

Frontline DLBCL: Are We Done With R-CHOP?

R-CHOP Remains Standard

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Conflict of Interest

- **Consulting:** Novartis, ADC Therapeutics, AbbVie, Genmab, Natera, and Tanabe Pharma Corporation
- **Research support:** ADC Therapeutics, Genmab, BeOne, Genentech, and Natera

CHOP CHEMOTHERAPY PLUS RITUXIMAB COMPARED WITH CHOP ALONE IN ELDERLY PATIENTS WITH DIFFUSE LARGE-B-CELL LYMPHOMA

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ABSTRACT

Background The standard treatment for patients with diffuse large-B-cell lymphoma is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, has therapeutic activity in diffuse large-B-cell lymphoma. We conducted a randomized trial to compare CHOP chemotherapy plus rituximab with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

Methods Previously untreated patients with diffuse large-B-cell lymphoma, 60 to 80 years old, were randomly assigned to receive either eight cycles of CHOP every three weeks (197 patients) or eight cycles of CHOP plus rituximab given on day 1 of each cycle (202 patients).

Results The rate of complete response was significantly higher in the group that received CHOP plus rituximab than in the group that received CHOP alone (76 percent vs. 63 percent, $P=0.005$). With a median follow-up of two years, event-free and overall survival times were significantly higher in the CHOP-plus-rituximab group ($P<0.001$ and $P=0.007$, respectively). The addition of rituximab to standard CHOP chemotherapy significantly reduced the risk of treatment failure and death (risk ratios, 0.58 [95 percent confidence interval, 0.44 to 0.77] and 0.64 [0.45 to 0.89], respectively). Clinically relevant toxicity was not significantly greater with CHOP plus rituximab.

Conclusions The addition of rituximab to the CHOP regimen increases the complete-response rate and prolongs event-free and overall survival in elderly patients with diffuse large-B-cell lymphoma, without a clinically significant increase in toxicity. (N Engl J Med 2002;346:235-42.)

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THE most frequent type of non-Hodgkin's lymphoma, diffuse large-B-cell lymphoma, accounts for approximately 40 percent of new cases of lymphoma.¹ More than half of patients with diffuse large-B-cell lymphoma are over 60 years of age,²⁻⁴ and the treatment of these elderly patients is a difficult challenge. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard of care for younger and elderly patients with diffuse large-B-cell lymphoma,⁵ but it induces complete responses in only 40 to 50 percent of elderly patients, with three-year

event-free and overall survival rates of 30 percent and 35 to 40 percent, respectively.⁶ Attempts to increase the efficacy of CHOP by adding other cytotoxic drugs have not succeeded, probably because these additional drugs cannot be administered unless the doses of cyclophosphamide and doxorubicin are reduced below those given in the CHOP regimen.^{6,7} Intensified chemotherapy regimens may improve the outcome in young patients with a poor prognosis,⁸ but they are not well tolerated by elderly patients. Indeed, CHOP itself may be too toxic for elderly patients.^{9,10} More easily tolerated regimens have been designed for elderly patients, but although they cause fewer side effects, they are less effective and no more beneficial than CHOP.^{6,11}

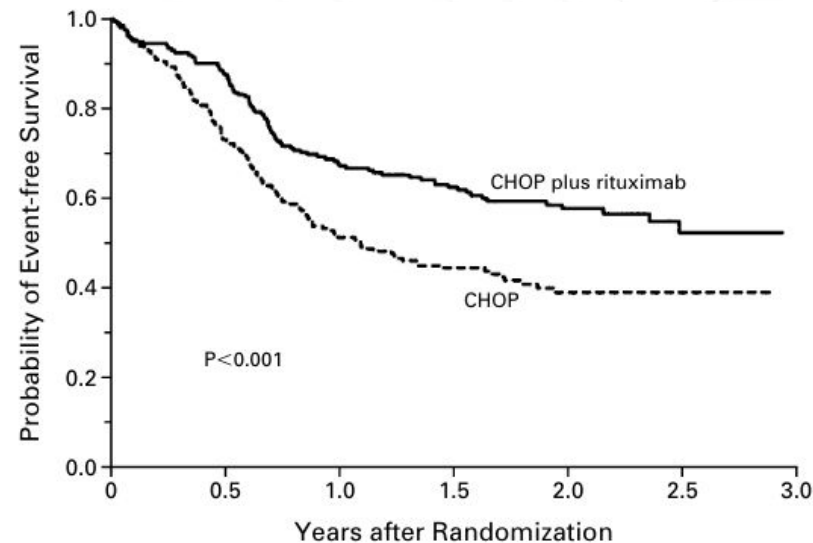
Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and has activity in relapsed or refractory diffuse large-B-cell lymphoma.¹²⁻¹⁵ CD20 is a cell-surface protein that occurs almost exclusively on mature B cells. The chimeric antibody is a human IgG1 in which the CD20-binding region was derived by genetic engineering from a mouse monoclonal antibody. On the basis of phase 2 studies in which rituximab in combination with CHOP had a good safety profile and induced responses in over 90 percent of patients with indolent or aggressive lymphoma,^{16,17} the Groupe d'Etude des Lymphomes de l'Adulte (GELA) undertook a study to compare CHOP plus rituximab with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

METHODS

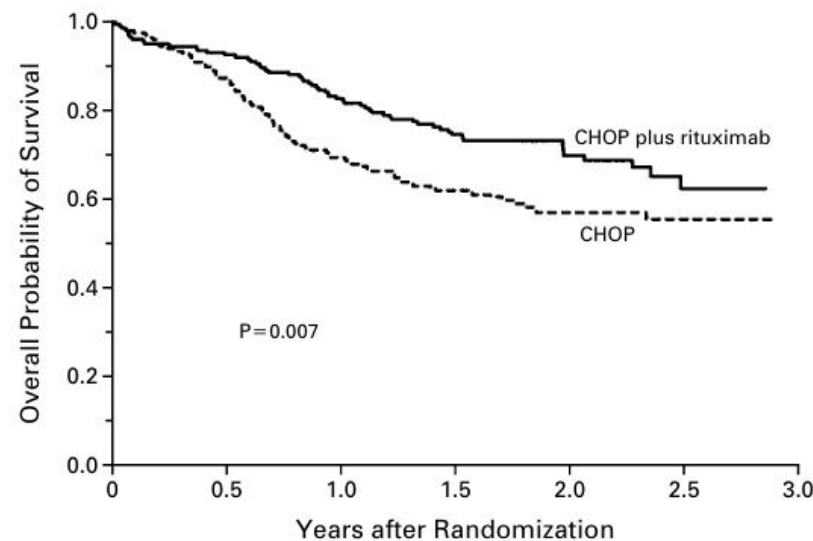
Patients

Patients were eligible if they were 60 to 80 years of age and had untreated diffuse large-B-cell lymphoma that had been diagnosed according to the Revised European-American Lymphoma clas-

From the Hospices Civils de Lyon and the Université Claude Bernard, Lyons (B.C., G.S.); Hôpital Henri-Mondor, Paris (E.L., P.G., F.R.); Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, Paris (J.B., C.G.); Hôpital de Hautepierre, Strasbourg (R.H.); the Centre Beccarel, Rouen (H.T.); the Institut Paoli-Calmette, Marseille (R.B.); and the Centre Hospitalier de Lens (P.M.) — all in France; and the Université Catholique de Louvain, Brussels, Belgium (E.N.). Address reprint requests to Dr. Coiffier at the Service d'Hématologie, Centre Hospitalier Lyon-Sud, 69495 Pierre Bénite CEDEX, France, or at bertrand.coiffier@chu-lyon.fr. Pierre Lederlin, Ph.D., Centre Hospitalier Universitaire de Brabois, Nancy, France, was also an author.



No. AT RISK						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17



No. AT RISK						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

What are we trying to beat?

60–65%

Cure rate

24 yrs

as frontline
standard-of-care

100+

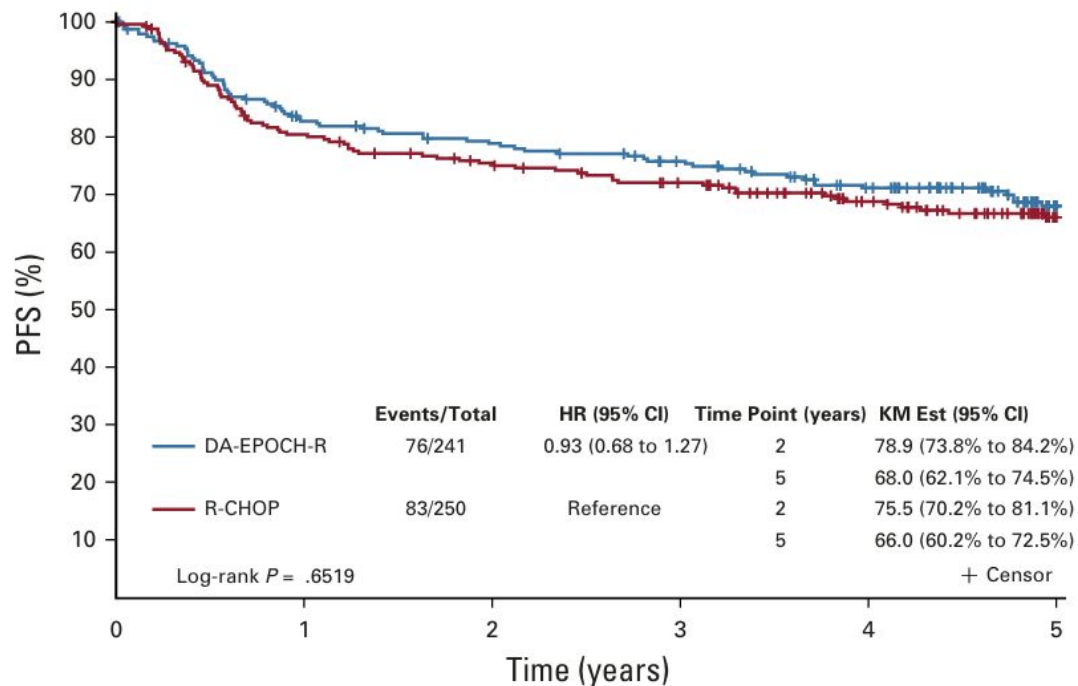
countries where it is
accessible & generic

6

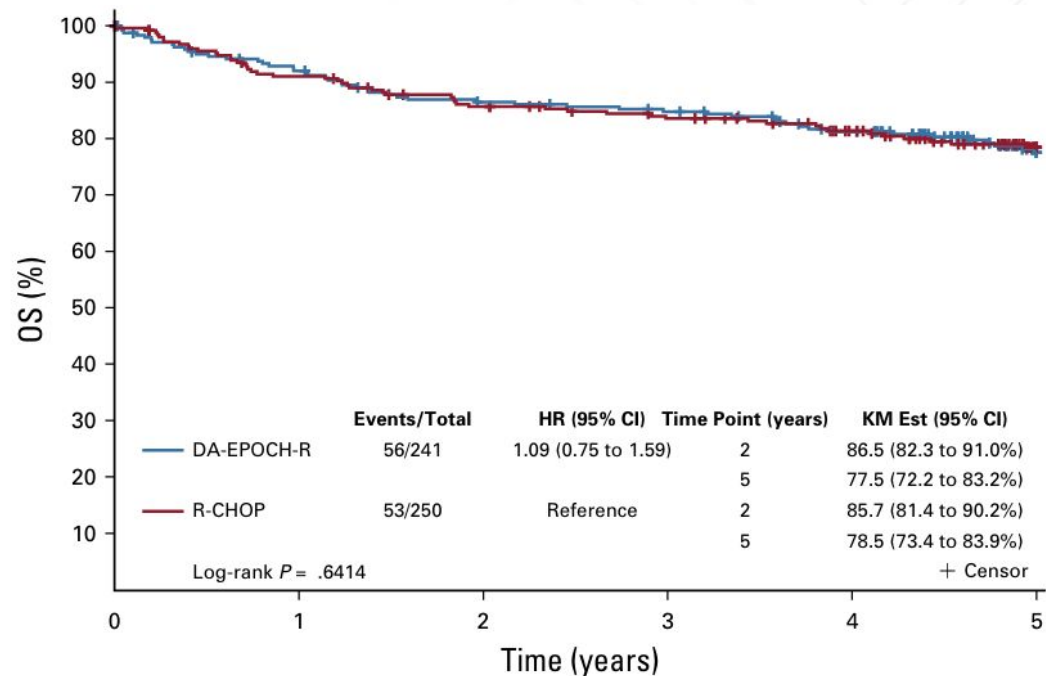
cycles — simple,
well-characterized
toxicity



Alliance/CALGB 50303: DA-EPOCH-R vs R-CHOP



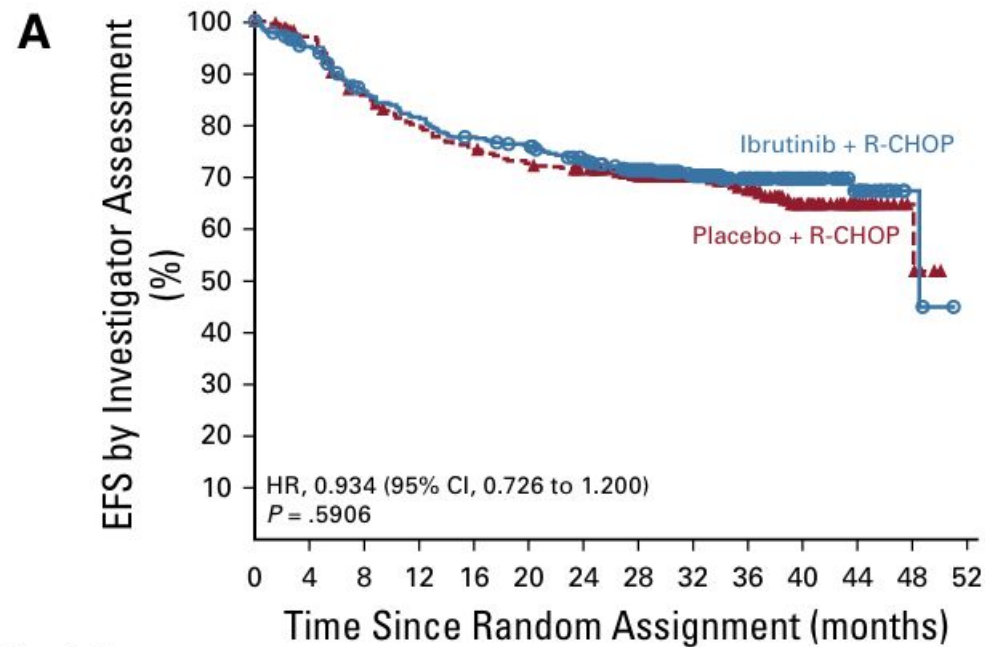
No. at risk:						
DA-EPOCH-R	241	193	181	168	146	88
R-CHOP	250	196	179	165	137	90



No. at risk:						
DA-EPOCH-R	241	218	202	196	181	128
R-CHOP	250	223	206	195	179	131

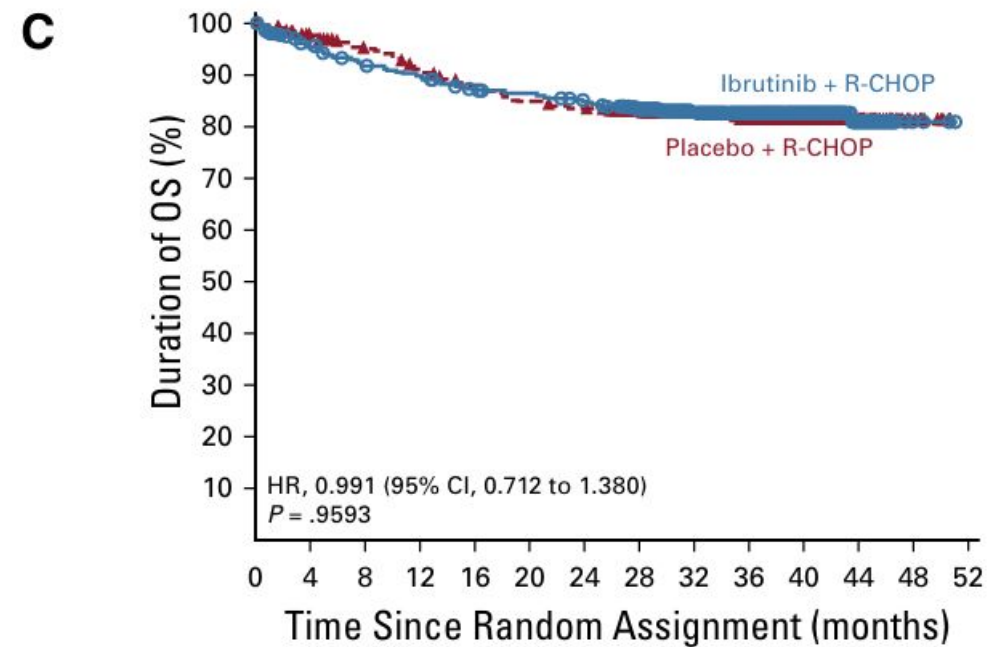
CTCAE Toxicity Grade	Treatment		Total (n = 480)*	P†
	R-CHOP (n = 243)*	DA-EPOCH-R (n = 237)*		
3/4/5 AE				<.001
No	53 (21.8)	4 (1.7)	57 (11.9)	
Yes	190 (78.2)	233 (98.3)	423 (88.1)	
3/4 Hematologic				<.001
No	64 (26.3)	6 (2.5)	70 (14.6)	
Yes	179 (73.7)	231 (97.5)	410 (85.4)	
3/4 Nonhematologic				<.001
No	138 (56.8)	66 (27.8)	204 (42.5)	
Yes	105 (43.2)	171 (72.2)	276 (57.5)	
3/4 Infection				.0494
No	217 (89.3)	197 (83.1)	414 (86.3)	
Yes	26 (10.7)	40 (16.9)	66 (13.8)	
3/4 Febrile neutropenia				<.001
No	200 (82.3)	154 (65.0)	354 (73.8)	
Yes	43 (17.7)	83 (35.0)	126 (26.3)	
3/4 Mucositis				.0017
No	238 (97.9)	217 (91.6)	455 (94.8)	
Yes	5 (2.1)	20 (8.4)	25 (5.2)	
1/2 Neuropathy				<.001
No	128 (52.7)	82 (34.6)	210 (43.8)	
Yes	115 (47.3)	155 (65.4)	270 (56.3)	
3/4 Neuropathy				<.001
No	235 (96.7)	193 (81.4)	428 (89.2)	
Yes	8 (3.3)	44 (18.6)	52 (10.8)	

Phoenix trial. Ibrutinib with R-CHOP



No. at risk:

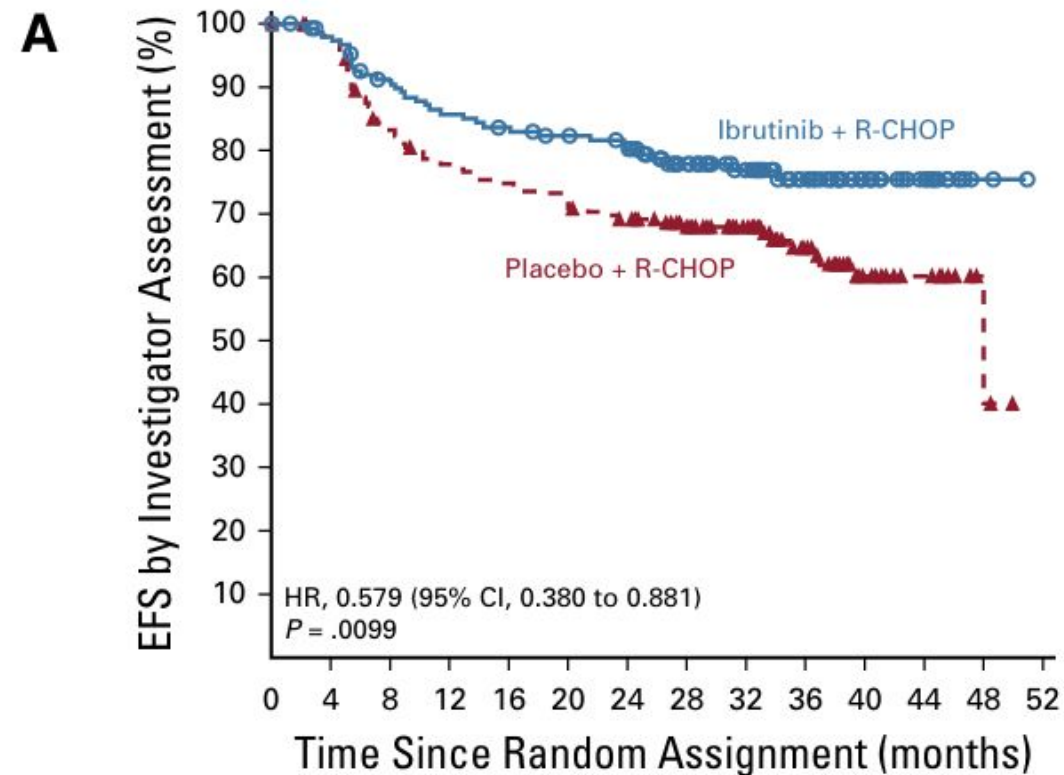
Ibrutinib + R-CHOP	419	374	336	316	300	291	276	233	179	120	63	25	3	0
Placebo + R-CHOP	419	390	341	316	297	286	277	244	184	118	60	33	5	0



No. at risk:

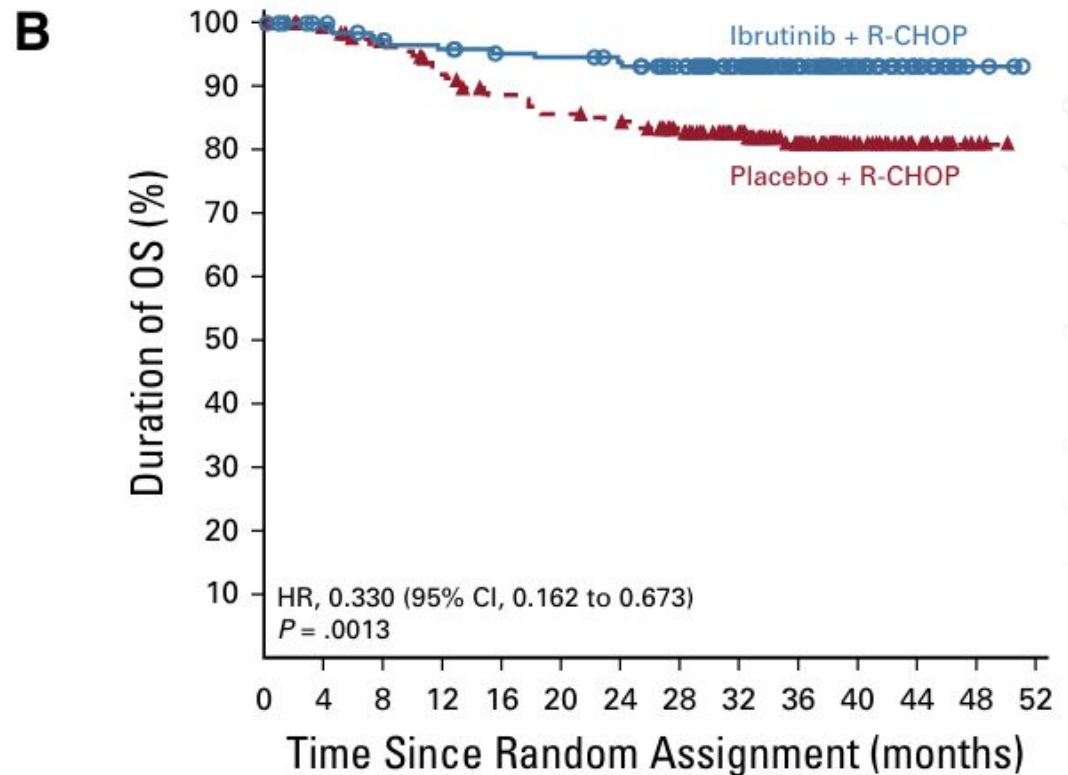
Ibrutinib + R-CHOP	419	384	365	356	342	337	328	309	236	159	100	38	4	0
Placebo + R-CHOP	419	400	382	363	347	335	329	301	237	157	99	51	12	0

Patients younger than 60 years



No. at risk:

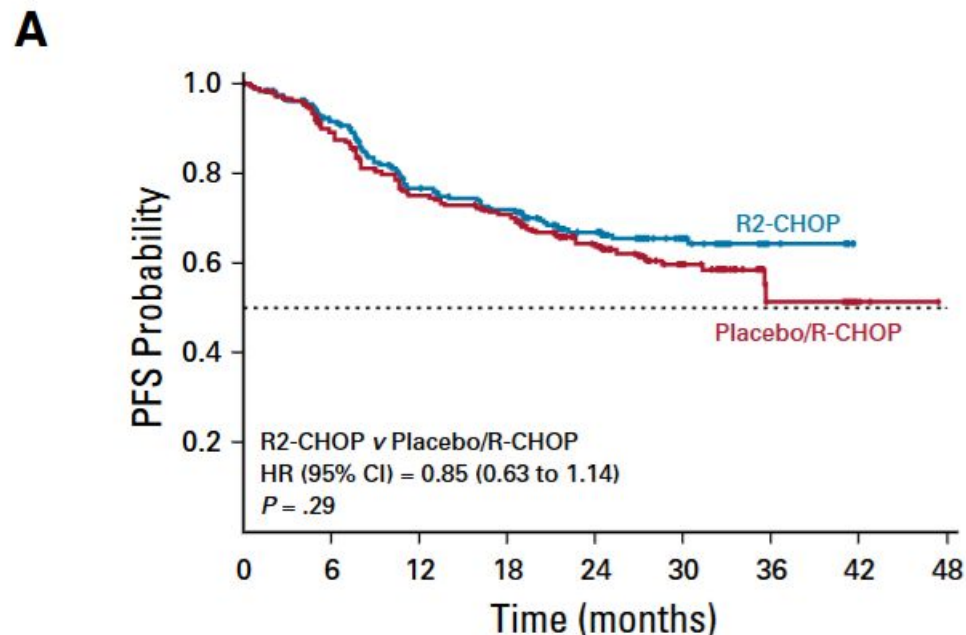
Ibrutinib + R-CHOP	156	146	133	125	121	117	113	93	72	44	27	13	2	0
Placebo + R-CHOP	186	177	148	137	132	127	120	104	78	52	24	16	3	0



No. at risk:

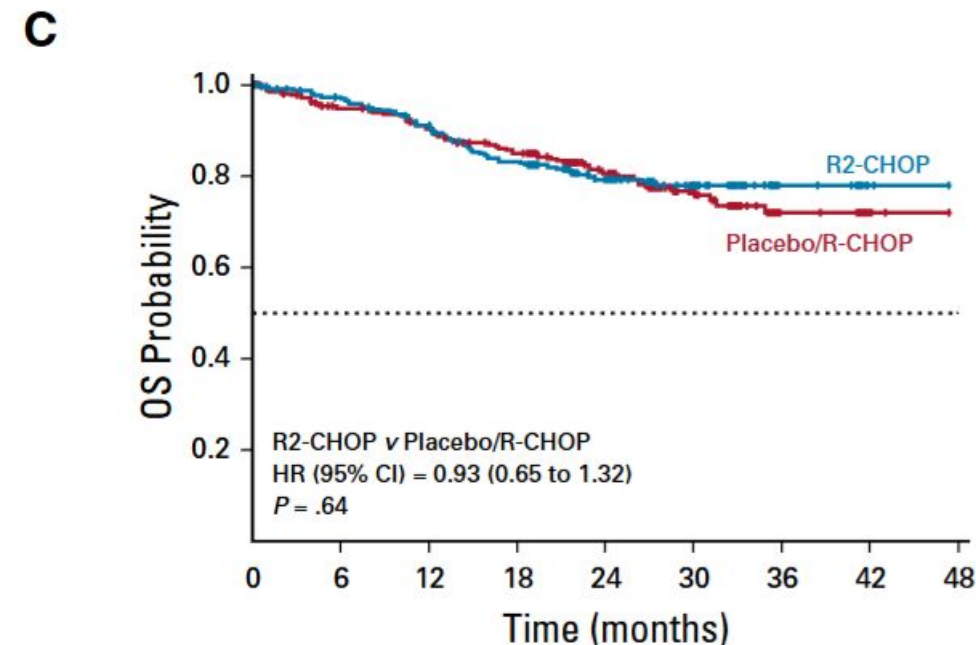
Ibrutinib + R-CHOP	156	151	145	142	138	137	134	125	96	62	39	18	3	0
Placebo + R-CHOP	186	181	173	161	153	148	145	130	101	70	38	21	5	0

ROBUST. Lenalidomide with R-CHOP



No. at risk:

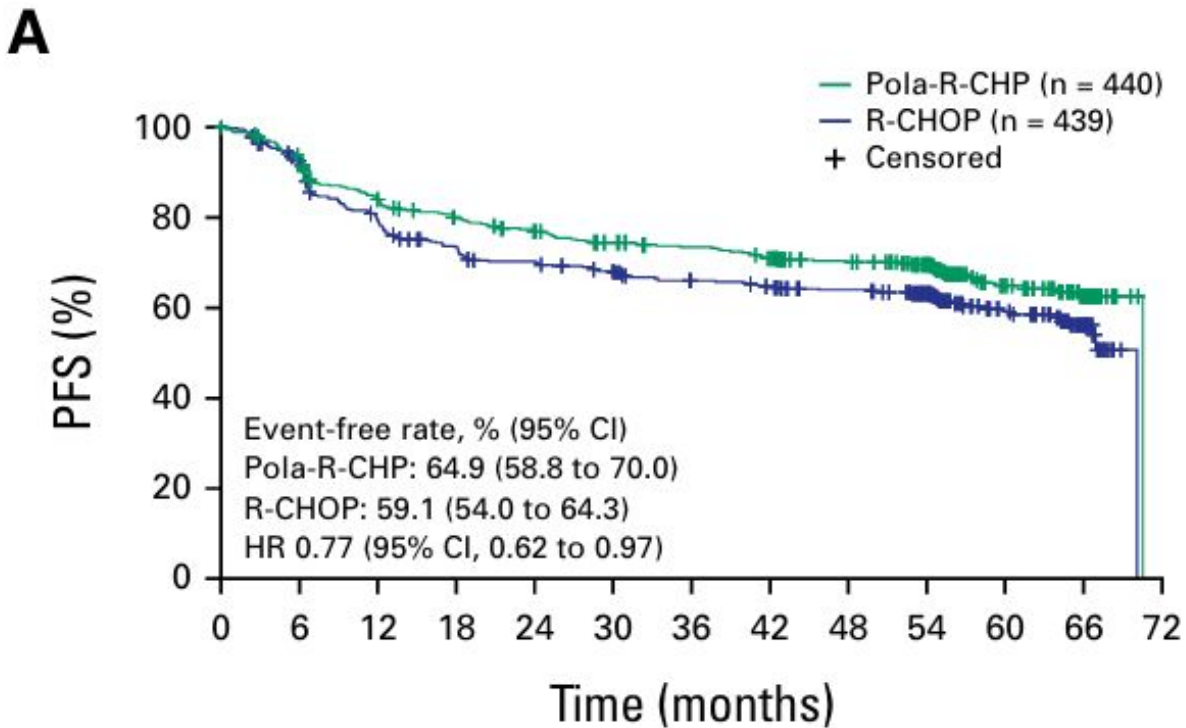
R2-CHOP	285	221	178	162	119	57	10	0
Placebo/R-CHOP	285	229	187	173	111	55	10	3



No. at risk:

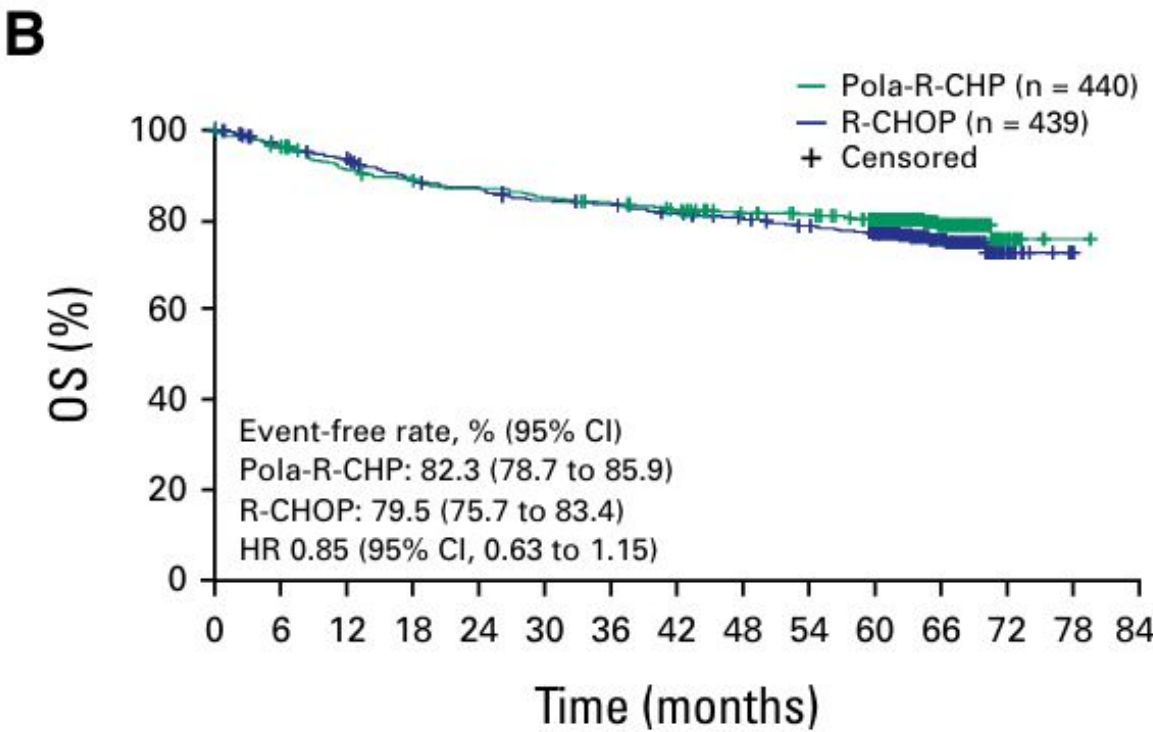
R2-CHOP	285	269	248	224	165	83	18	2	0
Placebo/R-CHOP	285	260	245	226	162	77	15	3	0

POLARIX. Polatuzumab vedotin with R-CHP



Number at risk

Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE



Number at risk

Pola-R-CHP	440	424	399	389	381	373	366	355	343	338	319	124	12	1	NE
R-CHOP	439	415	403	382	372	361	357	347	338	329	311	128	13	1	NE

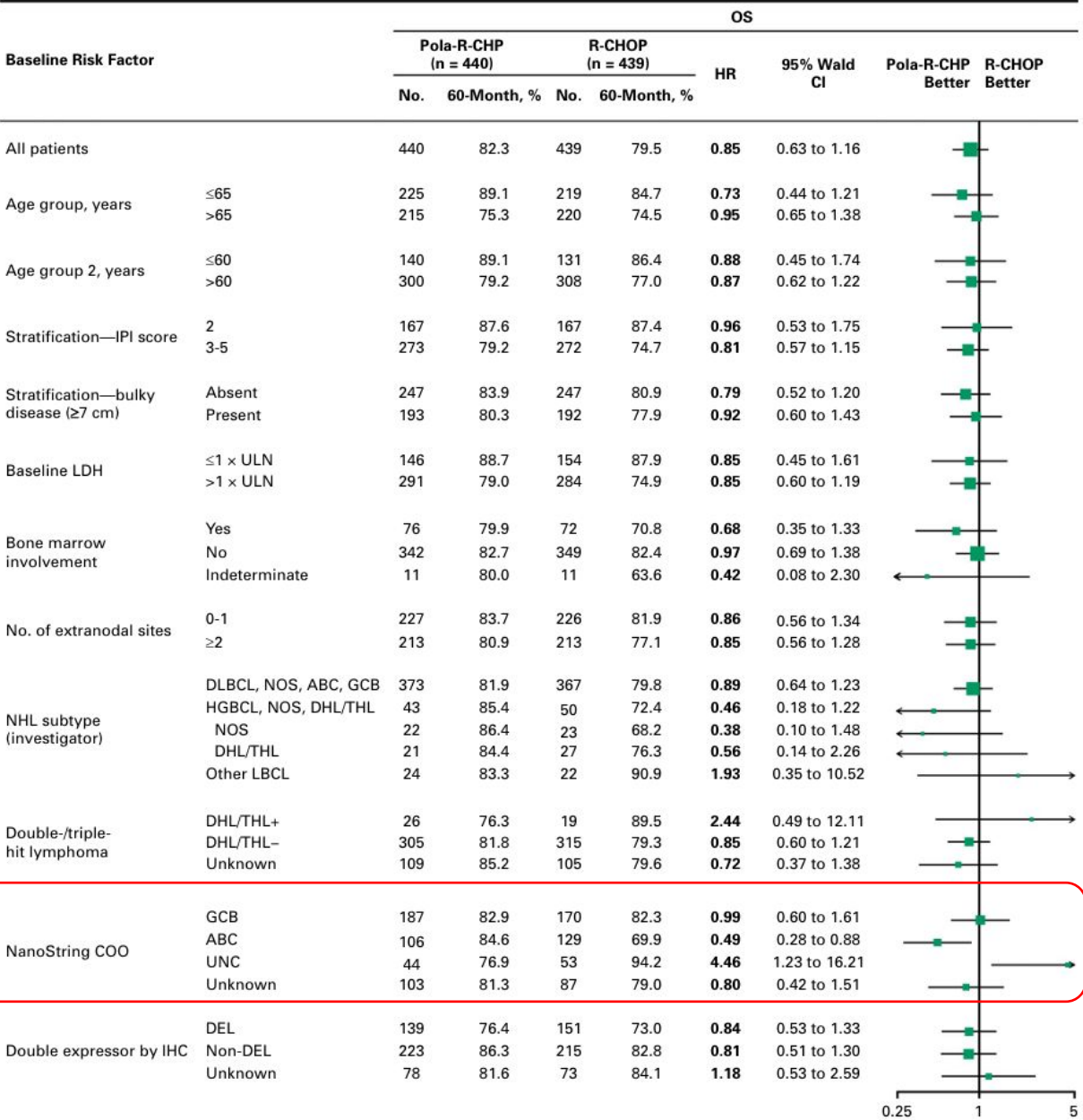
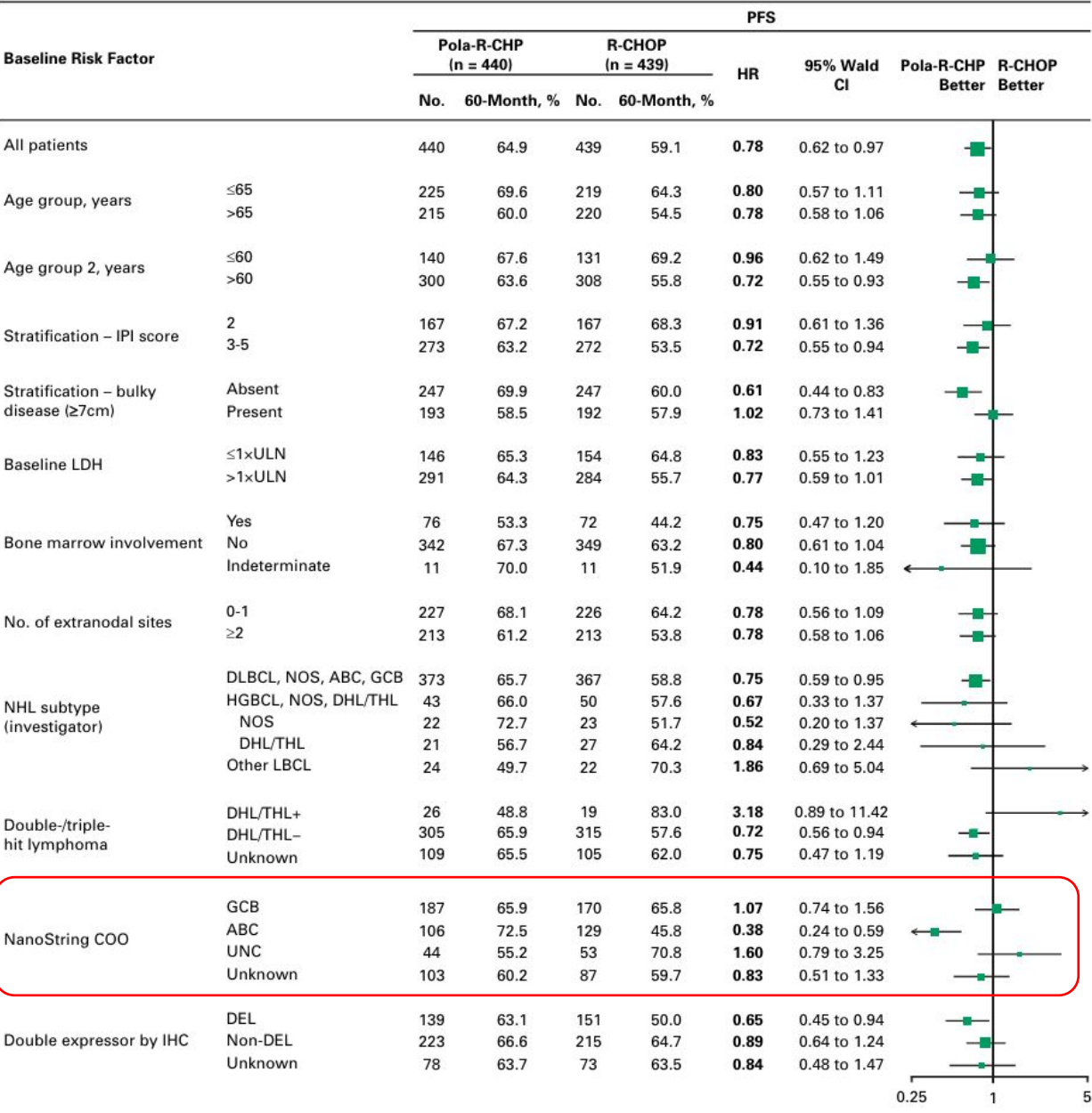
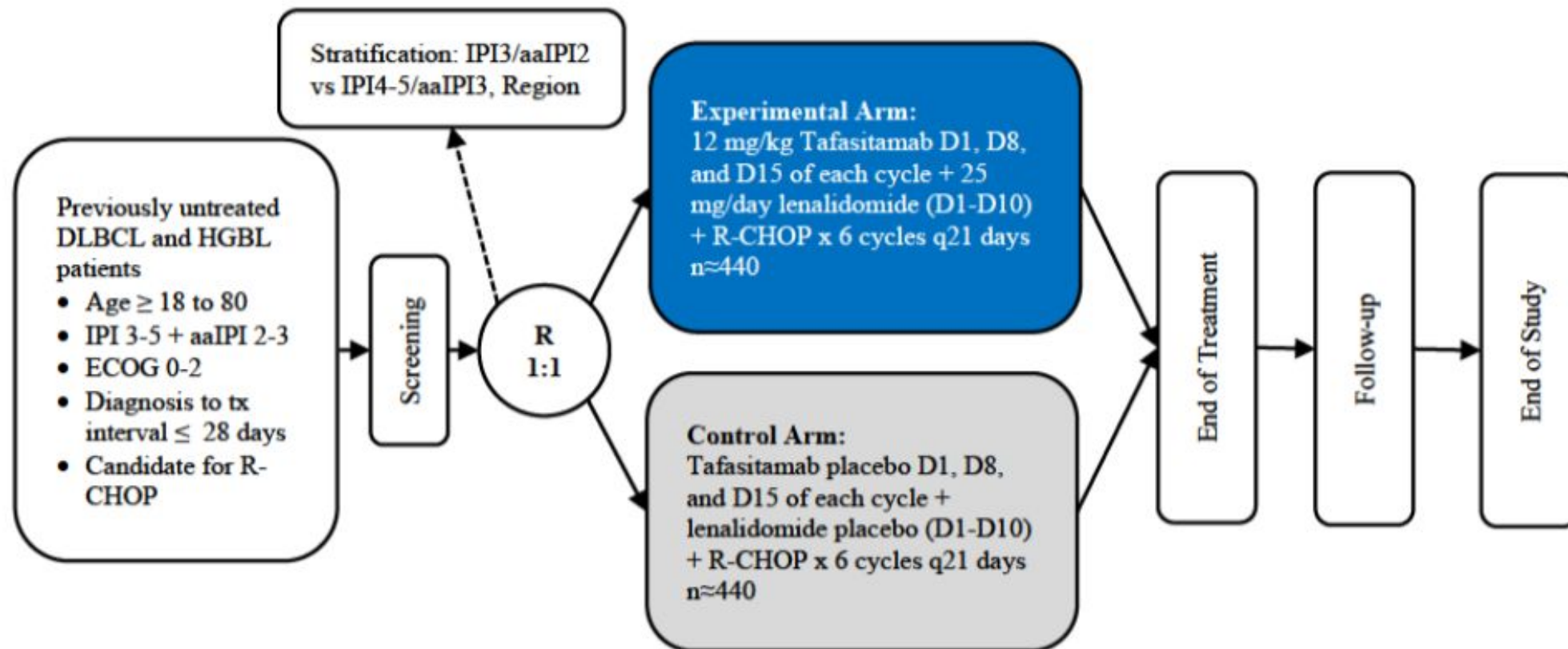


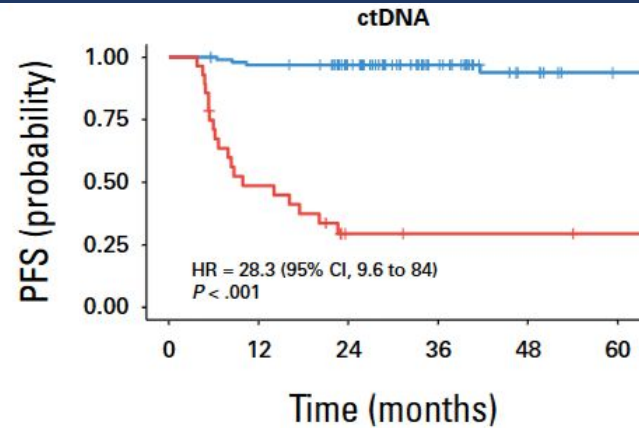
Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N = 435)		R-CHOP (N = 438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

FrontMIND. Tafa+len with R-CHOP

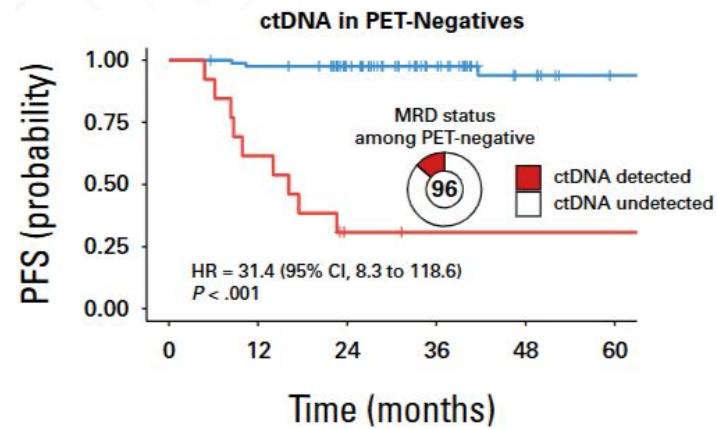


ctDNA



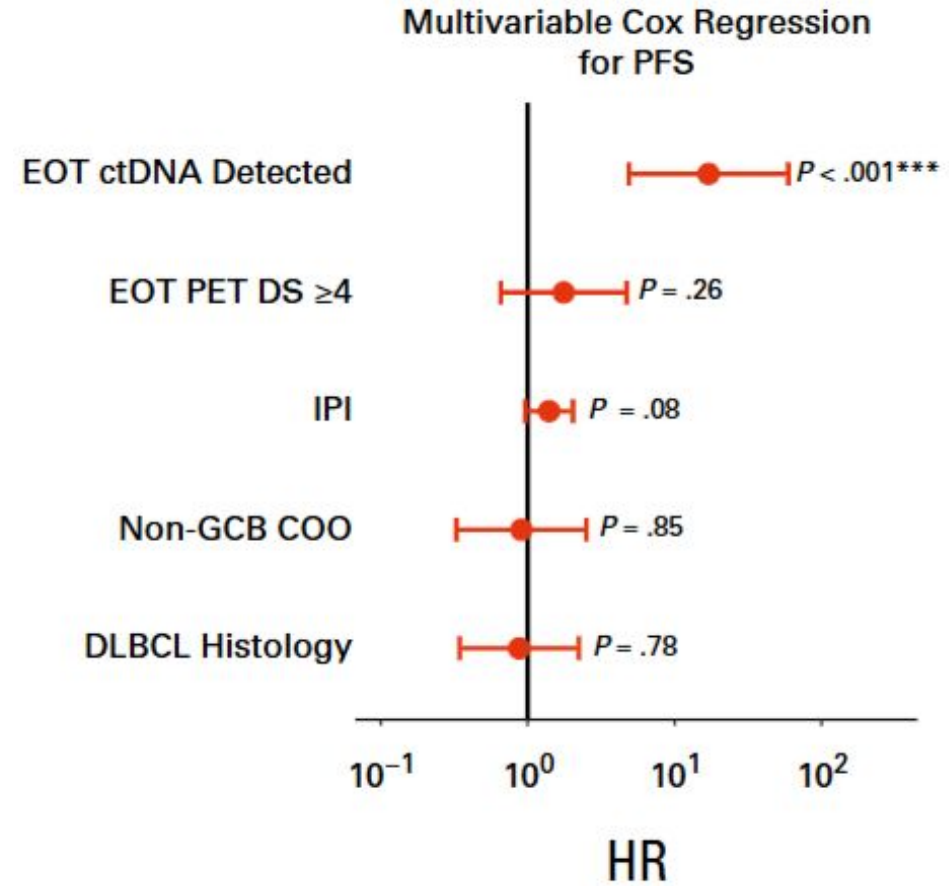
No. at risk

ctDNA not detected	97	93	77	46	28	21
ctDNA detected	28	13	4	3	3	2



No. at risk

ctDNA not detected	83	80	66	41	24	18
ctDNA detected	13	8	2	1	1	1



Do we need fixed-duration R-CHOP in 2026?

Trials	Experimental Arm	Control Arm	Eligibility criteria			Endpoint		Planned N	Hazard ratio	NCT
			Age	IPI	Other	Primary	Non-traditional Secondary			
Benchmark										
POLARIX	Polatuzumab vedotin + R-CHP	R-CHOP	18-80	2-5	No transformed lymphoma	PFS	PRO	1000	0.73	NCT03274492
Ongoing										
SKYGLO	Glofitamab + pola-R-CHP	Pola-R-CHP	18-80	2-5	No transformed lymphoma	PFS	PRO	1130		NCT06047080
OLYMPIA-3	Odronextamab + CHOP	R-CHOP	≥18	2-5		PFS	MRD, PRO	904		NCT06091865
EPCORE DLBCL-2	Epcoritamab + R-CHOP	R-CHOP	18-80	2-5		PFS	MRD	900		NCT05578976
ZUMA-23	Axicabtagene ciloleucel	R-CHOP or Pola-R-CHP	≥18	4-5	Post 1 cycle of R-chemo	EFS	PRO	300		NCT05605899
frontMIND	Tafasitamab + lenalidomide + R-CHOP	R-CHOP	18-80	3-5	DTI ≤ 28 days	PFS		899		NCT04824092
GolSeek-1	Golcadomide + R-CHOP	R-CHOP	18-80	3-5 1-2 with high risk features	No transformed lymphoma	PFS	MRD, PRO	850		NCT06356129
WaveLINE-010	Zilovetamab vedotin + R-CHP	R-CHOP	≥18	2-5		PFS	PRO	1046		NCT06717347
ESCALADE	Acalabrutinib + R-CHOP	R-CHOP	18-75	1-5	Non-GCB No double hit lymphoma	PFS		611		NCT04529772
BELIEVE-01	Orelabrutinib + R-CHOP	R-CHOP	18-80	2-5	MCD subtype	PFS, CRR		150		NCT05234684
ENGINE-1	Enzastaurin + R-CHOP	R-CHOP	≥18	3-5	Focus on biomarker (DGM1)	OS in DGM1+		256		NCT03263026
Tucidinostat + R-CHOP	Tucidinostat + R-CHOP	R-CHOP	18-80	2-4	MYC/BCL2 Double-Expressor	EFS		418		NCT04231448
GUIDANCE-02	R-CHOP + X	R-CHOP	18-80	2-5	Agent X guided by 38-gene “LymphPlex” algorithm	PFS		1100		NCT05351346

ctDNA-guided Therapy Optimization in Newly Diagnosed DLBCL

ClinicalTrials.gov ID ⓘ NCT06693830

Sponsor ⓘ Hua-Jay J Cherng, MD

Information provided by ⓘ Hua-Jay J Cherng, MD, Columbia University (Responsible Party)

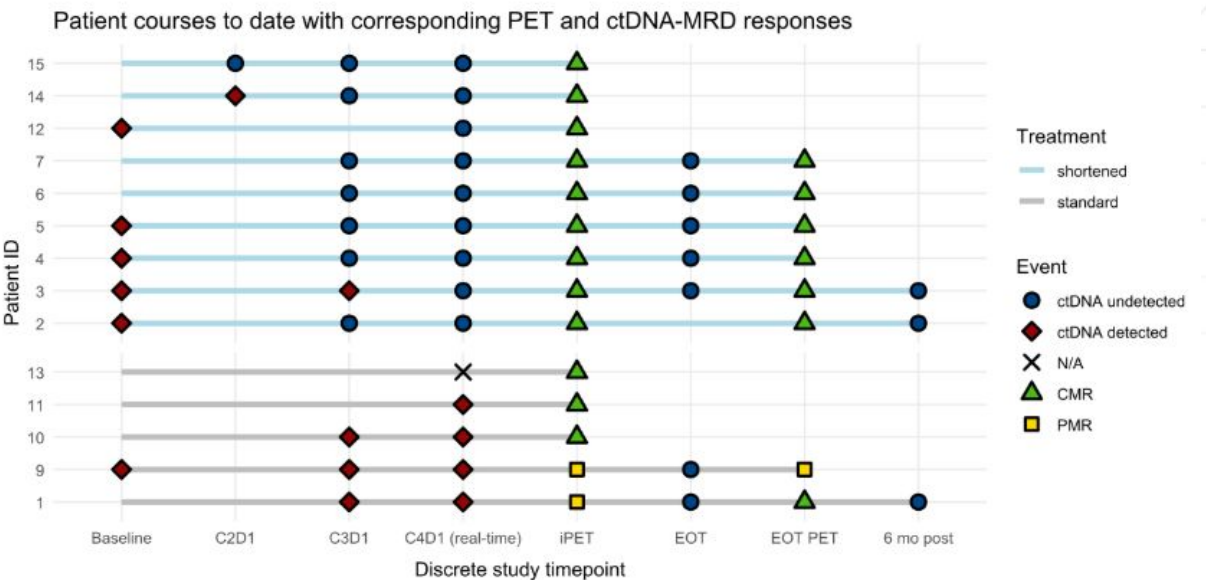
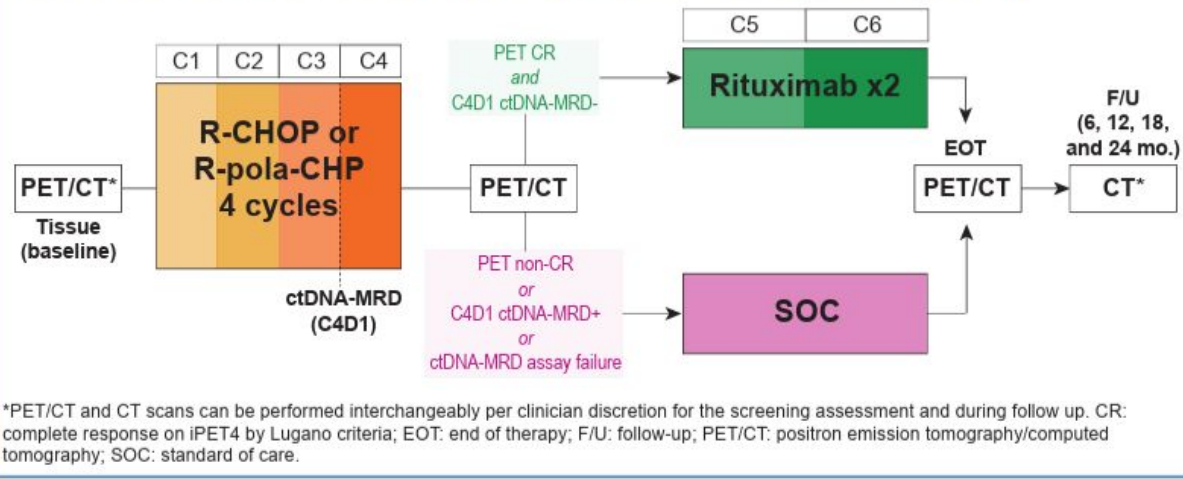
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Recruiting ⓘ

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Figure 1. Treatment and Response Assessment with ctDNA-Guided Treatment De-Escalation During Frontline DLBCL Therapy



Conclusions

- R-CHOP remains an appropriate frontline regimen for most patients
 - Highly effective regimen
 - Significant cure rates
 - Well-known toxicity profile
 - Administration across multiple practice settings
- Pola-R-CHP in patients with IPI score ≥ 2 and/or ABC subtype
- Emerging data supports de-escalation strategies integrating ctDNA into the decision-making
 - Personalized approach
 - Decrease treatment-related toxicity

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Thank you!

