Overview of Diffuse Large B-Cell Lymphoma

Notice

- The data and conclusions of the following referenced presentations and/or publications are those of the author(s) and are provided as they were presented and/or published

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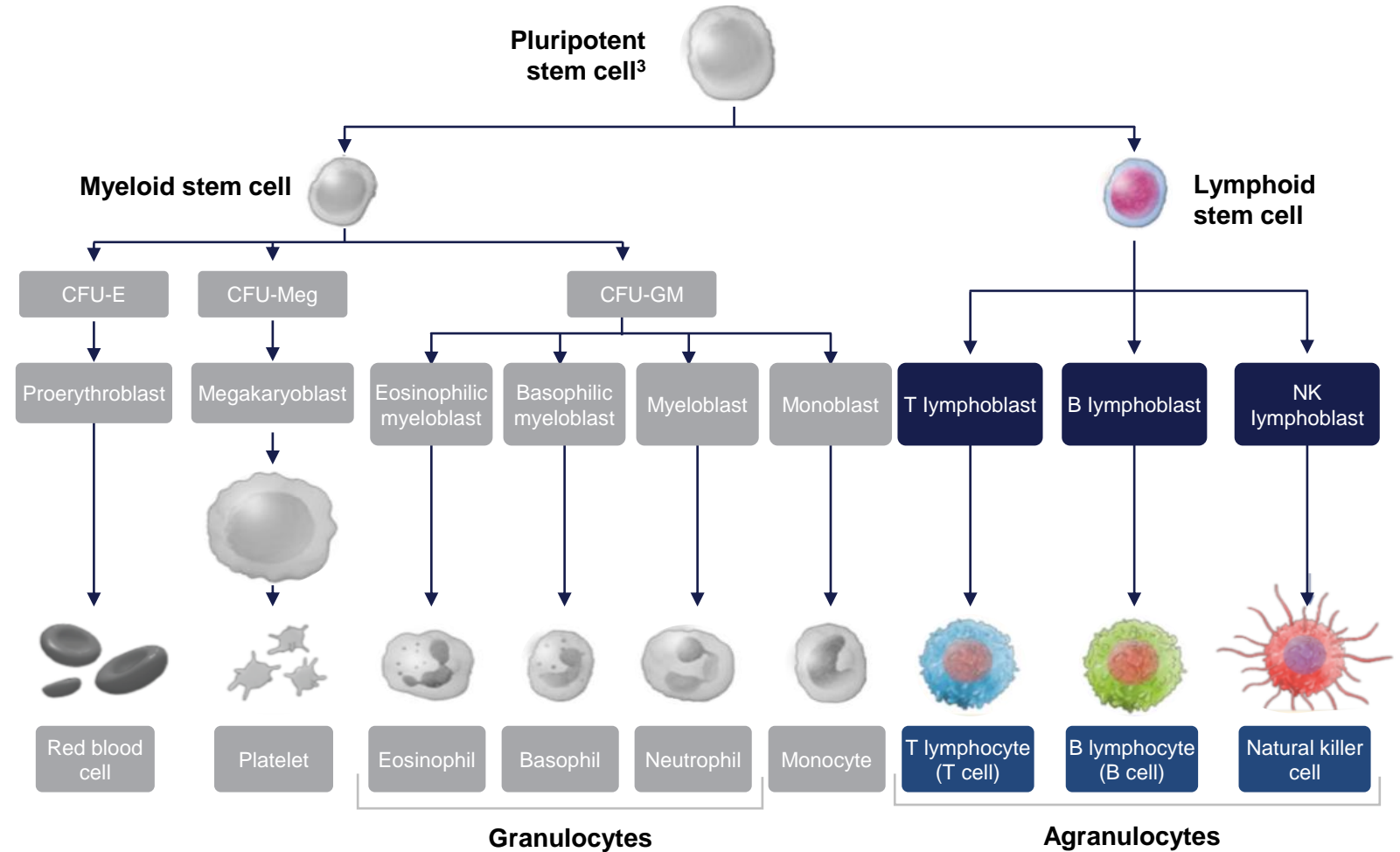Click the section tab of interest to be taken to the corresponding section of the deck

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Pathogenesis and Epidemiology of DLBCL

Lymphoid Cell Differentiation and Maturation

Lymphoid and myeloid lineages are separated at the progenitor level[1]

Lymphoid stem cells can differentiate into several types of lymphocytes, such as T cells, B cells, and NK cells[1]

Malignant tumors originating in lymphocytes are known as lymphomas and represent a diverse group of neoplastic disorders classified based on the cell of origin from which they arise[2]

Pluripotent stem cell[3]

Myeloid stem cell

Lymphoid stem cell

CFU-E

CFU-Meg

CFU-GM

Proerythroblast

Megakaryoblast

Eosinophilic myeloblast

Basophilic myeloblast

Myeloblast

Monoblast

T lymphoblast

B lymphoblast

NK lymphoblast

Red blood cell

Platelet

Eosinophil

Basophil

Neutrophil

Monocyte

T lymphocyte (T cell)

B lymphocyte (B cell)

Natural killer cell

Granulocytes

Agranulocytes

CFU-E, colony forming unit-erythroid; CFU-GM; colony-forming unit-granulocyte-macrophage; CFU-Meg, megakaryocytic colony forming unit; NK, natural killer.
1. Marti LC, et al. Lymphoid Hematopoiesis and Lymphocytes Differentiation and Maturation. *In Lymphocyte Updates: Cancer, Autoimmunity and Infection.* 2017. 2. Jiang M, et al. *Expert Rev Hematol.* 2017;10(5):405-415. 3. Lodish H, et al. *IUBMB Life.* 2010;62(7):492-6.
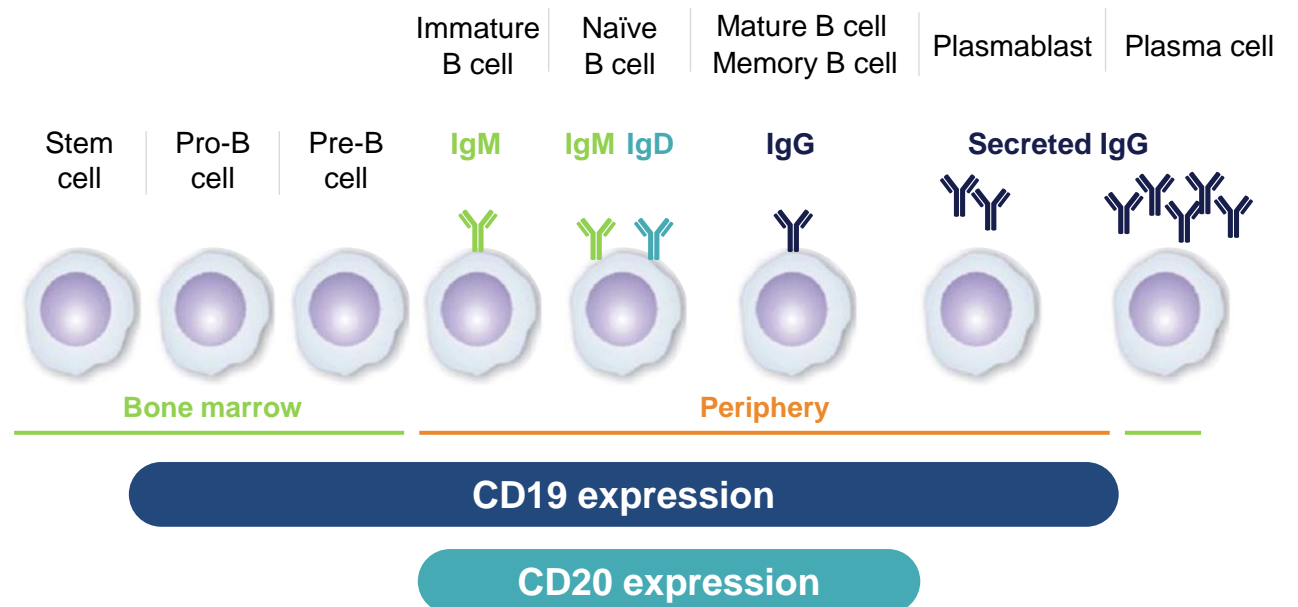
B-cell Development

B-cell development begins in the bone marrow and ends with their differentiation in the periphery (lymph nodes and/or spleen)[1]

The transmembrane protein CD19 is involved in B-cell fate and differentiation at multiple stages of B-cell development, and is also expressed during malignancy[2]

The transmembrane protein CD20 is also involved in B-cell development, differentiation, and malignancy[2,3]

- CD20 expression initiates later and is lost earlier than CD19[3]

Data suggests CD19 and CD20 exert their effects through interactions with B-cell receptor signaling[2,3]

Immature B cell | Naïve B cell | Mature B cell Memory B cell | Plasmablast | Plasma cell

Stem cell | Pro-B cell | Pre-B cell | **IgM** | **IgM IgD** | **IgG** | **Secreted IgG**

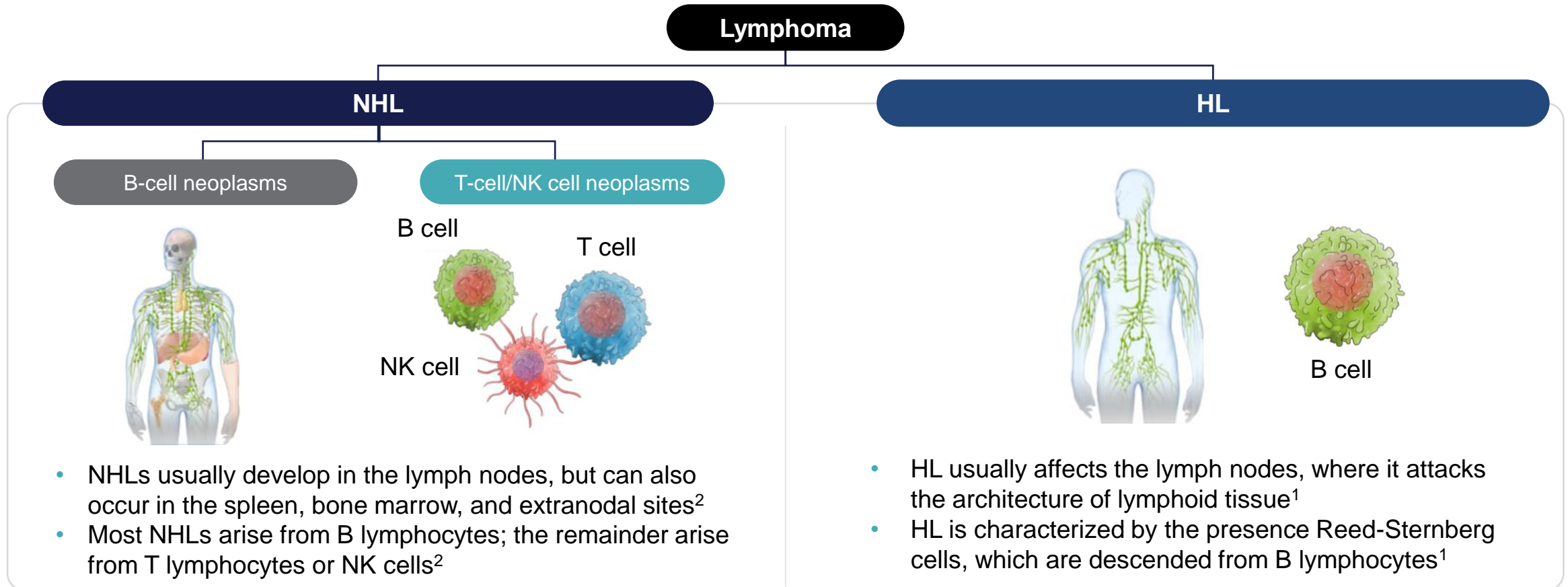**Bone marrow** | **Periphery**

CD19 expression

CD20 expression

CD, cluster of differentiation; IgD, immunoglobin D; IgM, immunoglobin M; IgG, immunoglobin G.

1. Marti LC, et al. Lymphoid Hematopoiesis and Lymphocytes Differentiation and Maturation. *In Lymphocyte Updates: Cancer, Autoimmunity and Infection.* 2017. 2. Blanc V, et al. *Clin Cancer Res.* 2011;17(20):6448-6458. 3. Forsthuber TG, et al. *Ther Adv Neurol Disord.* 2018;11:1756286418761697.

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Classification of Lymphoma

Traditionally, lymphomas are divided into HL and NHL[1,2]

NHL can be further classified as B-cell neoplasms or T-cell/NK cell neoplasms[2]

- NHLs usually develop in the lymph nodes, but can also occur in the spleen, bone marrow, and extranodal sites[2]
- Most NHLs arise from B lymphocytes; the remainder arise from T lymphocytes or NK cells[2]

- HL usually affects the lymph nodes, where it attacks the architecture of lymphoid tissue[1]
- HL is characterized by the presence Reed-Sternberg cells, which are descended from B lymphocytes[1]

HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

1. American Cancer Society. What is Hodgkin Lymphoma? https://www.cancer.org/cancer/types/hodgkin-lymphoma/about/what-is-hodgkin-disease.html. Accessed October 18, 2023. 2. American Cancer Society. What is Non-Hodgkin Lymphoma? https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/what-is-non-hodgkin-lymphoma.html. Accessed October 18, 2023.
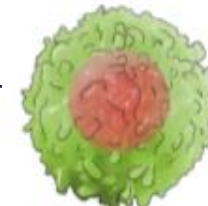
B-Cell Neoplasms

- B-cell neoplasms are divided into precursor and peripheral B-cell neoplasms, and can be further classified by morphology and immunophenotype
- Peripheral B-cell neoplasms can also be classified into indolent (usually not curable in advanced stages) and aggressive (potentially curable) forms

NHL

B-cell neoplasms   **T-cell/NK cell neoplasms**

Precursor B-cell Neoplasms

Example:
- B lymphoblastic leukemia/lymphoma

Indolent Peripheral B-cell Neoplasms

Examples:
- FL
- MZL
- Splenic MZL

Aggressive Peripheral B-cell Neoplasms

Examples:
- DLBCL
- MCL

FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.
National Cancer Institute. Adult Non-Hodgkin Lymphoma Treatment (PDQ®)–Health Professional Version. https://www.cancer.gov/types/lymphoma/hp/adult-nhl-treatment-pdq. Accessed October 18, 2023.

Pathogenesis of Different NHLs

NHLs Can Arise at Different Stages of B-Cell Differentiation
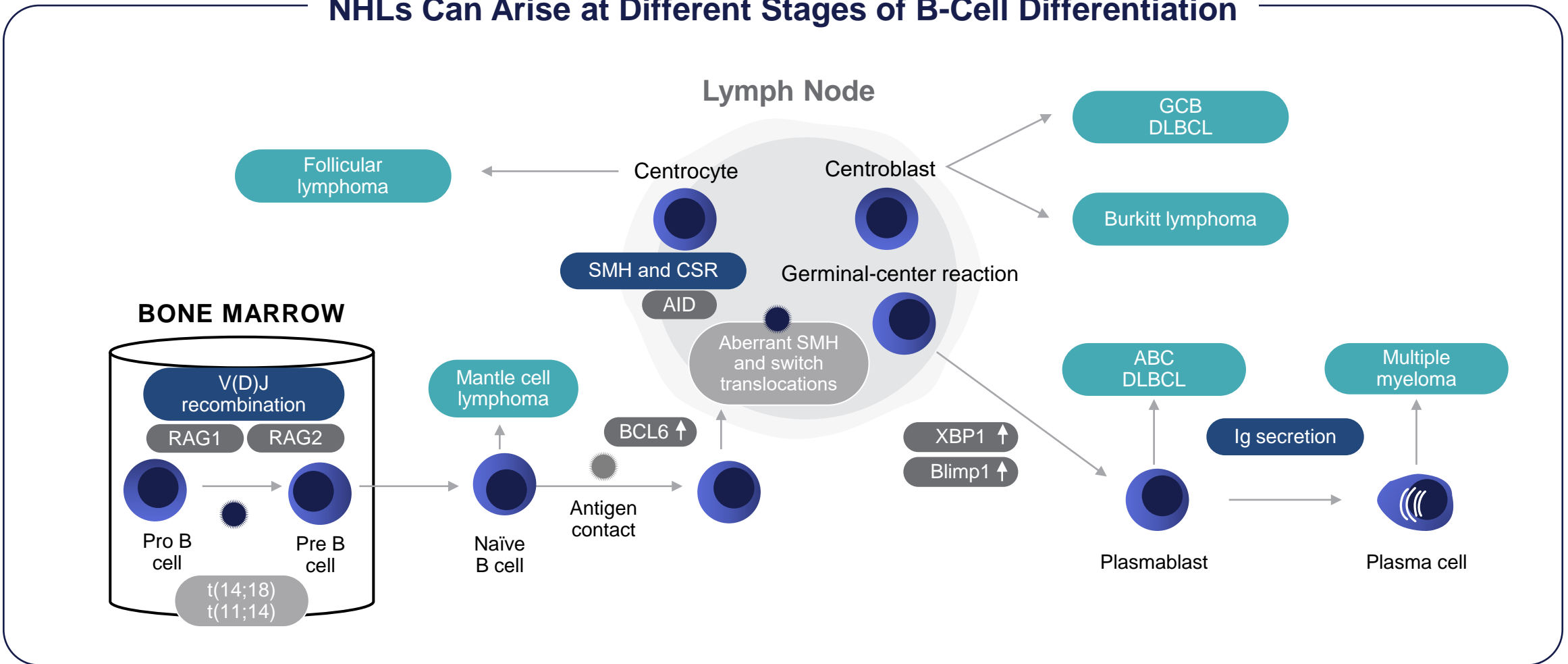
ABC, activated B-cell-like; AID, activation-induced cytidine deaminase; Blimp, B lymphocyte-induced maturation protein 1; BCL, B-cell lymphoma; CSR, class-switch recombination; GCB, germinal center B-cell-like; Ig, immunoglobulin; SMH, somatic hypermutation; t, translocation; XBP1, X box binding protein 1; V(D)J, variable diversity joining.
Nogai H, Dörken B, Lenz G. *J Clin Oncol*. 2011;29:1803-11.

B-cell Receptor Signaling in NHL

BCR signaling is a critical component of B cell activation, proliferation, survival, and migration in normal as well as malignant B cells

- BCR activation induces CD79A and B phosphorylation and subsequent recruitment of multiple kinases including SYK and the SRC family kinases (SFK)
- Activation of these kinases initiates the signaling cascade leading to phosphorylation, recruitment, and activation of other kinases and signaling molecules, including BTK, PLCγ2, PKC, and PI3K

The BCR signaling cascade ultimately activates multiple pro-survival pathways including ERK, NF-κB, and AKT signaling
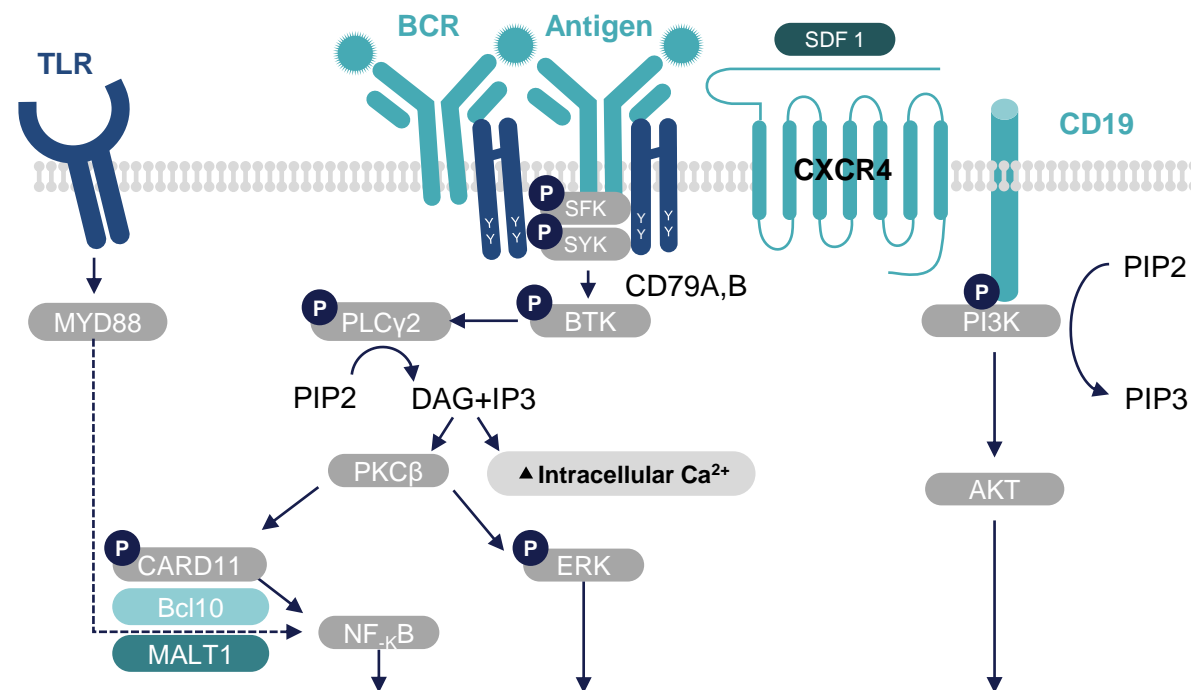
- Transcriptional activation
- Cell cycle progression/proliferation
- Integrin activation, chemokine-mediated migration

AKT, protein kinase B; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; Ca, calcium; CARD11, caspase recruitment domain family, member 11; CXCR4; chemokine receptor 4; DAG, diacyl-glycerol; ERK, extracellular signal-regulated kinase; IP3, inositol triphosphate; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; MYD88, myeloid differentiation primary response 88; NF-kB, nuclear factor kB; PIP2; phosphatidylinositol bisphosphate; PIP3; phosphatidylinositol triphosphate; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLCγ2, phospholipase Cγ2; SDF-1: stromal cell-derived factor 1; SYK, spleen tyrosine kinase; TLR, toll-like receptor.
Blum KA. *Hematology Am Soc Hematol Educ Program*. 2015;2015:82-91.

Incidence of NHL Subtypes and Plasma Cell Malignancies

2016 US NHL cases
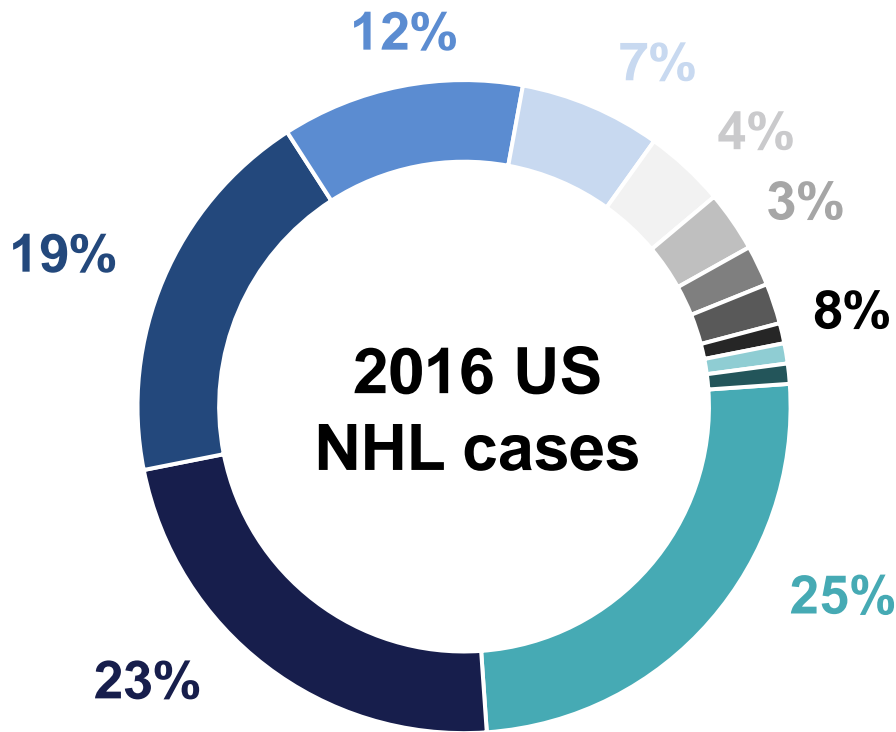
DLBCL is the most common type of NHL

| Subtype	Cases
DLBCL	27,650
Plasma cell neoplasms	25,980
CLL/SLL	20,980
Follicular Lymphoma	13,960
Marginal Zone Lymphoma	7,460
Peripheral T-cell Lymphoma	3,950
Mantle Cell Lymphoma	3,320
Lymphoplasmacytic lymphoma	2,330
Hairy Cell Leukemia	1,910
Mycosis Fungoides	1,620
Burkitt Lymphoma/Leukemia	1,480
Others	1,710
Total mature NHL	**112,380**

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Teras LR, et al. *CA Cancer J Clin*. 2016;66(6):443-459.

DLBCL Epidemiology

Rates of New DLBCL Cases and Associated Mortality

NCI SEER data based on the US population

Rate per 100k persons

■ Rate of New Cases   ▼ Death Rate
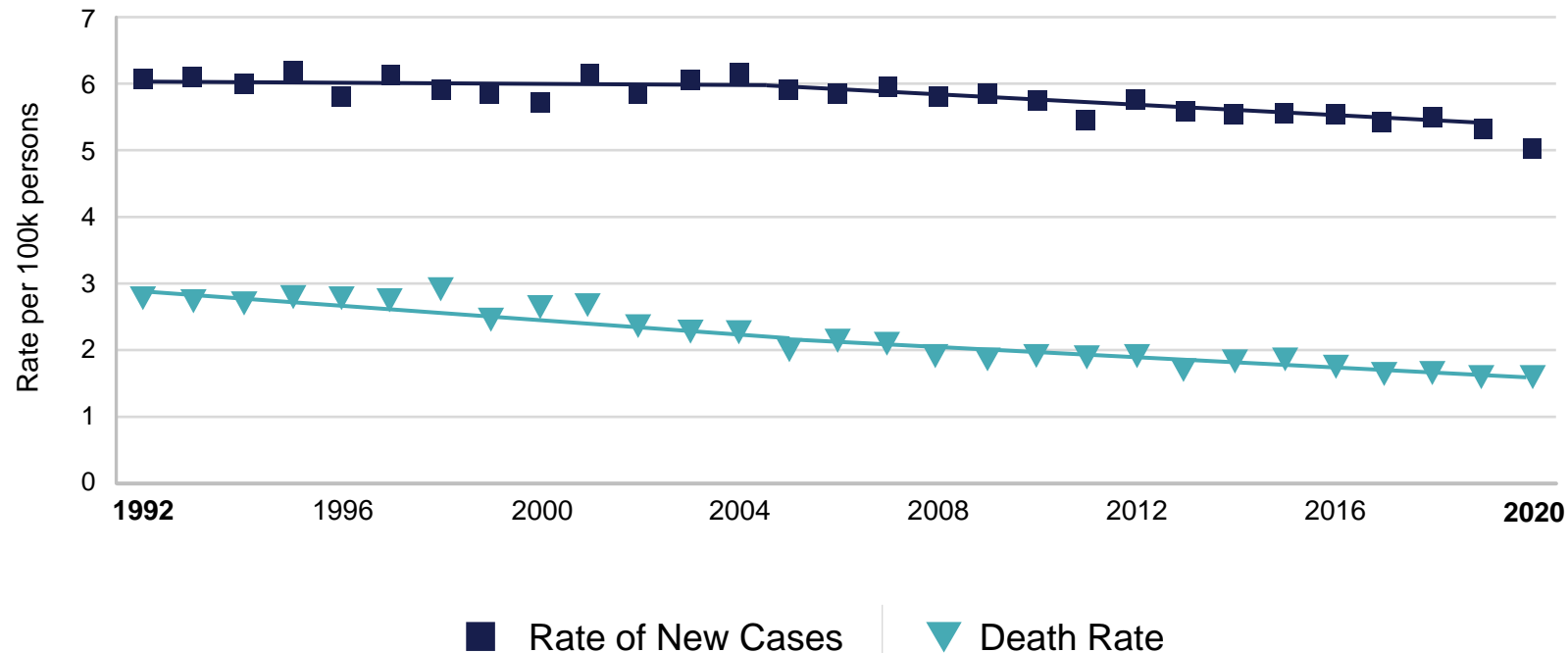
The rate of new cases of diffuse large B-cell lymphoma was 5.5 per 100,000 men and women per year

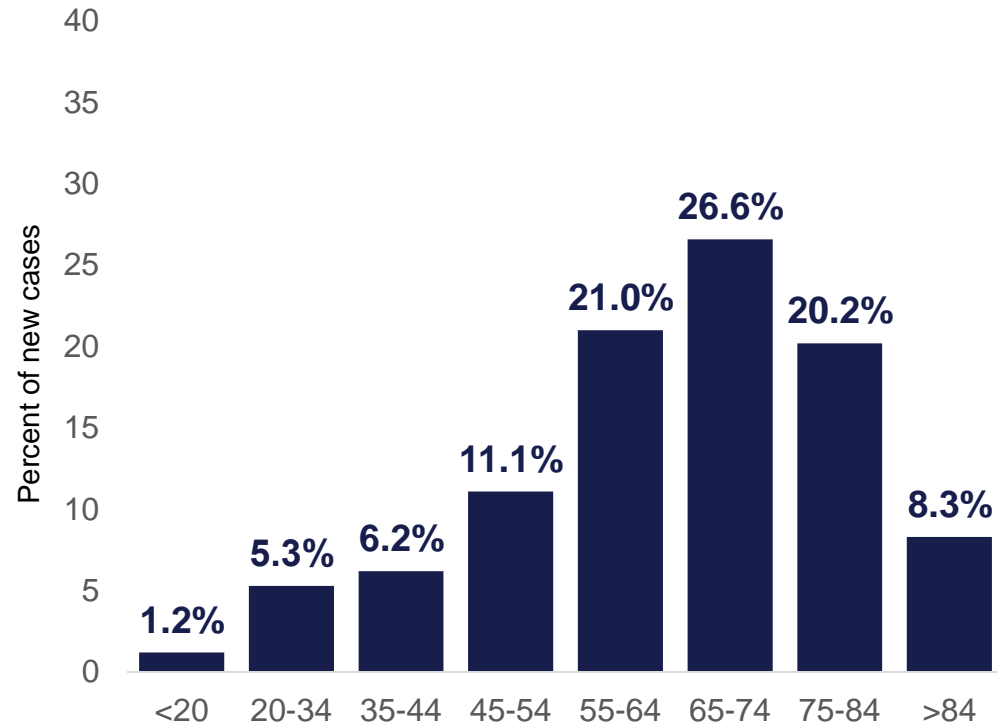The death rate was 1.7 per 100,000 men and women per year

These rates are age-adjusted and based on 2016–2020 cases and deaths

NCI, National Cancer Institute; SEER, surveillance, epidemiology, and end results.
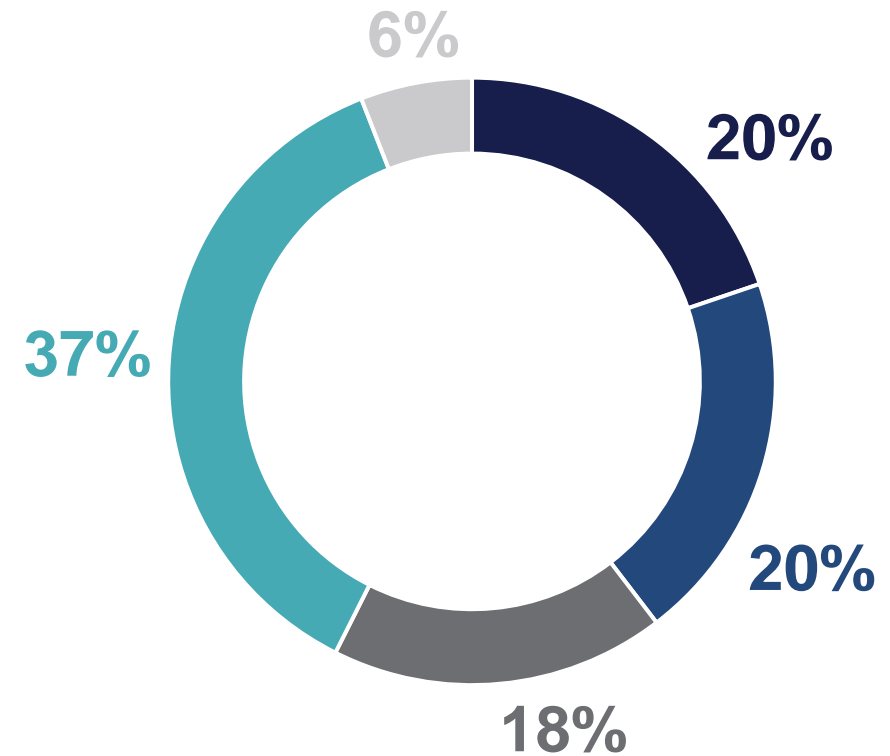National Cancer Institute. Cancer Stat Facts — Diffuse Large B-Cell Lymphoma (DLBCL). https://seer.cancer.gov/statfacts/html/dlbcl.html. Accessed October 18, 2023.

DLBCL Epidemiology (cont)

New DLBCL Cases by Age Group

- <20: 1.2%
- 20-34: 5.3%
- 35-44: 6.2%
- 45-54: 11.1%
- 55-64: 21.0%
- 65-74: 26.6%
- 75-84: 20.2%
- >84: 8.3%

Percent of new cases

MEDIAN AGE AT DIAGNOSIS | 66 years

Percent of DLBCL Cases by Stage

- 6%
- 20%
- 20%
- 18%
- 37%

■	Stage I	Confined to Single Region
■	Stage II	Involving Multiple Regions
■	Stage III	Spread to Both Sides of Diaphragm
■	Stage IV	Diffuse or Disseminated Involvement
■	Unknown	Unstaged

National Cancer Institute. Cancer Stat Facts — Diffuse Large B-Cell Lymphoma (DLBCL). https://seer.cancer.gov/statfacts/html/dlbcl.html. Accessed October 18, 2023.
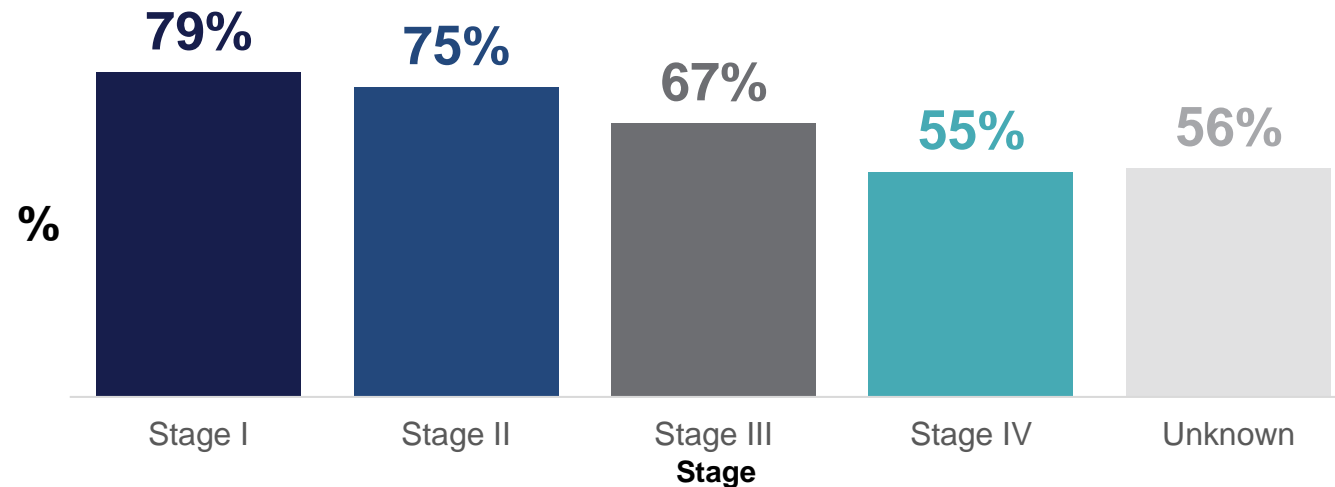
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DLBCL Epidemiology (cont)

5-Year Relative Survival Over Time (1975-2020)
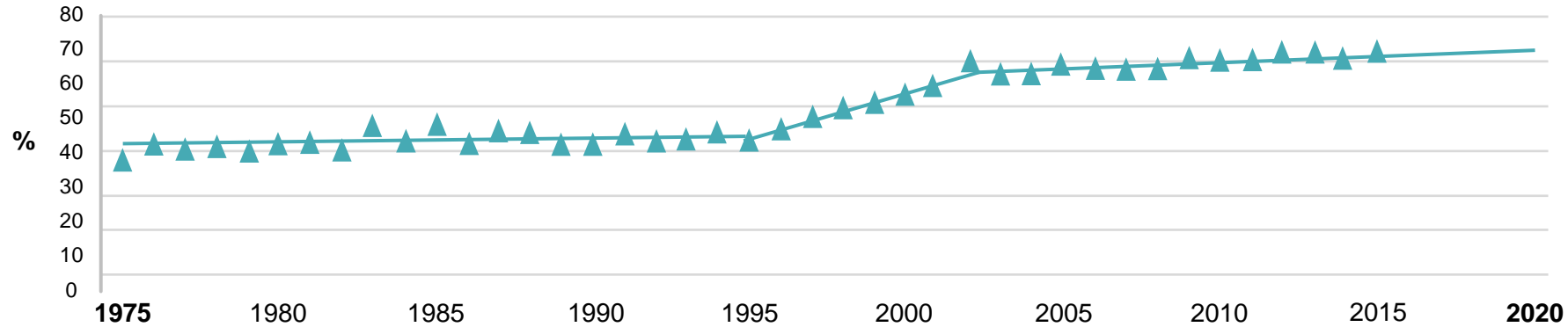
5-Year Relative Survival by Ann Arbor Stage

Stage I	Stage II	Stage III	Stage IV	Unknown
79%	75%	67%	55%	56%

Stage

Learn about DLBCL etiology and risk factors

National Cancer Institute. Cancer Stat Facts — Diffuse Large B-Cell Lymphoma (DLBCL). https://seer.cancer.gov/statfacts/html/dlbcl.html. Accessed October 18, 2023.

Primary vs Secondary DLBCL

Primary (de novo) DLBCL occurs spontaneously[1]
Secondary DLBCL occurs when less aggressive lymphomas are transformed by genetic mutations that cause them to grow faster and behave more aggressively[2]

- Approximately 5% of CLLs/SLLs transform into DLBCLs[3]
- Richter's transformation refers to the transformation of low-grade B-cell lymphoproliferative disorder to an aggressive lymphoma such as DLBCL[4]
- Approximately 3% of FLs transform into DLBCLs per year[5]
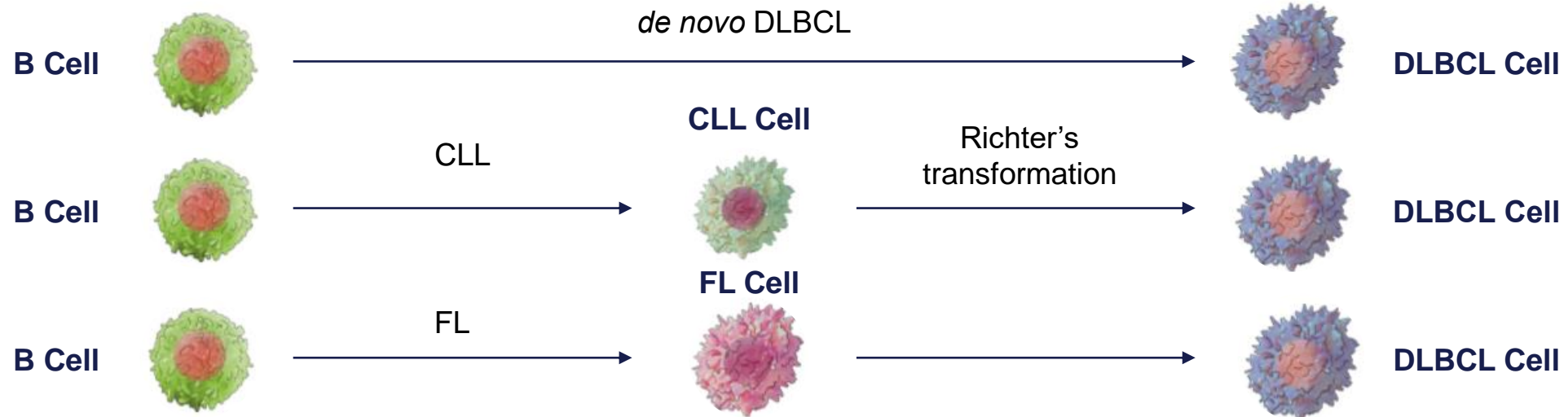

1. Martelli M, et al. *Crit Rev Oncol Hematol.* 2013;87(2):146-171. 2. Lymphoma Research Foundation. Understanding Transformed Lymphomas. https://lymphoma.org/wp-content/uploads/2022/05/LRF_Transformed_Lymphomas_Fact_Sheet.pdf. Accessed October 18, 2023. 3. Krause JR, et al. *Proc Bayl Univ Med Cent.* 2013;26:16-18. 4. Parikh SA, Kay NE, Shanafelt TD. *Blood.* 2014;123(11):1647-1657. 5. Lossos IS, Gascoyne RD. *Best Pract Res Clin Haematol.* 2011;24:147-163.

WHO Classification of DLBCL

DLBCL is a heterogeneous disease category, with prognostic groups identified based on morphology, phenotype, and genetic analysis[1,2]

DLBCL subtypes are characterized by unique clinical and pathological features[1,2]
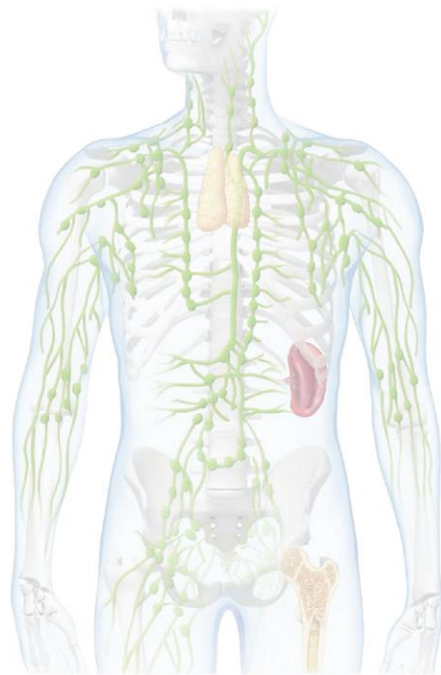
2022 Update of WHO Classification of Lymphoid Neoplasms

Included modification from "diffuse large B-cell lymphoma" to "large B-cell lymphoma"[2]

- This update was in recognition that a diffuse growth pattern is not apparent/present or cannot be assessed in some entities

Additional changes include a reframed and reassigned entity for high-grade B-cell lymphoma with dual rearrangements of *MYC* and *BCL2* and/or *BCL6*[2]

- This update was in recognition of their variable morphologies, but homogeneous dark zone biologic features and gene expression characteristics

CNS, central nervous system; DEL, double expressor lymphoma; EBV, Epstein-Barr virus; IRF4, interferon regulatory factor 4; WHO, World Health Organization.

1. Li S, Young KH, Medeiros LJ. *Pathology*. 2018;50(1):74-87. 2. Alaggio R, et al. *Leukemia*. 2022;36:1720-1748.

Two Subtypes of DLBCL NOS Based on COO

GCB DLBCL
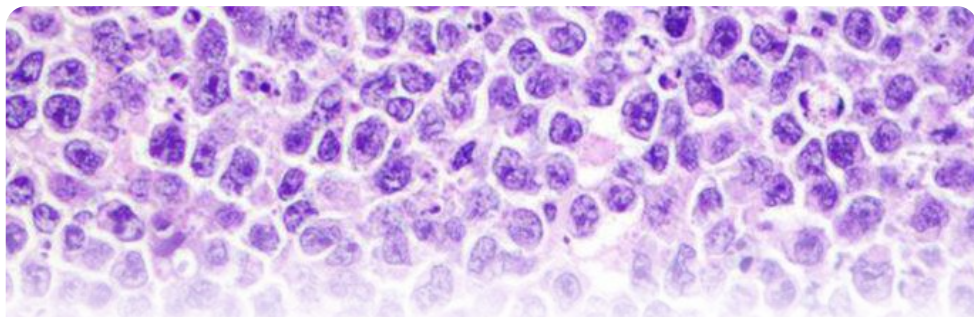
GCB DLBCL cells concentrate staining to the cell membrane and nucleus/nucleolus[1]

- Derived from germinal center B cells[2]
- A genetic abnormality detected in roughly 45% of GCB DLBCLs is the t(14;18) translocation; this leads to the deregulation of the antiapoptotic BCL2 protein and proliferation of abnormal cells[2]

ABC DLBCL
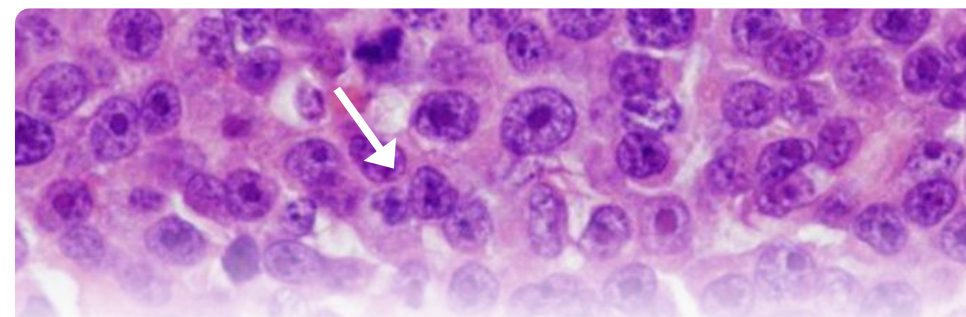
ABC DLBCL cells have abundant staining concentrated in the cytoplasm and nucleus/nucleolus (arrow)[1]

- Derived from B cells that are differentiating into plasma cells[2]
- Common mutations block differentiation, promote proliferation, and suppress apoptosis[2]
- Associated with a poorer outcome compared to GCB DLBCL, potentially due to gene expression patterns that reduce the efficacy of conventional therapy[2,3]

- While most of the non-germinal center tumors fall into the ABC category, others may fall into an <u>unclassifiable</u> category[4]

Learn how DLBCL molecular subtype affects prognosis

Reprinted from *Seminars in Hematology*, 52(2), Xie Y, et al. The Histological Classification of Diffuse Large B-cell Lymphomas, 57-66, Copyright (2015), with permission from Elsevier.
COO, cell of origin; NOS, not otherwise specified.
1. Xie Y, Pittaluga S, Jaffe ES. *Semin Hematol.* 2015;52(2):57-66. 2. Nogai H, Dörken B, Lenz G. *J Clin Oncol.* 2011;29(14):1803-1811. 3. Rosenwald A, et al. *N Engl J Med.* 2002;346(25):1937-1947. 4. Brown JR, et al. https://www.uptodate.com/contents/pathobiology-of-diffuse-large-b-cell-lymphoma-and-primary-mediastinal-large-b-cell-lymphoma. Accessed November 21, 2023.

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DHL and DEL DLBCL

DHL DLBCL involves co-rearrangement of the *MYC* gene with *BCL2*, often resulting in overexpression of the MYC and BLC2 proteins[1]

In a retrospective analysis, patients with DHL DLBCL frequently presented with:[1]

- Aggressive clinical features
- High-risk IPI score
- Elevated LDH levels

DEL DLBCL involves the co-expression of the MYC and BCL2 proteins, with or without underlying genomic rearrangement[1,2]

In a retrospective analysis, patients with DEL DLBCL were more likely to have:[1]

- Poor performance status
- Advanced stage disease
- High risk IPI scores
- Higher Ki-67 proliferative index
- Multiple extranodal sites of disease

80–90% of DHL cases occurred in GCB DLBCL, while 63% of DEL cases occurred in ABC DLBCL[1]

GCB — ABC
BCL2 rearrangement
DHL
MYC/BCL2 DEL
MYC rearrangement
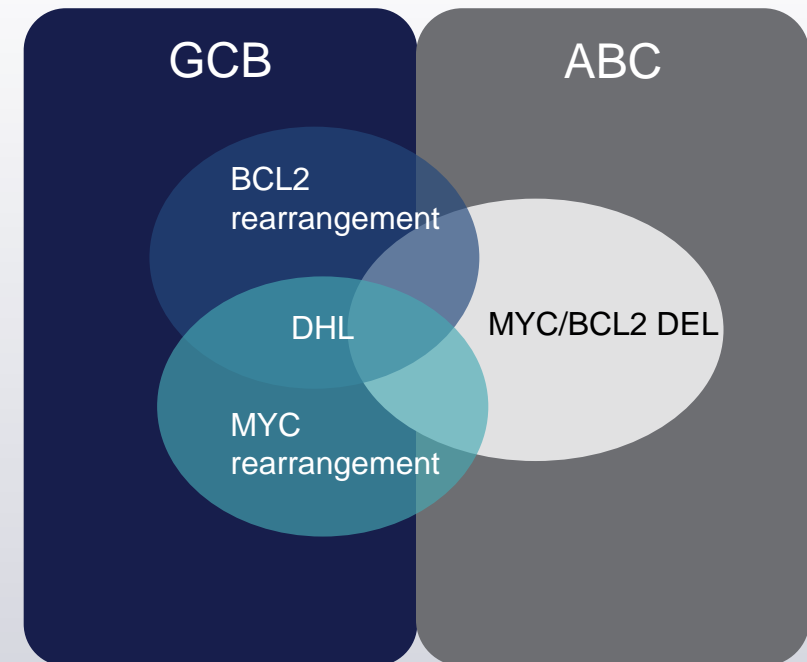
DEL, double expressor lymphoma; DHL, double-hit lymphoma; IPI, International Prognostic Index; Ki-67, marker of proliferation Kiel 67; LDH, lactate dehydrogenase.

1. Riedell PA, Smith SM. *Cancer*. 2018;124(24):4622-4632. 2. Li S, et al. *Pathology*. 2018;50(1):74-87.

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Presentation, Diagnosis, and Prognosis of Patients With DLBCL

# Clinical Presentation of Patients With DLBCL

The Clinical Presentation of DLBCL

Varies according to subtype, patient age, and immune status. Patients with DLBCL NOS typically present with rapidly enlarging tumor at ≥1 nodal or extranodal sites[1,2]

- Up to 40% of patients present with extranodal involvement[1]

Patients are generally asymptomatic, but B symptoms may be present at diagnosis[1,3]

- B symptoms are caused by the release of proinflammatory cytokines and chemokines by malignant B cells or host tissues, and are more common in advanced and aggressive subtypes[3,4]

Development of B symptoms

Release of pro-inflammatory cytokines and chemokines

B symptoms:[1,3]
- Weight loss (>10% body weight)
- Fever (>38°C)
- Night sweats

Malignant B cells

Release of pro-inflammatory cytokines and chemokines by malignant B cells or host tissues may produce B symptoms[1,3]
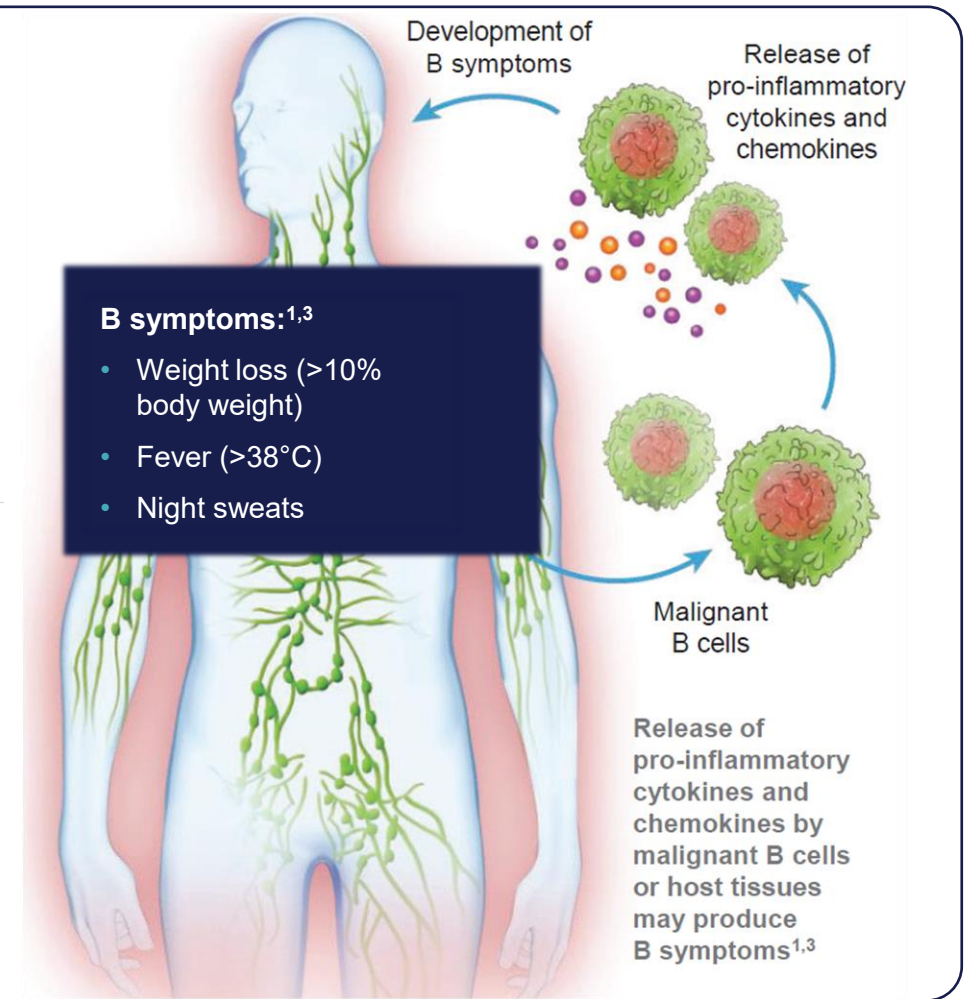
1. Martelli M, et al. *Crit Rev Oncol Hematol.* 2013;87:146-171. 2. Tilly H, et al. *Ann Oncol.* 2015;26(suppl 5):v116-v125. 3. Padala SA, Kallam A. Diffuse Large B-Cell Lymphoma. 2023 Apr 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32491728. 4. Sapkota S, Shaikh H. Non-Hodgkin Lymphoma. 2023 Feb 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32644754.

Overview of Workup for DLBCL[a]

Essential

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Uric acid
- PET/CT scan (preferred) or chest/abdominal/pelvic CT with contrast of diagnostic quality
- Calculation of IPI
- Hepatitis B testing[b]
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regime is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

Useful in Selected Cases

- Head CT/MRI with contrast or neck CT/MRI with contrast
- HIV testing
- Hepatitis C testing
- Beta-2-microglobulin
- Lumbar puncture for patients at risk for CNS involvement
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate; bone marrow biopsy is not necessary if PET/CT scan demonstrates bone disease. Bone marrow biopsy with a negative PET/CT scan may reveal discordant lymphoma
- Discuss fertility preservation[c]

Learn about performance status models for patient assessment

[a] All recommendations are category 2A unless otherwise indicated. [b] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consider consult with gastroenterologist. [c] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.
CBC, complete blood count; CT, computed tomography; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition; PET, positron emission tomography; RT, radiation therapy.
Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas. V.6.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed October 10, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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Overview of PET/CT
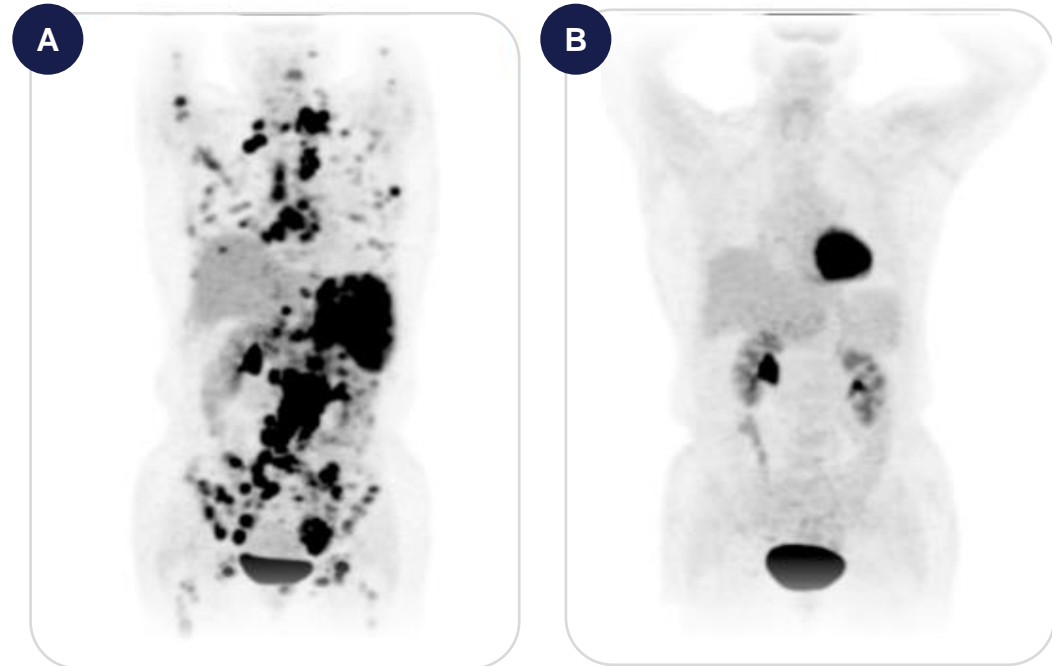
PET/CT of Stage IV GCB DLBCL[2]

PET/CT scans are essential for the initial staging of DLBCL and for response assessment after treatment[1]

Unlike conventional CT, PET/CT can provide functional and morphologic data. PET/CT is better able to assess:[2]

- Viable lesions
- Initial staging and restaging
- Treatment response
- Prognosis
- Post-treatment relapse/exacerbation

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend whole body PET/CT scan with or without chest/abdomen/pelvic CT with contrast of diagnostic quality for the initial workup[3]

A) PET/CT demonstrates 18F-FDG uptake in regional lymph nodes and multiple organs
B) Following first-line therapy, PET/CT shows no residual abnormal 18F-FDG uptake and the patient achieves complete remission

Kong Y, et al. *Medicine* (Baltimore). 2016; 95(6), 1-8. Figure reproduced under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND) (https://creativecommons.org/licenses/by-nc-nd/4.0/ [creativecommons.org]).
18F-FDG, fluorine-18-2-fluoro-2-deoxy-D-glucose; NCCN, National Comprehensive Cancer Network.
1. El-Galaly TC, et al. *J Int Med*. 2018;284:358-376. 2. Kong Y, et al. Medicine (Baltimore). 2016;95(6):1-8. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas. V.6.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed October 10, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.

Additional Diagnostic Testing[a]

Essential

- Adequate immunophenotyping to establish diagnosis and germinal center B-cell (GCB) versus non-GCB origin[b]
  - IHC panel: CD20, CD3, CD5, CD10, CD21, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, MYC with or without
  - Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20
- Karyotype or FISH for *MYC*; FISH for *BCL2*, *BCL6* rearrangements if *MYC* positive

Useful Under Certain Circumstances

- Additional immunohistochemical studies to establish lymphoma subtype
  - IHC panel: cyclin D1, kappa/lambda, CD30, CD138, anaplastic lymphoma kinase (ALK), human herpesvirus-8 (HHV8), SOX11
- EBV-encoded RNA (EBER) in situ hybridization (EBER-ISH)
- Karyotype or FISH for *IRF4/MUM1* rearrangements[c]

[a] All recommendations are category 2A unless otherwise indicated. [b] Typical immunophenotype: CD20+, CD45+, CD3-; additional markers are used for subclassification.
[c] LBCL with IRF4/MUM1 rearrangement are usually DLBCL but occasionally are purely FL grade 3b (ICC/FLBL [WHO]) and often DLBCL with FL grade 3b. Patients typically present with Waldeyer's ring involvement and are often children/young adults. These lymphomas are locally aggressive but respond well to chemotherapy ± RT. They do not have a BCL2 rearrangement and should not be treated as low-grade FL.
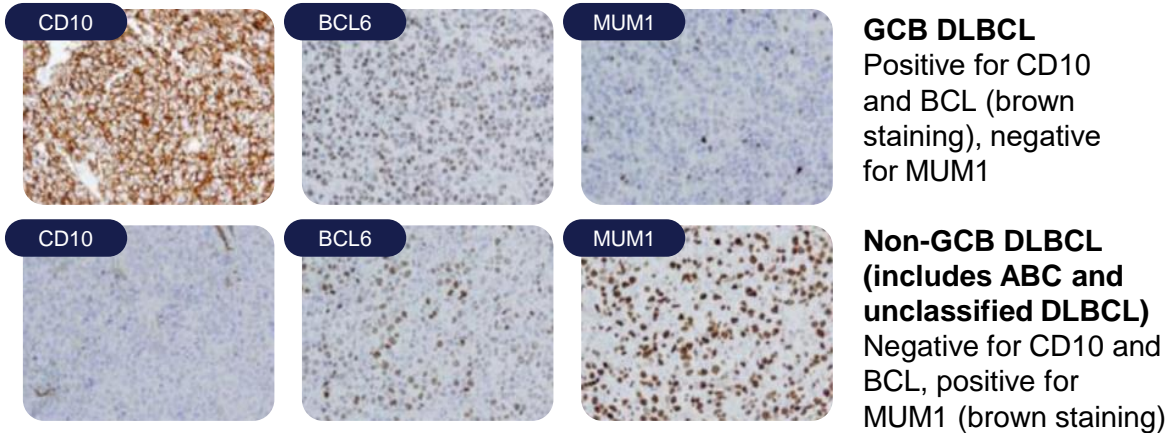MUM1, multiple myeloma oncogene-1; SOX11, SRY-related HMG-box 11.
Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas. V.6.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed October 10, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.
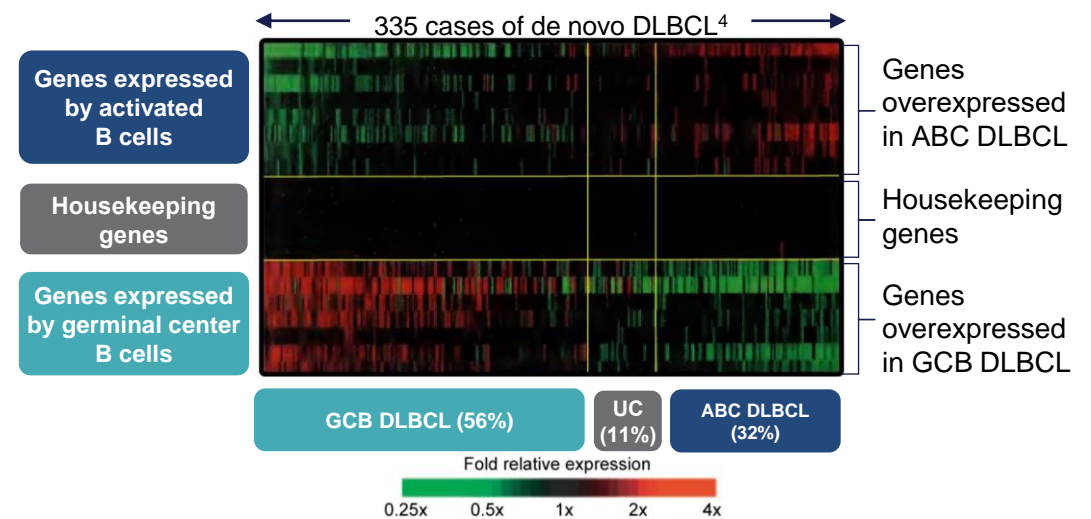
Approaches to Determine COO: IHC and GEP

IHC Panel

IHC uses antibodies to detect cells bearing a specific cell surface antigen, which can be used to distinguish between GCB and non-GCB subtypes[1,2]

GCB DLBCL
Positive for CD10 and BCL (brown staining), negative for MUM1

Non-GCB DLBCL (includes ABC and unclassified DLBCL)
Negative for CD10 and BCL, positive for MUM1 (brown staining)

IHC is a simple and widely available method used to identify the COO of DLBCL specimens[1,2]

Gene Expression Profiling

GEP is a robust method for determining COO in DLBCL NOS, but requires substantial time, technological expertise, and resources[3]

335 cases of de novo DLBCL[4]

Genes expressed by activated B cells

Housekeeping genes

Genes expressed by germinal center B cells

Genes overexpressed in ABC DLBCL

Housekeeping genes

Genes overexpressed in GCB DLBCL

GCB DLBCL (56%) | UC (11%) | ABC DLBCL (32%)

Fold relative expression
0.25x 0.5x 1x 2x 4x

GEP is not currently available in the clinic and is only used in clinical trials[5]

GEP, gene expression profiling.

1. Hans CP, et al. *Blood*. 2004;103(1):275-82. 2. Batlle-Lopez A, et al. *Oncotarget*. 2016;7(14):18036-49. 3. Choi WW, et al. *Clin Cancer Res*. 2009;15(17):5494-502. 4. Kridel R, et al. *Blood*. 2015;126(18):2118–2127. 5. Vodicka P, et al. *Onco Targets Ther*. 2022;15:1481–1501.

Ann Arbor Staging System for DLBCL

> DLBCL can be staged using the Ann Arbor staging system,
> which was originally developed for Hodgkin lymphoma

Stage	Involvement
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement extralymphatic organ or site and of 1 or more lymph node regions on the same side of the diaphragms (IIE)
III	Involvement of lymph node regions on both side of the diaphragm (III), which may be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS), or both (IIISE)
IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues with or without associated lymph node enlargement

National Cancer Institute. SEER Training Modules. Lymphoma Staging Scheme. https://training.seer.cancer.gov/staging/systems/schemes/lymphoma.html. Accessed October 20, 2023.

Lugano Staging System for DLBCL

> The Lugano modification of the Ann Arbor staging system was developed in order to improve the staging and response criteria for Hodgkin lymphoma and NHL

Stage	Involvement	Extranodal Status
LIMITED DISEASE		
I	1 node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	2 or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
ADVANCED DISEASE		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Extent of disease is determined by PET/CT for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
[a] Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.
Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-68.

International Prognostic Index: The Basis of Initial Risk Stratification for Patients With DLBCL[1]

Revised and NCCN IPI Scoring Systems: Efforts to improve the model's discrimination have focused on adding new clinical prognostic factor(s) to the initial index, regrouping the original IPI score, or specifically focusing on elderly patients[1]

IPI Risk Factors[2,3]

Age >60 years

Serum LDH > normal

Performance status 2–4

Ann Arbor stage III or IV

Extranodal involvement >1 site

Risk Group	Total # of Risk Factors[2]
Low	0 or 1
Low–Inter	2
High–Inter	3
High	4 or 5

Revised IPI Risk Factors[3]

Age >60 years

Serum LDH > normal

Performance status 2–4

Ann Arbor stage III or IV

Extranodal involvement >1 site

Risk Group	Total # of Risk Factors[3]
Very Good	0
Good	1 or 2
Poor	3, 4, or 5

NCCN-IPI Risk Factors[1]

		Score
Age, years	>40 to ≤60	1
	>60 to ≤75	2
	>75	3
LDH, normalized	>1 to ≤3	1
	>3	2
Ann Arbor stage III–IV		1
Extranodal disease[a]		1
Performance status ≥2		1

Risk Group	Total # of Risk Factors[1]
Low	0-1
Low–Inter	2-3
High–Inter	4-5
High	≥6

In these models, each risk factor is allocated 1 point and patients are stratified into 4 risk groups based on their total number of risk factors[1]

Learn about age-adjusted IPI

[a] Disease in bone marrow, CNS, liver/GI tract, or lung" per reference.[1]

1. Zhou Z, et al. *Blood.* 2014;123(6):837-842. 2. The International Non-Hodgkin's Lymphoma Prognostic Factors Project (INHLPFP). *N Engl J Med.* 1993;329(14):987-994. 3. Ruppert AS, et al. *Blood.* 2020;135(23):2041-2048.

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Appendix

DLBCL Etiology and Risk Factors

DLBCL Etiology is Poorly Understood

However, several factors thought to increase DLBCL risk have been identified[1,2]

Immunosuppression | Diet | Caucasian origin | UV radiation | Pesticides | EBV | Male sex
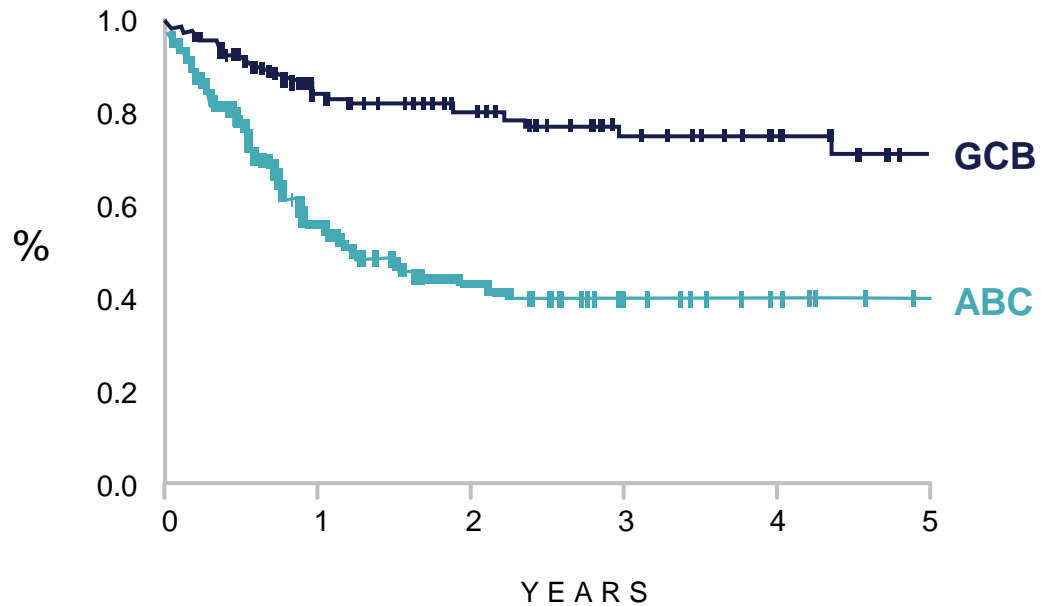
UV, ultraviolet.

1. National Cancer Institute. Cancer Stat Facts — Diffuse Large B-Cell Lymphoma (DLBCL). https://seer.cancer.gov/statfacts/html/dlbcl.html. Accessed October 18, 2023. 2. Blinder V, Fisher SG. *Cancer Invest*. 2008;26:306–316.
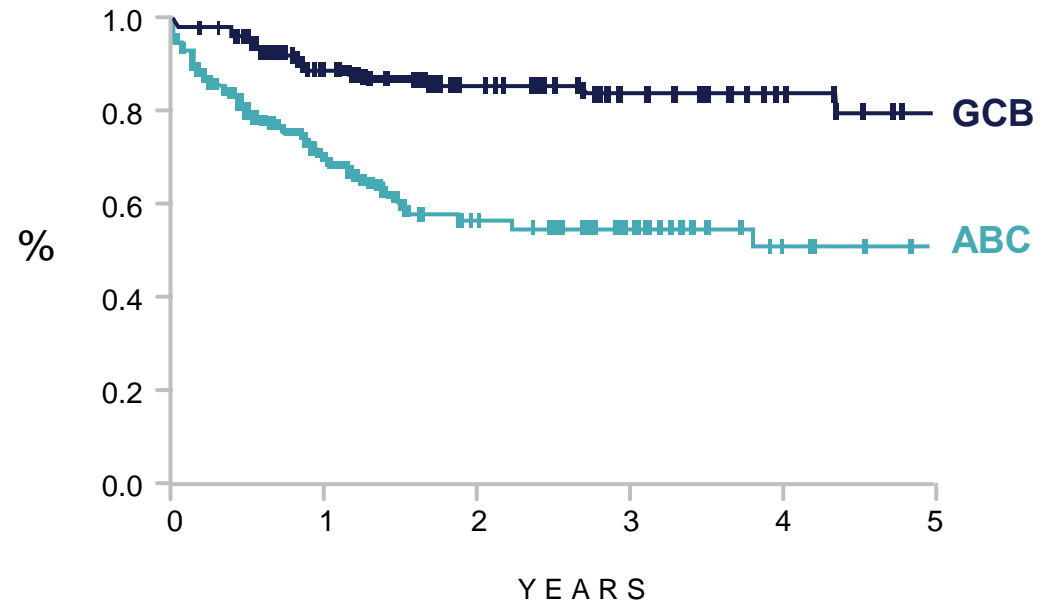
DLBCL Molecular Subtype Affects Prognosis

Probability of Progression-free Survival

Probability of Overall Survival

Gene expression profiling revealed rates of five-year overall survival and progression-free survival were lower for patients with ABC DLBCL compared to patients with GCB DLBCL

Lenz G, et al. *N Engl J Med.* 2008;359(22):2313-2323.

Performance Status Models

ECOG Performance Status[1]

0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Karnofsky Performance Status[2]

100	Normal, no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs of symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, but unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Disable; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death is not imminent
20	Very ill; hospitalization and active supportive care necessary
10	Moribund
0	Dead

The ECOG and Karnofsky performance status models are used to assess the ambulatory status of the patient[1,2]

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Age-Adjusted IPI for Patients ≤60 Years of Age

Age-Adjusted IPI Risk Factors

Serum LDH > normal	Performance status 2–4	Ann Arbor stage III or IV

Risk group	Number of risk factors
Low	0
Low-intermediate	1
High-intermediate	2
High	3

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