LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

LYMPHOMA CARE IN EUROPE

ONGOING EXPLORATION OF DISPARITIES IN CARE

SEPTEMBER 2019

LYMPHOMA COALITION

Vision:
Equity in lymphoma outcomes across borders.

Mission:
Enabling global impact by fostering a lymphoma ecosystem that ensures local change and evidence-based action.

Acknowledgments

LCE would like to thank all those whose collaboration and support assisted in the development of this report, as well as companies that provided grants to make this report possible.

Methodology

LCE reviewed the incidence and mortality data gathered by IARC for changes in incidence and mortality in lymphomas, including CLL, between 2012 and 2018[3]. The estimates provided by IARC were based on the most recent data available through collaborations with population-based cancer registries (the International Association of Cancer Registries) and with the World Health Organization or were based on information publicly available online.

To determine availability of phase II and III clinical trials, information was obtained from the LC Global Database which includes information from clinicaltrials.gov, the European Union Clinical Trials Register, the Australian Cancer Trials, the German Hodgkin Study Group and the World Health Organization website.

Availability of novel as well as standard therapies was determined through the LC Global Database, which is kept current through a quarterly review of member country regulatory and reimbursement websites, medical journals and general media press releases.

Assessment of quality of life issues was based on information from the 2018 GPS on Lymphomas and CLL[2] in which there were 6631 global respondents, of whom 1901 were from Europe.

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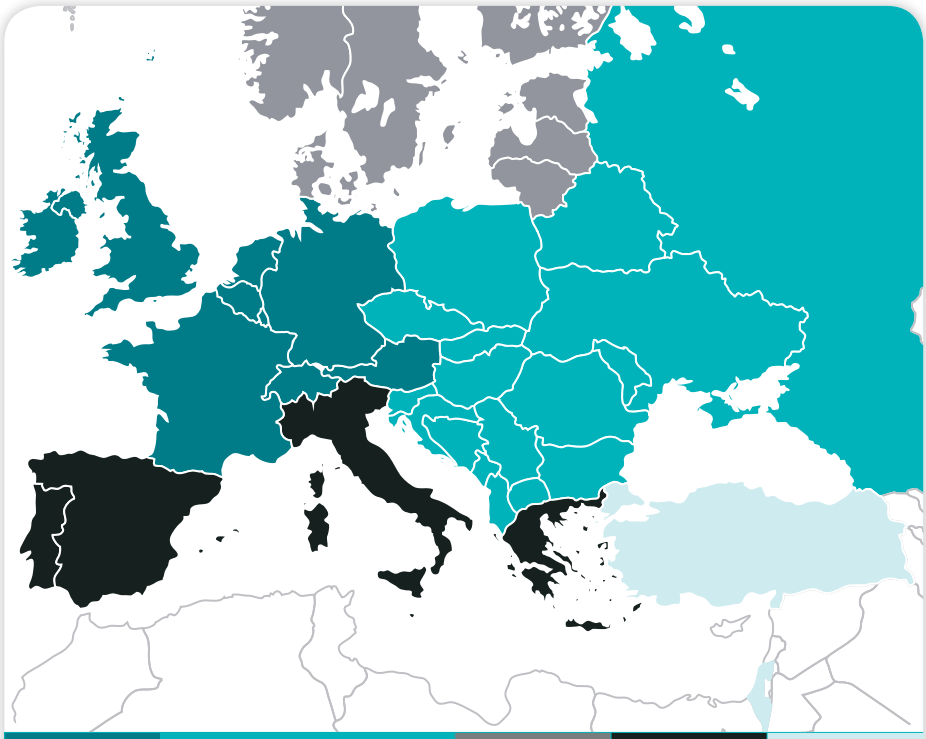
Objectives:

- Assess changes in incidence and mortality
- Identify disparities in treatment and care
- Analyse phase II and III clinical trials availability
- Report on the patient experience
- Identify and make recommendations for future lymphoma advocacy initiatives in Europe

Overview

The 2017 Lymphoma Care in Europe Report focused on the gaps and disparities in care in the different regions of Europe, including Israel and Turkey. The 2019 report builds on these findings, looking at differences between care in north, south, east and west Europe (Figure 1).

Figure 1: Regions in Europe



Western Europe	Eastern Europe		Northern Europe	Southern Europe	Other
Andorra	Albania	Macedonia	Denmark	Cyprus	Israel
Austria	Armenia	Moldova	Estonia	Greece	Turkey
Belgium	Azerbaijan	Montenegro	Finland	Italy	
France	Belarus	Poland	Iceland	Malta	
Germany	Bosnia and Herzegovina	Romania	Latvia	Portugal	
Ireland	Bulgaria	Russian Federation	Lithuania	San Marino	
Liechtenstein	Croatia	Slovakia	Norway	Spain	
Luxembourg	Czechia	Slovenia	Sweden		
Monaco	Hungary	Serbia			
Netherlands		Ukraine			
Switzerland					
United Kingdom					

Turkey and Israel are included in this analysis under an 'other' category due to their geographic location. There is a lack of consensus in how to list these two countries. For instance, the World Health Organization includes Israel and Turkey as part of Europe, but the United Nations lists them as part of Western Asia. They have to date been included in Lymphoma Coalition Europe initiatives. In addition, an in-depth examination of selected countries within each subregion and on certain lymphoma subtypes is an integral piece of this analysis. Table 1 shows the countries in each of the four regions selected for review. They were selected as they are viewed as being representative of the respective regions using a number of different criteria, including population size, geographical location, economic and political significance and the availability of relevant data on access to lymphoma therapies and clinical trials.

Table 1. Countries under In-Depth Review

Western Europe	Eastern Europe	Northern Europe	Southern Europe	Other
Austria Belgium France Germany Netherlands Switzerland UK	Bulgaria Czech Republic Hungary Poland Romania Serbia	Denmark Finland Lithuania Norway Sweden	Greece Italy Portugal Spain	Israel Turkey

UK = United Kingdom

Even though certain countries are profiled, Lymphoma Coalition Europe (LCE) is committed to ensuring efforts are undertaken in all countries to improve the care that patients with lymphoma receive. In countries where data is limited or hard to find, LCE is very keen to work with member organisations to understand fully the local situation on lymphoma care, clinical trial access and the current lymphoma patient experience.

Six subtypes were examined within each region. The subtypes selected are:

1. Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL);
2. Diffuse large B-cell lymphoma (DLBCL);
3. Follicular lymphoma (FL);
4. Hodgkin lymphoma (HL);
5. Mantle cell lymphoma (MCL);
6. Waldenström's macroglobulinaemia (WM).

These six subtypes were selected for reasons of clinical presentation, patient representation, incidence/prevalence and the availability of relevant data. Between them, the six subtypes represent a significant population of patients with lymphoma and cover both aggressive (high grade) and indolent (low grade) disease. Furthermore, thought was given to ensure the lymphoma subtypes chosen included variety in outcomes, diverse patient ages and areas of unmet need, particularly in the relapsed/refractory (R/R) settings. Finally, between them, the six subtypes represent 84% of Europe-based participants in the Lymphoma Coalition 2018 Global Patient Survey (GPS) on Lymphomas and CLL, thus providing a representative cohort of patients in terms of understanding the lymphoma patient experience.[2]

The objectives of the report were to:

- Identify disparities in treatment and care in Europe by;
  - Assessing changes in incidence and mortality in all lymphomas;
  - Reviewing the degree of access to novel and standard therapies;
  - Analysing the availability of phase II and III clinical trials for both novel therapies and standard therapies by country;
  - Examining the patient experience based on findings from the 2018 GPS on Lymphomas and CLL[2];
- Identify and make recommendations for future lymphoma advocacy initiatives in Europe.

In undertaking this review, LCE determined that:

- Based on data from the International Agency for Research (IARC), the incidence and mortality of lymphomas increased in more countries than it decreased between 2012 and 2018, regardless of region[3];
- Access to treatments, particularly novel therapies, varied considerably by region;
- Access to clinical trials varied not only by region but also by country within each region. Some countries will in fact have a difficult time finding participants to fill the available clinical trials as there aren't enough patients in country that match the trial criteria;
- Fear of relapse was the psychosocial issue of overriding concern to patients following completion of treatment, yet most did not feel they had the support needed to cope with this issue;
- There are other quality of life concerns related to the side effects patients experienced, in particular fatigue. Again, findings showed that while some patients sought help from their doctor, help was not always forthcoming;
- As in findings from previous surveys, the doctor remains the main source of information for the majority of patients although the internet is an important resource in some regions. At the same time, patients indicated a need for more understandable and credible information at diagnosis and through treatment, indicating there is a gap in the information currently being provided.

Key Lymphoma Statistics, Data and Metrics

Key data was accumulated for the countries previously identified in Table 1.

In assessing the significance of changes in incidence and mortality, the challenge is that the data are not gathered by individual subtype, with the exception of HL. All other lymphoma data are gathered under a non-Hodgkin lymphoma (NHL) category.

The high number of separate subtypes within this NHL category means that there are serious limits to the usefulness of the grouped incidence, prevalence and survival data since there is much variety amongst the subtypes.

While acknowledging the difficulties of collecting accurate data on a collection of individual rare lymphoma subtypes, there needs to be some change to data collection and reporting at a global and regional level if such data are going to be useful to those working in the field of lymphoma. At the very least, there should be some differentiation between, or specific data collection for, the most common subtypes such as DLBCL, FL and CLL. At a minimum it would be useful to understand the data differences between indolent and aggressive forms of lymphoma (given the different diagnostic, prognostic and treatment challenges) rather than using amalgamated data, which doesn't help one understand the characteristics of either group of lymphomas.

Another reason to gather incidence and mortality data by subtype is to help with future development of new treatments, to ensure patients with the greatest need have effective treatment options.

Of the 24 countries reviewed, only nine showed a decline in HL incidence between 2012 and 2018 and only 12 countries showed a decline in mortality (see Table 2. The countries with the biggest changes between 2012 and 2018).

Given the variety and complexity of the more than 80 different lymphoma subtypes, it is important to stop amalgamating data under the NHL umbrella and instead gather useful data by subtype.

- Within Western Europe, Austria was the only country to show a decline in both HL incidence and mortality. The country with the biggest decline in HL mortality was Belgium (39%) while Germany had the biggest increase between 2012 and 2018 at 19%.
- In Eastern Europe, Bulgaria had the biggest decline in incidence (29%), while Hungary had an increase of 44%. Except for Hungary and Serbia, HL mortality declined in all countries in Eastern Europe.
- In Northern Europe, the most notable increase in HL incidence was seen in Sweden (47%), while Norway had a 91% increase in mortality.
- In Southern Europe, Greece had a significant increase in incidence (95%) as well as mortality (46%). Both Portugal and Spain had a decline in mortality.
- While the incidence in HL declined in Israel, mortality increased by 15%. In Turkey, reported mortality decreased by 69%.

Within NHL, only two of the 24 countries had a decline in incidence (Switzerland and Romania) and only three countries showed a decline in mortality: namely Romania, Serbia and Turkey (see Table 2).

- Within Western Europe, while the UK had the biggest increase in incidence (35%), the biggest increase in mortality was in Germany (37%).
- In Eastern Europe, incidence increased significantly in Hungary (60%) while Poland saw a 39% increase in mortality.
- In Northern Europe, Lithuania had a 50% increase in incidence while there was a 33% increase in mortality in Finland.
- In Southern Europe, Greece had a 163% increase in incidence along with an 81% increase in mortality.
- Israel saw an increase in both incidence and mortality.

In terms of the actual IARC data, some caution needs to be exercised as to what it tells. While the data may appear to show shifts in disease presentation or changes in treatment and care outcomes, these may be due to improved data collection systems within national or regional registries. For instance, increases in incidence and mortality in a country may simply be the result of better reporting systems and more accurate data collection. Similarly, the methodology used to collect and report data may have an impact on how trends over time are reported. Some countries may extrapolate their national data from other sources, for instance from limited data collected at one hospital or from a neighbouring country that has a registry. If data is extrapolated from small patient populations, the sample sizes may mean it is easier for data to be skewed one way or the other.

If there was a better understanding of the incidence, mortality and prevalence of the different lymphomas, that information could be helpful in determining where more information is needed on up-to-date protocols, where access to new therapies is critical, where clinical trials would be of most benefit, and where to add in more patient support programs.

Table 2. HL and NHL Lymphomas: Changes in Incidence and Mortality between 2012 and 2018 [3,4,5,6]

			HL		NHL	
Region/ Country	GDP per capita, US$	Per capita spend on health, % of GDP	Incidence increase (+) or decrease (-) between 2012-2018	Mortality increase (+) or decrease (-) between 2012-2018	Incidence increase (+) or decrease (-) between 2012-2018	Mortality increase (+) or decrease (-) between 2012-2018
Western Europe						
Austria	$50,000	10.3%	-7%	-13%	+13%	+18%
Belgium	$46,600	10.5%	+17%	**-39%**	+29%	+24%
France	$43,800	11.1%	+2%	-11%	+28%	+32%
Germany	$50,400	11.2%	+15%	**+19%**	+17%	**+37%**
Netherlands	$53,600	10.7%	+19%	-1%	+19%	+32%
Switzerland	$61,400	12.1%	+5%	+9%	-0.4%	+16%
UK	$44,100	9.9%	**+27%**	+10%	**+35%**	+30%
Eastern Europe						
Bulgaria	$21,700	8.2%	**-29%**	-10%	+10%	+2%
Czech Republic	$35,500	7.3%	+9%	N/A	+32%	+12%
Hungary	$29,500	7.2%	**+44%**	+3%	**+60%**	+16%
Poland	$29,500	6.4%	+20%	-16%	+50%	**+39%**
Romania	$24,500	5.0%	-17%	-18%	-9%	-4%
Serbia	$15,000	9.4%	-10%	+5%	+3%	-5%
Northern Europe						
Denmark	$49,900	10.3%	0%	+29%	+26%	+5%
Finland	$44,300	9.5%	**+16%**	+63%	+9%	**+33%**
Lithuania	$32,300	6.5%	**-16%**	**-33%**	**+50%**	+19%
Norway	$71,800	10.0%	+12%	**+91%**	+21%	+17%
Sweden	$51,500	11.0%	+47%	+13%	+24%	+27%
Southern Europe						
Greece	$27,800	8.4%	**+94%**	**+46%**	**+163%**	**+81%**
Italy	$38,100	9.0%	+35%	-71%	+0.2%	+7%
Portugal	$30,400	9.0%	**-20%**	**-82%**	+13%	+45%
Spain	$38,300	9.2%	-17%	**-82%**	+27%	+30%
Other						
Israel	$36,300	7.4%	-11%	+15%	+8%	+21%
Turkey	$26,900	4.1%	-3%	**-69%**	+14%	-6%

Information as of November 30, 2018
GDP = gross domestic product; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; UK = United Kingdom

Key
Teal shading indicates an increase
Gray shading denotes a decrease
Percentages in **bold** denotes countries with the biggest changes between 2012 and 2018

There have been a number of new therapies for lymphoma in recent years and research continues.

The prospects of new treatments are exciting, but it can be challenging and frustrating waiting for those therapies to come to market and be reimbursed.

Treatment

The treatment of lymphoma has changed dramatically over the last 20 years, particularly since the approval and introduction of rituximab in the late 1990s.

Lymphoma has been and continues to be one of most active areas of new treatment development in the global pharmaceutical and healthcare sector.

The American Society of Hematology (ASH) has identified the following classes of lymphoma drugs as being currently under investigation in clinical trials or very recently approved (see ashclinicalnews.org/news/lymphoid-malignancies-pipeline):

Kinase Inhibitors

These drugs contain a substance that blocks a type of enzyme called a kinase. Human cells have many different kinases that control important functions (cell signalling, metabolism, division); however, certain kinases are more active in some types of cancer cells. Blocking these kinases may help keep the cancer cells from growing, and kinase inhibitors may also block the growth of new blood vessels that tumours need to grow.

Examples:
- BGB-3111
- ONC201
- SNS-062

Phosphatidylinositide 3 Kinase (PI3K) Inhibitors

Part of the family of kinase inhibitors, but specifically designed to inhibit a PI3K enzyme.

Examples:
- Apilimod dimesylate
- Bimiralisib
- Buparlisib
- Duvelisib

Monoclonal Antibodies

Antibodies are part of the immune system; an antibody is a protein that sticks to a specific protein called an antigen. Once attached, they can recruit other parts of the immune system to destroy the cells containing the antigen. Researchers can design antibodies that specifically target a certain antigen, such as one found on cancer cells. They can then make many copies of that antibody in the lab. These are known as monoclonal antibodies (mAbs).

Examples:

- AFM13
- Cirmtuzumab
- Epratuzumab
- Mogamulizumab

Checkpoint Inhibitors

Immune checkpoints help the immune system identify what is foreign and should be eliminated from the body. The immune system, when working properly, is able to identify and get rid of cancer cells. Research has shown that cancer can take over certain immune checkpoints to evade destruction and ensure survival. Checkpoint inhibitors stop this from happening and help kickstart an immune response against the cancerous cells.

Example:

- TTI-621

Antibody Drug Conjugates (ADC)

Agents that combine cytotoxic chemotherapy with a monoclonal antibody. The monoclonal antibody portion of the drug targets a protein on the surface of a cancer cell and attaches to it. The ADC is absorbed into the interior of the cell, which allows the cytotoxic chemotherapy portion of the drug to kill the cell. This type of targeted therapy limits the side effects that occur when cytotoxic chemotherapy is used alone.

Examples:

- AGS67E
- Polatuzumab vedotin

Chimeric antigen receptor T cell (CAR-T) Therapy

CAR-T is a type of therapy, known as immunotherapy, which uses a patient's own immune system to treat cancers. A key component of the immune system are T cells, which are white blood cells that can detect disease-causing pathogens in the body. CAR-T therapy involves enhancing a patient's T cells to be more effective at detecting and destroying lymphoma. T cells are enhanced by being genetically altered to produce a chimeric antigen receptor (CAR). This receptor helps T cells find lymphoma cells by detecting certain proteins on the tumour cells. Once the lymphoma cells are detected, they can then be destroyed by the immune system. CARs are synthetic receptors that reprogram immune cells for therapeutic purposes.

Examples:

- Axicabtagene ciloleucel
- Tisagenlecleucel
- JCAR017

Selective Inhibition of Nuclear Export (SINE) XPO1 Antagonist

Exportins are types of proteins that bind to certain large molecules, allowing the large molecules to move out of the nucleus of a cell (nuclear export) in a tightly regulated way. When working properly, this controls several cellular processes. One of these exportins is called Exportin 1 (XPO1). XPO1 is elevated in cancer cells, showing that the cancer cells have found a way to use XPO1 to move tumour suppressor proteins out of the cell nucleus so they won't work. This allows the cancer cells to avoid death, and grow and divide uncontrollably. An XPO1 antagonist inhibits XPO1 to restore the body's natural anti-cancer mechanisms.

Example:

- Selinexor

In addition, there are numerous treatments from many of these therapy classes that are now being used or trialled in combination with other new or existing treatments, or in different lymphoma subtypes, such as:

- Antibody treatments, e.g., rituximab, ofatumumab and obinutuzumab;
- Combination treatments or antibody drug conjugates, e.g., brentuximab vedotin and 90Y-ibritumomab tiuxetan;
- Drugs that act as signal blockers or inhibitors, such as:
  - Cell signal blockers, e.g., ibrutinib, idelalisib, acalabrutinib and temsirolimus;
  - Proteasome inhibitors, e.g., bortezomib;
  - Immunomodulators, e.g., lenalidomide.
- Programmed cell death inducers, which block proteins that keep lymphoma cells alive, e.g., venetoclax;
- Checkpoint inhibitors e.g., nivolumab and pembrolizumab.

The prospects of new treatments are exciting, but it can be challenging and frustrating waiting for those therapies to come to market and then be reimbursed for use in individual countries.

It is vital that lymphoma patient organisations work together to share knowledge of patients' and carers' experiences with these therapies so their impact in the real world is better understood, including how they affect patients' quality of life.

LCE is committed to bringing a stronger patient and carer perspective to the research and development pipeline, including via its Lymphoma and CLL Community Advisory Board initiative, which brings together leading patient/carer experts from across Europe to act as a professional resource for industry and research organisations working in the field of lymphoma treatment.

Levels of Access to New and Current Treatments

To form a baseline of what treatments should be available for the treatment of the six featured subtypes, the treatment guidelines developed by the European Society for Medical Oncology (ESMO) were reviewed.

In addition to reviewing the ESMO guidelines, the therapies that have funding and reimbursement approval in each country, i.e., are accessible to patients through public healthcare, were reviewed.

CLL: Access to Novel and Current Treatments

Table 3 shows the therapies recommended by ESMO[7] in both the first line and relapsed settings and Table 4 shows the treatments accessible through public healthcare in Europe including Israel and Turkey.

It should be borne in mind that the field of CLL treatment is in a state of flux, given the results and outcomes from a range of clinical trials that were reported on during 2018 and 2019. The standard of care is evolving fast and the sequencing of lines of treatment is still not clear. Although the most current ESMO guidelines from 2017 are used here, they are already out of date and highlight the need for clinical bodies to update their guidelines much more regularly, particularly in such a fast-moving field.

Table 3. CLL Treatment Guidelines[7]

First-Line Treatment		Relapsed Treatment	
Novel Therapy	**Standard Therapy**	**Novel Therapy**	**Standard Therapy**
Obinutuzumab + chlorambucil	FCR	Ofatumumab + chlorambucil	FCR
Ofatumumab + chlorambucil	Bendamustine ± rituximab	Ibrutinib	Bendamustine ± rituximab
Ibrutinib (17p or TP53)	Rituximab ± chlorambucil	Idelalisib + rituximab	Rituximab ± chlorambucil
Idelalisib + rituximab (17p or TP53)		Venetoclax	alloHSCT
Venetoclax			

alloHSCT = allogeneic haematopoietic stem cell transplantation; CLL = chronic lymphocytic leukaemia; FCR = fludarabine, cyclophosphamide, rituximab

Compared with the other subtypes, CLL has the most treatment options using a novel therapy.

A huge unmet need was previously identified within this community of patients, with the only existing treatments being chemoimmunotherapy regimens that did not work in patients with genetic mutations such as 17p deletion or TP53 mutations, nor could they be used in patients with certain comorbidities. Research conducted as a result has led to the development of several novel therapies in recent years.

All the novel therapies recommended by ESMO for CLL were accessible through public healthcare in one or more of the European countries under review. In addition to the therapies recommended by ESMO, a few other novel therapies were also accessible in some countries; namely FCO (fludarabine, cyclophosphamide, ofatumumab), bendamustine + ofatumumab and ofatumumab alone.

It is positive that ibrutinib, which was approved by the European Medicines Agency (EMA) in 2014 and provided a treatment option for patients with poor genetic markers, is widely available, with exceptions being Finland, where there is no access, and availability only through special access programmes in both the Czech Republic and Serbia.

Differences definitely come to light when overall access is analysed by region.

In Western Europe, Germany was the only country to have all 11 novel therapies accessible to patients through public healthcare. All countries had public access to at least one of the two rituximab biosimilars listed in Table 4 and all standard therapies recommended by ESMO were accessible.

A different picture emerges for treatment availability in Eastern Europe with no country in this region having public access to all novel therapies listed. While Bulgaria provided public access to six of the 11 novel therapies, in Hungary and Serbia only one novel therapy was available. Bulgaria and the Czech Republic were the only countries with access to both rituximab biosimilars, while Poland and Serbia had no access to either rituximab biosimilar. Among the standard therapies, FCR (fludarabine, cyclophosphamide, rituximab) was available in all countries, but bendamustine + rituximab could only be accessed in the Czech Republic through a special access programme; no information could be found on its availability in Romania.

Among the countries under review in Northern Europe, Sweden provided public access to 10 of the 11 novel therapies while Lithuania and Norway had access to only two. Aside from the availability of ibrutinib and obinutuzumab + chlorambucil in Norway, LCE was unable to determine what other novel therapies or rituximab biosimilars were available there. All other countries in this region had access to at least one rituximab biosimilar. All standard therapies were accessible in all countries.

In Southern Europe, Spain provided access to 10 of the 11 novel therapies through public healthcare while in Italy nine of the novel therapies were accessible. LCE was unable to determine which therapies were accessible to patients through public healthcare in Greece. In Italy, the two standard therapies could only be accessed through a special access programme. No country provided access to both rituximab biosimilars.

In Israel, seven of the 11 novel therapies were accessible through public healthcare but neither of the two rituximab biosimilars were accessible. It was difficult to find information in Turkey.

In summary, access to CLL novel therapies varied greatly by country and was inequitable across regions. Eastern European countries have significantly less access than any other region.

Table 4. CLL: Novel and Standard Therapies Accessible Through Public Healthcare

Region/ Country	Novel Therapies											Standard Therapies		Rituximab Biosimilars	
	B+ Ofa	FCO	IBR	Ib	Idela+O	Idela+R	Clb+G	Ofa	Clb+O	Ven	VR	BR	FCR	Biosimilar Truxima	Biosimilar Rixathon
Western Europe															
Austria															
Belgium															
France															
Germany															
Netherlands															
Switzerland															
UK															
Eastern Europe															
Bulgaria															
Czech Republic															
Hungary															
Poland															
Romania															
Northern Europe															
Denmark															
Finland															
Lithuania															
Norway															
Sweden															
Southern Europe															
Greece															
Italy															
Portugal															
Spain															
Other															
Israel															
Turkey															

Data as of March 2019

Key
- Defined as therapy available to patients through public healthcare
- Therapy available through a special access programme within that country
- Therapy not available/no evidence found
- No information found on therapy's availability

B+Ofa = bendamustine+ ofatumumab; BR = bendamustine + rituximab; Clb+O = Chlorambucil + ofatumumab; CLL = chronic lymphocytic leukaemia; FCO = fludarabine, cyclophosphamide, ofatumumab; FCR = fludarabine, cyclophosphamide, rituximab; Clb+G = chlorambucil + obinutuzumab; Ib = Ibrutinib; IBR = Ibrutinib, bendamustine, rituximab; Idela+ O Idela+R = idelalisib+ rituximab; Ofa = ofatumumab; UK = United Kingdom, Ven = venetoclax, VR = venetoclax + rituximab

DLBCL: Access to Novel and Current Treatments

The therapies recommended by ESMO[8] shown in Table 5 and Table 6 shows the treatments accessible through public healthcare in Europe, including Israel and Turkey.

DLBCL, an aggressive lymphoma, has a 5-year survival rate in the front-line setting of over 60%, yet nearly half of patients with this subtype relapse or are refractory to treatment.[9] This is an area of unmet need, with few novel therapies with either regulatory or reimbursement/funding approval. The ESMO guidelines list no novel therapies although two CAR T cell therapies along with pixantrone have received regulatory approval in Europe.

Of concern to LCE is that the ESMO guidelines have not been updated since 2015, thus they are not necessarily reflective of current clinical practice.

Of the 24 countries under review, nine did not have any of the three novel therapies available. Only one country in northern Europe had access to one of the novel treatments, the least availability across the four regions. CAR-T, a promising yet expensive option for relapsed/refractory patients, is not yet widely available in Europe. Of the two CAR T cell therapies that have been approved, Germany was the only country that provided access to both through public healthcare while France provided access to axicabtagene ciloleucel. In the UK, both CAR T cell therapies were available through a special access programme while tisagenlecleucel was available through a special access programme in Spain. Pixantrone, the other novel therapy, was also not widely available in any of the regions. This information was sourced and verified as of March 2019. Other countries may have since made decisions regarding the reimbursement of CAR-T.

Of the two biosimilars noted in Table 6, except for Israel, Poland and Serbia, all countries had at least one available. No information could be found on the availability of biosimilars in Norway and Turkey.

All standard therapies were available through public healthcare.

LCE tried to determine what therapies were accessible in Norway and Greece, but it was not possible to find this information.

Table 5. DLBCL Guidelines[8]

First-Line Treatment		Relapsed Treatment	
Novel Therapy	**Standard Therapy**	**Novel Therapy**	**Standard Therapy**
	R-CHOP		DHAP ± rituximab
	ACVBP		GDP ± rituximab
	R-CEOP		ICE ± rituximab
			BEAM
			AutoSCT
			AlloSCT
			GemOx ± rituximab

ACVBP = doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone; AlloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; BEAM = carmustine, etoposide, cytarabine and melphalan; DHAP = dexamethasone, cisplatin, cytarabine; DLBCL = diffuse large B-cell lymphoma; GDP = cisplatin, gemcitabine, dexamethasone; GemOx = gemcitabine, oxaliplatin; ICE = ifosfamide, carboplatin, etoposide; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine, prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Table 6. DLBCL: Novel and Standard Therapies Accessible Through Public Healthcare

Region/ Country	Novel Therapies			Standard Therapies					Rituximab Biosimilars	
	CAR T Axi-cel	CAR T Tisagenlecleucel	Pixantrone	CHOEP+R	CHOP+R	DHAP+R	EPOCH+R	R+ACVBP	Biosimilar Truxima	Biosimilar Rixathon
Western Europe										
Austria										
Belgium										
France										
Germany										
Netherlands										
Switzerland										
UK										
Eastern Europe										
Bulgaria										
Czech Republic										
Hungary										
Poland										
Romania										
Northern Europe										
Denmark										
Finland										
Lithuania										
Norway										
Sweden										
Southern Europe										
Greece										
Italy										
Portugal										
Spain										
Other										
Israel										
Turkey										

Data as of March 2019

Key
- Defined as therapy available to patients through public healthcare
- Therapy available through a special access programme within that country
- Therapy not available/no evidence found
- No information found on therapy's availability

Axi-cel = Axicabtagene Ciloleucel; CAR = chimeric antigen receptor; CHOEP = cyclophosphamide, vincristine, doxorubicin, etoposide, prednisone, rituximab; CHOP-R = cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab; DHAP-R = dexamethasone, cisplatin, cytarabine, rituximab; DLBCL = diffuse large B-cell lymphoma; EPOCH-R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; R-ACVBP = rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; UK = United Kingdom

FL: Access to Novel and Current Treatments

Table 7 shows the therapies recommended by ESMO[10] in both the first line and relapsed settings and Table 8 shows the treatments accessible through public healthcare in Europe including Israel and Turkey.

While several novel therapies have received regulatory approval, only idelalisib was noted in the ESMO guideline. Although obinutuzumab + bendamustine, obinutuzumab maintenance and idelalisib were approved by the EMA in 2014, LCE only found evidence of all three regimens being available in nine countries.

Among the other novel therapies with regulatory approval, obinutuzumab + CVP and obinutuzumab + CHOP were the two regimens with the least availability through public healthcare. In Western Europe, they were only accessible in four countries while in Eastern Europe they were not accessible in any country. In Northern Europe, they were accessible in only two countries and were not accessible in any countries in Southern Europe.

Standard therapies for FL were widely available and, with the exception of Poland, all countries had access to at least one biosimilar.

In general, countries in Eastern Europe had the least amount of access to therapies.

Table 7. FL Treatment Guidelines[10]

First-Line Therapy		Relapsed Therapy	
Novel Therapy	**Standard Therapy**	**Novel Therapy**	**Standard Therapy**
	Bendamustine + rituximab	Idelalisib	Bendamustine + rituximab
	R-CHOP		R-CHOP
	R-CVP		R-CVP
	Rituximab		Rituximab
	Chlorambucil + rituximab		Chlorambucil + rituximab
	Rituximab maintenance		AutoSCT
	Radioimmunotherapy		AlloSCT
			Rituximab maintenance
			Radioimmunotherapy

AlloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; FL = follicular lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

Table 8. FL: Novel and Standard Therapies Accessible Through Public Healthcare

Region/ Country	Novel Therapies				Standard Therapies						Rituximab Biosimilars	
	G + CVP	G + CHOP	G + B	Obinutuzumab Maintenance	Idela	BR	CHOP+R	CVP+R	R	Rituximab Maintenance	Biosimilar Truxima	Biosimilar Rixathon
Western Europe												
Austria												
Belgium												
France												
Germany												
Netherlands												
Switzerland												
UK												
Eastern Europe												
Bulgaria												
Czech Republic												
Hungary												
Poland												
Romania												
Northern Europe												
Denmark												
Finland												
Lithuania												
Norway												
Sweden												
Southern Europe												
Greece												
Italy												
Portugal												
Spain												
Other												
Israel												
Turkey												

Data as of March 2019

Key
- Defined as therapy available to patients through public healthcare
- Therapy available through a special access programme within that country
- Therapy not available/no evidence found
- No information found on therapy's availability

B = bendamustine; CHOP-R = cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab; CVP-R = cyclophosphamide, vincristine, prednisone, rituximab; FL = follicular lymphoma; G = obinutuzumab; Idela = idelalisib; UK = United Kingdom

HL: Access to Novel and Current Treatments

The therapies recommended by ESMO guidelines[11] are shown in Table 9 and the therapies with public access in each country are shown in Table 10.

Hodgkin lymphoma has one of the best 5-year survival rates after first-line treatment of any lymphoma subtype, but there are still patients for whom current therapy is ineffective in treating their disease.

Specifically, more treatment options are needed for patients who have relapsed or refractory HL or are over age 50 when diagnosed.

While few novel therapies are available for use in HL, the situation is improving especially in the R/R setting. The introduction of antibody-drug conjugates and PD1 inhibitors is positive. In the ESMO guidelines, the novel therapies were only recommended for use in the relapsed setting.

Within Western Europe, Germany was the only country in which all four novel therapies were accessible through public healthcare. Aside from Germany, no other country provided access to AVD-A (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine). France had the most restricted availability with pembrolizumab not being available and nivolumab only available through a special access programme. However in Eastern Europe, only brentuximab vedotin was available in all countries. In Northern Europe, while three of the four novel therapies were accessible in Denmark and Sweden, in Lithuania, only brentuximab vedotin (BV) was accessible. In Norway, LCE was only able to find information on the availability of nivolumab. Within Southern Europe, no country had access to all four novel therapies.

Apart from Greece, all standard therapies were available. LCE was unable to find information for Greece.

Israel had access to three of the four novel therapies noted but Turkey only had access to BV.

Table 9. HL Treatment Guidelines[11]

First-Line Therapy		Relapsed Therapy	
Novel Therapy	**Standard Therapy**	**Novel Therapy**	**Standard Therapy**
	ABVD	Brentuximab vedotin	DHAP
	BEACOPP	Pembrolizumab	ICE
	Radiation therapy	Nivolumab	IGEV
			Radiation therapy
			AutoSCT
			AlloSCT

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; alloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; DHAP = dexamethasone, cisplatin, high-dose cytarabine; HL = Hodgkin lymphoma; ICE = ifosfamide, carboplatin, etoposide; IGEV = ifosfamide, gemcitabine, vinorelbine

Table 10. HL: Novel and Standard Therapies Accessible Through Public Healthcare

	Novel Therapies				Standard Therapies	
	AVD-A	Brentuximab Vedotin Monotherapy	Pembrolizumab	Nivolumab	ABVD	BEACOPP
Western Europe						
Austria						
Belgium						
France						
Germany						
Netherlands						
Switzerland						
UK						
Eastern Europe						
Bulgaria						
Czech Republic						
Hungary						
Poland						
Romania						
Northern Europe						
Denmark						
Finland						
Lithuania						
Norway						
Sweden						
Southern Europe						
Greece						
Italy						
Portugal						
Spain						
Other						
Israel						
Turkey						

Data as of March 2019

Key
- Defined as therapy available to patients through public healthcare
- Therapy available through a special access programme within that country
- Therapy not available/no evidence found
- No information found on therapy's availability

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AVD-A = brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; HL = Hodgkin lymphoma; UK = United Kingdom

MCL: Access to Novel and Current Treatments

The therapies recommended by ESMO[12] are shown in Table 11 and those with public access in each country are shown in Table 12.

Mantle cell lymphoma can be very challenging to treat and there is a need for novel therapies to improve survival. To date, however, only three novel therapies have received regulatory approval for the treatment of MCL.

Among Western Europe countries, Germany and the Netherlands were the only ones with all three novel therapies accessible through public healthcare while lenalidomide was not available in Switzerland or the UK. Within Eastern Europe, no country had all three novel therapies available. Bulgaria was the only country in which ibrutinib was available although it could be accessed through a special access programme in the Czech Republic and Serbia. For four of the countries in this region, LCE was unable to find information on what therapies patients could access through public healthcare. Among Northern European countries, Sweden was the only country where all three novel therapies were accessible. No information could be found for Finland and Lithuania, and only limited information was available for Norway. In Southern Europe, all three novel therapies were available in Italy and Spain, but LCE was unable to determine a complete picture of availability in Portugal and no information could be found for Greece. In Israel, all three novel therapies were available.

Table 11. MCL Treatment Guidelines[12]

First-Line Therapy		Relapsed Therapy	
Novel Therapy	**Standard Therapy**	**Novel Therapy**	**Standard Therapy**
CAP-VcR	HyperCVAD ± rituximab	Ibrutinib	Bendamustine + rituximab
	R-CHOP		DHAP-R
	Rituximab maintenance		FC
	AutoSCT		Rituximab maintenance
	Bendamustine + rituximab		R-BAC
	R-BAC		AutoSCT
	Rituximab maintenance		AlloSCT

AlloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; CAP-VcR = bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone; DHAP = dexamethasone, cisplatin, high-dose cytarabine; FC = fludarabine, cyclophosphamide; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MCL = mantle cell lymphoma; R-BAC = rituximab, bendamustine, cytarabine; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Table 12. MCL: Novel and Standard Therapies Accessible Through Public Healthcare

Region/ Country	Novel Therapies			Standard Therapies		
	CAP-VcR	Ibrutinib	Lenalidomide	Bendamustine +Rituximab	CHOP+R	HyperCVAD+R
Western Europe						
Austria						
Belgium						
France						
Germany						
Netherlands						
Switzerland						
UK						
Eastern Europe						
Bulgaria						
Czech Republic						
Hungary						
Poland						
Romania						
Northern Europe						
Denmark						
Finland						
Lithuania						
Norway						
Sweden						
Southern Europe						
Greece						
Italy						
Portugal						
Spain						
Other						
Israel						
Turkey						

Data as of March 2019

Key
- Defined as therapy available to patients through public healthcare
- Therapy available through a special access programme within that country
- Therapy not available/no evidence found
- No information found on therapy's availability

CAP-VcR = cyclophosphamide, doxorubicin, bortezomib, prednisone, rituximab; CHOP-R = cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab; hyperCVAD-R = cyclophosphamide, vincristine, doxorubicin, rituximab and dexamethasone alternating with high dose methotrexate and cytarabine; MCL = mantle cell lymphoma; UK = United Kingdom

WM: Access to Novel and Current Treatments

The therapies recommended for Waldenström's macroglobulinaemia by ESMO[13] are shown in Table 13 and the therapies with public access in each country are shown in Table 14.

Only one novel therapy (ibrutinib) has, to date, received regulatory approval. It was available in all countries in Western Europe. Outside of Western Europe, it was only available in Bulgaria, Denmark, Israel, Portugal, Spain and Sweden. In the Czech Republic and Serbia, it was available through a special access programme.

It should be noted that R-CHOP as a therapy was available in all the countries we looked at where we were able to identify information on treatment access, even though it is not explicitly mentioned in ESMO's guidelines on WM.

This may be the result of outdated thinking on the treatment of WM, which can be a neglected or misunderstood subtype.

Table 13. WM Treatment Guidelines[13]

First-Line Therapy		Relapsed Therapy	
Novel Therapy	**Standard Therapy**	**Novel Therapy**	**Standard Therapy**
BDR	Bendamustine + rituximab	Ibrutinib	Alternate rituximab-based therapy not used in first line treatment
Bortezomib + Rituximab	DRC		
Ibrutinib	Rituximab		
	Fludarabine		
	Chlorambucil		

BDR = bortezomib, dexamethasone, rituximab; DRC = dexamethasone, rituximab, cyclophosphamide; WM = Waldenström's macroglobulinaemia

Table 14. WM: Novel and Standard Therapies Accessible Through Public Healthcare

Region/ Country	Novel Therapies	Current Therapies				
	Ibrutinib	CHOP-R	Bendamustine -Rituximab	Bendamustine	DRC	FCR
Western Europe						
Austria						
Belgium						
France						
Germany						
Netherlands						
Switzerland						
UK						
Eastern Europe						
Bulgaria						
Czech Republic						
Hungary						
Poland						
Romania						
Northern Europe						
Denmark						
Finland						
Lithuania						
Norway						
Sweden						
Southern Europe						
Greece						
Italy						
Portugal						
Spain						
Other						
Israel						
Turkey						

Data as of March 2019

Key
- Defined as therapy available to patients through public healthcare
- Therapy available through a special access programme within that country
- Therapy not available/no evidence found
- No information found on therapy's availability

CHOP-R = cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab; DRC = dexamethasone, rituximab, cyclophosphamide; FCR = fludarabine, cyclophosphamide, rituximab; UK = United Kingdom; WM = Waldenström's macroglobulinaemia

Access to Treatment Summary

Given the challenges LCE experienced in finding information on what is accessible in many of the countries under review, it likely means that patients face similar challenges. This can add unnecessary stress to an already stressful situation.

Overall, countries in Western Europe were more likely to provide access to novel therapies to patients, with Germany the only country to provide access to all the therapies under review.

Of the six ESMO treatment guidelines referred to in this report, only two – HL and WM – were updated in 2018.

If guidelines are meant to be a valid and trustworthy resource, they need to be updated regularly, particularly at a time of such fertile and productive pharmaceutical and clinical research and development in the lymphoma field.

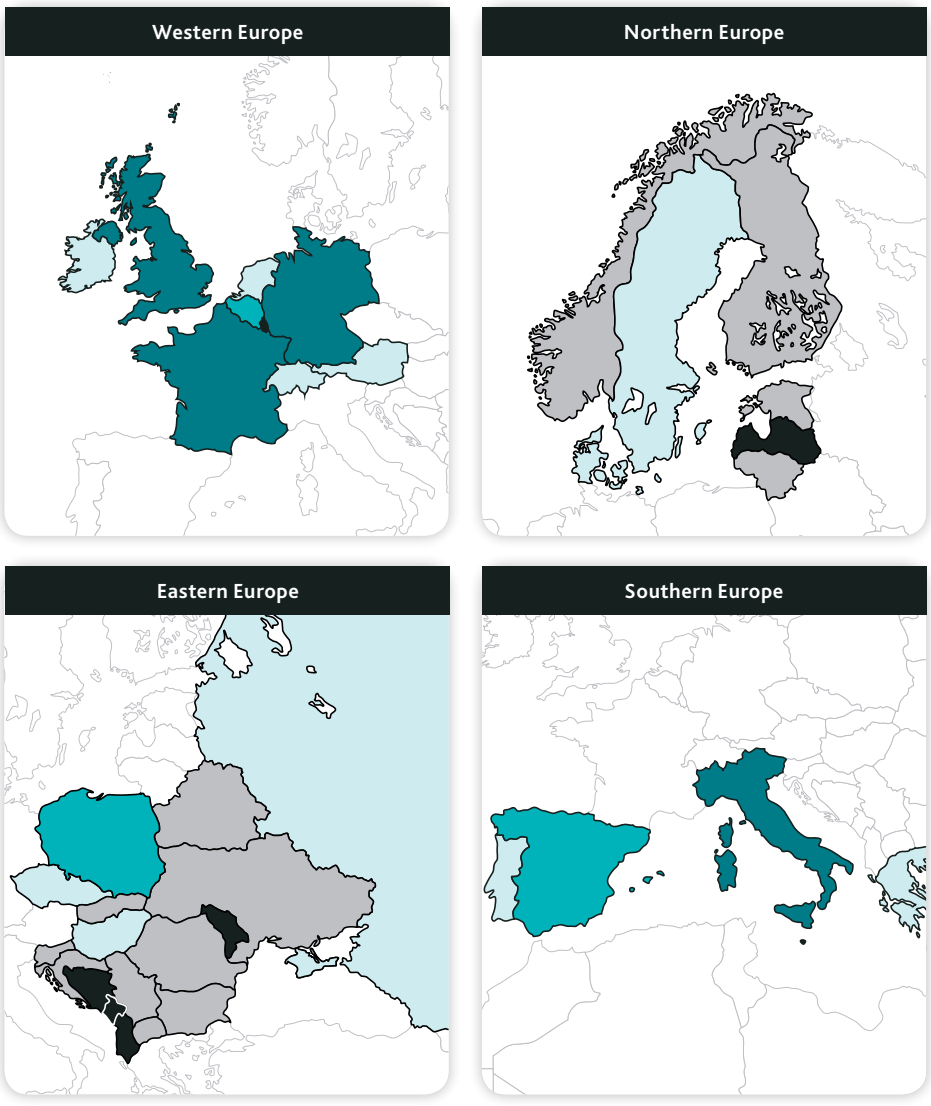
Having updated guidelines would likely help with advocacy initiatives as they can validate the need for the treatment to be accessible given that a rigorous review process is followed before a treatment is included in a treatment guideline.

Access to Clinical Trials

It is also important to review the availability of phase II and III clinical trials for both novel therapies and standard therapies across Europe. For patients whose disease does not respond to standard therapy, participation in clinical trials may be the best or only choice for a possible remission.

When comparing the degree of access to clinical trials among regions, countries in Western Europe had a much higher degree of access to both phase II and III trials as well as those involving a novel therapy.

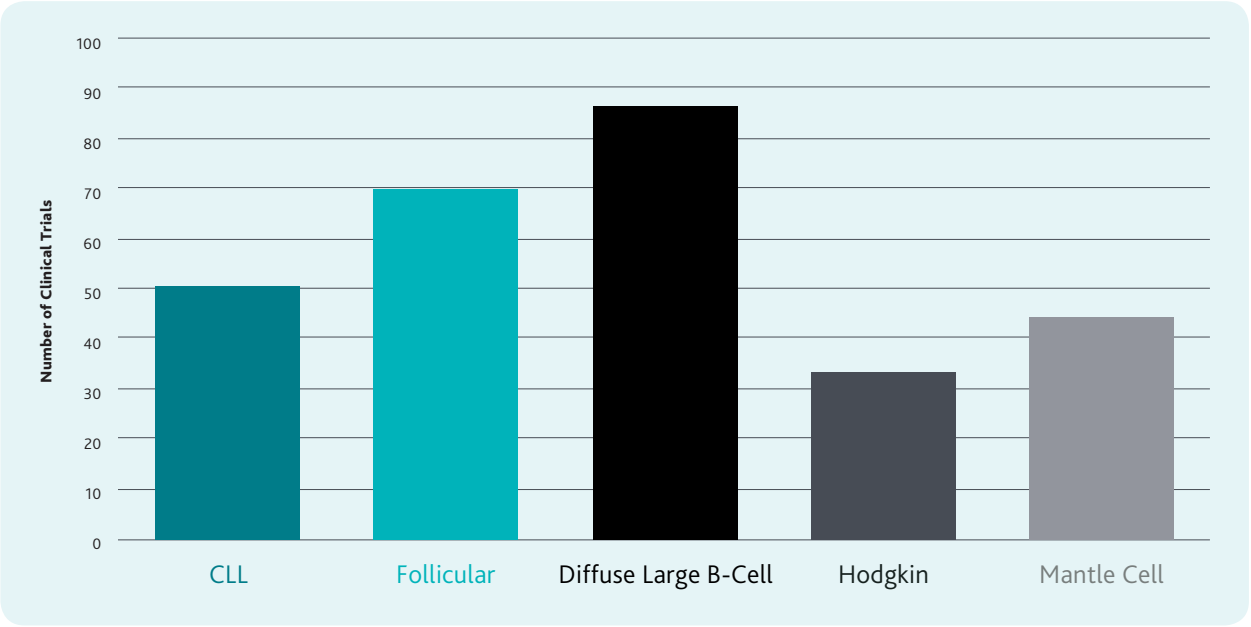
Figure 2: Number of Phase II and Phase III Clinical Trials by Region in Europe



Most clinical trials are in Western Europe, leaving patients in many countries struggling to receive experimental therapies that could be life-saving.

The majority of the trials being conducted are looking at novel therapies. Figure 3 below shows most of these are for DLBCL, followed closely by FL.

Figure 3: Novel Therapy Clinical Trials in Europe by Subtype



When comparing the degree of access to clinical trials among regions, countries in Western Europe had a much higher degree of access to both phase II and III trials as well as those involving a novel therapy. Within each region, the countries with the most clinical trials in each subtype are highlighted in **gray**. Note that the novel therapy trials may involve more than one subtype.

Table 15 also shows that population size does not necessarily link to the number of available trials.

There are countries with sizeable populations, like Romania and Turkey, that have very few trials in comparison to countries with a smaller population size like Denmark, Israel and Belgium.

Table 15. In Depth Clinical Trial Analysis by Select Countries

Region/ Country	Population as of 2017[3]	Total PII & PIII Trials	Novel Therapy Trials	CLL Novel Therapy Trials (n=50)	DLBCL Novel Therapy Trials (n=86)	FL Novel Therapy Trials (n=70)	HL Novel Therapy Trials (n=33)	MCL Novel Therapy Trials (n=44)	WM Novel Therapy Trials (n=14)
Western Europe									
Austria	8,793,370	35	33	12	11	8	2	4	1
Belgium	11,491,346	73	70	17	24	21	5	15	6
France	67,106,161	115	106	17	36	33	15	22	8
Germany	80,594,017	120	99	28	29	32	13	21	9
Netherlands	17,084,719	42	39	7	16	10	5	10	2
Switzerland	8,236,303	19	19	4	10	7	2	6	1
UK	65,648,100	102	91	25	34	27	7	14	7
Eastern Europe									
Bulgaria	7,101,510	14	12	2	4	8	1	3	5
Czech Republic	10,674,723	49	41	9	12	13	6	9	3
Hungary	9,850,845	30	28	7	10	11	3	7	4
Poland	38,476,269	67	60	17	17	16	5	12	8
Romania	21,529,967	11	9	3	2	3	1	1	2
Serbia	7,111,024	6	4	0	2	0	1	0	0
Northern Europe									
Denmark	5,605,948	27	24	9	5	3	2	4	2
Finland	5,518,371	12	10	2	4	5	0	3	2
Lithuania	2,823,859	1	1	0	0	1	0	0	1
Norway	5,320,045	15	14	1	2	5	2	2	0
Sweden	9,960,487	37	33	11	7	12	2	11	3
Southern Europe									
Greece	10,761,523	19	17	3	3	6	1	3	6
Italy	62,137,802	119	97	21	35	34	10	18	10
Portugal	10,839,514	16	15	5	5	7	0	3	3
Spain	48,958,159	97	88	19	32	27	9	18	6
Other									
Israel	8,299,706	39	37	11	14	12	3	7	3
Turkey	80,845,215	26	24	7	7	11	3	5	5

Data as of November 30, 2018

Countries with the most clinical trials in each subtype are highlighted in gray

CLL = chronic lymphocytic leukaemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; MCL = mantle cell lymphoma; PII = phase II; PIII = phase III; UK = United Kingdom; WM = Waldenström's macroglobulinaemia

Clinical Trial Availability by Region

Western Europe

France had access to the highest number of novel therapy trials (n=106) while Switzerland the fewest (n=19) (see Table 15). Among the subtypes, DLBCL had the most clinical trials involving a novel therapy (n=86). Of these 86 clinical trials, France had access to the most while Switzerland had access to the fewest. The subtype with the fewest clinical trials involving a novel therapy was WM (n=14) with Germany having access to the most (n=9). All countries examined in this region were involved in at least one novel therapy clinical trial for each subtype.

Eastern Europe

Poland had access to the highest number of novel therapy trials (n=60), while Serbia had access to only four. Neither Croatia nor Serbia were involved in a novel therapy trial for the subtypes under review.

Northern Europe

Sweden was involved in the highest number of novel therapy trials (n=33) while Lithuania was involved in only one which was looking at both FL and WM. In essence, no novel therapy trials for CLL, DLBCL, HL and MCL were available in Lithuania. Finland had at least one novel therapy available for each subtype under review except HL. A similar situation was seen in Norway where there were no novel therapy trials available for WM although at least one was available for the other subtypes.

Southern Europe

Most countries under review in this region were involved in at least one clinical trial involving a novel therapy with Italy having access to the highest number (n=97). Italy also had access to the highest number of novel therapy trials for DLBCL and FL. Conversely, Portugal had access to the fewest number of novel therapy trials with no novel therapy trials in HL.

Access to Clinical Trials Summary

While it is encouraging to see that most of the clinical trials underway focused on novel therapies, what is not so encouraging is their concentration in Western Europe. The role of population size appears not to be a factor. For example, both Germany and Turkey have populations of more than 80 million people, yet Turkey only has 26 phase II/III compared with 120 in Germany.

The lack of access to novel therapy clinical trials in countries outside of Western Europe likely means that patients in those regions are not receiving the best care especially those for whom a clinical trial may be their only treatment option.

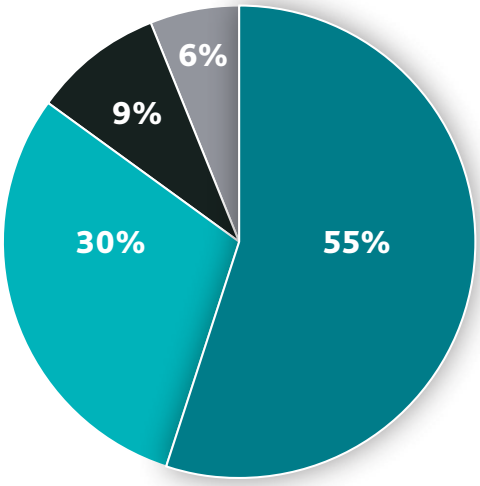
LCE recognises that the setting up of clinical trial research centres is expensive and requires significant clinical expertise; however, stronger efforts, support and development need to be made to make access to clinical trials easier so all those who wish to participate can.

Lymphoma Patient Experience and Quality of Life

To better understand the patient experience, LC conducted the GPS in 2018. This survey has been undertaken by LC every two years since 2008 and is now available in 19 languages. Its findings provide insights into the impact of treatment and care and the results are instrumental in helping LC and its members promote the patient voice and perspective.

Of the 6631 participants in the 2018 GPS, 1901 were from Europe. Of the 1901 European respondents, 1630 are included in this analysis who self-identified their country of residence. For this section of the report, given the sample size, LCE can only provide insights into each geographic subregion under review rather than country-specific findings.

Figure 4: Breakdown of Respondents by Region



Western Europe		Eastern Europe		Northern Europe	Southern Europe	Other
Andorra	Liechtenstein	Albania	Macedonia	Denmark	Cyprus	Israel
Austria	Luxembourg	Armenia	Poland	Finland	Greece	Turkey
Belgium	Monaco	Bulgaria	Romania	Lithuania	Italy	
France	Netherlands	Croatia	Slovakia	Norway	Portugal	
Germany	Switzerland	Czechia	Slovenia	Sweden	Spain	
Ireland	United Kingdom	Hungary	Serbia			

Initial Understanding of Diagnosis and Treatment

Survey respondents were asked to rate on a scale of 1-5 (1 being poor and 5 being very good) their understanding of their diagnosis and subtype after their initial diagnostic visit with their doctor. While the initial understanding of diagnosis was good or very good in all regions among 50% or more of respondents, the understanding of subtype characteristics was not, with only one-third of respondents indicating they had a good or very good understanding of their subtype's characteristics (see Table 16).

Table 16. Understanding of Diagnosis by Region

Region	Good/Very Good Understanding of Diagnosis, %	Good/Very Good Understanding of Subtype Characteristics, %
Western Europe	59	32
Eastern Europe	53	37
Northern Europe	52	33
Southern Europe	67	35

A similar pattern was seen when looking at understanding of diagnosis by subtype as well as subtype characteristics. Among respondents with HL, for instance, 65% indicated they had a good or very good understanding of their diagnosis but only 40% indicated they had a similar degree of understanding of their subtype's characteristics. HL was the most understood subtype (diagnosis and disease characteristics) with the least understood being mantle cell. For respondents diagnosed with MCL, 52% of respondents rated their understanding of their diagnosis as good or very good, but only one in four revealed a good/very good understanding of the specific characteristics of their type of lymphoma.

This shows there is scope for patient organisations and healthcare professionals to develop and disseminate more and better information on all subtypes.

Table 17 shows the degree of understanding of medical treatment options as well as the understanding of initial treatment if started immediately. Rating scale was the same 1 (poor) to 5 (very good) scale. While just half of respondents in Western and Southern Europe had a good or very good understanding of their medical treatment options, those in Eastern and Northern Europe did not. However, if treatment was started immediately, then the understanding was higher.

Table 17. Degree of Understanding of Medical Options

Region	Good/Very Good Understanding of Medical Treatment Options, %	Good/Very Good Understanding of Initial Treatment if Started Immediately, %
Western Europe	51	55
Eastern Europe	39	51
Northern Europe	39	49
Southern Europe	56	65

When looking at understanding of medical treatment options by subtype, 40% or more of respondents in all subtypes indicated they understood their treatment options well. However, when looking at understanding of initial treatment if started immediately, those with CLL and WM had the lowest understanding (31% and 32%, respectively), while those with HL and DLBCL had the highest level of understanding (64% for HL and 63% for DLBCL). It is perhaps not surprising that those with CLL and WM had the lowest level of understanding as often no treatment is initiated until active disease is present.

While 56% of respondents in Southern Europe had a good understanding of the side effects associated with their treatment, in the other regions less than half of respondents expressed a similar understanding (see Table 18). When looking at the degree of understanding as to how the side effects would be managed, while 43% of respondents in Southern Europe indicated they had a good or very good understanding, in the other regions, less than 40% indicated a similar understanding. In analysing the Southern Europe data in more detail, it may be relevant to note the high proportion of respondents based in Italy, which may have confounded the findings.

Table 18. Degree of Understanding of Potential Treatment Side Effects by Region

Region	Good/Very Good Understanding of Potential Side Effects, %	Good/Very Good Understanding of Initial Side Effect Management, %
Western Europe	47	37
Eastern Europe	43	39
Northern Europe	44	34
Southern Europe	56	43

Understanding of treatment side effects by subtype showed that those with aggressive lymphoma reported a higher level of understanding of potential side effects (over 53%) compared to those diagnosed with an indolent form. Within the indolent subtypes, there is a great deal of variance in their reported understanding. While 47% of respondents with FL indicated they had a good or very good understanding of potential side effects, only 28% of respondents with WM indicated the same degree of understanding. Understanding of side-effect management was under 50% for all subtypes with only 24% of WM respondents indicating they had a good or very good understanding.

These findings indicate there is significant scope for improving the quality of care and information when explaining side effects and their management to patients.

Physical Side Effects Affecting Quality of Life Since Diagnosis

LCE examined the three main physical side effects respondents indicated were affecting their quality of life by region (Table 19) and by subtype.

Findings showed that regardless of the region or subtype, fatigue was the physical side effect that affected the quality of life of most respondents. Respondents indicate that even if they raise this concern with their doctor, they are often not provided with helpful ways to manage their fatigue.

Hair loss was also an issue for respondents in all regions. While muscle weakness was an issue in Eastern, Northern and Southern Europe, in Western Europe changes in sleep patterns was reported more frequently.

Table 19. Top Three Physical Side Effects Affecting Well-being and Their Duration by Region

Region	%	Issue persisted 1-7 years, %
Western Europe		
Fatigue	79	60
Changes in sleep patterns	49	54
Hair loss	47	26
Eastern Europe		
Fatigue	71	57
Changes in sleep patterns	53	31
Hair loss	43	59
Northern Europe		
Fatigue	76	66
Changes in sleep patterns	55	55
Hair loss	53	23
Southern Europe		
Fatigue	70	55
Changes in sleep patterns	52	20
Hair loss	48	52

Side effects are the unwanted consequences of treatment and can be debilitating as well as an outward sign of illness, information that patients may not wish to make known.

Of greater concern, though, is that patients continue to experience side effects long after treatment is completed. When reviewing Tables 19, 20 and 21, please note many survey respondents had not yet reached 8 years post-diagnosis when completing the survey, which is why the data focuses on an upper limit of seven years. Some patients experience these issues for much longer.

For all respondents who indicated that fatigue was an issue, it remained so anywhere from one to seven years after treatment for more than 50% of respondents. Changes in sleep patterns and muscle weakness also continued to be bothersome.

Apart from fatigue, the physical side effects of greatest concern by subtype were hair loss (DLBCL, FL, HL, MCL) which is related to treatment often used for these subtypes, night sweats (CLL, WM), changes in sleep patterns (CLL, FL, WM), and muscle weakness (DLBCL, HL, MCL).

Medical Side Effects Experienced by Respondents

Table 20 shows the top three medical issues experienced by respondents both during and after treatment, as well as one to seven years following treatment.

Table 20. Top 3 Medical Side Effects and Their Duration by Region

Region	During treatment, %	After treatment, %	Issue persisted 1-7 years, %
Western Europe			
Neutropaenia	21	13	56
Tingling	17	12	57
Pain	18	10	57
Eastern Europe			
Stomach-related issues	22	10	51
Tingling	15	11	60
Issues with other organs	13	11	52
Northern Europe			
Stomach-related issues	33	14	58
Pain	29	14	33
Numbness	17	14	67
Southern Europe			
Stomach-related issues	24	12	66
Tingling	18	11	56
Numbness	18	11	54

Following completion of treatment, respondents indicated that medical issues did not go away and, in some cases, lasted for various lengths of time including up to eight or more years. When looking at the medical side effects by subtype, for the most part, neutropaenia was the most commonly experienced side effect followed by stomach-related issues and tingling. It is worth noting that neutropaenia is a common side effect of novel therapies, so it is likely this finding will continue in coming years.

While new and better treatments are needed, efforts are also needed to ensure that the associated side effects are not an impediment to improved care.

Given that the medical effects can endure for a long period after treatment, it is key that patients receive support and ongoing management.

Psychosocial Issues Experienced by Respondents

Table 21 shows the top three psychosocial issues experienced by respondents before, during and after treatment. The table also shows the percentage to which these psychosocial concerns remained a concern anywhere from one to seven years after treatment. While respondents did experience psychosocial issues prior to treatment, their prevalence or severity was relatively minimal when compared with respondents' experiences during and after treatment.

Fear of relapse was the psychosocial issue of greatest concern for all respondents.

Anywhere from one to seven years after treatment, it remained an issue for many of the respondents with those in Southern Europe reporting the highest degree of fear of relapse. Changes in relationships was also an issue for those in Western Europe, Northern Europe and Southern Europe. In Eastern Europe, financial stress was reported slightly more frequently than changes in relationships.

Table 21. Psychosocial Concerns by Region

Region	Before treatment, %	During treatment, %	After treatment, %	Issue persisted 1-7 years, %
Western Europe				
Anxiety	10	29	23	67
Changes in social relationships	8	32	25	49
Fear of relapse	4	21	35	69
Eastern Europe				
Changes in social relationships	5	31	16	53
Fear of relapse	3	21	29	68
Financial stress	10	26	13	56
Northern Europe				
Changes in social relationship	9	30	18	65
Concerns about body image/ physical appearance changes	3	29	24	62
Fear of relapse	1	16	37	69
Southern Europe				
Anxiety	20	28	23	63
Changes in social relationships	9	31	26	65
Fear of relapse	5	23	42	78

Within subtypes, changes in social relationships was a concern expressed by all. Fear of relapse was of concern for all subtypes except CLL. Within CLL the main three psychosocial concerns were depression, changes in social relationships and anxiety.

Information Sources

In all four regions, the doctor was the primary source of information during their patient experience, followed by websites (see Table 22).

When looking at the primary source of information by subtype, there was a slight difference with respondents with CLL tending to use a website more frequently than a doctor (67% vs. 64%, respectively) while respondents with WM used the doctor and websites equally, 69% for both.

It is worth noting the role of nurses here. In some countries the nurse may act as the provider of additional care and vital information. However, this will only be in countries where the role of nurse is clearly defined in this way, where the necessary training is provided, and the expertise acquired. In many countries, the profession of nursing may not be seen in that way and patients will depend entirely on their relationship with their doctor for any additional information or support about their disease. There is scope for future surveys to explore the nurse's role and how it varies from country to country.

Table 22. Primary Sources of Information during Patient Experience

Information Source	Western Europe, %	Eastern Europe, %	Northern Europe, %	Southern Europe, %
Doctor	73	76	74	83
Family/Friends	10	29	20	12
Nurse	38	20	39	28
Online blogs/social media	22	37	43	35
Other	5	4	10	5
Patient organisation	37	22	32	29
Website	64	58	73	61

Given that the doctor was the primary source of information, it is perhaps not surprising that over 60% of respondents in all regions told their doctor about their physical and/or medical side effects (see Table 23).

Unfortunately, less than 50% of respondents indicated that their doctor had been able to help.

Table 23. Communication of Topics of Concern during the Patient Experience

Topic	Western Europe, %	Eastern Europe, %	Northern Europe, %	Southern Europe, %
Told doctor about physical/medical issues	70	72	66	65
Doctor provided help for physical/medial issues	33	48	26	35
If fatigue was an issue, doctor/nurse provided referrals to usable support/information	22	34	14	24
Discussed fear of relapse with the doctor	43	37	39	38
Doctor helped alleviate the fear	18	28	21	23
Doctor/nurse provided referral to further usable support	40	32	26	38
Told doctor about emotional issues	36	34	30	33
Doctor helped with emotional issues	24	33	17	28
Clarification sought on things not understood	73	71	70	80
Doctor provided clarification/answered questions	61	56	52	55
Felt confident/comfortable voicing concerns to the doctor	54	50	44	48
Felt they had the right to take the doctor's time to discuss any of the above	55	55	53	66
Doctor encouraged discussion	38	43	27	29

For those in whom fatigue was an issue, few respondents in all regions indicated that their doctor or nurse had provided them with referrals to usable support or information, with only 14% of respondents in Northern Europe indicating they had received useful help.

While fear of relapse was discussed by some respondents in all regions, less than 40% of respondents in Eastern, Northern and Southern Europe raised the issue with their doctor (see Table 23). In Western Europe just over 40% of respondents discussed it with their doctor. In general, those who did raise their fear of cancer recurrence with their doctor did not find the doctor helpful, nor was referral to usable support particularly helpful.

Overwhelmingly, respondents in all regions sought clarification on issues they did not understand, yet only 61% of respondents in Western Europe, 56% in Eastern Europe, 52% in Northern Europe and 55% in Southern Europe indicated that their doctor was able to answer their questions (see Table 23).

When it came to talking about emotional issues with their doctor, less than 40% of respondents in all regions did and less than 40% felt that their doctor had been able to help.

Although respondents felt that they had the right to take the doctor's time to discuss their issues during their visit, very few respondents indicated that their doctor encouraged such discussions. This was especially noticeable in Northern and Southern Europe.

While doctors cannot be expected to give patients all the support they need, it would be helpful if they could refer them to resources where they can receive support. Patients need to be supported not only with treatment but also physically and psychosocially, and this support is needed throughout the patient experience.

Evaluation of Services

The 2018 GPS on Lymphomas and CLL investigated what other services respondents might find helpful (see Table 24). Respondents were asked to rate the services they had used using a scale of 1 to 5 with 5 indicating the service being of most help.

Table 24. Percentage of Respondents Who Rated Services as Level 5 (1 least helpful, 5 most helpful).

Service	Western Europe, %	Eastern Europe, %	Northern Europe, %	Southern Europe, %
Complementary therapist	14	6	14	11
Counsellor/psychologist	22	21	17	26
Dietitian/nutritionist	13	17	8	17
Pain management	9	14	9	12
Patient organisation/support group	35	33	19	27
Physical therapy	13	11	14	7
Social worker	7	6	6	8
Spiritual support	12	30	19	10

While the patient organisation/support group was viewed as being the most helpful service in Western, Eastern and Southern Europe, in Northern Europe respondents also found spiritual support to be helpful. In Western and Southern Europe, a counsellor/psychologist was viewed as being beneficial.

Table 26 shows the services respondents would be interested in accessing; the ones of greatest interest are highlighted in **gray**.

Regardless of the region, the service that all respondents were interested in was treatment information.

Other services in which there was great interest were complementary nutrition/fitness information, credible website links about the respondent's type of lymphoma and treatment suggestions, and patient organisation support. The service of least interest to all respondents in all regions was phone line support.

The services respondents expressed interest in are perhaps not surprising and are reflective of patients wanting information and support throughout their experience.

Table 25. Evaluation of Interest in Services

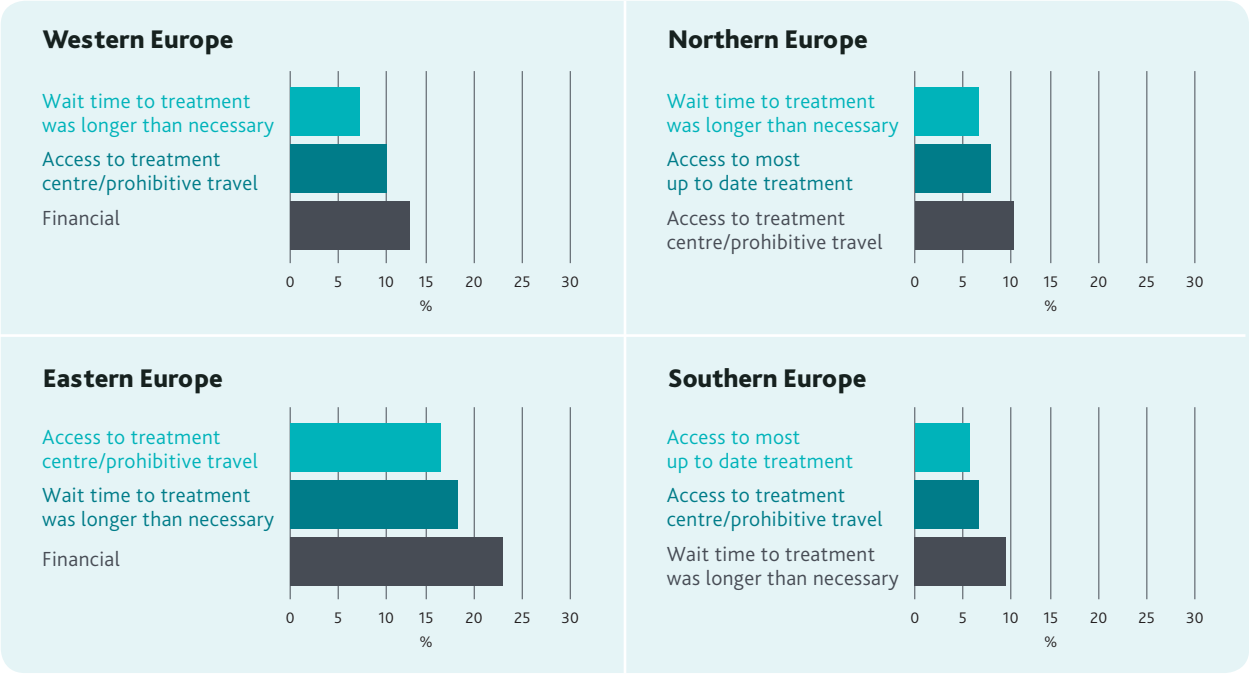
Service	Western Europe, %	Eastern Europe, %	Northern Europe, %	Southern Europe, %
Clinical trial options information	78	73	81	85
Complementary nutrition/fitness information	84	82	87	90
Credible website links about your type of lymphoma and treatment suggestions	84	82	87	90
Downloadable materials	83	79	82	86
Fatigue support	79	75	80	86
Hard copy material	72	73	67	68
If available, financial support	49	74	63	63
Support in navigating the insurance system (health, mortgage, life)	56	68	62	77
Treatment information	92	85	97	96
In-person support group	52	60	56	56
Information on available patient organisation services	80	77	81	89
Live education sessions	51	68	63	63
Online chat room and/or online patient support group	53	70	56	69
Patient organisation support	78	75	87	87
Phone line support	37	53	40	38
Professional emotional support	62	71	67	81
Professional physical support	59	69	67	82

Barriers to Care

Respondents were asked if they encountered any barriers to their care. The highest percentage (43) of respondents who did not experience any barriers to their care was in Northern Europe (see figure 5). Western (31%) and Southern Europe (36%) had similar percentages of their populations without any reported barriers.

The most barriers were reported in Eastern Europe, where 3/4 of patients indicated they had at least one barrier to care.

Figure 5: Top 3 Barriers to Care by Region (%)



The leading barrier in both Western (13%) and Eastern Europe (23%) was related to the financial impact of lymphoma. Access to treatment was the most reported barrier in Northern Europe (10%) and this was also a top issue in Western (10%), Southern (7%) and Eastern (16%) regions. For the Southern countries, wait time to treatment was the main concern (9% of respondents), also reported in Western (7%), Northern (7%) and Eastern (18%) Europe.

It is important to note that while all regions have patients reporting barriers to their care, the percentages of issues reported in Eastern Europe are at a much higher rate than anywhere else.

More needs to be done to ensure patients in these countries receive the treatment required in a timely manner, without causing undue financial stress for the patient and their family.

All patients with lymphoma deserve optimal care. Currently, there are significant disparities across Europe in accessing timely, adequate care. LCE is determined to improve this situation, working alongside other members of the lymphoma community.

Overall Conclusions & Recommendations

In summary, the 2019 Lymphoma Care in Europe Report demonstrates that patients in Europe continue to experience inequalities in accessing timely and adequate care.

Patients in Eastern Europe continue to have more challenges accessing care than anywhere else in Europe. Greater efforts are needed to improve uniform access to new therapies and find a way of making more clinical trials accessible so all patients in Europe can benefit.

While patients in Eastern Europe may have the above-mentioned challenges, they also report the most positive interactions with their doctor and are more likely to say their doctor was able to help them with their concerns. This points to the fact that even when therapy access is not ideal, patient-doctor communication is an important part of the patient experience and is valued.

Providing patients with the supportive care they need before, during and after treatment is a significant issue. Doctors cannot provide all the support a patient needs but effort can be made to ensure patients are referred to services that can help.

This includes ensuring patients have access to quality disease information, especially treatment information. Research has shown patients who feel well informed also report a better overall healthcare experience, regardless of the physical and medical issues they face as a result of their lymphoma and are significantly more likely to be active participants in their own care.

8 Areas of Need with Recommendations for Moving Forward

1 Credible, up-to-date, reliable statistics are difficult to find. The grouping of almost all lymphoma statistics under an NHL umbrella is unhelpful due to wide differences in symptoms, disease trajectory and treatment options amongst the more than 80 different subtypes.

Registries have a critical role, particularly for rare lymphomas. Information garnered from well-functioning registries that integrate patient-reported issues and clinical data can contribute to improved care and improved clinical trial design.

How LCE can help:

- LCE can provide perspective on what's important for a registry to include to maximise impact, how to best collect the required data, and how the registry could provide additional value to patients beyond data collection.
- LC is committed to providing an up-to-date, cohesive online resource centre that includes available lymphoma statistics and other relevant data in one place.

2 Four of the six clinical practice guidelines (CPG) reviewed have not been updated within the past two years, yet there have been new therapies approved for treating these lymphoma subtypes. Evidence-based CPGs must keep pace with regulatory approval of new therapy classes. Many doctors rely on guidelines to understand where a new treatment fits in the treatment paradigm to ensure they are providing optimal care to patients.

How LCE can help:

- LCE can provide input to the early-stage development and subsequent review of clinical guidelines to ensure the inclusion of patient-relevant topics, like appropriate symptom/side-effect burden tracking and long-term follow up needs.

3 Some countries do not publicise what lymphoma treatments are available. From the information that is publicly available on therapy access, it is apparent that therapies – especially novel treatments – are not uniformly available across Europe. There are pronounced access issues in Eastern Europe, but each of the other regions also have countries with limited access.

How LCE can help:

- LCE will devise individualised advocacy plans with interested members to improve transparency on what treatments are available to patients.
- LCE will work with members within Eastern Europe on individualised advocacy plans to improve the procedures used to determine the prices and reimbursement of medicinal products and improve access to therapies so patients receive optimal care.

4 A small number of countries have an abundance of clinical trials while others have very few. Many factors contribute to this. Regardless, if trials are held in communities where there is already an abundance of trials or a small population, it is very difficult to reach accrual targets and research becomes competitive. This seems counter-intuitive.

Most trials address relapsed/refractory disease, which LCE applauds as more treatment options are needed in all subtypes for patients whose lymphoma does not respond to therapy or where the disease returns. It is important to remember that patients, regardless of the line of therapy, continue to report short- and long-term issues that significantly impact their quality of life and future trials need to focus on therapies that have minimal or no side effects.

How LCE can help:

- LCE will partner with all relevant stakeholders to promote a regulatory change focused on reducing bureaucracy associated with clinical trials. This will encourage more doctors and patients to participate and will facilitate low- and medium-income countries to join clinical research.
- LCE is committed to finding ways to bring the clinical trial to the patient in need, on a country-by-country basis.
- Through the Lymphoma and CLL Community Advisory Board, LCE helps build research that answers questions and examines outcomes that are important to patients, their caregivers, and clinicians. LCE can helps to validate and integrate reliable Quality of Life and Patient Reported Outcomes (PRO) measurements to systematically capture meaningful health outcomes.

5 Fatigue is the most reported physical side effect that affects the quality of life for lymphoma patients, regardless of region or subtype. More needs to be done to alleviate the effects of fatigue.

How LCE can help:

- LCE champions the recognition of fatigue as a diminishing quality of life feature and will help to introduce active monitoring of fatigue in the lymphoma care pathway.
- LCE will create patient information about lymphoma-related fatigue, coupled with proven management strategies, to be disseminated widely through LCE member organisations.

6 Patients in Eastern Europe report more barriers to care than anywhere else, with financial issues being their primary concern.

How LCE can help:

- LCE can work alongside members to design policy proposals to address financial toxicity faced by lymphoma patients and their carers, such as tax reduction, reasonable accommodations at work (flexible work-schedules/working from home), insurance coverage and legal protection for employees.
- LCE can support patient and clinician awareness about available financial assistance.

7 Doctors and websites are the primary sources of information for patients, yet patients say the information they receive is often not enough (they want more) or doesn't answer their questions. It is critical that patients have access to credible, understandable information throughout their patient experience, but especially in the beginning.

A doctor's time may be limited in any appointment but if the doctor does not have the time to address all the patient's questions, they should direct them to other trustworthy sources of information and support. These could be other members of the medical team (i.e. nurses), local patient organisations, reliable websites, etc.

How LCE can help:

- LCE can help build an evidence-based framework of systematic questions to guide physician-patient communication that will facilitate a useful dialogue with patients about their emotional health, physical concerns and their individual treatment plan and personal care pathway, ensuring discussions with patients are conducted in a patient-centric manner.
- LCE can create plans with member organisations as needed to ensure the information on their websites and in resource materials is complete, medically vetted and up to date.
- LCE can connect doctors and clinics with local patient organisations who can provide additional information to patients, often without the time limitations experienced in clinic.

8 Most patients will not talk about their psycho-social concerns with their doctor, even if these issues are greatly impacting their quality of life. For the small percent that do, they report not receiving helpful information or referrals for useful support.

The psychosocial impact of the disease must be a focus of care even if it is something as simple as a referral to other places for support. It is important that physicians start the dialogue with patients by asking about their emotional health, let them know concerns like anxiety and fear of cancer recurrence are common and direct to other support when needed.

How LCE can help:

- LCE can help to build a systematic and comprehensive multidimensional follow-up for lymphoma patients, providing evidence-based information "beyond clinical care" to guide the choice on what should be included to meet patient expectations and unmet needs.
- LCE can connect doctors and clinics with local patient organisations who often are running successful support programs for patients that can help.

Glossary

AFM13: An anti-CD30 and anti-CD16A bispecific antibody for CD30-positive lymphomas.

AGS67E: An anti-CD37 ADC for NHL.

Apilimod dimesylate: A PIKfyve inhibitor for lymphoma.

Axicabtagene ciloleucel: Approved for DLBCL, transformed FL (TFL) or primary mediastinal large B-cell lymphoma (PMBCL) DLBCL, TFL or PMBCL not responding to chemotherapy (one or multiple therapy lines) and those ineligible for, or relapsing after, autologous stem cell transplant (ASCT); and in clinical trials for other lymphoma subtypes (MCL, indolent lymphomas), for R/R transplant-ineligible aggressive lymphoma or for R/R DLBCL in combination with a checkpoint inhibitor.

Bimiralisib: An oral selective dual PI3K/mTOR inhibitor in preclinical lymphoma models.

BGB-3111: A Bruton tyrosine kinase (BTK) inhibitor for DLBCL.

Buparlisib: A small molecule orally available PI3K inhibitor for DLBCL, MCL and FL.

Cirmtuzumab: An anti-ROR1 monoclonal antibody for B-cell CLL, SLL and MCL.

Duvelisib: A PI3Kδ and PI3Kγ inhibitor for previously untreated CD20-positive FL.

Epratuzumab: An anti-CD22 monoclonal antibody for previously untreated FL and NHL.

JCAR017: This treatment is being investigated in clinical trials for R/R patients with DLBCL not otherwise specified (de novo or transformed from indolent lymphoma), high-grade B-cell lymphoma, PMBCL or Grade 3B FL, after two prior lines of chemotherapy or failed ASCT. This CAR T cell product is also in clinical trial for patients with MCL who are R/R to one prior line of chemotherapy.

Mogamulizumab: An anti-CCR4 monoclonal antibody for cutaneous T cell lymphoma.

ONC201: An Akt/ERK inhibitor for the treatment of MCL and DLBCL.

Polatuzumab vedotin: An anti-CD79b ADC for DLBCL and FL.

Selinexor: A first-in-class SINE XPO1 antagonist for DLBCL

SNS-062: A BTK inhibitor for CLL, SLL, MCL, DLBCL and FL.

Tisagenlecleucel: Approved for DLBCL that does not respond to chemotherapy (one or multiple therapy lines) and those ineligible for, or relapsing after, ASCT.

TTI-621: A CD47-targeting recombinant fusion protein for DLBCL.

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LYMPHOMA COALITION

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Let's all ensure patients with lymphoma have access to accurate information on their specific subtype, their treatment options – including clinical trials – and are involved in the decision-making process when determining the course of their treatments.

know your subtype