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A multicenter, open-label, phase II study of tirabrutinib (ONO/GS-4059) in patients with Waldenström's macroglobulinemia

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Abstract

Tirabrutinib is a second-generation Bruton's tyrosine kinase inhibitor with greater selectivity than ibrutinib. Here, we conducted a multicenter, phase II study of tirabrutinib in patients with treatment-naïve (Cohort A) or with relapsed/refractory (Cohort B) Waldenström's macroglobulinemia (WM). Patients were treated with tirabrutinib 480 mg once daily. The primary endpoint was major response rate (MRR; ≥ partial response). Secondary endpoints included overall response rate (ORR; ≥ minor response), time to major response (TTMR), progression-free survival (PFS), overall survival (OS), and safety. In total, 27 patients (18 in Cohort A; 9 in Cohort B) were enrolled. The median age was 71 y, and the median serum immunoglobulin M level was 3600 mg/dL. Among the patients, 96.2% had the *MYD88*^{L265P} mutation. MRR and ORR were 88.9% and 96.3%, respectively (Cohort A: MRR, 88.9%; ORR, 94.4%; Cohort B: MRR, 88.9%; ORR, 100%). Median TTMR was 1.87 mo. PFS and OS were not reached with a median follow-up of 6.5 and 8.3 mo for Cohorts A and B, respectively. The most common adverse events (AEs) were rash (44.4%), neutropenia (25.9%), and leukopenia (22.2%), with most AEs classified as grade 1 or 2. Grade ≥ 3 AEs included neutropenia (11.1%), lymphopenia (11.1%), and leukopenia (7.4%). No grade 5 AEs were noted. All bleeding events were grade 1; none were associated with drug-related atrial fibrillation or hypertension. Although the follow-up duration was relatively short, the study met the primary endpoint. Therefore, tirabrutinib monotherapy is considered to be highly effective for both untreated and relapsed/refractory WM with a manageable safety profile. (JapicCTI-173646).

Abbreviations: AE, adverse event; AS-PCR, allele-specific polymerase chain reaction; BTK, Bruton's tyrosine kinase; CI, confidential interval; CLL, chronic lymphocytic leukemia; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IPSSWM, International Prognostic Scoring System for Waldenström's macroglobulinemia; IRC, independent review committee; MR, minor response; MRR, major response rate; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SPD, sum of the products of the greatest diameters; TTMR, time to major response; TTOR, time to overall response; VGPR, very good partial response; WHIM, warts, hypogammaglobulinemia infection, and myelokathexis syndrome; WM, Waldenström's macroglobulinemia.

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1 | INTRODUCTION

Waldenström's macroglobulinemia (WM) is a major type of lymphoplasmacytic lymphoma that is characterized by the infiltration of neoplastic B cells with plasmacytic differentiation into bone marrow and IgM monoclonal gammopathy.[1,2] Several treatment options for WM have been developed, including rituximab monotherapy, chemoimmunotherapy, and bortezomib-based treatments.[3-8] However, WM typically progresses despite treatment in most patients. In addition, hematologic and non-hematologic toxicities, including peripheral neuropathy, infections, and secondary malignancies, remain major concerns for these treatments.[9] Therefore, the development of new treatment strategies is necessary.

BTK is predominantly expressed in B cells, where it plays a critical role in B-cell development and function.[10-13] However, in B-cell lymphoma, the BTK-mediated signal cascade is constitutively activated,[14] and knockdown of BTK is shown to reduce the survival of malignant B cells. In WM, a mutation in $MYD88^{L265}$ serves to support the survival of lymphoplasmacytic cells via BTK activation. This mutation ($MYD88^{L265P}$) has been found to be present in the majority of patients with WM[15,16] and triggers nuclear factor kappa B activation via phosphorylated BTK.[17] Therefore, BTK inhibition is considered a promising therapeutic option for WM.

Ibrutinib is an irreversible selective inhibitor for BTK and has been shown to be highly effective for WM.[18,19] A randomized phase III trial demonstrated a higher response rate in patients treated with ibrutinib and rituximab compared with those treated with rituximab alone (iNNOVATE Study).[20] However, safety remains a major concern regarding ibrutinib treatment, with several adverse effects noted, including atrial fibrillation, bleeding events, and hypertension.[21-25] This is likely because ibrutinib has some off-target effects, including inhibition of other tyrosine kinases such as EGFR, tyrosine kinase expressed in hepatocellular carcinoma, the phosphoinositide 3-kinase/AKT cardio protective pathway, and interleukin-2-inducible T-cell kinase.[26] A systematic review and meta-analysis of ibrutinib treatment for patients with CLL demonstrated an increased risk of these toxicities, which led to the discontinuation of ibrutinib.[22,23] Thus, the development of an effective treatment for WM with a reduced incidence of these toxicities would contribute to a longer response duration.

Tirabrutinib (ONO/GS-4059) is a highly potent and selective second-generation BTK inhibitor.[27,28] Tirabrutinib forms a covalent bond with BTK and has demonstrated effective in vitro cytotoxicity in B-cell lymphoma and in vivo antitumor activity in mouse models.[27] Multicenter, dose-escalation phase I trials of tirabrutinib for relapsed or refractory CLL and B-cell lymphoma, including WM, have demonstrated the efficacy and tolerability of tirabrutinib.[29,30]

Therefore, we conducted a multicenter, open-label, phase II study of tirabrutinib to evaluate its efficacy and safety in patients with WM.

2 | MATERIALS AND METHODS

2.1 | Trial design and treatment

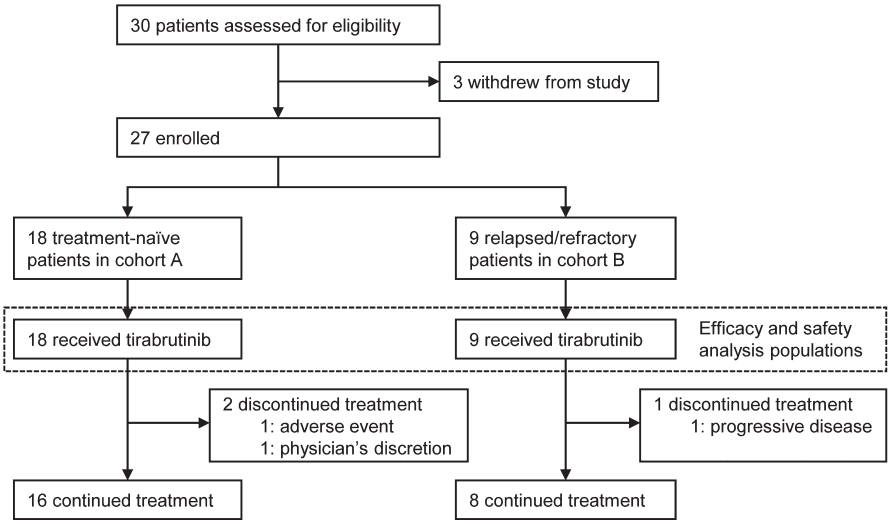
This phase II trial (Japan Pharmaceutical Information Center clinical trial ID: JapicCTI-173646) was conducted with an open-label and single-arm design at 19 sites in Japan. The enrollment of patients began on November 8, 2018 and closed on February 22, 2019. All authors had full access to the primary data.

Tirabrutinib was administered orally under fasting conditions at a daily dose of 480 mg for 28 d as 1 cycle. Tirabrutinib was continued until disease progression or clinically unacceptable toxicity. The dose was determined based on safety and efficacy data obtained in previous clinical trials.[29,30] During the study, the administration of tirabrutinib would be interrupted due to AEs and, after recovery, a reduced dose of 320 or 160 mg/d would be administered at the physician's discretion.

2.2 | Patients

Patients histologically diagnosed with WM were enrolled into 2 cohorts. Patients in Cohort A were treatment-naïve patients, and those in Cohort B were relapsed or refractory patients who received 1 or more lines of systemic treatment for WM. The inclusion criteria in Cohort A were either presence of symptomatic WM[31,32] or serum IgM levels of >4000 mg/dL. Other major eligibility criteria for both cohorts included age ≥ 20 y, monoclonal gammopathy with serum

FIGURE 1 Patient disposition



IgM levels of >500 mg/dL, an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1, and acceptable laboratory test results. The International Prognostic Scoring System for WM (IPSSWM) score was also categorized.[33] Major exclusion criteria were tumor lesions in the central nervous system and prior administration of BTK inhibitors.

2.3 | *MYD88* and *CXCR4* genotyping

Genomic DNA was isolated from bone marrow and/or tumor tissues. The L265P mutation in *MYD88* was specifically assessed by real-time polymerase chain reaction using an allele-specific oligonucleotide (AS-PCR).[34] Mutations in *CXCR4* were analyzed using the Ion Torrent PGM NGS system (Life Technologies Japan Ltd.).[35] The occurrence of warts, hypogammaglobulinemia infection, and myelokathexis syndrome (WHIM)-like mutations in *CXCR4*,[36,37] hereafter referred to as *CXCR4*^{WHIM}, were a particular focus of this study.

2.4 | Efficacy and safety

The primary endpoint of this study was MRR, as assessed by an IRC according to the consensus criteria of the VIth International Workshop for Waldenström's Macroglobulinemia.[38] The consensus categories for the response comprised CR, VGPR, PR, MR, stable disease, and PD. Major response was defined to include CR, VGPR, and PR. The overall response was defined to include the major response and MR. The major secondary endpoints were the ORR, TTMR, TTOR, duration of major response, PFS, OS, decreases in serum IgM and in the sizes of measurable lesions in the lymph nodes and extramedullary diseases by CT, and changes in primary disease-associated clinical symptoms, including hemoglobin levels. The lesion size was defined as the sum of the products of the greatest diameters (SPD). Serum IgM and SPD were monitored before the first administration, at the end of the first cycle, and at the beginning of each odd-numbered cycle.

AEs that occurred during administration, within 28 d after completion of administration of the study drug, and before the start of a subsequent therapy were evaluated, as were death and the data cutoff point. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[39]

2.5 | Statistics

The expected MRR of Cohorts A and B were 80.0% and 70.0%, respectively. The required number of patients in each cohort was 18 in Cohort A and 8 in Cohort B. This was calculated so that the study would show that the lower limit of the 95% CI for the MRR was higher than the threshold response rates of 45.0% (Cohort A) and 20.0% (Cohort B), with a probability of at least 80%.[40-42]

Baseline characteristics were analyzed for all enrolled patients, including the efficacy in patients having one or more response scores as evaluated by the IRC after the administration of tirabrutinib and the safety in patients administered with at least 1 dose of tirabrutinib. The data cutoff point was August 28, 2019, which was the first day of the seventh cycle for the latest-enrolled patient. The Clopper-Pearson method was used to estimate the 95% CIs for the MRR and ORR. No adjustments were made for covariates. The maximum reduction ratios of serum IgM levels and the measurable lesion sizes by CT were assessed using waterfall plots.

3 | RESULTS

3.1 | Patient characteristics

Among the 30 patients who provided informed consent, 18 treatment-naïve patients with WM were enrolled in Cohort A and 9 relapsed or refractory patients were enrolled in Cohort B (Figure 1;

TABLE 1 Baseline demographic and disease characteristics

	Cohort A Treatment-naïve *N* = 18	Cohort B Relapsed/refractory *N* = 9	Total *N* = 27
Sex			
Female	3 (16.7)	2 (22.2)	5 (18.5)
Male	15 (83.3)	7 (77.8)	22 (81.5)
Age			
Median (y)	70.5 (50-82)	71 (60-83)	71 (50-83)
IPSSWM			
Low risk	3 (16.7)	2 (22.2)	5 (18.5)
Intermediate risk	8 (44.4)	5 (55.6)	13 (48.1)
High risk	7 (38.9)	2 (22.2)	9 (33.3)
Serum IgM			
Median (mg/dL)	3787.5 (1392-6340)	2105.0 (730-6930)	3600.0 (730-6930)
≤4000 mg/dL	11 (61.1)	7 (77.8)	18 (66.7)
>4000 mg/dL	7 (38.9)	2 (22.2)	9 (33.3)
Hemoglobin			
Median (g/dL)	10.45 (8.0-15.3)	12.20 (9.1-13.9)	10.60 (8.0-15.3)
Platelet count			
Median (10^9/L)	257.5 (67-441)	206.0 (79-311)	257.0 (67-441)
β_2-microglobulin			
Median (mg/L)	3.150 (1.60-9.70)	3.200 (1.70-5.50)	3.200 (1.60-9.70)
Lymphadenopathy, Yes	8 (44.4)	6 (66.7)	14 (51.9)
Splenomegaly, Yes	10 (55.6)	4 (44.4)	14 (51.9)
Hyperviscosity, Yes	6 (33.3)	1 (11.1)	7 (25.9)
Gene mutations[a]			
MYD88^{L265P}	16 (94.1)	9 (100.0)	25 (96.2)
CXCR4^{WHIM}	4 (23.5)	0	4 (15.4)
MYD88^{WT}/*CXCR4*^{WHIM}	1 (5.9)	0	1 (3.8)
MYD88^{L265P}/*CXCR4*^{WT}	13 (76.5)	9 (100.0)	22 (84.6)
MYD88^{L265P}/*CXCR4*^{WHIM}	3 (17.6)	0	3 (11.5)
Number of prior therapies			
Median (range)	NA	2.0 (1-7)	NA
1	NA	3 (33.3)	NA
2	NA	3 (33.3)	NA
≥3	NA	3 (33.3)	NA
Prior therapies			
Rituximab	NA	8 (88.9)	NA
Bortezomib	NA	3 (33.3)	NA
Bendamustine	NA	3 (33.3)	NA
Other alkylating agents	NA	6 (66.7)	NA

Note: Data are numbers of patients (%) or median (range).

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IPSSWM, International Prognostic Staging System for Waldenström's Macroglobulinemia; NA, not applicable.

[a]Gene mutation data were missing in 1 patient in Cohort A.

Table 1). All 27 patients met the criteria for efficacy and safety analyses. At median follow-ups of 6.5 and 8.3 mo for Cohort A and Cohort B, respectively, 24 patients continued the administration (Figure 2). One patient in Cohort B discontinued the administration due to PD, 1 in Cohort A discontinued due to an AE, and another in Cohort A discontinued at the physician's discretion following the patient's request of study drug discontinuation after PR.

The baseline demographics, clinical characteristics, baseline laboratory values, IPSSWM scores, and genotypes of the enrolled patients are listed in Table 1. The overall median age was 71 y (range, 50-83), with the median age of Cohort A 70.5 y (range, 50-82) and that of Cohort B 71 y (range, 60-83). The overall median baseline serum IgM level was 3600 mg/dL (range, 730-6930), with that of Cohort A 3788 mg/dL (range, 1392-6340) and that of Cohort B 2105 mg/dL (range, 730-6930). The number of patients in whom the baseline serum IgM level was >4000 mg/dL was 9 (33.3%), with 7 (38.9%) in Cohort A and 2 (22.2%) in Cohort B. Prior systemic therapies administered to Cohort B included rituximab in 8 patients (88.9%), bortezomib in 3 patients (33.3%), bendamustine in 3 patients (33.3%), and other alkylating agents in 6 patients (66.7%). No patients received purine analogs, such as fludarabine, or autologous transplantation. The majority (96.2%) of the patients (16 in Cohort A and 9 in Cohort B) were identified to have a mutation in *MYD88*.

3.2 | Efficacy

The MRR and ORR in all patients were 88.9% and 96.3%, respectively. The MRR was 88.9% in both Cohort A (16 patients, including 3 patients exhibiting VGPR; 95% CI, 65.3-98.6) and Cohort B (8 patients; 95% CI, 51.8-99.7) (Table 2). The ORRs were 94.4% (17 patients; 95% CI, 72.7-99.9) and 100% (9 patients; 95% CI, 66.4-100.0) in Cohorts A and B, respectively. The median TTOR and TTMR in all patients were 0.95 (range, 0.9-3.9) and 2.00 (range, 1.0-5.7) mo; in Cohort A, 0.95 (range, 0.9-3.9) and 1.87 (range, 1.0-5.7) mo; and in Cohort B, 0.99 (range, 0.9-1.9) and 2.07 (range, 1.0-3.7) mo, respectively (Figure 2; Table 2). Because all the major responders, with 1 exception, achieved a major response by the data cutoff point, the median duration of the major response was not reached in either cohort.

The L265P mutation in *MYD88*, as assessed by AS-PCR, was found in 94.1% and 100% of patients in Cohorts A and B, respectively, whereas $CXCR4^{WHIM}$, as assessed by NGS, was only found in 23.5% of patients in Cohort A (Table 1). The IRC-assessed responses in the patient subpopulations were classified according to the mutations in *MYD88* and *CXCR4* and are summarized in Table 2 and Supporting Information, Table S1. Briefly, the MRRs in patients with $MYD88^{L265P}/CXCR4^{WT}$ (90.9%; 95% CI, 70.8-98.9) were relatively higher than those in patients with $MYD88^{L265P}/CXCR4^{WHIM}$ (66.7%; 95% CI, 9.43-99.2). The median TTMRs were comparable between

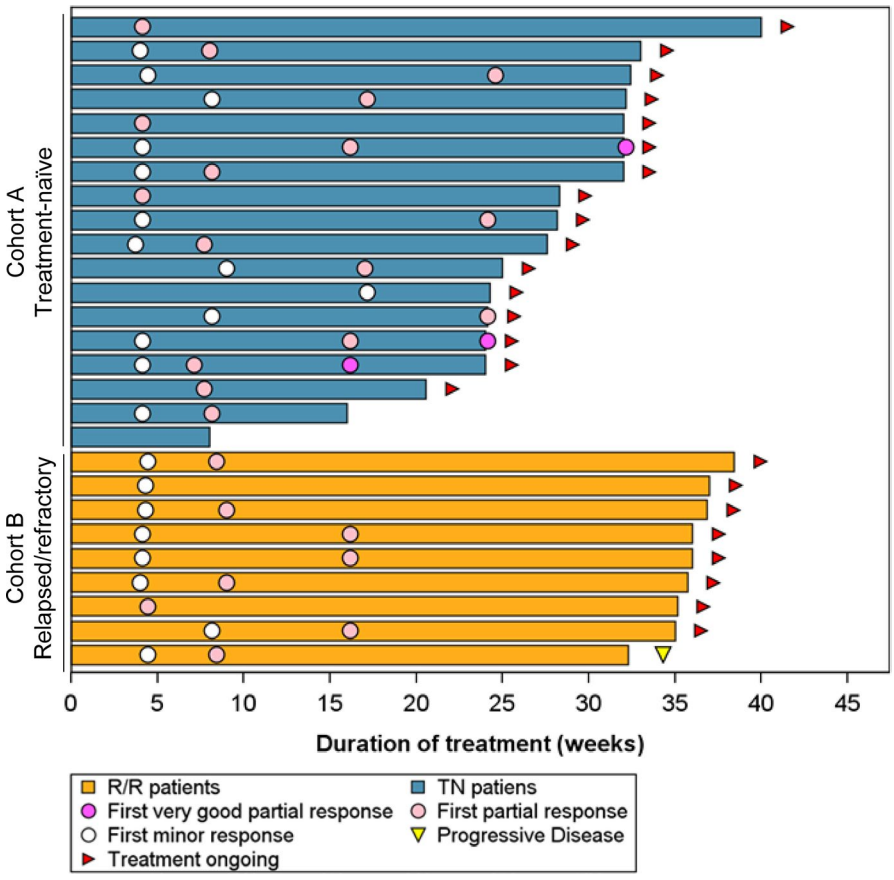


FIGURE 2 Duration of treatment and responses. A swimmer plot shows the duration of treatment, the first timings of better responses, and a progressive disease analysis for each patient

TABLE 2 IRC-assessed responses

Genotype	Cohort A *N* = 18	Cohort B *N* = 9	ALL *N* = 27	ALL *N* = 26[a]		
	All *N* = 18	All *N* = 9	All *N* = 27	*MYD88*^{WT} *CXCR4*^{WHIM} *N* = 1	*MYD88*^{L265P} *CXCR4*^{WT} *N* = 22	*MYD88*^{L265P} *CXCR4*^{WHIM} *N* = 3
Response rates – % (95% CI)						
MRR (CR + VGPR + PR)	88.9 (65.3-98.6)	88.9 (51.8-99.7)	88.9 (70.8-97.6)	100 (2.50-100)	90.9 (70.8-98.9)	66.7 (9.43-99.2)
ORR (CR + VGPR + PR + MR)	94.4 (72.7-99.9)	100 (66.4-100)	96.3 (81.0-99.9)	100 (2.50-100)	95.5 (77.2-99.9)	100 (29.2-100)
Best overall response – *n* (%)						
CR	0	0	0	0	0	0
VGPR	3 (16.7)	0	3 (11.1)	0	3 (13.6)	0
PR	13 (72.2)	8 (88.9)	21 (77.8)	1 (100)	17 (77.3)	2 (66.7)
MR	1 (5.6)	1 (11.1)	2 (7.4)	0	1 (4.5)	1 (33.3)
SD	1 (5.6)	0	1 (3.7)	0	1 (4.5)	0
PD	0	0	0	0	0	0
Median TTMR – mo (range)	1.87 (1.0-5.7)	2.07 (1.0-3.7)	2.00 (1.0-5.7)	5.55 (5.6-5.6)	1.94 (1.0-5.6)	2.89 (1.9-3.9)
Median TTOR — mo (range)	0.95 (0.9-3.9)	0.99 (0.9-1.9)	0.95 (0.9-3.9)	0.95 (1.0-1.0)	0.95 (0.9-1.9)	2.07 (1.0-3.9)

Abbreviations: 95% CI, 95% confidential interval; CR, complete response; MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTMR, time to major responses; TTOR, time to overall responses; VGPR, very good partial response

[a]Gene mutation data were missing in 1 patient in Cohort A.

patients with $MYD88^{L265P}/CXCR4^{WT}$ (1.94 mo) and those with $MYD88^{L265P}/CXCR4^{WHIM}$ (2.89 mo).

Regarding PFS and OS, no events were observed during the study period, with the exception that 1 patient (11.1%) in Cohort B, whose best overall response was PR, had PD at 240 d after the start of the study drug administration. All patients in both cohorts experienced a decrease in serum IgM levels (Figure 3A). The best reductions in individual serum IgM levels were greater than 50% in 25 (92.6%) patients in total, with 16 (88.9%) and 9 (100%) patients in Cohorts A and B, respectively. Among 14 patients in total with prior lymphadenopathy, SPD data were available for 13 patients (8 and 5 patients in Cohorts A and B, respectively). All the patients experienced marked shrinkage in lesion size, with > 50% best reduction in SPD observed in 87.5% and 80% of patients in Cohorts A and B, respectively (Figures 3B and S1). Low basal levels of hemoglobin, particularly in Cohort A, recovered during the treatment (Figure 3C).

Baseline clinical symptoms associated with WM were observed in 21 patients in total, with 16 and 5 patients in Cohorts A and B, respectively (Table S2). Among them, 15 patients (71.4%) in total, including 11 (68.8%) in Cohort A and 4 (80.0%) in Cohort B, experienced resolution of all symptoms at least once after administration of the study drug.

3.3 | Safety

All patients experienced AEs. The common AEs were rash (44.4%), neutropenia (25.9%), leukopenia (22.2%), and stomatitis (14.8%) (Table 3). Grade 3 and 4 AEs were observed in 8 patients (29.6%), including 3 with neutropenia (11.1%), 3 with lymphopenia (11.1%), and 2 with leukopenia (7.4%). No grade 5 AEs were identified. Serious AEs, including transient ischemic attack on day 49, classified as grade 2, and rhegmatogenous retinal detachment on day 184, classified as grade 3, were observed in 2 patients in Cohort A (7.4%). These serious AEs appeared to be unrelated to tirabrutinib treatment, and the patients recovered after treatment interruption. Three patients experienced tirabrutinib-related grade 1 bleeding events, including epistaxis (2 patients) and mouth hemorrhage (1 patient). These patients continued the study drug administration without interruption but were administered a reduced

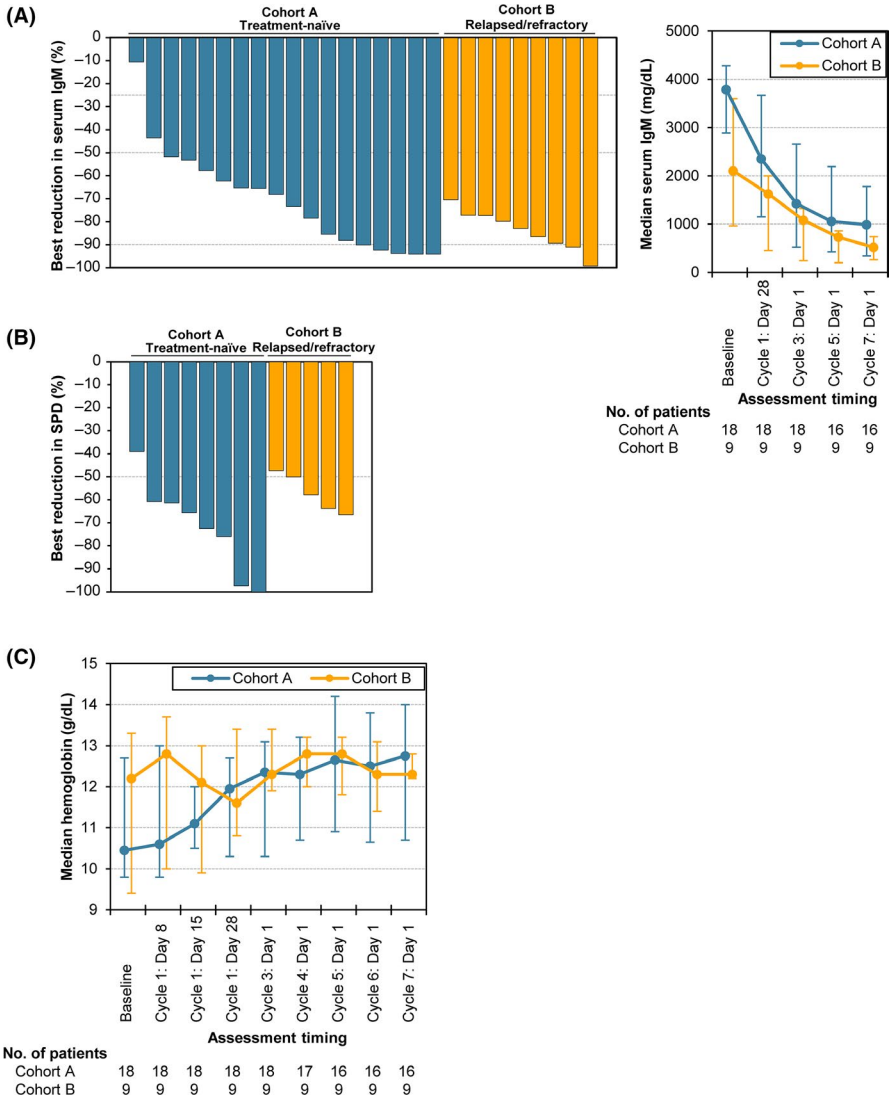


FIGURE 3 Best reductions in serum IgM and SPD and chronological changes in median hemoglobin levels. A, Left panel: A waterfall plot shows the best reductions in serum IgM level in each patient. Dotted lines represent 25%, 50%, and 90%, which are the thresholds of each response. Right panel: Chronological changes in median serum IgM levels are shown. The error bars represent the interquartile ranges. B, The best reductions in SPD are shown as a waterfall plot. The SPD data for 1 patient in Cohort B were missing. C, Chronological changes in median hemoglobin levels are shown. The error bars represent the interquartile ranges

TABLE 3 Common adverse events

Adverse events — *n* (%)		Cohort A Treatment-naïve *N* = 18	Cohort B Relapsed/refractory *N* = 9	Total *N* = 27
All		18 (100)	9 (100)	27 (100)
	Grade ≥ 3	4 (22.2)	4 (44.4)	8 (29.6)
Rash		11 (61.1)	1 (11.1)	12 (44.4)
Neutropenia		2 (11.1)	5 (55.6)	7 (25.9)
	Grade ≥ 3	0	3 (33.3)	3 (11.1)
Leukopenia		2 (11.1)	4 (44.4)	6 (22.2)
	Grade ≥ 3	0	2 (22.2)	2 (7.4)
Stomatitis		3 (16.7)	1 (11.1)	4 (14.8)
Thrombocytopenia		3 (16.7)	0	3 (11.1)
Rash maculopapular		3 (16.7)	0	3 (11.1)
Nausea		2 (11.1)	1 (11.1)	3 (11.1)
Nasopharyngitis		1 (5.6)	2 (22.2)	3 (11.1)
Lymphopenia		1 (5.6)	2 (22.2)	3 (11.1)
	Grade ≥ 3	1 (5.6)	2 (22.2)	3 (11.1)
Diarrhea		2 (11.1)	0	2 (7.4)
Urinary tract infection		2 (11.1)	0	2 (7.4)
Pruritus		2 (11.1)	0	2 (7.4)
Cataract		1 (5.6)	1 (11.1)	2 (7.4)
Constipation		1 (5.6)	1 (11.1)	2 (7.4)
Pyrexia		1 (5.6)	1 (11.1)	2 (7.4)
Weight decreased		1 (5.6)	1 (11.1)	2 (7.4)
Insomnia		1 (5.6)	1 (11.1)	2 (7.4)
Epistaxis		1 (5.6)	1 (11.1)	2 (7.4)
Bronchitis		0	2 (22.2)	2 (7.4)
Rhegmatogenous retinal	Grade ≥ 3	1 (5.6)	0	1 (3.7)
Atypical mycobacterial	Grade ≥ 3	1 (5.6)	0	1 (3.7)
Erythema multiforme	Grade ≥ 3	1 (5.6)	0	1 (3.7)
Rash erythematous	Grade ≥ 3	1 (5.6)	0	1 (3.7)
Type 2 diabetes mellitus	Grade ≥ 3	0	1 (11.1)	1 (3.7)

Note: Adverse events observed in more than 2 patients and those with grade ≥ 3 were listed.

dose of tirabrutinib. One patient was considered to have worsening chronic atrial fibrillation; however, electrocardiography and echocardiography revealed no apparent changes. The chronic atrial fibrillation was considered to be due to exercise reported by the patient and not due to drugs.

One patient discontinued tirabrutinib administration due to the worsening of an atypical mycobacterial infection at day 57 (grade 3), which resolved after discontinuation. AEs leading to study drug interruption were observed in 7 patients (38.9%) in Cohort A and 5 patients (55.6%) in Cohort B and included skin-related AEs in 5 patients and neutropenia in 2 patients. No noticeable symptoms associated with the primary disease, with the exception of a transient increase in IgM levels in 3 (25%) of the 12 patients, were observed during the study drug interruption. Upon resuming administration of the study drug, reduced doses were administered to 6 patients (33.3%) in Cohort A and temporarily to 1 patient (11.1%) in Cohort B.

No patients exhibited IgM flares during the study drug administration. The transient increases in IgM levels observed during the study drug interruption were resolved after resuming administration. Basal serum IgA and IgG levels were mostly sustained or slightly decreased during the administration (Figure S2), and no patients required new administration of globulin preparation. Basal IgG levels in 3 patients in Cohort A were beyond the upper normal limit but decreased to within the normal limit or lower upon tirabrutinib administration. Focusing on lymphocytosis after tirabrutinib administration, 1 patient had grade 2

treatment-related lymphocytosis (lymphocyte count: 5.5×10^9/L) at day 10, and the AE was resolved without discontinuation of tirabrutinib administration.

4 | DISCUSSION

In this study, we present the results of a prospective single-arm phase II study of tirabrutinib monotherapy in patients with treatment-naïve and relapsed or refractory WM. We observed high ORR (96.3%) and MRR (88.9%) in all patients. The TTOR and TTMR were 0.95 and 2 mo, respectively. Although the long-term survival could not be satisfactorily evaluated in the follow-up period, the rapid improvement in hemoglobin levels and the gradual decrease in serum IgM levels were noted. Indeed, the hemoglobin levels increased from 10.45 g/dL at baseline to 11.95 g/dL, and the median serum IgM levels decreased from 3788 mg/dL to 2350 mg/dL after 4 wk of tirabrutinib administration in Cohort A. Approximately half of the patients (51.9%) had lymphadenopathy, and all experienced immediate reduction in lesion size or resolution. These results are comparable with those obtained for ibrutinib monotherapy in treatment-naïve WM[19] and the rituximab-ibrutinib group in the iNNOVATE study.[20]

Our study has the limitation of tirabrutinib responses by *MYD88* and *CXCR4* mutational status because these mutations were assessed using different methods: *MYD88* using AS-PCR and *CXCR4* using NGS. Ibrutinib monotherapy responses have been reported to be affected by *MYD88* and *CXCR4* mutational status,[18,19] whereas the responses in patients treated with ibrutinib and rituximab appeared to be independent of mutational status.[20] In the present study, 25 of 26 patients (96.2%) with genetic mutational data had $MYD88^{L265P}$ mutation. Although only 4 patients had $CXCR4^{WHIM}$ mutation, including 3 with $MYD88^{L265P}$ mutation, the median times to response in these patients were comparable with those of the patients with $MYD88^{L265P}/CXCR4^{WT}$.

The efficacies and safeties of various BTK inhibitors, including ibrutinib for patients with WM, are summarized in Table S3. Ibrutinib is often accompanied by AEs such as atrial fibrillation, bleeding events, and hypertension, leading many patients to discontinue treatment.[21-25] For instance, with ibrutinib monotherapy,[18,19] grade 2 or higher AEs, including atrial fibrillation (5%-10%), bleeding events (6%-13%), and hypertension (5%-13%), have been reported, and 32% of patients discontinued ibrutinib treatment for any reason in relapsed or refractory WM. Mato et al. conducted a multicenter retrospective analysis of 616 patients with CLL treated with ibrutinib either commercially or in clinical trials.[22] In the report, 41% of the patients discontinued ibrutinib, with toxicity reported as the most common reason for discontinuation. The median time to ibrutinib discontinuation was 7 mo. In contrast, in the present study, tirabrutinib-related grade 1 bleeding events occurred in 3 patients, and there were no grade 2 or higher drug-related bleeding events. Three patients discontinued tirabrutinib during follow-up: 1 patient discontinued because of PD after exhibiting PR, whereas the other discontinuations were not because of tirabrutinib-related AEs. Thus, we conclude that tirabrutinib monotherapy was well tolerated, with no unexpected toxicities observed.

It is noteworthy that there were no incidents of drug-related atrial fibrillation or hypertension in response to tirabrutinib. In contrast, a systematic review and meta-analysis of WM and mantle cell lymphoma in addition to CLL showed that ibrutinib significantly increased the risk of both atrial fibrillation and hypertension.[23] Ibrutinib potently inhibits essential human EGFR-related tyrosine kinases such as HER2 and HER4.[43,44] Conversely, tirabrutinib may not affect these tyrosine kinases. Therefore, the difference in selectivity between ibrutinib and tirabrutinib may result in different influences on cardiovascular AEs.

In the present study, 1 case had transient grade 2 lymphocytosis after tirabrutinib administration, which was resolved without any specific treatment or discontinuation of tirabrutinib. Treatment-related lymphocytosis has not been reported as common or serious AEs in most of BTK inhibitor clinical trial for WM patients.[19,20,45] Thus, lymphocytosis accompanied by BTK inhibitor initiation in WM might not be a problematic issue, although further investigation will be required.

Second-generation BTK inhibitors, including tirabrutinib and acalabrutinib, have been designed to have fewer off-target effects,[21,28] with the goal of improving efficacy and reducing toxicity. Two reports of phase II studies of acalabrutinib monotherapy in ibrutinib-intolerant patients for relapsed or refractory CLL are available to date, and these studies reported high response rates and satisfied safety criteria.[46,47] Most recently, a phase II study of acalabrutinib monotherapy for mainly patients with relapsed or refractory WM demonstrated high efficacy and feasibility, with a low discontinuation rate.[45] Considering these reports, second-generation BTK inhibitors may contribute to reducing toxicities recognized by ibrutinib, with better dose adherence expected for patients with WM.

In summary, the present study demonstrated that tirabrutinib monotherapy is highly effective with rapid responses and is well tolerated in both treatment-naïve patients and those with relapsed/refractory symptomatic WM. The MRR as the primary endpoint was met. However, some efficacy endpoints, such as PFS and OS, could not be evaluated because of the limited observation period. Therefore, future studies with a longer follow-up period are warranted.

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DISCLOSURE

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ETHICAL CONSIDERATIONS

The institutional review board of each site approved this trial. This trial was conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient data through Clinical Study Data Request.com (https://www.clinicalstudydatarequest.com/). The policy for data sharing of the sponsor is available at https://www.ono.co.jp/eng/rd/policy.html.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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