Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in combination with venetoclax ± rituximab in relapsed/refractory chronic lymphocytic leukemia: Results from the BRUIN phase 1b study

Presented at: AACR Annual Meeting 2022
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**BACKGROUND**

- Pirtobrutinib (LOXO-305): a highly selective and potent non-covalent (reversible) Bruton tyrosine kinase (BTK) inhibitor
- Has high oral bioavailability and a long half-life, resulting in robust BTK target coverage regardless of high BTK protein turnover
- Is well-tolerated and exhibits promising efficacy in heavily pretreated relapsed/refractory (RR) chronic lymphocytic leukemia (CLL) patients, regardless of BTK C481S mutation status

**CT138**

- BRUIN (NCT03740529) is a multicenter, phase 1/2 dose escalation and expansion study evaluating pirtobrutinib in patients with previously treated, advanced B-cell malignancies

- Recent clinical studies reported on the safety and efficacy of time-limited venetoclax and constant BTK inhibitor combination regimens

- Due to its selectivity, pirtobrutinib may be an attractive partner for use in combination therapy strategies

- Here we evaluated the safety, efficacy, and pharmacokinetics of pirtobrutinib combined with venetoclax in patients with rr CLL

**Pirtobrutinib is a Highly Selective and Potent Non-Selective (Reversible) BTK Inhibitor**

- In vitro activity similarly efficacious as that of IR in C481S highly sensitive for BTK

**RESULTS**

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Combination Arm A</th>
<th>Combination Arm B</th>
<th>Total</th>
<th>Median age, years (range)</th>
<th>Female, n (%)</th>
<th>Male, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66 (59-77)</td>
<td>2 (13)</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>69 (62-79)</td>
<td>3 (20)</td>
<td>17 (70)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>60 (53-68)</td>
<td>1 (7)</td>
<td>13 (73)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td>7 (7-14)</td>
<td>8 (53)</td>
<td>16 (14)</td>
</tr>
<tr>
<td>High Risk Molecular Features, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (7)</td>
<td>2 (20)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>1q21 rearrangement</td>
<td></td>
<td></td>
<td></td>
<td>1 (7)</td>
<td>2 (20)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td></td>
<td></td>
<td></td>
<td>1 (7)</td>
<td>2 (20)</td>
<td>2 (20)</td>
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<tr>
<td>IGH translocation</td>
<td></td>
<td></td>
<td></td>
<td>1 (7)</td>
<td>2 (20)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>1q12 deletion</td>
<td></td>
<td></td>
<td></td>
<td>4 (20)</td>
<td>2 (20)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

**Response to Pirtobrutinib Combination Therapy per iwCLL**

**Safety of Pirtobrutinib Combination Therapy**

**Phase 1B BRUIN STUDY DESIGN**

- Phase 1A: Pirtobrutinib in combination with venetoclax in relapsed/refractory chronic lymphocytic leukemia (CLL)
- Phase 1B: Pirtobrutinib in combination with venetoclax in relapsed/refractory chronic lymphocytic leukemia (CLL)
- Phase 2: Pirtobrutinib in combination with venetoclax in relapsed/refractory chronic lymphocytic leukemia (CLL)

**ACKNOWLEDGEMENTS**

- BRUIN trial investigators and study staff
- Pharmacology and statistics was provided by Sonya C. Chapman, PhD, an employee of Eli Lilly and Company
- Medical writing assistance was provided by Hannah M. Messeranth, PhD, an employee of Eli Lilly and Company

**REFERENCES**


**CONCLUSIONS**

- Pirtobrutinib combined with venetoclax ± rituximab was well-tolerated with a safety profile consistent with known drug class findings and no new additive toxicities in patients with relapsed/refractory CLL
- Safety profiles were generally similar across both cohorts
- No DLTs were observed
- No prior discontinuation due to treatment-related AEs
- Early results demonstrate promising efficacy with combination therapy
- ORR was 95.5% (95% CI, 77-100)
- All responding patients except one remain on therapy
- There is no apparent drug-drug interaction between pirtobrutinib and venetoclax

**RESULTS**

**Venetoclax Pharmacokinetics**

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Median</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>4.0</td>
<td>5.0</td>
<td>4.0</td>
<td>2.0-7.0</td>
</tr>
<tr>
<td>20</td>
<td>4.0</td>
<td>5.0</td>
<td>4.0</td>
<td>2.0-7.0</td>
</tr>
<tr>
<td>30</td>
<td>4.0</td>
<td>5.0</td>
<td>4.0</td>
<td>2.0-7.0</td>
</tr>
</tbody>
</table>

**Patient Characteristics**

- Favorable pharmacologic properties allow sustained BTK inhibition
- >300-fold selectivity for BTK vs 370 other kinases

**Key Endpoints**

- Best response of CR and PR. Response status per iwCLL 2018 based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

**Compliance Arm B**

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