Aggressive Non-Hodgkin Lymphomas

Overview of Diseases and Treatment

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Leukemia and Lymphoma Society Conference

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Outline

- Overview of NHL
- Diffuse large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Mantle cell lymphoma
- Burkitt lymphoma
- T-cell lymphomas

Non Hodgkin Lymphoma

Definition

- A diverse group of cancers that arise from one of the following cells:
  - B-lymphocytes
  - T-lymphocytes
  - Natural killer cells
  - Precursors of these cells

Lymphoma
Epidemiology

Parameter (2014 estimates)	Non Hodgkin Lymphoma	Hodgkin Lymphoma
Number of new cases	70,800	9190
Number of deaths	18,990	1180
“Death rate”	27%	13%
M:F ratio	1.2	1.2
Median age		30 years

Siegel R et al. Cancer Statistics 2014. CA: Cancer J Clin 2014; 64:9-22.

WHO 2008 Classification of Lymphoid Neoplasms (1)

- Precursor lymphoid neoplasms (e.g. ALL)
- Mature B-cell neoplasms
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - Lymphoplasmacytic lymphoma
  - Mantle cell lymphoma
  - B-cell prolymphocytic leukemia
  - Follicular lymphoma
  - Diffuse large B-cell lymphoma (several subtypes)
  - Burkitt lymphoma/leukemia
  - Marginal zone lymphoma
  - Hairy cell leukemia
  - Plasma cell myeloma

WHO 2008 Classification of Lymphoid Neoplasms (2)

- Hodgkin lymphoma
- Mature T-cell and NK-cell neoplasms
  - Peripheral T-cell lymphoma (several subtypes)
  - Anaplastic large cell lymphoma
  - Primary cutaneous peripheral T-cell lymphomas
  - Adult T-cell leukemia/lymphoma
  - T-cell large granular lymphocyte leukemia
  - T-cell prolymphocytic leukemia
  - Natural killer cell large granular lymphocyte leukemia
  - Aggressive natural killer cell leukemia

Non Hodgkin Lymphoma

Classification Based on Growth Rate

- Indolent
  - Follicular
  - Small lymphocytic lymphoma/chronic lymphocytic leukemia
  - Marginal zone lymphoma
  - Occasionally mantle cell lymphoma
  - Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia)
- Aggressive
  - Diffuse large B-cell lymphoma
  - Mantle cell lymphoma
  - Peripheral T-cell lymphoma
  - Anaplastic large cell lymphoma
- Highly Aggressive
  - Burkitt lymphoma
  - Acute lymphoblastic leukemia

Lymphoma

Clinical Presentation

- Enlarging lymph node(s)
- B symptoms: fever, night sweats, weight loss
- Enlargement of liver
- Enlargement of spleen
- Others possible: bowel involvement, brain involvement

- Patients may have no symptoms
- Indolent much different from aggressive

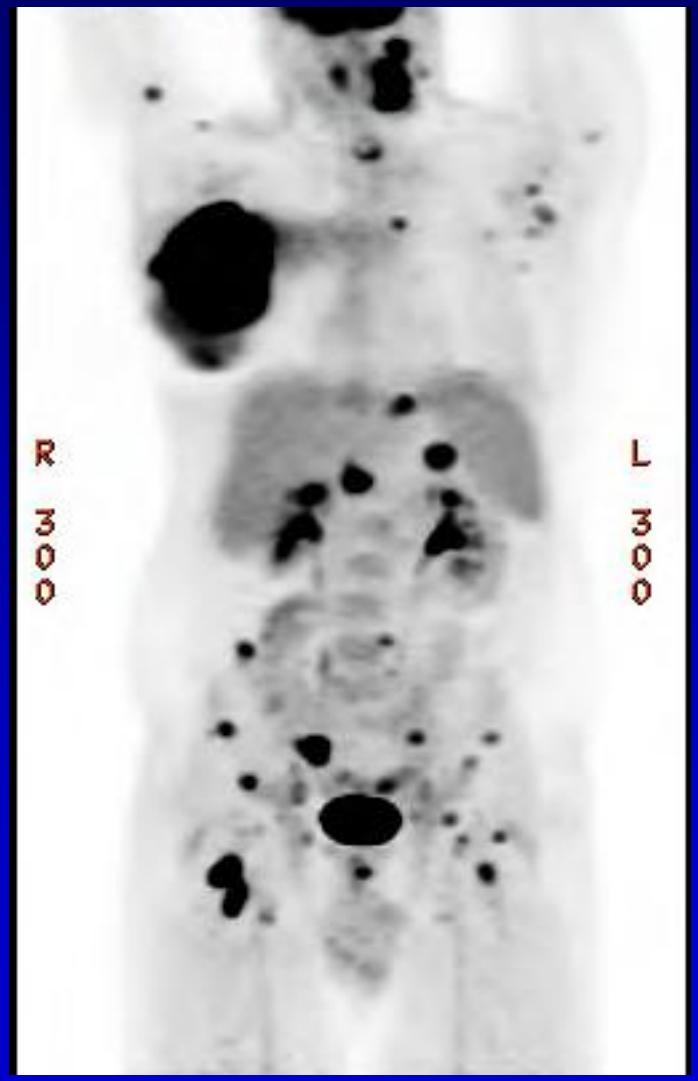
Lymphoma
Making the Diagnosis

- Lymph node biopsy
  - Fine needle aspiration usually inadequate but can be used for screening
  - Core needle biopsy often adequate
  - Excisional biopsy may be necessary
- Studies on tissue
  - Histology
  - Immunophenotype (flow cytometry)
  - Genetic studies
- Bone marrow examination can be diagnostic or used for staging

Lymphoma
Staging Evaluation

- Fertility preservation
- Labs
  - CBC, CMP, LDH
  - Immunoglobulin studies (esp. indolent NHL)
  - HIV, hepatitis B and C serologies
- CT chest, abdomen, pelvis
- PET/CT scan
  - Best in DLBCL, Hodgkin
  - No role in following patients in remission
- Bone marrow aspirate and biopsy
- Lumbar puncture in 4 high-risk groups
  - Testicular non Hodgkin lymphoma
  - Bone marrow involvement with DLBCL (not indolent)
  - Paranasal sinus non Hodgkin lymphoma
  - Immunodeficiency
- Echocardiogram if doxorubicin planned
- Pulmonary function tests if bleomycin planned

Example of a PET/CT scan in a patient with aggressive NHL



Cotswald Modification of Ann Arbor Staging

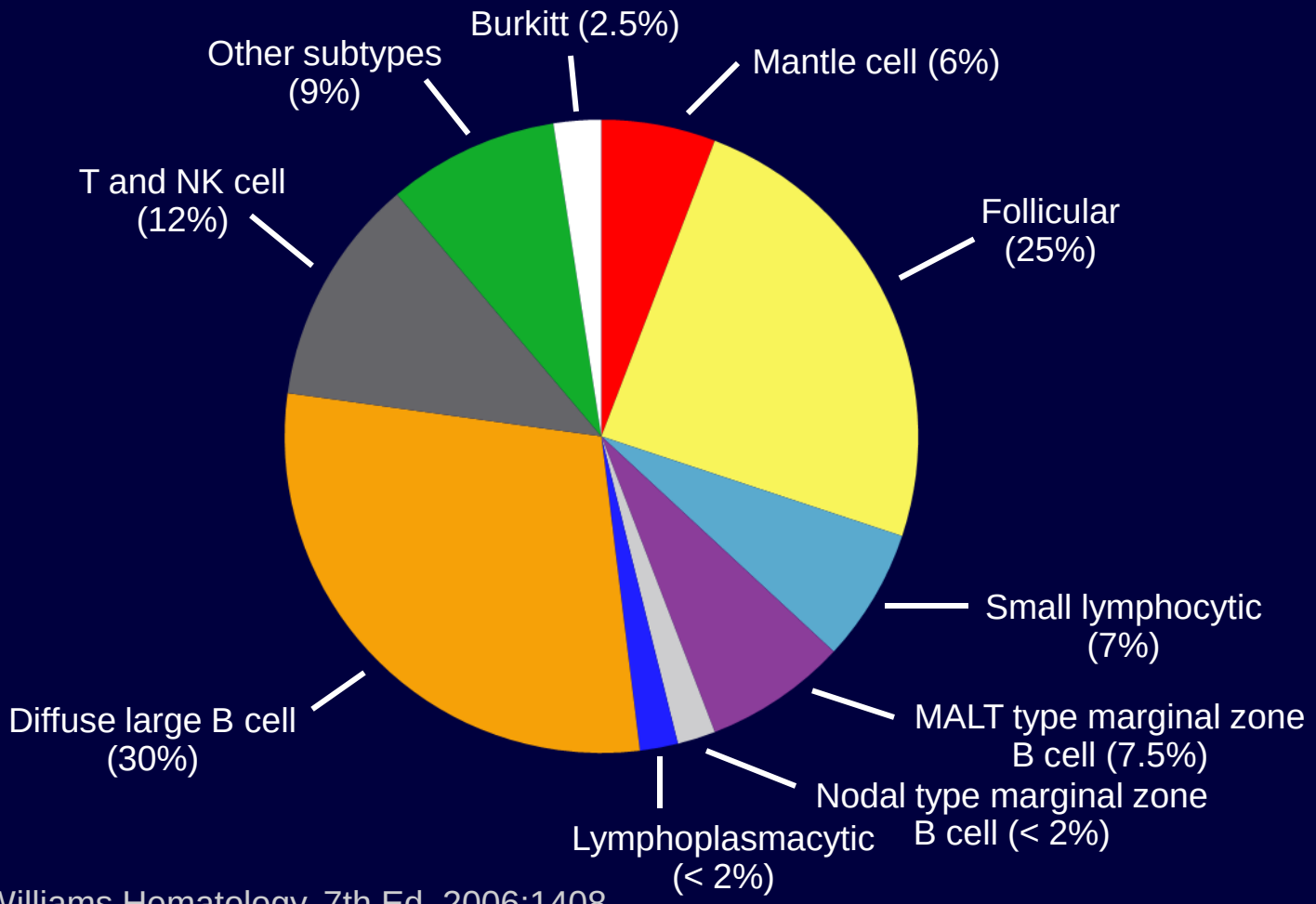
Stage	Description
I	Involvement of one lymph node region
II	Involvement of 2 or more lymph node regions on same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Involvement of extranodal sites beyond that designated as E (e.g. bone marrow, liver, lung)
	Other Designations Applicable to Any Stage
A	No B symptoms
B	Fever 100.4° or higher, drenching night sweats, unexplained weight loss > 10% of body weight
X	Bulky disease (> 10 cm)
E	Involvement of a single extranodal site adjacent to a known nodal site

Lister T, J Clin Oncol 1989; 7:1630 and 1990; 8:1602.

Outline

- Overview of NHL
- **Diffuse large B-cell lymphoma**
- Primary mediastinal large B-cell lymphoma
- Mantle cell lymphoma
- Burkitt lymphoma
- T-cell lymphomas

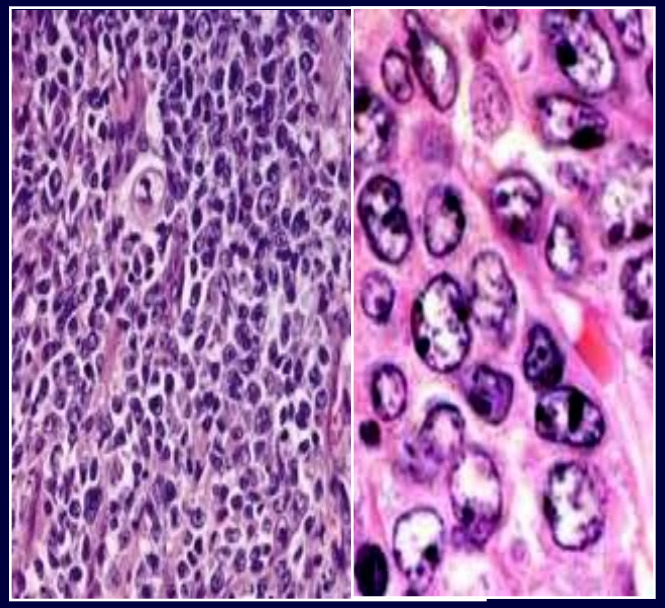
Diffuse Large B-Cell Lymphoma: Most Common Subtype of NHL



Lichtman. Williams Hematology, 7th Ed. 2006;1408.

Diffuse Large B-Cell Lymphoma

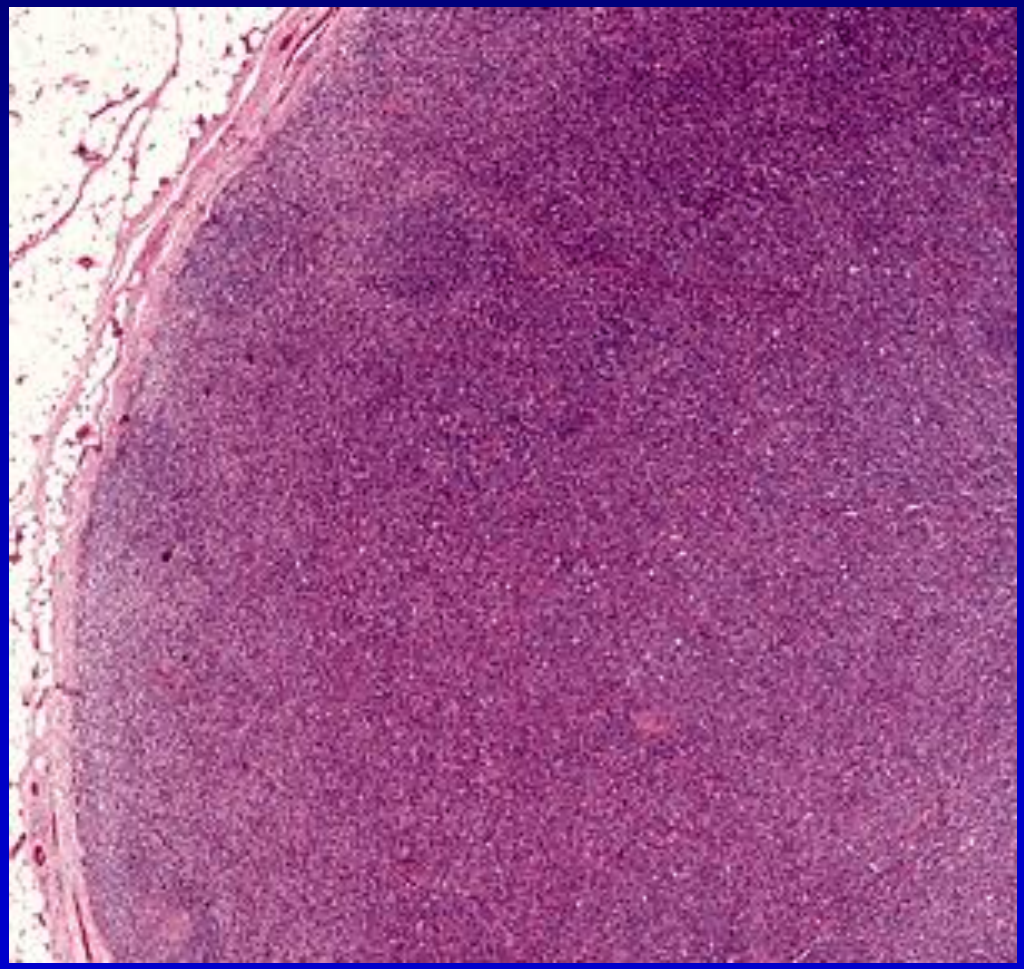
- Most common NHL: 31%
  - Peak incidence in sixth decade
- Clinical outcomes and molecular features highly heterogeneous
- Large cells with loss of follicular architecture
  - 30% to 40% present with rapidly enlarging, symptomatic mass with B symptoms
  - May present as extranodal disease (stomach, CNS, testis, skin)
- Curable in 50% or more of cases
- Median survival: wks to mos if not treated



Michallet AS, et al. Blood Rev. 2009;23:11-23.

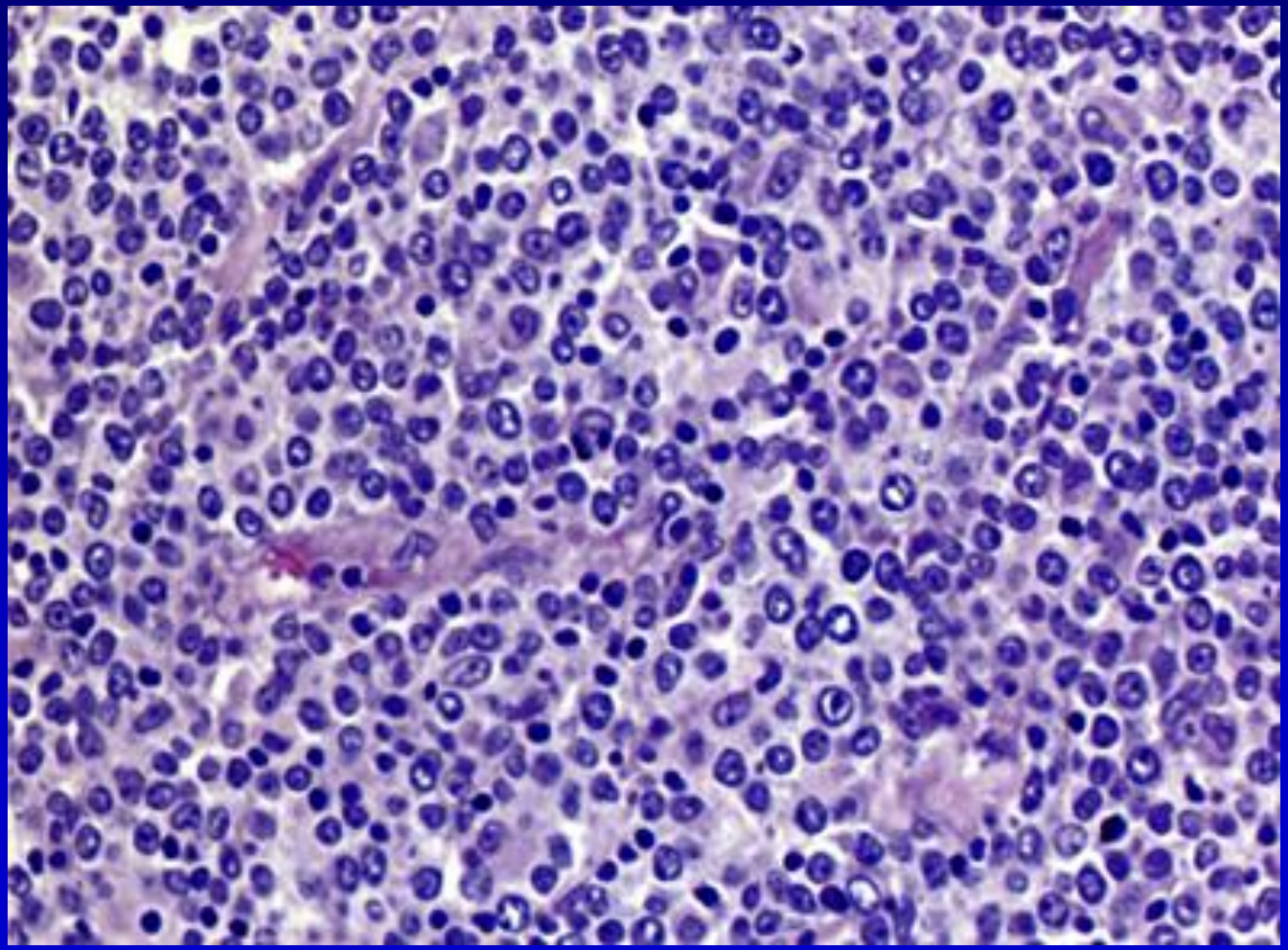
Diffuse Large B-Cell Lymphoma

Pathology, low-power view



Diffuse Large B-Cell Lymphoma

Pathology, high-power view



International Prognostic Index (1)

- Developed to identify factors related to the prognosis of DLBCL

- 5 factors with adverse implications identified (APLES)
  - Age > 60
  - ECOG performance status 2 or higher
  - LDH above normal range
  - Extranodal sites: 2 or more
  - Stage III or IV

N Engl J Med 1993

International Prognostic Index (2)

Risk level	IPI score	3-year OS
Low	0-1	91%
Low-intermediate	2	81%
High-intermediate	3	65%
High	4-5	59%

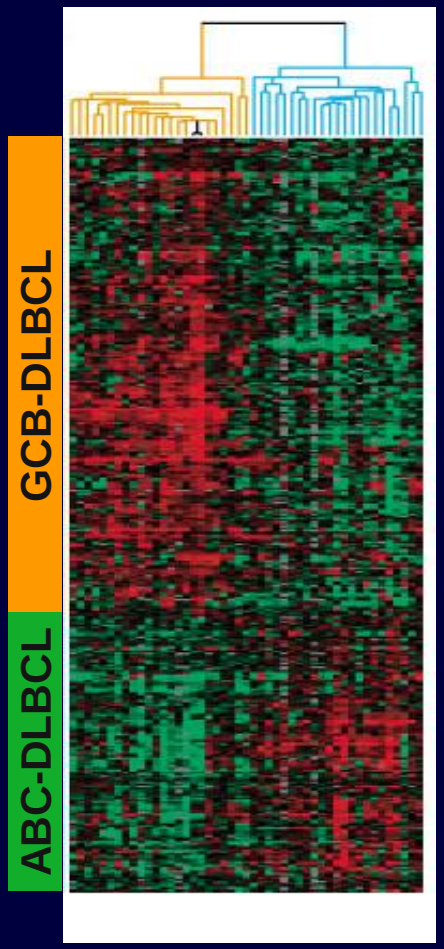
Ziepert M et al., JCO 2010.

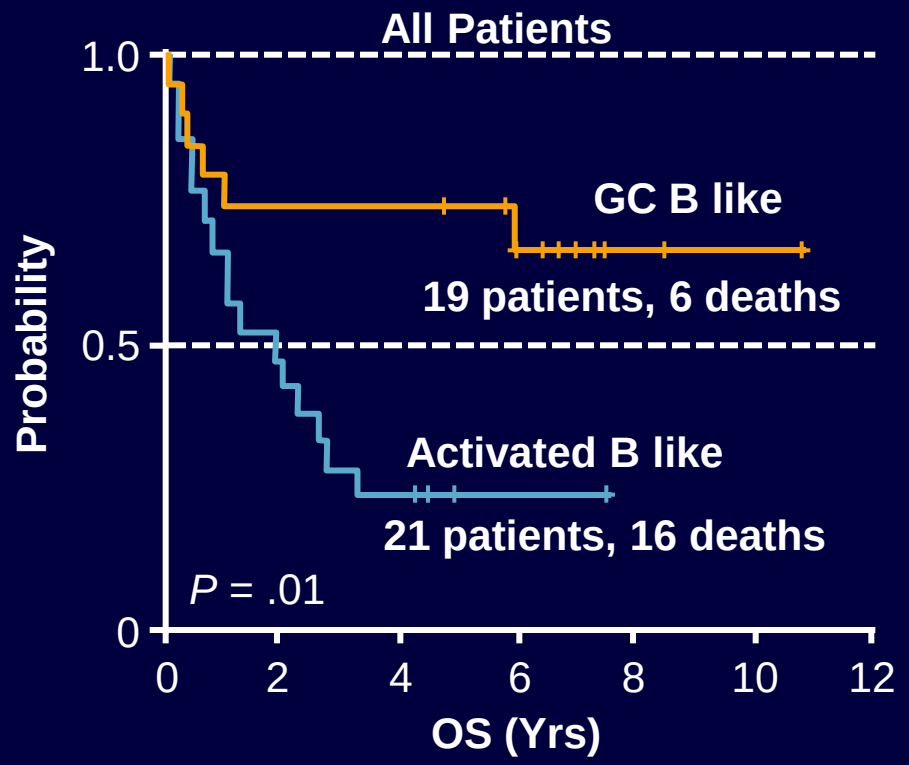
Gene Expression Profiling

- Uses DNA microarrays to characterize gene expression by tumor cells

- Identifies 3 major groups
  - Germinal center-type DLBCL
    - Profile similar to that of normal germinal center B cells
    - Better prognosis
  - Activated B-cell type DLBCL
    - Profile resembles that of activated B cell
    - Worse prognosis
  - Primary mediastinal

Microarray Analysis and Diffuse Large B-Cell Lymphoma Heterogeneity

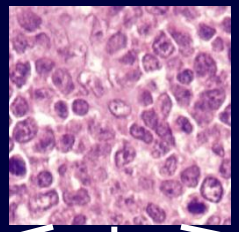


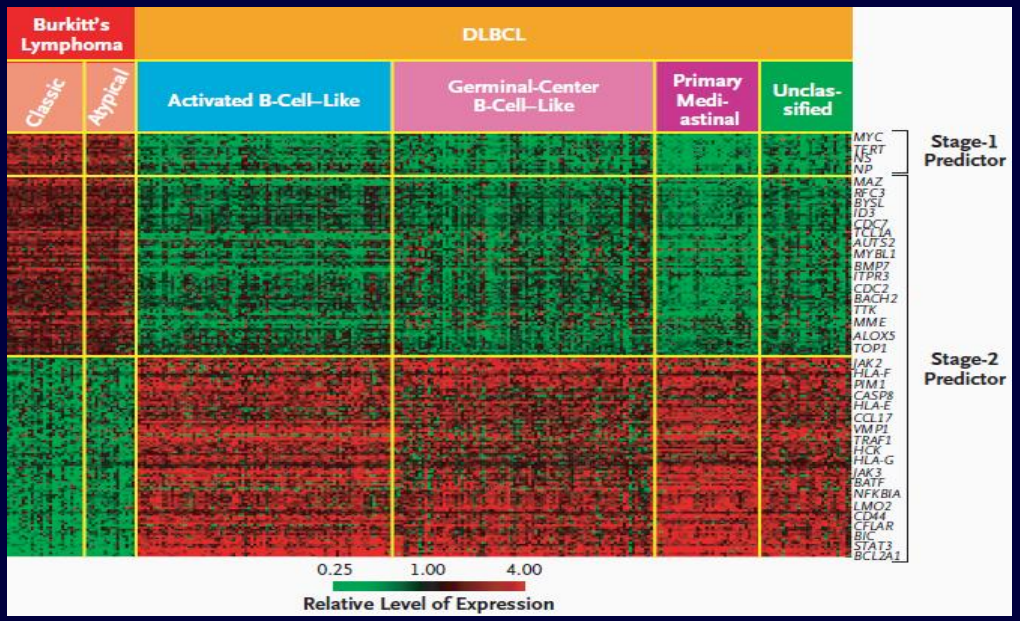


Alizadeh AA, et al. Nature. 2000;403:503-511.

Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL

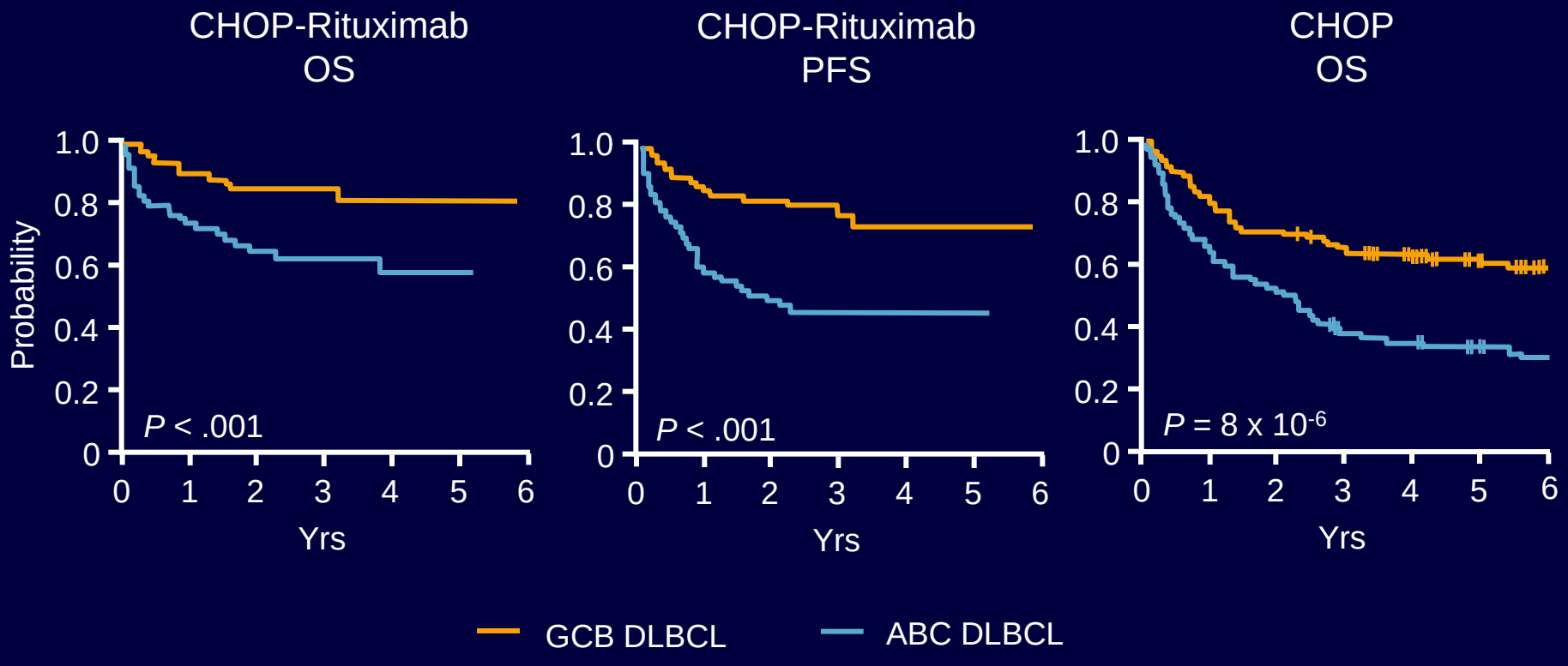
Diffuse Large
B-Cell Lymphoma





Dave SS, et al. N Engl J Med. 2006;354:2431-2442. Graphic reproduced with permission.

DLBCL Subtype Retains Prognostic Value With R-CHOP Therapy

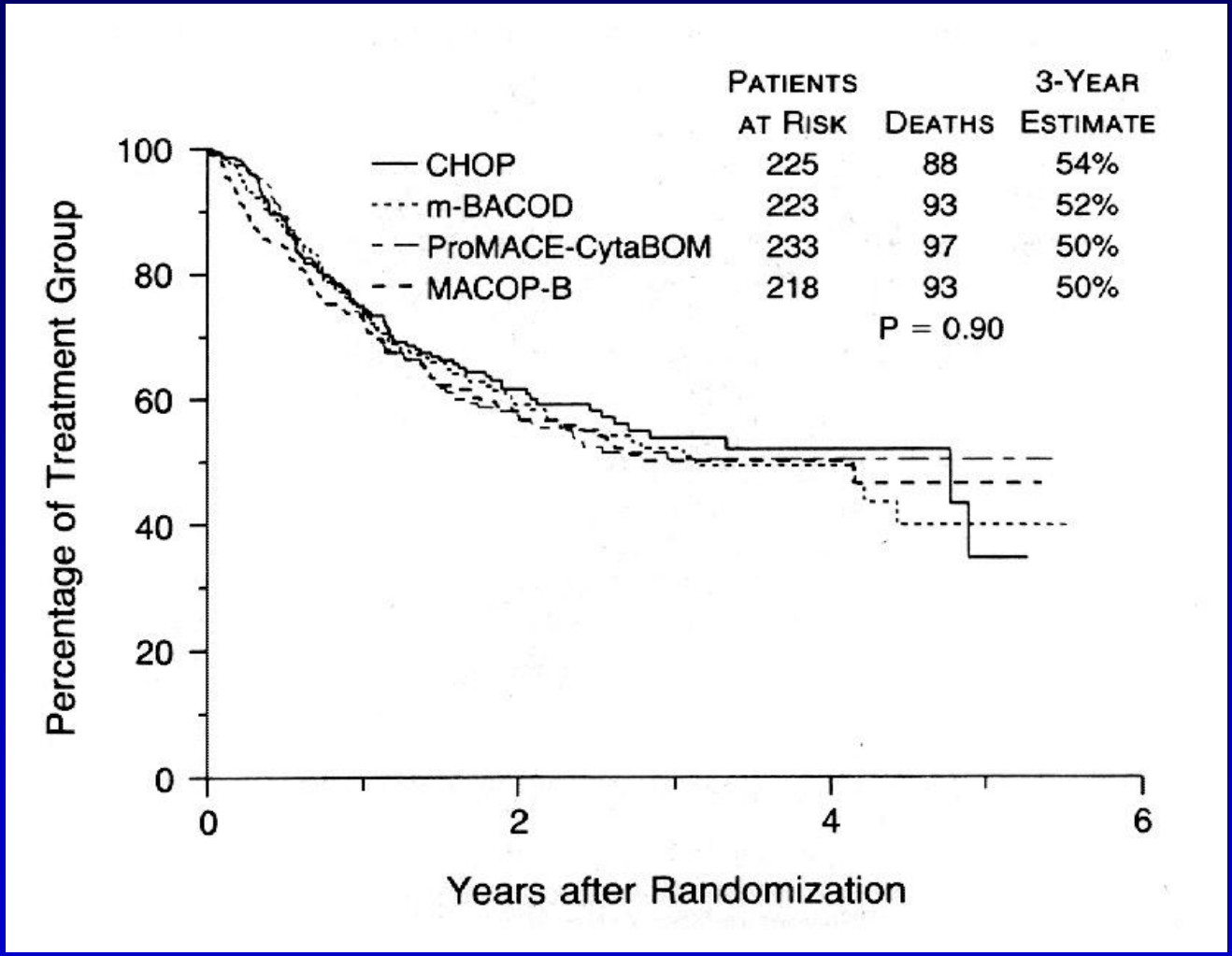


Lenz G, et al. N Engl J Med. 2008;359:2313-2323.

Treatment of DLBCL

- What is current standard treatment?
  - R-CHOP in previously untreated patients
  - Chemo then autologous transplant in relapsed patients
- How are we trying to improve on current standard treatment?

Increasing the intensity of chemotherapy by adding chemotherapy drugs to CHOP does not improve outcome in patients with DLBCL.



Fisher RI et al. N Engl J Med 1993;328:1002-1006.

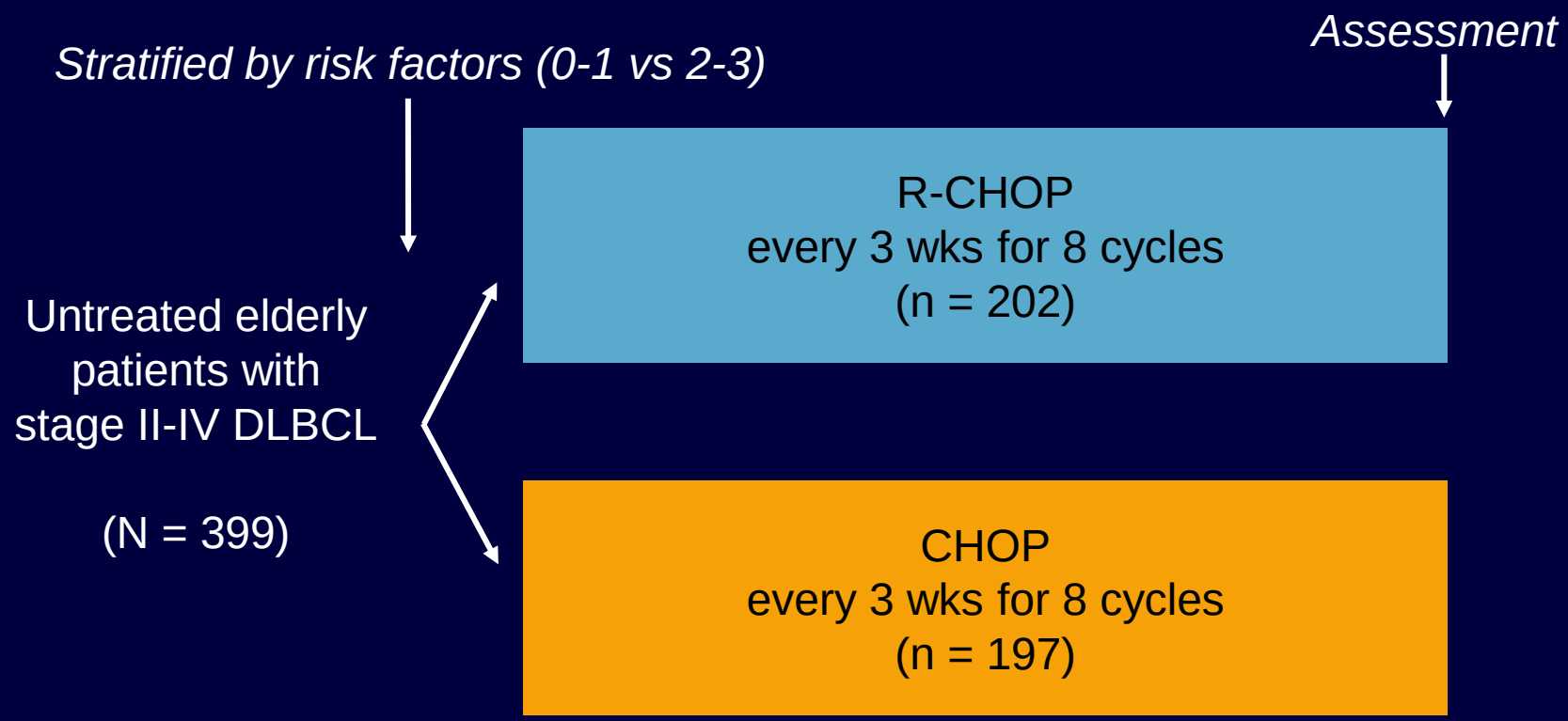
The NEW ENGLAND JOURNAL of MEDICINE

What is R-CHOP?

Name of Drug	Dose and Route of Administration
Rituximab	375 mg/m^2 IV on day 1
Cyclophosphamide	750 mg/m^2 IV on day 1
Doxorubicin	50 mg/m^2 IV push on day 1
Vincristine	2 mg IV push on day 1
Prednisone	50 mg/m^2 or 100 mg PO on days 1-5

- 1 cycle = 21 days
- 3-6 cycles administered, depending on stage
- Often administered with growth factor support (e.g. Neulasta 6 mg subcutaneously on day 6)

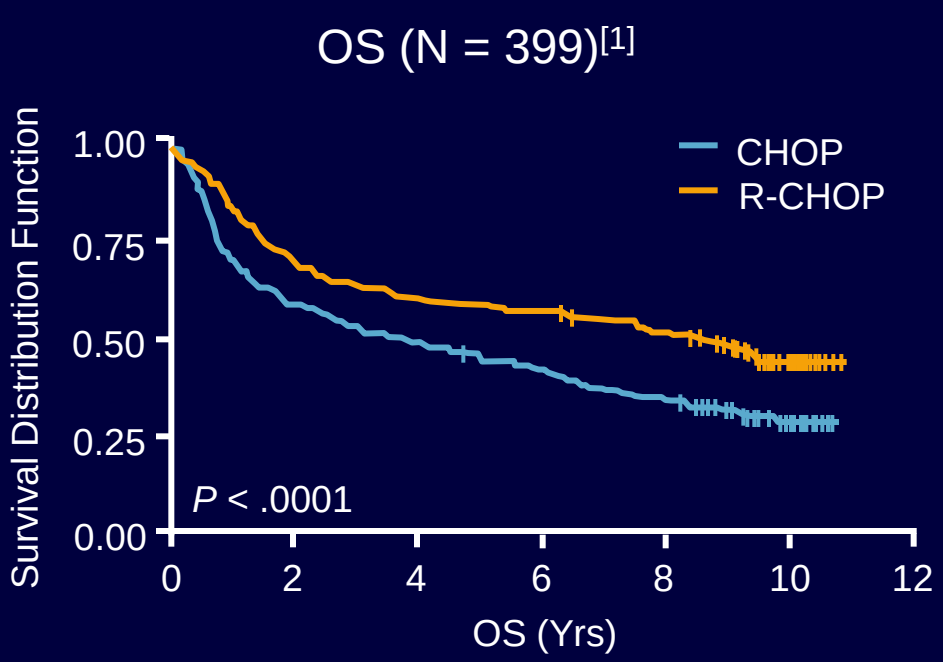
CHOP ± Rituximab in DLBCL: GELA LNH-98.5 Phase III Study



- Primary endpoint: EFS
- Secondary endpoints: OS, RR

Coiffier B, et al. N Engl J Med. 2002;346:235-242. Feugier P, et al. J Clin Oncol. 2005;23:4117-4126.

CHOP ± Rituximab in DLBCL: 10-Yr Survival Results (GELA LNH-98.5 Study)



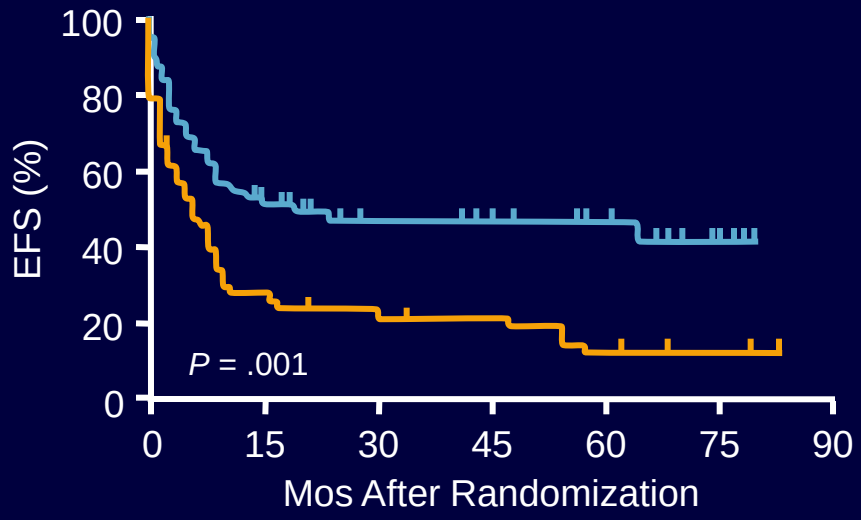
Parameter, %[2]	Low Risk	High Risk
Age, < 70 vs ≥ 70 yrs	58.0	49.0
LDH, NI vs > NI	69.0	45.0*
Stage, I/II vs III/IV	67.0	50.0
Bone marrow, yes vs no	60.0	34.5*
Tumor size, < 10 vs ≥ 10 cm	60.0	36.5
β_2-microglobulin, NI vs > NI	64.5	39.0*
Serum albumin, ≥ 35 vs < 35 g/L	60.0	40.0

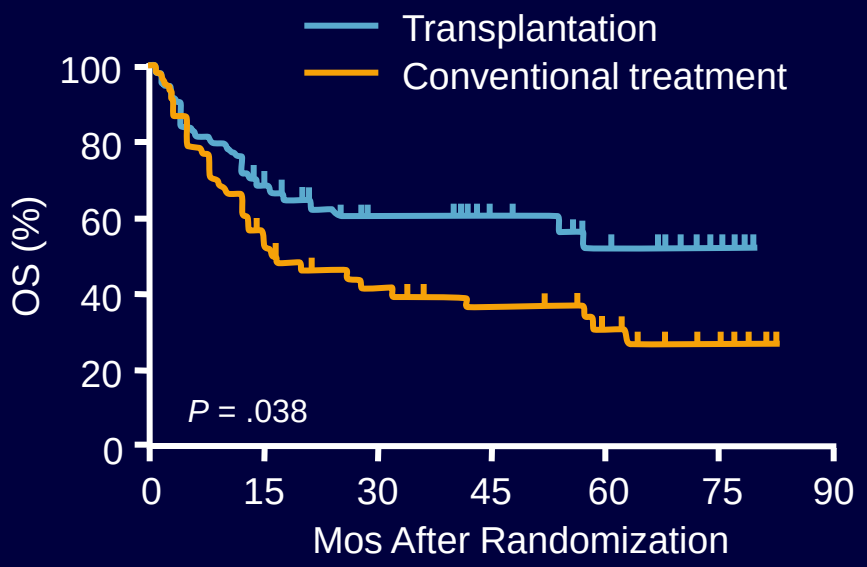
*P < .05 (multivariate analysis).

- Median OS: 3.5 yrs with CHOP vs 8.4 yrs with R-CHOP

1. Coiffier B, et al. Blood. 2010;116:2040-2045.
2. Coiffier B, et al. ASCO 2007. Abstract 8009.

PARMA Study: Bone Marrow Transplantation vs Salvage Chemotherapy





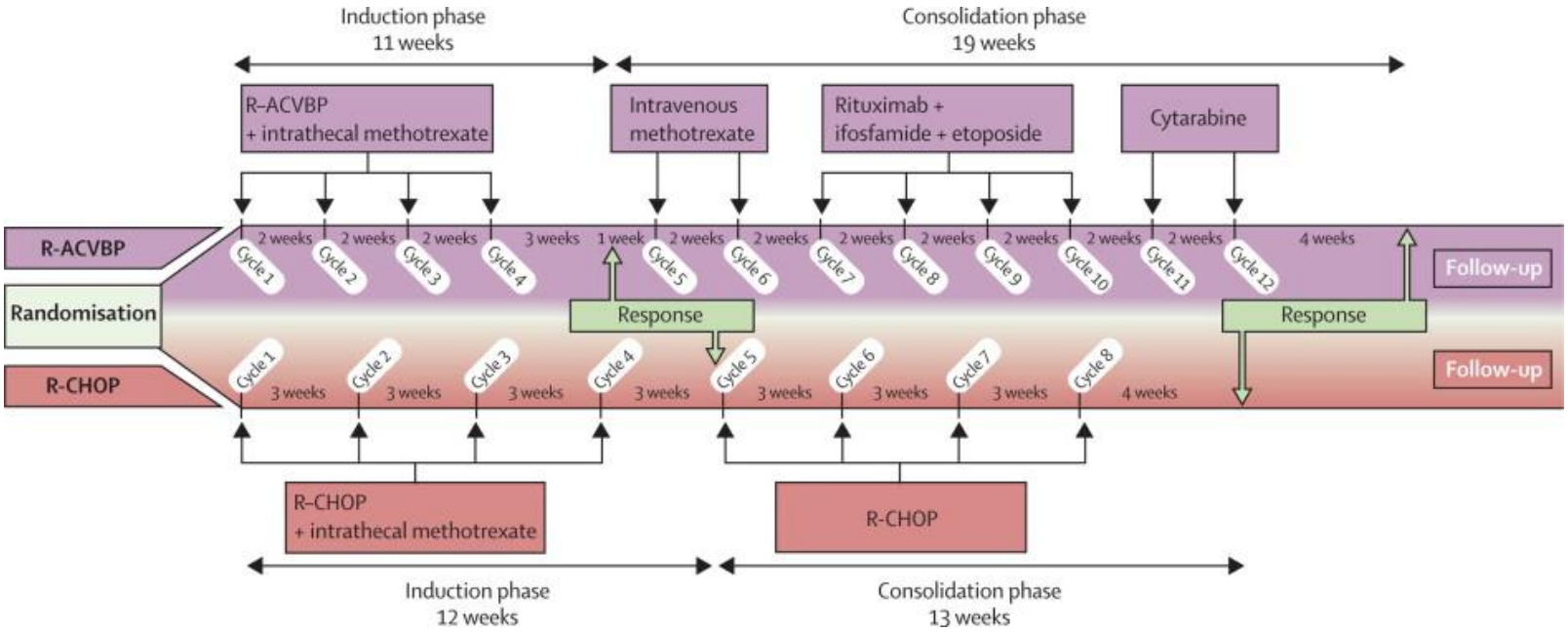
Philip T, et al. N Engl J Med. 1995;333:1540-1545.

Selected Investigational Therapies

- Targeting all subtypes
  - R-ACVBP
  - Dose-adjusted EPOCH-R
  - New anti-CD20 antibodies
  - Antibody-drug conjugates
  - CAR T-cell therapy
  - Many more!

- Targeting activated B-cell subtype with R-CHOP-X
  - Bortezomib (proteasome inhibitor)
  - Ibrutinib (Bruton tyrosine kinase inhibitor)
  - Lenalidomide (Cereblon inhibitor)

Design of study comparing R-ACVBP with R-CHOP for DLBCL.



Ages 18-59; median age 47 years

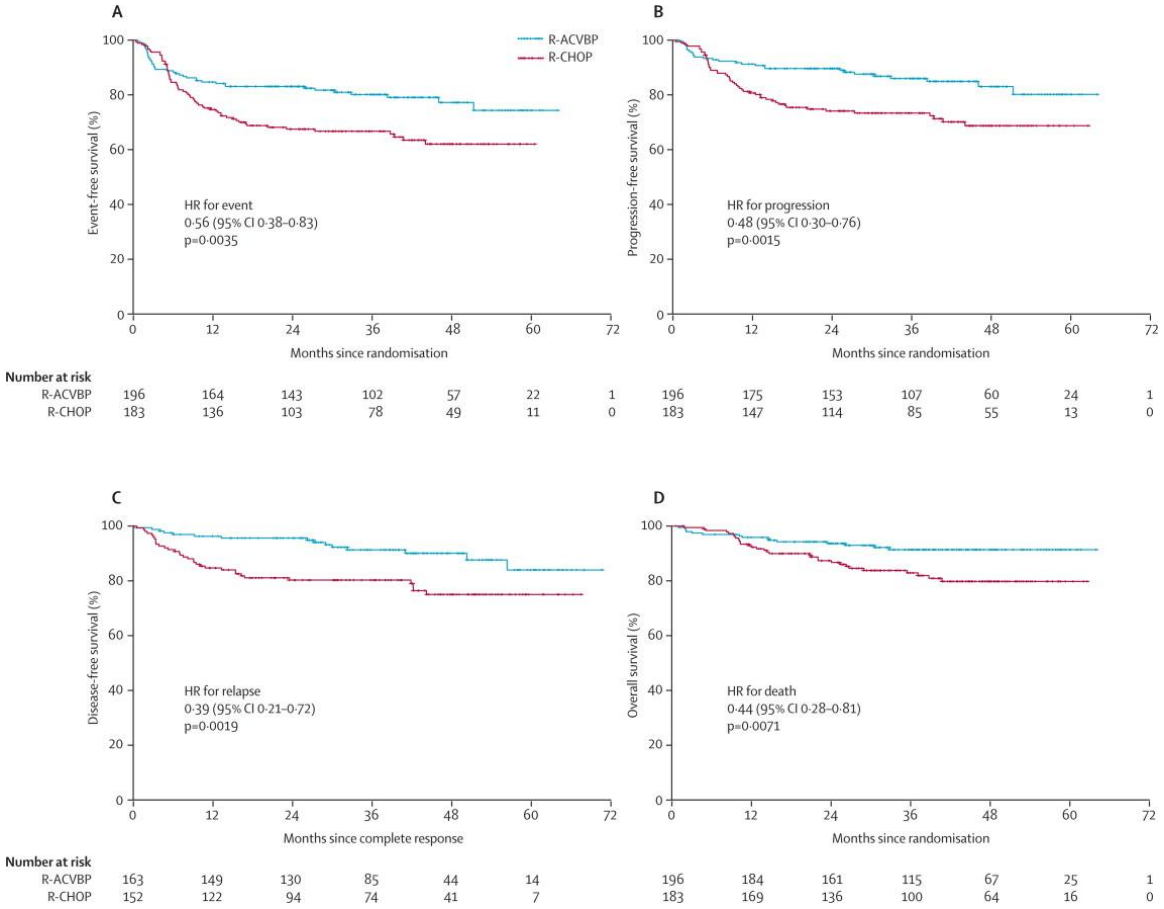
N = 380

About 96% had good prognosis (age-adjusted IPI 1)

Christian Récher , Bertrand Coiffier , Corinne Haioun , Thierry Jo Molina , Christophe Fermé , Olivier Casasnovas ...
Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial

The Lancet, Volume 378, Issue 9806, 2011, 1858 - 1867
http://dx.doi.org/10.1016/S0140-6736(11)61040-4

Compared with R-CHOP, R-ACVBP improves EFS, DFS, PFS, OS, but severe toxicity was increased.



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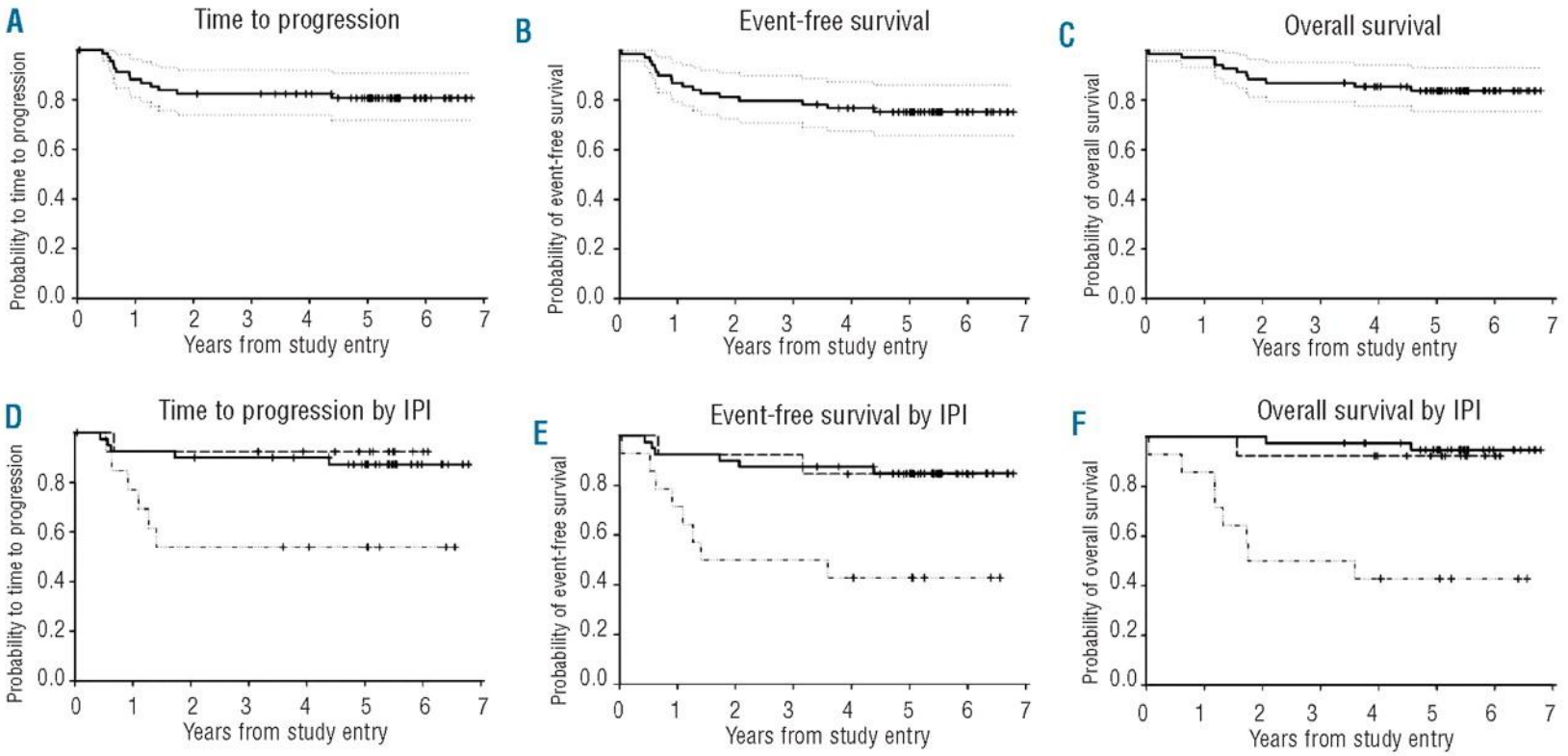
http://dx.doi.org/10.1016/S0140-6736(11)61040-4

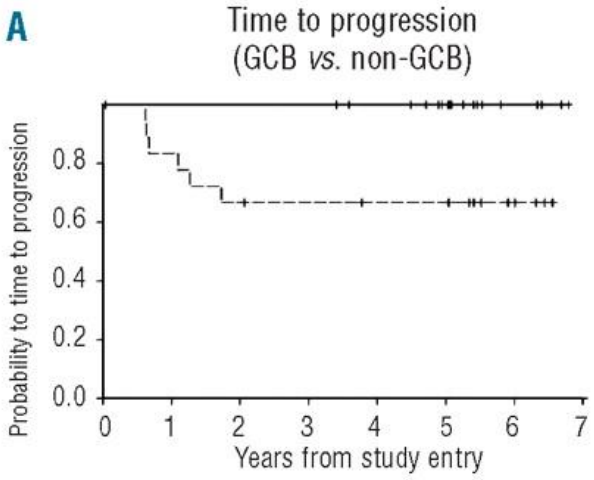
Dose-adjusted EPOCH-R results in good outcomes in patients with DLBCL, though patients with high-risk disease by IPI continue to fare poorly.

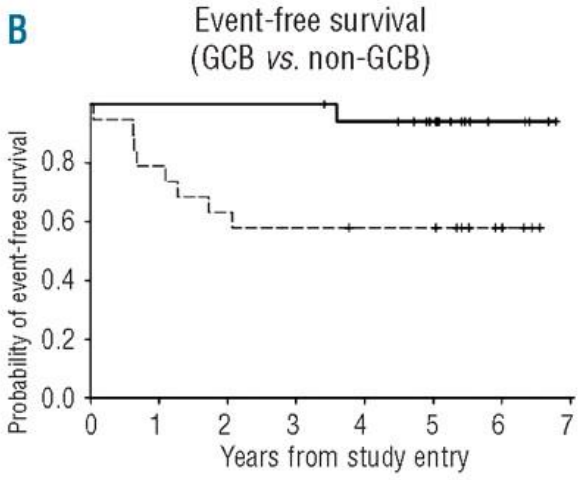


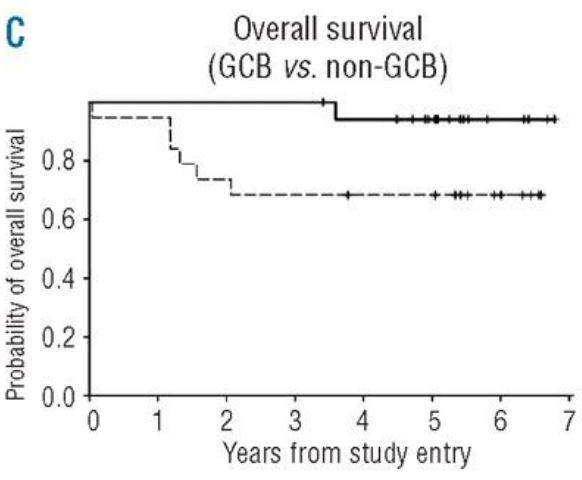
Wyndham H. Wilson et al. Haematologica 2012;97:758-765

haematologica
the hematology journal

Even with DA-EPOCH-R, patients with non-GCB subtype (dotted line) have worse outcomes than patients with GCB subtype (solid line).



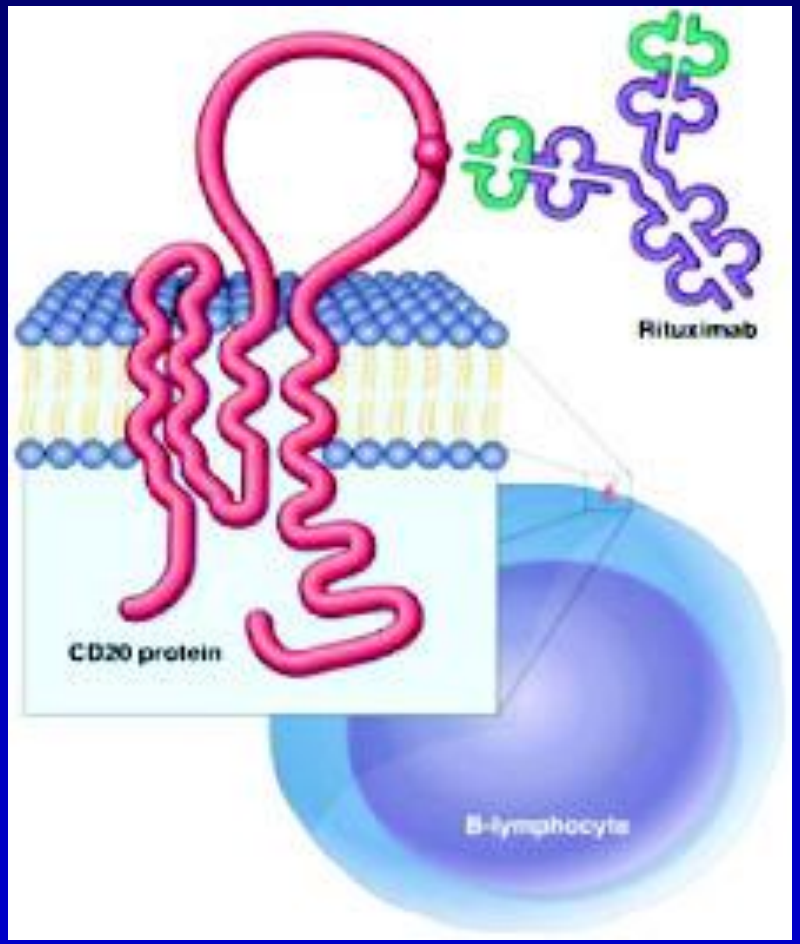


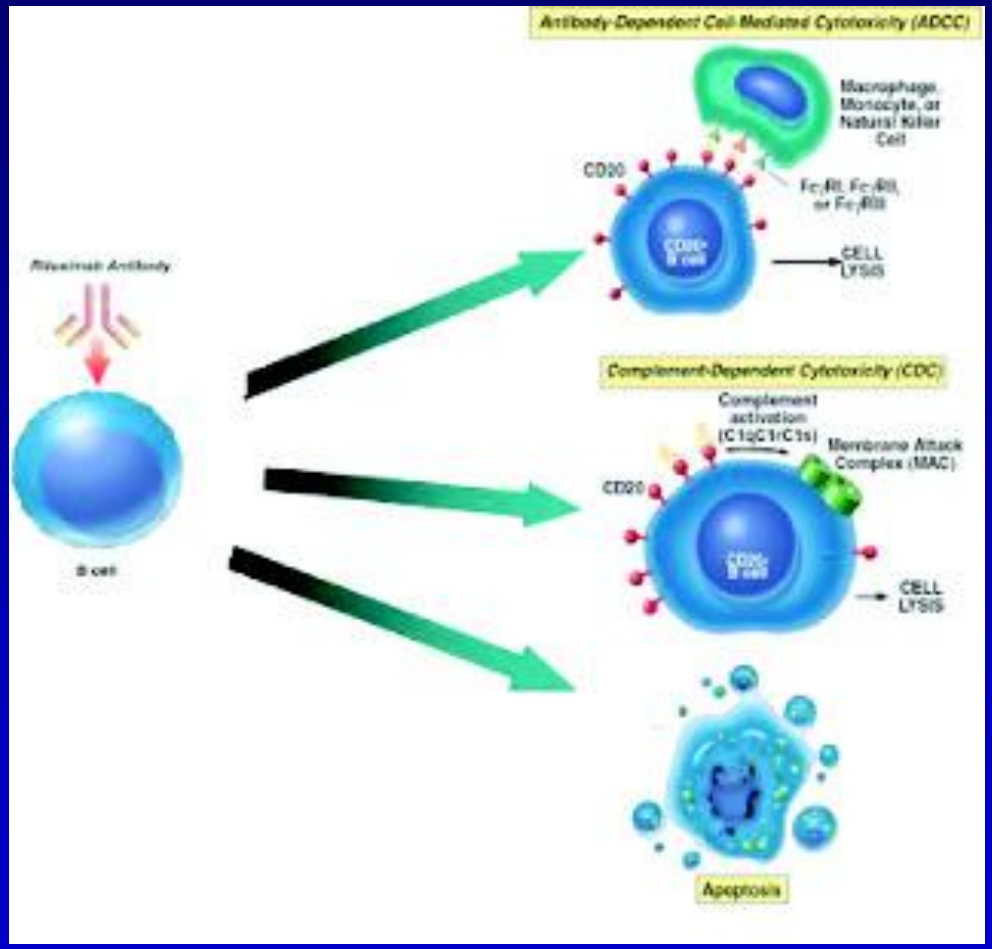


Wyndham H. Wilson et al. Haematologica 2012;97:758-765

haematologica
the hematology journal

Mechanism of action of anti-CD20 antibodies



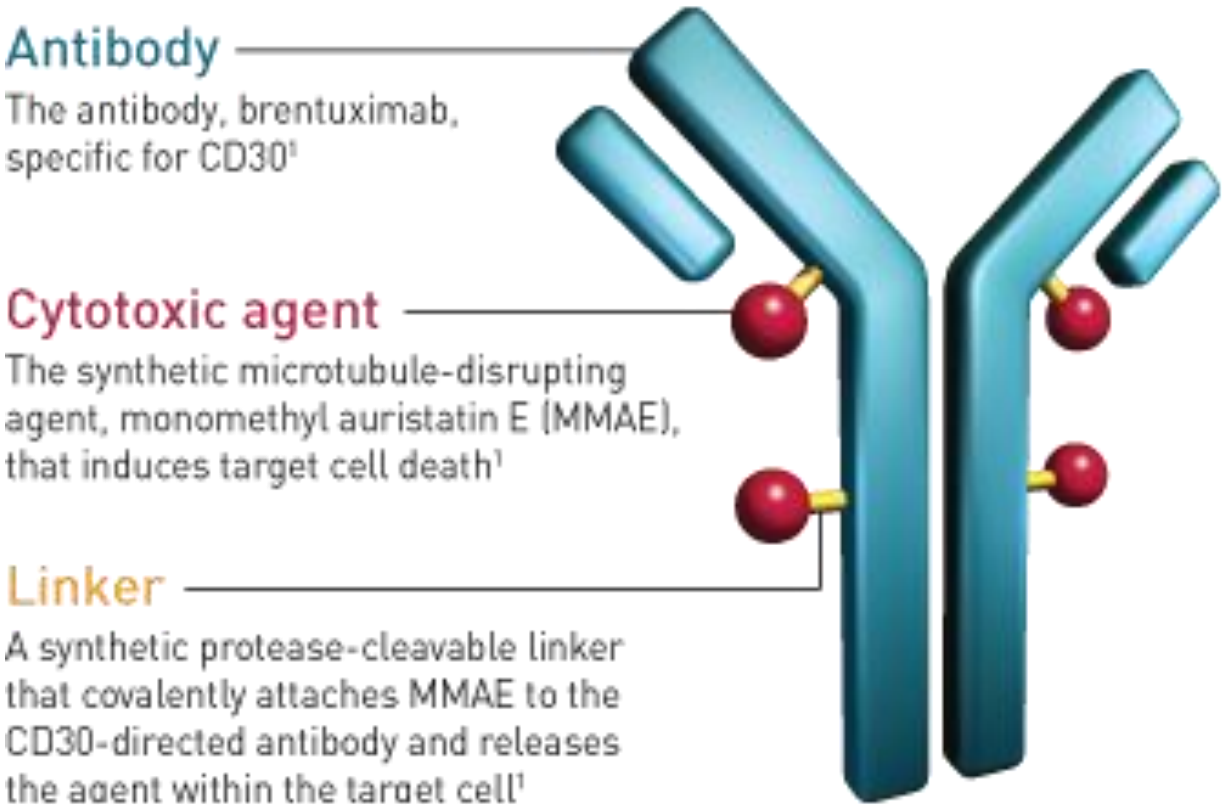


Pescovitz MD. Am J Transplantation 2006; 6:859-66.

Obinutuzumab (GA-101)

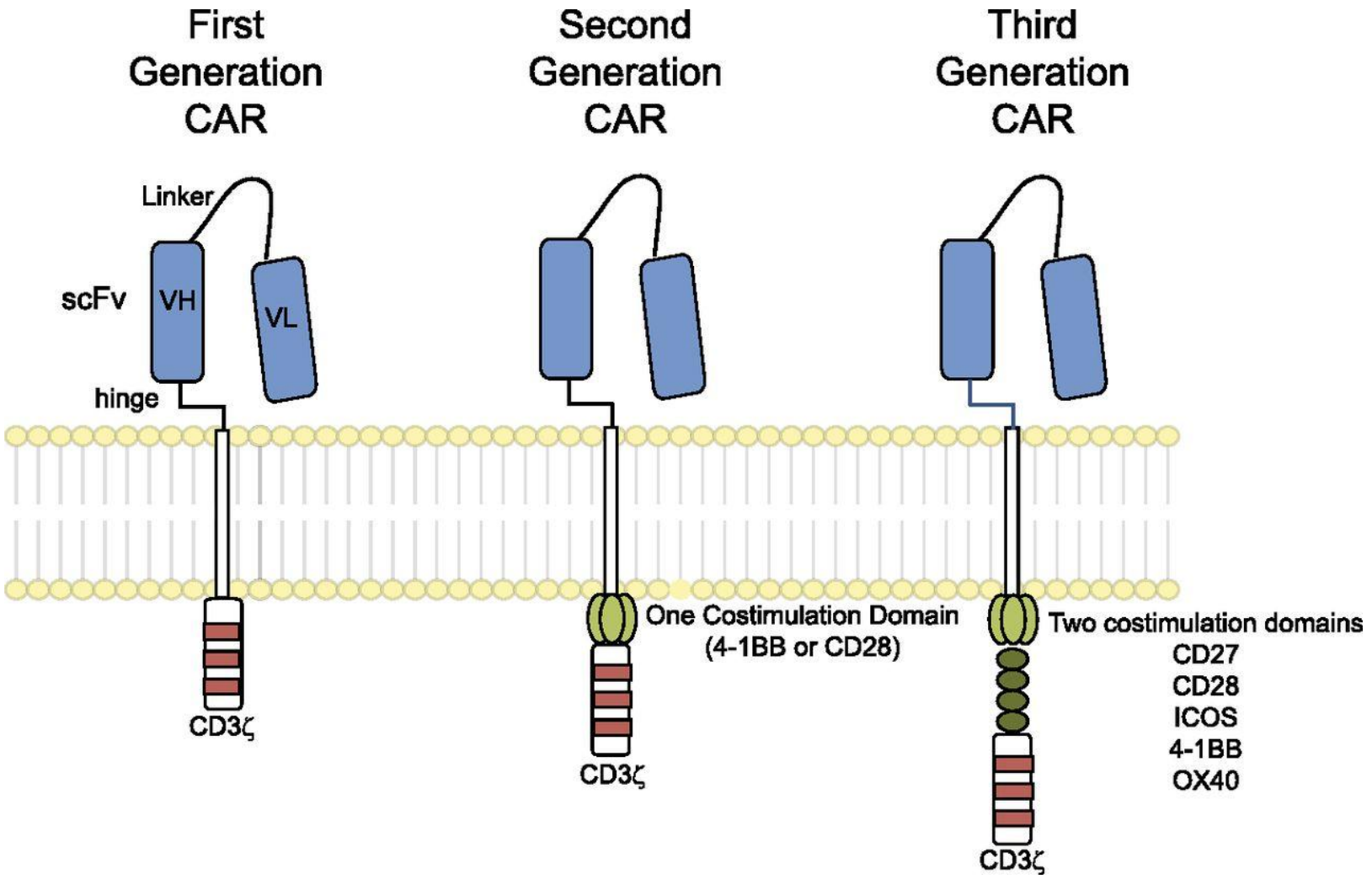
- Mechanism
  - Monoclonal antibody that binds to protein called CD20 on surface of B cells
  - “Glycoengineered”: sugar molecules removed from part of antibody that induces immune reaction
  - Glycoengineering makes it a better killer of cancer cells than rituximab

Structure of antibody-drug conjugates



http://www.adcetris.com/hcp/mechanism-of-action.php, accessed April 14, 2013

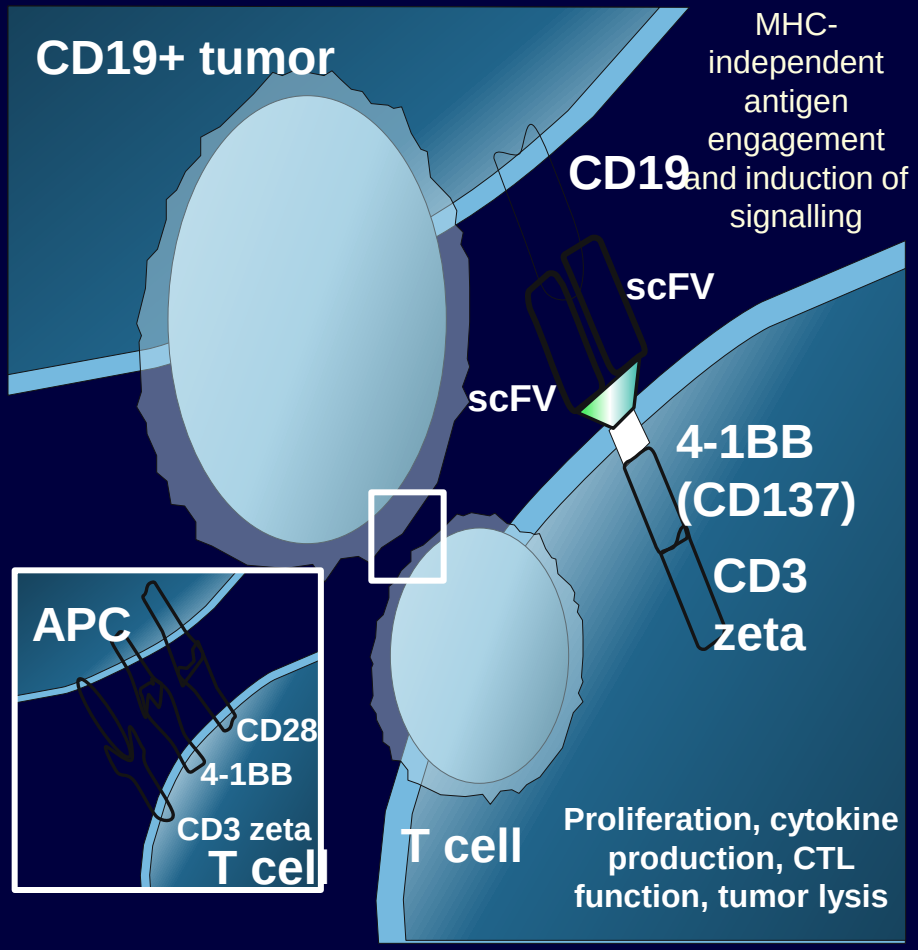
Chimeric antigen receptors.



Marcela V. Maus et al. Blood 2014;123:2625-2635

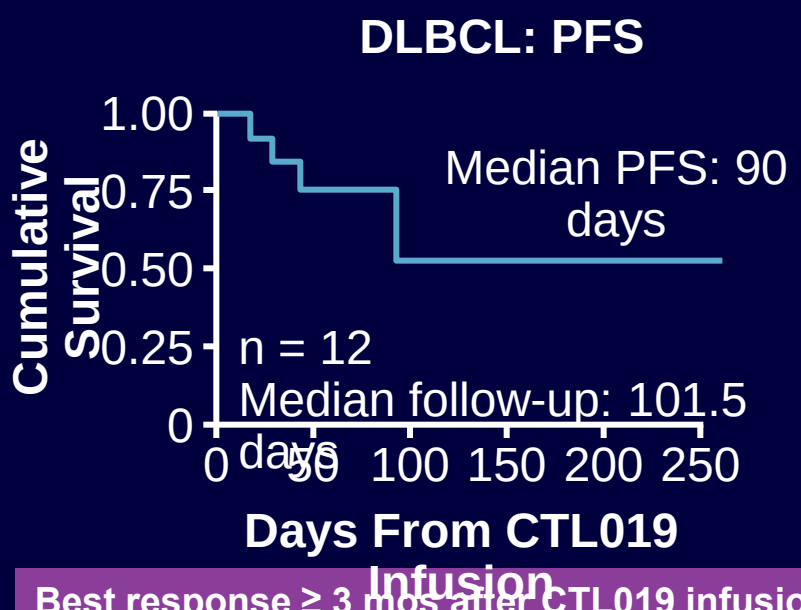
Chimeric Antigen Receptors: MOA

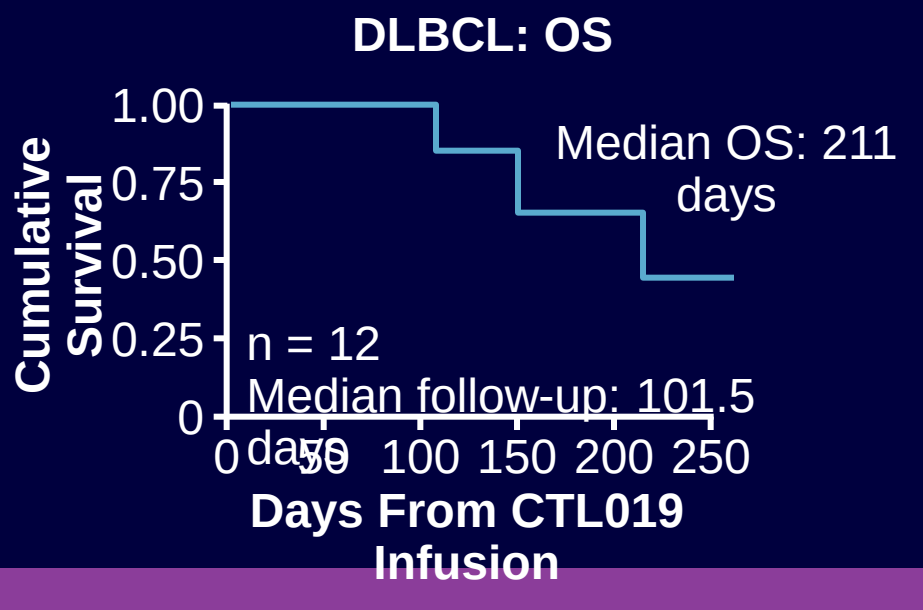
- Chimeric antigen receptors[1]
  - Genetically engineered receptors that combine anti-CD19 single chain variable fragment of an antibody with intracellular signaling domains of T cells
  - With the use of lentiviral-vector technology, CTL019 T cells express a CAR with CD3 zeta and 4-1BB (CD137) signaling domains[2]



1. Grupp S, et al. ASH 2014. Abstract 380.
2. Maude SL, et al. N Engl J Med. 2014; 371:1507-1517.

CAR T Cells Against CD19 in Rel/Ref CD19+ Lymphomas: Results



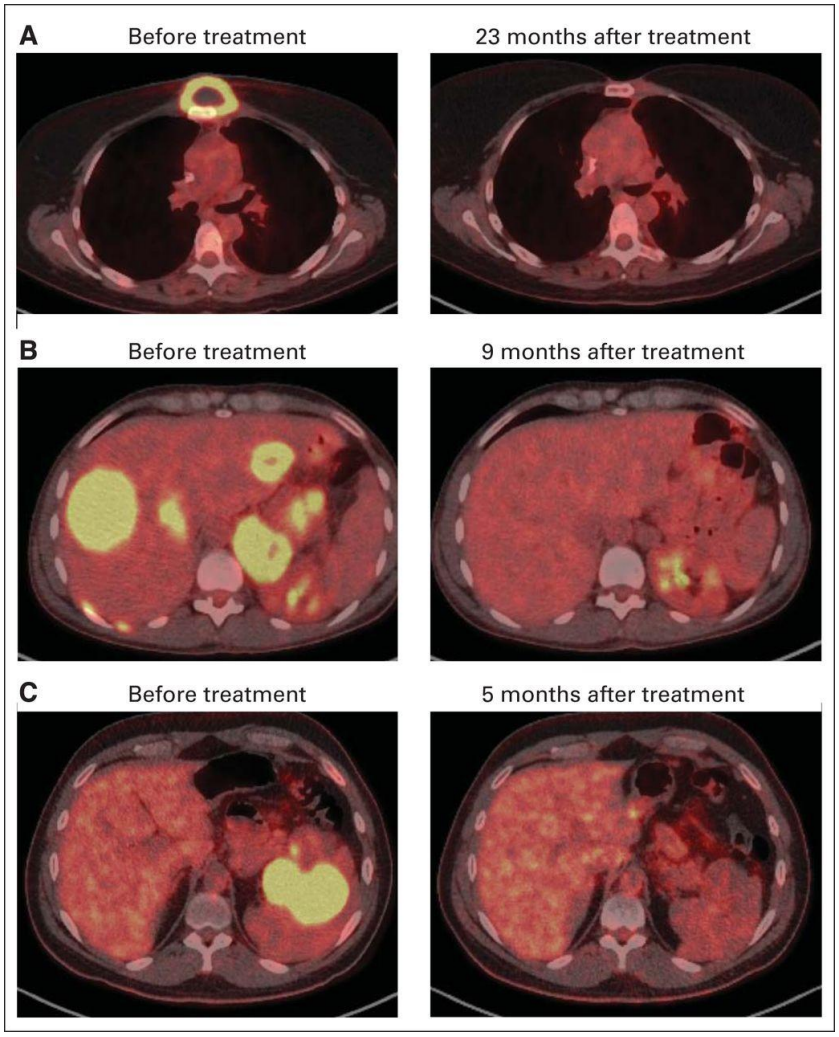


Best response ≥ 3 mos after CTL019 infusion

Pts, n	ORR	CR/CRu	PR	PD
FL n = 5	5	4	1	0
DLBCL n = 11	5	4	1	6

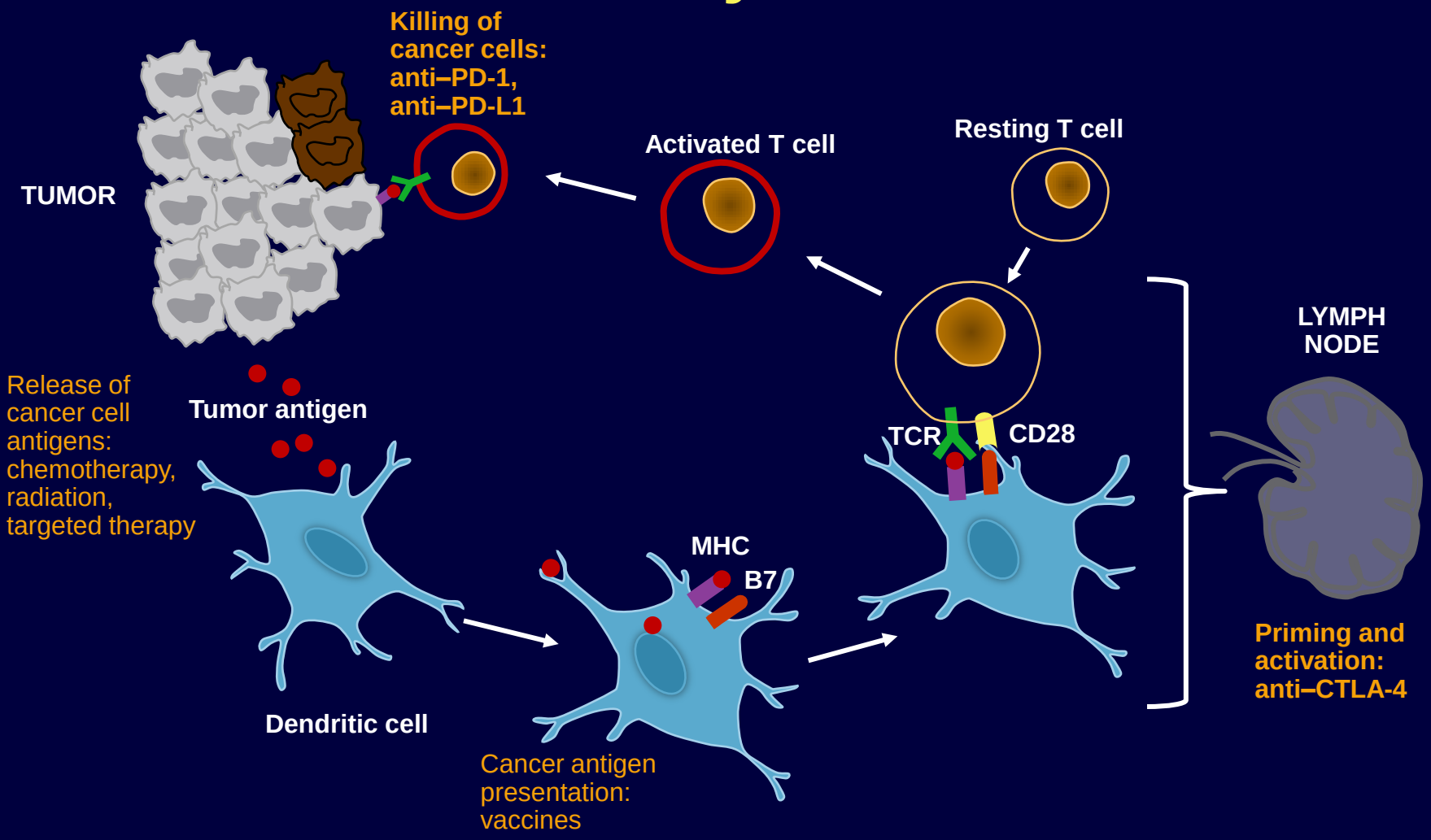
Schuster SJ, et al. ASH 2014. Abstract 3087.

Complete remissions (CRs) of chemotherapy-refractory large-cell lymphomas in patients receiving anti-CD19 chimeric antigen receptor T cells.

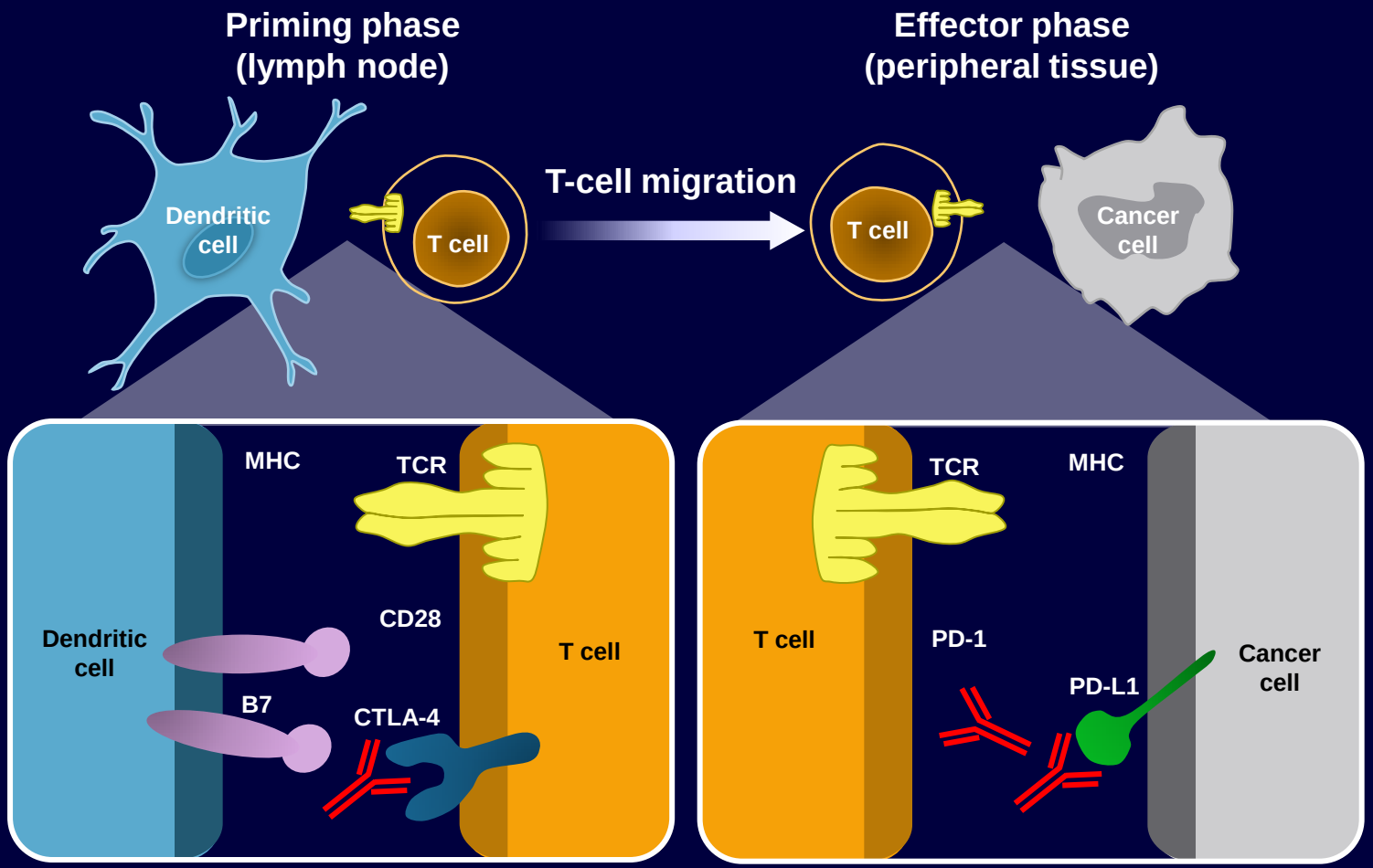


James N. Kochenderfer et al. JCO 2015;33:540-549

A Roadmap of Immunotherapy Agents in the Cancer: Immune System Interaction



CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment



Ribas A. N Engl J Med. 2012;366:2517-2519.

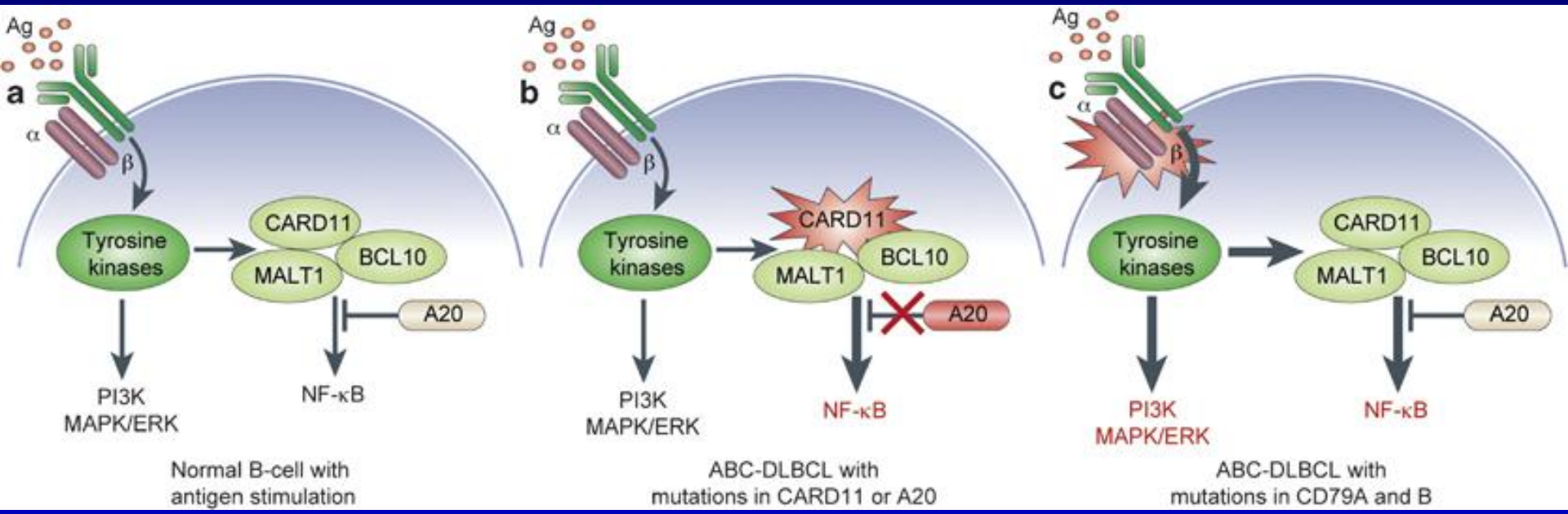
Examples of Companies Developing T-cell Treatments

- CAR T cell therapy
  - Novartis
  - Juno Therapeutics
  - Kite Pharmaceuticals
  - BluebirdBio

- PD1/PD-L1 Antibodies
  - BMS
  - Merck
  - Roche/Genentech
  - MedImmune

There is lots of enthusiasm and lots of research in this field!

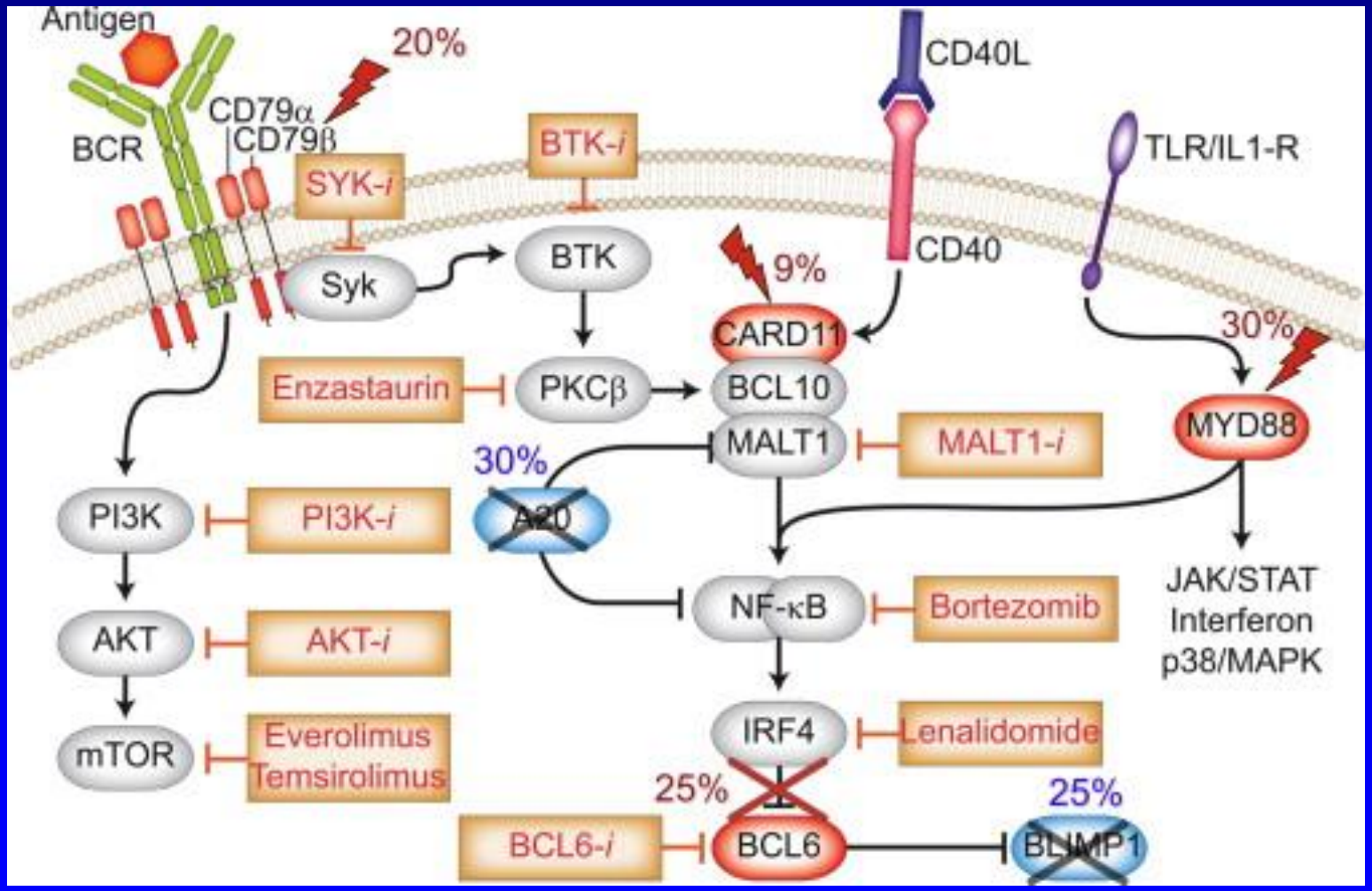
B-cell receptor signaling is derailed in lymphomas.



Klein U and Pasqualucci L. Immunology and Cell Biology 2010; 88:346.

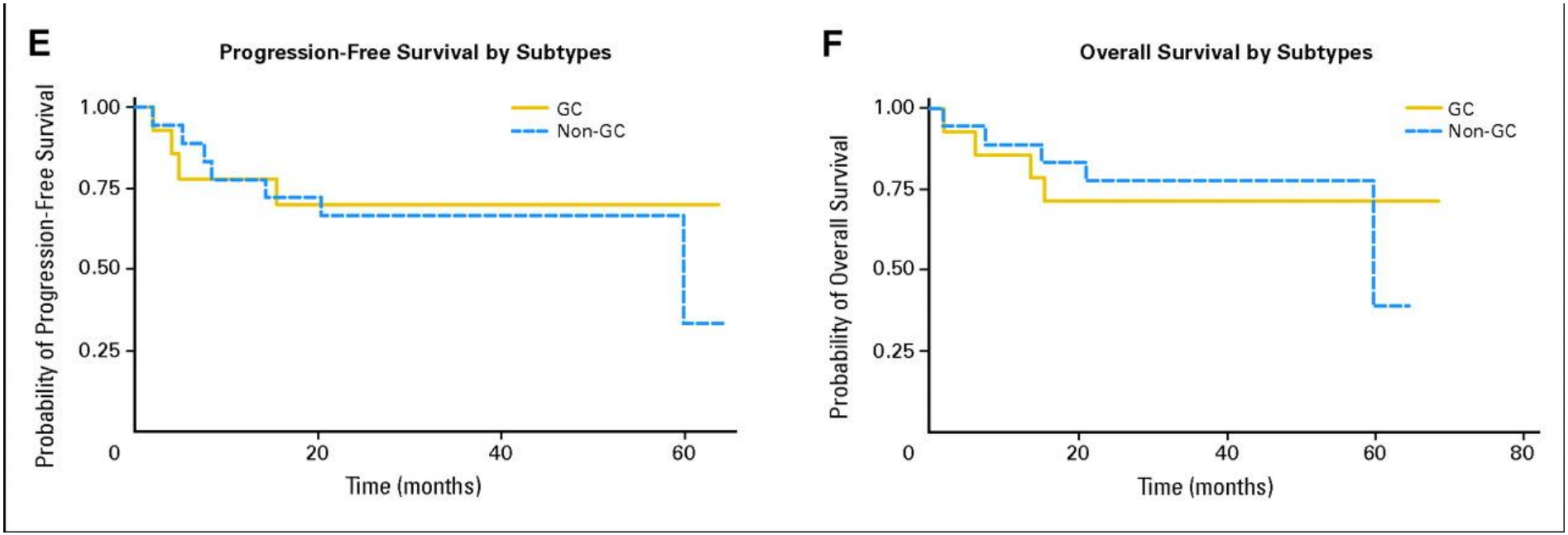
Targeting the ABC Subtype of DLBCL

ABC subtype has a unique biology



Pasqualucci L and Dalla-Favera R. Semin Hematol 2015; 52:67.

Adding bortezomib to R-CHOP may overcome the adverse prognostic significance of the ABC subtype.



Jia Ruan et al. JCO 2011;29:690-697

JOURNAL OF CLINICAL ONCOLOGY ASCO

Addition of lenalidomide to R-CHOP (R2-CHOP) may overcome adverse prognostic implications of ABC subtype.

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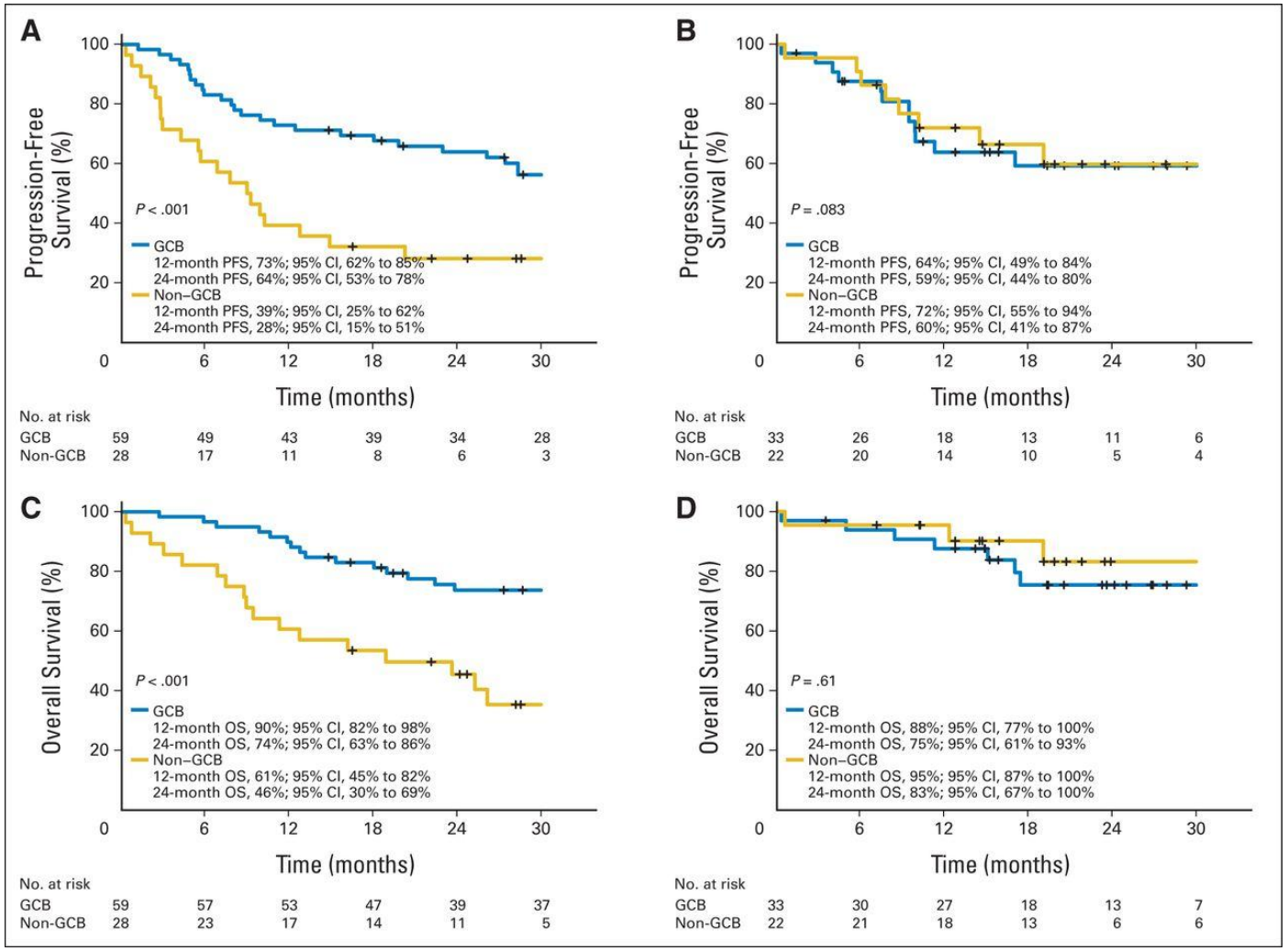


R2
C
H
O
P

Grzegorz S. Nowakowski et al. JCO 2015;33:251-257

JOURNAL OF CLINICAL ONCOLOGY ASCO

Ibrutinib

- Inhibitor of Bruton's tyrosine kinase
- Orally administered
- Approved by FDA in 2013 for relapsed mantle cell lymphoma
- Approved by FDA in February 2014 for previously treated chronic lymphocytic leukemia

Ibrutinib in de Novo DLBCL

- Relapsed/refractory de novo DLBCL (median number of previous systemic therapies: 3); ibrutinib 560 mg PO QD; CT and PET scanning pretreatment and every 2 cycles; primary endpoint: ORR, categorized by molecular subtype
- Ibrutinib showed a clinically meaningful response rate in relapsed/refractory ABC DLBCL, but not in other molecular subtypes

Response	ABC Subtype (n = 29)	GCB Subtype (n = 20)	Unclassifiable* (n = 16)	Unknown* (n = 5)	Total (N = 70)
Not evaluable for response, n	4	1	3	2	10
ORR (CR + PR, per protocol), n (%)	10 (40.0)	1 (5.3)	0	2 (66.7)	13 (21.7)
CR, n (%)	2 (8.0)	0	0	1 (33.3)	3 (5.0)
PR, n (%)	8 (32.0)	1 (5.3)	0	1 (33.3)	10 (16.7)

*GEP performed, but not assignable to ABC or GCB subtypes, or GEP not yet performed or tissue not available.

Wilson WH, et al. ASH 2012. Abstract 686.

Outline

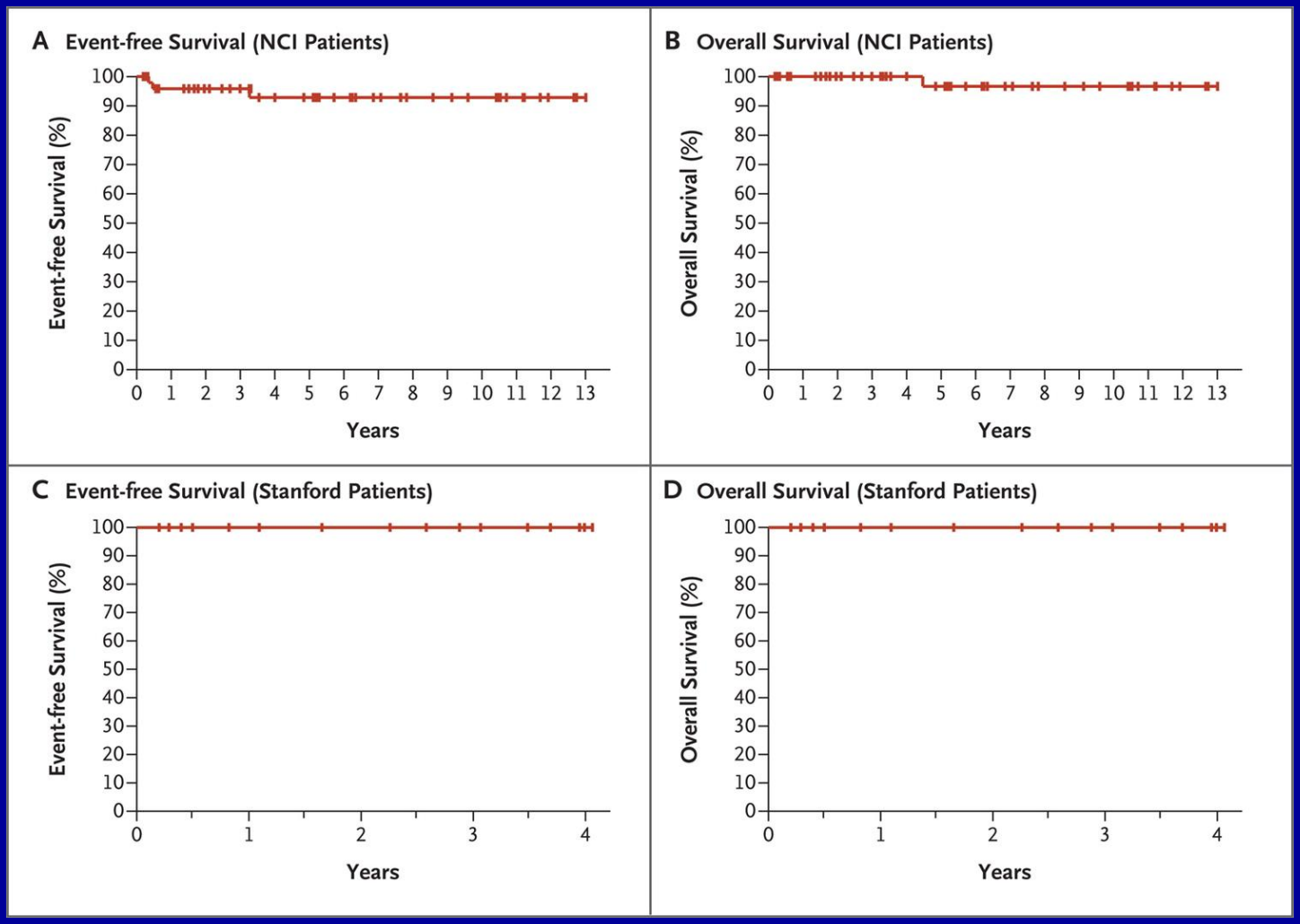
- Overview of NHL
- Diffuse large B-cell lymphoma
- **Primary mediastinal large B-cell lymphoma**
- Mantle cell lymphoma
- Burkitt lymphoma
- T-cell lymphomas

Primary Mediastinal Large B-cell Lymphoma

- Distinct subtype of DLBCL
- 10% of cases of DLBCL
- Arises in thymus
- Affects predominantly young women
- Bulky mass, possibly with pleural or pericardial effusions
- Unique gene mutations on molecular testing

Dunleavy K et al. N Engl J Med 2013;368:1408-1416.

DA-EPOCH-R leads to excellent outcomes in primary mediastinal DLBCL.



Dunleavy K et al. N Engl J Med 2013;368:1408-1416.

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Outline

- Overview of NHL
- Diffuse large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
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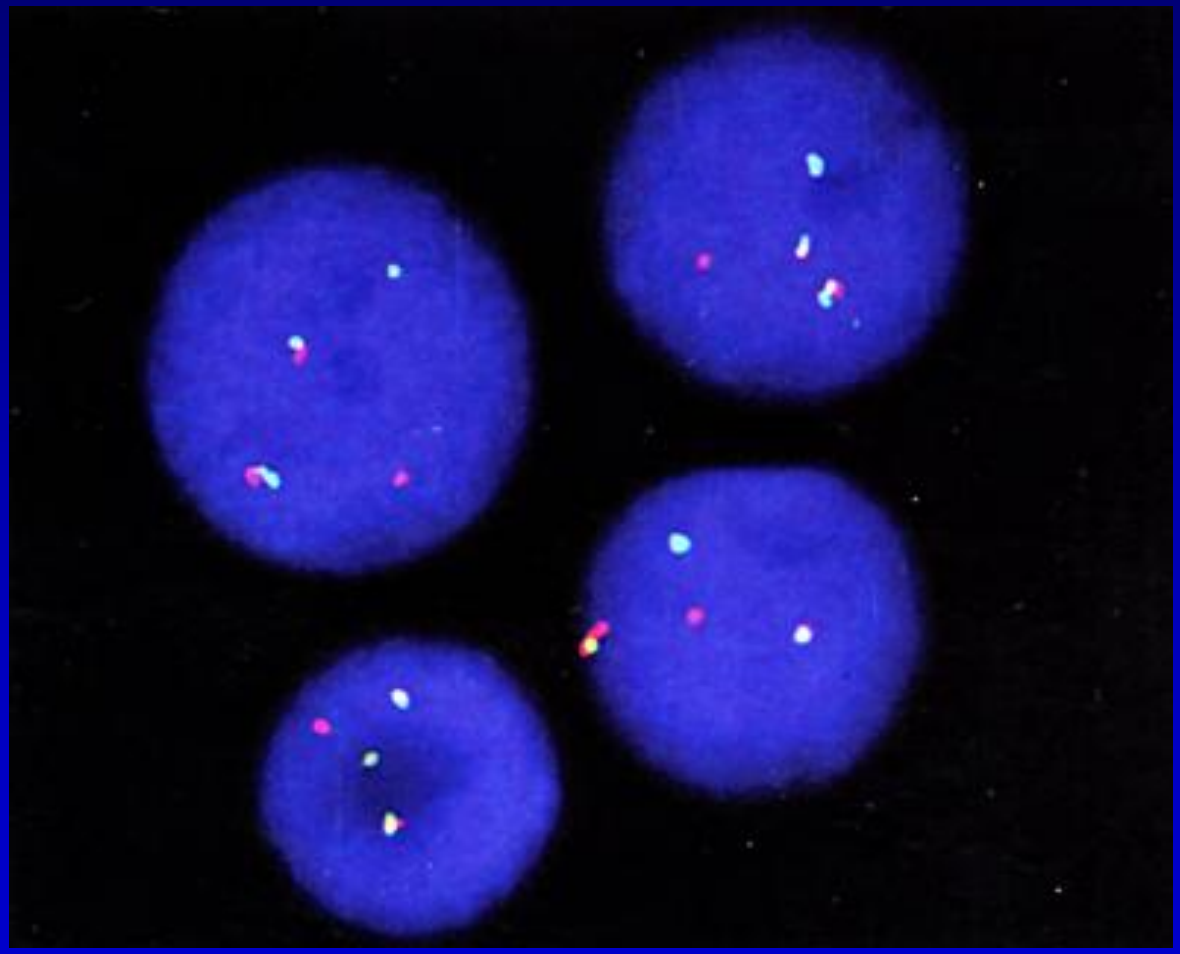
- T-cell lymphomas

Mantle Cell Lymphoma

- Usually aggressive, though can be indolent
- Characteristic immunophenotype: CD5, CD19, CD20 positive (like CLL) but CD23-negative. Cyclin D1-positive.
- Genetic feature: t(11;14) between cyclin D1 locus and Ig heavy chain locus

FISH showing t(11;14)



UpToDate, accessed 3/29/2012

Mantle Cell Lymphoma

Therapy

- Watchful waiting only rarely (elderly, indolent)
- Induction therapy options
  - R-bendamustine
  - VR-CAP
  - R-hyper CVAD
  - R-CHOP alternating DHAP
- Usually autologous transplantation offered in first remission
- Bortezomib, ibrutinib, and lenalidomide used in relapsed disease

Compared with R-CHOP, BR improves PFS in MCL.

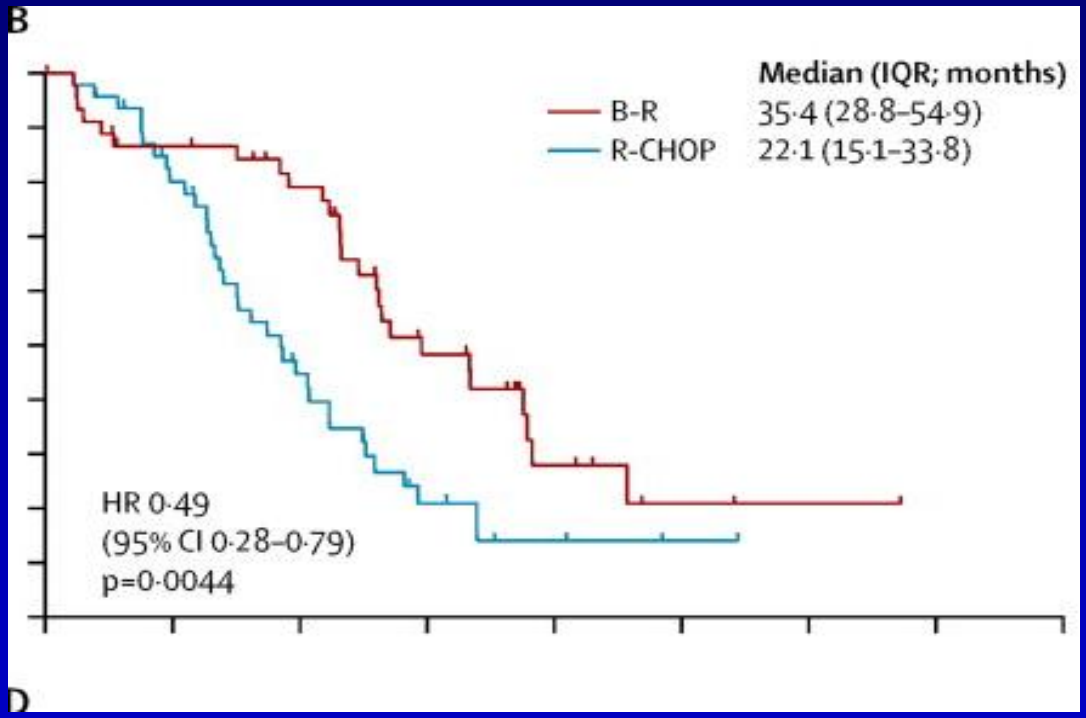


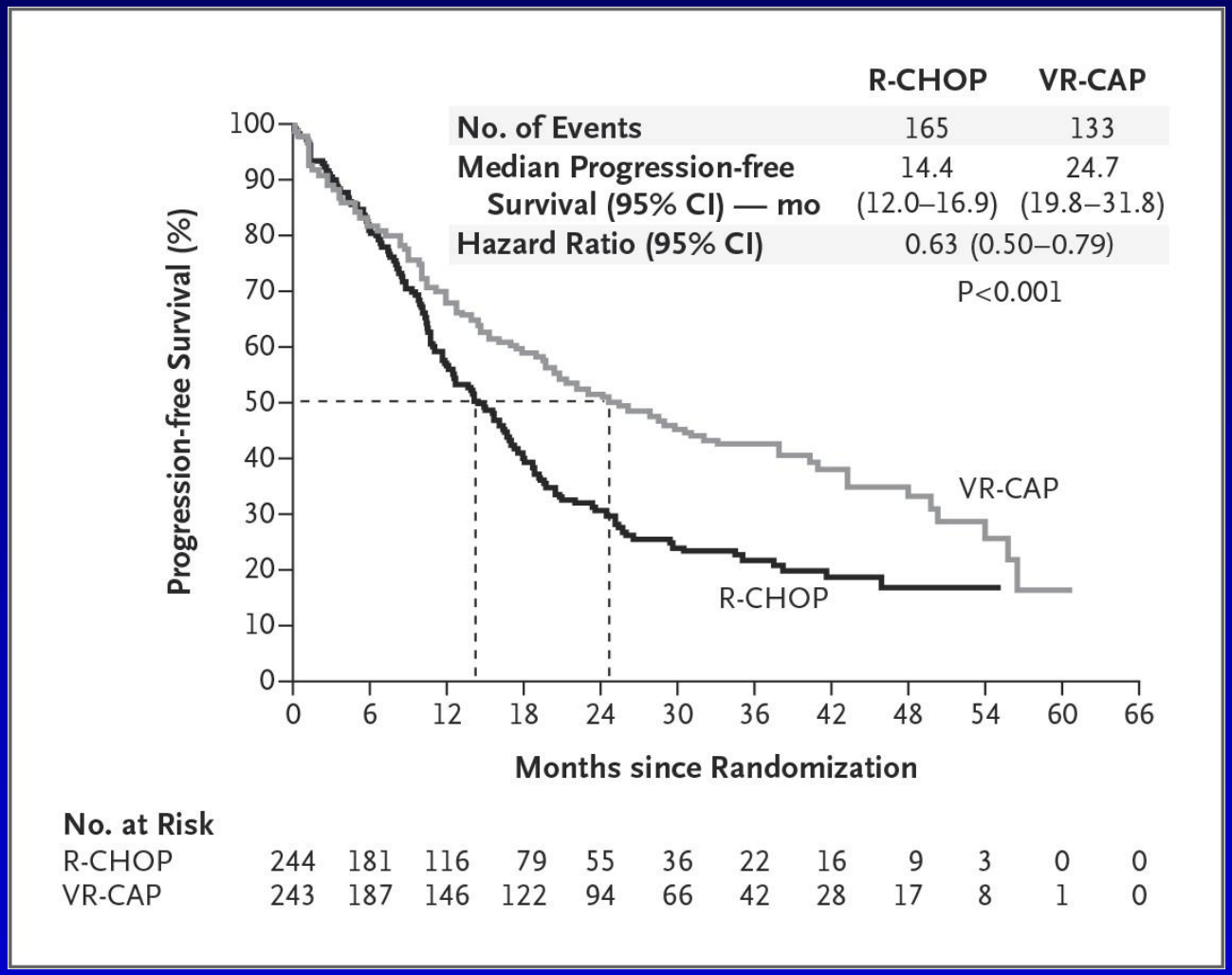
Figure 3 Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D) B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Mathias J Rummel , Norbert Niederle , Georg Maschmeyer , G Andre Banat , Ulrich von Grünhagen , Christoph Losem , ...

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

The Lancet, Volume 381, Issue 9873, 2013, 1203 - 1210
http://dx.doi.org/10.1016/S0140-6736(12)61763-2

Replacement of vincristine with bortezomib leads to improved PFS in patients with newly diagnosed MCL.



Robak T et al. N Engl J Med 2015;372:944-953.

The NEW ENGLAND JOURNAL of MEDICINE

Ibrutinib therapy results in a high response rate in patients with relapsed mantle cell lymphoma.

Table 3. Best Response to Therapy.*

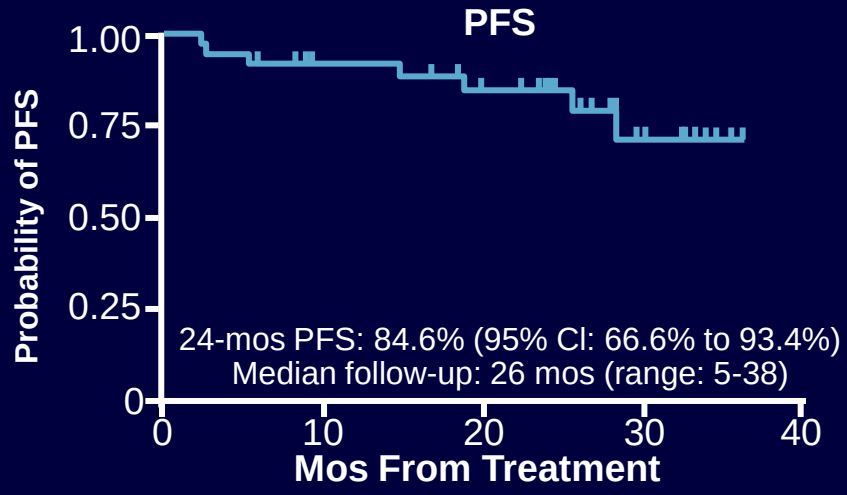
Variable	No Prior Treatment with Bortezomib (N=63)	Prior Treatment with Bortezomib (N=48)	All Patients (N=111)
Response — no. (%)			
Overall	43 (68)	32 (67)	75 (68)
Complete	12 (19)	11 (23)	23 (21)
Partial	31 (49)	21 (44)	52 (47)
None†	20 (32)	15 (31)	35 (32)
Response duration — mo			
Median	15.8	NR	17.5
95% CI	5.6–NR	NR–NR	15.8–NR
Progression-free survival — mo			
Median	7.4	16.6	13.9
95% CI	5.3–19.2	8.3–NR	7.0–NR
Overall survival — mo			
Median	NR	NR	NR
95% CI	10.0–NR	11.9–NR	13.2–NR

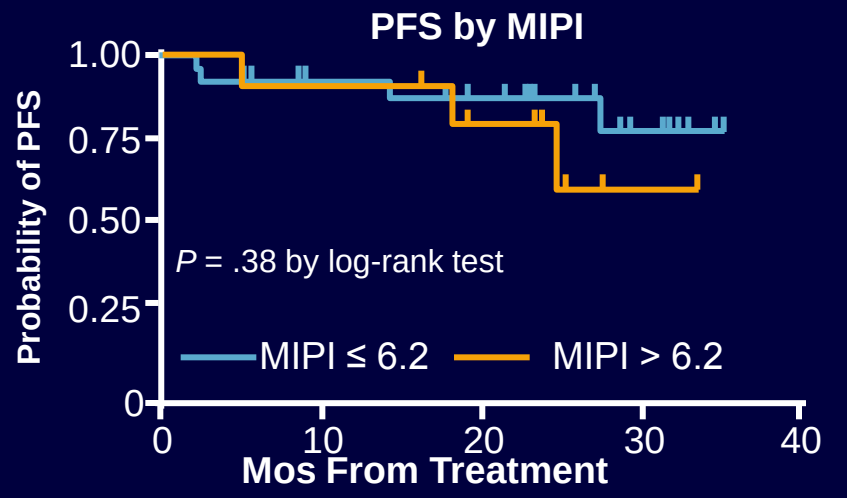
* Response data included only those patients who received ibrutinib and had at least one postbaseline efficacy assessment. CI denotes confidence interval, and NR not reached.
† No response was defined as stable or progressive disease.

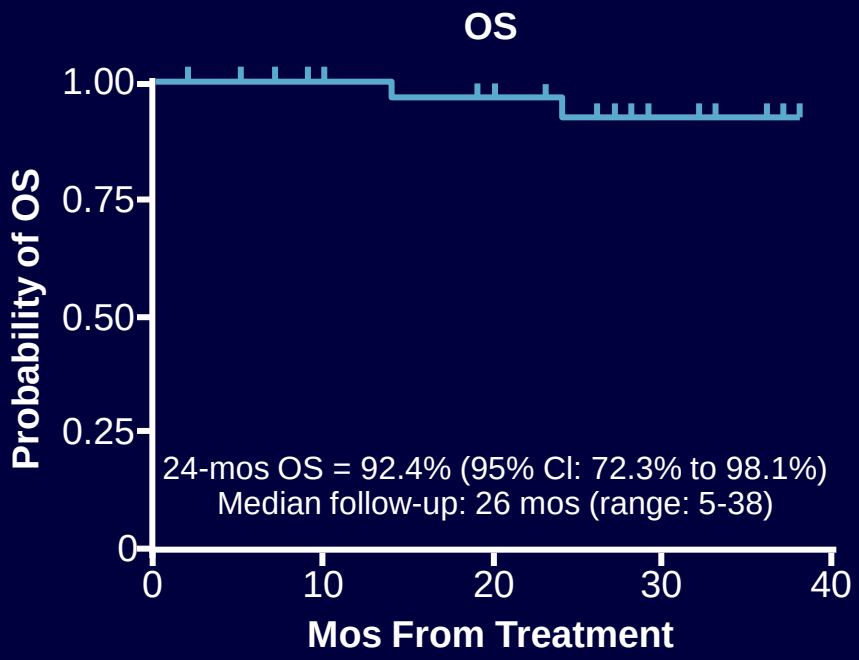
Wang ML et al. N Engl J Med 2013;369:507-516.

The NEW ENGLAND JOURNAL of MEDICINE

Lenalidomide + Rituximab for MCL: Efficacy







Ruan J, et al. ASH 2014. Abstract 625.

Outline

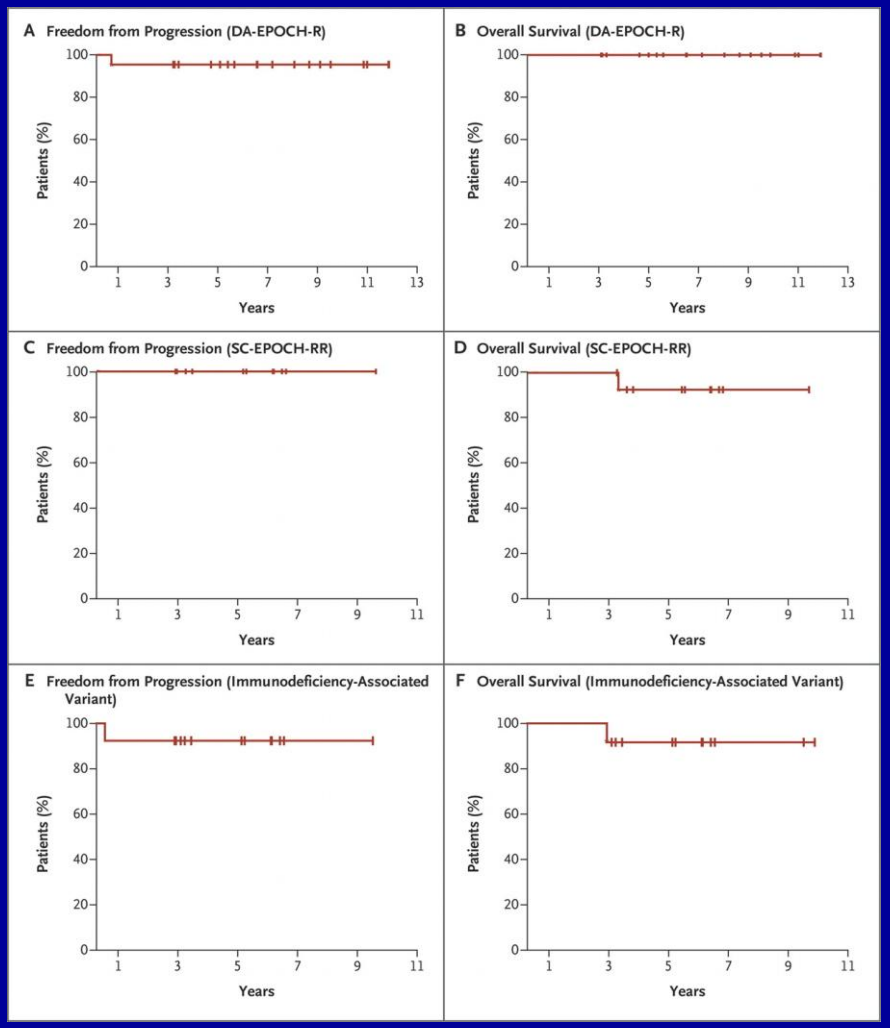
- Overview of NHL
- Diffuse large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Mantle cell lymphoma
- **Burkitt lymphoma**
- T-cell lymphomas

Burkitt Lymphoma

- Highly aggressive non-Hodgkin lymphoma
- 3 variants
  - Endemic (Africa)
  - Sporadic
  - Immune-deficiency-associated
- Characterized by translocation between chromosomes 8 and 14, which places *MYC* gene adjacent to Ig promoter region
- Historically treated with multi-agent chemotherapy regimens, as per ALL

Dunleavy K et al. N Engl J Med 2013;369:1915-1925.

Variants of EPOCH-R lead to favorable outcomes in patients with Burkitt lymphoma. Immune-deficiency-associated BL is shown in panels E-F.



Dunleavy K et al. N Engl J Med 2013;369:1915-1925.

The NEW ENGLAND JOURNAL of MEDICINE

Outline

- Overview of NHL
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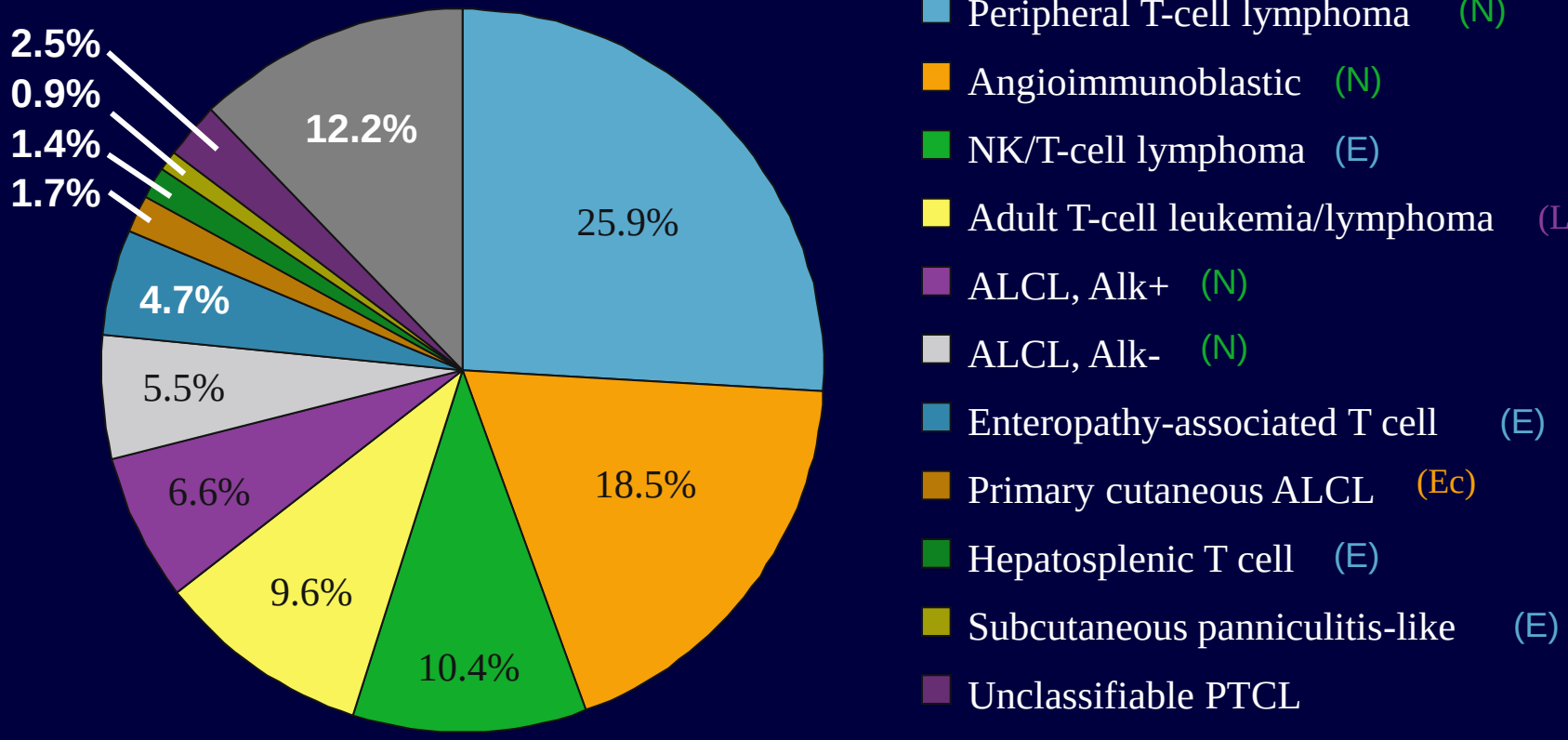
- Primary mediastinal large B-cell lymphoma
- Mantle cell lymphoma
- Burkitt lymphoma
- **T-cell lymphomas**

T-Cell Lymphoma

- Accounts for ~ 10% to 15% of all NHL
- Clinically and biologically heterogeneous group of disorders
- Classification relies on
  - Morphology
  - Immunophenotype
  - Clinical/anatomical presentation
- No recurrent genetic or molecular lesions
- Expert hematopathology review essential

NCCN. Clinical practice guidelines in oncology: non-Hodgkin's lymphoma. v.2.2013.

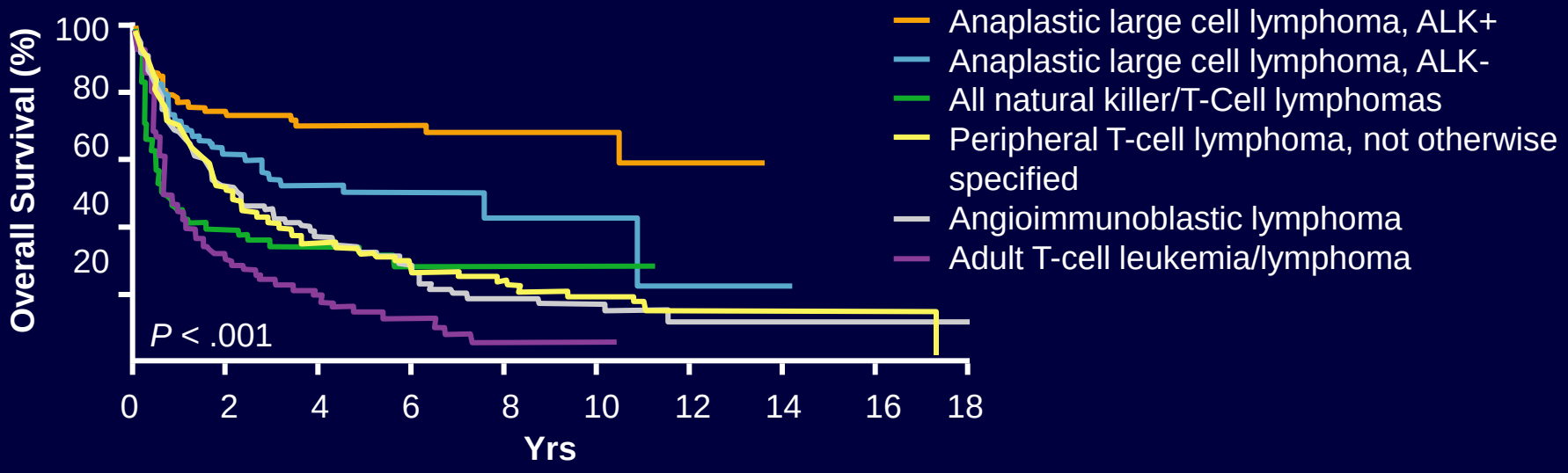
International T-Cell Lymphoma Project: PTCL Subtype Distribution



Vose J, et al. J Clin Oncol. 2008;26:4124-4130.

International T-Cell Lymphoma Project: OS in PTCL

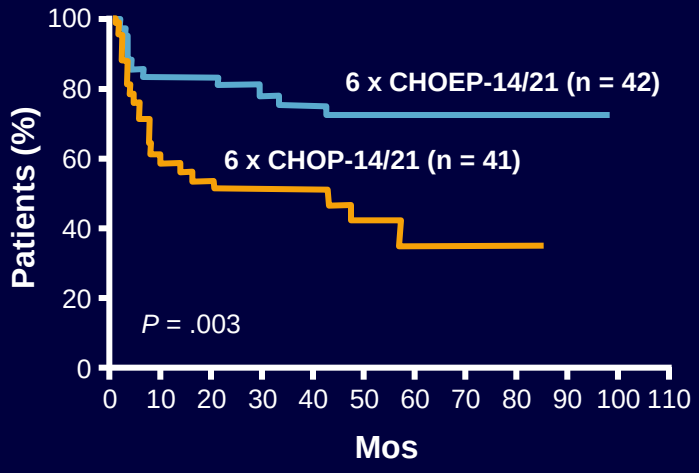
- Majority of patients (> 85%) received an anthracycline-containing regimen

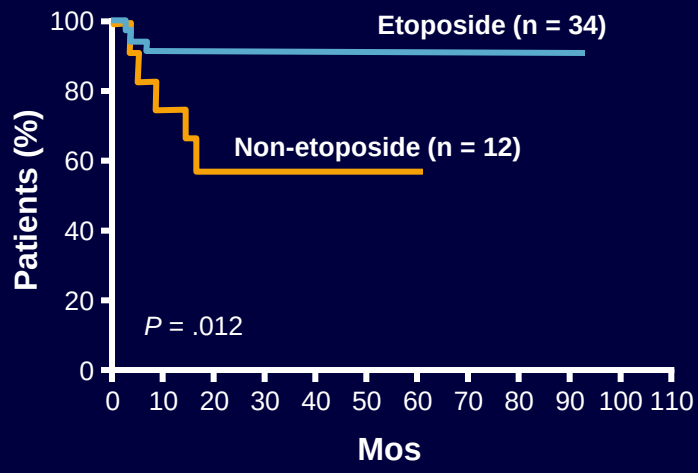


	PTCL Subtypes					
	Alk+ ALCL	Alk- ALCL	PTCL-NOS	AITL	NK/TCL	ATLL
5-yr OS, %	70	49	32	32	42	14

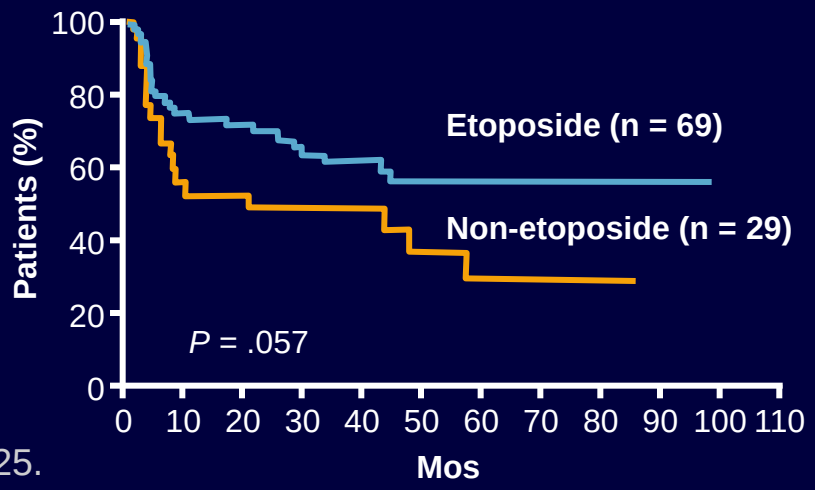
Vose J, et al. J Clin Oncol. 2008;26:4124-4130.

CHOP+ Etoposide: German High-Grade NHL Study Group Analysis





PTCL Subtype	n
ALCL, ALK+	78
ALCL, ALK-	113
PTCL-NOS	70
AITL	28
Other	31
Total	**320**



Schmitz N, et al. Blood. 2010;116:3418-3425.

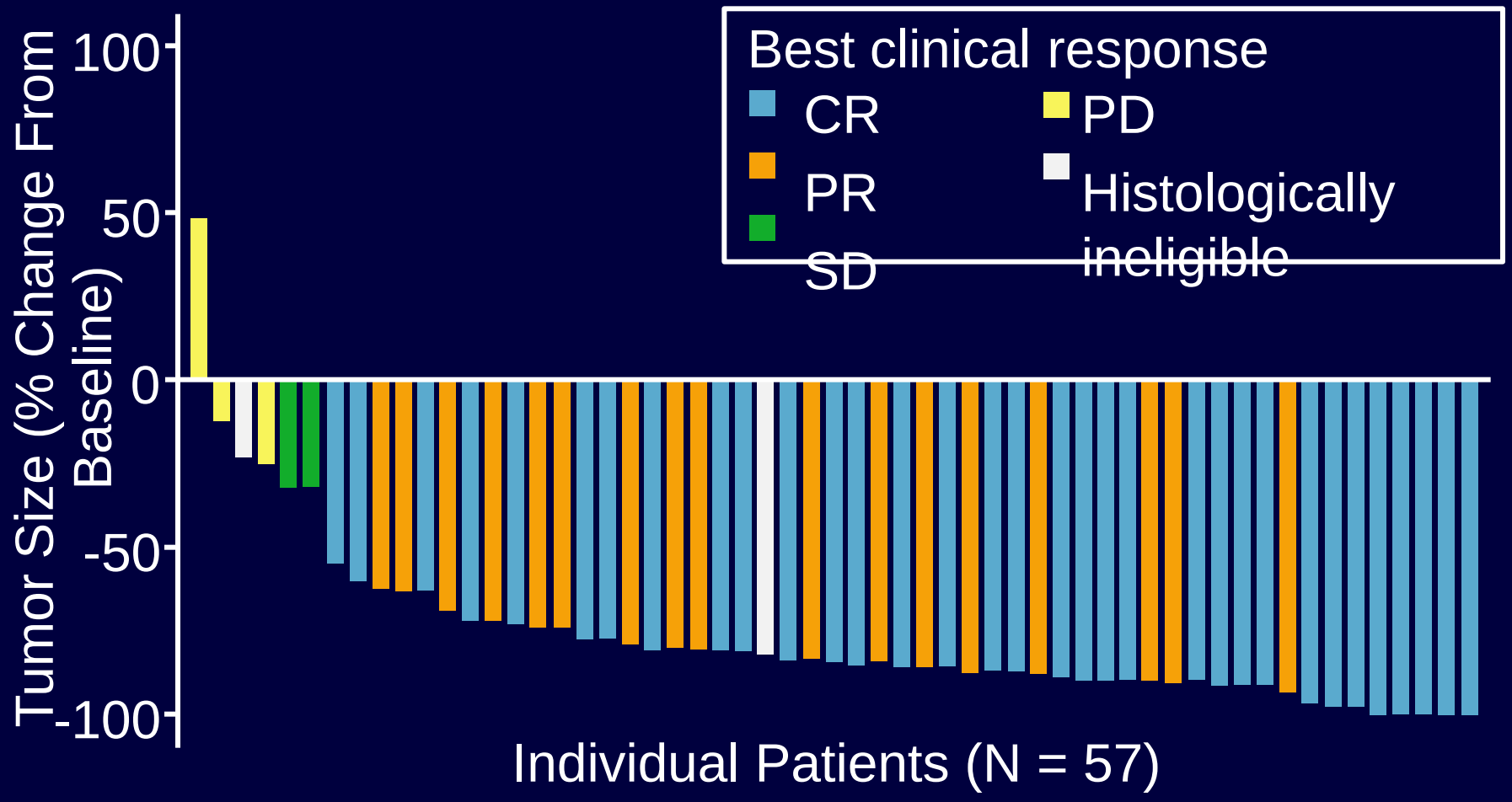
Relapsed/Refractory PTCL: FDA-Approved Agents

Agent	Dose/ Schedule	N	ORR, %	CR, %	DOR, Mos
Pralatrexate[1]	30 mg/m^2/wk x 6	111	29*	11	10.1
Romidepsin[2]	14 mg/m^2/wk x 3 q28 days	131	25	14	17
Brentuximab vedotin (ALCL)[3]	1.8 mg/kg q21 days	58	86	57	12.6

*ORR of 8% in AITL

1. O'Connor OA, et al. J Clin Oncol. 2011;29:1182-1189. 2. Coiffier B, et al. J Clin Oncol. 2012;30:631-636. 3. Pro B, et al. J Clin Oncol. 2012;30:2190-2196.

Phase II Study: Brentuximab Vedotin for R/R Systemic ALCL



31. Pro B, et al. J Clin Oncol. 2012;30:2190-2196.

Crizotinib in Advanced, Chemoresistant ALK+ Lymphoma Patients: Main Findings

Response, n(%)	Crizotinib (N = 11)
ORR	10 (90.5)
CR	9 (81.8)
PR	1 (10)

- At 40-mo follow-up
  - 4 patients in CR under continuous crizotinib treatment
  - 2 patients with DLBCL and 2 with ALCL had disease progression and 3 died
  - 2-yr PFS: 63.7% (95% CI: 30.8-89.2)
  - 2-yr OS: 72.7% (95% CI: 39.1-94.0)

Redaelli S, et al. ASH 2013. Abstract 368.

Summary

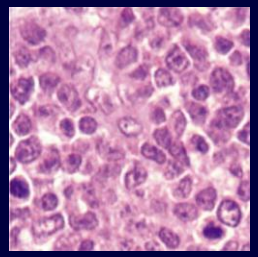
- DLBCL
  - Standard therapy is R-CHOP
  - Promising new therapies include R-ACVBP, EPOCH-R
  - ABC subtype may be susceptible to bortezomib, lenalidomide, ibrutinib
- MCL
  - Standard is chemo followed by ASCT
  - Effective targeted therapies include bortezomib, lenalidomide, ibrutinib
- Burkitt lymphoma – EPOCH-R very effective

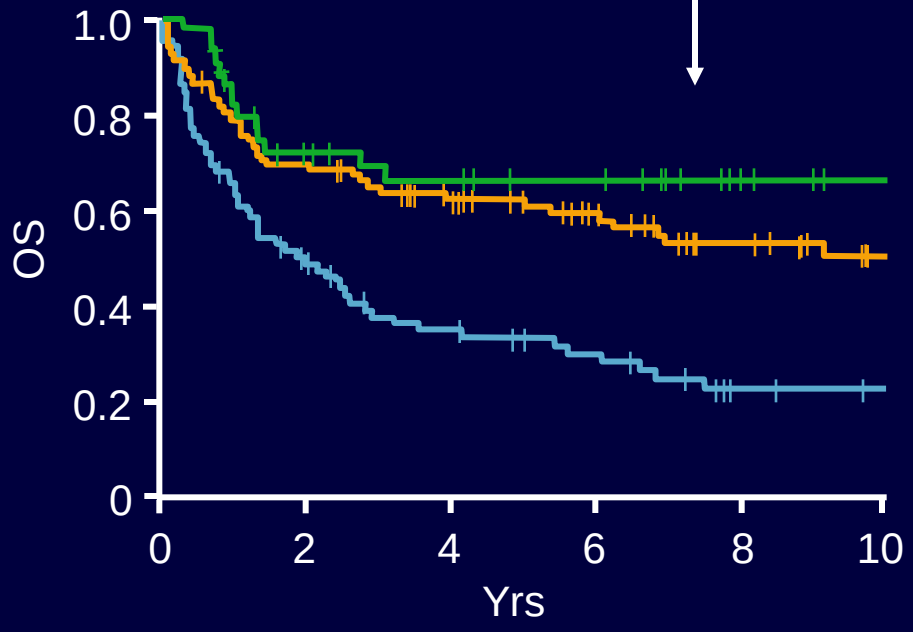
- **Better understanding of biology leading to new therapies**

Backup Slides

Survival by Subgroups in DLBCL

Diffuse Large
B-Cell Lymphoma





DLBCL Subgroup	5-Yr OS, %
PMBL	64
GCB DLBCL	59
ABC DLBCL	30

Rosenwald A, et al. J Exp Med. 2003;198:851-862.

Cytogenetic Changes Associated With Subgroups in DLBCL

Cytogenetic Change, %	GCB DLBCL	ABC DLBCL	PMBL
c-Rel amplification	16	0	25
Bcl-2 translocation	45	0	18
Gain of 3q	0	24	5
Gain/amplification of 9p24	0	6	43
Constitutive NF-κB activation	No	Yes	Yes

Bea S, et al. Blood. 2005;106:3183-3190.

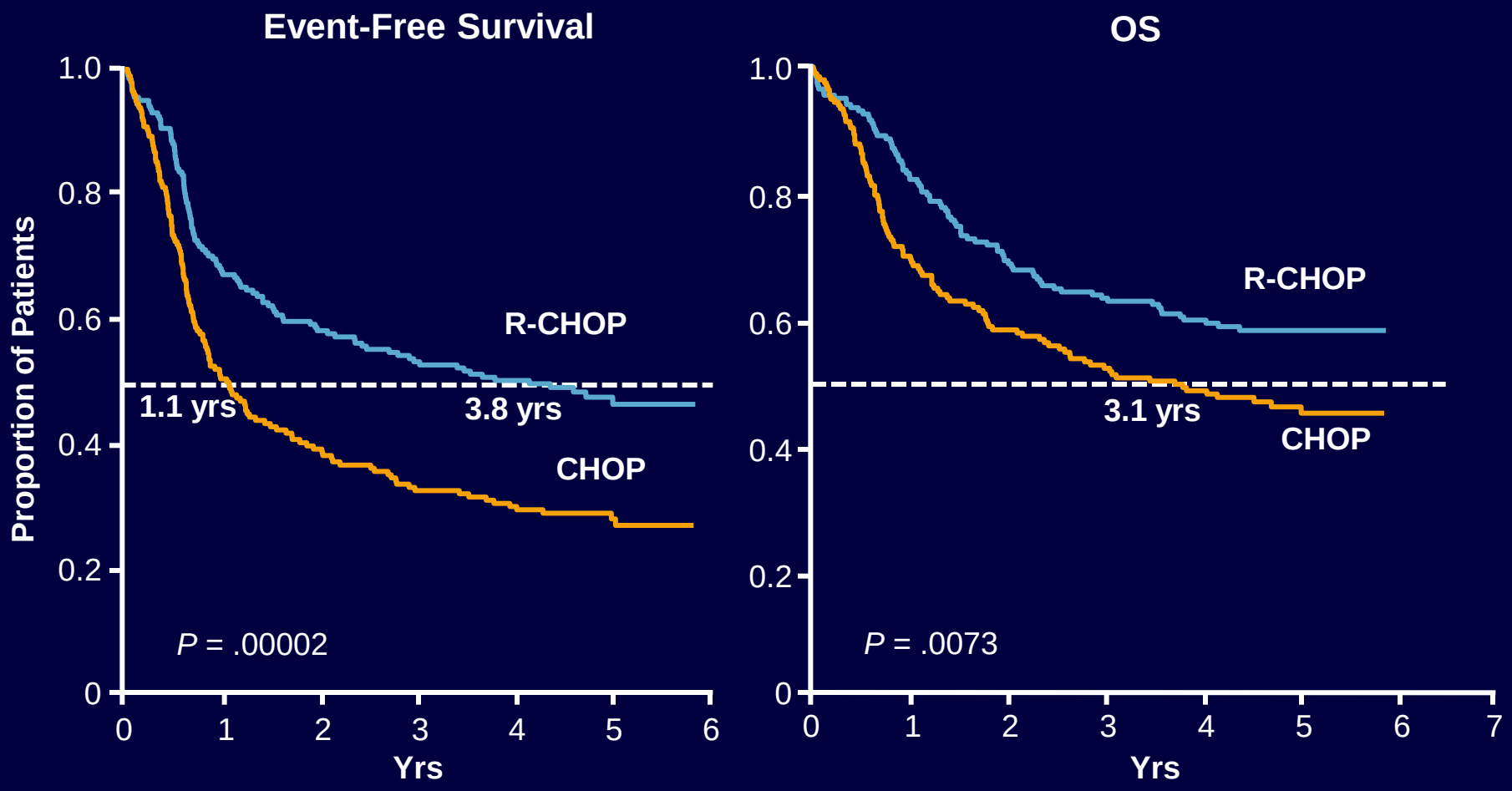
Molecular Changes Associated With DLBCL

- Prevalence of genetic abnormalities
  - Recurring chromosomal translocations: ~ 50%
  - DNA imbalances: up to 67%

Gene(s) Affected/Disregulated	Frequency, %	Predominant Causal Genetic Abnormality
Multiple	45	Aberrant SHM
Bcl-6	35-40	3q27 translocations
Bcl-2	13/24	t(14;18)/amplification
Fas(CD95)	20	10q24 mutations
p53	16	17p mutations/deletions
c-Myc	15	t(8;14) deregulation
Potentially *c-Rel*	14	2p13 amplification

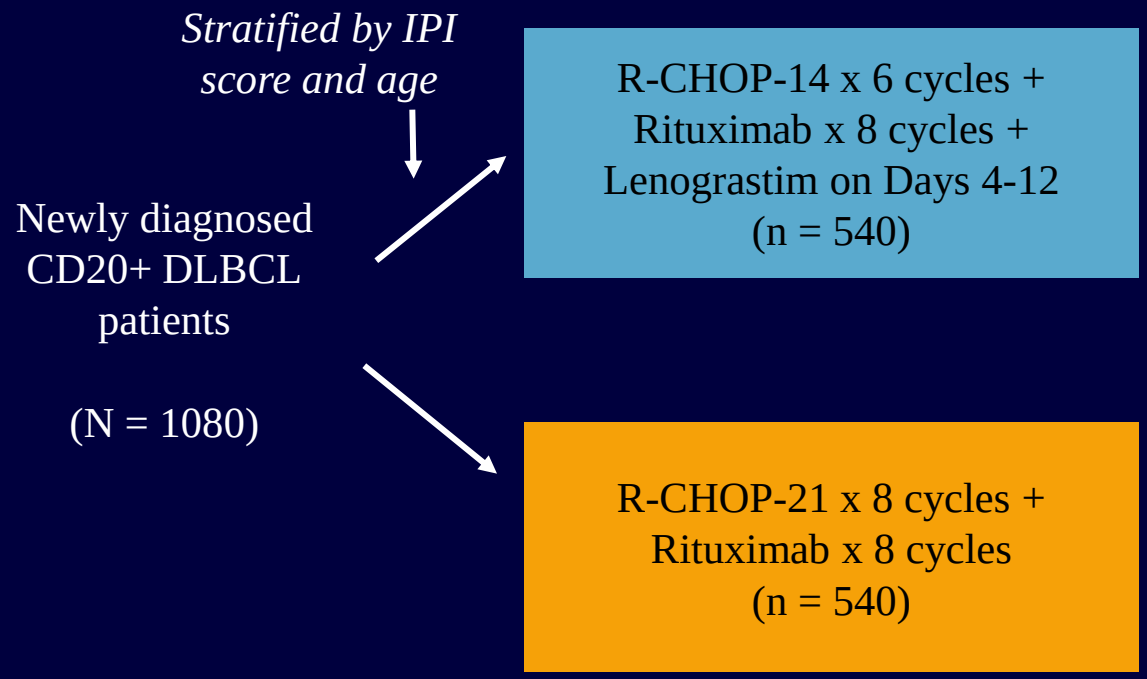
Abramson JS, et al. Blood. 2005;106:1164-1174.

GELA Study Median Follow-up: 5 yrs



Feugier P, et al. J Clin Oncol. 2005;23:4117-4126.

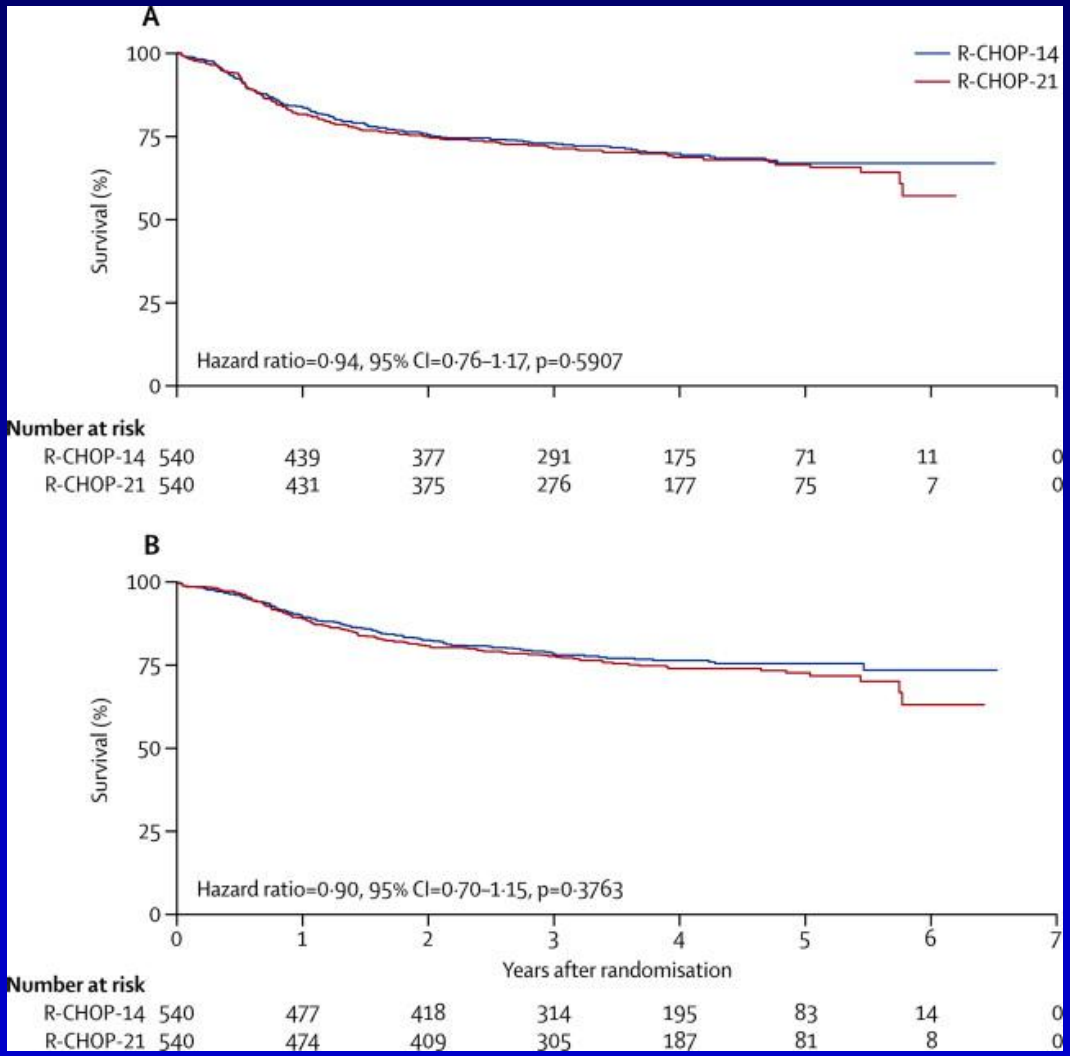
R-CHOP-14 vs R-CHOP-21 in Newly Diagnosed DLBCL (Phase III Study)



- Primary endpoint: OS
- Secondary endpoint: FFS, toxicity, response rates

Cunningham D, et al. ASCO 2011. Abstract 8000.

Giving R-CHOP every 14 days instead of every 21 days has no impact on PFS (A) or OS (B).



Cunningham D et al. Lancet 2013; 381:1817.

Crizotinib in Advanced, Chemoresistant ALK+ Lymphoma Patients: Study Design

- Crizotinib monotherapy administered at 250 mg BID; until disease progression
- ALK+ NHL patients; N = 11
  - Diagnosed by immunohistochemistry and/or FISH
  - Median age: 28 yrs (range: 19-55 yrs)
    - ALCL: 9 patients
    - DLBCL: 2 patients
- Criteria
  - Refractory/relapsed disease after at least 1 prior chemotherapy regimen (median: 3, including 3 patients who received autologous BMT and 2 allogeneic BMT)
  - Measurable disease; all pts had involvement at multiple sites (nodal and extranodal), B symptoms
  - ECOG PS: 1- 4; response to therapy assessed by RECIST

Redaelli S, et al. ASH 2013. Abstract 368.