First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab *versus* chlorambucil plus obinutuzumab: final analysis of the randomized, phase III iLLUMINATE trial

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Supplemental Methods

Statistical analysis

PFS and OS were analyzed using Kaplan-Meier estimates and log-rank test. Rates of undetectable minimal residual disease, hematologic improvement, and overall response rate were analyzed using chi-square test. Calculations of overall survival were not censored in the chlorambucil plus obinutuzumab arm at crossover.

Supplemental Figures and Tables

Figure S1. CONSORT diagram. AE, adverse event; ITT, intention-to-treat; NA, not applicable.

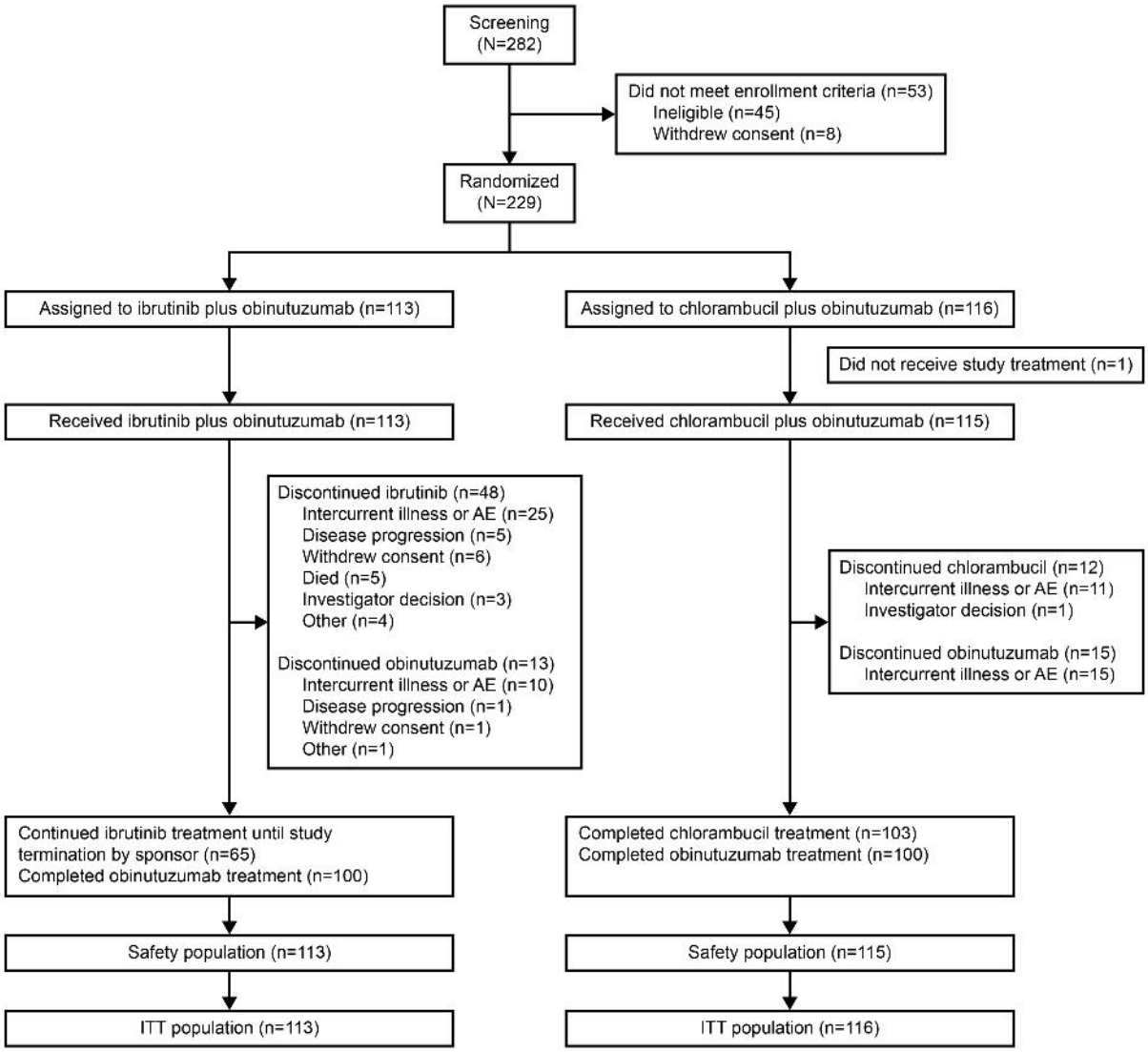
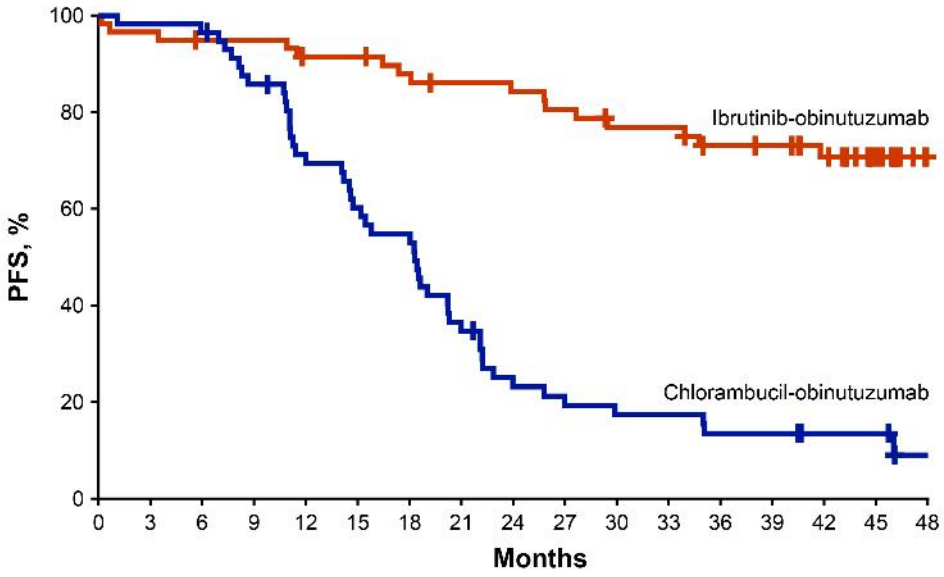


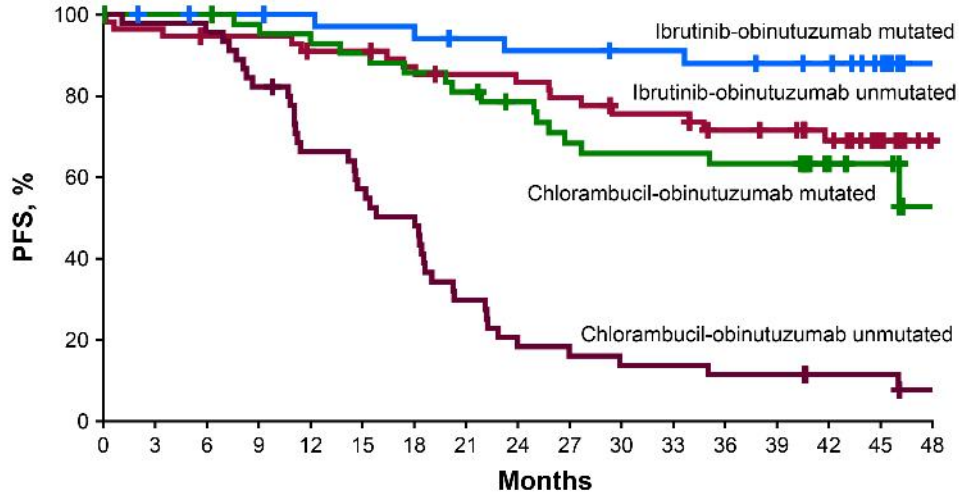
Figure S2. Progression-free survival per investigator assessment in the high-risk population of patients excluding del(17p) (patients with del(11q), *TP53* mutations, and/or unmutated *IGHV*). PFS, progression-free survival.



Patients at risk

Ibrutinib-obinutuzumab	59(0)	57(0)	55(1)	55(1)	52(2)	52(2)	49(3)	47(4)	46(4)	44(4)	41(5)	41(5)	37(7)	36(8)	30(13)	21(22)	4(39)
Chlorambucil-obinutuzumab	57(0)	56(0)	55(0)	48(1)	38(2)	33(2)	30(2)	19(2)	12(3)	10(3)	9(3)	9(3)	7(3)	7(3)	4(6)	4(6)	1(8)

Figure S3. Progression-free survival per investigator assessment according to *IGHV* status, excluding patients with del(17p). PFS, progression-free survival.



Patients at risk																	
Ibrutinib-obinutuzumab mutated	37	36	35	35	34	33	33	31	30	30	29	29	28	27	26	22	11
Ibrutinib-obinutuzumab unmutated	56	54	52	52	49	49	46	44	43	41	38	38	34	33	27	19	4
Chlorambucil-obinutuzumab mutated	45	43	43	41	39	38	36	34	31	27	26	26	25	25	14	11	2
Chlorambucil-obinutuzumab unmutated	45	44	43	37	29	25	22	13	8	7	6	6	5	5	3	3	1

Figure S4. Subgroup analyses of progression-free survival. Forest plot of hazard ratios for disease progression or death across patient subgroups. CI, confidence interval; Clb, chlorambucil; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; Ibr, ibrutinib; Ob, obinutuzumab.

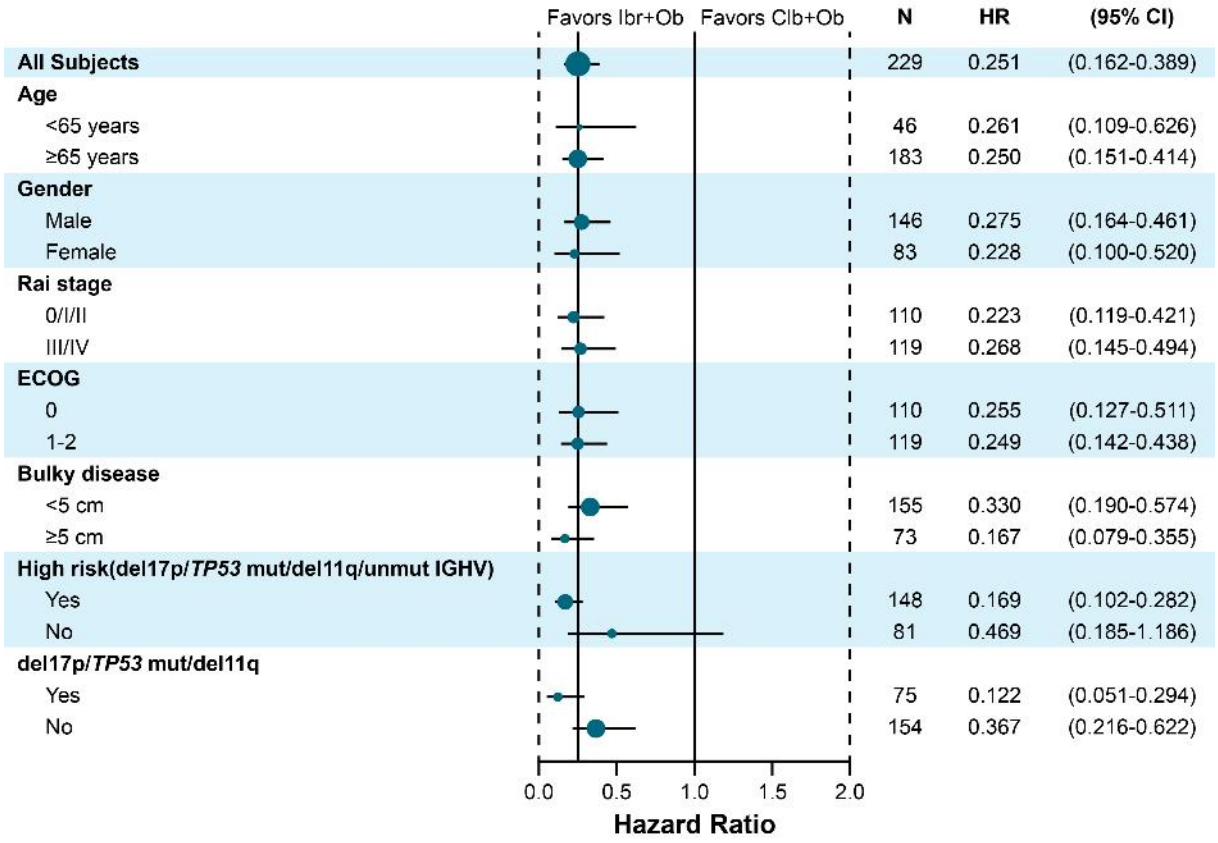
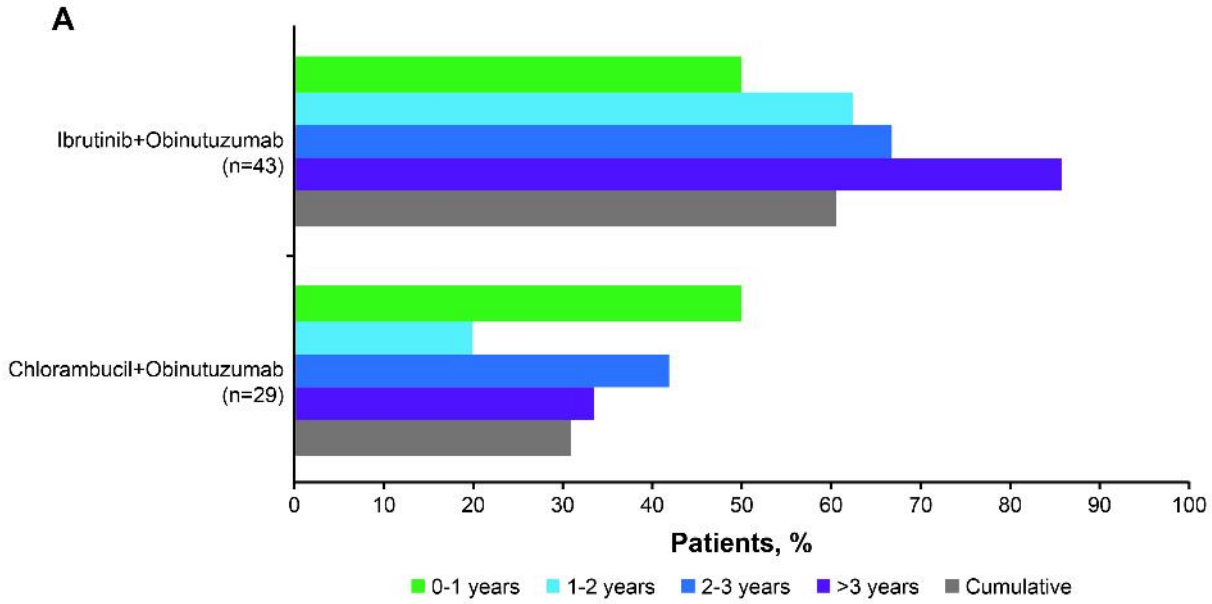
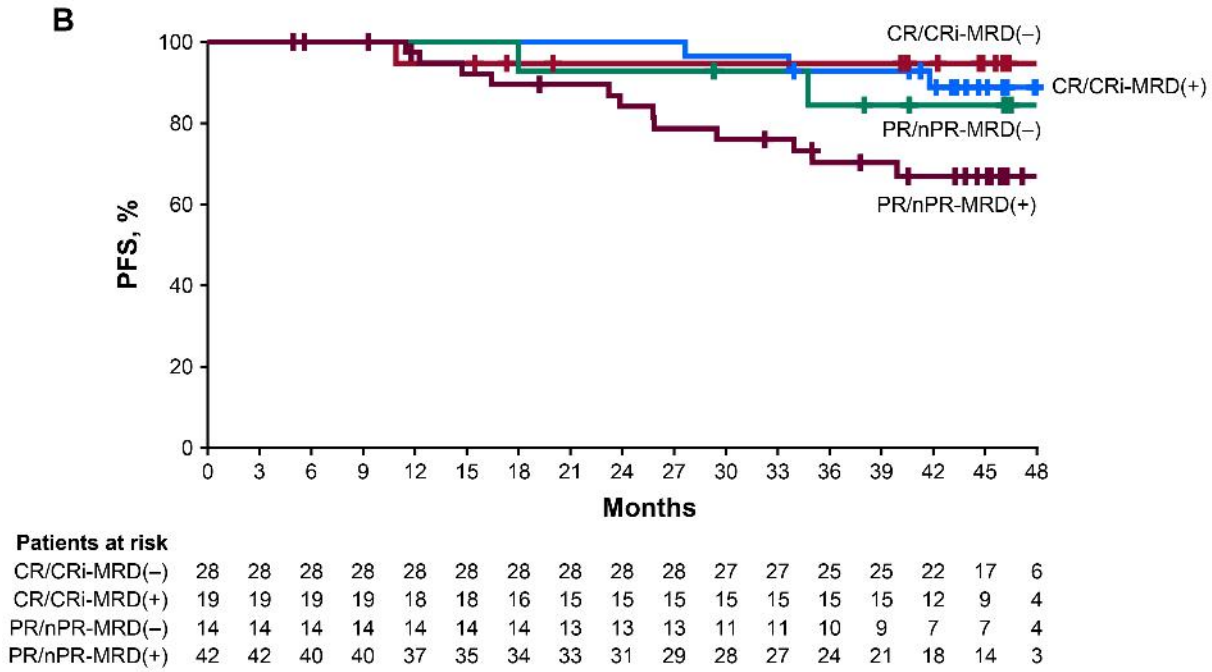


Figure S5. Progression-free survival (PFS) per investigator assessment according to MRD status. PFS in A) patients who remained MRD negative at last peripheral blood or bone marrow sample by follow-up time, B) patients treated with ibrutinib plus obinutuzumab, C) patients treated with chlorambucil plus obinutuzumab. CR, complete response; CRi, complete response with incomplete bone marrow recovery; MRD, minimal residual disease; nPR, nodular partial response; PR, partial response.





Patients at risk

CR/CRi-MRD(–)	28	28	28	28	28	28	28	28	28	28	27	27	25	25	22	17	6
CR/CRi-MRD(+)	19	19	19	19	18	18	16	15	15	15	15	15	15	15	12	9	4
PR/nPR-MRD(–)	14	14	14	14	14	14	14	13	13	13	11	11	10	9	7	7	4
PR/nPR-MRD(+)	42	42	40	40	37	35	34	33	31	29	28	27	24	21	18	14	3

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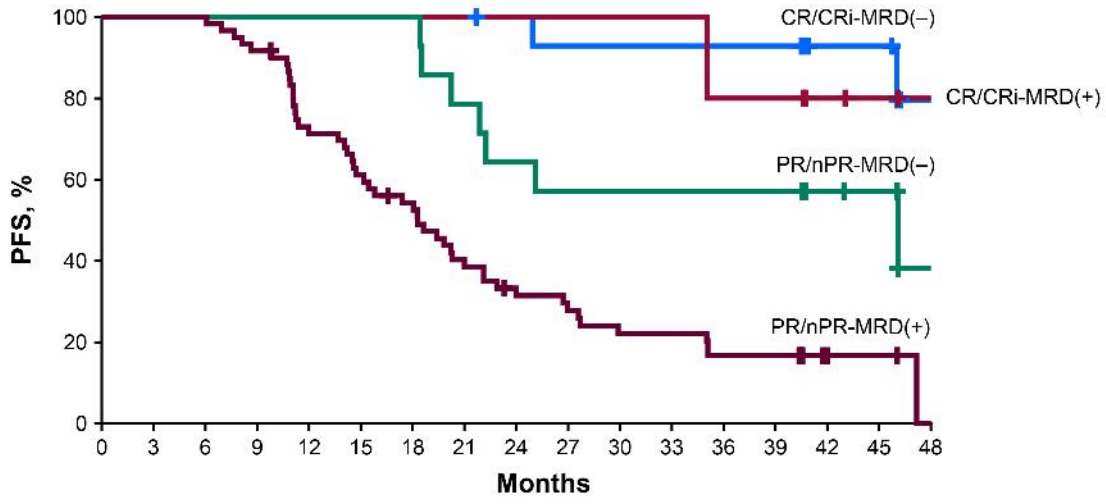

Patients at risk

CR/CRi-MRD(–)	15	15	15	15	15	15	15	15	14	13	13	13	13	13	8	8	3
CR/CRi-MRD(+)	5	5	5	5	5	5	5	5	5	5	5	5	4	4	2	1	0
PR/nPR-MRD(–)	14	14	14	14	14	14	14	11	9	8	8	8	8	8	5	4	1
PR/nPR-MRD(+)	60	60	60	55	42	36	31	22	17	15	12	12	9	9	4	3	0

Figure S6. Overall survival in patients treated with ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab. Patients in the chlorambucil plus obinutuzumab arm were permitted to crossover to ibrutinib therapy upon disease progression; 44% of patients initially randomized to chlorambucil plus obinutuzumab received second-line therapy with ibrutinib. CI, confidence interval; NE, not estimable; OS, overall survival.

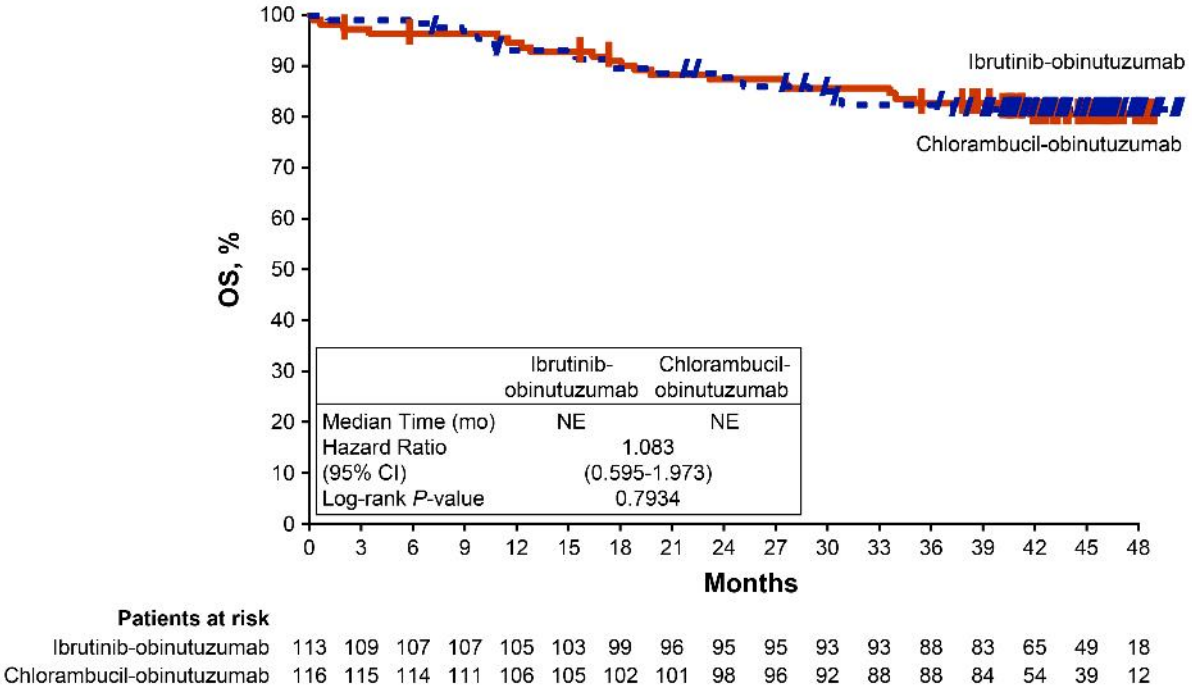

Figure S7. Duration and resolution status of AEs leading to ibrutinib dose reduction. Each bar depicts AE onset/grade with event duration shown in months. Bars denoted as arrows indicate AEs reported as not recovered/not resolved. Ibrutinib was reduced to 280 mg unless otherwise noted per the legend. AE, adverse event; G, grade.
[a]Ibrutinib 140 mg dose.
[b]Serious AE.

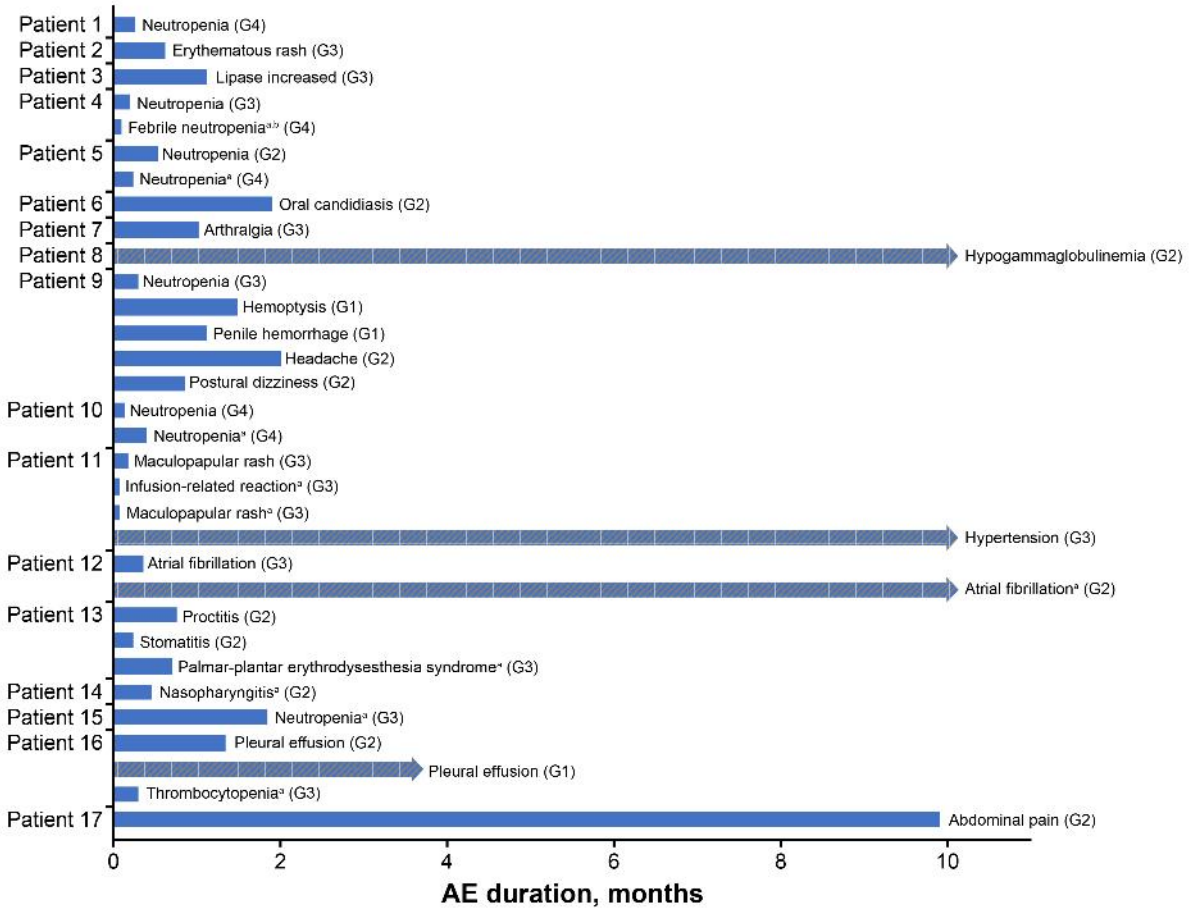

Table S1. Baseline patient and disease characteristics

	Ibrutinib plus obinutuzumab (N=113)	**Chlorambucil plus obinutuzumab (N=116)**
Median age (range), years	70 (47–87)	72 (40–86)
≥65 years, n (%)	91 (81)	92 (79)
Male, n (%)	67 (59)	79 (68)
Ethnicity n (%)		
White	109 (96)	111 (96)
Black or African American	2 (2)	2 (2)
Asian	1 (1)	2 (2)
Native Hawaiian or other Pacific Islander	1 (1)	1 (1)
ECOG performance status n (%)		
0	57 (50)	53 (46)
1	52 (46)	56 (48)
2	4 (4)	7 (6)
Diagnosis n (%)		
Chronic lymphocytic leukemia	107 (95)	107 (92)
Small lymphocytic lymphoma	6 (5)	9 (8)
Rai stage III/IV, n (%)	60 (53)	59 (51)
Bulky disease of ≥5 cm, n (%)	30 (27)	44 (38)
High risk features n (%)		
del(17p), *TP53*, del(11q), or unmutated *IGHV*	73 (65)	75 (65)
del(17p) or *TP53*	18 (16)	23 (20)
del(17p)	14 (12)	18 (16)
TP53 mutation[a]	13/112 (12)	16/110 (15)
del(11q)[b]	13 (12)	22 (19)
Unmutated *IGHV*	66/107 (62)	57/107 (53)
Any cytopenia at baseline, n (%)	63 (56)	62 (53)
Cumulative illness rating scale for geriatrics score		
Median (range)	4.0 (0–12)	4.0 (1-12)
>6, n (%)	37 (33)	36 (31)
Creatinine clearance		
Median, mL/min (range)	72.0 (32–151)	69.6 (31-198)
<60 mL/min, n (%)	26 (23)	38 (33)
Median time from initial diagnosis, months (range)	29.6 (0–192)	36.5 (0-480)

[a]Irrespective of del(17p), 4 of 112 patients in the ibrutinib plus obinutuzumab group and 5 of 110 patients in the chlorambucil plus obinutuzumab group had *TP53* mutations in the absence of del(17p). [b]Without del(17p); hierarchical categories according to Dohner classification.

ECOG, Eastern Cooperative Oncology Group; *IGHV*, immunoglobulin heavy-chain variable region; IQR, interquartile range.

Table S2. Patients who achieved MRD-negative response in peripheral blood or bone marrow

	Ibrutinib plus obinutuzumab (n=113)	**Chlorambucil plus obinutuzumab (n=116)**
Patients with MRD test performed, n (%)	101 (89)	92 (79)
Patients with PB or BM MRD negativity, n (%)	43 (38)	29 (25)
PB	37 (33)	23 (20)
BM	28 (25)	20 (17)
Patients with PB or BM MRD followed after first achieving negative, n (%)	39 (91)	25 (86)
Follow-up time after first achieving negative MRD, median (range)	23 (0.03-44)	30 (0.03-44)
Number of patients remaining negative at last PB or BM sample, n (%)	26 (60)	9 (31)
Number of patients with MRD relapsed in PB or BM, n (%)	5 (12)	7 (24)
Time to MRD relapse (months), median (range)	NE (0.03-44+)	37.5 (0.03-44+)

BM, bone marrow; MRD, minimal residual disease; NE, not estimable; PB, peripheral blood.

Table S3. Summary of most common AEs (≥10% of patients in either arm) during the TEAE period[a]

	Ibrutinib plus obinutuzumab (n=113)			Chlorambucil plus obinutuzumab (n=115)		
	Any grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Neutropenia	50 (44)	41 (36)	0	73 (63)	53 (46)	0
Thrombocytopenia	40 (35)	22 (19)	0	29 (25)	12 (10)	0
Diarrhea	39 (35)	3 (3)	0	12 (10)	0	0
Cough	33 (29)	1 (1)	0	14 (12)	0	0
Infusion-related reaction	28 (25)	2 (2)	0	67 (58)	9 (8)	0
Arthralgia	27 (24)	1 (1)	0	12 (10)	0	0
Pyrexia	22 (19)	2 (2)	0	30 (26)	1 (1)	0
Fatigue	22 (19)	1 (1)	0	19 (17)	2 (2)	0
Hypertension	22 (19)	4 (4)	0	5 (4)	4 (3)	0
Back pain	21 (19)	0	0	12 (10)	1 (1)	0
Anemia	19 (17)	4 (4)	0	30 (26)	9 (8)	0
Constipation	19 (17)	0	0	14 (12)	1 (1)	0
Upper respiratory tract infection	19 (17)	1 (1)	0	7 (6)	0	0
Pneumonia	18 (16)	9 (8)	1 (1)	8 (7)	4 (3)	1 (1)
Rash maculo-papular	17 (15)	2 (2)	0	2 (2)	0	0
Atrial fibrillation	17 (15)	7 (6)	0	0	0	0
Muscle spasms	16 (14)	0	0	7 (6)	0	0
Nausea	15 (13)	0	0	35 (30)	0	0
Nasopharyngitis	15 (13)	0	0	4 (3)	0	0
Hyperuricemia	15 (13)	1 (1)	0	0	0	0
Edema peripheral	14 (12)	0	0	8 (7)	0	0
Urinary tract infection	14 (12)	4 (4)	0	8 (7)	1 (1)	0
Insomnia	13 (12)	0	0	5 (4)	0	0
Asthenia	12 (11)	0	0	17 (15)	0	0
Dyspnea	12 (11)	2 (2)	0	15 (13)	1 (1)	0
Vomiting	12 (11)	0	0	14 (12)	0	0
Pain in extremity	12 (11)	1 (1)	0	10 (9)	2 (2)	0
Dizziness	12 (11)	0	0	7 (6)	0	0
Conjunctivitis	12 (11)	0	0	2 (2)	0	0
Cataract	12 (11)	2 (2)	0	1 (1)	0	0
Headache	9 (8)	0	0	13 (11)	1 (1)	0

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]TEAE period defined as time from first dose until 30 days after last dose of study drug or initiation of subsequent antitumor therapy, whichever occurred first. At final analysis,

median treatment exposure was 42.3 months in the ibrutinib plus obinutuzumab arm and 5.1 months in the chlorambucil plus obinutuzumab arm.

Table S4. Summary of study discontinuation and deaths.

	Ibrutinib plus obinutuzumab (n=113)		Chlorambucil plus obinutuzumab (n=116)	
All deaths, n (%)	21 (19)		21 (18)	
Adverse event	13 (12)		9 (8)	
Disease progression	2 (2)		4 (3)	
Unknown	5 (4)		3 (3)	
General health deterioration	1 (0.01)		1 (0.01)	
Accident	0		1 (0.01)	
Acute kidney failure + sepsis	0		1 (0.01)	
Gastric adenocarcinoma	0		1 (0.01)	
Ischemic stroke	0		1 (0.01)	
TEAEs leading to death	**All death (n1 [%])***	**Treatment-related n2†**	**All death (n1 [%])**	**Treatment-related n2†**
Any TEAE	14 (12)	5	3 (3)	1
Cardiac disorders	2 (2)	0	0	0
General disorders and administration site conditions	3 (3)	2	0	0
Infections and infestations	5 (4)	3	2 (2)	0
Neoplasms benign, malignant, and unspecified	2 (2)	0	1 (1)	1
Suicide	1 (1)	0	0	0

*n1; number of subjects with the specified event.

†n2; number of subjects with the specified event that were possibly related to study drug per investigator's judgement.