MANTLE CELL LYMPHOMA

Learning Objectives

After reviewing this slide deck, Health Care Professionals will be able to:

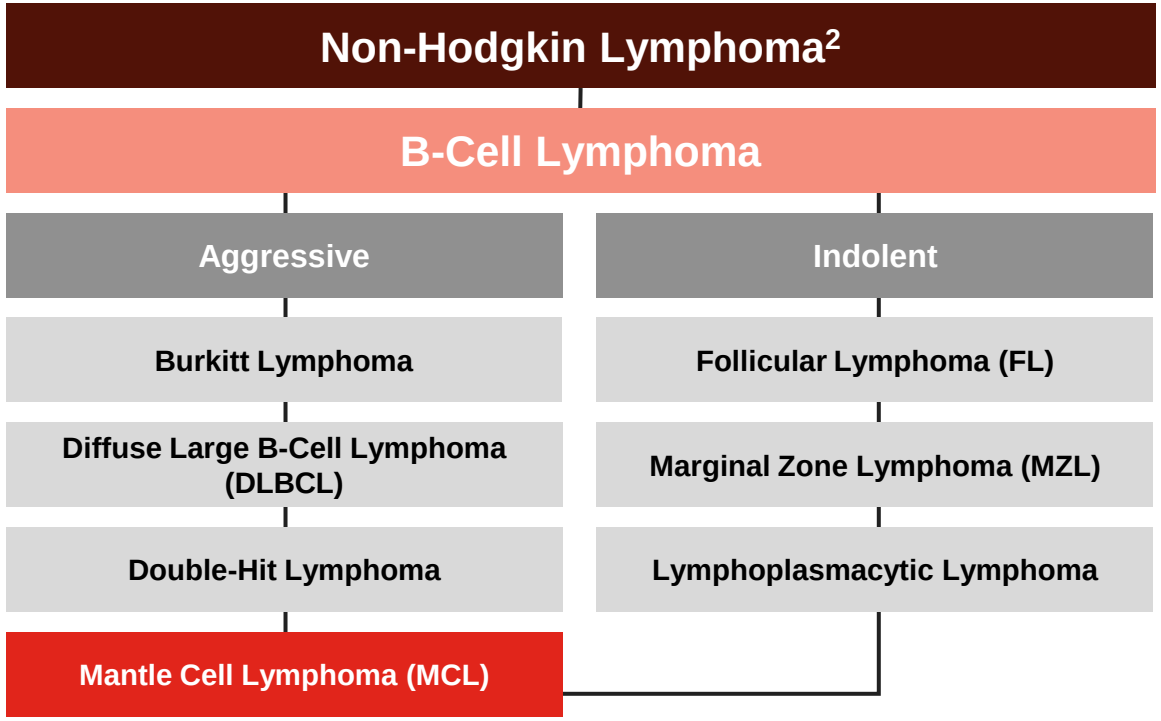
Gain deeper knowledge of Mantle Cell Lymphoma (MCL) including epidemiology, pathophysiology, and clinical presentation

Apply treatment guidelines for MCL into their practice

Understand the clinical evaluation in MCL and important prognostic indices

Background and Classification

- Aggressive B-cell malignancy that arises in the lymph node mantle zone[1]
- Characterized by a (11;14) translocation and overexpression of cyclin D1[1]
- Heterogenous disease with respect to clinical presentation and prognosis[1]
- Molecular variation creates treatment challenges and diverse outcomes[1]



1. Veloza L, et al. *Ann Lymphoma.* 2019;3(3):1-17. 2. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes (Accessed May 15, 2024).

Epidemiology (1/2)

Incidence

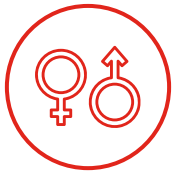
- ~1 case per 200,000 persons[1]
- ~3,320 cases per year in the US (~3% of all NHL cases)[2]
- Surveillance data indicate the incidence has increased among older patients[3]

Prevalence

- 3-10% of all NHL cases[4]
  - 7-9% of NHL cases in Europe[5]
  - ~6% of NHL cases in the US[5]

Median Overall Survival

- 4-5 years[6]
- MIPI intermediate-risk group: 51 months[6]
- MIPI high-risk group: 29 months[6]



Male-to-Female Ratio

- ~3x more common in males[7]

MIPI= Mantle Cell Lymphoma International Prognostic Index; NHL=Non-Hodgkin Lymphoma; US=United States.

1. https://rarediseases.org/rare-diseases/mantle-cell-lymphoma/ (Accessed February 4, 2022). 2. Teras LR, et al. *CA Cancer J Clin.* 2016;66:443-459. 3. Epperla N, et al. *Br J Haematol*. 2018;181(5):703-706. 4. Veloza L, et al. *Ann Lymphoma*. 2019;3(3):1-17. 5. Sandoval-Sus JD, et al. *Hematol Oncol Stem Cell Ther.* 2017;10(3):99-115. 6. Vose JM. *Am J Hematol*. 2017;92(8):806-813. 7. Dreyling M, et al. *Ann Oncol.* 2017;28(suppl_4):iv62-iv71.

Epidemiology (2/2)

Age

- Median age at diagnosis: 68 years[1]
- Age-adjusted incidence rates in the US per 100,000 person-years[2]
  - <50 years: 0.07
  - 50-59 years: 0.83
  - 60-69 years: 1.96
  - 70-79 years: 2.97
  - ≥80 years: 2.78

Race

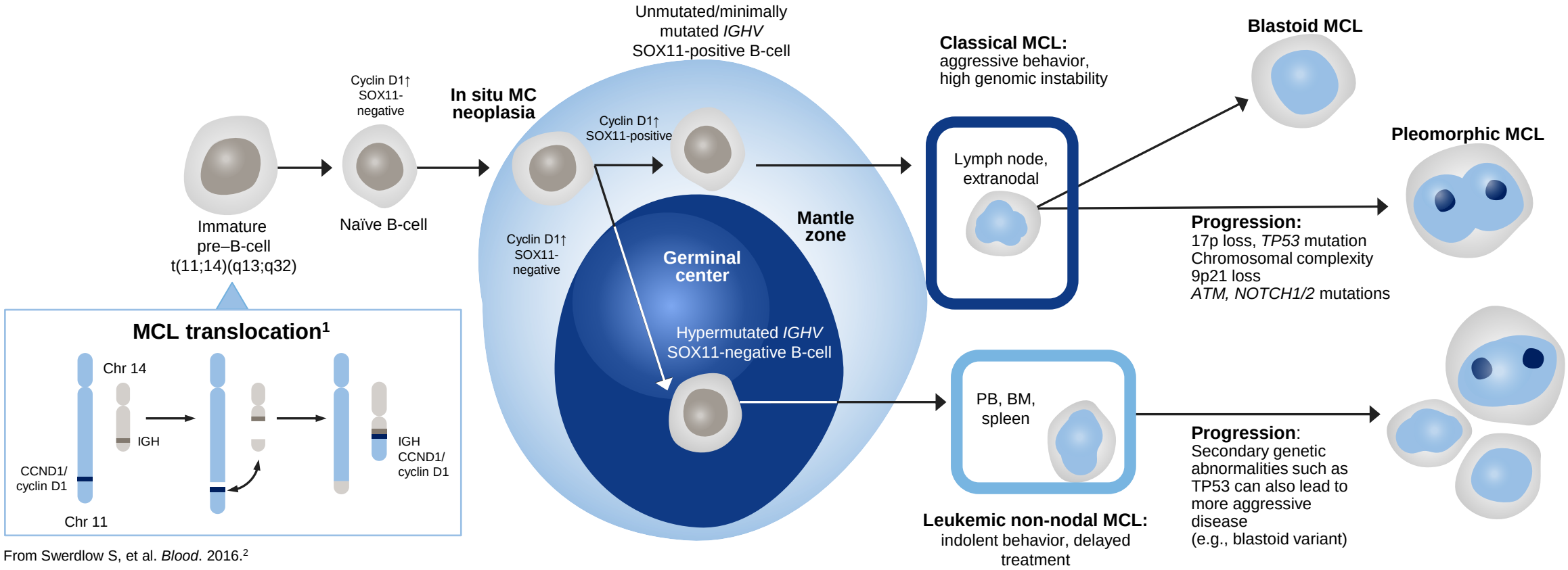
- Race-specific incidence rates in the US per 100,000 person-years[3]
  - Non-Hispanic White: 0.73
  - Hispanic White: 0.53
  - African American: 0.32
  - Asian or Pacific Islander: 0.29

US=United States.

1. Jain P, Wang, M. *Am J Hematol*. 2019;94:710-725. 2. Zhou Y, et al. *Cancer*. 2008;113(4):791-798. 3. Wang Y, Ma S. *BMC Cancer*. 2014;14:764.

Pathophysiology of MCL

Molecular Pathogenesis in Development and Progression of Major Subtypes of MCL[1,2]



From Swerdlow S, et al. *Blood*. 2016.[2]

BM=bone marrow; CCND1=cyclin D1 protein; chr=chromosome; cMCL=classical MCL; IGH=immunoglobulin heavy locus; IGHV=immunoglobulin heavy chain variable region gene; MC=mantle cell; MCL=mantle cell lymphoma; nnMCL=non-nodal MCL; PB=peripheral blood; SOX11=sex-determining region Y (SRY)-box transcription factor 11; t=translocation; TP53=tumor protein p53.

1. Veloza L, et al. *Ann Lymphoma*. 2019;3(3):1-17. 2. Swerdlow S, et al. *Blood*. 2016;127(20):2375-2390.

Classical MCL vs. Leukemic nnMCL

Classical MCL[1-3]

- Most common variant
- Generally aggressive
- Involves lymph nodes and extranodal sites
- Arises in mantle zone
- No or minimal IGHV mutation
- SOX11 expression
- High LDH
- Genetically unstable
- Potential to develop blastoid morphologyz

Leukemic nnMCL[1-3]

- 10-20% of cases
- Generally indolent
- Involves BM, PB, and spleen
- Develops through germinal center
- IGHV hypermutation
- Minimal SOX11 expression
- Low Ki-67 levels
- Genetically stable
- Potential to become aggressive disease

BM=Bone Marrow; IGHV=Immunoglobulin Heavy Chain Variable Region Gene; LDH=Lactate Dehydrogenase; MCL=Mantle Cell Lymphoma; nnMCL=Non-Nodal Mantle Cell Lymphoma; PB=Peripheral Blood; SOX11=Sex-Determining Region Y (Sry)-Box Transcription Factor 11.

1. Veloza L, et al. *Ann Lymphoma*. 2019;3(3):1-17. 2. Swerdlow S, et al. *Blood*. 2016;127(20):2375-2390. 3. Jain P, Wang, M. *Am J Hematol*. 2019;94:710-725.

Roles of t(11;14)(q13;q32) and SOX11

t(11;14)(q13;q32)[1-3]

- Initial oncogenic event
- Found in over 90% of MCL
- Occurs in pre-B stage
- Juxtaposes CCND1 at 11q13 to IGH complex at 14q32
- Results in overexpression of cyclin D1, not usually in B-cells, and cell cycle activation
- Overexpression of cyclin D1 can occur after amplification of translocated t(11;14) allele

SOX11[1-3]

- Neuronal transcription factor
- Found in ~90% of MCL
- Role in epigenetic regulators and oncogenesis; However, the clinical implications are not fully understood
- May augment BCR signaling and suppress BCL-6 to prevent transit to germinal center and block B-cell maturation
- Marker of classical MCL; not found in CLL, MZL, FL, or DLBCL

BCL-6=B-Cell Lymphoma-6; BCR=B-Cell Receptor; CCND1=Cyclin D1; CLL=Chronic Lymphocytic Leukemia; DLBCL=Diffuse Large B-Cell Lymphoma; FL=Follicular Lymphoma; IGH=Immunoglobulin Heavy Chain Locus; MCL=Mantle Cell Lymphoma; MZL=Marginal Zone Lymphoma; SOX11=Sex-Determining Region Y (Sry)-Box Transcription Factor 11.

1. Veloza L, et al. *Ann Lymphoma*. 2019;3(3):1-17. 2. Swerdlow S, et al. *Blood*. 2016;127(20):2375-2390. 3. Jain P, Wang, M. *Am J Hematol*. 2019;94:710-725.

Clinical Presentation

- B symptoms[1,2]
  - Drenching night sweats
  - Repeated fevers
  - Unintended weight loss of >10% of body weight over 6 months
- Lymphadenopathy (~90%)[1,3]
- Splenomegaly (~55%)[1,3]
- Hepatomegaly (~35%)[1,3]
- GI tract involvement (~25%)[1,3]
- Poor performance status[1]
- Can present as disseminated disease:[1-4]
  - Other organs and peripheral blood
  - Bone marrow involvement (60-75%)
  - CNS relapse (~4%)

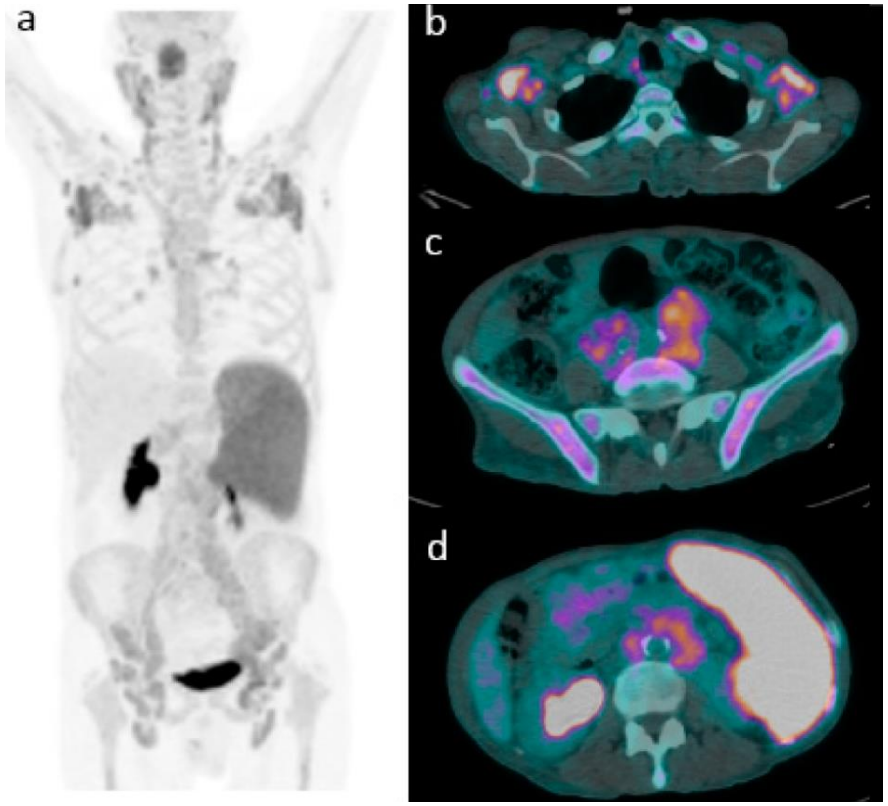
CNS=Central Nervous System; GI=Gastrointestinal.

1. Jain P, Wang, M. *Am J Hematol*. 2019;94:710-725. 2. https://rarediseases.org/rare-diseases/mantle-cell-lymphoma/ (Accessed February 4, 2022). 3. Meusers P, et al. *Leukemia*. 1997;11 Suppl 2:S60-S64. 4. Eyre TA, et al. *Blood*. 2022;139(5):666-677.

Clinical Evaluation

Diagnostic Workup[1]

- Physical exam
- Performance status
- CBC with differential
- Lactate dehydrogenase
- PET/CT imaging
- Hepatitis panel
- HIV status
- Electrocardiogram, echocardiogram
- Pregnancy testing in women of childbearing age
- Endoscopy/colonoscopy
- Bone marrow biopsy ± aspirate
- β2 microglobulin levels
- Lumbar puncture



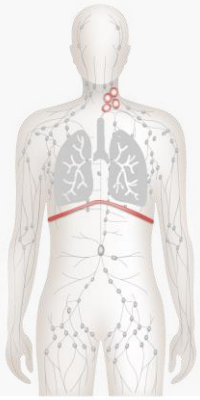
65-year-old male with stage III MCL. (a) Baseline maximum intensity projection showing diffuse hypermetabolic disease in (b) lateral cervical, axillary, (c) iliac and (d) inguinal nodes and in spleen.

CBC=Complete Blood Count; CT=Computerized Tomography; MCL=Mantle Cell Lymphoma; PET=Positron Emission Tomography.

1. Jain P, Wang, M. *Am J Hematol*. 2019;94:710-725. 2. Albano D, et al. *Cancers (Basel)*. 2019;11(12):1831.

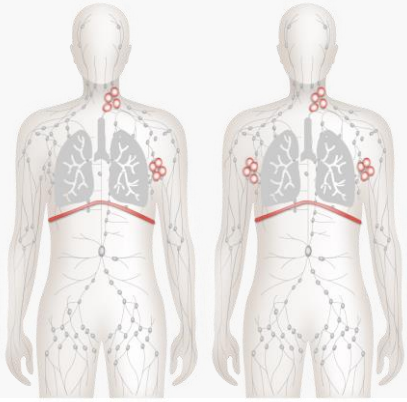
Staging System

Lugano Modification of Ann Arbor Staging System[1-2]



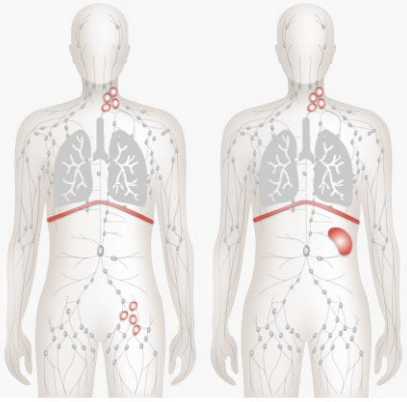
Stage I

- One node or group of adjacent nodes
- Single extranodal lesions without nodal involvement



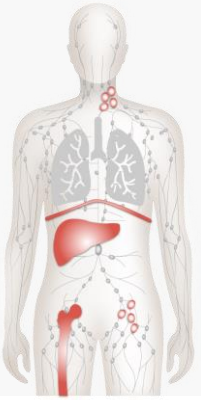
Stage II

- Two or more nodal groups on same side of diaphragm
- Limited contiguous extranodal involvement



Stage III

- Nodes on both sides of diaphragm
- Above diaphragm with spleen involvement



Stage IV

- Additional non-contiguous extralymphatic involvement

Adapted from Adult Non-Hodgkin Lymphoma Treatment (PDQ®): Health Professional Version. National Cancer Institute (US). 2022[2]

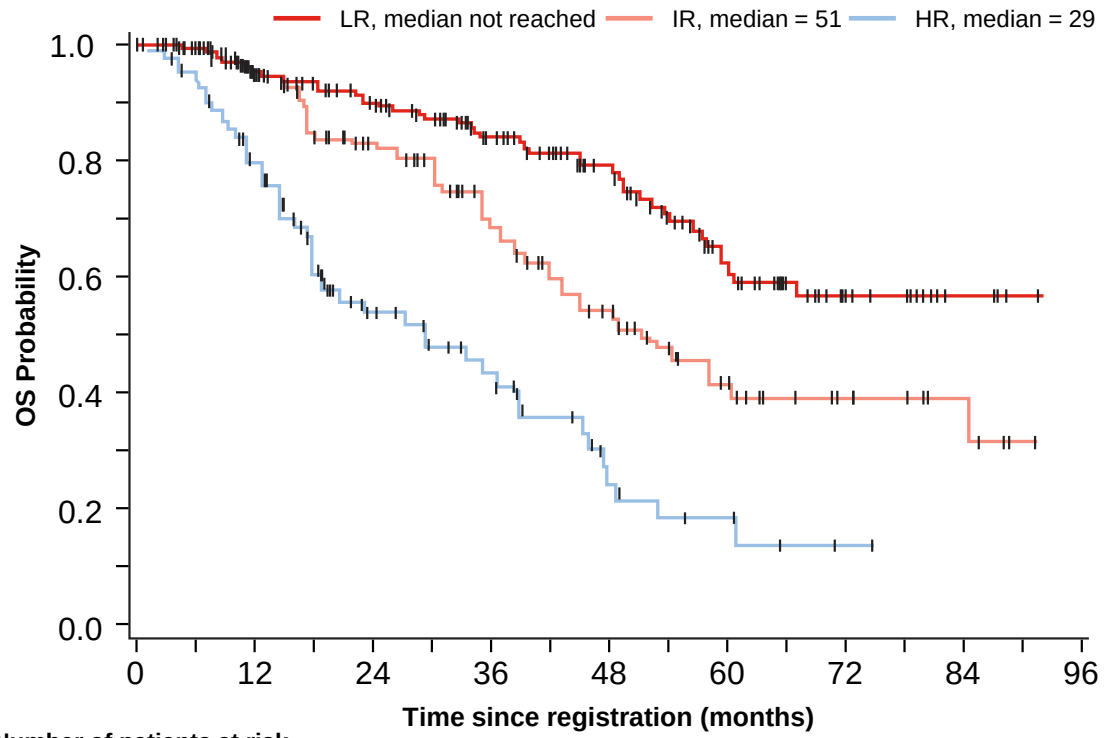
1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068. 2. https://www.ncbi.nlm.nih.gov/books/NBK66057/table/CDR0000062707__1075/ (Accessed March 3, 2022).

Prognostic Indices: MIPI and Ki-67

- MCL International Prognostic Index (MIPI) was developed to better characterize MCL prognosis:[1-4]
  - MIPI is prognostic for OS; not predictive of chemotherapy response or progression-free survival (PFS)
- Ki-67 index is used in conjunction with MIPI score to create a cumulative prognostic index called biologic MIPI[1,3]
  - Ki-67 ≥30% is high-risk

Points	Age, y	ECOG PS	LDH/ULN	WBC, 10^9/L
0	<50	0-1	<0.67	<6.700
1	50-59	—	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000-1.49	1.000-14.999
3	≥70	—	≥1.5000	≥15000

MIPI Score: 0-3 - Low Risk | 4-5 - Intermediate Risk | 6-11 - High Risk



Number of patients at risk:

LR	180	153	131	99	69	39	15	4
IR	145	116	83	57	37	19	9	5
HR	84	58	29	19	8	5	1	0

From Hoster E, et al. *Blood.* 2008[1]

ECOG PS=Eastern Cooperative Oncology Group performance status; HR=High Risk; IR=Intermediate Risk; LDH=Lactate Dehydrogenase; LR=Low Risk; MCL=Mantle Cell Lymphoma; MIPI=MCL International Prognostic Index; OS=Overall Survival; ULN=Upper Limit of Normal; WBC=White Blood Cell; y=Years.

1. Hoster E, et al. *Blood*. 2008;111:558-565. 2. Determann O, et al. *Blood*. 2008;111:2385-2387. 3. Jain P, et al. *Am J Hematol*. 2019;94:710-725. 4. Shah BD, et al. *Blood* 2010;116 (21): 5082.

MCL Treatments*

There is No Standardized Treatment Approach For MCL[1-5]

Precision Medicines

BTKis
- Acalabrutinib
- Pirtobrutinib
- Zanubrutinib

Proteasome inhibitor
- Bortezomib

IMiD
- Lenalidomide

BCL-2 inhibitor
- Venetoclax

Anti-CD20 monoclonal antibody
- Rituximab

Cell-based Therapy

CAR T-cell therapy
- Brexucabtagene autoleucel

HSCT
- Autologous stem cell transplant
- Allogeneic stem cell transplant

Chemoimmunotherapy

Common regimens:
- BR
- Hyper CVAD
- NORDIC regimen
- RBAC
- RCHOP
- RDHA
- RDHAP
- VR-CAP

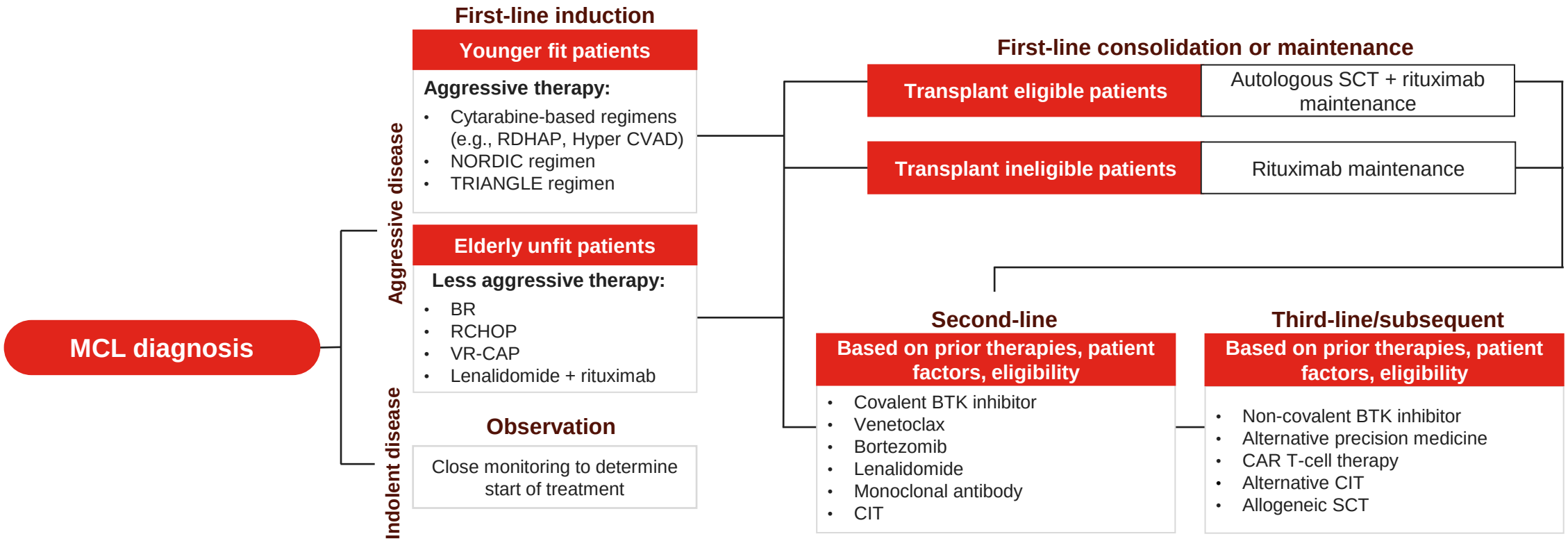
*The safety and efficacy of various treatments cannot be compared unless it is derived from head-to-head clinical trials and meets specific criteria. This information is based on scientific literature and is not a recommendation of treatments or a representation of all available treatment options.

BCL-2= B-Cell Leukemia/Lymphoma 2; BR=Bendamustine + Rituximab; BTK=Bruton's Tyrosine Kinase; CAR=Chimeric Antigen Receptor; CD=Cluster of Differentiation; HSCT=Hematopoietic Stem Cell Transplant; Hyper CVAD=Cyclophosphamide + Vincristine + Doxorubicin + Dexamethasone Alternating with High-Dose Methotrexate and Cytarabine; IMiD=Immunomodulatory Drugs; NORDIC regimen=Dose-Intensified Induction Immunochemotherapy with Rituximab + Cyclophosphamide, Doxorubicin + Vincristine _ Prednisone [maxi-CHOP] Alternating with High-dose Methotrexate and Cytarabine; RBAC=Rituximab + Bendamustine + Cytarabine; RCHOP=Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone; RDHA=Rituximab + Dexamethasone + Cytarabine + Platinum; RDHAP=Rituximab + Dexamethasone + Cytarabine + Cisplatin; VR-CAP=Bortezomib + Rituximab + Cyclophosphamide + Doxorubicin + Prednisone.

1. Silkenstedt E, Dreyling M. *Hematol Oncol*. 2021;39 Suppl 1:31-38. 2. Rule S. *Hematol Oncol*. 2019;37 (Suppl 1):66-69. 3. Hanel W, Epperla N. *J Hematol Oncol*. 2020;13(1):79. 4. Jain P, Wang M. *Am J Hematol*. 2019;94:710-725. 5. Pirtobrutinib [package insert]. Indianapolis, IN: Eli Lilly and Company; 2023.

MCL Treatments*

There is No Standardized Treatment Approach For MCL[1-7]



*The safety and efficacy of various treatments cannot be compared unless it is derived from head-to-head clinical trials and meets specific criteria. This information is based on scientific literature and is not a recommendation of treatments or a representation of all available treatment options.

BR=Bendamustine + Rituximab; BTK=Bruton's Tyrosine Kinase; CAR=Chimeric Antigen Receptor; CIT=Chemoimmunotherapy; Hyper CVAD=Cyclophosphamide + Vincristine + Doxorubicin + Dexamethasone Alternating With High-dose Methotrexate And Cytarabine; MCL=Mantle Cell Lymphoma; NORDIC regimen=Dose-intensified Induction Immunochemotherapy With Rituximab + Cyclophosphamide, Doxorubicin + Vincristine _ Prednisone [Maxi-chop] Alternating With High-dose Methotrexate And Cytarabine; RCHOP=Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone; RDHAP=Rituximab + Dexamethasone + Cytarabine + Cisplatin; SCT=Stem Cell Transplantation; TRIANGLE Regimen=R-CHOP/R-DHAP With Ibrutinib, With/Without Autologous SCT, + Ibrutinib Maintenance; VR-CAP=Bortezomib + Rituximab + Cyclophosphamide + Doxorubicin + Prednisone.

1. Silkenstedt E, Dreyling M. *Hematol Oncol*. 2021;39 (Suppl 1):31-38. 2. Rule S. *Hematol Oncol*. 2019;37 Suppl 1:66-69. 3. Hanel W, Epperla N. *J Hematol Oncol*. 2020;13(1):79. 4. Jain P, Wang M. *Am J Hematol*. 2019;94:710-725. 5. Pirtobrutinib [package insert]. Indianapolis, IN: Eli Lilly and Company; 2023. 6. Silkenstedt E, etl. *Hematol Oncol.* 2023;41 (Suppl 1):36-42. 7. Dreyling M, et al. *Blood.* 2022; 140 (Suppl 1): 1–3.

FDA Approved BTK Inhibitors for MCL*

BTK Inhibitor	Indication	Dosing	Study Which Led to Approval	Initial US Approval
Acalabrutinib[1,2]	Adult MCL after ≥1 prior therapy	100 mg PO every 12 hours	TY-004 (NCT02213926)	2017
Zanubrutinib[3,4]	Adult MCL after ≥1 prior therapy	160 mg PO BID or 320 mg PO once daily	BGB-3111-206 (NCT03206970)	2019
Pirtobrutinib[5,6]	Adult MCL after ≥2 prior therapy including a cBTKi	200 mg PO once daily	BRUIN 18001 (NCT03740529)	2023

***Direct comparison of efficacy results across clinical studies cannot be made due to differences in study populations, inclusion and exclusion criteria, and study endpoints.**

BID=Twice Daily; BTK=Bruton's Tyrosine Kinase; FDA=Food and Drug Administration; MCL=Mantle Cell Lymphoma; NCT=National Clinical Trial number; PO=Taken Orally; US=United States.

1. CALQUENCE® (Acalabrutinib) [PI]. Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2017. https://www.azpicentral.com/calquence/calquence.pdf. 2. https://clinicaltrials.gov/ct2/show/NCT02213926 (Accessed May 15. 2024). 3. BRUKINSA® (Zanubrutinib) [PI]. San Mateo, CA: BeiGene USA, Inc. 2019. Available from https://www.brukinsa.com/prescribing-information.pdf. 4. https://clinicaltrials.gov/ct2/show/NCT03206970 (Accessed May 15, 2024). 5. JAYPIRCA® (Pirtobrutinib) [PI}. Indianapolis, IN: Eli Lilly and Company, 2023. Available from https://pi.lilly.com/us/jaypirca-uspi.pdf?s=pi. 6. https://clinicaltrials.gov/study/NCT03740529 (Accessed May 15, 2024).

Measurement of Response (1/3)

Lugano Response Criteria for Non-Hodgkin Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Complete response	Lymph nodes and extralymphatic sites	Score 1, 2, 3[a] with or without a residual mass on 5-PS[b,c]	All the following: Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New Lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate and flow cytometry IHC negative
Partial response	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline. No new progressive lesions. At interim these findings suggest responding disease. At end of treatment these findings may indicate residual disease.	All the following: ≥50% decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value. When no longer visible, 0x0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New Lesions	None	None
	Bone marrow	Residual uptake higher than update in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the content of a nodal response, consider further evaluation with biopsy, or an interval scan.	Not applicable

[a]Score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where deescalation is investigated, it may be preferable to consider score 3 as an inadequate response (to avoid under-treatment). [b]PET Five-Point Scale (5-PS): 1) No uptake above background; 2) Uptake ≤ mediastinum; 3) Uptake > mediastinum but ≤ liver; 4) Uptake moderately > liver; 5) Uptake markedly higher than liver and/or new lesions; X) New areas of uptake unlikely to be related to lymphoma.[c]It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake.

5PS=5-Point Scale; CMR=Cardiovascular Magnetic Resonace; CT=Computed Tomography; FDG=Fluorodeoxyglucose; IHC=Immunohistochemistry; Ldi=Longest Transverse Diameter of a Lesion; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography; PPD=Cross Product of LDi and Perpendicular Diameter; Sdi=Shortest Axis Perpendicular to LDi; SPD=Sum of Product of Perpendicular Diameters for Multiple Lesions.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

Measurement of Response (2/3)

Lugano Response Criteria for Non-Hodgkin Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
No response/ stable disease	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment. No new or progressive lesions.	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New Lesions	None	None
	Bone marrow	No change from baseline	Not applicable

[a]Score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where deescalation is investigated, it may be preferable to consider score 3 as an inadequate response (to avoid under-treatment). [b]PET Five-Point Scale (5-PS): 1) No uptake above background; 2) Uptake ≤ mediastinum; 3) Uptake > mediastinum but ≤ liver; 4) Uptake moderately > liver; 5) Uptake markedly higher than liver and/or new lesions; X) New areas of uptake unlikely to be related to lymphoma.[c]It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake. 5PS=5-Point Scale; CT=Computed Tomography; FDG=Fluorodeoxyglucose; IHC=Immunohistochemistry; Ldi=Longest Transverse Diameter of a Lesion; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography; PPD=Cross Product of LDi and Perpendicular Diameter; Sdi=Shortest Axis Perpendicular to LDi; SPD=Sum of Product of Perpendicular Diameters for Multiple Lesions.

Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.

Measurement of Response (3/3)

Lugano Response Criteria for Non-Hodgkin Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Progressive disease	Lymph nodes and extralymphatic sites	Score 4 or 5b with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Requires at least one of the following PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
	New Lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

[a]Score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where deescalation is investigated, it may be preferable to consider score 3 as an inadequate response (to avoid under-treatment). [b]PET Five-Point Scale (5-PS): 1) No uptake above background; 2) Uptake ≤ mediastinum; 3) Uptake > mediastinum but ≤ liver; 4) Uptake moderately > liver; 5) Uptake markedly higher than liver and/or new lesions; X) New areas of uptake unlikely to be related to lymphoma.[c]It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake. 5PS=5-Point Scale; CT=Computed Tomography; FDG=Fluorodeoxyglucose; IHC=Immunohistochemistry; Ldi=Longest Transverse Diameter of a Lesion; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography; PPD=Cross Product of LDi and Perpendicular Diameter; Sdi=Shortest Axis Perpendicular to LDi; SPD=Sum of Product of Perpendicular Diameters for Multiple Lesions.

Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.