Zanubrutinib in Combination with Venetoclax for Patients with Treatment-Naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma and del(17p): Arm D of the SEQUOIA (BGB-3111-304) Trial

Constantine S. Tam, MBBS, MD1,2,3,4; Ian W. Flinn, MD, PhD5; Alessandra Tedeschi, MD6; Emmanuelle Ferrant, MD, PhD7; Jennifer R. Brown, MD, PhD8; Tadeusz Robak, MD, PhD9; Paolo Ghia, MD, PhD10; Sowmya B. Kuwahara, PharmD11; Jason C. Paik, MD, PhD11; Lei Hua, PhD11; Aileen Cohen, MD, PhD11; Jane Huang, MD11; and Peter Hillmen, MBChB, PhD, FRCP, FRCPath

1Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; 2University of Melbourne, Parkville, Victoria, Australia; 3St Vincent’s Hospital, Fitzroy, Victoria, Australia; 4Royal Melbourne Hospital, Parkville, Victoria, Australia; 5Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; 6ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; 7Centre Hospitalier Lyon-Sud, University Claude Bernard Lyon 1, Pierre-Bénite, France; 8Dana-Farber Cancer Institute, Boston, MA, USA; 9Medical University of Lodz, Lodz, Poland; 10Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; 11BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; 12Saint James’s University Hospital, Leeds, UK

Presented at the 62nd American Society of Hematology (ASH) Annual Meeting, December 5-8, 2020
Abstract: 1318
Introduction

- Targeted therapies have demonstrated improved outcomes for patients with del(17p) CLL/SLL\(^1,2\)

- Zanubrutinib (BGB-3111) is a highly selective next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target effects\(^3,4\)
  - Arm C of the SEQUOIA trial suggested that zanubrutinib monotherapy was active (ORR of 94.5%) and well-tolerated in treatment-naïve patients with del(17p) CLL/SLL\(^5\)

- In the ASPEN study of patients with Waldenström macroglobulinemia, zanubrutinib was associated with important safety advantages compared to ibrutinib, including atrial fibrillation (zanubrutinib 2% vs. ibrutinib 15%) and hypertension (zanubrutinib 6% vs. ibrutinib 11%)\(^6\)

AE, adverse event; BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; deletion 17p13.1, del(17p); ORR, overall response rate.

Rationale for Combining Zanubrutinib and Venetoclax

- Data from phase 2 studies combining BCL-2 and BTK inhibitors in patients with CLL suggest these regimens are tolerable with synergistic activity\(^1\)-\(^3\)

- Novel regimens that result in uMRD status have the potential to alter the CLL/SLL treatment landscape and may enable fixed duration therapy

- In the BOVen study, 62% of treatment-naïve patients with CLL administered zanubrutinib + venetoclax + obinutuzumab met the uMRD endpoint and discontinued treatment per protocol\(^4\)

  - 100% of patients had a best response of PR or higher, including 43% of patients with a best response of CR/CRi

---

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete blood count recovery; PR, partial response; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease.

SEQUOIA (BGB-3111-304)
Overall Study Design

Cohort 1
- without del(17p)
- n ~ 450

Arm A: zanubrutinib
Arm B: bendamustine + rituximab

Cohort 2
- with del(17p)
- n ~ 100

Arm C: zanubrutinib

Cohort 3
- with del(17p)
- n ~ 50

Arm D: zanubrutinib + venetoclax

Primary Endpoint (Cohort 1): PFS determined by IRC
Response Assessment: per modified iwCLL criteria for CLL\textsuperscript{1,2} and Lugano criteria for SLL\textsuperscript{3} (IRC and investigator assessments)

Recruiting

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IRC, independent review committee; iwCLL, international workshop on CLL; PFS: progression-free survival; R, randomized.

## Arm D Key Eligibility Criteria

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL or SLL by iwCLL criteria requiring treatment</td>
<td>Previous systemic treatment for CLL/SLL</td>
</tr>
<tr>
<td>Central assessment of del(17p) by FISH with &gt; 7% aberrant nuclei present</td>
<td>Prolymphocytic leukemia or Richter’s transformation</td>
</tr>
<tr>
<td>Measurable disease by CT/MRI</td>
<td>Clinically significant cardiovascular disease</td>
</tr>
<tr>
<td>ECOG PS ≤ 2</td>
<td>CNS involvement by leukemia or lymphoma</td>
</tr>
<tr>
<td>Adequate marrow and organ function</td>
<td>Active fungal, bacterial, or viral infection requiring systemic therapy</td>
</tr>
</tbody>
</table>

**Permitted medications**: anticoagulation and CYP3A inhibitors

**Prohibited medications**: warfarin and warfarin derivatives (venetoclax contraindication)
SEQUOIA (BGB-3111-304)
Arm D Secondary & Exploratory End Points

• Secondary End Points:
  – Overall response rate, determined by investigator review
  – Progression-free survival, determined by investigator review
  – Duration of response, determined by investigator review
  – Rate of undetectable MRD at <10^{-4} sensitivity at various timepoints
  – Safety summary
  – Pharmacokinetics of zanubrutinib

• Exploratory End Points:
  – Overall survival
  – Patient-reported outcomes
  – Pharmacokinetics of venetoclax
  – Time to recurrence of detectable MRD after discontinuation of zanubrutinib and/or venetoclax

MRD, minimal residual disease.
SEQUOIA (BGB-3111-304)
Arm D Treatment Regimen and Response Assessment Schedule

Venetoclax ramp-up cycle, then 400 mg once daily for 12-24 cycles

Zanubrutinib 160 mg twice daily for ≥27 cycles

Baseline & end of C3: TLS risk assessment

Discontinue venetoclax for confirmed uMRD (PB and BM)

Discontinue zanubrutinib for confirmed uMRD

Hematology / physical exam / imaging

MRD: peripheral blood

Bone marrow biopsy & aspirate for CR\(^a\)

MRD: bone marrow aspirate\(^b\)

BM, bone marrow; PB, peripheral blood; C, cycle; CR, complete response; CRi, CR with incomplete blood count recovery; PD, progressive disease; TLS, tumor lysis syndrome; uMRD, undetectable minimal residual disease (at <10\(^{-4}\) sensitivity by flow cytometry).

\(^a\)Bone marrow biopsy and aspirate are required to confirm a suspected CR/CRi, starting after cycle 9 and then annually if needed.

\(^b\)Patients with confirmed CR/CRi and two negative peripheral blood MRD tests must have two consecutive bone marrow aspirate MRD tests that meet uMRD requirements for dose stopping.
SEQUOIA (BGB-3111-304)  
Arm D Study Status and Enrollment

- Arm D enrollment began in November 2019; planned enrollment ~ 50 patients
- Recruitment is ongoing from sites in 8 countries:
  - US, UK, France, Sweden, Poland, Italy, Australia, New Zealand