ESMO PRECEPTORSHIP ON LYMPHOMA

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Treatment of DLBCL

Martin Hutchings
Rigshospitalet, Copenhagen, Denmark
EORTC Lymphoma Group

EORTC
The future of cancer therapy

Overview of this lecture

- Classification
- Epidemiology
- Staging and prognostic stratification
- History of CHOP
- Treatment
  - Young, low risk patients without bulky disease
  - Young, low-intermediate risk patients or low risk with bulky disease
  - Young high and high-intermediate risk patients
  - Patients aged 60-80 years
  - Patients older than 80 years
- Risk of CNS relapse and CNS prophylaxis
- Relapsed and refractory disease

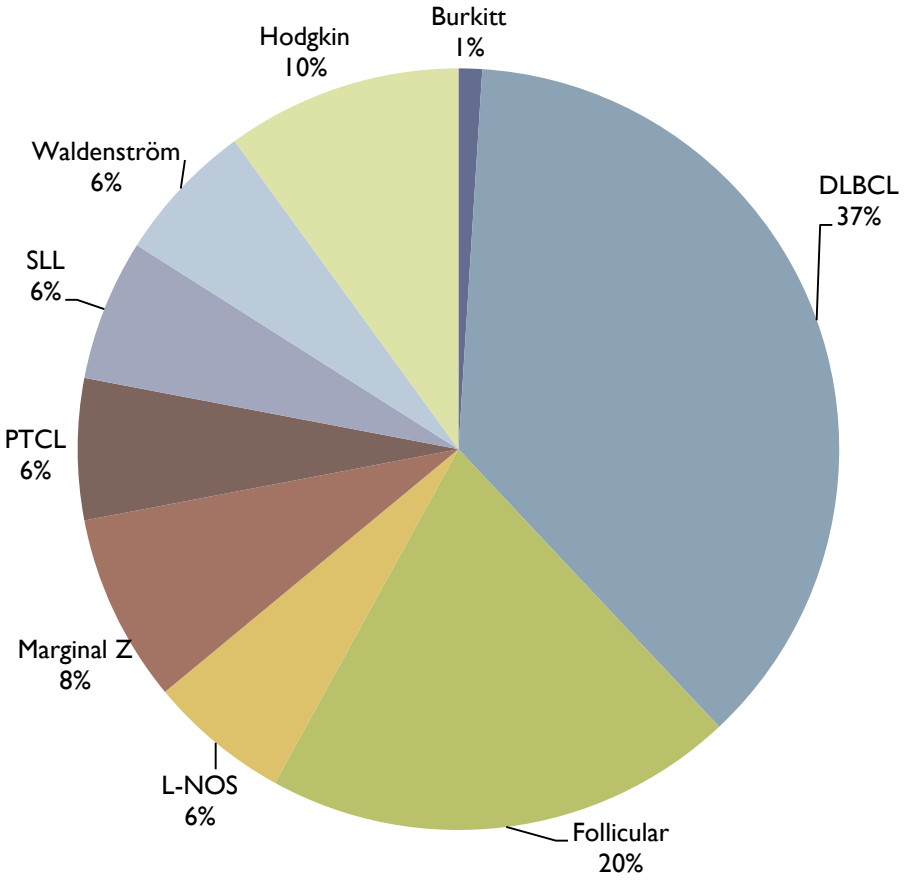
Classification[1]

- *Diffuse large B-cell lymphoma NOS*
  - Common morphologic variants
    - Centroblastic
    - Immunoblastic
    - Anaplastic
  - Rare morphologic variants
  - Molecular subgroups
    - Germinal centre B-cell-like (GCB)
    - Activated B-cell-like (ABC)
  - Immunohistochemical subgroups
    - CD5-positive DLBCL
    - Germinal centre B-cell-like (GCB)
    - Non-germinal centre B-cell-like (non-GCB)
- *Diffuse large B-cell lymphoma subtypes*
  - T-cell histiocyte-rich large B-cell lymphoma
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - EBV positive DLBCL of the elderly
- *Other lymphomas of large B-cells*
  - Primary mediastinal large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis
  - ALK-Positive LBCL
  - Plasmablastic lymphoma
  - Large B-cell lymphoma arising in HHV-8 associated multicentric Castleman disease
  - Primary effusion lymphoma
- *Borderline cases*
  - *B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma*
  - *B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Classical Hodgkin*

1. 2008 WHO classification of tumours of haematopoietic and lymphoid tissues

Epidemiology

- 30-50% af all non-Hodgkin lymphomas
- Incidence in Europe 4-8/100,000 per year[1]
- Risk factors of DLBCL:
  - Family history
  - Autoimmune diseae
  - HIV or HCV seropositivity
- Incidence is increasing
- Occurs in all age groups
- Median age 65-70 years



1. Sant, *et al.* Blood 2010; 116: 3724-34.
2. LYFO, Danish Lymphoma Registry

Staging and risk stratification

Lugano classification

- Ann Arbor stage I-IV
- PET/CT
- CeCT
- BMB only if
  - no PET-pos skeletal findings
  - findings would have therapeutic implications
- MRI and LP if suspected CNS involvement

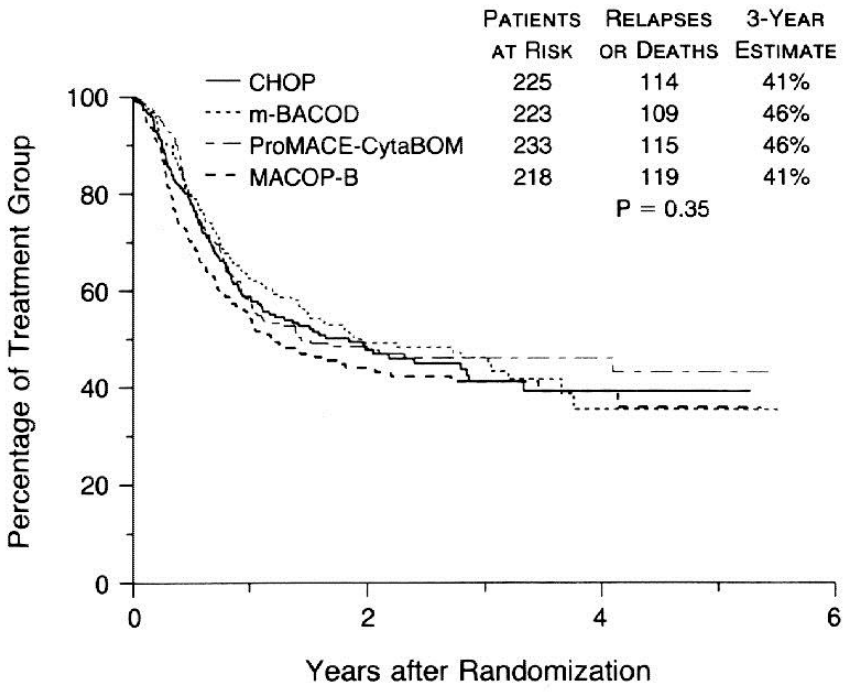
IPI, aaIPI

Risk factors	Age >60 years		
	Serum LDH > normal		
	Stage III–IV		
	Performance status 2–4		
	Extranodal sites >1		
Risk categories	Low	0–1	91 (89–94)
	Low intermediate	2	81 (73–86)
	High intermediate	3	65 (58–73)
	High	4–5	59 (49–69)
Age-adjusted international prognostic index (aaIPI) in patients ≤60 years			
Risk factors	Serum LDH > normal		
	Stage III–IV		
	Performance status 2–4		
Risk categories	Low	0	98 (96–100)
	Low intermediate	1	92 (87–95)
	High intermediate	2	75 (66–82)
	High	3	

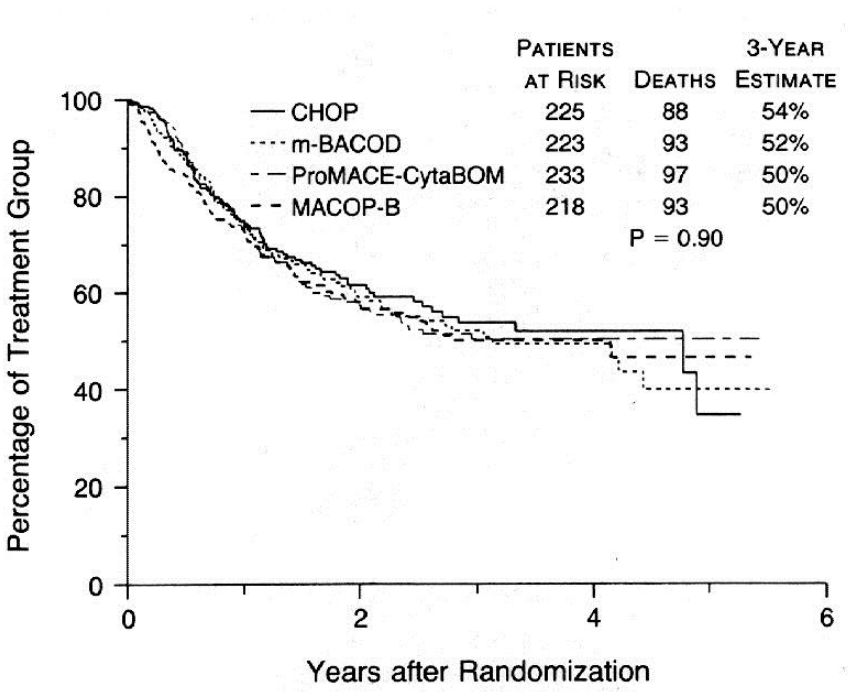
1. Cheson B, *et al.* JCO 2014, 32, 3059-68.
2. Shipp M, *et al.* NEJM 1993; 329, 987-94.

CHOP - backbone of aggressive NHL therapy

Time to treatment failure



Overall survival



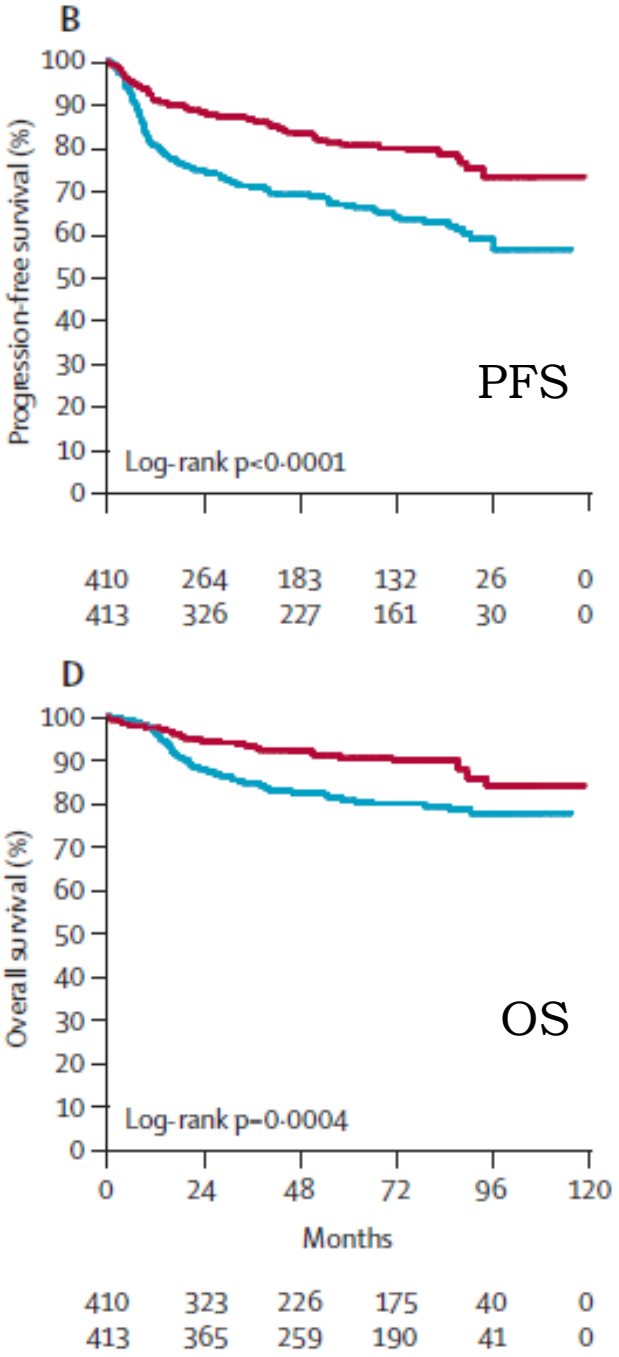
1. Fisher RI et al. N Engl J Med 1993;328:1002-1006.

Young, low-risk (aaIPI = 0), no bulk

MInT trial

- 18-60 years
- aaIPI 0-1
- Stage II–IV disease or stage I disease with bulk
- 6x CHOP(-like) chemotherapy +/÷ Rituximab
- Radiotherapy to sites of bulky or extranodal disease
- ITT population of 813 patients

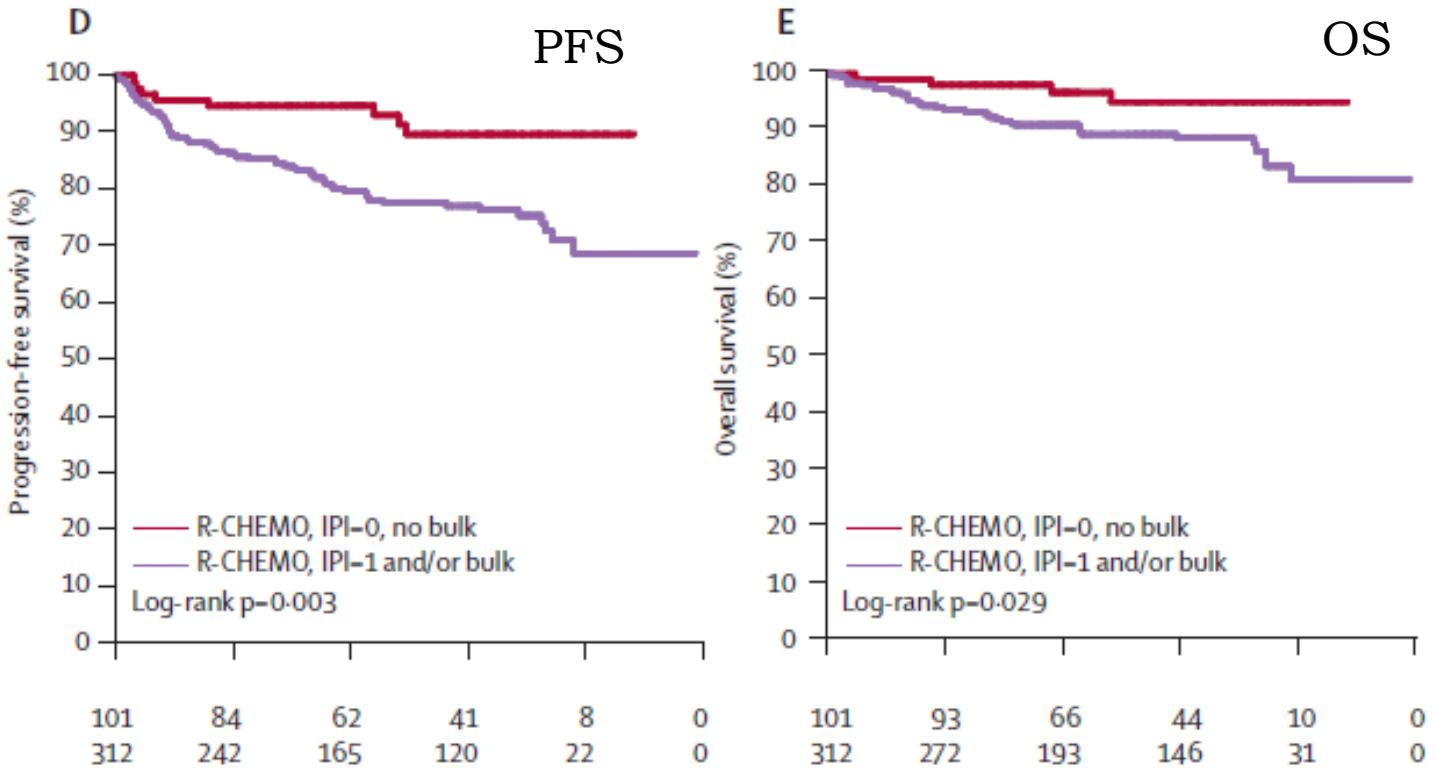
- Red: with rituximab
- Blue: without rituximab



1. Pfreundschuh M, *et al.* Lancet Oncol 2011; 12: 1013–22.

MInT trial

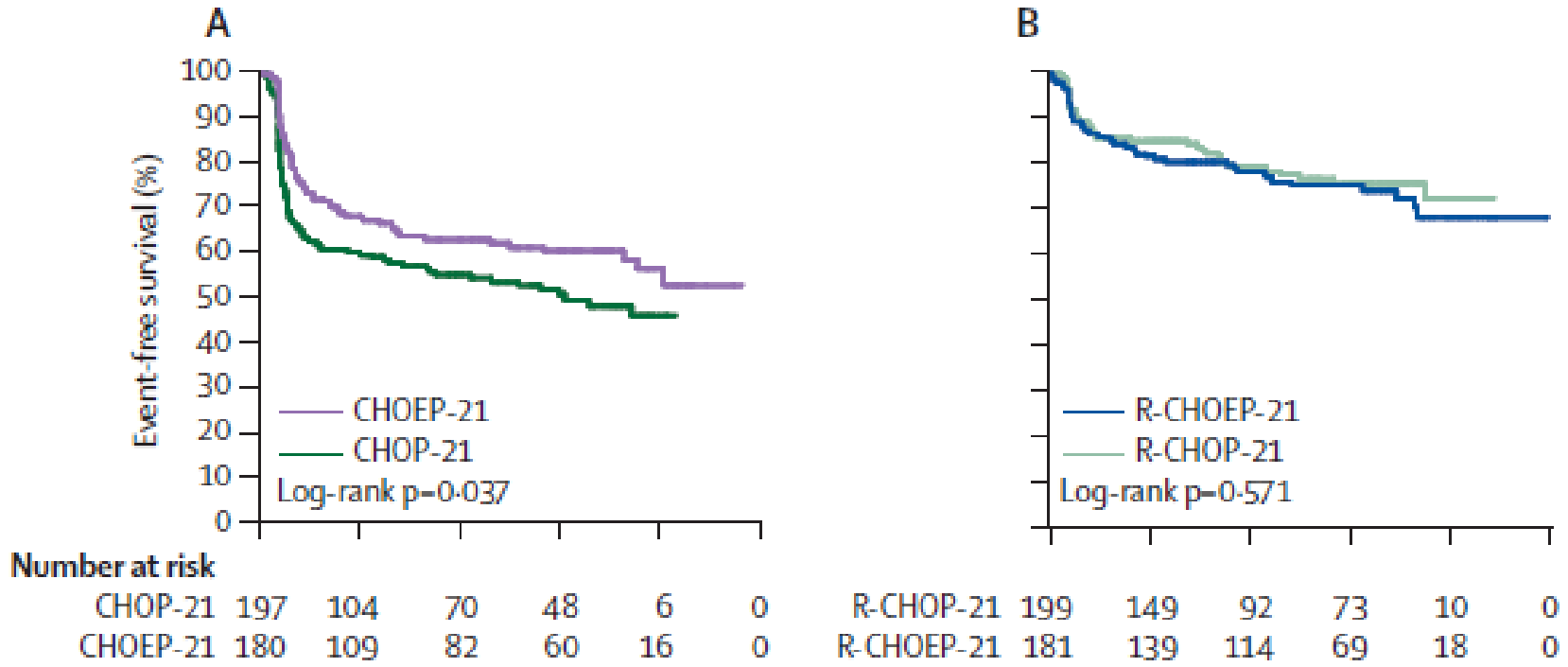
- Two distinct prognostic subgroups emerge when rituximab is added to CHOP or CHOEP



1. Pfreundschuh M, *et al.* Lancet Oncol 2011; 12: 1013–22.

MInT trial

- No difference between R-CHOP and R-CHOEP in this group



1. Pfreundschuh M, *et al.* Lancet Oncol 2011; 12: 1013–22.

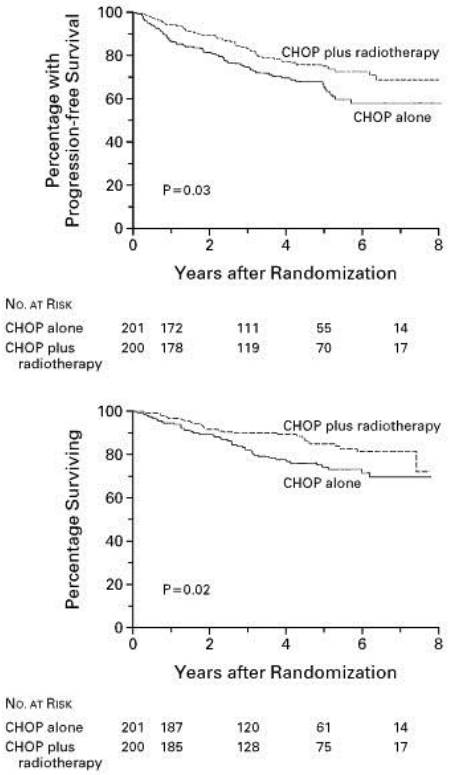
Young, low-risk (aaIPI = 0), no bulk

- Significant improvement of all outcome parameters after addition of rituximab[1]
- Outcome is extremely good for patients with aaIPI = 0 and no bulk[1]
- No advantage of R-CHOEP over R-CHOP[1]
- No advantage of radiotherapy to initial non-bulky sites[2]

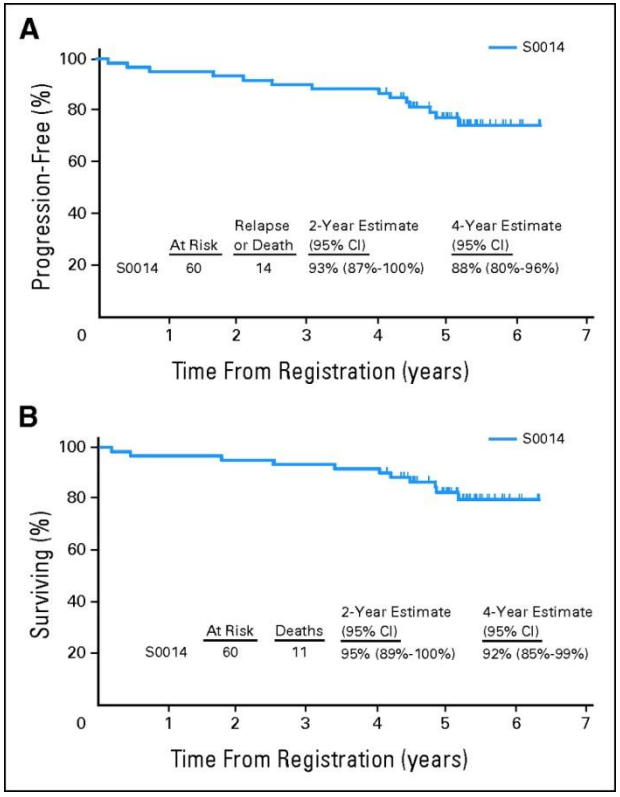
1. Pfreundschuh M, *et al.* Lancet Oncol 2011; 12: 1013–22.
2. Lamy T, *et al.* ASH 2014, abstract 393.

Localised DLBCL

201 Patients Receiving 8xCHOP and 200 Patients Receiving 3xCHOP plus Radiotherapy[1]



60 patients enrolled in a SWOG trial of 3xR-CHOP followed by involved-field radiation therapy[2]

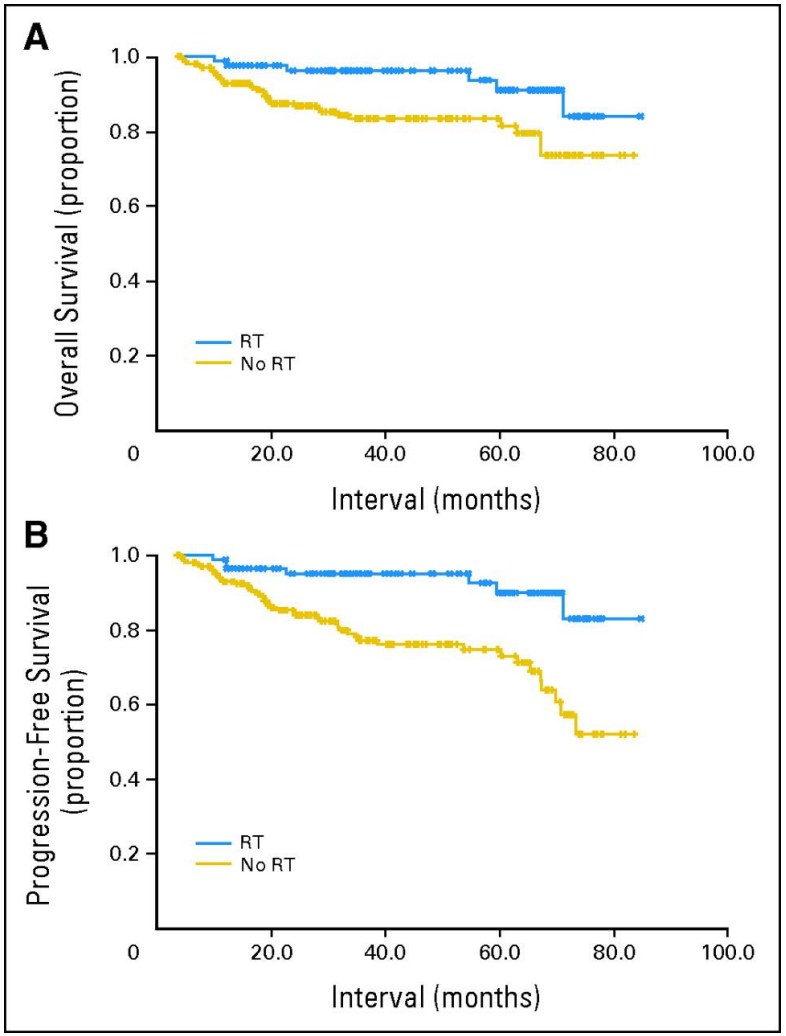


1. Miller TP, et al. N Engl J Med 1998;339:21-26.
2. Persky DO, et al. JCO 2008;26:2258-2263.

Young, low-intermediate risk patients (aaIPI = 1) or low risk (aaIPI = 0) with bulk

Young, low-intermediate risk patients (aaIPI = 1) or low risk (aaIPI = 0) with bulk

- The MInT trials showed significant improvement of all outcome parameters after addition of rituximab also in this group[1]
- Still no advantage of R-CHOEP over R-CHOP[1]
- Radiotherapy is recommended to bulky sites[2]
- R-ACVBP have shown superiority over R-CHOP in this group but no radiotherapy given in that trial



1. Pfreundschuh M, *et al.* Lancet Oncol 2011; 12: 1013–22.
2. Phan J, JCO 2010; 28(27): 4170-6.

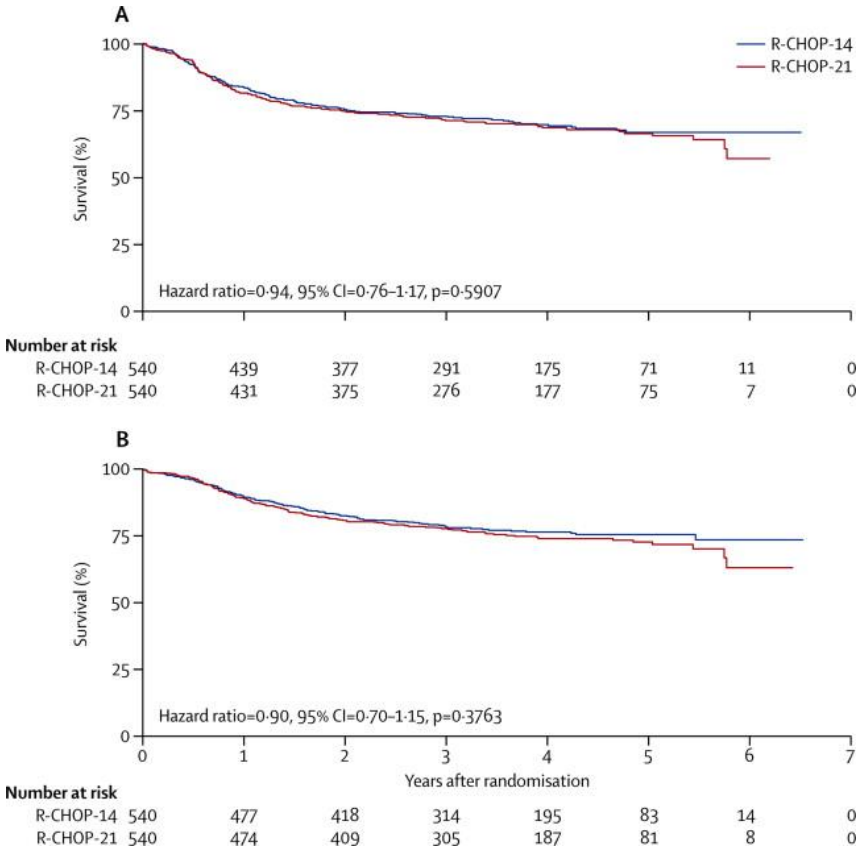
Young, high and high-intermediate risk patients (aaIPI ≥ 2)

No clear standard in this group

- R-CHOP14 vs. R-CHOP21?
- R-CHOEP vs. R-CHOP
- More intensive regimens?
- HDC+ASCT?

R-CHOP14 vs. R-CHOP21

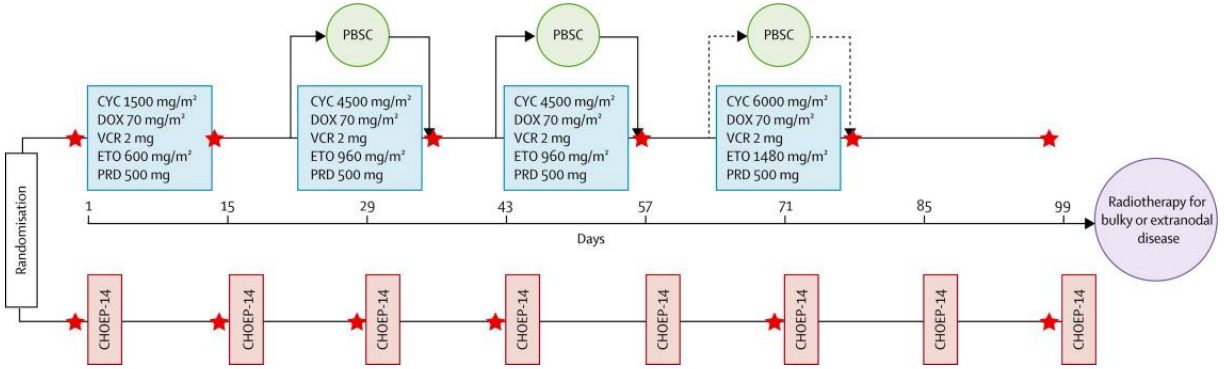
- All age groups
- Stage IA with bulk or stage IB-IV
- All IPI groups
- No advantage of R-CHOP14 over R-CHOP21 in any of the prognostic groups or age groups

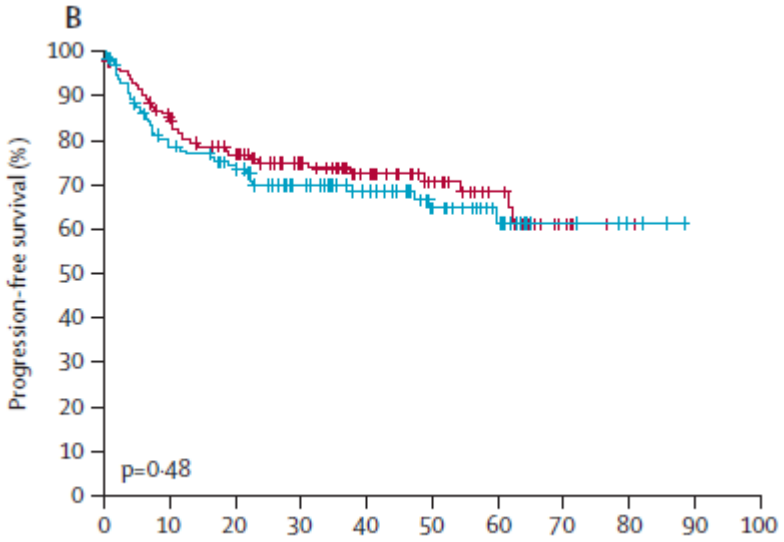


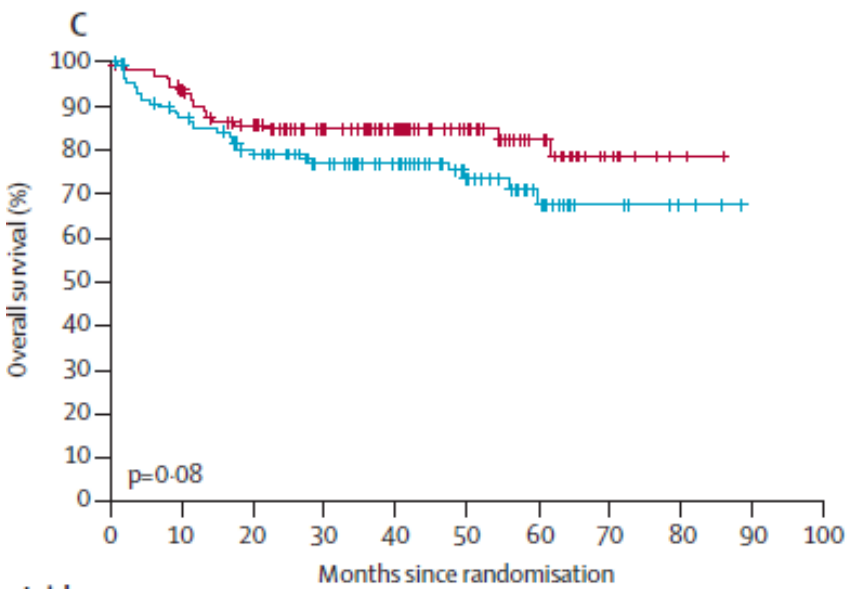
1. Cunningham D, *et al.* Lancet 2013; 381: 1817-26.

R-CHOEP?

- 18-60 years
- aaIPI 2 or 3
- No difference in PFS and OS







1. Schmitz N, *et al.* Lancet Oncol 2012; 13: 1250-59.

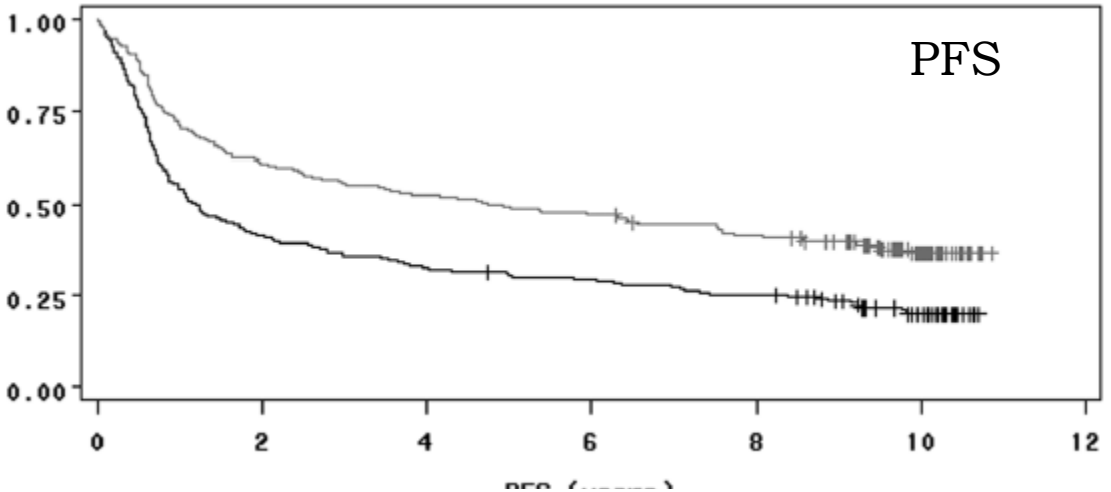
More intensive regimens?

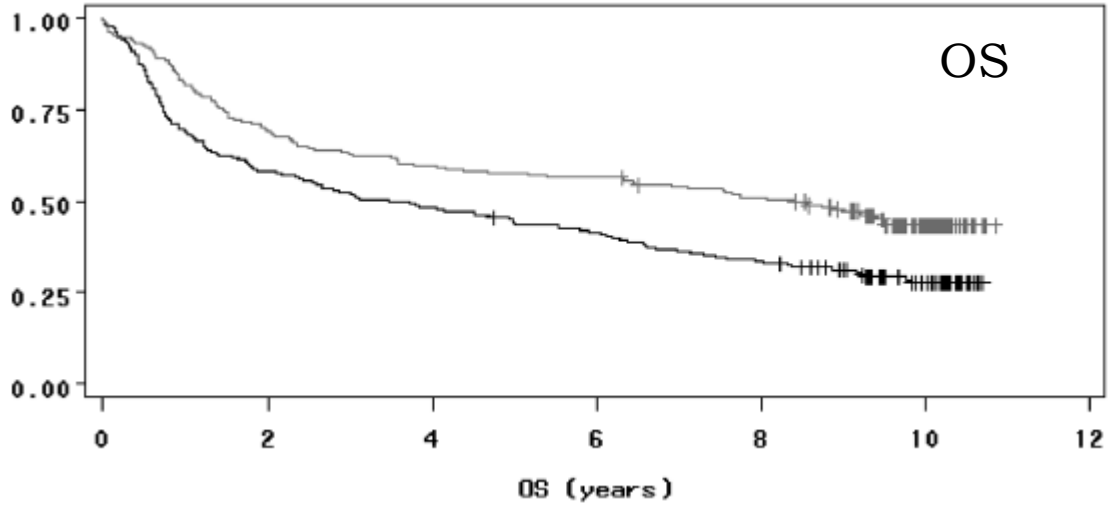
- No direct comparisons between R-CHOEP or R-ACBVP and R-CHOP in young, high-risk patients
- Four randomised trials have compared R-chemo with or without HDC+ASCT
  - Two trials show PFS benefit but not OS benefit
    - FIL DLCL04
    - SWOG-9704
  - Two trials show no benefit at all
    - DSHNHL 2002-1
    - GOELAMS 075

Patients aged 60-80 years

LNH 98.5: CHOP vs. R-CHOP

- 399 patients aged 60-80
- Stage II-IV DLBCL
- PS 0-2

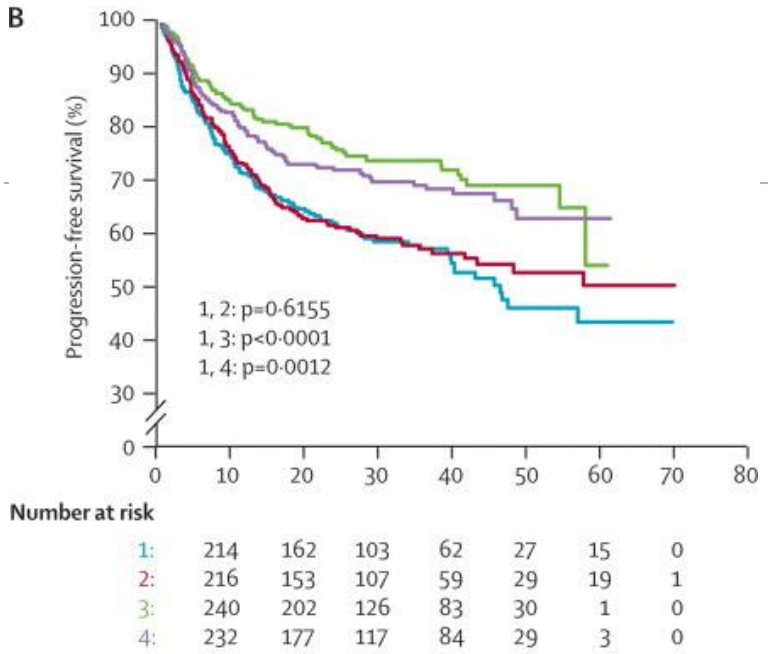


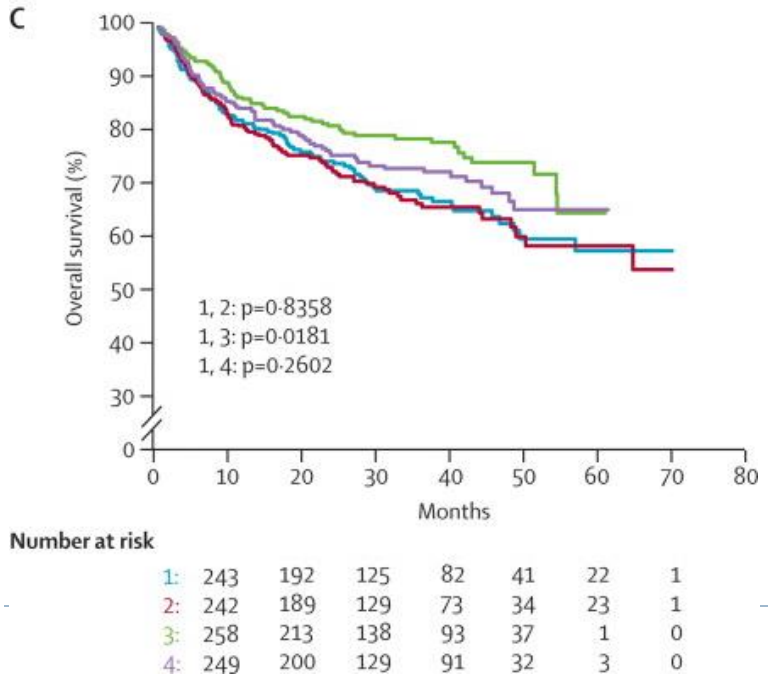


1. Coiffier B, *et al.* Blood 2010; 116: 2040-45.

RICOVER-60

- 1222 patients
- 61-80 years
- Randomised to
  - 6 x CHOP14
  - 8 x CHOP14
  - 6 x R-CHOP14
  - 8 x R-CHOP14

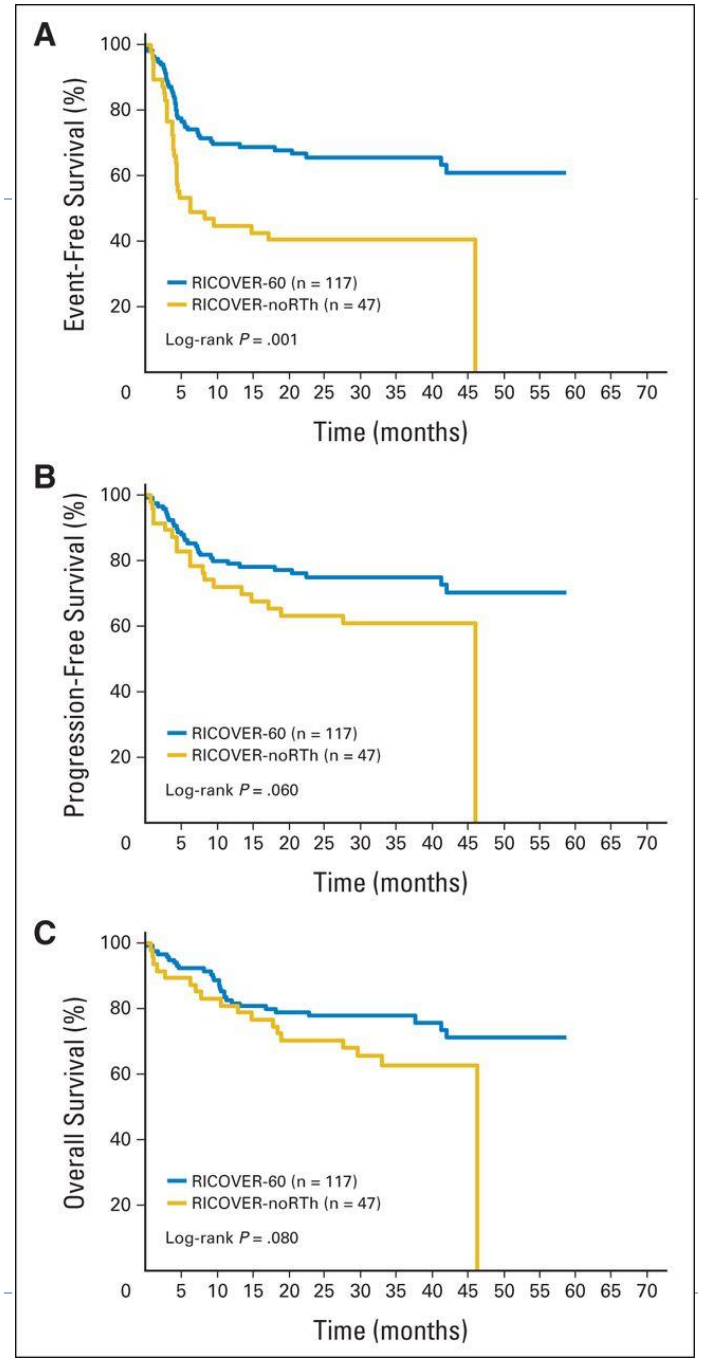




1. Pfreundschuh M, *et al.* Lancet Oncol 2008; 9: 105-116.

RICOVER-60: RT to bulky disease?

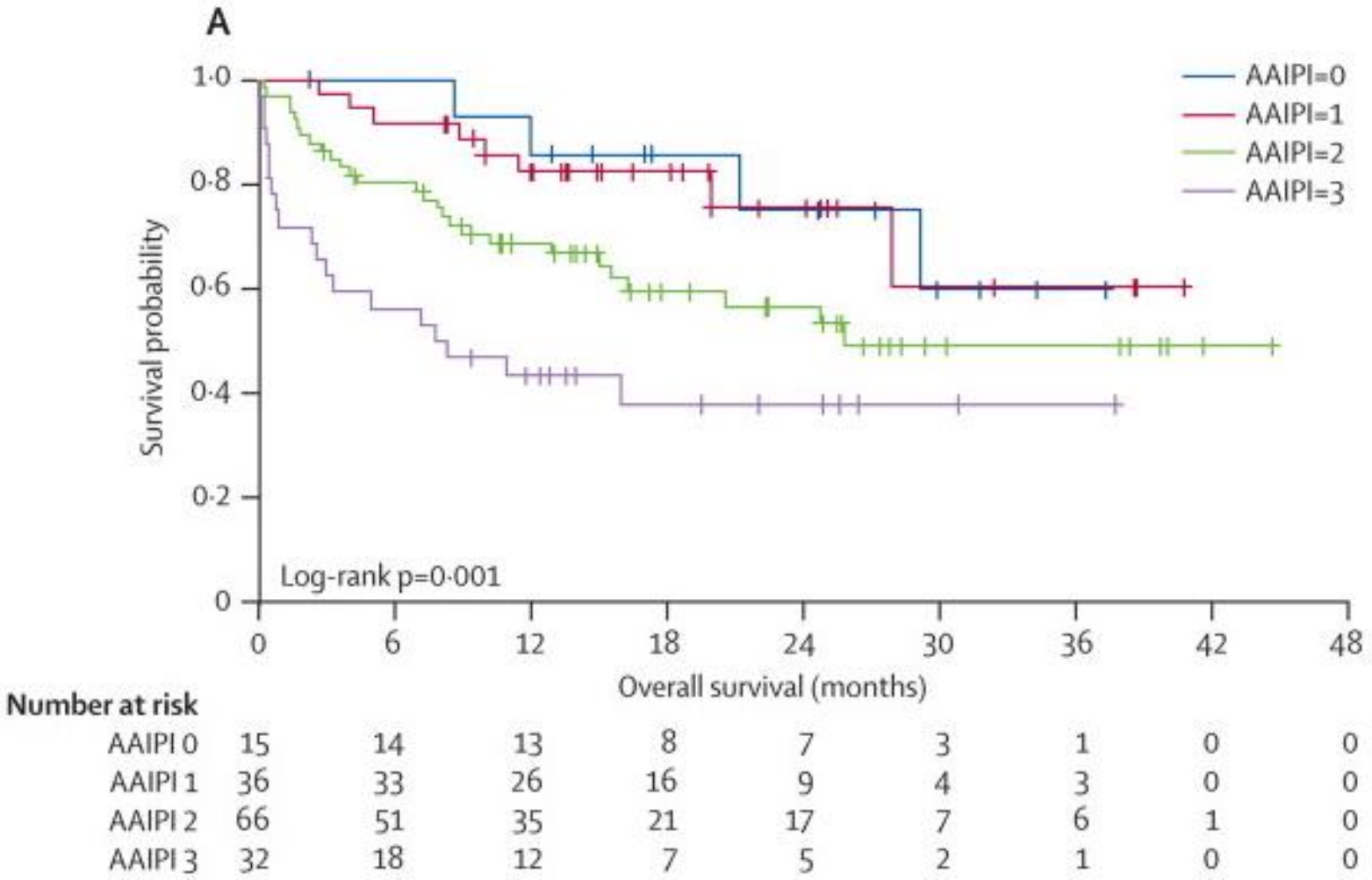
- The best arm of the RICOVER-60 trial (6×R-CHOP-14+2R plus involved-field RT [36 Gy] to sites of initial bulky [≥ 7.5 cm] disease and extralymphatic involvement) – versus
- A cohort receiving the same immunochemotherapy but without RT in an amendment to the RICOVER-60 trial (RICOVER-noRTh) in a prospective fashion



1. Held G, et al. JCO 2014;32:1112-1118

Patients over 80 years

R-mini-CHOP



1. Peyrade. Lancet Oncol. 2011 May;12(5):460-8

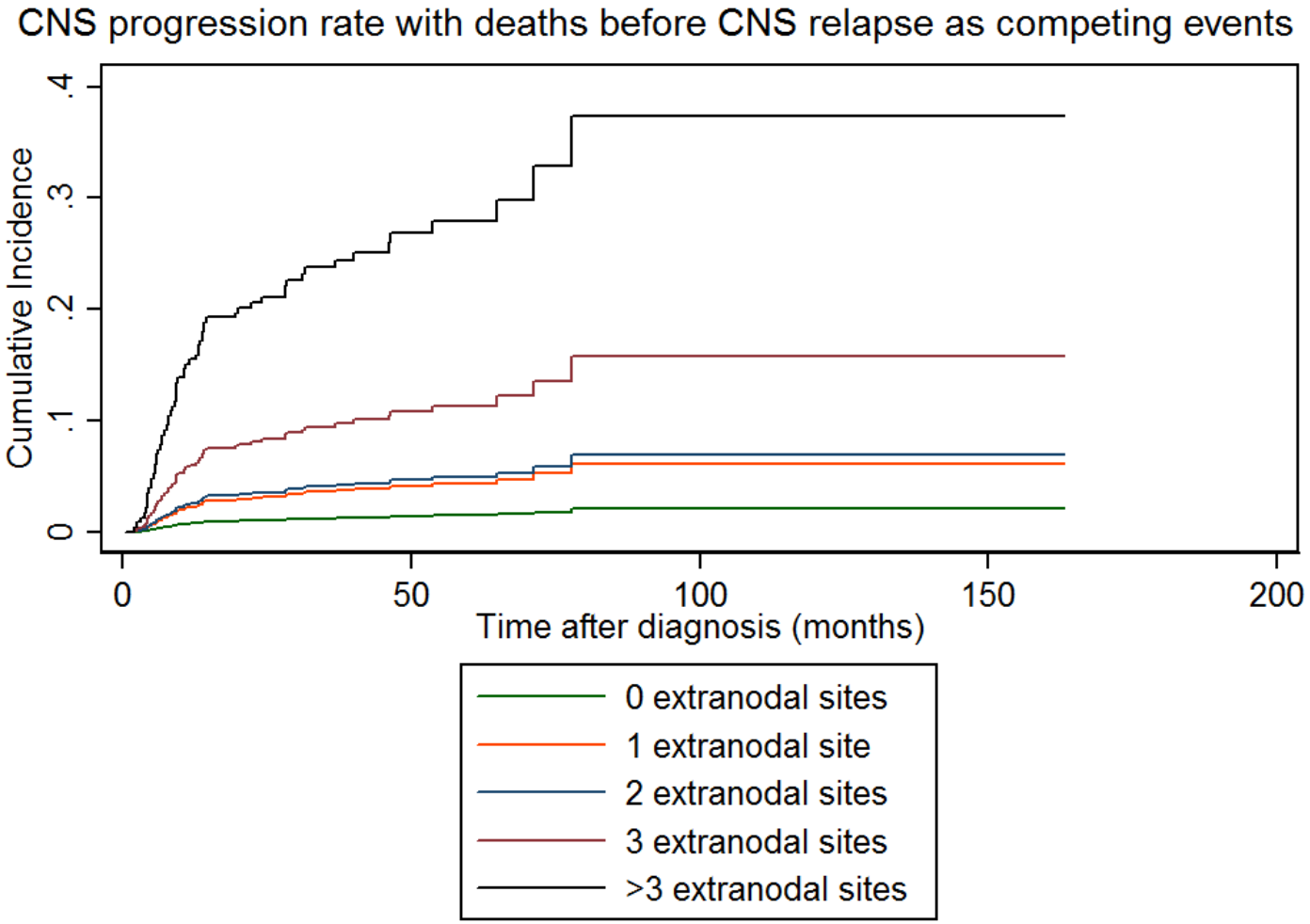
Risk of CNS relapse / CNS prophylaxis

CNS disease: analysis of patients treated on DSHNHL trials

aaIPI	All patients (n = 2196)		With rituximab (n = 620)		Without rituximab (n = 1576)	
	No.	Incidence	No.	Incidence	No.	Incidence
0	920	0,8%	166	0%	754	1,0%
1	858	2,0%	243	0,5%	615	2,6%
2	313	4,4%	157	4,2%	156	4,6%
3	104	11,4%	53	9,7%	51	13,20%

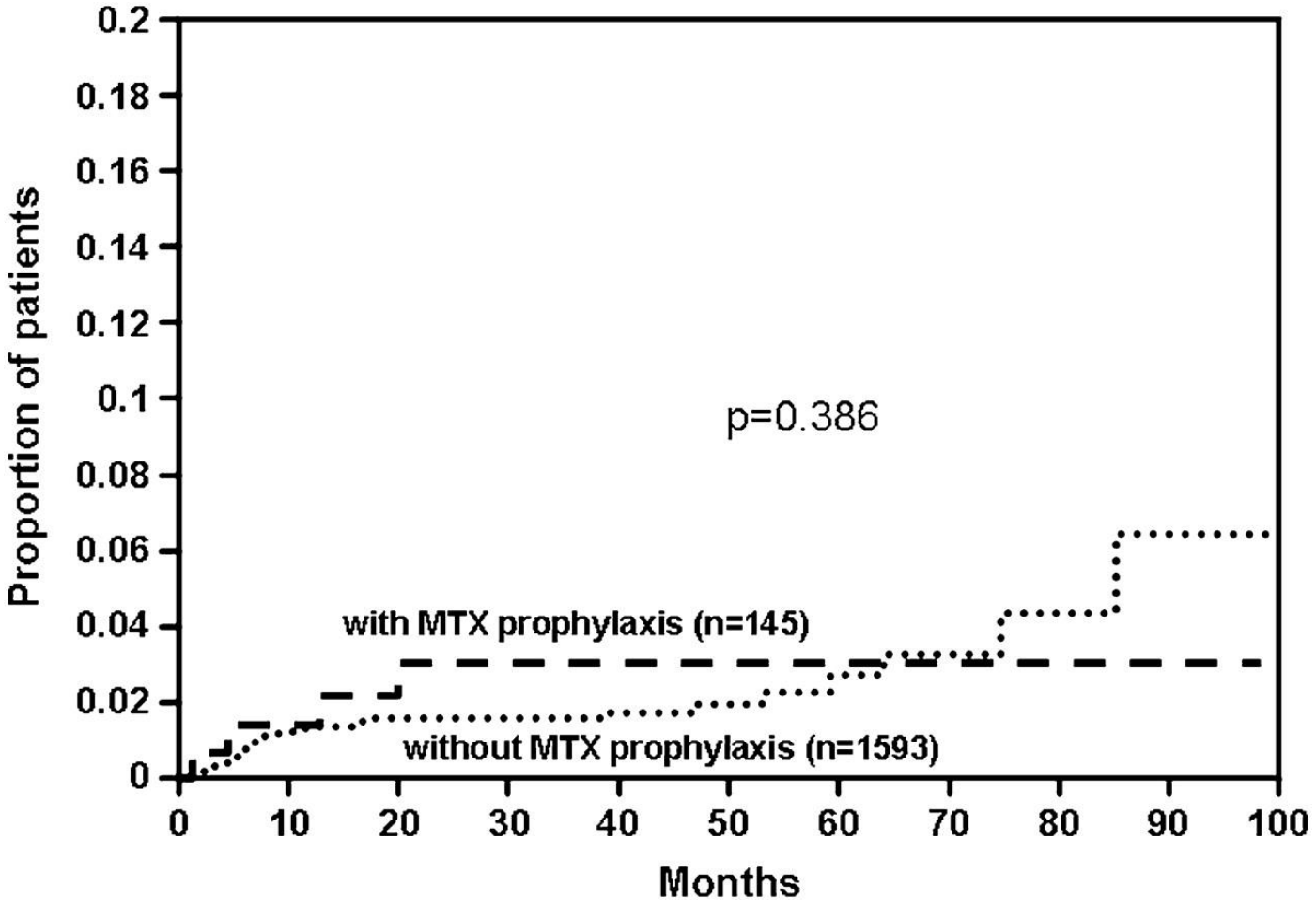
1. Schmitz N, *et al.* Ann Oncol. 2012 May;23(5):1267-73.

No. extranodal sites predicts CNS relapse



1. Chaeh C, *et al.* ASH 2015.

CNS disease: analysis of patients treated on DSHNHL trials



1. Schmitz N, *et al.* Ann Oncol. 2012 May;23(5):1267-73.

Indications for CNS prophylaxis

- IPI > 2
- PS >1 (HR) = 2.01
- Testicular (HR = 6.67)
- Kidney (HR = 20.14)
- Breast or Uterus involvement (HR = 6.14)
- CNS & Epidural lymphoma
- More than 2 extranodal sites*

- Use of IT prophylaxis does not appear to decrease CNS relapse

MORE MTX means LESS CNS relapses

Table 3. Overall and CNS relapse-free survival by group

	Group 1	Group 2	Group 3	
	CHOP ± R + IT MTX	CHOP ± R + IT + IV HD MTX	HyperCVAD or CODOXMIVAC ± R	*P*-value
Number	12	10	1	—
Localisation				
Leptomeningeal Parenchymal Both Unknown	5 4 2 1	1 5 0 4	0 0 0 1	0.16
3-Year cumulative incidence of CNS relapse (95% CI)	18.4% (9.5–33.1%)	6.9% (3.5–13.4%)	2.3% (0.3–15.4%)	**0.009**
3-Year overall survival	68.0% (52.4–79.3%)	85.9% (77.6–91.3%)	89.2% (73.7–95.8%)	**0.029**

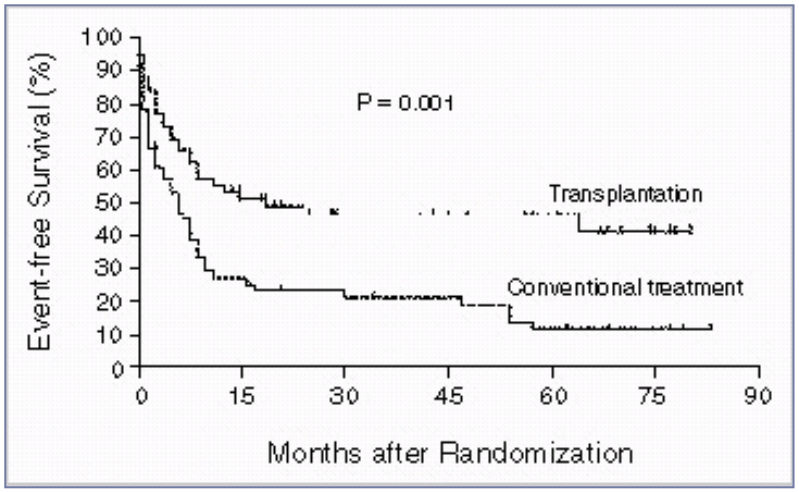
Abbreviations: CI = confidence interval; CNS = central nervous system; CODOXMIVAC = cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine; HD = high dose; IT = intrathecal; IV = intravenous; MTX = methotrexate; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-HyperCVAD = rituximab, hyper fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone; R-MTX-ara-c = rituximab, high-dose methotrexate, high-dose cytarabine. Bold denotes $P < 0.05$.

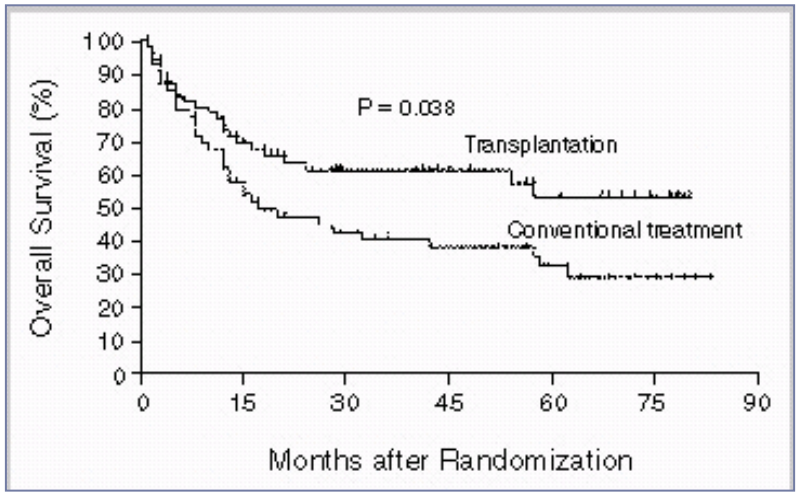
1. Cheah C,et al. British Journal of Cancer 2014; 111: 1072–1079.

Relapsed and refractory DLBCL

Parma trial

n=215. 2 x DHAP: response→ randomisation (n=109)

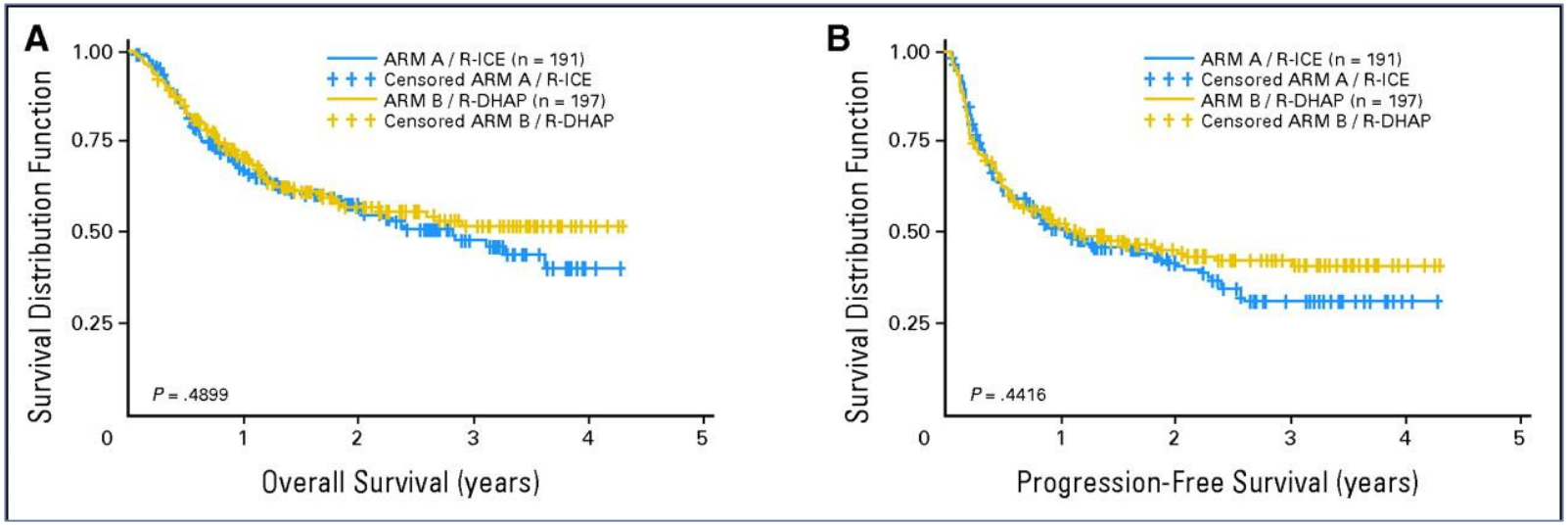




Conventional therapy: 4 x DHAP with or without RT
Autologous transplant: BEAC conditioning

1. Philip et al NEJM1995;333(23):1540-5.

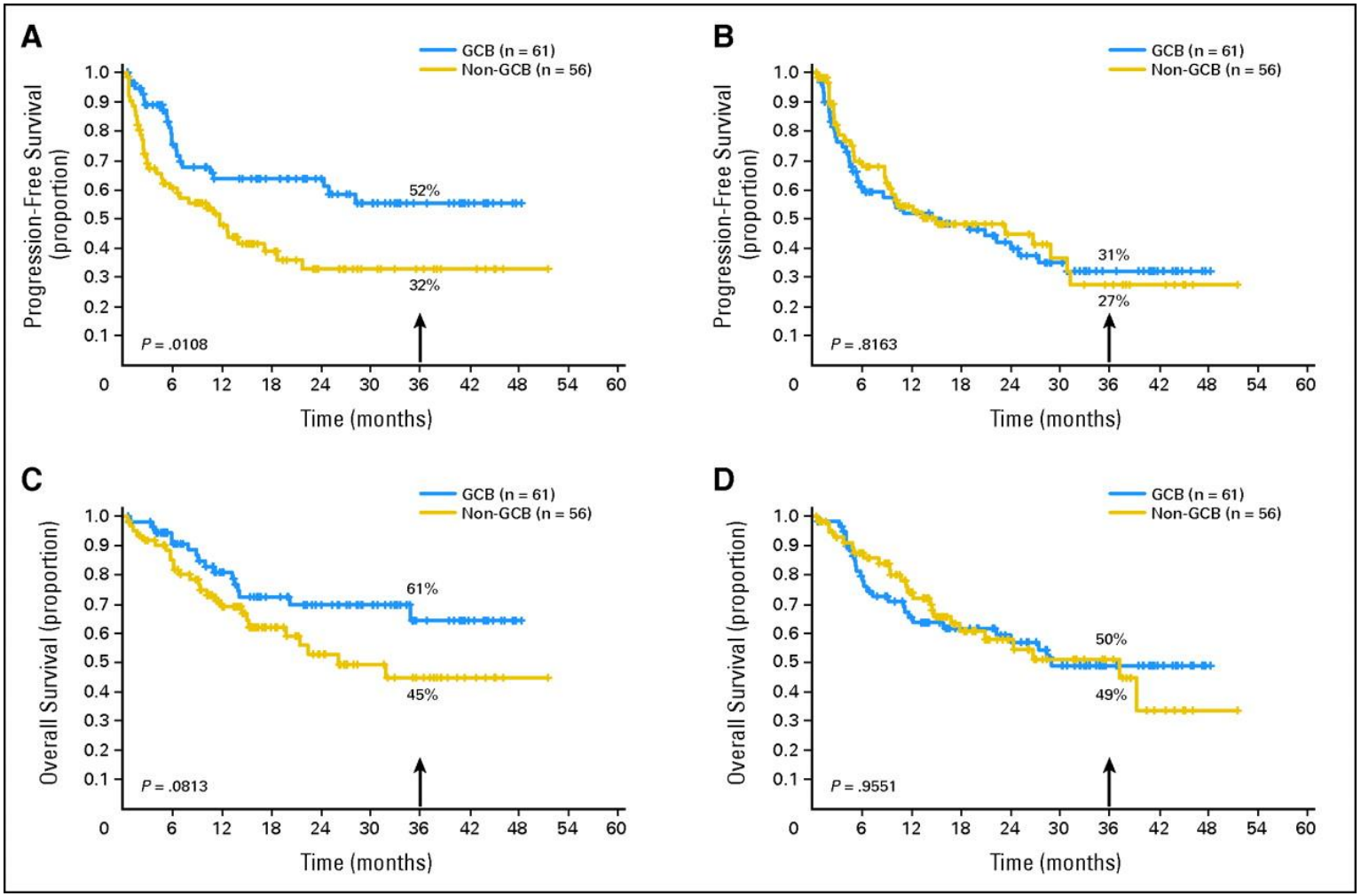
CORAL study



1. Gisselbrecht C et al. JCO 2010;28:4184-4190

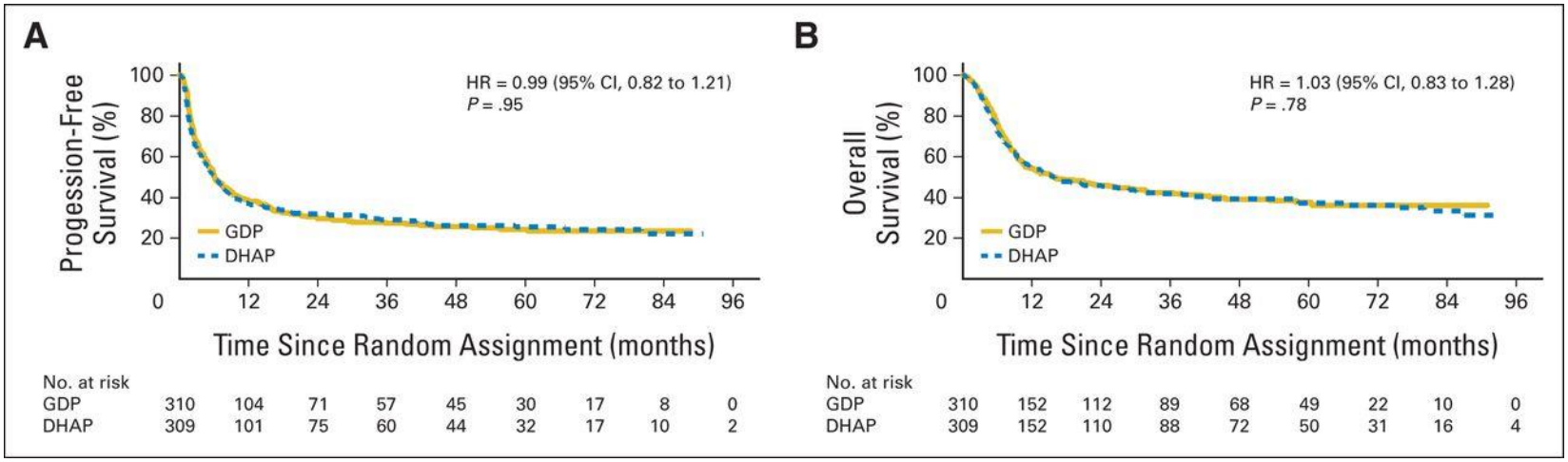
Bio-CORAL study

R-DHAP R-ICE



1. Thieblemont C et al. JCO 2011;29:4079-4087

R-DHAP VS R-GDP + BEAM



1. Crump M,et al. JCO 2014;32:3490-3496

R-DHAP VS R-GDP + BEAM

Table 3. Most Serious Adverse Events

Adverse Event	GDP (n = 306) No.	GDP (n = 306) %	DHAP (n = 304) No.	DHAP (n = 304) %	*P*
Thrombosis/embolism	18	6	18	6	NS
Fatigue	30	10	28	9	NS
Nausea	13	4	25	8	.04
Vomiting	22	7	21	7	NS
Infection					
With grade 3 to 4 neutropenia	18	6	28	9	NS
Without neutropenia	21	7	22	7	NS
Febrile neutropenia	28	9	70	23	< .001
Syncope	7	2	16	5	
Worst overall	143	47	186	61	< .001

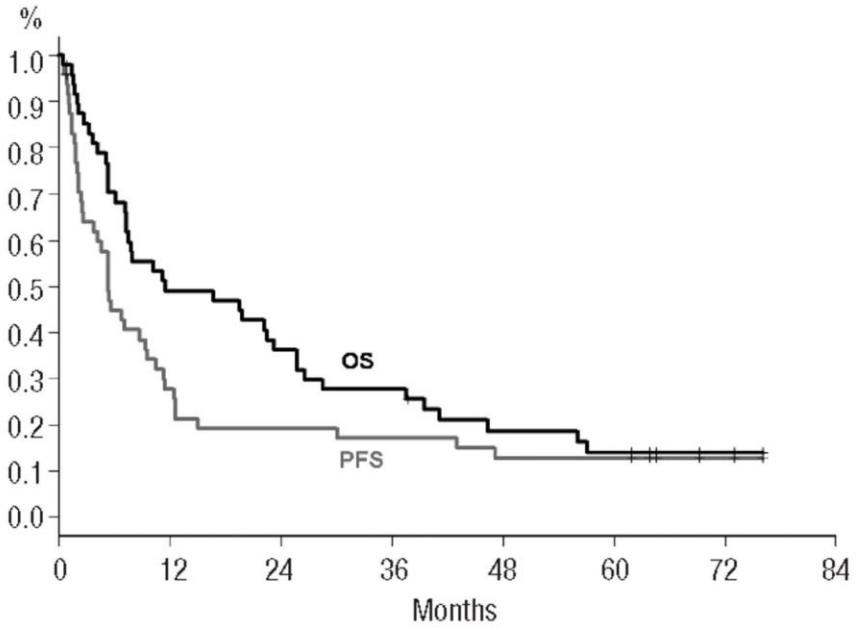
NOTE. Comparison of most frequently occurring serious adverse events, occurring in at least 5% of patients who received at least one dose of protocol therapy, at grade 3 or 4 (National Cancer Institute Common Toxicity Criteria version 2.0).

Abbreviations: DHAP, dexamethasone, cytarabine, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin; NS, not significant.

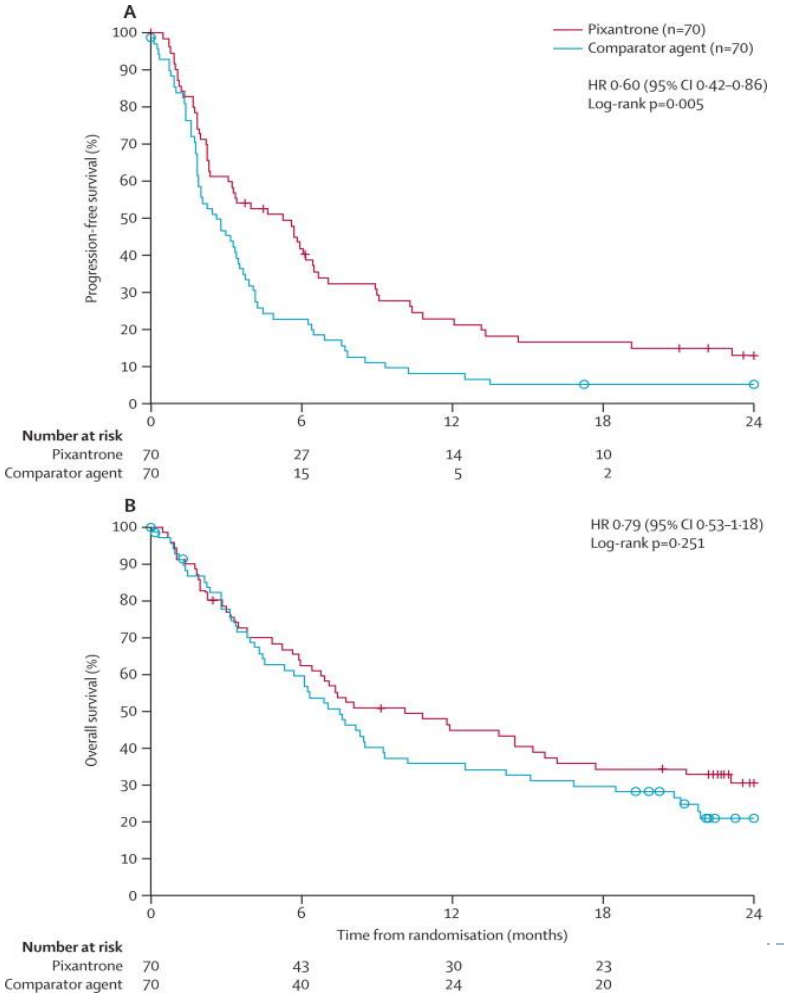
1. Crump M,et al. JCO 2014;32:3490-3496

Transplant-ineligible patients

- R-GemOx[1]



- Pixantrone[2]



1. Mounier N, *et al.* Haematologica 2013; 98: 1726-31.
2. Pettengell R, *et al.* Lancet Oncol 2012; 13: 696-706.

Further considerations

Open questions

- Ibrutinib may improve the efficacy of R-CHOP in 1st line treatment of ABC subtype DLBCL[1]
- The poor prognosis of double-hit, particularly MYC rearrangement/overexpression, is an unsolved issue
- PET-response adapted therapy?
- DA-EPOCH?
- Bortezomib (plasmablastic variant?)
- Lenalidomide and other ImIDs
- PI3K inhibition
- Syk/JAK inhibition (Cerdulatinib)
- Antibody-drug conjugates (CD19, CD79B)
- BCL2 inhibition (ABT-199)

1. Younes A, *et al.* Lancet Oncol 2014; 15: 1019-26.

2015 revised ESMO DLBCL guidelines

- For young, low-risk patients (aa-IPI = 0) without bulky disease:
  - six cycles of combination chemotherapy with CHOP treatment combined with six doses of rituximab given every 21 days is the current standard [I, A];
  - consolidation by radiotherapy to initial non-bulky sites has no proven benefit in patients treated with rituximab or not [I, A].
- For young low-intermediate-risk patients (aa-IPI = 1) or IPI low risk (aa-IPI = 0) with bulky disease:
  - either R-CHOP21 × 6 with radiotherapy to the sites of previous bulky disease or the intensified regimen R-ACVBP is recommended [II, B].
- For young high- and high-intermediate-risk patients (aa-IPI ≥ 2):
  - enrolment in clinical trials should be a priority;
  - six to eight cycles of chemotherapy with CHOP combined with eight doses of rituximab given every 21 days are most frequently applied [III, B];
  - dose dense treatment with R-CHOP given every 14 days has not demonstrated a survival advantage over standard R-CHOP given every 21 days [I, C];
  - intensive treatment with R-ACVBP or R-CHOEP is frequently used but these regimens have not been directly compared with R-CHOP in this category [II, B];
  - HDC with ASCT in first line remains experimental or may be proposed for selected high-risk patients [II, C];
  - the role of interim PET to select patients who could benefit from consolidative ASCT or from radiotherapy is under evaluation [I, C].
- For patients aged 60–80 years:
  - six to eight cycles of combination chemotherapy with CHOP plus eight doses of rituximab given every 21 days is the current standard [I, A];
  - if R-CHOP is given every 14 days, six cycles of CHOP with eight cycles of rituximab are sufficient [I, A];
  - a comprehensive geriatric assessment in order to ascertain comorbidities and functional decline is recommended to guide the choice of treatment in elderly poor-prognosis patients [III, A];
  - R-CHOP treatment can usually be used up to 80 years of age in fit patients [I, A], but modulation of treatment according to geriatric assessment is recommended [III, C].
- For patients aged >80 years:
  - the combination of rituximab with attenuated chemotherapy, such as R-miniCHOP, can induce complete remission and long survival in fit patients older than 80 years [III, B];
  - substitution of doxorubicin by gemcitabine, etoposide or liposomal doxorubicin, or even its omission, can be considered from the beginning or after a few cycles in patients with cardiac dysfunction or who are frail or unfit [III, C].

1. Tilly H, *et al.* Ann Oncol 2015; 26 (suppl5): v116-v125.

Thank you!