The effectiveness of ibrutinib in chronic lymphocytic leukaemia: a nationwide, population-based study in the Netherlands

At present, in the Netherlands, the application in daily practice of ibrutinib in patients with chronic lymphocytic leukaemia (CLL) is, as yet, restricted to CLL patients with del(17p) or a *TP53* mutation across all treatment lines, and in particular to patient subsets with previously treated CLL (Kersting *et al.*, 2018).

Efficacy data derived from the RESONATE trial (Byrd *et al.*, 2014) — which led to the approval of ibrutinib for the abovementioned indications — cannot always be readily extrapolated into "real-world" effectiveness. This issue relates to the restricted patient selection criteria in clinical trials (Meyer, 2010). Most population-based information on the effectiveness of ibrutinib in CLL currently derives from compassionate-use programmes (CUPs) and series in which patients were primarily managed in academic centres (Winqvist *et al.*, 2016; Ysebaert *et al.*, 2017; Hillmen *et al.*, 2018). Such series might also suffer from patient selection, as in clinical trials. Therefore, this nationwide, population-based study aimed to assess the effectiveness of ibrutinib among CLL patients in a post-approval setting in the Netherlands.

All CLL patients who initiated treatment with commercially available ibrutinib between 2015 and 2016 in the Netherlands were identified and queried via the Nationwide Registry of Hospital Discharges (i.e. inpatient and outpatient discharges) and the nationwide Netherlands Cancer Registry. Details about the registries are provided in the Supporting information.

The primary endpoint was progression-free survival (PFS). The secondary endpoints included assessment of the application of ibrutinib according to the Dutch guidelines by HOVON, duration and toxicity of ibrutinib treatment, overall survival (OS), and event-free survival (EFS). Survival distributions were constructed using the Kaplan-Meier method and compared using the log-rank test. Regression analyses were performed to assess various covariates associated with ibrutinib discontinuation and survival outcomes. Details about the endpoints (Table SI) and statistical methods are described in the Supporting information.

All 155 ibrutinib-treated CLL patients [median age 70 years (range: 48–91 years), 74% males; 67% Rai stage III–IV; 68% managed in non-university hospitals; 6% with small lymphocytic lymphoma] were included in the study. Patient characteristics are presented in Table SII.

At a median follow-up of 14·2 months (range 0·9–31·9), 75 (48%) patients were still receiving ibrutinib and 45 (29%) patients had died. Reasons for ibrutinib discontinuation and the best response rate are described in the Supporting information. Overall, the median time on ibrutinib was 11·6 months (range 0·1–30·9). Multivariable logistic regression showed that Rai stage III–IV — especially anaemia — was the sole covariate associated with ibrutinib discontinuation (Table SIII).

The median PFS (95% CI: 22·9, median not reached) and OS (95% CI: median not reached) were not reached (Fig 1). One-year PFS and OS were 73% (95% CI, 65–79%) and 77% (95% CI, 69–83%) respectively (Fig 1). Multivariable Cox regression analyses revealed that Rai stage III-IV (HR for PFS, 2·56; 95% CI: 1·26–5·19 and HR for OS, 2·54; 95% CI: 1·17–5·55) (Table IA) — particularly anaemia (HR for PFS, 4·09; 95% CI 2·02–8·28 and HR for OS, 3·61; 95% CI 1·69–7·70) (Table IB) — and the number of previous therapies per one treatment line increase (HR for PFS, 1·27; 95% CI: 1·04–1·55 and HR for OS, 1·29; 95%CI: 1·04–1·60) were associated with inferior PFS and OS, respectively. Besides, haepato- and/or splenomegaly (HR for OS, 3·16; 95% CI: 1·12–8·92) was only associated with inferior OS (Table IB).

The median EFS and one-year EFS were 18·2 months (95% CI, 11·6, median not reached) and 58% (95% CI, 50–66%), respectively (Fig 1). Multivariable Cox regression

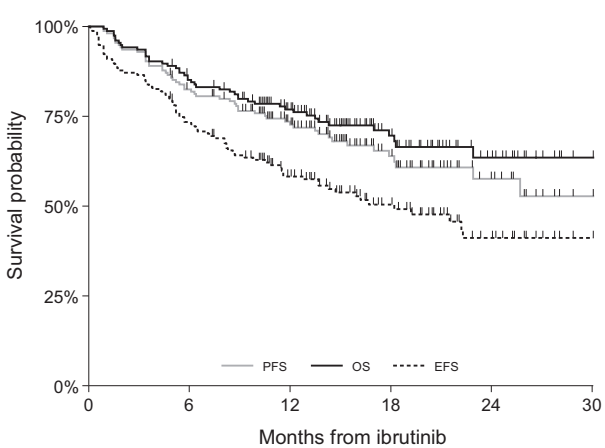

Fig 1. Survival outcomes. Abbreviations: PFS, progression-free survival; OS, overall survival; and EFS, event-free survival.

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Table I. Results of the multivariable Cox regression analysis for progression-free survival, overall survival, and event-free survival.

		Progression-free survival			Overall survival			Event-free survival		
Section	Covariate	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
A	Age*	0·98	0·94–1·02	0·252	0·99	0·95–1·03	0·670	1·00	0·97–1·03	0·877
	Female sex	0·78	0·40–1·50	0·454	0·90	0·44–1·80	0·758	0·85	0·50–1·44	0·538
	No. of comorbidities*	1·16	0·97–1·39	0·113	1·16	0·95–1·41	0·136	1·15	0·99–1·34	0·068
	RAI stage									
	0–IIs	1	(ref)		1·00	(ref)	1	(ref)		
	III–IV	**2·56**	**1·26–5·19**	**0·009**	**2·54**	**1·17–5·55**	**0·019**	1·63	0·94–2·84	0·082
	Treatment as per guidelines	1·75	0·99–3·09	0·055	1·73	0·93–3·21	0·081	1·39	0·87–2·22	0·168
	No. of previous therapies*	**1·27**	**1·04–1·55**	**0·020**	**1·29**	**1·04–1·60**	**0·019**	1·12	0·94–1·33	0·220
	Prior therapy with PA and/or B	0·94	0·47–1·90	0·870	1·13	0·52–2·48	0·754	0·87	0·50–1·51	0·618
B	Age*	0·97	0·93–1·01	0·160	0·99	0·95–1·03	0·596	1·00	0·97–1·04	0·858
	Female sex	0·63	0·30–1·29	0·204	0·69	0·32–1·51	0·353	0·73	0·41–1·31	0·293
	No. of comorbidities*	1·09	0·88–1·36	0·415	1·07	0·85–1·35	0·583	1·09	0·92–1·30	0·311
	Lymphadenopathy	0·93	0·27–3·25	0·915	0·99	0·22–4·47	0·988	1·21	0·42–3·45	0·720
	Haepato- and/or splenomegaly	2·25	0·94–5·38	0·068	**3·16**	**1·12–8·92**	**0·030**	1·45	0·76–2·76	0·254
	Anaemia†	**4·09**	**2·02–8·28**	**<0·001**	**3·61**	**1·69–7·70**	**0·001**	**1·96**	**1·15–3·34**	**0·014**
	Thrombocytopenia‡	0·90	0·48–1·70	0·748	0·94	0·48–1·84	0·855	1·07	0·64–1·79	0·798
	Treatment as per guidelines	**1·91**	**1·04–3·52**	**0·037**	1·82	0·95–3·49	0·072	1·48	0·91–2·40	0·112
	No. of previous therapies*	**1·43**	**1·15–1·79**	**0·001**	**1·46**	**1·16–1·84**	**0·002**	1·18	0·98–1·41	0·080
	Prior therapy with PA and/or B	0·75	0·36–1·56	0·448	0·89	0·40–2·01	0·782	0·83	0·47–1·47	0·529

In section B of this Table, the Rai stage was replaced with its parameters (i.e. presence of lymphadenopathy, haepato- and/or splenomegaly, anaemia, and thrombocytopenia) to delineate which parameter was most critical in predicting the outcome.

Hazard ratios (HRs) denoted in bold indicate variables that are significant at the level of $P < 0{\cdot}05$.

Abbreviations: B, bendamustine; CI, confidence interval; PA, purine analogue.

*Linear estimate per one unit increase.

†Anaemia defined as a haemoglobin level below 110 g/l.

‡Thrombocytopenia defined as thrombocytes below 100×10^9/l.

analyses showed that anaemia — but not Rai stage III–IV or thrombocytopenia — was the only covariate associated with inferior EFS (Table IA, B).

Exploratory survival analyses according to (i) the line of therapy, (ii) the presence of *TP53* aberrations or (iii) anaemia, (iv) the application of ibrutinib as per the Dutch guidelines by HOVON, and (v) the experience of a grade 3 or 4 adverse event (AE) are presented in the Supporting information.

Grade 3 or 4 AEs during ibrutinib treatment were noted in 73 (47%) patients and are listed in Table SIV. Of note, AEs occurred more abundantly in patients with anaemia, as compared to patients without anaemia (57% vs. 38%; $P = 0{\cdot}021$).

In our population-based study, one-year PFS and OS are slightly inferior to the one-year PFS (84%) and OS (90%) reported in the RESONATE trial (Byrd *et al.*, 2014), 10-months PFS (77%) and OS (83%) in the Swedish CUP (Winqvist *et al.*, 2016), and one-year PFS (74%) and OS (84%) in the international CUP (Hillmen *et al.*, 2018) respectively. However, as a result of a higher discontinuation rate in our study compared to the aforementioned studies, one-year EFS was 58%. Several arguments can be brought forward to discuss disparities related to these outcomes. In the aforementioned studies, patient inclusion relies on referral practices and relatively strict inclusion and exclusion criteria. Also, the median age of ibrutinib-treated CLL patients in a US study (Mato *et al.*, 2018) — who were managed mainly in academic hospitals and within the setting of clinical trials — was 10 years lower compared to our study population and the general CLL population (Kristinsson *et al.*, 2009; Van den Broek *et al.*, 2012). Collectively, our study represents general ibrutinib-treated CLL patients better. It therefore merits acknowledgement that our study might include a more inferior group of patients who were rather expeditiously treated with ibrutinib following its reimbursement as from late 2014 in the Netherlands. Indeed, the inclusion of older, often frail patients in our study might have contributed to early ibrutinib discontinuation. Moreover, the discontinuation rate in our study was higher (58%) compared to those reported in CUPs (range, 11–41%) and the RESONATE trial (14%) (Byrd *et al.*, 2014). The high discontinuation rate thus highlights the need for additional and accessible supportive-care measures in a daily practice setting to improve the tolerability of ibrutinib, which, in turn, may improve outcomes (Jain *et al.*, 2015).

An interesting novel finding that emerged from our study was that pretreatment anaemia — but not thrombocytopenia — was independently associated with inferior survival outcomes and ibrutinib discontinuation. Anaemia has hitherto not been reported as a specific predictor of outcome in ibrutinib-treated CLL patients. We strongly encourage that

the association of anaemia with outcome should be validated in forthcoming studies.

The key strength of our study includes the use of a nationwide registry that enabled us to identify all ibrutinib-treated CLL patients. The omission of genetic testing in most patients and the limited application of ibrutinib in the first-line setting prevented meaningful subgroup analyses.

In summary, in this nationwide, population-based study — which mainly included previously treated CLL patients — survival outcomes with ibrutinib were lower than reported in clinical trials and CUPs. Forthcoming population-based studies are imperative to assess whether the outcomes of ibrutinib-treated CLL patients will improve to the level of clinical studies.

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Conflict of interest

AGD received research funding from Janssen-Cilag. The other authors declare no conflict of interest.

Author contributions

M-DL, APK, and AGD designed the study; LvdS analysed the data; AGD supervised the data analyses; OV collected the data; LvdS wrote the manuscript with contributions from all authors, who also interpreted the data, and read, commented on, and approved the final version of the manuscript.

Lina van der Straten[1,2]
Mark-David Levin[2]
Otto Visser[3]
Nicole M.A. Blijlevens[4]
Jan J. Cornelissen[5]
Jeanette K. Doorduijn[5]
Arnon P. Kater[6]
Avinash G. Dinmohamed[1,5,7]

[1]Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands, [2]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands, [3]Department of Registration, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands, [4]Department of Haematology, Radboud University Medical Center, Nijmegen, The Netherlands, [5]Department of Haematology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [6]Department of Haematology, Cancer Center Amsterdam, Lymphoma and Myeloma Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands and [7]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands.
E-mail: a.dinmohamed@iknl.nl

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Primary and secondary endpoints.

Table SII. Patient characteristics.

Table SIII. Results of the logistic regression analysis for ibrutinib discontinuation.

Table SIV. Grade 3 and 4 adverse events during ibrutinib treatment.

Figure S1. Survival outcomes among ibrutinib-treated patients with chronic lymphocytic leukaemia according to the line of therapy (i.e. first-line therapy versus and subsequent lines of therapy).

Figure S2. Survival outcomes among ibrutinib-treated chronic lymphocytic leukaemia patients according to the presence of TP53 aberrations (i.e. deletion and/or mutation).

Figure S3. Survival outcomes among ibrutinib-treated chronic lymphocytic leukaemia patients according to the presence of anaemia.

Figure S4. Survival outcomes among ibrutinib-treated chronic lymphocytic leukaemia patients according to the receipt of ibrutinib within or outside the indications endorsed by the CLL working group of the Hemato-Oncology Foundation for Adults in the Netherlands (HOVON).

Figure S5. Survival outcomes among ibrutinib-treated patients with chronic lymphocytic leukaemia according to the experience of toxicity.

References

Van den Broek, E., Kater, A., van de Schans, S., Karim-Kos, H., Janssen-Heijnen, M., Peters, W., Nooijen, P., Coebergh, J. & Posthuma, E. (2012) Chronic lymphocytic leukaemia in the Netherlands: trends in incidence, treatment and survival, 1989–2008. *European Journal of Cancer*, **48**, 889–895.

Byrd, J.C., Brown, J.R., O'Brien, S., Barrientos, J.C., Kay, N.E., Reddy, N.M., Coutre, S., Tam, C.S., Mulligan, S.P., Jaeger, U., Devereux, S., Barr, P.M., Furman, R.R., Kipps, T.J., Cymbalista, F., Pocock, C., Thornton, P., Caligaris-Cappio, F., Robak, T., Delgado, J., Schuster, S.J., Montillo, M., Schuh, A., de Vos, S., Gill, D., Bloor, A., Dearden, C., Moreno, C., Jones, J.J., Chu, A.D., Fardis, M., McGreivy, J., Clow, F., James, D.F. & Hillmen, P.; RESONATE Investigators (2014) Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *New England Journal of Medicine*, **371**, 213–223.

Hillmen, P., Diels, J., Healy, N., Iraqi, W., Aschan, J. & Wildgust, M. (2018) Ibrutinib for chronic lymphocytic leukemia: international experience from a named patient program. *Haematologica*,

103, e204–e206. https://doi.org/10.3324/haematol.2017.178798.

Jain, P., Keating, M., Wierda, W., Estrov, Z., Ferrajoli, A., Jain, N., George, B., James, D., Kantarjian, H., Burger, J. & O'Brien, S. (2015) Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood*, **125**, 2062–2067. https://doi.org/10.1182/blood-2014-09-603670.

Kersting, S., Neppelenbroek, S.I., Visser, H.P., van Gelder, M., Levin, M.-D., Mous, R., Posthuma, W., van der Straaten, H.M. & Kater, A.P. (2018) Clinical practice guidelines for diagnosis and treatment of chronic lymphocytic leukemia (CLL) in the Netherlands. *Clinical Lymphoma Myeloma and Leukemia*, **18**, 52–57.

Kristinsson, S.Y., Dickman, P.W., Wilson, W.H., Caporaso, N., Björkholm, M. & Landgren, O. (2009) Improved survival in chronic lymphocytic leukemia in the past decade: a population-based study including 11 179 patients diagnosed between 1973–2003 in Sweden. *Haematologica*, **94**, 1259–1265.

Mato, A.R., Nabhan, C., Thompson, M.C., Lamanna, N., Brander, D.M., Hill, B., Howlett, C., Skarbnik, A., Cheson, B.D., Zent, C., Pu, J., Kiselev, P., Goy, A., Claxton, D., Isaack, K., Kennard, K.H., Timlin, C., Landsburg, D., Winter, A., Nasta, S.D., Bachow, S.H., Schuster, S.J., Dorsey, C., Svoboda, J., Barr, P. & Ujjani, C.S. (2018) Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica*, **103**, 874–879. https://doi.org/10.3324/haematol.2017.182907

Meyer, R.M. (2010). Generalizing the results of cancer clinical trials. *Journal of Clinical Oncology*, **28**, 187–189.

Winqvist, M., Asklid, A., Andersson, P.-O., Karlsson, K., Karlsson, C., Lauri, B., Lundin, J., Mattsson, M., Norin, S., Sandstedt, A., Hansson, L., &Österborg A. (2016) Real-world results of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia: data from 95 consecutive patients treated in a compassionate use program. A study from the Swedish Chronic Lymphocytic Leukemia Group. *Haematologica*, **101**, 1573–1580.

Ysebaert, L., Aurran-Schleinitz, T., Dartigeas, C., Dilhuydy, M.S., Feugier, P., Michallet, A.S., Tournilhac, O., Dupuis, J., Sinet, P. Albrecht, C. & Cymbalista, F. (2017) Real-world results of ibrutinib in relapsed/refractory CLL in France: early results on a large series of 428 patients. *American Journal of Hematology*, **92**, E166–E168.