Welcome & Introductions

Dr. Hagemeister’s slides are available for download at www.LLS.org/programs

Diagnosis and Treating Slow Growing Non-Hodgkin Lymphomas

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Lymphoma: A Model for Basic Science and Clinical Research

- “Staging” – does the extent of disease make a difference?
- Combinations of drugs - better than “single-agent” therapies?
- Cytogenetics – a tool for better classification and basic science?
- Radiotherapy – a useful treatment?
- Prognostic factors – determining outcome?
- Antibody therapy – new targeted treatment?
- Gene Microarray Studies – understanding the basic cause of cancer?
- Molecular Studies-testing minor variations that make a difference?

### Frequency of Lymphoma Subtypes in Adults

![Image of pie chart showing the frequency of different lymphoma subtypes in adults.]

- Follicular lymphoma (22%)
- Diffuse large B-cell (31%)
- Mantle cell (6%)
- Composite lymphomas (13%)
- Small lymphocytic lymphoma (6%)
- Marginal zone B-cell lymphoma MALT type (5%)
- Marginal zone B-cell lymphoma nodal type (1%)
- Lymphoplasmacytic lymphoma (1%)

Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas

- Diagnosis
  - Possible Causes
  - Pathology
  - Clinical Evaluation
- Therapy
  - Follicular Lymphomas
  - Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia
  - Mantle Cell Lymphomas
  - Marginal Zone Lymphomas
  - T Cell Lymphomas

Possible Causes of Lymphomas

- Aging
- Immunodeficiency/Immunosuppression
  - Congenital - Ataxia telangiectasia, Wiskott-Aldrich, SCID
  - Acquired – HIV infection, organ transplant, aging, autoimmune disease
  - Drug induced – Immunosuppressants, organ or allogeneic SC transplantation
- Environmental/Toxic Exposure
  - Agent orange, dioxins, PCBs, pesticides, herbicides, solvents
- Radiation
  - Atomic bomb exposure, Nuclear reactor accidents, Therapeutic RT
- Chemotherapy
  - Methotrexate and other immunosuppressive drugs suspected
- Viruses
  - EBV, HIV, HTLV-1, Hepatitis C, Human Herpesvirus 8
- Bacteria
  - H. Pylori, B. burgdorferi, C. jejuni, C. psittaci
Primary Immunodeficiency Disorders Associated with NHL

- Wiskott-Aldrich Syndrome
- Ataxia Telangiectasia
- Common Variable Immunodeficiency
- X-Linked Immunoproliferative Syndrome
- SCIDS – “Bubble Boy”
- Autoimmune Lymphoproliferative Syndrome (ALPS)
- Job’s Syndrome (subcutaneous abscesses)

Autoimmune Disorders Associated with Development of Lymphomas

- Hashimoto’s Thyroiditis
- Sjogren’s Syndrome
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Sprue, Inflammatory Bowel Disease
- Autoimmune Hemolytic Anemia and Immunopathic Thrombocytopenic Purpura
- Dermatitis Herpetiformis
Models for Increased Risk of NHL in Patients with Autoimmune Disorders

• Chronic Immune Stimulation by Self Antigens
  – Defective apoptosis of B-cells
  – Impaired T-Cell function
  – Secondary inflammation

• Genetic Factors
  – Defects in inherited self-tolerance genes (TNF and IL-10 polymorphisms) with increased TNF, and increased NF-KB
  – Other polymorphisms possibly associated (IL-7, IL-12, IL-13, and Interferon-gamma)

• Environmental Factors
  – Dietary antigens (as in gluten, intestinal inflammation, and lymphoma)
  – Abnormal response to viral or other infectious agents.

Relative Risks of NHL for Patients with Selected Autoimmune Diseases

<table>
<thead>
<tr>
<th>Disorder</th>
<th>DLBCL</th>
<th>CLL</th>
<th>T-Cell</th>
<th>MCL</th>
<th>MZL</th>
<th>LPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1.8*</td>
<td>1.4</td>
<td>1.9</td>
<td>1.2</td>
<td>1.4</td>
<td>2.5*</td>
</tr>
<tr>
<td>SS</td>
<td>11*</td>
<td>--</td>
<td>UD</td>
<td>UD</td>
<td>28*</td>
<td>--</td>
</tr>
<tr>
<td>SLE</td>
<td>6.2*</td>
<td>--</td>
<td>UD</td>
<td>UD</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Celiac Dz</td>
<td>2.8*</td>
<td>0.5</td>
<td>17*</td>
<td>3.3</td>
<td>UD</td>
<td>3.4</td>
</tr>
<tr>
<td>DM (Type1)</td>
<td>1.3</td>
<td>3.6*</td>
<td>UD</td>
<td>5.0*</td>
<td>2.8</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Autoimmune Diseases for which there are cases, but there either no cases in the “Control Group” or the Relative Risk of NHL is not statistically significant include: Crohn’s disease, Ulcerative Colitis, Sarcoidosis, and Psoriasis

* P < 0.05; UD: No cases in the control group; --: Too few cases in the AD or the control group

Clinical Features of 126 Patients with RA and Risk of Lymphoma (2905 Controls)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Risk of NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : Female</td>
<td>0.8 : 9.2</td>
</tr>
<tr>
<td>Duration of Disease &lt;5 : &gt;5 yrs</td>
<td>2.4 : 1.4</td>
</tr>
<tr>
<td>Family history Autoimmune Disorders</td>
<td>1.1</td>
</tr>
<tr>
<td>ESR &gt; 45</td>
<td>2.8</td>
</tr>
<tr>
<td>Severe Small : Severe Large Joint Damage</td>
<td>10.5 : 29.3</td>
</tr>
<tr>
<td>Steroids/NSAIDS Therapy</td>
<td>1.5</td>
</tr>
<tr>
<td>NSAIDS &gt; 10 yrs</td>
<td>1.9</td>
</tr>
<tr>
<td>Immunosuppressant Therapy</td>
<td>3.5</td>
</tr>
<tr>
<td>Immunosuppressants &gt; 10 yrs</td>
<td>5.8</td>
</tr>
</tbody>
</table>


Drugs Associated with Development of Lymphoproliferative Disorders

- TNF-Blockers (Used for other inflammatory disorders besides those listed)
  - Eternacept: Approved for RA, psoriasis, ankylosing spondylitis
  - Associated with NHL in RA (one study), maybe other solid tumors
  - Infliximab: For RA, Crohn’s, amylosing spondylitis, psoriasis, UC
  - Combined with azathioprine or 6-MP, associated with hepatosplenic T-cell NHL
  - Adalimumab: Same as eternacept
- Alemtuzumab
  - In combination With CHOP for aggressive T-cell NHL
  - 3/20 developed EBV+ lymphoproliferative disorders
- Methotrexate in rheumatoid arthritis patients
  - Reports of regression following discontinuation
  - WHO Latrogenic Immunodeficiency-associated LPD

Clinical Features of Lymphomas in 76 Patients with RA

<table>
<thead>
<tr>
<th>Feature</th>
<th>MTX-LPD</th>
<th>Non-MTX LPD</th>
<th>All Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Pts</td>
<td>48</td>
<td>28</td>
<td>76</td>
<td>150</td>
</tr>
<tr>
<td>Med. Age</td>
<td>67</td>
<td>66</td>
<td>66#</td>
<td>58</td>
</tr>
<tr>
<td>Percent male</td>
<td>32</td>
<td>19</td>
<td>28*</td>
<td>62</td>
</tr>
<tr>
<td>Mo from RA-LPD</td>
<td>132@</td>
<td>240</td>
<td>144</td>
<td>NA</td>
</tr>
<tr>
<td>Percent Stage I/II</td>
<td>38</td>
<td>40</td>
<td>38+</td>
<td>28</td>
</tr>
<tr>
<td>5 yr OS, %</td>
<td>59</td>
<td>53</td>
<td>59^</td>
<td>75</td>
</tr>
</tbody>
</table>

Comparisons with P = 0.05:
- # RA cases with LPDs were older than were controls
- More women had LPDs with RA than did men compared with controls
- @ MTX-LPDs occurred earlier in diagnosis of RA than did non-MTX-LPDs
- + RA-LPDs were more often early staged than controls
- ^ 5-yr OS rates were worse for RA-LPDs that were controls


Other Inflammatory Disorders for Which There May Be an Increased Risk of NHL

- Hashimoto’s thyroiditis (local MZL excepted)
- Polymyositis/Dermatomyositis (small #s)
- Psoriasis (problems in pathology)
- Spondylarthropathies (small #s)
- Systemic Sclerosis (small #s)
- Wegener’s granulomatosis (problems with pathology)
Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas

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Lymph Nodes and Lymphatic Vessels: Important Parts of the Immune System

- Lymph nodes
- Lymphatic vessels
- Blood vessel entering the lymphatic system
- Lymphocytes in outflowing lymph
- Effervescent lymph vessel
- Affterent lymph vessels
- Cortex
- Medulla
- Capsule
A Normal Lymph Node Under the Microscope

1. Capsule; 2. Subcapsular sinus; 3. Follicle (Germinal Center); 4. Lymphoid Nodule; 5. Trabeculae.

Some Lymphomas Get Their Names from Where the Normal Cell Counterpart Is Found

- Follicle Center
- Mantle Zone
- Marginal Zone
Examples of Various Proteins on the Surface of B Cell Lymphomas

- CD19
- CD22
- CD23
- CD40
- CD80
- CD20

An antibody that attaches to these proteins can be found under the microscope.

“Markers” That Make a Difference in Diagnosis of Indolent Lymphomas

- “Markers” are sugar/protein complexes that are produced by cells.
- They can be produced by both cancer cells and normal cells.
- These can be studied under the microscope to identify certain types of lymphomas.

<table>
<thead>
<tr>
<th>Marker</th>
<th>FL</th>
<th>SLL/CLL</th>
<th>MCL</th>
<th>MZL</th>
<th>T Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>CD10</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>CD5</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>CD23</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>t(14;18)</td>
<td>Various</td>
<td>Various</td>
<td>t(11;14)</td>
<td>Various</td>
</tr>
</tbody>
</table>

- CD: Cluster of Differentiation
- Not all are absolute: There are often variations in positivity/negativity.
- Note: The genetics are only in the cancer cells.
One of the best known cytogenetic abnormalities in cancer management is the t(14;18)(q32;q21) translocation in follicular lymphoma. This translocation results in the overexpression of the BCL-2 protein, which is important in the therapy of these specific diseases.

CD20 expression in B-cell malignancies is shown in a histogram where Hairy cell, Large cell, Burkitt’s lymphoma, Marginal zone, Follicular small cell, Small cleaved, LP/Waldenström’s, Mantle cell, CLL/PLL, and CLL are listed. The mean channel fluorescence ranges from 0 to 500, with values indicating the expression level of CD20. The histogram shows that different histologies have varying CD20 expression, which is important because it may suggest how well Anti-CD20 antibodies work in therapy of these specific diseases.

Adapted with permission from D. Maloney.
Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas

• Diagnosis
  • Possible Causes
  • Pathology
  • Clinical Evaluation

• Therapy
  • Follicular Lymphomas
  • Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia
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  • Marginal Zone Lymphomas
  • T Cell Lymphomas

How Are Patients Found to Have Slow-Growing (Indolent) Lymphomas?

The fastest growing cancer is a lymphoma; the slowest growing cancer is a lymphoma
The most common “presentation” is a painless lump, but pain can be an important initial clue to diagnosis in aggressive lymphomas
Other symptoms depend upon the location of the disease: back, chest, or abdominal pain can occur with slow-growing lymphomas
Bone marrow involvement can result in low blood counts (hemoglobin, platelets)
Unusual sites of disease: Gastrointestinal Tract, Kidney, Lung, and Other Organs
Tests in the Evaluation of Indolent NHL

- A Biopsy: The most important test
  - FNA (Fine needle aspirate)
    - Usually inadequate (loose cells)
  - "Excisional" biopsy recommended
  - CORE biopsy (larger needle) may be as good
    - Evaluates nodal "architecture"
- Xrays (Radiographs) and Other Tests
  - CAT (computerized axial tomography) Scan
    - Most common method to evaluate disease extent (nodes, organs)
  - PET (Positron Emission Tomography) not mandatory.
  - Bone Marrow Biopsy useful, and necessary in some
  - Other special tests may be useful
    - MRI (Magnetic Resonance Imaging)
    - Gastroscopy or Colonoscopy

Indolent Lymphomas: Problems and Questions

- Should FL, SLL/CLL, and MZLs be treated differently?
  A. Marrow Involvement
    1. Follicular Lymphomas rarely cause blood involvement although marrow is positive
    2. SLLs can be diseases with massive lymph node involvement, and yet very minimal marrow disease
    3. MZLs involve the bone marrow sometimes, but most often in the splenic type
Indolent Lymphomas: Problems and Questions

B. Extranodal Disease
1. FLs rarely present with disease outside of lymph nodes, esp. Gastrointestinal sites, until transformation
2. SLLs can be indistinguishable from MZLs when disease is present outside of nodes
3. MZLs often have disease outside of the lymph nodes, but the nodal form is poorly defined

Indolent Lymphomas: Problems and Questions

C. Risk of Transformation
1. FLs have the perhaps the highest risk, but when and how the diagnosis is made can be difficult: Bulkiness, Pure DLCL, CT type?
2. Grading of FLs is very subjective: FLCL?
3. Transformation may not be such a bad thing at initial diagnosis
4. SLL/CLLs transform infrequently and may be a very poor risk feature: Richter’s Syndrome
5. MZLs transform at an unknown rate, despite classic involvement outside of lymph nodes
Indolent Lymphoma: Treatment Choice Considerations

• Efficacy
• Patient’s age
• Prior therapies
• Safety profile
• The FLIPI (Follicular Lymphoma International Prognostic Index)
• Patient Choice
• Future therapies
• AE management
• QOL
• Treatment goals and expectations
• Even with advanced disease, Observation is an option

Indications for Treatment by GELF Criteria

Involvement of 3 nodal sites, each with a diameter of ≥ 3 cm
Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm
B symptoms
Splenomegaly
Pleural effusions or peritoneal ascites
Cytopenias (leukocytes < 1.0 × 10^9/L and/or platelets < 100 × 10^9/L)
Leukemia (> 5.0 × 10^9/L malignant cells)

**Standard Regimens for Therapy of Indolent Lymphomas**

- **Initial Therapy**
  - Single-Agent Rituximab
  - Bendamustine + Rituximab
  - R-CHOP
  - Fludarabine-like Regimens

- **Relapsed Disease**
  - Any of the above
  - Lenalidomide + Rituximab

- **Regimens not often used**
  - Platinum-, Gemcitabine-, Etoposide-Based Regimens

**Novel Therapies in Treatment of Lymphomas**

- **moAbs**
  - Anti-CD20 (obinutuzumab and ofatumumab), as well as other antigens on the cell surface (eg, CD19, CD22)

- **IMiDs**
  - Lead drug is lenalidomide, which has efficacy in multiple NHL subtypes (ie, MCL, FL, DLBCL, T-cell lymphoma)

- **PI3K and BTK Inhibitors**
  - Have effects in CLL and subtypes of aggressive and indolent lymphomas

- **BCL2 Inhibitors**
  - Induce expression of costimulatory molecules and tumor immunity in melanoma, Hodgkin lymphoma, and NHLs

- **PD-1 moAbs**
  - Effective in Hodgkin's and other lymphomas

- **CAR T-Cell Therapy**
  - Significant activity, especially in aggressive lymphomas and leukemias

Btk: Bruton’s tyrosine kinase; CAR: chimeric antigen receptor; CLL: chronic lymphocytic leukemia; IMiD: immunomodulatory drug; mAb: monoclonal antibody; MCL: mantle cell lymphoma; NHL: non-Hodgkin lymphoma; PI3k: phosphoinositide-3-kinase; PD-1: programmed death-1
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WHO Histologic Grading of Follicular Lymphoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histology</th>
<th>Clinical Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-5 centroblasts/HPF</td>
<td>Indolent</td>
</tr>
<tr>
<td>2</td>
<td>6-15 centroblasts/HPF</td>
<td>Indolent</td>
</tr>
<tr>
<td>3a</td>
<td>&gt;15 centroblasts/HPF, centrocytes present</td>
<td>Indolent-Aggressive</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;15 centroblasts/HPF, centrocytes absent; centroblasts in large sheets</td>
<td>Aggressive (similar to LCL)</td>
</tr>
</tbody>
</table>

Mortality According to FLIPI Index Using “NoLASH”

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Number Factors</th>
<th>% Patients (n = 1795)</th>
<th>5-year OS (%)</th>
<th>10-year OS (%)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>0-1</td>
<td>36</td>
<td>91</td>
<td>71</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>37</td>
<td>78</td>
<td>51</td>
<td>2.3</td>
</tr>
<tr>
<td>Poor</td>
<td>≥ 3</td>
<td>27</td>
<td>53</td>
<td>36</td>
<td>4.3</td>
</tr>
</tbody>
</table>

No = 5 or more Nodal Sites of Involvement

L = Elevated LDH  
A = Age Greater than 60  
S = Stage III – IV  
H = Hemoglobin 12 or Less


Prognosis of FL: OS Related to Duration of EFS Following Initial Therapy

- EFS: absence of progression, relapse, retreatment, or death

Patients with EFS > 1 Yr
Similar OS rate to that of the general US population

Patients with EFS < 1 Yr
Significantly inferior OS rate compared with the general US population

**Disease and Patient Features of FL with POD in 24 Months Versus Others**

- Retrospective analysis of patients in LymphoCare Study
- Therapy: R-CHOP-588 pt; R-CVP-280; R-Flu-207
- Comparison of those with POD < 24 vs > 24 mo (Reference)

<table>
<thead>
<tr>
<th>Features</th>
<th>Early POD, N (%)</th>
<th>Reference, N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pts Total</td>
<td>110</td>
<td>420</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38 (35)</td>
<td>200 (48)</td>
<td>NS</td>
</tr>
<tr>
<td>Gr 1-2</td>
<td>63 (66)</td>
<td>227 (60)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33 (34)</td>
<td>150 (40)</td>
<td>0.33</td>
</tr>
<tr>
<td>Missing</td>
<td>14</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>FLIPI 0-1</td>
<td>10 (12)</td>
<td>92 (26)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29 (34)</td>
<td>119 (34)</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>47 (55)</td>
<td>140 (40)</td>
<td>0.007</td>
</tr>
<tr>
<td>Missing</td>
<td>24</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

*Casulo et al. JCO 33: 2516-2522, 2015.*

**OS According to POD Less Than or More Than 24 Months From Start of Therapy**

The LymphoCare Database | U Iowa and Mayo Database (Validation Set)
--- | ---

By MVA, PS > 2, Age > 60 and ≥ 4 Nodal Sites (FLIPI features) and POD < 24 Mo were adverse features for OS.

*Casulo et al. JCO 33: 2516-2522, 2015.*
Transformed FL Outcomes from the LymphoCare Database

- PFS and OS rates were not statistically different for those with suspected (S) versus confirmed (biopsy-proven) T-FL.

- Clinical features of ST-FL (Vancouver): LDH >2XNL, rapid single node growth, new ENS, new B SX, hypercalcemia (not collected in this study).


The M7-FLIPI: A Prognostic Model for Prediction of POD24

- Evaluation of 74 genes from 151 pts with FL who received R-CHOP and interferon maintenance.
- Selected genes that appeared mutated in more than 5 patients.
- Calculated FFS models using high Risk FLIPI and other clinical and lab features.
- Generated models that incorporated molecular features of 7 genes providing best FFS discrimination.
- Validated: BCCA Cohort receiving R-CVP and MR.

**Foll05 Trial: R-CVP vs R-CHOP vs R-FN: 3 Year TTF and OS Results**

- **R-CHOP**
  - TTF: 64%
  - OS: 95%

- **R-CVP**
  - TTF: 46%
  - OS: 98%

- **R-FN**
  - TTF: 61%
  - OS: 93%

Federico et al. ASCO 2012 (abst 8006).

**BR vs R-CHOP for Indolent Lymphomas**

- **Follicular Lymphoma**
  - Median (Q1-Q3; months): 18.7 (0.8-42.0)
  - Hazard Ratio (95% CI): 0.64 (0.35-1.17)
  - p-value: 0.107

- **Mantle Cell Lymphoma**
  - Median (Q1-Q3; months): 29.1 (15.0-32.6)
  - Hazard Ratio (95% CI): 1.0 (0.38-2.86)
  - p-value: 0.964

- **Marginal Zone**
  - Median (Q1-Q3; months): 57.2 (26.0-72.0)
  - Hazard Ratio (95% CI): 0.49 (0.28-0.87)
  - p-value: 0.016

- **Waldenstrom’s**
  - Median (Q1-Q3; months): 18.1 (13.0-21.0)
  - Hazard Ratio (95% CI): 0.92 (0.52-1.60)
  - p-value: 0.806

R² for Untreated FL: Response by Tumor Burden and Molecular Features

By GELF Criteria (N=46)

<table>
<thead>
<tr>
<th>Tumor Burden</th>
<th>SD</th>
<th>PR</th>
<th>CR/CRu</th>
<th>ORR</th>
<th>SD</th>
<th>PR</th>
<th>CR/CRu</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>0</td>
<td>1</td>
<td>21(95%)</td>
<td>100%</td>
<td>1</td>
<td>4</td>
<td>19(79%)</td>
<td>96%</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>1</td>
<td>21(95%)</td>
<td>100%</td>
<td>1</td>
<td>4</td>
<td>19(79%)</td>
<td>96%</td>
</tr>
</tbody>
</table>

By Bulk of Disease (N=46)

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>SD</th>
<th>PR</th>
<th>CR/CRu</th>
<th>ORR</th>
<th>SD</th>
<th>PR</th>
<th>CR/CRu</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulky</td>
<td>1</td>
<td>12</td>
<td>92%</td>
<td>100%</td>
<td>1</td>
<td>4</td>
<td>28(85%)</td>
<td>97%</td>
</tr>
<tr>
<td>Non-Bulky</td>
<td>1</td>
<td>12</td>
<td>92%</td>
<td>100%</td>
<td>1</td>
<td>4</td>
<td>28(85%)</td>
<td>97%</td>
</tr>
</tbody>
</table>

Molecular Response (N=44 Evaluable, Marrow and Blood)

<table>
<thead>
<tr>
<th>PCR Status</th>
<th>PRETREATMENT</th>
<th>POST CYCLE 3</th>
<th>POST CYCLE 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR Positive</td>
<td>17(41%)</td>
<td>5(11%)</td>
<td>2(5%)</td>
</tr>
<tr>
<td>PCR Negative</td>
<td>26(59%)</td>
<td>39(89%)</td>
<td>42(95%)</td>
</tr>
</tbody>
</table>


R² for Untreated follicular and Other Indolent NHLs: PFS and OS Results

Obinutuzumab-CIT vs Rituximab-CIT for Untreated FL: The Gallium Study

Marcus et al. ASH 2016, abstract 6. Results for other iNHLs pending.

Phase 3 Obinutuzumab/Bendamustine vs Bendamustine for R-Refractory FL

Cheson et al. ASH 2016, abstract 615.
Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas

- Diagnosis
  - Possible Causes
  - Pathology
  - Clinical Evaluation

- Therapy
  - Follicular Lymphomas
  - Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia
  - Mantle Cell Lymphomas
  - Marginal Zone Lymphomas
  - T Cell Lymphomas

CLL Management—How Far We’ve Come

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>Wait and Watch or Alkylating Agents</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>5% CR</td>
</tr>
<tr>
<td></td>
<td>30%-50% ORR</td>
</tr>
<tr>
<td>1970s</td>
<td>Chemoimmunotherapy</td>
</tr>
<tr>
<td></td>
<td>FCR, FR, PCR, BR</td>
</tr>
<tr>
<td></td>
<td>41%-70% CR</td>
</tr>
<tr>
<td></td>
<td>90%-95% ORR</td>
</tr>
<tr>
<td>1980s</td>
<td>Purine Analog               Alkylators</td>
</tr>
<tr>
<td></td>
<td>Fludarabine, Pentostatin, Cladribine</td>
</tr>
<tr>
<td></td>
<td>20%-30% CR</td>
</tr>
<tr>
<td></td>
<td>50%-80% ORR</td>
</tr>
<tr>
<td>1990s</td>
<td>Purine Analogs + Alkylators</td>
</tr>
<tr>
<td></td>
<td>FC, PC</td>
</tr>
<tr>
<td></td>
<td>35% CR</td>
</tr>
<tr>
<td></td>
<td>75%-90% ORR</td>
</tr>
<tr>
<td>2000s</td>
<td>TKIs</td>
</tr>
<tr>
<td></td>
<td>Ibrutinib, acalabrutinib, idelalisib, duvelisib</td>
</tr>
<tr>
<td></td>
<td>mAb (anti-CD20)</td>
</tr>
<tr>
<td></td>
<td>Obinutuzumab, Ofatumumab</td>
</tr>
<tr>
<td>2005-2016</td>
<td>TKIs + Purine Analogs + Alkylators + mAb (anti-CD20)</td>
</tr>
</tbody>
</table>

Traditional and Newer PFs associated With Inferior OS in CLL

- **Traditional PFs**
  1. Advanced stage at diagnosis
  2. Short lymphocyte doubling time
  3. Diffuse pattern of bone marrow disease
  4. Advanced age / male
  5. $\uparrow$ $\beta$-2 microglobulin or circulating CD23
  6. $\uparrow$ prolymphs (PLL)

- **Newer PFs**
  1. FISH cytogenetics
     - 17p del: agg dz
     - 11q del: agg dz
     - 13q del: indolent dz
  2. Unmutated IgV<sub>H</sub> (<2% homology with germline)
  3. ZAP70 ($\geq$ 20% positive)
  4. CD38 ($\geq$ 30% positive)

---

FCR vs BR in Pts With Advanced CLL: PFS

**ITT PFS = Primary Endpoint**

- Median PFS:
  - FCR: 55.2 mos
  - BR: 41.7 mos

**PFS in IGHV-Matched Population**

- Median PFS:
  - FCR: NR
  - BR: 43.1 mos

MR After FCR for Untreated CLL: The French FILO CLL 2007 Trial

- 409 pts with untreated CLL, >65 yrs, in CR/PR. No del(17p).
- Therapy: 4 cycles of FCR, followed by MR (500 mg/m2 q 2 mo for 2 yr) vs Observation
- CR/CRi = 38%. Stratified by del(11q), CR/PR, and IGHV status.

<table>
<thead>
<tr>
<th>Maintenance R (202)</th>
<th>Observation (207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mo)</td>
<td>59.3</td>
</tr>
<tr>
<td>3 Yr PFS (%)</td>
<td>83</td>
</tr>
<tr>
<td>3 Yr OS (%)</td>
<td>92.6</td>
</tr>
<tr>
<td>Secondary Cancer</td>
<td>15.3</td>
</tr>
<tr>
<td>Heme SAEs*</td>
<td>6.9</td>
</tr>
<tr>
<td>Infectious SAEs*</td>
<td>18.8</td>
</tr>
</tbody>
</table>

- PFS also better with MR for those with/without del(11q) or unmutated IGHv

Dartigeas et al. ASCO 2016 (abst 7505). * P < 0.05.

Maintenance Ofatumumab vs Observation for 2nd or 3rd CR/PR: The PROLONG study

After a median follow-up of 19.1 months

Approved by FDA
Maintenance Len After Initial Therapy for “High –Risk” Disease: CLL M1 Study

- Median observation time of 17.7 months

Median PFS
Placebo group: 14.6 mos
Lenalidomide group: NR
HR 0.198
[95% CI: 0.083-0.475]

CLL11 Results: OS in Older Patients

Obinutuzumab-chlorambucil is associated with significant OS benefit vs chlorambucil

No statistically significant difference in OS is noted vs rituximab-chlorambucil

* OS results are not yet mature
Ibrutinib (BTK Inhibitor) for High-Risk CLL: RESONATE-2 Survival Outcomes

CR rate improved from 11% to 18% with longer f/u: at 29 mo: 88% reduction in risk of PD or death with ibrutinib vs CHL

Tedeschi A et al. ASH 2015. Abstract 495.

Ib + BR vs PL + BR for Rel CLL: HELIOS

- Investigator-assessed HR for ib + BR vs pl + BR: 0.201 (CI: 0.145-0.278)
- No Richter’s observed on the ib and 3 on the pl arms

Chanan-Khan et al. ASCO 2015; LBA 7005
Idelalisib (PI3Kδ Inhibitor): Phase 3 Summary in CLL

- Phase 3 summary of efficacy in relapsed/refractory CLL (N = 220)
- 150-mg BID dose tested
- Patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>Idelalisib + Rituximab</th>
<th>Rituximab</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>81</td>
<td>13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>Not reached</td>
<td>5.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12-month OS, %</td>
<td>92</td>
<td>80</td>
<td>.02</td>
</tr>
</tbody>
</table>

HR for PFS (progression or death) = 0.15
HR for OS (death) = 0.28


Idelalisib + BR for Relapsed/Refractory CLL

- Primary endpoint: PFS

- Reduced risk of both PD and death
- Increased PFS
- Increased OS (HR 0.55; stratified P = .008)

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + BR</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>23.1</td>
<td>11.1</td>
</tr>
<tr>
<td>HR, P</td>
<td>0.33, &lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

* Bendamustine 70 mg/m² days 1, 2 Q4W, cycles 1-6; rituximab 375 mg/m² cycle 1, 500 mg/m² cycles 2-6.

Zelenetz AD et al. ASH 2015. Abstract LBA-5.
Emerging Strategies for Therapy of Lymphomas: Bcl-2 Inhibition

Venetoclax: orally bioavailable, selective Bcl-2 inhibitor that induces apoptosis in CLL cells independent of p53
- 79% ORR in early clinical studies in relapsed/refractory CLL


Venetoclax Monotherapy: Phase 2 Study in Relapsed/Refractory del(17p) CLL (N = 107)

Response and Main Safety Findings

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>IRC</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>85 (79.4)</td>
<td>79 (73.8)</td>
</tr>
<tr>
<td>CR or CRi</td>
<td>8 (7.5)</td>
<td>17 (15.9)</td>
</tr>
<tr>
<td>nPR</td>
<td>3 (2.8)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>PR</td>
<td>74 (69.2)</td>
<td>58 (54.2)</td>
</tr>
</tbody>
</table>

Safety Summary

- 40% grade 3/4 neutropenia; 22.4% baseline neutropenia (any grade)
- Infections in 72% of patients (20% grade ≥3)
- Laboratory TLS in 5 patients during the ramp-up period; no clinical TLS
- Most common SAEs: pyrexia (7%), AIHA (7%), pneumonia (6%), FN (5%)

Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas

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  - T Cell Lymphomas

Diagnosis of Mantle Cell Lymphoma

- 5%-10% of B-cell NHL, with moderately aggressive course
- 74% male, median age 63 years
- >80% stage III/IV including marrow involvement
- Extranodal sites common: lymphomatous polyposis, gastrointestinal, soft tissue, or leukemic phase
- Classic translocation: >70% t(11;14); overexpression of cyclin D1 (bcl-1)
- CD19+, 20+, 5+, 23−, FMC7+, SOX11+
- In the past, prognosis was poor: chemoresponsive, but median survival 30 months with CHOP-type chemotherapy

MCL Histologic Subtypes

- Mantle Zone Nodular
- Diffuse
- Blastoid

Indolent Mantle Cell Lymphoma

- Characterization
  - Mantle Zone Lymphoma
    - With this pathology, only the Mantle Zone is involved by the disease
  - Any MCL (except Blastoid variant) with Ki-67 ≤ 10%
  - Mantle Cell Lymphoma involving the spleen and marrow only (usually do not have colon involvement)
  - Low MIPI and small tumor burden
- None of these have been studied in prospective trials
A Prognostic Index (M-IPI) for Patients With Advanced-Stage MCL

- Age (↑ 10 y, HR 1.42; \( P=0.0002 \))
- Sex
- ECOG PS (>1, HR 2.01; \( P=0.0088 \))
- Ann Arbor stage
- B-symptoms
- Number of ENS
- Number of involved nodal areas
- Tumor size
- Serum LDH (2 × ↑ LDH, HR 1.51; \( P<0.0059 \))
- WBC (10 × ↑ WBC, HR 2.56; \( P<0.0001 \))
- Platelet count
- Hemoglobin
- Albumin
- β2-microglobulin
- Ki-67

Patients with advanced MCL treated with first-line from 3 GLSG trials N=455

Analysis based on a list of prognostic factors*


Initial R-HyperCVAD had 97 pts
Median age 61 (range 41-80); 1/3 pts > 65 y

Pts > 65y worse: med PFS just over 2y (delays / dose reduction / toxicity)

VcR-CVAD and MR for Untreated MCL

Chang et al. ASH 2016, abstract 149.
Tolerance better with Bor 1.3 and Vin 1

BCR Inhibition in Relapsed MCL: Ibrutinib

Eligibility (N = 111)
- Patients with relapsed/refractory MCL
- 1–5 prior lines of treatment
- No significant CV or GI disease

Bortezomib-naive cohort (n = 63)
- Ibrutinib 560 mg/d PO
- 28-d cycle until PD

Bortezomib-exposed cohort (n = 48)
- Ibrutinib 560 mg/d PO
- 28-d cycle until PD


Note: 560-mg daily dose approved in MCL (differs from CLL dose)
Ibrutinib + Rituximab for Untreated MCL < 66: Responses by Features

CR 73%, ongoing. Better in those with high Ki-67%, but not affected by MIPI or degree of rash.

*Wang et al. ASH 2016, abstract 147.*

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**Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas**

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  - T Cell Lymphomas
### Outcome in Treatment Subsets of Stage IE Gastric MALT NHL: OS and EFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>5 Yr OS</th>
<th>5 Yr EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>45</td>
<td>67%</td>
<td>9%</td>
<td>24%</td>
<td>94%</td>
<td>75%</td>
</tr>
<tr>
<td>Local tx*</td>
<td>14</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>Chemo</td>
<td>8</td>
<td>50%</td>
<td>12%</td>
<td>38%</td>
<td>75%</td>
<td>49%</td>
</tr>
<tr>
<td>CMT†</td>
<td>5</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>74%</td>
<td>7%</td>
<td>19%</td>
<td>89%</td>
<td>72%</td>
</tr>
</tbody>
</table>

* Surgery alone (n = 11), surgery and XRT (n = 2), or XRT alone (n = 1)
† Surgery and adjuvant chemotherapy


### Nongastric MALT Lymphoma: Presenting Sites

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>30</td>
</tr>
<tr>
<td>Ocular adnexa</td>
<td>24</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
</tr>
<tr>
<td>Skin</td>
<td>12</td>
</tr>
<tr>
<td>Intestinal tract/GU</td>
<td>8/1</td>
</tr>
<tr>
<td>Thyroid/Breast</td>
<td>7/2</td>
</tr>
</tbody>
</table>

From International Extranodal Lymphoma Study Group (IELSG), others

Splenic Marginal-Zone Lymphoma: Clinical Presentation

- Typical presentation:
  - Splenomegaly
  - Circulating lymphoma cells
  - BM involvement
  - No enlarged nodes
- Rare lymphoma (<1% of all NHL)
- Also called splenic lymphoma with or without villous lymphocytes
- Was confused with Hairy Cell Leukemia

Nodal Marginal-Zone Lymphoma: Clinical Features

- B symptoms (14%)
- Stages I/II (29%) and III/IV (71%)
- Elevated LDH (36%)
- Bone marrow involvement (28%)
- 5-year survival (56%)

Therapy for Marginal Zone Lymphomas

- Few randomized trials
  - Good survival rates, even with active disease
  - Many different therapies work
  - Treatment depends on site of disease, and patient features
- Individualized Choices
  - Observation (no immediate therapy)
  - Radiation Therapy (often low dose)
  - Single-Agent Rituximab
  - Bendamustine/Rituximab
  - B-cell pathway drugs (Ibrutinib, Idelalisib)
  - Other novel agents being studied

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  - T Cell Lymphomas
The WHO Classification of PTCL

- **PTCL Leukemic**
  - Adult T cell leukemia/lymphoma (HTLV-1+)
- **PTCL, Predominantly Extranodal**
  - Extranodal NK/T cell lymphoma, nasal type
  - Enteropathy-type T cell lymphoma
  - Hepatosplenic T cell lymphoma (gamma/delta)
  - Subcutaneous panniculitis-type T cell lymphoma
  - **Indolent:** Mycosis fungoides/Sezary syndrome
  - Primary cutaneous ALCL
- **PTCL, Predominantly Nodal**
  - Peripheral T cell lymphoma, NOS
  - Angioimmunoblastic T cell lymphoma, AILD-like
  - Anaplastic large cell lymphoma (T and Null cell)

Initial Therapy of PTCL

- Relative rarity and heterogeneity of subtypes has limited clinical trials for these entities
  - Cell size does not correlate well with prognosis
- Most series indicate a higher relapse rate and poorer survival for PTCL, NOS vs DLBCL
  - Important to recognize ALCL, ALK+, containing the t(2;5) translocation → high curability with CHOP alone
- CHOP therapy has been the most commonly utilized front-line therapy
  - **ORR ~ 60-70%, CR ~ 40-60%**
  - Relapse @ 2 years > 70-80% in most series
Initial Therapy of PTCL

- HyperCVAD often used for ATCL and other highly aggressive variants: PTCL trial at MDACC demonstrated no real benefit
- ACVBP may be better than CHOP in GELA trials
- EPOCH has activity in both front-line and relapsed settings
- Nucleoside analogues (fludarabine, cladribine, pentostatin) are more often used in MF or PTCL with cutaneous involvement
  - Inhibit adenosine deaminase, high concentrations in T-cells
  - ORR 20-70%, CR 3-25%, DR often < 6 months
- Improved therapies are needed!

Q&A Session

Ask a question by phone:
  - Press star (*) then the number 1 on your keypad.

Ask a question by web:
  - Click "Ask a question"
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.
SUPPORT RESOURCES

- Online Chats: Online moderated chat forums: www.LLS.org/chat
- Questions to ask your treatment team: www.LLS.org/what_to_ask
- Free education materials: www.LLS.org/booklets
- Past NHL education programs: www.LLS.org/programs
- Additional information on NHL: www.LLS.org/NHL
- Information Resource Center: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - EMAIL: infocenter@LLS.org
  - TOLL-FREE PHONE: (800) 955-4572