SPOTLIGHT REVIEW ARTICLE

# Advances in biomarkers for mantle cell lymphoma in the era of targeted therapies

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## Abstract

Exciting therapeutic advances are transforming the mantle cell lymphoma (MCL) treatment landscape, with an expanding array of novel agents. Growing evidence demonstrates that MCL is a biologically heterogeneous disease ineffectively managed with historical uniform standard chemoimmunotherapy approaches. Furthermore, traditional prognosticators such as the MCL-International Prognostic index (MIPI), proliferation index Ki-67, and presence of *TP53* aberrations remain valuable but are insufficient to fully capture disease complexity or guide personalized therapy. Biomarker technologies are evolving rapidly. Reflecting this technological renaissance, recent studies have identified a range of novel molecular and cytogenetic alterations that carry prognostic or therapeutic relevance in the context of both chemotherapy and novel agent delivery. Advances in measurable residual disease detection using polymerase chain reaction analysis, next-generation sequencing, and circulating tumor DNA are reshaping risk stratification and offer the potential to guide therapy intensity and duration. New information is emerging regarding the critical role of the tumor microenvironment and immune dysregulation in driving treatment resistance. Additionally, the expanding utility of fluorodeoxyglucose positron emission tomography by harnessing quantitative parameters and radiomic data offers new opportunities for multimodality risk stratification. Here, we comprehensively review the literature beyond established MCL prognosticators and provide an overview of these newer prognostic and predictive biomarkers for MCL in modern treatment paradigms, and their role in informing treatment decisions and future research directions.

## Introduction

Mantle cell lymphoma (MCL) is a rare and biologically distinct subtype of non-Hodgkin lymphoma characterized by marked clinical heterogeneity, historically treated with rituximab-chemotherapy regimens of varying intensity, according to the patients' fitness. Recently, novel targeted and cellular therapies, such as Bruton tyrosine kinase (BTK) inhibitors, bispecific antibodies and chimeric antigen receptor T cells, have yielded excellent results.

Several established molecular prognosticators exist in MCL, such as the proliferation index (Ki-67) and genetic alterations in *TP53* and *SOX11*, yet their value in new treatment paradigms is more varied. The role of the tumor microenvironment (TME) has been heavily scrutinized in other B-cell lymphomas but data from MCL are less established. With the rising use of immunotherapies and integration of high-resolution genomic technologies, along with early insights into the TME and metabolic fluorodeoxyglucose positron emission tomography (FDG-PET) parameters, a broader array of biomarkers is emerging (Figure 1).

The most useful biomarkers in MCL should not only be clinically accessible and reproducible, but also help to delineate disease subgroups, guide therapeutic decisions such as selection for autologous stem cell transplant (ASCT) and maintenance therapy in the upfront setting, and identify patients more likely to benefit from specific targeted agents compared with chemoimmunotherapy. Establishing validated biomarkers in MCL faces several challenges inherent to rare cancers, including small numbers of patients, marked disease heterogeneity, variability in global treatment approaches, and lack of standardization of measurable residual disease (MRD) and genomic testing. Biomarkers can be broadly categorized as tumor-intrinsic or tumor-extrinsic. In this review article, we first review tumor-intrinsic markers such as PET imaging metrics that

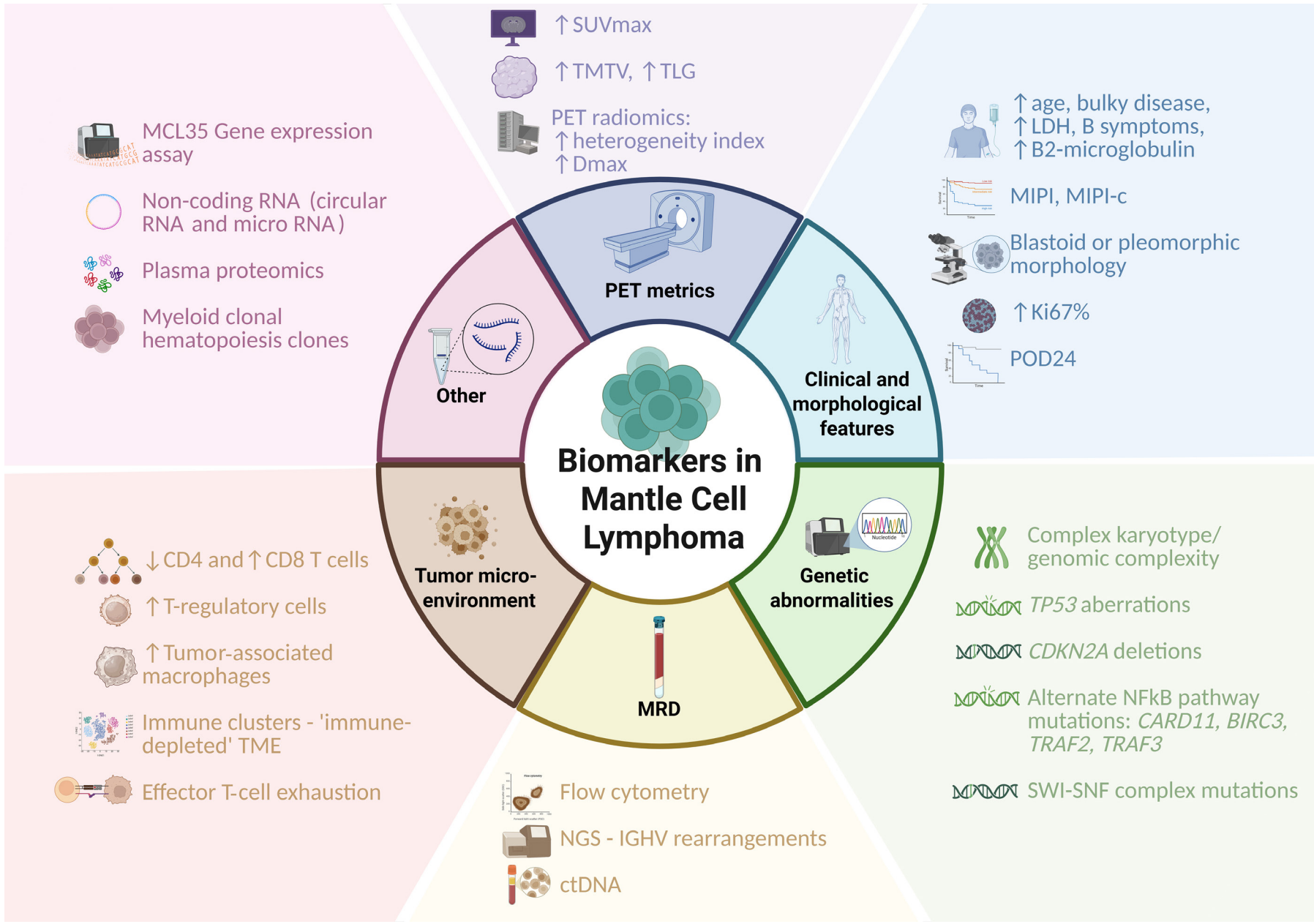


**Figure 1. Overview of current and emerging biomarkers in mantle cell lymphoma.** SUVmax: maximum standardized uptake value; TMTV: tumor metabolic tumor volume; TLG: total lesion glycolysis; PET: positron emission tomography; Dmax: maximum tumor dissemination; LDH: lactate dehydrogenase; MIPI: Mantle cell lymphoma International Prognostic Index; MIPI-c: combined MIPI; POD24: progression of disease within 24 months of treatment initiation; NGS: next-generation sequencing; IGHV: immunoglobulin heavy chain variable region; ctDNA: circulating tumor DNA; TME: tumor microenvironment; MRD: measurable residual disease. Figure created in *https://BioRender.com*

reflect tumor biology, as well as tumor genomic alterations, followed by tumor-extrinsic markers (gene expression assays, non-coding RNA, T cells and macrophages within the TME, and MRD dynamics), with a focus on their contribution to risk stratification and modern personalized MCL strategies (Tables 1 and 2). Some of these biomarker studies were performed using patients from the same clinical trial, or in real-world cohorts, but we have focused on their individual merits within those studies due to the significant variation across studies of which markers are, or are not, included (Table 3).

## Clinical features

Previously well-described prognostic features include prognostic indices developed for MCL such as the MCL-International Prognostic Index (MIPI)[1] and combined MIPI (MIPI-c).[2] The MIPI was created in the chemotherapy era and incorporates age, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase concentration and white cell count. It has retained prognostic capabilities in some BTK-inhibitor trials[3-5] but not in others.[6,7] The Ki-67 index, a measure of cell proliferation rate as the percentage of Ki-67-positive tumor cells determined by immunohistochemistry, is an established prognostic marker in MCL. Using a binary cutoff of 30%, Ki-67 was combined with the MIPI (i.e., MIPI-c) to further refine risk stratification.[2] More recently, a Ki-67 cutoff of 50% was found to be optimal for progression-free survival (PFS) and overall survival (OS), in an analysis of 385 patients (real-world cohort + CALBG 50403 trial of chemoimmunotherapy and ASCT); patients with Ki-67 >50% had an inferior PFS with an adjusted hazard ratio (HR) of 2.2 (95% confidence interval: 1.38-3.48) after adjusting for ECOG score, stage, lactate dehydrogenase concentration and MIPI.[8]

**Table 1.** Clinical data supporting emerging biomarkers in mantle cell lymphoma.

| Biomarker | Testing method | Author (year) | Clinical setting | Treatment | Clinical significance |
|---|---|---|---|---|---|
| **Clinical features** | | | | | |
| MIPI | Age, ECOG PS, LDH and WCC | Hoster (2008)[1] | Treatment-naïve N=455 | Chemotherapy | Low, intermediate and high MIPI risk groups associated with PFS and OS |
| MIPI-c | MIPI + Ki67 IHC | Hoster (2016)[2] | Treatment-naïve N=508 | Chemoimmunotherapy (MCL Younger and MCL Elderly trials) | Low, intermediate and high MIPI risk groups associated with PFS and OS |
| Blastoid/pleomorphic morphology | Histopathology | Gerson (2023)[9] | Treatment-naïve N=207 | Chemoimmunotherapy ± ASCT | Median PFS of 38 months and median OS of 68 months |
| POD24 | Progression of disease within 24 months | Bond (2021)[11] | Treatment-naïve N=1,168 | Chemoimmunotherapy | Inferior OS (<3 years *vs.* 8 years) |
| | | Sarkozy (2025)[12] | Treatment-naïve N=1,280 | Chemoimmunotherapy 6 RCT (LYMA, LYMA101, EU-MCL younger, EU-MCL Elderly, RiBVD, MCL-R2) | Inferior 2-year OS (27% *vs.* 79%) |
| | | He (2025)[13] | Treatment-naïve N=979 | Chemoimmunotherapy or novel agent | Inferior median OS (24 months *vs.* 122 months) |
| **PET metrics** | | | | | |
| TMTV, TLG and Dmax | PET | Albano (2025)[15] | Treatment-naïve N=120 | Chemoimmunotherapy ± ASCT | High baseline TMTV and TLG associated with inferior PFS (HR=2.3 and 2.2, respectively, *P*=0.001). High baseline Dmax associated with inferior OS (HR=1.6, *P*=0.039) |
| SUVmean and entropy | PET | Mayerhoefer (2019)[16] | Treatment-naïve N=107 | Chemoimmunotherapy | High baseline SUVmean and entropy associated with inferior 2-year PFS |
| Heterogeneity index | PET | Liu (2022)[17] | Treatment-naïve N=83 | Chemoimmunotherapy | High heterogeneity index associated with inferior PFS (HR=4.4, *P*=0.042) |
| **Molecular abnormalities** | | | | | |
| Genomic complexity | Conventional karyotyping | Greenwell (2018)[18] | Treatment-naïve N=274 | Chemoimmunotherapy ± ASCT | CK associated with inferior median OS (4.5 years *vs.* 11.6 years) |
| | FISH | Malarikova (2020)[19] | Treatment-naïve N=127 | R-CHOP-like therapy | CK associated with inferior EFS and OS (median OS 13 months *vs.* 47 months) |
| | Whole genome sequencing | Nadeu (2020)[20] | Treatment-naïve N=61 | Chemoimmunotherapy (60%) or observation (40%) | High number of copy number alterations (>7) associated with inferior OS |
| | Conventional karyotyping | Jain (2020)[21] | BTKi-treated N=396 | BTKi; karyotype tested either at diagnosis (N=304) or at relapse | CK associated with inferior OS (median OS 35 months *vs.* 101 months) |

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| Biomarker | Testing method | Author (year) | Clinical setting | Treatment | Clinical significance |
|---|---|---|---|---|---|
| **Molecular abnormalities** | | | | | |
| *TP53* mutations and deletions | NGS | Eskelund (2017)[25] | Treatment-naïve N=183 | Chemoimmunotherapy + ASCT (MCL2/MCL3 trials) | *TP53* mutations associated with inferior OS and PFS (median PFS 0.9 years *vs.* 10.2 years) |
| | NGS and WES | Wang (2022)[5] | Treatment-naïve N=131 | Ibrutinib then chemoimmunotherapy (WINDOW-1 trial) | *TP53* aberrations associated with lower CR rate (55% *vs.* 91%) and inferior PFS |
| | NGS | Freeman (2025)[40] | Treatment-naïve N=261 | Bendamustine rituximab ± ibrutinib (SHINE trial) | *TP53* aberrations associated with poorer PFS Benefit of ibrutinib seen only in *TP53* wildtype patients |
| | NGS | Wang (2025)[29] | R/R N=267 | Ibrutinib ± venetoclax (SYMPATICO trial) | *TP53* aberrations associated with inferior OS in ibrutinib + venetoclax group (median OS 37 months *vs.* NR), although outcomes were improved compared to the ibrutinib-only group (median OS 15 months *vs.* 53 months) |
| | NGS | Epstein-Peterson (2024)[30] | Treatment-naïve N=49 | Lenalidomide + R-CHOP | *TP53* aberrations associated with poorer PFS and OS (3-year OS 96% *vs.* 69%) |
| | Various methods | Wang (2023)[31] | R/R N=168 | Standard-of-care brexucabtagene autoleucel | *TP53* aberrations associated with poorer PFS (HR=1.98, *P*=0.008), OS (HR=2.56, *P*=0.003) and lower CR rate (72% *vs.* 88%, *P*=0.029) |
| *CDKN2A* deletions | NGS | Malarikova (2020)[19] | Treatment-naïve N=127 | R-CHOP-like therapy | *CDKN2A* deletion associated with inferior median OS (36 months *vs.* NR) and EFS (15 months *vs.* 54 months). Concurrent *CDKN2A* and *TP53* mutations associated with resistance to therapy (CR rate 17% *vs.* 56%) |
| *CARD11* mutations | NGS | Decombis (2023)[35] | Treatment-naïve N=17 | Obinutuzumab, ibrutinib and venetoclax (OAsIs trial) | *CARD11* mutations enriched at relapse leading to venetoclax resistance |
| | NGS | Song (2022)[36] | R/R N=86 | Zanubrutinib | *CARD11* mutations associated with inferior PFS (2.9 months *vs.* NR) and inferior ORR (33 months *vs.* 90 months) |
| *BIRC3* mutations and deletions | Hybrid capture NGS | Freeman (2022)[37] | R/R N=156 | Ibrutinib vs. temsirolimus (MCL3001 RAY trial) | *BIRC3* mutations associated with inferior PFS (HR=2.34, *P*<0.001) |
| SWI-SNF complex mutations | WES | Agarwal (2019)[38] | R/R N=24 | Ibrutinib + venetoclax | Del 9p21.1-24.3 and *SMARCA2*, *SMARCA4*, *ARID2* mutations associated with primary resistance to venetoclax + ibrutinib |
| MCL35 gene expression assay (17-gene proliferation signature) | Gene expression assay | Freeman (2025)[40] | Treatment-naïve N=261 | Bendamustine rituximab ± ibrutinib (SHINE trial) | Low, standard and high MCL35 risk groups associated with PFS (median PFS 81, 77 and 13 months, respectively) |
| | | Freeman (2022)[37] | R/R N=134 | Ibrutinib vs. temsirolimus (MCL3001 RAY trial) | MCL35 differentiates low-, standard- and high-risk groups for PFS more reliably than MIPI does |
| MicroRNA | qRT-PCR for miRNA | He (2021)[46] | Treatment-naïve N=75 | Chemoimmunotherapy | Low miRNA34a and elevated miRNA-155 associated with inferior OS |

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| Biomarker | Testing method | Author (year) | Clinical setting | Treatment | Clinical significance |
|---|---|---|---|---|---|
| **Molecular abnormalities** | | | | | |
| Circular RNA | Nanostring RNA profiling platform | Dahl (2022)[44] | Treatment-naïve N=163 | Chemoimmunotherapy + ASCT (MCL2&MCL3 trials) | High-risk circSCORE associated with inferior TTP, PFS, and OS, independent of MIPI and *TP53* mutation status |
| | | Salim (2025)[45] | R/R N=65 | Chemoimmunotherapy or BTKi | High-risk circSCORE associated with inferior PFS (HR=1.92, *P*=0.015) |
| **Other** | | | | | |
| Myeloid clonal hematopoiesis clones | Targeted NGS panel | Ragaini (2025)[57] | Treatment-naïve N=254 | Chemotherapy + ASCT ± lenalidomide maintenance (FIL MCL0208 trial) | Clonal hematopoiesis clones with VAF >10% associated with inferior PFS (HR=2.93, *P*=0.006) and OS (HR=3.02, *P*=0.02) |
| Plasma proteomics | Plasma proteomic profiling | Selvin (2024)[58] | Treatment-naïve N=75 | Chemoimmunotherapy ± BTKi | Expression of LRRN1 and IL-15 associated with POD12 (HR=18.1 and 17.4, respectively) |
| | | Lokhande (2020)[59] | R/R N=44 | Lenalidomide, rituximab + ibrutinib (MCL6 trial) | An immune signature score composed of 11 proteins associated with inferior OS (HR=3.32, *P*=0.03) |
| **Tumor microenvironment (TME)** | | | | | |
| CD4:CD8 ratio | Flow cytometry (tissue) | Nygren (2014)[50] | Treatment-naïve N=153 | Chemoimmunotherapy | Decreased CD4:CD8 ratio associated with inferior OS (HR=2.5, *P*=0.023) |
| | Flow cytometry (blood) | Lv (2022)[51] | Treatment-naïve N=198 | Chemoimmunotherapy | $CD4^+$ T cells <27% and $CD8^+$ T cells >44% associated with inferior OS |
| CD70 overexpression | IHC (FFPE tissue) | Balsas (2021)[48] | Treatment-naïve N=64 | Chemoimmunotherapy | CD70 overexpression associated with inferior OS (HR=1.29, *P*=0.004) |
| High $FOXP3^+$ | IHC (FFPE tissue) | Assis-Mendonca (2021)[47] | Treatment-naïve N=122 | Chemoimmunotherapy | High FOXP3 positivity (marker of Treg cell infiltration) associated with EFS (HR=5.03, *P*<0.001) |
| $CD68^+$ and $CD163^+$ macrophages | IHC (FFPE tissue) | Li (2021)[69] | Treatment-naïve N=82 | Chemoimmunotherapy | High $CD163^+$ M2 TAM and $CD68^+$ M1 TAM associated with inferior OS |
| $CD163^+$ on FFPE | IHC (FFPE tissue) | Rodrigues (2021)[55] | Treatment-naïve N=282 | Chemoimmunotherapy | CD163 expression >0.6% associated with OS (HR=2.48, *P*=0.02) |
| Soluble CD163 in serum | ELISA | Nikkarinnen (2023)[56] | Treatment-naïve (N=81) and relapsed (N=50) | Chemoimmunotherapy | High sCD163 associated with inferior 5-year OS (51% *vs.* 96%) |
| T-cell exhaustion | Flow cytometry | Minson (2024)[52] | R/R N=20 | CAR-T + ibrutinib (TARMAC trial) | Deep responders demonstrated a lower proportion of $CD8^+$/HLA–$DR^-$/$PD\text{-}1^+$ terminally differentiated effector memory subsets, consistent with a less exhausted $CD8^+$ T-cell phenotype |
| | Single-cell RNA sequencing | Jiang (2022)[53] | R/R N=15 | CAR-T | Acquired T-cell exhaustion (reduced CD4/CD8 cytotoxic T cells) seen at relapse after CAR-T |

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| Biomarker | Testing method | Author (year) | Clinical setting | Treatment | Clinical significance |
|---|---|---|---|---|---|
| **Tumor microenvironment (TME)** | | | | | |
| TME clusters | Bulk RNA sequencing | Jain (2023)[49] | R/R<br>N=41 | BTKi | 'Immune-depleted' TME subtype associated with primary resistance to BTKi and poorest OS |
| **Measurable residual disease (MRD)** | | | | | |
| MRD negativity | clonoSEQ NGS | Fenske (2024)[63] | Treatment-naïve<br>N=650 | Chemoimmunotherapy<br>(*ECOG-ACRIN EA4151 trial*) | No difference in 3-year OS between ASCT *vs.* no ASCT group if MRD negative at $10^{-6}$ after induction |
| | RT-qPCR ± NGS | Gine (2022)[3] | Treatment-naïve, indolent MCL<br>N=50 | Ibrutinib + rituximab<br>(*ICML-2015 trial*) | Treatment ceased in the 24 patients who achieved MRD negativity ($10^{-5}$) after 24 months; only 1 patient had clinical relapse after a median follow-up of 36 months |
| | RT-qPCR | Jerkeman (2024)[64] | R/R<br>N=59 | Lenalidomide, venetoclax + rituximab<br>(*VALERIA MCL7 trial*) | 89% who achieved MRD negativity ($10^{-5}$) remained in molecular remission, with a median follow-up of 14 months |
| | clonoSEQ NGS | Kumar (2025)[6] | Treatment-naïve, *TP53*-mutated<br>N=25 | Zanubrutinib, obinutuzumab + venetoclax (*BOVen trial*) | Treatment discontinued in the 15 patients who achieved MRD negativity ($10^{-6}$); 13 remain in remission after a median follow-up of 28 months |

MIPI: Mantle Cell Lymphoma International Prognostic Index; MIPI-c: combined Mantle Cell Lymphoma International Prognostic Index; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; WCC: white cell count; PFS: progression free survival; OS: overall survival; IHC: immunohistochemistry; MCL: mantle cell lymphoma; ASCT: autologous stem cell transplant; POD24: progression of disease within 24 months of treatment initiation; RCT: randomized controlled trial; PET: positron emission tomography; TMTV: total metabolic tumor volume; TLG: total lesional glycolysis; Dmax: maximum tumor dissemination; SUV: standardized uptake value; HR: hazard ratio; CK: complex karyotype; FISH: fluorescence in situ hybridization; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; EFS: event-free survival; BTKi: Bruton tyrosine kinase inhibitor; NGS: next-generation sequencing; WES: whole-exome sequencing; CR: complete remission; R/R: relapsed/refractory; NR: not reached; ORR: overall response rate; qRT-PCR: quantitative reverse transcriptase polymerase chain reaction; miRNA: microRNA; TTP: time to progression; VAF: variant allele frequency; LRRN1: leucine-rich repeat neuronal protein 1; IL-15: interleukin-15; POD12: progression of disease within 12 months of treatment initiation; FFPE: formalin-fixed paraffin-embedded; Treg: regulatory T cells; TAM: tumor-associated macrophages; ELISA: enzyme-linked immunosorbent assay; CAR-T: chimeric antigen receptor T cells.

**Table 2.** Current data for mantle cell lymphoma biomarkers according to treatment setting.

| Biomarker | Chemoimmuno-therapy | BTKi | BTKi + BCL2i | CAR-T |
|---|---|---|---|---|
| **Clinical features** | | | | |
| MIPI | | | | |
| MIPI-c | | | | |
| Blastoid/pleomorphic morphology | | | | |
| POD24 | | | | |
| **PET radiomics** | | | | |
| TMTV, TLG | | | | |
| Heterogeneity index | | | | |
| **Molecular markers** | | | | |
| Genomic complexity | P | | | |
| *TP53* mutation/deletions | P | P | | P |
| *CDKN2A* deletions | P | | | |
| NF-κB pathway mutations (*CARD11*, *BIRC3*) | | P | P | |
| SWI-SNF complex mutations | | | P | |
| MCL35 gene expression assay | | | | |
| circSCORE | | | | |
| Plasma proteomics | | | | |
| **TME** | | | | |
| Low $CD4^+$ T cells | | | | |
| Tumor-associated macrophages | | | | |
| $CD8^+/HLA\text{-}DR^-/PD1^+$ T cells | | | | P |
| TME immune clusters | | P | | |
| **MRD** | | | | |
| MRD negativity | P | P | P | |

| | |
|---|---|
| | Studies demonstrate prognostic effect |
| | Studies show no prognostic significance |
| | Insufficient data for prognostic effect |
| P | Studies demonstrate predictive effect |

BTKi: Bruton tyrosine kinase inhibitor; BCL2i: B-cell lymphoma-2 inhibitor; CAR-T: chimeric antigen receptor T cells; MIPI: Mantle Cell Lymphoma International Prognostic Index; MIPI-c: combined Mantle Cell Lymphoma International Prognostic Index; POD24: progression of disease within 24 months; PET: positron emission tomography; TMTV: total metabolic tumor volume; TLG: total lesional glycolysis; TME: tumor microenvironment; MRD: measurable residual disease.

Pleomorphic and blastoid morphological variants which account for 10-20% of cases have a distinct biology, aggressive clinical course and poor outcomes in patients treated with chemoimmunotherapy or BTK inhibitors.[9,10] As in follicular lymphoma, progression of disease within 24 months of treatment initiation (POD24) is a robust clinical marker of survival in MCL. A North American study of 455 cases of relapsed MCL demonstrated significantly inferior OS in POD24-positive patients compared to those relapsing >24 months after first-line therapy in both intensive and less intensive treatment groups.[11] The POD24 group had a median OS of <3 years, compared to 8 years for those relapsing beyond 2 years. This was validated externally in a subsequent analysis of six rituximab-era clinical trials (N=1,280 patients), in which 2-year survival of patients with POD24-positive MCL was 27%, while 79% of non-POD24 patients were alive at 7 years.[12] A Chinese study, in which 19% of patients received novel BTK inhibitors, lenalidomide or bortezomib induction therapy, confirmed these results.[13]

## Fluorodeoxyglucose positron emission tomography radiomic features

$^{18}$F-FDG-PET is the gold standard staging and response assessment imaging in most lymphoma subtypes. The

**Table 3.** Selected clinical trials in mantle cell lymphoma with biomarker inclusion.

| Clinical trial | Phase | Age, years | Treatment | Biomarker | Biomarker significance |
|---|---|---|---|---|---|
| **Frontline** | | | | | |
| Nordic MCL2 and MCL3 trials[25,44] | II | ≤65 | R-maxi CHOP/ R-HiDAC | MIPI and MIPI-c<br>Blastoid morphology (18%)<br>*TP53* mutation (11%)<br>*TP53* deletion (16%)<br>*CDKN2A* deletion (20%)<br>High-risk circSCORE (39%) | MIPI/MIPI-c risk groups associated with PFS and OS<br>Blastoid morphology: median OS 5.2 years *vs.* 12.8 years<br>*TP53* mutations associated with inferior OS and PFS (median PFS 0.9 years *vs.* 10.2 years)<br>*CDKN2A* and *TP53* deletions associated with inferior OS and PFS<br>High risk circSCORE: median PFS 4.5 years *vs.* 7.7 years |
| WINDOW-1[42] | II | ≥65 | Ibrutinib + rituximab → HCVAD/MA | *TP53* aberration (32%)<br>Blastoid/pleomorphic (12%)<br>Complex karyotype (15%)<br>Mutations identified by WES and RNA-sequencing | *TP53* aberration, blastoid/pleomorphic, complex karyotype associated with inferior PFS<br>*TP53* aberration associated with lower CR rate (55% *vs.* 91%) to IR<br>*NSD2, KMT2C* and *SMARCA4* mutations enriched in patients with late CR<br>*BTK, BANK1, BIRC3, CARD11, CCND1, CD79A, CD79B*, and *SMARCB1* aberrations found in patients who failed to reach CR |
| SHINE[40] | III | ≥65 | Bendamustine + rituximab ± ibrutinib | *TP53* mutation (10%)<br>Blastoid/pleomorphic morphology (9%)<br>High *MYC* mRNA expression (upper quartile)<br>MCL35 high-risk group (17%) | Inferior PFS for: *TP53* mutation (HR=1.7, *P*=0.02), blastoid/pleomorphic morphology (HR=2.7, *P*=0.0002) and high *MYC* (HR=1.5, *P*=0.03)<br>High-risk *vs.* low risk MCL35 group: median PFS 13 months *vs.* 81 months |
| ICML-2015[70] | II | All | Ibrutinib + rituximab<br>*blastoid and Ki67 >30% excluded | MRD negativity ($10^{-5}$) at 24 months (69%)<br>*TP53* alteration (15%) | Treatment ceased in the 24 patients who achieved MRD at 24 months; only 1 patient relapsed after a median of 36 months of follow-up<br>*TP53* mutations associated with inferior PFS |
| Lenalidomide-RCHOP *NCT0263313*[30] | II | All | Lenalidomide-RCHOP → HiDAC → lenalidomide-rituximab | *TP53* mutations and/or deletions (37%)<br>Blastoid (8%)<br>HIgh-risk MIPI (59%) | *TP53* aberrations associated with poorer PFS and OS (3-year OS 96% *vs.* 69%, *P*<0.001; 3-year PFS 78% *vs.* 38%, *P*=0.04) |
| EA4151[63] | III | <70 | If MRD negative after induction: ASCT *vs.* no ASCT | MRD negativity ($10^{-6}$) after induction (78%) | No difference in 3-year OS between ASCT *vs.* no ASCT group if MRD-negative after induction (82.1% and 82.7%) |
| ALTAMIRA[66] | II | >60 | Acalabrutinib + rituximab | *TP53* mutation (24%)<br>Ki67 >30% (22%)<br>Blastoid morphology (6%)<br>MRD negativity (59%) | 1-year PFS 87%, 1 year OS 93%<br>*TP53* mutation associated with inferior PFS at 1 year (69%)<br>*Outcomes of MRD-guided acalabrutinib cessation not yet reported* |
| FIL MCL0208[57] | III | <65 | Chemotherapy + ASCT ± lenalidomide maintenance | Myeloid clonal hematopoiesis mutations (13%)<br>Ki67 >30% (31%) | Clonal hematopoiesis clones with VAF >10% associated with inferior PFS (HR=2.93, *P*=0.006) and OS (HR=3.02, *P*=0.02)<br>Ki67 associated with worse PFS (HR=1.96, *P*=0.023) |
| BOVen[6] | II | All | Zanubrutinib + obinutuzumab + venetoclax in *TP53*-mutated MCL | Blastoid morphology (20%)<br>Biallelic *TP53* inactivation (48%)<br>High-risk MIPI (68%)<br>Ki67 >30% (52%)<br>MRD negativity ($10^{-6}$) at EOT (48%) | Blastoid/pleomorphic morphology associated with inferior PFS and OS<br>No effect of biallelic *TP53* inactivation, Ki67 or MIPI risk score on PFS or OS<br>Treatment discontinued in the 15 patients who achieved MRD negativity; 13 remain in remission after a median follow-up of 28 months |

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| Clinical trial | Phase | Age, years | Treatment | Biomarker | Biomarker significance |
|---|---|---|---|---|---|
| **Relapsed/refractory** | | | | | |
| AIM[38] | II | All | Ibrutinib + venetoclax | *TP53* aberrations (50%)<br>Ki67 <30% (43%)<br>SWI-SNF complex mutations | Del 9p21.1-24.3 and *SMARCA2*, *SMARCA4*, *ARID2* mutations associated with primary resistance to venetoclax + ibrutinib<br>Lower response rate for Ki67 >30%<br>All non-responders (N=5) were *TP53* mutant |
| MCL6 Philemon[59] | II | All | Ibrutinib + lenalidomide + rituximab | Immune signature score: 11 proteins identified via plasma proteomic profiling<br>*TP53* mutation (25%)/deletion (34%)<br>Ki67 >30% (42%)<br>High-risk MIPI (46%) | Immune signature score associated with inferior OS (HR=3.32, *P*=0.03)<br>Ki67 (HR=1.02, *P*=0.03) and MIPI (HR=1.97, *P*=0.007) associated with inferior OS<br>*TP53* mutation/deletion not associated with OS |
| MCL3001 RAY[37] | III | All | Ibrutinib *vs.* temsirolimus | *TP53* mutation (25%)<br>*BIRC3* mutation/deletion (34%)<br>Blastoid morphology (12%)<br>High-risk MIPI (21%)<br>MCL35 high-risk group (10%) | Inferior PFS for: blastoid morphology (HR=2.49, *P*<0.001), high-risk MIPI (HR=2.51, *P*=0.0002), *BIRC3* mutations/deletions (HR=2.34, *P*<0.001) and *TP53* mutations/deletion (HR=1.9, *P*=0.006)<br>MCL35 risk score retained prognostic significance for PFS after adjusting for above risk factors |
| OAsIs[35] | I/II | All | Ibrutinib + obinutuzumab + venetoclax | *TP53* mutation (17%)<br>17p deletion (19%)<br>Blastoid/pleomorphic (17%)<br>Mutations and CNV identified by sequencing | 5-year PFS of 80% in whole cohort<br>*CARD11* mutations enriched at relapse leading to venetoclax resistance |
| TARMAC[52] | II | All | Tisagenlecleucel + ibrutinib | Blastoid (15%)<br>*TP53* mutated or deleted (45%)<br>Ki67 >30% (71%)<br>POD24 (65%)<br>T-cell exhaustion | 88% of patients with *TP53* mutation achieved CR<br>Similar CR rate regardless of blastoid morphology, Ki67 or *TP53* mutation<br>Less exhausted $CD8^+$ T-cell phenotype found in deep responders |
| SYMPATICO[29] | III | All | Ibrutinib ± venetoclax | *TP53* mutations (29%)<br>Blastoid/pleomorphic (19%)<br>High-risk MIPI (34%) | *TP53* aberrations associated with inferior OS in ibrutinib + venetoclax group (median OS 37 months *vs.* NR), although outcomes were improved compared to the ibrutinib-only group (median OS 15 months *vs.* 53 months) |
| VALERIA MCL7[64] | Ib/II | All | Venetoclax + lenalidomide + rituximab | *TP53* mutation (30%)<br>MRD negativity ($10^{-5}$) at 6 months (94%) | *TP53* mutation associated with poorer response rate, PFS, OS and DOR<br>89% who achieved MRD negativity ($10^{-5}$) remained in molecular remission, with a median follow-up of 14 months |

MIPI: Mantle Cell Lymphoma International Prognostic Index; R-maxiCHOP: rituximab, cyclophosphamide, doxorubicin; vincristine; prednisone; R-HiDAC: rituximab, high-dose cytarabine; MIPI: Mantle Cell Lymphoma International Prognostic Index; MIPI-c: combined Mantle Cell Lymphoma International Prognostic Index; PFS: progression-free survival; OS: overall survival; HCVAD: hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MA: high-dose methotrexate and cytarabine; WES: whole-exome sequencing; CR: complete response; IR: ibrutinib + rituximab; HR: hazard ratio; MRD: measurable residual disease; ASCT: autologous stem cell transplant; VAF: variant allele frequency; MCL: mantle cell lymphoma; EOT: end of treatment; CNV: copy number variation; POD24: progression of disease within 24 months; NR: not reached; DOR: duration of response.

prognostic role of FDG-PET beyond the visual 5-point Deauville score in MCL is less defined than in other lymphomas. A systematic review of FDG-PET in MCL found that higher baseline PET maximum standardized uptake value (SUVmax) and post-treatment complete metabolic response were both inconsistently associated with PFS and OS.[14] Interim PET is used frequently in other lymphomas but rarely adopted in MCL.

Metabolic parameters that accurately quantify disease volume and activity, such as tumor metabolic tumor volume (TMTV) and total lesion glycolysis (TLG), are highly prognostic at baseline and in treatment response assessment for diffuse large B-cell lymphoma and Hodgkin lymphoma. More advanced radiomic parameters such as textural features and quantification of tumor dissemination are emerging as useful biomarkers in lymphoma.

In 120 chemoimmunotherapy-treated MCL patients, higher TMTV and TLG were independently associated with inferior PFS in a multivariate analysis.[15] Combining baseline TMTV with end-of-treatment PET response stratified patients into four distinct risk groups with markedly different PFS ranging from 8 months to 59 months; those with higher TMTV and an incomplete response had significantly inferior outcomes. In contrast, the only PET parameter independently associated with OS was maximum tumor dissemination (Dmax).

In another study (N=107), only high SUVmean and entropy – a measure of image heterogeneity – were significantly associated with 2-year PFS.[16] In this study, a composite radiomic signature combining dichotomized SUVmax and entropy outperformed the MIPI in predicting progression risk. Finally, in a separate study of 83 patients, high heterogeneity index (>1.94) was also identified as prognostic for PFS (HR=4.4, *P*=0.042), whereas TMTV and TLG were not.[17] PET radiomics are of potential value in MCL risk stratification, although larger series are required to confirm these findings.

# Molecular biomarkers

### Genomic complexity

Genetic complexity, defined by complex karyotype on conventional karyotyping or ≥3 copy number variations, is an independent poor prognostic marker in both the chemoimmunotherapy and BTK-inhibitor settings, with blastoid and pleomorphic MCL enriched for high degrees of complexity.[18-21] These results have been replicated using whole-genome sequencing.[20]

### Somatic mutations and copy number variations

A high burden of somatic variants and copy number variations on whole-exome sequencing is seen in MCL compared to other lymphomas, with a median of six driver mutations and nine copy number variations per tumor and 98% of cases having at least one copy number variation when analyzed at a genome scale.[20,22] However, not all aberrations carry prognostic implications. *TP53* mutations/deletions and *CDKN2A* deletions are the most robust molecular prognosticators, present in approximately 25% of patients at baseline.[19,23,24]

*TP53* aberrations confer poor survival and often treatment resistance.[19,25] While the prognostic impact of *TP53* deletions alone has previously been debated,[22] overall, the data suggest that that both *TP53* mutations and deletions each convey poor prognosis,[25,26] with *TP53* mutations being worse than deletions. In an analysis of 183 patients enrolled in the MCL2 and MCL3 trials, the median PFS was 1.8 years for *TP53*-mutated cases, compared to 3.1 years for those with deletions and 10.2 years for *TP53* wildtype cases.[25] *TP53* overexpression, determined by immunohistochemistry, has been used as a surrogate for *TP53* mutations with a reported sensitivity of 82%;[27] high *TP53* expression was prognostic in the MCL2 and MCL3 cohorts with a HR of 3.0 for OS compared to low expression.[28]

While inferior outcomes for *TP53*-mutated MCL remain evident in some trials of BTK-inhibitor monotherapy and BTK-inhibitor-containing regimens overall, in studies of pure novel therapy combinations, data are intriguing. The randomized SYMPATICO trial in relapsed/refractory MCL found improved PFS in the group treated with ibrutinib + venetoclax compared to the group given ibrutinib monotherapy; however, outcomes were still inferior compared to those of the *TP53*-wildtype patients.[29] Preliminary results from the front-line *TP53*-selected BOVen trial demonstrated a 2-year PFS of 72%.[6] These data suggest that the outcomes of BTK-inhibitor + BCL2-inhibitor treatment in *TP53*-mutated patients are superior to those of historical chemotherapy-treated patient cohorts, although this, too, needs confirmation in prospective, randomized studies. *TP53* was the only negative genetic prognostic marker for OS in a trial of lenalidomide added to induction and maintenance therapy.[30] Real-world brexucabtagene data (N=168) demonstrated inferior PFS and OS in *TP53*-mutated patients, despite high complete remission rates overall (72%).[31] *TP53* mutation status was unfortunately only available for 10% of patients in a recent phase I/II trial of glofitamab in relapsed/refractory MCL;[32] prioritization of molecular data is critical for future studies of bispecific antibodies. Challenges interpreting existing data include incomplete testing of trial populations, result interpretation in the context of other prognosticators, short-term follow-up and non-randomized studies. A comprehensive assessment of the prognostic impact of *TP53* mutation status requires future studies to evaluate not only mutations, but also deletions, biallelic inactivation, and variant allele frequency.

*CDKN2A* deletions are consistently and independently associated with shorter OS, an effect that is not overcome by treatment with intensive regimens. Importantly, concurrent

*TP53* aberration and *CDKN2A* deletion portended a highly chemoresistant phenotype, with complete responses in only 17% of patients receiving upfront chemoimmunotherapy.[24]

Preclinical studies demonstrated that BTK-inhibitor resistance is characterized by activation of the alternative NF-κB pathway, in contrast to the B-cell receptor-driven classic NF-κB pathway in BTK inhibitor-sensitive patients. Recurrent NF-κB pathway mutations (*TRAF2*, *TRAF3*, *BIRC3*, *CARD11*) are reported in both BTK-inhibitor-insensitive cell lines and patients' samples, mirrored in clinical studies.[33,34] Comprehensive genomic and single-cell RNA sequencing analysis of tissue from patients receiving first-line treatment with obinutuzumab + ibrutinib + venetoclax revealed enrichment of *CARD11* gain-of-function mutations at relapse, causing independence from B-cell receptors and thus ibrutinib resistance, along with induction of the anti-apoptotic protein BCL2A1, resulting in venetoclax resistance.[35] In zanubrutinib-treated relapsed/refractory MCL patients, *CARD11* mutations conferred inferior outcomes.[36]

In another study of relapsed/refractory MCL patients, the randomized MCL3001 RAY trial[37] evaluating ibrutinib *versus* temsirolimus, targeted hybrid capture-based next-generation sequencing demonstrated that *BIRC3* mutations/deletions were associated with inferior PFS.

In the WINDOW-1 trial of upfront ibrutinib + rituximab, patients with a late complete remission were enriched for *NSD2*, *KMT2C* and *SMARCA4* mutations on whole-exome sequencing, compared to those achieving early complete remission. Patients who never achieved complete remission had B-cell receptor signaling and MYC pathway gene upregulation and *BTK, BANK1, BIRC3, CARD11, CCND1, CD79A, CD79B*, and *SMARCB1* aberrations on gene expression profiling. Furthermore, *MS4A1* gene aberrations were associated with resistance to rituximab.[5]

In patients treated with ibrutinib + venetoclax, chromosome 9p21.1–24.3 deletion and mutations in the SWI-SNF chromatin remodeling complex (*SMARCA2, SMARCA4* and *ARID2*) were associated with primary and acquired resistance. *SMARCA4* resulted in increased Bcl-xL expression, thus conferring a survival advantage in the setting of therapeutic challenge.[38]

## Gene expression assays

The MCL35 NanoString gene expression-based assay used a 17-gene proliferation signature on RNA from formalin-fixed paraffin-embedded tissue to classify chemotherapy-treated patients into low-, standard- or high-survival groups.[39] A recent analysis of the SHINE trial population receiving bendamustine + rituximab ± ibrutinib demonstrated that MCL35 score was independently associated with PFS, with median PFS of 81, 77 and 13 months for low-, standard- and high-risk groups, respectively.[40]

In the relapsed/refractory MCL RAY study, MCL35 score outperformed MIPI in risk stratification and retained prognostic significance in multivariate analysis. The MCL35 high-risk group displayed higher levels of MYC expression, *TP53* aberrations, blastoid morphology and truncated CCND1 3' untranslated region. On multivariate analysis after adjusting for treatment, MIPI, *BIRC3*, *TP53* and blastoid morphology, the MCL35 risk category retained prognostic significance for PFS (HR=1.82, *P*=0.001).[37]

In a paper by Yi *et al.*, whole-exome sequencing was performed on 152 MCL tumor samples, with RNA-sequencing data in 48 matched samples. Four subsets were identified based on distinct genetic signatures; cluster 4 was enriched in mutations in *TP53* and *TRAF2*, and gene signatures of an active MYC pathway – this group had the worst clinical outcome with a median PFS of 16 months.[41]

Overexpression of the *MYC* transcription factor has been established as an adverse prognostic factor in other studies. In the SHINE trial, high (i.e., upper quartile) *MYC* mRNA expression was associated with inferior PFS (HR=1.5, *P*=0.03).[40] In the WINDOW-1 trial, bulk RNA-sequencing demonstrated that *MYC* pathways were enriched in the group of patients who did not achieve complete remission.[42] Finally, in 256 tumor samples from patients treated with immunochemotherapy, high *MYC* expression, as assessed by immunohistochemistry with a cutoff of 20%, was associated with inferior OS (median OS 2.2 years *vs*. 7.3 years) and poor prognostic factors such as Ki-67, non-classic morphology and *TP53* aberrations. In addition, those with concurrent MYC$^{high}$ and *TP53* aberrations had a particularly dismal median OS of 0.9 years.[43]

## Circular RNA and microRNA

Non-coding RNA – circular RNA (circRNA) and microRNA (miRNA) – appear relevant to MCL prognostication. CircRNA have disease-specific expression patterns and are particularly attractive due to their stability *in vivo*. A circRNA-based prognostic model, circSCORE, incorporating nine circRNA individually predictive of time to progression, was developed in MCL2 and MCL3 trial patients receiving cytarabine-based chemotherapy and ASCT. The circSCORE independently stratified patients into high- and low-risk groups for time to progression, PFS, and OS.[44] In an analysis of patients with relapsed/refractory MCL (N=65) from three prospective trials, one using ibrutinib, lenalidomide, and rituximab, the circSCORE retained prognostic significance for PFS but not OS.[45]

miRNA are involved in post-transcriptional gene regulation, influencing key cell proliferation and differentiation pathways. In MCL, specific miRNA have shown prognostic value. Notably, miR-34a, which modulates *TP53* through FOXP1 and BCL2, and miR-155-5p, implicated in *SOX11* regulation, have been associated with inferior clinical outcomes. In one study, expression levels above/below defined cut-offs (<0.215 for miR-34a and >2.11 for miR-155-5p) were associated with OS.[46] miR-34a retained significance in multivariate testing for OS.

# Tumor microenvironment

Initial MCL studies of checkpoint inhibitor therapy were disappointing, limiting early enthusiasm for exploring the TME. However, with the emergence of promising CAR-T and T-cell engaging bispecific antibodies, there is renewed focus on the TME. Increasing evidence indicates that complex interactions between malignant cells and the surrounding immune milieu promote tumor survival, immune evasion, and resistance to therapy.

## T cells

T-cell dysregulation is critical to MCL pathogenesis and treatment resistance. An "immune-depleted" TME, characterized by decreased T-cell numbers, downregulation of cytotoxic T cells, and increased numbers of regulatory cells (Treg) are all associated with adverse chemotherapy outcomes in MCL.[47-50]

In a flow cytometric analysis of 153 tissue samples, MCL lymph nodes had significantly lower T-cell counts compared to controls. A decreased tissue CD4:CD8 ratio correlated with more aggressive phenotypes and poorer OS.[50] Similarly, in a predominantly intensive chemoimmunotherapy-treated cohort (N=189), lower $CD4^+$ and higher $CD8^+$ T-cell counts in pre-treatment peripheral blood were independently associated with inferior OS. An immune-related prognostic index (IRPI), combining $CD4^+$ and $CD8^+$ T-cell counts with B symptoms, platelet count, and β2-microglobulin level, outperformed both MIPI and MIPI-c. Patients with a low-risk IRPI had a 5-year OS of 100%, compared to 65% and 32% in the groups with intermediate- and high-risk IRPI, respectively.[51]

Another study assessed T-cell function by immunohistochemistry and targeted gene expression profiling of 730 immune-related genes. SOX11-positive MCL showed reduced effector T-cell function, characterized by decreased $CD4^+$ T-cell infiltration, CD4:CD8 ratios, and cytotoxic T cells, compared to SOX11-negative MCL. Overexpression of CD70, which promotes Treg proliferation and differentiation, was strongly associated with inferior OS, consistent with the findings of other studies of aggressive lymphomas.[48]

Similarly, in 122 biopsies from patients with chemotherapy-treated MCL, immunohistochemistry analysis revealed that an 'inflammatory Treg phenotype' within the TME may contribute to disease progression. High numbers of Treg, characterized by FOXP3 positivity, and an elevated IL17A expression (produced by a subset of Treg to provide proliferative signals to neoplastic cells) were each independently linked to poor outcomes.[47]

T-cell exhaustion may also be a predictor of response to CAR-T therapy. A higher proportion of $CD8^+$/HLA-$DR^-$/$PD\text{-}1^+$ terminally differentiated effector memory T cells (i.e., exhausted $CD8^+$ T-cell phenotype) was associated with poorer treatment response and early failure in one small study of ibrutinib + tisagenlecleucel.[52] In a single-cell RNA-sequencing analysis of longitudinal samples from 15 brexucabtagene autoleucel-treated patients, acquired T-cell exhaustion was evident at relapse, demonstrated by reduced CD4/CD8 cytotoxic T cells and upregulation of immune checkpoint molecules (TIGIT, LAG3 and CD96) in these cells.[53]

## Tumor-associated macrophages

Tumor-associated macrophages (TAM) within the TME are important prognosticators in several lymphomas. TAM can be polarized into M1 type (anti-tumoral, pro-inflammatory) or M2 type (anti-inflammatory, pro-tumoral), which strongly expresses cell membrane CD163 in the presence of MCL tumor cells. M2 TAM promote MCL growth in murine models.[54] Increased CD163 expression, as determined by immunohistochemistry, was independently associated with all-cause mortality in multivariate models from population-based studies of chemotherapy-treated MCL.[55]

In a subset of patients from the MCL2/3 trials who were treated with intensive chemotherapy, both high $FOXP3^+$ cells (above a cutoff of 2% by immunohistochemistry) and CD163 (above 0.04%) had an additive poor prognostic effect with much shorter time to progression compared to that of patients with single-positive tumors.

Serum soluble CD163 (sCD163), a circulating (thus non-invasive) marker of TAM activation, is prognostic in diffuse large B-cell lymphoma and Hodgkin lymphoma, and appears prognostic in MCL. In a mixed cohort of 131 patients (81 at diagnosis before chemotherapy-based treatment, 50 at relapse after a median of 2 lines of therapy), elevated baseline sCD163 levels measured via enzyme-linked immunosorbent assay were significantly associated with inferior OS, after adjusting for established risk factors.[56] In the 29 patients for whom paired tissue and serum samples were available, a moderate correlation between sCD163 and tissue CD163 was seen (Spearman rank correlation r=0.64, *P*=0.014), with elevated tissue CD163 also significantly associated with inferior PFS (HR=4.0).

## Tumor microenvironment subtypes

Recent data suggest that specific TME clusters identified via bulk RNA-sequencing may serve as both prognostic and predictive biomarkers for primary resistance to BTK inhibitors. In one BTK inhibitor-treated MCL cohort, four distinct TME subtypes were identified: normal (N=27), immune-cell-enriched (N=45), mesenchymal (N=42), and immune-depleted (N=49). The immune-depleted subtype was associated with baseline adverse biological features, including high Ki-67, recurrent high-risk mutations (*TP53, NOTCH1, KMT2D, SMARCA4*), high degree of chromosomal instability, and reduced expression of immune checkpoint genes. This immune-depleted group demonstrated primary BTK-inhibitor resistance and had the poorest OS.[49]

Collectively, these studies support the notion of an immunosuppressive TME in MCL, with a functional deficit in

anti-tumor T-cell responses. Quantitative and qualitative T-cell and macrophage alterations within the TME may serve as valuable biomarkers for immune status and treatment response. Treg and M2 TAM may be potential future therapeutic targets.

## Other novel biomarkers

The myeloid compartment in MCL has also been evaluated. Myeloid clonal hematopoiesis mutations were analyzed by targeted next-generation sequencing in peripheral blood and bone marrow samples of patients in the FIL MCL0208 trial of lenalidomide maintenance.[57] Large clonal hematopoiesis clones (variant allele frequency ≥10%) were significantly associated with inferior PFS and OS (both $P$=0.006); these outcomes were driven by MCL progression rather than treatment-related toxicity or secondary malignancies. The association with PFS remained significant after adjusting for MIPI and blastoid histology, suggesting that clonal hematopoiesis may influence tumor progression through extrinsic mechanisms such as modulation of the TME.

Plasma proteomics is another emerging prognostication tool. In 75 Swedish patients, baseline plasma levels of 1,460 proteins were evaluated. Two proteins – LRRN1 and IL-15 – were strong predictors of progression within 12 months, with HR of 18.1 and 17.4, respectively. Combined, they achieved an area under the curve of 0.92, outperforming the MIPI.[58] Similarly, in the MCL6 Philemon trial of lenalidomide + rituximab + ibrutinib, proteomic analysis of 44 serum samples identified 11 proteins significantly associated with OS, most of which have a known role in the immune system but have not previously been studied in MCL.[59] These were used to create an immune signature score with a HR of 3.22 for OS, which remained significant after adjusting for MIPI and Ki-67. MIPI alone failed to stratify risk in this novel-therapy setting, underscoring the need for biomarkers reflective of tumor biology and immune landscape.

## Measurable residual disease

MRD is sensitive measure of disease response, and an established prognostic marker in MCL in numerous chemoimmunotherapy-based studies.[60] Consensus on optimal detection methods, testing timepoints, or sensitivity thresholds is lacking. Despite this, MRD via flow cytometry, quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) analysis and next-generation sequencing all have prognostic value, even though each method has specific strengths and limitations.[61]

Circulating tumor DNA (ctDNA) analysis using next-generation sequencing to track *IGHV* clonotypes is emerging as a precise and dynamic biomarker in MCL. In one study, baseline ctDNA levels were strongly correlated with tumor burden as measured by TMTV and TLG, and clinical risk factors, with median ctDNA concentrations of 143 lymphoma molecules per mL for low-risk MIPI and 6,519 for high-risk MIPI. Importantly, both pretreatment ctDNA levels and early ctDNA kinetics (after 1–2 cycles of induction) were predictive of PFS and OS. Failure to clear ctDNA early was associated with failure to achieve complete remission later in treatment.[62] Unlike other MRD modalities, ctDNA can track disease in nearly all patients, as it does not depend on the presence of circulating tumor cells, making it a highly promising biomarker for both prognostication and response monitoring.

MRD response-based adaptive approaches are being tested in several prospective novel therapy trials to inform treatment de-escalation.[3,6,52,63,64] The ECOG-EA4151 trial evaluated MRD-driven upfront consolidative ASCT based on post-induction MRD status using clonoSEQ next-generation sequencing.[63] Patients who achieved MRD negativity at $10^{-6}$ sensitivity were randomized to ASCT or no ASCT before maintenance rituximab. In the interim analysis with a median follow-up of 2.7 years, there was no difference in 3-year OS between those who received ASCT and those who did not, suggesting that ASCT does not benefit patients who achieve both MRD-negative and PET complete remission status following chemoimmunotherapy induction. Patients who remained MRD-positive were not randomized in this study, thus MRD cannot be used to guide treatment for this subgroup until further randomized studies are performed. Several trials have used molecular MRD to limit duration of therapy, including the BOVen trial of upfront zanubrutinib, obinutuzumab and venetoclax, Spanish ICML-2015 (ibrutinib + rituximab for indolent MCL), VALERIA MCL7 (lenalidomide, venetoclax + rituximab), ALTAMIRA (acalabrutinib + rituximab in elderly) and TRAVERSE trials. Preliminary results are promising although longer follow-up is required to validate this approach.[3,6,64–66]

Collectively, emerging data support MRD as a powerful predictive biomarker in MCL, with the potential to inform dynamic treatment strategies and reduce treatment burden for patients achieving deep molecular responses. The optimal timing for MRD assessment in MCL remains context-dependent and varies according to the biological activity of the treatment and clinical intent. Currently, the use of MRD in standard-of-care clinical practice globally is limited by several factors. Cost and access remain challenging with most MRD testing restricted to large academic centers with local testing capability. The varied methodologies and turn-around times restrict meaningful translation of clinical results from research into clinical care. These issues mean that MRD is not yet routinely used to guide treatment decisions outside of clinical trials or large academic centers. As testing methods become more standardized and data continue to mature, MRD is likely to move into routine care.

## Future directions

MCL prognostication is becoming more sophisticated, but also increasingly complex, as testing technologies become more advanced. Current prognostic tools largely reflect a composite of underlying biological features, yet remain imperfect and difficult to quantify (Table 4). While markers such as *TP53* mutation status and blastoid morphology are well established in the chemoimmunotherapy era, their relevance in the context of novel therapies, particularly immunotherapies, requires re-evaluation. The expanding range of treatment options, with associated cost, toxicity, and resource implications, makes predictive biomarkers especially critical. However, risk stratification remains underutilized in practice. A major challenge to this is that many recent international MCL trials reported *TP53* status in only a minority of patients,[4,5,32,67,68] reflecting difficulties with tissue availability, resources, and historically limited alternative treatment strategies.

Moving forward, obtaining sufficient tissue and blood at diagnosis and relapse for the relevant prognostic tests must be prioritized. Broader efforts to sequence tumor samples are needed to characterize the genomic complexity of MCL and define consistent, clinically relevant alterations. For future trials, international consensus on a core set of baseline biomarkers, standardized testing timepoints, and harmonized sample collection and storage will be essential. Regulatory bodies should incentivize industry to integrate biomarkers

**Table 4.** Key characteristics of emerging biomarkers in mantle cell lymphoma.

| Biomarker | Access | Cost | Turnaround time | Reproducibility | Benefits | Limitations |
|---|---|---|---|---|---|---|
| MRD (NGS or flow cytometry) | Limited to academic/ central laboratories, not widely routine yet | Moderate–high | Flow cytometry: 1-2 days<br>NGS: 3-4 weeks | High with standardized assays | Dynamic measure of treatment response<br>Can guide therapy intensity and duration | Limited availability<br>Assay variability<br>Result dependent on sample quality |
| *TP53* status | Mutations: Widely available via targeted sequencing panels | Moderate | 3-4 weeks | High | Strong prognostic/ predictive marker in chemoimmunotherapy thus may influence choice of upfront therapy | Prognostic value in novel therapies is unclear |
| | Deletions: Widely available via FISH or karyotype. Higher resolution assays (WES/WGS, qPCR, SNP arrays) only at specialized centers | Moderate (cytogenetics, SNP array) to high (NGS) | Days to weeks, depending on assay | High | | |
| NGS panels (wider genomic profiling) | Targeted panels increasingly accessible to diagnostic laboratories. WES/ WGS not available outside of research settings | High | 3–6 weeks | Good in accredited laboratories | Can identify novel targets and resistance mutations | Costly and often not reimbursed<br>Clinical utility in MCL still evolving<br>Need sufficient tissue for DNA extraction |
| PET radiomics | Currently limited to research; not routine in practice | Moderate | Days to weeks | Not yet standardized | Non-invasive<br>No additional testing required - uses standard-of-care PET scans<br>Can offer additional risk stratification at baseline and during treatment | Requires expertise and specific software – not widely available<br>Clinical utility in MCL still evolving |
| Tumor microenvironment | Research setting only | High | Weeks to months | No data | May predict response to immunotherapies<br>Potential to identify novel targets | Not clinically available<br>Heterogeneity of assays and lack of validation |

MRD: measurable residual disease; FISH: fluorescent in situ hybridization; NGS: next-generation sequencing, WES: whole-exome sequencing, WGS: whole-genome sequencing; qPCR: quantitative polymerase chain reaction; SNP: single nucleotide polymorphism; PET: positron emission tomography; MCL: mantle cell lymphoma.

into prospective studies and encourage collaboration with academic laboratories. Ultimately, the field must transition from descriptive to clinically actionable biomarkers that guide therapy intensity, select patients for novel strategies, and refine prognostication in real-world practice.

## Conclusion

MCL is a complex and biologically heterogeneous disease, and it is increasingly evident that traditional one-size-fits-all approaches do not adequately serve patients. As treatment options expand beyond chemoimmunotherapy, reliance on conventional clinical markers alone will be insufficient. Many of the biomarkers discussed in this review are not yet widely accessible or clinically implemented, but they provide a foundation for future development and validation in cohorts treated with novel and cellular therapies. Ultimately, the integration of clinical, radiomic, genomic, and immunological biomarkers in routine practice will be essential to refine prognostication, guide treatment intensity, and enable personalized strategies for both frontline and relapsed disease management.

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**Contributions**

*EAH designed the study and supervised the research. ZL wrote the manuscript. EAH, PY and CK edited and revised the manuscript.*

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