Zanubrutinib monotherapy for patients with treatment-naïve chronic lymphocytic leukemia and 17p deletion

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Adverse Events of Interest: Categories and Corresponding Search Criteria

AEI Category	Search Criteria
Bruising	Purpura PT, contusion PT, ecchymosis PT, increased tendency to bruise PT
Major bleeding	• Subdural hematoma PT or subdural hemorrhage PT • All hemorrhage PTs if AE SOC is "nervous system disorders" • Any serious or grade ≥ 3 hemorrhage PT if AE SOC is not "nervous system disorders"
Minor bleeding	Hemorrhage terms (excluding laboratory terms) (SMQ) Narrow, except for PTs in Bruising category, Major bleeding category, and petechiae
Atrial fibrillation and flutter	Atrial fibrillation PT, atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Other malignancies Skin cancers	Malignant Tumors (SMQ) Narrow Subcategory - skin cancers: skin malignant tumors (SMQ) Narrow
Infection Pneumonia Opportunistic infections	Infections: Infections and infestations SOC Subcategory – Pneumonia (SMQ) Narrow Subcategory – Opportunistic infections (SMQ) Narrow
Neutropenia	Neutropenia PT, neutrophil count decreased PT, febrile neutropenia PT, agranulocytosis PT, neutropenic infection PT, neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, platelet count decreased PT
Anemia	Anemia PT, hemoglobin decreased PT
Diarrhea	Diarrhea PT, diarrhea infectious PT, *Clostridium difficile* colitis PT, diarrhea hemorrhagic PT

AEI, adverse event of interest; CMQ, Company MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, Standardized MedDRA Query; SOC, system organ class.

Supplemental Table 2. Listing of Sites and Investigators by Number of Patients Enrolled

Site	PI	Country	Patients Enrolled
Peninsula Private Hospital	Walker, Patricia	Australia	6
St Vincent's Hospital	Tam, Constantine	Australia	6
Calvary Mater Hospital	Janowski, Wojciech	Australia	5
North Shore Hospital	Simpson, David	New Zealand	5
Fred Hutchinson Cancer Research Center	Shadman, Mazyar	United States	4
Peter MacCallum Cancer Centre	Tam, Constantine	Australia	4
AUSL Ravenna	Tani, Monica	Italy	3
Christchurch Hospital/Canterbury Health	Ganly, Peter	New Zealand	3
Concord Hospital	Verner, Emma	Australia	3
Copernicus Podmiot Leczniczy Sp. z o.o. Wojewódzkie Centrum Onkologii	Ciepluch, Hanna	Poland	3
Dana Farber Cancer Institute	Brown, Jennifer	United States	3
Monash Health	Opat, Stephen	Australia	3
Universitario Agostino Gemelli	Laurenti, Luca	Italy	3
Azienda Socio Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda	Tedeschi, Alessandra	Italy	2
University Hospital Hradec Kralove	Simkovic, Martin	Czech Republic	2
Russian Research Institute of Hematology and Transfusiology	Voloshin, Sergey	Russia	2
Karolinska Universitetssjukhuset	Osterborg, Anders	Sweden	2
Ordensklinikum Linz GmbH	Petzer, Andreas	Austria	2
Palmerston North Hospital	Baker, Bartrum	New Zealand	2
Royal Hobart Hospital	Harrup, Rosemary	Australia	2
Sahlgrenska University Hospital	Lewerin, Catharina	Sweden	2
Tauranga Hospital	Corbett, Gillian	New Zealand	2
Leeds Teaching Hospitals	Hillmen, Peter	United Kingdom	2
Uppsala University Hospital	Mattsson, Mattias	Sweden	2
Vseobecna fakultni nemocnice v Praze	Trneny, Marek	Czech Republic	2
University Hospital Southampton	Forconi, Francesco	United Kingdom	1
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia	Motta, Marina	Italy	1
Box Hill Hospital	Ting, Stephen	Australia	1
Cambridge Hospitals	Follows, George	United Kingdom	1
Centre Henri-Becquerel	Lepretre, Stephane	France	1
Centre Hospitalier Le Mans	Laribi, Kamel	France	1
Clinique Saint-Pierre	Connerotte, Thierry	Belgium	1
Fakultní nemocnice Olomouc	Papajik, Tomas	Czech Republic	1

N.N. Blokhin National Medical Research Center for Oncology	Tumyan, Gayane	Russia	1
Hopital Pontchaillou CHU	De Guibert, Sophie	France	1
Hospitalier du Haut Leveque	Dilhuydy, Marie-Sarah	France	1
Insitut d'Hématologie de Basse Normandie	Vilque, Jean-Pierre	France	1
Joe Arrington Cancer Research and Treatment Center	Quick, Donald	United States	1
Kent and Canterbury Hospital	Young, Moya	United Kingdom	1
Landeskrankenhaus Salzburg	Greil, Richard	Austria	1
Malopolskie Centrum Medyczne S.C.	Jurczak, Wojciech	Poland	1
Medizinische Universitaetsklinik Innsbruck	Wolf, Dominik	Austria	1
Mount Sinai School of Medicine	Shulman, Jonah	United States	1
National Taiwan University Hospital	Cheng, Chieh-Lung	Chinese Taipei	1
The Tweed Hospital	Sia, Hanlon	Australia	1
Oregon Health and Science University	Danilov, Alexei	United States	1
Ospedale San Raffaele	Ghia, Paolo	Italy	1
Plymouth Hospitals	Hutchinson, Claire	United Kingdom	1
Princess Alexandra Hospital	Marlton, Paula	Australia	1
Regional Clinical Hospital	Pristupa, Alexander	Russia	1
Royal Brisbane and Women's Hospital	Weber, Nicholas	Australia	1
Skånes Universitetssjukhus	Juliusson, Gunnar	Sweden	1
Sunderby Sjukhus	Lauri, Birgitta	Sweden	1
Sverdlovsk Regional Clinical Hospital # 1	Konstantinova, Tatiana	Russia	1
Tennessee Oncology	Flinn, Ian	United States	1
The Royal Marsden	Iyengar, Sunil	United Kingdom	1
Tula Regional Clinical Hospital	Volodicheva, Elena	Russia	1
University of Virginia Health System	Portell, Craig	United States	1
Wojewódzkie Wielospecjalistyczne Centrum Onkologii i Traumatologii im. M. Kopernika w Lodzi	Robak, Tadeusz	Poland	1

Supplemental Table 3. Sustained Hematologic Improvement

Sustained Improvements by Laboratory Parameter, n (%)[a]	
Absolute Neutrophil Count[b]	6/8 (75.0)
Hemoglobin[c]	37/43 (86.0)
Platelet count[d]	24/28 (85.7)

[a]Percentages calculated as percent of patients with the particular cytopenia at baseline. Cytopenia was defined as follows: anemia (≤ 110 g/L), thrombocytopenia (≤ 100 x 10^9/L), or neutropenia (≤ 1.5 x 10^9/L).
[b]Sustained improvement in absolute neutrophil count is defined as an increase to at least 1.5 × 10^9/L or increase of at least 50% over baseline, maintained for at least 56 days without growth factors during this period.
[c]Sustained improvement in hemoglobin defined as an increase of 20 g/L over baseline and maintained for at least 56 days without blood transfusion or growth factors during this period.
[d]Sustained improvement in platelet count is defined an increase to at least 100 × 10^9/L or an increase of at least 50% over baseline, maintained for at least 56 days without blood transfusion or growth factors during this period.

Supplemental Table 4. Disease Characteristics and Best Overall Response by del(17p) Frequency

Patients, n (%)	**del(17p) Result > 7% - < 20%**	**del(17p) Result ≥ 20%**
	59/109 (54.1)	50/109 (45.9)
Disease Characteristics		
Age, median (range), y	70.0 (42 – 84)	70.0 (45 – 86)
ECOG PS of 2, n (%)	6 (10.2)	8 (16)
Months since diagnosis, median (Q1 - Q3)	24.28 (8.28 – 51.22)	17.12 (5.39 – 56.21)
Binet stage C for patients with CLL, n (%)	20 (37.0)	20 (44.4)
β2-microglobulin[a] > 3.5 g/dL, n (%)	42/55 (76.3)	36/44 (81.8)
IGHV mutational[b] status		
Mutated	24/55 (43.6)	12/48 (25.0)
Unmutated[c]	31/55 (56.4)	36/48 (75.0)
Bulky disease[d], n (%) Any TL LDi ≥ 5 cm Any TL LDi ≥ 10 cm	 27 (45.8) 6 (10.2)	 15 (30.0) 5 (10.0)
Cytopenia present,[e] n (%)	34 (57.6)	27 (54.0)
Karyotype status, [f] n (%) Non-Complex (0 to 2 abnormalities) Complex (3 or more abnormalities)	 38/49 (77.6) 11/49 (22.4)	 16/37 (43.2) 21/37 (56.8)
Best response, n (%)		
ORR (CR, PR, or PR-L), n (%) [95% CI][g]	54 (92) [81 – 97]	49 (98) [89 – 100]
CR/CRi	1/59 (1.7)	3/50 (6.0)
PR	51/59 (86.4)	44/50 (88.0)
PR-L	2/59 (3.4)	2/50 (4.0)
SD	4/59 (6.8)	1/50 (2.0)
PD	1/59 (1.7)	0/50 (0.0)
Estimated 12-month PFS, % [95% CI][g]	95 [85 – 98]	94 [83 – 98]
Estimated 18-month PFS, % [95% CI][g]	88 [72 – 95]	89 [76 – 95]

CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; LDi, longest diameter; ORR, overall response rate; PD, progressive disease, PFS, progression-free survival, PR, partial response, PR-L, PR with lymphocytosis; SD, stable disease; TL, target lesion.

[a]10 patients had missing data.

[b]RNA quantity/quality not sufficient for PCR amplification of VH region for sequencing.

[c]Chi-square test for statistical significance; $P = 0.0478$.

[d]Patients with any target lesion with longest diameter presented.

[e]Patients with anemia (≤ 110 g/L), thrombocytopenia (≤ 100 x 10^9/L), or neutropenia (≤ 1.5 x 10^9/L)

[f]10 and 13 patients had insufficient metaphases available for analysis in the del(17p) result >7%-< 20% and del(17p) result ≥ 20% categories, respectively.

[g]Two-sided Clopper-Pearson 95% CIs.

Supplemental Table 5. Adverse Events of Interest Grouped by Category

Category	Grade 1/2	Grade 3 or Higher	All Grades
	n (%)		
Hematologic			
Neutropenia	5 (4.6)	15 (13.8)	20 (18.3)
Thrombocytopenia	6 (5.5)	1 (0.9)	7 (6.4)
Anemia	4 (3.7)	0 (0)	4 (3.7)
Nonhematologic			
Infections	55 (50.5)	15 (13.8)	70 (64.2)
Minor Bleeding	29 (26.6)	0 (0)	29 (26.6)
Bruising	27 (24.8)	0 (0)	27 (24.8)
Diarrhea	16 (14.7)	1 (0.9)	17 (15.6)
Nausea	15 (13.8)	0 (0)	15 (13.8)
Arthralgia	12 (11.0)	0 (0)	12 (11.0)
Fatigue	10 (9.2)	1 (0.9)	11 (10.1)
Dermatologic malignancies	8 (7.3)	2 (1.8)	10 (9.2)
Headache	8 (7.3)	1 (0.9)	9 (8.3)
Hypertension	6 (5.5)	3 (2.8)	9 (8.3)
Major bleeding	1 (0.9)	5 (4.6)	6 (5.5)
Other non-dermatologic malignancies	0 (0)	5 (4.6)	5 (4.6)
Myalgia	4 (3.7)	1 (0.9)	5 (4.6)
Atrial fibrillation and flutter	1 (0.9)	2 (1.8)	3 (2.8)

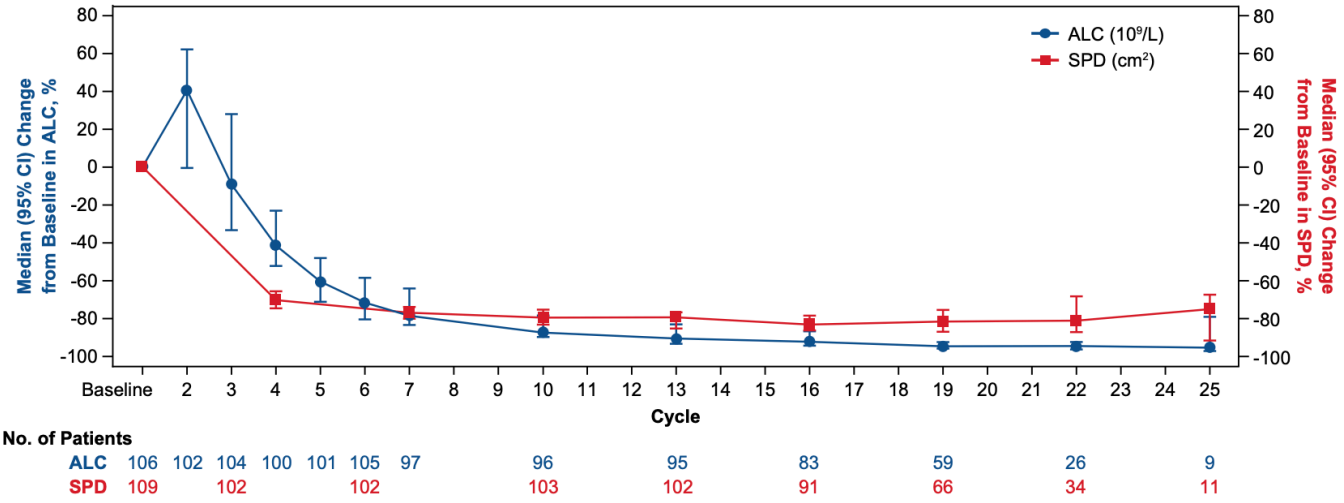
Supplemental Table 6. Description of Major Bleeding Adverse Events

Patient Characteristics	Adverse Event and CTCAE Toxicity Grade	Study Day Start and End of AE	SAE?	AE Relationship per Investigator	Confounding Factors
78 years Male	Pericholecystic hematoma, grade 3	292 – 295	Yes	Not related	Occurred in the setting of cholecystitis and coadministration of apixaban and heparin for 4 days prior to event given for atrial fibrillation. Last dose of study drug prior to event was given on study day 277.
72 years Female	Postoperative hemorrhage, grade 3	334 – 345	Yes	Not related	Occurred in the setting of removal of a melanoma lesion of the skin. Study drug was not held until day of event.
42 years Male	Epistaxis, grade 3	2 – 4	Yes	Not related	
78 years Male	Purpura, grade 1	16 – 43	Yes	Related	Occurred in the setting of mechanical fall and resultant hospitalization. AE was deemed serious due to hospitalization. Patient was on concurrent aspirin at time of event.
73 years Male	Macrohematuria, grade 3	201 – 201	No	Not related	Occurred in the setting of a transurethral resection of prostate gland. Study drug was not held until day of event. Patient was on concurrent aspirin at time of event.
72 years Male	Haematuria, grade 3	107 – 121	No	Not related	

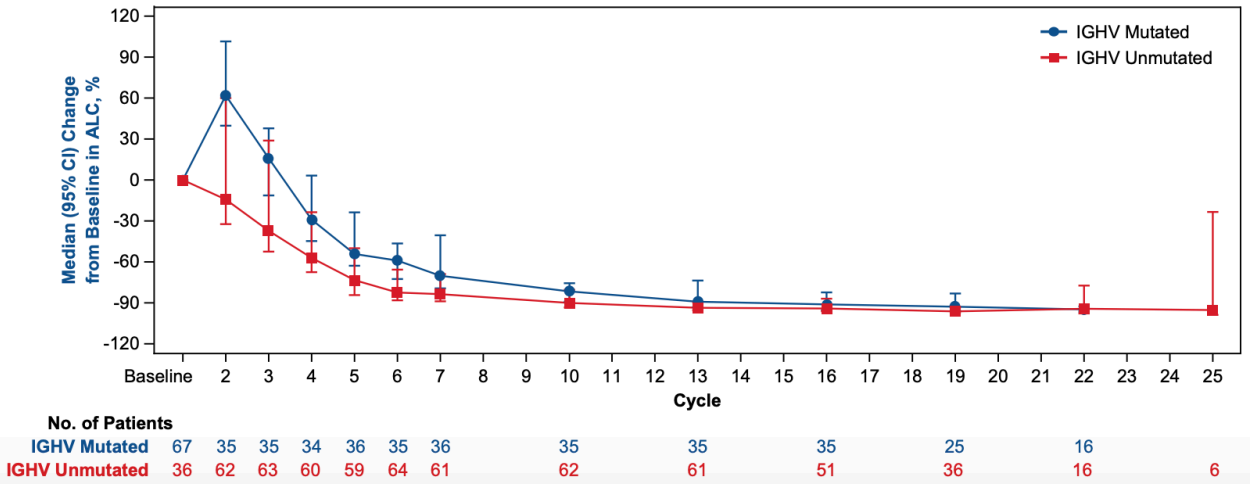
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious AE.

Supplemental Figure 1.

A. Change in ALC and SPD over time with zanubrutinib treatment. Graph plotted as median change from baseline ALC in red and baseline SPD in blue. Data points represent all data collected during the treatment cycle of 28 days. Bars represent 1 standard deviation; numbers represent individual patient data generated during each timepoint.



B. Effect of IGHV status on change in ALC over time with zanubrutinib treatment. Graph plotted as median change from baseline ALC of patients with IGHV mutated status in blue and IGHV unmutated status in red. Data points represent all data collected during the treatment cycle of 28 days. Bars represent 1 standard deviation; numbers represent individual patient data generated during each timepoint.



ALC, absolute lymphocyte count; SPD, sum of the products of lymph node diameters.