LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

# NHL & CLL

## Diagnosis and Treatment Update

Supported by a grant from
Genentech | biogen idec

In collaboration with
abrale | ALIANZA LATINA

**Christopher R. Flowers, MD, MS**

***Associate Professor of Hematology and Medical Oncology***
**Winship Cancer Institute**
**Emory University School of Medicine**
**Atlanta, Georgia**

EMORY WINSHIP CANCER INSTITUTE

*Advancing the possibilities…*

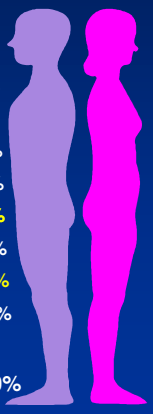
2

# Anyone can get blood cancer

## One million North Americans affected per year

### 2012 Estimated New Cancer Cases in United States

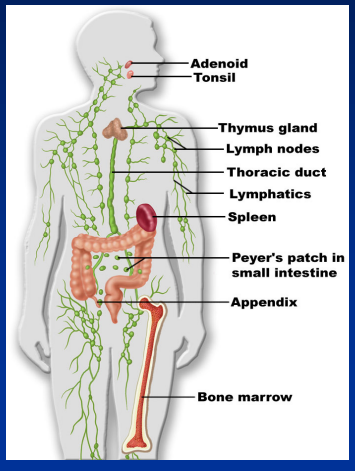
| Males | | | Females | | |
|---|---|---|---|---|---|
| Prostate | 241,740 | 29% | Breast | 226,870 | 29% |
| Lung & bronchus | 116,470 | 14% | Lung & bronchus | 109,690 | 14% |
| Colon & rectum | 73,420 | 9% | Colon & rectum | 70,040 | 9% |
| Urinary bladder | 55,600 | 7% | Uterine corpus | 47,130 | 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

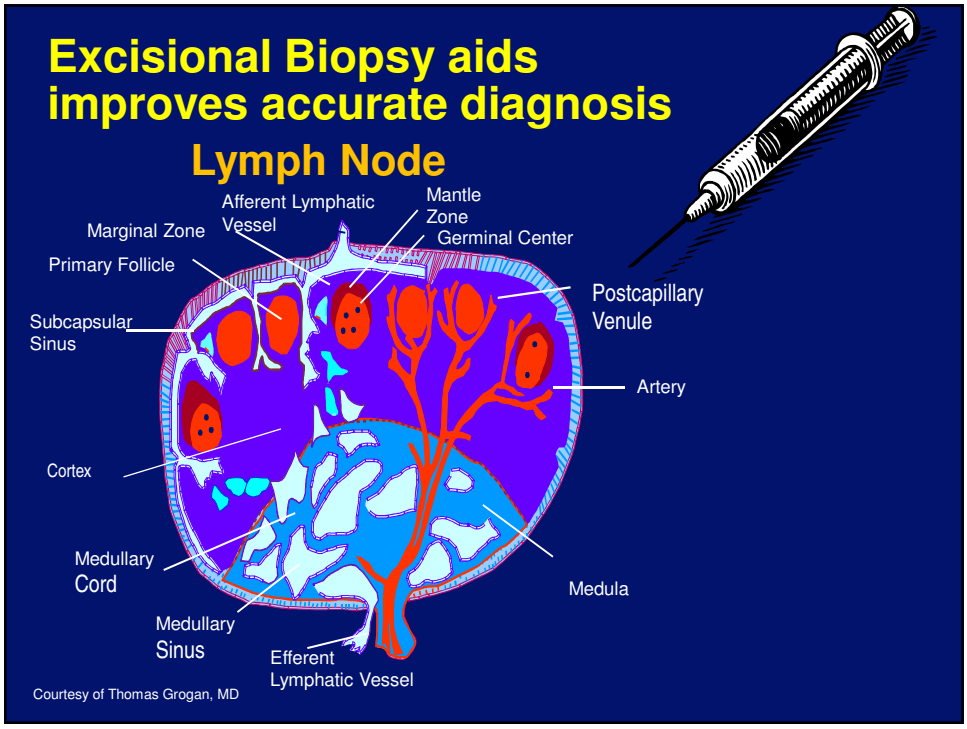
**B-cell**

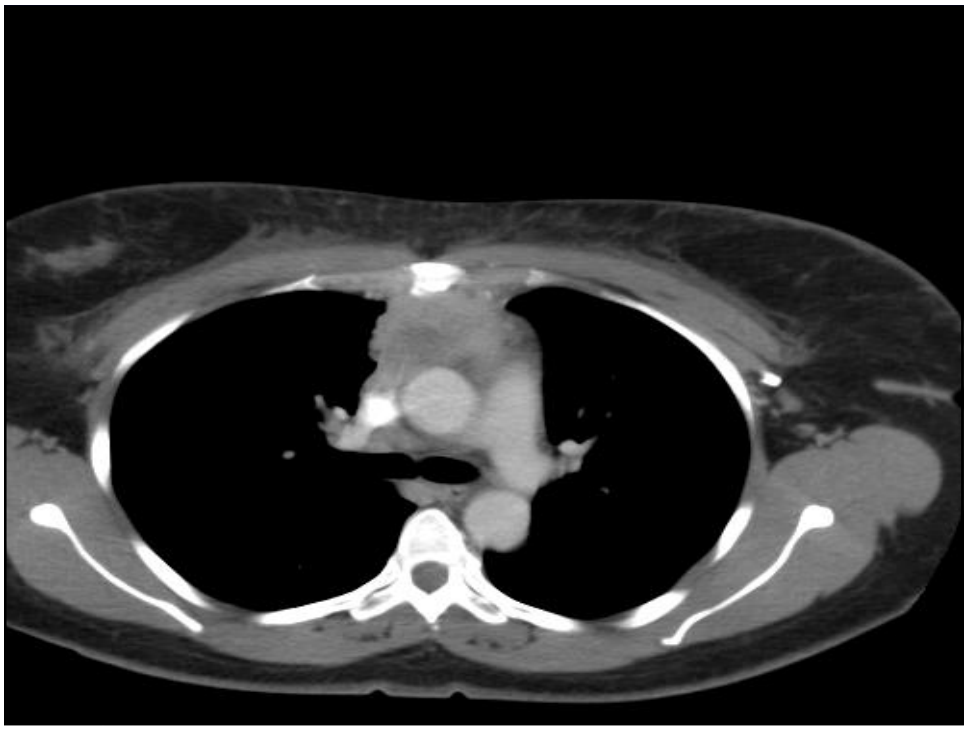
- Precursor B-cell neoplasms
  - B-acute lymphoblastic leukemia (B-ALL)
  - Lymphoblastic lymphoma (LBL)
- Peripheral B-cell neoplasms
  - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma/immunocytoma
  - Mantle cell lymphoma
  - 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 aids improves accurate diagnosis
Lymph Node
Afferent Lymphatic Vessel
Mantle Zone
Marginal Zone
Germinal Center
Primary Follicle
Postcapillary Venule
Subcapsular Sinus
Artery
Cortex
Medullary Cord
Medula
Medullary Sinus
Efferent Lymphatic Vessel
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

# WHO Classification

**B-cell**

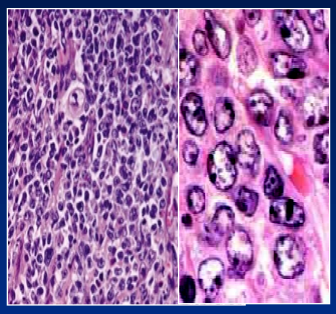
- Precursor B-cell neoplasms
  - B-acute lymphoblastic leukemia (B-ALL)
  - Lymphoblastic lymphoma (LBL)
- Peripheral B-cell neoplasms
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma/immunocytoma
  - Mantle cell lymphoma
  - 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.

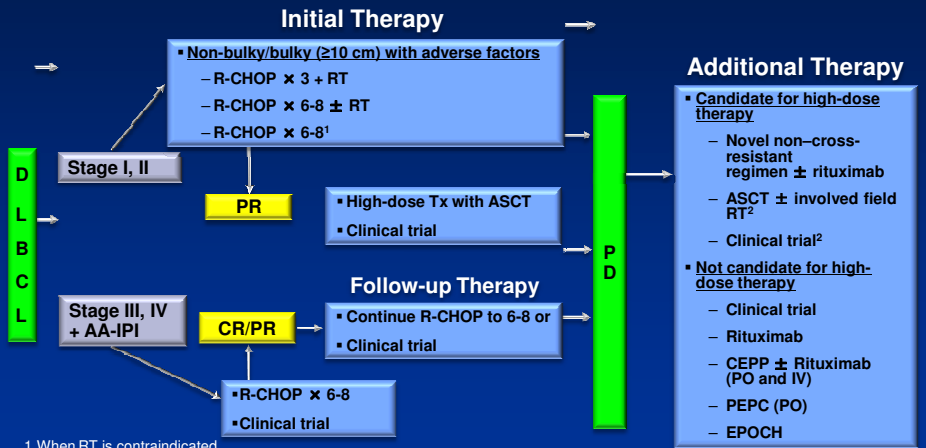
# Diffuse Large B-Cell Lymphoma



- 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)

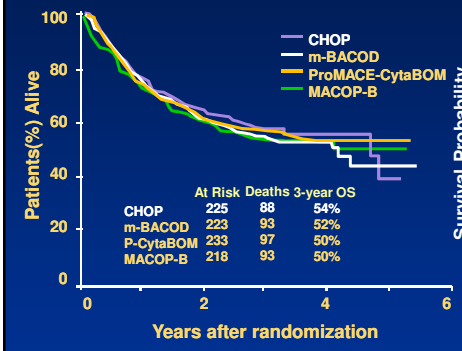
Michallet AS, et al. Blood Rev. 2009;23:11-23.

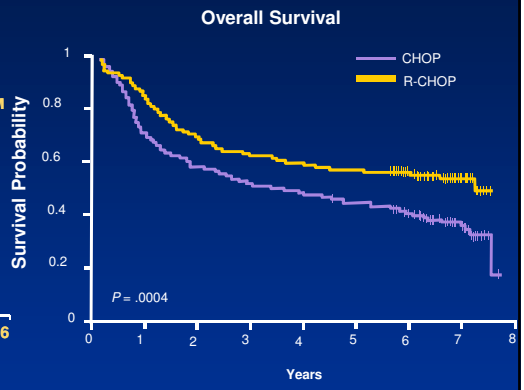
# DLBCL Management Strategy




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



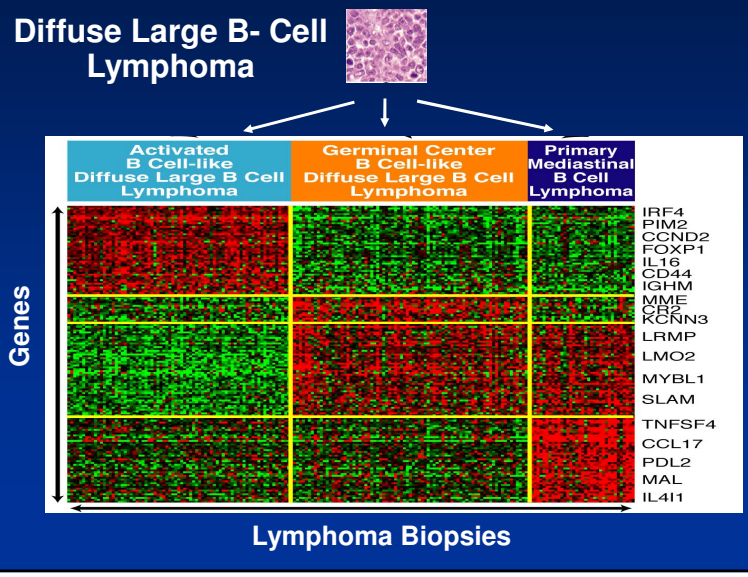




Fisher RI, et al. *N Engl J Med.* 1993

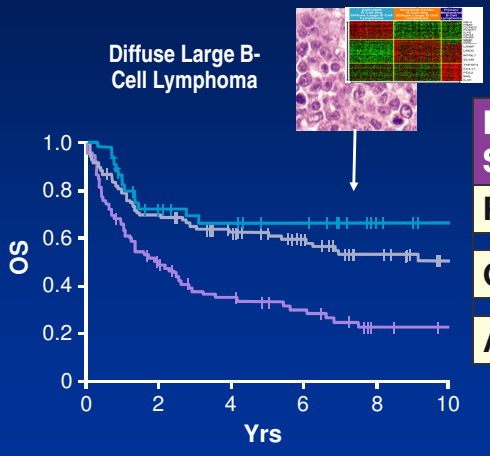
Coiffier B, et al. N Engl J Med. 2002.

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

# Genetic Testing Identifies Biologic and Clinically Different Types of DLBCL

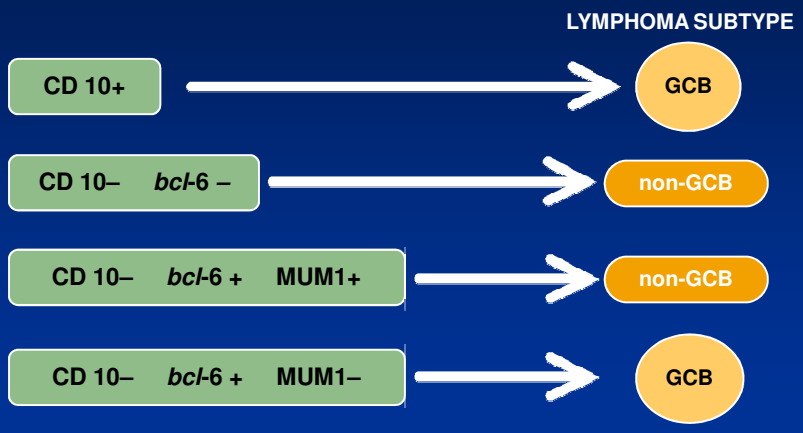


# Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL



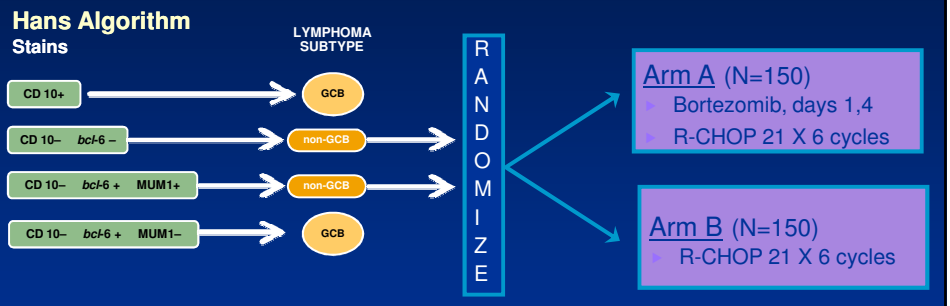

| DLBCL Subgroup | 5-Yr OS, % |
|---|---|
| PMBL | 64 |
| GCB DLBCL | 59 |
| ABC DLBCL | 30 |

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

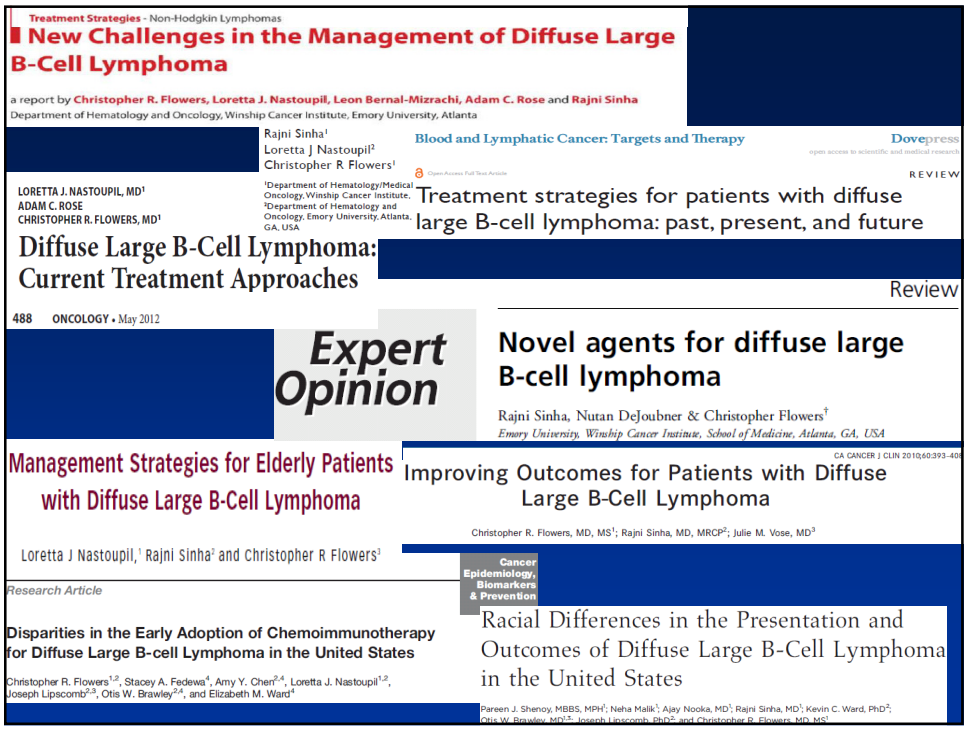



Hans et al. *Blood.* 2004;103:275.

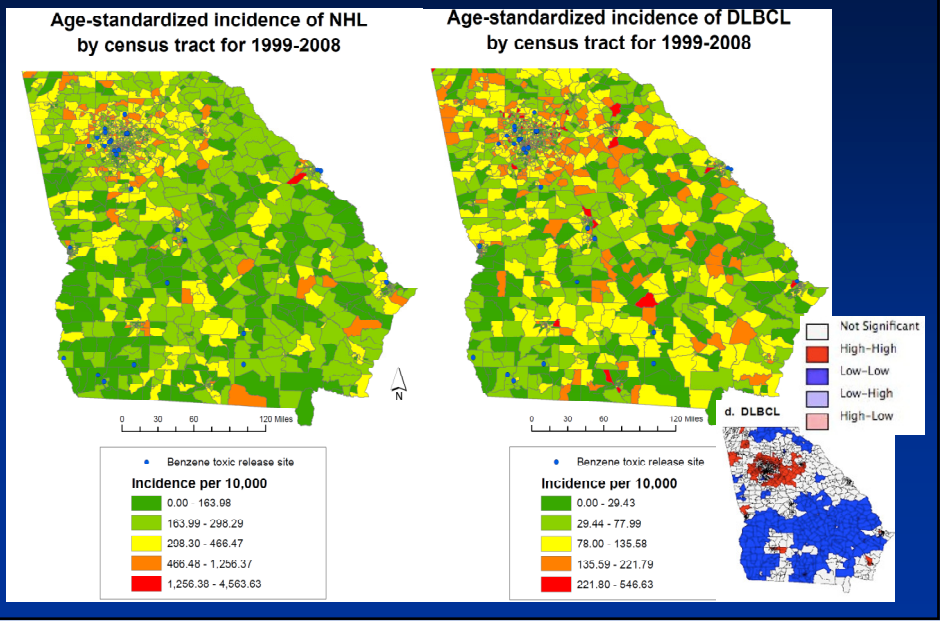
# Using DLBCL Biological Subtype to Choose Treatment




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

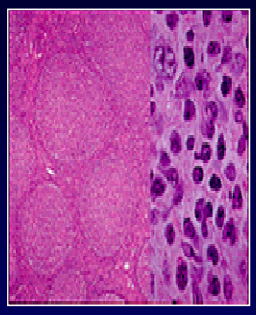


# Finding Causes for Lymphoma

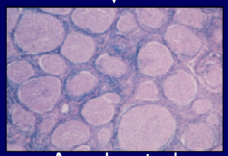



# Follicular Lymphoma (FL)

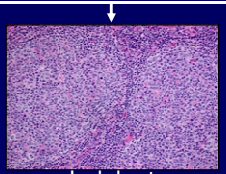
- Most common indolent NHL, accounts for ~22%-25% of NHL in North America
- Variable presentation and prognosis, but typically advanced stage at presentation
- Often asymptomatic
- Advanced stage FL not curable with standard therapy
- Median survival was about 10 years, but has increased with new treatments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



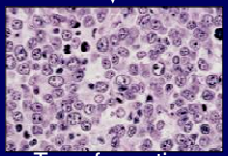
**Follicular Lymphoma**



Accelerated
10% to 15%



Indolent
40% to 65%

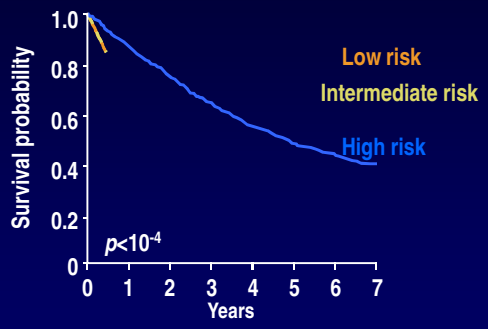


Transformation
20% to 60%

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

# Overall Survival According to FLIPI: Clinical Prognosis Factors

- No Nodal regions >4
- L LDH increased
- A Age ≥60
- S Stage III/IV
- H Hemoglobin <120 g/L

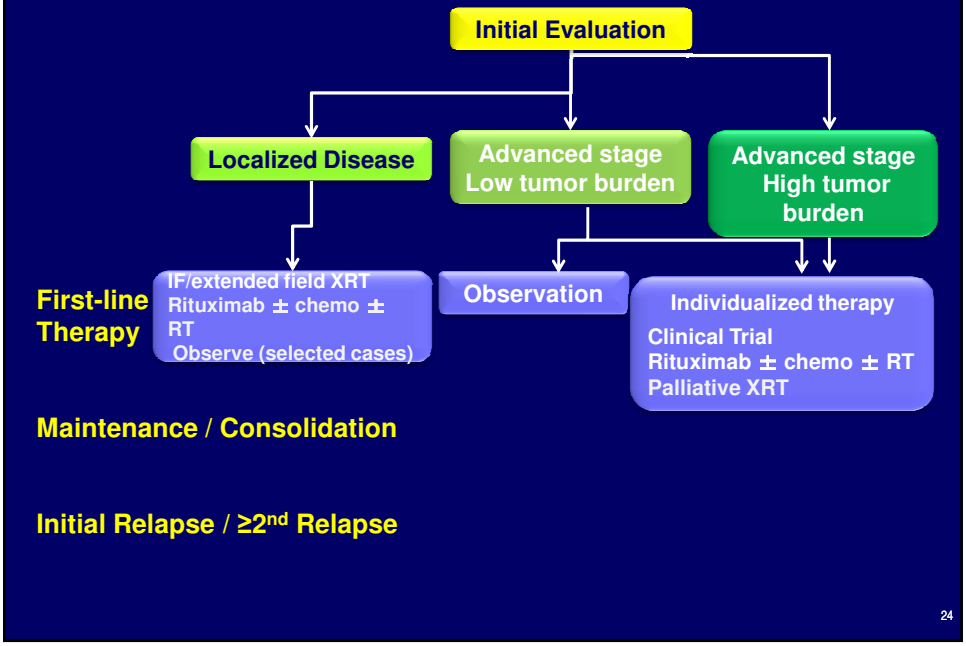



| Risk Group | No. of Factors | % of Pts | 5-y OS (%) | 10-y OS (%) |
|---|---|---|---|---|
| Low | 0-1 | 36 | 90.6 | 70.7 |
| Intermediate | 2 | 37 | 77.8 | 50.9 |
| High | 3-5 | 27 | 52.5 | 35.5 |

23

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

# A Management Approach for FL




24

# 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.

25

# 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).

26

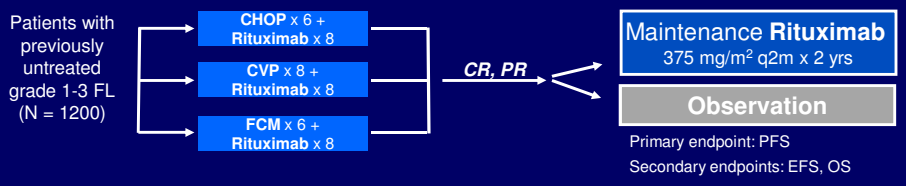
# Adding Rituximab to Front-Line Chemo for High Tumor Burden FL Improves Response Rates & Survival

| | | 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.

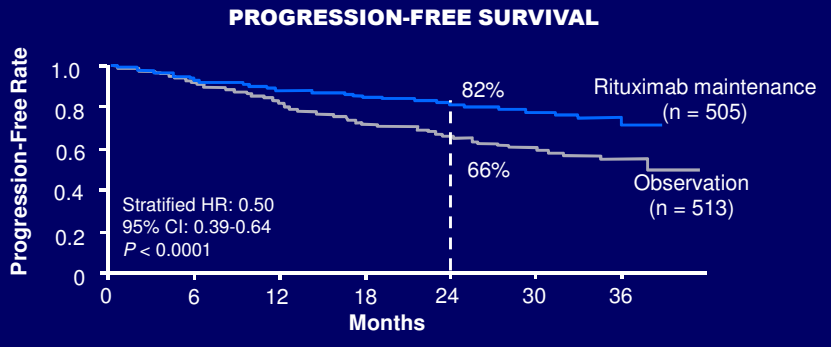
# Rituximab Maintenance vs Observation in FL

## GELA PRIMA Phase III Study




Primary endpoint: PFS

Secondary endpoints: EFS, OS




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

28

## 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

29

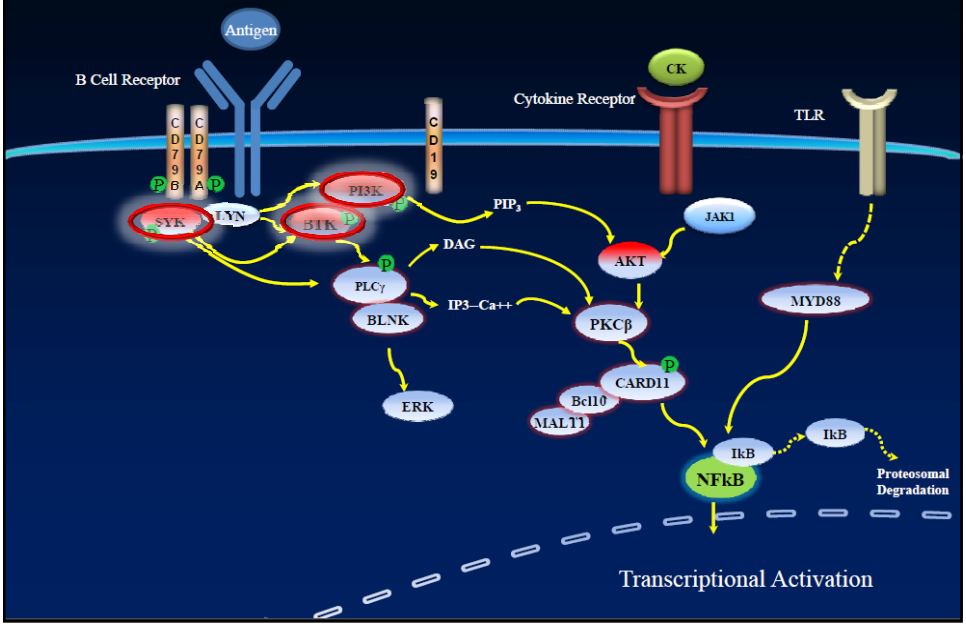
## Recurrent Follicular Lymphoma: Recommended Treatment

- 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.

30

# B-Cell Receptor Signaling




# 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

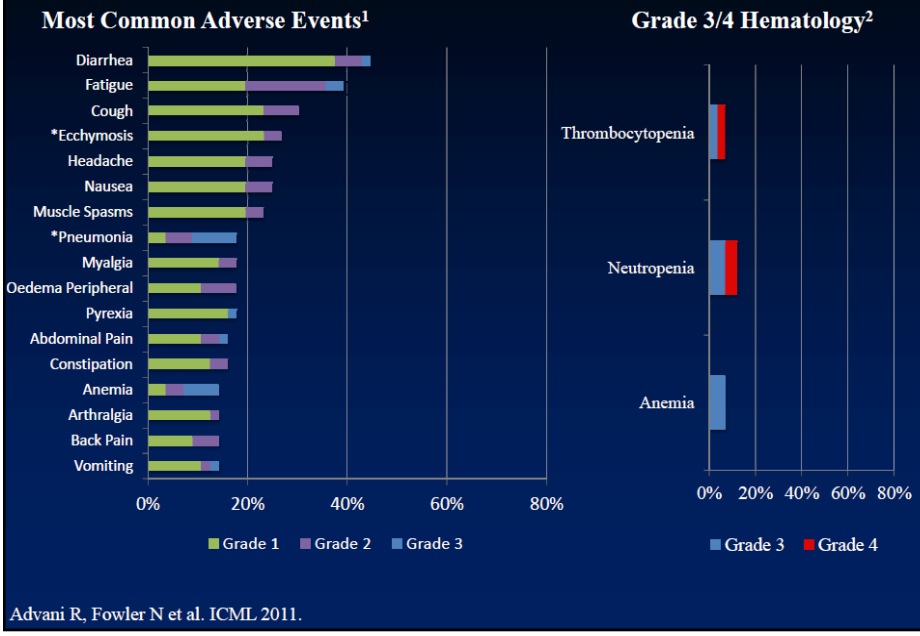
| Histology | N | CR | PR | SD | PD | NE | ORR% ITT (n=56) | ORR% Eval (n=50) |
|---|---|---|---|---|---|---|---|---|
| CLL/SLL | 16 | 1 | 10 | 3* | | 2 | 69% | 79% |
| MCL | 9 | 3 | 4 | 1 | 1 | | 78% | 78% |
| WM | 4 | | 3** | 1 | | | 75% | 75% |
| FL | 16 | 3 | 3 | 3 | 4 | 3 | 38% | 46% |
| MZL/MALT | 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

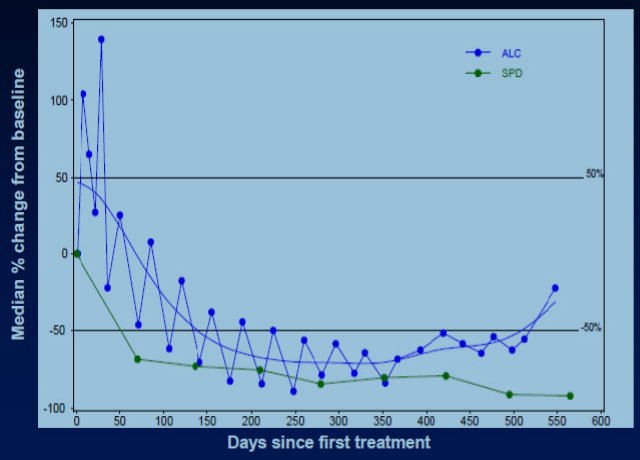
Advani R, Fowler N et al. ICML 2011.

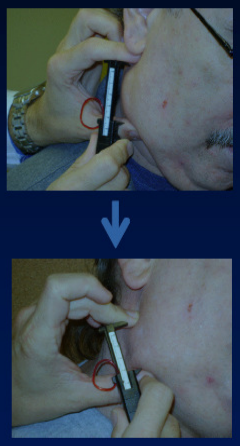
# Adverse Events: PCI-32765




Advani R, Fowler N et al. ICML 2011.

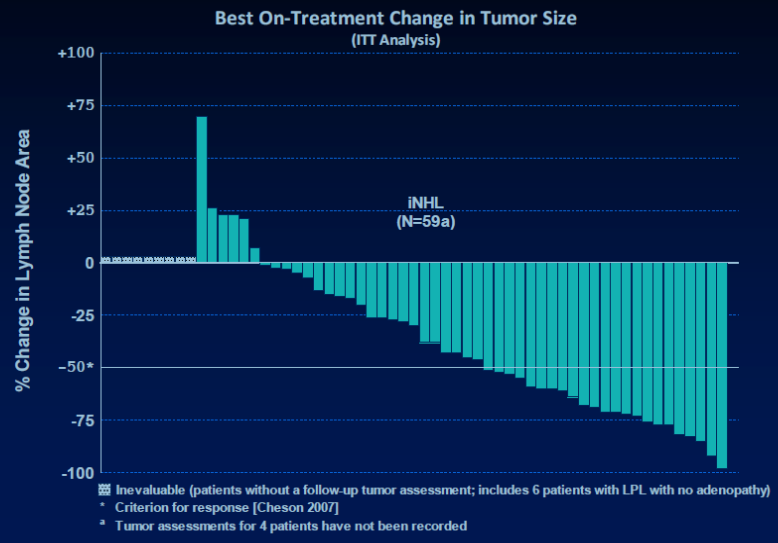
# Treatment-related Lymphocytosis: BTKi



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 |

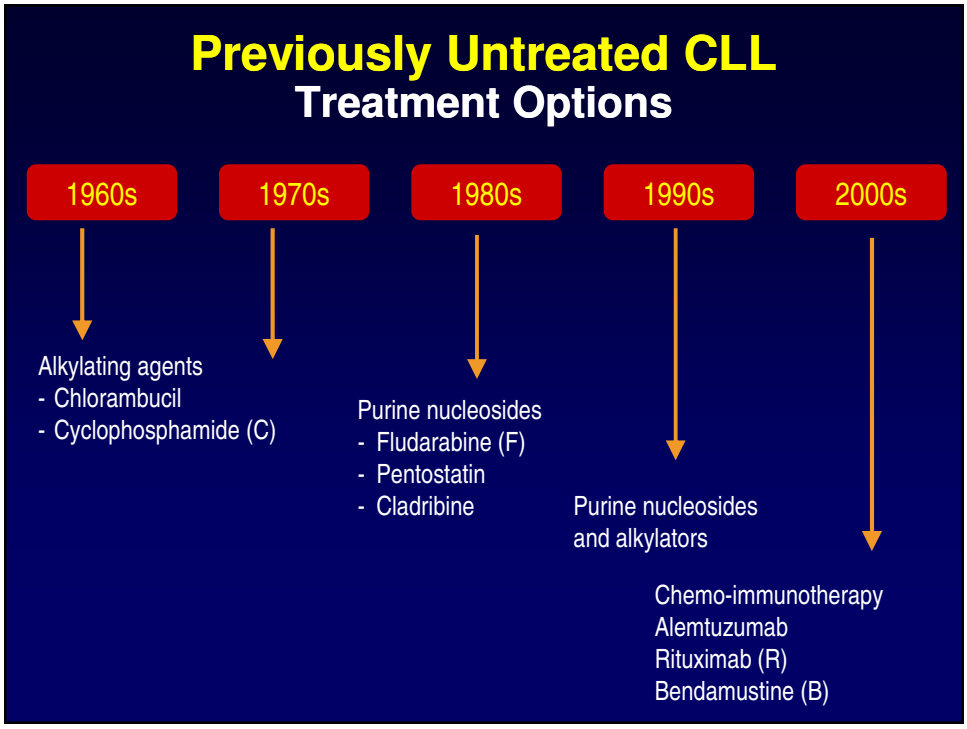
*Involved areas include cervical, axillary, or inguinal nodes, spleen, or liver.

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.




## 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

Hierarchy

Unfavorable

Favorable

- 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 $\beta_2$-microglobulin and soluble CD23

41

# 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

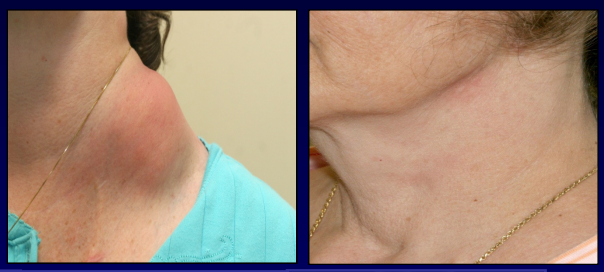
Relapse/Refractory
-FCR
-R-FCM
-CFAR
-Bendamustine
-Alemtuzumab
-Lenalidomide
-Ofatumumab
-Clinical Trial

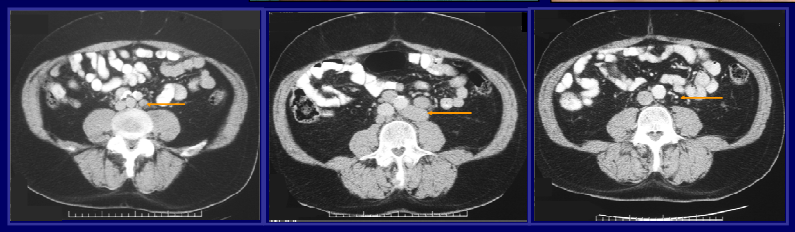
*Large phase III trials lacking for most of these approaches.

## 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**

NHL & CLL
*Diagnosis and Treatment Update*

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

# Question and Answer Session

NHL & CLL
*Diagnosis and Treatment Update*

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

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**