Zanubrutinib Versus Other Bruton Tyrosine Kinase Inhibitors in Relapsed/Refractory Chronic Lymphocytic Leukemia: A Multilevel Network Meta-Regression

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INTRODUCTION

- Improved understanding of the disease biology of chronic lymphocytic leukemia (CLL) resulted in the development of Bruton tyrosine kinase inhibitors (BTKis), which have been investigated in randomized clinical trials (RCTs) in relapsed/refractory (R/R) CLL. These include the ALPINE trial[1] (NCT03734016; zanubrutinib vs ibrutinib) and the ELEVATE-RR trial[2] (NCT02477696; acalabrutinib vs ibrutinib)
- Population-adjusted indirect treatment comparisons (ITC) can be conducted to estimate relative treatment effects between different BTKis that were not studied head-to-head, while adjusting for between-trial differences in important patient characteristics
- However, commonly used ITC methods are unable to estimate the relative effect in the true population of interest. Matching adjusted indirect comparisons (MAICs) for instance, reweight the individual patient data (IPD) from a given trial to reflect the population characteristics of a comparator trial
- Multilevel network meta-regression (ML-NMR) is a newly developed method that facilitates estimations of relative treatment effects between interventions for different target populations based on networks of any size, and with that provides an opportunity to overcome the common ITC limitations[3]
- With ML-NMR, at the minimum, the IPD for 1 trial in the network is needed so that relative treatment effects can be estimated as a function of patient characteristics[3]

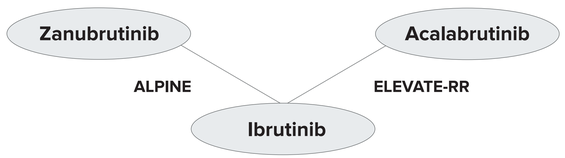
OBJECTIVES

- To estimate the treatment effect of zanubrutinib relative to other BTKis in R/R CLL patients with a profile similar to the ALPINE intention-to-treat (ITT) population by means of an ML-NMR
- Treatment effects were also predicted for ELEVATE-RR-like patients

METHODS

- The evidence base of this analysis included ALPINE and ELEVATE-RR, connected via their common comparator, ibrutinib, using the IPD for ALPINE and summary aggregate level data from the publication of ELEVATE-RR[1,2] (**Figure 1**)
- The key trial and patient characteristics at baseline are summarized in **Table 1**
- Selection of the relevant patient characteristics to incorporate in the adjustment of between-trial differences was based on a review of the literature and consultation with clinical experts and included the following treatment effect-modifiers: Rai/Binet stage, β_2-microglobulin, cytogenetic deletions/mutations (*TP53*, del(11q), del(17p)), immunoglobulin heavy-chain variable (IGHV) mutation status, and the number of prior treatment lines
- As IPD data was available for ALPINE but not ELEVATE-RR, it was not feasible to estimate a different effect of covariates on hazard ratios (HRs) for zanubrutinib vs ibrutinib and acalabrutinib vs ibrutinib
- Therefore, we assumed that the impact of covariates on the HRs of zanubrutinib vs ibrutinib and acalabrutinib vs ibrutinib are of the same magnitude i.e., shared effect modifiers assumption
- Fixed effect ML-NMR models, which assume shared effect modifiers for both direct comparisons as introduced above, were used to estimate the relative treatment effect between the competing interventions for progression-free survival (PFS) and overall survival (OS) for 2 target populations: the ALPINE ITT population and the ELEVATE-RR population, which consisted of high-risk patients defined as having del(17p) and/or del(11q)
- Given the timing of the included trials in relation to the COVID-19 pandemic, ALPINE PFS and OS data were adjusted for death due to COVID-19
- Analyses were implemented in a Bayesian framework, with parameters estimated using Markov Chain Monte Carlo method in R (packages: rstan and loo) and Stan[4,5]

Figure 1. Network Diagram of Included Trials



RESULTS

- Zanubrutinib was associated with a more favorable PFS than acalabrutinib in a population as in ALPINE (**Table 2**). **Figure 2** presents the corresponding predicted PFS curves and the observed Kaplan-Meier curves in ALPINE
- The analysis showed numerically favorable OS with zanubrutinib when compared to acalabrutinib for the ALPINE population, but differences were not statistically significant (**Table 2; Figure 3**)
- Treatment effect estimates with zanubrutinib vs ibrutinib and acalabrutinib vs ibrutinib were numerically different between the 2 target populations (**Table 2**)
- For both PFS and OS, the HRs of zanubrutinib vs acalabrutinib obtained with the indirect comparison were the same between the two target populations (**Table 2**)
  - Since it had to be assumed that the impact of covariates on the HRs of zanubrutinib vs ibrutinib and acalabrutinib vs ibrutinib are of the same magnitude (see Methods), the indirect comparison estimate of zanubrutinib vs acalabrutinib is independent of the patient characteristics in the analysis and therefore consistent across the target populations

Table 1. Key Trial and Patient Characteristics at Baseline

	ALPINE		ELEVATE-RR	
	Zanubrutinib	Ibrutinib	Acalabrutinib	Ibrutinib
Study characteristics				
Study phase and design	RCT phase III, open-label		RCT phase III, open-label	
Country/region	Multinational		Multinational	
Treatments	zanubrutinib 160 mg orally 2x daily ibrutinib 420 mg orally 1x daily		acalabrutinib 100 mg orally 2x daily ibrutinib 420 mg orally 1x daily	
Follow-up (months)	PFS: 44.2 OS: 45.8	PFS: 44.2 OS: 45.6	PFS: 40.9 OS: 41.1	PFS: 40.9 OS: 41.1
Sample size	327[a]	325[a]	268	265
Patient characteristics at baseline				
Age ≥65 years, n (%)	204 (62.3)	200 (61.5)	144 (53.7)	143 (54.0)
Male, n (%)	213 (65.1)	232 (71.4)	185 (69.0)	194 (73.2)
Region Europe, n (%) North America, n (%) Asia, n (%) Other, n (%)	 198 (60.6) 52 (15.9) 49 (15.0) 28 (8.6)	 191 (58.8) 59 (18.2) 45 (13.8) 30 (9.2)	 NR NR 0 (0)[b] NR	 NR NR 0 (0)[b] NR
ECOG PS ECOG 0-1, n (%) ECOG 2, n (%)	 0-1: 320 (97.9) 2: 7 (2.1)	 0-1: 312 (96.0) 2: 13 (4.0)	 0-1: 247 (92.2) 2: 20 (7.5)	 0-1: 243 (91.7) 2: 22 (8.3)
Rai stage 0-II, n (%) III-IV, n (%) Missing, n (%)	 182 (55.7) 145 (44.3) -	 189 (58.2) 135 (41.5) -	 130 (48.5); 131 (48.9) 7 (2.6)	 124 (46.8); 134 (50.6) 7 (2.6)
Bulky disease at least 5 cm, n (%)	145 (44.3)	149 (45.8)	128 (47.8)	136 (51.3)
TP53 mutation and/or del(17p), n (%)	75 (22.9)	75 (23.1)	136 (50.7)	135 (50.9)
Del(11q), n (%)	91 (27.8)	88 (27.1)	167 (62.3)	175 (66.0)
Del(17p), n (%)	45 (13.8)	50 (15.4)	121 (45.1)	120 (45.3)
TP53 mutated, n (%)	50 (15.3)	45 (13.8)	100 (37.3)	112 (42.3)
IGHV mutated, n (%)	79 (24.2)	70 (21.5)	44 (16.4)	28 (10.6)
β_2-microglobulin >3.5 mg/L, n (%)	176 (53.8)	183 (56.3)	207 (77.2)	214 (80.8)
>3 previous LOT, n (%)	24 (7.2)	33 (10.1)	33 (12.3)	28 (10.6)

[a] The sample size for the ALPINE population with complete data on all relevant patient characteristics was 265 for zanubrutinib and 251 for ibrutinib.
[b] Concluded based on the trial inclusion/exclusion criteria.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; LOT, line of treatment; NR, not reported.

Figure 2. Prediction of Progression-Free Survival; M-spline Model Adjusted for Rai/Binet Stage, β_2-microglobulin, Cytogenetic Mutations, Immunoglobulin Heavy-chain Variable, and the Number of Prior Line of Treatment – ALPINE Intention-to-treat Population

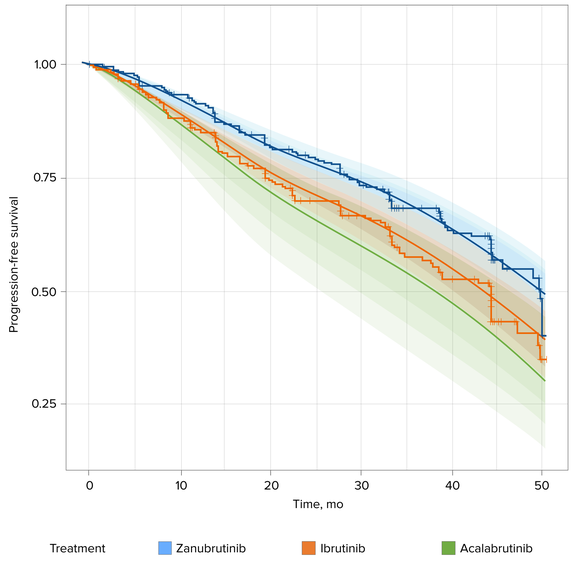
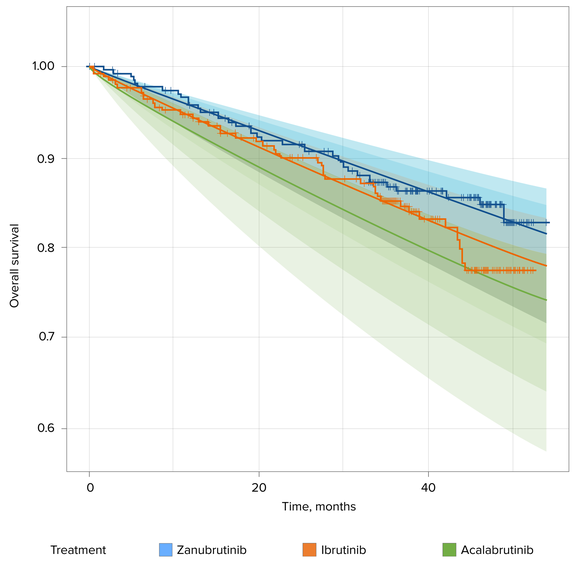


Figure 3. Prediction of Overall Survival; M-spline Model Adjusted for Rai/Binet stage, β_2-microglobulin, Cytogenetic Mutations, Immunoglobulin Heavy-chain Variable, and the Number of Prior Line of Treatment – ALPINE Intention-to-treat Population



CONCLUSIONS

- Our findings indicate that zanubrutinib had significantly greater PFS compared to acalabrutinib and ibrutinib in a R/R CLL population akin to that of the ALPINE trial as well as for ELEVATE-RR patients who were characterized by high-risk cytogenetics
- In terms of OS, zanubrutinib also demonstrated a potential improvement in OS compared to both ibrutinib and acalalabrutinib. However, the findings were not statistically significant, possibly due to the limitations in the number of studies available and their sample sizes
- As with any statistical technique, ML-NMR involves some assumptions. Among other assumptions described in the literature[3], the following should be noted for the current study:
  - Our analysis assumed that all relevant patient characteristics have been incorporated
  - Given the lack of IPD from the ELEVATE-RR trial, we assumed that the effect of covariates was the same in ALPINE and ELEVATE-RR (i.e., the shared effect modifier assumption)
- RCTs remain the gold standard of estimating relative treatment efficacy

Table 2. Progression-free Survival and Overall Survival per Treatment Comparison Across Different Target Populations

	Comparison	Population	
		ALPINE ITT	ELEVATE-RR
PFS HR, 95% CrI	zanubrutinib vs acalabrutinib[a]	0.57 (0.34, 0.98)	0.57 (0.34, 0.98)
	zanubrutinib vs ibrutinib	0.73 (0.55, 0.98)	0.56 (0.36, 0.86)
	acalabrutinib vs ibrutinib	1.27 (0.80, 2.00)	0.97 (0.73, 1.29)
OS HR, 95% CrI	zanubrutinib vs acalabrutinib[a]	0.66 (0.30, 1.46)	0.66 (0.30, 1.46)
	zanubrutinib vs ibrutinib	0.72 (0.41, 1.28)	0.52 (0.25, 1.04)
	acalabrutinib vs ibrutinib	1.09 (0.50, 2.35)	0.78 (0.48, 1.24)

[a] With the analysis, we assumed that the impact of patient characteristics on the treatment effect with zanubrutinib vs ibrutinib and acalabrutinib vs ibrutinib are of the same magnitude; therefore, the relative treatment effect of zanubrutinib vs acalabrutinib is independent of the patient characteristics included in the analyses.
CrI, credible interval.

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DISCLOSURES

MS: Consultancy for AbbVie, Genentech, AstraZeneca, Pharmacyclics, BeiGene, BMS, MorphoSys/Incyte, Kite, Eli Lilly, Genmab, Mustang Bio, Regeneron, ADC therapeutics, Fate Therapeutics, Janssen and MEI Pharma. Research funding from Mustang Bio, BMS, Pharmacyclics, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Genmab, MorphoSys/incyte, Vincerx. **WB**: Research funding from BeiGEne. **LM**: Employed by and owns equity in BeiGene. Previously employed by Evidera. **SX**: n/a. **MJ**: Research funding from BeiGene. **KY**: Employed by and owns equity in BeiGene. **RW**: Employed by and owns equity in BeiGene. **AC**: n/a **JJ**: Paid on a part time basis by Precision Medicine Group as Chief Scientist - HEOR. **CT**: Research funding from Janssen, AbbVie, BeiGene. Honararia from Janssen, AbbVie, BeiGene, LOXO, Novartis, Roche.

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