LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

NHL & CLL

Diagnosis and Treatment Update

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Diagnosis and Treatment Update

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Welcome and Introduction

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Senior Director, Patient Services Programs
The Leukemia & Lymphoma Society

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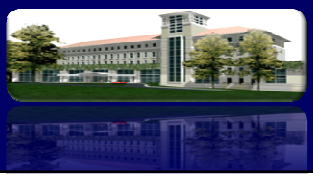
EMORY WINSHIP CANCER INSTITUTE

Advancing the possibilities…



Anyone can get blood cancer

One million North Americans affected per year

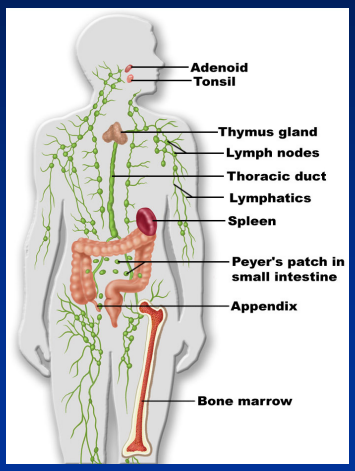
2012 Estimated New Cancer Cases in United States

	Males			Females	
Prostate	241,740	29%	Breast	226,870	29%
Lung & bronchus	116,470	14%	Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%	Colon & rectum	70,040	9%
Urinary bladder	55,600	7%	Uterine corpus	47,130	6%
Melanoma of skin	44,250	5%	Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%	Melanoma of skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%	Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%	Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%	Ovary	22,280	3%
Pancreas	22,090	3%	Pancreas	21,830	3%
ALL SITES	848,170	100%	ALL SITES	790,740	100%

CA: A Cancer Journal for Clinicians, Vol. 62, January/February 2012.

Lymphomas/Chronic Lymphocytic Leukemia

- Cancers of the cells of the immune system: Lymph system
- Classified by source of the cancer cell
- The causes for most lymphomas and CLL are unknown
- Usually start in the lymph nodes, but can involve tissues in the spleen, skin, GI tract, liver, bone marrow, or other sites
- May spread to these areas



Common Symptoms

63 yo man over the last 3 months:

- Feeling worn down, unable to go to work
- Sweats at night
- Lost 17 lbs
- Noticed a lump in his groin that keeps getting bigger
  - Now has lumps under left arm and left neck too
- Feels itchy all over

Common Symptoms

- painless swelling of the lymph nodes
- Nodes are movable and nontender
- Unexplained fever
- Night sweats
- Unexplained weight loss (>10% body weight)

B Symptoms

- Constant fatigue
- ETOH causes immediate pain @ involved site.
- Itchy skin
- Reddened patches on the skin

Diagnostic Evaluation

- Medical History
- Physical exam
- Laboratory:
  - Complete Blood Count (CBC), Metabolic Panel
  - Lactate Dehydrogenase (LDH), B_2 Microglobulin
- Lymph Node Biopsy
- Computed Tomography (CT) scan
- Positron Emission Tomography (PET)
- Bone Marrow Biopsy

WHO Classification

B-cell

- Precursor B-cell neoplasms
  - B-acute lymphoblastic leukemia (B-ALL)
  - Lymphoblastic lymphoma (LBL)
- Peripheral B-cell neoplasms
  - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma/immunocytoma
  - Mantle cell lymphoma
  - Follicular lymphoma
  - Extranodal marginal zone B-cell lymphoma of MALT type
  - Nodal marginal zone B-cell lymphoma
  - Splenic marginal zone lymphoma
  - Hairy cell leukemia
  - Plasmacytoma/plasma cell myeloma
  - Diffuse large B-cell lymphoma
  - Burkitt's lymphoma

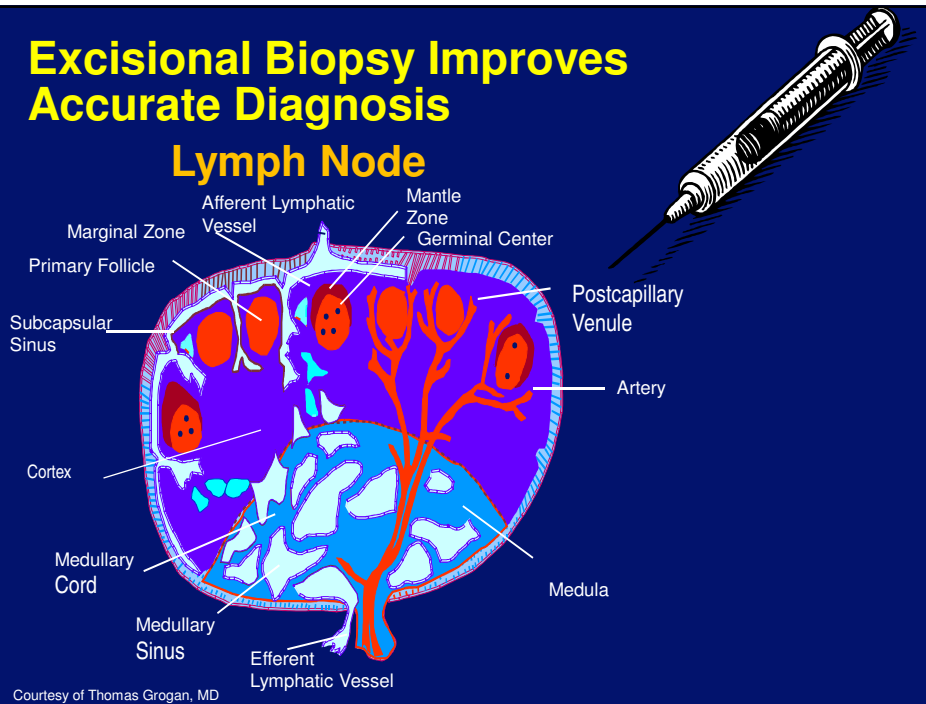
T-cell/NK-cell

- Precursor T-cell neoplasm
  - Precursor T-acute lymphoblastic leukemia (T-ALL)
  - Lymphoblastic lymphoma (LBL)
- Peripheral T-cell/NK-cell neoplasms
  - T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
  - T-cell granular lymphocytic leukemia
  - Mycosis fungoides/Sézary syndrome
  - Peripheral T-cell lymphoma not otherwise characterized
  - Hepatosplenic gamma/delta T-cell lymphoma
  - Angioimmunoblastic T-cell lymphoma
  - Extranodal T-/NK-cell lymphoma, nasal type
  - Enteropathy-type intestinal T-cell lymphoma
  - Adult T-cell lymphoma/leukemia (HTLV1+)
  - Anaplastic large cell lymphoma, primary systemic type
  - Anaplastic large cell lymphoma, primary cutaneous type
  - Aggressive NK-cell leukemia

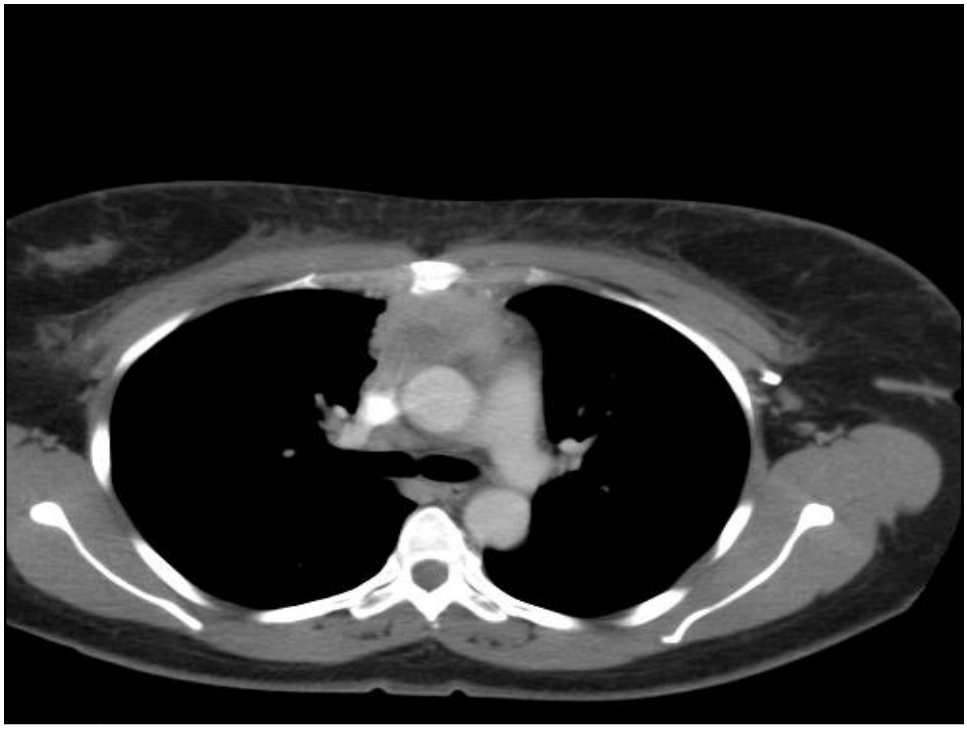
Fisher et al. In: DeVita et al, eds. *Cancer: Principles and Practice of Oncology*. 2005:1967.
Jaffe et al, eds. *World Health Organization Classification of Tumours*. 2001.

Excisional Biopsy Improves Accurate Diagnosis

Lymph Node



Courtesy of Thomas Grogan, MD



Ann Arbor Staging System

I. Involvement of 1 lymph node (I) or 1 extralymphatic organ or site (I_E)

II. Involvement of ≥2 lymph nodes on same side of diaphragm or localized extralymphatic organ or site and ≥1 involved lymph node on same side of diaphragm (II_E)

III. Involvement of lymph nodes on both sides of diaphragm (III) or same side with localized involvement of extralymphatic site (III_E), spleen (III_S), or both (III_{S+E})

IV. Diffuse or disseminated involvement of ≥1 extralymphatic organ or tissues with or without lymph node enlargement

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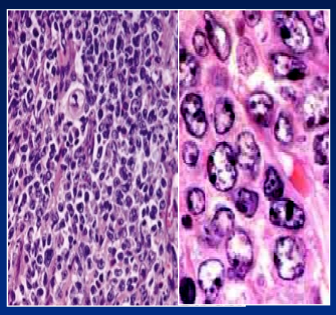
Fisher et al. In: DeVita et al, eds. *Cancer: Principles and Practice of Oncology*. 2005:1967.
Jaffe et al, eds. *World Health Organization Classification of Tumours*. 2001.

Diffuse Large B-Cell Lymphoma

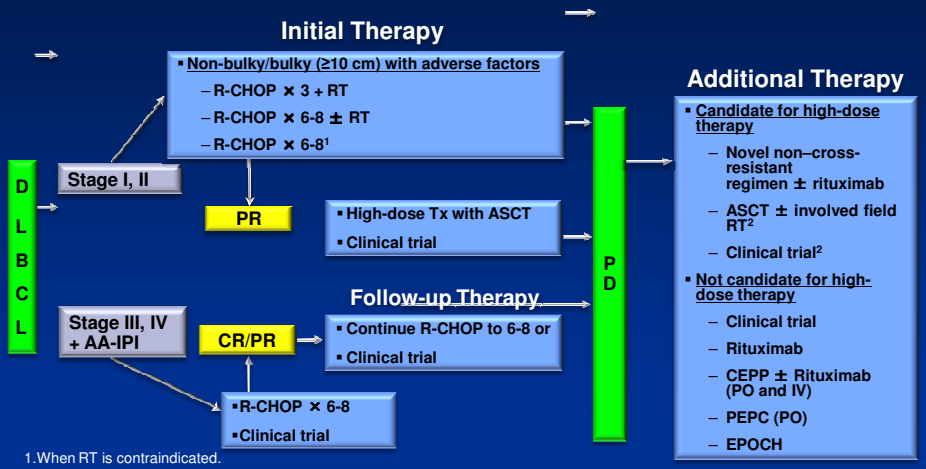
- Most common NHL: 31%
- Average survival: weeks to months if not treated
- Curable in 50% or more of cases
- **Clinical outcomes highly variable**



- 30% to 40% present with rapidly enlarging, mass with B symptoms
- May present outside of lymph nodes (stomach, brain, skin, other)
- Large cells with diffuse growth pattern (loss of follicule structure)

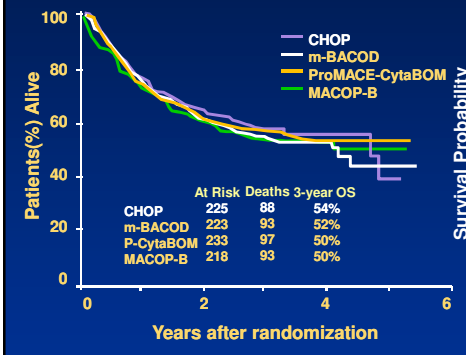
Michallet AS, et al. Blood Rev. 2009;23:11-23.

DLBCL Management Strategy

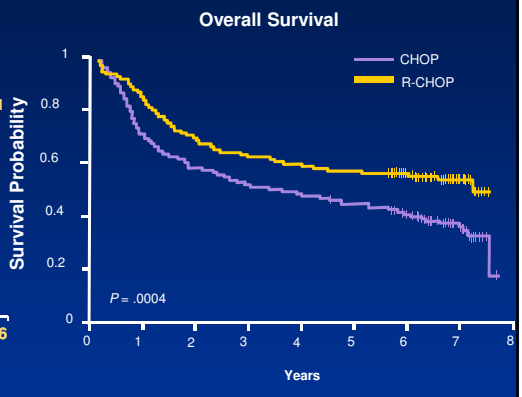


1.When RT is contraindicated.
2. In patients achieving CR or PR after second-line therapy
- AA-IPI = age-adjusted IPI.
- NCCN Practice Guidelines in Oncology, v.3.2010.

Advances in Treatment Improve Survival for Patients with Lymphoma



Fisher RI, et al. *N Engl J Med.* 1993

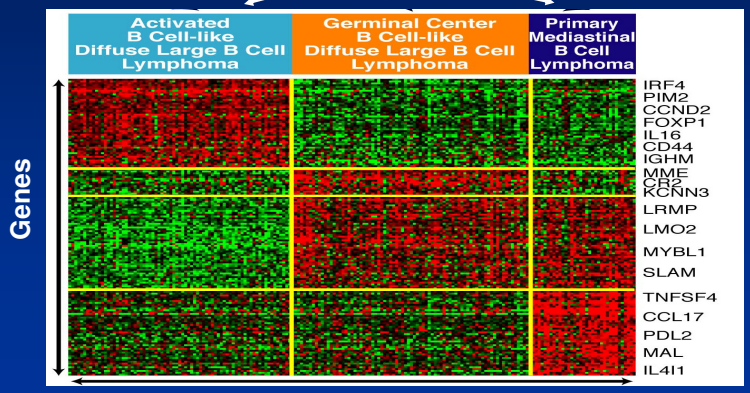


Coiffier B, et al. N Engl J Med. 2002.

Coiffier B, et al. ASCO 2007. Abstract 8009.

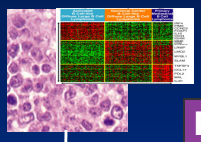
Genetic Testing Identifies Biologic and Clinically Different Types of DLBCL

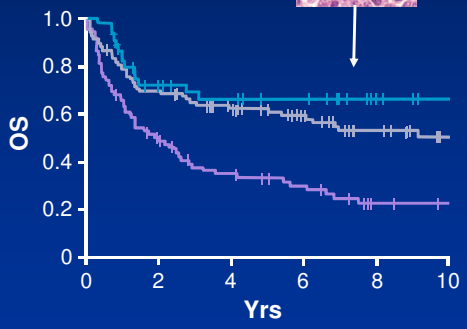
Diffuse Large B- Cell Lymphoma



Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL

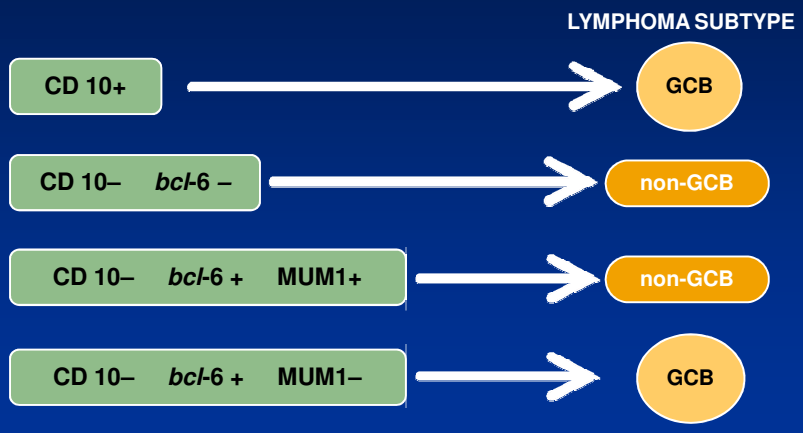
Diffuse Large B-Cell Lymphoma





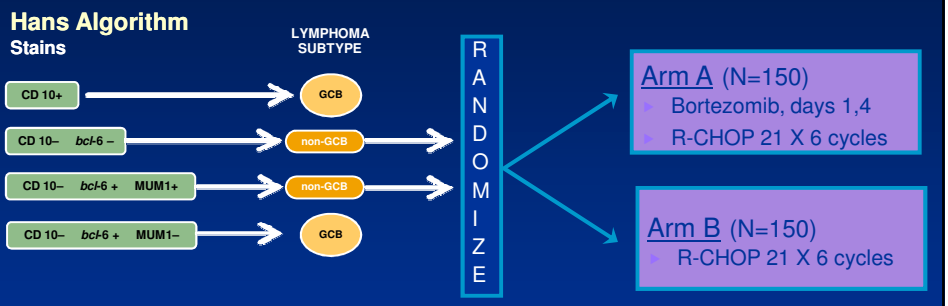
DLBCL Subgroup	5-Yr OS, %
PMBL	64
GCB DLBCL	59
ABC DLBCL	30

GCB vs Non-GCB Subtypes of DLBCL: Using Pathology Stains



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

Using DLBCL Biological Subtype to Choose Treatment



- Patients: 300, non-GCB DLBCL (by IHC)
- Primary Endpoint: PFS at 1 year; 80% power to detect an increase from 67% to 78%

Treatment Strategies - Non-Hodgkin Lymphomas

New Challenges in the Management of Diffuse Large B-Cell Lymphoma

a report by Christopher R. Flowers, Loretta J. Nastoupil, Leon Bernal-Mizrachi, Adam C. Rose and Rajni Sinha

Department of Hematology and Oncology, Winship Cancer Institute, Emory University, Atlanta

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ADAM C. ROSE
CHRISTOPHER R. FLOWERS, MD[1]

Diffuse Large B-Cell Lymphoma: Current Treatment Approaches

488 ONCOLOGY • May 2012

Rajni Sinha[1]
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Blood and Lymphatic Cancer: Targets and Therapy

Dovepress

REVIEW

Treatment strategies for patients with diffuse large B-cell lymphoma: past, present, and future

Review

Expert Opinion

Novel agents for diffuse large B-cell lymphoma

Rajni Sinha, Nutan DeJoubner & Christopher Flowers†

Emory University, Winship Cancer Institute, School of Medicine, Atlanta, GA, USA

Management Strategies for Elderly Patients with Diffuse Large B-Cell Lymphoma

Loretta J Nastoupil,[1] Rajni Sinha[2] and Christopher R Flowers[3]

CA CANCER J CLIN 2010;60:393–406

Improving Outcomes for Patients with Diffuse Large B-Cell Lymphoma

Christopher R. Flowers, MD, MS[1]; Rajni Sinha, MD, MRCP[2]; Julie M. Vose, MD[3]

Research Article

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

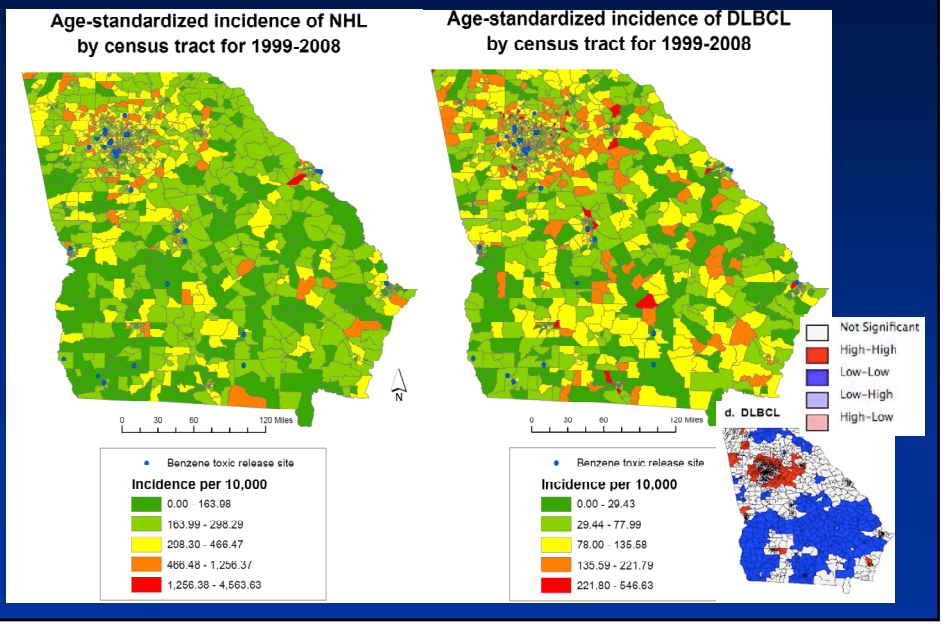
Christopher R. Flowers[1,2], Stacey A. Fedewa[4], Amy Y. Chen[2,4], Loretta J. Nastoupil[1,2], Joseph Lipscomb[2,3], Otis W. Brawley[2,4], and Elizabeth M. Ward[4]

Cancer Epidemiology, Biomarkers & Prevention

Racial Differences in the Presentation and Outcomes of Diffuse Large B-Cell Lymphoma in the United States

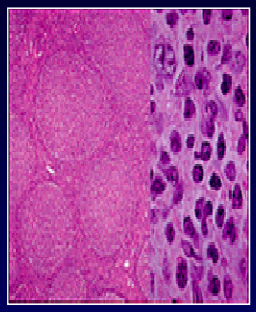
Pareen J. Shenoy, MBBS, MPH[1]; Neha Malik[1]; Ajay Nooka, MD[1]; Rajni Sinha, MD[1]; Kevin C. Ward, PhD[2]; Otis W. Brawley, MD[1,2]; Joseph Lipscomb, PhD[2]; and Christopher R. Flowers, MD, MS[1]

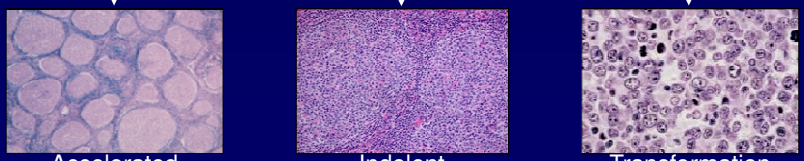
Finding Causes for Lymphoma



Follicular Lymphoma (FL)

- Most common indolent NHL, accounts for ~22%-25% of NHL in North America
- Variable presentation and prognosis, but typically advanced stage at presentation
- Often asymptomatic
- Advanced stage FL not curable with standard therapy
- Median survival was about 10 years, but has increased with new treatments
- Multiple therapies: no standard, how best to sequence
- Many new therapies in development

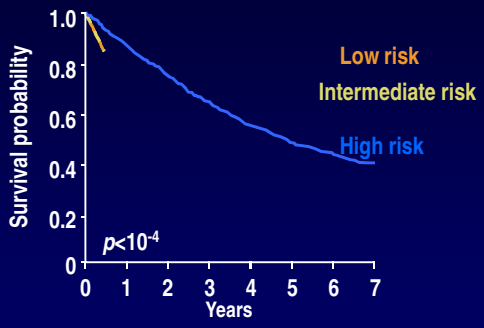




Modified from Skarin AT, Dorfman DM. *CA Cancer J Clin*. 1997;47:351-72.

Overall Survival According to FLIPI: Clinical Prognosis Factors

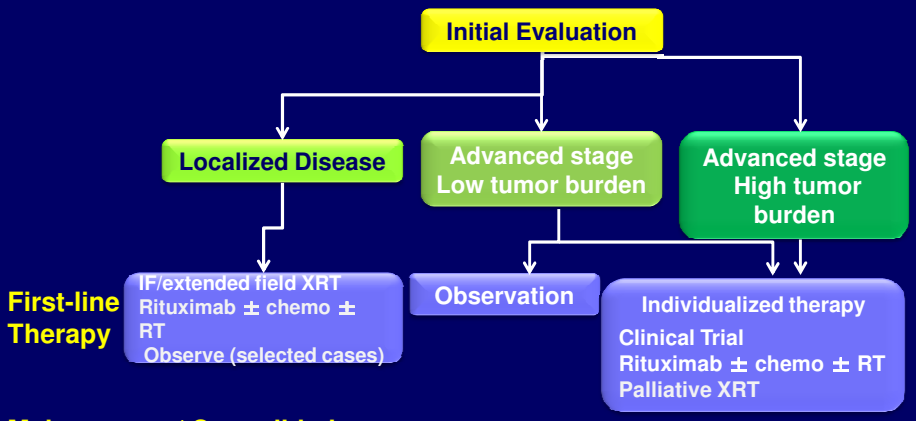
No **No**dal regions >4
L **L**DH increased
A **A**ge ≥60
S **S**tage III/IV
H **H**emoglobin <120 g/L



Risk Group	No. of Factors	% of Pts	5-y OS (%)	10-y OS (%)
Low	0-1	36	90.6	70.7
Intermediate	2	37	77.8	50.9
High	3-5	27	52.5	35.5

Adapted from Solal-Celigny P, et al. *Blood*. 2004;104:1258-65.

A Management Approach for FL



Criteria for Initiation of Treatment: Indolent NHL

GELF

- ≥3 nodal sites each with diameter ≥ 3 cm
- Any nodal/extranodal mass with diameter ≥ 7 cm
- B symptoms (fevers, night sweats, weight loss)
- Enlarged spleen
- Pleural effusions/ascites
- WBC < 1.0 x 10^9/L or platelets < 100 x 10^9/L
- Leukemia (> 5.0 x 10^9/L malignant cells)

NCCN

- GELF criteria
- Symptoms (fatigue, pain, fevers...)
- Threatened end-organ function/ compressive syndrome
- Steady progression
- Elevated LDH or β2-microglobulin
- Patient preference

J Natl Compr Canc Netw. 2010 8(3):288-334.

Rituximab (R) Compared with a "Watch and Wait" Strategy in Patients with Stage II-IV Asymptomatic, Nonbulky FL

Strategy	Observe	R x 4 weeks	R x 4 weeks
Maintenance	---	---	R q 2 mos. x 2 years
Number	187	84	192
CR/PR (%)	2/3	43/30	54/33
3-year PFS	33%	60%	81%
Time to next treatment	33 months	Not reached	Not reached

- Patients had: stage II–IV, asymptomatic, non-bulky low-grade FL
- Improved PFS in rituximab arms ($p \leq 0.001$)
- Time to initiation of new treatment in the rituximab arms
  - 33 months vs. not reached at 4 years ($p \leq 0.001$)
- No difference in OS ($p \geq 0.5$)
- Quality of life no different

Ardeshna KM, et al. *ASH* 2010. abstr 6 (oral, Plenary Session).

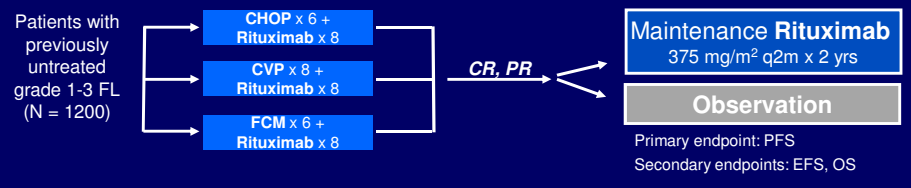
Adding Rituximab to Front-Line Chemo for High Tumor Burden FL Improves Response Rates & Survival

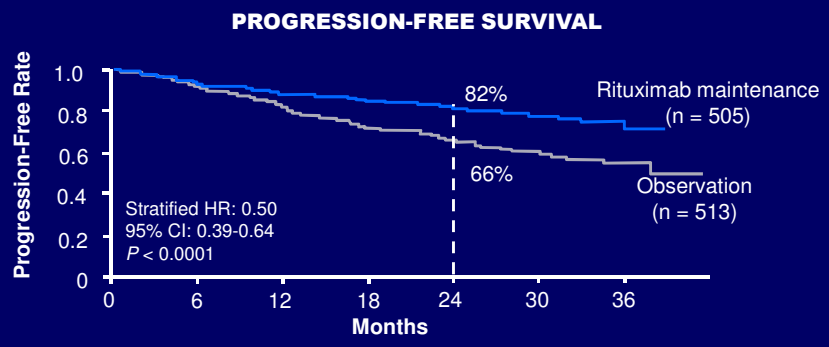
		Complete Response %		Endpoint, Years	Overall Survival %	
Regimen	N	R-Chemo	Chemo		R-chemo	Chemo
CHOP[1]	428	44	35	2	95*	90
CHVP-IFN[2]	358	63*	34	5	84	79
CVP[3]	321	41*	10	4	83*	77
MCP[4]	201	50*	25	4	87*	74

1. Hiddemann et al. *Blood*. 2005;106(12):3725-3732. 2. Salles et al. *Blood*. 2008;112(13):4824-4831. 3. Marcus et al. *J Clin Oncol*. 2008;26(28):4579-4586. 4. Herold et al. *J Clin Oncol*. 2007;25(15):1986-1992.

Rituximab Maintenance vs Observation in FL

GELA PRIMA Phase III Study





Salles et al. *Lancet*. 2011;377:42-51.

Relapsed Follicular Lymphoma

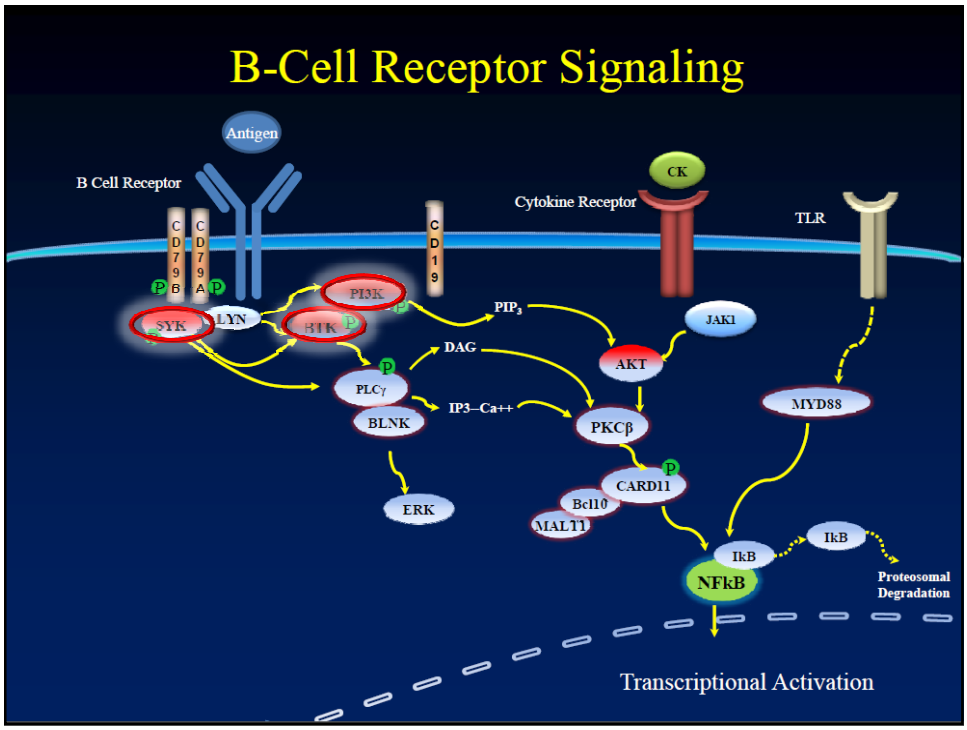
- All patients eventually relapse
- Considerations for retreatment
  - Is treatment currently needed? (GELF, BNLI, NCCN)
  - What previous therapies were given?
    - How well did they work?
  - What is the current clinical situation?
    - Patient age / comorbidities
    - Disease-related symptoms
    - Tumor burden
    - Prognostic factors (eg, LDH, β2M)
  - Patient's goals
- Options
  - Chemo ± Rituximab
  - Radioimmunotherapy
  - High dose CT ± SCT
  - Novel agent

30

Recurrent Follicular Lymphoma: Recommended Treatment

- Conventional strategies
  - Rituximab ± maintenance
  - Chemoimmunotherapy ± maintenance
  - Radioimmunotherapy
  - External-beam radiotherapy
  - Autologous transplantation
  - Allogeneic transplantation
- Novel strategies
  - Novel monoclonal antibodies
  - Bortezomib
  - Bendamustine
  - Lenalidomide
  - Others
- **Clinical trial**

NCCN. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf.



Syk Inhibition: Phase I Results

Overall Response and PFS by Group

Response	Group 1, DLBCL		Group 2, FL	Group 3		
	De novo (n = 17)	Transformed (n = 6)	(n = 21)	CLL/SLL (n = 11)	MCL (n = 9)	Other (n = 4)
CR, n	1	0	0	0	0	0
PR, n	3	1	2	6	1	0
SD, n	2	2	11	2	4	1
PD, n	8	3	7	3	4	2
Not evaluable, n	3	0	1	0	0	1
ORR (CR + PR), n (%)	4 (23.5%)	1 (16.7%)	2 (9.5%)	6 (54.5%)	1 (11.1%)	0
CR + PR + SD, n (%)	6 (35.3%)	3 (50.0%)	13 (61.9%)	8 (72.7%)	5 (55.6%)	1 (25.0%)
PFS, mo (95% CI)	–	–	4.6 (2.0-8.3)	6.4 (2.2-7.1)	3.8 (1.9-4.6)	1.9 (1.8-N/A)

- Most common adverse events were diarrhea, fatigue, cytopenias, hypertension, and nausea
  - 18% grade 3-4 neutropenia
  - 3% grade 3-4 thrombocytopenia

Friedberg J W et al. Blood 2010;115:2578-2585

Phase I Results
BTK Inhibitor: PCI-32765

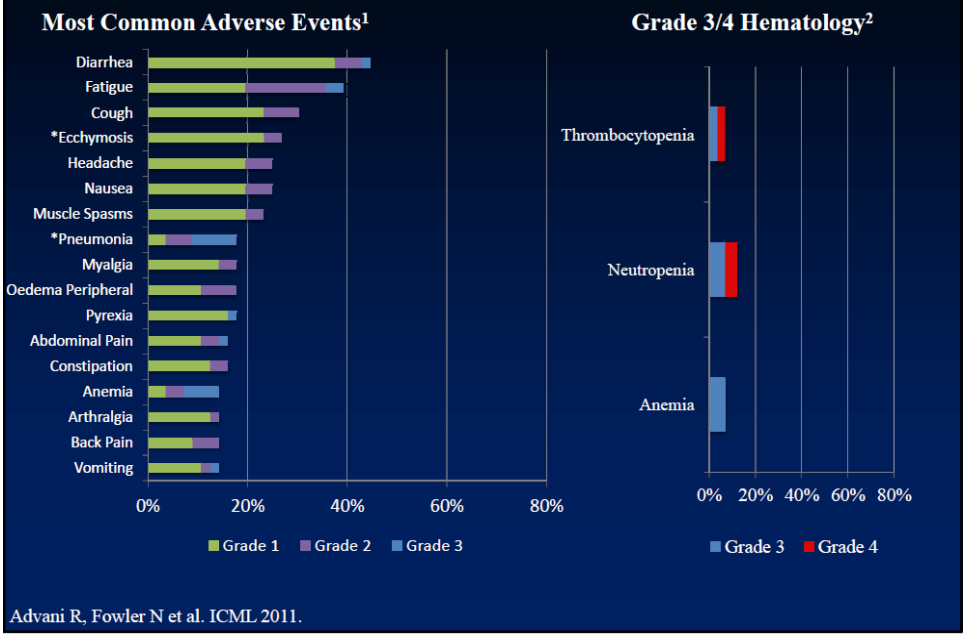
Histology	N	CR	PR	SD	PD	NE	ORR% ITT (n=56)	ORR% Eval (n=50)
CLL/SLL	16	1	10	3*		2	69%	79%
MCL	9	3	4	1	1		78%	78%
WM	4		3**	1			75%	75%
FL	16	3	3	3	4	3	38%	46%
MZL/MALT	4		1	1	1	1	25%	33%
DLBCL	7		2	1	4		29%	29%
TOTAL	56	7	24	9	10	6	55%	62%

* 1 CLL pt had nodal response with lymphocytosis;
** Based on IgM

NE = not evaluable; *includes 1 Nodal Responder; ** via IgM

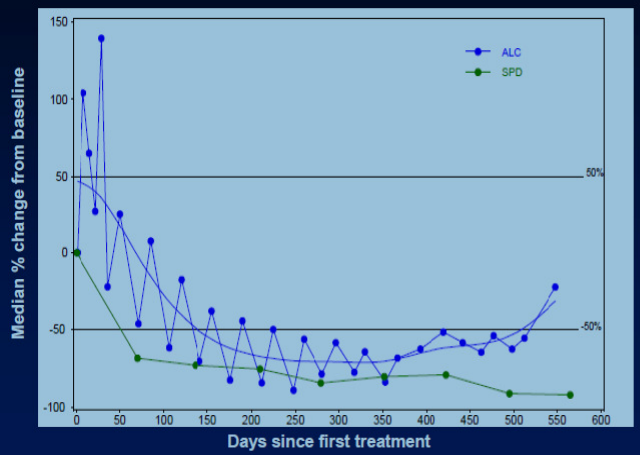
Advani R, Fowler N et al. ICML 2011.

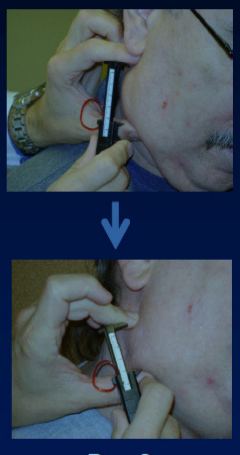
Adverse Events: PCI-32765



Advani R, Fowler N et al. ICML 2011.

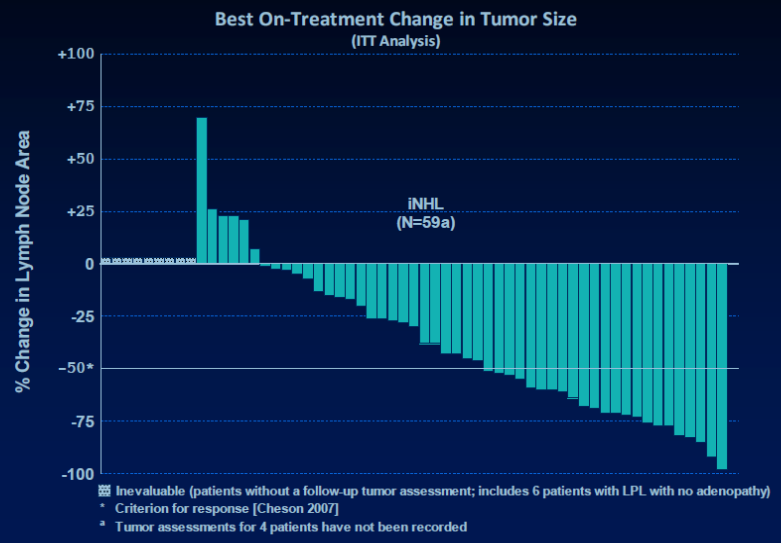
Treatment-related Lymphocytosis: BTKi





Day 2

GS-1101
Tumor Shrinkage in Indolent NHL



Khal. B et al. ICML 2011.

CLL Staging Systems

Rai	Findings	Survival (mo)
0	Lymphocytosis only	> 120
I	Lymphocytosis + lymphadenopathy	95
II	Lymphocytosis + > spleen and/or liver	72
III	Lymphocytosis + anemia (Hgb < 11.0 g/dL)	30
IV	Lymphocytosis + platelets < 100	30

Binet	Findings	Survival (mo)
A	Hgb ≥ 10, Plts ≥ 100, < 3 involved areas*	> 120
B	Hgb ≥ 10, Plts ≥ 100, ≥ 3 involved areas*	84
C	Hgb < 10, or Plts < 100	24

*Involved areas include cervical, axillary, or inguinal nodes, spleen, or liver.

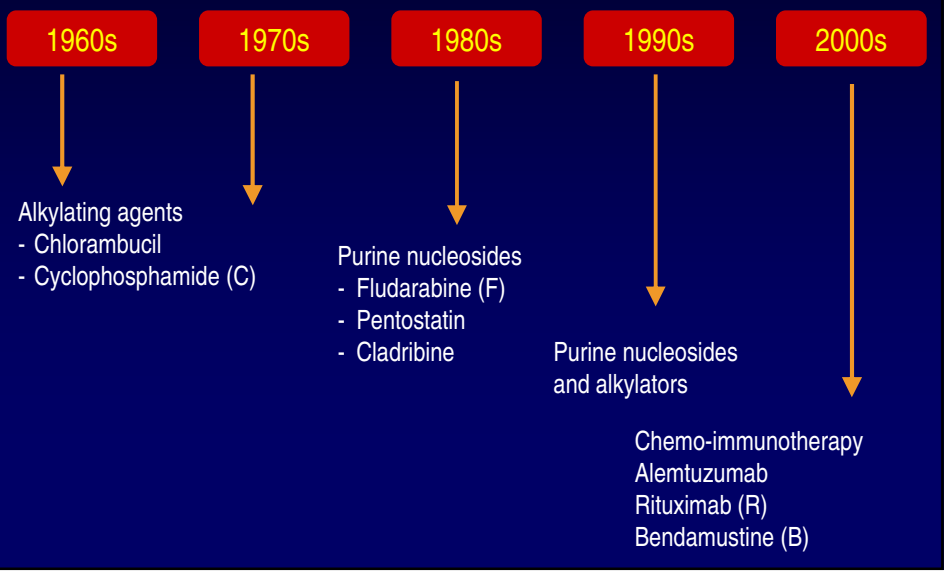
Rai KR, et al. *Blood*. 1975;46:219-234; Binet JL, et al. *Cancer*. 1981;48:198-206.

Chronic Lymphocytic Leukemia Overall Survival in Months by Stage and Year of Diagnosis

Rai Stage	Characteristic	Original Report 1975 (N = 125)	Mayo Clinic 1995-2009 (N = 2397)
0	Lymphocytosis only	150	130
I	Lymphadenopathy	101	106
II	Organomegaly	71	88
III	Hemoglobin < 11 g/dL	19	58
IV	Platelet < 100 x 10^9/L	19	69

Rai KR, et al. *Blood.* 1975;46:219-234;
Shanafelt TD. *Hematology Am Soc Hematol Educ Program.* 2009;421-429.

Previously Untreated CLL
Treatment Options



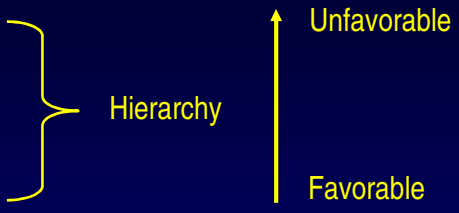
Traditional Prognostic Factors

- Advanced stage at diagnosis
- Short lymphocyte doubling time
- Diffuse bone marrow infiltration
- Older age, males
- Cytogenetic abnormalities

Rozman C, Montserrat E. *N Engl J Med.* 1995;333:1052-1057;
Cheson BD, et al. *Blood.* 1996;87:4990-4997.

Newer Prognostic Factors

- FISH defects
  - 17p deletion
  - 11q deletion
  - 12q trisomy
  - Normal
  - 13q deletions



- Immunoglobulin heavy chain variable region (IgVH) - ≤ 2% mutation = unmutated
  - Survival 7.5 years for unmutated vs 27 years for mutated
- CD38 status (≥ 30% = poor outcome)
- ZAP-70 status (≥ 20% = poor outcome)
- High serum β_2-microglobulin and soluble CD23

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Newly Diagnosed and Relapsed / Refractory CLL Patients

Initial Diagnosis → Stage Determination → Prognostic Determination

Frontline Options*:
- -FCR
- -PCR
- -FR
- -FC
- -Chlorambucil
- -Rituximab
- -Bendamustine
- -Alemtuzumab
- -Clinical Trial

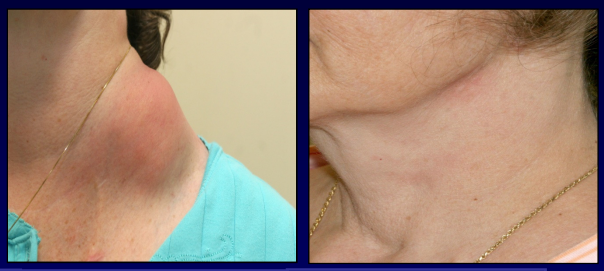
Relapse/Refractory
- -FCR
- -R-FCM
- -CFAR
- -Bendamustine
- -Alemtuzumab
- -Lenalidomide
- -Ofatumumab
- -Clinical Trial

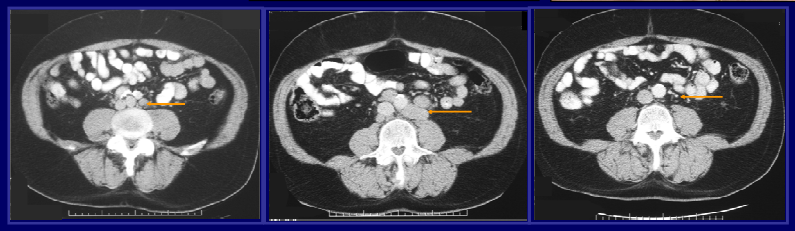
*Large phase III trials lacking for most of these approaches.

New Side Effects with New Therapies: Tumor Flare Reaction

Occasional

- Fever
- Bone pain
- ↑ WBC / ALC





Baseline | Flare reaction | Post-treatment

Patient-Clinician Communication

- Use communication approaches tailored to individual patient needs according to health literacy and numeracy, living circumstances, language barriers and decision-making capacity.
- Receive/Provide clear written instructions about when and how to contact healthcare practitioners.
- Recognize that coordination of care among providers is essential for high quality care
- Receive/Give written and/or electronic copies of management plans

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The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified NHL & CLL patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

For more information about NHL & CLL and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**