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            | Malignant Tumors (SMQ) Narrow  
                                Subcategory - skin cancers: skin malignant tumors (SMQ) Narrow                                                                               |
| Skin cancers                  |                                                                                                                                                   |
| Infection                     | Infections: Infections and infestations SOC  
                                Subcategory – Pneumonia (SMQ) Narrow  
                                Subcategory – Opportunistic infections (SMQ) Narrow                                                                                     |
| Pneumonia                     |                                                                                                                                                   |
| Opportunistic infections      |                                                                                                                                                   |
| 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, Peter                      | Australia        | 3                 |
| Copernicus Podmiot Leczniczy Sp. z o.o. Wojewódzkie Centrum Onkologi | 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                             | Leverin, 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                 |
| Vseobecná fakultní 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                 |
| Hospital Name                                                   | Name               | Country     | Code |
|----------------------------------------------------------------|--------------------|-------------|------|
| 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                                    | Juliussen, 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 Wielospecialistyczne Centrum Onkologii i Traumatologii im. M. Kopernika w Lodz | Robak, Tadeusz   | Poland      | 1    |
**Supplemental Table 3. Sustained Hematologic Improvement**

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

<sup>a</sup>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).

<sup>b</sup>Sustained improvement in absolute neutrophil count is defined as an increase to at least 1.5 x 10^9/L or increase of at least 50% over baseline, maintained for at least 56 days without growth factors during this period.

<sup>c</sup>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.

<sup>d</sup>Sustained improvement in platelet count is defined an increase to at least 100 x 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

| Characteristics                          | del(17p) Result > 7% - < 20% | del(17p) Result ≥ 20% |
|-----------------------------------------|-----------------------------|------------------------|
| 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<sup>a</sup> > 3.5 g/dL, n (%) | 42/55 (76.3)              | 36/44 (81.8)           |
| IGHV mutational<sup>b</sup> status      |                             |                        |
| Mutated                                 | 24/55 (43.6)                | 12/48 (25.0)           |
| Unmutated                               | 31/55 (56.4)                | 36/48 (75.0)           |
| Bulky disease<sup>d</sup>, n (%)        |                             |                        |
| Any TL LDi ≥ 5 cm                       | 27 (45.8)                   | 15 (30.0)              |
| Any TL LDi ≥ 10 cm                      | 6 (10.2)                    | 5 (10.0)               |
| Cytopenia present,<sup>e</sup> n (%)    | 34 (57.6)                   | 27 (54.0)              |
| Karyotype status,<sup>f</sup> n (%)     |                             |                        |
| Non-Complex (0 to 2 abnormalities)      | 38/49 (77.6)                | 16/37 (43.2)           |
| Complex (3 or more abnormalities)       | 11/49 (22.4)                | 21/37 (56.8)           |

### Best response, n (%)

| Response, n (%) | del(17p) Result > 7% - < 20% | del(17p) Result ≥ 20% |
|----------------|-------------------------------|-----------------------|
| ORR (CR, PR, or PR-L), n (%) [95% CI]<sup>g</sup> | 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]<sup>g</sup> | 95 [85 – 98] | 94 [83 – 98] |
| Estimated 18-month PFS, % [95% CI]<sup>g</sup> | 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.

<sup>a</sup>10 patients had missing data.

<sup>b</sup>RNA quantity/quality not sufficient for PCR amplification of VH region for sequencing.

<sup>c</sup>Chi-square test for statistical significance; P = 0.0478.

<sup>d</sup>Patients with any target lesion with longest diameter presented.

<sup>e</sup>Patients with anemia (≤ 110 g/L), thrombocytopenia (≤ 100 x 10<sup>9</sup>/L), or neutropenia (≤ 1.5 x 10<sup>9</sup>/L).

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

<sup>g</sup>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 (%)     |                   | 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.