Real-World Outcomes Among Medicare Beneficiaries Treated With First-Line Bruton Tyrosine Kinase Inhibitors for Chronic Lymphocytic Leukemia

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CONCLUSION

- In this large real-world cohort of patients aged ≥65 years with the longest follow-up to date, zanubrutinib monotherapy was associated with significantly better rwTTD, rwTTNT, and rwOS compared with ibrutinib and acalabrutinib
- Stratification by age group resulted in similar outcomes between treatment groups

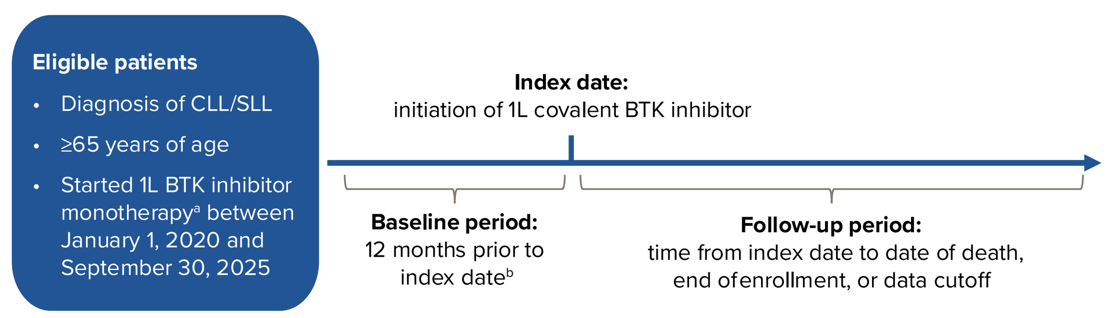
INTRODUCTION

- Covalent Bruton tyrosine kinase (BTK) inhibitor monotherapies are the standard of care for first-line (1L) treatment of chronic lymphocytic leukemia (CLL) in the US[1]; however, there is a lack of head-to-head trials comparing BTK inhibitors in the 1L setting
- Previous real-world studies were frequently limited by short follow-up, small sample sizes, or patient populations derived from a single institution
- In this study, we used Medicare, the largest payer for patients aged ≥65 years in the US,[2] to evaluate clinical outcomes in patients treated with BTK inhibitors for CLL in the 1L setting

METHODS

- This retrospective, observational, cohort study in patients with CLL/small lymphocytic lymphoma used the deidentified Medicare Fee-for-Service database (**Figure 1**)
- Outcomes included real-world time to treatment discontinuation or death (rwTTD), time to next treatment (rwTTNT), and overall survival (rwOS) from start of 1L treatment
  - Discontinuation was defined as having a subsequent systemic therapy after the current line of therapy (LOT), having a gap of >180 days with no systemic therapy after the last drug episode of the current LOT, or having a date of death
- Median time to event and landmark treatment and survival probabilities at 12 and 24 months were estimated using Kaplan-Meier methods
- Adjusted hazard ratios (aHRs) and 95% CIs were estimated using Cox proportional hazards models, adjusting for age, sex, race and ethnicity, Charlson Comorbidity Index, and year of 1L initiation
- Stratified analysis was performed by age group (65-74, 75-84, and ≥85 years)

Figure 1. Study Design



[a]Ibrutinib, acalabrutinib, or zanubrutinib. [b]Unless otherwise specified.
Abbreviations: 1L, first line; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

RESULTS

Patient Characteristics

- A total of 10,523 patients with CLL were included: 3006 received zanubrutinib, 4309 received acalabrutinib, and 3208 received ibrutinib
- Baseline demographics and clinical characteristics are summarized in **Table 1**
  - Median age at 1L initiation was 77 years for patients treated with zanubrutinib (IQR, 72-82) and acalabrutinib (IQR, 72-83) and 76 (IQR, 71-82) years for patients treated with ibrutinib
  - Most patients were male (58.3%), were non-Hispanic White (89.3%), and resided in urban areas (78.0%)
  - At baseline, hypertension was reported in 64.7% of patients overall, and atrial fibrillation was reported in 17.1%, 17.2%, and 11.6% of patients treated with zanubrutinib, acalabrutinib, and ibrutinib, respectively
- Median follow-up was 15.8 (range, 0.1-61.2) months for zanubrutinib, 20.7 (range, 0.0-69.2) months for acalabrutinib, and 34.9 (range, 0.0-69.4) months for ibrutinib

Table 1. Baseline Demographics and Clinical Characteristics

	Regimen at First LOT			
Characteristics	**Acalabrutinib (n=4309 [40.9%])**	**Ibrutinib (n=3208 [30.5%])**	**Zanubrutinib (n=3006 [28.6%])**	**Total (N=10,523)**
Age group, n (%)				
65-69 years	606 (14.1)	518 (16.1)	451 (15.0)	1575 (15.0)
70-74 years	1005 (23.3)	831 (25.9)	702 (23.4)	2538 (24.1)
75-79 years	992 (23.0)	792 (24.7)	706 (23.5)	2490 (23.7)
80-84 years	880 (20.4)	568 (17.7)	629 (20.9)	2077 (19.7)
≥85 years	826 (19.2)	499 (15.6)	518 (17.2)	1843 (17.5)
Sex, n (%)				
Female	1771 (41.1)	1379 (43.0)	1240 (41.3)	4390 (41.7)
Male	2358 (58.9)	1829 (57.0)	1766 (58.7)	6133 (58.3)
Race (RTI race code), n (%)				
Non-Hispanic White	3847 (89.3)	2863 (89.3)	2691 (89.5)	9401 (89.3)
Hispanic	90 (2.1)	72 (2.2)	68 (2.3)	230 (2.2)
Black	166 (3.8)	148 (4.6)	96 (3.2)	410 (3.9)
Asian/Pacific Islander	51 (1.2)	36 (1.1)	39 (1.3)	126 (1.2)
Other	27 (0.6)	18 (0.6)	20 (0.7)	65 (0.6)
Unknown	128 (3.0)	71 (2.2)	92 (3.0)	291 (2.8)
Socioeconomic status, n (%)				
Dual eligibility	384 (8.9)	357 (11.1)	216 (7.2)	957 (9.1)
Low-income subsidy	436 (10.1)	413 (12.9)	249 (8.3)	1098 (10.4)
Rural-urban community area, n (%)				
Urban	3425 (79.5)	2392 (74.6)	2386 (79.4)	8203 (78.0)
Rural	884 (20.5)	816 (25.4)	620 (20.6)	2320 (22.0)
CCI score, median[a]	4.0	3.0	4.0	4.0
CCI score, n (%)				
None (0)	416 (9.7)	322 (10.0)	277 (9.2)	1015 (9.6)
Mild (1/2)	1050 (24.4)	810 (25.2)	680 (22.6)	2540 (24.1)
Moderate (3/4)	1203 (27.9)	865 (27.0)	813 (27.1)	2881 (27.4)
Severe (≥5)	1640 (38.0)	1211 (37.8)	1236 (41.1)	4087 (38.8)
Comorbidities of interest, n (%)				
Atrial fibrillation	743 (17.2)	371 (11.6)	514 (17.1)	1628 (15.5)
Arrythmia	343 (8.0)	182 (5.7)	250 (8.3)	775 (7.4)
Cerebrovascular disease	56 (1.3)	37 (1.1)	41 (1.4)	134 (1.3)
Hypertension	2758 (64.0)	2106 (65.6)	1943 (64.6)	6807 (64.7)
Coronary artery disease (including MI)	1098 (25.5)	690 (21.5)	770 (25.6)	2558 (24.3)
Diabetes	1155 (26.8)	905 (28.2)	808 (26.9)	2868 (27.2)
Neutropenia	100 (2.3)	59 (1.8)	83 (2.8)	242 (2.3)
Headache	18 (0.4)	11 (0.3)	18 (0.6)	47 (0.4)
Migraine	51 (1.2)	38 (1.2)	50 (1.7)	139 (1.3)
Hepatic disease	181 (4.2)	112 (3.5)	164 (5.5)	457 (4.3)
GI bleeding	85 (2.0)	70 (2.2)	69 (2.3)	224 (2.1)
Time from initial diagnosis to index, median (range), months	33 (0-186.0)	28.9 (0-179.5)	27.6 (0-184.7)	30.2 (0-186.0)
Year of index event, n (%)				
2020	463 (10.7)	1282 (40.0)	0	1748 (16.6)
2021	889 (20.6)	876 (27.3)	36 (1.2)	1801 (17.1)
2022	875 (20.3)	549 (17.1)	183 (6.1)	1607 (15.3)
2023	580 (13.5)	196 (6.1)	806 (26.8)	1582 (15.0)
2024	779 (18.1)	202 (6.3)	1393 (46.3)	2374 (22.6)
2025 (through September 2025)	723 (16.8)	103 (3.2)	585 (19.5)	1411 (13.4)

[a]CCI excludes any B-cell malignancies.
Abbreviations: CCI, Charlson Comorbidity Index; GI, gastrointestinal; LOT, line of therapy; MI, myocardial infarction; RTI, Research Triangle Institute.

rwTTD and rwTTNT

- Median rwTTD was not reached (NR) (95% CI, NR-NR) in patients treated with zanubrutinib, 24 (95% CI, 22-25) months in patients treated with acalabrutinib, and 14 (95% CI, 13-15) months in patients treated with ibrutinib (**Figure 2**)
- Patients treated with zanubrutinib had a higher probability of remaining on treatment at 12 and 24 months (72.3% at 12 months and 63.2% at 24 months), followed by those treated with acalabrutinib (62.6% at 12 months and 48.9% at 24 months) and ibrutinib (52.9% at 12 months and 35.1% at 24 months) (**Table 2**)

Table 2. Analysis of rwTTD With Ibrutinib or Acalabrutinib as Reference vs Zanubrutinib

Outcome	Zanubrutinib	Ibrutinib[a]	Acalabrutinib[a]
12-month rwTTD (95% CI), %	72.3 (70.5-73.9)	52.9 (51.1-54.7)	62.6 (61.0-64.1)
24-month rwTTD (95% CI), %	63.2 (61.0-65.4)	35.1 (33.4-36.9)	48.9 (47.1-50.6)
Adjusted HR (95% CI)[b]	–	0.57 (0.51-0.64)	0.86 (0.78-0.94)
***P*-value (adjusted)**	–	<.0001	.0007

[a]Denotes reference group vs zanubrutinib. [b]Adjusted covariates included categorical age (65-74, 75-84, and ≥85 years), sex, race and ethnicity (non-Hispanic White vs other), year of index, and Charlson Comorbidity Index score (0, 1, 2, 3, ≥4).
Abbreviations: HR, hazard ratio; rwTTD, real-world time to treatment discontinuation or death.

- Median rwTTNT was NR (95% CI, 45 months-NR) in patients who received zanubrutinib, 40 (95% CI, 38-42) months with acalabrutinib, and 30 (95% CI, 29-32) months with ibrutinib (**Figure 3**)
- At 12 and 24 months, the probability of not advancing to the next treatment or dying was highest in patients treated with zanubrutinib (82.3% at 12 months and 71.3% at 24 months), followed by those treated with acalabrutinib (78.4% at 12 months and 66.7% at 24 months) and ibrutinib (73.8% at 12 months and 56.4% at 24 months) (**Table 3**)

Table 3. Analysis of rwTTNT With Ibrutinib or Acalabrutinib as Reference vs Zanubrutinib

Outcome	Zanubrutinib	Ibrutinib[a]	Acalabrutinib[a]
12-month rwTTNT (95% CI), %	82.3 (80.8-83.7)	73.8 (72.2-75.3)	78.4 (77.0-79.6)
24-month rwTTNT (95% CI), %	71.3 (69.1-73.4)	56.4 (54.6-58.1)	66.7 (65.1-68.3)
Adjusted HR (95% CI)[b]	–	0.63 (0.55-0.71)	0.87 (0.78-0.96)
***P*-value (adjusted)**	–	<.0001	.008

[a]Denotes reference group vs zanubrutinib. [b]Adjusted covariates included categorical age (65-74, 75-84, and ≥85 years), sex, race and ethnicity (non-Hispanic White vs other), year of index, and Charlson Comorbidity Index score (0, 1, 2, 3, ≥4).
Abbreviations: HR, hazard ratio; rwTTNT, real-world time to next treatment or death.

rwOS

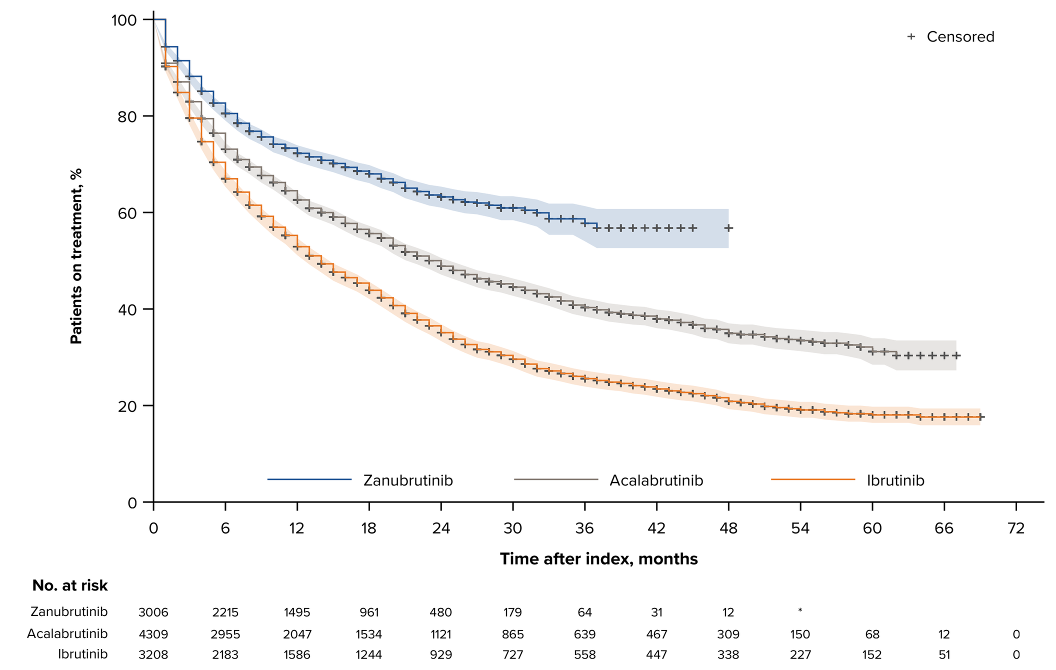
- Median rwOS was NR in all groups (**Figure 4**)
- At 12 and 24 months, patients treated with zanubrutinib had a higher probability of survival (90.8% at 12 months and 85.9% at 24 months) than those treated with acalabrutinib (86.9% at 12 months and 79.7% at 24 months) and ibrutinib (84.8% at 12 months and 75.4% at 24 months) (**Table 4**)

Table 4. Analysis of rwOS With Ibrutinib or Acalabrutinib as Reference vs Zanubrutinib

Outcome	Zanubrutinib	Ibrutinib[a]	Acalabrutinib[a]
12-month rwOS (95% CI), %	90.8 (89.7-91.9)	84.8 (83.5-86.0)	86.9 (85.8-87.9)
24-month rwOS (95% CI), %	85.9 (84.2-87.4)	75.4 (73.8-76.9)	79.7 (78.3-81.0)
Adjusted HR (95% CI)[b]	–	0.64 (0.54-0.77)	0.76 (0.66-0.88)
***P*-value (adjusted)**	–	<.0001	.0002

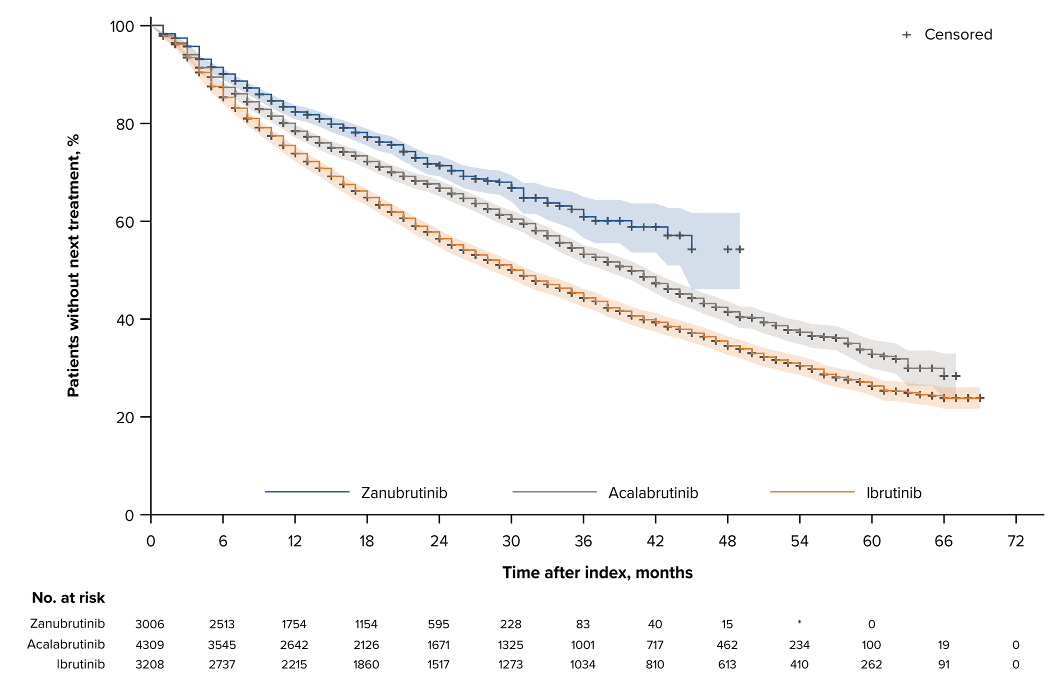
[a]Denotes reference group vs zanubrutinib. [b]Adjusted covariates included categorical age (65-74, 75-84, and ≥85 years), sex, race and ethnicity (non-Hispanic White vs other), year of index, and Charlson Comorbidity Index score (0, 1, 2, 3, ≥4).
Abbreviations: HR, hazard ratio; rwOS, real-world overall survival.

Figure 2. rwTTD by Covalent BTK Inhibitor



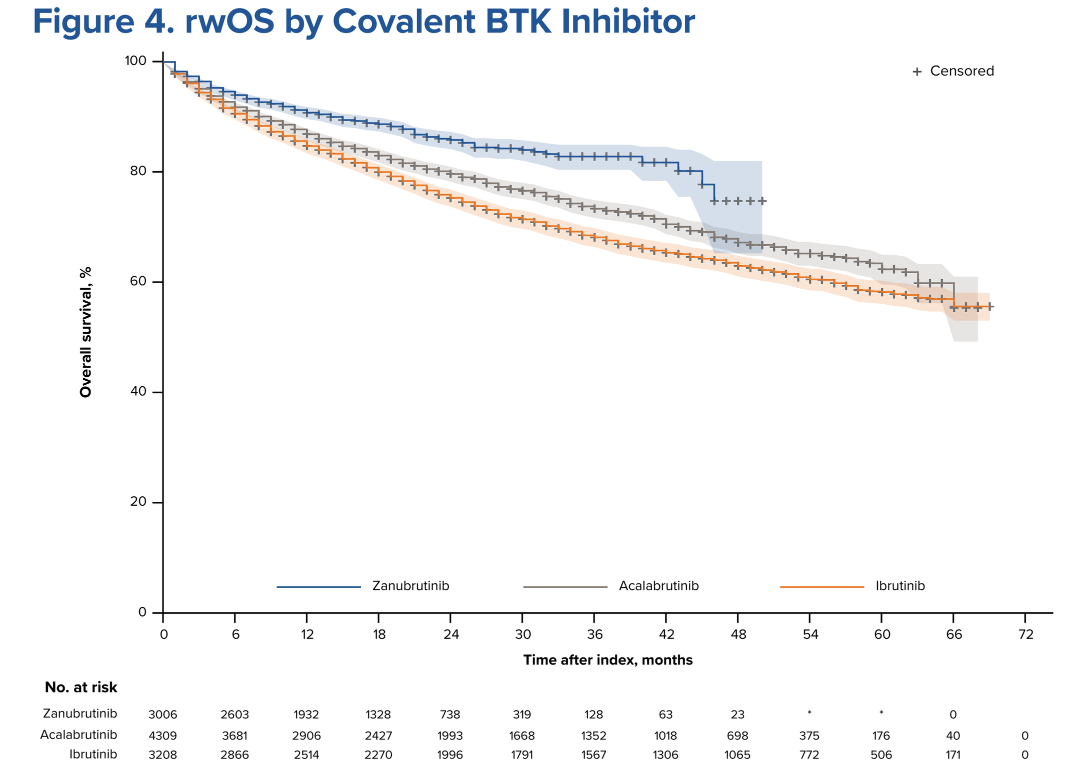
Patients at risk are blinded with an asterisk when n≤10.
Abbreviations: BTK, Bruton tyrosine kinase; rwTTD, real-world time to treatment discontinuation or death.

Figure 3. rwTTNT by Covalent BTK Inhibitor



Patients at risk are blinded with an asterisk when n≤10.
Abbreviations: BTK, Bruton tyrosine kinase; rwTTNT, real-world time to next treatment.

Figure 4. rwOS by Covalent BTK Inhibitor

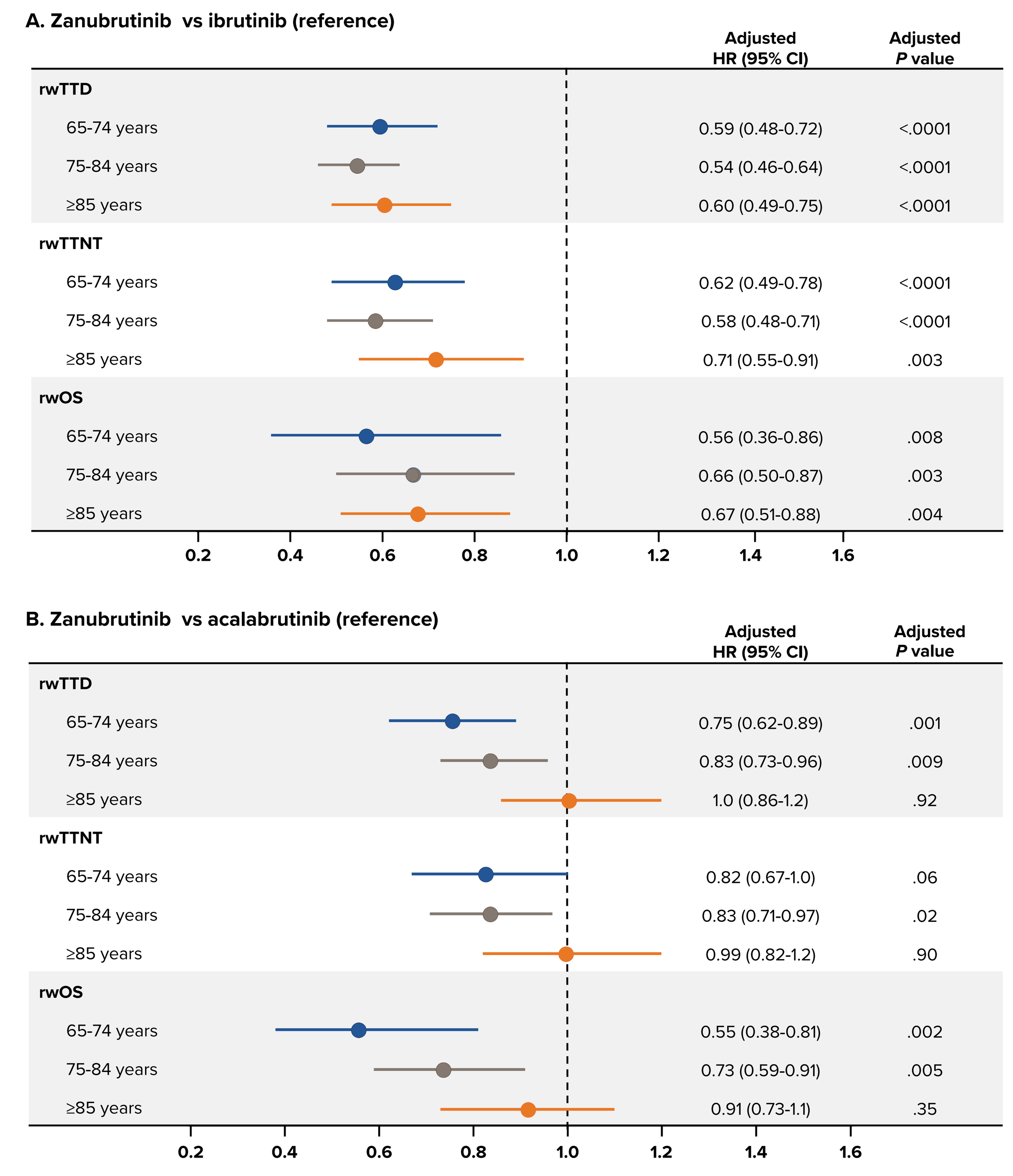


Patients at risk are blinded with an asterisk when n≤10.
Abbreviations: BTK, Bruton tyrosine kinase; rwOS, real-world overall survival.

Outcomes Stratified by Age Group

- Similar patterns in rwTTD, rwTTNT, and rwOS were observed between treatment groups when stratified by age group (**Figure 5**)
- Patients treated with zanubrutinib had statistically significantly longer rwTTD and rwTTNT compared with patients treated with ibrutinib across all age groups
- Patients treated with zanubrutinib had statistically significantly longer rwTTD and rwTTNT than those treated with acalabrutinib in the 65-74– and 75-84–year age groups
- Patients treated with zanubrutinib had 33%-44% lower risk of death compared with patients treated with ibrutinib across age groups
- Similarly, patients treated with zanubrutinib had 45% and 27% lower risk of death than those treated with acalabrutinib in the age groups of 65-74, respectively, but not in the ≥85 age group

Figure 5. rwTTD, rwTTNT, and rwOS Analyses by Age Group Using Cox Proportional Hazards Regression



Abbreviations: HR, hazard ratio; rwOS, real-world overall survival; rwTTD, real-world time to treatment discontinuation or death; rwTTNT, real-world time to next treatment.

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DISCLOSURE

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