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blood advances

Comparative efficacy of Bruton tyrosine kinase inhibitors in high-risk relapsed/refractory CLL: a network meta-analysis

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Key Points

- An NMA of BTKis found zanubrutinib to be the most efficacious treatment for patients with high-risk R/R CLL.
- Zanubrutinib demonstrated reduced risk of progression/death compared to ibrutinib, acalabrutinib, and bendamustine or idelalisib+rituximab.

Bruton tyrosine kinase inhibitors (BTKis) have led to changes in the treatment algorithm for patients with high-risk relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL), defined based on the presence of genetic mutations. Given the lack of head-to-head trials comparing next-generation BTKis used to treat high-risk R/R disease, a network meta-analysis (NMA) was performed to estimate their relative efficacy. High-risk populations were defined based on the prespecified definitions within each trial, including patients with del(17p) and/or *TP53* mutations in the ALPINE (n = 150) and ASCEND (n = 86) trials, and del(17p)/del(11q) in the ELEVATE-RR (n = 533) trial. Bayesian NMAs found zanubrutinib to be the most efficacious treatment for high-risk patients, with significantly reduced risk of progression or death compared with ibrutinib (hazard ratio [HR], 0.49; 95% credible interval [CrI], 0.31-0.78), acalabrutinib (HR, 0.55; 95% CrI, 0.32-0.94), and bendamustine + rituximab or idelalisib + rituximab (BR/IR; HR, 0.12; 95% CrI, 0.05-0.26). Differences in overall survival demonstrated a numerical trend favoring zanubrutinib (probability better than ≥80%) compared with ibrutinib (HR, 0.59; 95% CrI, 0.31-1.11), acalabrutinib (HR, 0.72; 95% CrI, 0.35-1.50), and BR/IR (HR, 0.65; 95% CrI, 0.23-1.75). Rates of response also demonstrated trends favoring zanubrutinib compared with acalabrutinib, with significant results compared with ibrutinib. The NMA suggests that the most efficacious BTKi for patients with high-risk R/R CLL is zanubrutinib.

Introduction

Chronic lymphocytic leukemia (CLL) is a hematologic malignancy characterized by progressive accumulation of phenotypically mature malignant B-cell lymphocytes in the peripheral blood, bone marrow, and lymph nodes.[1,2] CLL is the most common leukemia in adults, with a reported incidence of 5 per 100 000 people per year in Europe.[3] The incidence increases to >30 per 100 000 per year for people

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The full-text version of this article contains a data supplement.

aged >80 years, with a median age of diagnosis of 72 years.[4] The selection of treatment in advanced CLL is driven by disease characteristics and prior treatment exposure.[4,5] Various treatment options are available for patients with advanced CLL; however, most patients will relapse on, or after, treatment and will require multiple lines of therapy. After diagnosis, the Binet or Rai staging systems are used to determine the indication for treatment.[4] Patients with detectable 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 are likely to experience a more severe course of disease and have an unfavorable prognosis with some treatment strategies, which also factors into the choice of therapy.[4,6,7]

An improved understanding of the disease's biology and scientific innovation has led to the development and approval of several targeted therapies for relapsed/refractory (R/R) CLL over the last 10 years, including Bruton tyrosine kinase inhibitors (BTKis). The introduction of BTKis has led to increases in patient survival and delayed progression, even in patients with unfavorable prognoses.[4,7,8] Moreover, improved understanding of the CLL genome and advances in testing methodology have facilitated the identification of specific high-risk genetic features of the disease, thus allowing for a more personalized approach to treatment.

Guidelines recommend specific treatments for patients with R/R CLL who have del(17p) or *TP53* mutations, which include the first-generation BTKi ibrutinib, next-generation BTKis acalabrutinib and zanubrutinib, the B-cell lymphoma 2 inhibitor venetoclax with/without the anti-CD20 monoclonal antibody rituximab, and the phosphoinositide 3 kinase inhibitor idelalisib with/without rituximab.[2,4-6] However, differentiated treatment recommendations based on the presence of del(11q) or immunoglobulin heavy-chain variable region mutation status are not available for patients with R/R CLL.[4,6] Given the lack of head-to-head trials comparing next-generation BTKis approved and recommended for patients with high-risk R/R CLL, this study aimed to assess their comparative efficacy using network meta-analysis (NMA) methods.

Methods

Study identification

A systematic literature review (SLR) was conducted in accordance with the standards outlined in the "preferred reporting items for systematic reviews and meta-analyses" statement.[9] Systematic searches were conducted on 17 January 2023 to identify randomized controlled trials that reported overall survival (OS), progression-free survival (PFS), and response outcomes for approved and recommended BTKi treatments for patients with R/R CLL. Further details regarding the methods of the SLR are presented in the supplemental Materials.

Feasibility assessment

Studies of interest for the NMA were required to report hazard ratios (HRs) or Kaplan-Meier curves for PFS and/or OS, and/or overall response rates (ORR) or complete response (CR) rates for an approved/recommended BTKi (zanubrutinib, acalabrutinib, and/or ibrutinib) vs any approved comparator. The feasibility of performing an NMA was assessed to ensure that the assumptions underlying a valid NMA (homogeneity and transitivity) were met.[10-12] Differences in study design, patient populations, and outcome characteristics across comparisons that were likely modifiers of the relative treatment effects were identified a priori based on observed subgroup data and clinical expert opinion. The list of effect modifiers considered included: age, Eastern Cooperative Oncology Group (ECOG) status, bulky disease status, del(11q) status, del(17p) status, *TP53* status, refractory/relapse status, type of prior treatment (eg, fludarabine), and number of prior treatments. The recommendations and decisions made during the feasibility assessment and implications for analysis are summarized in "Results."

NMAs

Data inputs. NMAs were performed using available subgroup data reported based on mutation status across the included trials. High-risk populations were defined based on the prespecified subgroups within each trial, including patients with del(17p) and/or *TP53* mutations in the ALPINE and ASCEND trials, and del(17p)/del(11q) in the ELEVATE-RR trial (as per the study inclusion criteria). Additional analyses were also performed for subgroups based on del(17p) and *TP53* mutation status alone, when data were available.

Given the data from one of the clinical trials identified in the SLR (ALPINE) were collected during the COVID-19 pandemic, post hoc analysis of data from this trial were performed to adjust for COVID-19–related deaths.[13] The NMA was performed in the base case using the adjusted data and in a scenario analysis without.

Statistical methods. Analyses were performed in OpenBUGS (version 3.2.3). Fixed-effect Bayesian NMA models were used to simultaneously synthesize the relative treatment effects observed in each trial (ie, HRs) and obtain estimates of the relative treatment effects of all treatments in the network.[11,12,14,15] Survival outcomes were analyzed in terms of HRs and response outcomes in terms of odds ratios (ORs), each with the corresponding 95% credible intervals (95% CrIs) and the probability of zanubrutinib being better than each comparator in each analysis.

Statistical heterogeneity could not be explored because there was only 1 trial per comparison. Inconsistency could not be explored because there was no closed loop (ie, no indirect evidence was available for the comparison informed by direct/study effect and vice versa). Further details regarding the methods of the NMA methods are presented in the supplemental Materials.

Results

Feasibility assessment

A total of 3 unique trials (reported across 22 publications) were considered for the NMA feasibility assessment: ALPINE,[13] ELEVATE-RR,[16] and ASCEND.[17] All were large, multicenter, multinational, open-label randomized controlled trials that evaluated at least 1 BTKi and were considered sufficiently comparable regarding study size, study site geography, and the nature of the primary end points to permit synthesis.

The duration of follow-up of the trials varied: ALPINE had the shortest follow-up at 39 months, followed by ELEVATE-RR at 40.9 months, and ASCEND at 46.5 months (Table 1). The study periods also varied: ELEVATE-RR collected data between October

Table 1. Study and baseline characteristics of studies included in the NMA

Trial name	ALPINE	ELEVATE-RR	ASCEND
Study arms	Zanubrutinib vs Ibrutinib	Acalabrutinib vs Ibrutinib	Acalabrutinib vs BR/IR
Median follow-up, mo	39	40.9	46.5 (acalabrutinib) 45.3 (BR/IR)
Sample size	652	533	310
Median age (range), y	67 (35-90)	66 (28-89)	67 (32-90)
Male sex (%)	68	71	67
ECOG performance status score (%)	0-1: 97	0-1: 92	0: 36
	2: 3	2: 8	1: 51
			2: 13
Rai stage III-IV (%)	NR	50	42
Binet stage* (%)	A: 11	A: 11	NR
	B: 48	B: 41	
	C: 41	C: 41	
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 no. of prior lines (range)	1 (1-8)	2 (1-12)	2 (1-10)
No. of prior lines (%)	1: 59	1-3: 88	1: 48
	2: 24		2: 27
	3: 10		3: 13
Prior anti-CD20 Ab (%)	83	86	80

Ab, antibody; IGHV, immunoglobulin heavy-chain variable region gene; NR, not reported.
*Defined only for patients with CLL (percentage of categories reported are for the Binet stages among patients with CLL, in which ALPINE had 623 patients with CLL). Unknown or not done made the missing category, percentage of which is not presented here.

2015 and September 2020, ASCEND from February 2012 to September 2021, and ALPINE from November 2018 to September 2023.

Assessment of differences in potential effect modifiers deemed important by clinical experts found the trials to be sufficiently similar with regard to median patient age (range, 66-67 years), ECOG status (>87% had were ECOG performance status score of 0-1), and Rai stage (stage III-IV ranged from 42% to 50%). Key differences were identified with regard to del(17p), del(11q), and *TP53* mutation status (Table 1). The ELEVATE-RR trial included only patients with del(17p) or del(11q) mutations (64% del[11q] and 46% del[17p]), whereas the proportion in the other trials were consistent: 27% for del(11q) and 15% to 16% for del(17p) (Table 1). *TP53* mutation status varied from 15% in ALPINE to 40% in ELEVATE-RR. Given that analyses were performed using available subgroup data reported based on mutation status, the distribution of potential effect modifiers within those subgroups were unknown. It was therefore assumed that population characteristics within each prespecified subgroup of interest (based on del(17p), del (11q), and TP53 mutations status) would be more comparable than the intention-to-treat (ITT) populations presented in Table 1.

NMA

The network comprised a single trial per node, allowing for comparisons of zanubrutinib, ibrutinib, acalabrutinib, and bendamustine + rituximab or idelalisib + rituximab (BR/IR; Figure 1). The available data used as inputs for the analyses are presented by high-risk population of interest in Table 2. PFS and response outcomes were investigator assessed (INV). Limited data were reported for OS and response outcomes across individual mutation types (ie, del(17p) and *TP53* mutation).

In high-risk populations, findings vs ibrutinib were aligned with the results of the ALPINE trial, with zanubrutinib showing a more favorable investigator assessed ORR (ORR-INV, [range]; 3.09 [1.40-7.26]) and a trend favoring improvement in investigator assessed CR (CR-INV; 1.96 [0.55-8.14]; Figure 2). Compared with acalabrutinib, there were numerical trends favoring zanubrutinib in ORR-INV (OR, 1.91; 95% credible interval [CrI], 0.75-5.00) and CR-INV (OR, 2.07; 95% CrI, 0.50-9.67; Figure 2). Analyses of response were not feasible vs BR/IR or across specific mutation types given a lack of reported subgroup data. Findings for response were consistent with or without adjustment for COVID-19–related deaths in ALPINE (supplemental Table 2).

The results of the NMAs performed for investigator assessed PFS (PFS-INV) with COVID-19 adjustment of ALPINE data are presented in Figure 3. In high-risk populations, zanubrutinib was found to be significantly more efficacious than ibrutinib (HR, 0.49; 95% CrI, 0.31-0.78), acalabrutinib (HR, 0.55; 95% CrI, 0.32-0.94), and BR/IR (HR, 0.12; 95% CrI, 0.05-0.26). These differences represented risk reductions of 51%, 45%, and 88%, respectively (with a probability better than ≥99% across all comparisons). Results were similar when data from ALPINE were not adjusted for

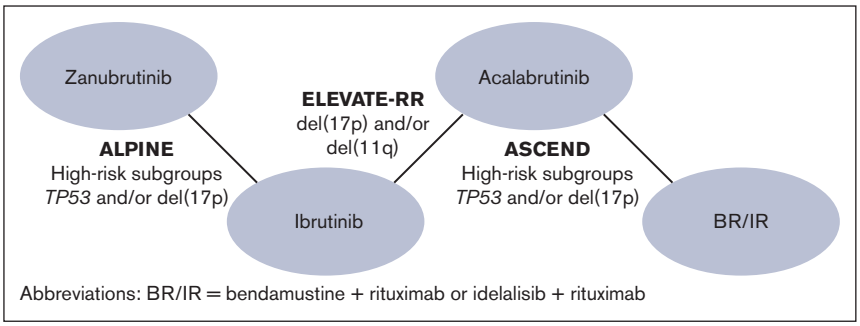

Figure 1. Network diagram.

COVID-19–related death, with PFS-INV HRs of 0.52 (95% CrI, 0.33-0.82) vs ibrutinib, 0.58 (95% CrI, 0.34-0.99) vs acalabrutinib, and 0.13 (95% CrI, 0.06-0.28) vs BR/IR; representing risk reductions of 48%, 42%, and 87%, respectively. For patients with del(17p) mutations, 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 ibrutinib and BR/IR, but not acalabrutinib when unadjusted data were used (HR, 0.53; 95% CrI, 0.28-1.03; supplemental Figure 1). For those with *TP53* mutations, zanubrutinib was found to be significantly more efficacious than ibrutinib and BR/IR, with trends favoring zanubrutinib over acalabrutinib with and without ALPINE data adjusted for COVID-19.

OS results showed a numerical benefit favoring zanubrutinib compared with ibrutinib (HR, 0.59; 95% CrI, 0.31-1.11; probability better than 94.8%), acalabrutinib (HR, 0.72; 95% CrI, 0.35-1.50; probability better than 81.5%), and BR/IR (HR, 0.65; 95% CrI, 0.23-1.75; probability better than 80.0%), although these findings were not statistically significant. Risk reductions were 41% vs ibrutinib, 28% vs acalabrutinib, and 35% vs BR/IR. When ALPINE data were not adjusted for COVID-19–related deaths, the OS benefit of zanubrutinib was maintained, but the magnitude of differences were slightly less across all comparisons (supplemental Figure 2).

Discussion

This study estimated the relative efficacy of approved/recommended therapies for high-risk R/R CLL using NMA. The findings suggest that zanubrutinib provides benefits over other approved covalent BTKis (acalabrutinib and ibrutinib) and BR/IR in terms of PFS, and over ibrutinib in terms of response. Furthermore, although results were not statistically significant, there was a numeric trend in favor of zanubrutinib over other BTKis and BR/IR in terms of OS. The ALPINE and ELEVATE-RR trials have been critical in demonstrating the efficacy of the next-generation BTKis for treatment of R/R CLL. However, ELEVATE-RR did not show the same sustained superior benefit over ibrutinib in high-risk patients when compared with the ALPINE trial. Findings from this NMA highlight this difference, along with the magnitude of relative benefit for zanubrutinib vs acalabrutinib in patients with high-risk mutations. To our knowledge, this is the first indirect treatment comparison to assess the comparative efficacy of BTKi therapies for patients with CLL considered to be at high risk based on the presence of specific genetic mutations.

Mutational profiling in CLL has led to improved decision-making and outcomes for patients.[18,19] However, a further understanding of how second-generation BTKis modify the natural course of disease for specific mutation subgroups is required; particularly mutations at codon L528 of BTK, which have been linked to disease progression with zanubrutinib.[20] This is particularly important given that most patients receive BTKis in earlier lines of therapy, and salvage therapies for patient's refractory to BTKis are limited.[18] Findings from this NMA use the available subgroup data reported from pivotal trials for patients with high-risk R/R disease, but given that limited sample sizes cannot provide a clear understanding of long-term survival outcomes. The outcomes included for analysis were those that reflected the primary end points of the pivotal trials included for analysis (PFS and ORR) as well as OS. Although the most important end point for evaluation of response to BTKis is an important open question, in particular given the high ORR observed and clinical benefits observed beyond response outcomes, our NMA aimed to maximize the reported subgroup data available for high-risk patients. The results provide insights that cannot be derived directly from assessment of the individual trial outcomes and were not previously known.

In the umbrella analysis by Marchetti et al, only 2 NMAs published between 2019 and 2020 included evidence on BTKis which were limited to ibrutinib, and made comparisons to rituximab plus venetoclax, BR, and ofatumumab. Additional pairwise meta-analyses included in the umbrella review compared BTKis (again limited to ibrutinib) to a mix of non-BTKi therapies and found a significant benefit in terms of PFS (HR, 0.24; 95% CrI, 0.19-0.30) and OS (HR, 0.58; 95% CrI, 0.46-0.73) in patients with R/R CLL.[21] None of the included meta-analyses or NMAs identified by Marchetti et al focused on high-risk patient populations. Results from another NMA by Chanan-Khan et al that used an earlier data cut from ALPINE than this analysis and data for the ITT populations across all trials, found zanubrutinib to be more efficacious than acalabrutinib (HR, 0.52; 95% CrI, 0.30-0.90), ibrutinib (HR, 0.47; 95% CrI, 0.29-0.76), and BR (HR, 0.13; 95% CrI, 0.06-0.26) in terms of PFS, with a similar trend in OS benefit for zanubrutinib over acalabrutinib (HR, 0.75; 95% CrI, 0.35-1.59), ibrutinib (HR, 0.62; 95% CrI, 0.31-1.22), and BR/IR (HR, 0.52; 95% CrI, 0.21-1.24).[22] A key limitation of this study relates to the fact that it was conducted based on the ITT populations from each trial, which varied significantly in terms of the proportion of patients with del(17p) mutations. Nonetheless, the findings of our analysis are similar, suggesting that the efficacy of zanubrutinib is consistent across various subgroups of patients with R/R CLL.

Table 2. Data inputs used for NMA

Trial	Comparators	High risk*						del(17p)		*TP53* mutation	
		n	OR (95% CI)		HR (95% CI)		n	HR (95% CI)	n	HR (95% CI)	
			ORR-INV	CR-INV	PFS-INV	OS		PFS-INV		PFS-INV	
ALPINE, 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, 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	

Ref, reference for the HR.
*Trial-defined definition of high risk.

Matching-adjusted indirect comparisons (MAICs) have also been performed using data from ALPINE and ASCEND, whereby individual patient data (IPD) from 1 trial are reweighted to reduce between-study differences in variables that are prognostic or effect modifying. Results from a MAIC using IPD from ASCEND found PFS-INV to be comparable between acalabrutinib vs zanubrutinib after matching (HR, 0.90; 95% confidence interval [CI], 0.60-1.36),[23] whereas a MAIC using IPD from a more recent data cut from ALPINE (median follow-up, 39 months) found zanubrutinib to be favorable vs acalabrutinib in terms of PFS (HR, 0.68; 95% CI, 0.46-0.99) and CR (OR, 2.90; 95% CI, 1.13-7.43).[24] The latter MAIC also found zanubrutinib to be associated with a potential OS benefit, although results were not statistically significant. Differences in the results of these 2 MAICs relate to the use of different data cuts from ALPINE and ASCEND, difference in approach to COVID-19–related events between the studies, and differences in the ability to match specific variables given published baseline characteristics. In our NMA, data from ALPINE were adjusted for COVID-19–related deaths in the base case, with additional analyses performed using unadjusted data. Findings from the unadjusted analysis produced slightly different point estimates but resulted in the same conclusions regarding the comparative efficacy of zanubrutinib vs other BTKis. Although PFS was not the primary end point in the ALPINE study, analyses of PFS should still be considered valid from an outcome definition and method of assessment perspective. The results of the NMA show statistically significant differences between treatments based on this outcome.

When interpreting the results of this study, the structure of the network must be considered; specifically for comparisons of zanubrutinib vs BR/IR, which rely on indirect evidence (via ibrutinib), thereby decreasing the certainty of relative effect estimates. When estimates are informed by a single study per node along a chain, differences in effect modifiers across studies within the chain may affect the observed relative effects that rely on those chains, thereby making results less reliable. Statistical heterogeneity, which is often used to assess the proportion of the variance in a set of estimates that is due to between-study heterogeneity (ie, the proportion of variation observed that is not explainable due to sampling error) can also not be estimated, because this requires enough studies (ideally, 3-4) per comparison to appropriately investigate.

Finally, the size of some of the subgroups used for the NMA was also limited, particularly those from ASCEND and the subgroups with del(17p) and *TP53* mutations from ALPINE. The ELEVATE-RR trial also exclusively enrolled patients with del(17p)/del(11q), whereas ALPINE and ASCEND did not restrict enrollment by these mutation types, nor did they report subgroup results for patients with del(11q). As a result, the definition of high risk for ELEVATE-RR varied from the definition used in the other trials. To test the impact of this difference, analyses were also performed for subgroups based on del(17p) and *TP53* mutation status separately, when data were available, although this was limited to PFS. Findings of these subgroup analyses were consistent with the base case, which focused on trial-defined definitions of high risk.

In this NMA, some assumptions were not tested; mainly the proportional hazard assumption, which determines whether the Cox regression models used to estimate HRs from the individual trials are appropriate summary statistics to use for NMA (ie, do relative

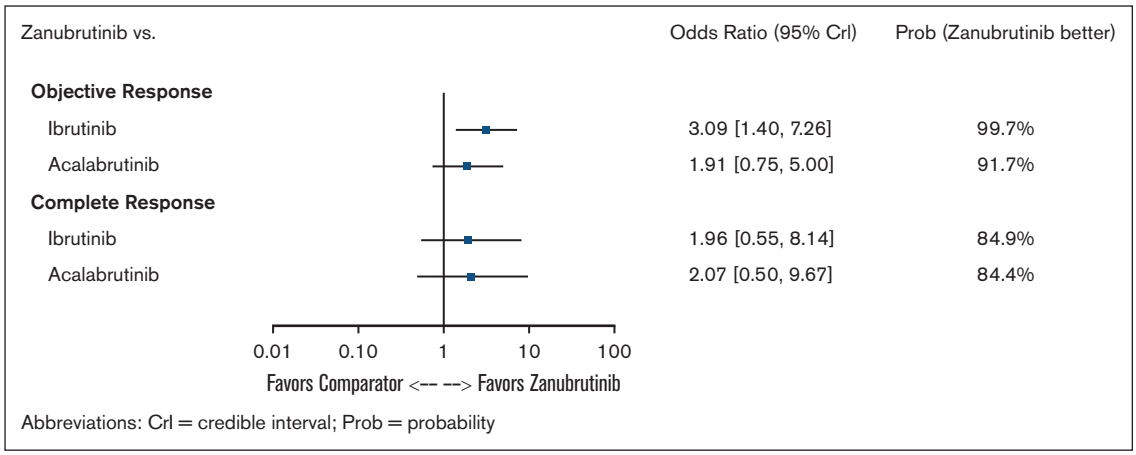

Figure 2. NMA results for response using COVID-19–adjusted data from ALPINE trial. ORs and Prob better for zanubrutinib vs comparators in high-risk patients.

hazards observed within each trial remain constant over time?). Violation of this assumption would require consideration of more advanced statistical models, such as fractional polynomial NMAs which estimate hazards for each treatment and HRs for each treatment comparison but demonstrate how those hazards vary by time.[25]

Another assumption not tested was that the population characteristics within each prespecified high-risk subgroup of interest would be more comparable than the ITT populations for which data were reported. Although the number of prior lines of therapy were known for the ITT populations, and were not identified as strong effect modifiers during the feasibility assessment; the distribution of this variable across the subgroups analyzed is unknown, as is the type of prior therapy received. The lack of information regarding the types of prior therapy across trials is a limitation.

A further limitation is how standard NMA methodology does not adjust for differences in baseline characteristics and the fact that the distribution of effect modifiers is unknown for the high-risk subgroups analyzed. Had there been more data available for each node of the network, it may have been possible for NMA meta-regression that adjusts for differences in baseline characteristics across studies to have been performed. It should be noted, however, that NMA meta-regression does not adjust the results of the included trials based on these differences but rather can be used to describe the impact/significance of specific covariates on the findings of the NMA. The lack of reporting of baseline

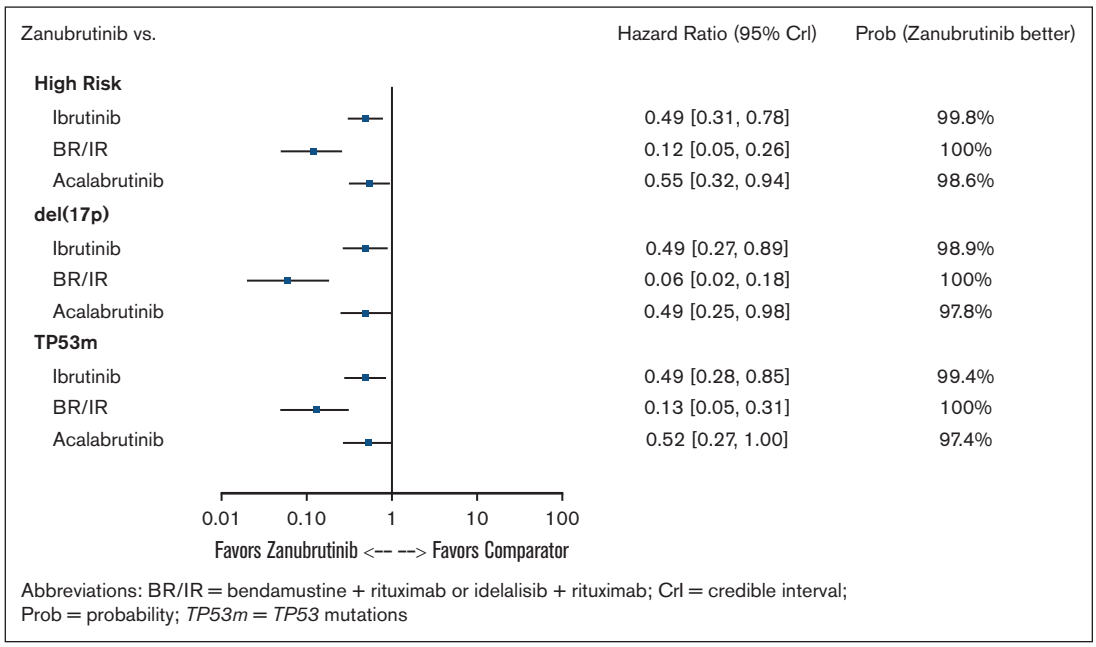

Figure 3. NMA results for PFS-INV using COVID-19–adjusted data from ALPINE trial. HRs and Prob better for zanubrutinib vs comparators.

characteristics for high-risk subgroups also meant that population-adjusted indirect comparison methods such as MAIC could not be applied.

In conclusion, this is the first NMA to compare the efficacy of zanubrutinib vs approved and recommended 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).

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Authorship

Contribution: L.M., K.Y., H.B., and B.N. conceptualized and designed the study; L.M., H.B., and B.N. acquired the data; H.B. and B.N. analyzed the data; and all authors interpreted the data, wrote the original manuscript draft, and reviewed and edited the manuscript.

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