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Original article

Post-marketing surveillance of tirabrutinib for Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma in Japan

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ABSTRACT

Tirabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, was approved in Japan for the treatment of Waldenström's macroglobulinemia (WM) and lymphoplasmacytic lymphoma (LPL). We report the findings of post-marketing surveillance (PMS) of tirabrutinib that was started following its approval. We conducted an all-case PMS of patients who started tirabrutinib treatment between August 21, 2020, and January 17, 2021 for WM/LPL in Japan. Safety and effectiveness data were recorded for up to 52 weeks after the first dose of tirabrutinib. Among 152 patients who started tirabrutinib, 67.1% were male, 77.6% were ≥ 65 years old, and 61.8% started treatment with tirabrutinib at 480 mg/day (once-daily). Among these 152 patients, any-grade and grade ≥ 3 adverse drug reactions (ADRs) occurred in 58.6% and 29.6% of patients, respectively. The main ADRs were platelet count decreased (9.2%) and rash (9.2%). Grade 5 ADRs were reported in four patients (2.6%). The outcomes of most ADRs associated with the safety specifications (myelosuppression, infections, interstitial lung diseases, clinically significant skin disorders, hemorrhages, hepatic function disorders, and hypersensitivities) were resolved or improved. The effectiveness was assessed by the physicians using the VIth International Workshop for Waldenström's Macroglobulinemia criteria. Among 85 patients (initial dose: 480 mg/day) included in the effectiveness analysis set, the major response and overall response rates were 63.5% and 74.1%, respectively. This PMS suggested that the safety profile of tirabrutinib for patients with WM/LPL in real-world clinical settings is in line with that observed in prior studies.

INTRODUCTION

Lymphoplasmacytic lymphoma (LPL) is low-grade B-cell lymphoma comprising small lymphocytes, lymphoplasmacytoid cells, and plasma cells.[1,2] Waldenström's macroglobulinemia (WM) is a major type of LPL characterized by infiltration of the bone marrow by LPL and the presence of immunoglobulin M-type monoclonal gammopathy.[1–3] WM and LPL are rare disorders; in 2016, 354 cases of WM or LPL were diagnosed in Japan, resulting in an annual incidence of 2.8 cases per 1,000,000 population.[4] Evidence suggests that WM is more common in older adults (age ≥ 65 years).[5]

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) and the Japanese Society of Hematology (JSH) guidelines for WM/LPL recommend using rituximab (anti-CD20 monoclonal antibody), alkylating agents, proteasome inhibitors, steroids, and Bruton's tyrosine kinase (BTK) inhibitors as primary therapy for patients with WM.[6,7] The BTK inhibitors listed in the NCCN Guidelines are the first-generation BTK inhibitor ibrutinib and the second-generation BTK inhibitor zanubrutinib, while those listed in the JSH guidelines are ibrutinib and the second-generation BTK inhibitor tirabrutinib.[6,7] BTK is a downstream mediator of the B-cell receptor that plays critical roles in the survival, proliferation, and differentiation of B cells.[8] Aberrant BTK activation is a key oncogenic driver in various B-cell malignancies.

Tirabrutinib is a potent, highly selective, irreversible oral BTK inhibitor.[9] It has been reported that tirabrutinib shows greater selectivity for BTK compared with ibrutinib.[10] In August 2020, tirabrutinib was approved in Japan for treating WM and LPL[11] based on the results of a multicenter, open-label, single-arm, phase 2 trial (ONO-4059-05) conducted in Japan.[12] However, only 27 patients were enrolled in that trial,[12,13] and data on the efficacy and safety

of tirabrutinib for WM/LPL are limited. As a condition of approval, the Pharmaceuticals and Medical Devices Agency requested an all-cases post-marketing surveillance (PMS) of tirabrutinib in patients with WM/LPL to collect safety and effectiveness data in a larger patient population.[14] Because WM/LPL is a rare hematologic malignancy, it is particularly challenging to conduct large-scale clinical studies in this patient population. Furthermore, the majority of patients with WM/LPL are elderly, and often have comorbidities or organ dysfunction, which frequently precludes their enrollment in clinical trials. Consequently, there are limited safety and efficacy data in patients with WM/LPL. Therefore, all-cases PMSs that collect data from large, unselected patient populations are essential to accurately characterize the safety and effectiveness of treatments in this patient population. Such data also complement the findings from single-arm clinical trials with limited patient numbers. Here, we report the safety and effectiveness of tirabrutinib in patients with WM/LPL, as collected through the PMS program.

The primary objective of this PMS was to assess the safety of tirabrutinib in patients with WM/LPL in a real-world clinical setting. Based on the findings from prior clinical trials of tirabrutinib,[12,15–17] specific adverse drug reactions (ADRs) requiring particular attention during treatment—myelosuppression, infections, interstitial lung diseases (ILDs), clinically significant skin disorders, hemorrhages, hepatic function disorders, and hypersensitivities—were identified and designated as safety specifications for this PMS. Accordingly, this PMS sought to characterize the ADRs associated with these safety specifications and to further elucidate the safety profile of tirabrutinib in the treatment of WM/LPL.

MATERIALS AND METHODS

Surveillance design

This prospective, noninterventional, observational PMS was designed to collect data regarding the safety and effectiveness of tirabrutinib for up to 52 weeks after the first dose in patients with WM/LPL in Japan. It was planned to register all patients who started treatment with tirabrutinib for this indication between August 2020 and January 2021.

No invasive or interventional procedures were performed as part of this PMS; all treatment decisions, including the use of tirabrutinib and other drugs, were at the physician's discretion. Clinical information obtained as part of routine medical practice was collected in adherence to the Japanese Good Post-Marketing Study Practice (GPSP) based on the Pharmaceuticals and Medical Devices Act. Data were collected anonymously. All institutions prescribing tirabrutinib entered into a contract with the sponsor before initiating its use. This PMS was registered with the Japan Registry of Clinical Trials (jRCT2011210005).

Patients

In accordance with the approved label in Japan, patients with WM/LPL were eligible for treatment with tirabrutinib. Tirabrutinib was administered orally, once daily. All patients who started treatment with tirabrutinib from August 21, 2020, were registered in the PMS and followed up for 52 weeks from the first dose. Patients who discontinued tirabrutinib within 52 weeks were to be followed up as far as possible.

The target sample size was set at 60 patients based on the following rationale. In the ONO-4059-05 trial, the least-frequent ADR associated with the safety specifications for tirabrutinib was hyperbilirubinemia, which occurred in 3.7% of patients (1/27).[11] Therefore, it was

necessary to register 60 patients to detect at least one case of this ADR with a 90% probability. It was originally planned to register patients through to January 2021. We analyzed the case-report forms (CRFs) collected from patients who started treatment with tirabrutinib up to January 17, 2021, when the planned number of patients had been reached. We excluded patients whose institution declined consent for publication of the PMS results, and evaluated the CRFs for all other patients.

Data collection and assessments

The baseline demographic characteristics included sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS), medical history, comorbidities, treatment history of tirabrutinib, number of prior systemic therapy regimens, plasmapheresis, hematopoietic stem cell transplantation (HSCT), and time from the primary diagnosis to the start of treatment with tirabrutinib. Tirabrutinib administration-related factors included the duration of administration, dose, and reason for discontinuation.

The clinicians recorded adverse events (AEs) in the CRFs. AEs for which a causal relationship with tirabrutinib could not be ruled out were defined as ADRs and tabulated. The primary outcome was the incidence of ADRs, which were classified using the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J) version 25.1 and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The Risk Management Plan of tirabrutinib specified the following safety specifications, which were specifically assessed in this PMS: infections, clinically significant skin disorders, myelosuppression, hypersensitivities, ILDs, hepatic function disorders, and hemorrhages. All ADRs related to these safety specifications were captured and analyzed, regardless of their severity.

The clinicians recorded the response to tirabrutinib according to the consensus criteria of the VIth International Workshop for Waldenström's Macroglobulinemia (IWWM),[18] as complete response (CR), very good partial response (VGPR), partial response (PR), minor response (MR), stable disease, or progressive disease at the time of best response. The effectiveness of tirabrutinib was evaluated in terms of the major response rate (MRR; sum of CR, VGPR, and PR), the overall response rate (ORR; sum of CR, VGPR, PR, and MR), and overall survival (OS).

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics, treatment status, safety (e.g. ADRs) and effectiveness (responses). The incidences of ADRs, the MRR, and the ORR were compared between subgroups of patients using Fisher's exact test or the Wilcoxon rank sum test. The level of significance was $P < 0.05$ (two-tailed). The 95% confidence intervals were determined using the Clopper–Pearson exact method. OS was defined as the time (days) from the start of tirabrutinib treatment to death. Survival curves were plotted using the Kaplan–Meier method. Patients were censored if their outcome was unknown, they were lost to follow-up, or they were transferred to another hospital. In these circumstances, the last observation date was used as the censor date. SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

RESULTS

Patient disposition

Treatment with tirabrutinib was started in 162 patients with WM/LPL between August 21, 2020, and January 17, 2021 (**Fig. 1**). CRFs were collected for 158 patients and 152 patients were included in the safety analysis set, after excluding one patient whose CRFs before and after hospital transfer were integrated into one form, and five patients from four institutions that declined to disclose their data for publication.

The effectiveness analysis set consisted of 85 patients. This set was formed from the safety analysis set by excluding patients (multiple reasons apply) with prior use of tirabrutinib or unknown tirabrutinib treatment history (*n* = 3) and those with indications other than WM/LPL (*n* = 1). To allow us to evaluate the real-world effectiveness of tirabrutinib under conditions comparable to those of pivotal clinical trials and the approved dosage and administration, patients who did not initiate tirabrutinib at 480 mg/day (*n* = 58) and those who concomitantly used other drugs for the treatment of WM/LPL (*n* = 14) were excluded from the primary effectiveness analysis.

Patient characteristics

Among 152 patients in the safety analysis set, 102 (67.1%) were male (**Table 1**). The median age was 73.0 years and 118 patients (77.6%) were ≥ 65 years old. PS was 0–1 in 122 patients (80.3%) and 2–4 in 29 patients (19.1%). A total of 108 patients (71.1%) had comorbidities such as neuropathies, renal disorders, infections, liver disorders, respiratory disorders, or visual impairments. The median number of prior systemic therapy regimens was 1.0, and 33 patients (21.7%) were naïve to systemic therapy for WM/LPL. The most common prior medication was rituximab, which was used in 72 patients (47.4%) (**Supplementary Table 1**).

Prior treatments included plasmapheresis in 13 patients (8.6%) and HSCT in 5 patients (3.3%). The median duration from the initial diagnosis of WM/LPL to the start of tirabrutinib treatment was 48.2 months. The baseline characteristics of the 85 patients included in the effectiveness analysis set are summarized in **Supplementary Table 2**. There were no notable differences in patient characteristics between the safety and effectiveness analysis sets.

Tirabrutinib administration status

Overall, 94 patients (61.8%) out of 152 patients in the safety analysis set received tirabrutinib at an initial dose of 480 mg/day and 58 patients (38.2%) received tirabrutinib at a dose < 480 mg/day (**Supplementary Table 3**). The tirabrutinib dose was reduced during treatment in 47 patients (30.9%). The most common reason for a dose reduction was AEs in 37 patients (78.7%). The median duration of tirabrutinib administration was 338.5 days, and 56 patients (36.8%) continued it for 365 days (**Table 2**).

At the end of the observation period, 92 patients (60.5%) were continuing tirabrutinib, with a median duration of 365.0 days (**Table 3**). Of these, 38 patients maintained the initial dose for 365 days and the other patients continued tirabrutinib until the end of the observation period with dose modifications or treatment interruptions **(Supplementary Fig. 1)**. Meanwhile, 60 patients (39.5%) had discontinued the treatment, with a median treatment duration of 70.0 days (**Table 3**). The most common reasons for discontinuing tirabrutinib were AEs in 30 patients (50.0%) and disease progression (including death) in 18 (30.0%).

Safety

Frequent ADRs

ADRs of any grade were reported in 89 patients (58.6%) and ADRs of grade ≥ 3 were

reported in 45 patients (29.6%) (**Table 4**). The most common ADRs were platelet count decreased in 14 patients (9.2%), rash in 14 patients (9.2%), and neutrophil count decreased in 7 patients (4.6%). The most common grade ≥ 3 ADR was neutrophil count decreased in 7 patients (4.6%). Grade 5 ADRs were reported in 4 patients (2.6%) and comprised disseminated cryptococcosis in 1 patient (0.7%); bronchopulmonary aspergillosis, sinusitis aspergillus and cerebral aspergillosis in 1 patient (0.7%); ILD in 1 patient (0.7%); and subdural hematoma in 1 patient (0.7%) (**Supplementary Table 4**). ADRs related to cardiac disorders and vascular disorders included palpitations in 4 patients (2.6%), atrial fibrillation in 2 patients (1.3%), and hypertension in 3 patients (2.0%) (**Table 4**). Among the ADRs related to cardiac disorders and vascular disorders, the only ADR that did not resolve or improve was one case of palpitations (**Supplementary Tables 5–7**).

ADRs by patient characteristics

Regarding the incidences of ADRs by patient characteristics, there were significant differences between patients divided by age (15–64 vs. ≥ 65 years: 76.5% vs. 53.4%, P = 0.016), PS (0–1 vs. 2–4: 62.3% vs. 41.4%, P = 0.040), and presence of neuropathy as a comorbidity (with vs. without: 79.2% vs. 54.7%, P = 0.040) (**Supplementary Table 8**). There were no significant differences in the incidences of ADRs among other patient characteristics.

ADRs associated with the safety specifications

The most frequent categories in the safety specifications were myelosuppression in 32 patients (21.1%) and clinically significant skin disorders in 30 (19.7%) (**Table 5**). Infections, hemorrhages, hepatic function disorders, ILDs, and hypersensitivities were observed in 14 patients (9.2%), 13 (8.6%), 5 (3.3%), 4 (2.6%), and 3 (2.0%), respectively.

A total of 114 patients (75.0%) received concomitant prophylactic anti-infection medications **(Supplementary Table 9)**. The most common was sulfamethoxazole/trimethoprim, which was administered to 82 patients (53.9%). The incidence of ADRs associated with infections was 7.9% among patients who did not receive prophylactic medication, compared to 9.6% among those who did **(Supplementary Table 10)**. Sixteen patients (10.5%) received concomitant anticoagulant or antiplatelet agents. Aspirin was the most common, being administered to 9 patients (5.9%) **(Supplementary Table 11)**. The incidence of ADRs associated with hemorrhages was 7.4% in patients who did not receive anticoagulant or antiplatelet agents, compared to 18.8% in those who did **(Supplementary Table 12)**.

ADRs associated with the safety specifications were observed throughout the 52-week observation period (**Fig. 2**). Myelosuppression and clinically significant skin disorders, the most frequent categories, mostly occurred within the first 8 weeks of tirabrutinib treatment.

Even among patients who experienced ADRs associated with the safety specifications, dose modifications of tirabrutinib were implemented in many patients (**Supplementary Table 13**). Many ADRs associated with the safety specifications resolved or improved (**Fig. 3**). However, there were ADRs that did not resolve or improve, including three cases of infections, five of clinically significant skin disorders, nine of myelosuppression, one of hypersensitivities, one of ILDs, two of hepatic function disorders, and three of hemorrhages. The median time to either resolution or remission was generally 14.5–50.0 days. However, some ADRs associated with the safety specifications, other than hypersensitivities, took ≥ 100 days for resolution or remission. In one patient, grade 3 toxic epidermal necrolysis was observed on Day 43 of administration and resolved 43 days after onset following steroid pulse therapy and

discontinuation of tirabrutinib treatment (**Supplementary Table 14**).

Effectiveness

Among 85 patients in the effectiveness analysis set, the MRR was 63.5% (*n* = 54) and the ORR was 74.1% (*n* = 63). CR was achieved in 4 patients (4.7%) and VGPR was achieved in 11 (12.9%) (**Table 6**). The MRR was also analyzed among subgroups of patients, and a significant difference was found between males and females (74.5% vs. 43.3%, *P* = 0.008) (**Supplementary Table 15**). The ORR was significantly different between males and females (81.8% vs. 60.0%, *P* = 0.038) and between subgroups of patients with a PS of 0–1 and 2–4 (77.3% vs. 44.4%, *P* = 0.035) (**Supplementary Table 16**). Median OS was not reached and the survival rate at 365 days was 92.7% (**Fig. 4**).

DISCUSSION

This PMS registered all patients with WM/LPL who were treated with tirabrutinib, with no specific exclusion criteria. However, five patients from four institutions were excluded from the safety analysis set due to lack of consent for data publication. Ultimately, data were collected for 158 patients from 117 institutions; the excluded patients and institutions accounted for 3.2% and 3.4% of the total numbers, respectively. Therefore, the impact of these exclusions on the overall results is considered to be minimal. The 152 patients included in the safety analysis set likely represent the broad characteristics of patients with WM/LPL who would be treated with tirabrutinib in clinical practice settings in Japan. This PMS included 19.1% of patients with a PS of 2–4, a subgroup of patients excluded from the ONO-4059-05 trial.[12] Therefore, the safety profile of tirabrutinib determined in this PMS can help fill the gap in evidence between the clinical trial and real-world conditions.

The most frequent ADRs with tirabrutinib were related to skin disorders or myelosuppression. This was similar to the results of the PMS of tirabrutinib in patients with primary central nervous system lymphoma (PCNSL).[19] The most common skin disorder was rash (9.2%). In clinical trials of each BTK inhibitor, rash was reported as an AE with an incidence rate of 3%–47% for ibrutinib, 6%–33% for acalabrutinib, 11%–34% for zanubrutinib, and 18%–44% for tirabrutinib.[20] Skin disorders may develop through a mechanism involving inhibition of epidermal growth factor receptor (EGFR).[20] The ratio of the half-maximal inhibitory concentration (IC_{50}) values for EGFR to BTK varies among BTK inhibitors: 7-fold for ibrutinib, > 2020-fold for acalabrutinib, 38-fold for zanubrutinib, and > 3597-fold for tirabrutinib.[10] The difference was greater for acalabrutinib and tirabrutinib compared to ibrutinib and zanubrutinib. It is unlikely that EGFR inhibition contributes to the rash caused by these two compounds. Other off-targets might be considered, although they are currently

unknown.

Regarding myelosuppression, the most frequent type of ADR was platelet count decreased (9.2%). Thrombocytopenia was also reported as an AE in clinical trials of other BTK inhibitors in patients with WM, with incidences of 10% for ibrutinib, 10% for zanubrutinib, and 4.7% for acalabrutinib.[21,22] BTK is also expressed in platelets.[23] Humans who carry X-linked agammaglobulinemia with a mutation in the *BTK* gene produce platelets with normal BTK and mutated BTK.[23] The *BTK* mutation in megakaryocytes is not considered a significant factor in the maturation of megakaryocytes and the production of platelets.[23] However, because thrombocytopenia was observed in clinical trials of multiple BTK inhibitors, the mechanism involved in thrombocytopenia caused by BTK inhibitors remains unclear.

ADRs related to cardiac and vascular disorders are a common concern for BTK inhibitors.[20] In this PMS, cardiac and vascular disorders that occurred with an incidence of ≥ 1% included palpitations (*n* = 4, 2.6%), hypertension (*n* = 3, 2.0%), and atrial fibrillation (*n* = 2, 1.3%). Notably, palpitations are an ADR that was not observed in the clinical trials of tirabrutinib[12,13,15–17] or the PMS of tirabrutinib in PCNSL.[19] Most ADRs related to cardiac and vascular disorders observed in this PMS resolved or improved. However, palpitations did not resolve in one patient. Therefore, although these ADRs are considered manageable with appropriate monitoring, attention should be paid to cardiac and vascular disorders in patients treated with tirabrutinib.

BTK is crucial for the development of B cells and the function of innate immunity, and its regulation increases the risk of infections.[24] AEs related to infections were reported in clinical

trials of ibrutinib, zanubrutinib, and acalabrutinib.[21,22,25,26] Reflecting on prior clinical trials of tirabrutinib,[12,15-17] infections were specified as safety specifications in this PMS. Among patients who developed infections, two resulted in death, and one recovered with sequelae (**Fig. 3**, **Supplementary Table 4**). Therefore, it is important to exercise caution regarding infections.

In this PMS, the incidence of ADRs associated with infections was similar between patients who received concomitant prophylactic anti-infection medications and those who did not (**Supplementary Table 10**). However, there was a bias in patient characteristics because prophylactic medications were administered to 11 out of 12 patients with comorbid infections and to all 10 patients with a PS ≥ 3. The patient characteristics collected in this PMS were limited, and only 14 patients experienced ADRs associated with infections (**Table 5**). Therefore, it is difficult to assess whether prophylactic medication reduced the incidence of infections in patients receiving tirabrutinib based on the present data. The incidence of ADRs associated with hemorrhages was numerically higher among patients who received concomitant anticoagulant or antiplatelet agents (**Supplementary Table 12**). However, because these agents were administered to only 16 patients, and ADRs associated with hemorrhages were observed in just three of them, these findings are based on a limited sample size. Therefore, it is difficult to draw definitive conclusions regarding an increased risk of ADRs associated with hemorrhages due to concomitant use of these agents. Nevertheless, our results suggest that careful monitoring for ADRs associated with hemorrhages is warranted in patients receiving concomitant anticoagulant or antiplatelet agents.

ADRs associated with the safety specifications were observed throughout the 52-week

observation period (**Fig. 2**). Many ADRs associated with this safety specification resolved or improved (**Fig. 3**), similar to the PMS of tirabrutinib in patients with PCNSL.[19] However, it took a long time for some ADRs to resolve or improve. Additionally, in some patients, the ADRs did not resolve, resolved with sequelae, or progressed to grade 5 (**Supplementary Table 4**). Therefore, careful management of ADRs during tirabrutinib treatment is essential.

Regarding the effectiveness of tirabrutinib in this PMS, the MRR was 63.5%, the ORR was 74.1%, and the survival rate at 365 days was 92.7%. The response rate was evaluated by the individual physicians in accordance with the IWWM criteria,[18] but was not assessed by a central independent review committee. Additionally, the study protocol did not specify the exact timing of the response assessments. Therefore, the effectiveness data should be interpreted with caution. The MRR (63.5%) and the ORR (74.1%) observed in this PMS were numerically lower than those reported in the ONO-4059-05 phase 2 trial (MRR 92.6%, ORR 96.3%).[13] It should be noted that the ONO-4059-05 phase 2 trial only enrolled patients who met predefined eligibility criteria, which included restrictions on PS and organ function, thereby excluding patients with PS 2–4,[12] whereas such patients accounted for 10.6% of the effectiveness analysis set in this PMS, reflecting routine clinical practice. Consistent with this difference in patient characteristics, subgroup analyses in this PMS demonstrated a significantly lower ORR in patients with PS 2–4 (**Supplementary Table 16**), suggesting that this imbalance may have contributed to the lower effectiveness-related parameters observed in the PMS compared with the clinical trial. In addition to PS, differences in tumor burden and other prognostic factors for WM, such as β_2-microglobulin levels, serum IgM levels, hemoglobin levels, and platelet count,[27] may also have influenced treatment outcomes. These variables were systematically collected in the ONO-4059-05 phase 2 trial[12] but were not captured in this PMS, precluding further assessment of their potential impact on the observed

differences in effectiveness. Furthermore, the ONO-4059-05 trial was conducted in a limited number of patients.[12] Taken together, these differences in study design and available data make it difficult to clearly delineate the reasons for the discrepancies in efficacy outcomes between this PMS and the clinical trial.

Limitations

All patients who started treatment with tirabrutinib in Japan between August 21, 2020, and January 17, 2021, were registered in this PMS. However, there were four patients whose CRFs were not returned and five patients whose institutions did not give consent to disclose their results in this publication; these patients were excluded from the safety analysis set. At the end of the observation period, more than half of the patients were continuing tirabrutinib treatment. This suggests that the 52-week observation period was insufficient to evaluate the safety of long-term administration of tirabrutinib. The clinical information for patients treated with tirabrutinib was collected using CRFs completed by the physicians. Therefore, only the information specified in the CRFs was collected, limiting the scope of information collected in this PMS. Additionally, central review of the tumor responses was not performed. Only best overall response data were collected to evaluate effectiveness. Furthermore, subsequent treatments were not recorded. Consequently, Kaplan–Meier curves for progression-free survival or time to next treatment could not be generated. Data for specific laboratory parameters, including serum IgM and hemoglobin, were not collected. Consequently, detailed evaluation of the effectiveness of tirabrutinib in patients with WM/LPL could not be performed.

Conclusion

This PMS evaluated the safety and effectiveness of tirabrutinib for WM/LPL in real-world clinical settings. The results suggested that the safety profile of tirabrutinib is in line with that observed in prior studies.

STATEMENTS

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CONFLICT OF INTEREST

Akira Kawasaki and Toshikazu Nagano are employees of Ono Pharmaceutical. Yudai Higuchi is an employee of Ono Pharmaceutical and holds stock in the company. Ryo Nishikawa has nothing to declare. Koji Izutsu has received grants/contracts (to the institution) from MSD, AstraZeneca, AbbVie, Incyte, Bristol Myers Squibb, Novartis, Bayer, Pfizer, Janssen Pharmaceutical, Yakult Honsha, Kyowa Kirin, Daiichi Sankyo, Chugai Pharmaceutical, BeiGene, Genmab, Loxo Oncology, Otsuka Pharmaceutical, Regeneron Pharmaceuticals, and Gilead Sciences; consulting fees from MSD, AstraZeneca, AbbVie, Bristol Myers Squibb, Novartis, Yakult Honsha, Kyowa Kirin, Chugai Pharmaceutical, BeiGene, Genmab, Otsuka Pharmaceutical, Ono Pharmaceutical, Mitsubishi Tanabe Pharma, Eisai, SymBio Pharmaceuticals, Takeda Pharmaceutical, Zenyaku Kogyo, Carna Biosciences, and Nippon Shinyaku; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, AbbVie, Bristol Myers Squibb, Novartis, Pfizer, Janssen Pharmaceutical, Kyowa Kirin, Daiichi Sankyo, Chugai Pharmaceutical, Genmab, Gilead Sciences, Ono Pharmaceutical, Nippon Kayaku, SymBio Pharmaceuticals, Takeda Pharmaceutical, Eli Lilly, Astellas Pharma, and Meiji Seika Pharma.

ETHICAL APPROVAL

This PMS was registered on the Japan Registry of Clinical Trials (jRCT2011210005). This PMS was conducted based on the approval conditions for tirabrutinib in Japan set by the Pharmaceuticals and Medical Devices Agency. The PMS adhered to the "Ministerial Ordinance on Standards for Conducting Post-Marketing Surveillance and Studies on Drugs" (GPSP) based on Article 14-4 or 14-6 of the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Pharmaceuticals and Medical Devices Act). No invasive or interventional procedures were performed for the purpose of this PMS. We only collected clinical information that was recorded as part of routine medical practice, while adhering to GPSP. Under GPSP, it is not necessary to obtain ethical approval for PMS conducted in compliance with GPSP. Under GPSP, it is not necessary to obtain patient consent for PMS conducted in compliance with GPSP. Therefore, patient consent was not obtained for this PMS. However, because publishing the results of this PMS in a scientific journal falls outside the scope of GPSP, we obtained written consent to disclose the results from the institutions that treated the patients. The data presented in this paper only includes information from patients whose institutions provided consent to disclose the results.

AUTHOR CONTRIBUTIONS

Akira Kawasaki and Toshikazu Nagano contributed to the conception and design of the PMS, data collection, and data analysis. Ryo Nishikawa and Koji Izutsu contributed to the conception and design of the PMS. All authors made significant contributions to the interpretation of the data. All authors reviewed the article for accuracy and provided constructive feedback. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant

changes introduced during the proofing stage. All authors agreed to take responsibility and be accountable for all aspects of the work, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors agreed on which journal to submit the article.

DATA AVAILABILITY

Qualified researchers may request Ono Pharmaceutical to disclose individual patient-level data from clinical studies through the following website: https://vivli.org/. For more information on Ono Pharmaceutical's Policy for the Disclosure of Clinical Study Data, please see the following website: https://www.ono.co.jp/eng/rd/policy.html.

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Table 1. Patient characteristics (safety analysis set, *N* = 152)

Characteristic		Value
Sex	Male	102 (67.1)
	Female	50 (32.9)
Age, years	Median (range)	73.0 (36–96)
	≤ 14	0
	15–64	34 (22.4)
	≥ 65	118 (77.6)
ECOG PS	0–1	122 (80.3)
	2–4	29 (19.1)
	Unknown	1 (0.7)
Medical history	No	65 (42.8)
	Yes	87 (57.2)
	Hemorrhagic events	12 (7.9)
Comorbidities (complications)*	No	44 (28.9)
	Yes	108 (71.1)
	Neuropathies	24 (15.8)
	Renal disorders	13 (8.6)
	Infections	12 (7.9)
	Liver disorders	11 (7.2)
	Respiratory disorders	11 (7.2)
	Visual impairments	11 (7.2)
	Blood coagulation disorders	0
	Others	86 (56.6)
Disease	WM/LPL	151 (99.3)
	Other	1 (0.7)
Interval from primary diagnosis to the start of tirabrutinib, months	Median (range)	48.2 (0.3–349.8)
Prior treatment with tirabrutinib	No	149 (98.0)
	Yes	2 (1.3)

	Unknown	1	(0.7)
Number of prior systemic therapy regimens	Median (range)	1.0 (0–8)	
	0	33	(21.7)
	1	49	(32.2)
	2	24	(15.8)
	≥ 3	43	(28.3)
	Unknown	3	(2.0)
Prior plasmapheresis	No	137	(90.1)
	Yes	13	(8.6)
	Unknown	2	(1.3)
Prior HSCT	No	147	(96.7)
	Yes	5	(3.3)

Values are presented as *n* (%) unless otherwise stated.

*If there were multiple cases for the same patient, each case was tabulated.

ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; WM/LPL, Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma.

Table 2. Duration of tirabrutinib treatment (safety analysis set, $N = 152$)

Duration of treatment, days*	**Value**
Median (range)	338.5 (2–365)
1–28	13 (8.6)
29–84	22 (14.5)
85–168	8 (5.3)
169–252	11 (7.2)
253–364	42 (27.6)
365	56 (36.8)

Values are presented as *n* (%) unless otherwise stated.

*Duration of treatment with tirabrutinib in days, excluding periods of drug interruption.

Table 3. Tirabrutinib treatment status (safety analysis set, *N* = 152)

Treatment status		**Value**
Treatment status at the end of the observation period	Continuation	92 (60.5)
	Discontinuation	60 (39.5)
Duration of tirabrutinib treatment, days*, median (range)	Continuation†	365.0 (71–365)‡
	Discontinuation†	70.0 (2–358)
Reasons for discontinuation§		
Adverse event		30 (50.0)‖
Disease progression (including death)		18 (30.0)‖
Transfer to another hospital		4 (6.7)‖
Response to treatment		2 (3.3)‖
Other reason		14 (23.3)‖

Values are presented as *n* (%) unless otherwise stated.

*Duration of treatment with tirabrutinib in days, excluding periods of drug interruption.

†Patients who were continuing/discontinuing treatment at the end of the observation period.

‡The duration of tirabrutinib treatment was 71 days in one patient, and ranged from 209 to 365 days in the other patients.

§If patients discontinued for multiple reasons, each reason was tabulated.

‖Percentages were calculated using number of patients who discontinued tirabrutinib as the denominator.

Table 4. ADRs in ≥ 1% of patients (safety analysis set, $N = 152$)

ADRs	Number of patients with the ADR, *n* (%)			
	Any grade		Grade ≥ 3	
Any ADR	89	(58.6)	45	(29.6)
Platelet count decreased	14	(9.2)	6	(3.9)
Rash	14	(9.2)	1	(0.7)
Neutrophil count decreased	7	(4.6)	7	(4.6)
Neutropenia	5	(3.3)	3	(2.0)
White blood cell count decreased	5	(3.3)	2	(1.3)
Interstitial lung disease	4	(2.6)	2	(1.3)
Hemorrhage subcutaneous	4	(2.6)	0	
Palpitations	4	(2.6)	0	
Pruritus	4	(2.6)	0	
Pneumonia	3	(2.0)	3	(2.0)
Anemia	3	(2.0)	2	(1.3)
Hepatic function abnormal	3	(2.0)	2	(1.3)
Eczema	3	(2.0)	1	(0.7)
Hypertension	3	(2.0)	1	(0.7)
Purpura	3	(2.0)	0	
Pyrexia	3	(2.0)	0	
Urticaria	3	(2.0)	0	
Leukopenia	2	(1.3)	2	(1.3)
Thrombocytopenia	2	(1.3)	2	(1.3)
Hematuria	2	(1.3)	1	(0.7)
Liver disorder	2	(1.3)	1	(0.7)
Nausea	2	(1.3)	1	(0.7)
Atrial fibrillation	2	(1.3)	0	
Blood creatinine increased	2	(1.3)	0	
Dyspnea	2	(1.3)	0	
Erythema	2	(1.3)	0	
Malaise	2	(1.3)	0	

ADRs were coded using MedDRA/J Ver. 25.1 and classified by preferred term. If the same ADR occurred multiple times in the same patient, it was included as a single event.

ADR, adverse drug reaction.

Table 5. ADRs associated with the safety specifications (safety analysis set, $N = 152$)

ADRs associated with the safety specifications	**Number of patients with the ADR, *n* (%)**	
	Any grade	**Grade ≥ 3**
Myelosuppression	32 (21.1)	22 (14.5)
Platelet count decreased	14 (9.2)	6 (3.9)
Neutrophil count decreased	7 (4.6)	7 (4.6)
Neutropenia	5 (3.3)	3 (2.0)
White blood cell count decreased	5 (3.3)	2 (1.3)
Anemia	3 (2.0)	2 (1.3)
Leukopenia	2 (1.3)	2 (1.3)
Thrombocytopenia	2 (1.3)	2 (1.3)
Febrile neutropenia	1 (0.7)	1 (0.7)
Lymphocyte count decreased	1 (0.7)	1 (0.7)
Clinically significant skin disorders	30 (19.7)	5 (3.3)
Rash	14 (9.2)	1 (0.7)
Pruritus	4 (2.6)	0
Eczema	3 (2.0)	1 (0.7)
Erythema	2 (1.3)	0
Erythema multiforme	1 (0.7)	1 (0.7)
Rash pruritic	1 (0.7)	1 (0.7)
Toxic epidermal necrolysis	1 (0.7)	1 (0.7)
Infections	14 (9.2)	9 (5.9)
Pneumonia	3 (2.0)	3 (2.0)
Bronchopulmonary aspergillosis	1 (0.7)	1 (0.7)
Cellulitis	1 (0.7)	1 (0.7)
Disseminated cryptococcosis	1 (0.7)	1 (0.7)
Nocardiosis	1 (0.7)	1 (0.7)
Pneumonia aspiration	1 (0.7)	1 (0.7)
Sepsis	1 (0.7)	1 (0.7)
Muscle abscess	1 (0.7)	1 (0.7)

Sinusitis aspergillus	1	(0.7)	1	(0.7)
Cerebral aspergillosis	1	(0.7)	1	(0.7)
Cutaneous nocardiosis	1	(0.7)	1	(0.7)
Coronavirus pneumonia	1	(0.7)	1	(0.7)
Hemorrhages	13	(8.6)	2	(1.3)
Hemorrhage subcutaneous	4	(2.6)	0	
Purpura	3	(2.0)	0	
Hematuria	2	(1.3)	1	(0.7)
Subdural hematoma	1	(0.7)	1	(0.7)
Hepatic function disorders	5	(3.3)	3	(2.0)
Hepatic function abnormal	3	(2.0)	2	(1.3)
Liver disorder	2	(1.3)	1	(0.7)
Interstitial lung diseases	4	(2.6)	2	(1.3)
Interstitial lung disease	4	(2.6)	2	(1.3)
Hypersensitivities	3	(2.0)	0	
Urticaria	3	(2.0)	0	

Seven categories of diseases (infections, clinically significant skin disorders, myelosuppression, hypersensitivities, interstitial lung diseases, hepatic function disorders, and hemorrhages) were defined as safety specifications. ADRs were coded using MedDRA/J Ver. 25.1 and classified by preferred term. The table lists all of the ADRs associated with safety specifications with a grade ≥ 3, as well as any ADRs (any grade) that were reported in ≥ 2 patients within each category. If the same ADR occurred multiple times in the same patient, it was included as a single event. If more than one ADR within the same category of safety specifications occurred in one patient, it was calculated as one safety specification.

ADR, adverse drug reaction.

Table 6. Best overall responses (effectiveness analysis set, $N = 85$)

Investigator-assessed responses		***n* (%)**
Best overall response	CR	4 (4.7)
	VGPR	11 (12.9)
	PR	39 (45.9)
	MR	9 (10.6)
	Stable disease	10 (11.8)
	Progressive disease	4 (4.7)
	Not evaluable	8 (9.4)
MRR (= CR + VGPR + PR)		54 (63.5)
ORR (= CR + VGPR + PR + MR)		63 (74.1)

The best overall response was assessed according to the consensus criteria of the VIth International Workshop for Waldenström's Macroglobulinemia.[18]

CR, complete response; MR, minor response; MRR, major response rate; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

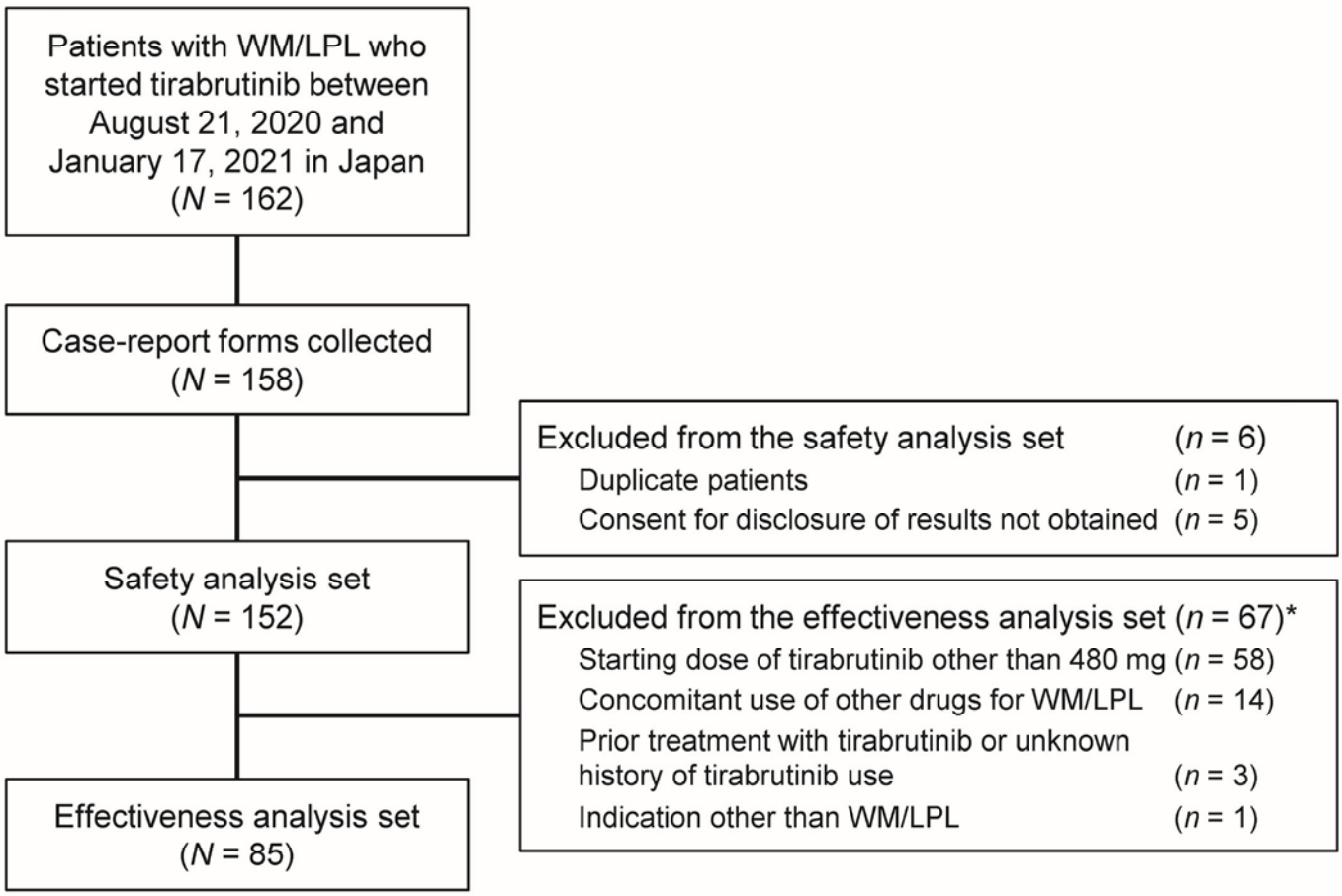

Fig. 1. Patient disposition. *Some patients were excluded for multiple reasons. WM/LPL, Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma.

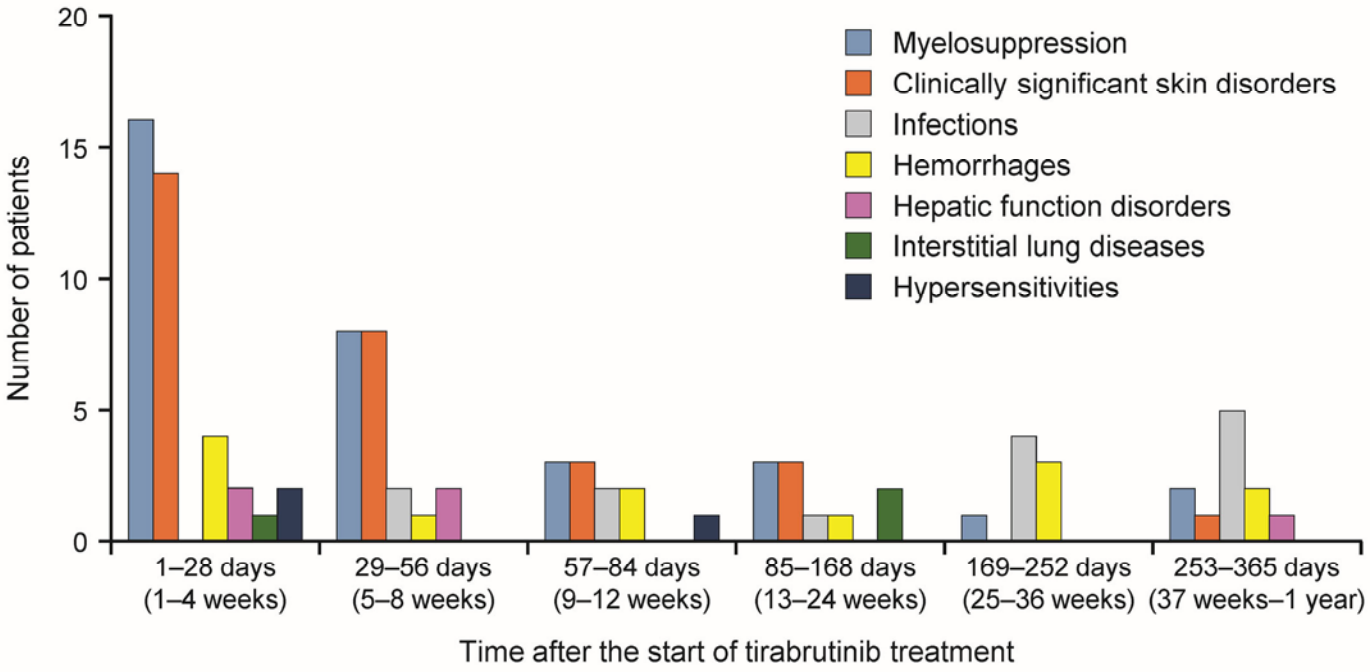

Fig. 2. Interval from the first dose of tirabrutinib to the onset of ADRs associated with the safety specifications (safety analysis set, $N = 152$). If the same ADR occurred more than once in the same patient, the first occurrence of that ADR was tabulated. ADR, adverse drug reaction.

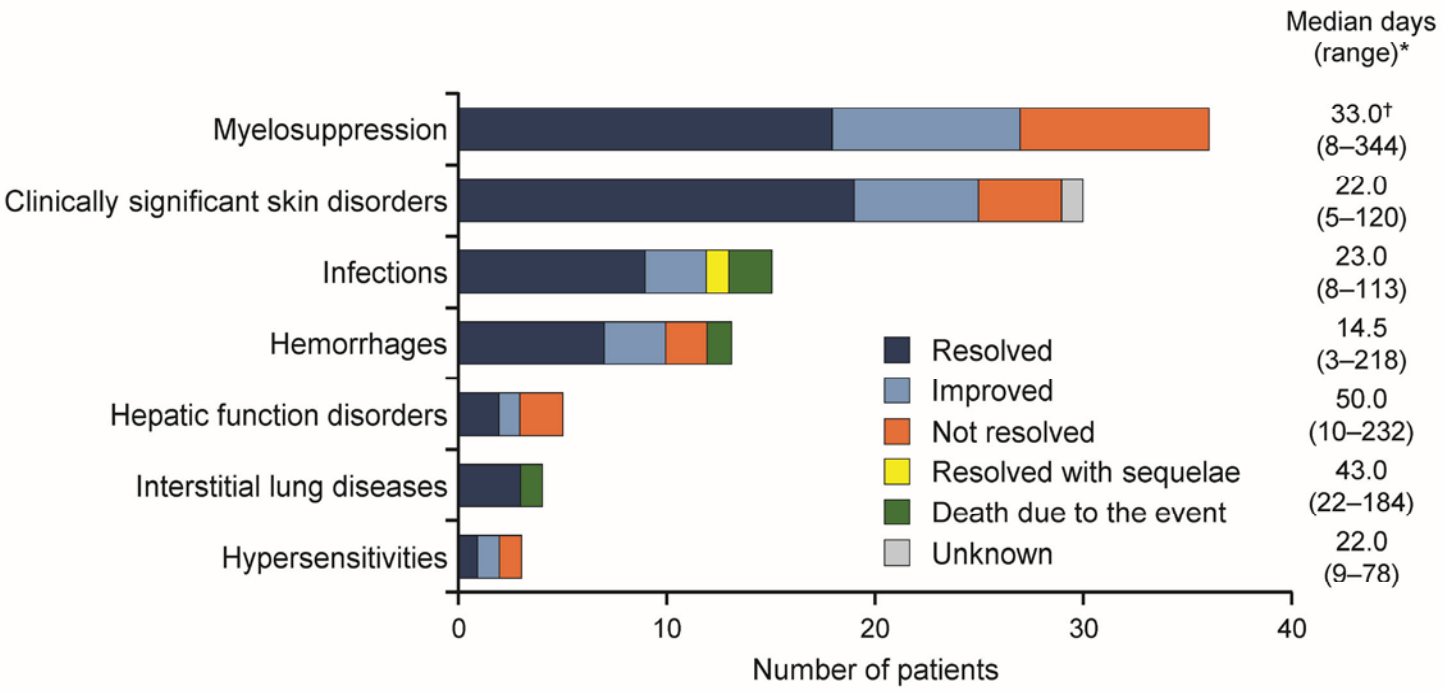

Fig. 3. Outcomes of ADRs associated with the safety specifications (safety analysis set, *N* = 152). If the same ADR occurred more than once in the same patient, that ADR was counted once according to the following hierarchy: death due to the event > resolved with sequelae > not resolved > improved > resolved > unknown. *Interval from the onset of the ADRs to improved/resolved status. †Number of days to improved/resolved status, excluding one patient with missing data. ADR, adverse drug reaction.

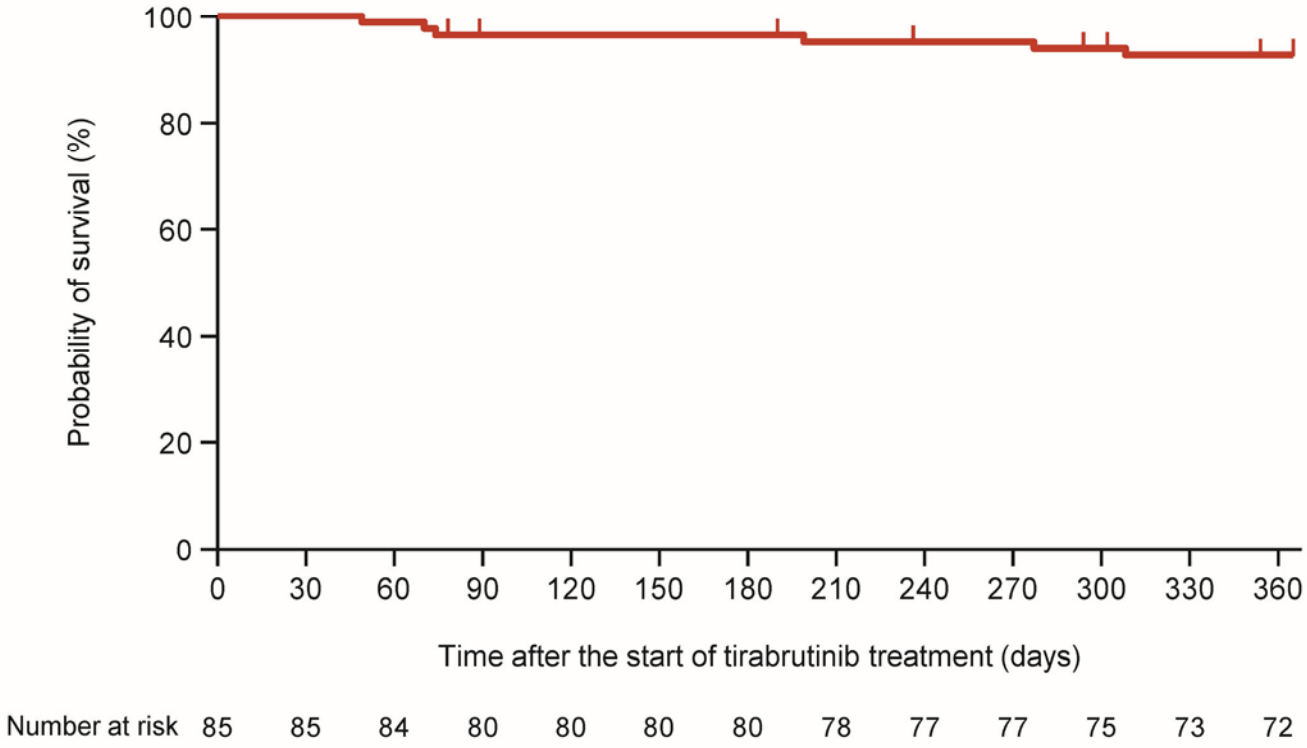

Fig. 4. Kaplan–Meier curve of overall survival (effectiveness analysis set, $N = 85$).