Efficacy and Safety of Zanubrutinib in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with del(17p): Follow-up Results from Arm C of the SEQUOIA (BGB-3111-304) Trial

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Abstract: 1306
Introduction

- Patients with CLL/SLL whose tumor exhibits the deletion of chromosome 17p13.1 [del(17p)] have an unfavorable prognosis and respond poorly to standard chemoimmunotherapy, even in the frontline setting\(^1,2\)

- BTK and Bcl-2 inhibitors have been shown to improve outcomes for patients with del(17p)\(^3,4\)

- Zanubrutinib (BGB-3111) is a second generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases\(^5,6\)

  - In the ASPEN study of patients with Waldenström macroglobulinemia, zanubrutinib was associated with important safety advantages compared with ibrutinib, including reduced rates of atrial fibrillation (2% vs 15%)\(^7\)

- Initial results from Arm C of the SEQUOIA (BGB-3111-304) trial of zanubrutinib in a large cohort of TN CLL/SLL patients with del(17p) were previously presented with a median follow-up of 10 months\(^8\); updated results with a median follow-up of 22 months are presented here

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BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; EGFR, epidermal growth factor receptor; TN, treatment-naïve.

SEQUOIA (BGB-3111-304)
Study Design

Key Eligibility Criteria

- TN CLL/SLL
- Met iwCLL criteria for treatment
- ≥ 65 y of age OR unsuitable for treatment with FCR
- Anticoagulation and CYP3A inhibitors allowed

ClinicalTrials.gov: NCT03336333

Endpoints for Arm C: ORR (IRC and investigator assessments), PFS, DOR, safety

Response assessment: per modified iwCLL criteria for CLL\(^2,3\) and Lugano criteria for SLL\(^4\) (IRC and investigator assessments)

bid, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DOR, duration of response; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in situ hybridization; IRC, independent review committee; iwCLL, international workshop on CLL; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; R, randomized; TN, treatment-naïve.

\(^a\) TP53 mutational status was not centrally assessed prior to enrollment.

Del(17p) enrolled/safety population
n = 109

Not evaluable for efficacy
n = 0

Off study treatment
n = 14 (5 AE, 8 PD, 1 WD)

On study treatment
n = 95

Median follow-up (range): 21.9 months (5.0 - 30.2)
Adverse Events of Interest

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1 %</th>
<th>Grade 2 %</th>
<th>Grade ≥ 3 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor bleeding(^b)</td>
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<td></td>
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<tr>
<td>Bruising(^c)</td>
<td></td>
<td></td>
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<tr>
<td>Neutropenia(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologic malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
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<td></td>
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<tr>
<td>Hypertension(^e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia(^g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation and flutter</td>
<td>Grade ≥3: 1.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Events, n (%)

- Treatment discontinuation due to AE\(^h\) 5 (4.6)
- Grade 5 AE\(^i\) 2 (1.8)


\(^a\) All infection terms pooled. \(^b\) Pooled term of bleeding not included in bruising, petechiae, or major bleeding. \(^c\) Purpura, contusion, ecchymosis or increased tendency to bruise. \(^d\) Neutropenia, neutrophil count decreased, or febrile neutropenia. \(^e\) Hypertension, blood pressure increased, or hypertensive crisis. \(^f\) Grade ≥ 3 hemorrhage, serious hemorrhage, or central nervous system hemorrhage of any grade were pooled. \(^g\) Thrombocytopenia or platelet count decreased. \(^h\) Pneumonia leading to sepsis and death (related), pseudomonal sepsis (related), melanoma (unrelated), renal failure in the context of disease progression (unrelated), and unknown at the data cutoff. \(^i\) Pneumonia leading to sepsis and death (related), and renal failure in the context of disease progression (unrelated), both of which also led to treatment discontinuation.
Best Overall Response
Investigator Assessment

- Duration of Response
  - DOR ≥12 mo [95% CI]<sup>a</sup>: 93.1% [86 - 97]
  - DOR ≥18 mo [95% CI]<sup>a</sup>: 87.7% [78 - 93]

- Compared to 2019 ASH presentation<sup>b</sup>
  - CR/CRi rate increased from 1.9% to 6.4%
  - PR-L rate decreased from 11.9% to 0.9%

- Features of patients achieving CR/CRi
  - 5 mutated IGHV, 2 unmutated IGHV
  - 4 noncomplex, 1 complex, and 2 unknown karyotype

- 5 additional patients had clinical CR but did not perform bone marrow assessment (some due to COVID precautions)

Data cutoff: August 10, 2020
CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; DOR, duration of response; IGHV, gene encoding for immunoglobulin heavy chain variable region; mo, months; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease.

<sup>a</sup> 2-sided Clopper-Pearson 95% confidence intervals.<sup>b</sup> Data cutoff for 2019 ASH presentation: August 7, 2019; Tam CS, et al. Blood. 2019;134(Supplement_1):499.
Progression-Free Survival and Overall Survival
Investigator Assessment

- 12 patients had investigator-reported PD
  - 5 patients had investigator-assessed RT
  - Median time to transformation was 13.6 mo (range, 3.9 - 15.7)
- 1 patient had PD after discontinuing study drug treatment due to AE

Data cutoff: August 10, 2020. Median follow-up (range): 21.9 months (5.0 – 30.2)
AE, adverse events; CI, confidence interval; mo, month(s); OS, overall survival; PD, progressive disease; PFS, progression-free survival; RT, Richter transformation.

* 2-sided Clopper-Pearson 95% confidence intervals.
Progression-Free Survival by IGHV and Karyotype Status

Investigator Assessment

Data cutoff: August 10, 2020. Median follow-up (range): 21.9 months (5.0 – 30.2)
CI, confidence interval; IGHV, gene encoding for immunoglobulin heavy chain variable region; mo, month; PFS, progression-free survival.

* 2-sided Clopper-Pearson 95% confidence intervals.  
  5 patients had RNA quantity/quality not sufficient for PCR amplification of heavy-chain variable (VH) region for sequencing.  
  23 patients had insufficient metaphases available for analysis.

IGHV mutational status^b, n (%)

<table>
<thead>
<tr>
<th>Mutated</th>
<th>Unmutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 /104 (33.7)</td>
<td>69 /104 (66.3)</td>
</tr>
</tbody>
</table>

Karyotype status^c, n (%)

<table>
<thead>
<tr>
<th>Non-Complex (0 to 2 abnormalities)</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or more abnormalities</td>
<td>5 or more abnormalities</td>
</tr>
<tr>
<td>32 / 86 (37.2)</td>
<td>23 / 86 (26.7)</td>
</tr>
</tbody>
</table>
Progression-Free Survival by IGHV and Karyotype Status
Investigator Assessment

Data cutoff: August 10, 2020. Median follow-up (range): 21.9 months (5.0–30.2) mo, month; PFS, progression-free survival.

CI, confidence interval; IGHV, gene encoding for immunoglobulin heavy chain variable region; mo, month; PFS, progression-free survival.

*2-sided Clopper-Pearson 95% confidence intervals. b 5 patients had RNA quantity/quality not sufficient for PCR amplification of heavy-chain variable (VH) region for sequencing. c 23 patients had insufficient metaphases available for analysis.

With limited follow-up, PFS appears similar at this time between patients with unmutated versus mutated IGHV as well as between patients with complex versus non-complex karyotype.
Summary

- With a median follow-up of 21.9 mo, zanubrutinib monotherapy demonstrated an ORR of 94.5%, 18-mo PFS of 90.6%, and 18-mo OS of 95.4% in a cohort of 109 TN CLL/SLL patients with del(17p)
  - PFS appears to be preserved in patients with unmutated IGHV and complex karyotype
- Zanubrutinib tolerability was generally consistent with previous reports of zanubrutinib treatment in patients with various B-cell malignancies¹,²,³,⁴
- Additional data from this cohort are now published online⁵


CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IGHV, gene encoding for immunoglobulin heavy chain variable region; mo, month(s); ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TN, treatment-naïve.
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Disclosures

- **JRB**: Consulting role with AbbVie, AstraZeneca, BeiGene, Catapult, Dynamo Therapeutics, Eli Lilly and Company, Juno/Celgene, Kite, MEI Pharma, Nextcea, Novartis, Octapharma, Pfizer, Rigel Pharmaceuticals, Sunesis, TG Therapeutics, Verastem; advisory role for Invectys (data safety monitoring committee); research funding from Acerta, Pfizer, Janssen, Morphosys, AbbVie, BeiGene, UCB, Roche, UTX-TGR, AstraZeneca, GSK, BMS; travel expenses from Roche, Janssen, and AbbVie

- **TR**: Honoraria from Janssen, AbbVie, Sandoz, Novartis, Octapharma; Consulting role with Janssen, Takeda, AbbVie, Momenta; research funding from Acerta, Pfizer, Janssen, Morphosys, AbbVie, BeiGene, UCB, Roche, UTX-TGR, AstraZeneca, GSK, BMS; travel expenses from Roche, Janssen, and AbbVie

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- **BSK**: Consulting role with BeiGene, AbbVie, Pharmacyclics, Janssen, Acerta, AstraZeneca; advisory role for BeiGene, Janssen, AstraZeneca; research funding from BeiGene, and Acerta

- **PW**: Employment with Alfred Health and Peninsula Health; travel expenses from Roche

- **WJ**: Consulting with AstraZeneca; advisory role for Celgene, Amgen, and Janssen

- **HChang**: Advisory role for Janssen and AbbVie; research funding and speakers' bureau with Janssen

- **MShadman**: Consulting and advisory role with AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, Verastem, ADC Therapeutics, BeiGene, Cellectar, BMS, Mophosys and Atara Biotherapeutics; research funding from Mustang Bio, Celgene, Pharmacyclics, Gilead, Genentech, AbbVie, TG therapeutics, BeiGene, AstraZeneca, and Sunesis

- **PSG**: Has nothing to disclose

- **LL**: Has nothing to disclose

- **SO**: Honoraria from Roche, AbbVie, Janssen, Merck, AstraZeneca; consulting role with AbbVie, Roche, BeiGene, Janssen, Gilead, Merck; advisory role with AbbVie, Merck, Janssen, AstraZeneca, BeiGene, Roche, CSL, Gilead; research funding from AbbVie, Merck, Janssen, Astra Zeneca, BeiGene, Roche, Epizyme, and Gilead

- **MT**: Has nothing to disclose

- **HC**: Employment with Copernicus Wojewódzkie centrum Onkologii

- **EV**: Employment with Concord Repatriation General Hospital; research funding from Janssen-Cilag Pty Ltd

- **Mš**: Honoraria from Janssen-Cilag, AbbVie; consulting role with Janssen-Cilag, AbbVie, Gilead, Acerta Pharma; advisory role with AbbVie; speakers' bureau with Janssen-Cilag, AbbVie; travel expenses from Janssen-Cilag, AbbVie, and Gilead

- **AO**: Employment with Karolinska University Hospital; research funding from BeiGene

- **MT**: Has nothing to disclose

- **AT**: Employment with Department of Hematology Niguarda Hospital Milano; speakers' bureau for Janssen spa; advisory role for Janssen spa, Astra Zeneca, BeiGene, and AbbVie

- **PB**: Has nothing to disclose

- **JP, SF, VR AND JH**: employment and equity ownership with BeiGene

- **FY**: employment with BeiGene; equity ownership with BeiGene and Arcus Biosciences; patents/royalties with Cornell University

- **PH**: Honoraria with Janssen, AbbVie, AstraZeneca, Roche; advisory role for Janssen, AbbVie; research funding from Janssen, Pharmacyclics, AbbVie, Gilead, Roche; travel expenses from Janssen and AbbVie

- **CT**: Honoraria with Janssen, AbbVie, BeiGene; research funding from Janssen and AbbVie
Supplemental Data
# SEQUOIA Arm C

## Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>70.0 (42-86)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>78 (71.6)</td>
</tr>
<tr>
<td>ECOG PS of 2, n (%)</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Months since diagnosis, median (Q1-Q3)</td>
<td>21.62 (7.69–54.77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLL, n (%)</td>
<td>10 (9.2)</td>
</tr>
<tr>
<td>Binet stage C for patients with CLL, n (%)</td>
<td>40 / 99 (40.4)</td>
</tr>
<tr>
<td>Absolute lymphocyte count (x10⁹/L), median</td>
<td>65.1</td>
</tr>
<tr>
<td>Hemoglobin (g/L), median</td>
<td>120.0</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L), median</td>
<td>154.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(13q), n (%)</td>
<td>72 (66.1)</td>
</tr>
<tr>
<td>del(11q), n (%)</td>
<td>37 (33.9)</td>
</tr>
<tr>
<td>Trisomy 12, n (%)</td>
<td>20 (18.3)</td>
</tr>
<tr>
<td>IGHV mutational status(^a), n (%)</td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>35 / 104 (33.7)</td>
</tr>
<tr>
<td>Unmutated</td>
<td>69 / 104 (66.3)</td>
</tr>
<tr>
<td>Bulky disease(^b), n (%)</td>
<td></td>
</tr>
<tr>
<td>Any target lesion LDi ≥ 5 cm</td>
<td>42 (38.5)</td>
</tr>
<tr>
<td>Any target lesion LDi ≥ 10 cm</td>
<td>11 (10.1)</td>
</tr>
<tr>
<td>Karyotype status(^c), n (%)</td>
<td></td>
</tr>
<tr>
<td>Non-Complex (0 to 2 abnormalities)</td>
<td>54 / 86 (62.8)</td>
</tr>
<tr>
<td>Complex</td>
<td></td>
</tr>
<tr>
<td>3 or more abnormalities</td>
<td>32 / 86 (37.2)</td>
</tr>
<tr>
<td>5 or more abnormalities</td>
<td>23 / 86 (26.7)</td>
</tr>
</tbody>
</table>

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CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, gene encoding for immunoglobulin heavy chain variable region; LDi, longest diameter; SLL, small lymphocytic lymphoma.

\(^a\) 5 patients had RNA quantity/quality not sufficient for PCR amplification of heavy-chain variable (VH) region for sequencing.

\(^b\) Patients with any target lesion with longest diameter presented.

\(^c\) 23 patients had insufficient metaphases available for analysis.
Common AEs Regardless of Causality
Any Grade ≥ 10% or Grade 3 or Higher ≥ 2%

Contusion
Upper respiratory tract infection
Diarrhea
Nausea
Back pain
Constipation
Rash
Cough
Neutropenia
Arthralgia
Pneumonia
Fall
Hypertension
Neutrophil count decreased

- Contusion
- Upper respiratory tract infection
- Diarrhea
- Nausea
- Back pain
- Constipation
- Rash
- Cough
- Neutropenia
- Arthralgia
- Pneumonia
- Fall
- Hypertension
- Neutrophil count decreased

AE, adverse event.
## Summary of Grade ≥ 3 and Serious AEs

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Grade ≥ 3 AE</td>
<td>57 (52.3)</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs that occurred in &gt; 2 patients</td>
<td></td>
</tr>
<tr>
<td>Neutropenia/decreased neutrophil count</td>
<td>17 (15.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Fall</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>42 (38.5)</td>
</tr>
<tr>
<td>Treatment discontinuation due to AE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Grade 5 AE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

AE, adverse event.

<sup>a</sup>Pneumonia leading to sepsis and death, pseudomonal sepsis, melanoma, renal failure in the context of disease progression, and unknown at the data cutoff.

<sup>b</sup>Pneumonia leading to sepsis and death, and renal failure in the context of disease progression, both of which also led to treatment discontinuation.