LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

2017

EUROPEAN

**SUBTYPE REPORT**

# Chronic Lymphocytic Leukaemia

The focus of this report is to review patient access to care in chronic lymphocytic leukaemia (CLL) in Europe; namely therapy access, clinical trials and aspects of the patient experience.

# Overview

Chronic lymphocytic leukaemia (CLL) is an incurable lymphoma found in the lymphocytes. The progression of CLL is extremely variable ranging from indolent disease not requiring treatment to one that progresses rapidly and is resistant to treatment. The average incidence of CLL varies between individuals in different geographic regions with incidence being lower in eastern Asia and slightly higher in Europe and the USA. Median age at diagnosis is 72 years.

Within CLL, there are two main subsets which are distinguished by whether the CLL cells express as unmutated or mutated immunoglobulin heavy-chain variable region gene (*IGHV*). Patients with CLL that expresses an unmutated *IGHV* usually have more aggressive disease than those that express a mutated *IGHV*.

Genetic factors play a role in the development of CLL with a six- to nine-fold increased risk for family members of patients with CLL. Approximately 80% of patients with CLL carry at least one or more common chromosomal alterations. The most common alterations are focal, i.e., limited to a specific area, deletions of chromosomes 13q14.3 (del(13q)), del(11q), del(17p) and trisomy 12.

Patients with CLL are often asymptomatic at the time of presentation and only become aware of the cancer following the detection of lymphocytosis during a routine blood count. CLL can, however, have a range of presentations with some patients feeling well and being fully active while others will have disease-related symptoms. Typical symptoms of CLL include fatigue, weight loss, night sweats, feeling of fullness while eating and increased frequency of infections. Patients may also have or develop enlarged lymph nodes, hepatomegaly or splenomegaly.

The management of CLL is determined by the stage and activity of the cancer. Two clinical staging systems are used to predict patient outcomes: the Binet staging system and the Rai staging system.

Significant advancements in the care of patients with CLL have occurred over the past decade. This is largely due to the ongoing investigation into the pathogenesis of CLL that has led to the development of novel treatments and therapeutic strategies. These efforts highlight a complex biology that includes inherited or acquired genetic changes, the role of the B-cell receptor (BCR) and BCR signalling, CLL cell make-up, and the interactions in the microenvironment between CLL cells and other immune cells.

Based on information gathered from the Lymphoma Coalition (LC) Global Database, there was a wide discrepancy among European countries in terms of treatment protocols with regulatory approval compared with those that were funded/reimbursed, especially the newer therapies. For example, venetoclax had regulatory approval in 21 Eastern and Western European member countries but only five countries funded/reimbursed it none of which were in Eastern Europe.

Globally, of the 211 clinical trials involving patients with CLL 78 were available in Europe. Of these 78 clinical trials, 64 were specifically for patients with CLL. All European countries had at least one CLL clinical trial available.

Key findings from the 2016 Lymphoma Global Patient Survey showed that 37% of respondents from Western Europe and 65% of respondents from Eastern Europe had experienced barriers to treatment. The biggest psychological concern for all respondents was the fear of relapse. Among Eastern European respondents, other

psychological concerns were changes in relationships, depression, concerns about body image and stress related to financial issues. For Western European respondents, changes in relationships and concerns about body image were of concern.

Fatigue was the physical effect of greatest concern for all respondents. In general, however, physical effects were a bigger issue in Eastern Europe than in Western Europe. Medical issues, however, were of greater concern among Western European respondents compared with those from Eastern Europe.

Respondents reported that they understood the characteristics of their subtype but those in Western Europe had a higher understanding of the side effects associated with treatment compared with those in Eastern Europe (81% versus 55%).

When seeking help, all respondents overwhelmingly indicated that their doctor had only been able to help them somewhat. Given that 80% of respondents reported that their doctor was their primary source of information means patients have to find information on their own.

This subtype report on CLL focuses on Europe. Table 1 lists the countries included in this report.

**TABLE 1. EASTERN AND WESTERN EUROPEAN LC MEMBER COUNTRIES[a]**

| Western Europe (n = 14) | Eastern Europe (n = 14) |
|---|---|
| Belgium | Bulgaria |
| Denmark | Croatia |
| Finland | Czech Republic |
| France | Hungary |
| Germany | Latvia |
| Ireland | Lithuania |
| Israel | Macedonia |
| Italy | Poland |
| Netherlands | Russian Federation |
| Portugal | Serbia |
| Spain | Slovakia |
| Sweden | Slovenia |
| Switzerland | Turkey |
| UK | Ukraine |

[a]Israel is included in Western Europe as its healthcare system is similar to those of Western European countries.

# Acknowledgements

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# What is Chronic Lymphocytic Leukaemia?

Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder hence it is classified as a lymphoma. It is an incurable lymphoma found in the lymphocytes, a type of white blood cell involved in the body's immune system. CLL is classified by the accumulation and rapid reproduction of clonal B cells in the blood, marrow and lymph nodes. The progression of CLL is extremely variable ranging from indolent (slow growing) disease not requiring treatment to one that progresses rapidly and is resistant to treatment.[1]

The average incidence of CLL varies between individuals in different geographic regions with incidence being lower in eastern Asia and slightly higher in Europe and the USA.[2] Median age at diagnosis is 72 years. Most cases of CLL are diagnosed in patients over the age of 55 years with approximately only 10% of CLL cases being diagnosed in patients younger than 55 years.[3] The risk of CLL developing in men is twice as high as it is in women.[2]

Within CLL, there are two main subsets. These subsets are distinguished by whether the CLL cells express as unmutated, i.e., genetic material in the cell is unchanged, or mutated, i.e., genetic material in the cell has changed, immunoglobulin heavy-chain variable region gene (*IGHV*). Those CLL cells that express an unmutated *IGHV* originate from the B cell that has not undergone differentiation (a cell changes from one cell type to another) in the germinal centres. Germinal centres are sites where B cells proliferate, i.e., they grow rapidly through the production of new cells and mutate during an immune response to an infection. Patients with CLL that expresses an unmutated *IGHV* usually have more aggressive disease than those that express a mutated *IGHV*.[2] *IGHV* status is determined by flow cytometry.[4]

Most cases of CLL are diagnosed in patients **over the age of 55 years**.[3]

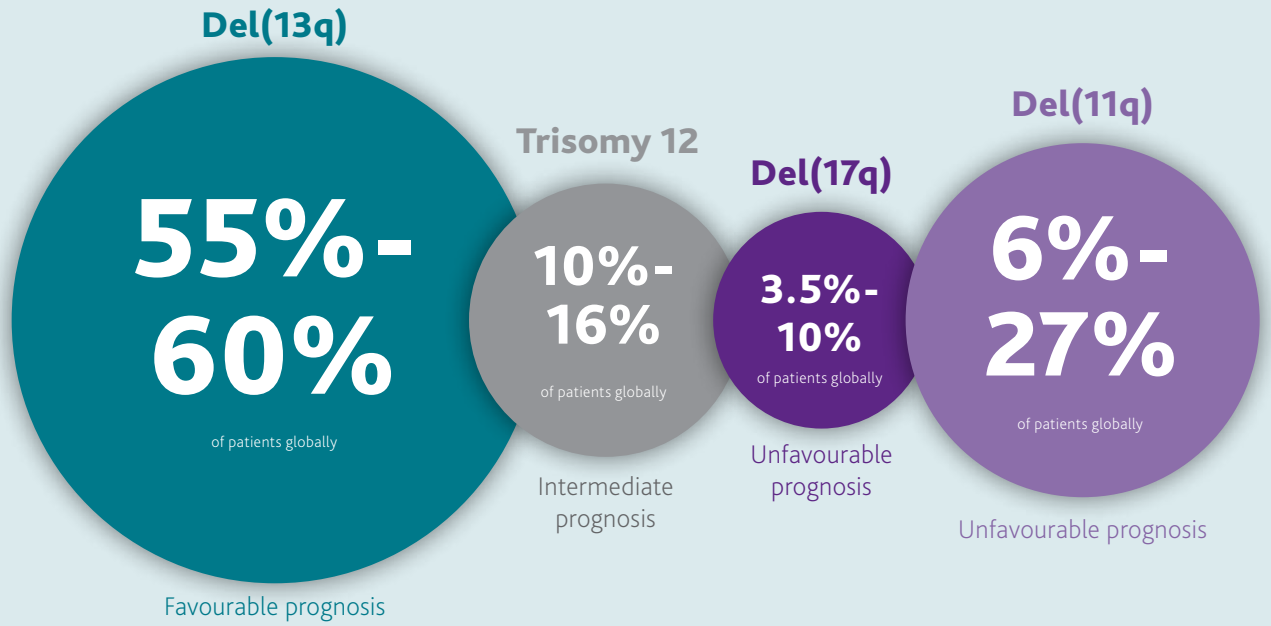

The risk of CLL developing in **men is twice as high** as it is in women.[2]

Genetic factors play a role in the development of CLL with a six- to nine-fold increased risk for family members of patients with CLL.[3] As well, among monozygotic (identical twins), if one has CLL the other is more likely to develop it compared with dizygotic (not identical) twins.[2]

Approximately 80% of patients with CLL carry at least one or more common chromosomal alterations. The most common alterations are focal, i.e., limited to a specific area, deletions of chromosomes 13q14.3 (del(13q)), del(11q), del(17p) and trisomy 12. Figure 1 shows the global prevalence of chromosomal alterations.

It is important to note that chromosomal abnormalities can change over time. These changes can be a result of therapy, in particular chemoimmunotherapy (a combination of chemotherapy and immunotherapy, CIT), where there may be a selection for cells that have del(17p).[5] Anecdotally, tests for mutations, markers and chromosomal abnormalities are not readily accessible in all countries. **This needs to change to ensure patients receive the best treatment otherwise they may not receive treatment that is appropriate for their type of CLL.**

**FIGURE 1. PREVALENCE OF CHROMOSOMAL ALTERATIONS[1,2]**




The understanding of the genetic diversity associated with CLL has greatly improved through the use of parallel as well as whole-exome sequencing. Recurrent mutations have been consistently observed in genes that play a role in DNA damage, e.g., *TP53* and *ATM*, mRNA processing, e.g., *SF3B1* and *XPO1*, chromatin modification, e.g., *HIST1H1E*, *CHD2* and *ZMYM3*, WNT signalling, Notch signalling, e.g., *NOTCH1*, and inflammatory pathways, e.g., MYD88. CLL is also associated with alterations in microRNA, specifically *mir-15a and mir-16-1*. They are deleted, altered or downregulated in approximately 60% of patients with CLL globally and dysfunctional in a few cases of familial CLL.[1,2]

Patients with CLL are often asymptomatic at the time of presentation and only become aware of the cancer following the detection of lymphocytosis (an increase in the number of lymphocytes in the bloodstream) during a routine blood count. CLL can, however, have a range of presentations with some patients feeling well and being fully active while others will have disease-related symptoms.

## Typical symptoms of CLL include:

- Fatigue;
- Weight loss;
- Night sweats;
- Feeling of fullness while eating;
- Increased frequency of infections.

Patients may also have or develop enlarged lymph nodes, hepatomegaly (abnormal enlargement of the liver) or splenomegaly (abnormal enlargement of the spleen).[2]

A complete blood count (CBC) with differential is undertaken as part of the diagnostic process. This routine test helps determine a patient's general health status. The presence of at least 5,000 abnormal B cells per microlitre of blood (≥5,000 monoclonal B lymphocytes/µl) for at least three months is required to make the diagnosis.[3,6] However, in practice, if the lymphocyte count is slightly lower and there are other indications that the patient has CLL, clinicians will not wait another three months before retesting the patient.[7]

The World Health Organization (WHO) recently modified its classification of lymphoid neoplasms. In 2008, it was unknown if monoclonal B-cell lymphocytosis (MBL) was a precursor of CLL. It is now clear that it is and that it precedes nearly all cases of CLL. The updated WHO guideline requires that low-count MBL (peripheral blood CLL count of $<0.5 \times 10^9$/L) must be differentiated from high-count MBL. Patients with high-count MBL require yearly follow-up; those with low-count MBL rarely develop CLL.[8]

As part of the diagnostic work-up, peripheral blood flow cytometry may be used to identify specific proteins that may be on the cell surface, such as CD5, CD19, CD20 and CD23. This is called immunophenotyping.[3]

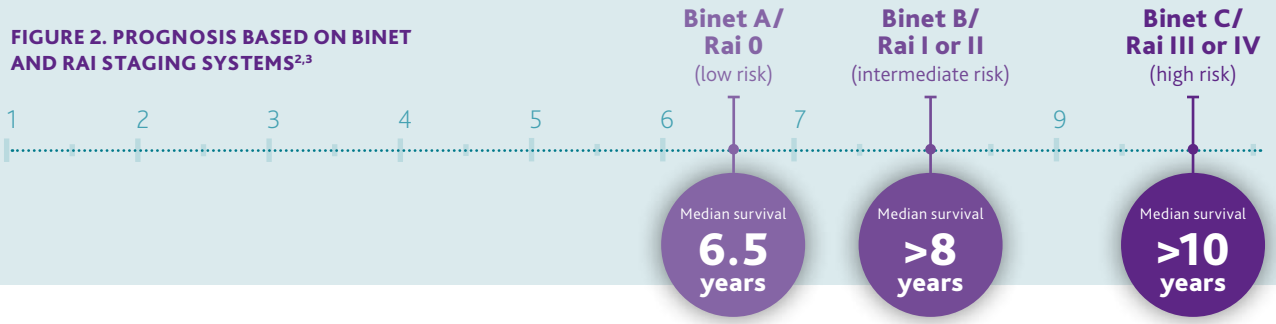
## Other tests that may have prognostic value and provide an overall idea of the patient's status prior to the start of treatment include:

- Genetic and cell protein tests;
- A comprehensive metabolic panel;
- Hepatitis B testing;
- An echocardiogram;
- Immunoglobulin testing may be indicated for patients who develop repeated infections.

For further information on testing for CLL, click here.

The management of CLL is determined by the stage and activity of the cancer. Two clinical staging systems are used to predict patient outcomes. In Europe, the Binet staging system is more widely used, whereas in North America, the Rai staging system is more commonly applied. Both systems recognise the importance of bone marrow function and define late-stage or high-risk disease through the presence of pronounced anaemia or thrombocytopenia (low blood platelet count). In addition, both the Binet and Rai staging systems separate patients into three groups with different prognoses (see Figure 2). The Binet and Rai staging systems provide general guidelines as each patient is different and needs to be treated accordingly.

**FIGURE 2. PROGNOSIS BASED ON BINET AND RAI STAGING SYSTEMS[2,3]**




It is not recommended that patients who are asymptomatic with early-stage or intermediate stage cancer (Binet stage A or B; Rai stage 0-II) receive treatment. This is typically called watch and wait, watchful waiting or active surveillance. Treatment should only be given if patients have symptoms or there is evidence of disease progression. Studies have not shown that treating patients with early-stage CLL resulted in a survival advantage. However, these patients should have CBCs and a clinical examination every three to 12 months.[2,3]

## Signs and symptoms of symptomatic disease or cancer progression may include:

- Enlarged lymph nodes, liver or spleen;
- Recurring infections;
- Loss of appetite or early satiety;
- Abnormal bruising (late-stage symptom);
- Fatigue;
- Night sweats.[2,6]

Once a patient has met the criteria for treatment, the choice of therapy is the next major decision. The key feature currently directing the choice of therapy is the presence of either del(17p) or mutated *TP53*. As well, in patients over the age of 65 years, the presence of comorbidities and the goal of treatment will play an important role in the choice of therapy.[2] Given the toxicities associated with therapies, it is helpful to predict which patients will need treatment as a way of ensuring the preservation of bone marrow function, reducing the exposure to treatment side effects, as well as reducing morbidity and mortality.

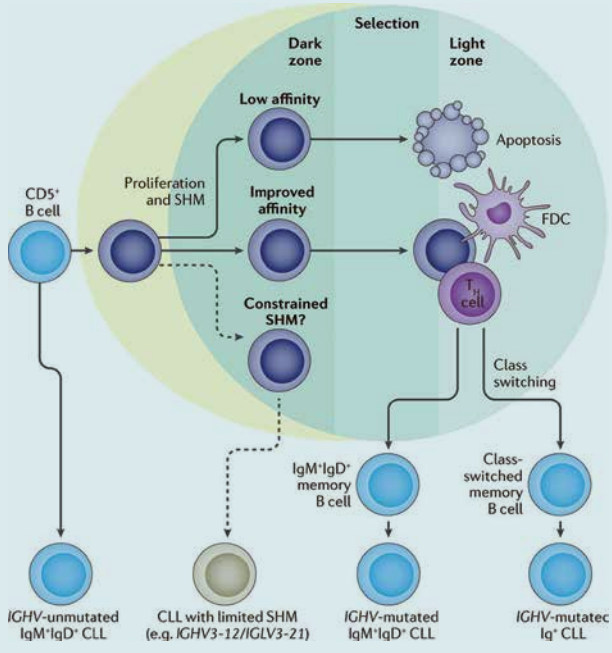
While the course of CLL is extremely variable, it is hoped that the improved understanding of the genetic diversity associated with CLL will lead to improved treatments as well as outcomes for patients.

# Understanding the Biology of CLL

## Significant advancements in the care of patients with CLL have occurred over the past decade. This is largely due to the ongoing investigation into the pathogenesis of CLL that has led to the development of novel treatments and therapeutic strategies.

Figure 3 provides an overview of the origins of CLL cells. These efforts highlight a complex biology that includes inherited or acquired genetic changes, the role of the B-cell receptor (BCR) and BCR signalling, CLL cell make-up, and the interactions in the microenvironment between CLL cells and other immune cells.

**FIGURE 3: CELLULAR ORIGINS OF CLL CELLS**

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Normal naive B cells that have undergone successful V(D)J recombination and express functional B cell receptors that are capable of binding to antigen interact with CD4+ T cells and accessory cells, which aggregate to form follicles that become germinal centres. Germinal cells each have a dark zone, comprising rapidly dividing B cells, and a light zone, comprising B cells mixed with follicular dendritic cells (FDCs), macrophages and helper T cells ($T_H$ cells). The B cells enter the dark zone of the germinal centre where they experience rapid proliferation and somatic hypermutation (SHM) in the genes encoding the immunoglobulin variable regions of the heavy chain (*IGHV*) and the light chain (*IGVL*). As they pass through to the light zone, the B cells that express the fittest B cell receptors for binding antigen are selected and may undergo immunoglobulin class-switch recombination. Chronic lymphocytic leukaemia (CLL) cells that use unmutated *IGHV* apparently originate from CD5+ B cells prior to experiencing SHM, whereas CLL cells that use mutated *IGHV* most likely originate from CD5+ B cells that have passed through and differentiated in the germinal centre. Some CLL cells might be derived from B cells that also have undergone immunoglobulin class-switch recombination and express immunoglobulin isotypes other than IgM and IgD, for example, IgG or IgA. Another subset is one with CLL cells that express immunoglobulin with only modest somatic mutations, such as CLL cells that use *IGHV3-21* with ~97% homology to the inherited *IGHV3-21* gene and an immunoglobulin light chain encoded by an unmutated *IGLV3-21*; these cells might derive from a B cell that has had constrained SHM, possibly owing to a limited need for immunoglobulin somatic diveresification and selection. Dashed arrows indicate speculated pathways.

**As the biology of CLL is further established, both molecular and cellular markers have been identified that may predict the tendency for cancer progression in patients with CLL. For example, the mutational profile of genes, in this instance, mutated CLL or unmutated CLL, will determine two separate subtypes. Progress continues to raise questions that warrant further research. These research areas are:**[7]

1. **Gaining a better understanding of the factors that contribute to the early pathogenesis of CLL to determine:**
   - Why people develop CLL;
   - Why CLL progresses;
   - The factors that regulate the rate of progression in patients who become symptomatic versus those remaining stable for many years.

2. **Determining optimal treatment:**
   - CIT versus the use of a targeted agent?
   - How to select the preferred targeted agent?
     - Are there subsets of patients where, because of their mutational profile, one targeted agent is better than another or are they equivalent?

3. **How to achieve the greatest efficacy from novel agents:**
   - Is combination treatment using ibrutinib plus venetoclax plus a CD20 antibody better than sequencing therapies?
   - What is the ideal combination regimen given the innumerable potential combinations?

4. **Continuous versus time-limited therapy:**
   - Do therapies need to be given continuously or, once remission is achieved, treatment stopped and only restarted at early evidence of progression?

5. **Mechanisms of resistance:**
   - How does CLL become resistant to the targeted agent?
   - Is it possible to identify the early development of resistance?
   - Can the emergence of resistance be used to pre-emptively switch treatments rather than waiting for profound resistance?

6. **Richter's transformation:**
   - What are the factors that lead to the development of Richter's transformation as it is the manifestation of CLL that is responsible for most deaths?

7. **Supportive care:**
   - How can infections be prevented as a result of treatment?
   - How can supportive care be optimised?
   - How can the development of secondary cancers be minimised?

**LC looks forward to the results of this research and how these findings may relate to the clinical setting.**

With increasing frequency, retrospective data show that patients with CLL have a threefold risk of developing a secondary malignancy and an eight- to 15-fold increased risk of developing skin cancers.

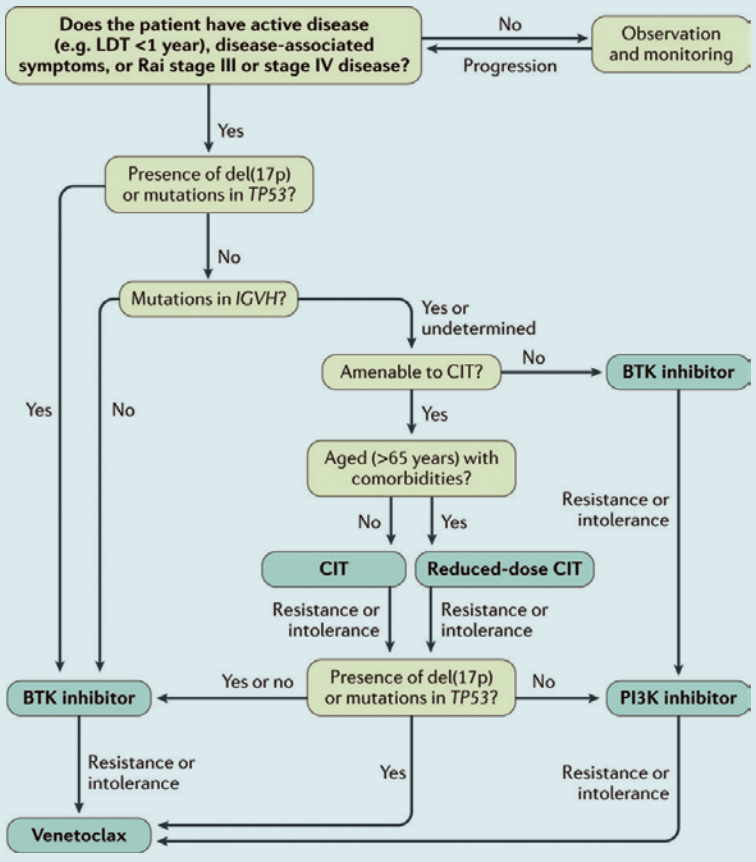
When skin cancers are excluded, the overall risk is twice that of age- and gender-matched control populations.[9,10] This risk is the same for men and women regardless of age or treatment history.[9] The risk of developing nonmelanoma skin cancer (NMSC) and prostate cancer is higher in men while women have a higher risk of developing breast, lung and gastrointestinal (GI) cancers.[9,11] This is a difficult outcome given that the average age of people diagnosed with CLL is 72 years. Among the commonly diagnosed secondary malignancies are NMSC, Kaposi sarcoma, malignant melanoma, lung cancer, GI malignancies, breast cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancers, and Richter's transformation to a very aggressive large B-cell lymphoma.[9,11-13]

Prolymphocytic transformation is rare occurring in less than 1% of patients. It is characterised by symptomatic splenomegaly and rapidly increasing number of leukaemia cells in the blood. Approximately 2% to 7% of patients will develop Richter's syndrome. This is the transformation of CLL to an aggressive lymphoma, usually diffuse large B-cell lymphoma. While it is possible for patients with CLL to develop acute leukaemia and myelodysplastic syndrome, it is uncommon.[2]

# Current Treatment Protocols

The treatment of CLL may include chemotherapy, CIT or treatments that target the signalling pathways that promote the growth and/or survival of CLL cells. Figure 4 provides an overview of the management for patients with CLL.

**FIGURE 4: MANAGEMENT ALGORITHM FOR PATIENTS WITH CLL**

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BTK = Bruton tyrosine kinase; CIT = chemoimmunotherapy; CLL = chronic lymphocytic leukaemia; IGHV = immunoglobulin heavy-chain variable region; LDT = lymphocyte doubling time; PI3K = phosphoinositode 3-kinase

Within chemotherapy, different kinds of chemotherapy are used depending on the situation. There are purine analogues (fludarabine, pentostatin, cladribine) and alkylating agents such as chlorambucil, cyclophosphamide or bendamustine. CIT includes the use of anti-CD20 monoclonal antibodies such as rituximab, obinutuzumab or ofatumumab in combination with chemotherapy.[2,14] There are no head-to-head randomised studies comparing obinutuzumab and ofatumumab. In clinical trials that have compared ofatumumab plus chemotherapy versus rituximab plus chemotherapy, primarily chlorambucil, efficacy appears to be similar. However, comparisons of obinutuzumab plus chemotherapy versus rituximab plus chemotherapy showed the use of obinutuzumab to be superior. While this is an indirect comparison, it is highly likely that obinutuzumab is superior to ofatumumab.[7]

**There are three main classes of drugs that can inhibit BCR signalling:**

- Bruton tyrosine kinase (BTK) inhibitors (ibrutinib);
- Phosphatidylinositol 3-kinase (PI3K) inhibitors (idelalisib);
- Spleen tyrosine (SYK) inhibitors.

CLL cells with unmutated *IGHV* appear to be more sensitive to inhibitors of BCR signalling than CLL cells with mutated *IGHV*. What is unclear is whether inhibitors, such as ibrutinib, are more effective in patients with CLL who have unmutated *IGHV*. This needs to be validated in clinical trials. Idelalisib is the only PI3K inhibitor with regulatory approval globally in 24 member countries; additional ones are being evaluated in clinical trials.[2,14]

In the updated treatment guidelines issued by the European Society of Medical Oncology (ESMO) in 2016, in patients with the *TP53* deletion/mutation who are not suitable for treatment with a BTK inhibitor, idelalisib plus rituximab is recommended for use in first-line treatment. Ibrutinib can be considered as an alternative treatment option to chlorambucil-based CIT as a first-line treatment option but the lack of long-term experience with the use of ibrutinib in first line must be taken into consideration.[15] SYK inhibitors are still being evaluated in clinical trials. Venetoclax is a B-cell lymphoma (BCL)-2 inhibitor that kills CLL cells. It is effective in relapsed/refractory disease as well as in patients who have relapsed and have del(17p).[2,14]

When determining which regimen to use, patients with del(17p) will likely be resistant to standard regimens involving either alkylating agents or purine analogues.[6] For these patients the use of a BTK inhibitor or a P13K inhibitor plus rituximab is recommended.[15] For CLL without del(17p), it is recommended that that the ESMO clinical practice guideline be followed.[7,15]

For the purpose of this review and to determine what treatment protocols should be accessible to patients with CLL, LC reviewed the information from both the ESMO clinical practice guideline and the National Comprehensive Cancer Network (NCCN) listing. The ESMO clinical practice guideline for first-line treatment was updated in 2016; NCCN's guideline was updated in 2017.[3,4,15] Given the complexity of CLL, the treatment regimens listed in Table 2 are not categorised by any particular subtype or prognostic factor. For more specific information, please refer to either the ESMO guidelines or the NCCN listing.[3,4,15]

**TABLE 2. NCCN LISTING AND ESMO GUIDELINE FOR CLL[3,4,15]**

| ESMO | | NCCN | |
|---|---|---|---|
| **First Line** | **Relapsed** | **First Line** | **Relapsed** |
| | | Alemtuzumab ± rituximab | Alemtuzumab ± rituximab |
| BR | BR | BR | BR |
| | | Ch | |
| Ch-R | Ch-R | Ch-R | Ch-R |
| | | | FCO |
| FCR | FCR | FCR | FCR |
| | | FR | |
| | | HDMP±R | HDMP±R |
| Ibr | Ibr | Ibr | Ibr |
| Id-R | Id-R | | Id-R |
| | | Lenalidomide maintenance | Lenalidomide maintenance |
| | | | LR |
| | | | Ob |
| Ob-Ch | | Ob-Ch | |
| | | | Of |
| | | | OFAR |
| | | | Ofatumumab maintenance |
| Of-Ch | Of-Ch | Of-Ch | |
| | | PCR | PCR |
| | | | R-CHOP |
| | | | Venetoclax ± rituximab |

BR = bendamustine±rituximab; Ch = chlorambucil; Ch-R = chlorambucil, rituximab; ESMO = European Society of Medical Oncology; FCR = fludarabine, cyclophosphamide, rituximab; FR = fludarabine, rituximab; HDMP±R = high-dose methylprednisolone + rituximab; Id-R = idelalisib, rituximab; Ibr = ibrutinib; LR = lenalidomide±rituximab; Ob-Ch = obinutuzumab, chlorambucil; NCCN = National Comprehensive Cancer Network; Of-Ch = ofatumumab, chlorambucil; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab; PCR = pentostatin, cyclophosphamide, rituximab

# Therapy Access

LC looked at access to treatment in LC member countries to determine what CLL therapies were available. A list of these treatment protocols is on the LC website. Table 3 shows which of the therapy protocols in the ESMO or NCCN listings had regulatory as well as funding/reimbursement approval in each member country. As the table shows, there was a wide discrepancy among countries in terms of the protocols with regulatory approval compared with those that were funded/reimbursed.

With the exception of Macedonia where none of the newer therapies had either regulatory or funding/reimbursement approval, many of the newer therapies had regulatory approval in Eastern Europe although not all had reimbursement/funding approval. Similarly in Western Europe, while most of the newer therapies had regulatory approval, not all were funded/reimbursed. This was particularly noticeable in Ireland. No reimbursement information was available for Portugal.

Venetoclax, indicated for del(17p), is one of the latest therapies to receive regulatory approval in 21 countries in Europe. However, it was not funded/reimbursed in any Eastern European country and funded/reimbursed in only five countries in Western Europe. A somewhat encouraging sign is that ibrutinib, another treatment indicated for relapsed/refractory CLL with del(17p), had regulatory approval in 24 countries in Europe and was funded/reimbursed in 20 countries, including eight countries in Eastern Europe. In the 2016 Lymphoma eInformation Project Report Card on Lymphomas, of the 12 countries examined, six of which were from Europe, all six had provided regulatory approval but it was only funded/reimbursed in France. It is critical that patients gain access to these new therapies to ensure they are receiving optimal treatment.

## TABLE 3. CLL: THERAPY ACCESS BY LC MEMBER COUNTRY

| | Therapies with Regulatory Approval | Therapies with Funding/ Reimbursement Approval |
|---|---|---|
| **Eastern Europe** | | |
| **Bulgaria** | B, B-Of, BR, Ch, CVP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, BR, Ch, CVP±R, F, FC, FCM±R, FCR, FR, Ibr, HDMP±R, Of, Of-Ch, R |
| **Croatia** | B, B-Of, BR, CFAR, Ch, Ch-R, CHOP-R, cladribine, CVP±R, EPOCH-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, hyperCVAD-R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, PCR, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | B, BR, Ch, Ch-R, CHOP-R, cladribine, EPOCH-R, FC, FCM±R, FCR, FR, HDMP±R, hyperCVAD-R, Ibr, Id-R, Ob-Ch, PCR, R, SCT |
| **Czech Republic** | B, B-Of, BR, Ch, Ch-R, cladribine, cyclophosphamide, DHAP±R, DRC, ESHAP-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, ICE-R, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | B, B-Of, BR, Ch, Ch-R, cladribine cyclophosphamide, DHAP±R, DRC, ESHAP-R, F, FC, FCM±R, FCR, FR, HDMP, Ibr, ICE-R, Id-R, Ob-Ch, Of-Ch, R, SCT |
| **Hungary** | B, B-Of, BR, Ch, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, BR, Ch, FC, FCM±R, FCR, FR, HDMP±R, Ibr, R |
| **Latvia** | B, B-Of, BR, Ch, F, FC, FCM, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | FC |
| **Lithuania** | B, B-Of, BR, Ch, Ch-R, CVP±R, FC, FCM±R, FCO, FCR, FNDR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCR, FNDR, FR, HDMP±R, Ibr, Id-R, Ob-Ch, Of-Ch, R |
| **Macedonia** | FC, FCR, FCM±R, F-prednisone, FR, HDMP±R | FC, FCR, FCM±R, F-prednisone, FR, HDMP±R |
| **Poland** | B, B-Of, BR, Ch, Ch-R, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, BR, Ch, Ch-R, FC, FCR, FR, HDMP±R, Ob-Ch |
| **Russian Federation** | BR, Ch, F, FC, FCMR, FCR, HDMP±R, Ibr, R | BR, Ch, F, FC, FCMR, FCR, HDMP±R, Ibr, R |
| **Serbia** | B, B-Of, BR, Ch, Ch-R, cyclophosphamide, F, FC, FCM±R, FCR, FR, Ibr, Ob-Ch, Of-Ch, R | B, BR, Ch, Ch-R, cyclophosphamide, F, FC, FCM±R, FCR, FR, R |
| **Slovakia** | B, B-Of, BR, Ch, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-R, Id-Of, Ob-Ch, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, BR, B-Of, Ch, Ch-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-Of, Id-R, Ob-Ch, Of-Ch, R |
| **Slovenia** | B, B-Of, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, B-Of, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Ob-Ch, Of, Of-Ch, R |
| **Turkey** | B, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Of, R | B, BR, Ch, Ch-R, CVP±R, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Of, R |
| **Ukraine** | Ch, CHOP-R, FC, FCR | No information available |

| | Therapies with Regulatory Approval | Therapies with Funding/ Reimbursement Approval |
|---|---|---|
| **Western Europe** | | |
| **Belgium** | B, B-Of, BR, Ch, Ch-R, CVP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, BR, Ch, Ch-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Ob-Ch, R |
| **Denmark** | Alemtuzumab, B, B-Of, BR, Ch, Ch-R, CHOP-R, cladribine, CVP±R, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | Alemtuzumab, BR, Ch, Ch-R, CHOP-R, cladribine, CVP±R, FC, FCM±R, FCR, FR, HDMP±R, Ibr, IBR, Id-R, Ob-Ch, Of, Of-Ch, R, venetoclax |
| **France** | Alemtuzumab, B, B-Of, BR, Ch, FC, FCO, FCM±R, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | Alemtuzumab, B, B-Of, BR, Ch, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, venetoclax |
| **Germany** | B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, SCT, venetoclax |
| **Ireland** | B, B-Of, BR, Ch, CVP±R, FC, FCM-R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | B, BR, Ch, CVP±R, FC, FCR, FR, HDMP, Ob-Ch, R, SCT |
| **Israel** | B, B-Of, BR, Ch, cladribine, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Ob-Ch, Of, Of-Ch, R, venetoclax | B, B-Of, BR, Ch, cladribine, F, FC, FCM±R, FCR, HDMP±R, Ibr, Ob-Ch, Of, R, venetoclax |
| **Italy** | B, B-Of, BR, Ch, cladribine, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | B, BR, B-Of, Ch, cladribine, F, FC, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Of, Of-Ch, R |
| **Netherlands** | Alemtuzumab, B-Of, BR, Ch, DHAP±R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | Alemtuzumab, B-Of, BR, Ch, DHAP±R, F, FC, FCM±R, FCR, HDMP±R, Ibr, Id-R, Ob-Ch, Of, Of-Ch, R, SCT, venetoclax |
| **Portugal** | B, B-Of, BR, Ch, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | No information available |
| **Spain** | Alemtuzumab, B, B-Of, BR, Ch, Ch-R, F, FC, FCM-R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, PCR, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | Alemtuzumab, B, BR, B-Of, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, PCR, R, SCT |
| **Sweden** | B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R, R biosimilars (Rixathon, Truxima), venetoclax | B, B-Of, BR, Ch, Ch-R, F, FC, FCM±R, FCO, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, R |
| **Switzerland** | B, B-Of, BR, Ch, Ch-R, CHOP-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id, Id-R, Ob-Ch, Of, Of-Ch, R, SCT | B, BR, Ch, Ch-R, CHOP-R, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id, Id-R, Ob-Ch, R, SCT |
| **UK** | B, B-Of, BR, Ch, Ch-R, cladribine±R, CVP±R, cyclophosphamide, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, IBR, Id-Of, Id-R, Ob-Ch, Of, Of-Ch, pentostatin, R, R biosimilars (Rixathon, Truxima), SCT, venetoclax | B-Of, BR, Ch, Ch-R, cladribine±R, CVP±R, cyclophosphamide, F, FC, FCM±R, FCR, FR, HDMP±R, Ibr, Id-R, Ob-Ch, Of, Of-Ch, pentostatin, R, SCT |

Source: LC Global Database June 2017

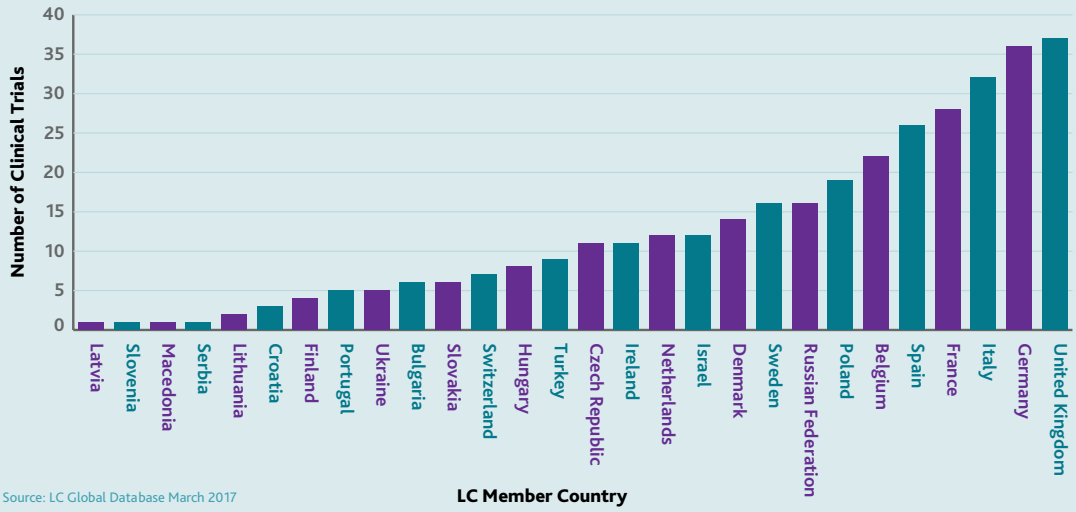
B = bendamustine; B-Of = bendamustine, ofatumumab; BR = bendamustine±rituximab; BRI = bendamustine, rituximab, idelalisib; CFAR = cyclophosphamide, fludarabine, alemtuzumab, rituximab; Ch = chlorambucil; Ch-R = chlorambucil+rituximab; ChIVPP = chlorambucil, vinblastine, procarbazine, prednisone; CHOP-R = cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab; CVP±R = cyclophosphamide, vincristine, prednisone±rituximab; DHAP±R = dexamethasone, cisplatin, cytarabine±rituximab; DRC = dexamethasone, rituximab, cyclophosphamide; EPOCH-R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; ESHAP-R = etoposide, methylprednisolone, cytarabine, cisplatin, rituximab; F = fludarabine; FC = fludarabine, cyclophosphamide; FCM±R = fludarabine, cyclophosphamide, mitoxantrone ± rituximab; FCO = fludarabine, cyclophosphamide, ofatumumab; FCR = fludarabine, cyclophosphamide, rituximab; FMD = fludarabine, mitoxantrone, dexamethasone; FMR = fludarabine, mitoxantrone, rituximab; FNDR = fludarabine, mitoxantrone, dexamethasone,rituximab; FP = fludarabine, prednisone; FR = fludarabine, rituximab; HDMP±R = high-dose methylprednisolone±rituximab; hyperCVAD-R = cyclophosphamide, vincristine, doxorubicin, rituximab and dexamethasone alternating with high dose methotrexate and cytarabine; Ibr = ibrutinib; IBR = ibrutinib, bendamustine, rituximab; ICE-R = ifosfamide, carboplatin, etoposide, rituximab; Id = idelalisib; Id-Of = idelalisib, ofatumumab; Id-R = idelalisib+rituximab; Id-Of = idelalisib, ofatumumab; Id-R = idelalisib, rituximab; LR = lenalidomide±rituximab; Ob-Ch = obinutuzumab+chlorambucil; Of = ofatumumab; Of-Ch = ofatumumab+chlorambucil; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab; PCR = pentostatin, cyclophosphamide, rituximab; R = rituximab; RT = radiation therapy; SCT = stem cell transplant

**Overall, more research needs to look at combinations of therapies and sequencing of therapies to perfect the ideal treatment pathway, especially with the new treatments now available.**

# Clinical Trial Activity

As of March 2017, there were 211 clinical trials underway globally involving patients with CLL of which 78 were available in Europe. This information is taken from the six clinical trial registries LC follows.[b] Of the 211 clinical trials available globally, 147 were specifically for patients with CLL of which 64 were available in Europe. All LC member countries in Europe had at least one clinical trial for CLL available (see Figure 5). The countries with the most clinical trials for patients with CLL were the UK (n = 37), Germany (n = 36) and Italy (n = 32).

**FIGURE 5. CLL CLINICAL TRIALS BY COUNTRY**

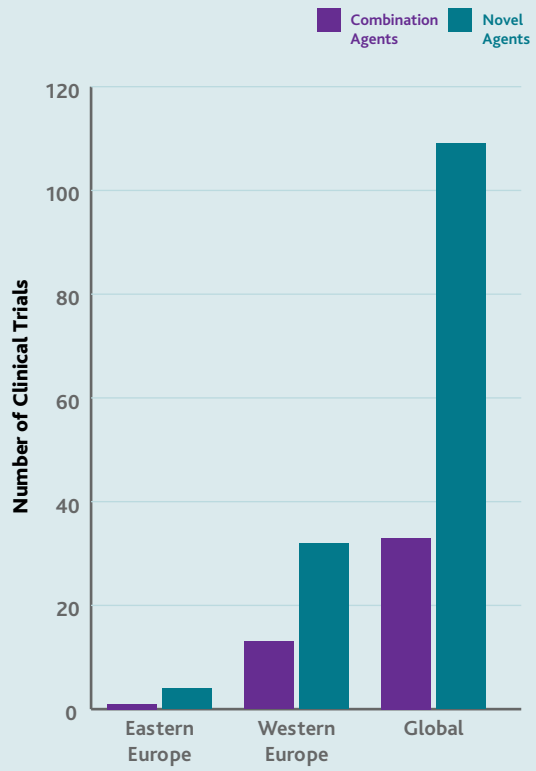



[b]The six clinical trial registries LC follows are Clinicaltrials.gov, Australian Cancer Trials, European Union Clinical Trials Register, World Health Organization, JAPIC Clinical Trials Information (Japan), Clinical Trials Registry, India

While the majority of the phase II clinical trials underway in CLL in Europe were studying the use of novel agents, compared with the number of phase II trials available globally (n = 109), there were only 32 available in Western Europe while Eastern Europe only had four (see Figure 6). This suggests that patients in Europe, especially Eastern Europe, likely do not have access to the latest developments. When looking at the availability of phase III clinical trials involving novel therapies, while fewer were available in Eastern Europe compared with Western Europe, the difference was not as stark as it was with the availability of phase II clinical trials (see Figure 7).

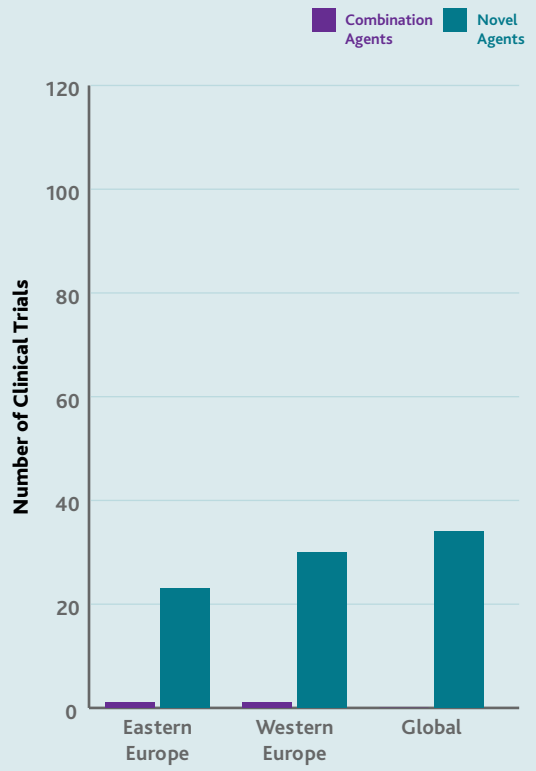
While it is encouraging to see the extent of clinical trial activity for CLL, what is of concern is that few of the clinical trials specifically examine issues as they pertain to the elderly with CLL. Most clinical trials involve younger patients (under the age of 65 years), yet the median age of diagnosis is 72 years with the average time to first treatment being four to five years from the time of diagnosis.[14] Of the 211 CLL clinical trials in LC's global database, only seven were exclusively for patients aged 65 years and older; of these seven two were available in Europe. Anecdotally, this has also been identified as an issue by the CLL Advocates Network (CLLAN), an international collective representing CLL patient groups. Most patients in CLL clinical trials are younger than the typical patient with CLL, consequently, there is an unmet need in the understanding of the true impact of therapies on older patients who have comorbidities.[16]

**FIGURE 6. REGIONAL AVAILABILITY OF PHASE II NOVEL THERAPY CLINICAL TRIALS**




Source: LC Global Database March 2017

**FIGURE 7. REGIONAL AVAILABILITY OF PHASE III NOVEL THERAPY CLINICAL TRIALS**




Source: LC Global Database March 2017

# Incidence and Mortality

Based on the information that has been collected in the LC Global Database, **CLL affected 5:100,000** each year (2010 and 2011) worldwide. Globally, the **average mortality rate was 2:100,000** in 2011. Among the 28 member countries in Europe, complete incidence and mortality information for 2010 and 2011 could only be obtained for 14 countries. Based on this information, the **average incidence of CLL in Europe in 2010 and 2011 was 5:100,000** while the **average mortality rate for both years was 2:100,000**. For more information on the incidence and mortality of CLL in Europe, click here.

# The Patient Experience

It is imperative that the patient experience is always front of mind when reviewing data and information. To better understand the patient experience, every two years, LC engages with the lymphoma community through a global survey. The results from this survey are then used to help guide LC and its member organisations in planning patient activities, advocacy efforts and support.

In the 2016 Lymphoma Global Patient Survey (GPS), of the 4,154 responders, 416 indicated they had CLL of which 41 were from Eastern Europe and 135 from Western Europe. This section will review the patient experience from the perspective of Eastern and Western Europe rather than individual member countries as the sample sizes were small.

Findings from the GPS indicated that globally, 39% of respondents had experienced barriers to treatment, while in Western Europe 37% had.

**When looking at Eastern Europe, however, a considerably higher percentage of respondents (65%) had experienced barriers, with access to the treatment centre and financial concerns being the biggest issues.**

LC undertook a review of several indicators to compare the experience of patients with CLL in Eastern and Western Europe, as well as globally. The concerns LC reviewed were:

- Barriers to treatment;
- Psychosocial effects;
- Physical and medical effects;
- Awareness and understanding about the CLL subtype;
- Level of support provided by respondent's physician.

# Barriers to Treatment

Globally, when looking at barriers to treatment, LC found that access to a specialty physician was an issue for 18% of all respondents with CLL, compared with 6% of respondents in Eastern Europe and 16% of respondents in Western Europe (see Figure 8).

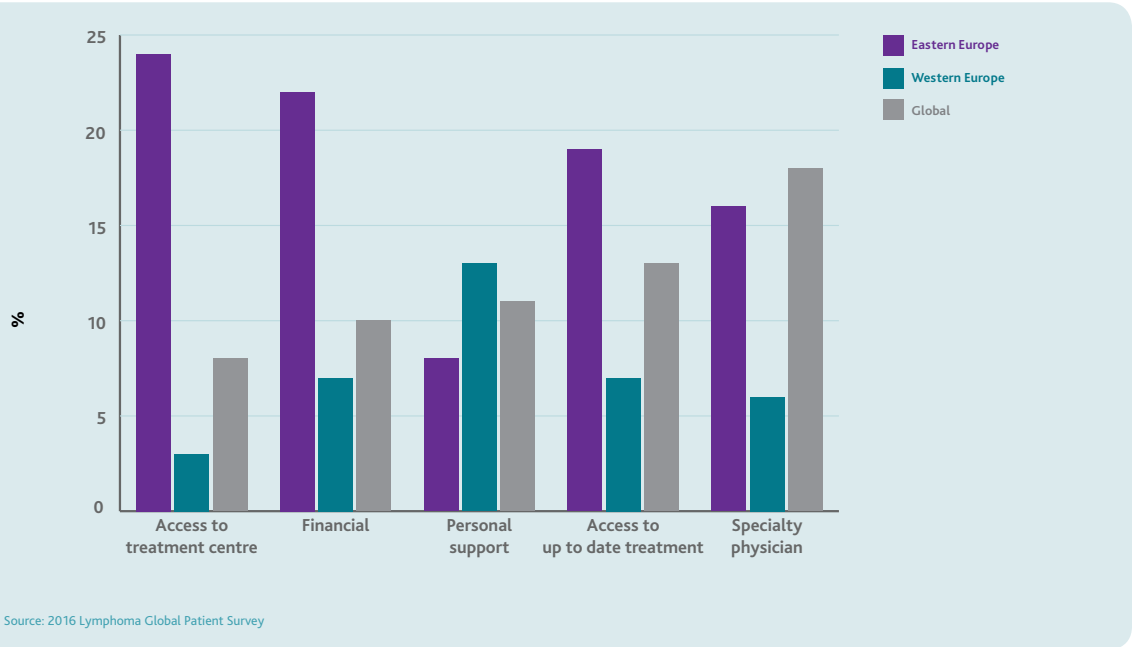
**Among respondents from Eastern Europe, the biggest barriers to treatment were access to a treatment centre (24%) and financial concerns (22%). Among respondents from Western Europe, the biggest barrier was lack of personal support.**

Within Eastern Europe, the difficulty to access the treatment centre likely means patients are not receiving treatment in a timely manner and, therefore, are not achieving optimal outcomes. In addition, if patients have far to travel to the treatment centre, they may incur additional expenses (travel and accommodation costs, unpaid leave, childcare, etc.). Another factor likely contributing to the financial concerns is that a number of the therapies, e.g., venetoclax, listed by either ESMO or NCCN for the treatment of CLL, were not funded/reimbursed in Eastern European countries.

**When comparing barriers by year of diagnosis, barriers to treatment appeared to be on the increase among respondents from Eastern Europe compared with those from Western Europe.**

For example, for respondents diagnosed between 2010 and 2016, 85% of Eastern European respondents experienced barriers as opposed to 15% who were diagnosed between 2003 and 2009. In Western Europe, 43% of respondents experienced barriers to treatment as compared with 33% who were diagnosed between 2003 and 2009.

**FIGURE 8. BARRIERS TO TREATMENT BY REGION**




Source: 2016 Lymphoma Global Patient Survey

# Psychosocial Effects

Psychosocial concerns look at the influence that psychological factors in combination with the surrounding social environment have on physical and mental wellness of patients. The top concerns for patients with CLL are shown in Figure 9.

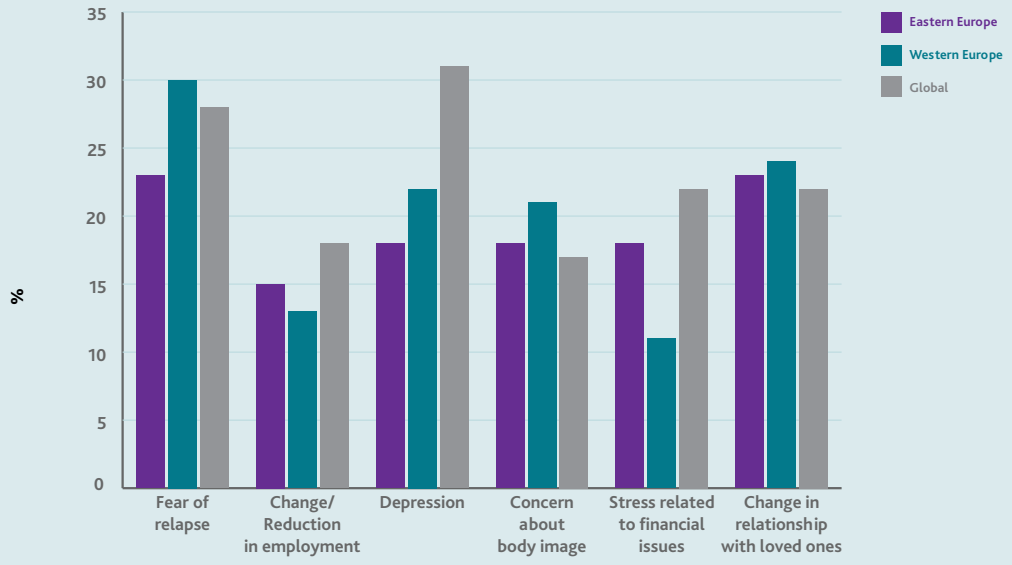
**Fear of relapse, depression and change in relationships with loved ones were the top challenges followed by stress related to financial issues, change/reduction in employment and concern about body image.**

Among respondents from Eastern Europe the biggest concerns were fear of relapse (23%), changes in relationship with loved ones (23%), depression (22%), concern about body image (18%) and stress related to financial issues (18%). In Western Europe, the greatest concern was fear of relapse (30%), changes in relationship with loved ones (24%) and concern about body image (21%).

Body image is of great importance as it can be a physical outward sign of being unwell, knowledge that not all patients may wish to share. Results from the 2016 Lymphoma GPS showed that concerns about body image affected one-third of all respondents.

Fear of relapse is a major concern for patients across all lymphoma subtypes. To date, it would appear that this topic is not discussed as frequently as it should be with healthcare professionals (HCPs). Referring patients to the social care department or to patient organisation is one way to begin the support.

**FIGURE 9. PSYCHOSOCIAL IMPACT BY REGION**



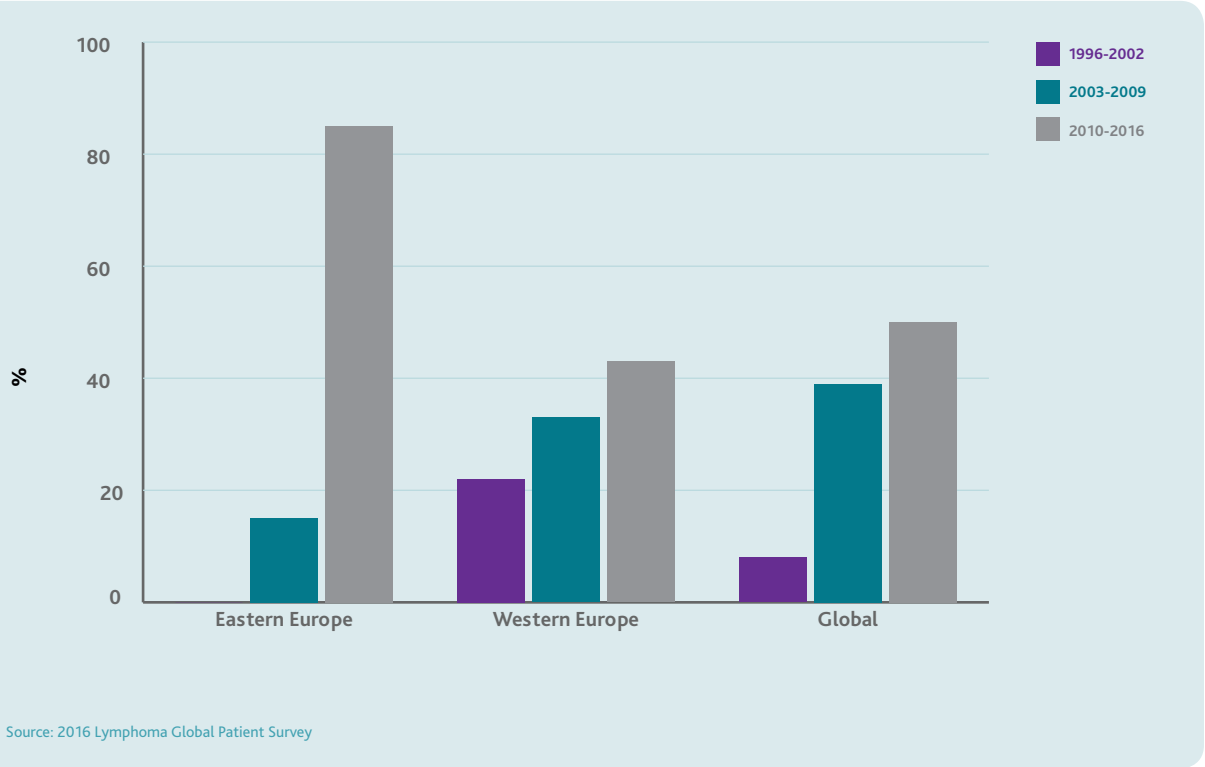

Source: 2016 Lymphoma Global Patient Survey

# Psychosocial Impacts: Loss/Reduction in Employment

When comparing responses, stress related to financial issues and change/reduction in employment were higher in Eastern Europe compared with Western Europe. When comparing concerns with employment with year of diagnosis, 39% of the patients diagnosed between 2003 and 2009 indicated they experienced loss/reduction in employment; this increased to 85% for patients diagnosed between 2010 and 2016. A similar trend was seen among respondents from both Eastern and Western Europe combined with the biggest increase among respondents from Eastern Europe: 15% for the diagnosis period 2003 and 2009 versus 85% for the diagnosis period 2010 and 2016 (see Figure 10).

Given the small sample it was not possible to determine whether loss or reduction in employment was worse before, during or after treatment as well as whether the respondent's age had an impact. Regardless, patients with CLL living in Eastern Europe are likely having financial difficulties because of the challenges they are experiencing on the work front.

**FIGURE 10. CHALLENGES WITH EMPLOYMENT BY YEAR OF DIAGNOSIS**




Source: 2016 Lymphoma Global Patient Survey

# Physical and Medical Side Effects

## Physical Side Effects

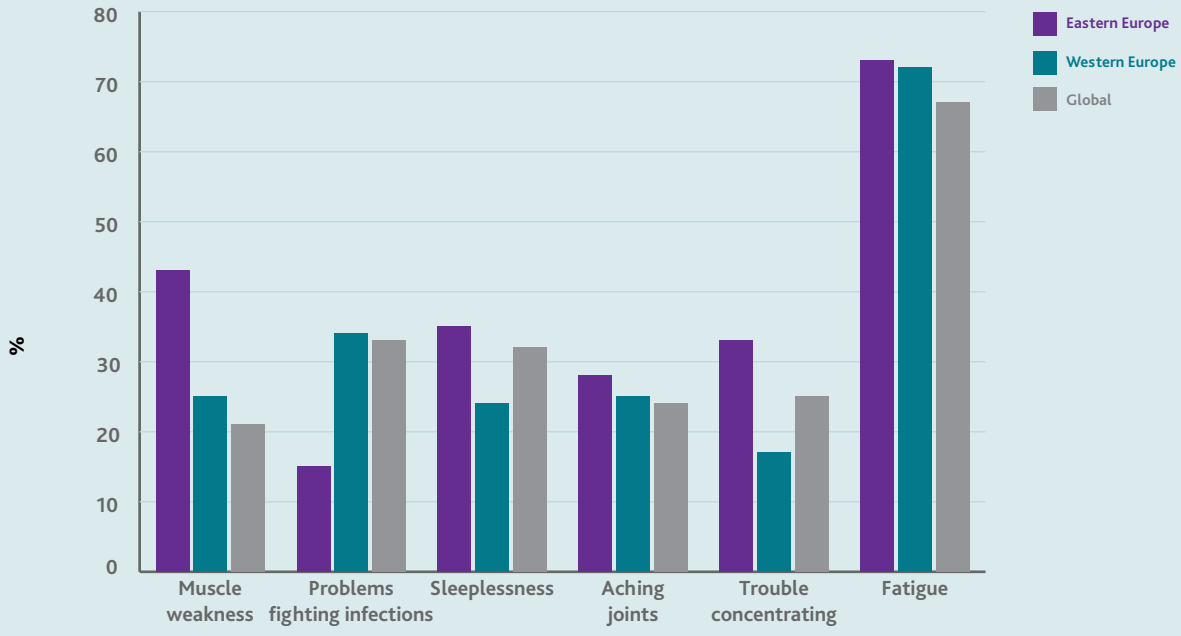
With the introduction of new therapies, the hope is that patients will not only achieve more enduring remissions but that they will also experience fewer side effects. To determine if newer therapies did result in any changes, respondents were asked to indicate what physical and medical side effects they had experienced.

**When looking at physical effects, overwhelmingly, all respondents with CLL, regardless of where they were from, indicated that fatigue was a concern (see Figure 11).**

The physical effects were higher in Eastern Europe compared with Western Europe with the exception of problems fighting infections, which was significantly lower in Eastern Europe compared with Western Europe.

On average, the physical side effects were higher in European countries compared with the rest of the world.

**FIGURE 11. PHYSICAL SIDE EFFECTS**




Source: 2016 Lymphoma Global Patient Survey

# Medical Side Effects

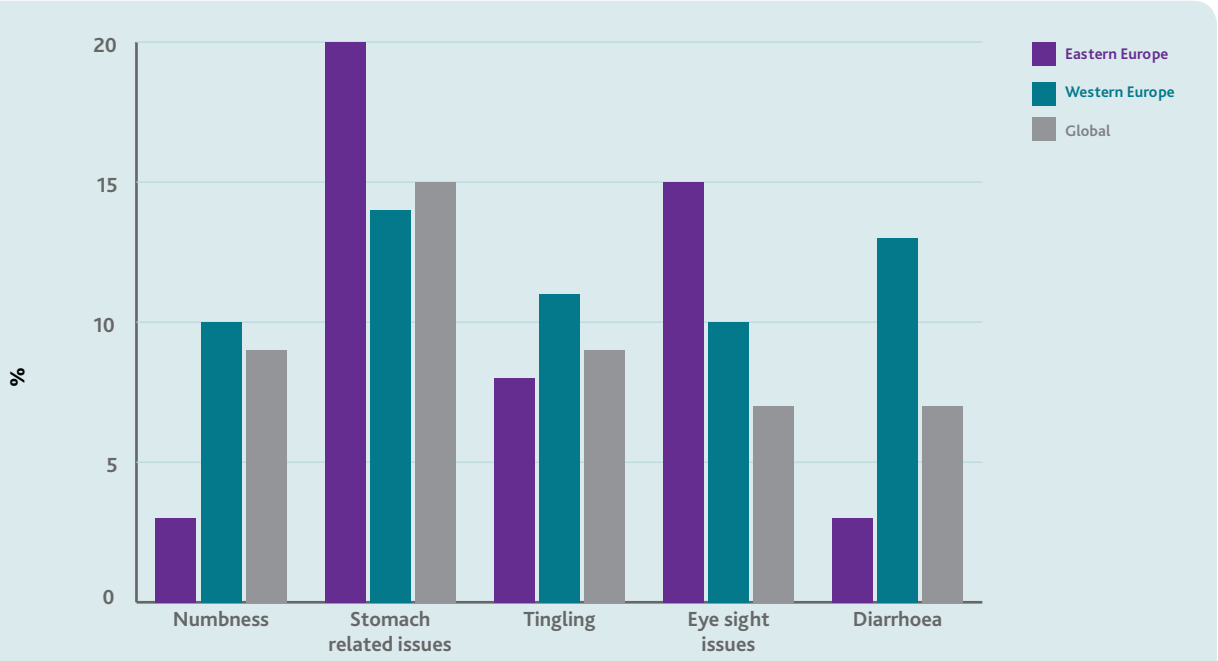
In the 2016 Lymphoma GPS respondents were asked if they had experienced any medical issues as a result of their lymphoma or treatment. The medical concern that was most reported by all respondents with CLL was stomach-related issues (see Figure 12).

Western Europe reported higher incidences of medical issues except for stomach-related issues while eye sight issues were higher among Eastern European respondents. Concerns such as diarrhoea and numbness were far lower in Eastern Europe (3% for both) than in Western Europe (13% and 10%, respectively).

On average, the medical issues faced by patients in Europe were higher than the global average.

While it is encouraging that efforts are underway to develop new therapies that will provide a more targeted approach to treatment, what is of concern is that results from clinical trials still show that physical effects such as fatigue and physical weakness (asthenia) remain common side effects. For example, with both obinutuzumab and ofatumumab, the newer monoclonal antibodies, fatigue is still one of the most common side effects.[17] New therapies, regardless of how effective they are, need to have fewer side effects so patients do not have to deal with them in addition to all the other factors they have reported.

**FIGURE 12. MEDICAL ISSUES BY REGION**




Source: 2016 Lymphoma Global Patient Survey

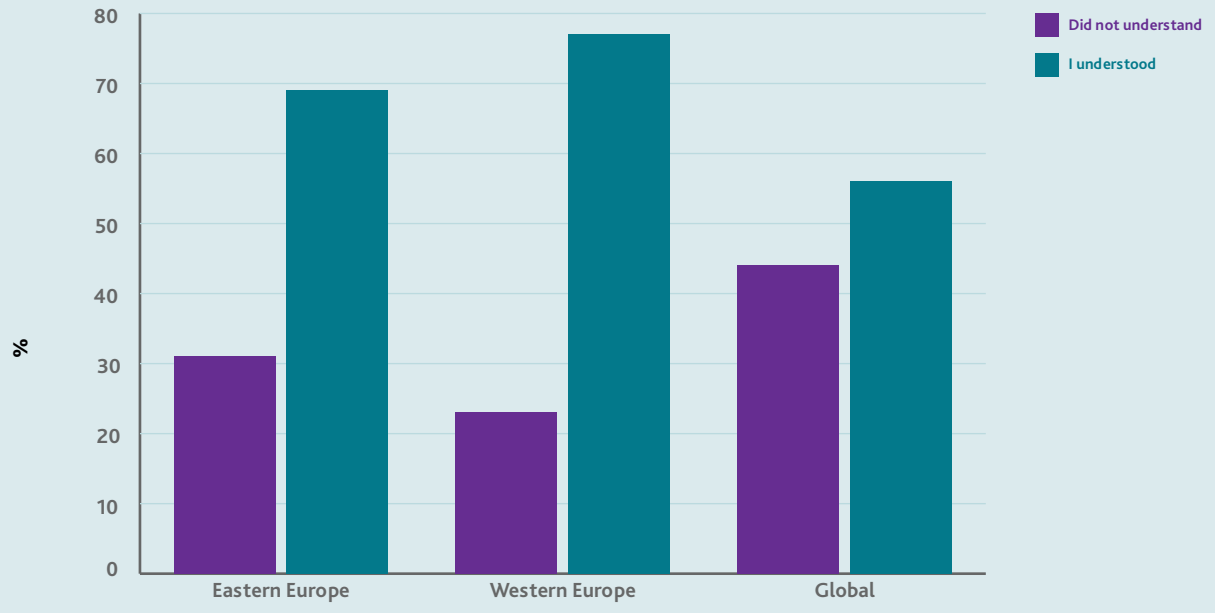
# Awareness and Understanding about the CLL Subtype

Key to ensuring effective treatment and care is for patients to know their subtype. Among those with CLL, respondents living in either Eastern or Western Europe reported they understood the characteristics of their subtype. This understanding was higher than that among CLL patients globally (see Figure 13).

**When looking at the understanding of the potential side effects associated with treatment options, respondents in Western Europe had a much higher understanding (81%) than those in Eastern Europe (55%).**

The level of understanding in both regions, however, was higher than the level of understanding globally among those with CLL (47%). Respondents in Western Europe also appeared to have a better understanding of the management of potential side effects (71%) compared with those in Eastern Europe (39%).

**FIGURE 13. UNDERSTANDING OF CLL SUBTYPE BY REGION**




Source: 2016 Lymphoma Global Patient Survey

# Support from Healthcare Professionals

**In the 2016 Lymphoma GPS, only 30% of respondents indicated that their doctor had been able to help them with their physical and emotional concerns.**

LC wanted to determine if the level of support received from doctors varied among those with CLL based on their region of residence. Overwhelmingly, respondents with CLL, regardless of where they lived, indicated that their doctor had only been able to help them somewhat or not at all (see Figure 14).

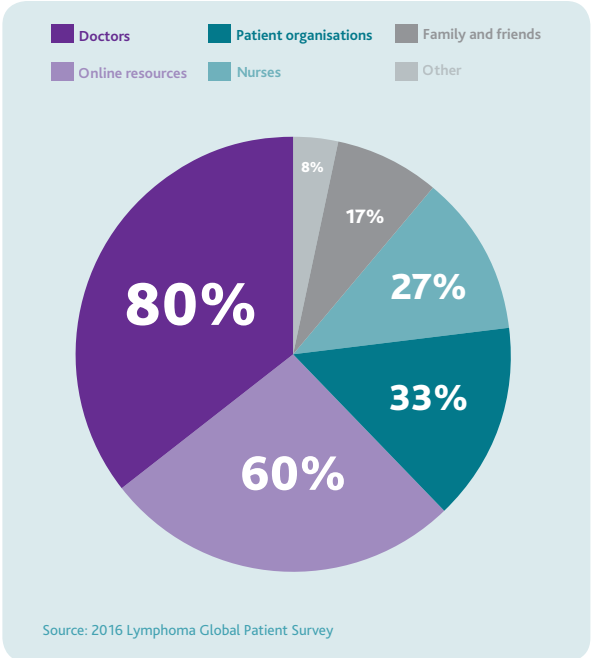
So, where are patients getting their information from? Findings from the GPS showed that after doctors, online resources were the most frequently accessed sources of information (60%) followed by patient organisations (33%) (See Figure 15).

Given that 80% of respondents reported that their doctor was their primary source of information but only 30% indicated that their doctor had been able to help means patients have to find information on their own. While the Internet is a good resource, it is not possible to ensure that all information patients gather is relevant or even helpful, and this is of greater concern in light of the evolving understanding about CLL and its biology. This situation presents an opportunity for HCPs and patient organisations to play a greater role together to help patients get the information they need. The HCPs cannot fulfil the role entirely on their own.

**FIGURE 14.**
**PATIENTS HELPED BY DOCTOR**


Source: 2016 Lymphoma Global Patient Survey

**FIGURE 15.**
**PRIMARY SOURCES OF INFORMATION FOR PATIENTS**




Source: 2016 Lymphoma Global Patient Survey

# Conclusion

To ensure patients with CLL receive the best possible care, it is key that the focus goes beyond the administration of therapy to include the psychological, emotional as well as physical effects associated with treatment. A multifaceted approach that provides information and care that corresponds to the patient's needs will likely result in patients being better able to cope with their lymphoma. There are services outside of the doctor's office that can provide such support and they should be used and recommended to patients. Given that CLL is a chronic as well as heterogeneous disease, this is of particular importance as each patient will present with their unique issues.

A number of barriers to treatment confront patients with CLL. Access to both specialty physicians and treatment centres are issues as are financial concerns. Those in Eastern Europe appear to be in particular need of more assistance in overcoming many of these barriers. Patient organisations and other social support systems may be able to play a bigger role in helping patients navigate through the intricacies of their respective country's healthcare systems.

While it is encouraging that a great deal of research is occurring to better understand this subtype resulting in new treatments, more research is needed that examines the combination as well as sequencing of therapies to perfect the treatment pathway. There are also areas of concern with treatment as they relate to providing patients with optimal care. Access to the newer therapies needs to improve. There is now information to show which types of CLL will respond to which treatments, and it is important that markers are verified. These markers dictate the course of therapy and they should be made available to patients who need them. It is not acceptable for these newer therapies not to be easily available to patients who need them. The availability of CLL clinical trials in countries where there are few needs to improve. Improving access to clinical trials will result in potentially better access to care and doctors having the experience of the novel treatment protocols.

Greater efforts are needed to ensure patients with CLL understand the nature of their subtype. Supporting patients while they are in the watch-and-wait phase of treatment is just as important as when they are undergoing treatment. Hence, the need for a holistic approach to treatment that encompasses both physical as well as psychological support.

A multifaceted approach that provides information and care that corresponds to the patient's needs will likely result in patients being better able to cope with their lymphoma.

There is now information to show which types of CLL will respond to which treatments and it is important that markers are verified. These markers dictate the course of therapy and they should be made available to patients who need them.

# Acronyms

| | |
|---|---|
| **B** | bendamustine |
| **BCL** | B-cell lymphoma |
| **BCR** | B-cell receptor |
| **B-Of** | bendamustine, ofatumumab |
| **BR** | bendamustine±rituximab |
| **BRI** | bendamustine, rituximab, idelalisib |
| **BTK** | Bruton tyrosine kinase |
| **CBC** | complete blood count |
| **CFAR** | cyclophosphamide, fludarabine, alemtuzumab, rituximab |
| **Ch** | chlorambucil |
| **CHOP-R** | cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab |
| **Ch-R** | chlorambucil+rituximab |
| **ChlVPP** | chlorambucil, vinblastine, procarbazine, prednisone |
| **CIT** | chemotherapy plus immunotherapy |
| **CLL** | chronic lymphocytic leukaemia |
| **CPR** | cyclophosphamide, prednisone±rituximab |
| **CVP±R** | cyclophosphamide, vincristine, prednisone±rituximab |
| **DHAP±R** | dexamethasone, cisplatin, cytarabine±rituximab |
| **DNA** | deoxyribonucleic acid |
| **DRC** | dexamethasone, rituximab, cyclophosphamide |
| **EPOCH-R** | etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab |
| **ESHAP-R** | etoposide, methylprednisolone, cytarabine, cisplatin, rituximab |
| **ESMO** | European Society of Medical Oncology |
| **F** | fludarabine |
| **FC** | fludarabine, cyclophosphamide |
| **FCM±R** | fludarabine, cyclophosphamide, mitoxantrone±rituximab |
| **FCO** | fludarabine, cyclophosphamide, ofatumumab |
| **FCR** | fludarabine, cyclophosphamide, rituximab |
| **FMD** | fludarabine, mitoxantrone, dexamethasone |
| **FMR** | fludarabine, mitoxantrone, rituximab |
| **FNDR** | fludarabine, mitoxantrone, dexamethasone, rituximab |
| **FP** | fludarabine, prednisone |
| **FR** | fludarabine, rituximab |
| **GI** | gastrointestinal |
| **GPS** | Global Patient Survey |
| **HCP** | healthcare provider |
| **HDMP±R** | high-dose methylprednisolone±rituximab |
| **hyperCVAD-R** | cyclophosphamide, vincristine, doxorubicin, rituximab and dexamethasone alternating with high-dose methotrexate and cytarabine |
| **Ibr** | ibrutinib |
| **IBR** | ibrutinib, bendamustine, rituximab |
| **ICE-R** | ifosfamide, carboplatin, etoposide, rituximab |
| **Id** | idelalisib |
| **Id-Of** | idelalisib, ofatumumab |
| **Id-R** | idelalisib+rituximab |
| **IGVH** | immunoglobulin heavy-chain variable region |
| **LC** | Lymphoma Coalition |
| **LR** | lenalidomide±rituximab |
| **MBL** | monoclonal B-cell lymphocytosis |
| **NCCN** | National Comprehensive Cancer Network |
| **NMSC** | nonmelanoma skin cancer |
| **Ob-Ch** | obinutuzumab+chlorambucil |
| **Of** | ofatumumab |
| **Of-Ch** | ofatumumab+chlorambucil |
| **OFAR** | oxaliplatin, fludarabine, cytarabine, rituximab |
| **PCR** | pentostatin, cyclophosphamide, rituximab |
| **PI3K** | phosphatidylinositol 3-kinase |
| **R** | rituximab |
| **RT** | radiation therapy |
| **SCT** | stem cell transplant |
| **SLL** | small lymphocytic leukaemia |
| **SYK** | spleen tyrosine |
| **UK** | United Kingdom |
| **USA** | United States of America |
| **WHO** | World Health Organization |

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To ensure patients with CLL receive the best possible care, it is key that the focus goes beyond the administration of therapy to include the psychological, emotional as well as physical effects associated with treatment. A multifaceted approach that provides information and care that corresponds to the patient's needs will likely result in patients being better able to cope with their lymphoma.