Phase III Trial of Pirtobrutinib versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent BTK Inhibitor–Pretreated CLL/SLL (BRUIN CLL-321)

Study Design and Patient Population

BRUIN CLL-321 is the first prospective, randomized ph3 study conducted exclusively in a cBTKi-pretreated CLL/SLL population

Patients with CLL/SLL previously treated with cBTKi N=238

Stratified by:
17p deletion (yes/no)
Prior venetoclax (yes/no)

R 1:1

Pirtobrutinib Monotherapy n=119
200mg PO QD

IdelaR/BR n=119
Idelalisib + Rituximab[a] n=82
Bendamustine + Rituximab[b,c] n=37

Optional Crossover (PD confirmed by IRC and eligibility criteria for treatment by iwCLL 2018 met)[d]

Key Eligibility

- Age ≥18
- ECOG PS 0-2
- Confirmed CLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**
- **Prior history of atrial fibrillation allowed**

Endpoints

- **Primary Endpoint: PFS assessed by IRC**
- PFS assessed by investigator
- Event-Free Survival
- Time to Next Treatment
- Overall survival
- Safety

Patient characteristics indicate a poor prognosis and heavily pre-treated population

Median of 3 prior lines of systemic therapy
(range 1-13 for pirtobrutinib arm, and 1-11 for IdelaR/BR arm)

~50% received prior BCL2i

>50% del(17p) and/or *TP53* mutation

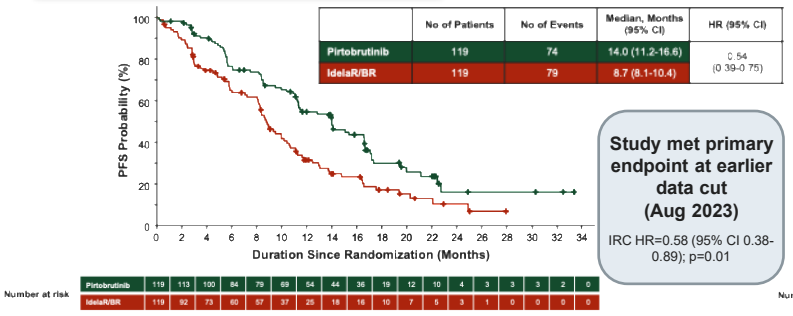
Statistical Analysis Plan

Primary PFS Analysis
7.5 months median follow-up
August 2023

Final OS Analysis
17.2 median follow-up
August 2024

Efficacy Analysis

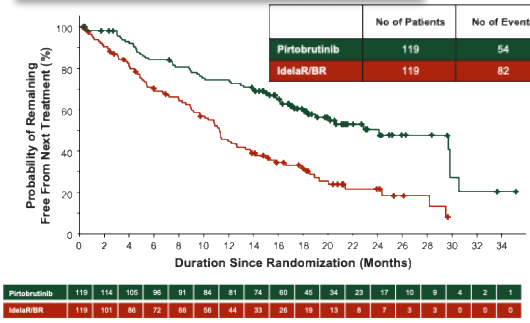
IRC-Assessed Progression-free Survival



	No of Patients	No of Events	Median, Months (95% CI)	HR (95% CI)
Pirtobrutinib	119	74	14.0 (11.2-16.6)	0.54 (0.39-0.75)
IdelaR/BR	119	79	8.7 (8.1-10.4)	

Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38-0.89); p=0.01

Time-To-Next-Treatment or Death



	No of Patients	No of Events	Median, Months (95% CI)	HR (95% CI)
Pirtobrutinib	119	54	24.0 (17.8-29.7)	0.37 (0.25-0.52)
IdelaR/BR	119	82	10.9 (8.7-12.5)	

Median TTNT was 24 months in the pirtobrutinb group vs 10.9 months with IdelaR/BR (HR, 0.37)

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 versus 8.7 months 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]

In venetoclax naïve patients, median TTNT was 29.5 mo in the pirtobrutinib group and 12.5 mo in the IdelaR/BR group (HR, 0.36 [95% CI, 0.21 to 0.61]). In venetoclax-treated patients, median TTNT was 20 mo in the pirtobrutinib group and 8.7 mo in the IdelaR/BR group (HR, 0.37 [95% CI, 0.23 to 0.60]).

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, 0.38-0.92]), unmutated IGHV (HR, 0.61 [95%CI, 0.42-0.88]), and complex karyotype (HR, 0.37 [95%CI, 0.23-0.58];

Overall Survival follow-up limited and confounded by high rate of post-progression crossover

- **18-month OS rate: Pirtobrutinib, 73.4%; IdelaR/BR, 70.8%**
- **76% effective crossover rate among INV PD patients[e]**
- **HR 1.09 (0.68-1.75). Crossover-adjusted HR <1.**

Safety Analysis

TEAEs Occurring in ≥ 15% of Patients	Pirtobrutinib (n=116)		IdelaR/BR (n=109)	
	Any Grade, n (%)	Grade 3/4, n (%)	Any Grade, n (%)	Grade 3/4, n (%)
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)

- **Median time on treatment with pirtobrutinib, IdelaR and BR was 15.1 months, 7.1 months and 4.7 months, respectively**
- **Treatment discontinuations due to AEs occurred in 20 (17.2%) treated with pirtobrutinib and 38 patients (34.9%) treated with IdelaR/BR. 6 (5.2%) and 23 (21.1%) discontinuations, respectively, were considered drug-related**
- **Dose reductions occurred in 13 (11.2%) patients receiving pirtobrutinib and 40 (36.7%) receiving IdelaR/BR**

TEAEs of Clinical Interest	Pirtobrutinib (n=116)		IdelaR/BR (n=109)	
	Any Grade, n (%)	Grade 3/4, n (%)	Any Grade, n (%)	Grade 3/4, n (%)
Anemia[f]	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[g]	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[h]	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[i]	74 (63.8)	25 (21.6)	54 (49.5)	21 (19.3)
w/o COVID-19	67 (57.8)	26 (22.4)	47 (43.1)	19 (17.4)
Neutropenia[j]	31 (26.7)	24 (20.7)	37 (33.9)	30 (27.5)
Thrombocytopenia[k]	11 (9.5)	9 (7.8)	17 (15.6)	8 (7.3)

2 of 3 patients with any grade atrial fibrillation during pirtobrutinib treatment had a past medical history of atrial fibrillation. 1 patient treated with IdelaR/BR had de novo atrial fibrillation. 3 patients on pirtobrutinib experienced grade 3 hemorrhage (n=1 each; vaginal hemorrhage, conjunctival hemorrhage, and subdural hematoma). 1 patient treated with IdelaR had grade 5 hemorrhage (hematoma).

Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. TTNT is defined as time from the date of randomization to the date of initiation of the subsequent anticancer therapy (including crossover) for CLL/SLL, or death due to any cause, whichever occurs first. [a]Idelalisib dosed at 150mg PO BID. Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 4 infusions at 500 mg/m^2 every 2 weeks, next 3 infusions at 500 mg/m^2 every 4 weeks. [b]Bendamustine (70 mg/m2) administered IV D1, D2 of cycles 1-6. [c]Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 5 infusions day 1 of cycle 2 through cycle 6 at 500 mg/m^2. [d]Eligible patients receiving investigator's choice of IdelaR/BR could crossover to receive pirtobrutinib upon confirmation of PD by IRC per protocol, and only if they met the eligibility criteria for treatment by iwCLL 2018. [e]Among patients whose event was INV PD and thus had the opportunity to crossover. [f]Includes anemia and iron deficiency anemia. [g]Includes contusion and ecchymosis. [h]Includes hemorrhage and hematoma. [i]Includes all infection events reported including COVID-19. [j]Includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis. [k]Includes thrombocytopenia and platelet count decreased.

NCTNCT04666038. Data cutoff: August 23, 2024.

Presentation by Lilly using data from Sharman et al. J Clin Oncol. 2025.
https://doi.org/10.1200/JCO-25-00166