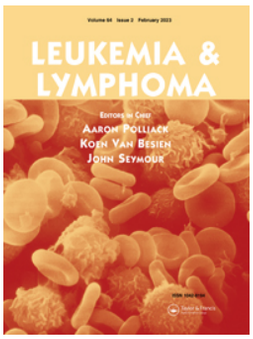

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: www.tandfonline.com/journals/ilal20

Real-world experience of Australian and New Zealand patients with chronic lymphocytic leukemia and mantle cell lymphoma accessing ibrutinib through a Named Patient Program

Stephen P. Mulligan, Stephen Opat, Chan Y. Cheah, Bryone Kuss, Mark Hertzberg, Paula Marlton, Sarah Poplar, Andrea Puig, Marija McGeachie, Robert Weinkove & Constantine S. Tam

To cite this article: Stephen P. Mulligan, Stephen Opat, Chan Y. Cheah, Bryone Kuss, Mark Hertzberg, Paula Marlton, Sarah Poplar, Andrea Puig, Marija McGeachie, Robert Weinkove & Constantine S. Tam (2023) Real-world experience of Australian and New Zealand patients with chronic lymphocytic leukemia and mantle cell lymphoma accessing ibrutinib through a Named Patient Program, Leukemia & Lymphoma, 64:2, 312-318, DOI: 10.1080/10428194.2022.2148220

To link to this article: https://doi.org/10.1080/10428194.2022.2148220

LEUKEMIA & LYMPHOMA
2023, VOL. 64, NO. 2, 312–318
https://doi.org/10.1080/10428194.2022.2148220

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Real-world experience of Australian and New Zealand patients with chronic lymphocytic leukemia and mantle cell lymphoma accessing ibrutinib through a Named Patient Program

Stephen P. Mulligan[a], Stephen Opat[b], Chan Y. Cheah[c,d,e], Bryone Kuss[f], Mark Hertzberg[g], Paula Marlton[h,i], Sarah Poplar[j], Andrea Puig[k], Marija McGeachie[l], Robert Weinkove[m,n] and Constantine S. Tam[o]

[a]Department of Haematology, Royal North Shore Hospital, Sydney, Australia; [b]Monash Health, Monash University, Melbourne, Australia; [c]Department of Haematology, Sir Charles Gairdner Hospital, Perth, Australia; [d]Department of Haematology, Pathwest Laboratory Medicine, Perth, Australia; [e]School of Medicine, University of Western Australia, Perth, Australia; [f]Flinders Medical Centre and Finders University, Bedford Park, Australia; [g]Department of Haematology, Prince of Wales Hospital, Sydney, Australia; [h]Department of Haematology, Princess Alexandra Hospital, Brisbane, Australia; [i]University of Queensland School of Medicine, Brisbane, Australia; [j]Northland Cancer and Blood Services, Northland District Health Board, Whangarei, New Zealand; [k]Real-world Evidence, Janssen-Cilag Pty Ltd, Sydney, Australia; [l]Medical and Scientific Affairs, Janssen-Cilag Pty Ltd, Sydney, Australia; [m]Te Rerenga Ora Blood & Cancer Centre, Wellington Hospital, Wellington, New Zealand; [n]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand; [o]Alfred Hospital and Monash University, Melbourne, Australia

ABSTRACT

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase indicated for the treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and mantle cell lymphoma (MCL). The Named Patient Program in Australia and New Zealand (ANZ NPP) provided access to ibrutinib treatment to 1126 R/R CLL/SLL and 330 R/R MCL patients, prior to Pharmaceutical Benefits Scheme listing. This study aimed to assess the duration of treatment for the ANZ NPP patients, as an indicator of efficacy and tolerability of ibrutinib in the real world. Based on the NPP data, ibrutinib provided a median of 47 months clinical benefit for participants with CLL/SLL and 14 months clinical benefit for those with MCL; outcomes that are consistent with the clinical trial results and further support the well-established efficacy and safety profile of ibrutinib in the real world.

ARTICLE HISTORY
Received 24 October 2022
Accepted 12 November 2022

KEYWORDS
Ibrutinib; real-world; mantle cell leukemia; chronic lymphocytic leukemia

Introduction

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK), an important signaling molecule of the B-cell antigen receptor (BCR) pathway [1]. The BCR pathway is involved in the pathogenesis of several B cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL) [1].

Ibrutinib has shown significant clinical benefit across multiple indications in B-cell malignancies. In the phase 3 RESONATE [NCT01578707], RESONATE-2 [NCT01722487, NCT01724346], and RAY [NCT01646021] studies, in the relapsed/refractory (R/R), front line (1L) CLL and R/R MCL indications, respectively, ibrutinib was found to significantly improve progression-free survival (PFS), overall survival (OS), and response rates when compared to standard of care treatments [2–5]. The long-term RESONATE-2 data show sustained PFS and OS benefits (medians not reached) for CLL patients receiving first-line ibrutinib treatment at eight years [6]. Further, a recently published, pooled analysis of three clinical trials of patients with R/R MCL provides nearly 10 years of follow-up data [7], the longest of any BTK inhibitor. The long-term data support the earlier trial findings regarding efficacy and tolerability of ibrutinib.

In Australia and New Zealand, ibrutinib is indicated for the treatment of R/R CLL/SLL and MCL, as well as previously untreated CLL/SLL and Waldenstrom's macroglobulinemia (WM). However, at present in Australia

CONTACT S. P. Mulligan stephen.mulligan@sydney.edu.au Department of Haematology, Royal North Shore Hospital, Sydney, Australia
Supplemental data for this article can be accessed online at https://doi.org/10.1080/10428194.2022.2148220.

ibrutinib is only reimbursed for R/R CLL/SLL and MCL indications and reimbursement in New Zealand is awaited.

Upon regulatory approvals in 2015 in Australia [1] and New Zealand [8], the ibrutinib Named Patient Program (NPP) commenced at a global level to enable patient access to R/R CLL/SLL and MCL, prior to ibrutinib reimbursement. The data collected from the NPP in Australia and New Zealand (ANZ NPP) provides valuable insight into the clinical use and treatment outcomes of ibrutinib in the real-world setting.

The aim of this study was to assess the real-world duration of ibrutinib treatment (DoT) for R/R CLL/SLL and R/R MCL patients enrolled in the ANZ NPP. For reference, DoT from the NPP analysis was compared to that of the RESONATE and RAY trials, for R/R CLL and R/R MCL, respectively. A secondary aim was to identify and examine predictors of ibrutinib treatment duration in this real-world dataset.

Methods

The multicenter NPP allowed patients with R/R CLL/SLL and MCL access to ibrutinib across Australia and New Zealand. Patients were enrolled in the NPP by their physicians via the Janssen Managed Access portal (MAcWeb). Key inclusion and exclusion criteria for the NPPs were consistent with those for the RESONATE and RAY studies (Supplementary Table 1).

Janssen-Cilag Pty Ltd commenced an NPP for patients with R/R CLL/SLL in New Zealand from September 2014, and in Australia from December 2014 (Figure 1). The NPP for patients with R/R MCL commenced in New Zealand from January 2016, and in Australia from December 2014 (Figure 1).

In Australia, the NPP continued to support patients on treatment until December 2017 and July 2018, when ibrutinib was first listed on the Pharmaceutical Benefits Scheme (PBS) for R/R CLL/SLL and R/R MCL, respectively. Once listed, patients requiring ongoing treatment were transitioned onto the PBS supply.

Similarly, in New Zealand, the NPP continued to support patients on treatment until Pharmac listing for R/R CLL/SLL on September 2019 and R/R MCL April 2017. This provided 60 and 16 months of data, respectively. However, within New Zealand, patients remained on the NPP until withdrawal by the treating physician, or until the patient decided to stop treatment. New Zealand NPP patients requiring ongoing ibrutinib treatment were censored at the date of last ibrutinib supply.

The NPP treatment start date was defined as the day that the supply of ibrutinib was commenced, while the treatment stop date was the date entered by the physician in MAcWeb. Where this information was missing, a three-month gap in refill request was considered treatment discontinuation. The NPP treatment duration was defined as the time-period between treatment start and stop dates, with the treatment duration being censored at the date of the last ibrutinib supply. It was compulsory for physicians to complete baseline information collection via a simple questionnaire, distributed through the MAcWeb portal (Supplementary Materials).

Enrolled patients self-administered oral ibrutinib once daily (QD), 420 mg for CLL/SLL and 560 mg for MCL, unless they experienced progressive disease (PD), unacceptable toxicity, or failed to achieve clinical benefit (in the absence of disease progression). Disease evaluation and adverse events (AEs) were monitored by physicians throughout the NPP.

Ethics approval was obtained from the local Ethics Committee (2021/ETH12084). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines have been used to ensure that an accurate and complete report of the study is provided [9].

Analyses

The NPP estimate of treatment duration was compared to time to treatment discontinuation in the ibrutinib arm of the RESONATE and RAY Phase 3 trials.

Time-on-treatment with ibrutinib was evaluated descriptively using Kaplan–Meier's curves for both the RESONATE and RAY trials and the NPP, and statistical testing was conducted using the log-rank test.

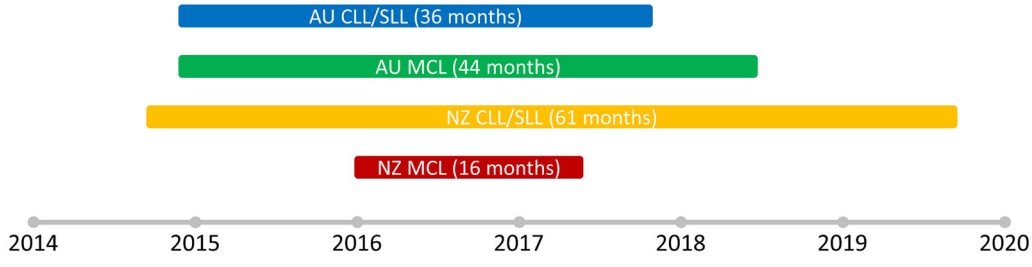

Figure 1. Length of operation of each NPP for ibrutinib in Australia and New Zealand.

Relevant baseline information collected at NPP enrollment was used to explore factors correlated with treatment duration. Univariate and multivariate Cox proportional hazards models were used to determine if any baseline characteristics affected treatment duration in the NPP.

Results

Baseline CLL/SLL

A total of 1126 patients were enrolled in the R/R CLL/SLL NPP across Australia and New Zealand. One thousand and fifteen patients were enrolled in the Australian NPP (77% with CLL and 23% with SLL diagnosis) and 111 patients were enrolled in the New Zealand NPP (80% with CLL and 20% with SLL diagnosis). The median age of patients was 72 years (range 26–94 years), and most patients were male (67%).

Baseline MCL

A total of 300 patients with R/R MCL were enrolled in the Australian NPP and 30 patients in the New Zealand NPP (total = 330 patients). The median age of patients was 73 years (range 33–95 years). Most patients were male (76%) and had advanced disease (involvement of the bone marrow, extra-nodal sites, or both; 82%).

Table 1 compares the available baseline data from both the CLL/SLL and MCL NPP populations with that of the RESONATE and RAY trials, respectively. In both the

Table 1. Patient characteristics at baseline.

	CLL/SLL		MCL	
Variable	NPP ($n = 1126$)	RESONATE ($n = 195$)	NPP ($n = 330$)	RAY ($n = 139$)
Median age, years (range)	72 (26–94)	67 (30–86)	73 (33–95)	67 (IQR 11)
Sex (male)	757 (67%)	129 (66%)	250 (76%)	100 (72%)
3 or more prior lines of therapy	489 (43%)	103 (53%)	131 (40%)	44 (31%)

n: number; NPP: Named Patient Program; ANZ: Australia and New Zealand; CLL/SLL: Chronic Lymphocytic Leukaemia / Small Lymphocytic Lymphoma

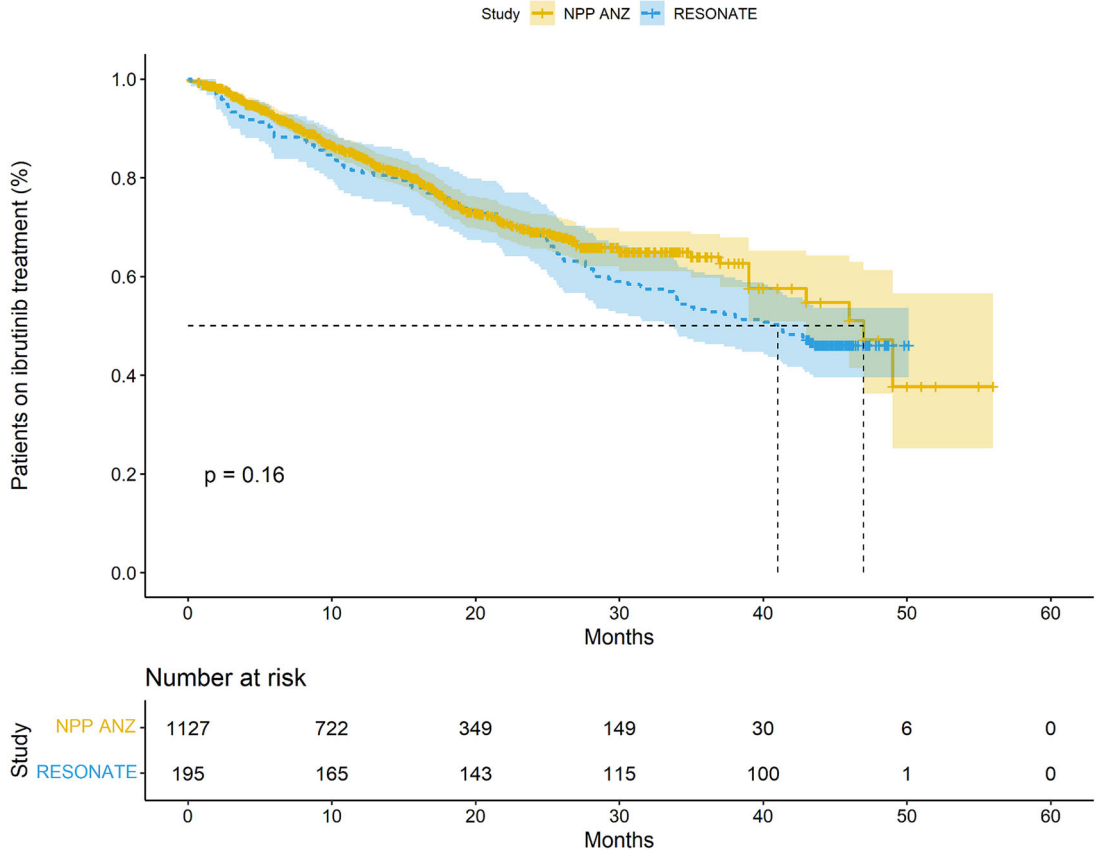

Figure 2. Kaplan–Meier's curve showing duration on ibrutinib treatment in the RESONATE study and the CLL/SLL ANZ-NPP.

CLL/SLL and MCL NPP cohorts, the patients were older than the randomized control trial (RCT) populations, while the gender split was comparable. The baseline characteristics of the patients enrolled in the NPP are given in Tables 2 and 3 of the supplementary materials.

Duration of treatment for patients with CLL/SLL

The median treatment duration for R/R CLL/SLL patients in the ANZ-NPP was 47 months (range 0–56 months), with no statistical difference in median treatment duration of 41 months (range 0.2–71.1) seen in the RESONATE study (Figure 2, HR: 0.84, 95% CI: 0.66–1.07, $p = 0.159$).

Duration of treatment for patients with R/R MCL

The median treatment duration for R/R MCL patients in the ANZ-NPP was 14 months (range 0–41 months) with no statistical difference in median treatment duration of 14.4 months (IQR 15.1) on the RAY study (Figure 3, HR: 0.936, 95% CI: 0.73–1.20, $p = 0.61$).

Predictors of ibrutinib treatment duration in the ANZ-NPP

The results of univariate Cox proportional hazards models of treatment duration performed to identify baseline characteristics associated with treatment duration for ANZ-NPP patients are presented in Figure 4.

For patients with CLL/SLL, those in the age groups 60–64 years and 65–69 years were significantly less likely to stop treatment versus the reference group of patients aged 85 years or older. MCL NPP patients who were diagnosed with MCL within the 2 years prior to NPP enrollment had a significantly shorter treatment duration.

Discussion

The ibrutinib ANZ NPP was one of the largest international ibrutinib programs that provided access for more than 1000 Australian and New Zealand patients with R/R CLL/SLL and MCL. The program continued to support these patients on treatment until either they experienced no further clinical benefit or government funding was attained. The ANZ NPP also provided data on the clinical use and treatment duration of ibrutinib in the real-world context. In this study, this data has enabled an indirect naïve comparison of the

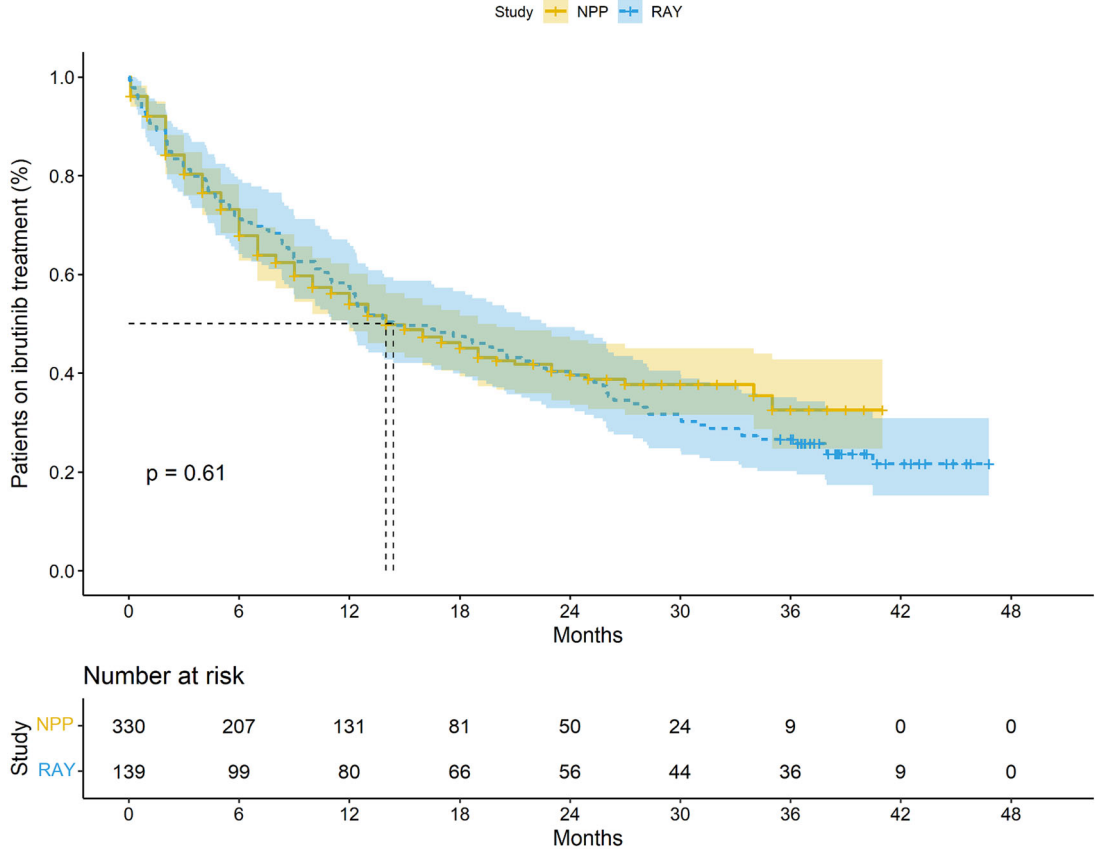

Figure 3. Kaplan–Meier's curve showing duration on ibrutinib treatment in the RAY study and the MCL ANZNPP.

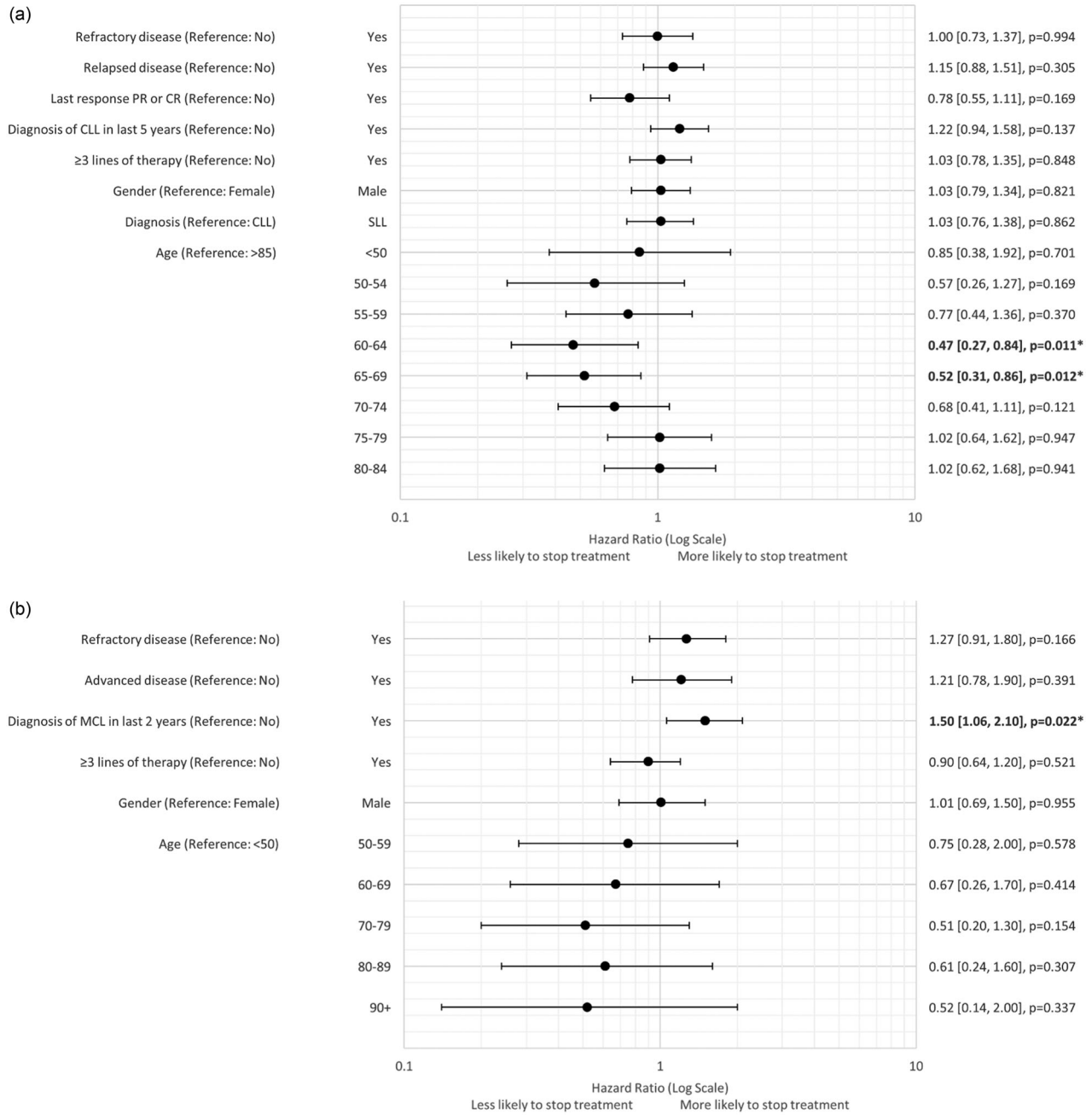

Figure 4. Forest plots of prognostic factors predicting duration on ibrutinib treatment in NPP in: (a) R/R CLL/SLL NPP and (b) R/R MCL.

treatment duration between patients in the real-world versus the clinical trial outcomes. Duration on treatment outcomes with a treat-to-progression drug, such as ibrutinib, provides valuable insight into the length of time patients experience clinical benefit from the treatment.

Analysis of real-world evidence for ibrutinib showed that the estimates of treatment duration for R/R CLL/SLL (median DoT 47 months) [10] and R/R MCL (median DoT 14 months) [11] patients were similar to those in the pivotal phase 3 trials, RESONATE (median DoT 41 months) [2] and RAY (median DoT 14.4 months) [4]. This indicates that ibrutinib treatment duration observed in clinical trials is reproducible in real-world clinical practice in Australia and New Zealand, despite the NPP patients being significantly older than patients in the respective clinical trials (CLL/SLL 72 years versus 67 years and MCL 73 years versus 67 years). This finding is surprising as typically, real-world patients tend to be more heavily pretreated, generally frailer and have more comorbid disease than patients in the clinical trials. We consider

that this likely reflects the efficacy and tolerability of ibrutinib, even in an older population. This is a clinically relevant and important outcome, as real-world results are often considered to be more representative of the day-to-day clinical practice than those from RCTs [12]. Despite these factors, the older NPP cohort nevertheless had essentially identical treatment duration due to ongoing benefit from therapy.

A secondary aim of the study was to search for predictors of ibrutinib treatment duration in this real-world dataset. Because the NPP did not capture comprehensive clinical data on each patient, the only observation that could be made was that CLL patients aged 60–69 years were less likely to stop treatment compared to older patients. It is not clear what factors led to this difference; however, it can be speculated that since the anticipated life expectancy for younger patients is longer and their fitness more favorable, this translated into a longer treatment duration. It is interesting to note that patients <60 years of age are no more likely to stop treatment than those in the >69 years cohort. This may reflect low subgroup numbers, with the majority of patients falling into older age groups (>60 years); an expected age range for patients with CLL.

MCL NPP patients who were diagnosed in the two years prior to NPP enrollment had a significantly shorter treatment duration in the adjusted analysis. This finding is not surprising, as MCL is considered a more aggressive disease than CLL. Further, those with high-risk genetic profiles and blastoid morphology are expected to progress faster than those with classical MCL [13]. Unfortunately, the NPP did not collect comprehensive genetic or histological data that would allow definitive conclusions to be drawn.

Analysis of the NPP data provides insightful information on the clinical use and treatment duration of ibrutinib in a real-world context. Tolerability and efficacy can be inferred from duration on treatment, however, in the absence of detailed systematic clinical data collection, the incidence of AEs and reasons for treatment discontinuation cannot be accurately assessed. While the NPPs were designed to have inclusion and exclusion criteria that closely mapped those of the relevant clinical trials to allow the comparison of findings, they were not designed to collect data in the form of a registry. Nevertheless, NPPs provide valuable insights and further validate other published outcomes from Australian real-world evidence data sources, particularly when they are the size of the ibrutinib ANZ-NPP [14].

It is generally acknowledged that RCTs provide gold standard evidence through the elimination of confounding factors, especially patients with significant comorbidities [12]. However, this inherent strength of RCTs can result in bias toward 'healthier' study cohorts. Due to the strict inclusion and exclusion criteria applied to RCT study populations, it may be difficult to make generalized conclusions for community patients. Studies using real-world data, can expand the knowledge of drug efficacy beyond what can be learnt from RCTs.

The limitations of this study include its retrospective design; the lack of detailed clinical data and baseline characteristics, reliance on physician reporting for completeness of the data; as well as unknown reasons for patient discontinuation within the NPP. These details could be addressed in future NPPs to improve the collection of real-world data. Furthermore, duration on treatment was estimated based on resupply data and does not necessarily reflect medication adherence.

Notwithstanding the limitations of this study, these findings provide a useful real-world estimate of the prolonged time-on-treatment with ibrutinib consistent with real clinically beneficial outcomes. Additionally, they demonstrate a rapid and extensive uptake of NPP access indicating a significant unmet medical need for CLL and MCL patients prior to regulatory authority approval and reimbursement of ibrutinib. Although these patients were not able to access ibrutinib through a clinical trial, they were able to experience the same clinical benefit through the NPP, which is the primary objective of these programs and a positive outcome for the CLL and MCL patients who participated in this program.

Acknowledgements

The authors thank Pippa Burns, PhD, CMPP & Anne Dyson MBBS, of WriteSource Medical Pty Ltd, Sydney, Australia, for providing medical writing support. Medical writing support was funded by Janssen-Cilag Australia in accordance with Good Publication Practice (GPP2022) guidelines (https://www.ismpp.org/gpp-2022).

Geolocation information

Australia and New Zealand.

Disclosure statement

SPM has acted as a consultant/advisor for AbbVie, AstraZeneca, BeiGene, Janssen, Gilead, and Roche. SO has acted as a consultant/advisor for AbbVie, AstraZeneca,

BeiGene, Janssen, Gilead, Roche, Mundipharma, Merck, and Bristol Myers Squibb; has received research funding from AbbVie, AstraZeneca, BeiGene, Janssen, Gilead, Roche, and Epizyme; and has received honoraria from AbbVie, AstraZeneca, BeiGene, Janssen, Gilead, Roche, Merck, and Bristol Myers Squibb. CYC has acted as a consultant/advisor/honoraria for Roche, Janssen, MSD, Gilead, AstraZeneca, Lilly, TG Therapeutics, BeiGene, Novartis, and BMS. BK notes honoraria, consultancy, and advisory boards for Roche, AbbVie, Janssen, Mundipharma, Takeda, Gilead, Merck, CSL, Pharamacyclics, and AstraZeneca, speaker fees from Gilead, Janssen, Roche, AbbVie, and AstraZeneca, and conference registration from AbbVie, Roche, and AstraZeneca. MH has acted as a consultant/advisor/honoraria for Roche, Janssen, Gilead, BeiGene, Novartis, Takeda, Otsuka, and MSD. PM has acted as a consultant/advisor/speaker/honoraria for AbbVie, Astellas, Astra Zeneca, Roche, Janssen, Jazz, Gilead, BeiGene, Novartis, and Otsuka. SP has nothing to declare. AP & MMcG are both employees of Janssen-Cilag Australia Pty Ltd. RW has received honoraria and speaker fees from Janssen, AbbVie, and speaker fees from Beigene. CT has received research funding from Janssen, AbbVie, and Beigene; honoraria from Janssen, AbbVie, and Beigene.

Funding

The study was sponsored by Janssen-Cilag Australia, the sponsor of ibrutinib (Imbruvica) in Australia and New Zealand.

ORCID

Stephen P. Mulligan http://orcid.org/0000-0003-1928-2098
Stephen Opat http://orcid.org/0000-0002-0308-6458
Chan Y. Cheah http://orcid.org/0000-0001-7988-1565
Robert Weinkove http://orcid.org/0000-0003-3645-7988

Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

References

[1] Therapeutic Goods Administration. Australian product information; IMBRUVICA® Ibrutinib capsules and tablets. Therapeutic Goods Administration; Canberra, ACT, Australia; 2021.
[2] Brown JR, Hillmen P, O'Brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. Leukemia. 2018;32(1):83–91.
[3] Barr PM, Robak T, Owen C, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica. 2018;103(9):1502–1510.
[4] Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet. 2016;387(10020):770–778.
[5] Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213–223.
[6] Barr PM, Owen C, Robak T, et al. Up to 8 years follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Adv. 2022;6(11):3440–3450.
[7] Dreyling M, Goy A, Hess G, et al. Long-term outcomes with ibrutinib treatment for patients with relapsed/refractory mantle cell lymphoma: a pooled analysis of 3 clinical trials with nearly 10 years of follow-up. Hemasphere. 2022;6(5):e712.
[8] Medsafe. IMBRUVICA® ibrutinib New Zealand Data Sheet. Medsafe; Wellington, New Zealand ; 2021.
[9] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] statement: guidelines for reporting observational studies. Gac Sanit. 2008;22(2):144–150.
[10] Weinkove R, Doocey R, Henderson R, et al. PB 1892 real world treatment persistence of New Zealand ibrutinib chronic lymphocytic leukaemia patients in a Named Patient Program. HemaSphere. 2019;3(S1):861–862.
[11] Hertzberg M, Cheah CY, Tam C, et al. Real-world experience of Australian and New Zealand relapsed or refractory mantle cell lymphoma patients on ibrutinib in a Named Patient Program. Haematology Society of Australia and New Zealand Annual Scientific Meeting. Blood. 2018. P070
[12] Blonde L, Khunti K, Harris SB, et al. Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther. 2018;35(11):1763–1774.
[13] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization Classification of Lymphoid Neoplasms. Blood. 2016;127(20):2375–2390.
[14] Mulligan SP, Opat S, Marlton P, et al. Ibrutinib use, treatment duration, and concomitant medications in Australian patients with relapsed or refractory chronic lymphocytic leukaemia. Br J Haematol. 2022;198(4):790–793.