THE
WHITE PAPER

chronic lymphocytic leukemia

Medical consultants:

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"The White Paper of CLL is the first of this kind, dedicated specifically to the issues of blood cancers. It describes the type of leukemia which is most prevalent among adult patients; the report also presents the current standards of diagnosis and treatment of CLL and the situation of patients in Poland against the background of other European countries, to highlight the need for a change to close the gap between treatment outcomes in Poland and across Europe. It is definitely a valuable and much-needed publication".

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"The White Paper is a unique report addressing the situation of patients with chronic lymphocytic leukemia in Poland. It stresses the need to improve access to hematologists, who are now responsible for correct diagnosis as well as patient follow-up and qualification for treatment. I believe that this analysis will be a practical instrument with which optimum therapies for chronic lymphocytic leukemia can be made more accessible".

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Hematology Clinic, the Institute of Hematology and Transfusion Medicine, Warsaw

"The White Paper reports on the existing standards in diagnosis and therapy of chronic lymphocytic leukemia, as well as practical solutions to facilitate their implementation in Poland. It shows the necessary corrective measures to be taken to improve the effectiveness of CLL management".

prof.
TADEUSZ ROBAK
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"This report provides comprehensive and up-to-date information about clinical settings and contemporary therapies for chronic lymphocytic leukemia. Particular emphasis is placed on the evaluation of accessibility of novel therapies among Polish patients".

MICHAŁ SUTKOWSKI
MD

Primary Care Physicians Council in Poland

"This is a hemato-oncological bestseller. The White Paper of CLL is an analysis illustrating the current and necessary clinical and therapeutic standards for patients and the changes to be implemented in the Polish healthcare".

prof.
DARIUSZ WOŁOWIEC
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Chair and Clinic for Hematology, Blood Cancer and Bone Marrow Transplants, Medical University in Wrocław

"Treatment of patients with chronic lymphocytic leukemia is a medical and logistical challenge. In the existing healthcare system, patients are not given access to the novel medical technologies that are confirmed to be effective. A major advantage of this White Paper is that it identifies key problems in this area of healthcare, which can be very helpful to individuals and institutions interested in improving the standards of care of patients who suffer from the most common type of leukemia among adults".

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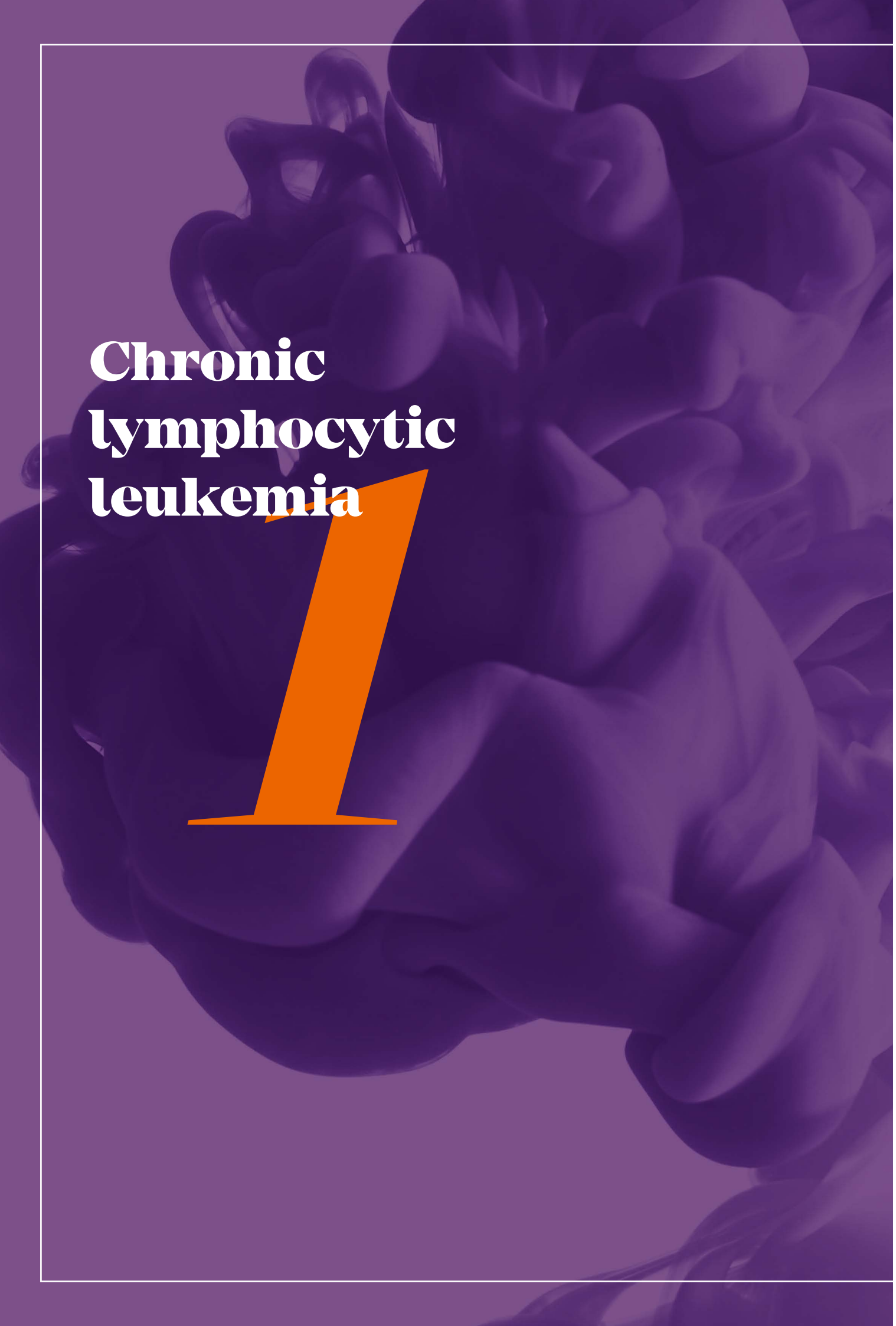


Chronic lymphocytic leukemia

1

What is chronic lymphocytic leukemia?

Chronic lymphocytic leukemia is a type of blood cancer in which lymphocytes become cancerous as they mature; they then grow and multiply uncontrollably and accumulate in blood, bone marrow and, over time, in lymph nodes, spleen, and liver. In this type of leukemia, lymphocytes present with surface B-cell antigens (CD19, CD20, CD23) in addition to a typical T-cell antigen (CD5)[1,2].

CLL continues to be an incurable disease except for few cases where bone marrow transplant can be performed from family or unrelated donor, which is referred to as an allogeneic stem cell transplant (alloSCT). This procedure is carried out in younger patients (< 65 years), it involves a high risk of complications and is associated with a high mortality rate. So far, therapies used in CLL were oriented towards eliminating general signs and symptoms of the disease, to prevent cytopenia and to control leucocyte count. With the introduction of new treatment options, the purpose of CLL treatment – with a focus on younger patients – is to obtain complete remission or to eradicate residual disease, which translates into longer disease-free survival and overall survival among CLL patients[3].

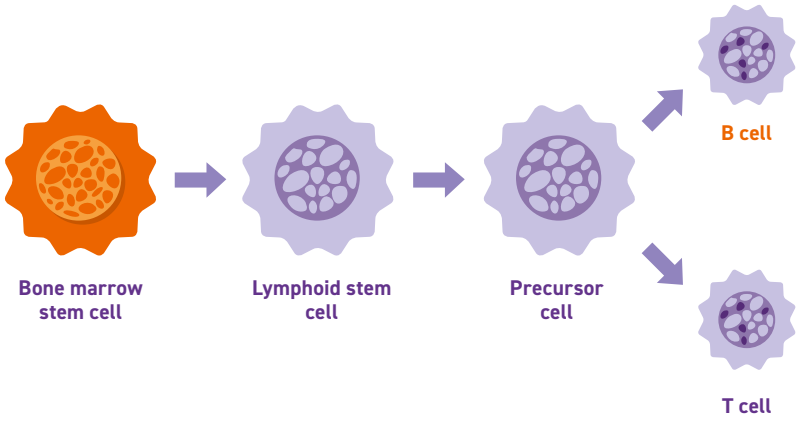
Hematologist: "The disease is often first diagnosed by chance, patients are surprised to have the condition – CLL is detected during routine blood tests, it is mostly asymptomatic and the newly diagnosed patients suddenly become ill with a fatal condition (...)"[5].

What are the symptoms of chronic lymphocytic leukemia?

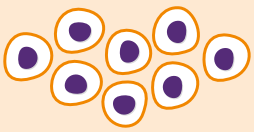
The course of chronic lymphocytic leukemia is very diversified and often asymptomatic. Around 30% of patients are symptom-free at diagnosis[4]. The condition is often detected by chance, during routine blood rests[5].

Other patients can develop very diversified and unspecific symptoms, depending on the stage of the disease. The most common symptoms in CLL include enlarged peripheral lymph nodes (lymphadenopathy) and fatigue (tiredness). Systemic symptoms, such as weight loss of more than 10% over 6 months, a fever that lasts for more than 2 weeks, night sweats – are experienced by around 10% of patients[4]. In other patients, CLL can be mainly manifested by CLL-related complications, such as decreased RBC and platelet count, reduced immunity, and frequent infections[6].

WHAT IS CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)?



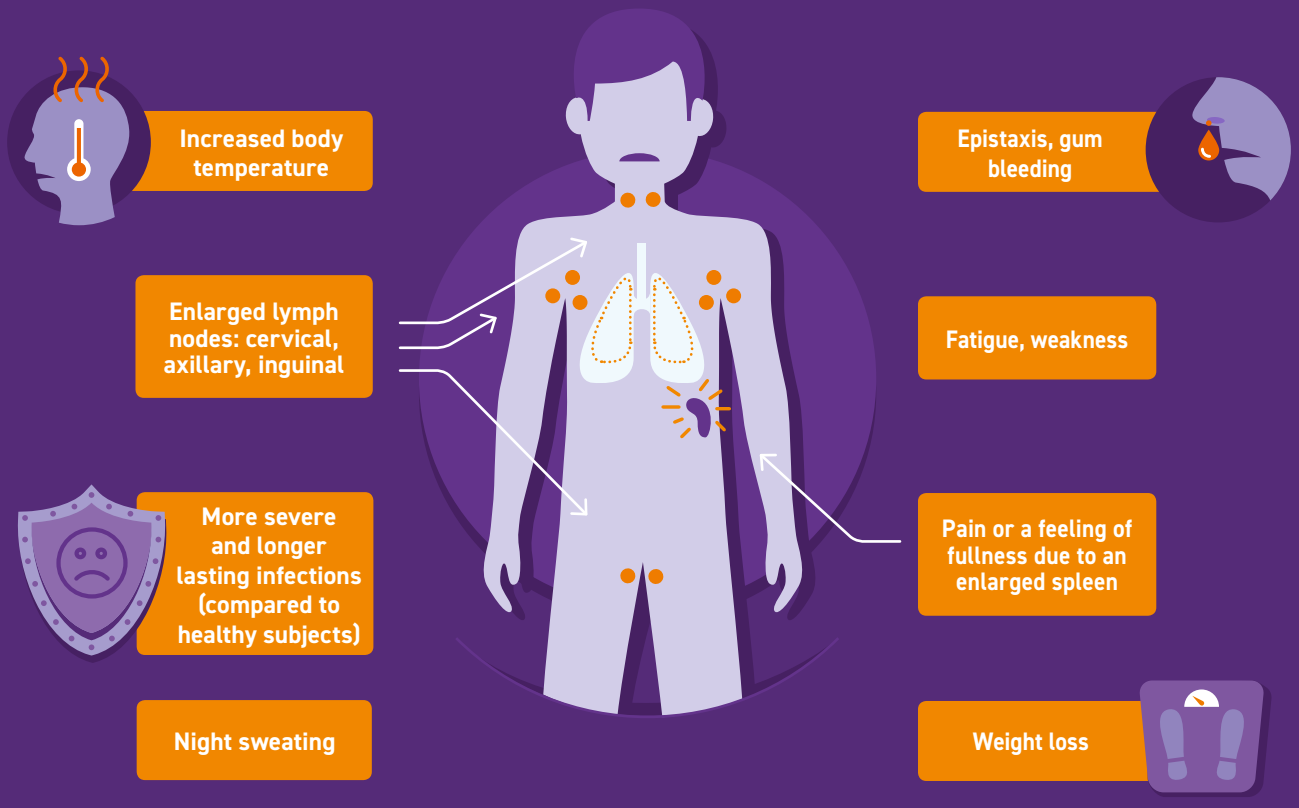
CLL is diagnosed when the bone marrow extensively produce white cells (lymphocytes).

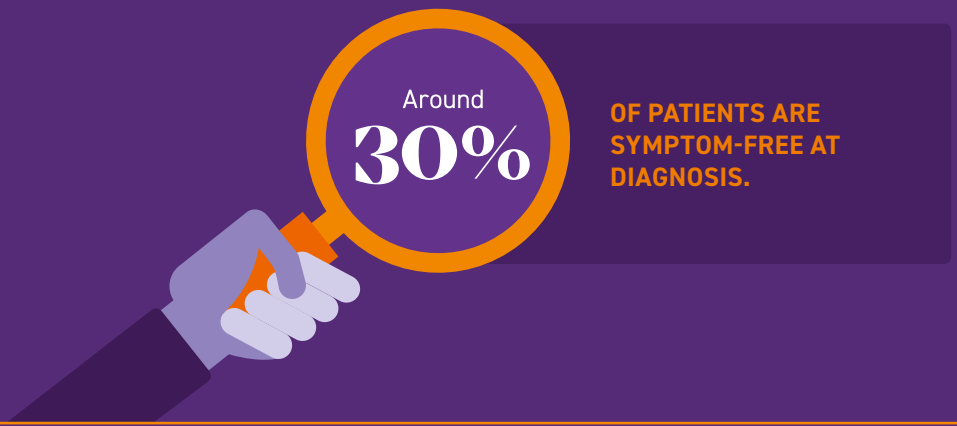


Malignant B cells have impaired signaling that controls proliferation. They exist in favourable microen-vironment of lymph nodes or bone marrow. There they continue to proliferate and cumulate.

Source: Chiorazzi M, et al. Mechanisms of disease Chronic Lymphocytic Leukemia. N Engl J Med. 2005;352:804-15.
Gore JM. Chronic myeloid leukemia and chronic lymphocytic leukemia. JAAPA. 2014;27(2).

CLL SYMPTOMS





Source: Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych – 2013 r. Warzocha K. Przewlekła białaczka limfocytowa.

Gore JM. Chronic myeloid leukemia and chronic lymphocytic leukemia. JAAPA. 2014;27(2).

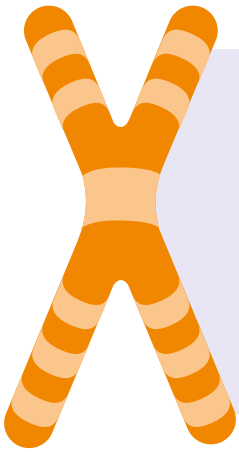
What is the cause of chronic lymphocytic leukemia?

The causes of chronic lymphocytic leukemia remain unknown. There is an increased family incidence, which may be indicative of a genetic predisposition to the development of CLL[1].

GENETIC ABNORMALITIES IN LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia is a **condition in which many genetic abnormalities are present.** Genetic aberrations detected in cancerous lymphocytes significantly affect the course of the disease, response to treatment, and the resulting prognosis.

Deletions of parts of chromosomes are detected in over 80% of CLL cases and are the most common identified genetic changes in newly diagnosed patients:



- 55% Deletion of the long arm of chromosome 13 (del13q) –55% of patients,
- 18% Deletion of the long arm of chromosome 11 (del11q) –18% of patients,
- 16% Chromosome 12 trisomy –16% of patients,
- 7% Deletion of the short arm of chromosome 17 (del17q) –7% of patients.

Source: Giannopoulos K. Biologia i rokowanie w przewlekłej białaczce limfocytowej. Acta Haematologica Polonia 2010; 41: 3, 433-440.
van Leeuwen JE, Samelson LE. T cell antigen-receptor signal transduction. Curr Opin Immunol. 1999; 11: 242-248.

High-risk chronic lymphocytic leukemia

In early 1980s, chronic lymphocytic leukemia was considered a homogenous, slowly progressing condition[7]. The presentday state of knowledge clearly indicates that CLL is a heterogenous condition both in terms of the clinical picture, and its genetic characteristics[8].

The varied course of CLL has been investigated for many years. A list of clinical and molecular criteria has been compiled, based on which patients are classified according to how the disease is anticipated to progress. High-risk CLL is defined as progressive disease and is associated with worse response to standard therapy and shorter survival as compared to patients with standard-risk CLL[9,10].

High-risk chronic lymphocytic leukemia is currently diagnosed in patients:[11,12]

- with a positive status of chromosome 17p deletion [del(17p)] and/or TP53 gene mutation in cancerous lymphocytes,
- who experience relapse within less than 24 months following intensive immunochemotherapy regimen,
- who are resistant to monotherapy with purine analogs – fludarabine.

From the clinical point of view, a deletion in the short arm of chromosome 17 (del17p) is the critical genetic aberration, signifying fast disease progression and shorter survival. As a consequence of del17p, leukemia cells lack the tumor suppressor gene TP53, which results in patient's resistance to chemotherapeutic agents whose mechanism of action largely depends on the correct tumor suppression function of the TP53 gene. This type of therapy includes purine analogs that are universally used in the management of CLL[13]. In general, poor response to standard intensive chemotherapy

regimens is often associated with quick relapse and shorter survival, even in patients who are found to be free of adverse genetic factors[12]. Over time, adverse genetic aberrations are found to accumulate in patients with CLL, particularly 17p and 11p deletions. Moreover, the higher the number of replaces, the higher resistance to subsequent lines of therapy[14].

It is estimated that patients with high-risk CLL account for around 10 – 15% of all individuals who receive first-line treatment[12]. Del17p is detected in 7–12% of individuals undergoing first-line treatment and in 23 – 50% of patients who experience relapse and require further treatment[10,15,16].

Population of patients with high-risk CLL is not extensive, but deserves special attention. In these patients, it is extremely difficult to achieve long-term remission with commonly used standard immunochemotherapy regimens[11]. In high-risk chronic leukemia, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently recommended, but this procedure is associated with high risk of death and is contraindicated in elderly patients, in patients in poor general condition, and in persons with comorbidities[4].

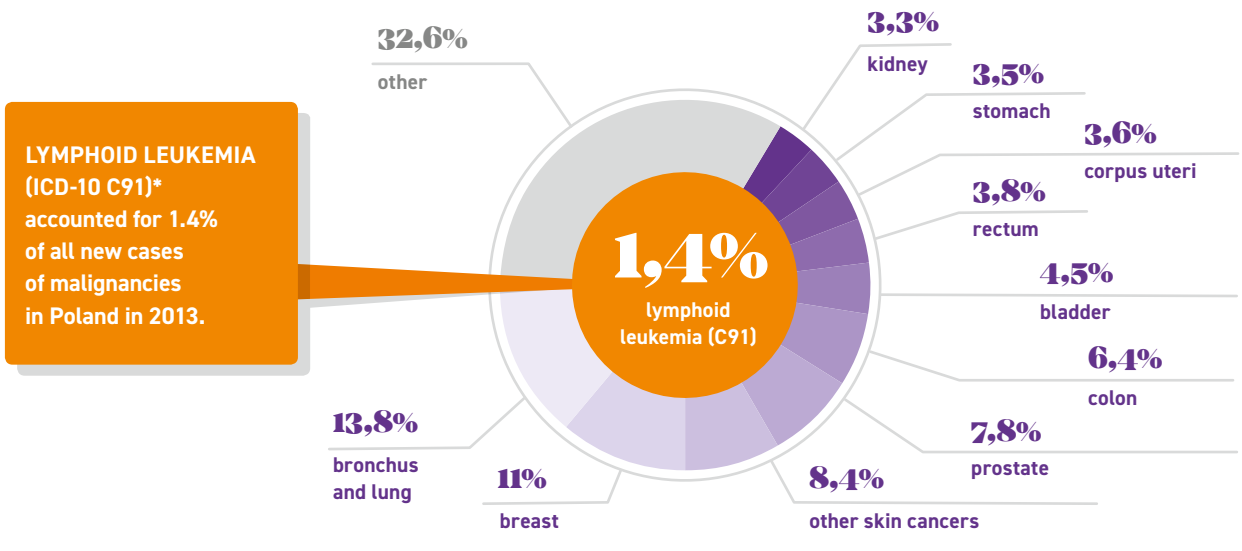
Tab. 1. Incidence and mortality in the most common types of malignancies and lymphocytic leukemia (ICD-10 C91) in Poland in 2013 [own estimates based on data collected by the National Cancer Registry (KRN)][118].

	ICD-10	Malignancies*	New cases	Mortality rate
1.	C34	Malignancy of bronchus and lung	21 524	22 628
2.	C50	Malignancy of breast	17 286	5881
3.	C44	Other skin cancers	13 196	189
4.	C61	Malignancy of prostate	12 162	4281
5.	C18	Malignancy of colon	10 001	7188
6.	C67	Malignancy of bladder	6965	3413
7.	C20	Malignancy of rectum	5898	3374
8.	C54	Malignancy of corpus uteri	5706	1243
9.	C16	Malignancy of stomach	5402	5232
10.	C64	Malignancy of kidney	5143	2584
...				
18.	**C91**	**Lymphoid leukemia**	**2234**	**1307**

What is the prevalence of chronic lymphocytic leukemia?

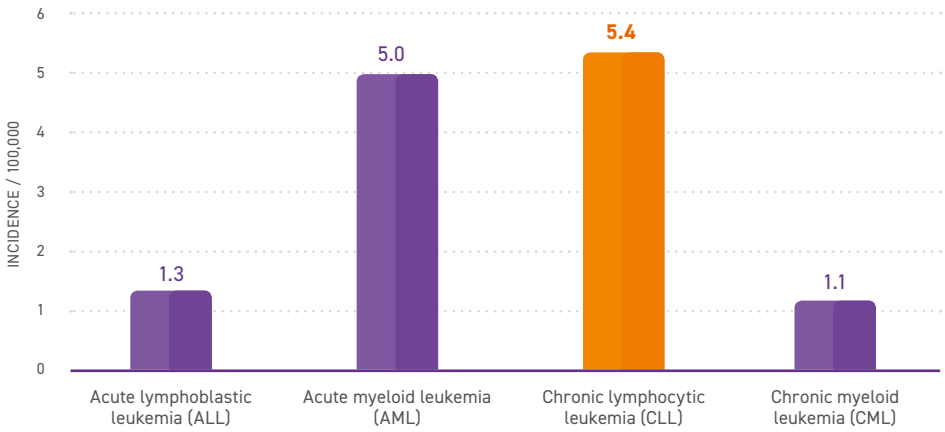
Chronic lymphocytic leukemia is the most commonly diagnosed type of leukemia affecting adults and accounts for 25-30% of all leukemia types[17] (compare Fig. 1). According to data compiled by the National Health Fund NFZ, there were 16.7 thousand people diagnosed with this condition in Poland in 2015[18]. The number of new cases estimated based on NFZ data in Poland has been stable over the past 10 years and amounts to around 1900 cases per year[19]. The incidence of CLL is estimated at around 4.2-5.0 new cases per 100,000 population per annum[4,19]. Poland's incidence rate is comparable to that in Europe (based on HAEMACARE study – 4.92 cases per 100,000 population per year)[20]. A more exact immunophenotyping study has demonstrated that the annual incidence of CLL is 7.99/100,000 and is twice as high as the one calculated from registry data[21].

MALIGNANT TUMOR INCIDENCE STATISTICS IN POLAND AS OF 2013



* KRN data are considered imprecise and apply to the main categories of medical conditions according to ICD-10 code. Thus, data on lymphoid leukemia (C91) include – apart from chronic lymphocytic leukemia of B-cell type (C91.1) – also other conditions from this group.

Fig. 1. Number of new cases of specific leukemia types per 100,000 population per year (incidence) in the UK between 2011 and 2013 [own summary based on data by Cancer Research UK][119].



Who develops chronic lymphocytic leukemia?

According to epidemiological data, chronic lymphocytic leukemia mainly affects elderly patients. Around 70% of patients are more than 65 years of age at the time of diagnosis[23]. Based on US data, median age at the time of CLL diagnosis is 70 years[24]. According to NFZ data, the age at diagnosis is slightly lower in Poland – 63 years in men and 66 years in women, on average[19].

The risk of developing CLL increases with age – incidence rate of CLL in individuals aged over 65 years is estimated at over 20 cases per 100,000 population and increases in older patients (refer to Fig 4)[20,23]. European epidemiological data indicate that patients with CLL are the oldest population of patients suffering from any type of leukemia (compare Fig. 2 and Fig. 3).

Chronic lymphocytic leukemia is 1.5 – 2 time more frequent in men than in women – the number of new cases in women and men per 100,000 population is 3.9 and 6.9, respectively[20,23].

Fig. 2. Average percentage of patients aged 65 and more who are diagnosed with leukemia [the UK, 2011 – 2013; own summary based on data by Cancer Research UK][119].

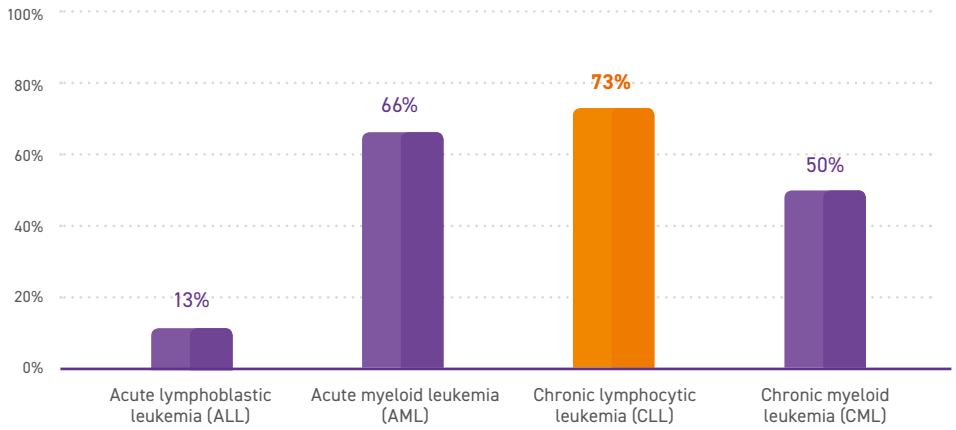


Fig. 3. Median age at diagnosis according to leukemia type [the US, 2009 – 2013; own summary based on data from SEER][120].

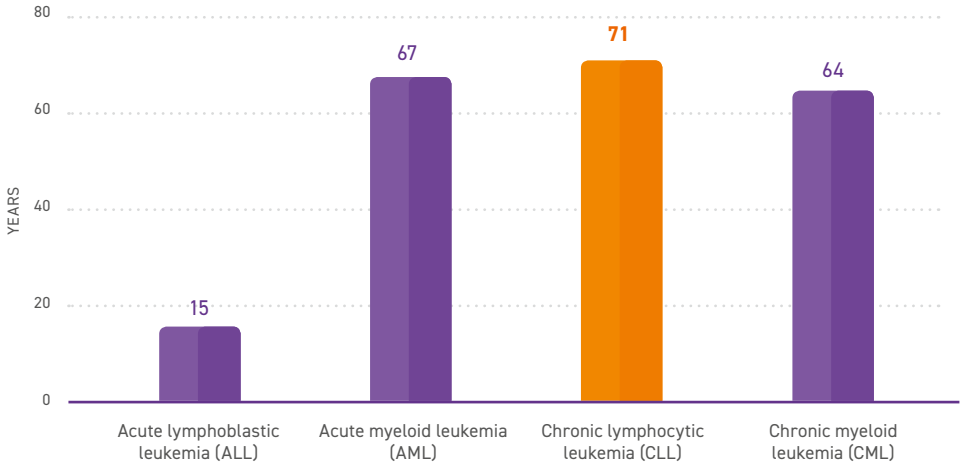
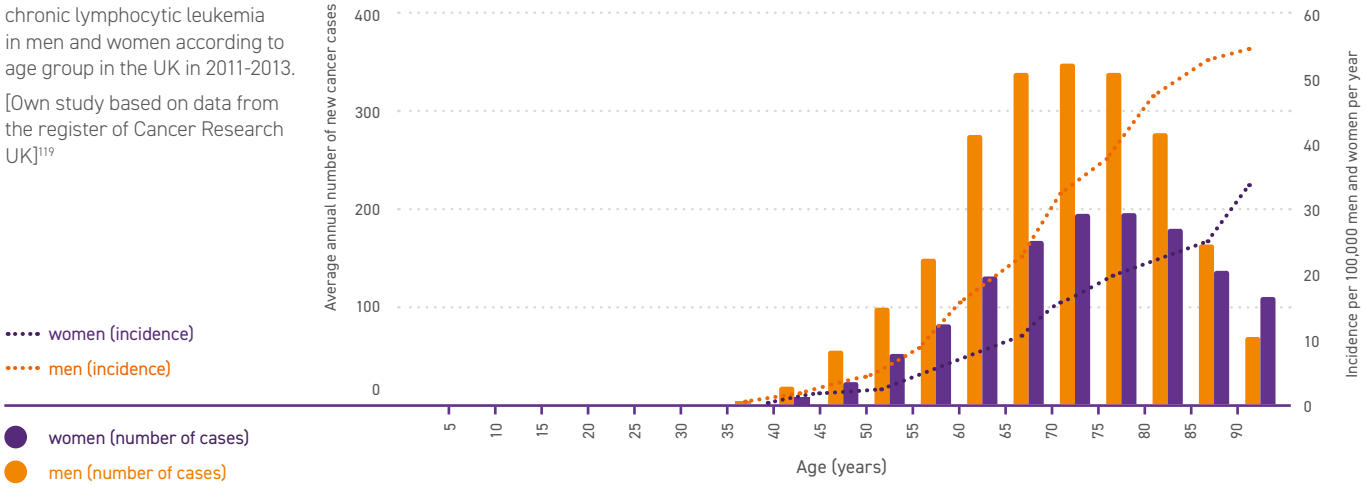


Fig. 4. Average number of new cases and annual incidence of chronic lymphocytic leukemia in men and women according to age group in the UK in 2011-2013.

[Own study based on data from the register of Cancer Research UK][119]



WHAT IS THE INCIDENCE OF CLL?

CLL affects men around
2 times
more often than women

CLL IS THE MOST RECOGNIZED TYPE OF LEUKEMIA IN ADULTS

Number of new cases of CLL in Poland per year:

in 100 000 inhabitants

AVERAGE AGE AT THE TIME OF CLL DIAGNOSIS IN POLAND:

men

63 years

66 years

women

Source: Brugiatelli M, Bandini G, Barosi G, et al. Management of chronic lymphocytic leukemia: practice guidelines from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica. 2006 Dec;91(12):1662-73.

Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010 Nov 11;116(19):3724-34.

Cancer Research UK. Statistics by cancer type. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type [dostęp: 10.05.2016]

Raport: Białaczka limfatyczna. Dane i Analizy, Kraków 2015, str. 1-53.

What are the prognoses in chronic lymphocytic leukemia?

In 1/3 of all cases, chronic lymphocytic leukemia is mild and has a survival time of 10-20 years. In other cases, the condition can be aggressive and cause death within a few years, or it can be initially mild to cause to severe complications and death over time[1,3].

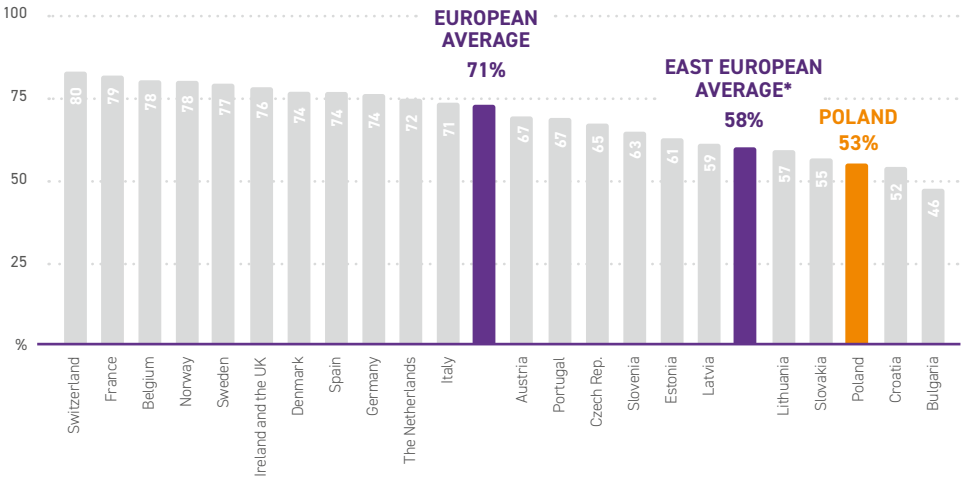
According to the results of "EUROCARE" epidemiological study on the survival of cancer patients in regions and countries of Europe, 5-year survival rate of patients with chronic lymphocytic leukemia in Poland counts among the lowest not only in Europe, but also in Central and Eastern Europe. European average 5-year survival rate of 71% is relatively high. However, Poland's average 5-year survival rate is only 53% and is by 18% lower than the European average and by 5% lower than the average 5-year survival rate in Central and Eastern Europe (compare Fig. 5)[22].

AVERAGE 5-YEAR SURVIVAL IN EUROPE AND IN POLAND

Source: De Angelis R, Minicozzi P, Sant M, et al. Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000-2007: Results of EUROCARE-5 population-based study. Eur J Cancer. 2015 Sep 6.

Fig. 5. Average 5-year survival of patients with CLL in Europe between 2000 and 2007, based on the results of EUROCARE-5 study[22].

* Countries included in the analysis of average 5-year survival rates in chronic lymphocytic leukemia in Central and Eastern Europe: Bulgaria, Czech Rep., Estonia, Lithuania, Latvia, Poland, and Slovakia[22].



* median survival time is the time of follow-up at which half of patients died.

[based on Fendler W, Chałubińska J, Młynarski W. Techniki analizy przeżycia stosowane w onkologii — założenia, metodyka i typowe problemy interpretacyjne. Onkol. Prak. Klin. 2011; 7, 2: 89–101]

HIGH-RISK FACTORS IN CHRONIC LYMPHOID LEUKAEMIA, PREVALENCE AND MEDIAN SURVIVAL IN PATIENTS PRESENTING WITH A SPECIFIC RISK FACTOR

	Risk factor	Prevalence (first-line treatment)	Median survival* (first-line treatment)
High-risk CLL (~10-15%)	17p deletion	5-8%	< 24 months
	TP53 mutation	4-5%	24-36 months
	Lack of response to purine analogs	5%	< 24 months
	Fast relapse (< 24/36 months)	14%	< 24 months

Source: Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:481-8.

Zenz T, Busch R, Fink A, et al. Genetics of patients with F-refractory CLL or early relapse after FC or FCR: Results from the CLL8 trial of the GCLLSG [Abstract] Blood 2010 116:2427.

Prognosis in chronic lymphocytic leukemia are less favourable in patients with high-risk factors (specific genetic mutations in cancerous lymphocytes, fast disease progression, weak response to purine analogs – refer to section “High-risk Chronic Lymphocytic Leukemia”). Overall survival in an “average” patient with CLL is estimated at almost 7 years, but patients with high-risk factors are likely to survive for no more than 3 years[12].

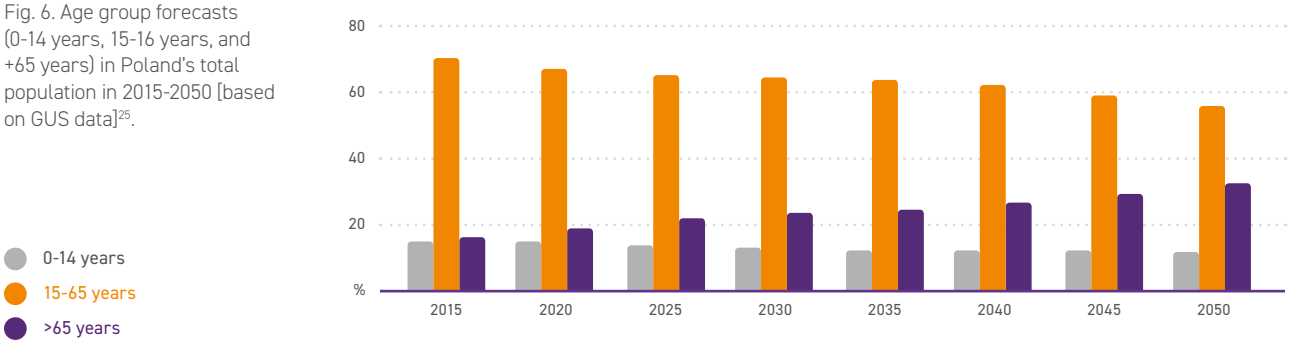
Chronic lymphocytic leukemia vs. ageing society

Epidemiological and demographic projections clearly indicate that the demographic changes in Poland will translate into a growing population of elderly people who are more vulnerable to the development of neoplasms[23].

According to the latest estimates by the Central Statistical Office GUS for the period 2014-2050, Poland will face deepening changes in its population structure – the number of people aged between 15 and 65 years will diminish, and the population aged 65 years and more will increase (compare Fig. 6). It is expected that in 10 years time, over 1/5 of Poland's population will be over 65 years old, and in 2050, over 65-year-olds will account for nearly 1/3 of the total Polish population[25]. The upcoming demographic developments will have an impact on the incidence of neoplastic diseases and cancer-related mortality rates over the coming decade. According to forecasts on the incidence of cancers, the current incidence level of 145,000 new cases of cancer annually can increase to around 185,000 per year in 2025[23,24].

In the face of ageing population and considering the fact that chronic lymphocytic leukemia is more common in elderly patients, it is expected that this condition will become an increasing health concern in Poland.

Fig. 6. Age group forecasts (0-14 years, 15-16 years, and +65 years) in Poland's total population in 2015-2050 [based on GUS data][25].



Treatment of chronic lymphocytic leukemia

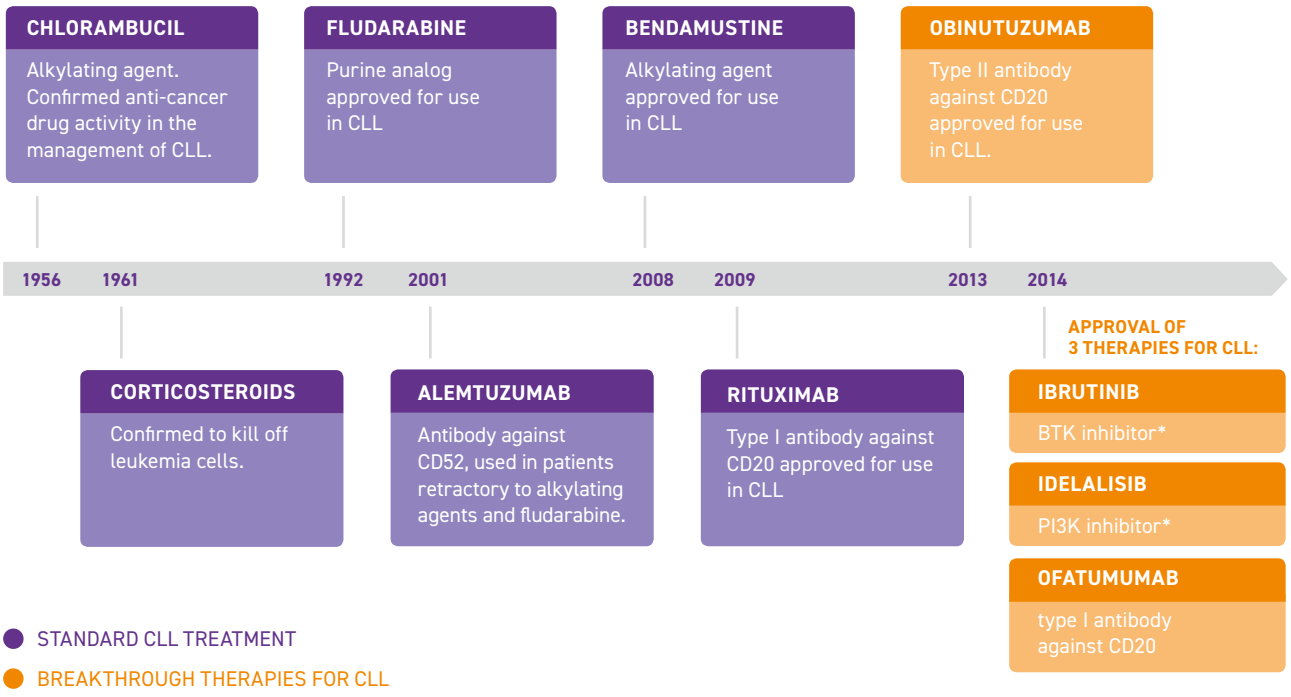
2

How is chronic lymphocytic leukemia managed?

Pharmacotherapy is the mainstay of chronic lymphocytic leukemia management; surgical treatment and radiation therapy are of limited use in CLL, unlike in solid tumors. Stem cell transplant is rarely used in the management of CLL[31]. Immunotherapy based on purine analogs, alkylating agents, and anti-CD20 monoclonal antibodies are the current standard of case in first-line treatment of chronic lymphocytic leukemia.

Treatment of chronic lymphocytic leukemia has evolved over the past decades[7]. In late 1980s, CLL treatment consisted of chemotherapy based on alkylating agents, such as chlorambucil and cyclophosphamide, the oldest group of anticancer drugs. However, even if patients with CLL responded to these medications, lasting disease remission was rarely achieved[26]. In 1990s, purine analogues were included to chemotherapy used in CLL, such as fludarabine, which is still used in first-line treatment. It improved a number of clinical outcomes, such as the percentage rates of remission and progression-free survival[7,27]. In early 21st century, monoclonal antibodies directed against the B cell surface antigen CD20 (anti-CD20) were introduced to the treatment of CLL and contributed to further improvements in patients' survival[26]. In the recent years, owing to the better understanding of the underlying biological mechanisms of chronic lymphocytic leukemia, we have witness another breakthrough in the management of this condition, especially among patients who poorly respond to standard therapy.

TIME AXIS ILLUSTRATING MILESTONES IN THE DEVELOPMENT OF PHARMACEUTICALS USED IN CHRONIC LYMPHOCYTIC LEUKAEMIA



* BTK – Bruton's tyrosine kinase
PI3K – Phosphoinositide 3-kinase

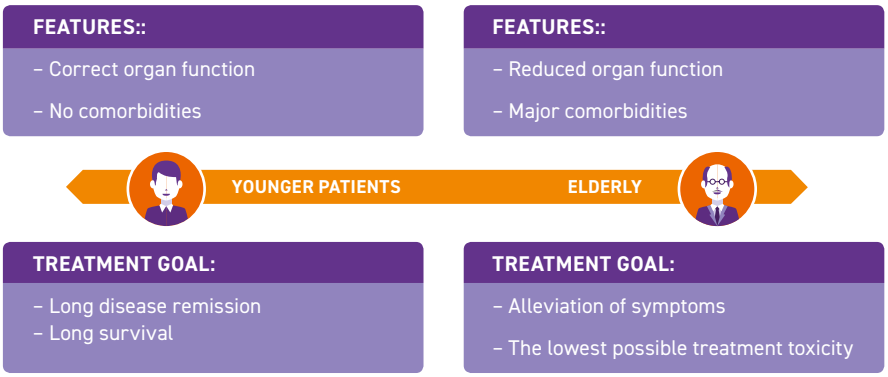
Source: Warzocha K, Lech-Marańda E, Budziszewska BK, et al. Rola bendamustyny w przewlekłej białaczce limfocytowej ze szczególnym uwzględnieniem chorych w podeszłym wieku. Hematologia 2014; 5, 4: 285–295.

With the current stage of knowledge and the existing treatment options, chronic lymphocytic leukemia continues to be an incurable condition using conventional treatment methods. Only autologous bone marrow transplant offers a chance of recovery. Initially, the most important decision in the management of CLL is whether to start cancer treatment or not. As a rule, newly diagnosed patients in early stages of the condition and no clinical symptoms are routinely monitored according to a "wait and watch" approach[28]. This "wait and watch" approach is based on the results of randomized studies showing no improvement in survival in patients undergoing treatment involving a risk of chemotherapy-related complications[29].

If the disease is found to progress and the patient is eligible for therapy, the next stage of patient care is to choose the most appropriate treatment regimen. Patients with chronic lymphocytic

leukemia are a heterogenous population comprising extreme groups of individuals – younger patients in good general condition, and elderly patients with comorbidities. Each of these groups have distinct therapeutic goals attributed to the general health condition of individual patients. However, the majority of CLL patients are somewhere between these two extremes and form a population that escapes easy classification. This means that treatment decisions are taken on a case-by-case basis[30].

POPULATION DIVERSITY OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA AND TREATMENT GOALS DEPENDING ON CLINICAL STATE



Source: Warzocha K, Lech-Marańda E, Budziszewska BK, et al. Rola bendamustyny w przewlekłej białaczce limfocytowej ze szczególnym uwzględnieniem chorych w podeszłym wieku. Hematologia 2014; 5, 4: 285–295.

The choice of treatment regimen depends on the general condition and physical functioning of individual patients[28]. According to the updated ESMO Clinical Practice Guidelines, an inherited genetic susceptibility for CLL, i.e. the presence of mutations associated with poor prognosis (del17p andTP53 mutations), should be also taken into a consideration in the choice of treatment of relapsed CLL[31]. In the majority of patients, the current standard of treatment consists of chemotherapy combined with immunotherapy, and the existing treatment regimens can be personalized to reflect the patient's clinical condition, comorbidities, and the results of auxiliary tests[28,30].

In relapsed patients, the therapeutic decision largely depends on the duration of remission and the general condition of a patient. In case of long-term remission (over 24-26 months) in patients without any adverse prognostic factors identified, the same treatment regimen is typically repeated. The choice of optimum therapy is less obvious in patients suffering from high-risk CLL. In patients with high-risk CLL, one feasible option is to qualify to clinical studies of innovative drugs or allogeneic hematopoietic cell transplantation – but this procedure is restricted to younger patients in good general condition[31]. If a patients does not qualify for a transplant, the main therapeutic goal is to improve quality of life through cytoreductive treatment and/or symptomatic treatment[4].

Since 2013, four innovative medications have been registered for CLL patients who were given a poor prognosis. These were "milestones" in the management of chronic lymphocytic leukemia that marked the beginning of a new era of treatment focused on specific molecular targets, a so-called targeted therapy.

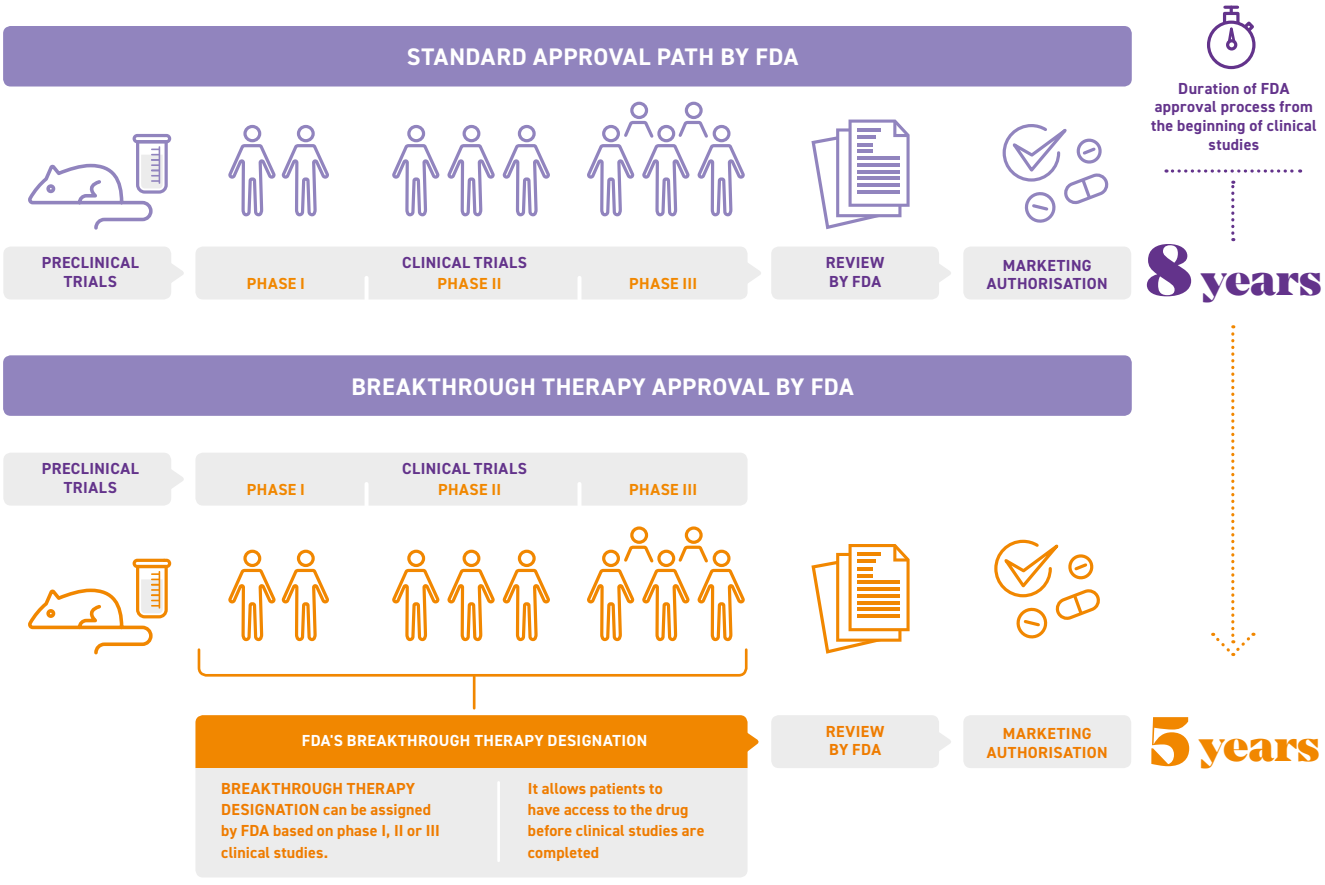
Breakthrough treatments of chronic lymphocytic leukemia

A breakthrough therapy designation has been awarded to drugs since 2012 by the Food and Drug Administration. It allows expedited approval and marketing authorization of a novel drug to make it available to patients as soon as possible.

* FDA defines a serious disease or a serious clinical condition as having a substantial impact on day-to-day functioning. A clinical condition or a disease is considered serious based on its effect on patient survival, day-to-day functioning, and likelihood of progression if untreated[35].

FDA's Breakthrough Therapy Designation is assigned to drugs intended to treat serious and life threatening conditions[32]. From among all early access and fast-track programs covering drug newly approved by FDA, the breakthrough therapy designation accelerates the approval process on the one hand, but on the other hand it is also the most restrictive approval process[33]. The key criterion that a drug has to meet to be designated as a breakthrough therapy is substantial improvement of at least one clinically significant endpoint as compared to the current standard of therapy. A clinically significant endpoint is defined as beneficial effects of treatment on morbidity, mortality or serious complications[34]. An application for a breakthrough therapy designation is filed by the drug's manufacturer; FDA can proactively

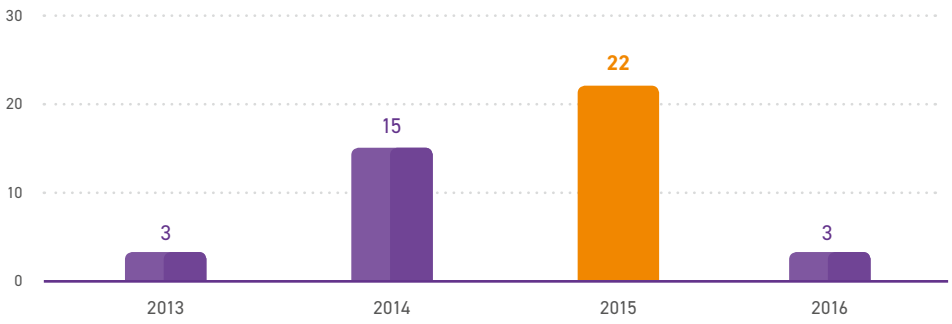
SUMMARY OF FDA DRUG APPROVAL PROCESS FOR REGULAR VS. BREAKTHROUGH THERAPY



Source: Subramanian R, et al. FDA's New Breakthrough Therapy Designation: What does it mean for Pricing and Market Access? OBRoncology.com September 2013 Edition | Vol. 7, Issue 8.
Shea M, Ostermann L, Hohman R, et al. Regulatory Watch: Impact of breakthrough therapy designation on cancer drug development. Nat Rev Drug Discov. 2016 Mar 2;15(3):152.

suggest this approval process based on a review of early scientific evidence[34]. A breakthrough therapy designation is given for a specific indication only; in other words, a single drug can be approved under separate breakthrough therapy designations for a number of different indications. In a standard approval process, it takes around 8 years for a drug to be approved, starting from phase I clinical studies until the final drug approval by FDA. With a Breakthrough Therapy Designation, this process is reduced to around 5 years[35].

Fig. 7. Number of indications approved by FDA under the breakthrough therapy designation between 2013 and 2016 (data as of April 2016)[36,37,38].



2012

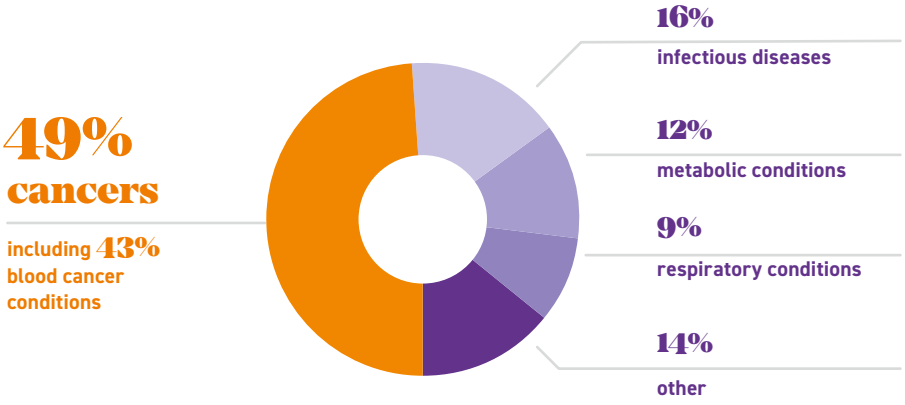
FDA approval pathway of a novel drug as a breakthrough therapy

Since then, altogether have been approved as breakthrough therapies

31 drugs and **2 vaccines**

in 43 indications

Fig. 8. Specific indications approved by FDA under the breakthrough therapy designation[36,37,38].



* The active substance of Venclyxto, venetoclax binds to a protein known as Bcl-2. This protein is abundant in the tumor cells of chronic lymphocytic leukemia, and contributes to prolong their survival in the body and makes them resistant to anticancer drugs. Venetoclax binds to the Bcl-2 protein and blocks its action, causing tumor cell death, and thereby slowing the progression of the disease.

Breakthrough therapies in CLL can be divided into two groups with three distinct mechanisms of action: anti-CD20 monoclonal antibodies (obinutuzumab and ofatumumab),B-cell receptor inhibitors (BCR) (ibrutinib and idelalisib) and inhibitors of Bcl-2 protein (venetoclax)*. Both antibodies are recommended as first-line treatment of CLL in patients eligible for intensive immunochemotherapy, whereas ofatumumab is also indicated in patients with CLL refractory to fludarabine and alemtuzumab.

A breakthrough therapy designation for chronic lymphocytic leukemia was first assigned to obinutuzumab, a drug authorized for use since 2013. In 2014, three more breakthrough therapies were approved for CLL: ibrutinib, idelalisib (small-molecule-targeted agents) and ofatumumab (Table 2). Ibrutinib became a breakthrough therapy in two indications referring to chronic lymphocytic leukemia and in one indication referring to another blood cancer – mantle cell lymphoma, MCL37. In June 2016, FDA recognized another breakthrough therapy for a chronic condition – graft-versus-host disease[39].

Table2. Breakthrough therapies approved by FDA for chronic lymphocytic leukemia.

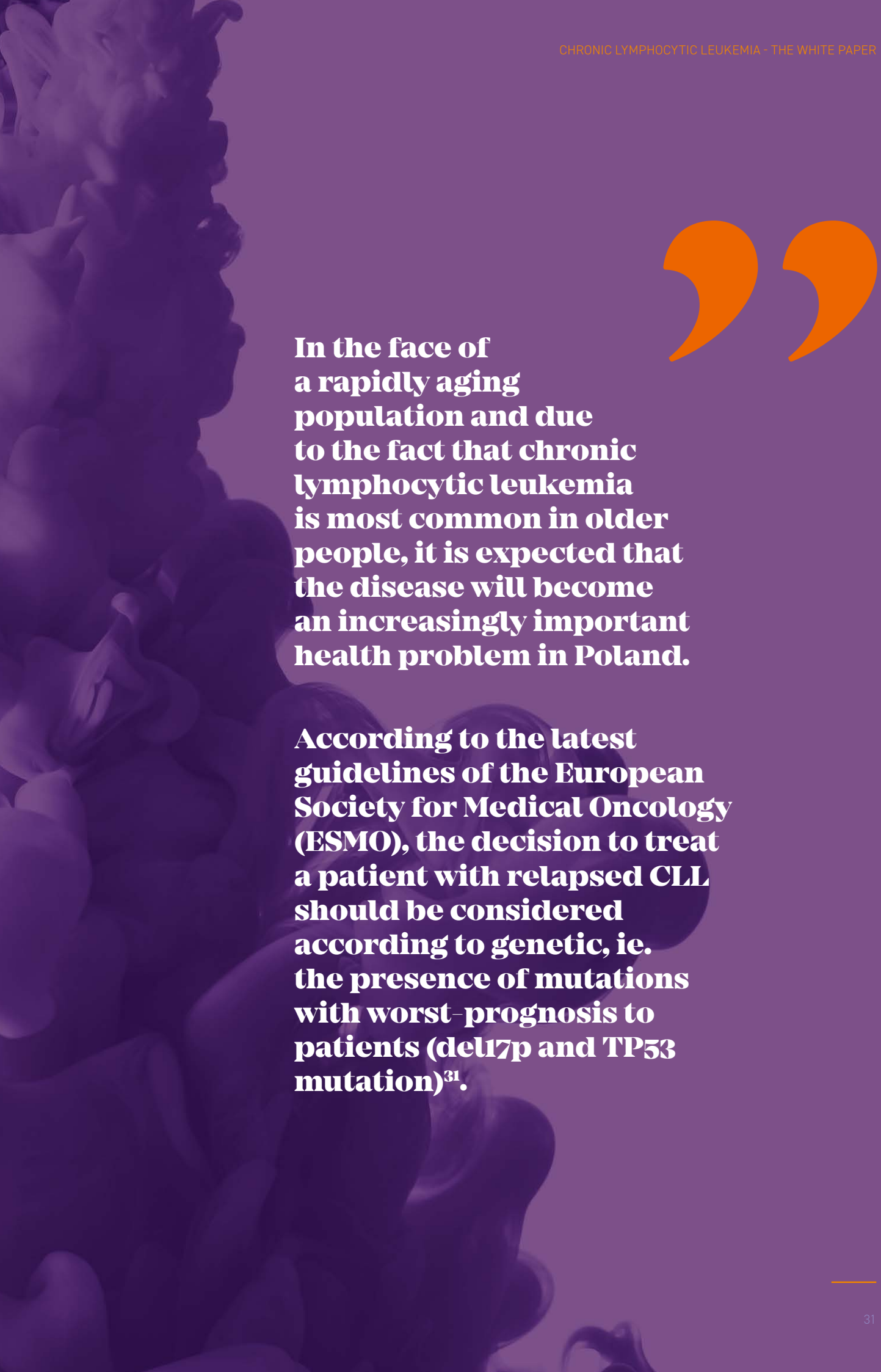
Medicinal product	Date of approval as a break-through therapy for CLL[37]	Marketing authorisation in the EU[40]
IBRUTINIB	13.11.2013 / 28.07.2014	21.10.2014
IDELALISIB	23.07.2014	18.09.2014
OBINUTUZUMAB	01.11.2013	23.07.2014
OFATUMUMAB	17.04.2014*	19.04.2010
VENETOCLAX	27.04.2015**	08.12.2016

* OFATUMUMAB was approved as a breakthrough therapy for **"the treatment of treatment-naive patients with CLL for whom fludarabine-based therapy was considered inappropriate"**. The drug was approved by FDA in 2009 for "patients with CLL refractory to fludarabine and alemtuzumab"; at that time, the breakthrough therapy designation was not yet introduced. Recently, based on the results of COMPLEMENT 2 study, FDA decided to expend ofatumumab indications to include relapsed and refractory CLL[41].

** breakthrough therapy status BY FDA in April 2015 - venetoclax in treatment of recurrent / refractory chronic lymphocytic leukemia in patients with del17p; January 2016 – venetoclax in combination with rituximab in the treatment of relapsed / refractory chronic lymphocytic leukemia. by: http://www.ac-cessdata.fda.gov/drugsatfda_docs/nda/2016/208573Orig1s000SumR.pdf

All novel therapies approved for CLL are targeted therapies as they are designed to modify specific cellular mechanisms that play a key role in a particular type of cancer. By blocking these mechanisms, the growth of tumor cells can be stopped[42,43]. Each FDA approved novel therapy for CLL has been introduced to standard clinical practice and included in the latest recommendations published

From 2013 there have been five innovative medicines registered for CLL patients with the worst prognosis. These are the next "milestones" in the treatment of this disease, opening stage therapies aimed at specific molecular targets so called targeted therapy.

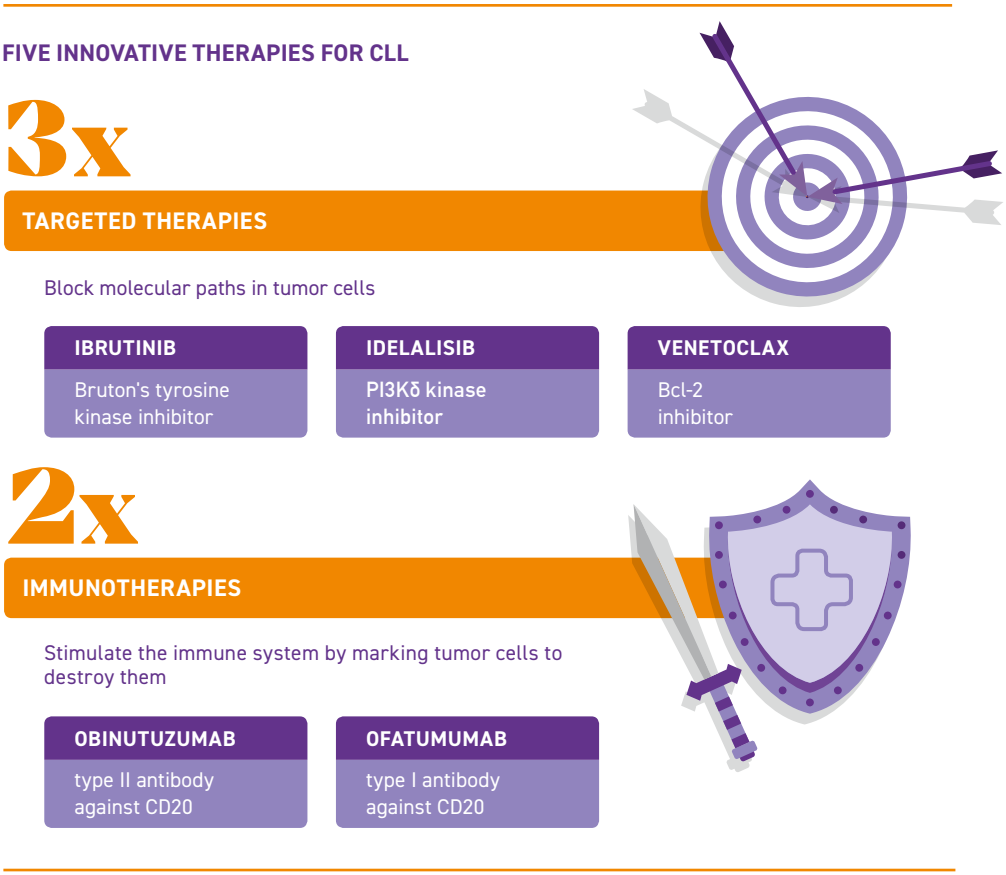


In the face of a rapidly aging population and due to the fact that chronic lymphocytic leukemia is most common in older people, it is expected that the disease will become an increasingly important health problem in Poland.

According to the latest guidelines of the European Society for Medical Oncology (ESMO), the decision to treat a patient with relapsed CLL should be considered according to genetic, ie. the presence of mutations with worst-prognosis to patients (del17p and TP53 mutation)[31].

by Polish, European, and American medical associations (Table 3, Table 4, Table 5, Table 6)[31,54].

Each breakthrough therapy has a different mechanism of action and is targeted at a slightly different population of CLL patients. In the first-line of CLL treatment, ibrutynib alone can be used without restrictions due to



Source: Opracowanie własne na podstawie: Robak T. Przewlekła białaczka limfocytowa wysokiego ryzyka. Acta Haematologica Polonica 2015;46:68-74. / Hill BT, Kalaycio M. Profile of obinutuzumab for the treatment of patients with previously untreated chronic lymphocytic leukemia. Onco Targets Ther 2015;8:2391-7. / Charakterystyka Produktu Leczniczego. Venclyxto®.

the presence of 17p deletion / mutation of p53 (as opposed to venetoclax and idelalisib)[45,121,46] or contraindication to immunochemotherapy (as opposed to ofatumumab and obinutuzumab)[47,48].

In the second and subsequent lines of CLL therapy, idelalisib must be used in combination with monoclonal antibody: anti-CD2046, ofatumumab - in combination with fludarabine and cyclophosphamide

or in patients refractory to fludarabine, and alemtuzumab - in monotherapy[48], obinutuzumab has no indication registered[47], venetoclax must be used after signaling pathway inhibitor of B-cell receptor (patients with no deletion in the region 17p and TP53 mutation – and after immunochemotherapy)[121]. Ibrutinib can be used in monotherapy regardless of the presence of del17p / TP53 mutation or in earlier application of fludarabine (although it can also be administered in combination with bendamustine and rituximab)[4545].

Obinutuzumab and ofatumumab are both monoclonal antibodies that identify CD20 antigen on the surface of cancerous B cells[49,52]. Anti-CD20 antibodies act by adhering to the surface of cancerous cells to induce immune response. As a result, cancer cells are eliminated from the body[52]. Ibrutinib and idelalisib inhibit proteins involved in B cell receptor (BCR) signaling pathway, which plays a key role in the pathogenesis of chronic lymphocytic leukemia[50].

The novel therapies are highly selective, the systemic toxicity is typically moderate and the treatment does not induce bone marrow suppression (myelosuppression). The drugs previously used in CLL are likely to be now combined with innovative therapies to produce long-term control of the disease and to help patients maintain the best possible quality of life[51]. Novel targeted therapies can translate into a more optimized management of chronic lymphocytic leukemia, both in terms of first-line treatment and in the treatment of relapsing CLL[52].

Breakthrough therapies are now included in diagnostic and therapeutic recommendations of the Polish Society of Haematologists and Transfusiologists (PTHiT) and the Polish Leukemia Group (PALG) of 2016 concerning new therapies used in progressive or symptomatic chronic lymphocytic leukemia (refer to Table 3 and Table 4.)[44].

Table3. Clinical Practice Recommendations by the Polish Society of Haematologists and Transfusiologists (PTHiT) and the Polish Leukemia Group (PALG) of 2016 for new therapies used in progressive or symptomatic CLL[44].

Therapies	Progressive or symptomatic CLL – first-line treatment				
	Absence of 17p deletion/TP53 mutation			17p deletion/TP53 mutation	
	younger patients, no comorbidities	elderly patients‡ no comorbidities and/or history of infections	elderly‡ and younger patients with comorbidities	younger patients, no comorbidities	elderly‡ patients with comorbidities
IBRUTINIB†				●	●
IDELALISIB				●*	●*
OBINUTUZUMAB or OFATUMUMAB**	●	●			●

‡ > 65 years; † as of the date of the latest guidelines, ibrutinib has not been authorized for use in first-line treatment in patients w/o del17p/TP53 mutations; * used in combination with rituximab if no other therapeutic options are available; recommendations on reduced infection risk according to EMA CHMP of 22.07.2016 should be followed; ** used in combination with chlorambucil

Table4. Clinical Practice Recommendations by the Polish Society of Haematologists and Transfusiologists (PTHiT) and the Polish Leukemia Group (PALG) of 2016 for new therapies used in relapsed refractory CLL (based on Fig. 2, page 180)[44].

Therapies	Relapsed or refractory CLL				
	relapse after 24 months from starting first-line treatment			relapse after 24 months from starting first-line treatment or lack of response	
	W/o 17p deletion/TP53 mutation		17p deletion/TP53 mutation	W/o 17p deletion/TP53 mutation	17p deletion/TP53 mutation
	younger patients, no comorbidities	elderly patients‡ with comorbidities			
IBRUTINIB			●	●	●
IDELALISIB			●		●

† as of the date of the 2015 guidelines, ibrutinib has not been authorized for use in first-line treatment in patients w/o del17p/TP53 mutations; while ofatumumab has not been approved for use in relapsed refractory CLL.

Table5. ESMO 2015 Clinical Practice Guidelines for novel therapies used in chronic lymphocytic leukemia[31] (including the updated 2016 version[53]).

Therapies	First-line treatment		Relapsed or refractory CLL		
	comorbidities, w/o 17p deletion/ *TP53* mutation	17p deletion/ *TP53* mutation	relapse within 24-36 months or resistance to therapy	relapse after at least 24-36 months	
				w/o 17p deletion/ *TP53* mutation	17p deletion/ *TP53* mutation
IBRUTINIB†	●	●	●	●	●
IDELALISIB*		●**	●	●	●
OBINUTUZUMAB***	●				
OFATUMUMAB***	●			●	

* used in combination with rituximab;

** because of high risk of infections, idelalisib in combination with rituximab is recommended only in patients who are unsuitable to receive Bruton's tyrosine kinase inhibitors (ibrutinib); anti-infectious prophylaxis is necessary;

*** used in combination with chlorambucil

Therapies	w/o 11q or 17p deletion/TP53 mutation					17p deletion/TP53 mutation		
	purine analogs contraindicated	First-line treatment age > 65 years or major comorbidities	First-line treat--ment, age < 65 years, no major comorbidities	relapsed / refractory CLL	maintenance treatment	First-line treat-ment	relapsed / refractory CLL	maintenance treatment
IBRUTINIB	●	●	●	●		●	●	
IDELALISIB + RITUXIMAB				●			●	
IDELALISIB*				●			●	
OBINUTUZUMAB + CHLORAMBUCIL	●	●				●		
OBINUTUZUMAB	●	●		●				
OFATUMUMAB + CHLORAMBUCIL	●	●						
OFATUMUMAB				●	●		●	●
RITUXIMAB + CHLORAMBUCIL	●	●						
RITUXIMAB	●	●		●				
CHLORAMBUCIL	●	●						
BENDAMUSTINE + RITUXIMAB		●						
CHEMOIMMUNOTHRAPY (FCR, FR, BR)			●	●				
VENETOCLAX				●			●	
LENALIDOMIDE + RITUXIMAB							●	
ALEMTUZUMAB + RITUXIMAB						●	●	
HDMP + RITUXIMAB				●		●	●	

* IDELALISIB can be used as first-line treatment if no other therapeutic options are available; infection prophylaxis is obligatory.

Table 6. American Clinical Practice Guidelines by the National Comprehensive Cancer Network (NCCN) as of September 2016 for chronic lymphocytic leukemia[54].

Anti-CD20 monoclonal antibodies

CD20 antigen is a transmembrane phosphoprotein expressed on the surface of B cells, both pre-B cells and mature B lymphocytes, and on the surface of malignant B cells. B-cell malignancies include chronic lymphocytic leukemia (low CD20 expression) and non-Hodgkin lymphomas (high CD20 expression). Once it binds to an antibody, CD20 antigen is no longer released from the surface of a cell nor does it move to the inside of a cell[48].

In 2009, the first anti-CD20 monoclonal antibody was approved for use in patients with CLL (rituximab), and was proved to extend survival among CLL patients[55].

Obinutuzumab – a glycoengineered humanized type II anti-CD20 monoclonal antibody – was approved four years later. It was engineered to produce significantly enhanced anti-body-dependent cellular cytotoxicity (ADCC) and to more effectively trigger direct cell death, as compared to rituximab[44,47].

Ofatumumab, second-generation type I human monoclonal antibody, was also approved by EMA as a first-line treatment of CLL. Ofatumumab binds to both large and small CD20 extracellular loops and is more potent than rituximab, inducing higher complement-dependent cytotoxic CDC)[44,48].

BCR pathway inhibitors in the treatment of CLL

B-cell receptor (BCR) signaling pathway plays a key role in the pathogenesis of chronic lymphocytic leukemia. BCR pathway in healthy B cells is involved in transmitting signals inside cells from the level of cellular membrane through a number of components, thereby activating or attenuating other cellular pathways. In healthy cells, BCR pathway is responsible for correct immune response, growth, survival, and migration of B cells[55]. In malignant B cells, BCR signaling pathway is compromised and characterized by a modified response of B cell receptor to antigen stimulation as well as tonic activation of signaling pathways to prevent cell apoptosis[56].

BCR signaling pathway is specific to B cells, and its role in CLL pathogenesis is increasingly well understood. In other words, the individual components of the BCR signaling pathway has become promising targets of therapies used in chronic lymphocytic leukemia[50,56]. For example, CLL therapy can be targeted at Bruton's tyrosine kinase (BTK), which plays an important role in regulating BCR pathway-mediated adhesion of malignant cells and their accumulation in lymph nodes – a microenvironment favourable for their growth and survival[50].

Therapy should be preferably administered in an out-patient setting. Hospitalizations are very depressing. Having to spend a weak at a hospital every month is really scary. I am very happy I can take this treatment at home and function normally[61].

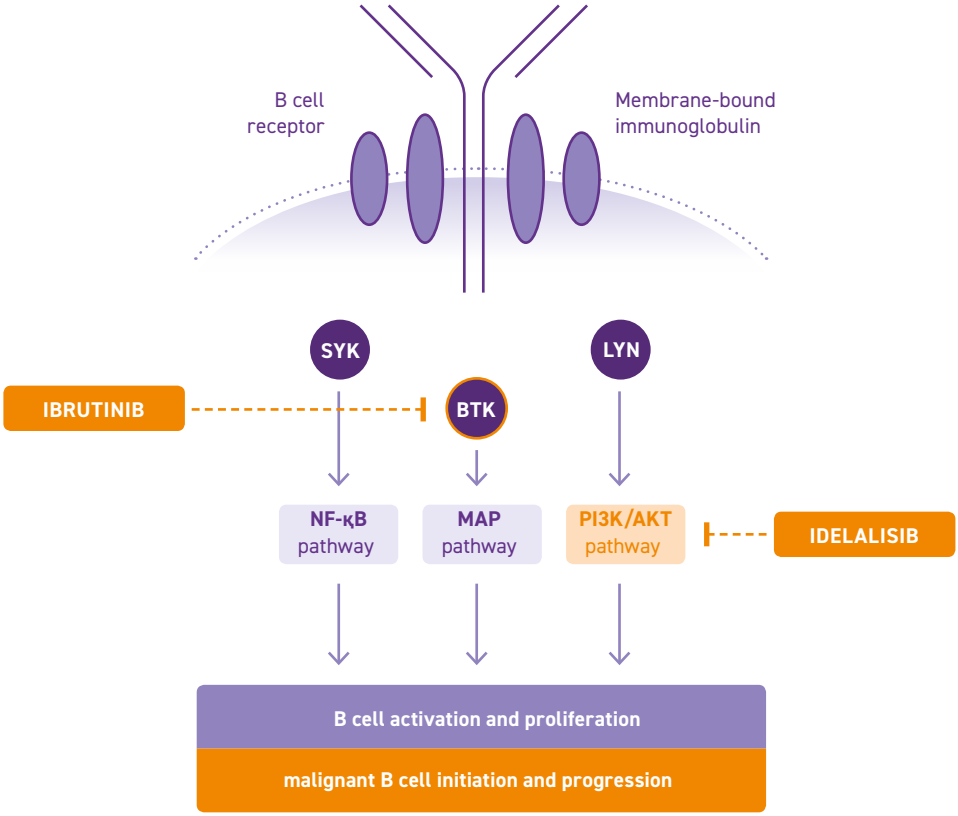
a patient receiving a breakthrough therapy
Lublin, Poland

This is a very comfortable solution. I only need to take 3 pills each day at about the same time. I make an appointment with my doctor when I run out of the pills, I do the medical tests, I get the prescription and collect the drug at the hospital's pharmacy [61].

a patient receiving a breakthrough therapy
Lublin, Poland

LYN, SYK	threonine kinases
BTK	Bruton's tyrosine kinase
NF-κB	transcription nuclear factor
MAPK	mitogen-activated protein kinase
PI3K/AKT	phosphoinositide 3-kinase / serine-threonine kinase

SIMPLIFIED DIAGRAM OF B CELL RECEPTOR SIGNALING PATHWAY

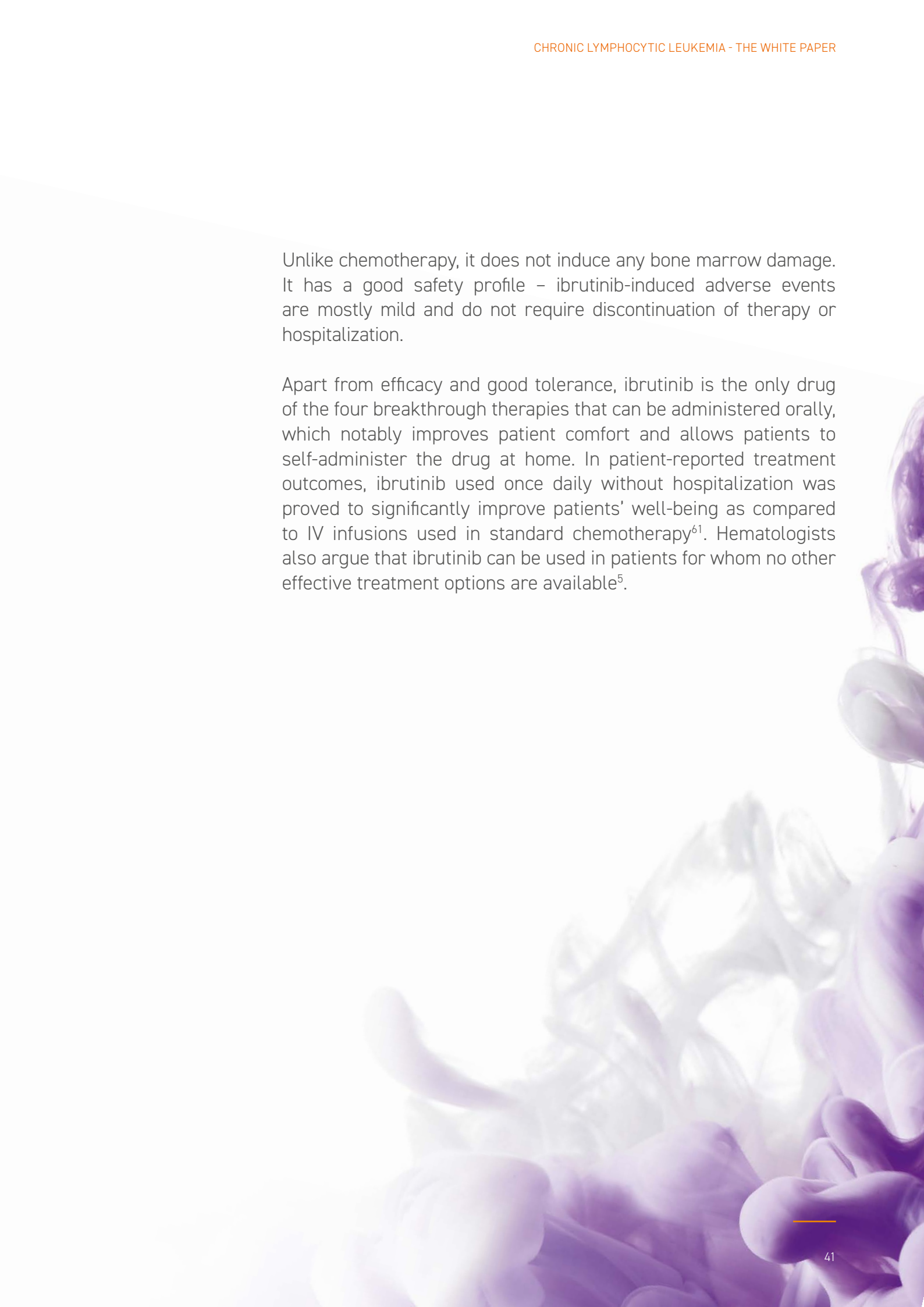


Source: Chung C, Lee R. Ibrutinib, obinutuzumab, idelalisib, and beyond: review of novel and evolving therapies for chronic lymphocytic leukemia. Pharmacotherapy. 2014 Dec;34(12):1298-316.

Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (BTK) that induces cell apoptosis and inhibits cell division[57]. Clinical studies have confirmed the efficacy and good tolerance of ibrutinib in patients with relapsed or refractory CLL[58]. As compared to ofatumumab, ibrutinib produced statistically significant improvement in patients' overall survival, and reduced the risk of death by 57%[59]. It is highly specific and only inhibits BTK kinase in B cells, thereby demonstrating lower toxicity as compared to standard chemotherapy[60].

Unlike chemotherapy, it does not induce any bone marrow damage. It has a good safety profile – ibrutinib-induced adverse events are mostly mild and do not require discontinuation of therapy or hospitalization.

Apart from efficacy and good tolerance, ibrutinib is the only drug of the four breakthrough therapies that can be administered orally, which notably improves patient comfort and allows patients to self-administer the drug at home. In patient-reported treatment outcomes, ibrutinib used once daily without hospitalization was proved to significantly improve patients' well-being as compared to IV infusions used in standard chemotherapy[61]. Hematologists also argue that ibrutinib can be used in patients for whom no other effective treatment options are available[5].



Treatment of chronic lymphocytic leukemia

from the Polish perspective

3

The past and present of CLL treatment in Poland

In Poland, the treatment of chronic lymphocytic leukemia (standard chemotherapy agents and rituximab-based immunotherapy) is currently delivered within the limits of guaranteed healthcare services[62]. In addition, specific patient populations are eligible for treatment under the so-called Drug Programs launched by the Ministry of Health at the request of drug manufacturers. Treatment delivered under a Drug Program involves the use of innovative and expensive medications that do not qualify for reimbursement within the framework of other healthcare services (Table 7). Drug Programs are only available for specific conditions and cover a strictly defined group of patients. To be qualified for treatment under a Drug Program, patients must meet predetermined in-clusion criteria[63]. There are currently 23 Drug Programs for cancer, including 7 Drug Programs dedicated to patients with blood cancers (Table 7). There is only one Drug Program for patients with CLL: obinutuzumab in treatment-naive patients not suitable for full-dose fludarabine-based regimen (due to comorbidities)[62]. Treatment is delivered free of charge, both chemotherapy and the Drug Programs. No other therapies approved for CLL are eligible for reimbursement, unless they are listed as chemotherapy or available under a Drug Program. These drugs are only accessible to patients in clinical trials or to those who can afford to buy them.

Guaranteed healthcare services available for CLL patients include allogeneic hematopoietic stem cell transplantation (allo-HSCT). In practical terms, allo-HSCT is only rarely used because of high risk of serious complications and death. According to NFZ data, altogether 22 allo-HSCT procedures were performed between 2009 and 2015, mainly in patients with chronic lymphocytic leukemia (around 3 procedures annually)[64].

Table 7. Drug Programs in Blood Cancers (as of 14.07.2016)[62].

Drug Program (Annex no. to the Decree of the Minister of Health)	Drug used in the Program
Treatment of malignant lymphomas (B.12).	RITUXIMAB
Treatment of chronic myelogenous leukemia (B.14).	DASATINIB, NILOTINIB
Lenalidomid in the treatment of refractory or re-lapsed multiple myeloma (B.54).	LENALIDOMID IN COMBINATION WITH DEXAMETHASONE
Dasatinib in Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (B.65).	DASATINIB
Bexarotene in the treatment of mycosis fungoides or Sézary disease (B.66).	BEXAROTENE
Treatment of refractory or relapsed CD30+ lymphomas (B.77).	BRENTUXIMAB VEDOTIN
Obinutuzumab in the treatment of chronic lymphocytic leukemia (B.79).	OBINUTUZUMAB

Access to innovative therapy of chronic lymphocytic leukemia

With the introduction of a Drug Program dedicated exclusively to a narrow population of CLL patients and following the elimination of non-standard chemotherapy program in 2015, the majority of breakthrough therapies are regrettably not available to patients[62,65,66]. Innovative therapies in any indication are typically expensive owing to a long-term and costly research and development phase before the drug is invented, studied for efficacy and authorized for marketing. In fact, innovative drugs are so expensive they are hardly affordable for patients and access to these drugs is highly restricted, unless a systemic funding is introduced[67]. The lack of access to innovative therapies for CLL, as recommended by the European Society for Medical Oncology, further constrains the already limited treatment options that meet the current European standards.

So far, the Agency for Health Technology Assessment and Tariff System AOTMiT has reviewed 3 innovative therapies for CLL: ibrutinib, obinutuzumab, and ofatumumab (Table 8). None of these drugs has received a positive recommendation decision for public reimbursement. AOTMiT explained that the main reason behind a negative recommendation for innovative therapies is that they exceeded the incremental cost-effectiveness ratio, as well as insufficient evidence and quality of clinical trials[68,69,70]. Foreign HTA agencies apparently apply less restrictive criteria and have issued positive or conditionally positive recommendations based on the same body of scientific evidence Table 8). This may be due to higher cost-effectiveness ratio for drugs adopted in individual countries and better recognition of the medical needs of patients with chronic lymphocytic leukemia. Despite the negative recommendations by AOTMiT for novel therapies in CLL, the Minister of Health set up the first Drug Program for CLL therapy, starting from 1 July 2016[62]. It

should be noted this Drug Program only includes obinutuzumab and is intended for a very specific population of patients (treatment-naive patients who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them) and do not take full advantage of the therapeutic potential of breakthrough therapies in CLL.

Budget constraints are the main factor limiting access to innovative treatment for patients suffering from chronic lymphocytic leukemia in Poland. Innovative therapies typically exceed the established break-even point for drug reimbursement, set at three times the GDP per 1 Quality Adjusted Life Year. In other words, despite the well-proven effectiveness of an innovative breakthrough therapy for the given condition, its reimbursement is not a matter of fact. One way to optimize the price of cancer drugs and facilitate favorable reimbursement-related decision-making is to establish separate HTA assessment algorithms for this category of medicines. This is the case in the UK (Cancer Drugs Fund), while European and American clinical oncology associations (ESMO and ASCO) work to set up similar mechanisms. An algorithm developed by the Polish Society of Clinical Oncology and the Polish Oncology Association (PTOK/PTO) allows an assessment of added value of a drug against the currently reimbursed standard of case in a particular condition. The algorithm takes account of prolonged survival, increase quality of life of patients, drug safety profile, cost effectiveness of therapy, and the quality of scientific evidence. A drug is assigned to one of five categories denoting the extent to which reimbursement is justified[67].

HTA Agency	Recommendations for public drug reimbursement				
				OFATUMUMAB	
	IBRUTINIB	IDELALISIB	OBINUTUZUMAB	treatment-naive patients with CLL who are not eligible for fludarabin-based therapy or bendamustine	patients with CLL refractory to fludarabine and alemtuzumab
AOTMiT (Poland)[68,69,70]	**Negative**	*Not evaluated*	**Negative**	Recommendation for the drug to be **removed from the list of guaranteed healthcare services** delivered within a non-standard chemotherapy program.	*Not evaluated*
HAS (France)[71,72,73,74,75]	**Positive** decision to add the drug to a **list of therapies eligible for reimbursement covered by social insurance** (fr. *assurés sociaux*) and a **list of therapies approved for use in in-patient settings in the prescribed indication**.	**Positive** decision to add the drug to a **list of therapies eligible for reimbursement covered by social insurance** (fr. *assurés sociaux*) and a **list of therapies approved for use in in-patient settings in the prescribed indication**.	**Positive** decision to add the drug to a **list of therapies approved for use in in-patient settings in the prescribed indication.**	**Positive** decision to add the drug to a **list of therapies approved for use in in-patient settings in the prescribed indication.**	**Positive** decision to add the drug to a **list of therapies approved for use in in-patient settings in the prescribed indication.**
NICE (UK)[76,77,78,79,80]	*Final recommendation in development.*	**Conditionally positive***	**Conditionally positive***	**Conditionally positive***	**Negative**
SMC (Scotland)[81,82,83,84,85]	*Recommendation in development.*	**Conditionally positive****	**Positive**	**Conditionally positive****	**Negative**
IQWIG. G-BA (Germany)[86,87,88,98,90]	**No additional benefit** according to IQWIG	**No additional benefit** according to IQWIG **Additional, unquantifiable benefit** according to IQWIG	Drug **eligible for reimbursement**.^	Not evaluated	*Not evaluated*
CADTH pCODR (Canada)[91,92,93,94]	**Conditionally positive†**	**Conditionally positive†**	**Positive**	**Negative**	*Not evaluated*
PBAC (Australia)[95,96,97,98]	**Decision postponed††**	**Decision postponed††**	**Positive under special conditions‡**	**Positive under special conditions‡**	*Not evaluated*

Table 8. Summary of recommendations for reimbursement of innovative therapies used in chronic lymphatic leukemia by Polish and foreign HTA agencies.

* This decision is subject to the condition that the company supplies the drug at a discount price, as previously agreed.

** This decision is subject to the condition that the therapy is continuously available under PAS (Patient Access Scheme) or through a list of reimbursed therapies, at the same or a lower price.

^ According to national legislation governing orphan drugs in Germany, obinutuzumab is found to offer a therapeutic benefit because it was approved for use in this indication.

† This decision is subject to the condition that the cost-effectiveness ratio is improved to an acceptable level.

†† This application should be postposed to make room for price negotiations to reduce ICER to a more reasonable level.

‡ The drug should be available within the framework of Section 100 (Items Available under Special Arrangement). Use of the drug on prior consent in writing will be acceptable in order to prevent its use outside the populations in which it was proved to be effective and cost-effective.

Table 9. Ibrutinib reimbursement in Europe[18,99].

GENERAL REIMBURSEMENT

AUSTRIA	DENMARK	THE NETHERLANDS	GERMANY	SWITZERLAND*
BELGIUM*	FRANCE*	IRELAND	NORWAY	SWEDEN
BULGARIA (CEE)*	GREECE	LIECHTENSTEIN	ROMANIA(CEE)	THE UK*
CROATIA(CEE)*	SPAIN*	LUXEMBURG	SLOVENIA (CEE)*	ITALY

INDIVIDUAL REIMBURSEMENT

CZECH REP. (CEE)	LITHUANIA(CEE)	
ESTONIA(CEE)	LATVIA(CEE)	SLOVAKIA (CEE)
FINLAND	PORTUGAL	HUNGARY (CEE)

NOT REIMBURSED

POLAND (CEE)

Negative reimbursement recommendation by the Agency for Health Technology Assessment and Tariff System AOTMiT

NO REIMBURSEMENT REQUEST FILED

SERBIA (CEE)

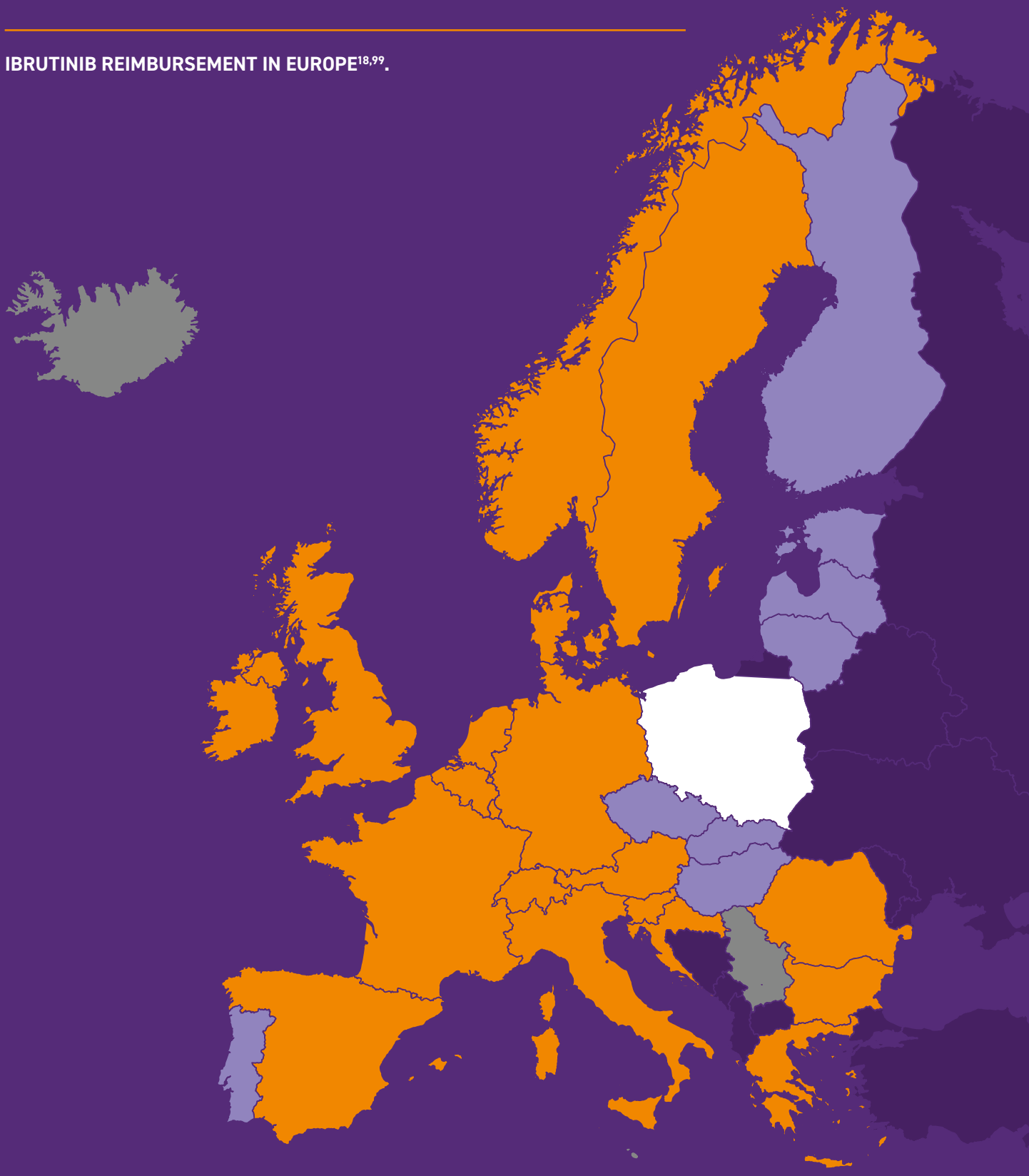
NO DATA

CYPRUS
ISLAND
MALTA

* Country	* Ibrutinib reimbursement terms
BELGIUM	- patients with a positive 17p deletion/TP53 mutation status (all lines of treatment) - patients not eligible for purine analog-based therapy in second-line treatment after chemoimmunotherapy and in third-line treatment after chemotherapy
BULGARIA	- patients with a 17p deletion (all lines of treatment)
CROATIA	- patients with a 17p deletion (first-line of treatment) - early relapse and/or refractory CLL
FRANCE	Under an Early Access Program
SPAIN	Relapsed or refractory CLL
SLOVENIA	high-risk patients (del17p/TP53 or del 11q or relapse within less than 24 months) who are not eligible for chemoimmunotherapy, who failed to respond to ofatumumab, or are candidates to allogeneic stem cell transplant
SWITZERLAND	- first-line treatment of CLL in patients with 17p deletion/TP53 mutation - second-line treatment of CLL in patient who relapsed within 36 months or patients who are not eligible for immunochemotherapy
THE UK	Product reimbursed from the dedicated Cancer Drug Fund
OTHER COUNTRIES	Drug used according to label instructions (SmPC).

Source: Data provided by: Janssen-Cilag Polska Sp. z o.o.

IBRUTINIB REIMBURSEMENT IN EUROPE[18,99].



Assumptions*	Findings	Ibrutinib vs. bendamustine + rituximab[100]	Ibrutinib vs. ofatumumab[59]	Idelalisib+ rituximab vs. rituximab +placebo[100,102]	Obinutuzumab + chlorambucil vs. rituximab + chlorambucil[103,104]	Obinutuzumab + chlorambucil vs. chlorambucil[103,104]	Ofatumuma + chlorambucil vs. chlorambucil[105,106] INDICATION: Treatment--naive patients with CLL not eligible for fludara-bine and bentamustine regimens	Ofatumumab (phase II uncontrolled study)[107,108] INDICATION: CLL re-fractory to fludarabine and alemtuzumab
cost-effectiveness for idelalisib, obinutuzumab, ofatumumab = 0 score	Category (score)	A (10 pts)	A (16 pts)	A (18 pts)	B (7.5 pts)	A (15.5 pts)	B (7.5 pts)	E (2 pts)
	Added value	Very high added value	Very high added value	Very high added value	High added value	Very high added value	High added value	Negligible added value
	Recommendations	**The drug should be reimbursed**	**The drug should be reimbursed**	**The drug should be reimbursed**	**Reimbursement hi-ghly recommended**	**The drug should be reimbursed**	**Reimbursement highly recommended**	**The drug should not be reimbursed**
cost-effectiveness for idelalisib, obinutuzumab, ofatumumab = -2 points	Category (score)	A (10 pts)	A (16 pts)	A (16 pts)	C (5.5 pts)	A (13.5 pts)	C (5.5 pts)	E (0 pts)
	Added value	Very high added value	Very high added value	Very high added value	Moderate added value	Very high added value	Moderate added value	Negligible added value
	Recommendations	**The drug should be reimbursed**	**The drug should be reimbursed**	**The drug should be reimbursed**	**Risk-sharing mechanism is recommended**	**The drug should be reimbursed**	**Risk-sharing mechanism is recommended**	**The drug should be reimbursed**

* Cost-effectiveness score: – 2 to +2 points. Because of the lack of cost-effectiveness data on idelalisib, obinutuzumab, and ofatumumab, this analysis included two different cost-effec-tiveness variants: each drug was assigned a neutral number of points (0 points) or the lowest possible number of points (–2), which corresponds to the cost-effectiveness of < PLN 170,000 – PLN 220,000 and > PLN 270,000, respectively.

Table 10. Summary of assessment results of breakthrough therapies for use in CLL, based on PTOK/ PTO algorithm [own estimations based on published clinical studies].

PTOK/PTO algorithm categories	Score	Added value	Reimbursement recommendations
Category A	> 9 pts	Very high added value	The drug should be reimbursed
Category B	7-8 pts	High added value	Reimbursement highly recommended
Category C	5-6 pts	Moderate added value	Risk-sharing mechanism is recommended; the manufacturer refunds treatment if it fails to produce therapeutic benefits
Category D	3-4 pts	Low added value	Reimbursement will only be possible if a risk-sharing mechanism is agreed with the manufacturer in order to safeguard cost-effectiveness against the established cost-effectiveness threshold.
Category E	0–2 pts	Negligible added value	The drug should not be reimbursed

In this report, an added value of breakthrough therapies used in CLL was evaluated using the algorithm developed by PTOK/PTO; the results of clinical studies in the registration dossiers of particular medicinal products were used as input data. Due to the lack of data on the cost effectiveness of idelalisib, ofatumumab, and obinutuzumab, the assessment was carried out for two cost-effectiveness variants, with 0 points (neutral value) or –2 points (the most unfavourable value) assigned to these drugs (Table 10). The results of this assessment based on PTOK/PTO algorithm clearly demonstrate that breakthrough therapies in CLL offer moderate to high added value and, in the majority of cases, it is perfectly justified to have them reimbursed. Depending on the adopted variant, the assessed drugs are assigned to category A (should be reimbursed) or B (reimbursement highly recommended) if their cost effectiveness equals 0, or to category A to C (risk-sharing mechanism recommended) for those with –2 points for the cost-effectiveness criterion. Irrespective of the cost-effectiveness variant, ofatumumab is assigned category E in "CLL refractory to fludarabine and alemtuzumab" – this is the indication approved based on an non-controlled study.

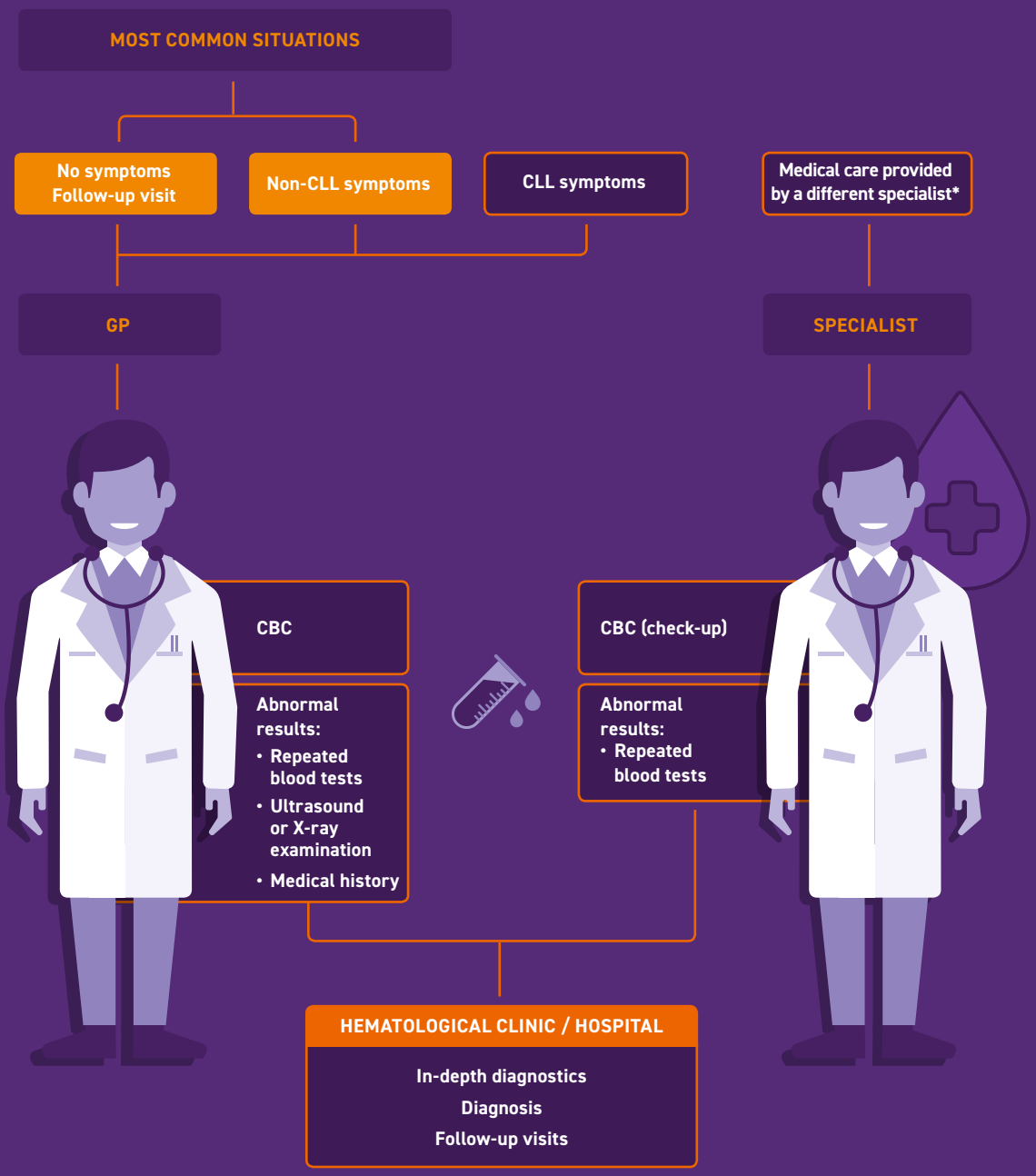
Diagnostic and therapeutic path for patients with CLL

Despite the systemic instruments established for the management of cancer patients, such as the "oncological fast-track system", we are now missing solutions specifically addressing medical care for patients with blood cancers.

Since January 1st 2015, patients can receive therapy for cancer under an "oncological fast-track system". The main assumption behind this healthcare package geared towards cancer patients is to fast-track diagnosis in order to be able to start treatment as soon as possible in patients diagnosed with cancer. Healthcare providers are bound to follow a strict timeline for cancer diagnostics. The time between the date on which a patient is enlisted on a waiting list to visit a specialist and the diagnosis should not be longer than 9 weeks[109].

A real-world picture of a CLL patient's pathway in Poland's healthcare system was produced from a qualitative study featuring in-depth interviews of both, patients suffering from CLL and HCPs: Gps, hematologists, and hematologist nurses[5,61]. The study revealed that patients with CLL are mostly diagnosed by chance, based on abnormalities in the results of blood tests. Primary care physicians and other medical specialists then refer patients to an hematology outpatient clinic or a hospital. The final diagnosis is made by a hematologist, based on additional tests. Individuals with confirmed CLL are managed by a hematologist for therapy and routine tests. In the majority of cases, primary care is separated from hematological care and is primarily focused on the general health, monitoring blood parameters, and the treatment of infections[5,61].

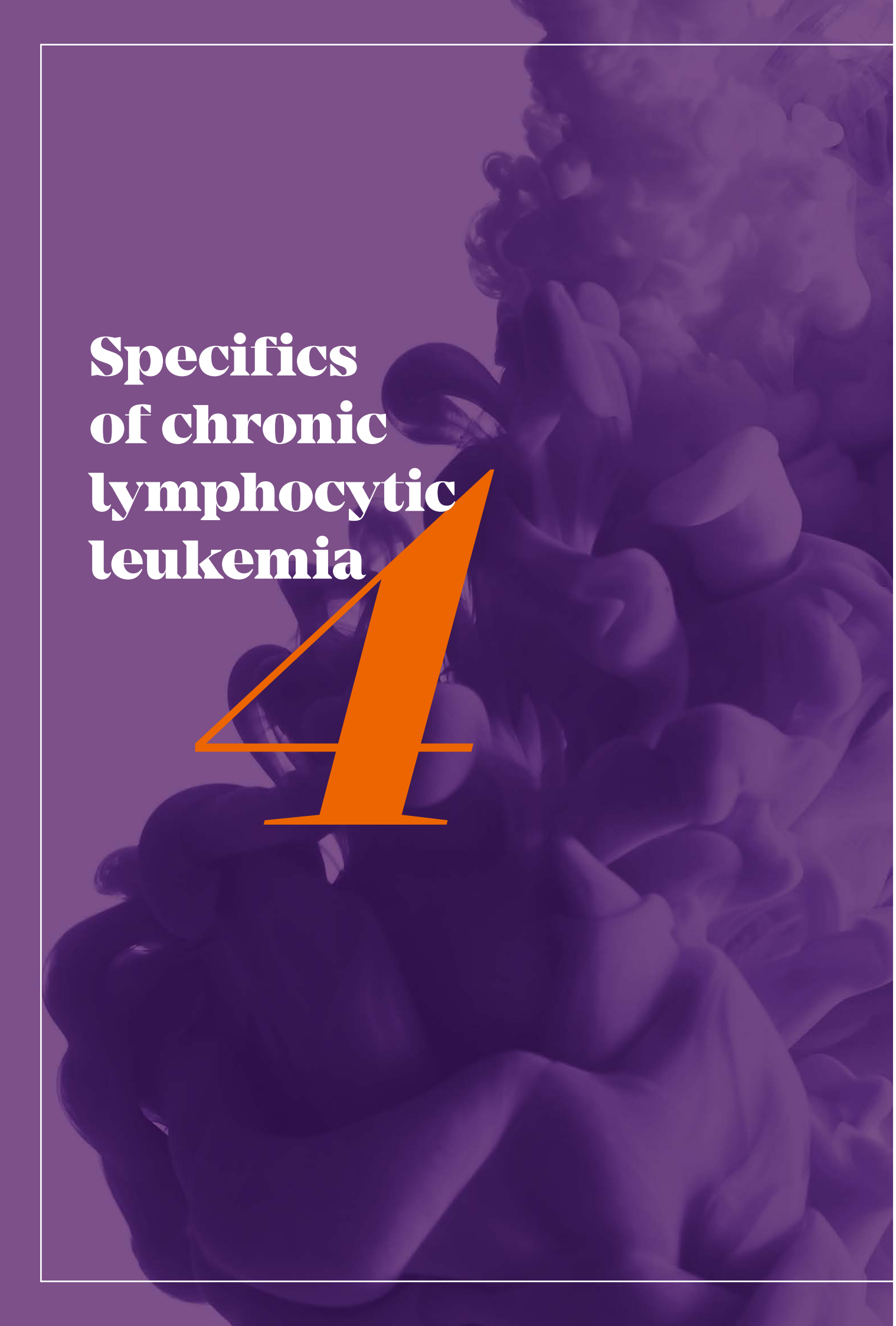
DIAGNOSTIC-THERAPEUTIC PATHWAY OF A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA



Source: Sequence. Diagnostyka, terapia i codzienność pacjentów z CLL. Pacjenci chorujący na CLL. Raport z badania jakościowego przeprowadzonego dla firmy Janssen. Luty 2016.

* patient under specialist care due to comorbidities

Specifics of chronic lymphocytic leukemia



Chronic lymphocytic leukemia is a heterogenous condition both in terms of the clinical picture and genetic basis, and needs a specific individual physician-to-patient approach.

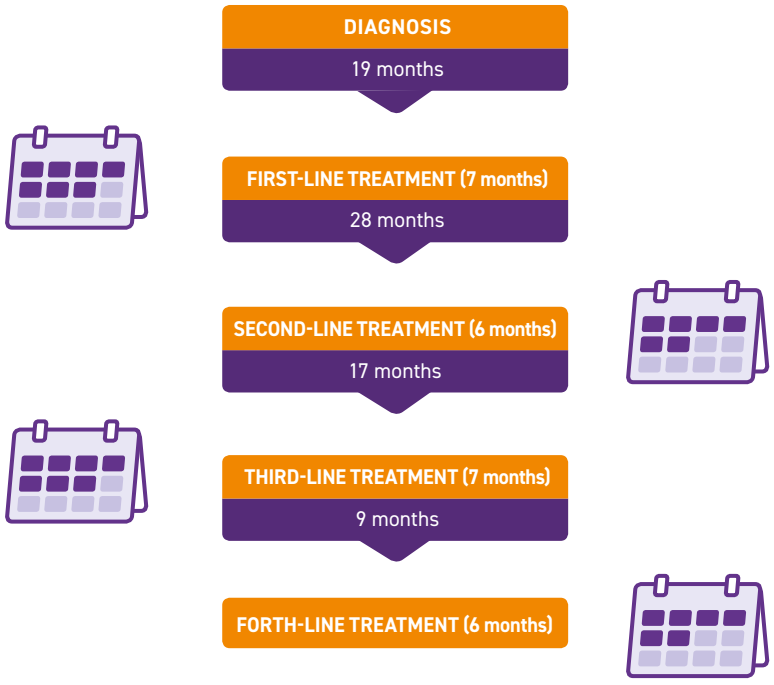
Patients with chronic lymphocytic leukemia are mostly retired or working part time. Only a small fraction of patients is fully professionally active – these are mostly younger patients, around 50 years old or younger. The majority of patients are self-dependent and enjoy a good general condition. Chronic lymphocytic leukemia is predominantly a long-term medical condition. As a result, patients become integrated with healthcare professionals and build a long-lasting relationship with the attending physician[5].

On the contrary to the majority of neoplastic diseases in which successful therapeutic outcomes or recovery largely depends on urgent initiation of therapy, many people with chronic lymphocytic leukemia in initial stages may not need treatment right away, unless the condition develops into an active form of CLL. The clinical stage of CLL is the main criterion based on which decision is taken on whether to initiate treatment[110]. From the patient's perspective, this situation is difficult to accept and highly problematic, but the negative feelings can be alleviated by good physician-patient communication and clear explanation of the condition to the affected patient[5,61].

Although CLL is rarely aggressive, it can be a very heavy burden to bear by patients. This is largely because of the accompanying symptoms (weight loss, tiredness, frequent infections, hospitalizations for infections), the time spent at healthcare facilities during medical checks and IV infusions[5]. Patients are faced with mental stress, being aware of having an incurable disease

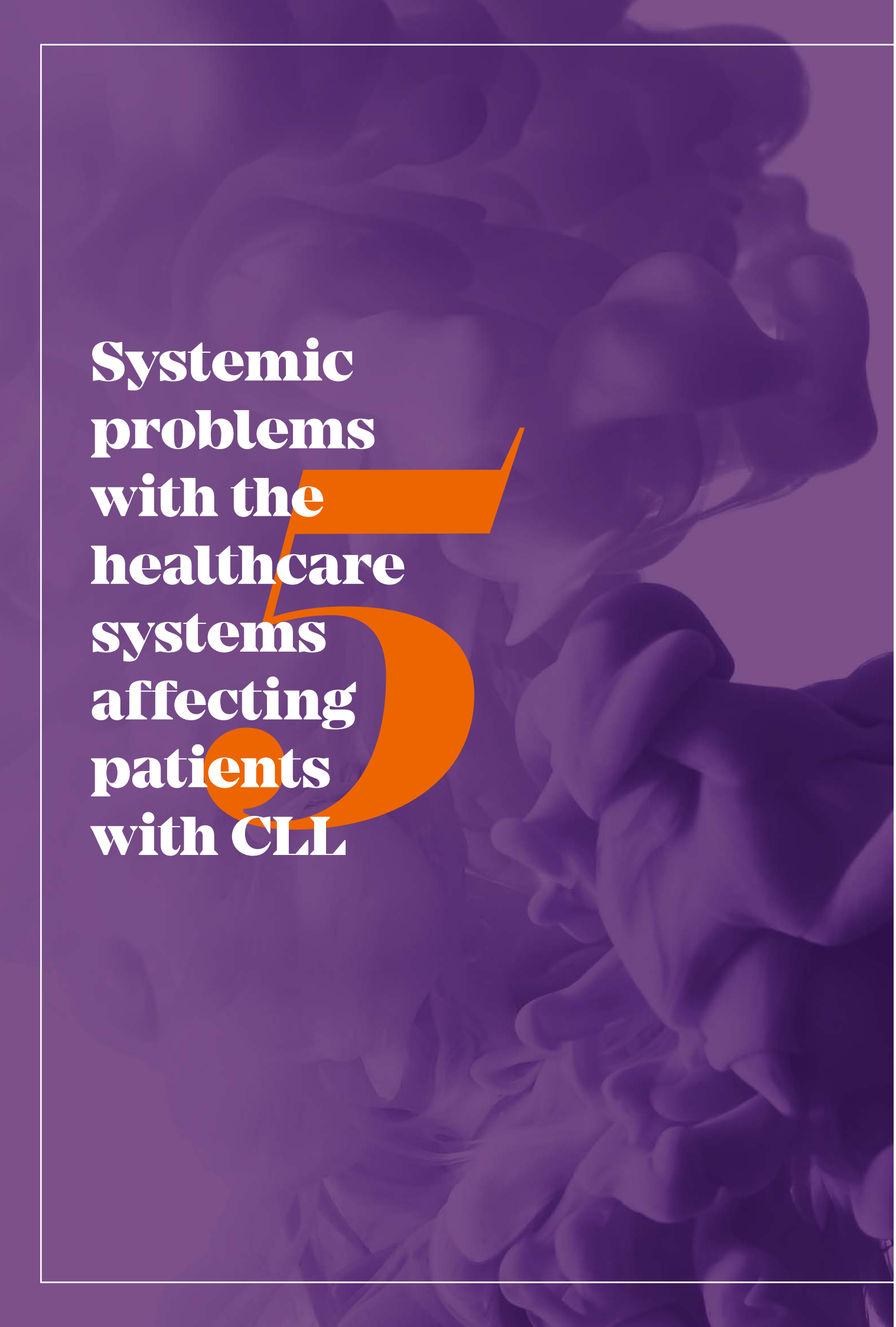
and having to cope with the resulting limitations in daily activities and professional work[61]. A quantitative study of 120 patients with CLL has demonstrated that the average time from diagnosis until initiation of fourth-line treatment is around 8 years. During this period, patients receive "lines" of treatment, and the intervals between subsequent treatment regimens tend to be increasingly shorter. The interval between first- and second-line treatment is around 2 years on average, but is reduced to around 9 months after the third therapy. Each line of chemo- or immunochemotherapy lasts around 6 months[111].

AVERAGE DURATION OF TREATMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA



Source: Sequence. Leczenie przewlekłej białaczki limfocytowej.
The report from the quantitative study conducted for Janssen. March 2016.

Despite the existing (immuno)chemotherapy regimens, the treatment of chronic lymphocytic leukemia is a major challenge for hematologists, especially in relapsed, refractory, and increasingly younger patients. According to reports by hematologists, a relapse of CLL following third-line treatment considerably narrows down the available therapeutic options. Likewise, standard therapy is not suitable for patients with a positive del17p status, which is associated with poor response[5]. In younger patients with chromosome 17p deletion, allogeneic hematopoietic stem cell transplantation (allo-HSCT) was proved to be the only treatment option offering a chance of recovery. In elderly patients and in patients in poor general condition, the only goal of therapy is to improve the quality of life by choosing more gentle therapies[6].



5 Systemic problems with the healthcare systems affecting patients with CLL

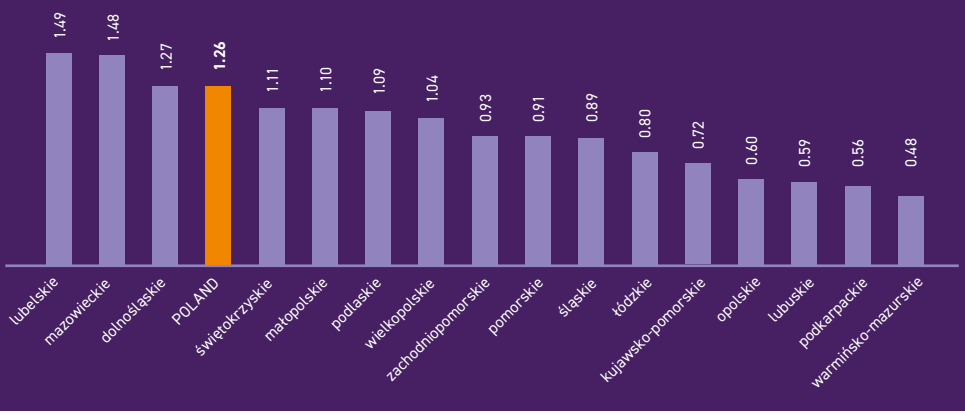
The systemic hardships affecting both patients and healthcare professionals can be grouped under three main headings: problems with how CLL patient care is organized, and the availability of CLL treatment options.

A qualitative study carried out among patients and physicians has shown that the major organizational problem is that there are too many CLL patients assigned to receive care from a limited number of specialist healthcare centers, which translates into long queues and wait times for a hematological consultation[5,61]. This is due to an insufficient number of hematologists available in Poland. Currently, there is little more than 1 hematologist (1.3) per 100,000 population in Poland, and more than 3 hematologists per 100,000 population in the Czech Republic, Bulgaria, or Lithuania[113]. In France, Austria, or Germany, the low rate of hematologists (less than 1 per 100,000 population) can be traced back to differences in the way healthcare is organized, with more patient care duties transferred from specialist to primary care HCPs. Moreover, there are considerable (as high as three-fold) internal differences in hematologist numbers between regions of Poland (Fig. 9).

In Poland, patients with CLL are attended to by a hematologist during periods of remission and relapse, and the primary care is limited to other internal diseases. Only rarely does a primary care physician runs tests to monitor the course of CLL[5,112]. On the other hand, under the current healthcare model in Poland, HCPs also point to the lack of good communication between specialist and primary care facilities, which may additionally impede the management of patients with CLL by a general practitioner[5].

HEMATOLOGISTS PER 100,000 POPULATION IN SELECTED EU COUNTRIES

Fig. 9. Hematologists per 100,000 population per region in 2014[112]

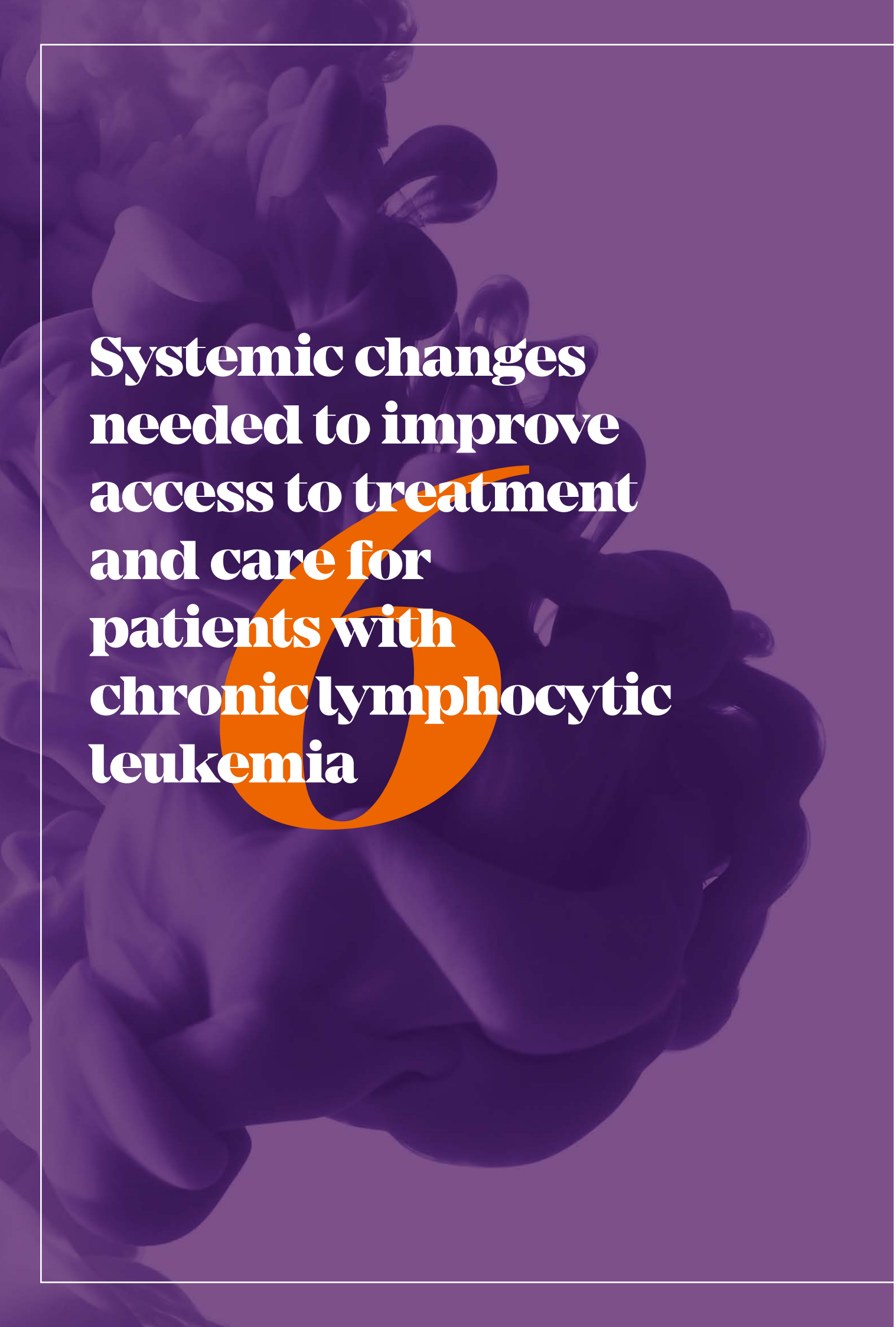


The current systemic solutions for cancer care fall short of what is needed for patients with blood cancers. The present-day cancer care package is not fully tailored to address the needs of patients with chronic lymphocytic leukemia. The timeline proposed in this package of healthcare services is applied universally across all types of cancer, and does not allow for the "watch and wait" approach in patients with CLL. The statutory composition of a medical council is not always appropriate for the management

of CLL patients. Also, the cancer package is designed for newly diagnosed patients instead of patients who have relapsed, progressed or require palliative care[114]. From November 1st 2015, the cancer package was modified to improve the situation, and the modifications introduced are likely to have a positive impact on the diagnosis and treatment in the future, also in patients with blood cancers[115].

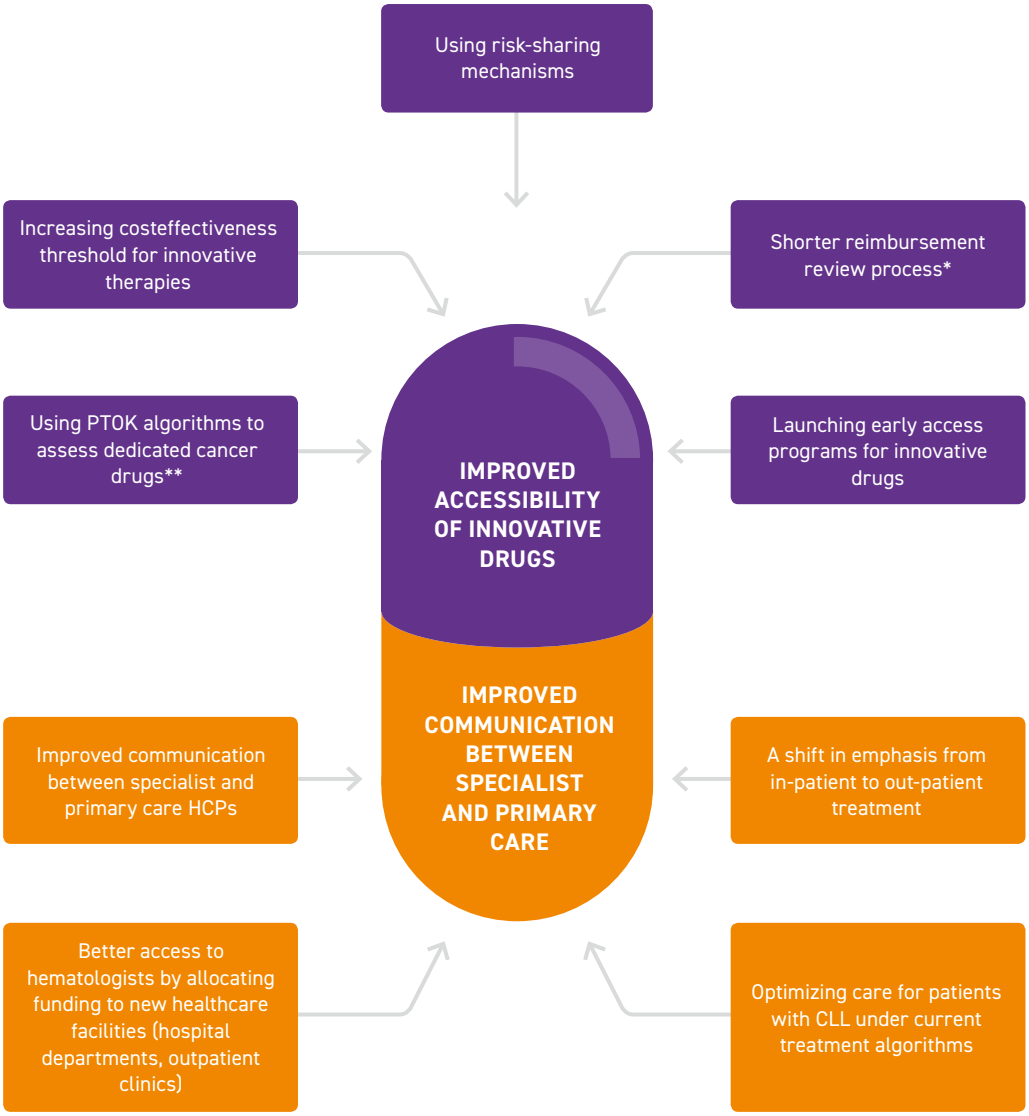
Moreover, there is the lack of sufficient funding and reimbursement of more expensive therapies and modern diagnostic technologies based on cytogenetic tests[66]. According to a qualitative study among physicians, cytogenetic tests are not universally used among patients with CLL[61]. Cytogenetic tests for chromosome 17p deletion are currently performed in around 18% of patients at the time of diagnosis and in around 20% of patients during initiation of subsequent lines of treatment[111]. According to the latest clinical practice guidelines, cytogenetic diagnostics is one of the criteria to make informed decisions about the type of treatment used in patients with CLL[31]. Unless cytogenetic tests are performed, there is little chance of fast and informed decision-making to choose the most effective treatment in patients with unfavourable genetic status.

In terms of how chronic lymphocytic leukemia is treated, the lack of access to reimbursed novel therapies as part of guaranteed healthcare services is especially acute for patients. Access to a medical technology in real-world settings largely depends on the drug's reimbursement status. Innovative therapies are too expensive to be affordable for patients and are considered to be available for a very small group of selected patients[61,113]. From the perspective of hematologists, the lack of access to novel therapies for CLL limits the choice of effective therapeutic solutions for patients with refractory CLL, short remission time, and comorbidities. Because of the inaccessibility of oral therapies, both innovative and traditional drugs used in CLL, patients cannot be offered an effective treatment regimens with a comfortable route of administration to avoid having to receive intravenous chemotherapy[5].



Systemic changes needed to improve access to treatment and care for patients with chronic lymphocytic leukemia

6



* Today, the time necessary for the decision-making in reimbursement issues under a Drug Program is 180 + 60 days[116].

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Conclusions

7

Chronic lymphocytic leukemia is the most common type of leukemia in adults with the incidence rate of 4.2–5 cases per 100,000 inhabitants/year. Because of the chronic course of the condition and the high incidence among elderly, CLL is likely to be a major challenge for the healthcare policy in view of the significant projected increase in the average age of Poland's population.

Chronic lymphocytic leukemia is a complex condition, characterized by varied clinical and genetic characteristics. CLL population includes asymptomatic patients in good general condition and elderly patients with major comorbidities. This translates into different survival rates among patients with CLL – from several years in individuals with unfavourable prognostic factors, to 10-20 years in people who do not experience fast disease progression.

Chemotherapy and immunotherapy used to be the standards of care in chronic lymphocytic leukemia. In the recent years, we have witnessed revolutionary changes in CLL management, which is now focused on precise molecular targets, such as the B cell receptor (BCR) signaling pathway. BCR inhibitors are currently one of the most promising therapies of B-cell cancers. They are highly selective, well tolerated, and convenient to use (oral route of administration). Clinical experts predict that BCR inhibitors are likely to be combined with the currently used chemotherapy or immunotherapy. The progress in the treatment of CLL is likely to be oriented towards deeper individualization of therapy, better combined therapies, and improved treatment outcome predictions based on molecular markers[52].

Despite the huge progress in the treatment of chronic lymphocytic leukemia over the recent years, novel therapies are in fact inaccessible to patients because of limited reimbursement options. A Drug Program dedicated to chronic lymphocytic leukemia started from July 1st 2016 is a positive signal and a response of the Ministry of Health to the unmet medical needs of this patient population. Although this Drug Program is dedicated to a small population

of CLL patients and only includes one breakthrough therapy, it perhaps paves the way for more innovative therapies to be available in the future. By introducing systemic instruments (such as PTOK/PTO algorithms) to support decision-making concerning reimbursement, tailored to novel cancer therapies, the availability of these drugs can be significantly improved. The funding of expensive novel cancer therapies is the only solution to address the unmet needs of patients with chronic lymphocytic leukemia. The 5-year survival rates of patients with CLL in Poland can hopefully be increased (which now counts among the lowest across Europe) if changes in the organization of medical care for patients with blood and lymphoid cancers – advocated by hematologists – are progressively introduced, accompanied by increased accessibility of novel therapies.

Table content

Figure contents

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8

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A preliminary version of the report was completed in July 2016 and presented to the review of clinical experts in August and September 2016. On 5 December 2016 the European Medicines Agency registered a new drug for the treatment of CLL (venetoclax).

In March 2017 the report was supplemented with information on venetoclax.