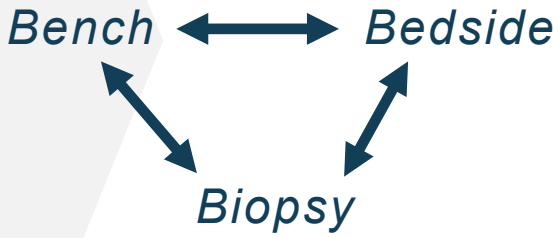
Nurses Brown Bag Update on Lymphomas in 2022



NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

Mark Roschewski, MD
Clinical Director, Lymphoid Malignancies Branch
Center for Cancer Research, NCI, NIH
Bethesda, MD, USA
@RoschewskiMD

Goals of NCI Lymphoma Branch

"What are the goals in diffuse large B-cell lymphomas?"

1. *Primary goal: improve the cure rate*
2. *Secondary goal: focus on those with the greatest need*

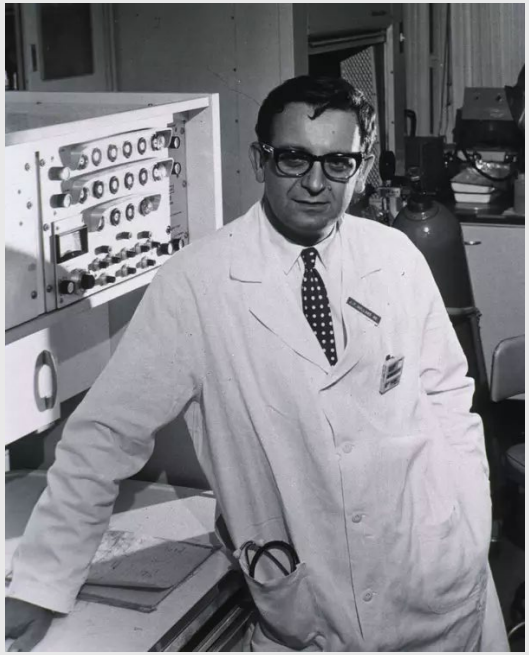
Translational Endpoints to Maximize Scientific Impact

1. High-risk disease subtypes – address unmet clinical needs

2. Innovative clinical trial designs: window of opportunity; response-adapted

3. Emphasis on molecular and immunologic correlates of response

History of Chemotherapy for Lymphomas



James F. Holland
Trailblazing Cancer Researcher, Dies 92
March 27, 2018 in *New York Times*
Co-founded CALGB

Emil Frei
Dana-Farber Cancer Institute
Co-founded CALGB

Emil J Freirich
MD Anderson Cancer Center

History of Chemotherapy #2

Vincent DeVita
Former NCI Director
At NCI, he developed MOPP and CMF

Epidemiology and Risk Factors

- **~8,500 new cases in U.S. into 2010 → 55% men**
  - Bimodal distribution
- **EBV associated in 40% of cases (higher in children)**
- **HIV associated → seen an increase with better viral control**
- **Associated with higher socioeconomic status**
- **Familial cases in about 4.5% - germline NPAT in LP**

Clinical Features of HL

- **Predilection for lymph nodes (rare extranodal, never leukemia)**
  - Left supraclavicular painless node in a female
- **Abdominal disease preceded by splenic involvement**
  - More common in elderly HL patients
- **Only 1/3 have B symptoms**
- **Paraneoplastic syndromes involve skin, CNS, and kidney**

Clinical features of histologic subtypes

TABLE 2. Major Categories of Hodgkin's Lymphoma

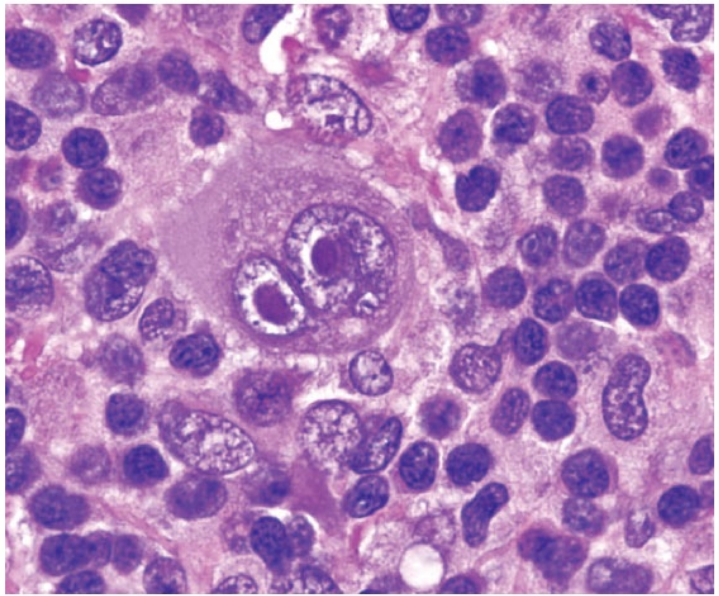
	NSCHL	MCCHL and LDCHL	NLPHL
Risk factors			
Socioeconomic status	High	Low	No risk factors
HIV infection	Negative	Positive	
Gender predominance	Female	Male	Male
Age	Young adults	Children or elderly	Young adults
EBV infection	Negative	Positive	Negative
Lymphoid tissue involved	Mediastinal, cervical and axial lymph nodes	Generalized disease, lymph nodes and bone marrow	Peripheral and mesenteric lymph nodes, no mediastinal involvement

NS is involving the mediastinum 80% of the time and 50% have stage II dz

Eberle et al. Cancer J. 2009 Mar-Apr;15(2):129-37.

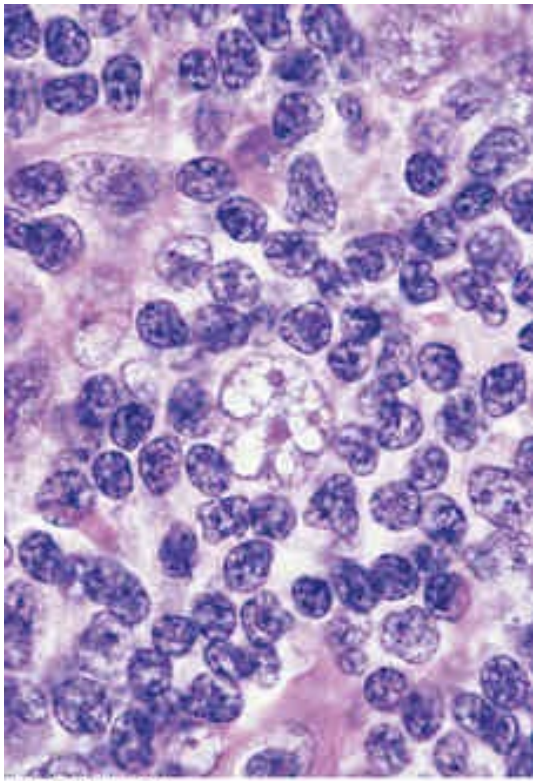
Malignant cell within appropriate tumor microenvironment

Reed-Sternberg cell (HRS)

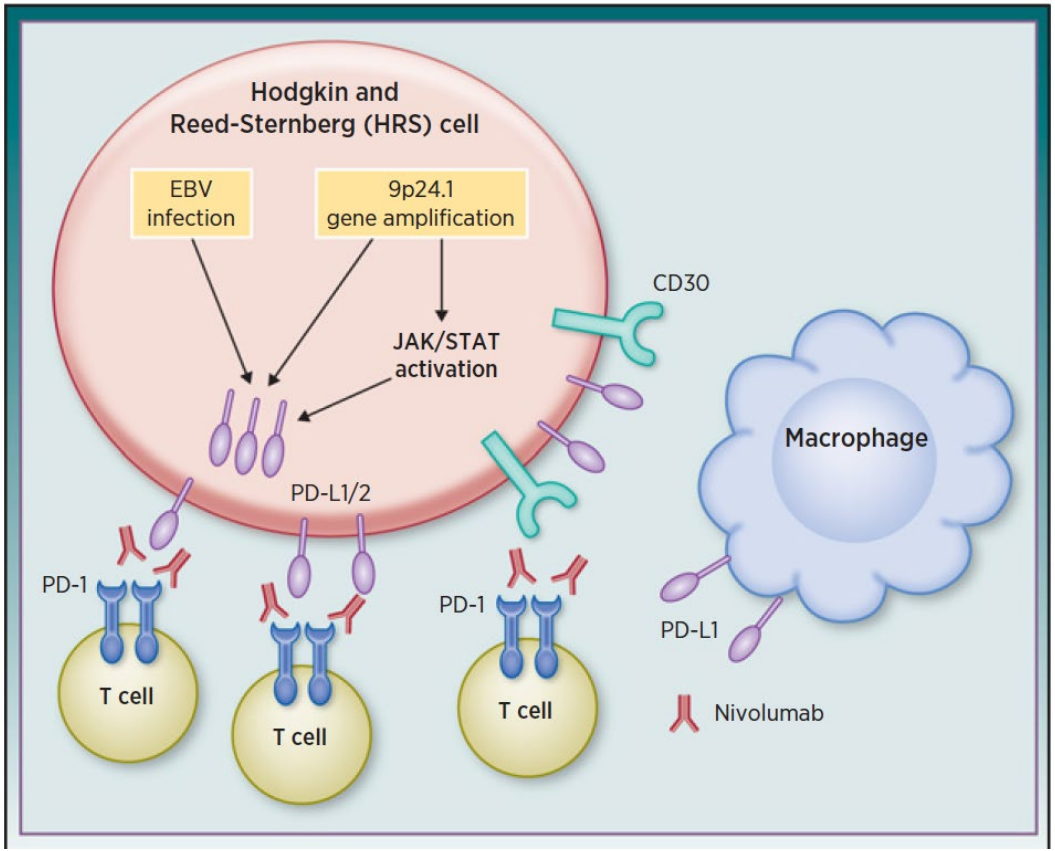


T-cells, histiocytes, eosinophils, and plasma cells

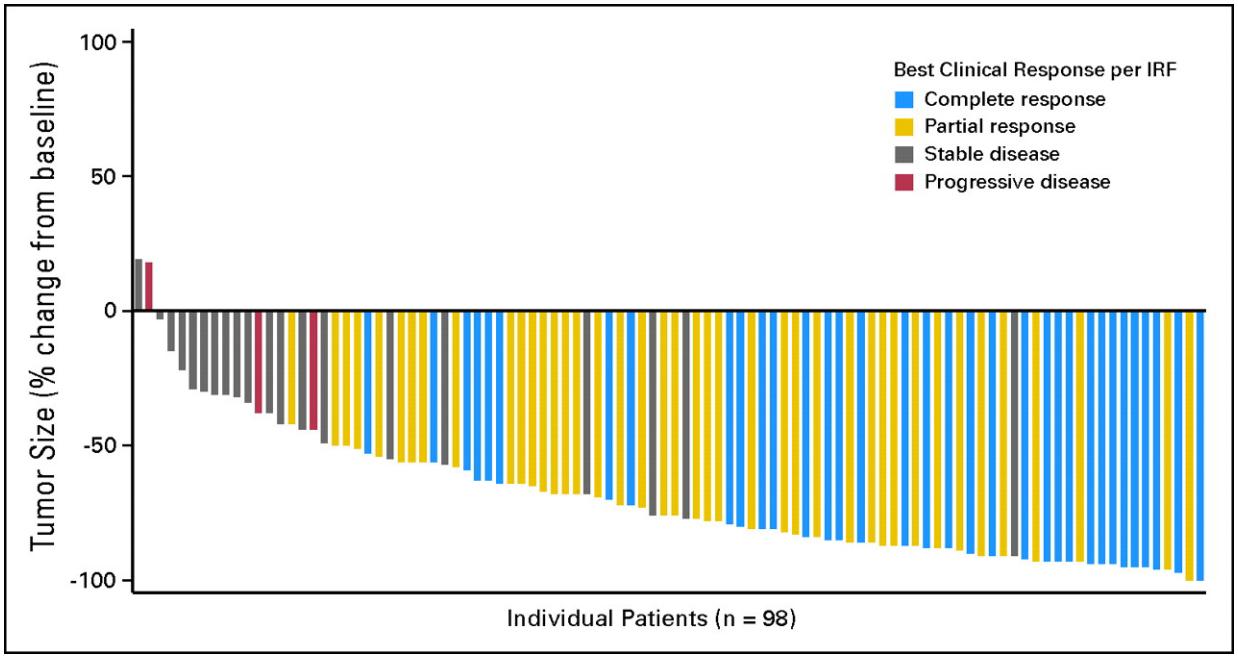
“Popcorn” cells



PD-1 blockade in HL

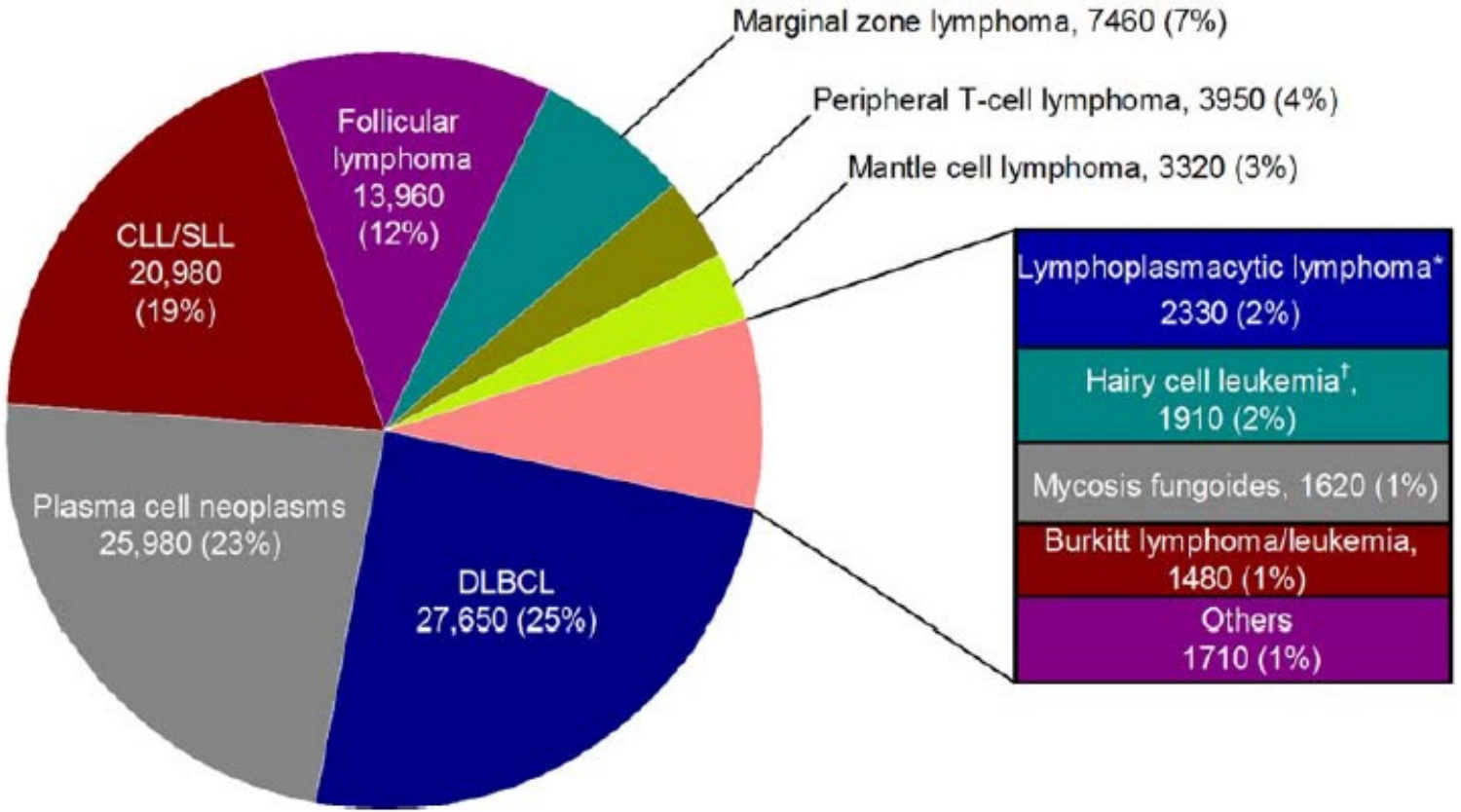


Brentuximab in relapsed HL



Younes et al. *J Clin Oncol*. 2012 Jun 20;30(18):2183-9

Diffuse Large B-cell Lymphoma common; Burkitt Lymphoma rare in Adults



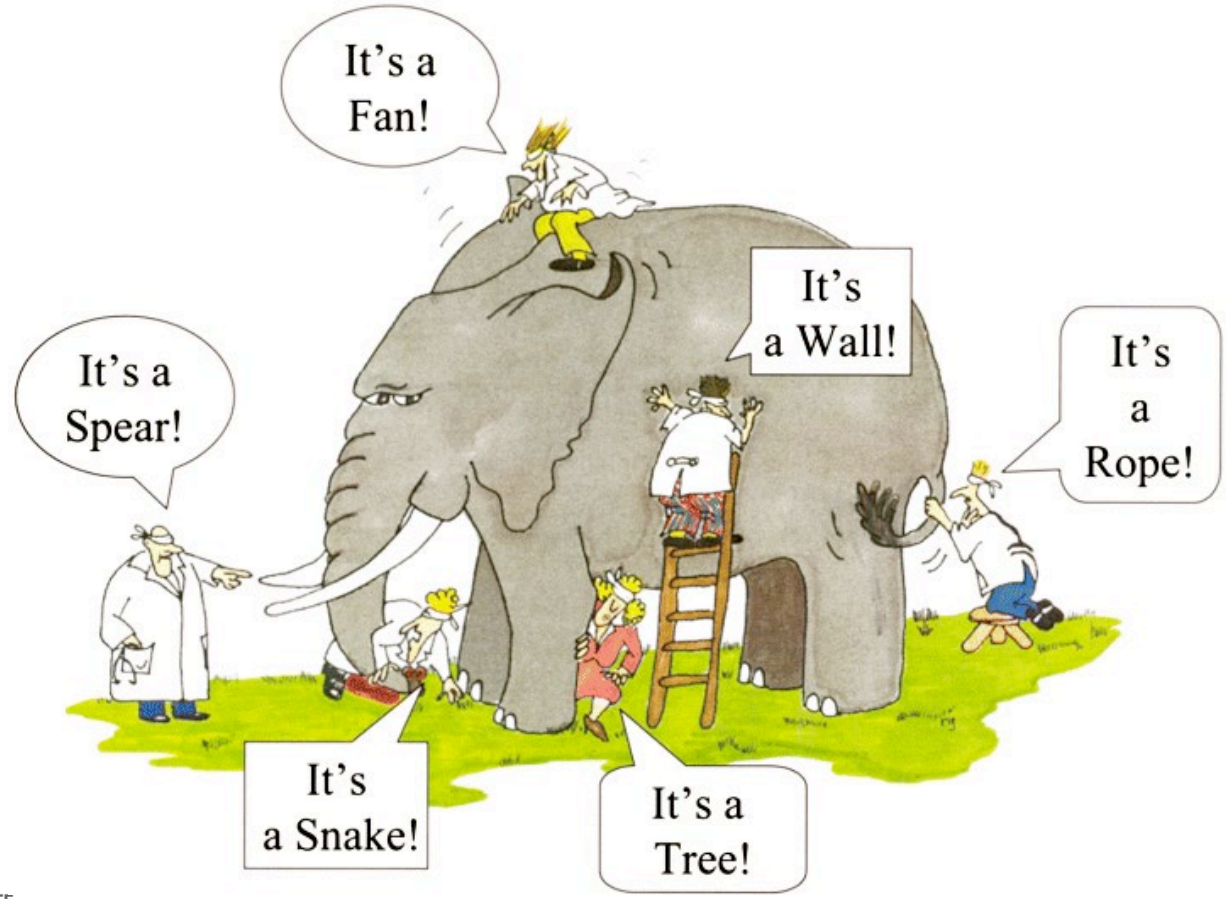
Teras LR, et al. *CA Cancer J Clin* 2016 Nov 12;66(6):443-459

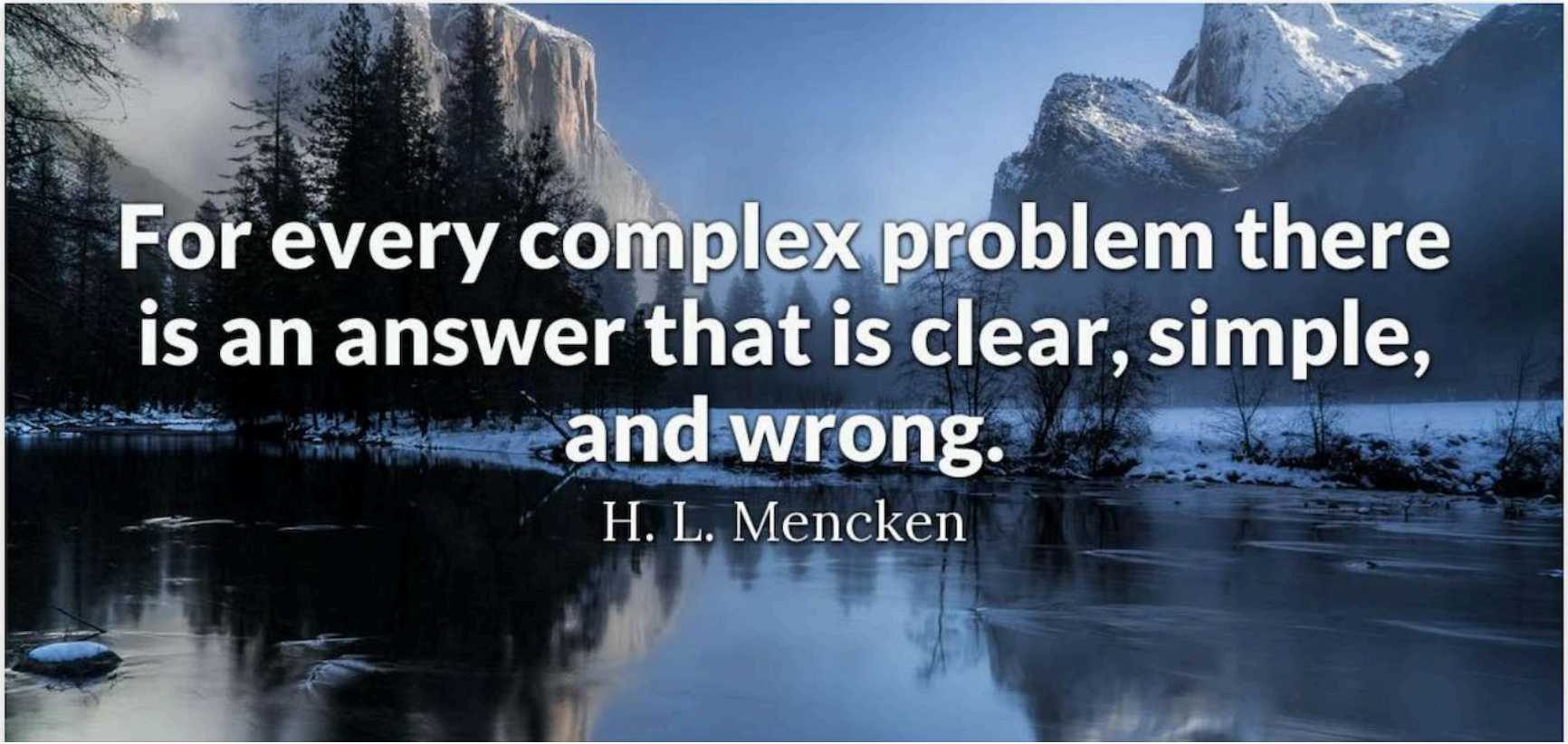
Precision Medicine Definition

NIH → *"an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"*

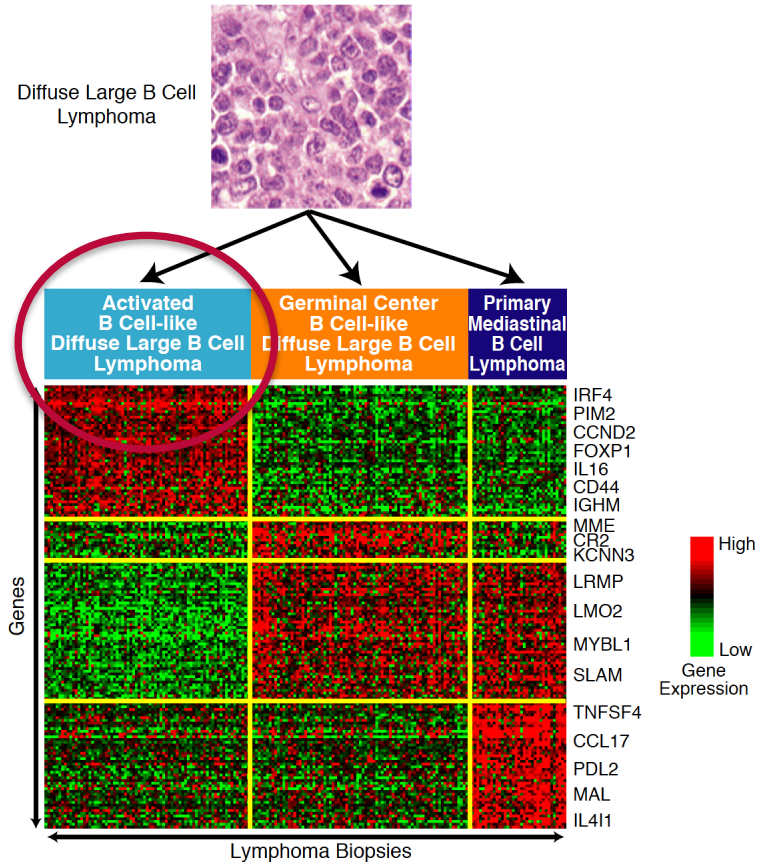
NCI → *“increased knowledge of the genetics and biology of lymphoma to find new, more effective treatments”*

Inherent Risk of Precision Medicine



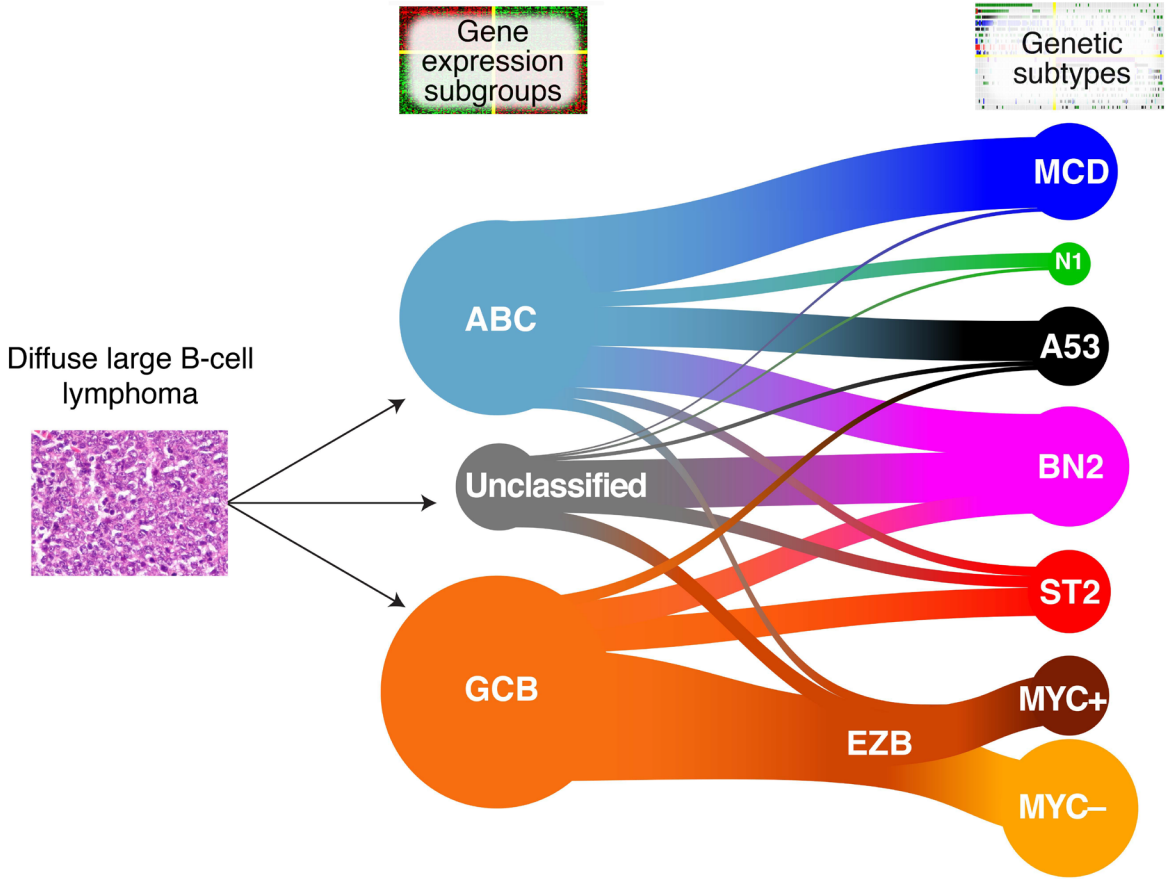

For every complex problem there is an answer that is clear, simple, and wrong.
H. L. Mencken

Molecular Subtypes of Diffuse Large B-cell Lymphoma



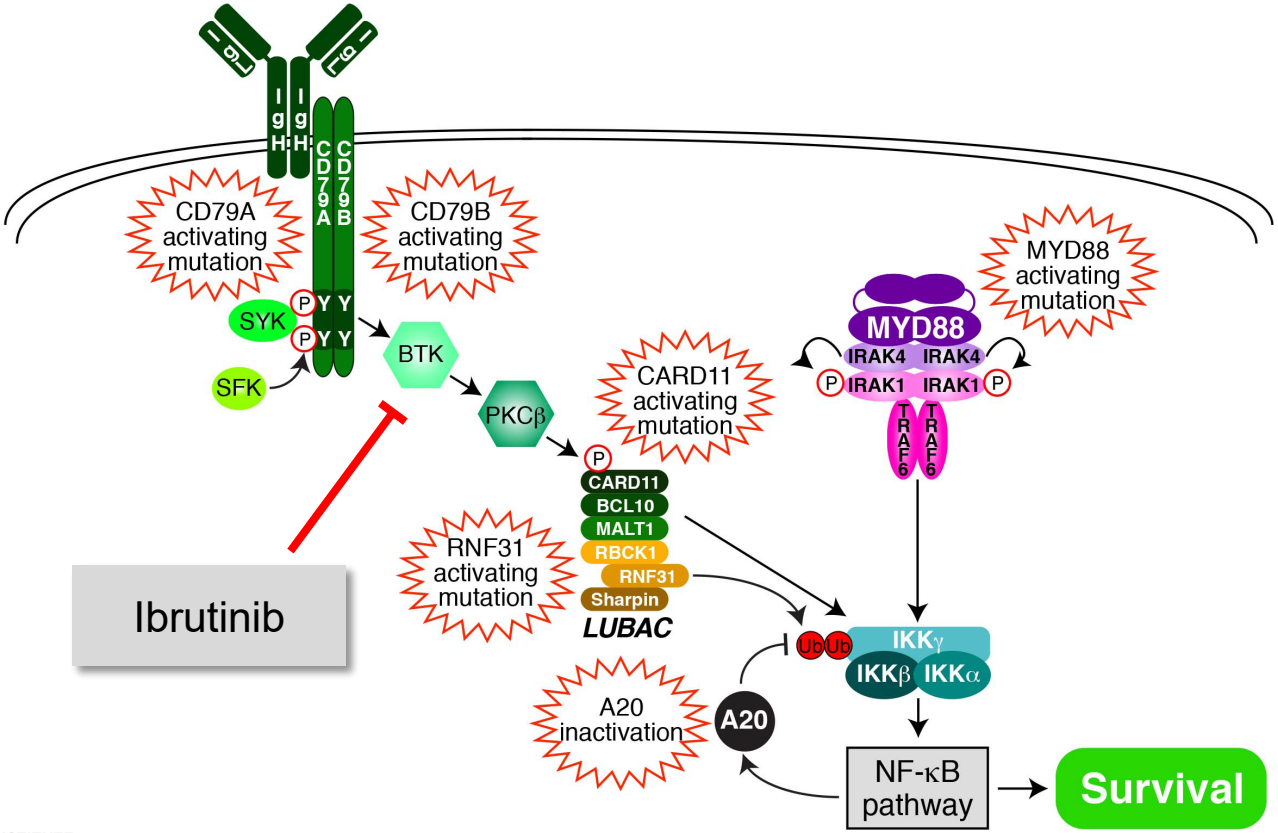
Roschewski et al. *Nat Rev Clin Oncol* 2014 Jan;11(1):12-23

The DLBCL Genetic Subtypes Subdivide the Gene Expression Subgroups

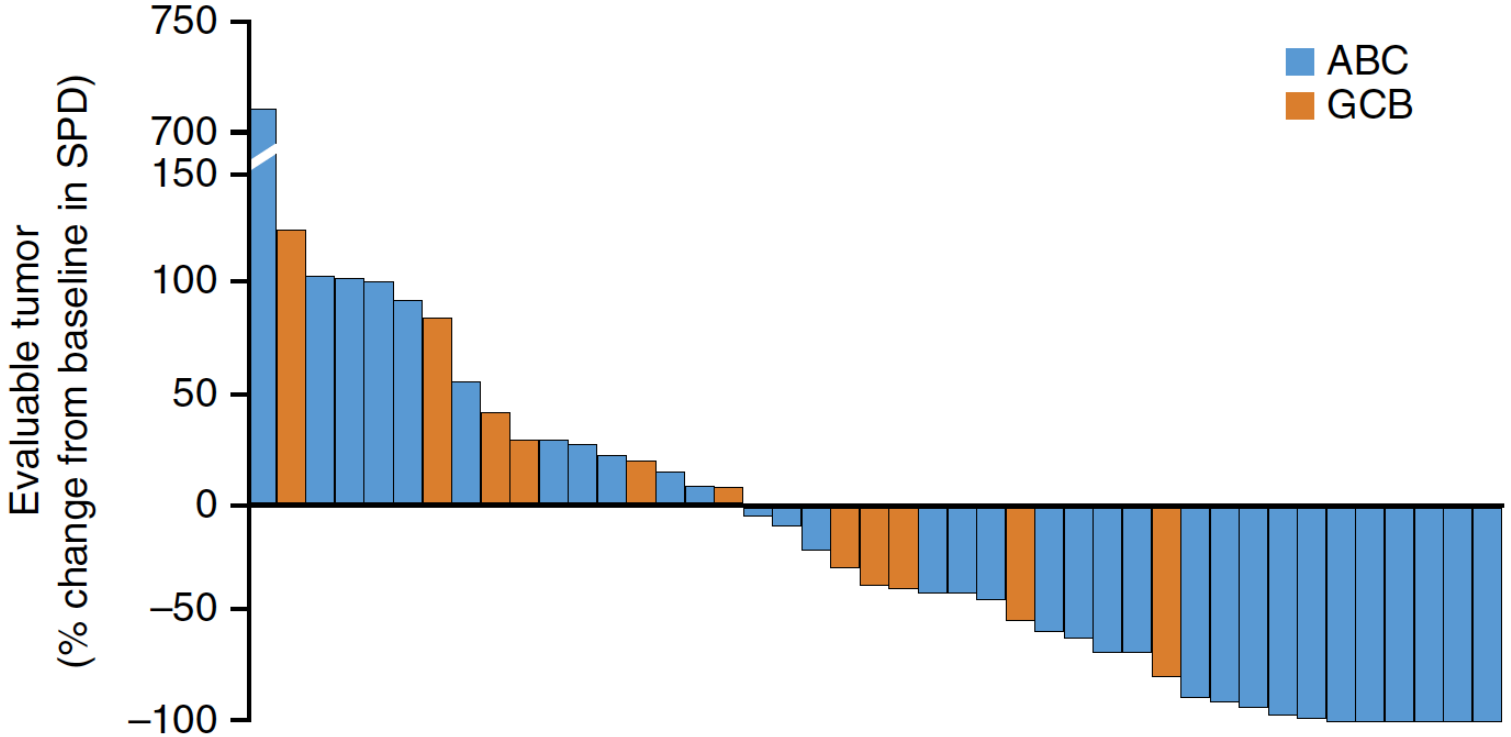


Schmitz et al. *N Eng J Med* 2018 Apr 12;378(15):1386-140
Wright et al. *Cancer Cell* 2020 Apr 13;37(4):551-568

Targeting Chronic Active BCR Signaling With Ibrutinib

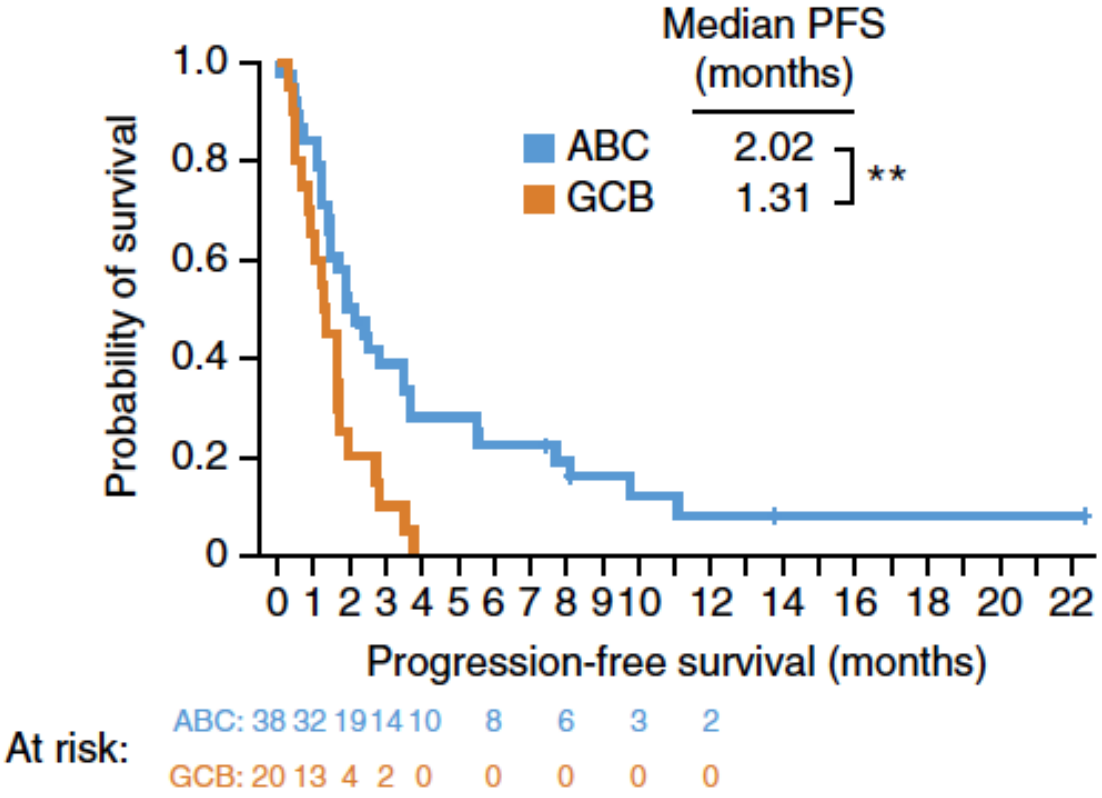


Ibrutinib Activity Specific for ABC DLBCL



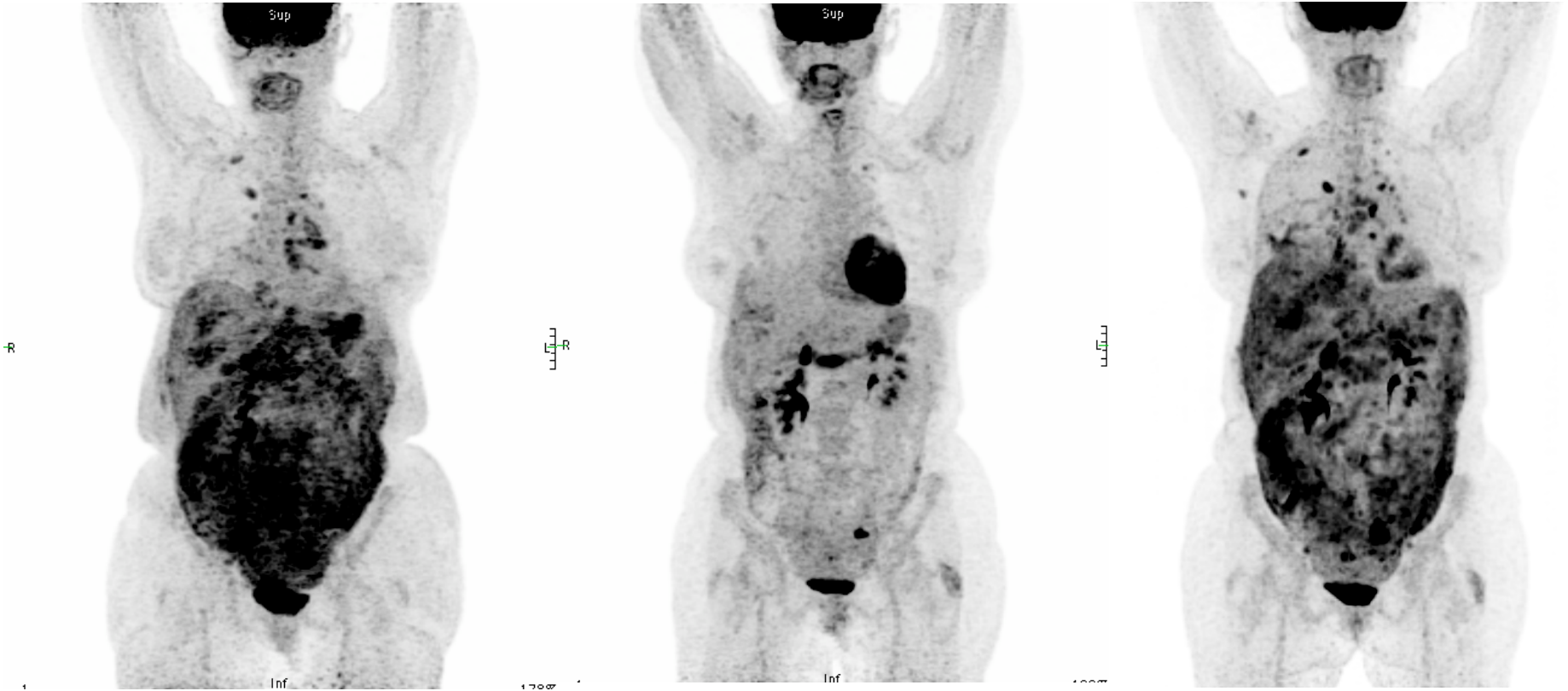
Wilson et al. *Nat Med* 2015; 21(8):922-926

Duration of response to ibrutinib very short



Wilson et al. *Nat Med* 2015; 21(8):922-926

PET/CT Scan of Patient #9 With ABC DLBCL
Before and On Treatment With a BTK Inhibitor (PCI-32765)

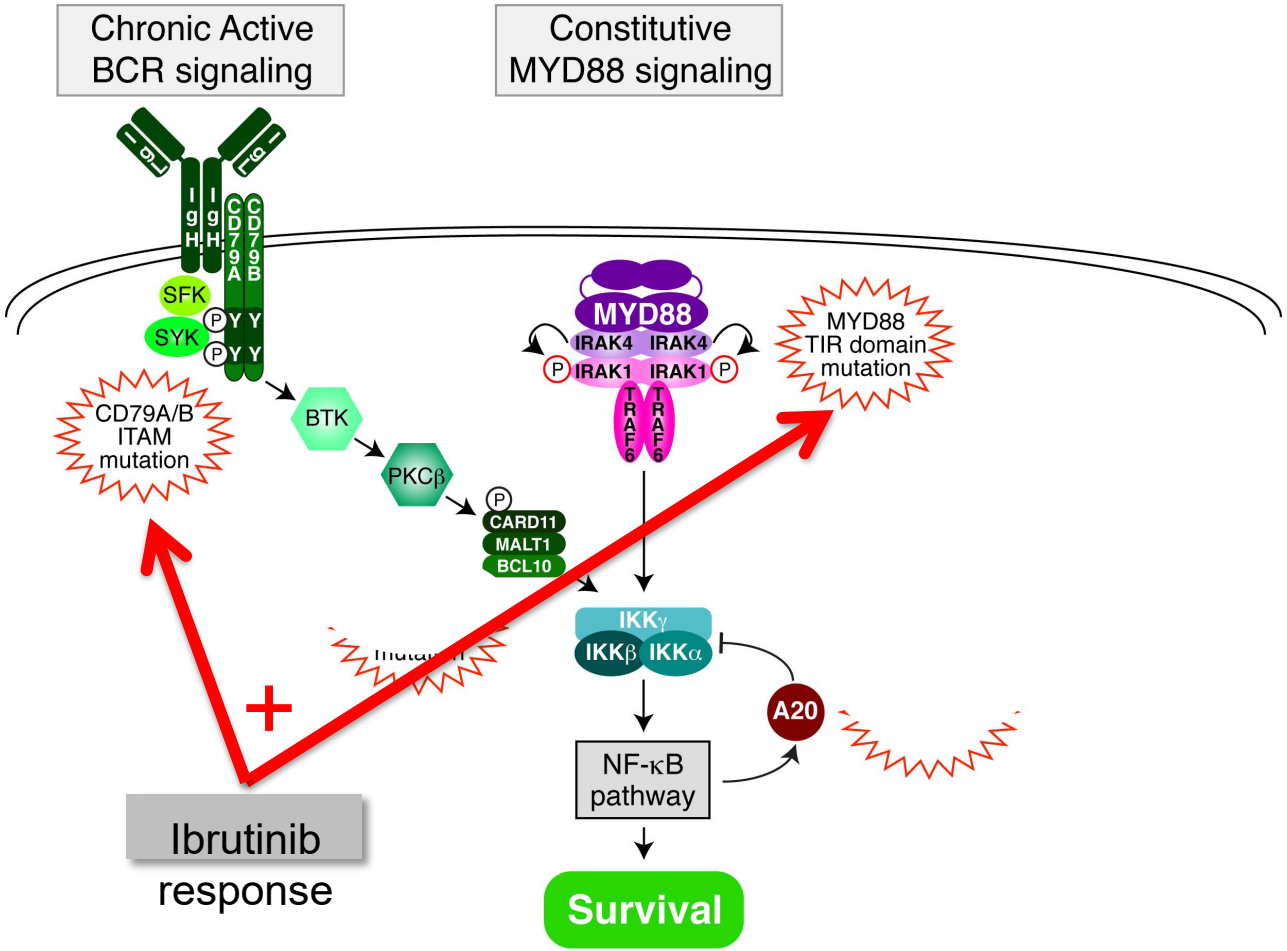


Before Rx: 9/26/11

On Rx: 10/19/11

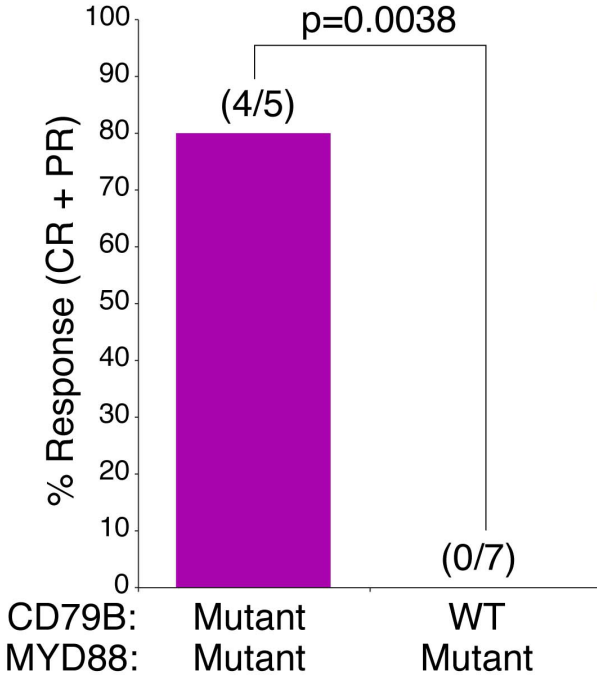
11/3/11

Do Mutations Predict Ibrutinib Response?



B-cell Receptor Mutations and MYD88 Mutations

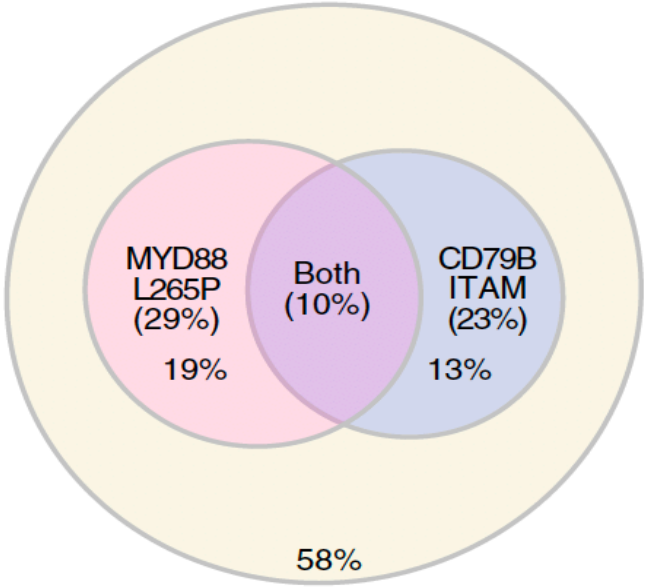
MYD88 TIR domain vs.
CD79A/B ITAM motif



Wilson et al. *Nat Med* 2015; 21(8):922-926

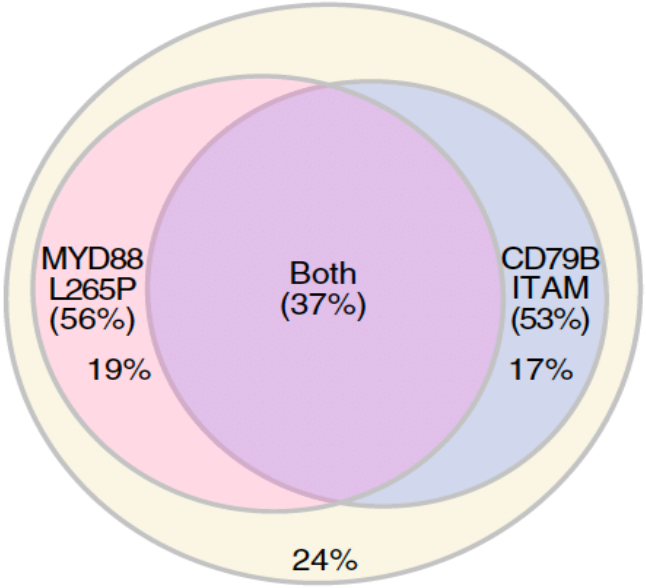
“Hyper-addiction” to BTK

“Nodal” ABC



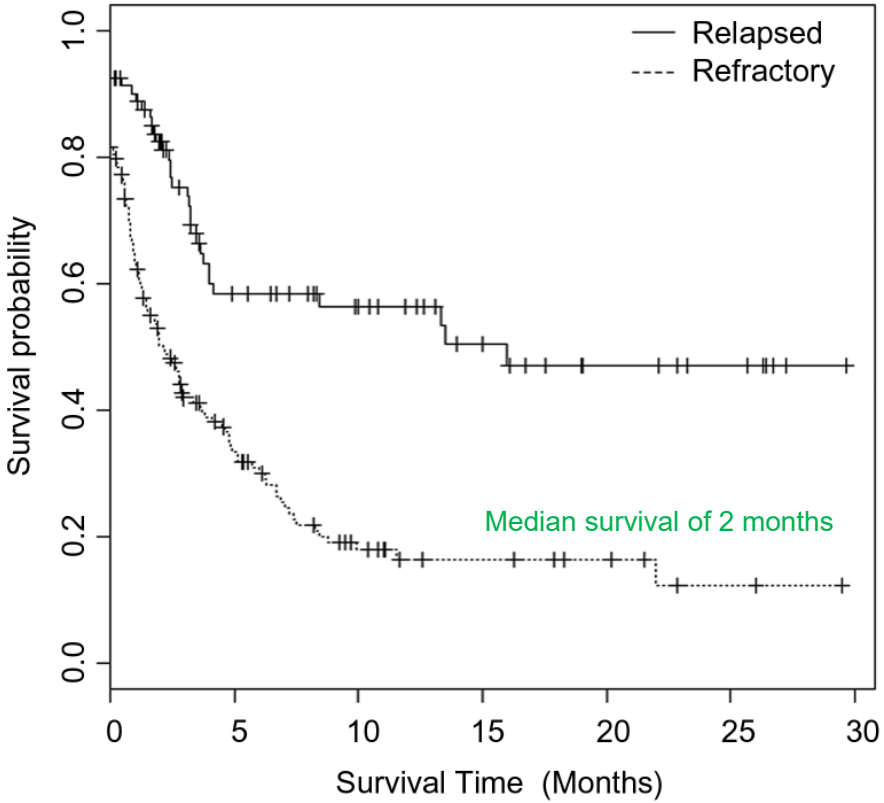
Nodal
ABC DLBCL
(n=155)

“Extra-nodal” ABC



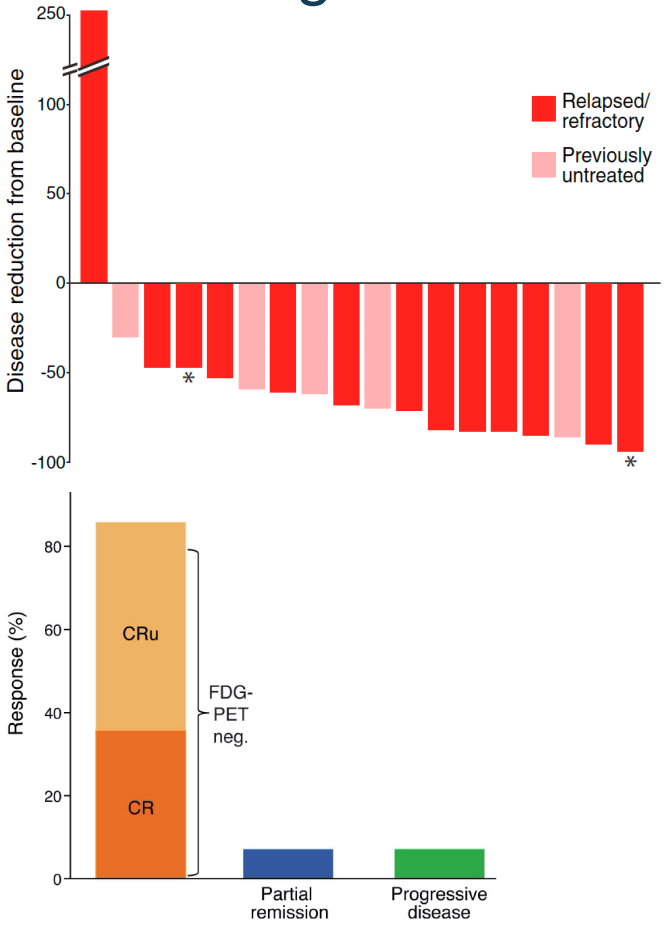
1° Central Nervous System
Lymphoma
(n=213)

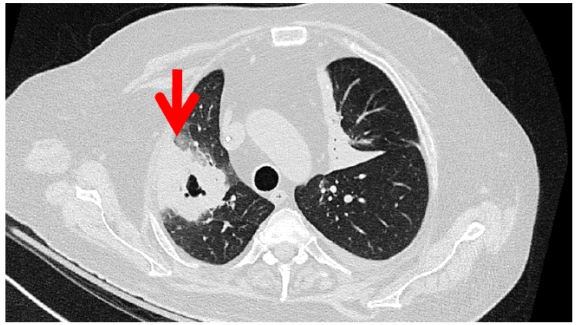
Urgent Unmet Need in PCNSL - Chemotherapy Refractory

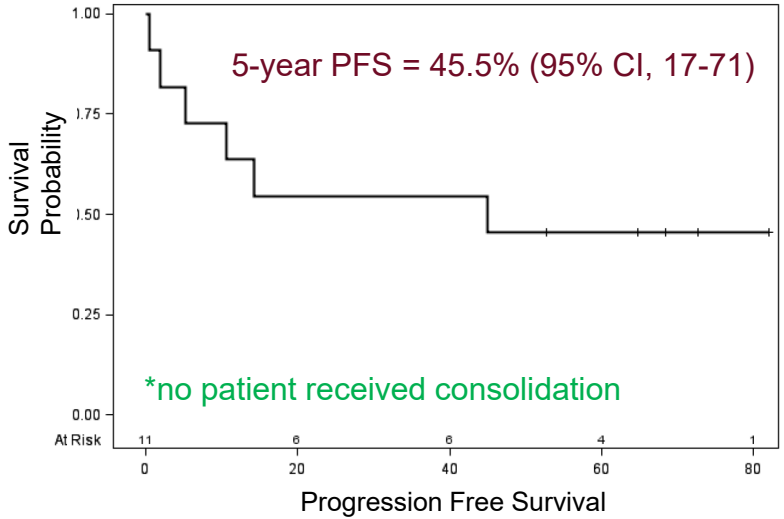


Langner-Lemercier et al. *Neuro Oncol* 2016; 18(9):1297-303

Original TEDDI-R study in PCNSL – Lessons Learned



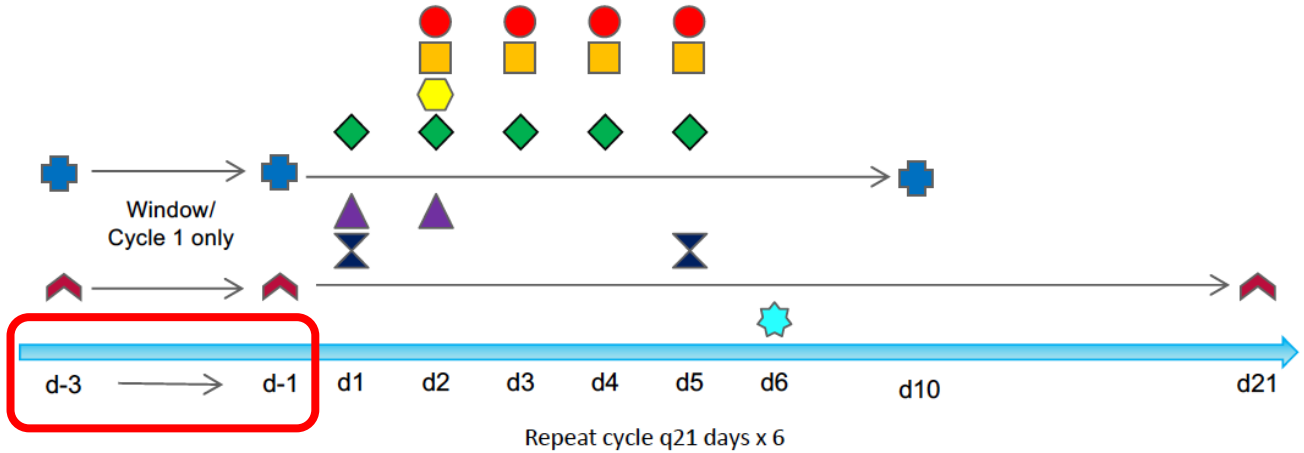




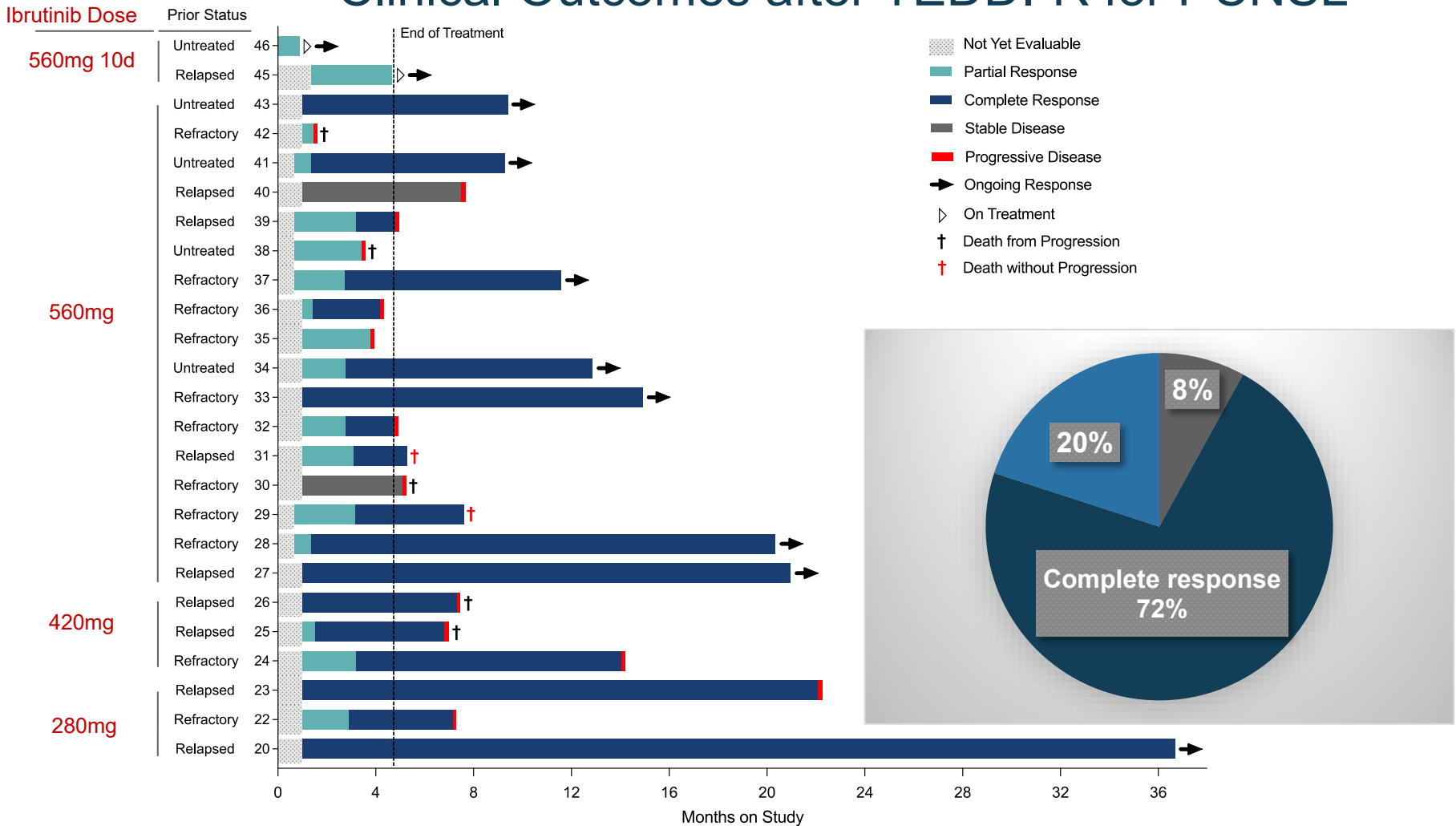
Optimizing the TEDDI-R regimen for CNS Lymphomas

- Temozolomide 90 mg/m^2/day IV days 2 thru 5*
- Etoposide 45 mg/m^2/day IV days 2 thru 5*
- Doxil 40 mg/m^2 IV day 2
- Dexamethasone 10 mg BID PO days 1 thru 5
- Ibrutinib 560 mg PO days -3 thru -1 (window)
- Ibrutinib 560 mg PO days 1 thru 10 (each cycle)
- Rituximab 375 mg/m^2 IV on days 1 and 2

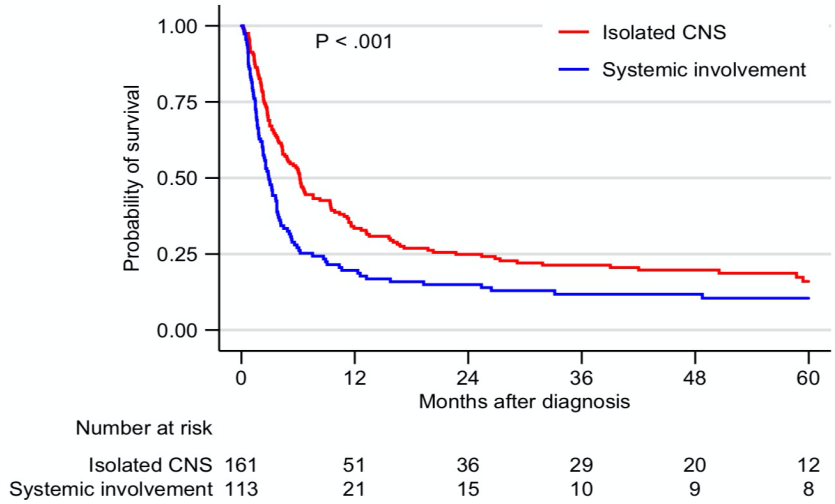
- Cytarabine 70 mg ICV or Methotrexate IT
  - Cycles 2-6: days 1 and 5
- Isavuconazole 200 mg PO BID/QD
  - Starts up to 7 days prior to day -14
  - Loading dose: 200 mg PO BID for 3 days
  - Followed by: 200 mg PO QD continuous
- Pegfilgrastim 6 mg SQ on day 6



Clinical Outcomes after TEDDI-R for PCNSL

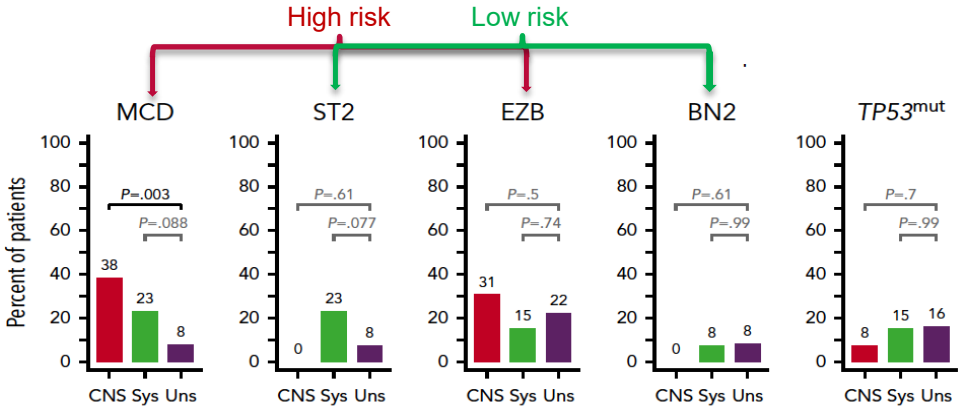


CNS Tropism Enriched in Genetic Subtypes of DLBCL



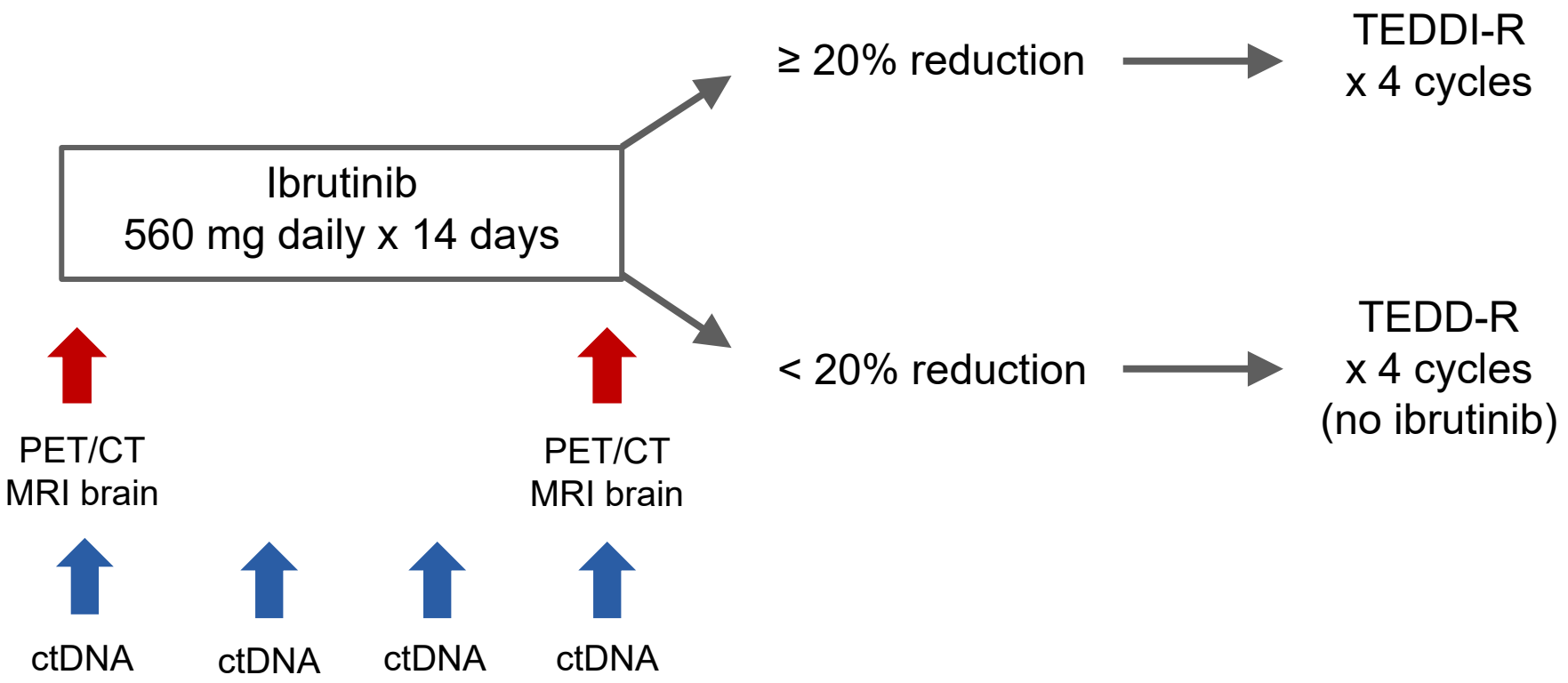
El-Galaly et al. *Eur J Cancer*. 2018 Feb 21;93:57-68

N=462 relapsed DLBCL

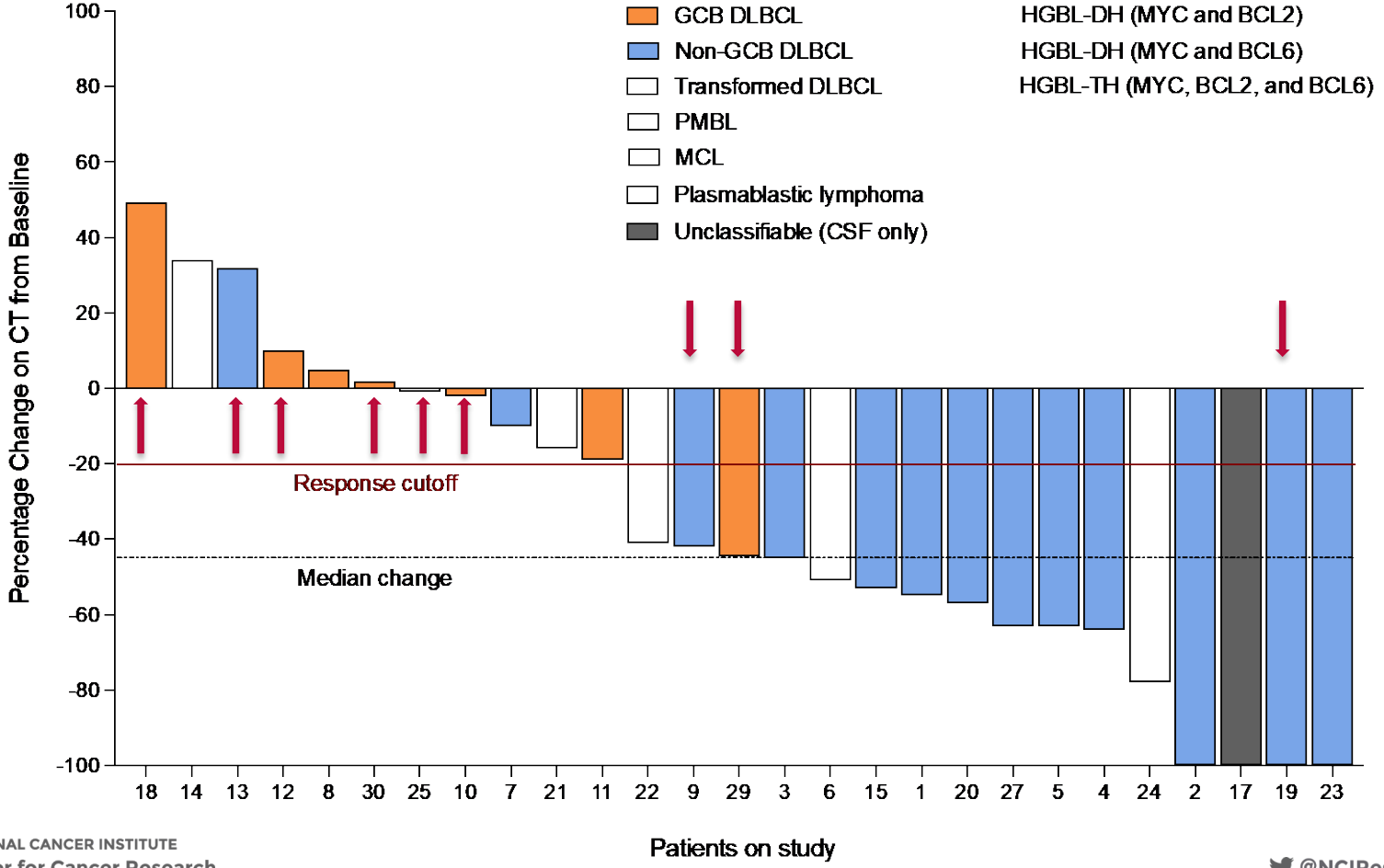


Ollila et al. *Blood* 2021 Feb 25;137(8):1120-1124

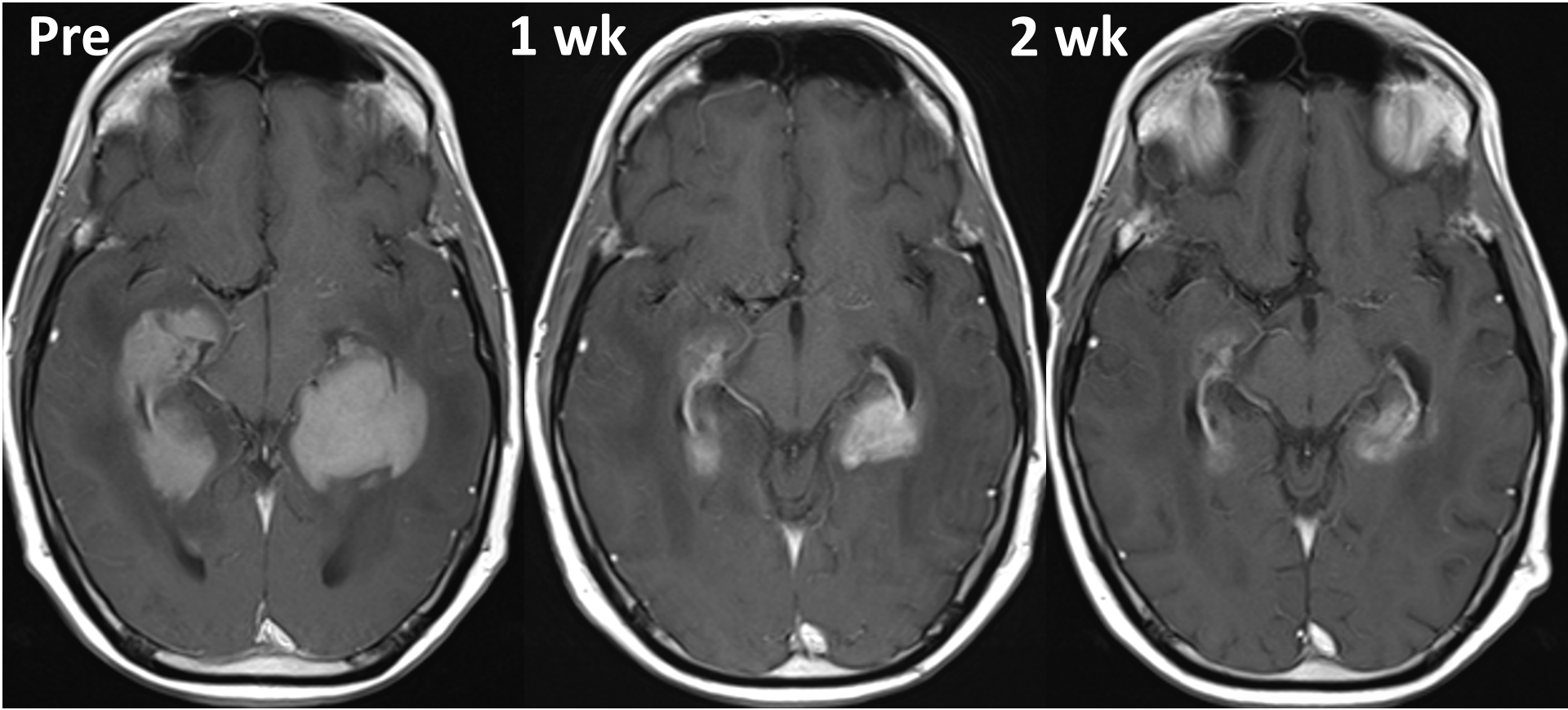
Response-Adapted TEDDI-R in Secondary CNS Lymphoma



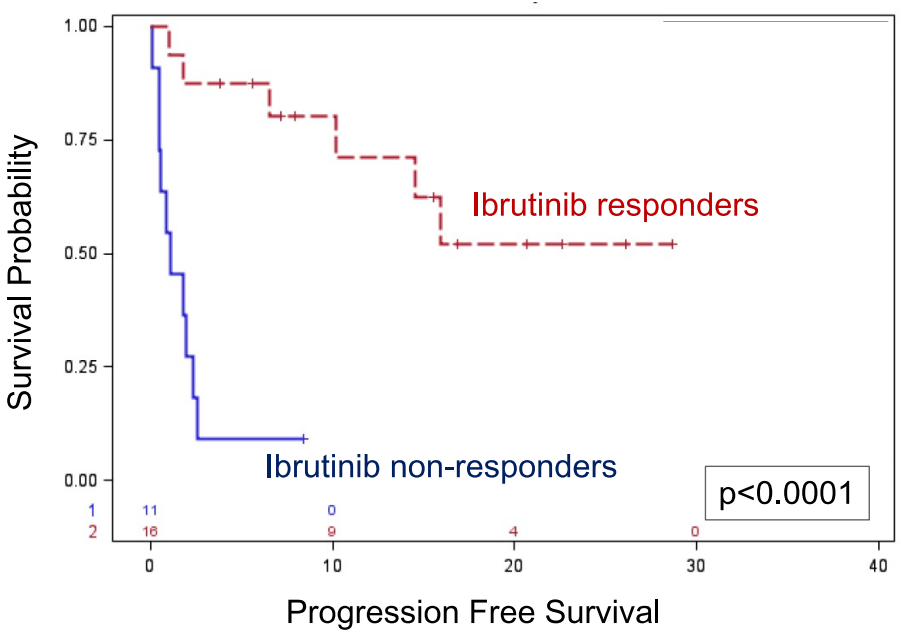
Response to Ibrutinib Monotherapy in 14 day Window

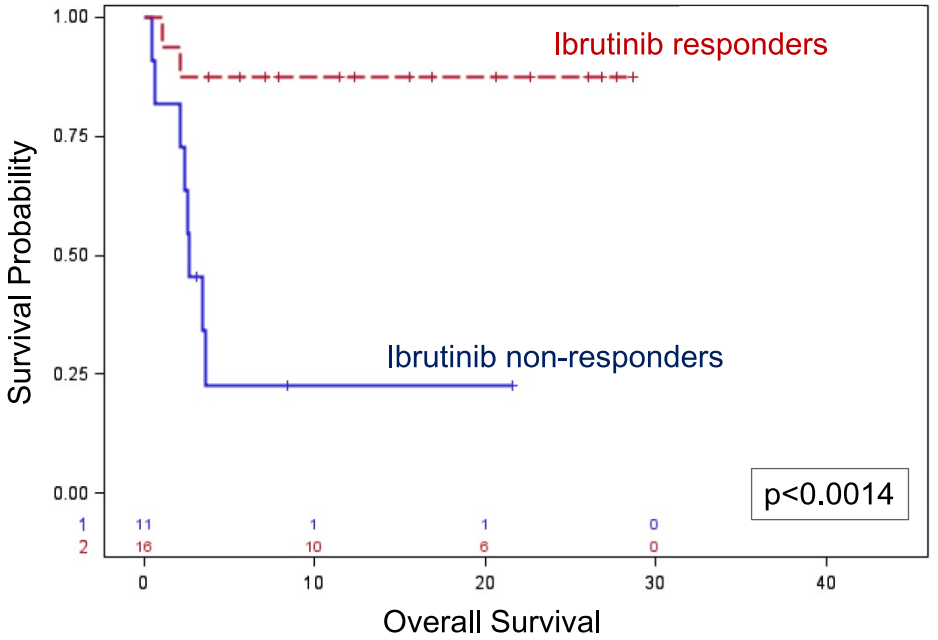


Improvement After Ibrutinib Window



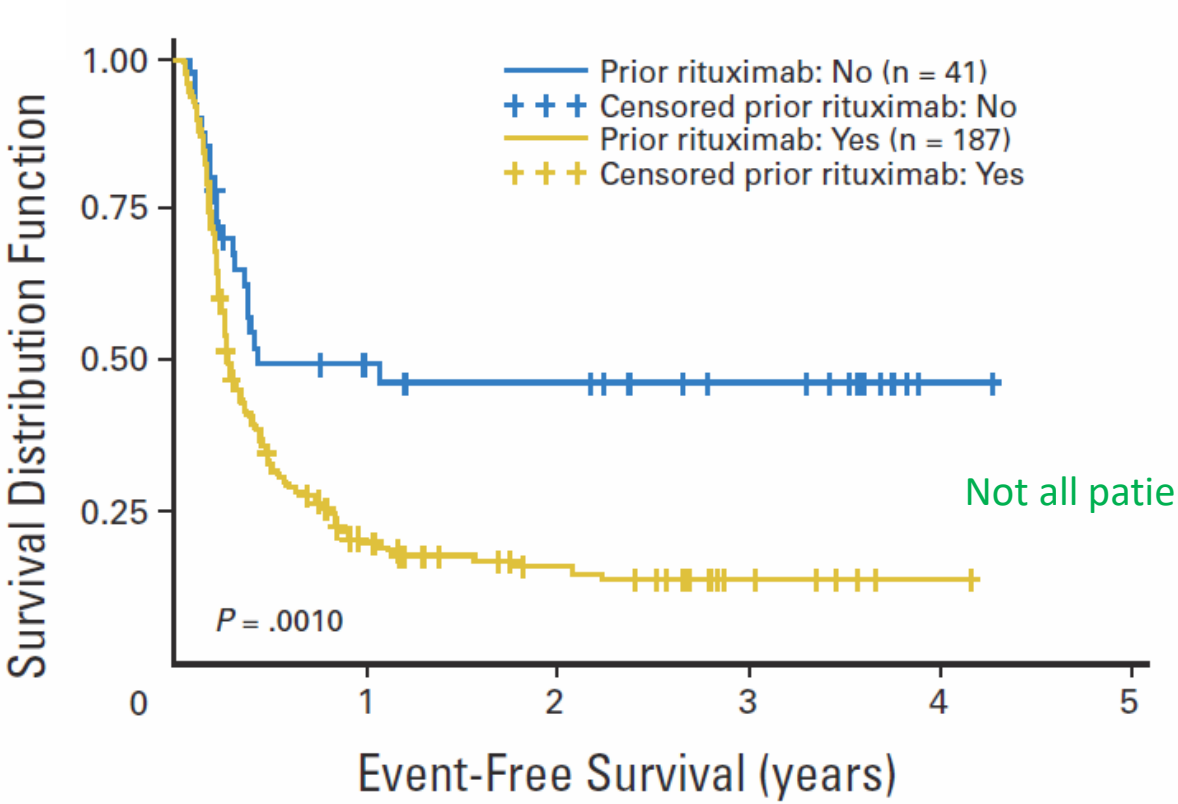
Improved Survival in Ibrutinib Responsive Tumors





Ongoing study: NCT03964090

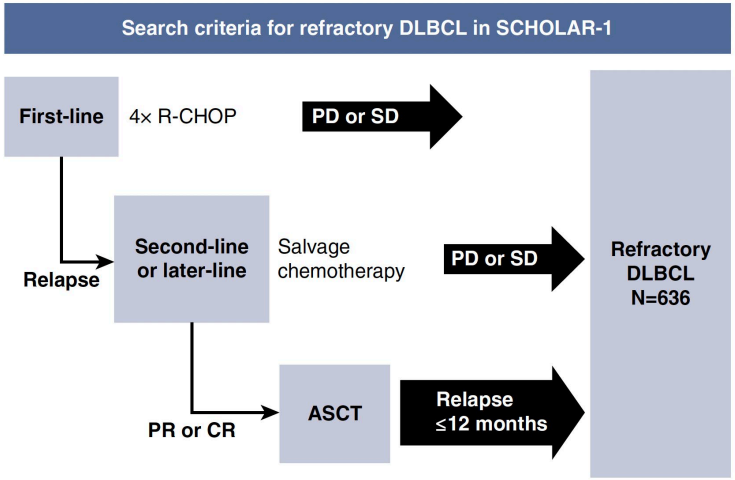
ASCT Largely Non-Curative for Relapsed Diffuse Large B-cell Lymphoma

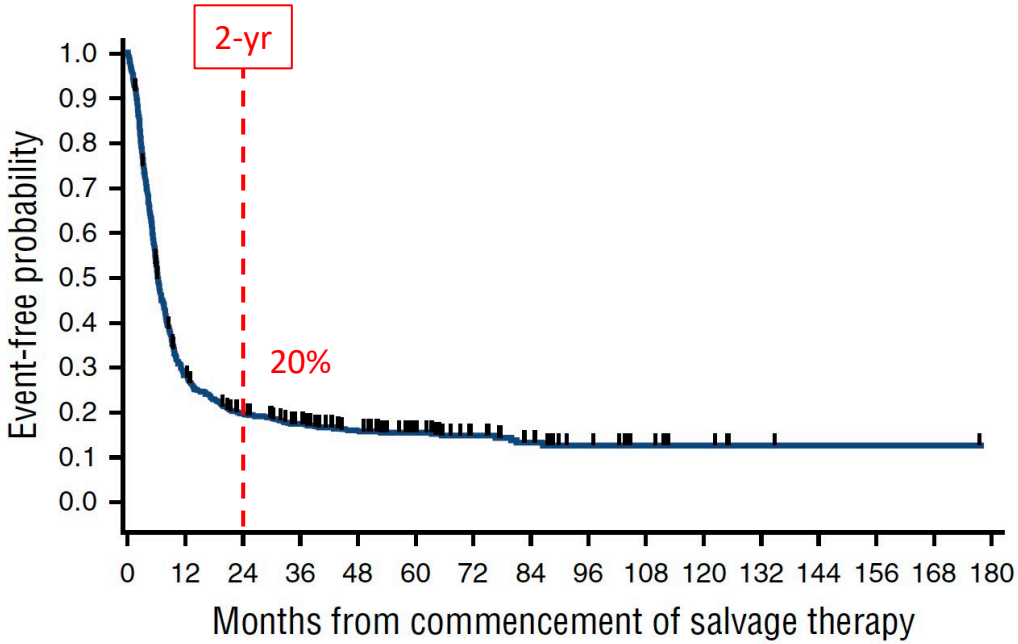


Not all patients ASCT-eligible

Gisselbrecht et al. *J Clin Oncol* 2010 Sep 20;28(27):4184-90

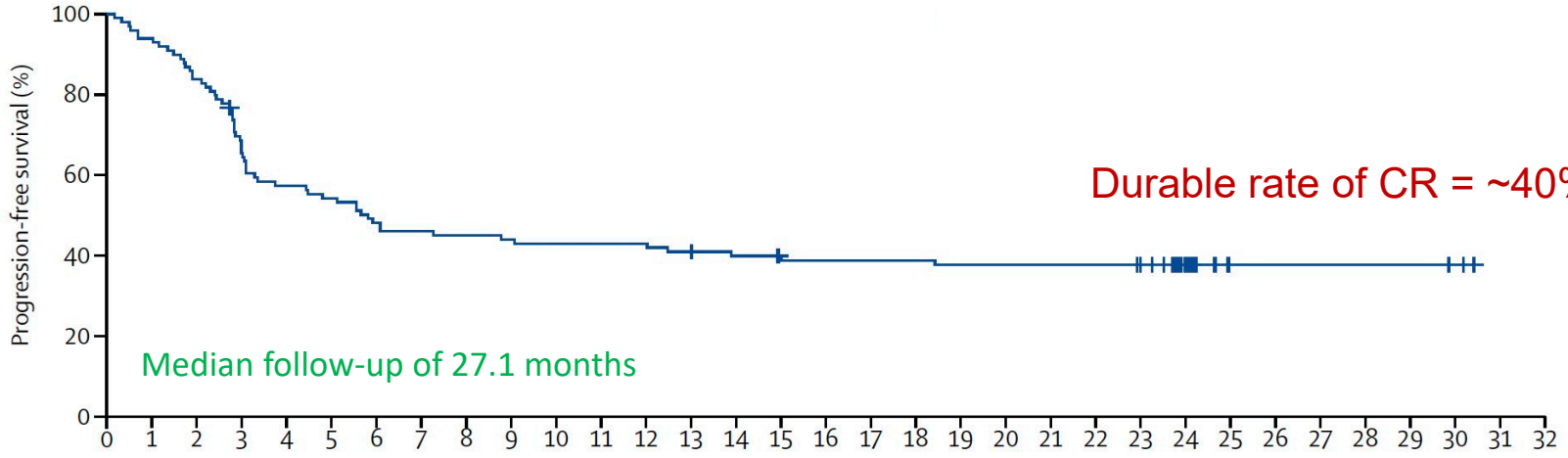
SCHOLAR-1 Established Benchmark for Refractory DLBCL





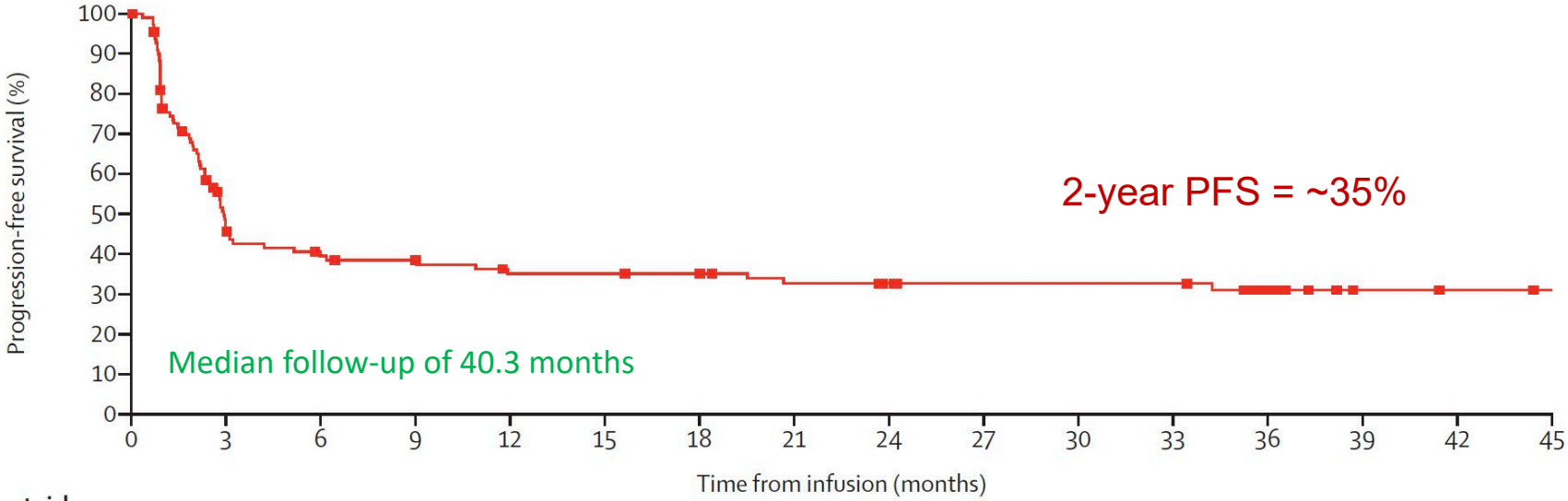
Crump et al. *Blood* 2017 Oct 19; 130(16):1800-08

Long-Term Follow-Up of ZUMA-1 (Axicabtagene ciloleucel)



Locke et al. *Lancet Oncol* 2019 Jan;20(1):31-42

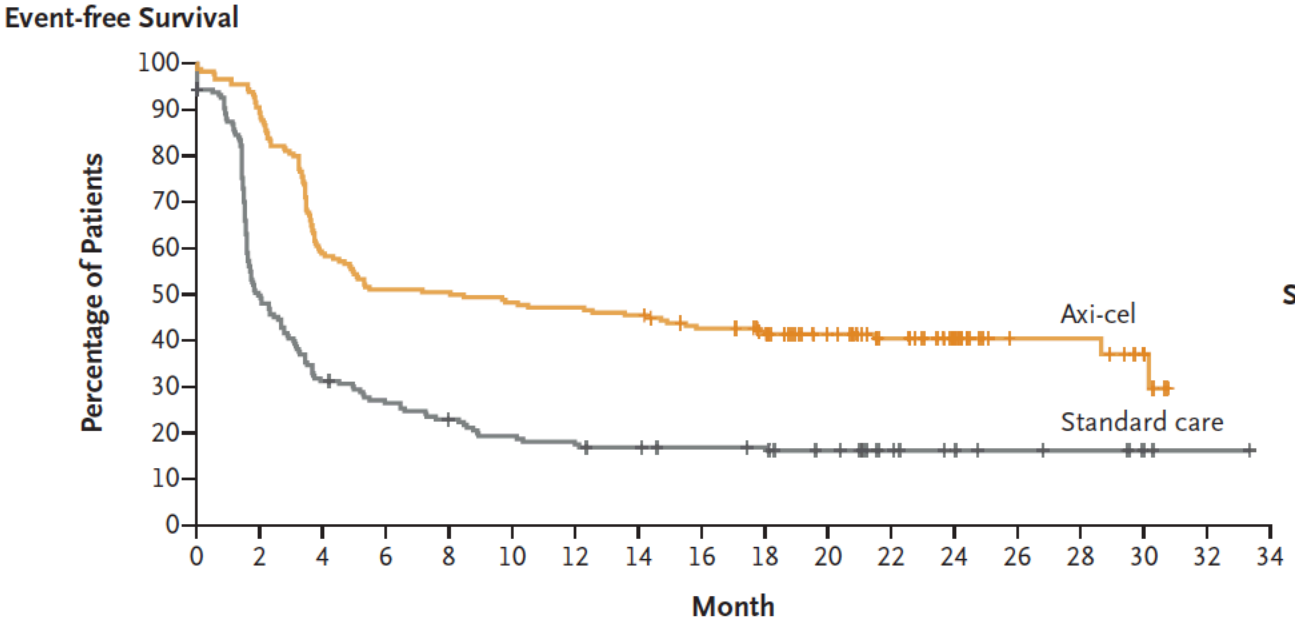
Long-Term Follow-Up of JULIET (Tisagenlecleucel)



Number at risk (number censored)															
All patients	115 (0)	47 (11)	38 (13)	36 (14)	31 (16)	31 (16)	30 (17)	26 (19)	24 (21)	21 (24)	21 (24)	21 (24)	11 (33)	2 (42)	1 (43)	0 (44)

Schuster et al. *Lancet Oncol* 2021 Oct;22(10):1403-1415

ZUMA-7 Did Meet Its Primary Endpoint



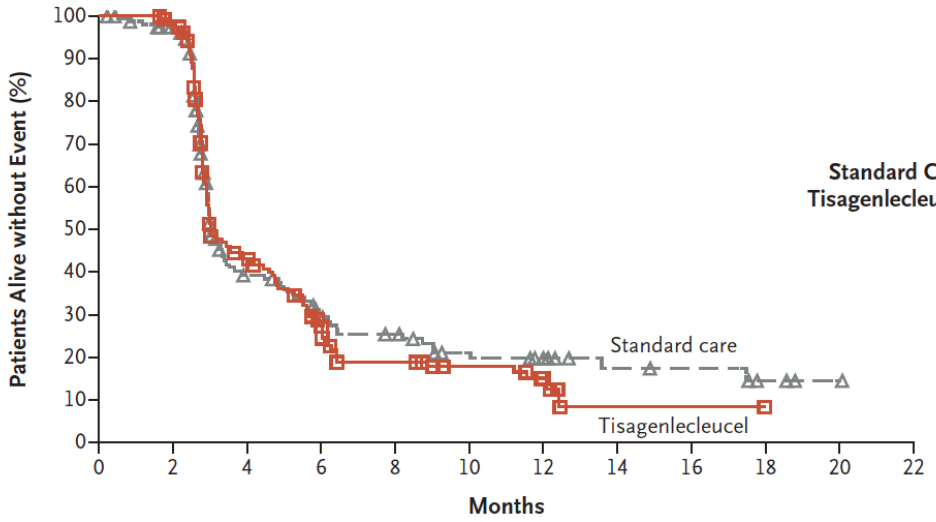
No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

Locke et al. *N Eng J Med* 2022 Feb 17;386(7):640-654

BELINDA Study Did Not Meet Its Primary Endpoint



	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

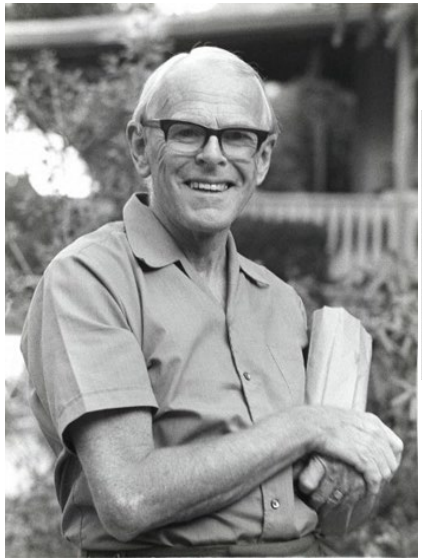
Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

Figure 2. Kaplan–Meier Plot of Event-free Survival.

An event was defined as progressive disease or stable disease on or after day 71 or death at any time (i.e., event-free survival at a given time point represents the estimated percentage of patients who had a complete or partial response at this time point among all randomly assigned patients). Responses were determined by an independent review committee whose members were unaware of the trial-group assignments. The triangles (standard-care group) and squares (tisagenlecleucel group) indicate censoring times.

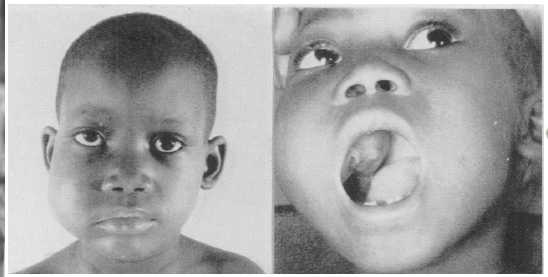
History of Burkitt Lymphoma

"Jaw lymphosarcoma"



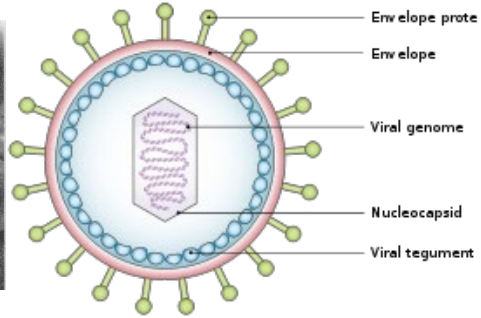
Denis P. Burkitt
(Irish Surgeon)

Rapidly proliferating tumors



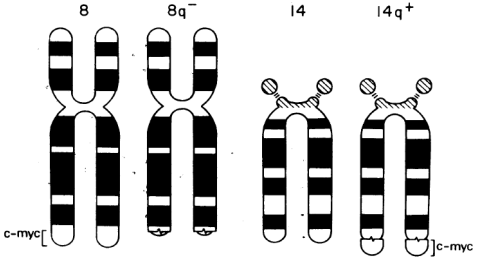
Endemic Burkitt Lymphoma

1st bona fide tumor virus



Epstein-Barr Virus

Oncogene activation



c-myc translocation

Burkitt D. *Br J Surg* 1958 Nov;46(197):218-23
Ngu VA. *Br J Cancer* 1965 Mar;19(1):101-7

Epstein MA. and Barr YM. *Lancet.* 1964 Feb 1;1(7327):252-3
Dalla-Favera R. et al. *Proc Natl Acad Sci.* 1982 Dec;79(24):7824-7

Clinical Features of Burkitt Lymphoma Variants

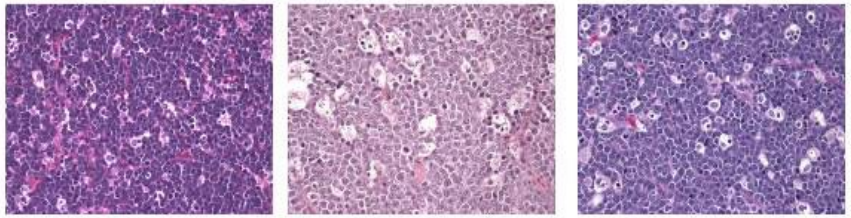
	Endemic	Sporadic	HIV-Associated
Annual Incidence	5-15/10^5	2-3/10^6	Unclear
Epidemiology	Equatorial Africa, malaria-endemic areas	Worldwide	Worldwide
Age	Median age, 4-7 y	Median age, 30 y	Median age, 44 y
Sex	M > F	M > F	M=F
Commonest Site(s)	Jaw/orbit	Ileocecal region	Extranodal sites
Bone Marrow	<10%	~30%	~30%
CNS (Leptomeningeal)	<10%	10%-20%	20%-30%
EBV-Associated	100%	~40%	25%-40%
c-MYC Translocation	~80% t(8;14); ~15% t(2;8); ~5% t(8;22)		

Cases of "possible BL" should be considered a medical emergency

Gastwirt J and Roschewski M. *Clin Adv Hematol Oncol* 2018 Dec;16(12):812-822

Pathology of Burkitt Lymphoma

Rapid diagnosis can be made on histology alone

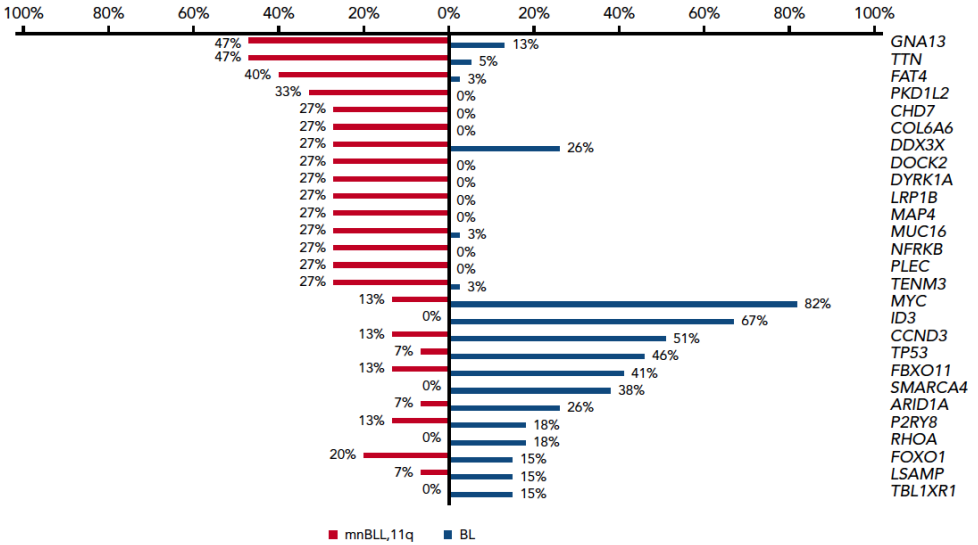


BL- endemic | BL-sporadic | BL- ID-HIV

- BL endemic is the prototype, similar in terms of morphology, phenotype, and genetics to sporadic and immunodeficiency-associated BL
- Plasmacytoid differentiation can be seen in some cases of HIV-BL
- Typical phenotype: CD20+, CD10+, BCL6+, and negative for TdT, BCL2 (weakly pos 20%)
- Proliferative rate close to 100%

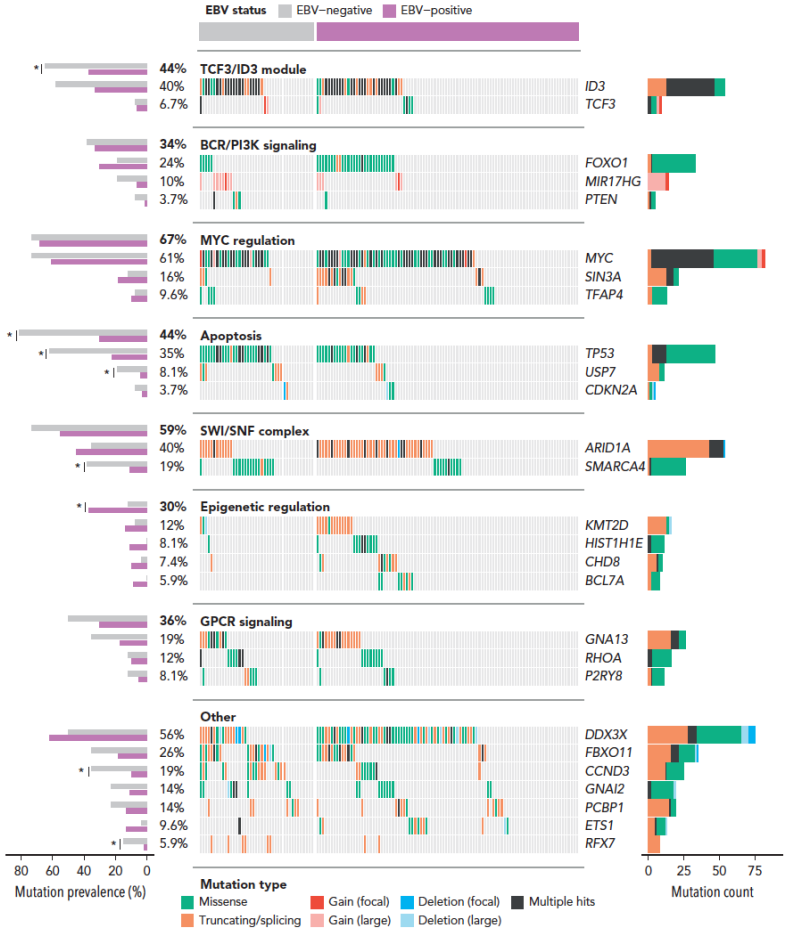
Images courtesy of Elaine Jaffe and Stefania Pittaluga

Burkitt-like lymphoma with 11q aberration



Wagener R et al. *Blood* 2019 Feb 28;133(9):962-966

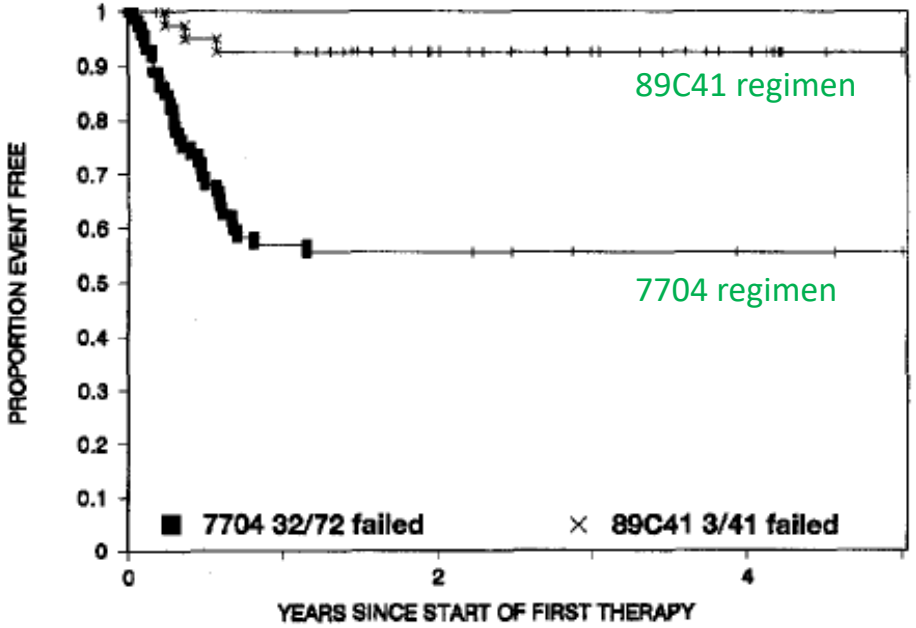
Genomic Landscape of Burkitt Lymphoma Differs by EBV status



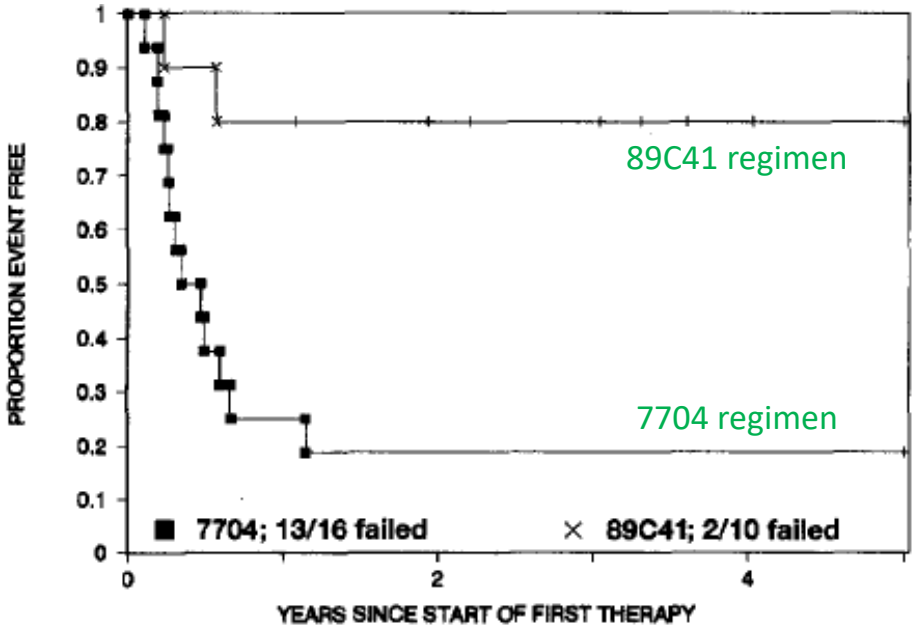
Grande BM, Gerhard DS et al. *Blood.* 2019 Mar 21;133(12):1313-1324

“Magrath” Regimen (CODOX-M/IVAC) for Burkitt Lymphoma

All patients



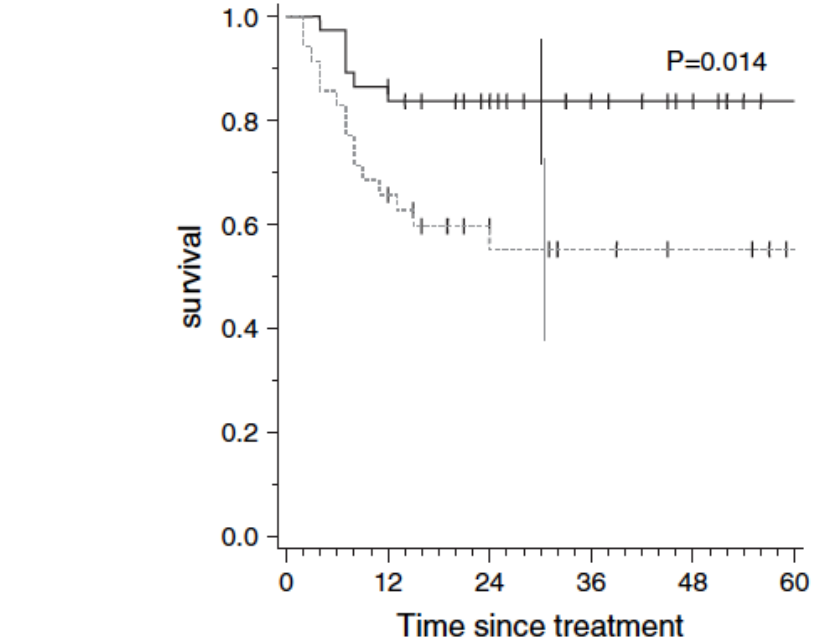
Stage IV patients



89C41: 21 pediatric and 20 adult patients with a median age of 25 years

Magrath I. et al. *J Clin Oncol.* 1996 Mar;14(3):925-34

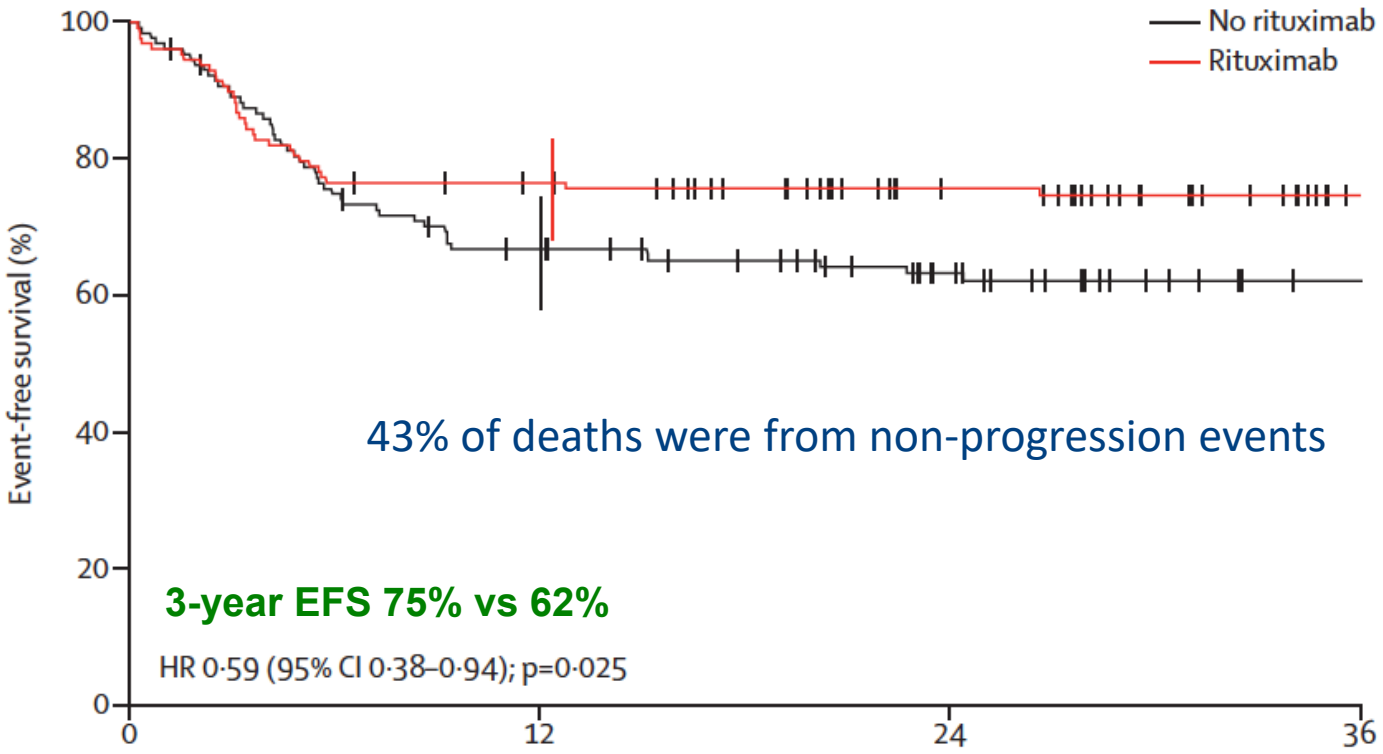
Age Strongly Predicts Survival with Pediatric Regimens in Burkitt Lymphoma



Overall survival curve of the 72 patients according to age.

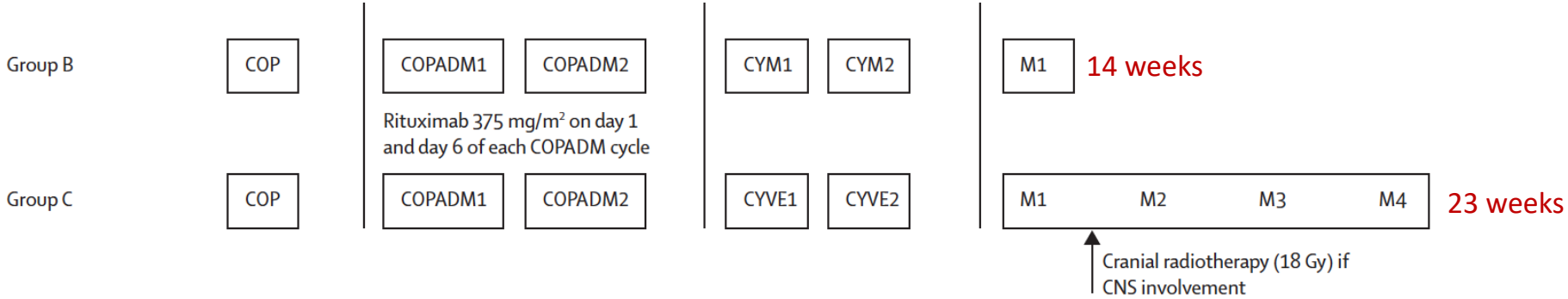
Divine M. et al. *Ann Oncol* 2005;6(12):1928-35

Rituximab Improves Outcomes for Adult Burkitt Lymphoma



Ribrag V. et al. *Lancet* 2016;387(10036):2402-11

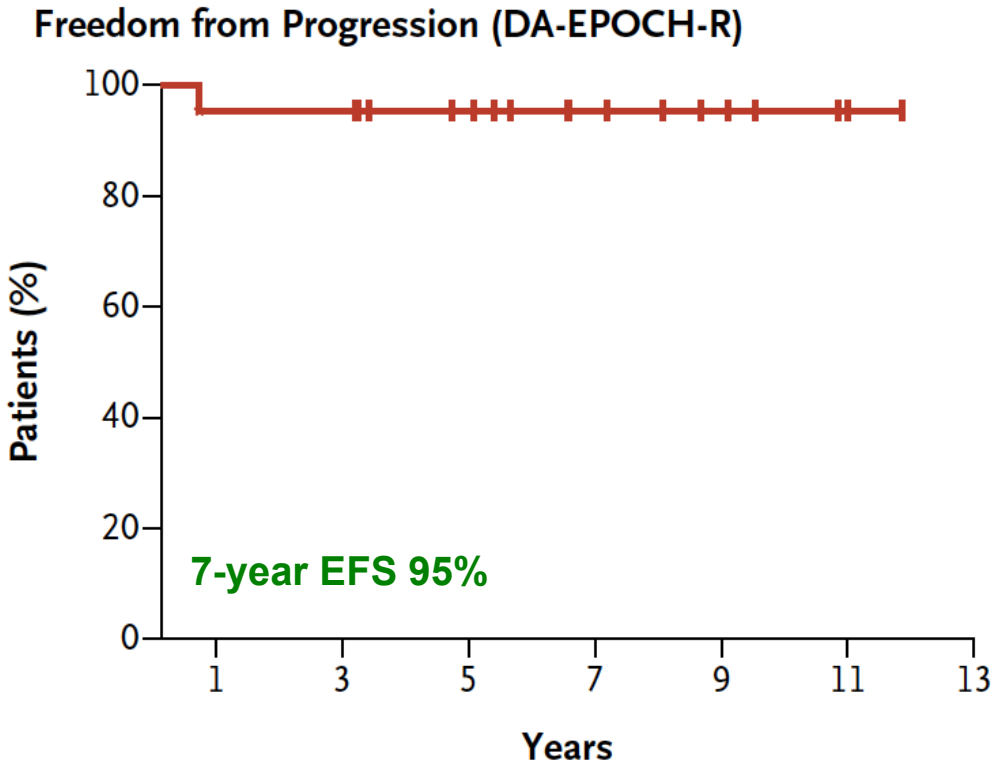
Highly-Intensive Treatment of Burkitt Lymphoma



Short-term toxicities → myelosuppression, infections, neuropathy
Long-term and late-onset toxicities → sterility, second malignancies, neuropathy, cancer survivorship

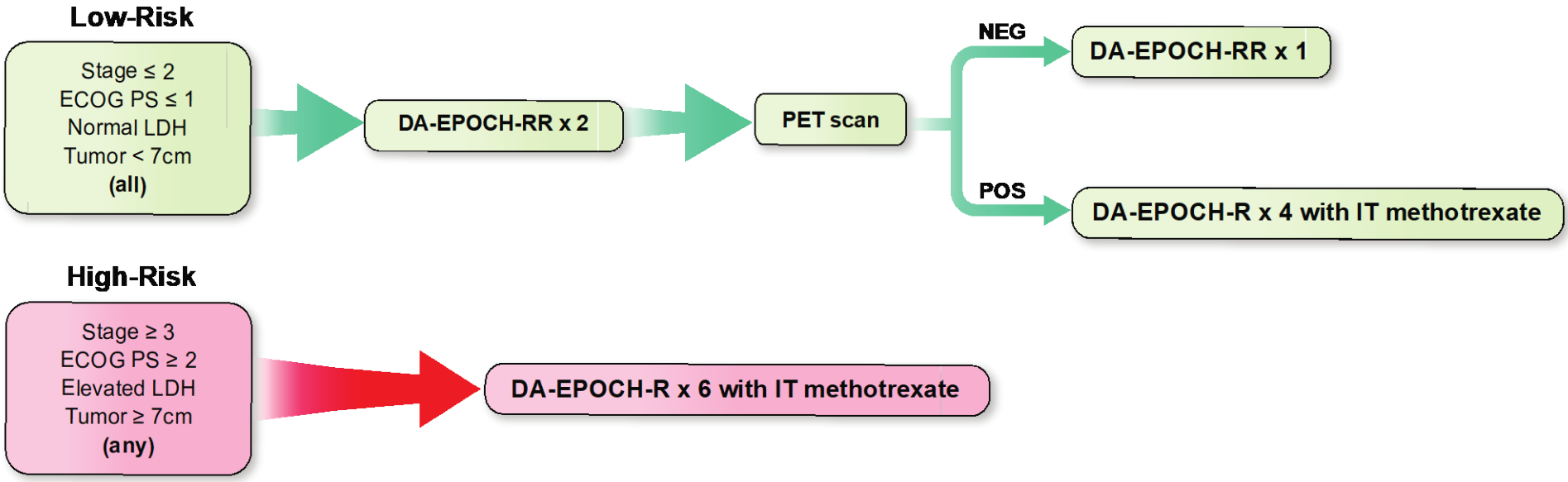
Ribrag V. et al. *Lancet* 2016;387(10036):2402-11

Low-Intensity Therapy for Burkitt Lymphoma



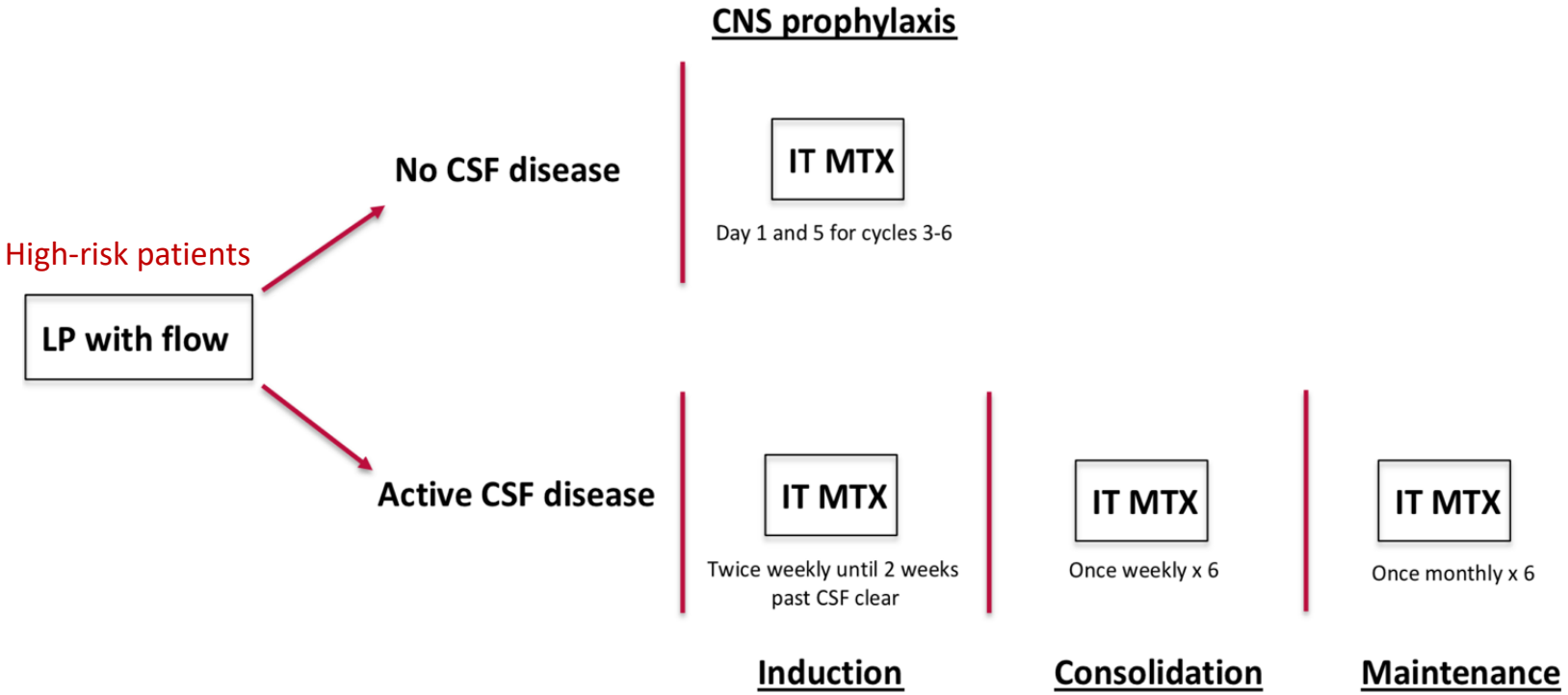
Dunleavy K. et al. *N Eng J Med* 2013;369(20):1915-25

NCI 9177: Risk-Adapted Study of DA-EPOCH-R for Adult Burkitt Lymphoma



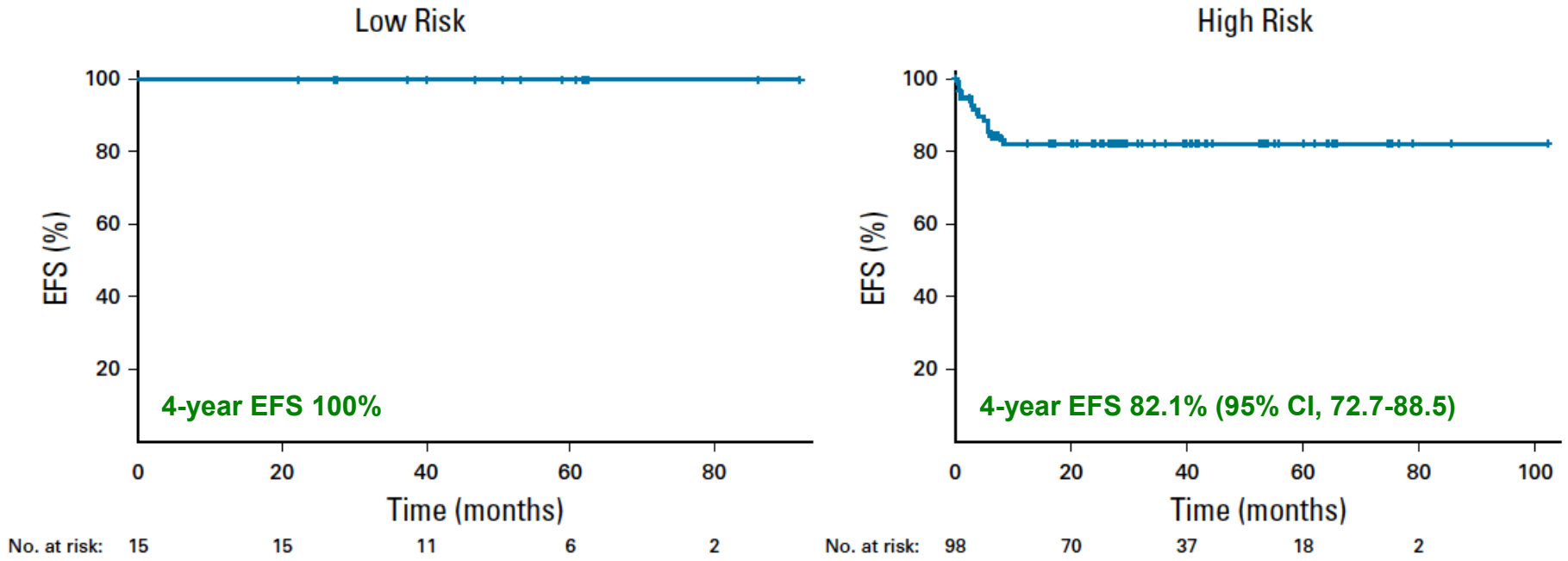
Roschewski M., Dunleavy K. et al. *J. Clin Oncol* 2020;38(22):2519-2529

Risk-Adapted Approach to CNS Management with DA-EPOCH-R



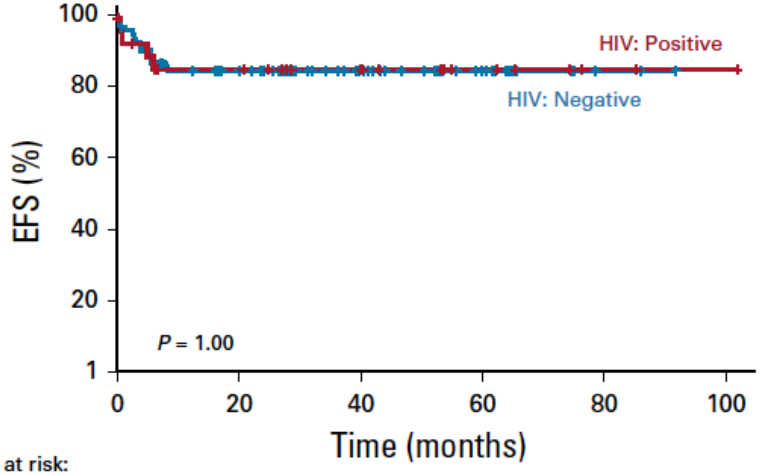
Roschewski M., Dunleavy K. et al. *J. Clin Oncol* 2020;38(22):2519-2529

Risk-Adapted Study of DA-EPOCH-R for Adult Burkitt Lymphoma



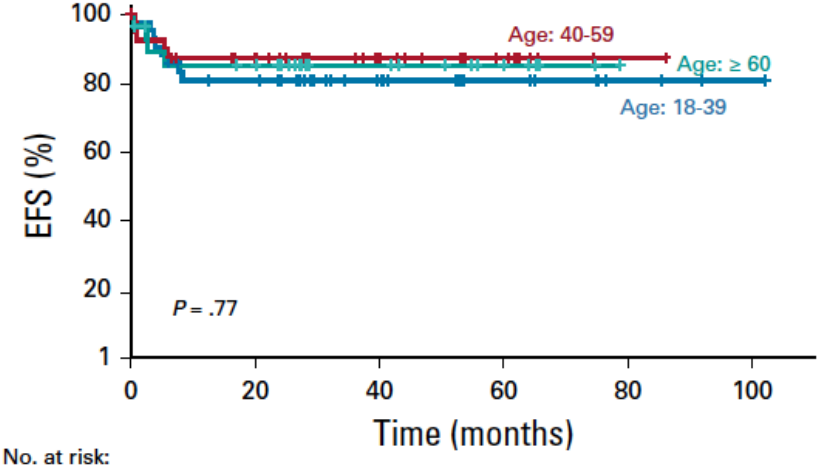
Roschewski M., Dunleavy K. et al. *J. Clin Oncol* 2020;38(22):2519-2529

Neither HIV Status Nor Age Affected Outcomes with DA-EPOCH-R



No. at risk:

HIV: Negative	85	65	35	18	2
HIV: Positive	28	20	13	6	2

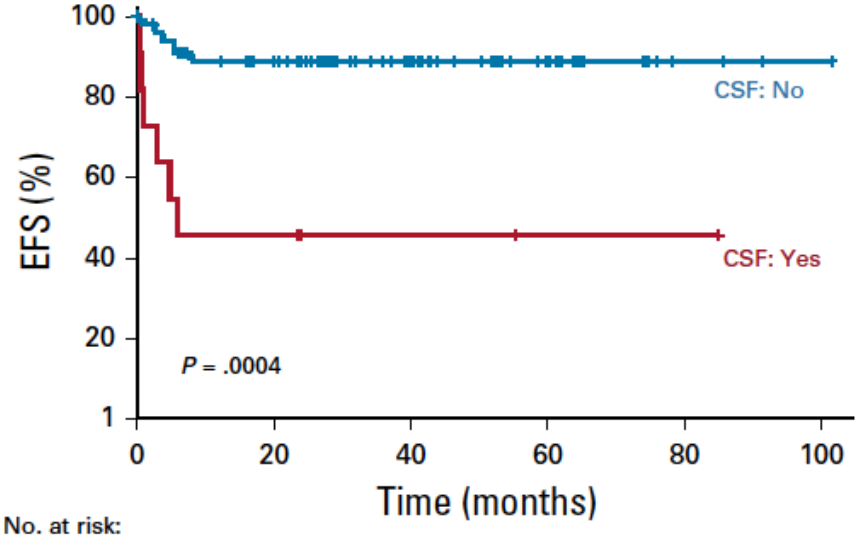


No. at risk:

Age: 18-39	43	32	19	9	3
Age: 40-59	41	31	18	9	1
Age: ≥ 60	29	22	11	6	0

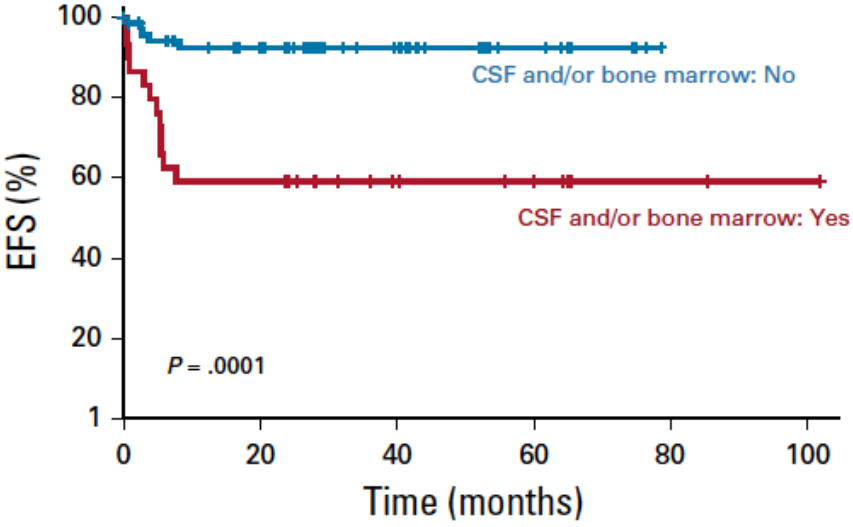
Roschewski M., Dunleavy K. et al. *J. Clin Oncol* 2020;38(22):2519-2529

High-Risk Subsets of Burkitt Lymphoma with DA-EPOCH-R



No. at risk:

CSF: No	102	80	46	23	3
CSF: Yes	11	5	2	1	1

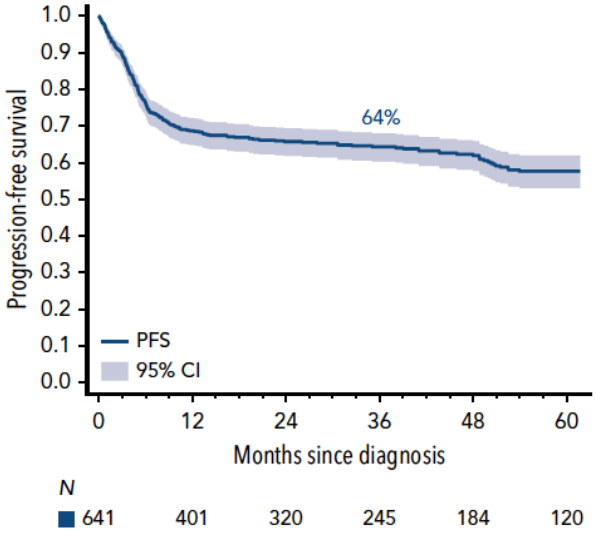


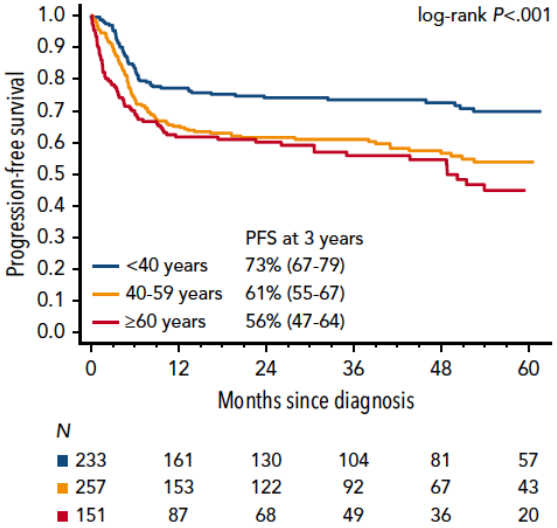
No. at risk:

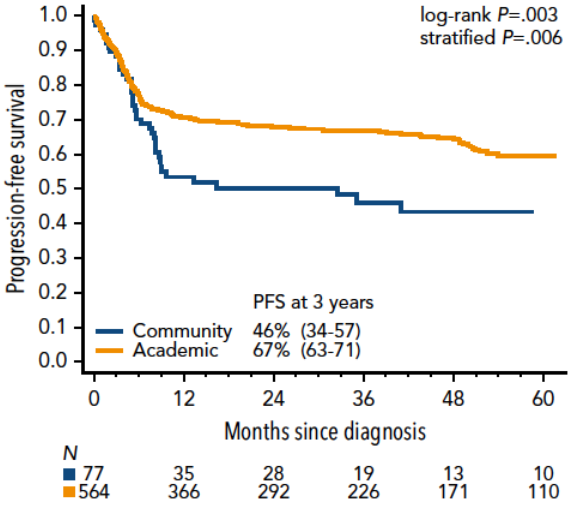
CSF and/or bone marrow: No	0	69	53	29	12	0
CSF and/or bone marrow: Yes	1	29	17	8	6	2

Roschewski M., Dunleavy K. et al. *J. Clin Oncol* 2020;38(22):2519-2529

“Real-World” Outcomes for Adult Burkitt Lymphoma in the U.S.



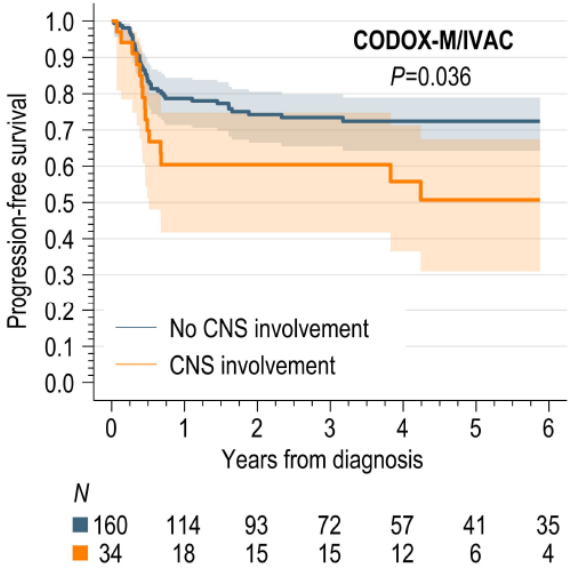


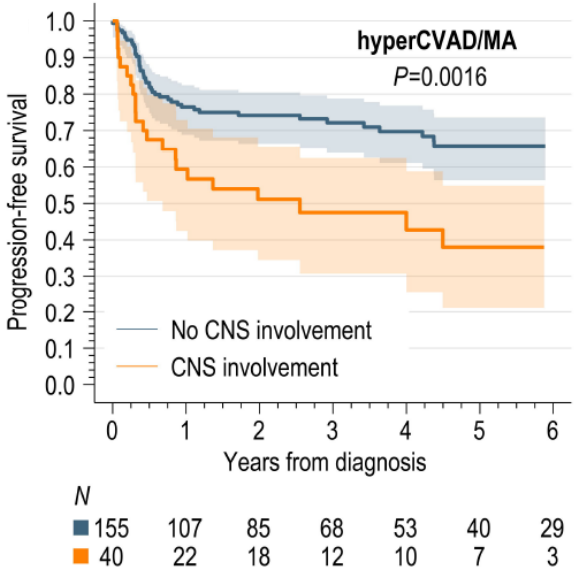


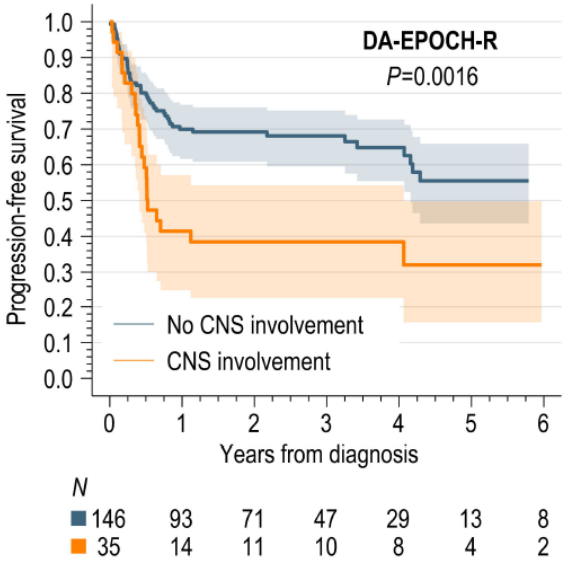
- Primary refractory = 14%
- Treatment-related mortality = 10%
- Rate of CNS involvement = 19%

Evens AM. et al. *Blood* 2021;137(3):374-386

Clinical Outcomes Affected by CNS Involvement Across Regimens







Baseline CNS involvement was more common with concomitant HIV infection

Zayac AS., Evens AM. et al. *Haematologica* 2021;Feb 4 (online only)

Conclusions

1. Strategies to increase cure rate in high-risk DLBCL include precision medicine

2. Genetic heterogeneity of DLBCL is a barrier to precision medicine

3. Precision medicine toolkit: technology, study designs, ***and*** novel agents

Thank you for your attention!