American Society of Hematology
Helping hematologists conquer blood diseases worldwide

ZANUBRUTINIB IN COMBINATION WITH VENETOCLAX FOR PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA WITH DEL(17P): EARLY RESULTS FROM ARM D OF THE SEQUOIA (BGB-3111-304) TRIAL

Alessandra Tedeschi, MD[1]; Emmanuelle Ferrant, MD[2]; Ian Flinn MD, PhD[3]; Constantine S. Tam MBBS, MD[4,5,6,7]; Paolo Ghia, MD, PhD[8]; Tadeusz Robak, MD, PhD[9]; Jennifer R. Brown, MD, PhD[10]; Vanitha Ramakrishnan, PhD[11]; Tian Tian, PhD[11]; Sowmya B. Kuwahara, PharmD[11]; Fangfang Yin, PhD[11]; Jason C. Paik, MD, PhD[11]; Aileen Cohen, MD, PhD[11]; Jane Huang, MD[11]; and Peter Hillmen, MBChB, PhD[12]

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

Saturday, December 11, 2021
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Combination Small Molecules

DISCLOSURES

Dr. Tedeschi has participated in advisory boards and speakers' bureaus for AbbVie, AstraZeneca, BeiGene, and Janssen; and has had travel, accommodations, or expenses paid for by AbbVie and Janssen

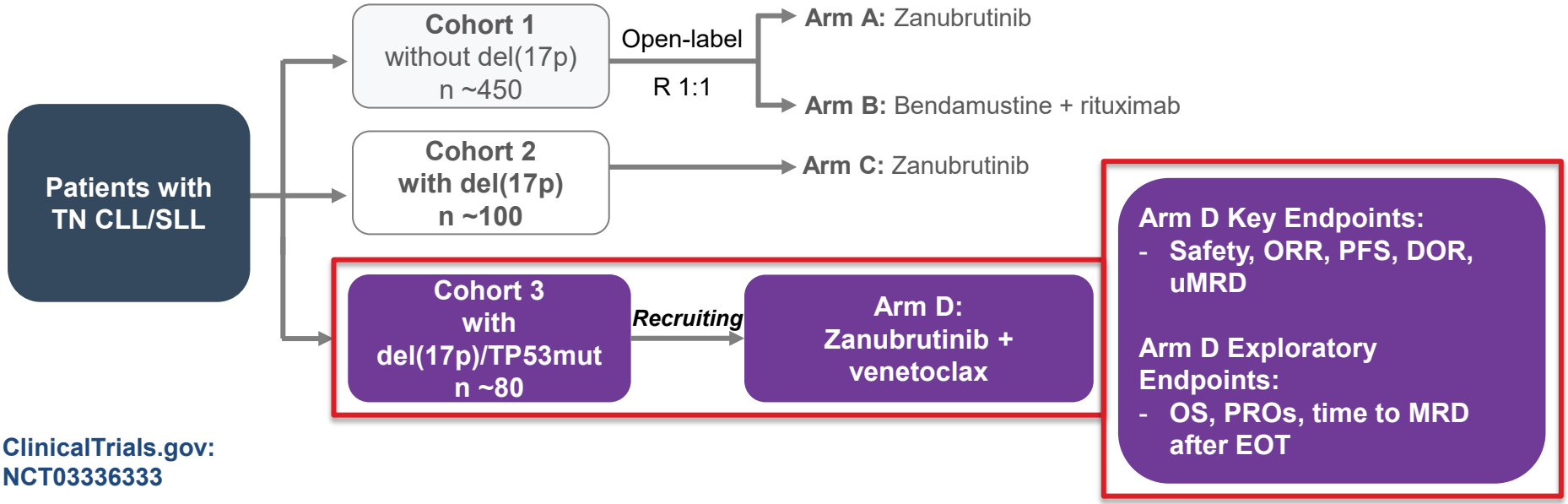
INTRODUCTION

- Patients with CLL/SLL with del(17p) and/or pathogenic TP53 variant(s) are a high-risk population and have an unfavorable prognosis, even in the front-line setting[1,2]
- Targeted therapies, such as BTK and BCL-2 inhibitors, have demonstrated improved outcomes for patients with TN CLL/SLL including high-risk populations with del(17p) and/or TP53 variant(s);[3,4] combinations of targeted therapies may be even more effective[5-8]
- Zanubrutinib (BGB-3111) is a highly selective second-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target effects;[9,10] results from Arm C of the SEQUOIA trial suggest that zanubrutinib monotherapy is active and well tolerated in patients with TN CLL/SLL with del(17p)[11,12]
- Here we present the early results from Arm D of the SEQUOIA trial of zanubrutinib in combination with venetoclax in TN CLL/SLL patients with del(17p) and/or TP53 variant(s)

BCL-2, B-cell lymphoma-2; BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; del(17p), chromosome 17p deletion; TN, treatment naive; TP53, gene encoding tumor protein p53.

1. Puiggros A, et al. *Biomed Res Int.* 2014;2014:435983. 2. Hallek M, et al. *Lancet*. 2010;376:1164-1174. 3. O'Brien S, et al. *Lancet Oncol.* 2016;17:1409-1418. 4. Stilgenbauer S, et al. *J Clin Oncol*. 2018;36:1973-1980. 5. Hillmen P, et al. *J Clin Oncol*. 2019;37:272-2729. 6. Jain N, et al. *N Engl J Med*. 2019;380:2095-2103. 7. Siddiqi T, et al. EHA 2020. Abstract S158. 8. Wierda WG, et al. *J Clin Oncol.* 2021 [epub ahead of print]. 9. Guo Y, et al. *J Med Chem*. 2019;62:7923-7940. 10. Tam CS, et al. *Blood*. 2019;134:851-859. 11. Tam CS, et al. *Haematologica*. 2021;106:2354-2363. 12. Brown JR, et al. ASH 2020. Abstract 1306.

SEQUOIA (BGB-3111-304)
Study Design



ClinicalTrials.gov: NCT03336333

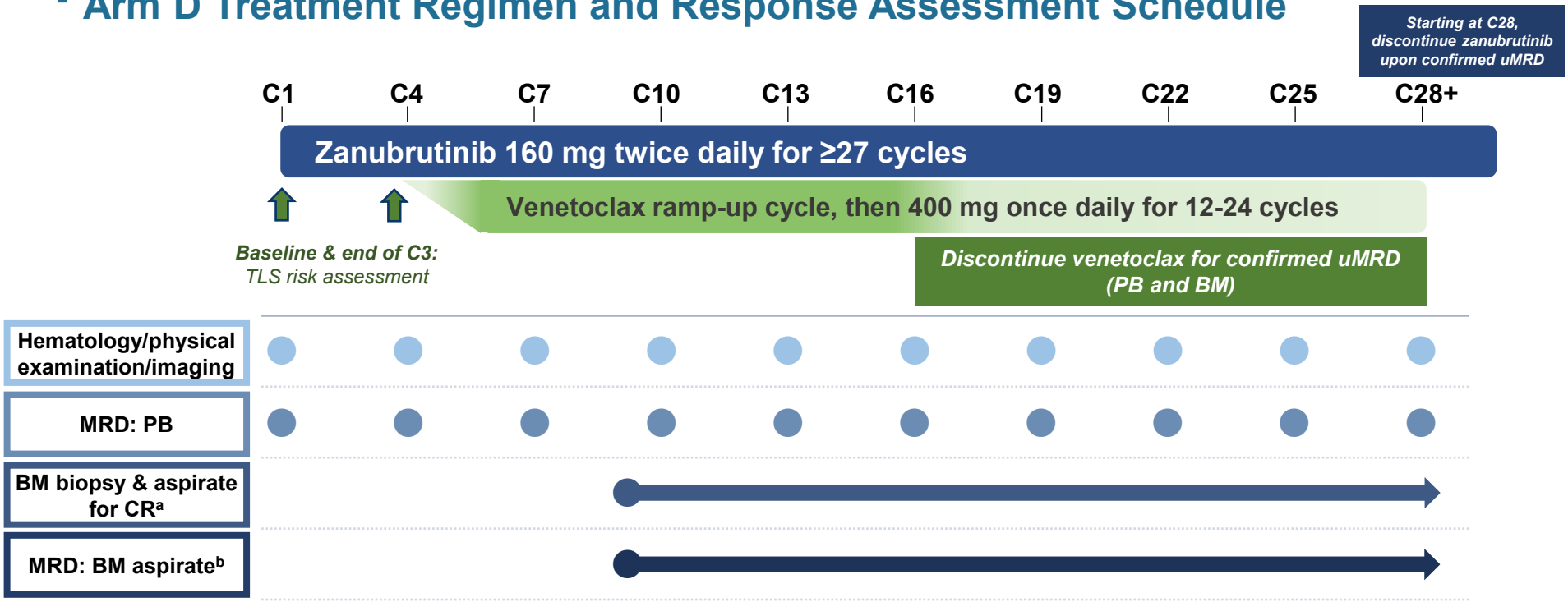
Response assessment: per modified iwCLL criteria for CLL[1,2] and Lugano criteria for SLL[3] (investigator assessments)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; del(17p), chromosome 17p deletion; DOR, duration of response; EOT, end of treatment; iwCLL, International Workshop on CLL; MRD, measurable residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R, randomized; TN, treatment naive; TP53mut, mutation in the gene encoding tumor protein p53; uMRD, undetectable measurable residual disease.

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 Treatment Regimen and Response Assessment Schedule



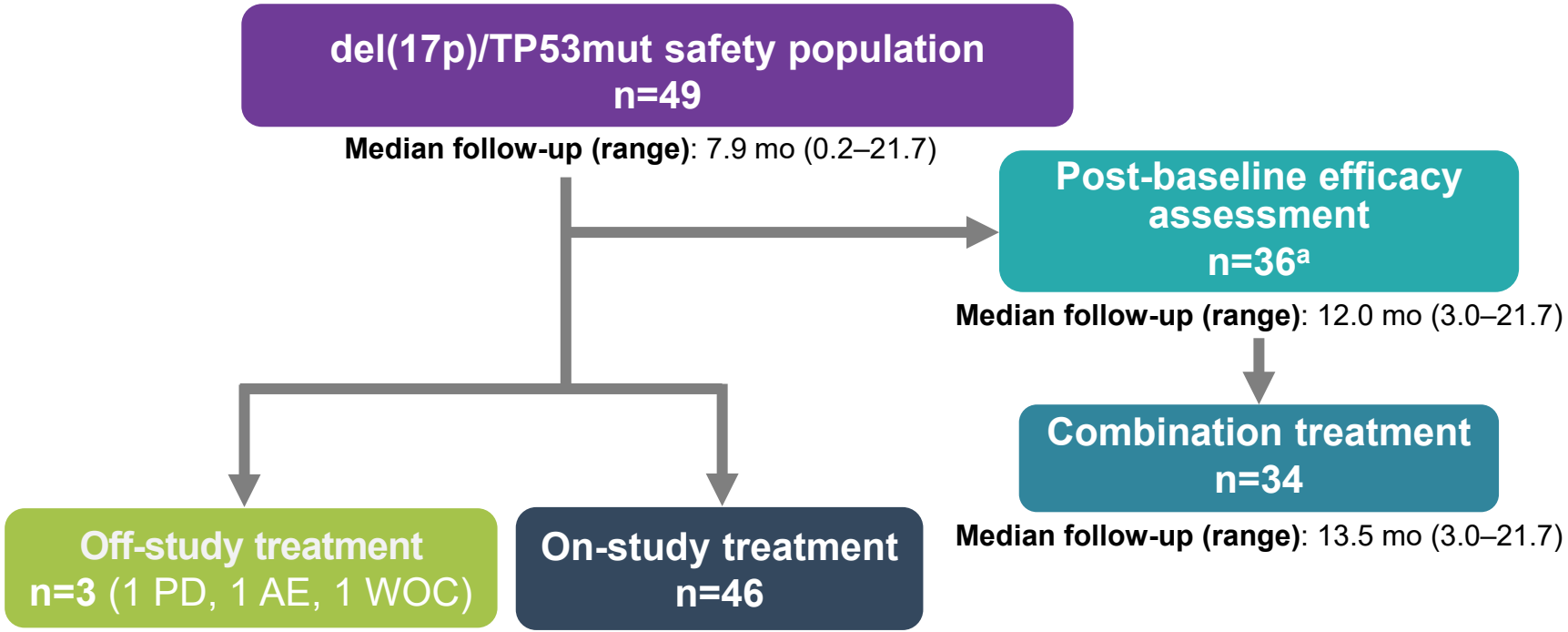
BM, bone marrow; C, cycle; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete bone marrow recovery; MRD, measurable residual disease; PB, peripheral blood; TLS, tumor lysis syndrome; uMRD, undetectable measurable residual disease (<1 CLL cell in 10,000 leukocytes at 10^{-4} sensitivity by 8-color 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 2 consecutive peripheral blood MRD tests plus 2 consecutive BM aspirate MRD tests with results that meet uMRD requirements for dose stopping.

SEQUOIA Arm D: Patient Disposition

Data Cutoff Date: September 7, 2021



AE, adverse event; del(17p): chromosome 17p deletion; PD, progressive disease; TP53mut, mutation in the gene encoding tumor protein p53; WOC, withdrawal of consent.
[a]Two patients had post-baseline efficacy assessment but ended study treatments prior to initiating venetoclax treatment; 1 due to withdrawal of consent and 1 due to AE of lung carcinoma.

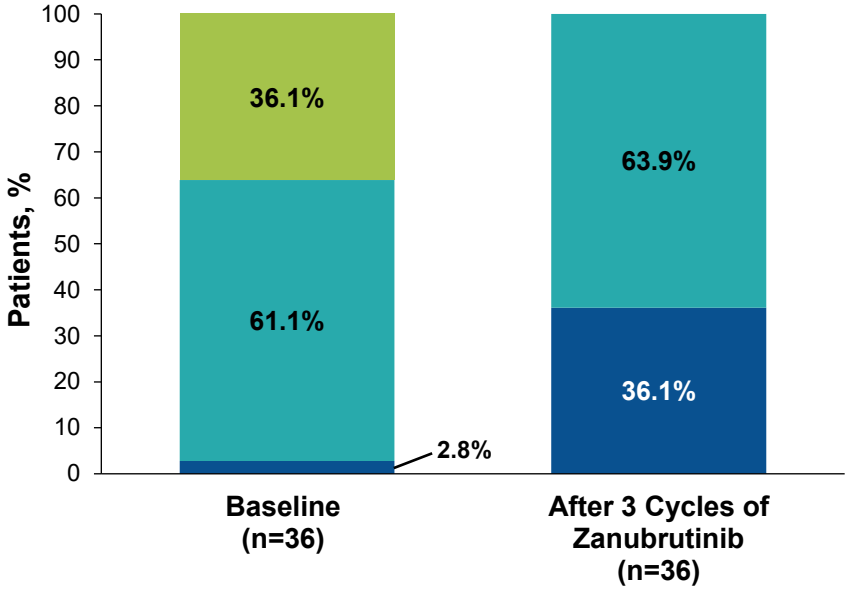
Demographics and Baseline Disease Characteristics

	n=49
Demographics	
Age, median (range), y	65.0 (25–86)
Male, n (%)	27 (55.1)
ECOG PS ≥1, n (%)	26 (53.1)
Months since diagnosis, median (Q1-Q3)	19.8 (5.7–38.1)
Disease characteristics	
SLL, n (%)	3 (6.1)
Binet stage C for patients with CLL, n/N (%)	22/46 (47.8)
Absolute lymphocyte count (×10^9/L), median	76.3
Hemoglobin (g/L), median	112.0
Platelet count (×10^9/L), median	159.0
Bulky disease, n (%)	
Any target lesion LDi ≥5 cm	20 (40.8)
Any target lesion LDi ≥10 cm	3 (6.1)

	n=49
Disease characteristics	
del(17p) by central lab FISH, n (%)	
Positive	46 (93.9)
Negative (eligible by local lab TP53 mutation)	3 (6.1)
del(17p) percent of abnormal nuclei, median	77.5
del(13q), n (%)	25 (51.0)
del(11q), n (%)	1 (2.0)
Trisomy 12, n (%)	11 (22.4)
Retrospective TP53 mutation,[a] n/N (%)	34/37 (91.9)
IGHV mutational status, n (%)	
Unmutated	43 (87.8)
Mutated	6 (12.2)
Complex karyotype,[b] n/N (%)	
Non-complex (0–2 abnormalities)	4/24 (16.7)
Complex (3 or more abnormalities)	20/24 (83.3)
Complex (5 or more abnormalities)	17/24 (70.8)

CLL, chronic lymphocytic leukemia; del(11q), chromosome 11q deletion; del(13q), chromosome 13q deletion; del(17p), chromosome 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence *in situ* hybridization; IGHV, gene encoding the immunoglobulin heavy chain variable region; lab, laboratory; LDi, longest diameter; Q, quartile; SLL, small lymphocytic lymphoma; TP53, gene encoding tumor protein p53.
[a]Ongoing analysis by next-generation sequencing. [b]Ongoing analysis.

Zanubrutinib 3-Cycle Lead-in Decreases Risk of TLS



TLS high risk: Presence of any LN ≥10 cm with the largest diameter by radiographic assessment OR presence of both ALC ≥25 ×10^9/L and one LN ≥5 cm

TLS medium risk: Presence of all measurable LNs with the largest diameter ≥5 cm and <10 cm by radiographic assessment OR ALC ≥25 ×10^9/L

TLS low risk: Presence of all measurable LNs with the largest diameter <5 cm by radiographic assessment AND ALC <25 ×10^9/L

- No clinical TLS has been reported

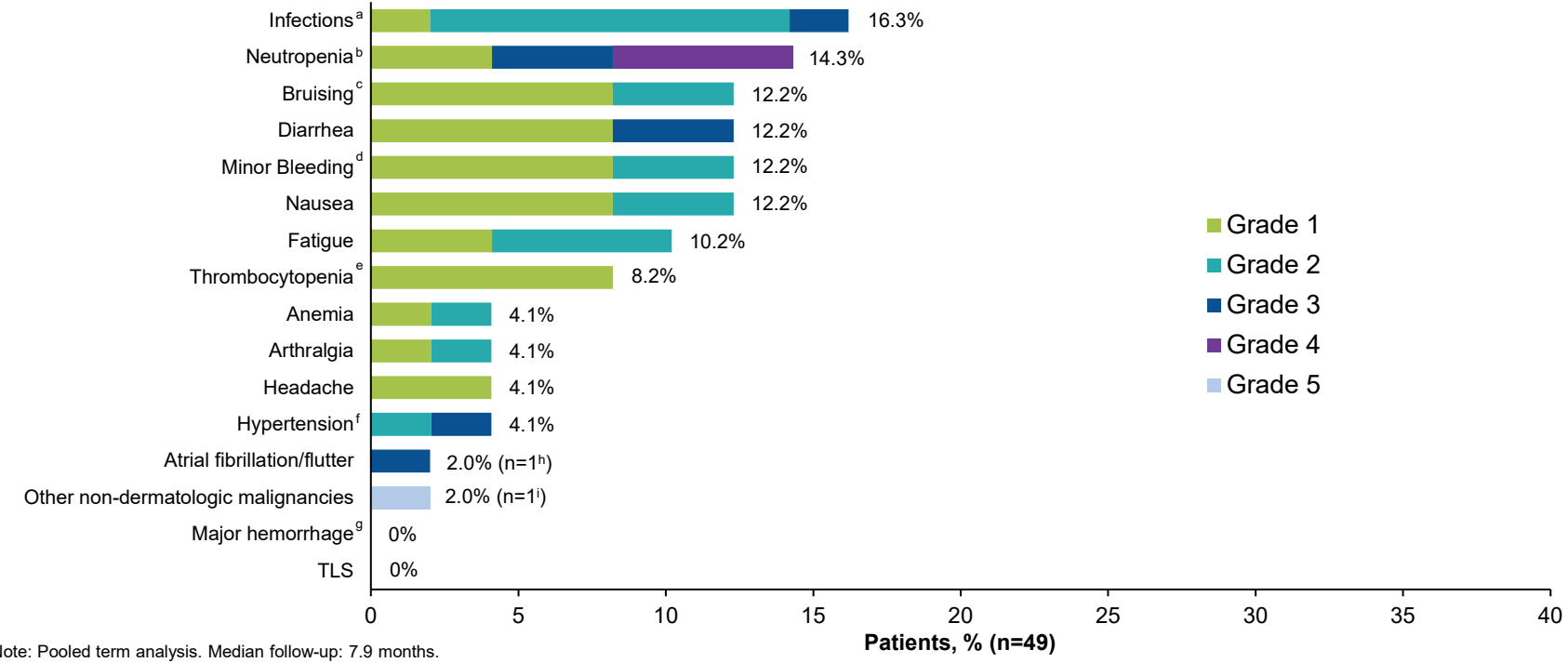
ALC, absolute lymphocyte count; LN, lymph node; TLS, tumor lysis syndrome.

Adverse Event Summary

n (%)	All Patients (n=49)	Patients on combination treatment (n=34)
Any AE	40 (81.6)	29 (85.3)
Grade ≥3 AE	16 (32.7)	13 (38.2)
Serious AE	4[a] (8.2)	3[c] (8.8)
Fatal AE	1[b] (2.0)	0 (0.0)
AE leading to dose interruption	10 (20.4)	10 (29.4)
AE leading to dose reduction	0 (0.0)	0 (0.0)
AE leading to treatment discontinuation	1[b] (2.0)	0 (0.0)

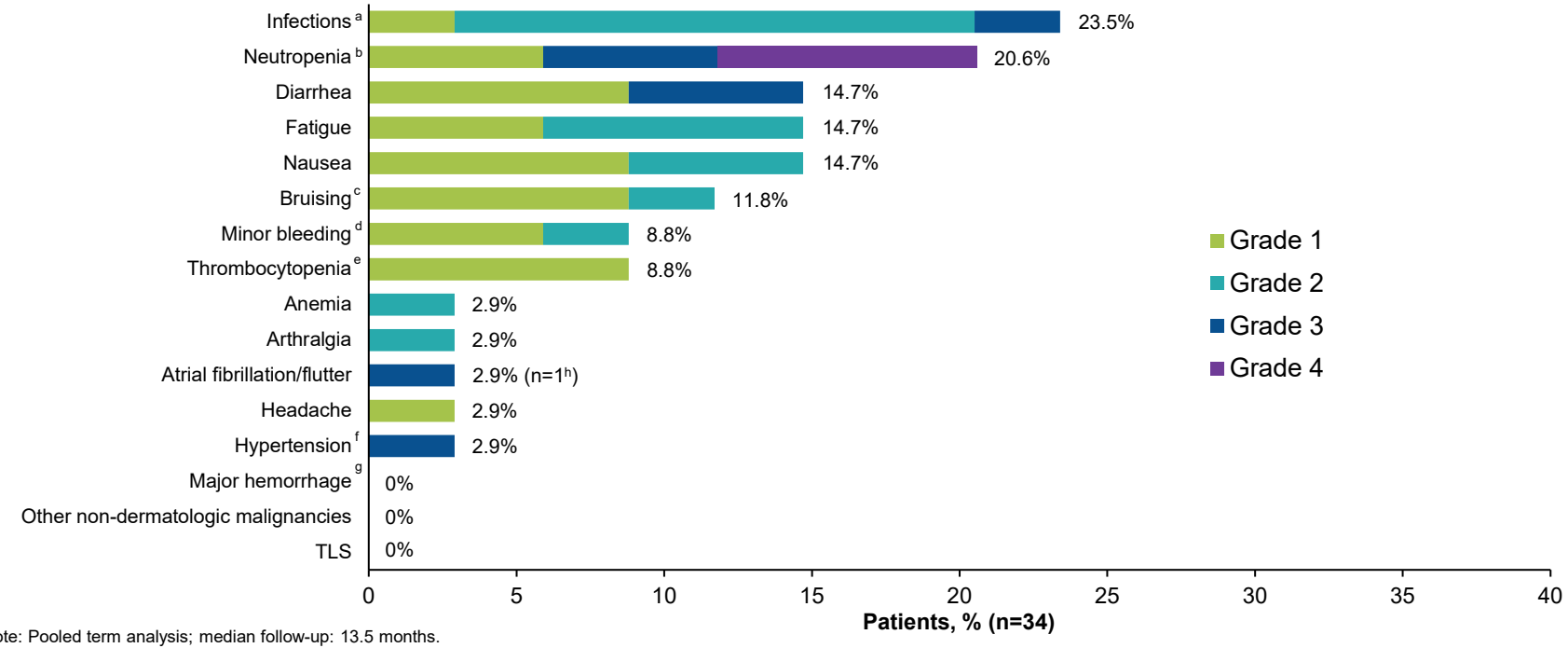
AE, adverse event.
[a]Serious AEs included anemia, drug hypersensitivity, COVID-19 pneumonia, thoracic vertebral fracture, and lung carcinoma. [b]Lung carcinoma (unrelated) leading to discontinuation of zanubrutinib and death prior to initiating venetoclax treatment. [c]Serious AEs included anemia, COVID-19 pneumonia, and drug hypersensitivity.

Adverse Events of Interest in All Patients



Note: Pooled term analysis. Median follow-up: 7.9 months.
TLS, tumor lysis syndrome.
[a]All infection terms pooled. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Purpura, contusion, ecchymosis or increased tendency to bruise. [d]Pooled term of bleeding not included in bruising, petechiae, or major bleeding. [e]Thrombocytopenia or platelet count decreased. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]Grade ≥3 hemorrhage, serious hemorrhage, and central nervous system hemorrhage of any grade were pooled. [h]One patient experienced atrial fibrillation that was worsened from a pre-existing condition. [i]Lung carcinoma (unrelated) leading to discontinuation of zanubrutinib and death prior to initiating venetoclax treatment.

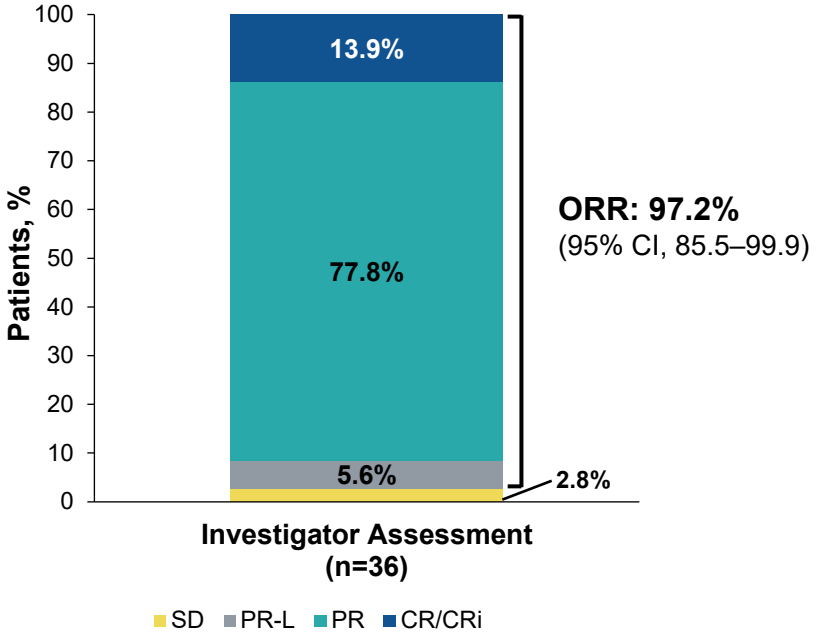
Adverse Events of Interest in Patients Receiving Combination Treatment



Note: Pooled term analysis; median follow-up: 13.5 months.
TLS, tumor lysis syndrome.
[a]All infection terms pooled. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Purpura, contusion, ecchymosis or increased tendency to bruise. [d]Pooled term of bleeding not included in bruising, petechiae, or major bleeding. [e]Thrombocytopenia or platelet count decreased. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]Grade ≥3 hemorrhage, serious hemorrhage, and central nervous system hemorrhage of any grade were pooled. [h]One patient experienced atrial fibrillation that was worsened from a pre-existing condition.

High Overall Response Rate Despite Short Follow-up

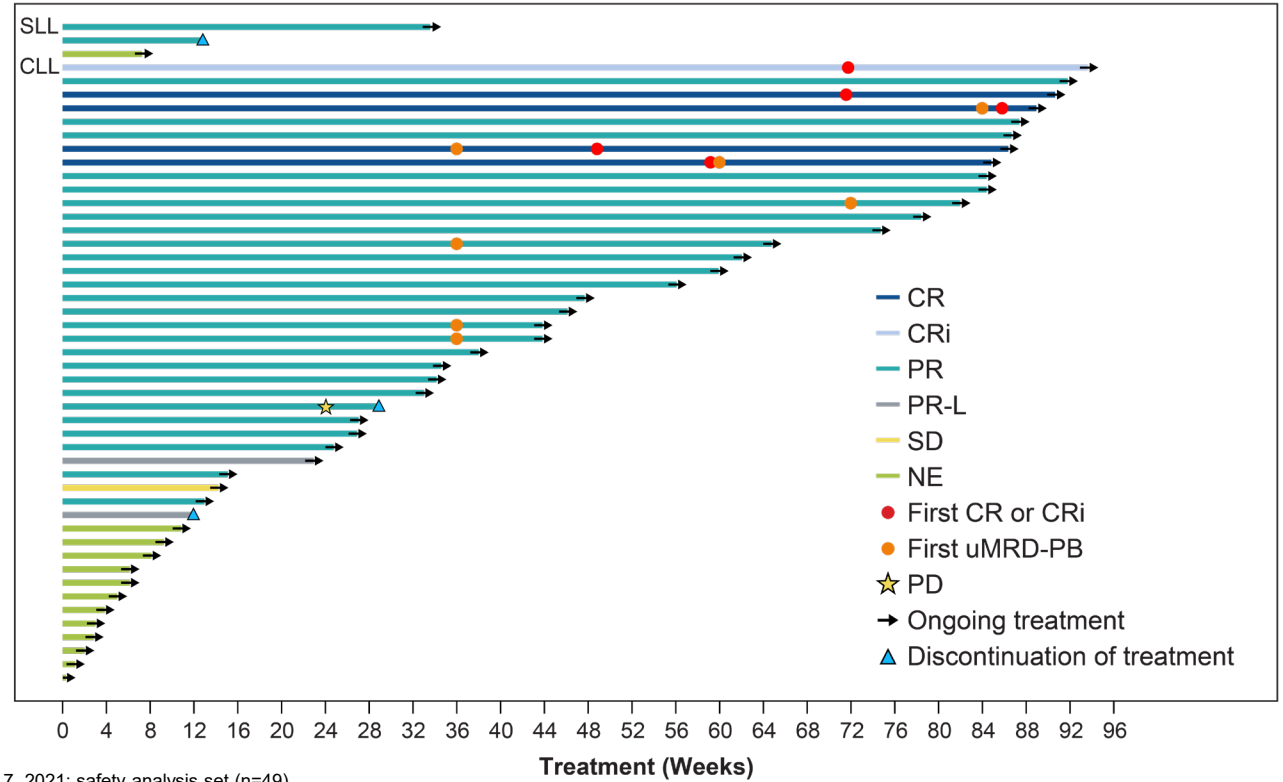
Median Follow-Up (Range): 12.0 Months (3.0–21.7)



- Thirty-six patients had post-baseline response evaluations by the data cutoff date
- Of 36 patients, 14 were treated with the combination therapy for at least 12 months
  - Five of 14 (36%) patients performed bone marrow assessment to assess CR, and all 5 patients achieved confirmed CR/CRi
  - Four additional patients in this subgroup met criteria for CR/CRi but did not perform bone marrow assessment to confirm CR/CRi, some due to COVID-19 restrictions

Data cutoff date: September 7, 2021.
CR, complete response; CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease.

Treatment Disposition by Patient



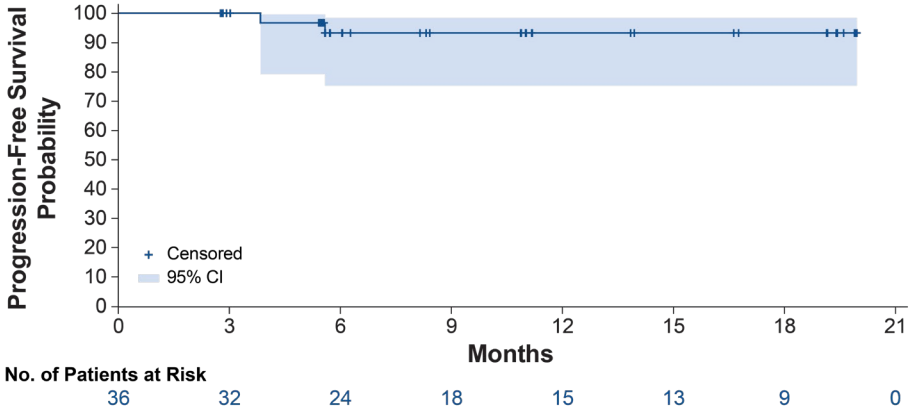
Data cutoff date: September 7, 2021; safety analysis set (n=49).

CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete bone marrow recovery; NE, not evaluable due to not reaching the first response assessment; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; uMRD-PB, undetectable measurable residual disease in peripheral blood.

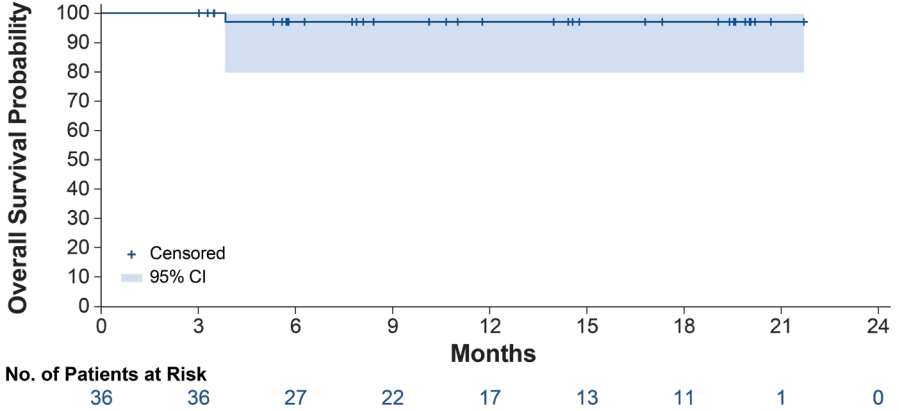
Progression-Free Survival and Overall Survival

Median Follow-Up (Range): 12.0 Months (3.0–21.7)

Progression-Free Survival



Overall Survival



- One patient had PD as assessed by investigator
  - PD based on enlargement of one non-target lesion, while all other compartments responded
  - No Richter transformation reported
  - No PLCG2, BTK, or BCL-2 gene mutations identified in post-PD sample
- One death due to lung carcinoma prior to initiating venetoclax treatment
- No reported sudden death

BCL-2, B-cell lymphoma-2; BTK, Bruton tyrosine kinase; PD, progressive disease; PLCG2, phospholipase C gamma 2.

Summary

- With relatively short follow-up, zanubrutinib plus venetoclax achieved a high response rate in this very high-risk del(17p)/TP53 mutant CLL/SLL patient population; responses appeared to deepen in patients treated with the combination for longer periods, as indicated by achievement of CR/CRi and undetectable measurable residual disease
- Zanubrutinib plus venetoclax appeared well tolerated with no reported clinical TLS, no dose reduction due to AE, and relatively low incidences of neutropenia, diarrhea, and nausea
- More mature follow-up is needed to fully assess depth of response and safety of zanubrutinib plus venetoclax in this high-risk TN CLL/SLL population

AE, adverse event; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; CRi, complete response with incomplete bone marrow recovery; del(17p), chromosome 17p deletion; TLS, tumor lysis syndrome; TN, treatment naive; TP53, gene encoding tumor protein p53.

ACKNOWLEDGMENTS

- We would like to thank the SEQUOIA Arm D investigators, site support staff, and especially the patients for participating in this study
- This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene

Corresponding Author:

Alessandra Tedeschi, MD, e-mail: alessandra.tedeschi@ospedaleniguarda.it