Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 2015;373:2425-37. DOI: 10.1056/NEJMoa1509388

SUPPLEMENTARY APPENDIX

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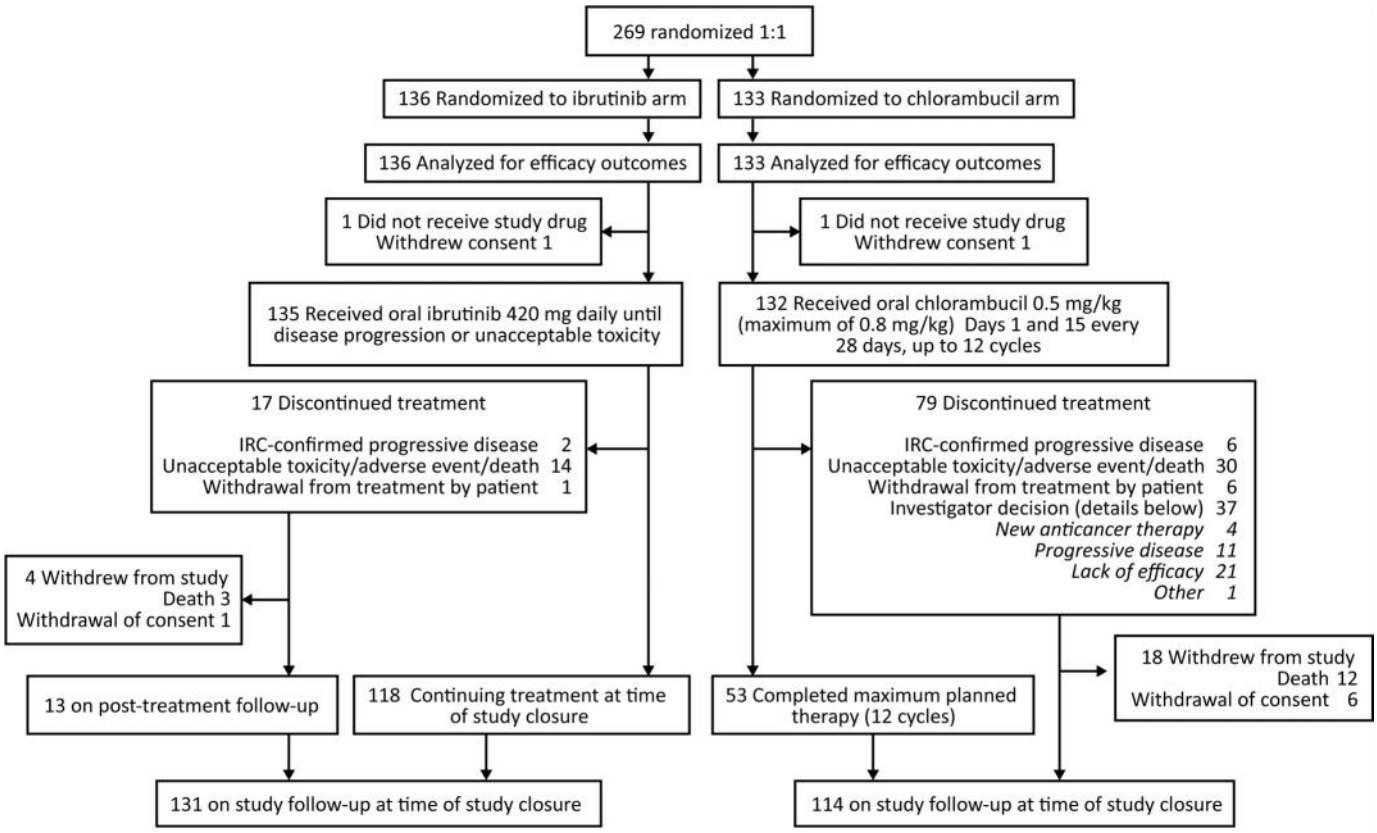
Country	**Number of Patients Enrolled**
United States	60
United Kingdom	30
Italy	27
Poland	20
Australia	18
Israel	16
New Zealand	13
Ukraine	13
Belgium	12
Spain	12
Canada	11
China	11
Czech Republic	10
Turkey	10
Ireland	5
Russia	1
Total	**269**

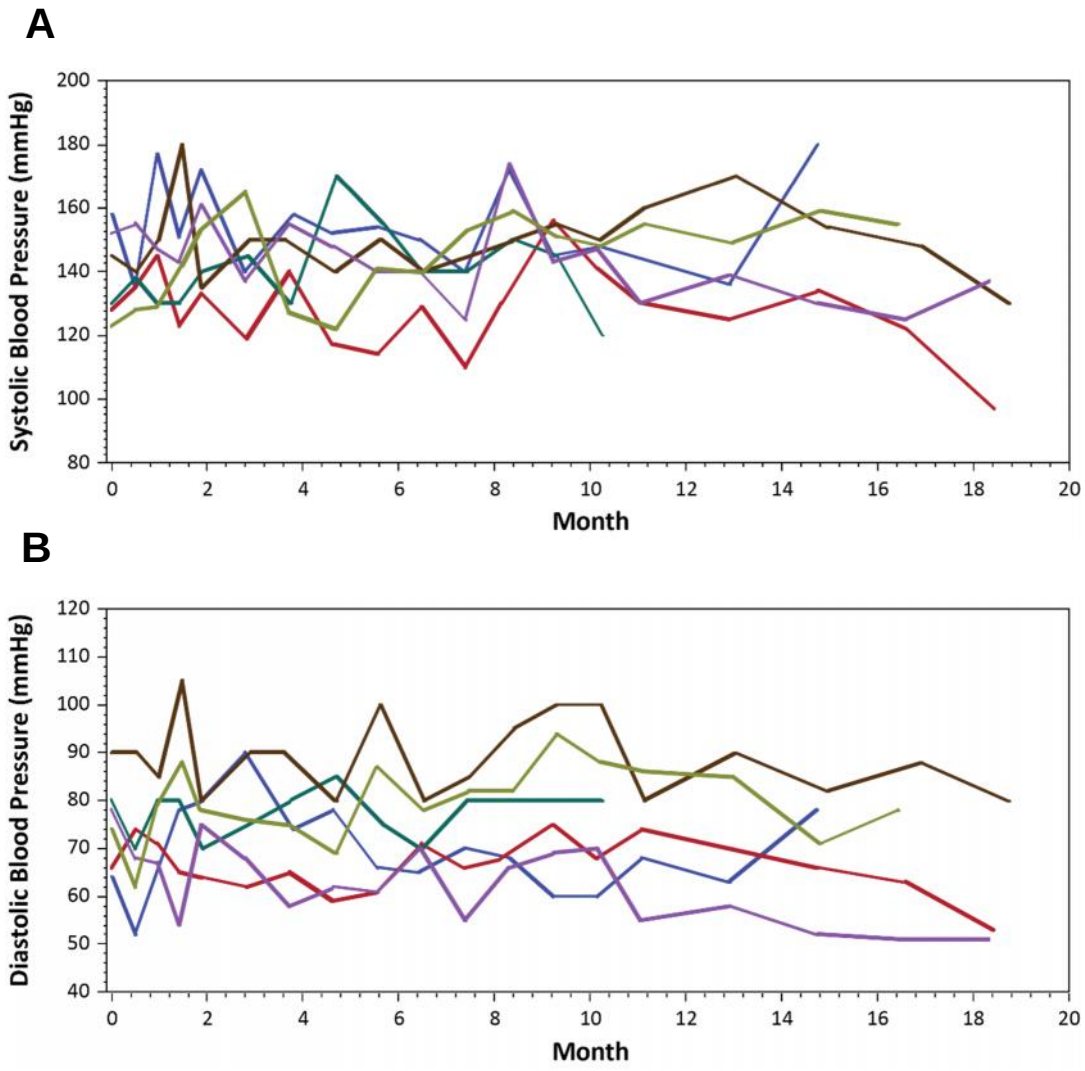
Supplementary Figures S1-S2

Figure S1. CONSORT Diagram*



*At the closure of this PCYC-1115-CA study (RESONATE-2™), all patients remaining on the study were transferred to the extension study, PCYC-1116-CA for long-term follow-up and ibrutinib treatment, as appropriate

Figure S2. Systolic and Diastolic Blood Pressure Among Patients with Grade 3 or Greater Hypertension with Ibrutinib. These graphs show systolic (Panel A) and diastolic (Panel B) blood pressure measurements over the course of study treatment in the six patients who had grade 3 or greater hypertension in the ibrutinib arm. Blood pressure measurements are plotted from baseline to 30 days after the last dose of study treatment or initiation of subsequent antitumor therapy, whichever occurred earlier.



Supplementary Tables S1-S8

Table S1. 2008 iwCLL Indication for Treatment[1]

Active disease meeting at least 1 of the following iwCLL criteria for requiring treatment[1]
• Evidence of progressive marrow failure as manifested by development of, or worsening of, anemia (hemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/µL)
• Massive (≥6 cm below left costal margin), progressive or symptomatic splenomegaly
• Massive (≥10 cm in longest diameter), progressive or symptomatic lymphadenopathy
• Progressive lymphocytosis with an increase of >50% over a 2-month period or lymphocyte doubling time (LDT)* of <6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months.
• Autoimmune hemolytic anemia and/or immune thrombocytopenic purpura that is poorly responsive to glucocorticoids or other standard therapy
• Constitutional symptoms, defined as one or more of the following disease-related symptoms or signs, documented in the patient's record prior to randomization – Unintentional weight loss (>10% within 6 months prior to screening) – Significant fatigue (inability to work or perform usual activities) – Fever (>100.5°F or 38.0°C for ≥2 weeks) without evidence of infection – Night sweats (>1 month prior to screening) without evidence of infection

* In patients with initial blood lymphocyte counts of <30,000/µL, LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.

Table S2. Criteria for Response Categories

Parameter	CR	PR	PD
Group A			
Lymphadenopathy*	None; ≤1.5 cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Increase ≥50% or new hepatomegaly
Splenomegaly	None	Decrease ≥50%	Increase ≥50% or new splenomegaly
Blood lymphocytes	<4000/μL	Decrease ≥50% from baseline. Lymphocytosis defines PR-L.	Increase ≥50% over baseline‡
Marrow†	Normocellular, <30% lymphocytes, no B lymphoid nodules. Hypocellular defines CRi. Presence of B lymphoid nodules defines nPR.		
Group B			
Platelet count	>100,000/μL	>100,000/μL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	>11g/dL	>11g/dL or increase ≥50% over baseline	Decrease of >2g/dL from baseline secondary to CLL
Neutrophils	>1500/μL	>1500/μL or increase ≥50% over baseline	N/A

*Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node.

†This parameter is not relevant for the PD category unless confirming cytopenic progression.

‡Patients with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease. Lymphocytosis should only be considered as the sole criteria for progression if no improvement in other disease parameters.

Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system.

CR: all of the criteria need to be met and patients have to lack disease related constitutional symptoms. Bone marrow and aspirate is required to confirm CR.

CRi: all of the criteria for CR need to be met, but bone marrow biopsy shows hypocellularity; patient continues to have cytopenias due to drug toxicity in the bone marrow and not due to evidence of disease.

nPR: all of the criteria for CR need to be met, but bone marrow biopsy shows B lymphoid nodules.

PR: at least 2 abnormal Group A criteria must meet be met plus one of the criteria from Group B must be met.

PR-L: only 1 abnormal Group A criteria met in the setting of lymphocytosis not meeting PR criteria

SD: absence of PD and the failure to achieve CR, CRi, nPR, PR, or PR with lymphocytosis.

PD: at least 1 of the above criteria from Group A or B are met or development of transformation to a more aggressive histology.

Table S3. Summary of Patients with Unknown Causes of Death in Ibrutinib Arm

Patient Age/Sex	Treatment Duration	Patient Narrative Surrounding Death
73 years/male	20 days	History of chronic obstructive pulmonary disease, hypertension, coronary artery disease, and type 2 diabetes mellitus. Ibrutinib treatment was ongoing at time of death. Patient experienced non-serious lobar pneumonia 8 days prior to death. Patient died at home due to unknown causes.
87 years/male	157 days	History of multiple medical conditions including pulmonary embolism, pleural and pericardial effusion, and hypoxia. Ibrutinib treatment was ongoing at time of death. Patient was found to have died during sleep and cause of death was unknown.

Table S4. Time to Response and Summary of Treatment-related Lymphocytosis with Ibrutinib

	PCYC-1115 ibrutinib arm
Median duration of follow-up — mo	18.4
Median time to initial response* (range) — mo	3.8 (3.2-14.8)
Patients who developed lymphocytosis† — no. (%)	77 (57)
Median duration of lymphocytosis‡ (range) — weeks	12 (0.1-78)
Patients who resolved lymphocytosis‡ — no. (%)	73 (95)

*First response assessment was performed at the end of month 4. These data pertain to patients who responded (PR with lymphocytosis or better) to ibrutinib per IRC assessment (n=117).
†Lymphocytosis was defined as ≥50% increase from baseline and above absolute lymphocyte count of 5,000/μL.
‡Among patients who developed treatment-related lymphocytosis in the ibrutinib arm (n=77).

Table S5. Sustained Hematologic Improvement* in Intent-to-Treat Population

Sustained Improvements by Laboratory Parameter	Ibrutinib (N = 136)	Chlorambucil (N = 133)	P Value†
	number of patients (percent)		
Platelet count	37 (27)	15 (11)	<0.001
Hemoglobin	62 (46)	27 (20)	<0.001
Absolute neutrophil count	45 (33)	14 (11)	<0.001

*Sustained improvement was defined as hematologic improvement that was sustained continuously for at least 56 days without transfusion or growth factors, as measured by: at least 50% improvement over baseline (or for hemoglobin, improvement of ≥2 grams per deciliter over baseline); or improvement in baseline cytopenia to hemoglobin >11 grams per deciliter, or platelet count >100,000 cells per mm^3, or absolute neutrophil count >1500 cells per mm^3.
†P value based on Chi-square test.

Table S6. Sustained Hematologic Improvement* in Subgroup of Intent-to-Treat Patients with Baseline Cytopenia

	Baseline Cytopenia		Hematologic Improvement in Patients with Baseline Cytopenia		
	Ibrutinib (N = 136)	Chlorambucil (N = 133)	Ibrutinib (N = 136)	Chlorambucil (N = 133)	P Value†
	number of patients with baseline cytopenia (percent)		*number of patients with improvement in each subgroup (percent)*		
Platelet count	35 (26)	28 (21)	27/35 (77)	12/28 (43)	0.005
Hemoglobin	51 (38)	55 (41)	43/51 (84)	25/55 (45)	<0.001
Absolute neutrophil count	10 (7)	7 (5)	10/10 (100)	5/7 (71)	0.07

*Sustained improvement was defined as hematologic improvement that was sustained continuously for at least 56 days without transfusion or growth factors, as measured by: at least 50% improvement over baseline (or for hemoglobin, improvement of ≥2 grams per deciliter over baseline); or improvement in baseline cytopenia to hemoglobin >11 grams per deciliter, or platelet count >100,000 cells per mm^3, or absolute neutrophil count >1500 cells per mm^3.
†P value based on Chi-square test.

Table S7. Summary of Most Common Adverse Events*

	Ibrutinib (N = 135)		Chlorambucil (N = 132)	
Median duration of treatment (range) — mo	17.4 (0.7-24.7)		7.1 (0.5-11.7)	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Adverse Event	***number of patients (percent)***			
Diarrhea	57 (42)	5 (4)	22 (17)	0
Fatigue	41 (30)	1 (1)	50 (38)	7 (5)
Cough	30 (22)	0	20 (15)	0
Nausea	30 (22)	1 (1)	52 (39)	1 (1)
Anemia	25 (19)	8 (6)	27 (20)	11 (8)
Peripheral edema	25 (19)	2 (1)	12 (9)	0
Dry eye	23 (17)	0	6 (5)	0
Pyrexia	23 (17)	0	19 (14)	2 (2)
Upper respiratory tract infection	23 (17)	3 (2)	23 (17)	2 (2)
Arthralgia	22 (16)	2 (1)	9 (7)	1 (1)
Constipation	21 (16)	1 (1)	21 (16)	0
Neutropenia	21 (16)	14 (10)	30 (23)	24 (18)
Vomiting	18 (13)	0	27 (20)	1 (1)

*This table summarizes adverse events that occurred in at least 15% of patients in either treatment arm.

Table S8. Summary of Major Bleeding Events in the Ibrutinib Arm

Patient Age/Sex	Preferred Term (severity grade)	Time of Onset	Relevant Medical History and Potential Confounding Factor(s)
67 years/female	Cerebral hemorrhage (grade 4)	Day 254	Diabetes, thrombocytopenia, concurrent use of aspirin, hemorrhagic transformation of ischemic stroke
75 years/male	Post-procedural hemorrhage (grade 3)	Day 244	Anemia, thrombocytopenia at the time of the event, excision of colonic adenoma, dalteparin for deep vein thrombosis prophylaxis
71 years/male	Vitreous hemorrhage (grade 3)	Day 310	Previous history of posterior retinal detachment with retina rupture, glaucoma
85 years/male	Hyphema (grade 2)	Day 155	Bilateral cataracts, and lens insertion
71 years/male	Traumatic hematoma (grade 3)	Day 24	Hematoma observed at the point of pacemaker insertion (insertion on Day -29) in left chest wall, concomitant use of tocopherol acetate (vitamin E)
84 years/female	Subarachnoid hemorrhage, subdural hematoma (grade 3, both)	Day 446	Advanced age, history of immune thrombocytopenia purpura, hemorrhage was secondary to trauma sustained by fall

Reference

1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56.