Pirtobrutinib monotherapy in Bruton tyrosine kinase inhibitor-intolerant patients with B-cell malignancies: results of the phase I/II BRUIN trial

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Abstract

Bruton tyrosine kinase inhibitors (BTKi) have transformed the treatment of B-cell malignancies, but intolerance has often led to their discontinuation. The phase I/II BRUIN study evaluated pirtobrutinib, a highly selective non-covalent (reversible) BTKi, in patients with relapsed / refractory B-cell malignancies (clinicaltrials.gov 03740529). Pirtobrutinib was investigated in 127 patients with intolerance to at least one prior BTKi therapy in the absence of progressive disease. The most common adverse event (AE) leading to BTKi discontinuation was cardiac disorders (N=40, 31.5%), specifically atrial fibrillation (N=30, 23.6%). The median follow-up was 17.4 months and the median time on pirtobrutinib was 15.3 months. The most common

reasons for pirtobrutinib discontinuation were progressive disease (26.8%), AE (10.2%) or death (5.5%). The most frequent treatment-emergent AE were fatigue (39.4%) and neutropenia (37.0%). Among patients who discontinued a prior BTKi for a cardiac issue, 75% had no recurrence of their cardiac AE. No patient discontinued pirtobrutinib for the same AE that led to discontinuation of the prior BTKi. In 78 chronic lymphocytic / small lymphocytic lymphoma (CLL/SLL) and 21 mantle cell lymphoma (MCL) patients intolerant to prior BTKi, overall response rate to pirtobrutinib was 76.9% and 81.0%, respectively. Median progression-free survival for CLL/SLL was 28.4 months but was not estimable for MCL. These results suggest that pirtobrutinib was safe, well-tolerated, and an efficacious option in patients with prior BTKi-intolerance.

Introduction

Covalent (c) Bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib, acalabrutinib and zanubrutinib have changed the treatment landscape for patients with B-cell malignancies. These cBTKi are commonly administered as monotherapy using continuous dosing. However, a significant number of patients develop cBTKi intolerance due to therapy-limiting adverse events (AE) such as atrial fibrillation, bleeding, diarrhea, rash, arthralgias, and infections.[1,2] Real-world analyses have suggested that intolerance accounts for about half of discontinuations for patients treated with ibrutinib.[3,4] AE that lead to BTKi discontinuation may limit efficacy, as continued inhibition of the B-cell receptor signaling pathway is key to its mechanism of action. Similarly, treatment interruptions and dose reductions due to AE may further reduce efficacy and impact long-term outcomes.[5] The toxicity profile of cBTKi agents has largely been attributed to the variable selectivity for BTK and binding to off-target kinases that leads to adverse off-target events.[1,2,6] The binding of cBTKi agents, for example, to epidermal growth factor receptor (EGFR) may lead to diarrhea and rash, whereas off-target tec protein tyrosine kinase (TEC) inhibition may lead to platelet dysfunction and bleeding.[2] Although later generation cBTKi appear to be more selective than ibrutinib, leading to a more favorable toxicity profile, intolerance still remains a concern. Phase II studies have examined acalabrutinib and zanubrutinib, which have been shown to have improved selectivity compared to ibrutinib, in patients that have demonstrated intolerance to a previous cBTKi. Despite improved toxicity profiles with reduced rates of recurrence of AE after intolerance to another cBTKi, therapy with these agents also resulted in some toxicity. For patients who received acalabrutinib after prior ibrutinib intolerance, 27 ibrutinib intolerance events occurred in 24/60 (40%) acalabrutinib-treated patients, with 18 events at a lower grade, 8 events at the same grade, and one event at a higher grade with acalabrutinib than had been observed with ibrutinib.[7] In addition, 7/34 ibrutinib intolerance events and 2/3 acalabrutinib events still recurred with a therapeutic switch to zanubrutinib.[8] Discontinuations after prior cBTKi intolerance due to AE occurred in 16.7% of patients that received acalabrutinib and in up to 20% of those who transitioned to zanubrutinib.[7,8]

Pirtobrutinib is a highly selective non-covalent (reversible) BTKi with favorable oral pharmacology that enables continuous BTK inhibition throughout the once daily dosing interval, regardless of intrinsic rate of BTK turnover. It has greater than 300-fold selectivity for BTK compared to 363 (98%) of 370 other kinases tested, thereby potentially lowering the risk of off-target toxicities.[9] Data also suggest that pirtobrutinib binding enhances the stability of BTK in its closed, inactive conformation whereas cBTKi binding favors the open active conformation.[10] The inactive BTK conformation by pirtobrutinib binding may interact with fewer cellular proteins than cBTKi-bound BTK, thereby inhibiting kinase-independent BTK cellular signaling, and potentially limiting toxicity.[10] Pirtobrutinib selectivity for BTK has translated into a tolerable safety profile across multiple B-cell malignancies, with low overall treatment-related AE and few discontinuations due to drug-related AE: 2.8% in patients with chronic lymphocytic / small lymphocytic lymphoma (CLL/SLL) and 3% in patients with relapsed / refractory mantle cell lymphoma (MCL).[11,12] In January 2023, pirtobrutinib received accelerated approval in the USA to treat relapsed or refractory MCL after at least 2 lines of systemic therapy including prior BTKi treatment.[13] On December 1, 2023, the US Food and Drug Administration (FDA) granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least 2 prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor.[14] Here we explored the safety and efficacy of pirtobrutinib in patients from the phase I/II BRUIN study who had previously demonstrated intolerance to BTKi therapy and were without progressive disease.

Methods

Patients

Patients previously treated for CLL/SLL, MCL, and other B-cell non-Hodgkin lymphoma (NHL) were enrolled in the open-label, multi-center phase I/II BRUIN study.[9,11] Patients received pirtobrutinib at doses ranging from 25 to 300 mg once daily in 28-day cycles in the phase I portion, and the recommended dose of 200 mg once daily in the phase II portion. The BRUIN study permitted enrollment of patients with ongoing anti-coagulation / anti-platelet treatment (excluding warfarin) and patients with controlled atrial fibrillation at the time of enrollment. Patients with a history of

atrial fibrillation on prior BTKi were also allowed to enter the study. Treatment with pirtobrutinib continued until disease progression, unacceptable toxicity, or withdrawal.

All patients who received at least one dose of pirtobrutinib comprised the overall safety population. Patients who had received prior BTKi and discontinued due to intolerance, defined as having discontinued treatment due to persistent / recurrent AE as assessed by the physician in the absence of progressive disease, comprised the prior BTKi-intolerant subgroup.

The institutional review boards or independent ethics committees overseeing each site approved the BRUIN study protocol, and the study was carried out in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws. All patients provided written informed consent.

Assessment of adverse events

The following reasons for discontinuing a prior BTKi due to intolerance were collected: bleeding, atrial fibrillation, neutropenia, cardiac events, diarrhea, arrhythmia, infection, and other events including rash, arthralgias / myalgias, fatigue, and pain. More than one AE could be reported in an individual patient. Data concerning the severity of the AE leading to discontinuation of a prior BTKi was not collected.

Safety with pirtobrutinib treatment was determined by frequency and severity of AE, graded according to the Common Terminology Criteria for Adverse Events version 5.0. Treatment emergent AE (TEAE) were defined as all AE reported from the date of the first dose through the date of the last dose plus 37 days or start of subsequent anticancer therapy, whichever was earlier. Treatment-related AE (TRAE) were defined as all TEAE with an investigator-determined attribution related to pirtobrutinib.

Statistical analysis

A data cutoff of 29 July 2022 was used for all analyses. The AE categories that led to discontinuation of a prior BTKi were summarized using frequencies and percentages. Atrial fibrillation was reported individually and also under the category of cardiac disorders. Diarrhea was reported individually and also under the category of gastrointestinal disorders. Pirtobrutinib TEAE recurring in the same patient as those leading to prior BTKi discontinuation were summarized. Pirtobrutinib TEAE and TRAE were also summarized by type and severity, according to maximum grade, using frequencies and percentages. In addition, efficacy data for patients in the prior BTKi intolerant subgroup who had CLL/SLL or MCL were determined. Overall response rate (ORR) as assessed by the investigator, and using either the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines[15] or the Lugano criteria[16] for CLL/SLL and MCL, respectively, was estimated with corresponding 95% two-sided exact Confidence Intervals (CI). The Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS). Analyses were performed using SAS version 9.4.

Table 1. Patients' characteristics.

Characteristics	Prior BTKi-intolerant N=127
Disease types, N (%)	
CLL/SLL	78 (61.4)
MCL	21 (16.5)
WM	16 (12.6)
RT	8 (6.3)
FL/MZL	4 (3.1)
Age in years, median (range)	70 (42-87)
<50	2 (1.6)
50-64	36 (28.3)
65-74	53 (41.7)
75-84	33 (26.0)
≥85	3 (2.4)
Male, N (%)	81 (63.8)
ECOG PS, N (%)	
0	70 (55.1)
1	48 (37.8)
2	9 (7.1)
Prior lines of systemic therapy, median (range)	3 (1-11)
Prior systemic therapy, N (%)	
BTKi	127 (100)
Anti-CD20 antibody	108 (85.0)
Chemotherapy	97 (76.4)
BCL2 inhibitor	34 (26.8)
PI3K inhibitor	24 (18.9)
Immunomodulator	13 (10.2)
Stem cell transplant	9 (7.1)
Autologous	7 (5.5)
Allogeneic	2 (1.6)
CAR T-cell therapy	9 (7.1)
Other systemic therapy	35 (27.6)
Prior lines of BTKi, N (%)	
1	81 (63.8)
2	34 (26.8)
≥3	12 (9.4)
Prior BTKi therapy with toxicity as reason for discontinuation, N (%)*	
Ibrutinib	120 (94.5)
Acalabrutinib	9 (7.1)
Nemtabrutinib	4 (3.1)
Zanubrutinib	3 (2.4)
DTRMWXHS-12	1 (0.8)
Time in months since end of last prior BTKi discontinued for toxicity to first pirtobrutinib dose, median (range)	18.8 (0.1-90.5)

*Sum >100% due to some patients having multiple prior Bruton tyrosine kinase inhibitors (BTKi). CLL: chronic lymphocytic lymphoma; SLL: small lymphocytic lymphoma; MCL: mantle cell lymphoma; WM: Waldenström macroglobulinemia; RT: Richter transformation; FL: follicular lymphoma; MZL: marginal zone lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; BTKi: Bruton tyrosine kinase inhibitors; BCL2: B-cell lymphoma 2; PI3K: phosphatidylinositol 3-kinase; CAR: chimeric antigen receptor; N: number.

Results

Patients and treatment

As of July 29, 2022, 773 patients with CLL/SLL, MCL, or other NHL were enrolled in the BRUIN study and received at least one dose of pirtobrutinib. Of these, 597 patients had received a prior BTKi-containing regimen, and 127 patients discontinued at least one prior BTKi-containing regimen in the absence of progressive disease (either as monotherapy or a combination regimen) (*Online Supplementary Table S1*) due to intolerance (cBTKi ibrutinib N=120, acalabrutinib N=9, zanubrutinib N=3, and DTRMWXHS-12 N=1 or non-covalent BTKi nemtabrutinib N=4) (Table 1, *Online Supplementary Figure S1*). At the time of enrollment to BRUIN, the median age for patients with prior BTKi intolerance was 70 years (range: 42-87), and Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0, 1, and 2 in 55.1%, 37.8%, and 7.1% of patients respectively, and was similar to the overall safety population (*Online Supplementary Table S2*). Median number of prior lines of systemic therapy for the BTKi intolerant subgroup was 3 (range: 1-11). The median time from the end of last BTKi containing-regimen discontinued due to intolerance to the first dose of pirtobrutinib was 18.8 months (range: 0.1-90.5). At the time of the data cutoff date, median study follow-up for all patients was 17.4 months (range: 0.5-39.9) and median time on pirtobrutinib treatment was 15.3 months (range: 0.2-39.9).

Adverse events leading to discontinuation of prior Bruton tyrosine kinase inhibitors

The most common AE that led to the discontinuation of a prior BTKi therapy (i.e., prior to participation in the BRUIN study) were cardiac disorders (N=40, 31.5%; [primarily atrial fibrillation: N=30, 23.6%]), infections (N=13, 10.2%), neutropenia (N=12, 9.4%), rash (N=11, 8.7%), arthralgias / myalgias (N=10, 7.9%), bleeding / hemorrhage (N=9, 7.1%), gastrointestinal disorders (N=8, 6.3%; [diarrhea: N=6, 4.7%]), fatigue (N=6, 4.7%), and pain (N=6, 4.7%) (Table 2). Other cardiac disorders included cardiac events that were not specified (N=5), atrial flutter (N=2), palpitations (N=2), cardiac failure (N=1), ventricular tachyarrhythmia (N=1), ventricular tachycardia (N=1). Though hypertension is commonly associated with cBTKi treatment, it was not a common AE that led to discontinuation of a prior BTKi therapy (N=3, 2.4%).

Recurrence of adverse events that had previously led to discontinuation of prior Bruton tyrosine kinase inhibitors

For a given patient and TEAE category that led to prior BTKi discontinuation, recurrence rates of the same TEAE

Table 2. Adverse events that led to discontinuation of prior Bruton tyrosine kinase inhibitors.[a]

Adverse events	AE by prior BTKi N (%)			
	Any BTKi N=127	Ibrutinib N=120	Acalabrutinib N=9	Zanubrutinib N=3
Cardiac disorders Atrial fibrillation	40 (31.5) 30 (23.6)	39 (32.5) 30 (25.0)	1 (11.1) -	- -
Infection	13 (10.2)	13 (10.8)	-	-
Neutropenia[b]	12 (9.4)	9 (7.5)	1 (11.1)	1 (33.3)
Rash	11 (8.7)	9 (7.5)	-	-
Arthralgias/myalgias	10 (7.9)	9 (7.5)	2 (22.2)	-
Bleeding/hemorrhage[c]	9 (7.1)	8 (6.7)	1 (11.1)	-
Gastrointestinal disorders Diarrhea	8 (6.3) 6 (4.7)	7 (5.8) 5 (4.2)	1 (11.1) 1 (11.1)	- -
Fatigue	6 (4.7)	5 (4.2)	-	1 (33.3)
Pain	6 (4.7)	6 (5.0)	1 (11.1)	-
Unknown	5 (3.9)	3 (2.5)	1 (11.1)	-
Depression	2 (1.6)	1 (0.8)	1 (11.1)	-
Headache	2 (1.6)	-	1 (11.1)	-
Joint effusion	1 (0.8)	-	-	1 (33.3)

[a]Common adverse event (AE) categories that led to prior Bruton tyrosine kinase inhibitor (BTKi) discontinuation in at least 5% of patients or that occurred with acalabrutinib or zanubrutinib are shown; an individual patient may be counted in more than one AE category. [b]Neutropenia is an aggregate of decreased neutropenia and neutrophil count. [c]Included bleeding events not specified, hemorrhage, hematoma, hematuria, and intracranial hemorrhage. N: number.

category in the same patient treated with pirtobrutinib are shown in Figure 1. Except for infections, neutropenia, and gastrointestinal disorders, the TEAE that led to discontinuation of a prior BTKi did not recur in the majority of patients receiving pirtobrutinib. If there was a recurrence, with the exception of infections and neutropenia, it was usually of low grade (grade 1 or 2; see Figure 1 light blue bars). The observed rates of high-grade events (i.e., grade 3 or higher; see Figure 1 orange bars) while on pirtobrutinib were 7.5% (3/40) for cardiac disorders (including sinus tachycardia N=1 and atrial fibrillation N=2) and 12.5% (1/8) for gastrointestinal disorders (small intestinal obstruction). Of the 30 patients who discontinued prior BTKi due to atrial fibrillation, 2 had recurrence that was grade 4. Of the 6 patients who discontinued prior BTKi due to diarrhea, one had grade 1 recurrence. In the 3 patients who discontinued prior BTKi due to hypertension, one had a grade 1 recurrence. No patient who discontinued a prior BTKi due to a TEAE discontinued pirtobrutinib for the same TEAE.

Since patients who start pirtobrutinib after an extended gap from their last prior BTKi therapy might be expected to have less toxicity than those who start pirtobrutinib soon after their last prior BTKi therapy, recurrence of AE that led to discontinuation of prior BTKi was examined according to subgroups categorized by the median duration from last prior BTKi therapy to start of pirtobrutinib (18.8 months). No patterns in toxicity were identified for any of these subgroups, although it should be noted that patient numbers were small (*Online Supplementary Table S3*).

Pirtobrutinib safety profile in prior Bruton tyrosine kinase inhibitor-intolerant patients

A summary of TEAE and TRAE occurring in the 127 patients with prior BTKi-intolerance and who were treated with pirtobrutinib is shown in Table 3. The most frequent TEAE of any grade included fatigue (39.4%), neutropenia (37.0%), and diarrhea (29.9%). Grade ≥3 infections occurred in 24.4% of patients. Dose reductions due to TRAE occurred in 9% (N=11) of patients. As reference, TEAE and TRAE for the overall safety population (N=773) were similar to those seen among the BTKi-intolerant patients and are included in *Online Supplementary Table S4*.

Among the patients with prior BTKi-intolerance, 65 (51.2%) remain on pirtobrutinib treatment with a median time on treatment of 15.3 months (range: 0.2-39.9). The most

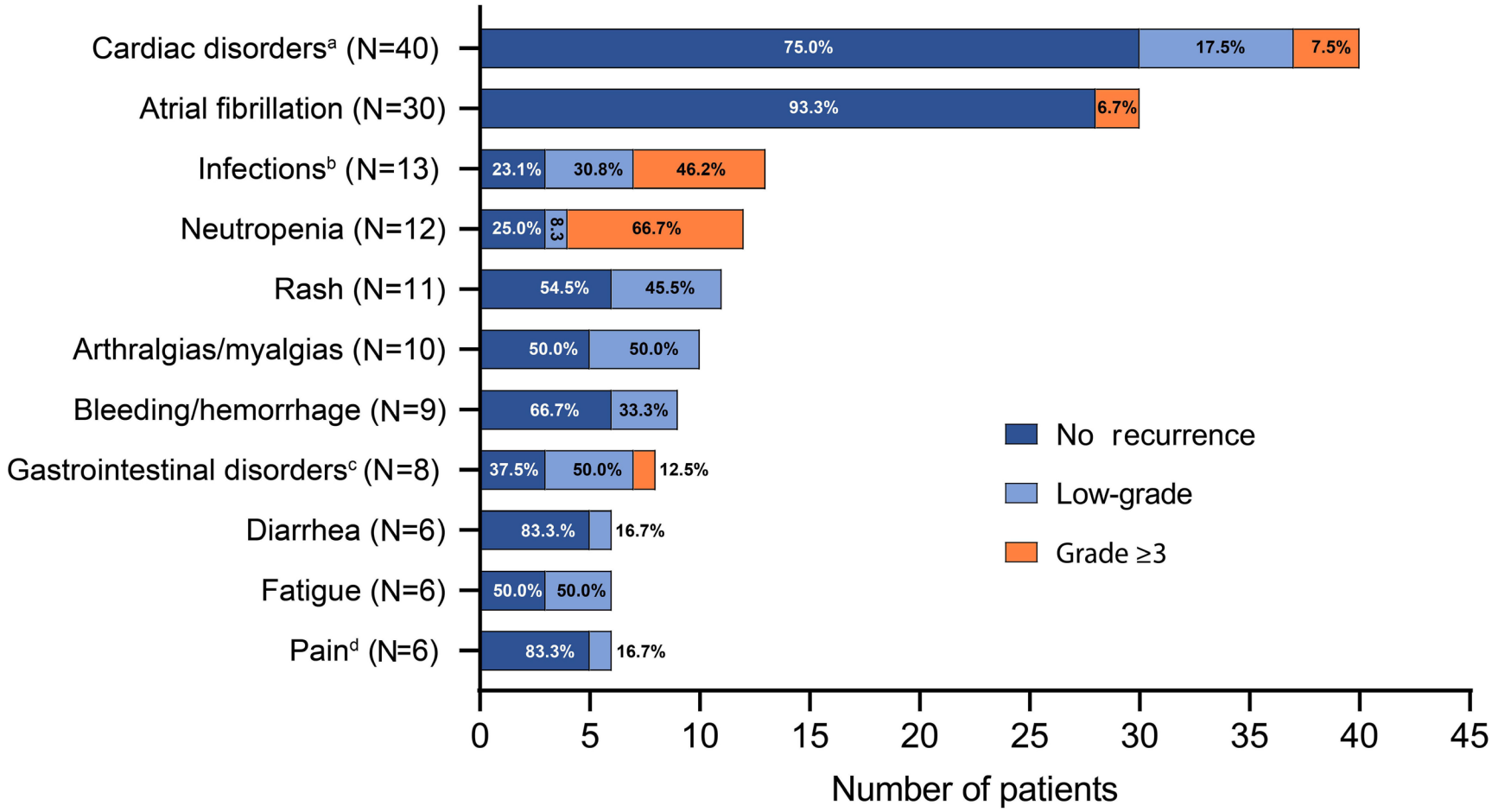


Figure 1. Recurrence with pirtobrutinib treatment of treatment emergent adverse events that had previously led to discontinuation of prior Bruton tyrosine kinase inhibitor within the same patient. Common treatment emergent adverse event (TEAE) categories that had led to discontinuation of prior Bruton tyrosine kinase inhibitor (BTKi) are shown; an individual patient may be counted in more than one category. [a]Cardiac disorders include atrial fibrillation. [b]Prior discontinuation infection types were not specified for most patients, so any infection recurrence was investigated. Among the 6 patients with a grade >3 infection recurrence, 11 grade ≥3 events were reported and included: diarrhea and salmonellosis in 1 patient; bacteremia, septic shock, and fungal pneumonia in 1 patient; pneumonia, COVID-19, and COVID-19 pneumonia in 1 patient; and pneumonia, viral pneumonia, and COVID-19 pneumonia each in 1 patient. [c]Gastrointestinal disorders include diarrhea. [d]One patient had recurrence of pain in the same site, 3 had new / different pain, and 2 had no pain; no patient discontinued pirtobrutinib for pain.

common reason for pirtobrutinib treatment discontinuation was progressive disease (N=34, 26.8%). Twenty (15.7%) patients discontinued pirtobrutinib treatment due to AE (N=13) or death (N=7) (*Online Supplementary Table S5*). Seven of these AE were considered related to pirtobrutinib treatment: COVID-19 pneumonia (grade 5), myalgia (grade 2), neutropenia (grade 3), platelet count decrease (grade 3), maculo-papular rash (grade 2), skin necrosis (grade 3), and staphylococcal sepsis (grade 3). Other reasons for discontinuation were intercurrent illness (N=1), alternative treatment per investigator (N=2), consent withdrawal (N=4), and other (N=1).

Table 3. Pirtobrutinib safety profile.

Adverse events	BTKi-intolerant N=127			
	All cause AE, %		Treatment-related AE, %	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	39.4	3.9	9.4	1.6
Neutropenia[a]	37.0	31.5	21.3	17.3
Diarrhea	29.9	1.6	12.6	0.8
Contusion	29.1	0.0	22.0	0.0
Cough	26.8	0.0	4.7	0.0
Headache	25.2	0.8	7.1	0.8
COVID-19	22.8	4.7	0.0	0.0
Abdominal pain	22.0	2.4	4.7	0.8
Dyspnea	22.0	2.4	5.5	0.0
Nausea	20.5	0.0	4.7	0.0
AE of interest[b]				
Infections[c]	68.5	24.4	14.2	5.5
Infections (excluding COVID-19)	59.8	17.3	14.2	5.5
Bruising[d]	36.2	0.0	26.8	0.0
Rash[e]	22.8	0.8	8.7	0.8
Arthralgia	21.3	0.8	4.7	0.0
Hemorrhage/hematoma[f]	14.2	3.1	4.7	0.8
Hypertension	7.9	0.8	3.1	0.0
Atrial fibrillation/flutter[g]	4.7	1.6	0.8	0.0

Median time on treatment for the BTKi-intolerant population was 15 months. [a]Aggregate of preferred terms including neutropenia or neutrophil count decreased. [b]Adverse events (AE) of interest are those that were previously associated with covalent Bruton tyrosine kinase inhibitors (BTKi). [c]Aggregate of all preferred terms indicating infection and including COVID-19. [d]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [e]Aggregate of all preferred terms including rash. [f]Aggregate of all preferred terms including hemorrhage or hematoma. [g]Aggregate of atrial fibrillation and atrial flutter. No occurrences of atrial flutter were reported. N: number.

Efficacy in prior Bruton tyrosine kinase inhibitor-intolerant patients

Within the subgroup of patients with prior BTKi-intolerance, there were 78 patients with CLL/SLL and 21 patients with MCL evaluated for efficacy. The ORR to pirtobrutinib treatment after prior BTKi intolerance for patients with CLL/SLL was 76.9% (95% CI: 66.0-85.7), including 58 (74.4%) patients with partial response and 2 (2.6%) with partial response including lymphocytosis. An additional 12 (15.4%) patients had stable disease. The ORR to pirtobrutinib treatment for patients with MCL after prior BTKi intolerance was 81.0% (95% CI: 58.1-94.6), including 9 (42.9%) patients with complete response and 8 (38.1%) with partial response (Table 4). The maximum percent change in the sum of the product diameters relative to baseline for patients with CLL/SLL or MCL is shown in Figure 2. With a median follow-up of 19.4 months for patients with CLL/SLL and 14.8 months for patients with MCL, median PFS for patients with CLL/SLL was 28.4 months (95% CI: 21.8-not estimable), while median PFS was not estimable for patients with MCL (Figure 3). The 18-month PFS rate was 74.2% (95% CI: 61.5-83.3%) for CLL/SLL and 61.9% (95% CI: 33.1-81.3%) for MCL. With a median follow-up of 20.8 months for the patients with CLL/SLL and 26.8 months for patients with MCL, the 18-month OS rates were 84.1% (95% CI: 72.9-90.9%) and 72.4% (95% CI: 45.6-87.6%), respectively. Median OS was not estimable for CLL/SLL or MCL.

Among the 78 patients with CLL/SLL, ORR rates were determined for the subgroups of patients categorized by the median duration from last prior BTKi therapy to start of pirtobrutinib (18.8 months). Although the ORR rate was numerically higher for patients with longer duration from last prior BTKi therapy to start of pirtobrutinib (81.8%, 95% CI: 67.3-91.8) compared to those with shorter duration from last prior BTKi therapy to start of pirtobrutinib (70.6%, 95%

Table 4. Pirtobrutinib efficacy in patients intolerant to prior Bruton tyrosine kinase inhibitor.

Response	CLL/SLL N=78	MCL N=21
Overall response rate,[a] % (95% CI)	76.9 (66.0-85.7)	81.0 (58.1-94.6)
Best response, N (%)		
Complete response	0 (0.0)	9 (42.9)
Partial response	58 (74.4)	8 (38.1)
Partial response with lymphocytosis	2 (2.6)	NA
Stable disease	12 (15.4)	1 (4.8)
Progressive disease	3 (3.8)	1 (4.8)
Not evaluable	3 (3.8)	2 (9.5)

[a]Response by investigator assessment based on International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2018 guidelines for chronic lymphocytic lymphoma (CLL) / small lymphocytic lymphoma (SLL) and Lugano 2014 criteria for mantle cell lymphoma (MCL), respectively. CI: Confidence Interval; N: number; NA: not applicable.

CI: 52.5-84.9), the Confidence Intervals overlapped (*Online Supplementary Table S6*).

Discussion

Covalent Bruton tyrosine kinase inhibitors are most commonly discontinued in clinical trial patients and real-world practice because of toxicities and disease progression.[17] Data suggest switching to acalabrutinib or zanubrutinib after ibrutinib intolerance may result in lower rates of AE recurrence caused by prior BTKi treatment.[1,7,8] In this retrospective analysis, we characterized the safety and efficacy of pirtobrutinib monotherapy in patients who had previously discontinued a BTKi due to intolerance. While the vast majority of patients (120/127) had discontinued a treatment containing the first-generation cBTKi ibrutinib,[18] we also examined a limited number of intolerant patients who had received acalabrutinib or zanubrutinib (only 5 patients received either acalabrutinib or zanubrutinib without first receiving ibrutinib). AE that led to the discontinuation of a prior BTKi were consistent with the toxicities associated with intolerance to ibrutinib, acalabrutinib, and zanubrutinib.[7,8] Overall, pirtobrutinib treatment was well tolerated, and recurrence of AE that commonly led to prior discontinuation were infrequent and of low grade.

Pirtobrutinib has been shown to be highly selective for BTK when evaluated against 370 kinases.[9] The highly selective nature of pirtobrutinib may account for the low rates of recurrence of most AE that previously led to a patient discontinuing a cBTKi. As an exception, neutropenia recurred in 75% (N=9, 8.3% low grade and 66.7% grade >3) of the 12 patients who had previously discontinued a cBTKi for neutropenia, and infections recurred in 77% (N=10, 30.8% low grade and 46.2% grade >3) of the 13 patients who previously discontinued a cBTKi for infection. This study was conducted mostly during the time of the COVID-19 pandemic before an active vaccine was available. Infections occurring in more than one of these 13 patients were COVID-19 (N=4), pneumonia (N=4), COVID-19 pneumonia (N=2), and urinary tract infection (N=2). The neutropenia and infection findings highlight the immunosuppressed nature of patients with hematologic malignancies, and show the importance of careful patient monitoring and vaccinations.

The most common reason for patients to discontinue a prior BTKi was a cardiac disorder. Only 10 of 40 patients (25%) had recurrence of any cardiac disorder with pirtobrutinib. Recognizing that an association between atrial fibrillation and the covalent BTKi agents has been observed across multiple studies,[19] among the 30 patients in this study who discontinued a prior cBTKi due to atrial fibrillation, recurrence with pirtobrutinib occurred in only 2 patients. These results are consistent with the broader BRUIN B-cell malignancy patient population where atrial fibrillation was reported in 21 of 773 (2.7%) patients receiving pirtobrutinib monotherapy. These results suggest that it may be possible to reduce the occurrence of atrial fibrillation induced by a cBTKi by using pirtobrutinib. As for AE of special interest, bleeding and hypertension have been commonly associated with cBTKi treatment.[2,20,21] Of the 9 patients in this study that previously discontinued a cBTKi due to bleeding/hemorrhage, 3 had recurrence but no major hemorrhage (grade ≥3) was reported.

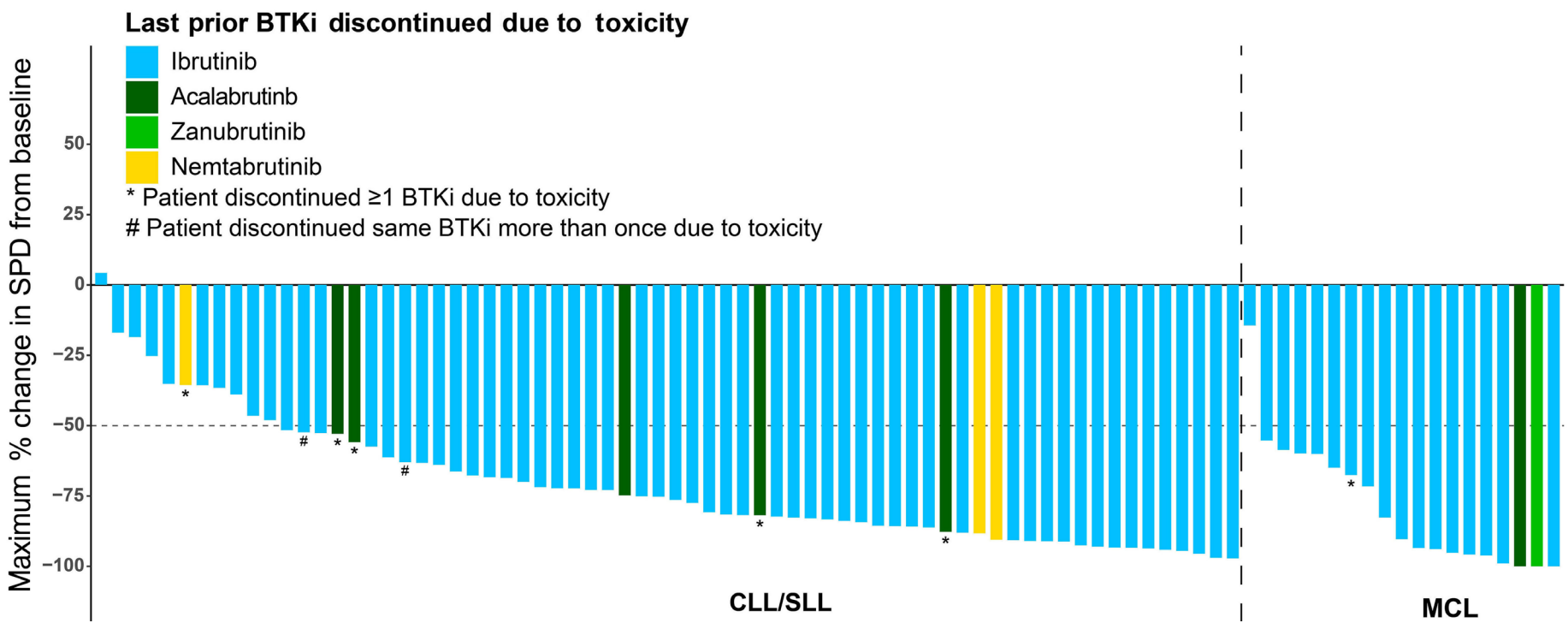
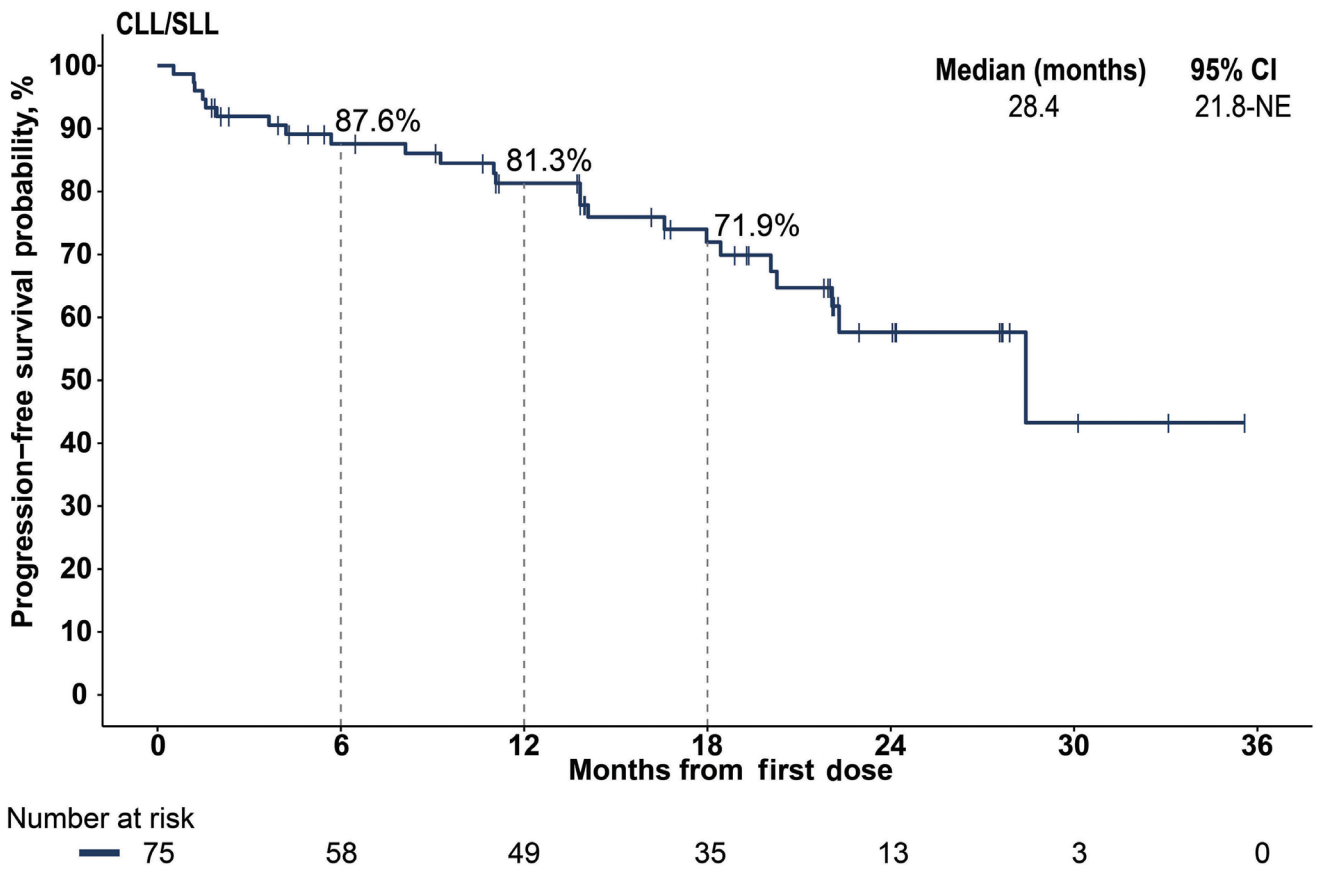


Figure 2. Pirtobrutinib efficacy in patients intolerant to prior Bruton tyrosine kinase inhibitor. Waterfall plot of best change in tumor burden based on investigator assessments. Best change in tumor size was defined as the maximum % change in the sum of product diameters (SPD) at a post-baseline assessment relative to baseline. Pirtobrutinib exhibited promising efficacy across B-cell malignancies among patients who experienced intolerance to prior Bruton tyrosine kinase inhibitor (BTKi). Data for 12 patients are not shown due to 6 patients having no target lesions identified at baseline, and 6 patients with no / incomplete post-baseline lesion measurements. CLL: chronic lymphocytic lymphoma; SLL: small lymphocytic lymphoma.

Similarly, of 3 patients who discontinued a prior cBTKi due to hypertension, one had grade 1 recurrence in this study. Overall, there was low frequency of pirtobrutinib discontinuations due to an AE. Discontinuation of pirtobrutinib due to TRAE occurred in 7 (5.5%) patients with B-cell malignancies who were previously intolerant to BTKi, which was consistent with the 2.6% discontinuation rate due to TRAE seen among all patients treated with pirtobrutinib monotherapy in the phase I/II BRUIN study.

The data presented here suggest pirtobrutinib may be an option after cBTKi intolerance as no patient stopped pirtobrutinib for the same AE that had led to prior BTKi intolerance. These low rates of discontinuation after prior intolerance may be important in the clinical management of B-cell malignancies by allowing BTK inhibition to be maintained without having to switch to another drug class.[7] In addition, pirtobrutinib was highly efficacious and extended BTK inhibition for these prior BTKi-intolerant patients as



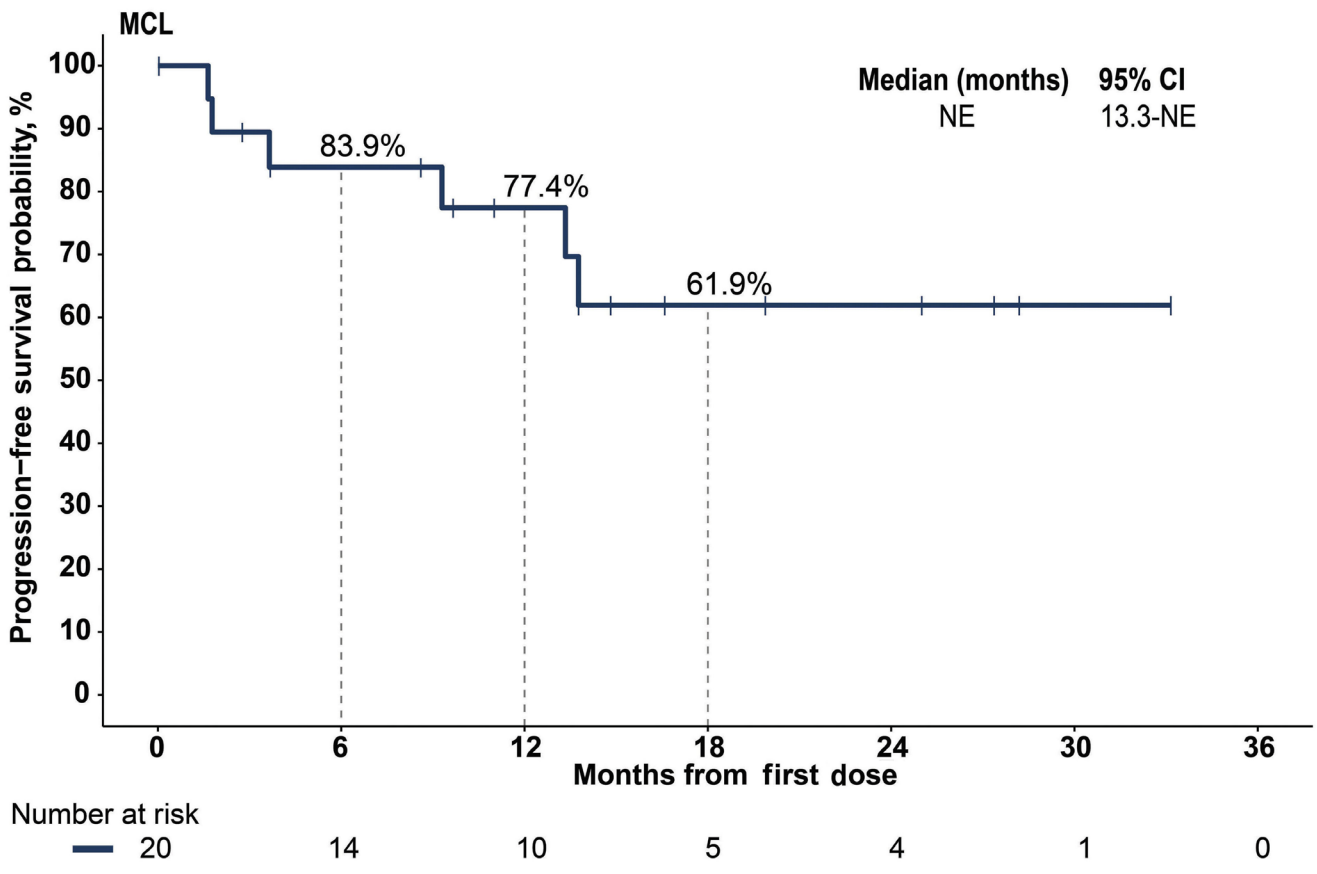


Figure 3. Progression-free survival in patients intolerant to prior Bruton tyrosine kinase inhibitor. Median progression-free survival (PFS) for patients with chronic lymphocytic lymphoma (CLL) / small lymphocytic lymphoma (SLL) was 28.4 months (95% Confidence Interval [CI]: 21.8-not estimable [NE]), while median PFS was not estimable for patients with mantle cell lymphoma (MCL). Median overall survival was not estimable for CLL/SLL or MCL.

demonstrated by a pirtobrutinib ORR of 76.9% and 81% for patients with CLL/SLL and MCL, respectively. Of note, for the 4 patients who discontinued prior nemtabrutinib for toxicity, 3 achieved a partial response to pirtobrutinib and one had stable disease. All 3 patients who achieved a partial response were still on treatment (17.2, 19.9, and 24.7 months) at the time of the data cutoff, and the one patient who had stable disease discontinued treatment after 19.8 months to start alternative therapy. For CLL specifically, this could delay switching to another class of drugs such as venetoclax-based treatment that often requires frequent initial visits and monitoring to reduce the risk of tumor lysis syndrome.[22-25]

This analysis of prior BTKi intolerant patients treated with pirtobrutinib has limitations. In particular, it was an exploratory subgroup analysis from a single-arm study, and data for AE while on prior BTKi treatment, including the grade of the AE that led to discontinuation, were limited. We also cannot be entirely certain if discontinuations from combination regimens were due to agents other than pirtobrutinib. It is important to note, however, that the vast majority (110/127, 86.6%) of the patients in this study discontinued prior BTKi given as a monotherapy, and the most common combination therapy previously administered was a BTKi plus a CD20 monoclonal antibody (16/127, 12.6%), in which the CD20 monoclonal antibody was given for a fixed number of cycles, while treatment with BTKi also continued until disease progression or intolerance, mitigating the concern for an underestimate of pirtobrutinib-related toxicities. Furthermore, the number of patients who received prior treatment with acalabrutinib and zanubrutinib, which are now more commonly prescribed due to an improved AE profile, was low relative to patients who received prior treatment with ibrutinib.

In summary, pirtobrutinib monotherapy was safe and well-tolerated in the majority of patients with B-cell malignancies with documented intolerance to prior BTKi therapy. Most patients did not experience recurrence of the same AE or AE category that had led to discontinuation of the prior BTKi, and among those who did, none discontinued pirtobrutinib for this AE. Patients who discontinued prior BTKi due to intolerance had high response rates with pirtobrutinib, suggesting that pirtobrutinib may be an important consideration to extend the benefit of BTK inhibition among patients without progressive disease that are intolerant to a prior BTKi.

Disclosures

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Contributions

WGW, IF and JRB are responsible for study concept and design. NNS, MW, LER, KP, JAW WGW, CSU, TAE, PLZ, AJA, NL, MSH, MRP, JNG, SM, CCC, CYC, ELM, BF, WSK JBC, WJ, TM and JRB acquired study data. NNS, MW, KP, JAW, WGW, CSU, TAE, AJA, PG, NL, MSH, MRP, IF, SM, CCC, BF, MAB, JBC, WJ, MCT and JRB analyzed and interpreted the study data. DET, KB, NAC, JFK, RAW, HH and ASR verified and interpreted the acquired study data, and carried out the analysis. ASR conducted statistical analyses. All authors vouch for the completeness and accuracy of the data and adherence to the protocol. All authors critically revised the manuscript and approved the final version.

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Data-sharing 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 six months after the indication studied has been approved in the US and EU, and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once 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, 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/ourmember/lilly/

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