LYMPHOMA COALITION

Worldwide Network of Lymphoma Patient Groups

SUBTYPE REPORT

Diffuse Large B-Cell Lymphoma

Review of patient access to care in Diffuse Large B-cell Lymphoma (DLBCL) including:

1. Understanding DLBCL
2. Therapy access
3. Patient experience

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Contents

Words in the text in *italics* are defined in the glossary.

Overview

Diffuse Large B-Cell Lymphoma (DLBCL) is a highly aggressive and *heterogenous* subtype of lymphoma.

DLBCL affects patients of all age groups and has a wide range of presentations (clinically, *morphologically*, and genetically).[1] Scientific advances have led to DLBCL being curable with combined *chemotherapy* and *immunotherapy*. **If properly treated and managed, the cure rate is as high as 70%.**[2]

Optimisation of front-line therapy and the development of more effective salvage strategies remain important objectives in DLBCL. Recent advances in *molecular genetics* have significantly improved our understanding of the biological diversity of DLBCL. Unique molecular targets and pathways have been identified that may be used to advance therapeutic interventions.[3] The main ongoing research challenges include accurately identifying these molecular subsets and determining if specific chemotherapy and targeted therapies offer distinct benefit.[4]

The focus of this report is to review DLBCL to:

- Provide a current understanding of DLBCL
- Outline DLBCL treatment options and protocols, including:
  - Therapy access in LC member countries
  - Clinical trial access in LC member countries
- Explore the DLBCL patient experience

Classifying the heterogenous group of DLBCL subtypes by risk is an evolving process. Therapy development is becoming more tailored according to the different cancer-causing pathways; however, gaps in therapy research, development, and access continue to exist.

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

- Improved treatment options for relapsed-refractory (RR) DLBCL, occurring in approximately one third of patients, who have less favourable survival outcomes.[5]
- A gold standard regimen for salvage chemotherapy does not exist and current salvage regimens benefit a relatively small proportion of RR patients.[5]
- Double-expresser and double/triple-hit lymphomas are areas requiring attention and therapy development.
- Prognostic and predictive tools must be further developed in order to improve the individualised application of new therapies.[4]
- Molecular testing for each patient to implement individualised therapy is the ideal, but it remains costly and highly inaccessible for many patients around the world.

Understanding Diffuse Large B-Cell Lymphoma (DLBCL)

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, which allows them to rapidly multiply indefinitely instead of self-destructing at the end of their normal limited life span.

Lymphoma is a cancer of lymphocytes, a type of white blood cell. Lymphocytes circulate in the body through a network referred to as the lymphatic system, which includes the bone marrow, spleen, thymus, and lymph nodes (figure 1). The organs and vessels of the lymphatic system work together to help fight infections throughout the body. When lymphoma occurs, lymphocytes begin to grow and multiply uncontrollably.[6]

There are two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells). B cells are responsible for creating *antibodies* or *immunoglobulins* which fight infections. T cells either directly destroy cancerous cells as well as virally or bacterially infected cells, or they play an important role in orchestrating an immune response. B cell lymphomas are much more common than T cell lymphomas, and account for over 90% of all lymphomas.[7]

FIGURE 1: LYMPHATIC SYSTEM

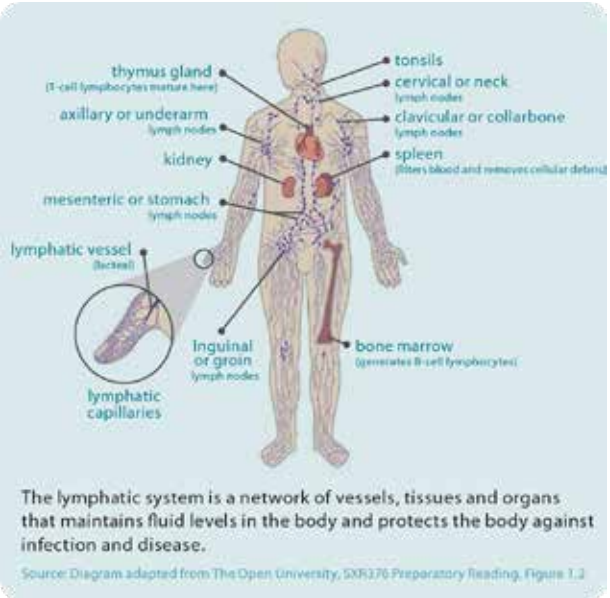
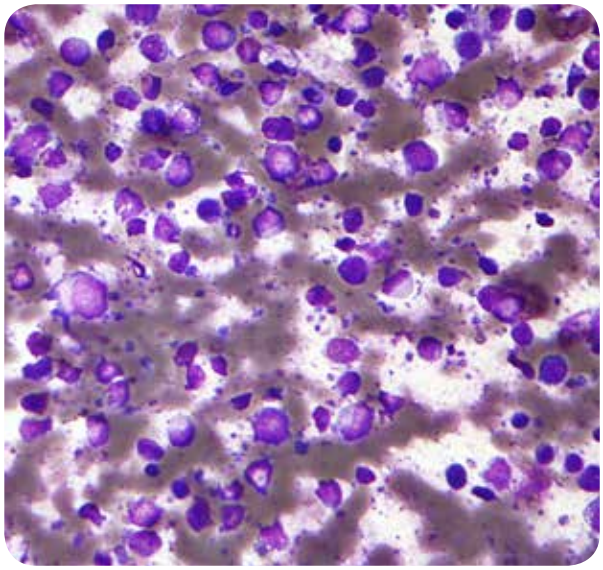


FIGURE 2: CELLS FROM A BIOPSY OF DLBCL SHOWING ABNORMAL, LARGE CELLS SPREAD DIFFUSELY



DLBCL is a cancer of B lymphocytes (B cells). In DLBCL, B cells stop responding to signals that usually limit the growth and reproduction of cells. This causes the B cells to undergo a *malignant* transformation where they become much bigger than normal lymphocytes.[4] Diffuse large B cell by definition is a large transformed B cell with nuclear diameter more than twice that of a normal lymphocyte.[5]

This subtype of lymphoma is called diffuse large B cell because of the way the cancerous large B cells are scattered throughout (diffuse) the lymph nodes when examined with a microscope (figure 2). This growth pattern contributes to the aggressive behaviour of DLBCL.

DLBCL is typically an aggressive (fast-growing) lymphoma (also known as high grade or acute). It can occur in lymph nodes ('nodal') or outside of the lymphatic system ('extranodal') in the gastrointestinal tract, testes, thyroid, skin, breast, bone or brain. About 70% of these lymphomas are nodal, and 30% extranodal. Extranodal disease usually indicates advanced stage disease.[7]

DLBCL can present de novo (new) or as a transformation of other low-grade B cell lymphomas like follicular or chronic lymphocytic leukaemia/small lymphocytic lymphoma.[5] The de novo DLBCL cases have better *prognoses* than the transformed cases.[5] There are many subtypes of DLBCL, which have common *histology* but unique biology, with differences in clinical outcomes.[8] A patient's DLBCL subtype may affect their prognosis, response to treatment, and treatment options.[1]

For more information on large B cell lymphoma subtypes, see Appendix A.

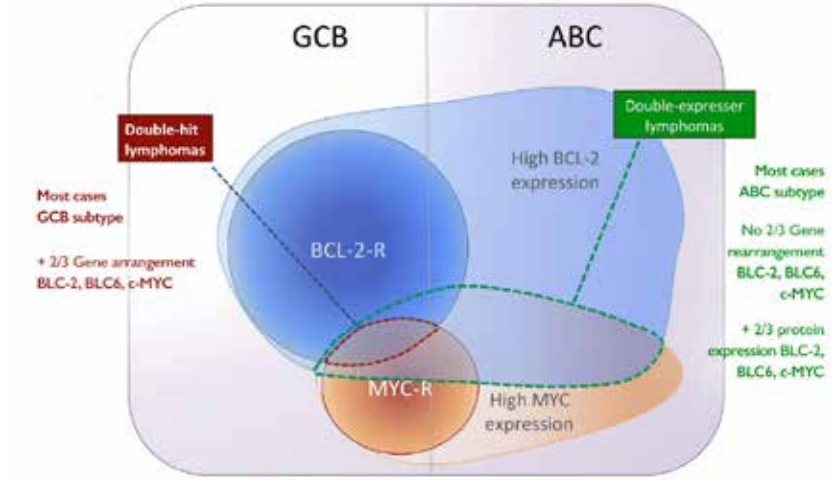
Most cases of DLBCL do not fall perfectly into a defined category, and they are considered DLBCL not otherwise specified (NOS). However, these NOS cases can be grouped into molecular subtypes according to their *cell of origin*.[2] Within the large category of DLBCL NOS, two distinct molecular subtypes have been recognised (with ~15% of patients remaining unclassifiable):

1. Germinal centre B cell (GCB): Patients with GCB type DLBCL generally have better outcomes compared to patients with the non-GCB type. GCB subtype has a complete response (CR) rate of about 70% to standard therapy.[3,9]

2. Activated B cell (ABC): ABC DLBCL has a more aggressive clinical course and a worse prognosis when treated with standard therapy. The complete response (CR) rate with standard therapy for ABC-type DLBCL is not more than 30% with a high chance of relapse within two years following treatment, hence patients with ABC subtype may benefit from clinical trial.[3,9]

Once cell of origin (GCB vs ABC) has been determined, it can then be determined if the DLBCL is a 'double-expresser' or a 'double-hit' (figure 3).[1] Double-expresser lymphomas express two proteins (MYC and BCL2) and are strongly associated with poor outcome in patients treated with immunochemotherapy. Double-expressers are observed in up to 25% of DLBCL patients.[8,10]

FIGURE 3: HIGH GRADE LYMPHOMA (DOUBLE/TRIPLE-HIT) VS DOUBLE-EXPRESSER DLBCL[1]



Surprisingly, most of these double/triple-hit lymphomas are of GCB type, which according to cell of origin classifications usually show a better *prognosis*.[1,2,8,10]

Diffuse large B-cell lymphoma (DLBCL) is the most common form of lymphoma, accounting for 30% to 40% of all newly diagnosed cases globally (excluding Hodgkin lymphoma cases).[2,3,5,11,12]

DLBCL affects patients of all age groups; however, the median age at diagnosis is roughly 60 years with slightly more males than females affected. Up to 50% of DLBCL patients have advanced disease (stage III or IV) at diagnosis.[8]

There is no known definite cause of DLBCL.

A family history of lymphoma, auto-immune disease, HIV infection, hepatitis C virus, a high body mass as a young adult and some occupational exposures have been identified as risk factors for DLBCL.[13] Indolent or slow-growing lymphomas can also sometimes transform or change into an aggressive lymphoma like DLBCL.

The first sign of DLBCL is often a painless, rapid swelling in the neck, underarms, or groin that is caused by enlarged lymph nodes. For some patients, the swelling may be painful.

Other symptoms may include[7]:

- night sweats
- fever
- unexplained weight loss
- fatigue
- loss of appetite
- shortness of breath
- pain

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

A biopsy is necessary to diagnose DLBCL.[6,14] For DLBCL, an incisional (removes only part of the tumour) or excisional (removes the whole tumour) is advised.[6,7] There are many biologic variants of DLBCL, so it is very important to have a big enough sample to make an accurate diagnosis under the microscope. An expert pathologic review is needed to confirm the diagnosis.

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, well as positron emission tomography (PET) and computed tomography (CT) scans to determine where the disease is present. *Gene-expression profiling* (GEP) and *immunohistochemistry* (IHC) are used to determine DLBCL molecular subtypes.

See Appendix B for more details on diagnostic testing.
For treatment planning, physicians will also assess a patient's prognosis using the cancer stage (see Appendix C) and the 'International Prognostic Index' (IPI) (see Appendix D).

Treatment

DLBCL is readily curable with immunochemotherapy in the majority of patients (~65-70%), even in the most advanced cases.[2]

Because DLBCL advances very quickly, it requires immediate treatment.

Different subtypes of DLBCL acquire different mutations that allow the cancer to multiply and be resistant to chemotherapy treatments. Sometimes when you introduce a novel treatment, it will only work for certain DLBCL subtypes, so **it's critically important to identify which subtype the patient has.**[1]

While conducting *molecular risk assessment* for each patient to adopt individualised therapy is ideal, it remains costly and highly inaccessible for many patients around the world. This leads to disparities in treatment and care.

Area of concern in DLBCL:

Molecular risk assessment is costly and highly inaccessible for many patients around the world.

There is an unacceptably high treatment failure rate in some DLBCL subsets.

Developing effective and personalised strategies for relapsed/refractory patients is an ongoing research challenge.

First-Line Therapy

First-line treatment options are partly based on cancer stage. **Approximately 75% of DLBCL patients present with advanced stage disease (stage III or IV), and roughly 25% with limited or early stage disease (stage I or II).**[4]

For a full account of first-line DLBCL treatment recommendations by stage (NCCN guidelines), please see Appendix F.

The current standard of care is to have 2 main ingredients:

1. anthracycline (doxorubicin)

2. immunotherapy (rituximab)

The most widely used treatment for DLBCL is the combination known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). This treatment is called immunochemotherapy as the 'R' is a *monoclonal antibody* (anti-CD20), a type of immunoglobulin, and the 'CHOP' is a chemotherapy regimen. R-CHOP can be given with or without radiation therapy. R-CHOP is usually given once every 21 days (may be called R-CHOP-21) for an average of 6 cycles; however, the length and number of cycles given can vary based on the patient's individual disease and health status.[7]

Despite extensive research into other treatment options, R-CHOP has remained the standard of care since the year 2000. Over the past decade, there have been several phase III clinical trials that have attempted to improve upon R-CHOP-21. Only one study[17] has demonstrated an overall survival (OS) benefit. A dose intensive regimen called R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) was compared with R-CHOP in a randomised phase III trial in a select population of DLBCL patients <60 years of age.[17] The R-ACVBP was associated with better OS; however, the median age of trial participants was younger than the median age of DLBCL patients generally.[17] Therefore, R-ACVBP has not become widely used as its value in a general population of patients remains unclear, and there is concern surrounding acute and delayed toxicity.[2]

Beyond R-ACVBP, there are many other drug combinations, which are variations of R-CHOP (either the drugs or the delivery) that are being used as first-line treatments for DLBCL. While there are differences in toxicities between these regimens, there are no current studies to suggest that one is better than another.[1] In certain cases, R-CHOP may be delivered in 14-day cycles (R-CHOP-14) rather than 21-day cycles. Sometimes, an additional chemotherapy drug, etoposide, is added to the R-CHOP regimen, resulting in drug combination called R-CHOEP. A related combination called EPOCH-R involves the same drugs administered as a continuous infusion over 4 days (sometimes called 'dose adjusted', or DA). Patients who cannot receive anthracycline may receive R-CEOP, R-CEPP or R-GCVP. Elderly patients (80 years and older) may receive R-Mini-CHOP, which is a lower dose version of R-CHOP.[1,2,6,7,14]

For a comprehensive list of first-line DLBCL treatment options (NCCN and ESMO guidelines), please see Appendix E.

Second-Line Therapy (Salvage Therapy)

Though outcomes in DLBCL have improved, 10% to 15% of patients exhibit primary refractory disease, and an additional 20% to 25% relapse following initial response to therapy.[2]

Relapsed (lymphoma responded to treatment but then returned) or refractory (lymphoma did not respond to initial treatment) DLBCL is diagnosed during treatment response assessment. Relapsed DLBCL is often diagnosed during a routine follow-up.

If clinical features and/or imaging indicate relapse, an excisional biopsy should always be performed. A CT (computed tomography) scan of the chest/abdomen/pelvis and a bone marrow biopsy should be conducted at relapse for re-staging. A PET-CT (positron emission tomography) can also be conducted to determine if there is a new lymphoma site and/or extranodal involvement. Patients with CNS (central nervous system) symptoms should be evaluated with a head-CT and lumbar puncture. The IPI should be re-calculated at relapse for all cases.[5]

Prognostic factors in relapsed/refractory DLBCL:

- Relapsed vs refractory: relapsed patients have higher overall response to treatment than refractory patients[5]
- Age-adjusted IPI: patients with more risk factors perform worse than patients with fewer risk factors[5]
- Rituximab status: patients who have not had rituximab before have a better response rate to additional treatment[15]
- Time to relapse: relapse within one year is a poor risk factor[16]

With standard chemoimmunotherapy, there is still an unacceptably high treatment failure rate in the following DLBCL subsets[4]:

- activated B cell (ABC),
- double-hit lymphoma,
- dual protein-expressing lymphomas,
- older patients, and
- those with central nervous system (CNS) involvement.

Managing relapsed and refractory disease continues to be a challenge to the treating physician. Current salvage regimens benefit a relatively small proportion of relapsed patients, and a gold standard regimen for salvage chemotherapy does not exist.[5]

High-dose chemotherapy followed by *autologous stem cell transplant* (HD-ASCT) is the main treatment for patients with chemotherapy-sensitive relapse. However, this is a very intensive approach that disqualifies many DLBCL patients due to advanced age and comorbidities. Further, many patients who are deemed transplant-eligible will also be disqualified because their disease will not respond to salvage chemotherapy. Of those who proceed to transplant, less than half will be cured.[2] Additionally, relapse post HD-ASCT is associated with extremely poor patient outcomes.

Relapsed/refractory (RR) patients who are candidates for HD-ASCT have several salvage regimens available to them, which have been developed to reduce tumour burden and confirm *chemosensitivity* prior to the ASCT.[2] The two most commonly used regimens are R-DHAP (rituximab, dexamethasone, Ara-C, cisplatin) and R-ICE (rituximab, ifosfamide, carboplatin, etoposide). The findings of two recently performed clinical trials suggest that these two regimens have similar response rates, event free survival (EFS) and OS.[5] However, patients with GCB DLBCL may benefit from R-DHAP rather than R-ICE.[5]

Relapsed/refractory (RR) patients who are not candidates for HD-ASCT do have various options that may be used for treatment. Chemotherapies such as bendamustine or gemcitabine, or targeted drugs like lenalidomide or ibrutinib, are alternative therapies that may be used in combination with rituximab or other monoclonal antibodies.[5,7] More information on new therapies is available in the next section of this report.

Select patients may be candidates for CAR-T (*chimeric antigen receptor T cells*) therapy. Patients must be carefully evaluated to determine eligibility for CAR-T. As CAR-T is a personalised treatment developed from the patient's own T cells, it can take many days to receive the modified T cells so they can be infused into the patient. In very aggressive DLBCL, it can be challenging to keep the lymphoma in control during this timeframe while the CAR-T cells are manufactured. The therapy has the potential to cause severe side effects, including cytokine release syndrome (CRS) and neurotoxicity in some patients. CAR-T therapy is a new type of treatment, so the long-term effects are unknown. Additionally, CAR-T is presently highly inaccessible in most countries around the world.

What is CAR-T therapy?

CAR-T is a type of therapy, known as immunotherapy, which uses a patient's own immune system to treat cancer. 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.

Developing effective and personalised strategies in the RR setting is an ongoing research challenge.[4] In the future, the treatment of DLBCL could be tailored according to risk of relapse. Until then, the search for predictors of RR disease in DLBCL continues. Some predictors under investigation include:

- IPI at presentation
- CNS status
- *immunoblastic* histology
- molecular markers
- *stromal signatures*
- *monocyte*/lymphocyte ratio at presentation.[5]

A relatively small proportion of patients are cured in the RR setting with the current recommended treatments. **Advances are needed to improve outcomes for RR DLBCL patients through developing newer and more effective drugs for salvage, and for optimising ASCT.[5]**

For a comprehensive list of second-line (relapsed and subsequent) DLBCL treatment options (NCCN and ESMO guidelines), please see Appendix G.

Novel Therapies

Next generation sequencing (NGS) technologies have revealed many complexities of DLBCL and identified unique targets that may be used for therapeutic benefit.[2] These findings have translated into a growing list of promising novel agents or novel drugs.

A novel drug, or a new molecular entity (NME) is an innovative product that serves a previously unmet medical need and helps to advance clinical care. NMEs have chemical structures that have never been approved before by regulatory agencies. Several novel agents are being investigated in randomised trials on patients with DLBCL, including:

- *kinase inhibitors*
- monoclonal antibodies
- antibody–drug conjugates
- *PD1 inhibitors*
- chimeric antigen receptor T cells (CAR-T)
- *immunomodulatory agents.*[6,7,14]

Many novel drugs have selective activity; therefore, it is important they be evaluated in patient populations who are most likely to benefit (i.e. particular molecular subgroups).[2] Some examples of novel drugs in development, or that have already been developed, are shown in table 1 according to their molecular subgroup of benefit.

TABLE 1: DLBCL NOVEL DRUGS (IN DEVELOPMENT OR ALREADY DEVELOPED) ACCORDING TO PATIENT SUBGROUP MOST LIKELY TO BENEFIT. ADAPTED FROM SEHN & GASCOYNE 2014.

Molecular Subgroup	Therapeutic Target	Novel Drug/Agent
ABC DLBCL	BTK	Ibrutinib
	Microenvironment, NF-κB	Lenalidomide
	SYK	Fostamatinib
	NF-κB	Bortezomib
	PKCß	Enzastaurin
GCB DLBCL	BCL6	BCL6 inhibitors
	EZH2	EZH2 inhibitors
	PI3K	Idelalisib*
	BCL2	ABT-199**
ALL DLBCL	CD20	Obinutuzumab
		Ofatumomab
	CD79b	Polatuzumab vedotin

* Potentially GCB

** Potentially GBC, also potentially dual expressers

These novel drugs may improve outcome when combined with standard therapy, provide an alternative for those who are too frail for R-CHOP, or provide effective options for patients in the relapsed/refractory setting.[2]

Much current DLBCL research is focused on using *precision medicine* to customise treatments based on a patient's specific DLBCL subtype.[4] For example, there are currently phase III clinical trials underway based on retrospective observations that a BTK inhibitor and an immunomodulatory agent appear to have selective activity in relapsed ABC-DLBCL. These trials are comparing standard chemotherapy with or without the BTK inhibitor, and with or without the immunomodulatory agent, in patients with non-GCB subtypes of DLBCL. Similarly, a line of research is evaluating chemotherapy with or without an antibody drug conjugate in populations enriched for higher IPI (International Prognostic Index) patients.[1,2,4,7]

Beyond the addition of novel drugs onto an R-CHOP backbone (i.e. R-CHOP + BTK inhibitor), current clinical trials for DLBCL are taking several other approaches, including testing dose-density delivery of R-CHOP with growth factor support, testing alternative anthracycline-based chemotherapy combinations, and evaluating infusional delivery of cytotoxic agents.[4]

While therapy development is becoming more tailored according to the different *oncogenic pathways* of GCB and ABC DLBCL, stratifying the heterogeneous group of DLBCLs by risk is an evolving process. The main research challenges include accurately identifying molecular subsets and determining if specific chemotherapy regimens and targeted agents offer different benefits.[4] Additionally, double-expresser and double/triple-hit lymphomas are areas requiring attention and risk-adapted therapy development.

Therapy Access

Lymphoma Coalition (LC) looked at access to current and novel treatment protocols in LC member countries to determine the availability of DLBCL therapies globally.

To determine what treatments should be accessible to DLBCL patients in member countries, LC reviewed information and guidelines from both the NCCN and the ESMO (Appendices E and G). This information was then compared against by-country data to determine accessibility.

Standard therapies included in the analysis were R-CHOP, R-CHOEP, R-DHAP, R-EPOCH, R-ACVBP. Novel therapies included were axicabtagene ciloleucel (Yescarta, CAR-T), tisagenlecleucel (Kymriah, CAR-T), and Pixantrone. The accessibility of certain rituximab *biosimilars* was also analysed, including Truxima and Rixathon. Accessibility was defined as 'therapy being available to a patient through public healthcare'.

When examined regionally (North America, Europe, South America, Asia-Pacific, Middle East & Africa), though some data could not be found, all the standard therapies appear to be readily accessible across all the regions. There are only a few exceptions: R-ACVBP is inaccessible in Canada, the US, and Korea. Interestingly, R-CHOP was made accessible through China's public healthcare system in 2017; however, only DLBCL patients and follicular lymphoma patients (stage III and IV) can be reimbursed after they use it.

Novel therapies are much less accessible across all regions.

While Pixantrone is accessible in many European countries, it is inaccessible across all the other regions. Additionally, beyond the US, Germany, the UK and France, both CAR-T therapies remain inaccessible across all regions. The use of rituximab biosimilars is expanding in member countries. Overall, they appear to be more popular for use in the public health sector in Europe but are also becoming available in the USA (with the recent approval of Rituximab-biosimilar production).

Detailed information on therapy access can be found in Appendix H (by country and grouped regionally).

Clinical Trial Analysis

There is significant clinical trial activity in the DLBCL space globally. There are currently 313 phase II and III clinical trials underway that involve DLBCL, of those, 116 are specific to DLBCL. Research objectives in DLBCL include the optimisation of first-line therapy, as well as the development of effective salvage strategies for relapsed/refractory patients.

At this time, the greatest need for improved therapies is within the relapsed/refractory setting, which is reflected in clinical trial activity: of the 313 DLBCL-related trials, 59 are first-line treatments and 235 are relapse. While some of these relapse trials are aimed at ABC DLBCL, they do not make up a significant portion, indicating a continued area of unmet need.

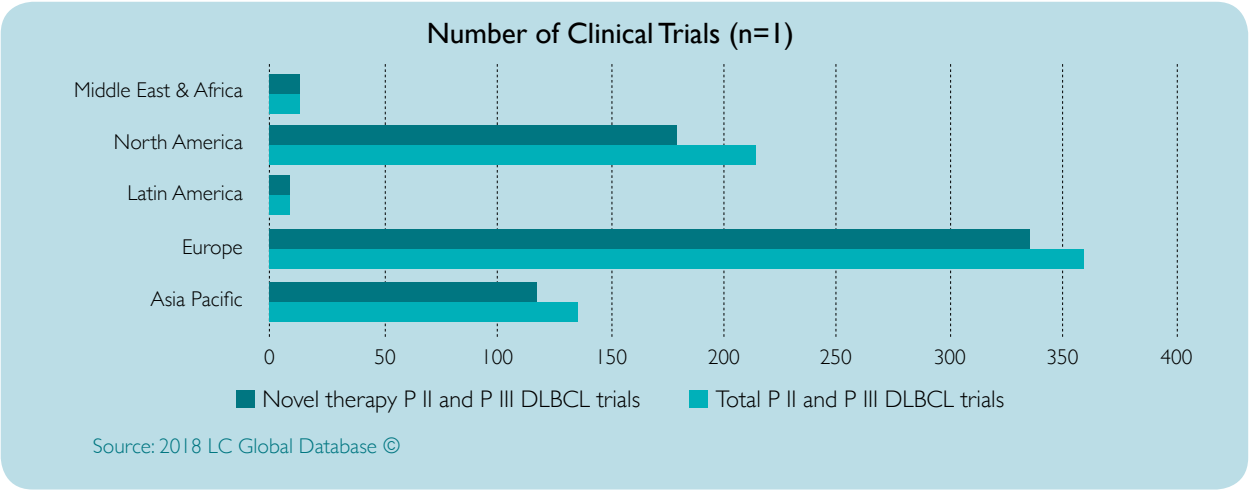
Of the 313 trials, 253 include novel therapies. The extensive pipeline for DLBCL is dominated by small molecule kinase inhibitors, monoclonal antibodies, and CAR-T therapies.[18] Of the 235 relapse trials, 56 involve a CAR-T product. The prominence of CAR-T is due to the successful FDA approvals that CAR-T therapy has already gained in this indication.[18]

The LC also examined DLBCL clinical trial activity by member country. The majority of phase II and III trials are occurring in the USA (n=186) and in China (n=55). When examined regionally (figure 4), Europe and North America have the most DLBCL-related trials occurring, while South America and the Middle East/Africa have the least. Despite having the most trials, when Europe is examined by-country, there is a large disparity in the trials underway in Western versus Eastern Europe. Compared to western Europe, there are far fewer eastern European countries with available trials, and far fewer trials available within these countries. Other such by-country disparities exist across the regions.

DLBCL patients continue to face unequal access to clinical trial enrolment and participation due to geography, preventing many patients from receiving the latest therapies.

Detailed analysis of clinical trial activity is available in Appendix I.

FIGURE 4: TOTAL NUMBER OF PHASE II AND PHASE III CLINICAL TRIALS INVOLVING DLBCL BY REGION, AND OF THESE TRIALS, HOW MANY ARE NOVEL THERAPIES



Source: 2018 LC Global Database ©

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. Through this survey, patient experience in lymphomas as well as the impact of treatment and care can be better understood, and LC and its global members can bring the patient voice forward.

The 2018 LC Global Patient Survey (GPS) result is used in this report to provide a sense of DLBCL patients' experience.

The 2018 LC Global Patient Survey (GPS) received 6,631 responses, with representation from 70+ countries around the world, of which 1478 (22%) were DLBCL patients.

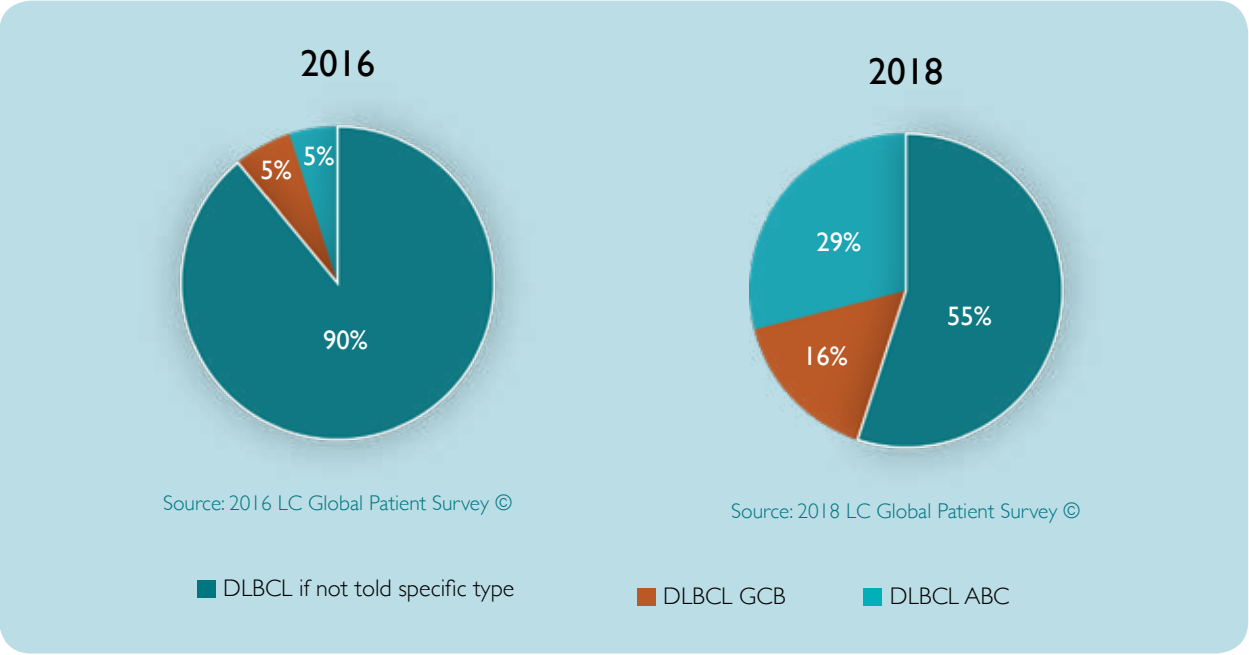
Patients were asked questions about their understanding and awareness, physical and psychosocial concerns, communication with the doctor, and barriers to care.

Understanding and Awareness

Approximately half (53%) of DLBCL patients were made aware of their lymphoma subtype during their initial diagnosis, whereas 33% were not informed and 14% were not sure.

Compared to the 2016 LC GPS, there was improvement in patient's awareness of their molecular subtype, or 'cell of origin' (figure 5).

FIGURE 5: DLBCL PATIENTS WHO WERE INFORMED OF THEIR CELL OF ORIGIN IN 2016 COMPARED TO 2018



Despite this increased awareness, DLBCL patients reported the most difficulty understanding the characteristics of their particular subtype (46%). Patients were asked to rate on a scale of 1-5 (5 being the highest) their understanding of various topics surrounding diagnosis and care following their initial diagnosis meeting with the doctor. Interestingly, more than 30% of DLBCL patients had difficulty understanding each of the different topics (responses 1+2) (table 2).

TABLE 2: DLBCL PATIENTS' UNDERSTANDING FOLLOWING THEIR INITIAL DIAGNOSIS MEETING WITH THE DOCTOR

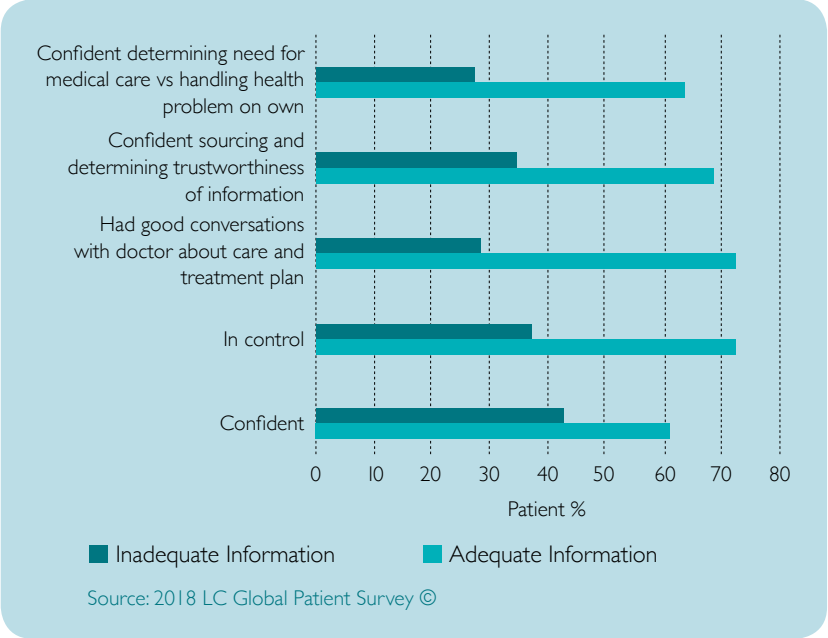
	Patient's Level of Understanding (%) (1 lowest, 5 highest)				
Topics Around Diagnosis and Care	1	2	3	4	5
Characteristics of your particular subtype	26	20	25	16	13
The different medical treatment options	24	15	25	18	18
The process and stages of care	15	16	26	21	22
Side effect management	20	18	25	18	18

Source: 2018 LC Global Patient Survey ©

The need for additional information at diagnosis was evident; 68% of DLBCL patients would have liked to receive additional medical and/ or associated support information at their diagnosis meeting.

Additionally, only 25% of DLBCL patients reported having an adequate level of information overall, whereas 48% reported having somewhat adequate information, and 27% inadequate information. Having a perceived adequate information level was correlated with more self-reported positive healthcare experiences (figure 6). Therefore, access to credible, timely information is an important aspect to a successful patient experience.

FIGURE 6: DLBCL PATIENTS' FEELINGS ACCORDING TO INFORMATION LEVEL



Source: 2018 LC Global Patient Survey ©

DLBCL patients reported being the most active in seeking information and support immediately upon diagnosis, and 1-3 months following diagnosis. DLBCL patients' primary sources for information were doctors, websites, and patient organisations. It is critical that the healthcare community work together to meet this need and provide patients with the information and support they require right from the beginning of their experience.

DLBCL patients' primary information sources:

- 68% Doctor
- 56% Websites
- 41% Patient Organisations
- 24% Nurse
- 23% family/friends
- 21% Online blogs/ social media
- 4% Other

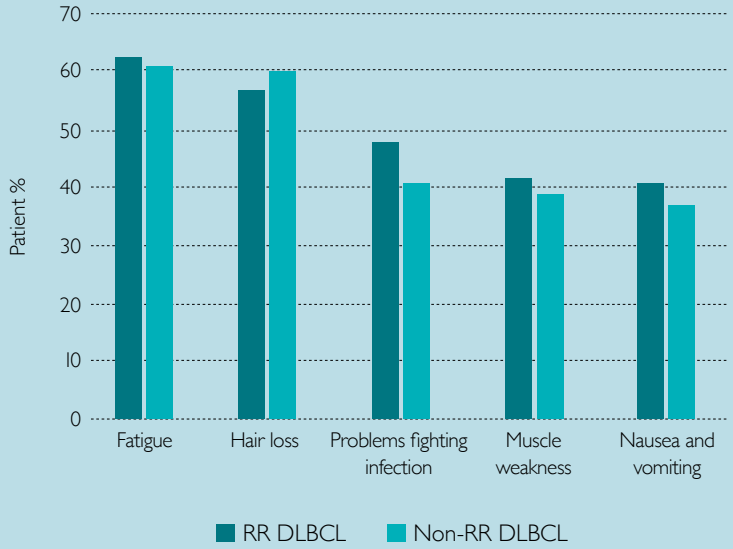
Physical and Medical Concerns

For this section, the LC compared the experience of relapsed/refractory (RR) DLBCL patients (n=167) against the rest of the DLBCL patient population (non-RR) (n=1285). Though there have been significant advances in the treatment of patients with DLBCL, relapse and/or transformation can occur. This means that patients must undergo additional rounds of treatment, which can intensify side effects and raise more concerns needing attention.

Physical and medical side effects have continued to negatively impact the lives of DLBCL patients. **The toxicity of DLBCL treatments has long since been a concern for patients, healthcare practitioners and researchers.**

When examining the physical conditions impacting well-being faced by patients (figure 7), both RR and non-RR DLBCL patients reported the same top conditions at comparable levels. These physical conditions were reported to last for many years (figure 8).

FIGURE 7: TOP PHYSICAL CONDITIONS AFFECTING WELLBEING REPORTED BY DLBCL PATIENTS



Source: 2018 LC Global Patient Survey ©

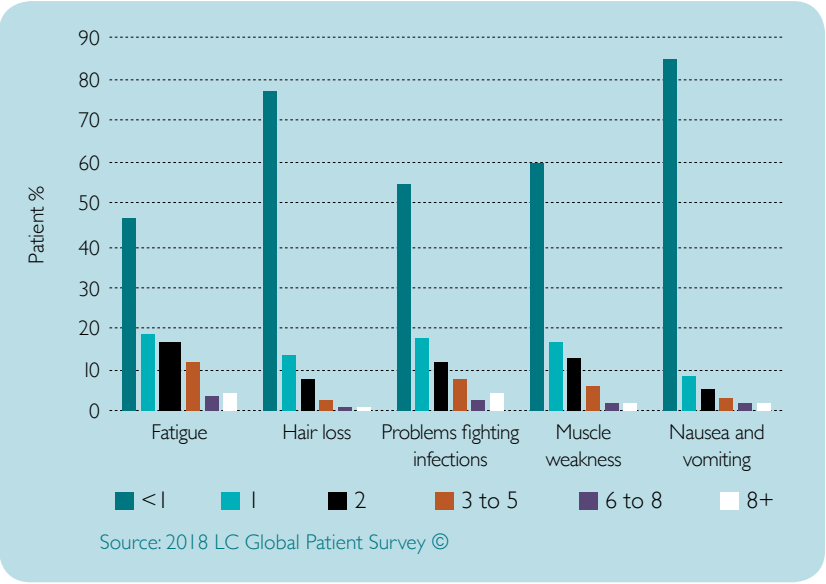
Primary physical condition affecting wellbeing reported by patients with DLBCL:

Fatigue

63% Relapsed/refractory patients

61% Rest of patients

FIGURE 8: TIME LENGTH (IN YEARS) OF TOP PHYSICAL CONDITIONS REPORTED BY ALL DLBCL PATIENTS (RR+NON-RR)

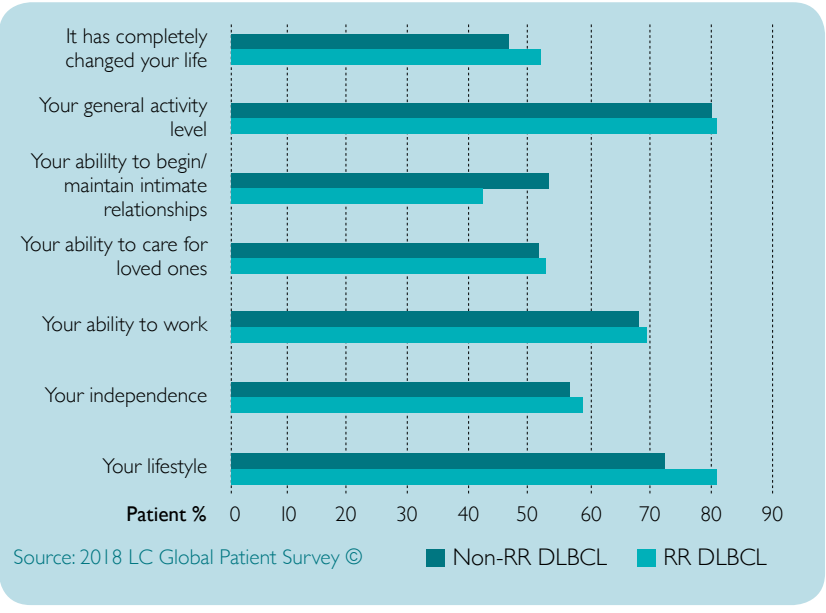


Source: 2018 LC Global Patient Survey ©

Fatigue was a major concern for all DLBCL patients, irrespective of their RR status. **Fatigue has a massive impact on many patient's quality of life. Understanding cancer-related fatigue and the repercussions it may have during and post treatment on patients is an important factor that needs to be addressed.**

Though the prevalence of fatigue was comparable between RR and non-RR DLBCL patients, RR patients reported a greater burden of this fatigue across various areas of their life (figure 9).

FIGURE 9: CHANGES IN LIFESTYLE IMPACTING QUALITY OF LIFE RESULTING FROM FATIGUE AMONG DLBCL PATIENTS



Source: 2018 LC Global Patient Survey ©

Primary medical condition during treatment:

Neutropenia

32% Relapsed/refractory patients

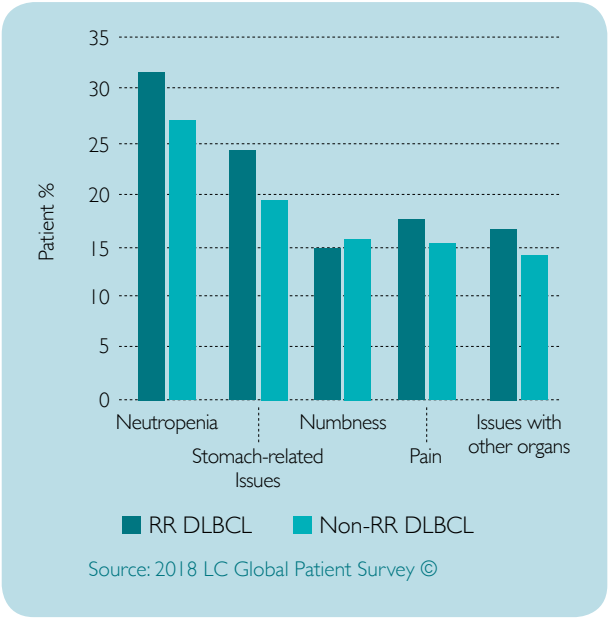
27% Rest of patients

Additionally, of those DLBCL patients (all, i.e. RR +non-RR) who experienced fatigue issues, only 43% were referred by their doctor or nurse onto further support. **Supporting patients in understanding and managing their fatigue is an area requiring attention and improvement.**

The top medical issues reported by DLBCL patients during and after treatment (figure 10 & 11) are commonly reported treatment side effects. This leads to the need for better treatment options with fewer side effects. Additionally, each of the top medical issues were reported up to 8+ years following treatment completion (figure 12), which leads to a discussion about what is an acceptable side effect both short and long-term.

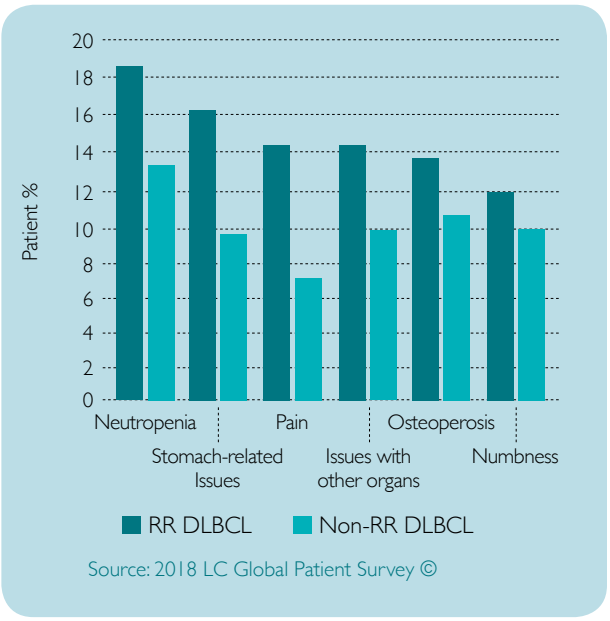
When comparing RR against non-RR DLBCL patients, the same top medical issues were reported both during and after treatment. However, the reported prevalence of medical issues was higher for RR patients than non-RR patients (figures 10 & 11). This was especially true for the medical issues reported after treatment. This increased prevalence could be attributed to disease progression, and/or to further treatment exposure and associated toxicities.

FIGURE 10: TOP MEDICAL ISSUES REPORTED DURING TREATMENT BY DLBCL PATIENTS



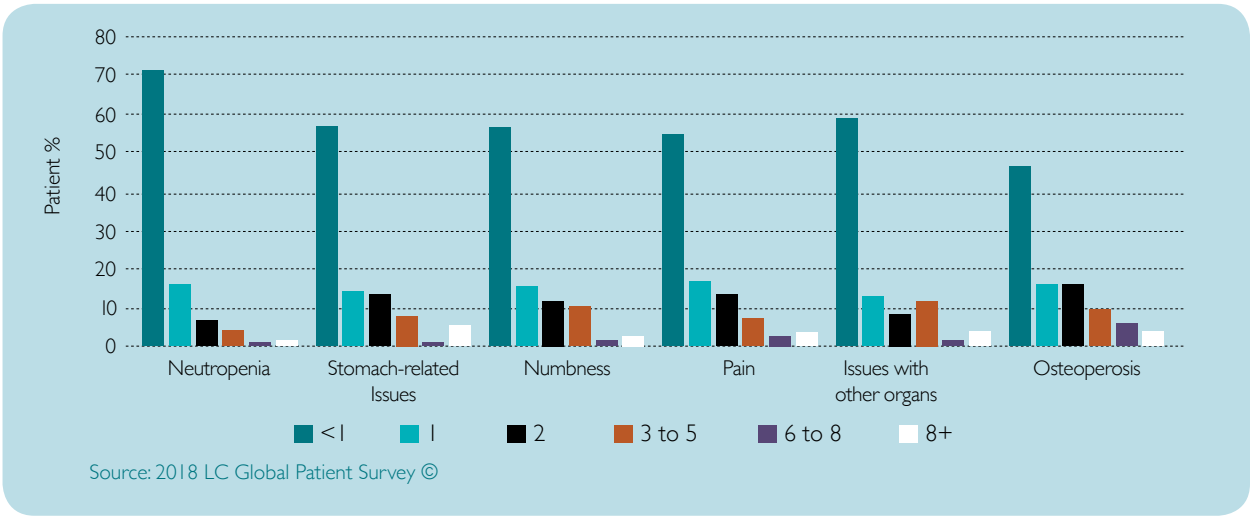
Source: 2018 LC Global Patient Survey ©

FIGURE 11: TOP MEDICAL ISSUES REPORTED AFTER TREATMENT BY DLBCL PATIENTS



Source: 2018 LC Global Patient Survey ©

FIGURE 12: TIME LENGTH (IN YEARS) OF TOP MEDICAL ISSUES FOLLOWING TREATMENT REPORTED BY ALL DLBCL PATIENTS (RR + NON-RR)



Source: 2018 LC Global Patient Survey ©

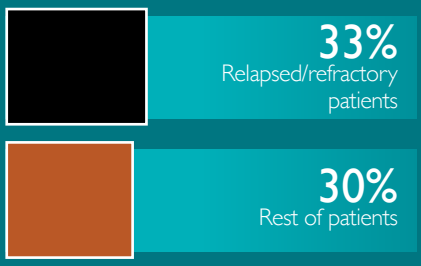
Psychosocial Effects

Psychosocial effects encompass the psychological and emotional well-being of the patient and how it impacts their day-to-day life. Both RR and non-RR DLBCL patients reported the same top psychosocial issues during and after treatment (figures 13 &14). **Important to note here is these top psychosocial issues are not seeing a large decrease in prevalence once treatment is completed. Many of these issues were reported on similar levels during and after treatment, and some see an increase in prevalence after treatment as patients adapt to life post-cancer.** Additionally, psychosocial issues are continuing to affect DLBCL patients long-term (figure 15).

Fear of relapse was the highest cause of concern for all DLBCL patients following treatment, irrespective of their RR status. Fear of relapse is concerning not only because of the distress it causes patients, but also because of its negative impacts on quality of life, healthcare service use, and adherence to follow-up recommendations. Despite being a common experience for which cancer survivors seek professional help or support, **studies indicate that fear of relapse is one of the most frequently cited unmet needs.** This was reflected in the DLBCL patient population (all, i.e. RR+ non-RR); though more than half of these patients discussed their fear of relapse with their doctor, only 40% felt it helped alleviate the fear, and only 43% were referred onto further support. Those who experience fear of relapse must be identified, supported, and directed to appropriate resources.

Primary Psychosocial concern for patients with DLBCL:

During treatment:
Change in relationships



After treatment:
Fear of relapse

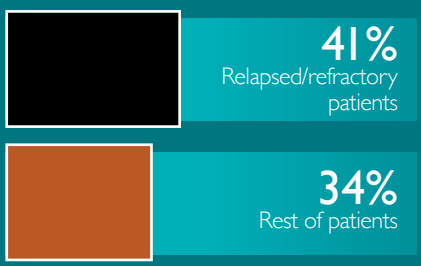


FIGURE 13: TOP PSYCHOSOCIAL ISSUES REPORTED DURING TREATMENT BY DLBCL PATIENTS

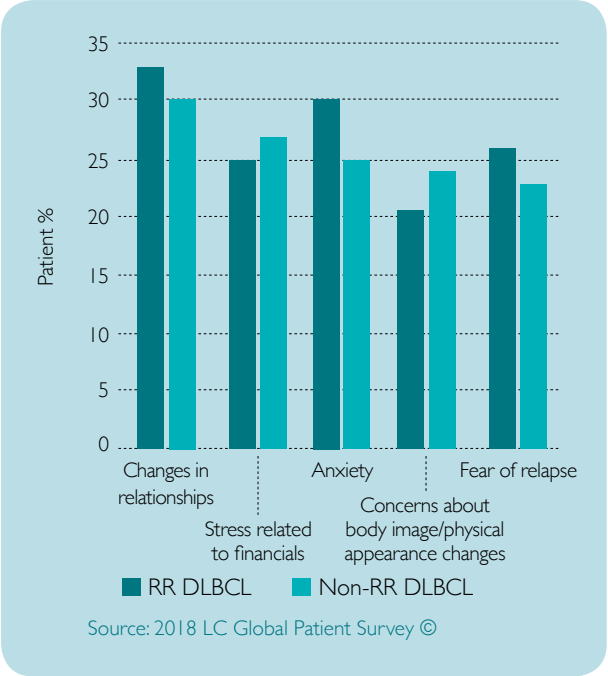


FIGURE 14: TOP PSYCHOSOCIAL ISSUES REPORTED AFTER TREATMENT BY DLBCL PATIENTS

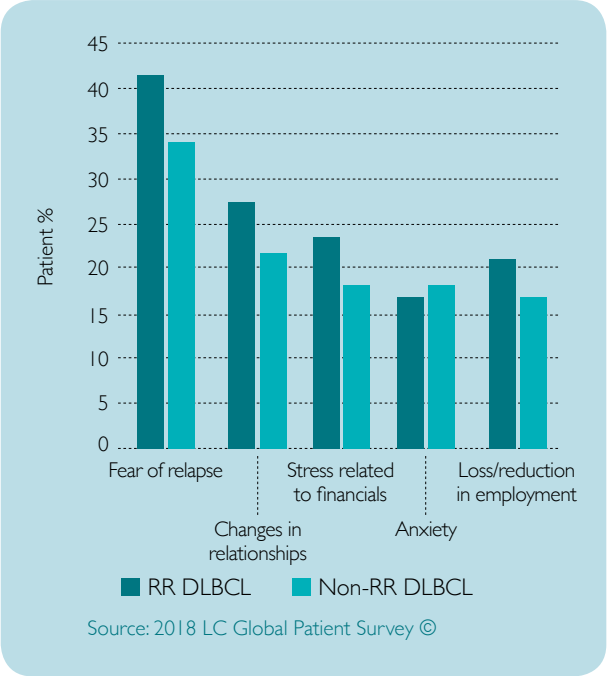
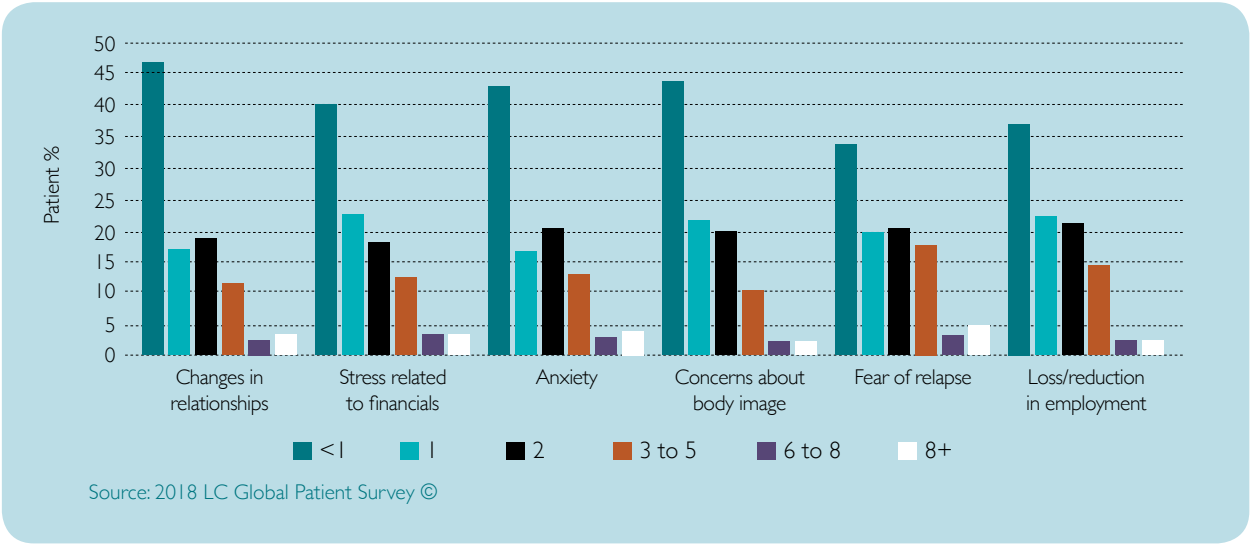


FIGURE 15: TIME LENGTH (IN YEARS) OF TOP PSYCHOSOCIAL ISSUES FOLLOWING TREATMENT REPORTED BY ALL DLBCL PATIENTS (RR + NON-RR)



Compared to non-RR DLBCL patients, **the reported prevalence of psychosocial issues was again higher across the majority of categories for RR DLBCL patients.** Changes in relationships are a prominent issue that RR patients experience. Many of these patients may feel as though people are tired and moving on, that people do not know how to support them any longer as their cancer persists, or that they are living in a different world than the one they previously shared. Additionally, given that RR patients are likely undergoing numerous rounds of treatment, it is not surprising that they are experiencing financial stress. This stress is not just related to therapy costs, but may also be attributed to time off work, travel costs, parking at hospitals/clinics, other hired assistance and so on.

Communication with Healthcare Professionals

Globally, there are many cultural, social, and healthcare system-based differences that can impact how patients communicate with healthcare professionals. For this section, the LC examined doctor-patient communication for the total DLBCL patient population (n=1478), as well as how this communication varied across geographic regions using the sample populations shown in table 3.

TABLE 3: NUMBER OF DLBCL PATIENTS PER GEOGRAPHIC REGION EXAMINED

Number of DLBCL Patients per Geographic Region					
	North America	South America	Asia Pacific	Eastern Europe	Western Europe
Countries Examined	CA 17 US 26	CO 12 AR 17	JP 40 NZ 25	BG 25 RS 16	GB 20 IT 35
Total DLBCL Patients	**43**	**29**	**65**	**41**	**55**

** CA Canada, US United States of America, CO Columbia, AR Argentina, JP Japan, NZ New Zealand, BG Bulgaria, RS Serbia, GB United Kingdom, IT Italy*

Source: 2018 LC Global Patient Survey ©

Healthcare professionals and palliative care providers can play a major role in easing physical and emotional concerns for patients. When asked specifically about the concerns they communicated to their doctor(s), **DLBCL patients (total) were much more likely to communicate their physical/medical issues (77%) than their emotional issues (38%). Additionally, DLBCL patients (total) received more help from the doctor with physical/medical issues than emotional issues, though support in both areas was insufficient (less than 50% felt helped in either area).**

When examined geographically, the majority of DLBCL patients in all regions reported communicating physical/medical issues to their doctor (figure 16). Many DLBCL patients in North and South America reported that the doctor was able to help with these issues. Fewer DLBCL patients in Western Europe and Asia Pacific reported being helped, and the least amount of DLBCL patients were helped in Eastern Europe.

Patient concerns communicated to doctor:

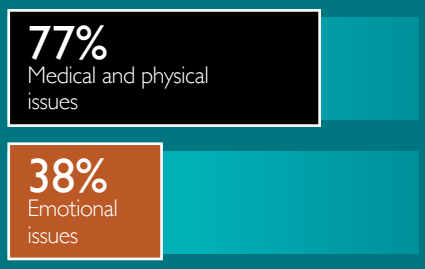


FIGURE 16: DLBCL PATIENT COMMUNICATION OF PHYSICAL/MEDICAL ISSUES TO DOCTOR BY REGION

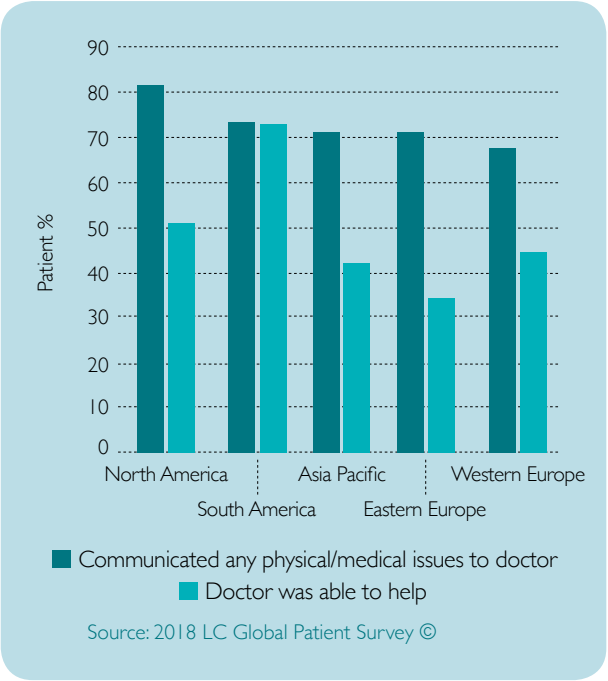
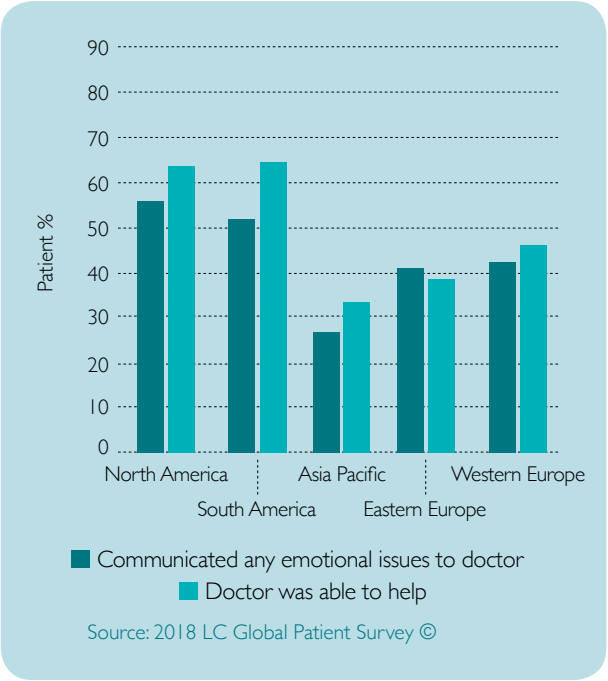


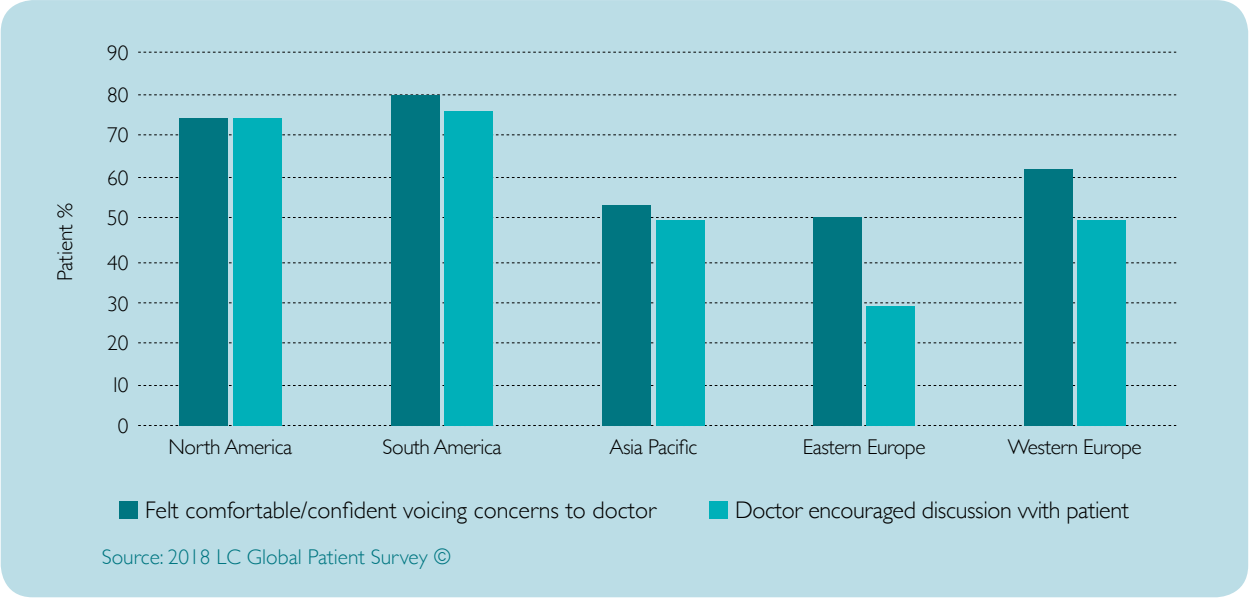
FIGURE 17: DLBCL PATIENT COMMUNICATION OF EMOTIONAL ISSUES TO DOCTOR BY REGION



Compared to physical/medical issues, emotional issues were less frequently communicated to doctors across all geographic regions (figure 17). DLBCL patients in Eastern and Western Europe were less likely to communicate and receive help for emotional issues than patients in North and South America. DLBCL patients in Asia Pacific seldom communicated or received helped for their emotional issues.

Of the total DLBCL patient population, **only 49% felt confident/comfortable voicing their concerns to their doctors. Additionally, only 45% indicated that the doctor encouraged discussion with them surrounding key issues (side effects, fear of relapse, fatigue, etc.).** When examined geographically, DLBCL patients in Asia Pacific and Eastern Europe reported feeling the least confident voicing concerns to their doctors (figure 18). Further, while most DLBCL patients in North and South America reported that their doctor encouraged discussion, less than half of DLBCL patients in Western Europe and Asia Pacific reported that their doctor(s) did so. Only 29% of DLBCL patients in Eastern Europe reported that their doctor encouraged discussion.

FIGURE 18: DLBCL PATIENT COMMUNICATION WITH DOCTOR BY REGION



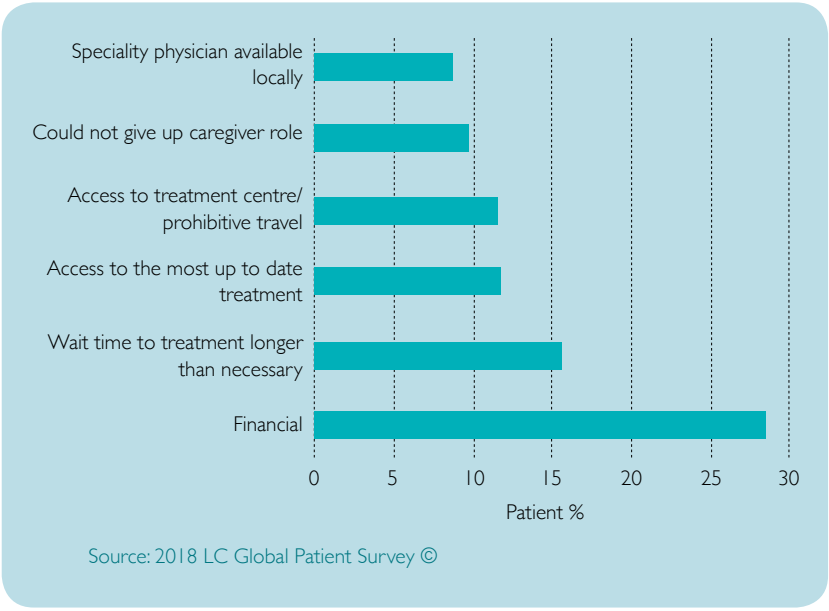
Source: 2018 LC Global Patient Survey ©

It is evident that a major two-way communication issue exists between patients and their doctors. Patients are not often communicating their emotional issues to the doctor, and when they do, they are met with inadequate support. To encourage communication, the emotional impact of a cancer diagnosis must be acknowledged at the outset, and the emotional cues from the patients must be recognised and responded to throughout their experience. Healthcare providers cannot be expected to provide all the information and support patients need; however, patients must be directed to the appropriate resources. This can include other resources that are hospital or community-based, as well as patient organisations.

Barriers to Care

There are many reasons why a patient may not be able to access treatment. The two main barriers reported by DLBCL patients were financials and wait time to treatment that was longer than necessary (figure 19). Other barriers concerning personal support (i.e. could not give up caregiver role) were reported, highlighting the fact that patients require both clinical as well as social support during their treatment.

FIGURE 19: TOP BARRIERS TO TREATMENT REPORTED BY DLBCL PATIENTS

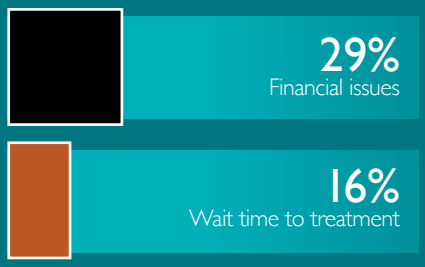


Source: 2018 LC Global Patient Survey ©

The numerous barriers patients face can be linked and can make other physical and emotional issues more pronounced. Living with any form of cancer can hinder a person's ability to make a living, either due to treatment side effects or because they need to take time off for treatment, tests, etc. This can cause financial stress, so too can undergoing multiple rounds of treatment, or travelling to receive a treatment that is not available locally. Additionally, since this DLBCL patient pool was global, access issues (approvals, reimbursements) can arise depending on geography. If personal support is lacking, or if patients cannot give up their caregiver role, then even if they can access treatment, they may not be able to receive it, or receive it in a timely manner due to their personal circumstances.

Patients face many challenges throughout their experience. The aim should be to provide optimal care with support structures in place allowing patients access to specialist physicians, up-to-date treatments, and adequate personal/social support.

Primary barriers to treatment:



Conclusion

While DLBCL is a curable disease in two thirds of patients, there is still considerable room for improvement in care.

- Access to equal, quality treatment needs to improve. It is imperative that novel therapies are made available to all patients no matter where they live.
- Healthcare providers should perform molecular risk assessment for every patient to adopt individualised therapy, requiring increased accessibility to these costly tests.
- A relatively small proportion of patients are cured in the RR setting with current treatments. Advances are needed to improve outcomes for RR DLBCL patients.
- Clinical trials should be made available in more countries to ensure novel therapies are widely researched and accessible to all.
- Finding effective, less-toxic treatments is a priority.
- Fatigue is the leading physical issue affecting wellbeing in patients before, during and after treatment. Patients need to be provided with strategies to help them cope with this issue for an overall improvement to their quality of life and new treatments need to be developed that don't exacerbate this disease symptom.
- Post-treatment, many patients experience fear of relapse. This fear needs to addressed and monitored to ensure it doesn't become overwhelming and life-impacting.
- The 2018 LC GPS indicated that financial constraint was the greatest barrier to treatment. This has the potential to lead to, or worsen, 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 - WHO Classification of DCBCL Subtypes

Since the last World Health Organization (WHO) classification in 2008 (of mature large B cell lymphoid neoplasms), the adoption of genomic technologies has become more widespread. This has provided new insights into DLBCL biology and has led to the identification of distinct molecular subtypes and novel pathogenic pathways. The updated 2016 WHO classification is reflective of these advancements (table A1).

One of the major things to note is that this updated classification now requires cell of origin identification. Most cases of DLBCL do not fall perfectly into a defined category, and they are considered DLBCL not otherwise specified (NOS). NOS cases can be grouped into molecular subtypes according to their cell of origin.[2] Within the large category of DLBCL NOS, two distinct molecular subtypes have been recognised (with ~15% of patients remaining unclassifiable):

1. **Germinal centre B cell (GCB):** GCB DLBCL derives from centroblasts, and therefore expresses genes which can be found in germinal centre B cells including: GCET1, CD10, and BCL6. Approximately one third of GCB DLBCL have c-rel amplification or a t(14;18) translocation, and 10-20% express mutations of the histone methyltransferase EZH2 or deletion of PTEN. Overexpression of BCL2 is also observed.[1,2,4,8]

2. **Activated B cell (ABC):** ABC DLBCL derives from plasmablastic cells before they exit the germinal centre, and therefore have a gene expression like that of mature plasma cells including MUM1 and FOXP1. The constitutive activation of the NF-kappaB signalling is typical, and more than 50% show mutations concerning the regulation of the NF-kappaB cascade. Roughly 30% have recurring mutations in MYD88, 20% show mutations in CD79A or CD79B, and 10% show activating mutations of CARD11. [1,2,4,8]

TABLE A1: WHO CLASSIFICATION OF MATURE LARGE B-CELL LYMPHOID NEOPLASMS IN 2008 VS 2016[10]

2008 WHO Classification	2016 WHO Revision	Comments
Diffuse large B-cell lymphoma (DLBCL), NOS	Diffuse large B-cell lymphoma, NOS - germinal centre B-cell type[a] - activated B-cell type[a]	- cell of origin is required. Use of IHC algorithm is acceptable - coexpression of MYC and BCL2 (DE) is prognostically relevant
T-cell/histiocyte rich large B-cell lymphoma	T-cell/histiocyte rich large B-cell lymphoma	- no major changes
Primary DLBCL of the central nervous system (CNS)	Primary DLBCL of the central nervous system (CNS)	- frequent *MYD88* L265P mutations
Primary cutaneous DLBCL, leg type	Primary cutaneous DLBCL, leg type	- *MYD88* L265P mutations in ~50% of cases
EBV+ DLBCL of the elderly	EBV+ DLBCL, NOS[a]	- change in nomenclature because it also occurs in younger patients - should be distinguished from other well characterised EBV-associated lymphomas
	EBV$^+$ *mucocutaneous ulcer*[a]	- new entity associated with iatrogenic immunosuppression and age-related immunosenescence
DLBCL associated with chronic inflammation	DLBCL associated with chronic inflammation	- no major changes
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis	- no major changes
Primary mediastinal large B-cell lymphoma	Primary mediastinal large B-cell lymphoma	- no major changes
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma	- no major changes
ALK+ large B-cell lymphoma	ALK+ large B-cell lymphoma	- no major changes
Plasmablastic lymphoma	Plasmablastic lymphoma	- *MYC* rearrangement in ~50% of cases - 70% EBV+ with latency I or II
Primary effusion lymphoma	Primary effusion lymphoma	- no major changes
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease	*HHV8+ DLBCL, NOS*[a]	- change in nomenclature
Burkitt lymphoma	Burkitt lymphoma	- *TCF3* or ID3 mutations in up to 70% of cases
	Burkitt-like lymphoma with 11q aberration[a]	- new provisional entity - resembles Burkitt lymphoma but lacks *MYC* translocation
B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma (BCLU)	High grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements[a] High grade B-cell lymphoma, NOS[a]	- new category for all double or triple hit lymphomas excluding transformed FL, lymphoblastic lymphoma and MCL - include cases with BCLU and blastoid morphology without gene rearrangements

The provisional entities are listed in italics, [a]Changes from the 2008 classification, NOS Not otherwise specified, EBV Epstein Barr virus

Appendix B - Diagnostic Testing for DLBCL

Protein Tests

For diagnosis, the proteins in the cell's surface (membrane) must be studied.[19] This is called immunophenotyping, and there are several tests that are regularly used (table B1). DLBCLs have a common pattern of proteins, which includes the presence of CD20 and CD45 and no CD3.[1,8,20] These proteins are also studied to learn cell of origin (ABC vs GCB).[21]

TABLE B1: PROTEIN TESTS FOR DLBCL DIAGNOSIS, NCCN 2017 GUIDE[6,20]

Protein Test	Definition	Protein to Test for
IHC Panel (immunohistochemistry)	A chemical marker is applied to cells and then they are examined under a microscope	BLC2, BCL6, CD3, CD5, CD10, CD20, CD45, IRF4/MUM1, ki-67, and MYC To learn specific DLBCL subtype: ALK, CD30, CD138, cyclin D1, EBER-ISH, HHV8, SOX11, kappa and lambda light chain proteins
Flow Cytometry	A light-sensitive dye is added to cells. Then, patients' blood is passed through a flow cytometry machine and it measures surface proteins on thousands of cells	CD45, CD3, CD5, CD10, CD19, CD20, kappa and lambda light chain proteins

Recent research concerning cellular expression has also identified CD37 and PD-L1 as proteins of prognostic value in DLBCL.[1] CD37 is an antigen expressed on the cell surface of mature B cells, which predicts significantly better survival.[22] PD-L1 is a protein expressed on the surface of cancer cells (either tumour cells or microenvironment cells) that is associated with poor overall survival.[1,23] This protein emits a 'don't touch me' signal so that the cancer cells are protected, which makes them more resistant to treatment.[23]

Genetic Tests

These tests are advised if the IHC (protein tests) finds GCB-like DLBCL with MYC, and BCL2 or BCL6. Genetic tests (FISH, Karyotype) will be used to asses for MYC, BCL2 and BCL6 gene rearrangements.[1,4,8,20] These are the double and triple-hit lymphomas. A double-hit lymphoma has a MYC rearrangement and either a BLC2 or BCL6 rearrangement. A triple-hit has all three rearrangements.[1,4,8,20]

All these lab results will be recorded in a pathology report, which will be vital to diagnosis and treatment planning.

Appendix C - DLBCL Staging

Staging allows an understanding of how much lymphoma is present and where it is in the body.[7] Because DLBCL is a blood cancer, the whole body must be examined to find all the lymphoma. This is done with a whole-body computed tomography (CT) scan, or a positron emission tomography (PET)/CT scan. A bone marrow biopsy may be done to look for lymphoma cells in the bone, and sometimes a spinal tap (lumbar puncture) is done to look for lymphoma cells in the spinal cord and brain. The results of these tests will be used to assess the stage of the lymphoma.[1,6,7,14] The Ann Arbor staging system (table C1) is used to stage DLBCL.

- Early stage lymphoma (stage I and II) represents lymphoma affecting only one area of the body (above or below the diaphragm).
- Advanced stage disease (stage III and IV) indicates that lymphoma has spread to both sides of the diaphragm, or outside of the lymphatic system to several organs. It is common for patients with DLBCL to present with advanced stage disease.[6]

TABLE C1: ANN ARBOR CLASSIFICATION[6]

Stage	Area of Involvement
I	Only one lymph node (or lymph structure) is involved
II	Two or more lymph nodes (or lymph structures) are involved but only on one side (above or below) of the diaphragm
III	Lymph nodes (or structures) on both sides of the diaphragm are involved
IV	The lymphoma is present in the bone marrow and/or tissues or organs other than lymph nodes or lymph structures

Lymphomas may also be given a designation of A or B, with A meaning there are no *B symptoms* and B indicating the presence of the B symptoms of lymphoma (unexplained fever >38°C, drenching night sweats, or loss of >10% body weight within 6 months).

Appendix D - International Prognostic Index (IPI) for DLBCL

The International Prognostic Index (IPI) is the primary clinical tool used to predict outcomes in patients with DLCBL.[3,6] There is now more than one version of the IPI (table D1). The standard version was developed prior to the availability of rituximab; however, it has been evaluated in patients treated with rituximab-based therapy and has proven to retain its prognostic utility.[2]

An age-adjusted version has been developed for people 60 years of age and younger. Additionally, an enhanced IPI has been recently developed using data from the National Comprehensive Cancer Network (NCCN-IPI). The NCCN-IPI was validated in a DLBCL patient population being treated in British Columbia, Canada.[2] When compared with the standard IPI, the NCCN-IPI was better able to provide a more clinically useful prediction of outcome.[2,3,6]

TABLE D1: THREE AVAILABLE VERSIONS OF THE IPI FOR DLBCL PROGNOSIS

Standard IPI	Age Adjusted IPI	NCCN-IPI
1 point is given for:	1 point is given for:	1 point is given for:
1. > 60 years of age 2. LDL* above normal 3. performance status* score ≥2 4. stage III or IV 5. > 1 extranodal site	1. stage III or IV 2. LDL above normal 3. performance status ≥2	1. ages 41 to 60 • 2 points given for 61-74 • 3 points given for ≥75 2. LDL between 1 and 3 • 2 points given for LDL > 3 3. stage III or IV 4. extranodal disease 5. performance status score ≥2
Scores: 0-1 = low risk 2 = low-intermediate risk 3 = high-intermediate risk ≥4 = high risk	Scores: 0= low risk 1= low-intermediate risk 2= high-intermediate risk 3= high-risk	Scores: 0-1 = low risk 2 or 3= low-intermediate risk 4 or 5 = high-intermediate risk ≥6 = high risk

**LDL: lactate dehydrogenase level*
**Performance status: how much a lymphoma has debilitated someone or not*

IPI gives an overall idea of the aggressiveness or the risk of the disease, it does not always work perfectly, and must be sensitively applied and analysed case-by-case.[14] Some other clinical factors that may contribute to a poorer outcome following rituximab-based therapy include male gender, bone marrow involvement with large cell lymphoma but not discordant small cells, maximum tumour diameter ≥ 10cm, low absolute lymphocyte/monocyte count, and vitamin D deficiency.[2]

Appendix E - NCCN and ESMO DLBCL First-Line Clinical Treatment Guidelines

NCNN Clinical Treatment Guidelines (2019)	ESMO Treatment Guidelines (2015)
First Line Treatment (Standard)	**First Line Treatment (Standard)**
R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)	R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
Dose-dense R-CHOP 14	Dose-dense R-CHOP 14
Dose-Adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituximab	R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone
First Line Treatment for Patients with Poor Left Ventricular Function	R-CHOEP (cyclophosphamide, vincristine, doxorubicin, etoposide, prednisone, rituximab)
R-CEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)	
RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone	
Dose-Adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituximab	
RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)	
RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone)	
First Line Treatment for Frail and Elderly Patients	
R-CEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)	
RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	
Low-dose CHOP + Rituximab	
RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone)	
First Line Consolidation	
Lenalidomide maintenance*	

**Therapy used "off-label" - no official indication for this subtype*

Appendix F - NCCN First-Line Treatment Guidelines (2017) for DLBCL Patients by Stage

For Stages I and II DLBCL patients

Option 1:		
Immunochemotherapy	**Results**	**Treatment**
6 cycles of: • R-CHOP or • RCEPP • RCDOP • DA-EPOCH-R • RCEOP • RGCVP • R-mini-CHOP	No signs of cancer	• Radiation therapy
	Cancer looks smaller on scans and no cancer found with biopsy	• Radiation therapy
	Cancer looks smaller on scans; cancer is found with biopsy or no biopsy done	• Higher-dose radiation therapy • Blood stem cell transplant ± radiation therapy • Clinical trial
	Cancer looks same or larger	• Second-line treatment • Radiation therapy in some cases

Option 2:		
Immunochemotherapy	**Results**	**Treatment**
3-4 cycles out of 6 planned cycles of: • R-CHOP or • RCEPP • RCDOP • R-DA-EPOCH + rituximab • RCEOP • RGCVP • R-mini-CHOP	No signs of cancer	• Complete treatment
	Cancer looks smaller	• Complete treatment
	Cancer looks the same or larger; no cancer is found with biopsy	• Complete treatment
	Cancer looks same or larger; cancer is found with biopsy or biopsy is not done	• Second-line treatment • Radiation therapy in some cases

Continued on next page

Appendix F (continued)

Option 3 (for small cancers):		
Immunochemotherapy	**Results**	**Treatment**
3 cycles of: • R-CHOP or • RCEPP • RCDOP • DA-EPOCH + rituximab • RCEOP • RGCVP • R-mini-CHOP	No signs of cancer	• Radiation therapy
	Cancer looks smaller on scans and no cancer found with biopsy	• Radiation therapy
	Cancer looks smaller on scans; cancer is found with biopsy or biopsy not done	• Higher-dose radiation therapy • Clinical trial
	Cancer looks same or larger	• Second-line treatment • Radiation therapy in some cases
For Stages III & IV DLBCL Patients		
Immunochemotherapy	**Results**	**Treatment**
2-4 cycles out of 6 planned cycles of: • R-CHOP or • RCEPP • RCDOP • DA-EPOCH + rituximab • RCEOP • RGCVP • R-mini-CHOP	No signs of cancer or cancer looks smaller on scans	• Complete treatment • Clinical trial
	Cancer looks the same or larger; no cancer found with biopsy	• Complete treatment • Clinical trial
	Cancer looks the same or larger; cancer is found with biopsy or biopsy not done	• Second-line treatment • Radiation therapy in some cases

Extra Treatment

- Watch and wait
- Consider radiation therapy
- Consider lenalidomide maintenance
- Consider blood stem cell transplant if likely to relapse

Appendix G - NCCN and ESMO DLBCL Second-Line Clinical Treatment Guidelines

NCNN Clinical Treatment Guidelines (2019)	Relapsed and Subsequent
Relapsed and Subsequent	**Relapsed and Subsequent**
DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab	R-DHAP (rituximab, dexamethasone, cisplatin, cytarabine)
DHAX (dexamethasone, oxaliplatin, cytarabine) ± rituximab	R-ICE (ifosfamide, carboplatin, etoposide, rituximab)
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab	R-GDP (gemcitabine, dexamethasone, cisplatin, rituximab)
GDP (gemcitabine, dexamethasone, cisplatin)	Stem Cell Transplant (Autologous or Allogeneic)
GemOx (gemcitabine, oxaliplatin) ± rituximab	
ICE (ifosfamide, carboplatin, etoposide) ± rituximab	
MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab	
Bendamustine ± rituximab	
Brentuximab vedotin* (For CD30+)	
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab	
CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab	
Dose-Adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituximab	
GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab	
Gemcitabine, vinorelbine ± rituximab	
Ibrutinib* (for non-GCB)	
Lenalidomide* ± rituximab	
Stem Cell Transplant (Autologous or Allogeneic)	
Chimeric Antigen Receptor Therapy (CAR T)	
axicabtagene ciloleucel	
tisagenlecleucel	

**Therapy used "off-label" - no official indication for this subtype*

NCCN Second Line Treatment Guidelines (2017) for Blood Stem Cell Transplant Planned vs not Planned

Blood stem cell transplant is planned:

Immunochemotherapy	Results	Treatment
• DHAP ± rituximab • ESHAP± rituximab • GDP ± rituximab • GemOx ± rituximab • ICE ± rituximab • MINE ± rituximab Other cancer drugs to treat CNS disease may also be received	No signs of cancer or cancer looks smaller	• Autologous blood stem cell transplant ± involved-site radiation therapy • Clinical trial • Allogenic blood stem cell transplant in some cases
	Cancer looks same or larger	• Clinical trial • Drug treatment • Radiation therapy • Best supportive care

Blood stem cell transplant is not planned:

- Clinical trial
- Drug treatment:
  - Bendamustine ± rituximab
  - Brentuximab vedotin for CD30+ disease
  - CEPP ± rituximab
  - CEOP ± rituximab
  - DA-EPOCH ± rituximab
  - GDP ± rituximab
  - GemOx ± rituximab
  - Lenalidomide ± rituximab
  - Rituximab
  - Other cancer drugs to treat CNS disease may also be received
- Radiation therapy
- Best supportive care

Appendix H - Therapy Access by LC Member Country for DLBCL

Accessible defined as therapy being available to patient through public healthcare
Therapy available through a special access program within that country
Therapy not available/no evidence found
No information found whether therapy is available for this subtype

Country	Novel Therapies			Standard Therapies					Rituximab Biosimilars	
EUROPE	CAR T AXICABTAGENE CILOLEUCEL	CAR T TISAGENLECLEUCEL	PIXANTRONE	CHOEP+R	CHOP+R	DHAP+R	EPOCH+R	R+ACVBP	BIOSIMILAR TRUXIMA	BIOSIMILAR RIXATHON
Belgium										
Bulgaria										
Croatia										
Czech Republic										
Denmark										
Finland										
France										
Germany										
Greece										
Hungary										
Ireland										
Italy										
Latvia										
Lithuania										
Macedonia										
Netherlands										
Norway										
Poland										
Portugal										
Romania										
Russian Federation										
Serbia										
Slovakia										
Slovenia										
Spain										
Sweden										
Switzerland										
Turkey										
Ukraine										
United Kingdom										

Country	Novel Therapies			Standard Therapies					Rituximab Biosimilars	
NORTH AMERICA	**CAR T AXICABTAGENE CILOLEUCEL**	**CAR T TISAGENLECLEUCEL**	**PIXANTRONE**	CHOEP+R	CHOP+R	DHAP+R	EPOCH+R	R+ACVBP	BIOSIMILAR TRUXIMA	BIOSIMILAR RIXATHON
United States										
Canada										
LATIN AMERICA	**CAR T AXICABTAGENE CILOLEUCEL**	**CAR T TISAGENLECLEUCEL**	**PIXANTRONE**	CHOEP+R	CHOP+R	DHAP+R	EPOCH+R	R+ACVBP	BIOSIMILAR TRUXIMA	BIOSIMILAR RIXATHON
Argentina										
Barbados										
Brazil										
Colombia										
Uruguay										
Venezuela										
Mexico										
ASIA PACIFIC	**CAR T AXICABTAGENE CILOLEUCEL**	**CAR T TISAGENLECLEUCEL**	**PIXANTRONE**	CHOEP+R	CHOP+R	DHAP+R	EPOCH+R	R+ACVBP	BIOSIMILAR TRUXIMA	BIOSIMILAR RIXATHON
China										
India										
Japan										
Republic of Korea										
Singapore										
Australia										
New Zealand										
MIDDLE EAST & AFRICA	**CAR T AXICABTAGENE CILOLEUCEL**	**CAR T TISAGENLECLEUCEL**	**PIXANTRONE**	CHOEP+R	CHOP+R	DHAP+R	EPOCH+R	R+ACVBP	BIOSIMILAR TRUXIMA	BIOSIMILAR RIXATHON
Israel										
Algeria										
Morocco										
South Africa										

Data as of March 2019

CHOEP-R - cyclophosphamide, vincristine, doxorubicin, etoposide, prednisone, rituximab
CHOP-R - cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab
DHAP-R - dexamethasone, cisplatin, cytarabine, rituximab
EPOCH-R - etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab
R-ACVBP - rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone

Appendix I - DLBCL Clinical Trial Activity by LC Member Country

LC Member Country	Total P2 and P3 DLBCL Trials	Novel Therapy P2 and P3 DLBCL Trials
EUROPE		
Belgium	25	25
Bulgaria	4	4
Czechia	13	12
Denmark	6	6
France	38	38
Finland	6	5
Germany	39	34
Greece	3	3
Hungary	10	10
Ireland	3	3
Italy	43	37
Latvia	0	0
Lithuania	0	0
Netherlands	20	19
Norway	4	3
Poland	19	18
Portugal	5	5
Romania	2	2
Slovakia	1	1
Slovenia	0	0
Spain	34	34
Sweden	10	8
United Kingdom	38	36
Croatia	2	1
Macedonia	0	0
Russian Federation	8	7
Serbia	3	2
Switzerland	9	9
Turkey	8	8
Ukraine	7	6

LC Member Country	Total P2 and P3 DLBCL Trials	Novel Therapy P2 and P3 DLBCL Trials
ASIA PACIFIC		
China	55	46
India	3	2
Japan	12	11
Republic of Korea	21	18
Singapore	8	7
Australia	29	27
New Zealand	8	8
LATIN AMERICA		
Argentina	1	1
Barbados	0	0
Brazil	5	5
Colombia	1	1
Uruguay	0	0
Venezuela	0	0
Mexico	2	2
NORTH AMERICA		
Canada	29	28
United States	186	152
MIDDLE EAST & AFRICA		
Israel	15	15
Algeria	0	0
Morocco	0	0
South Africa	0	0

Data as of March 2019

Glossary

Adverse effect: An unexpected medical issue that happens during treatment with a drug or other therapy. Adverse effects may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given.

Antibodies (also known as an immunoglobulin): A protein produced in response to and counteracting a specific antigen (e.g. bacteria, virus). The antibody attaches to the antigen and tags it for attack by either another part of the immune system or directly neutralises the antigen itself, making it ineffective.

Autologous stem cell transplant: A procedure in which blood-forming stem cells (cells from which all blood cells develop) are removed, stored, and later given back to the same person.

Biosimilars: Biosimilar or biosimilarity means that the biological product (in this case a drug) is highly similar to the reference product (the original biologic drug; also called the innovator product) and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, quality and effectiveness of the product.

Cell of origin: Cancers of distinct subtypes may derive from different 'cells of origin'. These cells acquire the first genetic hit(s) that culminate in the initiation of cancer. Identifying these crucial target cell populations may allow earlier detection of malignancies and better prediction of tumour behaviour.

Chemosensitivity: The susceptibility of tumour cells to the cell-killing effects of anticancer drugs.

Chemotherapy: Widely used treatment for cancer. Chemotherapy refers to the drugs that prevent cancer cells from dividing and growing, the drugs do this by killing the dividing cells. A wide range of drugs are used to achieve these goals.

Chimeric antigen receptor T cells (CAR-T): CAR-T is a type of therapy, known as immunotherapy, which uses a patient's own immune system to treat cancer. 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.

CNS status: Central nervous system (CNS) lymphoma is a rare lymphoma in which cancer cells from lymph tissue form in the brain and/or spinal cord (primary CNS), or spread from other parts of the body to the brain and/or spinal cord (secondary CNS). CNS status, or CNS involvement, has been identified as a prognostic factor in lymphomas.

Gene-expression profiling (GEP): Messenger RNA (mRNA) molecules carry the genetic information needed to make proteins. GEP examines the relative abundance of mRNA from the various genes. GEP can assist in making a diagnosis; it can also determine response to treatment.

Heterogenous: Consisting of parts or things that are very different from each other.

Histology: The structure, especially the microscopic structure, of organic tissues in the human body.

Immunoblastic: Immunoblastic lymphoma is one of 3 morphologic variants of diffuse large B cell lymphoma (DLBCL). The other 2 variants are centroblastic lymphoma and anaplastic B-cell lymphoma.

Immunohistochemistry (IHC): Immunohistochemistry means the composition and properties ('chemistry') of immune ('immuno') tissue ('histo'). IHC uses antibodies to test for certain markers, also called antigens, which are on or in a cell.

Immunomodulatory agents: Immunomodulatory agents or drugs (IMiDs) are a novel and promising class of therapeutics. Thalidomide is the parent compound of this group of drugs. The analogues of thalidomide, CC-5013 (lenalidomide, Revlimid) and CC-4047 (Actimid) are more potent regulators of cellular immune and cytokine response while lacking some of the dose limiting side effects of the parent compound, such as neurologic toxicity.

Immunotherapy: Treatment that uses certain parts of a person's immune system to fight diseases such as cancer. This can be done by either stimulating your own immune system to work harder/smarter to attack cancer cells or giving you immune system components (such as man-made immune system proteins).

Kinase inhibitors: 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.

Malignant: A tumour that is not self-limited in its growth, is capable of invading adjacent tissues and spreading to distant tissues

Molecular genetics: The branch of genetics that focuses on the chemical structure and the functions, replication, and mutations of the molecules involved in the transmission of genetic information, namely DNA and RNA.

Molecular risk assessment: A procedure in which biomarkers (for example, biological molecules or changes in tumour cell DNA) are used to estimate a person's risk for developing cancer. Specific biomarkers may be linked to particular types of cancer.

Monoclonal antibody: 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).

Monocyte: A type of immune cell made in the bone marrow. It travels through the blood tissues in the body where is becomes a macrophage. Macrophages surround and kill microorganisms, remove dead cells, ingest foreign material, and boost immune responses. A monocyte is a type of phagocyte and a type of white blood cell.

Morphological (Morphology): The branch of biology that deals with the form of living organisms, and with relationships between their structures.

Next generation sequencing (NGS): A DNA sequencing technology. With NGS, the human genome can be sequenced in one day. This is much faster than previously available technology.

Oncogenic pathway: Cancer-causing signalling pathway. Genetic alternations in signalling pathways that control cell-cycle progression, cell growth, and cell death are common hallmarks of cancer.

PD1 inhibitors: PD-1 is a checkpoint protein on immune cells called T cells. It normally acts as a type of "off switch" that helps keep the T cells from attacking other cells in the body, this happens when PD-1 binds to PD-L1 (a protein on some normal and cancer cells). Some cancer cells have large amounts of PD-L1, which helps them evade immune attack. Drugs that target either PD-1 or PD-L1 can block this binding and boost the immune response against cancer cells.

Precision medicine: Emerging approach for disease treatment and prevention that accounts for individual variability in genes, environment, and lifestyle for each person.

Prognosis: The forecast of the probable outcome or course of a disease; the patient's chance of recovery.

Stromal signatures: gene-expression signatures. Studies are examining whether gene-expression signatures correlate with survival after treatment of diffuse large-B-cell lymphoma. Stromal-1 signature has been found to be prognostically favourable, while stromal-2 signature has been found to be prognostically unfavourable.

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