SUPPLEMENTARY APPENDIX

Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2

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Supplementary Online Content

First-line Ibrutinib in Older Patients With Chronic Lymphocytic Leukemia: Extended Phase 3 Results From RESONATE-2

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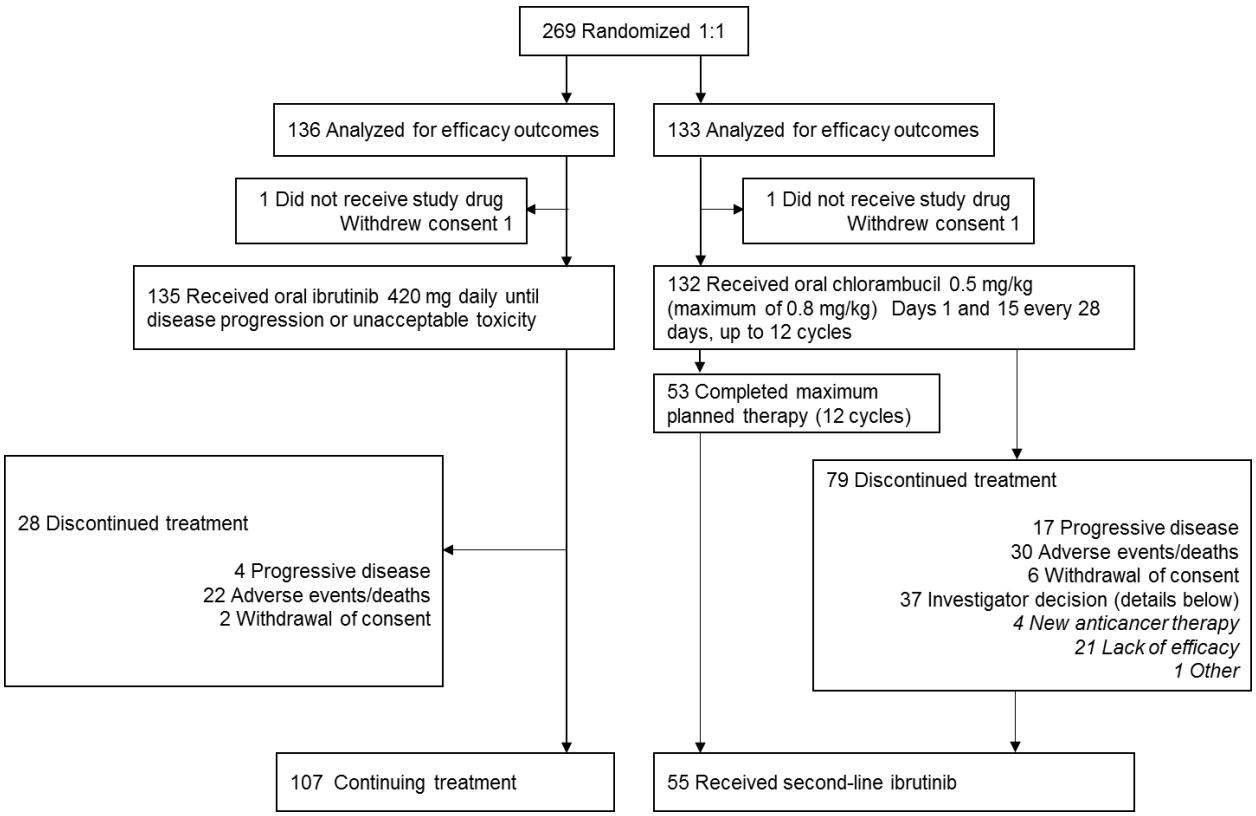
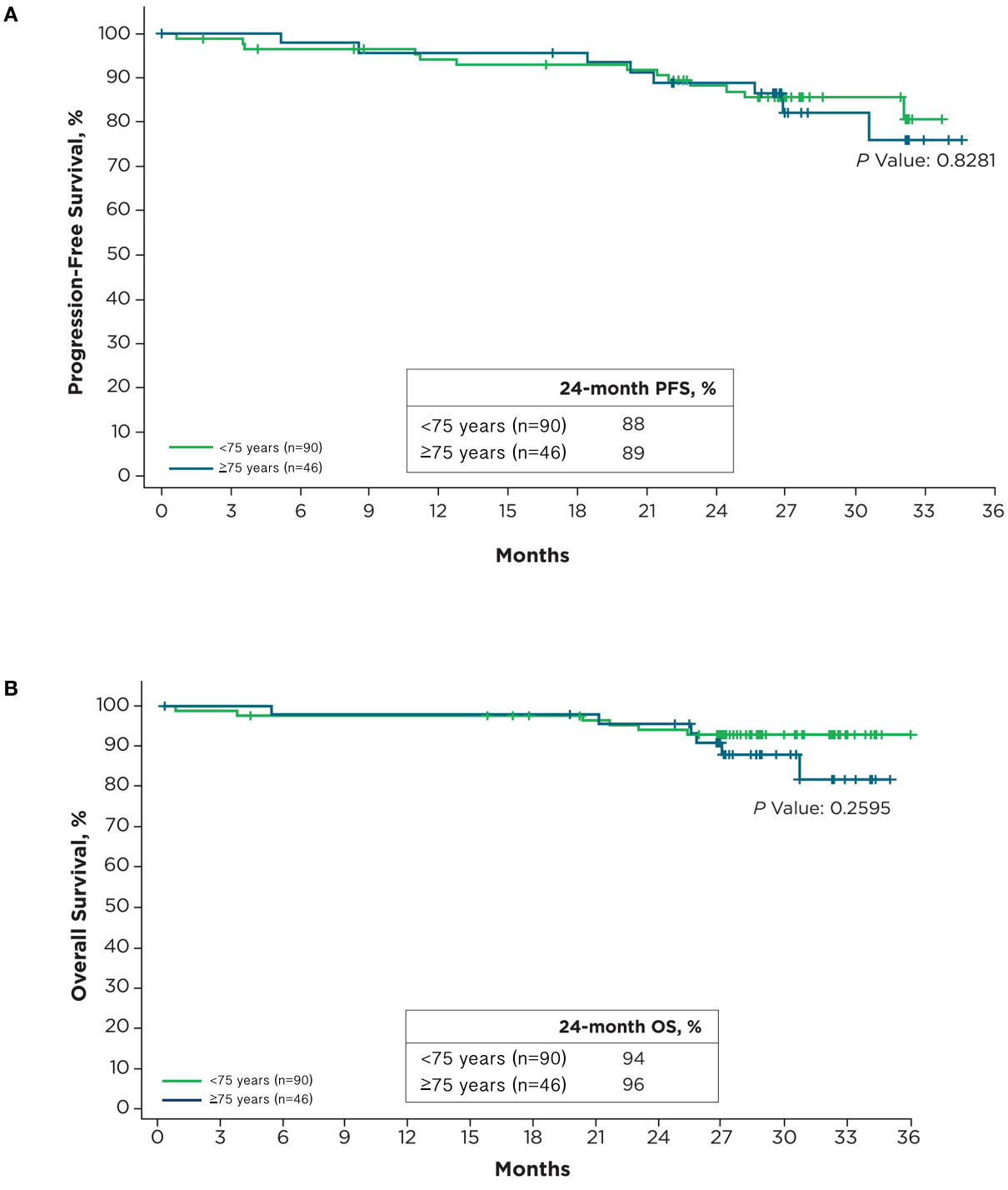
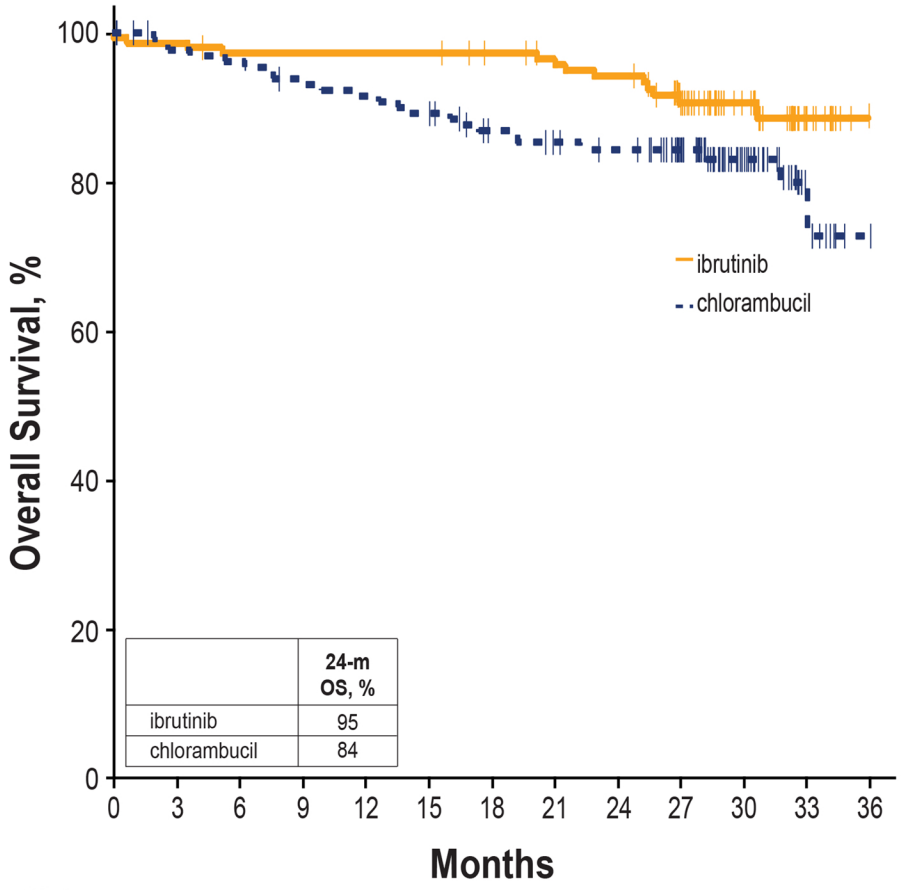
1. **Figure S1.** Patient flow with extended follow-up in the RESONATE-2 trial



2. **Figure S2.** PFS and OS for patients receiving ibrutinib by age subgroup



3. **Figure S3.** OS for the Intent-to-Treat Population



Patients at Risk

ibrutinib	136	134	131	131	131	131	128	124	122	87	50	16	0
chlorambucil	133	127	125	121	118	114	106	102	99	79	39	11	0

OS, overall survival.
Survival analyses from randomization until event or censored at last follow-up using the Kaplan-Meier method. Vertical ticks indicate censored patients.

4. **Table S1.** OS adjusted for crossover

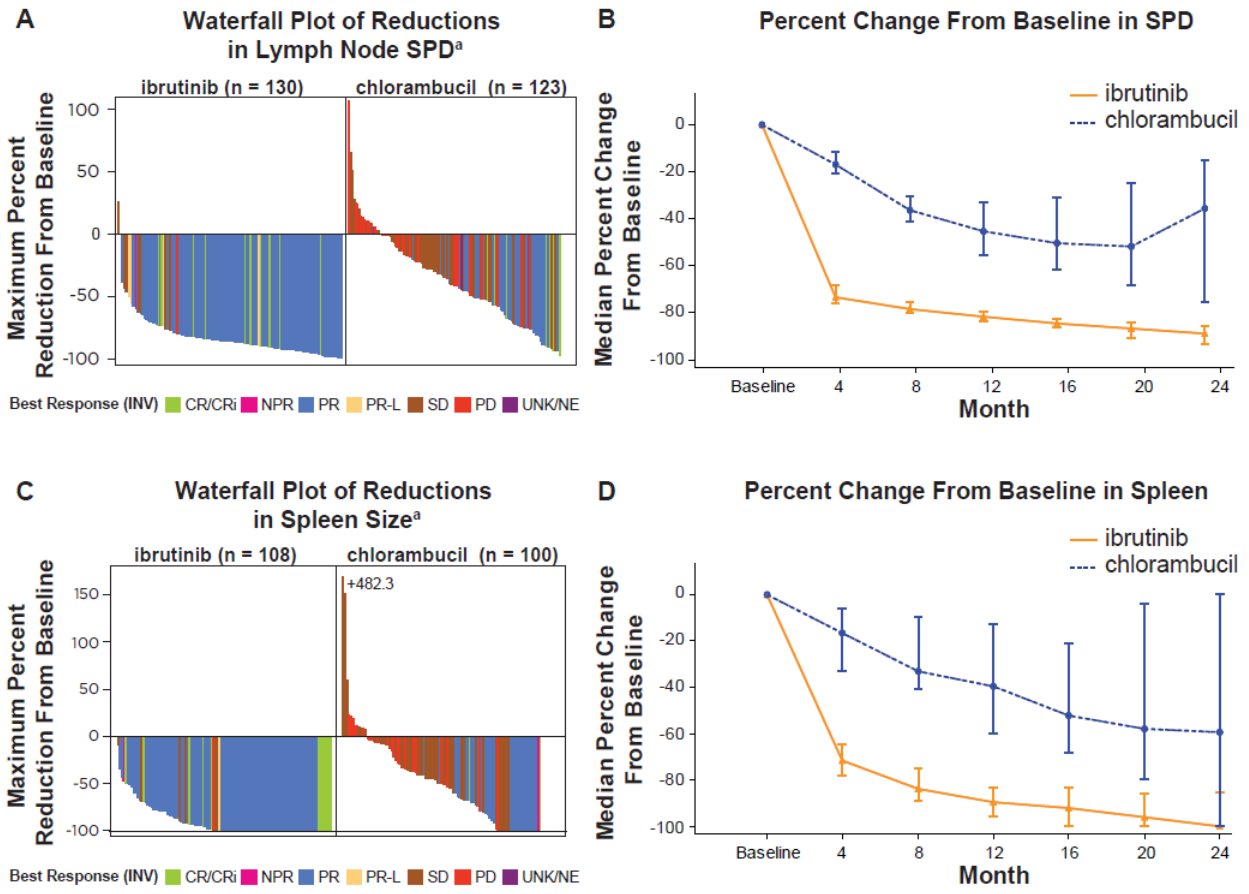
Method	Cox model		Log-rank *P* value
	HR	95% CI	
ITT	0.43	0.21-0.86	.0145
RPSFT model[a]	0.28	0.13-0.60	—
Excluding crossover patients[b]	0.31	0.15-0.66	.0013

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; RPSFT, rank-preserving structural failure time.

[a] Cox model including treatment and baseline covariates to compensate for any lack of balance between treatment arms and improve precision (ECOG PS, Rai stage, age, sex, bulky disease, del11q, region, ethnicity, lactate dehydrogenase, β2-microglobulin, creatinine clearance).

[b] Analysis stratified by 2 randomization factors: ECOG PS (0/1 vs 2) and Rai stage (0/I/II vs III/IV) at baseline as reported in the interactive web response system.

5. **Figure S4.** Reductions in lymphadenopathy and splenomegaly over time with ibrutinib treatment.

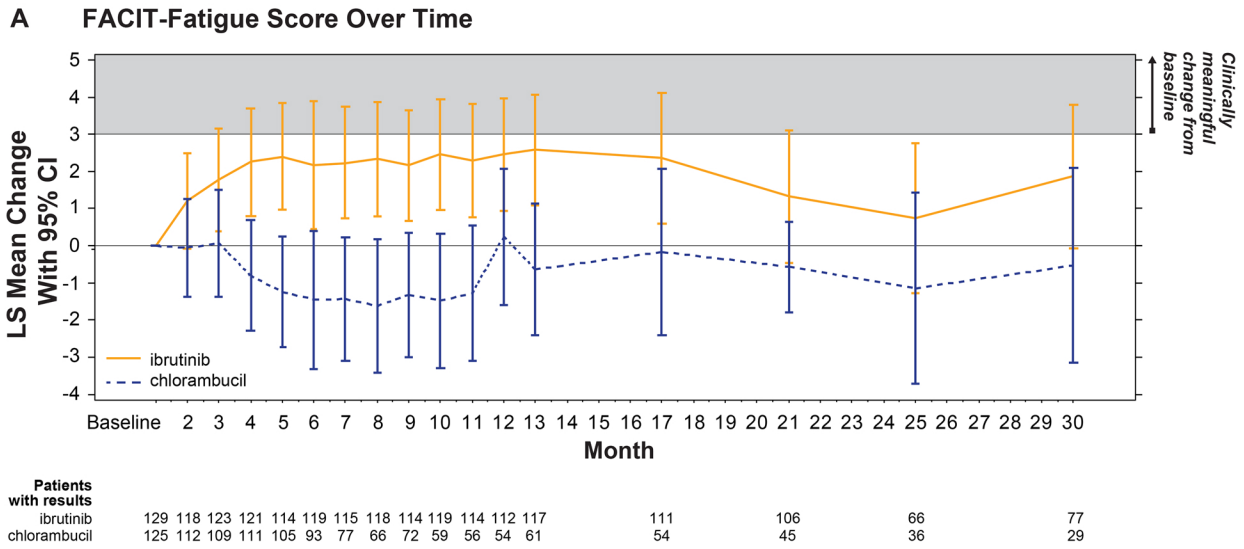


CRi, complete response with incomplete blood-count recovery; NPR, nodular partial response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SPD, sum of the product of perpendicular diameters of lymph nodes; UNK/NE, unknown/not evaluable.

Of patients with baseline lymphadenopathy, 95% (124/130) experienced a ≥ 50% reduction in the lymph node sum of the product of longest diameter (SPD) with ibrutinib versus 40% (49/123) of those treated with chlorambucil, with complete resolution in 42% (55/130) versus 7% (9/123), respectively (A and B). Of those with baseline splenomegaly, 95% (103/108) experienced a ≥ 50% reduction with ibrutinib versus 52% (52/100) with chlorambucil, with complete resolution in splenomegaly in 56% (60/108) versus 22% (22/100), respectively (C and D).

[a] For patients with measurable disease at baseline, reductions in lymphadenopathy and spleen size were measured by an Independent Review Committee at the time of primary analysis while best response was investigator assessed.

6. **Figure S5.** Patient-reported QOL measures over time.



CI, confidence interval; LS, least squares; QOL, quality of life.

7. Table S2. Most frequent AEs (≥15%) in ibrutinib-treated patients

AEs, n (%)	Ibrutinib-treated patients (n=135) Median duration of treatment = 28.5 months (range, 0.7-35.9 months)					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	61 (45)	40 (30)	16 (12)	5 (4)	0	0
Fatigue	44 (33)	29 (21)	13 (10)	2 (1)	0	0
Cough	38 (28)	30 (22)	8 (6)	0	0	0
Anemia	31 (23)	8 (6)	14 (10)	8 (6)	1 (1)	0
Nausea	31 (23)	21 (16)	9 (7)	1 (1)	0	0
Peripheral edema	29 (21)	20 (15)	7 (5)	2 (1)	0	0
Arthralgia	27 (20)	15 (11)	9 (7)	3 (2)	0	0
Pyrexia	27 (20)	17 (13)	9 (7)	0	0	1 (1)
URTI	26 (19)	7 (5)	16 (12)	3 (2)	0	0
Dry eye	25 (19)	23 (17)	2 (1)	0	0	0
Hypertension	24 (18)	4 (3)	13 (10)	7 (5)	0	0
Neutropenia	23 (17)	3 (2)	4 (3)	8 (6)	8 (6)	0
Vomiting	23 (17)	15 (11)	8 (6)	0	0	0
Constipation	22 (16)	16 (12)	5 (4)	1 (1)	0	0
Blurred vision	22 (16)	17 (13)	5 (4)	0	0	0

AE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

8. Frequent concomitant medications of clinical interest

Types of concomitant medications, n (%)	**Ibrutinib (n=135) median DOT = 28.5 months (range, 0.7-35.9 months)**	**Chlorambucil (n=132) median DOT = 7.1 months (range, 0.5-11.7 months)**
Antiplatelet agents	66 (49)	67 (51)
Acetylsalicylic acid (aspirin)	45 (33)	48 (36)
NSAIDs	35 (26)	23 (17)
Clopidogrel	8 (6)	4 (3)
Anticoagulants	28 (21)	13 (9)
LMWH	19 (14)	6 (5)
Heparin	5 (4)	1 (1)
Direct oral anticoagulants	6 (4)	6 (5)
Neutrophil growth factors	12 (9)	16 (12)
RBC transfusions	20 (15)	21 (16)
Platelet transfusions	2 (1)	3 (2)
Intravenous immunoglobulin	6 (4)	2 (2)

DOT, duration of treatment; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drug; RBC, red blood cell.

9. Table S4. Patients who discontinued ibrutinib due to AEs and died

Patient	AE leading to discontinuation	OS, months	Last dose of ibrutinib to death, days
1	Bilateral pneumonia (*Legionella pneumophylae*)	3.5	39
2	Secondary malignancy (non-small cell lung cancer)	20.2	180
3	Fever	21.5	5

AE, adverse event; OS, overall survival.

10. References

1. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.