Phase III Trial of Pirtobrutinib Versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor–Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321)

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DOI https://doi.org/10.1200/JCO-25-00166

ABSTRACT

PURPOSE Pirtobrutinib, a noncovalent, Bruton tyrosine kinase inhibitor (BTKi), has shown clinical efficacy and a favorable safety profile. BRUIN CLL-321 was an open-label, randomized phase III study conducted exclusively in patients with R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) previously treated with cBTKi, and compared pirtobrutinib with investigator's choice (IC) of idelalisib/rituximab (IdelaR) or bendamustine/rituximab (BR).

METHODS Patients were randomly assigned 1:1 to receive pirtobrutinib (200 mg once daily) or IC of IdelaR or BR, and were stratified by previous use of venetoclax and del(17p). The primary end point was independent review committee–assessed progression-free survival (PFS). Secondary end points included time to next treatment or death (TTNT), overall survival (OS), and safety. The primary PFS end point was met at the time of the primary analysis (August 29, 2023), and updated results are reported from the final OS analysis (August 29, 2024).

RESULTS A total of 238 patients were randomly assigned to receive pirtobrutinib (n = 119) or IC (n = 119; IdelaR [n = 82], BR [n = 37]). The PFS hazard ratio (HR) was 0.54 ([95% CI, 0.39 to 0.75]; P = .0002), with a median PFS of 14 months (95% CI, 11.2 to 16.6) in the pirtobrutinib group and 8.7 months (95% CI, 8.1 to 10.4) with IC. The unadjusted OS HR was 1.09 ([95% CI, 0.68 to 1.75]; P = .7202), and 18-month OS rate was 73.4% (95% CI, 63.9 to 80.7) in the pirtobrutinib group and 70.8% (95% CI, 60.9 to 78.7) with IC. Median TTNT was 24 months (95% CI, 17.8 to 29.7) with pirtobrutinib versus 10.9 months (95% CI, 8.7 to 12.5) with IC (HR, 0.37 [95% CI, 0.25 to 0.52]). At a median follow-up of 17.2 months, grade ≥3 treatment-emergent adverse events (AEs) were lower with pirtobrutinib (57.7%) than IC (73.4%). Treatment discontinuation due to AE occurred in 20 (17.2%) patients receiving pirtobrutinib and 38 (34.9%) patients receiving IC.

CONCLUSION Pirtobrutinib improved PFS and TTNT, and demonstrated favorable tolerability, versus IdelaR/BR in exclusively cBTKi pretreated patients with CLL/SLL.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

Accepted April 16, 2025
Published June 6, 2025

J Clin Oncol 43:2538-2549

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INTRODUCTION

Patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) usually receive a covalent Bruton tyrosine kinase inhibitor (cBTKi) as part of their first-line or second-line therapy.[1-3] Although cBTKis are effective, most patients experience disease progression (PD) or intolerance, leading to discontinuation.[2] While treatment with the B-cell lymphoma-2 inhibitor (BCL-2i) venetoclax has been used as an option for cBTKi-pretreated patients, there are no randomized data supporting the efficacy of venetoclax following a cBTKi. Additionally, recent

CONTEXT

Key Objective

To our knowledge, BRUIN CLL-321 is the first randomized, phase III clinical trial conducted exclusively in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) after treatment with a covalent Bruton tyrosine kinase inhibitor (cBTKi) to determine whether pirtobrutinib improved progression-free survival (PFS) compared with either idelalisib with rituximab (IdelaR) or bendamustine with rituximab (BR).

Knowledge Generated

In these heavily pretreated patients, treatment with pirtobrutinib was well tolerated and led to a significantly improved PFS versus IdelaR/BR.

Relevance *(C. Craddock)*

Pirtobrutinib represents an important new treatment option in patients with CLL/SLL which has progressed after prior treatment with a cBTKi.*

*Relevance section written by *JCO* Associate Editor Charles Craddock, MD.

real-world evidence reports with venetoclax-based therapies used after a cBTKi suggest outcomes are modest.[3-6]

Pirtobrutinib is a highly selective noncovalent BTKi that inhibits *BTK* throughout the dosing interval, with low nM potency.[7] Pirtobrutinib has shown promising safety and efficacy in the phase 1/2 BRUIN study in R/R patients with CLL/SLL, including patients previously treated with a cBTKi.[8] On December 1, 2023, the Food and Drug Administration granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two previous lines of therapy, including a BTKi and a BCL-2i. This indication is approved under accelerated approval on the basis of response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[9]

To date, to our knowledge, there have been no prospective, randomized controlled studies evaluating any therapy for R/R CLL after treatment with a cBTKi.[10-12] Importantly, the ASCEND study only assessed acalabrutinib in BTKi-naïve R/R patients with CLL/SLL compared against the same control group of idelalisib with rituximab (IdelaR)/bendamustine with rituximab (BR).[10] On the basis of real-world evidence, the median time to next treatment discontinuation after a cBTKi-based treatment in venetoclax-naïve patients was 9.5 months (95% CI, 8.8 to 10.4), and 5.6 months (95% CI, 4.3 to 6) after discontinuation from cBTKi and venetoclax.[13] As the number of patients with CLL/SLL in the post-cBTKi setting continues to increase, there is a greater need for therapies with proven benefit in this patient population. Here, we report the results from the randomized phase III study of pirtobrutinib versus investigator's (INV's) choice (IC) of IdelaR or BR therapy conducted entirely in patients with CLL/SLL previously treated with cBTKi (BRUIN CLL-321).

METHODS

Patients

Eligible patients were age 18 years and older with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2 and a diagnosis of CLL/SLL requiring treatment per International Workshop on CLL (iwCLL) 2018 criteria.[14] Patients must have been previously treated with a cBTKi, with no limit on the number of other previous therapies. Patients on concomitant anticoagulant therapy (excluding warfarin), receiving antiplatelet agents, and/or with a history of controlled atrial fibrillation at the time of enrollment were permitted. Complete inclusion/exclusion criteria can be found in the Protocol (online only).

Study Design and Treatment

LOXO-BTK-20020 (BRUIN CLL-321) is a phase III global, randomized, multicenter, open-label study (ClinicalTrials.gov identifier: NCT04666038). Patients were randomly assigned 1:1 to receive either pirtobrutinib or IC of IdelaR or BR (Fig 1). Randomization was performed using an interactive web response system and stratified by del(17p) status using fluorescence in situ hybridization from either local or central testing during screening (yes or no) and previous treatment with venetoclax (yes or no). Patients could cross over from IC to pirtobrutinib upon PD confirmation by independent review committee (IRC), and only if they met the eligibility criteria for treatment by iwCLL 2018 criteria. Patients could continue treatment beyond PD if the patient was tolerating treatment and, in the opinion of the INV, was deriving ongoing clinical benefit.

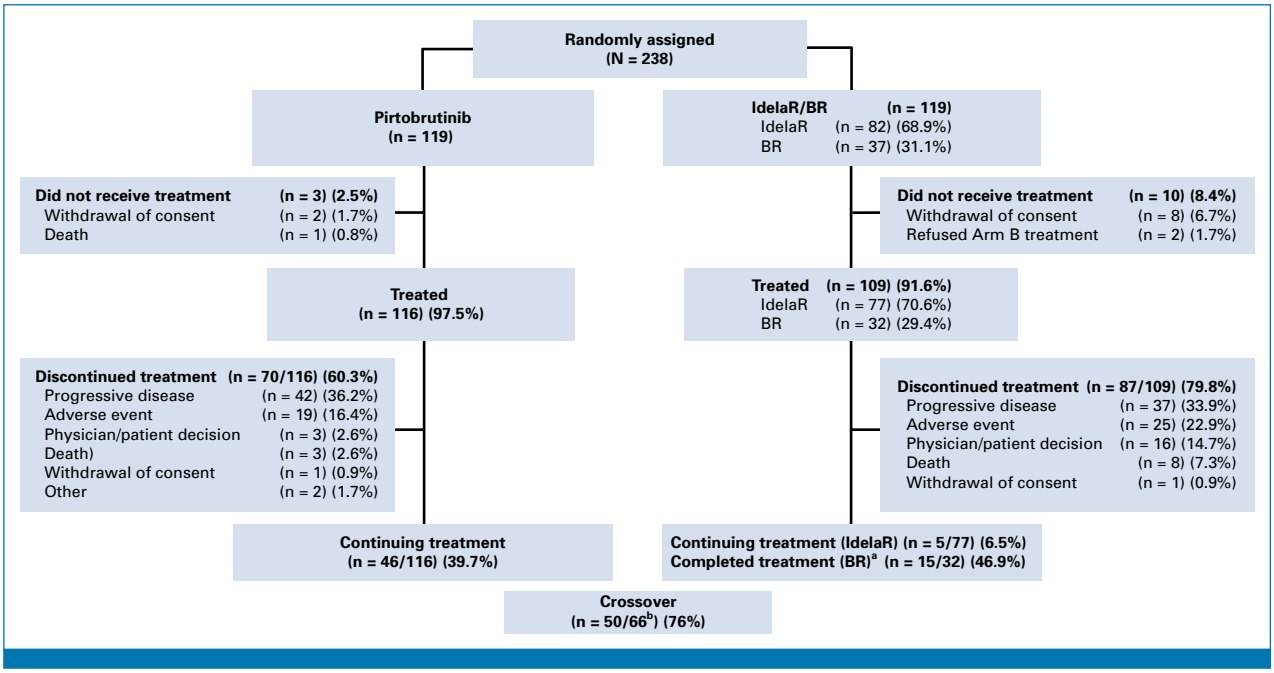

FIG 1. CONSORT diagram. Eligible patients receiving the investigator's choice could crossover to receive pirtobrutinib upon confirmation of PD by IRC per protocol. Visit cut: August 29, 2024. [a]The remaining 17 patients discontinued treatment. [b]Among patients whose event was investigator-assessed PD and thus had the opportunity to crossover. BR, bendamustine plus rituximab; IdelaR, idelalisib plus rituximab; IRC, independent review committee; PD, disease progression.

Pirtobrutinib was administered continuously at a 200 mg orally once daily. IdelaR patients received idelalisib 150 mg orally twice a day, continuously, and rituximab 375 mg/m² once at the first infusion, then 500 mg/m² once every 2 weeks at the following four infusions, then 500 mg/m² once every 4 weeks at the following three infusions.[15] BR patients received bendamustine 70 mg/m² intravenously once on days 1 and 2 of up to six total 28-day cycles, rituximab 375 mg/m² once at the first infusion, then 500 mg/m² once on day 1 of cycles 2-6. Patients on continuous treatment remained on treatment until PD or unacceptable toxicity. Dose modifications for adverse events (AEs) were allowed per protocol (Appendix Table A1, online only).

Peripheral blood samples collected during screening or cycle 1 day 1 were tested at a central laboratory to evaluate deletion status of 17p and 11q, and mutation of immunoglobulin heavy chain gene (IGHV) and *TP53*. *BTK* and *PLCγ* mutation status at baseline was assessed via next-generation sequencing of peripheral blood mononuclear cells at Foundation Medicine, Inc (Cambridge, MA). Screening bone marrow aspirates were evaluated for karyotype via G-banding in stimulated culture.

Site institutional review boards approved the trial protocol. The study was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice guidelines, and local laws. All patients provided written informed consent. The study was registered on ClinicalTrials.gov (identifier: NCT04666038).

Study End Points and Assessments

The primary end point was progression-free survival (PFS) as assessed by a blinded IRC using iwCLL 2018 criteria.[14] Overall survival (OS) was a key secondary end point. Additional secondary end points included PFS by INV, overall response rate (ORR), event-free survival (EFS), time to next treatment or death (TTNT), and safety. End points are defined in the protocol.

Treatment-emergent AEs (TEAEs) were defined as events that occurred or worsened in severity after the first dose of study treatment through 30 days (+7-day window) after the date of the last dose of study treatment, or the first date of starting new anticancer therapy for CLL/SLL, whichever is earlier. Treatment-related AEs are TEAE considered related to study drug treatment by the INV.

Statistical Analysis

A sample size of 250 patients, with an expected 88 events, was planned to achieve 90% power to detect a hazard ratio (HR) of 0.5 in PFS at the two-sided significance level of 0.05. The superiority of pirtobrutinib versus IC in OS was tested hierarchically after IRC-assessed PFS at a two-sided significance level of 0.05. Primary analysis was conducted on August 29, 2023, upon reaching predetermined events after only 238 patients were enrolled. Results from an updated descriptive analysis of PFS, the planned final analysis of OS, and other secondary end points using a data cutoff date of August 29, 2024, are reported here.

All efficacy analyses were performed in the intention-to-treat population, defined as all randomly assigned patients according to the assigned treatment group. More details describing the statistical analysis are provided in the protocol.

OS analysis included the crossover period, while all other efficacy analyses included data up until crossover. Additional sensitivity analyses of OS accounting for crossover included censoring patients at time of crossover, implementing the inverse probability of censoring weighted (IPCW) analyses to estimate the HR based on a reweighted pseudo population, and implementing the two-stage accelerated failure time (AFT) analyses which are based on counterfactual survival times that would have been observed without crossover.[16]

Safety analyses were performed on all randomly assigned patients who took at least one dose of study treatment, excluding the crossover period. Exposure adjusted incidence rate (IR) is based on first occurrence of the event and is calculated as number of events divided by sum of years at risk for a TEAE across all patients times 100. IR ratio (IRR) is based on pirtobrutinib IR relative to IdelaR/BR IR, and analyzed using Poisson regression. All *P* values presented are two-sided and all CIs are given at a two-sided 95% level (95% CI). Statistical analysis was performed using SAS software (SAS 9.4, SAS Institute Inc, Cary, NC).

RESULTS

Baseline Patient and Disease Characteristics

Between March 9, 2021, and July 17, 2023, 238 patients with R/R CLL/SLL were randomly assigned to receive pirtobrutinib (n = 119) or IC (n = 119) of IdelaR (n = 82) or BR (n = 37), hereafter referred to as IdelaR/BR (Fig 1). Three patients randomly assigned to pirtobrutinib, and 10 patients randomly assigned to IC (five IdelaR and five BR) did not receive any treatment. At the time of data cutoff, 46 of the 116 (39.7%) patients receiving pirtobrutinib remained on treatment, five (6.5%) of the 77 patients receiving IdelaR remained on treatment, and all 32 treated BR patients were off treatment, with 15 (46.9%) patients completing all six cycles of BR treatment. Of 66 patients on IdelaR/BR who experienced PD as assessed by INV, 50 with IRC-confirmed PD who met iwCLL criteria for requiring treatment crossed over to receive pirtobrutinib, for an effective crossover rate of 76% (n = 50/66). More than half of those who crossed over (n = 29/50, 58%) remained on pirtobrutinib at time of data cutoff. Continuation of treatment beyond INV assessed PD occurred in 38.6% (22/57) of patients receiving pirtobrutinib and once (1.5%, 1/66) with IdelaR/BR.

Median study follow-up for all patients was 17.2 months (95% CI, 9.7 to 23). Baseline patient characteristics were generally balanced between groups as well as stratification factors, with 50.4% of patients receiving previous venetoclax treatment in each group. Del(17p) was present in 46.2% and 44.5% of patients in the pirtobrutinib and IdelaR/BR groups, respectively (Table 1). The median age was 66 years (range, 42-90), 70% were male, and 58% had an ECOG PS ≥ 1 (Table 1). The prevalence of high-risk features was similar between pirtobrutinib and IdelaR/BR groups in patients with central results, including *TP53* mutation and/or del(17p) mutation (54% *v* 54%) and del(11q) (19% *v* 25%). Some high-risk genomic features appeared more prevalent in the pirtobrutinib group versus the IdelaR/BR, including complex karyotype (72% *v* 59%) and unmutated IGHV (93% *v* 80%). The median number of lines of previous therapy was three in both pirtobrutinib (range, 1-13) and IdelaR/BR (range, 1-11) groups. All patients had received previous cBTKi treatment. There were 17 and 18 patients in the pirtobrutinib and IdelaR/BR groups, respectively, who had received more than one previous cBTKi treatment. The most frequent reason for discontinuation of previous cBTKi in the pirtobrutinib and IdelaR/BR groups was PD (71% *v* 73%) and toxicity (17% *v* 18%).

Efficacy

At a limited median study follow-up of 7.5 months, the IRC-PFS primary analysis demonstrated superiority of pirtobrutinib versus IdelaR/BR (HR, 0.58 [95% CI, 0.38 to 0.89]; *P* = .0105). At the final OS analysis with a median study follow-up of 17.2 months, the median IRC-PFS in the pirtobrutinib group was 14 months (95% CI, 11.2 to 16.6) versus 8.7 months (95% CI, 8.1 to 10.4) with IdelaR/BR, resulting in a relative reduction in risk of relapse, PD, or death of 46% with pirtobrutinib (HR, 0.54 [95% CI, 0.39 to 0.75]; nominal *P* = .0002; Fig 2A). Of the 74 IRC-PFS events in the pirtobrutinib group, 60 were PD and 14 were death. Among the 79 events in the IdelaR/BR group, 66 were PD and 13 were death. INV-PFS was highly concordant to IRC, with a median PFS of 15.3 months (95% CI, 12.8 to 19.9) in the pirtobrutinib group and 9.2 months (95% CI, 7.3 to 10.6) in the IdelaR/BR group (HR, 0.48 [95% CI, 0.34 to 0.67]; Fig 2B). IRC-PFS benefit was consistently observed with pirtobrutinib among prespecified, clinically relevant patient subgroups, including those who had *TP53* mutation and/or del(17p) (HR, 0.59 [95% CI, 0.38 to 0.92]), unmutated IGHV (HR, 0.61 [95% CI, 0.42 to 0.88]), and complex karyotype (HR, 0.37 [95% CI, 0.23 to 0.58]; Appendix Fig A1). Pirtobrutinib also showed meaningful and consistent PFS improvement in both patients who received previous venetoclax (HR, 0.54 [95% CI, 0.35 to 0.83]) and were venetoclax-naïve (HR, 0.62 [95% CI, 0.39 to 1]).

EFS favored pirtobrutinib versus IdelaR/BR (HR, 0.39 [95% CI, 0.28 to 0.53]). Median EFS was 14.1 months (95% CI, 11.4 to 17) and 7.6 months (95% CI, 4.8 to 8.8) in the pirtobrutinib and IdelaR/BR groups, respectively (Fig 3A). Median TTNT was longer in the pirtobrutinib group at 24 months (95% CI, 17.8 to 29.7) versus 10.9 months (95% CI, 8.7 to 12.5) with IdelaR/BR (HR, 0.37 [95% CI, 0.25 to 0.52]; Fig 4A). In venetoclax-naïve patients, median TTNT was longer in the pirtobrutinib group with a median TTNT of 29.5 months

TABLE 1. Baseline Patient and Disease Characteristics

Characteristic	Pirtobrutinib (n = 119)	IdelaR/BR (n = 119)
Median age, years (range)	66 (42-90)	68 (42-85)
Male, No. (%)	83 (70)	83 (70)
Region, No. (%)		
North America	24 (20)	39 (33)
Europe	76 (64)	63 (53)
Asia	14 (12)	15 (13)
Australia	5 (4)	2 (2)
Histology, No. (%)		
CLL	109 (92)	108 (91)
SLL	10 (8)	11 (9)
Rai stage,[a] No. (%)		
0-II	58 (51)	62 (53)
III-IV	56 (49)	54 (47)
ECOG PS, No. (%)		
0	51 (43)	50 (42)
1	56 (47)	64 (54)
2	12 (10)	5 (4)
Bulky disease (lymph node), No. (%)		
<5 cm	67 (56)	53 (45)
≥5 cm	48 (40)	59 (50)
≥10 cm	14 (12)	18 (15)
No measurable target lesion at baseline	4 (3)	7 (6)
High-risk molecular features, No./n available (%)		
TP53 mutation	36/97 (37)	30/94 (32)
17p deletion	39/111 (35)	43/112 (38)
17p deletion and/or *TP53* mutation	51/94 (54)	53/98 (54)
Complex karyotype[b]	53/74 (72)	44/75 (59)
IGHV unmutated	90/97 (93)	74/93 (80)
11q deletion	19/101 (19)	25/99 (25)
Molecular characteristics, No./n available (%)		
BTK C481S	37/99 (37)	36/94 (38)
PLCγ2	15/99 (15)	11/94 (12)
β2 microglobulin, No. (%)		
≤3.5 mg/L	27 (23)	39 (33)
>3.5 mg/L	89 (75)	77 (65)
Median lines of previous systemic therapy, No. (range)	3 (1-13)	3 (1-11)
Previous therapy, No. (%)		
cBTKi	119 (100)	119 (100)
Ibrutinib	100 (84)	106 (89)
Acalabrutinib	17 (14)	20 (17)
Zanubrutinib	10 (8)	7 (6)
Other[c]	5 (4)	3 (3)
>1 previous cBTKi	17 (14)	18 (15)
BCL2 inhibitor[d]	60 (50)	62 (52)
Chemotherapy	81 (68)	83 (70)
Anti-CD20 antibody	86 (72)	83 (70)
PI3K agent	11 (9)	11 (9)
Immunomodulator	2 (2)	3 (3)
Autologous stem-cell transplant	1 (1)	0 (0)
Allogeneic stem-cell transplant	2 (2)	1 (1)
Reason for any previous cBTKi discontinuation,[e] No. (%)		
Disease progression	85 (71)	87 (73)
Toxicity	20 (17)	22 (18)
Other	14 (12)	8 (7)

(continued in next column)

NOTE. Data cutoff date of August 29, 2024.
Abbreviations: BCL-2i, B-cell lymphoma-2 inhibitor; BR, bendamustine plus rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IdelaR, idelalisib plus rituximab; IGHV, immunoglobulin heavy chain gene; SLL, small lymphocytic lymphoma.
[a]Rai stage at study entry; excludes patients with missing stage.
[b]≥3 abnormalities in same clonal population.
[c]Other includes orelabrutinib, tirabrutinib, zebutinib, and AVL-292-003.
[d]Two patients in the IdelaR/BR group received an investigational BCL-2i, all other patients received venetoclax.
[e]In the event more than one reason was noted for discontinuation, disease progression was prioritized, then toxicity, then other reasons.

(95% CI, 18.2 to not estimable [NE]) versus 12.5 months (95% CI, 9.5 to 18.4) with IdelaR/BR (HR, 0.36 [95% CI, 0.21 to 0.61]; Fig 4B). Venetoclax-treated patients also saw a longer median TTNT with 20 months (95% CI, 12 to NE) in the pirtobrutinib group versus 8.7 months (95% CI, 4.8 to 11.1) with IdelaR/BR (HR, 0.37 [95% CI, 0.23 to 0.60]; Fig 4C). TTNT subgroup analyses generally favored pirtobrutinib across clinically relevant subgroups (Appendix Fig A2). INV-assessed ORR, including partial response with lymphocytosis, was higher in the pirtobrutinib group (69% [95% CI, 60 to 77]) versus IdelaR/BR (50% [95% CI, 40 to 59]; Appendix Table A2).

At the prespecified final OS analysis, 18-month OS was 73.4% (95% CI, 63.9 to 80.7) in the pirtobrutinib group and 70.8% (95% CI, 60.9 to 78.7) with IdelaR/BR (unadjusted HR, 1.09 [95% CI, 0.68 to 1.75]; $P = .7202$; Fig 3B). OS assessment was confounded by a high effective crossover rate of 76%. Three sensitivity analyses adjusting for crossover were preformed, including a prespecified analysis censoring at crossover (adjusted HR, 0.99 [95% CI, 0.57 to 1.71]), and two post hoc analyses using the IPCW method (adjusted HR, 0.87 [95% CI, 0.51 to 1.50]) and the two-stage AFT method (adjusted HR, 0.78 [95% CI, 0.48 to 1.26]).

Safety

TEAE of any grade occurred in 108 (93.1%) patients receiving pirtobrutinib and 107 (98.2%) receiving IdelaR/BR (Appendix Table A3). Pneumonia was the most frequently occurring TEAE in patients receiving pirtobrutinib (22.4%)

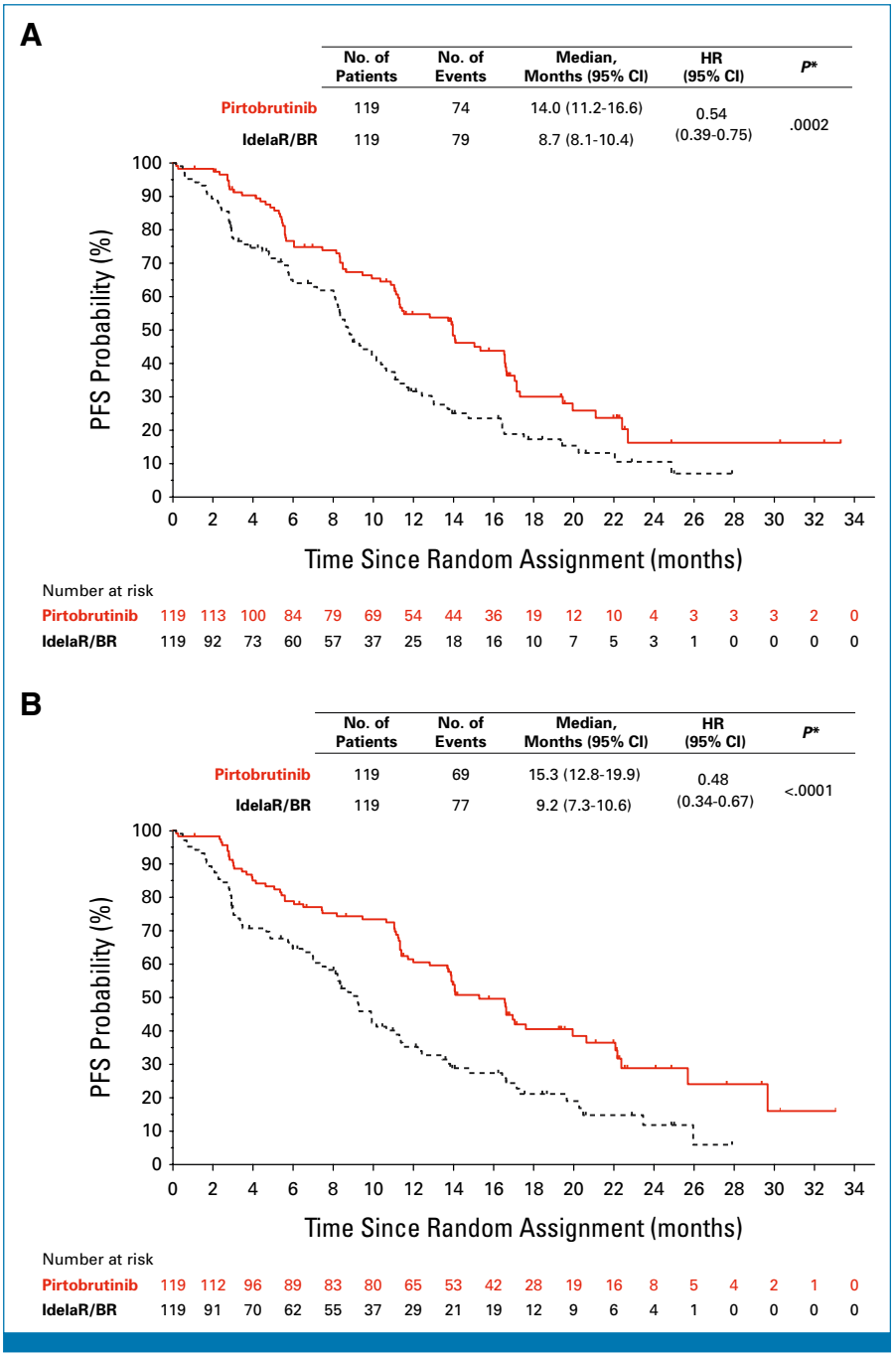

FIG 2. Kaplan-Meier curve of PFS as assessed by (A) IRC and (B) investigator. *Nominal *P* value. BR, bendamustine plus rituximab; HR, hazard ratio; IdelaR, idelalisib plus rituximab; IRC, independent review committee; PFS, progression-free survival.

versus IdelaR/BR (11.9%), followed by anemia (19.8%) and neutropenia (18.1%). The most frequently occurring AE in patients receiving IdelaR/BR were diarrhea (31.2%), pyrexia (26.6%), and fatigue and nausea (20.2% each). Since the median treatment duration was 15.1 months for patients on pirtobrutinib, and shorter with IdelaR (idelalisib = 7.1 months; rituximab = 5.5 months) and BR (bendamustine = 4.7 months; rituximab = 4.7 months), an exposure-adjusted safety analysis was conducted to account for these differences (Table 2). The IR of these TEAEs was lower with pirtobrutinib than with IdelaR/BR (Table 2), resulting in an IRR less than one for nearly all AEs including anemia (0.61 [95% CI, 0.33 to 1.12]) and neutropenia (0.60 [95% CI, 0.31 to 1.13]).

Bleeding AEs were primarily low-grade. Three patients on pirtobrutinib experienced grade 3 hemorrhage (n = 1 each; vaginal hemorrhage, conjunctival hemorrhage, and subdural hematoma) and one IdelaR-treated patient experienced grade 5 hemorrhage (hematoma). Three (2.6%) patients

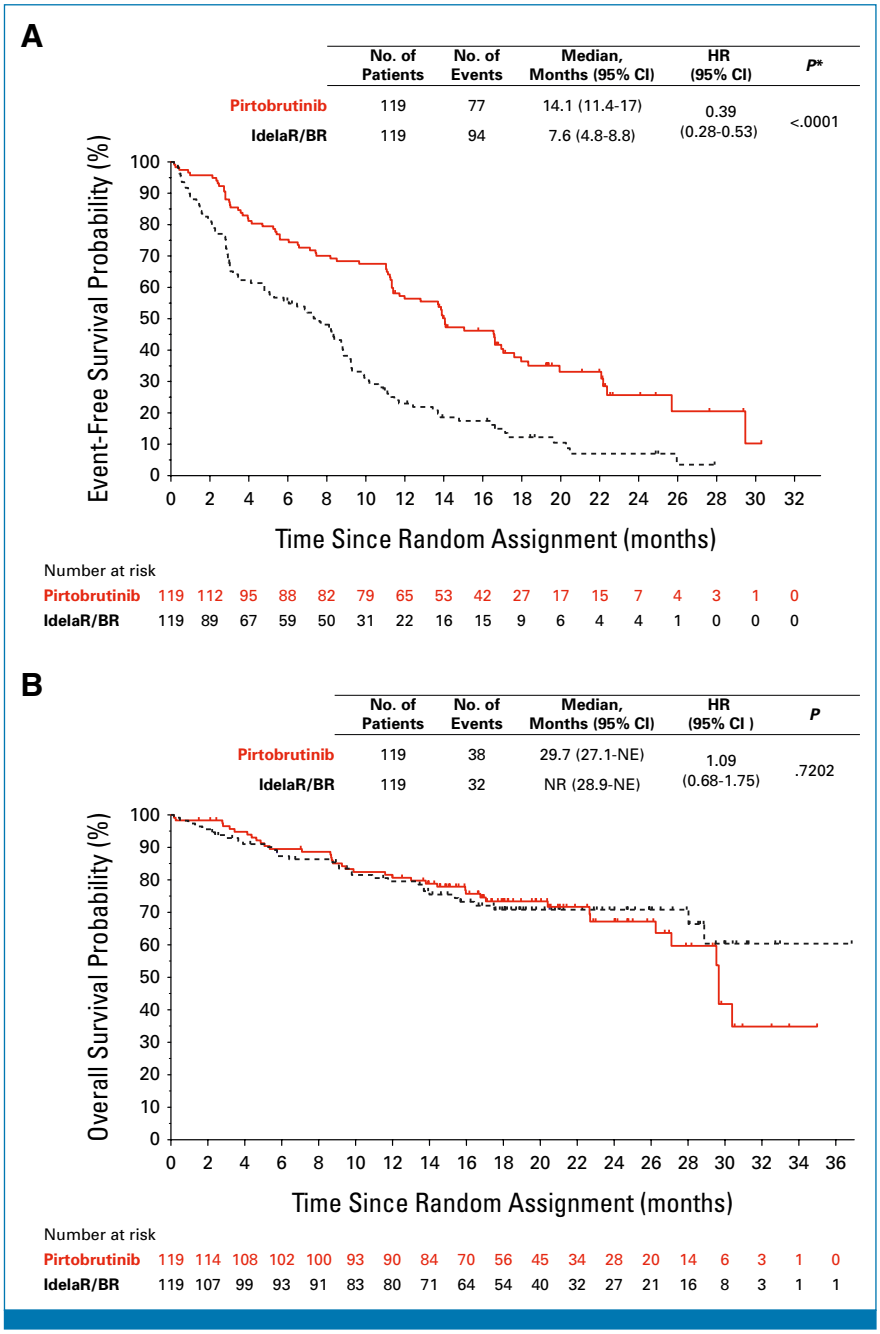

FIG 3. Kaplan-Meier curve of (A) event-free survival and (B) overall survival. *Nominal *P* value. BR, bendamustine plus rituximab; HR, hazard ratio; IdelaR, idelalisib plus rituximab; NE, not estimable.

experienced atrial fibrillation during pirtobrutinib treatment, two with previous history of atrial fibrillation associated with previous cBTKi exposure. One patient receiving IdelaR/BR experienced de novo atrial fibrillation. Hypertension of any grade was similar between groups, reported in eight (6.9%) patients receiving pirtobrutinib and four (3.7%) receiving IdelaR/BR.

Dose reductions occurred in 13 (11.2%) patients receiving pirtobrutinib and 40 (36.7%) receiving IdelaR/BR (Appendix Table A1). Treatment discontinuation due to AE occurred in 20 (17.2%) patients receiving pirtobrutinib, with six (5.2%) due to an AE considered treatment-related. Thirty-eight (34.9%) patients receiving IdelaR/BR discontinued treatment due to AE with 23 (21.1%) considered treatment-related (Appendix Table A4). Grade 5 TEAEs occurred in 12 (10.3%) patients receiving pirtobrutinib and 10 (9.2%) patients receiving IdelaR/BR, with none while on treatment in either group, none considered related to pirtobrutinib, and one considered related to BR treatment (Appendix Table A5). Grade 5 COVID-19 occurred in two (1.7%) patients receiving pirtobrutinib and one (0.9%) receiving IdelaR/BR. Three

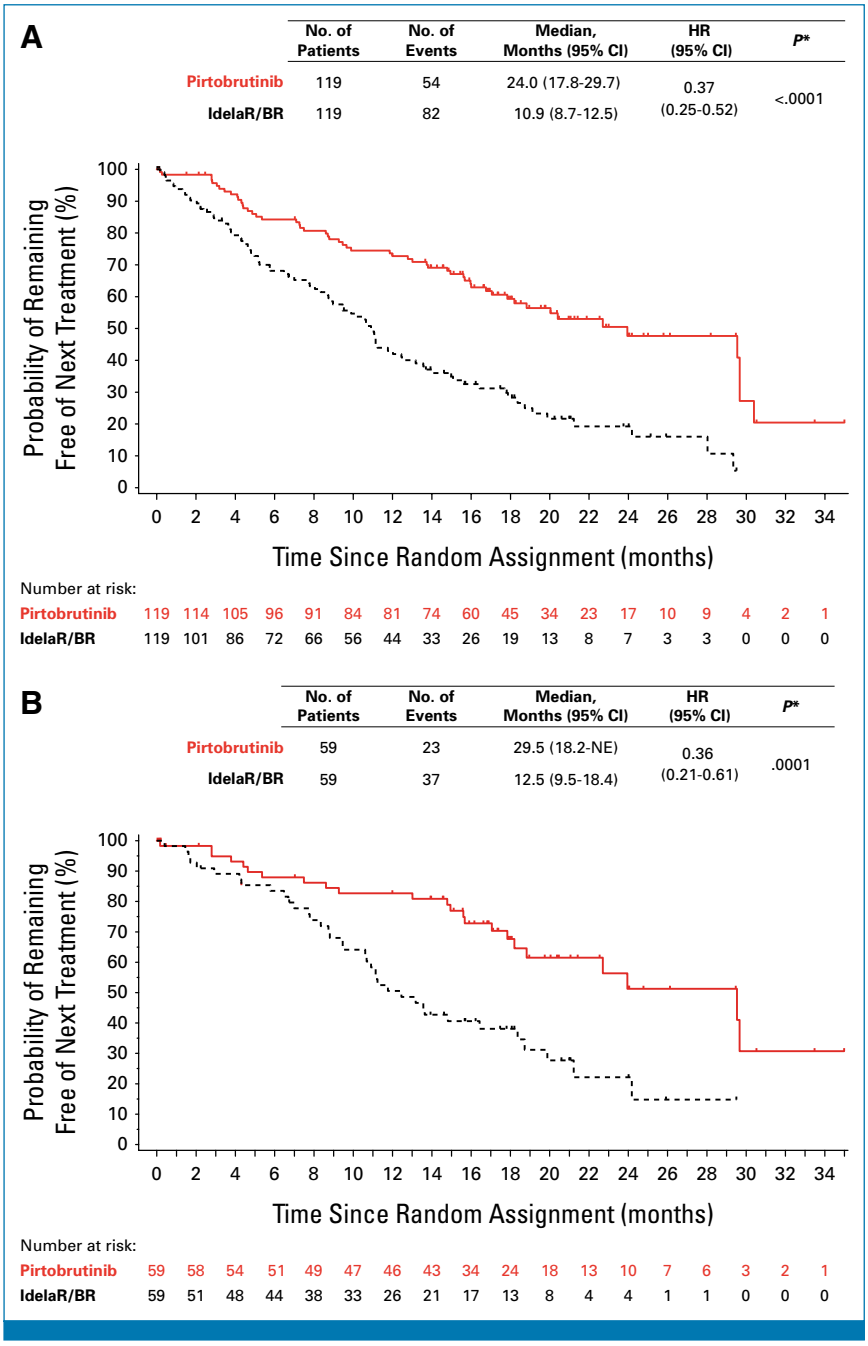

FIG 4. Time to next treatment or death in the (A) ITT population, (B) venetoclax-naïve patients, and (C) venetoclax-treated patients. *Nominal *P* value. BR, bendamustine plus rituximab; HR, hazard ratio; IdelaR, idelalisib plus rituximab; ITT, intention-to-treat; NE, not estimable. (continued on following page)

patients receiving IdelaR/BR experienced Richter transformation, while no patient receiving pirtobrutinib developed Richter transformation.

DISCUSSION

To our knowledge, BRUIN CLL-321 was the first prospective randomized phase III study conducted exclusively in patients with CLL/SLL previously treated with a cBTKi. The patients enrolled in this study were heavily pretreated, having received a median of three previous lines of therapy. Half had received venetoclax, and 70% had previous chemotherapy and/or anti-CD20 antibody. The majority had high-risk molecular features, often associated with more aggressive disease. In this poor-risk patient population, pirtobrutinib demonstrated a statistically significant and clinically meaningful improvement in PFS compared with IC, reducing the risk of relapse, PD, or death by 46%. A slight imbalance in the

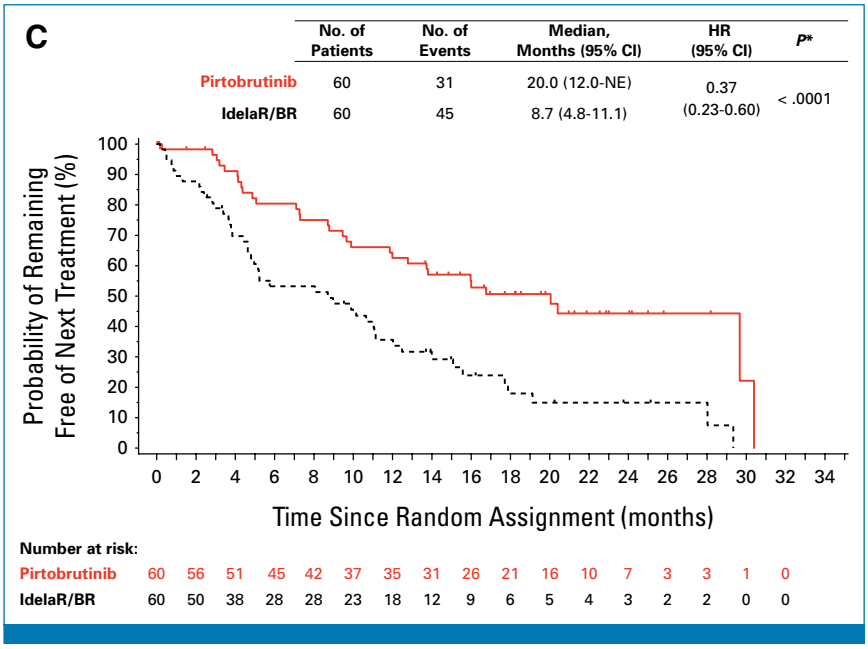

FIG 4. (Continued).

number of patients who withdrew early from the study without receiving pirtobrutinib (n = 3) versus IC (n = 10) is noted; however, the magnitude of benefit seen with pirtobrutinib is substantial and the potential impact of this imbalance from this small number of patients should not have meaningfully influenced the efficacy results of this study. Pirtobrutinib treatment benefit was observed across clinically relevant subgroups, including those with high-risk molecular features such as del(17p)/*TP53* mutations, complex karyotype, and unmutated IGHV. Pirtobrutinib also showed substantially

TABLE 2. Summary of TEAEs by Exposure-Adjusted IR

TEAE	Pirtobrutinib (n = 116), IR[a]	IdelaR or BR (n = 109), IR[a]	IRR (95% CI)[b]	*P*[c]
Infections[d]	94.5	125.5	0.75 (0.53 to 1.07)	.11
Pneumonia[e]	20.4	19.5	1.04 (0.54 to 2.03)	.90
COVID-19	11.1	33.4	0.33 (0.17 to 0.65)	.001
Anemia	18.5	30.3	0.61 (0.33 to 1.12)	.11
Neutropenia[f]	26.4	66.5	0.40 (0.25 to 0.64)	<.001
Cough	14.3	30.8	0.47 (0.25 to 0.88)	.02
Diarrhea	15.3	63.7	0.24 (0.14 to 0.42)	<.001
Pyrexia	11.1	52.4	0.21 (0.11 to 0.40)	<.001
Fatigue	9.5	34.2	0.28 (0.14 to 0.55)	<.001
Nausea	9.8	38.3	0.26 (0.13 to 0.51)	<.001
Vomiting	5.8	29.6	0.19 (0.08 to 0.44)	<.001
ALT increased	2.8	33.6	0.08 (0.03 to 0.25)	<.001
Weight decreased	2.8	28.5	0.10 (0.03 to 0.29)	<.001

Abbreviations: BR, bendamustine plus rituximab; IdelaR, idelalisib plus rituximab; IR, incidence rate; IRR, IR ratio; PYE, patient-years at risk; TEAE, treatment-emergent adverse event.

[a]IR is based on first occurrence of the event and is calculated as number of event (n) divided by sum of years at risk for a TEAE across all patients (PYE) times 100.

[b]IRR is based on pirtobrutinib IR relative to IdelaR/BR IR.

[c]The nominal two-sided *P* value and 95% CI for IRR are based on Poisson regression.

[d]Aggregate of all preferred terms indicating infection and including COVID-19. Grade ≥3 infection IR was 26.8 with pirtobrutinib and 43.5 with IdelaR/BR; the IRR was 0.62 (95% CI, 0.37 to 1.02), nominal *P* = .062.

[e]Grade ≥3 pneumonia IR was 15.2 with pirtobrutinib and 18 with IdelaR/BR; the IRR was 0.85 (95% CI, 0.41 to 1.73), nominal *P* = .646.

[f]Aggregate of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.

improved EFS versus IdelaR/BR. These EFS results demonstrate the clinically meaningful benefit and tolerability of pirtobrutinib over IdelaR/BR, including the impact of toxicity on a patient's ability to continue pirtobrutinib treatment.

Interestingly, investigation of the PFS curve in the pirtobrutinib group suggest that PD events occurred predominantly at time periods corresponding to protocol mandated study scans, conducted routinely regardless of signs or symptoms of PD. This trial allowed for continuation of study treatment beyond IRC-assessed PD if the INV determined continued clinical benefit, consistent with routine clinical practice. This occurred in 38.6% of patients who experienced IRC-assessed PD in the pirtobrutinib group, with many continuing treatment and not requiring a new therapy for considerable time, and in only one IdelaR/BR patient (1.5%).

To this end, TTNT is of clinical relevance, as patients in usual clinical practice do not have regular interval computed tomography scans in the absence of clinical signs of PD. Pirtobrutinib treatment resulted in a median TTNT of nearly 2.5 years in venetoclax-naïve and 1.7 years in venetoclax-pretreated patients. This TTNT improvement from pirtobrutinib treatment is much longer than the observed median PFS improvement seen in this study, and the differences in the rates of treatment beyond progression in each study group likely contribute to this observation. Although crossover to receive pirtobrutinib was allowed, it was only allowed when a patient required treatment per iwCLL criteria. This occurred in most eligible IdelaR/BR patients (75.8%, 50/66) in a short span of time after progression, suggesting that these progressions were likely clinically significant, and it is unlikely TTNT was confounded by a desire for early access to pirtobrutinib.

The TTNT data observed for pirtobrutinib in this post-BTKi population raise the proposition of sequencing pirtobrutinib treatment before venetoclax. This decision may rest, at least in part, on comfort in the efficacy of venetoclax after pirtobrutinib. Retrospective analyses by Thompson et al[17] suggest that more than 70% of patients respond to venetoclax after previous non-cBTKi therapy. However, to our knowledge, to date no significant prospective randomized data exist for the use of venetoclax after covalent or non-cBTKi treatment. Further studies on optimal treatment sequencing are needed. The BRUIN-322 study is evaluating the combined time-limited utilization of pirtobrutinib and venetoclax with rituximab in this setting (ClinicalTrials.gov identifier: NCT04965493).

The safety profile of patients receiving pirtobrutinib in this study was similar to what has been previously reported in phase 1/2 BRUIN studies of CLL/SLL with longer follow-up of patients.[8,18] Here, the safety profile of pirtobrutinib was more favorable than IdelaR/BR, a difference that was more pronounced when accounting for duration of drug exposure, with a low frequency of pirtobrutinib-related discontinuations (5.2%). AEs of interest associated with the cBTKi class such as atrial fibrillation, hypertension, and major bleeding were infrequent with pirtobrutinib.[8] Patients with a history of atrial fibrillation or atrial flutter were allowed enrollment on this study with only three events being observed in the pirtobrutinib group, two of the three patients already having a previous medical history of this event, and an overall rate difficult to distinguish from expected background incidence. Currently, there is no clear evidence that pirtobrutinib causes or exacerbates cardiac events. Similarly, the incidence of hypertension was low and comparable with levels observed in patients receiving IdelaR/BR, and not higher than expected in an elderly CLL population. Bleeding events were mostly low-grade, and usually did not require treatment interruption or modification. Notably, there were no cases of Richter transformation reported in the pirtobrutinib group, but three observed in the IdelaR/BR group.

Retrospective data suggested that outcomes are poor in subsequent lines of therapy post-cBTKi, and definitive data are needed to help guide treatment decisions. Studies supporting the use of idelalisib, bendamustine, and venetoclax in R/R CLL/SLL were conducted almost exclusively in BTK inhibitor-naïve populations.[15,19,20] The limited retrospective data align with data presented here, showing a short median PFS of 8.7 months with IdelaR/BR.[13] This contrasts with the median PFS of 16.8 months observed in patients treated with IdelaR/BR in the ASCEND study, which was conducted exclusively in a cBTKi-naïve patient population.[10]

In conclusion, to our knowledge, BRUIN-321 is the first prospective randomized trial ever conducted in a cBTKi-pretreated CLL/SLL population, providing definitive evidence of pirtobrutinib benefit after previous cBTKi therapy. This study demonstrated a significant, clinically meaningful improvement in PFS and a more favorable safety profile with pirtobrutinib versus IdelaR/BR in patients with CLL/SLL. TTNT and EFS showed robust benefit in this population where no effective standard of care exists. These data may be relevant for future treatment sequencing strategies.

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Presented in part at the American Society of Hematology 2024 Annual Meeting, San Diego, CA, December 7-10, 2024.

SUPPORT

Supported by Eli Lilly and Company.

CLINICAL TRIAL INFORMATION

NCT04666038 (BRUIN CLL-321)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-00166.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-00166. Eli 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 United States and the European Union 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, 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.

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ACKNOWLEDGMENT

The authors thank the BRUIN clinical trial participants and their caregivers, without whom this work would not be possible. The authors also thank the BRUIN trial investigators and study staff. The authors thank Min-Hua Jen and Yimei Han for their hard work providing statistical support for the OS sensitivity analyses reported in this study. Alyson L. Essex, PhD, employee of Eli Lilly and Company, provided medical writing support. Other company and product names are trademarks of their respective owners.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase III Trial of Pirtobrutinib Versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor–Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Dose Modifications

Dose Modification	Pirtobrutinib (n = 116), No. (%)	IdelaR (n = 77), No. (%)	BR (n = 32), No. (%)
Number of patients with dose reduction	13 (11.2)	34 (44.2)	6 (18.8)
Patient error	3 (2.6)	6 (7.8)	0
Adverse event	11 (9.5)	26 (33.8)	4 (12.5)
Other	0 (0)	10 (13)	3 (9.4)
Number of patients with dose hold	79 (68.1)	57 (74)	—
Patient error	23 (19.8)	7 (9.1)	—
Adverse event	60 (51.7)	54 (70.1)	—
Procedure	12 (10.3)	0	—
Other	21 (18.1)	15 (19.5)	—
Number of patients with dose delay	—	—	2 (6.3)
Adverse event	—	—	2 (6.3)
Other	—	—	1 (3.1)
Number of patients with infusion interruption	—	14 (18.2)	16 (50)
Adverse event	—	9 (11.7)	14 (43.8)
First dose split	—	4 (5.2)	2 (6.3)
Other	—	3 (3.9)	2 (6.3)

Abbreviations: BR, bendamustine plus rituximab; IdelaR, idelalisib plus rituximab.

TABLE A2. Best Overall Response, Overall Response Rate, and Duration of Response as Assessed by IRC and Investigator

	Pirtobrutinib (n = 119)		IdelaR or BR (n = 119)	
End Point	IRC	Investigator	IRC	Investigator
Best overall response, %				
CR, including CRi	2	6	4	6
PR, including nPR	59	61	48	43
PR-L	4	3	1	1
SD	23	15	13	13
PD	5	8	15	19
Other[a]	8	8	19	19
ORR including PR-L, % (95% CI)	65 (55 to 73)	69 (60 to 77)	53 (44 to 62)	50 (40 to 59)
Median DOR, including PR-L, months (95% CI)	13.8 (11.1 to 17.2)	13.9 (11.1 to 19.1)	10.9 (7.8 to 14.8)	9.4 (7.2 to 13.9)

NOTE. For IRC-assessed ORR, sensitivity analyses without requirement for two full postbaseline tumor assessments to confirm response.
Abbreviations: BR, bendamustine plus rituximab; CR, complete response; CRi, CR with incomplete bone marrow recovery; DOR, duration of response; IdelaR, idelalisib plus rituximab; IRC, independent review committee; nPR, nodular PR; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease.
[a]Other includes non-PD, unknown, nonestimable, and not available.

TABLE A3. Treatment-Emergent AEs Occurring in ≥15% of Patients in Either Treatment Group

	Pirtobrutinib (n = 116)		IdelaR/BR (n = 109)	
AE	Any Grade, No. (%)	Grade 3/4, No. (%)	Any Grade, No. (%)	Grade 3/4, No. (%)
Anemia	23 (19.8)	13 (11.2)	19 (17.4)	8 (7.3)
Pneumonia	26 (22.4)	18 (15.5)	13 (11.9)	9 (8.3)
Neutropenia	21 (18.1)	17 (14.7)	17 (15.6)	13 (11.9)
Diarrhea	19 (16.4)	0 (0)	34 (31.2)	6 (5.5)
Cough	19 (16.4)	0 (0)	19 (17.4)	0 (0)
COVID-19	15 (12.9)	0 (0)	20 (18.3)	4 (3.7)
Pyrexia	15 (12.9)	1 (0.9)	29 (26.6)	1 (0.9)
Fatigue	13 (11.2)	2 (1.7)	22 (20.2)	1 (0.9)
Nausea	13 (11.2)	1 (0.9)	22 (20.2)	0 (0)
Vomiting	8 (6.9)	1 (0.9)	19 (17.4)	0 (0)
ALT increased	4 (3.4)	1 (0.9)	19 (17.4)	10 (9.2)
Infusion-related reaction	0 (0)	0 (0)	19 (17.4)	3 (2.8)
Weight decreased	4 (3.4)	0 (0)	18 (16.5)	0 (0)
AE of interest				
Anemia[a]	24 (20.7)	13 (11.2)	19 (17.4)	8 (7.3)
Atrial fibrillation and atrial flutter	3 (2.6)	2 (1.7)	1 (0.9)	0 (0)
Bleeding	25 (21.6)	4 (3.4)	11 (10.1)	0 (0)
Bruising[b]	9 (7.8)	1 (0.9)	3 (2.8)	0 (0)
Petechiae and purpura	6 (5.2)	1 (0.9)	1 (0.9)	0 (0)
Hemorrhage[c]	18 (15.5)	3 (2.6)	8 (7.3)	0 (0)
Hypertension	8 (6.9)	3 (2.6)	4 (3.7)	1 (0.9)
Infections[d]	74 (63.8)	25 (21.6)	54 (49.5)	21 (19.3)
Infection without COVID-19	67 (57.8)	26 (22.4)	47 (43.1)	19 (17.4)
Neutropenia[e]	31 (26.7)	24 (20.7)	37 (33.9)	30 (27.5)
Thrombocytopenia[f]	11 (9.5)	9 (7.8)	17 (15.6)	8 (7.3)

Abbreviations: AE, adverse event; BR, bendamustine plus rituximab; IdelaR, idelalisib plus rituximab.
[a]Includes anemia and iron deficiency anemia.
[b]Includes contusion and ecchymosis.
[c]Includes hemorrhage and hematoma.
[d]Includes all infection events reported including COVID-19.
[e]Includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
[f]Includes thrombocytopenia and platelet count decreased.

TABLE A4. AEs of Any Grade Leading to Treatment Discontinuation

	Pirtobrutinib (n = 116)		IdelaR/BR (n = 109)	
AE	TEAE	TRAE	TEAE	TRAE
AE leading to discontinuation, No. (%)	20 (17.2)	6 (5.2)	38 (34.9)	23 (21.1)
Infections and infestations	11 (9.5)	0 (0)	10 (9.2)	2 (1.8)
COVID-19 pneumonia	3 (2.6)	0 (0)	1 (0.9)	1 (0.9)
Pneumonia	3 (2.6)	0 (0)	3 (2.8)	1 (0.9)
COVID-19	2 (1.7)	0 (0)	2 (1.8)	0 (0)
Anemia	2 (1.7)	1 (0.9)	0 (0)	0 (0)
Neutropenia	2 (1.7)	1 (0.9)	0 (0)	0 (0)
Thrombocytopenia	1 (0.9)	1 (0.9)	0 (0)	0 (0)
Cardiac disorders	2 (1.7)	2 (1.7)	1 (0.9)	0 (0)
Atrial fibrillation	1 (0.9)	1 (0.9)	0 (0)	0 (0)
GI disorders	1 (0.9)	1 (0.9)	9 (8.3)	8 (7.3)
Multiple organ dysfunction syndrome	1 (0.9)	0 (0)	0 (0)	0 (0)
Drug intolerance	0 (0)	0 (0)	1 (0.9)	0 (0)
Influenza-like illness	0 (0)	0 (0)	1 (0.9)	0 (0)
Mucosal necrosis	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Edema peripheral	0 (0)	0 (0)	1 (0.9)	0 (0)
Pyrexia	0 (0)	0 (0)	2 (1.8)	1 (0.9)
Lymphocyte count increased	1 (0.9)	1 (0.9)	0 (0)	0 (0)
ALT increased	0 (0)	0 (0)	5 (4.6)	5 (4.6)
AST increased	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Blood creatinine increased	0 (0)	0 (0)	1 (0.9)	0 (0)
Platelet count decreased	0 (0)	0 (0)	1 (0.9)	0 (0)
Squamous cell carcinoma	1 (0.9)	0 (0)	0 (0)	0 (0)
Acute interstitial pneumonitis	1 (0.9)	1 (0.9)	0 (0)	0 (0)
Respiratory failure	0 (0)	0 (0)	1 (0.9)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.9)	1 (0.9)	5 (4.6)	5 (4.6)
Vascular disorders	1 (0.9)	0 (0)	2 (1.8)	0 (0)
Hepatitis toxic	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Pneumothorax traumatic	0 (0)	0 (0)	1 (0.9)	0 (0)
Metabolism and nutrition disorders	0 (0)	0 (0)	4 (3.7)	2 (1.8)
Arthritis	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Lethargy	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Acute kidney injury	0 (0)	0 (0)	1 (0.9)	0 (0)

Abbreviations: AE, adverse event; BR, bendamustine plus rituximab; IdelaR, idelalisib plus rituximab; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

TABLE A5. Summary of Patients Who Experienced Fatal TEAE

Fatal TEAE	Pirtobrutinib (n = 116)	IdelaR/BR (n = 109)
Patients with fatal TEAE, No. (%)	12 (10.3)	10 (9.2)
COVID-19 pneumonia	3 (2.6)	1 (0.9)
Pneumonia	2 (1.7)	3 (2.8)
COVID-19	2 (1.7)	1 (0.9)
Clostridium difficile infection	1 (0.9)	0 (0)
Pneumonia viral	1 (0.9)	0 (0)
Multiple organ dysfunction syndrome	1 (0.9)	0 (0)
Squamous cell carcinoma	1 (0.9)	0 (0)
Tumor compression	0 (0)	1 (0.9)
Respiratory failure	1 (0.9)	1 (0.9)
Cardiac arrest	0 (0)	1 (0.9)
Pneumothorax traumatic	0 (0)	1 (0.9)
Hematoma	0 (0)	1 (0.9)

Abbreviations: BR, bendamustine plus rituximab; IdelaR, idelalisib plus rituximab; TEAE, treatment-emergent adverse event.

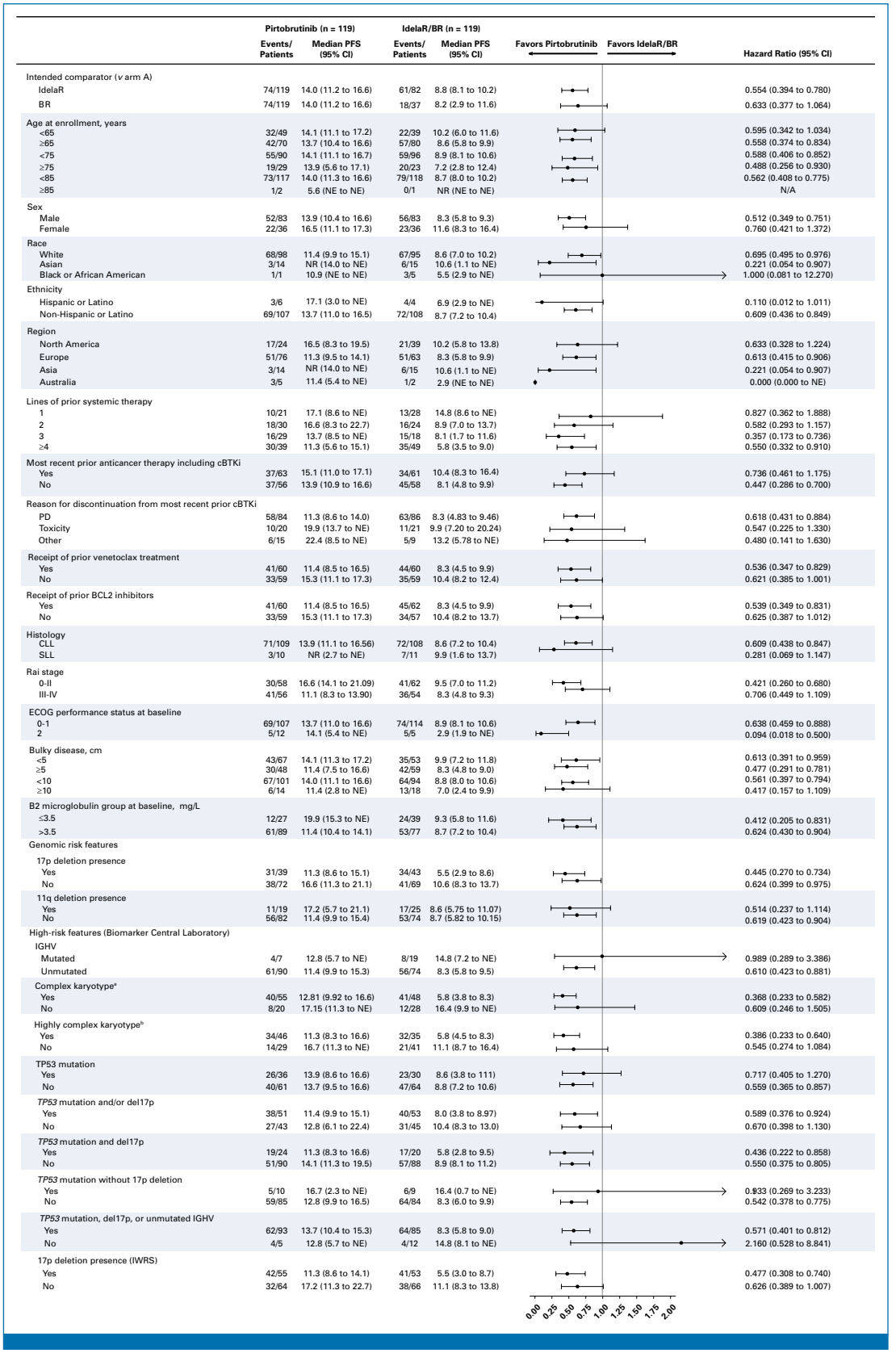

FIG A1. Forest plot of IRC-assessed PFS across patient subgroups treated. [a]Complex karyotype (yes = ≥3 chromosomal abnormalities; no ≤3 chromosomal abnormalities). [b]Highly complex karyotype (yes = ≥5 chromosomal abnormalities; no = <5 chromosomal abnormalities). BR, bendamustine plus rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; IdelaR, idelalisib plus rituximab; IGHV, immunoglobulin heavy chain gene; IRC, independent (continued on following page)

FIG A1. (Continued). review committee; IWRS, Interactive Web Response System; PD, progressive disease; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

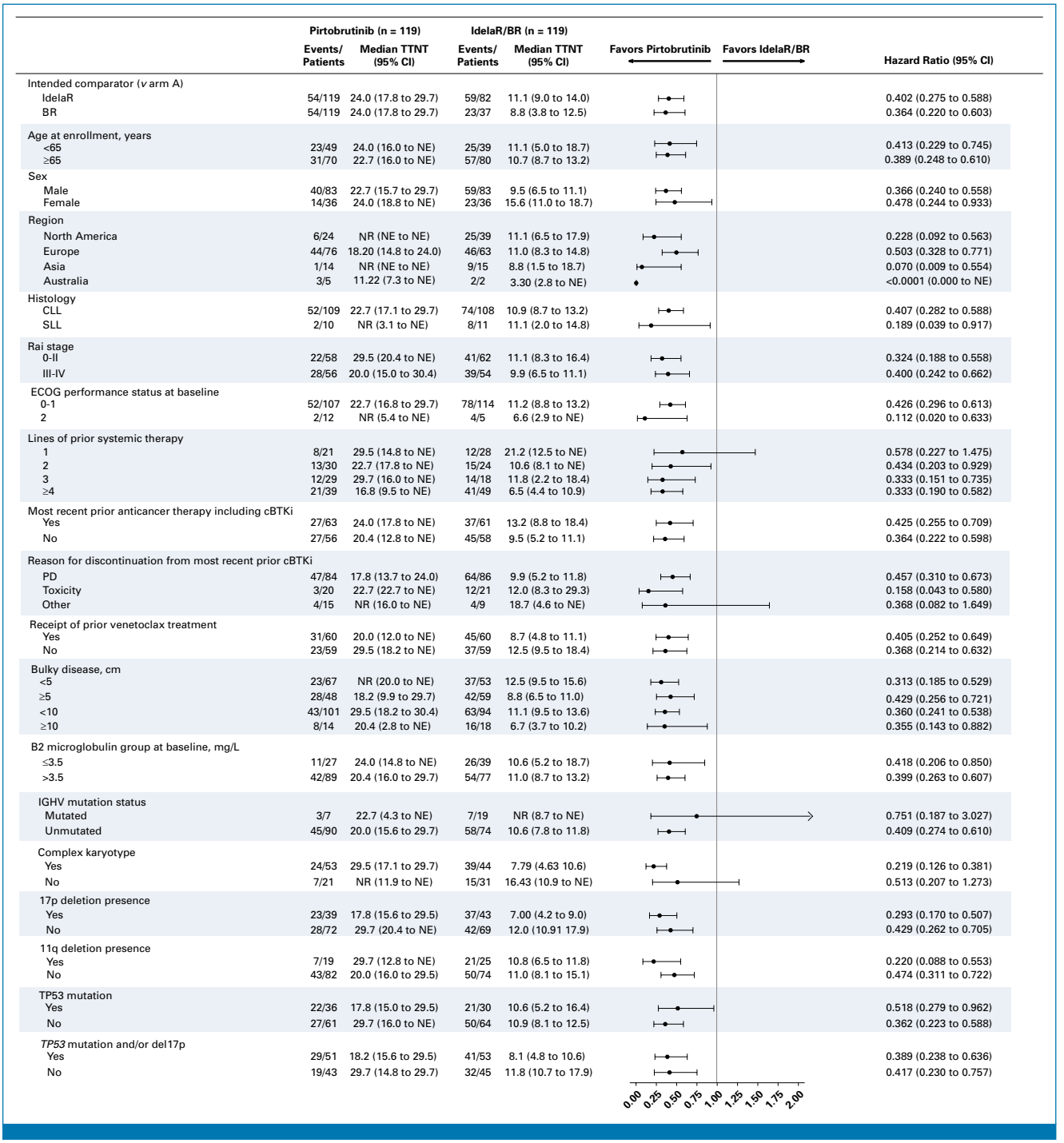

FIG A2. Forest plot of TTNT across subgroups. [a]≥3 abnormalities in same clonal population. BCL2, B-cell lymphoma-2; BR, bendamustine plus rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; IdelaR, idelalisib plus rituximab; IGHV, immunoglobulin heavy chain gene; IWRS, Interactive Web Response System; NE, not estimable; PD, progressive disease; SLL, small lymphocytic lymphoma; TTNT, time to next treatment or death.