How do we approach CNS prophylaxis in 2023?

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Disclosures

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

CNS Prophylaxis - Outline

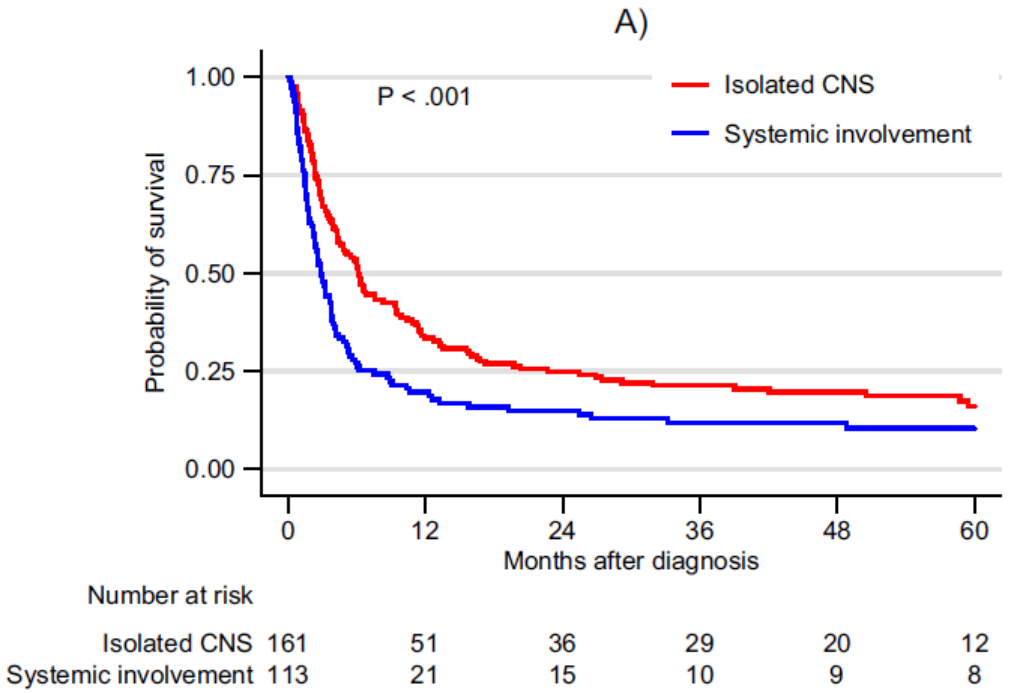
- WHO should receive CNS prophylaxis?
- WHAT should we give as CNS prophylaxis?
- WHEN should we give CNS prophylaxis?

- Should we give it at all?
  - Arguments for and against

- Future strategies
- Proposed approach(es) in 2023…

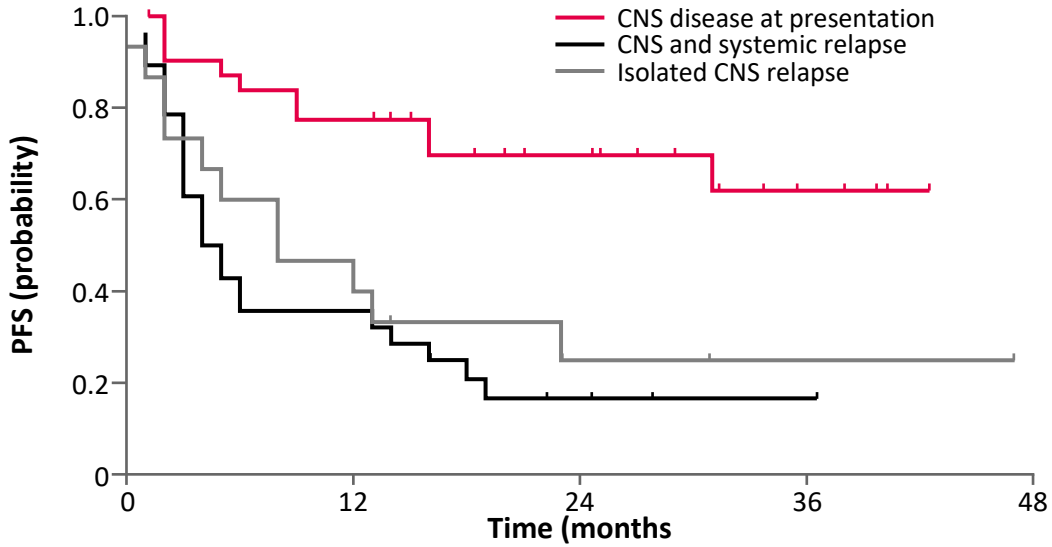
CNS prophylaxis: trying to prevent a devastating complication

Retrospective study[1] SCNSL n=291



Median OS post diagnosis of SCNSL = 3.9 months

MARIETTA Prospective Phase II trial[2]



2 year PFS ***71% if SCNSL de novo***

28% if SCNSL after R-CHOP

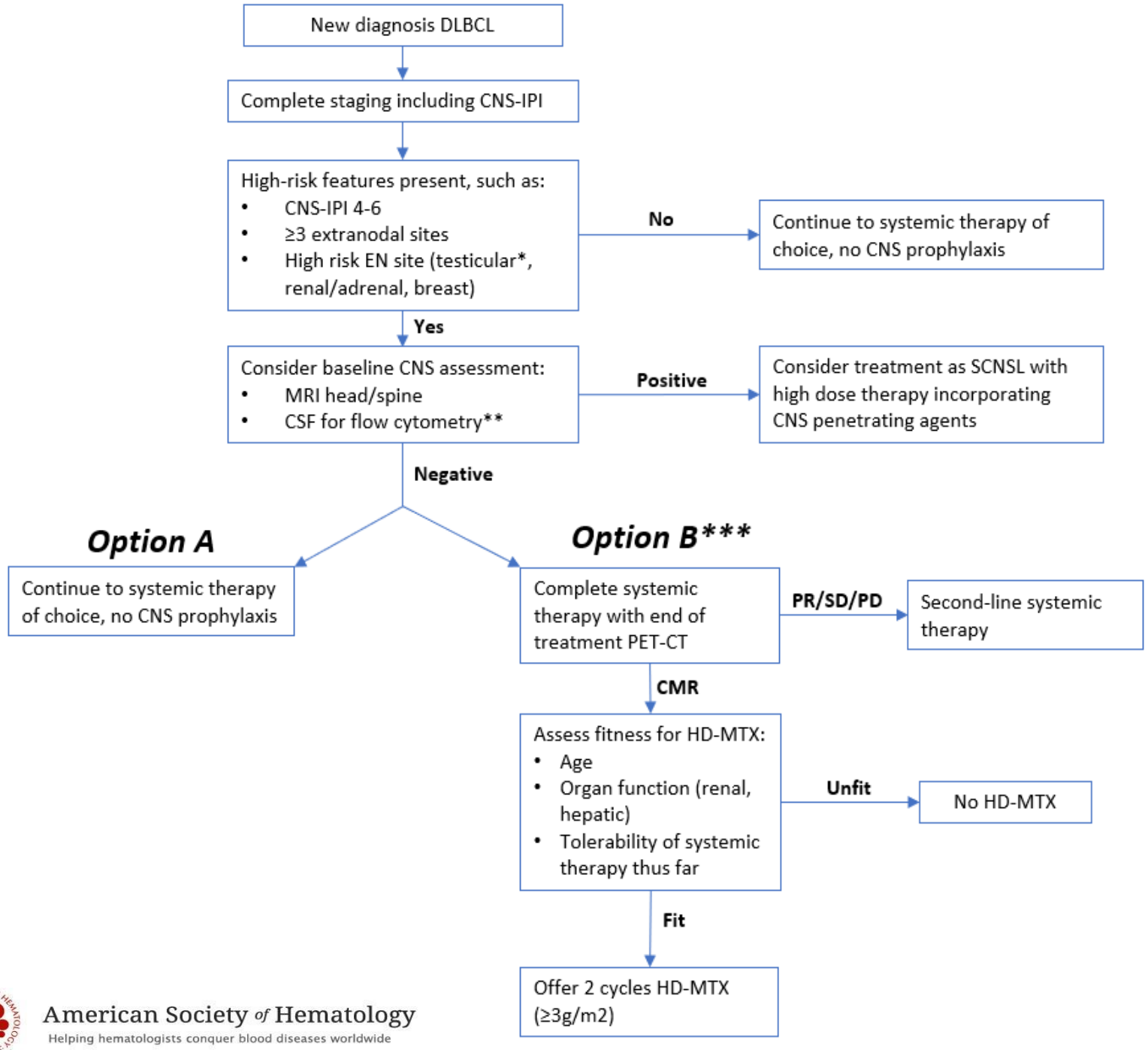
[1]El-Galaly *et al*, Eur J Cancer 2019 [2]Ferreri *et al*, Lancet Haem 2021

Variation in International Guidelines although CNS-IPI and HD-Methotrexate (HD-MTX) widely advocated

Guideline	Patient selection	Method for CNS prophylaxis suggested
British Society for Haematology (2021)[1]	Offer to: • High (4-6) CNS-IPI • ≥3 extranodal sites • High risk EN site involvement – testicular, renal/adrenal, intravascular Consider in: • Breast involvement • Uterine involvement	• HD-MTX (≥3g/m^2 for 2-3 cycles) as early as possible as part of first line therapy without compromising dose and time intensity of R-CHOP like treatment • IT prophylaxis not recommended if HD-MTX successfully delivered • Consider IT as well as systemic prophylaxis in testicular DLBCL
NCCN (2022)[2]	Consider in: • High (4-6) CNS-IPI • Double/triple-hit HGBL • High risk EN site involvement – testicular, renal/adrenal, breast, primary cutaneous	• HD-MTX (3-3.5g/m^2 for 2-4 cycles) during or after the course of treatment and/or • IT methotrexate and/or cytarabine (4-8 doses) during or after the course of treatment
ESMO (2018)[3]	Consider in: • High IPI • High risk EN site involvement – testicular, renal/adrenal, breast, bone marrow, bone	• HD-MTX is 'an option…even though the level of supporting evidence is low' • 'Little or no role' for IT therapy

[1]McKay *et al*, BJHaem 2020 [2]NCCP B-Cell Lymphomas. Version 3.2022-April 25, 2022. *https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf* [3]Tilly *et al*, Ann Oncol 2015

Proposed algorithm for CNS Prophylaxis in DLBCL in 2022



Consider IT therapy for Testicular DLBCL

***CSF ctDNA: currently being assessed prospectively in trials*

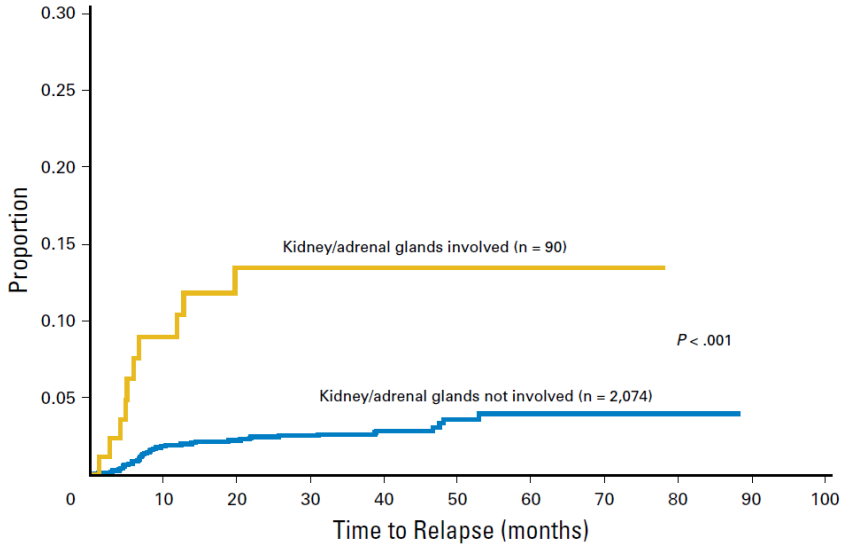
****Lack of evidence to suggest efficacy but consider for highest risk patients,*

e.g. CNS-IPI 5/6, renal/adrenal, testicular involvement

Wilson, Bobillo & Cwynarski,
Hematology Am Soc Hematol Educ Program, 2022

Extranodal sites associated with increased risk

Renal/adrenal: *Schmitz et al, JCO 2016*



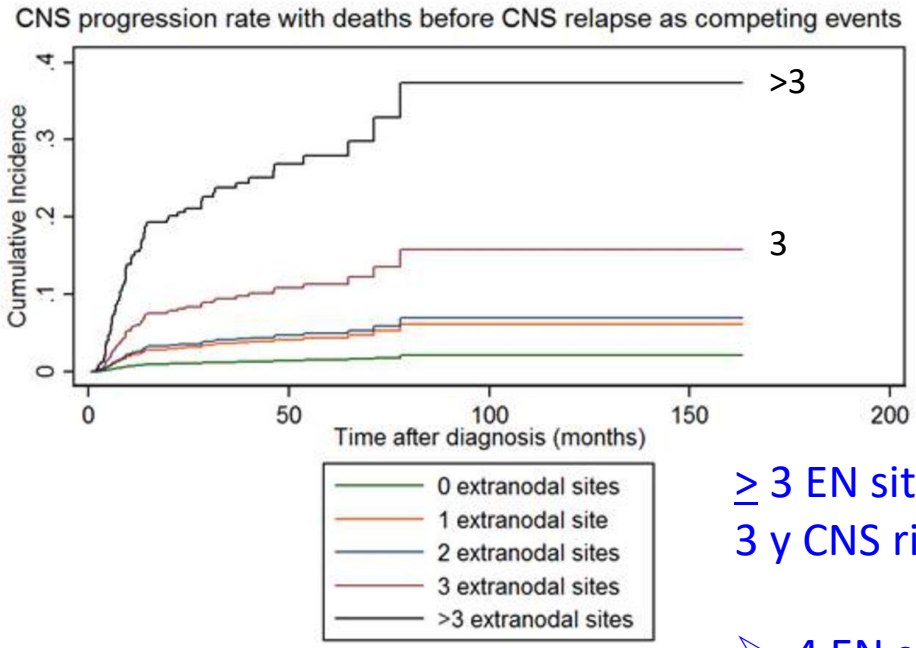
Testicular: *Kridel et al, Bjhaem 2016*

- BCCA series – 134 patients with testicular involvement (localised or advanced)
- 25% risk of CNS relapse:
  - Median time 2.3 years, longer in localised

Breast: *Hosein et al, Bjhaem 2014*

- Often localised, underrepresented in prospective trials
- Retrospective series report CNS relapse rates of ~15%

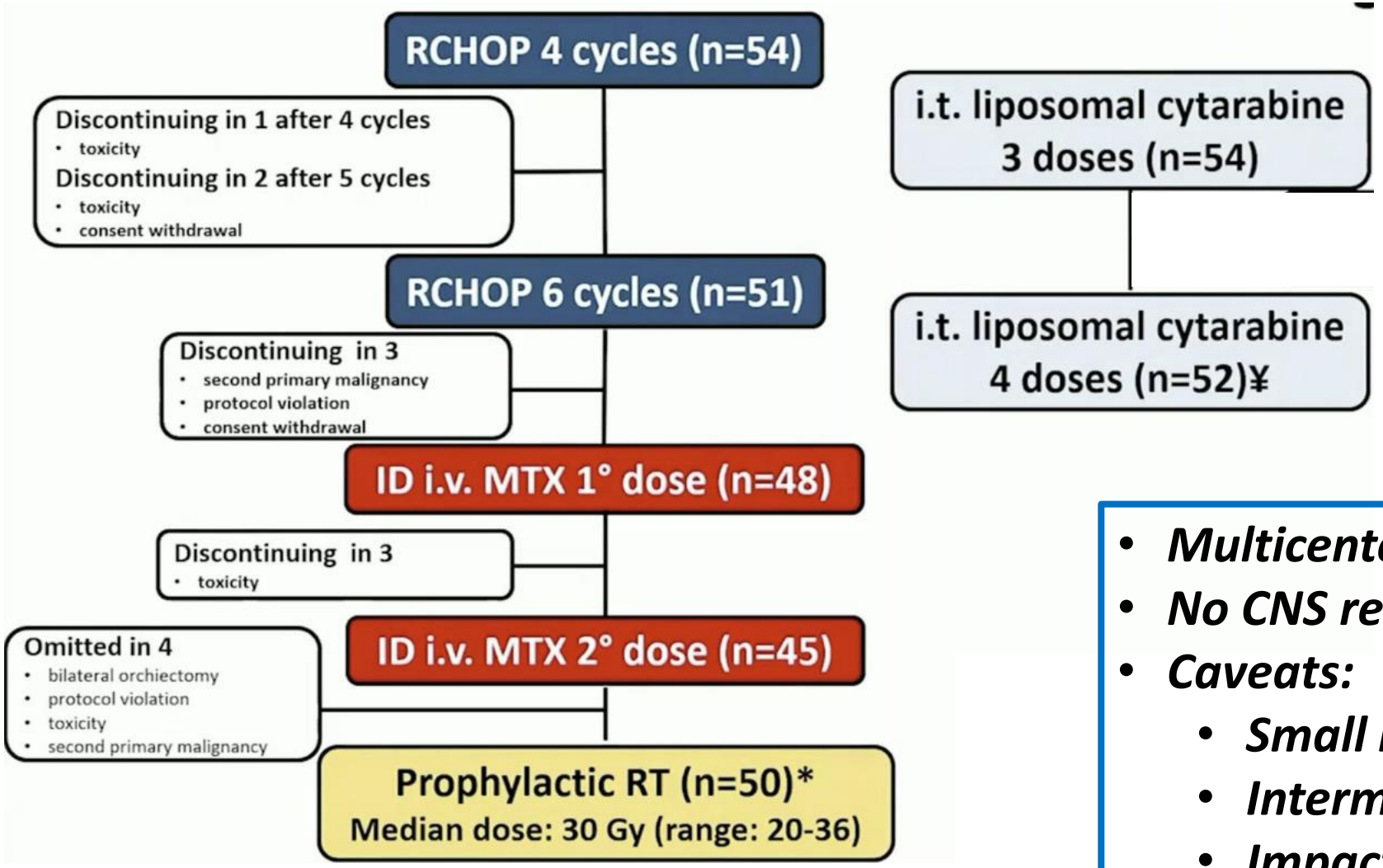
Total number of EN sites: *El-Galaly et al, Eur. Journal cancer 2017*



≥ 3 EN sites (6% pts)
3 y CNS risk 12.8%

➢ 4 EN sites (3% pts)
3 y CNS risk 32.1%
*Adjusted for LDH, age, PS

Testicular DLBCL: a distinct entity and approach?



- ***Multicenter Phase II prospective trial***
- ***No CNS relapses***
- ***Caveats:***
  - ***Small numbers***
  - ***Intermediate dose MTX?***
  - ***Impact of ITs and RT?***

Conconi *et al*, ICML 2021

Biological factors?

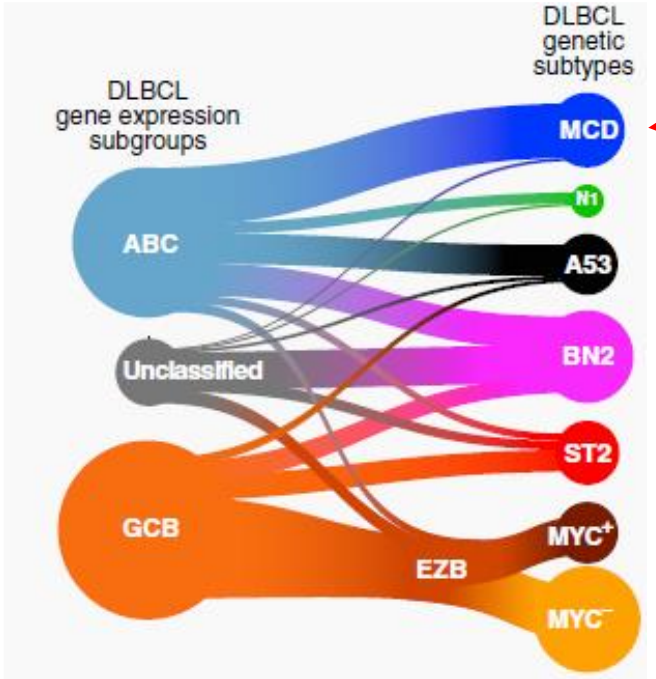
- HGBCL with *MYC* and *BCL2* translocations
  - Historically associated with high CNS relapse risk
  - but significant selection bias and non-uniform application of *FISH*

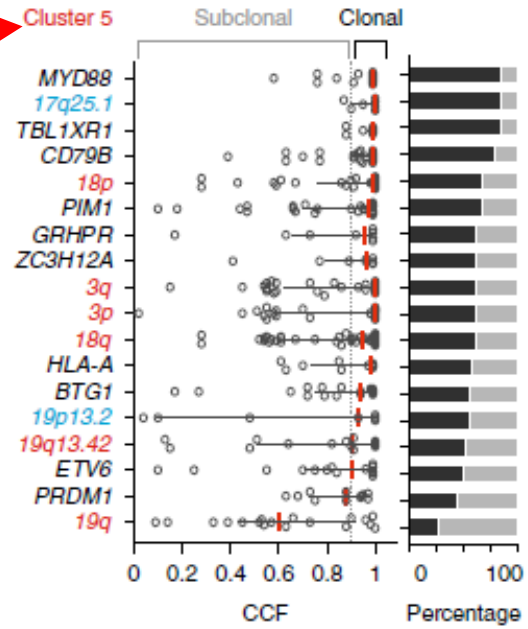
  - Risk may be related to high-risk clinical features rather than disease biology

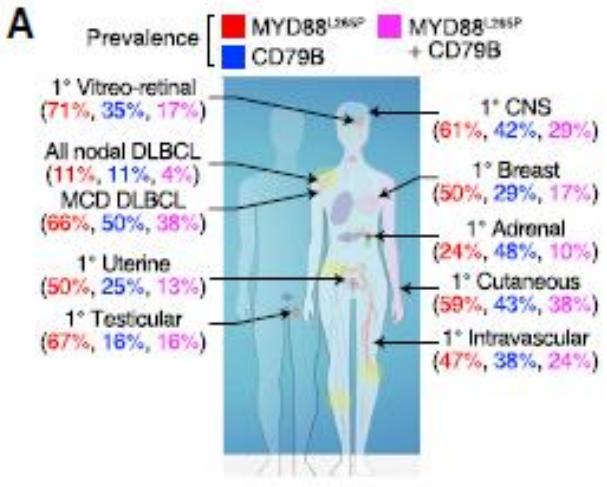
- Cell of origin (COO) – ABC subtype
  - GOYA study[1] combination of:
    - ABC subtype by Gene Expression Profiling + CNS-IPI
    - created group with 2y CNS relapse risk 15%
      - 8% of study population

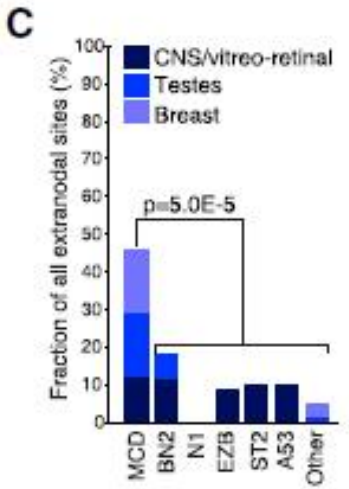
[1]Klanova *et al*, Blood 2019

New taxonomy of DLBCL: MCD/C5 CNS risk









MCD and Cluster 5

- ABC by expression profiling
- *MYD88*+ mutation frequent
- Predominance of 'immune privileged' extranodal subtypes (e.g. CNS, testes, intravascular)
- CNS risk elevated in MCD (38% vs 8% p=0.003)
- Present in almost 50% relapses

Schmitz *et al*. NEJM 2018; Wright *et al*. Cancer cell 2020; Chapuy *et al*. Nature Medicine 2018: Ollila *et al* Blood 2021

Intrathecal (IT) Therapy: no clear evidence of efficacy

- Majority of CNS relapses in Rituximab era are **parenchymal**
- Large systematic review of >7,000 patients:
- **NO** benefit of standalone IT prophylaxis[1]

Study (year)	Study design	n	Patients	Treatment	IT MTX prophylaxis	Time to CNS relapse	CNS relapse risk
Boehme V (2009)	*Post hoc* analysis RICOVER-60	1217	61-80y "aggressive"	CHOP vs. R-CHOP	57%	8 m	6.9% vs. 4.1% (2a) No benefit in the rituximab group
Tai WM (2011)	Retrospective	499	≥18y (R) -CHOP	18%*	6%* (2a)	6.7 m	No benefit
Villa D (2011)	Retrospective	435	>16y, III-IV or testicular	(R)-CHOP	4%*	6.7 m*	6.4% (R-CHOP) No benefit
Schmitz N (2012)	*Post hoc* analysis MinT trial and others	2210	18-60y	CHOP vs. R-CHOP	NR	7 m	2.3% (2y) No benefit in the rituximab group
Kumar A (2012)	Prospective NCCN database	989	≥18y	R-CHOP	11% (72% IT)	12.8 m	2% (2.5y) 5.4 px vs.1.4% no px No benefit
Tomita N (2015)	Retrospective	332	18-80y	R-CHOP	12%	8.2 m	3.6% (3y) 8.7 IT MTX vs. 2.9% no px (p=0.14) No benefit
Gleeson M (2017)	*Post hoc* analysis UK NCRI trials	984	≥18y, II-IV or I Bulky	R-CHOP 14 vs. R-CHOP 21	18%	8 m	1.9% (6y) No benefit No benefit by CNS-IPI
Klanova M (2019)	*Post hoc* analysis GOYA	1418	≥18y	R-CHOP vs. G-CHOP	10%	8.5 m	2.5% (2y) No benefit No benefit by CNS IPI
Eyre T I (2019)	Retrospective	690	>70y	R-CHOP	14%	9.4 m	3.1% (3y) No benefit

[1]*Eyre TA et al, Haematologica 2020*

Table courtesy of Dr Sabela Bobillo

International multicentre retrospective analysis: Timing of delivery: Intercalated vs EOT HD-MTX?

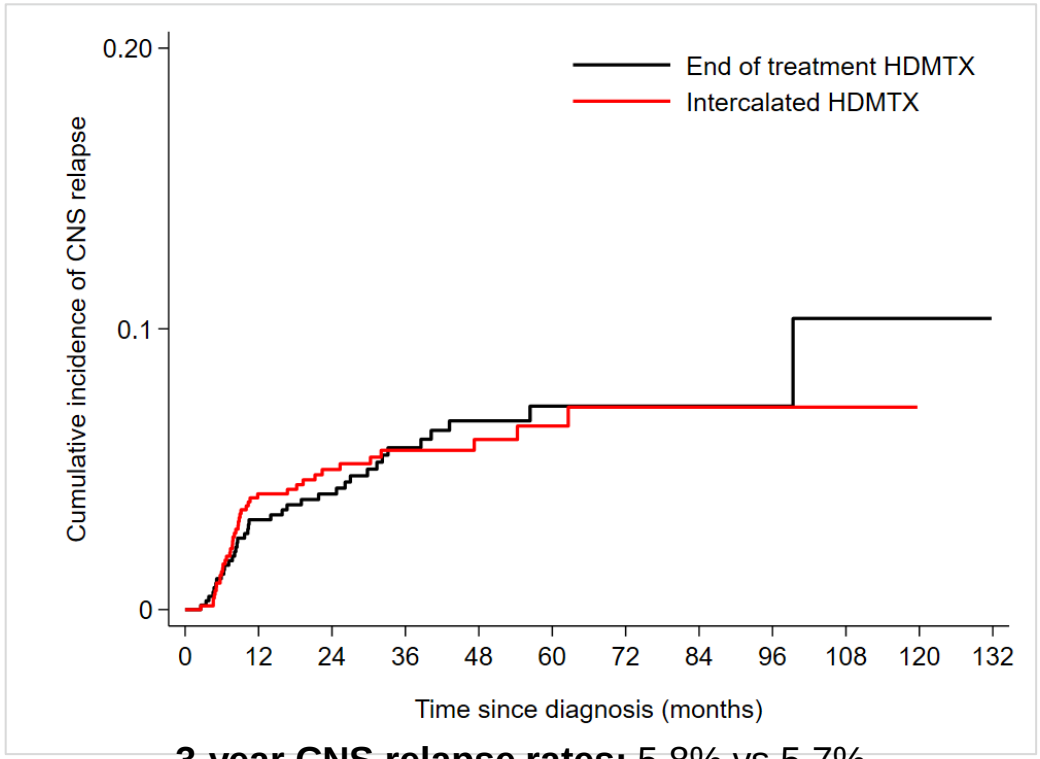
	All N=1384	End of treatment N=635	Intercalated N=749	P
Age (years), median (range)	62.5 (17 - 88)	63.0 (18 - 86)	62.0 (17 - 88)	0.065
Male sex, N (%)	840 (60.7)	393 (61.9)	447 (59.7)	0.40
Advanced stage, N (%)	1156 (83.5)	509 (80.2)	647 (**86.4**)	**0.0019**
Raised LDH baseline, N (%)	943 (70.0)	410 (68.0)	533 (71.5)	0.16
ECOG ≥2, N (%)	358 (25.9)	158 (25.0)	200 (26.7)	0.47
≥2 extra-nodal sites, N (%)	798 (57.6)	353 (55.6)	445 (59.4)	0.11
Renal/adrenal involvement, N (%)	240 (17.3)	102 (16.1)	138 (18.4)	0.25
Testicular involvement, N (%)	175 (12.7)	95 (**15.0**)	80 (10.7)	**0.016**
Breast involvement, N (%)	56 (4.1)	18 (2.8)	38 (**5.1**)	**0.037**
Double or triple hit, N (%)	66 (6.1)	32 (6.7)	34 (5.7)	0.47
CNS IPI, N (%)				
Low (0-1)	203 (14.9)	107 (17.5)	96 (12.9)	0.083
Intermediate (2-3)	555 (40.9)	241 (39.4)	314 (42.0)	
High (4-6)	600 (44.2)	263 (**43.0**)	337 (**45.1**)	

Wilson *et al*, ASH 2021; Wilson *et al*, Blood, 2022

No significant difference in CNS relapse: Intercalated vs EOT HD-MTX

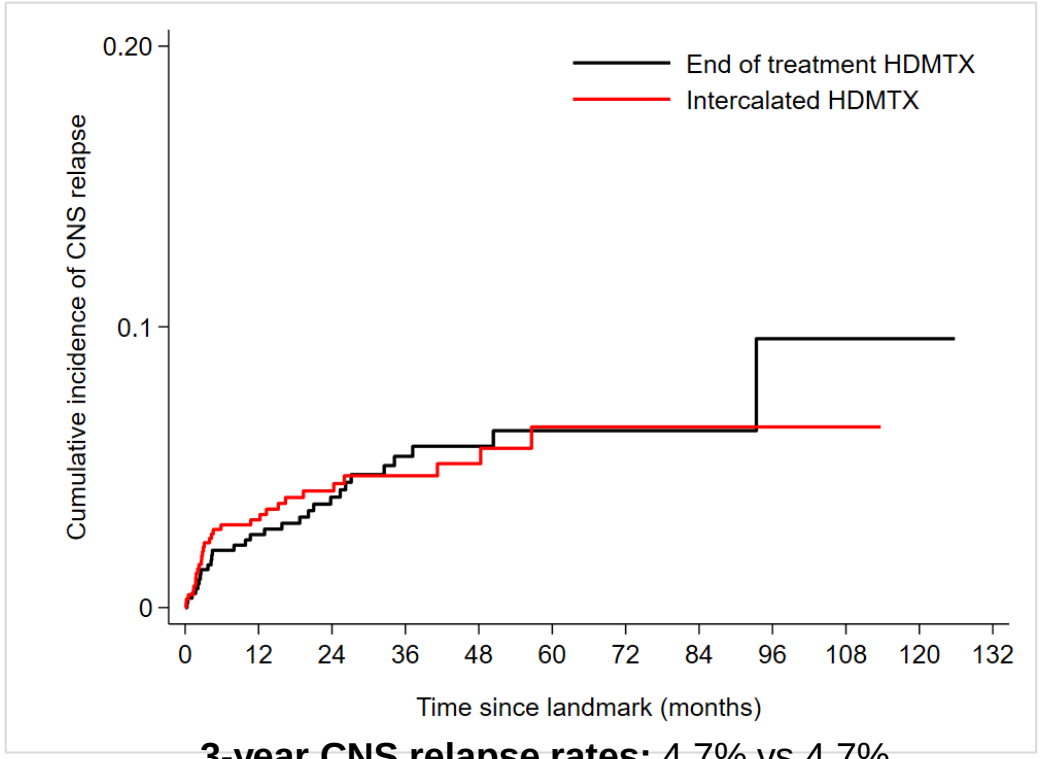
Primary endpoint: 3-year CNS relapse rate: 5.7% (all), 4.7% (landmark)

All patients (n=1,384)



3-year CNS relapse rates: 5.8% vs 5.7%
HR: 1.01 (95% CI: 0.65-1.57)
3-year difference: 0.04% (95% CI: -2.0 to 3.1)

Landmark analysis (n=1,253)



3-year CNS relapse rates: 4.7% vs 4.7%
HR: 0.99 (95% CI: 0.60-1.66)
3-year difference: -0.03% (95% CI: -1.0 to 3.0%)

Analyses restricted to isolated relapse showed no difference

Wilson *et al*, ASH 2021; Wilson *et al*, Blood, 2022

Delay in R-CHOP delivery with Intercalated HD-MTX

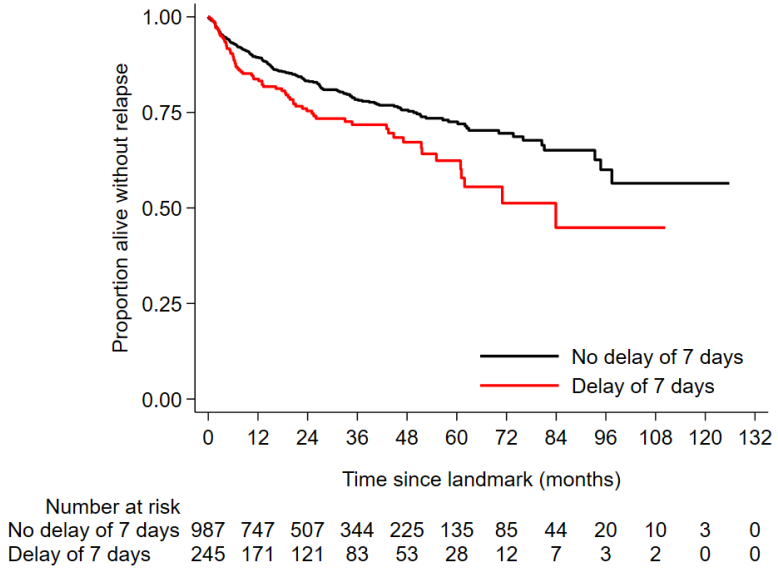
1,573 i-HD-MTX treatments delivered

19.6% (308/1573) **associated with next R-CHOP delay** (median delay 8 days)

Increasing Age: risk factor for delay on MVA

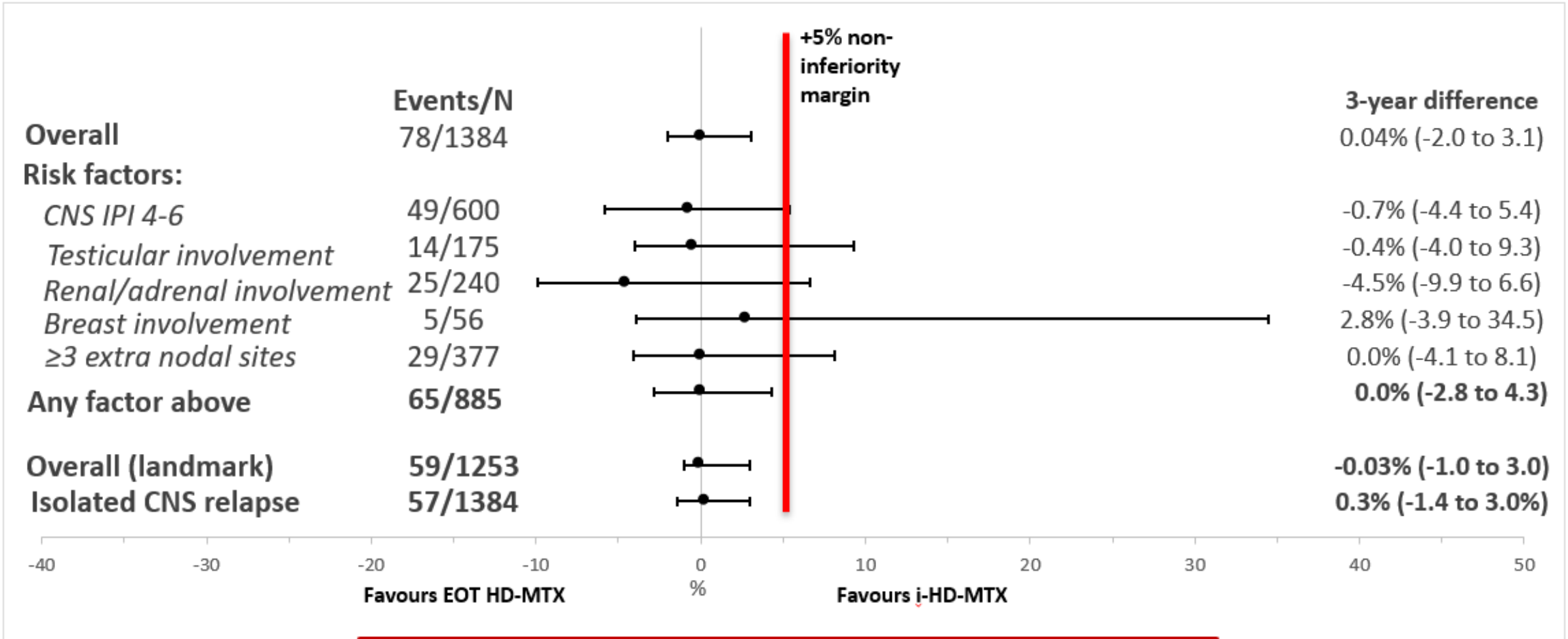
Reduction in delay risk when delivered before day 10 R-CHOP

Inferior PFS in patients experiencing any delay of ≥7 days (adjusted HR 1.52 (95% CI 1.15-2.03)



Wilson *et al*, ASH 2021; Wilson *et al*, Blood, 2022

High risk subgroups: Intercalated vs EOT HD-MTX



Overall 3-year rate CNS IPI 4-6: *9.1% (6.9 – 11.9)*

Wilson *et al*, ASH 2021; Wilson *et al*, Blood, 2022

Conclusions:
Intercalated vs EOT HD-MTX

- EOT HD-MTX did not increase risk of CNS relapse compared to early integration during R-CHOP/R-CHOP-like therapy

- Intercalated HD-MTX significantly increased risk of R-CHOP delay

- Overall rates of CNS relapse in high risk patients were relatively high despite the use of HD-MTX
  - ***Overall 3-year rate CNS IPI 4-6:*** *9.1% (6.9 – 11.9)*

Wilson *et al*, ASH 2021; Wilson *et al*, Blood, 2022

Is HD-MTX effective at all?
A large international retrospective analysis

Factor	No HD-MTX n=1875	HD-MTX n=392	p-value
HGBL with rearrangements of *MYC* + *BCL2* and/or *BCL6*, n (%)	124 (6.6)	40 (10.2)	0.018
Treatment, n(%)			0.303
R-CHOP-like*	1762 (94.0)	363 (92.6)	
DA-EPOCH-R	113 (6.0)	29 (7.4)	
Number of extranodal sites, n(%)			<0.001
0-1	565 (30.1)	57 (14.5)	
2	739 (39.4)	164 (41.8)	
3	343 (18.3)	90 (23.0)	
4	134 (7.2)	54 (13.8)	
>4	93 (5.0)	27 (6.9)	
High-risk extranodal site, n (%)			
Renal	287 (15.3)	107 (27.3)	<0.001
Adrenal	112 (6.0)	44 (11.2)	<0.001
Testicular	38 (3.9)	25 (10.6)	<0.001
Breast	23 (1.2)	9 (2.3)	0.104
CNS baseline assessment, n (%)			<0.001
Nil specific	960 (51.2)	181 (46.2)	
MRI or CT brain	50 (2.7)	27 (6.9)	
CSF analysis	291 (15.5)	119 (30.4)	
MRI/CT brain and CSF analysis	64 (3.4)	42 (10.7)	
Unknown	510 (27.2)	23 (5.9)	
CNS prophylaxis received, n (%)			N/A
None	1447 (77.2)	-	
Intrathecal MTX	428 (22.8)	-	
HD-MTX	-	254 (64.8)	
Intrathecal + HD-MTX	-	138 (35.2)	
Age>60	82.2%	72.2%	
ECOG 2-4	64.7%	41.9%	

DLBCL with CNS-IPI 4-6 OR
HGBL *MYC* + *BCL2* +/or *BCL6* OR
Breast/testicular DLBCL

HD-MTX vs none

≥3 : 43.7% vs 30.5%

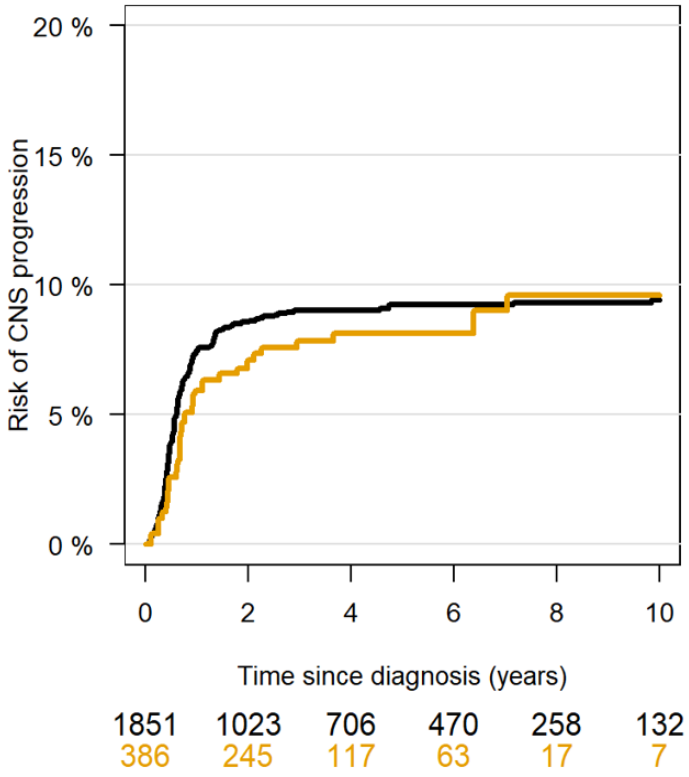
High risk : 51.4% vs 26.4%

Pre-planned power calc:
to detect CNS relapse rate 10% → 5%, α 0.05
→ 1300 patients (650 no/650 HD-MTX)

Lewis K…..El-Galaly, Cheah C , ASH 2021

No difference in incidence of CNS relapse

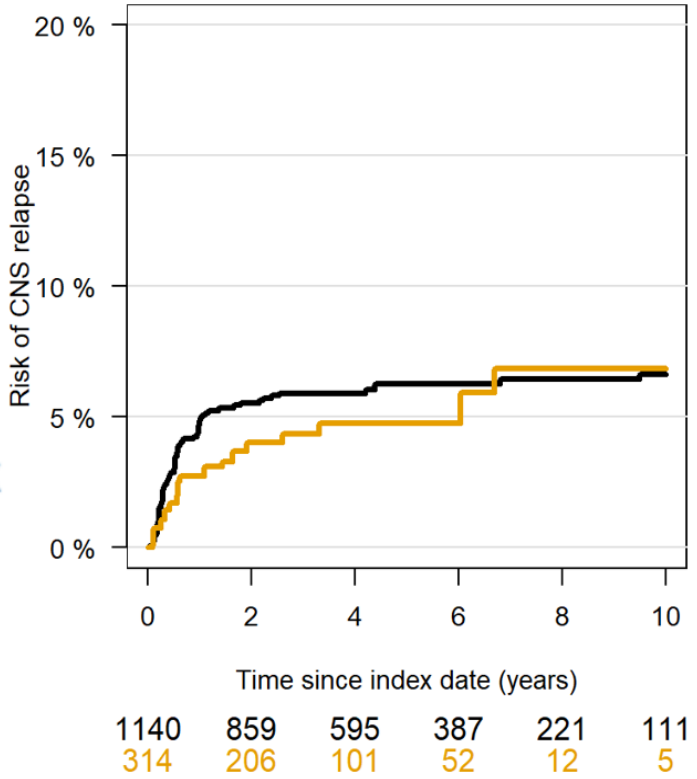
All patients (n=2267)
5 year risk: 9.2% (no HD-MTX) vs 8.1% (HD-MTX)
Adjusted HR: 0.68 (p=0.067)



Median time to CNS relapse from diagnosis:
HD-MTX 8.5 months
No HD-MTX 6.7 months

No HD MTX HD MTX

CR patients (n=1468)
Adjusted HR: 0.77 (p=0.381)



Median time to CNS relapse from diagnosis:
HD-MTX 11.5 months
No HD-MTX 10.3 months

Lewis *et al*, ASH 2021

No evidence of efficacy of HD-MTX in high-risk subgroup analyses

No difference in the rate of CNS relapse between HD MTX and no HD MTX for any of following subgroups:

Group	No HD MTX (n)	HD MTX (n)
Double/triple hit lymphoma	69	27
CNS-IPI 5/6	256	78
CNS-IPI 6/6	50	13
>4 extra-nodal sites	46	18
Renal	178	84
Adrenal	63	35
Breast	13	6
Testicular	22	21

Lewis *et al*, ASH 2021

Impact of HD-MTX: conclusions

- HD-MTX was not associated with reduction in CNS relapse:
  - Overall
  - For patients in CR at completion of frontline therapy
  - In any high-risk subgroup
- Overall incidence of CNS relapse was consistent with previously reported high-risk cohorts (9%)

Caveats:

- ***Underpowered HD-MTX arm?***
- ***Imbalance in baseline characteristics?***
- ***Small numbers in ultra high-risk groups***

Lewis *et al*, ASH 2021

DLBCL at risk of secondary CNS involvement: the inefficacy of intravenous HD-MTX CNS prophylaxis and the importance of baseline cerebrospinal fluid analysis

Rory Bennett, Anna Ruskova, Christin Coomarasamy, Edward Theakston, Leanne Berkahn, Sharon Jackson, Mina Christophers, Stephen Wong, and Samar Issa

Auckland City Hospital & Middlemore Hospital, Auckland New Zealand

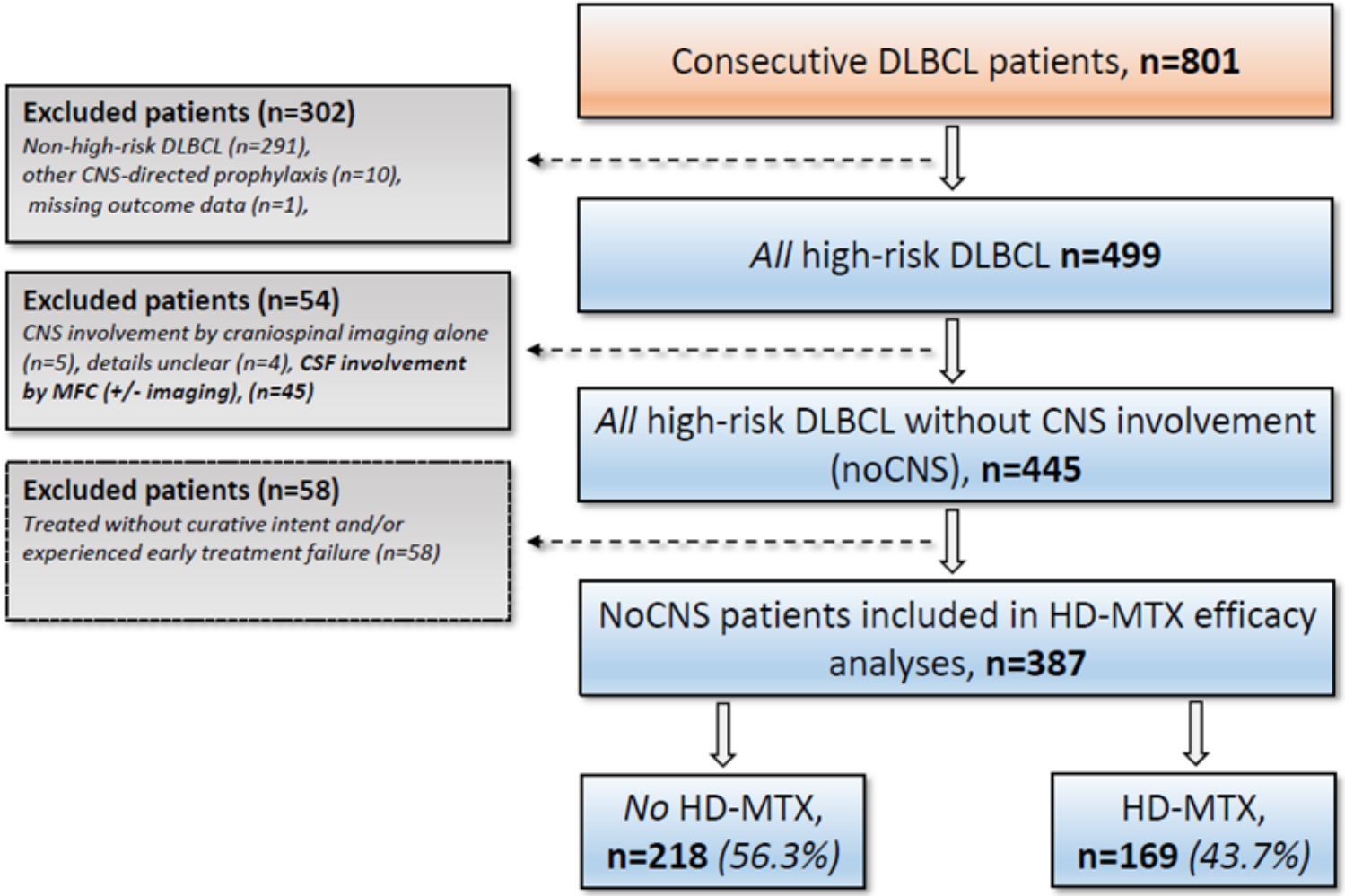
American Journal of Haematology May 2023

Regional practice

- CNS screening by CSF (cytology and flow cytometry) for all ‘at-risk’ patients
- +/- CNS imaging where indicated
- The high-risk criteria - any of:
  - High-risk CNS-IPI (score 4-6);
  - *MYC* and *BCL2* and/or *BCL6* rearrangements;
  - Involvement of $\geq$2 extra-nodal (EN) sites;
  - Inv of EN sites: testicular, breast, renal, adrenal, epidural, nasopharyngeal, endometrial

- Central review of pathology and radiology/MDT/Shared CNS proph guideline
- HD-MTX prophylaxis:
  - 2-4 cycles IV HD-MTX $\geq$3g/m^2
  - Administered either following or intercalated with systemic chemoimmunotherapy
  - Dose adjusted according to renal function as per guidelines.
    - Patients with creatinine clearance <30ml/min did not receive HD-MTX

Results – patient selection



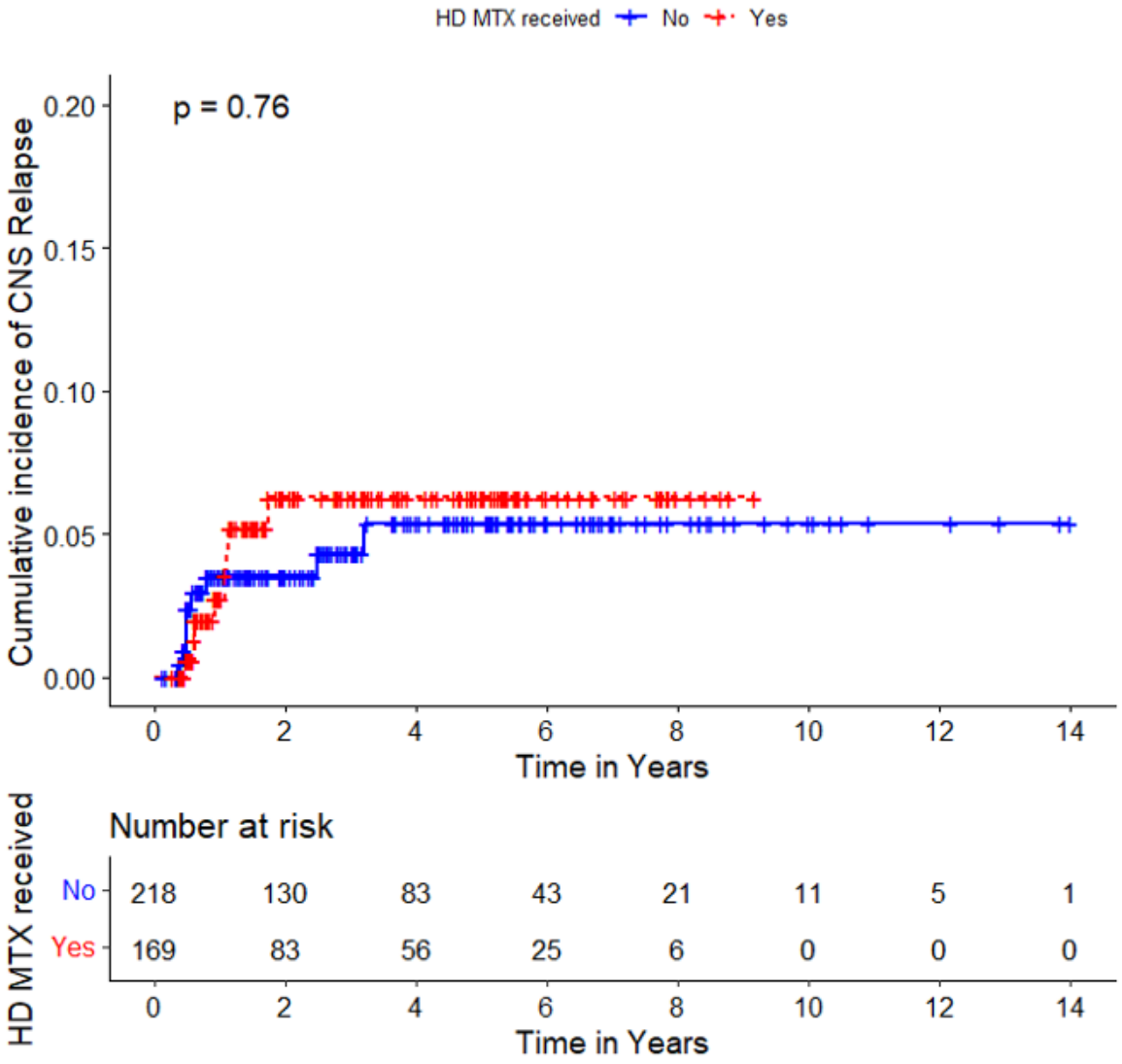
	NoCNS patients (n=387)		
Covariate	No CNS prophylaxis (n=218), n (%)	HD-MTX prophylaxis (n=169), n (%)	P-value
Age ≥60 years	148 (67.89)	100 (59.17)	0.076
Male gender	123 (56.42)	84 (49.7)	0.189
DLBCL	191 (87.61)	144 (85.21)	0.491
DH/TH cytogenetics by FISH	24 (13.71)	19 (13.29)	0.682
Cell of origin			
ABC	63 (28.9)	50 (29.59)	0.348
GCB	112 (51.38)	95 (56.21)	
UK/UC	43 (19.72)	24 (14.2)	
Preceding/concurrent indolent lymphoma	37 (16.97)	13 (7.69)	0.007
ECOG ≥2	73 (33.49)	53 (31.36)	0.658
Stage 3-4	161 (73.85)	134 (79.29)	0.213
LDH >ULN	139 (64.95)	125 (73.96)	0.058
≥2 extra-nodal sites	81 (37.16)	92 (54.44)	0.0007
CNS-IPI score risk			
Low risk	45 (20.64)	25 (14.79)	0.263
Intermediate risk	92 (42.2)	71 (42.01)	
High risk	81 (37.16)	73 (43.2)	
CSF analysis performed	187 (86.18)	166 (98.22)	<0.0001

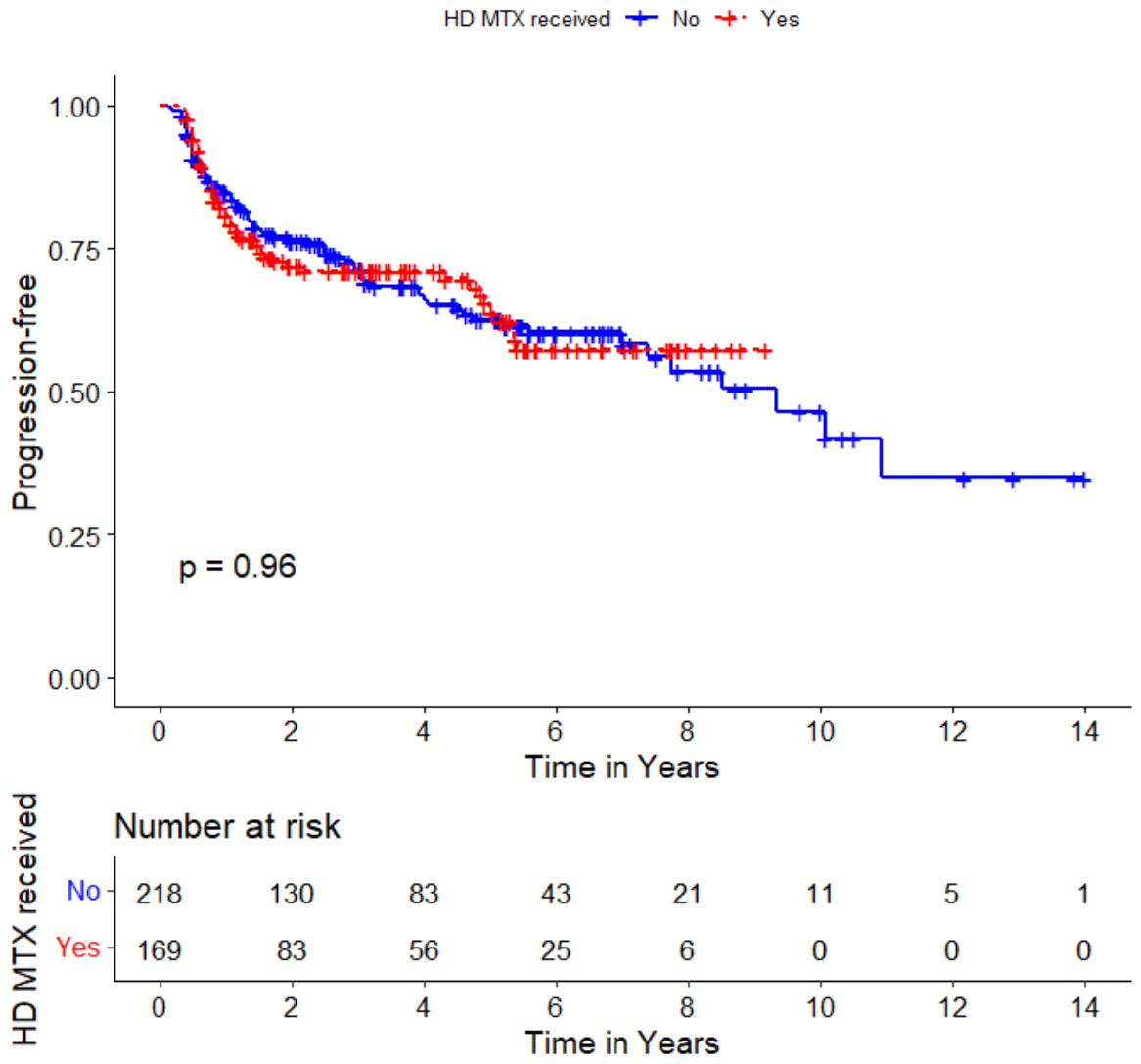
Covariate	CNSinv patients (n=45)	NoCNS patients (n=445)	P-value
Age ≥60	30 (66.7)	294 (66.1)	0.935
Male	28 (62.2)	238 (53.5)	0.262
DLBCL	34 (75.56)	379 (85.17)	0.091
DH/TH cytogenetics by FISH	10 (28.57)	55 (15.19)	0.032
Cell of origin			
ABC	14 (31.11)	126 (28.31)	0.744
GCB	25 (55.56)	240 (53.93)	
UK/UC	6 (13.33)	79 (17.75)	
ECOG 2-4	13 (28.89)	156 (35.06)	0.407
Stage 3-4*	36 (80)	344 (77.3)	0.679
Elevated LDH	34 (75.56)	307 (69.93)	0.431
≥2 extranodal sites	24 (53.33)	203 (45.62)	0.323
CNS-IPI[&]			
Low risk	8 (17.78)	77 (17.3)	0.661
Intermediate risk	15 (33.33)	178 (40)	
High risk	22 (48.89)	190 (42.7)	

CNSinv patients (+ve CSF) were more likely to have at least one (non-CNS) extra-nodal site of involvement (93.3% [n=42] vs. 75.3% [n=335], p=0.0031).

CNSinv patients: 31.8% [n=14] evaluable patients were neurologically symptomatic

Results – HD-MTX efficacy





Conclusions/Strengths/limitations

- **No benefit observed with use of HD-MTX for CNS prophylaxis in high-risk DLBCL**

- Strengths:
  - Routine screening for CNS involvement with flow cytometric CSF analysis in asymptomatic high risk DLBCL patients
  - Uniform use of single-route CNS prophylaxis

- Limitations:
  - retrospective analyses – potential for documentation error, missing data
  - expected selection bias affecting those who received HD-MTX prophylaxis compared with no prophylaxis.

- Detection of CNS involvement could be enhanced by
  - routine adjunctive cranial imaging for asymptomatic patients
  - Highest yield of CNS involvement at diagnosis in patients with extranodal disease
  - and/or use of more sensitive techniques to assess CSF such as analysis of CSF ctDNA

Bennett R… Issa S. American Journal of Haematology 2023

Study	n	Design	Risk factors	Treatment	CNS Prophylaxis	CNS relapse	Benefit?
Lewis K (2022)	2300	Retrospective	CNS-IPI ≥4 Testicular, breast involvement DHL	R-CHOP (94%) R-EPOCH (6%)	HD-MTX (18%) No HD-MTX (82%)	9.2% (5y) 8.1% (5y)	**No benefit HD-MTX**
Wilson MR (2022)	1384	Retrospective	High risk EN sites CNS-IPI ≥ 4 ≥2 EN and LDH ↑	R-CHOP	HD-MTX (all, intercalated or EOT)	5.7% (3y) 5.8% (3y)	No difference between EOT and intercalated HD-MTX
Orellana-Noia (2022)	1030	Retrospective	Not described	R-CHOP (48%) R-EPOCH (45%)	HD-MTX (20%) IT (77%)	6.8% 5.4%	**No benefit HD-MTX vs. IT.**
Puckrin R (2021)	326	Retrospective	CNS-IPI ≥ 4 Testicular DHL LDH ↑ + ECOG >1 + >1 EN	R-CHOP (85%) Intensive (15%)	HD-MTX (35%) No HD-MTX (65%)	12.2% 11.2%	**No benefit HD-MTX**
Bobillo S (2021)	585	Retrospective	CNS-IPI ≥ 4 High risk EN sites DHL	R-CHOP (68%) R-EPOCH (15%) Other (17%)	HD-MTX (7%) IT MTX (43%) None (50%)	7.5% (5y) 5.5% (3y) 5%	**No benefit (IT or HD-MTX)**
Ong SY (2021)	226	Retrospective	High risk EN sites CNS-IPI ≥ 4	R-CHOP	HD-MTX (29%) No HD-MTX (71%)	3.1% (3y, isolated) 14.6% (3y, isolated)	HD-MTX significantly reduced risk of isolated CNS relapse
Wilson MR (2020)	334	Retrospective	CNS-IPI ≥ 4 High risk EN sites ≥2 EN sites and LDH ↑	R-CHOP	HD-MTX (all, intercalated or EOT)	6.8% (3y) 4.7% (3y)	No difference between EOT and intercalated HD-MTX
Lee K (2019)	130	Retrospective	CNS-IPI ≥ 4 High risk EN sites ≥2 EN and LDH ↑	R-CHOP	HD-MTX (49%) None (51%)	6.9% (2y) 8.1% (2y)	**No benefit HD-MTX**
Goldschmidt N (2019)	480	Retrospective	High risk EN sites Stage IV, LDH ↑, ≥1 EN	CHOP +/- R (80%)	HD-MTX (27%) None (73%)	6.9% 6.3%	**No benefit HD-MTX**

Arguments for and against CNS prophylaxis

FOR

- Outcomes for SCNSL are historically v. poor
- HD-MTX has theoretical rationale and proven efficacy in CNS lymphoma
- Retrospective studies reporting no benefit may be subject to bias/imbalance in high-risk features
- 2 x prospective trials (Ph2) in testicular DLBCL suggest benefit of HD-MTX (+/- IT MTX)
- Delivery of HD-MTX at EOT results in no interruption to systemic therapy and can be well-tolerated in selected patients

AGAINST

- CNS relapse likely to occur due to occult/undetected disease at baseline
  - Need to improve detection methods e.g. ctDNA
  - Current risk models lack specificity
- Most CNS relapses occur w/ systemic relapse – i.e. failure of systemic therapy
- HD-MTX is toxic, difficult to deliver, often requires IP stay
- Cumulative data now suggesting lack of benefit of HD-MTX
- Increasing options for SCNSL treatment e.g. CAR T-cells
- New molecular classification implications:
  - More sensitive methods for risk stratification
  - Use of novel targeted agents e.g. BTKi, CELMoD

Novel therapy approaches in CNS prophylaxis

Prospective Trials

- BTKi and CELMoDs → CNS penetration

- PHOENIX trial (R-CHOP -/+ Ibrutinib) ABC DLBCL → low CNS relapse rates (2.4% vs. 3.8%)[1]
- ROBUST trial (R-CHOP -/+ Lenalidomide) CNS relapse rates not yet reported [2]
- Further studies of BTKi/CELMoDs with R-CHOP currently ongoing

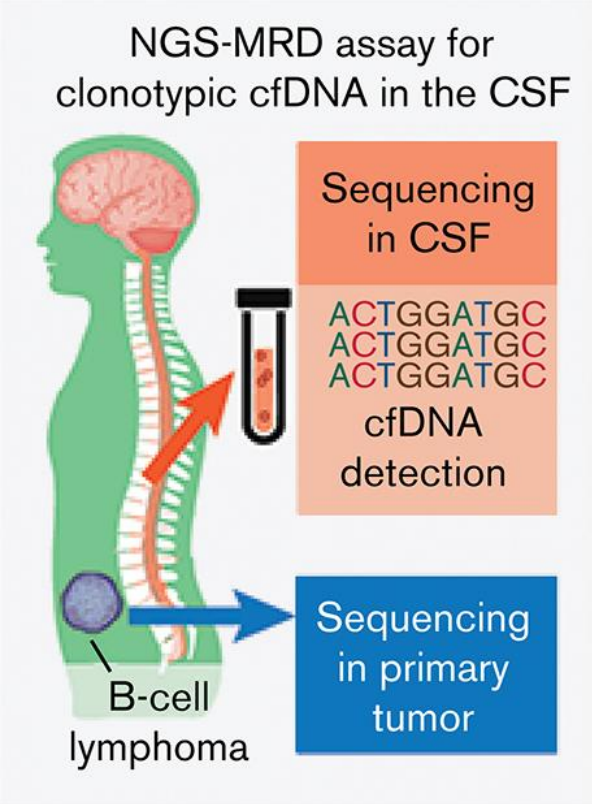
– **CAR T-cell therapy**

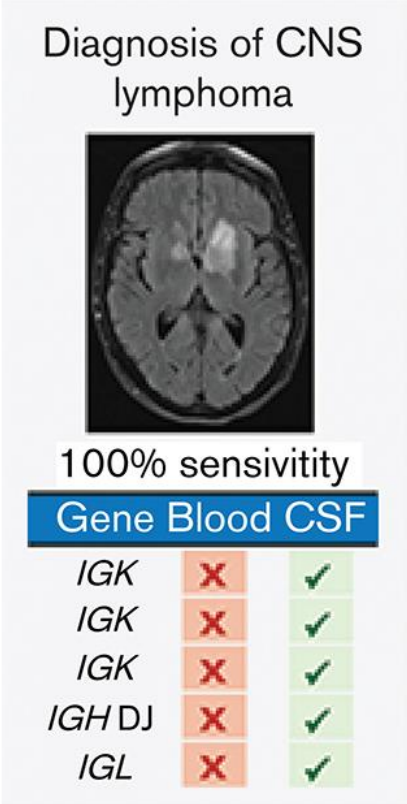
- Activity in relapsed CNS lymphoma[3]
- Clinical trials in 1st line ongoing[4]
- Role as prophylaxis?

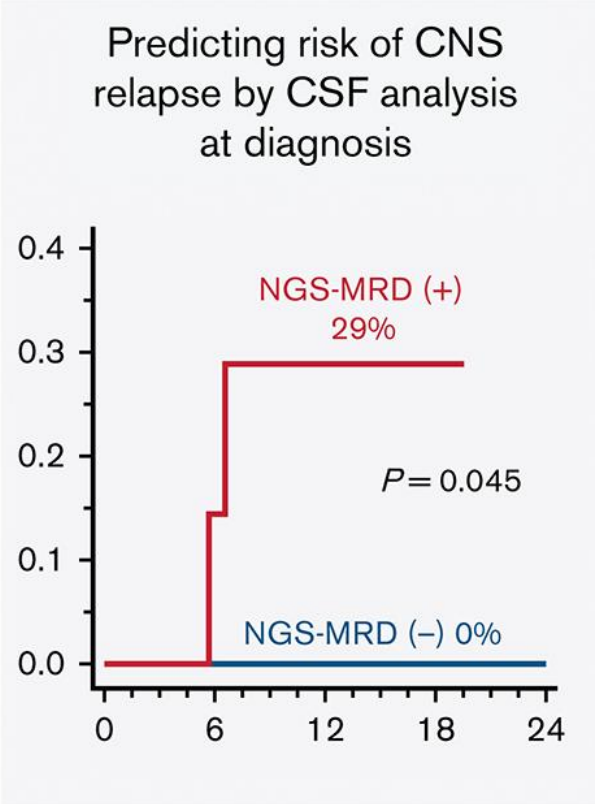
CNS-specific outcomes within genetically defined subtypes should be reported from clinical trials

[1]Younes A et al. J Clin Oncol 2019, [2]Nowakowski GS et al. J Clin Oncol 2021
[3]Siddiqi T et al. Blood Adv 2021[4]Neelapu SS et al. Nat Med 2022

Is the future: CSF ctDNA?







Olszewski et al, Blood Advances 2021:

- NGS-MRD assay detected clonotypic DNA in 100% of CSF samples from patients with known CSF involvement (7 parenchymal only)
- 8/22 high CNS risk patients had detectable CSF ctDNA
- Positive ctDNA → 29% risk CNS recurrence

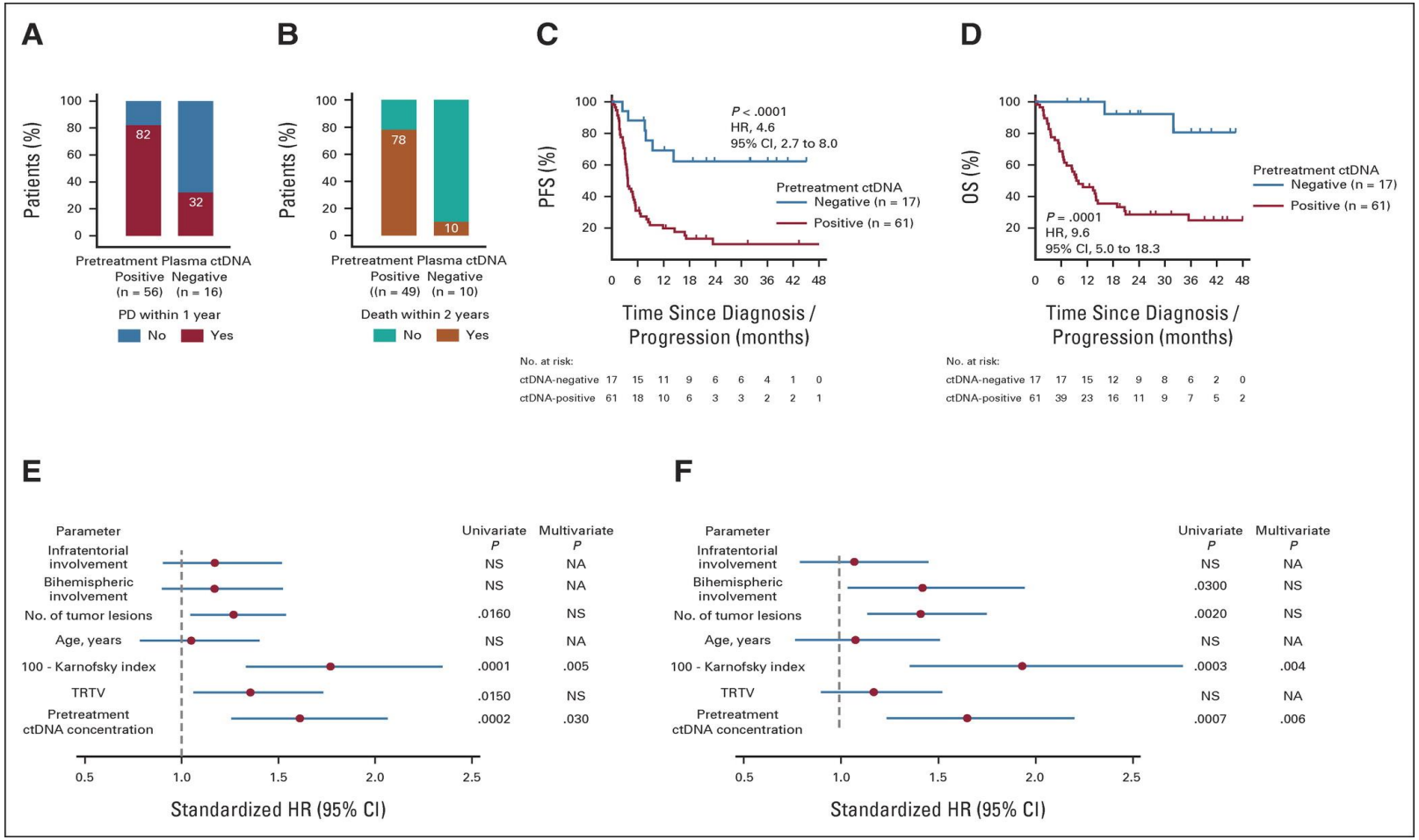
Bobillo et al, Haematologica 2021:

- CSF ctDNA analysed in 19 patients (systemic/CNS lymphoma n=1, systemic lymphoma n=12, CNS lymphoma n=6,
- Positive CSF ctDNA detected 3 months prior to CNS relapse in 1 patient with systemic lymphoma

Challenges

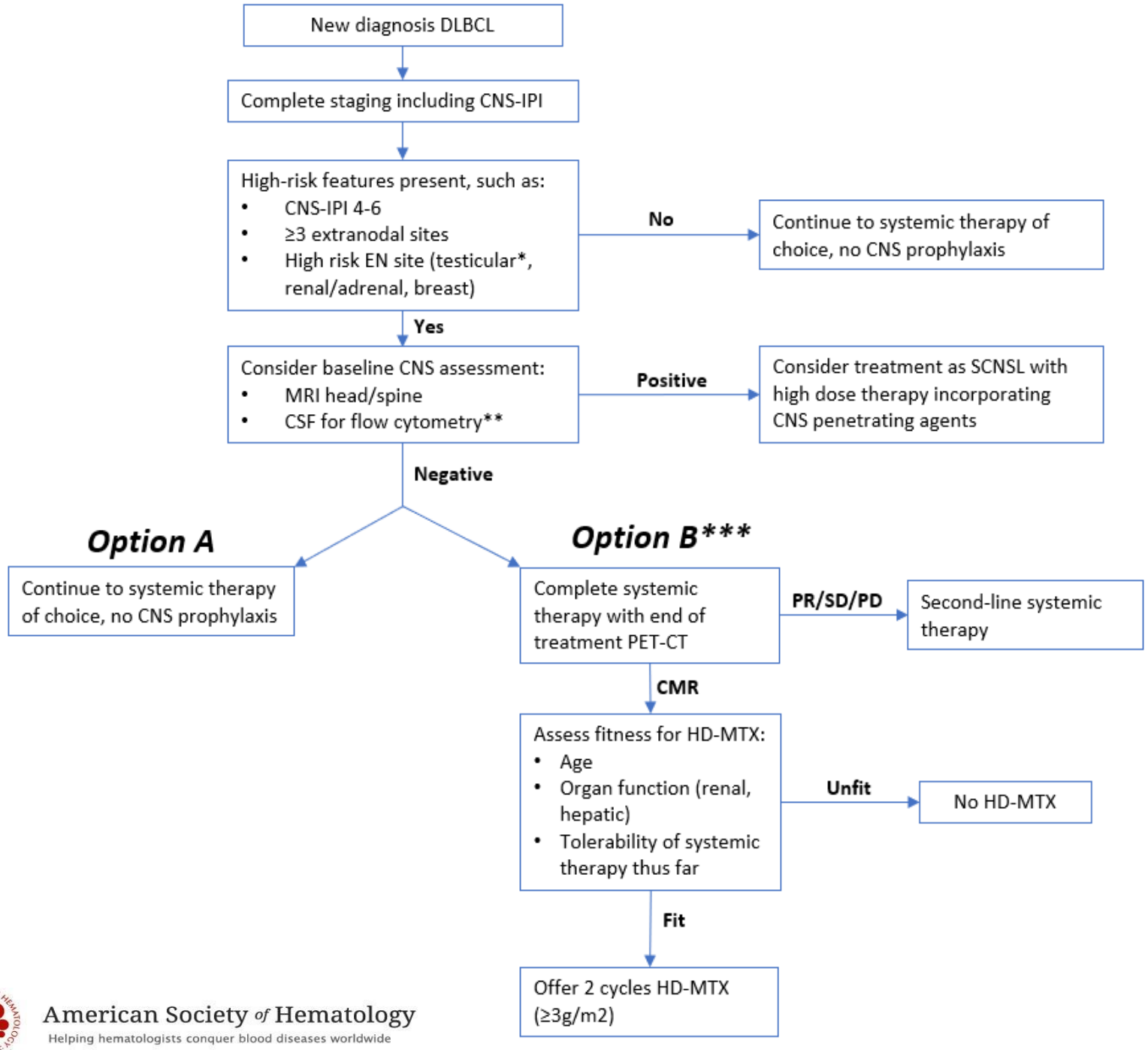
- Lumbar punctures prior to and during treatment
- Tumour heterogeneity
- Limited amount of ctDNA in the CSF

Prognostic value of ctDNA in pre-treatment plasma samples of patients with PCNSL



Mutter J *et al*, JCO 2023

Proposed algorithm for CNS Prophylaxis in DLBCL in 2022



Consider IT therapy for Testicular DLBCL

***CSF ctDNA: currently being assessed prospectively in trials*

****Lack of evidence to suggest efficacy but consider for highest risk patients,*

e.g. CNS-IPI 5/6, renal/adrenal, testicular involvement

Wilson, Bobillo & Cwynarski,
Hematology Am Soc Hematol Educ Program, 2022

Suggested approaches to CNS prophylaxis in 2023

- Greater emphasis on baseline screening – MRI + LP/CSF for high risk patients
  - CSF ctDNA once available
  - Do positive results warrant intensified treatment – e.g. MARIETTA, R-CODOX-M/R-IVAC?

- Reserve/discuss HD-MTX for 'ultra high-risk' – e.g.
  - Testicular, renal/adrenal, breast
  - ≥3 EN sites
  - *CNS-IPI 5-6*

- Discuss delivery of HD-MTX at EOT, ***after*** confirmation of systemic remission (CMR on PET)

- IT therapy only in Testicular DLBCL (IELSG30 data)

- Clinical trial enrolment – e.g. REMODL-A (+/- acalabrutinib), ESCALADE

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