Aggressive B and T cell lymphomas: Treatment paradigms in 2017

John P. Leonard M.D.

Richard T. Silver Distinguished Professor of Hematology and Medical Oncology

Associate Dean for Clinical Research

Interim Chairman, Joan and Sanford I. Weill Department of Medicine

Interim Physician-in-Chief, New York Presbyterian/Weill Cornell

Associate Director, Meyer Cancer Center

Weill Cornell Medicine

NewYork-Presbyterian

Disclosures

Consulting advice:

Teva, Gilead, Juno, Celgene, Kite, Genmab, Nanostring, Biotest, Regeneron, Abbvie, Sutro, Sunesis, BMS

WHO Lymphoma Classification 2016

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
*EBV$^+$ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*HHV8$^+$ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma

Table 1. (continued)

Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

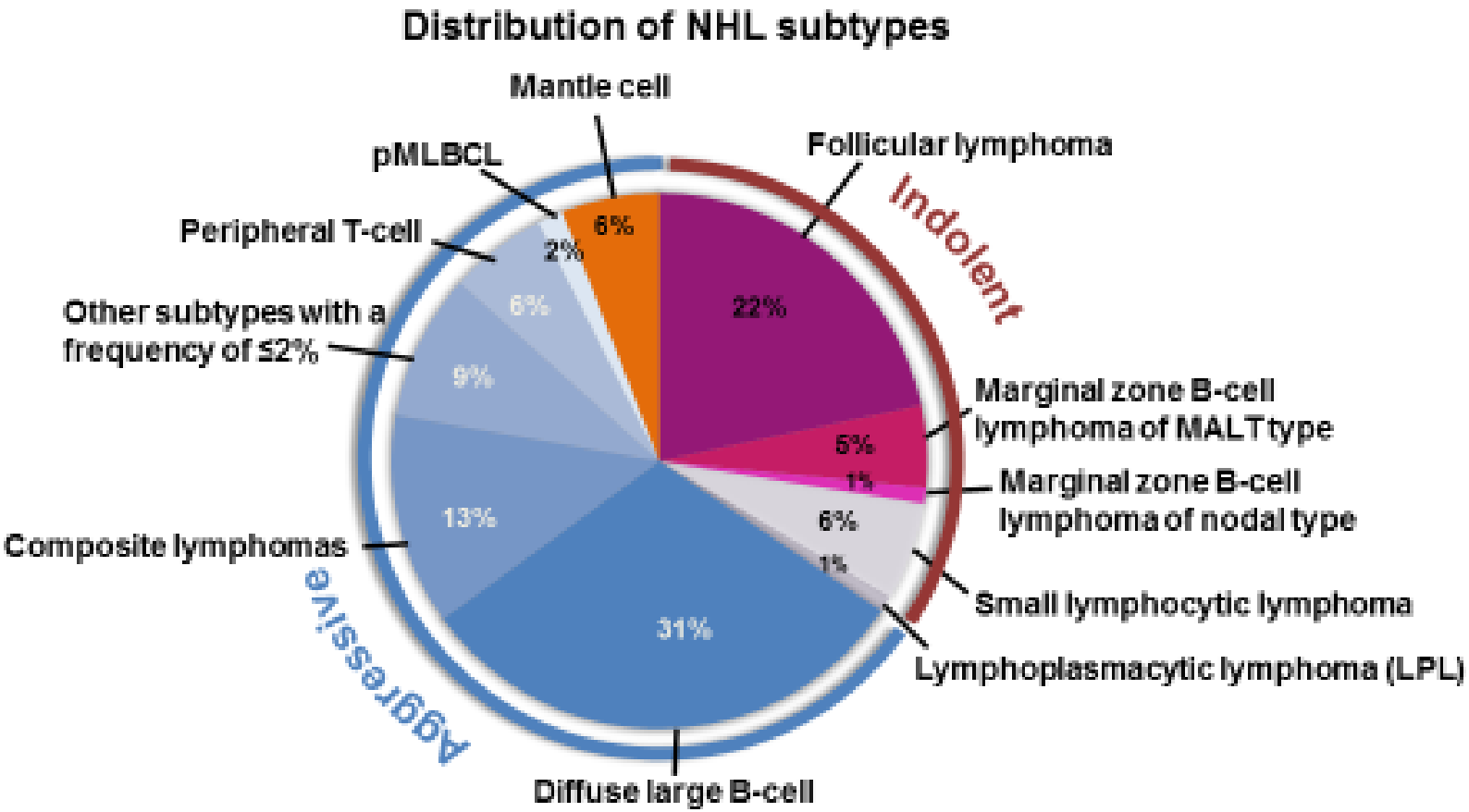
Provisional entities are listed in italics.
*Changes from the 2008 classification.

small population, but in others associated with a lymphocytosis.[4] Whereas in 2008 it was unknown whether MBL was a precursor of CLL, we now know that MBL precedes virtually all cases of **CLL/small lymphocytic lymphoma** (SLL).[5] The updated WHO will retain the current criteria for MBL, but will emphasize that "low-count" MBL, defined as a PB CLL count of $<0.5 \times 10^9$/L, must be distinguished from "high-count" MBL because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care.[6,7] In contrast, high-count MBL requires routine/yearly follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 CLL, although immunoglobulin heavy chain variable region (IGHV)-mutated cases are more frequent in MBL.[8] Also impacting our diagnostic criteria, the revision will eliminate the option to diagnose CLL with $<5 \times 10^9$/L PB CLL cells in the absence of extramedullary

100 + entities

Swerdlow et al, Blood 2016

Less precision in practice



MALT, mucosa-associated lymphoid tissue pMLBCL, primary mediastinal large B-cell lymphoma

Armitage JO, et al. *J Clin Oncol.* 1998;16(8):2780-2795.

Mantle cell lymphoma (10%)

Incurable, median survival 5-10 years

Key focus:

- **More vs less intensive initial therapies**
  - **Bendamustine based rx in older pts standard**
  - **Does SCT improve survival in younger patients?**
  - **Role of MRD?**
- **Development of novel agents and translational studies to understand resistance and advance rational combinations**

Rituximab maintenance after autologous stem cell transplantation prolongs survival in patients with mantle cell lymphoma (final result of the LyMa trial)

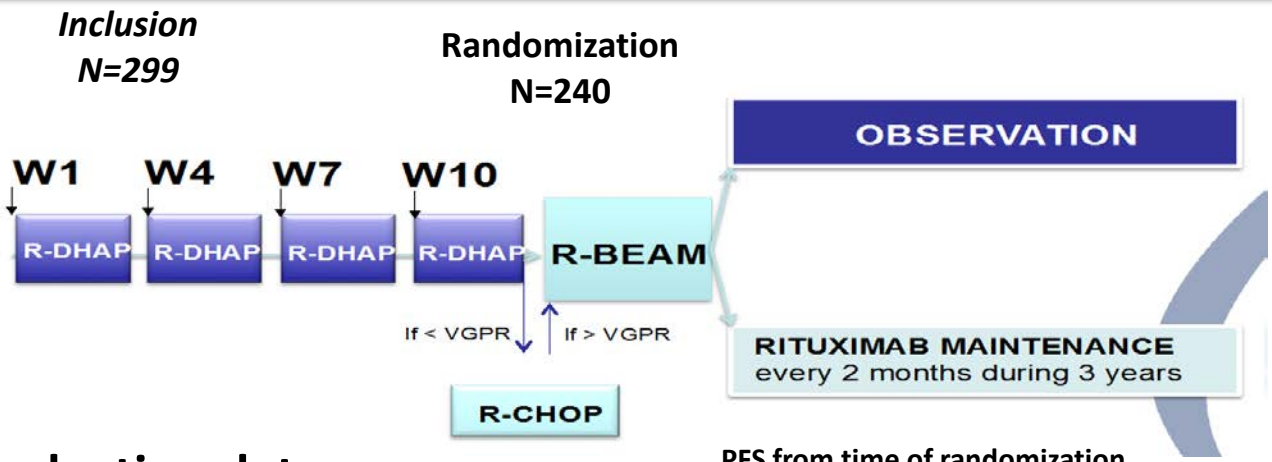
Steven Le Gouill, MD, PhD, Catherine Thieblemont, MD, PhD, Anne Moreau, MD, Lucie Oberic, MD, Krimo Bouabdallah, MD, Emmanuel Gyan, MD, PhD, Gandhi Damaj, MD, PhD, Vincent Ribrag, MD, PhD, Pierre Feugier, MD, PhD, Olivier Casasnovas, MD, Hacène Zerazhi, MD, Corinne Haioun, MD, PhD, Hervé Maisonneuve, MD, Eric Van Den Neste, MD, PhD, Olivier Tournilhac, MD, PhD, Katell Ledu, MD, Franck Morschhauser, MD, PhD, Bernard Christian, MD, Guillaume Cartron, MD, PhD, Luc Fornecker, MD, PhD, Danielle Canioni, MD, PhD, Marie-Christine Béné, MD, PhD, Gilles Salles, MD, PhD, Hervé Tilly, MD, PhD, Thierry Lamy, MD, PhD, Remi Gressin, MD, Olivier Hermine, MD, PhD, on behalf of the LYSA group

ClinicalTrials.gov, NCT00921414

Lysa
THE LYMPHOMA STUDY ASSOCIATION

Abstract # 145 ASH 2016

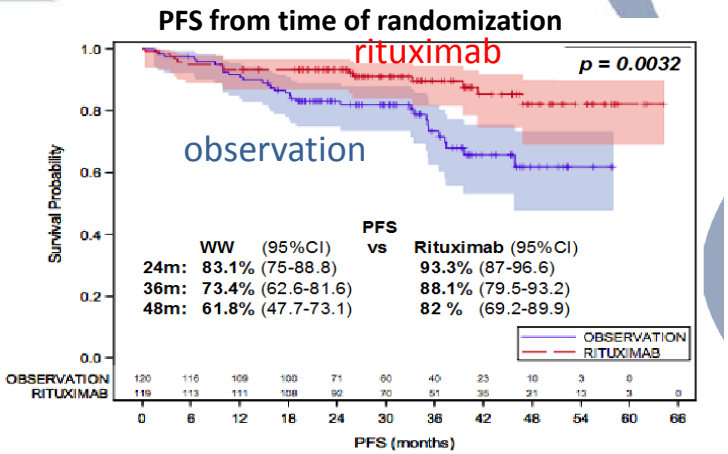
MCL: Role of Maintenance Therapy



Induction data presented ASH 2014:

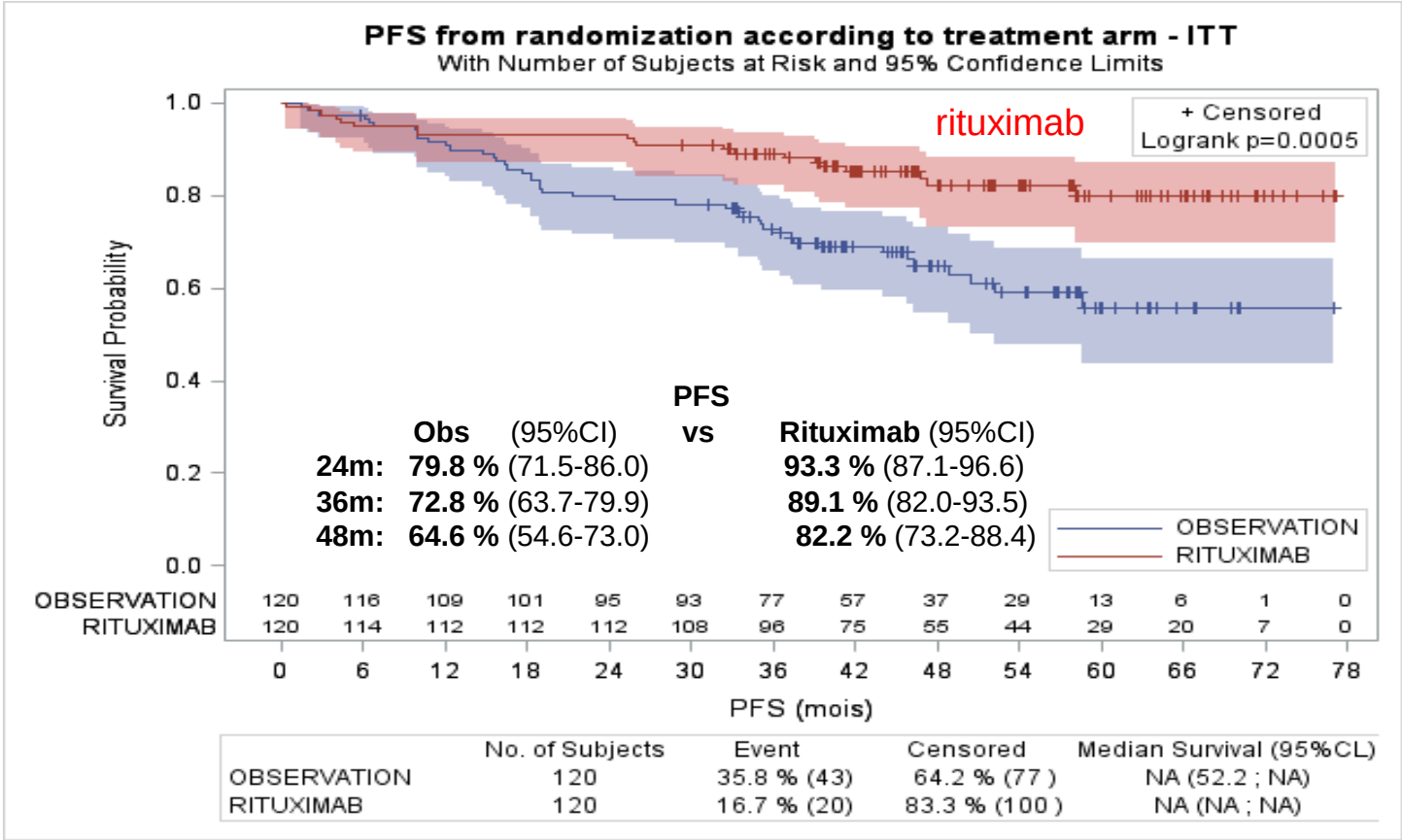
82% CR post-induction

93% post ASCT



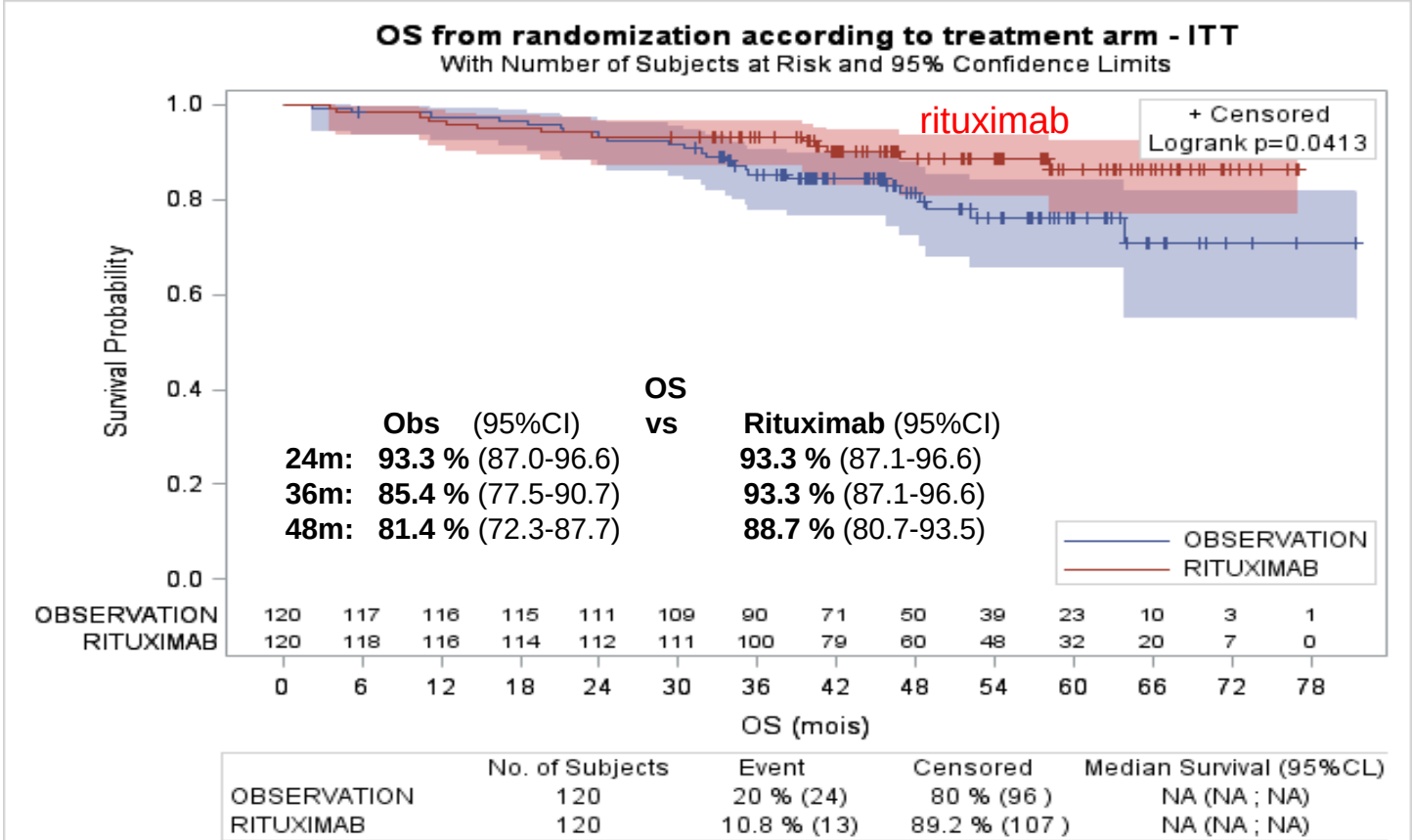
Le Gouill, Ash 2014 abst # 124

PFS from Randomization



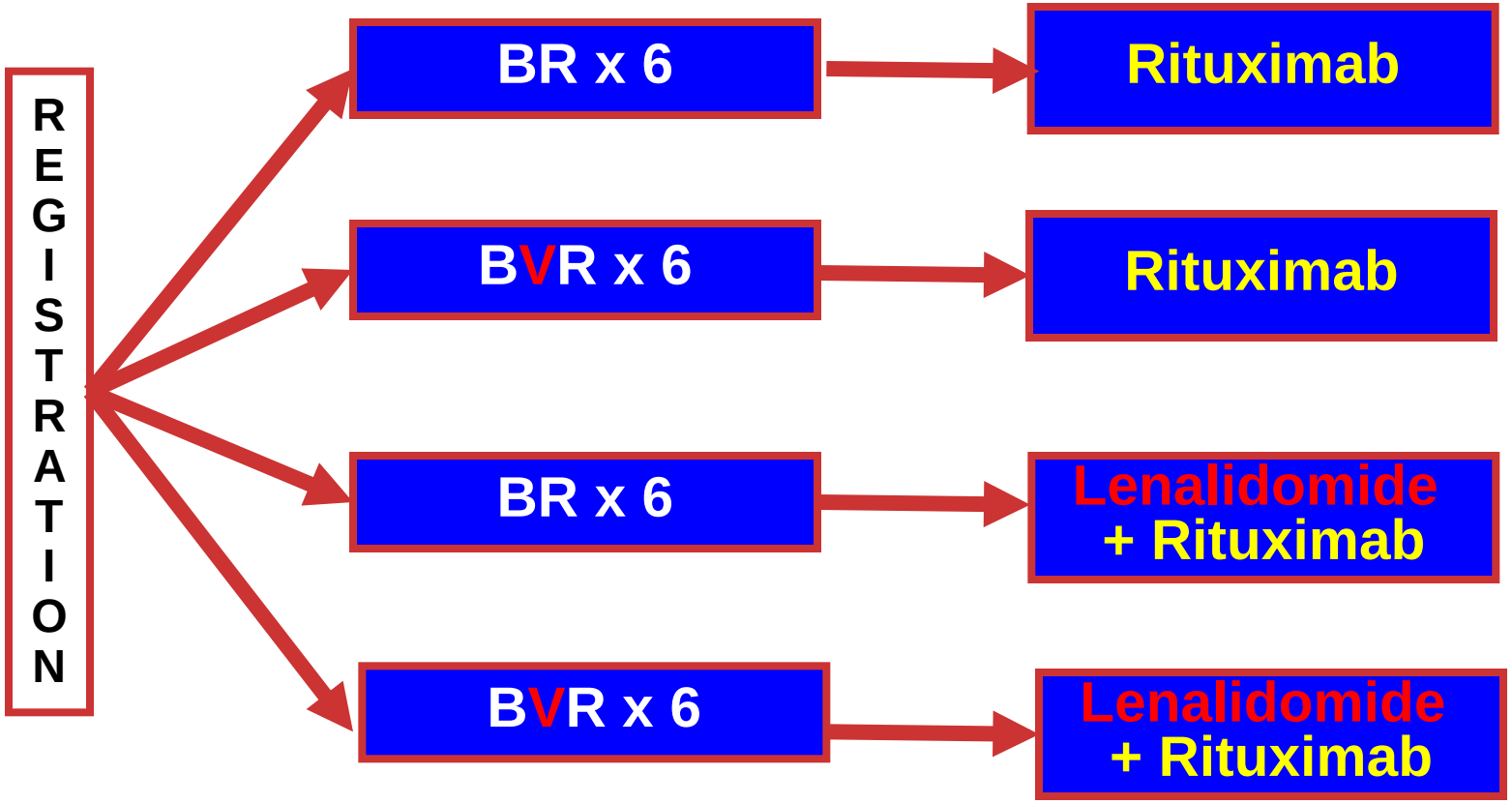
Median Follow up : 50.2m (46.4-54.2)

OS from Randomization

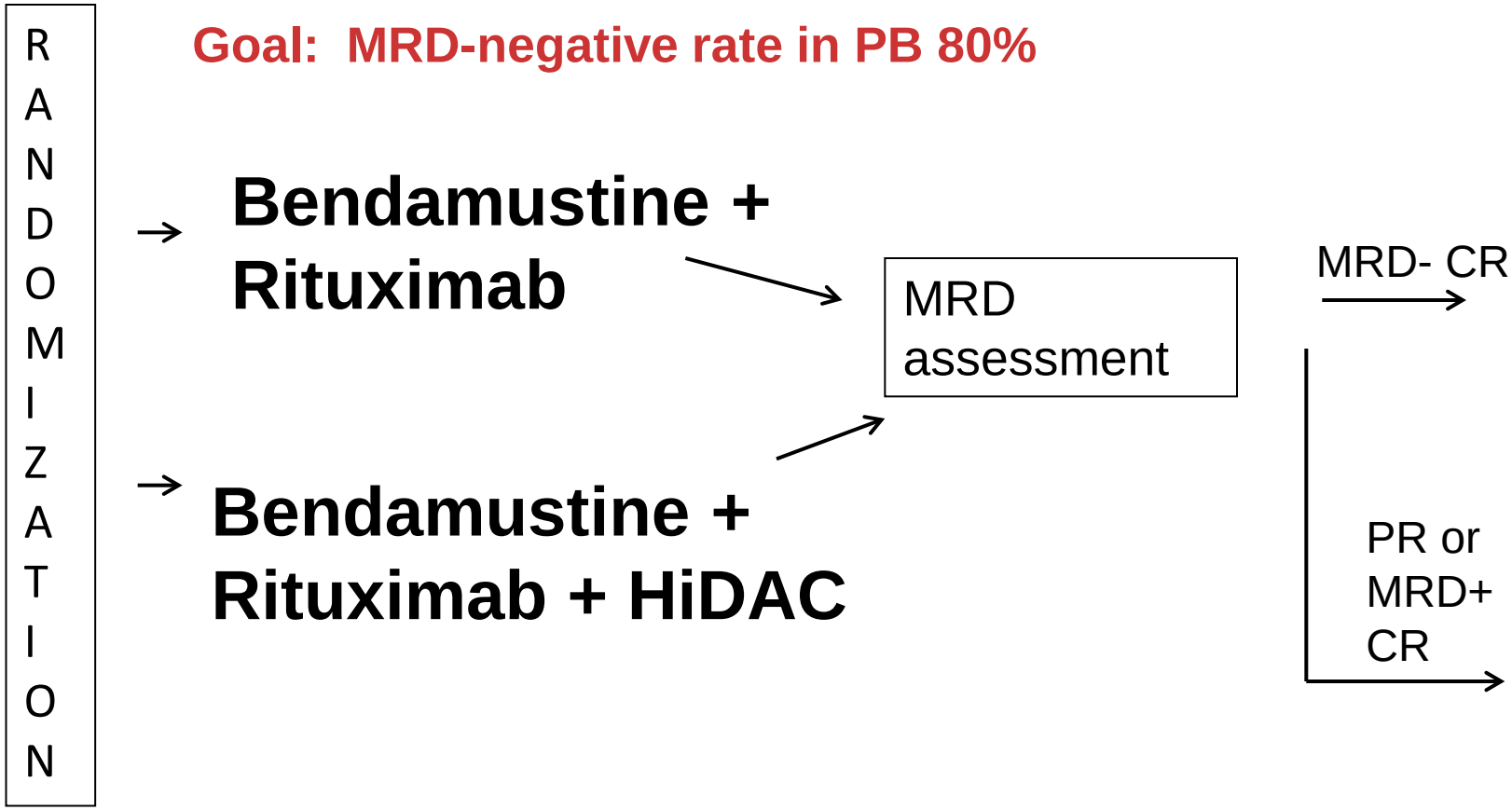


Median follow up: 50.2m (46.4-54.2)

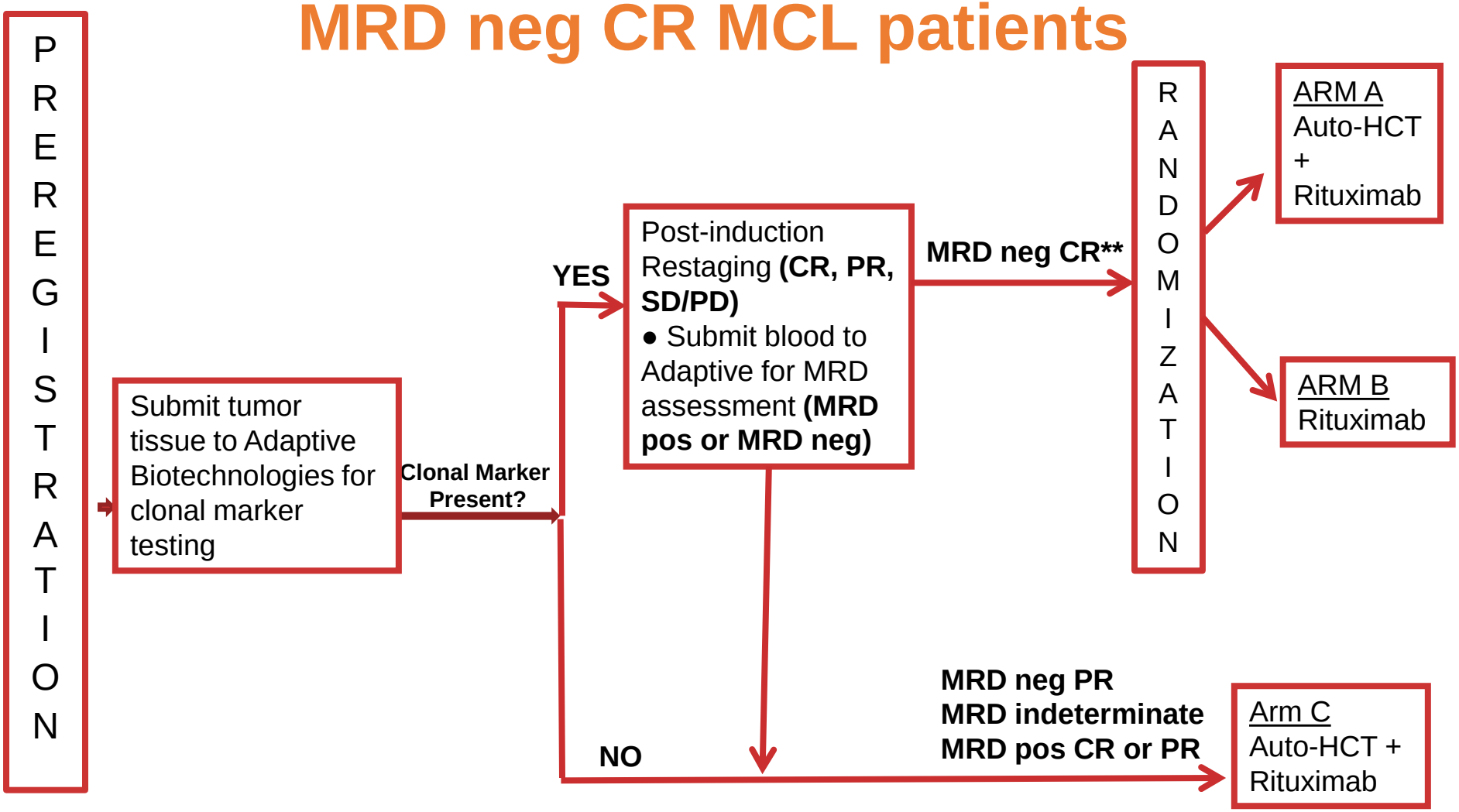
E1411: Randomized Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma



Intergroup Phase II trial in MCL



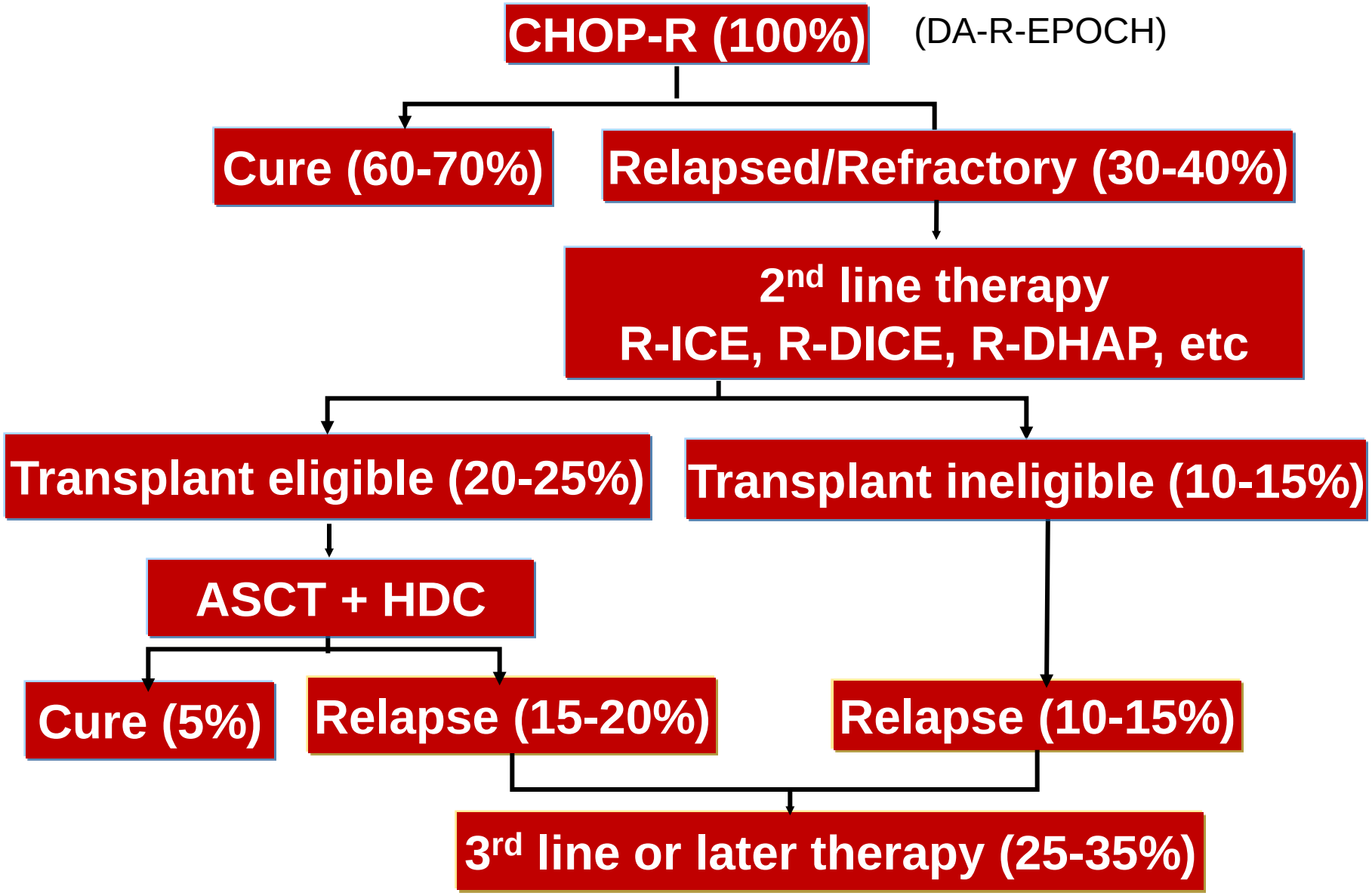
E4151: Randomized trial of SCT/R vs R in MRD neg CR MCL patients



Diffuse large B cell lymphoma

- Median age 60, usually with advanced stage disease
  - LAN, extranodal disease, symptoms
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
- Most patients treated same (R-CHOP)
- Unmet need – more cures, reduce toxicity
- Who should we treat differently?
- If refractory to second-line therapy, prognosis is poor

Treatment algorithm for DLBCL



Comparison of CHOP-R and EPOCH-R

R-CHOP

Rituximab 375 mg/m^2 d1
Cyclophosphamide 750 mg/m2 d1
Doxorubicin 50 mg/m^2 d1
Vincristine 1.4 mg/m^2 (2 mg cap) d1
Prednisone 40 mg/m^2 d1-5

q3w × 6

DA*-R-EPOCH

Rituximab 375 mg/m^2 d1
Etoposide 50 mg/m^2/d CI d1-4*
Doxorubicin 10 mg/m^2/d CI d1-4*
Vincristine 0.4 mg/m^2/d CI d1-4
Cyclophosphamide 750 mg/m^2 d5*
Prednisone 60 mg/m^2 bid d1-4
G-CSF 5 µg/kg d6-ANC recovery

q3w × 6

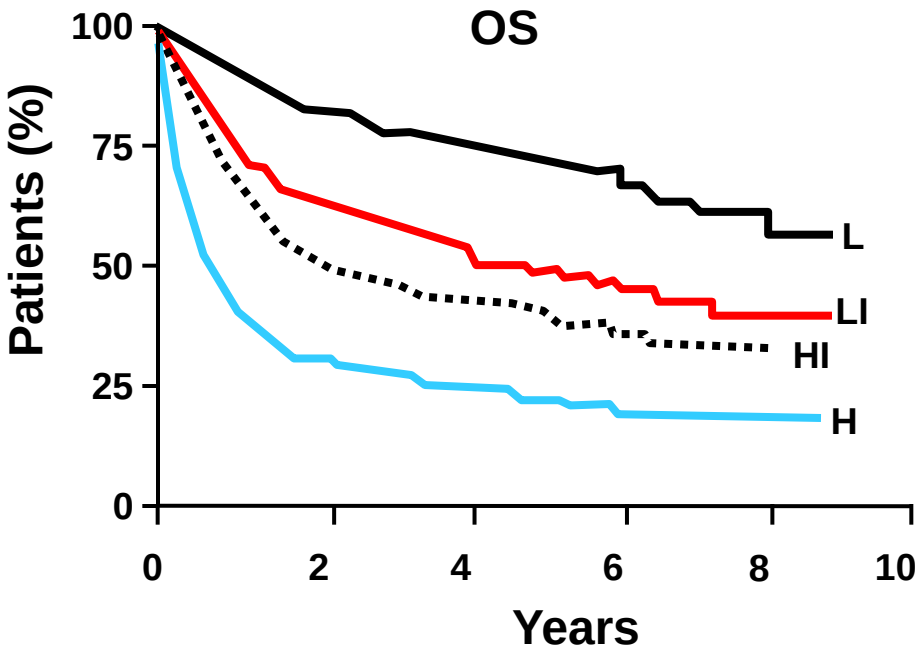
International Prognostic Index (IPI) in aggressive NHL

Prognostic factors (APLES)

- **A**ge >60 years
- **P**erformance status >1
- **L**DH >1× normal
- **E**xtranodal sites >1
- **S**tage III or IV

OR

Risk Category	Factors
Low (L)	0 or 1
Low intermediate (LI)	2
High intermediate (HI)	3
High (H)	4 or 5



International NHL Prognostic Factors Project. *N Engl J Med.* 1993;329:987.
Armitage. *CA Cancer J Clin.* 2005;55:368.

What does the physician need or want to know when approaching a new DLBCL patient?

- **Clinical features**
  - **International Prognostic Index**
  - **Primary mediastinal (R-EPOCH)**
  - **CNS, testicular (variations of rx)**
- **Pathological and molecular features**
  - **BM involvement (variations of rx)**
  - **Double hit (FISH) > Double protein (R-EPOCH)**
  - **Cell of origin (Germinal Center/Activated B Cell)**

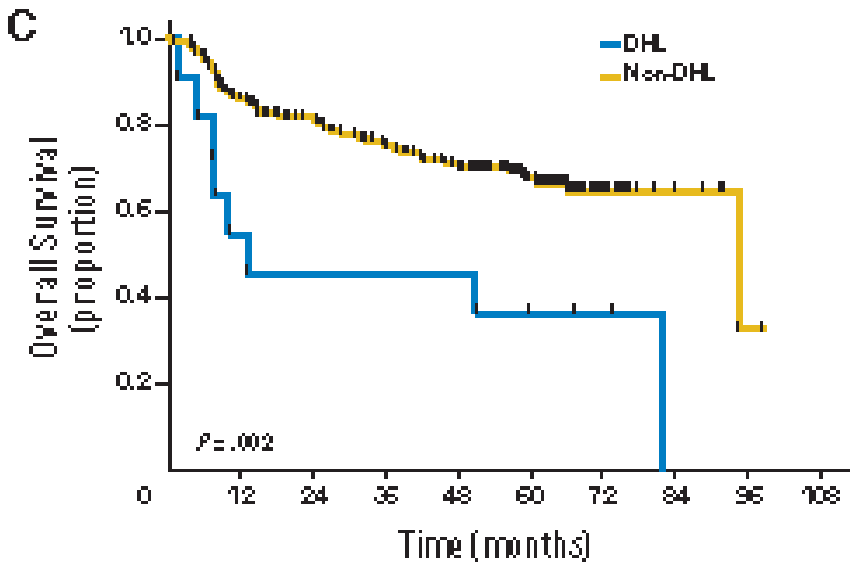
Double hit vs Double protein DLBCL 10-25% of DLBCL

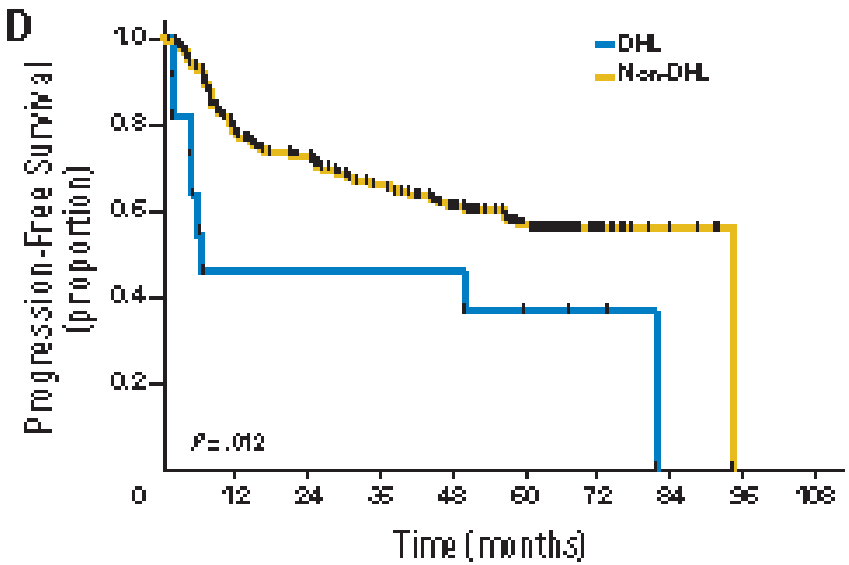
- **Double-hit lymphoma: High-grade B-cell lymphoma with translocations of MYC as well as BCL2, BCL6, or both ("triple-hit")**
  - **Histologically classified as DLBCL or B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt Lymphoma**
  - **Cell of origin: Virtually always germinal center subtype**
  - **Outcome poor with standard therapies**
- **Double-expressing lymphomas: DLBCL with dual immunohistochemical expression of MYC (≥40%) and BCL2 (≥70%) in the absence of translocations**
  - **Cell of origin: Usually activated B cell subtype**
  - **Outcome inferior to other DLBCLs, but not as poor as DHL**

Caveats in understanding clinical characteristics and outcomes in “double hit and double protein” lymphoma

- Clinical features of the subtype are less favorable
- Selection biases of series
- Variability in molecular testing
- Challenges and changes in morphologic/pathologic classification
- Non-uniform therapy
- Single vs multicenter
- Retrospective

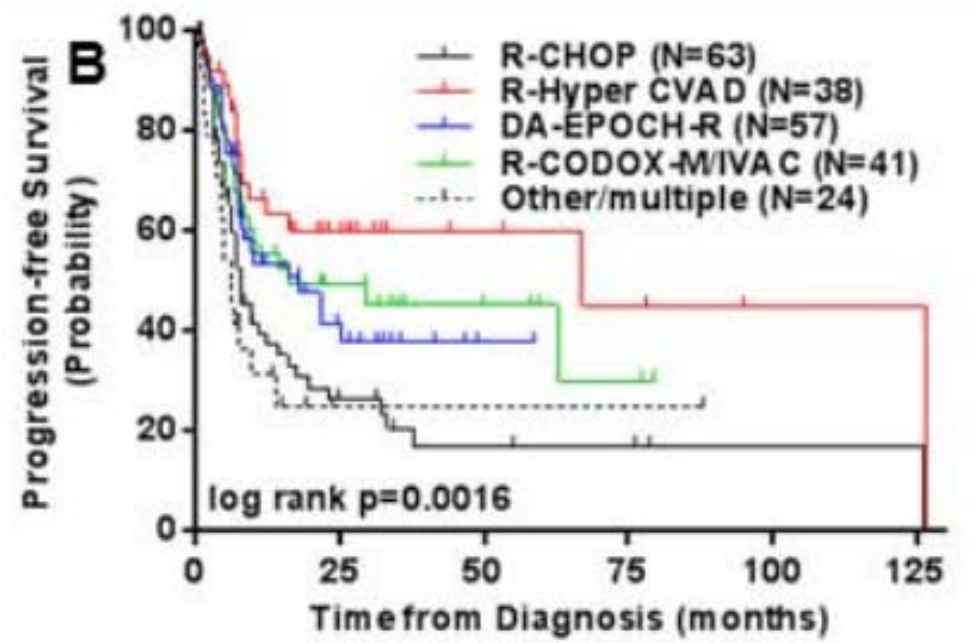
FISH DH DLBCL and treatment with R-CHOP

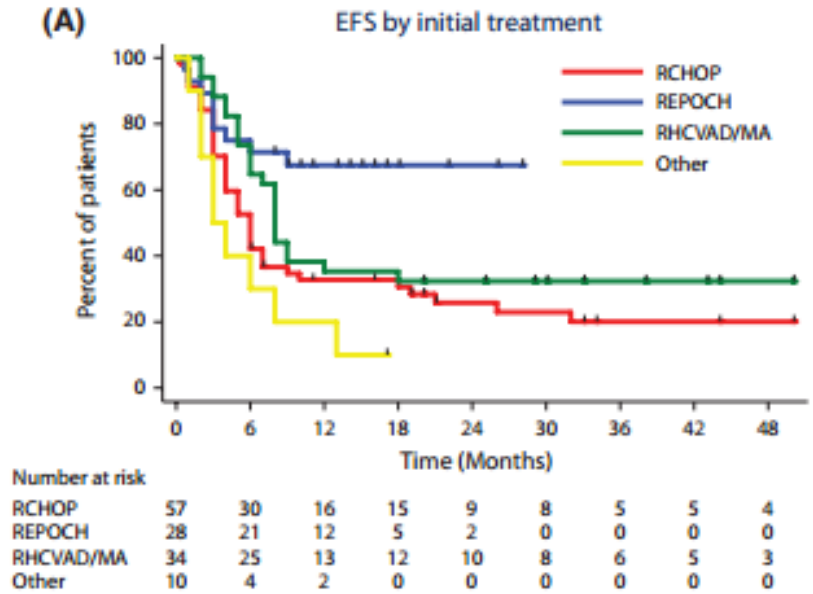




Green et al, JCO 2012

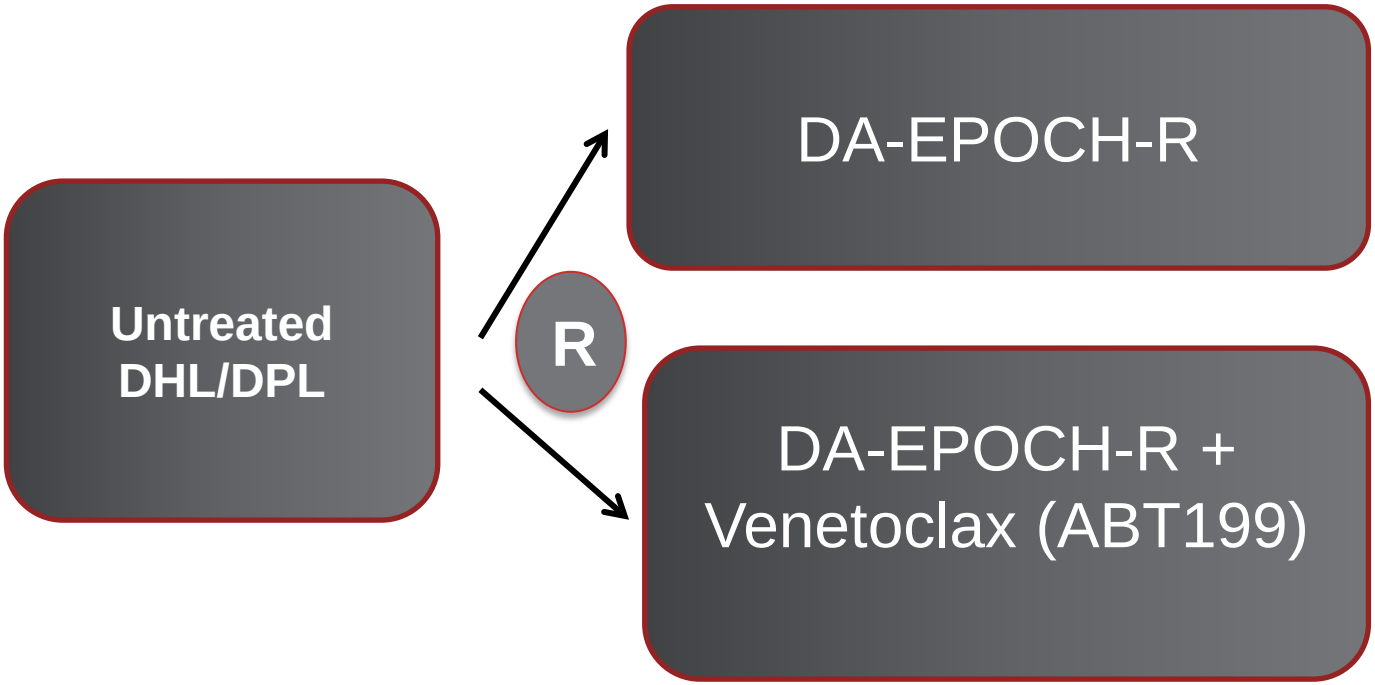
DA-EPOCH-R in double hit lymphoma





Petrich et al Blood 2014
Oki et al BJH 2014

Planned Intergroup Trial in DH/DP DLBCL
Phase I then Phase II-III
BCL-2 inhibitor Venetoclax



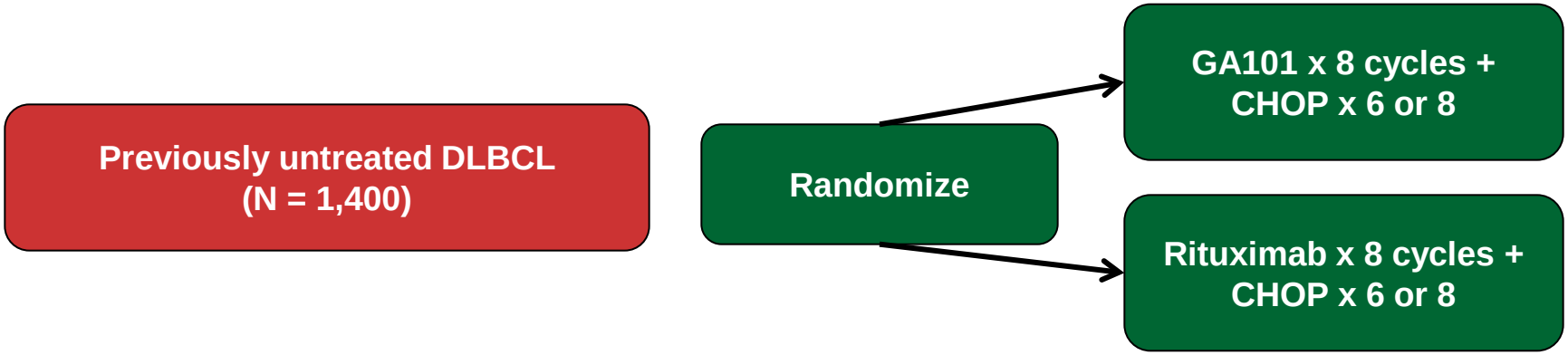
Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)

What about new approaches in DLBCL?

- **Strategies under investigation independent of cell of origin**

- **Strategies targeting specific cell of origin subtype**

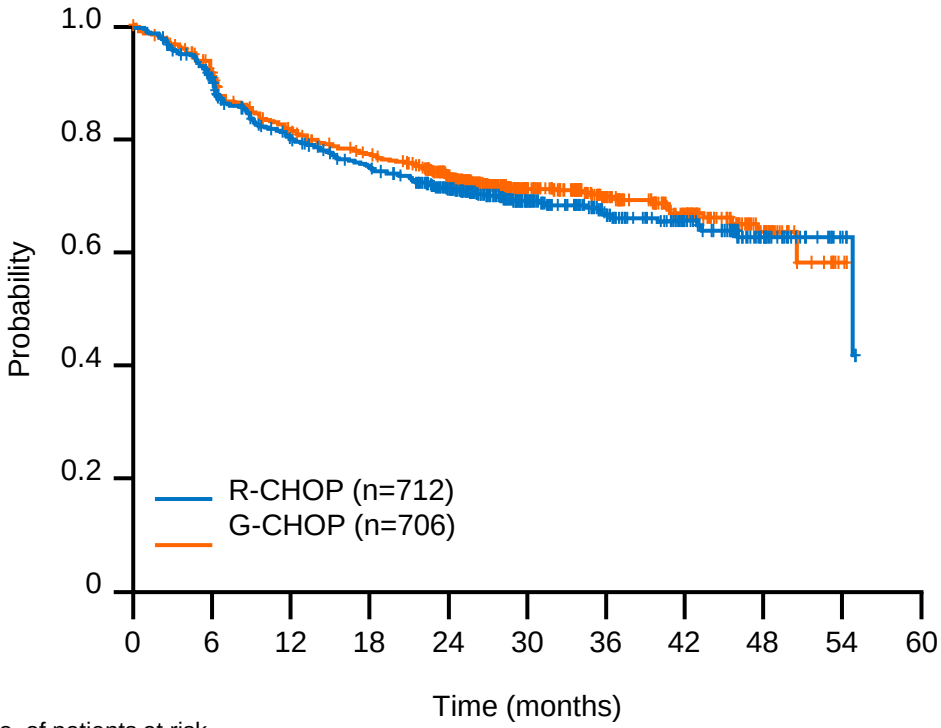
Roche GOYA Phase III: Study Design



GA101: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–8, every 21 days
Rituximab: 375 mg/m^2 d1, cycles 1–8, every 21 days

Other studies of "unselected" DLBCL patients
R-CHOP + (maintenance) enzastaurin, everolimus, lenalidomide

GOYA investigator-assessed PFS (ITT pop)



No. of patients at risk

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

KM plot of INV-assessed PFS by treatment arm

	R-CHOP, n=712	***G-CHOP, n=706***
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), stratified p-value	0.92 (0.76, 1.11), p=0.3868	

Median follow-up: 29 months

Vitolo et al, ASH 2016

Alliance/CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL

Untreated patients with newly diagnosed DLBCL

(N = 478)

R-CHOP
every 3 wks for 6 cycles

R-EPOCH
Doxorubicin, etoposide, vincristine Days 1-4;
cyclophosphamide Day 5;
prednisone Days 1-5

- Primary endpoints: EFS, molecular predictors of outcome for each regimen
- Secondary endpoints: RR, OS, toxicity, use of molecular profiling

Bartlett et al, ASH 2016

Clinical Trials.gov. NCT00118209. http://www.clinicaltrials.gov

Alliance 50303: Design

- N = 524; enrolled 2005 – 2013; Data cutoff November 2016

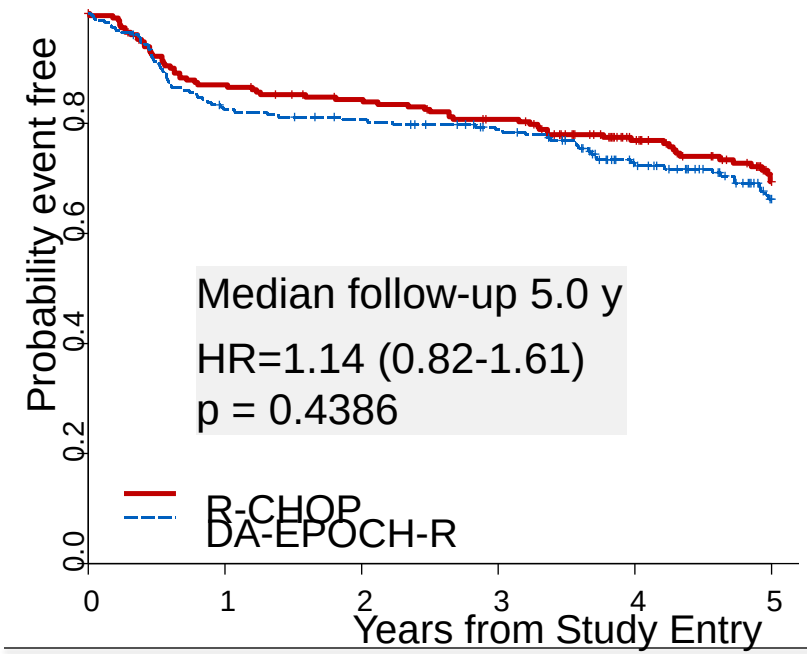
- Analysis planned after 242 events, but due to low event rate DSMB released data July 2016 with 167 events

Characteristic	R-CHOP (%)	DA-EPOCH R (%)	P-value
Median Age (range)	58 (18-86)	57 (19-84)	0.677
ECOG 0-1 vs. 2	88 vs. 12	87 vs. 13	0.518
Stage 3/4	73	77	0.641
IPI 0-2	65	61	0.405
GRADE ≥ 3 TOXICITY			
Treatment related deaths	2	2	0.975
Platelets	11	65	<0.001
Febrile neutropenia	17	35	<0.001
Infection	**11**	**14**	**0.169**
Neuropathy – sensory/motor	2/1	14/8	<0.001

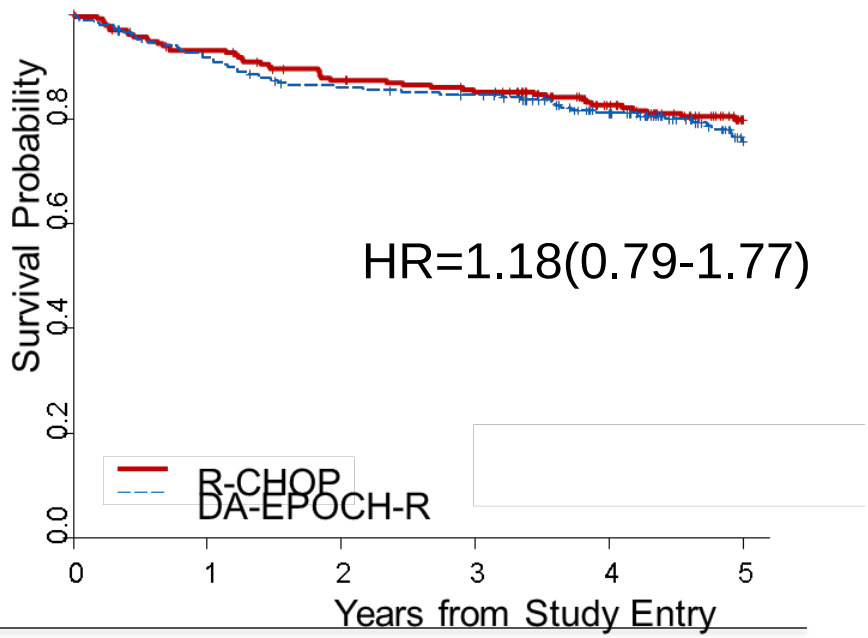
Alliance 50303: Outcomes

	R-CHOP	DA-EPOCH-R	P-value
ORR	89%	89%	0.983
CR/CRu	62%	61%	
PR	27%	27%	

Event Free Survival



Overall Survival



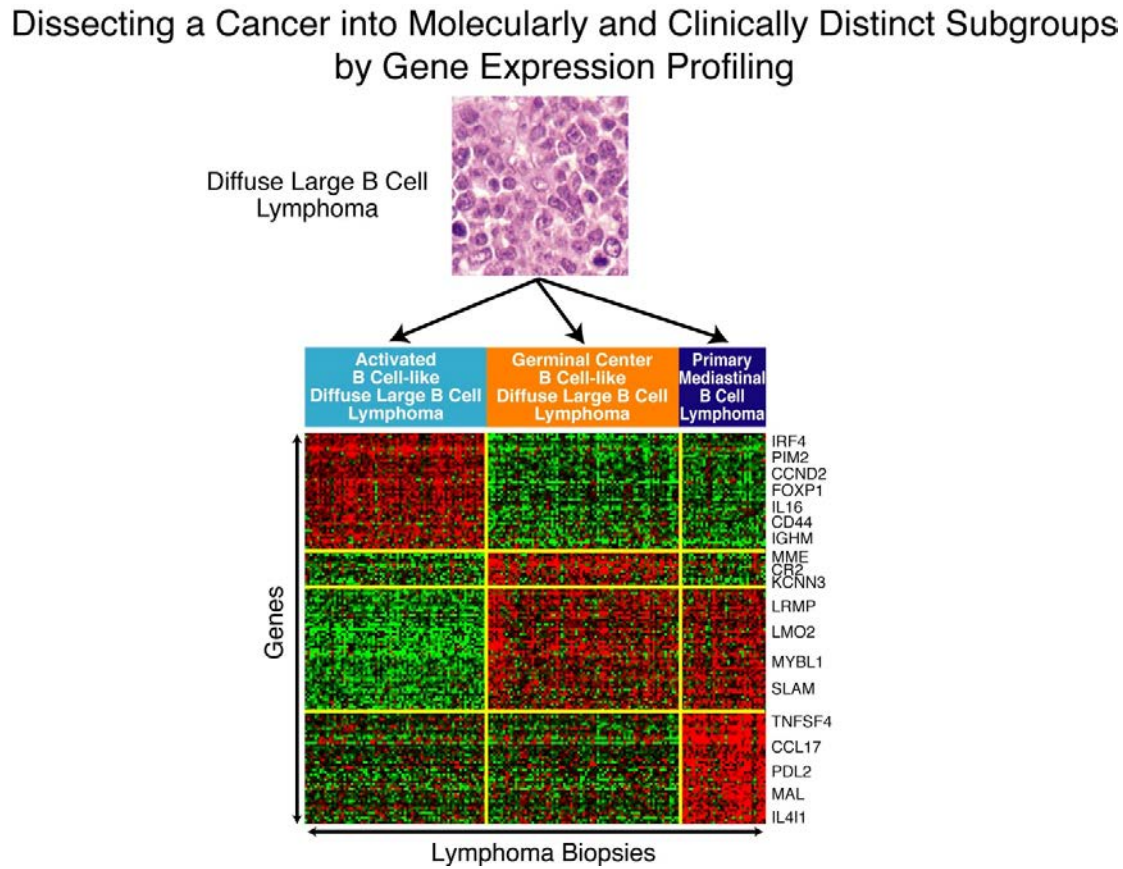
Weill Cornell Medicine NewYork-Presbyterian

What about new approaches in DLBCL?

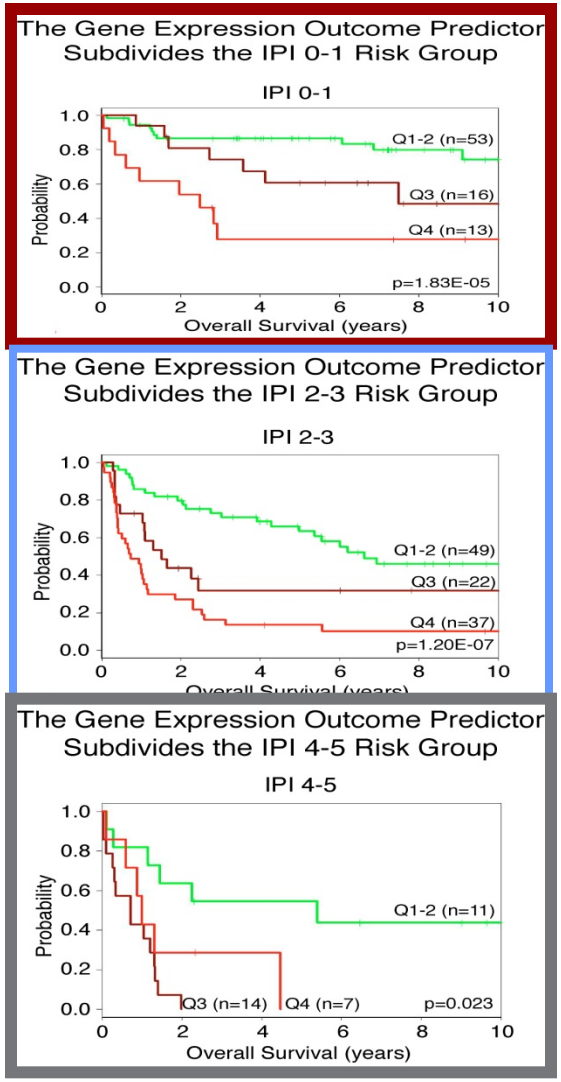
- **Strategies under investigation independent of cell of origin**

- **Strategies targeting specific cell of origin subtype**

Germinal Center vs Activated B Cell DLBCL



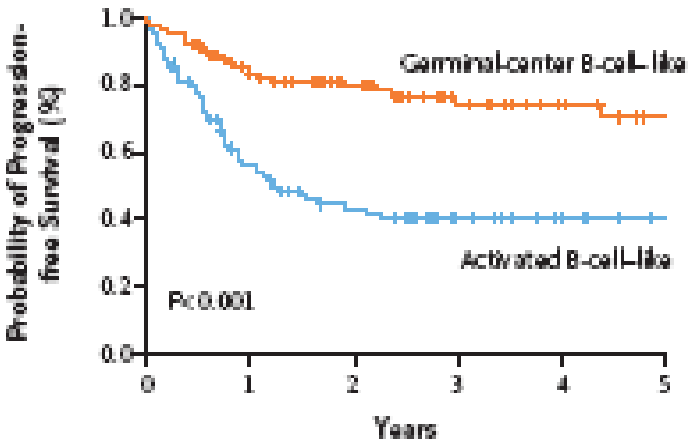
Rosenwald A et al. N Engl J Med. 2002;346:1937-1947



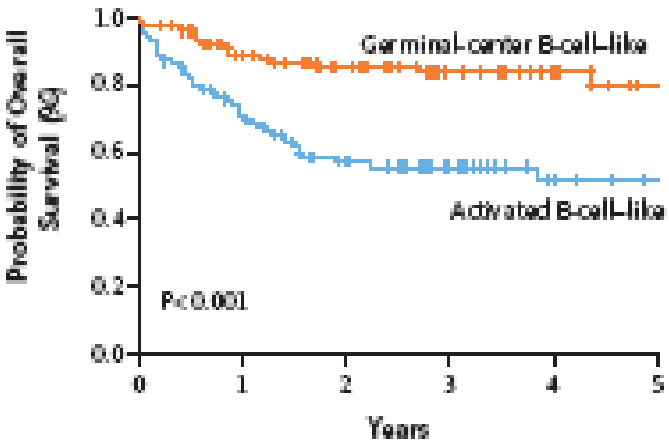
IHC surrogate (Hans) - CD10, bcl-6, MUM-1
GCB vs "non-GCB"

Outcome by GCB vs ABC gene signatures in DLBCL N=233 patients treated with R-CHOP

PFS



OS



No. at Risk												
Germinal-center B-cell-like	107	82	61	39	27	15	101	74	56	35	24	14
Activated B-cell-like	93	60	38	23	11	6	90	45	30	17	10	5

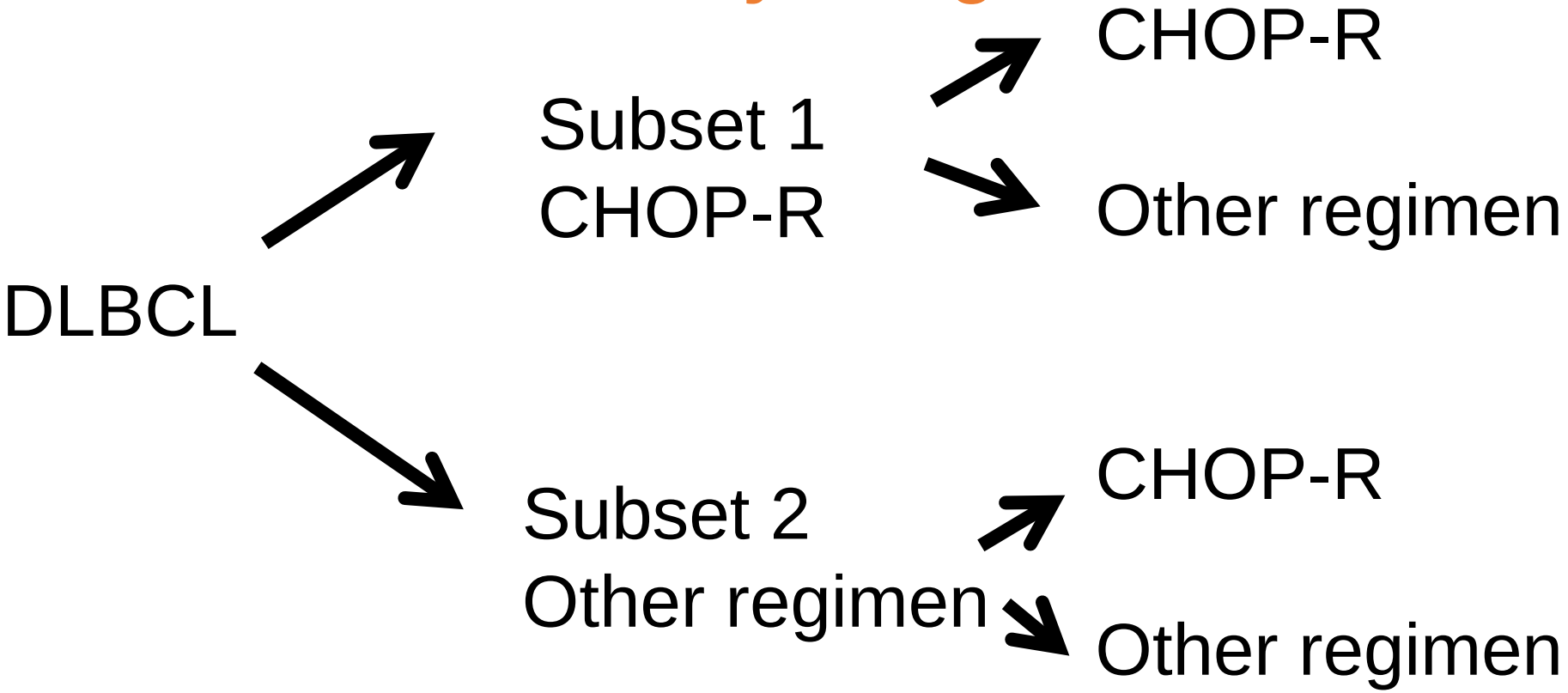
Lenz G, et al, NEJM 2008

Oncogenic mechanisms and potential therapeutic targets in GCB and ABC DLBCLs

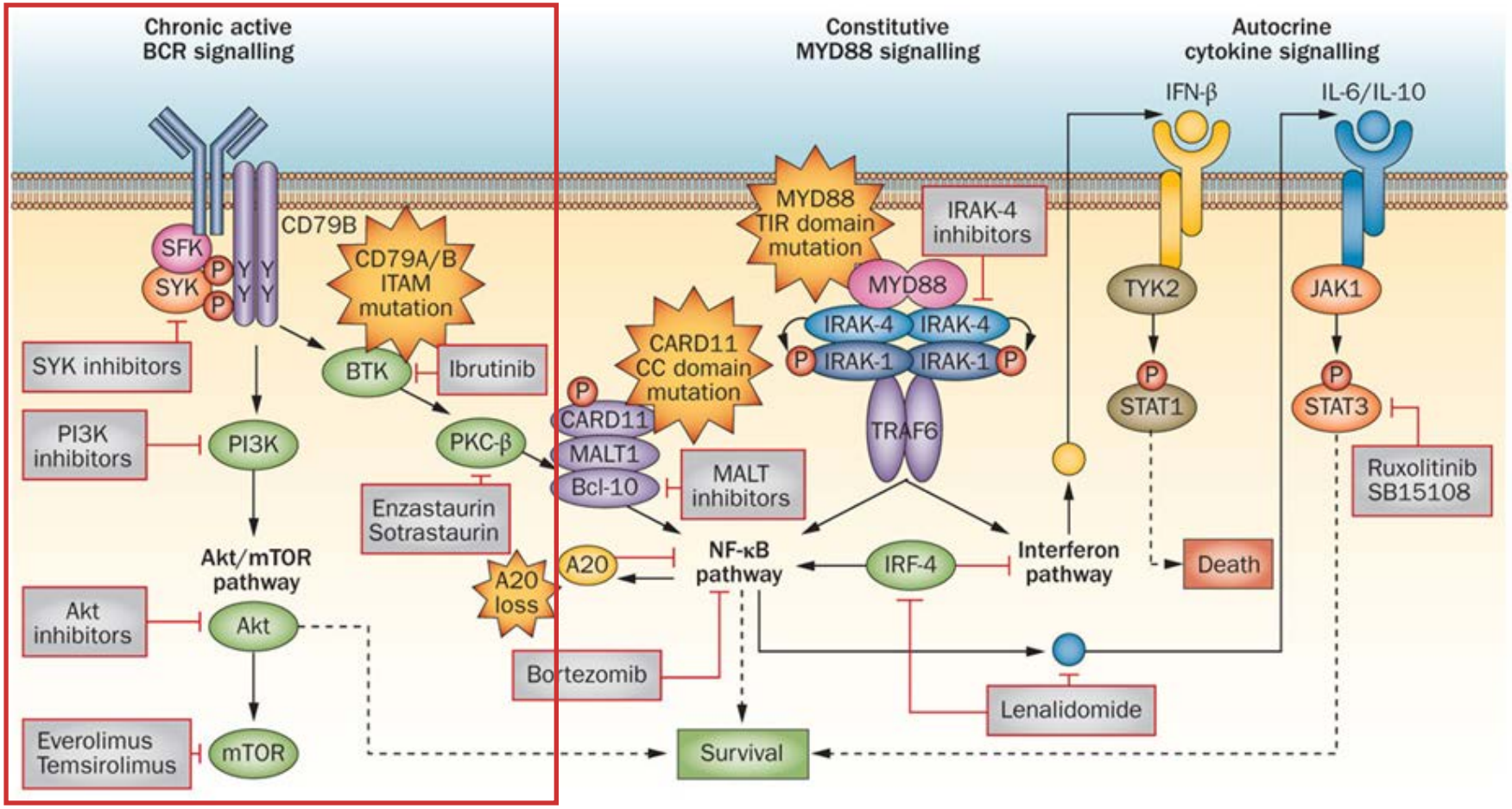
DLBCL subtype	Cell of origin	Oncogenic mechanisms	Potential targets
GCB	Germinal centre B-cell	*BCL2* translocation* *EZH2* mutations‡ *PTEN* deletions§ Loss of PTEN expression	BCL6 EZH2 PI3K/Akt
ABC	Post-germinal centre B-cell	NF-κB activation‖ *CARD11* mutations *MYD88* mutations *CD79B* mutations *A20* deletions	BCR CBM complex IRAK-4 JAK–STAT

Roschewski M. et al. *Nat. Rev. Clin. 2013;*11:12-23.

Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets
Study design



ABC DLBCL-associated signaling

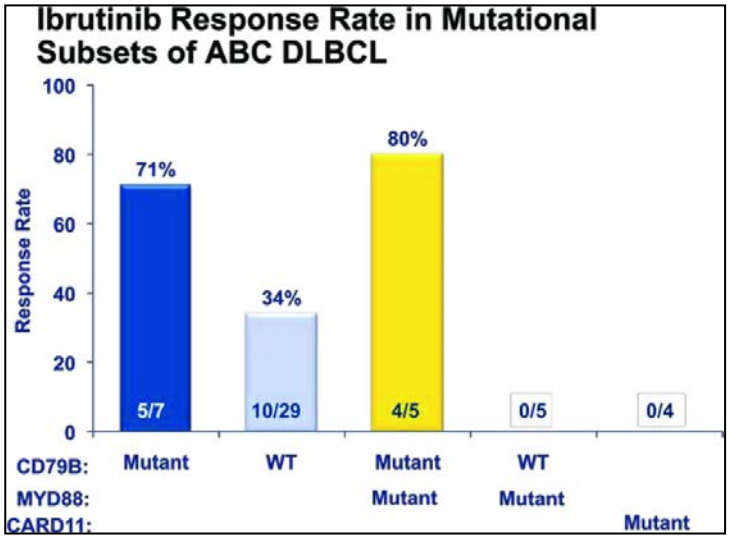


Roschewski M. et al. *Nat. Rev. Clin. 2013;*11:12-23.

Ibrutinib in relapsed DLBCL patients with ABC versus GCB subtype

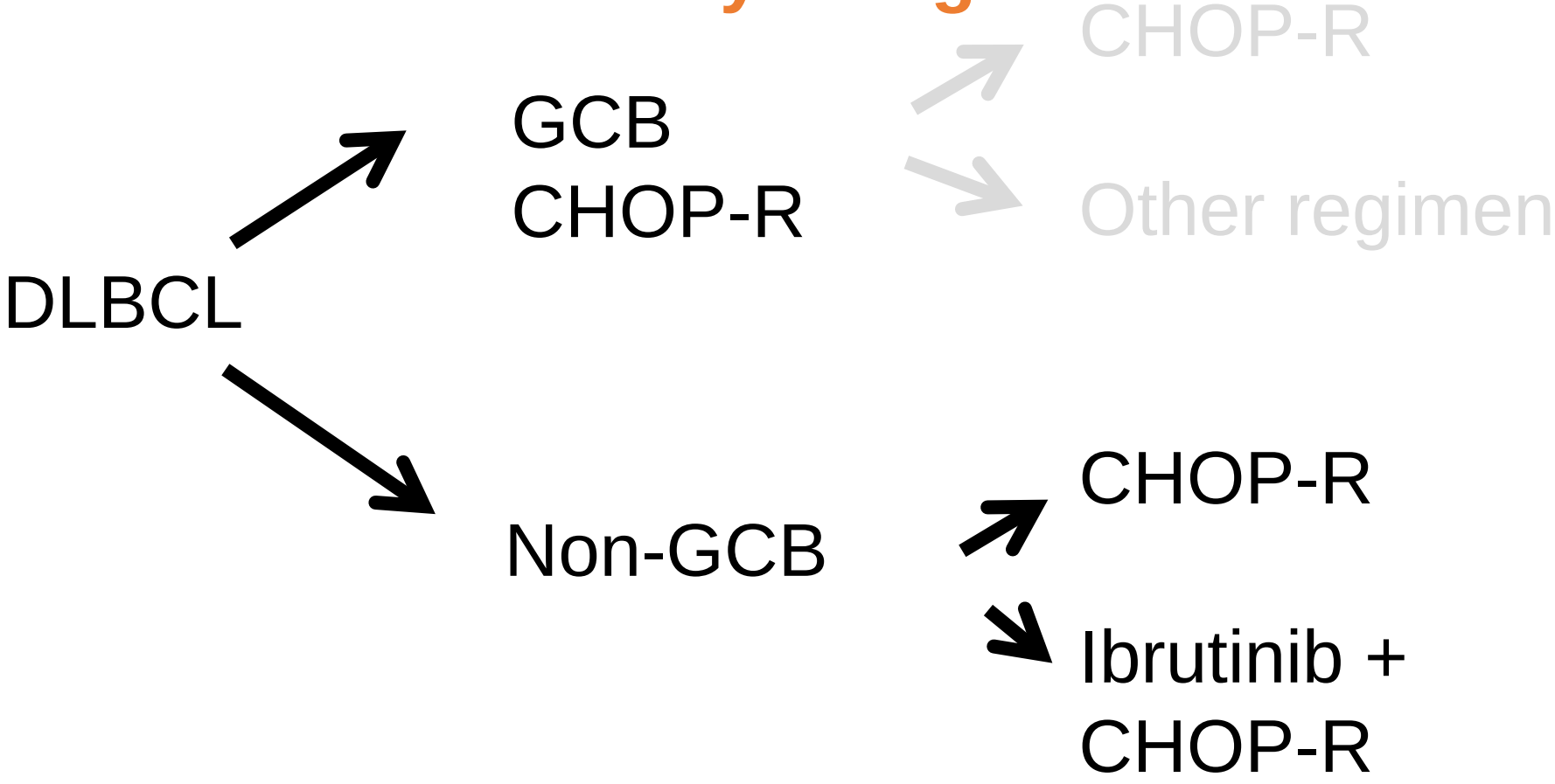
	ABC subtype (N=29)	GCB subtype (N=20)	Unclassifiable[1] (N=16)	Unknown[2] (N=5)	Total (N=70)
Not Evaluable for Response	4	1	3	2	10
PP ORR[4] (CR + PR)	**10 (40%)**	**1 (5.3%)**	0	2 (66.7%)	13 (21.7%)
Complete Response (CR)	**2 (8%)**	**0**	0	1 (33.3%)	3 (5%)
Partial Response (PR)	**8 (32%)**	**1 (5.3%)**	0	1 (33.3%)	10 (16.7%)
PFS (months)	2.5	1.28	0.95	NR[3]	1.64

N=70
Median age=63
Median prior treatments=3 (range 1-7)
IPI high-intermediate/high risk 59%

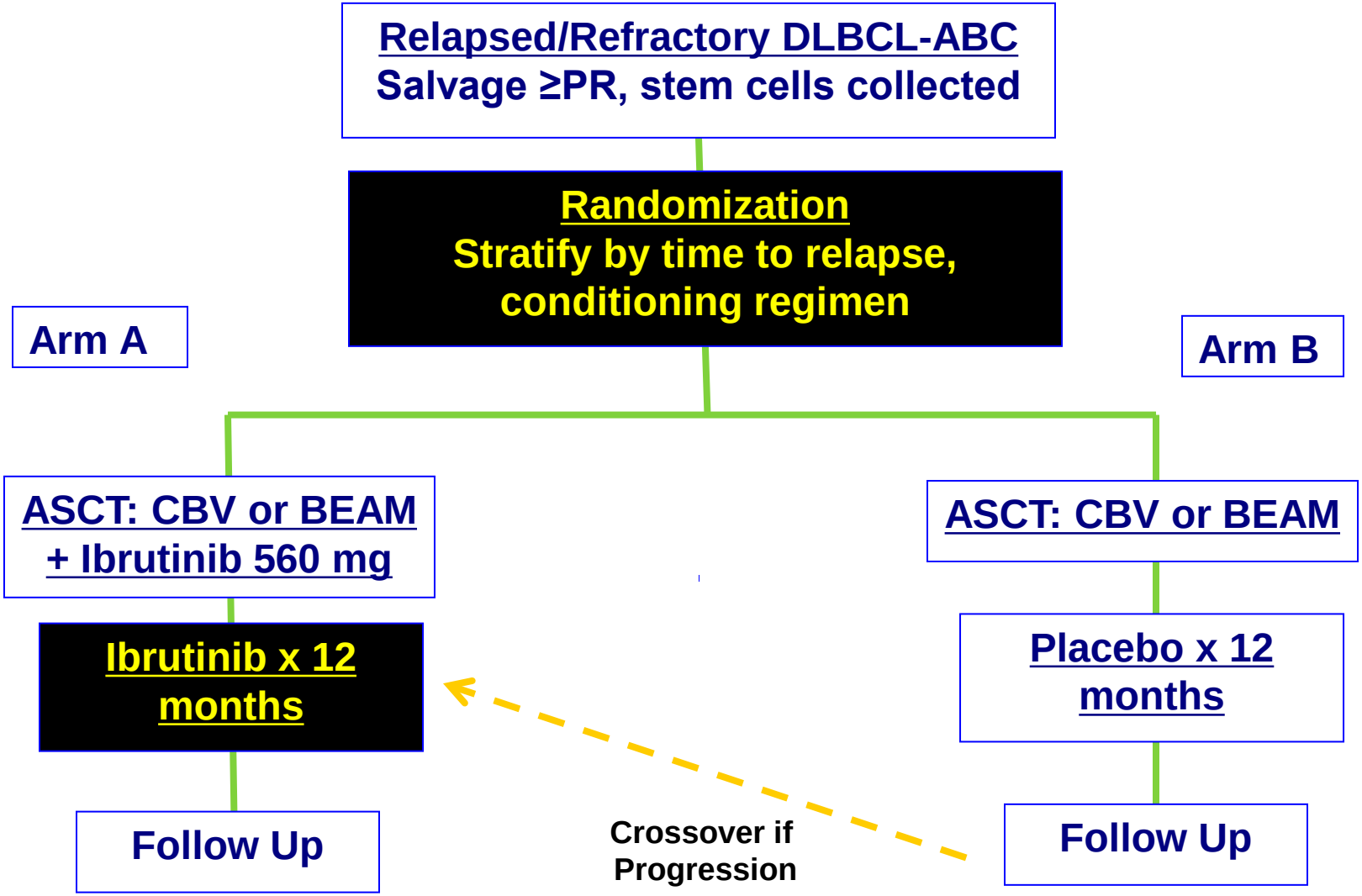


Wilson WH et al. *Blood*. 2012;120:686.

Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets
Study design



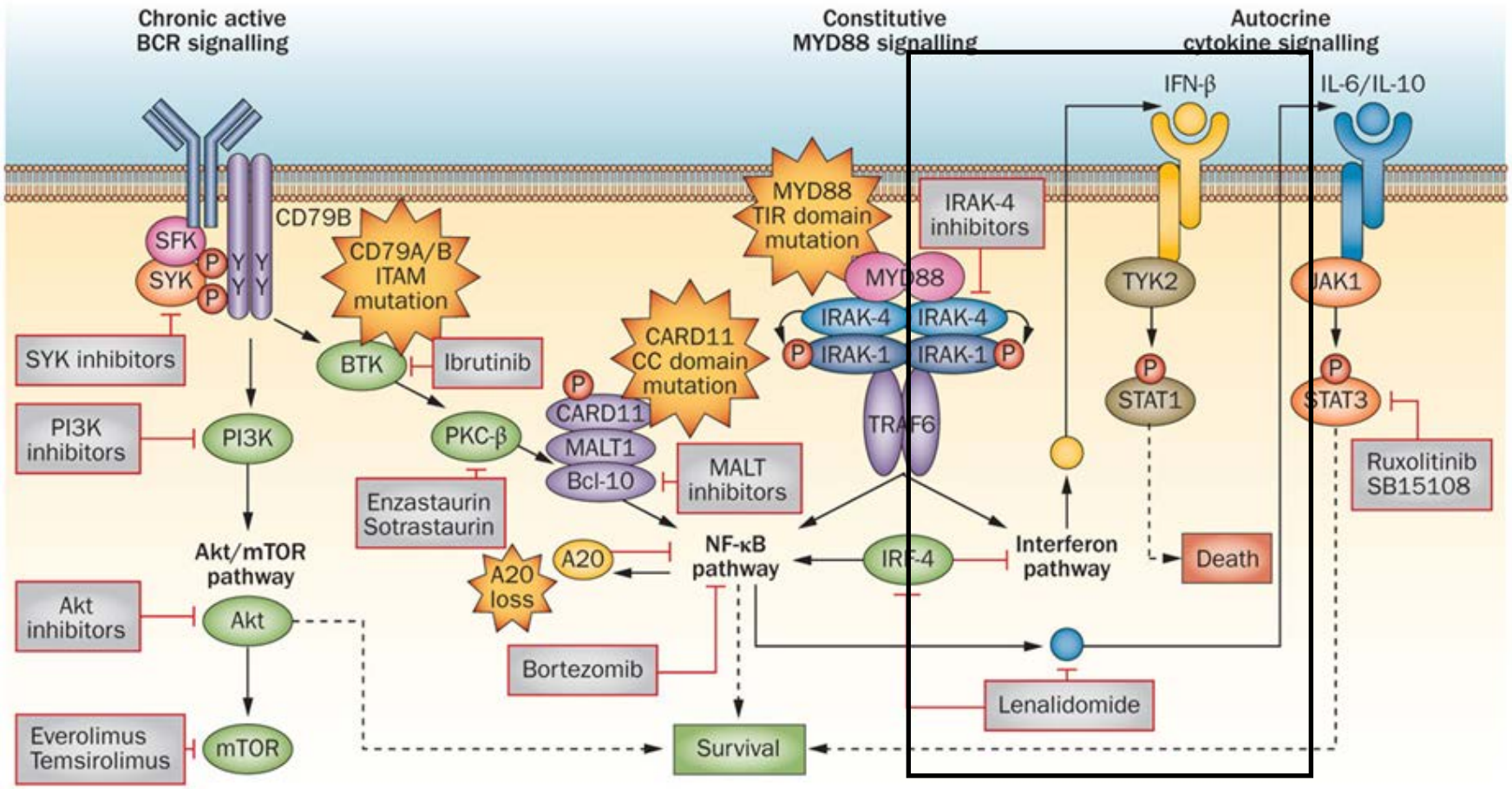
Alliance 51301 Study Schema



Ibrutinib in Relapsed or Refractory CNS Lymphoma

- Meaningful ibrutinib concentrations in CSF at 560 mg/day
- Interim analysis of the French *i*LOC phase 2 study, PCNSL:
  - Disease control rate 15/18 (83%); ORR 10/18 (55%) @ 2 months
  - Responses in 3 compartments: Brain, IO, CSF
  - Two aspergillosis cases
  - Final analysis is pending (n=52)
- MSKCC Phase 1B/2 Study, PCNSL and isolated CNS relapse:
  - Ibrutinib at 560 and 840mg with manageable toxicities, no DLTs, one case of aspergillosis
  - 15/20 (75%) ORR; mPFS of 5.4 month
  - Combination trial of Ibrutinib + methotrexate (-/+ rituximab) ongoing
- Single-agent Ibrutinib has therapeutic efficacy in recurrent/refractory PCNSL, and possibly SCNSL
- Need to define role of ibrutinib in therapeutic strategy of PCNSL

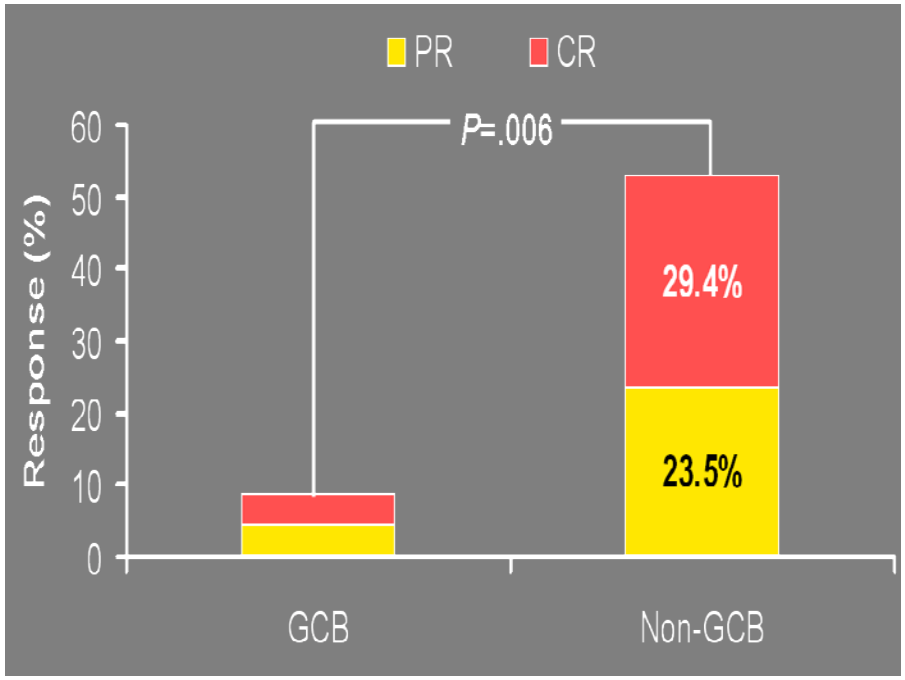
ABC DLBCL-associated signaling

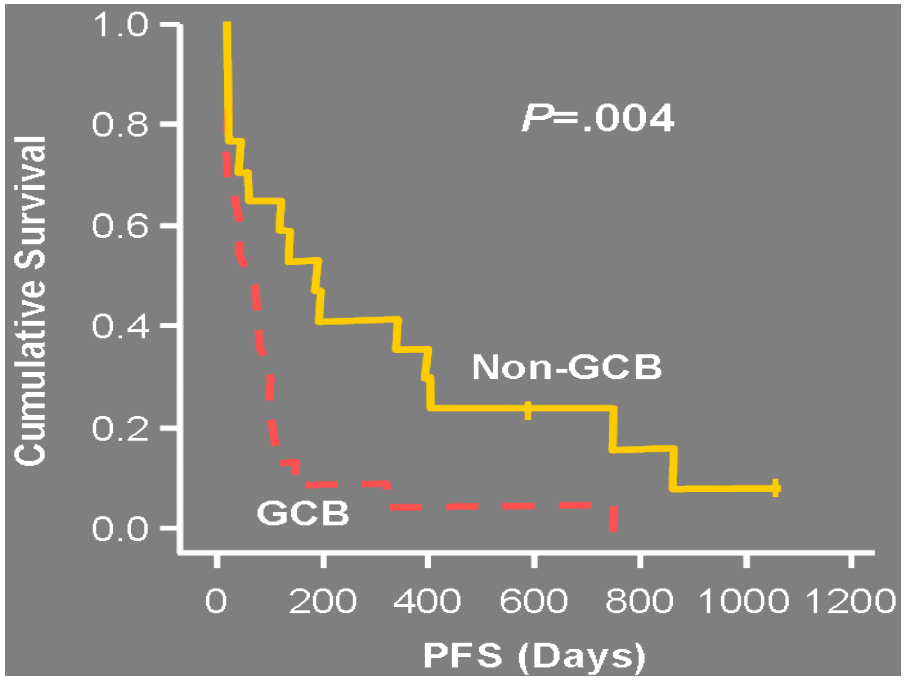


Roschewski M. et al. *Nat. Rev. Clin. 2013;*11:12-23.

Response to Lenalidomide in Relapsed and Refractory DLBCL Based on Subtype

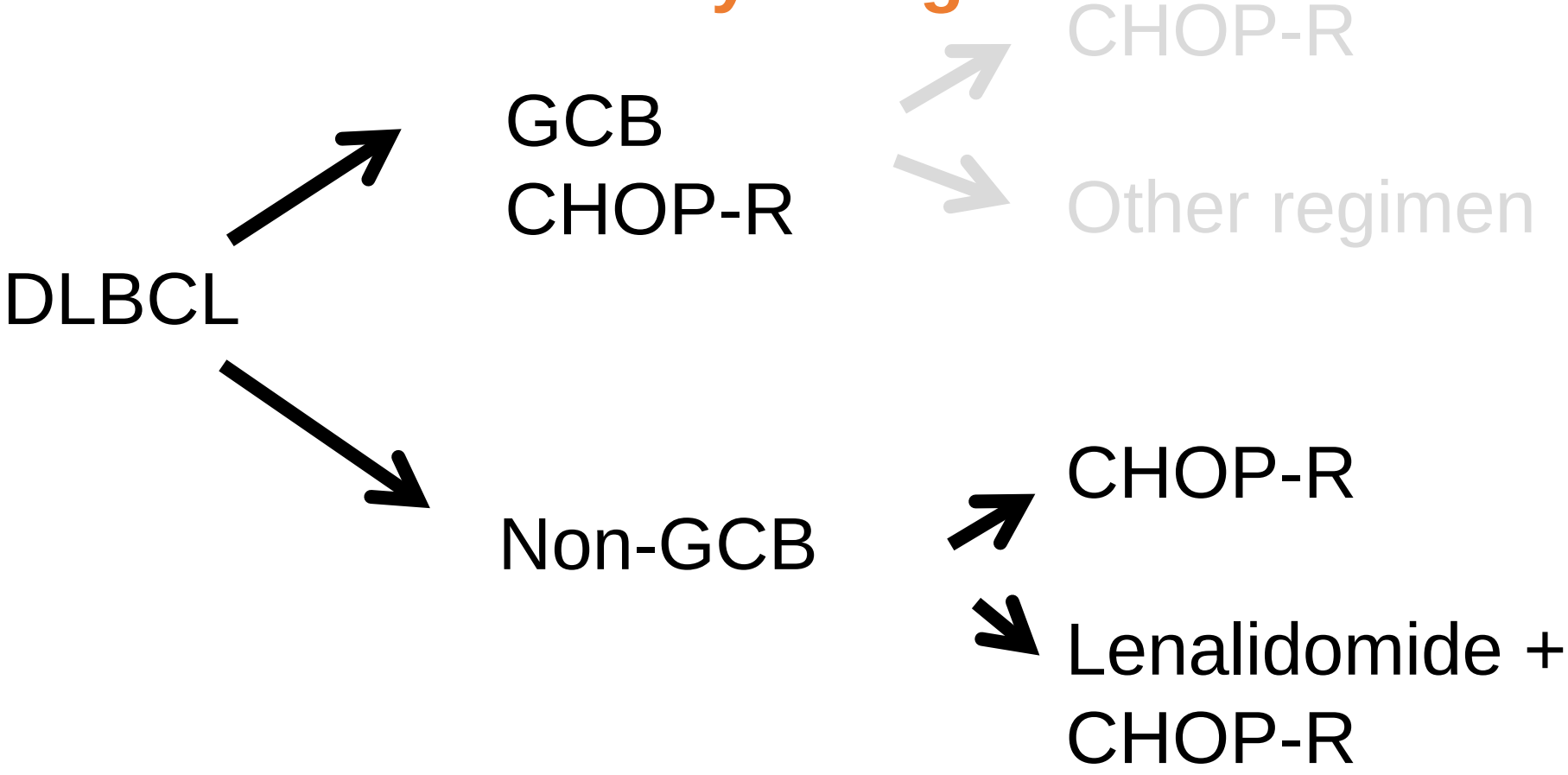
- Retrospective analysis of patients with relapsed DLBCL treated with lenalidomide as a single agent or in combination with rituximab/steroids at several institutions (N=56) suggests activity in the non-GCB subset





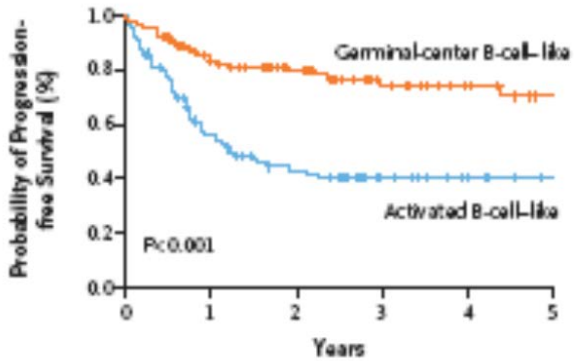
Hernandez-Illizaliturri et al. Cancer 2011

Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets
Study design

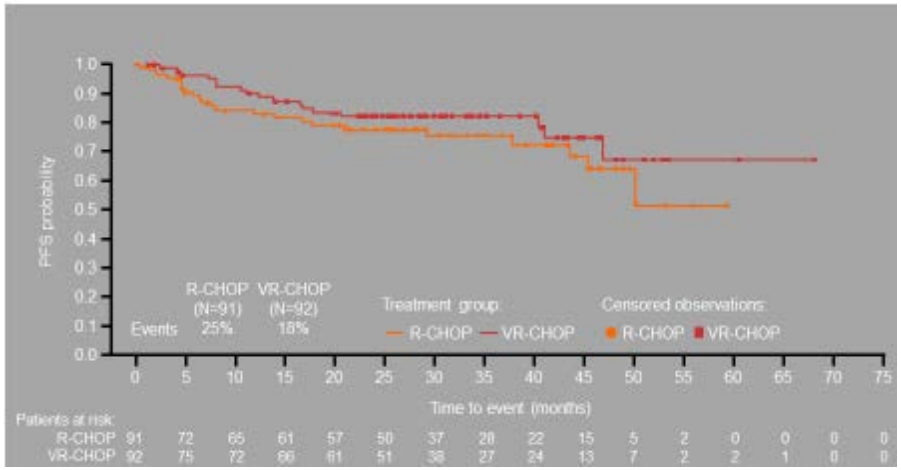


Comparison of R-CHOP in ABC/Non-GCB Retrospective vs Prospective studies

- **Retrospective (Lenz, NEJM 2008)**
  - **2-year PFS 40% ABC by GEP with R-CHOP, GCB > ABC subtype**
- **Prospective**
  - **2-year PFS 80% non-GCB by IHC with R-CHOP**



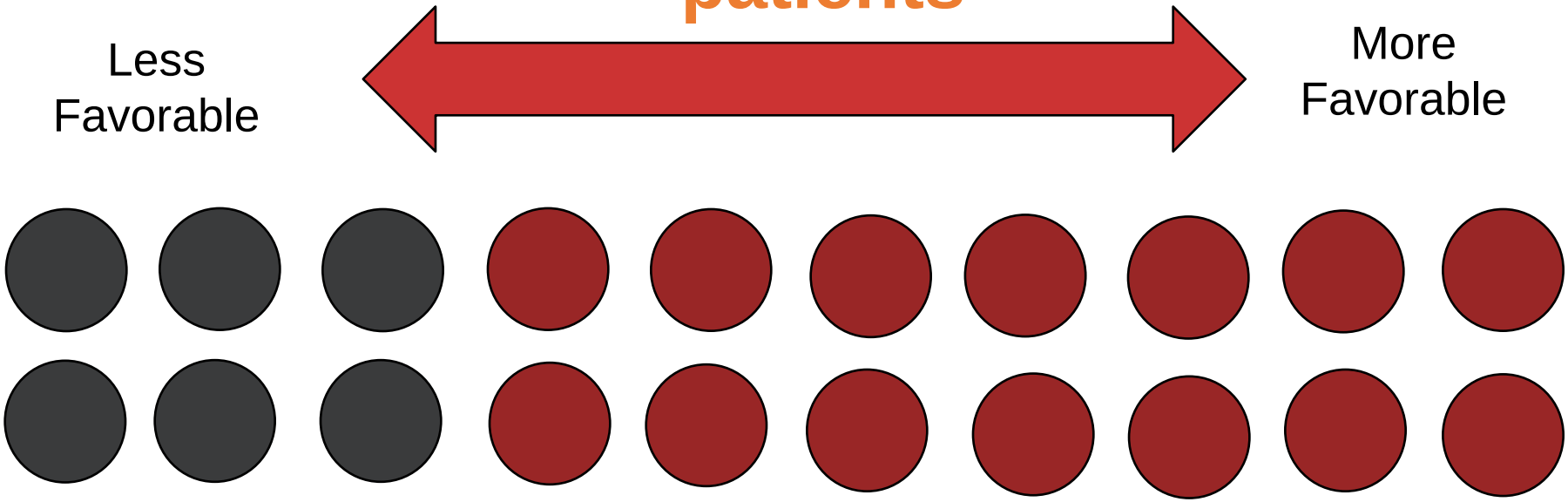
ter B-cell-like	107	82	61	39	27	15
ll-like	93	60	38	23	11	6



Lenz G, et al. N Engl J Med. 2008;359:2313–23.

Spectrum of ABC/Non-GCB DLBCL patients

Less Favorable



More Favorable

Excluded due to concerns about delays/risk

Randomized in a selected patient population (patients who could wait for screening/enrollment)

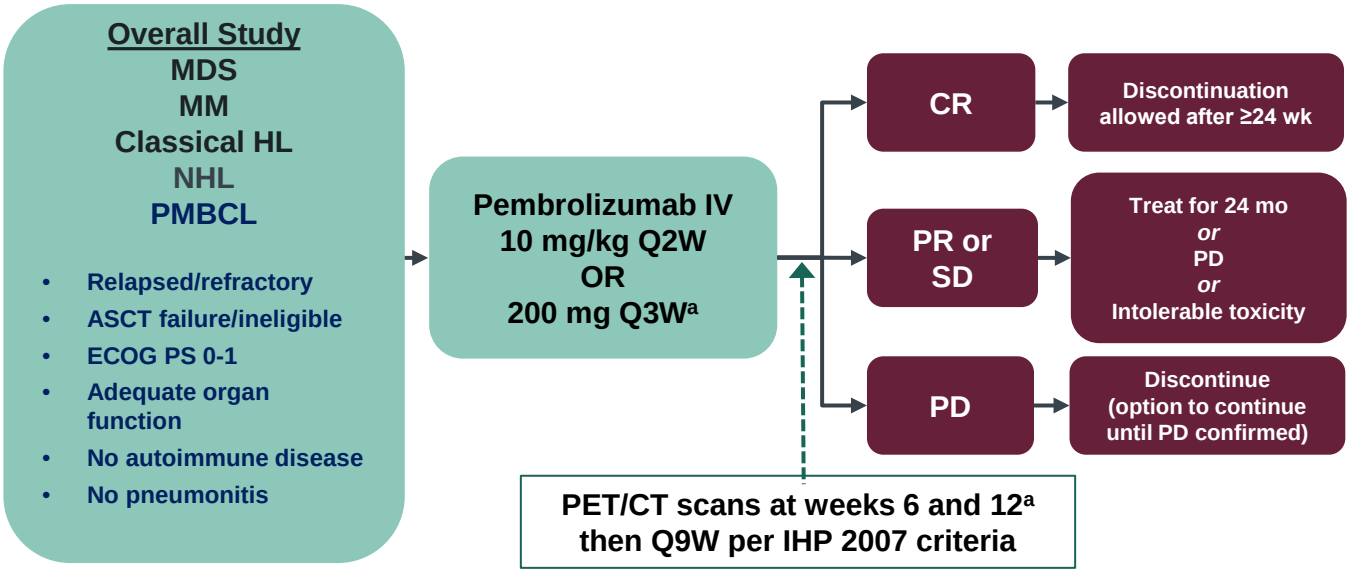
"Favorable outcome"

Phase 1b Study of Pembrolizumab in Patients with Relapsed/Refractory PMBCL: Results from the Ongoing KEYNOTE-013 Trial

Pier Luigi Zinzani,[1] Vincent Ribrag,[2] Craig H. Moskowitz,[3] Jean-Marie Michot,[2] John Kuruvilla,[4] Arun Balakumaran,[5] Yayan Zhang,[5] Patricia Marinello,[5] Sabine Chlosta,[5] Eric Gustafson,[5] Margaret A. Shipp,[6] Philippe Armand[6]

[1]Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna, Italy; [2]Institut Gustave Roussy, Villejuif, France; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Merck & Co., Inc., Kenilworth, NJ, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA

Phase 1b KEYNOTE-013 Study

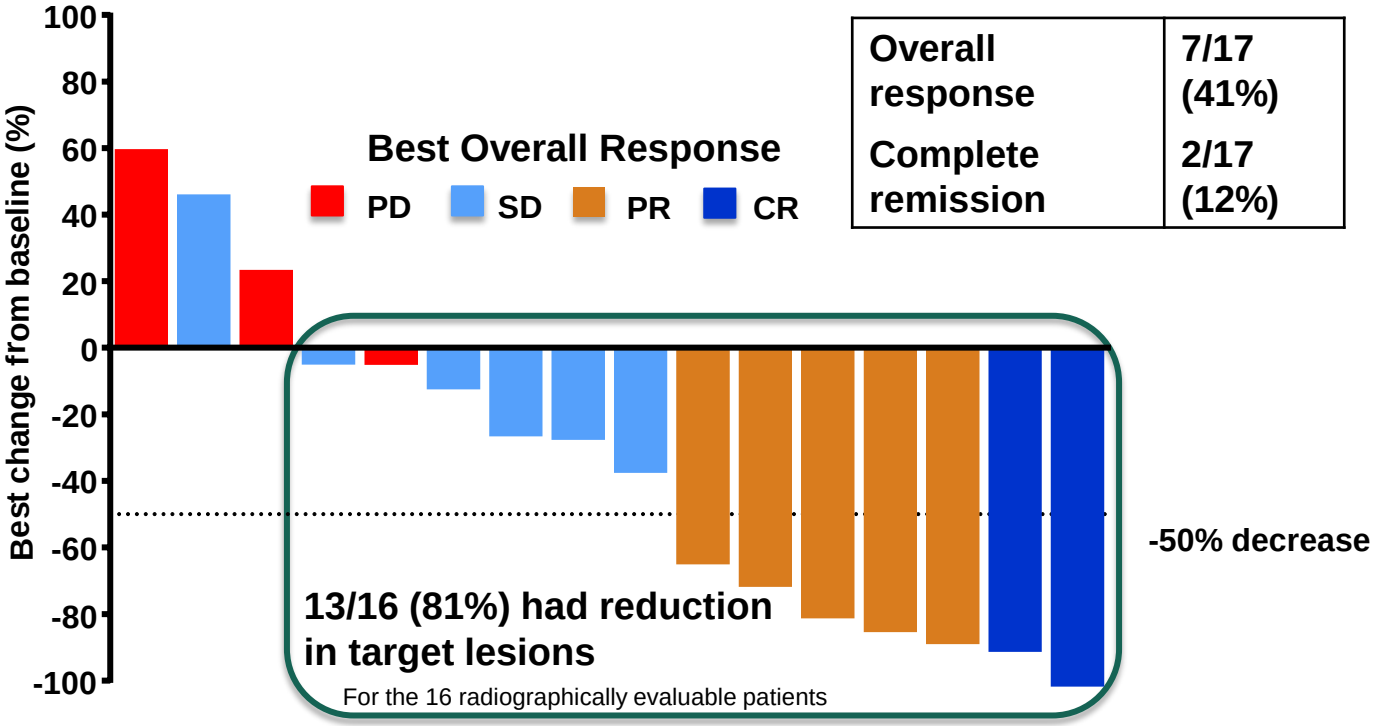


Primary endpoints: Safety; Objective response rate

N = 18 (13 women), median age 30.5 (22-62) yrs, all ECOG PS 0-1
Median prior lines of therapy 3 (range 2-6)

Clinicaltrials.gov NCT01953692
[a]The first 11 patients received 10 mg/kg Q2W with first response assessment at 12 weeks; the next 8 received 200 mg Q3W with first response assessment at 6 weeks. The two doses are equivalent based on PK/PD studies.

Best Percentage Change From Baseline in Tumor Size (Evaluable Patients)



Overall response	**7/17 (41%)**
Complete remission	**2/17 (12%)**

Median follow-up: 11 mo (range 3-27)
Median response duration: not reached (range 2-23 mo)
6/7 (86%) responses ongoing
2 reached the maximum 2 years of treatment, remain in remission (25.4 mo, 23.8 mo)

Abstract LBA-6

KTE-C19 Induces Complete Remissions in Patients with Refractory Diffuse Large B Cell Lymphoma: Interim Results from the Pivotal Phase 2 ZUMA-1

Sattva S. Neelapu[1*], Frederick L. Locke[2*], Nancy L. Bartlett[3], Lazaros J. Lekakis[4], David Miklos[5], Caron A. Jacobson[6], Ira Braunschweig[7], Olalekan Oluwole[8], Tanya Siddiqi[9], Yi Lin[10], John Timmerman[11], Patrick J. Stiff[12], Jonathan W. Friedberg[13], Ian Flinn[14], Andre Goy[15], Mitchell Smith[16], Abhinav Deol[17], Umar Farooq[18], Peter McSweeney[14], Javier Munoz[19], Irit Avivi[20], Januario E. Castro[21], Jason R. Westin[1], Julio C. Chavez[2], Armin Ghobadi[3], Krishna V. Komanduri[4], Ronald Levy[5], Eric D. Jacobsen[6], Patrick Reagan[13], Adrian Bot[22], John Rossi[22], Lynn Navale[22], Yizhou Jiang[22], Jeff Aycock[22], Meg Elias[22], Jeff Wiezorek[22], and William Y. Go[22]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA;[2]H, Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA;[3]Washington University, St. Louis, MO, USA;[4]University of Miami, Miami, FL, USA; [5]Stanford University, Stanford, CA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Montefiore Medical Center, Bronx, NY, USA; [8]Vanderbilt University Medical Center, Nashville, TN, USA; [9]City of Hope, Duarte, CA, USA; [10]Mayo Clinic, Rochester, MN, USA; [11]University of California at Los Angeles, Los Angeles, CA, USA; [12]Loyola University Medical Center, Maywood, IL, USA; [13]University of Rochester School of Medicine, Rochester, NY, USA; [14]Sarah Cannon Research Institute, Nashville, TN, USA; [15]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [16]Cleveland Clinic, Cleveland, OH, USA; [17]Karmanos Cancer Center, Wayne State University, Detroit, MI, USA; [18]University of Iowa Carver College of Medicine, Iowa City, IA, USA; [19]Banner M.D. Anderson Cancer Center, Gilbert, AZ, USA; [20]Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; [21]University of California at San Diego, San Diego, CA, USA; [22]Kite Pharma, Santa Monica, CA, USA

***Drs. Neelapu and Locke contributed equally to this work.**

This study is supported in part by funding from The Leukemia & Lymphoma Society (LLS) Therapy Acceleration Program®

ZUMA-1: Multicenter Trial of KTE-C19 in Refractory Aggressive NHL (NCT02348216)

Eligibility criteria

- Aggressive NHL: DLBCL, PMBCL, TFL
- Chemotherapy-refractory disease: no response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 mAb and anthracycline
- ECOG PS 0-1

Pre-specified interim efficacy analysis

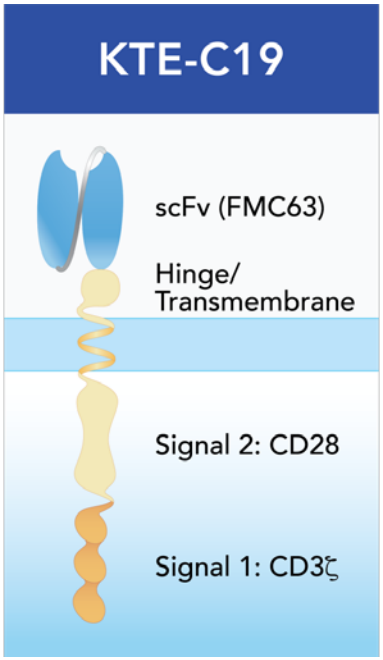
- Phase 2 cohort 1 (n=50 with ≥3mo follow-up)

Primary endpoint

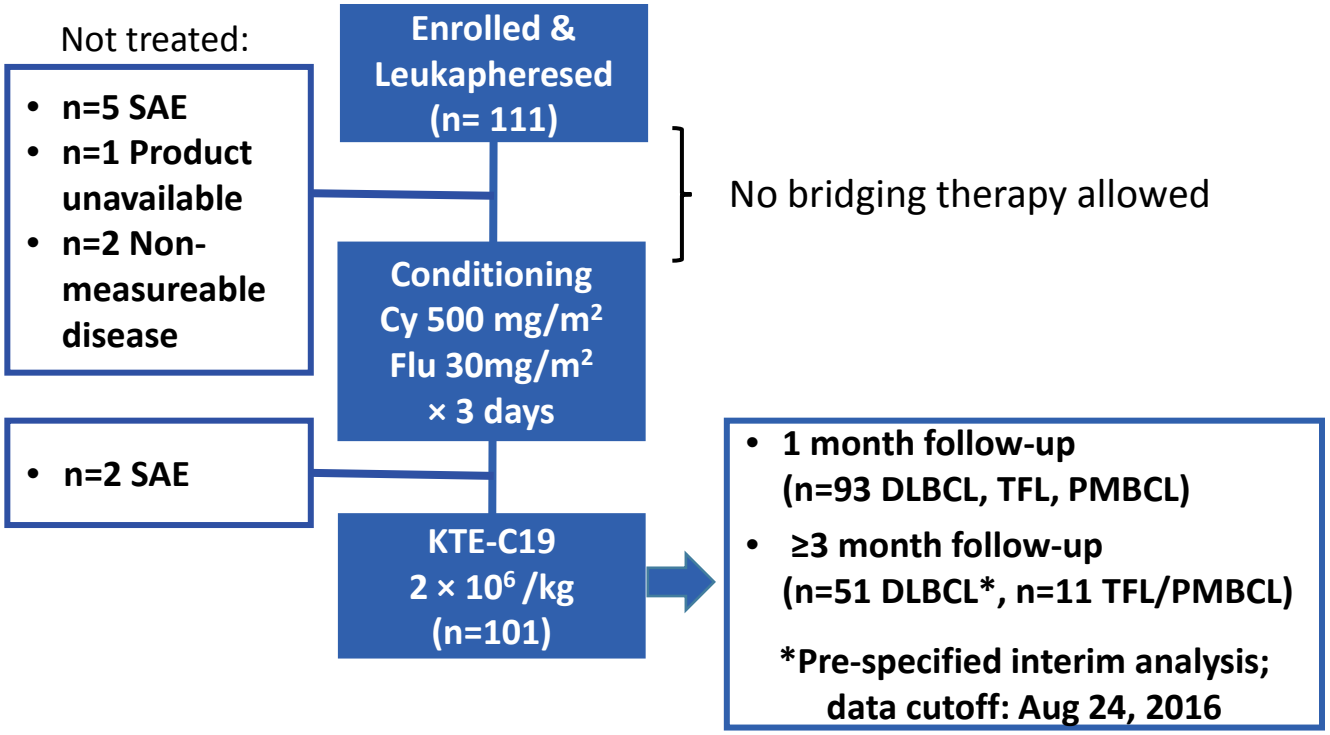
- Phase 2: ORR

Key secondary endpoints

- DOR, OS, Safety, Levels of CART and cytokines



ZUMA-1: Phase 2 CONSORT Diagram



ZUMA-1 Pivotal Trial: Response Rates and Toxicity

Best Overall Response in Patients with ≥3 Month Follow-up

Subgroup	Age (yrs) Median (range)	# prior Rx Median (range)	n	ORR	CR
DLBCL	59 (25-76)	3 (1-7)	51	76%*	47%
TFL / PMBCL	58 (28-76)	4 (2-12)	11	91%	73%
Total			**62**	**79%**	**52%**

***P*<0.0001 (exact binomial test comparing observed ORR to historical control assumption of 20%)**

Grade ≥3 Adverse Events, total N = 93 treated	n (%)
Cytokine release syndrome	12 (13)
Neurologic event	27 (29)
Fatal events (excluding PD)	3 (3)

Peak CART cell expansion (day 7-14) associated with ongoing CR at 3 months

Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T-Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): the Phase 3 ALCANZA study

Youn H. Kim,[1] Sean Whittaker,[2] Steven Horwitz,[3] Madeleine Duvic,[4] Reinhard Dummer,[5] Julia Scarisbrick,[6] Pietro Quaglino,[7] Pier Luigi Zinzani,[8] Pascal Wolter,[9] Yinghui Wang,[10] Maria Corinna Palanca-Wessels,[10] Erin Zagadailov,[11] William L. Trepicchio,[11] Yi Liu,[11] Meredith Little,[11] H. Miles Prince[12]

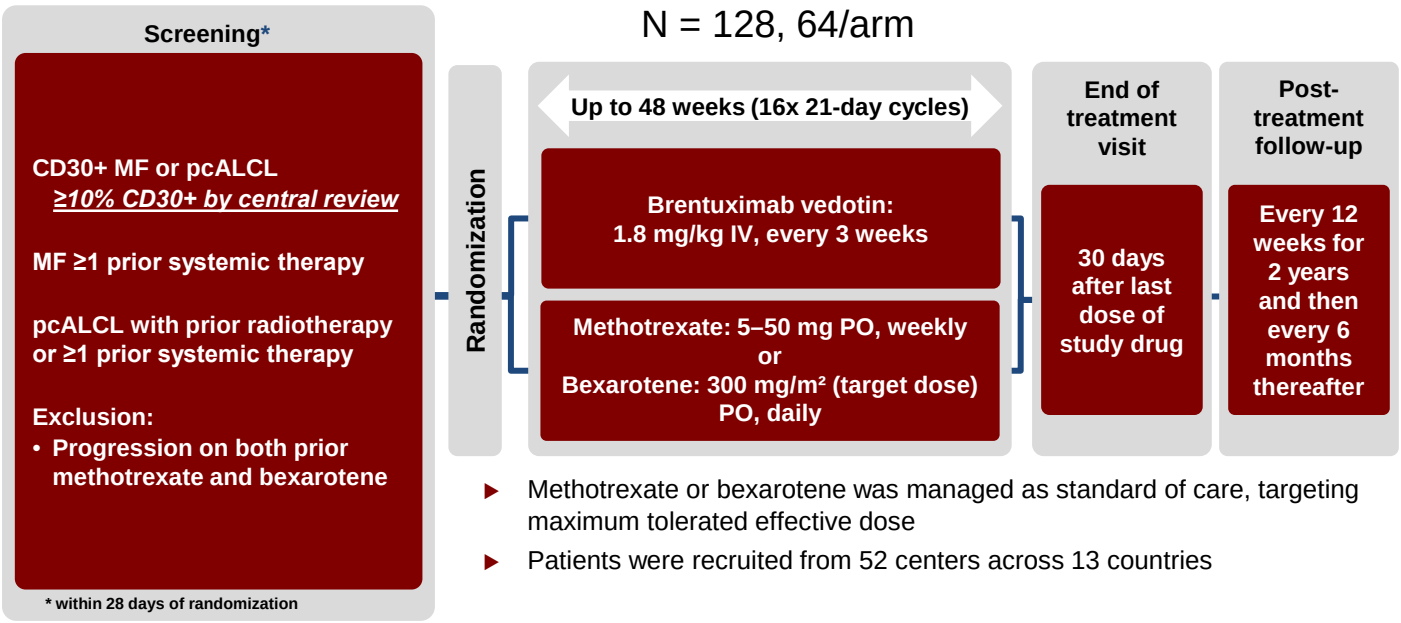
[1]Stanford Cancer Institute, Stanford, California, USA; [2]Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]Memorial Sloan Kettering Cancer Center, New York, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]University Hospital Zürich, Zurich, Switzerland; [6]University Hospital Birmingham, Birmingham, UK; [7]University of Turin, Turin, Italy; [8]Institute of Hematology "Seràgnoli" University of Bologna, Bologna Italy; [9]University Hospitals Leuven, Leuven, Belgium; [10]Seattle Genetics, Inc., Bothell, WA, USA; [11]Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA; [12]The University of Melbourne, Victoria, Australia

CTCL: Background and rationale

- CTCL, a heterogeneous group of T-cell lymphomas primarily involving skin
- Often a chronic course
- Current systemic therapies for CTCL rarely provide reliable and/or durable responses
- Mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) are the most common CD30 expressing CTCL
- Brentuximab vedotin, a CD30 targeting antibody-drug-conjugate, has clinical activity with acceptable safety in CTCL in two phase 2 studies
  - Duvic et al. ORR, MF 54%, pcALCL 100%;
  - Kim et al. ORR, MF/Sézary syndrome 70% [4,5]

Swerdlow SH, et al. Blood 2016;127:2375–90
Willemze R, et al. Ann Oncol 2013;24 Suppl 6:vi149–54
Jawed SI, et al. J Am Acad Dermatol 2014;70:223e1–17
Duvic M, et al. J Clin Oncol 2015;33:3759–65
Kim YH, et al. J Clin Oncol 2015;33:3750–8

ALCANZA: Randomized, open-label, phase 3 trial of brentuximab vedotin vs physician's choice (methotrexate or bexarotene) in CD30+ CTCL



- Methotrexate or bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- Patients were recruited from 52 centers across 13 countries

IV, intravenously; PO, orally

Median age 61 yrs; ECOG PS 0-1 in 96%
Median CD30 expression 32% (range 3-100)

Progression-free survival
(ITT population; independent review)

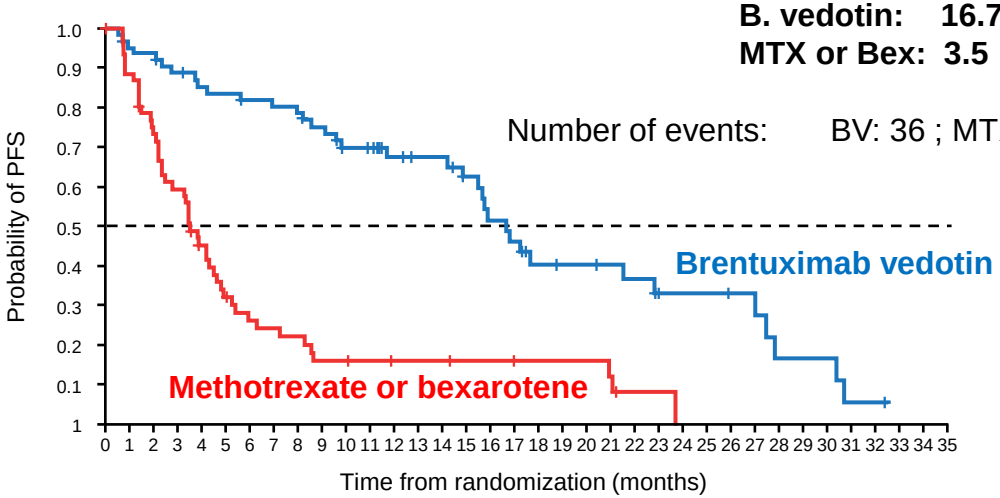
ORR 67% vs 20%

Log-rank test p-value: <0.001

Hazard ratio (95% CI): 0.270 (0.169, 0.430)

Median PFS (months):
B. vedotin: 16.7
MTX or Bex: 3.5

Number of events: BV: 36 ; MTX or Bex: 50



Number of patients at risk:

Brentuximab vedotin	64 59 58 54 51 50 48 47 46 43 38 38 29 27 27 23 19 17 13 12 12 11 10 8 7 7 7 6 3 3 3 1 1
Methotrexate or bexarotene	64 54 42 34 24 17 13 12 11 8 8 7 7 6 6 5 5 5 4 4 4 4 3 1 1

Some reasons why demonstrating benefits of cancer precision medicine may be challenging

- Targeted drug might not be effective
- Assay used to define subsets may not be sufficiently robust or rapid
- Patient selection issues

How do we go forward?

- Control groups
- Improved drugs and better/faster biomarker assays
- Innovative study designs