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[a], 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[b]	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, n (%)	61 (70.9)
Bone marrow involvement	39 (45.3)
Gastrointestinal involvement	15 (17.4)
MIPI-b, n (%)[c]	
Low risk	12 (14.0)
Intermediate risk	39 (45.3)
High risk	33 (38.4)
Missing	2 (2.3)

Characteristic	N = 86
Refractory disease[d]	45 (52.3)
TP53-mutated (N = 54)[e]	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.
[a]Categories are not mutually exclusive as patients may be included under multiple regimens.
[b]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)
[c]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.[44,45] 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.
[d]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.
[e]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 n (%)	
	Any grade	Grade 3 or higher
Patients with at least 1 AEI	76 (88.4)	34 (39.5)
Infections[a]	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)[b]	17 (19.8)[b]
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)[c]	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[d]	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)[e]	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)

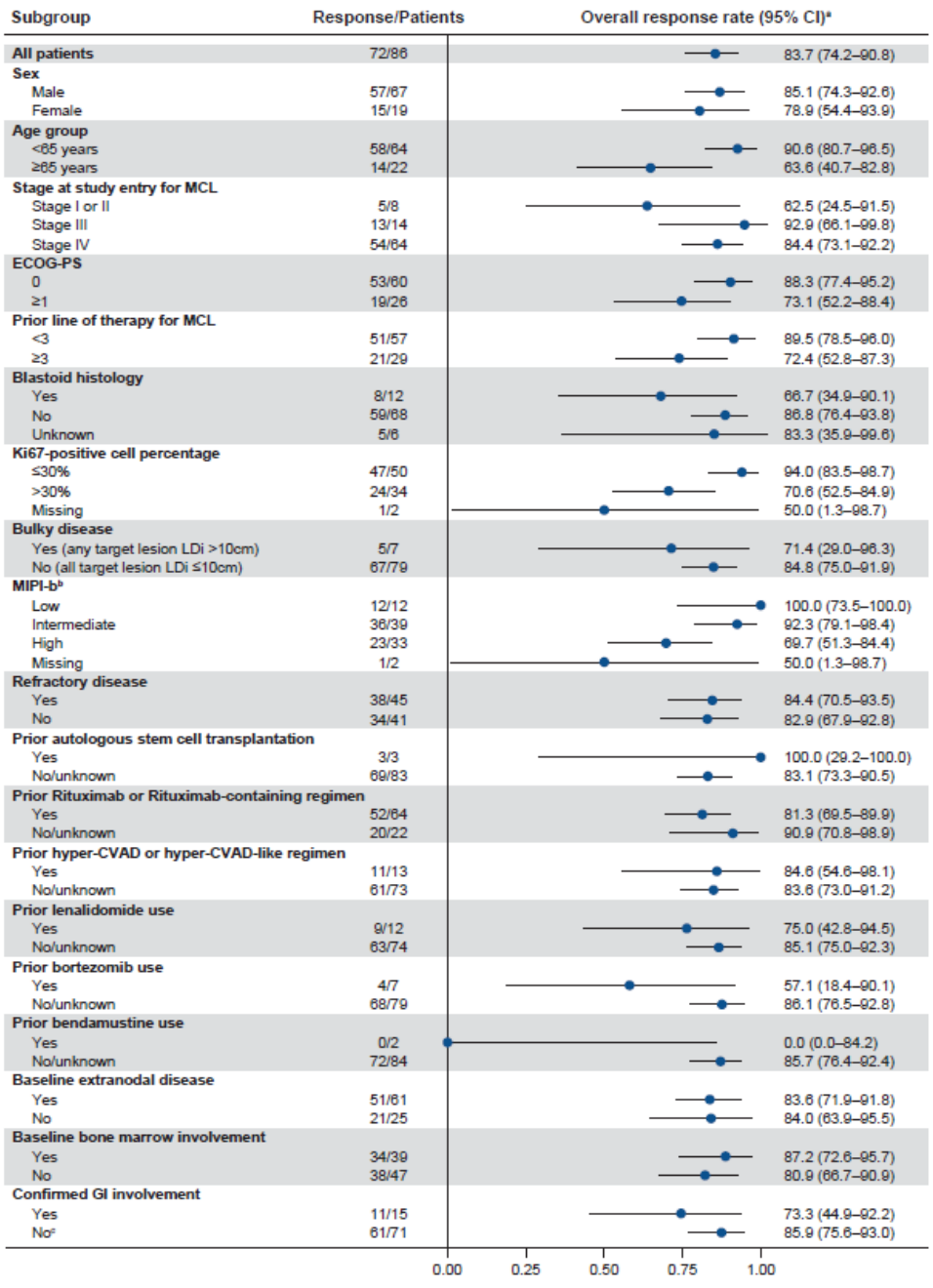
AEI, adverse event of interest; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SMQN, Standardized MedDRA Query Narrow; SOC, system organ class.

[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.

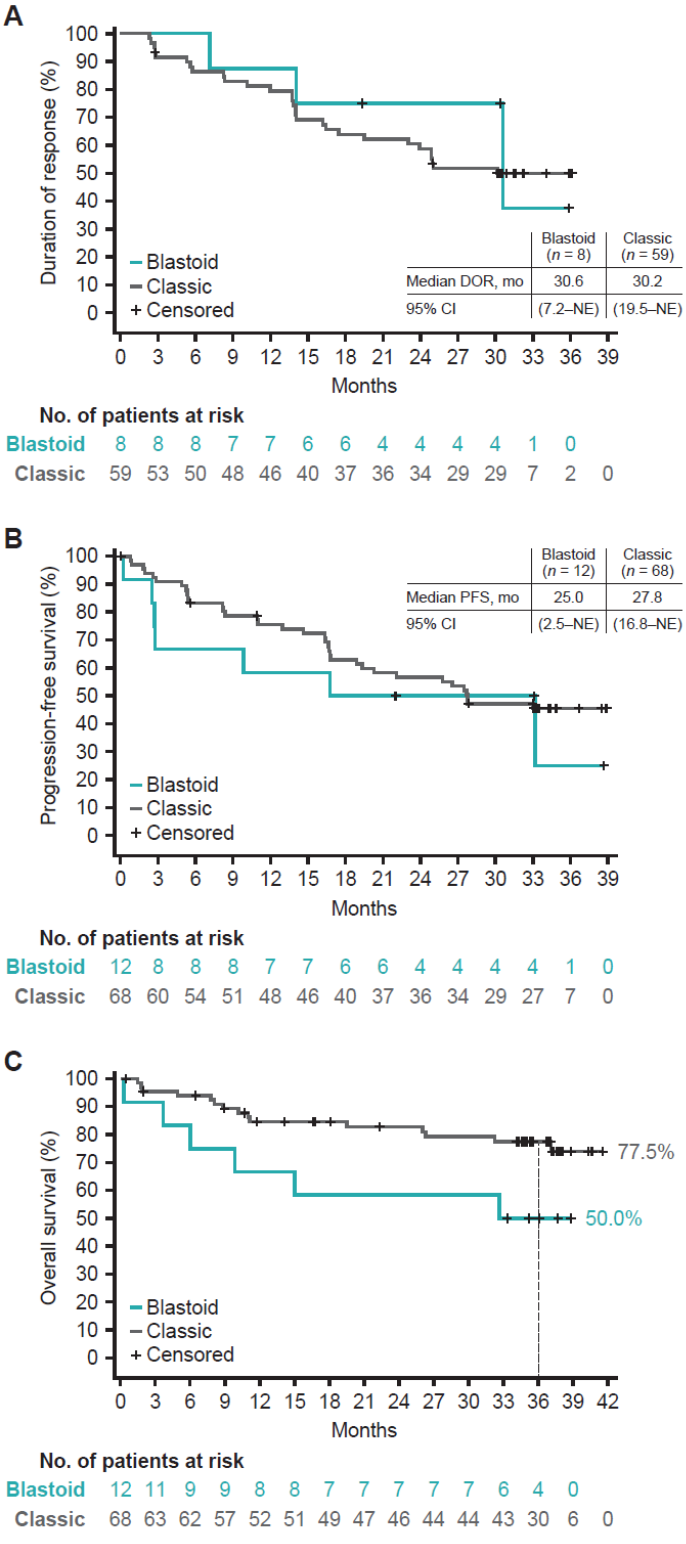
Supplemental Table : Adverse Events Leading to Death

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.



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.