LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

EUROPEAN

SUBTYPE REPORT

Hodgkin Lymphoma

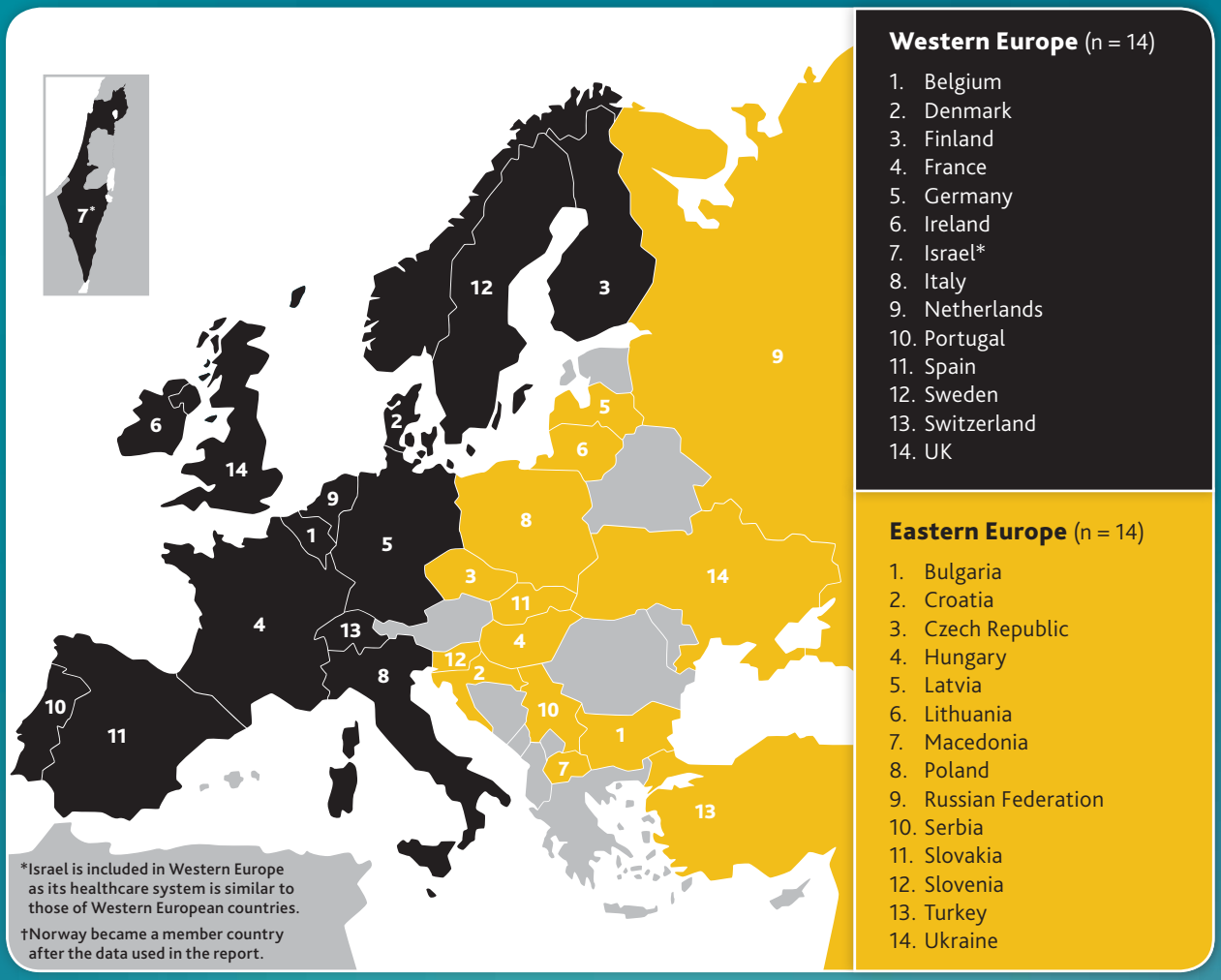
Review of patient access to care in Hodgkin Lymphoma (HL) in Europe, including:

1. Patient experience
2. Therapy access
3. Clinical trials

NOVEMBER 2017

This subtype report on HL focuses on Europe.

FIGURE 1: EASTERN AND WESTERN EUROPEAN LC MEMBER COUNTRIES



Acknowledgements

The Lymphoma Coalition would like to extend a special thanks to Prof. Engert whose collaboration and support greatly assisted our research and made this report possible.

Contents

Overview

Hodgkin lymphoma (HL) is a rare cancer that starts in B-lymphocytes. It can be classified into either nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) or classical Hodgkin lymphoma (CHL).

According to GLOBOCAN 2012, the last year data was reported, there were over 17,500 cases of HL diagnosed in Europe and 4,600 deaths due to HL. Incidence rates are higher in more developed regions and in males. It has two peaks of incidence by age, with a significant number diagnosed between the ages of 15-34 and another group diagnosed after age 50.

The overall 5-year survival rates of HL are high, being over 80%. Despite the success stories, there are still concerns:

- The long-term effects of treatment impacting overall quality of life. Patients are dealing with the effects of treatment for many years.
- Treating relapsed/refractory disease.

As well, there are discrepancies in incidence and mortality in Europe. Research studies have shown that countries with the lowest incidence rates of HL show the highest number of deaths and vice versa.[1] In 2012, Latvia, Serbia, Russia, Bulgaria and Macedonia had the highest HL mortality rates per 100,000 population amongst LC member countries.

There are continuing inequalities regarding treatment access amongst European countries. Eastern European countries overall have limited access to treatments (drugs and/or radiotherapy and/or adequate number of specialist healthcare professionals) compared to Western Europe.

Dr. Andreas Engert, Professor of Internal Medicine, Hematology, and Oncology at the University Clinic of Cologne and Chair, **German Hodgkin Study Group**, was interviewed to help identify recent improvements in care as well as disparities that require investigation.

Recent advances include:

- The identification of thymus and activation-regulated chemokine/CCL17 (TARC) as a possible biomarker.
- The increased use of PET scans to stage, restage and to guide response-adapted therapy.
- The introduction of immune checkpoint inhibitors to treat HL.

Major gaps that must be addressed in the treatment and care of HL patients include:

- Radiation use in early stage patients.
- Better treatment options for patients who are initially diagnosed with advanced stage disease.
- More treatment options for older HL patients (age 50+).
- More research into the long-term effects and outcomes of novel therapies.

While the overall survival rate for HL is good in relation to many other lymphomas, there is still work to do to ensure all patients can be effectively treated and enjoy a good quality of life post-treatment.

Hodgkin Lymphoma Overview

Hodgkin lymphoma is named after Dr. Thomas Hodgkin, a British pathologist who first described the disease in 1832. It is a cancer of the lymphatic system which originates in specialised white blood cells called B-cell lymphocytes. B-cells are responsible for creating antibodies or immunoglobulins which fight infections.

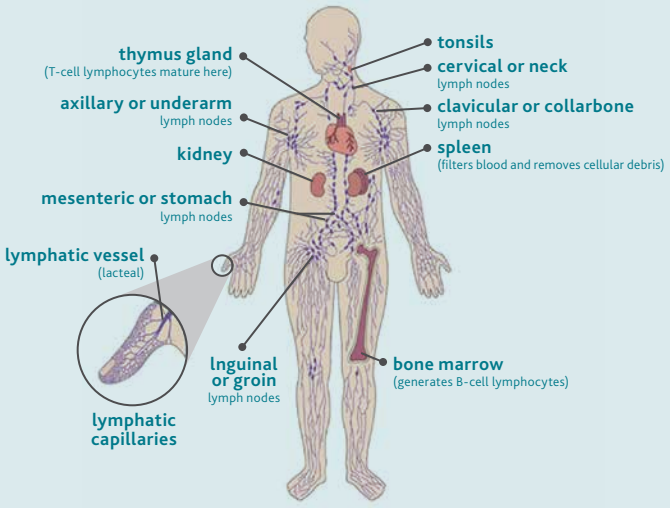
Cancer is the uncontrolled growth of abnormal cells. It is believed there is an error in the programming of cancerous cells caused by DNA damage that allows them to rapidly multiply indefinitely instead of self-destructing at the end of their normal limited lifespan.

In the case of HL, the abnormal cells usually present are called Hodgkin cells (named after Dr. Hodgkin) and Reed-Sternberg (RS) cells, named after Dorothy Reed who described the cells in 1902 and Carl Sternberg, who provided the first microscopic description of HL in 1898. These cells can only be found in Hodgkin lymphoma, which distinguishes it from other lymphomas and other diseases of the lymphatic system.

HL accounts for 10% of all lymphomas and less than 0.5% of all cancers diagnosed globally.[2] There are higher rates of HL in developed countries.

It is most common in young adults, primarily occurring in adults aged 20-34, and has a secondary peak of incidence after age 60.[5]

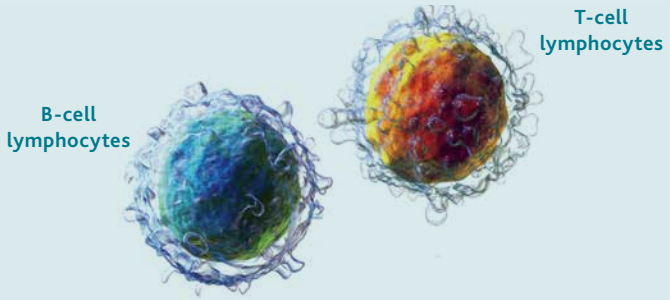
FIGURE 2: LYMPHATIC SYSTEM



The lymphatic system is a network of vessels, tissues and organs that maintains fluid levels in the body and protects the body against infection and disease.

Source: Diagram adapted from The Open University, SXR376 Preparatory Reading, Figure 1.2

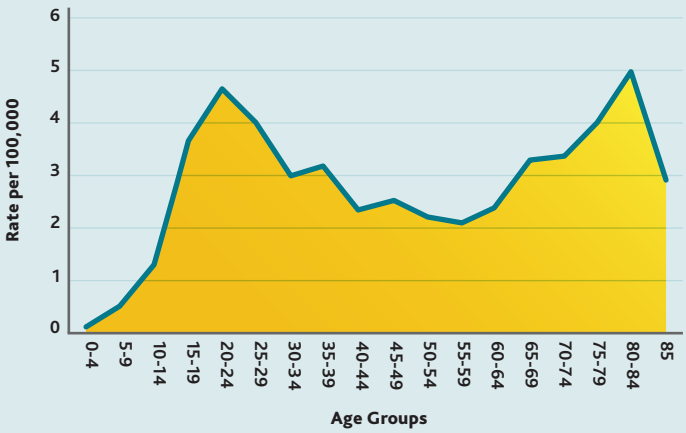
FIGURE 3: LYMPHOCYTES



Lymphocytes are types of white blood cells which help the body identify and get rid of foreign organisms like bacteria, viruses and parasites.

Source: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. - Own work

FIGURE 4 AGE SPECIFIC INCIDENCE OF HL[5]



Centre for Cancer Registry Data (ZfKD), Robert Koch-Institute

The World Health Organization classification of lymphoid neoplasms recognizes two major subtypes of HL.[6]

1. Classical Hodgkin lymphoma (CHL)

2. Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

It is not known what causes Hodgkin lymphoma.

- Siblings of HL patients have an above-average risk of developing this cancer but the significance of the family relationship as the primary cause is not known.
- The Epstein-Barr virus (EBV), which causes mononucleosis, is suspected to be linked to an increase in the risk of developing HL. The genetic material of EBV has been found in HRS cells. However, the fact remains that a clear majority of EBV infected people do not develop HL and more than half of all HL patients have no evidence of a previous EBV infection.

Potential factors that lead to the development of HL may be lifestyle-related, environment-related or changes that have occurred to the immune system.

Some patients will show no symptoms at all and will be diagnosed incidentally. In other instances, the patient may go to the doctor with one of the following common signs and symptoms:

- Painless swelling of lymph nodes in the neck, armpits or groin
- Persistent fatigue
- Fever and chills
- Night sweats
- Unexplained weight loss - as much as 10 percent or more of body weight
- Loss of appetite
- Pruritus (itchy skin)
- Alcohol intolerance or pain in lymph nodes after drinking alcohol

The presence of these symptoms cannot be the only basis of a HL diagnosis.

A biopsy is necessary to diagnose HL and determine the subtype. Other tests that might be performed include complete blood counts, erythrocyte sedimentation rate (ESR) that detects inflammation, metabolic panel to check liver and kidney function, testing for HIV and hepatitis B and C virus infections, as well as positron emission tomography (PET) and computed tomography (CT) scans to determine where the disease is present.

Classical Hodgkin lymphoma (CHL)

CHL is most commonly a B-cell derived cancer comprised of HRS cells. **Classical HL accounts for 90-95% of all HL diagnoses.**

The most common site for CHL are in the neck, under the arms and in the chest. CHL will typically start in the lymph nodes and often spreads through the lymph vessels from one lymph node to the next in a predictable order.[24] CHL may also spread to other areas and organs outside of the lymphatic system.[3]

TABLE 1. CHL SUBTYPES

Classical Hodgkin lymphoma (CHL) Subtypes	
Nodular Sclerosis	**Lymphocyte-Rich**
• Most common subtype, accounting for 60-80% of CHL. • Most common in adolescents and adults under age 50, but it can occur in people of any age. • More common in women than men. • Tends to start in lymph nodes in the neck or chest. • The involved lymph nodes contain HRS cells mixed with normal white blood cells. The lymph nodes often contain a lot of scar tissue, which is where the name nodular sclerosis (scarring) originates. • Most patients are cured with current treatments.[7]	• Accounts for less than 5% of CHL. • It usually occurs in the upper half of the body and is rarely found in more than a few lymph nodes. • The cancer may be diffuse (spread out) or nodular in form and is characterized by the presence of numerous normal appearing lymphocytes and classic HRS cells. • Lymphocyte-rich CHL has some features that are intermediate between other CHL and NLPHL. • This subtype of HL is usually diagnosed at an early stage in adults and has a low relapse rate.[7]
Mixed Cellularity	**Lymphocyte-Depleted**
• Accounts for about 15-30% of CHL. • Primarily affects older adults. • More common in men than in women. • It can start in any lymph node but most often occurs in the upper half of the body. • The lymph nodes contain many HRS cells in addition to several other cell types. • More advanced disease is usually present by the time this subtype is diagnosed.[7]	• Very rare; diagnosed in less than 1% of CHL. • It is seen mainly in older people. • More likely to be found in lymph nodes in the abdomen as well as in the spleen, liver, and bone marrow. • Abundant HRS cells and few normal lymphocytes are present in the lymph nodes. • Usually not diagnosed until it is widespread throughout the body. • Aggressive disease.[7]

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is rare, accounting for 5-10% all cases of HL.[3]

The cancer cells in NLPHL are variants of RS cells called LP cells (for 'lymphocyte-predominant') or popcorn cells (because they look like pieces of popcorn). Most patients present with enlarged lymph nodes in the neck or axilla (armpit) regions. It tends to grow at a slower rate than CHL and be diagnosed at an earlier stage. It can occur at any age and is much more common in men than women. Treatment is usually successful, however relapses are common, sometimes many years after the initial diagnosis.

NLPHL can have varied growth patterns, including diffuse areas and/or numerous T-cells. It is important for any patterns to be noted in the diagnostic report as some are associated with more advanced disease and higher rates of relapse. Overall, survival is still good with appropriate treatment.

Patients may have a T-cell histiocyte-rich large B-cell lymphoma (THRLBCL)-like transformation of NLHPL. Having features of THRLBCL is associated with a more aggressive disease, requiring different clinical management.

For more details on the Staging, Prognosis and Biology of HL please go to Appendix A, B & C.

The Patient Experience

It is important to understand the patient experience and their quality of life, from diagnosis through to the point they are no longer experiencing effects from their disease or any adverse effects from treatment. LC conducts a global survey of patients every two years, that is distributed within the patient community. The survey is evaluated and used to guide LC and its member organisations in planning patient activities and advocacy.

The 2016 LC Global Patient Survey (GPS) had over 4,000 respondents of which 933 were identified as HL patients. This includes 518 from Western Europe and 199 from Eastern Europe.

The patients and their caregivers were asked questions about their treatment, physical and psychosocial effects, barriers to care and factors affecting their well-being.

For this report LC compared the experience of patients in Western Europe and Eastern Europe to other non-European member countries.

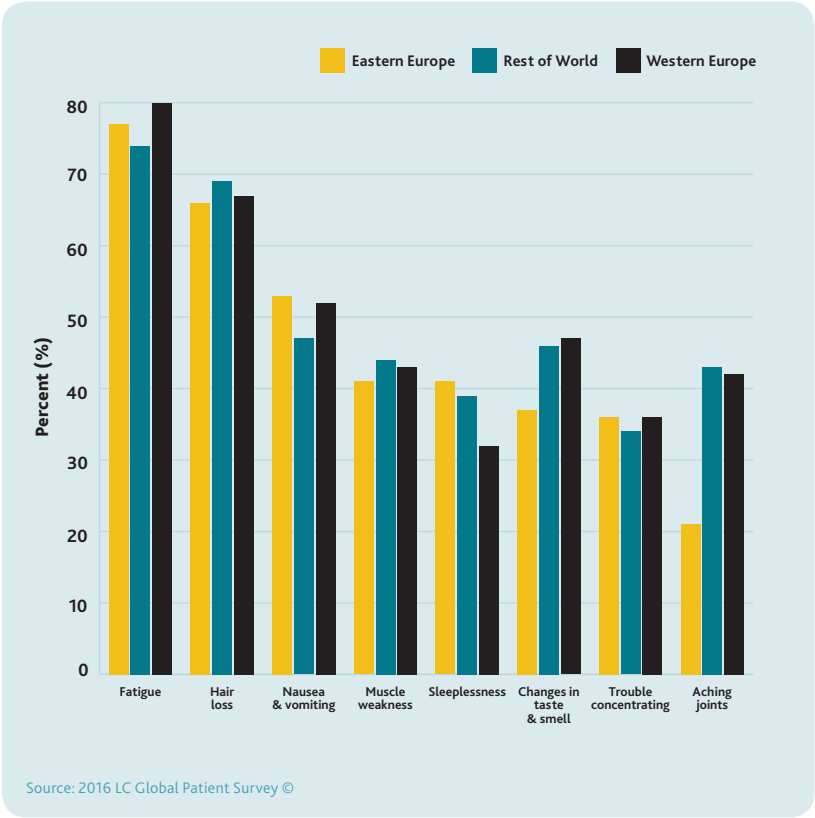
Physical and Medical Concerns

The toxicity of HL treatments has long been a concern for patients, healthcare practitioners and researchers. **91% of patients in Eastern Europe and 93% of patients in Western Europe reported experiencing physical conditions that impacted their well-being since diagnosis.**

Many new therapy combinations are looking to decrease the short-term and long-term side effects of treatments and the hope is that newer treatment protocols will see more remissions with fewer negative effects.

When looking at the physical issues impacting well-being faced by patients (Figure 5), fatigue is a major cause of concern for all respondents irrespective of region. Hair loss, nausea and vomiting are also major concerns for all respondents with HL during treatment. Aching joints was a greater cause of concern in Western Europe than in the Eastern European countries.

FIGURE 5. PHYSICAL CONDITIONS IMPACTING WELL-BEING SINCE DIAGNOSIS



Source: 2016 LC Global Patient Survey ©

Primary physical condition reported by patients:

Fatigue

Patients who reported fatigue as a physical condition;

77%
Eastern Europe

80%
Western Europe

Cancer-related fatigue occurs frequently in patients with HL and has a major impact on their quality of life. According to a study carried out by Behringer, Karolin, et al. fatigue is an important factor preventing survivors from social reintegration and may also have an impact on patients' treatment outcome.[14] **Understanding fatigue and the repercussions it may have during and post treatment on patients is an important factor that needs to be addressed particularly when treating HL survivors.[14]**

66% of patients in Eastern Europe and 58% of patients in Western Europe reported experiencing medical issues due to their HL or its treatment.

The medical concerns resulting from HL or its treatment faced by patients was more varied across the regions as seen in Figure 6. Stomach related issues were a much higher concern in Eastern Europe at 23%, while in Western Europe it was at 15%. Other concerns that were higher in Eastern Europe were problems concerning other organs, heart-related issues and diarrhoea.

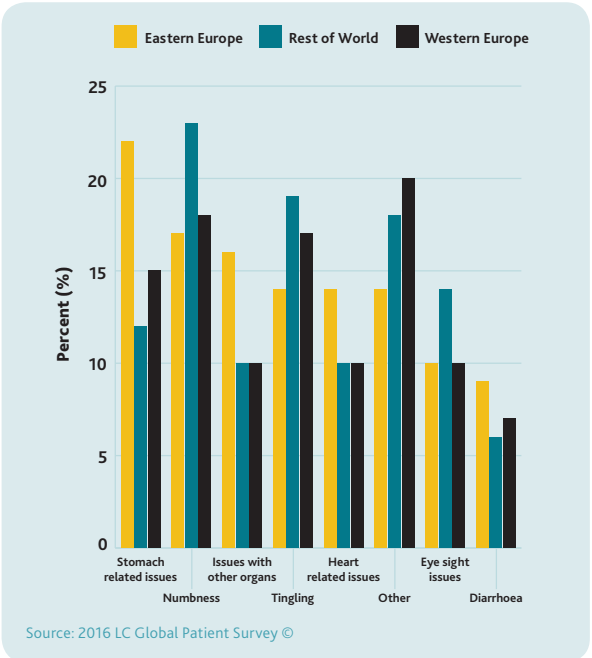
The burden of disease is carried for many years post treatment for some patients.

Long term survivors of HL are most at risk of developing secondary cancers, cardiovascular disease, hypothyroidism and fertility issues.

The incidence of these issues increases over time. A tailored monitoring programme needs to be established for each patient based on age and severity of symptoms as well as response to treatment.

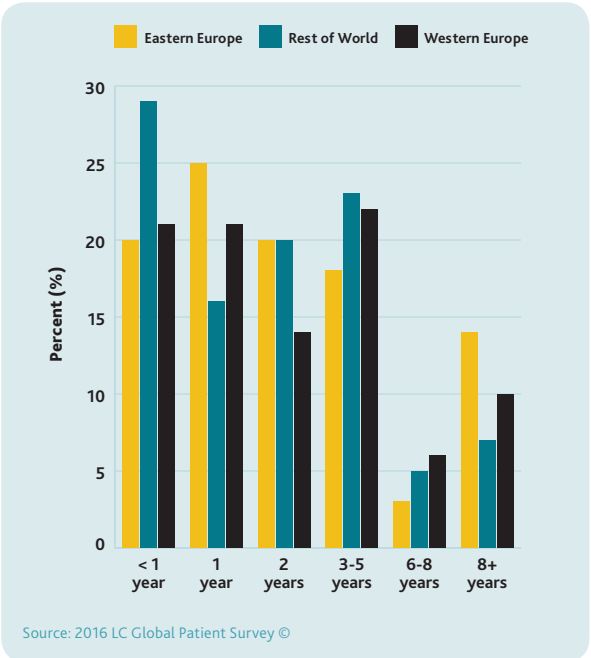
Over 20% of patients from Western Europe still suffered from issues 3-5 years after their treatment. The effects of treatment at the 8-years and onwards mark was felt most acutely by respondents in Eastern Europe.

FIGURE 6. MEDICAL ISSUES DUE TO HL OR ITS TREATMENT



Source: 2016 LC Global Patient Survey ©

FIGURE 7. TIME LENGTH OF ISSUES



Source: 2016 LC Global Patient Survey ©

Communication with Healthcare Professionals

Healthcare professionals and palliative care providers can play a major role in easing physical and emotional concerns for patients. The LC 2016 GPS asked patients if they had discussed their emotional and physical concerns with their doctor to determine if the level of support received from doctors was adequate. While most respondents regardless of region had said they communicated their concerns (Figure 8), overwhelmingly most responders indicated that the doctor had only been able to help them somewhat or not at all (Figure 9).

Healthcare providers are not always able to provide all the information patients need; often due to time constraints and limited availability of resources. Here too, healthcare practitioners have an opportunity to work with patient organisations to help patients with their emotional and physical concerns with timely and accurate information.

FIGURE 8. PATIENTS COMMUNICATING EMOTIONAL/PHYSICAL CONCERNS TO DOCTOR

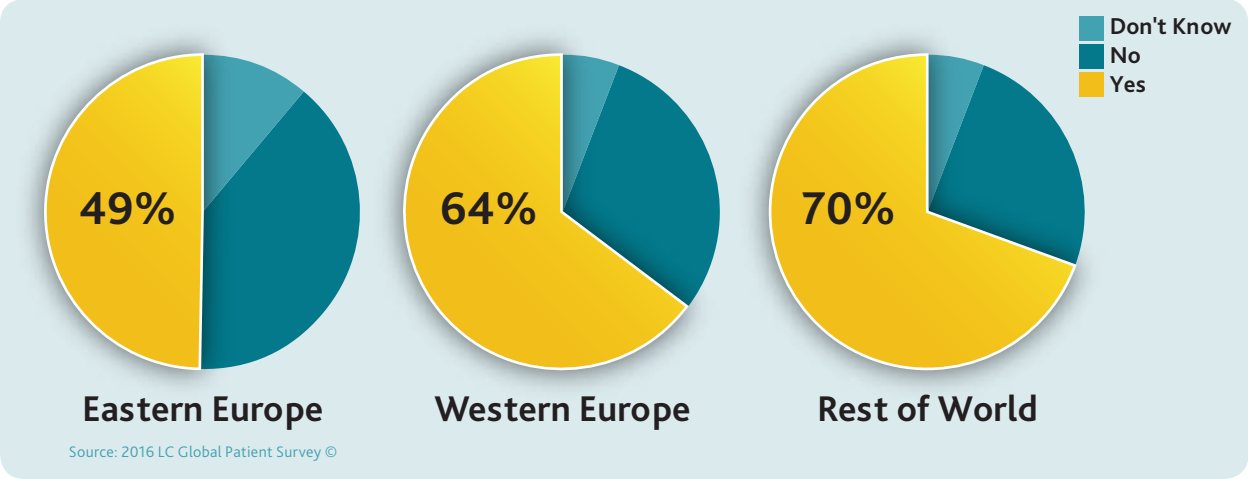
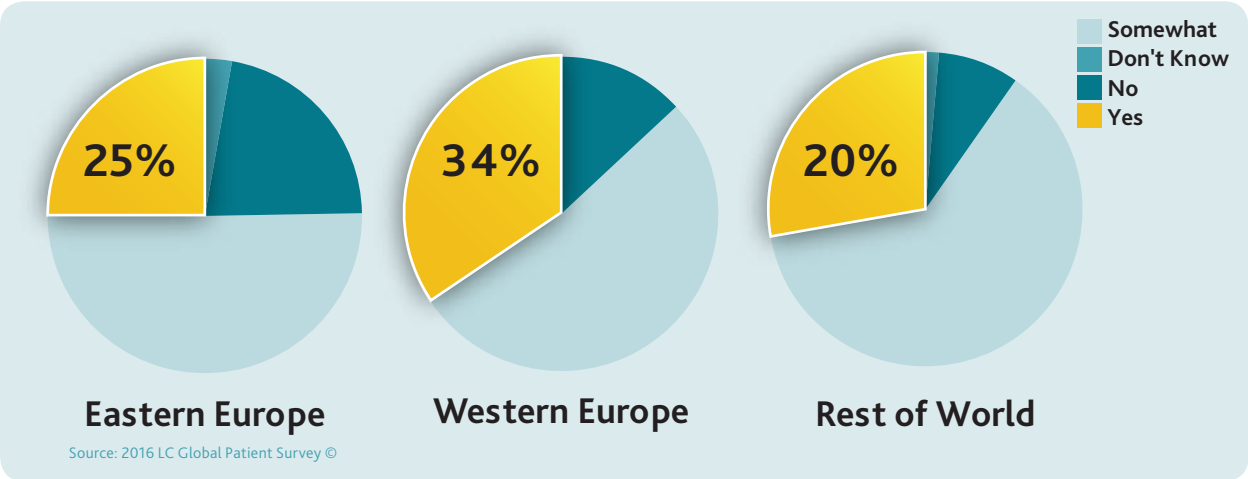


FIGURE 9. WAS THE DOCTOR HELPFUL?



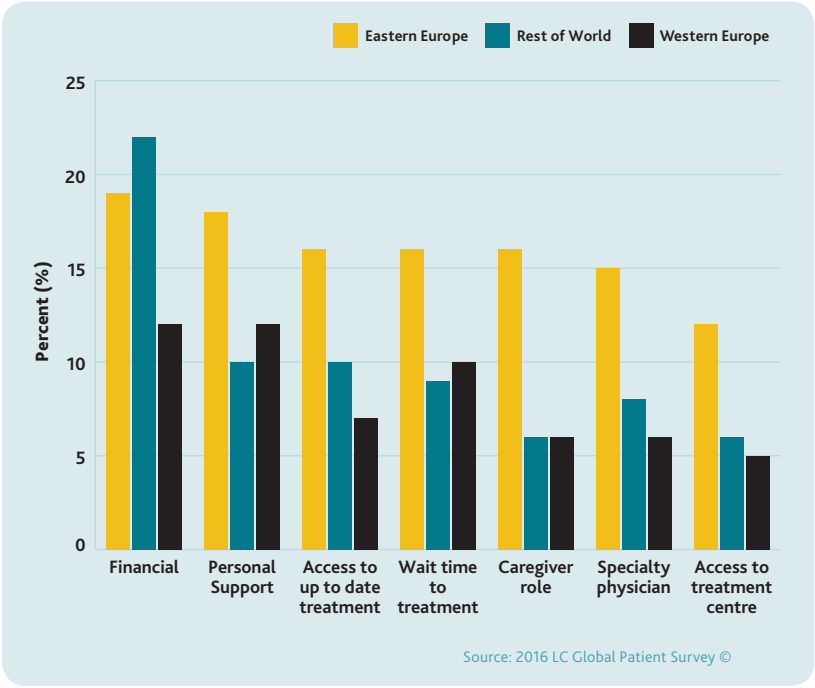
Barriers to Treatment

Overall the barriers to treatment were considerably higher in Eastern Europe than in Western Europe (Figure 10).

63% of patients in Eastern Europe reported experiencing barriers to treatment compared to 41% of patients in Western Europe.

There are many reasons why a patient may not be able to access treatment and the 2016 LC GPS aimed to highlight the main barriers they faced. The two main barriers in Europe are financial concerns and lack of personal support. This highlights the fact that patients require both clinical as well as social support during their treatment.

FIGURE 10. BARRIERS TO TREATMENT



The myriad of barriers faced by patients are intertwined and can make other physical and emotional issues more pronounced. Living with any form of cancer can impede a person's ability to earn a living, either due to the treatment side effects or because patients need to take time off for treatment, tests etc. If personal support is lacking or if a patient cannot give up their caregiver role, then even if they have access to treatment they can't receive it due to their personal circumstances. Patients face many challenges on their journey and the aim should be to provide optimal care with support structures in place allowing patients' access to not only a specialist physician but also up-to-date treatment.

Primary barriers to treatment:

- Financial
- Personal Support

Patients who reported financial issues as a primary barrier;

19% Eastern Europe

12% Western Europe

Patients who reported personal support as a primary barrier;

18% Eastern Europe

12% Western Europe

Psychosocial Effects

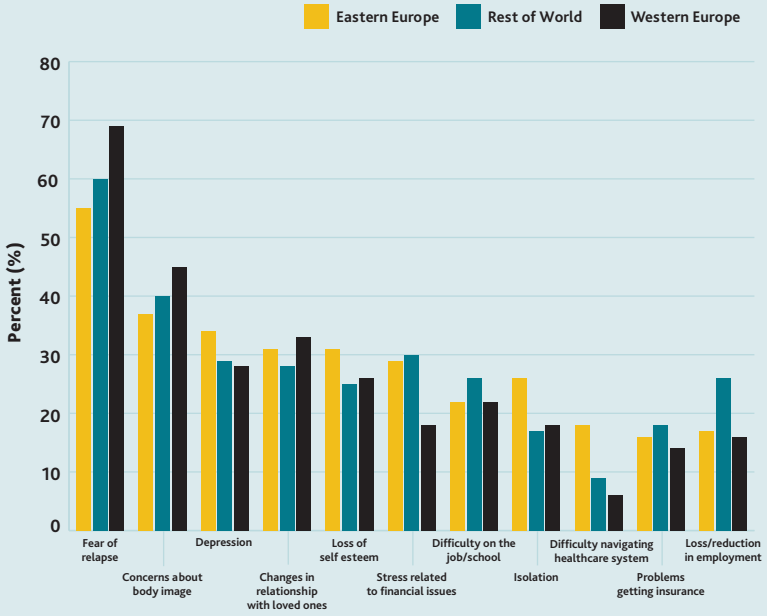
85% of patients in Europe reported experiencing psychosocial issues.

Psychosocial effects encompass the psychological and emotional well-being of the patient and how it impacts their day-to-day life. Questions were included in the 2016 LC GPS to assess the conditions that have had the greatest impact on the patients' sense of well-being.

As seen in Figure 11, fear of relapse is the highest cause of concern for patients globally, which is seen among patients with all lymphomas; followed by concern about body image.

Worldwide, the fear of relapse was highest in Western Europe, as was concern about body image. In Eastern Europe, higher rates of depression and loss of self-esteem were reported. Depression and the multitude of stressors at every stage of a patient's journey is especially important to highlight because it can lead to a sense of isolation and has the potential to aggravate psychological and physical symptoms. Healthcare professionals and palliative care providers can play a major role in easing patients' concerns, both physical and emotional. Healthcare providers and patient support organisations should work in tandem to create a more inclusive and comprehensive support structure for patients.

FIGURE 11. FACTORS AFFECTING SENSE OF WELL-BEING



Source: 2016 LC Global Patient Survey ©

Primary concern for patients:

Fear of Relapse

Patients who reported fear of relapse as a concern;

55%
Eastern Europe

69%
Western Europe

As a result of the numerous quality of life problems faced by HL patients, LC has developed a free patient support app called Lyfe. It offers:

- Insightful articles and practical tips designed to help during all stages of the patient journey;
- Relaxation tools;
- A community section, which allows patients and support-givers to share their stories and connect with others who are dealing with similar circumstances—locally, nationally and across the globe.

Lyfe is available in English, French, German and Spanish. Find out more about the app on the LC website or get in on Google Play or download on the App Store for iOS.

Treatment

Hodgkin lymphoma is a type of cancer with a high cure rate if the patient receives an optimal and consistent therapy by an experienced hospital or treatment centre.

- Approximately 80% of adult patients achieve a complete remission.[8]
- Patients with early stage Hodgkin lymphoma can be cured in over 90% of cases.
- Good long-term treatment results and complete recoveries can even be achieved in patients with relapsed Hodgkin lymphoma.

Multi-agent chemotherapy, often in combination with radiation therapy, is the mainstay of management of HL, and treatment intensity is tailored to the risk of relapse.[25]

Currently patients with limited stage HL are treated with ABVD, followed by involved field radiation therapy (IFRT).

In early stage patients, there is not enough evidence to suggest who will benefit from radiation therapy (RT) and who will not. As a result, doctors may be giving RT to those who don't need it and exposing them to unnecessary radiation.

It is the advanced stage HL (which are patients with disease staged III or IV or I and II with 'B') that may require more intensive therapy.

Diagnostic accuracy and assessing stage migration using PET scans are essential to provide the right level and dosage of treatment to reduce future comorbidities and toxicities related to therapies, particularly secondary cancers and cardiovascular disease.

The role of PET scans has been evolving recently in the treatment and evaluation of HL. It is an important tool in the initial staging and response assessment. PET scans have shown great accuracy when used to stage and restage patients with HL. The NCCN recommends that PET scans be used for initial staging and then again at the end of treatment to evaluate any residual mass.

Area of concern in HL:

Lack of evidence concerning who will benefit from radiation therapy.

Patients age 50+ often don't respond as well to treatment.

Patients diagnosed with advance stage HL require intensive treatment that is highly toxic.

Long-term outcomes of new therapies are unknown.

In 2007, Gallamini et al. published the dramatic results of a retrospective study describing the prognostic significance of an early interim PET scan in advanced HL.[11] Many healthcare practitioners will conduct an interim scan to assess whether the patient is responding to treatment and use it to guide dosage of the remaining cycles of treatment. Response adapted therapy can not only eliminate unnecessary treatments in low-risk patients but also give the opportunity to those experiencing treatment failures to try new approaches.

Intermediate stage patients, especially those who are under the age of 60 and have a higher tolerance for intensive treatment, can be treated with BEACOPP in escalated dose.

Patients age 50 and up often have a poorer prognosis and they suffer adverse reactions from the toxicity of chemotherapy more often than younger HL patients.

Advanced stage HL is usually treated by ABVD or BEACOPP and radiation therapy (RT) is only used if residual lymphoma is present. Current treatment available to patients with advance stage disease fails to cure as many as 20-30% of patients when treated with ABVD, leading to a secondary intensified treatment. This approach will often incur major toxicity and is only successful on average in 50% of patients.[12, 13]

For patients who are initially diagnosed in advanced stages and require more intensive treatment, the treatment has increased toxicity and often has long-term effects which can greatly impact quality of life. More research should be targeted to this group. Dr. Engert believes there is not enough of an impetus from research companies to fund trials to find less toxic first-line treatments for advanced stage patients due to the small population size.

As mentioned before the cure rate for HL is high, however, in the relapsed/refractory setting the survivorship is lower. For relapsed patients, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the recommended choice of treatment.[8]

Targeted therapies such as brentuximab vedotin are approved for treatment of patients failing ASCT and who have had multiple relapses.

To see what the current treatment recommendations are, as per ESMO and NCCN, please see Appendix D. It should be noted that the NCCN listing was updated in 2017. ESMO on the other hand has not updated its guidelines for the treatment of HL since 2014. In an email correspondence they have suggested that the guidelines will be updated late 2017 or early 2018.

Recent Developments in HL:

PET scans have shown great accuracy when used to stage and restage patients with HL.

Immune checkpoint inhibitors are one of the most exciting advances for patients.

Despite the use of best available therapies, some patients will develop relapsed or refractory HL for which effective treatment options are limited. To meet the needs of these patients, new therapies are being tested in patients with HL and results are encouraging. These include agents that deliver chemotherapy to the interior of cancer cells using specific targets on the cell surface (antibody-drug conjugates) and agents that enable the patient's immune system to eliminate HL cells (checkpoint inhibitors).[23]

The use of immune checkpoint blockades represents a new paradigm in the treatment of HL. Immune checkpoints help the immune system identify what is foreign and should be eliminated from the body. The immune system, when working properly, can identify and get rid of cancer cells. In recent years, research has shown that cancer can take over certain immune checkpoints to evade destruction and ensure survival. **The introduction of programmed cell death protein 1 (PD-1) inhibitors as a viable treatment for HL has been one of the most exciting advances for patients.**

Pembrolizumab is a PD-1 inhibitor that was approved by the European Commission (EC) in 2017 to treat adult patients with relapsed/refractory CHL, who have progressed after receiving an autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.[27] Another example of a PD-1 inhibitor approved by the EC is nivolumab, which has also been approved for patients that have relapsed or progressed despite a SCT and BV treatment.[28]

Trials are now underway to study the efficacy of nivolumab and pembrolizumab in a first line setting.[29,30]

How Do PD-1 Inhibitors Work?

PD-1 is a checkpoint protein on T-cells. They usually help the T-cells determine which cells to attack and which to leave alone. When the PD-1 on the T-cell binds to the target cell's receiver, called PD-L1, then the T-cell knows to leave the target cell alone. Many cancer cells have large amounts of PD-L1 which is how they evade an immune response.

Monoclonal antibodies (mABs) that target either PD-1 or PD-L1 can block this binding, T-cells can then detect cancer cells to be attacked, and help kickstart an immune response against the cancerous cells.

HL has a high cure rate and with the introduction of newer therapies the impression is that drugs are getting safer, but there aren't enough randomised trials to prove such is the case. Long-term outcomes cannot be ignored, and future research should be encouraged to analyse long-term effects, ensure improved survivorship results and lasting good quality of life.

Recent Advance: Biomarkers

Thymus and activation-regulated chemokine/ CCL17 (TARC) is highly and specifically elevated in this disease and has been proposed as a possible biomarker in HL patients.[10]

International Lymphoma Epidemiology Consortium (InterLymph) is an open scientific forum for epidemiologic research in lymphoproliferative disorders.

Established in 2001, the Consortium is an international group of scientists who undertake research projects that pool data across studies to better understand lymphoma causes and risk factors.

Listen to Prof. Ruth Jarrett talk about the significance of biomarkers, such as EBV and TARC and outlining the research being carried out by the Hodgkin Lymphoma Working Group from the InterLymph Consortium.

youtu.be/n5KMrk7dPgo

Therapy Access

LC looked at access to treatment protocols in LC member countries in Europe to determine the availability of HL therapies. A list of these treatment protocols can be found on the LC website.

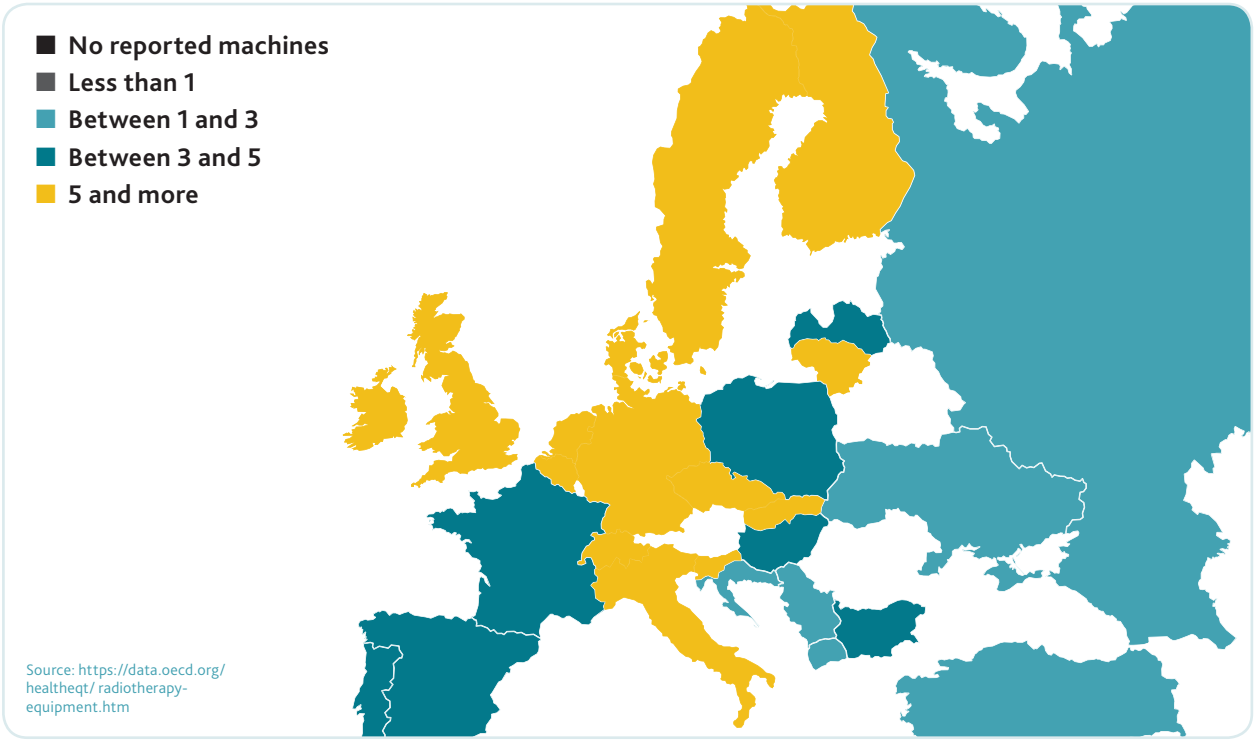
To determine what treatments should be accessible to HL patients in member countries, LC reviewed the information from both the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO), as shown in Appendix D, Table D1 and D2. Table D4 gives an overview by country of how many of the therapies that are recommended in the ESMO guidelines and the NCCN listings have regulatory and funding/reimbursement approval.

Standard therapies for front-line treatment of HL include the chemotherapy regimens ABVD and BEACOPP, and may include radiation therapy.

ABVD is currently available and fully funded in most European countries, except Slovakia, Bulgaria and Portugal. It is similar for BEACOPP, with the exceptions being Slovakia, Lithuania, and Portugal.

While analysing data on access to RT, we looked at the availability of RT equipment in Europe through the Directory of Radiotherapy Centres (DIRAC) database, managed by the International Atomic Energy Agency. As of July 2012, Europe had 1286 active radiotherapy centres. As seen in the Figure 12, Eastern Europe has far fewer machines per million people than Western Europe. The discrepancy can have major repercussions for patients who need to undergo RT. Some patients may not be able to travel long distances, while others may not be able to afford it. **Countries in Eastern Europe need to expand and modernize their equipment to ease the economic and psychological burden for patients.**[26]

FIGURE 12: NUMBER OF RADIOTHERAPY MACHINES PER MILLION PEOPLE



Treatment of relapsed or refractory disease may involve more chemotherapy, an autologous stem cell transplant (ASCT), or treatment with a novel therapy.

In the relapsed/refractory setting, there is a wide discrepancy among countries in terms of the protocols with regulatory approval compared with those that were funded/reimbursed.

For this report, access to the following novel therapies in Europe were tracked as shown in Figure 13: brentuximab vedotin; nivolumab; pembrolizumab.

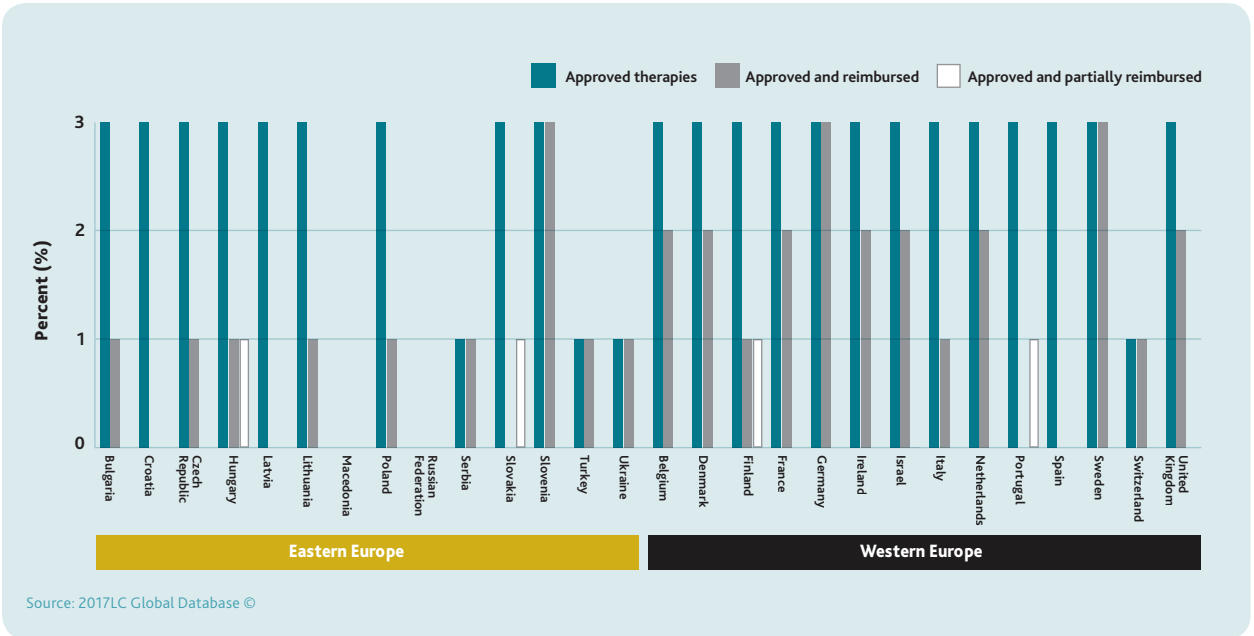
Brentuximab vedotin (BV) is a monoclonal antibody that attaches to a protein called CD30 on the surface of HL cells.[25] Once attached, it delivers a drug into the cancer cell that interferes with cell growth and causes it to die. It is used to treat adults with HL if the cancer has come back or has not responded to an autologous stem cell transplant (ASCT); when patients have had an ASCT but are considered to be at increased risk of the cancer coming back or not responding; when the cancer has come back or has not responded to at least two other therapies and when ASCT or multi-agent chemotherapy (a combination of cancer medicines) cannot be used.

Out of the three novel therapies examined, BV is approved and reimbursed most often. In Eastern Europe, nine out of the fourteen member countries provide funded access to the drug. The countries that **do not** provide access are: Croatia, Latvia, Macedonia, Russian Federation and Slovakia. BV is widely available In Western Europe, with only Spain and Portugal not providing reimbursement for this therapy.

Access to the PD-1 inhibitor nivolumab is still limited in many European countries. Russia, Serbia, Macedonia, Turkey, Ukraine, and Switzerland have not approved the drug for use. Nivolumab is not fully reimbursed in any Eastern European country though partial reimbursement is available in Hungary and Slovakia. Nine countries in Western Europe provide full reimbursement for nivolumab, while Finland and Portugal provide partial reimbursement. Spain and Italy do not provide any funding for this therapy.

Pembrolizumab is also limited in Europe through mainstream health care services. Sweden and Germany are the only countries that have full reimbursement for this this PD-1 immunotherapy.

FIGURE 13: APPROVED & REIMBURSED NOVEL THERAPIES

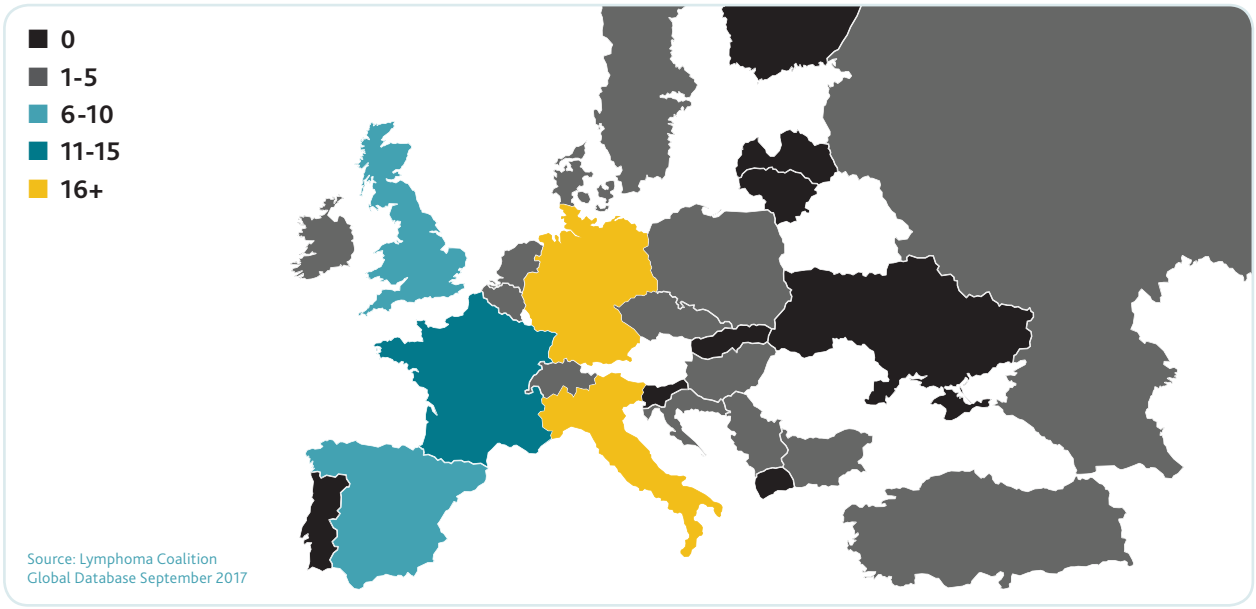


Source: 2017LC Global Database ©

Clinical Trials

There is significant clinical trial activity in the HL space globally. There are currently 126 HL trials underway in either Phase II or Phase III status, of which 43 are present in Europe. 28 trials are exclusive to Europe – a majority of which are researching brentuximab vedotin (BV). The majority of trials (93) are occurring in the USA.

FIGURE 14. HL CLINICAL TRIALS IN LC MEMBER COUNTRIES



Please note that a trial can be conducted simultaneously in multiple locations, so the total number of trials will not add up to the total of trials in individual countries.

If we look at Europe alone there is a huge disparity in the trials underway in Western Europe as opposed to Eastern Europe. The highest number of trials are in Germany (20), Italy (16) and France (15). There are only 9 trials available in all of Eastern Europe - 6 of which are studying brentuximab vedotin. The disparity suggests the patient population in Eastern Europe have limited access to enrolling in clinical trials and receiving the latest therapies.

The highest number of trials are in Germany (20), Italy (16) and France (15).

Looking at the availability of Phase II novel therapy trials, far more trials were available in Western Europe (27) as compared to Eastern Europe (5) both of which pale in comparison to the 63 trials available outside of Europe. In Phase III trials involving novel therapies, fewer trials were available in Europe (4) compared to the rest of the world (6).

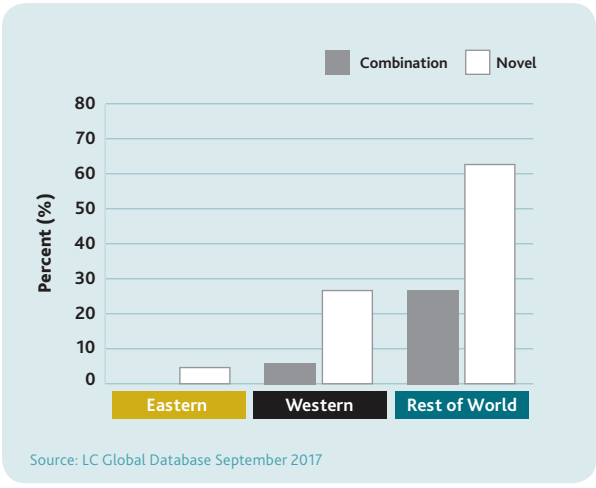
To improve the outcomes of patients with advanced-stage disease, novel agents need to be identified that can be integrated with standard chemotherapy during primary treatment.

The ECHELON -I trial is examining the potential for combining AVD with BV and eliminating bleomycin, which is associated with long-term toxicity. The use of A+AVD reduced the risk of progression and death by 23% in patients with advanced-stage HL compared with standard chemotherapy. A reduced need for further treatment was also indicated in patients treated with A+AVD. While the A+AVD shows positive outcomes, the results are not as remarkable as initially hoped, especially since the long-term toxicities of this combination are currently unknown.

Other areas of research include combining PD1s such as nivolumab and pembrolizumab with chemotherapy to reduce toxicity and intensity of treatment while increasing effectiveness.

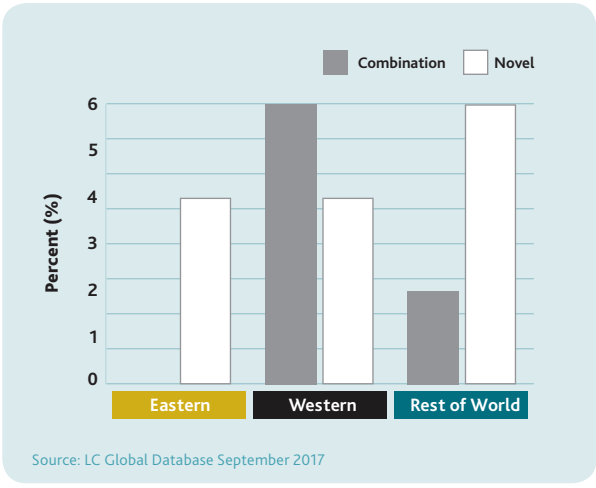
The greatest need for improved therapies for HL patients is within the relapsed/refractory setting. Within Europe there are 17 trials underway for relapsed patients of which 15 are studying novel therapies. There are no trials for relapsed patients in Eastern Europe in Phase II or in Phase III.

FIGURE 15. PHASE II HL TRIALS



Source: LC Global Database September 2017

FIGURE 16. PHASE III HL TRIALS



Source: LC Global Database September 2017

Conclusion

HL is a highly curable disease and early detection is the most important step in ensuring a favourable outcome for the patient.

There is still considerable room for improvement in care.

- Access to equal, quality treatment needs to improve, especially in Eastern Europe, where survival rates lag those observed in Western Europe.
- Healthcare providers should use evidence based guidelines and assessment tools to manage the treatment of HL with the aim of reducing the morbidity and mortality associated with treatment, especially for late stage and elderly patients.
- An improved understanding of biomarkers is needed for determining which patients are likely to respond to treatment and protect patients from over- or under-dosing of treatment.
- It is imperative that novel therapies are made available to all patients no matter where they live.
- More trials should be made available in Eastern Europe to ensure novel therapies are widely researched and accessible to all.
- Effort needs to be focused on improving results for relapsed/refractory patients who have poorer outcomes.
- Long-term survivorship issues continue for years for many patients; finding effective, less-toxic treatments is a priority.
- The LC GPS indicated that financial constraint was the greatest barrier to treatment in both Eastern and Western Europe. This has the potential to lead to, or exacerbate, already existing psychosocial issues.

LC members and the lymphoma community can work together to find solutions to improve treatment access and alleviate barriers for patients.

Appendix A - Staging

The management of HL is determined by the stage and activity of the cancer. Patients with HL are staged according to the Ann Arbor staging system with Cotswold's modifications.[15, 16]

The stage of the cancer depends on the extent to which it has spread in the body. In stages I and II, the cancer is limited to one or two areas of the body (early stage). In stages III and IV, the cancer is more widespread (advanced stage). Patients with early stage HL are then further stratified into favourable and unfavourable subsets, which is based on the presence or absence of other clinical features as seen in Table A2.[12]

A further revision was proposed to the Ann Arbor staging system in 2014, the Lugano classification, which proposes to clarify the role of positron emission tomography (PET) and better define extra nodal involvement.[17, 19] It also indicates the bone marrow biopsy is no longer necessary for routine staging of HL and discourages routine surveillance scans.

TABLE A1. STAGING SYSTEM FOR HL[17]

Stage	Nodal extent*	Extranodal extent (and suffix 'E' if present)
I	One node or a group of adjacent nodes	Single extranodal lesion with no nodal involvement
II	Two or more lymph node regions on the same side of the diaphragm	Stage I or II by nodal extent with contiguous extranodal extension
II bulky	As for II; definition of 'bulky' depends upon histology**	Not applicable
III	Nodes on both side of the diaphragm or nodes above the diaphragm with splenic involvement	Not applicable
IV	Noncontiguous extranodal involvement	Not applicable

*Tonsils, Waldeyer's ring and spleen are considered nodal
** ≥ 10 cm for Hodgkin lymphoma, 6-10 cm suggested for diffuse large B cell lymphoma ≥ 6 cm suggested for follicular lymphoma

Included in the staging system for HL are the suffixes A and B. This denotes if additional symptoms are involved as shown in Table A2.

TABLE A2. SUFFIX TO ADD FOR HL PATIENTS[19]

Suffix	Meaning
A	Absence of constitutional symptoms
B	Constitutional symptoms: fever (>38°C), drenching sweats, weight loss (10% body weight over 6 months)

Appendix B - International Prognostic Score (IPS)

Patients with advanced HL can be further risk stratified using the International Prognostic Score (IPS), which includes further risk factors outlined as:

- Albumin < 4 g/dL
- Haemoglobin < 10.5 g/dL
- Male
- Age ≥ 45y
- Stage IV disease
- Haemoglobin level below 10.5 d/dL
- Leukocytosis: white cell count (WBC) > 15,000/µL
- Lymphopenia: lymphocyte count < 8% of WBC count and/or absolute lymphocyte count < 600 cells/µL

The presence of any of the above factors counts as one point. A good risk profile would be IPS 0-1, fair risk would have a score of IPS 2-3 and poor risk is IPS 4-7.[18]

Appendix C - Cellular Biology of HL

The presence of HRS cells is characteristic of classical HL and a biopsy is necessary for diagnosis. It is recommended that a full lymph node or a sufficiently large specimen be removed surgically to ensure the laboratory has enough tissue to examine.[8] HRS cells stain consistently positive for the markers CD30 and CD15.[8,9]

RS (or HRS) cells are generally only 1-2% of the overall tumour mass, as they attract many other inflammatory cells which make up most of the mass.[3]

What HL looks like under the microscope will determine its vulnerability to certain drugs. Many studies in HL have focused on the cellular composition of the microenvironment, to not only better understand the cancer but also if the cells in the microenvironment in some way contribute to outcome prediction.

As an example, the number of tumour-associated macrophages has been identified as an adverse prognostic factor in many solid tumours.[20] Several molecules implicated in macrophage signalling might be promising targets for novel drug therapies.[21]

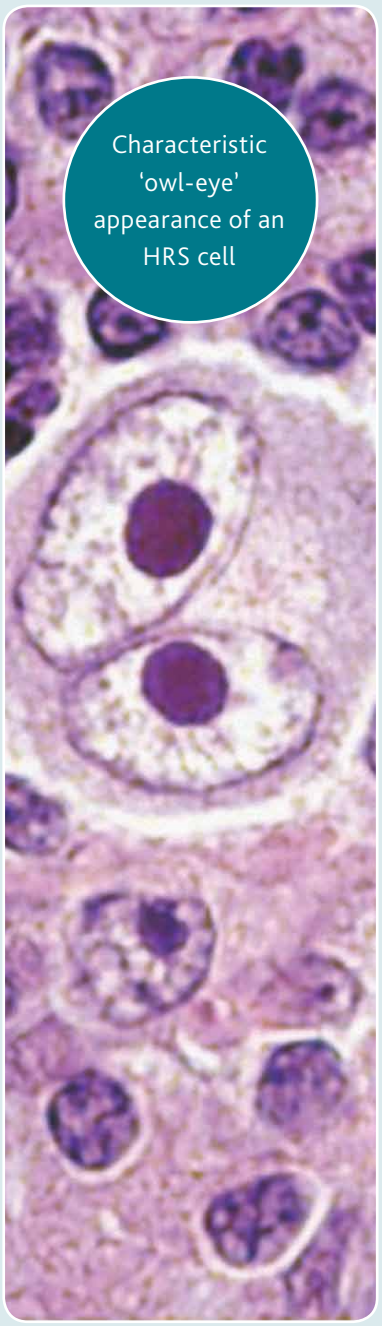
A major obstacle in identifying the origin of HRS cells was the rarity of their presence in affected tissues. Also, malignant HRS cells lose numerous B-cell markers making it difficult to identify its cell of origin.

HRS cells in classical HL have several characteristics that are unusual for lymphoid tumour cells, and understanding the biology is essential for the development of novel therapies.[22]

Almost all HRS cells are positive for CD30, expressed on the cell membrane as well as within the Golgi apparatus. CD30 can activate signalling pathways including PI3-kinase/Akt/mTOR, ERK/MAPK and NF-kB.[23] CD15 is also commonly expressed on HRS cells in a similar distribution to CD30. These cells also express other B-cell markers including the B-cell-specific activator protein PAX5/BSAP and the plasma cell transcription factor IRF4/MUM.[23]

It is still not known what causes HL, but in recent years improved understanding of the biology of HL has uncovered some potential targets for treatment. Clarification of the complex interactions between the HRS cell and the HL microenvironment have provided new insights into the molecular structures and signalling pathways that are essential for HRS survival.[23]

FIGURE 5.
HRS CELL UNDER THE MICROSCOPE



Source: ?

Appendix D - Current Treatment Recommendations

To determine what treatments should be accessible to HL patients in member countries, LC reviewed the information from both the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) and the treatment guidelines are shown in Table D1 and D2.

It should be noted that the NCCN listing was updated in 2017. ESMO on the other hand has not updated its guidelines for the treatment of HL since 2014. In an email correspondence they have suggested that the guidelines will be updated late 2017 or early 2018.

TABLE D1. ESMO TREATMENT GUIDELINES FOR HL[8]

Stage	Classic HL	NLPHL
Front-line Treatment		
Limited (no risk factors)	ABVD → RT	RT
Intermediate (≥1 risk factors)	Possible options: ABVD Or BEACOPPesc + ABVD → RT	ABVD Or BEACOPPesc + ABVD → RT
Advanced (large mediastinal mass; ≥50 y, elevated ESR, ≥4 nodal areas)		ABVD Or BEACOPPesc → RT
Relapsed Disease		
	DHAP or IGEV or ICE → high-dose chemotherapy → autoSCT Low-risk patients: BEACOPPesc	Rituximab alone Advanced disease: More aggressive salvage therapy + anti-CD20 antibody No data yet on efficacy of high-dose chemotherapy followed by autoSCT
	BV after autoSCT failure	

TABLE D2. NCCN TREATMENT GUIDELINE FOR HL[9]

	Classic HL	NLPHL
Front-line Treatment		
Stage I-II (bulky and non-bulky disease)	ABVD Or Stanford V Or BEACOPPesc + ABVD + RT	Non-bulky disease: Observation Or RT Bulky disease: ABVD + RT ± rituximab Or CHOP + RT ± rituximab Or CVP + RT ± rituximab
Stage III-IV	ABVD Or Stanford V Or BEACOPPesc	ABVD + RT ± rituximab Or CHOP + RT ± rituximab Or CVP + RT ± rituximab Or RT Or Rituximab
Relapsed Disease		
	HDT + autoSCT ± RT → BV Or Observation ± RT	Rituximab ± chemotherapy ± RT BV

TABLE D3. RECOMMENDED TREATMENT PROTOCOLS

NCCN (n-22)		ESMO (n-8)	
First Line	**Relapsed**	**First Line**	**Relapsed**
ABVD ± R	Bendamustine	ABVD	BV
BEACOPP	BV	BEACOPP	DHAP
CHOP-R	C-MOPP	Radiation Therapy	ICE
CVP-R	DHAP		IGEV
Radiation Therapy	ESHAP		Radiation Therapy
Rituximab	Everolimus		Stem Cell Transplant
Stanford V	GCD		
	GVD		
	ICE		
	IGEV		
	Lenalidomide		
	MINE		
	Mini-BEAM		
	Nivolumab		
	Pembrolizumab		
	Radiation Therapy		
	Rituximab		
	Stem Cell Transplant		

TABLE D4. THERAPY ACCESS BY LC MEMBER COUNTRY

Country	Approved therapies	Approved and reimbursed	Approved and partially reimbursed	Approved and not reimbursed
Eastern Europe				
Bulgaria	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	BEACOPP, BV, DHAP, GDP	ABVD, ESHAP, ICE, MINE	Nivolumab, Pembrolizumab
Croatia	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, Stanford V, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, ICE, MINE, MINI-BEAM, RT, Stanford V, SCT		GDP, Nivolumab, Pembrolizumab
Bulgaria	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	BEACOPP, BV, DHAP, GDP	ABVD, ESHAP, ICE, MINE	Nivolumab, Pembrolizumab
Croatia	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, Stanford V, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, ICE, MINE, MINI-BEAM, RT, Stanford V, SCT		GDP, Nivolumab, Pembrolizumab
Czech Republic	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MINI-BEAM, RT, SCT		Nivolumab, Pembrolizumab
Hungary	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, MINI-BEAM, RT, SCT	Nivolumab	Pembrolizumab
Latvia	ABVD, BEACOPP, BV, DHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, DHAP, ICE, RT		BV, GDP, MINE, Nivolumab, Pembrolizumab, SCT
Lithuania	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BV, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT	BEACOPP	COPP, Nivolumab, Pembrolizumab
Macedonia	ABVD, BEACOPP, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT, SCT	ABVD, BEACOPP, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT, SCT		
Poland	ABVD, BEACOPP, BV, DHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, GDP, ICE, MINE, RT, SCT		COPP, Nivolumab, Pembrolizumab
Russian Federation	ABVD, BEACOPP, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT	ABVD, BEACOPP, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT		
Serbia	ABVD, BEACOPP, BV, DHAP, ESHAP, ICE, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, ICE, MINE, RT, SCT		
Slovakia	ABVD, BEACOPP, Bendamustine, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, Pembrolizumab, RT, SCT	Bendamustine, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT, SCT	ABVD, BEACOPP, Nivolumab	BV, Pembrolizumab
Slovenia	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT		Nivolumab, Pembrolizumab
Turkey	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT, SCT		
Ukraine	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT		

TABLE D4. THERAPY ACCESS BY LC MEMBER COUNTRY (CONTINUED)

Country	Approved therapies	Approved and reimbursed	Approved and partially reimbursed	Approved and not reimbursed
Western Europe				
Belgium	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, RT, SCT		Pembrolizumab
Denmark	ABVD, ABVD-R, ASHAP, BEACOPP, Bendamustine, BV, CHOP, DHAP, ESHAP, GDP, GVD, ICE, IGEV, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, SCT	ABVD, ABVD-R, ASHAP, BEACOPP, Bendamustine, BV, CHOP, DHAP, ESHAP, GDP, GVD, ICE, IGEV, MINE, MINI-BEAM, Nivolumab, RT, SCT		Pembrolizumab
Finland	ABVD, BEACOPP, BV, CHOP, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, CHOP, DHAP, ESHAP, GDP, ICE, IGEV, MINE, RT, SCT	Nivolumab	Pembrolizumab
France	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, RT, SCT		Pembrolizumab
Germany	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, Pembrolizumab, RT, SCT		
Ireland	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, RT, SCT		COPP, Pembrolizumab
Israel	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, Nivolumab, RT, SCT		
Italy	ABVD, BEACOPP, Bendamustine, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MOPP, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, Bendamustine, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MOPP, RT, SCT		Nivolumab, Pembrolizumab
Netherlands	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MINI-BEAM, Nivolumab, RT, SCT		Pembrolizumab
Portugal	ABVD, BEACOPP, BV, DHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT		Nivolumab	ABVD, BEACOPP, BV, DHAP, GDP, ICE, MINE, Pembrolizumab, RT
Spain	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, Stanford V, SCT	ABVD, ASHAP, BEACOPP, DHAP, ESHAP, GDP, ICE, MINE, MINI-BEAM, RT, Stanford V, SCT		BV, Nivolumab, Pembrolizumab
Sweden	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, SCT	ABVD, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, IGEV, MINE, MINI-BEAM, Nivolumab, Pembrolizumab, RT, SCT		
Switzerland	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, RT, SCT		
United Kingdom	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, Pembrolizumab, RT, SCT	ABVD, ASHAP, BEACOPP, BV, DHAP, ESHAP, GDP, ICE, MINE, Nivolumab, RT, SCT		Pembrolizumab

Acronyms

ABVD±R	adriamycin, bleomycin, vinblastine, dacarbazine with/without rituximab
ASHAP	doxorubicin, methylprednisolone, cytosine arabinoside, cisplatinum
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
B±R	bendamustine with/without rituximab
Bortezomib+R	bortezomib, rituximab
BV	brentuximab vedotin
C-MOPP	cyclophosphamide, vincristine, procarbazine, prednisone
CEPP±R	cyclophosphamide, etoposide, procarbazine, prednisone with/without rituximab
ChIVPP	chlorambucil, vinblastine, procarbazine, prednisone
CHOP	cyclophosphamide, vincristine, doxorubicin, prednisone
CHOP±R	cyclophosphamide, vincristine, doxorubicin, prednisone with/without rituximab
COPP	cyclophosphamide, vincristine, procarbazine, prednisone
CT	clinical trial
CVP±R	cyclophosphamide, vincristine, prednisone with/without rituximab
DHAC	dexamethasone, doxorubicin, cytarabine, carboplatin
DHAP±R	dexamethasone, high-dose cytarabine, cisplatin, with/without rituximab
ESHAP±R	etoposide, methylprednisolone, cytarabine, cisplatin with/without rituximab
ESMO	European Society of Medical Oncology
EPOCH±R	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin with/without rituximab
FC	fludarabine, cyclophosphamide
FCM	fludarabine, cyclophosphamide, mitoxantrone
FCMR	fludarabine, cyclophosphamide, mitoxantrone, rituximab
FCR	fludarabine, cyclophosphamide, rituximab
FMR	fludarabine, mitoxantrone, rituximab
GDP	gemcitabine, dexamethasone, cisplatin
GVD	gemcitabine, vinorelbine, doxorubicin
HDT	high-dose therapy
HL	Hodgkin lymphoma
HyperCVAD+R	cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine, rituximab
ICE±R	ifosfamide, carboplatin, etoposide with/without rituximab
IGEV	ifosfamide, gemcitabine, vinorelbine
MCP±R	melphalan, chlorambucil, prednisone with/without rituximab
MINE	mesna, ifosfamide, mitoxantrone, etoposide
Mini-BEAM	carmustine, etoposide, cytarabine, melphalan
MOPP	mechlorethamine, vincristine, procarbazine, prednisone
NCCN	National Comprehensive Cancer Network
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
NORDIC	cyclophosphamide, vincristine, doxorubicin, prednisolone, rituximab, cytarabine
OPEC	vincristine, prednisolone, etoposide, chlorambucil
PCR	pentostatin, cyclophosphamide, rituximab
PEPC±R	prednisone, etoposide, procarbazine, cyclophosphamide with/without rituximab
R	rituximab
RICE	rituximab, ifosfamide, carboplatin, etoposide
RT	radiation therapy
SCT	stem cell transplant
Stanford V	mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

References

1. Massimiliano, Salati ,et al. "Epidemiological Overview of Hodgkin Lymphoma across the Mediterranean Basin." Mediterranean Journal of Hematology and Infectious Diseases 2014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103499
2. Ferlay J, et al. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2014.
3. Lymphoma Research Foundation – Understanding Hodgkin Lymphoma: http://www.lymphoma.org/atf/cf/%7Baaf3b4e5-2c43-404c-afe5-fd903c87b254%7D/UNDERSTANDING_HODGKIN_LYMPHOMA__BOOKLET.PDF
4. Ansell, Stephen. "Novel agents in the therapy of Hodgkin lymphoma." American Society of Clinical Oncology, 2015.
5. Pediatric Oncology – Special Section: Hodgkin Lymphoma http://telemedicina.med.muni.cz/pediatric-oncology/index.php?pg=special-section--hodgkin-lymphoma
6. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles G, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. Blood. 2016 May 19;127(20):2375-90
7. http://www.cancer.org/cancer/hodgkindisease/detailedguide/hodgkin-disease-what-is-hodgkin-disease
8. Eichenauer, D. A., A. Engert, and M. Dreyling. "Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Annals of Oncology-English Edition 22.6 (2011): vi55.
9. Hoppe RT, Advani RH, Ai WZ, Ambinder RF, Aoun P, Bello CM, et al. "Hodgkin Lymphoma Version 1.2017, NCCN Clinical Practice Guidelines in Oncology." J Natl Compr Cancer Netw. 2017;15:608–38
10. Sauer, Maike, et al. "Baseline serum TARC levels predict therapy outcome in patients with Hodgkin lymphoma." American journal of hematology 88.2 (2013): 113-115
11. Gallamini A, Hutchings M, Rigacci L, et al. "Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study." J Clin Oncol 2007;25:3746-3752
12. Alinari L, Blum KA. "How I treat relapsed classical Hodgkin lymphoma after autologous stem cell transplant." Blood. 2016;127(3):287-295.
13. Gerrie AS, Power MM, Shepherd JD, Savage KJ, Sehn LH, Connors JM. "Chemoresistance can be overcome with high-dose chemotherapy and autologous stem-cell transplantation for relapsed and refractory Hodgkin lymphoma." Ann Oncol. 2014;25(11):2218-2223.
14. Behringer, Karolin, et al. "Cancer-related fatigue in patients with and survivors of Hodgkin lymphoma: the impact on treatment outcome and social reintegration." Journal of Clinical Oncology 34.36 (2016): 4329-4337.
15. Carbone, Paul P., et al. "Report of the committee on Hodgkin's disease staging classification." Cancer research 31.11 (1971): 1860-1861.
16. Lister, T. A., et al. "Report of a Committee Convened To Discuss the Evaluation and Staging of Patients with Hodgkin's Disease Cotswolds Meeting." Journal of Clinical Oncology 8.9 (1990): 1602-1603.
17. http://bloodref.com/lymphoid/lymphoma-staging/lugano-classification
18. Hasenclever D, Diehl V. "A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease." N Engl J Med. 1998 Nov 19. 339(21):1506-14.
19. Cheson, Bruce D., et al. "Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification." Journal of clinical oncology 32.27 (2014): 3059-3067.
20. Qian BZ, Pollard JW. "Macrophage diversity enhances tumour progression and metastasis." Cell. 2010;141(1):39–51.
21. Steidl, Christian, Pedro Farinha, and Randy D. Gascoyne. "Macrophages predict treatment outcome in Hodgkin's lymphoma." Haematologica 96.2 (2011): 186-189.
22. Re D., Thomas R.K., Behringer K., Diehl V. (2005) "From Hodgkin disease to Hodgkin lymphoma: biologic insights and therapeutic potential." Blood 105: 4553–4560
23. Sweetenham, John W. "Novel therapies for Hodgkin lymphoma." Therapeutic advances in hematology 1.1 (2010): 23-29.
24. Jaffe, E, et al. Hematopathology E-Book, 2017; 529.
25. Villasboas, Jose C., and Stephen M. Ansell. "Recent advances in the management of Hodgkin lymphoma." F1000Research 5 (2016)
26. Rosenblatt, Eduardo, et al. "Radiotherapy capacity in European countries: an analysis of the Directory of Radiotherapy Centres (DIRAC) database." The lancet oncology 14.2 (2013): e79-e86.
27. EMA/CHMP/162113/2017 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/003820/WC500224298.pdf
28. EMA/CHMP/671272/2016 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/003985/WC500214219.pdf
29. https://clinicaltrials.gov/ct2/show/NCT03004833, https://clinicaltrials.gov/ct2/show/NCT02758717
30. https://clinicaltrials.gov/ct2/show/NCT03226249

LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

www.lymphomacoalition.org