Lymphoma and CLL Forms

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WHAT IS LYMPHOMA?

- Neoplasm of the lymphatic/immune system
  - Subtypes vary based on the cell of origin (most NHL are B-cell)
- Estimated 65,000 new cases in US
- 85% Non-Hodgkin lymphoma
### Normal lymph nodes

![Diagram of lymph nodes](image)

### Cancer Mortality in the United States*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>289,550</td>
<td>270,100</td>
</tr>
<tr>
<td>Prostate</td>
<td>31%</td>
<td>9%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Indications for Hematopoietic Stem Cell Transplantation in North America 2003

Allogeneic (Total N=7,300)

Autologous (Total N=9,600)

Allogeneic Hematopoietic Stem Cell Transplantation CIBMTR 2005

Related donor (Total N=8,326)

Unrelated donor (Total N=6,996)
How common is NHL?

United States

Year


Estimated annual incidence

0 15,000 30,000 45,000 60,000

~4% compound annual increase in incidence

Adapted from Greenlee et al. CA Cancer J Clin. 2001;51:15.
Adapted from Jemal et al. CA Cancer J Clin. 2006;56:106.

Hodgkin lymphoma

Thomas Hodgkin (1798-1866)
Hodgkin Lymphoma - epidemiology

- 8000 cases yearly in U.S.
- Patients at high risk?
  - Bimodal age distribution
    - Peak in 20s, second peak in 60s-70s
  - Family history: 7x increase for sibs, 100x for identical twins
  - HIV
  - EBV related (seen in about 30% of HL biopsies)

Pathology

Reed Sternberg cells:
large, bi- or multi-nucleated, abundant cytoplasm, two or more nucleoli. Surrounded by an inflammatory response.
Reed-Sternberg cell

Hodgkin lymphoma
Histologic subtypes

- Classical Hodgkin lymphoma
  - nodular sclerosis (most common subtype)
  - mixed cellularity
  - lymphocyte-rich
  - lymphocyte depleted
HL – clinical presentation

- Asymptomatic Lymph Node enlargement
- Mediastinal involvement can cause symptoms, but sometimes very bulky with minimal symptoms.
- Generalized pruritis is common, may precede Dx by months
- **B Symptoms**: Fever / Night Sweats / Weight loss in 25% - rare in early stage disease
- CNS involvement – very rare
- Most common sites involved are cervical, supraclavicular, and mediastinal
  - 2/3 will have mediastinal involvement at presentation

HL – Initial evaluation / staging

- History: esp B symptoms
- Good exam with Lymph node measurements
- **CT Scan Neck /C/A/Pelvis – Lymph Node Measurements**
- PET scan
- Ensure accurate pathology: r/o NHL, reactive node
- Marrow Biopsy
**Staging of lymphoma**

**Ann Arbor Staging**

- **Stage I**
- **Stage II**
- **Stage III**
- **Stage IV**

A: absence of B symptoms  
B: fever, night sweats, weight loss  

**Staging**

9. Did the recipient have any known organ involvement at diagnosis:
   1. □ I — Involvement of a single lymph node region or of a single organ or site and one or more lymph node regions on same side
   2. □ II — Involvement of two or more lymph node regions on same side
   3. □ III — Involvement of lymph node regions on both sides of diaphragm
   4. □ IV — Diffuse or disseminated involvement of one or more extranodal sites
   5. □ other organ involvement
   6. □ unknown

10. Specify organ involvement: __________

11. Did the recipient show any systemic symptoms at diagnosis:
   1. □ A — None of the symptoms listed in B below
   2. □ B — Unexplained weight loss > 10% body weight in six months

Did the recipient have any known extranodal or splenic involvement at diagnosis?

1. □ yes  
2. □ no  
3. □ unknown

Specify site(s) of involvement:

- 13. □ yes  □ no Bone
- 14. □ yes  □ no Bone marrow
- 15. □ yes  □ no Brain
- 16. □ yes  □ no Cerebrospinal fluid (CSF)
### How does NHL differ from HL?

<table>
<thead>
<tr>
<th></th>
<th>HL</th>
<th>NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtypes</strong></td>
<td>2</td>
<td>&gt;30</td>
</tr>
<tr>
<td><strong>Peak age</strong></td>
<td>20s</td>
<td>over age 60</td>
</tr>
<tr>
<td><strong>Cases / yr</strong></td>
<td>8,000</td>
<td>60,000</td>
</tr>
<tr>
<td><strong>Common sites</strong></td>
<td>Neck, mediastinum</td>
<td>Various</td>
</tr>
<tr>
<td><strong>S/Sx</strong></td>
<td>Usually mild</td>
<td>Often severe</td>
</tr>
<tr>
<td><strong>5 yr Survival</strong></td>
<td>80+ %</td>
<td>Varies</td>
</tr>
</tbody>
</table>
Age at Diagnosis for Hodgkin and Non-Hodgkin Lymphoma

Data for diagnoses from 1997 to 2001.

NHL Diagnosis

- Physical examination
- CT or PET scan
- Biopsy
  - Bone marrow biopsy may suffice in some cases.
- Specialized pathology tests may be key to determining the NHL subtype
  - Flow cytometry
  - Protein stains
  - Chromosome tests ("FISH")
  - Molecular tests
### REAL/WHO Classifications for B-Cell Neoplasms

#### Indolent (Low Risk)
- CLL/SLL* (IWF:A)
- Lymphoplasmacytic leukemia
- HCL
- Splenic marginal zone lymphoma
- Marginal zone B-cell lymphoma
  - Extr nodal
  - Nodal
- Follicular lymphoma, grades I-II (IWF:B-C)*

#### Aggressive (Intermediate Risk)
- Follicular lymphoma, grade III (IWF:D)*
- PLL
- Plasmacytoma/plasma cell myeloma
- MCL
- DLBCL*
  - Mediastinal large B-cell lymphoma
  - Primary effusion lymphoma

#### Very Aggressive (High Risk)
- Precursor B-lymphoblastic lymphoma/leukemia
- Burkitt's lymphoma/Burkitt's cell leukemia

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**Histology**

<table>
<thead>
<tr>
<th>Classical Hodgkin Lymphoma Codes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 nodular lymphocyte predominant Hodgkin lymphoma</td>
</tr>
<tr>
<td>02 lymphocyte-rich</td>
</tr>
<tr>
<td>03 nodular sclerosis</td>
</tr>
<tr>
<td>04 mixed cellularity</td>
</tr>
<tr>
<td>05 lymphocyte depleted</td>
</tr>
<tr>
<td>06 Hodgkin lymphoma, not otherwise specified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Hodgkin Codes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>07 lymphoplasmacytic lymphoma</td>
</tr>
<tr>
<td>08 splenic marginal zone B-cell lymphoma</td>
</tr>
<tr>
<td>09 extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type (MALT)</td>
</tr>
<tr>
<td>10 nodal marginal zone B-cell lymphoma (L monocyteoid B-cells)</td>
</tr>
<tr>
<td>11 follicular, predominantly small cleaved cell (Grade I follicle center lymphoma)</td>
</tr>
</tbody>
</table>

| 12 follicular, mixed, small cleaved and large cell (Grade II follicle center lymphoma) |
| 13 follicular, predominantly large cell (Grade III follicle center lymphoma) |
| 14 follicular, grade unknown |
| 15 mantle cell lymphoma |
| 16 diffuse, large B-cell lymphoma — intravascular large B-cell lymphoma subtype |
| 17 diffuse, large B-cell lymphoma — mediastinal large B-cell lymphoma subtype |
| 18 diffuse, large B-cell lymphoma — primary effusion lymphoma subtype |
| 19 Burkitt lymphoma / Burkitt cell leukemia |
| 20 high grade B-cell lymphoma, Burkitt-like (provisional entity) |
| 21 primary CNS lymphoma |
| 22 other B-cell lymphoma, specify above |
| 23 extranodal NK / T-cell lymphoma, nasal |

| 24 enteropathy-type T-cell lymphoma |
| 25 hepatosplenic gamma-delta T-cell lymphoma |
| 26 mycosis fungoides |
| 27 Sezary syndrome |
| 28 anaplastic large-cell lymphoma, T / null cell, primary cutaneous type |
| 29 anaplastic large-cell lymphoma, T / null cell, primary systemic type |
| 30 other T-cell / NK-cell lymphoma, specify above |
| 31 large T-cell lymphoma / leukemia |
| 32 other T-cell / NK-cell lymphoma, associated |
| 33 Waldenstrom macroglobulinemia |
The challenge of lymphoma classification

<table>
<thead>
<tr>
<th>Biologic relevance</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases that have distinct</td>
<td>Diseases that have distinct</td>
</tr>
<tr>
<td>• morphology</td>
<td>• clinical features</td>
</tr>
<tr>
<td>• immunophenotype</td>
<td>• natural history</td>
</tr>
<tr>
<td>• genetic features</td>
<td>• prognosis</td>
</tr>
<tr>
<td>• clinical features</td>
<td>• treatment</td>
</tr>
</tbody>
</table>

How clinicians think about lymphoma?

<table>
<thead>
<tr>
<th>Category</th>
<th>Survival</th>
<th>Cure</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Slow Growing</td>
<td>Years</td>
<td>Generally not curable</td>
</tr>
<tr>
<td>Aggressive</td>
<td>Months</td>
<td>Curable in some</td>
<td>Auto &gt;&gt; Allo</td>
</tr>
<tr>
<td>Very aggressive</td>
<td>Weeks</td>
<td>Curable in some</td>
<td>Allo or Auto</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>All types</td>
<td>Variable – months to years</td>
<td>Curable in most</td>
</tr>
</tbody>
</table>
Clinical Course of NHL

- **Indolent (low grade)**
  - Slowly progressive
  - Long natural history – "chronic disease"
  - Median survival: 6-10 years
    - 5-year OS: 53-91% (FLIPI)
  - Up to 50% risk of transformation
  - Treatable, but not curable
- **Aggressive (intermediate grade)**
  - Rapid clinical course
  - 5-year OS: 26-73% (IPI)
  - Potential long-term survival with treatment
- **Highly aggressive (high grade)**
  - Grows rapidly
  - Survival: 0.5-2 years
  - Potential long-term survival with treatment


Transformed Lymphoma

4. Is the current histology a transformation from CLL?
   1 □ yes □ no
   Also complete a Form 2000 — CLL insert

5. Did histologic transformation occur after diagnosis?
   1 □ yes □ no

6. Date of transformation: □□
   Month Day

7. Latest histology: □□
   (see codes at question 2)
47 yo male, with fatigue, night sweats, diffuse bone pains. Biopsy showed **Diffuse large B-cell lymphoma**
**Translocation in the Pathogenesis of FL**

14 18  →  t(14;18)  

↑Bcl-2  →  ↓Apoptosis  

Accumulation of mutations/transformation and proliferation

**Chromosomal Translocations Commonly Associated With Activation in B-Cell Malignancies**

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Protein</th>
<th>Translocation</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>bcl-1</td>
<td>Cyclin D₁</td>
<td>t(11;14)</td>
<td>MCL</td>
</tr>
<tr>
<td>bcl-2</td>
<td>BCL-2 (antiapoptosis)</td>
<td>t(14;18)</td>
<td>FL, some DLBCL</td>
</tr>
<tr>
<td>bcl-3</td>
<td>NF-κB inhibitor</td>
<td>t(11;19)</td>
<td>CLL</td>
</tr>
<tr>
<td>myc</td>
<td>Transcription factor</td>
<td>t(8;14)</td>
<td>Burkitt’s NHL</td>
</tr>
<tr>
<td>bcl-6</td>
<td>Zinc-finger transcription factor</td>
<td>t(3;14)</td>
<td>DLBCL (some follicular NHL)</td>
</tr>
</tbody>
</table>

Primary mediastinal DLBCL. 36 yo female, before and after R-CHOP. At diagnosis can see the mass penetrating through the anterior chest wall and bilateral (R>L) pleural effusion. Achieved CR with R-CHOP, went on to receive auto PBSC and consolidative XRT.

44 yo F, Dx with Stg IV mantle cell lymphoma in 8/05. WBC 40,000 (50% MCL). BMBx – 50% involved. Treated with Rituxan-HCVAD x8 (thru 1/06), followed by Auto PBSC on 2/15/06.
27 y/o F arthralgias, palpitations, SOB and chest pain. CT scan - large sternal mass. Biopsy Burkitt's lymphoma (with t(8;14) present).

25 y/o M
LE weakness and ataxia.
Multiple ring-enhancing parenchyma lesions with vasogenic edema.
Stereotactic biopsy of right parietal lobe lesion showed large B-cell lymphoma (primary CNS lymphoma)
Follicular Lymphoma Histology

Grade 1  Grade 2  Grade 3

- Numbers of centroblasts (large cells) increase with grade
- Criteria for grading*
  - Grade 1: 0-5 centroblasts/hpf; centrocytes predominate
  - Grade 2: 6-15 centroblasts/hpf
  - Grade 3: >15 centroblasts/hpf; centroblasts predominate


THERAPY OF INDOLENT NHL

- Paradoxical in that cure not obtained with conventional therapy
- Watchful waiting approach with therapy for symptomatic progression
- Radiation in limited disease
- Chemotherapy
- Biologic therapy (MoAb, IFN)
- Hematopoietic cell transplant (allo vs auto)
Overview of DLBCL

- Patients typically present with a rapidly enlarging mass
  - ~1/3 present with B symptoms
  - ~1/3 present with stage IV disease
  - More than 2/3 have any extranodal site
    - ~1/3 have >1 extranodal site
  - ~1/6 present with bone marrow involvement
- DLBCL is rapidly progressive if not treated
  - It follows a rapid clinical course
  - 75%-80% of patients respond well to treatment

Morphology
- Diffuse centroblastic, diffuse centroblastic/centrocytic, or immunoblastic

Clinical features
- Aggressive behavior
- Heterogeneous clinical response

Immune Phenotype
- Pan B-cell antigens (CD19, CD20, CD22, CD79a), surface IgM

Genetic features
- Most have somatic hypermutation of Ig variable region genes
  - t(14;18) (q32; q21) bcl-2 oncogene rearrangement
  - (3q27) bcl-6 oncogene rearrangement
  - t(1;14) (p22; q32) bcl-10 rearrangement
  - c-myc oncogene deregulation

The International Prognostic Index (IPI) for Aggressive NHL

Criteria
- Age (≤60 vs >60 years)
- Performance status (0 or 1 vs ≥2)
- LDH (≤ normal vs > normal)
- Extranodal sites (≤1 vs >1)
- Stage (I or II vs III or IV)

Age-adjusted criteria (patients ≤60 years)
- Performance status (0 or 1 vs ≥2)
- LDH (≤ normal vs > normal)
- Stage (I or II vs III or IV)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Factors</th>
<th>Patients (%)</th>
<th>2-year OS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>35</td>
<td>84</td>
<td>73</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>2</td>
<td>27</td>
<td>66</td>
<td>51</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>3</td>
<td>22</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
<td>16</td>
<td>34</td>
<td>26</td>
</tr>
</tbody>
</table>

THERAPY OF AGGRESSIVE NHL

- Aggressive therapy with curative intent
- CHOP-based therapy for B-cell neoplasms
- Adjunctive radiation to sites of bulk disease
- Risk stratification for patients to be considered for BMT in 1st remission
- Biologic therapy (anti-CD20 based therapy)
- Hyper-CVAD for mantle cell / highly aggressive diseases
Prior Therapy – Pre HSCT Treatment

- Wide Variety of Drugs used →
  - Antibody based strategies
  - Chemotherapy

<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Rituximab (Mabthera)</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid)</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Ibritumomab (Bexxar)</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Other monoclonal antibody</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Specify other antibody</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

- Bleomycin (BLM, Bleoroxane)
- Carmustine (BCNU, Gliadel)
- Carboplatin (Paraplatin)
- Cisplatin (Platinol, CDDP)
- Cytarabine (2-CDA, Leustatin)
- Cyclophosphamide (Cytoxan)
- Daunorubicin (Adriamycin)
- Doxorubicin (Adriamycin)
- Etoposide (VP-16, VePesid)
- Fludarabine (Fludara)
- Gemcitabine (Gemzar)
- Ifosfamide (Ifos)
- Methotrexate (MTX)
- Mitoxantrone (Novantrone)
- Nitrogen mustard (mustine)
- Pentostatin (Nipent)
- Procarbazine (Matulane)
- Vinblastine (Velban, VLB)
- Vincristine (NCR, Ovonal)
- Other treatment | 62 | 2 |

RadioImmunotherapy in the Treatment of NHL

Ibritumomab

- Chelator
- Tiuxetan
- 90Y Radionuclide

Tositumomab

- 131I radioisotope
Response

Best Response Definitions

1. Complete remission (CR) — complete disappearance of all known disease for ≥ 4 weeks
2. CR undetermined (CRU) — as above with the exception of persistent scan abnormalities of unknown significance
3. Partial remission (PR) — ≥ 50% reduction in greatest diameter of all sites of known disease and no new sites
4. No response / Stable disease (NR / SD) — < 50% reduction in greatest diameter of all sites of known disease
5. Progressive disease (Prog) — increase in size of known disease or new sites of disease
6. Not tested / Unknown

CRU???
Status reserved for patients having response typical of CR, but with residual lesion of uncertain significance

Example:
Large LN mass shrinks with each of first 4 cycles CHOP, no further shrinkage and small 2cm mass after therapy. Not amenable to biopsy. All other disease "gone".

Response to Pre HSCT Therapy !!

Start and Stop Date
Response
Response date
Relapse ?

Radiation Therapy: 64. 1 □ yes 2 □ no — cont. with q. 70

<table>
<thead>
<tr>
<th>Radiation Therapy</th>
<th>64.</th>
<th>1 □ yes</th>
<th>2 □ no</th>
<th>— cont. with q. 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date therapy started:</td>
<td>65.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date therapy stopped:</td>
<td>66.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mediastinum:</td>
<td>67.</td>
<td>1 □ yes</td>
<td>2 □ no</td>
<td></td>
</tr>
<tr>
<td>other site(s):</td>
<td>68.</td>
<td>1 □ yes</td>
<td>2 □ no</td>
<td></td>
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<tr>
<td>specify other site(s):</td>
<td>69.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery:</td>
<td>70.</td>
<td>1 □ yes</td>
<td>2 □ no — cont. with q. 75</td>
<td></td>
</tr>
<tr>
<td>Date of surgery:</td>
<td>71.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>splenectomy:</td>
<td>72.</td>
<td>1 □ yes</td>
<td>2 □ no</td>
<td></td>
</tr>
<tr>
<td>other site(s):</td>
<td>73.</td>
<td>1 □ yes</td>
<td>2 □ no</td>
<td></td>
</tr>
<tr>
<td>specify other site(s):</td>
<td>74.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was this line of therapy given for stem cell priming?</td>
<td>75.</td>
<td>1 □ yes</td>
<td>2 □ no</td>
<td></td>
</tr>
</tbody>
</table>

Best Response to Line of Therapy:
(see definitions at left)

<table>
<thead>
<tr>
<th>Best Response to Line of Therapy</th>
<th>76.</th>
<th>1 □ CR</th>
<th>4 □ NR / SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 □ CRU</td>
<td>77.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 □ PR</td>
<td>78.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 □ unknown</td>
<td>79.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date response established: 77.
Did disease relapse/progress following this line of therapy? 78.
Date of relapse/progression: 79.
### PET SCAN

129. Was a PET scan performed at any time between diagnosis and the start of the preparative regimen?
- 1. Yes
  - 130. Was the PET scan positive for lymphome involvement at any disease site?
    - 1. Yes
    - 2. No
- 2. No

131. Did the recipient have known nodal involvement at the time of the pre-HSCT disease status assessment?
- 1. Yes
- 2. No

132. Specify the total number of nodal regions involved:
- 1. One nodal region
- 2. Two or more nodal regions
- 3. Unknown

133. Specify the size of the largest nodal mass: \[
\text{cm} \times \text{cm}
\]

---

### Pretransplant Disease Status

Was molecular testing performed at the time of the pre-HSCT disease status determination?

What was the sensitivity of the lymphoma to chemotherapy prior to the preparative regimen? chemotherapy given prior to HSCT, treatment must be given ≤ 6 months prior to HSCT (see question 152)

1. Sensitive – ≥ 50% reduction in the bidimensional diameter of all disease sites with no new CR, CRU, REL, sen)
2. Resistant – < 50% reduction in the diameter of all disease sites, or development of new d
3. Untreated – no chemotherapy was given within 6 months prior to the preparative regimen
4. Unknown (PRI, unk, REL, unk)
**Remission State Pre HSCT**

1. What was the disease remission state immediately prior to the preparative regimen?
   - Disease untreated
   - PIF res
   - Primary induction failure - resistant: NEVER in COMPLETE remission on treatment
   - PIF sen / PR1
   - Primary induction failure - sensitive: NEVER in COMPLETE remission on treatment
   - PIF unk
   - Primary induction failure - sensitivity unknown
   - CR1
   - 1st complete remission: no bone marrow or extramedullary relapse
   - CR2
   - 2nd complete remission
   - CR3+
   - 3rd or subsequent complete remission
   - CRU1
   - 1st complete remission undetermined: as above with the exception of unknown significance
   - CRU2
   - 2nd complete remission undetermined
   - CRU3+
   - 3rd or subsequent complete remission undetermined
   - REL1
   - 1st relapse-untreated: includes either bone marrow or extramedullary relapse
   - REL1 res
   - 1st relapse-resistant: stable or progressive disease with treatment
   - REL1 sen
   - 1st relapse-sensitive: partial remission (if complete remission was achieved previously)
   - REL1 unk
   - 1st relapse-sensitivity unknown
   - REL2
   - 2nd relapse-untreated: includes either bone marrow or extramedullary relapse
   - REL2 res
   - 2nd relapse-resistant: stable or progressive disease with treatment
   - REL2 sen
   - 2nd relapse-sensitive: partial remission (if complete remission was achieved previously)
   - REL2 unk
   - 2nd relapse-sensitivity unknown
   - REL3+
   - 3rd or subsequent relapse-untreated: includes either bone marrow or extramedullary relapse
   - REL3+ res
   - 3rd or subsequent relapse-resistant: stable or progressive disease
   - REL3+ sen
   - 3rd or subsequent relapse-sensitive: partial remission (if complete remission was achieved previously)
   - REL3+ unk
   - 3rd or subsequent relapse-sensitivity unknown

**Pre HSCT disease status - Terms**

<table>
<thead>
<tr>
<th>Qn 1. Where is disease at?</th>
<th>Qn 2. How did it respond?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIF</strong> – never had a CR</td>
<td><strong>Sensitive</strong></td>
</tr>
<tr>
<td><strong>CR</strong> – can be 1, 2, 3+</td>
<td><strong>Resistant</strong></td>
</tr>
<tr>
<td><strong>REL</strong> – can be 1, 2, 3+</td>
<td><strong>Untreated</strong></td>
</tr>
<tr>
<td><strong>CRu</strong> – can be 1, 2, 3+</td>
<td><strong>Unknown</strong></td>
</tr>
</tbody>
</table>

e.g.
- PIF Sens → a PR to initial treatment then Tx = PR1
- REL1 Sens → CR, Relapse then PR to chemo pre transplant

CR – has to be sensitive!
PIF – can be sens, res, unt/unk
REL – can be sens/res/unt/unk
CRu – has to be sensitive

Looks more complicated than it actually is
**Pre HSCT disease status**

- 22 combinations offered
- Should cover all possible scenarios

<table>
<thead>
<tr>
<th>Disease Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td>20</td>
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<tr>
<td>21</td>
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<tr>
<td>22</td>
</tr>
</tbody>
</table>

- REL1 unk: 1st relapse-unintreated: includes either bone marrow or extramedullary relapse
- REL1 res: 1st relapse-resistant: stable or progressive disease with treatment
- REL1 sen: 1st relapse-sensitive: partial remission (if complete remission was achieved)
- REL1 unk: 1st relapse-sensitivity unknown

**Post Transplant - Response**

1. Compared to the disease status prior to the preparative regimen, what was the best response to HSCT since the date of the last report? (Include response to any post-HSCT treatment planned as of Day 0)
- CCR: continued complete remission (CCR) for patients transplanted in CR
- CR: complete remission (CR): complete disappearance of all known disease for ≥ 4 weeks
- CRu: complete remission undetermined (CRU), as above with the exception of persistent scan abnormalities of unknown significance
- PR: partial remission (PR): ≥ 50% reductions in greatest diameter of all sites of known disease and no new sites
- NR/SD: no response / stable disease (NR / SD): < 50% reduction in greatest diameter of all sites of known disease
- REL/PROG: relapse / progressive disease: increase in size of known disease, or new sites of disease
- NA: not assessed

2. Date the best response first began: [Month] [Day] [Year]
Post Transplant Treatment Maintenance / Consolidative

**Post-HSCT Planned Treatment for Lymphoma**

6. Was planned treatment given per protocol since the date of the last report?
   - [ ] yes
   - [ ] no

Specify planned treatment given:

Can be:
- Chemotherapy
- Radiation
- Immunotherapy – Rituximab/MabThera (antiCD20), Campath / Alemtuzumab (antiCD52), IL2/Aldesleukin

**Did the patient Relapse?**

Was a disease relapse or progression detected by any method since the date of the last report?
   - [ ] yes
   - [ ] no

Specify the total number of nodal sites involved:

Date
- How detected?
- Where – sites?
- Molecular studies
- FISH
- PET

Final Questions – Current Disease Status (time of reporting)
**CLL**

- **Most common leukemia**
- **8100-12,500 cases each year = 2.5/100,000**
- **Majority of patients have a cytogenetic abnormality**
  - Del 13q present in 55%
  - Del 11q23 present in 18%
  - Trisomy 12 in 16%
  - Mutation of p53 at 17p13.3 in 15%
- **3-15% will transform to a more aggressive form**
  - i.e. Richter syndrome
CLL Immune effects

Autoimmune disorder(s) at diagnosis:
- 1 □ yes 2 □ no 3 □ unknown Immune hemolytic anemia
- 1 □ yes 2 □ no 3 □ unknown Immune thrombocytopenia
- 1 □ yes 2 □ no 3 □ unknown Positive Coombs' test

- **HEMOLYSIS**
  - 20-30% have + Coombs test
  - 10-25% have evidence of hemolysis

- **PLATELET COUNT**
  - 2% develop ITP
  - 1% develop red cell aplasia (aka PRCA)

Also many other problems:
- Membranoproliferative glomerulonephritis/ angioedema/ pemphigus

### Staging of CLL

#### Staging: Rai and Binet staging systems for CLL

**Clinical staging systems for CLL**

<table>
<thead>
<tr>
<th>Value</th>
<th>Stage</th>
<th>Rai</th>
<th>Binet</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytosis (&gt;15,000/mm³)</td>
<td>I</td>
<td>A</td>
<td></td>
<td>101-109 months (6.5-9 years)</td>
</tr>
<tr>
<td>Lymphocytosis plus nodal involvement</td>
<td>II</td>
<td>B</td>
<td></td>
<td>60-71 months (5-6 years)</td>
</tr>
<tr>
<td>Lymphocytosis plus organomegaly</td>
<td>III</td>
<td></td>
<td></td>
<td>19-24 months (1.5-2 years)</td>
</tr>
<tr>
<td>Anemia (RBCs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hgb &lt;11 g/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hgb &lt;10 g/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytosis plus thrombocytopenia (platelets)</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT &lt;100,000/mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT &lt;100,000/mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SURVIVAL in the Five Genetic Categories of CLL

Cytogenetics is Important

Were cytogenetics tested (conventional or FISH)?

☐ yes ☐ no ☐ unknown

49. Results of test at diagnosis:

1 ☐ yes abnormalities identified
2 ☐ no evaluable metaphases
3 ☐ no abnormalities

Complete questions 51–60 in the table below

50. Results of tests after diagnosis to prior to the preparative regimen:

1 ☐ yes abnormalities identified
2 ☐ no evaluable metaphases on any tests
3 ☐ no abnormalities on any tests after diagnosis and before the preparative regimen

Specify abnormalities identified:

Cytogenetic abnormality

At diagnosis

Any test result between diagnosis and preparative regimen

Cytogenetics is Important!

Where do I look for these?
Addendum to marrow reports
Peripheral Blood FISH
Karyotype
Initial Consult note at Transplant Center

<table>
<thead>
<tr>
<th>Cytogenetic abnormality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy</td>
<td>+12</td>
</tr>
<tr>
<td>Translocation</td>
<td>t(11:14)</td>
</tr>
<tr>
<td>any translocation of 14</td>
<td></td>
</tr>
<tr>
<td>Deletion</td>
<td>del(11q)/11q– (ATM)</td>
</tr>
<tr>
<td></td>
<td>del(13q)/13q–</td>
</tr>
<tr>
<td></td>
<td>del(17p)/17(p53)–</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>abnormal 6</td>
<td></td>
</tr>
<tr>
<td>abnormal 8</td>
<td></td>
</tr>
<tr>
<td>Other abnormality</td>
<td></td>
</tr>
<tr>
<td>Specify other abnormality:</td>
<td></td>
</tr>
</tbody>
</table>

Sensitive Tests Pre Transplant

Was molecular testing/immunophenotyping performed at the time of disease assessment prior to the preparative regimen?

1. yes
2. no

Specify the testing method(s) used:

182. Immunophenotyping (4 color flow cytometry)

Specify the date immunophenotyping was performed:

183. Month: [ ]

184. Day: [ ]

185. Year: [ ]

186. Was disease detected?

1. yes
2. no

187. Heavy chain gene rearrangement (ASC-PCR)
CLL Response Criteria

- **Complete response (CR)** — no lymphadenopathy, no organomegaly, neutrophils > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin > 11 g/dL, lymphocytes < 4 x 10^9/L, bone marrow < 30% lymphocytes, absence of constitutional symptoms
- **Nodular partial response (NPR)** — complete response with persistent lymphoid nodules in bone marrow
- **Partial response (PR)** — ≥ 50% decrease in peripheral blood lymphocyte count from pretreatment value, ≥ 50% reduction in lymphadenopathy if present pretreatment, ≥ 50% reduction in liver and spleen size if enlarged pretreatment, one or more of the following: neutrophils ≥ 1.5 x 10^9/L or ≥ 50% improvement over baseline, platelets > 100 x 10^9/L or ≥ 50% improvement over baseline, hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline
- **Stable disease (SD)** — no change, partial response, or progressive disease
- **Progressive disease (Prog)** — one or more of the following: ≥ 50% increase in the sum of the products of ≥ 2 lymph nodes (nodes must be ≥ 2 cm or new nodes, ≥ 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly, ≥ 50% increase in absolute lymphocyte count to ≥ 5 x 10^9/L, transformation to a more aggressive histology

**Criteria for Response - Definitions**

- **Lymph Nodes**
- **Organomegaly**
- **Blood lymphocyte**
- **Marrow lymphocytes**
- **Neutrophils**
- **Platelets**
- **Hemoglobin**
- **B Symptoms**

- 50% reduction or increase (min 2cm to be significant)
- 50% change in size of liver /spleen
- PB lymphocytes -50% change (min ≥ 5x 10^9/L)
- **CBC Thresholds**
  - ANC 1.5, Platelets 100 x 10^9/L
  - Hemoglobin 11
- 50% CHANGE → PR
- Progression – NOT based on CBC!
- For CR – Marrow has to be <30% lymphocytes
CLL Response Criteria

- Complete response (CR) — no lymphadenopathy; no organomegaly; neutrophils > 1.5 x 10^9/L; platelets > 100 x 10^9/L; hemoglobin > 11 g/dL; lymphocytes < 4 x 10^9/L; bone marrow < 30% lymphocytes; absence of constitutional symptoms

- Partial response (PR) — complete response with persistent lymphoid nodules in bone marrow

- Partial response (PR) — ≥ 50% decrease in peripheral blood lymphocyte count from pretreatment value; ≥ 50% reduction in lymphadenopathy if present pretreatment; ≥ 50% reduction in liver and spleen size if enlarged pretreatment; one or more of the following: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets > 100 x 10^9/L or 50% improvement over baseline, hemoglobin > 11.0 g/dL or 50% improvement over baseline

- Stable disease (SD) — no change; not complete response, partial response, nor progressive disease

- Progressive disease (PD) — one or more of the following: ≥ 50% increase in the sum of the products of ≥ 2 lymph nodes ≥ 1 cm or 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly; ≥ 50% increase in absolute lymphocyte count to ≥ 5 x 10^9/L; transformation to a more aggressive histology

CLL Post Transplant

- Response to Transplant – Same criteria

- Reporting the best Response to Transplant is important

- i.e CR at day 120 but relapse at day 270 → important that the CR be reported as the best response

Best response is based on response to the HSCT, but does NOT include response to any therapy given for disease relapse or progression post-HSCT. When determining the best response to HSCT, compare the post-HSCT disease status to the status immediately prior to the preparative regimen, regardless of time since HSCT. This comparison is meant to capture the BEST disease status in response to HSCT that occurred in the reporting interval, even if a subsequent disease relapse or progression occurred during the same reporting interval. If a recipient already achieved their best response in a previous reporting interval, confirm the best response and check the box to indicate “data previously reported.”
CLL Post transplant

- Maintenance Therapy
- Molecular and Flow cytometry assessments
- Relapse/Progression ?
- Current Disease Status