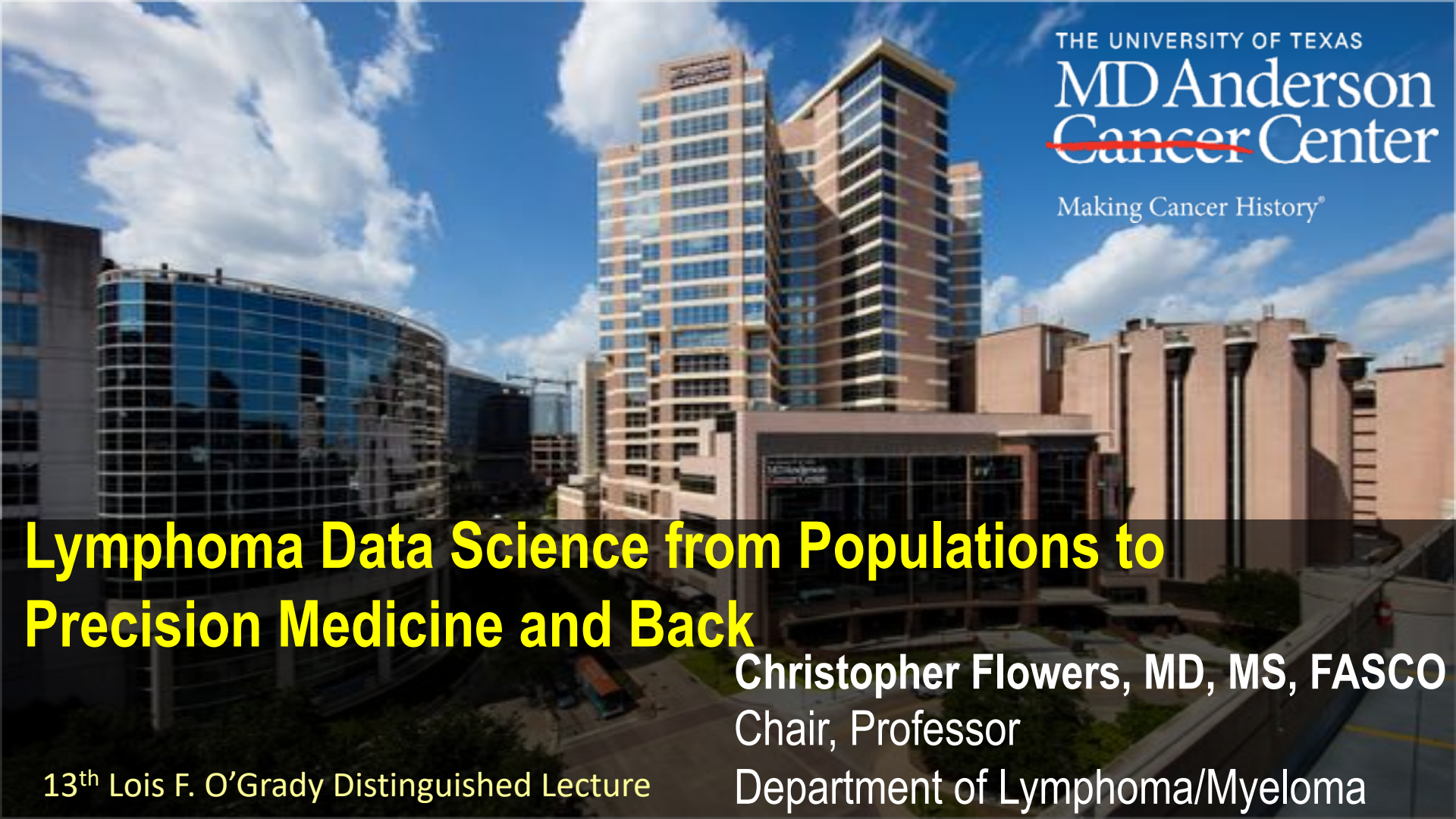
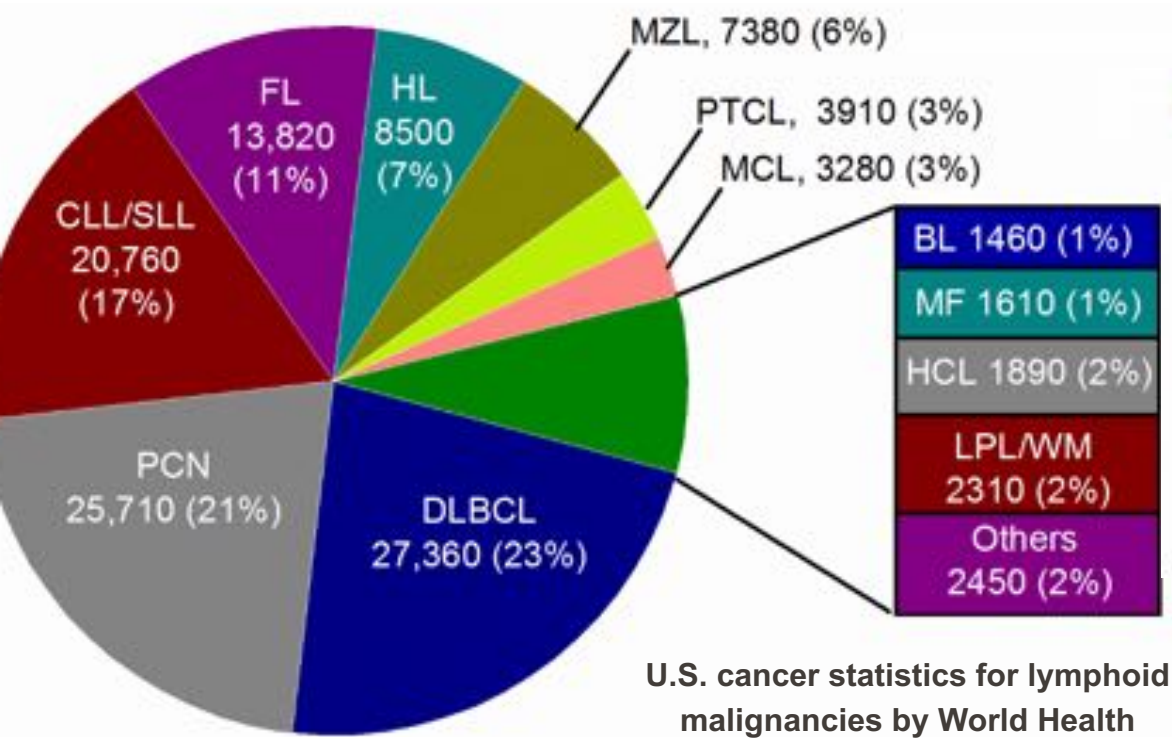


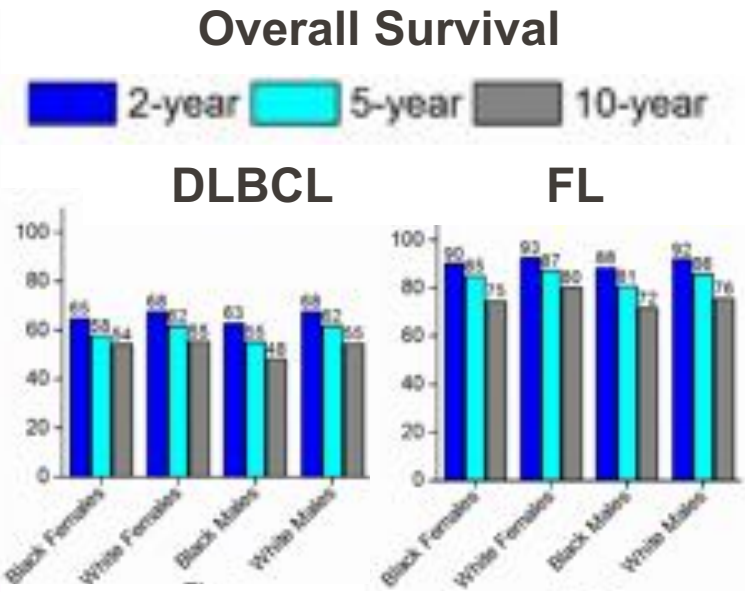
Lymphoma Data Science from Populations to Precision Medicine and Back

Christopher Flowers, MD, MS, FASCO
Chair, Professor
Department of Lymphoma/Myeloma

13th Lois F. O'Grady Distinguished Lecture

Annual Incidence of Lymphoid Cancers in the United States





U.S. cancer statistics for lymphoid malignancies by World Health Organization subtypes

Teras LR, DeSantis CE, Morton LM, Cerhan JR, Jemal A, Flowers CR
CA Cancer J Clin. 2016

Applying Population Sciences to Clinical Outcomes

- National Cancer DataBase
- SEER; SEER-Medicare
- NLCS Chair 2007 – 2014
- CONNECT CLL Chair
- CONNECT NHL Chair
- REAL-MIND Chair
- InterLymph
- FLASH Steering Comm.
  - (IPD 22 FL RCTs)
- SEAL Steering Comm.
  - (IPD 16 DLBCL RCTs)

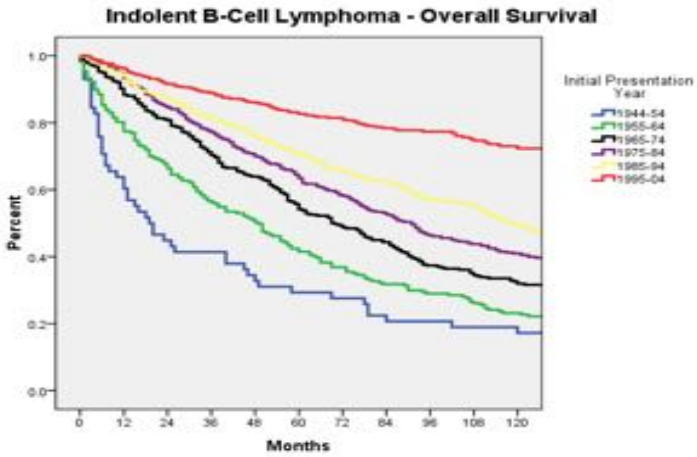
National LymphoCare Study FL (n = 2727)

Nastoupil Br J Haematol. 2016
Casulo Ann Oncol. 2015
Casulo J Clin Oncol. 2015
Wagner-Johnston Blood. 2015
Nabhan Br J Haematol. 2015
Nastoupil Leuk Lymphoma. 2015
Nastoupil Cancer. 2014
Martin Cancer. 2013
Nooka Ann Oncol. 2013
Friedberg J Clin Oncol. 2012
Nabhan Cancer. 2012
Friedberg J Clin Oncol. 2009

Follicular Lymphoma

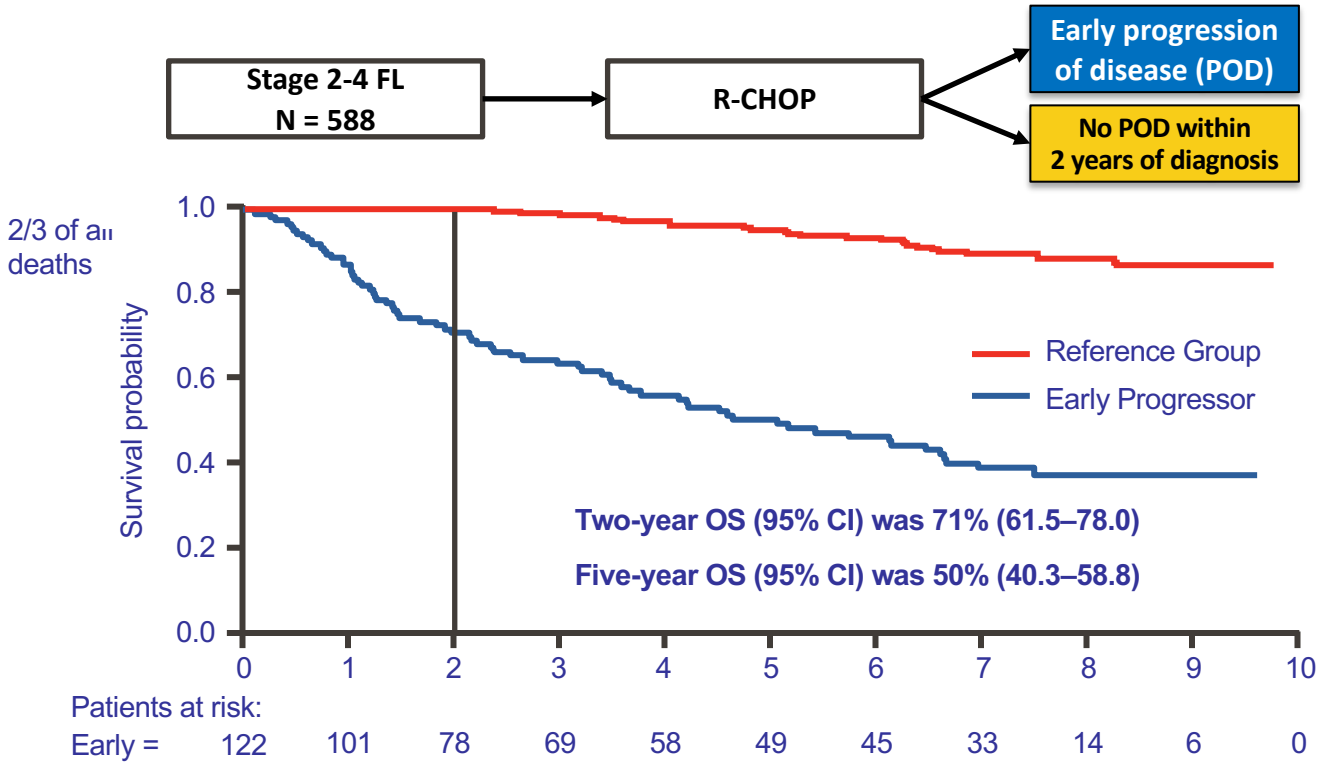
2nd most common NHL

- 30,000 new people diagnosed/year
- Indolent course with median survival 20+ yrs
- Incurable; Waxing and waning course
- Risk of transformation over time



Neelapu S. *60 Years of Survival Outcomes at the MD Anderson Cancer Center*. Springer. 2013. pp. 241-250.

OS of Patients With FL Who Relapsed Within 2 Years of R-CHOP ("Early POD")



Casulo C. et al. JCO 2015

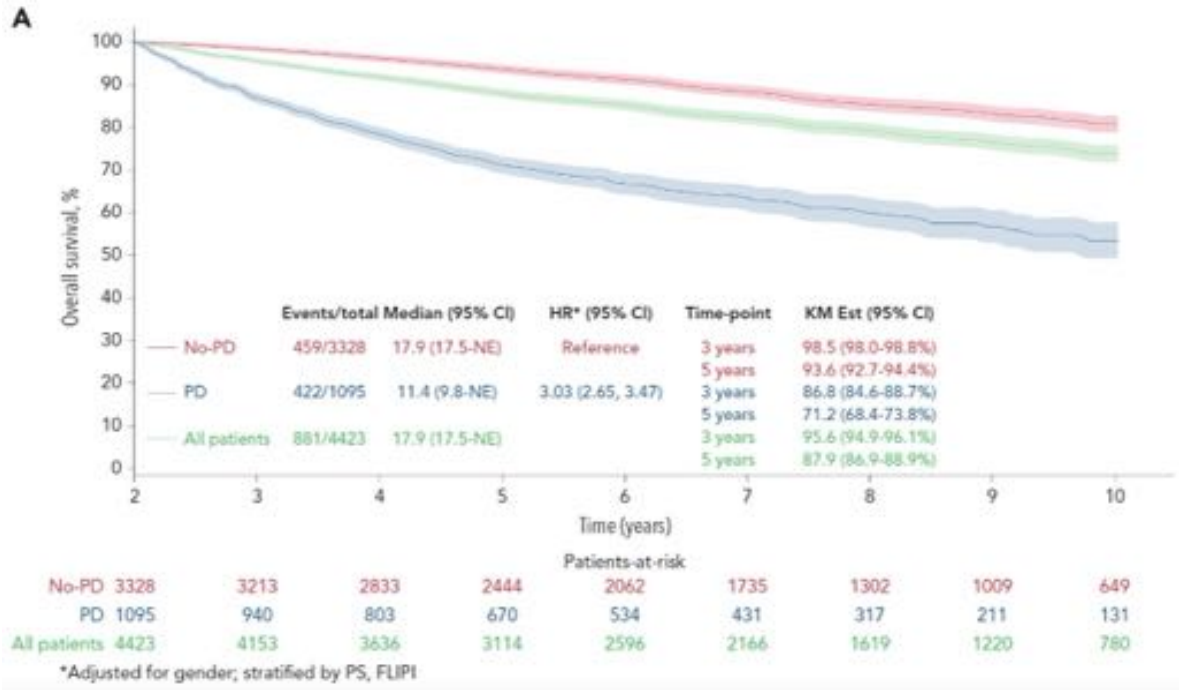
Progression of Disease in 24 Months Predicts Poor Survival

Analysis of >5000 patients on 13 clinical trials

- POD24 independently associated with increased risk of death or progression
- POD24 predicted by:
  - Male sex
  - Poor PS
  - High-risk FLIPI
  - Elevated ß2-macroglobulin

For patients with POD24, death more likely in the following:

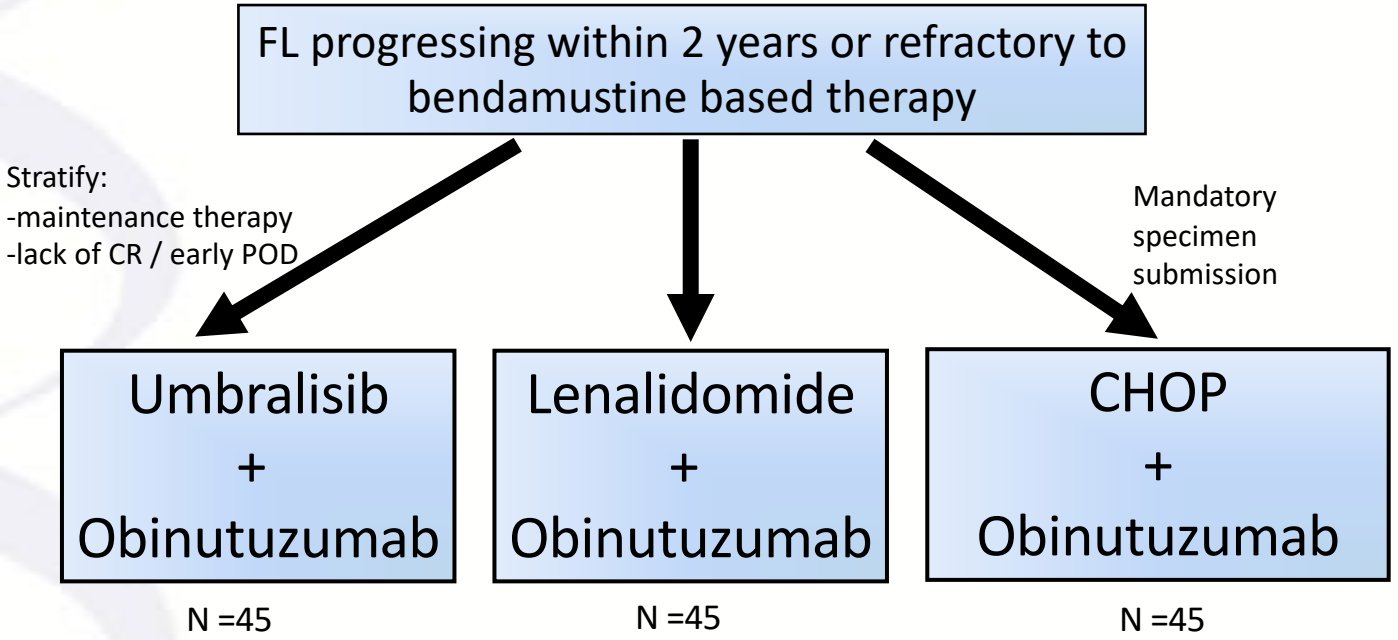
- Age >60
- Male sex
- PS ≥2
- High-risk FLIPI
- Hgb <12
- Elevated ß2-macroglobulin



Casulo et al, 2022

S1608: Randomized phase II trial in early progressing or refractory FL

Paul Barr (SWOG), Brian Link (Alliance), Chris Flowers (ECOG)



Primary clinical objective: CR by PET/CT

Primary translational objective: Validation of m7-FLIPI in this high-risk population

NOT the FLASH
I will discuss today…

Follicular Lymphoma Analysis of Surrogate Hypotheses (FLASH) Group Collaborators

Evaluation of Complete Response Rate at 30 Months as a Surrogate Endpoint for Progression-Free Survival in First-Line Follicular Lymphoma Studies: Analyses of Individual Patient Data of 3837 Patients From the FLASH Database

Follicular Lymphoma Analysis of Surrogate Hypotheses (FLASH) Group Collaborators

Academic collaboration of clinicians and statisticians with expertise in FL and/or surrogate endpoint assessment

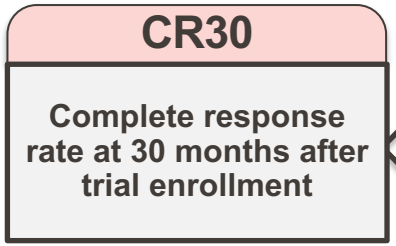
- Mayo Clinic independent statistical center; 13 Studies

Met with US FDA and the European Medicines Agency (EMA) to prospectively define meta-analysis approach and statistical methods

Objective

- Establish a surrogate endpoint for PFS to reduce duration of clinical trials and expedite patient access to effective new therapies

Principal Surrogacy Candidate



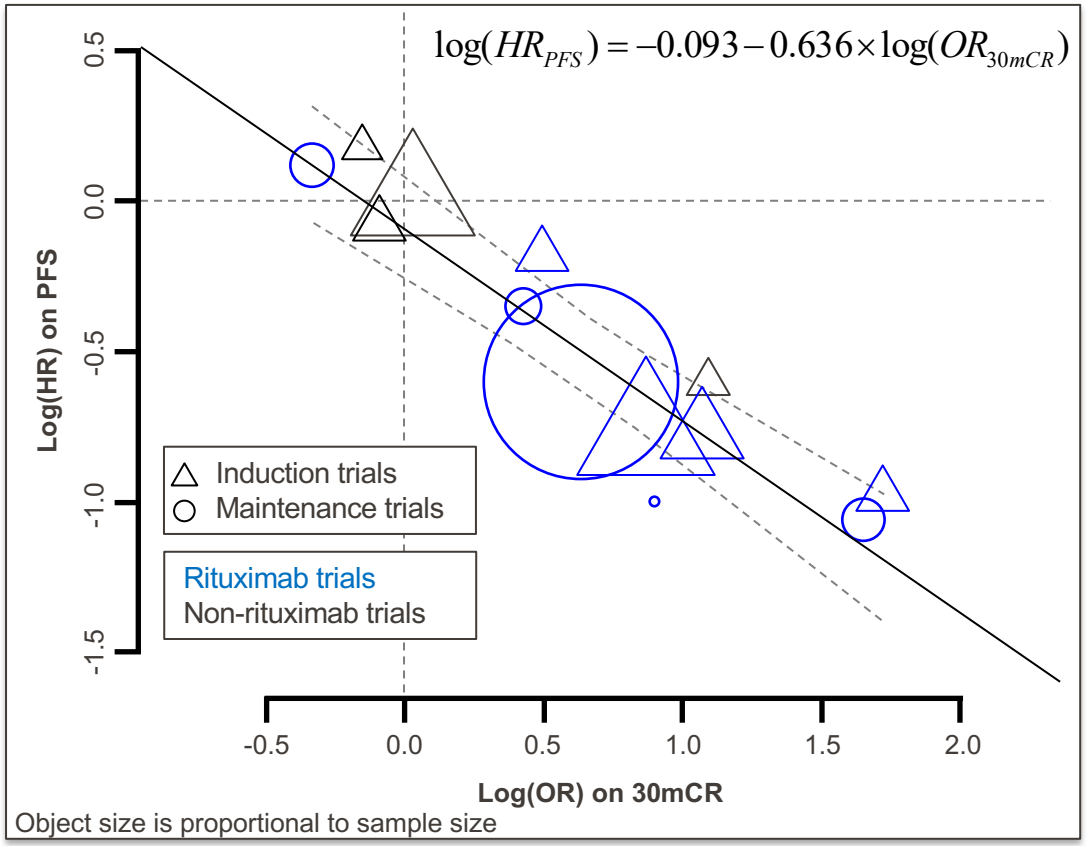
- Captures both induction (~6 months) and maintenance (~24 months) treatment effects
- Supported by preliminary clinical data showing that durable CR is associated with prolonged PFS[1]
- May allow reduction in clinical trial duration

1. Bachy et al. *J Clin Oncol.* 2010;28:822-829.

13 Studies and 26 Treatment Arms

		Line of Treatment	Control Arm		Experimental Arm	
Study Name	Reference		n	Treatment	n	Treatment
CALGB 7951	Peterson 2003	Induction	86	Cyclophosphamide	103	CHOP-B
ECOG 1496	Hochster 2009	Maintenance	113	CVP/observation	115	CVP/R maintenance
EORTC 20921	Hagenbeek 2006	Induction	117	CVP	114	F
FavId 06	Freedman 2009	Maintenance	130	Rituximab/placebo	127	Rituximab/idiotype vaccine
GOELAMS 064	Gyan 2009 Deconinck 2005	Induction	81	CHVP/CHVP-IFN-a	85	VCAP/ASCT
M39021	Marcus 2008	Induction	160	CVP	162	R-CVP
M39023/OSHO-39	Herold 2007	Induction	96	MCP/IFN-a	105	R-MCP/IFN-a
ML16865/NLG	Kimby 2015	Induction	117	Rituximab	111	Rituximab + IFN-a
ML17638/FIL	Vitolo 2013	Maintenance	101	R-FND/observation	101	R-FND/R maintenance
PRIMA	Salles 2010	Maintenance	513	R-chemo/observation	505	R-chemo/R maintenance
SAKK 35/98	Ghielmini 2004 Martinelli 2010	Maintenance	23	Rituximab/observation	22	Rituximab/R maintenance
STUDY 1/GLSG	Nickenig 2006	Induction	362	CHOP/ASCT, IFN-a	146	MCP/ASCT, IFN-a
STUDY A/GLSG	Hiddemann 2005	Induction	290	CHOP/ASCT, IFN-a	292	R-CHOP/ASCT, IFN-a

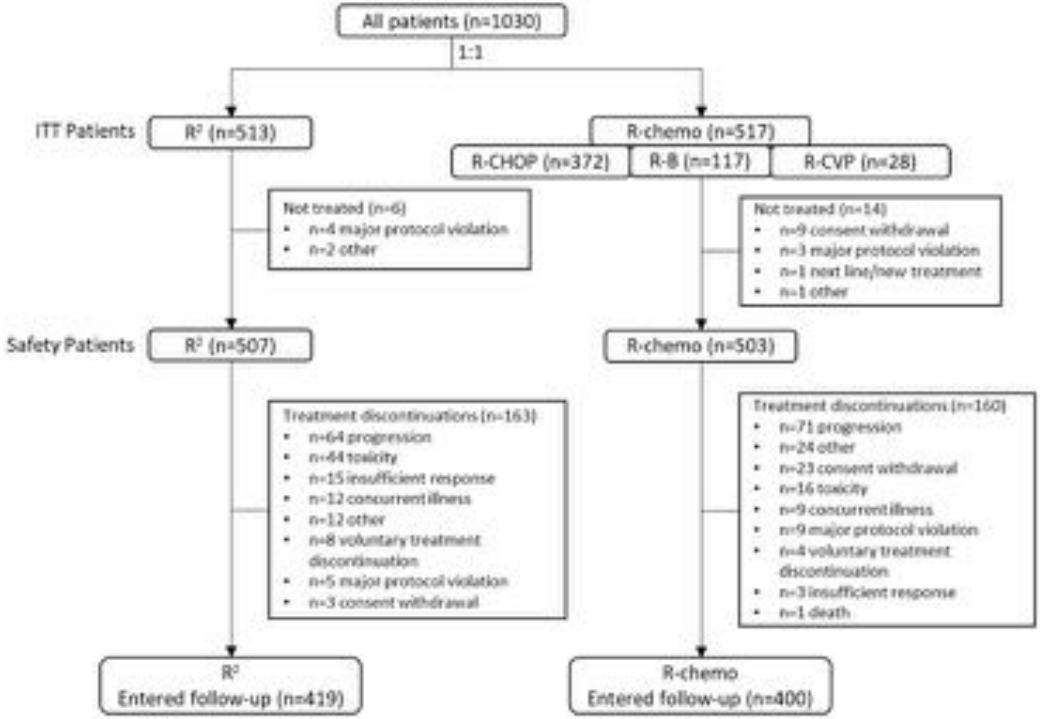
Results: Primary Surrogacy Evaluation

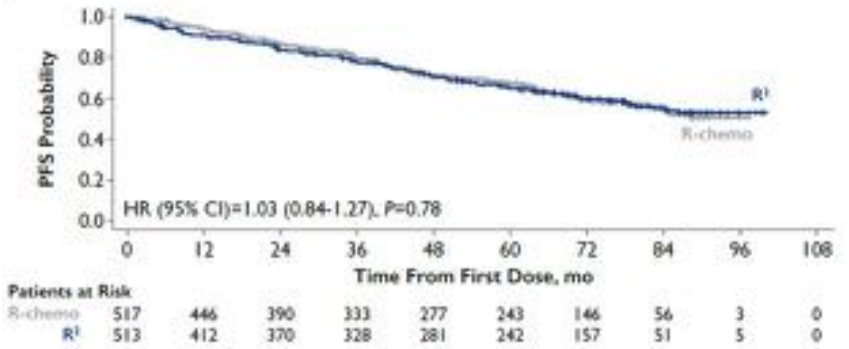


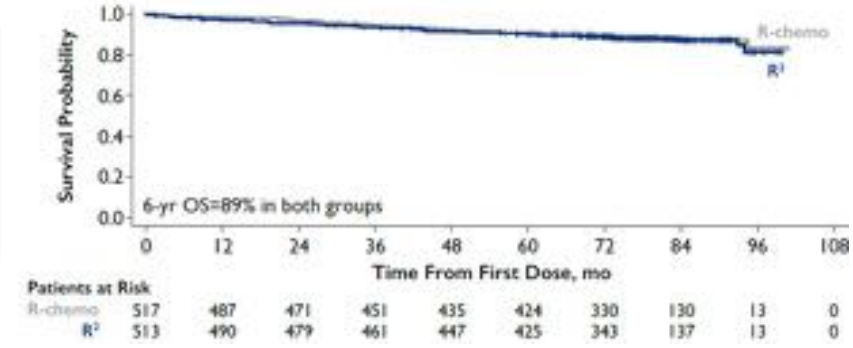
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.88 (0.77, 0.96)	0.86 (0.72, 1.00)

30 month complete response rate met the pre-specified surrogacy qualification criteria for PFS

RELEVANCE: R² vs R-chemo in Frontline FL



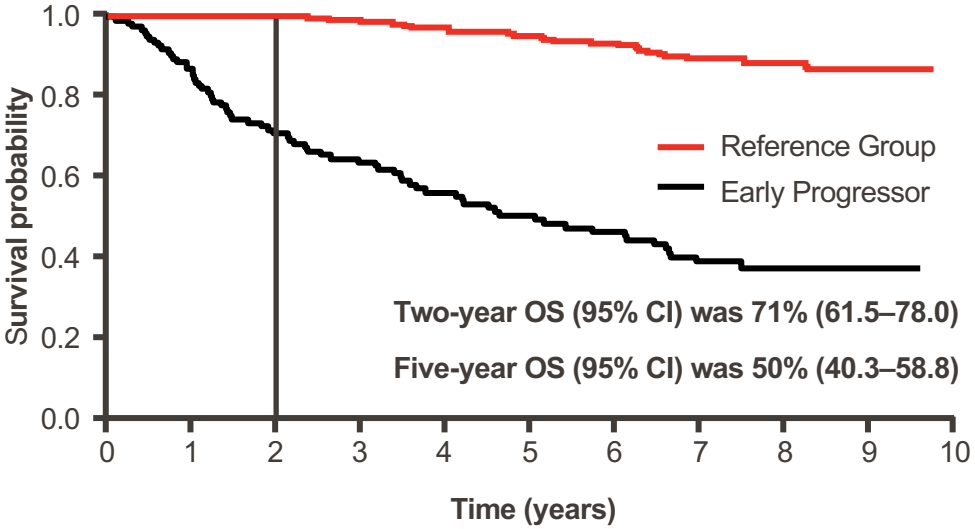




Morschhauser et al, 2018; Morschhauser et al, 2021.

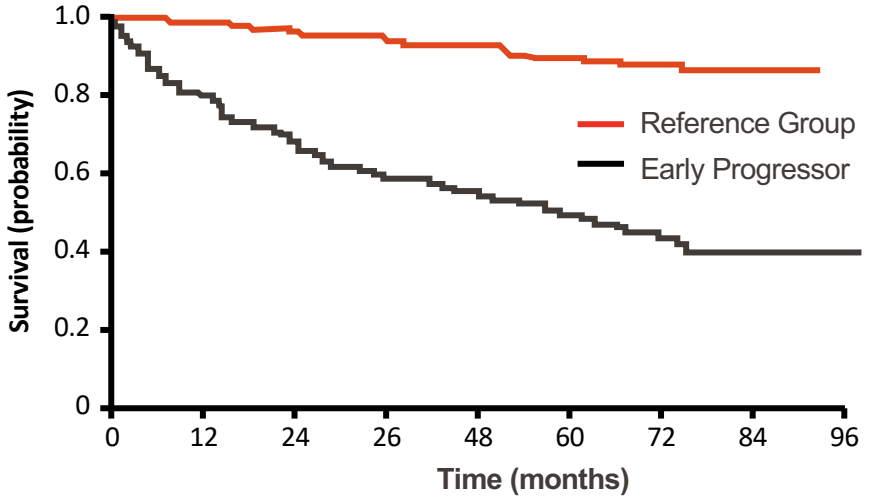
Example: Connections Between Cohort Study and RCTs

NLCS: Survival With POD24 (n=542)
(progression < 24 months after initial therapy)



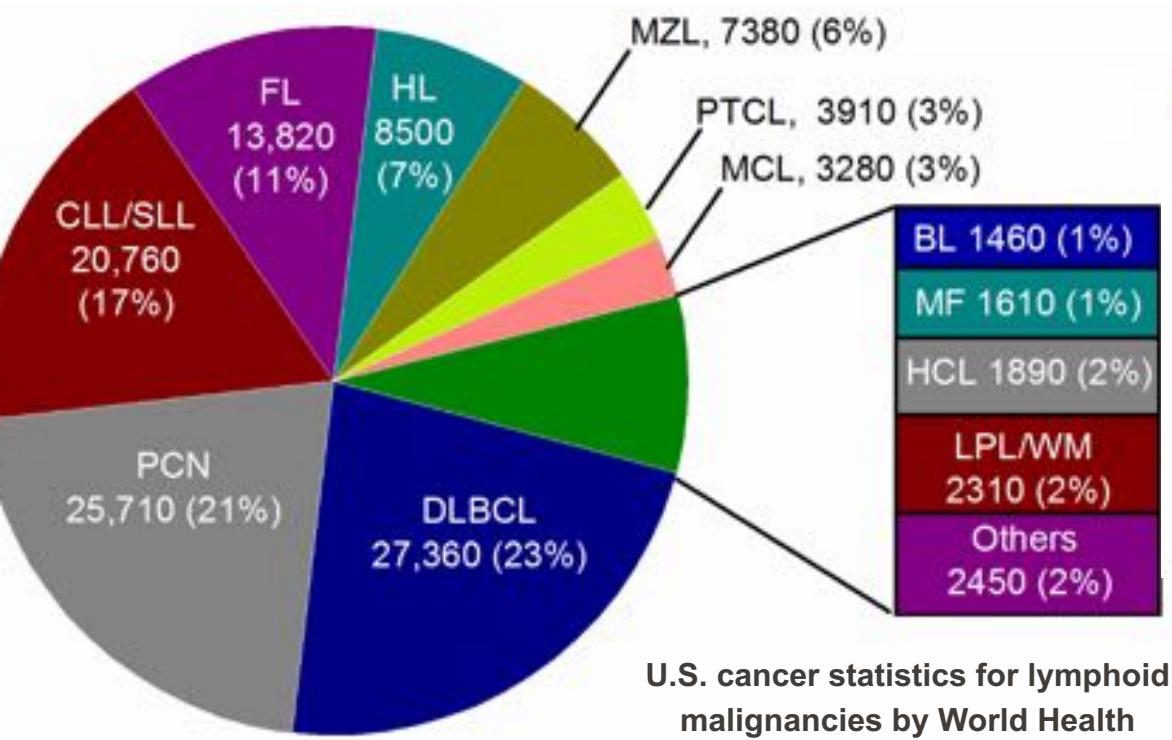
Casulo et al. *JCO.* 2015;33:2516.

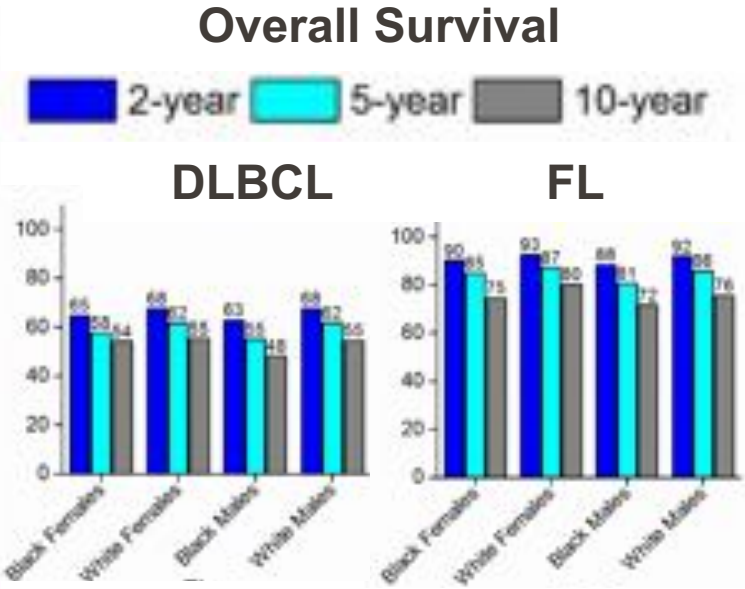
FLASH: Survival With POD24 (n=5,453)
(progression < 24 months after initial therapy)



Casulo et al. *Blood*. 2022

Annual Incidence of Lymphoid Cancers in the United States





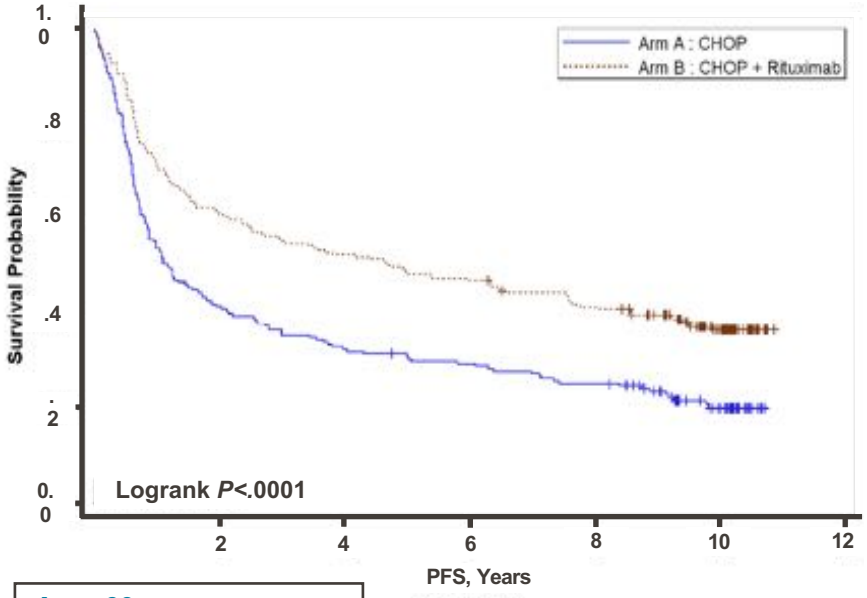
U.S. cancer statistics for lymphoid malignancies by World Health Organization subtypes

American Cancer Society®

Teras LR, DeSantis CE, Morton LM, Cerhan JR, Jemal A, Flowers CR
CA Cancer J Clin. 2016

Department of Lymphoma/Myeloma

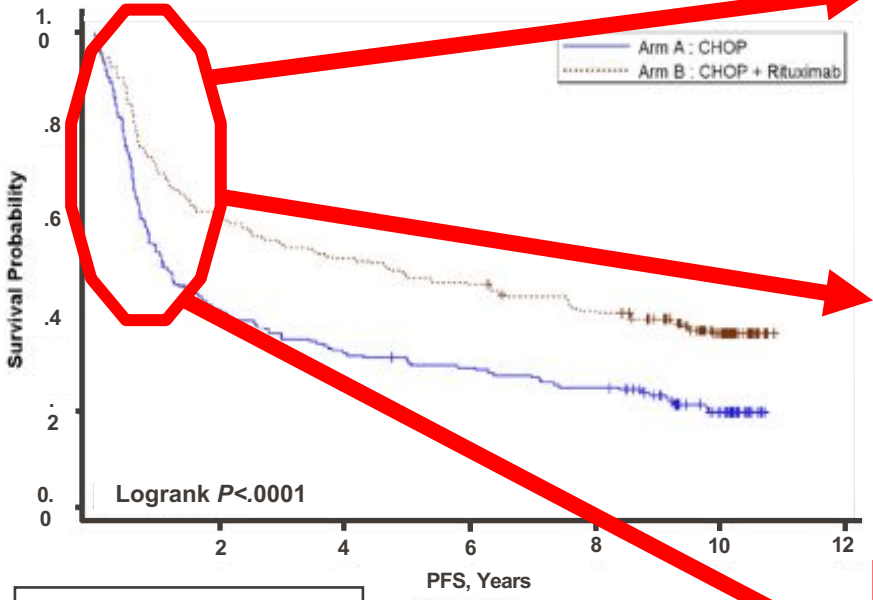
DLBCL: Strategies to Improve Beyond R-CHOP-21



Age>60 years
PS>2
Stage III-IV
Extranodal sites >2
LDH>Nml

IPI

DLBCL: Strategies to Improve Beyond R-CHOP-21



Age>60 years
PS>2
Stage III-IV
Extranodal sites >2
LDH>Nml

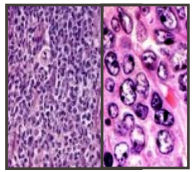
IPI

Intensification over R-CHOP-21?

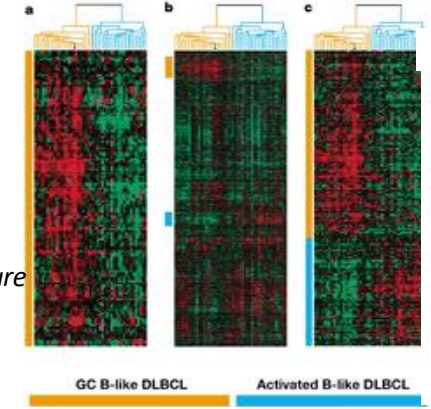
Better predict/evaluate quality of response?

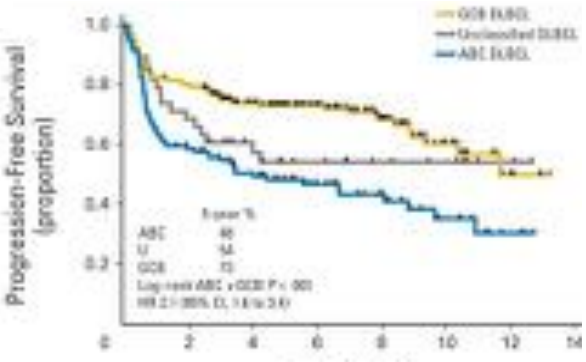
Take into consideration biological diversity of DLBCL

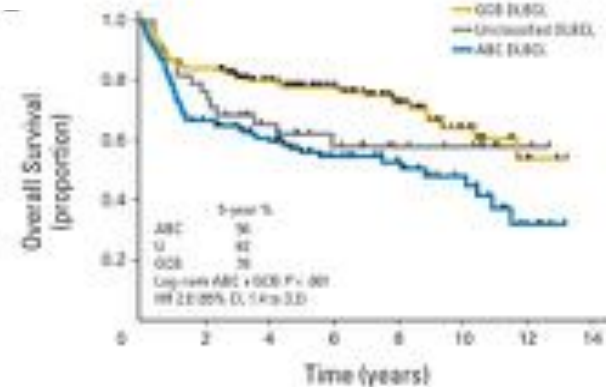
Molecularly and Clinically Distinct Subgroups in DLBCL



Alizadeh *et al. Nature* 2000

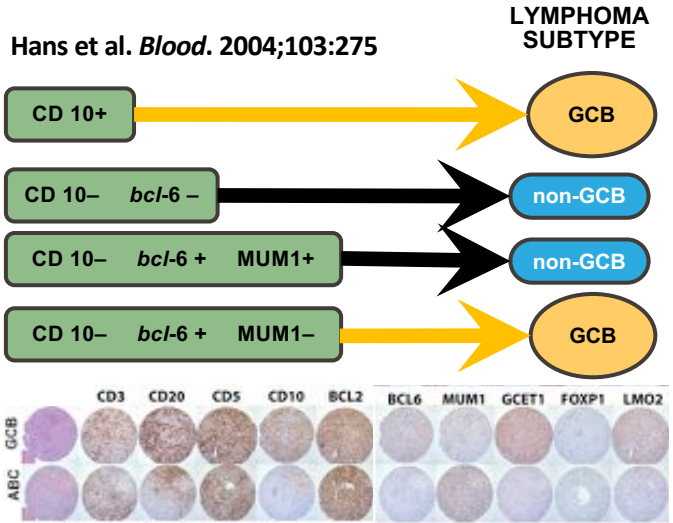






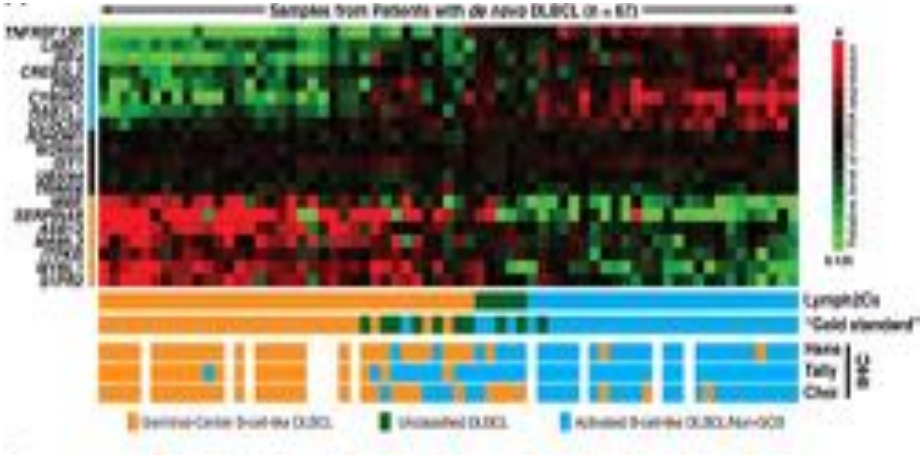
Immunophenotype Classification

Hans et al. *Blood*. 2004;103:275

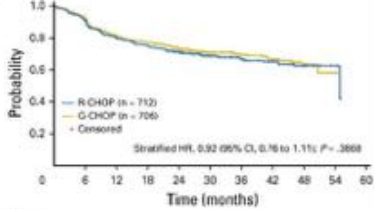


GEP from FFPE

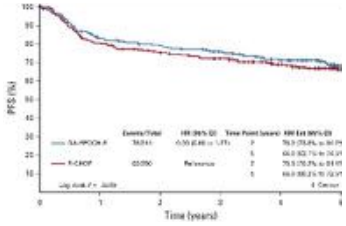
Scott et al. **Blood**. 2014



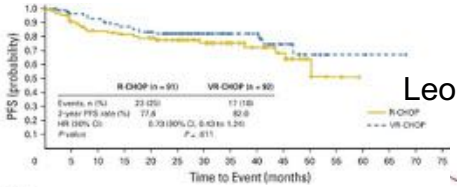
Trial	Comparison	Result
GOYA	R-CHOP vs. G-CHOP (n=1,418)	Negative
CALGB 50303	R-CHOP vs. R-DA-EPOCH (n=524)	Negative
PYRAMID (non-GCB)	R-CHOP vs. Bortezomib+R-CHOP (n=206)	Negative
REMoDL-B	R-CHOP vs. Bortezomib+R-CHOP (n=1,085)	Negative
LYM-2034 (non-GCB)	R-CHOP vs. Bortezomib+R-CHP (n=164)	Negative
PHOENIX (ABC)	R-CHOP vs. Ibrutinib+R-CHOP (n=838)	Negative
ECOG 1412	R-CHOP vs. Lenalidomide+R-CHOP (n=345)	*?Positive*
ROBUST (non-GCB)	R-CHOP vs. Lenalidomide+R-CHOP (n=570)	*Negative*



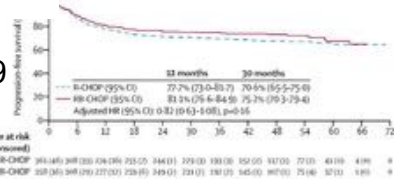
Vitolo *J Clin Oncol* 2017



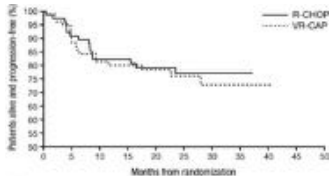
Bartlett *J Clin Oncol* 2019



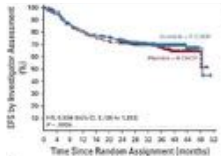
Leonard *J Clin Oncol* 2017



Davies Lancet Onc 2019



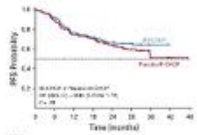
Offner *Blood* 2015



Younnes *J Clin Oncol* 2019

2-year OS: 87% len/R-CHOP
80% R-CHOP

Nowakowski *JCO* 2021



Nowakowski *J Clin Oncol* 2021

Progression-Free Survival as a Surrogate End Point for Overall Survival in First-Line Diffuse Large B-Cell Lymphoma: An Individual Patient - Level Analysis of Multiple Randomized Trials (SEAL)

Qian Shi, Norbert Schmitz, Fang-Shu Ou, Jesse G. Dixon, David Cunningham, Michael Pfreundschuh, John F. Seymour, Ulrich Jaeger, Thomas M. Habermann, Corinne Haioun, Hervé Tilly, Hervé Ghesquieres, Francesco Merli, Marita Ziepert, Raoul Herbrecht, Jocelyne Flament, Tommy Fu, Bertrand Coiffier, and Christopher R. Flowers

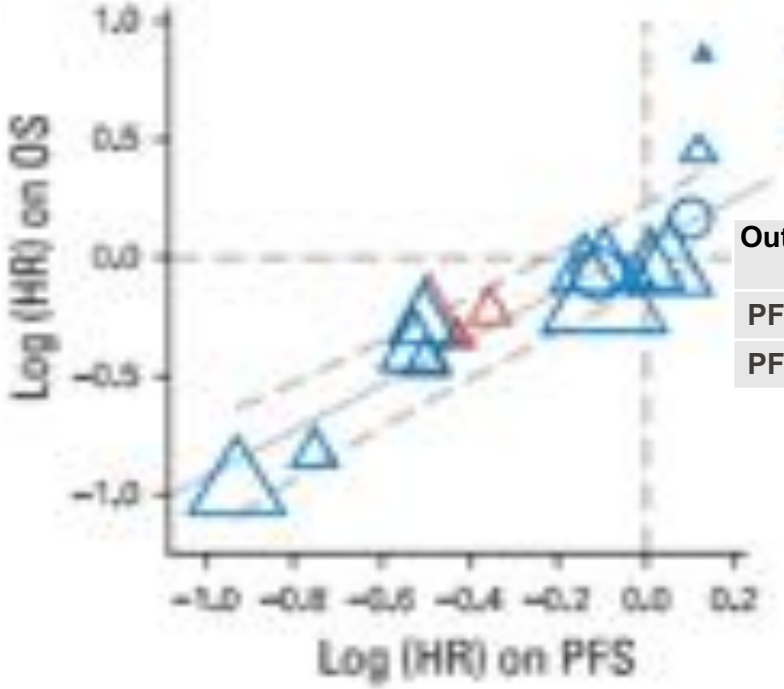
RCTs Included in the Analysis (n=13)

Age (categorical), years	Control (N=3,450)	Experimental (N=4,057)	Total (N=7,507)
<60	1,566 (45)	1,562 (39)	3,128 (42)
60-69	1,034 (30)	1,386 (34)	2,420 (32)
≥70	850 (25)	1,109 (27)	1,959 (26)
Sex			
Female	1,580 (46)	1,896 (47)	3,476 (46)
Male	1,870 (54)	2,161 (53)	4,031(54)
ECOG Performance Status			
Missing	3	1	4
0	1,627 (47)	1,837 (45)	3,464(46)
1	1,328 (38)	1,641 (40)	2,969 (40)
≥ 2	492 (14)	578 (14)	1,070 (14)
IPI score			
Missing	393	384	777
0-1	1,022(33)	1,217 (33)	2,239 (33)
2	734 (24)	968 (26)	1,702 (25)
3	768 (25)	878 (24)	1,646 (24)
4-5	533 (17)	610 (17)	1,143 (17)
Ann Arbor Stage			
Missing	14	9	23
I/II	1,223 (35)	1,492 (37)	2,715 (36)
III	787 (23)	1,022 (25)	1,809 (24)
IV	1,426 (41)	1,534 (38)	2,960 (40)

J Clin Oncol. 2018; 36(25): 2593-2602.

Progression-Free Survival is a Surrogate End Point for Overall Survival in First-Line Diffuse Large B-Cell Lymphoma

Trial-level treatment effect correlation between PFS and OS



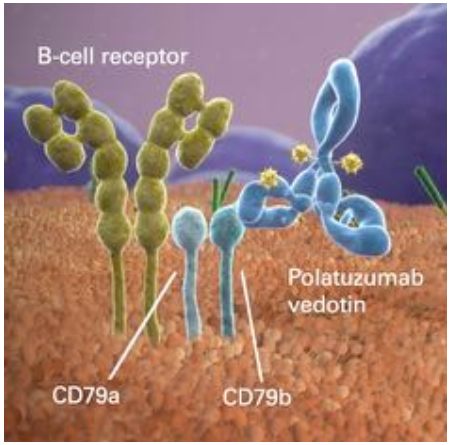
		Trial Level surrogacy:		Patient Level surrogacy:
Outcome	N Trials (N pts)	R^2WLS (95% CI)	R^2Copula (95% CI)	Global OR (95% CI)
PFS	17 (7,507)	0.83 (0.57-0.94)	**0.85 (0.73-0.98)**	0.85 (0.84-0.86)
PFS24	17 (6,882)	0.77 (0.51-0.92)	0.78 (0.59-0.96)	61.1 (52.6-69.6)

Prespecified criteria for surrogacy:

- R^2_{WLS} or $R^2_{Copula} \geq 0.80$ and neither < 0.7
- lower-bound 95% CI > 0.60

J Clin Oncol. 2018; 36(25): 2593-2602.

POLARIX: 1L DLBCL Phase 3



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trněný, J.P. Sharman, C. Herbaux, J.M. Burke, M. Matasar, S. Rai, K. Izutsu, N. Mehta-Shah, L. Oberic, A. Chauchet, W. Jurczak, Y. Song, R. Greil, L. Mykhalska, J.M. Bergua-Burgués, M.C. Cheung, A. Pinto, H.-J. Shin, G. Hapgood, E. Munhoz, P. Abrisqueta, J.-P. Gau, J. Hirata, Y. Jiang, M. Yan, C. Lee, C.R. Flowers, and G. Salles

Patients

- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

R 1:1

Pola-R-CHP

Polatuzumab vedotin (1.8mg/kg)* + **R-CHP + vincristine placebo**

R-CHOP

R-CHOP† + **polatuzumab vedotin placebo**

Cycles 1–6
(1 cycle=21 days)

Rituximab
375mg/m^2

Cycles 7 & 8

Primary endpoint

Progression-free survival (Investigator-assessed)

Secondary endpoints

- Event-free survival
- Complete response rate at end of treatment (PET/CT, IRC-assessed)
- Disease-free survival
- Overall survival

Safety endpoints

Incidence, nature, and severity of adverse events

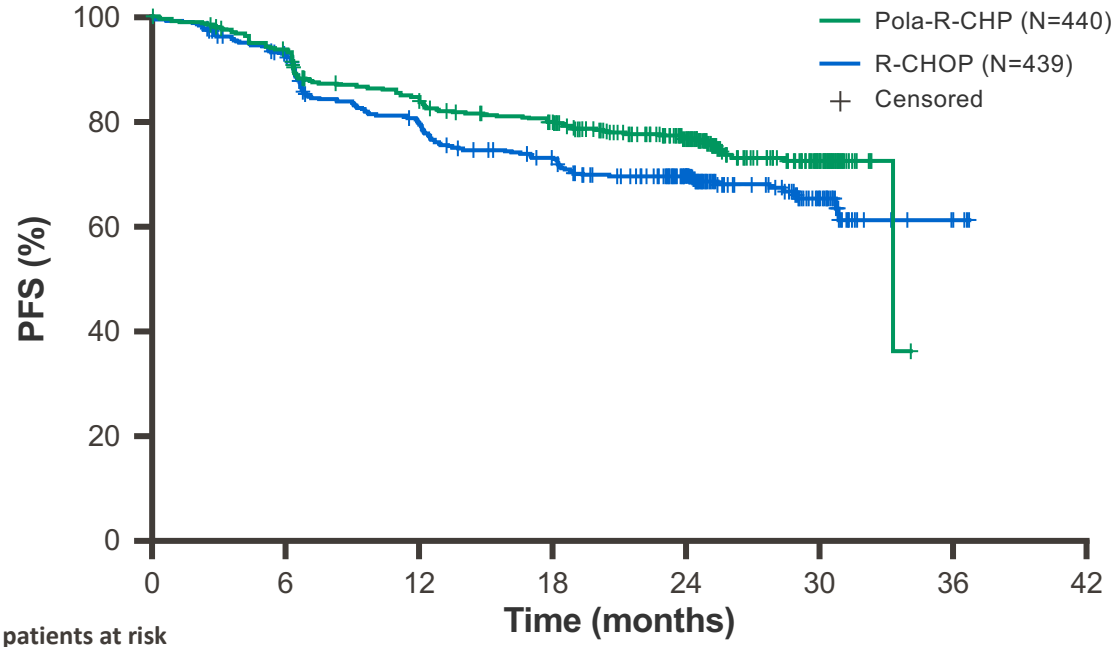
CCOD: June 28, 2021

Median follow up at the primary analysis: 28.2 months

Tilly et al. *NEJM* 2021

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS vs R-CHOP



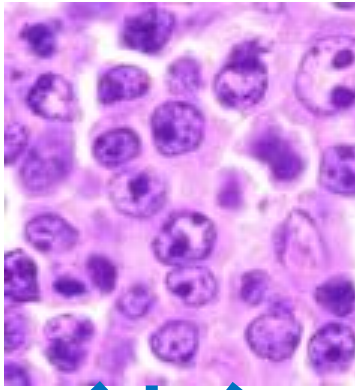
No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

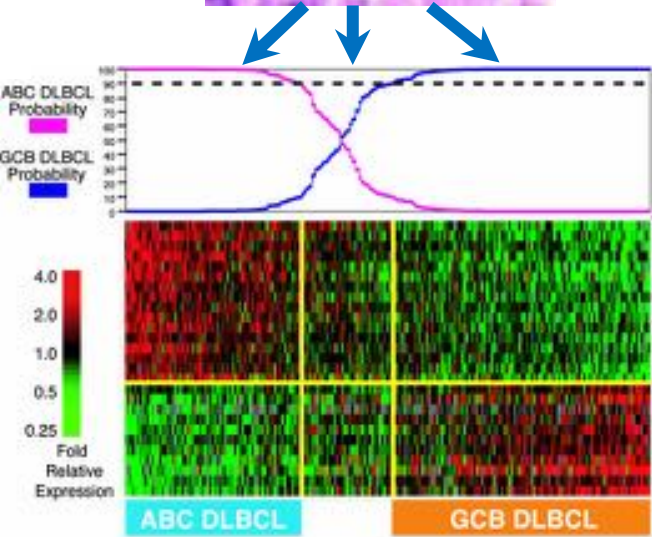
HR 0.73 **(P=0.02)**

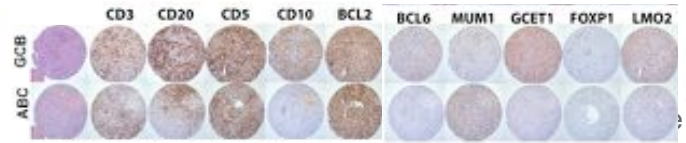
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** vs R-CHOP
- **24-month PFS:** 76.7% with Pola-R-CHP vs 70.2% with R-CHOP (**Δ=6.5%**)

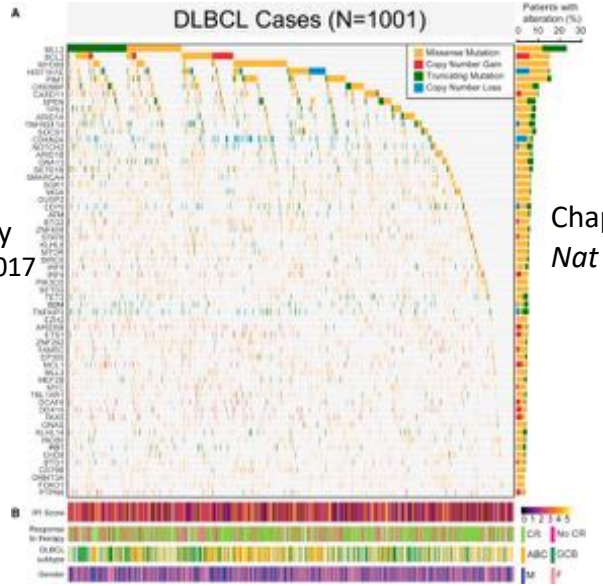
Tilly et al. *NEJM* 2021



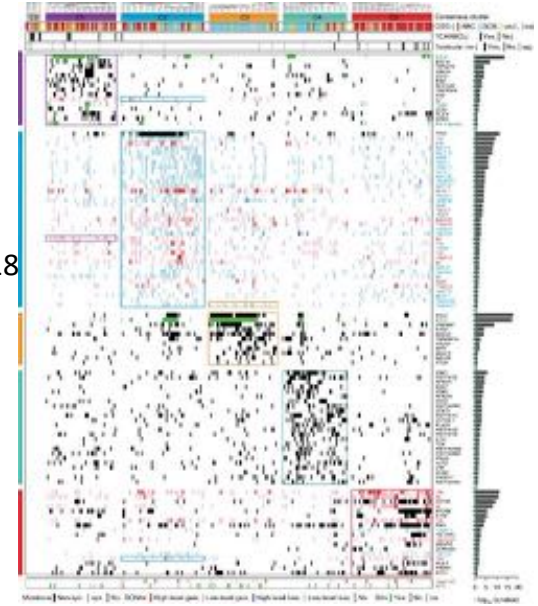




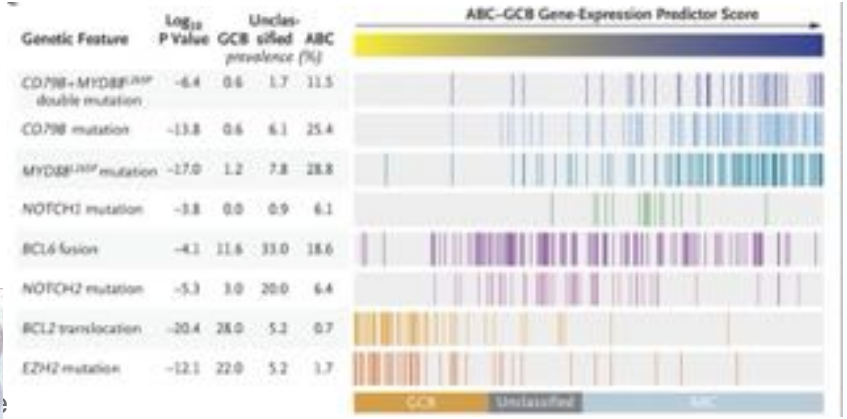
Reddy
Cell 2017

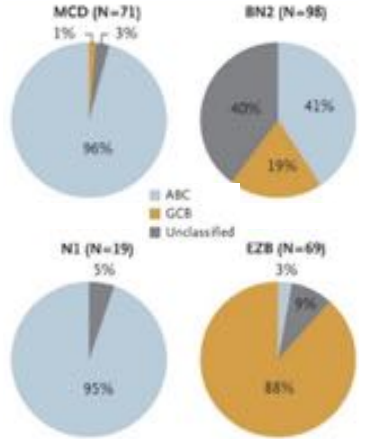


Chapuy
Nat Med 2018

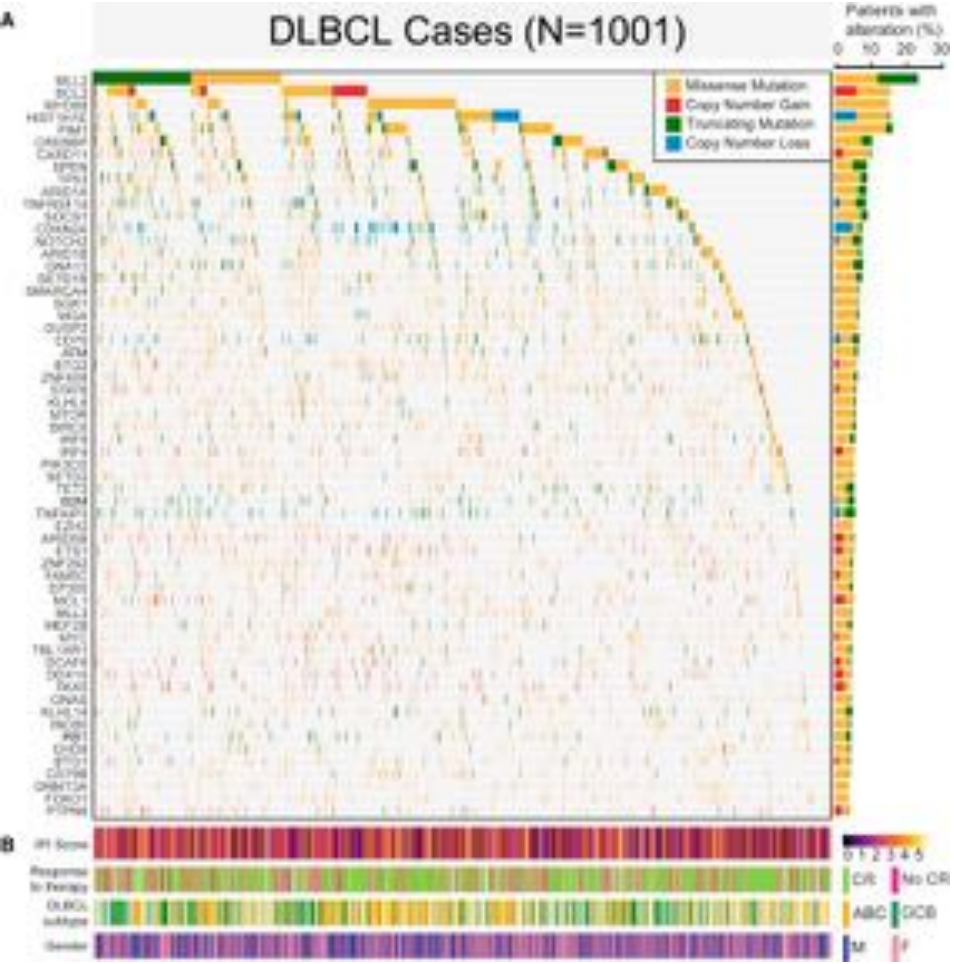


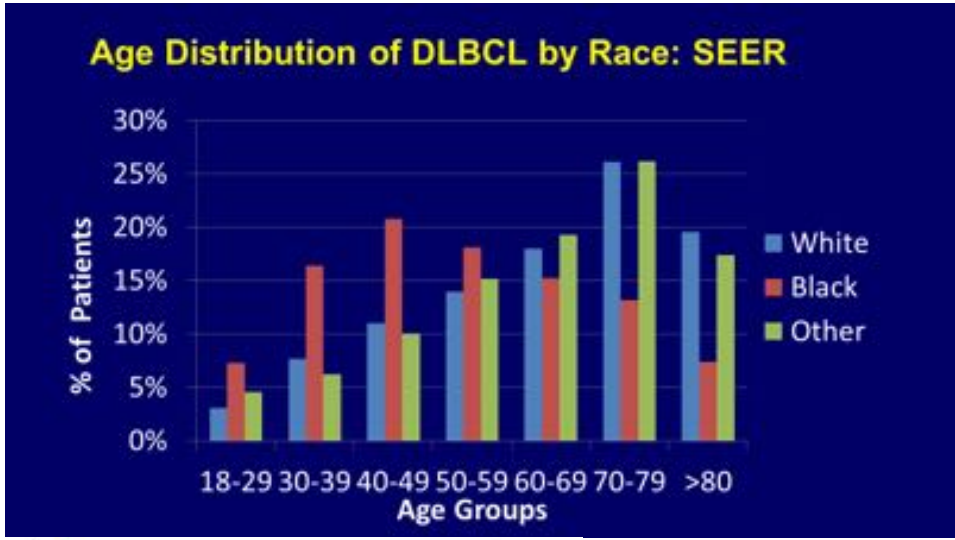
Schmitz NEJM 2018

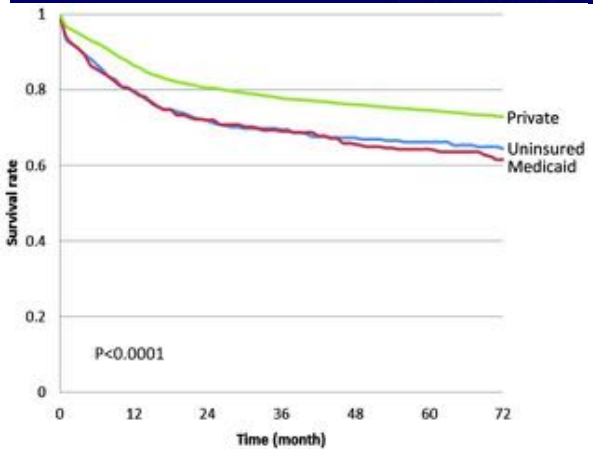




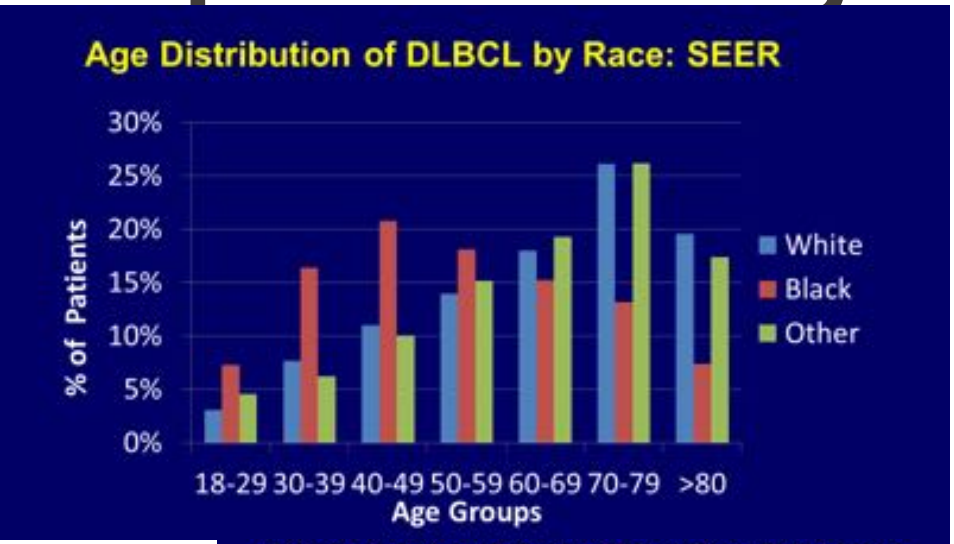
DLBCL Molecular AND Clinical Heterogeneity







Disparities in Lymphoma



African American Present 10 year Younger Across WHO Classified Lymphoid Malignancies

NHL Subtype	ICD-O-3	Median Age White	Black	Other
B-CELL NEOPLASM				
B-cell prolymphocytic leukemia	9833	75.5	57	46.5
Lymphoplasmacytic lymphoma	9671	71	60	69
Follicular lymphoma, NOS	9690	66	56	65
Follicular lymphoma Grade 1	9695	63	58	59
Follicular lymphoma Grade 2	9691	64	60	62
Follicular lymphoma Grade 3	9698	65	55	67
Diffuse large B-cell lymphoma	9680	68	52	66
Immunoblastic diffuse large B-cell lymphoma	9684	60	48	67
Primary effusion lymphoma	9678	58	50.5	
Mediastinal (thymic) large cell lymphoma	9679	35	21.5	39
Burkitt lymphoma	9687	41	39.5	49
T-CELL AND NK-CELL NEOPLASM				
Peripheral T-cell lymphoma, unspecified	9702	65	54	65.5
Classical Hodgkin lymphoma	9650	50	39	41

Disparities in survival by insurance status in follicular lymphoma. Goldstein JS, Nastoupil LJ, Han X, Jemal A, Ward E, **Flowers CR**. *Blood.* 2018 Sep 13;132(11):1159-1166

Impact of Treatment and Insurance on Socioeconomic Disparities in Survival after Adolescent and Young Adult Hodgkin Lymphoma: A Population-Based Study. Keegan TH, DeRouen MC, Parsons HM, Clarke CA, Goldberg D, **Flowers CR**, Glaser SL. *Cancer Epidemiol Biomarkers Prev.* 2016 Feb;25(2):264-73.

Population-specific prognostic models are needed to stratify outcomes for African-Americans with diffuse large B-cell lymphoma. Chen Q, Ayer T, Nastoupil LJ, Koff JL, Staton AD, Chhatwal J, **Flowers CR**. *Leuk Lymphoma.* 2016;57(4):842-51

Racial differences in chronic lymphocytic leukemia. Digging deeper. **Flowers CR**, Pro B. *Cancer.* 2013 Oct 15;119(20):3593-5.

Examining racial differences in diffuse large B-cell lymphoma presentation and survival. **Flowers CR**, Shenoy PJ, Borate U, Bumpers K, Douglas-Holland T, King N, Brawley OW, Lipscomb J, Lechowicz MJ, Sinha R, Grover RS, Bernal-Mizrachi L, Kowalski J, Donnellan W, The A, Reddy V, Jaye DL, Foran J. *Leuk Lymphoma.* 2013 Feb;54(2):268-76.

Disparities in the early adoption of chemoimmunotherapy for diffuse large B-cell lymphoma in the United States. **Flowers CR**, Fedewa SA, Chen AY, Nastoupil LJ, Lipscomb J, Brawley OW, Ward EM. *Cancer Epidemiol Biomarkers Prev.* 2012 Sep;21(9):1520-30

Racial differences in presentation and management of follicular non-Hodgkin lymphoma in the United States: report from the National LymphoCare Study. Nabhan C, Byrtek M, Taylor MD, Friedberg JW, Cerhan JR, Hainsworth JD, Miller TP, Hirata J, Link BK, **Flowers CR**. *Cancer.* 2012 Oct 1;118(19):4842-50.

Racial differences in the presentation and outcomes of chronic lymphocytic leukemia and variants in the United States.Shenoy PJ, Malik N, Sinha R, Nooka A, Nastoupil LJ, Smith M, **Flowers CR**. *CLML* 2011 Dec;11(6):498-506.

Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States. Shenoy PJ, Malik N, Nooka A, Sinha R, Ward KC, Brawley OW, Lipscomb J, **Flowers CR**. *Cancer.* 2011 Jun 1;117(11):2530-40.

Charting the Future of Cancer Health Disparities Research: A Position Statement from the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute. Polite BN, Adams-Campbell LL, Brawley OW, Bickell N, Carethers JM, **Flowers CR**, Foti M, Gomez SL, Griggs JJ, Lathan CS, Li CI, Lichtenfeld JL, McCaskill-Stevens W, Paskett ED. *J Clin Oncol.* 2017 Sep 10;35(26):3075-3082.

Insurance, Socioeconomic Disparities and Survival for Adolescent and Young Adult Hodgkin Lymphoma

Objective

Evaluate impact of sociodemographic characteristics (race/ethnicity, neighborhood SES, and health insurance) on survival among AYAs diagnosed with early- and late-stage Hodgkin lymphoma.

Approach

9,353 AYA patients (15-39 years) \diagnosed with Hodgkin lymphoma (1988 to 2011) from the California Cancer Registry.
Multivariate Cox proportional hazards regression

Keegan et al. Cancer Epidemiol Biomarkers Prev; 2016. 25(2); 264–73

Key Findings

- Improvements in HL-specific survival over time
- In multivariable analyses, HL–specific survival worse for Blacks than Whites with early-stage and late-stage disease and worse for Hispanics than Whites with late-stage disease.
- Worse survival if reside in lower SES neighborhoods.
- Worse survival with public health insurance or uninsured

Keegan et al. Cancer Epidemiol Biomarkers Prev; 2016. 25(2); 264–73

Age at Diagnosis by Race for InterLymph Clustering of WHO Classified Lymphoid Malignancies

NHL Subtype	ICD-O-3	White median Age	Black median Age	Other median age
B-CELL NEOPLASM				
B-cell prolymphocytic leukemia	9833	75.5	57	46.5
Lymphoplasmacytic lymphoma	9671	71	60	69
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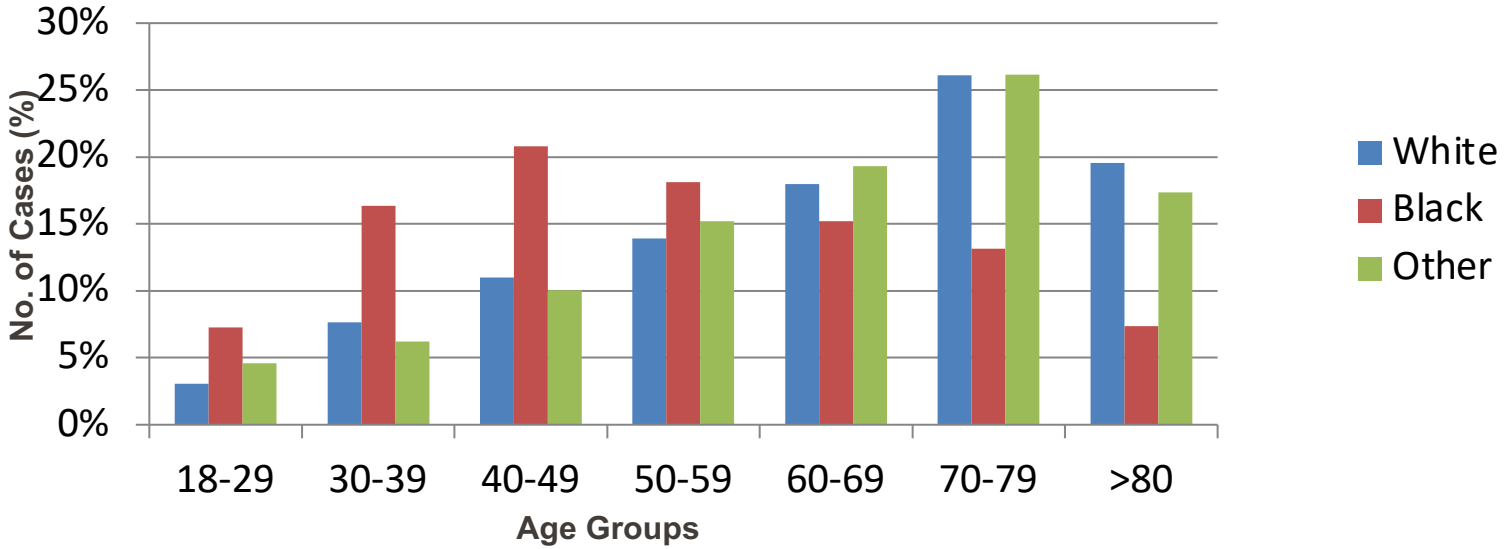
T-CELL AND NK-CELL NEOPLASM				
Precursor T-cell neoplasm				
Peripheral T-cell lymphoma, unspecified	9702	65	54	65.5
HODGKIN LYMPHOMA				
Classical Hodgkin lymphoma	9650	50	39	41
Lymphocyte-depleted classical Hodgkin lymphoma	9653	58.5	43	69

Shenoy et al. Cancer 2011.117(11) 2530-2540

Age distribution of DLBCL by Race



Shenoy et al. Cancer 2011.117(11) 2530-2540

Features at Presentation by Race

Black patients with DLBCL present:

- Younger age
- More Advanced stage
- Worse survival

Black patients with DLBCL:

- More likely uninsured
- More likely Medicaid insured
- Less likely to receive chemoimmunotherapy

Shenoy et al. Cancer 2011.117(11) 2530-2540; ; Flowers et al. Cancer Epidemiol Biomarkers Prev. 2012; Willians et al. Oncology 2020
Keegan et al. Cancer Causes Control. 2018; Ritter et al. Leuk Lymphoma. 2019; Lee et al. Cancer 2020

Disparities in the Early Adoption of Chemoimmunotherapy for Diffuse Large B-cell Lymphoma in the United States

Objective:

To investigate the factors affecting diffusion of chemoimmunotherapy for DLBCL.

Approach:

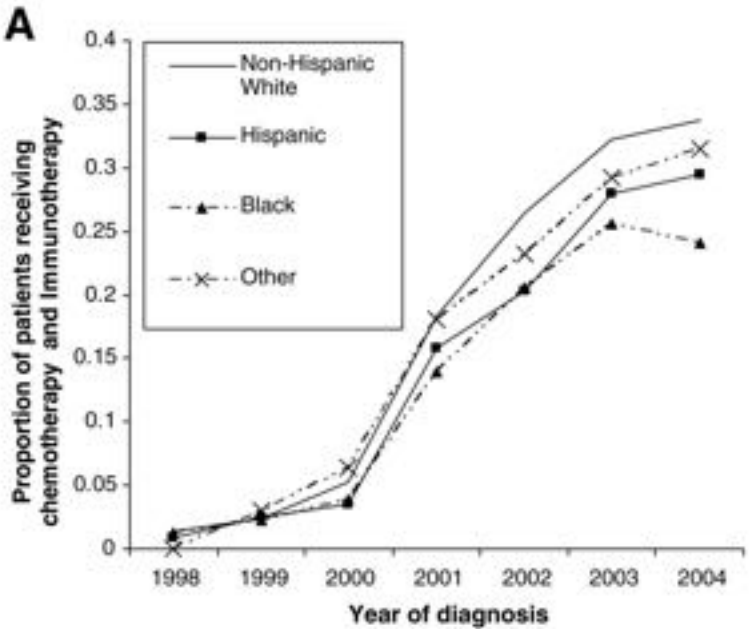
National Cancer Database (NCDB) to compare chemoimmunotherapy use with chemotherapy alone demographics, stage, health insurance, area-level socioeconomic status (SES), facility characteristics, and type of treatment for DLBCL patients diagnosed in 2001–2004.

- Among 38,002 patients with DLBCL, 27% received chemoimmunotherapy and 50% chemotherapy alone.

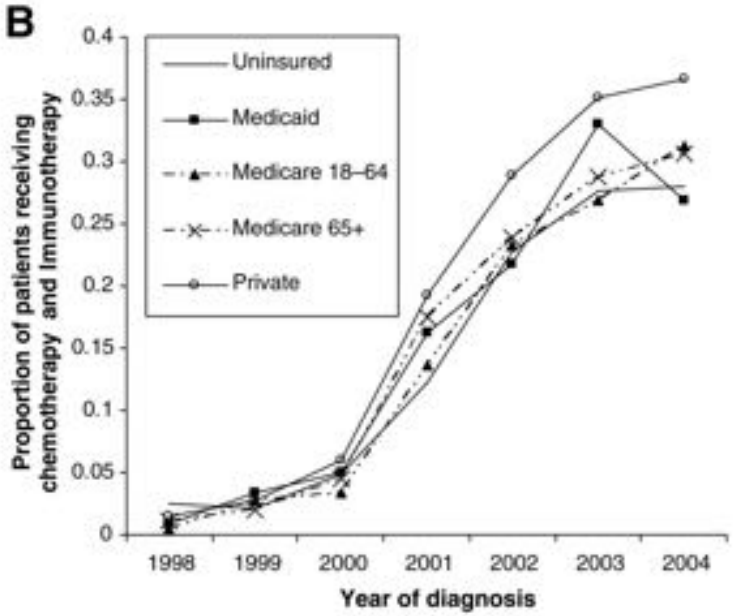
Flowers et al. Cancer Epidemiol Biomarkers Prev. 2012;21(9):1520-1530

Receipt of chemotherapy and immunotherapy

Race/ethnicity

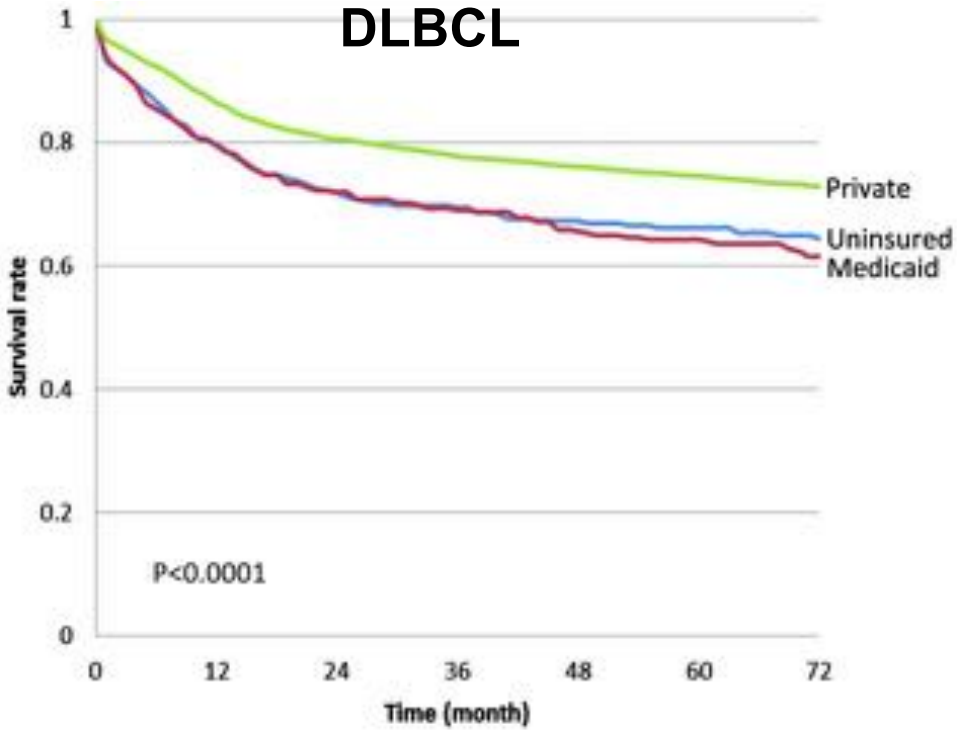


Insurance status



Flowers et al. Cancer Epidemiol Biomarkers Prev. 2012;21(9):1520-1530

Insurance status influences Lymphoma survival



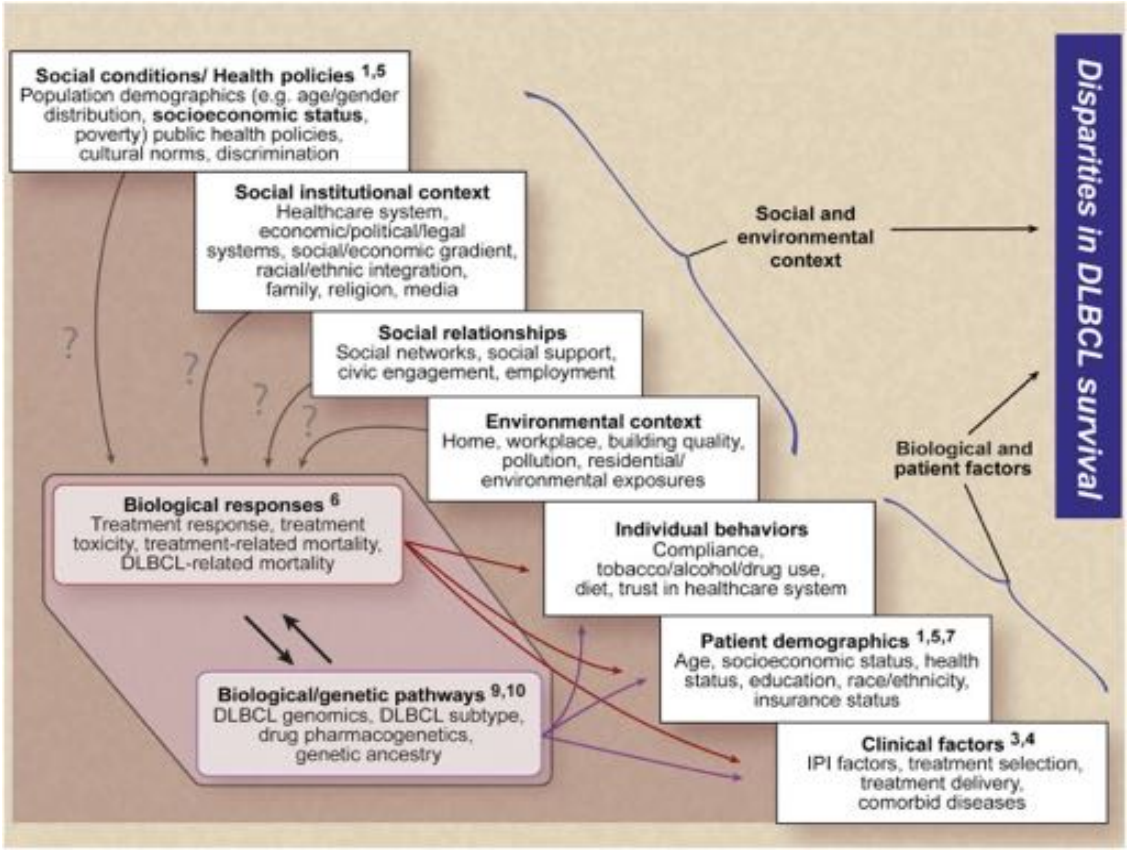
Han *et al. Cancer* 2014

Factor	Model 1	Model 2	Model 3	Model 4
Insurance status				
Private	1	1	1	1
Uninsured	**1.43** (1.18-1.74)	**1.39** (1.14-1.70)	**1.28** (1.05-1.57)	**1.28** (1.05-1.57)
Medicaid	**1.53** (1.29-1.83)	**1.48** (1.23-1.78)	**1.40** (1.16-1.68)	**1.37** (1.14-1.65)
% No HS Degree				
<14		1	1	1
14-19.9		**1.25** (1.05-1.48)	**1.23** (1.04-1.46)	**1.22** (1.03-1.45)
20-28.9		**1.33** (1.12-1.57)	**1.32** (1.11-1.56)	**1.31** (1.10-1.55)
≥29		**1.65** (1.37-1.99)	**1.61** (1.34-1.94)	**1.59** (1.32-1.92)
Stage				
I			1	1
II			1.10 (0.91-1.33)	1.06 (0.88-1.29)
III			1.66 (1.37-2.02)	1.57 (1.29-1.92)
IV			2.43 (2.08-2.84)	2.27 (1.93-2.66)

FL

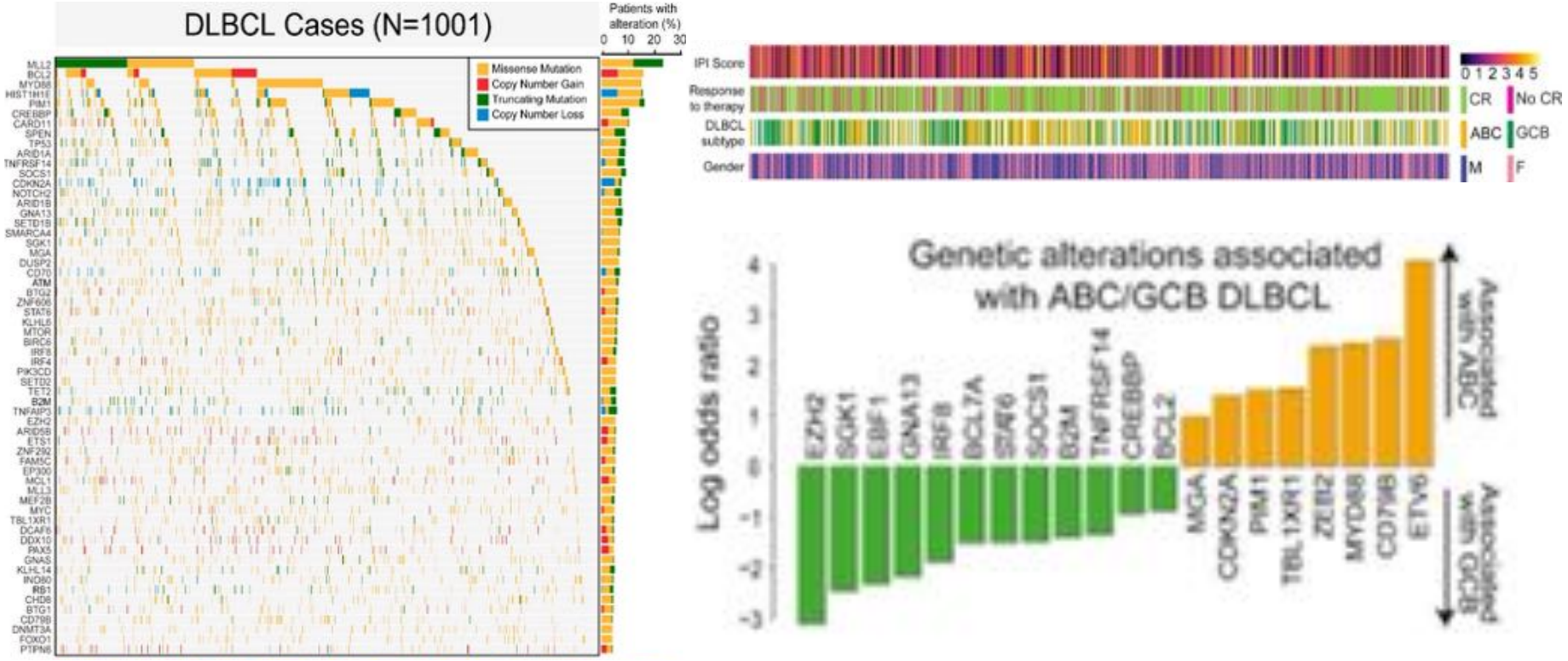
Goldstein et al. *Blood* 2018;132:1159-1166

Social, environmental, biological, and patient-related factors and disparities in DLBCL



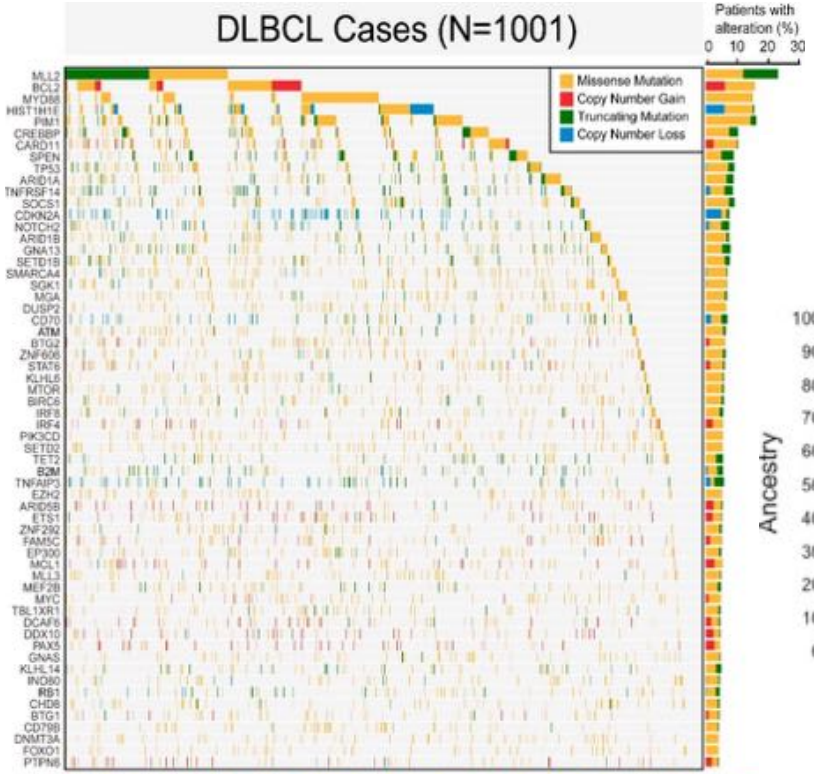
Flowers and Nastoupil. Blood 2014. 123(23):3530-3531

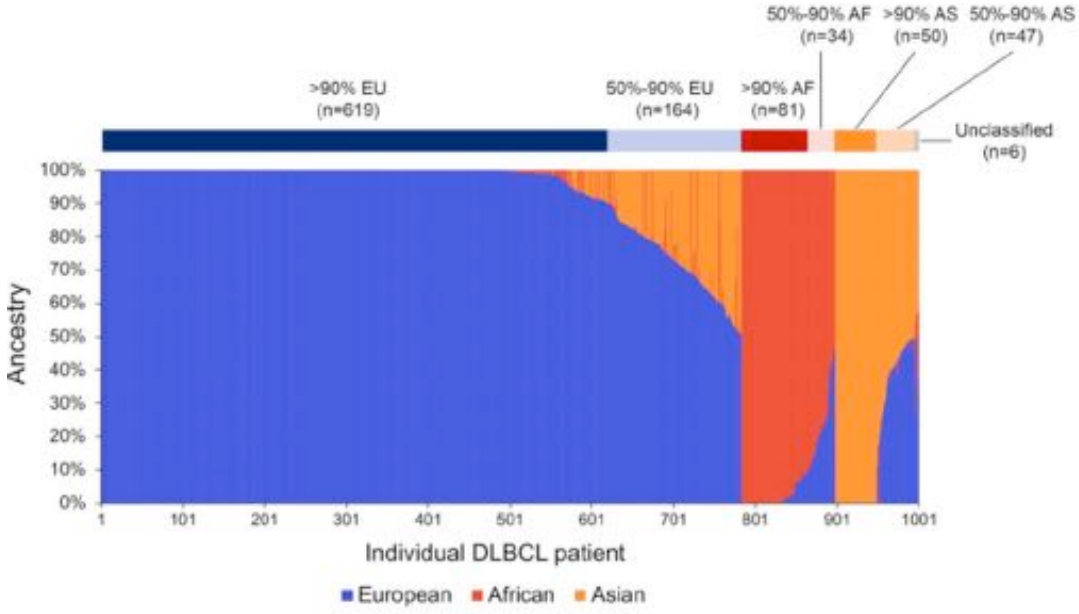
The Landscape of Genetic Drivers in 1,001 DLBCLs



Reddy et al. Cell 2017. 171(2) 481-494

Genetic ancestry analysis of 1001 DLBCL patients from Reddy





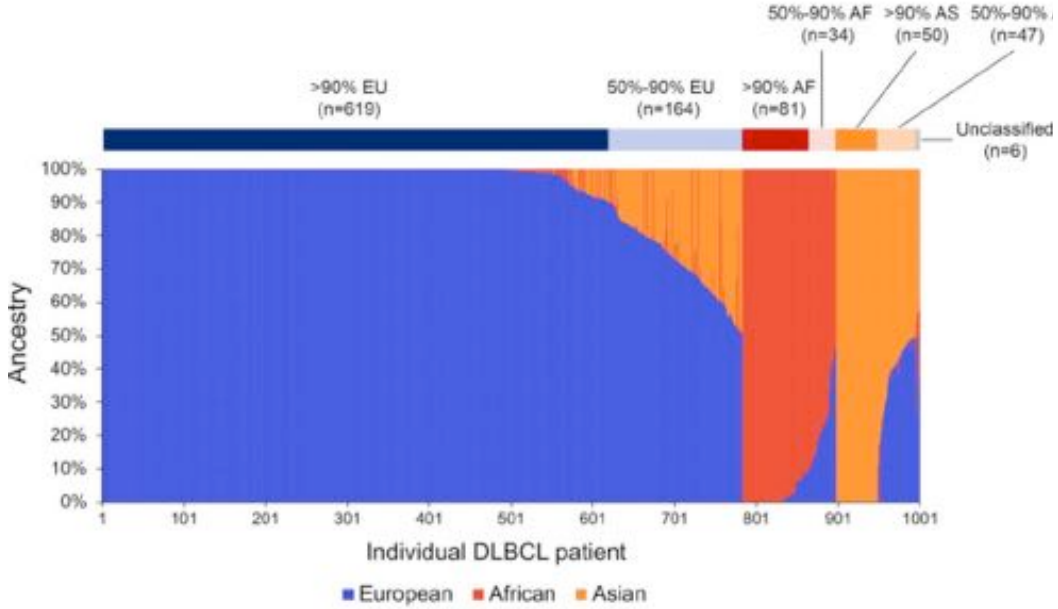
Lee et al. Cancer 2020

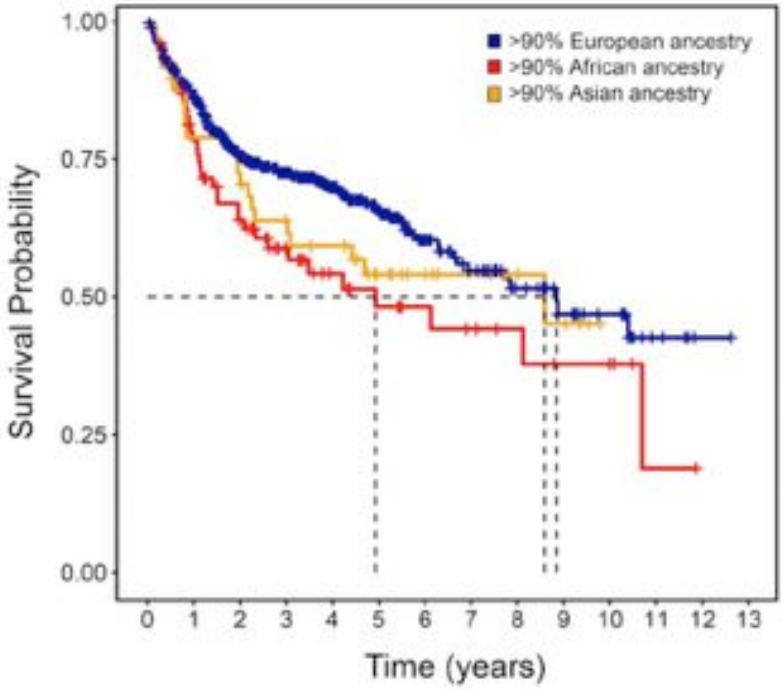
Genetic ancestry analysis of 1001 DLBCL patients from Reddy

Characteristics	No. of Patients (%)								$P^{a,b}$	
	All Patients N = 750		>90% EU N = 619		>90% AF N = 81		>90% AS N = 50		>90% AF vs >90% EU	>90% AS vs >90% EU
Age, y										
Mean	62		63		52		60		**<.001**	.91
≤60	318	(44.5)	244	(41.2)	52	(72.2)	22	(44.0)		
>60	396	(55.5)	348	(58.8)	20	(27.8)	28	(56.0)		
Sex										
Male	420	(56.1)	349	(56.5)	41	(50.6)	30	(60.0)	.38	.81
Female	329	(43.9)	269	(43.5)	40	(49.4)	20	(40.0)		
LDH										
Elevated	363	(54.8)	277	(50.7)	51	(76.1)	35	(71.4)	**<.001**	**.008**
Normal	299	(45.2)	269	(49.3)	16	(23.9)	14	(28.6)		
Stage of disease (Ann Arbor)										
I/II	277	(38.1)	242	(40.3)	18	(23.7)	17	(34.0)	**.007**	.47
III/IV	450	(61.9)	359	(59.7)	58	(76.3)	33	(66.0)		
ECOG PS										
0-2	488	(71.9)	396	(71.4)	51	(68.9)	41	(82.0)	.77	.15
3-4	191	(28.1)	159	(28.6)	23	(31.1)	9	(18.0)		
>1 Extranodal sites										
Yes	166	(23.8)	121	(20.6)	29	(46.8)	16	(34.0)	**<.001**	.05
No	531	(76.2)	467	(79.4)	33	(53.2)	31	(66.0)		
B symptoms										
Yes	252	(35.9)	205	(35.0)	28	(41.2)	19	(38.8)	**.001**	.71
No	450	(64.1)	380	(65.0)	40	(58.8)	30	(61.2)		
Subtype										
ABC	239	(40.0)	202	(39.8)	21	(42.9)	16	(40.0)	.31	.57
GCB	261	(43.7)	232	(45.7)	17	(34.7)	12	(30.0)		
Unclassified	97	(16.2)	74	(14.6)	11	(22.4)	12	(30.0)		

Lee et al. Cancer 2020

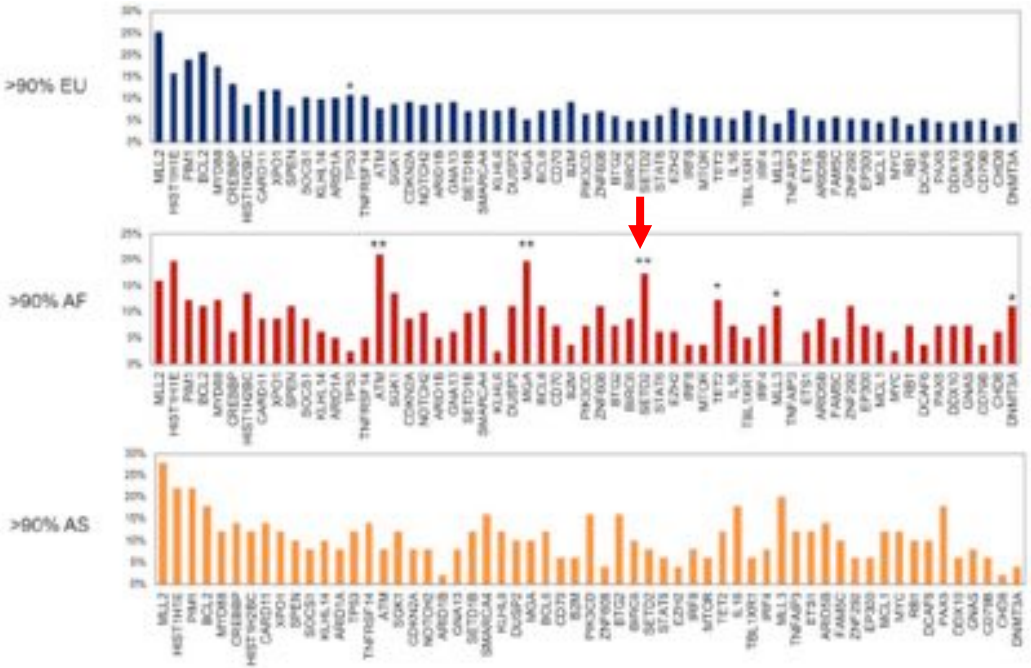
Genetic ancestry analysis of 1001 DLBCL patients from Reddy



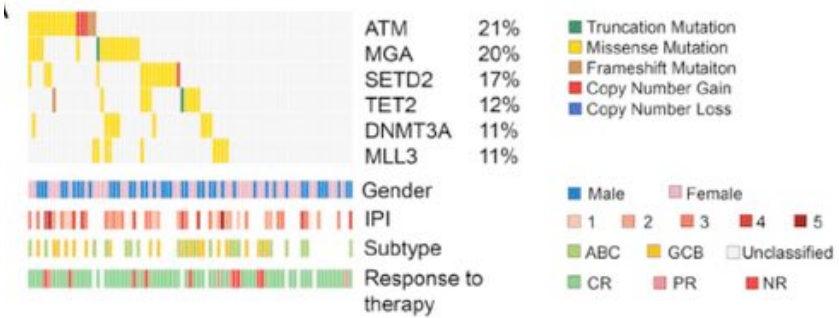


Lee et al. Cancer 2020

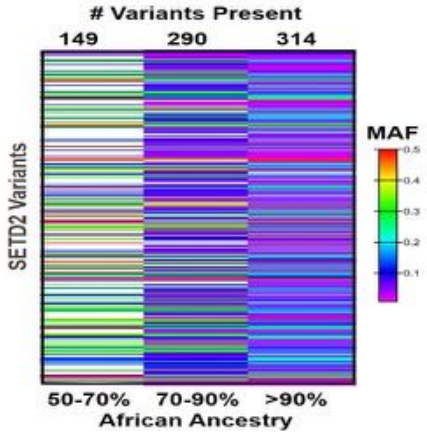
Genetic ancestry analysis of 1001 DLBCL patients from Reddy



Mutational analysis of 150 DLBCL driver genes



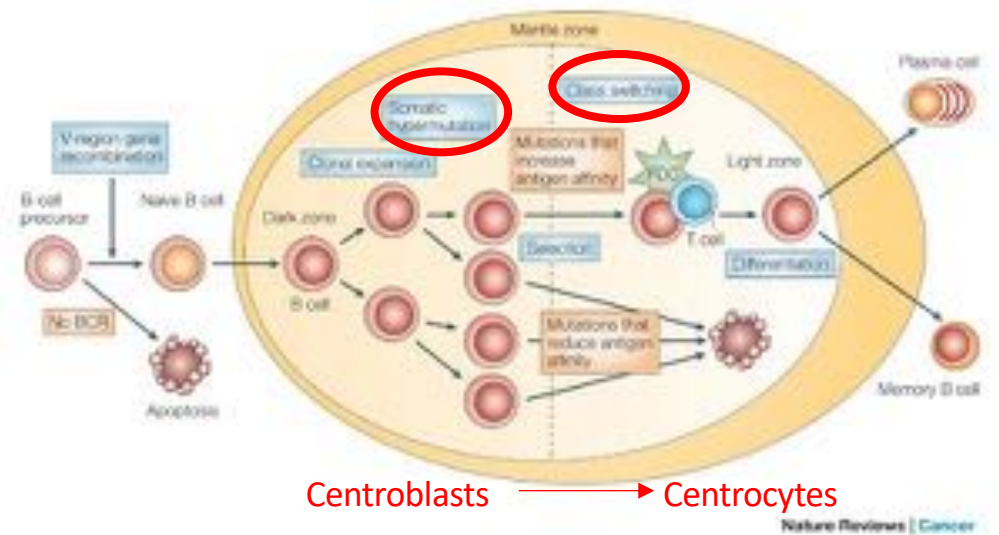
***SETD2* variants increase in number and decrease in MAF with increased African ancestry**



Lee et al. Cancer 2020

SETD2: Sole methyl transferase for H3K36m3 methylation

- SETD2 -/- = tumor suppressor
- **SETD2 +/-** = typical SET2 mutation in DLBCL
- **SETD2 +/-** = hyperplasia, competitive fitness & reduces checkpoint & apoptosis
  associated with ↑ AICDA somatic hypermutation, ↑ translocations *(Activation Induced RNA Cytidine Deaminase*
  Changes C:G into U:G mismatch, converting it to a T:A base pair; also converts C:G to A:T)
  ↑ non template strand H3K36me3 loss = DNA damage in non-template strand
  = greater RNA Pol II processivity
  = ↑ mutational burden



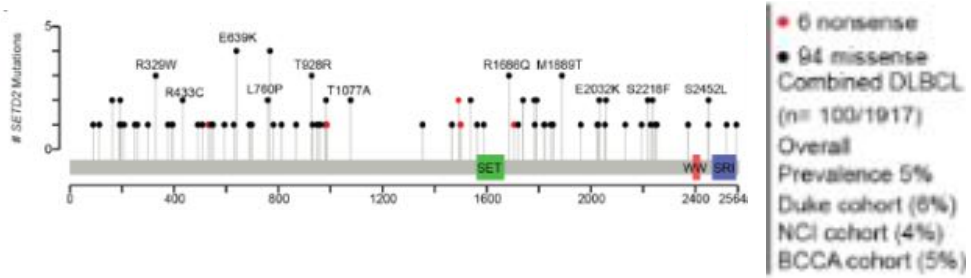
Centroblasts → Centrocytes

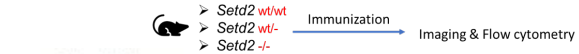
Dark zone → Light zone

Küppers R. et al. Nat Revs Cancer 2005

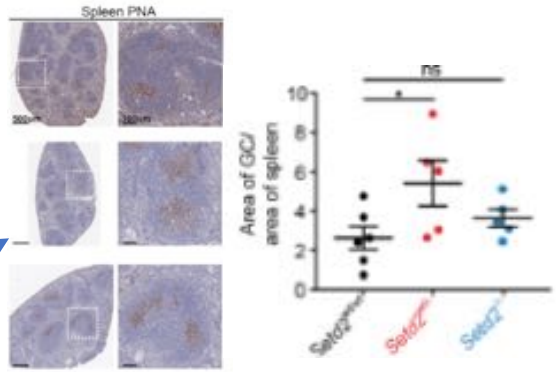
1. Setd2 haploinsufficiency induces GC hyperplasia and dark zone polarization

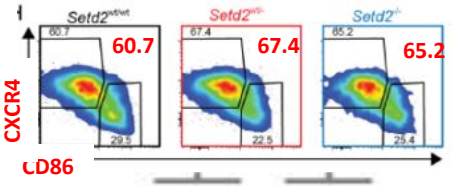
Available genomic profiling datasets **(n=1917 DLBCLs)** revealed the presence of missense (94%) and nonsense (6%) mutations of *SETD2* in 5% of cases overall):



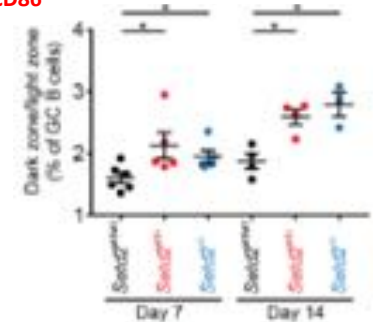


Enlarged GC in het, but not -/-





DZ polarization in both het, & -/-



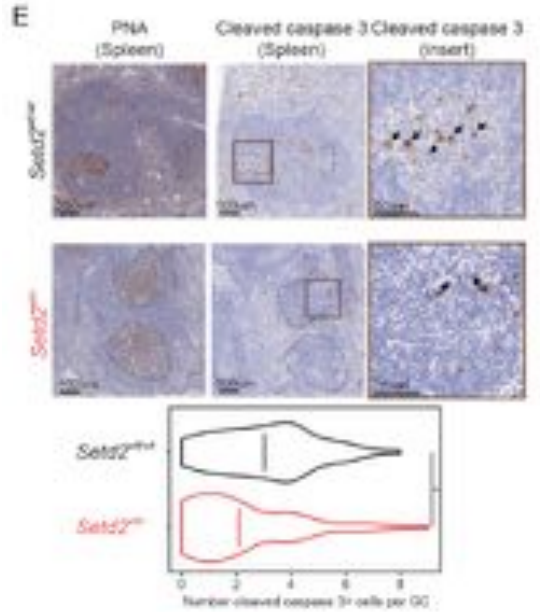
We focused in Setd2 +/- :

1. haploinsufficiency resulted in a **distinct** and **more clearly pre-neoplastic phenotype** than homozygous deletion, and
2. homozygous loss is deleterious to DLBCL cells
3. Failed to get homozygous human DLBCL cell lines (4/5)

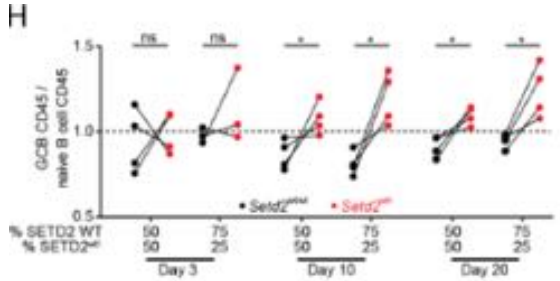
2. Setd2wt/- confers a fitness advantage to GCB cells, associated with reduced rates of apoptotic cell death

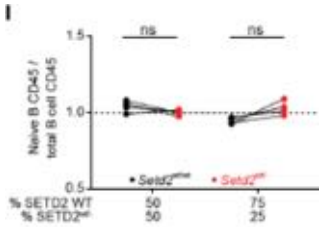
3. And with impaired DNA damage sensing

↓ Casp3 cleavage in GCs (also ↓ Annexin V)



In Mixed Chimeras: growth advantage for Set +/- GC B-cells (but no advantage for naiive B-cells)



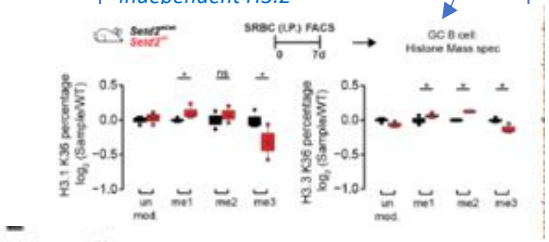


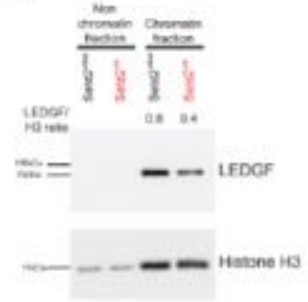
In Setd2+/- GC B cells:

↓ γH2AX DNA damage marker (but decrease only in non-dividing GC B cells)

↓ CHK1 phosphorylation (normally triggered by ssDNA damage during SHM)

↓ H3K36m3 in both replication dependent H3.1 and replication-independent H3.2



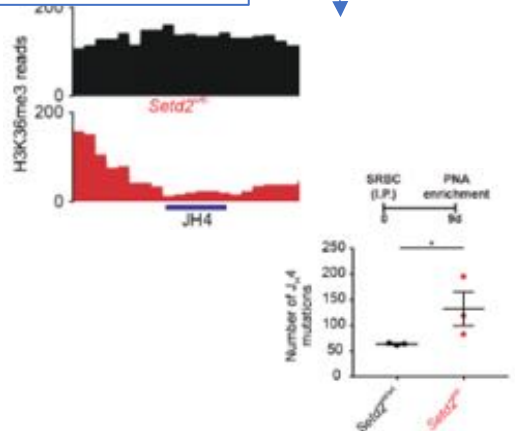


↓ LEGGF bound to chromatin (and consequently less H4K16 ac)

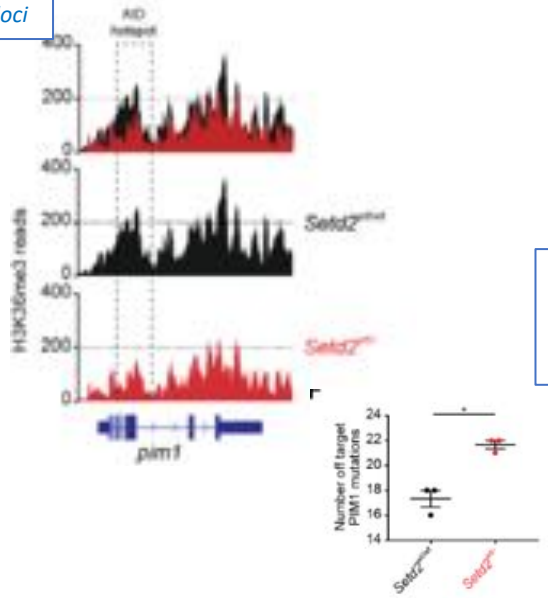
3. H3K36me3 loss is associated with increased SHM and off target AICDA mutations

AICDA
- SHM at Ig loci: eg: Ig J_H4 variable region
- Off target mutations at accessible chromatin (canonical targets include DLBCL oncogenes; eg. *PIM1*)

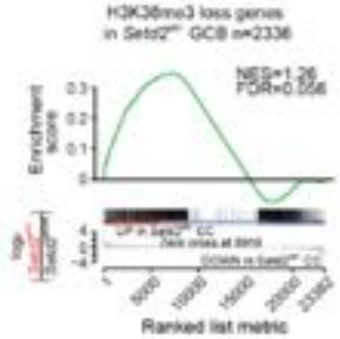
↓ H3K36m3 at J4H locus = ↑ # mutations at loci



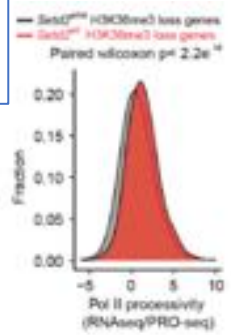
↓ H3K36m3 at PIM1 = ↑ # mutations at loci



↓ H3K36m3 in GC B cells = ↑ enriched induction of expression



↓ H3K36m3 = ↑ RNA Pol II Processivity (perturbing tx-coupled DNA damage sensing?)



AICDA: Activation –induced cytidine deaminase

4. *Setd2* haploinsufficiency results in accelerated lymphomagenesis: *Setd2 as tumor suppressor*

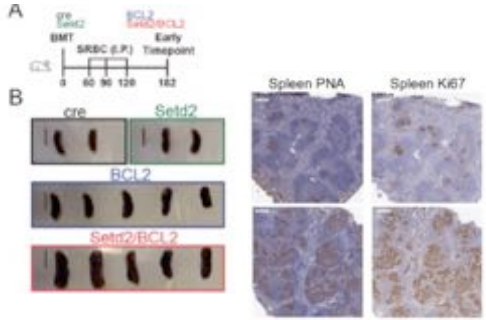
- Publicly available RNAseq datasets confirm BCL2 is highly expressed in *SETD2 mut* DLBCL patients
- Mouse model showed acceleration & dissemination of lymphomagenesis → highly malignant & invasive high grade DLBCL

Setd2 +/- strain x *Rosa26*lox-stop-lox-BCL2-IRES-GFP strain

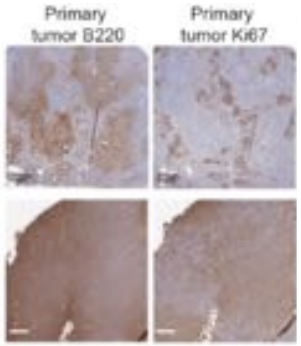
4 mouse strains

- Setd2/BCL2
- BCL2
- Setd2
- cre

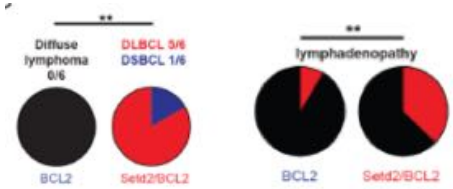
Setd2/BCL2 = enlarged spleens & disrupted GCs



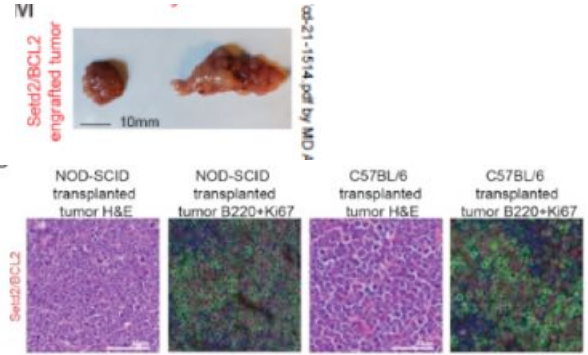
Setd2/BCL2 = total effacement of lymphoid tissue architecture



Setd2/BCL2 = 100% diffuse lymphoma penetrance & adenopathy

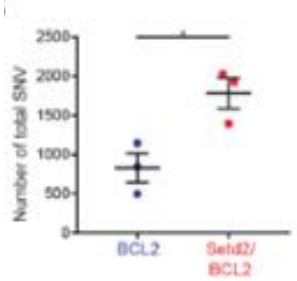


These lymphomas were distributed across the board as GCB, ABC and unclassified based on the cell of origin classification system & could be engrafted into RAG1 KO, NOD-SCID and C57BL/6 (immunocompetent) mice



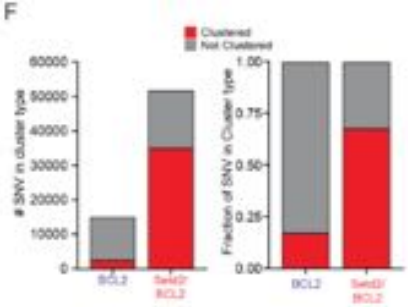
5. SETD2 lymphomas display a high abundance of clustered AICDA signature mutations skewed to non-template strand DNA.

Setd2/BCL2 = significant increase in global abundance of SNVs

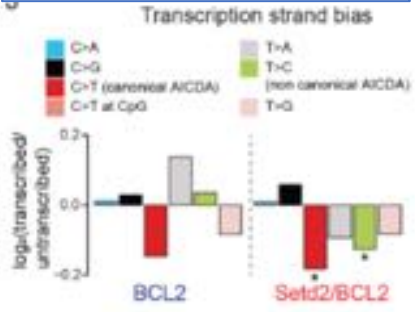


Setd2/BCL2 = 30 genes w/ exonic non-synonymous mutations, including canonical AICDA off target genes (vs. only 5 in BCL2)

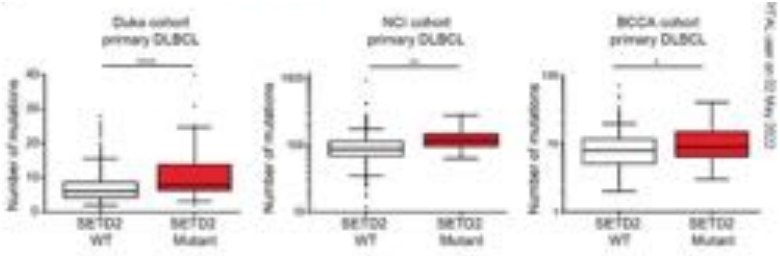
Setd2/BCL2 = mutations mainly due to clustered SNVs (<1kb)



Setd2/BCL2 =Off targeted AICDA mutations target non-transcribed strand= assoc. w/ Pol II elongation



Cohorts of human DLBCL patients also show increased SNVs in tumors that are SETD2 mutants



1679

A Phase 1/1b Open-Label, Multicenter, Two-Part Study of SETD2 Inhibitor EZM0414 in Patients With Relapsed/Refractory Multiple Myeloma or Diffuse Large B-Cell Lymphoma

Paul G. Richardson, MD[1]; Ruben Niesvizky, MD[2]; Richard Lin, PhD[3]; Neelu Yadav, PhD[3]; Yingxue Chen, PhD[3]; Coya Tapia, MD, PhD[3]; Helen Hsu, MD[3]; Christopher R. Flowers, MD[4]

[1]Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY; [3]Epizyme, Inc., Cambridge, MA; [4]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

OBJECTIVE

INTRODUCTION

Figure 1. SETD2 Therapeutic Target in Multiple Myeloma

METHODS

Study Design

Figure 2. SET-101 Study Design

Figure 3. MTD Workflow

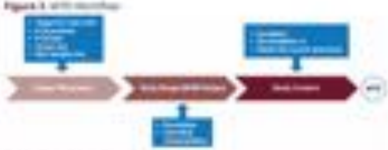


Figure 4. Dose Escalation Workflow

Endpoints

Translational Plan

METHODS, cont'd

Patient Population

CURRENT STATUS

References

Acknowledgments

Author Disclosures

(U01 CA195568) # The Lymphoma Epidemiology of Outcomes Cohort Study

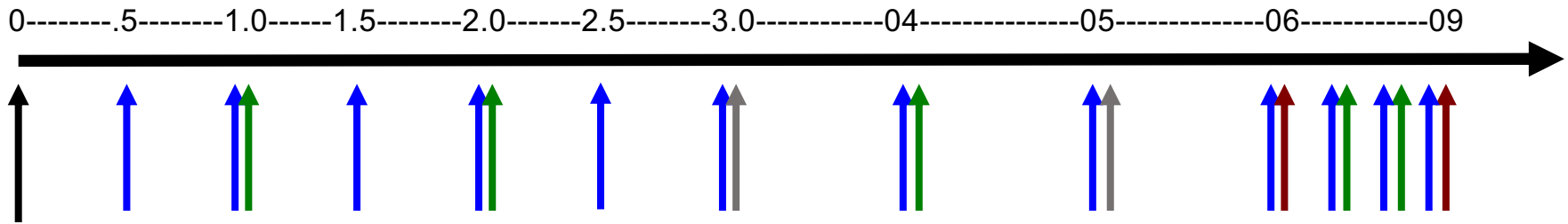
Chris Flowers MD, MS

Jim Cerhan MD, PhD

GOAL:

TO FACILITATE RESEARCH THAT USES **LEO** INFRASTRUCTURE AND SUPPORTS INTERACTION WITH LYMPHOMA TRIALS

LEO Study Design & Protocol



Baseline Enrollment:
(≤ 6 months from Dx)
Comorbidities
QoL (e.g. FACT-G, LASA)
Clinical & Path Data
Treatment
DNA & Serum
FFPE

Disease progression/ recurrence, 2nd cancer, MDS, new morbidity, death.
Validate new events.
Dr followup annually

FU 3 years / 5 years
QoL
Psychosocial
Health Behaviors
CAM
Screening

QoL

FU 6 9 & 12 years
QoL
Psychosocial
Health Behaviors

Medidata rave

LEO Lymphoma Epidemiology of Outcomes

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LEO

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SYLVESTER COMPREHENSIVE CANCER CENTER UNIVERSITY OF MIAMI HEALTH SYSTEM

Weill Cornell Medical College

LEO Overview

Figure A1. Schematic of the LEO Cohort Study, 2002-2026

LEO Cohort	2002	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
LEO-MER Subcohort	Enrollment† (N=4856)	Follow-up protocol*¶											
LEO - First 5 Years		Enrollment† (N=7781)						Follow-up protocol*§					
LEO - Renewal 5 Years									New Targeted Enrollment (N~3400)				
Funding Source	SPORE + other	U01 CA195568 + Bridge Funding‡						X	2U01 CA195568-A1				

†Baseline enrollment includes *Enrollment* and *Risk Factor* Questionnaires; clinical abstraction; plasma, serum, and DNA banking; pathology

*Follow-up every 6 months for the first 3 years, then annually thereafter for new events; survivorship survey at Follow-up 3 years after diagnosis

¶Survivorship Surveys at Follow-up 6 and 9 years

§Survivorship Surveys at Follow-up 3 and 5 years

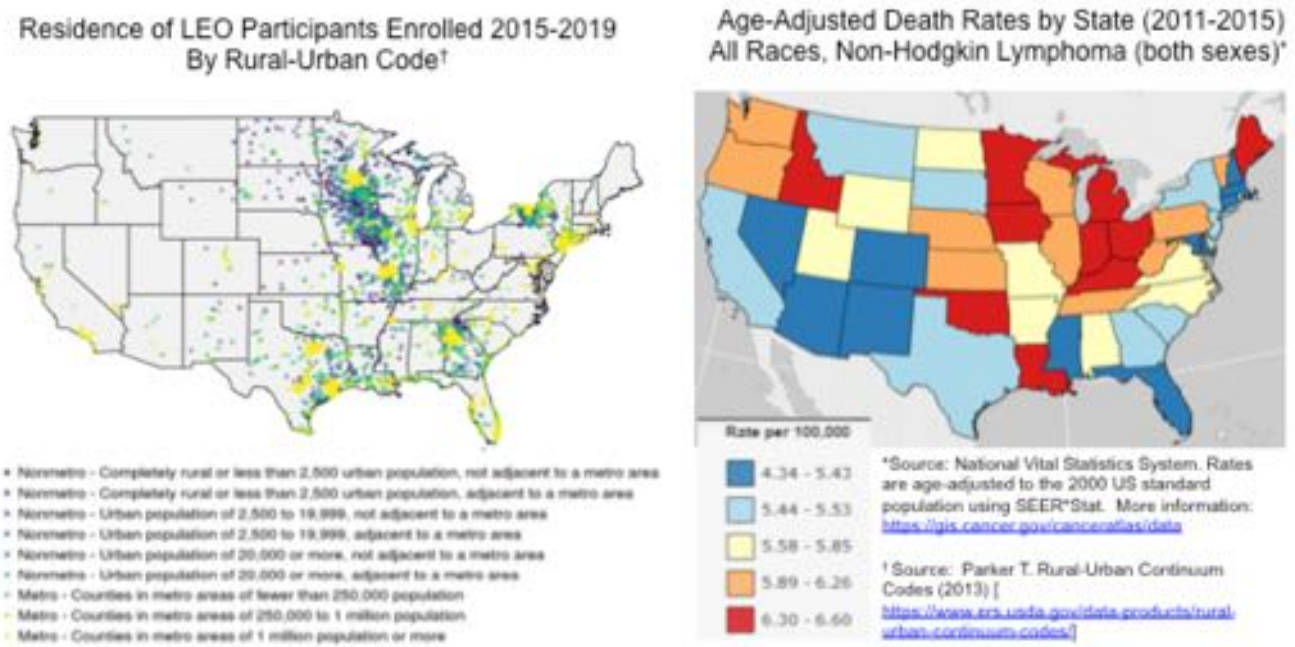
‡Bridge funding only covered basic maintenance of cohort (biorepository and data center) and follow-up

LEO Enrollment Reflects Demographics for Lymphoma in US

Comparison of LEO and SEER		
	LEO	SEER
	2015-2016	2011-2015
Gender: Female	44.1%	44.7%
Race: White	85.0%	83.1%
Black	7.4%	7.5%
Asian	2.6%	7.1%
>1 Race	3.5%	0.5%
Ethnicity: Hispanic	9.9%	13.1%
Age: <40 years	9.8%	6.9%
40-49	11.9%	8.4%
50-59	22.3%	17.6%
60-69	28.9%	25.1%
70-79	20.2%	23.5%
80+	6.8%	18.5%
Subtype: DLBCL	33.9%	37.2%
Follicular	22.2%	17.7%
Mantle cell	9.3%	4.5%
Marginal zone	8.3%	10.7%
PTCL	10.9%	10.2%
Other NHL	15.3%	19.6%

Addresses Rural Populations and High Mortality Regions

US NHL Mortality Rates and Residence at Diagnosis of LEO Cohort



Flowers et al. ASH Abstract 2018

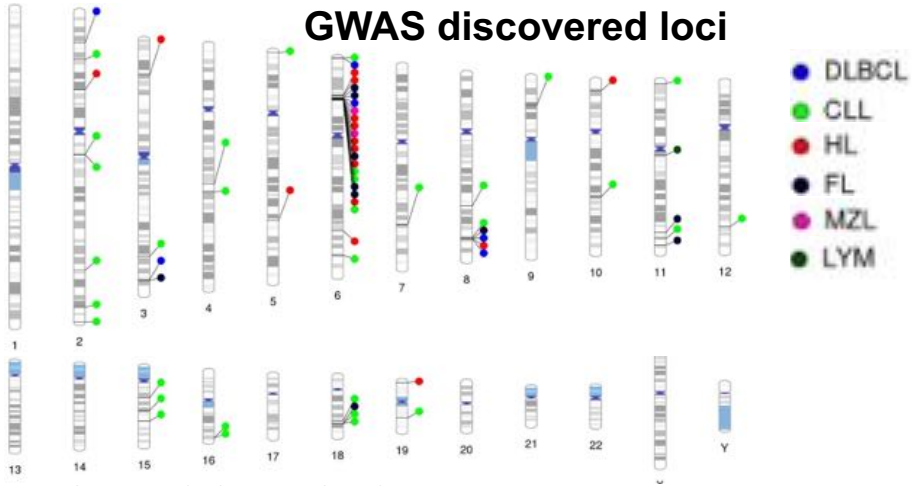
InterLymph
International Lymphoma Epidemiology Consortium

Identifying risk factors for Lymphoid Malignancies

DLBCL Risk Factors	OR	95% CI
B-cell activating autoimmune disease	2.36	1.80-3.09
Hepatitis C virus seropositivity	2.02	1.47-2.76
Family history of NHL	1.95	1.54-2.47
Higher young adult body mass index (≥35 vs 18.5 to 22.4 kg/m^2)	1.58	1.12-2.23
Field crop/vegetable farm worker	1.78	1.22-2.60
Hair dresser	1.65	1.12-2.41
Seamstress/embroiderer	1.49	1.13-1.97

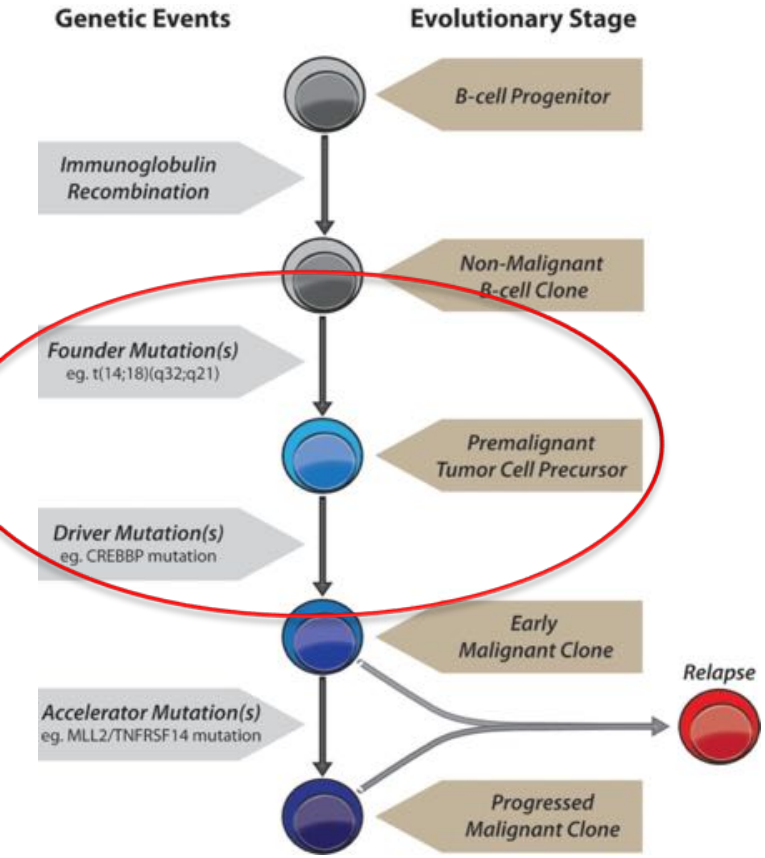
Cerhan et al. *J Natl Cancer Inst Monogr.* 2014

- 11 NHL subtypes; primary site of disease
- 23,096 controls : 14,129 cases
- 13 publications *JNCI Monograph* 2014
- Genome Wide Association studies of risk (GWAS)



Cerhan and Slager *Blood* 2015

Precursor Targeted Trials in At Risk Populations



Michael R. Green et al. Blood 2013;121:1604-1611

Identifying Individuals at Risk for FL

FL Risk Factors	OR	95% CI
women with Sjögren syndrome	3.37	1.23-9.19
spray painters	2.66	1.36-5.24
1° relative with NHL	1.99	1.55-2.54
↑young adult BMI per 5 kg/m^2 ↑	1.15	1.04-1.27

Linet et al. *J Natl Cancer Inst Monogr.* 2014

GWAS discovered loci (future)

- MHC Class I and II: 6p21.33, 6p21.32, (rs17203612), (rs3130437, near *HLA-C*), DRβ1
- Outside of HLA region: 11q23.3 (near *CXCR5*), 11q24.3 (near *ETS1*), 3q28 (in *LPP*), 18q21.33 (near *BCL2*), and 8q24 (near *PVT1*)

Cerhan and Slager *Blood* 2015

Precursor Screening At Risk Individuals

- e.g. t (14;18) + CREBBP mutation

Targeted Low Toxicity Therapy in At Risk Individuals

- e.g. HDAC3i

Research Leaders in Lymphoma/Myeloma

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Translational

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Myeloma

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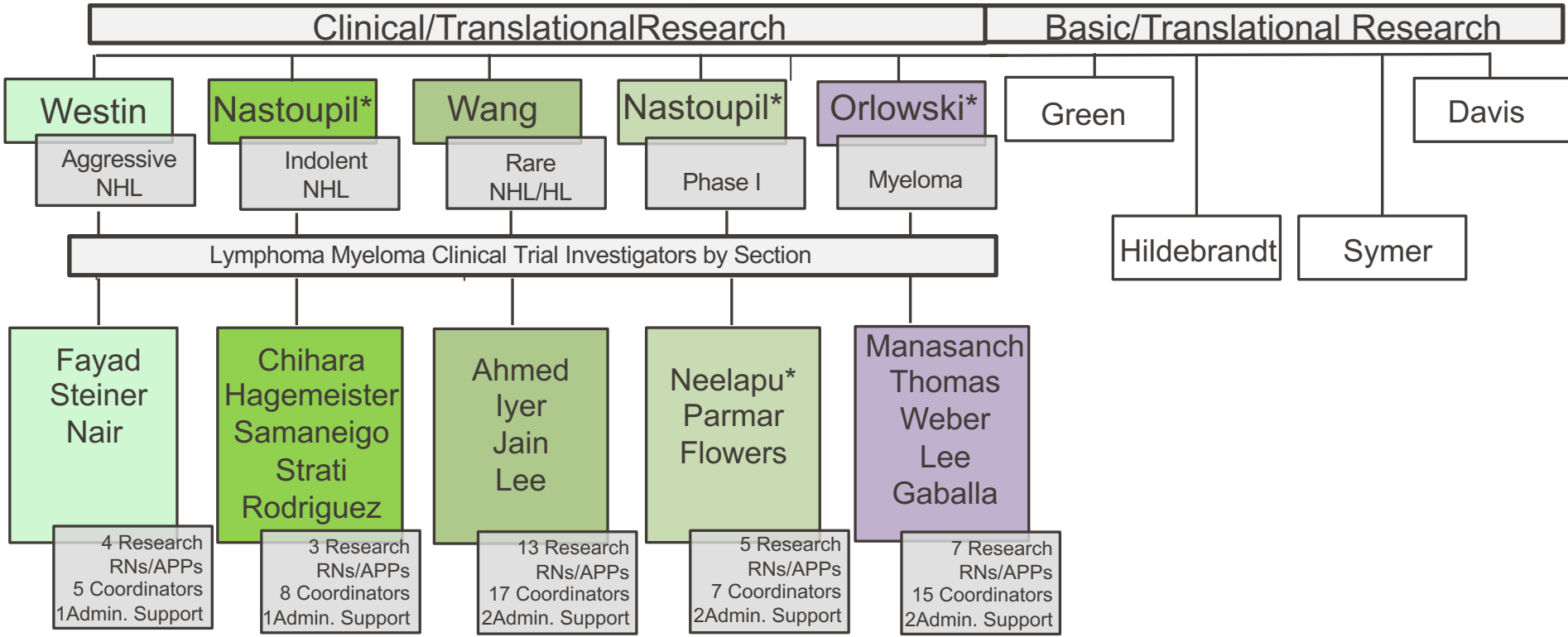
Research Leaders in Lymphoma/Myeloma



*Deputy Chair

Thank you!

Lymphoma Epidemiology of Outcomes

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K24CA208132
U01CA220401

Informatics Tools for Quantitative Digital Pathology Profiling and Integrated Prognostic Modeling (U01 CA220401)

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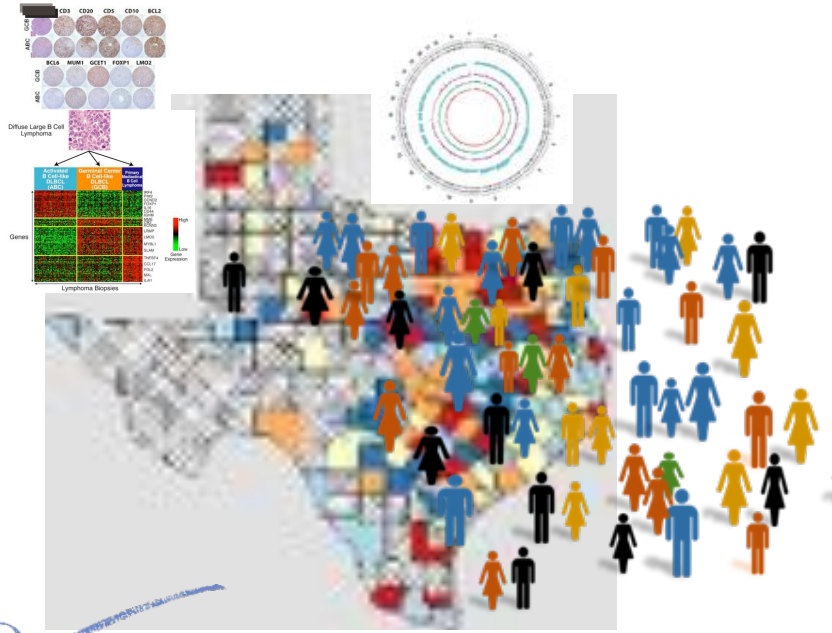

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Christopher Flowers, MD, MS, FASCO
Chair, Professor
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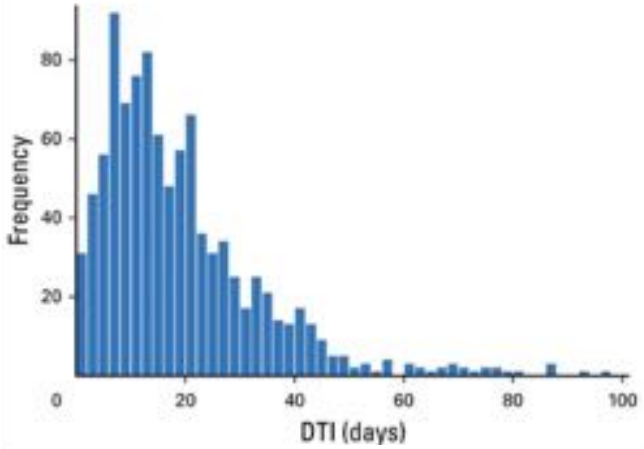
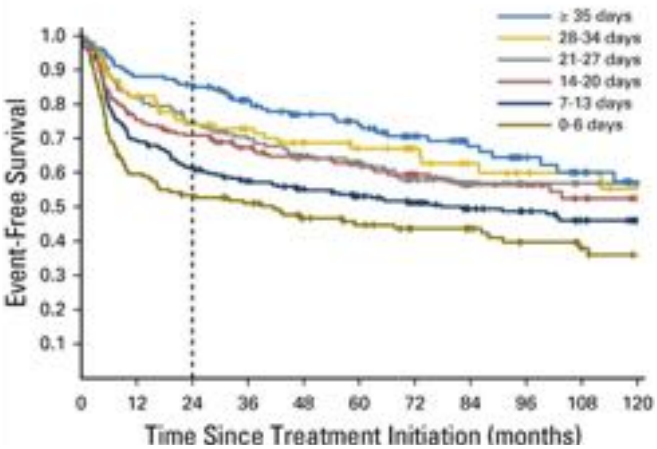
Contact: crflowers@mdanderson.org

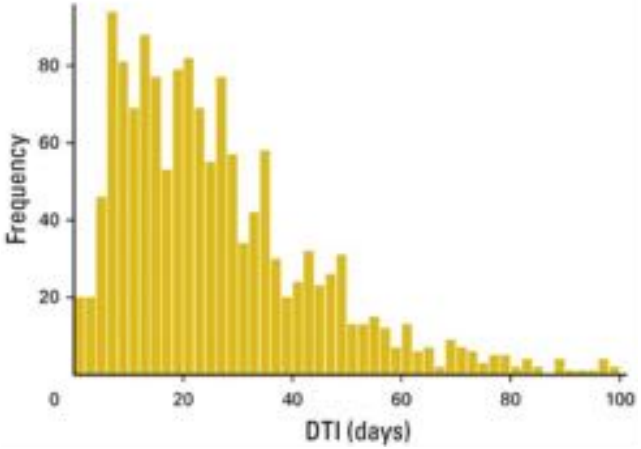
Diagnosis-to-Treatment Interval Is an Important Clinical Factor in Newly Diagnosed DLBCL and Has Implication for Bias in Clinical Trials

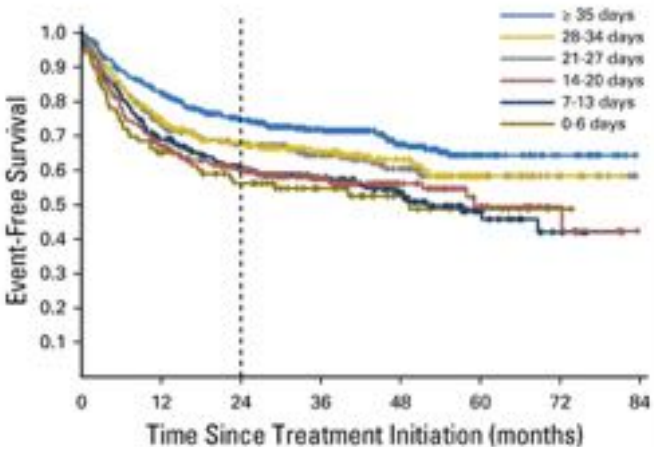
Mayo/Iowa DLBCL Cohort
(n=986)





LYSA DLBCL Cohort
(n=1446)





Maurer *J Clin Oncol.* 2018

Barriers to Clinical Trial Participation

- **Patient Issues**
  - Disinterest - “I don’t want to be a guinea pig”
  - Distance - “ I don’t live close to any site”
  - Debt - “ I cannot afford to come” - Dr. Barbara Bierer’s presentation
  - Distrust - “ I’ve done my own research and…”
- **Doctor, Institutional, or Insurance issues**
  - Time - “we are too busy”
  - Trial cost reimbursement - “we will lose money”
  - “My insurance company said I can only talk to you - no tests, no treatment and no trial” ☹

Barriers to Clinical Trial Participation

- **Pharmaceutical Industry**
  - No interest in that group of patients
  - Drug is going off patent
- **Government – National Clinical Trials Network**
  - CTEP “We do not have enough money to fund the trial”
  - NCTN Sites “I don’t think my site can accrue to that patient group - its not worth opening”
- **Bias against a people group or bias against an idea**
  - Subject of Dr. Barrett’s presentaiton

Protocol Design

- **Relevant issue?**
  - Is the problem important for patients or society? Worth it?
- **Do we have what it takes to answer this question?**
  - Technical advances can make an old idea now feasible
- **“Can we do it ourself or does it need NCTN?**
  - Ex. NCTN mantle cell trials - relevant questions that require the entire US
- **What is the optimal design? Dr. Winderlich’s talk**
- **“What do patient advocates thing? Would patients be interested**

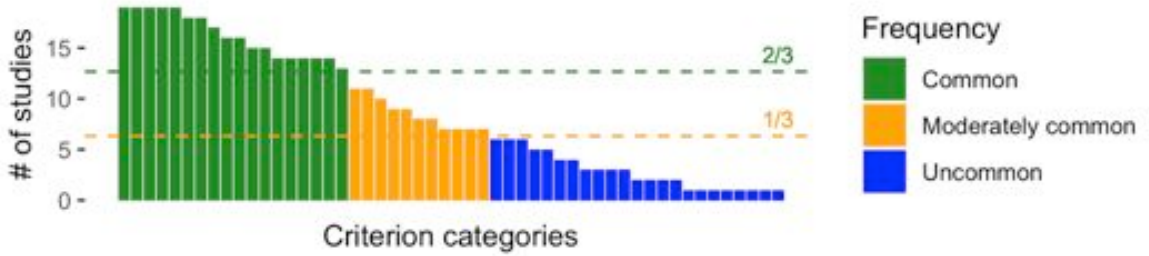
RCTs in DLBCL (n=19)

Study	Identifier	Accrual start year	Treatment	Reference
LNH 98-5	LYSARC	1998	CHOP21; R-CHOP21	Coiffier et al. (2002), Feugier et al. (2005), Coiffier et al. (2010)
E4494	NCT00003150	1998	CHOP21; R-CHOP21; 2nd Rand Observation; Rituximab	Habermann et al. (2006)
LNH 98-3	NCT00169169	1999	ACVBP; ACE; 2nd Rand Observation; Rituximab	Haioun et al. (2009)
RICOVER-60	NCT00052936	2000	6 cycles CHOP14; 8 cyclesCHOP14; 6 cycles R-CHOP14; 8 cycles R-CHOP14	Pfreundschuh et al. (2008)
MINT	NCT00064116	2000	CHOP-like; R-CHOP-like	Pfreundschuh et al. (2006) and (2011)
MegaCHOEP	NCT00129090	2003	R-CHOEP14; R-MegaCHOEP	Schmitz et al. (2012)
Anzinter 3	NCT01148446	2003	R-CHOP21; R-miniCEOP	Merli et al. (2012)
LNH 03-1B	NCT00140595	2003	ACVBP; R-ACVBP	Ketterer et al. 2012
LNH 03-2B	NCT00140595	2003	R-CHOP21; R-ACVBP	Récher et al (2011)
LNH 03-6B	NCT00144755	2003	R-CHOP21; R-CHOP14	Delarue et al. (2013)
NHL-13	NCT00400478	2004	Observation; Rituximab	Jaeger et al. (2015)
PIX203	NCT00268853	2005	R-CHOP21; R-CPOP	Herbrecht et al. (2013)
R-CHOP 14 vs. 21	ISCRTN 16017947	2005	R-CHOP21; R-CHOP14	Cunningham et al. (2013)
MAIN	NCT00486759	2007	R-CHOP (14/21); RA-CHOP (14/21)	Seymour et al. (2014)
Pyramid	NCT00931918	2009	RCHOP; Vc-RCHOP (bortezomib-RCHOP)	Leonard et al. (2017)
E1412	NCT01856192	2013	RCHOP; R2CHOP (lenalidome RCHOP)	King et al. (2018)
PHOENIX	NCT01855750	2013	RCHOP; RCHOP+ibrutinib	
ROBUST	NCT02285062	2015	R-CHOP vs. R-CHOP + lenalidomide	Nowakowski et al. 2016
POLARIX	NCT03274492	2017	R-CHOP; polatuzumab vedotin + R-CHP	

Common criteria (≥ 2/3 of studies)	Number of studies
Age (years)	19
Histology	19
History of other malignancies	19
Prior DLBCL treatment	19
Renal function	19
Hepatic function	18
HIV status	18
Cardiac function	17
CNS involvement by lymphoma	16
Performance status	16
Contraindications to study therapy	15
IPI score	15
Female reproductive	14
HBV status	14
Other organ dysfunction	14
Platelet count (platelets/µL)	14
WBC count (cells/µL)	14
Stage	13

Moderately common criteria (1/3–2/3)	Number of studies
HCV status	11
Participation in other study or treatment with other investigational drug	11
Other neurologic pathology	10
Immunologic history	9
Other infectious disease status	9
Imaging	8
Minimum life expectancy	8
Contraindicated therapies	7
History of transformed lymphoma	7
Male reproductive	7
Psychiatric history	7

Uncommon criteria (< 1/3)	Number of studies
Pulmonary function	6
Sex	6
Surgical history	6
Diabetes mellitus	6
Patient compliance	6
Adult patient under tutelage	4
Uncontrolled hypertension	4
Hemoglobin (g/dL)	3
History of PTLD	3
Hypercoagulability	3
Organ transplant history	3
Bone marrow infiltration	2
Coagulopathy	2
Gastrointestinal function	2
HTLV-1 status	2
Comprehensive Geriatric Assessment score	1
LDH level	1
Orthopedic history	1
Physical exam findings	1
Rheumatologic disease	1
Substance use	1
Tumor invasion of major blood vessels	1
Vaccination history	1



Department of Lymphoma/Myeloma

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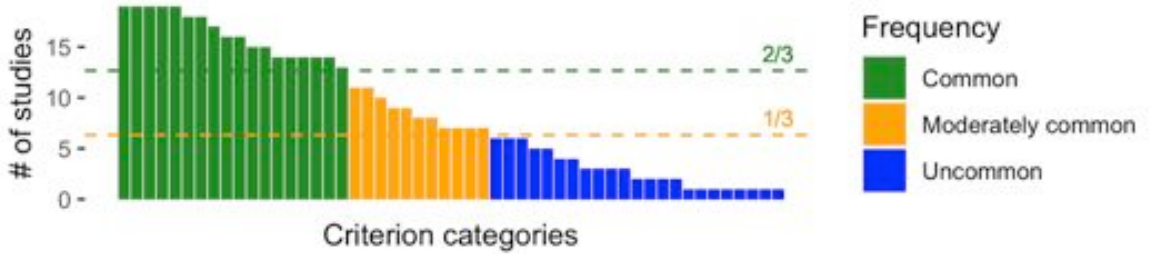
Vaccination history	1



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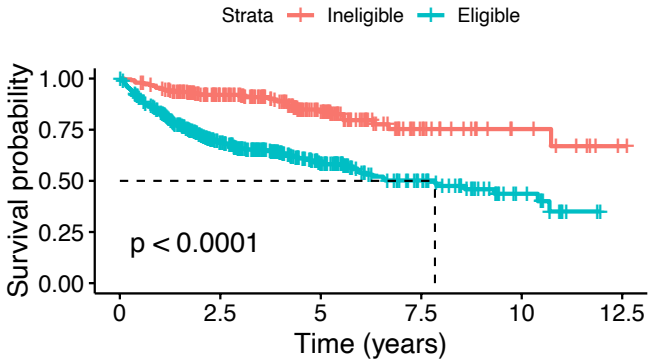
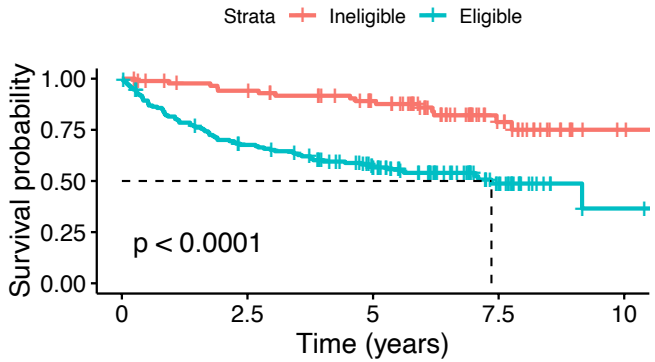
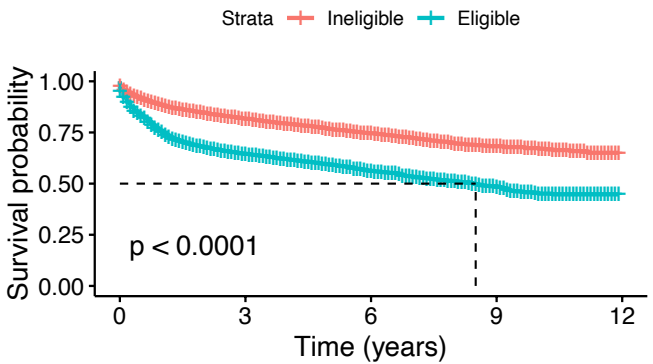
Impact of Eligibility Criteria on DLCBL outcomes: OS

Reddy et al.



Chapuy et al.





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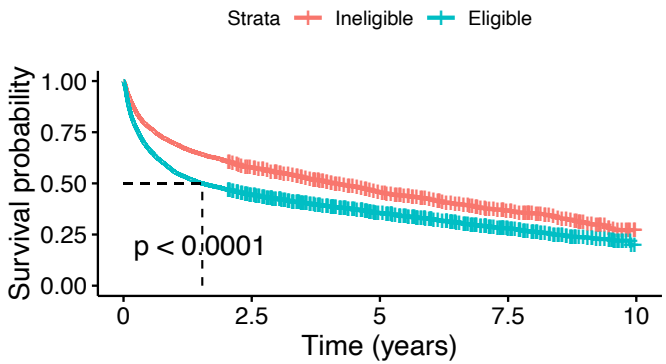
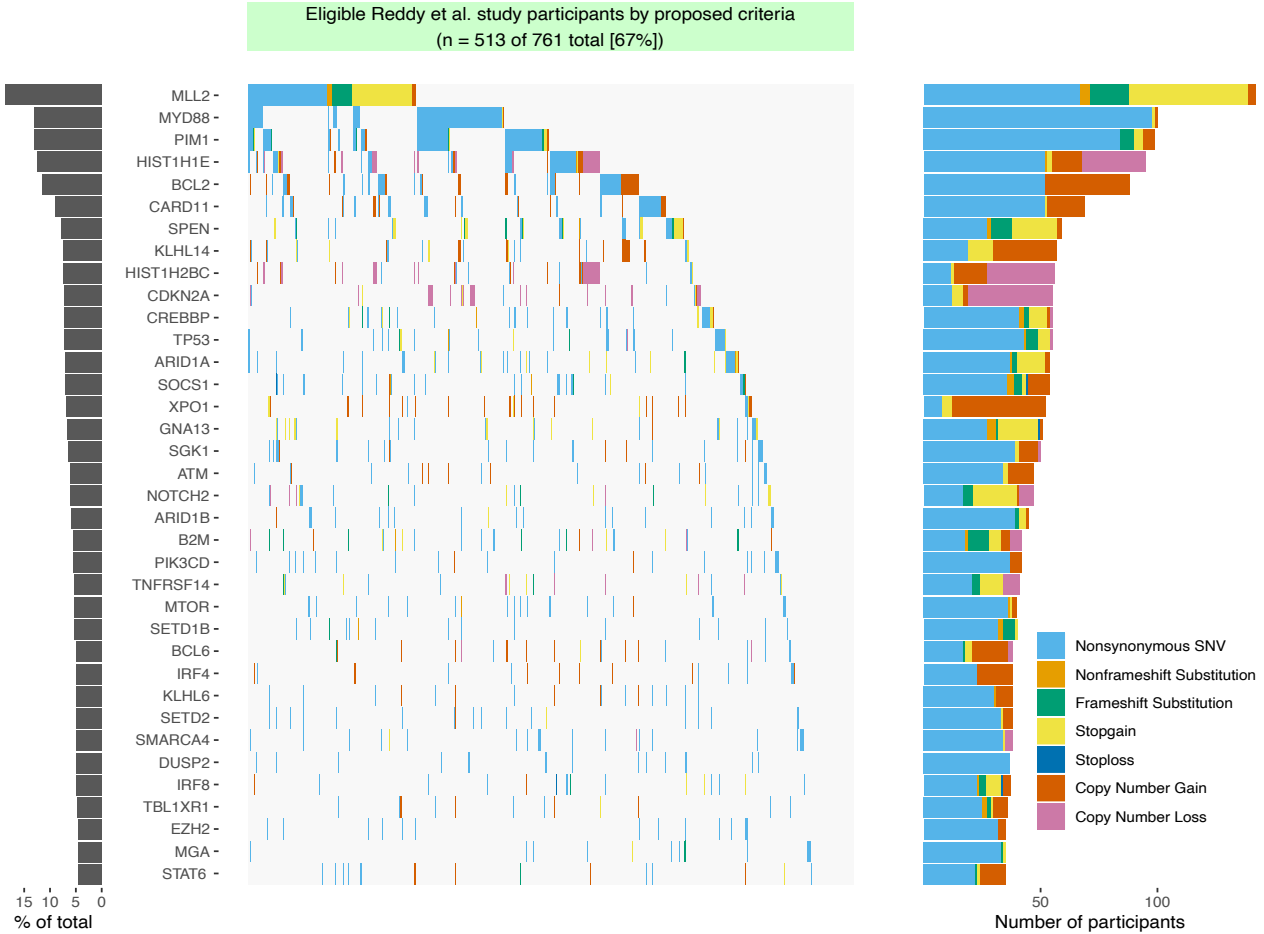


SEER-Medicare

Impact of Eligibility Criteria on DLCBL genetic alterations: Reddy et al.



Barriers to Lymphoma Trial Participation

TABLE 2. Organ Function–Based Exclusion Criteria in Various Frontline DLBCL Trials

Parameter	PHOENIX	ROBUST	ECOG 1412	REMoDL-B	GOYA	ENGINE	CALGB 50303
ANC (× 10⁹/L)	> 1,000	> 1,500 (> 1,000 for BM inv)	≥ 1,500	> 1,000 (lower unless because of lymphoma)	> 1,500	> 1,500	> 1,000
Platelets (× 10⁹/L)	> 75, unless BM inv	> 75 (> 50 for BM inv)	≥ 100	> 100	> 75	> 75	> 100
Bilirubin (mg/dL)	< 1.5 × ULN	< 1.5 × ULN or if total bilirubin is > 1.5 × ULN, the direct bilirubin must be normal	< 1.5 × ULN or if total bilirubin is > 1.5 × ULN, the direct bilirubin must be normal	< 3.5 mg/dL	< 1.5 × ULN	< 1.5 × ULN	< 2.0
CrCl (mL/min)	> 40	> 30	> 30	> 30	> 40	> 50	> 50
Hemoglobin (g/dL)	Not mentioned	> 7.5	Not mentioned	Not mentioned	> 9	> 10	Not mentioned

NOTE. Total bilirubin ULN 1.2 mg/dL.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; CrCl, creatinine clearance; DLBCL, diffuse large B-cell lymphoma; ULN, upper limit of normal.

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Barriers to Lymphoma Trial Participation

TABLE 3. Percent Estimation of Patient Exclusion From MER Cohort Based on the Trial-specific Organ Function–Based Exclusion Criteria

Parameter	PHOENIX	ROBUST	ECOG 1412	REMoDL-B	GOYA	ENGINE	CALGB 50303
Total, %	12.3	10.0	11.3	9.2	15.9	24.1	17.2
ANC, %	1.3	2.5	2.5	1.3	2.5	2.5	1.3
Platelets, %	3.2	3.2	4.7	4.7	3.2	3.2	4.7
Hepatic function, %	3.8	3.8	3.8	1.5	3.8	3.8	3.2
Renal function, %	5.2	2.0	2.0	2.0	5.2	10.5	10.5
Hemoglobin, %	0.0	1.3	0.0	0.0	6.3	12.7	0.0

Abbreviations: ANC, absolute neutrophil count; MER, Molecular Epidemiology Resource.

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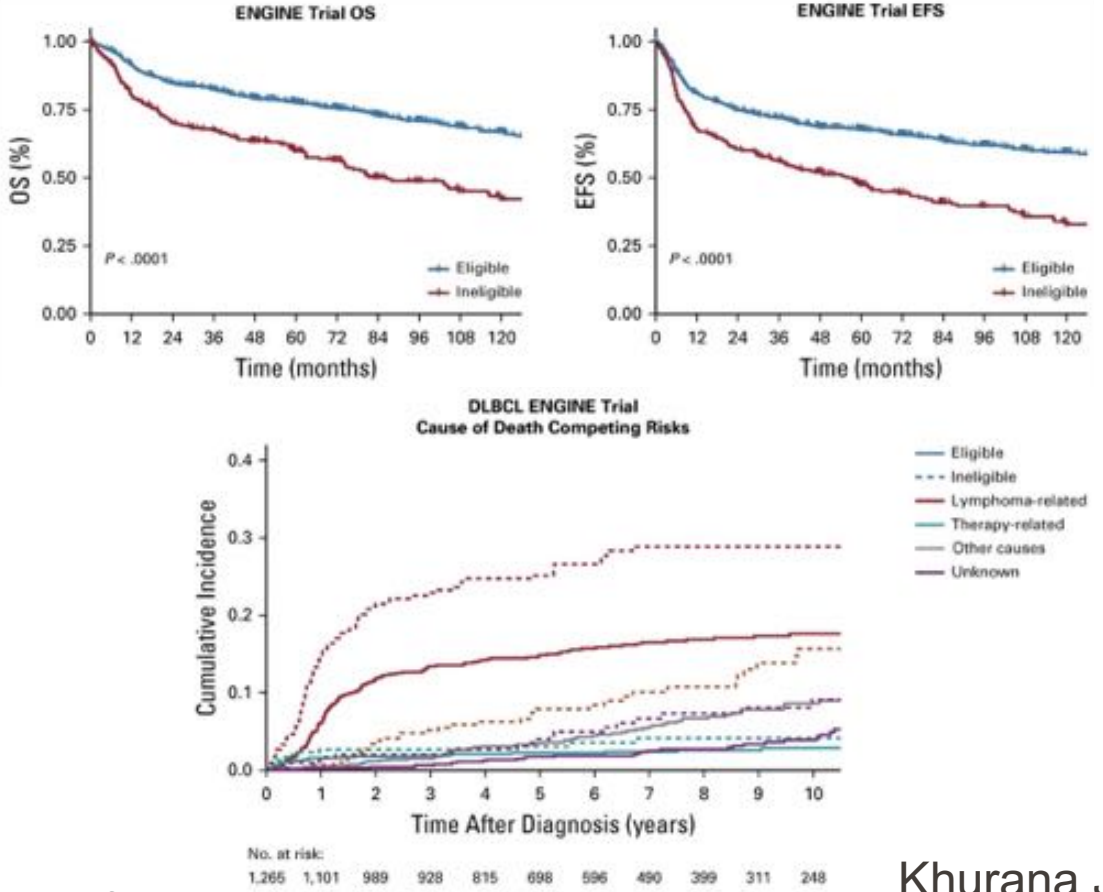
Barriers to Lymphoma Trial Participation



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Other “Protocol Busters”

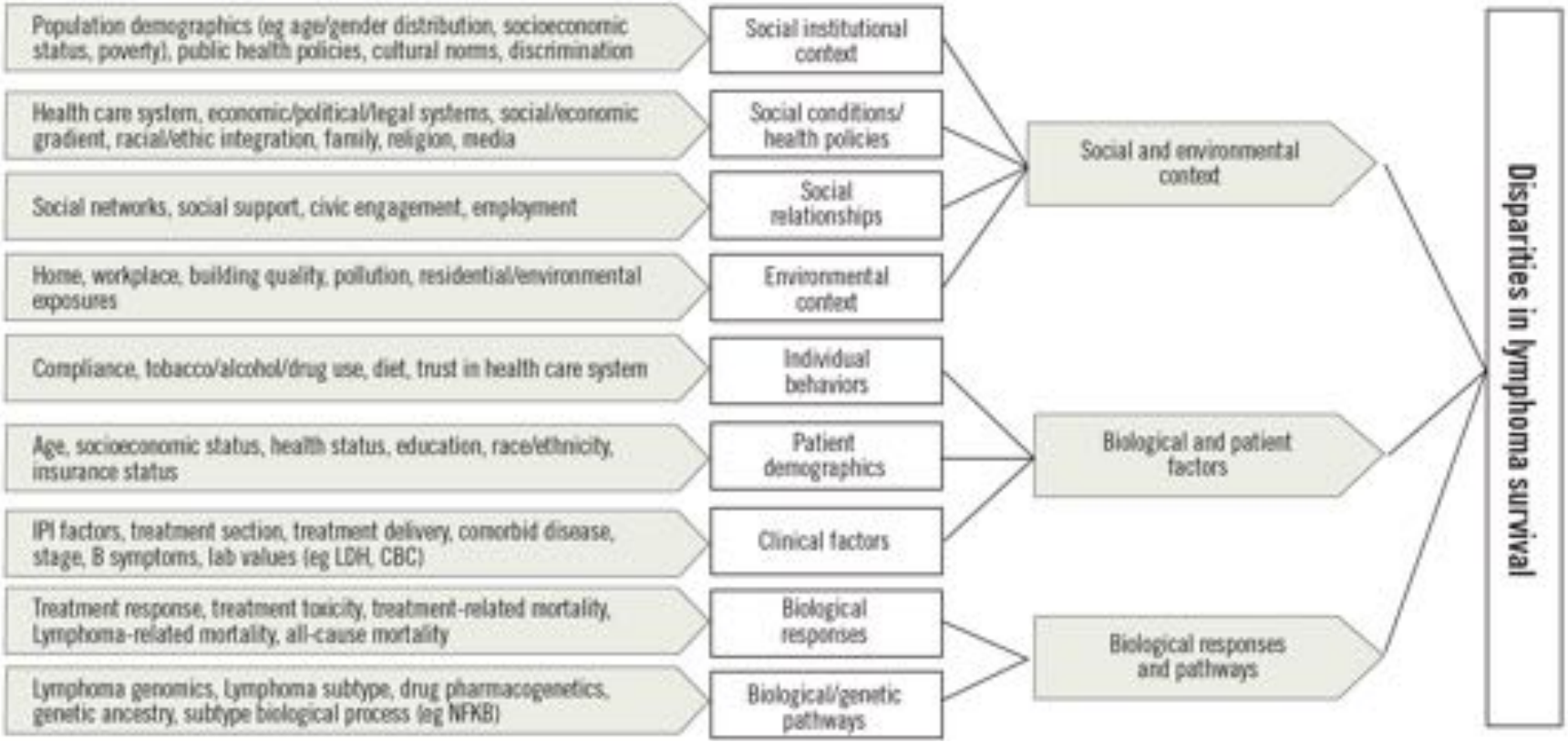
- Pathology eligibility too strict
  - And not reflective of real world
- Other cancer not allowed
  - Even though they may not interfere with the new cancer
- Eligibility test windows
  - What you write determines compliance or noncompliance
- Pre-phase therapy allowed?
- Regulatory issues

Consensus recommendations for eligibility criteria in first-line DLBCL RCTs based on a Delphi-method survey of lymphoma clinical trials experts

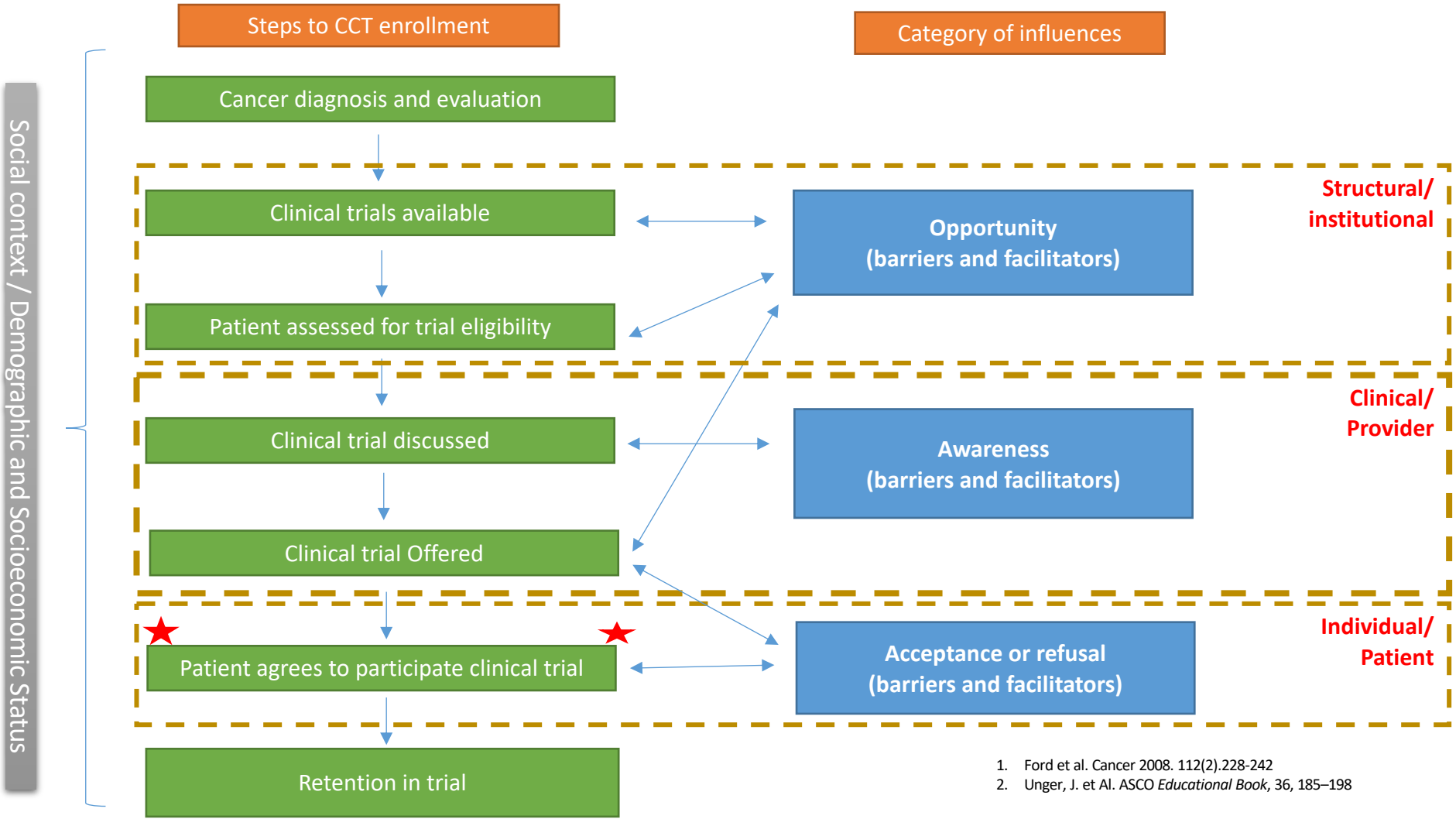
Criterion	Recommendation
Pregnancy status	Pregnant women should be excluded from enrollment.
Breastfeeding status	Breastfeeding should be prohibited during trial participation.
Female: contraception or abstinence	Effective contraception or abstinence from heterosexual intercourse is required for enrollment if of childbearing potential.
Male: contraception or abstinence	Effective contraception or abstinence from heterosexual intercourse is required for enrollment.
Participation in other study or treatment with other investigational drug	Study participants should receive no concurrent treatment OR have received no treatment within the last 30 days with any other investigational therapy. Participation in nontherapeutic studies (e.g., subject registries) is permitted.
IPI score	IPI score range should be determined based on the target population for a given study.
Ann Arbor Stage	Patients with Ann Arbor stages II–IV should be eligible for enrollment. Inclusion of patients with stage-I disease should depend on the study hypothesis and should be determined on a trial-by-trial basis.
Age at diagnosis	At baseline, patients aged ≥ 18 years should be eligible for trial participation. Determine final age range based on study intervention and target population
Performance status	Recommend including patients with PS of ECOG 0–2 and ECOG 3 if poor PS is due to lymphoma.
Renal function	Exclude patients based on a selected threshold value unless dysfunction is attributable to lymphoma. Selection of threshold value should take into account specific therapies in trial.
Hepatic function	
CNS involvement	No known CNS involvement by lymphoma permitted in frontline trials evaluating strategies to improve standard of care therapy. Testing for CNS lymphoma is not required for enrollment and should be performed only when based on clinical suspicion.
Presence of other significant, uncontrolled, concomitant disease	No other significant, uncontrolled, concomitant disease should be permitted at investigator's discretion.

Harkins *ASH*, 2020

Social, Biologic, and Environmental Factors That Contribute to Disparities in Lymphoma Survival



Williams et al., Oncology 2020



1. Ford et al. Cancer 2008. 112(2).228-242
2. Unger, J. et Al. ASCO *Educational Book*, 36, 185–198