



# A retrospective analysis of ibrutinib outcomes in relapsed or refractory mantle cell lymphoma

Yong-Pyo Lee<sup>1#</sup>, Ye Ji Jung<sup>2#</sup>, Junhun Cho<sup>3</sup>, Young Hye Ko<sup>3</sup>, Won Seog Kim<sup>2,4</sup>, Seok Jin Kim<sup>2,4</sup>, Sang Eun Yoon<sup>2</sup>

<sup>1</sup>Division of Hematology-Oncology, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Division of Hematology-Oncology, Departments of <sup>2</sup>Medicine, <sup>3</sup>Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, <sup>4</sup>Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea

p-ISSN 2287-979X / e-ISSN 2288-0011  
<https://doi.org/10.5045/br.2023.2023208>  
**Blood Res 2023;58:208-220.**

Received on October 26, 2023  
Revised on November 27, 2023  
Accepted on December 8, 2023

<sup>#</sup>These authors contributed equally to this work.

\*This study was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI22C0999). This study was also supported by grants from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (HR20C0025); a National Research Foundation of Korea grant funded by the Korean government (2022R1F1A1064058); and the Bio&Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. RS-2023-00222838).

## Correspondence to

Sang Eun Yoon, M.D., Ph.D.  
Division of Hematology-Oncology,  
Department of Medicine, Samsung  
Medical Center, Sungkyunkwan  
University School of Medicine, 81  
Irwon-ro, Gangnam-gu, Seoul 06351, Korea  
E-mail: starload0326@gmail.com

© 2023 Korean Society of Hematology

## Background

While treatment strategies for mantle cell lymphoma (MCL) have evolved, patients often experience disease progression and require additional treatment therapies. Ibrutinib presents a promising option for relapsed or refractory MCL (RR-MCL). This study investigated real-world treatment outcomes of ibrutinib in patients with RR-MCL.

## Methods

A single-center retrospective analysis investigated clinical characteristics and survival outcomes of patients with RR-MCL, treated with ibrutinib.

## Results

Forty-two patients were included, with 16 received rituximab and bendamustine, and 26 receiving anthracycline-based regimens as front-line treatment. During a median follow-up of 46.0 months, the response rate to ibrutinib was 69%, with 12 CRs and 8 partial responses. Disease progression (54.8%) and adverse events (11.9%) were the primary reasons for discontinuation. Median progression-free survival (PFS) and overall survival (OS) were approximately 16.4 and 50.1 months, respectively. Patients older than 70 years ( $P=0.044$  and  $P=0.006$ ), those with splenomegaly ( $P=0.022$  and  $P=0.006$ ), and those with a high-risk simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) ( $P<0.001$  and  $P<0.001$ ) exhibited significantly inferior PFS and OS. Notably, patients with a high-risk sMIPI relapsed earlier. Post-ibrutinib treatment yielded an OS of 12.2 months, while clinical trial participants demonstrated superior survival compared to those receiving chemotherapy alone.

## Conclusion

This study underscores the importance of considering patient characteristics before administering ibrutinib as salvage therapy. Early relapse was associated with poor outcomes, highlighting the need for novel therapeutic strategies.

**Key Words** Ibrutinib, Mantle-cell, Lymphoma, Relapsed or refractory

## INTRODUCTION

Mantle cell lymphoma (MCL) is a distinct subtype of non-Hodgkin's, accounting for approximately 2% of B-cell malignancies [1, 2]. According to an understanding of the developmental etiology of MCL, deregulation of B-cell receptor (BCR) signaling and Bruton tyrosine kinase (BTK) permits continuous B-cell proliferation, leading to MCL development in the pre-germinal center. BTK inhibitors block BCR signaling propagation, related to B-cell proliferation, and allow cancer cell apoptosis by ultimately reducing nuclear factor- $\kappa$ B pathway activity [3]. Thus, BTK is a key factor in BCR signaling and a therapeutic target for MCL. Several covalent (ibrutinib, acalabrutinib, and zanubrutinib) and non-covalent (pirtobrutinib) BTK inhibitors have been developed [4].

Among the various BTK inhibitors, ibrutinib, the first oral selective BTK inhibitor, has a favorable objective response rate (ORR) of 65–70% with a complete response (CR) rate of 19% and progression-free survival (PFS) of 12–15 months for relapsed/refractory MCL (RR-MCL) patients, who received more than two treatments prior [5–15]. Previous studies suggested that the response to ibrutinib depended on the simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI), which is calculated based on age, performance status, lactate dehydrogenase (LDH), and white blood cell (WBC) count. In addition to the sMIPI, other factors, predicting survival and therapeutic responses, have been suggested. However, their consistency has not been demonstrated across studies. Considering the various underlying conditions of non-selected patients, further retrospective studies, that accurately reflect real-world situations, are needed to identify clinical biomarkers, that directly predict the favorable outcomes of ibrutinib treatment, and treatment strategies need to be established accordingly.

The optimal timing of ibrutinib treatment is unknown due to the lack of consensus and the introduction of various novel agents. Owing to the limited efficacy of ibrutinib in achieving and maintaining disease remission, most patients experience disease progression, leading to poor survival. Chimeric Antigen Receptor (CAR)-T cell therapy is recommended for these patients [16, 17]. However, real-world constraints limit the accessibility of this cutting-edge treatment to a subset of patients. Thus, it is challenging to find definitive and palliative treatment schemes for patients with progressive disease due to the changing trends in the treatment of MCL treatment, caused by the development of various targeted agents and immune-cellular therapies.

Therefore, this retrospective study evaluated the clinical outcomes of 42 patients with RR-MCL, who received ibrutinib. This study presents the outcomes of ibrutinib treatment according to associated clinical variables and discusses subsequent therapeutic strategies for patients, who were refractory to ibrutinib treatment. In addition, the overall response and survival outcomes of patients, following the continuation and discontinuation of ibrutinib, were investigated.

## MATERIALS AND METHODS

### Study overview

This retrospective study investigated the characteristics and survival outcomes of patients with RR-MCL, treated with ibrutinib after at least one prior systemic therapy. By analyzing this comprehensive dataset, this study aimed to determine the benefits and outcomes, associated with salvage ibrutinib therapy in patients with RR-MCL. The study population was drawn from two prospective cohort studies (Institutional Review Board numbers: 2016-11-040 and 2022-05-078). Following a meticulous review of all tissue samples by pathology experts at our institution (J.C. and Y.H.K.), the diagnosis of MCL was conclusively established according to the WHO 2016 classification [18].

### Patients and data collection

The medical records of the patients were reviewed to collect the following clinical and laboratory data: age; sex; Eastern Cooperative Oncology Group Performance Status; Ann Arbor stage; presence of extra-nodal involvement; bone marrow (BM) involvement; splenomegaly, defined by a horizontal length greater than 11 cm; Ki-67 expression rate; sMIPI; complete blood count; LDH; and  $\beta$ -2 microglobulin (B2M). Unfortunately, *TP53* mutation evaluation using next-generation sequencing (NGS) was not performed in all patients due to lack of consent.

The study registration of patients was concluded in December 2021, and the data analysis was based on information available up to April 2023, which served as the cut-off date for this study. The IRB of the Samsung Medical Center approved this study (approval number. 2016-11-040-025), and all participants provided written informed consent before their enrollment. The study adhered to the ethical principles, outlined in the Declaration of Helsinki and the Korea Good Clinical Practice guidelines. Ethical considerations were strictly followed throughout this study.

### Ibrutinib therapy and response evaluation

Patients with RR-MCL received a prescribed daily dose of 560 mg of oral ibrutinib until disease progression or the emergence of intolerable toxicity. Dose adjustments, delays, and treatment discontinuation were decided at the physician's discretion, based on the severity of adverse events (AEs) or disease progression. According to the Lugano classification, treatment response was evaluated using computed tomography (CT) and/or  $^{18}\text{F}$ -fluorodeoxyglucose positron-emission tomography CT [19]. Patients, who achieved a CR or partial response (PR), were categorized as responders, while those with stable disease (SD) or disease progression were considered non-responders. The patients, who did not achieve disease control (CR, PR, or SD), were classified as primary non-responders. Moreover, those, with controlled diseases, that receded over time, were classified as secondary non-responders. Finally, those, whose controlled disease status was maintained until the last follow-up, were classified

as consistent responders. Early relapse was defined as disease recurrence within 12 months of ibrutinib administration.

The administration of the following first-line treatment options was confirmed: bendamustine and rituximab (BR); rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone (R-CHOP); and rituximab, cyclophosphamide, cytarabine, vincristine, and prednisolone (R-Hyper-CVAD). The regimens were classified as BR- or anthracycline-containing (R-CHOP or R-Hyper-CVAD) for analysis. None of the patients received cytarabine-containing first-line chemotherapy. A few patients eligible for autologous stem cell transplantation (ASCT) underwent high-dose chemotherapy, including cytarabine, followed by ASCT. None of the patients underwent allogeneic SCT.

### Statistical analysis

Descriptive statistics, including proportions and medians,

were used to analyze the data. Intergroup comparisons of categorical variables were performed using the Fisher's exact test. ORR was defined as the proportion of patients, who achieved CR or PR, with the best response obtained during ibrutinib treatment. PFS and OS were evaluated using the Kaplan-Meier method. The PFS was measured from the initiation of ibrutinib treatment to the date of disease progression or death. OS was measured from the date of ibrutinib initiation to the date of death due to any cause or last follow-up. Additionally, the OS of post-ibrutinib treatment patients was calculated from the starting date of next-line anti-cancer therapies after ibrutinib interruption to the date of death from any cause or last follow-up. The cumulative incidence of early relapse was estimated using the Kaplan-Meier method. The log-rank test was used for comparisons, and both univariate and multivariate analyses were performed to estimate the associations between the survival

**Table 1.** Baseline demographics and disease characteristics at diagnosis.

Characteristics		Total (N=42)	BR (N=16)	Anthracycline-based regimen (N=26)	P
Age (yr)	Median (range)	62 (38–78)	63 (50–78)	61 (39–70)	0.004
	< 60	17 (40.5%)	2 (12.5%)	15 (57.7%)	
	≥ 60	25 (59.5%)	14 (87.5%)	11 (42.3%)	
Gender	Male	30 (71.4%)	11 (68.7%)	19 (73.0%)	0.763
	Female	12 (28.6%)	5 (31.2%)	7 (27.0%)	
ECOG-PS	0–1	39 (92.9%)	14 (87.5%)	25 (96.2%)	0.290
	2–4	3 (7.1%)	2 (12.5%)	1 (3.8%)	
B symptom	Absence	37 (88.1%)	13 (81.2%)	24 (92.3%)	0.283
	Present	5 (11.9%)	3 (18.7%)	2 (7.7%)	
Leukocytosis	Absence	31 (73.8%)	8 (50.0%)	23 (88.5%)	0.006
	Present	11 (26.2%)	8 (50.0%)	3 (11.5%)	
Anemia	Absence	33 (78.6%)	9 (56.2%)	24 (92.3%)	0.006
	Present	9 (21.4%)	7 (43.7%)	2 (7.7%)	
Thrombocytopenia	Absence	36 (85.7%)	11 (68.7%)	25 (96.2%)	0.014
	Present	6 (14.3%)	5 (31.2%)	1 (3.8%)	
Serum LDH	Absence	23 (54.8%)	7 (43.7%)	16 (61.5%)	0.261
	Elevated	19 (45.2%)	9 (56.2%)	10 (38.5%)	
Serum $\beta$ -2 microglobulin	Absence	23 (54.8%)	5 (31.2%)	18 (69.2%)	0.016
	Elevated	19 (45.2%)	11 (68.7%)	8 (30.8%)	
Bone marrow involvement	Absence	13 (31.0%)	2 (12.5%)	11 (42.3%)	0.042
	Present	29 (69.0%)	14 (87.5%)	15 (57.7%)	
Number of extra-nodal involvement	Less than one	11 (26.2%)	2 (12.5%)	9 (34.6%)	0.113
	More than two	31 (73.8%)	14 (87.5%)	17 (65.4%)	
Bulky ( $\geq 7$ cm) mass	Absence	33 (78.6%)	10 (62.5%)	23 (88.5%)	0.046
	Present	9 (21.4%)	6 (37.5%)	3 (11.5%)	
Pathology	Classic type	41 (97.6%)	16 (100.0%)	25 (96.2%)	0.427
	Pleomorphic/blastoid type	1 (2.4%)	0 (0.0%)	1 (3.8%)	
Ki-67	< 30%	33 (78.6%)	12 (75.0%)	21 (80.8%)	0.658
	≥ 30%	9 (21.4%)	4 (25.0%)	5 (19.2%)	
Ann Arbor stage	I/II	5 (11.9%)	1 (6.3%)	4 (15.4%)	0.375
	III/IV	37 (88.1%)	15 (93.7%)	22 (84.6%)	
sMIPI score	Low (0–3)	19 (45.2%)	3 (18.7%)	16 (61.5%)	0.002
	Intermediate (4–5)	18 (42.9%)	8 (50.0%)	10 (38.5%)	
	High (6–11)	5 (11.9%)	5 (31.3%)	0 (0.0%)	

Abbreviations: ASCT, autologous stem cell transplantation; BR, bendamustine plus rituximab; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; sMIPI, simplified mantle cell lymphoma international prognostic index.

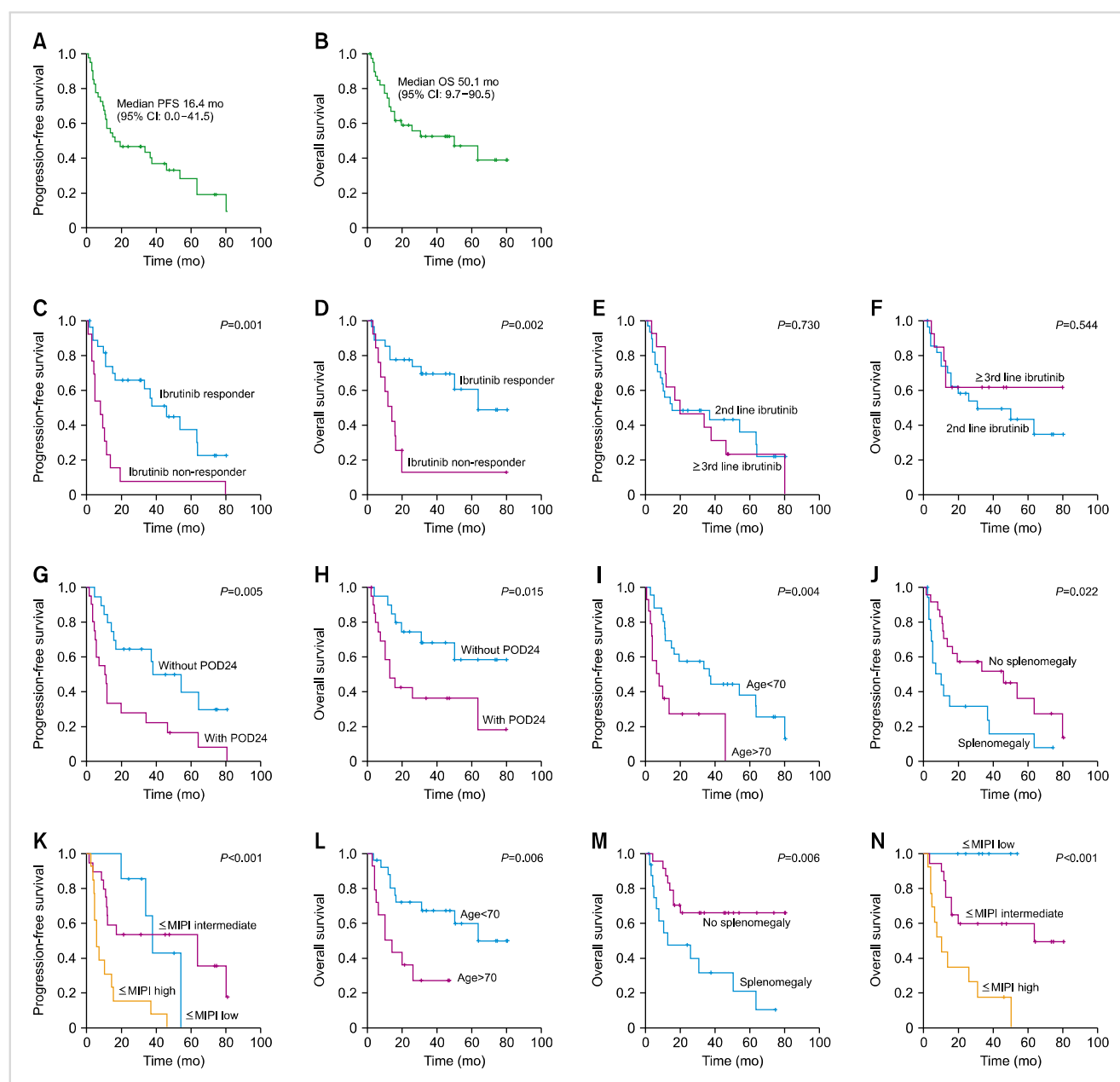
rate and variables, concerning the administration of salvage ibrutinib. Data were analyzed using the Statistical Package for Social Sciences software (version 24.0, IBM Corp., Armonk, NY, USA).

## RESULTS

### Patient characteristics at diagnosis and outcomes of front-line treatment

The baseline demographics of the 42 patients at the time

of their diagnosis are presented in Table 1. The median age was 62 years (range, 38–78 yr), and 25 patients (59.5%) were more than 60 years old. Most patients were male (N=30, 71.4%). Leukocytosis and elevated LDH levels were observed in 20% (N=11) and 45.4% (N=19) of the patients, respectively. Based on the pathologic reviews, most cases were documented as the classic MCL type (N=41, 97.6%), and 21.4% (N=9) presented with Ki-67 overexpression ( $\geq 30\%$ ). Among 37 patients (88.1%) diagnosed with stage III or IV disease, five (11.9%) presented with high-risk sMIPI, and most patients (N=37, 88.1%) were classified under low/intermediate-



**Fig. 1.** Kaplan-Meier curve of progression-free survival (PFS) (A) and overall survival (OS) for salvage ibrutinib therapy (B). Comparison of PFS and OS of ibrutinib treatment according to response (C, D), line of treatment (E, F), and progression of disease within 24 months of front-line treatment (G, H). Assessment of PFS according to age (I), presence of splenomegaly (J), and simplified mantle cell lymphoma international prognostic index (sMIPI) (K) and OS according to age (L), presence of splenomegaly (M), and sMIPI (N).

risk sMIPI.

Among the 42 patients, 16 (38.1%) received BR, and 26 (61.9%) were treated with an anthracycline-containing regimen as a front-line treatment. Patients older than 60 years ( $P=0.004$ ) with leukocytosis ( $P=0.006$ ), anemia ( $P=0.006$ ), thrombocytopenia ( $P=0.014$ ), elevated B2M ( $P=0.016$ ), BM involvement ( $P=0.042$ ), or low-/intermediate-risk sMIPI ( $P=0.002$ ) mainly received BR regimens rather than anthracycline-containing regimens (Table 1).

### Ibrutinib as a salvage treatment

The patient's characteristics at the start of ibrutinib treatment are presented in Supplementary Table 1. The patients received a median of one other treatment (range, 1–5) before ibrutinib administration. The ORR was 69% ( $N=29$ ), with 21 CR (50%) and eight PR (19%). Patients ( $N=29$ , 69.0%), who had previously received one line of treatment, were administered a median of 12 cycles of ibrutinib (range, 1–55), and they achieved an ORR of 72.4% ( $N=21$ ), with 16 CR (55.1%) and five PR (17.2%). Furthermore, patients ( $N=13$ , 31.0%), previously treated with more than two lines of treatment, received a median of 14 cycles of ibrutinib (range, 3–23), and they achieved an ORR of 61.5% ( $N=8$ ), with five CR (38.4%) and three PR (23%). The most common reasons for treatment discontinuation were disease progression ( $N=23$ , 54.8%) and severe AEs ( $N=5$ , 11.9%).

During a median follow-up of 46.0 months (95% CI, 1.9–80.5), the median PFS was 16.4 months (95% CI, 0.0–41.5), and the median OS was 50.1 months (95% CI, 9.7–90.5; Fig. 1A, B). The responders showed superior PFS (46.0 mo; 95% CI, 26.2–65.7 vs. 7.9 mo; 95% CI, 2.8–12.9;  $P=0.001$ )

and OS (63.5 mo; 95% CI, 42.9–67.3 vs. 13.6 mo; 95% CI, 7.3–19.9;  $P=0.002$ ), compared to poorly responding patients (Fig. 1C, D). There was no difference in PFS ( $P=0.730$ ) or OS ( $P=0.544$ ) according to the line of treatment (Fig. 1E, F). However, patients, who experienced disease progression within 24 months of front-line treatment (POD 24), exhibited inferior PFS (10.5 mo; 95% CI, 4.4–16.6 vs. 53.8 mo; 95% CI, 27.9–79.6;  $P=0.005$ ) and OS (12.6 mo; 95% CI, 4.5–20.7 vs. NR;  $P=0.015$ ) upon receiving salvage ibrutinib treatment (Fig. 1G, H).

Patients, who were older than 70 years at the initiation of ibrutinib treatment (7.9 mo; 95% CI, 1.3–14.4 vs. 36.6 mo; 95% CI, 9.8–63.5;  $P=0.004$ ), or those with splenomegaly (9.9 mo; 95% CI, 0.4–19.4 vs. 46.0 mo; 95% CI, 10.3–81.6;  $P=0.022$ ) or a high-risk sMIPI (5.0 mo; 95% CI, 2.3–7.7 vs. 37.4 mo; 95% CI, 29.4–45.4 vs. 63.5 mo; 95% CI, 0.0–152.8;  $P<0.001$ ) exhibited inferior PFS with ibrutinib treatment (Fig. 1I–K). Moreover, patients older than 70 years (13.6 mo; 95% CI, 6.7–20.5 vs. 63.5 mo; 95% CI, 9.8–63.5;  $P=0.006$ ) or those with splenomegaly (12.6 mo; 95% CI, 0.0–34.0 vs. not reached [NR];  $P=0.006$ ) or a high-risk sMIPI (9.9 mo; 95% CI, 3.4–16.4 vs. NR vs. NR;  $P<0.001$ ) displayed poorer OS (Fig. 1L–N). In the univariate and multivariate analyses, the duration of ibrutinib treatment and sMIPI were significant factors, influencing both OS and PFS (Table 2).

### Characteristics of the patients who experienced early relapse

An analysis was conducted to confirm the clinical markers, affecting early relapse during ibrutinib treatment ( $N=13$ , 30.9%). According to the independent samples t-test, only a high-risk sMIPI was correlated with early relapse ( $P=0.033$ ,

**Table 2.** Univariate and multivariate analyses for progression-free survival and overall survival with salvage ibrutinib treatment.

Variables	Overall survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age ( $\geq 70$ yr)	3.419 (1.340–8.726)	0.010	0.380 (0.106–1.358)	0.137	3.158 (1.395–7.146)	0.006	0.578 (0.201–1.661)	0.308
sMIPI score (high score)	5.325 (2.111–13.428)	$<0.001$	6.249 (2.067–18.892)	0.001	4.681 (2.086–10.501)	$<0.001$	2.874 (1.171–7.055)	0.021
Splenomegaly	3.303 (1.345–8.111)	0.009	1.983 (0.439–8.961)	0.374	2.338 (1.107–4.936)	0.026	1.373 (0.506–3.720)	0.534
Anthracycline-containing front-line treatment	0.197 (0.075–0.516)	0.001	1.282 (0.354–4.647)	0.705	0.159 (0.063–0.402)	$<0.001$	0.273 (0.081–0.921)	0.036
POD 24 of front-line treatment	3.013 (1.190–7.625)	0.020	0.991 (0.242–4.070)	0.991	2.858 (1.336–6.117)	0.007	1.895 (0.737–4.876)	0.185
Previous number of treatments ( $\geq 2$ lines)	0.730 (0.263–2.024)	0.546			1.230 (0.576–2.626)	0.593		
Underwent ASCT before ibrutinib treatment	0.692 (0.230–2.086)	0.513			1.068 (0.468–2.439)	0.876		
Duration of ibrutinib $> 12$ months	0.023 (0.003–0.179)	$<0.001$	0.011 (0.001–0.110)	$<0.001$	0.041 (0.011–0.154)	$<0.001$	0.042 (0.010–0.180)	$<0.001$
Grade 3/4 adverse events	3.185 (1.203–8.433)	0.020	1.884 (0.612–5.798)	0.269	1.977 (0.789–4.953)	0.146		

Abbreviations: ASCT, autologous stem cell transplantation; POD 24, disease progression within 24 months; sMIPI, simplified mantle cell lymphoma international prognostic index.



**Table 3).** Patients with early relapse had significantly poorer survival outcomes than those, who did not experience early relapse (12.6 mo; 95% CI, 7.9–17.3 vs. NR;  $P < 0.001$ , Fig. 2A). The primary non-responders had exceptionally poor survival compared to secondary non-responders and consistent responders (5.9 mo; 95% CI, 0.7–11.1 vs. 30.7 mo; 95% CI, 1.2–60.2 vs. NR;  $P = 0.002$ , Fig. 2B). In terms of cumulative incidence, patients who received BR as front-line treatment ( $P = 0.004$ ), those with high-risk sMIPI ( $P = 0.010$ ), and those older than 70 years ( $P = 0.011$ ) were strongly correlated with an increased cumulative incidence of early relapse (Fig. 2C–E). However, there was a weak correlation between early relapse, splenomegaly ( $P = 0.084$ ), and prior lines of treatment ( $P = 0.720$ ) (Fig. 2F, G).

### Post-ibrutinib survival outcomes

The median OS for patients, who discontinued ibrutinib treatment (N=37, 88.1%), was 9.8 months (95% CI, 0.6–19.0) (Fig. 3A). The ibrutinib responders had a better post-ibrutinib OS than the non-responders, but the difference was not statistically significant (20.0 mo; 95% CI, 0.0–43.0 vs. 5.7 mo; 95% CI, 0.0–13.2;  $P = 0.101$ ). The primary non-responders, who did not achieve disease control, had a median OS of only 2.6 months (95% CI, 0.0–10.4) after ibrutinib treatment.

Twenty-three patients (62.1%) received additional anti-cancer therapies after ibrutinib discontinuation, and the estimated median OS after ibrutinib was 12.2 months (95%

CI, 2.1–22.2). Sixty-five percent of patients (N=15) received bortezomib or novel agents, such as lenalidomide and venetoclax, and 21.7% (N=5) participated in clinical trials. Although statistical significance was not achieved, the patients assigned to clinical trials had improved survival outcomes, compared to those, who received conventional chemotherapy ( $P = 0.458$ , Fig. 3B). In terms of post-ibrutinib survival, the patients, who experienced early relapse, generally had an inferior OS (5.4 mo; 95% CI, 0.0–12.7 vs. 24.8 mo; 95% CI, 15.7–37.2;  $P = 0.012$ ) (Fig. 3C).

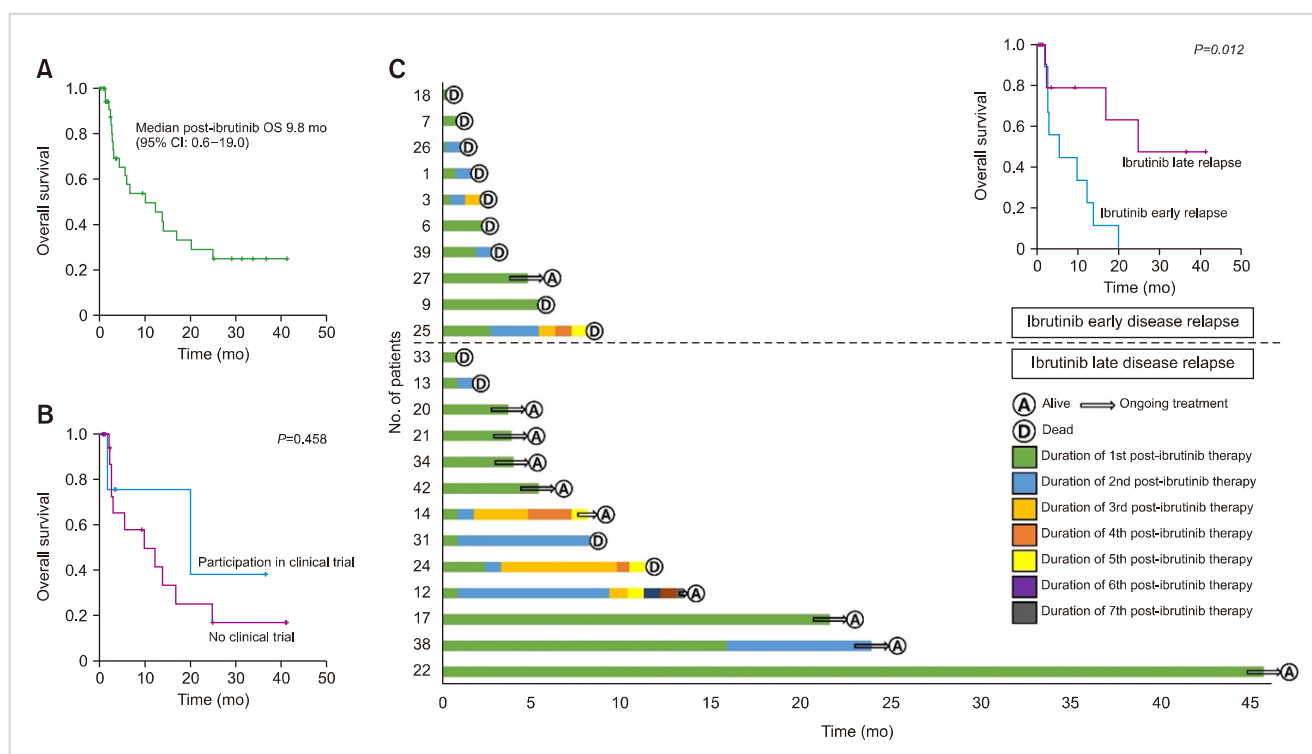
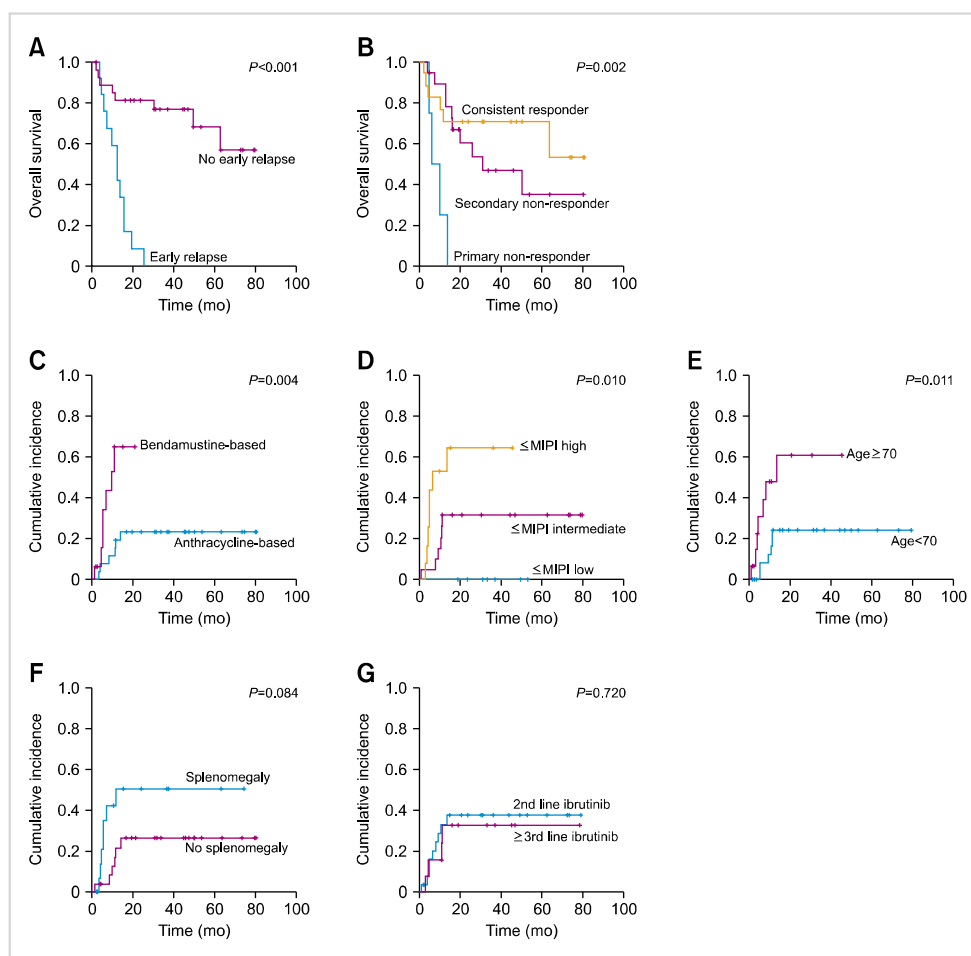
### Adverse events with ibrutinib treatment

During ibrutinib treatment, various hematologic and non-hematologic AEs were observed, but most were reported as grade 1 or 2 and were manageable. Six patients (14.3%) received a reduced ibrutinib dose, and five patients (11.9%) discontinued ibrutinib treatment due to toxicities (Supplementary Table 2). All grades of thrombocytopenia accounted for 11.9% of the hematologic AEs (N=5). In particular, grade  $\geq 3$  thrombocytopenia accounted for 7.1% (N=3). The incidence of all grades of anemia and neutropenia was 7.1%, and less than 5% had a grade  $\geq 3$ . The most common non-hematologic AE was skin rash (N=20, 47.6%), and only four patients (9.5%) presented with a grade  $\geq 3$ . Grade  $\geq 3$  fatigue and diarrhea were observed in approximately 9.5% (N=4) and 7.1% (N=3), respectively. Three patients (7.1%) had grade 1 or 2 atrial fibrillation, and all were adequately managed through medical intervention. Of the five patients who dis-

**Table 3.** Comparison of patients with and without early disease relapse.

Characteristics		Early relapse (N=13)	Late relapse or no relapse (N=29)	P
Age (yr)	Median (yr), range	67 (51–77)	67 (45–81)	0.101
	<70	6 (46.2%)	21 (72.4%)	
	$\geq 70$	7 (53.8%)	8 (27.6%)	
Gender	Male	10 (76.9%)	20 (69.0%)	0.598
	Female	3 (23.1%)	9 (31.0%)	
ECOG-PS	0–1	12 (92.3%)	29 (100.0%)	0.131
	2–4	1 (7.7%)	0 (0.0%)	
sMIPI score	Low (0–3)	0 (0.0%)	7 (24.1%)	0.033
	Intermediate (4–5)	6 (46.2%)	14 (48.3%)	
	High (6–11)	7 (53.8%)	8 (27.6%)	
Splenomegaly ( $\geq 11$ cm)	Absence	7 (53.8%)	11 (37.9%)	0.335
	Present	6 (46.2%)	18 (62.1%)	
Prior number of treatment	Prior 1 line	9 (69.2%)	20 (69.0%)	0.986
	Prior $\geq 2$ lines	4 (30.8%)	9 (31.0%)	
Front-line treatment	Anthracycline-based	6 (46.2%)	20 (69.0%)	0.159
	Bendamustine-based	7 (53.8%)	9 (31.0%)	
ASCT	Received	3 (23.1%)	7 (24.1%)	0.941
	Not received	10 (76.9%)	22 (75.9%)	
Ibrutinib dose adjustment	Dose reduction	1 (7.7%)	5 (17.2%)	0.414
	No dose reduction	12 (92.3%)	24 (82.8%)	
Ibrutinib discontinuation	Discontinuation	13 (100.0%)	24 (82.8%)	0.111
	No discontinuation	0 (0.0%)	5 (17.2%)	

Abbreviations: ASCT, autologous stem cell transplantation; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; sMIPI, simplified mantle cell lymphoma international prognostic index.



**Fig. 3.** Kaplan-Meier curves of overall survival for post-ibrutinib treatment (A). Comparison of overall survival according to participation in clinical trials (B). Swimmer plot of patients who received post-ibrutinib treatment (C).

continued ibrutinib, one ceased treatment due to a hematologic AE (grade 3 thrombocytopenia), while the remaining four stopped due to non-hematologic AEs (two patients with grade 3 diarrhea, one with grade 3 rash, and one with grade 3 fatigue). Among the consistent responders older than 70 years, those who were maintained on ibrutinib treatment with well-managed severe AEs had a more favorable PFS (36.6 mo; 95% CI, 12.3–60.9 vs. 11.4 mo; 95% CI, 0.0–23.1;  $P=0.234$ ) and OS (NR vs. 11.4 mo; 95% CI, 0.0–23.1;  $P=0.062$ ) (Supplementary Fig. 1A).

## DISCUSSION

This study evaluated the efficacy and survival outcomes of ibrutinib treatment, based on real-world clinical experience.

According to previous studies (Table 4) [5–14], patients with RR-MCL, treated with ibrutinib as a second- or third-line treatment, achieved an ORR of 69.7% and PFS of 12.5 months throughout a median follow-up period of two years. In this retrospective single-center study, the patients achieved an ORR of 69% and a PFS of 16.4 months within the same median follow-up period of two years. Patients, who were older than 70 years at the initiation of ibrutinib treatment, and those, who experienced POD 24, had poorer survival. In particular, having a high-risk sMPII had a negative impact on the survival outcomes, associated with salvage ibrutinib. Additionally, primary non-responders, who were refractory to ibrutinib, and patients, who experienced early relapse, experienced more significant adverse clinical outcomes. Patients, who were treated for a longer period with active management of severe AEs, had superior survival outcomes.

**Table 4.** Summary of previous studies on ibrutinib therapy in relapsed or refractory mantle cell lymphoma.

Study	Pt. number	Front-line Tx.	Refractory to front-line Tx.	Upfront ASCT	Prior Tx.	ORR	PFS (median)	OS (median)	Ref
Phase 2	111	R-containing therapy (N=99, 89%)	50 (45%)	8 (13%)	3 (1–5)	67% (CR, 23%)	13 mo	22.5 mo	[5, 6]
Phase 3	280	R-containing therapy (N=280, 100%)	36 (26%)	N/A	2 (1–9)	72% (CR, 19%)	14.6 mo	Not reached	[7]
Retrospective	97	Intensive induction therapy (N=52, 54%) (R±hyper-CVAD, R-maxi CHOP)	7 (7%)	38 (39%)	2 (1–8)	65% (CR, 33%)	15 mo	22 mo	[8]
Phase 2	16	R-containing therapy (N=16, 100%)	1 (6.2%)	N/A	2.5 (1–4)	87.5% (CR, 12.5%)	N/A	N/A	[9]
Retrospective	33	R-CHOP (N=33)	N/A	6 (18.1%)	1 (33.3%) 2 (36.4%) ≥ 3 (30.3%)	64% (CR, 15%)	27.4 mo	35.1 mo	[10]
Retrospective	65	R-CHOP, R-bendamustine and R-hyper-CVAD (87%)	N/A	N/A	2 (1–6)	N/A	12.0 mo	18.5 mo	[11]
Retrospective	88	R±CHOP (N=63) R±hyper-CVAD (N=13) BR (N=6) VR-CAP (N=3) CVP/bendamustine (N=3)	N/A	5 (5.6%)	1 (1–6)	64.8% (CR, N/A)	20.8 mo	2-yr OS rate 79.5%	[12]
Retrospective	211	R-CHOP/mini-CHOP (N=70, 33%) Cytarabine-based regimen (N=60, 28%) R-bendamustine (N=45, 21%) VR-CAP (N=5, 2%) Others (N=31, 15%)	38 (18%)	53 (25%)	1	69% (CR, 27%)	17.8 mo	23.9 mo	[13]
Retrospective	77	CHOP/CHOP-like (N=42, 54%) Cytarabine-based regimen (N=25, 33%) Non-anthracycline regimen (N=10, 13%)	15 (20%)	19 (25%)	1 (29%) 2 (30%) ≥ 3 (41%)	66% (CR, 31%)	10.3 mo	23.1 mo	[14]
Retrospective	42	R-CHOP (N=18, 43%) R-hyper-CVAD (N=8, 19%) R-bendamustine (N=16, 38%)	20 (47.6%)	6 (14.3%)	1 (1–5)	69% (CR, 50%)	19.2 mo	50.1 mo	Current study

Abbreviations: ASCT, autologous stem cell transplantation; BR, rituximab, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CVP, cyclophosphamide, vincristine, prednisone; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; LOT, line of therapy; N/A, non-available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Pt., patient; R, rituximab; Tx., treatment; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.



This highlighted the relevance of ibrutinib treatment duration.

Based on the CAN3001 study, which reported the long-term outcomes of salvage ibrutinib treatment with 10 years of follow-up [20], severe treatment-related AEs (TRAEs) were generally observed within one year of ibrutinib initiation, but it decreased annually thereafter. The AEs reported in this study were comparable to those, documented in previous studies, in terms of the type, timing of occurrence, and severity. This underscores that the prompt and proactive management of AEs during ibrutinib treatment alleviates the patient's symptoms and enhances survival outcomes. The patients, who received active toxicity management along with ibrutinib, had a stable treatment course and improved clinical outcomes despite AEs. Thus, to prevent treatment interruption and achieve favorable outcomes, acute and chronic AEs, associated with ibrutinib therapy, should be recognized, monitored, and managed.

In this study, ibrutinib monotherapy resulted in an ORR of approximately 70%, which was similar to or higher than the response rates, reported in other studies (Table 4). Ibrutinib was more efficacious in patients, older than 70 years, who received anthracycline-containing front-line treatment, than in those, who received bendamustine-based front-line treatment (Supplementary Fig. 1B). Patients, treated with a bendamustine-containing regimen, presented with unfavorable baseline characteristics, including age >70 years, elevated WBC count, BM involvement, and high-risk sMIPI at the time of diagnosis (Table 1). Based on this, less intensive chemotherapy is preferred as the front-line treatment for patients aged 70 or older as they have poor general health conditions or comorbidities. It was assumed that prior bendamustine exposure led to poor subsequent ibrutinib treatment outcomes, as observed in other studies [10]. In cases where POD 24 occurred, regardless of the front-line treatment, favorable survival outcomes were not guaranteed, even with ibrutinib treatment. In line with previous studies [20, 21], POD 24 persisted as an unfavorable prognostic indicator in the targeted agent era.

*TP53* mutation is a well-known biomarker, that predicts poor outcomes with conventional treatments in both newly diagnosed and RR-MCL patients. According to several retrospective studies [15, 22], the incidence of *TP53* mutations was approximately 14%, and patients with *TP53* mutations had lower response rates (55% vs. 70%) as well as shorter PFS (4 mo vs. 12 mo) and OS (10 mo vs. 34 mo) than patients with wild-type *TP53*. Unfortunately, this study was unable to include data on *TP53* mutation status due to limited tissue samples and the lack of patient consent. While the presence of *TP53* mutations impacts the prognosis of MCL, performing NGS on all MCL patients was not cost-effective in a real-world setting since only 14% were found to have *TP53* mutations. Instead, Eskelund *et al.* [23] suggested specific clinical factors, related to *TP53* mutation. These include a blastoid morphology, high-risk MIPI, and Ki67 >30%. In cases, where determining the *TP53* mutation status is challenging, establishing a treatment plan, based on the im-

plied factors, and defining the clinical signs of *TP53* mutations are essential.

In this study, early disease relapse was defined as disease relapse within 12 months of starting ibrutinib treatment since the reported median PFS of ibrutinib was 12.6 months (95% CI, 10.3–16.6). Patients with early relapse exhibited significantly shorter PFS than those, who did not experience early relapse (5.4 mo vs. 24.8 mo). High-risk sMIPI scores were correlated with early disease relapse. Unfortunately, these patients were unsuitable for any subsequent treatment due to rapid disease deterioration, and the post-ibrutinib survival outcomes were poor. Establishing optimal treatment strategies for patients, who were refractory to ibrutinib, remains challenging. Allogeneic SCT has demonstrated long-term disease control through the graft-to-host effect, but it is limited to patients with favorable general conditions for withstanding intensive induction therapy and life-threatening complications. Pirtobrutinib, a novel non-covalent BTK inhibitor, achieved an ORR of 58%. Patients with RR-MCL, who received a median of three prior treatment modalities, including ibrutinib, responded for 21.6 months [24]. Moreover, brexucabtagene autoleucel (brex-cel), an anti-CD19 CAR-T cell therapy, achieved an ORR of 93% and CR rate of 67% [16, 17]. After 12 months, 57% of patients remained in remission. The lisocaltagene maraleucel (liso-cel) was associated with a low incidence of grade ≥3 TRAEs, and it demonstrated promising clinical activity in a phase 1 study [25]. Thus, novel therapeutic approaches, including targeted agents and immunocellular therapies, should be utilized in the management of patients, experiencing early disease relapse. Additionally, the risk stratification system should be continuously validated and adjusted to improve treatment outcomes.

In conclusion, this study demonstrated the efficacy and safety of salvage ibrutinib in patients with RR-MCL, and the patients, who potentially benefit from salvage ibrutinib therapy, were identified by verifying prognostic factors. Favorable survival outcomes were more frequent among patients with an objective response or those, who remained in disease remission with continuous ibrutinib treatment. To maximize the benefits of ibrutinib treatment, the capacity of the patient to endure TRAEs and the specific characteristics of their disease should be considered. Since patients, who experience early disease relapse within 12 months, have poorer survival outcomes, groundbreaking treatment strategies should be identified.

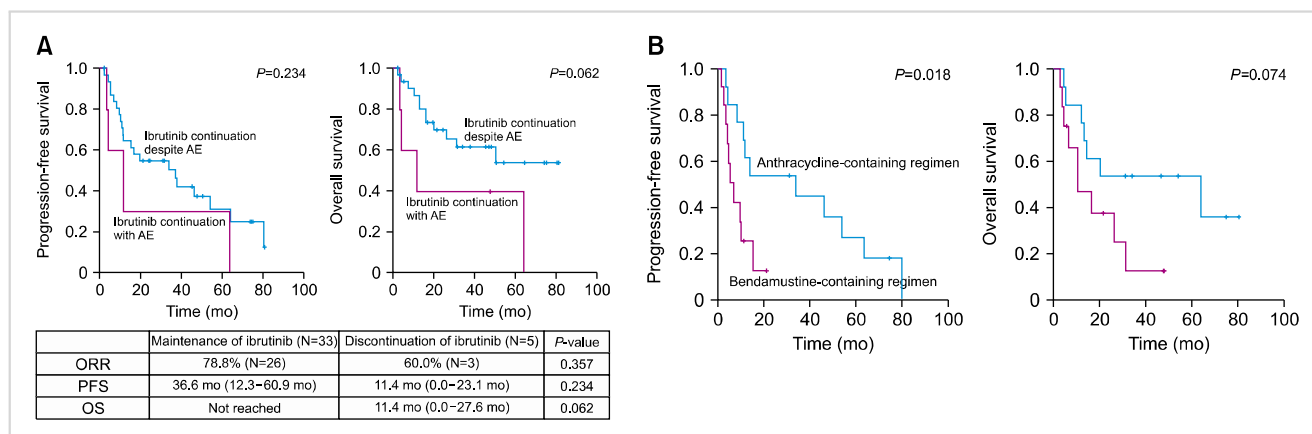
#### Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

#### REFERENCES

1. Armitage JO, Longo DL. Mantle-cell lymphoma. *N Engl J Med*

- 2022;386:2495-506.
2. Lee H, Park HJ, Park EH, et al. Nationwide statistical analysis of lymphoid malignancies in Korea. *Cancer Res Treat* 2018;50:222-38.
3. Merolle MI, Ahmed M, Nomie K, Wang ML. The B cell receptor signaling pathway in mantle cell lymphoma. *Oncotarget* 2018;9:25332-41.
4. Gu D, Tang H, Wu J, Li J, Miao Y. Targeting Bruton tyrosine kinase using noncovalent inhibitors in B cell malignancies. *J Hematol Oncol* 2021;14:40.
5. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013;369:507-16.
6. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood* 2015;126:739-45.
7. Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2016;387:770-8.
8. Epperla N, Hamadani M, Cashen AF, et al. Predictive factors and outcomes for ibrutinib therapy in relapsed/refractory mantle cell lymphoma-a "real world" study. *Hematol Oncol* 2017;35:528-35.
9. Maruyama D, Nagai H, Fukuhara N, et al. Efficacy and safety of ibrutinib in Japanese patients with relapsed or refractory mantle cell lymphoma. *Cancer Sci* 2016;107:1785-90.
10. Jeon YW, Yoon S, Min GJ, et al. Clinical outcomes for ibrutinib in relapsed or refractory mantle cell lymphoma in real-world experience. *Cancer Med* 2019;8:6860-70.
11. Tucker D, Morley N, MacLean P, et al. The 5-year follow-up of a real-world observational study of patients in the United Kingdom and Ireland receiving ibrutinib for relapsed/refractory mantle cell lymphoma. *Br J Haematol* 2021;192:1035-8.
12. Yi JH, Kim SJ, Yoon DH, et al. Real-world outcomes of ibrutinib therapy in Korean patients with relapsed or refractory mantle cell lymphoma: a multicenter, retrospective analysis. *Cancer Commun (Lond)* 2021;41:275-8.
13. McCulloch R, Lewis D, Crosbie N, et al. Ibrutinib for mantle cell lymphoma at first relapse: a United Kingdom real-world analysis of outcomes in 211 patients. *Br J Haematol* 2021;193:290-8.
14. Obr A, Benesova K, Janikova A, et al. Ibrutinib in mantle cell lymphoma: a real-world retrospective multi-center analysis of 77 patients treated in the Czech Republic. *Ann Hematol* 2023;102:107-15.
15. Rule S, Dreyling M, Goy A, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis. *Haematologica* 2019;104:e211-4.
16. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2020;382:1331-42.
17. Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. *J Clin Oncol* 2023;41:555-67.
18. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127:2375-90.
19. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;32:3059-68.
20. Dreyling M, Goy A, Hess G, et al. Long-term outcomes with ibrutinib treatment for patients with relapsed/refractory mantle cell lymphoma: a pooled analysis of 3 clinical trials with nearly 10 years of follow-up. *Hemasphere* 2022;6:e712.
21. Bond DA, Switchenko JM, Maddocks KJ, et al. Outcomes following early relapse in patients with mantle cell lymphoma. *Blood (ASH Annual Meeting Abstracts)* 2019;134(Suppl 1):753.
22. Lew TE, Minson A, Dickinson M, et al. Treatment approaches for patients with TP53-mutated mantle cell lymphoma. *Lancet Haematol* 2023;10:e142-54.
23. Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood* 2017;130:1903-10.
24. Wang ML, Jurczak W, Zinzani PL, et al. Pirtobrutinib in covalent bruton tyrosine kinase inhibitor pretreated mantle-cell lymphoma. *J Clin Oncol* 2023;41:3988-97.
25. Palomba ML, Gordon LI, Siddiqi T, et al. Safety and preliminary efficacy in patients with relapsed/refractory mantle cell lymphoma receiving lisocabtagene maraleucel in transcend NHL 001. *Blood (ASH Annual Meeting Abstracts)* 2020;136(Suppl 1):10-1.



**Supplementary Fig. 1.** Comparison of survival outcomes by maintenance versus interruption of ibrutinib in patients with adverse events (**A**). Comparison of ibrutinib efficacy according to front-line treatment in patients older than 70 years (**B**).

**Supplementary Table 1.** Demographics and disease characteristics at ibrutinib treatment (N=42).

Characteristics		N
Age (yr)	Median (range)	67 (45–81)
	<70	27 (64.3%)
	≥70	15 (35.7%)
Leukocytosis	Absence	33 (78.6%)
	Present	9 (21.4%)
Anemia	Absence	32 (76.2%)
	Present	10 (23.8%)
Thrombocytopenia	Absence	30 (71.4%)
	Present	12 (28.6%)
Serum LDH	Absence	10 (23.8%)
	Elevated	32 (76.2%)
Splenomegaly (≥11 cm)	Absence	24 (57.1%)
	Present	18 (42.9%)
Prior number of treatment	Prior 1 line	29 (69.0%)
	Prior ≥2 lines	13 (31.0%)
Best response to ibrutinib	Complete remission	21 (50.0%)
	Partial response	8 (19.0%)
	Stable disease	9 (21.5%)
	Progressive disease	4 (9.5%)
Post-ibrutinib management (N=23)	Novel agent &/or clinical trial	15 (65.2%)
	Conventional cytotoxic treatment only	8 (34.8%)

Abbreviations: LDH, lactate dehydrogenase.

**Supplementary Table 2.** Adverse events of ibrutinib treatment.

Hematologic adverse events	Total	Grade 1–2	Grade 3	Grade 4
Neutropenia	3 (7.1%)	1 (2.4%)	1 (2.4%)	1 (2.4%)
Anemia	3 (7.1%)	2 (4.8%)	1 (2.4%)	-
Thrombocytopenia	5 (11.9%)	2 (4.8%)	3 (7.1%)	-
Non-hematologic adverse events	Total	Grade 1–2	Grade 3–4	
General weakness/fatigue	14 (33.3%)	10 (23.8%)	4 (9.5%)	
Skin rash	20 (47.6%)	16 (38.1%)	4 (9.5%)	
Diarrhea	13 (30.9%)	10 (23.8%)	3 (7.1%)	
Heart failure	1 (2.4%)	1 (2.4%)	-	
Bleeding	3 (7.1%)	3 (7.1%)	-	
Sensory neuropathy	4 (9.5%)	4 (9.5%)	-	
Mucositis	5 (11.9%)	5 (11.9%)	-	
Atrial fibrillation (any degree)		3 (7.1%)		
Herpes zoster (any degree)		2 (4.8%)		
Treatment discontinuation due to toxicity		5 (11.9%)		
Dose reduction due to toxicity		6 (14.3%)		