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CORRESPONDENCE

Ibrutinib use, treatment duration, and concomitant medications in Australian patients with relapsed or refractory chronic lymphocytic leukaemia

Chemo-immunotherapy and the advent of small molecule inhibitors, including the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib,[1] have revolutionised the therapy of chronic lymphocytic leukaemia (CLL). In the original and pivotal RESONATE study, single agent ibrutinib was compared to ofatumumab in patients with relapsed/refractory CLL (R/R CLL), including those with high-risk prognostic factors, and demonstrated superior progression free survival (PFS), overall survival and overall response rate.[2]

It is recognised that clinical trial populations are highly selected and may not reflect those patients seen in the "real-world" clinical practice where patients are likely to be older and have more comorbidities. Currently, there is limited data with the use of ibrutinib in the general community, both in the Australian context, and from nationally representative datasets.

The primary objective of this study was to analyse ibrutinib utilisation patterns in Australia and to compare the duration on treatment to previously published data from the Phase 3 RESONATE clinical trial (RESONATE cohort).[2,3] An additional objective of this study was to develop an understanding of concomitant medication use in all Australian CLL patients who were treated with ibrutinib, under the national Pharmaceutical Benefits Scheme (PBS).

A retrospective cohort analysis of CLL/ small lymphocytic leukaemia (SLL) patients was undertaken using the PBS 10% dataset.[4] Information was accessed via the data custodian, Services Australia, and Prospection Pty Ltd performed the analysis under a licence agreement. Data from patients treated with ibrutinib in the RESONATE study were included as the comparison. Detailed information on the analytical methods and the PBS patient selection are reported in the Supplementary Text.

Between December 2017 and March 2021 (first date ibrutinib was available via the PBS to the latest data available at the time of the analysis), 683 patients in the PBS 10% dataset received treatment for CLL, of which 222 (32.5%) were being treated with ibrutinib. The median follow-up time for ibrutinib patients in the PBS sample was 18 months, and median age 74 years (range 30–97 years), with 64% being male. Baseline characteristics for the PBS cohort and the RESONATE cohort are presented in Table 1.

In the PBS cohort 65.8% of patients had received only one line of therapy prior to ibrutinib with the median number of prior lines being 1, in contrast to 17.9% of patients in the RESONATE cohort with one prior line of therapy. Over time, since ibrutinib became available in Australia, there has been an increasing trend in the use of ibrutinib in the second line (see Supplementary Text, Figure 1).

Duration on ibrutinib treatment was significantly longer in the PBS 10% sample compared to the RESONATE cohort (HR 0.65, 95% CI 0.46–0.92, $p = 0.01$) (Figure 1). At 1 year, 85% of patients in the PBS cohort remained on ibrutinib treatment, and at 2 years 74% remained on treatment compared to 81% and 69% at the same time points in the RESONATE study. At 3 years, a higher proportion of patients remained on ibrutinib treatment in the PBS cohort (64%) compared to patients in the RESONATE cohort (53%).

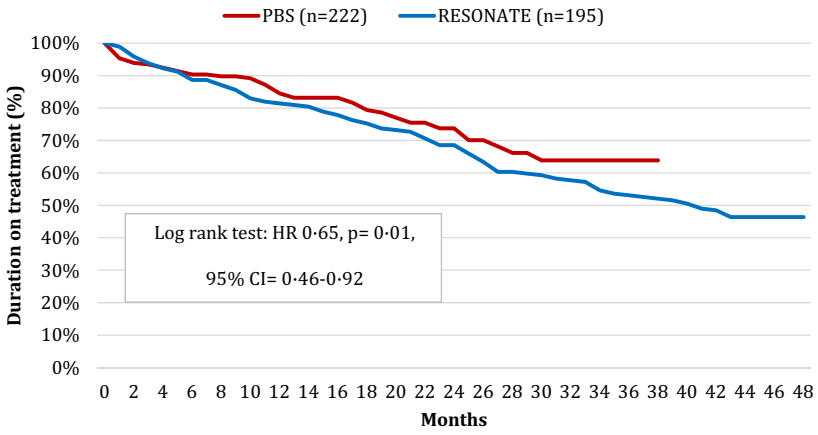
More than 90% of CLL patients in the PBS 10% dataset used concomitant medications. Similar levels of use of anti-hypertensives, anti-infectives, and hyperacidity and reflux medication were seen between ibrutinib only and entire CLL patient cohorts. A high proportion of the CLL patients were taking proton pump inhibitors, with no apparent differences between the ibrutinib and general CLL population (57.6% vs. 60.1%, respectively) (Supplementary Text, Table 1). No new safety signals were identified.

This study of a random Australian PBS 10% sample cohort of R/R CLL patients on ibrutinib indicates that by year three the duration of ibrutinib treatment in Australian real-world clinical practice is longer than that observed in the RESONATE clinical trial. At just over 3 years, the ibrutinib treatment duration in this real-world sample cohort is significantly longer than the median treatment duration seen in the RESONATE study. We hypothesise that many patients in the RESONATE study had received multiple lines of therapy before ibrutinib and therefore had more refractory disease, with only 17.9% of patients having received ibrutinib after one prior line of therapy. Indeed, long term analysis from the RESONATE study demonstrates that patients who commenced ibrutinib treatment in the second line had improved PFS compared to those who commenced treatment in later lines of therapy.[3]

TABLE 1 Baseline characteristics, patients with R/R CLL from the PBS 10% dataset and Phase 3 RESONATE study (ibrutinib arm only)

Variable	PBS 10% dataset (*N* = 222)	Phase 3 RESONATE (*N* = 195)
Median age (range), years	74 (30–97)	67 (30–86)
Sex, *n* (%)		
Male	143 (64.4)	129 (66.2)
Female	79 (35.6)	66 (33.8)
Prior lines, *n* (%)		
1 prior line	146 (65.8)	35 (17.9)
Proportion of patients receiving one prior line at Dec 2017 (%)	56	N/A
Proportion of patients receiving one prior line at Dec 2018 (%)	59	N/A
Proportion of patients receiving one prior line at Dec 2019 (%)	64	N/A
Proportion of patients receiving one prior line at Dec 2020 (%)	67	N/A
2 prior lines	36 (16.2)	57 (29.2)
3 or more prior lines	40 (18.0)	103 (52.8)

Abbreviations: PBS, Pharmaceutical Benefits Scheme; R/R CLL, relapsed/ refractory chronic lymphocytic leukaemia.



Persistence and numbers at risk at every 6-month interval									
Month	*0*	*6*	*12*	*18*	*24*	*30*	*36*	*42*	*48*
PBS Persistence (%)	100	90·3	84·5	79·4	73·7	63·9	63·9		
PBS Number at risk	222	172	130	107	84	58	28		
RESONATE Persistence (%)	100	89·7	81·4	75·3	68·6	59·3	53·1	48·5	46·4
RESONATE Number at risk	195	178	155	144	133	112	100	91	3

FIGURE 1 Comparison of duration on treatment between ibrutinib patients in the PBS 10% dataset compared to ibrutinib patients in the Phase 3 RESONATE study. PBS, Pharmaceutical Benefits Scheme. [Colour figure can be viewed at wileyonlinelibrary.com]

The proportion of patients treated with ibrutinib and concomitant medications is in line with previously published data.[5] However, the use of proton pump inhibitors was more common than previously published for other real-world cohorts[6–8] and no different between the ibrutinib PBS R/R CLL cohort and the total CLL population.

The result of this analysis further supports the available clinical trial data and demonstrates that in the real-world setting, similar, if not improved duration on ibrutinib treatment is being achieved in clinical practice.

Limitations of this dataset include the differences in the PBS population to that of the RESONATE study, which may have contributed to the differences in treatment persistence. Due to a limited number of variables captured in the PBS dataset, we were unable to undertake an adjusted analysis or assess the impact of other potential factors on treatment duration, such as high-risk genetics and therefore the results presented should be interpreted with care. We note that some of the patients in our dataset would have previously accessed ibrutinib via the named patient program or clinical trials.

The results of this study indicate that ibrutinib is commonly used as the first treatment option for R/R CLL in Australia, reflecting the clinical evidence supporting the benefits of ibrutinib use in earlier lines of therapy. This real-world dataset showed that the majority of patients continued ibrutinib treatment for more than 3 years, despite having a median age of 74 years and high rate of comorbidity as indicated by frequent concomitant medication use. Our real-world data supports the effectiveness and long-term tolerability profile of ibrutinib, as demonstrated in clinical trials.

AUTHOR CONTRIBUTIONS

Prospection Pty Ltd was contracted by Janssen-Cilag to carry out the methodology designed by authors Andrea Puig, Marija McGeachie, Poppy Gerungan, Stephen P. Mulligan, Stephen Opat, Paula Marlton, Bryone Kuss, Constantine S. Tam. The analysis was performed using Prospection's proprietary software PharmDash. All authors revised the draft article critically for important intellectual content and approved the final version of the article. All authors agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

SM notes honoraria/advisory or speaker services from Janssen, Abbvie, and AstraZeneca. SO notes consultancy for AbbVie, AstraZeneca, Janssen and Roche, research funding from AbbVie, AstraZenca, BeiGene, Gilead, Janssen, Pharmacyclics, Roche, Sandoz and Takeda, and honoraria from AbbVie, AstraZeneca, Celgene, CSL Behring, Gilead, Janssen, Merck, Roche, and Takeda. PM notes paid advisory/consulting or speaker services for AbbVie, Astellas, BeiGene, Gilead, Janssen, Novartis, Pfizer, and Roche. BK notes honoraria, consultancy, and advisory boards from 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. AM, MM and PG are employees of Janssen-Cilag Pty Ltd Australia. CT received honoraria from Janssen, AbbVie, BeiGene, Novartis, LOXO and research funding from Janssen, AbbVie, and BeiGene.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Services Australia. Restrictions apply to the availability of these data, which were used under licence for this study.

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