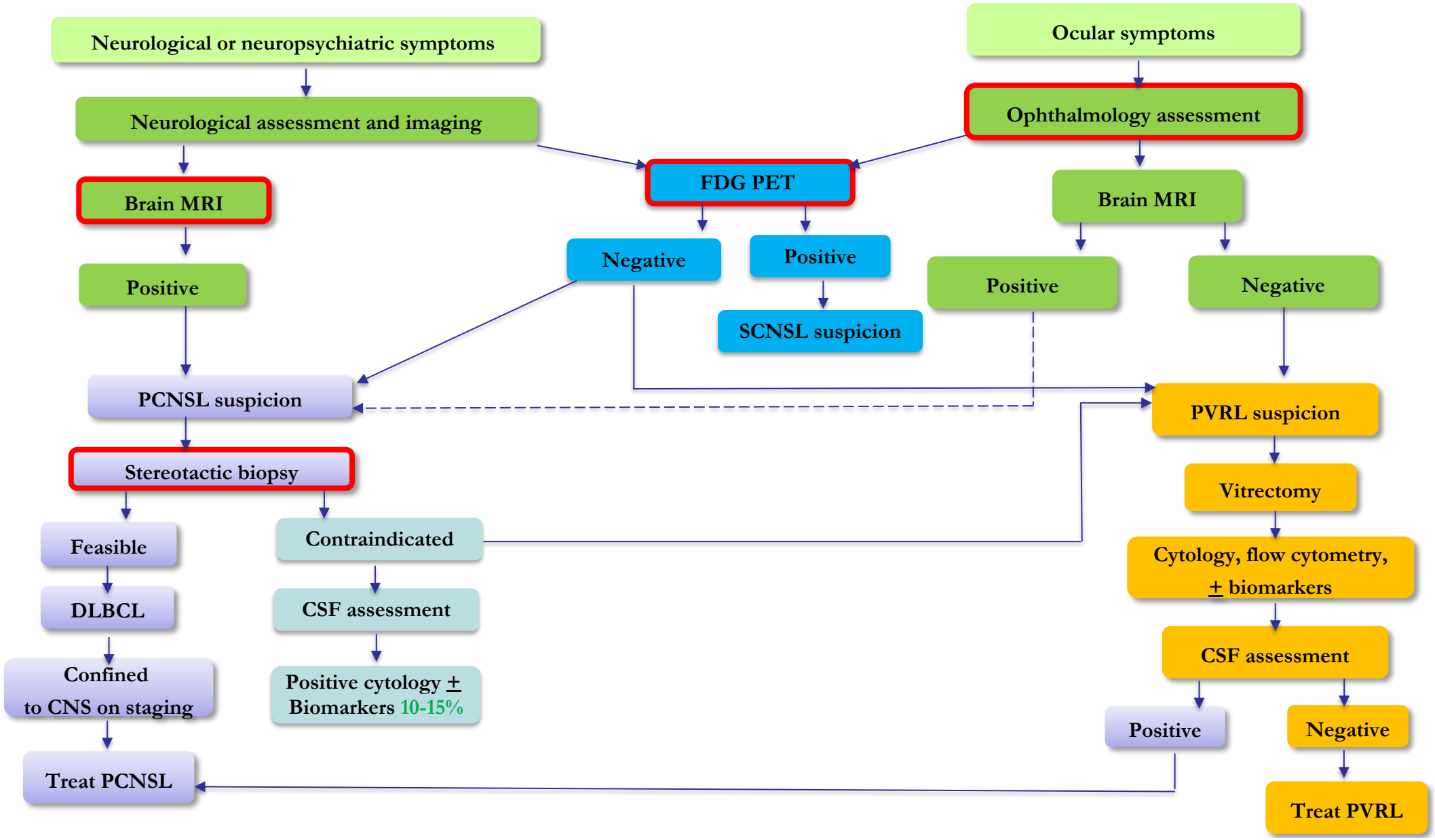
Primary CNS Lymphoma (PCNSL)

- **Rare**
  - 2% of all extra-nodal NHL
  - 4-6% of extranodal lymphomas
- **Rising incidence (in >60 years)**
  - 4-5 per million/year in Europe
- **Median age in ‘real world’ 68 years**
- **Treatment options have improved considerably over recent years**

Particular considerations in treating patients with PCNSL

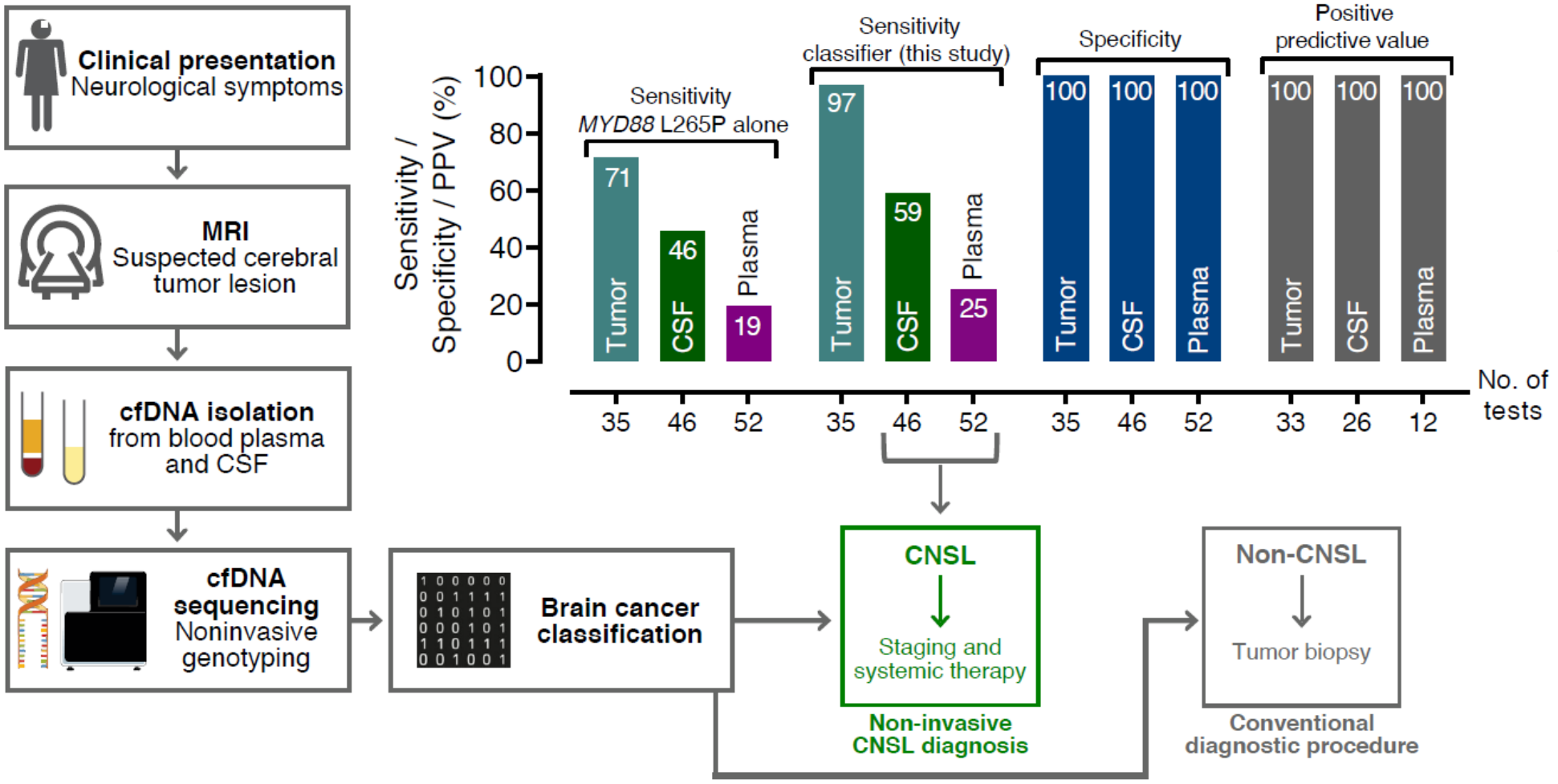
- Unique localisation of this aggressive lymphoma entity
- Challenges with drug delivery to CNS
- Surrounding brain tissue is highly vulnerable
- A ‘whole brain disease’ (>50% have multifocal disease on MRI)

Diagnostic Algorithm EHA/ESMO Guidelines 2024



Ferreri A *et al*, EHA/ESMO 2024. Annals Onc

Stereotactic biopsy is the standard-of-care for PCNSL diagnosis. Is biopsy-free CNSL identification a reality?



Turnaround time:
5-6 days (fastest)

Mutter…Scherer *et al*, JCO 2023

Staging evaluation

Clinical	Laboratory	Extent of disease	CNS
Age Performance status Physical Neurological, cognitive function, MMSE, QoL Steroid dose Drug history	FBC Renal/liver/LDH HIV, HBV, HCV, SPEP Echo/ECG	PETCT Ophthalmoscopy/ slit lap (15%) Fundoscopy Testicular US (BMAT)	MRI brain + gad (spine*) CSF (15%): cytology, flow cytometry, Ig gene rearrangement, MYD88, IL-10

* Spinal MRI only in symptomatic cases or if CSF+

Recent data: questions?

- **Is a brain biopsy 'required'?**
  - Promising data for the future
    Genomic & transcriptional landscape of PCNSL, Radke J *et al*, Nature Comms 2022
    Mutter J *et al*, JCO 2023

USUALLY

- **Is bone marrow biopsy 'helpful' for staging?**
  - In only 2 out of 352 (0.6%): impact on diagnosis and treatment
    Margold M *et al*, Neuro Oncol 2021

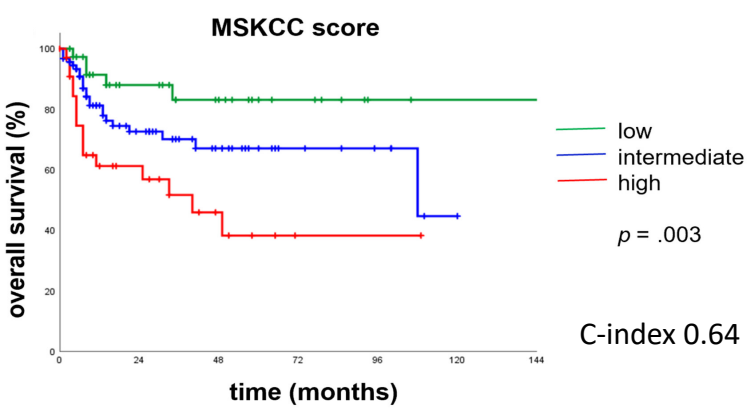
RARELY

- **Does HIV serostatus alter treatment?**
  - 'A distinct immunobiological entity'
    Gandhi MK *et al*, Blood 2021
  - Treatment: 'ART, rituximab and HD-MTX'
    Lurain K et al, Blood 2020

ALWAYS

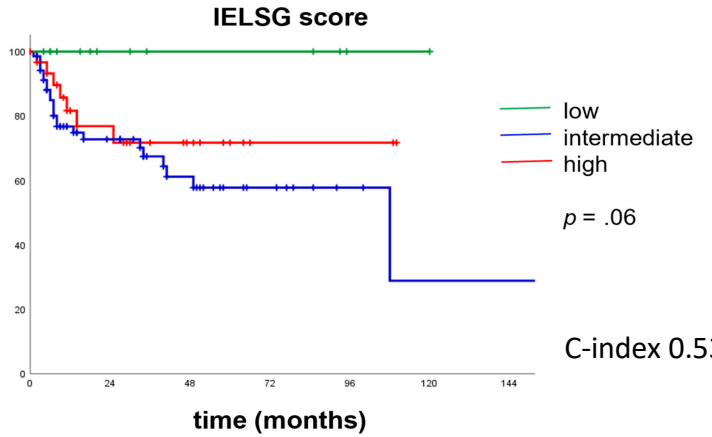
What factors are prognostic?

n=174



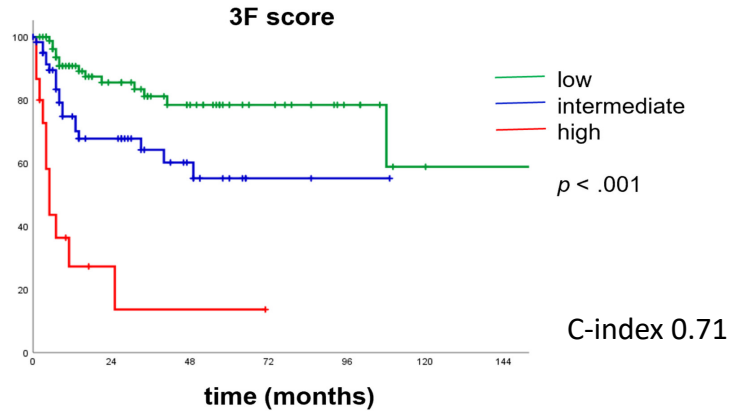
C-index 0.64

Age >50
KPS <70



C-index 0.53

Age >60
ECOG > 1
LDH & CSF protein
Deep brain lesions



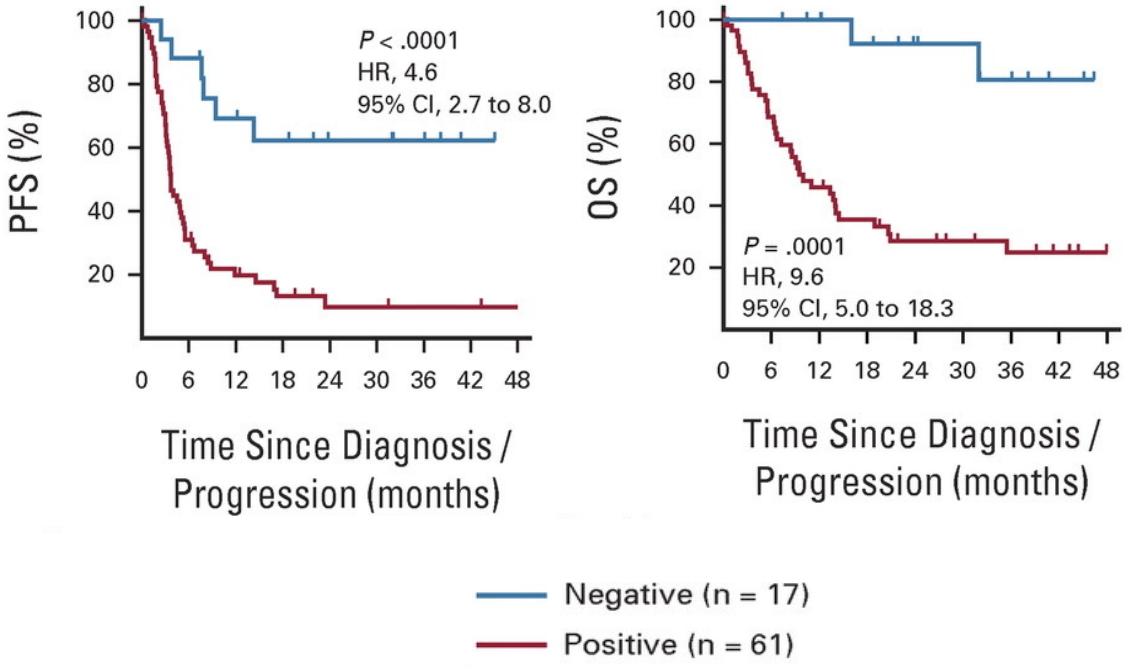
C-index 0.71

Age >50
ECOG ≥ 2
Lymphopenia

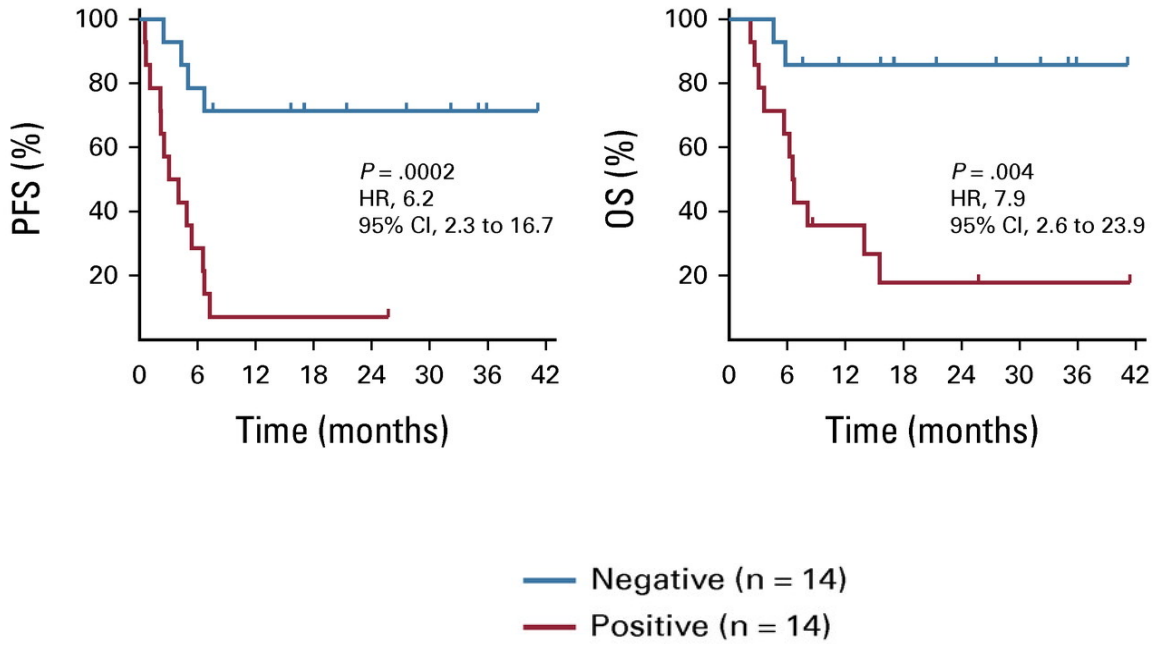
Zeremski V *et al*, European J of Haematology 2024

Plasma circulating tumour DNA (ctDNA)

Pretreatment ctDNA



ctDNA during induction



Mutter J *et al*, JCO 2023

Prognosis: Imaging, biology

- **Improved early outcome prediction by MRI-based 3D tumor volume assessment in patients with CNS lymphomas (n=93)**
  - Lauer E *et al*, Neuro Oncol 2024
  - Hatzoglou V *et a*l, J Neurooncol 2018

- **Interim FDG-PET improves treatment failure prediction in PCNSL: a LOC network prospective multicentric study**
  - Rozenblum L *et al*, Neuro Oncol 2024

- **Impact of MYC and BCL2 double expression on outcomes in PCNSL: a UK multicenter analysis**
  - Poynton E *et al*, Blood Advances 2024

Therapy for PCNSL

Induction

Well tolerated

Effective

Avoid progression during treatment

But what outcome?

CR vs PR (or SD)

Consolidation

Aim to reduce relapse

High Dose Therapy + Autologous-SCT

Whole Brain Radiotherapy

Conventional Chemotherapy

Aiming for cure?

Minimise neurocognitive toxicity

Therapy for PCNSL

Induction

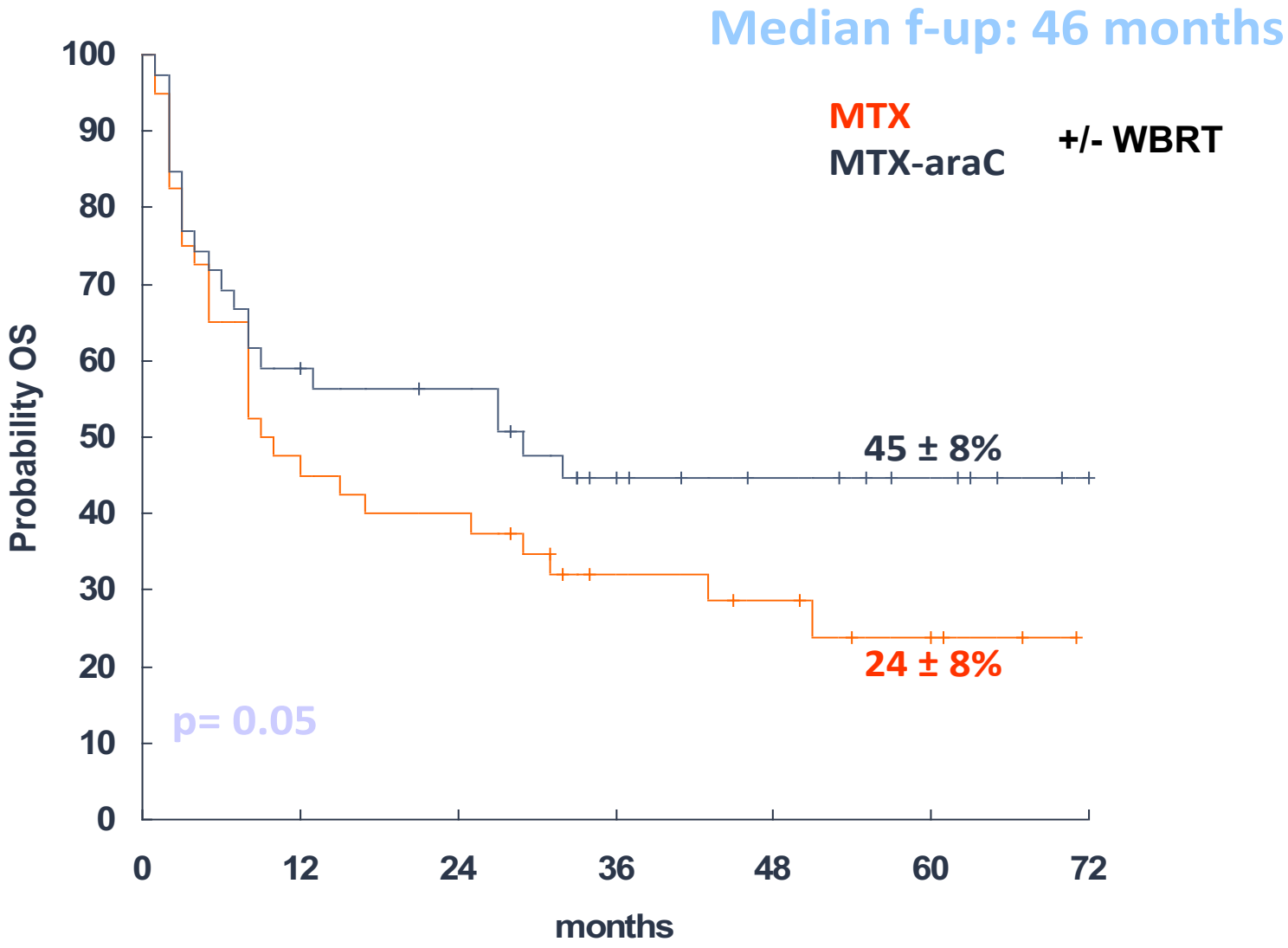
- High dose methotrexate
  ≥3g/m2 over 2-4hrs
- Cytarabine
  ≥2g/m2
- Ifosfamide
- Temozolamide
- Etoposide/Vincristine/Procarbazine
- Thiotepa
- Rituximab

CR (PR)

Consolidation

- High Dose Therapy + Autologous-SCT
- Whole Brain Radiotherapy
- Conventional Chemotherapy

Two drugs are better than one.....IELSG20

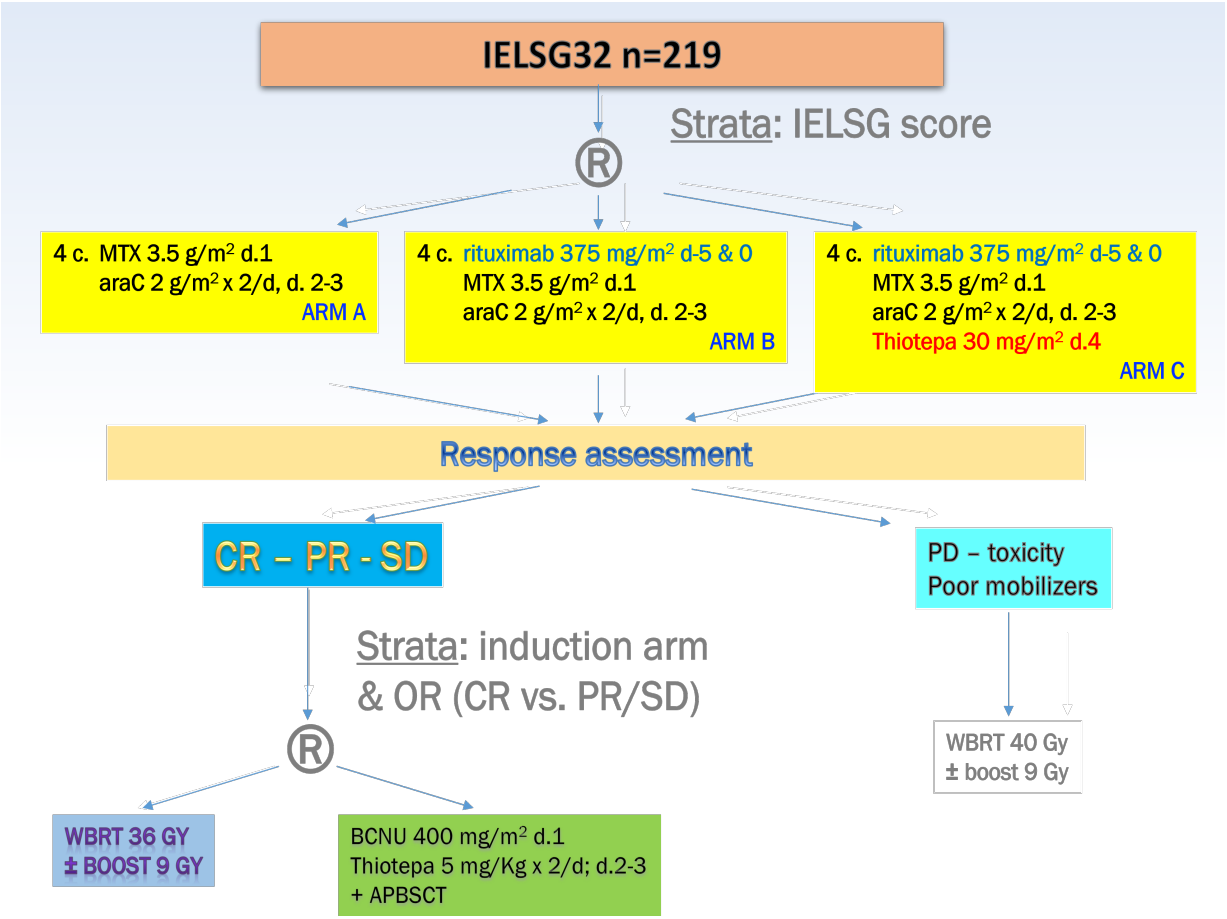


Ferreri et al, Lancet 2009 UPDATED FU

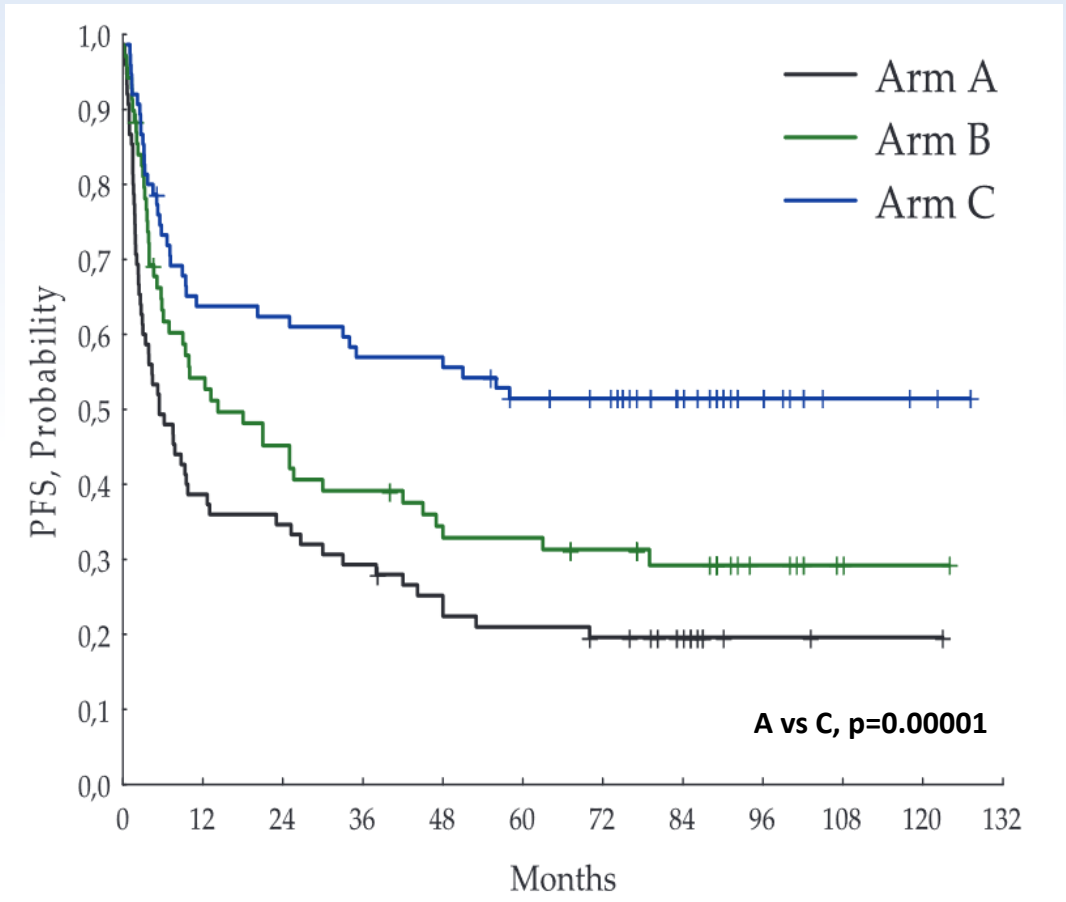
IELSG32: Addition of (cytarabine) thiotepa and rituximab (MATRix) induction is associated with improved outcome

Eligibility:

< 65 yrs & PS ≤3 OR < 70 yrs & PS ≤2

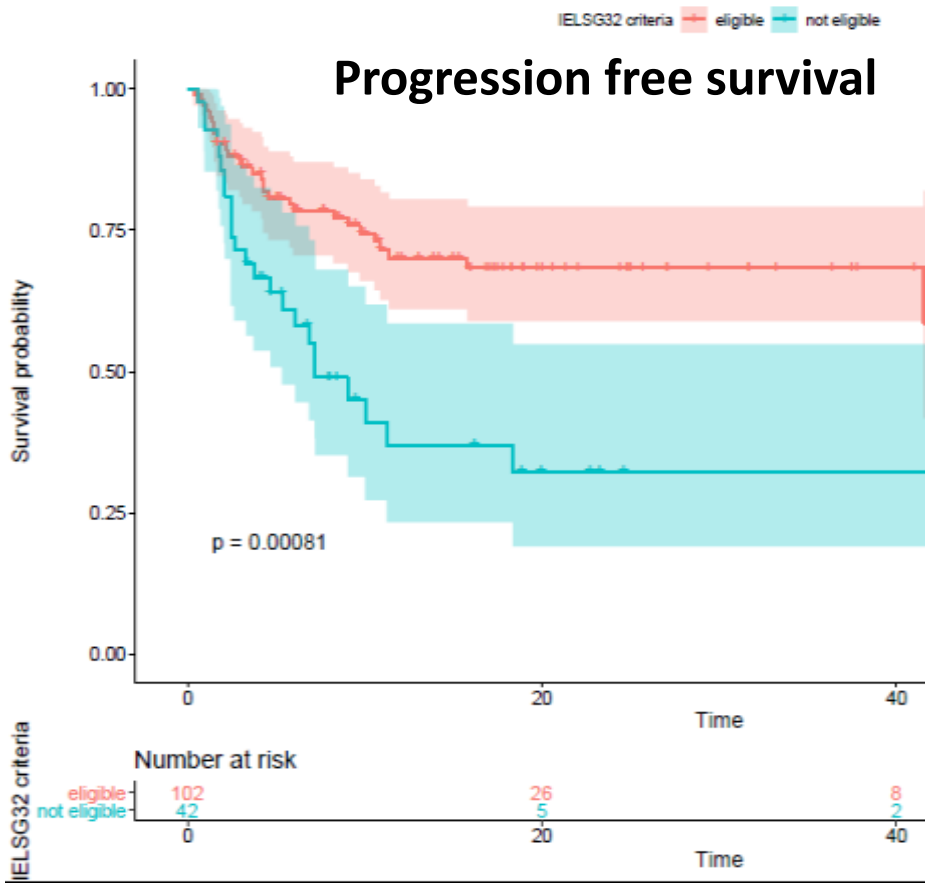


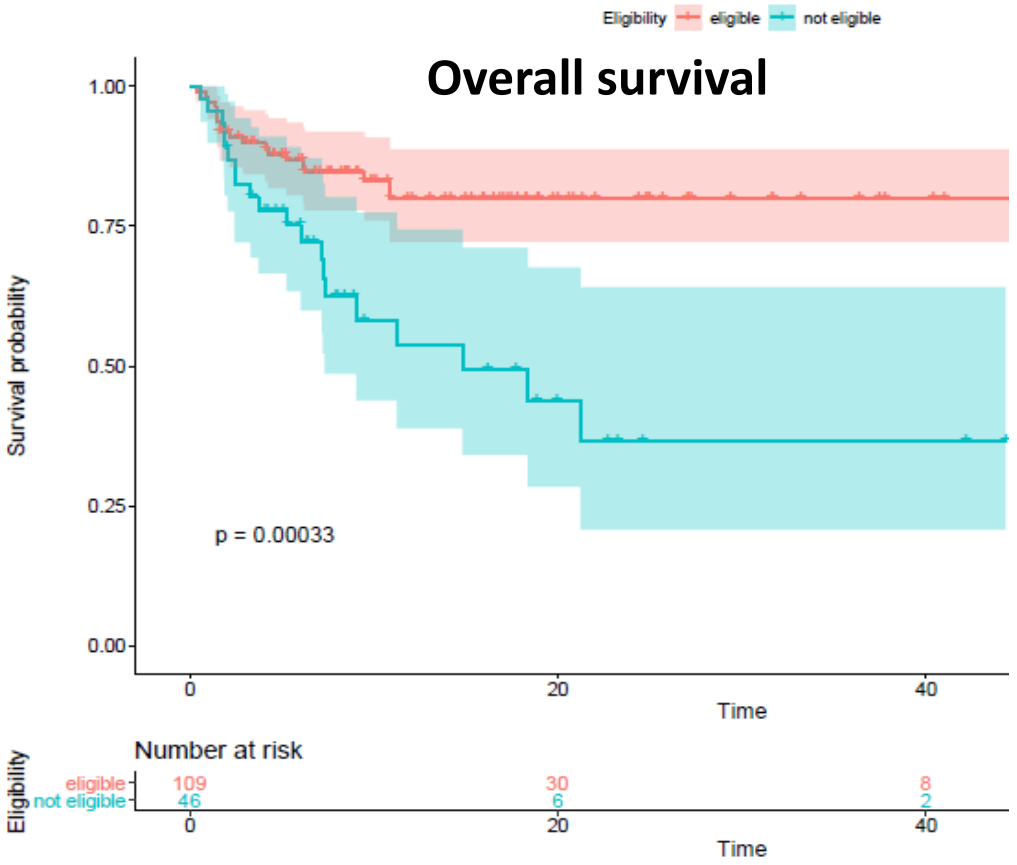
Median follow up: 88 months (IQR 77-99)



Ferreri A *et al*. The Lancet Haematology 2016, Leukemia 2022

MATRix in routine clinical practice (UK, Germany, Italy)
Inferior outcome if IELSG32 'ineligible' < 65yr PS ≤3; <70 yr PS ≤2





n=156
Median age 62 yr (28-78)

Suleman A *et al*, Haematologica 2023
n=33/37 1st line

Schorb *et al*, BJ Haem 2020

Induction regimens: There are NO randomised studies

	IELSG32 n=75	PRECIS n=132	CALGB51101 n=108
Induction	**MATRix**	**RMPV-A**	**MTRA**
Inclusion: Age / PS	**<70y PS 0-2 <65y PS <3**	**<60y PS 0-4**	**<75 y**
Median age	**57y**	**55y**	**61y**
PS > 1	**32%**	**39%**	Included KS PS ≥ 30 (≥ 50 if 60-75yrs)
ORR	**87%**	**70%**	
CR / PR / SD	**49% / 37%** /1%	**43% / 25%** / 2%	
% Proceeding with consolidation	**75% BCNU-TT**	**73% TBC (TT-Bu-CY)**	**66%**
Toxic deaths	**4%** (+3% ASCT)	**11%** (TBC)	

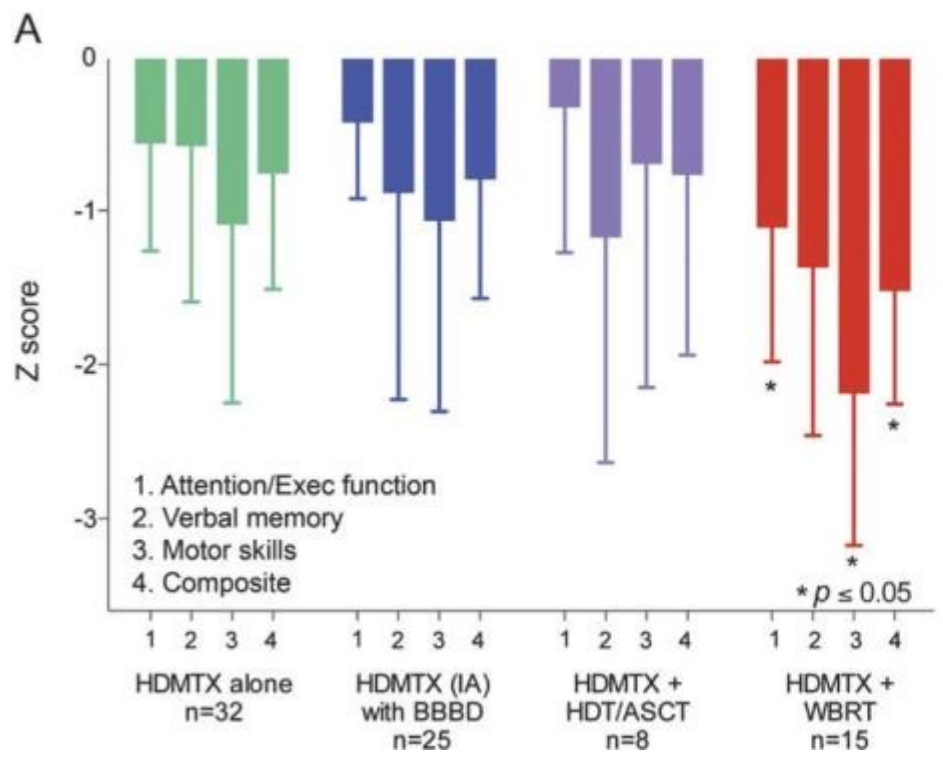
Ferreri A *et al.* Lancet Haem 2016, Leukaemia 2022; Houillier C *et al.* JCO 2016 & 2022, Batchelor T *et al*, Blood Advances 2024

First-line therapy: remission induction

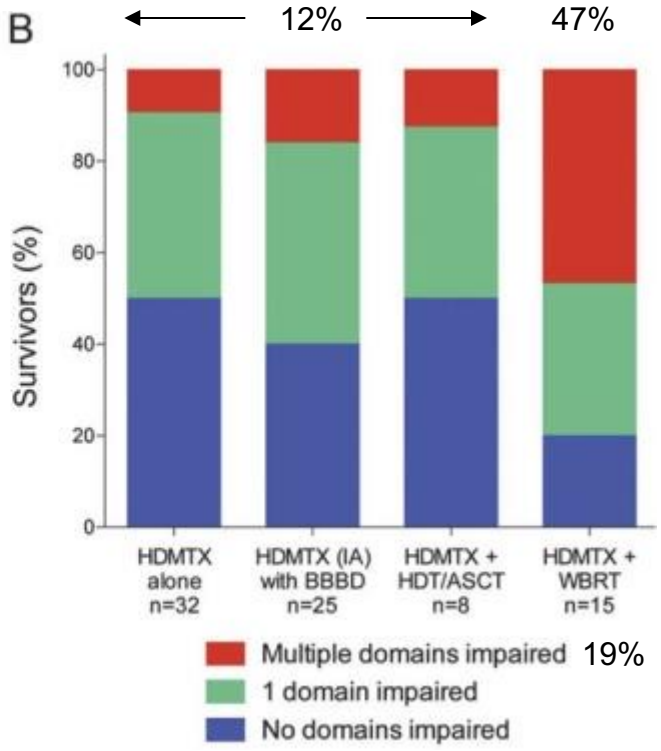
- **MATRix (*or MTX-combination chemoimmunotherapy*)**
  - If <65 yr PS 0-3 or <70 yr PS 0-2
- **Make appropriate dose reductions of Ara-C**
  - For 1st cycle (i.e omit 1-2 doses Ara-C if poor PS)
  - For subsequent cycles if symptomatic cytopenias ↓ dose 25% i.e omit 4th dose
- **Other induction regimens exist but no randomised studies**
  - **Utilise a R-MTX-chemo combination regimen you are familiar with**
- **Addition of novel agents?**
  - **Ongoing clinical trials: LYSA & US centres**

Ferreri A *et al*, Nature Rev Dis Primer 2023

Significantly increased neuropsychological impairment after HD-MTX & WBRT



Neuropsychological outcomes according to treatment group



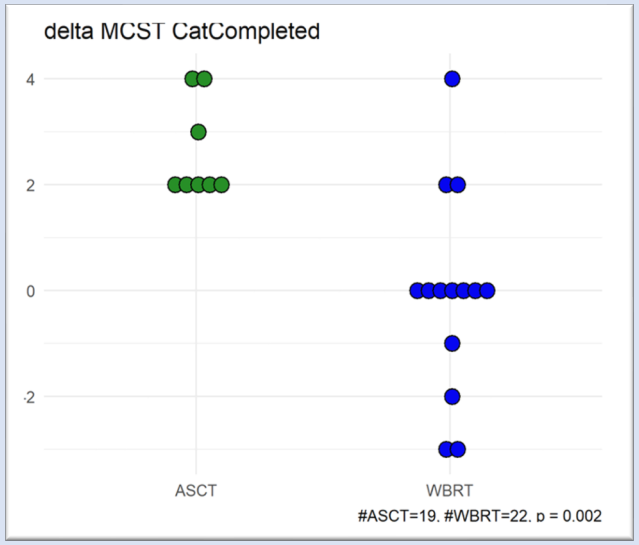
% survivors with neuropsych impairment

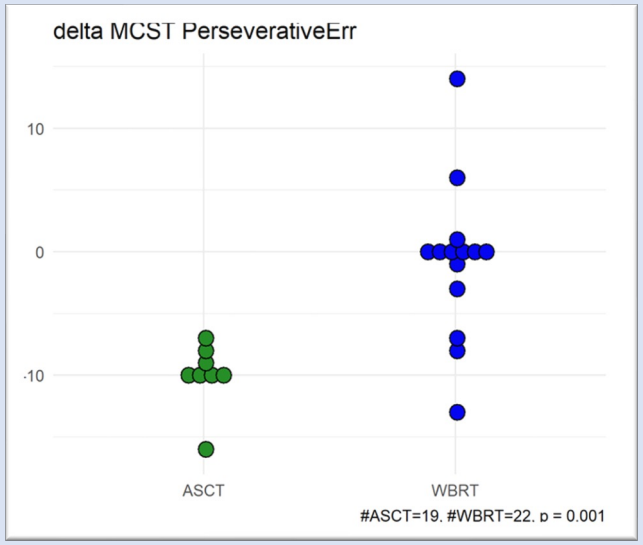
Doolittle *et al*. Neurology 2013

AMERICAN ACADEMY OF NEUROLOGY®

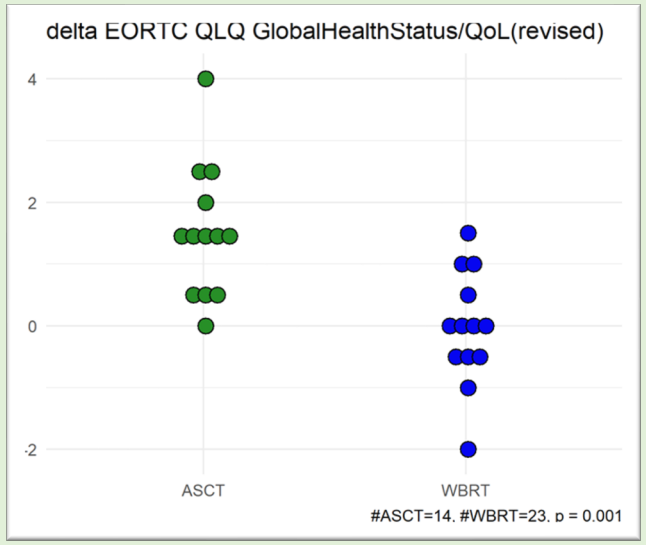
Consolidation:
Neurocognitive impairment post-WBRT

Attentive executive





Quality of Life

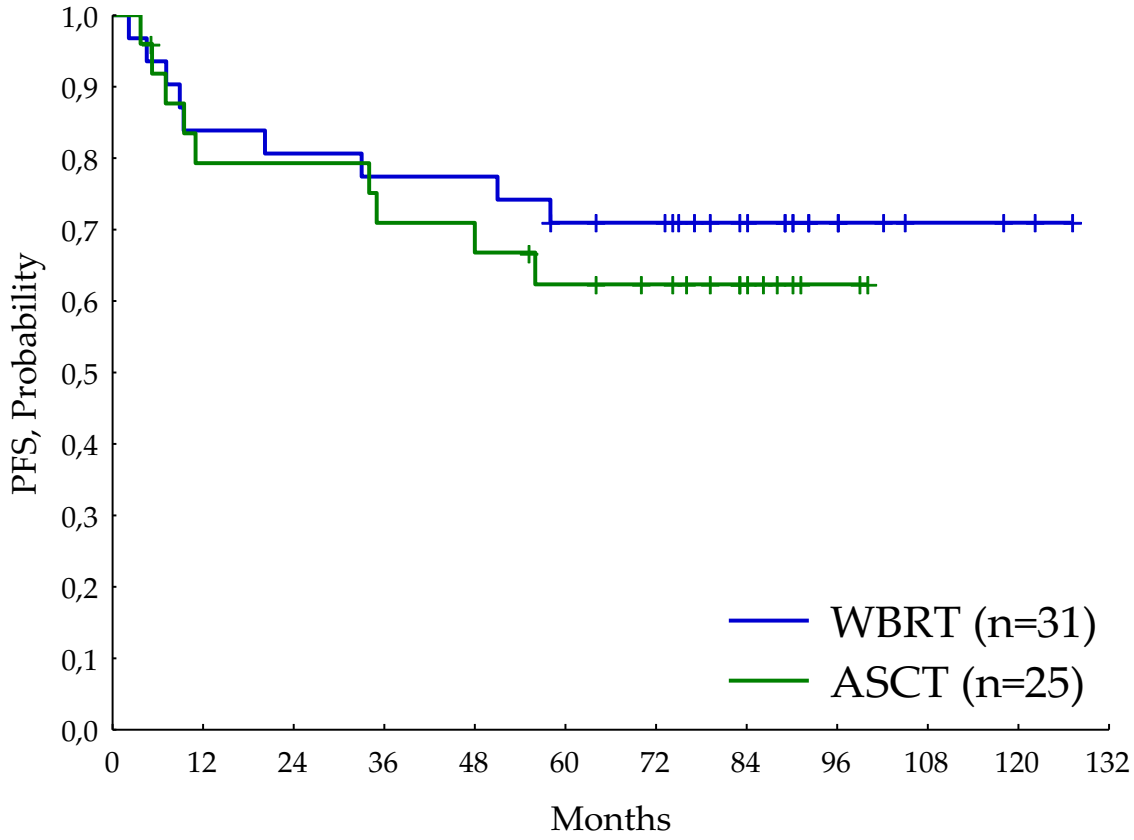


ASCT WBRT

Ferreri A *et al*. Leukemia 2022

PRECIS: Houillier C *et al.* JCO 2022

IELSG32: MATRix & Consolidation



Avoid WBRT
(at conventional doses)
in CR1

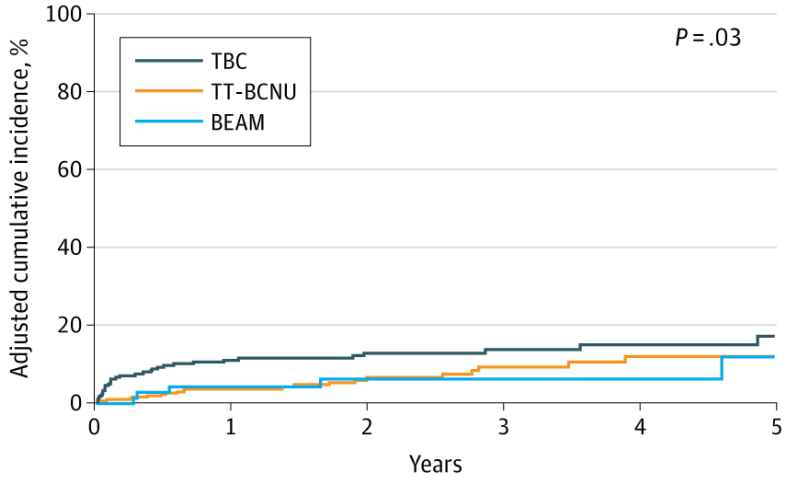
And 23.6Gy?

Ferreri A *et al*. Leukemia 2022

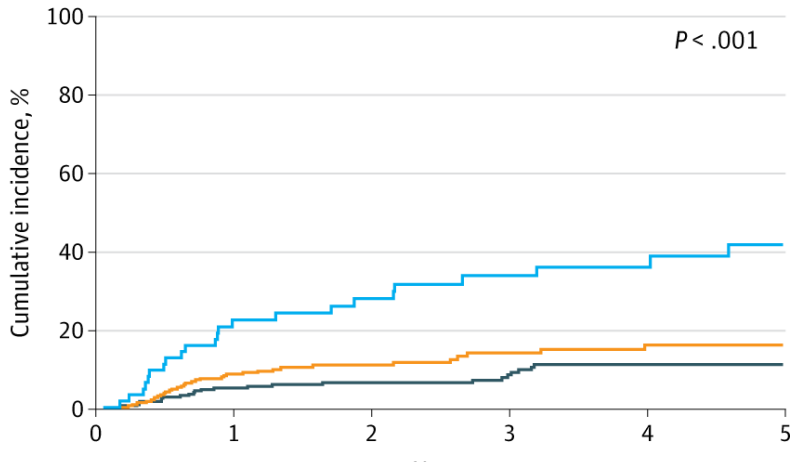
Correa DD *et al*, J Neurooncol 2019; Lesueur P *et al*. Blood Advances 202

Thiotepa-Based vs BEAM Conditioning

Non-Relapse Mortality



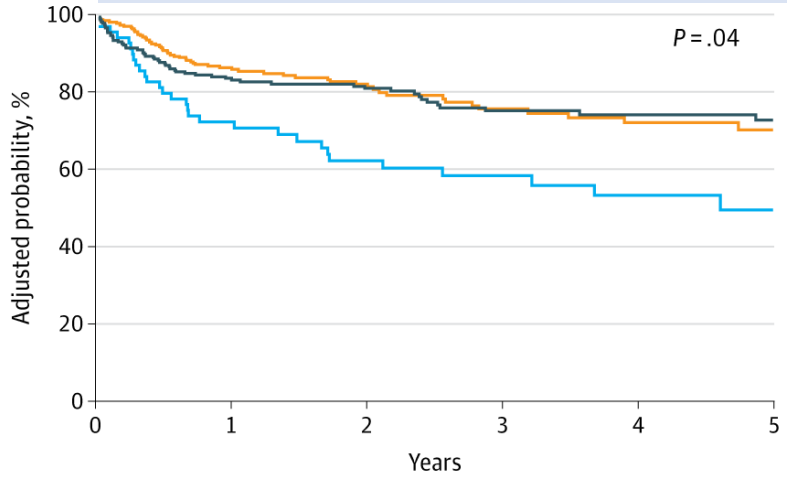
Relapse



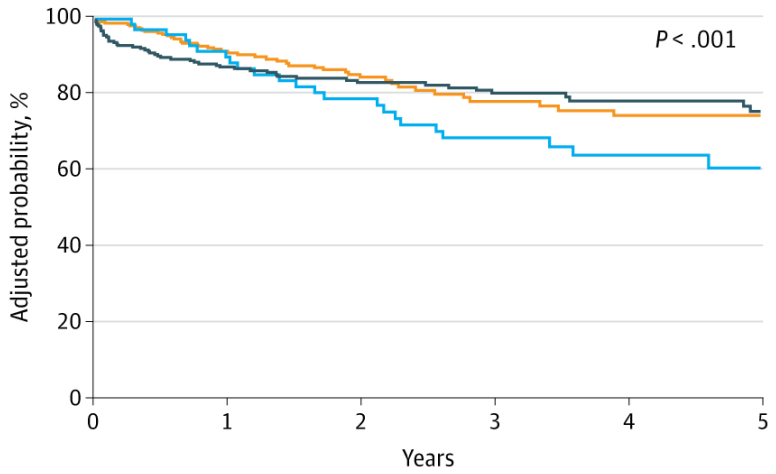
TBC
TT-BCNU
BEAM

TBC n = 263
TT-BCNU n = 275
BEAM n = 65

Progression Free Survival



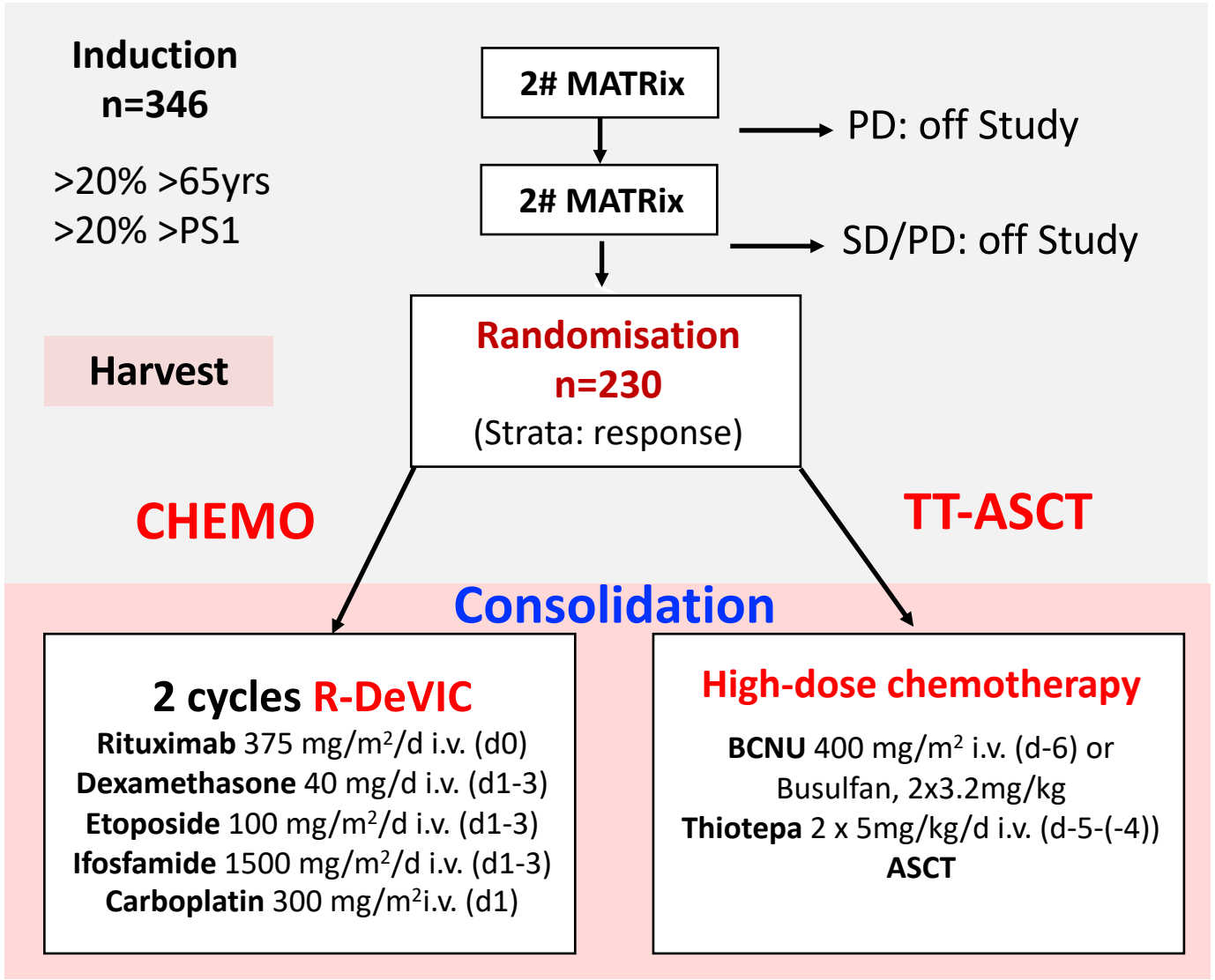
Overall Survival



TT dose-intensity (10mg vs 20mg/kg) does not impact outcomes Arshad S *et al*, BMT 2023

Scordo M *et al,* JAMA Oncol. 2021
Salim Akhtar O *et al*, EBMT 2024

Optimal Consolidation? MATRix/IELSG43 <70yrs



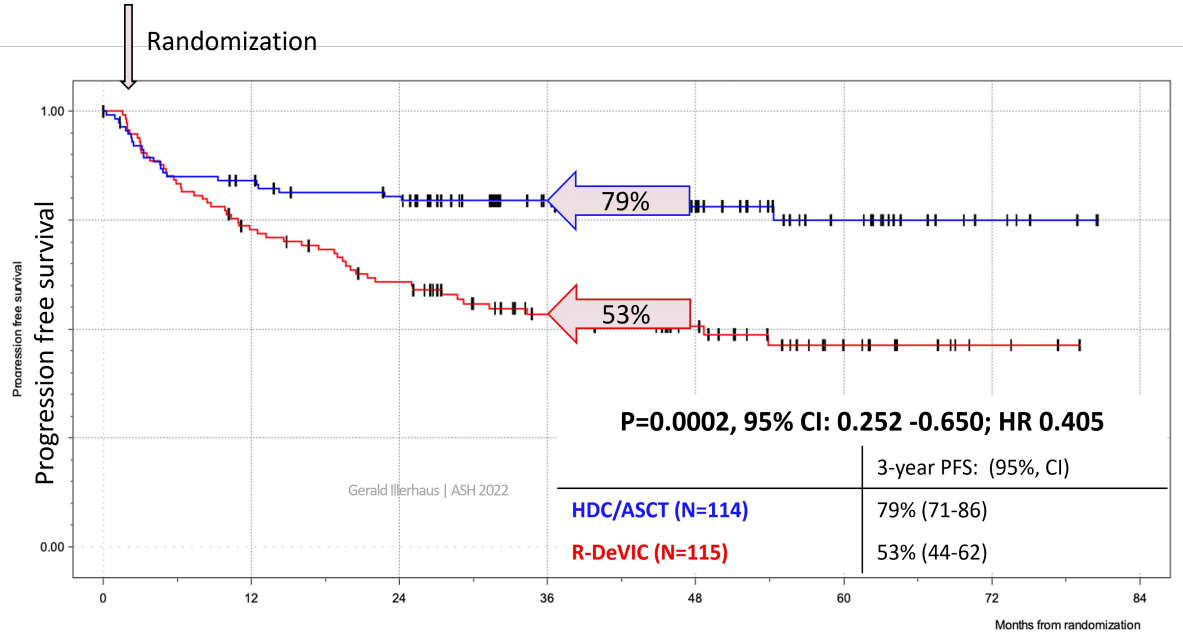
Median follow-up: 45 months (0.2-86)

Illerhaus G *et al* ASH 2022, ICML 2023

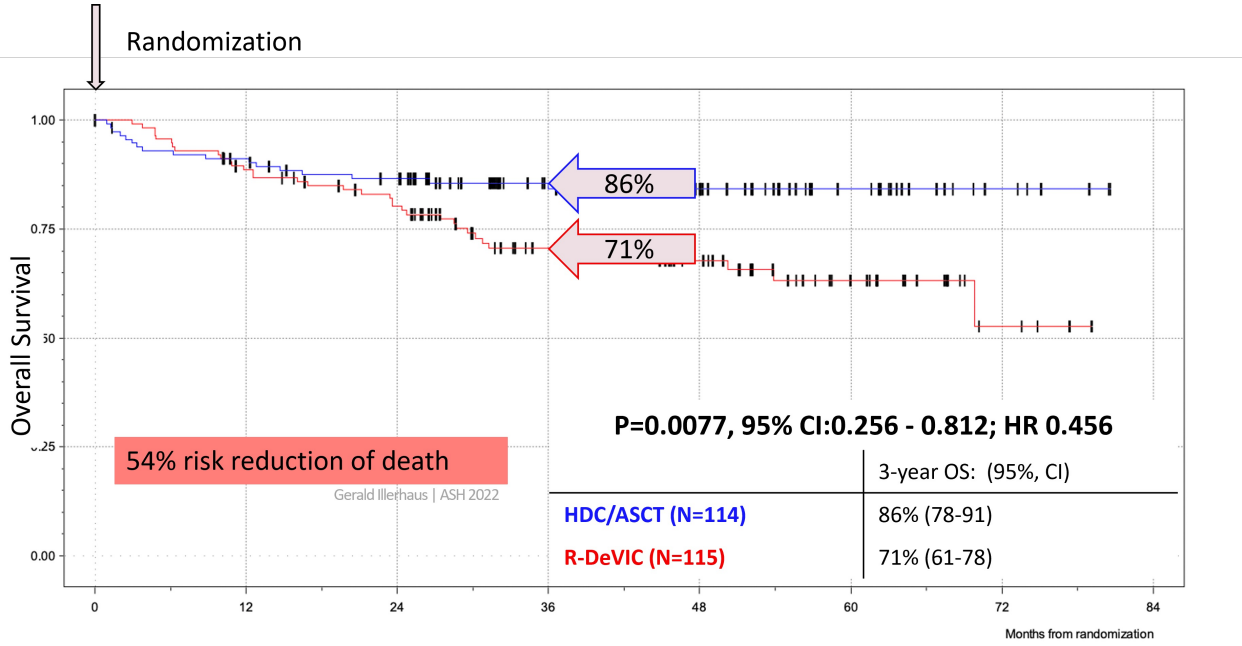
Superior PFS and OS (ITT) after BCNU-TT ASCT

Despite Similar Response Rates

Progression Free Survival



Overall Survival



Alliance 51101 Batchelor T et al, Blood Advances 2024

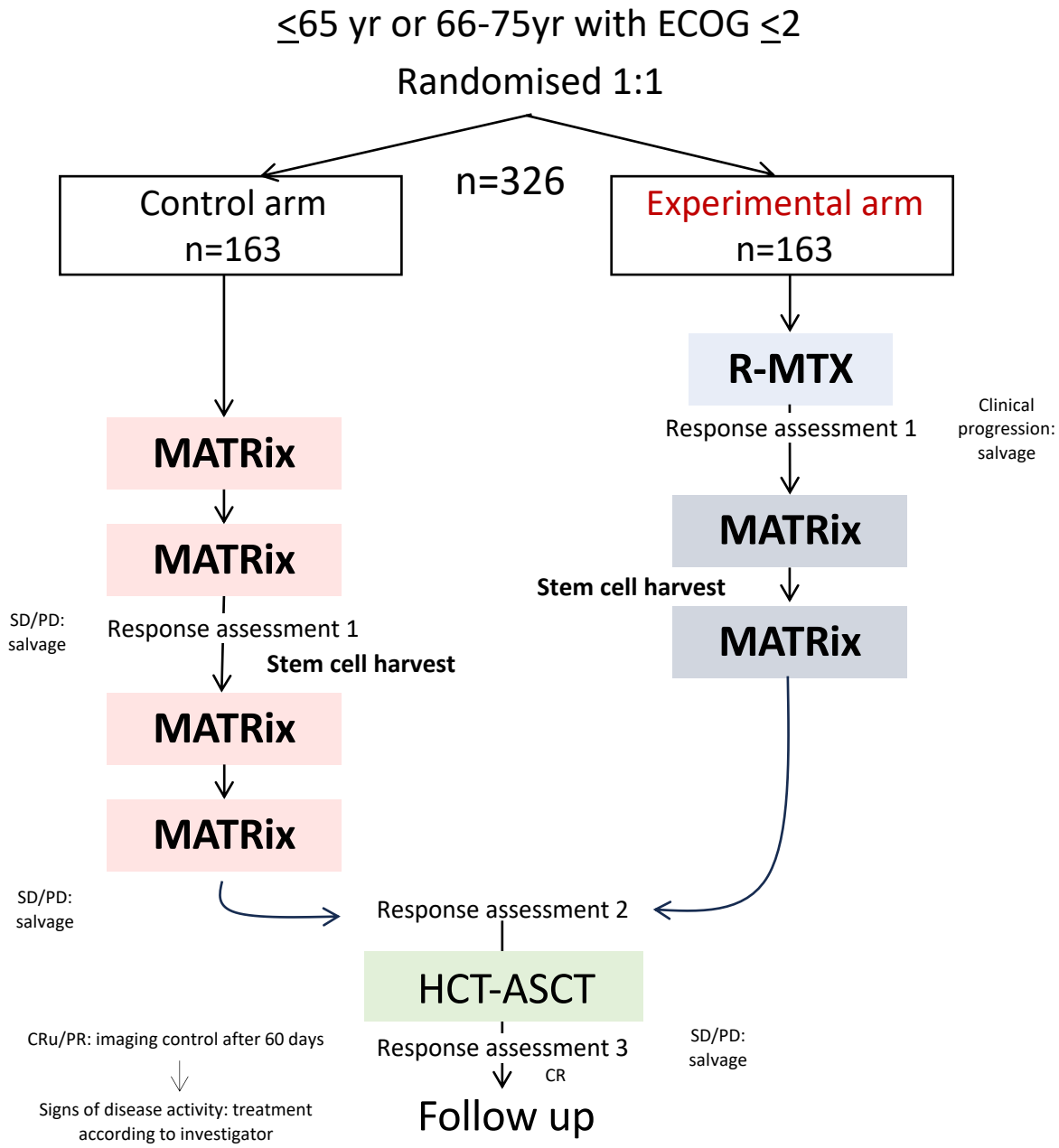
Illerhaus G *et al* ASH 2022, ICML 2023

OptiMATe

Optimizing MATRix as induction in newly diagnosed PCNSL:
Randomized phase III trial
De-escalated induction treatment

Multicentre international trial; Germany, Austria, Italy, UK

***Primary Objective**:* 2yr EFS (superiority)



Germany: G. Illerhaus, J. Wendler, S. Trefz, E. Schorb,
UK: C.P Fox, K. Cwynarski, J. Okosun, S. Thust

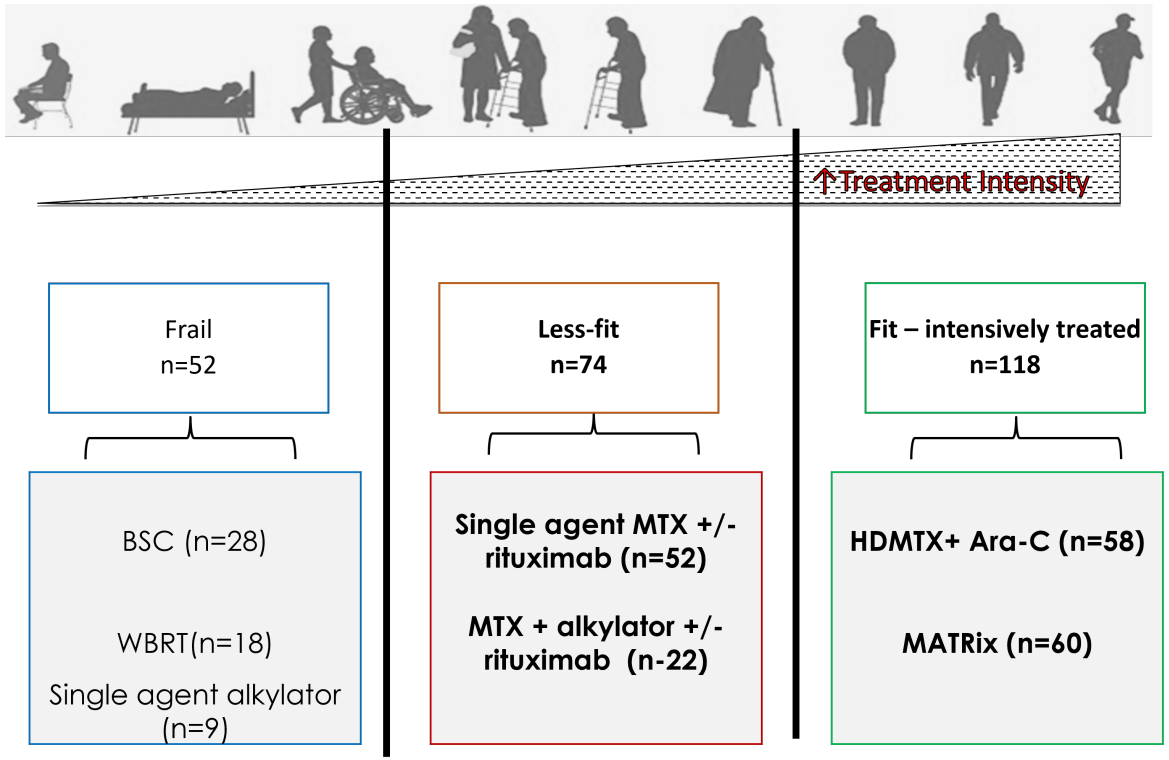
Ongoing questions

- Do we proceed to TT-ASCT in PR and CR? **YES**
  - *How many courses of Induction required?*
  - *In PD?*
- Role for further consolidation if PR pre TT-ASCT? **In a minority**
  - *Focal RT?*
  - *Additional agents: BTKi, CELMoDs?*
- Can we use the word(s) (potential) CURE? **YES**
- Is there an upper limit of age to consider TT-ASCT?

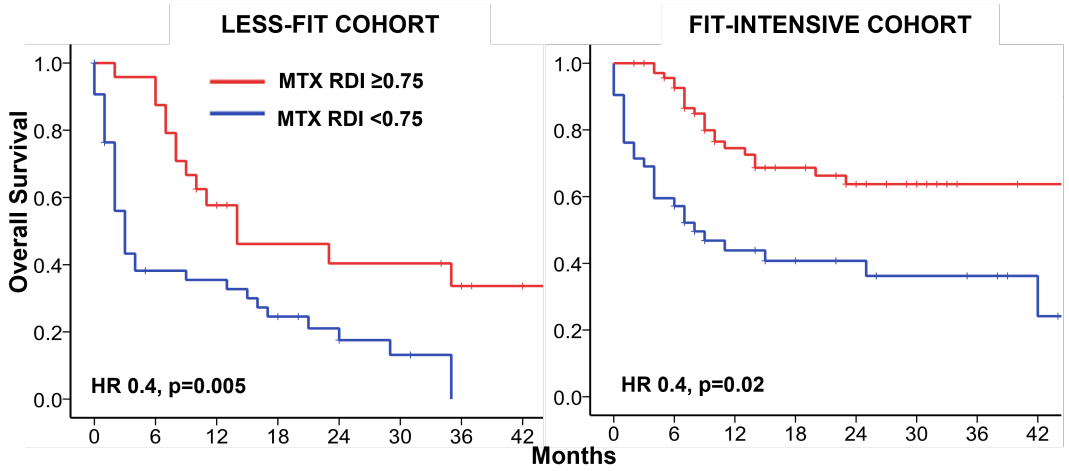
Ferreri A *et al*, Nature Rev Dis Primer 2023

Therapy for PCNSL: age > 65 yr

Multicentre retrospective UK study > 65 yr (n=244)
Newly diagnosed 2012 – 2017



Methotrexate dose intensity is associated with improved survival



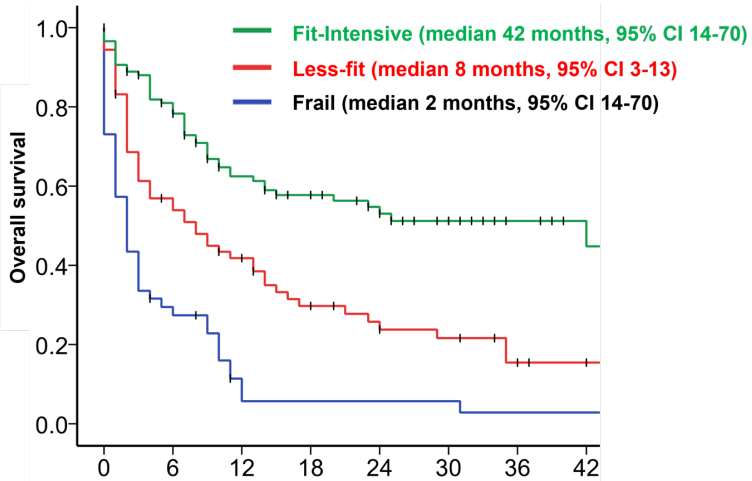
Improved overall survival in intensively treated cohort

HDMTX+ Ara-C (n=58)

MATRix (n=60)

Single agent MTX +/- rituximab (n=52)

MTX + alkylator +/- rituximab (n-22)

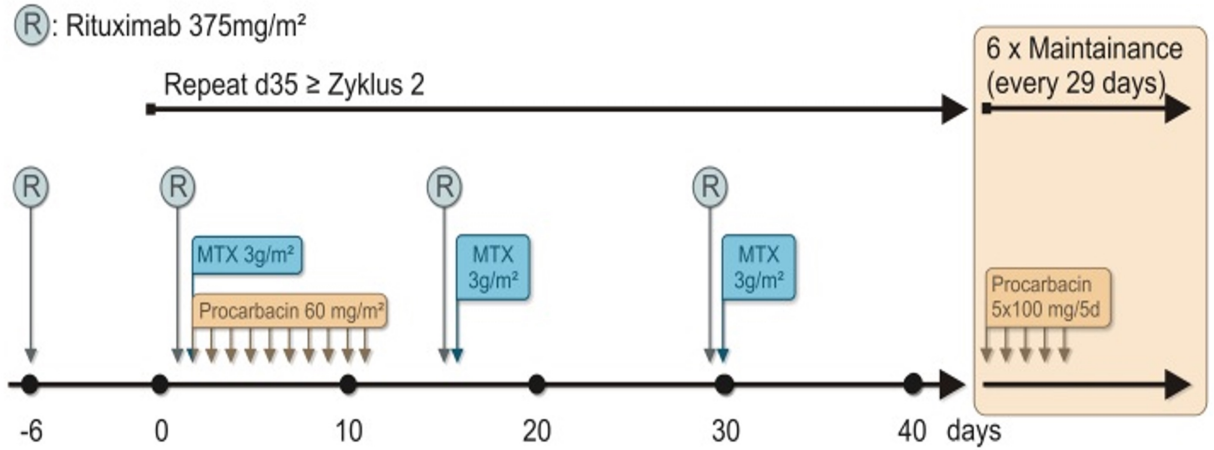


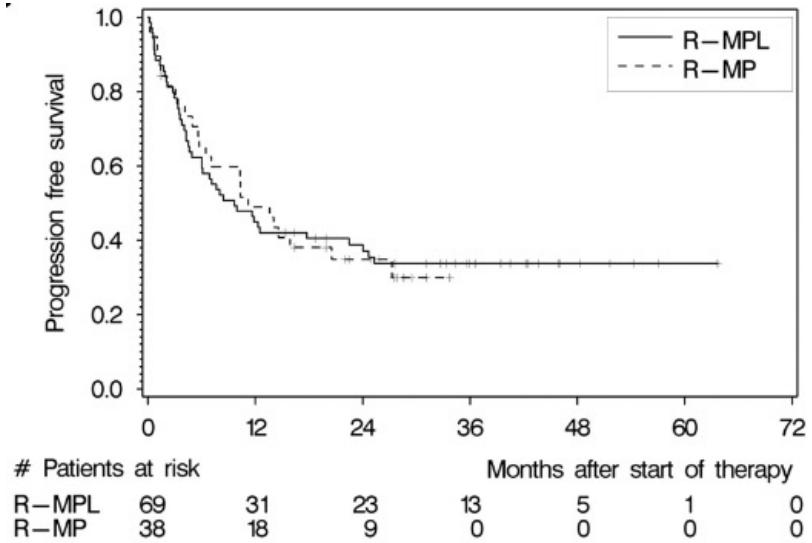
Martinez-Calle *et al*, BJ Haem 2020

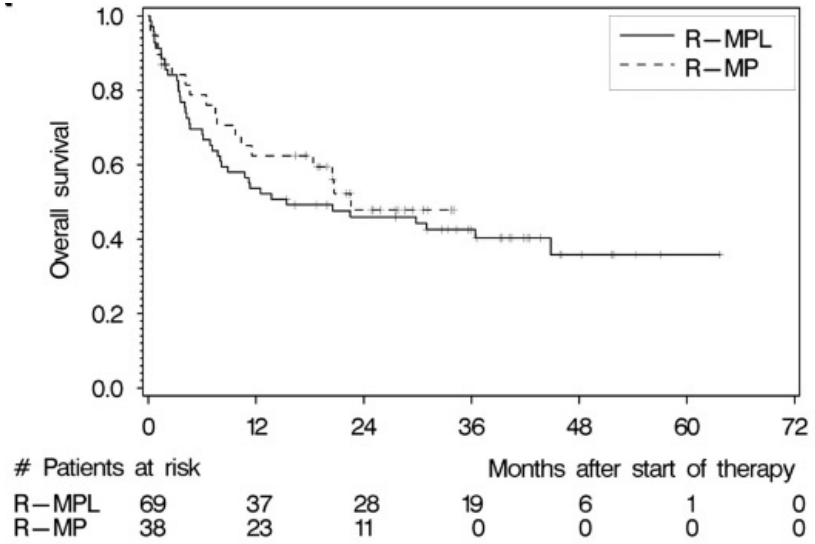
Treatment options for ‘older patients’?

PRIMAIN approach: R-MTX-Procarbazine and Procarbazine maintenance

Median age 75yr (65-83)

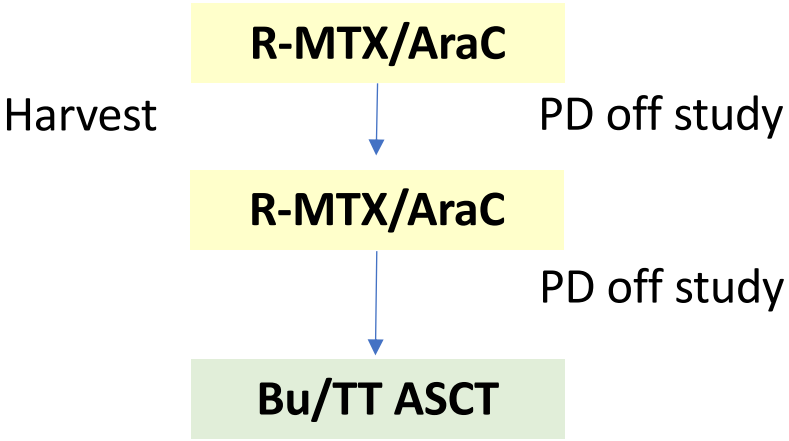






Fritsch *et al*. Leukemia 2017

MARTA: age-adapted HCT-ASCT in 1st line PCNSL > 65 yr



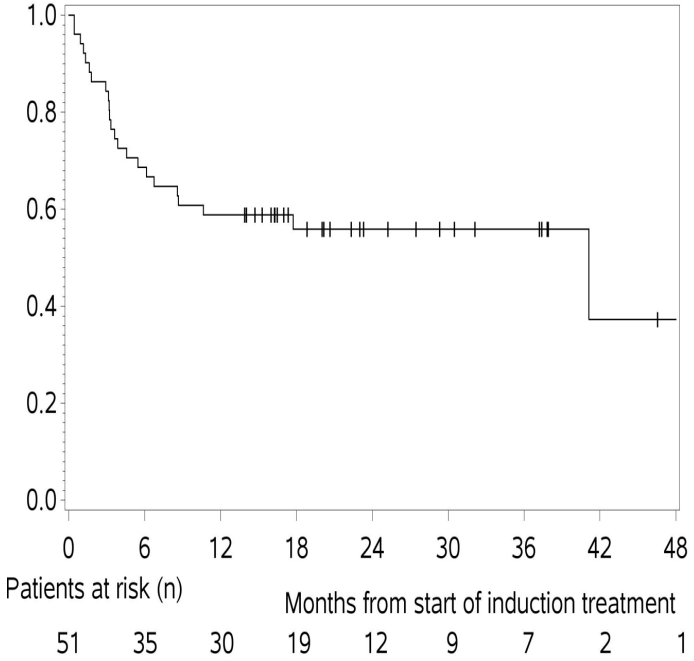
Median age 72yr (65-80)
70-74: 35%
75-80: 35%

36/51 patients: HCT-ASCT (71%)

Treatment related deaths	
Induction 3.7%	Consolidation 2.7%

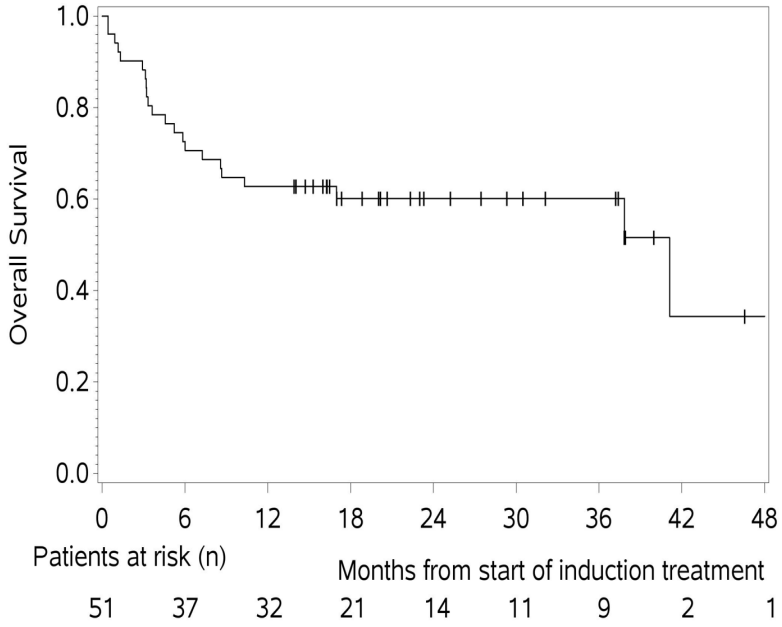
ITT

Progression free survival



1yr PFS 58.8% (95%CI 44-71)
Median PFS 41 months

Overall survival



1yr OS 62.7% (95%CI 48-74)
Median OS 41 months

Schorb E *et al*. Blood Advances 2020 & Lancet Haematology 2024

Thiotepa/BCNU-ASCT for CNSL at UCLH

Jan 2018 – Dec 2022

n=70

PCNSL n=42 (60%)

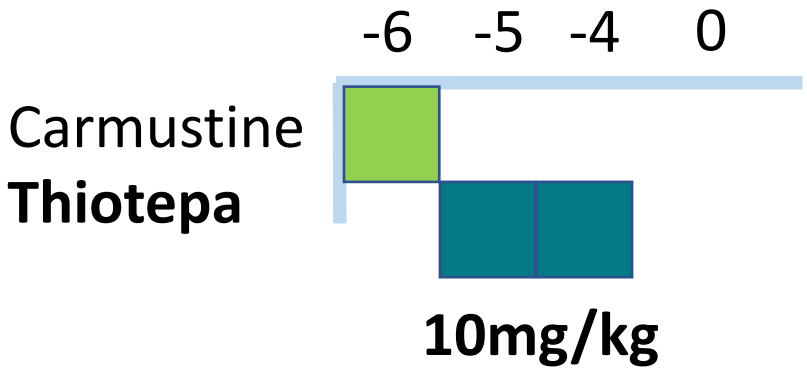
SCNSL n=28 (40%)

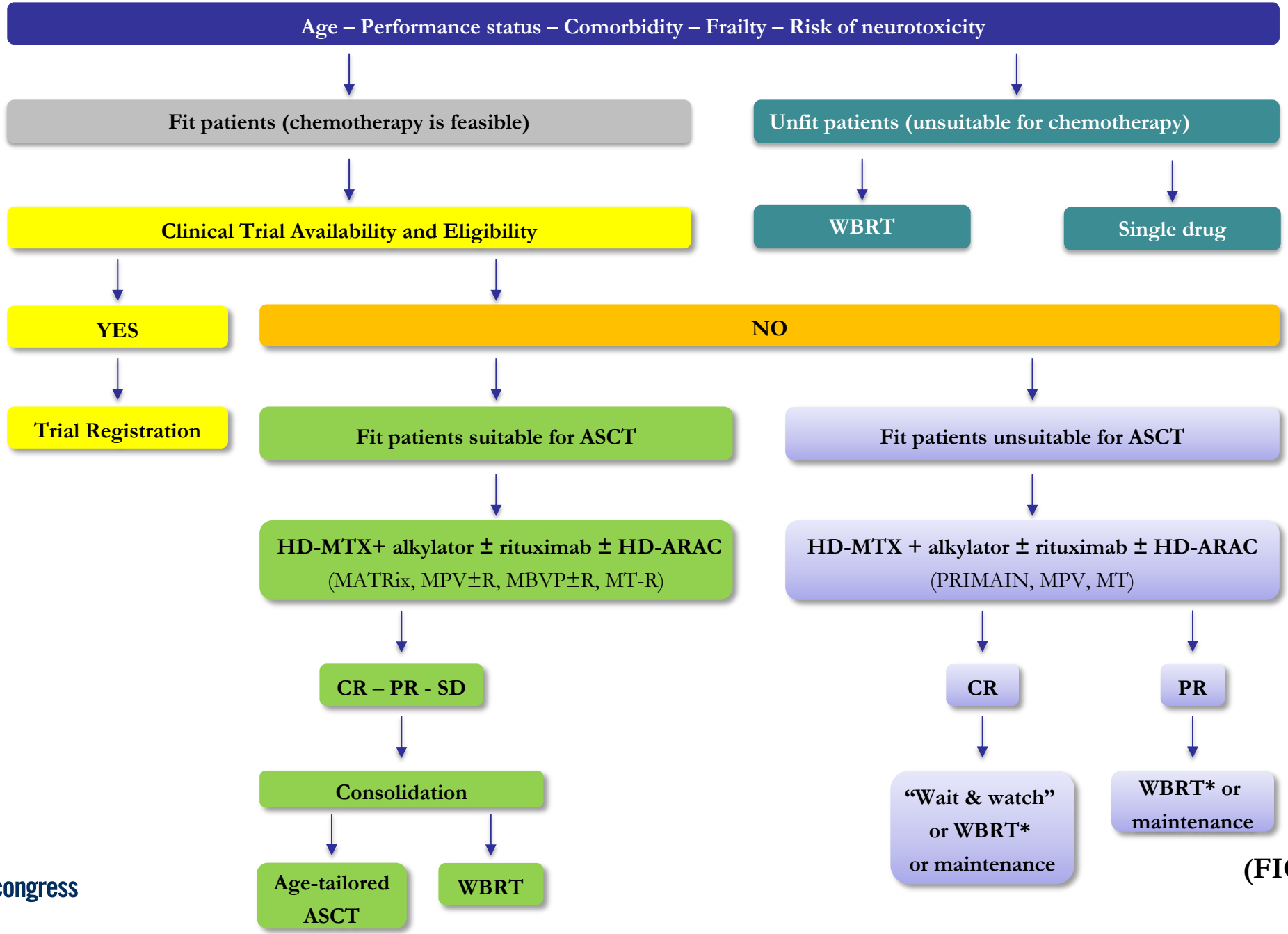
>65 years

n=20 (65-78 years)

1-year NRM

5%





PARIS 2022 ESMO congress

Ferreri A *et al*, EHA/ESMO 2024; Pulczynski E, *et al.* Haematologica 2015; Fritsch K *et al*, Leukemia 2017; Mishima K, *et al.* Neuro-Oncology 2022

What is the optimal treatment of PCNSL in HIV+ patients?

Risk group?

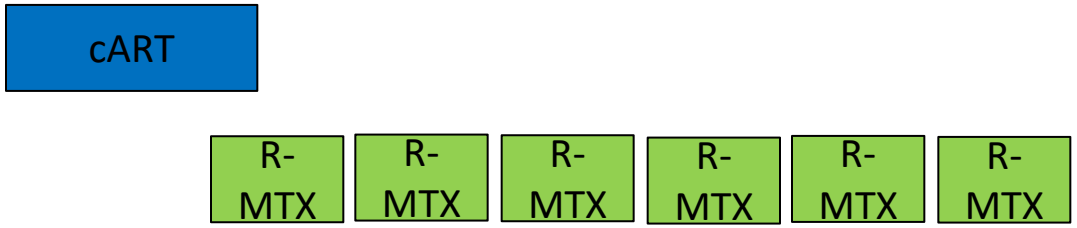
CD4 < 50 x 10^6/l

Is a biopsy necessary?

EBV PCR in CSF? YES – can be helpful

SPECT scan? May help but not diagnostic

Avoid awaiting Toxo treatment ‘failure’



Gupta et al, Neuro-Oncology 2016

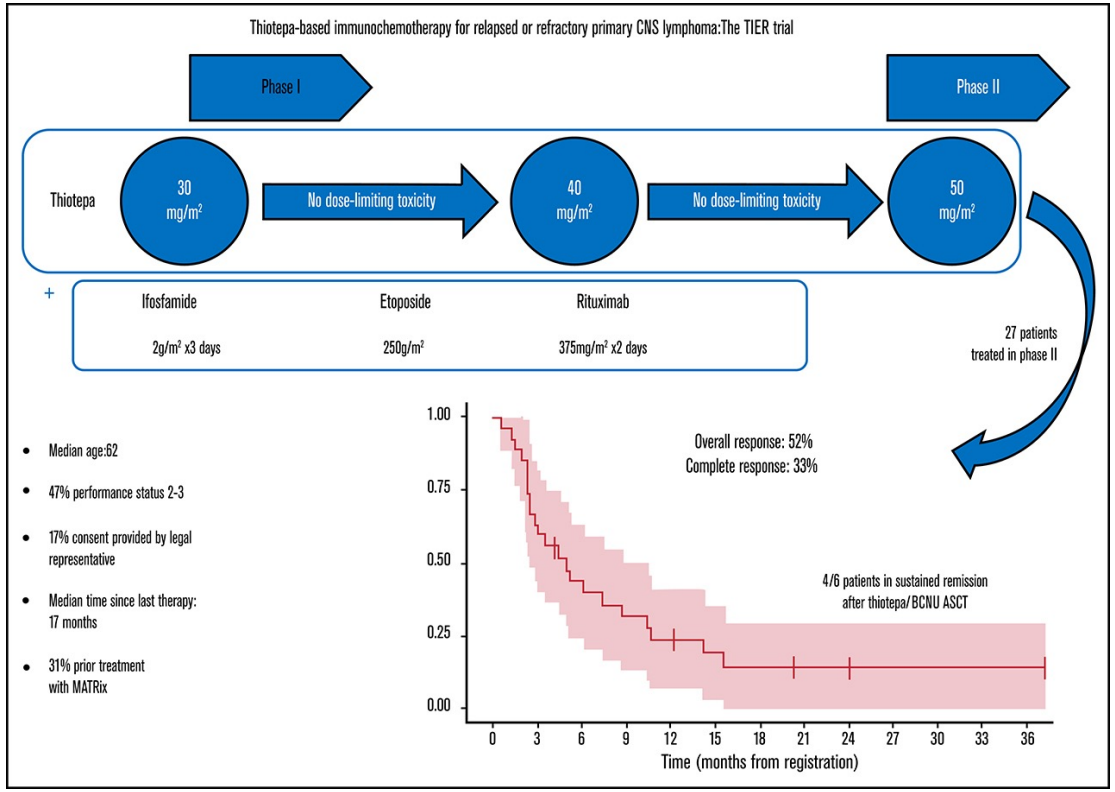
Moulignier et al, Neurology 2017

REGULAR ARTICLE

blood advances

A phase 1/2 study of thiotepa-based immunochemotherapy in relapsed/refractory primary CNS lymphoma: the TIER trial

Christopher P. Fox,[1,2] Ayesha S. Ali,[3] Graham McIlroy,[3] Steffi Thust,[4] Nicolás Martinez-Calle,[1] Aimee E. Jackson,[3] Louise M. Hopkins,[3] Catherine M. Thomas,[3] Shireen Kassam,[5] Josh Wright,[6] Sridhar Chaganti,[7] Jeffery Smith,[8] Ian Chau,[9] Dominic Culligan,[10] Kim M. Linton,[11] Graham P. Collins,[12] Andrés J. M. Ferreri,[13] David Lewis,[14] Andrew J. Davies,[15] Rod Johnson,[16] Dorothee P. Auer,[2,17] and Kate Cwynarski[18]



- Met primary endpoint with ORR 52%
- But very short PFS and poor outcomes
- Minority of patients who proceeded to HDT-ASCT had long-term survival

Relapsed/refractory PCNSL: agents in development

BTK inhibitors	CELMoDs	BTK degraders	Checkpoint inhibition
MYD88 and *CD79* mutations common Ibrutinib crosses BBB High responses to Ibrutinib in 3 different studies: short PFS PRiZM (Zanabrutinib): UK Explore combination regimens	Activity in early phase studies Parenchymal & CSF responses T cell compartment (CD4: CD8 ratio) may be important Role in the maintenance setting under evaluation in older patients	First-in-human Ph I trial of NX-2127 BTK degradation at similar rate/degree regardless of mutational status, mutation type & level of enzymatic activity (n=23) Trials ongoing in PCNSL & SCNSL	PD1 disruption common in PCNSL (copy number gain or rearrangement) Preliminary evidence of clinical activity with Nivolumab Global phase 2 trial results disappointing

Houllier *et al*, 2015; Chamoun *et al*, 2017; Nayak *et al*, 2017; Ghesquieres *et al*, 2019; Rubenstein *et al*, 2019, Soussain C *et al*. EJC 2023; Grommes C *et al*. Cancer Disc 2017; Lionakis *et al*. Cancer Cell 2017; Grommes C *et al* Blood 2019; Houillier C *et al*. Neurology 2021, Montoya *et al*, Science 2024; Villanueva MT, Nature Reviews Drug Discovery 2024

Relapsed and refractory PCNSL

Chief Investigator: Prof Chris Fox

PRiZM+

PRiZM+: A phase II platform study of zanubrutinib monotherapy and combination therapy for relapsed and refractory primary CNS lymphoma

Science lead:
Prof Jessica Okosun

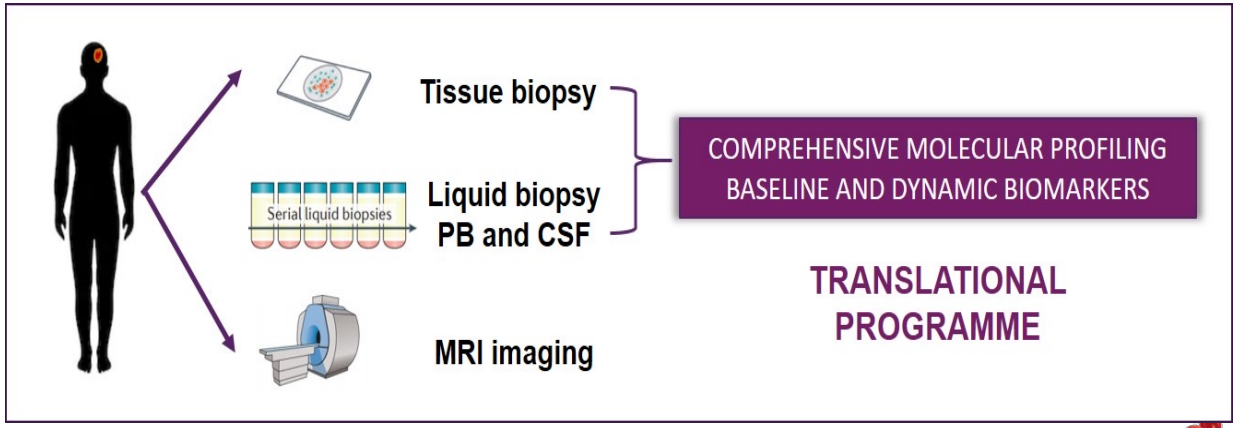
Design:

- Prospective, sequential, single arm, phase II study
- Each stage of trial will recruit 20 patients

- First cohort: Zanubrutinib monotherapy
- Platform design: planned combination therapy cohort 2+

Primary outcome:

- ORR (CR + CRu + PR) after 2# treatment



Funder: BeiGene **Sponsor**: UNIVERSITY OF BIRMINGHAM

cureleukaemia
the blood cancer charity

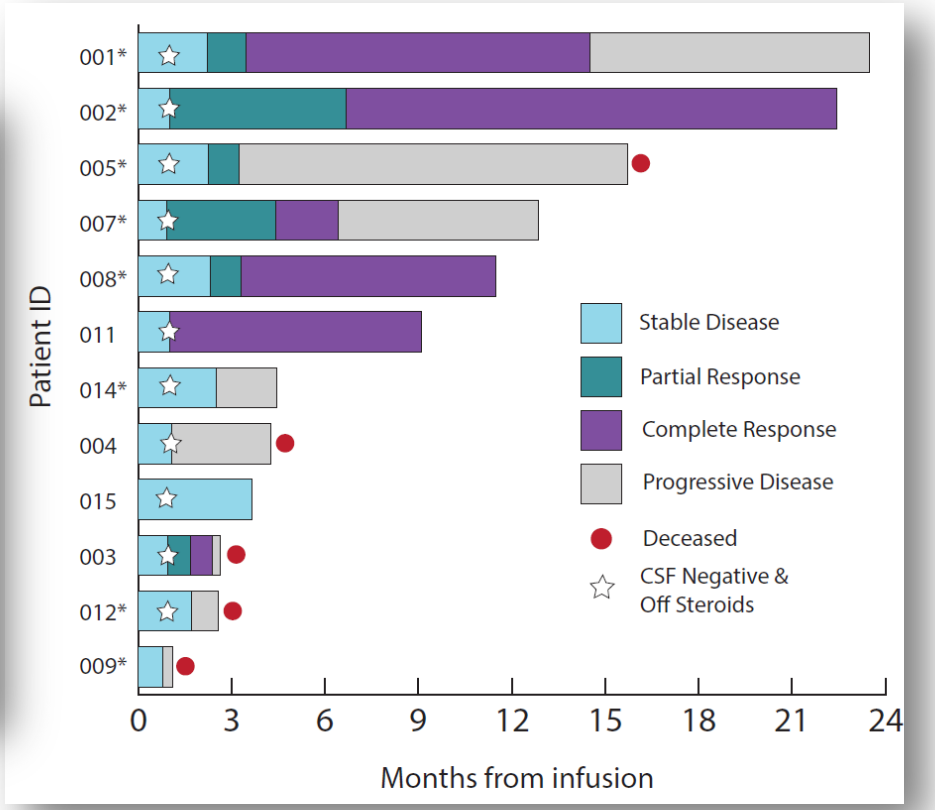
Cancer Research UK Clinical Trials Unit @CRCTU

TAP

Anti-CD19 CAR-T

Median age (range) – yr	63, (34-81)
Male:Female	7:5
Infused/Enrolled	12/13
ECOG performance status – no %	
• 0-1	7/12
• 2+	5/12
Disease location	
• Parenchymal	11/12
• Leptomeningeal enhancement/CSF+	2/12
Cell of origin	
• Germinal center B-cell type	1/12
• Non-germinal center B-cell type	11/12
Median no. of previous lines of anti-neoplastic therapy, (range)	4, (2-9)
Prior methotrexate-based regimen	
• Yes	12/12
• No	0/12
Prior thiotepa based ASCT	
• Yes	3/12
• No	9/12
BTKi refractory	
• Yes	12/12
• No	0/12
IMiD refractory$	
• Yes	4/12
• No	8/12
TEDDI-R refractory	
• **Yes**	6/12
• **No**	6/12
Prior radiotherapy	
• Yes	4/12
• No	8/12
Bridging therapy (including high dose steroids)	
• Yes	12/12
• No	0/12
Median Vein-to-Vein Time (days)	33, (27-37)

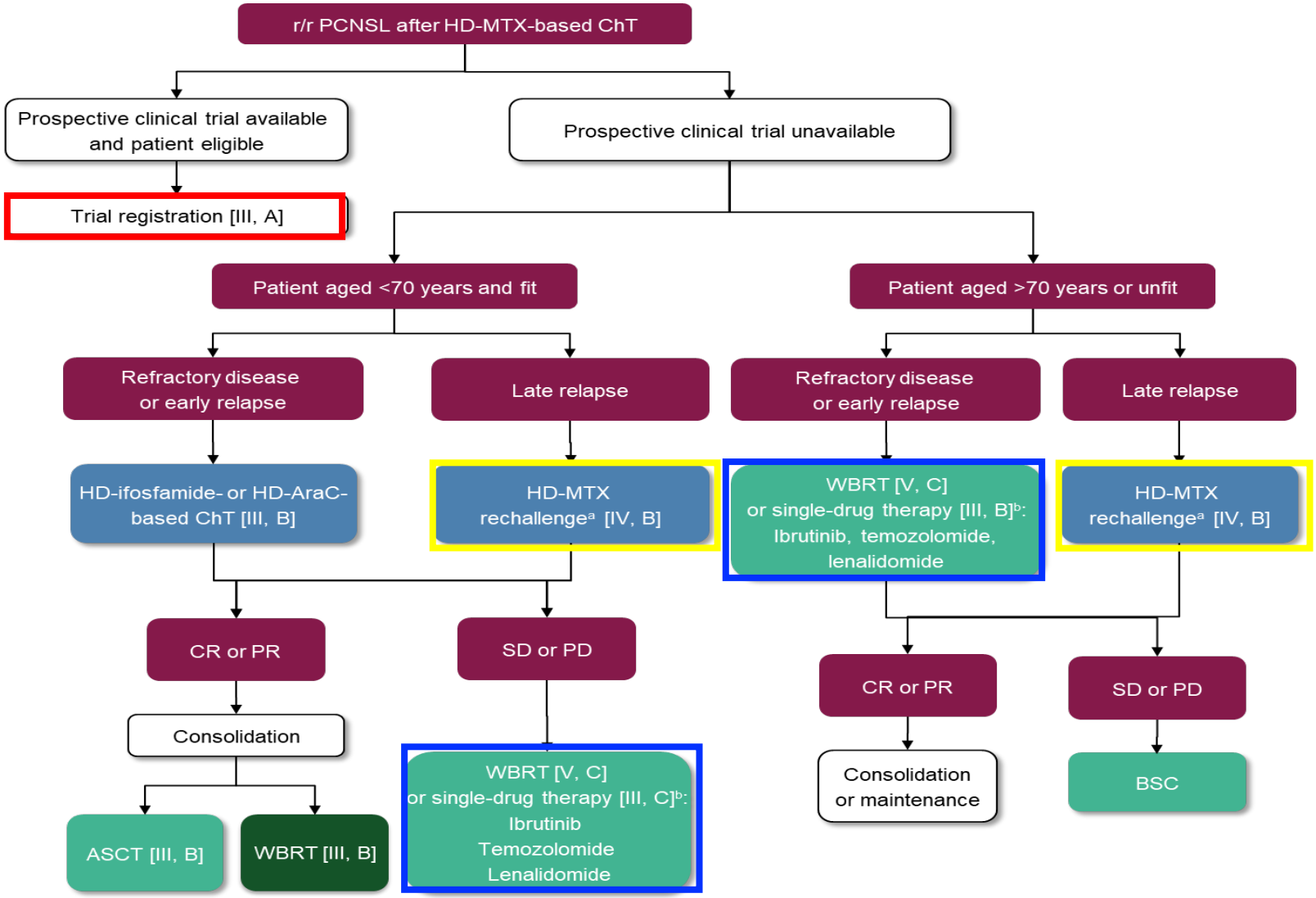
Cytokine release syndrome (CRS)$	
• Any CRS	7/12
• Grade 1	7/12
• Grade 2	-
• Grade 3	-
• Grade 4	-
Required tocilizumab	-
Median onset of CRS (day post infusion)	4
Median duration of CRS (day post infusion)	2
Immune Cell Associated Neurotoxicity Syndrome (ICANS)$	
• Any ICANS	6/12
• Grade 1	3/12
• Grade 2	2/12
• Grade 3	1/12
• Grade 4	-
Required corticosteroids	
• At time of infusion for disease control*	4/12
• Additional provided for ICANS following infusion	6/12
Median onset (day post infusion)	5
Median duration (day post infusion)	3



CAR-T cells radically modify the management of relapsed/refractory PCNSL (n=25)
Real life results of the French LOC network
Choquet S *et al* EHA/ ICML 2023

Frigault M, *et al*. Blood 2022

Treatment algorithm for R/R PCNSL



Ferreri A *et al*, EHA/ESMO 2024 Annals Onc

Ongoing challenges and questions in managing patients with PCNSL

- **Improved diagnosis and prognostic factors**
  Role of CSF & plasma ctDNA?, neuroimaging (MRI/PET)

- **Optimising induction**
  OptiMATe trial open in Germany/UK and IELSG

- **HDT-ASCT in first response: to be 'considered' for all suitable patients**

- **Optimising therapy for 'non-ASCT eligible' patients**
  Role of novel agents?

- **Relapsed/refractory PCNSL: clinical trials**
  Novel agents promising but short-lived responses as single-agent
  Combination trials ongoing
  CAR-T cell therapy promising

Ferreri A, *et al*. Nat Rev Dis Primers 2023; Ghione P, et al, Hem Onc 2023; Khwaja J, Cwynarski K. Hem Onc 2023

Challenges in managing Secondary CNS lymphoma

	CNS involvement prior to systemic lymphoma?[1]	CNS involvement secondary to systemic lymphoma?[1]	Meningeal involvement[2–13]	Systemic disease[2–13]	Systemic relapse[2–13]
PCNSL	✓	✗	~16%	~0%	~7%
SCNSL	✗	✓	**~35%**	**~35%**	**~50%**

3 modes of presentation of SCNSL

Synchronous

- Initial CNS presentation with systemic disease (**de novo**)

or

- CNS presentation with systemic relapse/refractory (prior/ongoing treatment)

Isolated

- CNS relapse (prior treatment for NHL)

Cwynarski K *et al*, SCNSL GPP Br J Haem 2023; How I treat SCNSL Alderuccio *et al* Blood 2023

Clinical practice: Diagnosis and staging in SCNSL

- Specialist haemato-pathology review
  - Systemic LN biopsy
  - CNS Parenchymal disease (stereotactic biopsy)
  - CSF (cytology/flow)
  - Vitrectomy specimen

- Contrast–enhanced MRI of brain +/- whole spine

- Imaging to exclude systemic disease:
  - PET/CT scan
  - Testicular US

Assessing fitness for therapy

- Patient fitness: Impaired PS
  - Associated with early toxicity and Rx related-mortality with intensive therapy
- Neurocognitive dysfunction
- Disease scenario/Previous treatment

  No randomised data

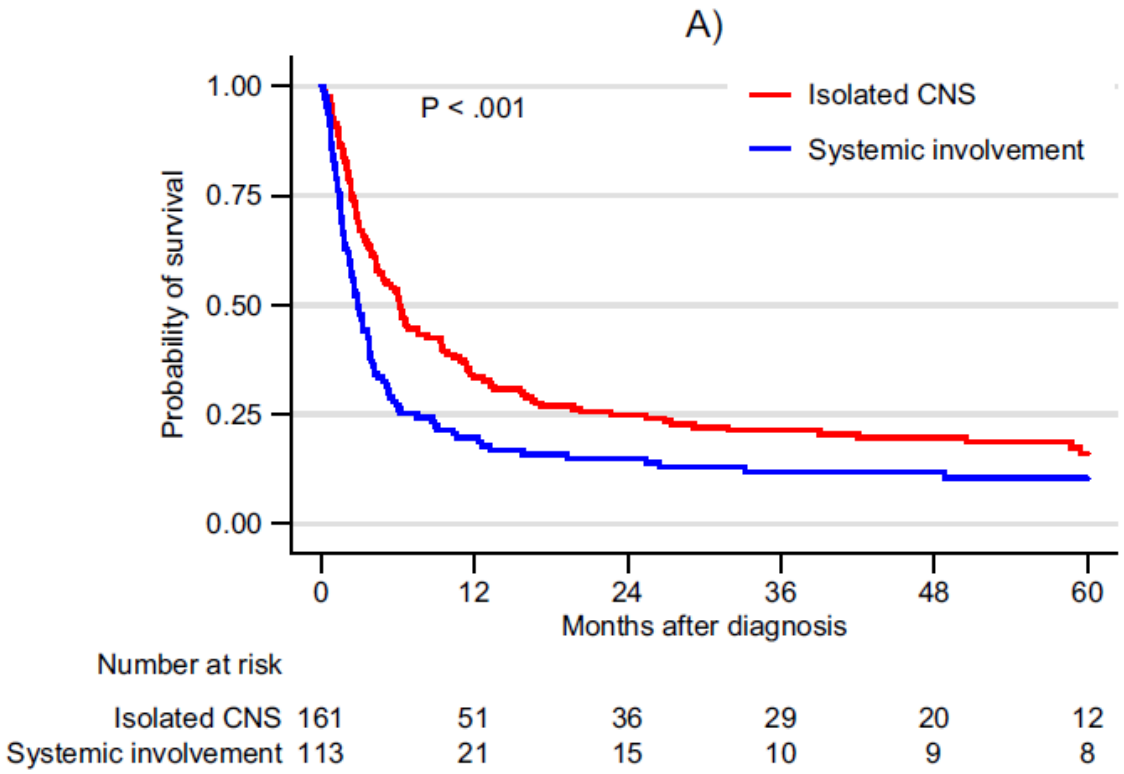
  Single arm phase 2 trials

- Short steroid pre-phase
- Consider dose reductions for C1 (and subsequent cycles)
- Continual re-assessment for treatment intensification including ASCT

- Frailty scores not specifically validated for SCNSL

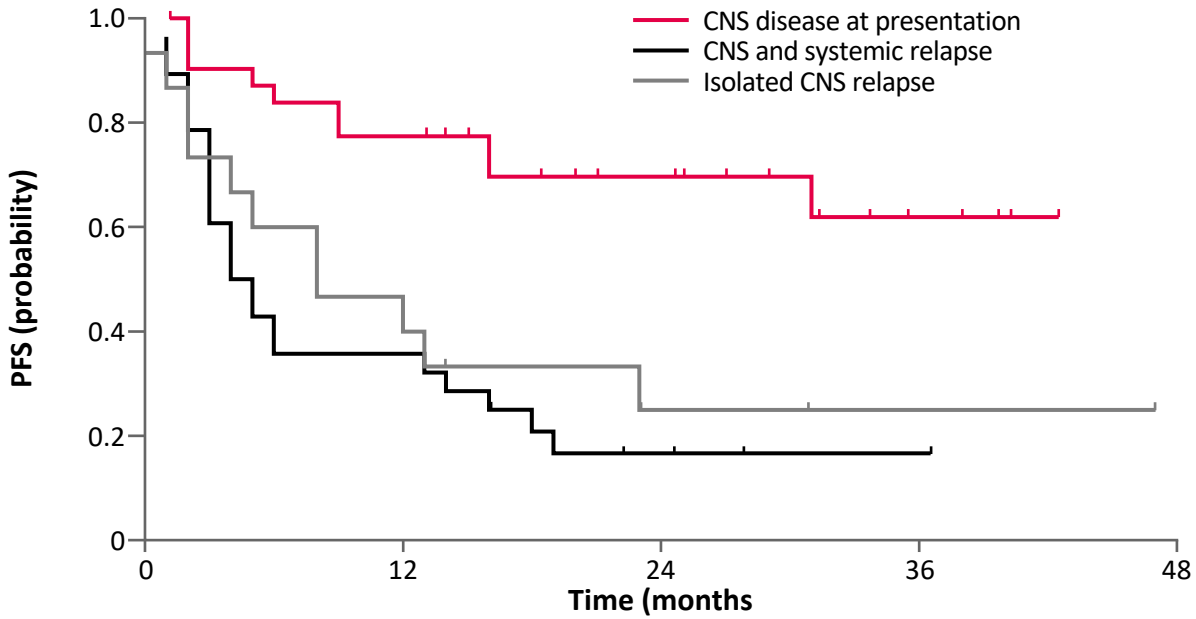
SCNSL after R-CHOP: a devastating complication

Retrospective study SCNSL n=291



Median OS post diagnosis of SCNSL = 3.9 months

MARIETTA prospective phase II trial



2 year PFS **71% if SCNSL de novo**
28% if SCNSL after R-CHOP

El-Galaly *et al*, Eur J Cancer 2019; Ferreri *et al*, Lancet Haem 2021

Prospective Phase II trials in SCNSL support TT-ASCT

Reference	Patients	Median age (range)	Treatment induction → consolidation (% completed)	IT therapy	Pre-ASCT ORR (CRR)	PFS	OS (*outcome in transplanted patients)	TRM
Korfel (2013)[1]	DLBCL (n=27) PTCL (n=3)	58 (29–65)	HD-MTX/IFO → HD-ARAC/TT → TT-ASCT (80%)	Liposomal ARAC (50 mg)	67% (23%)	2-year: 49%	2-year: 52% 2-year: 68%*	3%
Ferreri (2015)[2]	DLBCL (n=32) FL (n=3) MCL (n=3)	59 (36–70)	R-MTX-ARAC → R-HDS → TT-ASCT (53%)	Liposomal ARAC (50 mg)	63% (61%)	4-year: 50%	5-year: 41% 5-year: 68%*	10%
Doorduijn (2016)[3]	DLBCL (35) Grade 3 FL (n=1)	57 (23–65)	R-DHAP-HDMTX → BU-CY-ASCT (42%)	Rituximab	53% (22%)	**2-year: 14%**	2-year: 22%	8%
MARIETTA Ferreri (2021)[4]	DLBCL (n=75) 43% de novo 37% concom 20% isolated	58 (23–70)	MATRix → R-ICE → TT-ASCT (53%)	Liposomal ARAC or Triple	65% (39%)	2-year: 46% (2-year 71% de novo)	2-year: 46% 2-year: 83%*	5%

1. Korfel A, *et al*. Haematologica 2013
2. Ferreri AJM, *et al.* J Clin Oncol 2015
3. Doorduijn JK, *et al.* Hematol Oncol 2017
4. Ferreri A *et al,* Lancet Haematology 2021

Response to 2 courses of MATRix was a strong prognosticator

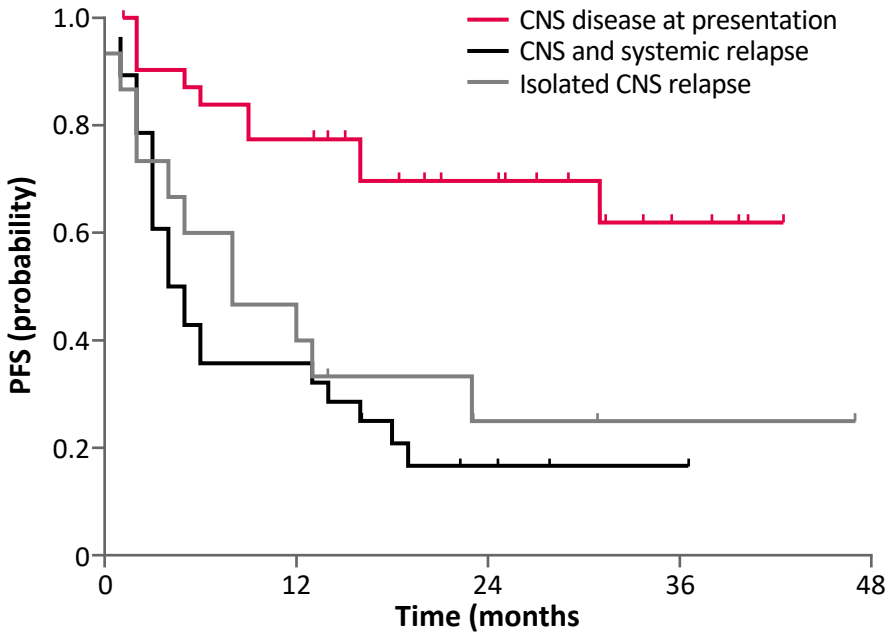
Response after MATRIX 1 & 2	RICE	Response after MATRIX-RICE	ASCT	After whole treatment	Failure-free
CR: 20 (27%)	**YES:** 17 pts	**CR:** 16 (94%)	14 (82%)	CR: 15 (88%)	11 pts
	NO: 3 pts	**CR:** 3 (100%)	1 pts	CR: 3 pts	2 pts
PR: 35 (47%)	**YES:** 31 pts	**CR:** 9 (29%) **PR:** 15 (50%)	7 (23%) 12 (39%)	**CR:** 9 (29%) **CR:** 11 (35%) **PR:** 2 (6%)	7 pts 8 pts
	NO: 4 pts	**PR:** 3 pts	0 pts	**PR:** 3 pts	1 ltf
SD: 3 (4%)	**YES:** 2 pts	**CR:** 1 pts **PR:** 1 pts	1 pts 1 pts	**CR:** 2 pts	2 pts
	NO: 1 pts	**PD:** 1 pts	0 pts	**PD:** 1 pts	
PD: 13 (17%)	**YES:** 5 pts	**PD:** 5 pts	0 pts	**PD:** 5 pts	
	NO: 8 pts	**PD:** 8 pts	0 pts	**PD:** 8 pts	

Patients with MATRix-refractory disease experienced no benefit from crossing to RICE

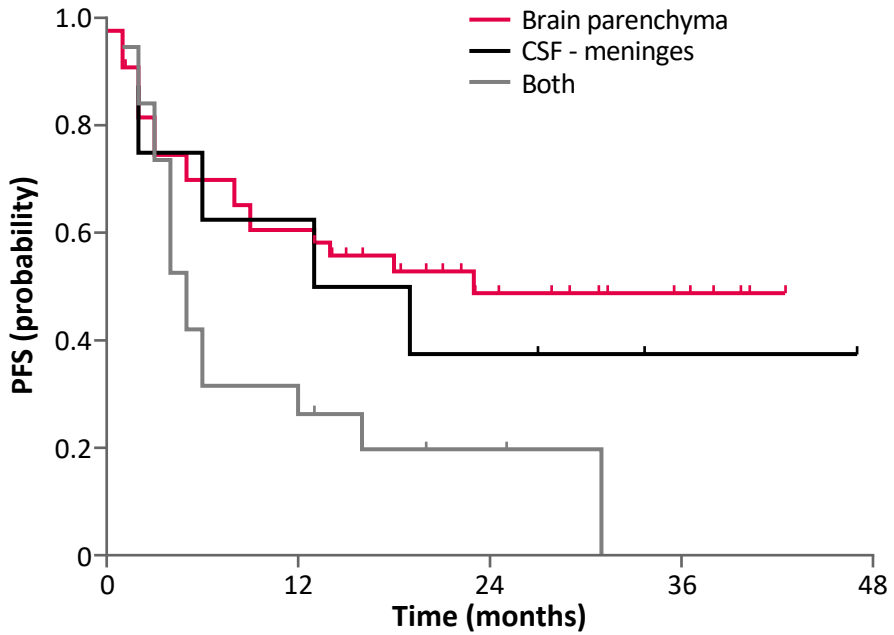
Ferreri AJM *et al,* Lancet Haematol 2021

Chemo-naïve patients or disease limited to a single CNS compartment had improved outcomes

PFS by CNS presentation and involvement



Patients with CNS disease at presentation had the best outcome



CSF/meningeal disease was associated with poor outcome

Ferreri AJM *et al,* Lancet Haematol 2021

Management of *treatment naïve* SCNSL

- **MARIETTA** (MATRix/R-ICE/ASCT) approach – fit patients, usually < 70years
  - Has ITs D4/5 of each cycle

- R-CODOX-M/R-IVAC, Ph 2 trial of untreated high IPI DLBCL 2
    - 10 cases with SCNSL – 2 year PFS of 70% without consolidation
    - If <50 years and PS <2?

Older, less fit patients

- R-MTX + cytarabine (2-3 doses) + reduced dose R-ICE and aim for ASCT

- R-CHOP + HD MTX– unfit for intensive approaches (+IT therapy?)

•Cwynarski K *et al*, SCNSL GPP Br J Haem 2023; How I treat SCNSL Alderuccio *et al* Blood 2023

Management of isolated SCNSL

- Outcomes appear better than those with concomitant relapse
- 2 year PFS of 60% (intensively treated); 70% (ASCT consolidation) [1, 2]
- MARIETTA: 20% (n=15) had isolated CNS relapse
  - 2 year PFS 40% vs 14% for concomitant systemic and CNS relapse
  - ? Role of R-ICE in this setting

- **MATRix if <70yrs**
- **R-MTX-AraC** – less intensive option for older (>70yrs)/less fit
  - **Plan for BCNU-TT ASCT**

- Clinical trials/novel therapy/RT (if unsuitable for intensive therapy)

1. Ferreri A.J…Cwynarski. The Lancet Haematology 2021; 2 El-Galaly TC *et al*, European J of Cancer 2018

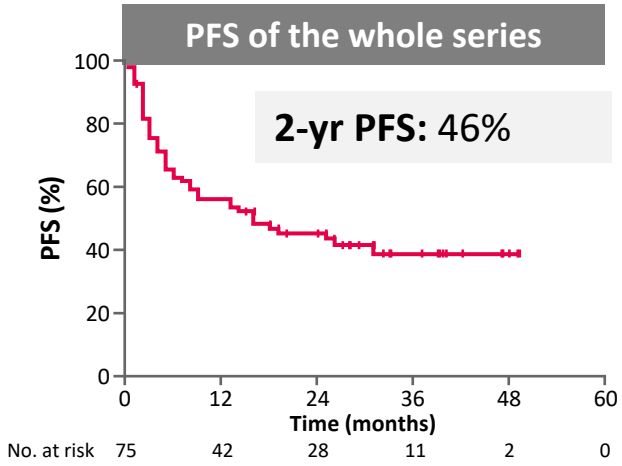
Management of relapsed concomitant SCNSL

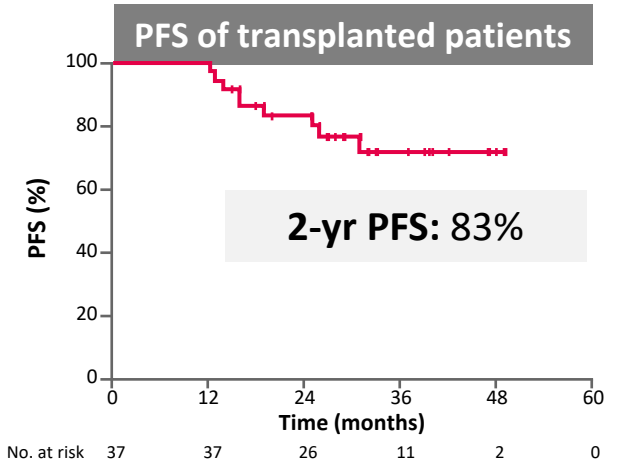
- Outcomes poor
- MARIETTA trial[1] n=28
  - ORR 46% but majority did not proceed to ASCT
  - 14% 2 year PFS
- 'Improved outcomes' if proceed to thiotepa consolidation-ASCT[2]
  - 46% 2 year PFS
- Other options
  - Clinical trials
  - Novel therapies: BTKi/CelMODs
  - CAR-T
  - Radiotherapy
  - Palliation – dexamethasone; RT; IT therapy

1. Ferreri….Cwynarski. The Lancet Haematology 2021; 2. How I treat SCNSL Alderuccio *et al* Blood 2023

Thiotepa-based ASCT in SCNSL

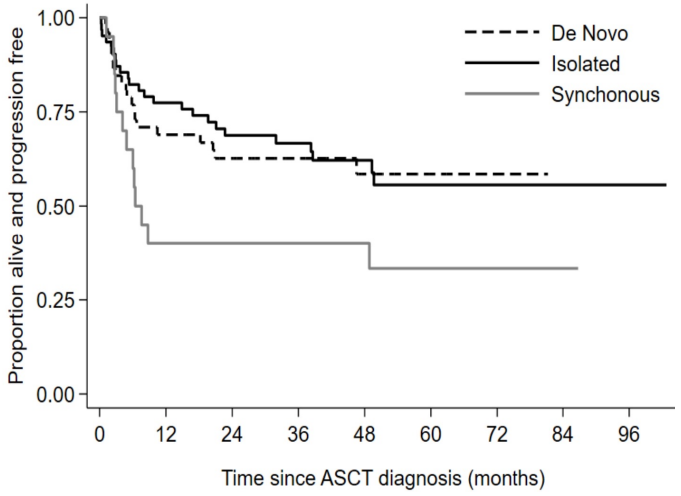
IELSG42 (MARIETTA) Trial (n=75)



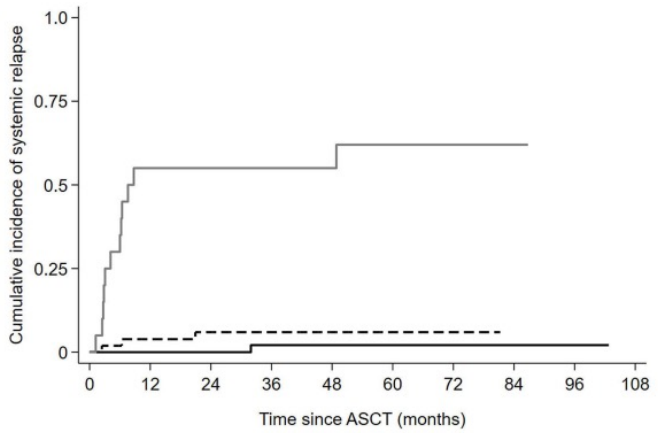


Thiotepa-based ASCT has efficacy in CR and PR

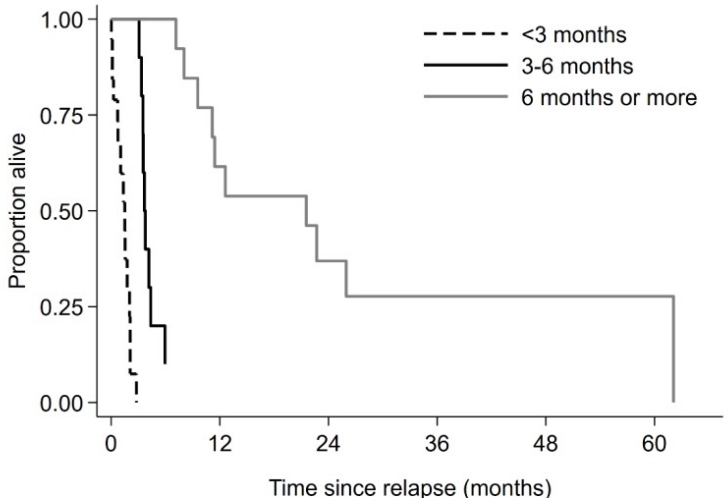
n=134



Systemic relapse post ASCT



Time to relapse post ASCT



Ferreri AJM *et al,* Lancet Haematol 2021

Khwaja J *et al*, Haematologica 2022

Clinical activity with novel agents in SCNSL

Ibrutinib for CNS lymphoma

- n=33, Ibrutinib ± other agents
- n=24 SCNSL
- ORR 58% (CR 55%)

SCNSL:

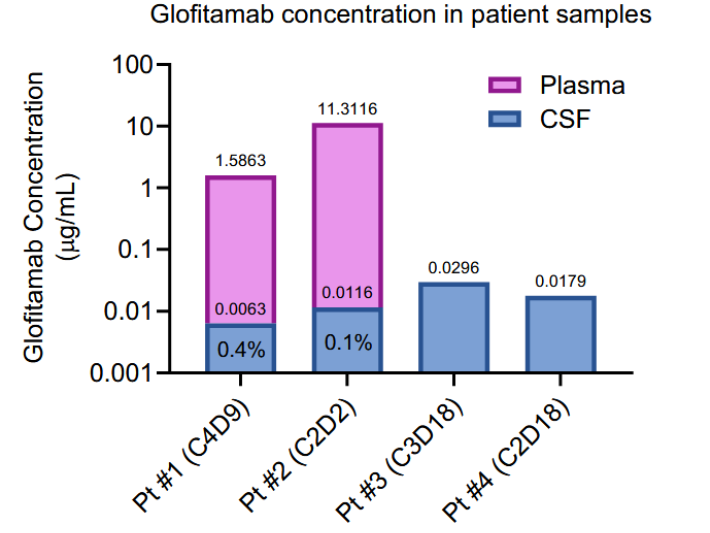
Median PFS: 10.2 months

Median OS: 11.5 months

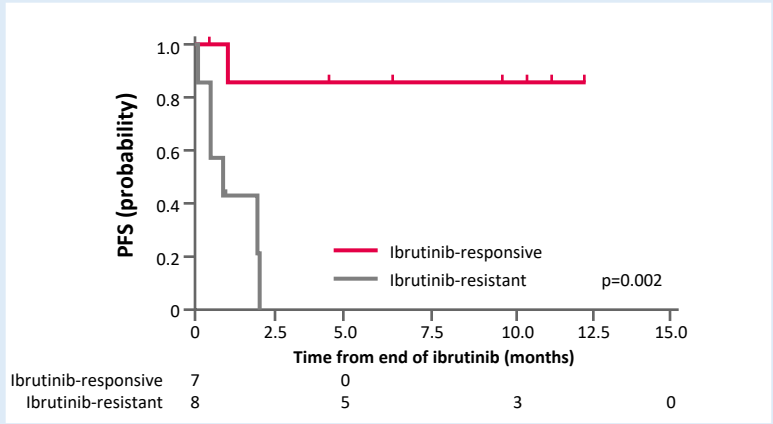
Australasian Lymphoma Alliance/MD Anderson Cancer Center

Glofitamab in SCNSL

n=4



Phase 2 Response-adapted Ibrutinib + TEDDI-R in SCNSL



- n=49; 5 untreated
- Toxicity assessed across 35 cycles:

  Grade 3/4 neutropenia: 40% of cycles

  Febrile neutropenia: 10% of cycle
- 24/42 evaluable patients were ibrutinib-responsive
- 88% Ibrutinib-responsive tumours = CD10 neg

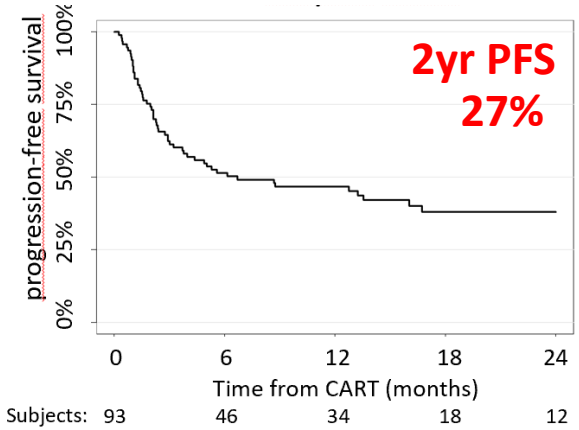
TEDDI-R, Isavuconazole with Temozolomide, Etoposide, Liposomal Doxorubicin, Dexamethasone, Rituximab;

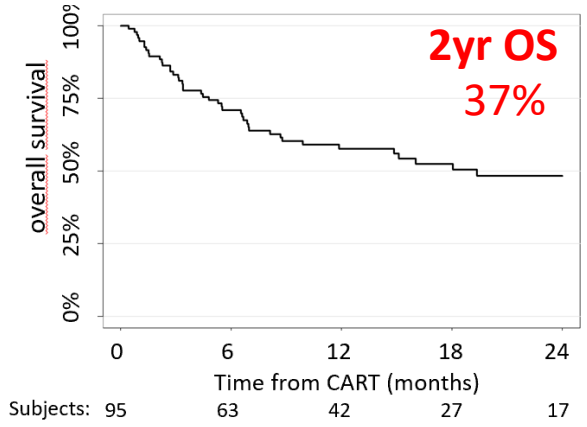
Lewis K *et al*, BJ Haem 2021; Roschewski M *et al*, ICML 2023; Godfrey JK *et al*, Blood 2024

ASH 2023/EHA 2024: Are CAR T effective for SCNSL?

EBMT data suggests YES but 'poorer outcomes' at EHA

n=95

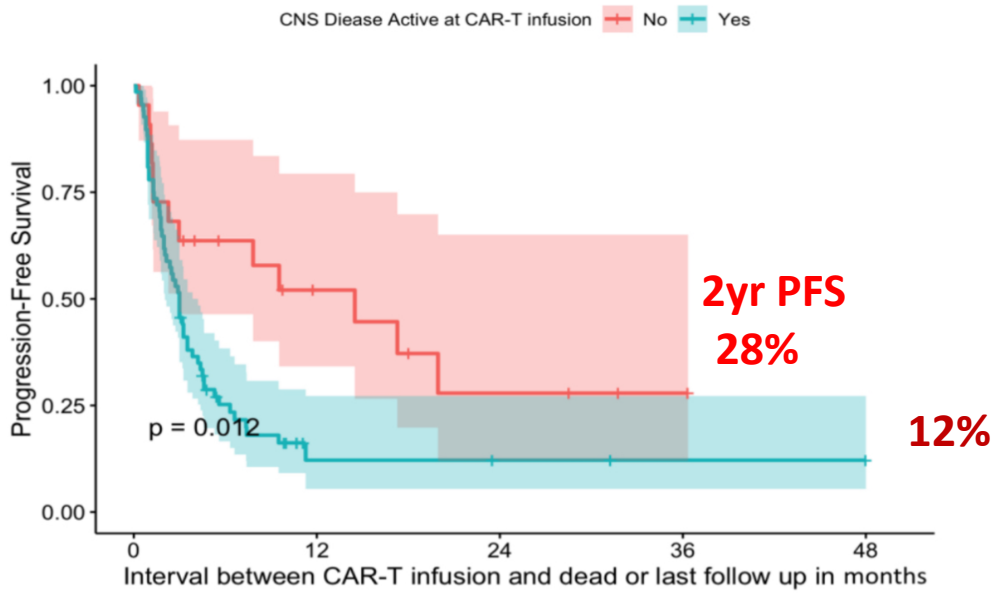




66% had active CNS involvement at time of CAR T infusion

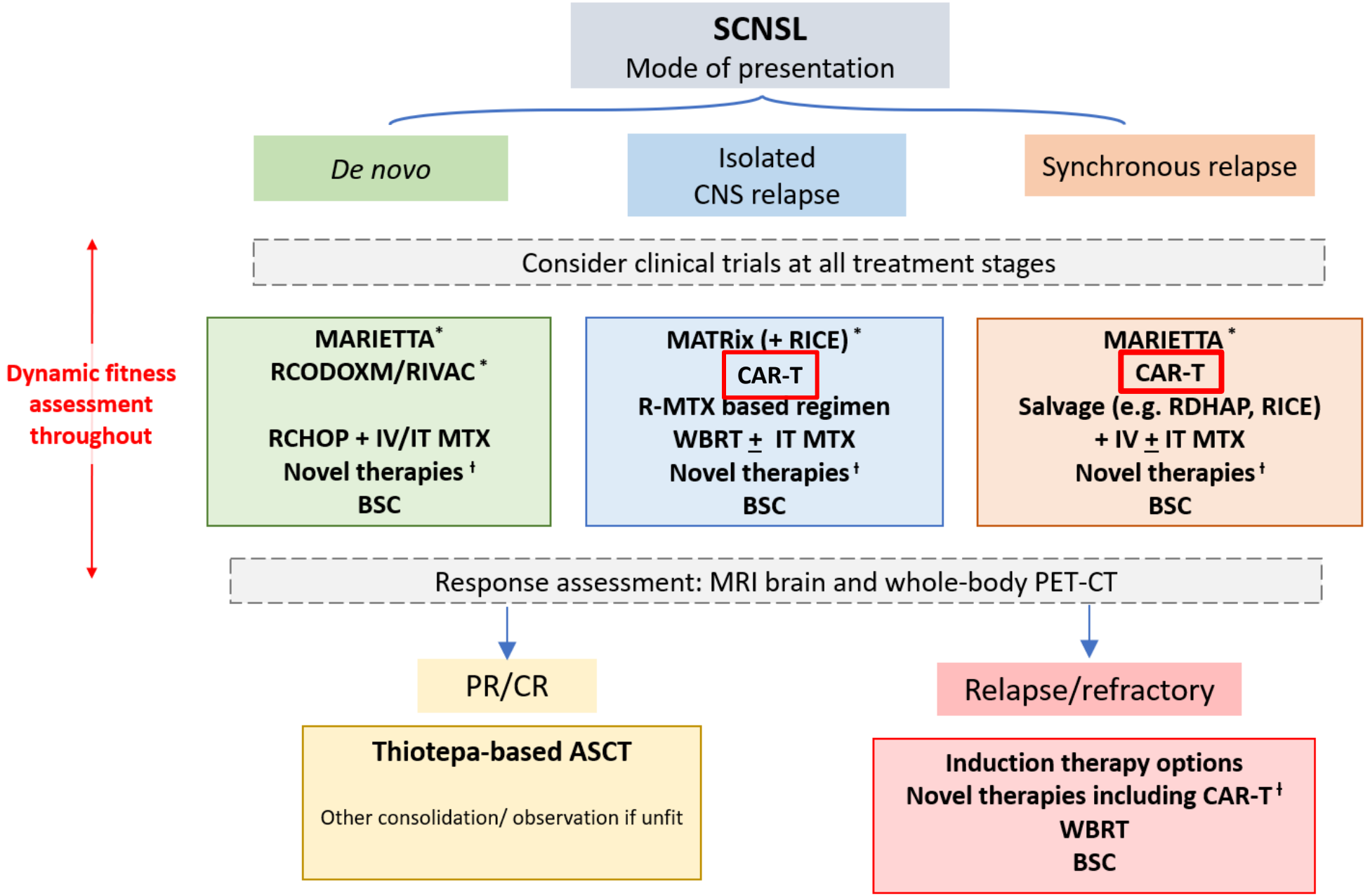
US data are NOT so optimistic

n=90



76% had active CNS involvement at time of CAR T infusion

Saidy AO *et al*, EHA 2024, Ahmed *et al* ASH 2023



Cwynarski K *et al*, SCNSL Good Practice Paper Br J Haem 2023; Khwaja J, Cwynarski HaemOnc 2023; How I treat SCNSL Alderuccio *et al* Blood 2023

Ongoing challenges and questions in managing patients with SCNSL

- Biology

- Relapsed Synchronous systemic and CNS disease an area of unmet need
- Access to treatments
  - CAR-Ts
  - Ibrutinib and CELMoDs have shown efficacy
  - Role of Radiotherapy for bridging?

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