A clinical practice comparison of patients with chronic lymphocytic leukemia with and without deletion 17p receiving first-line treatment with ibrutinib

Anthony R. Mato,[1] Boxiong Tang,[2] Soraya Azmi,[2] Keri Yang,[2] Xiaojuan Zhang,[3] Jennifer C. Stern,[4] Eric Hedrick,[4] Jane Huang,[5] and Jeff P. Sharman[6]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]BeiGene, Ltd., Emeryville, CA, USA; [3]BeiGene (Beijing) Co., Ltd, Beijing, China; [4]BeiGene, Ltd., Cambridge, MA, USA; [5]BeiGene USA, Inc., San Mateo, CA, USA and [6]Willamette Valley Cancer Institute / US Oncology Research, Eugene, OR, USA

Abstract

Among patients with chronic lymphocytic leukemia (CLL) with deletion 17p (del[17p]), evidence from clinical trials for the effectiveness of single-agent ibrutinib as first-line therapy is limited. This retrospective analysis compared real-world clinical outcomes among patients with CLL, with and without del(17p), treated with first-line ibrutinib monotherapy. Overall survival, time to next treatment, time to treatment discontinuation, and reasons for ibrutinib discontinuation were evaluated. Using data from a real-world database, patients included were aged ≥18 years, had been diagnosed with CLL between January 1, 2011 and December 31, 2019, had undergone cytogenetic testing, and had received first-line ibrutinib monotherapy. A total of 1,069 patients were included in the analysis (62.7% male; median age 69 years); 23.8% (n=254) had del(17p). The median overall survival was significantly shorter in patients with del(17p) than in patients without (57.7 months *vs.* not reached; *P*=0.0006). Similar results were observed for median time to next treatment (49.4 months *vs.* not reached, *P*=0.0330). The median time to treatment discontinuation was non-significantly shorter in the group of patients with del(17p) (32.5 months *vs.* 42.9 months, *P*=0.3370). Results of an adjusted Cox proportional hazards model showed that the group with del(17p) was at significantly higher risk of death than was the group without del(17p) (hazard ratio=1.70, *P*=0.0031). Event rates for switching to new treatment and discontinuation were higher but not statistically significantly so. The most common reason for discontinuing ibrutinib treatment in both groups was toxicity, but discontinuation due to progression was significantly more frequent among patients with del(17p) (20% *vs.* 6%; *P*<0.0001). This study identifies an unmet need for more effective first-line therapeutic options in patients with CLL/small lymphocytic lymphoma and del(17p), despite the advent of ibrutinib.

Introduction

In patients with chronic lymphocytic leukemia (CLL), the presence of molecular-cytogenetic lesions such as deletion 17p (del[17p]), *TP53* mutations, and/or expression of unmutated immunoglobulin heavy chain variable region (*IGHV*) confers a negative prognostic outcome.[1-3] Among these, del(17p) and *TP53* mutations are the least favorable, with patients considered at very high risk of having a poor response to initial chemoimmunotherapy or earlier relapse after achieving remission.[1,2] This unfavorable prognosis has been attributed to the del(17p)-mediated loss of one allele of *TP53*, a tumor suppressor that plays a crucial role in apoptosis, cell cycle arrest, and DNA repair in response to genotoxic insults.[4] Del(17p) is more common in relapsed/refractory CLL, but it does occur in treatment-naïve patients, albeit at lower rates.[5,6]

Overall, the prognosis for patients with CLL and small lymphocytic lymphoma (SLL) has improved with the advent of Bruton tyrosine kinase (BTK) inhibitors. The first drug in this class, ibrutinib, was approved by the US Food and Drug Administration (FDA) in February 2014 for the treatment of patients with relapsed/refractory CLL. This approval was based on results from the pivotal RESON-ATE trial, which showed that ibrutinib had efficacy in a heavily pretreated cohort of patients. However, this study included only patients with relapsed/refractory disease, and found that overall survival at 18 months was 86% and

progression-free survival was 76% in the ibrutinib arm, while in patients with del(17p) the corresponding values were 83% and 71%, respectively.[7,8] Following this, the RESONATE-2 trial was performed in the front-line setting and showed that ibrutinib was effective for treatment-naïve patients. Based on these data, FDA approval for ibrutinib was extended to first-line therapy.[9] However, RESONATE-2 excluded two key groups of patients: individuals younger than 65 years and those with del(17p).[10] Therefore, findings from this trial do not directly reflect and may not be generalizable to these high-risk patients.[11,12]

Additional research has shown favorable outcomes for patients with del(17p) CLL/SLL treated with ibrutinib, but has largely focused on patients with relapsed/refractory disease. The phase II RESONATE-17 trial was a single-arm open-label study including 144 patients with del(17p) CLL/SLL; it showed an estimated 24-month overall survival of 75% with ibrutinib monotherapy for this population of patients.[13] Likewise, an integrated analysis of three studies of ibrutinib in patients with relapsed/refractory del(17p) CLL/SLL found an estimated 12-month overall survival of 85%.[14] The Alliance trial provided some insight into front-line ibrutinib use in older patients.[15] However, the trial was not powered to compare results between patients with and without del(17p). Meanwhile, the phase II National Heart, Lung, and Blood Institute (NHLBI) trial investigating ibrutinib use in front-line treatment of CLL patients with *TP53* alterations is ongoing.[16] As such, options for front-line treatment of del(17p) CLL/SLL are largely extrapolated from experience in the relapsed/refractory setting. While ibrutinib has shown convincing data in this population to date, gaps still exist within the available data.

The aim of this observational retrospective study was to compare outcomes of patients with CLL/SLL, with and without del(17p), who received first-line ibrutinib monotherapy, in terms of the following outcomes: overall survival, time to next treatment, time to treatment discontinuation, and reasons for ibrutinib discontinuation. The study used information from the Flatiron Health electronic health record–derived database, one of the largest electronic datasets of community oncology practices in the USA.

Methods

Objectives
Study objectives were to (i) describe and compare baseline characteristics among patients with CLL/SLL with and without del(17p) receiving first-line ibrutinib monotherapy, (ii) compare real-world overall survival, time to next treatment, and time to treatment discontinuation, and (iii) evaluate the reasons for ibrutinib discontinuation in the two groups.

Study design and cohort selection
De-identified patients' data were obtained from the Flatiron Health electronic health record–derived database. The initial cohort of patients was selected based on CLL/SLL codes (ICD-9: 204.10-12, or ICD-10: C91.1x, C83.0x). Patients also had to have had two or more clinic encounters and one or more antineoplastic therapy order between January 1, 2011 and December 31, 2019, along with cytogenetic testing confirming del(17p) status at or before initiation of first-line ibrutinib therapy. Patients were included in the final analysis cohort only after manual chart review, including physician confirmation of diagnosis. Patients who initiated CLL/SLL treatment before entering the Flatiron Health network were excluded. Figure 1 illustrates the steps for selecting the patients.

Definitions
The index date was defined as the start of first-line ibrutinib monotherapy. Patients' characteristics of interest were: disease subtype; Rai stage at diagnosis; Eastern Cooperative Oncology Group (ECOG) status at index date; del(17p), del(11q), del(13q), trisomy 12, and *IGHV* mutation status; and time from diagnosis to, and follow-up from, index date.

Overall survival was defined as the time between the index date and death, with patients otherwise censored at their last date of confirmed electronic health record activity. Time to next treatment was the time from the index date to initiation of a subsequent non-ibrutinib line of therapy, or to date of death (patients with no subsequent line of therapy). Time to treatment discontinuation was the time from the index date to discontinuation of ibrutinib for any reason; discontinuation was defined as an abstraction-confirmed discontinuation episode, death, or lack of prescription despite structured activity within the Flatiron Health network in ≥120 days after the last ibrutinib treatment. Additional details regarding the definition of a discontinuation event are provided in the *Online Supplementary Material* (section 1). Reasons for ibrutinib discontinuation were classified as due to disease progression, toxicity, patient's request, financial reasons, disease-related symptoms not due to therapy, treatment completion, or other (including death).

Ethics review
Institutional Review Board approval of the study protocol was obtained prior to conducting the study and included a waiver of informed consent.

Statistical analysis
Descriptive statistics were used to summarize patients' characteristics. Between-group comparisons were based on the Kruskal-Wallis test for medians and the *t*-test for means.

Overall survival and time to next treatment were estimated using Kaplan-Meier curves, along with median durations and 95% confidence intervals (95% CI). Time to treatment discontinuation was modeled using non-parametric maximum likelihood estimator due to interval censoring. Outcomes were compared using log-rank testing or the Sun log-rank test (2-sided significance level, 0.05). The *Online Supplementary Material* (section 2) contains additional details regarding these statistical tests. Cox proportional hazards model comparisons (unadjusted and adjusted) were also conducted, with adjustments made for index year; sex; age; ECOG status; Rai stage; practice type; 11q, 13q, trisomy 12 deletion; and *IGHV* status. Descriptive statistics were used to summarize reasons for ibrutinib discontinuation, with comparisons made using the χ^2 or Fisher exact test (2-sided significance level, 0.05).

Results

The analysis cohort consisted of 1,069 patients; of these, 254 (23.8%) had a del(17p) and 815 (76.2%) patients did not have del(17p). The baseline characteristics of the patients, categorized by the presence or absence of del(17p), are shown in Table 1. The median age at diagnosis was similar for both groups of patients (70 years for those with del[17p]; 69 years for those without del[17p]). In terms of index year, only one patient entered the study in 2013, while the largest proportion of study patients (26.7%) enetered the study in 2018. Most patients were treated in community practices (94.6%), with the remainder (5.4%) treated in an academic setting.

At diagnosis, patients with del(17p) were more likely to be at a later Rai stage (*P*=0.0002); 9.1% and 10.2% of patients with del(17p) were at Rai stage 3 and 4, respectively, compared to 5.3% and 6.6% of patients without del(17p). Patients with del(17p) also received first-line ibrutinib sooner after diagnosis, with a median 0.8 years from diagnosis to index date, compared to 2.3 years for patients without del(17p) (*P*<0.0001). Overall, the median follow-up was 17.5 months. Meanwhile, the median follow-up was longer in the group with del(17p) (20.4 months) than in the group without del(17p) (16.3 months, *P*=0.0001). A majority of patients (58.2%) had ECOG performance status ≤1 at entry into the study, with no significant differences between the two groups. In terms of other genetic prognostic factors, as shown in Table 2, there was a statistically significant difference between the percentages of patients with and without del(17p) who also had deletion 11q (*P*<0.0001), deletion 13q (*P*=0.0238), trisomy 12 (*P*<0.0001), or *IGHV* mutated status (*P*=0.0227).

Outcomes of interest, including median overall survival, time to next treatment, and time to treatment discontinu-

ation, are summarized in Table 3. For the overall cohort, median overall survival and median time to next treatment were not reached, while the median time to treatment discontinuation was 38.6 months (95% CI: 33.4, 42.9). The
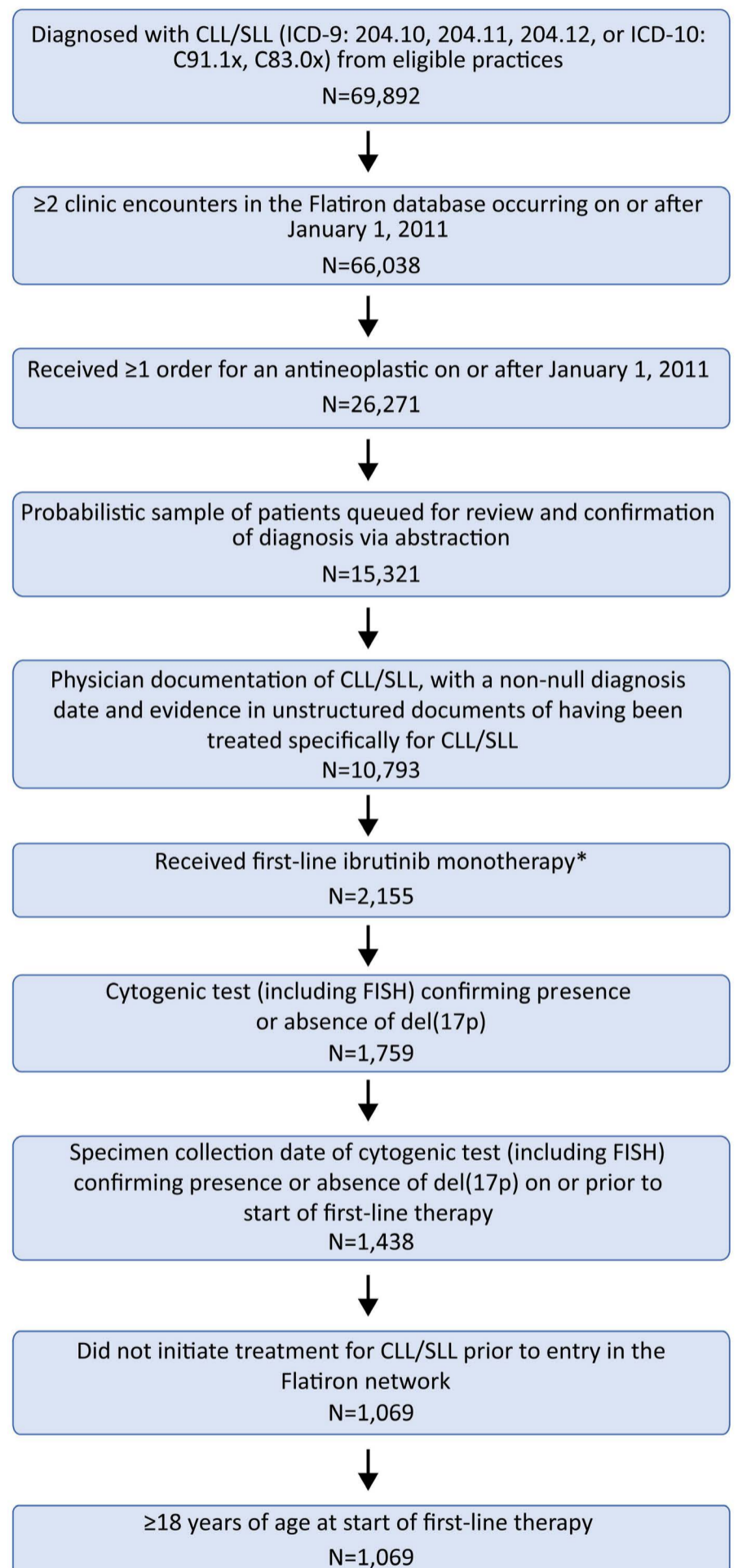

Figure 1. Selection of the study population. *One patient started ibrutinib in 2013, prior to its approval; the remainder started ibrutinib therapy between 2014-2019. CLL: chronic lymphocytic lymphoma; Del(17p): 17p deletion; FISH: fluorescence *in situ* hybridization; SLL: small lymphocytic lymphoma.

median overall survival was shorter in the group with del(17p) (57.7 months) than in the group without del(17p), in which the median was not reached (*P*=0.0006) (Table 3; Figure 2A). The median time to next treatment was also significantly shorter in the group with del(17p) than in the group without del(17p) (49.4 months *vs.* not reached; *P*=0.0330). The median time to treatment discontinuation was shorter in the group with del(17p) than in the group without del(17p); however, this difference was not statistically significant (32.5 months *vs.* 42.9; *P*=0.3370). In terms of event rates in the overall cohort, the rates of death, switching to a new treatment, and treatment discontinuation were 15.0%, 24.2%, and 32.1%, respectively (*data not shown*). As shown in Table 4, the rate of death

Table 1. Description and comparison of patients' characteristics.

Patients' characteristics	All N=1,069	Del(17p) present N=254	Del(17p) absent N=815	*P* value
Sex, n (%)				
Female	399 (37.3)	99 (39.0)	300 (36.8)	0.5331
Male	670 (62.7)	155 (61.0)	515 (63.2)	
Age in years at diagnosis				
Median (IQR)	69 (61-76)	70 (62-78)	69 (61-76)	0.2214
Range	31-85	35-85	31-85	
Disease subtype, n (%)				
CLL	884 (82.7)	211 (83.1)	673 (82.6)	0.9569
CLL/SLL	122 (11.4)	29 (11.4)	93 (11.4)	
SLL	63 (5.9)	14 (5.5)	49 (6.0)	
Rai stage at diagnosis, n (%)				
0	301 (28.2)	46 (18.1)	255 (31.3)	
I	171 (16.0)	39 (15.4)	132 (16.2)	
II	53 (5.0)	18 (7.1)	35 (4.3)	0.0002
III	66 (6.2)	23 (9.1)	43 (5.3)	
IV	80 (7.5)	26 (10.2)	54 (6.6)	
Unknown	398 (37.2)	102 (40.2)	296 (36.3)	
ECOG PS at index date, n (%)				
0	347 (32.5)	72 (28.3)	275 (33.7)	
1	275 (25.7)	66 (26.0)	209 (25.6)	0.1364
2+	92 (8.6)	18 (7.1)	74 (9.1)	
Unknown	355 (33.2)	98 (38.6)	257 (31.5)	
Year of index date, n (%)				
2013	1 (0)	0	1 (0)	
2014	26 (2.4)	12 (4.7)	14 (1.7)	
2015	53 (5.0)	37 (14.6)	16 (2.0)	
2016	183 (17.1)	46 (18.1)	137 (16.8)	<0.0001
2017	246 (23.0)	55 (21.6)	191 (23.4)	
2018	286 (26.7)	63 (24.8)	223 (27.4)	
2019	274 (25.6)	40 (15.7)	234 (28.7)	
Years from diagnosis to index date				
Median (IQR)	1.9 (0.3-4.8)	0.8 (0.1-3.0)	2.3 (0.4-5.5)	<0.0001
Mean (SD)	3.5 (4.7)	2.5 (4.7)	3.8 (4.7)	0.0002
Range	0.0-38.4	0.0-36.4	0.0-38.4	
Follow-up in months from index date				
Median (IQR)	17.5 (8.3-31.1)	20.4 (10.4-36.7)	16.3 (8.1-29.4)	0.0001
Mean (SD)	20.7 (14.9)	24.5 (16.8)	19.5 (14.0)	<0.0001
Range	0.2-72.1	0.3-72.1	0.0-70.5	
Practice type, n (%)				
Academic	58 (5.4)	16 (6.3)	42 (5.2)	0.4815
Community	1011 (94.6)	238 (93.7)	773 (94.8)	

CLL: chronic lymphocytic lymphoma; Del(17p): 17p deletion; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; PS: performance status; SD: standard deviation; SLL: small lymphocytic lymphoma.

Table 2. Mutation status based on fluorescence *in situ* hybridization and classical cytogenetic testing.

Mutation status		All N=1,069	Del(17p) present N=254	Del(17p) absent N=815	P value*
Deletion 11q, N (%)	Present	190 (17.8)	44 (17.3)	146 (17.9)	<0.0001
	Absent	856 (80.1)	193 (76.0)	663 (81.3)	
	Unknown	23 (2.2)	17 (6.7)	6 (0.7)	
Deletion 13q, N (%)	Present	502 (47.0)	122 (48.0)	380 (46.6)	0.0238
	Absent	549 (51.4)	123 (48.4)	426 (52.3)	
	Unknown	18 (1.7)	9 (3.5)	9 (1.1)	
Trisomy 12, N (%)	Present	286 (26.8)	49 (19.3)	237 (29.1)	<0.0001
	Absent	757 (70.8)	191 (75.2)	566 (69.4)	
	Unknown	26 (2.4)	14 (5.5)	12 (1.5)	
IGHV status, N (%)	Mutated	174 (16.3)	31 (12.2)	143 (17.5)	0.0227
	Unmutated	271 (25.4)	65 (25.6)	206 (25.3)	
	Indeterminate	33 (3.1)	3 (1.2)	30 (3.7)	
	Unknown	591 (55.3)	155 (61.0)	436 (53.5)	

*Evaluates comparison of distribution between groups in which del(17p) is present and absent. Del(17p): 17p deletion; *IGHV*: immunoglobulin heavy chain variable.

Table 3. Median overall survival, time to next treatment, and time to treatment discontinuation.

Outcome	Group	Number of patients	Number of events	Median months	95% CI months	Log-rank P value
OS	All	1,069	160	NR	63.2-NR	-
	Del(17p) present	254	64	57.7	51.8-NR	0.0006
	Del(17p) absent	815	96	NR	NR-NR	-
TTNT	All	1,069	259	NR	49.4-NR	-
	Del(17p) present	254	86	49.4	38.0-NR	0.0330
	Del(17p) absent	815	173	NR	NR-NR	-
TTD*	All	1,069	343	38.6	33.4-42.9	-
	Del(17p) present	254	95	32.5	24.0-39.4	0.3370†
	Del(17p) absent	815	248	42.9	38.1-48.4	-

*Time to treatment discontinuation was estimated using non-parametric maximum likelihood estimator. †Calculated with the Sun log-rank test for interval censoring. CI: confidence interval; Del(17p): 17p deletion; NR: not reached; OS: overall survival; TTNT: time to next treatment; TTD: time to treatment discontinuation.

among patients with del(17p) was higher at 25.2% *versus* 11.8%, as were rates of starting a new treatment and discontinuation (33.9% *vs*. 21.2% and 37.4% *vs*. 30.4%, respectively). Cox proportional hazard models showed that the hazard ratios (HR) for overall survival, time to next treatment, and time to treatment discontinuation were consistent with these findings. In the adjusted analysis, patients in the group with del(17p) were significantly more likely to die than those without del(17p) (HR=1.7; 95% CI: 1.20, 2.42; *P*=0.0031). Additionally, although not statistically significant, patients with del(17p) were 1.3 times more likely to receive subsequent therapy (95% CI: 0.97, 1.71; *P*=0.0784). At 1 year of treatment, patients with and with-

out del(17p) had overall survival rates of 88% (95% CI: 83.1, 91.6) and 92% (95% CI: 89.7, 93.8), respectively (*data not shown*). As shown in Table 5, out of 1,069 patients, 37% (n=395, including 52 with interval censorings) discontinued ibrutinib treatment for any reason. A significantly higher proportion of patients with del(17p) than without del(17p) discontinued ibrutinib treatment due to disease progression (20% *vs*. 6%; *P*<0.0001). When considering all other reasons for discontinuation (except for disease progression) overall discontinuation rates were higher in the group without del(17p) (81% *vs*. 94%; *P*<0.0001). Among all individual reasons given for discontinuation, toxicity was the most common (44% in

the overall group). Meanwhile, toxicity rates in patients with del(17p) were significantly lower than in those without del(17p) (35% *vs.* 48%; *P*=0.0357). Although numbers were small, our results indicate that patients without del(17p) were also more likely to discontinue ibrutinib treatment based on patients' request or disease-related symptoms not due to therapy. Both interval- and right-censored data effects existed in the discontinuation analysis. The *Online Supplementary Material* provides detailed outputs for the discontinuation analysis conducted using non-parametric maximum likelihood estimator. *Online Supplementary Table S1* shows sample distributions by censoring status, while *Online Supplementary Table S2* details quantile estimates for the population, stratified by del(17p) status.

Discussion

The initial management of patients with CLL/SLL with del(17p) requires special attention as they are at higher risk of rapid disease progression. Chemotherapy is no longer the standard of care in this population of patients, and the optimal treatment strategy for them is still evolving.[12] While BTK inhibitors are currently considered a standard of care for these patients in the first-line setting, there is still room for improvement in defining the best approach.[1-3,17] This retrospective cohort analysis was conducted to improve clinical understanding of the impact of first-line ibrutinib monotherapy for patients with CLL/SLL, particularly those with del(17p), in the real-world setting. As expected, our study showed that patients with del(17p) had poorer outcomes than those without del(17p). Specifically, the median overall survival and time to next treatment were significantly shorter for patients with del(17p) than for those without, while time to treatment discontinuation was non-significantly shorter with discontinuation mostly due to progression and toxicity. Furthermore, while the median overall survival and time to next treatment were not reached among patients without del(17p), among patients with the deletion, median survival following discontinuation of ibrutinib was relatively short (approximately 8 months) inferred from a median time to next treatment in this group of 49.4 months while the overall survival was 57.7 months.
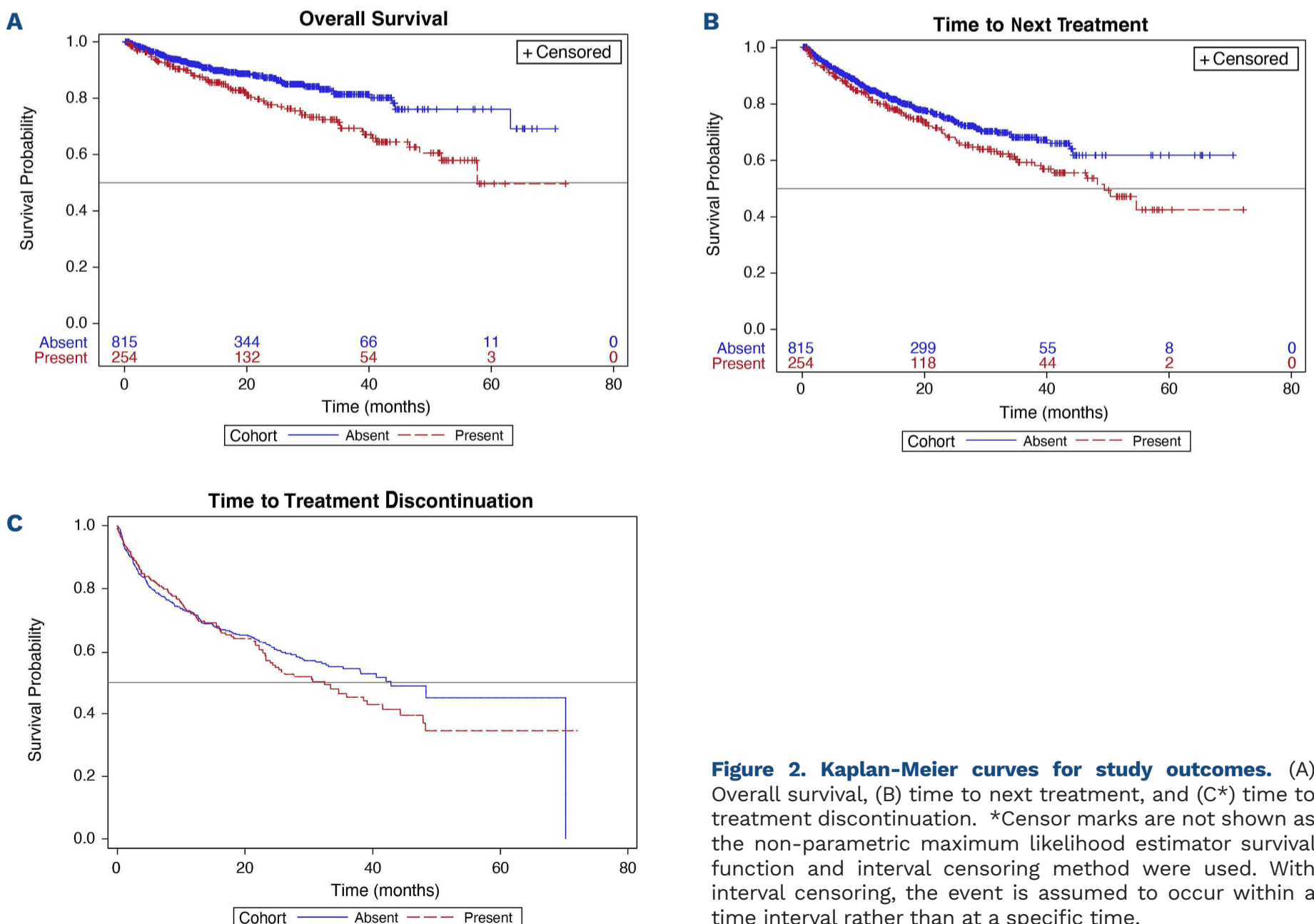

Figure 2. Kaplan-Meier curves for study outcomes. (A) Overall survival, (B) time to next treatment, and (C*) time to treatment discontinuation. *Censor marks are not shown as the non-parametric maximum likelihood estimator survival function and interval censoring method were used. With interval censoring, the event is assumed to occur within a time interval rather than at a specific time.

Table 4. Cox proportional hazards model results: del(17p) present *vs.* del(17p) absent.

	Outcome	Event rate, %	Hazard ratio	95% CI	*P* value
Unadjusted analyses					
OS	Del(17p) present	25.2	1.74	1.27-2.40	0.0007
	Del(17p) absent	11.8	(reference)		
TTNT	Del(17p) present	33.9	1.33	1.02-1.72	0.0336
	Del(17p) absent	21.2	(reference)		
TTD	Del(17p) present	37.4	1.08	0.87-1.34	0.4720
	Del(17p) absent	30.4	(reference)		
Adjusted analyses*					
OS	Del(17p) present	25.2	1.70	1.20-2.42	0.0031
	Del(17p) absent	11.8	(reference)		
TTNT	Del(17p) present	33.9	1.29	0.97-1.71	0.0784
	Del(17p) absent	21.2	(reference)		
TTD	Del(17p) present	37.4	1.11	0.88-1.39	0.3960
	Del(17p) absent	30.4	(reference)		

*The following covariates are included in the adjusted analyses: sex, age at index date, practice type, Rai stage at diagnosis, Eastern Cooperative Oncology Group performance status at index date, year of index date, deletion 11q status, deletion 13q status, trisomy 12 status, and *IGHV* mutation status. CI: confidence interval; Del(17p): 17p deletion; OS: overall survival; TTD: time to treatment discontinuation; TTNT: time to next treatment.

The current results support findings from a 2018 retrospective cohort analysis of treatment-naïve patients with CLL/SLL (n=391) who received first-line ibrutinib. The study utilized the eligibility criteria of the RESONATE-2 trial while expanding the inclusion criteria to two key groups: patients with del(17p) and individuals younger than 65 years. Overall, at 1 year, the overall survival and progression-free survival were 95% and 92%, respectively, and 81% of surviving patients remained on ibrutinib. However, patients with del(17p) (n=110; 28% of the study population) had inferior 1-year overall survival (89%, HR=3.9; *P*=0.001) and progression-free survival (87%, HR=1.9; *P*=0.04) compared to those without the deletion.[11] The study reported a 1-year overall survival that was very similar to the current results at 1 year (88%). The consistency of this finding is noteworthy for several reasons. First, the Flatiron Health electronic health record–derived database primarily represents patients from community practice settings, as opposed to academic centers, which were predominant in the earlier study, thus reflecting a consistency between both types of practices. In addition, these results may be somewhat more representative of the US population with CLL/SLL, a majority of whom would likely be treated in community practice.[18,19] This analysis also includes data that extend through 5 years of follow-up and is current through to the end of 2019. Finally, this research was based on real-world clinical practice patterns and was not limited by eligibility criteria

applied in prior clinical trials. Thus, compared with the findings of previous research, these results are representative of a broader patient experience with first-line ibrutinib.

Among all patients, toxicity was reported as the most common reason for ibrutinib discontinuation in 35% of patients with del(17p) and 48% without the deletion, which is comparable to findings in previously published studies.[20,21] It was notable that patients without del(17p) were more likely to discontinue due to toxicity than those with del(17p). On the other hand, patients with del(17p) were more likely to discontinue because of disease progression than were patients without the deletion. This could be explained by the fact that patients with del(17p) progress more quickly than those without, as demonstrated by the time to next treatment, a surrogate for progression-free survival, which was shorter in patients with del(17p). It may also reflect an unmet need as it is unlikely that patients with del(17p) experienced fewer toxicities than those without. Rather, this may reflect a choice by clinicians and patients to maintain treatment due to limited viable options within the timeframe of the study. Reducing discontinuations due to toxicity could help to improve overall outcomes. In the ongoing ELEVATE-RR head-to-head trial, acalabrutinib appears to cause lower rates of cardiac adverse events than ibrutinib.[22] In an interim analysis of the head-to-head phase III ALPINE study in patients with relapsed/refractory CLL/SLL,

Table 5. Reasons for discontinuation of ibrutinib treatment.

Reasons for discontinuation of ibrutinib episode*, N (%)	All N=1,069	Del(17p) present N=254	Del(17p) absent N=815	*P*-value
Discontinued for any reason[†] (% of subgroup)	395 (37)	113 (44)	282 (35)	0.0044
Progression	40 (10)	23 (20)	17 (6)	<0.0001
All reasons except progression[††]	357 (90)	91 (81)	266 (94)	<0.0001
Toxicity	174 (44)	39 (35)	135 (48)	0.0357
Patient request	21 (5)	2 (2)	19 (7)	0.0360
Financial reasons	4 (1)	1 (1)	3 (1)	0.1610
Disease-related symptoms not due to therapy	9 (2)	0 (0)	9 (3)	0.0286
Completed treatment	1 (0)	0 (0)	1 (0)	0.1203
Other	163 (41)	50 (44)	113 (40)	0.4460
Unknown	3 (1)	0 (0)	3 (1)	0.1101

*Patients could have multiple discontinuation episodes. The first discontinuation episode was used to define time to discontinuation. [†]Includes 52 interval censored patients. [††]Combined data for toxicity, patient request, financial reasons, disease-related symptoms, completed treatment, other, and unknown. Del(17p): 17p deletion.

zanubrutinib-treated patients had a lower rate of atrial fibrillation/flutter compared to those treated with ibrutinib, as well as a superior response rate and an improved progression-free survival.[23] Despite improved tolerability with next-generation BTK inhibitors, we believe there is still a need to define the best therapeutic approach to treating patients with del(17p).

Ongoing trials investigating combination therapy with targeted agents, including BTK inhibitors, B-cell lymphoma 2 (Bcl-2) antagonists, and/or anti-CD20 monoclonal antibodies may provide insight into improved therapeutic approaches for patients with del(17p). The SEQUOIA study (arm D - zanubrutinib plus venetoclax), the phase II AVO study (cohort 2 - acalabrutinib, venetoclax, and obinutuzumab), the BOVen trial (zanubrutinib, venetoclax, obinutuzumab), and the German CLL Study Group trial CLL-2 GIVe (ibrutinib, venetoclax, obinutuzumab) are directed at or have dedicated del(17p) cohorts.[24-27] These studies could help to distinguish the potential for overlapping toxicities while better defining effective first-line treatments for the management of high-risk CLL, but more time is needed to obtain follow-up data.[28]

Single-agent ibrutinib is currently the most frequently utilized BTK inhibitor as initial treatment for del(17p)-positive patients with CLL/SLL,[2,17] despite a paucity of data specific to this population of patients. In the past year, there has been an increasing number of patients treated with acalabrutinib following its approval in CLL although there are less data available for this agent in patients with del(17p).[29] Nevertheless, we believe that the differences in outcomes of patients with and without del(17p) described

in this study may be applicable to BTK inhibitors as a class and suggest that future randomized clinical studies limited to patients with del(17p) are needed to best define the ideal treatment for this high-risk population. As more treatments and combination regimens appear on the horizon to treat CLL, such as zanubrutinib and other novel agents,[30] opportunities to leverage data from real-world experience and ongoing clinical studies should continue to be taken to answer some of these key questions.

The question remains as to what regimen may work best in the del(17p) population.[3] Anti-CD20 monoclonal antibodies, including rituximab, ublituximab, and obinutuzumab, are under investigation for use in combination with BTK inhibitors, and have shown mixed results. In a randomized trial, the addition of rituximab to ibrutinib did not improve outcomes in previously untreated patients with del(17p).[15,31] However, in a single-arm study, the addition of ublituximab to ibrutinib was shown to safely produce high overall response rates among patients with relapsed/refractory del(17p) CLL/SLL.[32] The subsequent phase III GENUINE trial evaluated ublituximab plus ibrutinib *versus* ibrutinib alone in patients with high-risk relapsed/refractory CLL, defined as the presence of del(17p) and/or del(11q) deletions and/or the *TP53* mutation. Although this study was not powered to evaluate endpoints specific to individual mutation profiles, the authors affirmed that patients with del(17p) treated with ibrutinib alone showed inferior progression-free survival as compared to that of patients without the mutation, and that the addition of ublituximab to the treatment regimen improved these patients' outcomes.[33] In the phase III ELEVATE-TN trial, im-

provements in efficacy (assessed as progression-free survival) with the second-generation BTK inhibitor acalabrutinib, used with or without obinutuzumab, were observed in previously untreated patients with del(17p) compared to those receiving chemoimmunotherapy. In the del(17p) subset, there was no progression-free survival advantage from acalabrutinib-obinutuzumab *versus* acalabrutinib alone.[29] Combining ibrutinib and venetoclax in patients with del(17p) may address these inferior outcomes, while second-generation BTK inhibitors may be associated with fewer toxicity-related treatment discontinuations.

Some limitations of this study must be acknowledged. A key limitation is that this was a real-world study and results are not easily comparable to those of prospective clinical trials. Endpoints that are standard in trials may be lacking in real-world data. For example, our dataset did not contain information on progression in the same way as it is defined in clinical trials. Because progression-free survival data were not available, time to next treatment was used as an imperfect proxy. As mentioned above, our results were in line with those of an earlier retrospective study;[11] however, we note that the survival time after next treatment of 8 months in our study may seem poorer than anticipated based on the ongoing NHLBI phase II trial (n=34 patients with *TP53* alterations),[16] which reported a median post-progression survival of 25 months. In addition to differences in study approach, other factors, such as age (median 69 years in this study *vs.* 63 years in the NHBLI trial), may have led to differences in survival. Population differences in comorbid conditions and presence of other cytogenetic markers may also have shortened tail-end survival.

Other limitations of this study are the possibilities of inaccurate or incomplete data, similar to any retrospective database analysis,[34] and, potentially, the inclusion of patients with index dates that preceded the approval of ibrutinib for CLL. The possibility of inaccurate data is mitigated by the Flatiron Health cohort selection method, which combines structured and abstracted data to ensure accurate selection of patients. Our study included patients diagnosed from 2011 onward, while ibrutinib was not approved to treat CLL until 2014. This choice was made to allow the capture of community practice patterns while also ensuring the inclusion of all patients and maximum follow-up duration. Despite this, the analysis cohort contained only one patient who began treatment in 2013 while the others had index dates from 2014 onwards.

The rate of del(17p) has been reported as being between 5% to 7% in most populations of patients with previously untreated CLL/SLL.[18,35,36] Since our current study was focused on patients with del(17p) we note that the proportion of patients in this group may appear relatively high at 23.8%. This was due to selection criteria into the analysis cohort requiring availability of information on cytogenetic testing (including fluorescence *in situ* hybridization) (Figure 1). This was necessary in order to enable a meaningful comparison between patients with and without del(17p) and address the research question of interest. A similar rate of del(17p) positivity (29%) was observed in the prospective, USA-based, InformCLL Registry among previously untreated patients who had undergone fluorescence *in situ* hybridization testing.[19] A final study limitation is that this study did not assess presence or absence of the *TP53* mutation as a risk factor. *TP53* and del(17p) are closely linked (treatment resistance in patients with del[17p] has been attributed to the presence of a variant in a *TP53* allele),[6] and high concordance exists between these measures.[37] However, the Flatiron Health database does not routinely capture *TP53* mutation status and an effort to obtain *TP53* data would have been prohibitive. Similarly, there are several variables that have a high level of unknown status or missing data, such as *IGHV* status (>50%), ECOG score at index date (>33%), and Rai stage at diagnosis (>37%). Although these rates may seem relatively high, we believe this is consistent and not unexpected from data captured directly from day-to-day clinical practice patterns in the community as opposed to academic centers.[18,19] Despite these limitations, we believe these results are highly meaningful.

In conclusion, this real-world retrospective analysis of first-line treatment with ibrutinib suggests that patients with CLL/SLL with del(17p) had inferior survival and were more likely to discontinue treatment due to disease progression than were patients without del(17p) in this study population. Despite the advent of ibrutinib, which has changed the overall outlook for patients with CLL/SLL, there remains an unmet need among those with del(17p). The ideal treatment regimen for this group of high-risk patients is yet to be determined. Randomized clinical trials comparing novel agent-based therapies designed specifically for this high-risk patient population are needed.

Disclosures

Data-sharing statement

On request, and subject to certain criteria, conditions, and exceptions, BeiGene, Ltd., will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (i) for indications that have been approved or (ii) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to DataDisclosure@beigene.com. In addition, the data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be made available upon request, and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms.

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