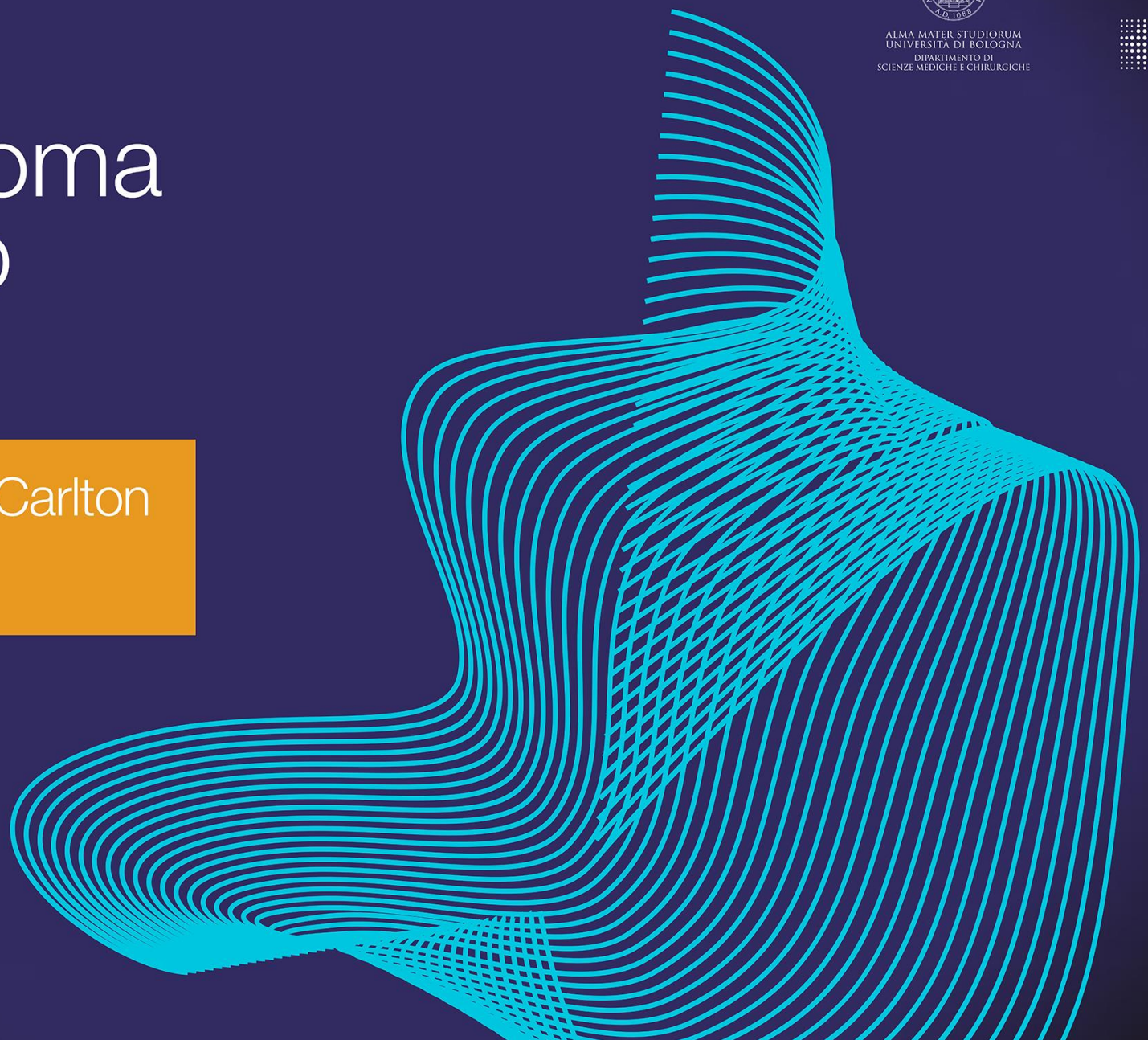
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Aggressive Lymphoma Workshop



Bologna, Royal Hotel Carlton

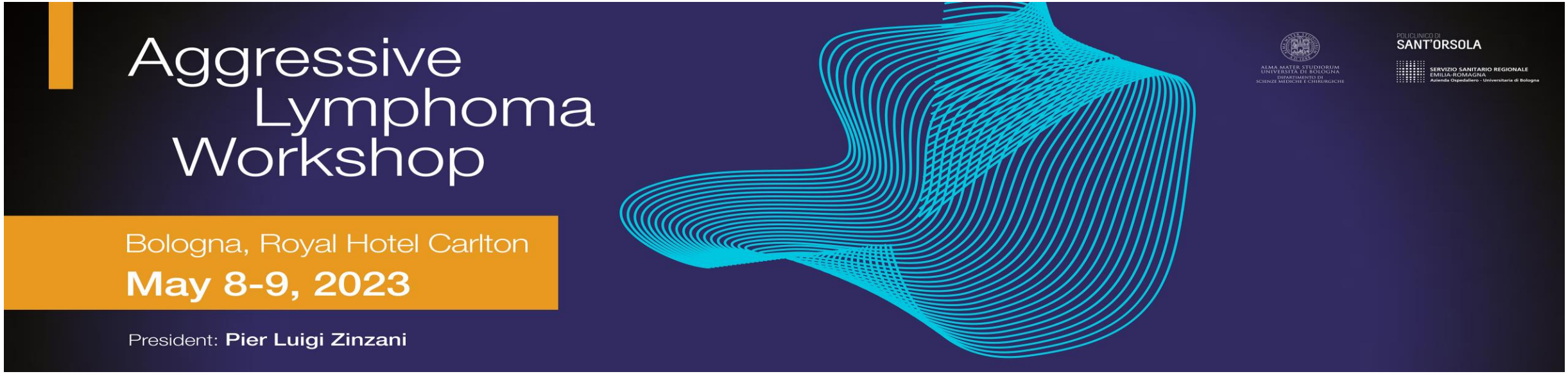
May 8-9, 2023

President: **Pier Luigi Zinzani**

SESSION IV: UPDATE ON FRONTLINE TREATMENTS AND BEYOND

Chairmen: G.S. Nowakowski, A. Pinto

02.45 pm How to treat early stage DLBCL A. Lopez-Guillermo



Disclosures of Armando López-Guillermo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche	X		X			X	
Gilead/Kite	X		X			X	X
BMS/Celgene	X					X	
Janssen						X	
Incyte						X	
Abbvie						X	

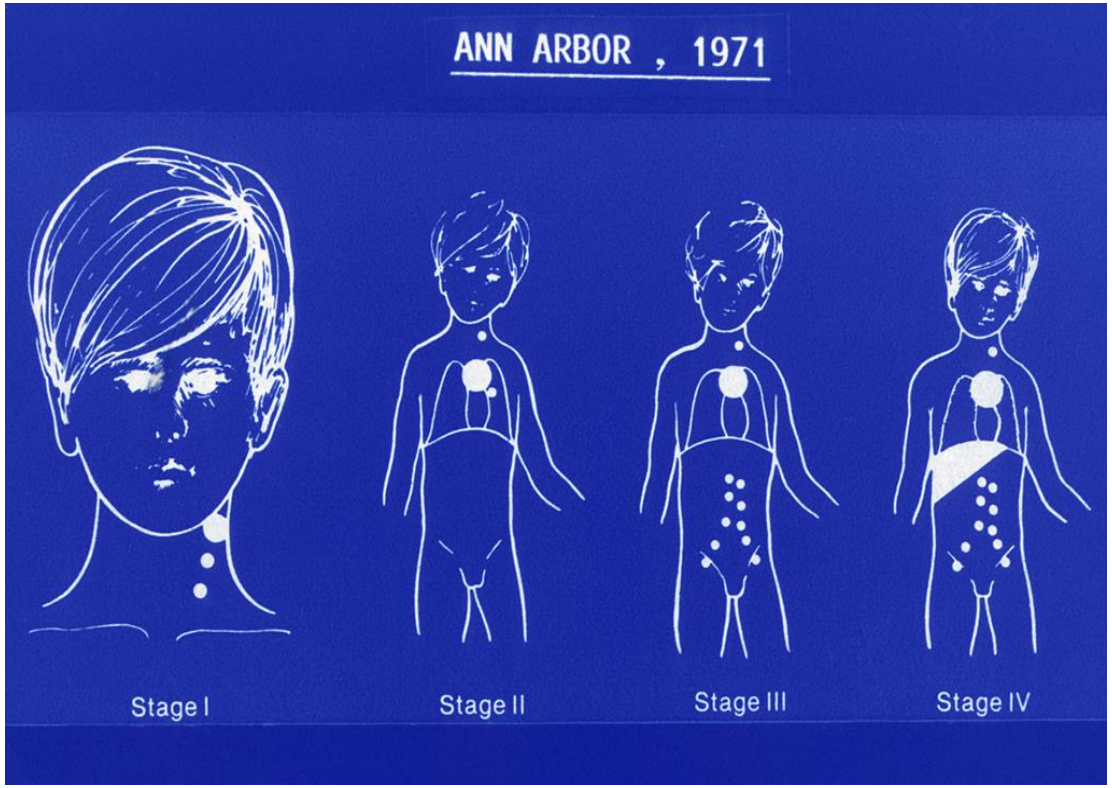
Outline

- Staging (Lugano classification) and prognostic impact
- Treatment before Rituximab
- Treatment in the Rituximab era
- Specific situations

Outline

- Staging (Lugano classification) and prognostic impact
- Treatment before Rituximab
- Treatment in the Rituximab era
- Specific situations

Staging in lymphomas



- Defines disease location and extend
- Suggests prognostic information
- Allows comparisons among studies
- Provides a baseline against which response or disease progression can be compared

- Initial staging criteria were designed for HL and superseded by the Ann Arbor classification

- Staging remains according to Ann Arbor

Resenberg SA, Cancer Res 1971; Carbone PP, Cancer Res 1971;
Rosenberg SA, Cancer Treat Rep 1977; Cheson BD 2014

Early stage DLBCL

- “Limited”, “localized” or “early” stage DLBCL occurs in 25-30% of DLBCL
- Overall, the outcome of these patients is good (10-yr OS 80%)
- No standard definition of early stage
  - In general: stages I or II, in absence of bulky disease (10cm?)
- Few specific studies on prognosis and low number on treatment
- Important issue: how to assess staging (PET/CT)

Le Guyader-Peyrou S, Haematologica 2017;102:584-92; Cheson BD, J Clin Oncol 2014;32:3059-67

Revised staging system (Lugano classification)

Revised staging system for primary nodal lymphomas		
Stage	Involvement	Extranodal (E) status
Limited I II	One node or a group of adjacent nodes 2 or more nodal groups on the same side of the diaphragm	Single E lesions without nodal involvement Stage I or II nodal extend with limited contiguous E involvement
II bulky	II as above with “bulky” disease	n/a
Advanced III IV	Nodes on both sides of diaphragm; nodes above diaphragm with spleen involvement Additional noncontiguous extralymphatic involvement	n/a n/a

Cheson BD, J Clin Oncol 2014;32:3059-67

Prognosis of early stage DLBCL

- Overall, the outcome is good: 10-year OS 80%
- However, there is a continuous pattern of relapse beyond 5 years
  - 20% at 5 years – 30% at 10 years
  - Related to more localized therapies?
  - Are relapses or second lymphomas?
- Scores better than IPI: stage modified IPI or NCCN-IPI
- Extranodal sites?
- Subdiaphragm sites (SEER database)?
- No influence of COO, double hit or double expression?

Stephens DM, J Clin Oncol 20167;34:1997-3004; Miller TP, N Engl J Med 1998;339:21-6; Xia Y, Cancers 2021;13:3954; Barraclough A, Blood Adv 2019;3:2013-21; Bobillo S, Blood 2021;137:39-48; Hawkes EA, Blood 2022;139:822-34

Stage-modified International Prognostic Index (smIPI)

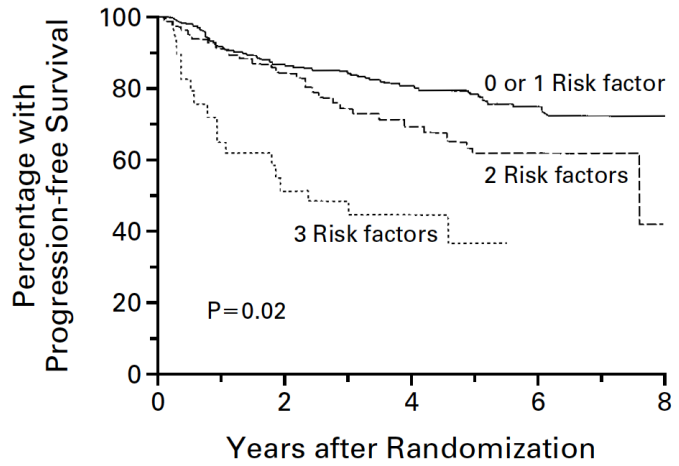
IPI

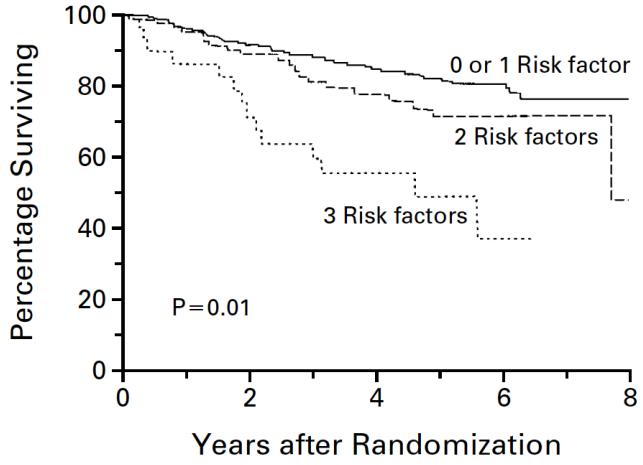
Age (≤60 vs. >60 yrs)
PS (ECOG 0-1 vs. 2-4)
Extranodal involvement (0-1 vs. ≥2)
Ann Arbor stage (I-II vs. III-IV)
Serum LDH (N vs. High)

smIPI

Age (≤60 vs. >60 yrs)
PS (ECOG 0-1 vs. 2-4)

Ann Arbor stage **(I vs. II)**
Serum LDH (N vs. High)





No. at Risk

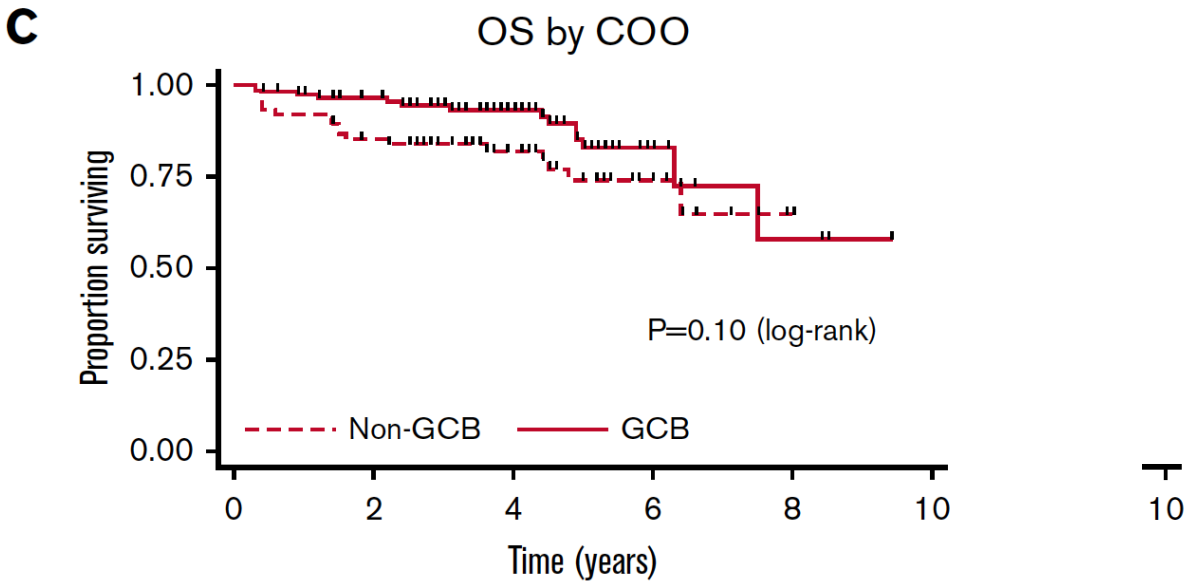
0 or 1 Risk factor	289	257	172	94	7
2 Risk factors	82	74	47	26	10
3 Risk factors	28	18	10	4	0

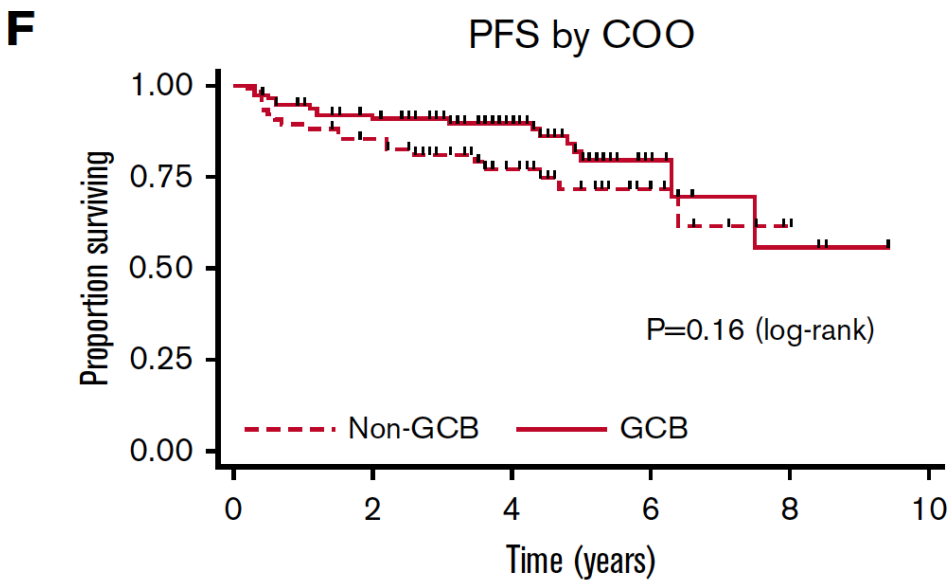
No. at Risk

0 or 1 Risk factor	289	272	182	99	21
2 Risk factors	82	77	51	30	19
3 Risk factors	28	23	14	6	0

Miller TP, N Engl J Med 1998;339:21-6

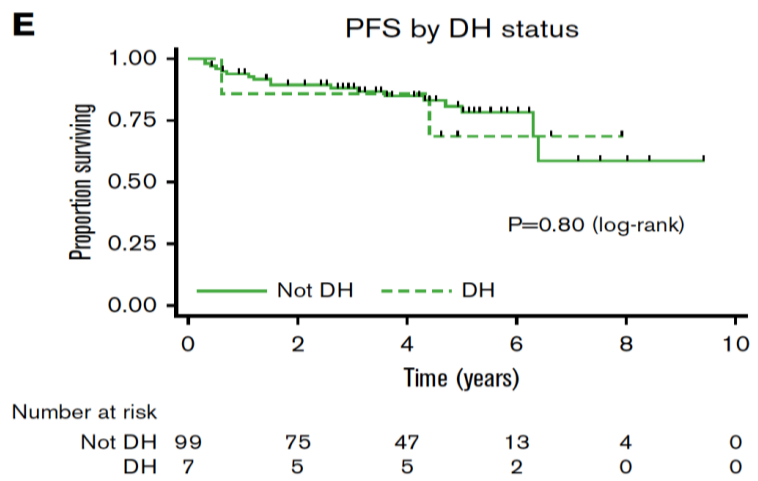
Cell of origin (COO) does not predict outcome in stage I-II patients with DLBCL

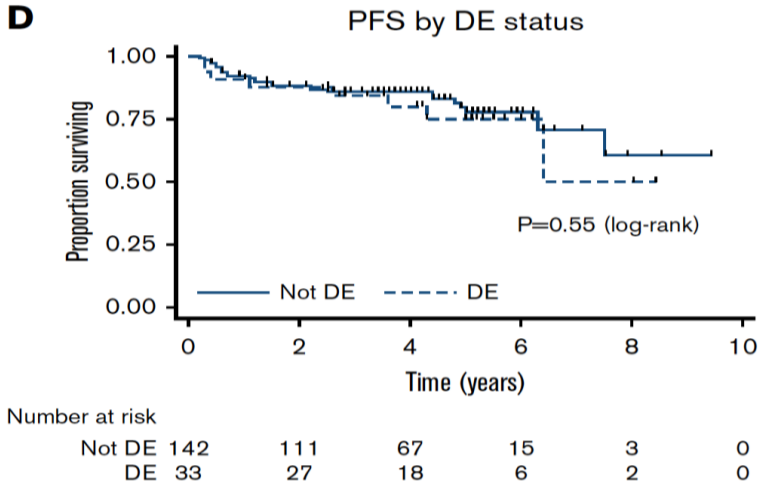


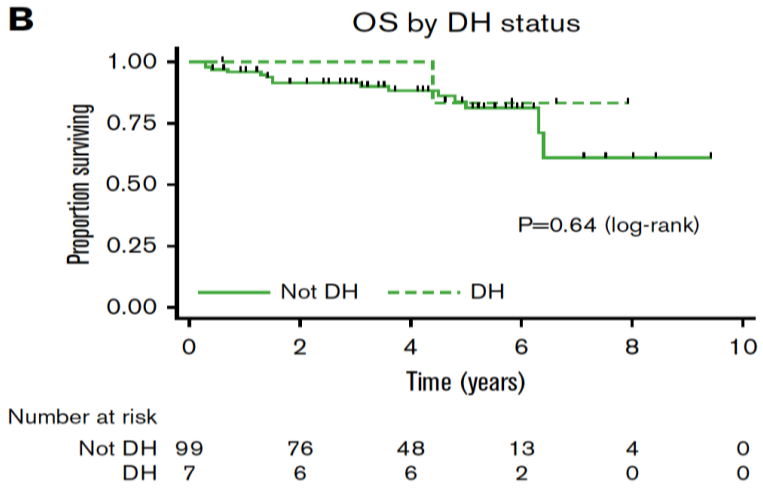


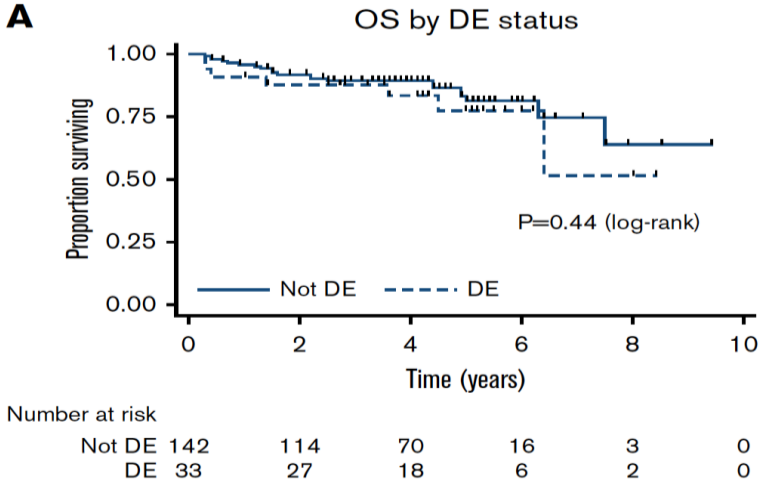
Barraclough A, Blood Adv 2019;3:2013-21

Double-hit or double-expresion do not predict outcome in stage I-II patients with DLBCL









Barraclough A, Blood Adv 2019;3:2013-21

Outline

- Staging (Lugano classification) and prognostic impact
- Treatment before Rituximab
- Treatment in the Rituximab era
- Specific situations

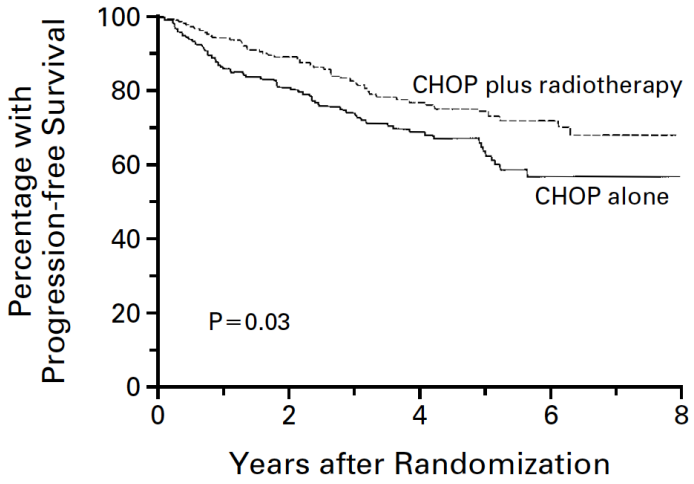
Selected randomized trials in early-stage DLBCL before Rituximab

Reference	N	Stage	Treatment arms	5-year PFS (%)	Other details
Miller 1998 Stephens 2016	401	I or II nonbulky	CHOPx8 CHOPx3 + IFRT	64 77*	No differences with long follow-up (median PFS: 11.1 vs. 12 years)
Bonnet 2007	576	I-II (with no risk factors of IPI)	CHOPx4 CHOPx4 + IFRT	61 64	≥60 years

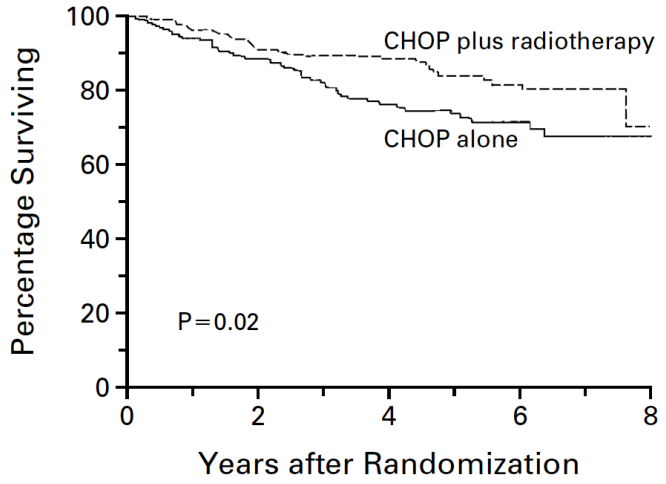
Miller TP, N Engl J Med 1998;339:21-6; Stephens DM, J Clin Oncol 2016;34:2997-3004; Bonnet C, J Clin Oncol 2007;25:787-92

CHOP x 8 *vs.* CHOPx3 plus RT in early stage aggressive lymphoma

- Biopsy-proven intermediate or high-risk NHL
- I – IE non bulky; II – IIE non bulky
- CT scan
- RT: involved field radiotherapy (40 to 55 Gy)



No. at Risk					
CHOP alone	201	172	111	55	14
CHOP plus radiotherapy	200	178	119	70	17



No. at Risk					
CHOP alone	201	187	120	61	14
CHOP plus radiotherapy	200	185	128	75	17

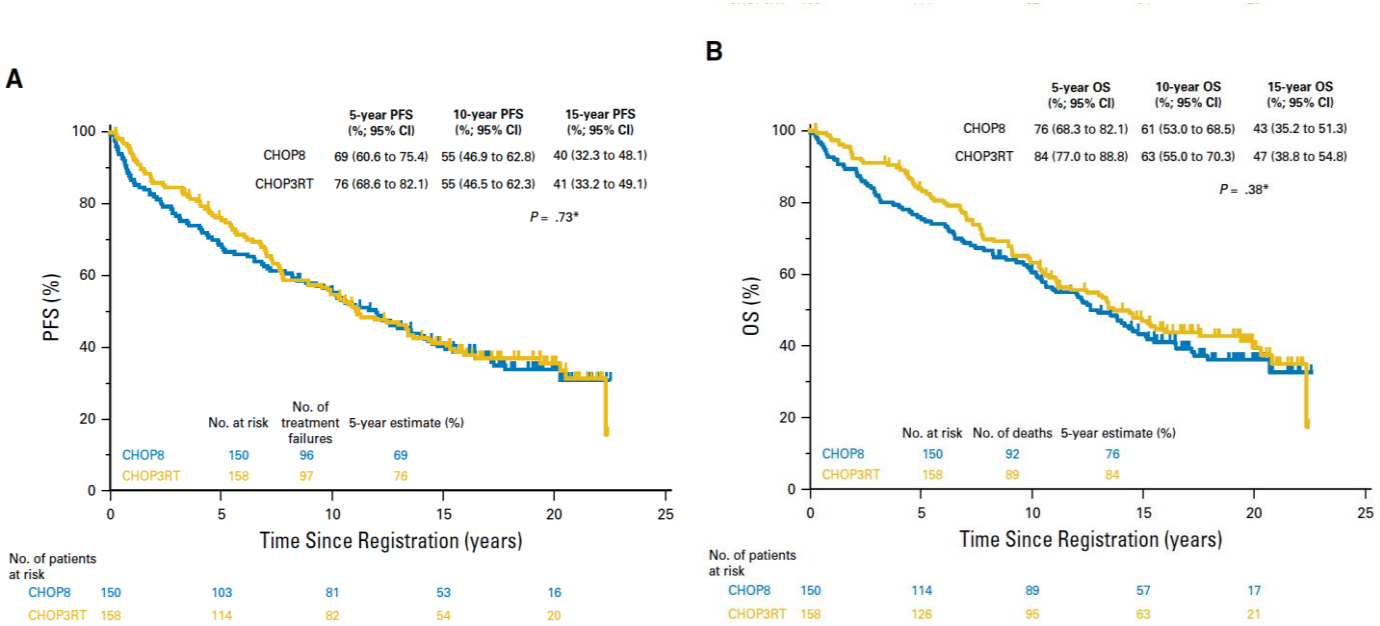
CHOP+RT:

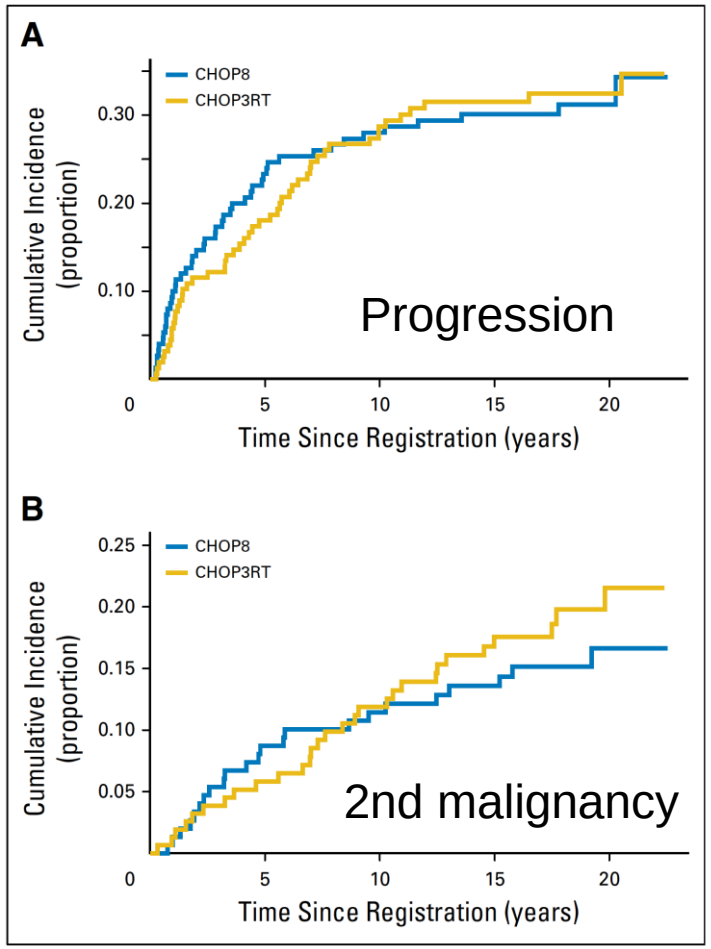
- = CR rate
- Less toxic (neutropenia or ventricular function)
- ↑ PFS and OS

Miller TP, N Engl J Med 1998;339:21-6

CHOP x 8 *vs.* CHOPx3 plus RT in early stage aggressive lymphoma

- Biopsy-proven intermediate or high-risk NHL
- I – IE non bulky; II – IIE non bulky
- CT scan
- RT: involved field radiotherapy (40 to 55 Gy)





Stephens DM, J Clin Oncol 2016;34:2997-3004

Outline

- Staging (Lugano classification) and prognostic impact
- Treatment before Rituximab
- Treatment in the Rituximab era
- Specific situations

Key strategies to improve the outcome in early stage DLBCL

1. Standard chemotherapy (CT) (MInT)
2. Combined modality (CT +- abbreviated + IFRT) (SWOG S0014)
3. Abbreviated CT (FLYER)
4. PET-adapted treatment

Hawkes EA, Barraclough A, Sehn LH, Blood 2022;139:822-38

R-CT > CT in early stage DLBCL

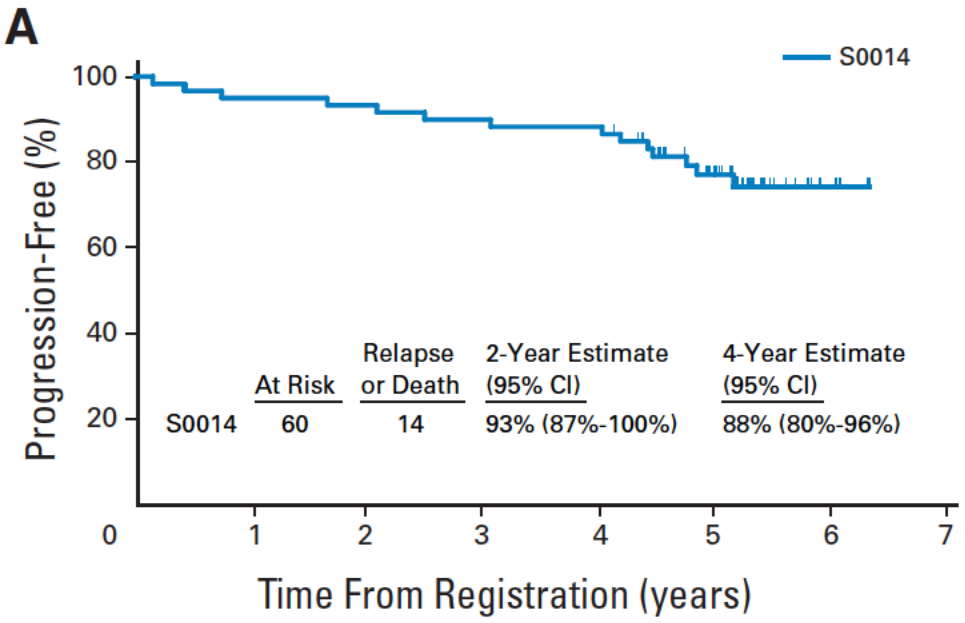
- SWOG S0014[1] (phase 2) R-CHOPx3 + IFRT (>CHOPx3 +RT)
- MInT[2,3] (phase 3)* R-CHO(E)Px6 > CHO(E)Px6

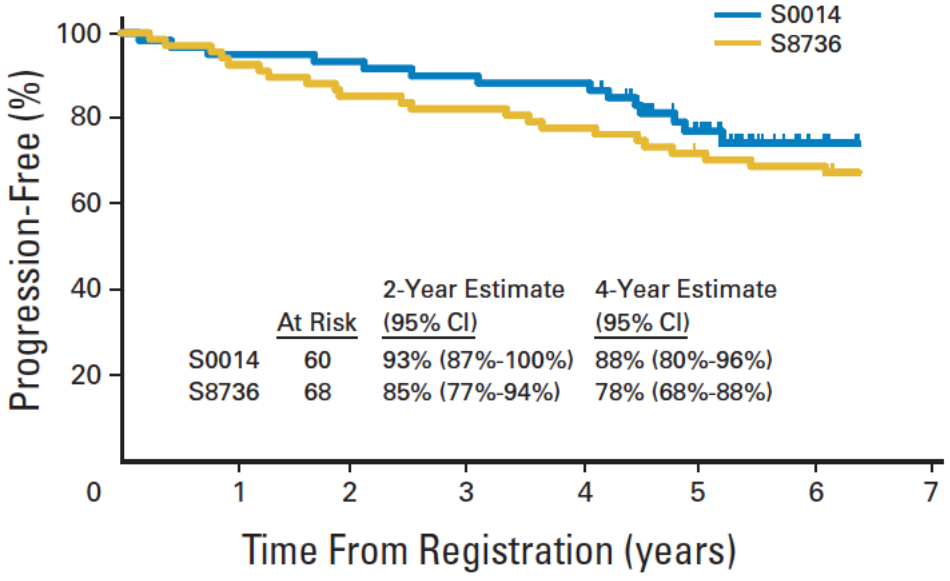
* Not exclusively early stage, but favorable (about 70%)
Bulk received RT 30-40 Gy

1) Persky DO, J Clin Oncol 2008;26:2258-63; 2) Pfreundschuh M, Lancet 2006;7:379-91; 3) Pfreundschuh M, Lancet Oncol 2011;12:1013-22

R-CT > CT in early stage DLBCL

- SWOG S0014[1] (phase 2) R-CHOPx3 + IFRT (>CHOPx3 +IFRT)
- MInT[2,3] (phase 3)* R-CHO(E)Px6 > CHO(E)Px6



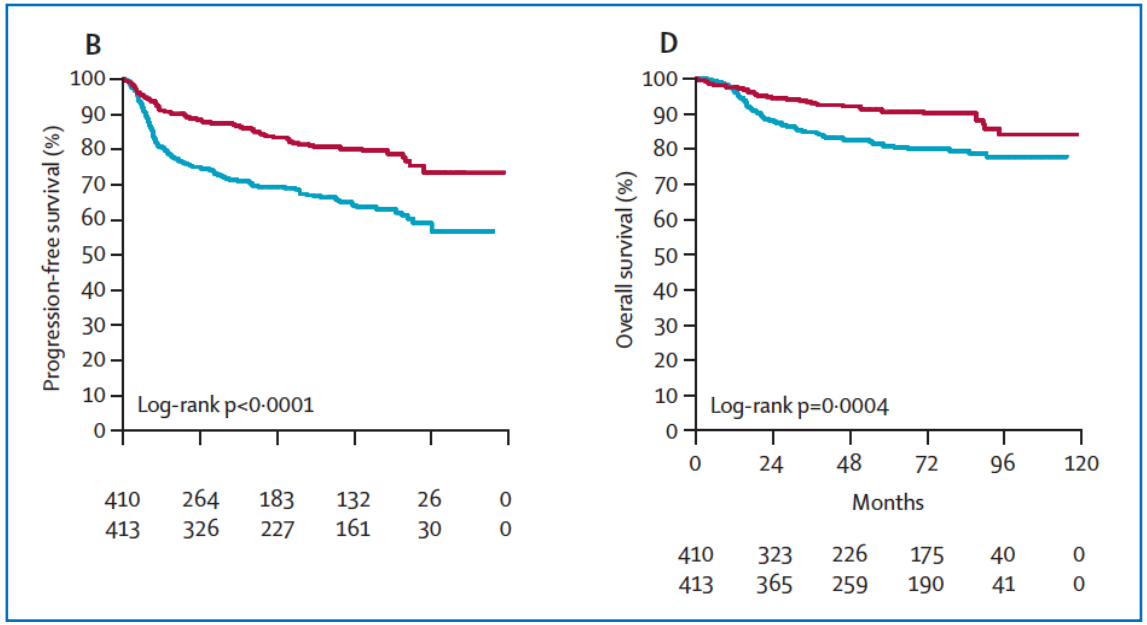


1) Persky DO, J Clin Oncol 2008;26:2258-63; 2) Pfreundschuh M, Lancet 2006;7:379-91; 3) Pfreundschuh M, Lancet Oncol 2011;12:1013-22

R-CT > CT in early stage DLBCL

- SWOG S0014[1] (phase 2) R-CHOPx3 + IFRT (>CHOPx3 +IFRT)
- MInT[2,3] (phase 3)* R-CHO(E)Px6 > CHO(E)Px6

* Not exclusively early stage, but favorable (about 70%)
Bulk received IFRT 30-40 Gy

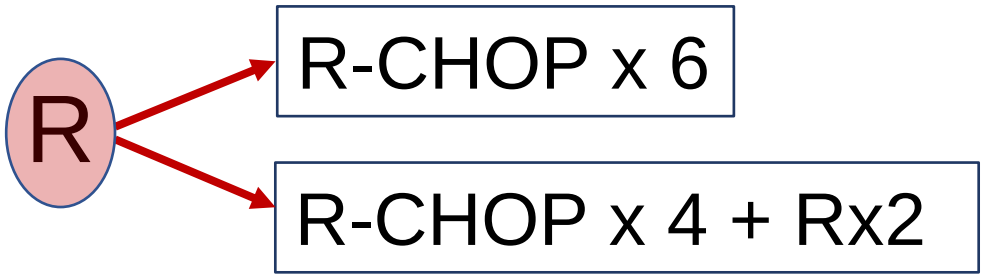


1) Persky DO, J Clin Oncol 2008;26:2258-63; 2) Pfreundschuh M, Lancet 2006;7:379-91; 3) Pfreundschuh M, Lancet Oncol 2011;12:1013-22

R-CHOPx6 *vs.* R-CHOPx4 + Rx2 in early stage DLBCL (FLYER trial)

ClinicalTrials.gov NCT00278421

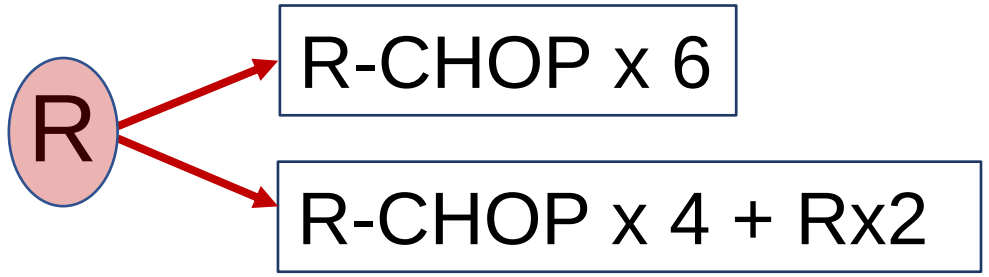
- DLBCL
- 18-60 years
- Stage I or II
- No IPI risk factor
- No bulky



Non-inferiority trial (margin -5.5%)
End-point: PFS (3 years)
No radiotherapy (except for testicular lymphoma)

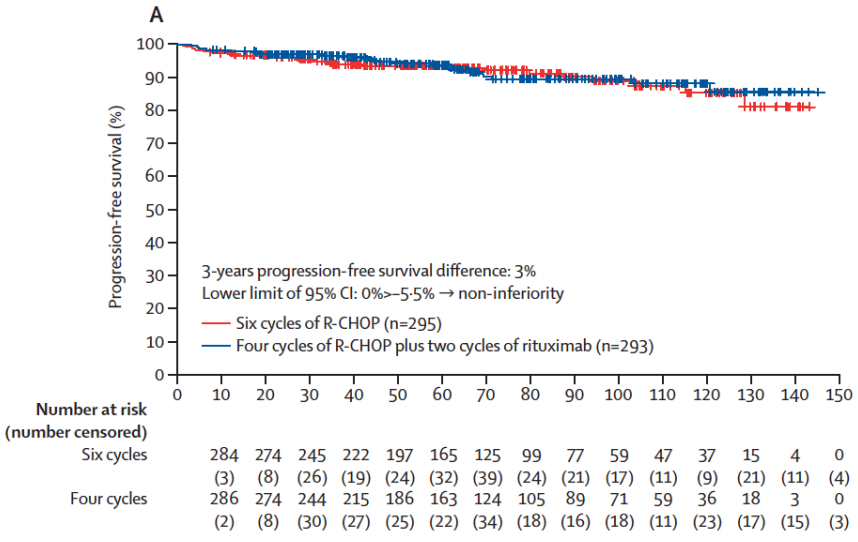
Poeschel V, Lancet 2019;394:2271-81

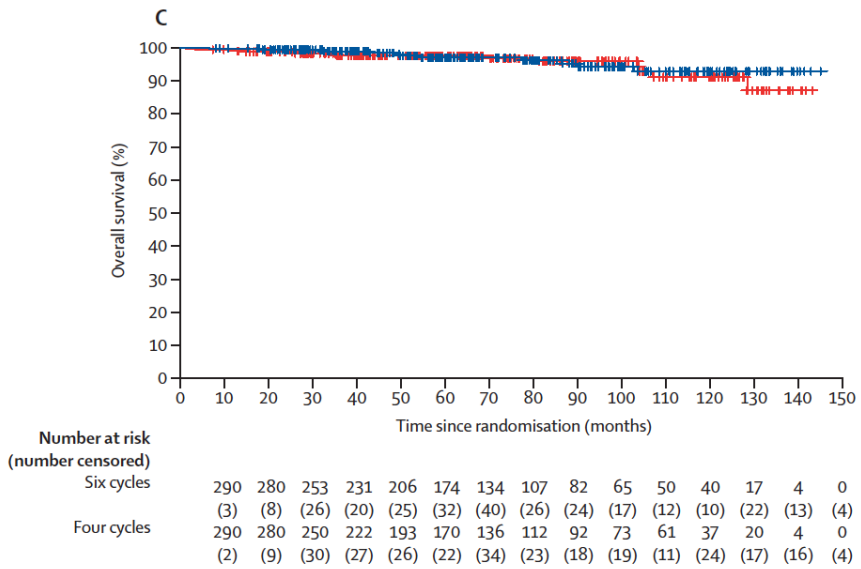
R-CHOPx6 *vs.* R-CHOPx4 + Rx2 in early stage DLBCL (FLYER trial)

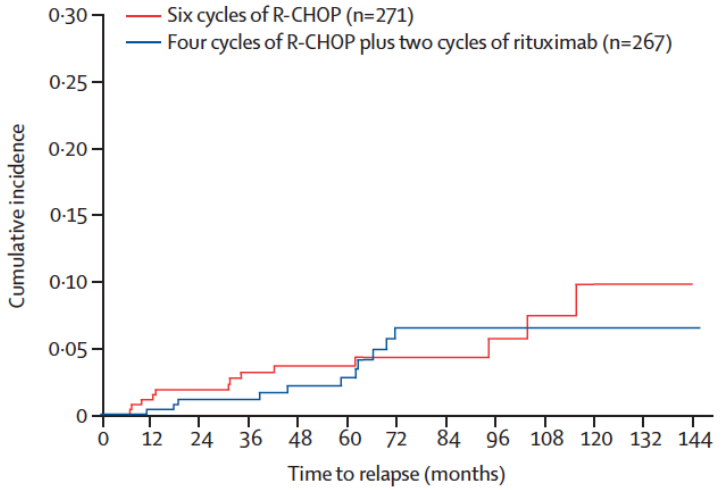


ClinicalTrials.gov NCT00278421

CR rate: 91% vs. 92%







Poeschel V, Lancet 2019;394:2271-81

Key strategies to improve the outcome in early stage DLBCL

1. Standard chemotherapy (CT) (MInT)
2. Combined modality (CT +- abbreviated + RT) (SWOG S0014)
3. Abbreviated CT (FLYER)
4. PET-adapted treatment

Hawkes EA, Barraclough A, Sehn LH, Blood 2022;139:822-38

CLINICAL TRIALS AND OBSERVATIONS

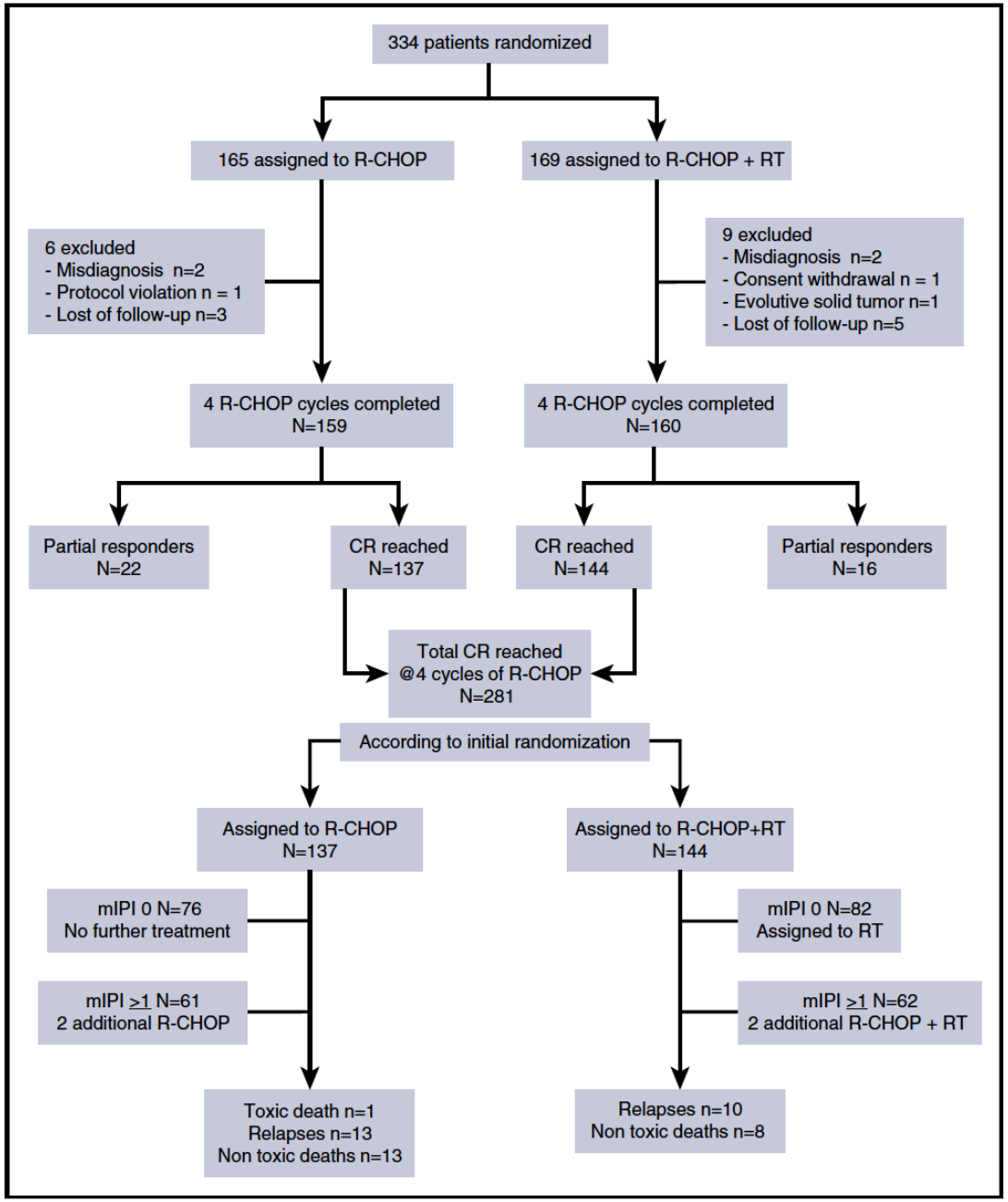
R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma

Thierry Lamy,[1] Gandhi Damaj,[2] Pierre Soubeyran,[3] Emmanuel Gyan,[4] Guillaume Cartron,[5] Krimo Bouabdallah,[6] Rémy Gressin,[7] Jérôme Cornillon,[8] Anne Banos,[9] Katell Le Du,[10] Mohamed Benchalal,[11] Marie-Pierre Moles,[12] Steven Le Gouill,[13] Joel Fleury,[14] Pascal Godmer,[15] Hervé Maisonneuve,[16] Eric Deconinck,[17] Roch Houot,[18] Kamel Laribi,[19] Jean Pierre Marolleau,[20] Olivier Tournilhac,[21] Bernard Branger,[22] Anne Devillers,[23] Jean Philippe Vuillez,[24] Thierry Fest,[25] Philippe Colombat,[26] Valérie Costes,[27] Vanessa Szablewski,[27] Marie C. Béné,[28] and Vincent Delwail,[29] on behalf of the LYSA Group

Blood 2018;131:174-81

- DLBCL
- 18-75 years
- Stage I or II
- No bulky

- Involved field RT
- 40Gy in 20 fractions
- 4 weeks after last R-CHOP

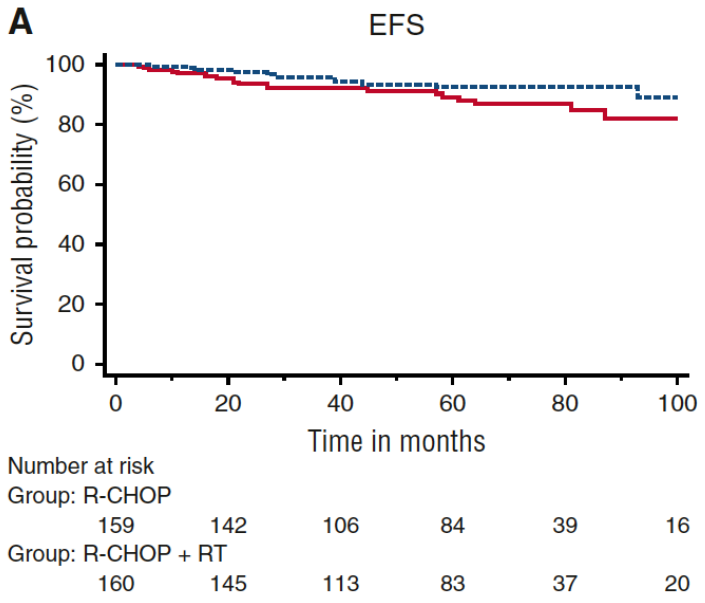


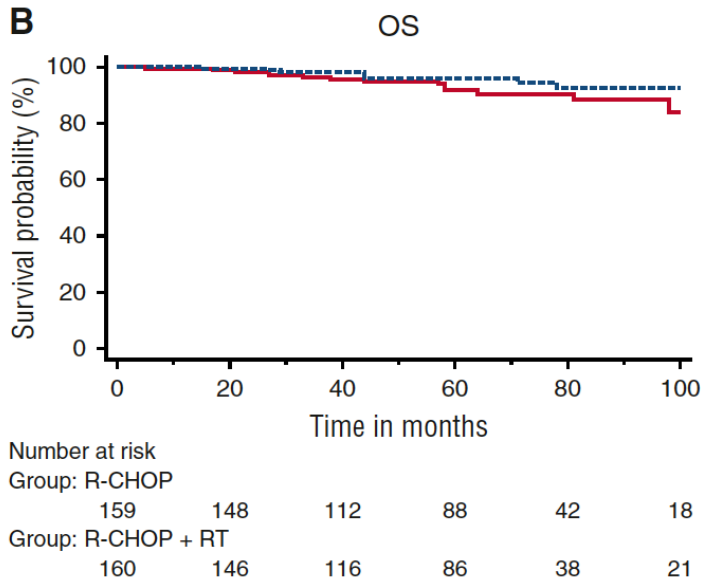
CLINICAL TRIALS AND OBSERVATIONS

R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma

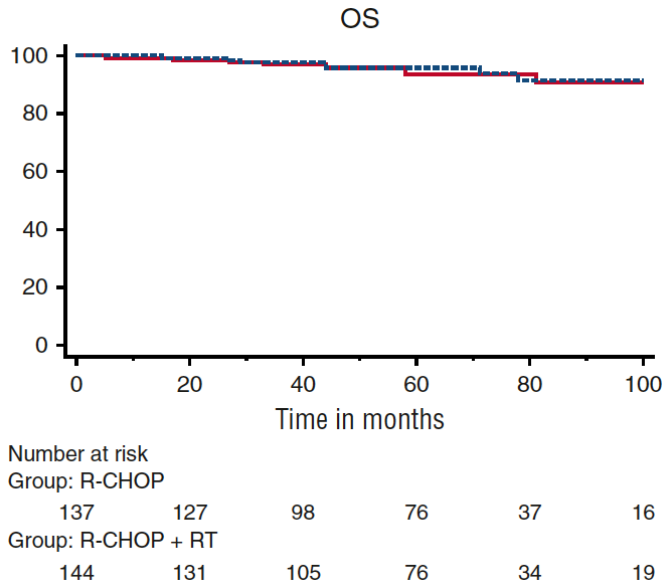
Thierry Lamy,[1] Gandhi Damaj,[2] Pierre Soubeyran,[3] Emmanuel Gyan,[4] Guillaume Cartron,[5] Krimo Bouabdallah,[6] Rémy Gressin,[7] Jérôme Cornillon,[8] Anne Banos,[9] Katell Le Du,[10] Mohamed Benchalal,[11] Marie-Pierre Moles,[12] Steven Le Gouill,[13] Joel Fleury,[14] Pascal Godmer,[15] Hervé Maisonneuve,[16] Eric Deconinck,[17] Roch Houot,[18] Kamel Laribi,[19] Jean Pierre Marolleau,[20] Olivier Tournilhac,[21] Bernard Branger,[22] Anne Devillers,[23] Jean Philippe Vuillez,[24] Thierry Fest,[25] Philippe Colombat,[26] Valérie Costes,[27] Vanessa Szablewski,[27] Marie C. Béné,[28] and Vincent Delwail,[29] on behalf of the LYSA Group

Blood 2018;131:174-81

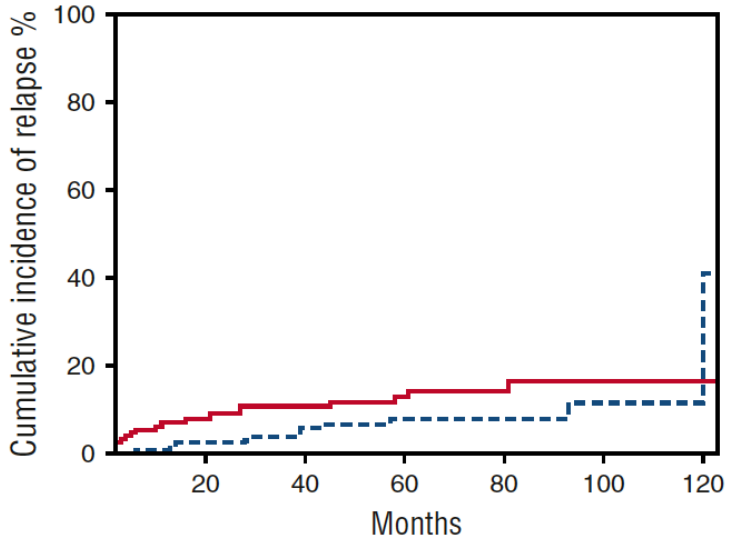




From time of inclusion



Patients in CR after 4th cycle



Abbreviated R-CHOP with PET-directed IFRT

- DLBCL
- Stage I or II
- No bulky

R-CHOP x 3

N=319

PET

\- **80%** R-CHOP x 1

5-yr PFS: 88%
5-yr OS: 90%

\+ **18%** IFRT

5-yr PFS: 74%
5-yr OS: 77%

Single center experience (British Columbia)
IFRT: involved-site radiotherapy

Sehn LH, Blood 2019;134(suppl 1):401

original reports

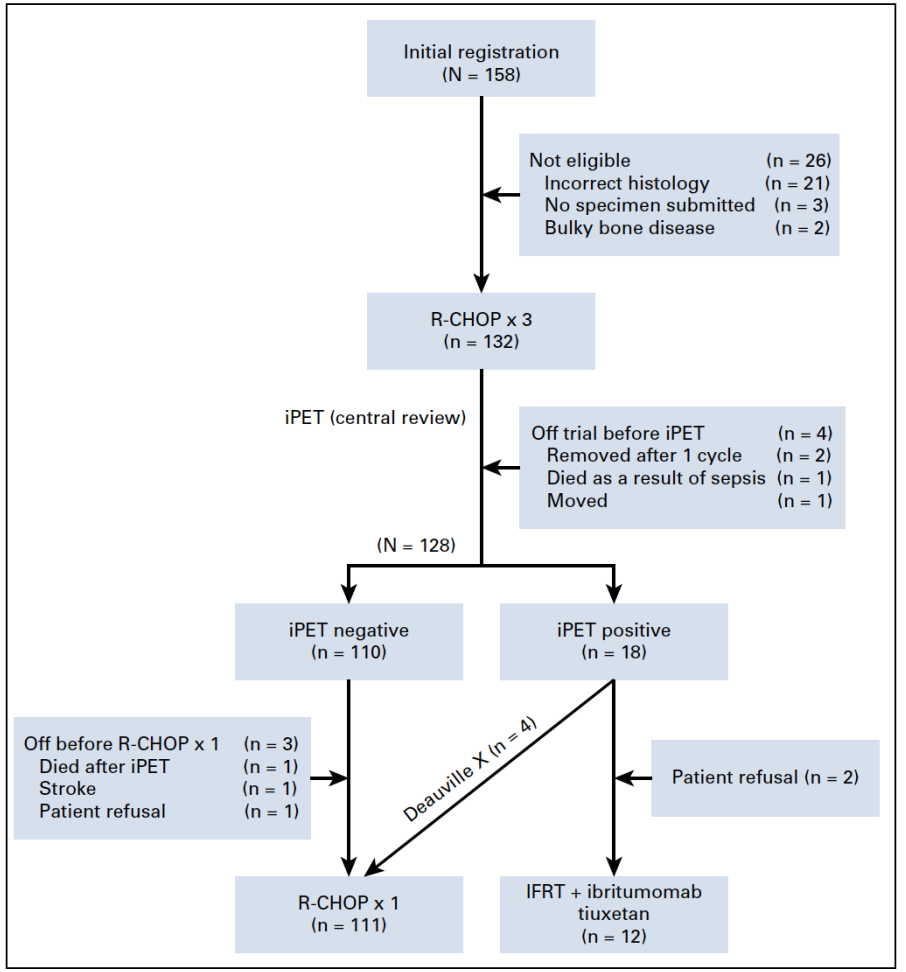
Positron Emission Tomography–Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001

Daniel O. Persky, MD[1]; Hongli Li, MS[2]; Deborah M. Stephens, DO[3]; Steven I. Park, MD[4,5]; Nancy L. Bartlett, MD[6]; Lode J. Swinnen, MD[7]; Paul M. Barr, MD[8]; Jerome D. Winegarden III, MD[9]; Louis S. Constine, MD[10]; Thomas J. Fitzgerald, MD[11]; John P. Leonard, MD[12]; Brad S. Kahl, MD[6]; Michael L. LeBlanc, PhD[2]; Joo Y. Song, MD[13]; Richard I. Fisher, MD[14]; Lisa M. Rimsza, MD[15]; Sonali M. Smith, MD[16]; Thomas P. Miller, MD[1]; and Jonathan W. Friedberg, MD[8]

J Clin Oncol 2020;38:3003-11

- DLBCL
- Stage I or II
- Age >18
- ECOG 0-2
- No bulky (10 cm)

R-CHOP x 3 → PET → - R-CHOP x 1 / + IFRT + Zevalin

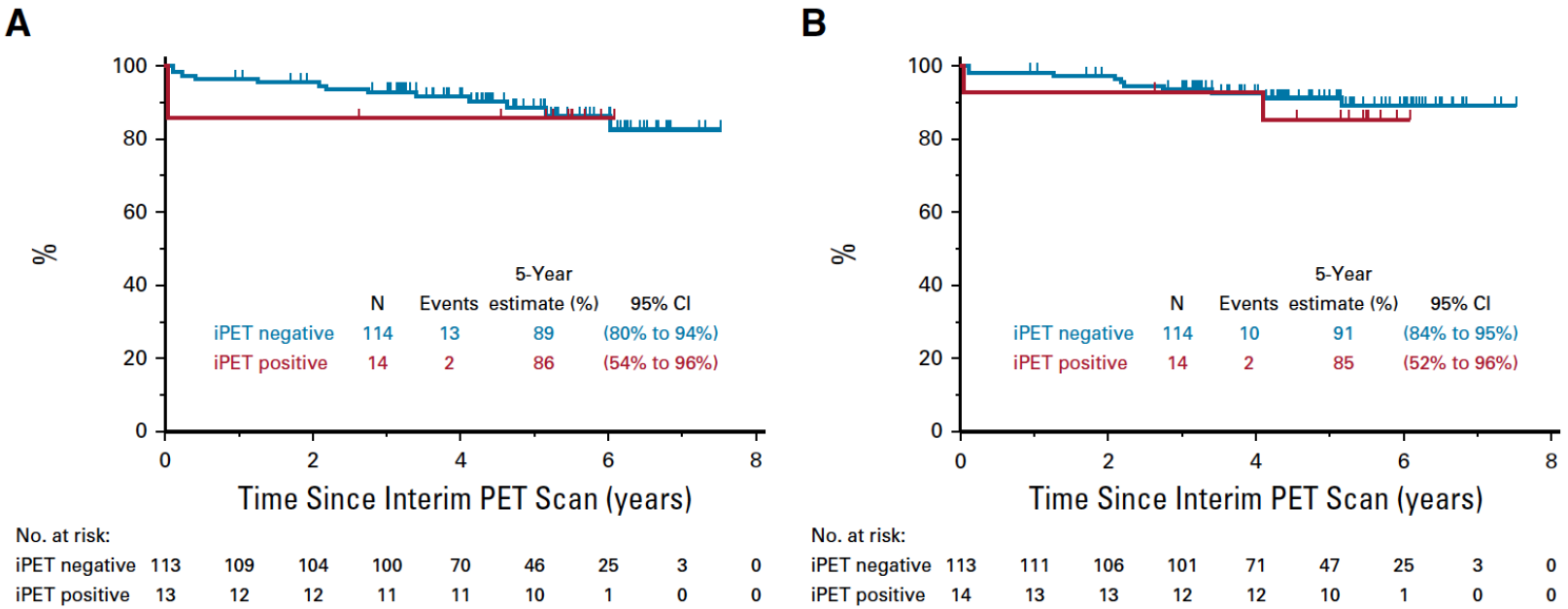


original reports

Positron Emission Tomography–Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001

Daniel O. Persky, MD[1]; Hongli Li, MS[2]; Deborah M. Stephens, DO[3]; Steven I. Park, MD[4,5]; Nancy L. Bartlett, MD[6]; Lode J. Swinnen, MD[7]; Paul M. Barr, MD[8]; Jerome D. Winegarden III, MD[9]; Louis S. Constine, MD[10]; Thomas J. Fitzgerald, MD[11]; John P. Leonard, MD[12]; Brad S. Kahl, MD[6]; Michael L. LeBlanc, PhD[2]; Joo Y. Song, MD[13]; Richard I. Fisher, MD[14]; Lisa M. Rimsza, MD[15]; Sonali M. Smith, MD[16]; Thomas P. Miller, MD[1]; and Jonathan W. Friedberg, MD[8]

J Clin Oncol 2020;38:3003-11

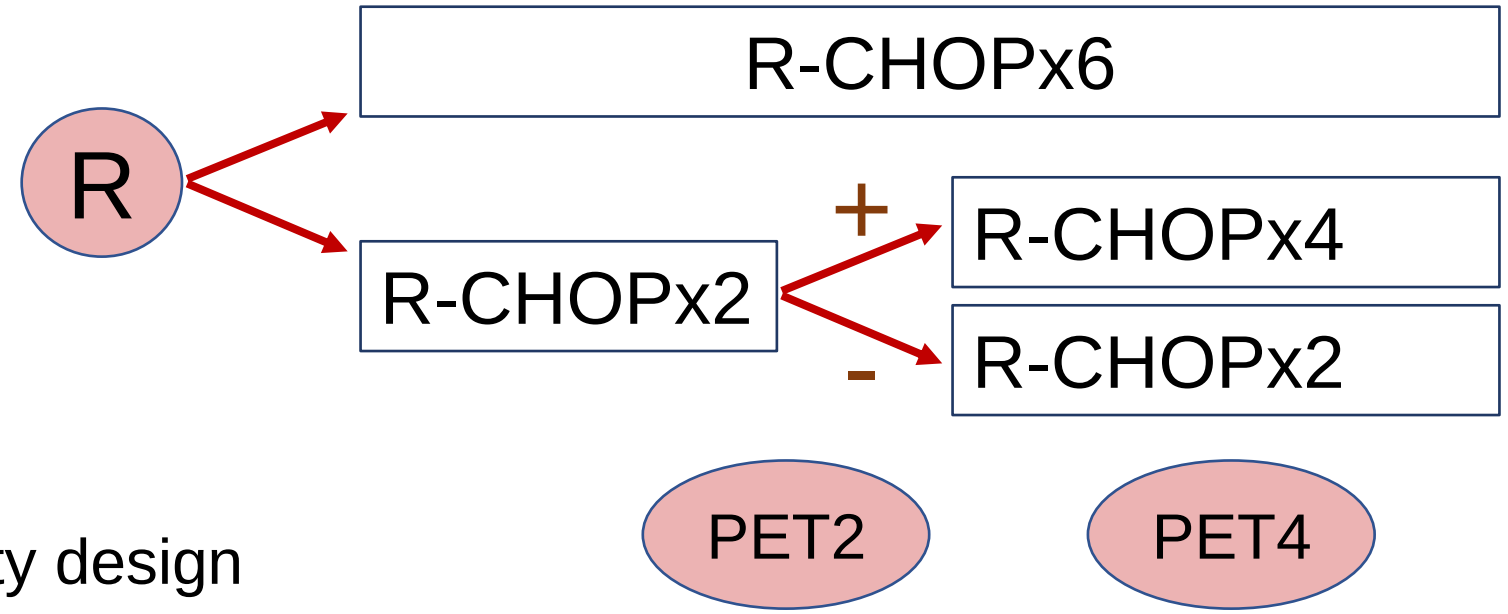


CONCLUSION To our knowledge, S1001 is the largest prospective study in the United States of limited-stage DLBCL in the rituximab era, with the best NCTN results in this disease subset. With PET-directed therapy, 89% of the patients with a negative iPET received R-CHOP × 4, and only 11% had a positive iPET and required radiation, with both groups having excellent outcomes. The trial establishes R-CHOP × 4 alone as the new standard approach to limited-stage disease for the absolute majority of patients.

005 | **EARLY POSITRON EMISSION TOMOGRAPHY RESPONSE-ADAPTED TREATMENT IN LOCALIZED DIFFUSE LARGE B-CELL LYMPHOMA (AAIPI=0) : RESULTS OF THE PHASE 3 LYSA LNH 09-1B TRIAL**

S. Bologna[1], T. Vander Borght[2], J. Briere[3], V. Ribrag[4], G. L. Damaj[5], C. Thieblemont[6], P. Feugier[7], F. Peyrade[8], L. Lebras[9], D. Coso[10], D. Sibon[11], C. Bonnet[12], F. Morschhauser[13], H. Ghesquieres[14], S. Becker[15], P. Olivier[16], B. Fabiani[17], H. Tilly[18], C. Haioun[19], J. N. Bastie[20]

- DLBCL
- Stage I or II
- 18-80 years
- aaIPI=0

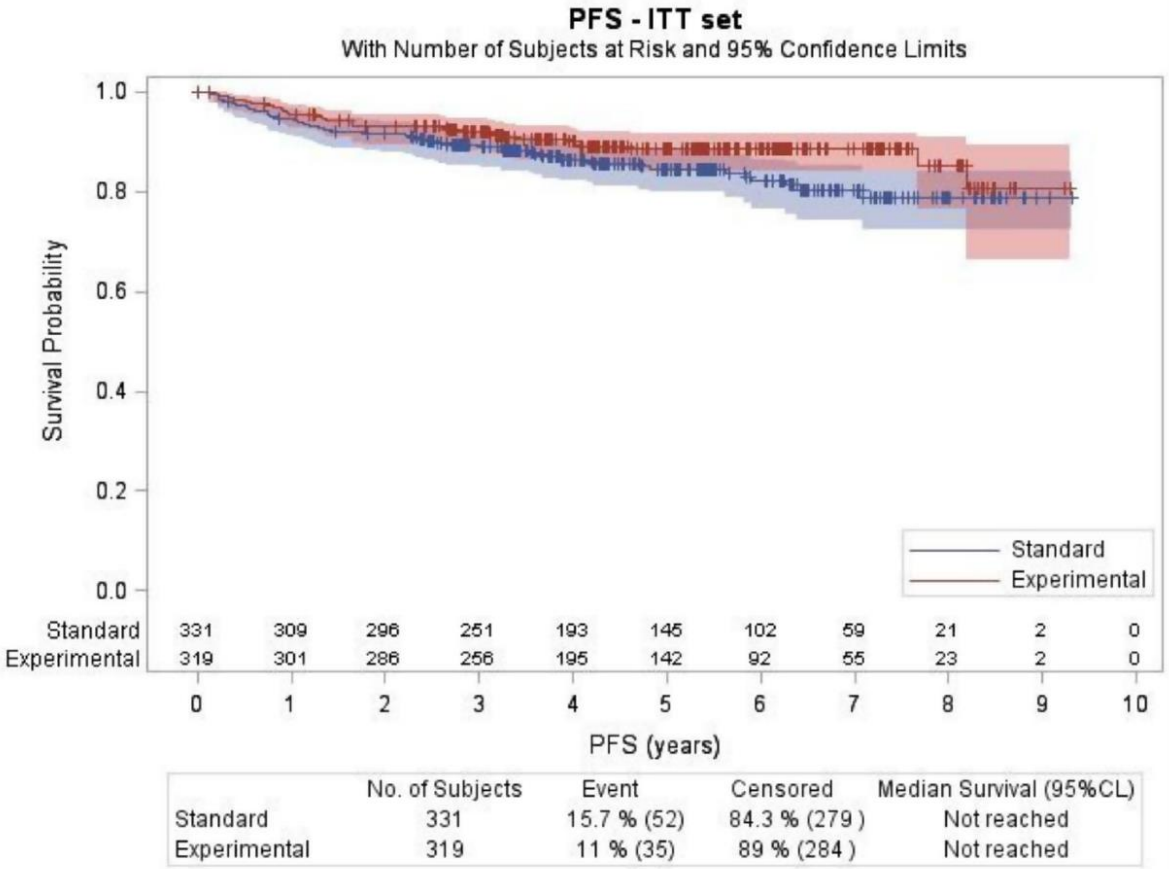


Non inferiority design

Bologna S, ICML 2021; Hematol Oncol 2021;31-2

005 | **EARLY POSITRON EMISSION TOMOGRAPHY RESPONSE-ADAPTED TREATMENT IN LOCALIZED DIFFUSE LARGE B-CELL LYMPHOMA (AAIPI=0) : RESULTS OF THE PHASE 3 LYSA LNH 09-1B TRIAL**

S. Bologna[1], T. Vander Borght[2], J. Briere[3], V. Ribrag[4], G. L. Damaj[5], C. Thieblemont[6], P. Feugier[7], F. Peyrade[8], L. Lebras[9], D. Coso[10], D. Sibon[11], C. Bonnet[12], F. Morschhauser[13], H. Ghesquieres[14], S. Becker[15], P. Olivier[16], B. Fabiani[17], H. Tilly[18], C. Haioun[19], J. N. Bastie[20]



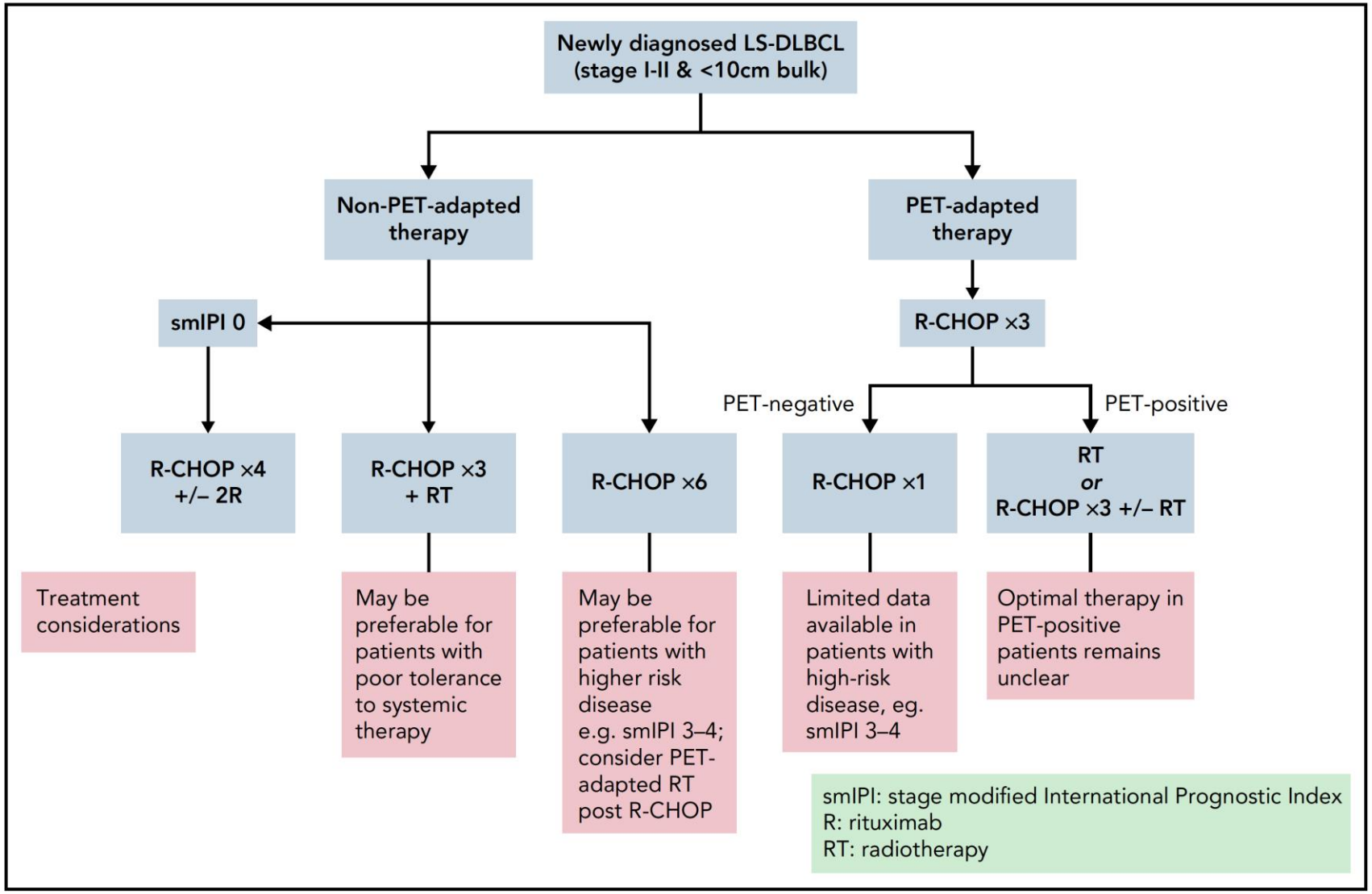
	No. of Subjects	Event	Censored	Median Survival (95%CL)
Standard	331	15.7 % (52)	84.3 % (279)	Not reached
Experimental	319	11 % (35)	89 % (284)	Not reached

- Experimental arm: 80% negative PET2
- Overall, PET2 does not predict outcome
- Patients with positive PET4 in either arm taken off study

Non inferiority: HR 0.724 (90%CI: 0.504-1.040)

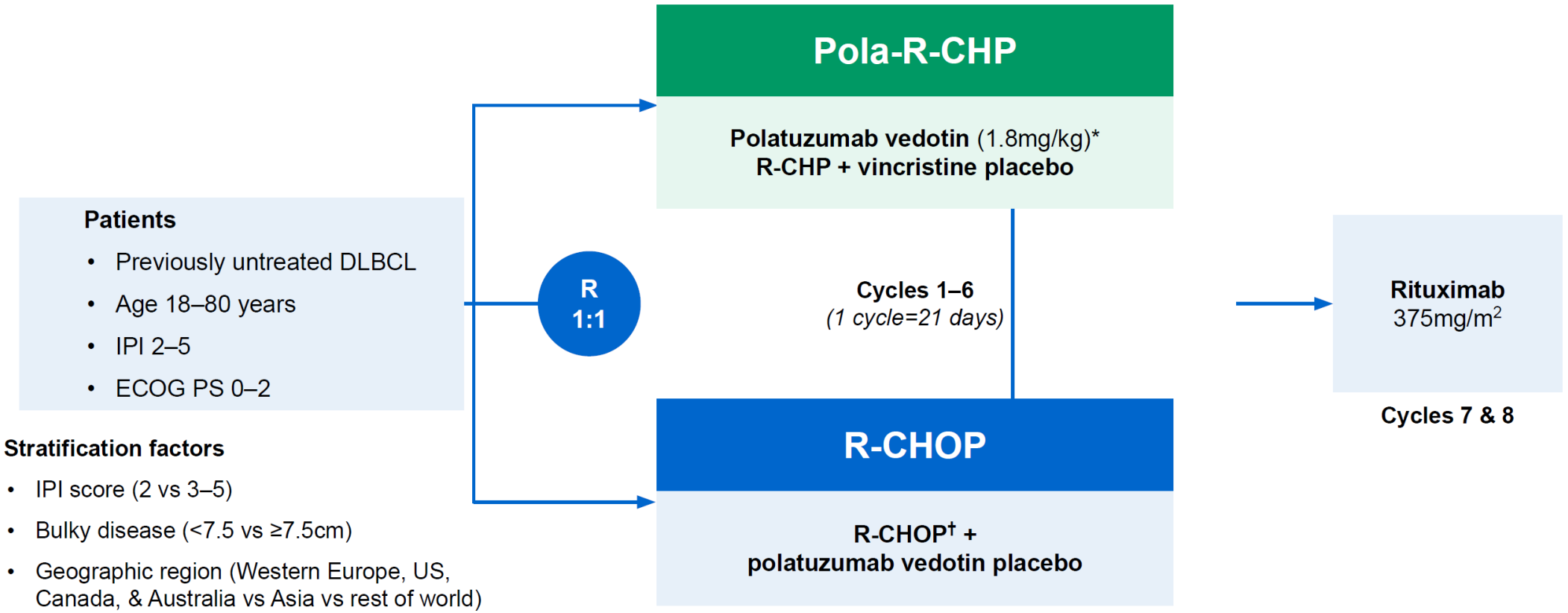
Bologna S, ICML 2021; Hematol Oncol 2021;31-2

Treatment of limited-stage DLBCL



Hawkes EA, Barraclough A, Sehn LH, Blood 2022;139:822-38

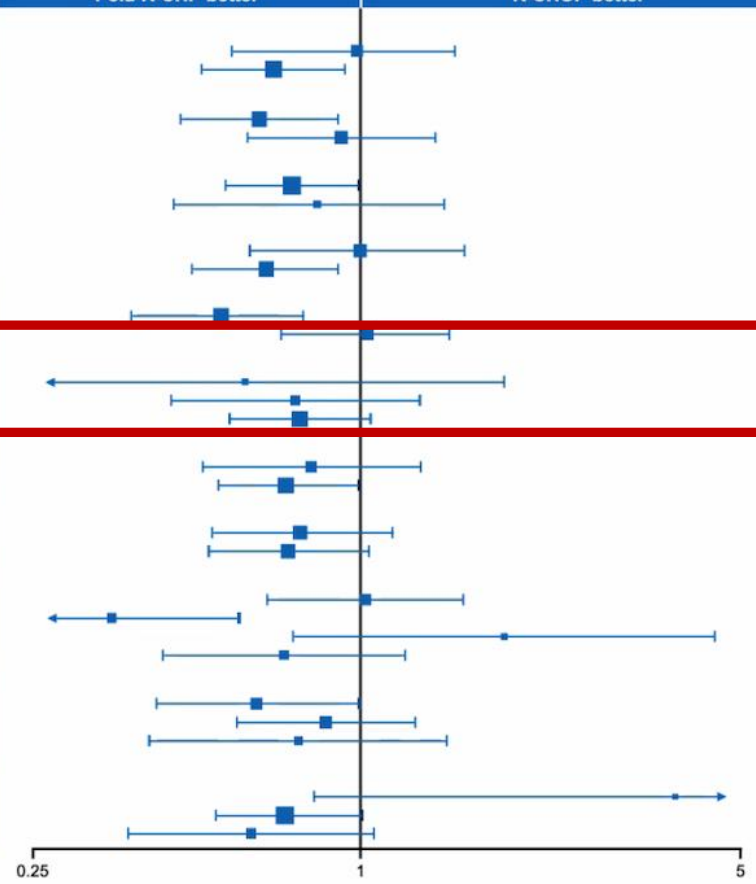
POLARIX: A randomized double-blinded study



*IV on Day 1; †R-CHOP: IV rituximab 375mg/m^2, cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2, and vincristine 1.4mg/m^2 (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

PFS (by INV) by subgroup (unstratified)

Baseline Risk Factors	Total N	Pola-R-CHP (N = 440) n	Pola-R-CHP (N = 440) 2-year rate	R-CHOP (N = 439) n	R-CHOP (N = 439) 2-year rate	Hazard ratio	95% Wald CI
Age group							
≤60	271	140	74.1	131	71.9	0.9	(0.6 to 1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5 to 0.9)
Sex							
Male	473	239	75.9	234	65.9	0.7	(0.5 to 0.9)
Female	406	201	77.7	205	75.2	0.9	(0.6 to 1.4)
ECOG PS							
0–1	737	374	78.4	363	71.2	0.8	(0.6 to 1.0)
2	141	66	67.2	75	65.0	0.8	(0.5 to 1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6 to 1.6)
IPI 3–5	545	273	75.2	272	65.1	0.7	(0.5 to 0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4 to 0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7 to 1.5)
Ann Arbor stage							
I–II	99	47	89.1	52	85.5	0.6	(0.2 to 1.8)
III	232	124	80.7	108	73.6	0.8	(0.5 to 1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6 to 1.1)
Baseline LDH							
≤ULN	300	146	78.9	154	75.6	0.8	(0.5 to 1.3)
>ULN	575	291	75.4	284	67.2	0.7	(0.5 to 1.0)
No. of extranodal sites							
0–1	453	227	80.2	226	74.5	0.8	(0.5 to 1.1)
≥2	426	213	73.0	213	65.8	0.7	(0.5 to 1.0)
Cell-of-origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7 to 1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2 to 0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8 to 4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4 to 1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4 to 1.0)
Non DEL	438	223	77.7	215	75.7	0.9	(0.6 to 1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4 to 1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8 to 17.6)
No	620	305	76.8	315	70.3	0.7	(0.5 to 1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4 to 1.1)



Outline

- Staging (Lugano classification) and prognostic impact
- Treatment before Rituximab
- Treatment in the Rituximab era
- Specific situations

Early stage DLBCL in special populations

- Aggressive lymphomas other than DLBCLnos
  - In S1001: 22 patients (17%) had high-grade B-cell lymphoma “nos” and 4 (3%) double hit (DH)[1]
  - The outcome was similar (i.e., 4/4 DH in maintained CR)[1]
  - Other histologic subtypes did not confer unique outcome in early stage aggressive lymphomas[2]
- *MYC* rearrangement +/- *BCL2* and/or *BCL6*[3]
- No differences in the outcome according to COO, DH or DE[4]

1) Persky DO, J Clin Oncol 2020;38:3003-11; 2) Spier CM, Blood 2004; 3) Turka P, Blood Adv 2020;4:253-62; 4) Barraclough A, Blood Adv 2019;3:2013-21

Targeted drugs according to molecular classification

Cell of origin	Molecular classification	Genetic alterations	Drugs
GCB	EZB / C3	*EZH2*, *BCL2*, *CREBBP*	▪ iBCL2 (venetoclax) ▪ imTOR (tensirolimus, everolimus) ▪ iEZH/iHDAC (tazemetostat, …) ▪ iPI3K (idelalisib, copanlisib, …)
	C4	Core histone genes, Immune evasion *JAK/STAT, BCR/PI3K, NFkB*	▪ iPI3K (idelalisib, copanlisib, …) ▪ iproteasoma (bortezomib, carfilzomib) ▪ JAK/STAT (ruxolotinib) ▪ iPD-1 (nivolumab, pembrolizumab)
Unclas. GCB/ABC	B2N / C1	*BCL6; NOTCH2*	▪ iBTK (ibrutinib, acalabrutinib) ▪ Iproteasoma (botezomib,carfilzomib) ▪ iPD1 (nivolumab, pembrolizumab)
	C2	*TP53*	▪ APR-246 ▪ MDM2/MDM$ ▪ XPO1 (selinexor)
ABC	MCD / C5	*MYD88, CD79B, BCL2, MALT1*	▪ iBTK (ibrutinib, acalabrutinib) ▪ iSYK (entospletinib, fosfamatinib) ▪ iPD1 (nivolumab, pembroluzumab) ▪ iMALT1 (fenotiacines, MI-1)
	N1	*NOTCH1*	▪ iNOTCH ▪ Lenalidomida

Schmitz R, N Engl J Med 2018; Chapuy B, Nat Med 2018; Wright GW, Cancer Cell 2020; Sehn LH & Salles G, N Engl J Med 2021; Campo E, Blood 2022

Conclusions

- Limited stage DLBCLs have good prognosis with current R-CHOP-based +-IFRT treatment.
- R-CHOPx4 (+Rx2) is adequate for low-risk (smIPI 0) cases.
- PET-based strategy is useful, since it allows to tailor the number of cycles or the use of IFRT in cases with insufficient metabolic response.
- The development of new biomarkers could guide the use of novel targeted therapies.