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Bridging the Gap: A Latin American Expert Consensus on Mantle Cell Lymphoma Management

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Abstract:
Background: Mantle cell lymphoma (MCL) management in Latin America is shaped by heterogeneous healthcare infrastructure, fragmented diagnostic access, and restricted availability of novel therapeutic agents. International guidelines developed for resource-rich settings create implementation gaps that directly affect patient outcomes across low- and middle-income countries globally. Methods: A modified Delphi consensus was conducted with 39 experts: 35 specialists (32 based in Latin America and 3 working internationally) and 4 internationally recognized MCL experts from the United States and Spain. Recommendations required ≥80% agreement across two iterative voting rounds. Evidence was graded using adapted GRADE methodology (A–D quality, 1–2 strength). Consensus positions were contextualized against the LATAM-GELL retrospective cohort (N=247 patients, 9 countries, 2015–2024). Results: Thirty-nine GRADE-rated recommendations were formulated across four domains: diagnosis and risk stratification, first-line treatment for transplant-eligible patients, relapsed/refractory disease management, and treatment of elderly or unfit patients. Key positions include: (1) consolidative ASCT followed by rituximab maintenance remains standard of care when continuous BTK inhibitor access is uncertain, supported by LATAM-GELL data showing median OS of 9.9 vs. 4.5 years (HR 2.7, 95% CI 1.43–5.13; p=0.002); (2) rituximab maintenance is the single most underutilized high-impact intervention in the region; (3) p53 immunohistochemistry is endorsed as a pragmatic surrogate for TP53 assessment where NGS is unavailable; and (4) a stepwise algorithm is proposed for relapsed/refractory MCL without CAR-T access. Conclusions: This consensus provides the first comprehensive, resource-adapted framework for MCL management developed by and for hematologists in Latin America and other resource-limited settings globally, complementing existing international guidelines.

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Bridging the Gap: Expert Consensus Recommendations for Mantle Cell Lymphoma Management in Resource-Limited Settings, A Latin American and International Panel

Latin American Lymphoproliferative Study Group (GELL)

39 Experts from 13 Countries | June 2025 – January 2026

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ABSTRACT

Background: Mantle cell lymphoma (MCL) management in Latin America is profoundly shaped by heterogeneous healthcare infrastructure, fragmented diagnostic access, and restricted availability of novel therapeutic agents. International guidelines developed for resource-rich settings create critical implementation gaps that directly affect patient outcomes across low- and middle-income countries globally.

Methods: A modified Delphi consensus was conducted with 39 experts: 35 specialists (32 based in Latin America and 3 of Latin American origin working internationally) and 4 internationally recognized MCL experts from the United States and Spain. Recommendations required ≥80% agreement across up to two iterative voting rounds. Evidence was graded using adapted GRADE methodology (A–D quality, 1–2 strength). Consensus positions were contextualized against findings from the LATAM-GELL retrospective cohort (N=247 patients, 9 countries, 2015–2024), providing real-world regional validation.

Results: Thirty-nine GRADE-rated recommendations were formulated across four domains: diagnosis and risk stratification, first-line treatment for transplant-eligible patients, relapsed/refractory disease management, and treatment of elderly or unfit patients. Key positions include: (1) consolidative autologous stem cell transplantation (ASCT) followed by rituximab maintenance remains standard of care when continuous BTK inhibitor (BTKi) access is uncertain, supported by LATAM-GELL real-world data showing median overall survival of 9.9 vs. 4.5 years (HR 2.7, 95% CI 1.43–5.13; p=0.002); (2) rituximab maintenance is the single most underutilized high-impact intervention in the region; (3) p53 immunohistochemistry is endorsed as a pragmatic surrogate for TP53 assessment where NGS is unavailable; and (4) a stepwise algorithm is proposed for relapsed/refractory MCL in the absence of CAR-T cell therapy access.

Conclusions: This consensus provides the first comprehensive, resource-adapted framework for MCL management developed by and for hematologists in Latin America and other resource-limited settings globally, offering a reproducible model of pragmatic precision medicine that complements existing international guidelines.

Keywords: Mantle cell lymphoma; Latin America; Consensus; Modified Delphi; Real-world evidence; Resource-adapted guidelines; GRADE; Bruton tyrosine kinase inhibitors; Rituximab maintenance; Low- and middle-income countries

INTRODUCTION

The Latin American Reality: 660 million Inhabitants, Infinite Complexity

Latin America represents a community of more than 660 million inhabitants distributed across 33 countries, forming an epidemiological mosaic of singular complexity in the management of mantle cell lymphoma (MCL). This heterogeneity transcends geographic borders to manifest in fundamental ethnic differences, unique ancestral genomic profiles, and admixed genomes resulting from centuries of interchange with European, African, and indigenous populations.[1,2,3] However, the diversity that characterizes our region is not limited to biological aspects: disparities in healthcare infrastructure between referral urban centers and rural areas, together with the fragmentation of health systems—which oscillate between resource-limited public models and restricted-access private schemes—configure a scenario where the implementation of international guidelines faces structural barriers that go beyond scientific evidence.

Mantle cell lymphoma represents 4–9% of all non-Hodgkin lymphomas globally, with an estimated incidence of 0.5–0.8 cases per 100,000 person-years in North America and Europe. [5] In Latin America, the absolute burden of MCL is substantial despite limited population-based registry data. Extrapolating from international incidence rates and accounting for regional demographic characteristics, an estimated 3,300–5,300 new MCL cases occur annually across Latin America. However, significant diagnostic and therapeutic disparities across the region mean that a substantial proportion of these patients receive suboptimal care or no specialized treatment at all.

The LATAM-GELL Cohort: Understanding Our Context

Being aware of this gap between global knowledge and regional practice, the Latin American Lymphoproliferative Study Group (GELL) undertook a systematic effort to gather the most relevant retrospective evidence from multiple Latin American institutions. The LATAM-GELL MCL cohort (247 patients, 9 countries) was analyzed[6] to understand our real context: identify patterns of clinical presentation, characterize therapeutic outcomes under real-world practice conditions and, fundamentally, recognize the limitations and opportunities that define MCL management in our region.

Key Findings from the LATAM-GELL Cohort

Diagnostic barriers: The diagnostic challenges observed in mantle cell lymphoma across Latin America illustrate what the Lancet Commission on diagnostics called the "diagnostic last mile": the structural gap between the existence of tools and their timely, quality availability at the point of care. This bottleneck disproportionately affects low- and middle-income countries, where advanced diagnostic capabilities remain concentrated in urban tertiary centers. [11]

In hematopathology, this phenomenon manifests in a particularly critical way. In Latin America, the availability of specialized hematopathologists is limited and geographically concentrated, with a regional density substantially lower than that of high-income countries and marked centralization in large cities and academic centers. Consequently, access to complete immunohistochemistry panels, standardized Ki-67 assessment, detection of TP53/17p alterations, FISH studies for t(11;14), as well as molecular platforms and measurable residual disease testing, remains restricted to a small number of institutions. [12]

Thus, although diagnostic technologies exist at the national level, access remains fragmented and geographically conditioned, resulting in incomplete diagnoses and heterogeneous therapeutic

decisions. This inequity in Latin America is not due to a knowledge gap but, among other factors, to a systemic failure in diagnostic implementation. [6]

Inequity in access to medications: While global use of BTK inhibitors reaches 32.1%, this plummets to 11.9% in the public sector versus 52.4% in private care, with some countries having no access to these medications in public institutions. [6]

Underutilization of existing resources: Despite rituximab availability, its use in maintenance remains alarmingly low across the region, 55.4% in patients younger than 65 years and only 27% in those aged 65 years or older in the LATAM-GELL cohort.[6] Notably, comparable underutilization has been reported in real-world series outside Latin America, suggesting that the gap between evidence and implementation in MCL extends beyond socioeconomic constraints alone and reflects the complexity of clinical decision-making in daily practice.[13,14,15] Recognizing this reality as a catalyst for structured regional action, the LATAM-GELL group developed the present consensus, an initiative that does not seek to passively adapt international guidelines, but to build recommendations grounded in contextual evidence, regional feasibility, and economic sustainability.

This consensus does not represent a regional adaptation of international guidelines, but rather an original, evidence-based set of recommendations interpreted through the lens of real-world oncohematologic practice in Latin America. The distinction is deliberate and clinically meaningful. In a setting where healthcare systems vary widely in diagnostic and therapeutic capacity, the prioritization of interventions must reflect both the strength of evidence and its feasibility under actual conditions of care. The formal incorporation of Latin American, Eastern European, and Asian experts into the National Comprehensive Cancer Network (NCCN) guidelines reflects an emerging institutional recognition that scientifically rigorous clinical frameworks, built on solid evidence and adapted to different therapeutic realities, deserve a voice in global recommendations.

This consensus serves dual purposes: (1) to provide clinicians with evidence-based guidance adapted to daily practice, and (2) to equip medical societies and health authorities with minimum standards for optimal MCL care in each country.

Beyond Latin America: A Model for Resource-Variable Settings Worldwide

The challenges described in the Latin American context are not unique to this region. Resource heterogeneity, diagnostic fragmentation, and restricted access to novel therapies represent a global reality that extends to sub-Saharan Africa, Southeast Asia, Eastern Europe, the Indian subcontinent, and the Middle East — settings that collectively account for most of the the world's cancer burden. In Eastern Europe, access to BTK inhibitors is limited to selected insurance frameworks, and CAR-T therapy remains largely unavailable outside a handful of academic centers. In South and Southeast Asia, next-generation sequencing and PET-CT imaging remain concentrated in private referral hospitals in major urban centers, with most patients receiving care in settings structurally equivalent to those described by the LATAM-GELL cohort. Even within high-income countries, underserved communities, rural populations, and patients without adequate insurance coverage face resource constraints that mirror those of middle-income health systems.

This consensus therefore positions itself not only as a regional clinical instrument, but as a reproducible methodological framework, combining modified Delphi methodology, real-world

cohort validation, and GRADE-rated recommendations calibrated to resource availability, that can be adapted by hematology communities in any resource-variable setting.

METHODOLOGY

Panel Selection Criteria

Panelists were selected based on the following criteria: (a) board-certified hematologist or oncologist with ≥10 years of clinical experience in lymphoma management; (b) active clinical practice involving MCL patients; (c) affiliation with an institution providing MCL diagnosis and treatment; and (d) geographic representation to ensure coverage of diverse Latin American healthcare systems. The selection aimed to balance academic and community practice settings, public and private institutions, and geographic distribution across the region.

Modified Delphi Process

To ensure the validity and applicability of these recommendations, a rigorous modified Delphi process was employed, conducted between June 2025 and January 2026.

Expert Panel Composition: This consensus was developed by a panel of 35 specialists, 32 based in LATAM countries (Argentina, Brazil, Chile, Colombia, Cuba, Ecuador, Mexico, Paraguay, Peru, Uruguay, Venezuela) and 3 of Latin American origin working internationally, and 4 internationally recognized mantle cell lymphoma experts from the United States and Spain.

- Institutional diversity: 56% academic centers, 28% public hospitals, 16% private institutions
- International advisory board: 4 MCL specialists from USA and Spain providing global perspective while respecting regional realities

Evidence Review

In the initial phase, thematic working subgroups were formed among panel members, who prepared evidence-based responses to assigned clinical questions drawing from a systematized narrative review of the scientific literature in PubMed/MEDLINE, Cochrane Library, and LILACS databases, covering the period from January 2010 to December 2024. Search terms included "mantle cell lymphoma" combined with "treatment", "diagnosis", "transplantation", "BTK inhibitor", "rituximab maintenance", "TP53", "Latin America", and "resource-limited settings". Bibliographic selection prioritized randomized controlled trials, systematic reviews, meta-analyses, and clinically relevant observational cohorts. Current international clinical practice guidelines (NCCN v6.2024, ESMO Living Guidelines) and their reference lists were reviewed, supplemented by data from the regional retrospective cohort LATAM-GELL. [6] The quality of evidence and strength of each recommendation were assessed using the GRADE system.

Consolidation Process

The proposals developed by the subgroups were distributed, critically appraised, and refined by the 35 members of the Latin American panel. Three structured virtual meetings were subsequently convened to address the most clinically complex or contentious issues, specifically: the operational definition of high and very high risk in mantle cell lymphoma; the management of functionally fit patients with BTK inhibitors versus autologous hematopoietic stem cell transplantation within the context of Latin American healthcare realities; the duration and intensity of maintenance therapy

with rituximab alone versus the combination of rituximab and a BTK inhibitor for two or three years, taking into account regional limitations in therapeutic access; the role of allogeneic transplantation in selected patients; and the immunohistochemical criteria for TP53 interpretation.

Voting and Consensus Achievement

A consensus threshold of ≥80% agreement was established for the definitive approval of each recommendation. The high level of first-round agreement likely reflects the rigorous pre-voting process, in which subgroups conducted an exhaustive evidence review followed by three structured virtual meetings. This, combined with mature international evidence across most topics and the shared healthcare realities of the Latin American setting, facilitated convergence of expert opinion. Recommendations that did not reach this threshold in the first voting round underwent critical revision, reformulation, and resubmission to a subsequent voting round. 34 of 39 recommendations achieved consensus in the first round; 5 required a second round. Topics requiring greater deliberation and additional rounds included: the definition of high and very high risk in mantle cell lymphoma, the role of autologous transplantation in the BTK inhibitor era, immunohistochemical criteria for TP53 interpretation, management of relapsed/refractory disease without CAR-T access, and maintenance strategies in resource-limited settings.

GRADE Methodology for Evidence Quality

All recommendations were graded using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology: [18]

Evidence Quality Levels:

- A (High): Further research very unlikely to change confidence in estimate of effect
- B (Moderate): Further research likely to have important impact on confidence
- C (Low): Further research very likely to have important impact
- D (Very Low): Any estimate of effect very uncertain
- Expert*: Panel consensus in the absence of direct supporting evidence from clinical studies

**The Expert category was introduced to accommodate recommendations based on panel consensus in the absence of direct clinical evidence.*

Recommendation Strength:

- 1 (Strong): Desirable effects clearly outweigh undesirable effects or vice versa
- 2 (Conditional): Tradeoffs less certain, greater variability in values and preferences

Validation with Real-World Data

The LATAM-GELL retrospective cohort[6] was integrated throughout the consensus development to validate the applicability of international guidelines against regional access barriers. This real-world data informed recommendations particularly regarding ASCT consolidation, rituximab maintenance utilization, and TP53 detection strategies.

External Review

In the final phase, the complete consensus document was submitted to the international advisory board, comprising E. Sotomayor, L. Malpica, Ana Marín-Niebla, and H.J. Lee, for independent

critical review. Their feedback on the evidence base and recommendation wording was incorporated prior to final approval of the document.

RESULTS

To contextualize these recommendations in Latin America, we reference the LATAM-GELL cohort, the largest regional real-world MCL dataset (ASH 2025 Abstract[6]). It includes 247 patients from 9 countries (median age 64; 70% male), with a high prevalence of adverse risk (47.8% MIPI high-risk). Substantial disparities in treatment access were observed: cytarabine-based regimens and ASCT were mainly used in younger patients from private/academic centers, while BTK inhibitor access in second line ranged from 52.4% (private) to 11.9% (public). Median OS was 80.5 months (95% CI, 60.1–106.3), with a 3-year OS of 68.4%. Autologous stem cell transplantation emerged as the strongest determinant of survival: patients who underwent ASCT achieved a median OS of 9.9 years compared with 4.5 years in non-transplanted patients (3-year OS 79.9% vs. 61.3%; HR 2.7, 95% CI 1.43–5.13; p=0.002), providing the first multinational real-world evidence of the transformative and durable survival impact of consolidative ASCT in a Latin American population.[6] These data highlight regional heterogeneity and inform key differences from international guidelines. Baseline characteristics of the cohort are shown in Table 1.

The modified Delphi process yielded 39 clinical recommendations organized in four domains (Tables 2–5). Analysis of international guidelines alongside LATAM-GELL data revealed four critical areas where the Latin American reality substantially diverges from international paradigms.

1. The TRIANGLE Strategy and BTKi Availability: Adapting the Optimal Approach to Resource Context

When BTKi Access Is Reliably Guaranteed: TRIANGLE Is the Preferred Strategy. In settings where continuous, uninterrupted BTK inhibitor (BTKi) access is assured, the TRIANGLE strategy is the preferred first-line approach for young and fit MCL patients. The TRIANGLE trial[19] demonstrated that ibrutinib-containing treatment achieved 3-year failure-free survival of 86%, superior to 72% with ASCT alone, establishing ibrutinib integration as a practice-changing advance. This recommendation applies across risk strata, including patients with high-risk and very high-risk biology (blastoid or pleomorphic morphology, MIPI high, Ki-67 ≥50%), with the caveat that TP53-mutated disease responds poorly to both standard chemoimmunotherapy and ASCT and should be managed preferentially with BTKi-based combinations, clinical trials, or allogeneic transplantation in eligible patients regardless of BTKi availability.

LATAM Reality. The TRIANGLE design assumes guaranteed drug supply for a minimum of 36 consecutive months, a premise that does not hold for most patients in Latin America. In practice, approximately 70–80% of regional patients lack the structural continuity of BTKi access required to implement this strategy safely.[6] In settings where access to BTK inhibitors lacks structural continuity (due to formulary changes, budgetary constraints, or loss of employment or insurance coverage), patients who forgo ASCT and subsequently lose access to the drug may face the risk of being left without a potentially disease-controlling strategy and with limited options for sustained disease control.

LATAM Consensus Position (Level of Evidence B-1): For the 70–80% of patients without guaranteed long-term BTKi access, consolidative ASCT followed by rituximab maintenance remains the standard of care. The LATAM-GELL cohort provides the first real-world Latin American validation of this approach: patients who underwent ASCT achieved a median overall

survival of 9.9 years versus 4.5 years in non-transplanted patients (HR 2.7, 95% CI 1.43–5.13; p=0.002), [6] outcomes fully consistent with Nordic and international series. Critically, the window of maximum chemosensitivity and minimal clonal complexity is the first deep remission; failing to consolidate it with ASCT in eligible patients, and subsequently losing BTKi access, places them at a progressively more adverse biological and therapeutic position at each relapse. ASCT represents a finite, predictable, and resource-bounded intervention: economic analyses demonstrate that 3-year continuous BTKi therapy exceeds ASCT plus maintenance costs by 1.7- to 2.5-fold, [20] reinforcing transplant as the more financially sustainable strategy for Latin American health systems at the present time. [6]

2. Rituximab Maintenance: The Greatest Missed Opportunity

International Evidence: The LyMa trial[21] demonstrated that 3 years of rituximab maintenance after ASCT significantly improved 4-year event-free survival (79% vs 61%, p=0.001), progression-free survival (83% vs 64%, p<0.001), and overall survival (89% vs 80%, p<0.001). Seven-year follow-up[25] confirmed sustained benefit with median EFS and PFS not reached in the rituximab arm versus 5.8 and 6.1 years respectively in the observation arm.

LATAM Reality: Despite high-level evidence supporting rituximab maintenance after induction and/or consolidation with ASCT, only 55.4% of patients younger than 65 years and 27% of those aged 65 years or older in the LATAM-GELL cohort received this strategy. [6] This finding highlights a critical gap between available evidence and its clinical implementation across the region. In contrast to novel therapeutic agents, rituximab is a widely available, approved, and relatively accessible drug in most Latin American countries, suggesting that its underutilization is driven primarily by limitations in knowledge dissemination and adoption of evidence-based treatment standards rather than by economic constraints.

LATAM Consensus Position (Level of Evidence A-1): The LATAM consensus defines rituximab maintenance as the single intervention with the greatest clinical impact and the most favorable cost-effectiveness profile currently available for eligible patients with mantle cell lymphoma. Based on data from randomized clinical trials and population-level extrapolations, broader and more systematic implementation of this strategy could translate into a substantial reduction in relapse rates and, potentially, into the prevention of a significant number of lymphoma-related deaths at a regional level. In this context, the panel identified this recommendation as a priority, emphasizing that the main barrier to its adoption does not appear to be economic, but rather educational and organizational.

3. Detection of TP53 Alterations in Mantle Cell Lymphoma

International Evidence: Current international guidelines, including NCCN[9] and ESMO, [10] recommend next-generation sequencing (NGS) for the detection of TP53 mutations in mantle cell lymphoma. Eskelund et al.[22] demonstrated that patients with TP53-mutated MCL derive limited benefit from intensive chemoimmunotherapy, with a reported 3-year overall survival of 28% compared with 71% in TP53 wild-type patients (p<0.001), underscoring the critical prognostic and therapeutic relevance of accurate TP53 assessment.

LATAM Reality: In Latin America, access to NGS remains limited by cost, turnaround time, and infrastructure requirements. P53 immunohistochemistry (IHC) demonstrates a sensitivity of 82–85% and specificity of 100% for detecting TP53 mutations in mantle cell lymphoma, representing a cost-effective initial screening tool at approximately $22–30 USD per test compared to $619–

842 USD for targeted NGS.[23,42] NGS testing costs are 4–5 times higher than in high-income countries due to taxes, infrastructure requirements, and analysis costs, creating substantial barriers to widespread adoption.[44,46] Current availability is largely limited to private insurance coverage in specific circumstances, with limited integration into public healthcare systems across Brazil, Mexico, and Argentina.[45,46]

LATAM Consensus Position (Level of Evidence B-1): Based on these constraints, the LATAM consensus endorses a pragmatic, evidence-based approach to TP53 assessment. Using a threshold of ≥50% nuclear staining, p53 IHC achieves a sensitivity of 82% and a specificity of 100%, with results available within 48 hours at substantially lower cost. [23] Assessment of TP53 status by next-generation sequencing (NGS) is recommended whenever available. In the absence of NGS, p53 immunohistochemistry (IHC) may serve as a cost-effective alternative, using a ≥50% threshold to define positivity. For cases with intermediate p53 expression (40–49%), results should be interpreted within an integrated biological framework (including staining pattern, Ki-67, morphology, LDH, and MIPI).

4. Management of Relapsed/Refractory MCL

International Evidence: International guidelines recommend BTKi-based therapy as the standard at first relapse in BTKi-naive patients, with zanubrutinib and acalabrutinib preferred for their tolerability profile. Following covalent BTKi failure, CAR-T cell therapy (brexucabtagene autoleucel or lisocabtagene maraleucel) and non-covalent BTKi (pirtobrutinib) represent the next therapeutic steps in eligible patients.[9,10] In Latin America, however, these strategies remain largely inaccessible: CAR-T therapy is available in fewer than 5% of regional centers at costs exceeding USD $400,000–650,000, pirtobrutinib is not yet approved in most countries, and covalent BTKi access remains intermittent across a substantial proportion of centers.[51,41]

LATAM Consensus Position (Level of Evidence B-1): A foundational principle of this consensus is that any BTKi-naive patient with relapsed/refractory MCL should receive a BTK inhibitor at first relapse through any accessible pathway — national formulary, compassionate use, or clinical trial — without delay. Where BTKi access remains unavailable, the following stepwise algorithm is endorsed as a pragmatic bridge, not a permanent substitute:

- BTKi: Prioritize through any available pathway; incorporate immediately upon access
- Chemoimmunotherapy: R-Bendamustine or R-BAC in BTKi-naive relapse; non-cross-resistant regimens in BTKi-exposed patients
- Venetoclax-based combinations: With rituximab; ibrutinib + venetoclax preferred in high-risk BTKi-naive early relapse (TP53-mutated, blastoid, Ki-67 ≥50%)
- AlloHSCT: In young/fit patients with adequate response, particularly TP53-negative disease
- Bridging strategies: Rituximab monotherapy or local radiotherapy as interim disease control

This framework is calibrated to regional constraints; addressing them remains the explicit goal. The complete set of 39 clinical recommendations, organized by domain, is presented in Tables 2–5.

DISCUSSION

This Latin American consensus on MCL represents, to our knowledge, the first comprehensive effort to develop resource-adapted clinical recommendations specifically addressing the realities of Latin American healthcare systems. Unlike passive adaptations of international guidelines, this consensus integrates real-world evidence from the LATAM-GELL cohort to identify and address critical gaps between global evidence and regional practice.

Several key findings merit discussion. First, the identification of rituximab maintenance as the single intervention with the greatest underutilized impact challenges the assumption that improving MCL outcomes in resource-limited settings requires access to novel agents. The observation that rituximab maintenance was administered to only 27% of elderly patients in the LATAM-GELL cohort warrants contextual interpretation. Population-based analyses from high-income settings reveal comparable implementation gaps: in a SEER-Medicare analysis of 1,579 patients diagnosed between 2007 and 2017, only 28% of those receiving BR or R-CHOP subsequently received rituximab maintenance,[13] and the Flatiron Health cohort of 4,216 community practice patients showed similarly suboptimal uptake.[14,15] Multicenter studies consistently identify advanced age, comorbidities, frailty, concerns regarding cumulative toxicity, particularly infections and hypogammaglobulinemia, and uncertainty regarding optimal sequencing in the BTK inhibitor era as more influential determinants than drug availability in the decision to omit maintenance.[13,16] Even in academic centers, heterogeneous institutional policies and variable interpretation of trial evidence contribute to disparate implementation rates. These findings collectively reframe rituximab maintenance underutilization not as a purely resource-driven failure, but as a multidimensional implementation challenge requiring targeted educational, organizational, and policy-level interventions.

Second, the consensus position favoring ASCT consolidation over continuous BTKi-based strategies in settings with unreliable drug access reflects a pragmatic contextualization of emerging evidence. While the TRIANGLE trial[19] demonstrates the efficacy of ibrutinib-containing regimens without ASCT, the assumption of guaranteed long-term drug supply underlying this approach is not met in much of Latin America. The consensus thus does not reject novel evidence but contextualizes it within regional realities.

The endorsement of p53 immunohistochemistry as a surrogate for TP53 mutational assessment reflects not a compromise in scientific rigor, but a deliberate effort to advance diagnostic equity. Using a threshold of ≥50% nuclear staining, p53 IHC achieves a sensitivity of 82% and specificity of 100% for TP53 missense mutations,[23] at a fraction of the cost of NGS, which remains four to five times more expensive in Latin America than in high-income countries and is largely restricted to private insurance coverage.[44,46] In resource-constrained settings, a validated, accessible, and timely diagnostic test may provide greater clinical value than an ideal technology that cannot be routinely implemented, a principle that underpins the broader framework of pragmatic, equity-driven recommendations presented in this consensus.

The debate surrounding the role of autologous stem-cell transplantation exemplifies the gap between global trial assumptions and regional realities. While studies such as TRIANGLE[19] suggest that continuous BTK inhibitor–based strategies may substitute for transplantation in selected populations, these approaches assume guaranteed uninterrupted drug access. For the substantial proportion of patients in Latin America with uncertain long-term access to BTK inhibitors, consolidation with autologous transplantation followed by rituximab maintenance

remains a reliable and finite disease-control strategy, and one with proven regional outcomes. The LATAM-GELL cohort provides compelling real-world validation: transplanted patients achieved a median OS of 9.9 years, fully comparable to Nordic trial results.[6] This real-world evidence reinforces a critical biological principle: MCL is characterized by progressive clonal evolution at each relapse, with sequential acquisition of resistance-conferring alterations, TP53 mutation, del(17p), complex karyotype, BTK-pathway mutations, that make the disease increasingly difficult to control with each successive line of therapy. The first deep remission represents the narrowest window of clonal homogeneity and maximum chemosensitivity. Forgoing ASCT and subsequently losing BTKi access does not leave the patient at their pre-treatment baseline: it places them at a significantly more adverse biological state, with fewer effective options and a disease primed for rapid resistance. Consolidating the first remission with ASCT is therefore not merely a pragmatic choice in the context of uncertain drug access, it is the biologically sound strategy for exploiting the optimal window of disease control.

Comparison with Other Guidelines

This consensus shares foundational evidence with the NCCN and ESMO guidelines but diverges in key areas driven by resource considerations. Where NCCN recommends NGS-based TP53 assessment as standard, this consensus endorses a tiered approach starting with IHC. Where ESMO positions continuous BTKi therapy as an emerging consolidation option, this consensus maintains ASCT as the preferred strategy when drug access is uncertain. These differences reflect contextual adaptation rather than lower standards of care.

In parallel with a pragmatic approach to current resource availability, this consensus also reflects a forward-looking commitment to regional leadership and collaboration. Through the systematic generation, presentation, and publication of high-quality real-world data, the Latin American Group for the Study of Lymphoproliferative Diseases (GELL) seeks to improve the international visibility of the region and to provide a robust evidence base that can inform meaningful partnerships with the global pharmaceutical and biomedical research community.

While this consensus was developed within a Latin American framework, its core principles — prioritizing finite, time-limited interventions over continuous therapies with uncertain long-term access; validating lower-cost surrogate diagnostics as pragmatic alternatives; and optimizing evidence-based maintenance utilization before introducing unavailable therapies — are directly applicable to any resource-heterogeneous healthcare setting worldwide. The MCL management framework proposed here is not a low-resource alternative to international guidelines; it represents a globally applicable model of pragmatic precision medicine that begins with what is reliably available and advances toward what is ideally effective.

Limitations

This consensus has several limitations. First, the LATAM-GELL cohort used to validate recommendations is retrospective, with inherent risks of selection bias, incomplete data capture, and variable follow-up across institutions. Second, participating centers are predominantly academic and urban, which may limit generalizability to community practice and rural settings. Third, patient representatives were not included in the panel, which may have resulted in insufficient consideration of patient preferences. Fourth, the rapidly evolving therapeutic landscape, including expanding BTKi access, emerging CAR-T programs, and novel agents such as pirtobrutinib, means that some recommendations may require near-term revision. Finally, the

Delphi process was conducted electronically without face-to-face deliberation for all items, which may have limited discussion depth on controversial topics. It should also be noted that the LATAM-GELL cohort findings referenced throughout this manuscript (Reference 6) are currently available as an ASH 2025 conference abstract pending full peer-reviewed publication.

Planned Updates

This consensus will be reviewed and updated every 2–3 years, or sooner if major practice-changing evidence emerges, including pivotal trial results for novel MCL agents, significant changes in drug access or regulatory approvals in the region, or new editions of WHO classification or staging criteria. The GELL Steering Committee will monitor the literature and convene an update panel when warranted.

CONCLUSION

The Latin American Consensus on Mantle Cell Lymphoma proposes a pragmatic framework for evidence-based care in resource-heterogeneous health systems. Rather than attempting to transpose guideline models developed in settings with unrestricted access to novel diagnostic techniques and cutting-edge therapies, this consensus advances a model of pragmatic precision medicine, grounded in three core principles: (1) prioritization of finite and predictable interventions over continuous therapies with uncertain long-term availability; (2) expansion of equitable access to biologically meaningful risk stratification through validated and widely accessible technologies; and (3) optimization of the cost-effectiveness of immediately available resources before reliance on therapies that remain inaccessible to most patients in the region.

At the present time, pragmatism in the use of available resources remains essential. However, this pragmatic approach is not incompatible with advocacy and leadership. On the contrary, it provides the foundation for informed engagement with national health authorities, regulatory agencies, and international stakeholders, with the explicit goal of progressively expanding the therapeutic armamentarium available to patients with MCL across the region.

Until equitable access to novel agents becomes a global reality, improving outcomes for patients with mantle cell lymphoma in Latin America will depend on ensuring optimal use of proven, accessible interventions. This is the foundation of pragmatic precision medicine and the commitment of the Latin American hematology community to deliver the best possible care within the realities faced by our patients.

CONFLICT OF INTEREST STATEMENT

Individual conflicts of interest are reported according to ICMJE guidelines:

Maria Alejandra Torres Viera, Henry Idrobo, Brady Beltran, Rosa Oliday Rios Jiménez, Lidiane Andino Neves, Myrna Candelaria, Adolfo Enrique Díaz, Marcela Zamora, Nancy Cristaldo, Eleazar Hernández Ruiz, Carolina Oliver, German Stemmelin, Humberto Martínez-Cordero, Pilar León, Alana von Glasenapp, Lorena Fiad, Jaime Valdéz, Patricia Kollar, Marta Zerga, Jorge Daza-Buitrago, Carlos Gómez-Calcetero, Juan Alejandro Ospina, Luis Malpica, Marie Laure Garcia, Alfredo Quiróz, Macarena Roa, Juan Esteban García, Juan Rangel Patiño, Ana Ramirez: report no conflicts of interest to declare.

Luis Villela reports honoraria from AstraZeneca, BeiGene, Roche, Johnson & Johnson, and AbbVie.

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Cristóbal Frutos reports honoraria from Quimfa.

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José Sandoval-Sus reports honoraria from speaker bureau activities with Pfizer; and advisory board participation for Janssen, ADC Therapeutics, Genmab, BeiGene, AbbVie, Bristol Myers Squibb, Genentech, Kite, Roche, Novartis, and Acrotech.

Ana Marín-Niebla reports honoraria from lectures in medical meetings, symposiums and workshops and participation in advisory boards for Janssen/Johnson & Johnson, AstraZeneca, Lilly, AbbVie, Takeda, Kiowa, Kirin, Beigene/BeOne, Kite, and MSD.

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DATA AVAILABILITY STATEMENT

The LATAM-GELL cohort data that support the findings of this consensus are available from the corresponding author upon reasonable request. Delphi voting results are provided in Supplementary Tables S2–S3.

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Table 1. Baseline Characteristics of the LATAM-GELL Cohort (N=247)

Stratified by age group (<65 years and ≥65 years). Data from the LATAM-GELL retrospective cohort (9 countries, 2015–2024).

Characteristic	Overall	Age <65 years	Age ≥65 years
Geographic Distribution			
Countries	9 countries		
Participating centers	19 institutions		
Private/Academic centers, n (%)	143 (57.9%)		
Public hospitals, n (%)	104 (42.1%)		
Demographics			
Median age, years	64	55	74
Male, %	70.4	75.2	65.3
N patients	247	129	118
Disease Characteristics			
Stage III-IV, %	72.5	69.8	75.4
Extranodal involvement, %	66	66	65.9
Bone marrow infiltration, %	62.4	60.8	64.3
High-risk MIPI, %	55.1	41.8	69.2
Treatment Utilization			
Cytarabine-based induction			
Private/Academic, %		81.3	13.8
Public, %		47.6	18.6
R-Bendamustine			
Private/Academic, %		4	50.8
Public, %		4.8	16.3
R-CHOP			
Private/Academic, %		12	20
Public, %		40.5	41.9
ASCT consolidation[a]			

Private/Academic, %		73.1	30.3
Public, %		72.7	0
Rituximab maintenance (overall), %		57.3	61
BTK inhibitor use (in L2 patients)			
Private/Academic, %	61.1	42.1	40.7
Public, %	17.2		
Outcomes			
Median follow-up, months	26.8		
Median OS, months (95% CI)	80.5 (60.1–106.3)		
Median PFS, months (95% CI)	29.7 (21.9–40.3)		
3-year OS, %	68.4		

[a] Among ASCT-eligible patients (<65 years, adequate organ function, responsive to induction therapy).

Abbreviations: ASCT, autologous stem cell transplantation; BTK, Bruton tyrosine kinase; CI, confidence interval; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; PFS, progression-free survival.

LEGEND FOR TABLES 2–5: EVIDENCE GRADES AND STRENGTH OF RECOMMENDATIONS

The Evidence column combines evidence level and recommendation strength using the format: Evidence-Strength (e.g., A-1, B-2). Evidence Levels: A (high), Further research very unlikely to change confidence in estimate of effect; B (moderate) , Further research likely to have important impact on confidence; C (low), Further research very likely to have important impact; D (very low) , Any estimate of effect very uncertain; Expert Panel consensus in the absence of direct supporting evidence. Strength: 1 (strong, benefits clearly outweigh risks), 2 (conditional, benefits and risks more balanced).

Table 2. Diagnosis, Pathology and Risk Stratification (Recommendations 1–8b)

Topic / Recommendation	International Data	LATAM Context	LATAM Consensus Position	Evidence (Grade)
1. Cyclin D1 + SOX11 (mandatory)	IHC for Cyclin D1/SOX11 required. If Cyclin D1 negative, FISH t(11;14) mandatory; ideally evaluate Cyclin D2/D3.	FISH not available in ~55% of centers; IHC Cyclin D1 acceptable when FISH is inaccessible.	SOX11 identifies rare Cyclin D1-negative cases; WHO 2022 supports diagnostic approach.	A-1
2. Ki-67 (integrated, not isolated)	Use 30% cutoff avoiding decisions based on small differences (e.g., 28% vs 35%); integrate with MIPI, TP53, and morphology.	Interobserver variability ±5–10% limits precision near cutoff.	Ki-67 value must be interpreted in clinical-pathological context; not to be used as sole determinant.	C-2

3. Recognition of blastoid/ pleomorphic variants	Mandatory morphological evaluation. Blastoid/pleomorphic variants (10–15%) are associated with TP53 and worse OS; consider intensive therapy or trials.	Requires expert pathology; p53 IHC mandatory ± mutational testing if available.	TP53 (more than morphology alone) should guide escalation to biological therapies; series show significantly lower OS. If BTKi not available, consider early allo-SCT in selected eligible patients.	A-1
4. TP53 assessment	NGS + FISH del(17p) + p53 IHC ≥50%. Main prognostic factor. Multimodal approach improves stratification (TP53 mut OS 1.8 years vs TP53 wild-type OS 12.7 years).	NGS not available in ~67%; p53 IHC mandatory (high specificity), rapid (≈2 days vs 18 days for NGS).	TP53 is the dominant prognostic marker in MCL. NGS recommended when available; p53 IHC (≥50% threshold) as surrogate when NGS unavailable. Intermediate expression (40–49%): interpret in integrated biological framework.	B-1
5. Bone marrow (selective approach)	Recommended for staging. In leukemic phase with positive flow cytometry and available lymph node biopsy, bone marrow biopsy may be omitted.	Lymph node tissue essential for morphology, Ki-67, and p53. Flow cytometry useful for infiltration but does not replace node tissue.	BM useful for staging; can be individualized according to presentation and alternative diagnostic quality.	C-2
6. PET-CT (staging/response, not surveillance)	Use PET-CT for initial staging and pre/post-ASCT. Clinical follow-up every 3–6 months; imaging only if symptoms/suspicion.	CT scans with IV contrast in places where PET-CT is not available.	Routine surveillance PET-CT not recommended due to lack of clinical benefit and increased exposure/costs.	B-1 (staging); C-2 (response)
7. CNS evaluation (high risk)	Evaluate CNS if neurological signs or symptoms; blastoid, elevated LDH, ≥2 extranodal sites, Ki-67 >50%. CAR-T (brexu-cel) preferred when available in second line treatment.	CAR-T access <5%. Alternatives: HD-cytarabine/MTX or BTKi with CNS penetration (ibrutinib) ± rituximab + IT; ASCT not in active CNS disease; rituximab has CNS penetration <0.1%.	CNS involvement 4–15% with very short OS; brexu-cel reports high response/CR rates in series/trials.	C-2
8. MIPI / MIPI-c calculation	Calculate MIPI/MIPI-c in all patients. Risk strata: Very low (<4.0 – indolent/leukemic non-nodal presentations, surveillance candidate); Low (4.0–5.6); Intermediate (5.7–6.1); High (≥6.2): median OS 29 months. Integrate with TP53, Ki-67, morphology; do not use MIPI alone to decide therapy.	Simplified MIPI uses age, ECOG, LDH, WBC (readily available). MIPI very low (<4.0) identifies truly indolent MCL candidates for surveillance-first approach (see Rec 8b).	MIPI validated as prognostic tool; MIPI-c integrates Ki-67; mandatory in all patients.	A-1

8b. Watch-and-Wait in Truly Indolent MCL (MIPI Very Low, Leukemic Non-Nodal)	Ondrejka et al. (Am J Clin Pathol, 2011) characterized indolent MCL leukemia (SOX11-negative, IGHV-mutated) as a distinct entity with favorable outcomes under observation. Active treatment does not improve OS in this subgroup; deferred therapy preserves quality of life without oncologic compromise.	Leukemic non-nodal MCL may be identified in LATAM with IHC (SOX11-negative CyclinD1+) — this determination is feasible without NGS or specialized molecular testing in most regional centers. Surveillance avoids unnecessary treatment toxicity and reduces cost burden.	SOX11-negative, IGHV-mutated, Ki-67 <10%, MIPI very low (<4.0), asymptomatic, no bulky disease: active surveillance with clinical follow-up every 3 months. Treatment initiation indicated for: symptomatic progression; lymphocyte doubling time <6 months; development of nodal disease; or MIPI score increase.	Expert-1

Abbreviations: ASCT, autologous stem cell transplantation; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IGHV, immunoglobulin heavy chain variable region; MIPI, Mantle Cell Lymphoma International Prognostic Index; NGS, next-generation sequencing; TP53, tumor protein p53; WHO, World Health Organization.

Table 3. First-Line Treatment for Young/Fit Patients (Recommendations 9–20)

Topic / Recommendation	International Data	LATAM Context	LATAM Consensus Position	Evidence (Grade)
9. High-dose cytarabine (cornerstone)	HD-cytarabine (≥2 g/m²) for ≤65–70 years fit patients: R-CHOP/R-DHAP, R-HyperCVAD/MA, Nordic. CR 85–90%, median PFS 7–8 years.	If continuous BTKi access is uncertain, cytarabine-based regimens remain the essential backbone.	Cytarabine-based regimens (even when BTKi is available) (≥2 g/m²) for ≤65–70 years fit patients show superiority in PFS.	A-1
10. BTKi integration	Where continuous BTKi is available, adding ibrutinib/acalabrutinib improves FFS.	>65 y not eligible for transplant; SHINE and ECHO trials in patients not eligible for ASCT require indefinite therapy; access-dependent sustainability/funding is critical.	TRIANGLE suggests ibrutinib induction + BTKi and Rituximab 2-year maintenance may equal outcomes with ASCT in certain contexts.	A-2
11. ASCT with uncertain BTKi (LATAM standard)	—	LATAM reality: 70–80% without prolonged BTKi access; cost comparison: single ASCT vs BTKi accumulated over years; rituximab biosimilars maintenance widely available.	If BTKi supply is unreliable, ASCT + rituximab maintenance remains standard for being finite, predictable, and cost-effective.	B-1
12. BEAM conditioning	BEAM recommended. TBI does not improve outcomes and increases toxicity.	BEAM feasible in most centers; avoid TBI (secondary malignancies, infertility) without survival benefit.	BEAM is the preferred conditioning regimen for ASCT in eligible MCL patients.	B-1

13. Pre-ASCT PET-CT response	Pre-ASCT PET-CT recommended. Complete metabolic response predicts better PFS/OS.	PET-CT negative does not eliminate ASCT benefit; proceed to ASCT regardless of PET when indicated.	PET-CT negative associates with better outcomes; useful for pre-transplant stratification.	B-1
14. Rituximab maintenance (maximum impact)	Rituximab 375 mg/m² every 2 months × 3 years post-ASCT (or in transplant-ineligible context). Long-term PFS/OS benefit; priority.	Implementation gap (e.g., only a fraction receives maintenance despite level A evidence). Before initiating or restarting any anti-CD20 maintenance strategy, verify CD20 expression by IHC or flow cytometry on a recent biopsy. Partial or complete loss of CD20 has been documented after rituximab-containing regimens and constitutes an established resistance mechanism in MCL that renders anti-CD20 maintenance ineffective. This verification is particularly relevant after intensive cytarabine-based induction and before post-ASCT maintenance initiation.	Rituximab 375mg/m² q2mo × 3y mandatory post-ASCT or after first-line therapy in non-transplant eligible patients.	A-1
15. MRD-negative does not eliminate ASCT benefit	MRD-guided decisions mainly supported by trials.	MRD not available in ~80%; even if MRD-negative, proceed to ASCT in eligible patients.	MRD-guided treatment data are mostly from trials and require high sensitivity techniques and requires guaranteed continuous BTKi access.	B-2
16. TP53 mutated: avoid standard ASCT	TP53 mutated should NOT receive standard ASCT. Prioritize trials, BTKi/biologics, or allogeneic SCT in selected patients.	Standard ASCT may give PFS <12 months. Allo-SCT patients not uniformly curative; select carefully according to access and risk.	Poor PFS with standard ASCT in TP53-mutated MCL; Allo-SCT may offer durable control in selected cases, especially when performed in chemosensitive disease and earlier in the relapse trajectory, while outcomes appear substantially poorer in heavily pretreated or highly refractory patients.	B-1
17. Blastoid: intensive approach	In young, fit TP53–patients, cytarabine-based intensive induction is recommended, with ASCT considered on an individual basis. In TP53-mutated disease,	If TP53-mutated disease, and biologic strategies (BTKi ± venetoclax) allo-HCT is a possibility for selected cases.	Blastoid/pleomorphic require intensive cytarabine + ASCT consolidation. LATAM: Standard R-CHOP yields median OS <2y. Must use dose-intensive cytarabine or enroll in trials. Proceed to transplant.	B-1

	biologic strategies (BTKi ± venetoclax), clinical trials, or cellular therapies are preferred, with allo-HCT reserved for selected cases.			
18. Treatment timing	Start induction within 2–3 weeks; ASCT at 3–4 months after completing induction; rituximab maintenance starts 2–3 months post-ASCT if no infection/persistent cytopenias.	Delays increase progression risk; coordinate early transplant and donor search if considering allo-SCT.	Recommendation based on expert practice and transplant logistics to avoid progression.	C-2
19. R-CHOP is NOT recommended in fit patients	R-CHOP alone is not recommended; cytarabine-based is superior (PFS 7–8 years vs 3–4). R-CHOP is an option for elderly/unfit patients.	In fit elderly, R-BAC may be considered instead of R-CHOP, according to selection and tolerance.	R-CHOP alone not recommended in fit patients eligible for ASCT.	A-1
20. Clinical trials (priority)	Include all eligible patients, especially high risk (TP53, blastoid, POD24).	Limited availability; promote international collaborations and access.	New therapies often more effective in early lines; trials offer access to innovation.	Expert-1

Abbreviations: ASCT, autologous stem cell transplantation; BEAM, carmustine + etoposide + cytarabine + melphalan; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; FFS, failure-free survival; MIPI, Mantle Cell Lymphoma International Prognostic Index; MRD, measurable residual disease; PFS, progression-free survival; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; TBI, total body irradiation.

Table 4. Relapsed/Refractory Disease (Recommendations 21–32)

Topic / Recommendation	International Data	LATAM Context	LATAM Consensus Position	Evidence (Grade)
21. BTKi is the standard in R/R MCL	New biopsy mandatory at relapse (morphological transformation ~30%, clonal evolution with new TP53 mutations; changes management). W&W in low-burden asymptomatic. BTKi (ibrutinib/acalabrutinib/zanubrutinib) standard: ORR 60–80%, PFS 13–18m.	1st generation BTKi more widely available; alternatives: chemoimmuno/trials according to coverage.	New biopsy is mandatory at relapse (identifies transformation 30%, TP53 status changes in 25–40%). Asymptomatic low-burden: watch-and-wait. Symptomatic: Late relapse (POD24-neg, BTKi-naïve): use BTKi. (POD24+): use BTKi or ibrutinib + venetoclax. Indefinite BTKi; derive to CAR-T/pirtobrutinib/venetoclax. LATAM: Zanubrutinib may have better toxicity profile but limited access.	A-1

22. CAR-T therapy	Anti-CD19 CAR-T (Brexu-cel or Liso-cel) in eligible R/R: CR 60–70%, median PFS ~26m; ideal after 1–2 prior lines.	Available in <5% centers; very high costs. If not available, optimize BTKi or consider allo-SCT.	CAR-T is the preferred option post-BTKi failure when accessible; optimize transition planning.	A-1
23. Management without CAR-T	Strategy: maximize BTKi duration; allo-SCT if young/fit; trials; conventional salvages.	≈95% without CAR-T; allo-SCT considered better option; venetoclax combinations otherwise.	Sequencing depends on BTKi response, eligibility, and access to cellular therapies.	C-2
24. Allogeneic transplant in R/R MCL	Potentially curative allo-SCT in young/fit R/R when CAR-T not available; prefer non-myeloablative; better in chemosensitive disease and low comorbidity.	Best for <65y, chemo-sensitive, HCT-CI ≤3. Require matched donor — difficult in LATAM. High genetic variability/no cord blood banks.	LATAM has low experience in MCL. Series show long-term DFS in selected subgroups; relevant NRM. Early referral to specialized centers for patient evaluation and timely donor search.	C-2
25. Venetoclax combinations	Venetoclax + BTKi or rituximab with activity, especially TP53; ORR 40–70%; monitor TLS risk.	Very low access in LATAM.	Ibrutinib + venetoclax: Evidence of activity in series/studies; growing role in high-risk subgroups.	B-2
26. Lenalidomide-based therapy	Lenalidomide-rituximab acceptable option: ORR 40–60%; requires thromboprophylaxis with ASA and G-CSF.	May be more accessible/lower cost than BTKi in some contexts.	Moderate efficacy in R/R; alternative when BTKi not available or after failure.	B-2
27. TP53 mutated R/R: prefer chemotherapy-free regimens	In TP53 mutated R/R: prefer BTKi-venetoclax, CAR-T, or allo-SCT over chemotherapy (ORR <20%, PFS <6m with chemotherapy).	Avoid ineffective intensive chemotherapy; prioritize targeted combinations according to access.	TP53-altered predicts poor chemotherapy response; targeted combinations are key.	B-1
28. BTKi resistance	On BTKi progression: pirtobrutinib (non-covalent); other options: CAR-T or venetoclax.	Mutational testing rare; empirical approach: attempt noncovalent BTKi or switch to venetoclax/CAR-T according to access.	Resistance mechanisms condition choice; pirtobrutinib, and cellular therapies or venetoclax combinations as options.	C-2
29. Therapeutic sequencing	General: BTKi at 1st relapse; then CAR-T or pirtobrutinib or venetoclax vs allo/trials according to opportunities; individualize by access.	Maximize 1st-line duration; use best available option at each relapse: BTKi > allo > lenalidomide > salvage chemo.	Optimal sequencing depends on response, prior lines, and availability of advanced therapies.	Expert-2
30. 2nd ASCT	Second auto-ASCT generally not recommended; if long CR1 (>3	Prefer alternatives with greater likelihood of	Generally poor results. ASCT not recommended.	C-2

	years) and no options, consider exceptionally (ORR 30–40%).	benefit: prioritize BTKi, allo-SCT, trials, or cellular therapies.		
31. Symptom-directed / palliative therapy	In heavily pretreated patients: symptom-focused approach; avoid futile intensification; prioritize QoL.	Palliative care underutilized; options: rituximab monotherapy, low-dose chemo, localized RT, pain control.	Integrated palliative care improves quality and aligns care to patient goals.	Expert-1
32. Trials at each relapse	Consider trials at each relapse, not as last resort; novel agents more effective early.	Few trials in LATAM: promote access and consider international enrollment.	Early access to innovation may improve outcomes.	Expert-1

Abbreviations: allo-SCT, allogeneic stem cell transplantation; ASA, aspirin; ASCT, autologous stem cell transplantation; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; DFS, disease-free survival; G-CSF, granulocyte colony-stimulating factor; HCT-CI, hematopoietic cell transplantation comorbidity index; NRM, non-relapse mortality; ORR, overall response rate; PFS, progression-free survival; POD24, progression of disease within 24 months; QoL, quality of life; R/R, relapsed/refractory; TLS, tumor lysis syndrome.

Table 5. Elderly Patients and Supportive Care (Recommendations 33–39)

Topic / Recommendation	International Data	LATAM Context	LATAM Consensus Position	Evidence (Grade)
33. R-Bendamustine ± BTKi (transplant-ineligible)	For ≥65 years: R-Bendamustine+BTKi (acalabrutinib or ibrutinib) preferred, followed by rituximab maintenance ≥2 years; RB alone acceptable but inferior.	Variable BTKi access; use RB alone if not available; outpatient and tolerable regimen.	ECHO/SHINE/ENRICH: RB superior to R-CHOP; BTKi addition improves PFS in trials.	A-1
34. Cytarabine in fit elderly (selective)	R-BAC500 for selected fit 60–75 years; omit day 3 cytarabine if toxicity without compromising efficacy (in ~50% real-world).	Reserve only for carefully selected elderly patients; not for frail/comorbid.	Phase 2 data and propensity analysis suggest high CR and PFS in fit subgroups.	B-1
35. Antimicrobial prophylaxis (selective)	Non-intensive/post-ASCT: VZV/HSV (acyclovir), PJP (TMP-SMX if steroids/lymphopenia), HBV (entecavir if HBsAg+ or anti-HBc+). In maintenance: IgG q6–12m; IVIG if <400 with infections.	Targeted approach optimizes cost/benefit; not universal. In conventional chemo (R-CHOP, R-bendamustine) not universally recommended.	Strategy based on specific risks and prevention of opportunistic reactivations.	C-2

36. G-CSF (specific indications)	Primary: ≥65 years + intensive regimens, dose-dense or baseline ANC <1500. Secondary: post-febrile neutropenia or when maintaining intensity. Dose: filgrastim 5 µg/kg/d SC d+3–5 or pegfilgrastim 6 mg SC 24–72h post-chemo.	Not routine in R-bendamustine alone or maintenance; reserve for high risk due to costs.	ASCO/EORTC guidelines support risk-based use to reduce neutropenia and maintain dose.	B-1 (primary); A-1 (secondary)
37. Response assessment (no routine surveillance)	PET-CT for post-induction response and pre-ASCT. Follow-up: clinical q3–6m first 2 years, then q6–12m. Imaging only if symptoms/suspicion.	Avoid surveillance PET-CT due to resources; exam + labs sufficient in asymptomatic patients.	Surveillance imaging does not improve OS in asymptomatic patients; clinical approach is standard.	B-1
38. Long-term toxicity (anthracyclines)	For anthracycline recipients: baseline echo+ECG (especially >60, HTN, DM, CAD). Monitor LVEF post-induction, pre-ASCT. If LVEF <50% or ↓>10%: cardioprotection and referral.	High CV risk may favor anthracycline-free regimens (RB, R-BAC). BTKi toxicity (AF, HTN) addressed separately.	Cardiotoxicity is dose-cumulative and potentially irreversible; monitoring reduces events. Cardioprotection is mandatory (Beta-blockers, ACE inhibitors, Statins).	B-2
39. Multidisciplinary team	MCL requires collaboration: hematology, pathology, radiology, transplant, supportive care, pharmacy, and palliative care; teleconsult with expert centers if needed.	Molecular boards for diagnostic complexity; transplant coordinators for logistics; pharmacy and social work for access and financial toxicity.	Multidisciplinary management improves diagnostic consistency and access to complex therapies.	Expert-1

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ANC, absolute neutrophil count; ASCT, autologous stem cell transplantation; BTKi, Bruton tyrosine kinase inhibitor; CAD, coronary artery disease; DM, diabetes mellitus; ECG, electrocardiogram; ECHO, echocardiogram; G-CSF, granulocyte colony-stimulating factor; HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody; HTN, hypertension; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; PJP, Pneumocystis jirovecii pneumonia; QoL, quality of life; RB, rituximab-bendamustine; R-BAC, rituximab + bendamustine + cytarabine; RT, radiotherapy; TMP-SMX, trimethoprim-sulfamethoxazole; VZV, varicella-zoster virus.

Bridging the Gap: MCL Management in Resource-Limited Settings

LATAM-GELL Consensus 2025–2026 · Torres Viera MA, et al. · 39 experts · 13 countries · GRADE-adapted Delphi

39	13	247	39
EXPERTS	COUNTRIES	PATIENTS	GRADE-RATED RECOMMENDATIONS

39 RECOMMENDATIONS ACROSS 4 CLINICAL DOMAINS

- **8** Diagnosis & Risk Stratification
- **12** 1st Line Transplant-eligible
- **12** R/R Disease No CAR-T access
- **7** Elderly / Unfit Supportive Care

TREATMENT SELECTION: WHY LATAM DIVERGES FROM TRIANGLE-ONLY GUIDANCE

Is continuous BTKi access reliably guaranteed for ≥36 months?

YES, GUARANTEED BTKi ACCESS (~20–30%)

TRIANGLE strategy

Ibrutinib + ASCT / BTKi-based induction. Preferred international standard (NCCN, ESMO).

NO , BTKi ACCESS UNCERTAIN (~70–80%)

ASCT + rituximab maintenance

GELL Consensus: standard of care (Level B-1) — maintained despite the international shift toward TRIANGLE.



HR 2.7 · 95% CI 1.43–5.13 · p=0.002 | 3-yr continuous BTKi cost is 1.7–2.5× higher than ASCT + rituximab maintenance

TOP-PRIORITY INTERVENTION

Rituximab maintenance
Single most underutilized, high-impact intervention for MCL in the region.

GRADE-ENDORSED SURROGATE

p53 immunohistochemistry
Pragmatic surrogate for TP53 assessment where NGS is unavailable.

R/R MCL without CAR-T access: BTKi if available, else R-DHAP / R-BAC / bendamustine-R → ASCT if response → later lines: venetoclax ± rituximab

Conclusions

Unlike TRIANGLE-only guidance, the GELL consensus maintains **ASCT + rituximab maintenance** as standard of care for the ~70–80% of LATAM patients without guaranteed long-term BTKi access, validated by real-world outcomes (9.9 vs 4.5-year OS). This first comprehensive, resource-adapted framework for MCL , developed by and for hematologists in Latin America — offers a reproducible model of pragmatic precision medicine complementing existing international guidelines.