Management of Lymphoma of the Central Nervous System

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DISCLOSURES

- No conflicts of interest to declare

AGENDA

Primary CNS lymphoma

CNS prophylaxis in DLBCL

Secondary CNS lymphoma

PCNSL - epidemiology

Rising incidence

- ~4 per million/year in Europe
- 4.8 per million/year in US
  - Not solely explained by improved diagnostics

2-5% of brain tumours / 2% of all extra-nodal NHL

Immunocompetent patients

Median age at diagnosis >60yrs

- Median age in recent large French study = 68 years
- Median age at diagnosis in East Midlands, UK = 70 years

PCNSL – increasing age at diagnosis

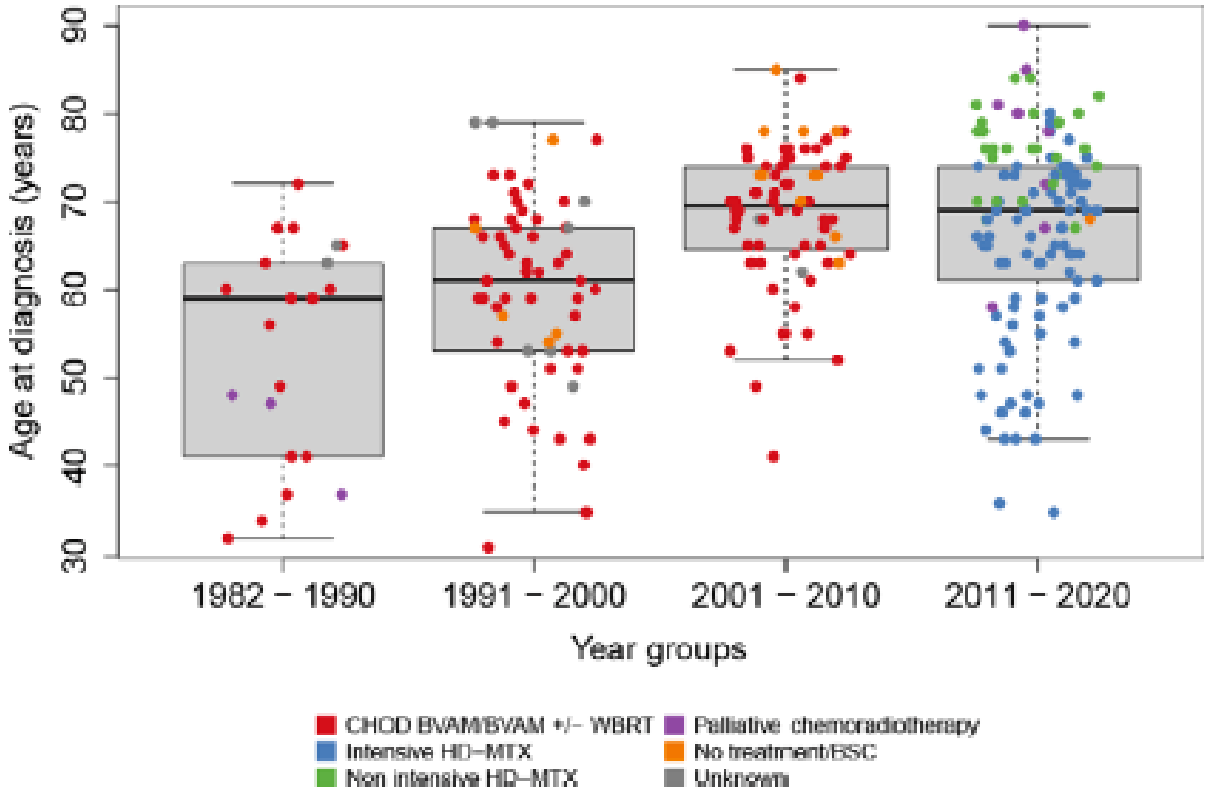
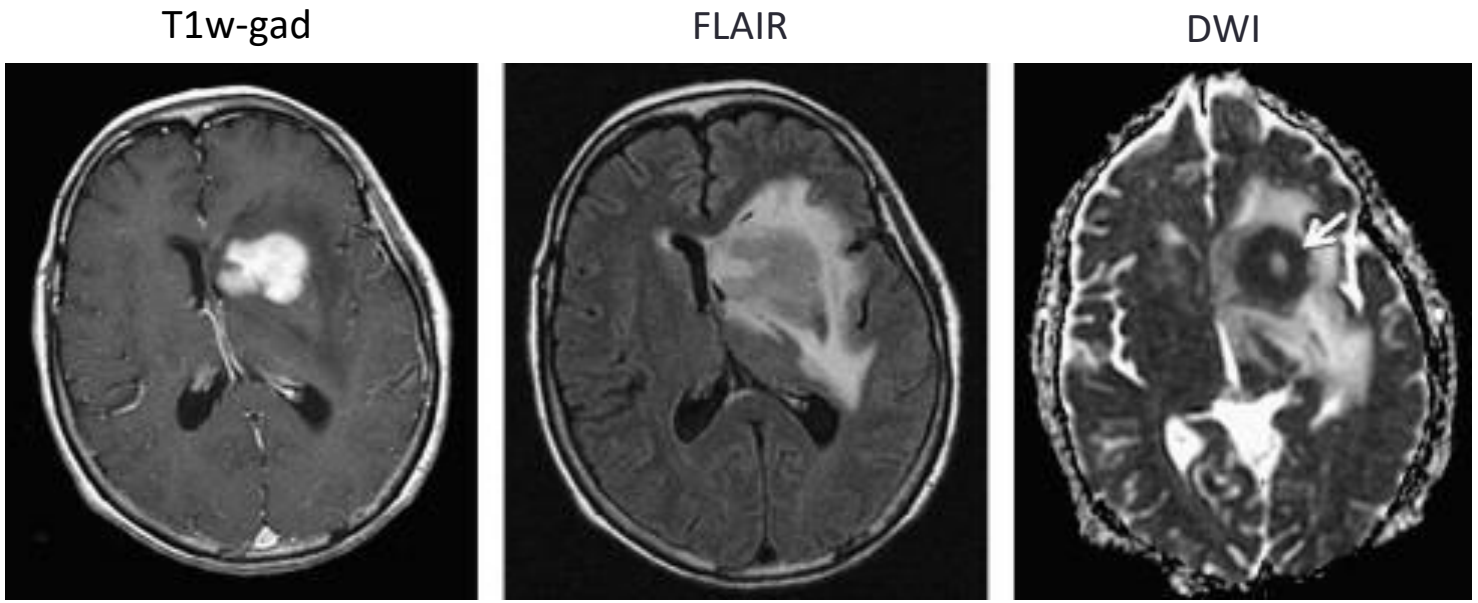


Fig 2. Box plots depicting distribution of ages within the period studied, divided by year groups. Individual data points are displayed by treatment type. Palliative chemoradiotherapy refers to the use of temozolomide (TMZ) + dexamethasone, TMZ + whole brain radiotherapy (WBRT), TMZ + rituximab (R), or the use of WBRT alone. BSC, best supportive care. [Colour figure can be viewed at wileyonlinelibrary.com]

Kaji, F et al BJHaem 2021

Particular considerations in PCNSL

- Unique clinical sequelae of this aggressive lymphoma entity
- Challenges with drug delivery to the CNS
- Surrounding brain tissue is highly vulnerable to treatment toxicities



Biology of PCNSL

BCR/NF-κB

MYD88 (30-80%)
CD79B (30-88%)
CARD11
TNFAIP3

Epigenetic modifiers & Transcription

KMT2D
CREBBP
MEF2B
TBXL1R1 (30%)
HIST1H1E

Immune escape

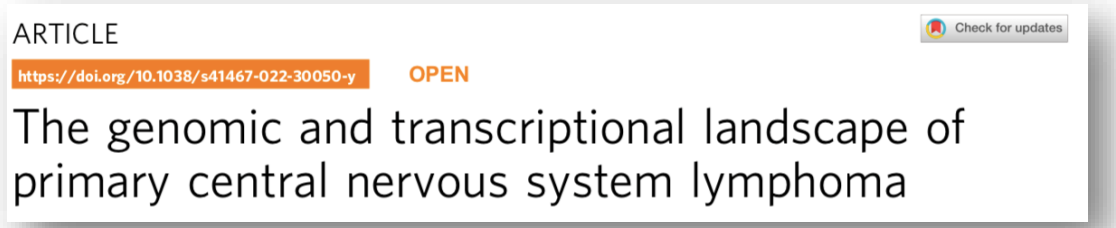
CIITA
B2M
HLA loss
PDL1/PDL2 gain
CD58

Cell cycle

TP53
CDKN2A

aSHM

PIM1 (30-100%)
BTG2
BTG1
IGLL5

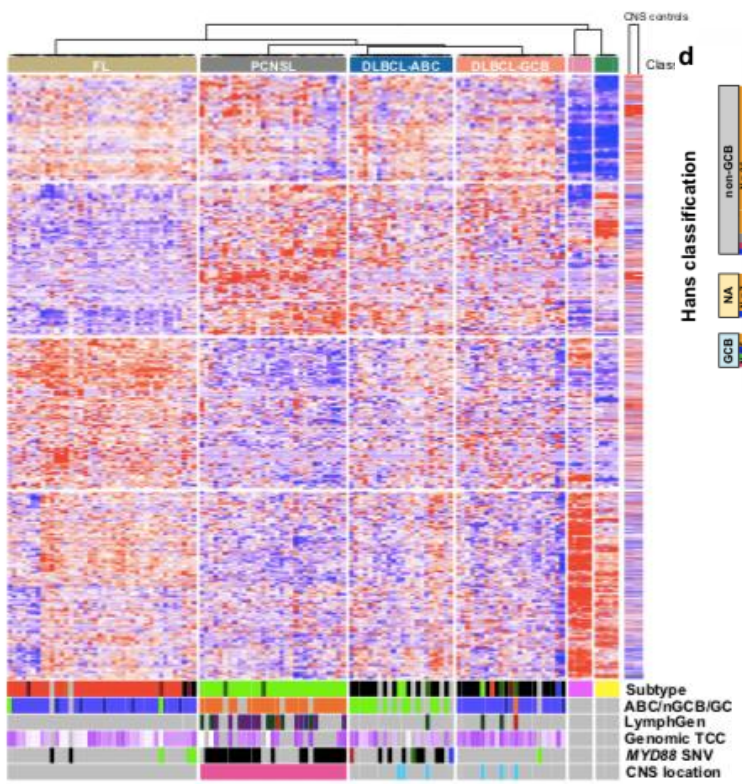

ARTICLE

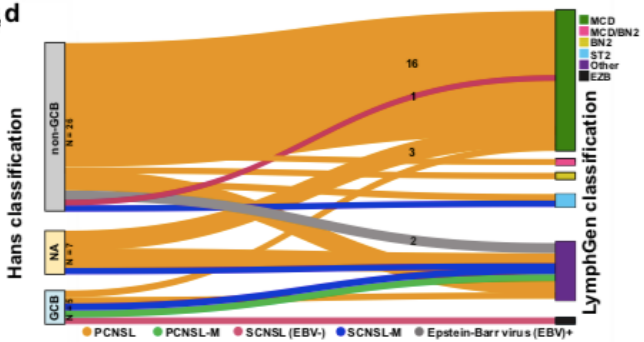
https://doi.org/10.1038/s41467-022-30050-y OPEN

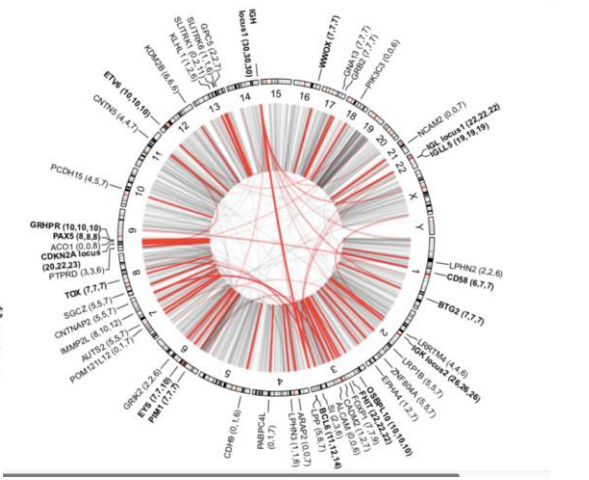
Check for updates

The genomic and transcriptional landscape of primary central nervous system lymphoma

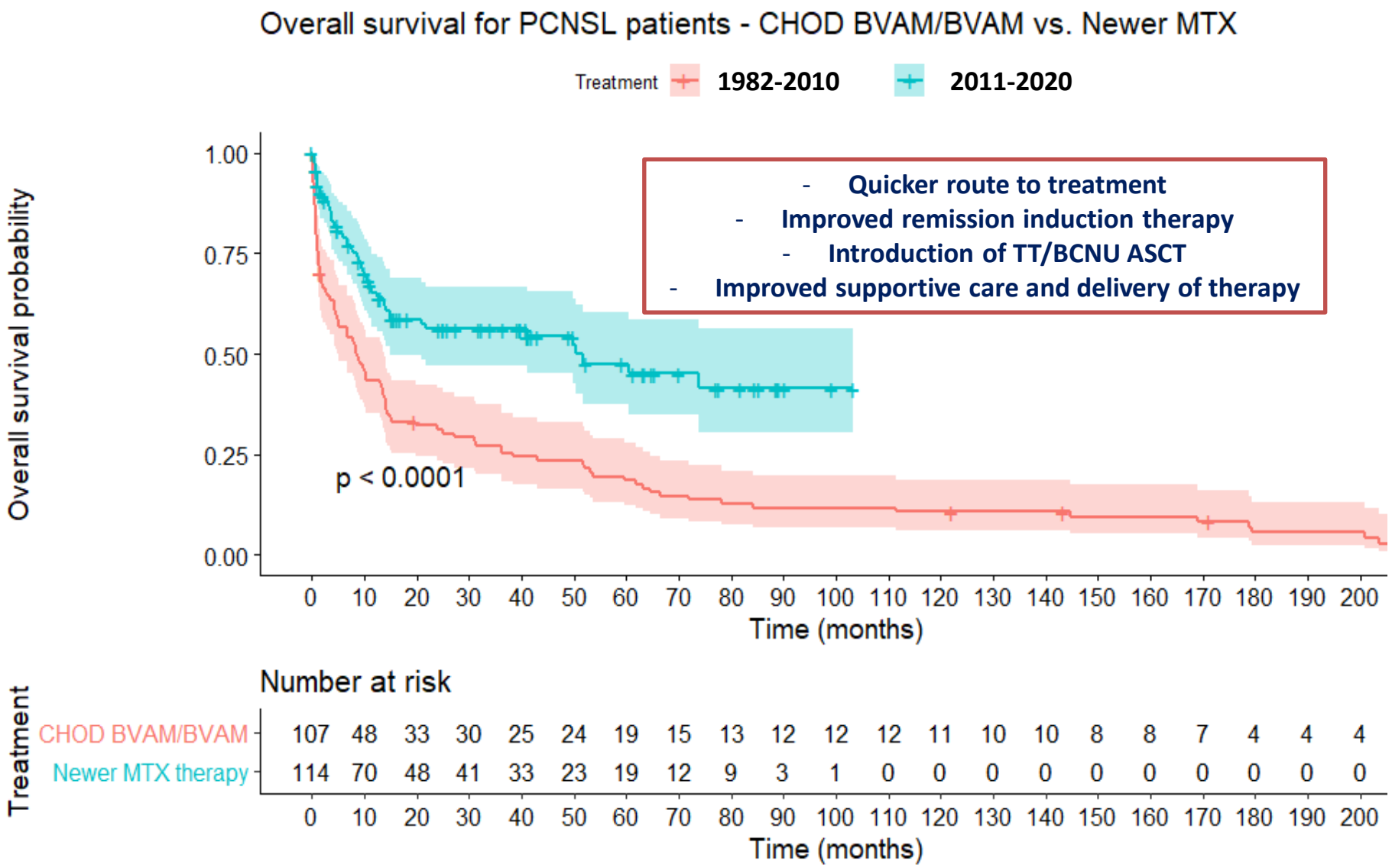
Radke et al. Nat Comm, 2022







Population-based survival data – era by era analysis from Nottingham, UK



Consecutive patients treated

<u>1982-2010</u>
CHOD BVAM/BVAM +WBRT

<u>2011 onwards</u>
MTX+Arac / MATRix
+TT/BCNU ASCT

RMP/PRIMAIN for less fit older patients

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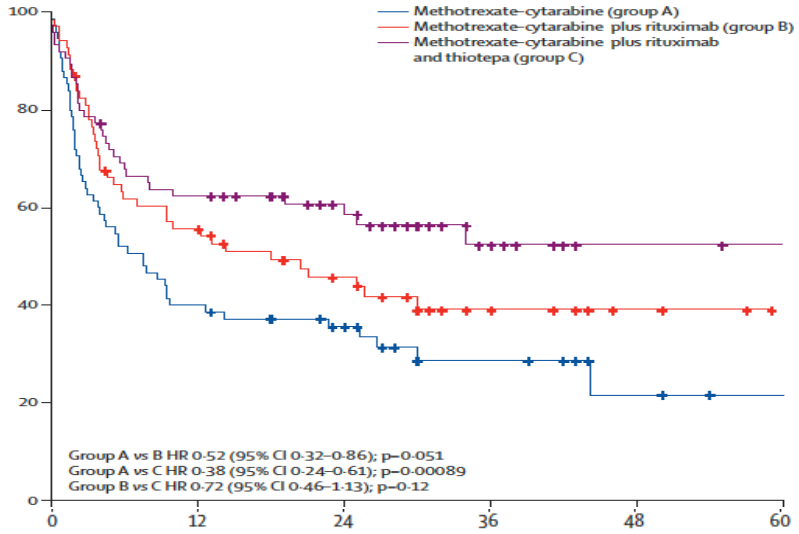
Treatment paradigm for PCNSL

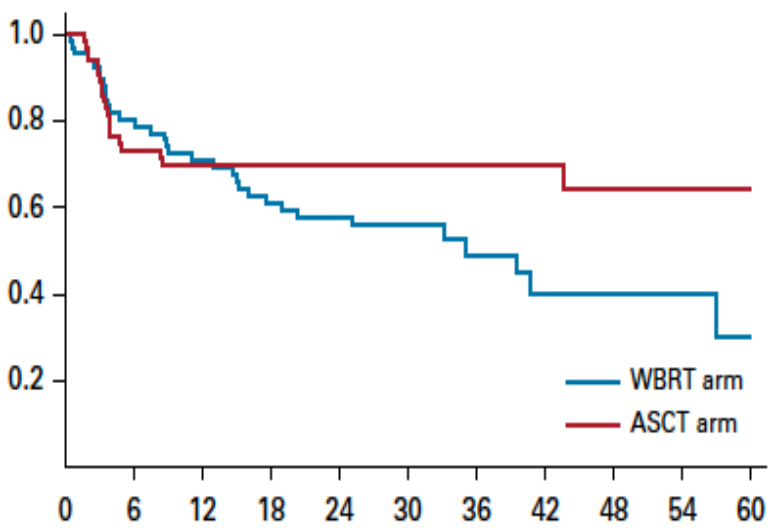
A ’two-phase’ treatment strategy (remission induction & consolidation) is widely adopted internationally



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

*Andrés J M Ferreri, Kate Cwynarski, Elisa Pulczynski, Maurilio Ponzoni, Martina Deckert, Letterio S Politi, Valter Torri, Christopher P Fox, Paul La Rosée, Elisabeth Schorb, Achille Ambrosetti, Alexander Roth, Claire Hemmaway, Angela Ferrari, Kim M Linton, Roberta Rudà, Mascha Binder, Tobias Pukrop, Monica Balzarotti, Alberto Fabbri, Peter Johnson, Jette Sønderskov Gørløv, Georg Hess, Jens Panse, Francesco Pisani, Alessandra Tucci, Stephan Stilgenbauer, Bernd Hertenstein, Ulrich Keller, Stefan W Krause, Alessandro Levis, Hans J Schmoll, Franco Cavalli, Jürgen Finke, Michele Reni, Emanuele Zucca, Gerald Illerhaus, for the International Extranodal Lymphoma Study Group (IELSG)**

Ferreri et al Lancet Haematology 2016

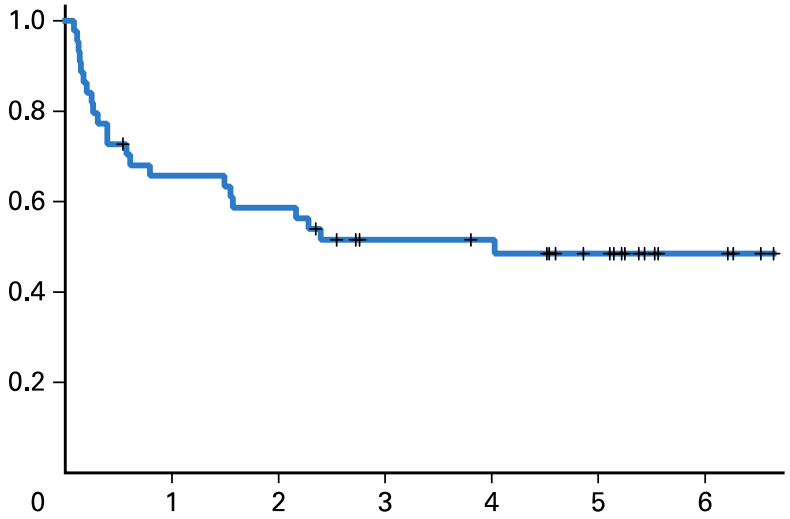


original report

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

Caroline Houillier, MD[1]; Luc Taillandier, PhD[2]; Sylvain Dureau, PharmD[3]; Thierry Lamy, MD, PhD[4]; Mouna Laadhari, MD[3]; Olivier Chinot, MD, PhD[5]; Cecile Moluçon-Chabrot, MD[6]; Pierre Soubeyran, MD, PhD[7]; Remy Gressin, MD[8]; Sylvain Choquet, MD[1]; Gandhi Damaj, MD, PhD[9]; Antoine Thyss, MD[10]; Julie Abraham, MD[11]; Vincent Delwail, MD[12]; Emmanuel Gyan, MD, PhD[13]; Laurence Sanhes, MD[14]; Jérôme Cornillon, MD, PhD[15]; Reda Garidi, MD[16]; Alain Delmer, MD, PhD[17]; Marie-Laure Tanguy, PharmD[13]; Ahmad Al Jijakli, MD[18]; Pierre Morel, MD[19]; Pascal Bourquard, MD[20]; Marie-Pierre Moles, MD[21]; Adrien Chauchet, MD[22]; Thomas Gastinne, MD[23]; Jean-Marc Constans, MD, PhD[9]; Adriana Langer, MD[3]; Antoine Martin, MD, PhD[24]; Patricia Moisson, MD[3]; Lucette Lacomblez, PhD[1]; Nadine Martin-Duvemeuil, 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

Hoillier et al JCO 2019



Intensive Chemotherapy and Immunotherapy in Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202)

James L. Rubenstein, Eric D. Hsi, Jeffrey L. Johnson, Sin-Ho Jung, Megan O. Nakashima, Barbara Grant, Bruce D. Cheson, and Lawrence D. Kaplan

Rubenstein et al JCO 2013

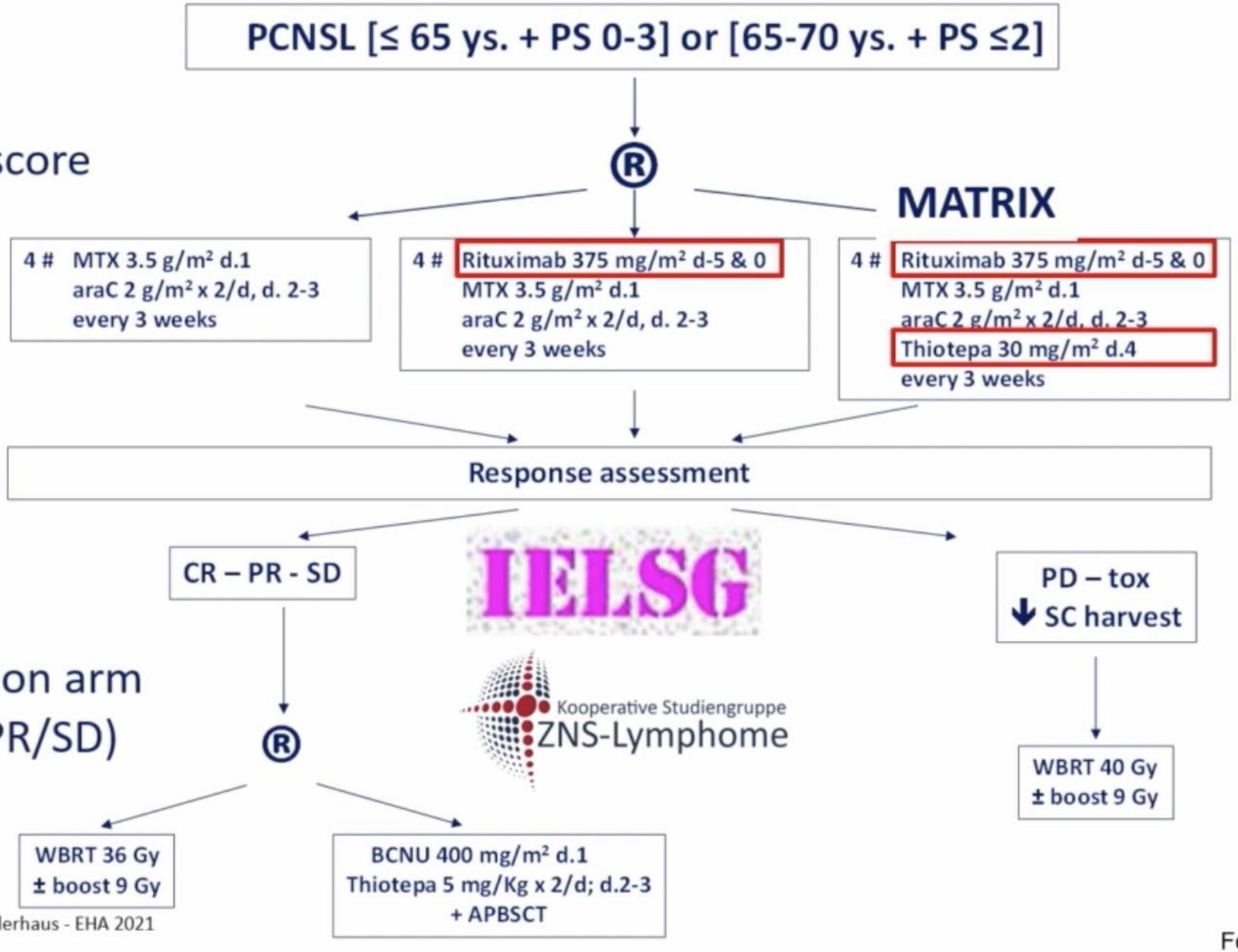
Choice of treatment

	Intensive treatment	Fit for HD-MTX, no ASCT	Unfit for intensive chemo*
		WBRT	* ECOG, renal function, LVEF
	MATRIX -> ASCT R-MTX/AraC -> ASCT R-MBVP -> AraC	R-MP RMVP-A	R-TMZ PCZ WBRT BSC
	MTR -> RT or HD AraC/Etoposide	MTR -> RT WBRT	R-TMZ PCZ WBRT BSC

MATRix followed by autologous transplant is associated with excellent survival and Neurotolerability in Primary CNS Lymphoma: Resulty of the IELSG32 Trial at a median Follow-up of 88 Months

G. Illerhaus, K. Cwynarski, E. Pulczynski, C.P. Fox, E. Schorb, P. C. Celico, M. Falautano, A. Nonis, La Rosée, M. Binder, A. Fabbri, F. Ilariucci, A. Ambrosetti, A. Roth, C. Hemmaway, P. Johnson, K. Linton, T. Pukrop, J. Sonderskov Gorlov, M. Balzarotti, G. Hess, U. Keller, S. Stilgenbauer, J. Panse, A. Tucci, L. Orsucci, F. Pisani, A. Levis, S. Krause, H.J. Schmoll, B. Hertenstein, M. Rummel, J. Smith, M. Pfreundschuh, G. Cabras, F. Angrilli, M. Ponzoni, M. Deckert, L.S. Politi, J. Finke, K. Cozen, E. Burger, N. Ielmini, F. Cavalli, E. Zucca, A.J.M. Ferreri

IELSG32 Trial



Gerald Illerhaus - EHA 2021

Ferreri et al, Lancet Hematology 2016

IELSG32 Initial publications

2016

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

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Ferreri et al, Lancet Hematology 2016

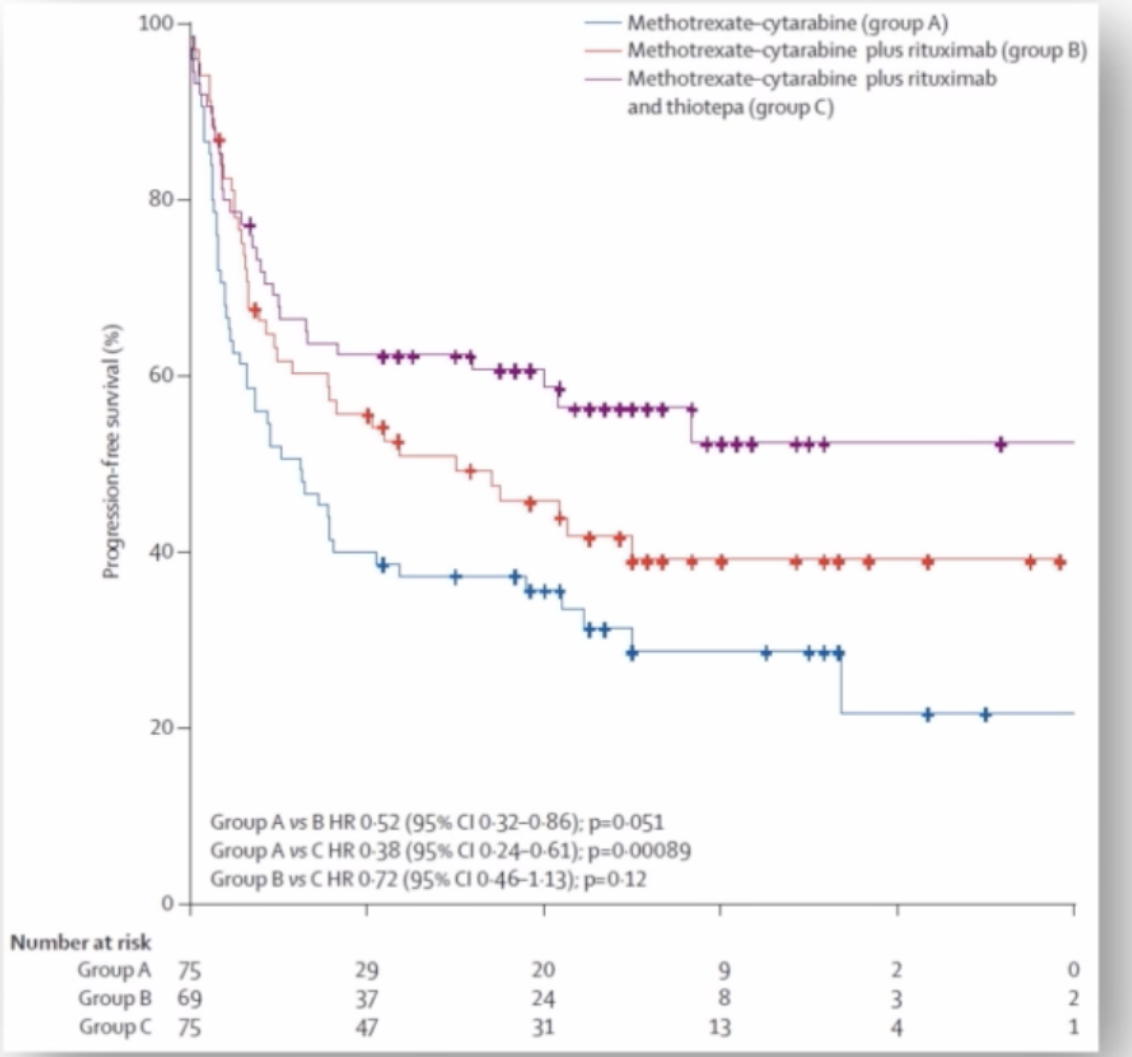
2017

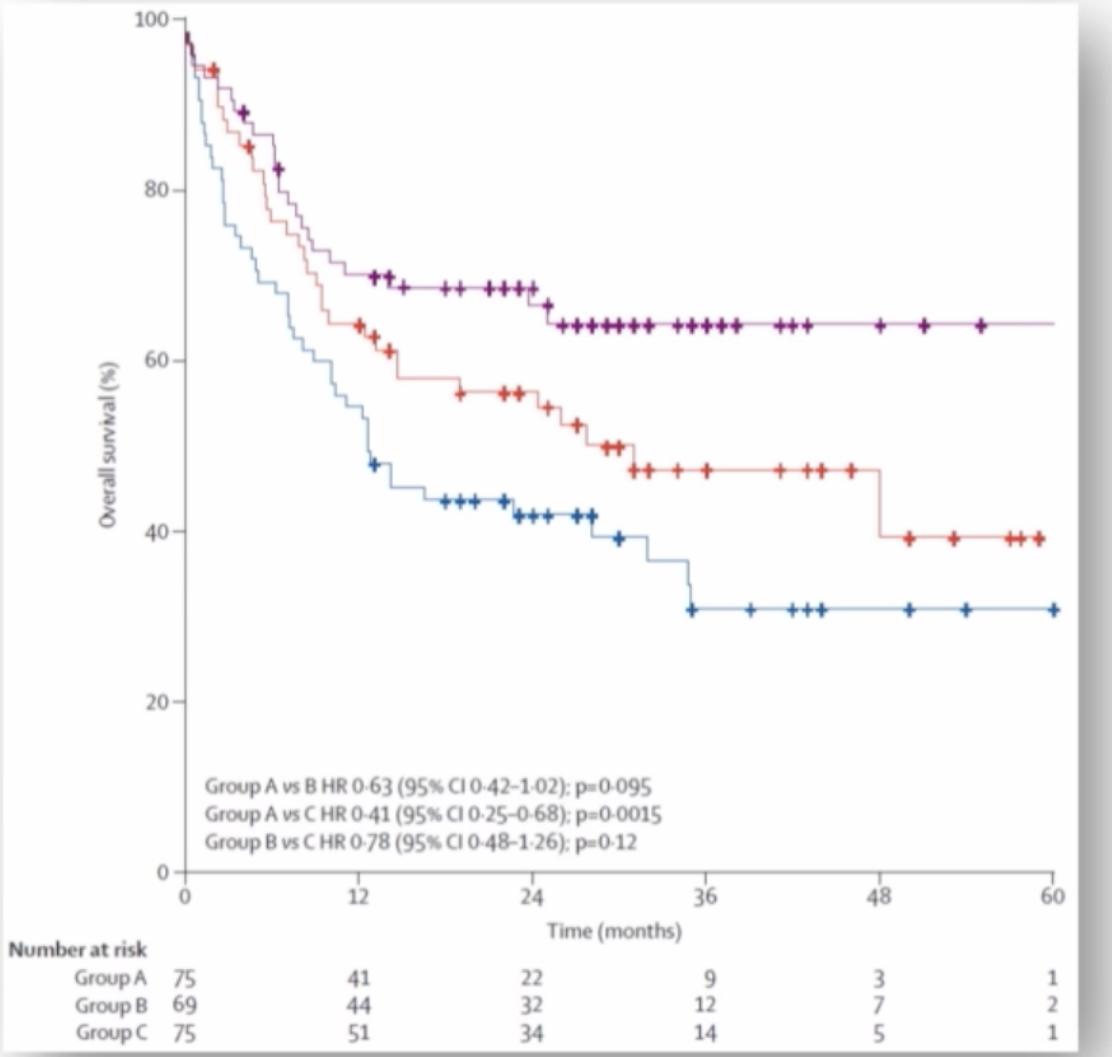
Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial

Andrés J M Ferreri, Kate Cwynarski, Elisa Pulczynski, Christopher P Fox, Elisabeth Schorb, Paul La Rosée, Mascha Binder, Alberto Fabbri, Valter Torri, Eleonora Minacapelli, Monica Falautano, Fiorella Ilariucci, Achille Ambrosetti, Alexander Roth, Claire Hemmaway, Peter Johnson, Kim M Linton, Tobias Pukrop, Jette Sønderskov Gørløv, Monica Balzarotti, Georg Hess, Ulrich Keller, Stephan Stilgenbauer, Jens Panse, Alessandra Tucci, Lorella Orsucci, Francesco Pisani, Alessandro Levis, Stefan W Krause, Hans J Schmoll, Bernd Hertenstein, Mathias Rummel, Jeffery Smith, Michael Pfreundschuh, Giuseppina Cabras, Francesco Angrilli, Maurilio Ponzoni, Martina Deckert, Letterio S Politi, Jürgen Finke, Michele Reni, Franco Cavalli, Emanuele Zucca, Gerald Illerhaus, for the International Extranodal Lymphoma Study Group (IELSG)

Ferreri et al, Lancet Hematology 2017

1st Randomization: Arms Activity

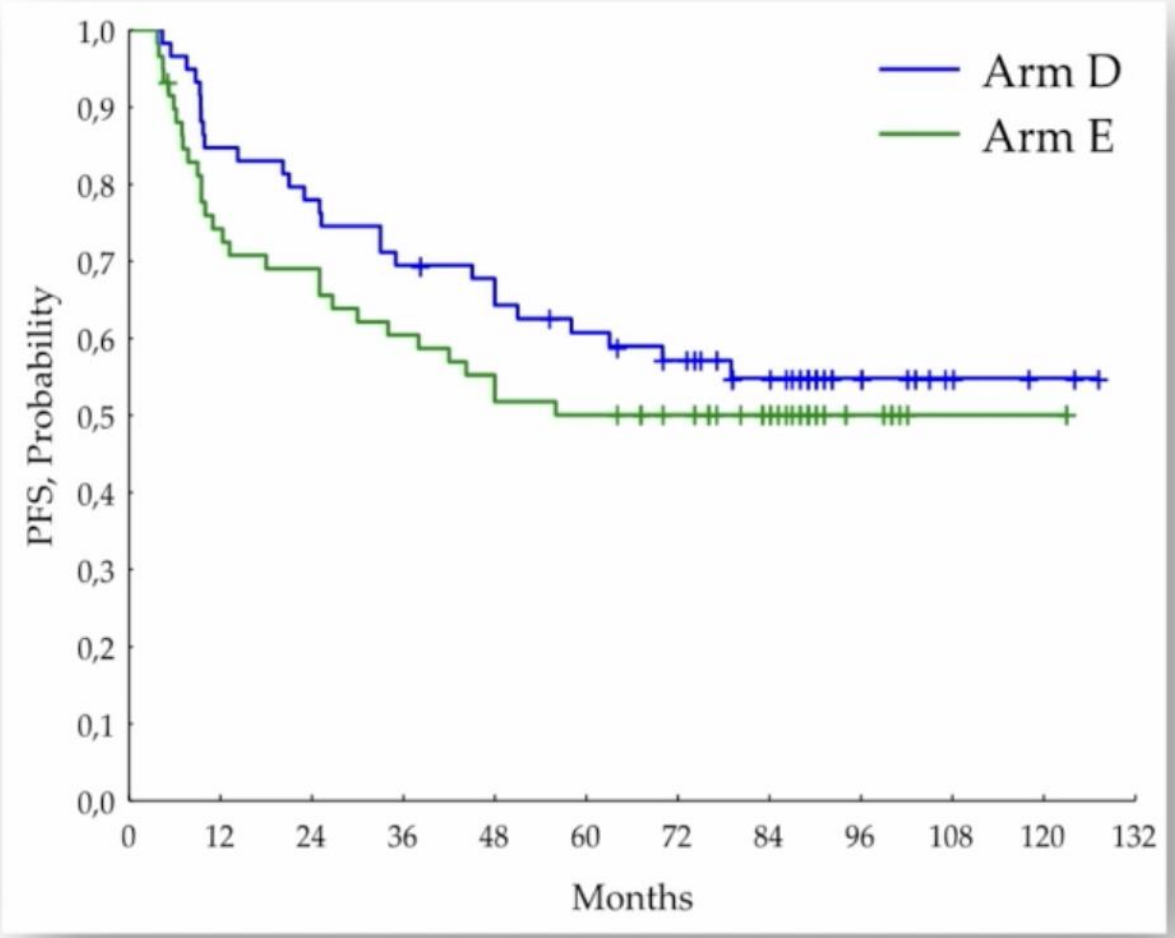




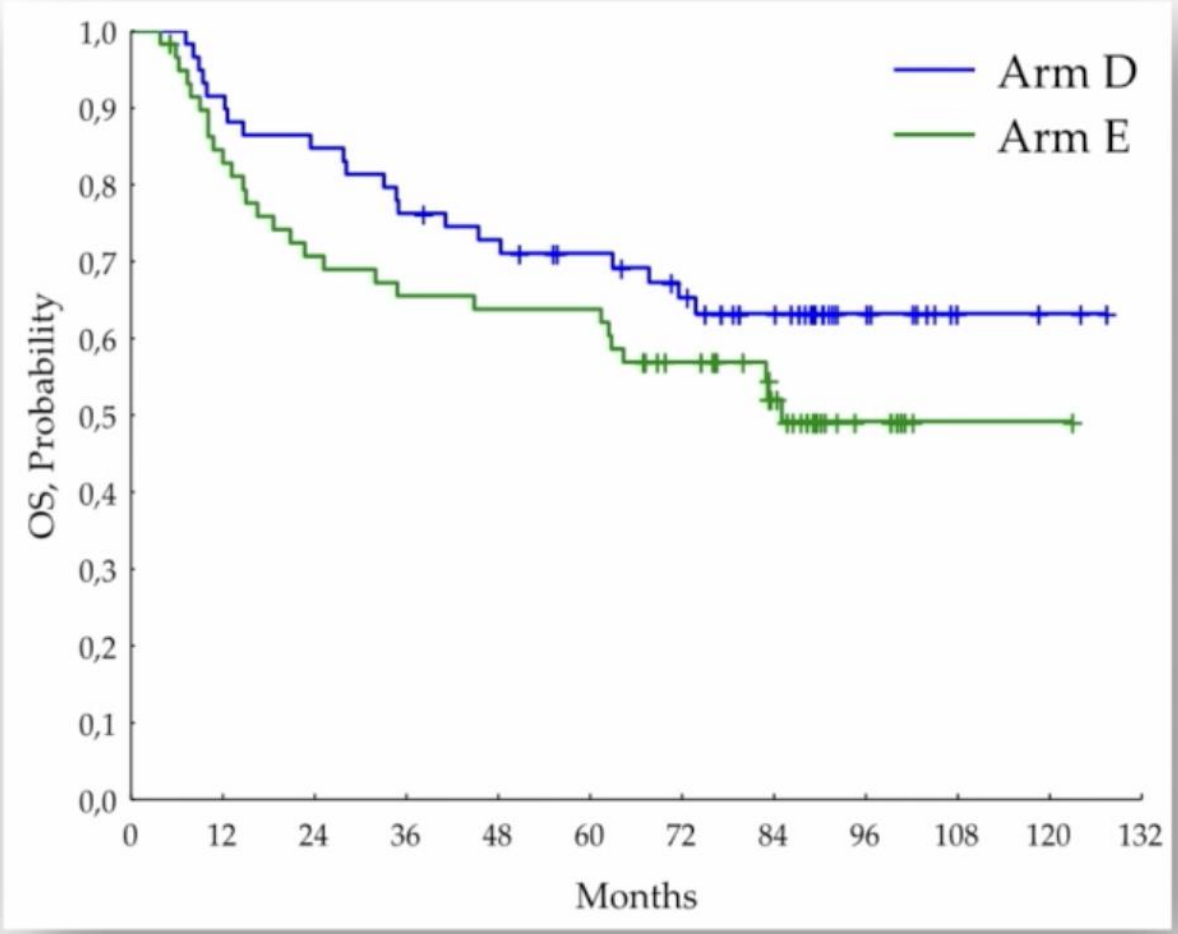
Ferreri et al, Lancet Hematology 2017

CONSOLIDATION

MEDIAN FOLLOW-UP: 88 MONTHS (IQR 77-99)

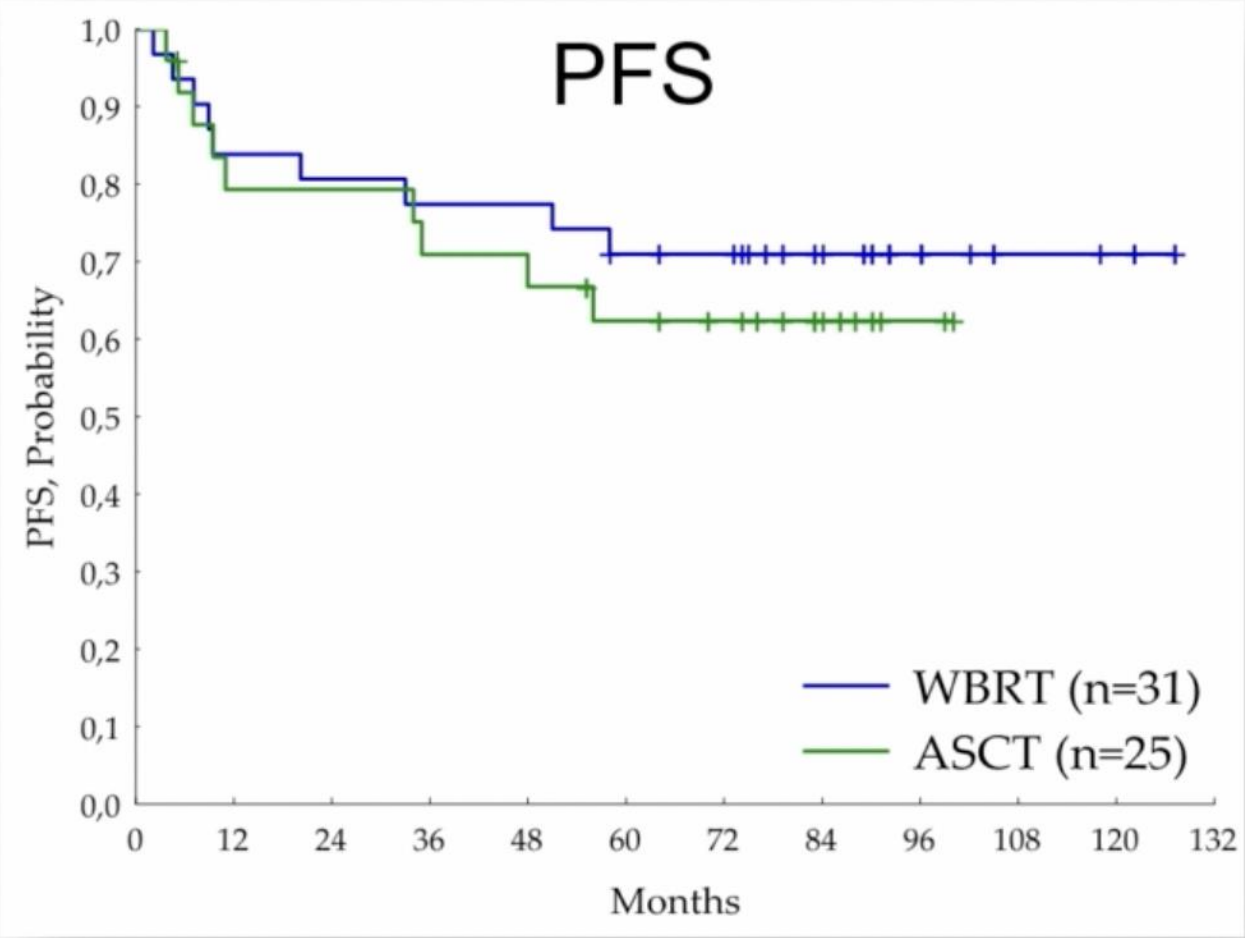


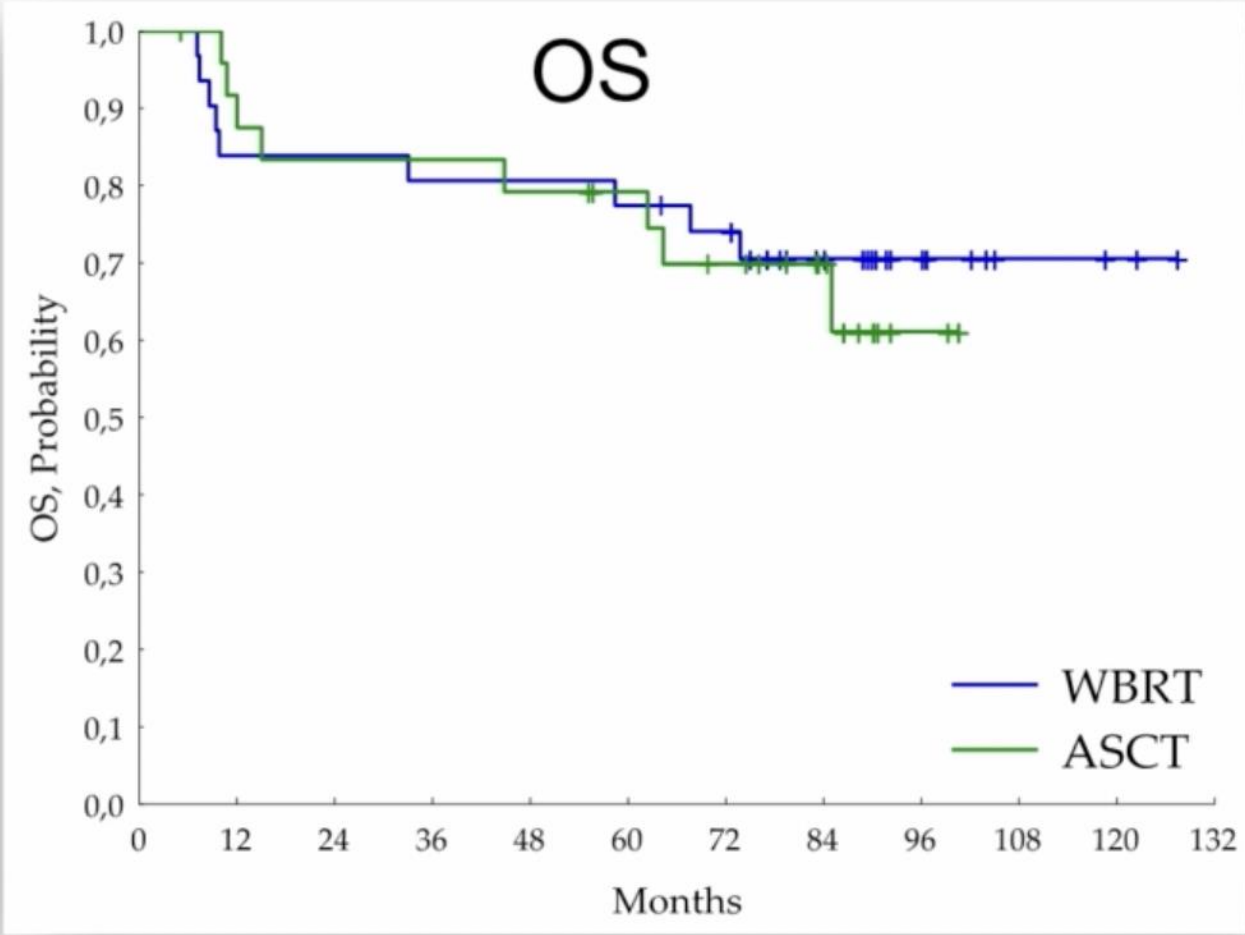
	HR	95%CI	p
D vs. E	1·15	0·78 - 1·68	0·46



	HR	95%CI	p
D vs. E	1·25	0·84 - 1·88	0·26

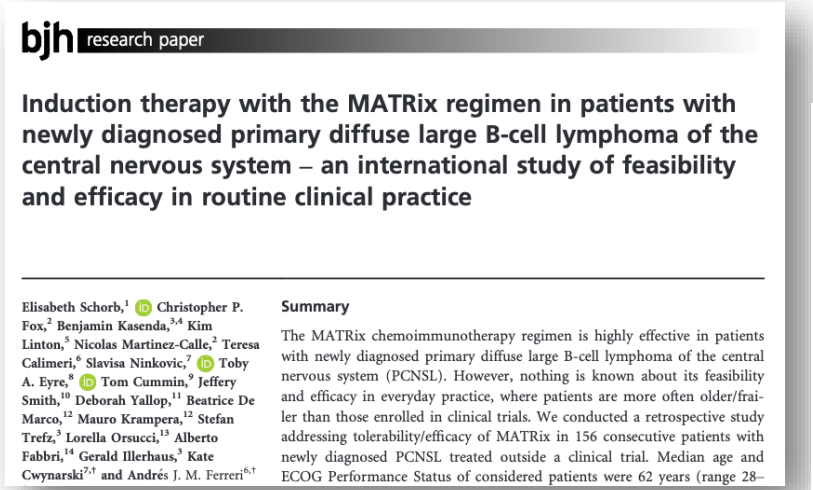
Consolidation After MATRix





Pts treated with MATRix and consolidation had a 7-yr OS of 70%, without a difference between WBRT and ASCT.

IELSG32: dose intensity of MATRIX



bjh research paper

Induction therapy with the MATRix regimen in patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system – an international study of feasibility and efficacy in routine clinical practice

Elisabeth Schorb,[1] Christopher P. Fox,[2] Benjamin Kasenda,[3,4] Kim Linton,[5] Nicolas Martinez-Calle,[2] Teresa Calimeri,[6] Slavisa Ninkovic,[7] Toby A. Eyre,[8] Tom Cummin,[9] Jeffery Smith,[10] Deborah Yallop,[11] Beatrice De Marco,[12] Mauro Krampera,[12] Stefan Trefz,[3] Lorella Orsucci,[13] Alberto Fabbri,[14] Gerald Illerhaus,[3] Kate Cwynarski[7,†] and Andrés J. M. Ferreri[6,†]

Summary

The MATRix chemoimmunotherapy regimen is highly effective in patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system (PCNSL). However, nothing is known about its feasibility and efficacy in everyday practice, where patients are more often older/frailer than those enrolled in clinical trials. We conducted a retrospective study addressing tolerability/efficacy of MATRix in 156 consecutive patients with newly diagnosed PCNSL treated outside a clinical trial. Median age and ECOG Performance Status of considered patients were 62 years (range 28–

Schorb et al, BJH, 2020

Delivery of 4 cycles in 62% of patients (3-4 in 75%)

Cycle 1	Inclusion criteria fulfilled (n = 110)	Inclusion criteria not fulfilled (n = 46)	All (n = 156)	P value
Patients with dose reduced 25% or more	28 (25·5)	35 (76·1)	63 (40·4)	0·001
Cycle 2	**Inclusion criteria fulfilled (n = 96)**	**Inclusion criteria not fulfilled (n = 40)**	**All (n = 136)**	**P value**
Patients with dose reduced 25% or more	41 (42·7)	26 (65·0)	67 (49·3)	0·02918
Cycle 3	**Inclusion criteria fulfilled (n = 88)**	**Inclusion criteria not fulfilled (n = 28)**	**All (n = 116)**	**P value**
Patients with dose reduced 25% or more	37 (42·0)	17 (60·7)	54 (46·6)	0·1317
Cycle 4	**Inclusion criteria fulfilled (n = 75)**	**Inclusion criteria not fulfilled (n = 22)**	**All (n = 97)**	**P value**
Patients with dose reduced 25% or more	34 (45·3)	14 (63·6)	48 (49·5)	0·205

Numbers are frequencies (column percentages).

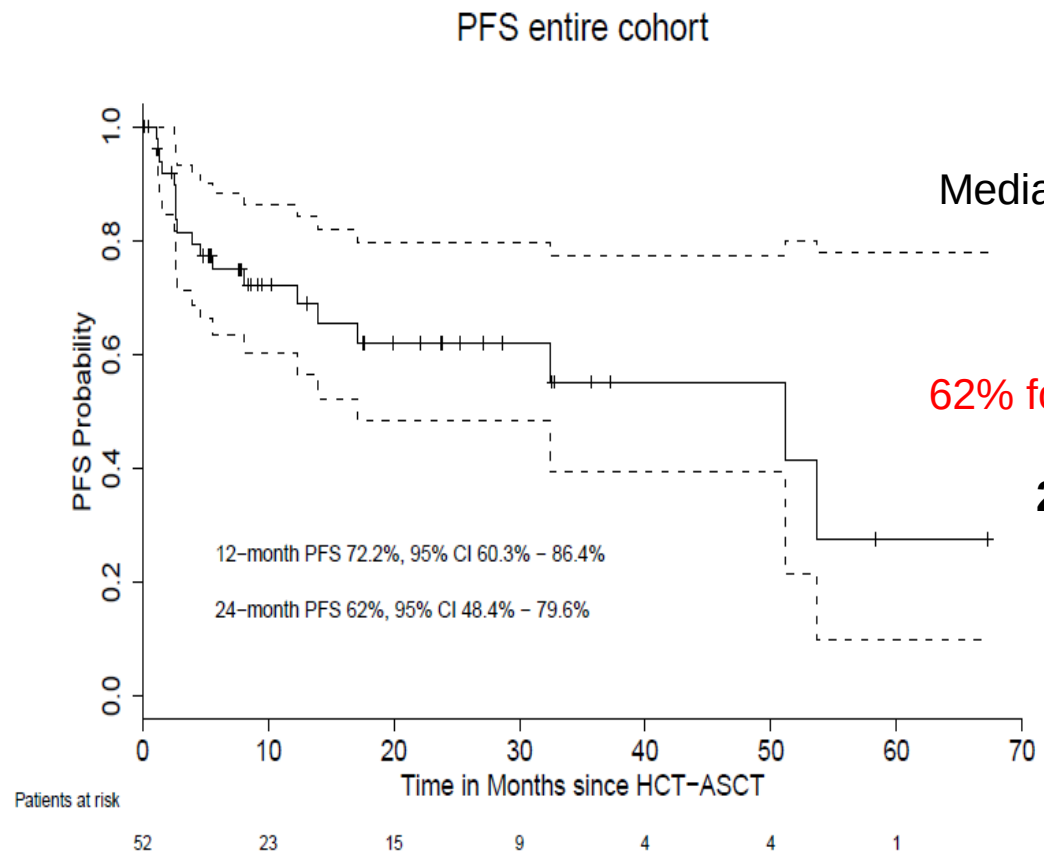
How we treat…

1) Delivery of MTX is key (Cummulative dose + schedule)
2) Biggest issue is haematological toxicity + neutropenic sepsis **(MTX not implicated)**

Dose intensity is tailored by modifying AraC doses (agent with highest Haem Tox) -> Thiotepa
Admission for neutropenic care

Age limit for HD-ASCT consolidation

IELSG32
Below 65y PS 1-3
65-70y PS1



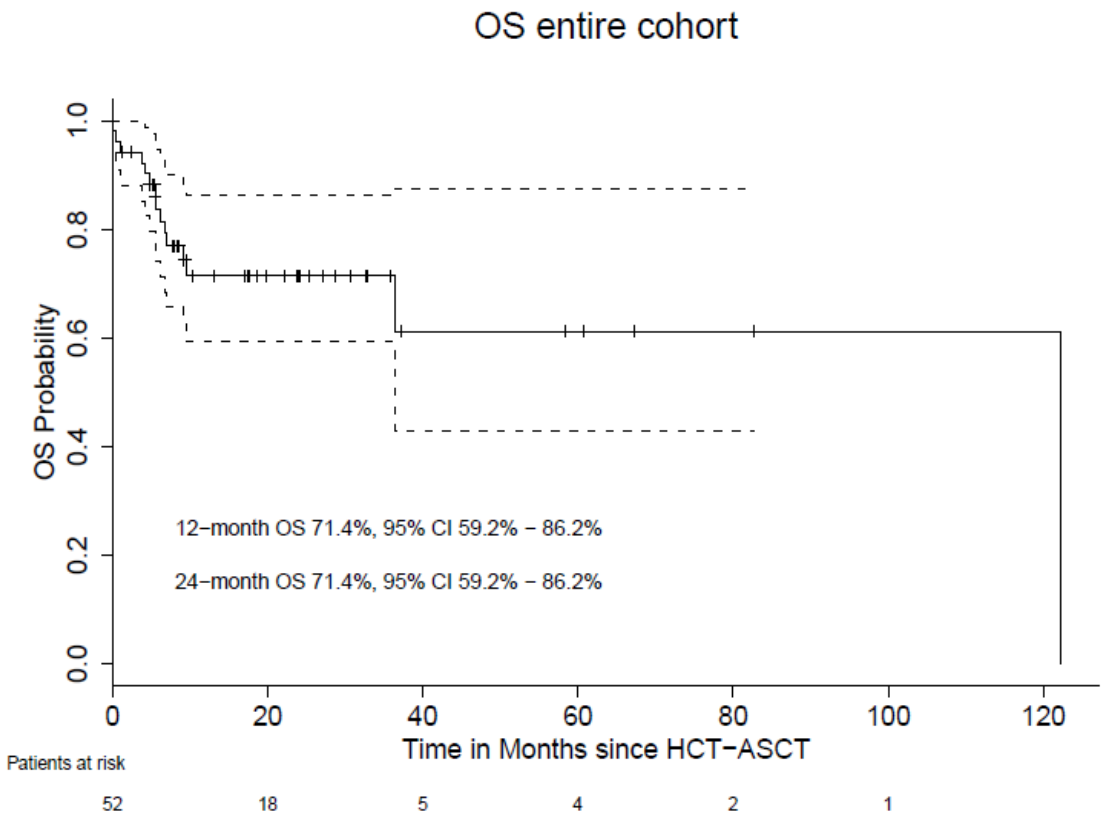
Median 69 years (65-77)

38% first-line

62% for relapsed disease

2 yr PFS 62%

TRM 3.8%

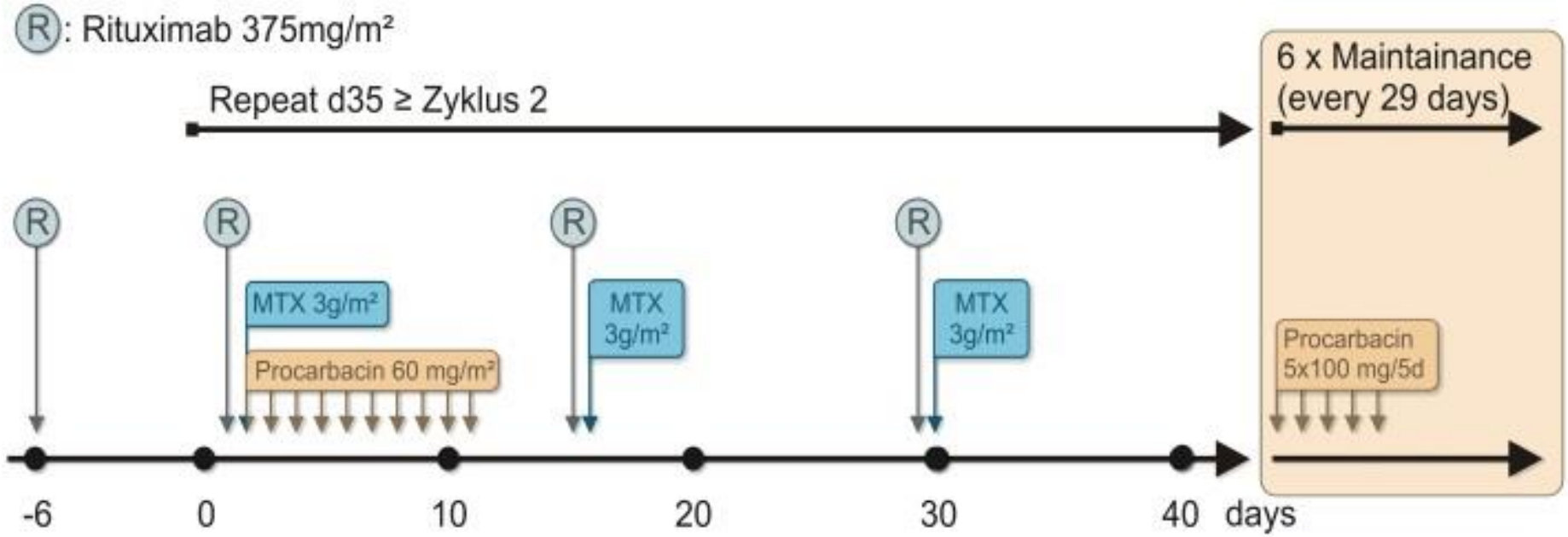


Schorb E, Fox CP *et al* BMT 2017

Older patients with PCNSL (non ASCT candidates)

German PRIMAIN protocol (older, HDT-ineligible patients)

From Gerard Illerhaus

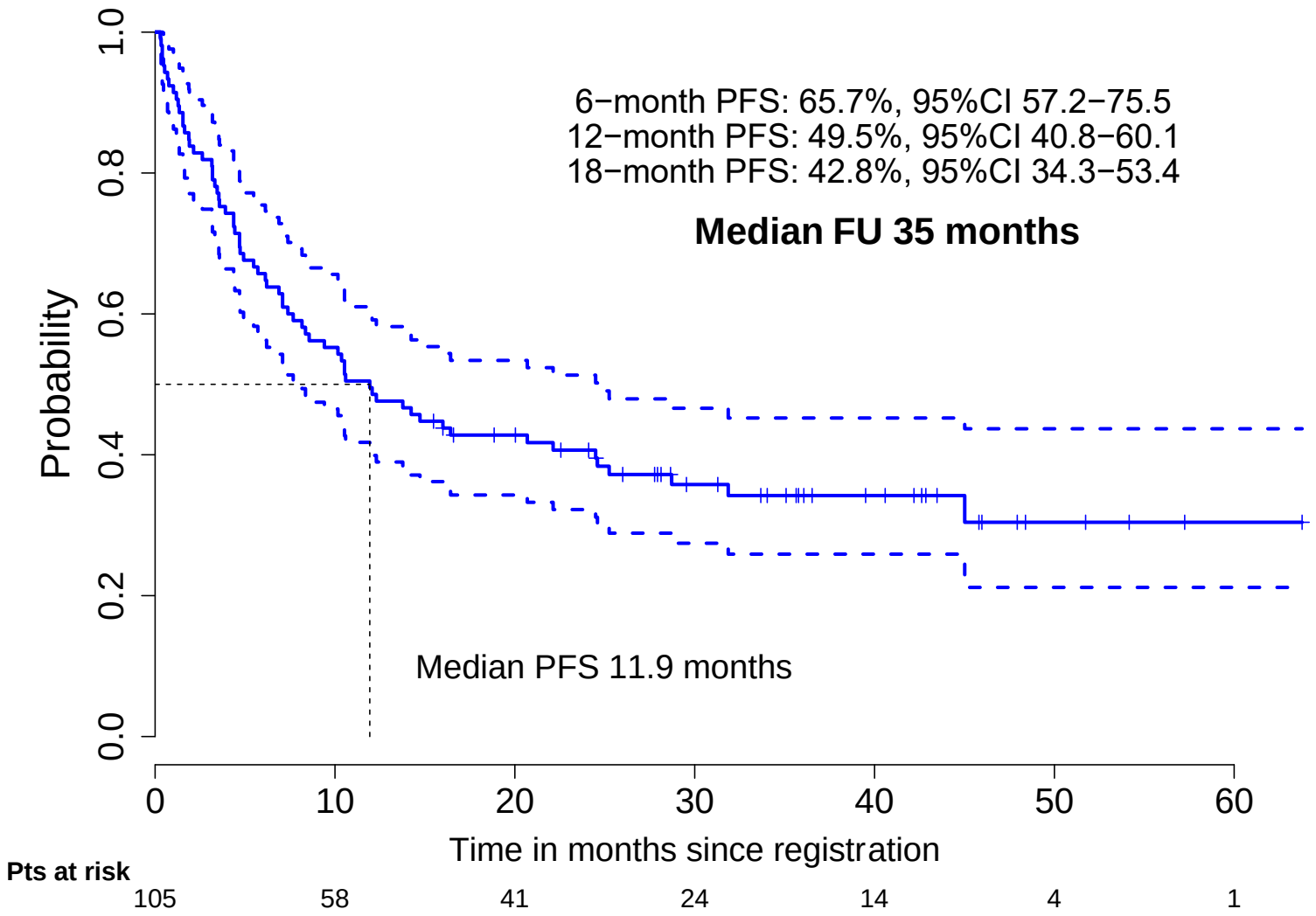


Median age 75yrs (65-83)

Cooperative Study Group
CNS-Lymphoma

Klinikum Stuttgart

German PRIMAIN protocol (older, HDT-ineligible patients)



Fritsch K *et al* Leukemia 2011

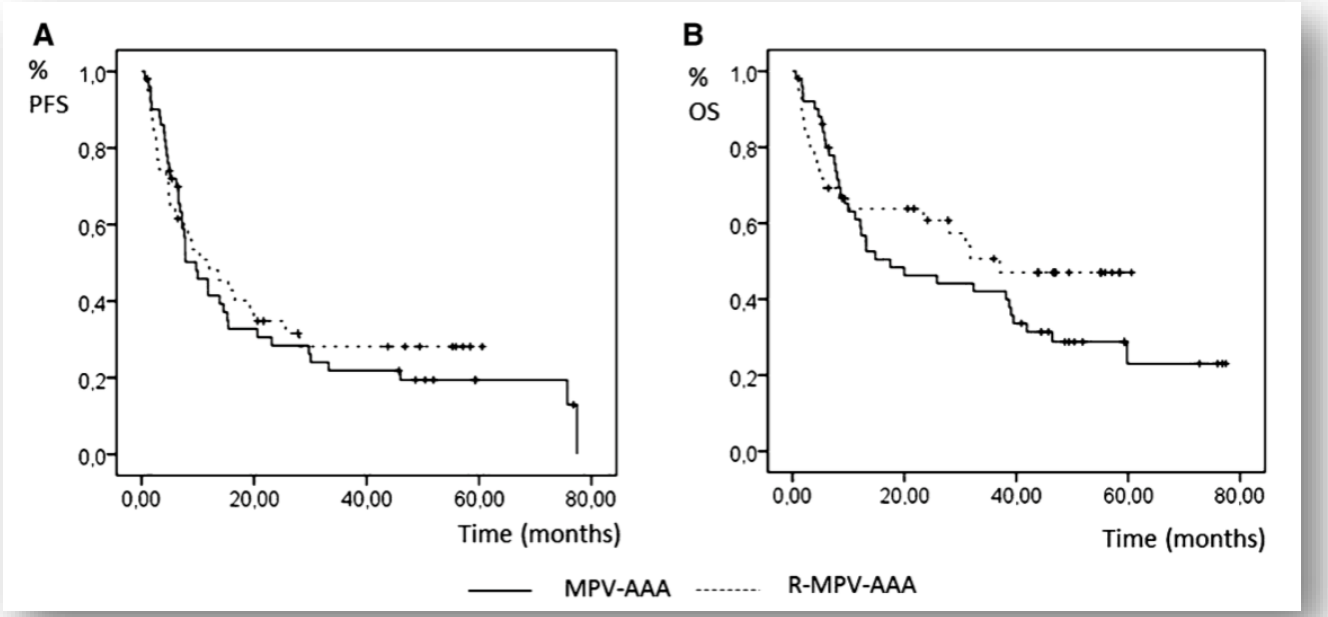
MVP-A

Houillier et al, Neuro Oncology, 2017

MVP x3 -> AraC x3

Pts Above 60y

Median age 68
CR rate 55%
40% discontinued (PD or death)
Median PFS 10m, 4-yr PFS 22%

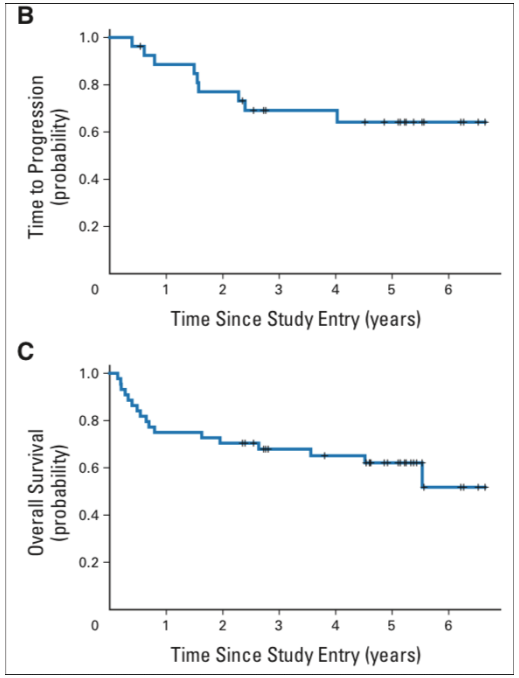


MTR

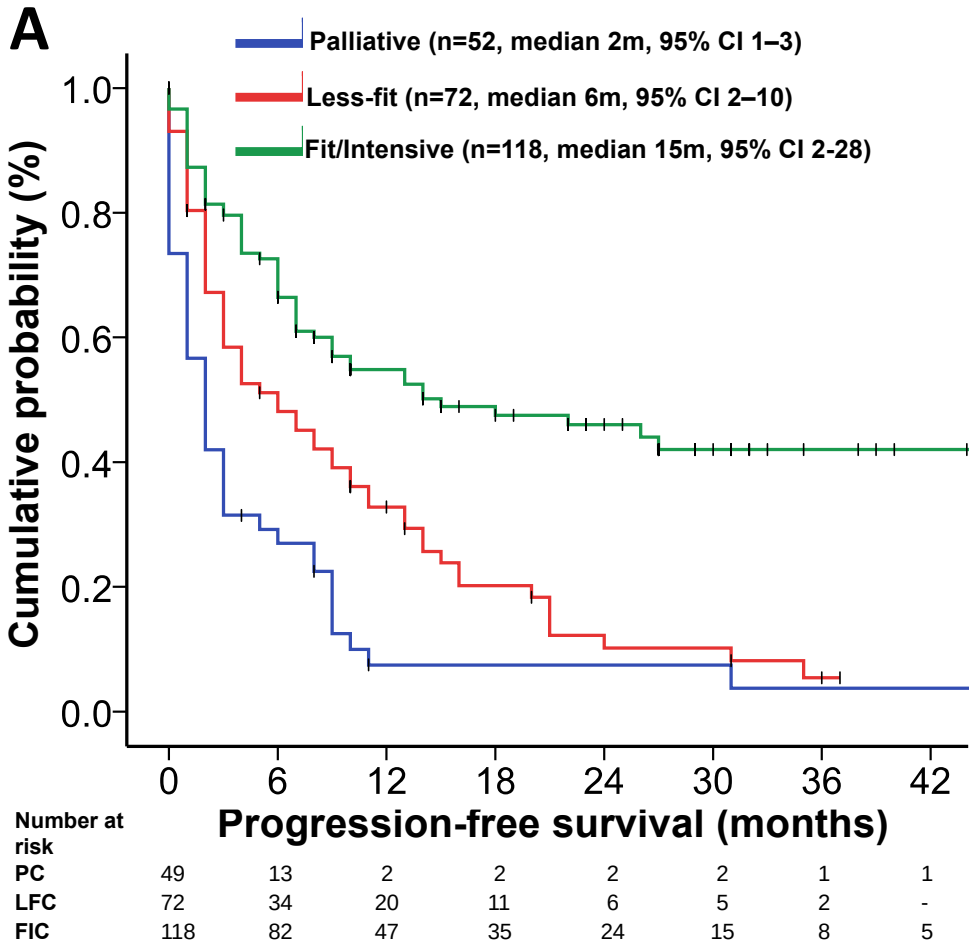
R + MTX 8gr/m2 x7 -> Etoposide/AraC

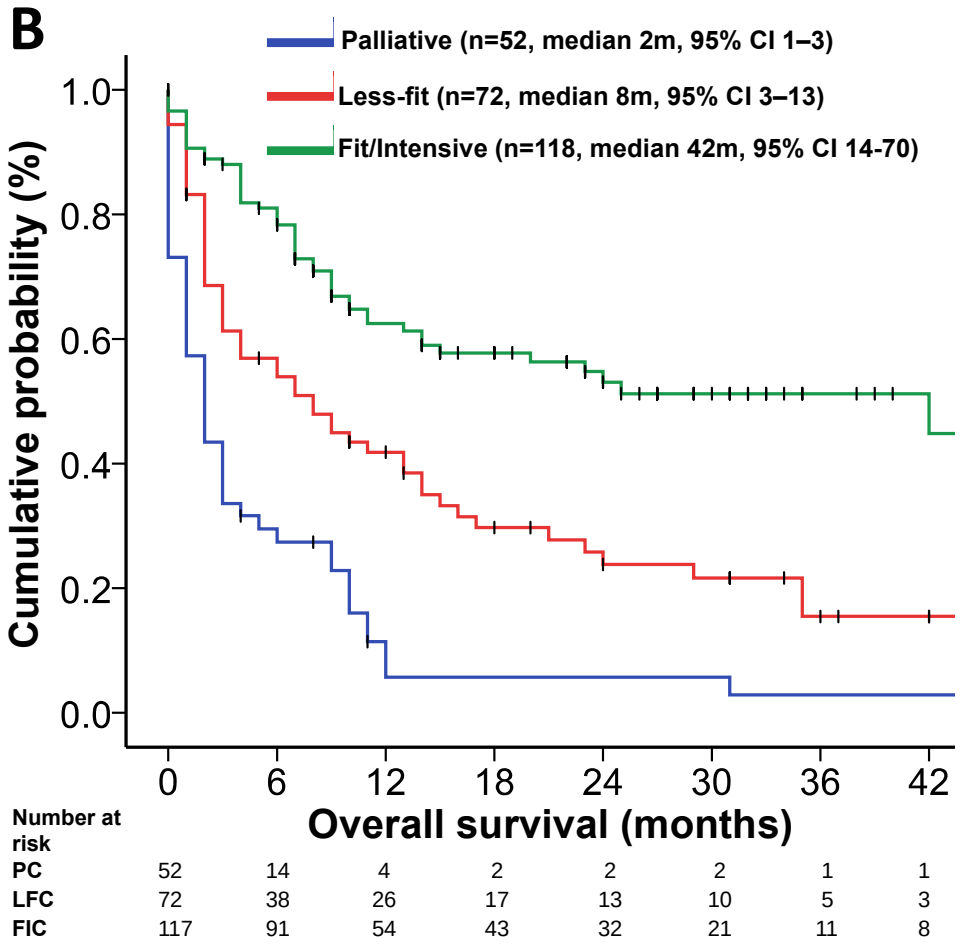
Any age
PS 1-2

Median Age 61, Max 76
CR rate (66% CR after MTR, 55%
20% discontinued PD
Median PFS 2.4Yr , 2-yr 57%



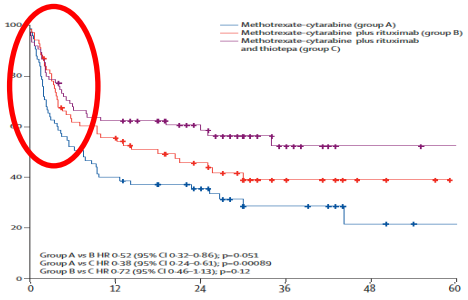
UK real-world study >65 years PCNSL





Martinez-Calle et al – BJHaem 2020

Early treatment failure despite modern intensive PCNSL therapy



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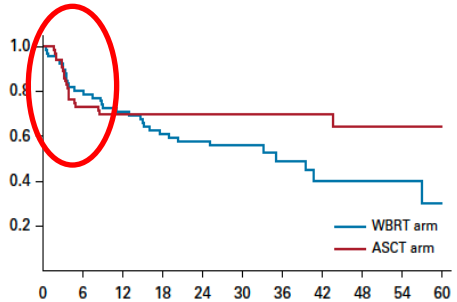
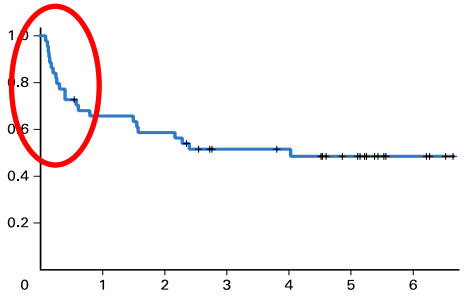
Ferreri et al Lancet Haematology 2016



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]; Mounia Laadhari, MD[5]; Olivier Chinot, MD, PhD[6]; Cecile Molucon-Chabrot, MD[6]; Pierre Soubeyran, MD, PhD[7]; Remy Gressin, MD[8]; Sylvain Choquet, MD[9]; Gandhi Damaj, MD, PhD[10]; Antoine Thyss, MD[10]; Julie Abraham, MD[11]; Vincent Delwail, MD[12]; Emmanuel Gyan, MD, PhD[13]; Laurence Sanhes, MD[14]; Jérôme Cornillon, MD, PhD[15]; Reda Garsi, MD[16]; Alain Delmer, MD, PhD[17]; Marie-Laure Tanguy, PharmD[18]; Ahmad Al Jijakli, MD[19]; Pierre Morel, MD[20]; Pascal Bourguard, MD[20]; Marie-Pierre Moles, MD[21]; Adrien Chauchet, MD[22]; Thomas Gastinne, MD[23]; Jean-Marc Cavaliere, MD, PhD[24]; Adriana Langer, MD[1]; Antoine Martin, MD, PhD[25]; Patricia Moisson, MD[1]; Lucette Lacombrez, PhD[1]; Nadine Martin-Duverneuil, MD[2]; Daniel Delgadille, PhD[1]; Isabelle Turbiez, HDR[1]; Loic Feuvret, MD[1]; Nathalie Cassoux, MD, PhD[3]; Valérie Touitou, MD, PhD[3]; Damien Ricard, MD, PhD[26]; Khê Hoang-Xuan, MD, PhD[2]; and Carole Soussain, MD, PhD[2] on behalf of the Integroupe GOELAMS–ANOCEF and the LOC Network for CNS Lymphoma

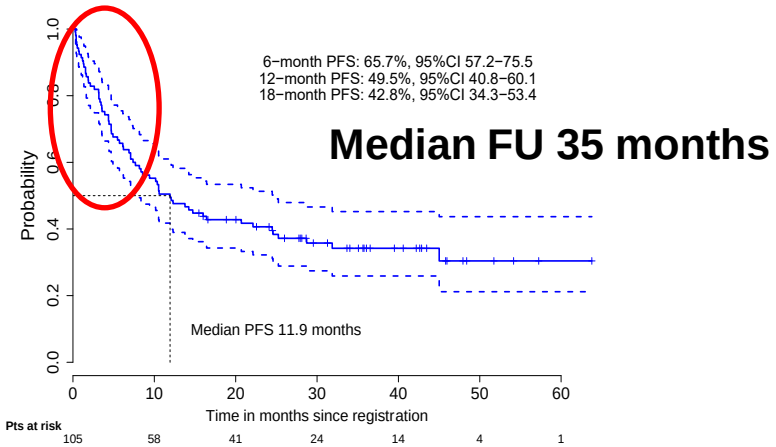
Hoillier et al JCO 2019



Intensive Chemotherapy and Immunotherapy in Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202)

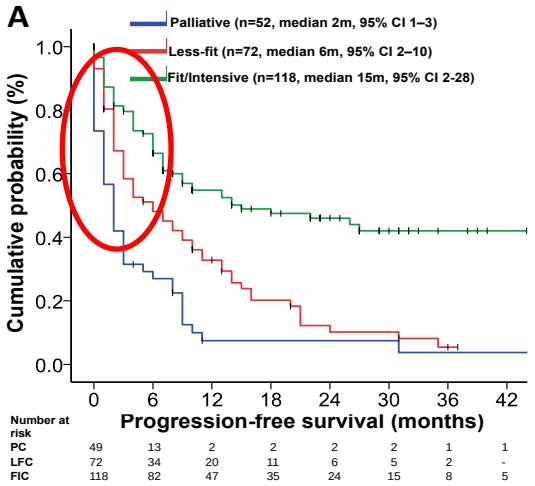
James L. Rubenstein, Eric D. Hsi, Jeffrey L. Johnson, Sin-Ho Jung, Megan O. Nakashima, Barbara Grant, Bruce D. Cheson, and Lawrence D. Kaplan

Rubenstein et al JCO 2013



Median FU 35 months

Fritsch K *et al* Leukemia 2011



Martinez-Calle et al – BJHaem 2020

Early progression/toxicity remains the biggest unmet need

Early treatment failure despite modern intensive PCNSL therapy

The majority (70%) of deaths in IELSG32 (≡ other PCNSL studies) were due to lymphoma

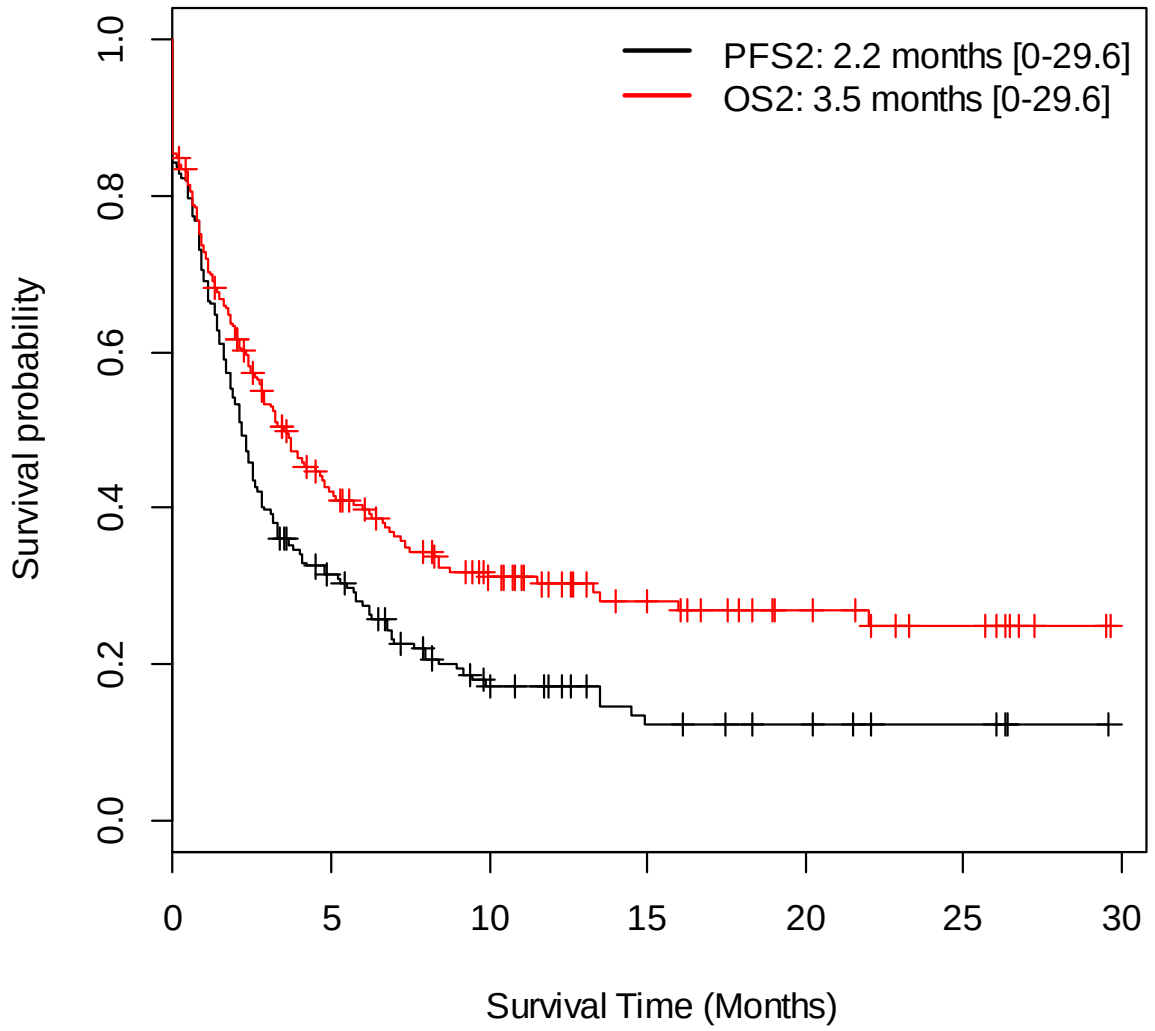
1. Failure of remission induction

- High ORR with MATRix, yet significant rates of early treatment failure
- 62% of MATRix arm proceeded to consolidation
  - TRM and lymphoma progression
  - Outcomes may vary according to clinician/centre experience

2. Early relapses after consolidation

- ~20% of patients
- Difficult to predict -> Advanced MR techniques
- Achieving a second durable remission very challenging
- Consolidation questions being investigated in two active RCTs
  - MATRix/IELSG43 and Alliance NCT01511562

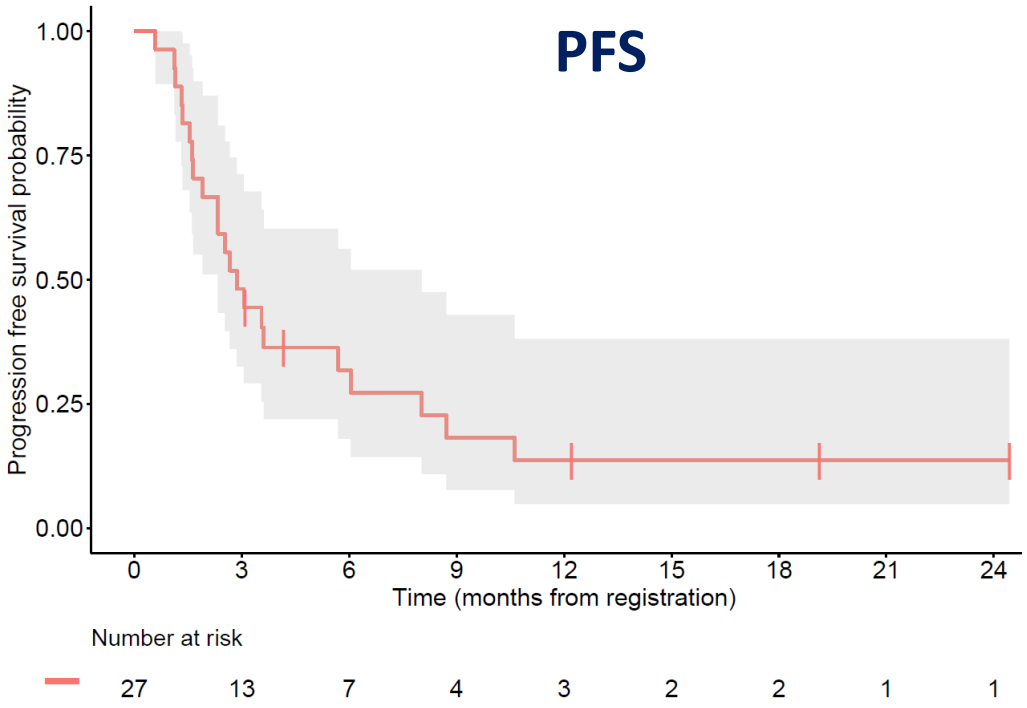
Relapsed & refractory PCNSL – French population-based data

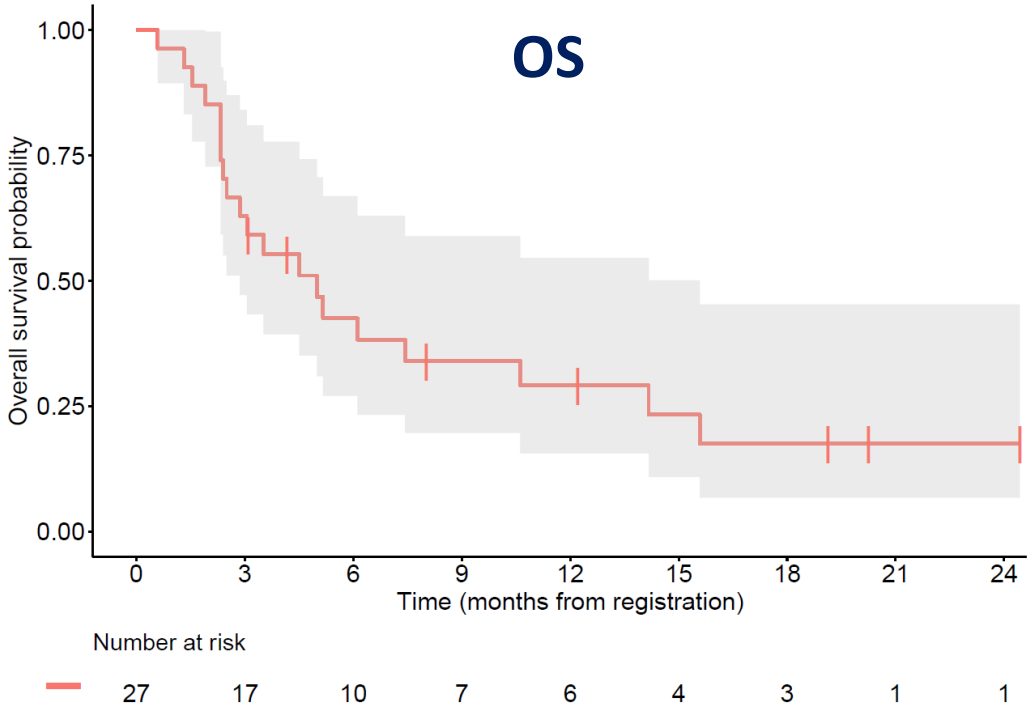


Langner-Lemercier et al NeuroOncology 2017

TIER phase I/II study for r/r PCNSL

- Median PFS = 2.9 months (95% CI 2.34, 8.02)
- Median OS = 5 month (95% CI 2.86, 15.58)





UNIVERSITY OF BIRMINGHAM
@CRCTU Cancer Research UK Clinical Trials Unit
TAP Bloodwise Beating blood cancer since 1960

Fox *et al* Blood Advances 2021

New agents in development for PCNSL

- **BTK inhibitors**
  - MYD88 and CD79 mutations very common in PCNSL
  - Ibrutinib crosses BBB in meaningful concentrations
  - High responses to ibrutinib but short PFS

- **IMIDs/PPMs**
  - Evidence of Lenalidomide activity in PCNSL in early phase studies
    - Parenchymal and CSF responses
  - T cell compartment (CD4: CD8 ratio) may be important
  - Role in the maintenance setting under evaluation in older patients

- **Checkpoint inhibition**
  - PD1 disruption common in PCNSL (copy number gain or rearrangement)
  - (very) preliminary evidence of clinical activity with Nivolumab
  - Global phase 2 trial results awaited..

CNS Prophylaxis for High-grade B-NHL

The matter of CNS prophylaxis in DLBCL

An estimated risk 3-4% of CNS relapse is generally accepted for DLBCL across all risk groups.

- 9-10% for High-risk group (CNS-IPI 4-6), 15%-18% for CNS-IPI 5-6 + high-risk sites included

Variable practice: Use of HD-MTX +/- IT MTX **(Health care resources)**

Retrospective data has set **doubts on HD-MTX efficacy**

Risk stratification is far from ideal (CNS-IPI, Schmitz et al)

- Not on rituximab and PET era
- Selection bias: True denominator of high-risk patients remains unknown

The matter of CNS prophylaxis

Imperfect risk stratification

CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP

Norbert Schmitz, Samira Zeynalova, Maike Nickelsen, Roopesh Kansara, Diego Villa, Laurie H. Sehn, Bertram Glass, David W. Scott, Randy D. Gascoyne, Joseph M. Connors, Marita Ziepert, Michael Pfreundschuh, Markus Loeffler, and Kerry J. Savage

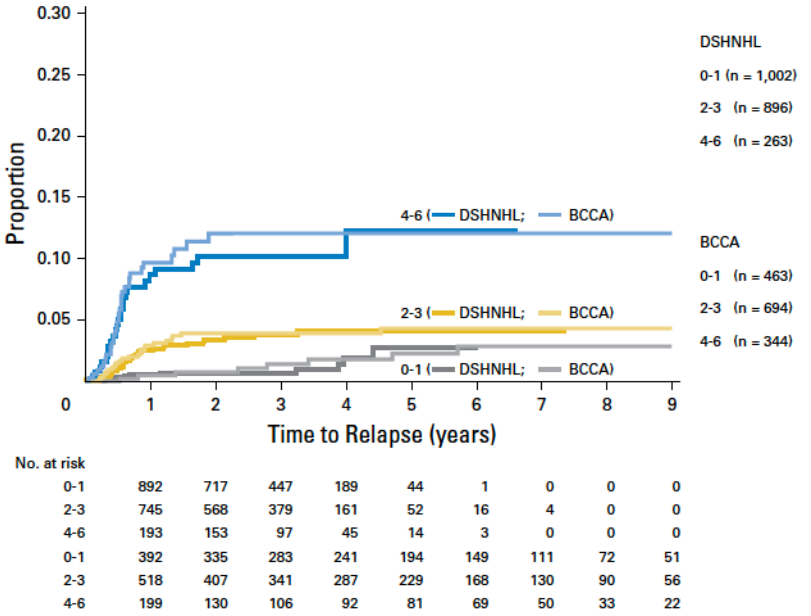
J Clin Oncol 34:3150-3156. © 2016 by American Society of Clinical Oncology

~1 in 5 patients fall into the high-risk group by CNS-IPI.
***CT staging: NB* EN sites & renal/adrenal underestimated**

Table 1. Major Clinical Characteristics of Patients Representing the Training Set (German High-Grade Non-Hodgkin Lymphoma Study Trial) and the Validation Set (British Columbia Cancer Agency)

Cohort Characteristic	DSHNHL/MInT, n = 2,164 (%)	BCCA, n = 1,597 (%)
Age, years, median (range)	58 (18-80)	65 (16-94)
Age > 60 years	974 (45)	1,035 (65)
Male	1,244 (58)	915 (57)
LDH > normal*	1,147 (53)	737 (49)
ECOG PS > 1	247 (11)	584 (37)
Stage III/IV disease	1,148 (53)	916 (57)
Extranodal site > 1	479 (22)	396 (25)
Bulky disease, > 7 cm*	1,027 (48)	636 (41)
Kidney/adrenal glands	90 (4)	56 (4)
IPI score*		
0, 1	1,009 (47)	463 (31)
2	523 (24)	359 (23)
3	398 (18)	350 (23)
4, 5	231 (11)	329 (22)

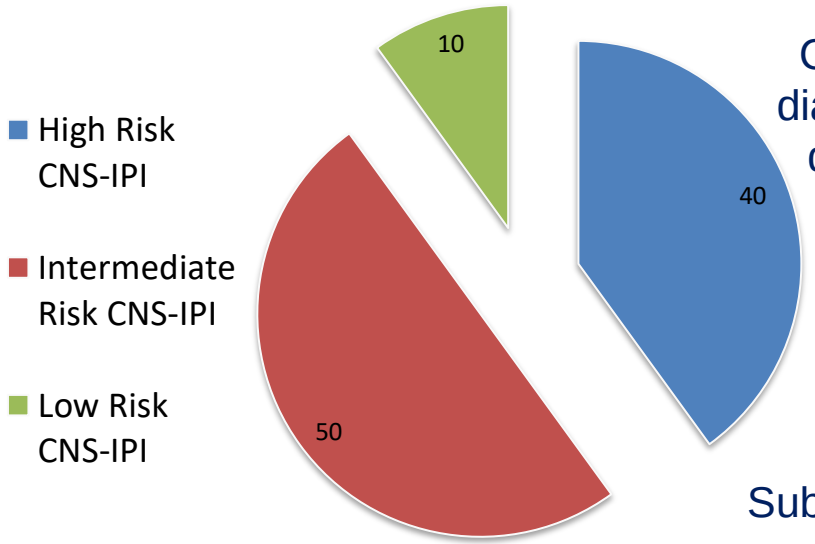
CNS-IPI score 4-6	263 (12.3%)	344 (23%)
CNS-IPI score 5-6	75 (3.4%)	



The matter of CNS prophylaxis

Imperfect risk stratification

Patients destined to CNS relapse

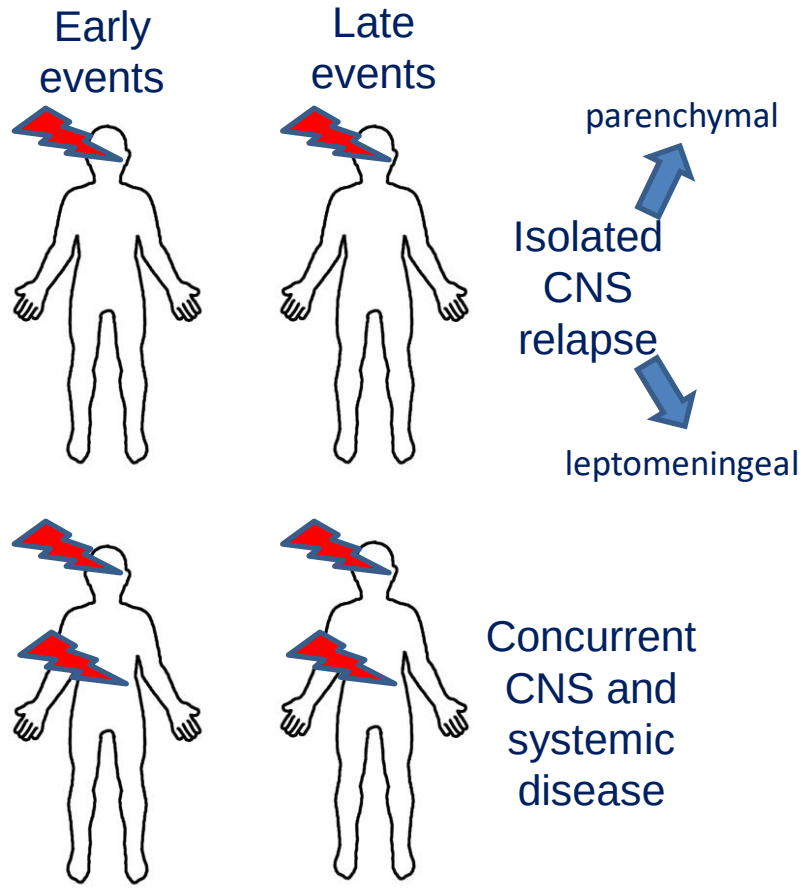


CNS seeded at diagnosis or early during therapy

Driver or acquired mutations?

Disease Burden

Sub-clones destined or selected to invade CNS at relapse



The matter of CNS prophylaxis

10000 DLBCL patients (1100 High-risk)

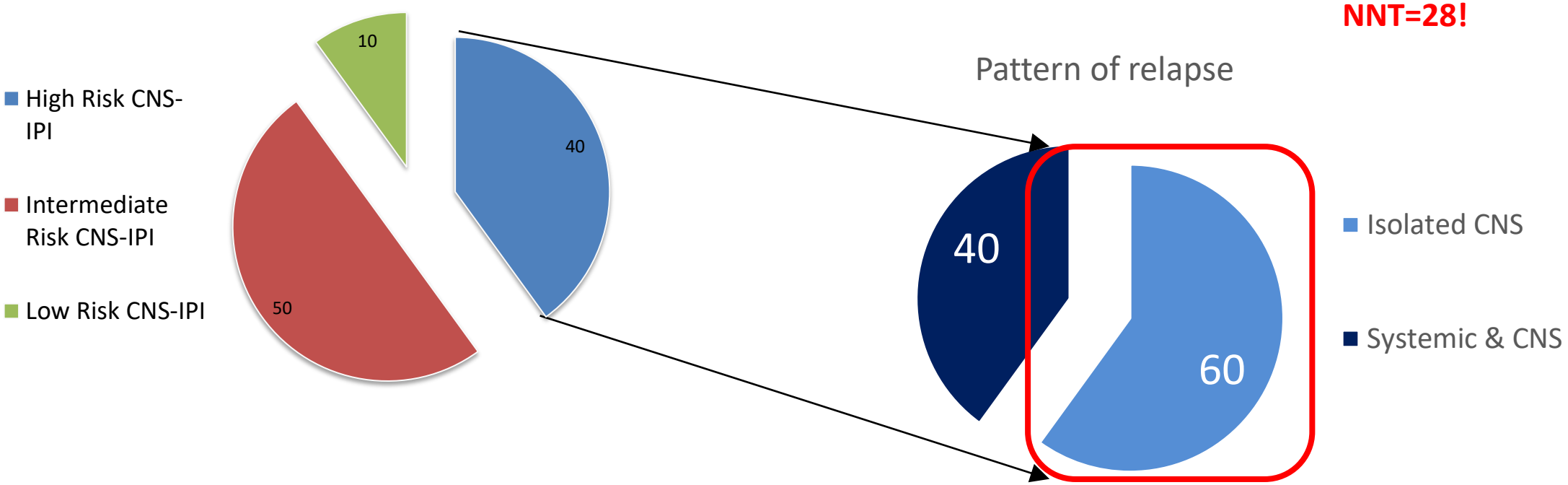
300 CNS relapse events
(120 High-risk, 150 Int-risk, 30 Low-risk)

↓

72 Isolated CNS relapses (7% of High-risk)

NNT=28!

Patients destined to CNS relapse

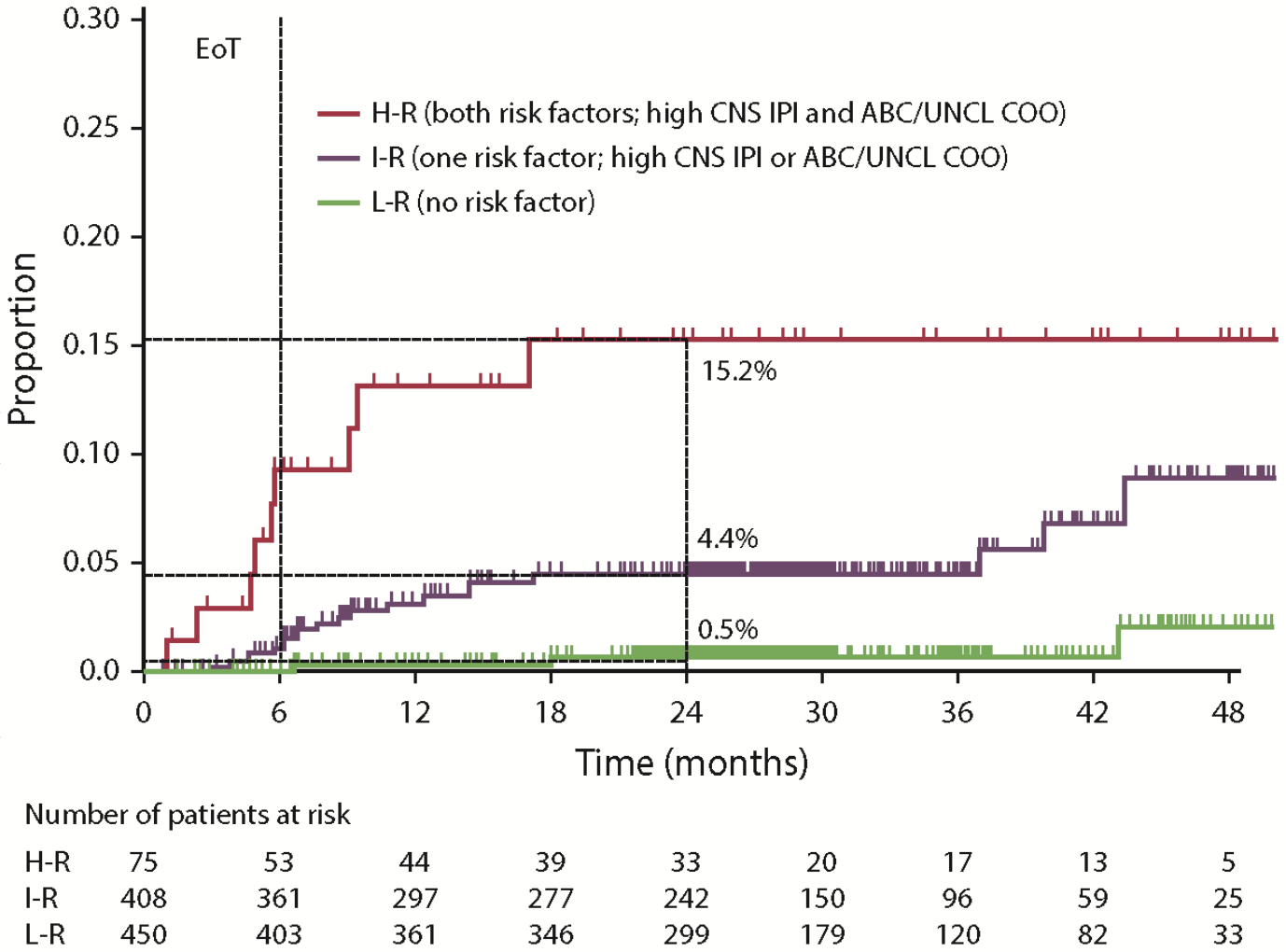


Number of relapses higher in Intermediate-risk group -> No prophylaxis
PPV of High-Risk CNS-IPI is 7% for parenchymal relapse -> NNT
No studies segregate by systemic/isolated CNS relapse

Can CNS-IPI be improved?

Table 4. Results of multivariate Cox regression analysis on factors associated with CNS relapse in the COO and BCL2/MYC dual-expression status-available population (n = 688), CNS relapses (n = 22)

Factor	HR*	95% CI	*P* value
CNS-IPI intermediate (*v* low)	0.75	0.23□2.45	.6378
CNS-IPI high (*v* low)	2.76	0.81□9.42	.1042
ABC COO (*v* GCB)	**4.78**	**1.49□15.29**	**.0084**
Unclassified COO (*v* GCB)	**4.24**	**1.32□13.61**	**.0151**
BCL2/MYC dual expresser (*v* non-dual expresser)	0.83	0.34□2.06	.6931

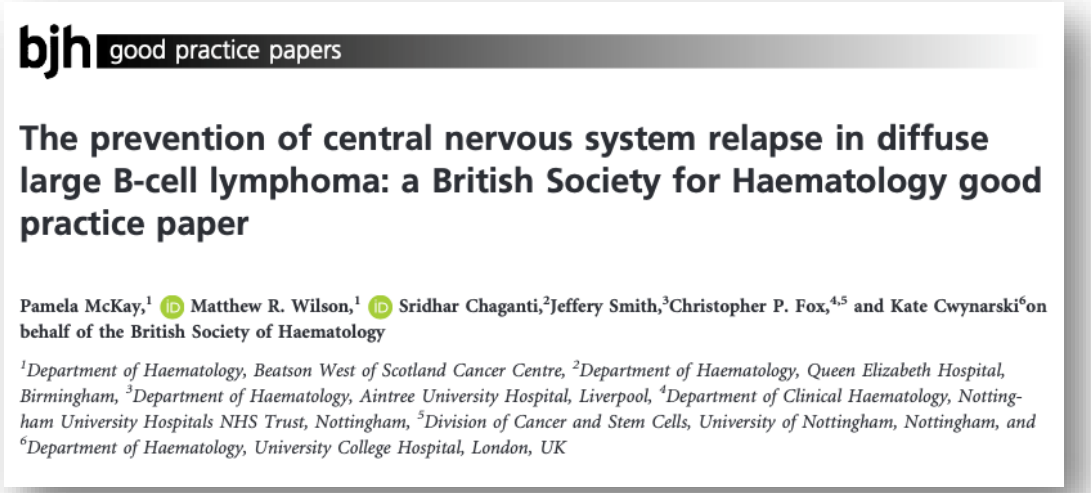


Klanova *et al*, Blood 2019 Fox CP Blood 2019

How to give CNS prophylaxis

HD-MTX

- At least 2 doses of HD-MTX (3gr/m2 or above)
- Rapid infusion MTX 2-4h

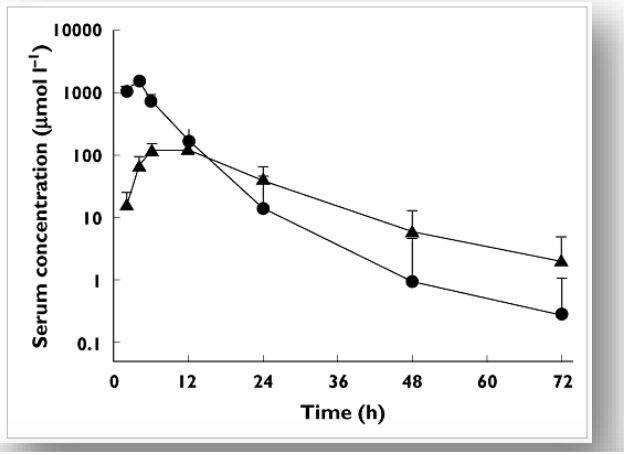


bjh good practice papers

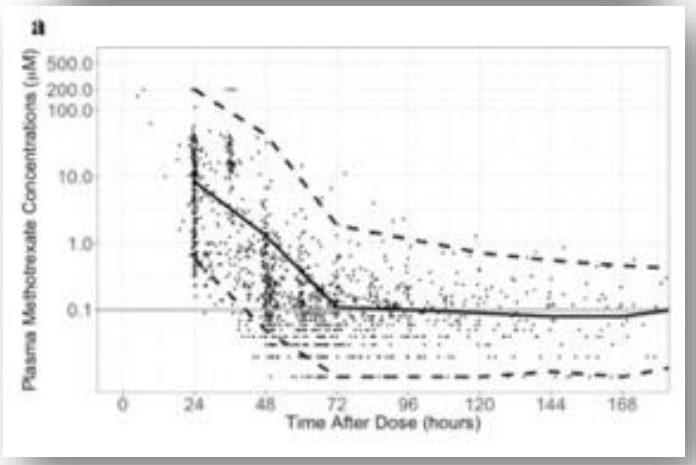
The prevention of central nervous system relapse in diffuse large B-cell lymphoma: a British Society for Haematology good practice paper

Pamela McKay,[1] Matthew R. Wilson,[1] Sridhar Chaganti,[2] Jeffery Smith,[3] Christopher P. Fox,[4,5] and Kate Cwynarski[6] on behalf of the British Society of Haematology

[1]Department of Haematology, Beatson West of Scotland Cancer Centre, [2]Department of Haematology, Queen Elizabeth Hospital, Birmingham, [3]Department of Haematology, Aintree University Hospital, Liverpool, [4]Department of Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, [5]Division of Cancer and Stem Cells, University of Nottingham, Nottingham, and [6]Department of Haematology, University College Hospital, London, UK



Rapid Infusion

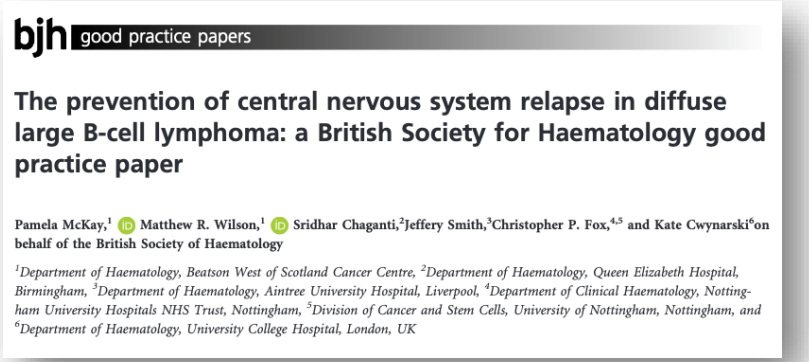


24-h infusion

Holmboe *et al*, BJCP, 2011

Kawatkatsu et al, Canc Chemother Pharmacol, 2019

How to give CNS prophylaxis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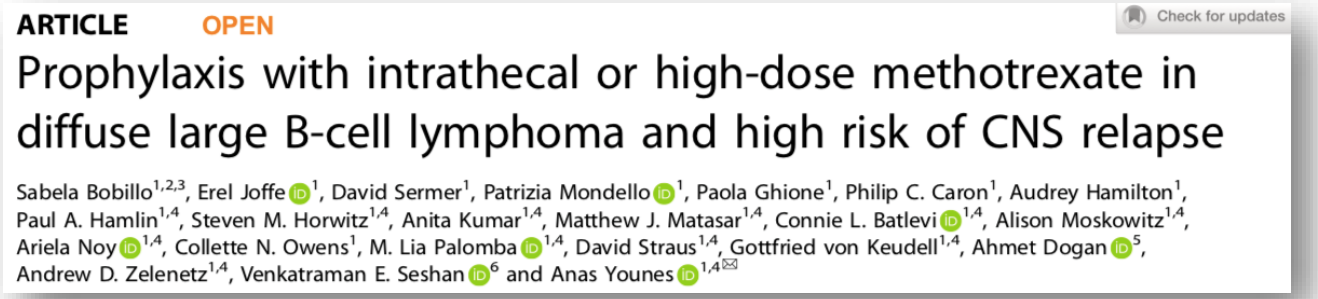
Intrathecal chemotherapy


ARTICLE OPEN

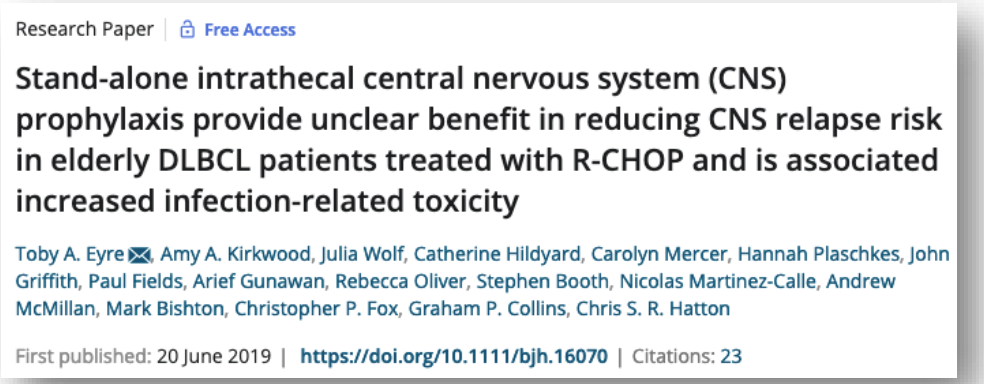
Check for updates

Prophylaxis with intrathecal or high-dose methotrexate in diffuse large B-cell lymphoma and high risk of CNS relapse

Sabela Bobillo[1,2,3], Erel Joffe[1], David Sermer[1], Patrizia Mondello[1], Paola Ghione[1], Philip C. Caron[1], Audrey Hamilton[1], Paul A. Hamlin[1,4], Steven M. Horwitz[1,4], Anita Kumar[1,4], Matthew J. Matasar[1,4], Connie L. Batlevi[1,4], Alison Moskowitz[1,4], Ariela Noy[1,4], Collette N. Owens[1], M. Lia Palomba[1,4], David Straus[1,4], Gottfried von Keudell[1,4], Ahmet Dogan[5], Andrew D. Zelenetz[1,4], Venkatraman E. Seshan[6] and Anas Younes[1,4]✉

N=2002 (585 High Risk)

N	CNS events (5y)
290/50% (No prophylaxis)	7.1%
253/43% (IT prophylaxis)	5.6%
42/7% (HD-MTX)	5.2%


Research Paper | Free Access

Stand-alone intrathecal central nervous system (CNS) prophylaxis provide unclear benefit in reducing CNS relapse risk in elderly DLBCL patients treated with R-CHOP and is associated increased infection-related toxicity

Toby A. Eyre✉, Amy A. Kirkwood, Julia Wolf, Catherine Hildyard, Carolyn Mercer, Hannah Plaschkes, John Griffith, Paul Fields, Arief Gunawan, Rebecca Oliver, Stephen Booth, Nicolas Martinez-Calle, Andrew McMillan, Mark Bishton, Christopher P. Fox, Graham P. Collins, Chris S. R. Hatton

First published: 20 June 2019 | https://doi.org/10.1111/bjh.16070 | Citations: 23

N	CNS events (5y)
559/81% (No prophylaxis)	2.7%
99/14% (IT prophylaxis)	5.5%
31/4.4% (HD-MTX)	3.9%

N=690 (277 High Risk)

***aHR for IT prophylaxis: 1.34 (0.8 – 5.5)**

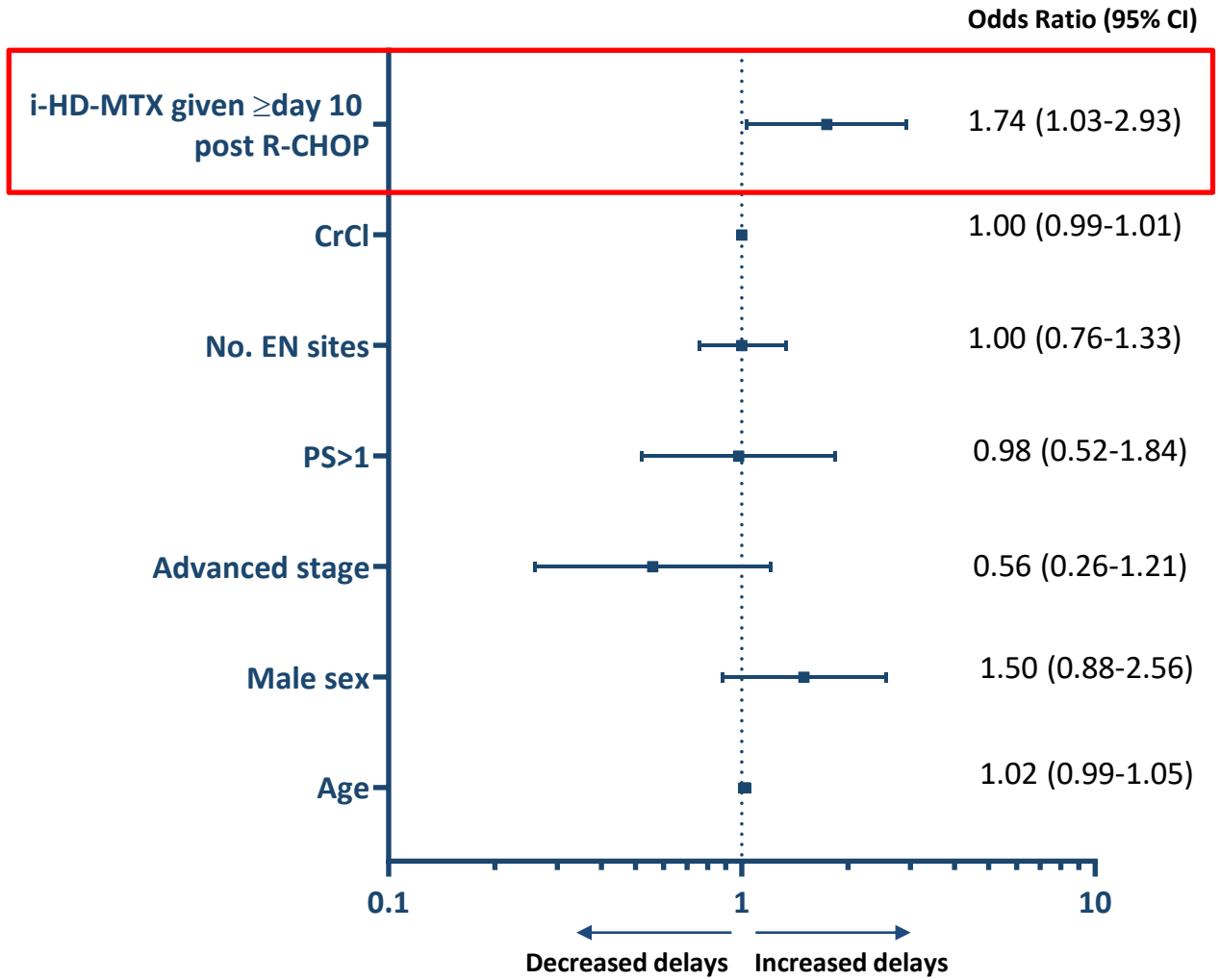
When to give HD-MTX prophylaxis

N=1324

409 Cycles HD-MTX intercalated with R-CHOP

82 (20%) associated with delay in next R-CHOP
Median delay 7 days (range 2-150)

56 (14%) delays directly attributed to MTX (clinician judgement)



Multivariable analysis: factors influencing delay of R-CHOP after intercalated HD-MTX

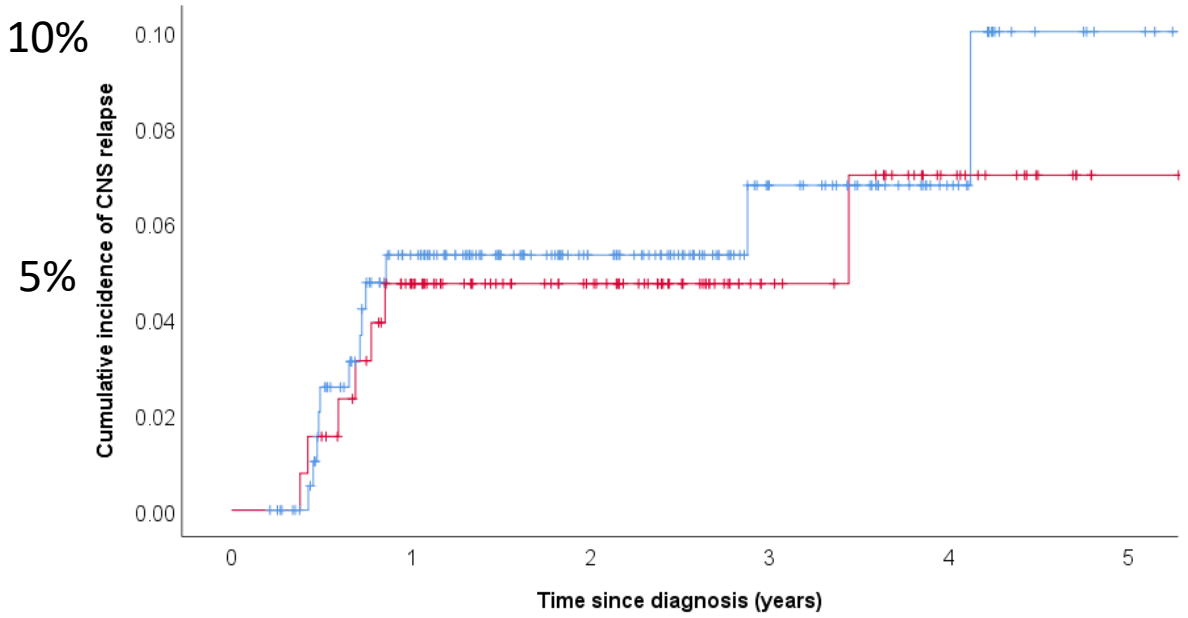
Wilson M *et al*, Blood Advances 2020

When to give HD-MTX prophylaxis

	All (n=729)	Intercalated (n=409)	End of treatment (n=320)	P value
Number inpatient days (median, range)	5 (2-60)	5 (2-60)	4 (3-80)	**<0.001**
Toxicity:				
Renal (any)	38 (5%)	21 (5%)	17 (5%)	0.92
Grade 1 (Creat 1.5-1.9 x baseline)	22 (3%)	12 (3%)	10 (3%)	
Grade 2 (Creat 2-2.9 x baseline)	6 (1%)	3 (1%)	3 (1%)	
Grade 3 (Creat >3 x baseline)	10 (1%)	6 (1%)	4 (1%)	
Liver (grade 2 or worse)	17 (2%)	7 (2%)	10 (3%)	0.21
Mucositis	54 (7%)	42 (10%)	12 (4%)	**0.001**
Neutropenic fever	49 (7%)	42 (10%)	7 (2%)	**<0.001**

Wilson M *et al*, Blood Advances 2020

When to give HD-MTX prophylaxis



Number at risk

Intercalated:	204	158	101	58	33	15
End of treatment:	130	111	82	45	30	15

Group	CNS relapses	3 year cumulative incidence	95% CI	P-value
All (n=334)	19 (5.7%)	5.9%	3.0-8.8	
Intercalated (n=204)	12 (5.9%)	6.8%	2.9-10.7	0.69
EOT (n=130)	7 (5.4%)	4.7%	1.0-8.4	

No benefit if IT MTX
3-yr rate 4.4% no IT / 5.2% for IT MTX.

Wilson M *et al*, Blood Advances 2020

Secondary CNS lymphoma

DOI: 10.1111/bjh.18128

REVIEW

Rare central nervous system lymphomas

Furqaan Ahmed Kaji[1] | Nicolás Martinez-Calle[1] | Vishakha Sovani[2] | Christopher Paul Fox[1]

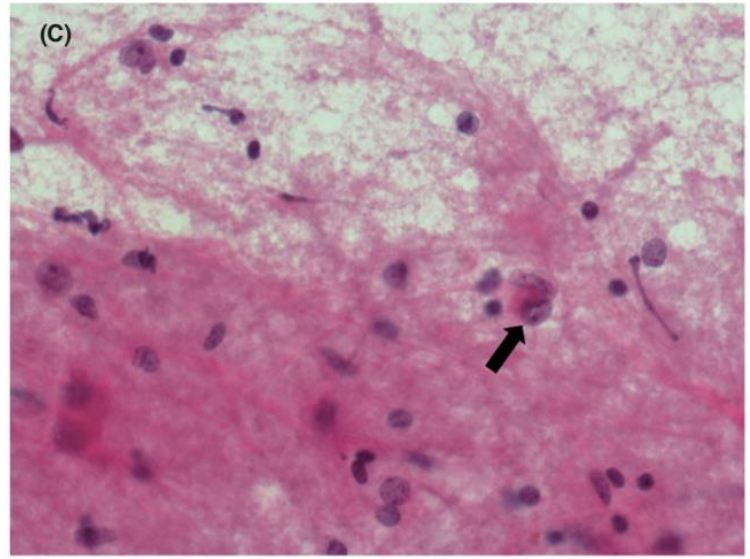
Kaji et al. BJH 2021

Hodgkin´s lymphoma

Median onset 45y

Parenchymal disease

Associated with immunosuppressive states (EBV)



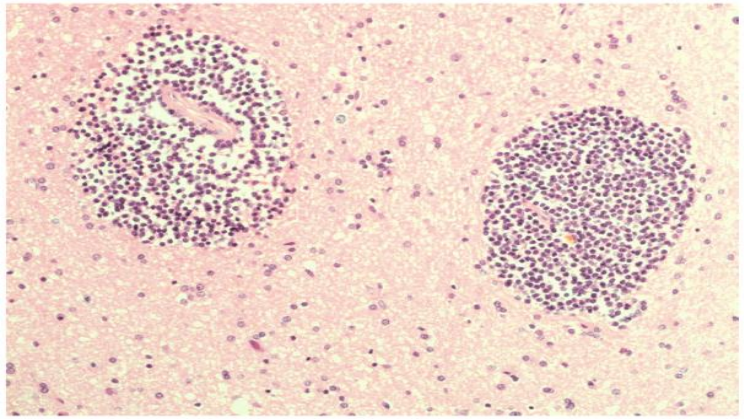
Incidentally Excision +RT -> 90% PFS at 28m (N=16)

CNS penetrating chemo -> ICE

Marginal Zone Lymphoma

Rarely true parenchymal, most of times leptomeningeal/dural disease

Frequently mistaken as meningioma



Remains an indolent disease

Treatment:

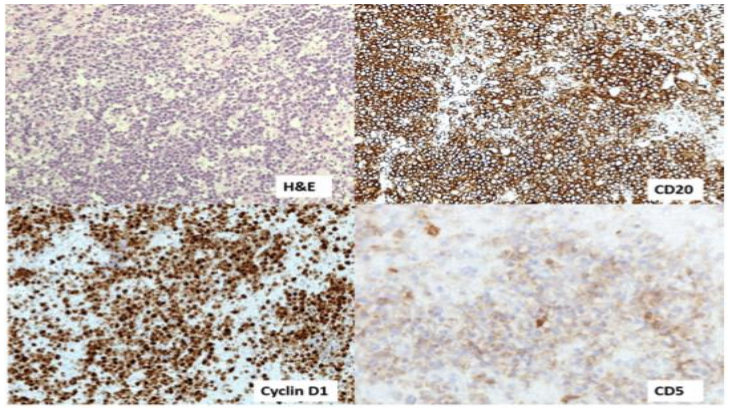
- Can you wait?
- RT most frequently used

High rates of response and long remission

Mantle Cell lymphoma

Typically relapse disease (Median time from diagnosis >12m)

IBR and AraC have CNS activity



Blastoid, high LDH, B-symptoms

R-HyperCVAD; HDMTX/AraC; HR 0.42 for TT based ASCT *(N=57; Cheah et al, Ann Oncol, 2013)*

Role of BTKi is promising, CNS activity is widely recognised *(Rusconi et all, Blood, 2022)*

N=29 in both IBR and CIT group. CNS involvement at relapse

PFS 13 vs 3m; OS 17 vs 4m

Follicular Lymphoma

Never assume low grade disease – biopsy

True FL has frequent dural involvement

Treatment

- RCHOP-like/HD-MTX alternating regimens
- **Bendamustine-based regimens**
- Rituximab-Lenalidomide

66% 5-year OS *(N=4000, Chihara et al, Oncotarget, 2018).*

Waldenstrom´s

Bing-neel syndrome: Clonal LPL cells in tissue biopsy or CSF

Typically diffuse infiltration (brain/meninges), less common as mass

Treatment (71% OS at 5 years, 70% ORR)

Simon et al, Haematologica 2015.

HD-MTX based treatment

Bendamustine

ASCT 13/14 long term remission *(Simon et al Am J Hematol, 2019)*

Ibrutinib (N=28, 2-year EFS 80% - *Castillo et al, BJH, 2019*)

CNS lymphoma: future pospects

- Optimisation of current therapies (Early efficacy/Toxicity)
- Novel agents: Comprehensive understanding of disease biology
- Minimally invasive diagnosis (ctDNA)
- Application of advanced imaging technologies to measure disease response, detect early relapse.
- CAR-T therapy

Acknowledgements

UK PCNSL working group

Dr Kate Cwynarski
Dr Jessica Okosun
Dr Christopher Fox

Dr Steffi Thust
Prof Dorothee Auer

University of Birmingham CRCTU
University of Southampton CTU

International Colaborators

Prof Andres Ferreri (Milan)
Prof Gerald Illerhaus (Stuttgart)
Dr Elisabeth Schorb (Freibrug)
Dr Benjamin Kasenda (Basel)

Thank you for your attention