Zanubrutinib + Venetoclax for Treatment-Naive CLL/SLL With del(17p) and/or *TP53*: Preliminary Results From SEQUOIA Arm D

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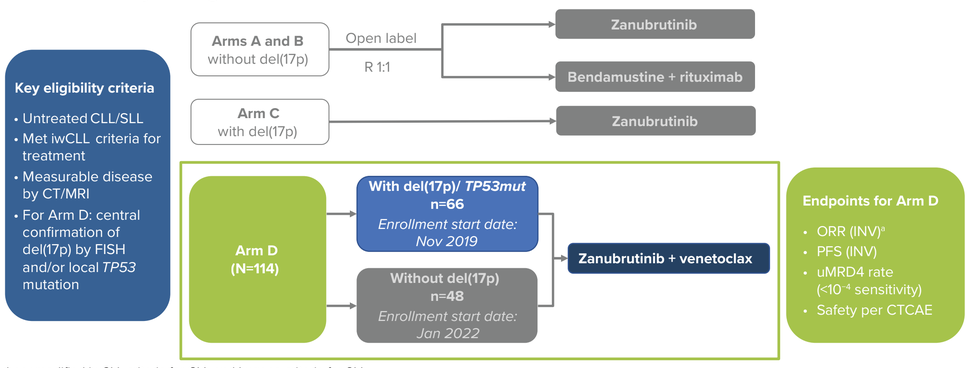
INTRODUCTION

- Zanubrutinib is a highly potent and selective next-generation Bruton tyrosine kinase (BTK) inhibitor approved in treatment-naive and relapsed/refractory chronic lymphocytic leukemia (CLL) as monotherapy[1,2] that was designed to provide complete and sustained BTK occupancy, with fewer off-target adverse events and improved efficacy compared with other BTK inhibitors[3,4]
- In Arm C of the phase 3 SEQUOIA trial, zanubrutinib monotherapy was well tolerated and achieved a high overall response rate (ORR; 95%) and an estimated 18-month progression-free survival (PFS) rate of 89%, in patients who had untreated CLL/small lymphocytic lymphoma (SLL) with deletion in chromosome 17p [del(17p)][5], which were consistent with outcomes in patients without del(17p)[6]
- Monotherapy with venetoclax, the first-generation B-cell lymphoma-2 (BCL2) inhibitor, has also been shown to be well tolerated with durable responses achieved in patients with del(17p) and/or *TP53* mutation,[7] but data on venetoclax + ibrutinib combination therapy in this high-risk population have been limited
- Combination therapy with a BCL2 inhibitor in patients with high-risk CLL may provide deep responses and improve outcomes in patients treated with zanubrutinib
- Preliminary results in patients with del(17p) and/or *TP53* mutation who received zanubrutinib + venetoclax combination treatment in Arm D of the SEQUOIA trial are presented

METHODS

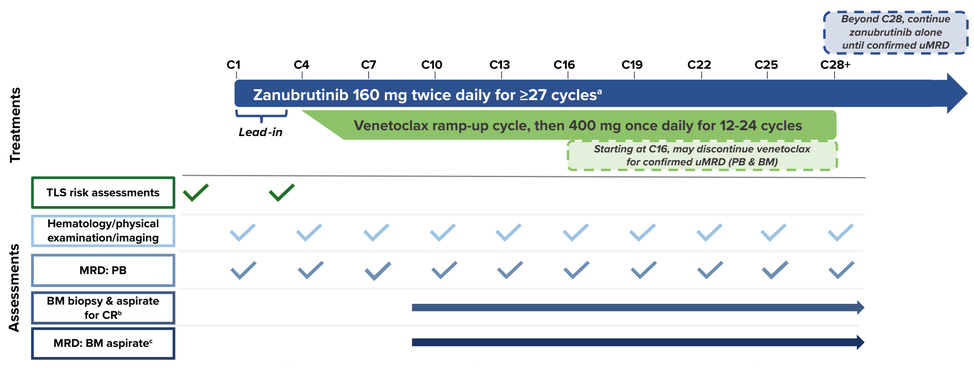
- The SEQUOIA study design, including Arm D is summarized in **Figure 1**
- For Arm D, the treatment schedule was as follows: zanubrutinib monotherapy lead-in (3 cycles) followed by zanubrutinib + venetoclax (12-24 cycles, dependent on rules for stopping venetoclax early guided by undetectable minimal residual disease [uMRD]), then zanubrutinib monotherapy until disease progression or unacceptable toxicity, or until rules for stopping zanubrutinib early based on uMRD were met (**Figure 2**)

Figure 1. SEQUOIA Study Design



[a] Reponses assessed per modified iwCLL criteria for CLL and Lugano criteria for SLL.
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; del(17p), deletion in chromosome 17p; FISH, fluorescence in situ hybridization; INV, investigator; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; mut, mutation; ORR, overall response rate; PFS, progression-free survival; R, randomized; uMRD4, undetectable minimal residual disease <1×10⁻⁴.

Figure 2. SEQUOIA Arm D: Treatment Regimen and Assessment Schedule



[a] Early zanubrutinib or venetoclax stopping rules were guided by uMRD (assessed by flow cytometry). Zanubrutinib or venetoclax can be stopped early if all of the following conditions are met: response assessed as CR/CRi confirmed by a bone marrow biopsy, uMRD4 achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart, uMRD4 achieved in 2 consecutive bone marrow aspirate MRD tests conducted ≥12 weeks apart, patients received ≥12 cycles of venetoclax (to stop venetoclax early), and patients received ≥27 cycles of zanubrutinib (to stop zanubrutinib early). [b] BM biopsy and aspirate are required to confirm a suspected CR/CRi (bone marrow collection timepoint not defined per protocol), starting after cycle 9 and then annually if needed. [c] Patients with confirmed CR/CRi and 2 consecutive peripheral blood uMRD ≥12 weeks apart.
BM, bone marrow; C, cycle; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; MRD, minimal residual disease; PB, peripheral blood; TLS, tumor lysis syndrome; uMRD4, undetectable minimal residual disease (<1×10⁻⁴).

RESULTS

Patients

- From November 2019 to June 2022, 66 patients with centrally assessed del(17p) and/or *TP53* mutation were enrolled into Arm D of the SEQUOIA trial
- By January 31, 2024 (median follow-up, 31.6 months; range, 0.4-50.5 months), 55 out of 63 patients (87%) who initiated zanubrutinib + venetoclax remained on treatment
  - This included 8 patients receiving zanubrutinib + venetoclax and 47 patients recieving zanubrutinib monotherapy after discontinuing venetoclax
- Overall, 6 patients discontinued the study (4 deaths; 1 withdrawal; 1 loss to follow-up); 3 patients discontinued treatment during the zanubrutinib lead-in
- Baseline demographics and disease characteristics are shown in **Table 1**
- After the zanubrutinib lead-in, the proportion of patients at high risk for tumor lysis syndrome decreased by 91%

Table 1. Patient Baseline Demographics and Disease Characteristics

Characteristic	Zanubrutinib + Venetoclax (n=66)
Age, median (range), years	66 (26-87)
≥65 Years, n (%)	36 (55)
Male sex, n (%)	34 (52)
White race, n (%)	58 (88)
ECOG performance status, n (%)	
1	32 (48)
2	2 (3)
SLL, n (%)	3 (5)
Bulky disease, n (%)	
Any target lesion LDi ≥5 cm	29 (44)
Any target lesion LDi ≥10 cm	5 (8)
Genotype status, n (%)	
del(17p) positive and/or *TP53* mutated	66 (100)
del(17p) positive and *TP53* mutated	42 (64)
del(17p) positive and *TP53* wild type	17 (26)
del(17p) negative and *TP53* mutated	7 (11)
Unmutated IGHV	56 (85)
Complex karyotype, n (%)	
≥3 Abnormalities	33 (50)
≥5 Abnormalities	24 (36)
del(17p) % of abnormal nuclei, median (range)	60.5 (1-98)

del(17p), deletion in chromosome 17p; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain variable region; LDi, longest diameter; SLL, small lymphocytic lymphoma.

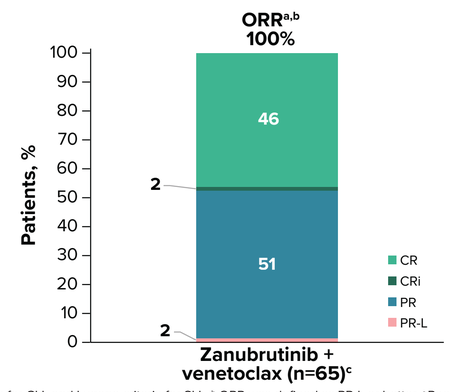
Efficacy

- In 65 response-evaluable patients with del(17p) and/or *TP53* mutation, the ORR was 100% and the complete response/complete response with incomplete hematopoietic recovery rate was 48% (**Figure 3**)
- Rates of uMRD in peripheral blood increased with longer treatment duration (**Figure 4**)
  - Best uMRD rate was 59% (39/66 patients) in ≥1 peripheral blood sample, and 37% (13/35 patients) in ≥1 bone marrow sample
- Median PFS was not reached; estimated 12-month and 24-month PFS rates were 95% and 94%, respectively (**Figure 5**)

CONCLUSIONS

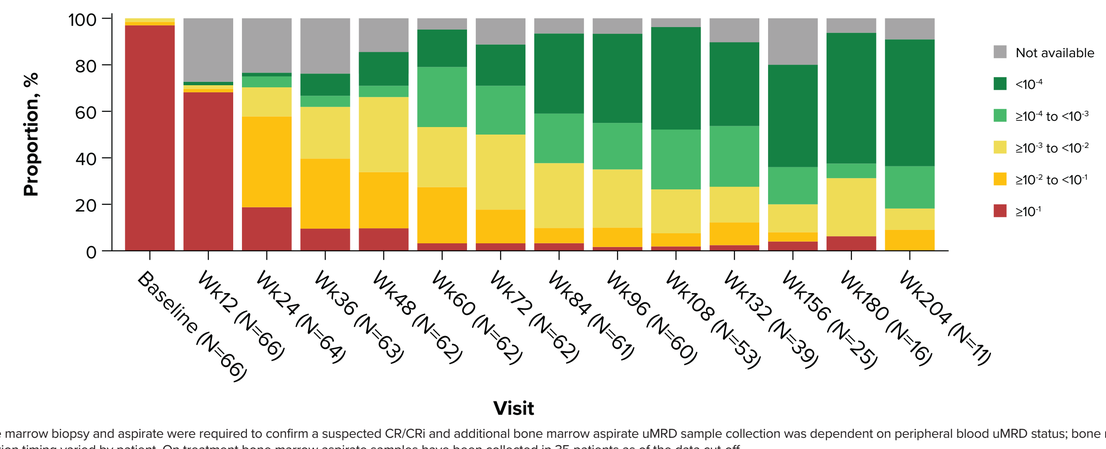
- Preliminary results for treatment with zanubrutinib + venetoclax in patients with high-risk treatment-naive CLL/SLL with del(17p) and/or *TP53* mutation showed favorable safety and tolerability
  - Rates of atrial fibrillation/flutter and hypertension were low (2% and 9%, respectively)
- Promising efficacy was seen in this high-risk population, with deep and durable responses
  - An ORR of 100% and a high rate of uMRD were achieved
  - With a median follow-up of 31.6 months, high estimated 12- and 24-month PFS rates were seen (95% and 94%, respectively)
- The study is ongoing, and results in patients who meet MRD-guided early stopping rules will be reported as data mature
- The ongoing phase 3 CELESTIAL-TNCLL trial (BGB-11417-301) is evaluating zanubrutinib in combination with sonrotoclax, a next-generation and potent BCL2 inhibitor, as fixed duration therapy in patients with treatment-naive CLL

Figure 3. Response Rates



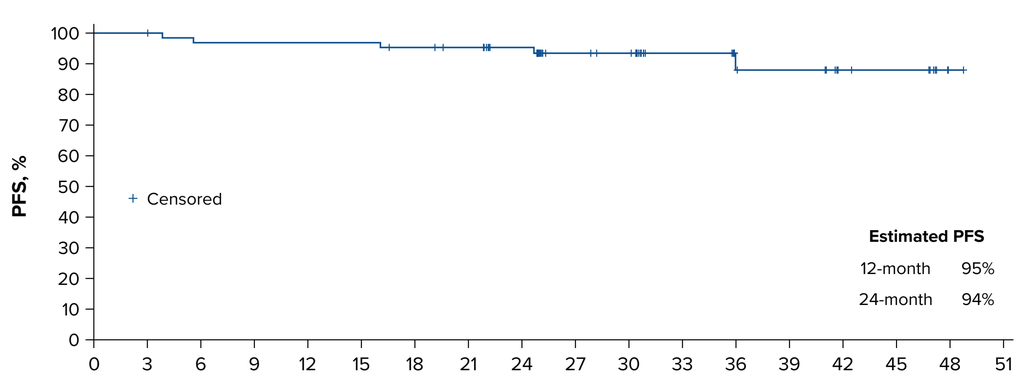
[a] Responses assessed by investigator per modified iwCLL criteria for CLL and Lugano criteria for SLL. [b] ORR was defined as PR-L or better. [c] Received ≥1 dose of zanubrutinib with ≥1 post-baseline disease assessment. The 1 patient who was not response-evaluable died during cycle 1.
CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SLL, small lymphocytic lymphoma.

Figure 4. MRD Rates in Peripheral Blood[a]



[a] Bone marrow biopsy and aspirate were required to confirm a suspected CR/CRi and additional bone marrow aspirate uMRD sample collection was dependent on peripheral blood uMRD status; bone marrow collection timing varied by patient. On treatment bone marrow aspirate samples have been collected in 35 patients as of the data cut-off.
CR, complete response; CRi, complete response with incomplete hematopoietic recovery; MRD, minimal residual disease; uMRD, undetectable minimal residual disease.

Figure 5. PFS

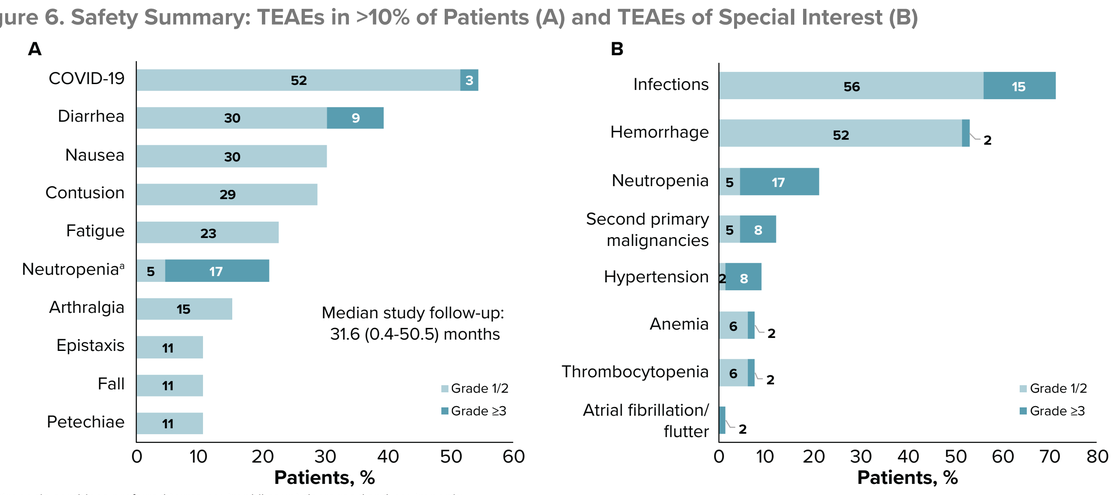


PFS, progression-free survival.

Safety

- The most common all-grade treatment-emergent adverse events (TEAEs) were COVID-19 (55%), diarrhea (39%), nausea (30%), and contusion (29%); the most common grade ≥3 TEAE was neutropenia (17%) (**Figure 6A**)
- For all-grade TEAEs of special interest, infections (71%) and hemorrhage (54%) were the most common (**Figure 6B**)
  - Of all patients with infections, 36 (55%) had COVID-19, 2 (3%) of whom experienced a grade ≥3 event
- TEAEs led to zanubrutinib and venetoclax discontinuation in 5 (8%) and 2 (3%) of patients, respectively; TEAEs led to death in 3 patients

Figure 6. Safety Summary: TEAEs in >10% of Patients (A) and TEAEs of Special Interest (B)



[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.
TEAE, treatment-emergent adverse event.

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DISCLOSURES

AT: Consultant: AstraZeneca, AbbVie, BeiGene, Janssen, Lilly; Speakers bureau: AbbVie, BeiGene, Janssen. **SM:** Consultant, membership on an entity's board of directors or advisory committee, research funding and/or speakers bureau: AstraZeneca, BeiGene, Lilly, Janssen Pharmaceuticals, Juno/BMS, AbbVie, Genentech. **TM:** Honoraria: BeiGene, AstraZeneca, Sobi, Roche, Janssen, AbbVie, Lilly; Consultant: AbbVie, BeiGene, Sobi, Alexion, Novartis, Janssen, AstraZeneca, Lilly, Roche; Research grants: Janssen, AbbVie; Travel, accommodations, or expenses: Alexion, BeiGene, AbbVie, Janssen, AstraZeneca; Advisory board: AbbVie, BeiGene, AstraZeneca, Janssen. **ML:** Travel, accommodations, or expenses: Celgene. **MS:** Consultant: AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeiGene, BMS, MorphoSys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nurix, Merck; Research funding: Mustang Bio, Genentech, AbbVie, BeiGene, AstraZeneca, Genmab, Morphosys/Incyte, Vincerx; Stock: Koi Biotherapeutics; Employment: BMS (spouse). **EF:** Honoraria: AbbVie, Janssen, AstraZeneca, BeiGene. **IWF:** Research grants (all payments made to institution): AbbVie, AstraZeneca, BeiGene, BMS, Celgene, City of Hope National Medical Center, Epizyme, Fate Therapeutics, Genentech, Gilead Sciences, IGM Biosciences InnoCare Pharma, Incyte, Janssen, Kite Pharma, Loxo, Marker Therapeutics, Merck, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Roche, Seattle Genetics, TG Therapeutics, Vincerx Pharma, 2seventy bio; Consultant fees (all payments made to physician): Abbvie, BeiGene, Genentech, Genmab, KITE, Vincerx; Board of Directors or advisory committee: Vincerx Adv Committee. **WJ:** Honoraria and consulting or advisory role: BeiGene, AstraZeneca, Janssen. **MT:** No disclosure. **TR:** Current employment: Medical University of Łódź, Copernicus Memorial Hospital; Consultant: Johnson and Johnson, BeiGene, AstraZeneca; Research funding: Johnson and Johnson, BeiGene, AstraZeneca, Lilly, OctaPharma, MSD; Honoraria: Johnson and Johnson, BeiGene, AstraZeneca. **JRB:** Consultant: AbbVie, Acerta/AstraZeneca, Alloplex Biotherapeutics, BeiGene, Galapagos NV, Genentech/Roche, Grifols Worldwide Operations, InnoCare Pharma Inc, iOnctura, Kite, Loxo@Lilly, Merck, Numab Therapeutics, Pfizer, Pharmacyclics; Research funding: BeiGene, Gilead, iOnctura, Loxo@Lilly, MEI Pharma, TG Therapeutics. **CST:** Research funding: Janssen, AbbVie, BeiGene; Honoraria: Janssen, AbbVie, BeiGene, Lilly, AstraZeneca. **TT:** Employment and may own stock: BeiGene. **EM:** Employment and may own stock: BeiGene.
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