BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib versus Idelalisib plus Rituximab (IdelaR) or Bendamustine plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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)[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**

Key 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

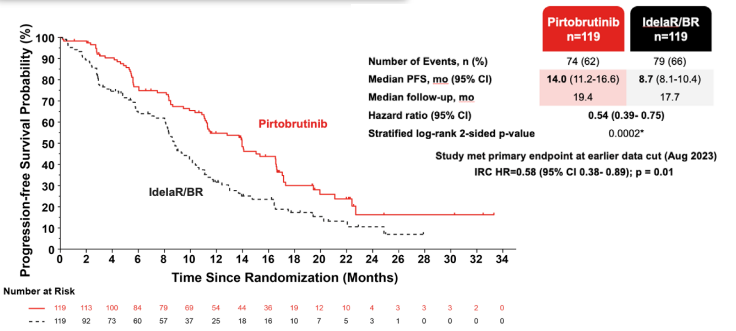
- 33% received ≥ 4 prior lines of therapy
- ~50% received prior BCL2i
- >50% del(17p) and/or *TP53* mutation and complex karyotype

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

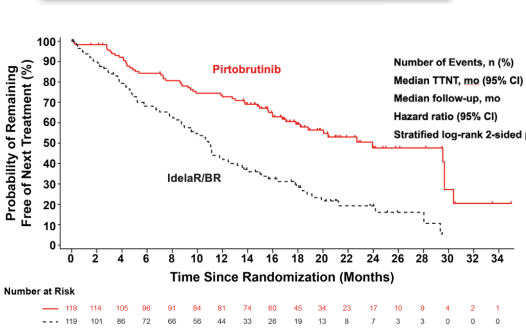


	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39- 0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

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

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

Time-To-Next-Treatment or Death



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	54 (45)	82 (69)
Median TTNT, mo (95% CI)	**23.9** (17.8-29.7)	**10.9** (8.7-12.5)
Median follow-up, mo	20.0	20.2
Hazard ratio (95% CI)	**0.37 (0.25-0.52)**	
Stratified log-rank 2-sided p-value	<0.0001*	

Pirtobrutinib reduced the risk of starting next treatment or death by 63% with a median TTNT of ~24 months

Consistent benefit of pirtobrutinib among subgroups (including presence of high-risk features, prior BCL2i, and IdelaR/BR)

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

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

Safety Analysis

Treatment-Emergent Adverse Event (≥20%)	Pirtobrutinib (n=116)		IdelaR or BR (N=109)	
	Any grade, n (%)	Grade 3+, n (%)	Any grade, n (%)	Grade 3+, n (%)
Subjects with ≥ 1 TEAE	108 (93.1)	67 (57.7)	107 (98.2)	80 (73.4)
Infections[e]	74 (63.8)	34 (29.3)	54 (49.5)	26 (23.9)
Pneumonia	26 (22.4)	20 (17.2)	13 (11.9)	12 (11.1)
COVID-19	15 (12.9)	2 (1.7)	20 (18.3)	5 (4.6)
Anemia	23 (19.8)	13 (11.2)	19 (17.4)	8 (7.3)
Neutropenia[f]	31 (26.7)	24 (20.7)	37 (33.9)	30 (27.5)
Cough	19 (16.4)	0	19 (17.4)	0
Diarrhea	19 (16.4)	0	34 (31.2)	6 (5.5)
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

- **Median time on treatment with pirtobrutinib, Idela, and BR was 15.1 months, 7.1 months and 4.7 months, respectively**
- **When adjusting for exposure, the incidence rate of TEAEs was lower with pirtobrutinib than with IdelaR/BR**
- **Overall pirtobrutinib treatment-emergent AESI rates were comparable to those seen in the Phase 1/2 BRUIN Study (any grade, grade 3+)**
  - **Infection (63.8%, 29.3%)**
  - **Bleeding (21.6%, 3.4%)**
  - **Hypertension (6.9%, 2.6%)**
  - **Atrial fibrillation & atrial flutter (2.6%, 1.7%)** (2 of 3 patients with any grade atrial fibrillation had a past medical history of atrial fibrillation)
  - **Neutropenia (26.7%, 20.7%)**
  - **Anemia (20.7%, 11.2%)**
  - **Thrombocytopenia (9.5%, 7.8%)**
- **Drug-related AEs led to discontinuation in 6 (5.2%) and 23 (21.1%) patients treated with pirtobrutinib and IdelaR/BR**

Summary

Pirtobrutinib demonstrated superior PFS in this cohort of heavily pretreated, R/R CLL/SLL patients previously treated with cBTKi. This benefit was seen in patients across all key risk-factors

Patients in the pirtobrutinib arm were able to delay next therapy or death for a median of approximately 2 years

Pirtobrutinib was well-tolerated, with low rates of treatment-related discontinuation

NCTNCT04666038. Data cutoff: August 23, 2024.
Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. [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. [e]Aggregate of all preferred terms indicating infection and including COVID-19. [f]Aggregate of neutropenia, neutrophil count decreased, febrile neutropenia and neutropenic sepsis. *Nominal p-value for August 2024 data cut

Reference: ASH 2024 Presentation, Abstract 886. Sharman JP, Munir T, Grosicki S, et al. BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib Versus Idelalisib Plus Rituximab (IdelaR) or Bendamustine Plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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