MOHSIN HAEMATOLOGY ACADEMY

UK-Oriented Clinical Practice Guide

Mantle Cell Lymphoma

Diagnosis, Risk Stratification, and Management in Adults — UK Practice-Oriented Evidence Guide

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Tool Metadata

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Intended users	UK consultant haematologists, haematology registrars and SHOs, CNS teams, haemato-oncology pharmacists, and MDT coordinators. Not for direct patient use.
Evidence base	BSH 2024 (Eyre et al, primary UK standard) · NICE TA502 ibrutinib · NICE TA1081 zanubrutinib · NICE TA677 brexucabtagene autoleucel · ESMO Clinical Practice Guidelines (Dreyling et al) · NCCN B-Cell Lymphomas · key RCTs (TRIANGLE, SHINE, LYMA, ZUMA-2, SYMPATICO, ECHO, BRUIN, MCL Younger, Nordic MCL2).
Tags	Interpretation · MDT · BSH 2024 · NICE TA502/TA1081/TA677 · Pathology · CAR-T

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1. Executive Summary

Mantle cell lymphoma (MCL) is an uncommon, biologically heterogeneous mature B-cell neoplasm defined by the t(11;14)(q13;q32) translocation and cyclin D1 overexpression. Although historically considered incurable with standard chemoimmunotherapy, sequential adoption of Bruton tyrosine kinase inhibitors (BTKi), chimeric antigen receptor T-cell therapy (CAR-T), and rational combination strategies has materially improved outcomes.

This evidence guide synthesises high-quality evidence and UK regulatory positions into a practical, NHS-facing framework for adults with MCL. It distinguishes verified, practice-defining evidence from emerging signals that may inform MDT discussion, trial referral, or access planning but should not be used as the sole basis for routine treatment outside approved access routes.

Key Practice Points

- Adequate diagnostic work-up requires excisional or generous core biopsy with full immunohistochemistry — CD20, CD5, cyclin D1, SOX11 — Ki-67 reported as a percentage, and TP53 assessment by both IHC and molecular (NGS) testing.
- Risk stratification at diagnosis using MIPI-c, Ki-67, TP53 mutation status, and morphological variant drives treatment intent. Each patient should be assigned a documented MDT risk category: standard-risk MCL, indolent/non-nodal MCL suitable for observation, high-risk MCL, TP53-aberrant MCL, or blastoid/pleomorphic MCL.
- Watch and wait remains appropriate for asymptomatic, low-burden, indolent-phenotype MCL (low Ki-67, SOX11 negative, IGHV mutated, leukaemic non-nodal).
- **TRIANGLE — practice-changing evidence benchmark, transitional UK position:** Ibrutinib-integrated induction and maintenance is now the key evidence benchmark for fit patients with newly diagnosed MCL. This approach is not yet uniformly embedded as a routine commissioned UK first-line pathway, but access is increasingly being explored through non-routine routes — compassionate access, manufacturer-supported programmes, individual funding mechanisms, clinical trials, or locally approved exceptional pathways. Cytarabine-containing immunochemotherapy with or without ASCT remains relevant where BTKi integration is not accessible. MDT discussion should explicitly consider whether BTKi-integrated induction is accessible and clinically appropriate, with documentation of evidence basis, funding route, patient suitability, toxicity considerations, and informed consent.
- For older or less fit patients, bendamustine-rituximab (BR) remains a UK standard. SHINE (ibrutinib + BR) has not been adopted as routine UK practice (no overall survival benefit, excess toxicity). ECHO (acalabrutinib + BR) has demonstrated PFS benefit; full UK NICE appraisal in this indication is pending.
- TP53-mutated MCL has poor outcomes with intensive chemoimmunotherapy and ASCT; ASCT should not be relied upon as the primary risk-overcoming strategy. These patients should be prioritised for clinical trials, BTKi-based approaches, and early cellular therapy planning where appropriate.
- For relapsed/refractory MCL after one previous line of therapy, two covalent BTKi are NICE-recommended in the UK: ibrutinib (NICE TA502, January 2018) and zanubrutinib (NICE TA1081, published 10 July 2025). TA1081 directs healthcare providers to use the least-expensive option of

suitable treatments, having discussed advantages and disadvantages with the patient. Choice should additionally consider cardiovascular and bleeding risk, drug interactions, comorbidity, and local formulary.

- On post-BTKi disease, brexucabtagene autoleucel under NICE TA677 (within the Cancer Drugs Fund and subject to the managed access agreement) is the established CAR-T option in the UK. A review of TA677 is in development; confirm the live NICE / NHS England commissioning position before referral or publication.
- Pirtobrutinib has clinically meaningful activity after covalent BTKi exposure, but routine UK NHS access should not be assumed. One NICE appraisal in MCL (ID3975) has been suspended pending company engagement; a separate appraisal (ID6493, BTKi-naive R/R MCL) is in development. Access should be checked through NICE, local formulary, compassionate, EAMS, clinical trial, or IFR routes at the time of decision-making.

1A. UK Access / Commissioning Snapshot

This snapshot summarises the principal NICE / NHS England access positions used as a reference for this evidence guide. Implementation may differ in Scotland (SMC), Wales (AWMSG), and Northern Ireland (HSCNI); local formulary positions should be checked. The list is not exhaustive; access positions change frequently and must be verified at the time of prescribing or referral.

Therapy	Indication and access position	Reference
Ibrutinib (R/R MCL)	Recommended after one previous line of therapy, subject to the commercial access agreement with NHS England.	NICE TA502 (31 Jan 2018; last reviewed 8 Jul 2021)
Zanubrutinib (R/R MCL)	Recommended after one line of treatment only; use least-expensive option of zanubrutinib or ibrutinib per TA1081 direction; subject to simple discount patient access scheme.	NICE TA1081 (10 Jul 2025)
Brexucabtagene autoleucel (R/R MCL)	Recommended within the Cancer Drugs Fund for adults previously treated with a BTK inhibitor, subject to the managed access agreement. A review of TA677 (for use after two or more prior systemic treatments) is in development — verify live position.	NICE TA677 (review in development)
Acalabrutinib + bendamustine-rituximab (untreated MCL)	NICE appraisal in development. Expected publication 4 June 2026 (may be rescheduled). Not adopted as routine UK standard before final NICE guidance.	NICE GID-TA11091 (ID6155)
Pirtobrutinib (R/R MCL)	Routine UK NHS access should not be assumed. As of May 2026, NICE appraisal ID3975 is reported as suspended pending company evidence submission; ID6493 (BTKi-untreated R/R MCL) is in development. Verify before prescribing.	NICE appraisals in development / suspended
TRIANGLE-style first-line ibrutinib-integrated induction	Practice-changing evidence benchmark in fit patients; not uniformly commissioned as routine UK first-line. Access via compassionate, manufacturer-supported, IFR, clinical trial, or locally approved exceptional pathways.	Dreyling et al, The Lancet 2024

NICE and NHS England positions are used as the principal access reference throughout this guide. Implementation may differ in Scotland, Wales and Northern Ireland; clinicians should check SMC, AWMSG, HSCNI and local formulary positions where relevant.

1B. Visual Decision Support Summary

This section provides a printable equivalent of the web-version sidebar. It is intended as a rapid MDT decision-support layer, not a substitute for the full evidence sections below.

MCL First-Line Algorithm

1. Confirm diagnosis, morphology, Ki-67, and TP53.

2. If indolent / non-nodal and asymptomatic: observe.

3. If fit / intensive: cytarabine-containing pathway ± ASCT; consider TRIANGLE-style BTKi integration where legitimate access exists.

4. If older / less fit: BR remains current UK standard; ECHO / acalabrutinib-BR is evidence-supported but access-dependent.

5. If TP53-mutated, blastoid, pleomorphic, or high-risk: prioritise trial, BTKi access route, and early CAR-T planning.

6. Document evidence basis, funding/access route, toxicity, alternatives, and consent.

Treatment Flowchart

New MCL diagnosis → Indolent / asymptomatic? — Yes: observe; No: assess fitness → Fit vs older / less fit — Fit: cytarabine ± ASCT (TRIANGLE if accessible); Older: BR standard (ECHO if accessible) → High-risk biology overlay: trial / BTKi access / early CAR-T pathway mapping.

MCL Pathway at a Glance

Stage	Meaning
Diagnosis	Tissue, cyclin D1 / SOX11, t(11;14)
Biology	Ki-67, TP53, morphology
Fitness	Frailty, renal, cardiac, transplant suitability
Access	NICE, formulary, trial, compassionate / IFR
MDT	Pathway category and consent
Follow-up	Response, relapse, supportive care

Access Status Legend

- Green — NICE-recommended / commissioned.
- Amber — evidence-supported but access-dependent.
- Red — investigational / not routine NHS-funded.
- Grey — emerging / conference-level.

Evidence-supported does not equal NHS-commissioned.

High-Risk MCL Reminder

High-risk features:

- TP53 mutation or TP53-aberrant IHC pattern.
- Blastoid / pleomorphic morphology.
- High Ki-67.
- High MIPI-c.
- Complex karyotype.

Action: trigger early trial discussion, BTKi access review, and CAR-T pathway mapping. ASCT should not be relied upon as the primary risk-overcoming strategy.

MDT Documentation Checklist (Sidebar Quick Reference)

- Diagnosis and morphology.
- Ki-67 percentage.
- TP53 NGS result.
- MIPI / MIPI-c.
- Fitness / frailty.
- Pathway category (routine / evolving access-dependent / selected alternative / not routine).
- Access / funding route.
- Alternatives and toxicity.
- Consent and patient preference.
- CAR-T / trial discussion where relevant.

2. Scope and Purpose

2.1 Population

Adults (≥18 years) with a histologically confirmed diagnosis of mantle cell lymphoma, including classical, blastoid, pleomorphic, and leukaemic non-nodal variants, and in situ mantle cell neoplasia (ISMCN).

2.2 Clinical Setting

UK National Health Service haematology services, encompassing district general hospital units, tertiary cancer centres, and JACIE-accredited cellular therapy centres.

2.3 Domains Covered

- Diagnostic pathology and minimum work-up
- Staging and risk stratification
- First-line treatment in fit and unfit patients
- Consolidation and maintenance strategies
- Relapsed and refractory disease, including CAR-T cell therapy
- CNS prophylaxis
- Supportive care, infection prophylaxis, vaccination
- Surveillance and survivorship
- Service-level implementation and audit standards

2.4 Out of Scope

- Paediatric and adolescent MCL (extremely rare)
- Detailed pharmacology of every cytotoxic and targeted agent (refer to BNF and SmPC)
- Allogeneic stem cell transplant donor selection (refer to BSBMT guidance)

3. Methodology

3.1 Evidence Sources

This guideline draws upon a structured review of the following sources, ranked by hierarchy of authority for UK practice:

- **Tier 1 — UK regulatory and society:** NICE Technology Appraisals, NHS England Clinical Commissioning Policy documents, and British Society for Haematology (BSH) guidelines — most recently Eyre TA, Bishton MJ, McCulloch R, O'Reilly M, Sanderson R, Menon G, Iyengar S, Lewis D, Lambert J, Linton KM, McKay P. Diagnosis and management of mantle cell lymphoma: a British Society for Haematology Guideline. British Journal of Haematology 2024;204(1):108–126 (online October 2023). The earlier 2018 BSH guideline (McKay et al, BJH 2018;182:46–62) is superseded but cross-referenced where relevant.
- **Tier 2 — International haematology society guidelines:** European Society for Medical Oncology (ESMO) MCL Clinical Practice Guidelines (Dreyling et al), European Hematology Association (EHA)

consensus and education programme materials, National Comprehensive Cancer Network (NCCN) Guidelines for B-Cell Lymphomas.

- **Tier 3 — Key randomised controlled trials:** TRIANGLE, SHINE, LYMA, MCL Younger, Nordic MCL2/MCL3, VR-CAP (LYM-3002), SYMPATICO, ECHO, ZUMA-2, TRANSCEND NHL 001, BRUIN/BRUIN MCL-321.
- **Tier 4 — Conference proceedings and emerging evidence:** ASH and EHA annual meetings 2023–2025. Emerging data are flagged [EMERGING] and may inform MDT discussion, trial referral, or access planning, but are not used as the sole basis for strong recommendations.

3.2 Evidence Grading

Recommendations are graded according to a GRADE-adapted framework consistent with BSH methodology:

Evidence Quality	Definition
High	Further research is very unlikely to change confidence in the estimate of effect. Typically supported by multiple consistent randomised trials or meta-analysis of randomised trials.
Moderate	Further research is likely to have an important impact on confidence and may change the estimate. Typically a single RCT, or RCTs with some limitations.
Low	Further research is very likely to have an important impact. Observational evidence or RCTs with serious limitations.
Very Low	Any estimate of effect is very uncertain. Case series, expert opinion, indirect evidence.

Recommendation strength is reported as:

- **Strong recommendation:** Benefits clearly outweigh harms or vice versa. Applies to most patients in most circumstances.
- **Conditional recommendation:** Benefits probably outweigh harms but with greater uncertainty. Shared decision-making is appropriate.
- **Good practice statement (GPS):** Action considered necessary by consensus despite limited direct evidence.

3.3 Limitations

A formal de novo systematic review was not undertaken; this guideline integrates existing high-quality syntheses and major trial data. Where the evidence base is rapidly evolving (notably bispecific T-cell engagers, MRD-guided strategies, and second-generation BTKi combinations), recommendations are explicitly conditional.

Evidence Integrity Statement

Every named trial, regulatory document, or society guideline cited in this document has been included on the basis that it is well established and verifiable in the public domain. Where any specific NICE Technology Appraisal number, abstract identifier, or numerical estimate could not be confirmed to a level of consultant defensibility, it is flagged with [VERIFY] for the user to cross-check before publication or clinical use.

Emerging evidence is included for consultant-level awareness and may inform MDT discussion, trial referral, or access planning, but should not be used as the sole basis for routine treatment outside approved access routes. Such evidence is segregated into the Emerging Evidence section and labelled [EMERGING].

4. Disease Overview

4.1 Definition

MCL is a mature B-cell non-Hodgkin lymphoma derived from a naive or post-germinal-centre B cell, defined by the chromosomal translocation t(11;14)(q13;q32) leading to juxtaposition of CCND1 with the immunoglobulin heavy chain locus and consequent constitutive cyclin D1 overexpression. SOX11 expression is characteristic of conventional and aggressive MCL and supports diagnosis in cyclin D1 negative cases.

4.2 Epidemiology

- Comprises 5–7% of adult non-Hodgkin lymphoma in the UK.
- Median age at diagnosis approximately 65–70 years.
- Male predominance (M:F approximately 3:1).
- Most patients (70–80%) present with Ann Arbor stage III–IV disease, often with bone marrow, peripheral blood, and gastrointestinal involvement.

4.3 Biological Variants

Variant	Key Features	Clinical Implication
Classical nodal MCL	Lymphadenopathy dominant, SOX11+, IGHV unmutated, t(11;14)	Standard treatment pathways
Blastoid	Cells resembling lymphoblasts, very high Ki-67, frequent TP53 abnormalities, complex karyotype	Aggressive; consider BTKi-based or CAR-T-anchored pathway
Pleomorphic	Large pleomorphic cells, high proliferation	Aggressive course; intensify therapy
Leukaemic non-nodal	Peripheral blood and splenic disease, SOX11-, IGHV mutated, often asymptomatic	Often indolent; observe initially if asymptomatic
In situ MCN (ISMCN)	Cyclin D1+ cells confined to mantle zone of otherwise reactive node	Often incidental; surveillance only in most cases

4.4 Pathogenesis Key Pathways

- Cyclin D1 overexpression drives cell cycle dysregulation via CDK4/6 activation.
- Chronic active B-cell receptor (BCR) signalling underpins sensitivity to BTK inhibition.
- ATM, TP53, CDKN2A, and NOTCH1/2 mutations contribute to genomic instability and treatment resistance.
- TP53 alterations (mutation, 17p deletion) are the strongest validated adverse molecular biomarker.

5. Diagnosis and Pathology Requirements

5.1 Minimum Tissue and Diagnostic Requirements

A confident diagnosis requires adequate tissue with a panel of confirmatory tests. Fine needle aspirate alone is insufficient.

- Excisional or generous core needle biopsy of an involved nodal or extranodal site.
- If diagnosis on bone marrow only, paired peripheral blood flow cytometry and molecular cyclin D1 confirmation are required.
- Histological review by a lymphoma-specialist haematopathologist within an MDT framework.

5.2 Immunohistochemistry and Flow Cytometry

Marker	Expected in MCL	Comment
CD20	Positive	Surface B-cell marker
CD5	Positive (aberrant)	Helpful in differential from CLL/SLL and other small B-cell lymphomas
Cyclin D1 (BCL1)	Positive (nuclear)	Diagnostic. Rare cyclin D1-negative cases exist (test SOX11, cyclin D2/D3)
SOX11	Positive in classical/aggressive MCL	Negative in leukaemic non-nodal indolent MCL
CD23	Usually negative or weak	Distinguishes from CLL (typically CD23+)
CD10	Negative (usually)	Distinguishes from follicular and Burkitt lymphoma
BCL6	Negative	
LEF1	Negative	Useful to distinguish from CLL (LEF1+)
Ki-67	Variable (report as percentage)	Strong independent prognostic marker; ≥30% adverse

Pattern Recognition — When to Suspect MCL

Middle-aged or older patient with widespread lymphadenopathy, splenomegaly, and lymphocytosis.

Frequent gastrointestinal involvement (multiple lymphomatous polyposis) — biopsy if symptomatic or radiologically suspicious.

B-symptoms with rapid progression — particularly consider blastoid or pleomorphic MCL.

Aberrant CD5-positive B-cell lymphoma that is CD23 negative or weak — think MCL, not CLL.

Mnemonic — Diagnostic Minimum (CCSKT)

C — CD20, CD5, CD23 (CLL distinction)

C — Cyclin D1 (BCL1) nuclear positivity

S — SOX11 (classical / aggressive MCL) — negative supports indolent / leukaemic non-nodal phenotype

K — Ki-67 percentage (≥30% adverse; report as a number, not 'high')

T — TP53 (by IHC AND molecular NGS — do not rely on IHC alone)

5.3 Pathology Reporting Minimum Dataset

Each pathology report for newly diagnosed MCL should explicitly include:

- Morphological variant: classical, blastoid, pleomorphic, or leukaemic non-nodal.
- Ki-67 proliferation index reported as a percentage (not just as low / intermediate / high).

- Cyclin D1 and SOX11 status.
- TP53 IHC pattern and molecular (NGS) mutation result.
- FISH confirmation of t(11;14) where cyclin D1 IHC is negative or equivocal.
- Bone marrow and peripheral blood involvement where assessed.
- Comment on differential diagnosis where relevant: CLL/SLL, marginal zone lymphoma, follicular lymphoma, cyclin D1-positive DLBCL, and in situ mantle cell neoplasia.

5.4 Molecular and Cytogenetic Testing

- FISH for t(11;14)(q13;q32) IGH-CCND1, mandatory if cyclin D1 IHC is equivocal or negative.
- TP53 mutation analysis by next-generation sequencing on diagnostic tissue or peripheral blood.
- TP53 immunohistochemistry as a screening surrogate (strong diffuse positivity or complete absence of expression suggests TP53 abnormality).
- Conventional karyotype where feasible (complex karyotype ≥3 aberrations is adverse).
- Consider a broader NGS lymphoma panel covering ATM, CDKN2A, NOTCH1, NOTCH2, NSD2, KMT2D where locally available.

5.5 Baseline Clinical Work-Up

- Full clinical history including B symptoms, performance status, comorbidity, frailty (Clinical Frailty Scale).
- FBC, U&E, LFT, LDH, urate, calcium, magnesium, phosphate, beta-2 microglobulin, immunoglobulins, hepatitis B surface antigen and core antibody, hepatitis C antibody, HIV serology.
- ECG, echocardiogram if anthracycline or BTKi planned; baseline blood pressure.
- Pregnancy test in women of childbearing potential.

5.6 Imaging and Endoscopy

- Contrast-enhanced CT of neck, chest, abdomen, and pelvis.
- 18F-FDG PET-CT recommended at baseline (BSH, ESMO). PET avidity is typical except in some indolent variants.
- Bone marrow aspirate and trephine with flow cytometry and IHC for cyclin D1.
- Upper and lower GI endoscopy with biopsy where clinically indicated; multiple lymphomatous polyposis is common.
- MRI brain and CSF examination by flow cytometry if blastoid morphology, high MIPI, neurological symptoms, or relapse with high-risk features.

Diagnostic Pitfalls

Cyclin D1 negative MCL exists; do not exclude MCL solely on a negative IHC. Test SOX11, FISH, and consider cyclin D2/D3.

CLL/SLL with cyclin D1 positivity is rare but reported; LEF1 negativity and t(11;14) confirmation help differentiate.

Reactive cyclin D1 staining can occur in occasional germinal centre cells; nuclear staining of mantle/lesional cells is required.

In situ MCN is often an incidental finding and does not in itself mandate treatment; correlate with imaging and clinical assessment.

6. Staging and Risk Stratification

6.1 Anatomical Staging

The Lugano modification of the Ann Arbor staging system is used. The majority of MCL presents at stage III or IV.

6.2 Mantle Cell Lymphoma International Prognostic Index (MIPI)

The MIPI score (Hoster et al, Blood 2008) integrates age, ECOG performance status, lactate dehydrogenase, and white cell count.

Risk Group	MIPI Score	Approximate Median OS (chemoimmunotherapy era)
Low risk	< 5.7	Not reached at long follow-up in fit population
Intermediate risk	5.7 – 6.2	Approximately 5–7 years
High risk	≥ 6.2	Approximately 2–3 years

6.3 MIPI-c

MIPI-c (Hoster et al, JCO 2016) incorporates the Ki-67 proliferation index and yields improved discrimination, particularly for high-risk patients.

- Ki-67 ≥30% is incorporated as an adverse feature.
- MIPI-c high risk patients have markedly inferior outcomes with conventional chemoimmunotherapy alone.

6.4 TP53 Status

TP53 mutation is the single most powerful adverse molecular biomarker in MCL. Eskelund et al (Blood 2017) demonstrated that TP53-mutated MCL had a median OS of less than four years in the Nordic MCL2/MCL3 cohorts, despite intensive cytarabine-containing induction and ASCT consolidation.

- **Recommendation:** All patients with MCL should undergo TP53 mutation testing at diagnosis (Strong; Moderate quality evidence).
- **Recommendation:** TP53-mutated patients should be prioritised for BTKi-based regimens and early consideration of clinical trials or CAR-T pathways rather than intensive chemoimmunotherapy alone (Conditional; Moderate quality evidence).

6.5 Morphological Risk Modifiers

- Blastoid or pleomorphic morphology: classify as high risk regardless of MIPI.
- Complex karyotype (≥3 cytogenetic aberrations): adverse.
- CDKN2A deletion and complex genomic instability: adverse.

6.6 MDT Risk Category Assignment

At first treatment decision, each patient should be assigned a documented MDT risk category. This is an operational categorisation derived from MIPI-c, TP53 status, morphology, and clinical phenotype, and should drive treatment intent:

- **Standard-risk MCL:** Symptomatic, no TP53 mutation, non-blastoid/pleomorphic morphology, Ki-67 < 30%. Standard first-line pathway applies.
- **Indolent / non-nodal MCL suitable for observation:** Asymptomatic, low Ki-67, SOX11 negative, IGHV mutated, leukaemic non-nodal phenotype. Watch and wait is the appropriate strategy.
- **High-risk MCL:** High MIPI-c, Ki-67 ≥ 30% without TP53 mutation. Consider TRIANGLE-anchored BTKi-integrated approaches where accessible, and earlier CAR-T pathway discussion.
- **TP53-aberrant MCL:** TP53 mutation by NGS or strong/absent TP53 IHC pattern. Prioritise clinical trials, BTKi-based approaches, and early cellular therapy planning. ASCT should not be relied upon.
- **Blastoid / pleomorphic MCL:** Aggressive variant. High-risk pathway with consideration of CNS prophylaxis and early CAR-T referral.

6.7 Minimal Residual Disease (MRD)

MRD assessment by allele-specific oligonucleotide PCR or, increasingly, by next-generation sequencing of immunoglobulin gene rearrangements (e.g. clonoSEQ-style assays), is a strong prognostic marker after induction. MRD-guided treatment intensification or de-escalation remains under investigation; outside clinical trials, MRD is a useful adjunct rather than a treatment trigger.

7. First-Line Management

This section presents first-line management as a stepwise MDT algorithm. For each fitness group, options are separated into four practical categories: (A) current UK standard / routine, (B) evolving evidence-standard / access-dependent, (C) high-risk biology / selected alternative, and (D) historical / not routine. Evidence-supported does not equal NHS-commissioned — access route must be documented for any non-routine option.

7.0 Treatment Decision at Diagnosis — MDT Algorithm

Step 1 — Is this indolent/non-nodal MCL suitable for observation?

- Asymptomatic; low tumour burden; non-bulky.
- Low Ki-67; non-blastoid / non-pleomorphic.
- SOX11 negative and IGHV mutated leukaemic non-nodal phenotype where available.

Decision: watch and wait, not immediate treatment.

Step 2 — Is the patient fit for intensive / cytarabine-based treatment?

- ECOG performance status and frailty (Clinical Frailty Scale).
- Renal function (eGFR / creatinine clearance) and cardiac fitness.
- Transplant fitness and end-organ reserve.
- Comorbidity burden and patient preference.

Step 3 — Is there high-risk biology?

- TP53 mutation or TP53-aberrant pattern by IHC.
- Blastoid or pleomorphic morphology.
- High Ki-67 proliferation index.
- High MIPI-c.
- Complex karyotype (≥ 3 cytogenetic aberrations).

Decision: do not assume ASCT will overcome adverse biology. Prioritise clinical trial, BTKi-based approach where accessible, and prospective CAR-T pathway planning.

Step 4 — Check access

Before final recommendation, confirm:

- NICE Technology Appraisal status.
- NHS England / local commissioning position.
- Local formulary approval.
- Compassionate / manufacturer-supported route availability.
- Individual Funding Request / exceptional funding route.
- Clinical trial availability.
- SmPC and patient-specific toxicity, interaction, and renal/hepatic considerations.

7.1 Observation Pathway

A minority of patients present with biologically indolent disease that can be safely observed.

- Who to observe: asymptomatic patients with non-blastoid, low Ki-67, non-bulky MCL — particularly leukaemic non-nodal phenotype (SOX11 negative, IGHV mutated).
- What to monitor: clinical assessment, FBC, U&E, LFT, LDH; imaging only on clinical suspicion.
- When to treat: development of MCL treatment triggers — B-symptoms, progressive cytopenias attributable to marrow or splenic disease, symptomatic or bulky nodal disease, threatened organ function, rapidly progressive disease, symptomatic splenomegaly, gastrointestinal complications, or unequivocal clinical or radiological progression.
- Median time to treatment with watch-and-wait may exceed 2–4 years in selected patients.

> **Common Pitfall — Indolent MCL**
>
> Lymphocytosis alone does not mandate treatment in indolent leukaemic non-nodal MCL.
>
> Treat when symptoms, cytopenias, bulky or progressive disease, organ compromise, or clinically meaningful progression emerges.

- **Recommendation 7.1.1:** Offer initial observation to asymptomatic patients with non-blastoid, low Ki-67, non-bulky MCL, particularly those with leukaemic non-nodal phenotype (Conditional; Moderate quality evidence; BSH 2024 / ESMO endorsed).

7.2 Fit / Intensive / Transplant-Eligible Pathway

Defined pragmatically as patients fit for cytarabine-based induction and, where applicable, autologous stem-cell transplant. Age alone is not the sole determinant; biological fitness, end-organ reserve, and comorbidity guide selection. The four categories below should be considered in order at MDT.

7.2.A Current UK standard / routine pathway

- Cytarabine-containing immunochemotherapy (e.g. R-CHOP/R-DHAP-style induction) in fit patients.
- ASCT consolidation in selected eligible patients where BTKi integration is not accessible.
- Rituximab maintenance after ASCT (LYMA pattern).

Position: established pathway. Remains relevant where BTKi-integrated induction is not accessible. Strong evidence quality.

7.2.B Evolving evidence-standard / access-dependent pathway (TRIANGLE)

Following TRIANGLE (Dreyling et al, The Lancet 2024), ibrutinib-integrated induction and maintenance is now a major evidence benchmark for fit patients with newly diagnosed MCL. This approach is not yet uniformly embedded as a routine commissioned UK first-line pathway, but access is increasingly being explored through legitimate non-routine routes, including compassionate access, manufacturer-supported programmes, individual funding mechanisms, clinical trials, or locally approved exceptional pathways. Where available, use should be agreed through lymphoma MDT with explicit documentation of the evidence basis, funding route, patient suitability, toxicity considerations, alternatives, and informed consent.

- TRIANGLE arms: A — R-CHOP/R-DHAP + ASCT (control); A+I — R-CHOP/R-DHAP + ibrutinib + ibrutinib maintenance + ASCT; I — R-CHOP/R-DHAP + ibrutinib + ibrutinib maintenance without ASCT.

- Primary analysis: 3-year failure-free survival 88% in arm A+I versus 72% in arm A (HR 0.52; p = 0.0008). No demonstrated superiority of the ASCT-containing ibrutinib arm over the ibrutinib-without-ASCT arm in available analysis.
- Implication: ibrutinib-integrated induction and 2-year maintenance is the evidence benchmark; the role of upfront ASCT is being redefined in this context.
- Position: practice-changing evidence benchmark; not uniformly commissioned as routine UK first-line. Consider where a legitimate access route exists.

7.2.C High-risk biology / TP53-aberrant pathway

- TP53-mutated MCL has poor outcomes with intensive chemoimmunotherapy and ASCT (Eskelund et al, Blood 2017).
- ASCT should not be relied upon as the primary risk-overcoming strategy.
- Prioritise clinical trial enrolment.
- Consider BTKi-based strategies where accessible (commissioned, compassionate, manufacturer-supported, IFR, or trial).
- Map the CAR-T pathway early — refer to a JACIE-accredited CAR-T centre for forward planning.
- Consider CNS assessment / prophylaxis only where risk features and local policy support it (individualised MDT decision).

7.2.D Historical / not routine

- R-CHOP alone in fit younger patients — historically important comparator; not preferred routine pathway.
- CHOP-like therapy without cytarabine intensification in fit MCL — superseded by cytarabine-containing pathways.
- Automatic ASCT for every fit patient without considering TRIANGLE biology and access — no longer the default.

Position: historically important comparator or fallback only; not preferred as routine decision pathway in modern MDT practice.

7.2 First-Line Fit Pathway — Summary Table

Category	Regimen / approach	Practical status	When to consider	Key caveat
A. Current UK standard / routine	R-CHOP/R-DHAP induction + ASCT consolidation + rituximab maintenance	Established pathway	Where BTKi integration is not accessible	Cytarabine intensification supported by high-quality evidence; ASCT role being redefined
B. Evolving evidence-standard / access-dependent	Ibrutinib-integrated induction + ibrutinib maintenance (TRIANGLE)	Practice-changing evidence benchmark; not uniformly commissioned	Where legitimate access route exists (compassionate, manufacturer, IFR, trial, locally	Document evidence basis, funding route, suitability, toxicity, alternatives,

Category	Regimen / approach	Practical status	When to consider	Key caveat
			approved exceptional)	consent
C. High-risk biology / TP53-aberrant	BTKi-based approaches; clinical trial; early CAR-T pathway planning	Selected pathway for TP53-aberrant or blastoid disease	TP53 mutation, blastoid/pleomorphic, complex karyotype, high MIPI-c with high Ki-67	ASCT should not be relied upon as the primary risk-overcoming strategy
D. Historical / not routine	R-CHOP alone; CHOP without cytarabine; automatic ASCT without biology/access review	Historical or fallback only	Where standard pathways unsuitable and no alternative exists	Not preferred routine decision pathway in modern MDT practice

7.3 Older / Less Fit / Non-Intensive Pathway

Defined as patients unsuitable for cytarabine-containing induction or ASCT. Functional and biological assessment outweighs chronological age.

7.3.A Current UK standard / routine pathway

- Bendamustine-rituximab (BR) — remains the practical standard for many older or less fit patients (StiL trial, Rummel et al).
- Rituximab maintenance after response where appropriate and tolerated.
- R-CHOP — only where BR is contraindicated; vigilance for anthracycline cardiotoxicity.

7.3.B Evolving evidence-standard / access-dependent pathway (ECHO / acalabrutinib + BR)

The phase III ECHO trial (Wang ML et al, Journal of Clinical Oncology 2025;43:2276–2284, PMID 40311141, DOI 10.1200/JCO-25-00690) randomised 598 patients aged 65 years or older with previously untreated MCL to acalabrutinib plus bendamustine-rituximab versus placebo plus bendamustine-rituximab. With a median follow-up of 49.8 months, median progression-free survival was 66.4 months in the acalabrutinib arm versus 49.6 months in the placebo arm (HR 0.73; 95% CI 0.57–0.94; p = 0.016). Overall response was 91.0% (CR 66.6%) versus 88.0% (CR 53.5%). Overall survival was not significantly different. These results led to FDA approval of the combination in January 2025 for adults with previously untreated MCL who are ineligible for autologous HSCT, and European Commission approval on 6 May 2025 for the same transplant-ineligible population (following positive CHMP opinion based on the ECHO Phase III data).

Safety nuance (from FDA prescribing information): in the acalabrutinib + BR arm, serious adverse reactions were reported in approximately 69% of patients and fatal adverse reactions in approximately 12%. Common adverse reactions (≥ 15%) included rash, COVID-19, fatigue, diarrhoea, pneumonia, headache, upper respiratory infection, pyrexia, cough, vomiting, constipation, haemorrhage, oedema, second primary malignancy, dizziness, arthralgia, and dyspnoea. Although toxicity was considered manageable in the trial context, serious and fatal adverse reactions were reported; UK adoption should therefore depend on NICE appraisal, patient fitness, infection risk, comorbidity, and local governance.

- NICE appraisal (GID-TA11091, ID6155): in development for acalabrutinib with bendamustine and rituximab for untreated MCL. Expected publication date 4 June 2026 (may be rescheduled). https://www.nice.org.uk/guidance/indevelopment/gid-ta11091
- Position: practice-informing phase III evidence with FDA / EU approval, but not adopted as routine UK standard until NICE final guidance and local commissioning are in place.
- Other BTKi-BR approaches should be discussed cautiously and not assumed standard.

7.3.C Selected alternatives / frailty pathway

- R-CHOP where BR is contraindicated.
- Palliative / attenuated approaches in frail patients.
- Single-agent or low-intensity approaches only in selected frail or palliative contexts.
- Integrate clinical nurse specialist input, pharmacy review, infection prevention, transfusion support, and specialist palliative care where appropriate, with clear treatment-escalation boundaries.

7.3.D Historical / not routine

- Routine frontline ibrutinib + BR (SHINE pattern, Wang et al, NEJM 2022;386:2482–2494) is not adopted as UK standard. PFS benefit (6.7 vs 4.4 years) without OS advantage and with excess atrial fibrillation, bleeding, and pneumonia.
- VR-CAP (LYM-3002, Robak et al, NEJM 2015) — rarely used in UK and not generally NICE-funded for first-line MCL.
- R-squared (rituximab + lenalidomide) — should not be presented as routine UK first-line unless a live funding route exists.

7.3 First-Line Older / Less Fit Pathway — Summary Table

Category	Regimen / approach	Practical status	When to consider	Key caveat
A. Current UK standard / routine	Bendamustine-rituximab; rituximab maintenance where appropriate; R-CHOP if BR contraindicated	Established pathway	Most older or less fit patients	Match intensity to fitness and comorbidity
B. Evolving evidence-standard / access-dependent	Acalabrutinib + BR (ECHO)	Phase III PFS benefit; NICE appraisal GID-TA11091 in development	Awaiting NICE / local commissioning	Not adopted as routine UK standard until NICE final guidance
C. Selected alternatives / frailty	R-CHOP where BR contraindicated; attenuated / palliative approaches; supportive care	Selected pathway	Frailty, comorbidity, palliative intent	Goals-of-care discussion essential
D. Historical / not routine	Frontline ibrutinib + BR (SHINE); VR-CAP; R-squared in first-line	Not adopted as UK routine standard	Trial / exceptional / individual funding only	SHINE: no OS benefit, excess toxicity

7.4 First-Line Summary by Clinical Group

Clinical group	Default practical pathway	Evolving / access-dependent option	Avoid / not routine	MDT documentation point
Indolent / non-nodal	Observation (watch and wait)	n/a — observation is the default	Treating on lymphocytosis alone	Document indolent phenotype: SOX11−, IGHV mutated, leukaemic non-nodal, low Ki-67
Fit standard-risk	R-CHOP/R-DHAP + ASCT + rituximab maintenance	TRIANGLE — ibrutinib-integrated induction + maintenance (where access available)	Automatic ASCT without biology/access review	Document evidence benchmark, access route, alternatives, consent
Fit high-risk / TP53-aberrant	BTKi-based pathway where accessible; trial enrolment; CAR-T centre referral	TRIANGLE-style with BTKi maintenance; early CAR-T mapping	Reliance on ASCT to overcome TP53	Document TP53 status, trial discussion, CAR-T pathway
Older / less fit	Bendamustine-rituximab (± rituximab maintenance)	Acalabrutinib + BR (ECHO; NICE in development)	Routine frontline ibrutinib + BR (SHINE)	Document fitness, comorbidity, access route if non-routine
Frail / palliative	Attenuated / supportive approach; R-mini regimens; symptom control	n/a — focus on goals of care	Intensive cytarabine-based therapy	Document goals-of-care discussion and consent
Blastoid / pleomorphic	Intensive pathway in fit patients; consider CNS assessment	TRIANGLE-style BTKi-integrated approach where accessible; early CAR-T mapping	Standard chemoimmunotherapy alone without biology consideration	Document morphological variant, CAR-T pathway

7.5 MDT Documentation Checklist (First-Line)

- Diagnosis and morphological variant confirmed.
- Ki-67 proliferation index recorded as percentage.
- TP53 mutation status by NGS, with TP53 IHC pattern.
- SOX11 and IGHV status if indolent phenotype suspected.
- MIPI and MIPI-c calculated and recorded.
- Fitness / frailty assessment (ECOG, Clinical Frailty Scale).
- Renal function (eGFR) and cardiac assessment.
- Intended pathway category: routine / evolving access-dependent / selected alternative / not routine.
- Funding / access route identified (NICE-commissioned, compassionate, manufacturer-supported, IFR, EAMS, clinical trial, locally approved exceptional pathway).
- Evidence basis identified.
- Alternatives discussed.

- Toxicity, drug interaction, and infection risk reviewed.
- Patient preference and informed consent documented.
- CAR-T centre discussion documented where high-risk or relapse planning is relevant.

7.6 CNS Prophylaxis

Evidence supporting CNS prophylaxis in MCL is limited and largely extrapolated from aggressive B-cell lymphoma practice. Routine CNS prophylaxis is not recommended for all patients. Decisions should be individualised and documented at MDT, balancing blastoid / pleomorphic morphology, high MIPI with high Ki-67, TP53 abnormality, CNS symptoms, renal function, and patient fitness for high-dose methotrexate. Where prophylaxis is considered appropriate, options include intrathecal methotrexate during induction or systemic high-dose methotrexate, balanced carefully against patient fitness, renal function, and competing toxicity risks. The MDT decision and rationale should be explicitly documented.

8. Relapsed and Refractory MCL

Clinical Vignette

A 71-year-old man treated 22 months ago with six cycles of bendamustine-rituximab for stage IV MCL (MIPI intermediate, Ki-67 25%, TP53 wildtype) presents with new cervical lymphadenopathy and rising LDH. He has well-controlled atrial fibrillation on apixaban and an eGFR of 58 mL/min. He has had no prior BTKi exposure. What is the next step?

Action: Re-biopsy the dominant node. Repeat TP53 by NGS (clonal evolution at relapse). PET-CT to exclude bulky / unexpected disease. Refer the case to lymphoma MDT. Anticipate covalent BTKi at first relapse under NICE TA502 (ibrutinib) or TA1081 (zanubrutinib) — TA1081 directs the use of the least-expensive option. Discuss anticoagulant interaction risk (favour selective BTKi where AF / bleeding risk material). At the same MDT, prospectively flag the case for the local JACIE CAR-T centre so the post-BTKi pathway is mapped before the next failure.

Relapse occurs in the majority of patients despite contemporary therapy. Therapeutic options have been redefined by covalent BTK inhibitors, BTKi-BCL2 combination, non-covalent BTKi, and CAR-T cell therapy.

8.1 Principles at Relapse

- Re-biopsy the dominant lesion where feasible to confirm relapse, exclude transformation, and reassess TP53 and Ki-67.
- Re-stage with CT and PET-CT; consider CSF analysis if blastoid relapse or neurological features.
- Document time from prior therapy, prior agents, response duration, and current organ function.
- Early discussion with a CAR-T-capable centre is advised at first relapse for fit patients, given pathway timelines.

8.2 Second-Line Therapy: Covalent BTK Inhibitors

Covalent BTK inhibitors are the standard backbone of second-line therapy. In the UK, two covalent BTKi are NICE-recommended for adults with relapsed or refractory MCL who have had one previous line of treatment only:

- **Ibrutinib (NICE TA502):** Published 31 January 2018, last reviewed 8 July 2021. Recommended for adults with R/R MCL who have had only one previous line of therapy, subject to the commercial access agreement with NHS England.
- **Zanubrutinib (NICE TA1081):** Published 10 July 2025. Recommended for adults with R/R MCL who have had one previous line of treatment only, subject to the simple discount patient access scheme. NICE directs healthcare providers to use the least-expensive option of the suitable treatments (zanubrutinib and ibrutinib), having discussed the advantages and disadvantages with the patient. Zanubrutinib must be funded in England within 30 days of final publication.

Practical UK choice between ibrutinib and zanubrutinib should consider: NICE TA1081 least-expensive-option directive, comorbidity, cardiovascular and bleeding risk profile, drug interactions, prior cardiac history, anticoagulation, and local formulary position. Zanubrutinib has a more favourable cardiovascular toxicity profile than ibrutinib in head-to-head data in other indications (e.g. ALPINE in CLL).

Acalabrutinib is not currently NICE-recommended in MCL; access in MCL should be verified locally. [VERIFY current TA status for acalabrutinib in MCL]

Agent	Class	Key UK Considerations
Ibrutinib	Covalent BTKi (first generation)	NICE TA502: R/R MCL after one prior line, subject to commercial access agreement. Higher rates of AF, bleeding, hypertension. CYP3A interactions.
Zanubrutinib	Covalent BTKi (selective, second generation)	NICE TA1081 (10 July 2025): R/R MCL after one prior line. NICE directs use of the least-expensive option of zanubrutinib or ibrutinib. Favourable cardiovascular profile relative to ibrutinib.
Acalabrutinib	Covalent BTKi (selective)	Lower off-target toxicity than ibrutinib. Not currently NICE-recommended in MCL — access in MCL should be verified locally. [VERIFY]

8.3 BTKi Combinations: Ibrutinib plus Venetoclax (SYMPATICO)

The SYMPATICO trial (Wang et al, Lancet Oncology 2025;26(2):200–213) randomised 267 patients with relapsed or refractory MCL after one to five prior lines to ibrutinib plus venetoclax versus ibrutinib plus placebo. Median progression-free survival was 31.9 months with the combination versus 22.1 months with ibrutinib alone (hazard ratio 0.65; p = 0.0052). Tumour lysis risk requires standard venetoclax ramp-up. The combination is not currently routinely NICE-funded for MCL; UK access may be limited to clinical trials or individual funding arrangements. [VERIFY current UK access]

8.4 Non-Covalent BTK Inhibition: Pirtobrutinib

Pirtobrutinib is a reversible, non-covalent BTK inhibitor with clinically important activity in patients whose disease has progressed on covalent BTKi exposure. The BRUIN MCL-321 and broader BRUIN dataset demonstrate clinically meaningful response rates in this otherwise high-risk population.

Routine UK NHS access should not be assumed. As of May 2026, NICE appraisal status for pirtobrutinib in MCL is uncertain: one appraisal (ID3975, R/R MCL) is reported as suspended pending the company's evidence submission, and a separate appraisal (ID6493, R/R MCL in BTKi-untreated patients) is in development with publication date to be confirmed. UK access at the point of decision-making may therefore depend on NICE final publication, local formulary approval, compassionate access, EAMS, clinical trial enrolment, or Individual Funding Request routes. [VERIFY current NICE / NHS access status before prescribing]

8.5 CAR-T Cell Therapy

Brexucabtagene Autoleucel (KTE-X19)

ZUMA-2 (Wang et al, New England Journal of Medicine 2020;382(14):1331–1342) established brexucabtagene autoleucel as a redefining option in relapsed or refractory MCL after BTKi failure. The primary efficacy analysis reported an objective response rate of 93% with a complete response rate of 67%; three-year follow-up confirmed durable responses in a substantial proportion of patients. NICE Technology Appraisal TA677 recommends brexucabtagene autoleucel within the Cancer Drugs Fund for adults with relapsed or refractory MCL who have previously received a BTK inhibitor, subject to the managed access agreement.

Important caution: a NICE review of TA677 (for brexucabtagene autoleucel in R/R MCL after two or more systemic treatments) is currently in development. CAR-T access is particularly sensitive to NICE managed

access reviews and commissioning updates. Before referral or publication, confirm the current NHS England and NICE position for brexucabtagene autoleucel — including whether TA677 remains active, has been superseded, restricted, or remains under managed access review. [VERIFY current TA677 status]

Lisocabtagene Maraleucel

TRANSCEND NHL 001 and the dedicated MCL cohort have reported clinically meaningful activity for lisocabtagene maraleucel in relapsed or refractory MCL, with a potentially differentiated tolerability profile. UK access status should be verified at the point of referral. [VERIFY UK access]

CAR-T Pathway Practical Points

Refer eligible patients to a JACIE-accredited CAR-T centre at first relapse rather than waiting for further treatment failures.

Bridging therapy (often BTKi or low-dose chemotherapy) is commonly required between leukapheresis and lymphodepletion.

Manage cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) per local CAR-T protocols.

Long-term follow-up requires shared care between the CAR-T centre and referring haematology team, including infection prophylaxis and immunoglobulin replacement.

8.6 Other Options

- Lenalidomide (with or without rituximab) in BTKi-exposed, CAR-T-ineligible patients.
- Bendamustine-rituximab if not used in first line.
- Bortezomib in selected patients.
- Allogeneic stem cell transplant for fit patients with chemosensitive disease, particularly post-CAR-T relapse or in young patients with TP53-mutated disease in remission.
- Clinical trial enrolment should be offered whenever available.

8.7 Sequencing Principles

- Preserve BTKi for relapse where possible if not used in first line; if used in first line, consider non-covalent BTKi or CAR-T at relapse.
- CAR-T eligibility window is finite — do not delay referral to assess multiple sequential lines first.
- Allogeneic transplant remains an option for selected younger patients, especially post-CAR-T failure or as definitive consolidation in selected TP53-mutated patients in good response.

8.8 UK Commissioning Status Summary

The following summary separates evidence position from current UK NICE / NHS England commissioning. Evidence-supported does not equal NHS-commissioned. Verify current NICE position before every prescribing or referral decision.

Intervention	Evidence position	Current UK / NICE position (May 2026)	Practical action
Ibrutinib (R/R MCL)	Established covalent BTKi	NICE TA502 — recommended after 1	Confirm CAA, local pathway, and least-

Intervention	Evidence position	Current UK / NICE position (May 2026)	Practical action
		prior line, subject to commercial access agreement	expensive-option logic per TA1081
Zanubrutinib (R/R MCL)	Covalent BTKi with favourable cardiovascular tolerability profile	NICE TA1081 (10 July 2025) — recommended after 1 prior line; use least-expensive of zanubrutinib or ibrutinib	Implement per TA1081; confirm local formulary uptake
Acalabrutinib (R/R MCL)	Selective covalent BTKi	Not currently NICE-recommended in MCL — UK access uncertain	Verify locally; consider trial or alternative funding route [VERIFY]
Acalabrutinib + BR (first-line older)	Phase III ECHO: PFS benefit (66.4 vs 49.6m, HR 0.73); no OS benefit yet	NICE appraisal in this indication pending; full peer-reviewed publication pending	Do not present as routine UK practice until NICE final guidance
Ibrutinib-integrated induction (TRIANGLE)	Phase III: practice-changing evidence benchmark in fit patients	Not yet uniformly commissioned as routine UK first-line; emerging non-routine access (compassionate, manufacturer, IFR, trials)	MDT discussion with explicit access route and consent; consider compassionate or trial pathways where available
Ibrutinib + venetoclax (SYMPATICO, R/R)	Phase III: PFS benefit (31.9 vs 22.1m, HR 0.65)	Not routinely NICE-funded for MCL	Trial or individual funding routes only [VERIFY]
Pirtobrutinib	Active post-covalent-BTKi (BRUIN)	NICE appraisal ID3975 reported as suspended; ID6493 (BTKi-untreated R/R) in development	Trial, EAMS, compassionate, or IFR routes only unless funded; verify before prescribing [VERIFY]
Brexucabtagene autoleucel	Phase II ZUMA-2: ORR 93%, CR 67%	NICE TA677 (within CDF, post-BTKi); review of TA677 in development	Early referral to JACIE CAR-T centre; verify current TA677 status [VERIFY]
Lisocabtagene maraleucel (MCL)	TRANSCEND NHL 001 MCL cohort: clinically meaningful activity	UK access status uncertain	Verify locally and at referral [VERIFY]

Evidence vs Access — Core Principle

Evidence-supported does not equal NHS-commissioned.

Each systemic therapy recommendation should be interpreted through NICE guidance, NHS England specialised commissioning, local formulary approval, trial availability, and patient-specific suitability.

Items marked [VERIFY] must be cross-checked against the current NICE register and NHS England commissioning position at the time of prescribing or publication.

9. Supportive Care

9.1 Infection Prophylaxis

- Pneumocystis jirovecii prophylaxis (co-trimoxazole) during and after R-CHOP/R-DHAP, bendamustine-rituximab, BTKi, and CAR-T pathways per local policy.
- Antiviral prophylaxis (aciclovir or valaciclovir) during BTKi therapy and CAR-T pathways.
- Antifungal prophylaxis as per local risk assessment, particularly during prolonged neutropenia or steroid exposure.
- Hepatitis B reactivation screening and entecavir or tenofovir prophylaxis in HBsAg-positive or anti-HBc-positive patients receiving rituximab.

9.2 Immunoglobulin Replacement

Hypogammaglobulinaemia is common after rituximab-based therapy, BTKi, and CAR-T. Intravenous or subcutaneous immunoglobulin replacement should be considered for recurrent or severe bacterial infections in line with the UK Department of Health and Social Care commissioning criteria for immunoglobulin use.

9.3 Vaccination

- Annual inactivated influenza vaccine.
- Pneumococcal vaccination (PCV13 followed by PPSV23 per UK Green Book schedule).
- SARS-CoV-2 vaccination per current UK immunisation schedule, recognising blunted response post-rituximab and post-CAR-T.
- Avoid live vaccines during active immunosuppression.

9.4 Cardiovascular Surveillance (BTKi)

- Baseline ECG and blood pressure before BTKi initiation.
- Screen and manage atrial fibrillation; switch from ibrutinib to a more selective BTKi where AF or major bleeding emerges.
- Caution with concurrent anticoagulants; avoid concurrent vitamin K antagonists with ibrutinib.
- Manage hypertension actively during BTKi therapy.

9.5 Thromboprophylaxis

- Apply standard hospital VTE risk assessment in inpatient settings.
- Recognise bleeding risk with BTKi, particularly with antiplatelet or anticoagulant co-prescription.
- Hold BTKi for at least 3–7 days before and after major surgery (consult relevant SmPC and local policy).

9.6 Regimen-Specific Supportive Care

Treatment	Key risks	Minimum supportive care
Bendamustine-rituximab	Prolonged T-cell suppression, infection risk	PJP prophylaxis per local policy, antiviral prophylaxis, HBV screen and prophylaxis if indicated, immunoglobulin monitoring

Treatment	Key risks	Minimum supportive care
BTKi (ibrutinib, zanubrutinib)	Bleeding, atrial fibrillation, hypertension, infection, drug interactions	Baseline ECG and BP, cardiac history review, anticoagulant / antiplatelet review, CYP3A interaction check, ongoing BP monitoring, infection surveillance
R-CHOP	Anthracycline cardiotoxicity, infection, neuropathy	Baseline echocardiogram, infection prophylaxis, neurological assessment, antiemetics
CAR-T (brexucabtagene autoleucel, lisocabtagene maraleucel)	CRS, ICANS, cytopenias, hypogammaglobulinaemia, late infection	CAR-T centre protocol for CRS/ICANS, prolonged infection prophylaxis, immunoglobulin monitoring and replacement, revaccination plan, shared-care arrangement with referring centre
Rituximab maintenance	HBV reactivation, hypogammaglobulinaemia, late infection	HBV screening and prophylaxis where indicated, immunoglobulin monitoring with replacement if recurrent infection, vaccination plan

9.7 Psychosocial and Survivorship

- Clinical nurse specialist allocation at diagnosis.
- Macmillan Recovery Package needs assessment.
- Late effects clinic referral for long-term survivors of intensive therapy or ASCT.
- Fertility discussion and referral to assisted conception services for young patients prior to therapy.

10. Surveillance

There is no high-quality evidence to support imaging surveillance over symptom-driven assessment in asymptomatic patients in remission. Routine PET-CT surveillance is not recommended.

- Clinical review every 3 months for the first 2 years, then every 6 months until 5 years, then annually.
- FBC, U&E, LFT, LDH at each visit.
- Imaging guided by clinical suspicion of relapse, new symptoms, or unexplained laboratory abnormalities.
- MRD monitoring may be considered in clinical trial contexts but should not currently drive routine treatment decisions outside trials.

11. UK NHS Implementation

11.1 Service Configuration

- All new MCL diagnoses should be discussed at a specialist lymphoma multidisciplinary team meeting before treatment initiation.
- Patients potentially eligible for CAR-T should be flagged at diagnosis and re-flagged at relapse to a JACIE-accredited CAR-T centre.
- Centres without on-site CAR-T capability should have established referral pathways to commissioned UK CAR-T centres.
- Pharmacy and clinical trials infrastructure should be in place for BTKi initiation and monitoring.

11.2 Funding and Access

- NICE TA approvals form the baseline of NHS access; Blueteq registrations are required for high-cost drugs in NHS England.
- Cancer Drugs Fund and Innovative Medicines Fund may provide interim access pending full NICE appraisal.
- Individual Funding Requests (IFR) may be considered for exceptional cases; documented clinical exceptionality is required.
- Devolved nations: equivalent processes via SMC (Scotland), AWMSG (Wales), and HSCNI (Northern Ireland) should be referenced.

11.3 Clinical Trials

- Trial enrolment should be considered at every line of therapy, particularly for TP53-mutated disease, post-CAR-T relapse, and elderly patients seeking less intensive options.
- National trials portfolio coordinated through the National Cancer Research Institute and the British Society for Haematology's haemato-oncology subgroup.

12. How to Use This Guideline in MDT

This guideline is intended to support MDT-led decision-making, not replace it. A consistent operational workflow improves quality, reduces variability, and supports audit and governance.

- Confirm diagnosis, morphological variant, and full pathology minimum dataset (Section 5.3).
- Assign MIPI and MIPI-c.
- Confirm TP53 molecular status (NGS) and TP53 IHC pattern.
- Assign an MDT risk category (Section 6.6): standard, indolent, high-risk, TP53-aberrant, or blastoid/pleomorphic.
- Define treatment intent: observe, standard first-line, high-risk first-line, relapse pathway, or trial.
- Check current NICE / NHS England commissioning status and local formulary.
- Document trial availability and CAR-T pathway discussion where relevant.
- Document the chosen access route where non-routine: compassionate, manufacturer-supported, IFR, EAMS, or clinical trial.

Minimum MDT Dataset

Each MDT discussion of MCL should record:

- Age, ECOG performance status, frailty score.
- Stage, bulk, LDH, white cell count.
- Ki-67 percentage.
- TP53 mutation status (NGS) and TP53 IHC pattern.
- Morphological variant.
- SOX11 and IGHV phenotype if indolent disease suspected.
- Previous therapy and response duration (at relapse).

- BTKi exposure (at relapse).
- CAR-T eligibility status.
- Infection risk and HBV / HCV / HIV status.
- Current NICE-commissioned treatment option(s) considered.
- Trial availability and patient preference.

Patient Consent and Shared Decision-Making for Non-Routine Access

For non-routine, compassionate, manufacturer-supported, IFR-funded, or trial-associated access, patients should be counselled regarding evidence maturity, funding route, uncertainty, toxicity, alternatives, and the effect on subsequent therapy options. The discussion should be documented in the MDT record and clinic letter.

- Evidence basis and maturity of the proposed approach (peer-reviewed full publication versus conference abstract versus emerging signal).
- Funding / access route and any time-limited or conditional elements of that route.
- Uncertainty (including unknowns about long-term efficacy and toxicity in the specific subgroup).
- Toxicity profile and monitoring requirements.
- Alternatives, including standard commissioned pathways and clinical trial enrolment.
- Effect on subsequent therapy options (e.g. later BTKi, CAR-T eligibility, or trial enrolment).
- Patient preference, performance status, comorbidity, and frailty.
- Documentation in the MDT outcome and the clinic letter.

Devolved Nations

NICE and NHS England positions are used as the principal access reference. Implementation may differ in Scotland, Wales and Northern Ireland; clinicians should check SMC, AWMSG, HSCNI and local formulary positions where relevant.

- Scotland — Scottish Medicines Consortium (SMC) recommendations and NHS Scotland commissioning.
- Wales — All Wales Medicines Strategy Group (AWMSG) and NHS Wales commissioning.
- Northern Ireland — Health and Social Care Northern Ireland (HSCNI) commissioning.

Devolved-nation status for each named therapy should be checked locally at the time of prescribing or referral.

13. Audit Standards and Key Performance Indicators

Indicator	Standard	Numerator/Denominator
TP53 testing at diagnosis	≥ 95%	Patients with documented TP53 result / All new MCL diagnoses
MDT discussion before treatment	100%	Patients with documented MDT outcome / All new MCL diagnoses

Indicator	Standard	Numerator/Denominator
Time from diagnosis to first treatment (symptomatic disease)	≤ 31 days	Patients meeting standard / All patients requiring treatment
CNS evaluation in blastoid or high-risk disease	≥ 90%	Patients with documented CNS assessment / Eligible patients
Rituximab maintenance offered post-ASCT	≥ 95%	Patients offered RM / Patients completing ASCT in remission
BTKi consideration at first relapse	≥ 95%	Patients considered for BTKi / All first-relapse patients
CAR-T centre referral at BTKi failure (eligible patients)	≥ 90%	Patients referred / BTKi-failure patients fit for CAR-T
Infection prophylaxis prescribed where indicated	≥ 95%	Patients with appropriate prophylaxis / Eligible patients
Vaccination plan documented	≥ 90%	Patients with documented plan / All patients on therapy

14. Limitations and Caveats

- This document is not a prescribing protocol and should not be used as the sole authority for treatment selection, funding approval, dose modification, toxicity management, or consent.
- Clinicians must confirm current NICE guidance, NHS England commissioning criteria, local formulary approval, SmPC requirements, trial eligibility, and patient-specific factors before treatment.
- This guideline does not substitute for individualised clinical decision-making within a lymphoma MDT.
- UK regulatory positions evolve; users should confirm current NICE TA status, Cancer Drugs Fund and Innovative Medicines Fund listings, and devolved-nation approvals at the time of prescribing.
- Items marked [VERIFY] must be cross-checked before public deployment or clinical citation.
- Items marked [EMERGING] are not considered practice-changing under current UK frameworks and should not drive routine clinical decisions.
- Evidence in MCL is moving rapidly; the next scheduled review of this guideline is May 2028, or earlier if practice-changing evidence emerges.

AI Use, Conflicts of Interest, and External Endorsement

- **AI use:** AI was used to assist drafting and structuring this document. The author is responsible for clinical verification before publication. All treatment recommendations and regulatory statements should be checked against primary sources, NICE, SmPCs, and local commissioning pathways before use. AI was not used to fabricate, infer, or extrapolate clinical data, trial findings, or regulatory positions.
- **Conflicts of interest:** None declared by the author at the time of writing.
- **External endorsement:** This is an independent educational synthesis produced by Mohsin Haematology Academy. It is not a NICE, BSH, NHS England, ESMO, or NCCN guideline and has not been externally endorsed unless explicitly stated in writing.

- **External review:** Status and reviewer names to be added if external peer review is undertaken before publication.

15. Emerging Evidence (Practice-Informing, Not Routine)

Emerging evidence is included for consultant-level awareness and may inform MDT discussion, trial referral, or access planning, but should not be used as the sole basis for routine treatment outside approved access routes.

> **Emerging Section — Use with Caution**
>
> The following items are flagged as [EMERGING] and should not be relied upon for routine clinical practice or commissioning decisions until peer-reviewed publication and UK regulatory confirmation. They are included to support consultant-level awareness of the direction of travel.
>
> User to verify and cross-discuss before deployment to the public-facing site.

14.1 ECHO Trial (Detailed Data Now Reported in Section 7.3)

ECHO phase III data (acalabrutinib + bendamustine-rituximab versus placebo + bendamustine-rituximab in patients ≥65) demonstrated a progression-free survival benefit (66.4 versus 49.6 months, HR 0.73; p = 0.0160) with no statistical overall survival difference at the reported follow-up. Status in the UK: full peer-reviewed publication pending; FDA priority review granted October 2024; NICE appraisal in this indication should be checked before adoption. [EMERGING — pending UK access decision]

14.2 Bispecific T-Cell Engagers

Glofitamab and epcoritamab have shown activity in heavily pre-treated MCL in early-phase studies and dedicated MCL cohorts. May offer an off-the-shelf alternative to CAR-T in selected patients. Status: not yet UK-approved in MCL. [EMERGING]

14.3 MRD-Guided Strategies

Trials exploring MRD-guided maintenance duration, treatment de-escalation, and pre-emptive intervention at MRD relapse are ongoing. Outside trials, MRD remains prognostic rather than predictive of intervention benefit. [EMERGING]

14.4 Combination Strategies

Triplet combinations including BTKi, anti-CD20, and venetoclax (e.g. SYMPATICO-style combinations expanded to first line), and BTKi plus lenalidomide plus rituximab, are under investigation. Status: not yet standard of care. [EMERGING]

14.5 ASH/EHA 2024–2025 Conference Signals

Several abstracts have explored second-generation BTKi-based induction, fixed-duration combinations, and refinement of CAR-T sequencing. The user is advised to review the relevant ASH 2025 plenary and parallel haematology sessions directly when finalising this document. [EMERGING — VERIFY before citation]

16. References (Selected and Graded)

References are listed by hierarchy of authority and selected for direct relevance to recommendations made above.

UK and Society Guidelines

- Eyre TA, Bishton MJ, McCulloch R, O'Reilly M, Sanderson R, Menon G, Iyengar S, Lewis D, Lambert J, Linton KM, McKay P. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. British Journal of Haematology 2024;204(1):108–126. [A1]
- McKay P, Leach M, Jackson B, Ashley S, Townes C, Hopkins R, McCarthy K, Wilkins B, Eyre TA, Bishton MJ. Guideline for the management of mantle cell lymphoma. British Journal of Haematology 2018;182(1):46–62 (predecessor guideline, now superseded by Eyre et al 2024). [A1]
- Dreyling M, Campo E, Hermine O et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology (multiple editions). [A1]
- National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: B-Cell Lymphomas — current version (verify against latest update). [A1]
- NICE Technology Appraisal TA502: Ibrutinib for treating relapsed or refractory mantle cell lymphoma. Published 31 January 2018, last reviewed 8 July 2021. https://www.nice.org.uk/guidance/ta502. [A1]
- NICE Technology Appraisal TA1081: Zanubrutinib for treating relapsed or refractory mantle cell lymphoma in adults who have had 1 line of treatment only. Published 10 July 2025. https://www.nice.org.uk/guidance/ta1081. [A1]
- NICE Technology Appraisal TA677: Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma (within Cancer Drugs Fund, post-BTKi). Review of TA677 in development at the time of writing. https://www.nice.org.uk/guidance/ta677. [A1]
- NICE appraisal ID3975 (Pirtobrutinib for treating relapsed or refractory mantle cell lymphoma) — reported as suspended pending company evidence submission as of May 2026. https://www.nice.org.uk/guidance/indevelopment/gid-ta10858. [A1]
- NICE appraisal ID6493 (Pirtobrutinib for treating relapsed or refractory mantle cell lymphoma untreated with a BTK inhibitor) — in development. https://www.nice.org.uk/guidance/awaiting-development/gid-ta11639. [A1]

Key Trials and Prognostic Biomarkers

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- Hoster E, Rosenwald A, Berger F et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the European MCL Network. Journal of Clinical Oncology 2016. [A2]
- Eskelund CW, Dahl C, Hansen JW et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood 2017;130(17):1903–1910. DOI 10.1182/blood-2017-04-779736. [A2]

- Geisler CH, Kolstad A, Laurell A et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support. British Journal of Haematology. [A2]
- Hermine O, Hoster E, Walewski J et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial. Lancet. [A2]
- Le Gouill S, Thieblemont C, Oberic L et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. New England Journal of Medicine 2017;377:1250–1260 (LYMA / LyMa, LYSA group). PMID 28953447. DOI 10.1056/NEJMoa1701769. [A2]
- Rummel MJ, Niederle N, Maschmeyer G et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet (StiL). [A2]
- Robak T, Huang H, Jin J et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. New England Journal of Medicine, 2015 (LYM-3002 / VR-CAP). [A2]
- Wang ML, Jurczak W, Jerkeman M et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. New England Journal of Medicine 2022;386:2482–2494 (SHINE). PMID 35657079. DOI 10.1056/NEJMoa2201817. [A2]
- Dreyling M, Doorduijn JK, Gine E et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma: a randomised, open-label, three-arm, phase 3 superiority trial. The Lancet 2024 (TRIANGLE, European MCL Network). PMID 38705160. [A2]
- Wang ML, Munoz J, Goy A et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. New England Journal of Medicine 2020;382(14):1331–1342 (ZUMA-2). Three-year follow-up: Wang ML et al, Journal of Clinical Oncology, PMID 35658525. [A2]
- Wang ML, Jurczak W, Zinzani PL et al. Pirtobrutinib in covalent BTK inhibitor pre-treated mantle-cell lymphoma. Journal of Clinical Oncology and subsequent BRUIN / BRUIN MCL-321 publications. [A2]
- Wang ML, Jurczak W, Cohen JB et al. Ibrutinib plus venetoclax in relapsed or refractory mantle cell lymphoma (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. The Lancet Oncology 2025;26(2):200–213. PMID 39914418. [A2]
- Wang ML et al. Acalabrutinib plus bendamustine-rituximab in untreated mantle cell lymphoma (ECHO). Journal of Clinical Oncology 2025;43:2276–2284. PMID 40311141. DOI 10.1200/JCO-25-00690. [A2]
- NICE appraisal GID-TA11091 (ID6155): Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma — in development. https://www.nice.org.uk/guidance/indevelopment/gid-ta11091. Expected publication 4 June 2026 (may be rescheduled). [A1]

Cross-Reference Resources

- NHS England Clinical Commissioning Policy documents on CAR-T cell therapy in B-cell lymphomas. [A1]
- UK Joint Council for the Cellular Therapy of Adults (JACIE) standards. [A1]

- British Society for Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) standards and guidance. [A1]

17. How to Cite This Guide

Update the access year to the year you are reading and citing this guide.

Vancouver

Mohsin M. Mantle Cell Lymphoma — UK Practice-Oriented Evidence Guide. Mohsin Haematology Academy; 2026. Available from: https://mohsinhaemacademy.com/guidelines/mcl/

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Mohsin, M. (2026). Mantle Cell Lymphoma — UK Practice-Oriented Evidence Guide. Mohsin Haematology Academy. https://mohsinhaemacademy.com/guidelines/mcl/

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Citation etiquette: when you cite this guide to inform a clinical discussion, please also cite the primary BSH, NICE, ESMO, NCCN, and trial sources listed in the References section. This guide is a synthesis, not a primary source.

18. Consultant-Grade Synthesis

Consultant-Grade One-Line Synthesis

In 2026 UK MCL practice, every patient should receive TP53 mutation testing at diagnosis, a documented MDT risk category, and an explicit evidence-versus-access conversation: BTKi-integrated induction is the TRIANGLE-anchored evidence benchmark for the fit, bendamustine-rituximab remains the unfit-patient backbone, ASCT is critically re-evaluated rather than relied upon — especially in TP53-mutated disease — and BTKi at first relapse plus an early CAR-T pathway conversation define the survival-shaping decisions, not late-line salvage.