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Safety of Extended Pirtobrutinib Exposure in Relapsed and/or Refractory B-Cell Malignancies

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Bruton tyrosine kinase inhibitor · B-cell malignancies · Long-term safety · Toxicity

Abstract
Introduction: Pirtobrutinib, a highly selective, noncovalent (reversible) Bruton tyrosine kinase inhibitor, has demonstrated promising efficacy in B-cell malignancies and is associated with low rates of discontinuation and dose reduction. Pirtobrutinib is administered until disease progression or toxicity, necessitating an understanding of the safety profile in patients with extended treatment. ***Methods:*** Here we report the safety of pirtobrutinib in patients with relapsed/refractory B-cell malignancies with extended (≥12 months) drug exposure from the BRUIN trial. Assessments included median time-to-first-occurrence of adverse events (AEs), dose reductions, and discontinuations due to treatment-emergent AEs (TEAEs) and select AEs of interest (AESIs). ***Results:*** Of 773 patients enrolled, 326 (42%) received treatment for ≥12 months. In the extended exposure cohort, the median time-on-treatment was 19 months. The most common all-cause TEAEs were fatigue (32%) and diarrhea (31%). TEAEs leading to dose reduction occurred in 23 (7%)

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and discontinuations in 11 (3%) extended exposure patients. One patient had a fatal treatment-related AE (COVID-19 pneumonia). Infections (73.0%) were the most common AESI with a median time-to-first-occurrence of 7.4 months. Majority of TEAEs and AESIs occurred during the first year of therapy. ***Conclusions:*** Pirtobrutinib therapy continues to demonstrate an excellent safety profile amenable to long-term administration without evidence of new or worsening toxicity signals.

Introduction

Studies have highlighted the critical role of Bruton tyrosine kinase (BTK) in B-cell development and function, and particularly in B-cell receptor signaling [1–4]. The introduction and availability of covalent BTK inhibitors (cBTKis), starting with the approval of ibrutinib in 2013 by the United States Food and Drug Administration (FDA) and in 2014 by the European Medicines Agency (EMA), advanced the standard of care for patients with B-cell malignancies [5, 6]. However, while cBTKis can induce sustained remissions, a significant number of patients develop therapy-limiting adverse events (AEs) such as atrial fibrillation, bleeding, diarrhea, rash, fatigue, cytopenia, pneumonia, infection, hypertension, and arthralgias [7]. Real-world analyses suggest that up to 40% of patients treated with ibrutinib discontinue the treatment, with toxicity being the most common reason for discontinuation [8–10]. Moreover, early cBTKi discontinuation can adversely impact continued efficacy [11]. Although later generation cBTKis, including acalabrutinib and zanubrutinib, are more selective than ibrutinib leading to a more favorable toxicity profile, long-term safety and late-effect toxicities, including cardiotoxicities, remain a concern [12–14]. Long-term tolerability is critical for adherence, maintaining dose intensity and thus delivering durable disease control [15].

Pirtobrutinib is a highly selective, noncovalent (reversible) BTK inhibitor (BTKi) that was developed to address several of the limitations of currently available cBTKis [16]. In preclinical studies and in vitro binding experiments, pirtobrutinib showed favorable pharmacokinetics with high oral bioavailability and a half-life of approximately 20 h, achieving sustained plasma drug levels that enabled continuous BTK inhibition (>90%) throughout the dosing interval. This may be important in the setting of an accelerated intrinsic rate of BTK turnover in highly proliferative tumors [17]. Pirtobrutinib also inhibited both wild-type and C481-mutant BTK with equal low nM potency and appeared to stabilize BTK in a closed, inactive conformation. This stabilization may lead to fewer interactions with cellular proteins, thereby inhibiting kinase-independent BTK cellular signaling [16]. In addition, it is suggested that pirtobrutinib's high selectivity minimizes off-target inhibition, reducing the risk of toxicity [18]. Efficacy data from the phase 1/2 BRUIN study indicated robust and durable antitumor activity against a variety of B-cell malignancies in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [17] and mantle cell lymphoma (MCL) [18] who were previously treated with cBTKis. Pirtobrutinib was well tolerated with low rates of discontinuation due to drug-related toxicities. In 2023, pirtobrutinib received approval from the FDA and EMA for relapsed or refractory MCL [19, 20]. On December 1, 2023, the FDA granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least 2 prior lines of therapy, including a BTKi and a B-cell lymphoma 2 inhibitor [21]. This accelerated approval is based on the response rate and may be contingent upon verification and description of clinical benefit in a confirmatory trial. Here, we describe the safety profile in patients who have been on treatment with pirtobrutinib for a minimum of 12 months (the extended exposure cohort) in the context of the overall safety population ($n = 773$) from the phase 1/2 BRUIN trial.

Methods

Study Design and Patients

The overall BRUIN trial design and full eligibility criteria have been previously reported [17]. In brief, patients with previously treated CLL/SLL or other non-Hodgkin lymphomas, 18 years of age or older, and with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 2 were enrolled. There was no limit on prior lines of therapy (number or type), and prior treatment with a cBTKi was permitted. Patients with cardiac comorbidities such as prior and active controlled atrial fibrillation (including due to prior BTKi treatment) and ongoing anticoagulation/antiplatelet treatment, except warfarin, were also eligible. Patients with significant cardiovascular disease or a major bleeding event with a prior BTKi were excluded. Treatment continued until disease progression, unacceptable toxicity effects, or patient withdrawal. Patients with disease progression could continue treatment if ongoing clinical benefit was evident according to the investigator's opinion. Patient allocation by study phase and B-cell malignancy type is shown in Figure 1.

The prespecified overall safety population consisted of all patients from the phase 1/2 BRUIN trial who received at least 1 dose of pirtobrutinib (regardless of dosage strength) by the data cutoff of July 29, 2022. The extended exposure cohort was defined post hoc as all patients who had been exposed to pirtobrutinib for at least 12 months. The phase 1/2 BRUIN protocol was approved by the Institutional Review Boards or Independent Ethics Committees overseeing each geographic region. The trial (NCT03740529) was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws. All patients provided

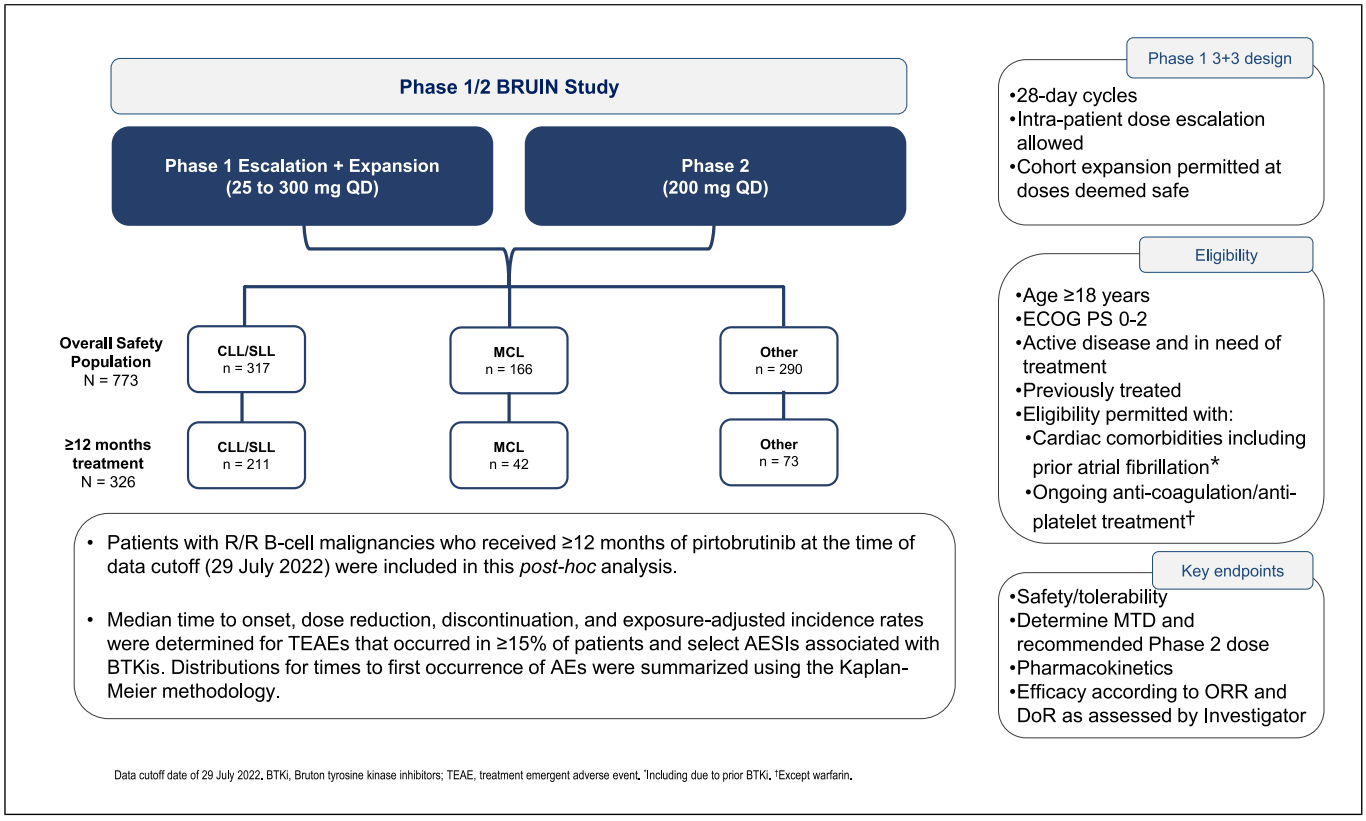

Fig. 1. Study design. Data cutoff date of July 29, 2022. DoR, duration of response; MTD, maximum tolerated dose; ORR, objective response rate; QD, once daily; R/R, relapsed/refractory. *Including due to prior BTKi. †Except warfarin. "Other" includes Waldenstrom macroglobulinemia, Richter transformation, and marginal zone lymphoma.

written informed consent. The manuscript was written by all authors and medical writers employed by Syneos Health. All authors made the decision to submit the manuscript for publication.

Statistical Analysis

This post hoc analysis aimed to characterize the safety and tolerability of pirtobrutinib in patients exposed to at least 12 months of pirtobrutinib therapy, in the context of the overall safety population treated with pirtobrutinib monotherapy in the phase 1/2 BRUIN trial. Treatment-emergent AEs (TEAEs) for both the overall safety population and the extended exposure cohort were defined as all AEs reported from the date of the first dose until the date of the last dose plus 37 days or the start of subsequent anticancer therapy, whichever was earlier. TEAEs were graded according to the National Cancer Institute Common Terminology for Adverse Events, version 5.0. The attribution of causality for treatment-related AEs was determined by the investigator. The reported AE term was coded using version 24.0 of the Medical Dictionary for Regulatory Activities.

Descriptive statistics were used to summarize patient disposition, demographics, and baseline disease characteristics. TEAE rates were summarized by type and severity using frequencies and percentages. Exposure-adjusted incidence rates (calculated as the occurrence of each AE per 100 person-months of pirtobrutinib exposure) were determined for TEAEs occurring in ≥15% of patients and select AEs of special interest (AESIs; those previously associated with the cBTKi class). The time to first occurrence of select TEAEs was estimated using the cumulative incidence function. Death due to any cause prior to the occurrence of the AE was treated as a competing event, and cumulative incidence rates were estimated with 95% confidence intervals at landmark timepoints [22]. The frequency and percentage of patients experiencing dose reductions or discontinuation of pirtobrutinib treatment due to AEs were summarized. Analyses were performed using SAS software, version 9.4 (SAS Institute).

Results

Patient Characteristics and Study Status

From March 21, 2019, to July 29, 2022, 773 patients with B-cell malignancies (317 with CLL/SLL, 166 with MCL, and 290 with other B-cell lymphomas) were enrolled in the BRUIN trial and comprised the overall safety population (shown in Fig. 1). A total of 326 patients

Table 1. Demographics, baseline disease characteristics, and prior therapy

Characteristics	Overall safety population (*N* = 773)	Extended exposure cohort (*N* = 326)	≥12-month treatment	Extended exposure CLL/SLL cohort (*n* = 211)
			Extended exposure MCL cohort (*n* = 42)	
Age, years, median (range)	68 (26–95)	69 (38–88)	70 (51–87)	69 (38–88)
Male, *n* (%)	516 (66.8)	213 (65.3)	36 (85.7)	136 (64.5)
ECOG PS, *n* (%)				
0	385 (49.8)	186 (57.1)	25 (59.5)	120 (56.9)
1	343 (44.4)	126 (38.7)	17 (40.5)	78 (37.0)
2	45 (5.8)	14 (4.3)	0 (0)	13 (6.2)
No. of prior lines of systemic therapy, median (range)	3 (0–13)	3 (1–13)	2 (1–9)	3.0 (1–11)
Prior therapy, *n* (%)				
Anti-CD20 antibody	723 (93.5)	297 (91.1)	42 (100)	187 (88.6)
Chemotherapy	668 (86.4)	282 (86.5)	40 (95.2)	176 (83.4)
BTKi	597 (77.2)	253 (77.6)	31 (73.8)	182 (86.3)
BCL2 inhibitor	228 (29.5)	75 (23.0)	1 (2.4)	68 (32.2)
PI3K inhibitor	126 (16.3)	46 (14.1)	2 (4.8)	36 (17.1)
Immunomodulator	100 (12.9)	32 (9.8)	5 (11.9)	15 (7.1)
Hematopoietic cell transplant	75 (9.7)	26 (8.0)	14 (33.3)	5 (2.4)
Autologous	59 (7.6)	20 (6.1)	14 (33.3)	0
Allogeneic	21 (2.7)	8 (2.5)	2 (4.8)	5 (2.4)
CAR T-cell therapy	55 (7.1)	12 (3.7)	2 (4.8)	8 (3.8)
Other systemic therapy	213 (27.6)	79 (24.2)	13 (31.0)	37 (17.5)
Reason discontinued any prior cBTKi*, *n* (%)				
Progressive disease	468 (60.5)	184 (56.4)	20 (47.6)	136 (64.5)
Toxicity	95 (12.3)	57 (17.5)	9 (21.4)	41 (19.4)
Other	28 (3.6)	12 (3.7)	2 (4.8)	5 (2.4)

Data cutoff date of July 29, 2022. Total % may be different from the sum of the individual components due to rounding. BCL2, B-cell lymphoma 2; CAR, chimeric antigen receptor; *N*, number of patients, *n*, number of patients in subgroup; P13K, phosphoinositide 3-kinase. [a]In the event, more than 1 reason was noted for discontinuation, and disease progression took priority.

(42.2%) (211 with CLL/SLL, 42 with MCL, and 73 with other non-Hodgkin lymphoma) were treated with pirtobrutinib for ≥12 months at the time of data cutoff and defined the extended exposure cohort. Among all patients in the extended exposure cohort, 287 patients (88.0%) received 200 mg of pirtobrutinib daily. Baseline demographics, disease characteristics, and prior therapies for the overall safety population and the extended exposure cohort (also by histological subtype) are provided in Table 1. With respect to the extended exposure cohort, the majority of patients were male (*n* = 213, 65.3%) with a median age of 69 years (range 38–88). Almost all patients had an ECOG PS of 0 or 1 (*n* = 312, 95.7%). The median number of previous lines of therapy was 3 (range: 1–13). Most patients (*n* = 253, 77.6%) had received a prior cBTKi, and of these, 184 (56.4%) had discontinued their prior cBTKi due to progressive disease and 57 (17.5%) had discontinued their prior cBTKi due to toxicity (Table 1). The median time on pirtobrutinib treatment for the extended exposure cohort was 19.4 months (interquartile range [IQR]: 16.0–25.4). As expected, patients with MCL (median 16.6 months, IQR: 13.6–28.0) were on treatment for a shorter duration than patients with CLL/SLL (median 19.9 months, IQR: 16.5–25.6).

At data cutoff, most patients in the extended exposure cohort (*n* = 231, 70.9%) remained on pirtobrutinib, including patients with CLL/SLL (*n*/*N* = 141/211, 66.8%) and MCL (*n*/*N* = 32/42, 76.2%). After ≥12 months of treatment with pirtobrutinib, the primary reason for pirtobrutinib discontinuation was progressive disease in 62 patients (19.0%). TEAEs accounted for only 3.4% (*n* = 11) of discontinuations, suggesting that most patients who remained on treatment for at least a year were able to continue until progression without discontinuation due to tolerability issues (Table 2).

Table 2. Pirtobrutinib exposure and treatment status

Treatment exposure	Overall safety population (N = 773)	≥12-month treatment		
		extended exposure cohort (N = 326)	extended exposure MCL cohort (n = 42)	extended exposure CLL/SLL cohort (n = 211)
Median time on pirtobrutinib, months (IQR)	9.6 (3.5–18.1)	19.4 (16.0–25.4)	16.6 (13.6–28.0)	19.9 (16.5–25.6)
Treatment discontinuation, n (%)				
Progressive disease	311 (40.2)	62 (19.0)	6 (14.3)	45 (21.3)
AE	58 (7.5)	11 (3.4)	3 (7.1)	7 (3.3)
Death	34 (4.4)	9 (2.8)	1 (2.4)	6 (2.8)
Physician decision	18 (2.3)	5 (1.5)	0	5 (2.4)
Withdrawal by patient	13 (1.7)	2 (0.6)	0	2 (0.9)
Dose reductions due to TEAE, n (%)	42 (5.4)	23 (7.1)	3 (7.1)	15 (7.1)
Dose discontinuations due to TEAE, n (%)	58 (7.5)	11 (3.4)	3 (7.1)	7 (3.3)
Dose reductions due to TRAE, n (%)	35 (4.5)	18 (5.5)	2 (4.8)	11 (5.2)
Dose discontinuations due to TRAE, n (%)	20 (2.6)	4 (1.2)	2 (4.8)	2 (0.9)

Data cutoff date of July 29, 2022. TRAE, treatment-related AE.

Overview of Adverse Events

The most commonly reported TEAEs in the extended exposure cohort and overall safety population are described in Table 3. Among the 326 patients in the extended exposure cohort, fatigue (n = 105, 32.2%), diarrhea (n = 100, 30.7%), contusion (n = 84, 25.8%), cough (n = 80, 24.5%), arthralgia (n = 69, 21.2%), and back pain (n = 68, 20.9%) were the most commonly observed any-grade TEAEs and were primarily low grade. The median time to the first occurrence of most TEAEs was within 6 months of treatment initiation: fatigue (5.1 months), diarrhea (4.2 months), and contusion (2.1 months). Among the extended exposure cohort, majority of TEAEs had their first occurrence within a year of treatment initiation (shown in Fig. 2). The median time to the first occurrence of COVID-19 was 14.3 months, with the pandemic's onset occurring during the second year of the study. The median time to the first occurrence of AEs in the overall safety population is described in the online supplementary Fig. 1 (for all online suppl. material, see https://doi.org/10.1159/000539587). TEAEs experienced by patients with MCL and CLL/SLL in the extended exposure cohort are presented in Tables 4 and 5.

In the extended exposure cohort, 187 (57.4%) and 77 patients (23.6%) had grade ≥3 TEAEs and treatment-related grade ≥3 TEAEs, respectively. The most commonly reported grade ≥3 TEAEs were pneumonia (6.4%, n = 21), COVID-19 pneumonia (6.1%, n = 20), anemia (4.9%, n = 16), COVID-19 (4.3%, n = 14), leukocytosis (2.8%, n = 9), and urinary tract infections (2.8%, n = 9) (Table 3). Sixteen patients (38.1%) with MCL and 134 patients (63.5%) with CLL/SLL reported grade ≥3 TEAEs (Tables 4, 5). Serious AEs were reported for 130 patients (39.9%) in the extended exposure cohort, and 19 serious AEs (5.8%) were treatment related. Serious TEAEs in the MCL and CLL/SLL extended exposure cohorts were observed in 13 (31.0%) and 94 patients (44.5%), respectively (2.4% and 6.2% were treatment related, respectively).

A total of 12 fatal AEs (3.7%) occurred in the 326 patients in the extended exposure cohort. In the overall safety population (n = 773), there were 47 fatal AEs (6.1%), and in the 447 patients who were exposed to less than 12 months of pirtobrutinib treatment, there were 35 fatal events (7.8%). In the extended exposure cohort, fatal events were observed in 1 patient with MCL due to COVID-19 pneumonia (2.4%) and in 10 patients with CLL/SLL due to COVID-19 (2.8%, n = 6), sepsis (0.9%, n = 2), pneumonia (0.5%, n = 1), and transitional cell carcinoma (0.5%, n = 1). One fatal case of treatment-emergent COVID-19 was observed among the non-Hodgkin lymphoma patient population with extended exposure to pirtobrutinib.

Table 3. All-grade and grade ≥3 TEAEs and AESIs reported in the extended exposure and overall safety population

	Extended exposure cohort (≥12 months) (*N* = 326)		Overall safety population (*N* = 773)	
	any-grade	grade ≥3	any-grade	grade ≥3
TEAEs, *n* (%)				
Fatigue	105 (32.2)	4 (1.2)	222 (28.7)	16 (2.1)
Diarrhea	100 (30.7)	4 (1.2)	187 (24.2)	7 (0.9)
COVID-19	93 (28.5)	14 (4.3)	129 (16.7)	21 (2.7)
Contusion	84 (25.8)	0	150 (19.4)	0
Cough	80 (24.5)	0	135 (17.5)	1 (0.1)
Arthralgia	69 (21.2)	2 (0.6)	111 (14.4)	5 (0.6)
Back pain	68 (20.9)	3 (0.9)	98 (12.7)	4 (0.5)
Rash[a]	64 (19.6)	1 (0.3)	98 (12.7)	4 (0.5)
Headache	60 (18.4)	2 (0.6)	101 (13.1)	4 (0.5)
Upper respiratory tract infection	59 (18.1)	0	76 (9.8)	1 (0.1)
Nausea	57 (17.5)	1 (0.3)	125 (16.2)	1 (0.1)
Dyspnea	56 (17.2)	2 (0.6)	120 (15.5)	8 (1.0)
Constipation	53 (16.3)	0	105 (13.6)	2 (0.3)
Abdominal pain	53 (16.3)	3 (0.9)	101 (13.1)	8 (1.0)
Edema peripheral	48 (14.7)	0	90 (11.6)	1 (0.1)
Dizziness	46 (14.1)	0	80 (10.3)	0
Pyrexia	46 (14.1)	4 (1.2)	106 (13.7)	8 (1.0)
Fall	42 (12.9)	0	58 (7.5)	0
Pneumonia	41 (12.6)	21 (6.4)	77 (10.0)	46 (6.0)
Urinary tract infection	41 (12.6)	9 (2.8)	70 (9.1)	14 (1.8)
Anemia	39 (12.0)	16 (4.9)	119 (15.4)	68 (8.8)
Vomiting	34 (10.4)	0	57 (7.4)	0
Insomnia	34 (10.4)	0	56 (7.2)	0
AESIs[b], *n* (%)				
Infections[c]	238 (73.0)	73 (22.4)	430 (55.6)	165 (21.3)
Neutropenia[d]	93 (28.5)	76 (23.3)	187 (24.2)	158 (20.4)
Thrombocytopenia[e]	38 (11.7)	16 (4.9)	117 (15.1)	63 (8.2)
Bruising[f]	100 (30.7)	0	183 (23.7)	0
Hemorrhage/hematoma[g]	54 (16.6)	7 (2.1)	88 (11.4)	14 (1.8)
Hypertension	52 (16.0)	11 (3.4)	71 (9.2)	18 (2.3)
Atrial fibrillation/flutter[h]	9 (2.8)	3 (0.9)	22 (2.8)	9 (1.2)

Events include multiple preferred terms within the Medical Dictionary for Regulatory Activities. TEAEs reported in ≥10% of patients are shown. [a]Aggregate of rash, rash maculopapular, rash macular, rash pruritic, rash erythematous, rash pustular, rash papular, injection site rash, and medical device site rash. [b]AESIs are those previously associated with cBTKi. [c]Aggregate of all infections. [d]Aggregate of neutropenia and decreased neutrophil count. [e]Aggregate of thrombocytopenia and decreased platelet count. [f]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [g]Aggregate of all preferred terms including hematoma or hemorrhage. [h]Aggregate of atrial fibrillation and atrial flutter.

TEAEs leading to dose reduction in the extended exposure cohort occurred in 23 patients (7.1%); TEAEs leading to dose reduction in the extended exposure cohort and deemed by the investigator to be related to pirtobrutinib occurred in 18 patients (5.5%). In the overall safety populations, 4.5% (*n* = 35) of patients had dose reductions. TEAEs leading to discontinuation occurred in 11 patients (3.4%) in the extended exposure cohort and were treatment related in 4 patients (Table 6). Treatment-related AEs leading to drug discontinuation included thrombocytopenia (0.3%) and neutropenia (0.3%). As expected, there were fewer treatment discontinuations (3.4%, *n* = 11) due to TEAEs in the extended exposure cohort than the overall safety population (10.5%, *n* = 47) as the patients were able to remain on treatment for at least a full year. The 2

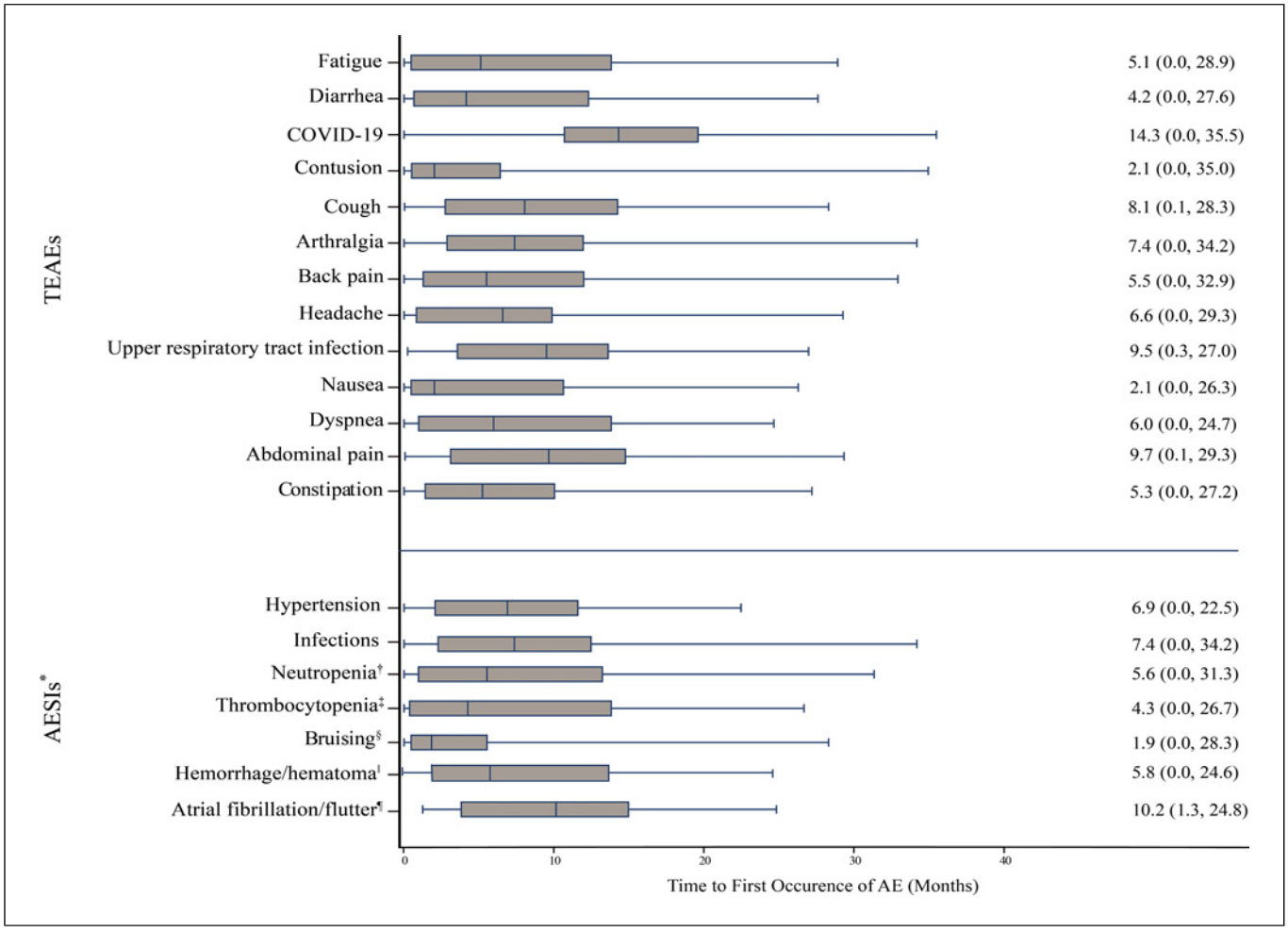

Fig. 2. Time to first occurrence of TEAEs and AESIs in the extended exposure cohort. Data cutoff date of July 29, 2022. *AESIs are those previously associated with cBTKi. †Aggregate of neutrophil count decreased and neutropenia. ‡Aggregate of platelet count decreased and thrombocytopenia. §Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. ‖Aggregate of all preferred terms including hematoma or hemorrhage. ¶Aggregate of atrial fibrillation and atrial flutter.

largest cohorts in this extended exposure data set, the MCL and CLL patient cohorts, demonstrate similar safety profiles, with no unique differential toxicities observed (Tables 4, 5).

Adverse Events of Special Interest

The most common AESIs are summarized in Table 3. The rate of any-grade neutropenia in the extended exposure cohort was 28.5% (n = 93), with 23.3% of patients experiencing grade ≥3 neutropenia. There were 4 patients (1.2%) with febrile neutropenia in the extended exposure cohort. Similar rates of any-grade (24.2%) and grade ≥3 (20.4%) neutropenia were observed in the overall safety population. The median time to the first occurrence of neutropenia was 5.6 months, and 74.2% (n = 69) of cases occurred before 12 months. The exposure-adjusted incidence rate of neutropenia was observed to be lower in patients with prolonged pirtobrutinib treatment in the extended exposure cohort (1.7 per 100 person-months) than in the overall safety population (2.5 per 100 person-months). Among the extended exposure cohort, treatment-emergent any-grade and grade ≥3 thrombocytopenia was observed in 11.7% and 4.9% of patients, respectively. Any-grade and grade ≥3 thrombocytopenia was reported in 15.1% and 8.2% of the overall safety population, respectively. In the extended exposure cohort, the median time to the first occurrence of thrombocytopenia was within the

Table 4. Any-grade and grade ≥3 TEAEs and AESIs reported in the extended exposure MCL cohort and overall MCL safety population

	Extended exposure MCL cohort (≥12 months) (*n* = 42)		Overall MCL safety population (*n* = 166)	
	any-grade	grade ≥3	any-grade	grade ≥3
TEAEs, *n* (%)				
Fatigue	14 (33.3)	0	52 (31.3)	5 (3.0)
Diarrhea	12 (28.6)	0	37 (22.3)	0
Back pain	10 (23.8)	0	20 (12.0)	1 (0.6)
Contusion	9 (21.4)	0	24 (14.5)	0
Cough	9 (21.4)	0	22 (13.3)	1 (0.6)
COVID-19	9 (21.4)	2 (4.8)	15 (9.0)	4 (2.4)
Anemia	7 (16.7)	2 (4.8)	28 (16.9)	12 (7.2)
Dyspnea	7 (16.7)	0	27 (16.3)	2 (1.2)
Upper respiratory tract infection	7 (16.7)	0	11 (6.6)	0
Paresthesia	6 (14.3)	0	16 (9.6)	1 (0.6)
Pneumonia	5 (11.9)	3 (7.1)	19 (11.4)	16 (9.6)
Peripheral swelling	5 (11.9)	0	13 (7.8)	0
Joint swelling	5 (11.9)	0	9 (5.4)	0
Fall	5 (11.9)	0	8 (4.8)	0
Stomatitis	5 (11.9)	0	8 (4.8)	1 (0.6)
Rash[a]	5 (11.9)	0	14 (8.4)	1 (0.6)
AESIs[b], *n* (%)				
Infections[c]	25 (59.5)	8 (19.0)	67 (40.4)	32 (19.3)
Bruising[d]	10 (23.8)	0	27 (16.3)	0
Neutropenia[e]	5 (11.9)	4 (9.5)	23 (13.9)	22 (13.3)
Thrombocytopenia[f]	3 (7.1)	2 (4.8)	30 (18.1)	16 (9.6)
Hemorrhage/hematoma[g]	5 (11.9)	1 (2.4)	17 (10.2)	4 (2.4)
Hypertension	3 (7.1)	0	6 (3.6)	0
Atrial fibrillation/flutter[h]	0	0	6 (3.6)	3 (1.8)

Events include multiple preferred terms within the Medical Dictionary for Regulatory Activities. TEAEs reported in ≥10% of patients are presented. [a]Aggregate of rash, rash maculopapular, rash macular, rash pruritic, rash erythematous, rash pustular, rash papular, injection site rash, and medical device site rash. [b]AESIs are those previously associated with cBTKi. [c]Aggregate of all infections. [d]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [e]Aggregate of neutropenia and decreased neutrophil count. [f]Aggregate of thrombocytopenia and decreased platelet count. [g]Aggregate of all preferred terms including hematoma or hemorrhage. [h]Aggregate of atrial fibrillation and atrial flutter.

first 5 months of treatment with pirtobrutinib (4.3 months) and 63.2% (*n* = 24) of patients had the first occurrence of thrombocytopenia within the first 12 months. A reduced exposure-adjusted incidence rate of thrombocytopenia was observed in patients in the extended exposure cohort (0.6 per 100 person-months) than in the overall safety population (1.4 per 100 person-months).

Rates of all-grade infection events were 73.0% and grade ≥3 events were 22.4% in the extended exposure cohort (Table 3). COVID-19 was the most commonly observed type of all-grade infection (28.5%, *n* = 93) and 62 (66.7%) of these patients had more than one type of infection. In the overall safety population, 55.6% reported all-grade infections, and COVID-19 was observed in 16.7% of patients. The other most commonly observed types of infections in the extended exposure cohort were infections of the respiratory system including upper respiratory tract infections (18.1%, *n* = 59), pneumonia (12.6%, *n* = 41), sinusitis (7.7%, *n* = 25), and bronchitis (3.1%, *n* = 10). Among patients in the extended exposure CLL/SLL and MCL cohorts, 78.7% and 59.5% had treatment-emergent infections, respectively. The CLL/SLL patient population, as expected, was at high risk for infection. Twenty-eight patients (13.3%) in the extended exposure cohort had prior hypogammaglobulinemia, and 43 (20.4%) were on concomitant immunoglobulin therapy. Fifty-nine patients (28.0%) received a concomitant growth factor. In the

Table 5. Any-grade and grade ≥3 TEAEs and AESIs reported in the extended exposure CLL/SLL cohort and overall CLL/SLL safety population

	Extended exposure CLL/SLL cohort (≥12 months) (*n* = 211)		Overall CLL/SLL safety population (*n* = 317)	
	any-grade TEAEs	grade ≥3 TEAEs	any-grade TEAEs	grade ≥3 TEAEs
TEAEs, *n* (%)				
Fatigue	72 (34.1)	4 (1.9)	100 (31.5)	6 (1.9)
COVID-19	65 (30.8)	12 (5.7)	76 (24.0)	16 (5.0)
Diarrhea	66 (31.3)	2 (0.9)	84 (26.5)	2 (0.6)
Cough	61 (28.9)	0	77 (24.3)	0
Contusion	57 (27.0)	0	77 (24.3)	0
Arthralgia	49 (23.2)	2 (0.9)	58 (18.3)	3 (0.9)
Upper respiratory tract infection	47 (22.3)	0	52 (16.4)	1 (0.3)
Rash[a]	45 (21.3)	0	54 (17.0)	1 (0.3)
Back pain	44 (20.9)	3 (1.4)	51 (16.1)	3 (0.9)
Abdominal pain	42 (19.9)	2 (0.9)	57 (18.0)	5 (1.6)
Headache	42 (19.9)	1 (0.5)	55 (17.4)	2 (0.6)
Constipation	41 (19.4)	0	46 (14.5)	1 (0.3)
Dyspnea	38 (18.0)	2 (0.9)	55 (17.4)	3 (0.9)
Nausea	37 (17.5)	0	60 (18.9)	0
Dizziness	37 (17.5)	0	45 (14.2)	0
Edema peripheral	36 (17.1)	0	45 (14.2)	0
Pneumonia	31 (14.7)	17 (8.1)	43 (13.6)	25 (7.9)
Pyrexia	31 (14.7)	2 (0.9)	45 (14.2)	4 (1.3)
Urinary tract infection	30 (14.2)	5 (2.4)	38 (12.0)	8 (2.5)
Insomnia	30 (14.2)	0	36 (11.4)	0
Fall	29 (13.7)	0	34 (10.7)	0
Vomiting	24 (11.4)	0	27 (8.5)	0
Hyperuricemia	23 (10.9)	0	29 (9.1)	0
Anemia	23 (10.9)	10 (4.7)	48 (15.1)	28 (8.8)
Nasal congestion	21 (10.0)	0	23 (7.3)	0
AESIs[b], *n* (%)				
Infections[c]	166 (78.7)	54 (25.6)	225 (71.0)	89 (28.1)
Neutropenia[d]	71 (33.6)	56 (26.5)	103 (32.5)	85 (26.8)
Thrombocytopenia[e]	28 (13.3)	11 (5.2)	51 (16.1)	28 (8.8)
Bruising[f]	70 (33.2)	0	96 (30.3)	0
Hemorrhage/hematoma[g]	33 (15.6)	6 (2.8)	39 (12.3)	7 (2.2)
Hypertension	39 (18.5)	9 (4.3)	45 (14.2)	11 (3.5)
Atrial fibrillation/flutter[h]	9 (4.3)	3 (1.4)	12 (3.8)	4 (1.3)

Events include multiple preferred terms within the Medical Dictionary for Regulatory Activities. TEAEs reported in ≥10% of patients are presented. [a]Aggregate of rash, rash maculopapular, rash macular, rash pruritic, rash erythematous, rash pustular, rash papular, injection site rash, and medical device site rash. [b]AESIs are those previously associated with cBTKi. [c]Aggregate of all infections. [d]Aggregate of neutropenia and decreased neutrophil count. [e]Aggregate of thrombocytopenia and decreased platelet count. [f]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [g]Aggregate of all preferred terms including hematoma or hemorrhage. [h]Aggregate of atrial fibrillation and atrial flutter.

extended exposure cohort, the median time to the first occurrence of infections was 7.4 months and 14.3 months for COVID-19. A reduced exposure-adjusted incidence rate of infections was observed in patients in the extended exposure cohort (6.5 per 100 person-months) than in the overall safety population (8.2 per 100 person-months) (Table 7).

Any-grade and grade ≥3 treatment-emergent hemorrhage/hematoma was observed in 16.6% and 2.1% of patients in the extended exposure cohort, respectively. Similar rates of any-grade (11.4%) and grade ≥3 (1.8%) hemorrhage/hematoma were reported for the overall safety population. Any-grade treatment-emergent bruising events were observed in 100 patients

Table 6. Any-grade and grade ≥3 TEAEs and AESIs leading to dose reductions and dose discontinuations in the extended exposure, MCL, and CLL/SLL cohorts following ≥12 months of treatment

	Extended exposure cohort (*N* = 326)		Extended exposure MCL cohort (*n* = 42)		Extended exposure CLL/SLL cohort (*n* = 211)	
	leading to dose reduction	leading to dose discontinuation	leading to dose reduction	leading to dose discontinuation	leading to dose reduction	leading to dose discontinuation
TEAEs						
Fatigue	0	0	0	0	0	0
Diarrhea	1 (0.3)	0	0	0	1 (0.5)	0
COVID-19	1 (0.3)	0	1 (2.4)	0	0	0
Contusion	1 (0.3)	0	0	0	1 (0.5)	0
Cough	0	0	0	0	0	0
Back pain	0	0	0	0	0	0
Headache	0	0	0	0	0	0
Upper respiratory tract infection	0	0	0	0	0	0
Nausea	0	0	0	0	0	0
Dyspnea	1 (0.3)	0	1 (2.4)	0	0	0
Abdominal pain	0	0	0	0	0	0
Constipation	0	0	0	0	0	0
Rash[a]	0	0	0	0	0	0
AESIs[b]						
Infections[c]	1 (0.3)	2 (0.6)	1 (2.4)	0	0	2 (0.9)
Neutropenia[d]	10 (3.1)	2 (0.6)	0	1 (2.4)	7 (3.3)	1 (0.5)
Thrombocytopenia[e]	2 (0.6)	1 (0.3)	0	1 (2.4)	2 (0.9)	0
Bruising[f]	1 (0.3)	0	0	0	1 (0.5)	0
Hemorrhage/ hematoma[g]	0	0	0	0	0	0
Hypertension	1 (0.3)	0	0	0	1 (0.5)	0
Atrial fibrillation/ flutter[h]	0	0	0	0	0	0

Data cutoff date of July 29, 2022. [a]Aggregate of rash, rash maculopapular, rash macular, rash pruritic, rash erythematous, rash pustular, rash papular, injection site rash, and medical device site rash. [b]AESIs are those previously associated with cBTKi. [c]Aggregate of all infections. [d]Aggregate of neutropenia and decreased neutrophil count. [e]Aggregate of thrombocytopenia and decreased platelet count. [f]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [g]Aggregate of all preferred terms including hematoma or hemorrhage. [h]Aggregate of atrial fibrillation and atrial flutter.

(30.7%) in the extended exposure cohort; however, no grade ≥3 events were observed in this cohort. Among patients in the extended exposure CLL/SLL and MCL cohort, 15.6% and 11.9% of patients had treatment-emergent hemorrhage/hematoma, respectively. In the extended exposure CLL/SLL cohort, 36.5% (*n* = 77) of patients received concomitant anticoagulants or antiplatelet agents. No patients in the overall safety population or the extended exposure cohort required dose discontinuations or reductions due to hemorrhage/hematoma. In the extended exposure cohort, the median time to the first occurrence of hemorrhage/hematoma was 5.8 months after treatment with pirtobrutinib, and 65% of these patients had an event of hemorrhage/hematoma during the first year, while the median time to the first occurrence of bruising was within the first 2 months of treatment with pirtobrutinib, and 88% of patients had the first occurrence during the first year. Exposure-adjusted incidence rates of hemorrhage/hematoma in patients with extended exposure (0.87 per 100 person-months) were similar to the overall safety population (1.07 per 100 person-months), suggesting that prolonged treatment with pirtobrutinib did not increase the rate of hemorrhage/hematoma. Cumulative incidence rates for hemorrhage/hematoma in the overall safety population at 6, 12, 18, and 24 months of exposure were 7.6%, 9.2%, 11.6%, and 12.6%, respectively. Similar results were reported for patients with CLL/SLL and MCL. There

Table 7. Exposure-adjusted incidence rates[a] for AESIs following ≥12 months of treatment with pirtobrutinib in the extended exposure, MCL, and CLL/SLL cohorts, compared with the overall safety population

AESIs[b]	Extended exposure cohort (N = 326)		Overall safety population (N = 773)		Extended exposure MCL cohort (n = 42)		Extended exposure CLL/SLL cohort (n = 211)	
	TEAE incidence rate	TRAE incidence rate	TEAE incidence rate	TRAE incidence rate	TEAE incidence rate	TRAE incidence rate	TEAE incidence rate	TRAE incidence rate
Infections[c]	6.50	0.82	8.17	1.12	4.59	1.85	7.39	0.73
Bruising[d]	1.99	1.21	2.69	1.55	1.50	0.97	2.16	1.24
Neutropenia[e]	1.66	1.04	2.54	1.43	0.62	0.37	1.99	1.20
Thrombocytopenia[f]	0.60	0.32	1.41	0.59	0.37	0.24	0.67	0.35
Hemorrhage/ hematoma[g]	0.87	0.30	1.07	0.36	0.65	0.38	0.80	0.25
Hypertension	0.85	0.23	0.87	0.30	0.37	0.25	0.97	0.20
Atrial fibrillation/ flutter[h]	0.13	0.04	0.25	0.07	—	—	0.20	0.07

Data cutoff date of July 29, 2022. [a]Exposure-adjusted incidence rate is calculated as the first occurrence of each AESI per 100 person-months of pirtobrutinib exposure. [b]AESIs are those previously associated with cBTKi. [c]Aggregate of all infections. [d]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [e]Aggregate of neutropenia and decreased neutrophil count. [f]Aggregate of thrombocytopenia and decreased platelet count. [g]Aggregate of all preferred terms including hematoma or hemorrhage. [h]Aggregate of atrial fibrillation and atrial flutter.

was no increase in the incidence of new (not previously occurring) hemorrhage/hematoma events after 12 months (extended exposure cohort data shown in Fig. 3 and online suppl. Fig. 2).

Any-grade and grade ≥3 hypertension were reported in 52 (16.0%) and 11 patients (3.4%) in the extended exposure cohort, respectively (shown in Fig. 3). Three patients (7.1%) with MCL and 39 patients (18.5%) with CLL/SLL reported hypertension in the extended exposure cohort (Tables 4, 5). In the overall safety population, 9.2% of patients had hypertension and 2.3% had grade ≥3 hypertension. The impact on treatment administration in the extended exposure cohort was also minimal as only 1 patient (0.3%) and 2 patients (0.6%) required a dose reduction or interruption of pirtobrutinib, respectively, due to treatment-emergent hypertension. No patients in the extended exposure cohort discontinued pirtobrutinib due to hypertension, while the median time to the first occurrence of hypertension was 6.9 months (shown in Fig. 2), and 75.0% of cases (n = 39) occurred in the first 12 months. In the extended exposure cohort, 42.3% of the patients with treatment-emergent hypertension had a preexisting medical history of hypertension (n/N = 22/52). Among patients in the extended exposure cohort without baseline hypertension, 30 cases of treatment-emergent hypertension were reported, of which 7 cases were new and developed after 1 year. Similar exposure-adjusted incidence rates of treatment-emergent hypertension were reported for the overall safety population (0.87 per 100 person-months) and the extended exposure cohort (0.85 per 100 person-months), while the exposure-adjusted incidence rate of treatment-related hypertension in the extended exposure cohort was only 0.23 per 100 person-months (Table 7). Cumulative incidence rate estimates of hypertension in the overall safety population at 6, 12, 18, and 24 months of exposure were 5.0%, 7.8%, 9.5%, and 10.4%, respectively. Similar results were reported for patients with CLL/SLL and MCL. The results indicate that cumulative incidence of hypertension was low with the incidence of new (not previously occurring) AESIs plateauing after 12 months (extended exposure cohort data shown in Fig. 3 and online suppl. Fig. 2).

Atrial fibrillation was reported in 9 patients (2.8%) in the extended exposure cohort, all of whom had CLL/SLL (Table 3) and 3 (0.9%) events were grade ≥3. One patient in the extended exposure cohort with atrial fibrillation had a history of prior atrial fibrillation. Similar rates of all-grade (2.8%, n = 22) and grade ≥3 (0.9%, n = 9) atrial fibrillation/flutter were observed in the overall safety population. In the extended exposure cohort, atrial fibrillation or flutter did not cause any dose reductions or discontinuations, but 2 cases (0.6%) did lead to dose interruptions. In the extended

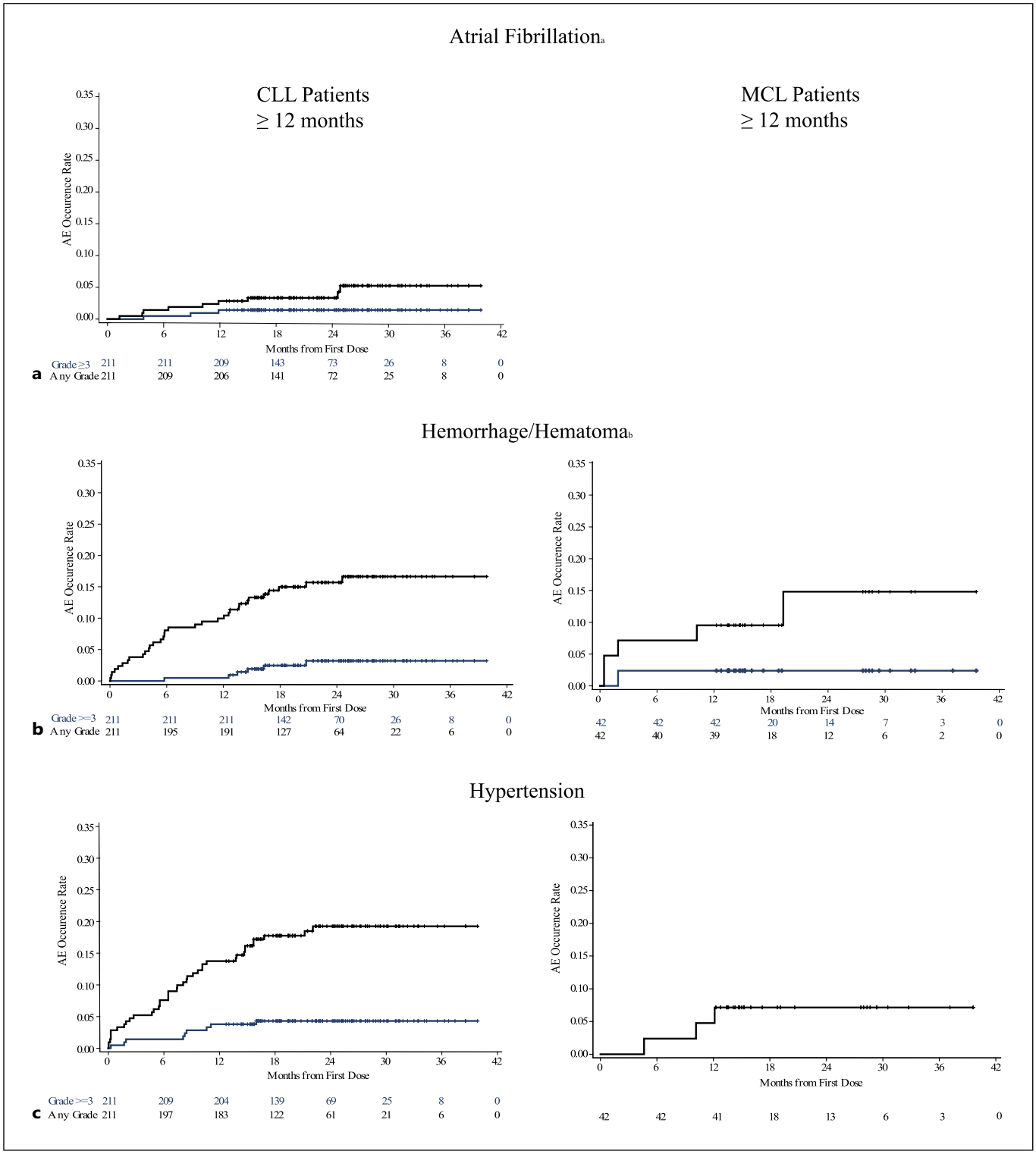

Fig. 3. Cumulative incidence curves illustrating the temporal relationship between selected AESIs and pirtobrutinib exposure in the extended exposure MCL and CLL population. **a** Aggregate of atrial fibrillation and atrial flutter. **b** Aggregate of all preferred terms including hematoma or hemorrhage. **c** Hypertension. A cumulative incidence curve for atrial fibrillation was not estimable for the MCL cohort as no events occurred. Data cutoff date of July 29, 2022.

Table 8. Time to first occurrence of TEAEs and AESIs in the extended exposure MCL and CLL/SLL cohorts following ≥12 months of treatment

	Extended exposure MCL cohort (*n* = 42)			Extended exposure CLL/SLL cohort (*n* = 211)		
	patients experiencing TEAEs, *n*	Median time to onset, months	Min, max, months	patients experiencing TEAEs, *n*	Median time to onset, months	Min, max, months
TEAEs						
Fatigue	14	2.6	0.0, 17.5	72	7.7	0.0, 28.9
Diarrhea	12	4.9	0.0, 27.6	66	3.8	0.0, 27.5
COVID-19	9	12.7	6.5, 35.5	65	14.7	1.0, 33.8
Contusion	9	3.1	0.7, 28.3	57	2.0	0.0, 35.0
Cough	9	6.1	0.6, 22.4	61	9.5	0.1, 28.3
Back pain	10	2.4	0.0, 27.3	44	5.5	0.0, 32.9
Headache	4	14.0	0.1, 21.6	42	6.0	0.0, 29.3
Upper respiratory tract infection	7	2.3	0.6, 19.2	47	10.1	0.4, 27.0
Nausea	3	0.1	0.0, 1.4	37	6.1	0.0, 26.3
Dyspnea	7	3.7	1.0, 22.4	38	9.0	0.0, 24.7
Abdominal pain	3	13.1	12.9, 21.8	42	8.0	0.1, 29.3
Constipation	4	5.5	4.1, 10.6	41	5.3	0.0, 27.2
AESIs[a]						
Bruising[b]	10	2.1	0.0, 28.3	70	1.9	0.0, 25.7
Infections[c]	25	4.8	0.4, 34.2	166	7.6	0.0, 27.8
Neutropenia[d]	5	4.6	0.0, 27.6	71	5.6	0.0, 31.3
Thrombocytopenia[e]	3	2.8	0.4, 26.7	28	5.6	0.0, 26.6
Hemorrhage/ hematoma[f]	5	1.9	0.4, 19.3	33	5.8	0.0, 24.6
Hypertension	3	10.2	4.6, 12.1	39	7.4	0.0, 22.1
Atrial fibrillation/ flutter[g]	0	—	—	9	10.2	1.3, 24.8

Data cutoff date of July 29, 2022. [a]AESIs are those previously associated with cBTKi. [b]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [c]Aggregate of all infections. [d]Aggregate of neutropenia and decreased neutrophil count. [e]Aggregate of thrombocytopenia and decreased platelet count. [f]Aggregate of all preferred terms including hematoma or hemorrhage. [g]Aggregate of atrial fibrillation and atrial flutter.

exposure cohort, the median time to atrial fibrillation onset was 10.2 months and 66.7% of cases occurred before the first 12 months (shown in Fig. 2; Table 8). The exposure-adjusted incidence rate for treatment-emergent atrial fibrillation was lower (0.13 per 100 person-months) in the extended exposure cohort compared to the overall safety population (0.25 per 100 person-months). Cumulative incidence rate estimates generated for the overall safety population to evaluate the onset of atrial fibrillation at 6, 12, 18, and 24 months of exposure were 1.6%, 2.6%, 2.7%, and 2.7%, respectively. The results indicate that cumulative incidence of atrial fibrillation was low with the incidence of new (not previously occurring) AESIs plateauing after 12 months (extended exposure cohort data shown in Fig. 3 and online suppl. Fig. 2).

Discussion

Pirtobrutinib is the first noncovalent BTKi to be approved that has promising efficacy in heavily pretreated patients with B-cell malignancies, even those with prior covalent BTKi exposure. Initial publications demonstrated pirtobrutinib to be well tolerated with a favorable AE profile [16–18]. Data presented in this publication expand on the existing literature and demonstrate that pirtobrutinib can be safely administered to patients in a continuous manner. These safety data after extended pirtobrutinib exposure did not identify significant new AEs developing after 1 year, and the cumulative incidence of AESIs remained low over time, plateauing after 12 months. These data are particularly important in diseases such as CLL/SLL where patients can be treated with a

single-agent targeted therapy for prolonged periods of time. Although CLL/SLL is incurable, novel agents have led to improved long-term survival for patients [23, 24]. BTKis require chronic administration for the treatment of CLL; thus, long-term tolerability of the therapeutic agent is essential in order to fully realize treatment benefit. Pirtobrutinib has shown a high degree of BTK selectivity and minimal off-target inhibition that may lead to reduced toxic side effects [16]. Specifically, pirtobrutinib has demonstrated low rates of key critical AEs such as atrial fibrillation and major hemorrhage across several B-cell malignancies [25], although extended exposure data have been lacking.

The incidence of AEs in patients with extended dosing of pirtobrutinib was consistent with findings from the overall patient population, and no new AEs were observed after 1 year of continuous therapy. Notably, patients in both the extended exposure cohort and overall safety population were heavily pretreated (median of 3 prior lines of therapy), with the majority having at least 1 prior BTKi and associated toxicities. Moreover, despite prolonged drug dosing, the analysis of rates of early-onset toxicities, including grade ≥3 AESIs, showed a plateau over time indicating the relatively low frequency of events occurring after 1 year of therapy, and very few treatment discontinuations and reductions. AEs leading to dose reductions (0.9%) or discontinuations (6.6%) were also low after 1 year of therapy among patients in the extended exposure CLL/SLL cohort, critical for success with oral continuous targeted agents.

Infections were the most common AE observed in the extended exposure cohort (73.0%), particularly respiratory tract infections such as COVID-19 infections that were observed in over 30% of patients. Infections were also the most common fatal AE among patients in the extended exposure cohort (11 patients). One patient (0.3%) required a dose reduction and 2 patients (0.6%) required dose discontinuations due to infections in the extended exposure cohort. Neutropenia and dysfunction of normal B cells contributed to the risk of infection [26, 27]. The increased risk of infection due to immunosuppression and prior treatments also remains a challenge for patients with hematologic malignancies. Additionally, since the study was conducted prior to widespread availability of the COVID-19 vaccine, complete information regarding the impact of vaccination is unknown.

Prolonged use of the BTKi class has shown the potential for emergent off-target toxicities such as bleeding and cardiac toxicities, including atrial fibrillation [28–30]. However, long-term administration of pirtobrutinib in BRUIN, which enrolled older patients with a history of atrial fibrillation and on concomitant anticoagulation therapy, resulted in low incidences of atrial fibrillation and hemorrhage/hematoma. Cardiovascular AEs such as atrial fibrillation and hypertension were reported in 4.3% and 18.5% of patients in the CLL-extended exposure cohort. These rates are generally consistent with the incidence of atrial fibrillation and hypertension reported in the untreated CLL population [31, 32]. Atrial fibrillation and hypertension are also more commonly observed in older individuals who are representative of those requiring therapy for CLL/SLL [33]. The cumulative incidence for these AEs did not indicate a relationship between new AE incidence and time on drug. The eventual plateauing of these curves may also indicate minimal concern over the late onset of these AEs. The rates of these cardiovascular AEs in the overall safety population were generally similar to those seen in other long-term follow-up studies with covalent BTK inhibitors such as acalabrutinib and zanubrutinib [13, 34], although some of these studies were in BTKi-naïve patients and did not select for patients with extended exposure. While encouraging and illustrative of the minimal off-target effects of pirtobrutinib, a continued follow-up is required to fully characterize long-term cardiovascular toxicity and bleeding profiles.

When interpreting the results presented in this post hoc exploratory analysis, the following limitations should be considered. The cohort of patients receiving pirtobrutinib for at least 12 months included patients who did not discontinue treatment due to progression or AEs within the first 12 months, resulting in an inherent selection bias. The BRUIN trial lacked an active control group, and the near absence of prospective data for other modern therapies following the use of BTKis limits direct comparisons with available therapeutics in this clinical context. A longer-term follow-up of the patients in the extended exposure cohort and the 5 ongoing phase 3 randomized trials utilizing pirtobrutinib is warranted.

The data presented here, including adjusted AE rates evaluating the cumulative effects of prolonged exposure and defining the onset timing, demonstrate the safety and tolerability of extended exposure to pirtobrutinib and offer the most comprehensive evaluation of safety to date for pirtobrutinib monotherapy. Prolonged pirtobrutinib therapy continues to demonstrate a favorable safety profile consistent with that observed in the overall safety population, without evidence of new or worsening toxicity.

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Statement of Ethics

This study protocol was reviewed and approved by ethics committees at each of the participating sites. This full list of participating site and ethics committees can be found in the online supplementary material. The trial (NCT03740529) was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws. Written informed consent was obtained from all the patients.

Conflict of Interest Statement

L.E.R. has served as a consultant for AbbVie, Ascentage, AstraZeneca, BeiGene, Janssen, Loxo Oncology, Pharmacyclics, Pfizer, and TG Therapeutics; has served as a CME speaker for DAVA, Curio, Medscape, and PeerView; holds minority ownership interest in Abbott Laboratories; has received travel support from Loxo Oncology; and has received research funding (paid to institution) from Adaptive Biotechnologies, AstraZeneca, Genentech, AbbVie, Pfizer, Loxo Oncology, Aptose Biosciences, Dren Bio, and Qilu Puget Sound Biotherapeutics. C.C.C. has received honoraria/served as a consultant for AbbVie, Allogene, AstraZeneca, BeiGene, Genentech, Janssen, Loxo/Eli Lilly and Company, MEI Pharma, MingSight, Octapharma, and TG Therapeutics; has served on speaker's bureau for AbbVie, AstraZeneca, BeiGene, and Genentech; and has received research funding (paid to institution) from AbbVie and Loxo/Eli Lilly and Company. 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Conception and design: C.E.M., S.A., and M.W. Acquisition and analysis of data: L.E.R., C.C.C., N.N.S., W.J., J.A.W., C.Y.C., K.P., Y.W., T.M., Y.K., C.E.M., C.W., R.S., S.H., D.E.T., T.A.E., and M.W. Interpretation of data: L.E.R., C.C.C., N.N.S., W.J., K.P., K.M., Y.W., P.L.Z., M.C.T., C.E.M., C.W., R.S., S.A., S.H., T.A.E., and M.W. Manuscript writing and critical revisions to manuscript; all authors provided final approval of the manuscript: L.E.R., C.C.C., N.N.S., W.J., J.A.W., C.Y.C., K.P., K.M., Y.W., P.L.Z., T.M., Y.K., M.C.T., C.E.M., C.W., R.S., S.A., S.H., D.E.T., T.A.E., and M.W.

Data Availability Statement

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once the data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org. Further inquiries can be directed to the corresponding author.

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