Chronic Lymphocytic Leukemia
A six-word narrative about living with blood cancer from patients in our LLS Community

Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/happy I’m alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don’t look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith, nutrition and optimism. Finding the joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I’m more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.

Discover what thousands already have at www.LLS.org/Community

Join our online social network for people who are living with or supporting someone who has a blood cancer. Members will find

- Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff
- Accurate and cutting-edge disease updates
- The opportunity to participate in surveys that will help improve care.
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## Acknowledgement

The Leukemia & Lymphoma Society (LLS) appreciates the review of this material by

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New treatments may have been approved since this book was printed. Check [www.LLS.org/DrugUpdates](http://www.LLS.org/DrugUpdates) or call (800) 955-4572.

This publication is designed to provide accurate and authoritative information about the subject matter covered. It is distributed as a public service by LLS, with the understanding that LLS is not engaged in rendering medical or other professional services.
Introduction

This booklet provides information about chronic lymphocytic leukemia (CLL) for patients and their families. It includes brief descriptions of normal blood and bone marrow and the lymphatic system, as well as definitions of medical terms. All LLS publications mentioned in this booklet are available at www.LLS.org/booklets as downloadable PDFs.

Approximately 20,720 new cases of CLL are expected to be diagnosed in 2019. As of 2015, the latest year for which statistics are available, an estimated 179,683 people are either living with or are in remission from CLL.¹

Doctors have learned a great deal about CLL in the last few decades. Advances in the treatment of CLL have resulted in improved remission rates, quality of life and outcomes for patients. This is due to the large number of approved therapies and new drug combinations. New therapies are under study in clinical trials.


Leukemia

Leukemia is a cancer of the blood and bone marrow. The four major types of leukemia are chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).

Leukemia is classified as “lymphocytic” or “lymphoblastic” if the cancerous change takes place in a blood-forming adult stem cell in the bone marrow that normally gives rise to a type of white blood cell called a lymphocyte. To help distinguish the types of leukemia, leukemia is classified as “myeloid” or “myelogenous” when the cell change takes place in a marrow cell that would normally go on to form other types of blood cells: red blood cells, white blood cells (other than lymphocytes) and platelets.

Acute leukemias progress rapidly and affect cells that are not fully developed. These cells cannot carry out their normal functions. Chronic leukemias usually progress more slowly than other types of leukemia, and patients have greater numbers of mature cells. In general, these more mature cells can carry out some of their normal functions (see Normal Blood and Bone Marrow on page 39 of this booklet and Where do Blood Cancers Develop? at www.LLS.org/booklets).
The four main types of leukemia are further classified into subtypes based on specific features of the leukemia cells. Knowing the subtype of your disease is important because your treatment approach may be based on your subtype.

**Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).** According to the World Health Organization (WHO), CLL and SLL are considered different manifestations of the same disease. Both diseases are the result of a change (called a mutation) to a cell that was supposed to become a healthy lymphocyte. The abnormal (leukemic) lymphocyte begins to multiply uncontrollably, causing leukemic cells to accumulate in the blood, bone marrow and lymphoid tissues. The leukemic lymphocytes observed in people with SLL are identical to those observed in patients with CLL.

In CLL, the disease manifests as significant accumulations of abnormal lymphocytes in the blood, bone marrow, spleen and lymph nodes. In SLL, abnormal lymphocytes are primarily found in the lymph nodes. The diagnosis of SLL requires the presence of less than 5,000 abnormal B-cells per microliter of blood (5,000/μL).

Talk to your doctor if you have questions about your specific diagnosis and treatment. Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to find more information about SLL in the free LLS booklet *Non-Hodgkin Lymphoma.*
Signs and Symptoms

Many people with CLL are diagnosed with the disease before they have any symptoms. The disease may be suspected because of abnormal results from blood tests that were ordered either as part of an annual physical or a medical examination for an unrelated condition. An unexplained elevated white blood cell (lymphocyte) count is the most common finding that leads a doctor to consider a diagnosis of CLL.

Generally, CLL symptoms develop over time. As the disease progresses, a person may experience symptoms such as

- Fatigue
- Shortness of breath during normal physical activity
- Anemia (decreased red blood cell count)
- Lymph node enlargement (particularly in the neck)
- Decreased platelet count
- Low-grade fever
- Unexplained weight loss
- Night sweats
- Feeling of fullness (due to an enlarged spleen or liver)
- Infection of the skin, lungs, kidneys or other organs as a result of low immunoglobulin levels and decreased neutrophil counts

Diagnosis

An accurate diagnosis of the type of leukemia is important. The exact diagnosis helps the doctor to

- Estimate how the disease will progress
- Determine the appropriate treatment

**Blood Cell Count and Examination.** A diagnosis of CLL is usually based on the results of blood cell counts and an examination of blood cells. A person with CLL will have increased numbers of lymphocytes. Low platelet and red blood cell counts may also be noted; these are usually only slightly decreased in the early stage of the illness.
Immunophenotyping. Lymphocyte immunophenotyping is an important test used to diagnose CLL and other types of leukemia and lymphoma, by comparing the cancer cells to normal immune cells. The test results indicate whether the person’s lymphocytes are derived from either a single cancer cell (leukemia) or from other noncancerous conditions. This test is especially important if the number of lymphocytes in the blood is only slightly elevated. Immunophenotyping also determines whether the abnormal cells originated from a B cell or a T cell.

Immunophenotyping is done with an instrument called a “flow cytometer.” A flow cytometry test can measure the number of cells in a sample, as well as specific characteristics of the cells, including size, shape and the presence of specific markers on the cell surface. A sample of cells from blood or bone marrow is tagged with an antibody that is specific for a site on the cell surface. The cells are stained with a light-sensitive dye and pass through a laser beam in the flow cytometer. If they have the antibody-specific surface feature, the cells light up and are counted. The diagnosis of CLL requires the presence of 5,000 or more abnormal B-cells per microliter of blood (5,000/μL).

Quantitative Immunoglobulin Test. This important test provides a measurement of the concentration of immunoglobulins in the blood. Immunoglobulins are proteins, called “antibodies,” that are made by B cells in healthy individuals to protect the body from infection. There are three major types of antibodies in the blood: IgG, IgA and IgM. A blood test can be used to measure the amount of each type of antibody.

CLL cells do not make effective antibodies and also interfere with the ability of the normal lymphocytes to make antibodies. As a result, people with CLL often have low levels of immunoglobulins, which causes immune deficiency and increases the risk of getting infections.

Bone Marrow Examination. Generally, if the red blood cells and platelets are normal, a bone marrow aspiration and biopsy are not needed to make a diagnosis of CLL. However, bone marrow aspiration and biopsy may be recommended before treatment begins. The test results can help rule out other diseases during the diagnostic stage and they can also be used later, during treatment, to evaluate the effectiveness of therapy.
Treatment Planning

A diagnosis of CLL is associated with a wide range of outcomes. For the best outcome, patients are encouraged to seek treatment in a center where specialized doctors, called hematologist-oncologists, are experienced in the diagnosis and care of patients with chronic leukemia.

Treatment for CLL is always changing, with new treatments and research emerging from clinical trials. The outlook for people with CLL is improving. New approaches to therapy are being studied in clinical trials for patients of all ages and at every stage of treatment.

The tests described in this section are not essential to diagnose CLL, but may help predict the likely outcome (called “prognosis”) for the patient, assess the extent of the disease and determine the patient’s readiness for certain treatments.

**Fluorescence in situ hybridization (FISH).** This is a test that studies chromosomes in tissue using DNA probes tagged with fluorescent molecules that emit light of different colors. The DNA-tagged probes bind to specific genes or areas in the chromosomes within the cells and light up when viewed under a microscope. It is very common for CLL cells to have abnormal chromosomes. In CLL cells, the chromosomes that generally have defects include chromosomes 11, 12, 13 and 17 (see Table 1 on page 8). FISH can be done with samples of either blood or bone marrow cells.

About 80 percent of CLL patients who undergo FISH testing have cytogenetic abnormalities in their leukemia cells. Cytogenetics is the study of chromosomes. Cytogenetic abnormalities can help the doctor identify people with CLL who are more likely to progress to the point of requiring treatment and those who may benefit most from the use of certain types of drug therapy.

**Karyotyping.** This test provides a snapshot of the chromosomes by pairing and arranging all the chromosomes of a cell in order. The test can show if there is an abnormality in the size, shape or number of chromosomes. A blood or bone marrow sample from the patient can be used. In CLL, a “complex karyotype” is associated with a poorer prognosis. A complex karyotype is defined by the presence of three or more unrelated defects in chromosomes that occur in more than one cell. The FISH and karyotyping tests can help distinguish CLL from other lymphoproliferative diseases.

**DNA Sequencing.** This lab test uses blood or marrow samples to look for mutations in genes. In CLL, DNA sequencing is used to test for mutations in the immunoglobulin heavy chain variable (IGHV) region and NOTCH1, SF3B1 and TP53 genes. Normal immunoglobulins or antibodies are made of two heavy chain proteins and two light chain proteins. The IGHV region genes in B cells
give instructions for making the heavy chain component. These genes may or may not be mutated in individuals with CLL; the patient’s prognosis is better if the IGHV gene is mutated. The TP53 gene makes a protein that signals for either the repair or the destruction of abnormal cells. It helps prevent tumors from forming. In CLL, mutated TP53 is associated with a poor prognosis. See Table 2 on pages 8 and 9 for more information about these factors.

During the last decade, numerous markers have been discovered that can help identify patients who have different rates of disease progression requiring therapy. Examples of these markers include:

- Serum markers, such as beta-2 microglobulin
- Genetic markers, including immunoglobulin heavy chain variable (IGHV) region and TP53 gene mutational status
- Genetic abnormalities detected by “fluorescence in situ hybridization” (FISH) or metaphase cytogenetics
- Protein markers, such as zeta-chain-associated protein kinase 70 (ZAP-70), cluster designation 38 (CD38) or CD49d

See Table 2 on pages 8 and 9, Tables 3A and 3B on pages 10 and 11 and the Health Terms section on page 45 for more information on these factors.

**Hepatitis B Testing.** It is important for your treatment team to know if you have ever been infected with hepatitis B because CLL and some of its treatments can cause the hepatitis B virus to reactivate.

**Beta-2 Microglobulin.** This small protein is made by many types of cells, including CLL cells. The protein can be measured through a blood chemistry test. High levels of beta-2 microglobulin (B2M) are associated with a type of CLL that is harder to treat.

**Lactate Dehydrogenase (LDH).** This protein is present in most cells. It gets into the bloodstream when a cell becomes damaged. A high level of LDH, detected by a blood test, indicates cell damage and may also indicate the presence of cancer or other health conditions. When related to cancer, a high level of this protein may be a sign that treatment may be needed soon.
### Table 1. Common Cytogenetic Abnormalities in CLL

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Features</th>
<th>Frequency</th>
<th>Associated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(13q)</td>
<td>Deletion in the long arm of chromosome 13</td>
<td>55%</td>
<td>Favorable outcome if not associated with any other abnormality</td>
</tr>
</tbody>
</table>
| Trisomy 12  | Three copies of chromosome 12                 | 16%       | • If by itself, associated with intermediate-risk CLL  
|             |                                               |           | • If in conjunction with other abnormalities, associated with higher-risk CLL |
| Del(11q)    | • Deletion in the long arm of chromosome 11   | 18%       | High risk                                                |
|             | • Often associated with extensive lymph node involvement |           |                                                          |
| Del(17p)    | • Deletion in short arm of chromosome 17      | <10% at diagnosis | High risk                                                |
|             | • Critical *TP53* gene in the region is deleted | Up to 30% in relapse/refractory cases |                                                          |
|             | • Does not respond well to chemotherapy or chemoimmunotherapy |           |                                                          |

**Table 2, below,** lists other factors that may be signs of faster-growing (higher-risk) CLL and indicate the need for closer monitoring of the patient.

### Table 2. Some Factors Associated with Higher-Risk CLL

<table>
<thead>
<tr>
<th>Factor</th>
<th>Features and Associated Outcomes</th>
</tr>
</thead>
</table>
| Blood lymphocyte doubling      | • People with CLL whose lymphocyte count doubles in one year have higher-risk CLL and may need closer monitoring.  
|                                | • A lymphocyte count that remains stable generally indicates a relatively lower risk.              |
| CD38                           | • CD38 expression is an indicator of higher-risk CLL.*                                             |
| Beta-2 microglobulin (B2M)      | • Beta-2 microglobulin (B2M) is a protein that is shed from CLL cells.  
|                                | • It is associated with a greater extent of disease.                                                |
| CD49d                          | • CD49d expression is an indicator of higher-risk disease.*                                        |

*CD is the abbreviation for “cluster designation,” a term that denotes a specific molecule on the surface of an immune cell.*
### Table 2 (con't). Some Factors Associated with Higher-Risk CLL

<table>
<thead>
<tr>
<th>Factor</th>
<th>Features and Associated Outcomes</th>
</tr>
</thead>
</table>
| **IGHV**        | • The unmutated immunoglobulin heavy chain variable (IGHV) region gene is associated with higher-risk disease.  
                  • About 40% of CLL patients have unmutated IGHV status at diagnosis, while the other 60% have the more favorable IGHV-mutated disease.  
                  • Testing for IGHV mutational status is necessary for treatment when considering chemoimmunotherapy.  
                  • IGHV is a stable marker (does not tend to change over time), so this mutation should only need to be checked once.                                                                 |
| **ZAP-70**      | • ZAP-70 is the abbreviation for zeta-chain-associated protein kinase 70.  
                  • Protein expressed near the surface membrane of T-cells  
                  • Plays a key role in T-cell signaling  
                  • Increased expression of ZAP-70 may be associated with higher-risk disease.                                                                                                                                               |
| **NOTCH1 gene mutations** | • NOTCH1 is a gene involved in the development of different types of blood cells.  
                  • Approximately 10%-15% of CLL patients have this mutation.  
                  • CLL patients who have NOTCH1 gene mutations may have a faster progression of disease and a less favorable outcome.  
                  • Associated with increased risk of transformation to diffuse large B-cell lymphoma (Richter’s transformation)                                                                                                           |
| **SF3B1 gene mutations** | • The SF3B1 gene is involved in the formation of certain proteins in CLL and other blood cancers.  
                  • Approximately 10%-15% percent of CLL patients have this mutation, which results in dysfunctional protein processing.  
                  • CLL patients who have SF3B1 gene mutations may have a faster progression of disease and a less favorable outcome.  
                  • Associated with resistance to treatment with fludarabine                                                                                           |
| **TP53 gene mutations** | • The TP53 gene is considered the gatekeeper that protects cell DNA from damage.  
                  • In cancer cells, this mutation leads to increased cell growth and resistance to chemotherapy.  
                  • Mutation of the TP53 gene is very commonly seen in patients who also have deletion 17p (del 17p).  
                  • CLL patients who have this mutation may have a faster progression of disease that is resistant to traditional therapy and a less favorable outcome.  
                  • The recommended regimens for the treatment of patients with del(17p) or TP53 gene mutations are ibrutinib, venetoclax and idelalisib.                                                                 |


Commonly Used Staging Systems for CLL. Staging helps doctors to assess how the disease is expected to progress over time and also to develop a treatment plan. Two staging systems, the Rai system and the Binet system, have been used throughout the world in both clinical practice and in clinical trial settings. In 2016, a new prognostic model called the CLL International Prognostic Index (CLL-IPI) was released, enabling a more targeted management of CLL.

The Rai and Binet staging systems for CLL are both based on the following factors:

- Abnormal increase in number of lymphocytes (lymphocytosis)
- Presence of enlarged lymph nodes
- Presence of enlarged spleen and/or liver
- Presence of anemia (abnormal decrease in the number of red blood cells)
- Presence of thrombocytopenia (abnormal decrease in the number of platelets)

The Rai staging system categorizes patients into three separate risk groups, as shown in Table 3A, below.

Table 3A. Rai Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (Stage 0)</td>
<td>Abnormal increase in the number of lymphocytes in the circulating blood and marrow</td>
</tr>
</tbody>
</table>
| Intermediate Risk (Stages I & II) | • Abnormal increase in the number of lymphocytes in the circulating blood and marrow  
|                               | • Enlarged lymph nodes                                                           |
|                               | OR                                                                              |
|                               | • Abnormal increase in the number of lymphocytes in the circulating blood and marrow  
|                               | • Enlarged spleen and/or liver                                                   |
| High Risk (Stages III & IV)  | • Abnormal increase in the number of lymphocytes in the circulating blood and marrow  
|                               | • Anemia (hemoglobin < 11 g/dL)                                                 |
|                               | OR                                                                              |
|                               | • Abnormal increase in the number of lymphocytes in the circulating blood and marrow  
|                               | • Thrombocytopenia (platelet counts < 100,000/μL)                              |
The Binet system (see Table 3B below) is based on the number of involved areas (defined as a lymph node larger than 1 cm), the enlargement of organs (liver and spleen) and whether there are reduced numbers of red blood cells and/or platelets.

### Table 3B. Binet Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| A     | • No anemia (hemoglobin ≥ 10 g/dL)  
       | • No thrombocytopenia (platelets ≥ 100,000/mm³)  
       | • Less than 3 areas of lymphoid tissue enlargement |
| B     | • No anemia (hemoglobin ≥ 10 g/dL)  
       | • No thrombocytopenia (platelets ≥ 100,000/mm³)  
       | • 3 or more areas of lymphoid tissue enlargement |
| C     | • Anemia (hemoglobin < 10 g/dL)  
       | • Thrombocytopenia (platelets < 100,000/mm³)  
       | • Any number of areas of lymphoid tissue enlargement |

Although the Rai and Binet staging systems are still widely used, they have shown certain limitations in the ability to predict which patients will have a more aggressive progression and which will have less favorable responses to treatment. These staging systems were developed before the discovery of genetic and molecular prognostic features of CLL and therefore cannot be used to estimate the risk of disease progression in patients with early-stage disease, or to predict responses to therapy.

To produce a more comprehensive prognostic system, some of these genetic features have been integrated into the CLL International Prognostic Index (CLL-IPI). The CLL-IPI combines genetic, biochemical and clinical parameters into a prognostic model, categorizing patients into four prognostic subgroups: low, intermediate, high and very high risk. Five independent prognostic factors were identified:

- **TP53** deleted or mutated = 4 points
- Unmutated **IGHV** = 2 points
- Serum beta-2 microglobulin concentration > 3.5 mg/L = 2 points
- Rai I-V or Binet B-C = 1 point
- Patient age > 65 years = 1 point

The CLL-IPI also provides treatment recommendations for the different patient risk groups (see Table 4 on page 12).
Table 4. CLL International Prognostic Index (CLL-IPI) Categories

<table>
<thead>
<tr>
<th>CLL-IPI Category</th>
<th>Risk Score</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>0-1</td>
<td>Do not treat</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>2-3</td>
<td>Do not treat unless the disease is highly symptomatic</td>
</tr>
<tr>
<td>High Risk</td>
<td>4-6</td>
<td>Treat unless the patient is asymptomatic</td>
</tr>
<tr>
<td>Very high risk</td>
<td>7-10</td>
<td>If the decision is made to treat, use novel agents or treatment in a clinical trial rather than chemotherapy</td>
</tr>
</tbody>
</table>

Types of Treatment for CLL

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Patients have two treatment options: standard therapies or treatment in a clinical trial. It is important to talk to your healthcare team about the best treatment option for you.

Speak with your doctor about treatment sequencing (the determination of the best first-line treatment and the order of additional therapies once treatment begins). This is likely to change as new treatments/drug combinations are approved.

Also talk to your doctor or healthcare team about the cost of treatment and how long treatment will last. Once these factors are understood, you can begin to plan how to pay for your treatment.

Treatment options for CLL have evolved during the last several decades. The development of targeted therapies has led to the design of new and more effective regimens, resulting in better outcomes for patients. Examples of targeted therapies are monoclonal antibodies that target cell surface antigens and immunomodulating agents that work with the patient’s own immune system to attack leukemic cells. The field of CLL treatment is moving away from chemotherapy to targeted therapies.

Although current therapies do not offer patients a cure for CLL, there are now many treatment options that have the potential to give patients longer remissions and a better quality of life. Treatment options for CLL include

- The watch-and-wait approach
- Single or combination drug therapy
- Chemoimmunotherapy
Targeted therapies

- Monoclonal antibody therapies
- A clinical trial (at any point treatment is being discussed; see Research and Clinical Trials on page 31)
- Radiation therapy (rarely used)
- Splenectomy (rarely used)
- Allogeneic stem cell transplantation

The goals of CLL treatments are to

- Stop the CLL cells from reproducing
-Activate programmed cell death (apoptosis)
- Provide long periods of remission (when there are no signs or symptoms of CLL)
- Improve survival
- Help people manage symptoms and complications of the disease

A person with CLL is usually treated by a hematologist/oncologist. Patients are advised to consult with a doctor who specializes in CLL and to discuss their most appropriate treatment options—including whether participation in a clinical trial is recommended.

**Watch and Wait.** In this approach, also called “active surveillance,” people with CLL are observed regularly by their hematologist-oncologist. This approach includes

- Regular medical examinations (check size of lymph nodes, spleen, etc.)
- Regular testing (blood work) to determine whether the disease is stable or beginning to progress

You will not be treated with drugs or other therapies during the watch-and-wait period. People are often concerned when they receive a diagnosis of CLL and then learn that they will not begin treatment right away. The watch-and-wait approach is the current standard of care when there are minimal changes to a person’s red blood cell and platelet counts and no symptoms. A rapidly rising lymphocyte count in patients without symptoms may not necessitate treatment.

- Are you concerned that you will not begin treatment right away? Speak to your doctor to get more information.

This approach may seem scary and counterintuitive. Many people who are diagnosed with cancer begin drug treatment right away. But CLL can be a very slow-progressing disease, and in many patients the disease will not be serious enough to warrant treatment with drugs at the time of diagnosis. In addition, a small proportion of patients may never need therapy for their CLL.
Many studies have compared the watch-and-wait approach to an early treatment approach for people with low-risk CLL. Study findings include the following information:

- To date, clinical trials have shown no benefit to early treatment.
- Several studies have confirmed that patients with early-stage disease do not benefit from the use of alkylating agents (see Table 6 on page 19) or aggressive chemotherapy, and these treatments do not prolong survival.
- There are risks to early treatment, including potential side effects and treatment complications.
- Patients may build up a resistance to the drugs used and may not be able to use them again when treatment for progressive disease is necessary.

For more information, visit www.LLS.org/booklets to read the free LLS fact sheet *Watch and Wait*.

**When to Start Treatment.** Some people with CLL can be managed with a watch-and-wait approach for years before their disease progresses. The decision to treat a person with CLL is based on a number of factors that indicate the disease is progressing. According to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines, the following conditions define active disease, and the patient should meet at least one of these criteria:

- Extranodal (outside of lymph nodes) involvement in skin, kidneys, lungs and spine
- Enlarging lymph nodes (at least 10 cm) noted over a series of clinical exams
- Enlarging spleen noted over a series of clinical exams
- Evidence of progressive marrow failure by the development or worsening of
  - Anemia (red blood cell count of less than 10 g/dL), and/or
  - Thrombocytopenia (platelet count of less than 100,000/μL)
- Autoimmune anemia and/or thrombocytopenia with poor response to corticosteroids
- Lymphocyte doubling time of less than 6 months, or progressive lymphocytosis with an increase of more than 50 percent over a two-month period
- Presence of CLL symptoms
  - Significant fatigue
  - Night sweats (more than 1 per month without evidence of infection)
  - Unexplained weight loss (10% or more of baseline weight over the course of less than 6 months)
  - Fever (higher than 100.5°F for 2 or more weeks) without other evidence of infection
Table 5, below, summarizes the tests to be done before a patient begins treatment.

### Table 5. Baseline Evaluation of Patients with CLL

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>General Practice</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tests to establish the diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count and differential count</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Immunophenotyping of peripheral blood lymphocytes</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Assessment prior to treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History and physical; performance status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Complete blood count and differential count</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Marrow aspiration and biopsy</td>
<td>When clinically indicated (unclear cytopenia)</td>
<td>Desirable</td>
</tr>
<tr>
<td>Serum chemistry, serum immunoglobulin and direct antiglobulin test</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Infectious disease status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Additional tests prior to treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p) and add(12) in peripheral blood lymphocytes</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)</td>
<td>NGI</td>
<td>Desirable</td>
</tr>
<tr>
<td>TP53 gene mutation</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>IGHV mutational status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Serum beta-2 microglobulin</td>
<td>Desirable</td>
<td>Always</td>
</tr>
<tr>
<td>CT scan of chest, abdomen and pelvis</td>
<td>NGI</td>
<td>Desirable</td>
</tr>
<tr>
<td>MRI and PET scans</td>
<td>NGI</td>
<td>NGI</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Possible</td>
<td>NGI</td>
</tr>
</tbody>
</table>

“General practice” is defined as the use of accepted treatment options for a CLL patient not enrolled in a clinical trial. Abbreviations: FISH, fluorescence in situ hybridization; del, a change in the number of DNA bases by the removal of a piece of DNA; add, the addition of an extra copy of a chromosome; NGI, not generally indicated; IGHV, immunoglobulin heavy chain variable; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

**Initial Treatment of Symptomatic CLL.** Treatment of CLL is started when symptoms develop that are associated with active disease.

Before beginning therapy, it is important for patients to have:

- Cytogenetic testing (FISH) to determine if del(17p) or del(11q) is present
  - If this test was not done at the time of the initial diagnosis, it should be done at this time.
  - If previous testing was done months or years ago, this test should be repeated.
- Testing to assess *IGHV* and *TP53* gene mutational status
- Testing for prior hepatitis B exposure
- A bone marrow aspiration and biopsy
- A direct antibody test (DAT, also known as the “direct Coombs test”)
  - If anemia is present
  - To identify possible hemolysis (red blood cell destruction)

Because CLL is typically a disease of elderly patients (median age at diagnosis is 70 years, although it has been diagnosed in people as young as 30), the evaluation of a patient’s fitness and the identification of other medical conditions or problems (comorbidities) that may affect CLL treatment is very important. CLL treatment options are determined by the patient’s age, fitness and health.

Another important factor for the choice of treatment is the patient’s genetic risk profile. For instance, the deletion of the short arm of chromosome 17, abbreviated as del(17p), is associated with a less favorable prognosis and resistance to chemotherapy. Thus, the presence or absence of del(17p) is essential information that must be taken into account when determining the choice of treatment. Testing for *IGHV* mutational status is also necessary when considering chemoimmunotherapy.

After all these tests are completed, patients are typically classified into one of three categories: the “FIT” category, the “OLDER OR LESS FIT” category or the “HIGH-RISK” category.

**THE FIT CATEGORY:** CLL Patients Younger Than 65 to 70 Years Without Del(17p) or TP53 Mutations. Suggested first-line treatment regimens for this group of patients include the following:

- Ibrutinib (Imbruvica®)
- Venetoclax (Venclexta®) in combination with obinutuzumab (Gazyva®)
- Ibrutinib in combination with rituximab
○ FCR (fludarabine [Fludara®], cyclophosphamide [Cytoxan®] and rituximab [Rituxan®])
○ FR (fludarabine [Fludara®] and rituximab [Rituxan®])
○ Bendamustine hydrochloride (Bendeka®) plus anti-CD20 monoclonal antibody
○ High-dose methylprednisolone (HDMP) plus rituximab
○ PCR (pentostatin, cyclophosphamide, rituximab)

Patients classified in the fit category typically do not have significant comorbidities. The first treatment options prescribed to many patients in this category include ibrutinib, either alone or in combination with rituximab, and venetoclax in combination with obinutuzumab. However, some patients may be eligible for intensive chemoimmunotherapy. These patients are generally treated with a combination called FCR (see Chemoimmunotherapy on page 23 and Monoclonal Antibody Therapies on page 21). This therapy is very effective at reducing disease and, for most patients, the treatment is tolerable. Studies have shown that this combination is particularly effective in patients with the *IGHV* gene mutation but without the del(17p) or *TP53* mutations.

Results from longer follow-up studies have shown that a significant number of patients who received FCR continue to have no detectable disease 10 years after the end of treatment. However, there are some complications associated with this therapy. Some studies have indicated a higher incidence of neutropenia and a more frequent occurrence of viral and bacterial infections for up to 2 years after the completion of treatment. Recent research has also indicated that up to 5 percent of patients may develop therapy-related myelodysplastic syndrome or acute myeloid leukemia. Despite the potential complications, FCR remains a very good option given the achievement of long-term remission in a majority of patients. Many of these patients had no evidence of minimal residual disease (expressed as MRD negative or MRD−) as detected by polymerase chain reaction (PCR) testing, which raises the possibility of a cure. This combination should only be used for patients who have the *IGHV* gene mutation but do not have the del(17p) or *TP53* mutations.

**OLDER OR LESS-FIT CATEGORY: CLL Patients Older Than 65 to 70 Years Without Del(17p) or TP53 Mutations.** Older adults and patients with significant comorbidities are considered to be in the “older or less-fit” category. For both fit and less-fit older patients who have CLL, the following combinations of drugs are recommended for first-line treatment:

○ Venetoclax (Venclexta®) and obinutuzumab (Gazyva®)
○ Ibrutinib (Imbruvica®)
○ Chlorambucil plus anti-CD20 monoclonal antibody
○ High-dose methylprednisolone (HDMP) plus rituximab
Ibrutinib and obinutuzumab

Obinutuzumab

Chlorambucil

Rituximab (Rituxan®)

Bendamustine plus anti-CD20 monoclonal antibody

Ibrutinib (Imbruvica®), given by mouth, is approved for first-line treatment. Venetoclax (Venclexta®), given by mouth, is approved in combination with obinutuzumab (Gazyva®), given by IV, for the treatment of people with previously untreated CLL or small lymphocytic lymphoma (SLL). This combination is a chemotherapy-free option that has a 12-month fixed duration of therapy. Results showed that patients achieved durable progression-free survival after 12 months and a higher rate of MRD negativity compared to obinutuzumab plus chlorambucil.

For some older patients, the combination of bendamustine with rituximab (BR) may be a good option. Examples of this might include cases when renal insufficiency is present or autoimmune complications develop.

HIGH-RISK CATEGORY: All CLL Patients Who Have Del(17p) or TP53 Mutations.

Both young and older patients who have del(17p) or TP53 mutations do not respond well to any type of chemoimmunotherapy treatment, or are likely to have early relapses if the first-line therapy is chemoimmunotherapy. The following treatments are approved for patients with del(17p) and should be used as a first option, unless there are contraindications:

- Ibrutinib (Imbruvica®), given by mouth
- Venetoclax (Venclexta®) plus obinutuzumab (Gazyva®), given by IV

Rituximab (Rituxan®) plus high-dose methylprednisolone is a regimen that is effective for reducing CLL in this patient group. Other options include alemtuzumab (Campath®), with or without rituximab and obinutuzumab.

If these treatments are not appropriate, a clinical trial should be considered. Allogeneic stem cell transplantation may also be an option in this patient group (see page 26).
Table 6. Some Drugs Approved or in Clinical Trials for the Treatment of CLL

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Antitumor Antibiotics</th>
<th>DNA-Damaging Agents</th>
<th>Antimetabolites</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ibrutinib (Imbruvica®)</td>
<td>- Doxorubicin (Adriamycin®)</td>
<td>- Cyclophosphamide (Cytoxan®)</td>
<td>- Cladribine (2-CdA; Leustatin®)</td>
<td>- Prednisone</td>
</tr>
<tr>
<td>- Venetoclax (Venclexta®)</td>
<td></td>
<td></td>
<td>- Fludarabine (Fludara®)</td>
<td>- Dexamethasone</td>
</tr>
<tr>
<td>- Idelalisib (Zydelig®)</td>
<td></td>
<td></td>
<td>- Pentostatin (Nipent®)</td>
<td></td>
</tr>
<tr>
<td>- Acalabrutinib (Calquence®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lenalidomide (Revlimid®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monoclonal Antibodies
- Alemtuzumab (Campath®)
- Obinutuzumab (Gazyva®)
- Ofatumumab (Arzerra®)
- Rituximab (Rituxan®)
- Rituximab and hyaluronidase human (Rituxan Hycela®)

Alkylating agents
- Bendamustine hydrochloride (Bendeka®)
- Chlorambucil (Leukeran®)

*After the first dose of Rituxan, patients may be switched to Rituxan Hycela.

It is possible for patients to be treated with drugs that are not listed in this table and still receive appropriate and effective treatment for CLL.

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Targeted Therapies. The drugs used in these therapies target specific parts of cancer cells. In most cases, the drugs administered in targeted therapies are given orally and are generally better tolerated than agents used in chemotherapy.

Kinase Inhibitors. Kinases are enzymes that are found in both normal cells and cancer cells. Kinases move chemicals called phosphates from one molecule to another. Kinase inhibitors stop the phosphates from being moved and block growth signals and pathways within cancer cells. These drugs are associated with fewer side effects than chemotherapy agents. There are many different kinases in CLL cells, including phosphatidylinositol 3-kinase (PI3-kinase) and Bruton tyrosine kinase (BTK), which are the focus of several targeted therapies.

- **Ibrutinib (Imbruvica®)**
  - It is an oral targeted therapy that is taken once a day.
  - It is an inhibitor drug that targets Bruton’s tyrosine kinase (BTK).
It is FDA-approved for the treatment of CLL patients with or without del(17p) as first-line therapy and for relapsed or refractory CLL. It is approved as a single agent and in combination with bendamustine and rituxan or with obinutuzumab.

Patients with del(17p) or a complex karyotype (presence of three or more mutations) still have a higher risk of relapsing than patients in other genetic profile groups.

Symptomatic patients with CLL take ibrutinib continuously until it does not work anymore, or until side effects occur that require them to stop taking it.

Thus far, patients have taken ibrutinib for more than 5 years without any long-term side effects.

Unlike chemotherapy, ibrutinib initially causes the leukemia cell count to increase as lymph nodes shrink due to the lymphocytes being pushed into the blood.

In most patients, this is followed by a decline in the number of leukemia cells in the blood, which may take several months.

The common side effects of ibrutinib are rash, loose stools, heartburn, fatigue, infections and joint aches. These symptoms generally subside with time.

Serious but uncommon side effects include bleeding, atrial fibrillation and kidney problems.

Ibrutinib can increase the risk of bleeding and should not be used with medicines that may increase the risk of bleeding, including aspirin and anti-inflammatories, blood thinners and supplements such as fish oil, vitamin E and flaxseed.

Because of the risk of bleeding, for minor surgeries, ibrutinib should be stopped for 3 days before and 3 days after surgery; for major surgeries it should be stopped for 7 days before and 7 days after surgery.

Idelalisib (Zydelig®) is a targeted therapy that blocks the kinase protein known as PI3K. This oral medication has been approved for the treatment of relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities. See page 25 for more information on this medication.

**BCL2 proteins and cell death.** B-cell lymphoma 2 (BCL2) proteins are a family of proteins that regulate cell growth and cell death. In CLL, abnormal function of BCL2 proteins prevents normal cell death, resulting in the uncontrolled growth of cancer cells.
Venetoclax (Venclexta®)

- It is an oral targeted therapy that is taken once a day.
- It is a small-molecule inhibitor that targets the BCL2 protein, a protein overexpressed in CLL.
- It is FDA approved for the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL). It is approved in combination with obinutuzumab (Gazyva®) for the treatment of people with previously untreated CLL or SLL. This treatment combination allows patients to stop treatment after 12 months. Results of studies showed durable progression-free survival after 12 months and a higher rate of MRD negativity compared to obinutuzumab plus chlorambucil. It is approved in combination with rituximab (Rituxan®) for the treatment of patients whose cancer has progressed after at least one prior treatment, regardless of whether their cancer cells have del(17p). This treatment combination allows patients to stop treatment after approximately two years.
- It is not a chemotherapy. It is a pill that works differently than other treatments to help restore apoptosis, a natural process that is disrupted when you have cancer. Through apoptosis, your body kills cancer cells.
- Common side effects include low blood cell counts, diarrhea, nausea, upper respiratory infection and fatigue.
- There is a risk of tumor lysis syndrome, but this can be prevented through appropriate monitoring and prophylaxis measures (see page 30). Talk to your doctor about what this means in your case.

Monoclonal Antibody Therapies. Monoclonal antibodies are proteins made in the laboratory that either react with or attach to specific antigens on the target cells. Examples of antibody therapies that target CD20 and CD52 include the following:

Monoclonal antibodies that target CD20

- Rituximab (Rituxan®)—Rituximab has become one of the standard treatments for CLL. It is approved for both previously untreated and previously treated CD20-positive CLL in combination with fludarabine (Fludara®) and cyclophosphamide. It is also being combined with other targeted agents to treat CLL. Rituximab is a liquid that is slowly administered via intravenous (IV) infusion. It is used in combination therapies, either as part of initial treatment or as part of a second-line regimen, but it may be also used as monotherapy.
- Rituximab and hyaluronidase human (Rituxan Hycela®)—Given subcutaneously, this drug is approved for patients with previously untreated or previously treated CLL in combination with fludarabine and cyclophosphamide (FC). Treatment with Rituxan Hycela should be used only after patients have received at least one full dose of a rituximab product intravenously.
Obinutuzumab (Gazyva®)—This is approved in combination with venetoclax (Venclexta®) for the treatment of people with previously untreated CLL or small lymphocytic lymphoma (SLL). This treatment combination allows patients to stop treatment after 12 months. It is also approved in combination with chlorambucil for the treatment of patients with previously untreated CLL. It is a liquid that is administered by slow injection into a vein (by IV infusion) over a period of a few hours.

Ofatumumab (Arzerra®)—Generally, ofatumumab is used if CLL does not respond to other treatments, such as other monoclonal antibodies or chemotherapy. Like rituximab (Rituxan®), ofatumumab is administered via IV infusion. It takes about 6 hours to receive the first dose. Ofatumumab is approved

- In combination with chlorambucil for previously untreated patients for whom fludarabine-based therapy is considered inappropriate
- In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL
- For extended treatment of patients who have had complete or partial response after at least two lines of therapy for recurrent or progressive CLL
- For the treatment of patients with CLL that is refractory to fludarabine and alemtuzumab (Campath®)

Monoclonal antibodies that target CD52

Alemtuzumab (Campath®)—This drug targets the CD52 antigen found on the surface of CLL cells. It is indicated as a single agent for the treatment of B-cell CLL.

Chemotherapy. Chemotherapy drugs are designed to kill cancer cells. Some drugs kill cancer cells by damaging the DNA of the cancer cells or by disrupting the process of making DNA. Other drugs interfere with cell components that are needed for making new cells. Chemotherapy is typically given in cycles, with each period of treatment followed by a rest period. There are many types of chemotherapeutic agents, including the following:

Antimetabolites

- Cladribine (Leustatin®)
- Fludarabine (Fludara®)
- Pentostatin (Nipent®)
Alkylating agents
- Bendamustine hydrochloride (Bendeka®)
- Chlorambucil (Leukeran®)
- Cyclophosphamide (Cytoxan®)

Corticosteroids may also be given with chemotherapy. Examples of corticosteroids include
- Prednisone
- Dexamethasone

**Chemioimmunotherapy.** With the introduction of the anti-CD20 monoclonal antibody rituximab (Rituxan®), chemoimmunotherapy regimens combining chemotherapy drugs with rituximab were established. Examples of these are
- FCR: fludarabine (Fludara), cyclophosphamide and rituximab (Rituxan)
- BR: bendamustine (Bendeka®) and rituximab

Before the introduction of newer targeted agents, younger patients with CLL who required treatment were offered a chemoimmunotherapy regimen, provided they were in good health and had no major comorbidities. The goal of these higher-intensity treatments was to induce deep and durable remissions for patients. With the advent and approval of new targeted agents, there are additional treatment options for patients. Currently, first-line chemoimmunotherapy is considered for young, fit patients with low-risk disease—patients with mutated IGHV but without del(17p) or TP53 mutations—given the excellent long-term outcomes for these patients.

**Radiation Therapy.** Radiation therapy uses high-energy rays to destroy cancer cells. It is not part of standard treatment for CLL, but it is sometimes used to shrink an enlarged spleen, large lymph node masses, or masses in locations that interfere with the function of a neighboring body part, such as the kidney, the gastrointestinal tract or the throat. It can also be helpful in treating pain from bone damage caused by leukemia cells growing in the marrow. Radiation is rarely used in CLL.

**Splenectomy.** In some patients, CLL cells can accumulate in the spleen. Sometimes the spleen becomes so enlarged that it starts pressing on nearby organs, causing discomfort. If it is very enlarged, surgical removal of the spleen (splenectomy) may improve blood cell counts and reduce the need for transfusions. This approach is used selectively for patients who have severe recurrent bouts of autoimmune diseases that target either the red blood cells—causing autoimmune hemolytic anemia (AIHA)—or the platelets, causing immune thrombocytopenic purpura (ITP). In such cases, removal of the spleen can help reduce the severity of the anemia (in AIHA) or low platelet count (in ITP).
Treatments for Relapsed or Refractory CLL

The term “relapsed” is used to refer to cases in which the CLL responded to therapy but, after 6 or more months, became active again. “Refractory” is the term used when treatment does not result in a remission (but the disease may be stable), or the disease gets worse within 6 months of the last treatment.

Patients who are treated for relapsed or refractory CLL often have good quality of life during years of remission after receiving this additional treatment. **Patients should be re-tested to find out if their mutation profile has changed before planning their next treatment.** If symptoms return, treatments similar to those used initially can be considered.

Abnormalities that involve the short arm of chromosome 17 are reported in about 5 percent of patients at the time of diagnosis; in patients with relapsed or refractory disease, the prevalence can increase to as high as 30 to 40 percent of patients. This can happen as a result of disease progression or past treatments.

The following drugs and treatments can be used to treat relapsed or refractory CLL:

- Ibrutinib (Imbruvica®) alone
- Venetoclax (Venclexta®) alone or with rituximab (Rituxan®)
- Duvelisib (Copiktra™)
- Idelalisib (Zydelig®) with rituximab
- Ofatumumab (Arzerra®)
- Combinations of ibrutinib or venetoclax with anti-CD20 antibodies
- Allogeneic stem cell transplantation
- Alemtuzumab (Campath®) alone or in combination

There is no role for chemoimmunotherapy in the relapsed/refractory CLL patient. See pages 19-23 and 25-26 for more information about the above list of treatments.

Ibrutinib (Imbruvica®) is approved for treatment of relapsed CLL patients. Idelalisib (Zydelig®), given in combination with rituximab, is approved for patients who have received at least one prior form of treatment. Idelalisib is given as an oral pill twice daily, and rituximab is given intravenously (IV) intermittently.

Idelalisib is continued indefinitely, as long as there is a good treatment response. Patients who have signs of disease progression while they are taking any of these medications should keep taking them until a new therapy is started. When relapse occurs during treatment with ibrutinib, it is mainly due to the acquisition of additional mutations. Some patients can have rapid tumor growth when these agents are stopped without the start of a new therapy.
Patients with del(17p) do respond to ibrutinib, but they may have a higher relapse rate than other patients. Venetoclax (Venclexta®) plus rituximab (Rituxan®) is approved as a treatment for patients who have CLL with or without del(17p) who have had at least one prior treatment. It contains no chemotherapy and is given for 24 months. Duvelisib (Copiktra™) is approved for treatment of relapsed and refractory CLL patients after at least two prior therapies.

Doctors deciding whether to treat with ibrutinib, idelalisib, venetoclax or duvelisib will consider the side effects of these medications and tailor the treatment to the individual patient. For more information about ibrutinib and venetoclax, see pages 19-21.

Patients who relapse are advised to speak to their doctors about whether treatment in a clinical trial is a good option. Clinical trials involving drug therapies or allogeneic stem cell transplantation may offer more appropriate treatment options (see Research and Clinical Trials on page 31).

Information about idelalisib (Zydelig®)

- It is an oral targeted therapy.
- It is an inhibitor of the kinase called phosphoinositide 3-kinase (PI3K)-delta.
- It is FDA approved for the treatment of relapsed CLL, given in combination with rituximab.
  - Patients with del(17p) or a complex karyotype (presence of three or more mutations) still have a higher risk of relapsing than patients in other genetic profile groups.
- Symptomatic patients with relapsed CLL are given idelalisib twice daily continuously until it does not work anymore, or until side effects occur that require them to stop taking it.
- Similar to ibrutinib, idelalisib initially causes the leukemia blood cell count to increase as lymph node size decreases. In most patients, this is followed by a decline in the number of leukemia blood cells over time.
- The most common side effects are fatigue, liver function abnormalities, loose stools, heartburn and infection. Liver function abnormalities can be very serious, and it is important to monitor liver function with blood tests during the first several months of therapy.
- Idelalisib can cause an immune-related colitis associated with diarrhea that often shows up after 9 to 12 months (or longer) on therapy. Patients should be seen by the doctor if diarrhea develops.
- Idelalisib is not known to cause any excess bleeding and it can be given together with blood thinners. This is probably the best initial therapy for patients with relapsed CLL who require blood thinners or have a risk factor for excessive bleeding (for example, hemophilia).
○ Common side effects include low blood cell counts, diarrhea, nausea, upper respiratory infection and fatigue.

○ It also increases the risk for tumor lysis syndrome (see page 30). Talk to your doctor about what this means in your case.

**Information about Duvelisib (Copiktra™)**

○ It is an oral targeted therapy that is taken twice a day.

○ It is a dual inhibitor of the kinase called phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma.

○ It is FDA-approved for the treatment of relapsed or refractory chronic CLL or small lymphocytic lymphoma (SLL) after at least two prior therapies.

○ Common side effects include diarrhea, neutropenia, rash, fatigue, fever, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain and anemia.

**Stem Cell Transplantation.** Allogeneic stem cell transplantation is a treatment option for people who have relapsed or refractory high-risk CLL. Allogeneic transplantation is a kind of stem cell transplant that requires a matching donor. It may be an appropriate therapy for carefully selected younger people with CLL who can be matched with a stem cell donor. Talk to your doctor about the best treatment option for you.

A modified form of allogeneic stem cell transplantation called a “reduced-intensity” or “nonmyeloablative” allogeneic stem cell transplantation may be another transplant option for CLL patients who do not respond to other treatments. This type of transplant is generally done for high-risk CLL patients who have del(17p) or TP53 gene mutations identified early in the course of CLL. It is also done for relapsed patients who have received multiple therapies. Even if transplant is not eventually pursued, it is important for patients with high-risk CLL who require therapy, and also patients with relapsed CLL, to be evaluated for potential transplantation relatively early in the course of the disease.

**Please visit www.LLS.org/booklets to view the free LLS booklet Blood and Marrow Stem Cell Transplantation for more information.**

**CAR T-Cell Therapy.** This is a type of immunotherapy that consists of engineering a patient’s own immune cells to first recognize and then attack cancerous cells. This approach has shown very promising results in patients with blood cancers. The T cells are genetically engineered to produce receptors on their surface called “chimeric antigen receptors” (CARs). These receptors recognize and bind to a specific target found on the cancerous cells. Clinical trials are in progress to study the use of CD19-directed CAR T-cell therapy in the treatment of chemotherapy-resistant, relapsed CLL, or CLL that has not responded to ibrutinib.
treatment. The results of recent trials have demonstrated that this new approach can induce long-term, disease-free remissions in CLL patients.

For more information on this type of therapy, please see the free LLS booklet Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts.

Please call (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials.

Financial Challenges for CLL Patients

There have been significant advances in CLL therapy in the past few years. Novel oral targeted agents, such as ibrutinib (Imbruvica®), idelalisib (Zydelig®), venetoclax (Venclexta®) and duvelisib (Copiktra™), have demonstrated remarkable outcomes for patients with CLL, improving survival and quality of life. However, the price of these targeted medications is significantly higher than previous standard treatments, which raises concerns for both patients and providers.

Ibrutinib, idelalisib, venetoclax and duvelisib are costly medications. Ibrutinib, idelalisib and duvelisib require continuous daily use until the treatment no longer works or the disease progresses. Venetoclax therapy can be completed in a set amount of time: 1 year for front-line treatment and 2 years for relapsed/refractory cases. The economic impact of these medications could result in financial burden for patients, limited access to medications and lower adherence to treatments.

Speak to your doctor if you have any concerns about being able to afford your CLL medication. A member of your treatment team may be able to provide information and resources that can help. Health insurance plans may not cover all the costs of cancer care, but there are many resources to find assistance in paying for prescription drugs.

In addition, several major pharmaceutical manufacturers currently provide patient assistance or prescription assistance programs. These companies may be able to help by providing both insured and uninsured patients with free or reduced-cost medications.

For more assistance, call our LLS Information Specialists at (800) 955-4572 for information about patient prescription assistance programs, copay programs and LLS financial programs.

For more information and resources to cope with the financial aspects of cancer care, please visit www.LLS.org/booklets to see the LLS booklet Cancer and Your Finances.
Complications of CLL and Its Treatment

**Infection.** CLL patients may be more susceptible to infections caused by either the CLL itself and/or its treatment. A higher risk of infection is caused by

- The inability of the person’s CLL cells to make antibodies needed to fight infections
- The effect of treatment, which causes reduced numbers of certain infection-fighting white blood cells in the blood, specifically neutrophils and monocytes

Because of the increased risk for infection, vaccination for pneumococcal pneumonia (repeated every 5 years) and a yearly flu vaccine is recommended. CLL patients should never receive live vaccines (such as Zostavax, a live shingles vaccine) but can receive Shingrix® because it is an inactivated shingles vaccine.

Antibiotic therapy is usually required to treat bacterial or fungal infections that may occur during the course of the disease. People who get recurrent infections may also receive injections of immunoglobulin (gamma globulin) on a regular basis to correct the immune deficiency. This treatment is expensive, but it does help decrease the frequency of infections in CLL patients with low levels of immunoglobulin in their blood.

Cytomegalovirus (CMV) reactivation can occur in about 10 to 25 percent of patients with relapsed or refractory CLL treated with alemtuzumab. Rates of reactivation as high as 6 percent have also been reported in patients treated with idelalisib (Zydelig®). It is important to monitor for this potential problem during alemtuzumab or idelalisib therapy. Appropriate anti-infection prevention and routine monitoring for early signs of infection should be considered when patients receive therapy with alemtuzumab or idelalisib.

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy, with or without immunotherapy agents. It has also been reported in patients treated with alemtuzumab, ibrutinib and idelalisib. Prophylactic antiviral care and continuous monitoring for HBV are recommended for high-risk patients receiving therapy with CD20 monoclonal antibodies, alemtuzumab, ibrutinib and/or idelalisib.

**Low Blood Cell Counts.** Supportive (palliative) care for CLL may include administering blood cell growth factors to improve low blood cell counts. The use of white blood cell growth factors may benefit patients who experience prolonged low white blood cell counts after treatment. Examples of white blood cell growth factors are

- Granulocyte-colony stimulating factors (G-CSF)—filgrastim (Neupogen®) or pegfilgrastim (Neulasta®)—that can increase the number of neutrophils
Granulocyte macrophage-colony stimulating growth factor (GM-CSF)—sargramostim (Leukine®)—that can increase the number of neutrophils and monocytes

**Richter Transformation.** In about 2 to 10 percent of people with CLL, the disease transforms into something more complex. Of this relatively small group, the vast majority (95 percent) may develop diffuse large B-cell lymphoma (DLBCL) and the other 5 percent may develop Hodgkin lymphoma during the course of their disease and treatment. This is known as “Richter transformation” or “Richter’s syndrome.” This syndrome is much more common in patients with high-risk factors, such as: advanced Rai stage; del(17p), trisomy 12, *TP53* or *NOTCH1* mutations; and *IGHV*-unmutated CLL.

Richter transformation generally occurs between 2 and 6 years after the CLL diagnosis. Patients may have significantly enlarged lymph nodes, and they may experience fevers and weight loss. Lymphocyte masses may also develop in parts of the body other than the lymph nodes.

Patients with Richter transformation whose CLL has transformed into DLBCL are typically treated with regimens designed for DLBCL. Allogeneic stem cell transplantation may be considered following a response to initial therapy.

Standard Hodgkin lymphoma therapy is used for patients with Richter transformation whose CLL has transformed into Hodgkin lymphoma. With aggressive therapy, these patients tend to do better and may be cured of the lymphoma, although they will not be cured of the underlying CLL.

Recently, some treatment responses have been reported with the use of checkpoint inhibitors and CAR T-cell therapy. Patients should consider a clinical trial as a treatment option. If remission is achieved, patients should consider an allogeneic stem cell transplant, which represents the only curative option.

Call 800-955-4572 or visit www.LLS.org/CTSC for more information about clinical trials.

**Autoimmune Cytopenias.** Autoimmune hemolytic anemia (AIHA), immune-mediated thrombocytopenia (also known as “immune thrombocytopenic purpura” or ITP), and pure red blood cell aplasia (PRCA) are the most frequent autoimmune cytopenias in CLL patients. Autoimmune cytopenias occur in 4 to 10 percent of patients with CLL. Bone marrow tests are used to confirm the presence of these conditions.

AIHA is the most common form of autoimmune cytopenia. Patients who have AIHA produce antibodies that work against their own cells. These “autoantibodies” are usually directed against the patient’s own red blood cells, causing them to be eliminated rapidly from the blood. The loss of these red blood cells can worsen the effects of already low red blood cell counts.
The direct antiglobulin test (DAT, also known as the “direct Coombs test”) is used to identify the autoantibodies; however, most patients with AIHA have a negative DAT test result. In these cases, additional serum markers, such as low haptoglobin (a blood protein) and elevated reticulocyte (immature red blood cell) levels, are required to make the diagnosis. Other patients who are also more likely to develop AIHA include those with advanced disease and high-risk factors such as unmutated IGHV gene status, increased serum beta-2 microglobulin levels and high expression of ZAP-70. Less often, the antibody works against the platelets. This condition, called “immune thrombocytopenic purpura” (ITP), results in significantly decreased platelet counts.

The drugs prednisone, rituximab (Rituxan®) and cyclosporine are sometimes used to treat AIHA and ITP. Splenectomy should be considered in cases in which the patient does not respond to steroid therapy. The drugs romiplostim (Nplate®) and eltrombopag (Promacta®) are both FDA approved for the treatment of thrombocytopenia in patients with ITP that is resistant to other treatments.

**Tumor Flare Reactions.** Tumor flare is a painful enlargement of the lymph nodes that may be accompanied by elevated lymphocyte counts, enlarged spleen, low-grade fever, rash and bone pain. These reactions are commonly seen in CLL patients treated with lenalidomide (Revlimid®). Use of steroid medications to control the inflammation, and antihistamines to manage the rash, is recommended.

**Tumor Lysis Syndrome.** Tumor lysis syndrome (TLS) is a potentially life-threatening condition that occurs when large amounts of tumor cells are killed at the same time by the cancer therapy, releasing their content into the bloodstream. Patients with bulky lymph nodes are considered at high risk for developing TLS, which is best managed if anticipated and treatment is started before chemotherapy. Treatment for TLS includes increased hydration, monitoring and treatment of electrolyte imbalances and abnormal uric acid levels, and therapy with the drug rasburicase (Elitek®), as needed.

**Second Cancer Risk.** People with CLL have a higher risk than those in the general population of developing a second cancer. This may be due to abnormalities in immune function associated with the disease and to the use of chemotherapeutic agents, which can induce potentially long-lasting remissions but are also associated with prolonged immunosuppression.

Second cancers are present at the time of CLL diagnosis in 15 to 18 percent of patients. The second cancers that are seen most frequently in CLL patients are acute myeloid leukemia, myelodysplastic syndromes, melanoma, gastrointestinal cancer, breast cancer, lung cancer, non-melanoma skin cancer, prostate cancer, kidney cancer, bladder cancer, and head and neck cancers.
Acute myeloid leukemia or myelodysplastic syndromes can develop in people diagnosed with CLL, whether they receive treatment or not. These complications are more common after treatment with fludarabine (Fludara) and cyclophosphamide (FC) or with FCR: fludarabine, cyclophosphamide and rituximab (Rituxan).

Although all CLL patients should be counseled about their increased risk for developing a second cancer, studies indicate there are some factors that may help predict the development of other malignancies in CLL patients. These include:

- Older age (older than 60 years)
- Male gender
- Elevated levels of certain blood markers, such as beta-2 microglobulin, lactate dehydrogenase and serum creatinine

It is important to have follow-up appointments with your hematologist-oncologist on a regular basis because of the increased risk of second cancers associated with CLL.

Visit www.LLS.org/booklets to find more information about long-term and late effects in the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Research and Clinical Trials

New approaches to CLL treatment are being studied in clinical trials that hold the promise of increasing the rate of remission, finding a chemotherapy-free treatment and eventually finding a cure for CLL. Many of these clinical trials are being supported by LLS research programs.

**Clinical Trials.** Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.
Research Approaches. A number of approaches are under study in clinical trials for the treatment of patients with CLL.

New Targeted Treatments. Specific new drug therapies under study in clinical trials for people with CLL include

- **Kinase Inhibitor Therapy.** Some types of cancer can be treated by kinase inhibitor drugs that target specific enzymes within the cancer cells that are involved in cell growth and death. These drugs may be associated with fewer side effects than traditional chemotherapy agents.
  - Ibrutinib (Imbruvica®)
  - Acalabrutinib (Calquence®)
  - Zanubrutinib (BGB-3111)
  - Entospletinib (GS-9973)
  - Tirabrutinib (ONO-4059 or GS-4059)
  - Duvelisib (Copiktra®)
  - Umbralisib (TGR-1202)

- **Monoclonal Antibodies**
  - Ofatumumab (Arzerra®)
  - Cirmtuzumab (UC-961)
  - Obinutuzumab (Gazyva®)
  - Ublituximab (TG-1101)

- **Combinations of Antibodies with Other Targeted Drugs Being Investigated in Clinical Trials**
  - Combinations with immunomodulatory drugs
  - Combination regimens of 3 or 4 drugs
  - Combinations with venetoclax (Venclexta®)

**Immunomodulatory Drug.** Lenalidomide (Revlimid®) is a targeted oral drug that is used to treat patients with myeloma. It stimulates a person’s own immune system to attack cancer cells. It also interferes with a wide variety of the components of the CLL microenvironment, the network of cells and molecules that allow CLL cells to survive and grow.

**Early Treatment in CLL.** Several ongoing trials are investigating the potential benefit of early treatment intervention, particularly in high-risk patients, with the use of less toxic novel agents.

**National Veteran Affairs Tumor Registry Study.** Exposure to Agent Orange has been associated with the development of CLL. This multi-center, retrospective
study focused on assessing the impact of Agent Orange exposure on the prognosis and management of CLL, using data from the National Veteran Affairs Tumor Registry. According to the study’s findings, exposure to Agent Orange was not associated with either unfavorable prognostic factors or shortened survival in the large veteran population examined.

**CLL Natural History Study.** This study helps researchers understand how CLL cells behave, which ultimately should help to develop new and better treatments for CLL patients. Applying new technologies to investigate the molecular basis and clinical indicators of CLL and small lymphocytic lymphoma (SLL) can clarify processes involved in disease progression and possibly lead to the discovery of targeted treatments. Patients may qualify for this clinical trial if they have never received treatment for their CLL.

**CAR T-Cell Therapy.** This type of immunotherapy consists of engineering a patient’s own immune cells to first recognize and then attack cancerous cells. This approach has shown very promising results in patients with blood cancers. The T cells are genetically engineered to produce receptors on their surface called “chimeric antigen receptors” (CARs). These receptors recognize and bind to a specific target found on the cancerous cells.

**For more information on this type of therapy, please see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts.***

**PD-1 Checkpoint Inhibitors.** A vital part of the immune system is its ability to distinguish healthy cells in the body from those that it recognizes as foreign or harmful. The immune system depends on multiple checkpoints—molecules on certain immune cells that need to be either activated or turned off in order to start an immune response. Cancer cells sometimes take advantage of these checkpoints to escape the detection of active immune cells. Programmed cell death 1 (PD-1) is a checkpoint protein that is found on the surface of T cells. It normally acts as a type of “off switch” that helps keep immune cells from attacking healthy cells in the body. It accomplishes this when it attaches to a PD-L1, a protein found on some normal cells and also in some cancer cells. When PD-1 binds to PD-L1, a message is sent to the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1 receptors, which help them avoid an immune attack.

Checkpoint inhibitors are drugs created to target PD-1 or PD-L1, blocking their actions and allowing the immune system to recognize and eliminate cancer cells. Two examples are

- **Nivolumab (Opdivo®)**
- **Pembrolizumab (Keytruda®)**

We encourage you to contact our Information Specialists and visit www.LLS.org/CTSC for more information about finding a clinical trial.
Treatment Response and Follow-Up Care

Treatment Outcomes. Treatment outcomes for people with CLL vary widely, and expected outcomes are influenced by the stage of the disease, the presence or absence of various factors associated with higher-risk disease, the overall health of the patient and other considerations. Current research suggests that newer treatment combinations and approaches may improve the length of survival. People with CLL should consult with their doctors to discuss individual potential outcomes.

Minimal Residual Disease. Some people who have been treated for CLL have such a low level of remaining CLL cells after treatment that these cells cannot be detected by the usual clinical tests, such as blood and bone marrow examinations. This is called “minimal residual disease” (MRD). Therefore, more sensitive tests may be performed to detect the presence of abnormal cells. The methods generally used to detect MRD in people with CLL are four-color flow cytometry and allele-specific polymerase chain reaction (AS-PCR). These tests are reliably sensitive to a level of less than one CLL cell in 10,000 leukocytes. Patients are classified as having an MRD-negative (MRD–) remission when they have less than one CLL cell per 10,000 leukocytes in blood or bone marrow cell samples (blood samples can generally be used to make this determination). However, some therapies clear CLL cells from the blood but not the bone marrow, which is the case when monoclonal antibody treatment is used. It may therefore be necessary to confirm that the bone marrow aspirate is also MRD negative when the blood has become MRD negative.

Having MRD-negative status after the end of treatment is emerging as an important factor that can predict the effectiveness of the treatment received. In addition, assessing MRD status can provide information to help the doctor recognize a disease relapse and decide if the continuation of treatment is necessary. Another proposed goal of MRD assessment is to eventually develop risk-adapted treatment strategies for CLL patients. Patients who have MRD after the end of treatment could be candidates for treatment intensification, consolidation and maintenance strategies. Those who achieve early MRD-negative status may be candidates for treatment de-escalation. However, to achieve this long-term goal, highly sensitive and specific MRD detection methods must be available, and further study on the predictive capacity of these methods will be necessary. There are some patients who may only achieve a partial response on a targeted therapy, but may do very well for a long period of time without the disease progressing. There are clinical trials underway to find the most effective way to deepen the response. Please visit www.LLS.org/booklets to view the free LLS booklet Minimal Residual Disease for more information.
**Table 7, below,** describes the criteria for various types of CLL treatment responses. Stable disease is the absence of progressive disease (PD) and the failure to achieve at least a partial response (PR).

### Table 7. Responses to CLL Treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>CR (Complete Response)</th>
<th>PR (Partial Response)</th>
<th>PD (Progressive Disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Lymph nodes</td>
<td>None ≥ 1.5 cm</td>
<td>Decrease ≥ 50% from baseline</td>
<td>Increase ≥ 50% from baseline or from response</td>
</tr>
<tr>
<td></td>
<td>Liver and/or spleen size (spleen size considered normal if &lt; 13 cm)</td>
<td>Spleen size &lt; 13 cm; liver size normal</td>
<td>Decrease ≥ 50% from baseline</td>
<td>Increase ≥ 50% from baseline or initial response</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Circulating lymphocyte count</td>
<td>Normal</td>
<td>Decrease ≥ 50% from baseline</td>
<td>Increase ≥ 50% from baseline</td>
</tr>
<tr>
<td>B</td>
<td>Platelet count</td>
<td>≥ 100,000/μL</td>
<td>≥ 100,000/μL or increase ≥ 50% from baseline</td>
<td>Decrease ≥ 50% from baseline secondary to CLL*</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin</td>
<td>≥ 11.0 g/dL (untransfused and without erythropoietin)</td>
<td>≥ 11.0 g/dL or increase ≥ 50% from baseline</td>
<td>Decrease ≥ 2 g/dL from baseline secondary to CLL*</td>
</tr>
<tr>
<td></td>
<td>Marrow</td>
<td>Normocellular, no CLL cells, no B–lymphoid nodules</td>
<td>Presence of CLL cells or B–lymphoid nodules, or test was not done</td>
<td>Increase ≥ 50% in CLL cells based on successive biopsies</td>
</tr>
</tbody>
</table>

Abbreviations and qualifications: CR, complete response (all of the criteria have to be met); PR, partial response (at least 1 of the parameters of group A and 1 of group B needs to improve if previously abnormal; if only 1 parameter of both groups A and B are abnormal prior to therapy, only 1 needs to improve); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met; constitutional symptoms alone do not indicate PD).

*“Secondary to CLL” means that this decrease in platelets or hemoglobin is due to the CLL and not from something else (for example, autoimmune disorder, treatment, etc.).

Follow-Up Care. After treatment, patients who are in remission and have completed therapy continue to be examined regularly by their doctors. Careful periodic assessment of the patients’ health, blood cell counts and, if indicated, other testing may be required to assess the full effect of therapy, as well as to identify signs of disease relapse. Patients need to keep their doctors informed of any changes they notice (for example, infections, lymph nodes, etc.). As time progresses, assessments may become less frequent.

People who have been treated for CLL are encouraged to

- Keep a record of the treatments they have received. This information can help the doctor follow up on specific late effects that may be associated with those treatments, as well as develop a follow-up schedule.
  - Records should include the following: the patient’s diagnosis; the names of all drugs taken; information about any radiation, surgery or transplantation therapy received; information about any other treatments; and the names and dates of any significant complications and the treatment received for those complications.

- Receive periodic screening and monitoring for skin, gastrointestinal, kidney, blood, bladder, prostate, breast, lung, head and neck and other types of cancer because of the increased risk of second cancers associated with CLL (see Second Cancer Risk on page 30).

- Consider cancer risk-reduction strategies, such as smoking cessation, skin protection against prolonged sun exposure, healthy eating and exercising.

For additional information, including risks of specific treatments, visit www.LLS.org/booklets to see the free LLS booklet Long-Term and Late Effects of Treatment in Adults Facts.

Related Diseases

Diseases related to CLL, such as prolymphocytic leukemia, result from the cancerous transformation of a type of lymphocyte. The accumulation of these cancer cells occurs mainly in the bone marrow, the blood and the spleen.

There are distinguishing characteristics that enable the hematologist-oncologist to identify each disease, including: the appearance and the immunophenotype of the cancer cells; the cancer cells’ varying effects on normal bone marrow and blood cell development; and the cancer cells’ varying effects on other parts of the body, such as the kidneys, bowels and nervous system.
The related diseases listed in Table 8 below have a range of clinical severity. At one end of the range are the diseases that may be stable and may not advance in severity for some months or years or, occasionally, indefinitely. At the other end of the range are diseases associated with complications that may be present at diagnosis and that can possibly get worse without rapid intervention, requiring immediate treatment and frequent observation.

<table>
<thead>
<tr>
<th>Table 8. Diseases Related to CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Less rapidly progressive</strong></td>
</tr>
<tr>
<td>• Hairy cell leukemia*</td>
</tr>
<tr>
<td>• Large granular lymphocytic leukemia†</td>
</tr>
<tr>
<td>• Waldenström macroglobulinemia*</td>
</tr>
<tr>
<td><strong>More rapidly progressive</strong></td>
</tr>
<tr>
<td>• Prolymphocytic leukemia</td>
</tr>
<tr>
<td>• Mantle cell lymphoma*</td>
</tr>
<tr>
<td><strong>Most rapidly progressive</strong></td>
</tr>
<tr>
<td>• Acute lymphoblastic leukemia*</td>
</tr>
</tbody>
</table>

* For more information, please see the free LLS booklet or factsheet about this disease.
† For more information, please visit the webpage www.LLS.org/LGL.

**Incidence, Causes and Risk Factors**

**Causes and Risk Factors.** There are few known risk factors for CLL.

Some studies have associated exposure to Agent Orange, an herbicide used during the Vietnam War, with an increased risk of CLL. The Health and Medicine Division (formerly known as the Institute of Medicine) of the National Academy of Sciences, Engineering and Medicine issued a report titled Veterans and Agent Orange: Update 2008, which concluded that there was “sufficient evidence of an association” between herbicides used in Vietnam and CLL, hairy cell leukemia and other chronic B-cell leukemias. A recent study focused on investigating the impact of Agent Orange exposure on the prognosis and treatment of patients with CLL. Veterans with Agent Orange exposure may be eligible for additional VA benefits. If you fall into this group of patients, it is worth getting a formal evaluation at the US Department of Veteran Affairs. For more information, please visit www.publichealth.va.gov/exposures/agentorange/.

Some studies suggest that exposure to benzene in the workplace increases the risk of CLL, however, the evidence is not as strong for CLL as with other blood cancers.

Genetic factors likely play a role in the development of CLL, as some families have more than one affected family member with the disease. First-degree
relatives of patients with CLL are approximately four times more likely to develop CLL than people who do not have first-degree relatives with the disease. However, the risk is small. For example, the 60-year-old sibling or child of someone with CLL would have three to four chances in 10,000 of developing the disease, compared with one chance in 10,000 for a 60-year-old person without a family history of the disease.

For information on studies about the occurrence of the same type of blood cancer in two or more blood relatives, please visit www.LLS.org/DiseaseRegistries.

**Incidence.** CLL is the most common type of leukemia in Western countries, accounting for nearly 45% of all leukemias. The disease generally affects older individuals, with more than 70% of patients being older than 65 years (see Figure 1 below). The median age at diagnosis is 72 years.

CLL affects more men than women. CLL incidence is substantially lower among Asian individuals and higher among Ashkenazi Jews. The reason for these differences is not known.

**Figure 1. Chronic Lymphocytic Leukemia (CLL): Age-Specific Incidence Rates 2011-2015**

The frequency of new cases of CLL per 100,000 people, by 5-year age groups.


**Feedback.** To give suggestions about this booklet, visit www.LLS.org/PublicationFeedback.
Normal Blood and Bone Marrow

**Blood.** Blood is the liquid that flows through a person’s arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

**Plasma.** Plasma is largely made up of water, in which many chemicals are dissolved. These chemicals each have a special role. They include

- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors) made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B12
- Electrolytes, such as calcium, potassium and sodium

**Blood cells.** Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called “hematopoiesis.” The blood cells are suspended in the plasma. See **Figure 2** on page 40.

Once the blood cell is created, it will develop into one of the three types of blood cells:

1. Red blood cells (the cells that carry oxygen)
   - These make up a little less than half of the body’s total blood volume.
   - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO2 is removed from the lungs.

2. Platelets (cells that help blood clot)
   - These are small cells (one-tenth the size of red blood cells).
   - They help stop bleeding from an injury or cut.
   - They stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot, with the help of proteins, such as fibrin, and electrolytes, such as calcium.
3. White blood cells (or WBCs, the cells that fight infections), including
   - Neutrophils and monocytes. These are cells called “phagocytes” that ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
   - Eosinophils and basophils. These are the WBCs that respond to allergens or parasites.
   - Lymphocytes. These are the WBCs found mostly in the lymph nodes, spleen and lymphatic channels that are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
     - T lymphocytes (T cells)
     - B lymphocytes (B cells)
     - Natural killer cells (NK cells)

![Figure 2. Blood Cell & Lymphocyte Development](image)

Stem cells develop into blood cells (hematopoiesis) and lymphocytic cells.

In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the marrow and then circulates throughout the body.

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.
Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

The Lymphatic System

The marrow is really two organs in one: 1) the organ that forms blood cells; and 2) the organ that forms lymphocytes, which make up part of the immune system.

The marrow produces three main types of lymphocytes. They are

- B lymphocytes (B cells), which make antibodies in response to foreign antigens, especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell (ingest it) along with its attached microbe. The white blood cell then kills and ingests the microbe.
- Natural killer (NK) cells, which attack virus-infected cells or tumor cells without requiring an antibody or other mediation. T cells and NK cells have other functions as well, and are important elements in research efforts to design immunotherapies to treat lymphoma and other cancers.

The lymphocytes circulate through channels called “lymphatics,” which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system, such as the skin, spleen, tonsils and adenoids, intestinal lining, and (in young people) the thymus.
Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions and to make the most of the knowledge and skills of the members of your healthcare team.

For Help and Information

Consult With an Information Specialist. Information Specialists are master’s level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (Monday through Friday, 9 am to 9 pm ET)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
- Visit: www.LLS.org/InformationSpecialists

Clinical Trials Support Center. Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Free Information Booklets. LLS offers free education and support booklets that can be either read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.


Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/copay

One-on One Nutrition Consultations. Access free one-on-one nutrition consultations by a registered dietitian with experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side
effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

**Podcast.** The Bloodline with LLS is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other health care professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

**Suggested Reading.** LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

**Continuing Education.** LLS offers free continuing education programs for health care professionals. Please visit www.LLS.org/ProfessionalEd for more information.

**Community Resources and Networking**

**LLS Community.** The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

**Weekly Online Chats.** Moderated online chats can provide support and help cancer patients to reach out and share information. Please visit www.LLS.org/chat to join.

**LLS Chapters.** LLS offers community support and services in the United States and Canada, including the Patti Robinson Kaufmann First Connection Program (a peer-to-peer support program), in-person support groups and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

**Other Helpful Organizations.** LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to obtain our directory.

**Advocacy.** The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new
treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

**Additional Help for Specific Populations**

**Información en español (LLS information in Spanish).** Please visit www.LLS.org/espanol for more information.

**Language Services.** Let members of your healthcare team know if you need a language interpreter or other assistance, such as a sign language interpreter. Often, these services are free.

**Information for Veterans.** Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

**World Trade Center (WTC) Survivors.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

**People Suffering from Depression.** Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a 2-week period. For more information, please

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov. Enter “depression” in the search box
Health Terms

**Allogeneic Stem Cell Transplantation.** A treatment that uses stem cells from a healthy donor to restore a patient’s bone marrow and blood cells. It uses high doses of chemotherapy and sometimes radiation to “turn off” a patient’s immune system so that the donor cells are not rejected. See the free LLS booklet *Blood and Marrow Stem Cell Transplantation.*

**Anemia.** A health condition that occurs when a person has a low number of red blood cells and therefore a low hemoglobin concentration. When this happens, it is hard for the blood to carry oxygen. People with severe anemia can be pale, weak, tired and become short of breath.

**Antibodies.** A type of protein created by blood cells when they are invaded by bacteria, viruses or other harmful foreign substances called “antigens.” Antibodies help the body fight against invaders that cause illness. Antibodies can also be made in the lab and are used to help detect certain types of cancer and to treat other diseases.

**Antigen.** Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses or other substances that come from outside the body.

**Apheresis.** A process using a machine to take out needed parts of a donor’s blood and return the unneeded parts to the donor. This process makes it possible to remove certain blood components (including red blood cells, white blood cells and platelets) separately and in large volumes.

**Basophil.** A type of white blood cell present in certain allergic reactions.

**Beta-2 microglobulin (B2M).** A small protein normally found on the surface of many cells, including lymphocytes, and in small amounts in the blood and urine. An increased amount in the blood or urine may be a signal of certain diseases, including some types of cancer, such as multiple myeloma or lymphoma. The degree of elevation of serum B2M levels appears to correlate with *IGHV* mutation status and ZAP-70 protein expression. Patients with a high level of ZAP-70 expression or an unmutated *IGHV* gene status are more likely to have a high B2M level. The test to measure B2M is available in most laboratories in the United States.

**Bone Marrow.** A spongy tissue in the hollow central cavity of the bones where blood cells are made. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in
blood cell formation. In adults, the bones of the hands, feet, legs and arms no longer contain blood-forming marrow—these bones are filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried in the bloodstream throughout the body.

**Bone Marrow Aspiration.** A test to find abnormal marrow cells. The area around the hip bone is numbed and then a special needle is inserted and a marrow sample (fluid) is drawn out. Usually this test is done at the same time as a bone marrow biopsy.

**Bone Marrow Biopsy.** A test to find abnormal marrow cells. The area around the hip bone is numbed and then a special needle is inserted and a sample of bone containing marrow is withdrawn. Usually this test is done at the same time as a bone marrow aspiration.

**Bone Marrow Transplantation.** See Allogeneic Stem Cell Transplantation.

**CD38.** An antigen on CLL cells and other cells. The expression of CD38 may be a marker to assist in predicting CLL progression. See Cluster Designation.

**Chemotherapy.** A treatment that uses chemical agents (medications) to kill cancer cells.

**Chromosome.** Thread-like structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes: the chromosome pairs numbered 1 to 22 and a 23rd pair that contains the sex chromosomes (XX for females and XY for males).

**Clonal.** The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers are derived from a single cell with an injury (mutation) to its DNA and thus are monoclonal. Leukemia, lymphoma, myeloma and myelodysplastic syndromes are examples of clonal cancers, meaning they are derived from a single abnormal cell.

**Cluster Designation (CD).** A term used with a number to identify a specific molecule on the surface of an immune cell. It is commonly used in its abbreviated form, for example, “CD20”—the target of the monoclonal antibody therapy rituximab (Rituxan®)—and “CD52,” the target of the monoclonal antibody therapy alemtuzumab (Campath®).

**Colony-Stimulating Factor.** See Growth Factor.
**Cytogenetic Analysis.** A type of test that looks at the number and size of the chromosomes in cells. It is often used in cancer treatment to see changes in the cells before and after treatment.

**Differentiation.** When stem cells develop and mature and take on a new function. Stem cells mature into red blood cells, platelets or white blood cells. See Hematopoiesis.

**Eosinophil.** A white blood cell that helps fight some parasitic infections and participates in allergic responses.

**Erythrocytes.** See Red Blood Cells.

**FISH (Fluorescence In Situ Hybridization).** A technique to study chromosomes in cells and tissues. It uses probes with fluorescent molecules that emit light of different wavelengths and colors. The probes bind to the chromosomes within the cells, and the chromosomes fluoresce in color. FISH can be helpful in assessing risk and treatment needs and for monitoring treatment effectiveness by detecting abnormal cells, such as those with 17p deletion.

**Flow Cytometry.** A test that finds specific cell types within a cell sample. During this test, cells flow through the instrument called a “flow cytometer.” When the cells pass through its laser beam, those with the antibody-specific features light up and can be counted. This test may be used to examine blood cells, marrow cells or cells from a biopsy.

**G-Banding Karyotyping.** A testing method that makes a certain characteristic of chromosomes easier to see. A “karyotype” is the systematic arrangement, using images, of the 46 human chromosomes of a cell. Karyotypes are examined for deviations from the expected arrangement, number, size, shape or other characteristics of the chromosomes. Each chromosome pair has a characteristic banding pattern. To make the banding pattern easier to see, a dye called “Giemsa” may be used as a stain. This process is also referred to as “G-banding.” G-banding karyotyping and other cytogenetic tests provide doctors with information that contributes to determining the best treatment approach for individual patients. It takes longer than the FISH test, but has the advantage of being able to detect any changes that are visible because it does not rely on specific probes. Usually, both tests are done on samples from the marrow, especially at the time of diagnosis. See Kayotype.
**Gene.** A small section of DNA that is passed from parent to child. Most genes provide instructions for making specific proteins that are used in one or more types of cells in the body. These proteins perform many important roles in the body, including breaking down food, carrying oxygen and detecting and destroying bacteria and viruses.

**Granulocyte.** A type of white blood cell with many particles (granules) in the cell body. Neutrophils, eosinophils and basophils are the three types of granulocytes.

**Growth Factor.** A substance used to increase the numbers of neutrophils after chemotherapy. Granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) are growth factors that can be made in the lab.

**Hematologist.** A doctor who specializes in blood cell diseases.

**Hematopoiesis.** The formation of all types of blood cells that starts in the marrow. For the blood cell development process, see *Normal Blood and Bone Marrow* on page 39.

**Immunoglobulin Heavy Chain Variable (IGHV) Region Gene Status.** A marker that can distinguish between CLL subtypes (unmutated IGHV and mutated IGHV). CLL patients with unmutated IGHV gene status may have a more progressive form of the disease.

**Immunophenotyping.** A process used to find specific types of cells within a blood sample. It looks at antigens or markers on the surface of the cell to identify antibodies.

**Karyotype.** The order, number and appearance of chromosomes within a cell. There are 46 human chromosomes: 22 pairs called “autosomes” and a 23rd pair, shown separately, with the sex chromosomes (either XX or XY). See FISH (Fluorescence In Situ Hybridization) and G-banding Karyotyping.

**Lymph Nodes.** Small structures, the size of beans, that contain large numbers of lymphocytes and are connected with each other by small channels called “lymphatics.” These nodes are distributed throughout the body. In patients with lymphoma and some types of lymphocytic leukemia, the malignant lymphocytes grow inside the lymph nodes, which become enlarged.
Lymphatic System. The system comprising the lymph nodes, the thymus gland (in the first several decades of life), the lymphatic channels, the lymphatic tissue of the marrow, the gastrointestinal tract, the skin and the spleen, along with the T lymphocytes, B lymphocytes and natural killer (NK) lymphocytes contained in those sites.

Lymphocyte. A type of white blood cell that is important to the body’s immune system. There are three major types of lymphocytes: 1) B lymphocytes, which produce antibodies to help combat infectious agents, such as bacteria, viruses and fungi; 2) T lymphocytes, which have several functions, including assisting B lymphocytes in making antibodies; and 3) natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Lymphocytosis. An increase in the number of lymphocytes in the blood.

Macrophage. Called a “scavenger cell,” a macrophage is a type of white blood cell that surrounds and kills microorganisms, removes dead cells and stimulates the action of other immune system cells. See Monocyte.

Minimal Residual Disease (MRD). The small amount of cancer cells that may remain after treatment. These cells can only be identified by sensitive molecular techniques.

Monoclonal. See Clonal.

Monocyte. A type of white blood cell that is made in the bone marrow and travels through the blood to tissues in the body, where it becomes a macrophage. See Macrophage.

Mutation. A change in the DNA that makes up a gene.

Neutropenia. An abnormal decrease in the number of neutrophils, a type of white blood cells, in the blood. See Neutrophil.

Neutrophil. A kind of white blood cell, and the main type that works to fight infection. People with some blood cancers, or those who have received treatment (such as chemotherapy) for cancer, often have low neutrophil counts. People with low neutrophil counts are very susceptible to infections.


Peripheral Blood. Blood circulating throughout the body.
**Phagocytes.** Cells that protect the body from infection by eating and killing microorganisms, such as bacteria and fungi. Neutrophils and monocytes are the two main types of phagocytes (also called “eating cells”). Once an infection occurs, phagocytes migrate from the bloodstream and enter the infected tissue. Chemotherapy and radiation can decrease the numbers of these cells, making patients more likely to get an infection.

**Platelets.** Small, colorless blood cells that travel to and clump together at the site of a wound. At the site of the injury, the platelets’ sticky surface helps them form clots and stop bleeding. Platelets make up about one-tenth of the volume of red blood cells. Also called “thrombocytes.”

**Polymerase Chain Reaction (PCR).** A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied.

**Red Blood Cells.** Blood cells that contain a substance called hemoglobin, which carries oxygen from the lungs to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people. Also called “erythrocytes.”

**Refractory.** The term used to describe a disease that does not go away and/or improve significantly after initial treatment.

**Relapse/Recurrence.** A return of the disease after it has been in remission following therapy.

**Remission.** When signs of a disease disappear, usually after treatment. Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is significantly improved by treatment, but residual evidence of the disease is present.

**Resistance to Treatment.** When cancer cells continue to grow even after administration of strong drugs and/or treatments, the disease is said to be “resistant.”

**Richter Transformation.** In a small number of patients, CLL takes on the characteristics of an aggressive lymphoma. This change is not a second cancer, but a transformation of the CLL cells.

**Spleen.** This organ, in the left upper portion of the abdomen just under the left side of the diaphragm, acts as a blood filter. Enlargement of the spleen is called “splenomegaly.” Surgical removal of the spleen is known as “splenectomy.”
**Stem Cell Transplantation.** See Allogeneic Stem Cell Transplantation.

**Stem Cells.** Immature marrow cells that mature into red blood cells, white blood cells and blood platelets. Stem cells are mostly found in the marrow, but some leave the marrow and circulate in the bloodstream. Stem cells can be collected, preserved and used for stem cell therapy. See Hematopoiesis.

**Thrombocytopenia.** A disorder characterized by having too few platelets in the blood.

**White Blood Cells.** The five types of infection-fighting cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. Also called “leukocytes.”

**ZAP-70.** An abbreviation for the cell protein called “zeta-chain-associated protein kinase 70.” A high level of ZAP-70 expression on the cells of patients with B-cell CLL is one of several factors that may predict more progressive disease. Outside of a research laboratory, this test is generally not very reliable and should not be used.
References


Hallek M. Role and timing of new drugs in CLL. *Hematological Oncology*. 2017;35(suppl 1):30-32.


Get support. Reach out to our INFORMATION SPECIALISTS

The Leukemia & Lymphoma Society team consists of master’s level oncology social workers, nurses and health educators who are available by phone Monday through Friday, 9 a.m. to 9 p.m. (ET).

• Get one-on-one personalized support and information about blood cancers
• Know the questions to ask your doctor
• Discuss financial resources
• Receive individual clinical-trial searches

Contact us at 800-955-4572 or www.LLS.org/informationspecialists (Language interpreters can be requested)
For more information, please contact our Information Specialists 800.955.4572 (Language interpreters available upon request).

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The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin’s disease and myeloma, and improve the quality of life of patients and their families. Find out more at www.LLS.org.