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Title: 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 personalised 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 PCR, next-generation sequencing, and circulating tumour 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 tumour microenvironment and immune dysregulation in driving treatment resistance. Additionally, the expanding utility of FDG-PET 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 characterised by marked clinical heterogeneity, historically treated with rituximab-chemotherapy regimens of varying intensity, according to patient fitness. Recently, novel targeted and cellular therapies as Bruton Tyrosine Kinase inhibitors (BTKi), bispecific antibodies and CAR-T have yielded excellent results.

Several established molecular prognosticators exist in MCL, such as 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 tumour microenvironment has been heavily scrutinised 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 tumour microenvironment(TME) and metabolic FDG-PET (fludeoxyglucose positron emission tomography) 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 delineate disease subgroups, to 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 patient numbers, marked disease heterogeneity, variability in global treatment approaches, and lack of standardisation of measurable residual disease (MRD) and genomic testing.

Biomarkers can be broadly categorised as tumour-intrinsic or tumour-extrinsic. In this review article, we first review tumour-intrinsic markers such as PET imaging metrics that reflect tumour biology, as well as tumour genomic alterations, followed by tumour-extrinsic markers (gene expression assays, non-coding RNAs, T cells and macrophages within the TME, and MRD dynamics), with a focus on their contribution to risk stratification and modern personalised MCL strategies (Table 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 MIPI-c[2]. The MIPI was created in the chemotherapy era and incorporates age, ECOG performance status, LDH and white cell count. It has retained prognostic capabilities in BTKi trials[3–5] but not others[6,7]. The Ki-67 index, a measure of cell proliferation rate as the percentage of Ki-67 positive tumour cells by immunohistochemistry (IHC), is an established prognostic marker in MCL. Using a binary cutoff of 30%, Ki-67 was combined with the MIPI (ie. MIPI-c) to further refine risk stratification[2]. More recently, a Ki-67 cutoff of 50% was found to be optimal for PFS and 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 adjusted HR of 2.2 (1.38-3.48) after adjusting for ECOG, stage, LDH and MIPI[8].

Pleomorphic and blastoid morphological variants that comprise 10-20% of cases have a distinct biology, aggressive clinical course and poor outcomes in patients treated with chemoimmunotherapy or BTKi[9,10]

Similar to follicular lymphoma, 'POD24' (Progression of Disease within 24 months of treatment initiation) is a robust clinical marker of survival in MCL. A North American study of 455 relapsed MCL demonstrated significantly inferior overall survival (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 median OS of <3 years, compared to 8 years for those relapsing beyond 2 years. This was validated externally in a subsequent analysis of 6 rituximab-era clinical trials (n=1280), in which 2-year survival of POD24-'positive' MCL was 27%, while 79% of non-POD24 patients were alive at 7 years[12]. A Chinese study confirmed these results where 19% received novel BTKi, lenalidomide or bortezomib induction therapy[13].

FDG-PET radiomic features

^{18}F-FDG-PET is the gold standard staging and response assessment imaging in most lymphoma subtypes. The 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 SUVmax and post-treatment complete metabolic response were both inconsistently associated with progression-free survival (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 tumour metabolic tumour volume (TMTV) and total lesion glycolysis (TLG) are highly prognostic at baseline and in treatment response assessment for diffuse large B cell lymphoma (DLBCL) and Hodgkin Lymphoma (HL). More advanced radiomic parameters such as textural features and quantification of tumour 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-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 Dmax (maximum tumour dissemination).

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 dichotomised SUVmax and entropy outperformed the MIPI in predicting progression risk. Finally, in a separate study of 83 patients, high heterogeneity index (>1.94) was again 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, however larger series are required to confirm these findings.

Molecular biomarkers

Genomic complexity

Genetic complexity, defined by complex karyotype on conventional karyotyping or $\geq$3 copy number variations (CNV), is an independent poor prognostic marker in both the chemoimmunotherapy and BTKi setting, 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 CNVs on whole exome sequencing (WES) is seen in MCL compared to other lymphomas, with a median of 6 driver mutations and 9 CNVs per tumour and 98% having at least one CNV when analysed at 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 both *TP53* mutations or deletions 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* wild-type[25]. *TP53* overexpression by IHC 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 cohort with a hazard ratio (HR) of 3.0 for OS compared to low expression[28].

While inferior outcomes for *TP53*-mutated MCL remain evident in some trials of BTKi monotherapy and BTKi-containing regimens overall, in studies of pure novel therapy combinations, data are intriguing. The randomised SYMPATICO trial in relapsed/refractory MCL (RRMCL) reported improved PFS in the ibrutinib-venetoclax group compared to ibrutinib monotherapy, however outcomes were still inferior compared to 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 BTKi+BCL2i outcomes in *TP53*-mutated patients are superior compared to historical chemotherapy-treated patient cohorts, however this needs confirmation in prospective randomised 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 (CR) rates overall (72%)[31]. *TP53* mutation status was unfortunately only available for 10% of a recent RRMCL phase I/II glofitamab trial[32]; prioritisation of molecular data is critical for future bispecific studies. Challenges interpreting existing data include incomplete testing of trial populations, result interpretation in the context of other prognosticators, short-term follow-up and non-randomised studies. A comprehensive assessment of the prognostic impact of *TP53* requires future studies to evaluate not only mutations, but also deletions, biallelic inactivation, and variant allele frequency (VAF).

CDKN2A deletions are consistently and independently associated with shorter OS and are not overcome by intensive regimens. Importantly, concurrent *TP53* aberration and *CDKN2A* deletion portends a highly chemoresistant phenotype, with complete responses in only 17% receiving upfront chemoimmunotherapy[24].

Pre-clinical studies demonstrated BTKi resistance is characterised by activation of the alternative NF-kB pathway, in contrast to the BCR (B cell receptor)-driven classic NF-kB pathway in BTKi-sensitive patients. Recurrent NF-kB pathway mutations (*TRAF2*, *TRAF3*, *BIRC3*, *CARD11*) are reported in both BTKi-insensitive cell lines and patient samples, mirrored in clinical studies[33,34].

Comprehensive genomic and single-cell RNA sequencing analysis of tissue from patients receiving first-line obinutuzumab-ibrutinib-venetoclax revealed enrichment of *CARD11* gain-of-function mutations at relapse, causing BCR-independence and thus ibrutinib resistance, along with induction of the anti-apoptotic protein BCL2A1, resulting in venetoclax resistance[35]. In zanubrutinib-treated RRMCL, *CARD11* mutations conferred inferior outcomes[36]. In the RRMCL randomised MCL3001 RAY trial[37] evaluating ibrutinib versus temsirolimus, targeted hybrid capture-based next generating sequencing(NGS) demonstrated that *BIRC3* mutations/deletions were associated with inferior PFS.

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

In patients treated with ibrutinib+venetoclax, chromosome 9p21.1–24.3 deletion and mutations in the SWI-SNF chromatin re-modelling 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 FFPE tissue to classify chemotherapy-treated patients into low-, standard- or high- survival groups[39]. Recent analysis in the SHINE trial population receiving bendamustine-rituximab +/- ibrutinib demonstrated that MCL35 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 RRMCL 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' UTR. On multivariate analysis after adjusting for treatment, MIPI, *BIRC3, TP53* and blastoid morphology, the MCL35 risk category retained prognostic significance for PFS (HR1.82, p=0.001)[37].

In a paper by Yi et al, WES was performed on 152 MCL tumour samples, with RNA-Seq data in 48 matched samples. 4 subsets were identified based on distinct genetic signatures; cluster 4 was enriched in mutations in *TP53* and *TRAF2*, and gene signatures of 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 (ie upper quartile) *MYC* mRNA expression was associated with inferior PFS (HR1.5, p=0.03)[40]. In the WINDOW-1 trial, bulk RNA-seq demonstrated that *MYC* pathways were enriched in the group who did not achieve CR[42]. Finally, in 256 tumour samples from patients treated with immunochemotherapy, high *MYC* expression, as assessed by IHC 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 RNAs and miRNAs

Non-coding RNAs - circular RNAs (circRNAs) and microRNAs (miRNAs) - appear relevant to MCL prognostication. CircRNAs have disease-specific expression patterns and are particularly attractive due to their stability in vivo. A circRNA-based prognostic model, circSCORE, incorporating nine circRNAs individually predictive of time-to-progression (TTP), 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 TTP, PFS, and OS[44]. In a RRMCL analysis (n=65) from 3 prospective trials, one using ibrutinib, lenalidomide, and rituximab, circSCORE retained prognostic significance for PFS but not OS[45].

miRNAs are involved in post-transcriptional gene regulation, influencing key cell proliferation and differentiation pathways. In MCL, specific miRNAs 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.

Tumour 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 bispecifics, there is renewed focus on the TME. Increasing evidence indicates that complex interactions between malignant cells and surrounding immune milieu promote tumour survival, immune evasion, and resistance to therapy.

T cells

T-cell dysregulation is critical to MCL pathogenesis and treatment resistance. An "immune-depleted" TME, characterised by decreased T-cell numbers, downregulation of cytotoxic T-cells, and increased numbers of regulatory T-cells (Tregs) 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-cells with B symptoms, platelet count, and β2-microglobulin level, outperformed both MIPI and MIPI-c. Low risk IRPI yielded a 5-year OS of 100%, compared to 65% and 32% in intermediate- and high-risk IRPI, respectively[51].

Another study assessed T-cell function by IHC and targeted GEP of 730 immune-related genes. SOX11+ MCL showed reduced effector T-cell function, characterised by decreased CD4+ T-cell infiltration, CD4:CD8 ratios, and cytotoxic T-cells, compared to SOX11- MCL. Overexpression of CD70, which promotes Treg proliferation and differentiation, was strongly associated with inferior OS, consistent with other aggressive lymphoma studies[48]. Similarly, in 122 chemotherapy-treated MCL biopsies, IHC analysis revealed that an 'inflammatory Treg phenotype' within the TME may contribute to disease progression. High numbers of Tregs, characterised by FOXP3 positivity, and an elevated IL17A expression (produced by a subset of Tregs to provide proliferative signals to neoplastic cells) were each independently linked to poor outcomes[47].

T-cell exhaustion may also be a predictor of CAR-T response. 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].

Tumour associated macrophages

Tumour associated macrophages (TAMs) within the TME are important prognosticators in several lymphomas. TAMs can be polarised into M1 type (anti-tumoural, pro-inflammatory) or M2 type (anti-inflammatory, pro-tumoural), which strongly expresses cell membrane CD163 in the presence of MCL tumour cells. M2 TAMs promote MCL growth in murine models[54]. Increased CD163 IHC expression is independently associated with all-cause mortality in multivariate models from population-based studies of chemotherapy-treated MCL[55]. In subset of intensive chemotherapy-treated patients from MCL2/3 trials, both high FOXP3+ cells (above a cutoff of 2% by IHC) and CD163 (above 0.04%) had an additive poor prognostic effect with much shorter TTP compared to single-positive tumours.

Serum soluble CD163 (sCD163), a circulating (thus non-invasive) marker of TAM activation, is prognostic in DLBCL and HL, 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 with paired tissue and serum samples, 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).

TME subtypes

Recent data suggest specific TME clusters identified via bulk RNAseq may serve as both prognostic and predictive biomarkers for primary BTKi resistance. In one BTKi-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 BTKi 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-tumour 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. Targeting Tregs and M2 TAMs may be potential future therapeutic targets.

Other novel biomarkers

The myeloid compartment in MCL has also been evaluated. Myeloid clonal haematopoiesis (CH) mutations were analysed by targeted NGS in peripheral blood and bone marrow samples from the FIL MCL0208 trial of lenalidomide maintenance[57]. Large clonal haematopoiesis clones (VAF$\geq$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 CH may influence tumour 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 hazard ratios of 18.1 and 17.4, respectively.

Combined, they achieved an AUC 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 tumour 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, RT-qPCR and NGS all have prognostic value, even though each method has specific strengths and limitations[61].

Circulating tumour DNA (ctDNA) analysis using NGS to track IGHV clonotypes is emerging as a precise and dynamic biomarker in MCL. In one study, baseline ctDNA levels were strongly correlated with tumour 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 6519 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 tumour 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 NGS[63]. Patients who achieved a MRD negativity at 10^{-6} sensitivity were randomised to ASCT or no ASCT before maintenance rituximab. In the interim analysis with a median follow-up 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 CR status post chemoimmunotherapy induction. Patients who remained MRD-positive were not randomised in this study, thus MRD cannot be used to guide treatment for this subgroup until further randomised 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 however 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 centres 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 centres. As testing methods become more standardised 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 underutilised 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 prioritised. Broader efforts to sequence tumour samples are needed to characterise the genomic complexity of MCL and define consistent, clinically-relevant alterations. For future trials, international consensus on a core set of baseline biomarkers, standardised testing timepoints, and harmonised sample collection and storage will be essential. Regulatory bodies should incentivise industry to integrate biomarkers 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 immunologic biomarkers in routine practice will be essential to refine prognostication, guide treatment intensity, and enable personalised strategies for both frontline and relapsed disease management.

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Figure 1: Overview of current and emerging biomarkers in Mantle Cell Lymphoma

Caption: Created in https://BioRender.com

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-naive 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-naive 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=1168	Chemoimmunotherapy	Inferior OS (<3 years vs 8 years)
		Sarkozy (2025) [12]	Treatment-naïve N=1280	Chemoimmunotherapy *6 RCTs (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 (24mths vs 122mths)
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 (HR1.6, 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	Complex karyotype (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 13mths vs 47mths)
	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 35mths vs 101mths)
***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 aberration 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 37mths vs NR), although outcomes were improved compared to the ibrutinib-only group (median OS

					15mths vs 53mths)
	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 = .029)
***CDKN2A* deletions**	NGS	Malarikova (2020) [19]	Treatment-naïve N=127	R-CHOP-like therapy	*CDKN2A* deletion associated with inferior median OS (36mths vs NR) and EFS (15mths vs 54mths). 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 (2.9mths vs NR) and inferior ORR (33mths vs 90mths)
***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 81mths, 77mths and 13mths)
		Freeman (2022) [37]	R/R N=134	Ibrutinib vs temsirolimus *(MCL3001 RAY trial)*	MCL35 more reliably differentiates low, standard and high risk groups for PFS than MIPI
MicroRNAs	qRT-PCR for miRNA	He (2021) [46]	Treatment-naïve N=75	Chemoimmunotherapy	Low miRNA34a and elevated miRNA-155 associated with inferior OS
Circular RNAs	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 haematopoiesis clones	Targeted NGS panel	Ragaini (2025) [57]	Treatment-naïve N=254	Chemotherapy + ASCT+/-lenalidomide maintenance *(FIL MCL0208 trial)*	Clonal haematopoiesis 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)
Tumour 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+	IHC (FFPE	Li (2021) [69]	Treatment-naïve	Chemoimmunotherapy	High CD163+ M2 TAMs (tumour-associated macrophages) and

macrophages	tissue)		N=82		CD68+ M1 TAMs 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-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 post CAR-T
TME clusters	Bulk RNA sequencing	Jain (2023) [49]	R/R 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 N=650	Chemoimmunotherapy *(ECOG-ACRIN EA4151 trial)*	No difference in 3-yr OS between ASCT vs no ASCT group if MRD negative at 10^{-6} post induction
	RT-qPCR +/- NGS	Gine (2022) [3]	Treatment-naïve, indolent MCL N=50	Ibrutinib + rituximab *(ICML-2015 trial)*	Treatment ceased in the 24 patients who achieved MRD negativity at 10^{-5} after 24 months; only 1 patient had clinical relapse after median 36mth follow up
	RT-qPCR	Jerkeman (2024) [64]	R/R N=59	Lenalidomide, venetoclax + rituximab *(VALERIA MCL7 trial)*	89% who achieved MRD negativity (10^{-5}) remained in molecular remission, with median 14 months follow up
	clonoSEQ NGS	Kumar (2025) [6]	Treatment-naïve, TP53-mutated N=25	Zanubrutinib, obinutuzumab + venetoclax *(BOVen trial)*	Treatment discontinued in the 15 patients who achieved MRD negativity at 10^{-6}; 13 remain in remission after median follow up of 28 months

MCL = mantle cell lymphoma; R/R = relapsed/refractory; MIPI = MCL international prognostic index; ASCT = autologous stem cell transplant, TMTV = total metabolic tumour volume; TLG = total lesional glycolysis; PET = positron emission tomography; NR = not reached; OS = overall survival; PFS = progression free survival; TTP = time to progression; EFS = event free survival, IHC = immunohistochemistry, NGS = next generation sequencing, BTKi = Bruton Tyrosine Kinase inhibitor

Table 2: Current data for MCL biomarkers according to treatment setting

Biomarker	Chemoimmunotherapy	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-kB pathway mutations (*CARD11, BIRC3*)		P	P	
SWI-SNF complex mutations			P	
MCL35 gene expression assay				
circSCORE				
Plasma proteomics				
TME				
Low CD4+ T cells				
Tumour associated macrophages				
CD8+/HLA-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; MIPI = Mantle Cell Lymphoma International Prognostic Index; POD24 = progression of disease within 24 months; PET = positron emission tomography; TMTV = total metabolic tumour volume; TLG = total lesional glycolysis; TME = tumour microenvironment; MRD = measurable residual disease

Table 3: Selected clinical trials in MCL with biomarker inclusion

Clinical trial	Phase	Age	Treatment	Biomarker	Biomarker significance
Frontline					
Nordic MCL2 and MCL3 trials [25,44]	II	≤65	R-maxiCHOP/R-HiDAC	MIPI and MIPI-c Blastoid morphology (18%) *TP53* mutation (11%) *TP53* deletion (16%) *CDKN2A* deletion (20%) High risk circSCORE (39%)	• MIPI/MIPI-c risk groups associated with PFS and OS • Blastoid morphology: median OS 5.2 yrs vs 12.8yrs • *TP53* mutations associated with inferior OS and PFS (median PFS 0.9 years vs 10.2 years) • *CDKN2A* and *TP53* deletions associated with inferior OS and PFS • High risk circSCORE: median PFS 4.5yrs vs 7.7yrs
WINDOW-1[42]	II	≥65	Ibrutinib + rituximab -> HCVAD/MA	*TP53* aberration (32%) Blastoid/pleomorphic (12%) Complex karyotype (15%) Mutations identified by WES and RNA-seq	• *TP53* aberration, blastoid/pleomorphic, complex karyotype associated with inferior PFS • *TP53* aberration associated with lower CR rate (55% vs 91%) to IR • *NSD2*, *KMT2C* and *SMARCA4* mutations enriched in patients with late CR • *BTK, BANK1, BIRC3, CARD11, CCND1, CD79A, CD79B,* and *SMARCB1* aberrations found in patients failed to reach CR
SHINE[40]	III	≥65	Bendamustine + rituximab +/- ibrutinib	*TP53* mutation (10%) Blastoid/pleomorphic morphology (9%) High *MYC* mRNA expression (upper quartile) MCL35 high-risk group (17%)	• Inferior PFS for: *TP53* mutation (HR1.7, p=0.02), blastoid/pleomorphic morphology (HR2.7, p=0.0002) and high *MYC* (HR1.5, p=0.03) • High-risk vs low risk MCL35 group: median PFS 13mths vs 81mths
ICML-2015[70]	II	All	Ibrutinib + rituximab *blastoid and Ki67>30% excluded	MRD negativity (10^{-5}) at 24mths (69%) *TP53* alteration (15%)	• Treatment ceased in the 24 patients who achieved MRD at 24 months; only 1 patient relapsed after median 36mth follow up • *TP53* mutations associated with inferior PFS
Lenalidomide-RCHOP *NCT0263313* [30]	II	All	Lenalidomide-RCHOP -> HiDAC -> lenalidomide-rituximab	*TP53* mutations and/or deletions (37%) Blastoid (8%) 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 post induction: ASCT vs no ASCT	MRD negativity (10^{-6}) post induction (78%)	• No difference in 3-yr OS between ASCT vs no ASCT group if MRD negative post induction (82.1% and 82.7%)
ALTAMIRA[66]	II	≥60	Acalabrutinib + rituximab	*TP53* mutation (24%) Ki67 >30% (22%) Blastoid morphology (6%) MRD negativity (59%)	• 1 year PFS 87%, 1 year OS 93% • *TP53* mutation associated with inferior PFS at 1 year (69%) • *Outcomes of MRD-guided acalabrutinib cessation not yet reported*
FIL MCL0208[57]	III	≤65	Chemotherapy + ASCT+/- lenalidomide maintenance	Myeloid clonal haematopoiesis mutations (13%) Ki67>30% (31%)	• Clonal haematopoiesis clones with VAF>10% associated with inferior PFS (HR 2.93, p=0.006) and OS (HR 3.02, p=0.02) • Ki67 associated with worse PFS (HR1.96, p=0.023)
BOVen[6]	II	All	Zanubrutinib + obinutuzumab + venetoclax in *TP53*-mutated MCL	Blastoid morphology (20%) Biallelic *TP53* inactivation (48%) High risk MIPI (68%) Ki67>30% (52%) MRD negativity (10^{-6}) at EOT (48%)	• Blastoid/pleomorphic morphology associated with inferior PFS and OS • No effect of biallelic *TP53* inactivation, Ki67 or MIPI risk score on PFS or OS • Treatment discontinued in the 15 patients who achieved MRD negativity; 13 remain in remission after median follow up of 28 months
Relapsed / Refractory					

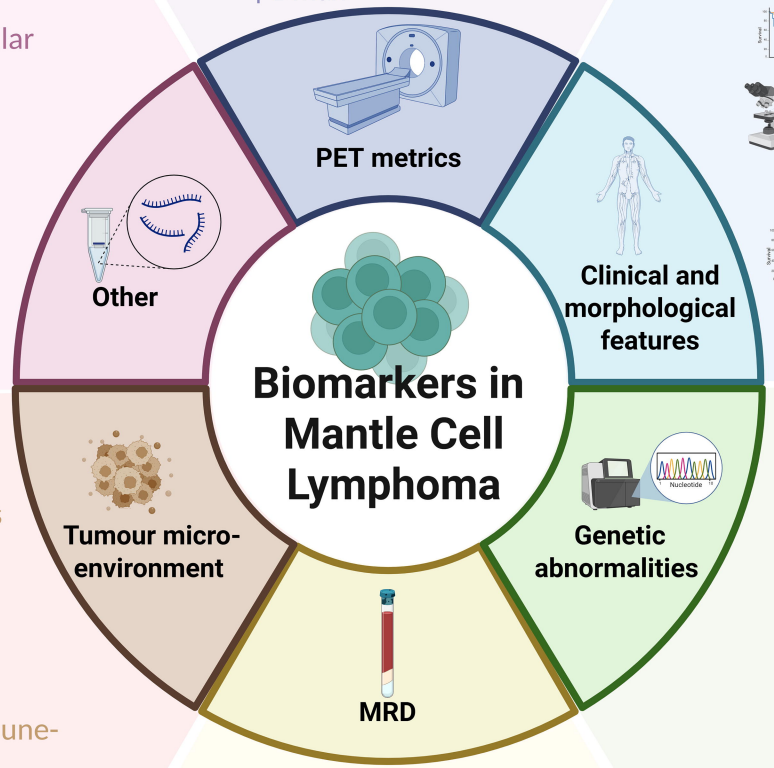
Emerging biomarkers for MCL

AIM[38]	II	All	Ibrutinib + venetoclax	*TP53* aberrations (50%) Ki67 <30% (43%) SWI-SNF complex mutations	• Del 9p21.1-24.3 and *SMARCA2*, *SMARCA4*, *ARID2* mutations associated with primary resistance to venetoclax + ibrutinib • Lower response rate for ki67>30% • 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 *TP53* mutation (25%) / deletion (34%) Ki67>30% (42%) High risk MIPI (46%)	• Immune signature score associated with inferior OS (HR 3.32, p=0.03) • Ki67 (HR1.02, p=0.03) and MIPI (HR1.97,p=0.007) associated with inferior OS • *TP53* mutation/deletion not associated with OS
MCL3001 RAY [37]	III	All	Ibrutinib vs temsirolimus	*TP53* mutation (25%) *BIRC3* mutation/deletion (34%) Blastoid morphology (12%) High risk MIPI (21%) 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 (HR1.9, p=0.006) • 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%) 17p deletion (19%) Blastoid/pleomorphic (17%) Mutations and CNVs identified by sequencing	• 5-year PFS of 80% in whole cohort • *CARD11* mutations enriched at relapse leading to venetoclax resistance
TARMAC [52]	II	All	Tisagenlecleucel + ibrutinib	Blastoid (15%) *TP53* mutated or deleted (45%) Ki67 >30% (71%) POD24 (65%) T cell exhaustion	• 88% of patients with *TP53* mutation achieved CR • Similar CR rate regardless of blastoid morphology, Ki67 or *TP53* mutation • Less exhausted CD8+ T cell phenotype found in deep responders
SYMPATICO[29]	III	All	Ibrutinib +/- venetoclax	*TP53* mutations (29%) Blastoid/pleomorphic (19%) High risk MIPI (34%)	• *TP53* aberrations associated with inferior OS in ibrutinib + venetoclax group (median OS 37mths vs NR), although outcomes were improved compared to the ibrutinib-only group (median OS 15mths vs 53mths)
VALERIA MCL7[64]	Ib/II	All	Venetoclax + lenalidomide + rituximab	*TP53* mutation (30%) MRD negativity (10^{-5}) at 6 months (94%)	• *TP53* mutation associated with poorer response rate, PFS, OS and DOR • 89% who achieved MRD negativity (10^{-5}) remained in molecular remission, with median 14 months follow up
MIPI = MCL international prognostic index; OS = overall survival, PFS = progression free survival; WES = whole exome sequencing; CR = complete response; MRD = measurable residual disease; ASCT = autologous stem cell transplant; VAF = variant allele frequency; EOT = end of treatment; CNV = copy number variations; DOR = duration of response					

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 NGS: 3-4 weeks	High with standardised assays	Dynamic measure of treatment response Can guide therapy intensity and duration	Limited availability Assay variability 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 specialised centres	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 setting	High	3–6 weeks	Good in accredited laboratories	Can identify novel targets and resistance mutations	Costly and often not reimbursed Clinical utility in MCL still evolving Need sufficient tissue for DNA extraction
PET radiomics	Currently limited to research; not routine in practice	Moderate	Days to weeks	Not yet standardised	Non-invasive No additional testing required - uses standard-of-care PET scans Can offer additional risk stratification at baseline and during treatment	Requires expertise and specific software – not widely available Clinical utility in MCL still evolving
Tumour microenvironment	Research setting only	High	Weeks to months	No data	May predict response to immunotherapies Potential to identify novel targets	Not clinically available Heterogeneity of assays and lack of validation

MRD = measurable residual disease; NGS = next generation sequencing, WES = whole exome sequencing, WGS = whole genome sequencing; PET = positron emission tomography



↑SUVmax

↑TMTV, ↑TLG

PET radiomics:
↑heterogeneity index
↑Dmax

↑age, bulky disease,
↑LDH, B symptoms,
↑B2-microglobulin

MIPI, MIPI-c

Blastoid or pleomorphic morphology

↑Ki67%

POD24

Complex karyotype/ genomic complexity

TP53 aberrations

CDKN2A deletions

Alternate NFkB pathway mutations: *CARD11, BIRC3, TRAF2, TRAF3*

SWI-SNF complex mutations

Flow cytometry

NGS - IGHV rearrangements

ctDNA

↓CD4 and ↑CD8 T cells

↑T-regulatory cells

↑Tumour associated macrophages

Immune clusters - 'immune-depleted' TME

Effector T cell exhaustion

MCL35 Gene expression assay

Non-coding RNAs (circular RNAs and micro RNAs)

Plasma proteomics

Myeloid clonal haematopoiesis clones