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Real-World Outcomes for 205 Patients with Chronic Lymphocytic Leukemia Treated with Ibrutinib

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Running title: Patients with CLL treated with Ibrutinib

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Novelty statement:

1. What is the NEW aspect of your work?

We here present the first population-based study exploring the outcomes of patients diagnosed with CLL and treated with ibrutinib in clinical practice in Denmark.

2. What is the CENTRAL finding of your work?

We find 1) comparable, though slightly inferior, overall and progression-free survival compared with clinical trials, 2) an increased risk of infections during the first six months 3) and, although similar rate of adverse events, a high discontinuation rate compared with clinical trials.

3. What is (or could be) the SPECIFIC clinical relevance of your work?

Our findings warrant for further investigations of prophylactic strategies upon ibrutinib initiation, and illustrate the importance of patient training and information to improve treatment adherence outside clinical trials.

Abstract:

Ibrutinib has now been approved for treatment of chronic lymphocytic leukemia (CLL) in both front-line setting and as later-line treatment. However, knowledge about the outcomes and adverse events (AE) among patients at a population-based level are still limited.

Objectives: To report outcomes and AEs in a population-based cohort treated with ibrutinib outside clinical trials.

Methods: We conducted a multicenter, retrospective cohort study including all patients with CLL treated with ibrutinib.

Results: In total, 205 patients were included of whom 39 (19%) were treatment-naïve. The median follow-up was 21.4 months (IQR, 11.9-32.8), and the estimated overall survival at 12 months was 88.8% (95%CI: 84.3-93.3) and the estimated progression-free survival at 12 months was 86.3% (95% CI: 81.3-91.2%). During follow-up, 200 (97.6%) patients had at least one AE and 100 (48.8%) patients had at least one grade grade ≥3 AE. Eigthy-six patients (42.0%) discontinued ibrutinib, hereof 47 (54.7%) due to AEs and 19 (22.1%) had progression of CLL or Richter transformation.

Conclusions: In our study, we find comparable, though slightly inferior**,** overall and progression-free survival, but discontinuation due to toxicity was higher compared with clinical trials. Patient training and information may improve treatment adherence outside clinical trials.

Keywords: Chronic Lymphocytic Leukemia, Epidemiology, Targeted Therapy

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world; worldwide 191.000 persons are diagnosed each year (1). The treatment of CLL has developed rapidly during the last two decades from chemo- to chemoimmunotherapy to targeted therapy (2). Many of the new drugs target the B-cell receptor pathway (BCR), which when activated fosters proliferation and differentiation of selected B-cells (3). Ibrutinib, targets BCR signaling through irreversible inhibition of Bruton's tyrosine kinase (BTK). In clinical trials ibrutinib has demonstrated high efficacy among both relapsed/refractory (R/R) and treatment-naïve (TN) patients (4,5), and is now approved for both indications. Remarkably, ibrutinib has shown to be superior among high-risk patients with *TP53*-abberations (del(17p) and/or *TP53*-mutations) and has led to a paradigm shift in treatment of CLL (4,6).

In contrast to established treatment regimens with chemo- and chemoimmunotherapy, treatment with ibrutinib is lifelong. This has led to an increased focus on adverse events (AE) of ibrutinib and management of these. Discrepancies in baseline characteristics and outcomes among patients in clinical trials and patients in routine clinical practice have previously been reported, emphasizing the importance of assessing data on outcomes at a population-based level (7–9). We here present data on overall survival (OS), progression-free survival (PFS), adverse events and rate of discontinuation for a population-based cohort of patients diagnosed with CLL and treated with ibrutinib in routine clinical practice.

Methods

We conducted a multicenter and retrospective study including patients diagnosed with CLL or small lymphocytic lymphoma (SLL) who were treated with ibrutinib prior to February 2019 outside clinical trials at 8 hospitals across Denmark. Danish guidelines for CLL treatment recommend treatment with ibrutinib as first-line only for patients a TP53-aberration. Patients were identified by one physician from each hospital through hospital records and registries. Patients receiving ibrutinib in clinical trials and patients with missing medical record data were excluded from the study. Patients receiving ibrutinib for Richter transformation (RT) were also excluded.

Data collection

All medical records were retrospectively reviewed to obtain information regarding date of CLL/SLL diagnosis, comorbidities, genetic and biological characteristics, previous treatment regimens, ibrutinib treatment, response to ibrutinib treatment, discontinuation, reason for discontinuation, infections, adverse events, progression and survival. Biochemistry and microbiology data were retrieved from the PERSIMUNE data warehouse, where data were available until 31/12/2018 (10).

To evaluate the comorbidities at time of ibrutinib treatment, the cumulative illness rating scale (CIRS) was used (11,12). Comorbidities prior to ibrutinib treatment initiation were registered from the medical records and the CIRS-score was calculated. We followed all patients from ibrutinib treatment initiation until death or end of follow-up whichever came first. AEs and infections were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (13). The International Workshop of Chronic Lymphocytic Leukemia (IWCLL) 2018 guidelines were used for grading hematologic toxicities (14). Assessment of best response followed the IWCLL 2018 guidelines and was defined based on clinical description and biochemistry (14) as bone marrow biopsy and CT-scan are not required in clinical practice to evaluate response. Overall response rate (ORR) included clinical complete remission (CR), partial remission (PR) and partial remission with lymphocytosis (PR-L). Progression during ibrutinib treatment was assessed following the IWCLL 2018 guidelines (14). The study was approved by the Data Protection Agency, and the National Ethics Committee. According to Danish legislation, these types of studies do not require informed consent from individual patients. To assure full anonymization, results for groups with less than 5 patients are summarized as such rather than reporting the exact number.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. OS was defined as time from ibrutinib start to death from any cause, while PFS was defined as time from ibrutinib start to progression or death from any cause. PFS and OS were analyzed with the Kaplan-Meier method, and the log-rank (LR) test was used to compare differences between patients with TN and patients with R/R CLL. Cox proportional hazards regression model was used to calculate univariate hazard ratios (HR) and adjusted HR. Estimates of cumulative incidence were calculated with the Aalen-

Johansen estimator. P-values <0.05 were considered statistically significant. Data were analyzed using R version 3.5.2.

Results

Study population

We identified 205 patients treated with ibrutinib, of whom 199 were diagnosed with CLL and 6 with SLL. Of the 205 patients, 39 (19.0%) were TN and 166 (81.0%) had R/R CLL. Baseline characteristics at the time of ibrutinib initiation are presented in Table 1. The median age at ibrutinib initiation was 73 years, 47.4 % had Binet stage C disease, 13.0 % had CIRS above 6, 27.2% were IGHV unmutated and 54.4% had TP53 aberrations. The median follow-up from time of treatment initiation was 21.4 months (IQR, 11.9-32.8); 23.7 months (IQR, 12.6-34.5) for the R/R patients and 17.5 (IQR, 9.6-25.1) for the TN patients. Median time of ibrutinib treatment was 16.8 months (IQR, 5.9-28.1); 17.6 months (IQR, 6.0-30.3) for patients with R/R CLL and 14.3 (IQR, 5.9-28.1) for patients with TN CLL. Types of prior treatment regimens are listed in Supplementary Table 1 and visualized in Supplementary Figure 1.

At treatment initiation, biochemistry data were available for 147 patients. The mean hemoglobin concentration was 11.2 g/dl (IQR, 9.7, 12.6), the mean platelet count was 138.1 x 10^9/L (IQR, 80.5, 185.0), the mean leukocyte count was 77.4 x 10^9/L (IQR, 12.1, 108.0) and the mean lymphocyte count (data missing for 20) was 54 x 10^9/L (IQR, 5.0, 78.5). The development of hematologic parameters during the first 12 months of treatment is visualized in Supplementary Figure 2.

Outcomes

The median OS was 48.3 months (IQR, 28.4, not reached (NR)). The estimated OS at 12 and 24 months were 88.8% (95%CI: 84.3-93.3%) and 76.8% (95%CI: 70.4-83.2%) for the total cohort. The OS at 12 and 24 months for patients with TN CLL was 91.0% (95%CI: 81.3-100.0%) and 78.3% (95%CI: 62.5-94.1%), respectively. The OS at 12 and 24 months for patients with R/R CLL was 88.3% (95%CI: 83.2-93.4%) and 76.4% (95%CI: 69.3-83.4%), respectively. Median PFS was

41.2 months (IQR:19.7, NR), while the estimated PFS at 12 and 24 months were 86.3% (81.3-91.2%) and 71.5% (95%CI: 64.6-78.4%) for the total cohort. The PFS at 12 and 24 months for patients with TN CLL was 82.9% (95%CI: 70.4-95.4%) and 67.6% (95%CI: 50.6-84.6%), respectively. The PFS at 12 and 24 months for patients with R/R CLL was 87.0% (95%CI: 81.7-92.3%) and 72.4% (95%CI: 64.9-79.9%), respectively. We did not have enough data to support any statistically significant differences in either OS or PFS between patients with TN CLL and R/R CLL (Figure 1A-D).

Higher age and higher CIRS-score at the time of ibrutinib treatment start as well as the combination of *TP53*-mutation and del(17p) were significantly associated with inferior OS (Table 2). Adjusting for age and sex, CIRS was no longer statistically significant associated with inferior OS (Table 2). Only age and the combination of *TP53*-mutation and del(17p) were independently associated with inferior PFS (supplementary Table 2). Interestingly, the presence of either del(17p) or *TP53*-mutation was not statistically significant related to OS or PFS (Table 2 and supplementary Table 2), even when including patients with missing data on either del(17p) or *TP53*-mutation (data not shown). We found no significant differences in OS nor PFS between patients with del(11q), del(13q) or tri12 as compared to the patients without these specific genetic aberrations. (data not shown).

Information regarding response was available for 191 (93.2%) patients. ORR was 76.4% (17.8% PR-L, 43.4% PR, and 15.2% clinical CR) for the patients with available response data. The cumulative best-responses were evaluated at 6, 12, 18 and 24 months as illustrated in Supplementary Figure 3.

Adverse events and infections

In total, 200 (97.6%) patients had at least one AE reported and 100 (48.8%) patients had at least one grade 3 or above AE. In total, <5 patients had a non-infectious grade 5 AE, and 6 patients died of an infection equivalent to a grade 5 AE. The most common grade ≥3 non-infectious AEs were hemorrhage, diarrhea and myalgia (Table 3 and supplementary Table 3). Hemorrhage appeared most frequently within the first months of treatment while atrial fibrillation appeared at a steady rate during follow up (Figure 2A). Infections were seen in 137 (66.8%) patients during follow-up, and 80 (39.0%) patients were hospitalized with a grade ≥3 infection. The incidence of infections

was 16.0 per 100 patient-months during the first 6 months of treatment and 8.3 per 100 patient-months thereafter. Airway and urinary tract infections appeared more frequent during the first months of treatment while skin infections appeared steadily during follow up (Figure 2B).

A blood culture sample was collected for 102 (49.7%) patients during follow-up on ibrutinib. The median time until first sample was 95.5 days (IQR, 36.25, 289.0 days). Of the 102 patients, 19 patients had at least one event with a positive microbiology verified bloodstream infection (BSI) with a total of 26 positive distinct BSI events. Twenty-one of the BSI were with gram-negative pathogens and five with gram-positive pathogens. The most common finding was *Escherichia coli* (n=5), no fungal infections were identified. Sample material from sputum, tracheal secretion and Broncho-alveolar lavage was available for 40 patients; 10 had at least one positive test with a fungal microorganism, <5 of the events were non-*Candida* species while no *Pneumocystis* were identified.

Discontinuation of ibrutinib

In total, 86 (42.0%) patients discontinued ibrutinib permanently during follow-up. Of those, 73 patients started ibrutinib due to R/R CLL (44% of all patients with R/R CLL) and 13 patients were TN (33.3% of all patients with TN CLL), though the median follow-up time was shorter for TN patients. Of the 86 patients discontinuing, 47 (54.7%) were due to AEs, 19 (22.1%) due to progressive disease where 12 (14.0%) discontinued due to progression of CLL and seven (8.1%) due to RT. Thirteen (15.1%) patients discontinued due to professional and/or patient preference and seven (8.1%) due to other reasons. The three most common AEs leading to discontinuation were atrial fibrillation (n=7), infections (n=6) and gastrointestinal AEs (n=5).

The median time to ibrutinib discontinuation was 9.3 months (IQR, 3.0- 23.2 months), with a median time of 5.5 months (IQR, 2.2-13.2 months) for patients discontinuing due to AEs, 25.1 months (IQR, 20.8, 37.3 months) for patients discontinuing due to progression of CLL and 7.0 months (IQR, 4.7-19.9 months) for patients discontinuing following RT. The estimated cumulative incidence for discontinuation at 12 and 24 months was 24.8% (95%CI: 18.6-30.9%) and 36.2% (95%CI: 29.0-43.3%) (Figure 3). New treatment regimens were initiated for 52 (60.5%) of the patients that discontinued ibrutinib, most commonly was venetoclax-based treatment (n=22) and idelalisib-based treatment (n=10). The median OS following ibrutinib discontinuation was 18.2 months (IQR, 7.1, NR) (supplementary Figure 4A). We found no statistically significant

difference in OS between patients discontinuing because of AEs, progression or other reasons (supplementary Figure 4B). Patients discontinuing because of adverse events were statistically significant older and more comorbid at baseline compared with patients discontinuing due to of progression.

Discussion

This is the first population-based study exploring the outcomes of patients diagnosed with CLL and treated with ibrutinib in clinical practice in Denmark. We found OS at 12 months to be 88.8%, which is in line with the 12 months OS at 90% reported in the RESONATE study (4). However, in the final analysis from the RESONATE study the median OS in the ibrutinib-arm was 68 months, which is higher than the estimated 48 month median OS in our study (15). Older and more comorbid patients in routine care could in part explain the inferior OS seen in clinical practice. In our study patients had a median age of 72.8 years compared with 67 years in the RESONATE trial (4), while larger proportion of patients had a CIRS-score >6 in the RESONATE trial (32% as compared to 13% in the present study). However, we assessed CIRS score based on hospital medical record review in our study, and therefore information regarding milder comorbidities may be underreported.

In the real-world study from the UK CLL forum (7) the OS at 12 months was 83.3% and from the Swedish real-world study (9) the OS at 10 months was 83%, both slightly inferior to what we find. These studies only include patients with R/R CLL, while we found no significant difference in OS between patients receiving ibrutinib as first-line or later-line treatment. This probably reflects that in the Danish guidelines for CLL treatment first-line ibrutinib is only recommended when patients have a *TP53*-abberation (16).Therefore, the first-line population in our study represents a high-risk population with expected inferior OS (17,18). Presence of both *TP53*-mutation and del(17p), was associated with inferior OS and PFS. No difference in OS and PFS was observed between patients with del(17p) or *TP53*-mutation and patients without. The RESONATE study reported similar results with an association among patients with both aberrations and poorer PFS, but not for either of the aberrations alone compared with patients without any of the aberrations (19).

The ORR (including PR-L) was 76.4% in our study; somewhat lower than reported in clinical trials (85%-86%) (4,5) and real-world studies from Sweden and the UK CLL forum (84%-85%) (7,9). The lower ORR in our study may be due to the retrospective nature of data, and the lack of

routine response evaluation for patients who discontinued early. However, bone marrow biopsy and a CT scan are not required in clinical practice to evaluate response (14), and patients categorized as in clinical CR includes patients who may have been categorized as PR if bone marrow biopsy and CT scans had been performed as in the clinical trial populations.

We found that the types of AEs were comparable with clinical trial data (4,5). Differences in frequencies of AEs compared with clinical trials may reflect lesser focus and non-systematic reporting of this in routine practice in general. The most commonly reported AEs in clinical trials such as fatigue, nausea, diarrhea as well as pyrexia (4,5) were seldom reported in our study. We believe that this discrepancy can partially be explained by the approach of collecting data from medical journals. Nevertheless, this would only be true for milder AEs, as the more severe AEs were always reported. We identified 6.8% patients with any grade hypertension, which is remarkably lower than previously reported; a recent study reported 71.6% patients developing de novo hypertension during ibrutinib treatment(20), whereas in the RESONATE and RESONATE-2 studies 21%-26% reported hypertension (15,21). The difference probably reflects the retrospective nature of this study and that hypertension primarily is managed in general practice, thus not fully documented in hospital records. The cumulative incidence of hemorrhage plateaued after six months in accordance to previously reported data (22), while atrial fibrillation appeared at a steady rate during follow up. The proportion of patients with an infection of any grade are comparable to what have been reported in the RESONATE trial (70%) (4). However, we found 39.0% of all patients had at least one grade ≥3 infection , which is higher than reported in the RESONATE study (24%) (4), but in line with the long-term follow-up Swedish real-world study (23) reporting 51% of the patients with a grade 3-4 infection. This illustrates the importance of real-world studies, since the results likely reflects how older and more frail patients included in real-world studies are at higher risk of infections. We further demonstrated that the rate of infections was highest during the first six months, similar to what has been reported in previous clinical trials (24,25). This may indicate that infections are related to the CLL-derived immune dysfunction rather than ibrutinib treatment per se. Prophylactic antibiotics may be considered during the first six months of ibrutinib treatment, for frail patients at higher risk of infection.

The overall discontinuation of ibrutinib was 42%; comparable, though slightly higher, than other real-world studies (24-41%) (7,9,26), probably reflecting the longer median follow-up in our

study. In the long-term follow-up (65.1 months) of the RESONATE trial (27) 53% of the patients discontinued ibrutinib; the majority due to progressive disease. This is in contrast to our study and other real-world studies where the majority of patients discontinue due to toxicities (7,9,26). This discrepancy could be due to older and more comorbid patients but also differences in management of ibrutinib in clinical trials and in clinical practice. We found the first six months of ibrutinib treatment to be critical, as the majority of discontinuations due to AEs appear in this time period. Thus, improved patient education and information about management of possible AEs especially during start of treatment may increase treatment adherence. This is of particular importance due to the inferior outcome for patients who discontinue ibrutinib where median OS is only 18 months, irrespective of if the cause for discontinuation was due to AEs or disease progression. The similar dismal outcome, whether discontinuing due to AEs or progression, is in contrast with prior studies reporting inferior OS for patients with progressing on ibrutinib compared with patients discontinuing due to AEs (26,28). This inter-study difference may in part be due to improved later-line treatment options with other targeted agents such as venetoclax upon progression on ibrutinib. Our results are however limited by the rather short follow-up time after discontinuation and the small number of patients.

The present study was limited by its inherent retrospective nature. Information regarding AEs, infections, and clinical examination was dependent on the information from the patient records. Furthermore, we identified patients treated with ibrutinib from multiple different sources, including hospital registries, medical records, and inputs from individual physicians. As the number of identified ibrutinib-treated patients from some hospitals was lower than expected, a reporting bias cannot be excluded. This could be due to inclusion of a high proportion of patients in clinical studies during the same period, or due to lack of identification of patients on ibrutinib, especially for patients with short duration of ibrutinib treatment. Thus, the study may be biased towards reporting patients with longer survival and less discontinuation. However, as 87% of the Danish CLL population (29) are covered by the hospitals included in this study, and CLL treatment is solely managed at public hospitals in Denmark, we believe the impact of these potential shortcomings may be small.

In conclusion, TN and R/R CLL patients treated with ibrutinib in clinical practice at the population-based level have comparable, though slightly inferior, outcomes regarding OS and PFS

compared with clinical trials. Ibrutinib can generally be safely managed in routine clinical practice, though the increased risk of infections during the first six months warrants further investigation of prophylactic strategies upon ibrutinib initiation. AEs are a major cause of discontinuation in this study leading to higher discontinuation rates than reported in clinical trials. This finding warrants improved patient education and information about management of ibrutinib and possible adverse events.

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Tables:

Variable	Level	Total
Age	Median (IQR)	72.8 (65.7, 77.8)
Age interval	>65 years	160 (78.0)
Sex	Male	128 (62.4)
CIRS-G score	0-3	96 (53.3)
	4-6	61 (33.9)
	>6	23 (12.8)
	Missing	25
Binet stage	A	64 (36.6)
	B	28 (16.0)
	C	83 (47.4)
	Missing	30
IGHV-unmutated		40 (27.2)
	Missing	58
TP53-mutation		51 (52.0)
	Missing	107
Cytogenetics		
Del(17p)		80 (39.6)
	Missing	<5
Del(11q)		39 (19.4)
	Missing	<5
Del(13q)		103 (51.2)
	Missing	<5
Trisomy 12		38 (18.9)
	Missing	<5
Normal FISH		21 (10.4)
	Missing	<5
Start dose	420 mg	190 (92.7)
Number of prior therapies for R/R patients	Median (IQR)	2.0 (1.0, 3.0)
Number of prior therapies	1-2	111 (66.9)
	3-4	46 (27.7)
	≥5	9 (5.4)
Time since last therapy (months)	Median (IQR)	17.5 (9.6, 32.8)

| | Missing | <5 |

Table 1. Baseline characteristics for the total cohort of patients at start of ibrutinib treatment. Percentages are based on patients with available data. 8.8% had both TP53-mutation and del(17p).

Baseline factor	Units	HR	95% CI	P	Adj. HR	95% CI	P
Age		1.06	[1.03;1.09]	<0.001			
Sex		0.83	[0.48;1.42]	0.49			
CIRS		1.14	[1.03;1.27]	0.01	1.07	[0.96;1.20]	0.20
Binet	A	Ref					
	B	0.88	[0.37;2.09]	0.77	0.86	[0.36;2.08]	0.74
	C	1.04	[0.54;1.98]	0.91	0.91	[0.47;1.75]	0.77
Number of therapies		1.07	[0.89;1.29]	0.46	1.08	[0.90;1.30]	0.39
IGHV-unmutated		0.81	[0.38;1.73]	0.58	1.02	[0.47;2.23]	0.96
Del(17p) or *TP53*-mutation		0.77	[0.34;1.74]	0.54	0.77	[0.34;1.73]	0.52
Both *TP53*-aberrations		2.67	[1.32;5.37]	0.006	2.97	[1.43;6.14]	0.003

Table 2. Cox proportional regression hazards model of baseline factors on OS for patients with CLL/SLL treated with ibrutinib in routine care. The adjusted (adj.) HR is adjusted for age and sex. HR: Hazard ratio.

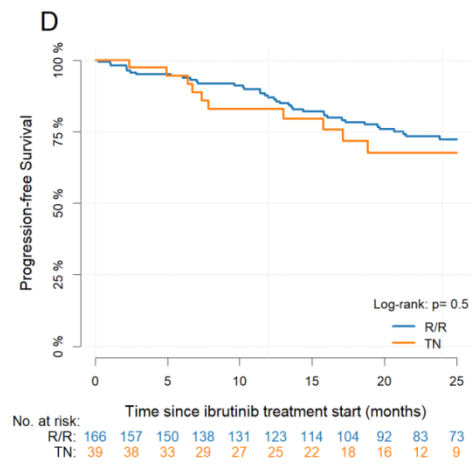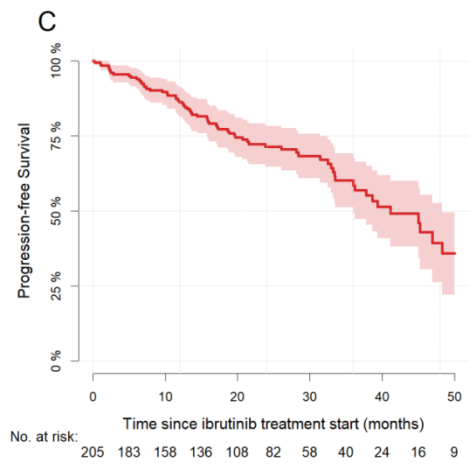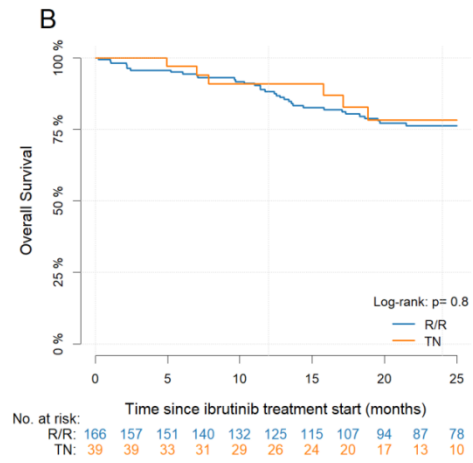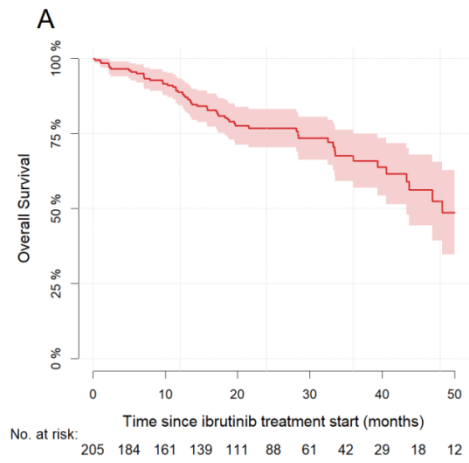| Non-hematologic AEs	Any grade (n)	Any grade (%)	Grade ≥3 (n)	Grade ≥3 (%)
Hemorrhage	86	42.0	6	2.9
Diarrhea	39	19.0	#	#
Myalgia	37	18.0	#	#
Atrial fibrillation	32	15.6	0	0
Arthralgia	28	13.7	0	0
Rash maculo-papular	21	10.2	0	0
Dizziness	20	9.8	0	0
Muscle cramp	18	8.8	0	0
Fatigue	17	8.3	0	0
Headache	16	7.8	0	0
Hematologic AEs				
Anemia	24	11.7	#	#
Neutropenia	21	10.2	14	6.8
Thrombocytopenia	14	6.8	#	#
Infections				
Lung infection	88	42.9	61	29.8
Urinary tract infection	41	20.0	15	7.3
Skin infection	39	19.0	5	2.4
Other infections	29	14.1	10	4.9
Upper respiratory infection	13	6.3	6	2.9

Table 3. The 10 most common non-hematologic AEs, hematologic AEs and the 5 most common infections for patients with CLL/SLL treated with ibrutinib in routine care. The AEs are registered in hospital records. Hemorrhage included all-type of bleeding-related adverse event (e.g. tendency to bruise, hematoma, epistaxis). # are groups including <5 patients.

Figure legends:

Figure 1. A. Overall survival for the whole cohort of patients with CLL/SLL treated with ibrutinib in routine care. B. Overall survival for patients with R/R CLL and for TN patients. C. Progression-free survival for the whole cohort. D. Progression-free for patients with R/R CLL and for TN patients. The shorter observation time for figure 1B and 1D is due to censoring as all curves are censored when one group includes <5 patients due to anonymization requirements.

Figure 2. A. Cumulative incidence of first event for the 4 most common reported AEs (any grade) for patients with CLL/SLL treated with ibrutinib in routine care. B. Cumulative incidence of first event for the 3 most common infections (any grade).
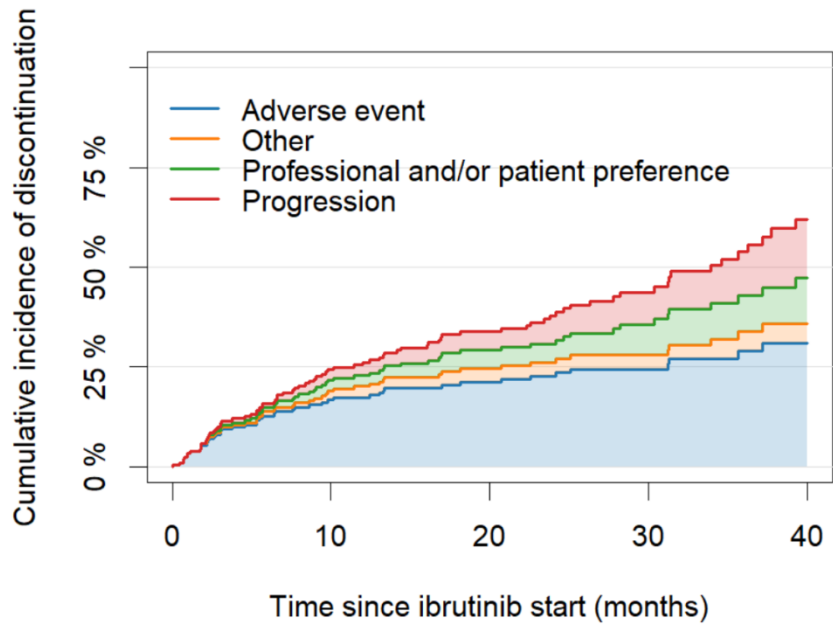
Figure 3. Cumulative incidence of discontinuation stratified by reason for discontinuation for patients with CLL/SLL treated with ibrutinib in routine care. Progression includes both progression of CLL and Richter transformation.

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Cumulative incidence of discontinuation

Time since ibrutinib start (months)
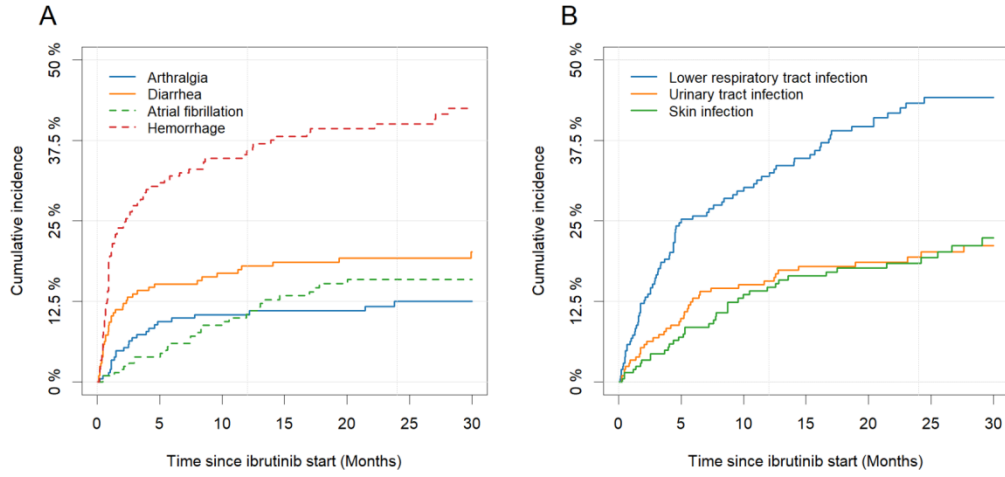
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