Comparative Efficacy of Bruton Tyrosine Kinase Inhibitors in the Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia: A Network Meta-Analysis

Mazyar Shadman¹, Jennifer R. Brown², Leyla Mohseninejad³, Keri Yang⁴, Heather Burnett⁵, Binod Neupane⁵, Rhys Williams⁴, Nicole Lamanna⁶, Susan M. O'Brien⁷, Alessandra Tedeschi⁸, Constantine S. Tam⁹

¹Fred Hutchinson Cancer Center and University of Washington, Seattle, WA; ²Chronic Lymphocytic Leukemia Center, Division of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; ³BeiGene Netherlands B.V., Schiphol, Netherlands; ⁴BeiGene USA, Inc, San Mateo, CA; ⁵Evidera, Montreal, Canada; ⁶Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY; ⁷University of California, Irvine, CA; ⁸ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; ⁹Alfred Hospital and Monash University, Melbourne, VIC, Australia

BACKGROUND

- Next-generation Bruton tyrosine kinase inhibitors (BTKis) have led to changes in the treatment
 algorithm for patients with high-risk relapsed/refractory chronic lymphocytic leukemia (R/R CLL)¹
- Moreover, improved understanding of the CLL genome has facilitated the identification of specific high-risk genetic features of disease, allowing a more personalized approach to treatment^{2,3}
- Patients with deletion of chromosome 17p (del[17p]), deletion of chromosome 11q (del[11q]), mutations in the TP53 gene, and unmutated immunoglobulin heavy-chain variable region gene (IGHV) are likely to experience a more severe course of disease and have an unfavorable prognosis with some treatment strategies⁴⁻⁶
- There is a current lack of understanding around how BTKis compare in R/R CLL patients with high-risk disease features
- Therefore, a network meta-analysis (NMA) was performed to estimate relative efficacy of approved and recommended BTKis used to treat high-risk R/R disease

METHODS

Feasibility Assessment

- A systematic literature review was conducted in in July 2022⁷ (updated January 2023) to identify randomized controlled trials (RCTs) that reported overall survival (OS), progression-free survival (PFS), and response outcomes for approved and recommended BTKi treatments (zanubrutinib, acalabrutinib, and/or ibrutinib) versus any approved comparator for patients with R/R CLL
- The feasibility of performing an NMA was assessed to ensure that the assumptions underlying a valid NMA (homogeneity and transitivity of data from included studies) were met⁸⁻¹⁰
- A total of three unique trials (reported across 22 publications) were considered for the NMA: ALPINE,¹¹
 ELEVATE-RR,¹² and ASCEND¹³
- Assessment of differences in potential effect modifiers deemed important by clinical experts found the trials to be sufficiently similar with regards to most factors including age, Eastern Cooperative Oncology Group (ECOG) status, bulky disease status, R/R status, type of prior treatment (eg, fludarabine), and number of prior treatments (Table 1)
- Key differences were identified in terms of del(17p), del(11q), and TP53 mutation status across the trials (Table 1)
- The ELEVATE-RR trial included only patients with del(17p) or del(11q) mutations (46% del[17p] and 64% del[11q]) while the proportion of patients with del(17p) and del(11q) mutations was similar in the other 2 trials: 15-16% and 27%, respectively (Table 1)
- Given these differences, NMAs were performed using available subgroup data reported based on mutation status
- High-risk populations were defined based on the pre-specified subgroups within each trial, including
 patients with del(17p) and/or *TP53* mutations in ALPINE and ASCEND, and del(17p)/del(11q) in ELEVATERR (as per the study inclusion criteria). Additional analyses were also performed for subgroups based on
 del(17p) and *TP53* mutation status alone, where data were available

 Table 1. Study and Baseline Characteristics of Studies Included in NMA

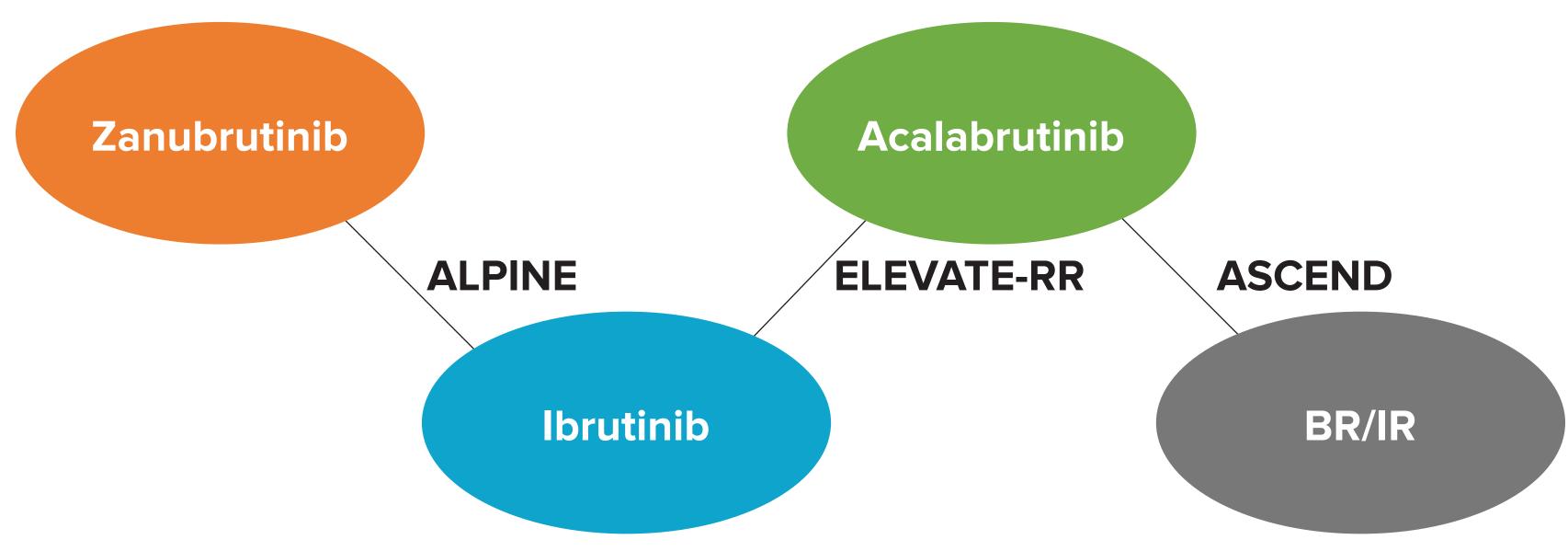
Trial Name	ALPINE	ELEVATE-RR	ASCEND		
Study arms	Zanubrutinib vs Ibrutinib	Acalabrutinib vs Ibrutinib	Acalabrutinib vs BR/IR		
Median follow-up in months	39	40.9	46.5 (acalabrutinib) 45.3 (BR/IR)		
Sample size	652	533	310		
Median age (range)	67 (35–90)	66 (28-89)	67 (32–90)		
% male	68	71	67		
ECOG (%)	0-1: 97 2: 3	0-1: 92 2: 8	0: 36 1: 51 2: 13		
Rai stage III–IV (%)	NR	50	42		
del(11q) (%)	27	64	27		
del(17p) (%)	15	46	16		
TP53 (%)	15	40	24		
del(17p) and/or TP53	23	51	28		
Unmutated IGHV (%)	73	86	74		
Median number of prior lines (range)	1 (1-8)	2 (1-12)	2(1-10)		
No. prior lines (%)	1: 59 2: 24 3: 10	1-3: 88	1: 48 2: 27 3: 13		
Prior anti-CD20 Ab (%)	83	86	80		

Ab, antibody; BR/IR, bendamustine + rituximab or idelalisib + rituximab; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy-chain variable region gene; NMA, network meta-analysis.

Network Meta-Analysis

- Fixed effect Bayesian NMA models were used to simultaneously synthesize the relative treatment
 effects observed in each trial (i.e., hazard ratios [HRs]) and obtain estimates of the relative treatment
 effects of all treatments in the network (Figure 1)
- Analyses were performed in OpenBUGS (version 3.2.3)
- Survival outcomes were analyzed in terms of HRs and response outcomes in terms of odds ratios (ORs), each with the corresponding 95% credible intervals (Crl), which reflect the range of true underlying effects with 95% probability. The probability that zanubrutinib was better than each comparator treatment was also estimated for each analysis
- Given that data from ALPINE were collected during the COVID-19 pandemic, data were analyzed with and without adjustment for COVID-19-related deaths

Figure 1. Network Diagram



BR/IR, bendamustine + rituximab or idelalisib + rituximab.

RESULTS

Available data used as inputs for the analyses are presented by high-risk population of interest in Table 2
 Response

- In high-risk populations as defined by the individual trials, zanubrutinib versus ibrutinib showed a more favorable investigator-assessed overall response rate (ORR-INV) and a trend favoring improvement in investigator-assessed complete response (CR-INV) (Table 3)
- These findings were aligned with the results of the ALPINE trial
- Findings versus acalabrutinib showed trends favoring zanubrutinib in terms of ORR-INV and CR-INV; these findings were not statistically significant
- Findings for response were consistent with or without ALPINE data adjusted for COVID-19 (Table 3)

Table 2. Data Inputs Used for NMA

			High Risk ^a			Del(17p)		TP53 mutation		
	Comparators	N	OR [95% CI]		HR [95% CI]			HR [95% CI]		HR [95% CI]
Trial		N	ORR-INV	CR-INV	PFS-INV	OS	N	PFS-INV	N	PFS-INV
ALPINE COVID- adjusted	Zanubrutinib	75	3.02 [1.35, 6.73]	1.89 [0.53, 6.75]	0.49 [0.31, 0.78]	0.59 [0.31, 1.12]	45	0.49 [0.27, 0.89]	50	0.49 [0.28, 0.86]
	Ibrutinib	75	Ref	Ref	Ref	Ref	50	Ref	45	Ref
ALPINE COVID- unadjusted	Zanubrutinib	75	2.64 [1.07, 6.54]	1.67 [0.52, 5.37]	0.52 [0.33, 0.82]	0.69 [0.38, 1.24]	45	0.53 [0.30, 0.94]	50	0.52 [0.30, 0.90]
	Ibrutinib	75	Ref	Ref	Ref	Ref	50	Ref	45	Ref
ELEVATE-RR	Acalabrutinib	268	1.61 [1.01, 2.56]	0.95 [0.53, 1.68]	0.90 [0.70, 1.16]	0.82 [0.58, 1.15]	124	1.00 [0.73, 1.37]	100	0.95 [0.68, 1.33]
	Ibrutinib	265	Ref	Ref	Ref	Ref	121	Ref	112	Ref
ASCEND	Acalabrutinib	44	NR	NR	0.22 [0.12, 0.40]	0.90 [0.45, 1.79]	28	0.13 [0.06, 0.29]	39	0.25 [0.14, 0.45]
	BR/IR	42	NR	NR	Ref	Ref	21	Ref	34	Ref

^aTrial-defined definition of high risk. BR/IR, bendamustine + rituximab or idelalisib + rituximab; CI, confidence interval; CR, complete response; HR, hazard ratio; INV, investigator assessed; NR, not reported; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ref, reference for the HR

 Table 3. NMA Results for Response – Odds Ratios and Probability Better for Zanubrutinib vs

 Comparators in High-Risk Patients

	Odds ratio [95% Crl], Probability Better (%)					
	High Risk With COVID-19 Adjustment	High Risk Without COVID-19 Adjustment				
Zanubrutinib vs ibrutinib ^a						
ORR-INV	3.09 [1.40, 7.26], 99.7	2.73 [1.11, 7.29], 89.7				
CR-INV	1.96 [0.55, 8.14], 84.9	1.73 [0.54, 6.23], 82.3				
Zanubrutinib vs acalabrutinib ^a						
ORR-INV	1.91 [0.75, 5.00], 91.7	1.69 [0.61, 4.97], 84.4				
CR-INV	2.07 [0.50, 9.67], 84.4	1.84 [0.50, 7.20], 81.6				

^aAnalyses of response were not feasible versus BR/IR or across specific mutation types given a lack of reported subgroup data. CR, complete response; CrI, credible interval; INV, investigator assessed; ORR, overall response rate.

Progression-Free Survival

- The NMA results in terms of PFS-INV are presented in Figure 2
- In high-risk populations as defined by the individual trials, zanubrutinib was found to be significantly
 more efficacious than ibrutinib, acalabrutinib, and bendamustine + rituximab or idelalisib + rituximab (BR/
 IR), representing risk reductions of 51%, 45%, and 88% respectively, with COVID-19 adjustment, and 48%,
 42%, and 87% without
- Findings were consistent when data from ALPINE were and were not adjusted for COVID-19-related deaths
- Similarly, for patients with del(17p), zanubrutinib was found to be significantly more efficacious than all
 other treatments in the network when data from ALPINE were adjusted for COVID-19, and all treatments
 except acalabrutinib when unadjusted data were used
- For those with TP53 mutations, zanubrutinib was found to be significantly more efficacious than ibrutinib and BR/IR, with trends in favor of zanubrutinib versus acalabrutinib

Overall Survival

- The NMA results in terms of OS are presented in **Figure 3**
- In high-risk populations as defined by the individual trials, although not statistically significant, there
 were trends showing numerical benefit with zanubrutinib compared to ibrutinib, acalabrutinib, and BR/IR,
 representing risk reductions of 41%, 28%, and 35%, respectively, with COVID-19 adjustment, and 31%,
 16%, and 24% without
- Findings were slightly less favorable for zanubrutinib when ALPINE data were not adjusted for COVID-19-related deaths
- OS analyses were not feasible across individual mutation types (del[17p] and TP53) given a lack of reported subgroup data

Figure 2. NMA Results for PFS Using COVID-19 Adjusted and Unadjusted Data from ALPINE Trial – Hazard Ratios and Probability Better for Zanubrutinib vs Comparators

Progression-Free Survival

Zanubrutnib vs.		Hazard ratio (95% Crl)	Prob (zanubrutinib better)
High Risk			
Ibrutinib: Adjusted		0.49 [0.31, 0.78]	99.8%
Ibrutinib: Unadjusted		0.52 [0.33, 0.82]	99.7%
BR/IR: Adjusted		0.12 [0.05, 0.26]	100%
BR/IR: Unadjusted	_	0.13 [0.06, 0.28]	100%
Acalabrutinib: Adjusted		0.55 [0.32, 0.94]	98.6%
Acalabrutinib: Unadjusted		058 [0.34, 0.99]	97.8%
del(17p)			
Ibrutinib: Adjusted		0.49 [0.27, 0.89]	98.9%
Ibrutinib: Unadjusted		0.53 [0.30, 0.94]	98.4%
BR/IR: Adjusted	_	0.06 [0.02, 0.18]	100%
BR/IR: Unadjusted	_	0.07 [0.02, 0.19]	100%
Acalabrutinib: Adjusted		0.49 [0.25, 0.98]	97.8%
Acalabrutinib: Unadjusted		0.53 [0.28, 1.03]	97.0%
TP53 mutation			
Ibrutinib: Adjusted		0.49 [0.28, 0.85]	99.4%
Ibrutinib: Unadjusted		0.52 [0.30, 0.90]	98.9%
BR/IR: Adjusted		0.13 [0.05, 0.34]	100%
BR/IR: Unadjusted		0.14 [0.06, 0.33]	100%
Acalabrutinib: Adjusted		0.52 [0027, 1.00]	97.4%
Acalabrutinib: Unadjusted		0.55 [0.29, 1.05]	96.6%
	0.01 0.10 1	10 100	

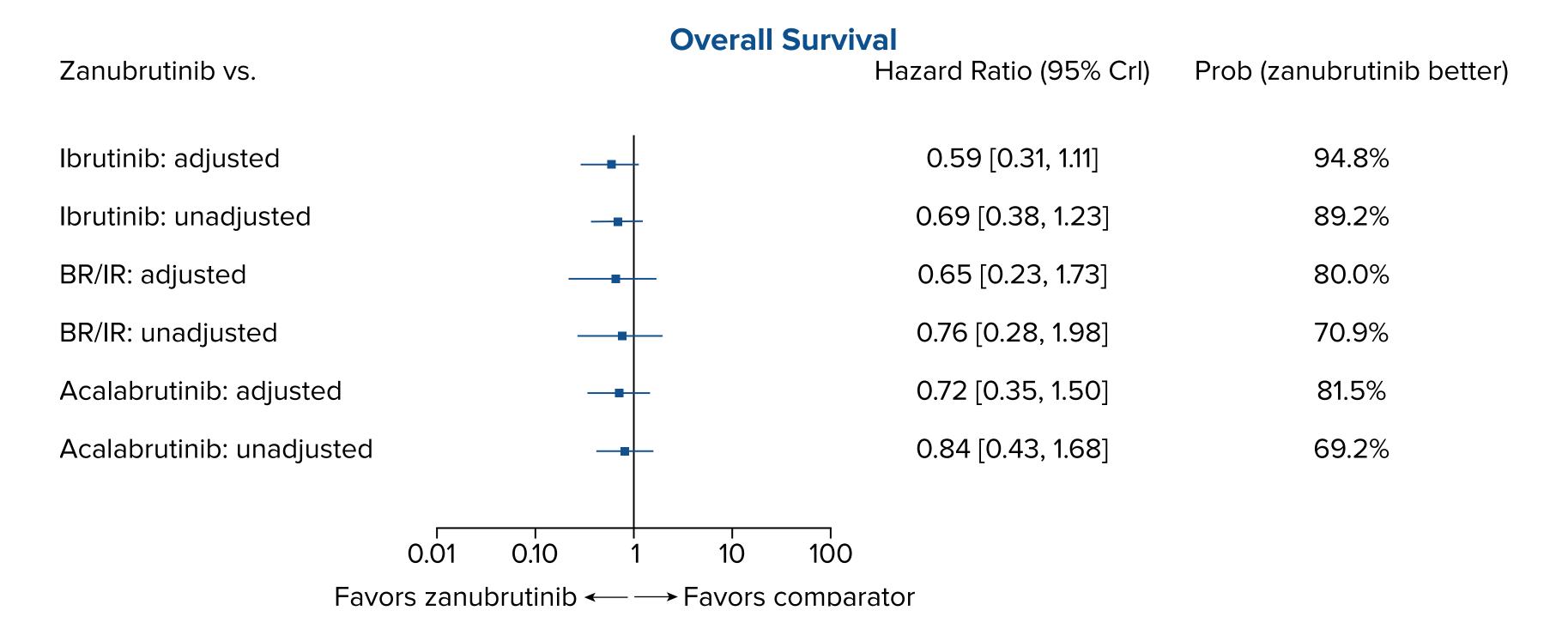
Favors zanubrutinib \longleftarrow \longrightarrow Favors comparator

BR/IR, bendamustine + rituximab or idelalisib + rituximab; CrI, credible interval; Prob, probability better.

CONCLUSIONS

- This is the first NMA to compare the efficacy of BTKis in high-risk patients with R/R CLL
- Findings suggest that zanubrutinib is likely to be the most efficacious BTKi for patients with genetic high-risk features such as the presence of *TP53* mutations and/or del(17p)

Figure 3. NMA Results for OS Using COVID-19 Adjusted and Unadjusted Data from ALPINE Trial – Hazard Ratios and Probability Better for Zanubrutinib vs Comparators in High-Risk Patients



BR/IR, bendamustine + rituximab or idelalisib + rituximab; Crl, credible interval; Prob, probability better.

LIMITATIONS

- The structure of the network must be considered in the context of our findings, specifically for comparisons of zanubrutinib versus BR/IR, which relies on indirect evidence (via ibrutinib), thereby decreasing the certainty of relative effect estimates
- The size of some of the subgroups used for NMA were limited, particularly those from ASCEND and the separate del(17p) and TP53 mutated groups from ALPINE
- The definition of high-risk varied between the studies included in this NMA. The ELEVATE-RR trial
 exclusively enrolled patients with del(17p)/del(11q), while ALPINE and ASCEND did not limit enrollment to
 this population, nor did they report subgroup results for patients with del(11q)
- Despite this limitation, findings of analyses for PFS based on del(17p) and TP53 mutation status separately, were consistent with the base case

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