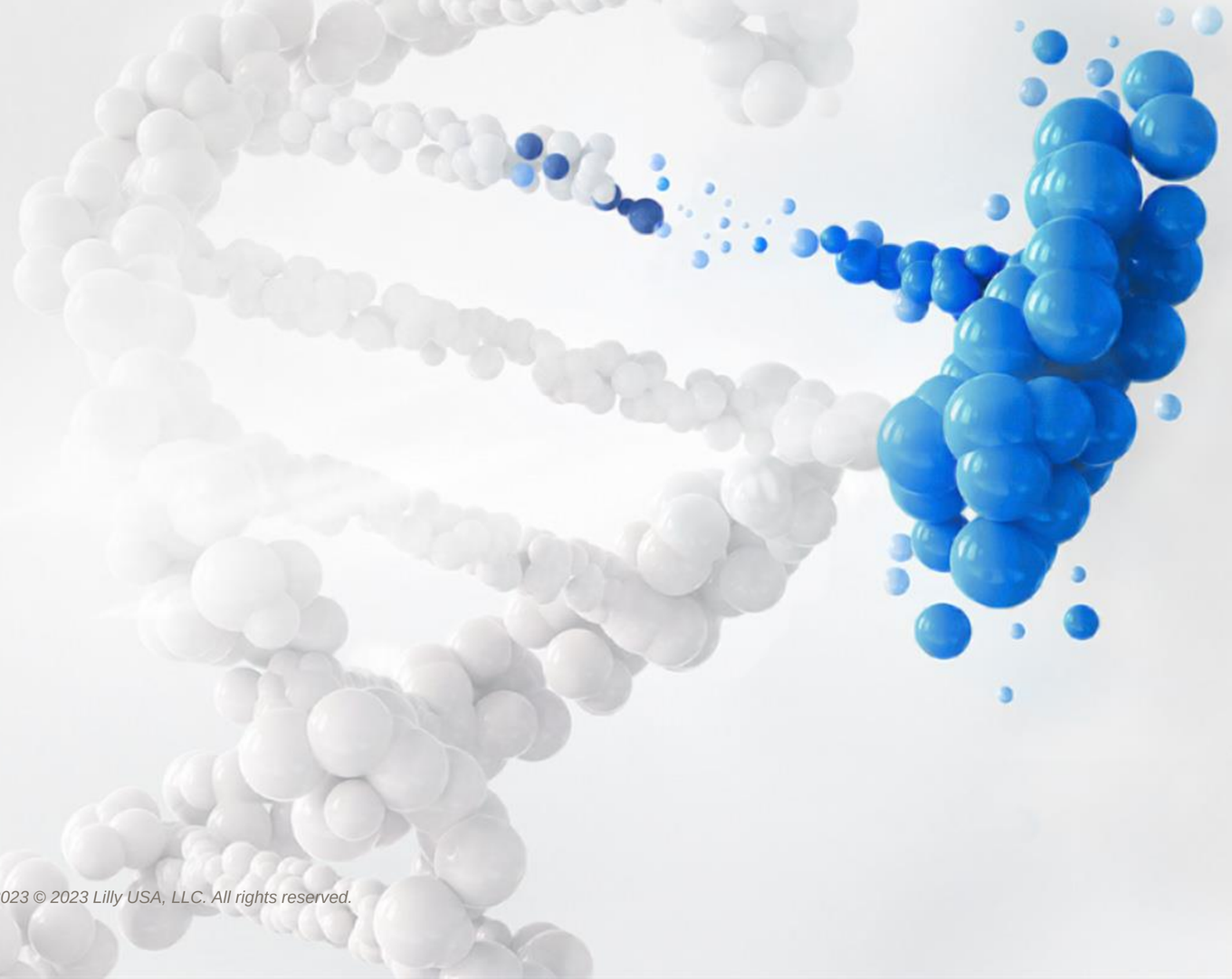
Mantle Cell Lymphoma

Biomarkers and Other Prognostic Factors



Learning Objectives

- Describe the pathophysiology and etiology of Mantle Cell Lymphoma (MCL)
- Recognize the importance of prognostic factors (eg, subtypes, karyotypic abnormalities, MIPI scores, molecular biomarkers) for inferring likely disease outcomes
- Understand that testing for molecular aberrations, such as *TP53*, *SOX11*, *and IGHV* mutations, may help improve upon current prognostic indices and better guide treatment decisions

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Pathophysiology and Etiology of MCL

- Pathophysiology of MCL
  - An aggressive B-cell malignancy, arising in the lymph node mantle zone[1]
  - Characterized by (11;14) translocation and cyclin D1 overexpression[1]
  - Heterogenous molecular alterations and clinical presentation lead to diverse outcomes and treatment challenges[1]

- Incidence
  - ≈1 case per 200,000 persons globally[2]
  - ≈4 to 8 cases per million persons per year in the United States[3]
  - Incidence has increased in the past 7 years[4]

- Prevalence[1]
  - 3% to 10% of all NHL cases

- Median overall survival
  - 4 to 5 years[5]

NHL, non-Hodgkin's Lymphoma.

1. Veloza L, et al. *Ann Lymphoma*. 2019;3(3):1-17. 2. Mantle Cell Lymphoma. NORD. Accessed June 28, 2023. https://rarediseases.org/rare-diseases/mantle-cell-lymphoma. 3. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656. 4. Epperla N, et al. *Br J Haematol.* 2018;181(5):703-706. 5. Vose JM. *Am J Hematol*. 2017;92(8):806-813.

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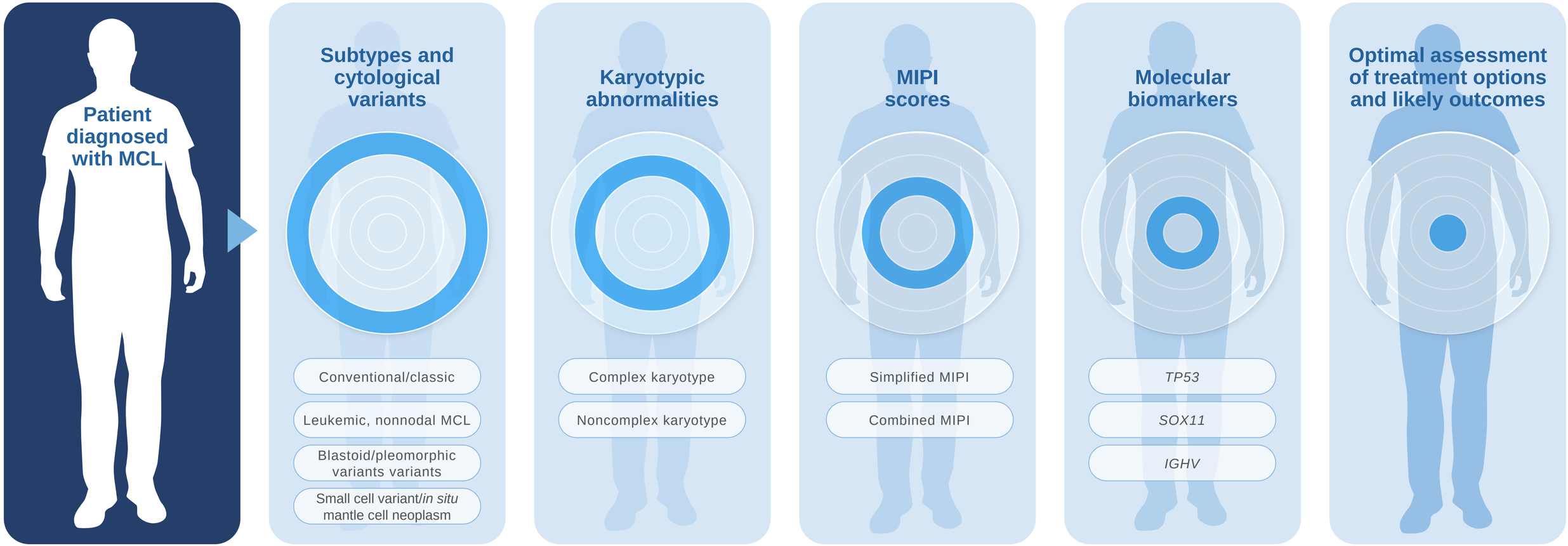
Prognostic Factors Can Help Inform Treatment Decisions and Patient Outcomes



IGHV, immunoglobulin heavy chain variable region gene; MIPI, MCL International Prognostic Index; *SOX11*, *TP53*, tumor promoter 53, .

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Prognostic Factors Can Help Inform Treatment Decisions and Patient Outcomes

Patient diagnosed with MCL

Subtypes and cytological variants

- Conventional/classic
- Leukemic, nonnodal MCL
- Blastoid/pleomorphic variants
- Small cell variant/*in situ* mantle cell neoplasm

Karyotypic abnormalities

- Complex karyotype
- Noncomplex karyotype

MIPI scores

- Simplified MIPI
- Combined MIPI

Molecular biomarkers

- *TP53*
- *SOX11*
- *IGHV*

Optimal assessment of treatment options and likely outcomes

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Subtypes and Cytological Variants

- MCL is dichotomized into 2 subtypes by the World Health Organization, and has a unique set of cytological variants with different clinical and biological characteristics[1-3]

More aggressive

Conventional (classic) MCL[1-3]

- Most common subtype
- Generally aggressive
- Involves lymph nodes and extranodal sites
- Arises in mantle zone
- No or minimal *IGHV* mutation
- *SOX11* expression
- High Ki-67 expression (proliferative index)
- Genetically unstable
- Associated with blastoid/pleomorphic cytological variants

Less aggressive

Leukemic nnMCL[1-3]

- 10% to 20% of cases
- Generally indolent
- Involves BM, PB, and spleen
- Develops in germinal center
- *IGHV* hypermutation
- Minimal *SOX11* expression
- Low Ki-67 expression (proliferative index)
- Genetically stable
- Associated with small cell variant/in situ mantle cell neoplasm

Subtype and histology can distinguish more aggressive disease, potentially requiring different treatment strategies[2]

BM, bone marrow; nnMCL, non-nodal mantle cell lymphoma; PB, peripheral blood.

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

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Complex Karyotype Is Associated With Poor Prognosis

Patient diagnosed with MCL

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Optimal assessment of treatment options and likely outcomes

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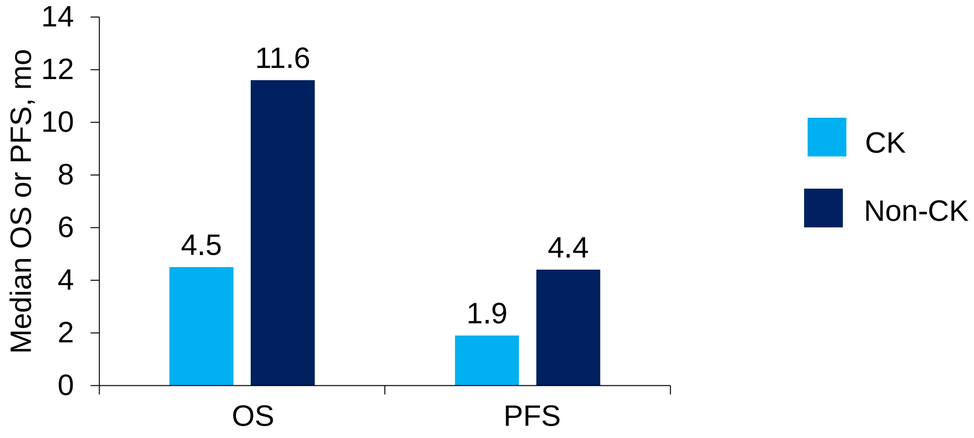
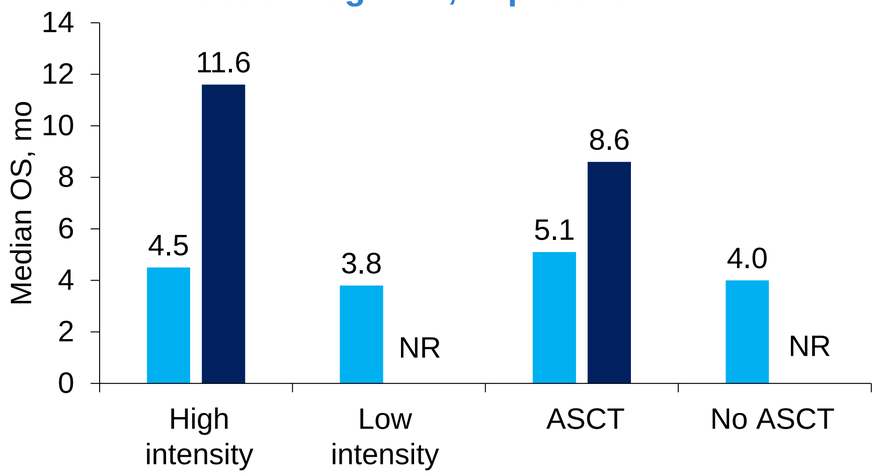
Complex Karyotype

- Defined as having ≥3 chromosomal abnormalities in addition to t(11;14)[1,2]
- Chromosomal imbalances and genetic instability are associated with more aggressive cytological variants and occur more frequently in the conventional subtype[1]

CK is associated with poor OS and PFS[2]



Poor OS was observed, regardless of induction regimen, in patients with CK[2]



Complex karyotype is associated with shorter survival regardless of the subtype and induction regimen[2]

ASCT; autologous stem-cell transplant; CK, complex karyotype; NR, not reached; OS, overall survival; PFS, progression-free survival.

1. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656. 2. Greenwell IB, et al. *Cancer*. 2019;124(11):2306-2315.

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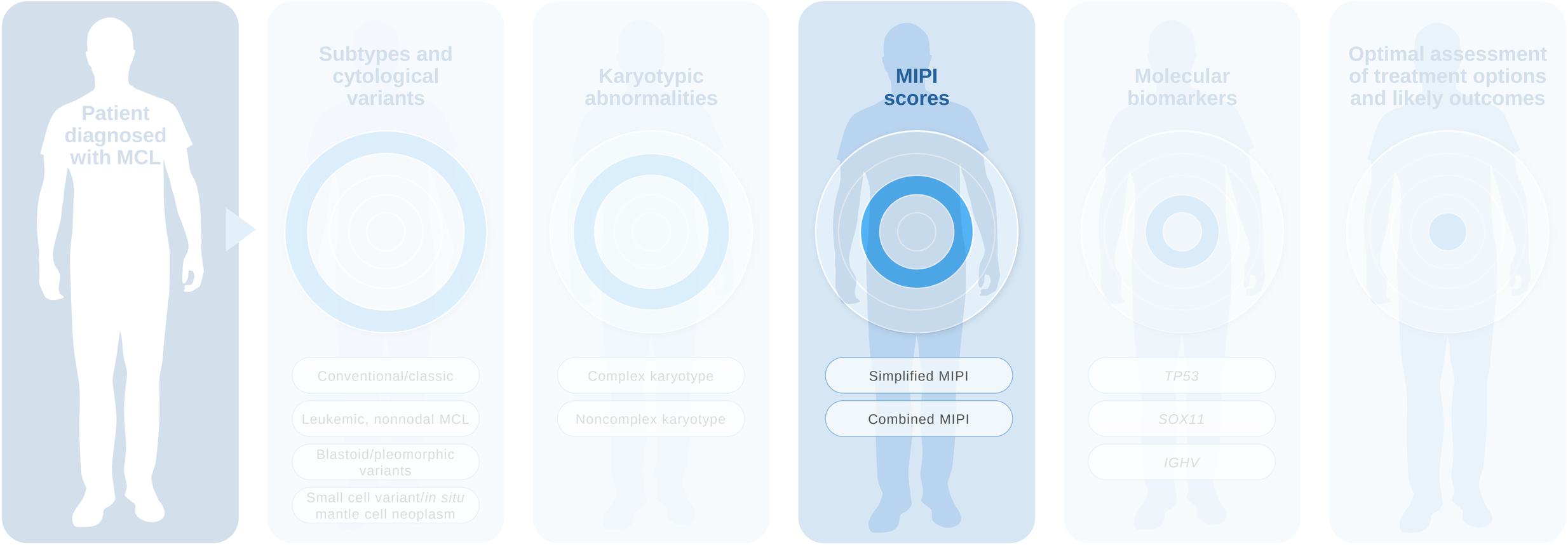
MIPI Score Is a Widely Used Prognostic Tool



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Simplified MCL International Prognostic Index

- Simplified MIPI was devised to better characterize prognosis[1,2]
  - Variables: age, ECOG PS, LDH, and WBC count[1,2]
  - Prognostic for OS[1,2]
    - 5-year OS rate (median)[1,2]
      - Low risk: 81% (Not reached)
      - Intermediate risk: 63% (51 mo)
      - High risk: 35% (29 mo)
    - Not predictive of chemotherapy response or PFS[3]

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	1.00-1.49	1.000-14.999
3	≥70	–	≥1.50	≥15.000

Table reproduced with permission from Hoster E, et al.[1]

MIPI score: 0-3 = Low risk | 4-5 = Intermediate risk | 6-11 = High risk

Simplified MIPI fails to consider known prognostic factors (eg, Ki-67, cytological variant)[3]

ECOG PS, Eastern Cooperative Oncology Group performance score; HR, high risk, IR, intermediate risk; LR, low-risk; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cell.

1. Hoster E, et al. *Blood*. 2008;111(2):558-565. 2. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656. 3. Hoster E, et al. *J Clin Oncol.* 2016;34(12): 1386-1394.

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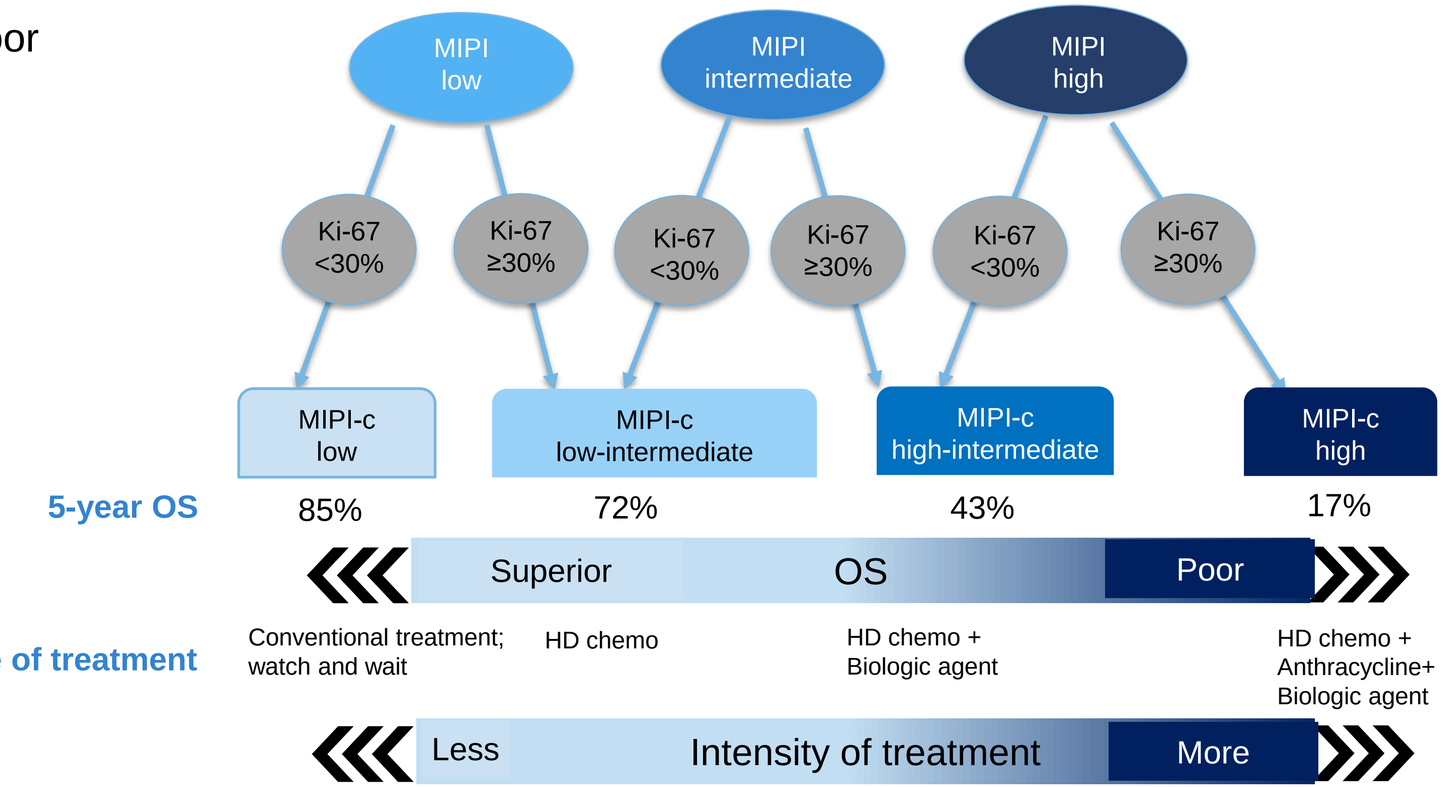
Combined MIPI: MIPI + KI-67 Proliferative Index

- High (>30%) Ki-67 index is associated with poor outcomes and blastoid variant[1-4]
- Ki-67 index is a powerful prognostic factor, independent of MIPI[1-3]
- Combining MIPI with Ki-67 index improves prognostic power[1-4]
  - Prognostic for OS[1,3,4]



Further refinement of MIPI to account for proliferative index can improve risk stratification, with potential implications for treatment selection[2]

Chemo, chemotherapy; HD, high dose; MIPI-c, combined MCL International Prognostic Index.

1. Hoster E, et al. *J Clin Oncol.* 2016;34(12):1386-1394. 2. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656. 3. Determann O, et al. *Blood*. 2008;111(4):2385-2387. 4. Dreyling M, et al. *Haemtaologica.* 2016;101(2):104-114.

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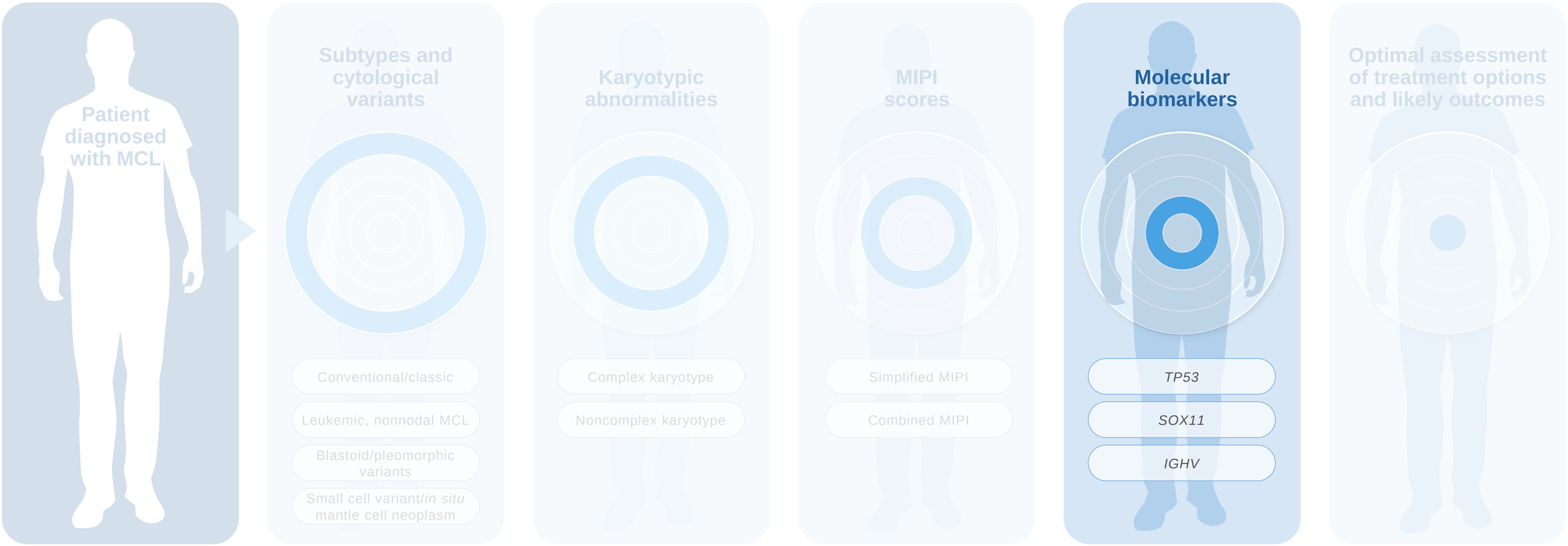
Testing for Molecular Aberrations May Help Improve Upon Current Prognostic Indices and Aid in Optimal Treatment Selection



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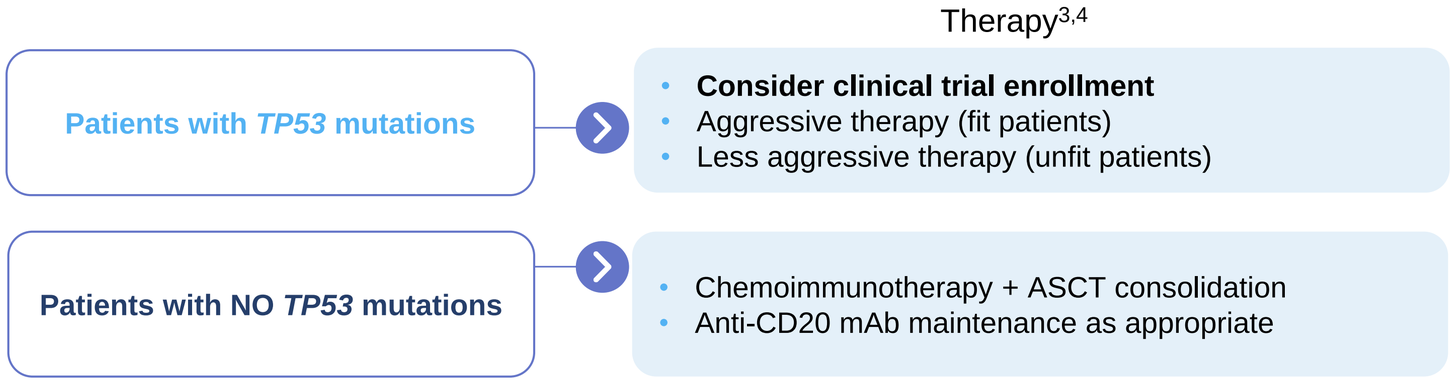
TP53

- *TP53* mutations are associated with poor clinical outcomes (median OS, 1.8 mo vs 12.7 mo)[1,2]
- Mutations in *TP53* are the only independent molecular marker that can improve the prognostic value of MIPI[1,3]
- *TP53* mutations are associated with[2]*:*
  - Blastoid morphology
  - High Ki-67
  - High-risk MIPI
- Because patients with *TP53* mutations have historically responded poorly to chemoimmunotherapy + ASCT, treatment considerations may be stratified by *TP53* mutation status[3]



_TP53_ mutations are associated with poor response to chemotherapy and poor outcomes[2,3]

BCL2, B-cell lymphoma 2; BCR, B-cell receptor; CD, cluster of differentiation; IHC, immunohistochemistry.; mAb, monoclonal antibody.

1. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656 2. Maddocks K. *Blood*. 2018;132(16):1647-1656. 3. Lew TE, et al. *Lancet Haematol.* 2023;10(2):e142-e154. 4. Robak T, et al. Leuk Lymphoma. *2019;60(11):2622-2634.*

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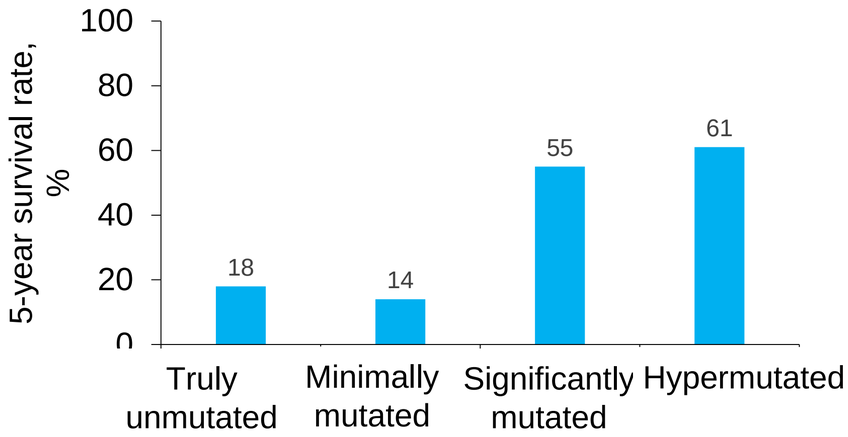
IGHV

- Unmutated *IGHV* MCL is associated with poor prognosis[1-3]
  - Minimally or truly mutated *IGHV* is detected in 24% to 40% of patients with MCL[2]
- Nodal presentation of patients with MCL was less common in mutated *IGHV* than unmutated *IGHV* (*P*<0.001)[2]
  - Hypermutated *IGHV* was associated with an absence of blastoid/pleomorphic variants[2]

Patients with mutated and unmutated *IGHV* had 5-year OS of 59% and 40%, respectively following induction therapy[2]



Unmutated IGHV is associated with a lack of response to induction chemotherapy (AraC or anti-CD20 mAb) and poor outcomes[1,2]

1. Li X, et al. *Medicine (Baltimore).* 2019;98(22):e15811. 2. Navarro A, et al. *Cancer Res.* 2012;72(20):5307-5316. 3. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656.

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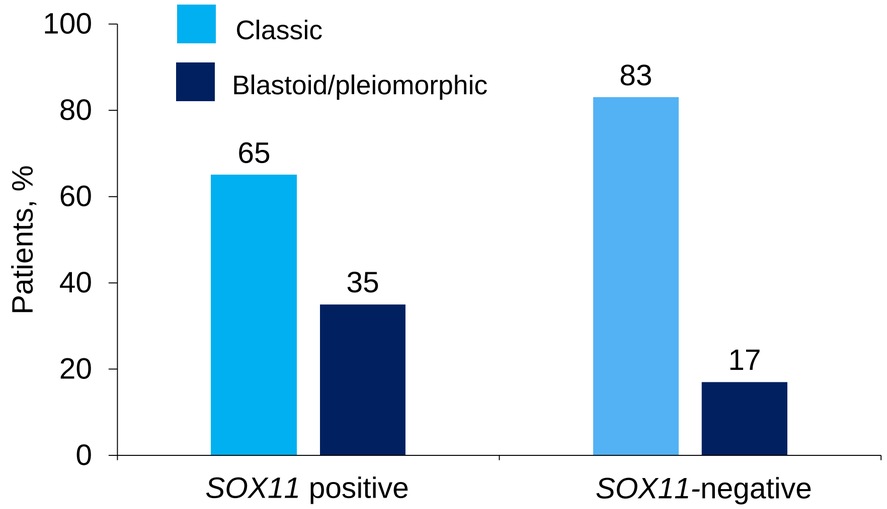
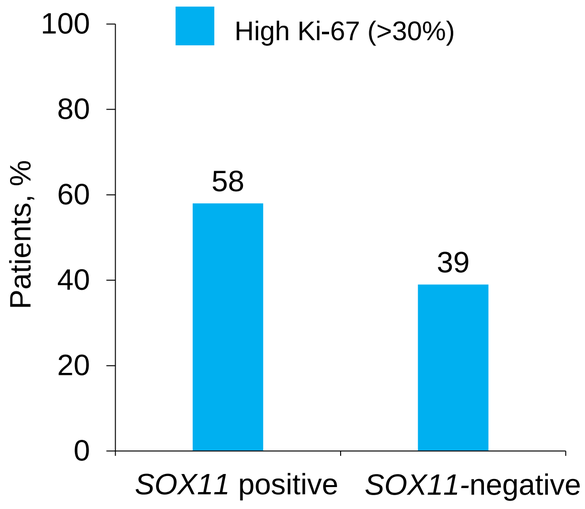
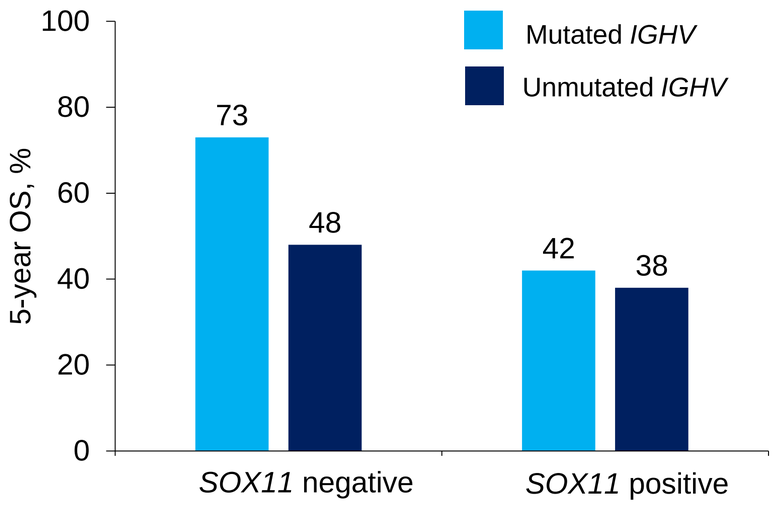
SOX11

- *SOX11* overexpression is associated with[1,2]:
  - Aggressive disease course
  - Conventional subtype
  - Blastoid morphology
  - High Ki-67
- *SOX11* expression may not directly impact prognosis, but is prognostic with other factors (*IGHV* mutation or 17p/*TP53*)[3]







SOX11-negative aids in identifying a subgroup of patients with less aggressive disease[2,3]

1. Inamdar A, et al. *Oncotarget*. 2016;7(30):48692-48731. 2. Xu J, et al. *Am J Surg Pathol*. 2019;43(5):710-716. *3.* Navarro A, et al. *Cancer Res.* 2012;72(20):5307-5316.

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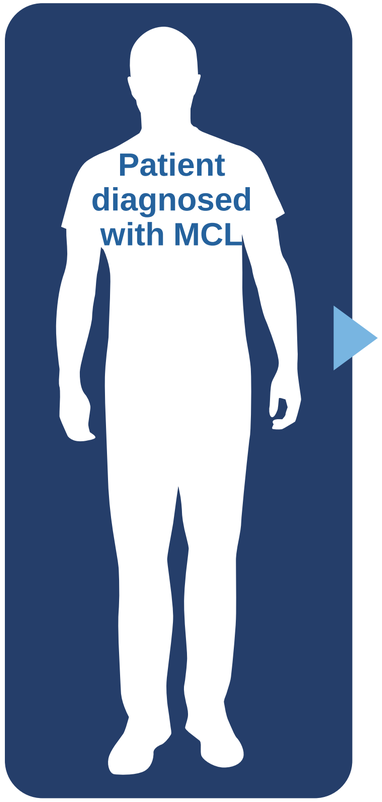
Collective Impact of Prognostic Factors on Treatment Decisions



Subtypes and cytological variants

- Conventional/classical
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- Blastoid/pleomorphic variants
- Small cell variant/*in situ* mantle cell neoplasm

Subtype and **histology** can distinguish more aggressive disease, potentially requiring different treatment regimens[1]

Karyotypic abnormalities

- Complex karyotype
- Non-complex karyotype

Complex karyotype is associated with shorter survival regardless of the subtype and induction regimen[1,2]

MIPI scores

- Simplified MIPI
- Combined MIPI

Also considering Ki-67 index can improve the capacity of the **MIPI score** to identify high-risk patients requiring treatment intensification[3]

Molecular biomarkers

- *TP53*
- *SOX11*
- *IGHV*

The most clinically relevant **biomarkers** in MCL based on outcomes and treatment responsiveness are *TP53*, *IGHV* and *SOX11*[1]

Optimal assessment of treatment options and likely outcomes

When evaluated in composite, prognostic factors provide the most robust assessment of likely clinical outcome, with implications for treatment selection

1. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656. 2. Greenwell IB, et al. Cancer. 2019;124(11):2306-2315. 3. Hoster E, et al. *J Clin Oncol.* 2016;34(12): 1386-1394.

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Future Directions: Prognostic Factors in MCL

- Recent genomic and transcriptomic profiling of samples from 134 patients with MCL identified 4 genetic subsets or clusters associated with OS[1,2]

Cluster	Description	5-year OS rate
Cluster 1	Mutated *IGHV*, *CCND1* mutation, amp(11q13), and active BCR signaling	**100%**
Cluster 2	Del(11q)/*ATM* mutations and upregulation of NF-κB and DNA repair pathways	**56.7%**
Cluster 3	Mutations in *SP140, NOTCH1*, and *NSD2*, with downregulation of BCR signaling and MYC targets	**48.7%**
Cluster 4	Del(17p)/*TP53* mutations, del(13q), del(9p), and active MYC pathway and hyperproliferation signatures	**14.2%**

- IRPI is a novel prognostic index that integrates clinical and immune parameters to predict OS[3]

IRPI	5-year OS rate
Low risk	**100%**
Intermediate risk	**65.3%**
High risk	**32%**

1. Jain P, Wang M. *Am J Hematol*. 2019;94:710-725. 2. Yi S, et al. *J Clin Invest*. 2022;132(3):e153283. 3. Lv H, et al. *Hematol Oncol.* 2022;40(3):343-355

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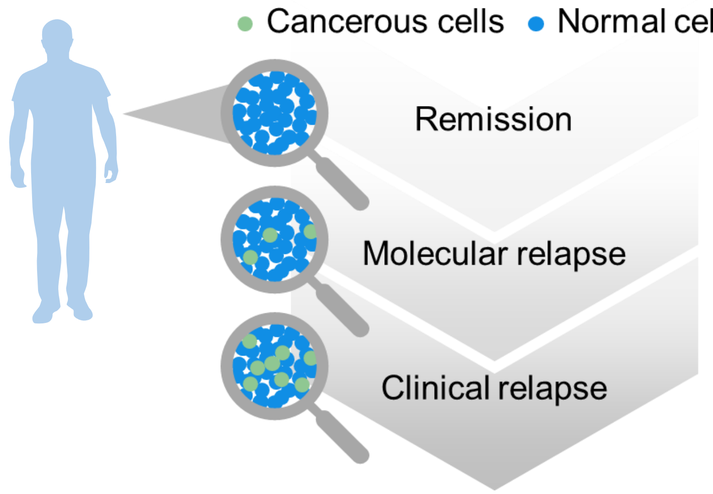
Future Directions: Prognostic Factors in MCL

- Although technologically achievable, MRD is investigational for MCL and is <u>not</u> yet recommended in clinical practice[1-3]



- Available evidence suggests mutational frequencies of critical biomarkers increase at the time of disease progression vs at baseline (eg, *TP53*: 26.8% at diagnosis vs 43.0% at relapse), reinforcing the need for serial testing to optimally inform treatment decisions[4]

Emerging technologies (eg, whole-exome sequencing, liquid biopsy) may facilitate further refinement of prognostic insights with potential implications for treatment selection[1-5]

1. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656. 2. Maddocks K. *Blood*. 2018;132(16):1647-1656. 3. Hoster E, Pott C. *Hematology Am Soc Hematol Educ Program.* 2016(1): 437-445. 4. Hill HA, et al. *Blood Adv.* 2020;4(13):2927-2938. 5 Yi S, et al. *J Clin Invest*. 2022;132(3):e153283.

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Summary

- MCL is an aggressive NHL subtype, characterized by overexpression of cyclin D1 and t(11;14)
- Prognostic factors, such as subtype and cytological variants, complex karyotype, MIPI score, and molecular biomarkers, can help infer likely disease outcomes
- Improved prognostic tools afford the potential to optimize treatment decision-making

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