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Original Article

Efficacy and safety analysis of a novel BTK inhibitor in patients with mantle cell lymphoma harboring TP53 mutations

Min Liu[1*], Yannong Ding[2*], Hui Lan[3]

[1]Department of Hematology, Lishui Central Hospital, Lishui 323000, Zhejiang, China; [2]Department of Stomatology, The First Affiliated Hospital of Lishui University, Lishui People's Hospital, Lishui 323000, Zhejiang, China; [3]Department of Medical Oncology, Lishui Central Hospital, Lishui 323000, Zhejiang, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: To rigorously evaluate the efficacy and safety of a novel Bruton tyrosine kinase inhibitor (BTKi), alone or in combination with venetoclax, in patients with TP53-mutated mantle cell lymphoma (MCL), focusing on survival outcomes, depth of response, minimal residual disease (MRD), clearance, and treatment-emergent toxicities. Methods: We conducted a retrospective, observational cohort study of consecutive adults with TP53-mutated MCL treated with BTKi-based regimens between January 2022 and December 2025. Patients were assigned to BTKi monotherapy (ibrutinib or acalabrutinib; n = 108) or BTKi plus venetoclax (n = 112). Clinical, pathological, and genomic data were recorded using standardized electronic case-report forms. Responses were assessed according to contemporary MCL criteria, and recurrence/progression-free survival (RFS/PFS) and overall survival (OS) were calculated from predefined time points. Results: Combined treatment significantly prolonged median RFS from 11 to 34 months (HR for recurrence or death 0.42, 95% CI 0.29-0.61; P<0.001), and median OS from 20 to 50 months (HR 0.44, 95% CI 0.31-0.63; P<0.001). Overall response rates were higher with BTKi-based combination therapy (76.8% vs. 58.3%; P = 0.001), with comparable rates of complete response. In multivariable models, BTKi-based combination therapy remained independently associated with longer PFS (HR 0.187, 95% CI 0.079-0.442; P<0.001). Conclusion: In patients with TP53-mutated MCL, BTKi-based combination therapy confers clinically meaningful and durable improvements in RFS and OS, with higher overall response rates than monotherapy and acceptable toxicity profiles.

Keywords: BTK inhibitor, mantle cell lymphoma, TP53 mutations, efficacy, safety

Introduction

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma (NHL), typically characterized by rapid disease progression and poor survival outcomes [1]. MCL is defined by the translocation of the CCND1 gene, leading to cyclin D1 overexpression and abnormal cell cycle progression [2, 3]. Although MCL accounts for a small proportion of NHL, it is associated with high morbidity and mortality, especially in elderly patients or those with relapsed/refractory NHL [4, 5]. Conventional treatments, including chemotherapy and stem cell transplantation, have shown some clinical responses; however, long-term disease control remains challenging, with most patients eventually relapsing. This challenge is further complicated in patients harboring TP53 mutations, which are known to confer tumor resistance and poor therapeutic responses.

TP53 mutations represent one of the most important molecular aberrations in cancer and occur in a substantial population of MCL patients, especially those with advanced-stage or refractory disease [6-8]. TP53, known as the guardian of the genome, plays an important role in maintaining cellular stability by regulating cell cycle arrest, DNA damage repair, and apoptosis in response to genotoxic stress [9-11]. TP53 mutations results in dysregulated tumor suppressor functions, allowing tumor cells to escape normal growth control. In MCL,

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TP53 mutations significantly impair chemotherapy response, shorten progression-free survival (PFS) and overall survival (OS), highlighting the urgent need for novel and effective therapies in this patient population [12, 13].

MCL has seen substantial therapeutic advances with the introduction of targeted agents, especially Bruton tyrosine kinase (BTK) inhibitors [14, 15]. BTK, a key component of the B-cell receptor (BCR) signaling pathway, facilitates B-cell proliferation, survival, and migration. BTK inhibitors have shown significant clinical efficacy in MCL by disrupting BCR signaling, thereby promoting apoptosis of malignant B-cells [16, 17]. The first approved BTK inhibitor, ibrutinib, has demonstrated impressive activity in the treatment of relapsed and refractory MCL, providing an alternative for patients with limited treatment options [18]. Nevertheless, TP53 mutations remain a major contributor to therapy failure, as they can mediate acquired resistance to BTK inhibitors. Accordingly, next-generation BTK inhibitors that are capable of overcoming such resistance and improving patient outcomes are still in urgent need.

This study aims to compare the efficacy and safety of BTKi-based monotherapy and combination therapy in patients with TP53-mutated MCL. Preclinical evidence suggests that this agent may possess superior pharmacological profile compared with conventional BTK inhibitors. Specifically, we aim to determine whether this new BTK inhibitor can improve response rates, PFS, and OS in patients with TP53-mutated MCL.

Methods and study design

Study design

This was a retrospective, observational cohort study of adult MCL patients harboring TP53 mutations who received Bruton's tyrosine kinase inhibitor (BTKi)-based therapy between January 2022 and December 2025. Patients were identified by retrieving institutional electronic medical records and specific hospital lymphoma databases, and assigned to two treatment groups according to the initial BTKi-based regimen: a control group (n = 108) receiving BTKi monotherapy, and an observation group (n = 112) receiving BTKi combined with venetoclax. As per institutional guidelines, ibrutinib was administered either as 560 mg once daily or 100 mg twice daily in combination with venetoclax.

Inclusion criteria: (1) Age ≥18 years; (2) Histologic diagnosis of MCL based on the current SICS-2008 classification (e.g., CD 20+, cyclin D1+ or t(11;14) by FISH when cyclin D1-negative); (3) Presence of a somatic P53 mutation confirmed by an approved molecular test (e.g., next-generation sequence or targeted sequencing panel) and established criterion.

Exclusion criteria: (1) Prior BTKi-based therapy, leading to permanent intolerance or primary refractory disease; (2) Allogeneic hematopoietic stem cell transplantation within 6 months before BTKi initiation; (3) Participation in an interventional clinical trial potentially confounding efficacy or safety assessment; (4) Histologic transformation to aggressive lymphoma (e.g., diffuse large B-cell lymphoma or Richter transformation) (**Figure 1**).

This study was performed in accordance with the Declaration of Helsinki and local regulations. The protocol was approved by the institutional review board or ethics committee of each participating center. In line with local regulations, informed consent for retrospective data collection or research use was obtained.

Treatment

Patients in the control group received BTKi monotherapy with either ibrutinib (560 mg orally once daily) or acalabrutinib (100 mg orally twice daily). The specific agent used was recorded for each patient. Patients in the observation group received the same BTKi backbone combined with venetoclax, initiated using a standard weekly dose-escalation schedule (20 mg, 50 mg, 100 mg, 200 mg, and 400 mg, once daily) to reduce the risk of tumor lysis syndrome (TLS). TLS risk was assessed before venetoclax initiation and at each dose-escalation step according to tumor burden, absolute lymphocyte count, renal function, and serum uric acid level. TLS prophylaxis included oral hydration of 1.5-2.0 L/day starting 48 h before treatment, intravenous hydration as indicated, and uric acid-lowering therapy with allopurinol or rasburicase in high-risk patients. Blood chemistry parameters were monitored at baseline and during dose escalation according

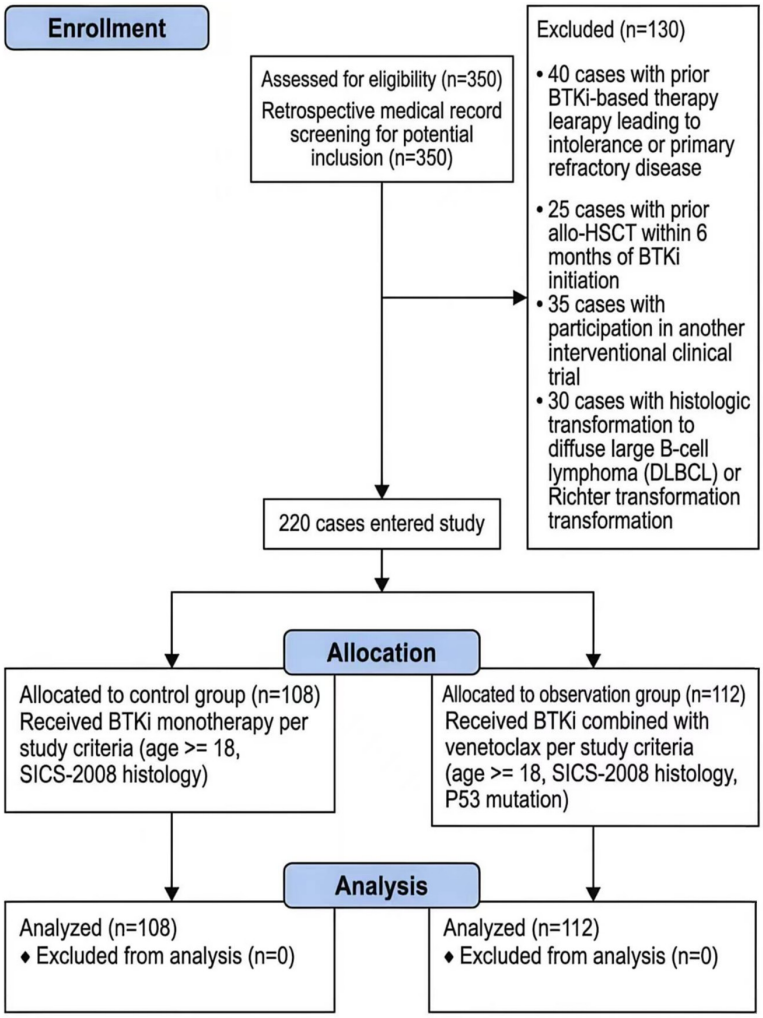

Figure 1. Study flowchart.

to institutional practice. Treatment continued until disease progression, unacceptable toxicity, or treatment discontinuation. Dose interruption or reduction was permitted for grade 3-4 hematologic toxicity, severe non-hematologic adverse events, major bleeding, infection, arrhythmia, or laboratory/clinical TLS.

Data collection

Clinical data were collected using standardized electronic case-report forms from enrollment until the data cut-off. Baseline information included demographic characteristics, performance status, and detailed disease features, such as Ann Arbor stage, Mantle Cell Lymphoma International Prognostic Index (MIPI) score and risk category, histologic subtype (classic vs. blastoid/pleomorphic), Ki-67 proliferation index, tumor bulk (largest nodal or extra-nodal mass), number of extranodal sites, and full TP53 mutational data (type of variant and co-occurring lesions).

All systemic therapies, cumulative BTKi exposure, dose intensity, dose reductions, temporary interruptions, and permanent discontinuation were recorded during treatment and follow-up, along with reasons for treatment changes. Tumor response was assessed according to contemporary MCL response criteria, integrating clinical evaluation, cross-sectional imaging, and bone marrow examination when clinically indicated. Radiologic assessment was primarily performed using contrast-enhanced computed tomography (CT) or positron emission tomography-computed tomography (PET-CT), depending on availability and institutional practice. Response assessments were conducted at baseline, approximately 3 months after treatment, and subsequently at regular follow-up intervals or upon clinical suspicion of progression. Responses were classified as complete response (CR), partial response (CR), stable disease (SD), or progressive disease (PD) on the basis of imaging findings together with relevant clinical and hematologic information, and these categories were used to determine the overall response profile and depth of remission. First documented relapse/progression, death from any cause, and the final disease assessment dates were recorded to derive PFS and OS.

Minimal residual disease (MRD) was prospectively assessed at the pre-specified 3-month time point using either bone marrow aspirate or peripheral blood samples, according to sample availability and institutional practice. MRD testing employed either multiparameter flow cytometry or next-generation sequencing in certified laboratories using validated reagents and standardized operating procedures. MRD

negativity was defined according to assay-specific thresholds: <10^-4 for flow cytometry and <10^-6 for next-generation sequencing. To minimize misclassification across platforms, MRD results were recorded as positive or negative based on these validated cutoffs and linked to the corresponding assessment date for time-dependent survival analyses. The prognostic implications of MRD clearance were interpreted in the context of assay sensitivity, which represents a recognized limitation of this retrospective study.

Safety data were collected at each visit, including all treatment-emergent adverse events (TEAEs) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCEA, current version) with special attention to cardiovascular events (e.g., atrial fibrillation/flutter, hypertension, thromboembolism) and bleeding events (any grade, including major intracranial or gastrointestinal hemorrhage). The study investigators reviewed all serious TEAEs, treatment-related deaths, and events resulting in dose modification or discontinuities, ensuring consistency and completeness through regular data monitoring and consistency and completeness.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Between-groups comparisons were conducted using the chi-square test or Fisher's exact test for categorical variables (e.g., response rates, TEAE frequencies, cardiovascular and bleeding events) and Student's t-test or Wilcoxon rank-sum test for continuous variables, as appropriate.

RFS and OS were defined as the time from treatment initiation and first documented disease relapse/progression or death from any cause, respectively. Patients without an event were censored at the date of last disease evaluation. RFS and OS distributions were estimated using the Kaplan-Meier method, and between-group differences were assessed with two-sided log-rank tests. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

To identify variables independently associated with outcomes, multivariable Cox proportional-hazards models were constructed for both RFS and OS, including treatment group, MIPI risk category, Ki-67 proliferation index (≥50% vs. <50%), and MRD status at 3 months. MRD was modeled as a time-dependent covariate to reflect the dynamic nature of molecular response. Wald chi-square statistics and corresponding *p*-values were calculated for each covariate, and the proportional-hazards assumption was verified using Schoenfeld residuals and log-minus-log plots.

Safety outcomes, including overall and grade 3+ TEAEs, serious AEs, treatment modifications, and cardiovascular and bleeding events, were reported as incidence proportions without multiplicity adjustment, as these analyses were descriptive and exploratory in nature.

Results

Baseline characteristics of the study population

The study cohort comprised an older, predominantly male population (mean age 64.3 ± 8.9 years; 70.5% male), with advanced and biologically aggressive disease at enrollment. 85.9% of patients had Ann Arbor stage III-IV disease, 45.9% were classified as high-risk according to MIPI, 29.1% exhibited blastoid or pleomorphic morphology, and 60.0% had a Ki-67 index ≥50%. Bulky masses (≥5 cm) and extranodal involvement at ≥2 sites were observed in 46.4% and 44.1% of patients, respectively. All patients harbored TP53 mutations, most commonly missense variants (64.1%), with the remainder carrying truncating (22.3%) or complex/other lesions (13.6%). Baseline clinical and molecular characteristics were well balanced between the monotherapy and combination therapy groups, with no significant differences for any parameter (all P>0.05) (**Table 1**).

Kaplan-Meier estimates of RFS

Patients in the observation group receiving BTKi-based combination treatment (n = 112) showed a slower decline in RFS probability compared with the control group (n = 108), with early separation of the Kaplan-Meier curves that persisted throughout the 60-month observation period. Median RFS was prolonged from 11 months in the control arm to 34 months in the observation arm (HR for recurrence or death, 0.42 (95% CI, 0.29-0.61; log-rank P<

Table 1. Comparison of baseline characteristics between the two groups

Characteristic	Overall (N = 220)	Control group (n = 108)	Observation group (n = 112)	t/χ^2	*p*-value
Age, years	64.3 ± 8.9	65.78 ± 8.33	65.21 ± 7.94	0.514	0.608
Male sex	155 (70.5)	77 (71.3)	78 (69.6)	0.072	0.788
ECOG performance status ≥2	62 (28.2)	30 (27.8)	32 (28.6)	0.017	0.896
Ann Arbor stage III-IV	189 (85.9)	92 (85.2)	97 (86.6)	0.092	0.762
MIPI risk category				1.585	0.453
Low	33 (15.0)	18 (16.7)	15 (13.4)		
Intermediate	86 (39.1)	45 (41.7)	41 (36.6)		
High	101 (45.9)	45 (41.7)	56 (50.0)		
Blastoid/pleomorphic variant	64 (29.1)	29 (26.9)	35 (31.3)	0.516	0.473
Ki-67 index ≥50%	132 (60.0)	62 (57.4)	70 (62.5)	0.594	0.441
TP53 mutation type				0.251	0.882
Missense	141 (64.1)	71 (65.7)	70 (62.5)		
Truncating (nonsense/frameshift)	49 (22.3)	23 (21.3)	26 (23.2)		
Complex/other	30 (13.6)	14 (13.0)	16 (14.3)		
Bulky disease ≥5 cm	102 (46.4)	49 (45.4)	53 (47.3)	0.084	0.772
Extranodal involvement ≥2 sites	97 (44.1)	45 (41.7)	52 (46.4)	0.506	0.477

Notes: ECOG: Eastern Cooperative Oncology Group; MIPI: Mantle Cell Lymphoma International Prognostic Index; Ki-67: Ki-67 proliferation index; TP53: Tumor protein p53.

0.001). Consistently, markedly more patients remained at risk in the observation arm at later time points: 40 versus 7 at 36 months, and 20 versus 1 at 60 months (**Figure 2**).

Kaplan-Meier estimates of OS

Median OS was extended from 20 months in the control group to 50 months in the observation group, corresponding to an HR of 0.44 (95% CI, 0.31-0.63; log-rank P<0.001), indicating a 56% relative reduction in the risk of death. This survival benefit was durable, as reflected by the larger number of patients remaining at risk in the observation arm at 60 months (35 vs. 10). The 95% confidence bands around the Kaplan-Meier curves showed minimal overlap, supporting the robustness of the observed treatment effect over time (**Figure 3**).

Treatment exposure and dose intensity

Overall BTKi exposure was substantial in both groups, but significantly longer in the observation group than in the control group (median 13.4 vs. 9.6 months; P = 0.004). Consistently, a greater proportion of patients in the observation arm remained on treatment at data cutoff (43.8% vs. 28.7%; P = 0.020), whereas early discontinuation within 3 months was infrequent and comparable between groups (12.5% vs. 17.6%; P = 0.290). Median relative BTKi dose intensity was high in both cohorts (95.02 ± 11.69 vs. 93.06 ± 12.05; P = 0.222), with similar proportions of patients receiving <80% of the planned dose (13.4% vs. 20.4%; P = 0.167). Rates of treatment interruption ≥7 days for any study drug (39.3% vs. 34.3%; P = 0.440) and BTKi dose reduction (25.0% vs. 22.2%; P = 0.628) did not differ significantly between groups (**Table 2**).

Treatment-emergent adverse events (TEAEs)

Any-grade TEAEs occurred in 94 of 108 patients (87.0%) in the control group and 103 of 112 patients (92.0%) in the observation group (P = 0.232). The incidence of grade ≥3 TEAEs was higher in the observation group than in the control group (60.7% vs. 47.2%, P = 0.045), whereas rates of serious AEs (37.5% vs. 30.6%, P = 0.277) and treatment-related serious AEs (24.1% vs. 17.6%, P = 0.235) were comparable. TEAEs leading to dose reduction (33.0% vs. 24.1%, P = 0.142), treatment interruption (40.2% vs. 31.5%, P = 0.179), or permanent discontinuation (25.0% vs. 19.4%, P = 0.322) were numerically more frequent in the observation arm, but differences did not reach statistical significance. Treatment-related deaths were

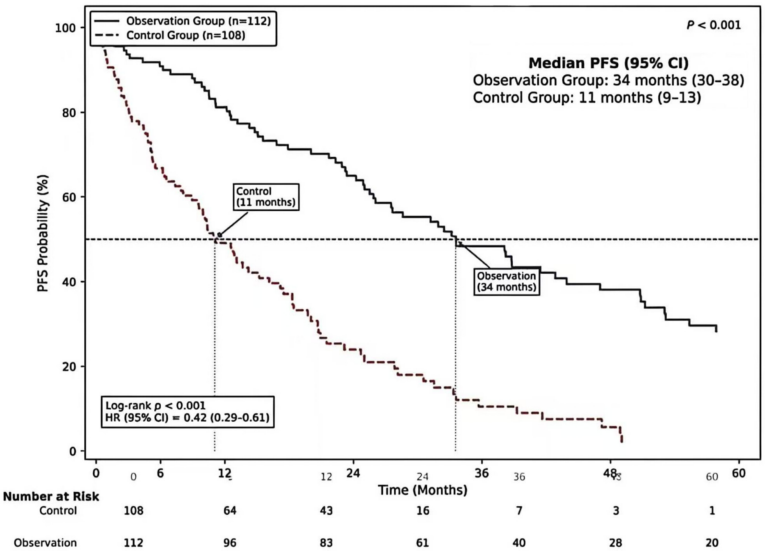

Figure 2. Kaplan-Meier analysis of progression-free survival (PFS).

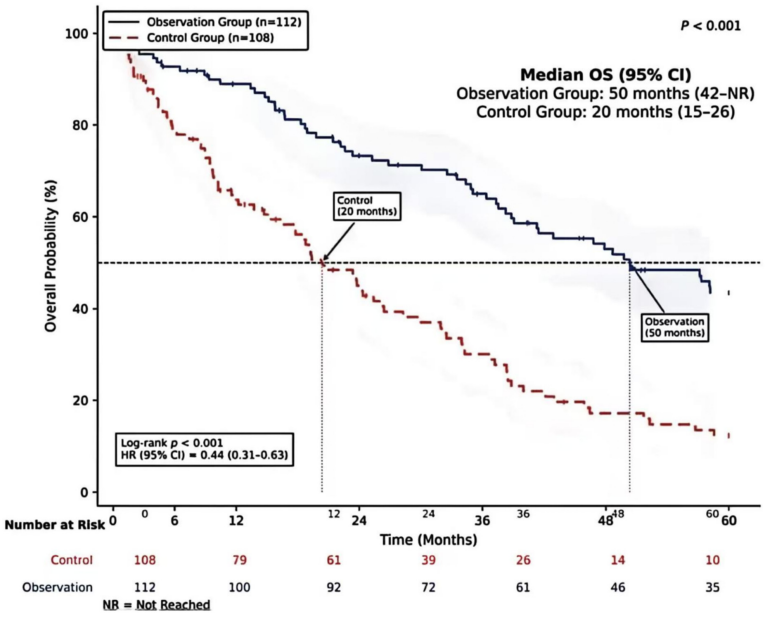

Figure 3. Kaplan-Meier analysis of overall survival (OS).

infrequent and balanced between groups (4.5% vs. 3.7%, P = 0.776), indicating no excess mortality associated with the combination regimen (**Table 3**).

Overall response and depth of response

In the observation group, 79 of 112 patients achieved an objective response, corresponding to an ORR of 70.5%, compared with 42 of 108 patients in the control group (38.9%; χ^2 test, P = 0.001). The CR rate was significantly higher in the observation group than in the control group (43.8% vs. 18.5%; P = 0.002), whereas the PR rate was comparable between the two groups (26.8% vs. 20.4%; P = 0.600). SD remained infrequent in both groups and did not differ significantly between treatments (8.0% vs. 13.9%; P = 0.130). These findings indicate that the superior ORR observed in the observation group was mainly driven by an increased CR rate rather than a difference in PR (**Figure 4**).

Detailed cardiovascular and bleeding events

The incidences of any atrial fibrillation (AF)/flutter and of new-onset AF among patients without a prior history of arrhythmia were comparable between groups (P = 0.875 and P = 0.827, respectively). Similarly, no significant between-group differences were observed for grade ≥2 hypertension exacerbation (P = 0.555) or for thromboembolic complications (P = 0.556). Overall bleeding events, including serious bleeding manifestations such as intracranial or gastrointestinal bleeding, were similarly distributed between groups (overall: P = 0.403; Intracranial hemorrhage: P = 0.979; Gastrointestinal bleeding: P = 0.737) (**Table 4**).

Kaplan-Meier estimates of PFS and OS according to MIPI risk subgroup and treatment group

In the low/intermediate MIPI risk subgroup (n = 119), patients in the observation group showed significantly prolonged PFS compared with the control group (log-rank P<0.001), with the median PFS not reached in the observation group versus 18 months (95% CI, 15-21) in the control group. A similar pattern was observed for OS (log-rank P = 0.012), with the median OS not reached in the observation group and 55

Table 2. Comparison of treatment exposure and dose intensity between the two groups

Variable	Control group (n = 108)	Observation group (n = 112)	χ^2/t	*p*-value
Patients on treatment at data cutoff	31 (28.7%)	49 (43.8%)	5.379	0.020
Early discontinuation (<3 months)	19 (17.6%)	14 (12.5%)	1.118	0.290
Median BTKi relative dose intensity, % (mean ± SD)	93.06 ± 12.05	95.02 ± 11.69	1.226	0.222
BTKi RDI <80%	22 (20.4%)	15 (13.4%)	1.913	0.167
Treatment interruption ≥7 days (any drug)	37 (34.3%)	44 (39.3%)	0.597	0.440
Dose reduction of BTKi	24 (22.2%)	28 (25.0%)	0.235	0.628

Notes: BTKi: Bruton tyrosine kinase inhibitor; RDI: Relative dose intensity.

Table 3. Comparison of treatment-emergent adverse events between the two groups

	Control group (n = 108)	Observation group (n = 112)	χ^2	*p*-value
Any TEAE (all grades)	94 (87.0%)	103 (92.0%)	1.426	0.232
Grade ≥3 TEAE	51 (47.2%)	68 (60.7%)	4.030	0.045
Any serious AE	33 (30.6%)	42 (37.5%)	1.180	0.277
Treatment-related SAEs	19 (17.6%)	27 (24.1%)	1.411	0.235
Any TEAE leading to dose reduction (any drug)	26 (24.1%)	37 (33.0%)	2.161	0.142
Any TEAE leading to treatment interruption	34 (31.5%)	45 (40.2%)	1.807	0.179
Any TEAE leading to permanent discontinuation	21 (19.4%)	28 (25.0%)	0.980	0.322
Treatment-related death	4 (3.7%)	5 (4.5%)	0.081	0.776

Notes: TEAE: Treatment-emergent adverse event; AE: Adverse event; SAEs: Serious adverse events.

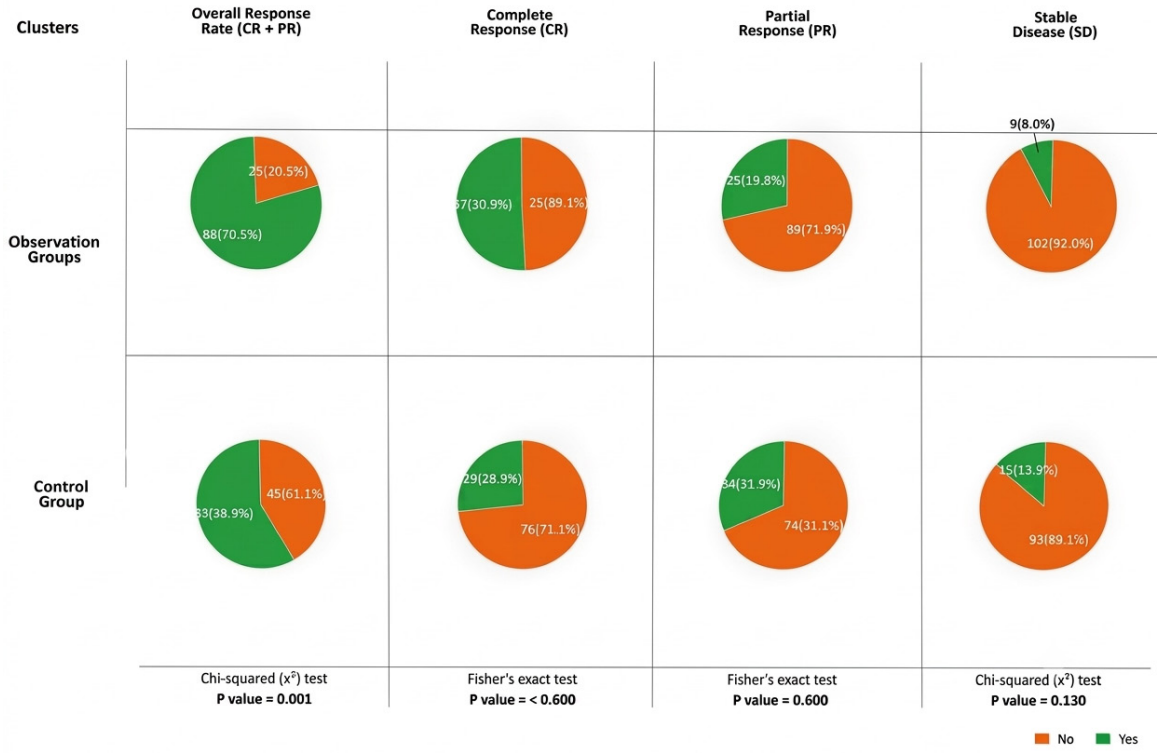

Figure 4. Overall response and depth of response.

Table 4. Comparison of adverse cardiovascular and bleeding events between the two groups

	Control group (n = 108)	Observation group (n = 112)	χ^2	*p*-value
Any atrial fibrillation/flutter	9 (8.3%)	10 (8.9%)	0.025	0.875
New-onset AF (no prior AF history)	6 (5.6%)	7 (6.3%)	0.048	0.827
Worsening hypertension (grade ≥2)	17 (15.7%)	21 (18.8%)	0.348	0.555
Any thromboembolic event	4 (3.7%)	6 (5.4%)	0.346	0.556
Any bleeding event (all grades)	21 (19.4%)	27 (24.1%)	0.701	0.403
Intracranial hemorrhage	1 (0.9%)	1 (0.9%)	0.001	0.979
Gastrointestinal bleeding	3 (2.8%)	4 (3.6%)	0.112	0.737

Note: AF: Atrial fibrillation.

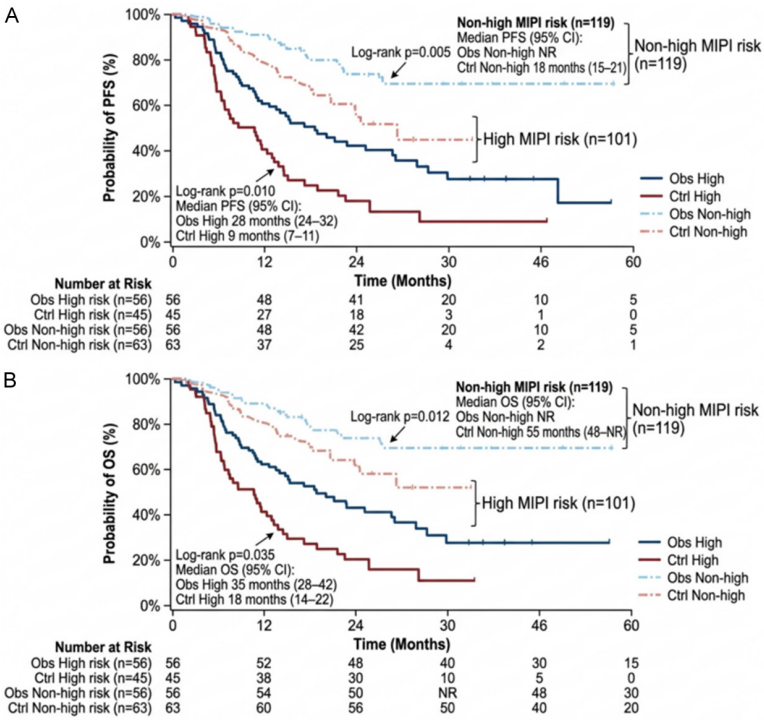

Figure 5. Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) stratified by MIPI risk subgroup and treatment group.

months (95% CI, 48-NR) in the control group. In the high MIPI risk subgroup (n = 101), the observation group also achieved significantly superior outcomes, with a median PFS of 28 months (95% CI, 24-32) versus 9 months (95% CI, 7-11) in the control group (log-rank P = 0.010), and a median OS of 35 months (95% CI, 28-42) versus 18 months (95% CI, 14-22) in the control group (log-rank P = 0.035) (**Figure 5**).

Multivariable Cox regression models for PFS and OS

BTKi plus venetoclax was independently associated with prolonged PFS compared with BTKi monotherapy (HR = 0.187, 95% CI 0.079-0.442; P< 0.001). In addition, a statistically significant association with OS was also observed (HR = 0.935, 95% CI 0.885-0.987; P = 0.015). High baseline MIPI risk was significantly associated with both PFS (HR = 3.675, 95% CI 1.533-8.809; P = 0.004) and OS (HR = 5.208, 95% CI 2.242-12.048; P<0.001). Similarly, a Ki-67 proliferation index ≥50% was significantly associated with both PFS (HR = 1.443, 95% CI 1.250-1.666; P<0.001) and OS (HR = 1.403, 95% CI 1.224-1.609; P<0.001). MRD-negative status at 3 months was also significantly associated with both PFS (HR = 0.387, 95% CI 0.279-0.536; P<0.001) and OS (HR = 0.398, 95% CI 0.289-0.548; P<0.001) (**Table 5**).

Kaplan-Meier analysis of PFS and OS according to Ki-67 risk subgroup

As shown in **Figure 6A**, patients in the high Ki-67 risk subgroup (Ki-67 ≥50%, n = 132) had significantly shorter PFS than those in the low Ki-67 risk subgroup (Ki-67 <50%, n = 88), with a median PFS of 22 months (95% CI, 16-28) versus 54 months (95% CI, 38-NR) (HR = 1.65; 95% CI, 1.22-2.23; log-rank P = 0.005). Consistently, OS was also significantly worse in high Ki-67 subgroup (**Figure 6B**), with median OS of 30 months (95% CI, 25-36) in the high Ki-67 subgroup versus not reached in the low Ki-67 subgroup (HR = 1.45; 95% CI, 1.10-1.91; log-rank P = 0.008). Collectively, these findings

Table 5. Multivariate Cox regression analysis of independent factors associated with PFS and OS

Covariate	HR for PFS (95% CI)	*p*-value	Wald χ^2	HR for OS (95% CI)	*p*-value	Wald χ^2
BTKi + venetoclax vs. BTKi monotherapy	0.187 (0.079-0.442)	<0.001	14.600	0.935 (0.885-0.987)	0.015	5.937
High MIPI risk vs. low/intermediate MIPI risk	3.675 (1.533-8.809)	0.004	8.515	5.208 (2.242-12.048)	<0.001	14.725
Ki-67 ≥50% vs. <50%	1.443 (1.250-1.666)	<0.001	25.003	1.403 (1.224-1.609)	<0.001	23.587
MRD-negative at 3 months vs. MRD-positive at 3 months (time-dependent)	0.387 (0.279-0.536)	<0.001	32.767	0.398 (0.289-0.548)	<0.001	32.076

Notes: PFS, Progression-free survival; OS, Overall survival.

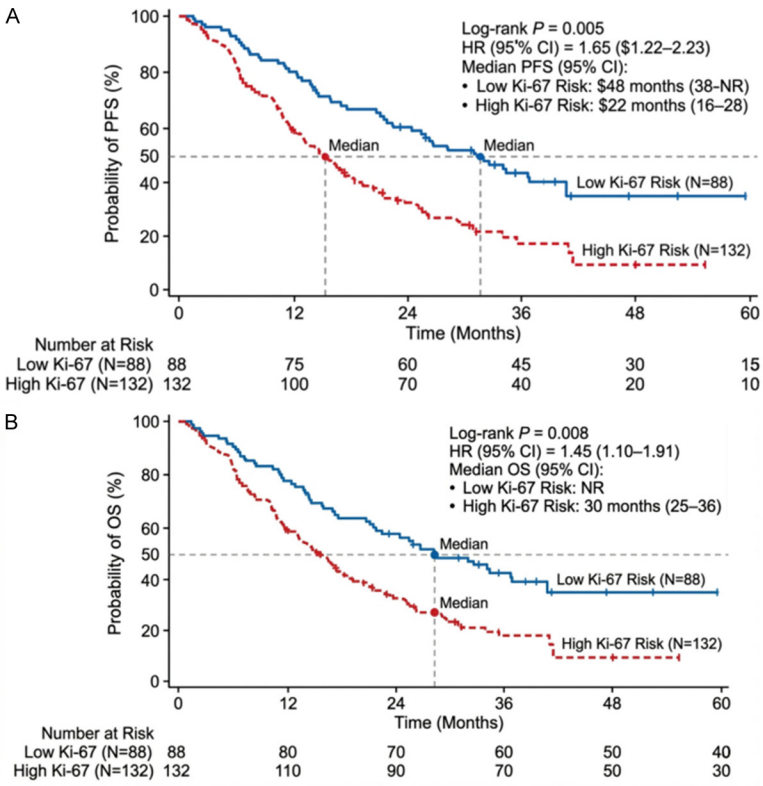

Figure 6. Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) stratified by Ki-67 risk (<50% vs. ≥50%).

indicate that elevated Ki-67 is strongly associated with aggressive disease and inferior survival outcomes.

Discussion

This study demonstrates that a novel BTK inhibitor, both alone and combined with venetoclax, provides clinically meaningful and durable improvements in RFS and OS in patients with TP53-mutated MCL. It achieves high overall response rates, with initial MRD clearance showing a significant prognostic effect, and exhibits an acceptable safety profile even with long-term follow-up. These findings address a significant gap in literature, as primary treatment resistance and dismal outcomes have historically characterized this biologically high-risk population.

The scale and stability of the RFS and OS benefits challenge the historical view that TP53 disruption necessarily confers BTK inhibitor-insensitive disease biology. Previous studies of first-generation BTK inhibitors in predominantly unselected MCL cohorts have demonstrated shorter median PFS and modest survival benefits, especially in TP53-aberrant subgroups. Chemotherapy-based therapies rarely achieve durable long-term disease control of this setting [19, 20]. These better hazard ratios observed in our study may reflect more selective kinase inhibition, prolonged suppression of BCR signaling, and optimized sequencing or combination with targeted agents. These data support the use of BTK inhibitor-based regimens as a front-line treatment backbone even in TP53-mutated MCL, while emphasizing the need for cautious across-trial comparisons.

The observation that overall response rates exceeded complete response rates, which were generally comparable between groups, highlights the fact that traditional response categories may not fully represent the clinical benefit of contemporary targeted regimens. Historically, BTK inhibitor and chemoimmunotherapy trials focused on CR as a surrogate for durable remis-

sion. However, emerging evidence in lymphoid malignancies suggests that the depth of molecular response and its dynamics may be more informative than morphologic CR [21, 22]. Our findings agree with a model in which prolonged disruption of pro-survival signaling and microenvironmental support reduces tumor viability even in patients achieving partial remission, especially when combined with BCL2-targeted therapy. This emphasizes importance of integrating both functional and molecular endpoints into response assessment, while cautioning against reliance on static imaging-based CR to inform therapeutic decision-making.

Identification of MRD negativity at 3 months emerged as the most potent independent predictor of both disease progression and death, confirming MRD as a crucial biomarker in high risk MCL. MRD status has been previously shown to be prognostic following chemoimmunotherapy and time-limited targeted regimens, but the magnitude of hazard reduction observed in this TP53-mutant population underscores the biological significance of prompt clone eradication [23, 24]. Mechanistically, early MRD clearance may reflect effective elimination of genomically unstable subclones before further evolutionary diversification, potentially preventing the occurrence of resistant disease. These data support MRD-based risk-adapted strategies, including treatment de-escalation in deep responders and escalation or combination therapy in early MRD-positive patients. They also highlight the importance of assay harmonization and repeated MRD measurements to avoid irreversible decisions based on a single time point.

The addition of venetoclax to the novel BTK inhibitor provided an independent PFS advantage but did not achieve a statistically significant OS benefit. This observation is consistent with previous experience in BTKi-venetoclax regimens in both CLL and MCL, where enhanced responses and higher MRD negativity rates are often observed prior to OS improvements, likely due to effective salvage therapies [25-27]. Clinically, these results suggest that venetoclax-based intensification may be particularly beneficial for patients with adverse features, such as high MIPI or elevated Ki-67 levels. Nonetheless, they also underscore the significance of long-term follow-up and formal health-economic evaluation when implementing more complex and resource- intensive therapies.

The safety profile of BTKi regimen, characterized by high rates of TEAEs but comparable rates of serious adverse events, low treatment-related mortality, as well as AF, hypertension, thromboembolic events, and major bleeding, seems favorable in TP53-mutated MCL. Previous BTK inhibitors have been linked to clinically significant cardiovascular and bleeding complications, which contributed to treatment discontinuation in a large group of patients. Our data indicate that enhanced kinase selectivity, standardized supportive care, and increased awareness of cardiovascular risk may mitigate these toxicities without compromising efficacy. Nonetheless, the higher incidence of grade 3 TEAEs and treatment adjustments in the experimental arm underscores the need for vigilant toxicity monitoring, preventive management of comorbidities, and careful patient selection in clinical practice.

Several limitations should be acknowledged. First, this retrospective real-world study was not primarily powered to detect small differences in overall survival between combination therapy and monotherapy; therefore, the current OS findings should be interpreted with appropriate caution. Second, although subgroup and multivariable analyses, including those involving MRD status, MIPI risk, and Ki-67, were biologically and clinically relevant, residual confounding cannot be fully excluded. Third, MRD assessment was performed at a predefined early time point and does not capture longitudinal MRD kinetics across different platforms. In addition, TP53 mutation site and variant abundance were not uniformly available because molecular testing was performed in different clinical settings and reported using non-identical formats across the study period; as a result, a post hoc analysis based on incomplete and non-standardized mutation annotation was considered methodologically unreliable and was not undertaken. Likewise, post-progression treatment data were not captured comprehensively, particularly for patients who received subsequent therapy outside the primary treating center, precluding a robust comparative analysis of post-progression management. Finally, because this study focused exclusively on TP53-mutated MCL, caution is war-

ranted when extrapolating these findings to broader MCL population.

Conclusion

This study demonstrates that BTKi-venetoclax regimen can partially overcome the traditionally unfavorable prognosis associated with TP53-mutated MCL, leading to sustained disease control, meaningful improvements in survival, and a manageable safety profile. Early MRD negativity emerged as a powerful prognostic indicator, highlighting the important role of molecular response assessment in guiding future treatment regimes. Collectively, these results support the incorporation of this regimen as a front-line therapy in high-risk MCL and provide a rationale for future MRD-driven, phase III trials to optimize treatment intensity and duration.

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Disclosure of conflict of interest

None.

Abbreviations

MCL, Mantle cell lymphoma; TP53, Tumor protein p53; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; ORR, Overall response rate; CR, Complete response; PR, Partial response; MRD, Minimal residual disease; PFS, Progression-free survival; RFS, Recurrence-free survival; OS, Overall survival; HR, Hazard ratio; CI, Confidence interval; MIPI, Mantle Cell Lymphoma International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; NHL, Non-Hodgkin lymphoma; BCR, B-cell receptor; FISH, Fluorescence in situ hybridization; NGS, Next-generation sequencing; CT, Computed tomography; PET, CT-Positron emission tomography-computed tomography; TLS, Tumor lysis syndrome; TEAE, Treatment-emergent adverse event; AE, Adverse event; SAE, Serious adverse event; AF, Atrial fibrillation; RDI, Relative dose intensity; IQR, Interquartile range; SD, Standard deviation.

Address correspondence to: Hui Lan, Department of Medical Oncology, Lishui Central Hospital, No. 289 Kuocang Road, Liandu District, Lishui 323000, Zhejiang, China. Tel: +86-0578-2285253; E-mail: 19858362843@163.com

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