Efficacy and Safety of Zanubrutinib in Patients With Treatment-Naive Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) With Del(17p): Initial Results From Arm C of the SEQUOIA (BGB-3111-304) Trial

Constantine S. Tam, MBBS, MD[1-4]; Tadeusz Robak, MD, PhD[5]; Paolo Ghia, MD, PhD[6]; Brad S. Kahl, MD[7]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[8]; Wojciech Janowski, MBChB, FRCPA, FRACP[9]; David Simpson, MBChB, FRACP, FRCPA[10]; Mazyar Shadman, MD, MPH[11,12]; Peter S. Ganly, BMBCh, PhD[13,14]; Luca Laurenti, MD[15]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[16,17]; Monica Tani, MD[18]; Hanna Ciepluch, MD[19]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[20]; Martin Šimkovič, MD, PhD[21,22]; Anders Österborg, MD, PhD[23, 24]; Marek Trněný, MD[25]; Alessandra Tedeschi, MD[26]; Jason Paik, MD, PhD[27]; Carol Marimpietri[27]; Shibao Feng, PhD[27]; Jane Huang, MD[27]; Peter Hillmen, MBChB, PhD, FRCP, FRCPath[28]; and Jennifer R. Brown, MD, PhD[29]

[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]Medical University of Lodz, Lodz, Poland; [6]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [7]Washington University School of Medicine, St Louis; MO, USA; [8]Peninsula Private Hospital, Frankston, Victoria, Australia; [9]Calvary Mater Newcastle, Waratah, NSW, Australia; [10]North Shore Hospital, Auckland, New Zealand; [11]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [12]Department of Medicine, University of Washington, Seattle, WA, USA; [13]Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; [14]Department of Pathology and Biomedical Science, University of Otago, Christchurch, New Zealand; [15]Fondazione Policlinico Universitario A Gemelli-Roma IRCCS, Rome, Italy; [16]Monash Health, Clayton, Victoria, Australia; [17]Monash University, Clayton, Victoria, Australia; [18]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [19]Copernicus Wojewódzkie Centrum Onkologii, Gdánsk, Poland; [20]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [21]4th Department of Internal Medicine - Hematology, University Hospital, Hradec Kralove, Czech Republic; [22]Faculty of Medicine, Charles University, Prague, Czech Republic; [23]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [24]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [25]First Department. of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [26]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [27]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [28]St James's University Hospital, Leeds, United Kingdom; and [29]Dana-Farber Cancer Institute, Boston, MA, USA

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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]

- Targeted therapies have been shown to improve outcomes for patients with del(17p), who have historically had few treatment options[3]
  - BTK is a critical component of the B-cell receptor signaling pathway mediating B-cell proliferation, migration, and adhesion[4,5]
  - Ibrutinib, a first-generation BTK inhibitor, has shown activity in treatment-naïve and relapsed/refractory CLL, and has become a standard of care in patients with del(17p) CLL[6,7]

BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

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. Woyach JA, et al. *Blood*. 2012;120:1175-1184. 5. Rickert RC. *Nat Rev Immunol*. 2013;13:578-591. 6. Imbruvica® (ibrutinib) [package insert]. Sunnyvale, CA, USA: Pharmacyclics LLC; Horsham, PA, USA: Janssen Biotech, Inc; 2019. 7. Imbruvica® (ibrutinib) [summary of product characteristics]. Beerse, Belgium: Janssen-Cilag International NV; 2019.

Zanubrutinib (BGB-3111)

- Zanubrutinib is an investigational next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases[1,2]

- In a phase 1/2 study (BGB-3111-AU-003), zanubrutinib monotherapy was generally well tolerated in patients with B-cell malignancies
  - Durable responses were achieved in patients with TN and R/R CLL/SLL, irrespective of del(17p) status[2-4]

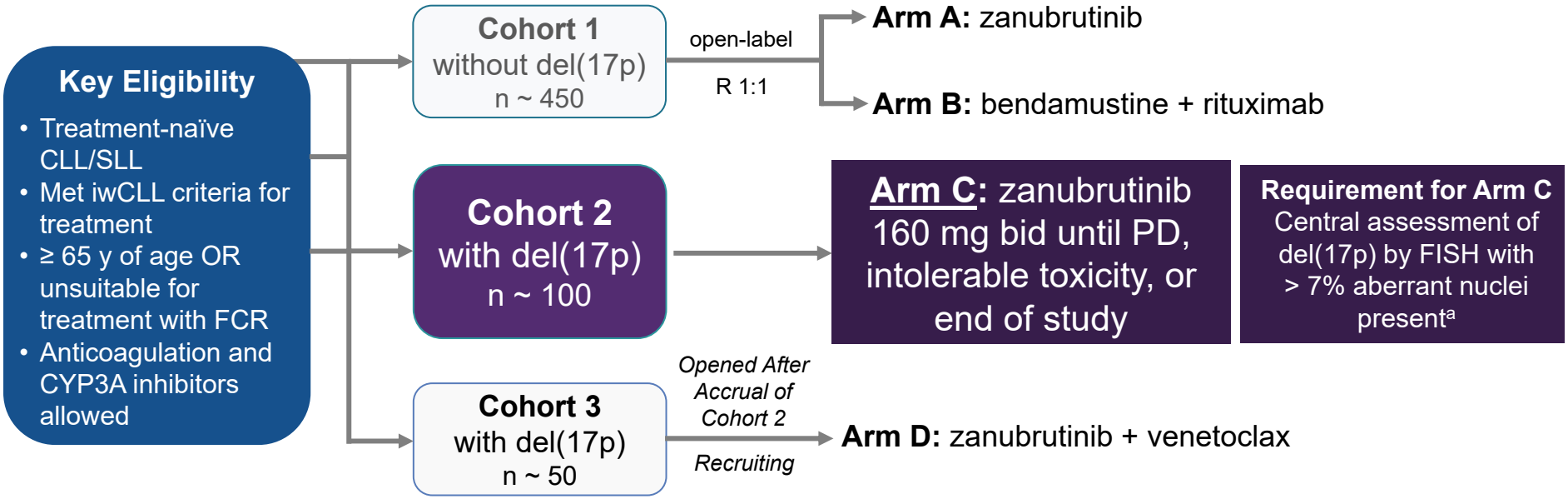
- Zanubrutinib was recently approved in the United States under accelerated approval for the treatment of relapsed/refractory mantle cell lymphoma in adults[5]

BTK, Bruton's tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; R/R relapsed/refractory; TN, treatment-naive.

1. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 2. Tam CS, et al. *Blood*. 2019;134:851-859. 3. Tam CS, et al. *Blood*. 2015;126(suppl, abstr); 832. 4. Cull G, et al. ASH 2019, Abstract 500. 5. Brukinsa® (zanubrutinib) [U.S. prescribing information]. San Mateo, CA, USA: BeiGene USA, Inc.; 2019.

SEQUOIA (BGB-3111-304)
Study Design

NCT03336333



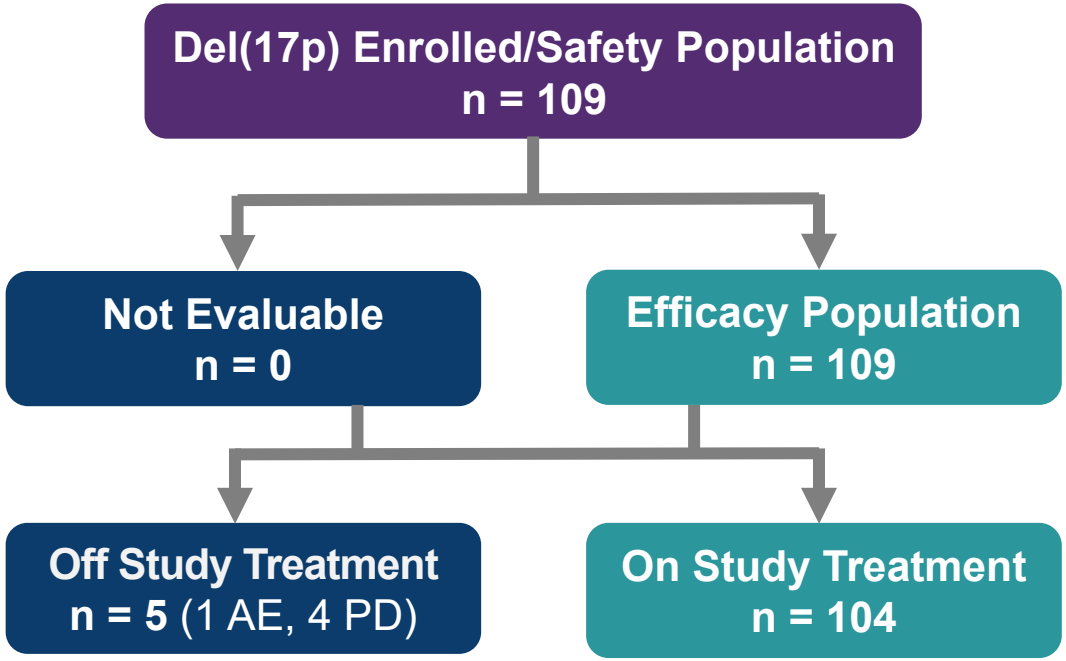
- **Endpoints for Arm C**: ORR (IRC and investigator assessments), PFS, DOR, safety
- **Response assessment:** per modified iwCLL criteria for CLL[1,2] and Lugano criteria for SLL[3] (IRC and investigator assessments)

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.

[a] *TP53* mutational status was not centrally assessed prior to enrollment.

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 Arm C: Patient Disposition
Data Cutoff: August 7, 2019



Median follow-up (range): 10.0 months (5.0-18.1)

AE, adverse event; PD, progressive disease.

SEQUOIA Arm C
Baseline Demographics and Disease Characteristics

	n = 109
Demographics	
Age, median (range), y	70.0 (42-86)
Men, 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

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; SLL, small lymphocytic lymphoma; TN, treatment naive.

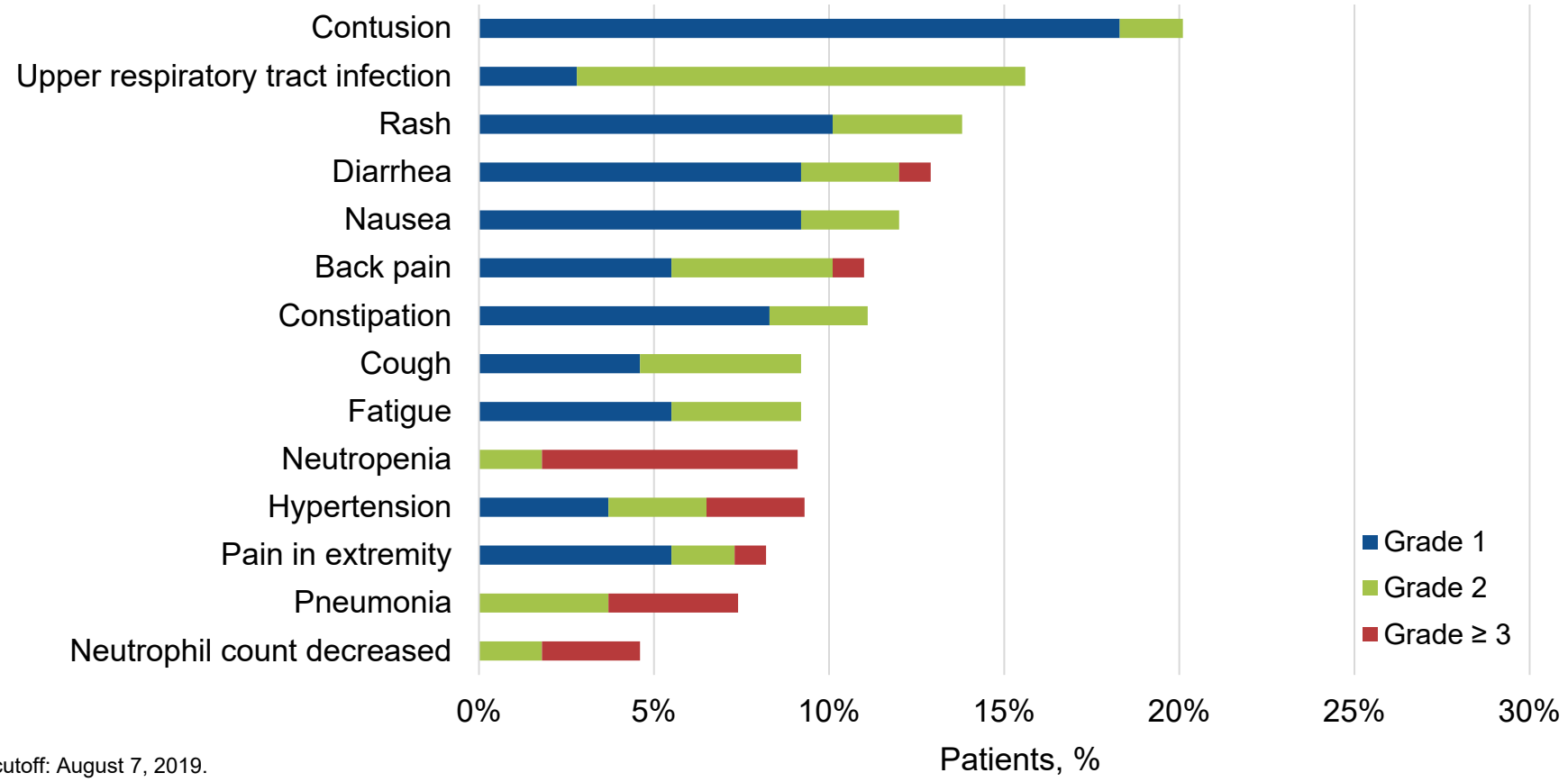
SEQUOIA Arm C
Baseline Disease Characteristics

	n = 109
Disease characteristics	
Del(13q), n (%)	72 (66.1)
Del(11q), n (%)	37 (33.9)
Trisomy 12, n (%)	20 (18.3)
β2 microglobulin[a] > 3.5 g/dL, n (%)	77 / 98 (78.6)
IGHV mutational status, n (%)	
Mutated	36 (33.0)
Unmutated	67 (61.5)
QNS[b]	6 (5.5)
Bulky disease[c], n (%)	
Any target lesion LDi ≥ 5 cm	42 (38.5)
Any target lesion LDi ≥ 10 cm	11 (10.1)

LDi, longest diameter; QNS, quantity not sufficient;
[a]11 patients had missing data. [b]RNA quantity/quality not sufficient for PCR amplification of VH region for sequencing. [c]Patients with any target lesion with longest diameter presented.

Common Adverse Events Regardless of Causality

Any Grade ≥ 7.5% or Grade 3 or Higher ≥ 2%



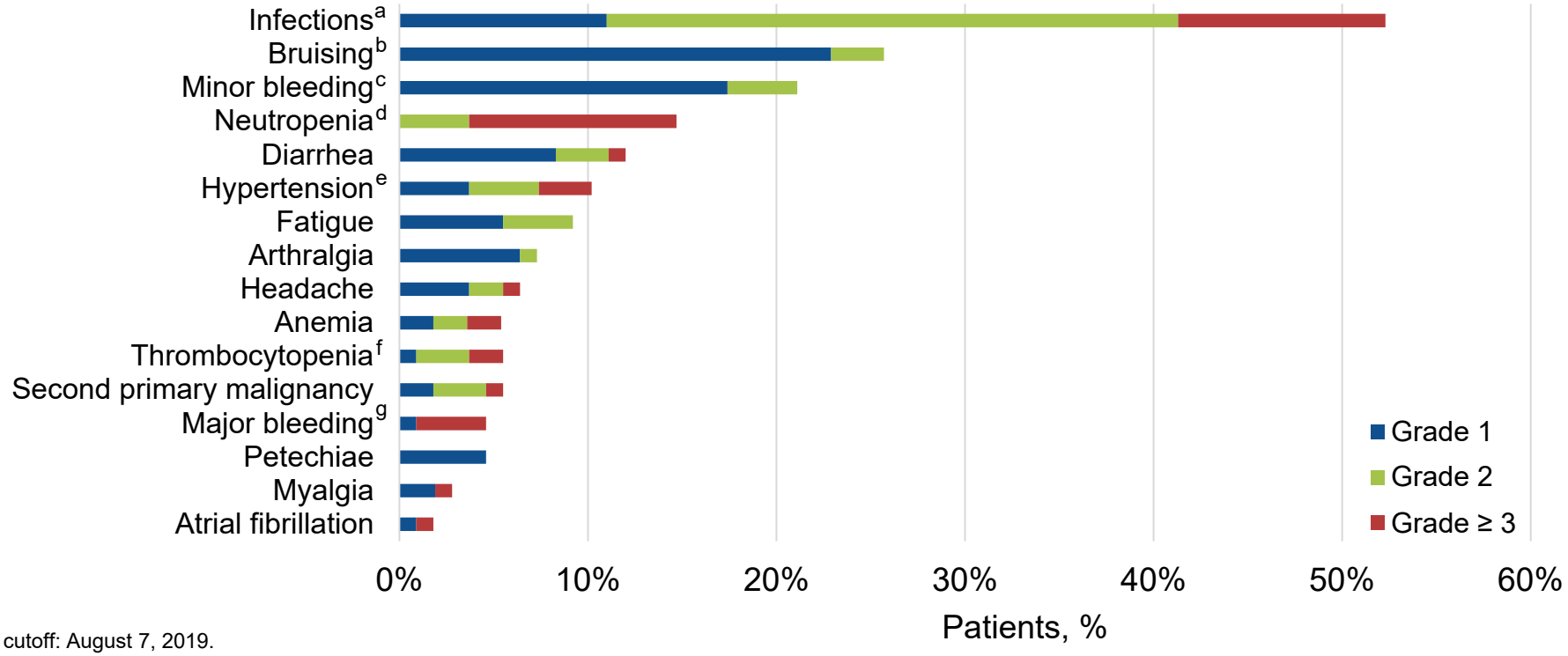
Data cutoff: August 7, 2019.

Summary of Grade ≥ 3 and Serious Adverse Events

Events, n (%)	n = 109
Patients with Grade ≥ 3 AE	40 (36.7)
Grade ≥ 3 AEs that occurred in > 2 patients	
Neutropenia/decreased neutrophil count	11 (10.1)
Pneumonia	4 (3.7)
Hypertension	3 (2.8)
Serious AE	26 (23.9)
Treatment discontinuation due to AE[a]	3 (0.9)
Grade 5 AE[b]	1 (0.9)

Data cutoff: August 7, 2019.
AE, adverse event
[a] Malignant pleural effusion in the context of suspected transformation, tumor pain/peripheral edema in the context of Richter transformation, pneumonia leading to sepsis and death. [b] Pneumonia leading to sepsis and death, which also led to treatment discontinuation..

Key Adverse Events of Interest
Pooled Term Analysis



Data cutoff: August 7, 2019.

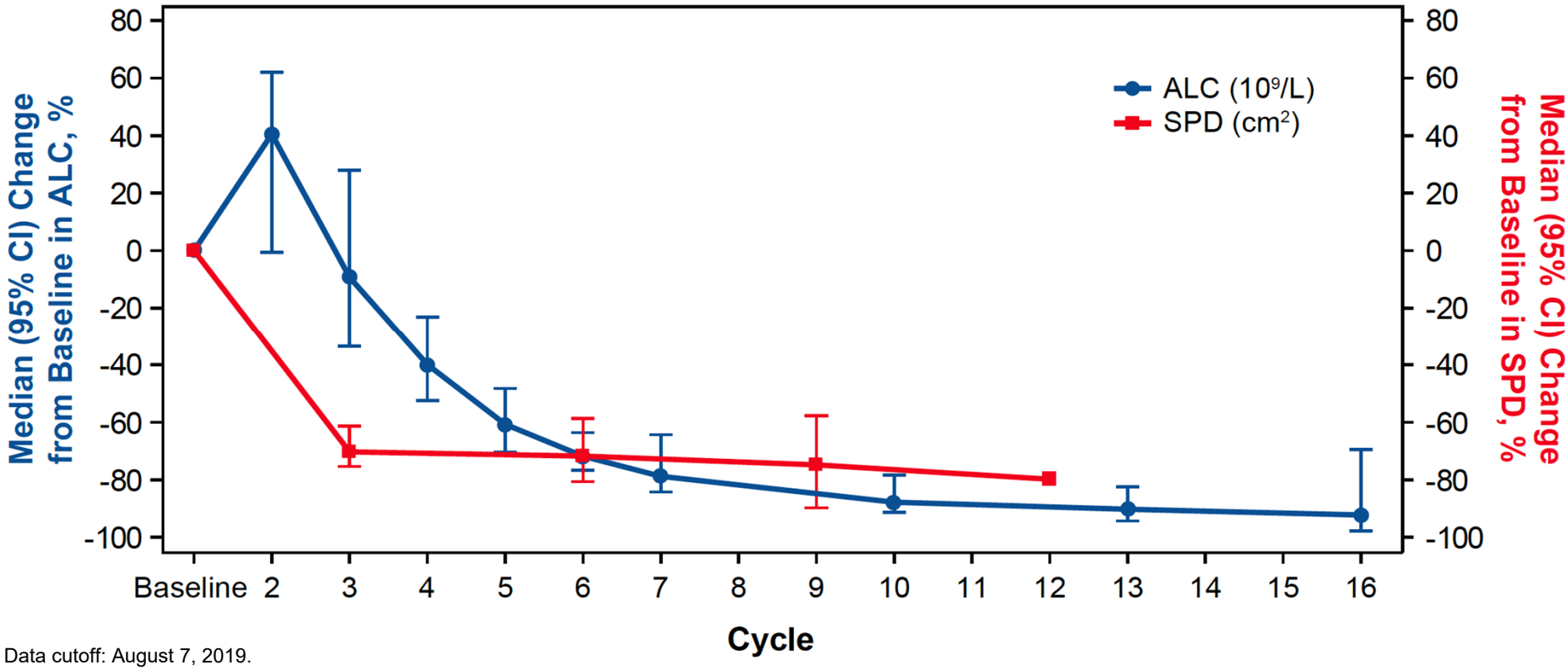
[a]All infection terms pooled. [b]Purpura, contusion, ecchymosis, or increased tendency to bruise. [c]Pooled term of bleeding not included in bruising petechiae, or major bleeding. [d]Neutropenia, neutrophil count decreased, or febrile neutropenia. [e]Hypertension, blood pressure increased, or hypertensive crisis. [f]Thrombocytopenia or platelet count decreased. [g]Grade ≥ 3 hemorrhage, serious hemorrhage, or central nervous system hemorrhage of any grade were pooled. No central nervous system hemorrhage was reported.

Best Overall Response
Investigator Assessment

Best Response, n (%)	n = 109
ORR (CR, PR, or PR-L), n (%) [95% CI][a]	**101 (92.7) [86.0-96.8]**
CR	2 (1.9)
PR	86 (78.9)
PR-L	13 (11.9)
SD	6 (5.6)
PD	1 (0.9)
Data Pending[b]	1 (0.9)
Months to response, PR-L or higher, median (range)	2.79 (1.9-11.0)
Months to response, PR or higher, median (range)	2.81 (1.9-11.1)
Duration of response ≥ 6 mo, % [95% CI][a]	95 [88-98]

Data cutoff: August 7, 2019.
[a]2-sided Clopper-Pearson 95% confidence intervals.
[b]Patient missed first 2 response assessments due to injury and inability to undergo imaging. After data cutoff, best response assessment was reported as PR.
CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease.

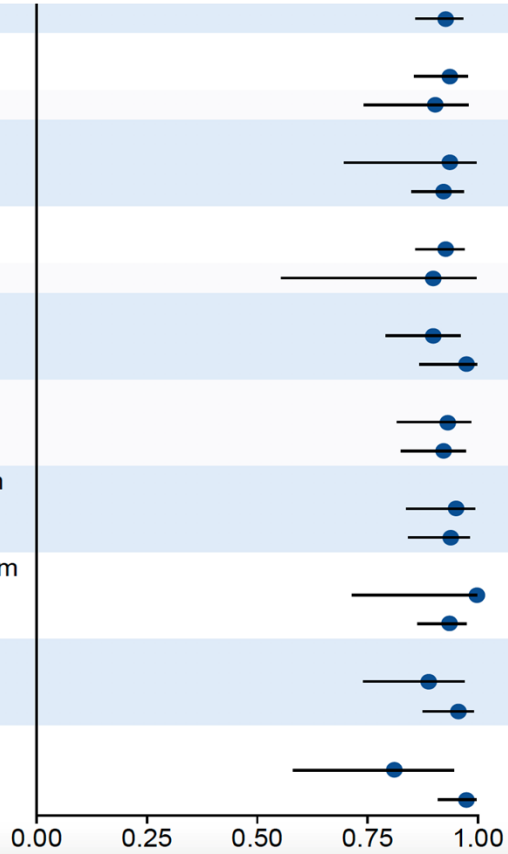
Change in Lymphocyte Count and Target Lesion Size



Data cutoff: August 7, 2019.
Cycle length is 28 days; 2-sided Clopper-Pearson 95% confidence internals are used.
ALC, absolute lymphocyte count (data collected on the first day of the indicated cycle); SPD, sum of the perpendicular diameters (imaging data collected during the indicated cycle for patients with measurable disease).

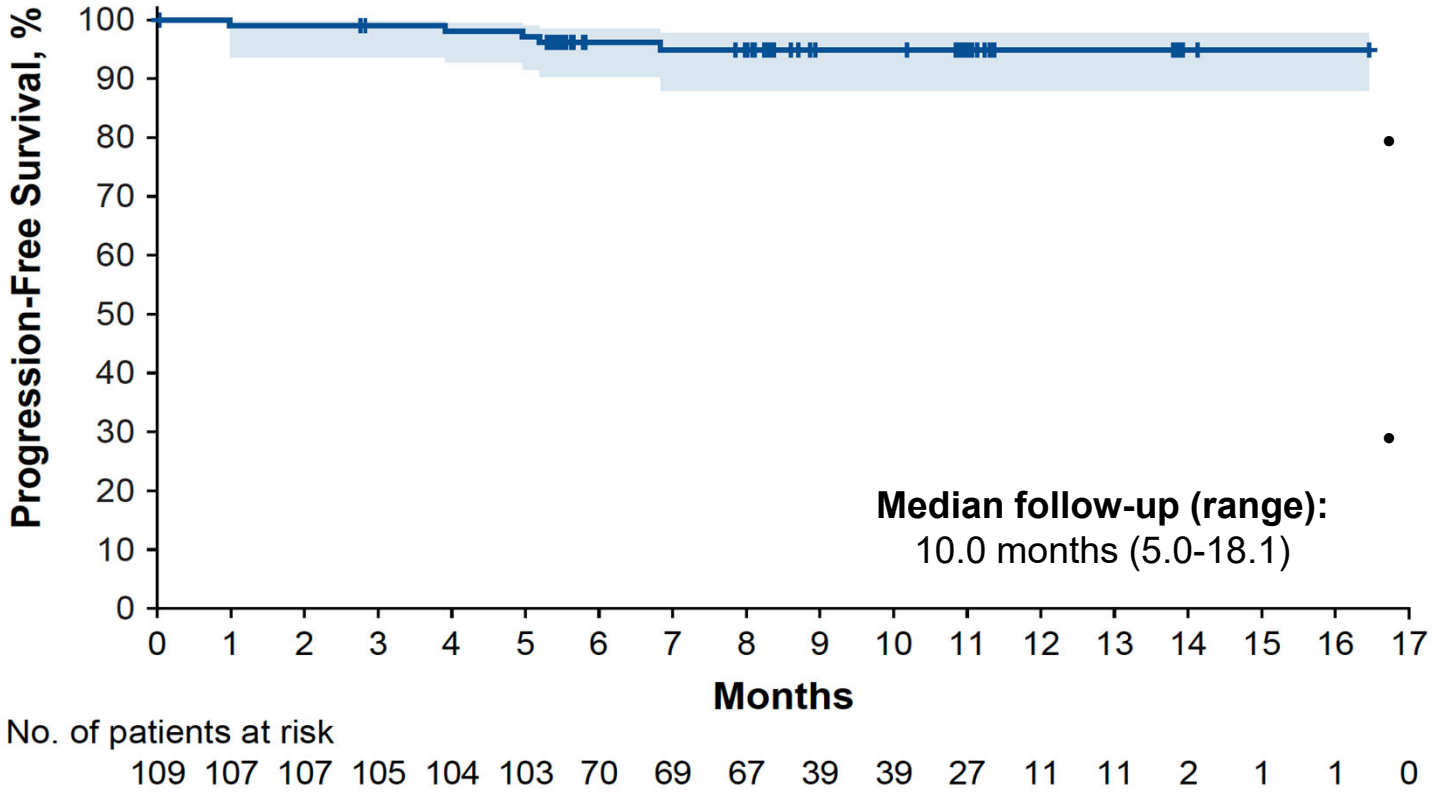
Subgroup Analysis of Overall Response Rate

Subgroup	Response/Patients	ORR (95% CI)
All patients	101/109	0.93 (0.86-0.97)
Sex		
Male	73/78	0.94 (0.86-0.98)
Female	28/31	0.90 (0.74-0.98)
Age group		
< 65	15/16	0.94 (0.70-1.00)
≥ 65	86/93	0.92 (0.85-0.97)
Cancer type		
CLL	92/99	0.93 (0.86-0.97)
SLL	9/10	0.90 (0.55-1.00)
Binet stage for CLL		
Stage A or B	53/59	0.90 (0.79-0.96)
Stage C	39/40	0.98 (0.87-1.00)
ECOG PS		
0	42/45	0.93 (0.82-0.99)
≥ 1	59/64	0.92 (0.83-0.97)
Bulky disease with any target lesion LDi ≥ 5 cm		
Yes	40/42	0.95 (0.84-0.99)
No	61/67	0.91 (0.82-0.97)
Bulky disease with any target lesion LDi ≥ 10 cm		
Yes	11/11	1.00 (0.72-1.00)
No	90/98	0.92 (0.85-0.96)
IGHV mutational status		
Mutated	32/36	0.89 (0.74-0.97)
Unmutated	64/67	0.96 (0.87-0.99)
Serum beta 2 microglobulin		
≤ 3.5 mg/L	17/21	0.81 (0.58-0.95)
> 3.5 mg/L	75/77	0.97 (0.91-1.00)



Data cutoff: August 7, 2019.
2-sided Clopper-Pearson 95% confidence internals are used.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDi, longest diameter.

Progression-Free Survival
Investigator Assessment



- 4 patients had investigator-reported progression of disease (1 confirmed RT, 3 suspected RT)
- One patient died due to AE (grade 5 pneumonia)

Data cutoff: August 7, 2019. Shaded area indicates the 95% CI.
AE, adverse event; PD, progressive disease; RT, Richter's transformation.

Summary

- In this prospective cohort of 109 patients with del(17p) treatment-naïve CLL/SLL with a median follow-up of 10 months, zanubrutinib demonstrated an overall response rate of 92.7%

- Zanubrutinib tolerability was generally consistent with previous reports of zanubrutinib treatment in patients with various B-cell malignancies[1]

- Updated results from a separate ongoing phase 1/2 study of zanubrutinib in patients with treatment-naïve and relapsed/refractory CLL/SLL will also be presented in this oral session[2]

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ORR, overall response rate.

1. Tam C, et al. ICML 2019, Abstract 191. 2. Cull G, et al. ASH 2019, Abstract 500.

Acknowledgements

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