**Supplemental Table 1. Baseline demographic and disease characteristics**

| Characteristic                                      | N = 86 |
|------------------------------------------------------|--------|
| Sex, n (%)                                           |        |
| Male                                                 | 67 (77.9) |
| Female                                               | 19 (22.1) |
| Race, n (%)                                          |        |
| Chinese                                              | 86 (100) |
| Age, years                                           |        |
| Median (range)                                       | 61 (34–75) |
| ≥65 years, n (%)                                     | 22 (25.6) |
| ECOG performance status, n (%)                       |        |
| 0/1                                                   | 82 (95.3) |
| 2                                                     | 4 (4.7) |
| Patients with prior systemic therapies, n (%)         | 86 (100.0) |
| Median (range) number of prior therapies              | 2.0 (1–4) |
| ≥3 prior therapies, n (%)                            | 29 (33.7) |
| Prior regimens<sup>a</sup>, n (%)                    |        |
| Patients with ≥ 1 rituximab-containing regimen       | 64 (74.4) |
| R-CHOP, R-CHOP-like                                  | 46 (53.5) |
| CHOP, CHOP-like                                      | 31 (36.0) |
| High-dose cytarabine-containing regimen<sup>b</sup>   | 33 (38.4) |
| (R) hyperCVAD (A)/EPOCH                              | 23 (26.7) |
| Lenalidomide                                         | 12 (14.0) |
| Bortezomib                                           | 7 (8.1) |
| Stem cell transplant                                 | 3 (3.5) |
| Blastoid histology                                   | 12 (14) |
| Bulky disease                                        |        |
| >5 cm tumor mass, n (%)                              | 37 (43) |
| Extranodal disease                                   |        |
| Bone marrow involvement                              | 39 (45.3) |
| Gastrointestinal involvement                         | 15 (17.4) |
| MIPI-b, n (%)<sup>f</sup>                            |        |
| Low risk                                             | 12 (14.0) |
| Intermediate risk                                    | 39 (45.3) |
| High risk                                            | 33 (38.4) |
| Missing                                              | 2 (2.3) |
| Characteristic                          | N = 86 |
|---------------------------------------|--------|
| Refractory disease<sup>d</sup>        | 45 (52.3) |
| TP53-mutated (N = 54)<sup>e</sup>     | 15 (27.8) |

CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin and dexamethasone; MIPI-b, Combined Biologic Mantle-Cell Lymphoma International Prognostic Index; (R), (rituximab); R-CHOP, rituximab plus CHOP.

Percentages may not add up to 100% because of rounding.

<sup>a</sup>Categories are not mutually exclusive as patients may be included under multiple regimens.

<sup>b</sup>High-dose cytarabine-containing regimens included dexamethasone, cytarabine and cisplatin (DHAP; etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP); methotrexate and cytarabine (HyperCVAD B); cyclophosphamide, etoposide, cytarabine, methylprednisolone, vincristine, nedaplatin (CDEADP).

<sup>c</sup>MIPI-b score was derived with the use of four baseline clinical prognostic factors (age, ECOG performance status, lactate dehydrogenase level, and white blood cell count) plus percent Ki-67 expression in tumor cells, and its range depends on the range of these characteristics.<sup>44,45</sup> The index classifies patients as having low-, intermediate-, or high-risk disease, as defined by scores of <5.7, ≥5.7 to <6.5 and ≥6.5, respectively.

<sup>d</sup>Refractory disease was defined as the lack of at least a partial response to the last therapy before study entry, as assessed by the investigator.

<sup>e</sup>54 patients had baseline sequencing. For the remaining patients, 21 did not provide consent, 9 lacked adequate tumor tissue, and for 2, the assay failed at the library preparation step.
**Supplemental Table 2. Efficacy outcomes by subgroup**

| Efficacy outcome | Bulky tumor, LDi ≤10 cm (n = 79) | Bulky tumor, LDi >10 cm (n = 7) |
|------------------|----------------------------------|---------------------------------|
| ORR, % (95% CI)  | 84.8 (75.0–91.9)                 | 71.4 (29.0–96.3)                |
| CR, % (95% CI)   | 78.5 (67.8–86.9)                 | 71.4 (29.0–96.3)                |
| Median DOR, months (95% CI) | NE (24.0–NE) | NE (10.2–NE) |
| Median PFS, months (95% CI) | 27.8 (18.9–NE) | NE (0.9–NE) |
| 36-month OS, % (95% CI) | 74.2 (62.4–82.7) | 83.3 (27.3–97.5) |

| Prior lines of therapy <3 (n = 57) | Prior lines of therapy ≥3 (n = 29) |
|------------------------------------|-----------------------------------|
| ORR, % (95% CI)                    | 89.5 (78.50–96.0)                 | 72.4 (52.8–87.3) |
| CR, % (95% CI)                     | 84.2 (72.1–92.5)                 | 65.5 (45.7–82.1) |
| Median DOR, months (95% CI)        | NE (24.9–NE)                     | 25.1 (16.2–NE) |
| Median PFS, months (95% CI)        | NE (19.4–NE)                     | 22.1 (5.4–33.1) |
| 36-month OS, % (95% CI)            | 79.6 (66.1–88.2)                 | 64.7 (42.7–80.0) |

| Ki67 ≤30% (n = 50) | Ki67 >30% (n = 34) |
|--------------------|--------------------|
| ORR, % (95% CI)    | 94.0 (83.5–98.7)   | 70.6 (52.5–84.9) |
| CR, % (95% CI)     | 90.0 (78.2–96.7)   | 61.8 (43.6–77.8) |
| Median DOR, months (95% CI) | NE (NE–NE) | 16.3 (13.7–30.2) |
| Median PFS, months (95% CI) | NE (NE–NE) | 16.6 (5.3–19.4) |
| 36-month OS, % (95% CI) | 87.0 (73.3–94.0) | 55.6 (36.5–71.1) |

| Low-/intermediate-risk MIPI-b (n = 51) | High-risk MIPI-b (n = 33) |
|----------------------------------------|---------------------------|
| ORR, % (95% CI)                        | 94.1 (83.8–98.8)          | 69.7 (51.3–84.4) |
| CR, % (95% CI)                         | 88.2 (76.1–95.6)         | 63.6 (45.1–79.6) |
| Median DOR, months (95% CI)            | NE (25.1–NE)              | 16.5 (5.8–NE) |
| Median PFS, months (95% CI)            | NE (27.8–NE)              | 9.1 (5.3–26.5) |
| 36-month OS, % (95% CI)                | 85.2 (71.5–92.7)         | 58.0 (38.6–73.3) |

CI, confidence interval; CR, complete response; DOR, duration of response; LDi, longest transverse diameter of a lesion; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
### Supplemental Table 3: Adverse Events of Interest Reported in >1 Patient

| AESI category | Preferred term                                      | N = 86 | Any grade | Grade 3 or higher |
|---------------|-----------------------------------------------------|--------|-----------|-------------------|
|               | **Patients with at least 1 AEI**                   | 76 (88.4) | 34 (39.5) |                   |
|               | **Infections**                                      | 56 (65.1) | 16 (18.6) |                   |
|               | Upper respiratory tract infection                   | 33 (38.4) | 1 (1.2)   |                   |
|               | Pneumonia                                           | 14 (16.3) | 11 (12.8) |                   |
|               | Urinary tract infection                             | 10 (11.6) | 1 (1.2)   |                   |
|               | Nasopharyngitis                                     | 5 (5.8)   | 0 (0.0)   |                   |
|               | Asymptomatic bacteriuria                            | 4 (4.7)   | 0 (0.0)   |                   |
|               | Otitis media                                         | 4 (4.7)   | 0 (0.0)   |                   |
|               | Pharyngitis                                         | 4 (4.7)   | 0 (0.0)   |                   |
|               | Folliculitis                                         | 3 (3.5)   | 0 (0.0)   |                   |
|               | Bronchitis                                           | 2 (2.3)   | 1 (1.2)   |                   |
|               | Influenza                                            | 2 (2.3)   | 0 (0.0)   |                   |
|               | **Neutropenia**                                      | 43 (50.0) | 17 (19.8) |                   |
|               | Neutrophil count decreased                           | 40 (46.5) | 16 (18.6) |                   |
|               | Neutropenia                                         | 7 (8.1)   | 1 (1.2)   |                   |
|               | **Thrombocytopenia**                                 | 34 (39.5) | 6 (7.0)    |                   |
|               | Platelet count decreased                             | 28 (32.6) | 6 (7.0)    |                   |
|               | Thrombocytopenia                                     | 8 (9.3)   | 0 (0.0)   |                   |
|               | Hemorrhage (including minor bleeds involving mucous membranes and skin) | 31 (36.0) | 1 (1.2)   |                   |
|               | Blood urine present                                  | 11 (12.8) | 0 (0.0)   |                   |
|               | Hematuria                                            | 6 (7.0)   | 0 (0.0)   |                   |
|               | Petechia/purpura/contusion                           | 5 (5.8)   | 0 (0.0)   |                   |
|               | Epistaxis                                            | 3 (3.5)   | 0 (0.0)   |                   |
|               | Hemorrhage subcutaneous                              | 3 (3.5)   | 0 (0.0)   |                   |
|               | Upper gastrointestinal hemorrhage                    | 3 (3.5)   | 0 (0.0)   |                   |
|               | Contusion                                             | 2 (2.3)   | 0 (0.0)   |                   |
|               | Ecchymosis                                           | 2 (2.3)   | 0 (0.0)   |                   |
|               | Hemoptysis                                           | 2 (2.3)   | 0 (0.0)   |                   |
|               | Purpura                                               | 2 (2.3)   | 0 (0.0)   |                   |
| AESI category Preferred term       | N = 86 n (%)                      |
|-----------------------------------|----------------------------------|
|                                  | Any grade | Grade 3 or higher |
| Anemia                           | 15 (17.4) | 5 (5.8)           |
| Anemia                           | 15 (17.4) | 5 (5.8)           |
| Hypertension                     | 14 (16.3) | 3 (3.5)           |
| Hypertension                     | 13 (15.1) | 3 (3.5)           |
| Blood pressure increased         | 2 (2.3)   | 1 (1.2)           |
| Major Hemorrhage                 | 3 (3.5)   | 1 (1.2)           |
| Upper gastrointestinal hemorrhage| 2 (2.3)   | 0 (0.0)           |

AEI, adverse event of interest; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SMQN, Standardized MedDRA Query Narrow; SOC, system organ class.

a The “Infections” AEI category is summarized under the Infections and Infestations SOC.
b Included 1 patient with febrile neutropenia.
c The “Haemorrhage” AEI category is summarized under the Haemorrhage terms (excluding laboratory terms) SMQN.
d Included patients with any of the 3 preferred terms.
e Included 2 patients with an event that met the criteria for major hemorrhage.
## Supplemental Table : Adverse Events Leading to Death

| Sex/Age (years) | Preferred Term (verbatim term) | Last Dose (study day) | Death Date (study day) | Relationship to Zanubrutinib | Additional Information |
|-----------------|--------------------------------|-----------------------|------------------------|-----------------------------|------------------------|
| Male/54         | Road traffic accident (Death [car accident]) | 149                   | 149                    | Not related                | Unrelated to study drug. |
| Female/66       | Death (Death with unknown reason) | 54                    | 56                     | Possibly related            | On day 53, the patient presented with fever of 40.1°C with infection of undetermined origin (grade 4). On day 56, the patient died at home. |
| Male/74         | Pneumonia fungal (Fungal pneumonia) | 170                   | 236                    | Unlikely related            | Death after more than 30 days from the last dose of zanubrutinib. |
| Female/64       | Death (Death [the cause of the death is unknown]) | 32                    | 53                     | Not related                | The next line of chemotherapy started on day 34 after progressive disease. The patient died after beginning this treatment. |
| Male/70         | Cerebral haemorrhage (Cerebral hemorrhage) | 6                     | 8                      | Possibly related            | The patient experienced a left occipital lobe hemorrhage 6 days after initiation of zanubrutinib, which led to treatment discontinuation and subsequent death. With the available information the correlation with zanubrutinib cannot be completely ruled out. It is notable that the patient had blastic histology and a high-risk MIPI-b score which are risk factors for central nervous system MCL. |
| Male/47         | Pneumonia (Pneumonia) | 88                    | 111                    | Possibly related            | On day 86, the patient presented with grade 4 pneumonia and, on day 88, disease progression was confirmed. The patient died due to complications from pneumonia in the setting of disease progression. |
| Female/61       | Death (Death with unknown reason) | 280                   | 300                    | Possibly related            | On day 280, the patient presented with grade 4 thrombocytopenia and was hospitalized due to lung infection and pancytopenia (HB 63 g/L x 10^9/L, ANC 1.11 PLT 9 x 10^9/L). The patient was discharged without improvement and died at home with no reason provided. |
Supplemental Figure 1. Forest plot of investigator-assessed overall response rate by subgroup. CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; LDi, longest transverse diameter of a lesion; MCL, mantle cell lymphoma; MIPI-b, Combined Biologic Mantle Cell Lymphoma International Prognostic Index. *2-sided Clopper-Pearson 95% confidence intervals. †MIPI-b score is calculated if Ki67 is available with cut-offs as low (<5.7), intermediate (≥5.7 and <6.5), and high (≥6.5). ‡Represents either no GI involvement as confirmed by endoscopy/biopsy, or no endoscopy/biopsy performed to confirm GI involvement.

| Subgroup                        | Response/Patients | Overall response rate (95% CI)* |
|---------------------------------|-------------------|---------------------------------|
| All patients                    | 72/65             | 63.7 (74.3–50.9)                |
| **Sex**                         |                   |                                 |
| Male                            | 51/57             | 85.1 (74.3–50.5)                |
| Female                          | 21/19             | 78.9 (74.4–50.9)                |
| **Age group**                   |                   |                                 |
| <65 years                       | 56/64             | 60.6 (50.7–50.9)                |
| ≥65 years                       | 16/22             | 63.8 (40.7–90.9)                |
| **Stage at study entry for MCL**|                   |                                 |
| Stage I or II                   | 59                | 62.5 (42.5–91.9)                |
| Stage III                       | 13/14             | 92.9 (90.0–99.8)                |
| Stage IV                        | 5/4               | 84.4 (73.1–94.2)                |
| **ECOG PS**                     |                   |                                 |
| 0                               | 53/66             | 66.3 (77.4–56.2)                |
| ≥1                              | 19/66             | 73.1 (52.2–90.4)                |
| **Prior line of therapy for MCL**|                   |                                 |
| <3                              | 51/57             | 89.5 (78.5–99.0)                |
| ≥2                              | 21/20             | 72.4 (52.8–92.7)                |
| **Histologic histology**        |                   |                                 |
| Yes                             | 8/12              | 60.7 (54.9–66.1)                |
| No                              | 59/66             | 66.8 (76.0–80.3)                |
| Unknown                         | 5/6               | 63.3 (55.8–66.8)                |
| **Ki67 positive cell percentage**|                   |                                 |
| <20%                            | 47/60             | 94.0 (83.5–96.7)                |
| >50%                            | 24/94             | 70.6 (62.5–80.1)                |
| Missing                         | 1/2               | 50.0 (1.5–98.7)                 |
| **Bulky disease**               |                   |                                 |
| Yes (any target lesion LDi >10cm)| 57                | 71.4 (69.0–81.3)                |
| No (all target lesion LDi ≤10cm)| 81/79             | 64.8 (75.0–91.9)                |
| **MIPI-b**                      |                   |                                 |
| Low                             | 12/12             | 100.0 (73.5–100.0)              |
| Intermediate                    | 8/92              | 82.3 (70.9–92.6)                |
| High                            | 23/13             | 92.9 (71.1–98.4)                |
| Missing                         | 1/2               | 50.0 (1.5–98.7)                 |
| **Refractory disease**          |                   |                                 |
| Yes                             | 50/65             | 64.4 (70.0–95.1)                |
| No                              | 34/41             | 62.9 (56.0–82.0)                |
| **Prior autologous stem cell transplantation** | | 83.1 (63.7–88.0) |
| Yes                             | 3/3               | 100.0 (92.2–130.0)              |
| No                              | 56/63             | 83.1 (72.2–98.0)                |
| **Prior Rituximab or Rituximab-containing regimen** | | 80.7 (70.5–85.9) |
| Yes                             | 23/24             | 81.3 (72.6–85.0)                |
| No                              | 57/62             | 90.0 (71.0–100.0)               |
| **Prior hyper-CVAD or hyper-CVAD-like regimen** | | 83.6 (54.8–99.9) |
| Yes                             | 11/13             | 91.6 (79.7–99.9)                |
| No                              | 81/73             | 86.4 (72.3–90.4)                |
| **Prior lenalidomide use**      |                   |                                 |
| Yes                             | 9/12              | 75.0 (42.5–99.5)                |
| No                              | 88/94             | 85.1 (75.0–90.4)                |
| **Prior bendamustine use**      |                   |                                 |
| Yes                             | 47                | 57.1 (38.4–79.1)                |
| No                              | 88/76             | 86.1 (83.2–89.0)                |
| **Prior bendamustine use**      |                   |                                 |
| Yes                             | 47                | 57.1 (38.4–79.1)                |
| No                              | 88/76             | 86.1 (83.2–89.0)                |
| **Baseline extramedul disease** |                   |                                 |
| Yes                             | 31/41             | 83.6 (71.5–91.9)                |
| No                              | 21/26             | 64.0 (50.3–86.5)                |
| **Baseline bone marrow involvement** | | 72.2 (58.5–87.5) |
| Yes                             | 34/41             | 87.7 (72.5–95.7)                |
| No                              | 21/26             | 90.0 (90.0–90.0)                |
| **Confirmed GI involvement**    |                   |                                 |
| Yes                             | 11/16             | 79.7 (44.9–29.2)                |
| No                              | 5/7               | 89.5 (83.5–85.9)                |
Supplemental Figure 2. (A) Duration of response, (B) progression-free survival, and (C) overall survival by MCL histology.
Supplemental Figure 3. (A) Duration of response, (B) progression-free survival, and (C) overall survival by TP53 mutation status.