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BRUIN CLL-322: A Phase 3 Open-Label, Randomized Study of Fixed Duration Pirtobrutinib plus Venetoclax and Rituximab versus Venetoclax and Rituximab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Trial in Progress)

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Background

- Covalent (c) Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but these agents are not curative
- The MURANO study established 2-year fixed duration venetoclax plus rituximab as a standard of care regimen for patients with relapsed or refractory CLL/SLL;[1] however, its efficacy has not been formally assessed in CLL/SLL patients treated with a cBTKi, a common setting where this regimen is used in contemporary practice
- Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover
- In the phase 1/2 BRUIN study, pirtobrutinib had a durable overall response rate and progression-free survival and was well tolerated in patients with pre-treated CLL/SLL regardless of prior therapy (including cBTKi), number of prior therapies, BTK C481 mutation status, or reason for prior cBTKi discontinuation[2]
- In the phase 1b BRUIN study, pirtobrutinib combined with venetoclax +/- rituximab was well tolerated with a safety profile consistent with known drug class findings and no clear additive toxicities in patients with relapsed/refractory CLL[3]
- The study's objective is to assess the superiority of adding time-limited pirtobrutinib to the MURANO regimen, hypothesized to delay disease progression in a largely BTKi-pretreated population

Study Design

BRUIN CLL-322 is a Randomized, Open-label, Global, Phase 3 Study (NCT04965493)

Key Inclusion Criteria

- Confirmed CLL/SLL requiring treatment per iwCLL 2018[4]
- ≥1 prior line of therapy (cBTKi-naïve patients limited to 20% of total enrollment)
- Known 17p status
- ≥18 years old and ECOG 0-2

N=600

1:1 Randomization

Arm A

- **Pirtobrutinib**
  - 200 mg orally once daily from C1—C28
- **Venetoclax**
  - 20-400 mg 5-week dose ramp from C4
  - 400 mg orally once daily from C5—C28
- **Rituximab**
  - 375 mg/m^2 intravenously on C1
  - 500 mg/m^2 on D1 of C2—C6

Arm B

- **Venetoclax**
  - 20-400 mg 5-week dose ramp from C1
  - 400 mg orally once daily from C2—C25
- **Rituximab**
  - 375 mg/m^2 intravenously on C2
  - 500 mg/m^2 on D1 of C3—C7

Stratification factors

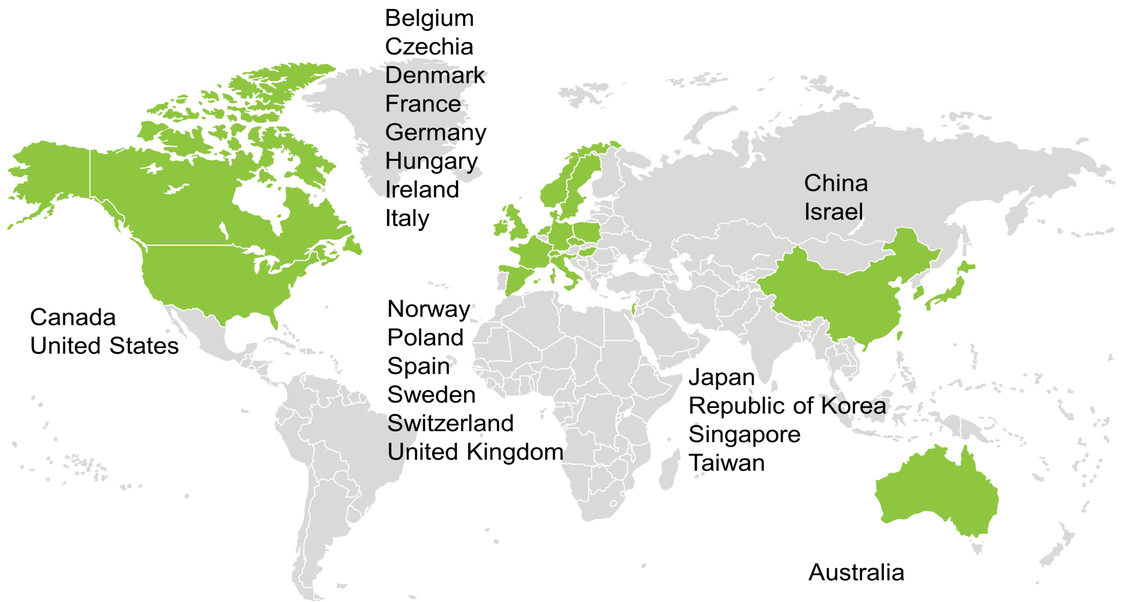
- 17p status (deleted/wildtype)
- Prior BTKi experience (discontinuation due to PD or other reasons versus no prior BTKi)

Each cycle is 28 days; C1 of Arm B is 35 days

Study Endpoints

- **Primary Endpoint**
  - Progression-free survival (PFS) per iwCLL 2018[4], as assessed by Independent Review Committee (IRC)
- **Secondary Endpoints**
  - PFS, as assessed by investigator
  - Overall response rate, as assessed by investigator and IRC
  - Overall survival and time to next treatment
  - Event-free survival, as assessed by investigator
  - Safety and tolerability
  - Patient-reported outcomes

Study Sites



Key Exclusion Criteria

- CNS involvement by CLL/SLL
- Richter transformation
- Prior BCL2 inhibitor or non-covalent BTK inhibitor
- Major bleeding event on prior cBTKi
- Recent history (within the last 60 days) of HCT or CAR T-cell therapy

Trial Progress Update

- Enrollment is ongoing for patients previously treated with cBTKi
- Enrollment is complete for cBTKi-naïve patients

Abbreviations: C, cycle; CAR, chimeric antigen receptor; CNS, central nervous system; D, day; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PD, progressive disease; PFS, progression-free survival; HCT, hematopoietic cell transplantation

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