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

Abstract: 1306

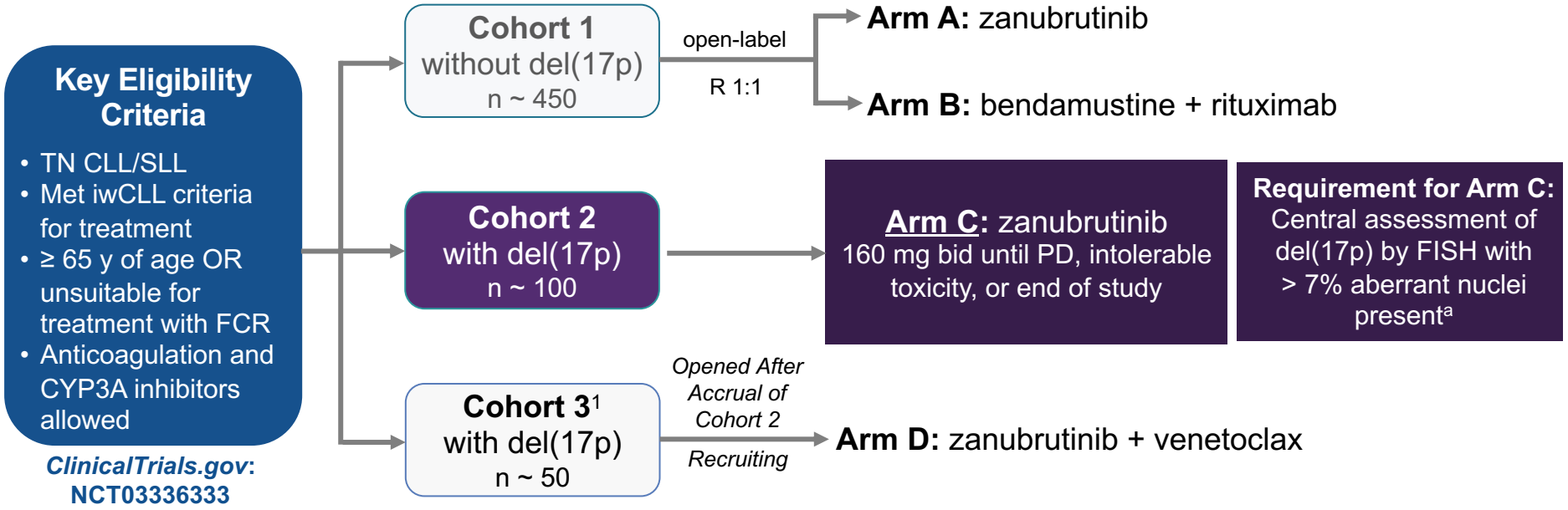
Introduction

- 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

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

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. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 6. Tam CS, et al. *Blood*. 2019;134:851-859. 7. Tam CS, et al, *Blood.* 2020;136:2038-2050. 8. Tam CS, et al. *Blood*. 2019;134(Supplement_1):499.

SEQUOIA (BGB-3111-304)
Study Design



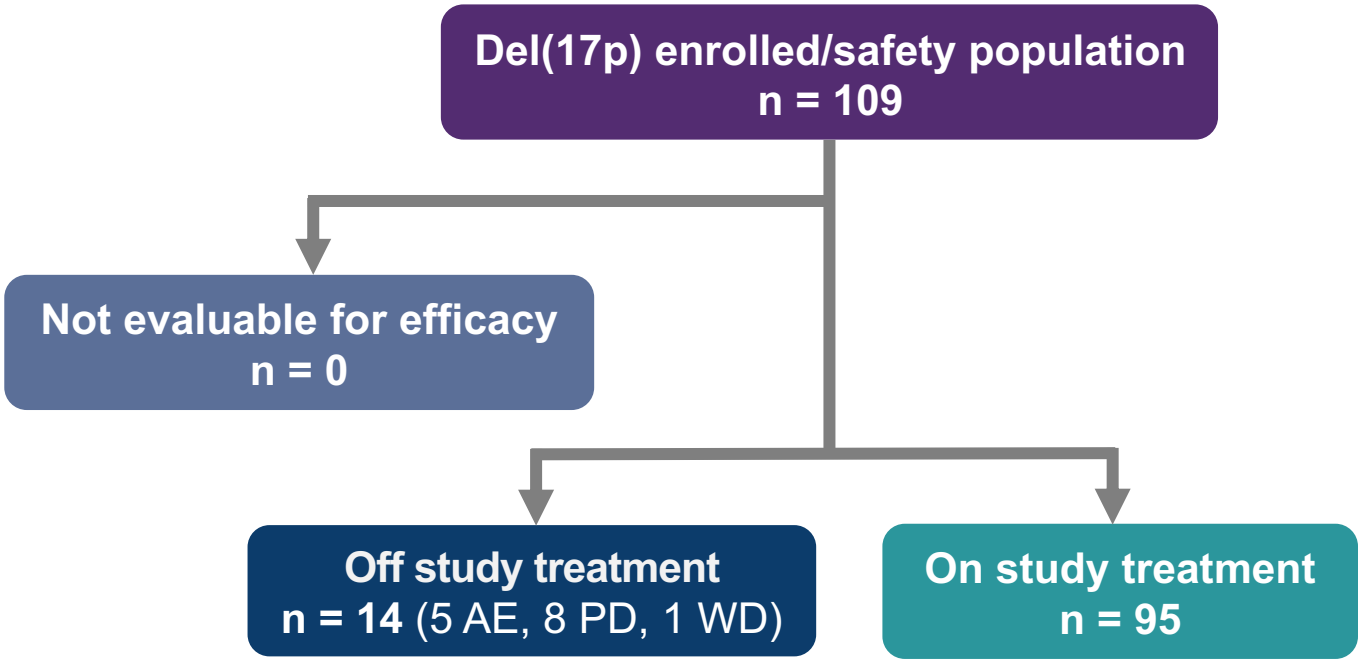
- **Endpoints for Arm C**: ORR (IRC and investigator assessments), PFS, DOR, safety
- **Response assessment:** per modified iwCLL criteria for CLL[2,3] and Lugano criteria for SLL[4] (IRC and investigator assessments)

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.

1. Tam CS, et al. *ASH.* 2020; Abstract: 1318. 2. Hallek M, et al. *Blood*. 2008;111:5446-5456. 3. Cheson BD, et al. *J Clin Oncol.* 2012;30:2820-2822. 4. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3067.

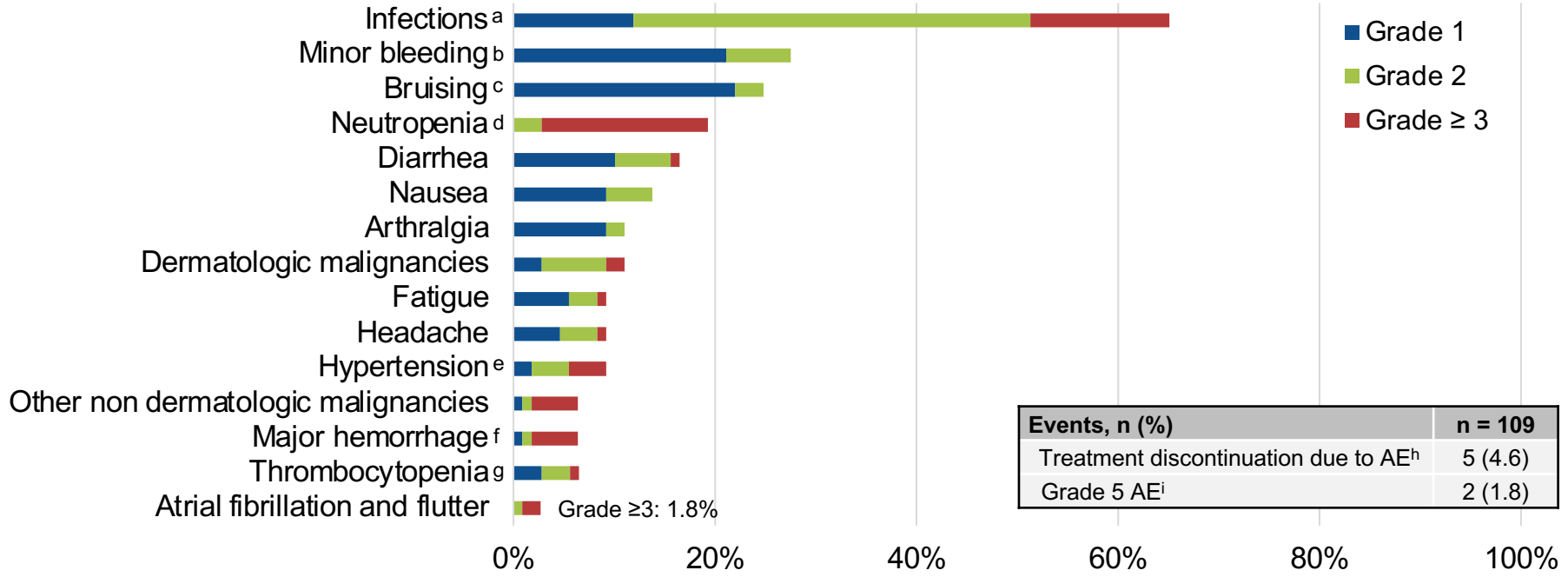
SEQUOIA Arm C: Patient Disposition
Data Cutoff: August 10, 2020



Median follow-up (range): 21.9 months (5.0 - 30.2)

AE, adverse event; PD, progressive disease; WD, withdrawal by subject.

Adverse Events of Interest

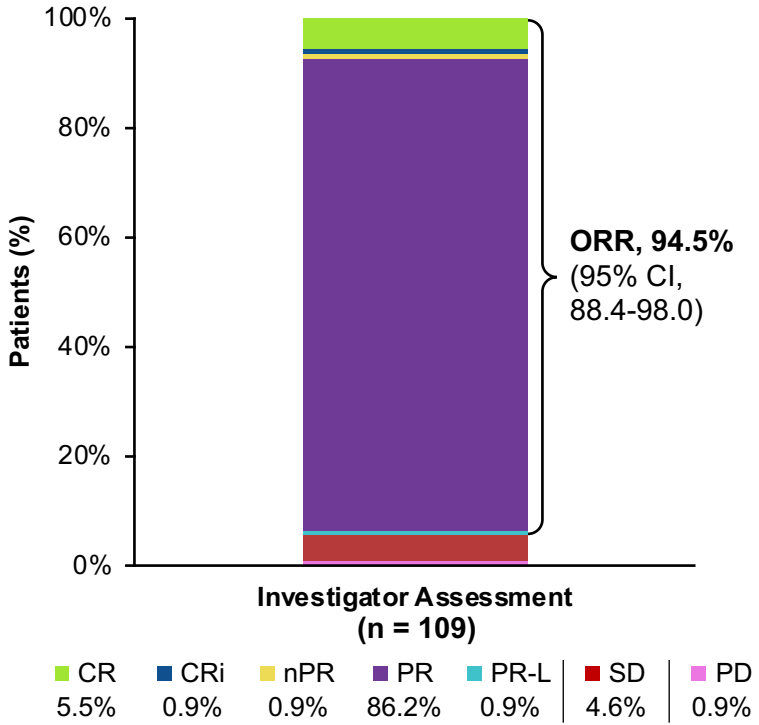


Events, n (%)	n = 109
Treatment discontinuation due to AE[h]	5 (4.6)
Grade 5 AE[i]	2 (1.8)

Data cutoff: August 10, 2020. Note: Pooled term analysis.
AE, adverse events.

[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



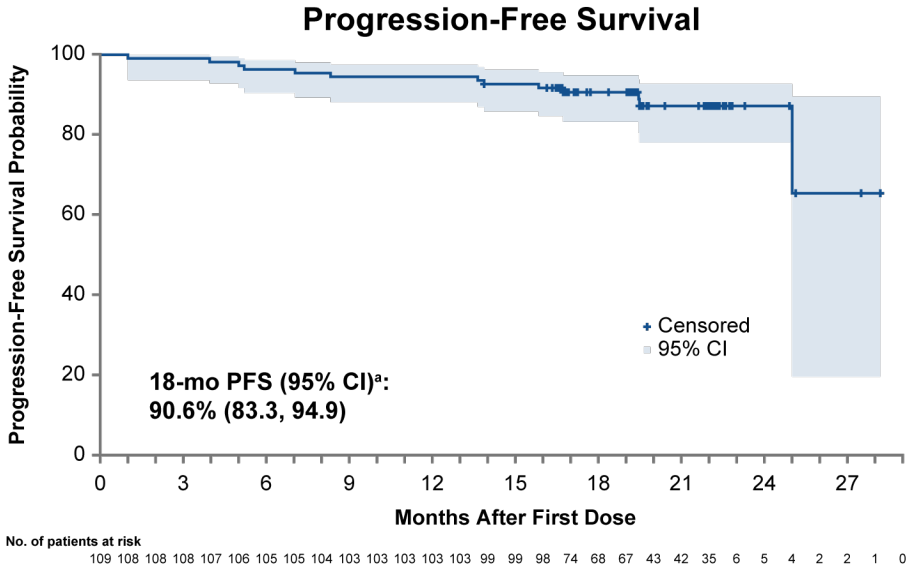
- Duration of Response
  - DOR ≥12 mo [95% CI][a]: 93.1% [86 - 97]
  - **DOR ≥18 mo [95% CI][a]: 87.7% [78 - 93]**
- Compared to 2019 ASH presentation[b]
  - **CR/CRi rate increased from 1.9% to 6.4%**
  - PR-L rate decreased from 11.9% to 0.9%
- Features of patients achieving CR/CRi
  - 5 mutated IGHV, 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)

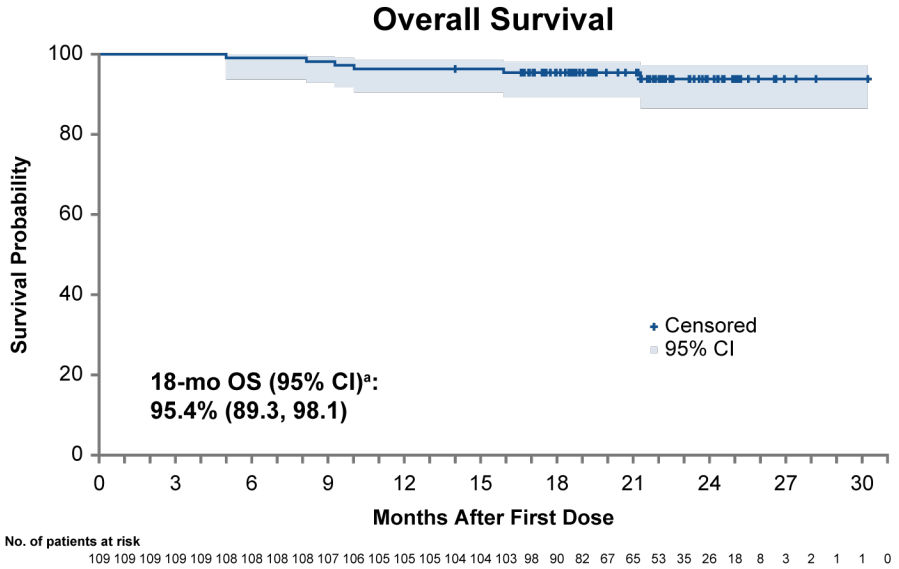
Data cutoff: August 10, 2020

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.

[a] 2-sided Clopper-Pearson 95% confidence intervals. [b] 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





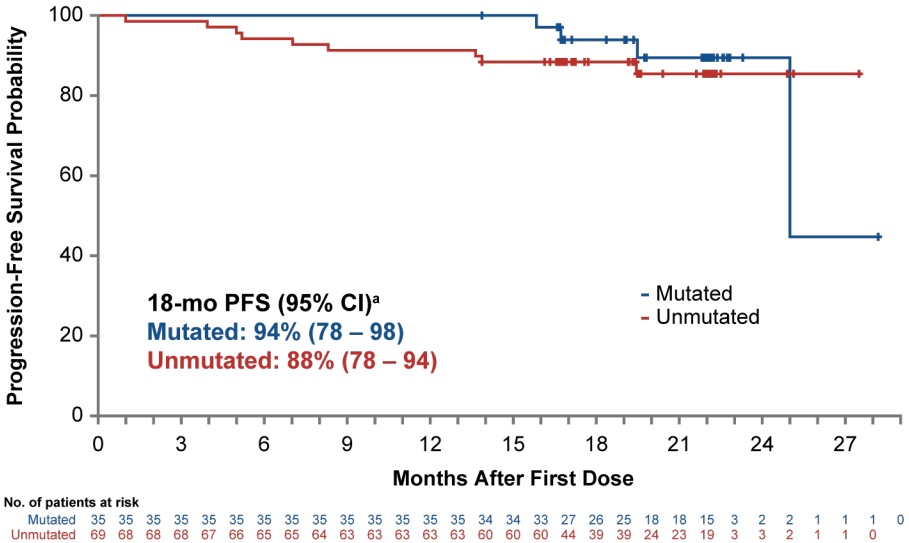
- 12 patients had investigator-reported PD
  - 5 patients had investigator-assessed RT
  - Median time to transformation was 13.6 mo (range, 3.9 - 15.7)
- 1 patient had PD after discontinuing study drug treatment due to AE

- Reasons for death
  - 2 AE (pneumonia, renal failure (in the context of PD))
  - 3 PD (2 RT)
  - 1 sepsis after PD due to RT
- No reported sudden deaths

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.
[a] 2-sided Clopper-Pearson 95% confidence intervals.

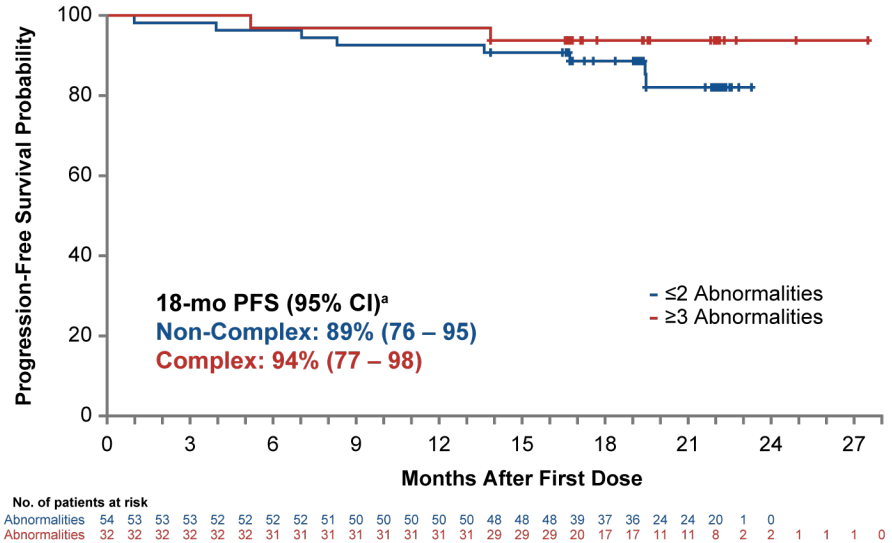
Progression-Free Survival by IGHV and Karyotype Status
Investigator Assessment

Progression-Free Survival by IGHV Mutation Status



IGHV mutational status[b], n (%)	
Mutated	35 /104 (33.7)
Unmutated	69 /104 (66.3)

Progression-Free Survival by Complex Karyotype Status



Karyotype status[c], n (%)	
Non-Complex (0 to 2 abnormalities)	54 / 86 (62.8)
Complex	
3 or more abnormalities	32 / 86 (37.2)
5 or more abnormalities	23 / 86 (26.7)

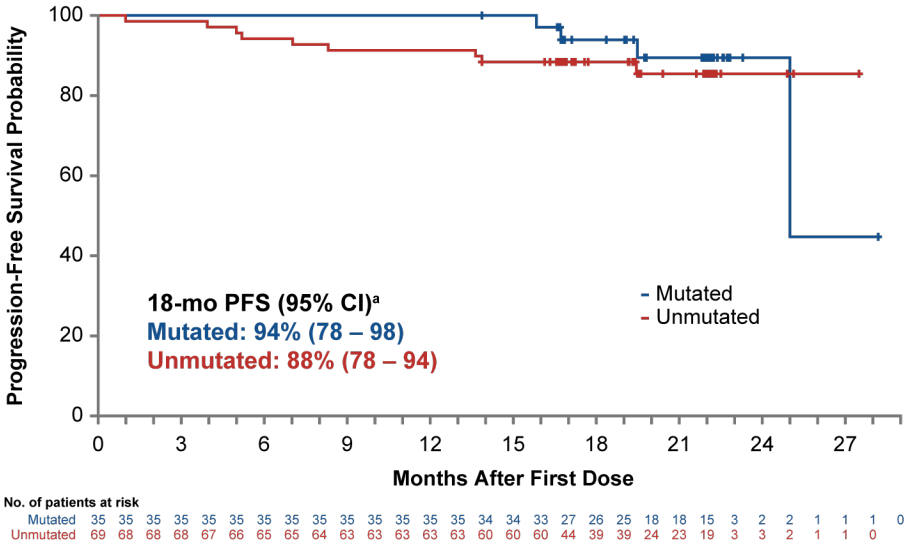
Data cutoff: August 10, 2020. Median follow-up (range): 21.9 months (5.0 – 30.2)

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

[a] 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.

Progression-Free Survival by IGHV and Karyotype Status
Investigator Assessment

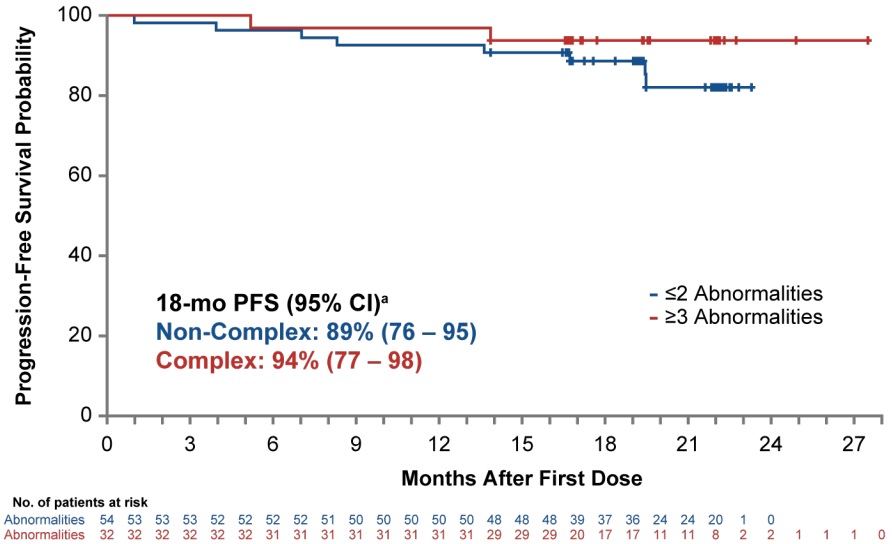
Progression-Free Survival by IGHV Mutation Status



No. of patients at risk

Mutated	35	35	35	35	35	35	35	35	35	35	35	35	35	35	34	34	33	27	26	25	18	18	15	3	2	2	1	1	1	0
Unmutated	69	68	68	68	67	66	65	65	64	63	63	63	63	63	60	60	60	44	39	39	24	23	19	3	3	2	1	1	0	

Progression-Free Survival by Complex Karyotype Status



No. of patients at risk

<=2 Abnormalities	54	53	53	53	52	52	52	52	51	50	50	50	50	50	48	48	48	39	37	36	24	24	20	1	0			
>=3 Abnormalities	32	32	32	32	32	32	31	31	31	31	31	31	31	31	29	29	29	20	17	17	11	11	8	2	2	1	1	1	0

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

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.
[a] 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.

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 malignancies[1,2,3,4]
- Additional data from this cohort are now published online[5]

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.

1. Tam CS, et al. *Blood*. 2020;136:2038-2050. 2. Song Y, et al. *Clin Cancer Res*. 2020;26:4216-4224. 3. Tam CS, et al. *Blood*. 2019;134:851-859. 4. Tam CS, et al. *EHA*. 2019;Abstract: PS1159. 5. Tam CS, et al. *Haematologica*. 2020;[epub ahead of print].

Acknowledgements

- We thank the investigators, site support staff, and especially the patients and their caretakers for participating in the SEQUOIA study
- This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene

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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 Gilead, Loxo, Sun, and Verastem
- **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
- **PG**: Honoraria and consulting role with AbbVie, ArQule, AstraZeneca, BeiGene, Gilead, Janssen, Juno, Lilly, MEI, Sunesis; Research funding from AbbVie, Gilead, Janssen, and Sunesis
- **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, AstraZenca; 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

	n = 109
Demographics	
Age, median (range), y	70.0 (42-86)
Male, n (%)	78 (71.6)
ECOG PS of 2, n (%)	14 (12.8)
Months since diagnosis, median (Q1-Q3)	21.62 (7.69–54.77)
Disease characteristics	
SLL, n (%)	10 (9.2)
Binet stage C for patients with CLL, n (%)	40 / 99 (40.4)
Absolute lymphocyte count ($\times 10^9$/L), median	65.1
Hemoglobin (g/L), median	120.0
Platelet count ($\times 10^9$/L), median	154.0

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

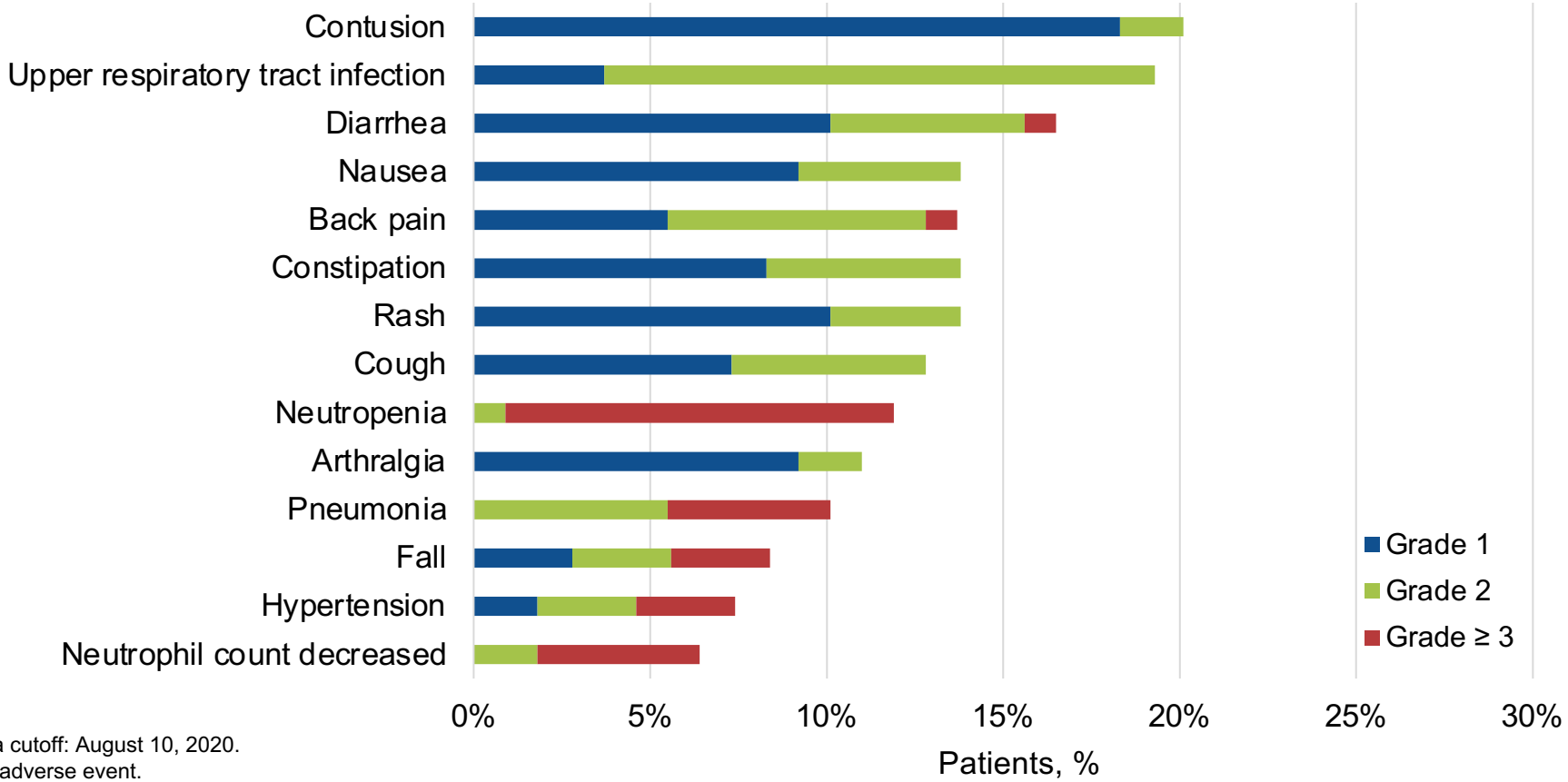
CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, gene encoding for immunoglobulin heavy chain variable region; LDi, longest diameter; SLL, small lymphocytic lymphoma.

[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%



Data cutoff: August 10, 2020.
AE, adverse event.

Summary of Grade ≥ 3 and Serious AEs

Events, n (%)	n = 109
Patients with Grade ≥ 3 AE	57 (52.3)
Grade ≥ 3 AEs that occurred in > 2 patients	
Neutropenia/decreased neutrophil count	17 (15.6)
Pneumonia	5 (4.6)
Fall	3 (2.8)
Hypertension	3 (2.8)
Serious AE	42 (38.5)
Treatment discontinuation due to AE[a]	5 (4.6)
Grade 5 AE[b]	2 (1.8)

Data cutoff: August 10, 2020.

AE, adverse event.

[a] Pneumonia leading to sepsis and death, pseudomonal sepsis, melanoma, renal failure in the context of disease progression, and unknown at the data cutoff. [b] Pneumonia leading to sepsis and death, and renal failure in the context of disease progression, both of which also led to treatment discontinuation.