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Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients

UK CLL Forum

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Ferrata Storti Foundation

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ABSTRACT

In 2014, ibrutinib was made available for relapsed/refractory chronic lymphocytic leukemia patients. The UK Chronic Lymphocytic Leukaemia Forum collected data from UK/Ireland patients with a minimum of 1 year follow-up with pre-planned primary endpoints; the number of patients still on therapy at 1 year "discontinuation-free survival" and 1 year overall survival. With a median of 16 months follow up, data on 315 patients demonstrated a 1 year discontinuation-free survival of 73.7% and a 1 year overall survival of 83.8%. Patients with better pre-treatment performance status (0/1 *vs.* 2+) had superior discontinuation-free survival (77.5% *vs.* 61.3%; $P<0.0001$) and overall survival (86.3% *vs.* 76.0%; $P=0.0001$). In univariable analysis, overall survival and discontinuation-free survival were not associated with the number of prior lines of therapy or 17p deletion. However, multivariable analysis identified an interaction between prior lines of therapy, age and 17p deletion, suggesting that older patients with 17p deletion did worse when treated with ibrutinib beyond the second line. Overall, 55.6% of patients had no first year dose reductions or treatment breaks of >14 days and had an overall survival rate of 89.7%, while 26% of patients had dose reductions and 13% had temporary treatment breaks of >14 days. We could not demonstrate a detrimental effect of dose reductions alone (1 year overall survival: 91.7%), but patients who had first year treatment breaks of >14 days, particularly permanent cessation of ibrutinib had both reduced 1 year overall survival (68.5%), and also a statistically significant excess mortality rate beyond one year. Although outcomes appear inferior to the RESONATE trial (1 year overall survival; 90%: progression-free survival; 84%), this may partly reflect the inclusion of performance status 2+ patients, and that 17.5% of patients permanently discontinued ibrutinib due to an event other than disease progression.

Introduction

The RESONATE trial established the efficacy and tolerability of ibrutinib in relapsed/refractory chronic lymphocytic leukemia (CLL) and led to the licensing of ibrutinib for this indication in the USA and Europe.[1,2] In 2014, a named patient scheme (NPS) made ibrutinib available for relapsed/refractory CLL patients in the UK and Ireland who broadly matched RESONATE trial entry criteria. Following closure of the scheme, the UK CLL Forum initiated a service evaluation of data from patients who commenced treatment on the scheme in 2014 with a minimum follow-up of 1 year. Accepting the limitations of retrospective data analysis, the UK CLL Forum executive committee pre-planned the two most objective primary endpoints for the evaluation: 1. Percentage of patients alive and still taking ibrutinib at 1 year (discontinuation-free survival; DFS) and 2. Percentage of 1 year overall survival (OS). As data collection was >12 months after all patients commenced ibrutinib, the 1 year DFS and OS are therefore absolute values that cannot change with further follow-up. The broad proposal with this service evaluation was to assess how the primary endpoints were influenced by basic patient demographics and per-

Correspondence:

george.follows@addenbrookes.nhs.uk

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formance status, aspects of CLL biology and treatment-related variables.

Methods

All clinicians entering patients into the CLL ibrutinib NPS were asked whether they wished to contribute anonymized data to the UK CLL Forum ibrutinib service evaluation. To meet entry criteria for the evaluation, patients had to have relapsed/refractory CLL having received prior immunochemotherapy, and had at least 1 day of ibrutinib treatment in the NPS, commencing treatment in 2014. Twelve months after the closure of the scheme, the participating clinicians were sent a questionnaire requesting 25 data points per patient, roughly grouped into 9 categories, as set out in the *Online Supplementary Table S1*.

Clinicians were given a further opportunity to update their data in March 2016. Clinicians were asked to report any clinically significant adverse event (AE) which was possibly related to ibrutinib, and to provide a best response to therapy. Inevitably, there are limitations to the accuracy of AE reporting and response assessments in retrospective analysis, particularly as there is very variable use of CT scanning and bone marrow assessments in non-trial practice. Defining accurate complete and partial remission rates was therefore not possible. Patients were grouped as 'responder' if clinicians graded the response to therapy as partial remission (PR) (including PR + lymphocytosis), or 'better', or 'non-responder' for stable disease or worse. Kaplan-Meier survival analyses, Cox regression and log-rank tests were used for time-to-event analyses, and the assumption of proportional hazards was checked using Schoenfeld residuals. Where the assumption of proportional hazards did not hold, 16 month rates are presented. Data were analyzed using Stata version 14.1.

Results

Demographics, disease and patient characteristics

Patient data were returned on 315 patients who met entry criteria from 62 hospitals from across the UK (England, Scotland, Wales, Northern Ireland) and the Republic of Ireland. Contributing hospitals, patient numbers contributed and responsible clinicians are detailed in the *Online Supplementary Table S2*. The median age of patients on the first day of treatment was 69 (range: 42-93), with 69% male. The median prior lines of therapy was 2 (range: 1-14), with 48% of patients having received 3 or more prior lines. Specific data on types of prior therapy were not collected. Fluorescence *in situ* hybridization (FISH) data were provided for 263/315 patients (83.5%). All 263 patients had FISH for 17p deletion, but testing for other loci was variable between centers. Testing for mutation of *TP53* was limited to a small number of academic centers, and the number of patients tested for this mutation is not known, although 3 patients were reported with a TP53 mutation. In total, 90 patients were identified with

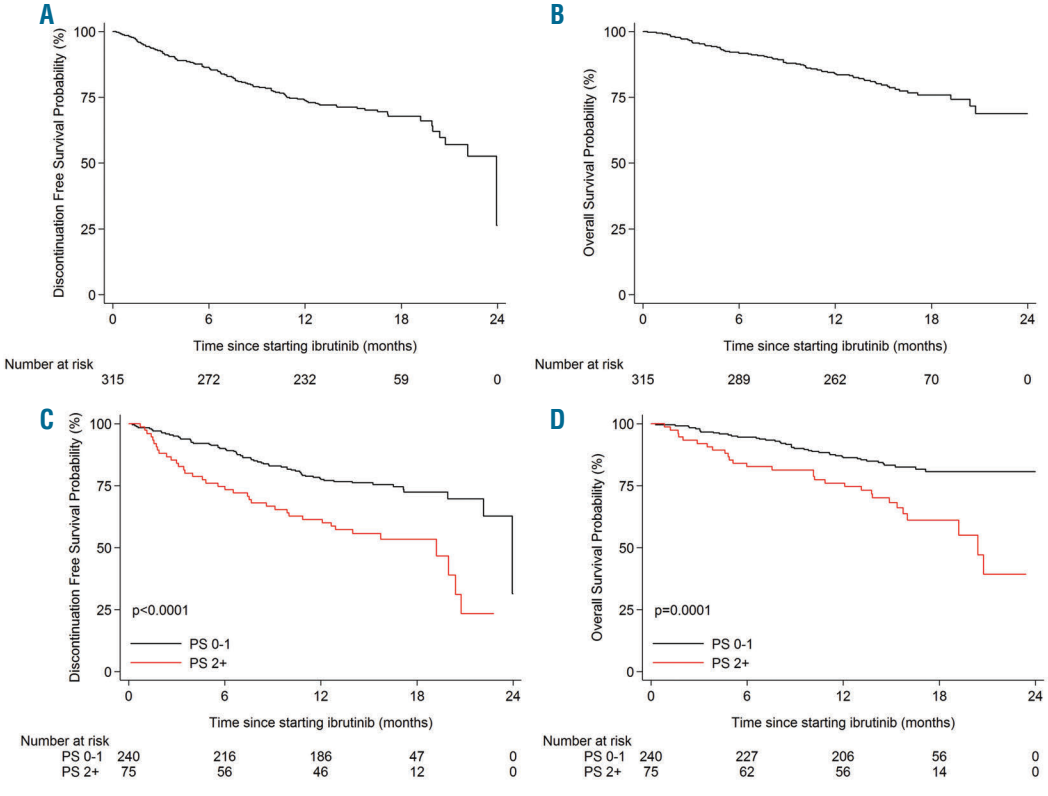

Figure 1. Kaplan-Meier plots of (A) discontinuation-free survival (DFS) and (B) overall survival (OS) for the whole cohort of 315 patients. Patient outcomes as per pre-ibrutinib performance status showing (C) DFS and (D) OS. PS: performance status.

a 17p deletion (90/263; 34.2%); Clinician assessed ECOG performance status (PS) was 0/1 in 240 (76.2%) patients (0=78, 1=162) and 2/3 in 74 (23.5%) patients (2=62, 3=12). One patient was PS 4.

Discontinuation-free and overall survival data

From the entire cohort, 73.7% (232/315) of patients were still on therapy at 1 year with an absolute one year survival rate of 83.8% (264/315) (Figure 1A,1B). At the median follow-up of 16 months, OS was 77.4% (95% CI: 71.9–81.9). The primary endpoints of 1 year DFS and OS were then analyzed by demographic, disease-specific and treatment-related criteria. The hazard ratios for this data with 95% confidence limits are presented in Table 1. Patients with a better performance status pre-treatment had better outcomes, with poorer performance status patients having more than double the risk of discontinuation and/or death: 1 year DFS for PS 0/1 was 77.5% and for PS 2+ was 61.3%; $P<0.0001$, and OS rates were 86.3% and 76.0% respectively; $P=0.0001$ (Figure 1C,1D).

Younger patients (median age of 69 or below) fared better in terms of both DFS (1 year rates: 80.7% and 68.2%; $P=0.024$) and OS (86.7% and 81.2%; $P=0.10$, Figure 2A) although this did not reach significance for OS. When age was analyzed as a continuous variable, the detrimental consequences for each additional 10 years was statistically significant for both DFS and OS (DFS HR=1.43 (1.14 – 1.80), $P=0.01$; OS HR=1.51 (1.15 – 1.98), $P=0.0025$). Male and female patients had no difference in DFS and OS. Although 1 year DFS and OS appeared inferior for 17p- patients compared with wild-type 17p, this was not statistically significant (DFS: 71.1% *vs.* 77.5%; $P=0.74$, OS: 84.4% *vs.* 86.7%; log-rank $P=0.86$, Figure 2B). It is noteworthy that patients with no FISH data available had a worse DFS and OS. There is no clear explanation for this observation. When the effect of prior therapies was analyzed, no differences could be demonstrated for either DFS or OS for patients treated with 1 prior, 2 prior or 3+ prior lines of therapy (OS: 83.5% 1 line, 82.9% 2 lines and 84.3% 3+ lines; $P=0.997$, Figure 2C). Furthermore, there was no suggestion of any separation of the DFS or OS Kaplan-Meier survival curves beyond one year. No data were available on types of prior therapy. Response assessments were available for 311 patients, with 266/311 (85.5%) classified as 'responder' by their clinician and 45/311 (14.5%) classified as 'non-responder'. Responding patients had a markedly superior 1 year DFS and OS compared with non-responding patients (OS: 90.2% *vs.* 46.7%, $P<0.0001$, Figure 2D).

All five pre-treatment variables from Table 1 were included in a mutivariable model. When fitted, it became apparent that there were significant interactions for DFS between age and number of prior lines and 17p and number of prior lines (*Online Supplementary Table S3*). If patients had received 1 line of prior therapy, then the older group patients had similar DFS and OS outcomes to younger patients. However, for patients with 2 prior lines of therapy, age was significantly associated with inferior DFS (a more than 4-fold increase in risk) and showed the same trend with OS (a 2-fold increase, $P=0.17$). For patients receiving 3 or more prior lines the same trend was seen, but the effect size was much smaller and did not reach statistical significance (a 71% increase in risk of discontinuation or death ($P=0.26$) and a 76% in the risk of death, $P=0.13$). The Kaplan-Meier OS plots for younger and older patients separated by prior lines of therapy are shown in Figure 3A and Figure 3B, respectively, while the corresponding DFS curves are shown in the *Online Supplementary Figures S1A* and *S1B*. 17p deletion showed a very similar pattern; if patients had received only 1 prior line of therapy, there was no evidence that 17p deletion had a detrimental effect, but with 2 prior lines the risk of discontinuation or death was 4 times higher ($P=0.006$) and the risk of death was more than double ($P=0.13$). For 3+ prior lines there was a non-significant increase of 71% in the risk of discontinuation or death ($P=0.12$) and 82% in the risk of death ($P=0.13$). It is not clear why the effect was less marked in 3+ prior lines compared with 2 prior lines, and there remains a possibility that there are unknown confounding factors. The Kaplan-Meier OS plots for wild-

Table 1. Univariable analysis of pre-treatment parameters for DFS and OS. *Compares patients with 17p results only **One patient was performance status (PS) 4.

Variable	DFS Events/N	HR(95% CI)	p-value	OS Events/N	HR(95% CI)	P
Age						
≤median (69 years)	39/150	1.00	0.024	27/150	1.00	0.10
>median	55/148	1.60 (1.06 – 2.42)		40/148	1.50 (0.92 – 2.43)	
TP53						
No 17p deletion	50/173	1.00	0.74*	34/173	1.00	0.86*
17p deletion	30/90	1.08 (0.68 – 1.71)		19/90	1.05 (0.60 – 1.84)	
Missing	22/52	1.56 (0.94 – 2.57)		18/52	1.95 (1.10 – 3.45)	
Prior therapies						
1	25/85	1.00	0.71	19/85	1.00	0.997
2	26/76	1.25 (0.72 – 2.18)		17/76	0.97 (0.51 – 1.87)	
3+	47/146	1.09 (0.67 – 1.77)		34/146	0.98 (0.56 – 1.73)	
Performance status						
0-1	64/240	1.00	<0.0001	42/240	1.00	0.0001
2+**	38/74	2.30 (1.54 – 3.44)		29/75	2.47 (1.54 – 3.96)	
Sex						
Female	26/93	1.00	0.63	19/93	1.00	0.65
Male	66/203	1.12 (0.71 – 1.76)		49/203	1.13 (0.67 – 1.92)	

HR: hazard ratio; OS: overall survival; CI: confidence interval; DFS: discontinuation-free survival.

type 17p and 17p deleted patients separated by prior lines of therapy are shown in Figure 3C and Figure 3D, respectively, while the corresponding DFS curves are shown in the *Online Supplementary Figures S1C* and *S1D*.

The association of prior lines with DFS and OS is complicated by the two interactions of age and 17p deletion status. Given the small numbers of events in the subsets of patients it is hard to draw firm conclusions, though it appears clear that for patients who are older and have 17p deletion, the risk of death or discontinuation increases dramatically with more lines of prior therapy (at least a 4-fold increase, HRs range from 4.34 to 17.04). The same more than 2-fold increase in the risk for both DFS and OS for PS 2+ patients was seen in both the multivariable and univariable analysis. There was no evidence of an association (or any interactions) with sex in the multivariable model. As there was missing data for a small group of patients, this variable has not been included in the model presented in the *Online Supplementary Table S3*. A number of clinicians included individual case histories describing marked quality of life (QoL) improvements in their patients, and 85.2% of patients (248/291) were reported to have an improved QoL with ibrutinib therapy. Clinical suspicion of Richter's transformation was reported in 9.2% of the whole patient cohort (29/315). Of these 29 patients, the transformation was biopsy-confirmed in 18 patients, i.e., 5.7% of all patients, with 13 biopsy-proven in the first year. Of the 29 patients clinically suspected of Richter's transformation, 22 (76%) had died by the time of data collection.

Table 2. Dominant reason given for permanently stopping ibrutinib in 83 patients who stopped the drug within the first year of treatment.

Dominant reasons given for stopping ibrutinib before 1 year	Number of patients
Infection	15
Progressive or refractory disease	14
Richter's transformation	14 (biopsy proven in 12)
Hemorrhage/bleeding-related/anticoagulation-related	9
General debility	6
2nd cancer	6
Lower / upper GI toxicity	2 / 1
Cytopenias	2
Cardiac issues	2
Dermatological	1
Neuropathy	1
Reason for stopping ibrutinib not provided	10 (including 3 patients who died on therapy)

GI: gastro-intestinal.

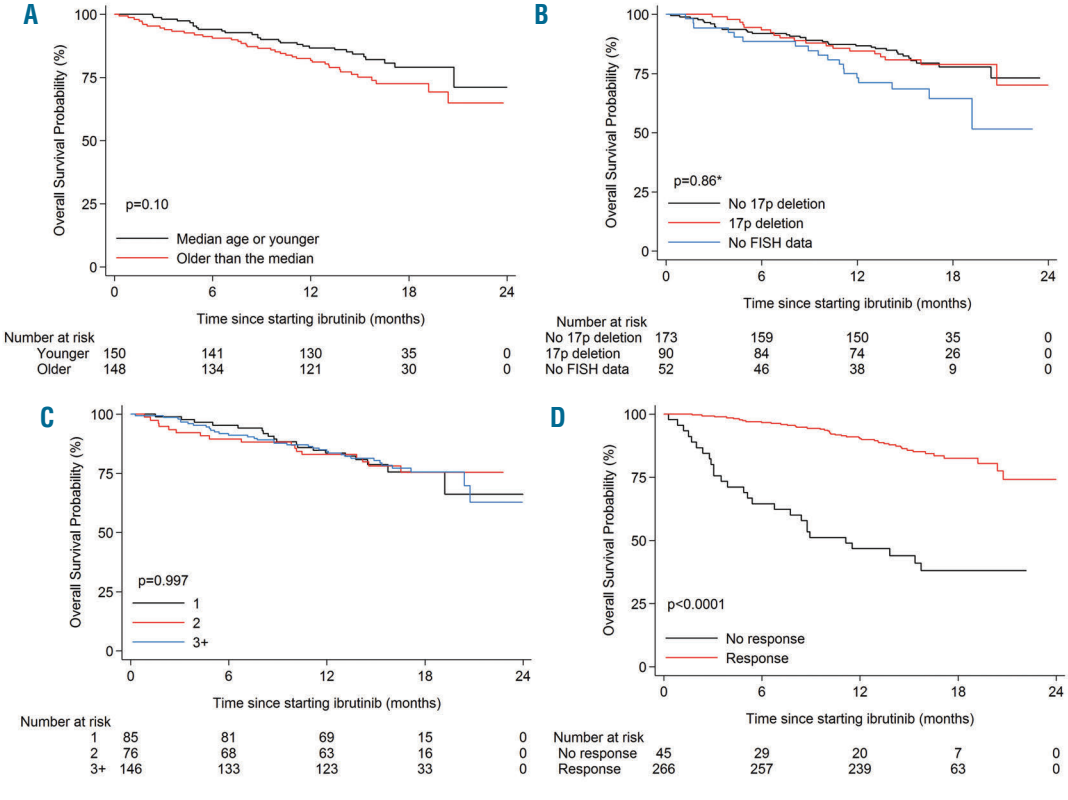

Figure 2. Kaplan-Meier plots of (A) overall survival (OS) of patients older than median age and median age or younger, (B) OS with or without 17p deletion (**P*-value for the comparion of patients with and without 17p deletion) (C) OS of patients by number of prior lines of therapy and (D) OS of patients classified by local clinician as 'responder' or 'non-responder' to ibrutinib therapy. FISH: fluorescence *in situ* hybridization.

Treatment discontinuation and dose reduction

Survival was poor for the 83 patients who stopped ibrutinib permanently within the first year. Of these patients, 11 died on therapy (median 153 days from the first dose (range: 46-363)), and of the remaining 72 patients, 40 died before 1 year and 8 died within the period of data collection. The median survival for these 72 patients was 95 days after stopping ibrutinib and 319 days from the first dose. Of the 83 patients who permanently stopped ibrutinib in the first year, 28 were broadly due to disease (refractory disease, progressive disease or Richter's transformation) and 55 due to other causes (summarized in Table 2). Clinicians were asked if the drug was stopped permanently due to an ibrutinib-related AE. For 56/83 patients, the local clinician classified the main reason for stopping was due to an ibrutinib-related AE, while for 27/83 patients the local clinician did not classify the reason for stopping as AE-related. There was a striking difference in the 1 year OS between these 2 groups. Of the patients who stopped for a 'clinician-defined' AE, 29/56 (51.8%) died before 1 year, but for the patients who stopped the drug for reasons other than an AE, mortality was much higher, with 22/27 (81.5%) dying before 1 year.

Thirty four patients had treatment breaks of 14 days or less. Temporary treatment breaks between 15 days and 6 months (median = 28 days) were reported in 41 patients. The five commonest primary reasons given for these longer treatment breaks were: infection (12 cases), hemorrhage/bruising (9 cases), cytopenias (4 cases), lower gastro-intestinal (GI) toxicity (3 cases), and skin rash/dermatological conditions (3 cases). Dose reductions were relatively common, with 26% of patients (82/315) being reduced to 280mg (42 patients) or 140mg (40 patients) lasting from 1 week to permanent dose reduction (median = 6 months). 32 of these 82 patients also had additional treatment breaks ranging from 15 days to permanent discontinuation. The primary reasons given for dose reductions are given in Table 3.

Overall, clinicians reported clinically significant AEs in 56.5% of patients, although a number of these events did not require either dose reduction or treatment breaks. The overall profile of AEs was similar to those in published studies, and included atrial fibrillation (AF) in 5.1% of patients.

We wanted to analyze whether any alterations in therapy potentially compromised outcomes. To assess whether dose reductions/treatment breaks could impact on outcome, we defined a reference group of patients (group A) who had minimal alterations to therapy, defined as having received standard dose ibrutinib with no dose reductions and total treatment breaks no greater than 14 days in the first year. Group B were patients with any dose reductions but no treatment breaks greater than 14 days. Group C included any patient where ibrutinib was withheld for longer than 14 days, either temporarily or permanently, whether or not the patient had any ibrutinib dose reduc-

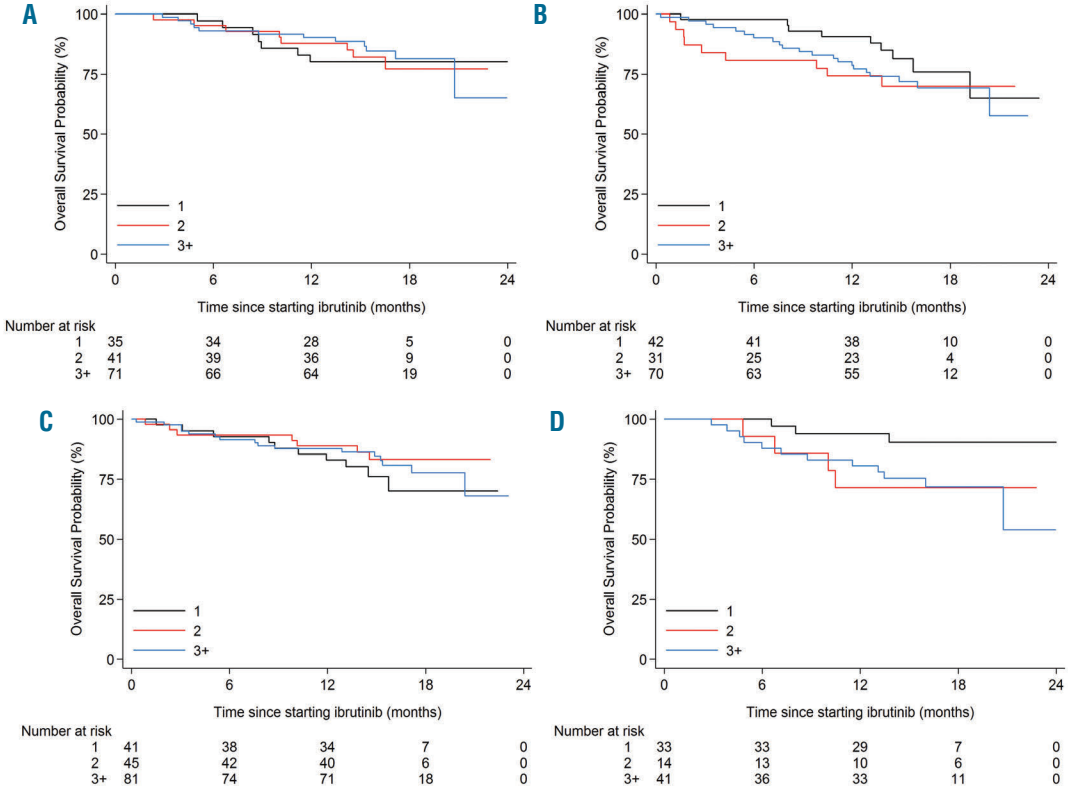

Figure 3. Kaplan-Meier plots of overall survival (OS) for (A) patients equal to or younger than the median age and (B) patients older than the median age and (C) patients without 17p deletion and (D) patients with 17p deletion stratified by the number of prior lines of therapy.

tions. Kaplan-Meier DFS and OS curves for the 3 groups are presented in Figure 4.

The total number of group A patients was 175, which included 136 patients who continued on ibrutinib unchanged for the whole year, and 21 patients who had up to 14 days temporarily off therapy. PS 0/1 patients were over-represented in group A with 141 PS 0/1 patients (80.6%), compared with 38 (79.2%) in group B and 61 (66.3%) in group C (Chi square P=0.03). There were 18 deaths in group A before 1 year, with 8 patients dying on therapy and 10 patients dying within 14 days of stopping therapy. Of the 18 deaths in group A, major AEs associated with the final illness were: infection (6), progressive CLL (4), Richter's transformation (2), cardiac problems (1), hemorrhage (1), general debility (1), and not given (3). Group A DFS and OS were both 89.7%. The total number of group B patients was 48, with 18 patients having dose reductions for less than or equal to 6 months (lowest dose 140mg in 11 and 280mg in 7) and 30 patients with dose reductions of >6 months (lowest dose 140mg in 16 and 280mg in 15). There were 4 deaths before 1 year in group B, 2 patients dying on therapy and 2 within 14 days of stopping. Major AEs associated with the final illness were infection (1), upper GI toxicity (1), and not given (2). All 4 deaths occurred in patients who were dose reduced to 140mg. Group B DFS and OS were 89.6% and 91.7%, respectively. There were 92 patients in group C, which included 58 patients with treatment breaks but no dose reductions, and 34 patients who had breaks in therapy and dose reductions. From group C, 32/92 patients were still on ibrutinib at 1 year with 29 patients having died before 1 year. Of the 92 group C patients, 42 were identified by their clinician as having temporary treatment breaks of >14 days in the first year. Of these 42 patients, 8 died before 1 year. Group C DFS and OS were 34.8% and 68.5%, respectively.

Assessing the consequences of dose modifications in a retrospective analysis is inevitably challenging owing to multiple confounding factors, primarily due to the fact that the most ill patients are inevitably the most likely to 'self-select' themselves to be dose reduced/stopped early. In an attempt to control for this, we carried out a post 1 year analysis of patients from group A, B and C, only analyzing patients who were alive in their specific group at 1 year. To be included in this post 1 year analysis, group A patients had to be alive on ibrutinib at the 1 year point with no modifications or breaks of >14 days in the first year, group B had to be alive on ibrutinib at 1 year having had (or having ongoing) dose reductions but no breaks of >14 days. With this prospective analysis from 1 year, we could also split group C into group C1, who were patients who had had temporary breaks of >14 days in the first year, but were alive and taking ibrutinib at 1 year, and group C2, who were patients who had stopped ibrutinib permanently before 1 year, but were alive at 1 year. The split of these patient groups are shown in a flow chart (*Online Supplementary Figure S2*). Patient numbers were: A=157, B=44, C1=32 and C2=31. The hazard ratios for DFS and OS beyond 1 year are shown in Table 4 and the Kaplan-Meier plots for DFS and OS beyond 1 year are shown in Figure 5.

Patients who have had dose reductions in the first year (group B), rather than treatment breaks (groups C1 and C2) appear to have very similar outcomes to patients who have been treated with no dose reductions (group A), within the constraints of the limited follow-up of this study. However, patients who have had temporary treatment breaks (>14 days) within the first year (group C1) appear to have an almost 4-fold increase in the risk of stopping ibrutinib beyond one year. The same trend is seen for the risk of death post 1 year (P<0.0001), though the assumption of proportional hazards does not hold for this comparison (P=0.015) so the hazard ratios are not valid; at the median follow-up of 16 months the OS rates in groups A and B are very similar (96.5% and 100%, respectively), but these drop to 85.4% in group C1 and just 68.1% in group C2. These combined results suggest that post 1 year survival does not appear to be compromised by dose reductions in ibrutinib, but does appear to be compromised by both temporary and permanent breaks in ibrutinib therapy.

By analyzing the patients alive at one year, we were also able to see whether the number of prior lines of therapy or pre-treatment performance status had any correla-

Table 3. Dominant reason given for ibrutinib dose reductions in 82 patients who dose reduced within the first year of treatment.

Dominant reasons given for dose reducing ibrutinib	Number of patients
Lower / upper GI toxicity	15 / 2
Cytopenias	14
Infection	14
Physician decision due to general debility	10
Abnormal liver function tests	6
Atrial fibrillation / coagulation issues	6
Hemorrhage / bruising	5
Arthralgias / musculo-skeletal	4
Mouth ulcers	2
Dermatological	1
Cardiac failure	1
Deterioration of Parkinson's disease	1
Not specified	1

GI: gastro-intestinal.

tion with the first year dose reductions and treatment breaks. We could not demonstrate any statistically significant association between the number of prior lines of therapy and either dose reductions or treatment breaks. However, there did appear to be a correlation between poorer performance status and higher frequency of treatment breaks. Of the 207 PS 0/1 patients alive at one year, they were split between groups A to C2 as follows: 62.8% (A); 17.4% (B); 10.1% (C1); 9.7% (C2). The 58 PS2+ patients alive at one year were split as follows: 48.3% (A); 13.8% (B); 19% (C1); 19% (C2), indicating that less than half of the poor performance status patients had no treatment modifications by one year, and twice as many had temporary and permanent treatment breaks in the first year compared to PS 0-1 (P=0.033).

Discussion

The RESONATE trial established ibrutinib as an effective therapy for relapsed/refractory CLL,[1] and ibrutinib is now a recommended therapy in this setting in European

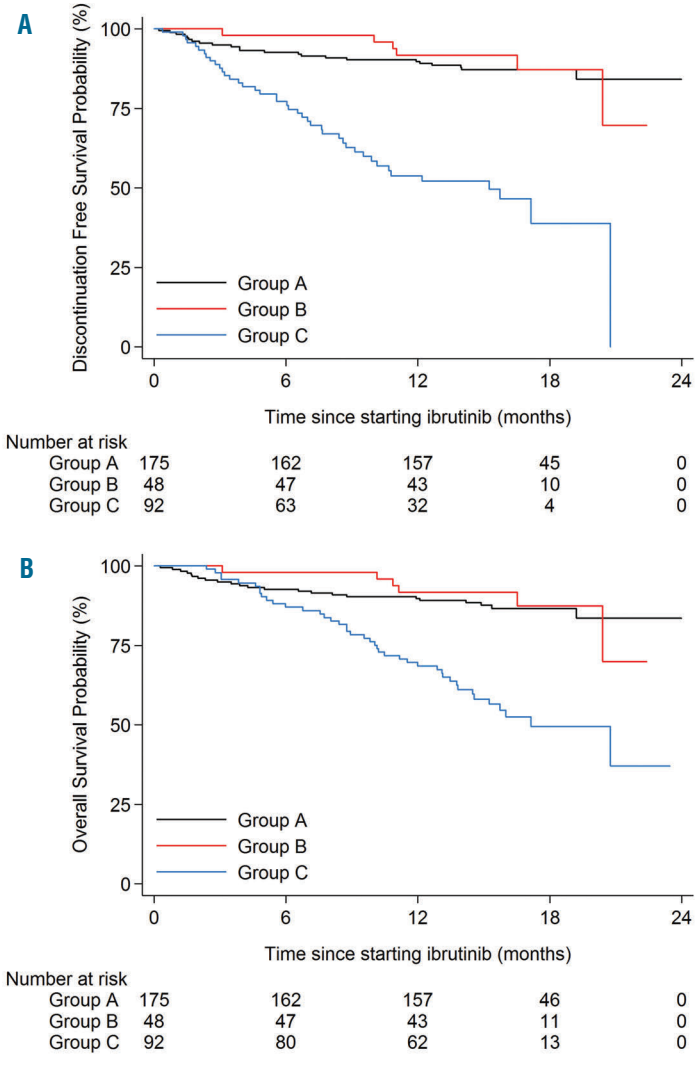

Figure 4. Kaplan-Meier plots of discontinuation-free survival (DFS) (A) and overall survival (OS) (B) of patients divided into group A, B or C as per definition in the text.

Table 4. Hazard ratios with 95% confidence intervals for OS and DFS for the 4 separate treatment compliance groups.

	DFS			OS*		
	Events/N	HR(95% CI)	*P*	Events/N	HR(95% CI)	*P*
Treatment group						
A	11/157	1.00	0.045	5/157	1.00	<0.0001
B	4/44	1.58 (0.49 – 5.06)		2/44	1.38 (0.27 – 7.12)	
C1	5/32	3.76 (1.24 – 11.39)		5/32	5.76 (1.65 – 20.08)	
C2	-	-		8/31	9.30 (3.04 – 28.45)	

*For this analysis, the origin time for DFS and OS was taken as the 1 year time point. *Fails the proportional hazards assumption – HR can only be interpreted as an average over time. HR: hazard ratio; OS: overall survival; CI: confidence interval; DFS: discontinuation-free survival.*

and US clinical guidelines.[3,4,5] There is considerable interest in real-world experience with this drug outside clinical trials, and this UK/Ireland evaluation represents the largest multi-center dataset of ibrutinib patients treated off-trial with a median follow-up of 16 months for surviving patients. Patients in this analysis were treated in 62 centers, ranging from small district general hospitals to large university teaching centers. The 1 year overall survival for the cohort was strikingly better than patients treated in historical relapsed/refractory CLL trials,[6,7] however, the patients in this evaluation appeared to fare less well than patients treated in the RESONATE trial. The patients in this study were similar in terms of age, number of prior therapies and 17p deletion status to the patients recruited into the RESONATE trial, which has now been presented with 16 months median follow-up with a 12 month progression-free survival (PFS) of 84% and overall survival of 90%.[2] Although our UK/Ireland dataset does not have a PFS, the 1 year absolute survival was inferior to the RESONATE 1 year PFS. Although DFS and PFS are only approximate equivalents, it does appear that the real-world rate of ibrutinib discontinuation rate and death rate appear higher than patients treated within the RESONATE trial. This real-world observation is not limited to the UK/Ireland data. The single-center Mayo clinic data included 124 relapsed/refractory CLL patients with a median follow-up of 6.4 months and has been presented as an abstract.[8] The estimated proportion of patients continuing ibrutinib at 6 months was 84% (95% CI: 77-92%) and at 12 months was 70% (95% CI: 59-83%), both figures being similar to the UK/Ireland data. Furthermore, the multi-center Swedish experience presented data on 95 CLL patients treated for a median of 10.2 months, with a 10 month PFS of 77% and OS of 83%.[9]

There are a number of potential reasons why the rates of ibrutinib discontinuation and survival are likely to be worse in a real-world setting than in a clinical trial. Patients treated outside of a clinical trial are more likely to have poorer performance status and more comorbidities. Nearly a quarter of the UK/Ireland patients had a pre-treatment performance status that would have excluded them from the RESONATE trial, and 45% of the Swedish patients had pre-treatment criteria that would have excluded them from RESONATE. If only PS 0/1 patients from the UK data are considered, then DFS of 77.5% and OS of 86.3% are closer to the figures from the RESONATE trial. Our data are the first to confirm that a poorer pre-treatment PS (2+) is significantly associated with reduced discontinuation-free and overall survival (16.2% and 9.3% lower at 1 year, respectively). We have also shown that of the patients who were alive at 1 year, the PS 2+ group were significantly more likely to have had treatment breaks during the first year of therapy. Interestingly, there appears to be an ongoing divergence of survival curves beyond 1 year for good and poor PS patients, suggesting ongoing consequences for patients who are less well when therapy commences.

Patients treated within a clinical trial have more stringent rules for dose modifications/dose interruptions that are likely to translate into higher levels of drug compliance. Dose reductions/breaks were reported in 4% of patients in the RESONATE trial and 10% in the Ohio State series,[10] whereas 26% of the UK/Ireland cohort had a dose reduction of ibrutinib (with or without treatment breaks), and 19% of patients had treatment breaks (temporary and permanent) with no dose reductions. It is difficult to compare the relative frequency of dose modifications with the clinical trial data exactly, as treatment breaks in particular can be classified in different ways. However, it seems clear that the extent of dose modification was much higher in this UK/Ireland series than in the published trials. The reasons given for dose reductions and treatment breaks predominantly fit within the expected AE profile of relapsed/refractory CLL patients treated with ibrutinib, with infection, cytopenias, bleeding issues, and gastro-intestinal toxicity being the recurring reasons cited for both temporary and permanent dose reductions and therapy breaks. It is not clear why the rates of modifications were so high in our study, although the inclusion of poorer PS patients was a likely contributing factor, and there was variation in practice between centers. We could not, however, demonstrate clear differences in outcomes between centers grouped by size/number treated/university hospital status etc. (*data not shown*). It seems unlikely that these dose modifications would have been permitted within the context of a clinical trial, and although a direct causal link between dose modifications and inferior outcomes cannot be made from our data, it does appear from our data that treatment breaks in particular are associated with inferior outcomes both at 1 year, and beyond 1 year for patients who were alive and had re-started ibrutinib by the 1 year

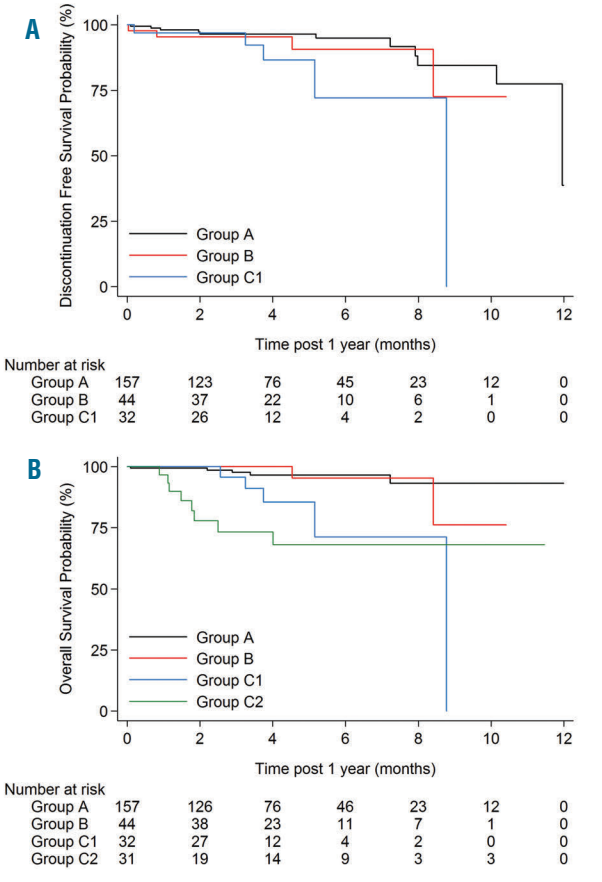

Figure 5. Kaplan-meir plots of discontinuation-free survival (DFS) (A) and overall survival (OS) (B) for groups A, B, C1 and C2 showing survival beyond one year.

time point. In contrast, we could not identify any statistically significant inferiority for DFS and OS up to and beyond 1 year for patients who were only dose reduced but had minimal treatment breaks. Our data therefore suggest that continuous therapy with ibrutinib (excepting minimal breaks) throughout the first year is required for optimal outcomes, but raises the question as to whether 420mg is required to gain maximal benefit from the drug. Therefore, if clinicians feel the need to dose modify therapy due to an AE, dose reduction may potentially be preferable to treatment cessation. Of course, there are major limitations to our retrospective dataset, particularly the limited follow-up, thus, whether or not dose reductions compromise longer term outcomes will only be answered by prospective clinical trials which are currently recruiting.

With regards to the permanent discontinuation of ibrutinib, it is clear that the drug was stopped in far fewer patients due to an AE in the RESONATE and Ohio State trials (4% and 12% with 9.4 months and 3 years follow-up, respectively) than in real-world datasets. Despite shorter follow-up in the Swedish and Mayo Clinic datasets, 10.5% and 12.1%, respectively, of patients in these real-world series stopped ibrutinib for an AE other than progressive disease, although both these figures are smaller than the 17.5% observed in the UK/Ireland series. Together these results suggest that higher rates of ibrutinib discontinuation are to be expected when patients are treated off-trial. When the reasons for permanent discontinuation of ibrutinib are compared between real-world datasets, there are some similarities. In the UK/Ireland, Swedish and Mayo clinic series, infection is the commonest single reason other than Richter's transformation/progressive CLL for permanent discontinuation of ibrutinib, and infection is also the dominant cause of death, other than Richter's transformation/progressive CLL in the UK/Ireland and Swedish series. After stopping ibrutinib within the first year of treatment, a notable feature of our dataset is the short OS. If patients who died while still taking the drug are excluded from the analysis, the median survival was 95 days, which appears shorter than reported in other series.[8] The reasons for this are not clear, but the lack of access to alternative non-chemotherapy treatments in the UK/Ireland after ibrutinib discontinuation could be a contributing factor.

Although our data suggested a slightly inferior 1 year DFS for 17p deleted patients (71.1% *vs.* 77.7%), this was not statistically significant, and OS at 1 year was similar (84.4% *vs.* 86.7%). This contrasts with published data, where, with longer follow-up, patients with TP53 disruption have worse PFS and OS.[10] Potentially, this separation could be seen with our data with a longer follow-up period. Our data contrasts markedly with the Swedish data, where Kaplan-Meier plots of PFS and OS show very early divergence for patients with 17p deletion. The reasons for these differences are not clear. We also looked at the effect of prior lines of therapy on 1 year outcomes. With the updated abstract presentation of RESONATE at 16 months median follow-up, there is a suggestion that patients treated with 1 prior line of therapy compared with 2+ prior lines of therapy had a statistically meaningful PFS advantage at 12 months (94% *vs.* 82%). Although it would be reasonable to expect a more heavily pre-treated group of patients to be enriched for poorer prognostic features such as poorer PS and higher levels of 17p deletion, with univariable analysis we could not see any outcome differences for more or less heavily pre-treated patients. With our data, DFS and OS were highly similar for patients treated with 1, 2 or 3+ prior lines of therapy with no suggestion of divergence of survival curves beyond 1 year, although these curves could potentially separate with longer follow-up. However, when pre-treatment variables of age, sex, PS, 17p status and prior lines of therapy were subject to multivariable analysis, significant interactions were uncovered. PS remains statistically significant, but it also appears that older patients and those with 17p deletion have inferior DFS and OS when treated beyond first relapse. These results are biologically plausible. It is highly likely that a 17p- patient treated with ibrutinib beyond the second line of therapy would have had a subclone of 17p- CLL cells when treated with earlier lines of chemotherapy. Potentially, these earlier lines of treatment could contribute to more genomic complexity and worse outcomes when treated with ibrutinib including and beyond the third line of therapy, although this remains speculation at this stage.

As response assessments in routine practice do not include bone marrow biopsy and CT scan assessments, it was not possible to accurately verify remission status in this evaluation. We therefore grouped all patients who achieved at least a partial remission (or PR + lymphocytosis) together as responding patients. Overall, the response rate of 85% in this study was identical to the investigator-assessed response rate in the RESONATE trial. As expected, patients who were classified by their clinician as responding to therapy demonstrated a markedly superior DFS and OS compared with non-responding patients. Although we could not demonstrate any clear differences in the incidence of dose reductions/temporary treatment breaks between patients classified as responder or non-responder (*data not shown*), the DFS and OS rates for responding patients who had no dose reductions and no treatment break of >14 days were excellent, with 95% (152/160) of patients in this group alive and continuing on ibrutinib treatment at 1 year.

In conclusion, with this presentation of the largest non-trial multi-center dataset of ibrutinib-treated relapsed/refractory CLL patients, we confirm that ibrutinib is a highly effective, generally well tolerated drug in this population, although our data and other real-world datasets suggest overall outcomes in routine clinical practice are inferior to those observed in the pivotal clinical trials. While it seems likely that some of the inadequecy reflects the treatment of poorer PS patients in the non-trial setting, it also remains possible that the unexpectedly high incidence of treatment breaks in the UK/Ireland practice could have been contributory. The lack of access to other CLL therapies in the UK/Ireland could also have contributed to the short OS observed following ibrutinib cessation.

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