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, MD[1,2,3,4]; Ian W. Flinn, MD, PhD[5]; Alessandra Tedeschi, MD[6]; Emmanuelle Ferrant, MD, PhD[7]; Jennifer R. Brown, MD, PhD[8]; Tadeusz Robak, MD, PhD[9]; Paolo Ghia, MD, PhD[10]; Sowmya B. Kuwahara, PharmD[11]; Jason C. Paik, MD, PhD[11]; Lei Hua, PhD[11]; Aileen Cohen, MD, PhD[11]; Jane Huang, MD[11]; and Peter Hillmen, MBChB, PhD, FRCP, FRCPath[12]

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

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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.

1. O'Brien S, et al. *Lancet Oncol*. 2016;17:1409-1418. 2. Stilgenbauer S, et al. *J Clin Onc.* 2018;36(19):1973-1980. 3. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 4. Tam CS, et al. *Blood*. 2019;134:851-859. 5. Tam C, et al. *Haematologica*. 2020 epub ahead of print. 6. Tam CS, et al. *Blood*. 2020;136:2038-2050.

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

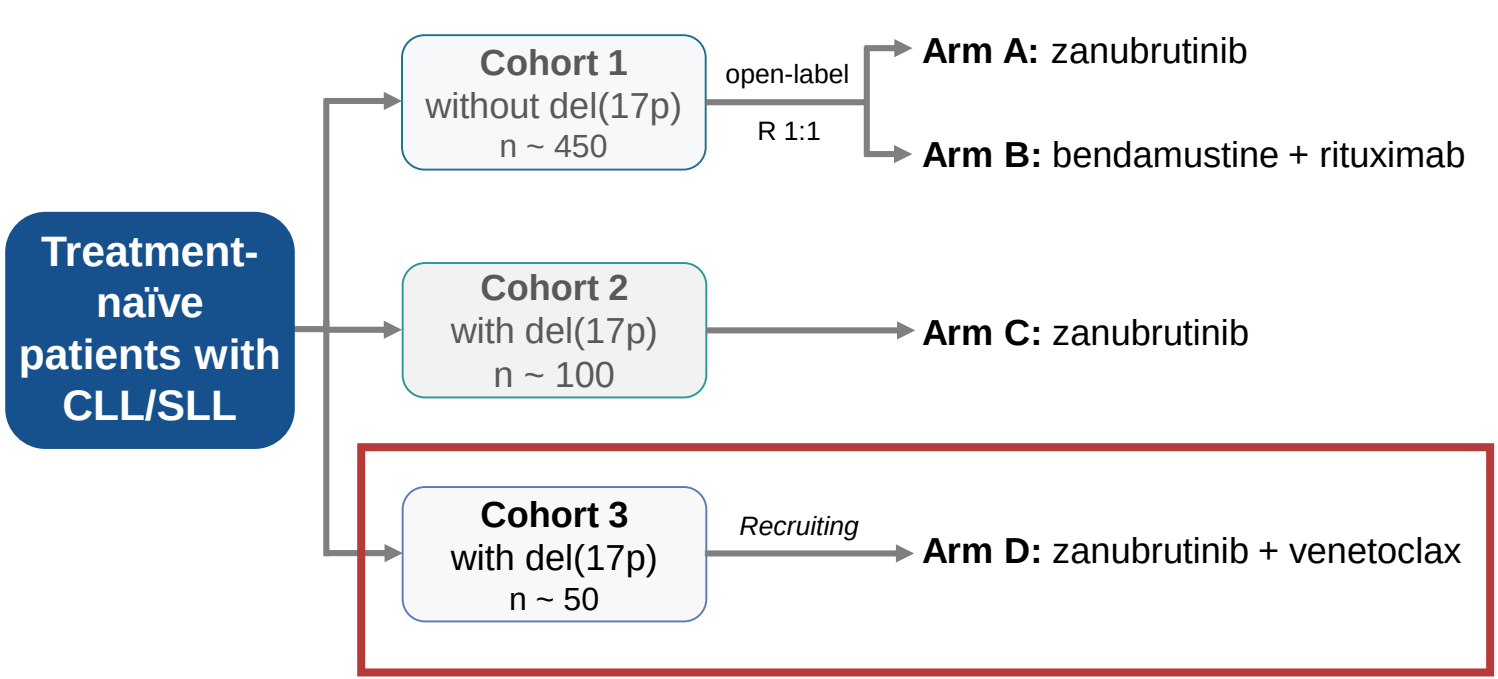
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete blood count recovery; PR, partial response; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease.

1. Hillmen P, et al. *J Clin Oncol*. 2019;37:272-2729. 2. Jain N, et al. *N Engl J Med*. 2019;380:2095-2103. 3. Siddiqi T, et al. EHA 2020. abstract #S158.

4. Soumerai JD, et al. ASCO 2020. abstract #8006.

SEQUOIA (BGB-3111-304)
Overall Study Design

NCT03336333



Primary Endpoint (Cohort 1):
PFS determined by IRC

Response Assessment:
per modified iwCLL criteria for CLL[1,2] and Lugano criteria for SLL[3] (IRC and investigator assessments)

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

1. Hallek M, et al. *Blood*. 2008;111:5446-5456. 2. Cheson BD, et al. *J Clin Oncol.* 2012;30:2820-2822. 3. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3067.

SEQUOIA (BGB-3111-304)
Arm D Key Eligibility Criteria

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

Permitted medications: anticoagulation and CYP3A inhibitors
Prohibited medications: warfarin and warfarin derivatives (venetoclax contraindication)

CLL, chronic lymphocytic leukemia; CNS, central nervous system; CT/MRI, computed tomography/magnetic resonance imaging; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; iwCLL, international workshop on CLL; SLL, small lymphocytic lymphoma; TN, treatment naive.

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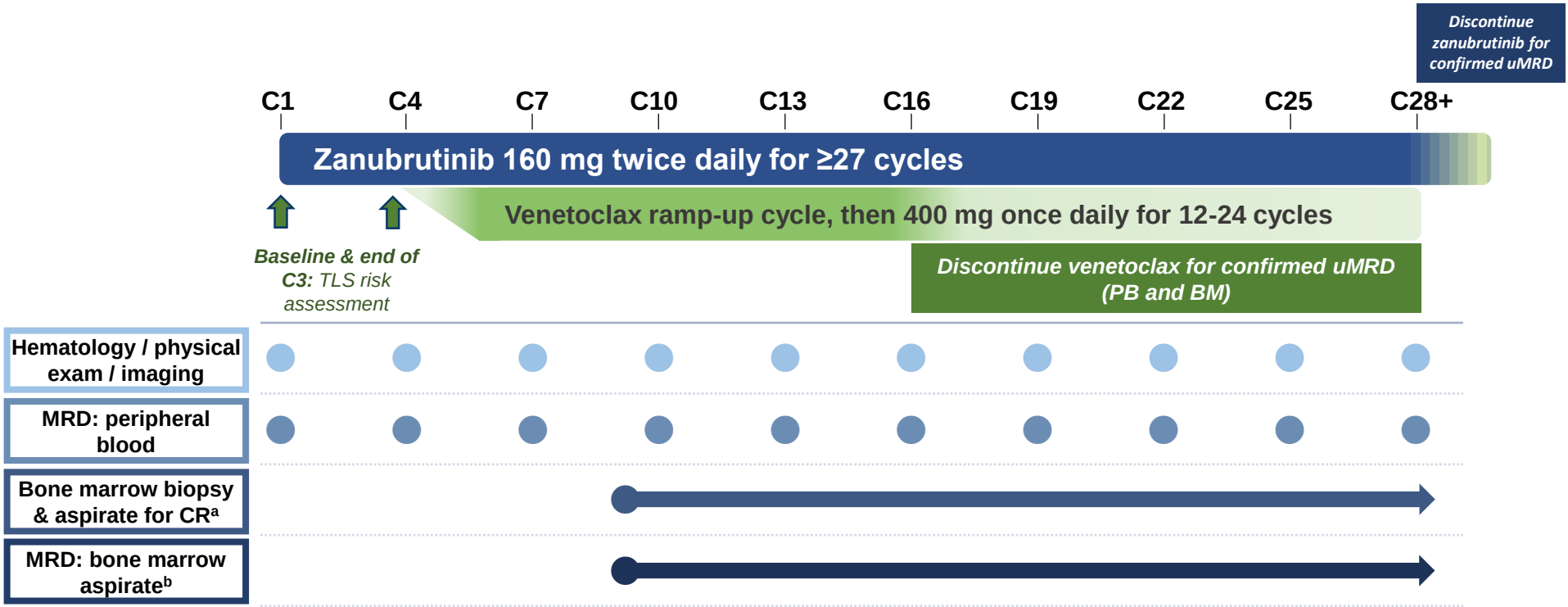
Arm D Secondary & Exploratory End Points

- **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



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