Review Report

January 19, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Imbruvica Capsules 140 mg
Non-proprietary Name	Ibrutinib (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	June 10, 2022
Dosage Form/Strength	Capsules, each containing 140 mg of ibrutinib
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 339 of 2014 [*26 yaku*]; PFSB/ELD Notification No. 0611-1 dated June 11, 2014 by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of treatment-naïve mantle cell lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions

Indications

1) Chronic lymphocytic leukemia (including small lymphocytic lymphoma)
2) Primary macroglobulinemia and lymphoplasmacytic lymphoma
~~2~~3) ~~Relapsed or refractory m~~Mantle cell lymphoma
~~3~~4) Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)

(Underline denotes additions. Strikethrough denotes deletions. Double underline denotes changes made as of December 23, 2022 after submission of the present application.)

Dosage and Administration

1) Chronic lymphocytic leukemia (including small lymphocytic lymphoma), primary macroglobulinemia, and lymphoplasmacytic lymphoma

   The usual adult dosage is 420 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

2) ~~Relapsed or refractory m~~Mantle cell lymphoma

   - Treatment-naïve diseases

     In combination with bendamustine hydrochloride and rituximab (genetical recombination), the usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

   - Relapsed or refractory diseases

     The usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

3) Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)

   The usual dosage in adults and children aged ≥12 years is 420 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

(Underline denotes additions. Strikethrough denotes deletions. Double underline denotes changes made as of December 23, 2022 after submission of the present application.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

November 22, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Imbruvica Capsules 140 mg
Non-proprietary Name	Ibrutinib
Applicant	Janssen Pharmaceutical K.K.
Date of Application	June 10, 2022
Dosage Form/Strength	Capsules, each containing 140 mg of ibrutinib.
Proposed Indications	1) Chronic lymphocytic leukemia (including small lymphocytic lymphoma) 2) ~~Relapsed or refractory m~~Mantle cell lymphoma 3) Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids) (Underline denotes additions. Strikethrough denotes deletions.)

Proposed Dosage and Administration

1) Chronic lymphocytic leukemia (including small lymphocytic lymphoma)
   The usual adult dosage is 420 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.
2) ~~Relapsed or refractory m~~Mantle cell lymphoma

- Treatment-naïve diseases
  In combination with bendamustine hydrochloride and rituximab (genetical recombination), the usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.
- Relapsed or refractory diseases
  The usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

3) Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)
   The usual dosage in adults and children aged ≥12 years is 420 mg of

ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

(Underline denotes additions, Strikethrough denotes deletions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Ibrutinib is a small-molecule inhibitor against Bruton's tyrosine kinase (BTK) discovered by Celera Genomics Inc. in the US. BTK plays a role in signaling pathways downstream of B-cell receptors (BCR) and chemokine receptors expressed in B cells. Ibrutinib is considered to form a covalent bond with a cysteine residue at position 481 in the BTK active site and inhibit BTK activity, thereby suppressing malignant B-cell proliferation, etc.

In Japan, ibrutinib was approved for the indications of "relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)" in March 2016, "relapsed or refractory mantle cell lymphoma" in December 2016, "chronic lymphocytic leukemia (including small lymphocytic lymphoma)" in July 2018, and "chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)" in September 2021.

1.2 Development history etc.

As a part of the clinical development project of ibrutinib for treatment-naïve mantle cell lymphoma (MCL), Janssen Research & Development, LLC (US) initiated a global phase III study in patients with treatment-naïve MCL (Study PCI-32765MCL3002 [Study 3002]) in April 2013.

In the EU, an application was submitted for the indication of treatment-naïve MCL in March 2022 with pivotal data from Study 3002, and is currently under review.

As of October 2022, ibrutinib has not been approved for the indication of treatment-naïve MCL in any country or region.

In Japan, the applicant initiated patient enrollment in Study 3002 in [redacted] 20[redacted].

Recently, the applicant has submitted an application for partial change of ibrutinib for the additional indication of treatment-naïve MCL and the dosage regimen, with pivotal data from Study 3002.

Of note, ibrutinib was designated as an orphan drug for the intended indications of "chronic lymphocytic leukemia, small lymphocytic lymphoma, and mantle cell lymphoma" in June 2014 (Orphan Drug Designation No. 339 of 2014 [*26 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

The present application pertains to the new indication and new dosage, and no quality-related data were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The present application pertains to the new indication and new dosage. Non-clinical pharmacology data were evaluated in the review process for the initial approval, and thus no new data were submitted.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The present application pertains to the new indication and new dosage. Non-clinical pharmacokinetic data were evaluated in the review process for the initial approval, and thus no new data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application pertains to the new indication and new dosage, and thus no toxicity data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The present application pertains to the new indication and new dosage. Data from biopharmaceutic studies and associated analytical methods were evaluated in the review process for the initial approval, and thus no new data were submitted.

6.1 Clinical pharmacology

Pharmacokinetics (PK) of ibrutinib in patients with cancer was investigated after the administration of ibrutinib/BR (concomitant use of ibrutinib with bendamustine plus rituximab).

6.1.1 Global phase III study (CTD 5.3.5.1-1, Study 3002, ongoing since April 2013 [data cut-off on June 30, 2021])

A randomized, double-blind study was conducted in 523 patients with treatment-naïve MCL aged ≥65 years (519 included in the PK analysis) to compare the efficacy and safety of ibrutinib/BR with placebo/BR. The patients orally received ibrutinib 560 mg or the placebo QD in combination with BR[1)] in 28-day cycles to investigate plasma ibrutinib concentrations. In addition, plasma bendamustine concentrations were investigated in 7 Japanese patients.

The applicant's explanation:

Plasma ibrutinib concentrations (mean ± standard deviation [SD]) before the administration of ibrutinib on Day 2 of Cycle 2 (n = 235) and on Day 2 of Cycle 3 (n = 218) were 6.60 ± 14.2 and 6.19 ± 12.1 ng/mL, respectively. In a foreign phase II study in patients with relapsed or refractory MCL (Study PCYC-1104-CA [Study 1104]), pre-dose steady state plasma ibrutinib concentrations during treatment with ibrutinib 560 mg alone were 6.36 to 11.3 ng/mL,[2)] which did not clearly differ from those during treatment with ibrutinib/BR.

Table 1 shows plasma bendamustine concentrations. Plasma bendamustine concentrations did not clearly differ between the ibrutinib/BR and placebo/BR groups.

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1) Bendamustine 90 mg/m^2 was intravenously administered on Days 1 and 2 of Cycles 1 to 6 and RIT 375 mg/m^2 on Day 1 of Cycles 1 to 6. For patents who had achieved complete response (CR) or partial response (PR) after the end of Cycle 6, RIT 375 mg/m^2 was intravenously administered as maintenance therapy on Day 1 of Cycles 8 to 30 (once every 2 cycles) up to 12 doses.

2) Range of mean plasma ibrutinib concentrations before administration on Days 8, 15, and 22 in cohorts of patients previously untreated and treated with bortezomib in Study 1104

Table 1. Plasma bendamustine concentrations

Measuring point	Ibrutinib/BR		Placebo/BR	
	n	Plasma concentration (ng/mL)	n	Plasma concentration (ng/mL)
End of bendamustine administration on Day 2 of Cycle 1	3	4,830 ± 1,904	4	4,858 ± 1,032
2 hours after bendamustine administration on Day 2 of Cycle 1	3	1,012 ± 683	4	727 ± 649
4 hours after bendamustine administration on Day 2 of Cycle 1	3	27.9 ± 20.1	4	31.4 ± 32.2

Mean ± SD

6.1.2 Association between exposure and efficacy or safety

Association between exposure and efficacy or safety of ibrutinib were investigated based on results from the global phase III study (Study 3002).

The applicant's explanation:
(a) In terms of efficacy, no clear relation was indicated between exposure and overall survival (OS) or progression free survival (PFS). (b) Safety related outcomes revealed a tendency of increased incidences of atrial fibrillation and bleeding events with increasing exposure.

6.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA has concluded that the applicant's explanation about clinical pharmacology of ibrutinib is acceptable.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data from the global phase III study outlined in Table 2.

Table 2. List of clinical study for efficacy and safety

Data category	Region	Study identifier	Phase	Study population	Number of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Global	Study 3002	III	Patients with treatment-naïve MCL aged ≥65 years	523 (a) 261 (b) 262	Oral administration of (a) ibrutinib 560 mg or (b) the placebo in combination with BR* QD in 28-day cycles	Efficacy Safety PK

* Bendamustine 90 mg/m^2 was intravenously administered on Days 1 and 2 of Cycles 1 to 6 and RIT 375 mg/m^2 on Day 1 of Cycles 1 to 6. For patients who had achieved CR or PR after the end of Cycle 6, RIT 375 mg/m^2 was intravenously administered as maintenance therapy on Day 1 of Cycles 8 to 30 (once every 2 cycles) up to 12 doses.

The following is the summary of the clinical study. Major adverse events other than deaths reported in the clinical study are reviewed in Section "7.2 Adverse events observed in clinical studies."

7.1 Evaluation data

7.1.1 Clinical study

7.1.1.1 Global phase III study (CTD 5.3.5.1.1, Study 3002, ongoing since April 2013 [data cut-off on June 30, 2021])

A randomized, double-blind study was conducted in patients with treatment-naïve MCL aged ≥65 years[3)] (target sample size, 520 patients) at 182 study sites in 28 countries or regions including Japan to compare the efficacy and safety of ibrutinib/BR with placebo/BR.

Ibrutinib 560 mg or the placebo was orally administered QD in combination with BR[1)] in 28-day cycles until disease progression or the discontinuation criteria were met.

A total of 523 patients enrolled and randomized in the study (261 in the ibrutinib/BR group, 262 in the placebo/BR group) were included in the intend-to-treat (ITT) population and were subjected to the efficacy analysis (7 Japanese in the ibrutinib/BR group, 4 Japanese in the placebo/BR group). Of the ITT population, 519 patients (259 in the ibrutinib/BR group, 260 in the placebo/BR group) were included in the safety analysis (6 Japanese in the ibrutinib/BR group, 4 Japanese in the placebo/BR group), excluding 2 patients each in the groups who did not receive the study drug.

The primary endpoint of the study was PFS assessed by investigator per Revised Response Criteria for Malignant Lymphoma (Revised RC) (*J Clin Oncol.* 2007;25:579-86). The PFS analysis was scheduled when the number of observed events reached 265. At the beginning of the study, only a single interim analysis was scheduled aiming to evaluate the futility and efficacy when the number of PFS events reached 134 (approximately 50% of the target count of events). After that, however, other clinical studies on ibrutinib yielded new data and, the incidence of PFS events was found to be lower than the expectation at the beginning of study. Therefore, assuming an extended interval between the interim analysis and the final analysis (with 265 PFS events), the second interim analysis was additionally scheduled for futility and efficacy evaluations when the number of PFS events reached 180 (68% of the target count of events) (the protocol, revised version No. [redacted] dated [redacted], 20[redacted]). The type I error probability associated with the interim analyses was adjusted using O'Brien-Fleming α-spending function according to the Lan-DeMets approach.

Table 3 and Figure 1 show final analysis results and Kaplan-Meier curve, respectively, on investigator-assessed PFS, the primary endpoint, demonstrating superiority of ibrutinib/BR to placebo/BR.

3) Patients at Stages II to IV according to the Ann Arbor staging classification were included.

Table 3. Final analysis results on PFS
(ITT population, investigator-assessed, data cut-off on June 30, 2021)

	Ibrutinib/BR	Placebo/BR
Number of patients	261	262
Death or disease progression (%)	116 (44.4)	152 (58.0)
Median [95% CI] (months)	80.6 [61.9, NE]	52.9 [43.7, 71.0]
Hazard ratio [95% CI]*1	0.75 [0.59, 0.96]*2	
P value (one-sided)*3	0.011	

*1 Calculated from a stratified Cox proportional hazards model using the simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score (0-3, 4 and 5, 6-11) as a stratification factor
*2 The upper limit of the one-sided 97.7% confidence interval (CI) corresponding to the significance level is 0.96
*3 Stratified log-rank test (the same stratification factor as that for the Cox proportional hazards model), one-sided significance level of 0.023

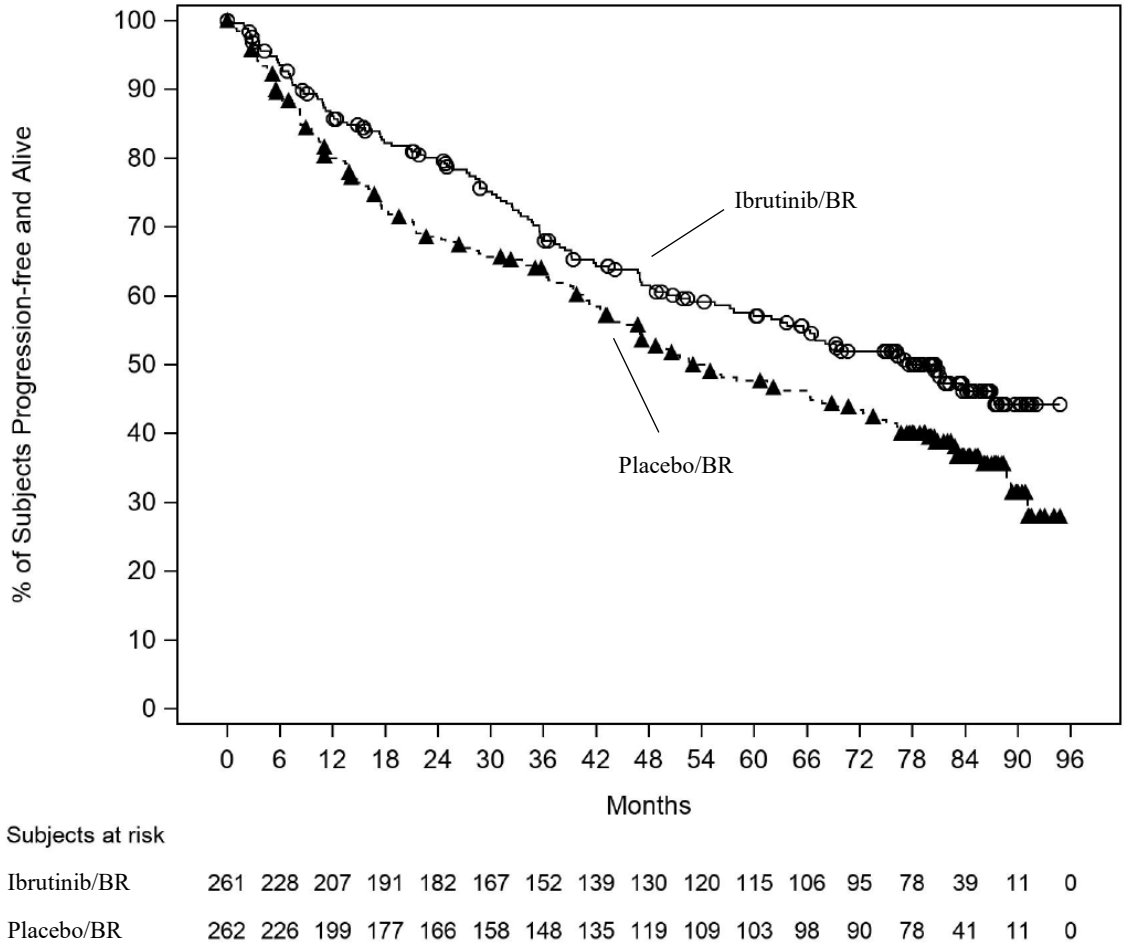

Figure 1. Kaplan-Meier curve on PFS at the final analysis
(ITT population, investigator-assessed, data cut-off on June 30, 2021)

The safely analysis revealed deaths of 29 patients (11.2%) in the ibrutinib/BR group and 19 (7.3%) in the placebo/BR group during the study treatment or follow-up period.[4)] The deaths were caused by disease progression (1 patient in the ibrutinib/BR group, 3 patients in the placebo/BR group) and other events including death in 3 patients, pneumonia, multiple organ dysfunction syndrome, sudden death, and cardiac arrest in 2 each, and bronchopulmonary aspergillosis, COVID-19, COVID-19 pneumonia, hepatitis B, nosocomial infection, pneumocystis jirovecii pneumonia, pneumonia fungal, pneumonia viral, sepsis, suspected COVID-19, general physical health deterioration, cardio-respiratory arrest, traumatic intracranial haemorrhage, tumour lysis syndrome, acute myeloid leukaemia, ischaemic stroke,

4) Period until 30 days after the last dose of the study drug or until the start of the next systemic treatment for MCL, whichever came first.

and respiratory failure in 1 patient each in the ibrutinib/BR group; and cardiopulmonary failure and myocardial infarction in 2 patients each, and pneumonia, sepsis, pseudomembranous colitis, pulmonary sepsis, septic shock, cardiac arrest, tumour lysis syndrome, acute myeloid leukaemia, myelodysplastic syndrome, haemorrhagic stroke, acute respiratory distress syndrome, and chronic obstructive pulmonary disease in 1 patient each in the placebo/BR group. A causal relationship to ibrutinib or the placebo could not be ruled out for pneumonia in 2 patients, and bronchopulmonary aspergillosis, pneumonia fungal, nosocomial infection, general physical health deterioration, tumour lysis syndrome, ischaemic stroke, and cardio-respiratory arrest in 1 patient each in the ibrutinib/BR group; and sepsis, septic shock, pseudomembranous colitis, acute myeloid leukaemia, and myelodysplastic syndrome in 1 patient each in the placebo/BR group (No deaths occurred in Japanese patients in either group).

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA decided to evaluate the efficacy and safety of ibrutinib mainly based on data from Study 3002, and to evaluate efficacy in Japanese patients systematically based on data from Study 3002, etc. in accordance with "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Amendment to 'Basic Principles on Global Clinical Trials (Reference Cases)'" (Administrative Notice dated December 10, 2021), and "General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018).

7.R.2 Efficacy

As a result of its review presented below, PMDA has concluded that ibrutinib/BR has efficacy in the treatment of treatment-naïve MCL.

7.R.2.1 Control group

The applicant's explanation about the rationale for the inclusion of the control group in Study 3002:
In 20[redacted] when Study 3002 was planned, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas (NCCN guidelines, non-Hodgkin's lymphoma) (v.[redacted]. 20[redacted]) and guidelines issued by the European Society of Medical Oncology (ESMO) (*Ann Oncol.* 20[redacted];[redacted]:[redacted]) recommended BR as one of the treatment options for patients with treatment-naïve MCL aged ≥65 years, the target patient population of Study 3002. In addition, RIT was recommended as maintenance therapy for patients with MCL who had responded to RIT used in combination with chemotherapy. Therefore, Study 3002 included the control group to be treated with BR and subsequent maintenance therapy with RIT.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the efficacy endpoints in Study 3002:
Where there were no curative treatments for treatment-naïve MCL, prolonged PFS was expected to delay the worsening of clinical symptoms caused by MCL such as anemia, and was considered clinically meaningful. For this reason, PFS was selected as the primary endpoint In Study 3002.

PMDA's view:
The applicant's explanation is largely understandable. However, OS is an important factor in the treatment of treatment-naïve MCL that aims to prolong survival. Therefore, OS will also be checked, while investigator-assessed PFS, the primary endpoint, remains as the main focus in the efficacy evaluation of ibrutinib/BR.

7.R.2.3 Efficacy evaluation results

In Study 3002, results of investigator-assessed PFS according to the Revised RC, the primary endpoint, demonstrated superiority of ibrutinib/BR to placebo/BR [see Section 7.1.1.1].

Table 4 shows results of PFS assessed by the independent review committee (IRC) according to the Revised RC, which were obtained for a sensitivity analysis.

Table 4. Final analysis results on PFS (ITT population, IRC-assessed, data cut-off on June 30, 2021)

	Ibrutinib/BR	Placebo/BR
Number of patients	261	262
Death or disease progression (%)	119 (45.6)	144 (55.0)
Median [95% CI] (months)	77.3 [57.3, NE]	52.9 [43.7, 72.7]
Hazard ratio [95% CI]*1	0.82 [0.64, 1.05]	
P value (two-sided)*2	0.055	

*1 Calculated from a stratified Cox proportional hazards model using the simplified MIPI score (0-3, 4 and 5, 6-11) as a stratification factor.
*2 Stratified log-rank test (the same stratification factor as that for the stratified Cox proportional hazards model)

The applicant's explanation about disagreement between the investigator assessment and the IRC assessment about the between-group difference in PFS:
Both ibrutinib/BR and placebo/BR groups showed high agreement rates between the investigator and IRC assessments in PFS event assessment (95.0% in the ibrutinib/BR group, 96.9% in the placebo/BR group). Among patients who had conflicting outcomes of PFS event assessments, the percentage of patients with a PFS event identified by the investigator but not by IRC was similar in the ibrutinib/BR and placebo/BR groups (4.3% [5 of 116] of patients in the ibrutinib/BR group, 5.3% [8 of 152] of patients in the placebo/BR group), while the percentage of patients with a PFS event identified by IRC but not by the investigator tended to be high in the ibrutinib/BR group than in the placebo/BR group (5.5% [8 of 145] of patients in the ibrutinib/BR group,[5)] 0% of patients in the placebo/BR group). These results were considered the major cause of the disagreement between the investigator- and IRC-assessed between-group difference in PFS.

When a statistically significant difference was observed in the primary endpoint in Study 3002, hypothesis tests were to be performed on the secondary endpoints, i.e., (a) complete response rate, (b) time to the start of the next treatment, (c) OS, (d) response rate, (e) minimal residual disease (MRD) negative rate, and (f) time to worsening of the score of functional assessment of cancer therapy-lymphoma (FACT-Lym), hierarchically in this order. The analysis on (a) did not show a statistically significant difference.

5) In Study 3002, the IRC assessment was first performed by 2 radiologists based on image data. When their judgements conflicted, the third radiologist decided which judgment to adopt. In the ibrutinib/BR group, of 8 patients with a PFS event identified only by the IRC but not by the investigator, 5 patients had conflicting judgments of 2 radiologists. All 8 patients with a PFS event identified only by IRC but not by the investigator in the ibrutinib/BR group did not undergo the subsequent treatment for MCL during the follow-up period.

Table 5 and Figure 2 show analysis results and Kaplan-Meier curve, respectively, on OS, the secondary endpoint.

Table 5. Analysis results on OS (ITT population, data cut-off on June 30, 2021)

	Ibrutinib/BR	Placebo/BR
Number of patients	261	262
Number of deaths (%)	104 (39.8)	107 (40.8)
Median [95% CI] (months)	NE [81.1, NE]	NE [86.1, NE]
Hazard ratio [95% CI]*	1.07 [0.81, 1.40]	

* Calculated from a stratified Cox proportional hazards model using the simplified MIPI score (0-3, 4 and 5, 6-11) as a stratification factor.

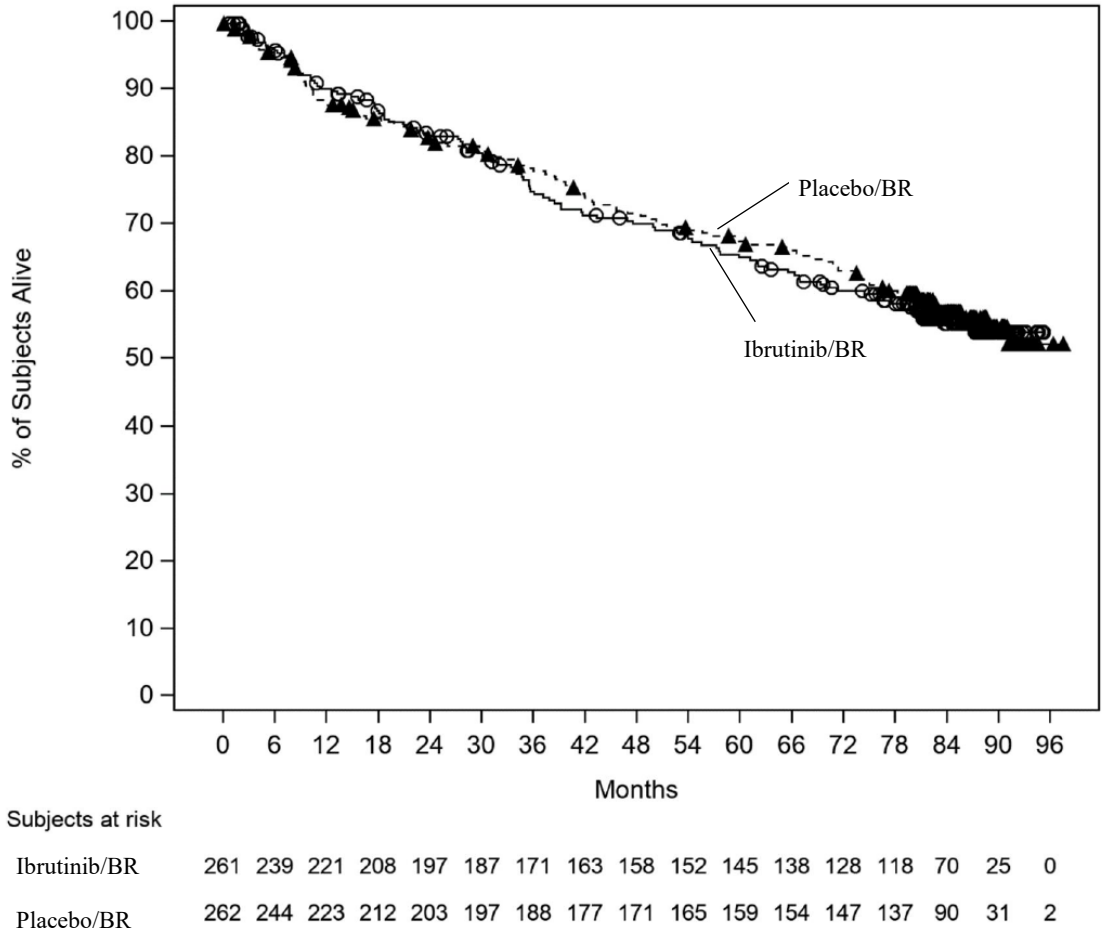

Figure 2. Kaplan-Meier curve on OS at the main analysis (ITT population, data cut-off on June 30, 2021)

Table 6 and Figure 3 show final analysis results and Kaplan-Meier curve, respectively, on investigator-assessed PFS according to the Revised RC in the Japanese population in Study 3002.

Table 6. Final analysis results on PFS in the Japanese population (ITT population, investigator-assessed, data cut-off on June 30, 2021)

	Ibrutinib/BR	Placebo/BR
Number of patients	7	4
Death or disease progression (%)	3 (42.9)	2 (50.0)
Median [95% CI] (months)	69.3 [46.8, NE]	76.4 [1.0, NE]
Hazard ratio [95% CI]*	0.79 [0.13, 4.94]	

* Calculated from a non-stratified Cox proportional hazards model.

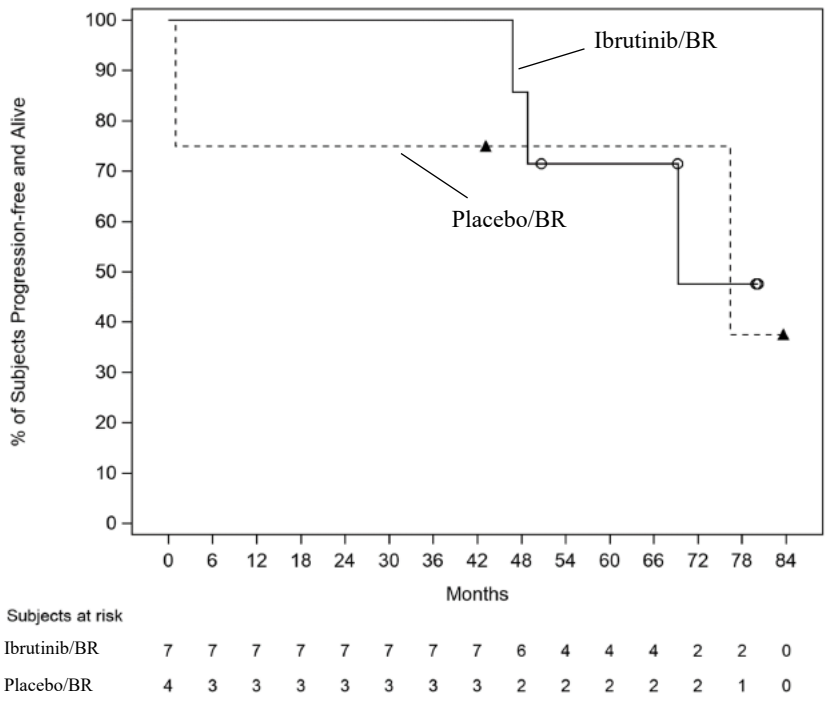

Figure 3. Kaplan-Meier curve on PFS in Japanese at the final analysis (ITT population, investigator-assessed, data cut-off on June 30, 2021)

PMDA's view:

The following outcomes has indicated that ibrutinib/BR has efficacy in the treatment of treatment-naïve MCL.

- The primary endpoint of Study 3002, investigator-assessed PFS according to the Revised RC, demonstrated the superiority of ibrutinib/BR to placebo/BR, with clinically meaningful PFS prolongation. Although there was a gap between the investigator- and IRC-assessed between-group difference in PFS, the results of IRC-assessed PFS also indicated potential efficacy of ibrutinib/BR.
- A secondary endpoint of Study 3002, OS, showed that ibrutinib/BR did not tend to shorten OS clearly as compared with placebo/BR.
- PFS results in the Japanese population of Study 3002 did not show a clearly different trend from that in the overall population, although the limited number of Japanese patients precluded thorough evaluation.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events observed in clinical studies"]

PMDA's conclusions:

As a result of its review in the following subsection, the use of ibrutinib/BR in patients with treatment-naïve MCL require special attention to adverse events, namely, haemorrhage, myelosuppression, infections, arrhythmia, secondary malignancies, eye disorders, leukostasis,[6)] tumour lysis syndrome, hypersensitivity, Stevens-Johnson syndrome [SJS], hepatic failure, hepatic dysfunction, and interstitial lung disease [ILD]. They were identified as such previously in the process of reviews for the approved indications. Attention must be paid to these adverse events during the treatment with ibrutinib.

6) A condition accompanied by leukocytosis and characterized by leukocyte aggregation and stagnation in microvessels that adversely affect organs such as brain and lungs

At the same time, despite the need of vigilance against the above-mentioned adverse events during the treatment, ibrutinib is tolerable when physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies take appropriate measures such as monitoring and management of adverse events and interruption, dose reduction, or discontinuation of ibrutinib.

7.R.3.1 Safety profile of ibrutinib/BR and difference in safety between Japanese and non-Japanese populations

The applicant's explanation about safety profile of ibrutinib based on the safety information in Study 3002:

Table 7 outlines the safety in Study 3002.

Table 7. Outline of safety (Study 3002)

	Number of Patients (%)	
	Study 3002	
	Ibrutinib/BR	Placebo/BR
	n = 259	n = 260
All adverse events	259 (100)	257 (98.8)
Grade ≥3 adverse events	240 (92.7)	220 (84.6)
Adverse events resulting in death	29 (11.2)	19 (7.3)
Serious adverse events	197 (76.1)	156 (60.0)
Adverse events leading to discontinuation of the study drug*1	20 (7.7)	9 (3.5)
Adverse events leading to interruption of the study drug*2	203 (78.4)	184 (70.8)
Adverse events leading to dose reduction of the study drug*3	87 (33.6)	59 (22.7)

*1 Discontinuation of all study drugs
*2 Interruption of ≥1 of study drugs
*3 ≥1 of study drugs reduced (Because dose reduction of RIT was not accepted, the figures include adverse events leading to dose reduction of ibrutinib, placebo, or bendamustine.)

In Study 3002, adverse events of any grade with a ≥10% higher incidence in the ibrutinib/BR group than in the placebo/BR group were pneumonia (87 patients in the ibrutinib/BR group [33.6%], 61 patients in the placebo/BR group [23.5%]) and rash (98 [37.8%], 57 [21.9%]). Grade ≥3 adverse events with a ≥5% higher incidence in the ibrutinib/BR group than in the placebo/BR group were anaemia (40 patients [15.4%], 23 patients [8.8%]), pneumonia (54 [20.8%], 38 [14.6%]), and rash (31 [12.0%], 5 [1.9%]). Adverse events resulting in death occurring in >1 patient and at a higher incidence in the ibrutinib/BR group than in the placebo/BR group were death (3 patients [1.2%], 0 patients), multiple organ dysfunction syndrome (3 [1.2%], 0), pneumonia (2 [0.8%], 1 [0.4%]), cardiac arrest (2 [0.8%], 1 [0.4%]), and sudden death (2 [0.8%], 0). Adverse events resulting in death with the highest incidence were infection-related events,[7] which occurred in 12 patients (4.6%) in the ibrutinib/BR group and 5 patients (1.9%) in the placebo/BR group. A serious adverse event with a ≥5% higher incidence in the ibrutinib/BR group than in the placebo/BR group was pneumonia (55 patients [21.2%], 34 patients [13.1%]). Adverse events leading to the interruption of any study drug with a ≥5% higher incidence in the ibrutinib/BR group than in the placebo/BR group were pneumonia (42 patients [16.2%], 28 patients [10.8%]), rash (27 [10.4%], 8 [3.1%]), and pyrexia (24 [9.3%], 11 [4.2%]). There were no adverse events leading to discontinuation of all study drugs or leading to dose reduction of any study drug[8] with a ≥5% higher incidence in the ibrutinib/BR group than in the placebo/BR group.

7) Classified into the system organ class (SOC) of "Infections and infestations" in the Medical Dictionary for Regulatory Activities (MedDRA).
8) Because dose reduction of RIT was not accepted, the figures include adverse events leading to dose reduction of ibrutinib (or the placebo) or bendamustine.

Adverse events of any grade with a ≥30% higher incidence in Japanese patients than in non-Japanese patients in the ibrutinib/BR group in Study 3002 were constipation (6 Japanese patients [100.0%], 45 non-Japanese patients [17.8%]), anaemia (4 [66.7%], 81 [32.0%]), upper respiratory tract infection (4 [66.7%], 67 [26.5%]), pruritus (4 [66.7%], 42 [16.6%]), neutrophil count decreased (4 [66.7%], 34 [13.4%]), conjunctivitis (4 [66.7%], 22 [8.7%]), lymphocyte count decreased (3 [50.0%], 29 [11.5%]), leukopenia (3 [50.0%], 23 [9.1%]), aspartate aminotransferase (AST) increased (3 [50.0%], 22 [8.7%]), nasopharyngitis (3 [50.0%], 21 [8.3%]), hyperuricaemia (3 [50.0%], 19 [7.5%]), stomatitis and dry skin (3 [50.0%] each, 18 [7.1%] each), lymphopenia (3 [50.0%], 15 [5.9%]), paronychia (2 [33.3%], 8 [3.2%]), abdominal distension, oral herpes and peripheral sensory neuropathy (2 [33.3%] each, 7 [2.8%] each), dental caries, purpura, and hypogammaglobulinaemia (2 [33.3%] each, 6 [2.4%] each). Grade ≥3 adverse events with a ≥10% higher incidence in Japanese patients than in non-Japanese patients in the ibrutinib/BR group in Study 3002 were neutrophil count decreased (4 [66.7%], 28 [11.1%]), lymphocyte count decreased (3 [50.0%], 26 [10.3%]), lymphopenia (3 [50.0%], 13 [5.1%]), white blood cell count decreased (1 [16.7%], 16 [6.3%]), leukopenia and rash maculo-papular (1 [16.7%] each, 11 [4.3%] each), hyponatraemia (1 [16.7%], 9 [3.6%]), cataract (1 [16.7%], 8 [3.2%]), nausea and hyperuricaemia (1 [16.7%] each, 5 [2.0%] each), lymphadenitis and decreased appetite (1 [16.7%] each, 3 [1.2%] each), stomatitis (1 [16.7%], 2 [0.8%]), anxiety (1 [16.7%], 1 [0.4%]), dental caries, Clostridium difficile colitis, cytomegalovirus infection, paronychia and sinusitis fungal (1 [16.7%] each, 0). Serious adverse events with a ≥10% higher incidence in Japanese patients than in non-Japanese patients in the ibrutinib/BR group in Study 3002 were nausea (1 [16.7%], 3 [1.2%]), lymphadenitis (1 [16.7%], 2 [0.8%]), Clostridium difficile colitis, cytomegalovirus infection, paronychia, sinusitis fungal, dental caries and organising pneumonia (1 [16.7%] each, 0). Adverse events leading to the interruption of any study drugs with a ≥10% higher incidence in Japanese patients than in non-Japanese patients in the ibrutinib/BR group in Study 3002 were pneumonia (2 [33.3%], 40 [15.8%]), diarrhoea (2 [33.3%], 20 [7.9%]), nausea (1 [16.7%], 11 [4.3%]), upper respiratory tract infection and rash maculo-papular (1 [16.7%] each, 10 [4.0%] each), bronchitis (1 [16.7%], 9 [3.6%]), anaemia (1 [16.7%], 8 [3.2%]), herpes zoster (1 [16.7%], 5 [2.0%]), sinusitis (1 [16.7%], 4 [1.6%]), dental caries (1 [16.7%], 3 [1.2%]), pneumonitis (1 [16.7%], 2 [0.8%]), oral candidiasis, paronychia and decreased appetite (1 [16.7%] each, 1 [0.4%] each), Clostridium difficile colitis, cytomegalovirus infection, oral herpes, sinusitis fungal, lymphadenitis, hyperuricaemia, palpitations, pneumatosis, Aspergillus test positive, anxiety and artery dissection (1 [16.7%] each, 0). Adverse events leading to dose reduction[8)] of any study drugs with a ≥10% higher incidence in Japanese patients than in non-Japanese patients in the ibrutinib/BR group in Study 3002 were pyrexia (1 [16.7%], 2 [0.8%]), lymphopenia (1 [16.7%), 1 [0.4%]), and liver disorder and anxiety (1 [16.7%] each, 0). There were no adverse events resulting in death or leading to discontinuation of all study drugs with a ≥10% higher incidence in Japanese patients than in non-Japanese patients in the ibrutinib/BR group in Study 3002.

The applicant's explanation about differences in the safety profiles of ibrutinib[9] between treatment-naïve MCL and approved indications (relapsed or refractory MCL, chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL]) and Waldenström's macroglobulinemia (WM)[10]:
Table 8 outlines the safety in patients with treatment-naïve MCL, patients with relapsed or refractory MCL, those with CLL/SLL, and patients with WM.

Table 8. Outline of safety in patients with treatment-naïve MCL, patients with relapsed or refractory MCL, patients with CLL/SLL, and patients with WM

	Number of patients (%)			
	Treatment-naïve MCL*1	Pooled analysis in patients with relapsed or refractory MCL*2	Pooled analysis in patients with CLL/SLL*3	Pooled analysis in patients with WM*4
	n = 259	n = 155	n = 349	n = 91
All adverse events	259 (100)	154 (99.4)	346 (99.1)	91 (100)
Grade ≥3 adverse events	240 (92.7)	102 (65.8)	209 (59.9)	64 (70.3)
Adverse events resulting in death	29 (11.2)	18 (11.6)	15 (4.3)	1 (1.1)
Serious adverse events	197 (76.1)	72 (46.5)	141 (40.4)	42 (46.2)
Adverse events leading to treatment discontinuation*5	20 (7.7)	20 (12.9)	31 (8.9)	1 (1.1)
Adverse events leading to treatment interruption*6	203 (78.4)	72 (46.5)	150 (43.0)	59 (64.8)
Adverse events leading to dose reduction*7	87 (33.6)	7 (4.5)	24 (6.9)	18 (19.8)

*1 Ibrutinib (560 mg)/BR
*2 Ibrutinib (560 mg) alone
*3 Ibrutinib (420 mg) alone
*4 Ibrutinib (420 mg)/RIT
*5 Discontinuation of all study drugs
*6 Interruption of ≥1 of study drugs
*7 Because dose reduction of RIT was not accepted in Study 3002, WAL2002, or PCYC-1127-CA (1127), the figures include adverse events leading to dose reduction of ibrutinib or bendamustine.

Adverse events of any grade with a ≥10% higher incidence in patients with treatment-naïve MCL than in patients with any tumor type mentioned in the approved indications (relapsed or refractory MCL, CLL/SLL) and WM[10] were pneumonia (87 patients with treatment-naïve MCL [33.6%], 15 patients with relapsed or refractory MCL [9.7%], 41 patients with CLL/SLL [11.7%], 10 patients with WM [11.0%]), nausea (107 [41.3%], 22 [14.2%], 83 [23.8%], 17 [18.7%]), pyrexia (95 [36.7%], 23 [14.8%], 73 [20.9%], 17 [18.7%]), neutropenia (111 [42.9%], 23 [14.8%], 70 [20.1%], 13 [14.3%]), anaemia (85 [32.8%], 29 [18.7%], 76 [21.8%], 19 [20.9%]), and rash (98 [37.8%], 21 [13.5%], 27 [7.7%], 8 [8.8%]). Likewise, Grade ≥3 adverse events with a ≥5% higher incidence in patients with treatment-naïve MCL were neutropenia (101 [39.0%], 19 [12.3%], 49 [14.0%], 11 [12.1%]), anaemia (40 [15.4%], 12 [7.7%], 17 [4.9%], 9 [9.9%]), febrile neutropenia (21 [8.1%], 3 [1.9%], 7 [2.0%], 1 [1.1%]), lymphopenia (16 [6.2%], 0, 2 [0.6%], 0), pneumonia (54 [20.8%], 11 [7.1%], 31 [8.9%], 9 [9.9%]), neutrophil count decreased (32 [12.4%], 7 [4.5%], 7 [2.0%], 4 [4.4%]), lymphocyte count decreased (29 [11.2%], 0, 0, 2 [2.2%]), white blood cell count decreased (17 [6.6%], 2 [1.3%], 0, 0), and rash (31 [12.0%], 1 [0.6%], 1 [0.3%], 0). Serious adverse events with a ≥5% higher incidence in patients with treatment-naïve MCL

9) (a) Results in patients with relapsed or refractory MCL were based on the pooled analysis of a Japanese phase II study (Study PCI-32765MCL2002) and a foreign phase III study (Study PCI-32765MCL3001 [Study 3001]) in patients with relapsed or refractory MCL. (b) Results in patients with CLL/SLL were based on the pooled analysis of a Japanese phase I study in patients with relapsed or refractory mature B cell tumor (Study PCI-32765-JPN-101), a foreign phase III study in patients with relapsed or refractory CLL/SLL (Study PCYC-1112-CA), a Japanese phase I study (Study 54179060LEU1001), and a foreign phase III study (Study PCYC-1115-CA) in patients with treatment-naïve CLL/SLL. (c) Results in patients with WM were based on the pooled analysis of a Japanese phase II study in patients with WM (Study WAL2002) and a foreign phase III study in patients with WM (Study 1127) (randomized part).

10) A partial change application for ibrutinib to add the indication of WM/lymphoplasmacytic lymphoma (LPL) was submitted on April 22, 2022.

were pneumonia (55 [21.2%], 12 [7.7%], 32 [9.2%], 9 [9.9%]) and pyrexia (19 [7.3%], 3 [1.9%], 7 [2.0%], 2 [2.2%]). Adverse events leading to the interruption of any study drug with a ≥5% higher incidence in patients with treatment-naïve MCL were pneumonia (42 [16.2%], 8 [5.2%], 20 [5.7%], 8 [8.8%]), rash (27 [10.4%], 4 [2.6%], 1 [0.3%], 0), and pyrexia (24 [9.3%], 0, 5 [1.4%], 3 [3.3%]). Adverse events leading to dose reduction[11] of any study drug with a ≥2% higher incidence in patients with treatment-naïve MCL were neutropenia (16 [6.2%], 0, 0, 3 [3.3%]), thrombocytopenia (7 [2.7%], 1 [0.6%], 1 [0.3%], 0), rash (12 [4.6%], 1 [0.6%], 0, 0), and diarrhoea (9 [3.5%], 1 [0.6%], 4 [1.1%], 1 [1.1%]). There were no adverse events resulting in death or leading to discontinuation of all study drugs with a ≥2% higher incidence in patients with treatment-naïve MCL than in patients with any tumor type mentioned in the approved indications.

PMDA's view:
Adverse events observed at a higher incidence in the ibrutinib/BR group than in the placebo/BR group in Study 3002 require attention as events attributable to ibrutinib/BR. The limited number of Japanese patients in the study precluded a definitive conclusion on the differences in the safety profiles of ibrutinib/BR between Japanese and non-Japanese patients based on the results of Study 3002. Nevertheless, vigilance is needed against the adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients.

The adverse events occurring at a higher incidence in patients with treatment-naïve MCL than in patients with relapsed or refractory MCL, CLL/SLL, or WM[10] require attention, although different concomitant medications used, etc. precluded precise safety comparison.

However, considering that the above-mentioned are mostly known events of ibrutinib or BR, ibrutinib/BR will be tolerable for patients with treatment-naïve MCL, where appropriate measures are taken against adverse events, including monitoring and management, by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

The incidences of adverse events resulting in death, serious adverse events, etc. tended to be higher in the ibrutinib/BR group than in the placebo/BR group in Study 3002. Detailed occurrence, etc. of the adverse events in Study 3002 should be appropriately communicated to healthcare professionals through written materials, etc.

7.R.4 Clinical positioning and indication

The proposed indication of ibrutinib was "mantle cell lymphoma." In addition, the following statement was proposed for the "Precautions Concerning Indications" section.

- For treatment-naïve mantle cell lymphoma, eligible patients must be selected by physicians with a full understanding of the descriptions in the "Clinical Studies" section and the efficacy and safety of ibrutinib, and after careful consideration of the use of treatment options other than ibrutinib.

[11] Because dose reduction of RIT was not accepted in Study 3002, WAL2002, or 1127, the figures include adverse events leading to dose reduction of ibrutinib or bendamustine.

As a result of discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following review, PMDA has concluded that the "Indications" and "Precautions Concerning Indications" section should be described as proposed.

7.R.4.1 Clinical positioning and indication of ibrutinib/BR

The Japanese and foreign clinical practice guidelines[12] and standard textbooks for hematology and clinical oncology[13] do not refer to the use of ibrutinib/BR for treatment-naïve MCL.

The applicant's explanation about clinical positioning of ibrutinib/BR for treatment-naïve MCL and the indication of ibrutinib:

Prior to chemotherapy for treatment-naïve MCL, the therapeutic strategy is first determined based on the age and general condition, then based on eligibility for intensive chemotherapy and high-dose chemotherapy with autologous stem cell transplantation (HDC/AHSCT). Study 3002 was primarily aimed to evaluate the efficacy of ibrutinib/BR, a regimen with ibrutinib added to BR. BR is a treatment option for patients with Stage II to IV treatment-naïve MCL according to the Ann Arbor staging classification, who are ineligible for intensive chemotherapy or HDC/AHSCT. Study 3002 included patients aged ≥65 years as ineligible patients for intensive chemotherapy or HDC/AHSCT.

Study 3002 demonstrated clinical benefits of ibrutinib/BR [see Sections 7.R.2 and 7.R.3], and thus ibrutinib/BR will be regarded as one of treatment options for patients with treatment-naïve MCL ineligible for intensive chemotherapy or HDC/AHSCT.

In contrast, currently there are no clinical study data on clinical benefits of ibrutinib/BR in the populations excluded from Study 3002, i.e., (a) patients with treatment-naïve MCL[14] at Stage I according to the Ann Arbor staging classification and (b) patients with MCL aged <65 years eligible for intensive chemotherapy and HDC/AHSCT. Ibrutinib/BR, therefore, will not serve as a treatment option for these patients.

In terms of choice between ibrutinib/BR and other antineoplastic drugs, the Japanese clinical practice guidelines (Practical Guidelines for Hematological Malignancies Supplemented version 2018 [edited by Japanese Society of Hematology]) recommend BR therapy, R-CHOP therapy (a combination therapy comprised of RIT, cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone), and VR-CAP therapy (a combination therapy comprised of bortezomib, RIT, cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone) as treatment options for patients with treatment-naïve MCL ineligible for HDC/AHSCT. However, there are no clinical study data comparing the clinical benefits of ibrutinib/BR with these combination therapies. Thus, choice of therapy should be individualized according to the patient's condition based on physicians' full understanding of the efficacy and safety of each therapy.

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12) Practice Guidelines for Hematological Malignancies Supplemented version 2018 (edited by Japanese Society of Hematology), NCCN guidelines (B-cell lymphomas) (v.5. 2022) and ESMO guidelines (*Ann Oncol.* 2017;28 Suppl 4:iv62–71)

13) Textbook of Hematology, 3rd edition (edited by Japanese Society of Hematology, 2019) and Williams Hematology 10th edition (USA, McGraw Hill Medical, 2021)

14) At the planning stage of Study 3002, a therapy including radiotherapy was recommended for patients at Stage I according to the Ann Arbor staging classification (NCCN guidelines [Non-Hodgkin's lymphoma] [v.[redacted] 20[redacted]], etc.) and thus this population was excluded from Study 3002.

The applicant's explanation about the indications of ibrutinib:
Ibrutinib was approved for the indication of "relapsed or refractory mantle cell lymphoma," and Study 3002 has demonstrated its clinical benefits for treatment-naïve MCL, and thus the proposed indication was defined as "mantle cell lymphoma," removing "relapsed or refractory" from the approved indication.

As mentioned earlier on the clinical positioning of ibrutinib/BR, ibrutinib/BR will not be a treatment option for all patients with treatment-naïve MCL. Ibrutinib, however, will be used by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies. In this view, the proposed indication will adequately serve to determine patients' eligibility when proper information and advice are offered via the package insert, i.e., target patient population of Study 3002 in the "Clinical Studies" section and a cautionary statement in the "Precautions Concerning Indications" section, which requires physicians to have a full understanding of the descriptions in the "Clinical Studies" section and of the efficacy and safety of ibrutinib, as well as careful consideration of the use of treatment options other than ibrutinib before patient selection.

PMDA's view:
The explanation about clinical positioning of ibrutinib/BR is acceptable. Eligibility for intensive chemotherapy and HDC/AHSCT is comprehensively determined for individual patients with their age and comorbidity taken into account, and thus eligible patients cannot be precisely defined only by the indication. In this view, the indications of ibrutinib and the "Precautions Concerning Indications" section may be described as proposed, with a note in the "Clinical Studies" section of the package insert that the target population of Study 3002 was patients with treatment-naïve MCL aged ≥65 years at Stage II, III, or IV according to the Ann Arbor staging classification.

7.R.5. Dosage and administration

The dosage and administration of ibrutinib for treatment-naïve MCL was "in combination with bendamustine hydrochloride and rituximab (genetical recombination), the usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition."
The proposed "Precautions Concerning Dosage and Administration" section included the following statements.

Precautions Concerning Dosage and Administration
All indications[15)]
- Dose adjustment in response to adverse drug reactions
- Dose adjustment in concomitant use with a cytochrome P450 (CYP) 3A inhibitor

Mantle cell lymphoma
- Concomitant use of antineoplastic drugs with ibrutinib must be determined based on a full understanding of the descriptions in the "Clinical Studies" section, especially about the dosage regimens.

15) The common part follows the precautions for relapsed or refractory MCL, approved indication.

As a result of discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the review in the subsection below, PMDA has concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" for treatment-naïve MCL should be described as follows, as per the proposal.

Dosage and Administration

In combination with bendamustine hydrochloride and rituximab (genetical recombination), the usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

All indications[15)]

- If a Grade ≥3* adverse drug reaction occurs, ibrutinib should be interrupted until it improves to Grade ≤1. The treatment should be resumed where necessary at reduced dose, or discontinued according to the following criteria.

  * As per Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0)

Dose adjustment guidelines

Occurrence	Resumed dose after improvement
First	560 mg QD
Second	420 mg QD
Third	280 mg QD
Fourth	Discontinue

- The following concomitant CYP3A inhibitors may increase blood ibrutinib concentrations. Ibrutinib should be used according to the concomitant drug as shown below.

Dose adjustment criteria for concomitant use with CYP3A inhibitors

Concomitant drug	Regimen
Voriconazole	140 mg of ibrutinib orally administered once daily
Posaconazole	140 mg of ibrutinib orally administered once daily

Treatment-naïve mantle cell lymphoma

- Antineoplastic drugs should be used in combination with ibrutinib based on a full understanding of the descriptions in the "Clinical Studies" section, especially about the dosage regimens.

7.R.5.1 Dosage and administration of ibrutinib

The applicant's explanation about the dosage regimen of ibrutinib:

In Study 3002, ibrutinib 560 mg was orally administered QD in combination with BR[1)] in view of the following outcomes.

- In a foreign phase II study in patients with relapsed or refractory MCL (Study 1104), ibrutinib 560 mg administered alone QD was highly effective for a long time and tolerable.
- In an investigator-initiated foreign phase Ib study in patients with treatment-naïve or relapsed or refractory Non-Hodgkin's lymphoma, a 28-day cycle of ibrutinib 560 mg QD in combination with BR[16)] demonstrated its efficacy and tolerability (*Blood.* 2012;120:1643, *Blood.* 2015;125:242-8).

[16)] Intravenous Bendamustine 90 mg/m^2 on Days 1 and 2 of Cycles 1 to 6 and intravenous RIT 375 mg/m^2 on Day 1 of Cycles 1 to 6

In Study 3002 employing the above dosage regimen, ibrutinib/BR was demonstrated to be clinically useful in patients with treatment-naïve MCL [see Sections 7.R.2 and 7.R.3]. Therefore, the proposed dosage and administration of ibrutinib was defined based on the dosage regimen of the study.

In Study 3002, ibrutinib was administered in combination with bendamustine plus RIT in 28-day cycles repeated for 6 times, then patients achieving complete response (CR) or partial response (PR) were to continue with ibrutinib in combination with RIT maintenance therapy. Therefore, the dosage regimen of ibrutinib for treatment-naïve MCL will be defined so as to make clear that ibrutinib be administered in combination with bendamustine plus RIT. The "Clinical Studies" section of the package insert will present the dosage regimen of bendamustine plus RIT used in Study 3002, noting that ibrutinib was administered in combination with RIT maintenance therapy after the 6 cycles with ibrutinib/BR. The "Precautions Concerning Dosage and Administration" section will also offer the following cautionary advice.

The dose adjustment criteria of ibrutinib in the clinical study were largely similar to that for the approved indications,[17] and thus the proposed dose adjustment criteria follow that for the approved indications.

- Antineoplastic drugs should be used in combination with ibrutinib based on a full understanding of the descriptions in the "Clinical Studies" section, especially about the dosage regimens.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation:

For the reasons below, there are no newly identified safety concerns in the present partial change application and thus post-marketing surveillance needs not be conducted immediately after approval to investigate the safety of ibrutinib in patients with treatment-naïve MCL, and the safety information will be collected through the regular pharmacovigilance activities.

- There are adverse events with a higher incidence in the ibrutinib/BR group than in the placebo/BR group in Study 3002, but they are mostly known events of ibrutinib or BR, indicating that the safety profile in the ibrutinib/BR group in Study 3002 did not clearly differ from that of ibrutinib for the approved indications [see Section 7.R.3].
- The post-marketing surveillance has been completed in patients with relapsed or refractory MCL and patients with relapsed or refractory CLL/SLL who received ibrutinib as per the approved indications, yielding a certain amount of safety information of ibrutinib in Japanese patients. The existing safety information does not indicate any new safety concerns.

PMDA accepted the applicant's explanation.

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[17] In the clinical study, the interruption criteria applied only to some of Grade ≥3 adverse drug reactions. In contrast, the interruption criteria for the approved indications uniformly apply to all Grade ≥3 adverse drug reactions because of the higher incidence of myelosuppression in Japanese patients than in the overall study population. This trend was also true in patients with treatment-naïve MCL, thus the proposed interruption criteria followed that for the approved indications.

7.2 Adverse events observed in clinical studies

Deaths reported in the clinical study submitted as the safety evaluation data are presented in Section "7.1 Evaluation data." The following summarizes major adverse events other than death.

7.2.1 Global phase III study (Study 3002)

Adverse events occurred in 259 of 259 patients (100%) in the ibrutinib/BR group and 257 of 260 (98.8%) in the placebo/BR group. A causal relationship of events to the study drug could not be ruled out in 237 of 259 (91.5%) in the ibrutinib/BR group and 214 of 260 (82.3%) in the placebo/BR group. Table 9 shows adverse events with an incidence of ≥10% in either group.

Table 9. Adverse events with an incidence of ≥10% in either group

SOC PT (MedDRA/J ver.24.0)	Number of patients (%)			
	Ibrutinib/BR n = 259		Placebo/BR n = 260	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	259 (100)	240 (92.7)	257 (98.8)	220 (84.6)
Infections and infestations				
Pneumonia	87 (33.6)	54 (20.8)	61 (23.5)	38 (14.6)
Upper respiratory tract infection	71 (27.4)	4 (1.5)	68 (26.2)	4 (1.5)
Bronchitis	38 (14.7)	6 (2.3)	38 (14.6)	6 (2.3)
Urinary tract infection	38 (14.7)	11 (4.2)	33 (12.7)	6 (2.3)
Sinusitis	28 (10.8)	2 (0.8)	34 (13.1)	3 (1.2)
Nasopharyngitis	24 (9.3)	0	28 (10.8)	0
Herpes zoster	15 (5.8)	2 (0.8)	28 (10.8)	10 (3.8)
Conjunctivitis	26 (10.0)	0	6 (2.3)	0
Gastrointestinal disorders				
Diarrhoea	120 (46.3)	18 (6.9)	96 (36.9)	10 (3.8)
Nausea	107 (41.3)	6 (2.3)	107 (41.2)	3 (1.2)
Constipation	51 (19.7)	0	68 (26.2)	1 (0.4)
Vomiting	58 (22.4)	7 (2.7)	48 (18.5)	0
Abdominal pain	26 (10.0)	6 (2.3)	30 (11.5)	2 (0.8)
General disorders and administration site conditions				
Pyrexia	95 (36.7)	5 (1.9)	83 (31.9)	5 (1.9)
Fatigue	79 (30.5)	8 (3.1)	77 (29.6)	6 (2.3)
Oedema peripheral	51 (19.7)	3 (1.2)	42 (16.2)	0
Chills	18 (6.9)	1 (0.4)	39 (15.0)	1 (0.4)
Asthenia	30 (11.6)	2 (0.8)	25 (9.6)	3 (1.2)
Blood and lymphatic system disorders				
Neutropenia	111 (42.9)	101 (39.0)	105 (40.4)	100 (38.5)
Anaemia	85 (32.8)	40 (15.4)	61 (23.5)	23 (8.8)
Thrombocytopenia	62 (23.9)	23 (8.9)	44 (16.9)	24 (9.2)
Leukopenia	26 (10.0)	12 (4.6)	14 (5.4)	10 (3.8)
Skin and subcutaneous tissue disorders				
Rash	98 (37.8)	31 (12.0)	57 (21.9)	5 (1.9)
Pruritus	46 (17.8)	6 (2.3)	56 (21.5)	1 (0.4)
Rash maculo-papular	26 (10.0)	12 (4.6)	10 (3.8)	3 (1.2)
Respiratory, thoracic and mediastinal disorders				
Cough	77 (29.7)	1 (0.4)	85 (32.7)	2 (0.8)
Dyspnoea	26 (10.0)	2 (0.8)	46 (17.7)	5 (1.9)
Epistaxis	31 (12.0)	0	12 (4.6)	0
Metabolism and nutrition disorders				
Decreased appetite	56 (21.6)	4 (1.5)	36 (13.8)	3 (1.2)
Hypokalaemia	39 (15.1)	19 (7.3)	31 (11.9)	14 (5.4)
Investigations				
Neutrophil count decreased	38 (14.7)	32 (12.4)	44 (16.9)	34 (13.1)
Platelet count decreased	41 (15.8)	13 (5.0)	28 (10.8)	11 (4.2)
White blood cell count decreased	30 (11.6)	17 (6.6)	34 (13.1)	20 (7.7)
Lymphocyte count decreased	32 (12.4)	29 (11.2)	26 (10.0)	23 (8.8)
Weight decreased	26 (10.0)	3 (1.2)	20 (7.7)	1 (0.4)
Musculoskeletal and connective tissue disorders				
Arthralgia	45 (17.4)	3 (1.2)	44 (16.9)	0
Back pain	36 (13.9)	2 (0.8)	37 (14.2)	1 (0.4)
Myalgia	31 (12.0)	0	30 (11.5)	3 (1.2)
Nervous system disorders				
Headache	33 (12.7)	0	40 (15.4)	1 (0.4)
Injury, poisoning and procedural complications				
Infusion related reaction	21 (8.1)	2 (0.8)	30 (11.5)	5 (1.9)
Vascular disorders				
Hypertension	35 (13.5)	22 (8.5)	29 (11.2)	15 (5.8)
Cardiac disorders				
Atrial fibrillation	36 (13.9)	10 (3.9)	17 (6.5)	2 (0.8)
Psychiatric disorders				
Insomnia	29 (11.2)	0	28 (10.8)	0

Serious adverse events occurred in 197 of 259 patients (76.1%) in the ibrutinib/BR group and 156 of 260 patients (60.0%) in the placebo/BR group. Serious adverse events with an incidence of ≥5% in each group were pneumonia in 55 patients (21.2%), pyrexia in 19 patients (7.3%), febrile neutropenia in 16 patients (6.2%), and atrial fibrillation in 13 patients (5.0%) in the ibrutinib/BR group and pneumonia in 34 patients (13.1%) and pyrexia in 14 patients (5.4%) in the placebo/BR group. A causal relationship to the study drug could not be ruled out for pneumonia in 38 patients (14.7%), pyrexia in 14 patients (5.4%), febrile neutropenia in 13 patients (5.0%), and atrial fibrillation in 8 patients (3.1%) in the ibrutinib/BR group and pneumonia in 24 patients (9.2%) and pyrexia in 7 patients (2.7%) in the placebo/BR group.

Adverse events led to study drug discontinuation in 20 of 259 patients (7.7%) in the ibrutinib/BR group and 9 of 260 (3.5%) in the placebo/BR group. Adverse events leading to study drug discontinuation reported by ≥2 patients were sepsis in 3 patients (1.2%), pneumonia, thrombocytopenia, diarrhoea, and ischaemic stroke in 2 patients (0.8%) each in the ibrutinib/BR group and pneumonia and pyrexia in 2 patients (0.8%) each in the placebo/BR group. A causal relationship to the study drug could not be ruled out for sepsis in 3 patients (1.2%), thrombocytopenia and diarrhoea in 2 patients (0.8%) each, and pneumonia in 1 patient (0.4%) in the ibrutinib/BR group and pneumonia in 2 patients (0.8%) and pyrexia in 1 patient (0.4%) in the placebo/BR group.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that ibrutinib has efficacy in the treatment of treatment-naïve MCL, and that ibrutinib has acceptable safety in view of its benefits. Ibrutinib/BR is considered clinically meaningful as one of treatment options for treatment-naïve MCL. Efficacy, clinical positioning, and indication need to be further investigated.

PMDA has concluded that ibrutinib may be approved if ibrutinib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

January 18, 2023

Product Submitted for Approval

Brand Name	Imbruvica Capsules 140 mg
Non-proprietary Name	Ibrutinib
Applicant	Janssen Pharmaceutical K.K.
Date of Application	June 10, 2022

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that ibrutinib/BR has efficacy in patients with treatment-naïve MCL, because a global phase III study in patients with treatment-naïve MCL (Study 3002) demonstrated superiority of ibrutinib/BR to placebo/BR in terms of investigator-assessed PFS according to the Revised RC, the primary endpoint.

The expert advisors supported the PMDA's conclusion at the Expert Discussion.

1.2 Safety

As a result of its review in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention in the use of ibrutinib/BR in patients with treatment-naïve MCL are haemorrhage, myelosuppression, infections, arrhythmia, secondary malignancies, eye disorders, leukostasis, tumour lysis syndrome, hypersensitivity, SJS, hepatic failure, hepatic dysfunction, and ILD, which were identified as such previously in the process of reviews for the approved indications.

PMDA has also concluded that, although the above-mentioned adverse events require attention in the use of ibrutinib, ibrutinib will be tolerable where appropriate measures, including monitoring and management, are taken against adverse events by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

The expert advisors supported the PMDA's conclusion at the Expert Discussion.

1.3 Clinical positioning and indication

As a result of its review in Section "7.R.4 Clinical positioning and indication of ibrutinib/BR" of the Review Report (1), PMDA has concluded that the indication of ibrutinib may be defined as "mantle cell lymphoma" as proposed, with a note in the "Clinical Studies" section of the package insert that the Study 3002 targeted patients with treatment-naïve MCL aged ≥65 years at Stage II, III, or IV according to the Ann Arbor staging classification, and the following cautionary statement in the "Precautions Concerning Indications" section.

Precautions Concerning Indications

- For treatment-naïve mantle cell lymphoma, eligible patients must be selected by physicians with a full understanding of the descriptions in the "Clinical Studies" section and the efficacy and safety of ibrutinib, and after careful consideration of the use of treatment options other than ibrutinib.

The expert advisors supported the PMDA's conclusion, and further made the following comment at the Expert Discussion:

- PMDA have reached a reasonable conclusion on the recommended target population of ibrutinib. However, the "Precautions Concerning Indications" section should more clearly convey the caution that ibrutinib is not recommended for the population excluded from Study 3002, i.e., (a) patients with treatment-naïve MCL at Stage I according to the Ann Arbor staging classification or (b) patients with treatment-naïve MCL who are eligible for intensive chemotherapy, owning to the lack of clinical study data on clinical benefits of ibrutinib/BR in these population at present.

PMDA's view:

In view of the comment at the Expert Discussion, the "Precautions Concerning Indications" section should provide the caution that the efficacy and safety of ibrutinib have not been established in (a) patients with treatment-naïve MCL eligible for intensive chemotherapy and (b) patients with treatment-naïve MCL at Stage I according to the Ann Arbor staging classification.

PMDA requested the applicant to take an appropriate action in response to the above conclusion, and the applicant agreed.

1.4 Dosage and administration

As a result of its review in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" statement for treatment-naïve MCL should be defined as follows, as per the proposal.

Dosage and Administration

In combination with bendamustine hydrochloride and rituximab (genetical recombination), the usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

All indications[15)]

- If a Grade ≥3* adverse drug reaction occurs, ibrutinib should be interrupted until it improves to Grade ≤1. The treatment should be resumed where necessary at reduced dose, or discontinued according to the following criteria.

  * As per CTCAE v4.0

Dose adjustment guidelines

Occurrence	Resumed dose after improvement
First	560 mg QD
Second	420 mg QD
Third	280 mg QD
Fourth	Discontinue

- The following concomitant CYP3A inhibitors may increase blood ibrutinib concentrations. Ibrutinib should be used according to the concomitant drug as shown below.

Dose adjustment criteria for concomitant use with CYP3A inhibitors

Concomitant drug	Regimen
Voriconazole	140 mg of ibrutinib orally administered once daily
Posaconazole	140 mg of ibrutinib orally administered once daily

Treatment-naïve mantle cell lymphoma

- Antineoplastic drugs should be used in combination with ibrutinib based on a full understanding of the descriptions in the "Clinical Studies" section, especially about the dosage regimens.

The expert advisors supported the PMDA's conclusion at the Expert Discussion.

1.5 Risk management plan (draft)

As a result of its review in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA has concluded that post-marketing surveillance may need not to be conducted immediately after approval for the purpose of safety investigation of ibrutinib in patients with treatment-naïve MCL. Regular pharmacovigilance activities will serve to collect safety information.

The expert advisors supported the PMDA's conclusion at the Expert Discussion.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for ibrutinib should include the safety specification presented in Table 10, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 11.

Table 10. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Haemorrhage • Myelosuppression • Infections • Arrhythmia • Hypersensitivity • Tumour lysis syndrome • Eye disorders • Hepatic failure, hepatic dysfunction • ILD • Secondary malignancies • Drug-drug interactions with CYP3A inhibitors • Use in patients with hepatic impairment	• Leukostasis • SJS	Not applicable
Efficacy specification		
Not applicable		

No change for the present partial change application

Table 11. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Post-marketing database survey in patients with chronic graft-versus-host disease • Drug use-results survey in patients with WM or LPL	Not applicable	• Organize and disseminate materials for healthcare professionals

Underline denotes activities planned for the newly added indication and dosage regimen.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that ibrutinib may be granted approval for the indication and dosage regimen below with the following approval condition, provided that necessary cautions are given via the package insert while information on proper use is offered to healthcare professionals in the post-marketing setting, and that ibrutinib is properly used by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies and at medical institutions capable of emergency response. The re-examination period for the present application is the remainder of the re-examination period (until December 1, 2026).

Indications (Underline denotes additions. Strikethrough denotes deletions. Double underline denotes changes made as of December 23, 2022 after submission of the partial change application.)

1) Chronic lymphocytic leukemia (including small lymphocytic lymphoma)
2) Primary macroglobulinemia and lymphoplasmacytic lymphoma
~~2~~3) ~~Relapsed or refractory m~~Mantle cell lymphoma
~~3~~4) Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)

Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions. Double underline denotes changes made as of December 23, 2022 after submission of the partial change application.)

1) Chronic lymphocytic leukemia (including small lymphocytic lymphoma), primary macroglobulinemia, and lymphoplasmacytic lymphoma
   The usual adult dosage is 420 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.
2) ~~Relapsed or refractory m~~Mantle cell lymphoma
   - Treatment-naïve diseases
     In combination with bendamustine hydrochloride and rituximab (genetical recombination), the usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.
   - Relapsed or refractory diseases
     The usual adult dosage is 560 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.
3) Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)
   The usual dosage in adults and children aged ≥12 years is 420 mg of ibrutinib orally administered once daily. The dose may be reduced according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warnings (no change)

The administration of ibrutinib should be exclusively limited to patients found to be eligible for the treatment with the product, under the supervision by a physician with adequate knowledge and experience in the treatment of hematopoietic malignancies and hematopoietic stem cell transplant, and at medical institutions capable of emergency response. The efficacy and risks of treatment should be thoroughly explained to the patients or their family, and consent should be obtained prior to the treatment.

Contraindications (no change)

1. Patients with a history of hypersensitivity to any ingredient of the product
2. Patients with moderate or severe hepatic impairment
3. Patients currently receiving ketoconazole, itraconazole, or clarithromycin
4. Pregnant women or women who may possibly be pregnant

Precautions Concerning Indications (Underline denotes additions. Strikethrough denotes deletions.)

Chronic lymphocytic leukemia (including small lymphocytic lymphoma)

1. For treatment-naïve chronic lymphocytic leukemia (including small lymphocytic lymphoma), eligible patients must be selected by physicians with a full understanding of the descriptions in the "Clinical Studies" section and the efficacy and safety of ibrutinib, and after careful consideration of the use of treatment options other than ibrutinib.

Mantle cell lymphoma

2. The efficacy and safety of ibrutinib in patients with treatment-naïve mantle cell lymphoma eligible for intensive chemotherapy have not been established.
3. The efficacy and safety of ibrutinib in patients with treatment-naïve mantle cell lymphoma at Stage I according to the Ann Arbor staging classification have not been established.

Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)

~~2~~4. Eligible patients must be selected by physicians with a full understanding of the descriptions in the "Clinical Studies" section and of the efficacy and safety of ibrutinib.

Precautions Concerning Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions. Double underline denotes changes made as of December 23, 2022 after submission of the partial change application.)

All indications

1. If a Grade ≥3[Note)] adverse drug reaction occurs, ibrutinib should be interrupted until it improves to Grade ≤1. The treatment should be resumed where necessary at reduced dose, or discontinued according to the following criteria.

   Note) As per Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0)

Dose adjustment guidelines

Occurrence	Resumed dose after improvement	
	Chronic lymphocytic leukemia Primary macroglobulinemia and lymphoplasmacytic lymphoma Chronic graft-versus-host disease	Mantle cell lymphoma
First	420 mg QD	560 mg QD
Second	280 mg QD	420 mg QD
Third	140 mg QD	280 mg QD
Fourth	Discontinue	

2. The following concomitant CYP3A inhibitors may increase blood ibrutinib concentrations. Ibrutinib should be used according to the concomitant drug as shown below.

Dose adjustment criteria for concomitant use with CYP3A inhibitors

Indications	Concomitant drug	Regimen
Chronic lymphocytic leukemia (including small lymphocytic lymphoma), primary macroglobulinemia and lymphoplasmacytic lymphoma, and ~~relapsed or refractory~~ mantle cell lymphoma	Voriconazole	140 mg of ibrutinib orally administered once daily
	Posaconazole	140 mg of ibrutinib orally administered once daily
Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)	Voriconazole	280 mg of ibrutinib orally administered once daily
	Posaconazole	140 mg of ibrutinib orally administered once daily

Chronic lymphocytic leukemia (including small lymphocytic lymphoma) and relapsed or refractory mantle cell lymphoma

3. The efficacy and safety of ibrutinib used in combination with other antineoplastic drugs have not been established.

Primary macroglobulinemia and lymphoplasmacytic lymphoma

4. Rituximab (genetical recombination) should be used in combination with ibrutinib unless its use is difficult.
5. The efficacy and safety of ibrutinib used in combination with the antineoplastic drugs other than rituximab (genetical recombination) have not been established.

Treatment-naïve mantle cell lymphoma

6. Antineoplastic drugs should be used in combination with ibrutinib based on a full understanding of the descriptions in the "Clinical Studies" section, especially about the dosage regimens.

Chronic graft-versus-host disease after hematopoietic stem cell transplant (for patients who have an inadequate response to steroids)

7~~6~~4. The efficacy and safety of ibrutinib used in combination with other antineoplastic drugs have not been established.

List of Abbreviations

AST	aspartate aminotransferase
BCR	B cell receptor
Bendamustine	Bendamustine hydrochloride
BR	Concomitant use of bendamustine and RIT
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
COVID-19	Infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ESMO	European Society of Medical Oncology
FACT-Lym	Functional assessment of cancer therapy-lymphoma
HDC/AHSCT	high-dose chemotherapy with autologous stem cell transplantation
Ibrutinib	Ibrutinib
Ibrutinib/BR	Concomitant use of ibrutinib and BR
Ibrutinib/RIT	Concomitant use of ibrutinib and RIT
ILD	interstitial lung disease
IRC	Independent review committee
ITT	intent-to-treat
LPL	lymphoplasmacytic lymphoma
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NCCN guidelines (B-cell lymphomas)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-cell Lymphomas
NCCN guidelines (Non-Hodgkin's lymphoma)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas
NE	not estimable
OS	overall survival
Partial change application	Application for partial changes
PFS	progression free survival
PK	pharmacokinetics
Placebo/BR	Concomitant use of the placebo and BR
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
QD	quaque die
R-CHOP	Concomitant use of RIT, cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone
Revised RC	Revised Response Criteria for Malignant Lymphoma
RIT	rituximab (genetical recombination)
SJS	Stevens-Johnson syndrome
SLL	small lymphocytic lymphoma
SOC	system organ class
Study 1104	Study PCYC-1104-CA

Study 1127	Study PCYC-1127-CA
Study 3001	Study PCI-32765MCL3001
Study 3002	Study PCI-32765MCL3002
Study WAL2002	Study 54179060WAL2002
VR-CAP	Concomitant use of bortezomib, RIT, cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone
WM	Waldenström's macroglobulinemia