A cross-trial comparison of single-agent ibrutinib *versus* chlorambucil-obinutuzumab in previously untreated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma

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Supplemental Methods

Clinical Studies

Both the RESONATE-2 and iLLUMINATE multi-center studies[1, 2] were conducted in accordance with International Conference on Harmonization Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by institutional review boards or independent ethics committees of all participating institutions for each study, and all patients provided written, informed consent.[1, 2]

In the randomized, open-label, RESONATE-2 (PCYC-1115/1116) phase III study,[1] previously untreated patients age ≥65 years with chronic lymphocytic leukemia/small lymphocytic lymphoma and without deletion of chromosome 17 (del[17p]) were randomly assigned 1:1 to receive single-agent ibrutinib (420 mg once daily continuously) until disease progression or toxicity or up to 12 cycles of chlorambucil (0.5 mg/kg on days 1 and 15 of each 28-day cycle, up to a maximum of 0.8 mg/kg).

In the randomized, open-label, iLLUMINATE (PCYC-1130) phase III study,[2] previously untreated patients with chronic lymphocytic leukemia/small lymphocytic lymphoma age ≥65 or <65 years with coexisting conditions were randomly assigned 1:1 to receive either ibrutinib-obinutuzumab (ibrutinib [420 mg once daily continuously] plus 6 cycles of intravenous obinutuzumab [100 mg on day 1, 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 of cycle 1, then 1000 mg on day 1 of each 28-day cycle for cycles 2-6]) or chlorambucil-obinutuzumab (6 cycles of oral chlorambucil [0.5 mg/kg on days 1 and 15 of each 28-day cycle] and intravenous obinutuzumab [same treatment schedule as above]).

Statistical Methods

This cross-trial analysis was a pre-specified analysis prior to the unblinding of the iLLUMINATE study. Progression-free survival was analyzed according to the Kaplan-Meier method and treatment effect of ibrutinib *versus* chlorambucil-obinutuzumab on progression-free survival was tested with an unstratified log-rank test. Hazard ratios were calculated based on an unstratified Cox regression model with treatment as the only covariate. Medical resource utilization, development and resolution of lymphocytosis, objective response rate and complete response rate, and safety are summarized by treatment group using descriptive statistics.

The efficacy population included all patients randomly assigned to ibrutinib from RESONATE-2 and patients without del(17p) in the iLLUMINATE study. The safety population included patients who received at least 1 dose of study treatment (ibrutinib, chlorambucil, or obinutuzumab).

Data Sharing Statement

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu

Supplemental Table 1. Medical resource utilization during the first 6 months on study treatment[a]

	Ibrutinib N=136	**Chlorambucil-obinutuzumab N=98**
Number of hospitalizations, n (%)	36 (26)	27 (28)
Median number of hospitalizations (range)	1.5 (1-4)	1.0 (1-5)
Median duration of hospitalization, days (range)	9.5 (3-46)	7.0 (1-99)
Use of blood supportive products,[b] n (%)	22 (16)	20 (20)
Use of any growth factors,[c] n (%)	8 (6)	40 (41)

[a]Medical resource usage within 183 days of first dose of any study treatment and prior to or on the date of initiating subsequent antineoplastic treatment.
[b]Packed red blood cells, fresh-frozen plasma, factor infusions, immunoglobulin.
[c]Neutrophil growth factor, erythropoietin-stimulating agents, thrombopoietin mimetics.

Supplemental Table 2. Baseline patient demographics and disease characteristics for ibrutinib and ibrutinib-obinutuzumab groups

	Ibrutinib N=136	**Ibrutinib-Obinutuzumab N=99**
Age, y Median (range) ≥70, n (%)	 73 (65-89) 96 (71)	 70 (47-87) 55 (56)
Time since initial diagnosis, months, median (range)	30.5 (1-241)	32.4 (0-192)
Rai stage III/IV at screening, n (%)	68 (50)	52 (53)
ECOG performance status, n (%) 0 1-2	 61 (45) 75 (55)	 51 (52) 48 (48)
Bulky disease (lymph node ≥5 cm), n (%)	54 (40)	26 (26)
High-risk features (unmutated *IGHV*, del(11q), and/or *TP53* mutation), n (%) unmutated *IGHV*, n/N[a] (%) del(11q), n/N[a] (%) *TP53* mutation, n/N[a] (%)	 74/135 (55) 58/98 (59) 29/130 (22) 12/124 (10)	 59 (60) 56/93 (60) 13/99 (13) 4/98 (4)
Any cytopenias, n (%) Anemia (hemoglobin ≤11 g/dL) Thrombocytopenia (platelets ≤100×10^9/L)Neutropenia (absolute neutrophil count ≤1.5×10^9/L)	72 (53) 51 (38) 35 (26) 10 (7)	54 (55) 43 (43) 23 (23) 6 (6)

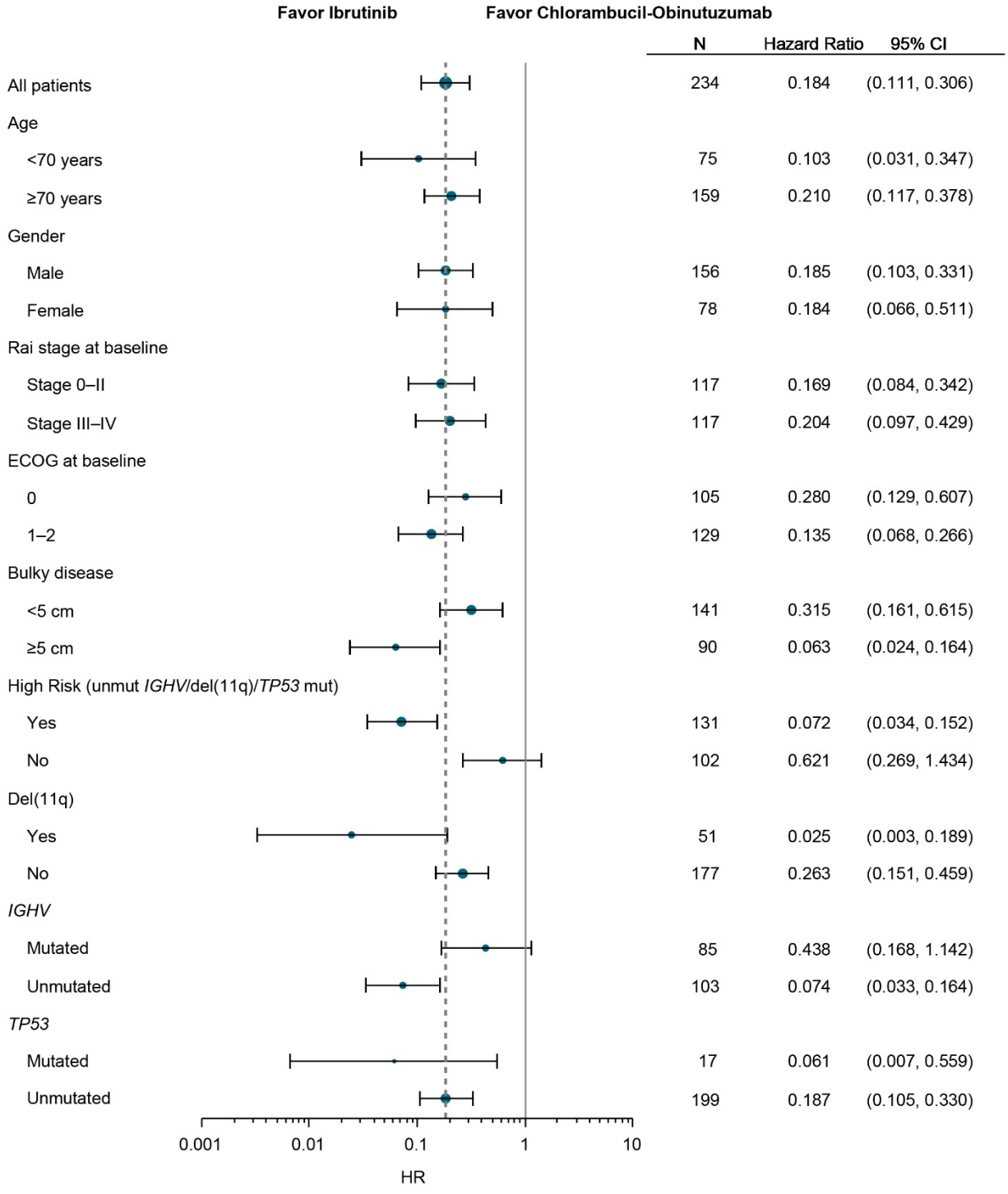
[a]N=patients with available data.

Supplemental Table 3. Summary of lymphocytosis[a] and normalization of ALC

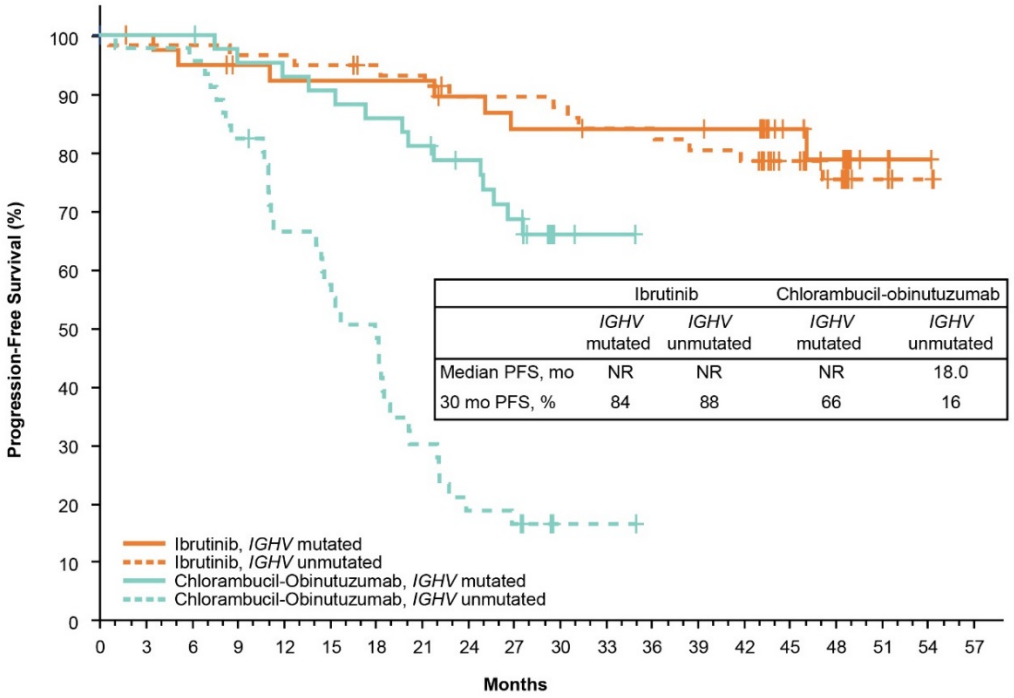
	Ibrutinib N=135	**Ibrutinib-Obinutuzumab N=99**
Patients with lymphocytosis, n/N[b] (%)	77/135 (57)	8/97 (8)
Patients with resolved lymphocytosis, n/N (%)	73/77 (95)	8/8 (100)
Median duration of lymphocytosis[c], weeks (range)	12.4 (0.1+ to 89.1+)	3.1 (1.3-19.0)
Normalization of ALC (<4×10^9/L) post-baseline Overall population, n (%) With elevated ALC (≥4×10^9/L) at baseline, n/N (%)	 110 (81) 103/128 (80)	 97(98) 92/94 (98)

ALC, absolute lymphocyte count; + indicates censored observation.
[a]Defined as ALC increasing ≥50% from baseline and achieving level ≥5×10^9/L.
[b]Of patients with baseline and any post-baseline ALC measurements.
[c]Number of weeks from first post-baseline ALC, which met the lymphocytosis criteria to the earliest date of the following ALC, which met the resolution of lymphocytosis criteria or date of censoring (date of last non-missing ALC). The Kaplan-Meier method was used to estimate the median time.

Supplemental Figure 1. **Subgroup analysis of PFS (investigator assessment) with single-agent ibrutinib *versus* chlorambucil-obinutuzumab.** Forest plot shows hazard ratios for disease progression or death across patient subgroups. Sizes of circles are proportional to the sample size for each subgroup. Error bars indicate 95% CIs.



Supplemental Figure 2. **Progression-free survival (investigator assessment) by *IGHV* mutation status with single-agent ibrutinib *versus* chlorambucil-obinutuzumab.** Vertical tick marks indicate patients with censored data.

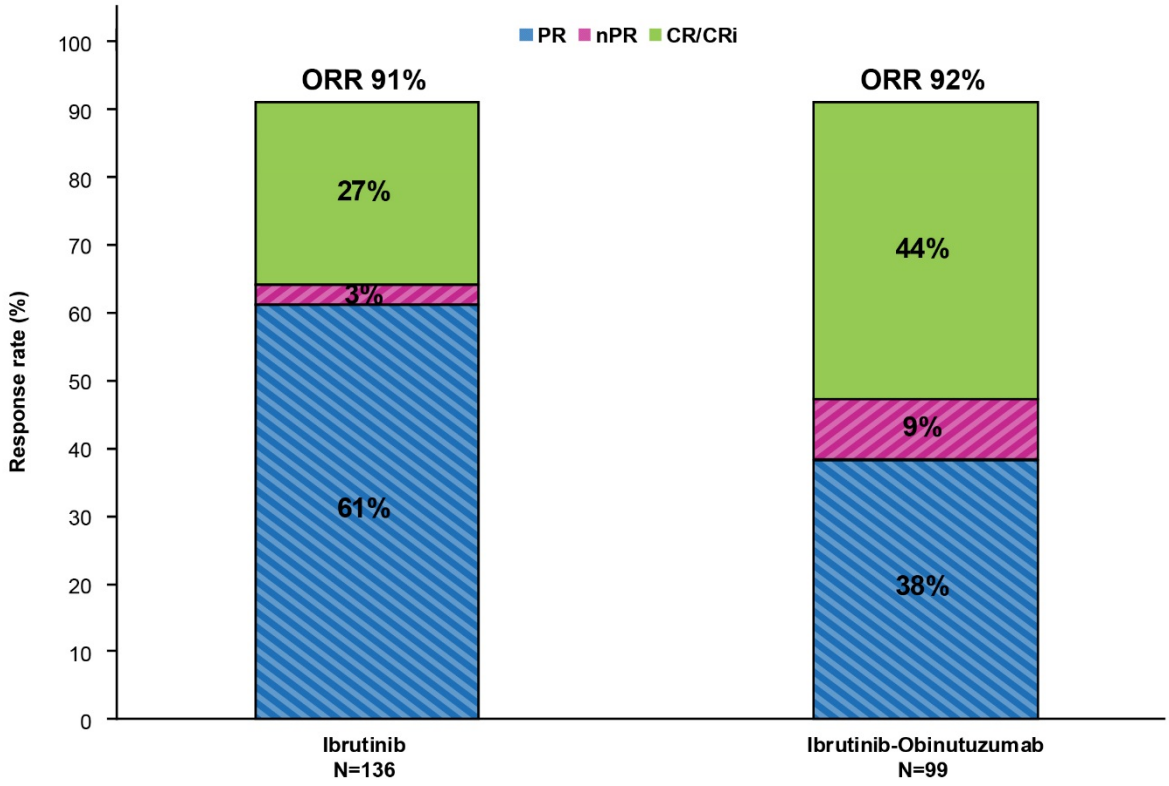


	Ibrutinib		Chlorambucil-obinutuzumab	
	IGHV mutated	*IGHV* unmutated	*IGHV* mutated	*IGHV* unmutated
Median PFS, mo	NR	NR	NR	18.0
30 mo PFS, %	84	88	66	16

Patients at Risk

Ibrutinib, *IGHV* mutated	40	39	37	35	34	34	34	34	32	30	30	30	30	30	29	18	15	3	1	0
Ibrutinib, *IGHV* unmutated	58	57	57	56	56	55	53	52	49	49	48	45	45	43	42	33	23	8	2	0
Chlorambucil-obinutuzumab, *IGHV* mutated	45	43	43	41	39	38	36	34	31	27	4	3	0							
Chlorambucil-obinutuzumab, *IGHV* unmutated	45	44	43	37	29	25	22	13	8	7	1	1	0							

Supplemental Figure 3. **Best response (investigator assessment) with single-agent ibrutinib and ibrutinib-obinutuzumab.** CR/CRi, complete response/complete response with incomplete bone marrow recovery; ORR, overall response rate; nPR, nodular partial response; PR, partial response.



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