

## ORIGINAL ARTICLE

# Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia

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## ABSTRACT

**BACKGROUND**

Patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) have poor outcomes after the failure of covalent Bruton's tyrosine kinase (BTK) inhibitor treatment, and new therapeutic options are needed. Pirtobrutinib, a highly selective, noncovalent (reversible) BTK inhibitor, was designed to reestablish BTK inhibition.

**METHODS**

We conducted a phase 1–2 trial in which patients with relapsed or refractory B-cell cancers received pirtobrutinib. Here, we report efficacy results among patients with CLL or SLL who had previously received a BTK inhibitor as well as safety results among all the patients with CLL or SLL. The primary end point was an overall response (partial response or better) as assessed by independent review. Secondary end points included progression-free survival and safety.

**RESULTS**

A total of 317 patients with CLL or SLL received pirtobrutinib, including 247 who had previously received a BTK inhibitor. Among these 247 patients, the median number of previous lines of therapy was 3 (range, 1 to 11), and 100 patients (40.5%) had also received a B-cell lymphoma 2 (BCL2) inhibitor such as venetoclax. The percentage of patients with an overall response to pirtobrutinib was 73.3% (95% confidence interval [CI], 67.3 to 78.7), and the percentage was 82.2% (95% CI, 76.8 to 86.7) when partial response with lymphocytosis was included. The median progression-free survival was 19.6 months (95% CI, 16.9 to 22.1). Among all 317 patients with CLL or SLL who received pirtobrutinib, the most common adverse events were infections (in 71.0%), bleeding (in 42.6%), and neutropenia (in 32.5%). At a median duration of treatment of 16.5 months (range, 0.2 to 39.9), some adverse events that are typically associated with BTK inhibitors occurred relatively infrequently, including hypertension (in 14.2% of patients), atrial fibrillation or flutter (in 3.8%), and major hemorrhage (in 2.2%). Only 9 of 317 patients (2.8%) discontinued pirtobrutinib owing to a treatment-related adverse event.

**CONCLUSIONS**

In this trial, pirtobrutinib showed efficacy in patients with heavily pretreated CLL or SLL who had received a covalent BTK inhibitor. The most common adverse events were infections, bleeding, and neutropenia. (Funded by Loxo Oncology; BRUIN ClinicalTrials.gov number, NCT03740529.)

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A complete list of the BRUIN investigators is provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

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**C**HRONIC LYMPHOCYTIC LEUKEMIA (CLL) and small lymphocytic lymphoma (SLL) are neoplastic diseases resulting in a clonal proliferation of B cells. CLL is the most common form of leukemia in Western countries.<sup>1</sup> The disease is called SLL when the dominant clinical manifestation of disease is lymphadenopathy, but both CLL and SLL involve malignant transformation of the same type of B cell. Although chemoimmunotherapy remains an important option for a subset of patients, the international standard of care for most patients with CLL or SLL has gradually moved during the past decade toward targeted therapies such as covalent Bruton's tyrosine kinase (BTK) inhibitors and the B-cell lymphoma 2 (BCL2) inhibitor venetoclax.<sup>2-5</sup>

Among the covalent BTK inhibitors, the first approved was ibrutinib. More recently, the covalent BTK inhibitors acalabrutinib and zanubrutinib have shown safety or efficacy advantages over ibrutinib in the context of relapsed or refractory disease.<sup>6-10</sup> Although covalent BTK inhibitors have dramatically improved outcomes for patients with CLL or SLL, they are not curative. The available covalent BTK inhibitors all share common resistance mechanisms and therefore are not effective when used in sequence in the context of drug resistance to another member of the drug class.<sup>11-13</sup> Consequently, once patients have disease progression while receiving any of these agents, the remaining therapeutic options are limited. Both chemoimmunotherapy and phosphatidylinositol 3-kinase (PI3K) inhibitors have shown limited durability of efficacy, unacceptable adverse events, or both in this context.<sup>14</sup>

Venetoclax has shown efficacy in patients with relapsed CLL or SLL after covalent BTK inhibitor therapy, with a response occurring in 65 to 85% of such patients.<sup>15,16</sup> A limitation is that venetoclax can induce a rapid tumor lysis syndrome that necessitates careful dose escalation and inpatient monitoring for some patients.<sup>17</sup> These logistic challenges can be difficult to manage, particularly in patients with limited access to health care resources and in those with clinically significant coexisting conditions. Even among patients who do receive venetoclax, the duration of disease control is approximately 2 years, and a growing number of patients have now received both a covalent BTK inhibitor and a BCL2 inhibitor.<sup>15,18</sup> Outcomes in these heavily pretreated patients are extremely poor, with a median time

to subsequent treatment failure or death of less than 6 months.<sup>19,20</sup>

Pirtobrutinib is a selective, noncovalent (reversible) BTK inhibitor that inhibits both wild-type and C481-mutant BTK (the most common mutation associated with resistance to covalent BTK inhibitors) with equal low nanomolar potency and is designed to address several of the limitations of covalent BTK inhibitors.<sup>21</sup> Pirtobrutinib recently received Food and Drug Administration approval for the treatment of relapsed or refractory mantle-cell lymphoma after two lines of systemic therapy including a BTK inhibitor. We conducted a phase 1-2 trial (BRUIN) in which patients with relapsed or refractory B-cell cancers received pirtobrutinib. Here, we report efficacy results among patients with CLL or SLL who had previously received a BTK inhibitor as well as safety results among all the patients with CLL or SLL.

## METHODS

### PATIENTS

Patients with relapsed or refractory B-cell cancers were eligible for treatment with pirtobrutinib in the phase 1-2 BRUIN trial, the results of which have been previously published in part.<sup>22</sup> Patients with controlled atrial fibrillation and concomitant anticoagulant (excluding warfarin) and antiplatelet agents at the time of enrollment were permitted. Full eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org. The protocol was approved by the institutional review boards or independent ethics committees overseeing each site. The trial was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws. All the patients provided written informed consent.

### TRIAL DESIGN AND TREATMENT

This trial was designed jointly by the sponsor (Loxo Oncology, a wholly owned subsidiary of Eli Lilly) and the investigators. The sponsor collected, analyzed, and interpreted the trial data in collaboration with the authors. The manuscript was written by the authors with writing assistance funded by the sponsor. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

This phase 1-2 trial was conducted at 49 sites

in 10 countries (Australia, France, Italy, Japan, Poland, South Korea, Sweden, Switzerland, United Kingdom, and United States). Patients received pirtobrutinib monotherapy in either the phase 1 portion or phase 2 portion of the trial. In the phase 1 portion, patients received pirtobrutinib at doses ranging from 25 to 300 mg once daily in 28-day cycles. In the phase 2 portion, patients received the recommended dose of 200 mg once daily. Treatment continued until disease progression, unacceptable toxic effects, or patient withdrawal occurred. Patients with disease progression could continue treatment if ongoing clinical benefit was evident according to the investigator's opinion.

Among patients with CLL or SLL, the primary end point was an overall response (partial response or better) according to the 2018 International Workshop on Chronic Lymphocytic Leukemia response criteria,<sup>23</sup> which are summarized in the trial protocol. Additional end points were overall response including partial response with lymphocytosis, progression-free survival, overall survival, safety, and an exploratory analysis of biomarkers. All efficacy data except for overall survival were assessed by an independent review committee whose members were unaware of the investigator assessments. Safety was assessed according to adverse events reported from the date of the first dose through the date of the last dose plus 37 days or the start of subsequent anticancer therapy, whichever was earlier.

#### TRIAL ASSESSMENTS

Response assessments were performed by means of computed tomography (CT) every 8 weeks for the first year, every 12 weeks for the second year, and every 6 months thereafter. Bone marrow samples were obtained only to confirm a hematologic or radiologic complete response. Molecular characteristics were determined centrally in those patients with a sufficient sample to pass assay quality control. Deletion of 17p and 11q were assessed by means of fluorescence in-situ hybridization. Genetic mutations in *BTK*, *PLCG2*, and *TP53* were analyzed by means of next-generation sequencing with a limit of detection of 5% variant allele frequency. Status with respect to somatic hypermutation in the gene encoding the immunoglobulin heavy-chain variable region (*IGHV*) was evaluated with next-generation or Sanger sequencing. Further trial procedures are

outlined in the protocol. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 5.0. Relatedness of adverse events to treatment was determined by the investigator.

#### STATISTICAL ANALYSIS

All the analyses were conducted in accordance with the prespecified statistical analysis plan (available with the protocol), as reviewed by international health authorities. Safety was summarized in all the patients with CLL or SLL who received at least one dose of pirtobrutinib monotherapy as of the data-cutoff date of July 29, 2022. According to the statistical analysis plan, the full safety cohort consisted of all the patients, regardless of the type of B-cell cancer, who received at least one dose of pirtobrutinib as of the data cut-off date. The efficacy cohort consisted of the patients with CLL or SLL pretreated with BTK inhibitors who were enrolled across both the phase 1 and phase 2 portions of the BRUIN trial and who received pirtobrutinib at any starting dose on or before May 11, 2021. The enrollment-cutoff date and data-cutoff date for the efficacy cohort ensured that the majority of patients in the efficacy cohort would have had a minimum of 15 months of follow-up and that a sufficient number of patients would be available for a prespecified subgroup analysis involving those who had previously received both a BTK inhibitor and a BCL2 inhibitor (i.e., dual-treated patients).

According to the original statistical analysis plan, a sample of 68 dual-treated patients was estimated to provide the trial with approximately 91% power to have the lower boundary of the two-sided 95% exact binomial confidence interval for the percentage of patients with a response exceed 30% if the true percentage was 50%. Ruling out a lower limit of 30% for the percentage of patients with a response was considered to be clinically meaningful for patients with CLL or SLL who had discontinued previous BTK inhibitor therapy, because incidences of response of 25 to 36% have been reported for this patient population.<sup>24</sup> After input from health authorities, the target sample size for the dual-treated patients was subsequently increased to 100. The reported confidence intervals have not been adjusted for multiplicity.

Baseline demographic and clinical character-

istics, best overall response, and the occurrence of adverse events were summarized descriptively. The percentages of patients with an overall response and with a response including partial response with lymphocytosis were estimated with exact two-sided 95% confidence intervals. The Kaplan–Meier method was used to analyze progression-free and overall survival. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### PATIENT CHARACTERISTICS

From March 21, 2019, through July 29, 2022, a total of 773 patients with B-cell cancers were enrolled in the trial, including 317 with relapsed or refractory CLL or SLL. A total of 247 patients with CLL or SLL who had previously received at least one BTK inhibitor (ibrutinib in 216 patients, acalabrutinib in 44, zanubrutinib and nemtabrutinib in 7 each, vecabrutinib and spebrutinib in 3 each, and tirabrutinib in 1) were treated with pirtobrutinib across both the phase 1 portion (86 patients) and the phase 2 portion (161 patients) of the trial and were included in the efficacy cohort (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

Baseline characteristics are shown in Table 1 and Table S1. The vast majority of patients who were pretreated with a BTK inhibitor received at least one dose of pirtobrutinib at the recommended phase 2 dose of 200 mg once daily (210 patients [85.0%]). The median age was 69 years (range, 36 to 88), and the median number of previous therapies was 3 (range, 1 to 11). In addition to previous BTK inhibitor therapy, patients had also received anti-CD20 antibody (in 87.9%), chemotherapy (in 78.9%), BCL2 inhibitors (in 40.5%), PI3K inhibitors (in 18.2%), chimeric antigen receptor (CAR) T-cell therapy (in 5.7%), and allogeneic stem-cell transplantation (in 2.4%). Most patients had discontinued previous BTK inhibitor therapy owing to disease progression (190 patients [76.9%]), and the remaining had discontinued owing to toxic effects or other reasons (57 patients [23.1%]). In a finding that was consistent with a heavily pretreated population with advanced disease, high-risk molecular features were common, including the presence of a del(17p) or TP53 mutation or both (in 90 of 193 patients [46.6%]), complex karyotype

(in 24 of 57 [42%]), and unmutated IGHV (in 168 of 198 [84.8%]).

### EFFICACY

Among the patients who had previously received a BTK inhibitor, an overall response occurred in 73.3% (95% confidence interval [CI], 67.3 to 78.7), including 4 complete responses (in 1.6%), 1 nodular partial response (in 0.4%), and 176 partial responses (in 71.3%) (Table 2). When partial response with lymphocytosis was considered, an overall response occurred in 82.2% of the patients (95% CI, 76.8 to 86.7). The percentage of patients with a response including partial response with lymphocytosis was consistent across most subgroups defined according to patient demographic characteristics, molecular features, or the extent of additional previous therapy, and the percentage was 56% (95% CI, 31 to 79) in the small number of patients (18) with *PLCG2* mutation (Fig. 1). In the subgroup of patients who had previously received both a BTK inhibitor and a BCL2 inhibitor, an overall response occurred in 70.0% (95% CI, 60.0 to 78.8); the percentage was 79.0% (95% CI, 69.7 to 86.5) when partial response with lymphocytosis was included. As shown in a waterfall plot (Fig. 2A), the majority of patients with available data (216 of 223 patients [96.9%]) had a decrease in the size of the target lesions, regardless of the reason for discontinuation of previous BTK inhibitor therapy and regardless of previous BCL2 treatment.

In the overall efficacy cohort, the median progression-free survival was 19.6 months (95% CI, 16.9 to 22.1) at a median follow-up of 19.4 months (Fig. 2B). A median progression-free survival of 16.8 months (95% CI, 13.2 to 18.7) was observed in the subgroup of patients who had previously received both a BTK inhibitor and a BCL2 inhibitor; the median progression-free survival was 22.1 months (95% CI, 19.6 to 27.4) among patients who had received a BTK inhibitor but not a BCL2 inhibitor (Fig. S2). Among patients who had received all five classes of available CLL or SLL therapy, including BTK, BCL2, and PI3K inhibitors as well as chemoimmunotherapy (chemotherapy and an anti-CD20 antibody), the median progression-free survival was 13.8 months (95% CI, 10.3 to could not be estimated) (Fig. S3A). Similar estimates of progression-free survival were observed regardless of BTK C481 mutation status or patient age (<75 vs.



≥75 years), with estimates ranging from 17.5 to 20.0 months (Fig. S3B and S3C). In subgroups defined according to the presence or absence of high-risk molecular features, estimates of median progression-free survival were 16.9 months among patients with *del*(17p) or *TP53* mutation and 18.7 months among those with unmutated *IGHV* (Fig. S3D and S3E).

At a median follow-up of 22.6 months, the 12-month overall survival among all the patients who had previously received a BTK inhibitor was 86.0% (95% CI, 81.0 to 89.8). The 18-month overall survival was 80.5% (95% CI, 74.8 to 85.0) (Fig. S4).

#### SAFETY

Among the 317 patients with CLL or SLL treated with pirtobrutinib as of the data-cutoff date, 277 (87.4%) had received at least one dose of pirtobrutinib at the recommended phase 2 dose of 200 mg once daily, and the median duration of treatment was 16.5 months (range, 0.2 to 39.9). The most common adverse events and adverse events of special interest (those previously associated with BTK inhibitors) are shown in Table 3. Overall, the most common adverse events were infections (in 71.0% of patients), bleeding (in 42.6%), and neutropenia (in 32.5%). The most frequently reported adverse events of grade 3 or higher were infections (in 28.1% of patients) and neutropenia (in 26.8%), and the most frequently reported treatment-related adverse event of grade 3 or higher was neutropenia (in 14.8%). Treatment-related lymphocytosis occurred early in the first treatment cycle (Fig. S5).

No sudden cardiac deaths were observed; a complete list of causes of death, regardless of attribution, is provided in Table S4. In total, 16 patients died while receiving pirtobrutinib for causes other than disease progression, including coronavirus disease 2019 (Covid-19) or Covid-19–related pneumonia (8 patients), pneumonia or fungal pneumonia (2 patients), septic shock or shock (2 patients), and other causes (4 patients). Treatment-related adverse events led to dose reductions in 15 patients (4.7%) and permanent discontinuation of pirtobrutinib in 9 patients (2.8%).

The safety profile that was observed in all the patients with B-cell cancers treated with pirtobrutinib (773 patients) was similar to findings from the safety population of patients with CLL or SLL; however, the incidence of infections was

higher among those with CLL or SLL (occurring in 71.0%) than among all the patients with B-cell cancers (in 55.6%) (Table S3). Moreover, no drug-related case of ventricular fibrillation or ventricular tachycardia had been observed among all the patients at the time of the data-cutoff date. Treatment-related adverse events led to dose reductions in 35 patients (4.5%) and permanent discontinuation of pirtobrutinib in 20 (2.6%).

#### DISCUSSION

In the phase 1–2 BRUIN trial, pirtobrutinib showed efficacy in patients with CLL or SLL who had previously received a BTK inhibitor. These data suggest that CLL and SLL tumors maintain nearly universal dependency on B-cell receptor signaling mediated by BTK, despite previous exposure to a covalent inhibitor. Sequential use of a covalent BTK inhibitor followed by pirtobrutinib may therefore meaningfully extend the total period of clinical benefit of targeting this critical pathway dependency. Importantly, recent data suggest that venetoclax maintains efficacy in patients previously treated with a noncovalent BTK inhibitor.<sup>25</sup> The appropriate sequencing and combination of pirtobrutinib with other active agents has not been established. These data show that pirtobrutinib therapy is efficacious in patients with CLL or SLL after treatment with a covalent BTK inhibitor. No information is currently available on the efficacy of covalent BTK inhibitors in patients who receive pirtobrutinib first and in whom resistance develops. More data are needed on mechanisms of resistance to pirtobrutinib.

The percentage of patients with a response including partial response with lymphocytosis ranged from 70 to 80% across clinically relevant subgroups defined according to patient demographic characteristics, molecular features, or the extent of additional previous therapy, with the exception of patients with tumors expressing mutated *PLCG2*, among whom the percentage was 56%. This efficacy profile compares favorably with previously reported incidences of response to other available therapies among patients who had received previous covalent BTK inhibitor treatment, although additional data are needed in patients with *PLCG2* mutations in order to more thoroughly evaluate efficacy in this subgroup.<sup>24</sup> Similarly, a favorable median progression-free survival of 19.6 months was observed in this heavily

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.\***

Characteristic	Patients (N=247)
Median age (range) — yr	69 (36–88)
Sex — no. (%)	
Male	168 (68.0)
Female	79 (32.0)
World Health Organization classification — no. (%)	
CLL	246 (99.6)
SLL	1 (0.4)
Rai stage — no. (%)	
0–II	131 (53.0)
III or IV	102 (41.3)
Missing data	14 (5.7)
Bulky disease ≥5 cm — no. (%)	78 (31.6)
ECOG performance-status score — no. (%)†	
0	133 (53.8)
1	97 (39.3)
2	17 (6.9)
No. of previous lines of systemic therapy	
Median (range)	3 (1–11)
Distribution — no. (%)	
1	19 (7.7)
2	55 (22.3)
3	57 (23.1)
≥4	116 (47.0)
Previous therapy — no. (%)	
BTK inhibitor‡	247 (100)
Anti-CD20 antibody	217 (87.9)
Chemotherapy	195 (78.9)
BCL2 inhibitor	100 (40.5)
PI3K inhibitor	45 (18.2)
CAR T-cell therapy	14 (5.7)
Allogeneic stem-cell transplantation	6 (2.4)
Median time from diagnosis to first dose of pirtobrutinib (IQR) — yr	11 (8–15)
Reason for discontinuation of any previous BTK inhibitor — no. (%)§	
Disease progression	190 (76.9)
Toxic effects or other reason	57 (23.1)
Mutation status — no./total no. (%)	
<i>BTK</i> C481	
Mutated	84/222 (37.8)
Not mutated	138/222 (62.2)
<i>PLCG2</i>	
Mutated	18/222 (8.1)
Not mutated	204/222 (91.9)

**Table 1. (Continued.)**

Characteristic	Patients (N=247)
High-risk molecular features — no./total no. (%)¶	
17p deletion	51/176 (29.0)
<i>TP53</i> mutation	87/222 (39.2)
17p deletion, <i>TP53</i> mutation, or both	90/193 (46.6)
Both 17p deletion and <i>TP53</i> mutation	48/170 (28.2)
Unmutated <i>IGHV</i>	168/198 (84.8)
Complex karyotype	24/57 (42)
11q deletion	44/176 (25.0)

\* Data are for the BRUIN trial patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who had previously received a Bruton's tyrosine kinase (BTK) inhibitor. Percentages may not total 100 because of rounding. BCL2 denotes B-cell lymphoma 2, CAR chimeric antigen receptor, IQR interquartile range, and PI3K phosphatidylinositol 3-kinase.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

‡ Ten patients who had received previous covalent BTK inhibitor therapy had also received previous noncovalent BTK inhibitor therapy.

§ In the event that more than one reason for discontinuation was noted, disease progression took priority.

¶ Molecular characteristics were determined centrally and are presented on the basis of data availability, in those patients with a sufficient sample to pass assay quality control.

|| Complex karyotype was defined as the presence of three or more chromosomal abnormalities.

**Table 2. Efficacy of Pirtobrutinib in Patients with CLL or SLL Who Had Previously Received a BTK Inhibitor.\***

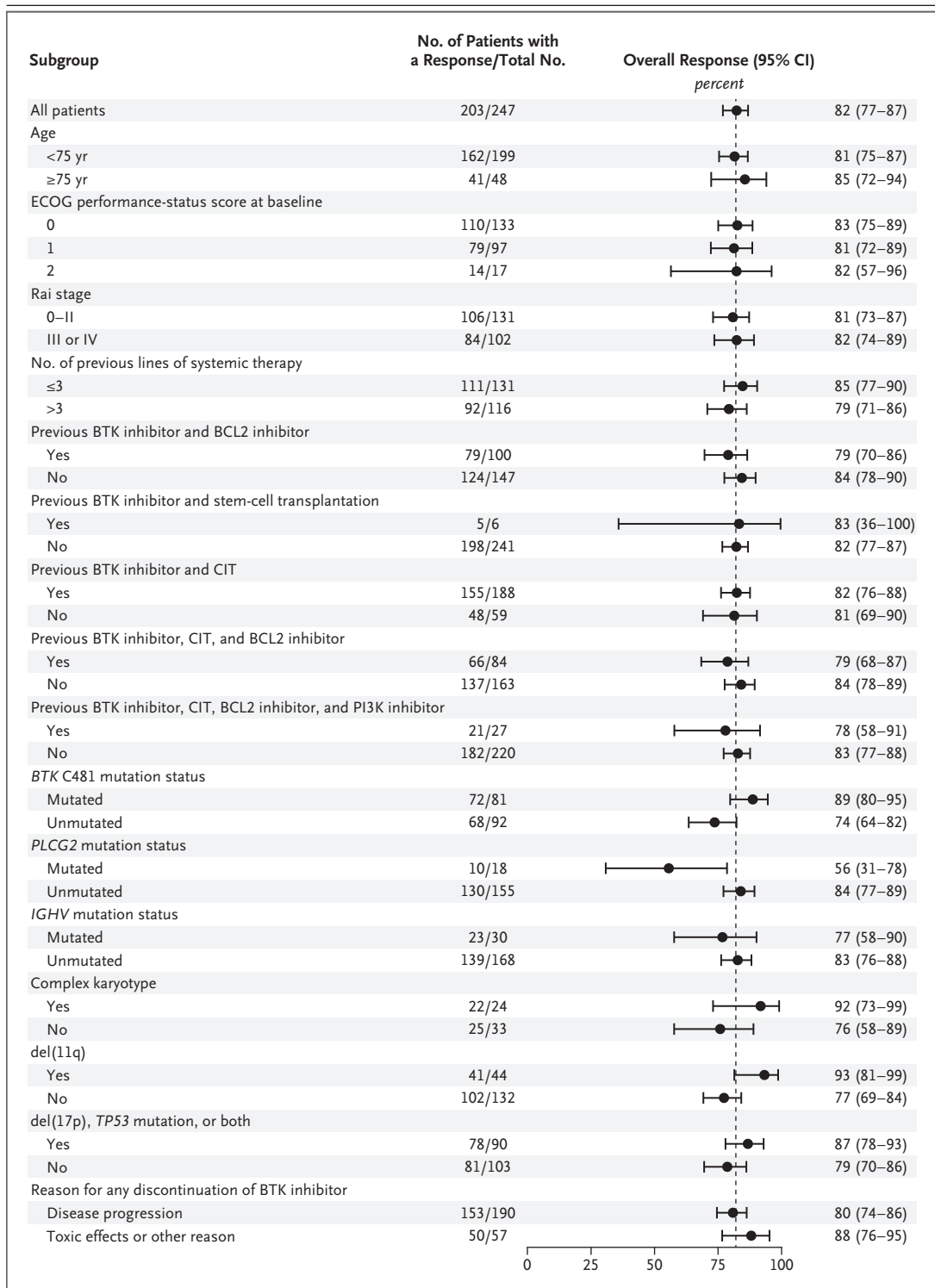
Variable	Previous BTK Inhibitor (N=247)	Previous BTK Inhibitor + BCL2 Inhibitor (N=100)
Overall response — % (95% CI)		
Including complete response, nodular partial response, or partial response	73.3 (67.3–78.7)	70.0 (60.0–78.8)
Including complete response, nodular partial response, partial response, or partial response with lymphocytosis	82.2 (76.8–86.7)	79.0 (69.7–86.5)
Best response — no. (%)		
Complete response	4 (1.6)	0
Nodular partial response	1 (0.4)	0
Partial response	176 (71.3)	70 (70.0)
Partial response with lymphocytosis	22 (8.9)	9 (9.0)
Stable disease	26 (10.5)	11 (11.0)
Progression-free survival		
Median (95% CI) — mo	19.6 (16.9–22.1)	16.8 (13.2–18.7)
Patients with censored data — no. (%)	126 (51.0)	44 (44.0)
Median follow-up — mo	19.4	18.2

\* Response status was assessed by an independent review committee in accordance with the criteria from the 2018 International Workshop on Chronic Lymphocytic Leukemia.

pretreated group of patients, among whom more than 40% had received a BCL2 inhibitor such as venetoclax. Consistent progression-free survival results were observed across various subgroups,

including patients with poor prognostic markers and those with heavily pretreated disease.

Infections, bleeding, and neutropenia occurred commonly during treatment with pirtobrutinib.



Only 2.8% of patients with CLL or SLL discontinued the drug because of a treatment-related adverse event. Moreover, the low incidences of atrial fibrillation, major hemorrhage, and hyper-

tension are encouraging as compared with other agents in the BTK inhibitor class, although additional long-term follow-up is needed to further assess the incidence of these important adverse

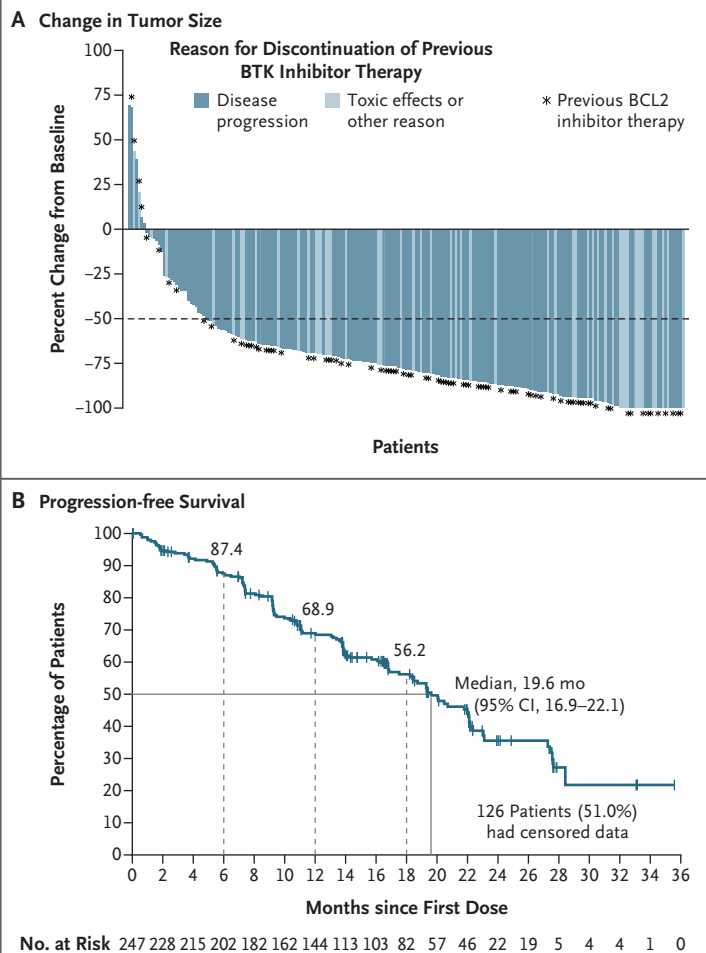


**Figure 1 (facing page). Subgroup Analysis of Overall Response to Pirtobrutinib.**

Shown are data for overall response (defined here as complete response, nodular partial response, partial response, or partial response with lymphocytosis) among 247 patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who had previously received a covalent Bruton's tyrosine kinase (BTK) inhibitor. Response status was assessed by an independent review committee in accordance with the criteria from the 2018 International Workshop on Chronic Lymphocytic Leukemia. Two-sided 95% confidence intervals were calculated with the use of the exact binomial distribution. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Labels for previous BTK inhibitor therapy and other therapies indicate that patients received at least those therapies; the combinations of therapies are not mutually exclusive. Data for *BTK* C481 or *PLCG2* mutation status are for patients with available mutation data who had disease progression while receiving any previous BTK inhibitor therapy. In the event that more than one reason for discontinuation for any BTK inhibitor was noted, disease progression took priority. BCL2 denotes B-cell lymphoma 2, CIT chemoimmunotherapy (chemotherapy and an anti-CD20 antibody), and PI3K phosphatidylinositol 3-kinase.

events.<sup>26,27</sup> The more favorable toxic-effect profile that was observed in this analysis is consistent with the high degree of BTK selectivity of pirtobrutinib and a relative absence of off-target inhibition.<sup>28</sup>

Pirtobrutinib has favorable pharmacokinetic properties with high oral bioavailability and an extended half-life (approximately 19 hours) that achieves sustained plasma drug levels, enabling continuous BTK inhibition throughout the administration interval, regardless of the intrinsic rate of BTK turnover. In addition to permitting tonic BTK target coverage, the selectivity profile of pirtobrutinib minimizes off-target inhibition that may lead to toxic effects and compromise dose intensity. Previous reports have also identified *BTK* C481 mutations as a common and shared mechanism of resistance to all available covalent BTK inhibitors.<sup>12,29</sup> By comparison, the reversible binding mode of pirtobrutinib does not require covalent modification of the C481 residue; therefore, pirtobrutinib retains potency in the context of these mutations. Mechanisms of acquired resistance to newer BTK inhibitors, both covalent (zanubrutinib) and noncovalent (pirtobrutinib), are still being investigated.<sup>30-32</sup> Small case series



**Figure 2. Change in Tumor Size and Progression-free Survival.**

The waterfall plot in Panel A depicts the change in tumor size after pirtobrutinib therapy among 223 patients with CLL or SLL who had previously received BTK inhibitor therapy. Data for 24 patients are not shown owing to no measurable target lesions identified by computed tomography at baseline, discontinuation before the first response assessment, or a lack of adequate imaging during follow-up. Tumor size was calculated as the sum of product diameters of the target lesions. Panel B depicts the Kaplan-Meier curve for progression-free survival among all 247 patients with CLL or SLL treated with pirtobrutinib monotherapy who had previously received BTK inhibitor therapy. Tick marks indicate censored data.

have been reported,<sup>30,31</sup> but more data are needed to better inform appropriate treatment sequencing and understand patterns of potential cross-resistance.

This trial has some important limitations. The lack of an active control group and the near-absence of prospective data for other modern therapies after the use of BTK inhibitors limit direct comparisons with other available thera-

**Table 3. Safety Profile of Pirtobrutinib in Patients with CLL or SLL.**

Event	Adverse Events (N = 317)		Treatment-Related Adverse Events (N = 317)*	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse events†				
Fatigue	100 (31.5)	6 (1.9)	11 (3.5)	1 (0.3)
Diarrhea	84 (26.5)	2 (0.6)	28 (8.8)	1 (0.3)
Contusion	77 (24.3)	0	52 (16.4)	0
Cough	77 (24.3)	0	5 (1.6)	0
Coronavirus disease 2019	76 (24.0)	16 (5.0)	5 (1.6)	0
Nausea	60 (18.9)	0	10 (3.2)	0
Abdominal pain	57 (18.0)	5 (1.6)	7 (2.2)	1 (0.3)
Dyspnea	55 (17.4)	3 (0.9)	2 (0.6)	0
Headache	55 (17.4)	2 (0.6)	17 (5.4)	1 (0.3)
Upper respiratory tract infection	52 (16.4)	1 (0.3)	11 (3.5)	0
Back pain	51 (16.1)	3 (0.9)	3 (0.9)	0
Anemia	48 (15.1)	28 (8.8)	15 (4.7)	7 (2.2)
Adverse events of special interest‡				
Atrial fibrillation or flutter§	12 (3.8)	4 (1.3)	4 (1.3)	1 (0.3)
Bleeding	135 (42.6)	7 (2.2)	75 (23.7)	3 (0.9)
Bruising¶	96 (30.3)	0	62 (19.6)	0
Hemorrhage	67 (21.1)	7 (2.2)	22 (6.9)	3 (0.9)
Hypertension	45 (14.2)	11 (3.5)	12 (3.8)	1 (0.3)
Infections	225 (71.0)	89 (28.1)	39 (12.3)	12 (3.8)
Neutropenia	103 (32.5)	85 (26.8)	62 (19.6)	47 (14.8)

\* Relatedness of adverse events to treatment was determined by the investigator.

† Shown are events that were reported in at least 15% of the patients.

‡ Adverse events of special interest are those that were previously associated with covalent BTK inhibitors. All terms are composite terms, except hypertension.

§ Of the 12 cases of atrial fibrillation or flutter in the overall safety population, 3 occurred in patients with a medical history of atrial fibrillation.

¶ Bruising included contusion, petechiae, ecchymosis, and increased tendency to bruise.

|| This term is an aggregate of neutropenia and decreased neutrophil count.

pies in this clinical context. Moreover, some of the subgroups that were defined according to previous therapy or molecular findings have a limited sample size, which led to wide confidence intervals around key efficacy measures. Finally, because many patients with CLL or SLL will be treated with BTK inhibitors for a considerable duration, the long-term safety of pirtobrutinib remains to be defined.

In this phase 1–2 trial, the noncovalent (reversible) BTK inhibitor pirtobrutinib showed efficacy in patients with heavily pretreated CLL or SLL who had had disease progression during

previous treatment with a covalent BTK inhibitor. These findings indicate that reestablishing BTK inhibition with pirtobrutinib is a potential therapeutic option regardless of whether previous covalent BTK inhibitor therapy is discontinued owing to disease progression, toxic effects, or other reasons. Several ongoing clinical trials are evaluating pirtobrutinib in the treatment of B-cell cancers, including four phase 3, international, randomized trials evaluating pirtobrutinib in patients with CLL or SLL (ClinicalTrials.gov numbers, NCT05023980, NCT05254743, NCT04666038, and NCT04965493).

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## APPENDIX

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