Treatment With First-Line Ibrutinib Improves Overall Survival in Patients With Chronic Lymphocytic Leukemia and High-Risk Genomic Features to Rates Approximating an Age-Matched US Population: Pooled Analysis of Phase 3 Trials With 10 Years of Follow-Up

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OBJECTIVE

To evaluate long-term overall survival (OS) outcomes in a pooled population of patients with previously untreated chronic lymphocytic leukemia (CLL), including those with high-risk genomic features, who received first-line ibrutinib treatment in 2 phase 3 trials with survival estimates compared with that of the US age-matched general population

CONCLUSIONS

With the longest follow-up time of any commercially available targeted therapy for CLL, this pooled analysis demonstrates that firstline treatment with ibrutinib provided long-term OS benefit in patients with CLL, with survival estimates that appear similar to those of a US age-matched general population

OS estimates for patients treated with ibrutinib appear similar to those of the age-matched general population regardless of evaluation from randomization or initial diagnosis and irrespective of age or high-risk features

With additional follow-up, active management of adverse events (AEs) through dose reductions continues to result in AE resolution in most patients, allowing patients to remain on ibrutinib treatment and potentially maximizing benefit



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INTRODUCTION

- Ibrutinib, a Bruton tyrosine kinase inhibitor (BTKi), changed the treatment landscape by demonstrating improved overall survival (OS) compared with chemotherapy/chemoimmunotherapy across multiple phase 3 trials in patients with chronic lymphocytic leukemia (CLL), including those with highrisk genomic features¹⁻⁷
- Recently, data were reported for patients treated with ibrutinib in the phase 3 RESONATE-2 trial with up to 10 years of follow-up, representing the longest follow-up of any BTKi used in first-line treatment of CLL⁸
- With the most robust long-term follow-up data among BTKis, ibrutinib therapy trials are uniquely positioned to assess the long-term OS benefit of first-line BTKi treatment in patients with CLL across patient subgroups

RESULTS

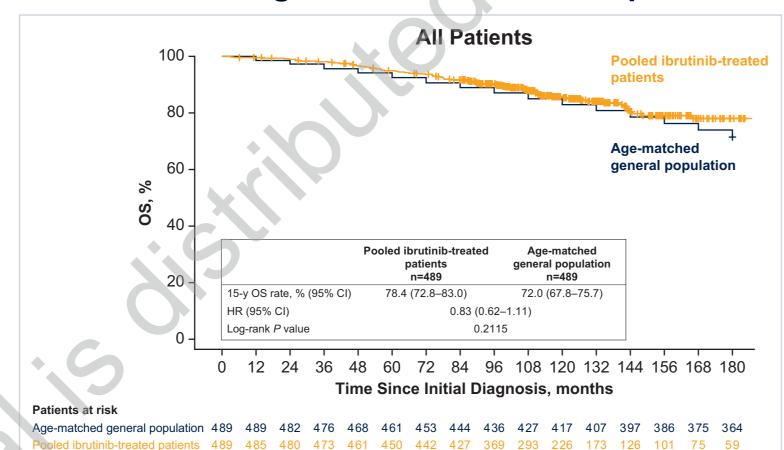
- 490 patients were pooled across the 2 studies - 352 patients (71.8%) were treated with ibrutinib + rituximab
- in E1912, and 135 patients (27.6%) were treated with single-agent ibrutinib in RESONATE-2
- 2 patients in E1912 and 1 patient in RESONATE-2 did not receive study treatment
- OS was analyzed in the intention-to-treat population
- Median follow-up was 10.3 years (123.5 months) from initial diagnosis and 8.3 years (99.2 months) from randomization
- At the time of analysis, study treatment had been discontinued in 293 of 490 (59.8%) pooled ibrutinib-treated patients
- 126 of 293 patients (43.0%) discontinued treatment due to AEs and 60 of 293 patients (20.5%) discontinued treatment due to progressive disease
- Study treatment was ongoing in 156 of 490 patients (31.8%)

Baseline Characteristics of Pooled Ibrutinib-Treated Patients

Characteristic	Pooled Ibrutinib-Treated Patients N=490
Age at randomization	
Median (range), years	61.0 (31–89)
≥65 years, n (%)	179 (36.5)
Age at diagnosis	
Median (range), years	59.0 (30–87)
≥65 years, n (%)	128 (26.1)
Median time from initial diagnosis to randomization (range), months	20.9 (0.0–341.8)
Male sex, n (%)	324 (66.1)
Baseline ECOG PS, n (%)	
0 or 1	468 (95.5)
2	22 (4.5)
CIRS score, n (%) ^a	
≤6	410 (83.7)
>6	56 (11.4)
IGHV, n (%)ª	
Unmutated	268 (54.7)
Mutated	109 (22.2)
No amplification	20 (4.1)
Polyclonal	3 (0.6)
del(11q), n (%) ^a	
Yes	107 (21.8)
No	375 (76.5)
del(17p), n (%) ^a	
Yes	2 (0.4)
No	483 (98.6)
TP53 mutated, n (%) ^a	
Yes	38 (7.8)
No	391 (79.8)

CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status. ^aBaseline data were missing for CIRS score (n=24), IGHV (n=90), del(11q) (n=8), del(17p) (n=5) and TP53 (n=61)

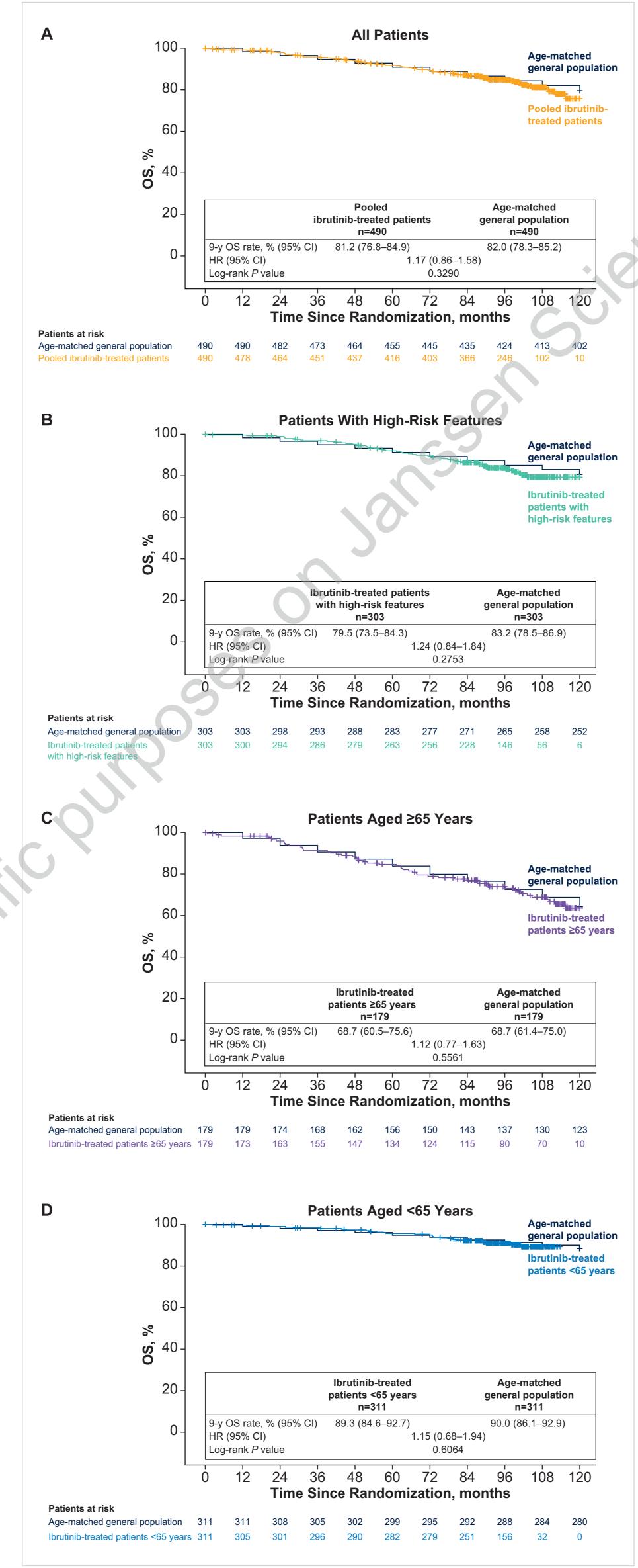
Estimated OS From Initial Diagnosis in Ibrutinib-Treated Patients Also Appeared Similar to That of an Age-Matched General Population



• Estimated OS from the time of initial diagnosis appeared similar between ibrutinib-treated patients versus the age-matched general population irrespective of high-risk features or age (Supplement)

- over longer follow-up durations
- clinical outcomes¹³⁻¹⁵

Estimated OS From Randomization in Ibrutinib-Treated Patients Was Similar to That of an Age-Matched General **Population Irrespective of High-Risk Features^a or Age**



HR, hazard ratio. ^aDefined as those with del(11q), del(17p), mutated TP53, and/or unmutated IGH\

• We previously demonstrated that first-line ibrutinib is associated with OS rates that appear similar to those in the age-matched general population, with a median follow-up of 5.9 years since initial diagnosis.⁹ It remains unclear whether this holds true for patients with high-risk genomic features

• In previous studies, continuation of ibrutinib treatment was associated with better survival outcomes¹⁰⁻¹²; active management of adverse events (AEs) by dose modification might facilitate continued ibrutinib treatment and maximize

METHODS

- Data were pooled for patients with previously untreated CLL who received first-line treatment with single-agent ibrutinib in the RESONATE-2 study (NCT01722487)¹ or ibrutinib + rituximab in the ECOG-ACRIN E1912 study (NCT02048813)⁵
- Detailed methods and results from these studies were previously described^{1,5} • OS probabilities from the time of randomization and from the time of initial diagnosis for ibrutinib-treated patients were compared with an agematched general population using 2021 life tables for the total US population published by the Centers for Disease Control and Prevention (CDC; www.cdc.gov/nchs/products/life_tables.htm)
- OS was estimated using the Kaplan-Meier method
- Estimated OS from the time of randomization was also similar between ibrutinib-treated patients versus the age-matched general population when analyzed according to individual high-risk features (del(11q), del(17p), mutated TP53, and/or unmutated IGHV)
- In patients with del(11q) (n=107), estimated 9-year OS rates were 75.2% (95% CI, 64.7–83.0) versus 80.4% (95% CI, 71.5–86.7), with an HR of 1.37 (95% CI, 0.75–2.51)
- In patients with unmutated IGHV (n=268), estimated 9-year OS rates were 81.6% (95% CI, 75.3–86.4) versus 83.6% (95% CI, 78.6–87.5), with an HR of 1.17 (95% CI, 0.76–1.80)
- Analysis of OS for patients with del(17p) or mutated *TP53* was precluded by small numbers of patients in these subgroups

Dose Modifications

- Active dose management for the prevention of AE recurrence or worsening (through dose reductions and dose holds) may allow patients to remain on ibrutinib, thereby contributing to an OS benefit
- Of 135 patients treated with single-agent ibrutinib in RESONATE-2, 34 (25.5%) had AEs leading to dose reductions

Any AEs Leading to Dose Reductions in Ibrutinib-Treated Patients

AEs Leading to Dose Reduction	
Any AE leading to dose reduction, n (%)	
Median time on study after first dose reduction (range), months	
First dose reduced to, n (%) ^a	
280 mg	
140 mg	
Resolution of first AE leading to dose reduction, n/N (%) ^a	
Recurrence of first AE leading to dose reduction, n/N (%) ^a	
No recurrence or recurred at lower grade	
Recurred at same or higher grade ^b	
AEs leading to dose reduction by SOC, n (%) ^c	
Hematologic	
Dermatologic	
Infection	
Cardiac	
Gastrointestinal	
Musculoskeletal	
Injuries	
Neoplasms	
Other	
Grade of AE leading to dose reduction, n (%) ^c	
Grade 1	
Grade 2	
Grade 3	
Grade 4	

SOC, system organ class.

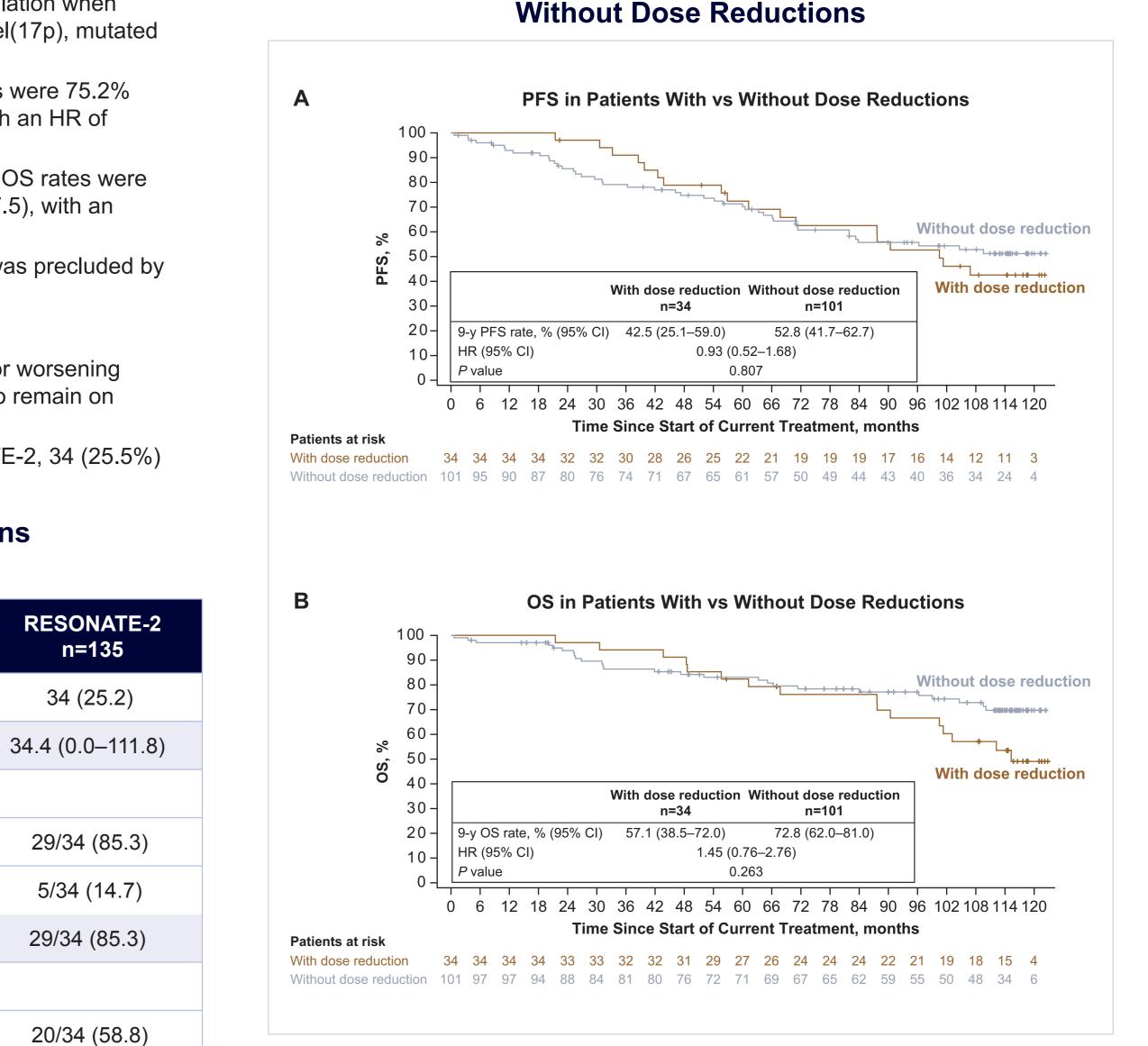
^aDenominator is patients with any AE leading to dose reduction. ^bOf the 14 AEs that recurred at same/higher grade at any point during treatment, 2/14 were cardiac, 1/14 was gastrointestinal, 3/14 were hematologic, 3/14 were infections, 1/14 was neoplasms, and 4/14 were other. °The same patient may be counted in ≥ 1 category due to multiple events.

Strengths and Limitations

- Strengths of this study include the relatively large number of patients and the long duration of follow-up
- characteristics
- time of initial diagnosis is subject to immortal time bias
- account for this may improve the estimation of confidence intervals; however, overall conclusions would likely remain consistent collected during the COVID-19 pandemic and includes deaths occurring from COVID-19
- The generation of the general population dataset is based on population data, and variances may be overestimated when treated as a patient-level dataset. Approaches to • This updated analysis incorporates data from ibrutinib-treated patients and the US age-matched general population (obtained from the CDC 2021 life tables), which was
- Confidence intervals may overlap due to limited sample size and power; as a result, we can only conclude failure to detect a statistically significant difference

- Subgroup analyses were performed for patients with high-risk genomic features, defined as those with del(11q), del(17p), mutated *TP53*, and/or unmutated IGHV, and for patients aged ≥65 or <65 years
- AEs leading to dose reductions were assessed in ibrutinib-treated patients from the RESONATE-2 study
- Patients from the E1912 study were excluded from the analysis due to limitations in details of AE data collection

PFS and OS in Patients With Versus



PFS, progression-free surviva

14/34 (41.2)

7 (5.2)

5 (3.7)

5 (3.7)

4 (3.0)

2 (1.5)

2 (1.5)

1 (0.7)

1 (0.7)

11 (8.1)

11 (8.1)

15 (11.1)

12 (8.9)

2 (1.5)

AEs With Recommended Dose Reductions per Ibrutinib USPI^{a,16} in Ibrutinib-Treated Patients

10 (7.4) 34.4 (0.0–111.8) 8/10 (80.0)	
8/10 (80 0)	
8/10 (80 0)	
0,10 (0010)	
1/10 (10.0)	
1/10 (10.0)	
10/10 (100.0)	
Recurrence of first AE leading to dose reduction, n/N (%) ^b	
7/10 (70.0)	
3/10 (30.0)	

^aAEs for which dose reductions are recommended in the ibrutinib USPI (grade 2 cardiac failure, grade 3 cardiac arrhythmia, grade 3 or 4 nonhematologic AEs [excluding cardiac failure and cardiac arrhythmia], grade 3 or 4 neutropenia with infection or fever, and grade 4 hematologic AEs).¹ ^bDenominator is patients with dose reductions because of AEs per recommendations in the ibrutinib USPI.

°Of the 3 AEs that recurred at same/higher grade at any point during treatment, 1/3 was cardiac and 2/3 were other.

• Because of limitations in data availability, the pooled ibrutinib-treated population was matched to the general population only for age and not for other individual patient

• The pooled ibrutinib-treated population included only patients who survived from initial diagnosis to study enrollment and randomization; as such, analysis of OS from the

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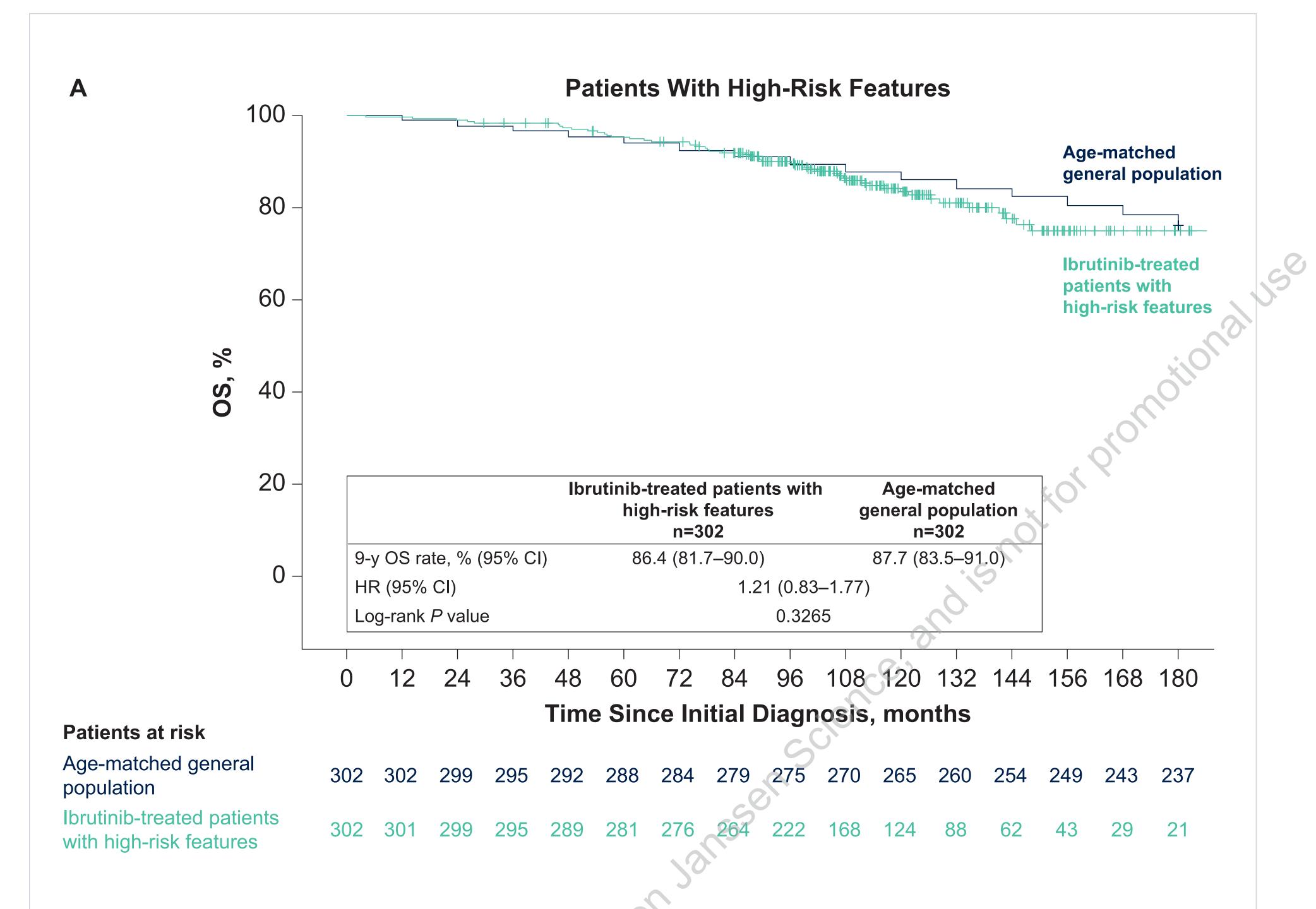
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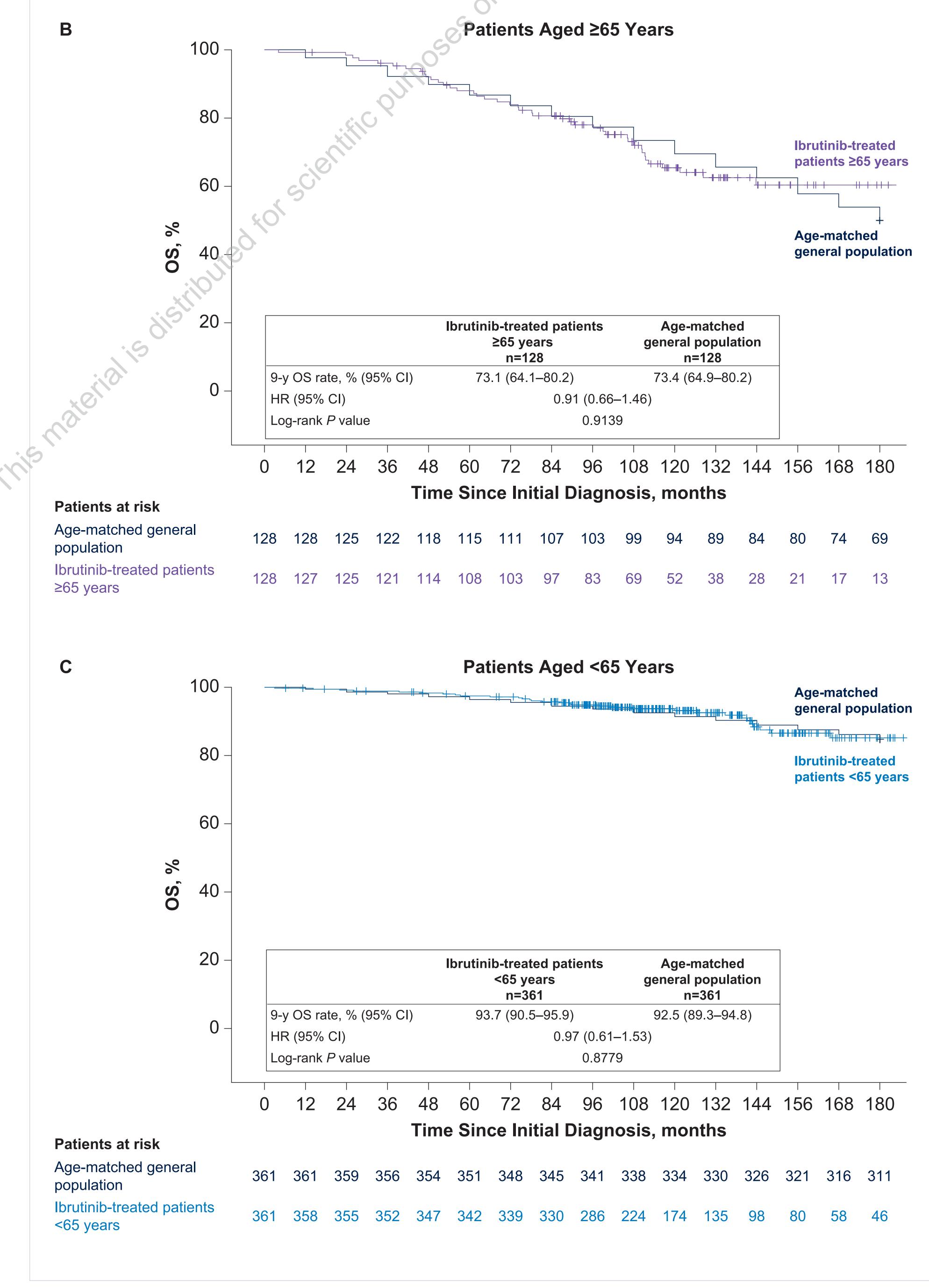
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SUPPLEMENTAL INFORMATION

Estimated OS From Initial Diagnosis in Ibrutinib-Treated Patients Was Similar to That of an Age-Matched General

Population Irrespective of High-Risk Features^a or Age





HR, hazard ratio; OS, overall survival.

^aDefined as those with del(11q), del(17p), mutated TP53, and/or unmutated IGHV.