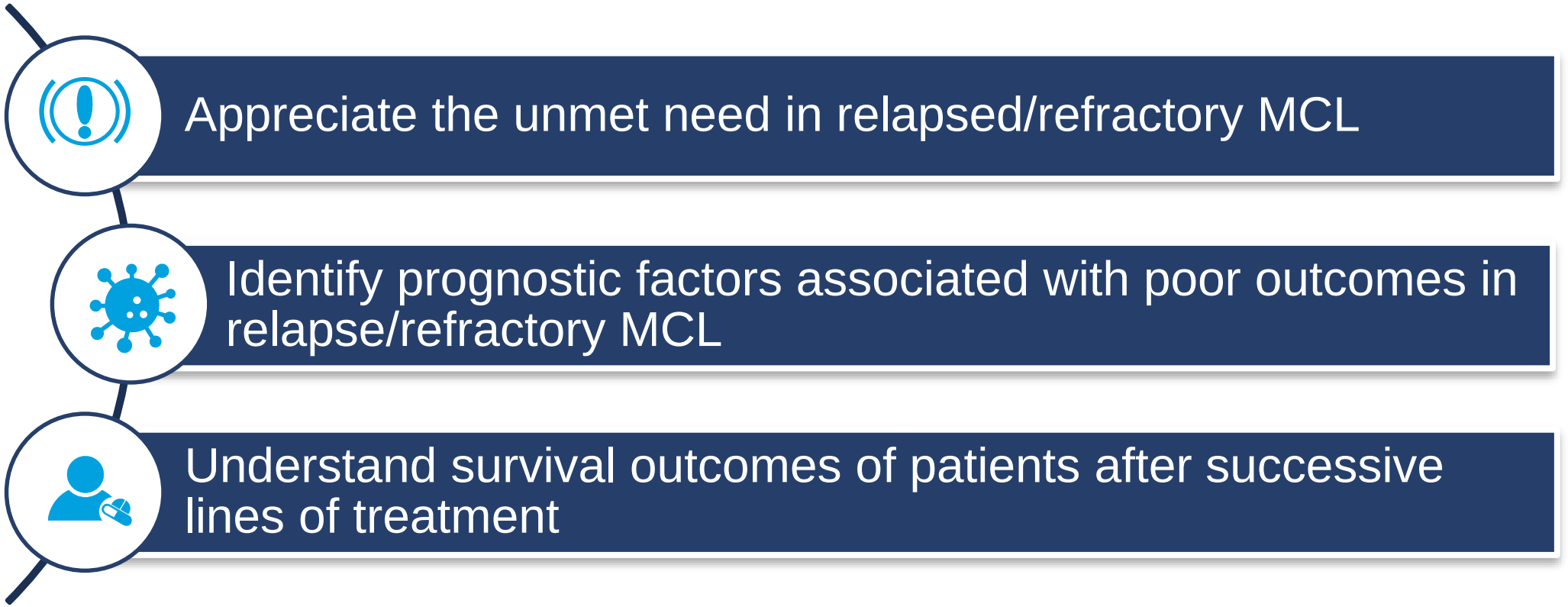
Understanding the Poor Prognosis in Mantle Cell Lymphoma

Learning Objectives

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



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Clinical Evaluation

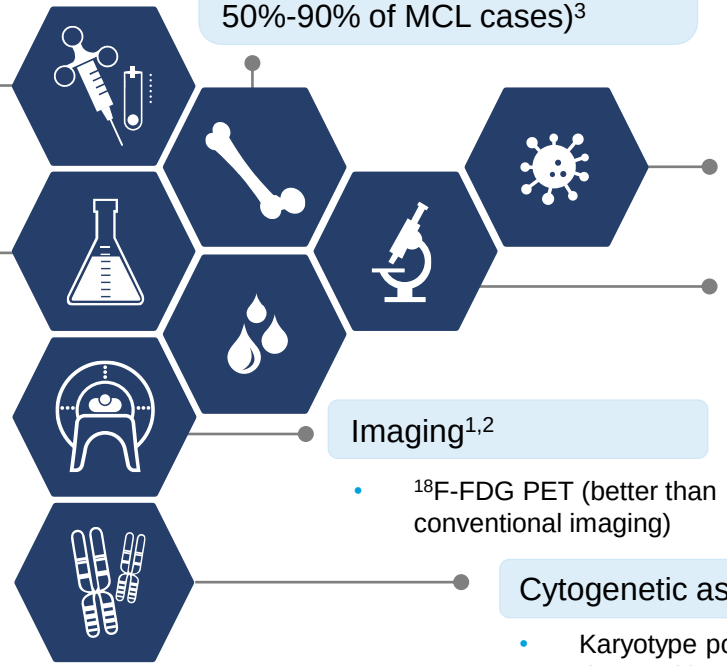
MCL is a clinically heterogeneous disease, and no single marker or aberration can be a diagnostic in all cases

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

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[1,2]

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

Cytogenetic assessment[1,3]

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

Abbreviations are provided in the speaker notes.

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.

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Clinical Evaluation: Relapsed/Refractory MCL[1-3]

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. Geisler CH, et al. *Blood.* 2010;115(8):1530-1533. 3. Jain P, et al. *Blood*. 2020;136(Suppl. 1):32-33.

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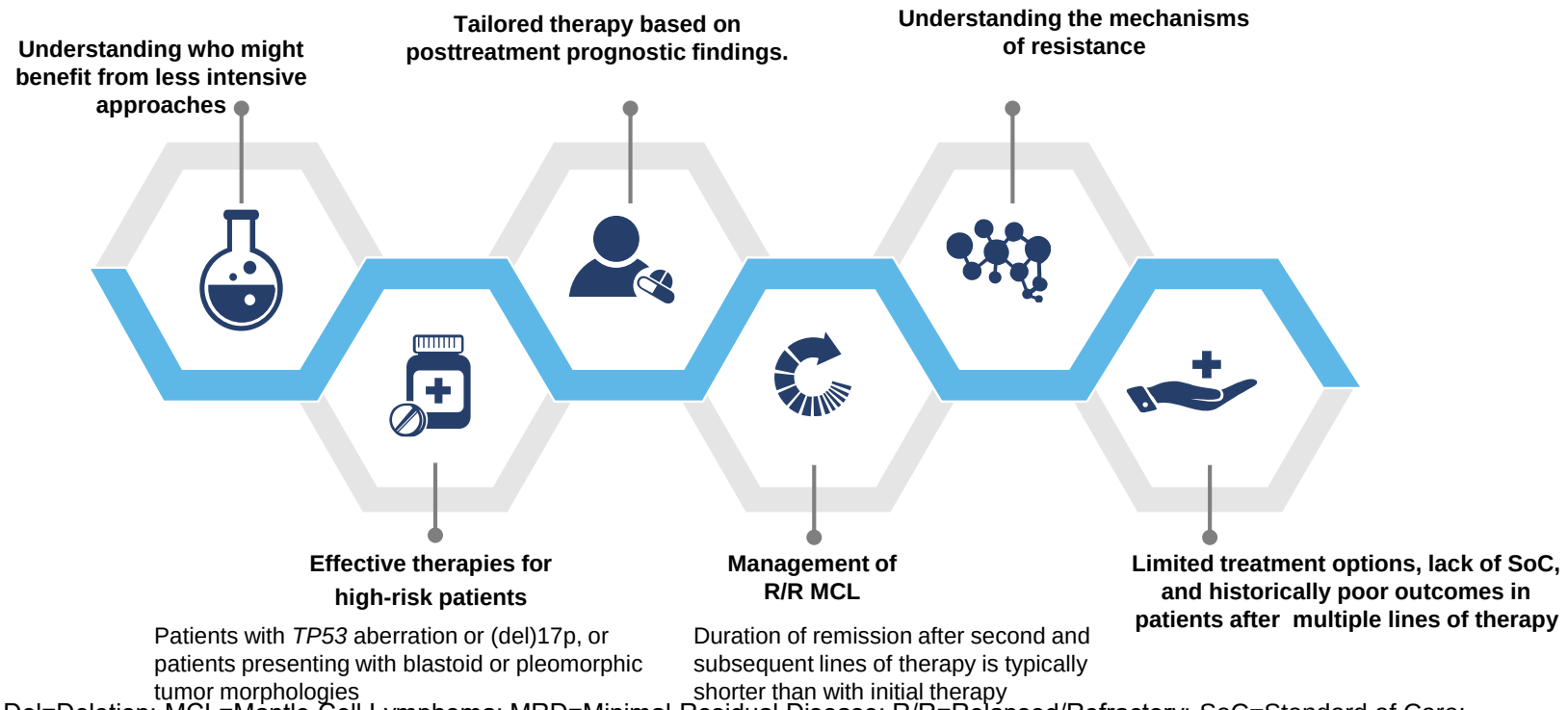
Unmet Need[1-6]



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

1. https://expertperspectives.com/Oncology/Mantle%20Cell%20Lymphoma/persistent-challenges-and-unmet-needs-in-mantle-cell-lymphoma. (Accessed April 14, 2022). 2. McCulloch R, et al. *Br J Haematol.* 2020;189(4):684-688. 3. Cheah CY, et al. *Ann Oncol.* 2015;26(6):1175-1179. 4. Epperla N, et al. *Hematol Oncol.* 2017;35(4):528-535. 5. Martin P, et al. *Blood.* 2016;127(12):1559-1563. 6. 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 (range: 29-85 years)[1,3]

Gender

2.5:1 (male to female ratio)[3]

Family History

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

Others[4]

- 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. Skibola CF, et al. *J Natl Cancer Inst Monogr*. 2014;2014(48):76-86.
4. Smedby KE, et al. *Cancer Biol.* 2011;21(5):293-298.

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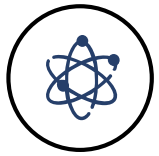
Prognostic Factors[1,2]

- The simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) was used to stratify patients into risk groups according to the 4 prognostic factors
- The patient's proliferative activity of lymphoma cells calculated indirectly through Ki67 positive cells. When known, a biologic MIPI (MIPIb) can be calculated

sMIPI

Age

WBC count



Serum concentration of LDH

ECOG PS

MIPIb

Ki67 score[a]

Simplified MIPI	Risk Level
0-3	Low
4-5	Intermediate
6-11	High

Points	Age	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	1.0-1.49	10.000-14.999
3	≥70	-	≥1.5	≥15.000

[a]Obtained from lymphoma-rich areas on non-bone marrow involved tissue biopsies. Ki-67% >30% is considered to be the high-risk category.
ECOG PS=Eastern Cooperative Oncology Group Performance Status; LDH=Lactate Dehydrogenase; MIPI=Mantle Cell Lymphoma International Prognostic Index;
MIPb=Mantle Cell Lymphoma International Prognostic Index Biological; ULN=Upper Limit of Normal; WBC=White Blood Cell.

1. Jain P et al. *Am J Hematol*. 2019;94(6):710-725. 2. Geisler CH, et al. *Blood.* 2010;115(8):1530-1533.

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MIPI Scores

- Older age, poor ECOG performance score, high LDH, and high white blood cell count at the time of diagnosis are some factors associated with poor survival of MCL patients

Simplified MIPI Scores

Total Score	Risk Groups	Median Survival (mo)	Overall Survival (%)
0-3	Low	Not reached	60
4-5	Intermediate	58	35
6-12	High	37	20

ECOG=Eastern Cooperative Oncology Group; LDH=Lactate Dehydrogenase; MCL=Mantle Cell Lymphoma; Mo=Month; OS=Overall Survival; PFS=Progression-free Survival.

Hoster E, et al. *Blood.* 2008;111(2):558-565.

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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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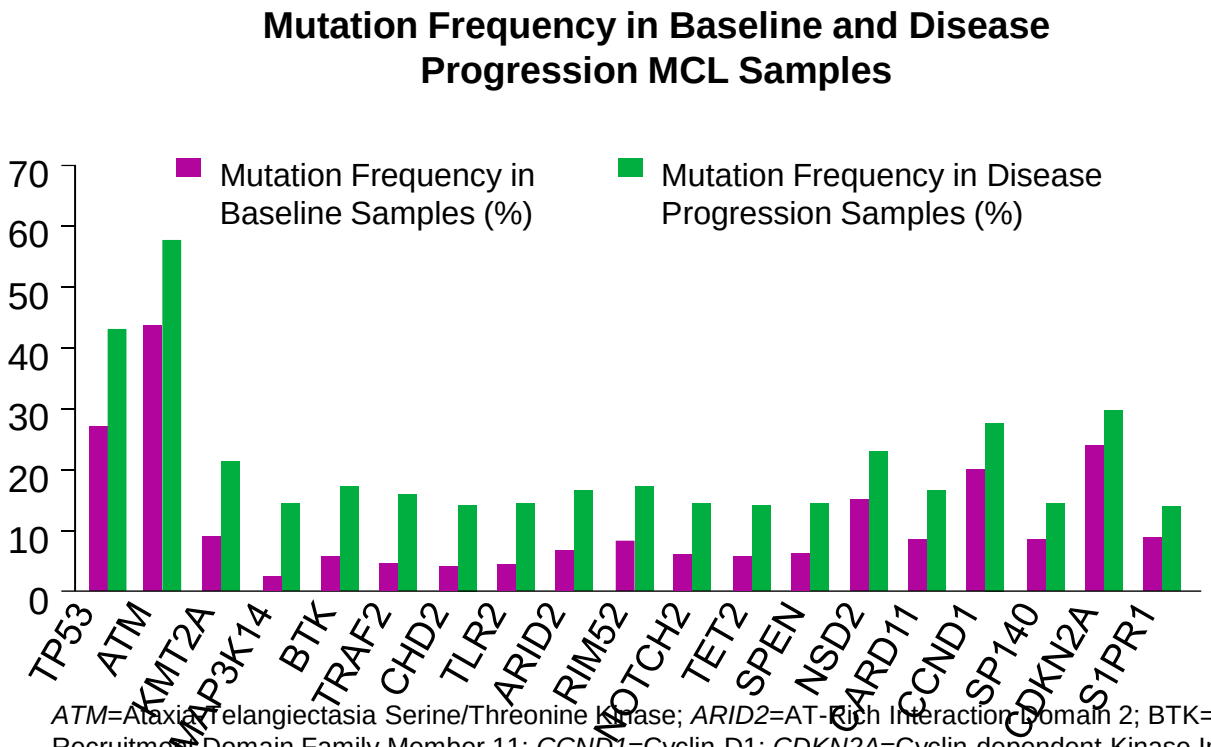
Mutation Frequency at Progression



- 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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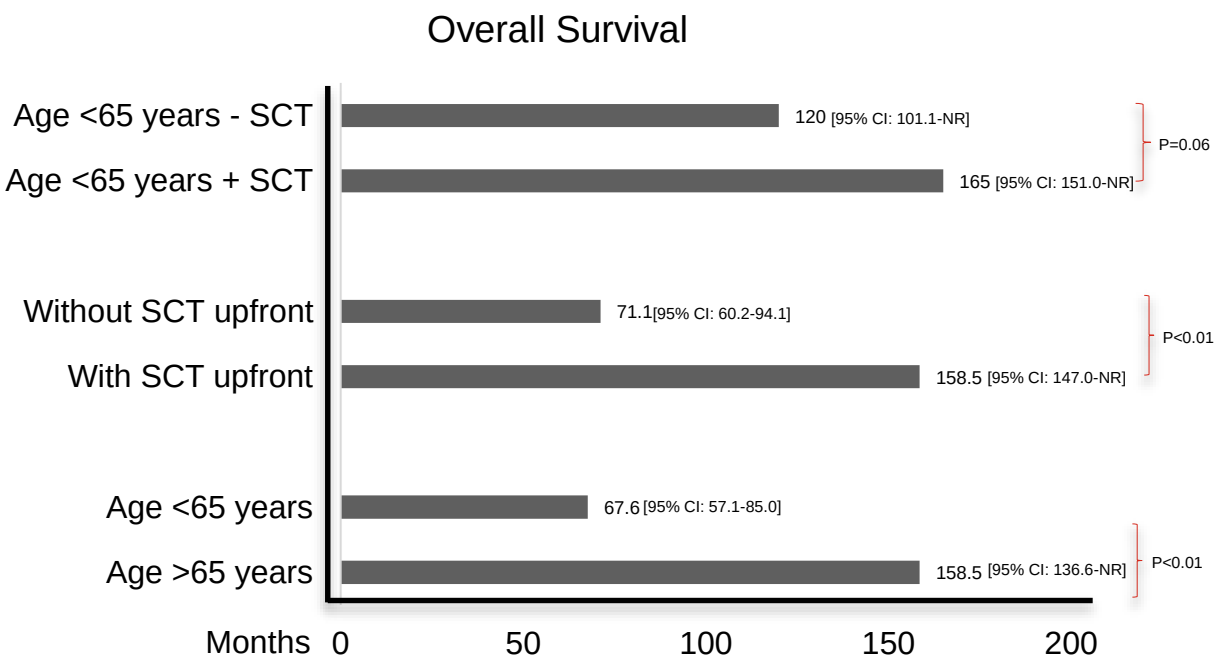
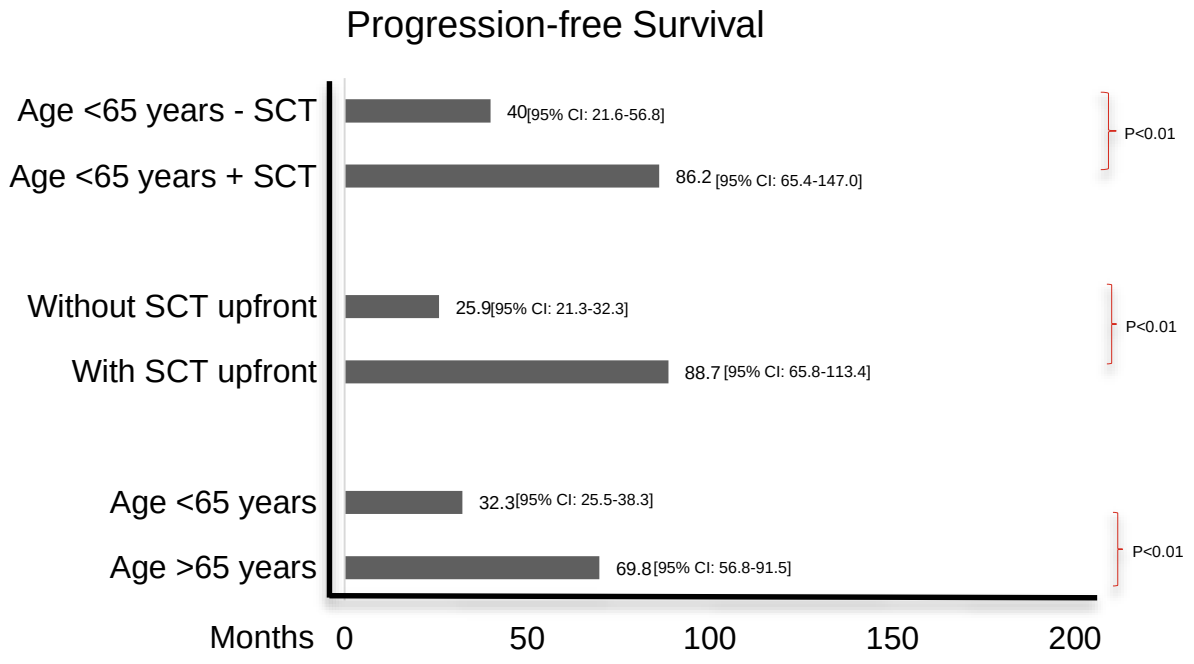
Median OS and PFS With First-line Treatment





- 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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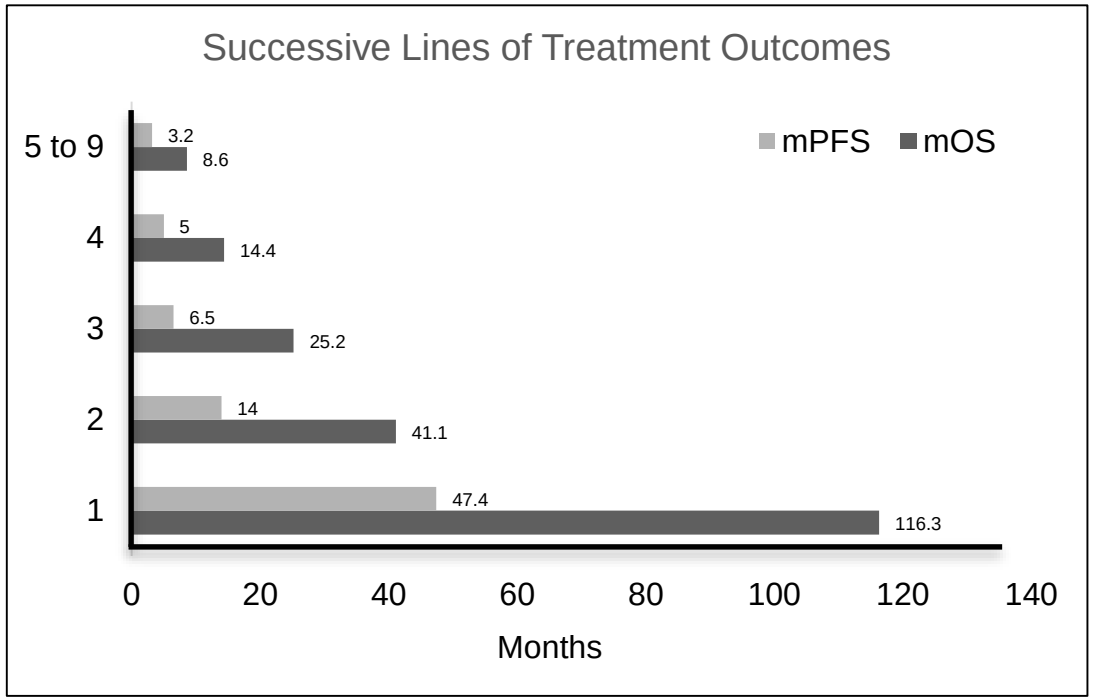
OS and PFS of MCL Patients Treated With Successive Treatment Lines



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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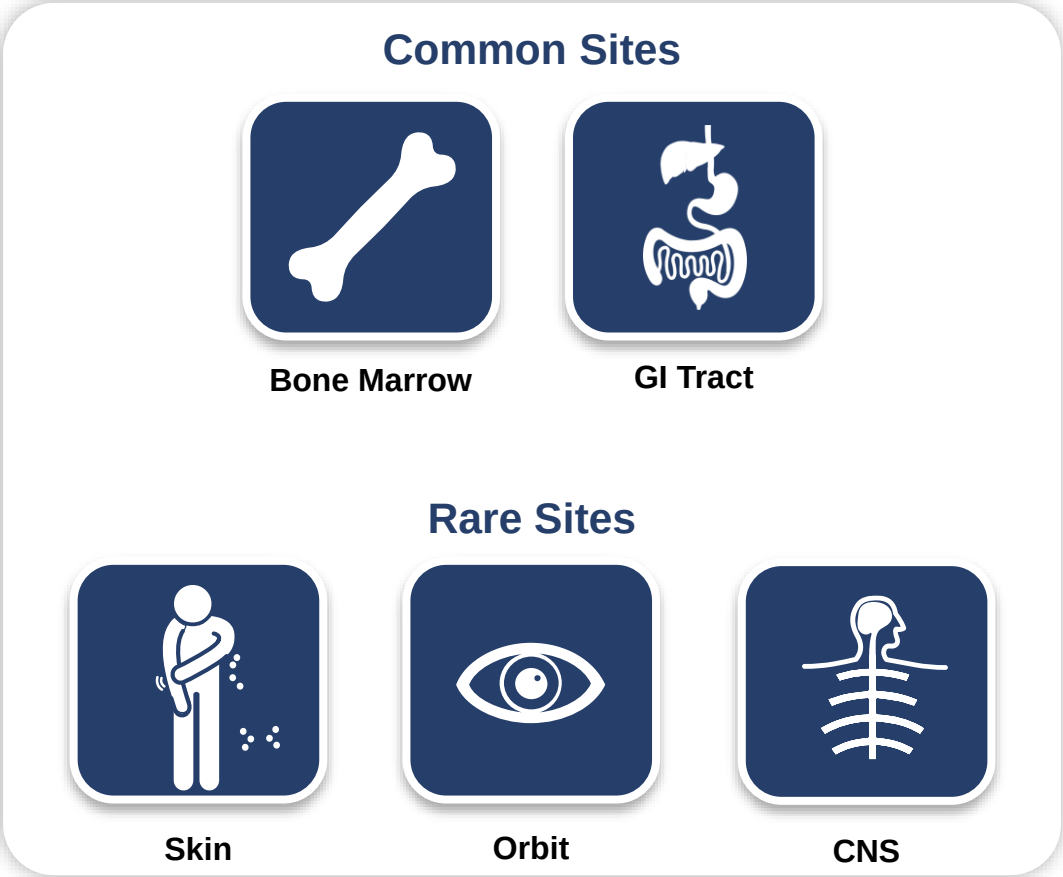
Extra-nodal Involvement



- 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[2]:
  - 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 with or without whole-brain irradiation and consolidated with autologous or allogeneic transplantation 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.

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Conclusion

Despite treatment advances, patients with high-risk subset, *TP53* aberrations, and blastoid histology experience limited long-term benefit[1-3]

Patients who have progressed through multiple lines of therapy have poor outcomes[2,3]

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

Additional therapies are needed to address the challenges and unmet need of R/R MCL patients[3]

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

FIX CITATION FOR 3RD BULLET: 1. Kahl BS. *Curr Hematol Malig Rep.* 2009;4(4):213-217. 2. Cheah CY, et al. *Ann Oncol.* 2015;26(6):1175-1179. 3. Jain P, et al. *Am J Hematol.* 2022;97(5):638-656. 4. Pease DF, et al. *J Geriatr Oncol.* 2018;9(4):308-314.

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