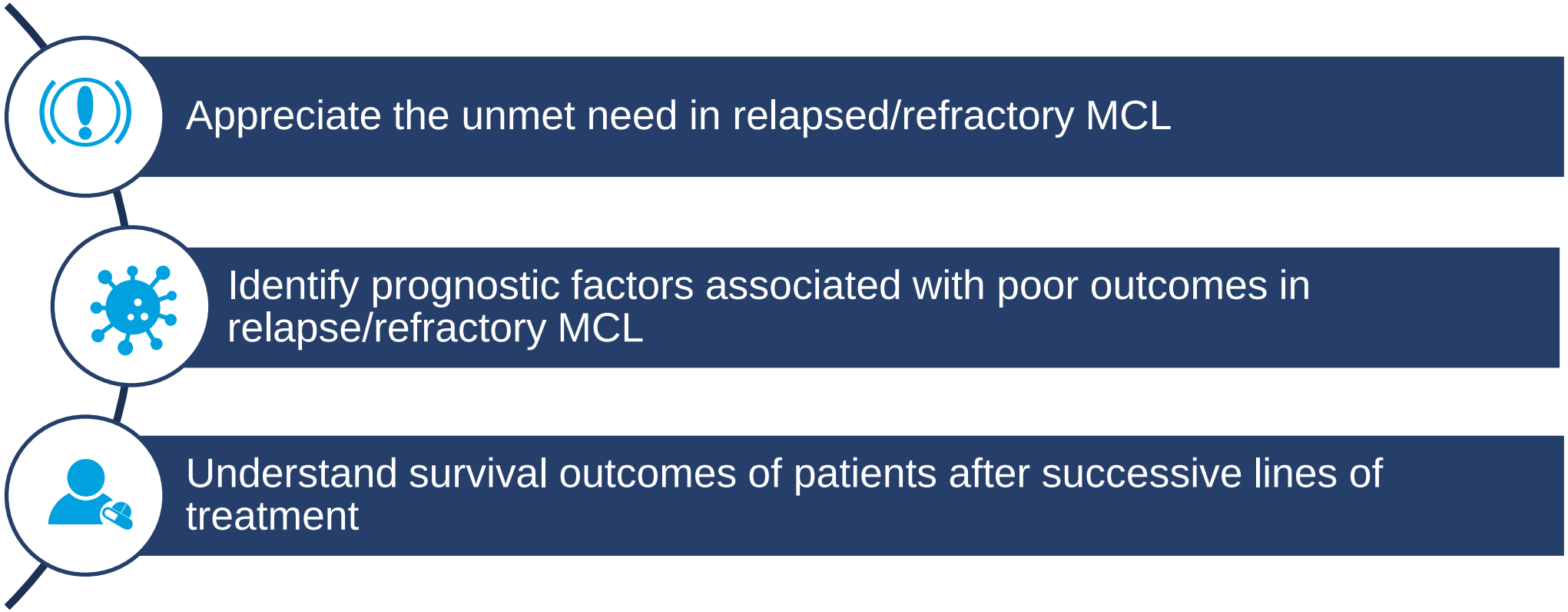
Understanding the Poor Prognosis in Mantle Cell Lymphoma

Learning Objectives

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



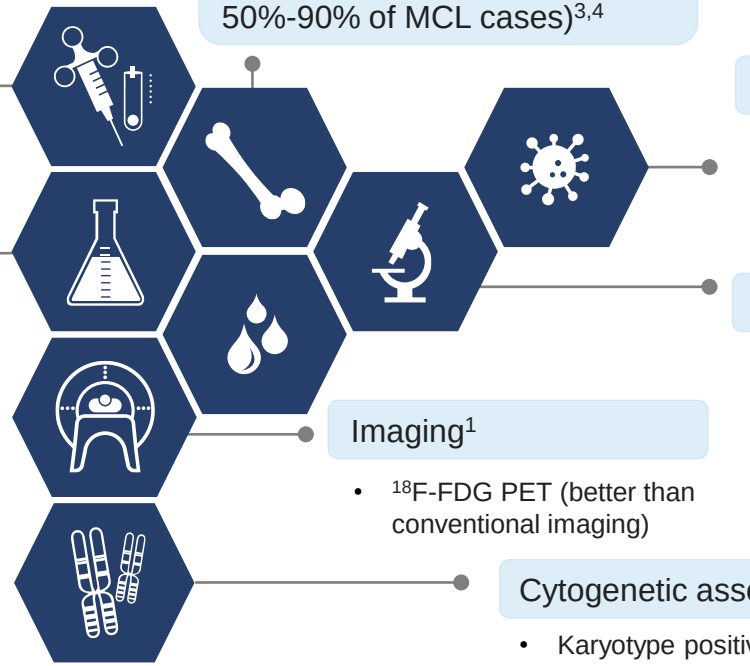
Mantle Cell Lymphoma

Clinical Evaluation

MCL is a clinically heterogeneous disease, and no single marker or aberration can be a diagnostic in all cases

Bone marrow biopsy (bone marrow infiltration is present in 50%-90% of MCL cases)[3,4]

Excisional biopsy of lymph node[1]



Laboratory measures[1,3]

- Differential CBC
- LDH
- CMP
- β-2 microglobulin
- Hepatitis B testing

Prognostic markers[1-3]

- Ki-67 index
- SOX-11 expression
- Mutation status (*TP53,* IGHV, *NOTCH1/2, BIRC3, CDKN2A, NSD2, BTK, and ATM*)

Immunophenotype evaluation[1,3]

- B-cell markers: CD19, CD20, CD22, *PAX5,* CD79a
- Pan-T cell marker CD5 and Cyclin D1
- CD43, *BCL2*, *SOX11*, and *FMC7 (CD20)*

Imaging[1]

- ^{18}F-FDG PET (better than conventional imaging)

Cytogenetic assessment[1,3]

- Karyotype positive for translocation t(11;14) (q13; q32) detected in 90-95% cases using FISH

ATM=Ataxia-Telangiectasia Serine/Threonine Kinase; *BCL2*=B-cell Lymphoma 2; *BIRC3*=Baculoviral IAP Repeat Containing 3; *BTK*=Bruton Tyrosine Kinase; CBC=Complete Blood Count; CD=Cluster of Differentiation; *CDKN2A*=Cyclin-Dependent Kinase Inhibitor 2A; CMP=Complete Metabolic Panel; CT=Computed Tomography; FDG-PET/CT=18f-Flourodeoxyglucose Positron Emission Tomography/Computed Tomography; FISH=Fluorescence In Situ Hybridization; IHC=Immunohistochemistry; LDH=Lactate Dehydrogenase; MCL=Mantle Cell Lymphoma; *NOTCH1/2*=Neurogenic Locus Notch Homolog Protein 1; *NSD2*=Nuclear Receptor Binding SET Domain Protein 2; *PAX5*=Paired Box Protein; *SOX11*=SRY-box Transcription Factor 11; *TP53*=Tumor Protein 53.

1. Jain P et al. *Am J Hematol*. 2022;97:638-656. 2. Bond DA, *et al*. *J Clin Med.* 2021;10(6):1207. 3. Inamdar AA, et al. *Oncotarget*. 2016;7(30):48692-48731. 4. Cohen PL, et al. *Br J Haematol*. 1998;101:302-310.

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Clinical Evaluation: Relapsed/Refractory MCL[1,2, 3]

Patients with R/R MCL require:

- Another biopsy to confirm diagnosis and assess for potential transformation
  - Complex Karyotype
    - High risk: ≥3 cytogenetic abnormalities
- Full restaging to assess disease burden
- TP53 status evaluation and other molecular testing
- Symptoms assessment
- Organ function tests
- Comorbidity status evaluation

- Relapsed/Refractory assessment: Assessment of initial tumor burden and treatment response
  - Obtain serial plasma samples, imaging and tissue biopsies (as needed) for MRD analysis.
  - Clonal evolution tracking by ctDNA testing
- TP53: Associated with therapy resistance, negative prognosis, and aggressive disease
  - Include 17p deletion, TP53 deletions/mutations, p53 overexpression
- Ki67 analysis: independent prognostic factor
  - Low risk: <30%
  - Moderate risk: 30%-50%
  - High risk: ≥50%

ctDNA=Circulating Tumor Deoxyribonucleic Acid; MCL=Mantle Cell Lymphoma; MRD=Minimum Residual Disease; POD24=Disease Progression Within 24 Months; R/R=Relapsed/Refractory; *TP53*=Tumor Protein 53.

1. Bond DA, *et al*. *J Clin Med.* 2021;10(6):1207. 2. Jain P, et al. *Blood*. 2020;136(Suppl. 1):32-33. 3. Eyre TA, et al. *Blood*. 2022;139(5):666-677.

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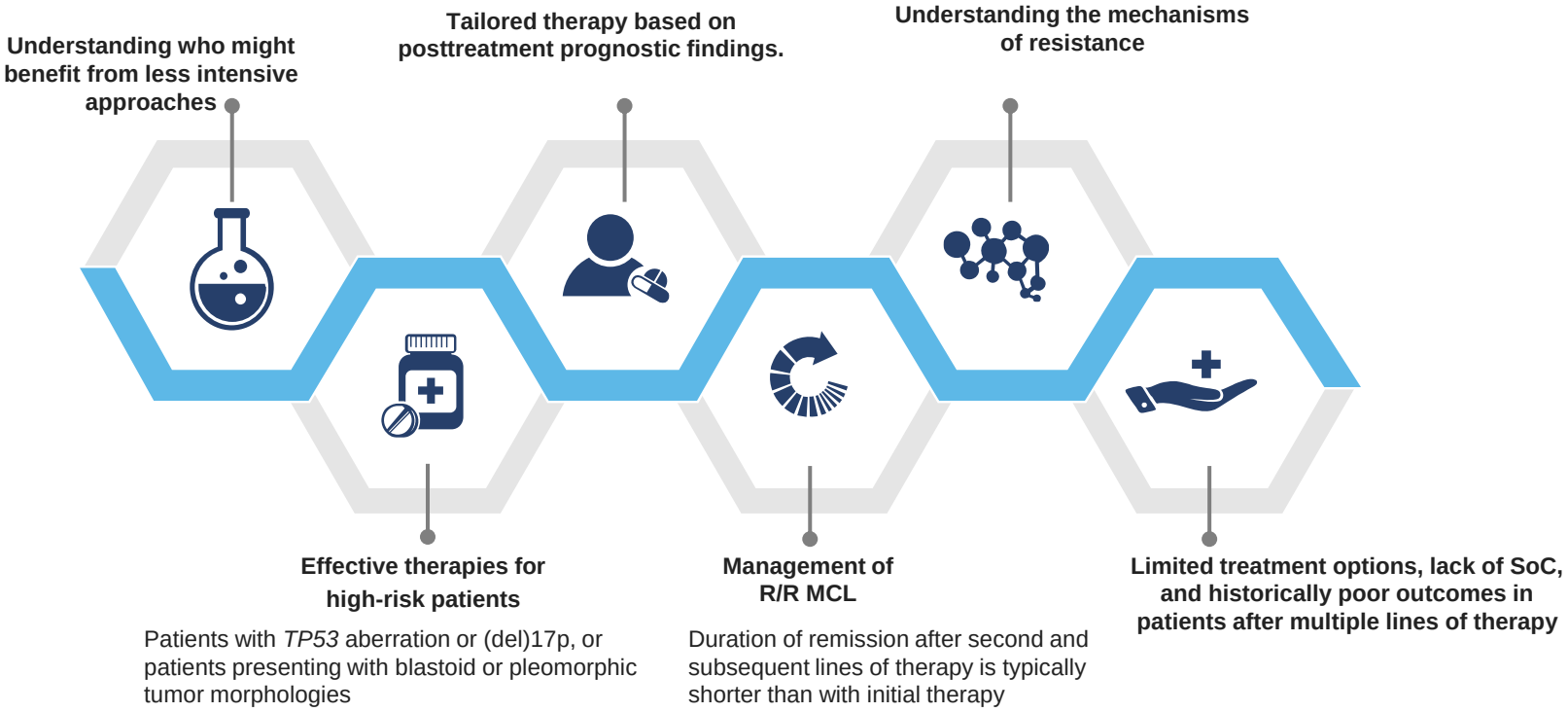
Unmet Need[1-5]



BTK=Bruton's Tyrosine Kinase; Del=Deletion; MCL=Mantle Cell Lymphoma; R/R=Relapsed/Refractory; SoC=Standard of Care; *TP53*=Tumor Protein p53.

1. McCulloch R, et al. *Br J Haematol.* 2020;189(4):684-688. 2. Cheah CY, et al. *Ann Oncol.* 2015;26(6):1175-1179. 3. Epperla N, et al. *Hematol Oncol.* 2017;35(4):528-535. 4. Martin P, et al. *Blood.* 2016;127(12):1559-1563. 5. Sharman J, et al. *Br J Haematol.* 2021;192(4):737-746.

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Risk Factors*

Race

2:1 (Caucasian to African American)[1]

- Race-specific incidence rate (per 100,000 person-years)[2]
  - Non-Hispanic white: 0.73
  - Hispanic white: 0.53
  - Black: 0.32
  - Asian/Pacific Islander: 0.29

Age

Median age of diagnosis is 68 years[1]

Gender

2.5:1 (male to female ratio)[1,2]

Family History

2x the risk if a first-degree relative has MCL[2,3]

Others[3]

- Immunosuppressed conditions (eg, HIV infection)
- EBV infection
- *Borrelia burgdorferi* infection
- Radiation exposure
- Variation in the IL-10 and *TNF* gene families
- Smoking

*United States.

EBV=Epstein Barr Virus; HIV=Human Immunodeficiency Virus; IL=Interleukin-10; MCL=Mantle Cell Lymphoma; *TNF*=Tumor Necrosis Factor.

1. Zhou Y, et al. *Cancer.* 2008;113(4):791-798; 2. Wang Y, Ma S. *BMC Cancer.* 2014;14:764. 3. Smedby KE, et al. *Cancer Biol.* 2011;21(5):293-298.

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	10.000-14.999
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

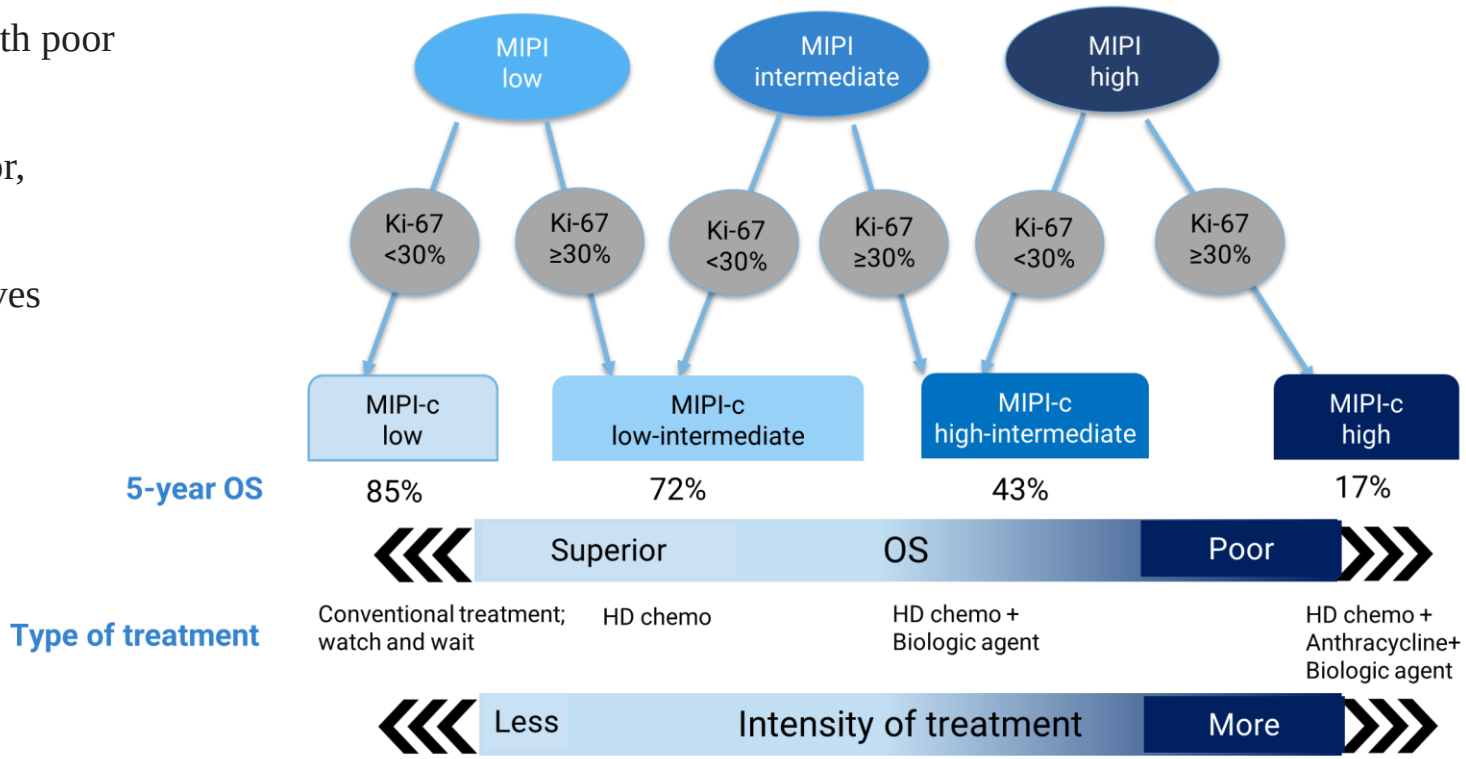
Simplified MIPI fails to consider known prognostic factors (eg, Ki-67, cytological variant)[3]

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.

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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Mutations and Survival

- Molecular aberrations in MCL affect pathogenesis, prognosis, and therapeutic response[1]
- TP53-mutated MCL patients have a poor prognosis and response to standard frontline chemotherapy[2]
- BIRC3 mutations are seen in 10%-15% of patients with MCL, which have decreased response to BTK inhibition[3]
- SWI/SNF mutations lead to decreased response to targeted therapy in MCL[4]
- AKT3, BCL2, BTK, CD79B, PIK3CD, and SYK are associated with poor outcomes, although may be sensitive to BTK inhibition[5]
- TP53 and ATM mutations in patients who have progressed and TP53 and NSD2 mutations in patients who developed blastoid transformation could be useful for evaluating novel agents[6]

AKT3=AKT Serine/Threonine Kinase 3; *ATM*=Ataxia-Telangiectasia Serine Tyrosine Kinase; *BCL2*=B-cell Lymphoma 2; *BIRC3*=Baculoviral IAP Repeat Containing 3; *BTK*=Bruton Tyrosine Kinase; CD79B= Cluster of Differentiation 79B; MCL=Mantle Cell Lymphoma; *NSD2*=Nuclear Receptor Binding SET Domain Protein 2; *PIK3CD*=Phosphatidylinositol 4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta Isoform; *SWI/SNF*=SWItch/Sucrose Non-Fermentable; *SYK*=Spleen Tyrosine Kinase; *TP53*=Tumor Protein 53.

1. Bond DA, et al. *J Clin Med.* 2021;10(6):1207. 2. Aukema SM, et al. *Blood.* 2018;131(4):417-420. 3. Rahal R, et al. *Nat Med.* 2014;20(1):87-92. 4. Agarwal R, et al. *Nat Med.* 2018;25(1):119-129. 5. Bomben R, et al. *Haematologica*. 2018;103(5):849-856. 6. Jain P, et al. *Br J Haematol*. 2018;183(4):578-587.

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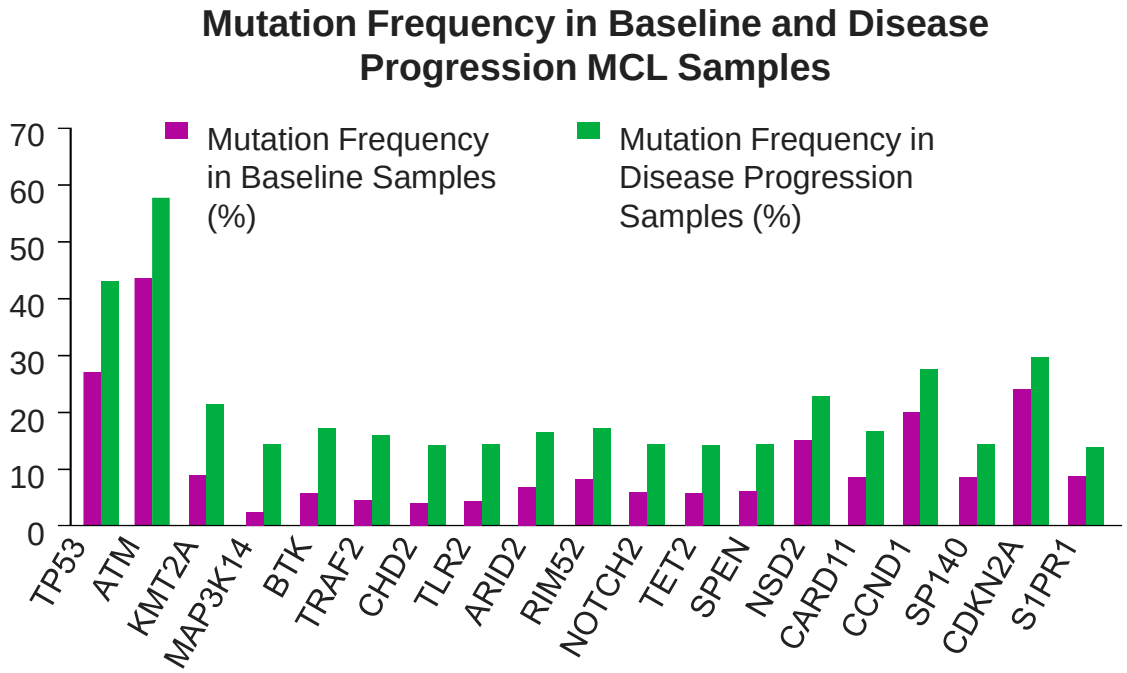
Mutation Frequency at Progression



- The mean mutation frequencies of genes at baseline across 25 studies from 2006 to 2019 were evaluated
- Highest mutation rate observed for ATM at baseline was 37.0% (95% CI: 33.7-40.5). Relapse/progression rate was 57.6% (95% CI: 46.6-68.1)
- The data showed alterations in mutational status from baseline to progressed state in MCL patients

ATM=Ataxia-Telangiectasia Serine/Threonine Kinase; *ARID2*=AT-Rich Interaction Domain 2; BTK=Bruton Tyrosine Kinase; *CARD11*=Caspase Recruitment Domain Family Member 11; *CCND1*=Cyclin D1; *CDKN2A*=Cyclin-dependent Kinase Inhibitor 2A; *CHD2*=Chromodomain-Helicase-DNA-binding Protein; CI=Confidence Interval; *KMT2A*=Histone-Lysine N-methyltransferase 2A; *MAP3K14*=Mitogen-activated Protein Kinase Kinase Kinase 14; MCL=Mantle Cell Lymphoma; *NOTCH2*=Neurogenic Locus Notch Homolog Protein 2; *NSD2*=Nuclear Receptor-binding SET Domain Protein 2; *S1PR1*=Sphingosine-1-Phosphate Receptor 1; *SP140*=Nuclear Body Protein; *SPEN*=Spen Family Transcriptional Repressor; *TET2*=Tet Methylcytosine Dioxygenase 2; *TLR2*=Toll-like Receptor 2; *TP53*=Tumor Protein 53; *TRAF2*=TNF Receptor-associated Factor 2.

Hill HA, et al. *Blood Adv.* 2020;4(13):2927-2938.

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Median OS and PFS With First-line Treatment

- Patients older than 65 years of age have poor outcomes
- SCT improves the outcome of patients when included upfront for first-line treatment
- Younger patients (<65 years) showed improved outcomes with SCT consolidation as part of first-line treatment

Adapted from Kumar A, et al. *Blood J*. 2019;9(6):50.
CI=Confidence Interval; OS=Overall Survival; PFS=Progression-free Survival; SCT=Stem Cell Transplant; NR=Not Reached.
Kumar A, et al. *Blood Cancer J.* 2019;9(6):50.

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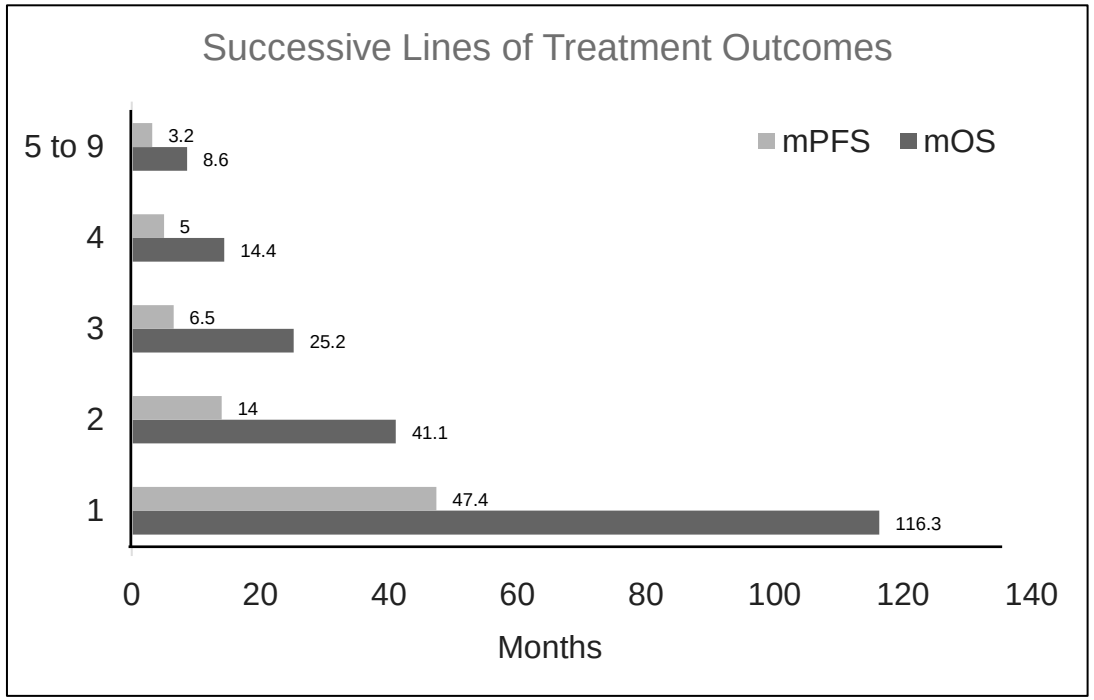
OS and PFS of MCL Patients Treated With Successive Treatment Lines



Overall Survival for Recurrent MCL Patients

- **First Line:** 9.7 years
- **Second Line:** ~3.4 years
- **Third Line:** 2.1 years
- **Fourth Line:** 1.2 years

Progression-free Survival for Recurrent MCL Patients

- **First Line:** 4.0 years
- **Second Line:** ~1.2 years
- **Third Line:** ~0.5 year
- **Fourth Line:** 5 months

- Patients failing third-line and beyond require different treatment strategies or novel therapies

Adapted from Kumar A, et al. *Blood J*. 2019;9(6):50.

MCL=Mantle Cell Lymphoma; OS=Overall Survival; mOS=Median Overall Survival; PFS=Progression-Free Survival; mPFS=Median Progression-Free Survival.

Kumar A, et al. *Blood Cancer J.* 2019;9(6):50.

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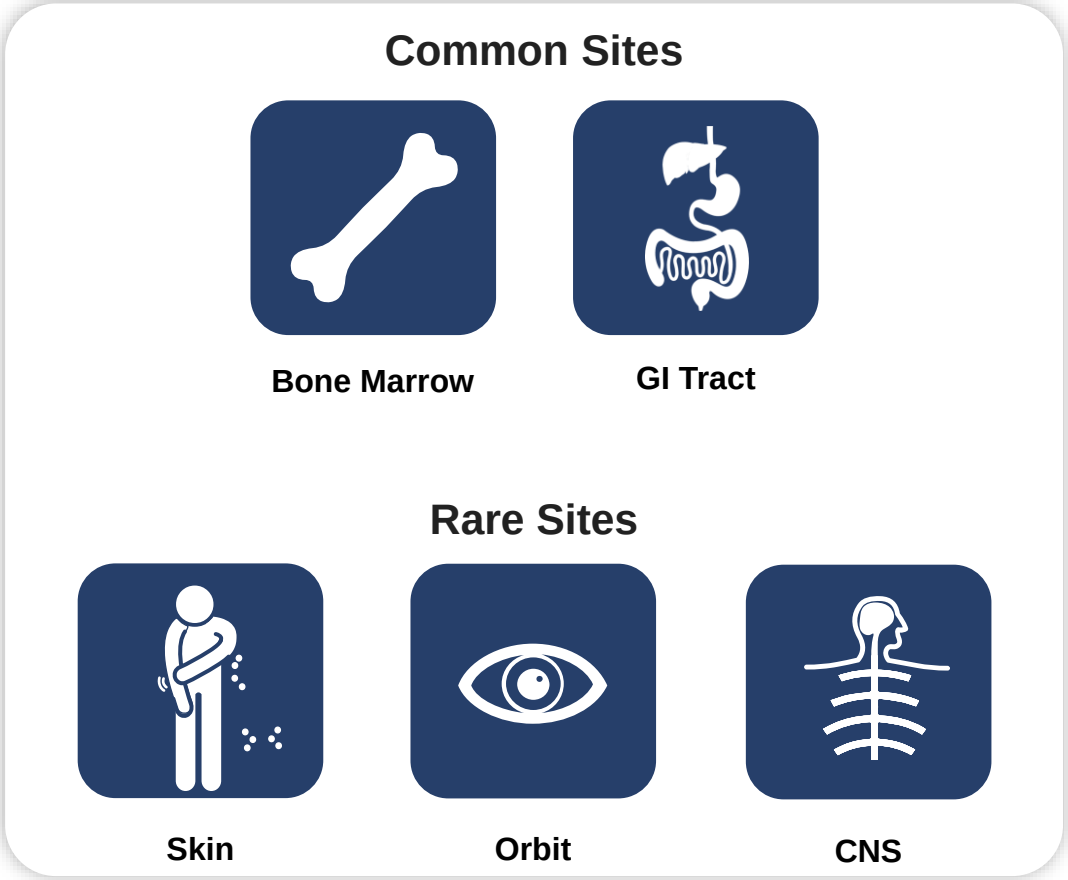
Extranodal Involvement



- MCL is a classical nodal disease; however, it frequently affects extra-nodal sites[1]
- CNS has a rare occurrence, yet it worsens the outcome of high-risk patients[1]
- It occurs in ~4%-23% of patients with systemic disease and median survival of 3 months[2]
- CNS involvement defined by at least one of the following[1]:
  - Histological confirmed CNS
  - Neuroimaging findings
  - Positive CSF
- Possible risk factors for CNS involvement[1]:
  - Blastoid histology
  - B-symptoms
  - Increased serum LDH
  - Poor ECOG performance
  - High MIPI score
- Despite high-dose antimetabolite treatment (eg, cytarabine, methotrexate) prognosis remains poor for patients with CNS involvement[3]
- Intrathecal chemotherapy has been a treatment option[3]

CNS=Central Nervous System; CSF=Cerebrospinal Fluid; ECOG=Eastern Cooperative Oncology Group; GI=Gastrointestinal; LDH=Lactate Dehydrogenase; MCL=Mantle Cell Lymphoma; MIPI=Mantle Cell Lymphoma International Prognostic Index.

1. Cheah CY, et al. *Ann Oncol.* 2013;24(8):2119-2123. 2. Faivre G, et al. *J Neurol.* 2014;261(5):1018-1020. 3. Ferrer A, et al. *Ann Onco.* 2008;19(1):135-141. 4. Shaikh H. et al. *J Hematol*. 2018;7(1):38-42.

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Conclusion

Despite treatment advances, patients with high-risk subset, *TP53* aberrations, and blastoid histology experience limited long-term benefit[1,2]

Patients who have progressed through multiple lines of therapy have poor outcomes[1,2]

It is important to understand somatic mutations in MCL as they can help assign a personalized prognostic risk at diagnosis and throughout treatment[1,2]

Additional therapies are needed to address the challenges and unmet need of R/R MCL patients[2]

BTKis=Bruton Tyrosine Kinase Inhibitors; MCL=Mantle Cell Lymphoma; *TP53*=Tumor Protein 53.

1. Cheah CY, et al. *Ann Oncol.* 2015;26(6):1175-1179. 2. Jain P, et al. *Am J Hematol.* 2022;97(5):638-656.