FRONTLINE DLBCL

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March 2, 2024

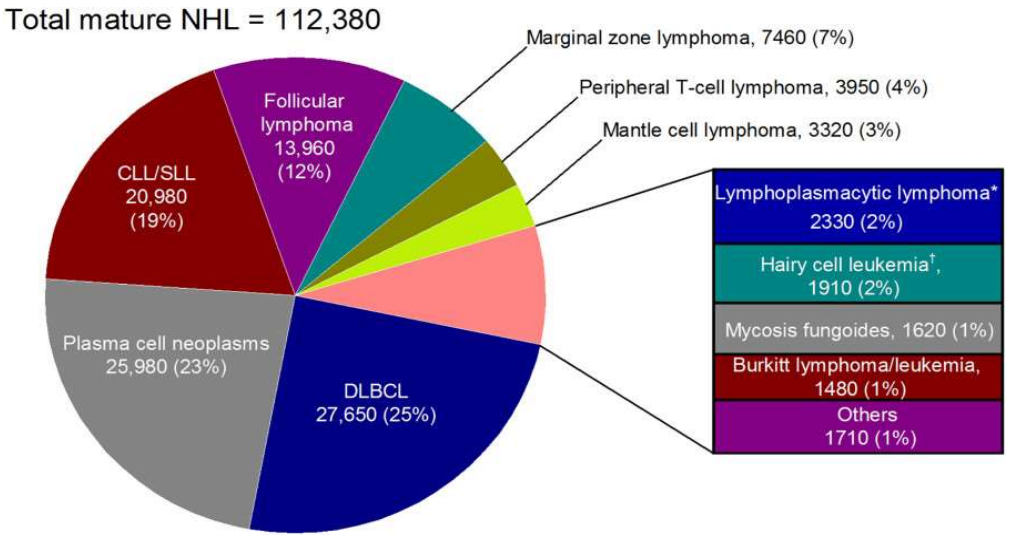
DISCLOSURES

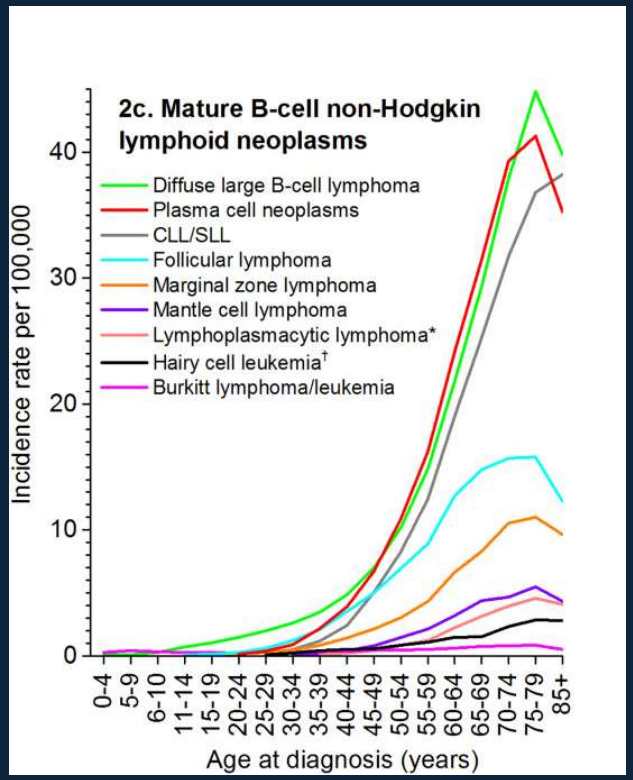
- No financial relationships that impact this presentation

DIFFUSE LARGE B-CELL LYMPHOMA

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

- Aggressive form of NHL
- Most common NHL in adults
- Peak incidence in 6th decade





CA A Cancer J Clin, 2016, 66(6): 443-459.

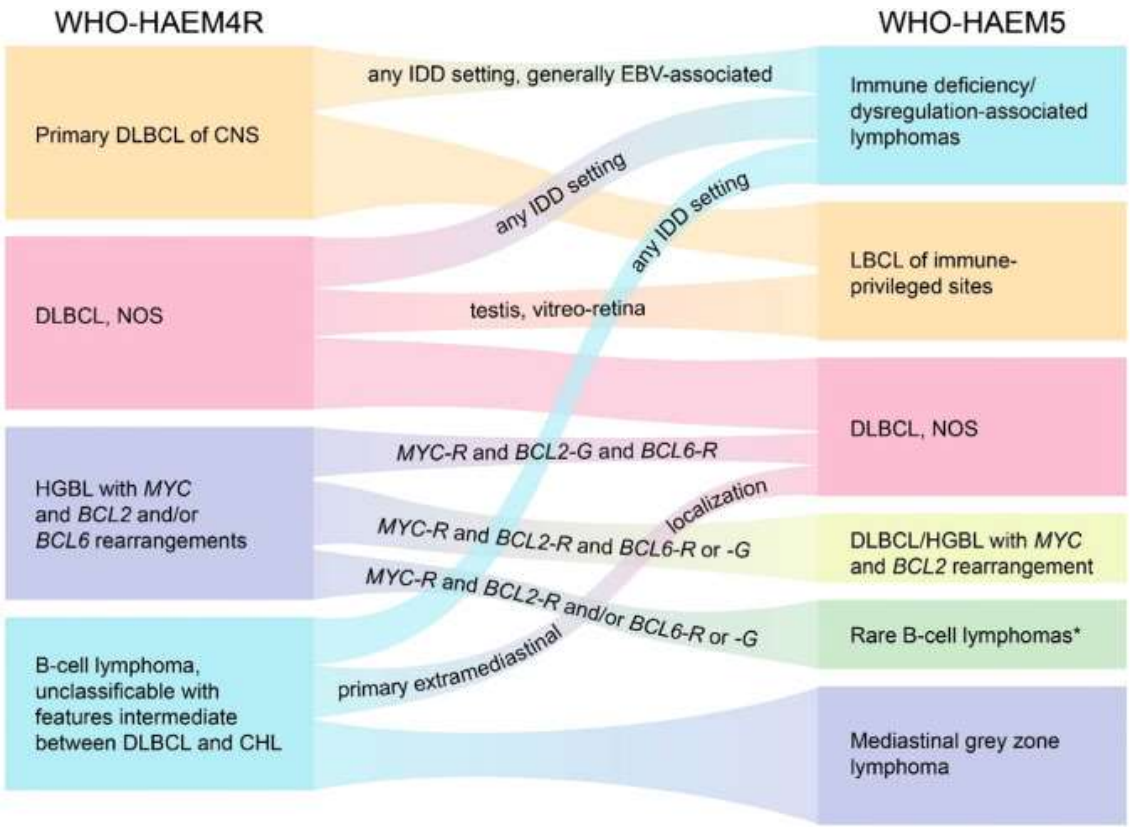
WHO CLASSIFICATION

- What has changed?

WHO Classification, revised 4th edition	WHO Classification 5th edition
High-grade B-cell lymphoma with *MYC* and *BCL2* **and/or *BCL6* rearrangements**	Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
Not previously included, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (*plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis)*	Primary large B-cell lymphoma of immune-privileged sites

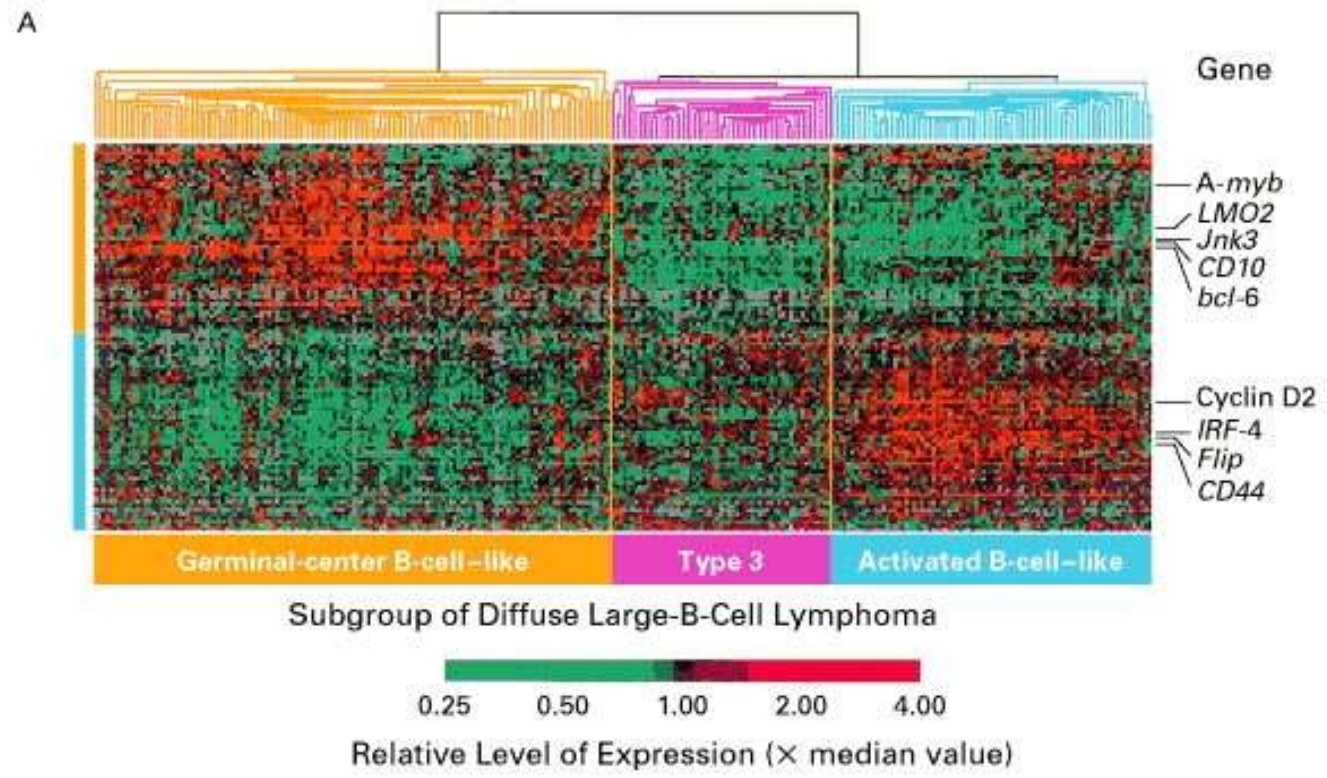
Leukemia, 2022; 36: 1720–1748.

WHO CLASSIFICATION



Leukemia, 2022; 36: 1720–1748.

GENE EXPRESSION PROFILING (GEP)



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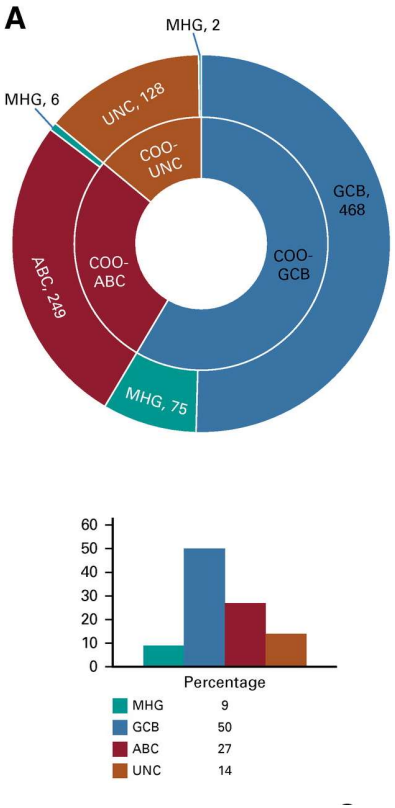
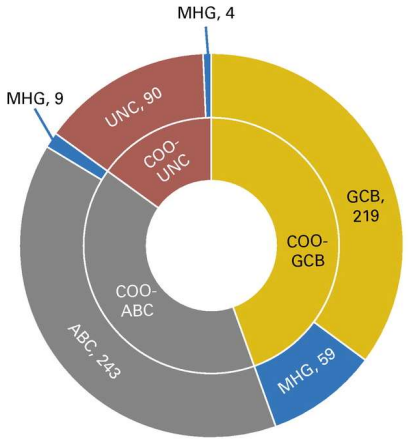
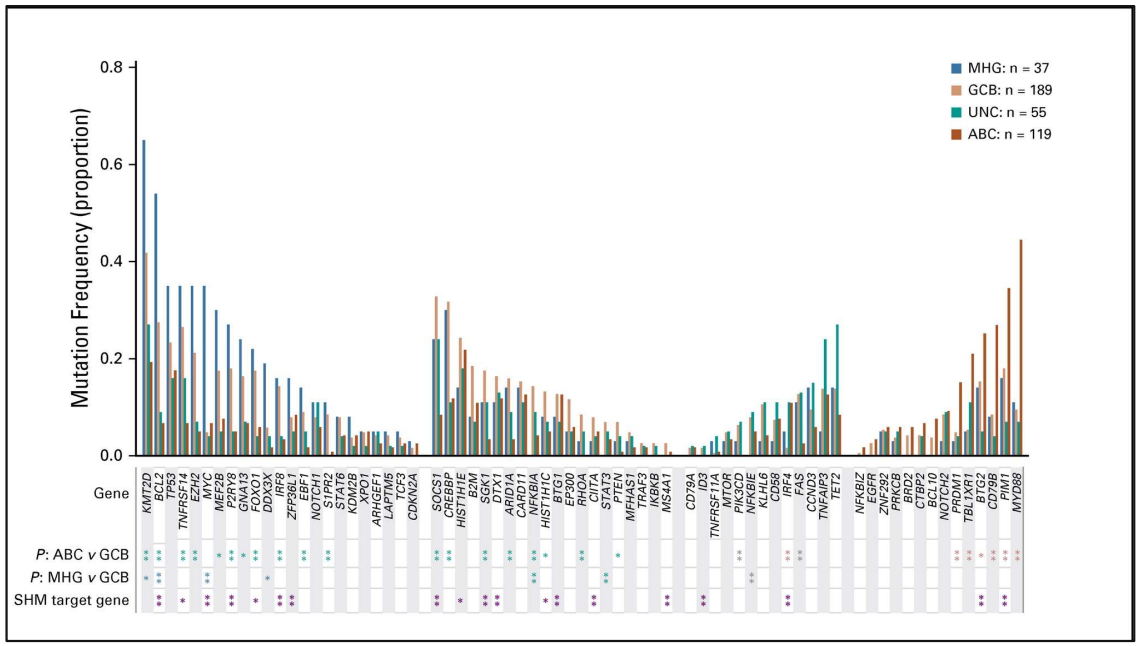
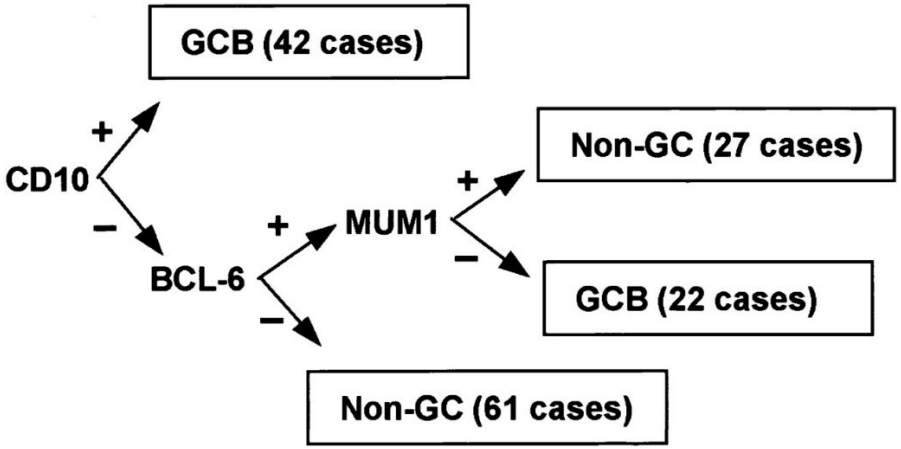






CELL OF ORIGIN - IHC

- Immunohistochemistry (IHC)
  - Hans algorithm – IHC based decision tree to classify GCB and non-GCB tumors
    - ~70% concordance with GEP
    - Does not recognize the 10-15% of tumors unclassified by GEP
    - Some indeterminate cases seen clinically

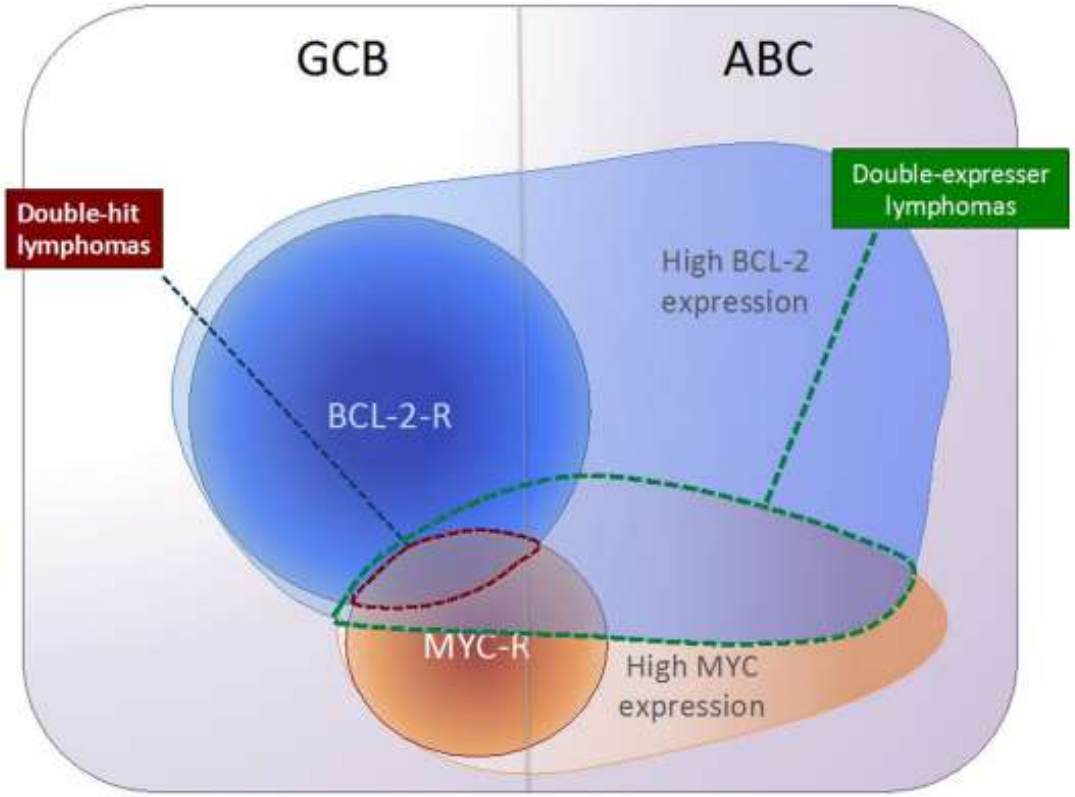


Blood 2004; 103(1):275-282

DLBCL: A HETEROGENEOUS DISEASE

GCB
favorable prognosis as compared to ABC.

Double HIT (MYC and BCL2 rearrangement by FISH)
Very poor prognosis. CNS involvement likely



ABC
poor prognosis as compared to GCB. CNS involvement could be more likely

Double Expresser (High MYC and BCL2 protein expression).
Poor prognosis

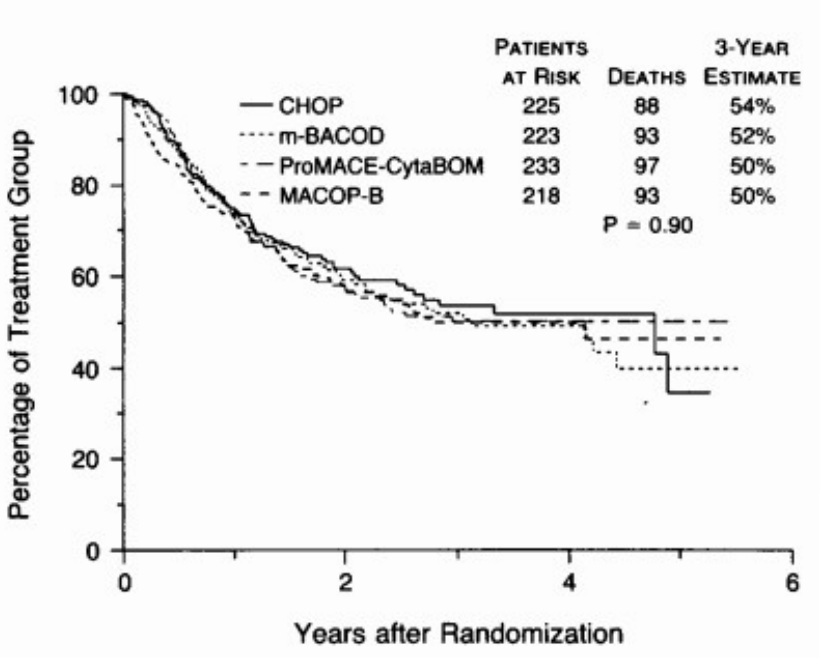
*Unclassified
Heterogenous population with intermediate prognosis

DIFFUSE LARGE B-CELL LYMPHOMA

Treatment

- Chemoimmunotherapy backbone
- Early Stage
- Advanced Stage

CHOP BACKBONE

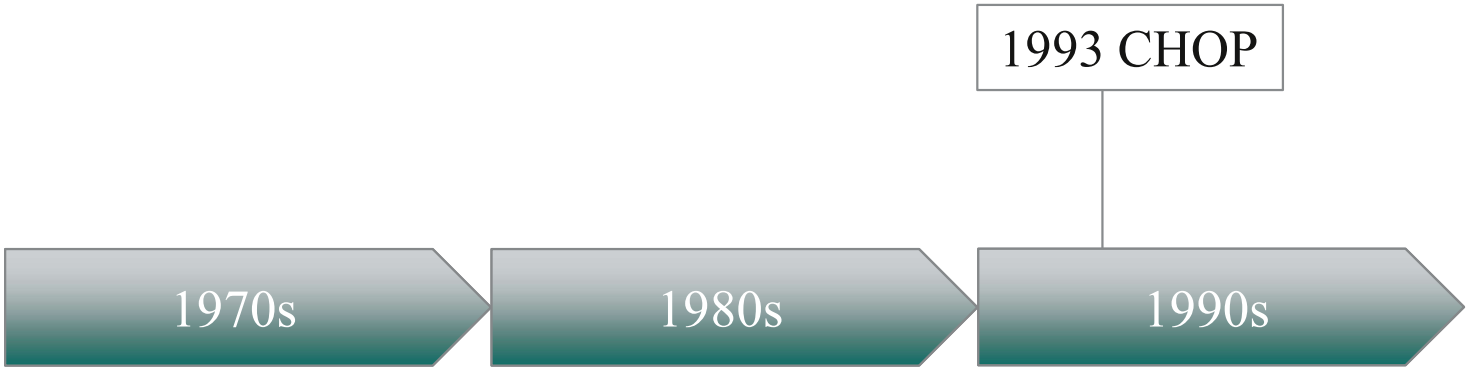


- Phase III, SWOG 8516 trial
- N=1138
- Overall survival
- CHOP best available tx

Toxicity	CHOP	m-BACOD	ProMACE-CytaBOM	MACOP-B
Death	1%	5%	3%	6%
G4	31%	54%	29%	43%

NEJM 1993;328:1002-1006

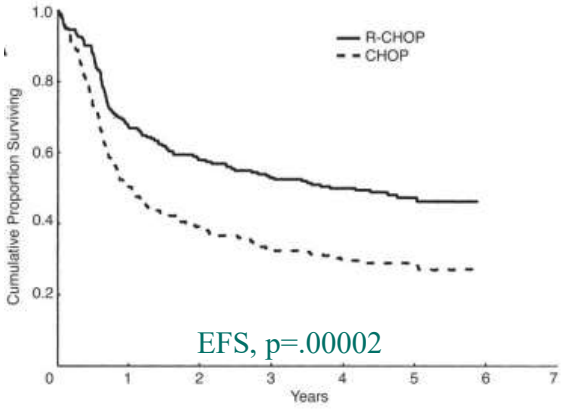
EVOLUTION OF DLBCL THERAPY

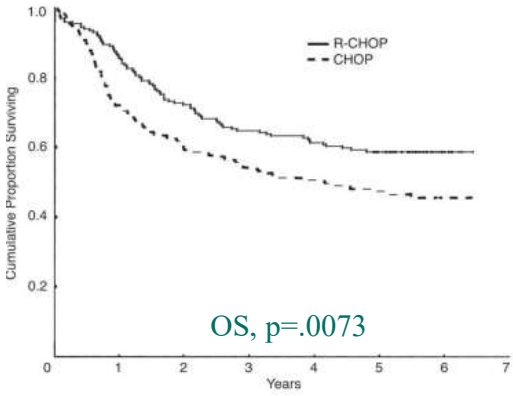


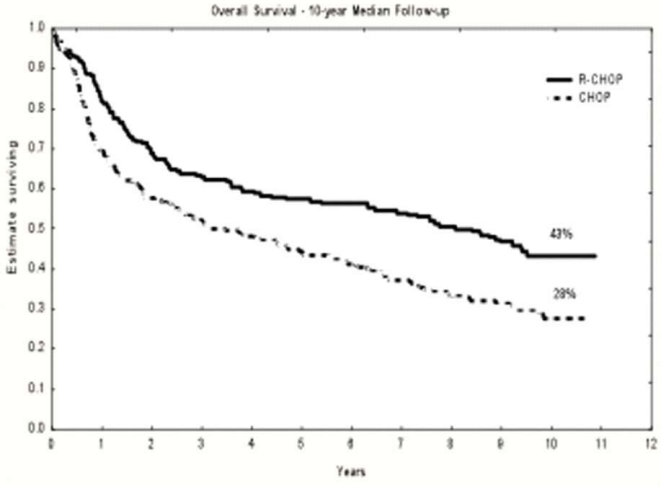
CHOP VS RCHOP

Groupe d'Etude des Lymphomes de l'Adulte	**GELA PHASE III TRIAL** • Elderly age 60-80 yrs. • Stage II-VI DLBCL • Stratified by aaIPI
MabThera International Trial	**MInT Trial** • Young, age 18-60 yrs. • Stage II-IV, or stage I-bulky • aaIPI 0-1
Eastern Cooperative Oncology Group Cancer and Leukemia Group B	**Intergroup study (ECOG4494/CALGB9793)** • Age >60 yrs. • Stage I-VI • Stratified by IPI

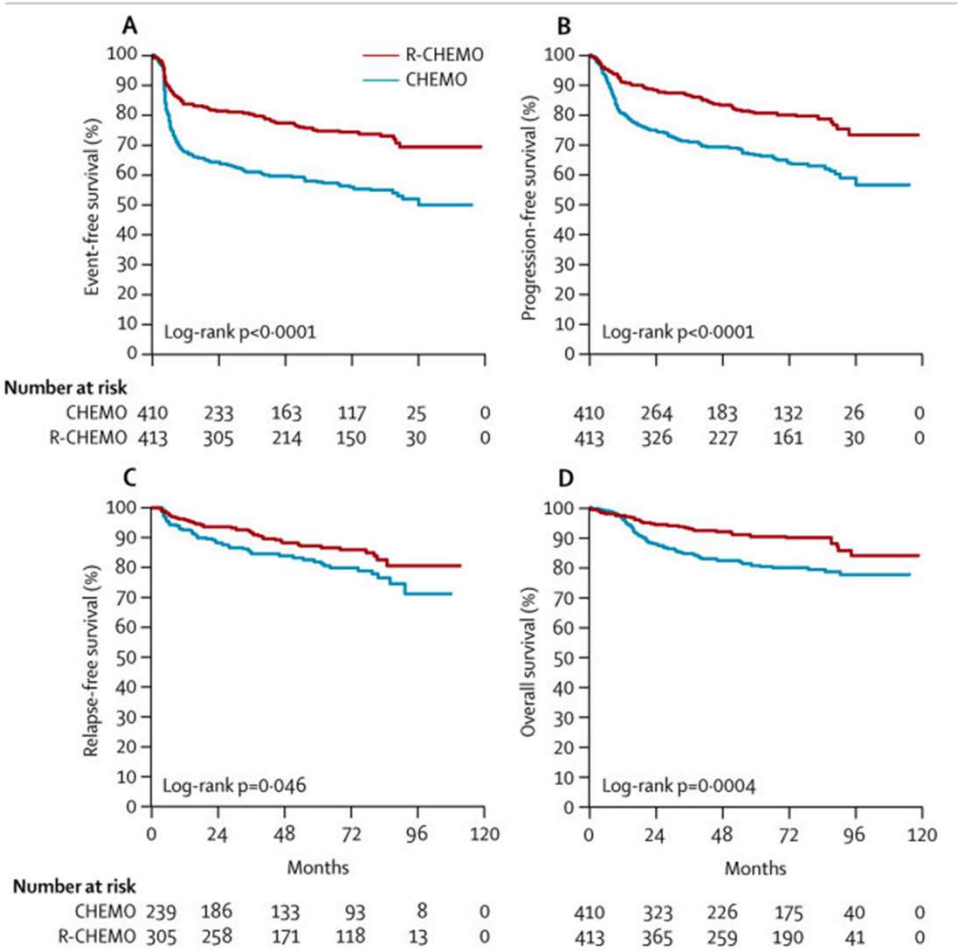
GELA TRIAL 5 & 10 YEAR FOLLOW-UP







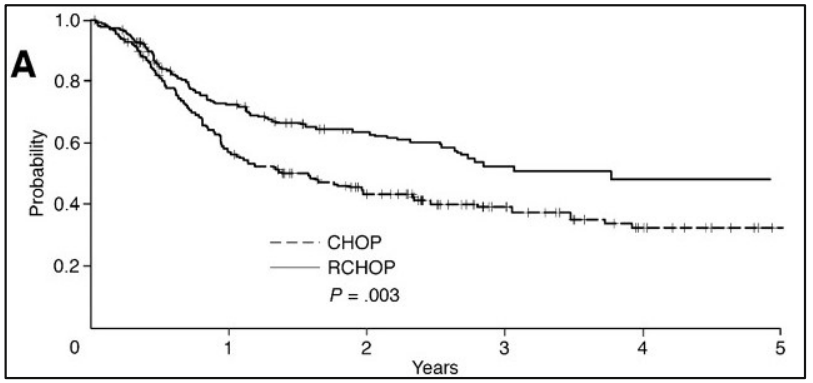
JCO 2005;23:4117-4126
Blood 2009;114:3741

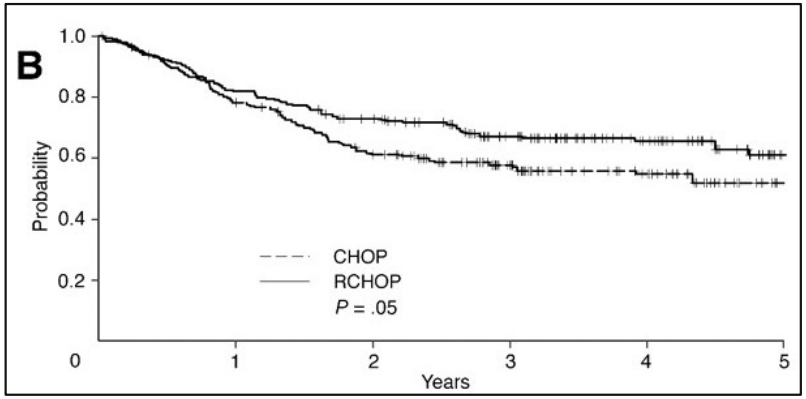


MINT TRIAL
6-YR FOLLOW UP

Lancet, 2011; 12(11): 1013-1022

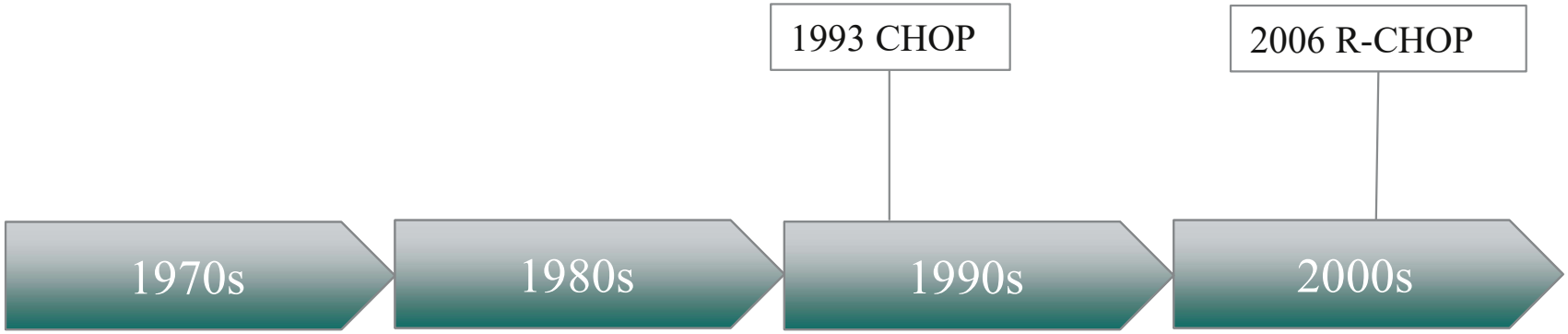
ECOG4494/ CALGB9793





JCO, 2006;24(19): 3121-3127

EVOLUTION OF DLBCL THERAPY



Chemoimmunotherapy backbone

Limited Stage

Advanced Stage

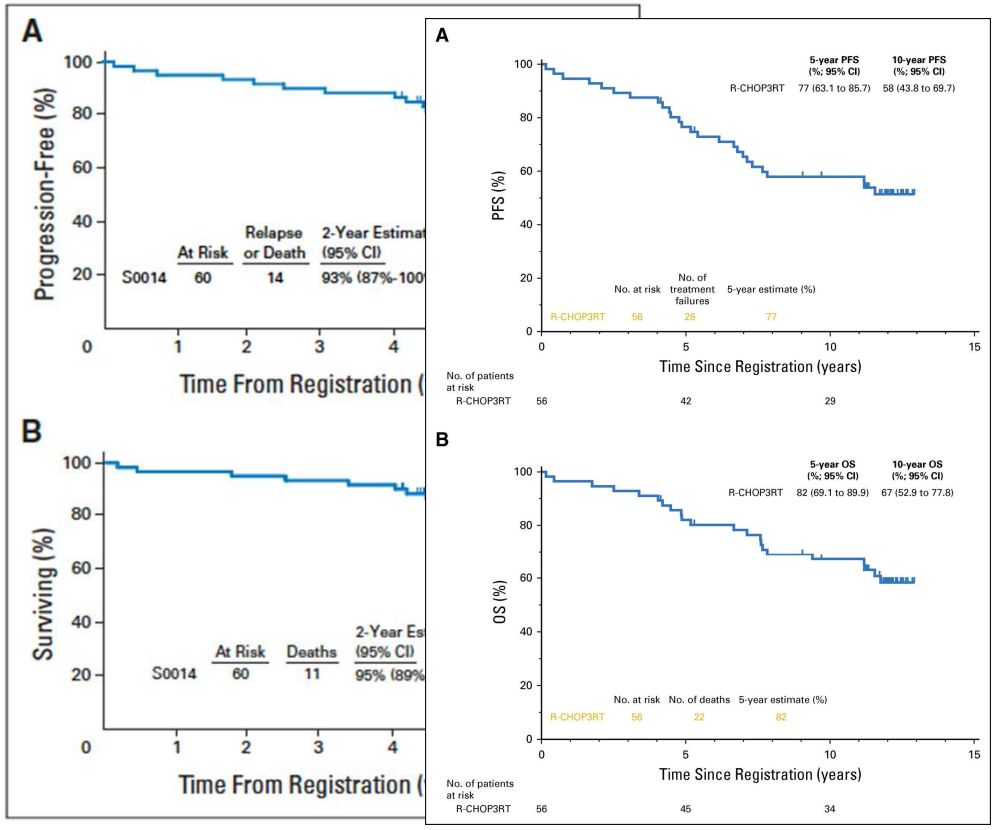
Treatment

LIMITED STAGE TREATMENT

Chemotherapy + RT	SWOG 8736 (pre-rituximab era) SWOG 0014
Chemotherapy alone	LYSA/GOELAMS 02-03 FLYER study
PET adaptive	NCTN S1001 BC Cancer study

- Limited stage (AA I-II)
  - No B-symptoms
  - Non-bulky
    - NCCN >7.5cm
    - Other >10cm
- Curative intent therapy

DLBCL: LIMITED STAGE – CHEMO + RT

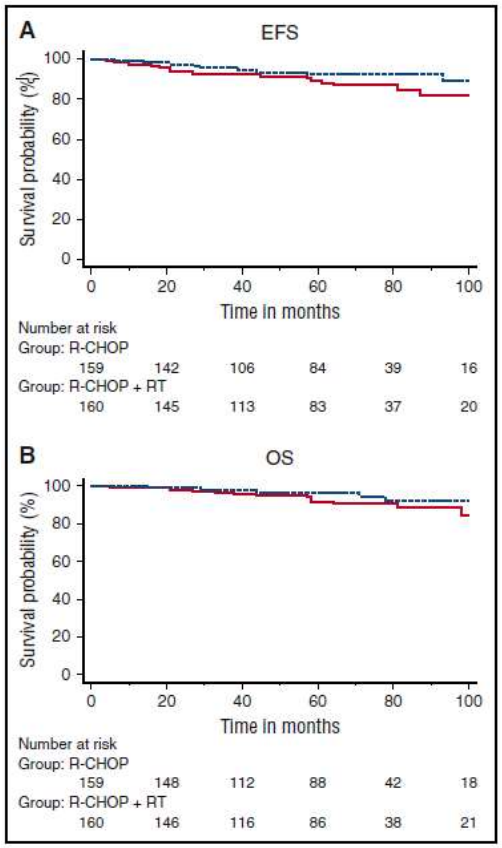


SWOG 0014 study

- Goal addition of ritux to SOC
- R-CHOP x 3 → IFRT (40-46Gy)
- Stage I-II (non-bulky, <10cm)
- One adverse RF (stage II, age >60, PS 2, LDH>ULN)
- Overall Survival
  - 4-yr 92%; 5-yr 82%; 10yr 67%
- Pattern – continuing relapse (even with rituximab)

JCO 2008;26:2258-2263
JCO 2016;34(25):2997-3004

DLBCL: LIMITED STAGE – CHEMO VS CHEMO-RT

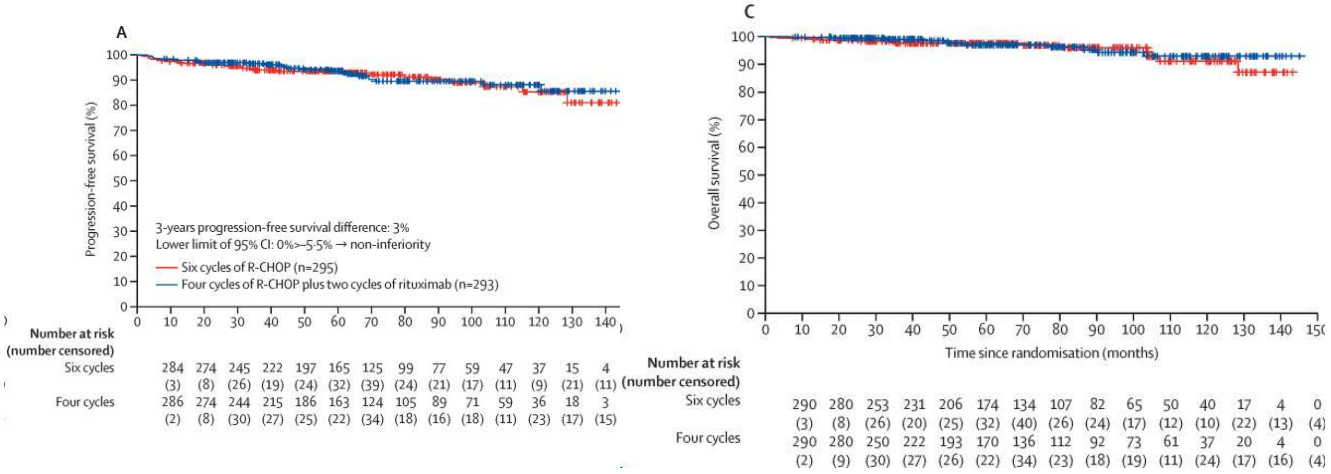


LYSA/GOELAMS 02-03

- Prospective, randomized study, N = 334
- Patient characteristics
  - Age 18-75
  - Stage I-II, non-bulky (max diameter <7cm)
- Treatment: R-CHOP14 x 4 or 6 vs R-CHOP14 x 4 or 6 + IFRT (40Gy)

Blood. 2018;131(2):174-181

DLBCL: LIMITED STAGE – CHEMO ONLY



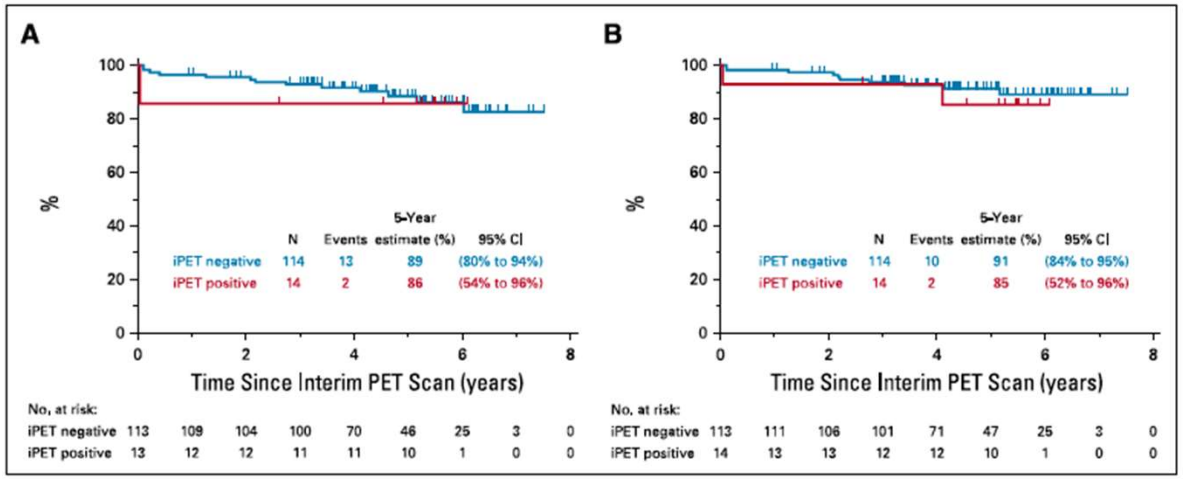
	3 year		5 year	
	R-CHOP4 + 2 ritux	R-CHOP6	R-CHOP4 + 2 ritux	R-CHOP6
CR	91%	92%		
PFS	96%	94%	94%	94%
OS	99%	98%	97%	98%

FLYER STUDY

- Two-arm, open-label , multicenter, prospective phase III study
- Performed in Europe 2005-2016
- Non-inferiority trial
- Patient characteristics
  - Age 18-60
  - Stage I-II, non-bulky (<7.5cm)
  - Normal LDH
  - ECOG 0-1
- Treatment: R-CHOP x 6 vs R-CHOP x 4 + Rituximab x 2
- N=592

Lancet 2019;394:2271-81

DLBCL: LIMITED STAGE – PET ADAPTED



5-yr	R-CHOP x 4	R-CHOP x 3 + RT and radioimmunotherapy
PFS	86%	89%
OS	85%	91%

S1011- PET adapted

- N=158 patients
- Stage I-II, nonbulky (<10cm)
- Patient characteristics
  - Age >18
  - PS 0-2
  - smIPI (Age>60, stage II, LDH>ULN, PS 2) >0 in 74%
- R-CHOP x 3 followed by PET
  - PET negative (DS 0-3) → R-CHOP x 1 additional cycle
  - PET positive → IFRT followed by ibritumomab tiuxetan radioimmunotherapy

JCO 2020;38(26):3003-3011

LIMITED STAGE DLBCL: TREATMENT

Optimal therapy – individualize to the patient

- Abbreviated chemotherapy in conjunction with radiation therapy has shown a pattern of continuing relapse.
- Tailor treatment to the patient and tolerance to chemoimmunotherapy +/- radiation

Treatment

Chemoimmunotherapy backbone

Early Stage

Advanced Stage

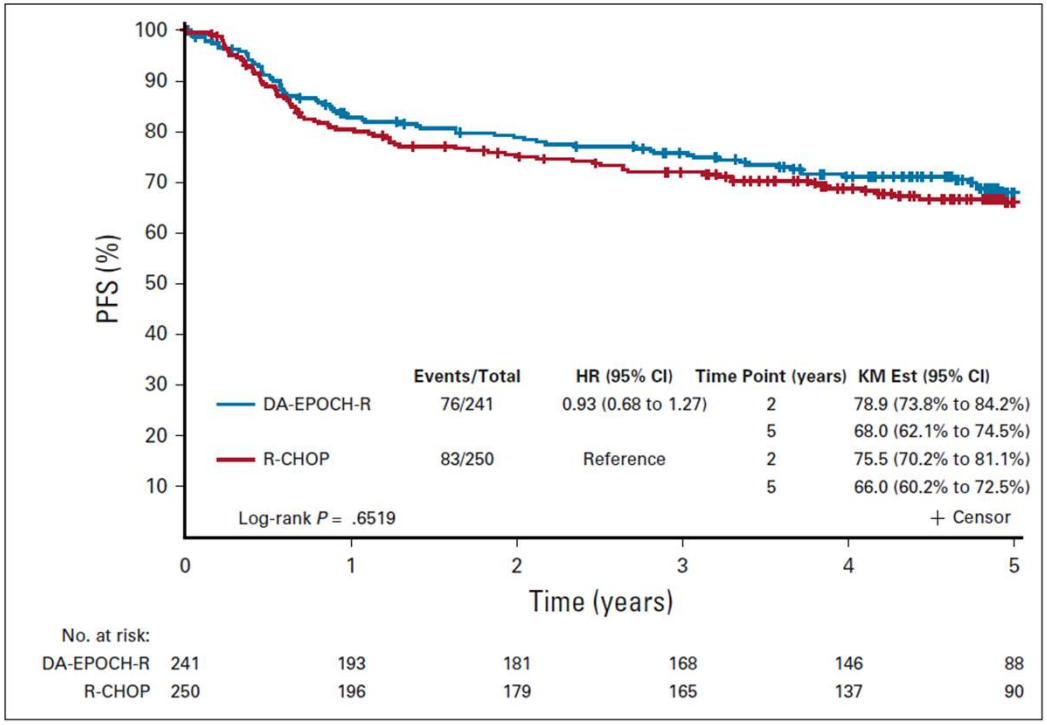
ADVANCED STAGE DLBCL

- Is there anything better than R-CHOP-21?
- Is R-CHOP the only option?

CAN WE BEAT R-CHOP-21?

- DA-EPOCH-R
- Next generation anti-CD20 mAB (i.e. obinutuzumab)
- Pola-R-CHP

IS DA-EPOCH-R BETTER?

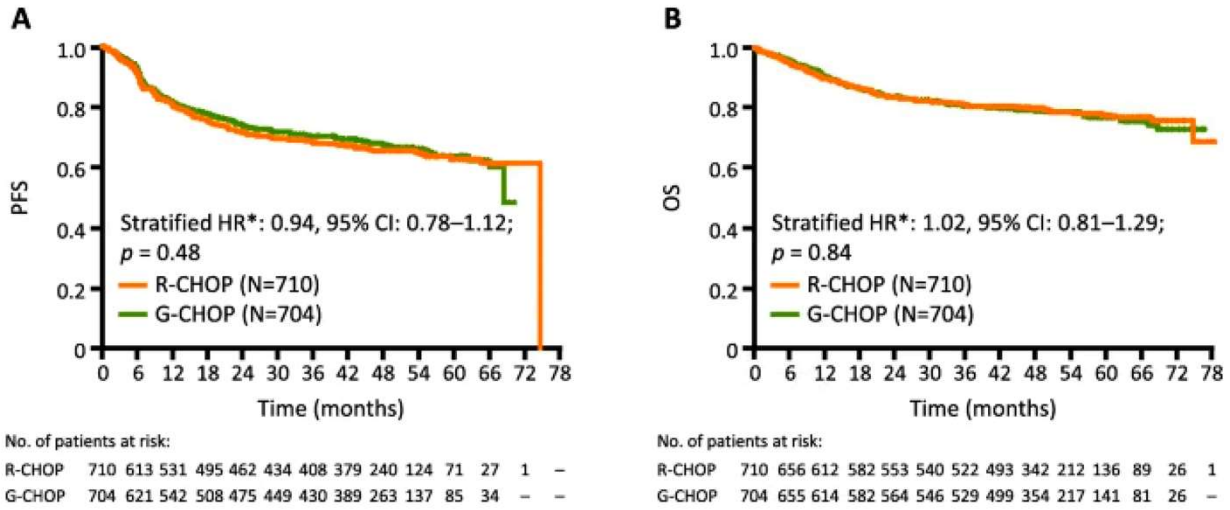


CALGB 50303: Phase III Randomized Study of R-CHOP vs DA-EPOCH-R with microarray in DLBCL

- No benefit DA-EPOCH-R over R-CHOP
- Increased toxicity with DA-EPOCH-R
- Will certain subgroups benefit?
  - MYC rearrangements N=13
    - 3 cases with BCL-2 or BCL-6
    - 10 incomplete data

JCO, 2019;37:1790-1799

RITUXIMAB VS OBINUTUZUMAB

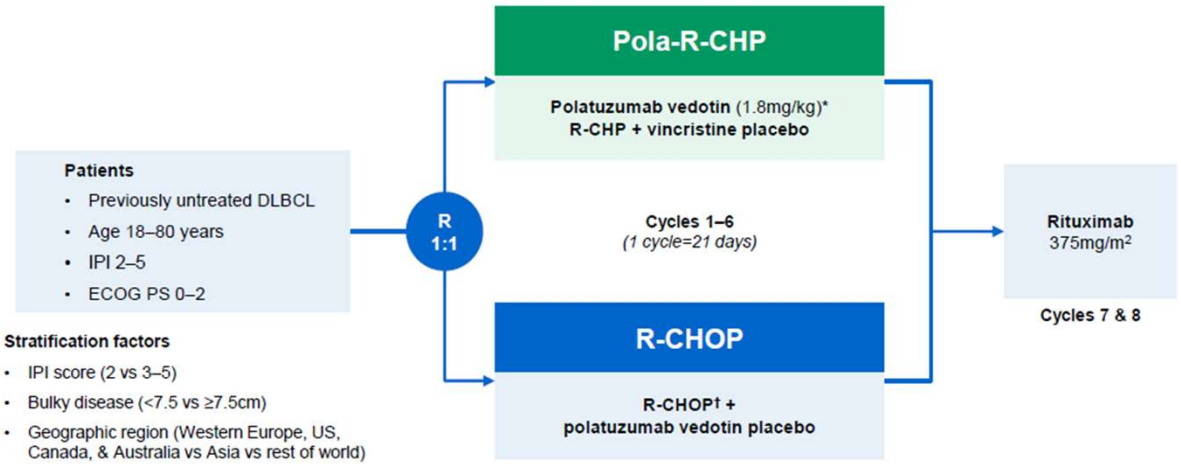


GOYA Phase III Study

- No difference R-CHOP vs G-CHOP

J Hematol Oncol, 2020; 13(1):71

R-CHOP VS POLA-R-CHP



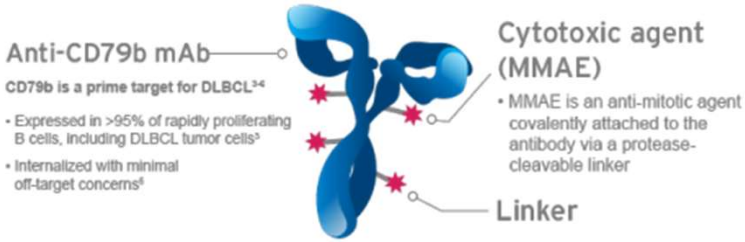
*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

POLARIX TRIAL

Randomized
Double blind
Phase III study

HervéTilly, et al.,Presented at ASH2021; No. LBA-1

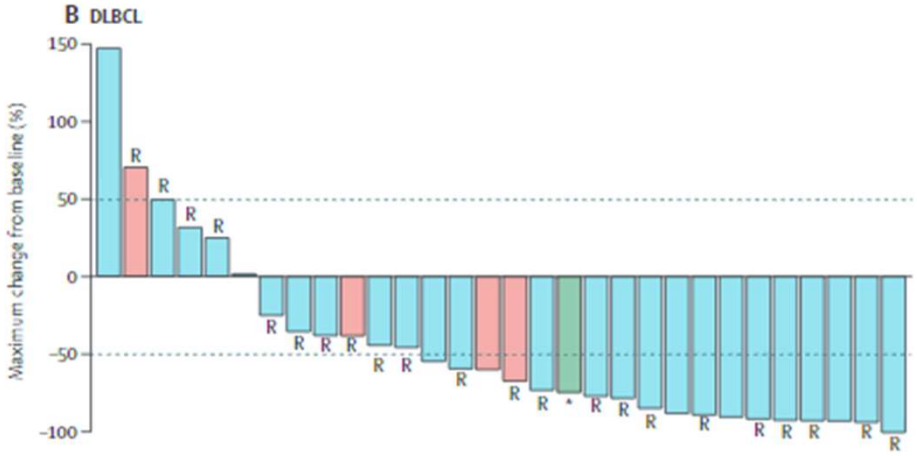
POLATUZUMAB VEDOTIN



- Antibody Drug Conjugate (ADC)
  - Humanized anti-CD79b monoclonal antibody
  - Conjugated with a monomethyl auristatin E (MMAE) payload
    - MMAE → Microtubule inhibitor
  - Phase 1 study
  - Dose >1.8 mg/m2

ORR	CR	mDOR
52%	13%	5.2 mo

  - Main AEs
    - Neutropenia (G3-4)
    - Peripheral neuropathy (G1-2)



Lancet Oncol 2015;16:704-15

Table 1. Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Pola-R-CHP (N = 440)	R-CHOP (N = 439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)
ECOG performance status score — no. (%)¶		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)‖		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)†**		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)††		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)††	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)††	26/331 (7.9)	19/334 (5.7)

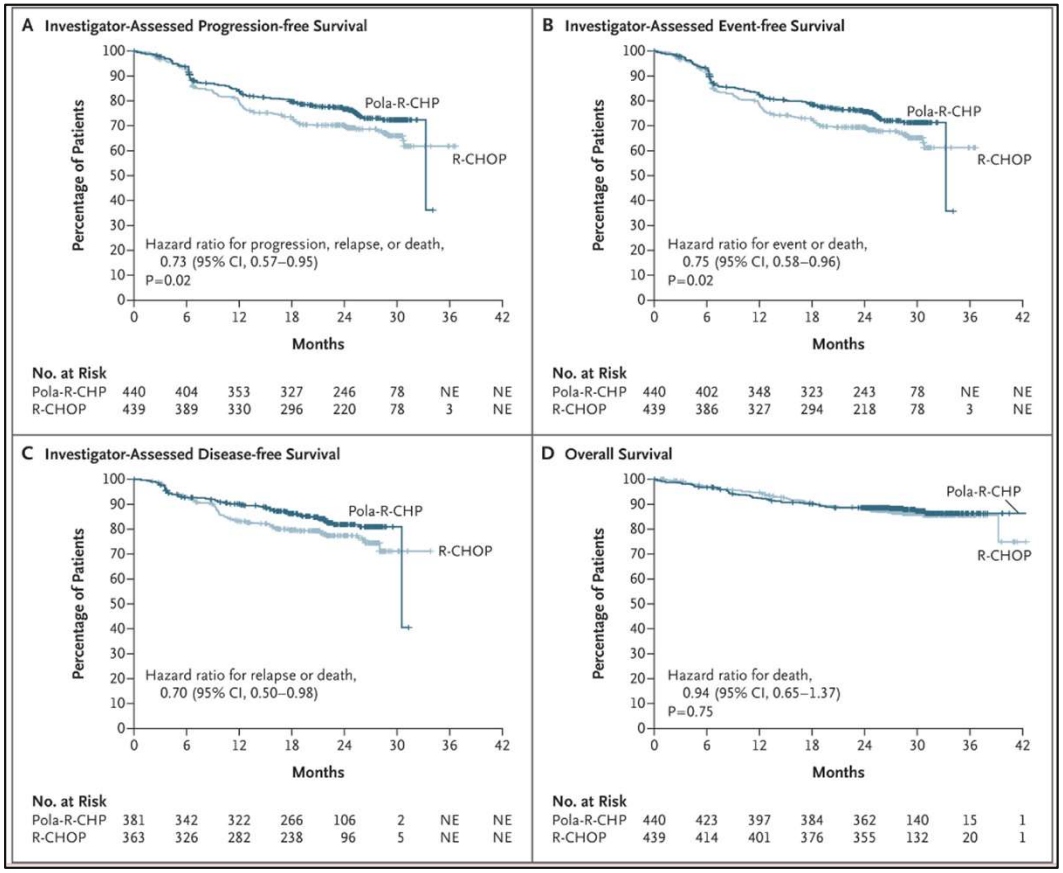
NEJM, 2022; 386: 351-363.

Table 2. Efficacy (Intention-to-Treat Population).

Variable	Pola-R-CHP (N=440)	R-CHOP (N=439)	Hazard Ratio (95% CI)	P Value
Progression-free survival*				
Patients who died or had progression or relapse — no. (%)	107 (24.3)	134 (30.5)	0.73 (0.57–0.95)	0.02
Earliest event — no.				
Death	19	20		
Progression or relapse	88	114		
Estimate at 1 year (95% CI) — %	83.9 (80.4–87.4)	79.8 (75.9–83.6)		
Estimate at 2 years (95% CI) — %	76.7 (72.7–80.8)	70.2 (65.8–74.6)		
Event-free survival*				
Patients who died, had progression or relapse, or had other events — no. (%)†	112 (25.5)	138 (31.4)	0.75 (0.58–0.96)	0.02
Earliest event — no.				
Death	18	20		
Progression or relapse	86	106		
Other†	8	12		
Estimate at 2 years (95% CI) — %	75.6 (71.5–79.7)	69.4 (65.0–73.8)		
Response status at treatment completion‡				
Overall response — no. (%)	376 (85.5)	368 (83.8)		
Complete response	343 (78.0)	325 (74.0)		
Partial response	33 (7.5)	43 (9.8)		
Stable disease — no. (%)	8 (1.8)	6 (1.4)		
Progressive disease — no. (%)	22 (5.0)	28 (6.4)		
Not evaluated or data missing — no. (%)	34 (7.7)	37 (8.4)		
Overall survival				
Patients who died — no. (%)	53 (12.0)	57 (13.0)	0.94 (0.65–1.37)	0.75
Estimate at 2 years (95% CI) — %	88.7 (85.7–91.6)	88.6 (85.6–91.6)		
Disease-free survival§				
No. of patients who could be evaluated¶	381	363		
Patients who died or had relapse — no. (%)	62 (16.3)	79 (21.8)	0.70 (0.50–0.98)	
Earliest event — no.				
Death	8	13		
Relapse	54	66		

NEJM, 2022; 386: 351-363.

POLARIX TRIAL

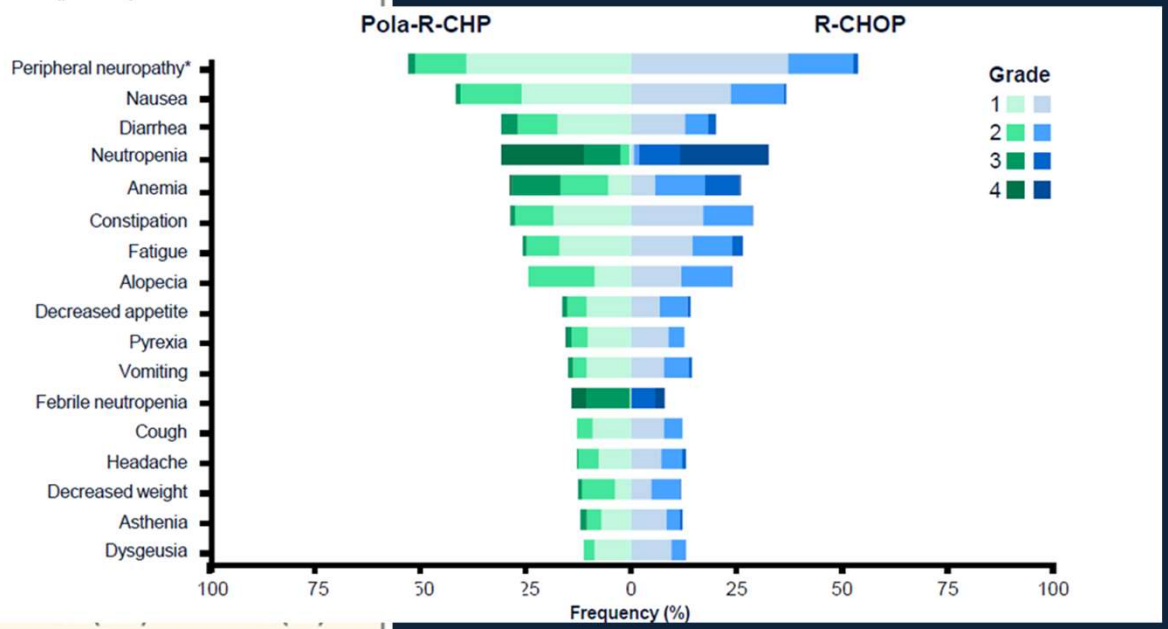


- Pola-R-CHOP demonstrated a 27% reduction in the relative risk of disease progression, relapse, or death when compared to R-CHOP.
- 2-yr PFS 76.7% vs 70.2%
- **FDA Approved Regimen in April 2023.**

NEJM, 2022; 386: 351-363.

Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)		
Nausea	181 (41.6)	5 (1.1)		
Neutropenia	134 (30.8)	123 (28.3		
Diarrhea	134 (30.8)	17 (3.9)		
Anemia	125 (28.7)	52 (12.0		
Constipation	125 (28.7)	5 (1.1)		
Fatigue	112 (25.7)	4 (0.9)		
Alopecia	106 (24.4)	0		
Decreased appetite	71 (16.3)	5 (1.1)		
Pyrexia	68 (15.6)	6 (1.4)		
Vomiting	65 (14.9)	5 (1.1)		
Febrile neutropenia	62 (14.3)	60 (13.8		
Headache	56 (12.9)	1 (0.2)		
Cough	56 (12.9)	0		
Decreased weight	55 (12.6)	4 (0.9)		
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

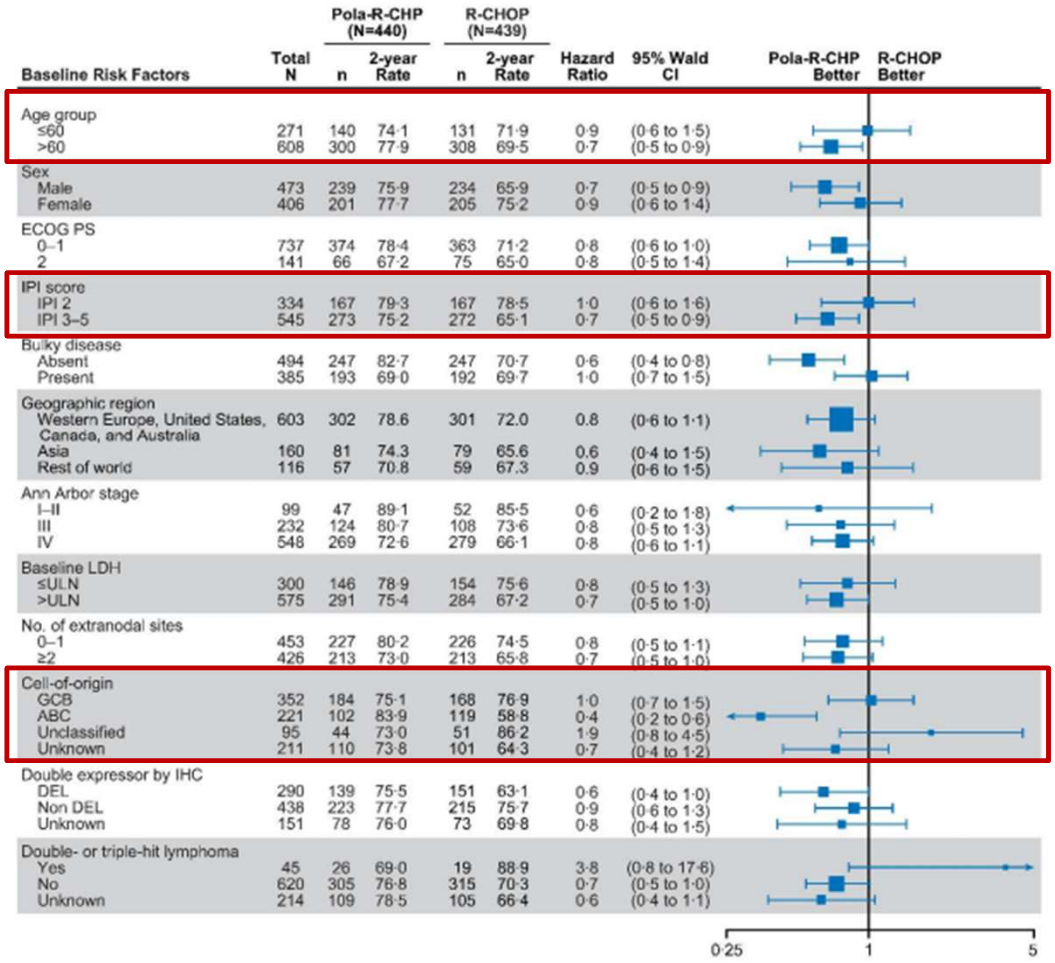


NEJM, 2022; 386: 351-363.

HervéTilly, et al. Presented at ASH2021; No. LBA-1

POLARIX TRIAL: SUBGROUP EXPLORATORY ANALYSIS

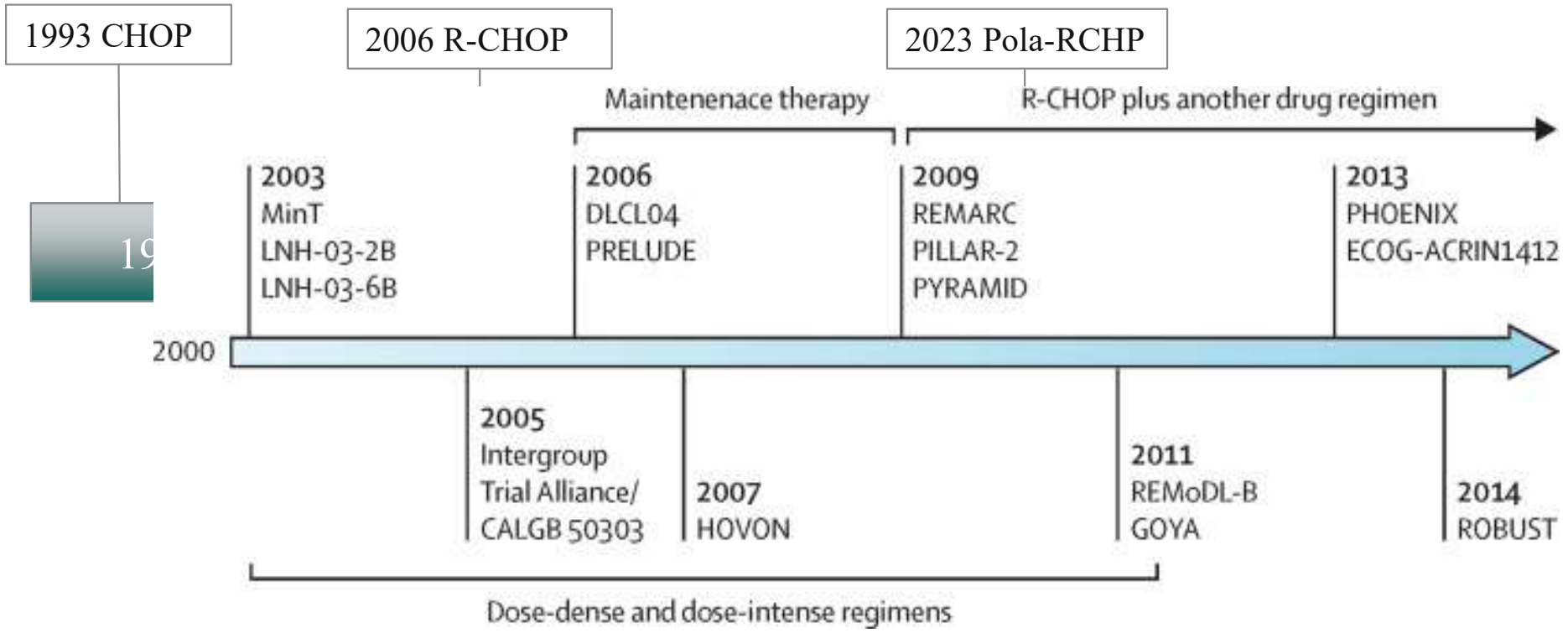
Figure S1. Subgroup Analysis of Investigator-assessed PFS (ITT Population).



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)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 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)

NEJM, 2022; 386: 351-363.

EVOLUTION OF DLBCL THERAPY



DLBCL – TAKE HOME POINTS

- DLBCL is a heterogeneous disease with at least 150 genetic drivers. Despite advancements in molecular profiling and trialing targeted agents, our mainstay of treatment is largely unchanged.
- Limited stage DLBCL:
  - Abbreviated chemotherapy in conjunction with radiation therapy has shown a pattern of continuing relapse.
  - Tailor treatment to the patient and tolerance to chemoimmunotherapy
- Advanced stage DLBCL:
  - Options available!


Incidence/Classification
Treatment
Future Directions

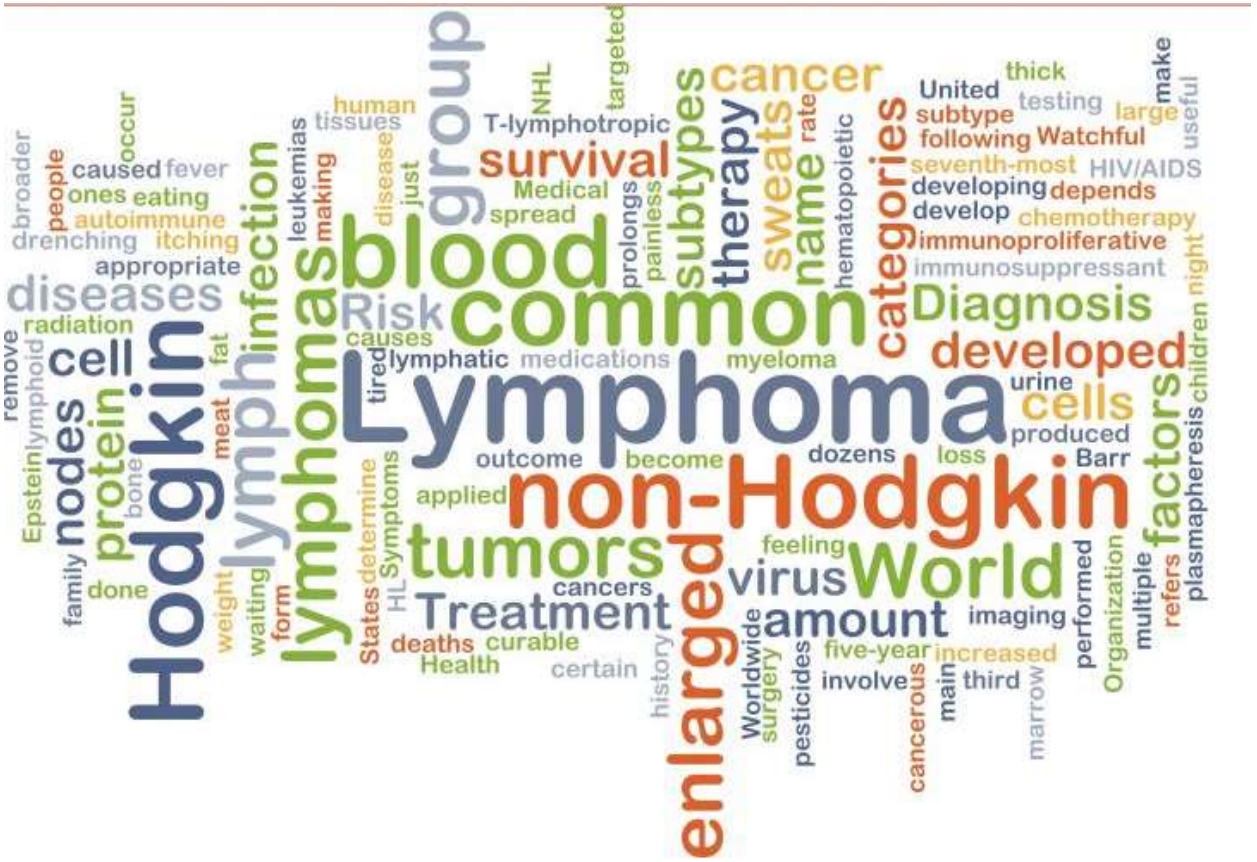
FUTURE DIRECTIONS

- Targeted approaches
  - BiTE therapy added to front line
    - COALITION STUDY: Glofitamab + R-CHOP vs Pola-R-CHP
  - CD19 Monoclonal Ab added to front line
    - FIRST MIND TRIAL: Tafasitamib + R-CHOP
- Elderly approaches
  - Split dose R-CHOP (MCW & UW Madison Clinical trial)
  - Unfit/Frail
    - Loncastuximab/Rituximab (LOTIS-9)
    - BiTE therapy with lenalidomide
    - BiTE therapy with polatuzumab and rituximab

MCW TRIALS

- Split dose R-CHOP (MCW & UW Madison Clinical trial)
  - Elderly, unfit/frail
- Loncastuximab with da-EPOCH-R
  - High-grade B-cell lymphoma with MYC and B-cell lymphoma 2 (BCL2) and/or B cell lymphoma 6 (BCL6) rearrangements
  - High-grade B-cell lymphoma, not otherwise specified
  - Primary mediastinal diffuse large B-cell lymphoma
  - Burkitt lymphoma
  - Diffuse large B-cell lymphoma with MYC rearrangement
  - Cluster of Differentiation 19 (CD19) -positive plasmablastic lymphoma.

QUESTIONS?


Lymphoma
Hodgkin
non-Hodgkin
blood
common
group
lymphoma
lymphomas
infection
enlarged
tumors
Treatment
virus
World
amount
cancer
survival
therapy
subtypes
sweats
name
categories
Diagnosis
developed
cells
factors
Risk
cell
nodes
protein
diseases
Hodgkin
T-lymphotropic
NHL
targeted
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leukemias
making
disease
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Medical
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prolongs
painless
hematopoietic
rate
United
subtype
following
Watchful
seventh-most
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immunoproliferative
immunosuppressant
thick
testing
large
make
useful
night
children
plasmapheresis
refers
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Organization
performed
marrow
cancerous
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third
involve
five-year
increased
imaging
Worldwide
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pesticides
history
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Health
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States
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Symptoms
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form
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Epstein
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radiation
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drenching
itching
appropriate