Ibrutinib for chronic lymphocytic leukemia: international experience from a named patient program

After first approval of ibrutinib for patients with B-cell malignancies in the US, an international named patient program (NPP) was initiated to provide ibrutinib to patients before local country approval. In this observational retrospective analysis of data collected from the NPP, estimated time on treatment and its relationship with baseline characteristics were analyzed for patients with relapsed/refractory chronic lymphocytic leukemia (CLL). Ibrutinib outcomes were compared with those from the phase III RESONATE™ study. Our findings suggest that ibrutinib is effective and well tolerated in the real world, with time on treatment similar to the clinical trial setting; younger age and complete response (CR)/partial response (PR) to prior therapy were predictive of longer time on treatment.

In B-cell malignancies such as CLL, Bruton's tyrosine kinase (BTK) is a rational target for therapy because it is needed for B-cell receptor signaling, plays a key role in B-cell maturation, and is overexpressed.[1,2] Benefits of ibrutinib, a first-in-class, once-daily, oral, covalent inhibitor of BTK,[1] have been demonstrated in phase II and III studies across multiple B-cell malignancies.[3-6] Ibrutinib is approved in the EU, US and elsewhere to treat patients with CLL, Waldenström's macroglobulinemia and relapsed/refractory mantle cell lymphoma.[7,8] It is also indicated for marginal zone lymphoma in the US.[7]

NPPs enable controlled access to treatments that have shown a positive benefit-risk ratio for life-threatening conditions, in response to unsolicited requests by physicians and on behalf of patients, before the drug is licensed or commercially available in their country. NPPs can provide data on the clinical use, treatment duration, efficacy and relative safety of a drug in a real-world context. After the first approval of ibrutinib in the US in November 2013,[9] an international ibrutinib NPP was initiated for patients with B-cell malignancies who met respective phase III trial eligibility criteria.

Here we describe an observational retrospective analysis of data from patients with relapsed/refractory CLL enrolled in the international ibrutinib NPP from March 2014 through October 2015, to estimate time on treatment and explore related patient characteristics. Time on ibrutinib treatment in the international NPP was compared with the phase III RESONATE™ (PCYC-1112) study of ibrutinib *versus* ofatumumab in patients with relapsed/refractory CLL.[4]

Inclusion criteria for the NPP were based on RESONATE™: age ≥18 years; confirmed diagnosis of CLL/small lymphocytic lymphoma (including patients with 17p deletion); Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of <2; relapsed/refractory disease after ≥1 prior therapy, defined as failure to achieve a PR with, or documented progression after, the most recent treatment regimen.[4]

Participation was approved by the local independent ethics committee or institutional review board as needed, and the enrolling physician obtained patients' informed consent.

Patients received oral ibrutinib 420 mg once daily continuously until progressive disease (PD) or unacceptable toxicity. Disease evaluations and safety monitoring were conducted by enrolling physicians, according to local standard of care. Ibrutinib was provided through the NPP until commercially available, at which point patients were transferred to commercial drug if appropriate, and follow up stopped.

Data on the ordering/reordering of ibrutinib were collected. Treatment start and stop (discontinuation) dates were entered by the physician via a simple questionnaire on the Janssen Managed Access portal (MAcWeb; if not entered, reordering data were censored at the date of last ibrutinib supply). Patient baseline characteristics and reasons for stopping orders were collected from physicians at enrollment and treatment discontinuation, respectively, also via MAcWeb.

Kaplan-Meier analysis and Cox proportional hazards regression were used to estimate time on treatment. Relationships between baseline characteristics and time on treatment were explored via multivariate analyses, included categorical variables of age, sex, number of prior therapy lines, time since CLL diagnosis, PD on prior therapy in the past 3 months, CR or PR to last therapy, relapsed disease and refractory disease.

In total, 2908 patients with CLL from 30 countries were enrolled in the NPP. Baseline demographic and disease characteristics are shown in Table 1. Naïve comparison with patient baseline characteristics of the RESONATE™ study ibrutinib arm suggests median age and proportion of males were similar, however, the proportion of patients with ≥3 prior lines of therapy was higher in the NPP (63% *vs.* 53% for NPP *vs.* RESONATE™). Fewer patients in the NPP relapsed after purine analogues (70% *vs.* 85%, respectively) or anti-CD20 therapy (68% *vs.* 94%, respectively).

The estimated proportion of patients on treatment at 12 months was 77.3% (95% confidence interval [CI]: 74.7, 79.6) in the NPP, similar to RESONATE™ (actual 12-month time on treatment rate, 81.5%; 95% CI: 75.3, 86.3).[10] Time on treatment for the international CLL NPP and RESONATE™ populations were not statistically different (hazard ratio, 1.20 [95% CI: 0.86, 1.67]) (Figure 1). The median duration of follow up was 5.78 (range, 0.03-18.73) months in the NPP, and 9.4 (range, 0.1-16.6) months in RESONATE™.[4]

In the multivariate analysis, younger age (<50 years) and achievement of CR/PR as a response to prior therapy were independent factors significantly associated with longer time on treatment. Having a CLL diagnosis for >5 years

Table 1. Baseline patient characteristics (international CLL NPP population).

Characteristics	N=2908
Median age, years (range)	69 (19-96)
Male sex, n (%)	1863 (64.1)[a]
≥3 prior lines of therapy, n (%)	1767 (62.9)[a]
CLL diagnosis in the last 5 years, n (%)	1437 (51.1)[a]
PD within 3 months prior to ibrutinib, n (%)	1714 (61.0)[a]
Last response CR/PR, n (%)	1826 (65.0)[a]
Relapsed disease, n (%)	
After purine analogue[b]	1969 (70.0)[a]
After CD20 antibody[c]	1921 (68.3)[a]
Refractory disease[d]	1554 (55.3)[a]

[a]Patients with missing values (n=97) are excluded. [b]Defined as failed ≥2 previous treatments, including ≥1 with a purine analogue (e.g., fludarabine). [c]Defined as progression-free interval of <24 months from treatment with a nucleoside analogue or bendamustine-containing regimen in combination with an anti-CD20 monoclonal antibody (e.g., rituximab). [d]Defined as failure to respond to any prior chemotherapy-based therapy (stable disease or PD on treatment). CLL: chronic lymphocytic leukemia; CR: complete response; NPP: named patient program; PD: progressive disease; PR: partial response.

showed a trend toward being associated with longer time on treatment. Patient sex, refractory disease, experiencing relapse within 24 months, PD within 3 months prior to ibrutinib or number of prior therapies (≥3 *vs.* <3; same categorization as used in the RESONATE™ interim analysis) had no effect (Figure 2).

In the NPP, 332 patients (11.4%) discontinued ibrutinib, most commonly due to death (n=123; 4.2%), PD (n=55; 1.9%) and adverse events (AEs) (n=50; 1.7%). In RESONATE™, the discontinuation rate due to AEs was 4% of patients.

In summary, this international, observational, retrospective analysis (the largest series reported to date for ibrutinib in a real-world setting) showed that estimated time on treatment did not differ statistically from RESONATE™. The median duration of follow up was 5.78 months in the NPP and 9.4 months in RESONATE™.[4] An independent analysis on a subset of the UK/Ireland NPP patients (n=315) showed that 73.7% of patients were still on ther-

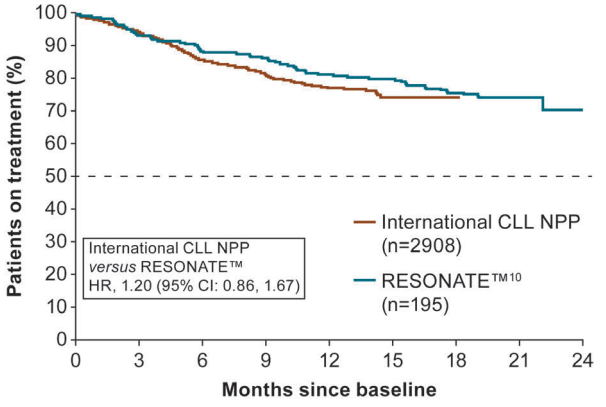

Figure 1. Time on treatment for the international CLL NPP population *versus* the RESONATE™ study population. CI: confidence interval; CLL: chronic lymphocytic leukemia; HR: hazard ratio; NPP: named patient program.

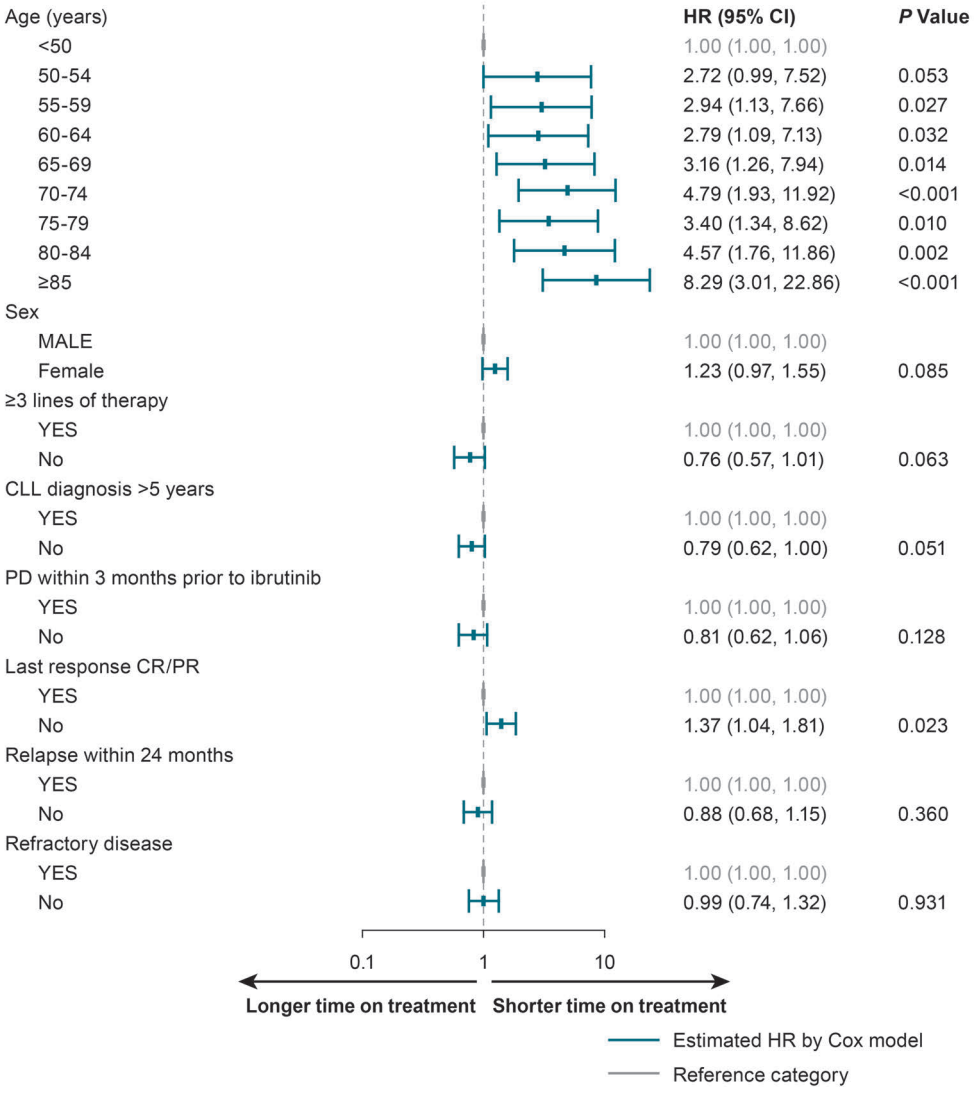

Figure 2. Multivariate analysis of time on treatment for the international CLL NPP population. CI: confidence interval; CLL: chronic lymphocytic leukemia; CR: complete response; HR: hazard ratio; NPP: named patient program; PR: partial response.

apy at 1 year, with a 1-year overall survival (OS) rate of 83.8%.[11] These results are comparable with the 1-year time on treatment rates observed in the international NPP population (77.3%) and the 1-year OS reported in RESONATE™ (90%).[4]

Multivariate analysis indicated that patient sex, prior treatment outcomes (relapse, PD or refractory disease) and number of previous therapies did not affect time on treatment. Achievement of CR/PR with prior therapy was significantly predictive of longer time on ibrutinib. Patients with more heavily pretreated or refractory disease were continuing on ibrutinib treatment for a similar duration as those with less severe or pretreated disease.

The RESONATE™ interim analysis (median follow up 9.4 months) showed that the progression-free survival (PFS) benefit with ibrutinib compared with ofatumumab did not differ between patients who received <3 *versus* ≥3 prior lines (hazard ratios, 0.19 and 0.21, respectively).[4] However, longer follow up of the RESONATE™ study (median 16 months) demonstrated that patients who received only 1 prior therapy had better efficacy outcomes than those who received ibrutinib in later lines (12-month PFS of 94% *vs.* 84% *vs.* 80%, for 1 *vs.* 2 *vs.* ≥3 prior lines, respectively; P=0.01 for 1 prior therapy *vs.* >1).[12] Patients receiving 1, 2 or ≥3 prior lines had a 24-month PFS of 89%, 80% and 69% and a 30-month OS of 93%, 83% and 82%, respectively.[13]

Interestingly, the NPP analysis by the UK CLL Forum showed that OS and PFS were not associated with number of prior lines of therapy or 17p deletion using univariate analysis, though multivariate analysis identified that older patients with 17p deletion had inferior survival when treated with ibrutinib beyond second line.[11] In our multivariate analysis of time on treatment in the international NPP, older age was significantly associated with shorter time on ibrutinib; RESONATE™ reported a positive effect of younger age (<65 years) on PFS with ibrutinib *versus* ofatumumab in patients with relapsed/refractory CLL.[4] These findings suggest that younger patients may have an "easier-to-treat" or more indolent form of disease and/or may be better able to tolerate treatment-related AEs. Further analysis of independent clinical variables and their influence on treatment duration and effectiveness may help to identify patient subgroups that have the greatest potential for improved outcomes with ibrutinib.

The NPP data also suggested a lower rate of discontinuation due to AEs than in RESONATE™.[4] RESONATE™ was a controlled clinical trial, therefore it is likely that patients were more closely monitored, and investigators were more likely to recognize AEs leading to cessation of therapy (including those reported by patients at regular study visits). Data collection on reasons for discontinuation was not mandatory in the NPP.

This study has some limitations. NPP data were based on physician declarations and hence did not provide a way of monitoring patients' adherence to the prescribed dose; variations in adherence are inherent to non-interventional, real-world studies.[14] Furthermore, although the NPP enrollment criteria were largely consistent with RESONATE™, comparisons of time on treatment were not adjusted for possible differences in baseline characteristics.

In conclusion, international CLL NPP data suggest that time on treatment for relapsed/refractory patients receiving ibrutinib is similar in clinical practice to the randomized controlled trial setting.

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Acknowledgments: the authors would like to thank all participating physicians, patients and their families.

Funding: writing and editorial assistance was provided by Jean Turner and Jennifer Fuchs of PAREXEL, funded by Janssen Research & Development, LLC.

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doi:10.3324/haematol.2017.178798

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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