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

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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 strategies[4-6]
- 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 2022[7] (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 met[8-10]
- A total of three unique trials (reported across 22 publications) were considered for the NMA: ALPINE,[11] ELEVATE-RR,[12] and ASCEND[13]
- 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 ELEVATE-RR (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

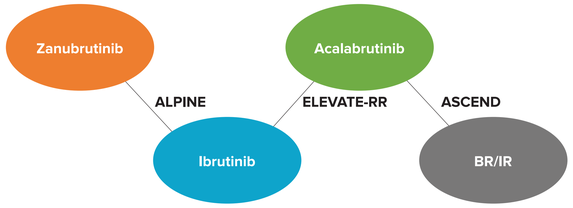
Trial Name	ALPINE	ELEVATE-RR	ASCEND
Study arms	Zanubrutinib vs Ibrutinib	Acalabrutinib vs Ibrutinib	Acalabrutinib vs BR/IR
Median follow-up in months	39	40.9	46.5 (acalabrutinib) 45.3 (BR/IR)
Sample size	652	533	310
Median age (range)	67 (35–90)	66 (28-89)	67 (32–90)
% male	68	71	67
ECOG (%)	0-1: 97 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 (CrI), 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

Trial	Comparators	N	High Risk[a] OR [95% CI] ORR-INV	OR [95% CI] CR-INV	HR [95% CI] PFS-INV	HR [95% CI] OS	Del(17p) N	Del(17p) HR [95% CI] PFS-INV	*TP53* mutation N	*TP53* mutation HR [95% CI] 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
ELE-VATE-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

[a]Trial-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% CrI], 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

[a]Analyses 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.

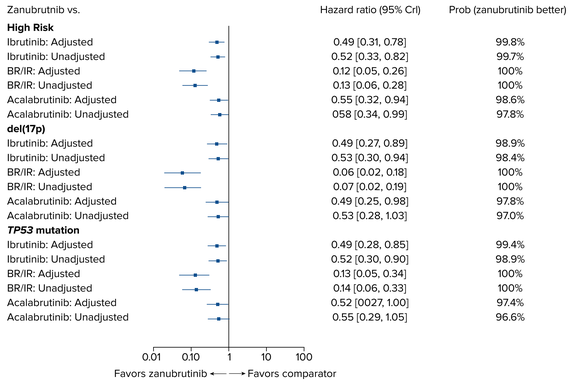
Progression-Free Survival

- 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

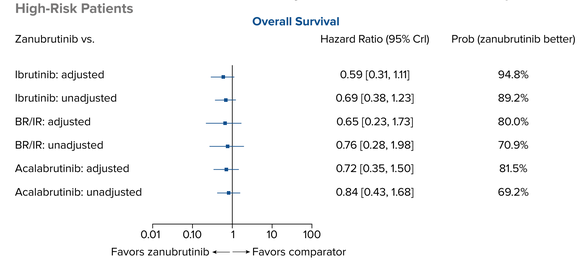


BR/IR, bendamustine + rituximab or idelalisib + rituximab; CrI, credible interval; Prob, probability better.

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; CrI, 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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DISCLOSURES

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