

IN PURSUIT OF *YOUR CURE.*[®]

Treatment of Primary CNS Lymphoma

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@SylvesterCancer



Disclosures

- AdBoard

- Genentech, Lilly, Amgen, TG Therapeutics, Incyte, BeiGene, Janssen, Epizyme, SeaGen, Kite, ADC Therapeutics

- Research Funding

- Lilly, Incyte, BeiGene, BostonGene, ONO Therapeutics

Primary CNS Lymphoma – Treatment goals

- Minimize neurotoxicity and toxicity

- 2 phases
 - Induction
 - Consolidation

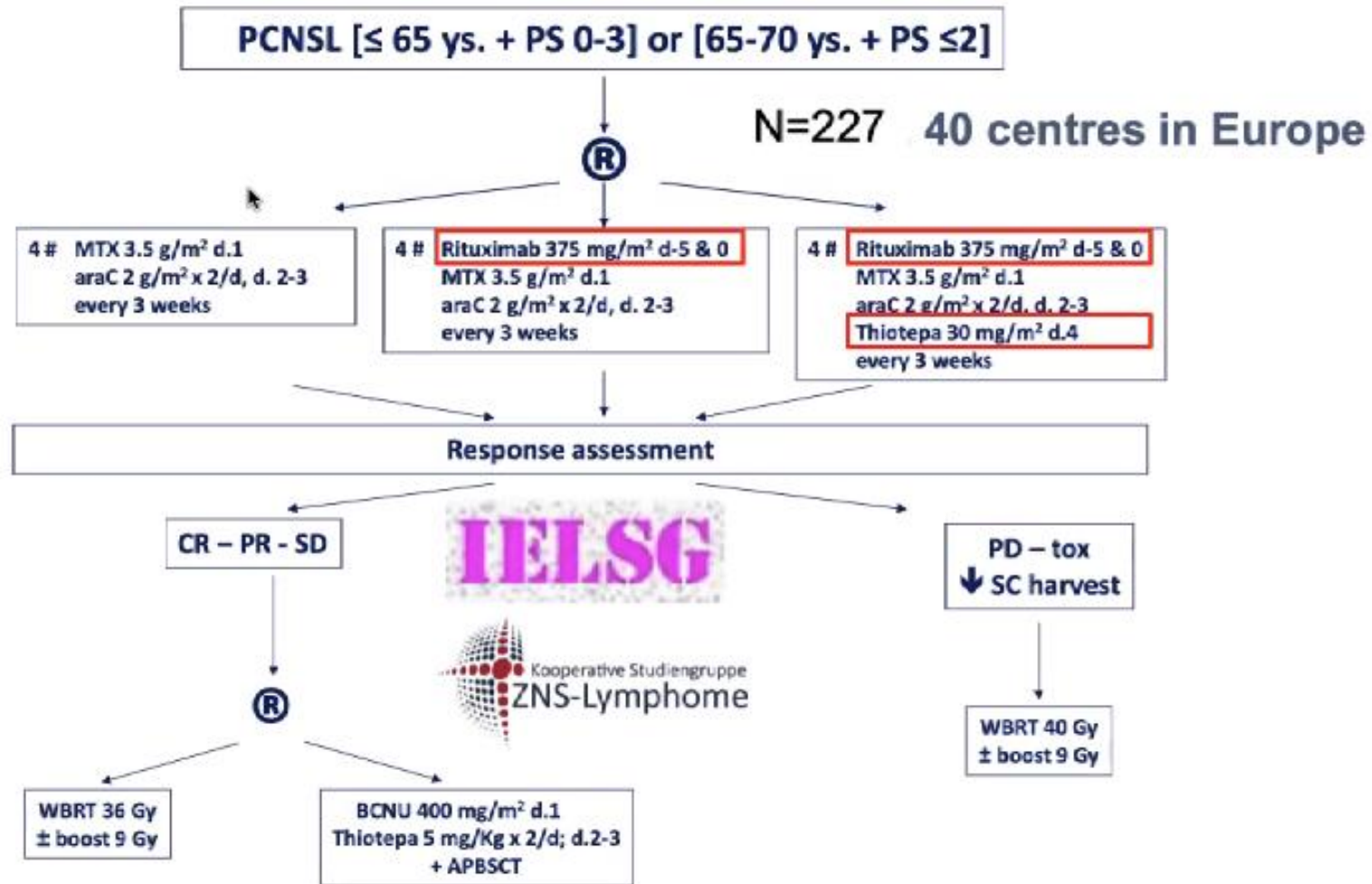
- Achieve adequate disease control
 - Neurologic recovery
 - HD MTX based therapy – high response rate
 - Combination – higher response, higher toxicity
 - Frequent recurrence

- Decrease/delay recurrence
 - Consolidation therapy
 - Maintenance therapy

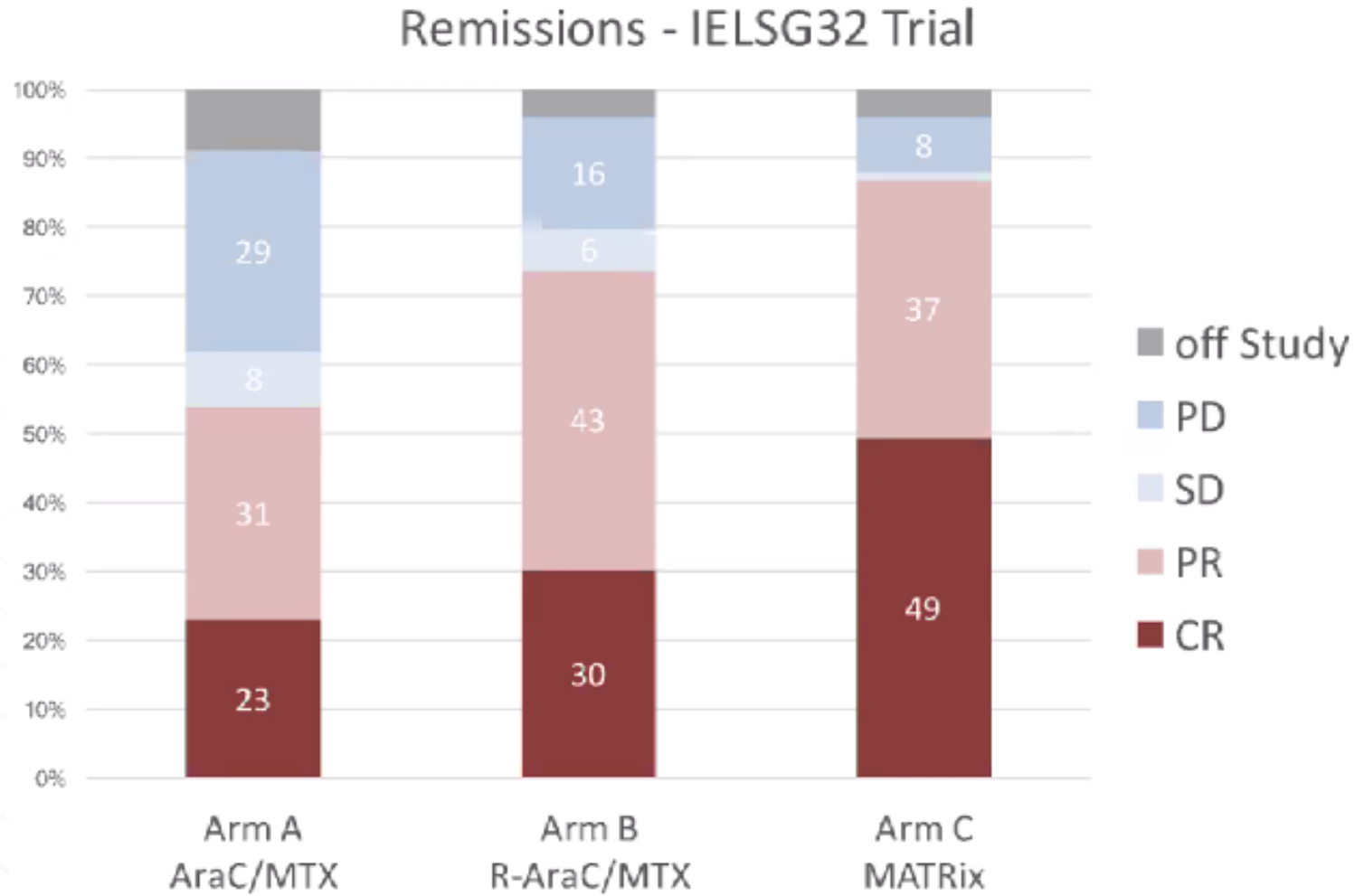
Primary CNS Lymphoma – Radiation therapy

- WBRT
 - No clear role for focal XRT/radiosurgery
- Responses but early relapse
- Neurotoxicity
 - Cognitive deficit, memory loss, ataxia, incontinence
- Avoided as single modality
 - Consolidation
 - Palliation in relapsed disease

Primary CNS Lymphoma – MATRix



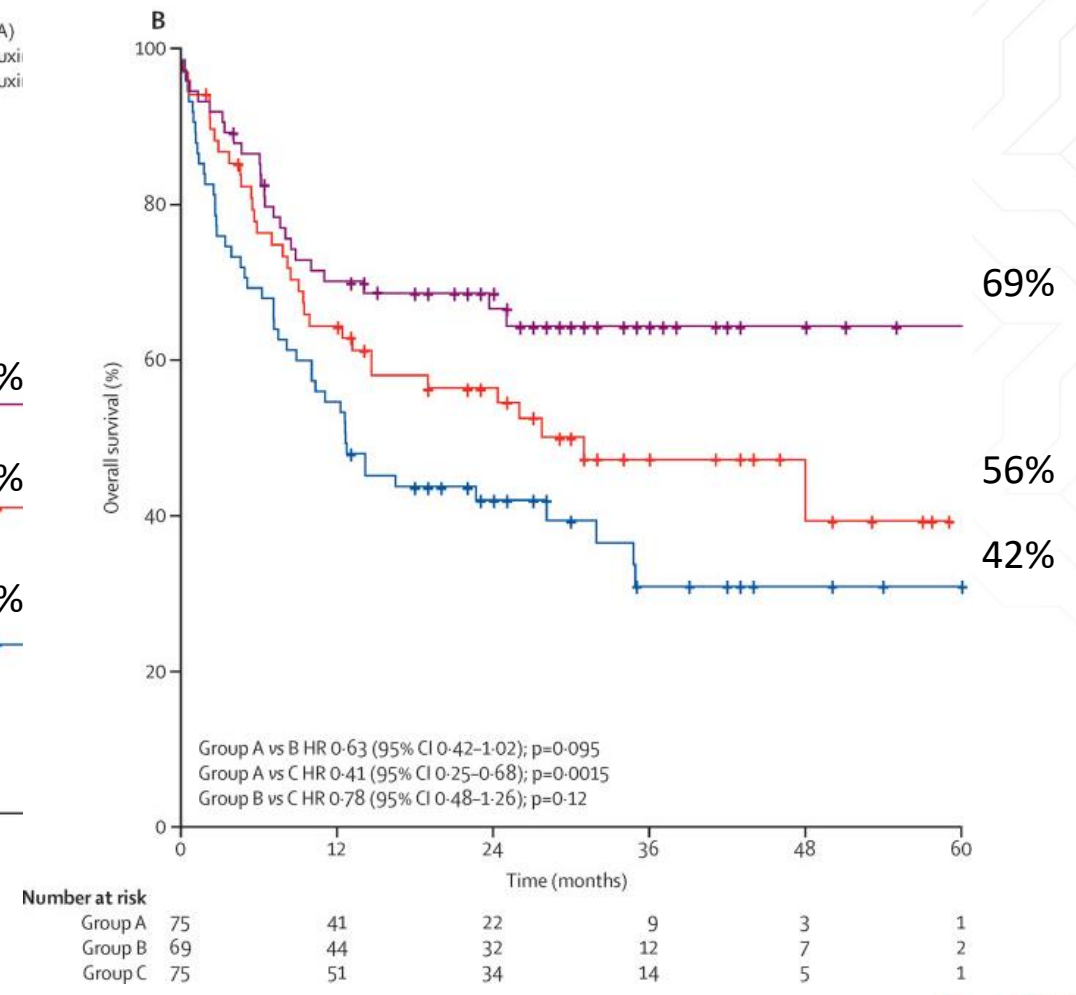
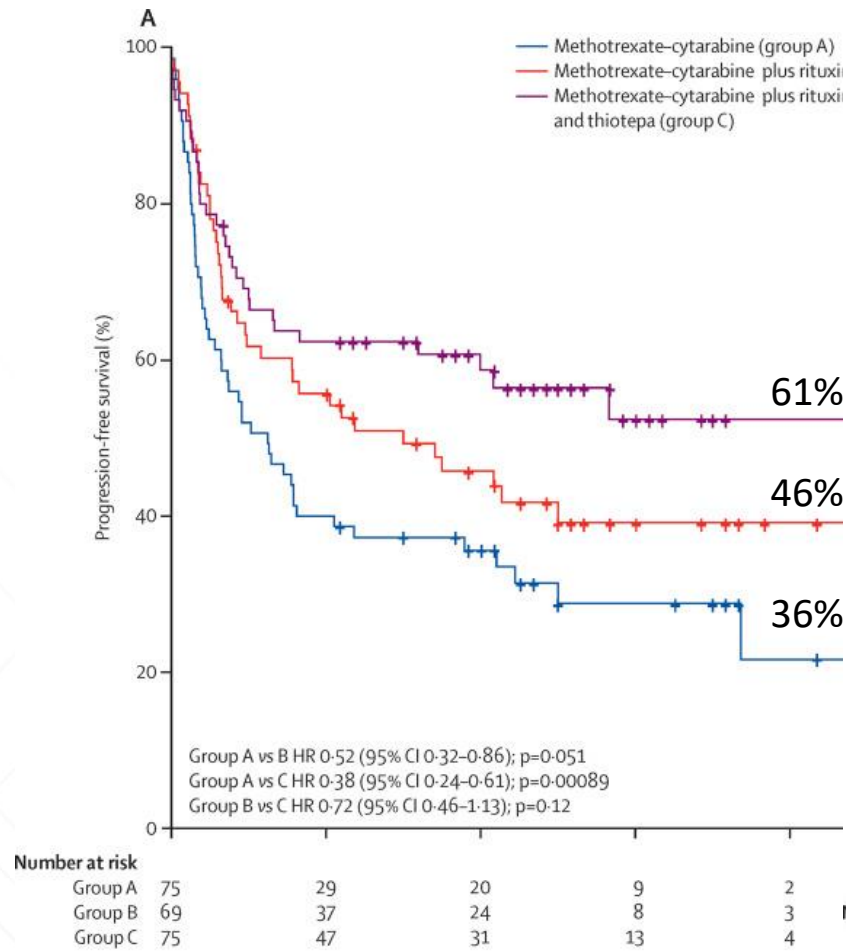
Primary CNS Lymphoma – MATRix



Lancet Haematol 3:e217, 2016

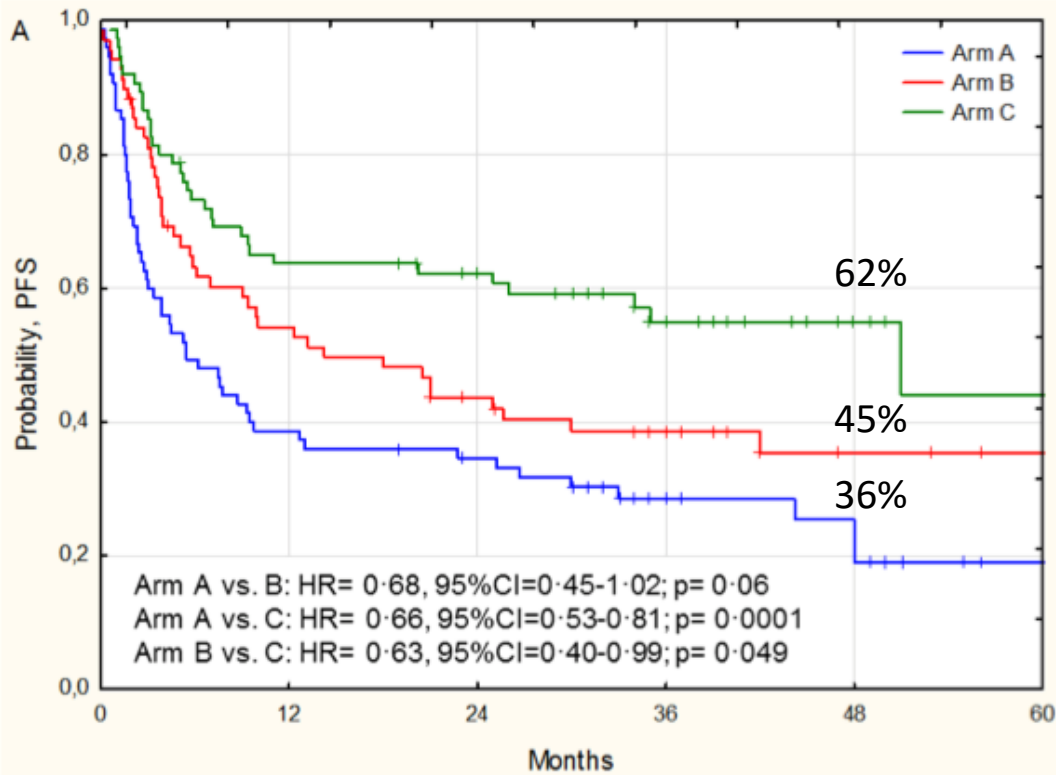
Primary CNS Lymphoma – MATRix

Median
f/u 30 mos

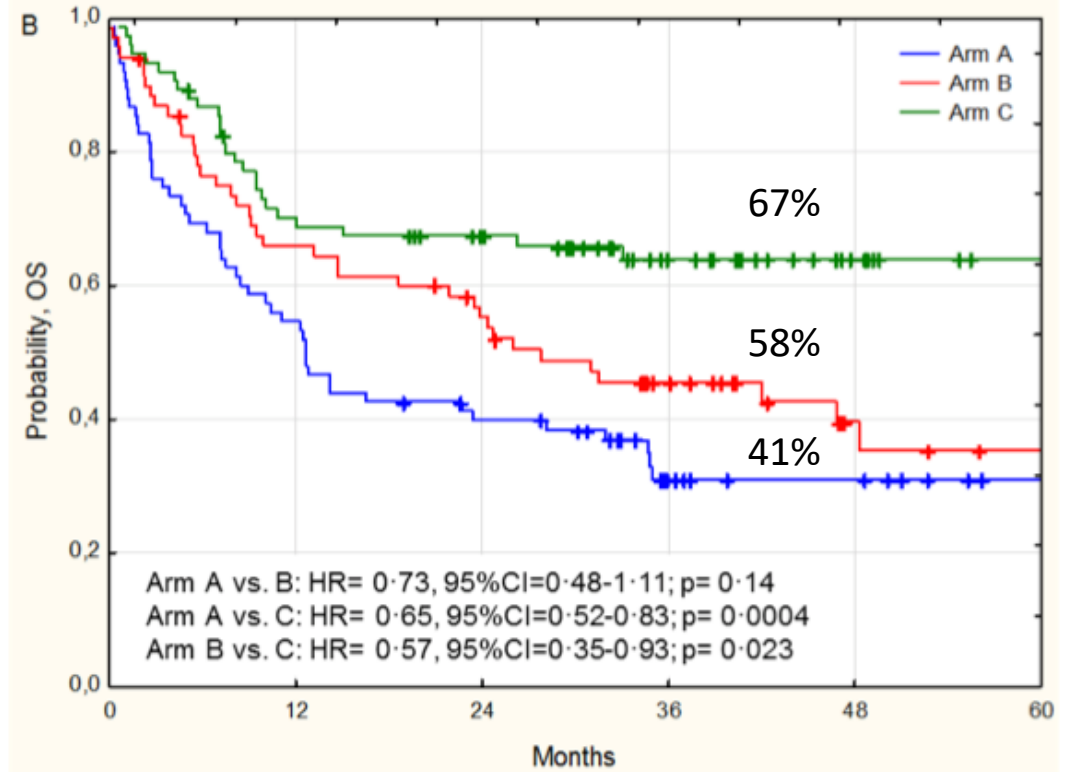


Primary CNS Lymphoma – MATRix

Median
f/u 40 mos



Months	0	12	24	36	48	60
Arm A	75	29	27	13	8	1
Arm B	69	36	30	19	5	3
Arm C	75	47	44	23	10	4



Months	0	12	24	36	48	60
Arm A	75	41	30	13	9	2
Arm B	69	44	37	24	9	6
Arm C	75	51	47	26	10	4

Primary CNS Lymphoma – MATRix

	Methotrexate–cytarabine (group A; n=75); 223 (74%) courses delivered*				Methotrexate–cytarabine plus rituximab (group B; n=69); 236 (86%) courses delivered*				Methotrexate–cytarabine plus rituximab and thiotepa (group C; n=75); 274 (91%) courses delivered*			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Neutropenia	12 (5%)	18 (8%)	99 (44%)	0	24 (10%)	15 (6%)	119 (50%)	0	14 (5%)	31 (11%)	153 (56%)	0
Thrombocytopenia	18 (8%)	43 (19%)	116 (52%)	0	27 (11%)	36 (15%)	140 (59%)	0	21 (8%)	27 (10%)	200 (73%)	0
Anaemia	115 (52%)	63 (28%)	9 (4%)	0	124 (53%)	77 (33%)	6 (3%)	0	131 (48%)	116 (42%)	14 (5%)	0
Febrile neutropenia/ infections	11 (5%)	32 (14%)	10 (4%)	6 (3%)	21 (9%)	23 (10%)	7 (3%)	2 (<1%)	18 (7%)	42 (15%)	3 (1%)	0
Hepatotoxicity	71 (32%)	20 (9%)	6 (3%)	0	76 (32%)	25 (11%)	3 (1%)	0	77 (28%)	19 (7%)	1 (<1%)	0
Nephrotoxicity	28 (13%)	3 (1%)	0	0	31 (13%)	4 (2%)	0	0	17 (6%)	2 (<1%)	1 (<1%)	0
Cardiotoxicity	0	0	0	0	0	2 (<1%)	0	0	0	2 (<1%)	1 (<1%)	0
Coagulopathy/deep vein thrombosis (including pulmonary embolism)	2 (1%)	3 (1%)	0	0	3 (1%)	3 (1%)	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)	2 (<1%)
Gastrointestinal	35 (16%)	1 (<1%)	0	0	106 (45%)	5 (2%)	1 (<1%)	0	81 (30%)	9 (3%)	1 (<1%)	0
Mucositis	20 (9%)	3 (1%)	0	0	37 (16%)	2 (<1%)	2 (<1%)	0	45 (16%)	1 (<1%)	0	0
Acute neurotoxicity	28 (13%)	3 (1%)	3 (1%)	0	34 (14%)	4 (2%)	0	0	19 (7%)	6 (2%)	2 (<1%)	0
Hyperglycaemia	0	4 (2%)	0	0	0	0	0	0	0	0	1 (<1%)	0
Sudden death†	1 (<1%)	0	1 (<1%)
Non-lethal interruptions	0	0	2 (<1%)	0	0	0	2 (<1%)	0	0	0	1 (<1%)	0

Lancet Haematol 3:e217, 2016

Primary CNS Lymphoma – HD MTX w XRT

- RTOG/SWOG 93-10

- ph 2
- WBRT 45 Gy
- CR - hyperfractionated WBRT 36 Gy

Methotrexate IV 2.5 g/m²
 Vincristine IV 1.4 mg/m²
 Procarbazine PO 100 mg/m²/d for 7 days
 Methotrexate Intra-Ommaya 12 mg
 Leucovorin 20 mg PO every 6 hours for 12 doses
 Leucovorin 10 mg PO bid for 8 doses
 Decadron, mg/d for 7 days
 Whole-brain RT
 Cytarabine 3 mg/m²/d for 2 days

	Weeks																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Methotrexate IV 2.5 g/m ²	X		X		X		X		X										
Vincristine IV 1.4 mg/m ²	X		X		X		X		X										
Procarbazine PO 100 mg/m ² /d for 7 days	X				X				X										
Methotrexate Intra-Ommaya 12 mg		X		X		X		X		X									
Leucovorin 20 mg PO every 6 hours for 12 doses	X		X		X		X		X										
Leucovorin 10 mg PO bid for 8 doses		X		X		X		X		X									
Decadron, mg/d for 7 days	16	12	8	6	4	2													
Whole-brain RT											X	X	X	X	X				
Cytarabine 3 mg/m ² /d for 2 days																X			X

Primary CNS Lymphoma – HD MTX w XRT

- RTOG/SWOG 93-10

- severe delayed neurologic toxicity (12 of 82 [15%])
 - Leukoencephalopathy
 - onset median 504 days (80-1540 days) after the start of XRT
 - Similar younger/older than 60
 - Eight fatal (10%)

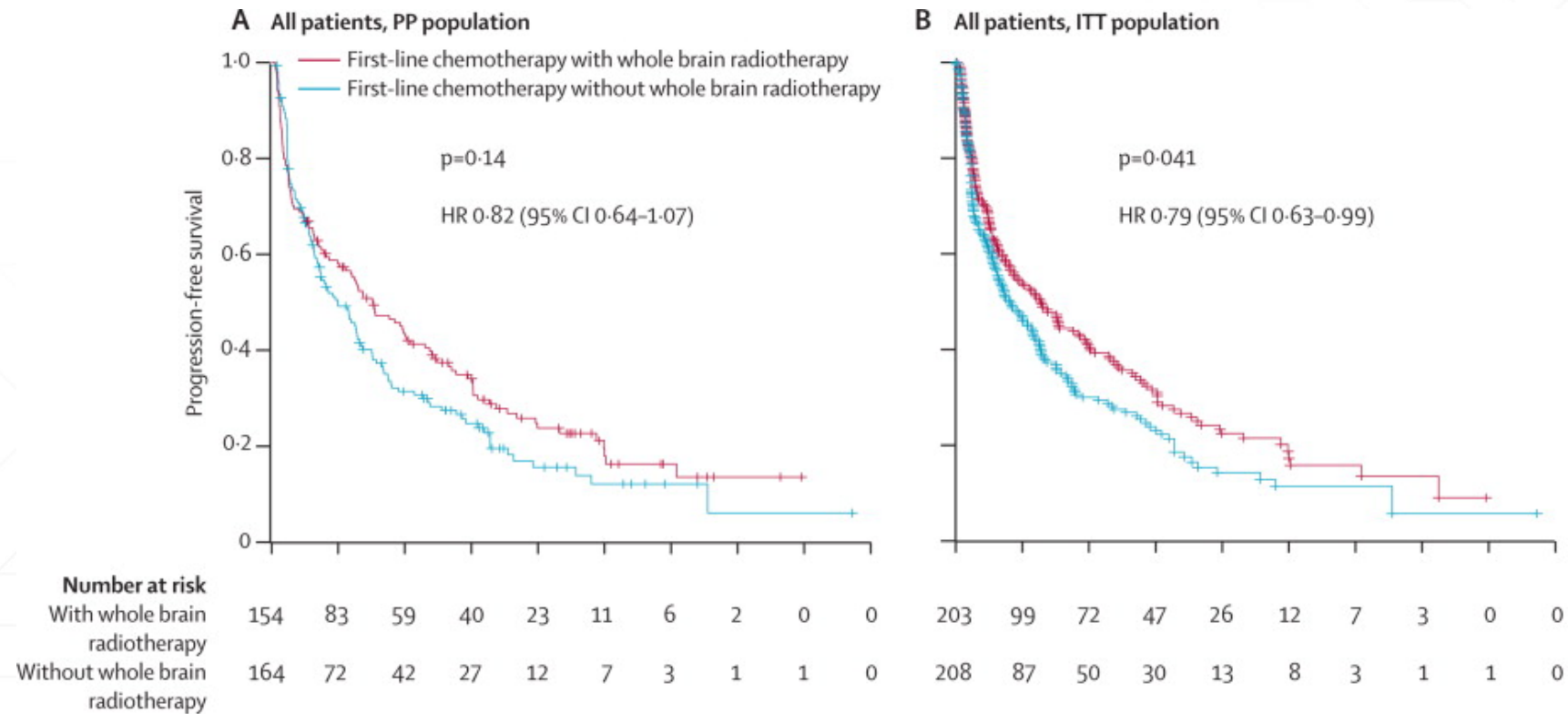
Primary CNS Lymphoma – HD-MTX + Ifos +/- XRT

■ G-PCNSL-SG-1

- Non-inferiority ph 3
- Omission of XRT would not impact OS
 - **MTX 4 g/m² D1 + ifos 1.5 g/m² D3-5 q2w x 6 → WBRT 45 Gy**
 - vs
 - **MTX 4 g/m² D1 + ifos 1.5 g/m² D3-5 q2w x 6 → cytarabine (if no CR)**
- n=551, median age 63 (55-69)
 - 318 treated per protocol

Primary CNS Lymphoma – HD-MTX + Ifos +/- XRT

median PFS 18.3 mos WBRT vs 11.9 mos no XRT (p=0.14)



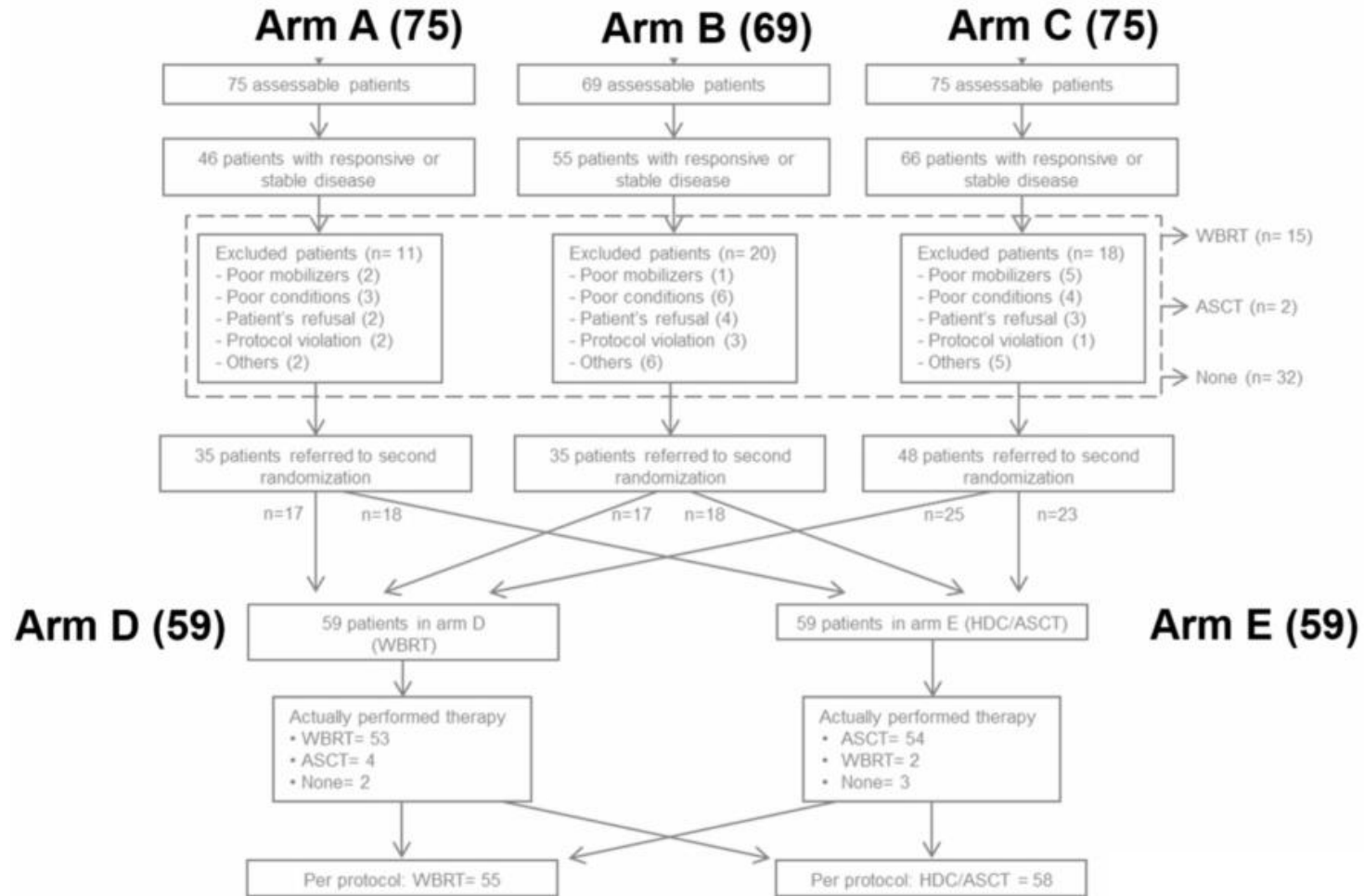
Lancet Oncol 11:1036-1047, 2010

Primary CNS Lymphoma – HD-MTX + Ifos +/- XRT

- Longer follow-up - neurotoxicity
 - WBRT (49% clinical assessment; 71% neuroradiology)
 - no XRT (26% clinical assessment; 46% neuroradiology)

- QoL/MMSE exploratory data in 318 PP patients 2 years after randomization
 - Worse cognitive functioning (p = 0.004)
 - Global health status reduced (p = 0.022)
 - Worse fatigue (p = 0.037)
 - Appetite loss (p = 0.006)
 - Hair loss (p = 0.002)
 - Lower MMSE (p = 0.002)
 - mixed model analysis favored no WBRT in 15 of 26 QoL dimensions

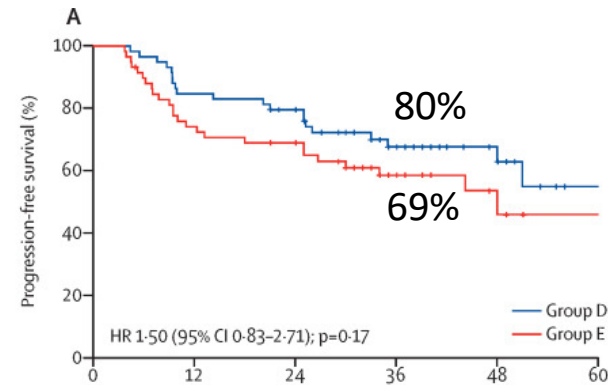
Primary CNS Lymphoma – MATRix



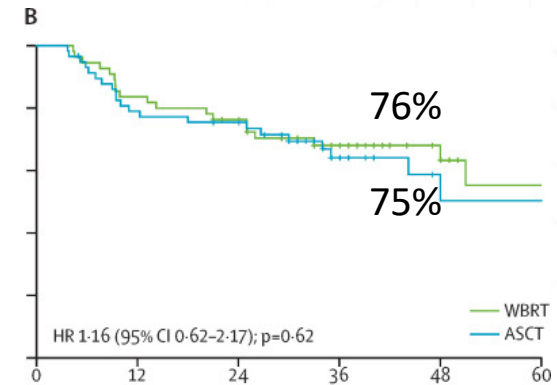
Primary CNS Lymphoma – MATRix

Median f/u 40 mos

ITT

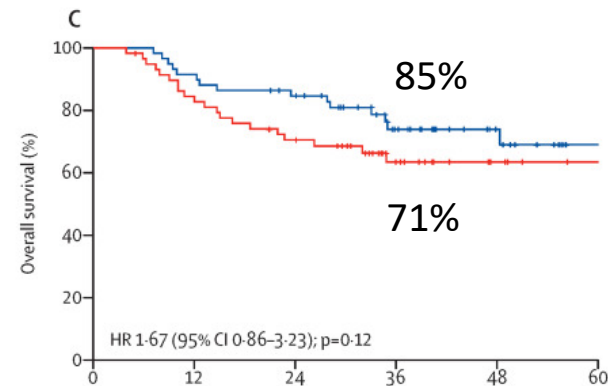


Number at risk	0	12	24	36	48	60
Group D	59	50	45	26	14	3
Group E	59	43	40	20	7	3

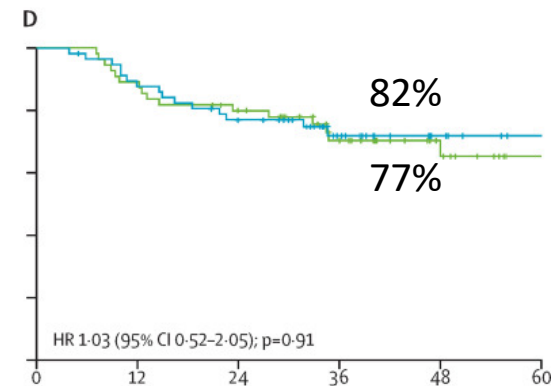


Number at risk	0	12	24	36	48	60
WBRT	55	46	40	25	14	3
ASCT	58	45	43	21	7	3

PP



Number at risk	0	12	24	36	48	60
Group D	59	54	48	30	16	3
Group E	59	49	41	22	9	5

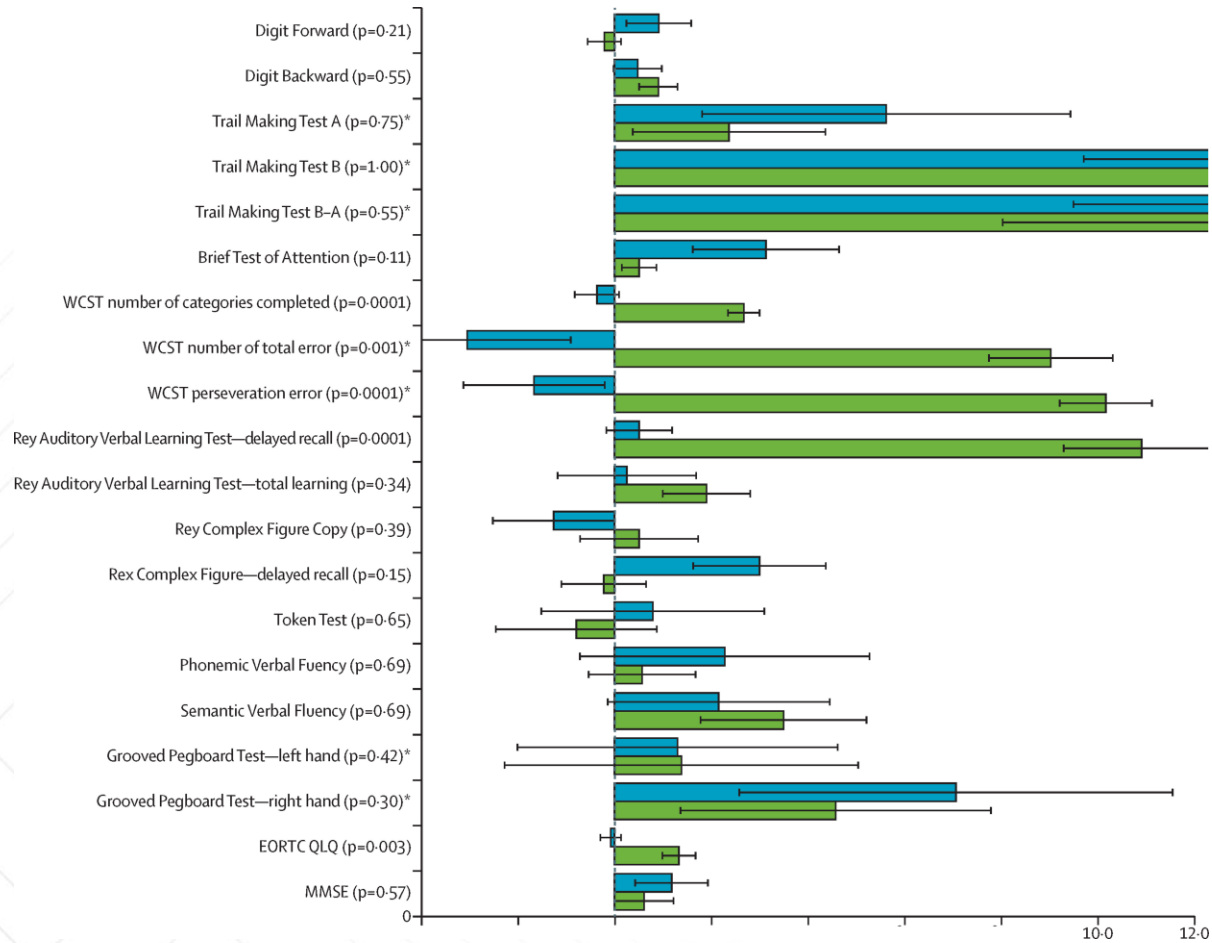


Number at risk	0	12	24	36	48	60
WBRT	55	49	42	27	15	3
ASCT	58	51	44	24	10	5

Lancet Haematol 4:e510, 2017

Primary CNS Lymphoma – MATRix

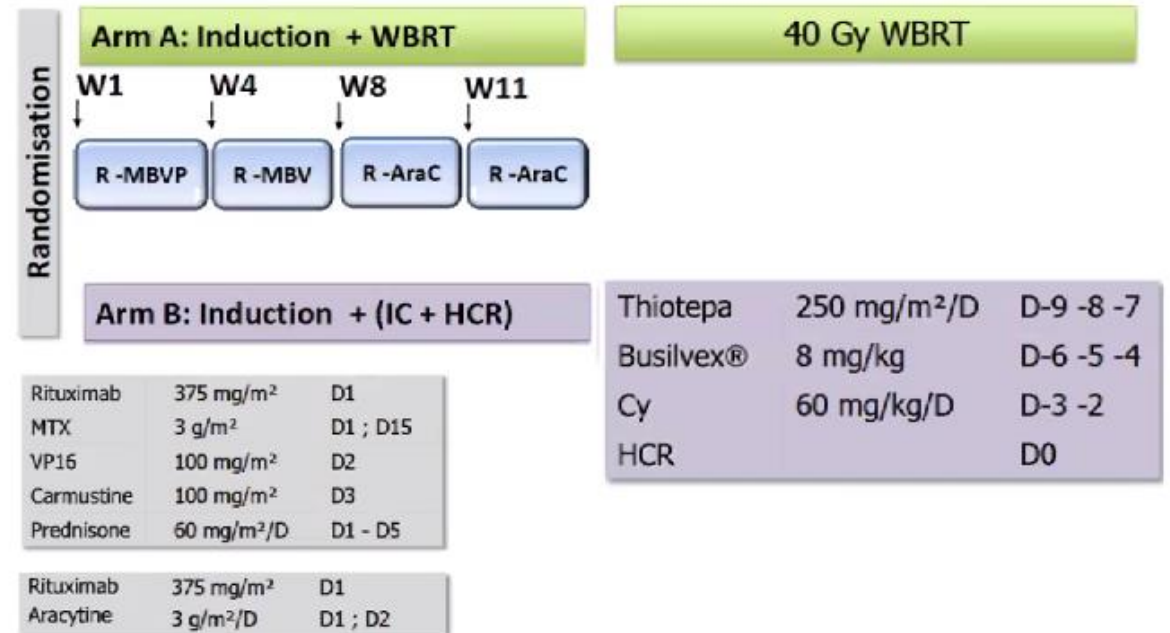
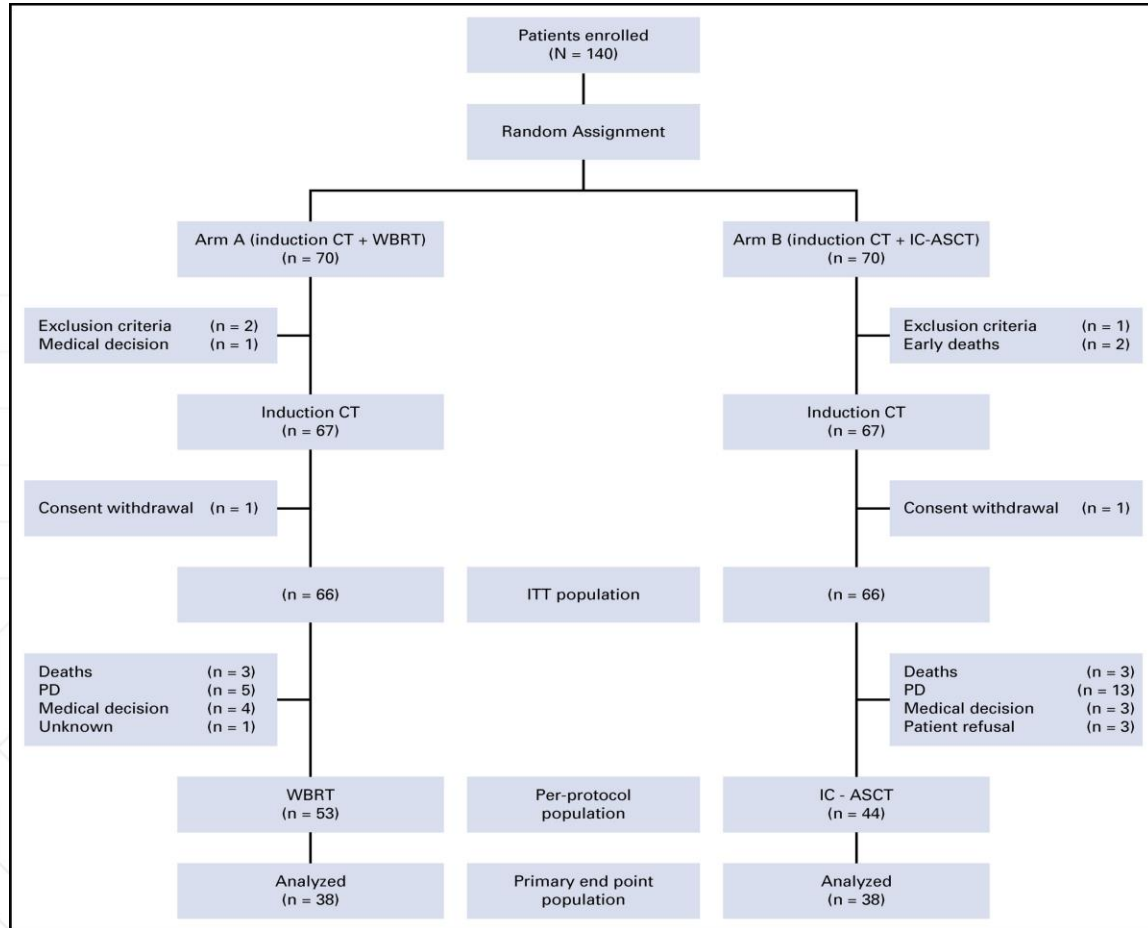
Cognitive function – 2 yrs f/u



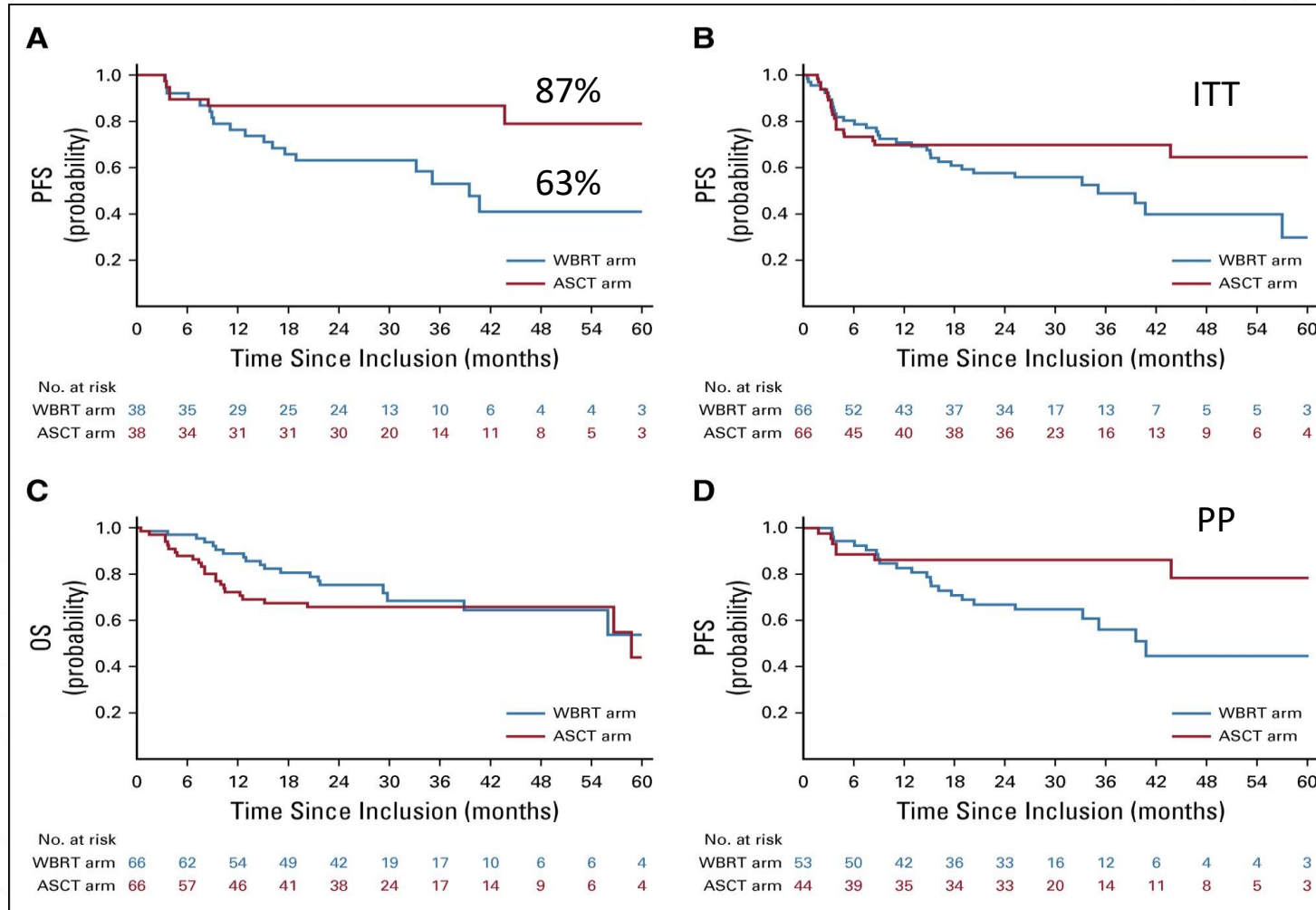
Blue bar – WBRT

Green bar – ASCT

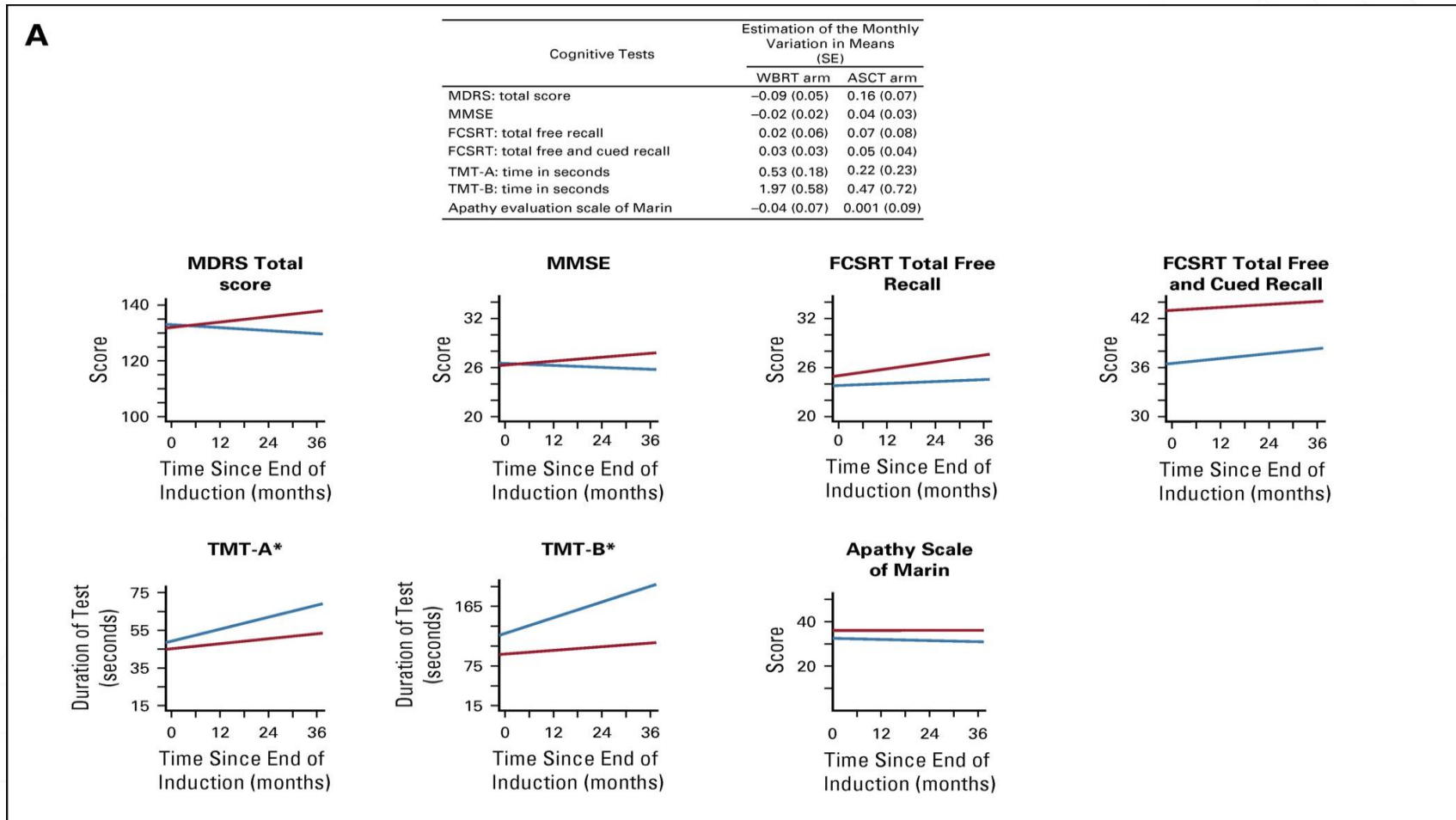
Primary CNS Lymphoma – ASCT vs WBRT - PRECIS



Primary CNS Lymphoma – ASCT vs WBRT - PRECIS

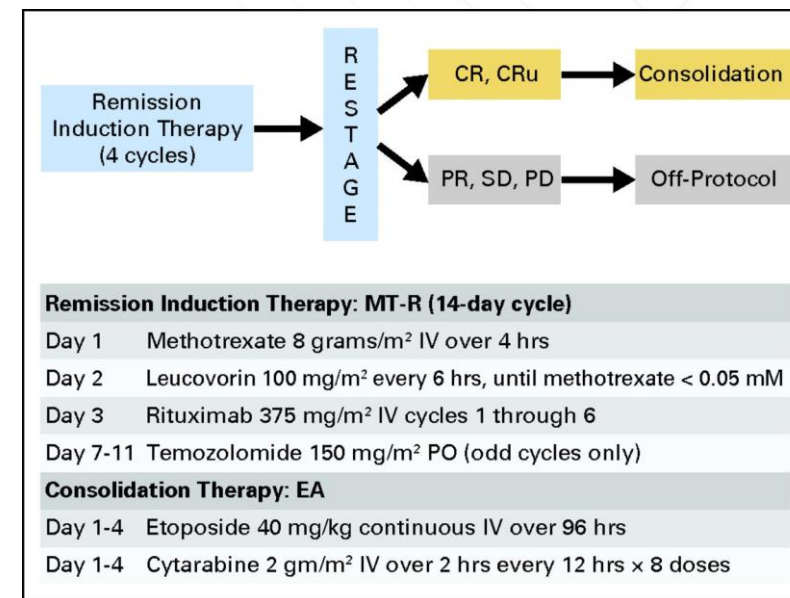


Primary CNS Lymphoma – ASCT vs WBRT - PRECIS



Primary CNS Lymphoma – MA vs non-myeloablative

- Alliance 51101
 - Ph 2 study
 - N=113, median age 61 (33-75)
 - MT-R- x 4 → ASCT (TC) vs EA



Response to Treatment

End of Induction

Group	N	CR/CRu, %	95% CI
All Subjects	108	50	40 - 60
Myeloablative	54	56	41 - 69
Non-Myeloablative	54	44	31 - 59

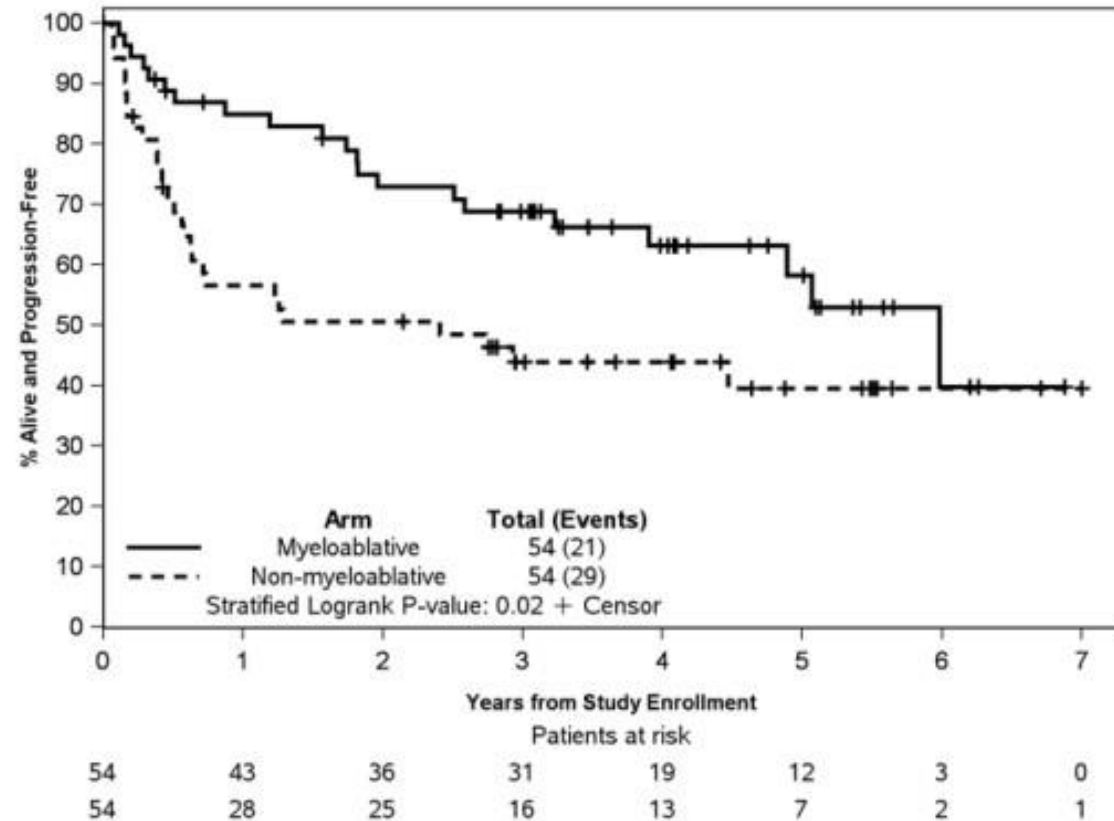
End of Consolidation

Group	N	CR/CRu, %	95% CI
All Subjects	108	60	50 - 69
Myeloablative	54	70	56 - 82
Non-Myeloablative	54	50	36 - 64

Primary CNS Lymphoma – MA vs non-myeloablative

■ Alliance 51101

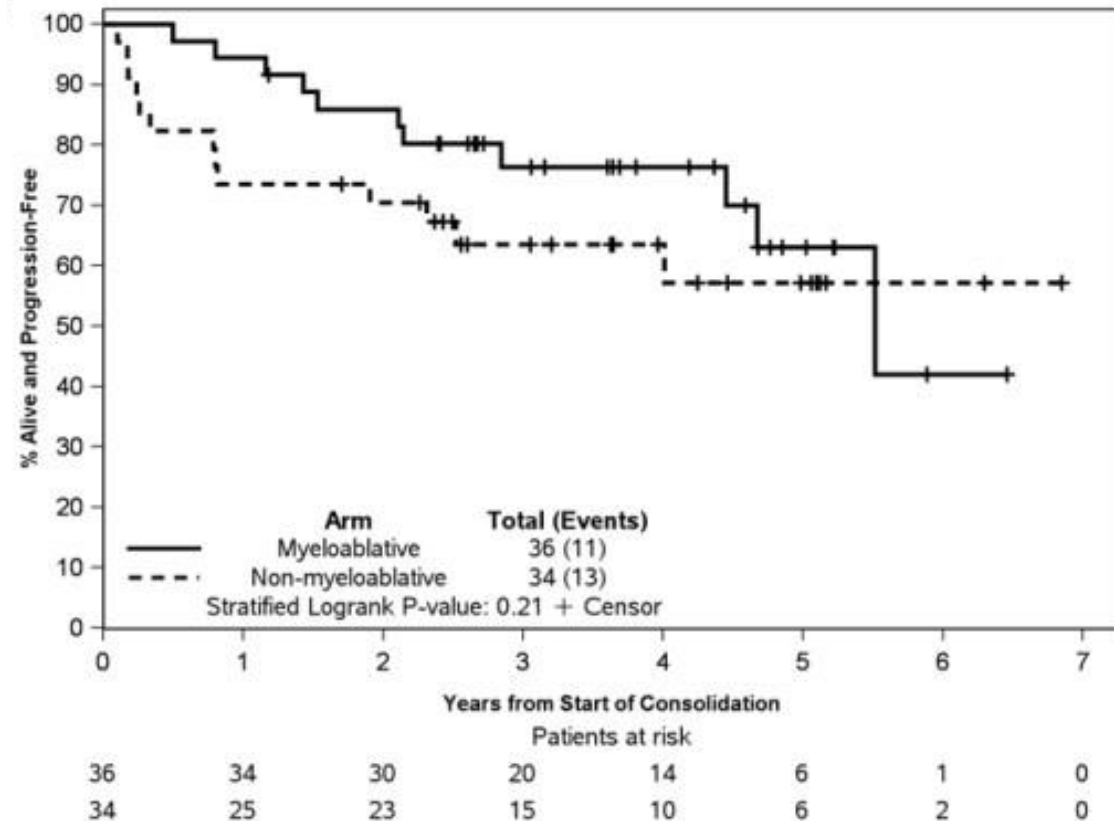
- Median f/u 4.1 yrs
- PFS at 2 yrs (p=0.02)
 - ASCT 73% (59-83%)
 - EA 51% (36-63%)



Primary CNS Lymphoma – MA vs non-myeloablative

■ Alliance 51101

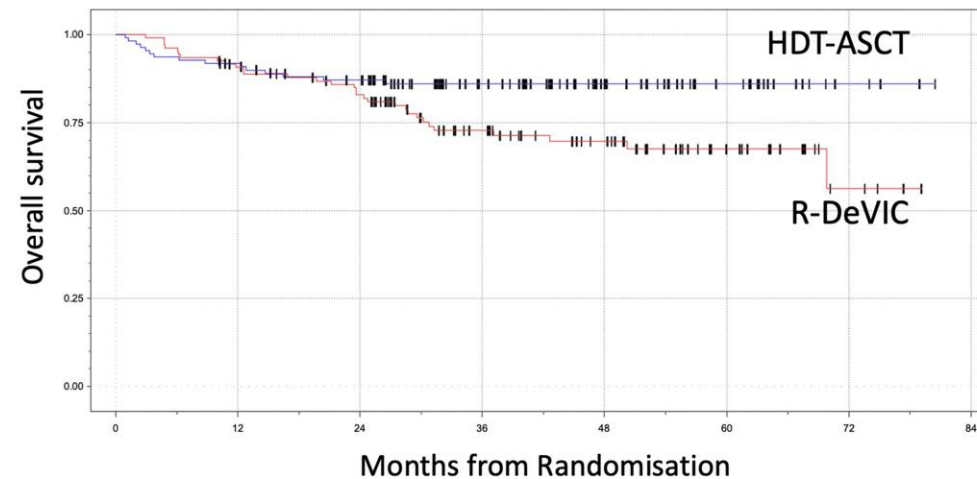
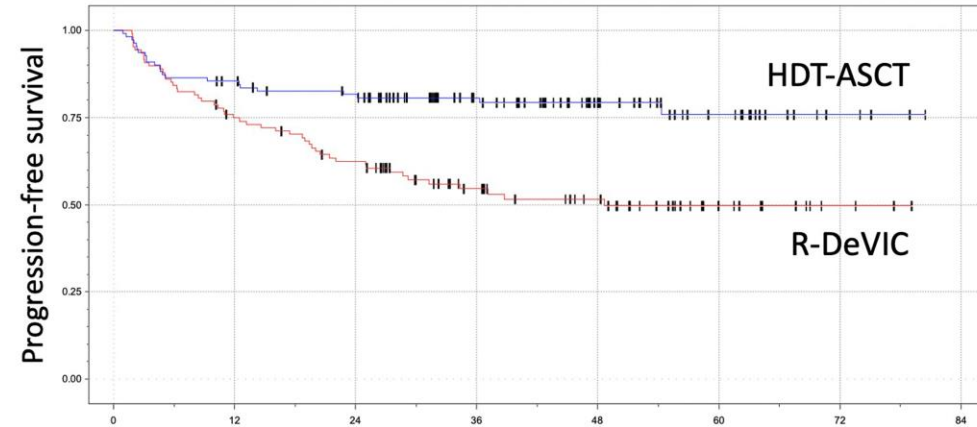
- Median f/u 4.1 yrs
- PFS at 2 yrs (p=0.21)
 - ASCT 86%
 - EA 71%



Primary CNS Lymphoma – IELSG43 - MA vs non-myeloablative

- Randomized phase III trial

- Age 18-65
- MATRix x 4
- R-DeVIC x 2 vs ASCT (TC)
- primary endpoint - PFS



Primary CNS Lymphoma – Current approach - Young

- MTX-based combinations
 - R-MPV (rituximab, methotrexate, procarbazine, vincristine)
 - MT-R (methotrexate, temozolomide, rituximab)

- Consolidation ASCT
 - TC (thiotepa, carmustine)
 - TBC (thiotepa, busulfan, cyclophosphamide)

- WBRT
 - Less utilized
 - At most rdWBRT

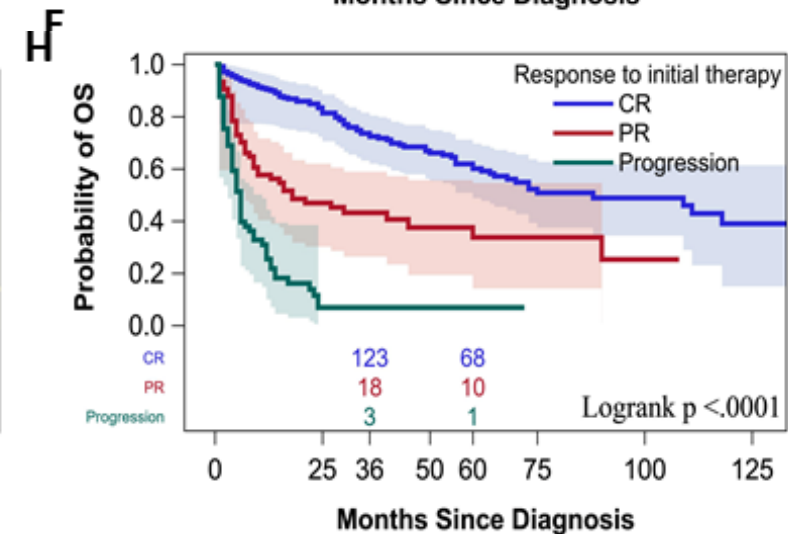
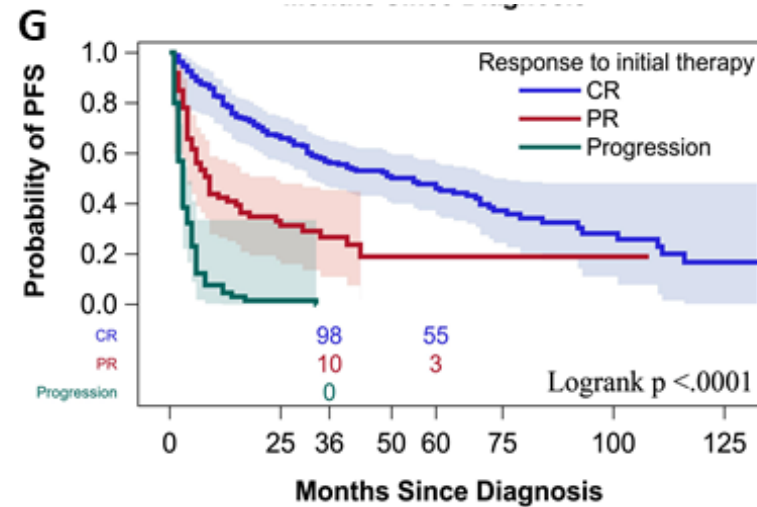
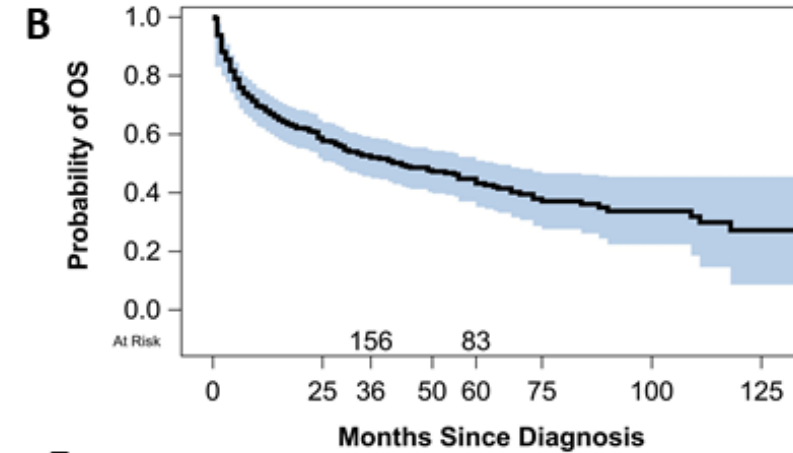
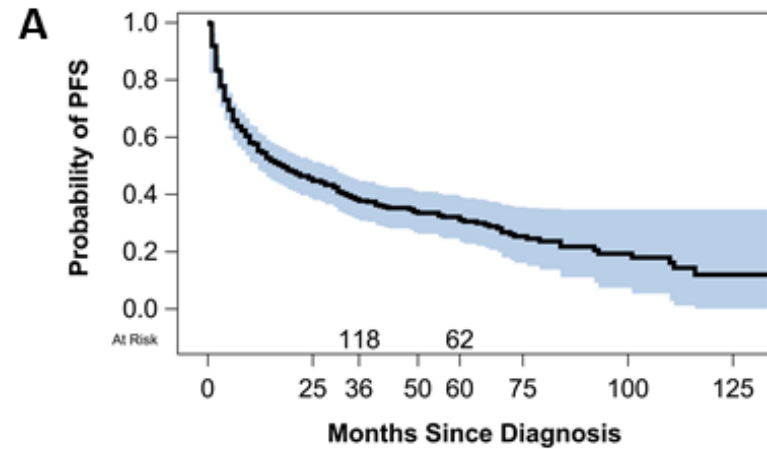
Elderly

Primary CNS Lymphoma – Elderly

- Dose-intensive chemotherapy not an option
 - 1-year PFS ~40%
 - Median OS 14-30 months
 - MTX is most active agent
- n=450
 - median age 71 (60-88)
 - CrCl <60 ml/min 20% (median 81 ml/min)
 - median CIRS-G score 6 (range 0-27)
 - impaired ADLs in 36%
 - geriatric syndrome in 45%
- CT in 91%, median MTX 3.5 g/m² (range 1-8 g/m²)
 - 60% CR, 18% PR
 - 6% SD, 16% primary refractory

Primary CNS Lymphoma – Elderly

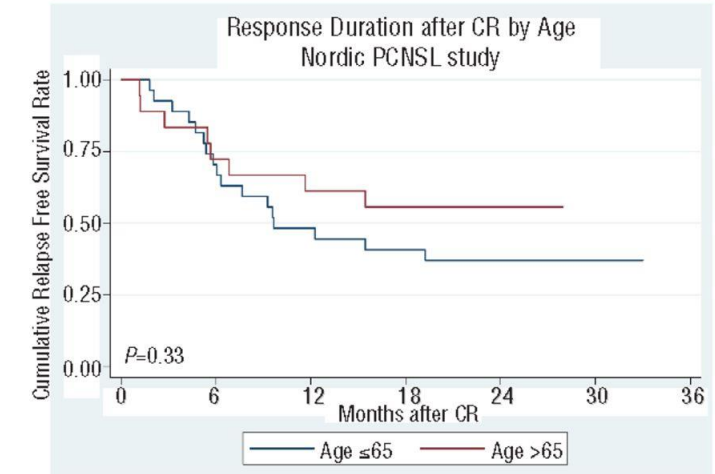
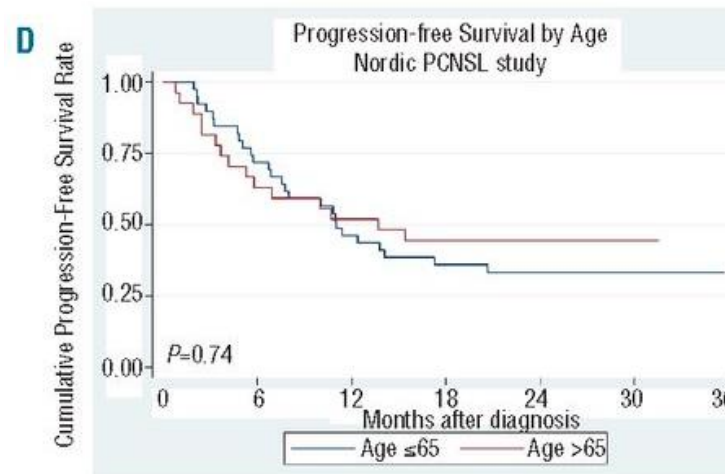
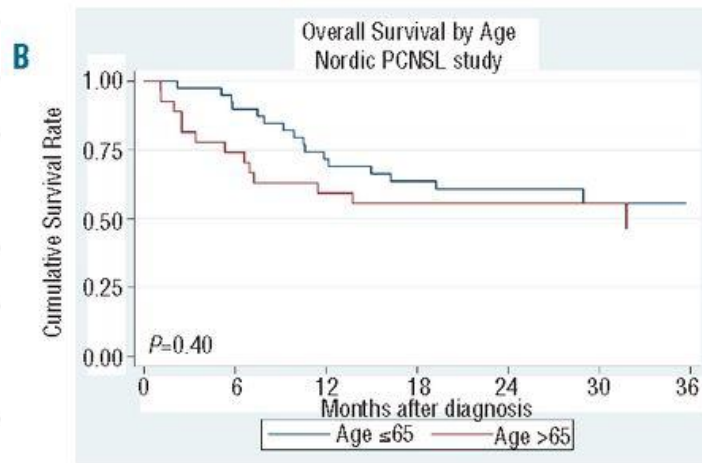
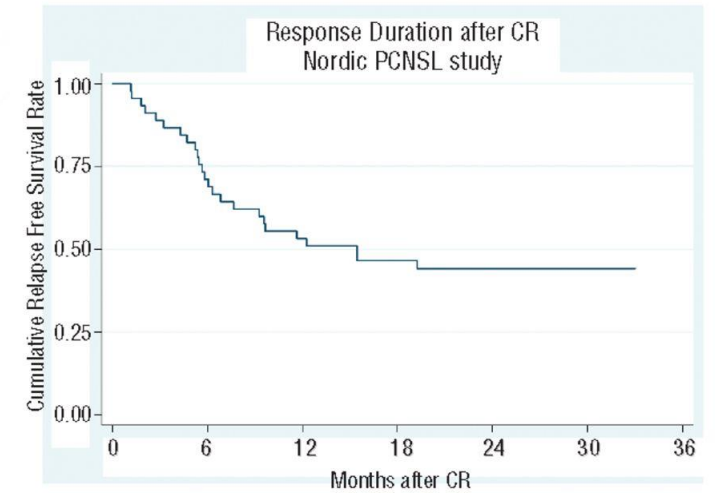
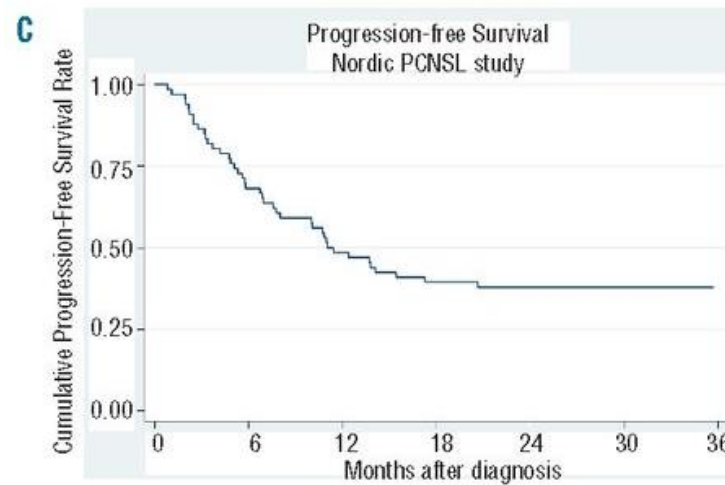
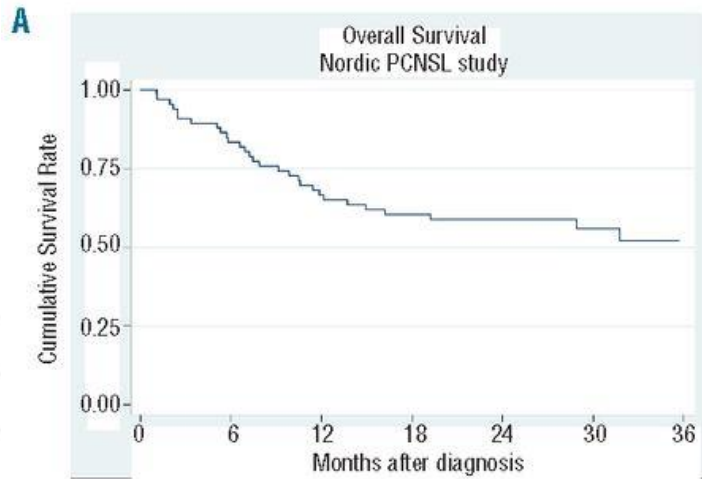
- median f/u 42 mos
- 3-yr PFS 38%
- 3-yr OS 52%
- increasing MTX dosing
- rituximab
- CR



Primary CNS Lymphoma – Elderly - maintenance

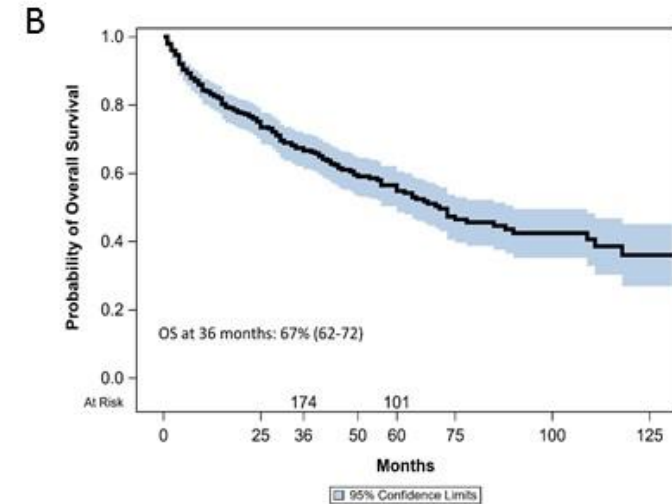
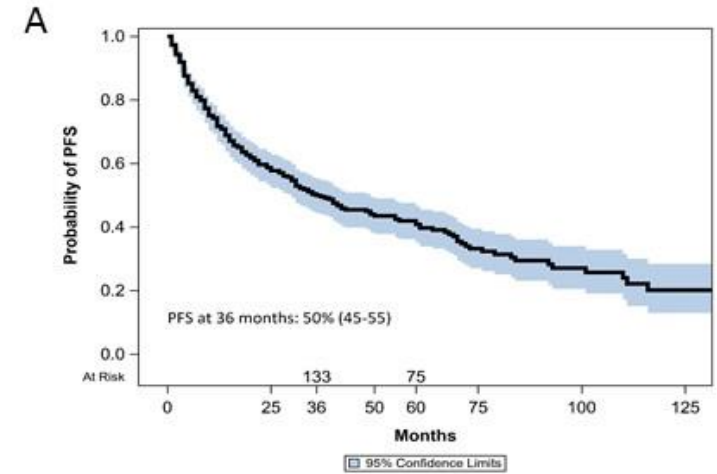
- Ph2 Nordic Lymphoma Group
 - induction based on HD-MTX and cytarabine
 - N=66, age 18-75 (median 66 years)
 - Age>65 (n=27, median 70 yrs) - age-adjusted induction
 - Elderly with maintenance temozolomide 150 mg/m² x 5 d q 28 d x 1 yr
 - Median maint 11 mos
- despite less intense induction, survival similar
 - 2-yr OS 58.7% (60.7% <66 yrs, 55.6% >65 yrs , p=0.4)
- relapse p CR
 - 63% in younger patients (17/27)
 - 28% in older patients (5/18)

Primary CNS Lymphoma – Elderly - maintenance



Primary CNS Lymphoma – Elderly - maintenance

- n=539, mean age 70 (60-88)
 - 70% CR or PR (n=376, 77% CR, 23% PR)
- Post-induction maintenance
 - 90 pts (24%), mean age 72 yrs (60-86)
 - temozolomide (31%)
 - lenalidomide (23%)
 - MTX (17%)
- Median f/u 56 mos
- Median PFS 36 mos (95% CI 30-49)
- Median OS 71 months (95% CI 60-90)



Primary CNS Lymphoma – Lenalidomide

- immunomodulatory agent

- Low dose LEN leads to immune reconstitution in elderly (Huang, 2011)

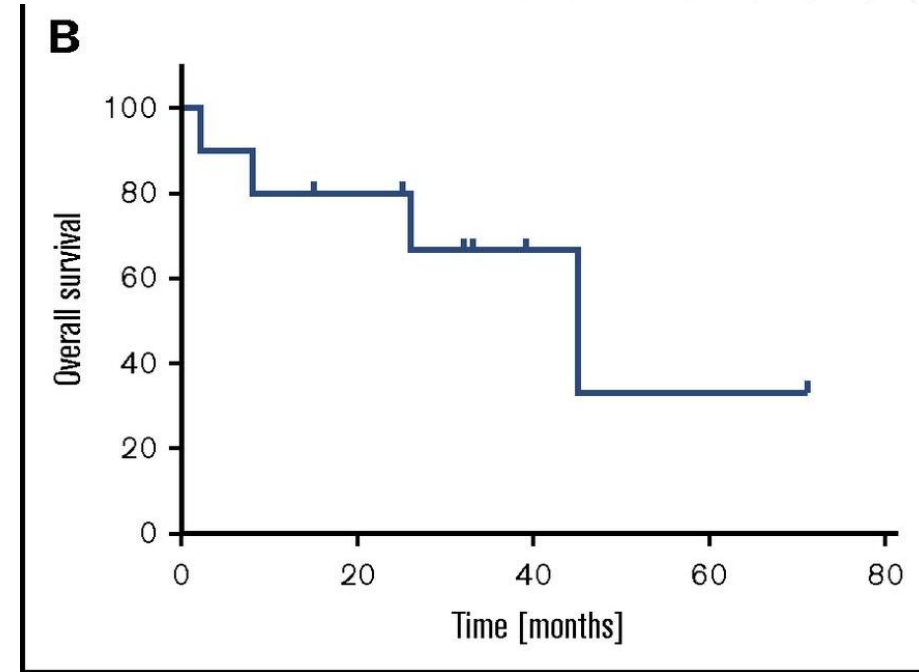
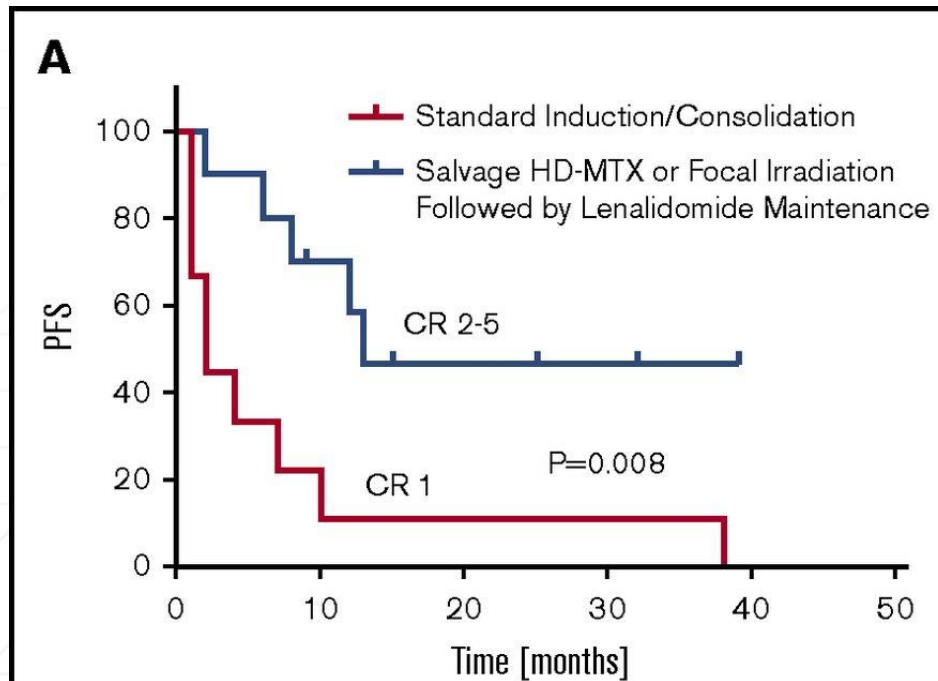
- LEN maintenance

- REMARC – len 25 mg maint – 60% d/c, 70% dose adjustment (median dose 19 mg)
- Low dose maintenance LEN SOC in MM with low discontinuation rate

Primary CNS Lymphoma – Lenalidomide

- LEN activity in PCNSL even at lower dose

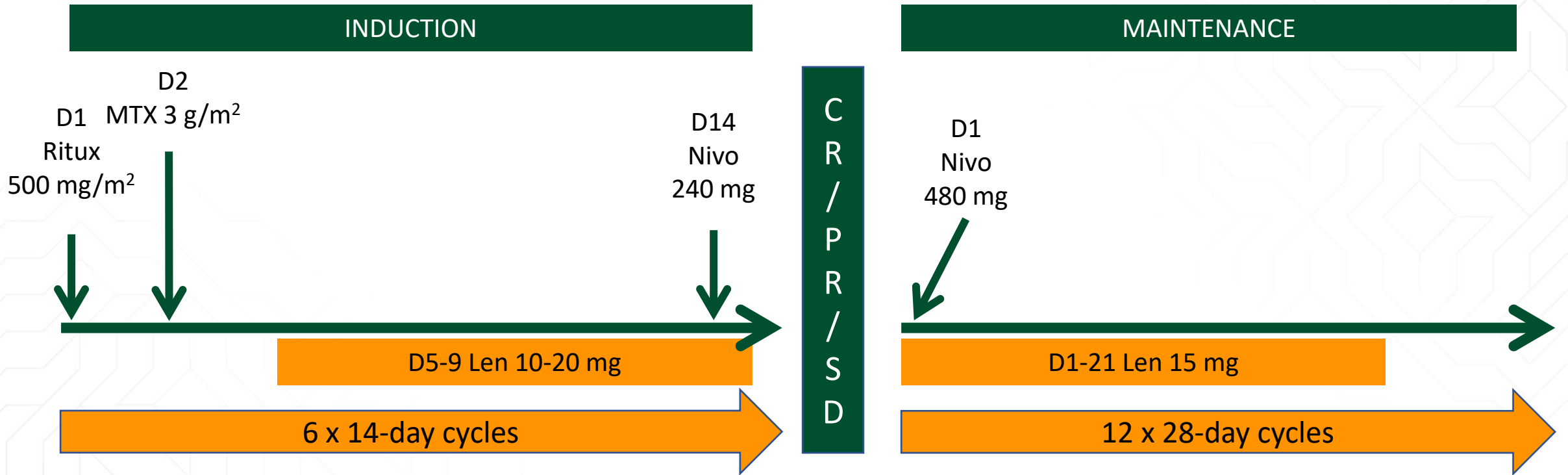
- Low dose LEN maintenance after MTX-based salvage with PFS after CR2>CR1 (Blood Adv 2018)
- Low dose LEN maintenance in elderly PCNSL (Br J Haematol, 2019; ASH 2020)



Primary CNS Lymphoma – CPI

- CPI activity in PCNSL reported
 - Anecdotal report of response (Nayak, Blood 2017)
- CPI mediated immune response enhanced by LEN (Görgün, 2015)
 - Increase inflammatory cytokines interferon-gamma, IL-2
 - Enhance cytotoxic T-cell and NK-cell activity

A51901 – Nivo-MR2 in 1L elderly PCNSL



	MTX	Lenalidomide	Nivolumab
Level -1	3 g/m ²	5 mg	-
Level 1	3 g/m²	10 mg	-
Level 2	3 g/m ²	15 mg	-
Level 3	3 g/m ²	20 mg	-
Level 4	3 g/m ²	MTD	240 mg

Conclusion

- Rare lymphoma
- Large proportion - elderly patients
- HD-MTX-based therapy
 - combination likely better
- Consolidation ASCT
- Adjustment for elderly patients
 - Potential role of maintenance therapy

Thank you

