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Welcome & Introductions

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Update on Aggressive Non-Hodgkin Lymphoma (NHL): Diagnosis and Treatment

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Wednesday, February 24, 2016

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Disclosure

David C. Fisher, MD, has affiliations with Genetics Institute and Celgene (*Consultant*).

DANA-FARBER CANCER INSTITUTE
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HARVARD MEDICAL SCHOOL

An Overview and Management of High Grade Lymphoma

February 24, 2016

David C. Fisher, MD

Agenda

- Classification of lymphoma
- Diffuse large B-cell lymphoma subtypes:
  - Germinal center subtype
  - Activated B-cell subtype
  - Primary mediastinal large B-cell lymphoma
  - "double-hit" lymphoma
  - Double protein expresser
- Novel therapeutic approaches

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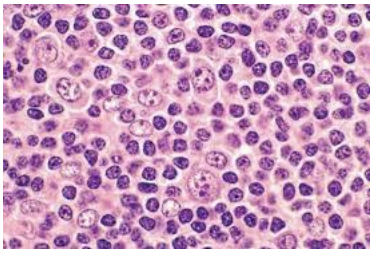
Classification of lymphoma

- Malignancies of normal lymphoid cells which reside predominantly in lymphoid tissues (nodes, spleen, marrow)
- WHO classification based on morphology, immunophenotype, cytogenetics and clinical factors
- Non-Hodgkin's lymphoma
  - B-cell
    - Precursor
    - Mature
  - T and NK-cell
    - Precursor
    - Mature
- Hodgkin lymphoma



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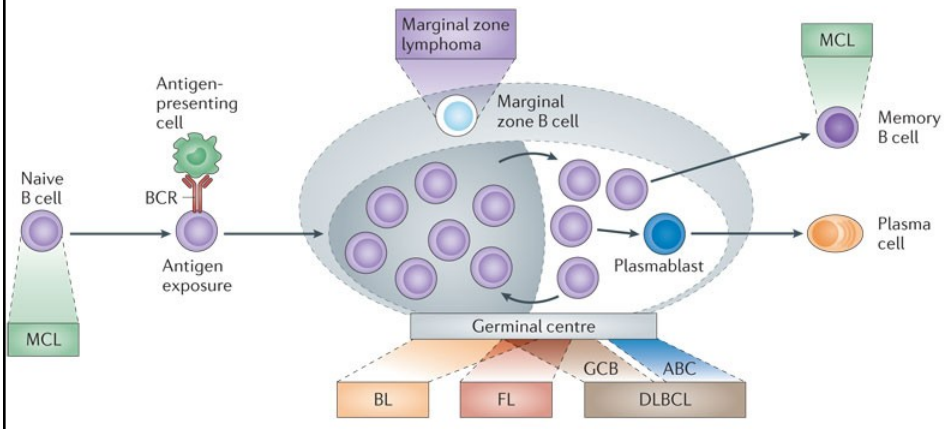
B-cell maturation



Nature Reviews | Cancer

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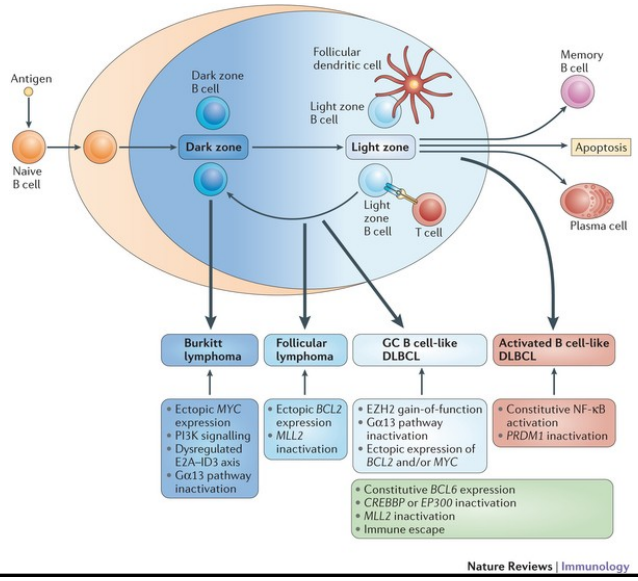
Pathogenesis of B-cell lymphomas



Subsets of lymphoma identified by corresponding normal counterpart in B-cell development

Nature Reviews | Immunology

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Non-Hodgkin's Lymphoma

- Most common hematologic malignancy
- 72,000 cases/year in the US
- 5th most common cause of cancer deaths
- 2nd fasting growing malignancy in terms of mortality
- 85% are of B-cell origin

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Presentation

- Lymphadenopathy (2/3)
- B symptoms - fever (>38), drenching night sweats, weight loss > 10% in 6 months
- Extra nodal sites - GI tract, skin, bone
- Rare - kidney, bladder, adrenal, heart, lungs, breast, testes, thyroid

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Biopsy

- Supraclavicular > cervical/axillary > inguinal
- Excisional biopsy when possible
- CT guided core needle
- Send for pathology, immunohistochemistry/flow cytometry

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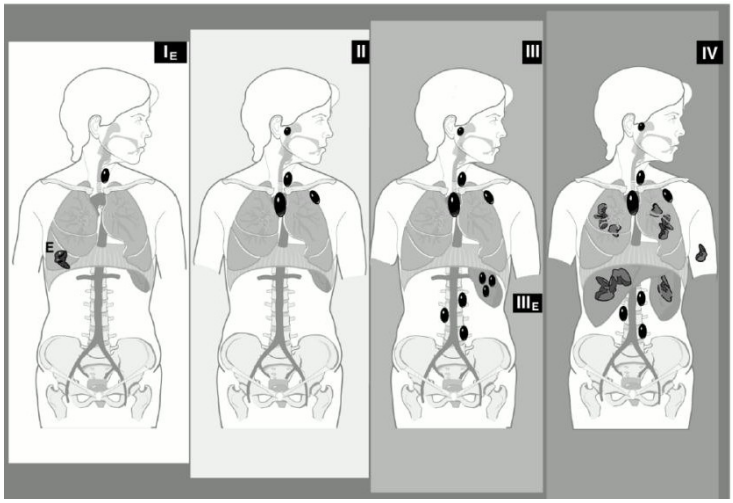
Staging system



A – asymptomatic; B- fever, night sweats, 10% wt loss

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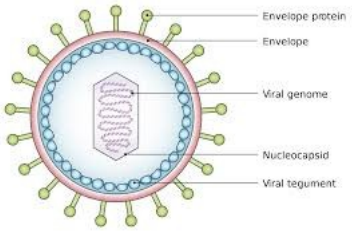
Infectious associations

EBV:
- Burkitt lymphoma
- DLBCL
- NK-T cell lymphoma
- Hodgkin lymphoma
- Plasmablastic lymphoma

HTLV-1:
- Adult T-cell leukemia/lymphoma

HHV-8:
- Primary effusion lymphoma
- Large B cell lymphoma associated with Castlemans



Marginal zone lymphoma :
- H pylori
- B burgdorferi
- C jejuni
- Hepatitis C

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Risk factors

Exposures:
- Occupational
- Environmental
- Prior RT, chemotherapy

Immune dysfunction:
- Autoimmune disease
- Immunodeficiency
- Immune suppression

Genetics:

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Clinical behavior of non-Hodgkin's lymphoma

	Indolent	Aggressive	Highly aggressive
Survival untreated	Years	Months	Weeks
Response to chemotherapy	Not curable	Curable	Curable
Example	Follicular lymphoma	Diffuse large B-cell lymphoma	Burkitt lymphoma

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High grade lymphoma

Highly aggressive lymphoma

B-cell:
Burkitt lymphoma
Precursor B Lymphoblastic lymphoma

T-cell:
Precursor T lymphoblastic lymphoma
Adult T-cell leukemia lymphoma

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Aggressive lymphoma

B-cell:
Diffuse large B-cell lymphoma
Follicular lymphoma grade 3 (A+B)

T-cell:
Peripheral T-cell lymphoma, NOS
Anaplastic large cell lymphoma
Angioimmunoblastic T-cell lymphoma
NK/T cell lymphoma

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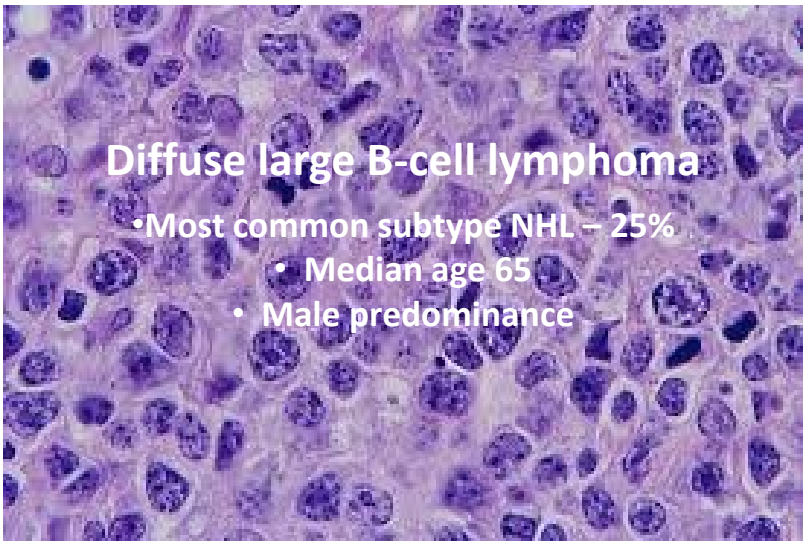

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Therapy for DLBCL

- 1970's - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- 1980's – 2nd and 3rd generation regimens (addition of other active agents, modification of doses and schedules) with improved CR rates and survivals in pilot studies
- 1990's – prospective randomized trials demonstrate 2nd and 3rd generation regimens are no better than CHOP

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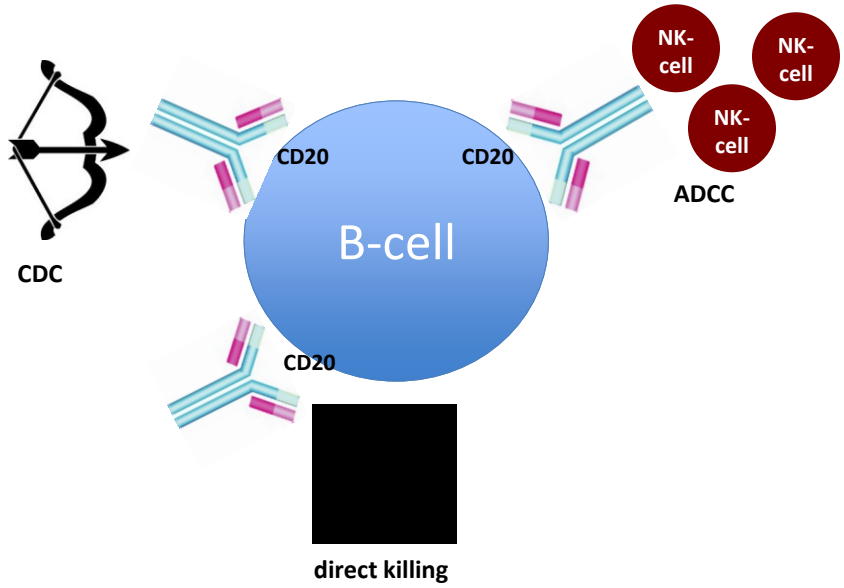
Rituximab – anti CD20 monoclonal antibody



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International Prognostic Index

Pre-Rituxan Era

Risk factors	5 yr OS
0-1	73%
2	51%
3	42%
4-5	26%

Rituxan Era

Risk factors	4 yr DFS	4 yr OS
0	94%	94%
1-2	80%	79%
3-5	53%	55%

Risk factors: age > 60, stage III/IV, >1 EN site, PS, LDH

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Gene expression profiling in DLBCL

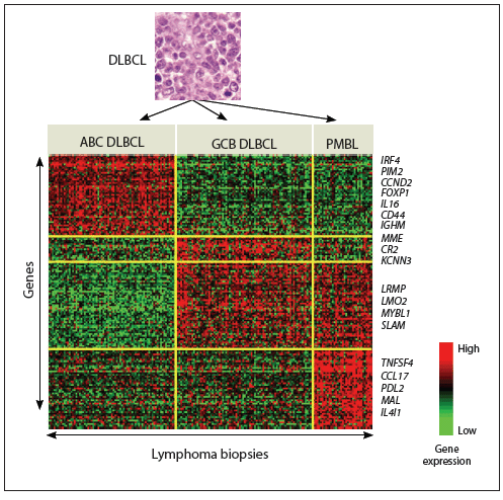
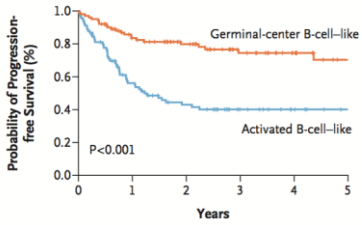


Figure 1: Differentiating Diffuse Large B-Cell Lymphoma (DLBCL) Into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling—The heat map shows differential expression of genes in activated B-cell–like (ABC), germinal center B-cell–like (GCB), and primary mediastinal B-cell lymphoma (PMBL) DLBCL subtypes.

Dunleavy and Wilson. Oncology. 2014



Lenz et al. NEJM. 2008

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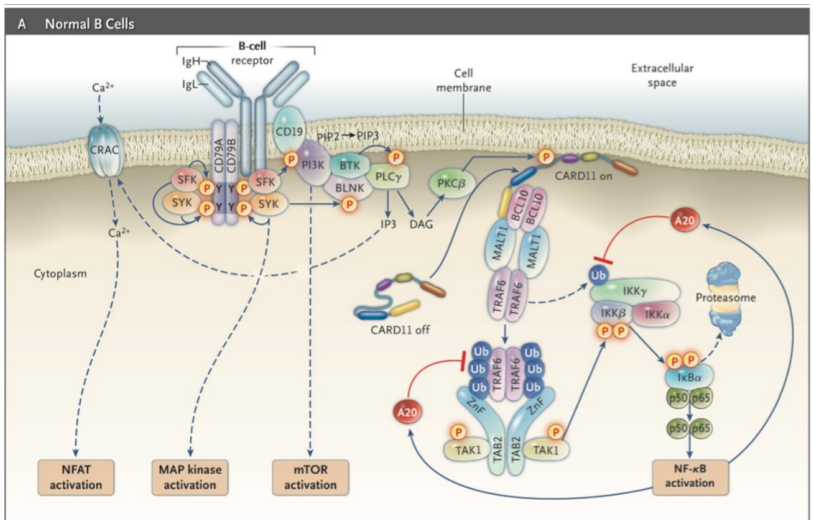
B-cell receptor signaling



Lenz et al. NEJM 2010

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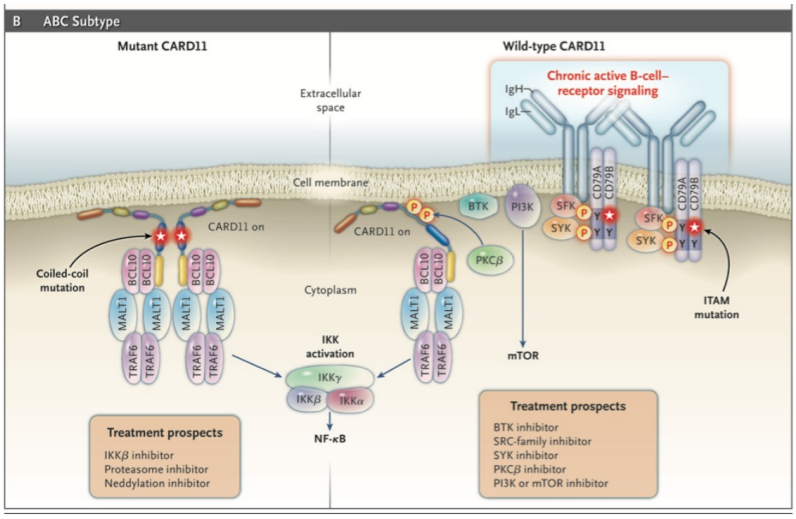
Novel targets in ABC DLBCL



Lenz et al. NEJM 2010

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Can we improve on RCHOP?

R-CHOP	DA*-R-EPOCH
Rituximab 375 mg/m² d1 Cyclophosphamide 750 mg/m2 d1 Doxorubicin 50 mg/m² d1 Vincristine 1.4 mg/m² (2 mg cap) d1 Prednisone 40 mg/m² d1-5 q3w × 6	Rituximab 375 mg/m² d1 Etoposide 50 mg/m²/d CI d1-4* Doxorubicin 10 mg/m²/d CI d1-4* Vincristine 0.4 mg/m²/d CI d1-4 Cyclophosphamide 750 mg/m² d5* Prednisone 60 mg/m² bid d1-4 G-CSF 5 µg/kg d6-ANC recovery q3w × 6

*Doses increased or decreased based on degree of neutropenia

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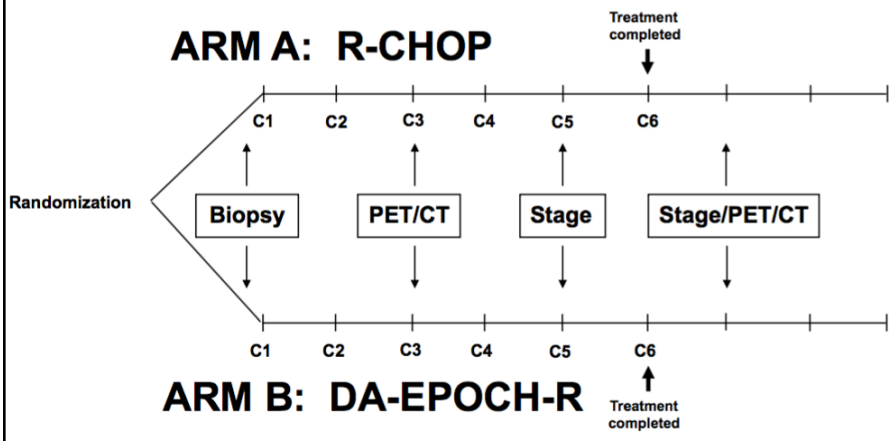
U.S. intergroup study

Treatment flow chart CALGB 50303



Correlatives include gene expression profiling

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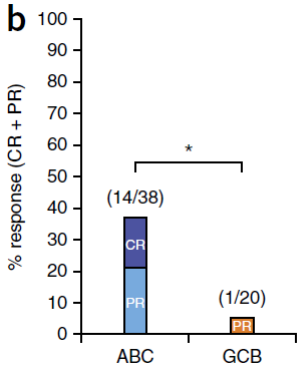
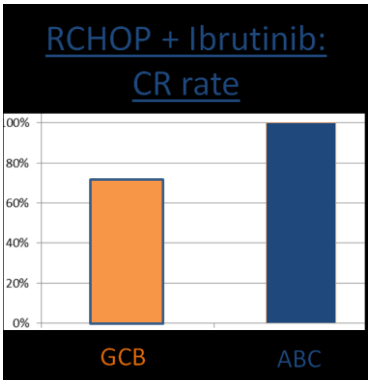
Ibrutinib in relapsed/refractory DLBCL





Wilson et al. Nature Medicine 2015

Younes et al. Lancet Oncology 2015

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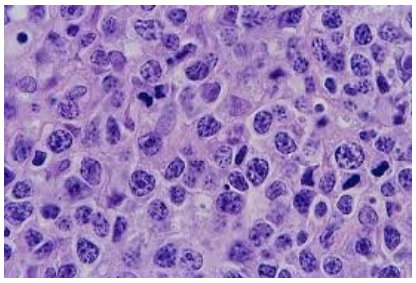
Definition of double hit lymphoma (DHL)

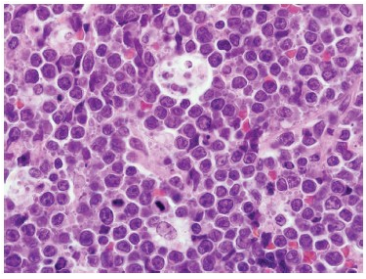
MYC rearrangement with other specified chromosomal rearrangements

- **BCL-2 mostly common (60%)**
- **BCL-6 rearrangement (<10%)**
- **BCL-2 and bcl-6 (up to 20%)**

Histologically:



Diffuse large B-cell lymphoma



B-cell lymphoma unclassifiable with features intermediate between DLBCL/BL (Gray zone lymphoma)

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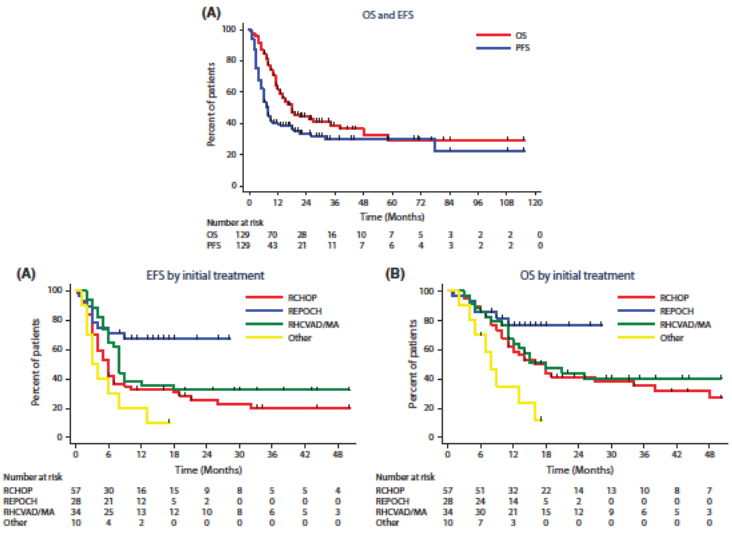
DHL has poor prognosis



Oki et al. BJH. 2014

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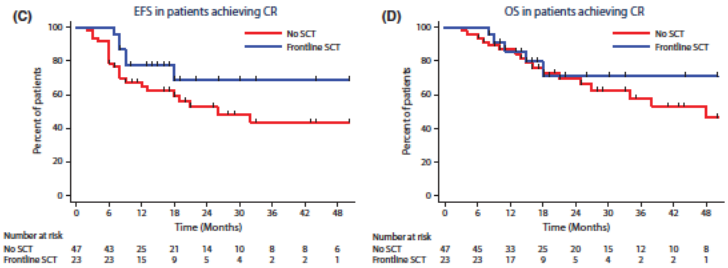
No overall survival benefit of transplant



Oki et al. BJH. 2014

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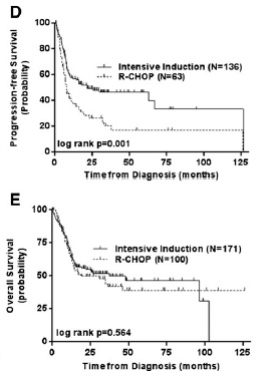
Intensive chemotherapy associated with improved PFS

Table 2. Treatment patterns (N = 311)

	n (%)
Induction regimen	
R-CHOP	100 (32)
R-Hyper-CVAD	65 (21)
DA-EPOCH-R	64 (21)
R-CODOX-M/IVAC	42 (14)
R-ICE	9 (3)
Other/multiple	31 (10)
Rituximab included	
Yes	268 (86)
No	15 (5)
NA	27 (9)
Median # Cycles administered (range)	5 (0-9)
CNS prophylaxis	
None	130 (42)
MTX	102 (33)
Ara-C	6 (2)
Both	66 (21)
NA	7 (2)
Stem cell transplantation	
At any time	83 (27)
In first CR	53 (17)
Autologous SCT in first CR	39 (13)
Allogeneic SCT in first CR	14 (5)
Salvage chemotherapy	
R-ICE	50 (16)
R-ESHAP	6 (2)
R-DHAP	2 (<1)
Other	48 (15)
NA	203 (65)



Petrich et al. Blood. 2014

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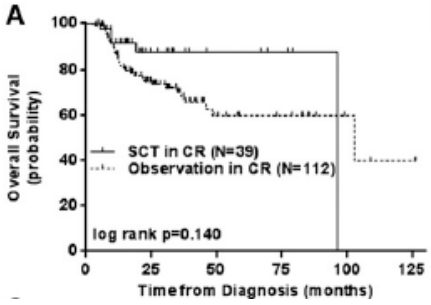
No clear benefit to upfront transplantation



Petrich et al. Blood. 2014

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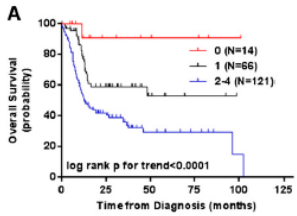
Prognostic factors

Table 3. Prognostic factors with associated hazard ratios and *P* values, by both univariate and multivariate analyses

Variable	Risk factor	Reference univariate analysis	Hazard ratio (95% CI)	*P* value
Age	≥60	<60	1.622 (1.177, 2.234)	.003
ECOG PS	2-4	0-1	1.772 (1.304, 2.805)	.001
WBC	$\geq 10^3$	$<10^3$	2.249 (1.694, 4.349)	<.001
Albumin	<4	≥4	1.864 (1.318, 3.026)	.001
LDH	>3× ULN	≤3× ULN	1.907 (1.131, 2.609)	.011
B symptoms	Present	Absent	1.587 (1.083, 2.414)	.019
Extranodal disease	>1 site	0-1 site	1.518 (1.099, 2.294)	.014
Ann Arbor Stage	3-4	1-2	2.007 (1.373, 3.138)	.001
Bone marrow involvement	Positive	Negative	1.906 (1.357, 2.851)	<.001
CNS involvement	Present	Absent	4.700 (3.763, 24.77)	<.001
Multivariate analysis				
WBC	$\geq 10^3$	$<10^3$	1.710 (1.001, 2.923)	.05
LDH	>3× ULN	≤3× ULN	1.721 (1.666, 3.013)	.03
Ann Arbor Stage	3-4	1-2	1.585 (1.351, 3.138)	.014
CNS involvement	Present	Absent	2.000 (1.169, 3.423)	.011

ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count, in 10^9 cells/mL; LDH, lactate dehydrogenase, in U/L; CNS, central nervous system; ULN, upper limit of nc



Petrich et al. Blood. 2014

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Response to initial chemotherapy predicts outcome

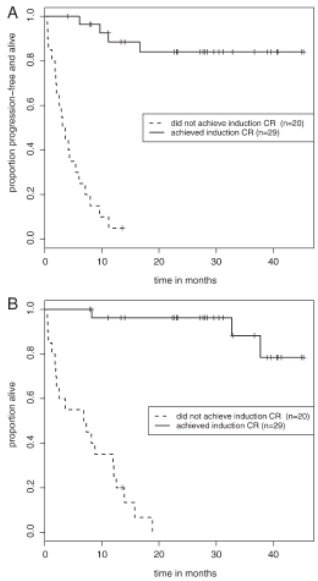

TABLE 4. Multivariable Analysis of the Factors Associated With Progression-Free Survival

	PFS		OS	
Factor	HR	*P*	HR	*P*
Induction CR	0.027	<.00001	0.01	.00002
Translocation t(14;18)	4.46	.033	–	–
Age >60 y at diagnosis	4.98	.004	4.46	.009

Cohen et al. Cancer. 2014

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DA-EPOCH-R in MYC-R DLBCL N=52

Characersitics	%
Median (range) age (years)	61y (29-80y)
Male sex	71%
Stage III or IV	73%
High LDH	59%
CNS disease	6%
IPI score	
0-2	35%
3-5	65%
Histology	
DLBCL	86%
BCL-U	14%
MYC + by FISH or cytogenetics	100%
BCL2 + by FISH	45%*
BCL2 – High by IHC	56%

* Of 31 cases tested

Dunleavy et al. ASH 2014

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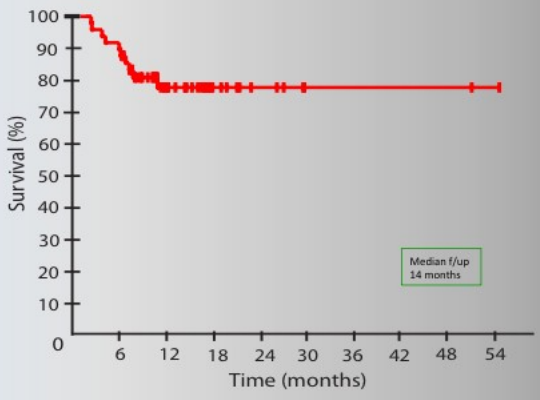
Progression-free survival – All patients



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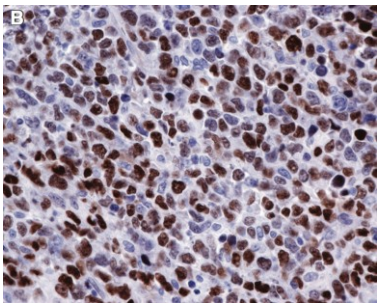
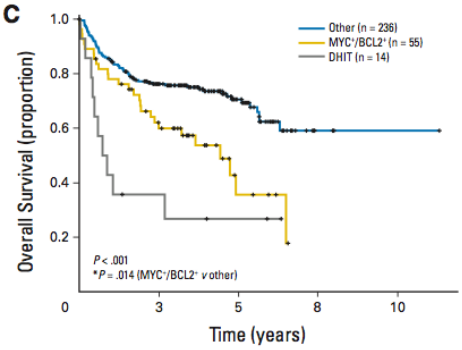
Over-expression of MYC and bcl-2 protein associated with inferior outcomes





Johnson et al. JCO. 2012

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Double expresser DLBCL

Table 3. Frequency, pathologic characterization, and impact of DE large B-cell lymphoma

Reference*	Frequency (type of lymphomas studied)†	% GC based on GEP or phenotype	Therapy‡	Significant impact on overall survival‡
Johnson et al, 2012[18]	19% (DLBCL)	24%	R-CHOP	Adverse
Green et al, 2012[19]	29% (DLBCL)	37%	R-CHOP	Adverse
Hu et al, 2013[17]	34% (DLBCL)	34%	R-CHOP	Adverse
Dunleavy et al, 2013[36]	20%§ (DLBCL, includes 33% HIV+)	42%	DA-EPOCH-R or short course EPOCH-RR	None
Perry et al, 2014[47]	27% (DLBCL)	64%	R-CHOP or CHOP-like	Adverse
Friedberg et al, 2014[35]	20% (advanced stage DLBCL)	N/A	R-CHOP + iodine-131 tositumomab	None

Definition of MYC positivity = 40% in most series, though BCL2 positivity varied

20-35% of DLBCL associated with adverse outcome in patients treated RCHOP and variants

Swerdlow. ASH 2014

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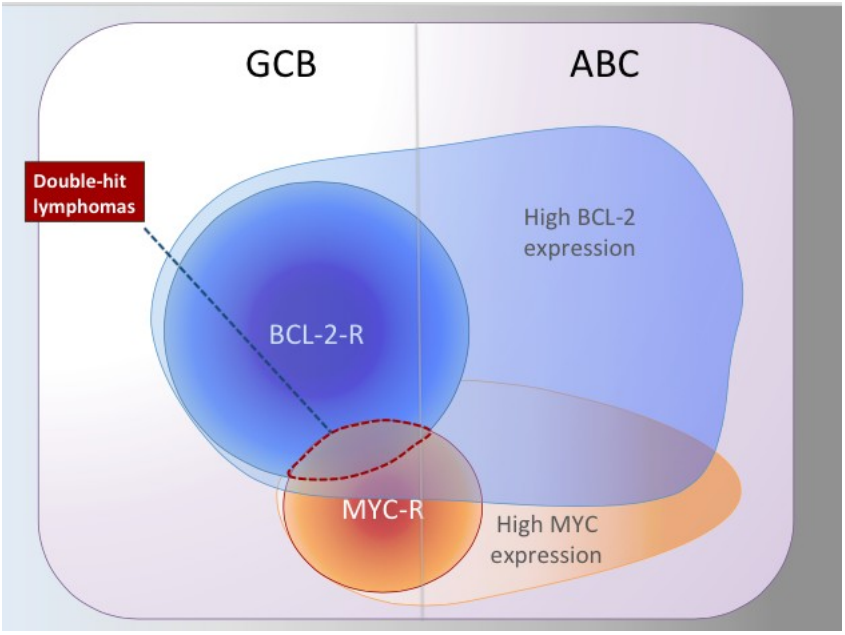

Dunleavy et al. ASH 2014

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DHL/DEL lymphoma summary

- Double hit (<10% of DLBCL) and double expresser (up to 30% of DLBCL) represent distinct subsets of aggressive lymphoma
- Outcomes with chemotherapy poor, particularly in patients with DHL
- Retrospective data mixed on benefit of intensified regimens
- No clear benefit of transplantation CR 1
- DA-REPOCH promising in small phase 2 study of MYC rearranged DLBCL
- DHL inherently chemotherapy resistant and improved outcomes will require novel agents

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Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- Comprise approximately 7% of DLBCL
- Female predominance
- Median age 30-40's
- SVC syndrome common
- 50% pts with pleural or pericardial effusion
- Cough, dyspnea, hoarseness and dysphagia
- B symptoms common

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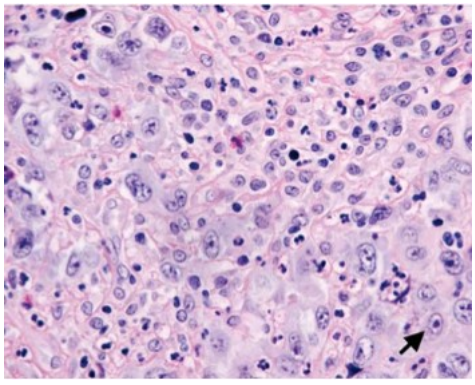
Pathology



Savage. Oncologist 2006

Predominantly diffuse infiltrate comprised of large-sized cells with round to irregular nuclei, vesicular chromatin, prominent nucleoli and moderate amounts of cytoplasm with sclerotic stroma is some areas

Immunohistochemical studies reveal the neoplastic cells to be CD20-positive B cells co-expressing CD10 (weak), Bcl-2, and Bcl-6. Immunostain for CD30 is weakly positive in scattered neoplastic cells.

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Possible diagnostic clues: PMBCL

pericardial or pleural effusion

elevated LDH

extranodal sites of disease outside the chest

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Clinical and pathologic distinction between NSHL and PMBCL

Table 1. Comparison of clinical and pathological features of primary mediastinal large B-cell lymphoma (PMBCL) and nodular sclerosis classic Hodgkin's lymphoma (NScHL)

Feature	PMBCL	NScHL
Age distribution	Third to fourth decade	Peak at 15–35 years
Gender	Female predominance	Slight female predominance
Site of disease	Anterior mediastinum	Anterior mediastinum most common
Pathology	Sclerosis	Sclerosis
Immunophenotype	CD30 variable and weak; surface Ig absent in ~70%	CD30 usually strong; surface Ig absent in all
Genetics	2p (*REL*) and 9p (*JAK-2*) amplification	2p (*REL*) and 9p (*JAK-2*) amplification

Savage. Oncologist 2006

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original article

Annals of Oncology 22: 664–670, 2011
doi:10.1093/annonc/mdq518
Published online 19 August 2010

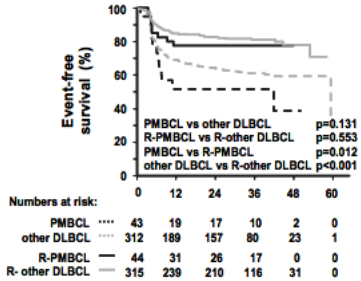
Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study

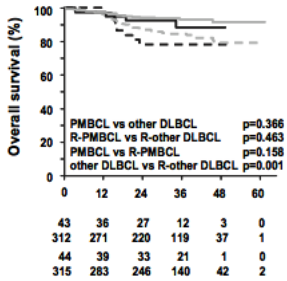
M. Rieger[1*], A. Österborg[2], R. Pettengell[3], D. White[4], D. Gill[5], J. Walewski[6], E. Kuhnt[7], M. Loeffler[8], M. Pfreundschuh[9] & A. D. Ho[1], for the MabThera International Trial (MInT) Group

EFS PMBCL approximately 80% with RCHOP +/- RT

Table 3. Response after chemo(immuno)therapy and before intended radiotherapy

	PMBCL	
	CHOP-like $n = 43$	CHOP-like + rituximab $n = 44$
Remission status after chemo(immuno)therapy		
CR/CRu	14 (32.6%)	23 (52.3%)
PR	17 (39.5%)	14 (31.8%)
NC	2 (4.7%)	4 (9.1%)
PD	7 (16.3%)	0
Death	0	1 (2.3%)
Unknown	3 (7.0%)	2 (4.5%)
RT intended	39 (90.7%)	37 (84.1%)
RT intended and given	29 (67.4%)	31 (70.5%)
RT intended and not given	10 (23.3%)	6 (13.6%)
RT not intended	4 (9.3%)	6 (13.6%)
RT not intended and given	0	1 (2.3%)
RT not intended and not given	4 (9.3%)	6 (13.6%)





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The NEW ENGLAND JOURNAL of MEDICINE

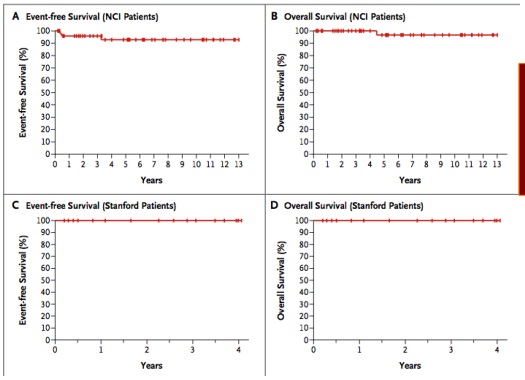
ORIGINAL ARTICLE

Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Lauren S. Maeda, M.D., Ranjana Advani, M.D., Clara C. Chen, M.D., Julie Hessler, R.N., Seth M. Steinberg, Ph.D., Cliona Grant, M.D., George Wright, Ph.D., Gaurav Varma, M.S.P.H., Louis M. Staudt, M.D., Ph.D., Elaine S. Jaffe, M.D., and Wyndham H. Wilson, M.D., Ph.D.

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Prospective NCI Cohort (N=51)	Retrospective Stanford Cohort (N=16)	P Value between Study Cohorts
Female sex — no. (%)	30 (59)	9 (56)	1.00
Age — yr			0.04
Median	30	33	
Range	19–52	23–68	
Bulky tumor, ≥10 cm			0.57
Patients — no. (%)	33 (65)	9 (56)	
Maximal diameter range — cm	5–18	7–18	
Stage IV disease — no. (%)	15 (29)	7 (44)	0.36
Elevated lactate dehydrogenase level — no. (%)	40 (78)	11 (69)	0.51
Extranodal site — no. (%)	27 (53)	3 (19)	0.02
Pleural effusion — no. (%)	24 (47)	10 (62)	0.39
CD20+ malignant cells — no. (%)	51 (100)	16 (100)	1.00
BCL6+ malignant cells — no. (%)	33/37 (89)	ND	ND



Extremely high PFS and OS with DA-REPOCH

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Diagnosis large cell lymphoma 2015

Table 10.14 Diffuse large B-cell lymphoma: variants, subgroups and subtypes/entities.

Diffuse large B-cell lymphoma, not otherwise specified (NOS)

- Common morphologic variants
  - Centroblastic
  - Immunoblastic
  - Anaplastic
- Rare morphologic variants
- Molecular subgroups
  - Germinal centre B-cell-like (GCB)
  - Activated B-cell-like (ABC)
- Immunohistochemical subgroups
  - CD5-positive DLBCL
  - Germinal centre B-cell-like (GCB)
  - Non-germinal centre B-cell-like (non-GCB)

Diffuse large B-cell lymphoma subtypes

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly

Other lymphomas of large B cells

- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- ALK-positive LBCL
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma

Borderline cases

- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

from www.pubcan.org

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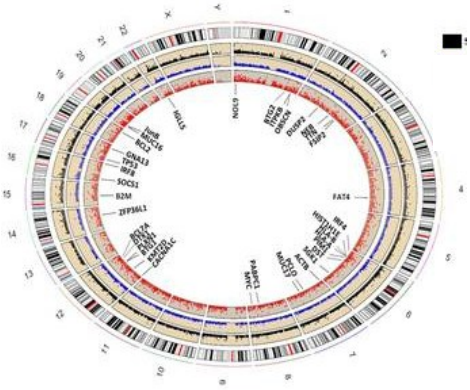
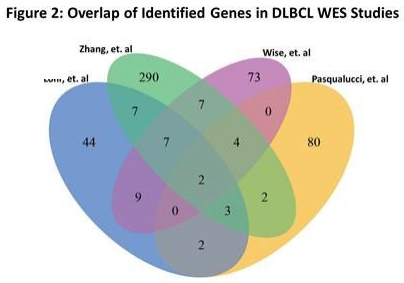
What about precision medicine in DLBCL?



MLL2, B2M, CD58, MEF2B, FOXO1, TP53, PIM1, SOCS1, MYC, GNA13, SGK1, TNFAIP3, MYD88, PRDM1, CDKN2A, EZH2 and CIITA.



102 potential "driver" mutations

Wise et al, ASH 2015, abstract 110

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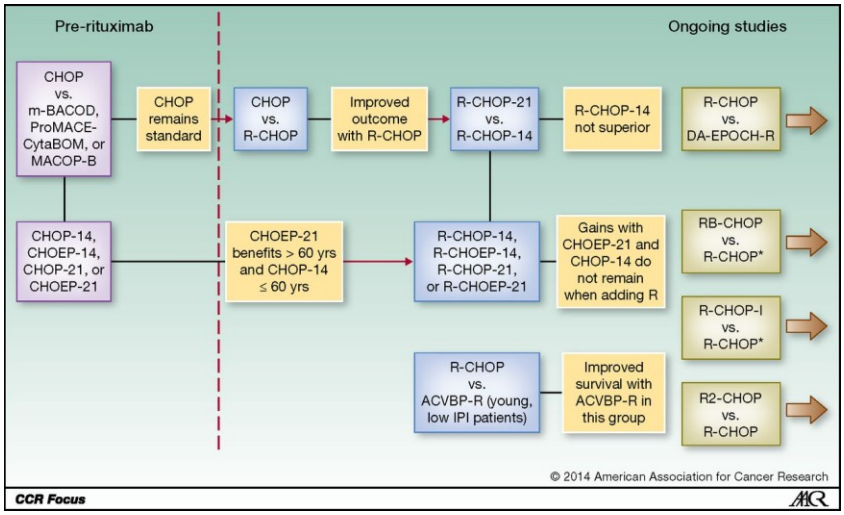
Evolution of trials in DLBCL



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Diagnosis

- **When to consider MCL?**
  - **Pathology**
    - Intermediate size monomorphic infiltrate
    - CD5+ CD10- CD20+ CD23- Bcl-2+ Bcl6- CyclinD1+
    - Cytogenetics=t(11;14)
    - FISH=IGH-CCND1 rearrangement
  - **DDx**

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Prognosis

- Pathological variants
- Prognostic factors
  - MIPI and derivatives
  - Ki67 (Mib-1) index
  - MIPI/Ki67 widely applied
    - At diagnosis with different therapies
    - At relapse?

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First-Line Therapy

- The Basics
  - R improves EFS in meta-analysis
  - RCHOP PFS 1.5y
  - RCHOP + Autologous SCT
    - European MCL network RCT
      - (R)CHOP + ASCT versus Interferon maintenance
      - 3y PFS 54% versus 25%

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First-Line Therapy

- The Basics
  - RCHOP PFS 1.5y
  - RCHOP + ASCT PFS 4y
- The role of Cytarabine
  - R-HCVAD
    - OR 97% CR 87%;
    - mFFS ~5y (5.9y in <65yo, 4y >65yo)
    - Outside MDACC mPFS ~5y, 5.5y <65yo
    - 39% could not complete for toxicity…

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First-Line Therapy

- The role of Cytarabine
  - R-HCVAD PFS 5.5y
  - R-CHOP + ASCT ~ R-HCVAD PFS 4y
  - RHCVAD + ASCT
    - Good single arm results, PFS>5y
    - Unclear benefit in comparative studies
    - Toxicity clear

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First-Line Therapy

- The role of Cytarabine
  - R-HCVAD PFS 5.5y
  - R-CHOP + ASCT ~ R-HCVAD PFS 4y
  - RHCVAD + ASCT PFS>5y
  - R-MegaCHOP/RHIDAC + ASCT PFS 7.5y
  - RCHOP/RDHAP + ASCT PFS 7y
    - Benefit in all MIPI groups
    - If CR before ASCT no difference

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First-Line Therapy

- The role of Cytarabine
- The wonders of bendamustine
  - R-Benda versus R-CHOP
    - R-Benda superior
    - PFS 35 v 22m
    - Less toxic

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First-Line Therapy

- Current concepts
  - R-Benda + Ara-C 2y PFS 95%
  - DFCI protocol 12-168: BRAC
    - Transplant eligible; R-Benda x3 + R-HIDAC x 3
    - OR 96% CR 96%

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Salvage

- Available agents
  - "Targeted Therapy"

Agent	OR/CR	PFS
Y90-Ibritumomab	30/15	6m
Lenalidomide*	30-50/10	6-12m
Temsirolimus*	40/5	6m
Bortezomib*	50/10-40	12m
Idelalisib	40/5	4m
Ibrutinib	70/20	14m
ABT-199	100/0	?

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Q&A Session

Dr. Fisher's slides are available for download at
www.LLS.org/programs

Update on Aggressive Non-Hodgkin Lymphoma (NHL): Diagnosis and Treatment

The Leukemia & Lymphoma Society (LLS) offers:

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- **What to ask:** For a list of suggested questions to ask about certain topics, download and print any of the guides found at:
  - **WEBSITE: www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/booklets**
- **Past NHL education programs: www.LLS.org/programs**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
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