CLL-269

# Pirtobrutinib in Relapsed/Refractory CLL/SLL: Results From BTKi Naïve Cohort in the Phase 1/2 BRUIN Study

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## CONCLUSIONS

- Pirtobrutinib demonstrated promising efficacy in patients with BTKi naïve CLL/SLL
  - 24-month PFS rate of 74.7% (95%CI: 55.7-86.5) and 81.8% (95%CI: 63.9-91.4) as assessed by IRC and INV: respectively
  - ORR including PR-L of 91.4% (95%CI: 76.9-98.2) and 94.3% (80.8-99.3) as assessed by IRC and INV: respectively
  - 24-month overall survival rate of 88.0% (95%CI: 71.2-95.3)
- Pirtobrutinib also demonstrated promising efficacy in R/R BTKi naïve CLL/SLL patients with high-risk molecular features: although the number of patients was small
- Pirtobrutinib was well-tolerated in this cohort of BTKi naïve CLL/SLL patients with low rates of discontinuation due to drug-related toxicity
  - Safety findings were similar to the larger BRUIN CLL/SLL patient population
- Ongoing Phase 3 clinical trials are assessing the efficacy of pirtobrutinib monotherapy in treatment naïve patients with CLL/SLL (BRUIN CLL-313: NCT05023980): as well as patients with CLL/SLL who are treatment naïve or received a prior non-BTKi therapy (BRUIN CLL-314: NCT05254743)

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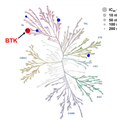
## BACKGROUND

### BTKi Have Transformed the Treatment Landscape of CLL/SLL

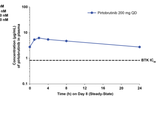
- Covalent BTKi (cBTKi) are effective therapeutic strategies for treatment with CLL/SLL: and are commonly being used to treat patients with CLL/SLL
- cBTKi have limitations in their long-term use for patients with CLL/SLL: as most patients discontinue cBTKi for either progression or intolerance[1-3]
- cBTKi share pharmacologic liabilities: including low oral bioavailability and a short half-life[4]
- These may lead to suboptimal BTK coverage
- This study aims to assess the efficacy and safety of pirtobrutinib in patients with relapsed/refractory (R/R): BTKi naïve CLL/SLL

### Pirtobrutinib is a Highly Selective: Non-Covalent (Reversible) BTK Inhibitor

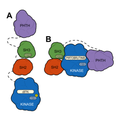
Highly selective for BTK[5,6]




Plasma exposures exceeded BTK $IC_{95}$ throughout dosing interval




Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]

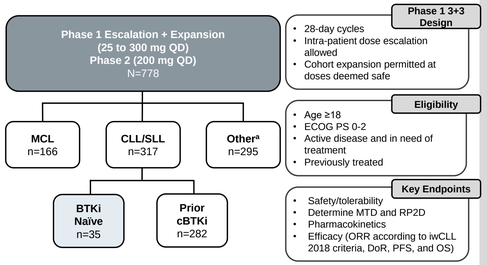



- Inhibits both WT and C481-mutant BTK with equal low nM potency[7]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[7]
- In contrast to cBTKi (A): pirtobrutinib (B) appears to stabilize BTK in a closed: inactive conformation: blocking access to upstream kinases and phosphorylation of Y551; thus, inhibiting scaffolding interactions that support kinase-independent BTK signaling[7]
- On December 1, 2023, the FDA granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy: including a BTK inhibitor and a BCL2 inhibitor[8:a]

[a]Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

## METHODS / STUDY DESIGN

### Phase 1/2 BRUIN Study: Design: Eligibility and Enrollment




A data cutoff of 05 May 2023 was used for all analyses. (NCT03740529)

[a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

## RESULTS

### Baseline and Disease Characteristics

| Characteristics | BTKi Naïve (n=35) |
|---|---|
| **Median age:** years (range) | 67 (38-81) |
| **Male:** n (%) | 18 (51) |
| **Rai Staging:** n (%) | |
| 0-II | 22 (63) |
| III-IV | 12 (34) |
| Missing | 1 (3) |
| **Bulky Lymphadenopathy ≥5 cm:** n (%) | 15 (43) |
| **ECOG PS:** n (%) | |
| 0 | 17 (49) |
| 1 | 16 (46) |
| 2 | 2 (6) |
| **Median number of prior lines of systemic therapy:** (range) | 2 (1-8) |
| **Prior therapy:** n (%) | |
| Chemotherapy | 35 (100) |
| Anti-CD20 antibody | 34 (97) |
| PI3K inhibitor | 8 (23) |
| BCL2 inhibitor | 3 (9) |
| Other Systemic Therapies | 2 (6) |
| **Median time from diagnosis to first dose:** months (IQR) | 112.5 (67-152) |
| **High Risk Molecular Features[a]:** n/n available (%) | |
| Complex Karyotype | 3/7 (43) |
| IGHV Unmutated | 20/25 (80) |
| *TP53* Mutated | 7/30 (23) |
| *del(17p)* | 7/26 (27) |
| *TP53* and/or *del(17p)* | 10/27 (37) |

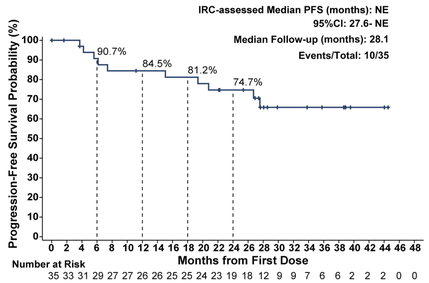
[a]Molecular characteristics were determined centrally and are presented based on data availability: in those patients with sufficient sample to pass assay quality control.

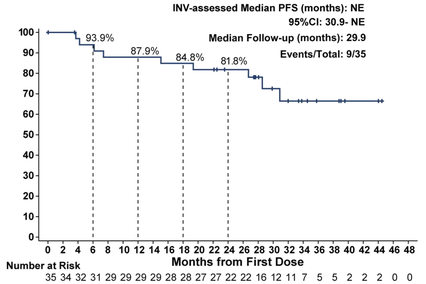
### Overall Response Rate

| | BTKi Naïve (n=35) | |
|---|---|---|
| | IRC-assessed | INV-assessed |
| **ORR[a]:** % (95%CI) | 91.4 (76.9-98.2) | 94.3 (80.8-99.3) |
| **Best Overall Response**: n (%) | | |
| CR | 1 (2.9) | 1 (2.9) |
| PR | 30 (85.7) | 27 (77.1) |
| nPR | - | 2 (5.7) |
| PR-L | 1 (2.9) | 3 (8.6) |
| SD | 2 (5.7) | 1 (2.9) |
| NE | 1 (2.9) | 1 (2.9) |
| **Subgroups** | Responders/Total With Characteristic | **ORR:** % (95%CI) |
| *TP53* mut. | 6/7 | 85.7 (42.1-99.6) |
| *del(17p)* | 7/7 | 100 (59.0-100.0) |
| Unmutated IGHV | 18/20 | 90.0 (68.3-98.8) |
| Complex Karyotype | 3/3 | 100 (29.2-100.0) |

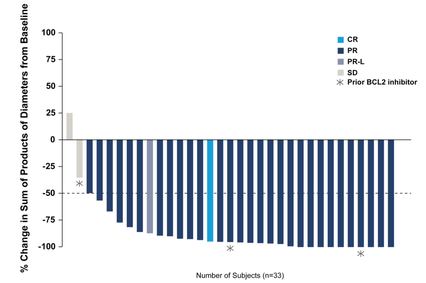
[a]ORR calculated by dividing the patients with a response of PR-L or better by total number of patients.

### PFS in Patients with R/R BTKi Naïve CLL/SLL Treated with Pirtobrutinib



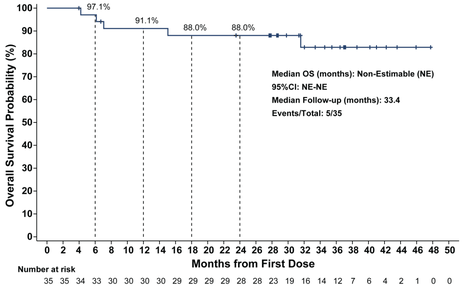




### Best Change in Tumor Burden in Patients with R/R BTKi Naïve CLL/SLL Treated with Pirtobrutinib




Two patients were non-evaluable due to lack of post-baseline assessment .

### OS in Patients with R/R BTKi Naïve CLL/SLL Treated with Pirtobrutinib




### Pirtobrutinib Safety Profile in Patients with R/R BTKi Naïve CLL/SLL

| Adverse Event | Treatment-Emergent AEs in Patients with BTKi Naïve CLL/SLL (n=35) | | | |
|---|---|---|---|---|
| | All Cause AEs: (≥20%): % | | Treatment-Related AEs: % | |
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| COVID-19 | 45.7 | 8.6 | 8.6 | 0.0 |
| Neutropenia[a] | 42.9 | 34.3 | 40.0 | 28.6 |
| Diarrhea | 31.4 | 5.7 | 20.0 | 2.9 |
| Anemia | 20.0 | 8.6 | 11.4 | 8.6 |
| Fatigue | 20.0 | 2.9 | 8.6 | 2.9 |
| Cough | 20.0 | 0.0 | 5.7 | 0.0 |
| Contusion | 20.0 | 0.0 | 14.3 | 0.0 |
| Pyrexia | 25.7 | 0.0 | 5.7 | 0.0 |
| **AEs of Interest[b]** | **Any Grade** | **Grade ≥3** | **Any Grade** | **Grade ≥3** |
| Infections[c] | 80.0 | 45.7 | 25.7 | 2.9 |
| Rash[e] | 31.4 | 0.0 | 17.1 | 0.0 |
| Hypertension | 28.6 | 8.6 | 5.7 | 0.0 |
| Hemorrhage[f] | 14.3 | 2.9 | 2.9 | 0.0 |
| Bruising[d] | 20.0 | 0.0 | 14.3 | 0.0 |
| Arthralgia | 14.3 | 0.0 | 5.7 | 0.0 |
| Atrial Fibrillation/ Flutter[g] | 5.7 | 2.9 | 2.9 | 0.0 |

**Median time on treatment was 28.8 months**

**TRAEs leading to pirtobrutinib dose reduction occurred in 4 (11.4%) patients**

**TRAEs leading to pirtobrutinib discontinuation in 2 (5.7%) patients**

**Safety profiles of BTKi naïve patients with CLL/SLL similar to overall BRUIN cohort**

Two grade 5 events: both COVID-19: occurred and were determined by investigator to be not related to treatment. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of all preferred terms indicating infection and including COVID-19. [d]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion. [e]Aggregate of all preferred terms including rash. [f]Aggregate of all preferred terms including hemorrhage or hematoma. [g]Aggregate of atrial fibrillation and atrial flutter.

**Abbreviations:**

**CLL:** chronic lymphocytic leukemia; **SLL:** small lymphocytic lymphoma; **cBTKi:** covalent Bruton tyrosine kinase inhibitor; **BTK:** Bruton tyrosine kinase; **WT:** wild-type; **FDA:** Food and Drug Administration; **BCL2:** B-cell leukemia/lymphoma 2; **QD:** once daily; **MCL:** Mantle Cell Lymphoma; **ECOG PS:** Eastern Cooperative Oncology Group performance status; **MTD:** maximum tolerated dose; **RP2D:** recommended phase 2 dose; **ORR:** overall response rate; **DOR:** duration of response; **PFS:** progression-free survival; **OS:** overall survival; DLBCL: diffuse large B-cell lymphoma; **WM:** Waldenström's macroglobulinemia; **FL:** follicular lymphoma; **MZL:** marginal zone lymphoma; **B-PLL:** B-Cell prolymphocytic leukemia; **CZOD:** cluster of differentiate 20; **PCNSL:** primary central nervous system lymphoma; **PI3K:** phosphoinositide 3-kinase; **IQR:** interquartile range; **IRC:** independent review committee; **INV:** investigator; **CR:** complete response; **PR:** partial response; **nPR:** nodular partial response; **PR-L:** partial response with lymphocytosis; **SD:** stable disease; NE: not evaluable; **AE:** adverse event; **TRAE:** treatment-related adverse event.

**Disclosures:**

**TB:** Loxo Lilly: Membership on an entity's Board of Directors or advisory committees; Speakers Bureau; KITE: Consultancy: Honoraria: Membership on an entity's Board of Directors or advisory committees; Speakers Bureau; Autolus: Consultancy; Janssen: Consultancy: Honoraria: Speakers Bureau; Gilead: Consultancy: Honoraria: Membership on an entity's Board of Directors or advisory committees; Speakers Bureau; Eli Lilly and Company: Consultancy: Honoraria: Speakers Bureau; PeerView: Speakers Bureau; Medscape: Speakers Bureau; Secura Bio: Consultancy: Honoraria: Membership on an entity's Board of Directors or advisory committees; Speakers Bureau; Beigene: Consultancy: Honoraria: Membership on an entity's Board of Directors or advisory committees; Speakers Bureau; AstraZeneca: Consultancy: Honoraria: Membership on an entity's Board of Directors or advisory committees; Research Funding; Speakers Bureau; Roche: Consultancy: Honoraria: Membership on an entity's Board of Directors or advisory committees; 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## REFERENCES

1. Woyach et al. J Clin Oncol. 2017; 35:1437–43.
2. Barr et al. Blood Adv. 2022; 6:3440-50.
3. Byrd et al. Blood 2022; 140 (Supplement 1): 9865–9867.
4. Patel et al. Clin Cancer Res. 2017; 23(14): 3734–3743.
5. Mato et al. Lancet 2021; 397: 892–901.
6. Brandhuber et al. Clin Lymphoma Myeloma Leuk 2018; 18(Suppl.1):S216.
7. Gomez et al. Blood.2023; 142(1):62-72.
8. Jaypirca [US Prescribing Information]. Indianapolis: IN: Eli Lilly and Company: 2023.

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