NEW MAIC ANALYSIS

MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC) OF BRUKINSA AND ACALABRUTINIB PHASE 3 R/R CLL TRIALS

Efficacy of Zanubrutinib Versus Acalabrutinib in the Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia (R/R CLL): A Matching-Adjusted Indirect Comparison (MAIC)

Shadman M, Brown JR, Williams R, et al.

Presented at: 28th International Congress on Hematologic Malignancies; February 29-March 3, 2024.

This analysis suggested an improved progression-free survival (PFS) and complete response (CR) advantage for BRUKINSA vs acalabrutinib[1]

There are no randomized controlled trials between BRUKINSA and acalabrutinib.

MAICs are hypothesis generating and do not establish superior efficacy or safety of one drug over another. The results should be viewed in the context of the limitations of the analysis and randomized clinical trial data.[1-3]

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.8% of patients treated with BRUKINSA in clinical trials, with fatalities occurring in 0.2% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 32% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days before and after surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher infections occurred in 26% of patients, most commonly pneumonia (7.9%), with fatal infections occurring in 3.2% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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METHODOLOGY MATTERS

- This MAIC was performed to address the significant methodological limitations of the ALPINE vs ASCEND MAIC published in the *American Journal of Hematology* by Kittai et al, which prevented a robust efficacy comparison. Several of these limitations were acknowledged by the authors[1-3]
- MAICs are intended to be hypothesis generating, provided they are conducted with appropriate rigor to minimize potential biases[1-3]

Head-to-head randomized controlled trials are the gold standard when it comes to evaluating the potential impact of individual treatments for patients[4]

Comparison of BRUKINSA vs acalabrutinib MAIC methodologies (ALPINE vs ASCEND)

	Kittai et al *American Journal of Hematology;* 2023	Shadman et al *International Congress on Hematologic Malignancies;* 2024
Median follow-up[1,2] *Length of follow-up is a known treatment-effect modifier*	**Disparate data cutoffs: ~17-month difference** **29.6 months with ALPINE vs 46.5 months with ASCEND** *The efficacy data cutoff for ASCEND that was used was much longer than the published cutoff for ALPINE at the time*	**Closely matched data cutoffs: 3-month difference** **39 months with ALPINE vs 36 months with ASCEND** *The latest ALPINE efficacy data cutoff and ASCEND published data were used to ensure follow-ups were balanced*
Matching criteria[1,2] *Ignoring or simplifying matching criteria could impact the results of unanchored MAICs*	**Limited** *Subcategories of variables with significant differences across trials (eg, previous therapies) were not included**	**Comprehensive** *Comprehensive selection of all categories identified as prognostic or predictive of treatment effect were considered†*
Adjusted for COVID-19[1,2,5] *In March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic*	**No** *The data cutoff used for ALPINE was August 2022 (post-pandemic), while the cutoff for ASCEND was February 2020 (pre-pandemic), with no adjustments for the disproportionate effects of COVID-19 on ALPINE patients* *Kittai et al acknowledged that comparing studies pre- and post-COVID era can be particularly problematic*	**Yes** *As the COVID-19 pandemic almost entirely overlapped with the ALPINE trial, all COVID-19–related events from ALPINE were censored*
Effective sample size (ESS)[1,2] *(after statistical weighting)*	**Imbalanced** **ALPINE** *ITT population* **N=327** **ASCEND** *adjusted population* **ESS=99**	**Balanced** **ALPINE** *adjusted population* **ESS=185** **ASCEND** *ITT population* **N=155**
Efficacy comparison	**PFS** *(by investigator)*	**PFS** *(by investigator)‡* **CR** *(odds ratio; weighted logistic regression model)*
Safety[1,2]	**Assessed** *ASCEND (ESS=99) was too small for a robust safety comparison with ALPINE (N=327), and a narrow and artificial data cutoff was created by adjusting only the median treatment exposure for acalabrutinib to match that of BRUKINSA; key adverse events were omitted, including anemia, pyrexia, pneumonia, and URTI, among others*	**Not assessed** *The limited patient numbers under analysis make MAICs problematic to use for robust safety comparisons given the need to assess safety across a large number of potential adverse events. In the absence of head-to-head data, comparative safety is best evaluated via meta-analyses using all available clinical trial results*

*Full matching criteria for Kittai et al were age, gender, ECOG PS, geographic region, IgHV, del(17p), del(11q), del(17p) and/or TP53 mutations, TP53 mutations without del(17p), bulky disease, Rai stage, prior chemoimmunotherapy use, and number of prior therapies.[2]

†Full matching criteria for Shadman et al were age, gender, ECOG PS, geographic region, mutated IgHV, del(17p), del(11q), TP53 mutation status, complex karyotype (covariates not matched in the base case), cancer type, beta$_2$-microglobulin (covariates not matched in base case), bulky disease, Rai/Binet stage, number and type of prior therapies, absolute lymphocyte and neutrophil counts, and platelet count.[1]

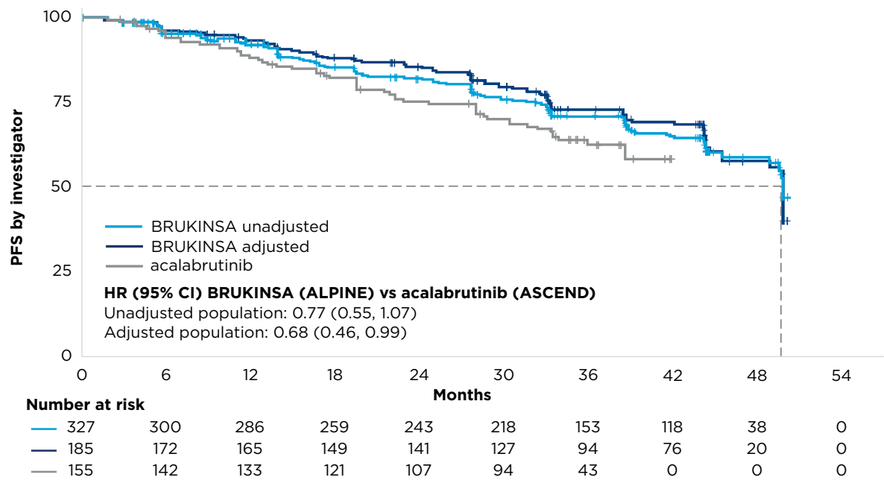
‡PFS was not analyzed by independent review committee due to unavailability of data in ASCEND and the latest ALPINE data cutoff.

ALPINE was a global Phase 3, randomized, open-label, multicenter trial evaluating BRUKINSA vs ibrutinib in 652 patients with relapsed/refractory CLL/SLL who received ≥1 prior systemic therapy.[6]

ASCEND was a global Phase 3, randomized, open-label, multicenter trial evaluating acalabrutinib vs investigator's choice of idelalisib+rituximab (IR) or bendamustine+rituximab (BR) in 310 patients with relapsed/refractory CLL/SLL who received ≥1 prior systemic therapy.[7]

MAIC ANALYSIS SUGGESTED IMPROVED EFFICACY OUTCOMES FOR BRUKINSA vs ACALABRUTINIB[1]

PFS for BRUKINSA vs acalabrutinib[1]



CR advantage for BRUKINSA vs acalabrutinib[1]

Unadjusted population (N=327)	Adjusted population (ESS=185)
BRUKINSA odds ratio to achieve a CR vs acalabrutinib: 2.88 (95% CI: 1.18, 7.02)	**BRUKINSA odds ratio to achieve a CR vs acalabrutinib: 2.90** (95% CI: 1.13, 7.43)

BRUKINSA was ~3 times more likely to achieve a CR

BTKi=Bruton's tyrosine kinase inhibitor; CI=confidence interval; COVID-19=coronavirus disease 2019; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; ITT=intent to treat; URTI=upper respiratory tract infection.

There are no randomized controlled trials between BRUKINSA and acalabrutinib.

There is a potential for bias resulting from the strong assumption that cross-trial differences can be entirely explained by variables selected for matching.

BRUKINSA is the only BTKi to have demonstrated superiority vs ibrutinib in R/R CLL[8]

See the ALPINE data at BRUKINSA.com

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Infections (continued)

Consider prophylaxis for herpes simplex virus, *pneumocystis jirovecii* pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (21%), thrombocytopenia (8%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA. Grade 4 neutropenia occurred in 10% of patients, and Grade 4 thrombocytopenia occurred in 2.5% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA. The most frequent second primary malignancy was non-melanoma skin cancers (8%), followed by other solid tumors in 7% of the patients (including melanoma in 1% of patients) and hematologic malignancies (0.7%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 4.4% of patients treated with BRUKINSA, including Grade 3 or higher cases in 1.9% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.3% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including BRUKINSA.

Evaluate bilirubin and transaminases at baseline and throughout treatment with BRUKINSA. For patients who develop abnormal liver tests after BRUKINSA, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold BRUKINSA. Upon confirmation of DILI, discontinue BRUKINSA.

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions (≥30%), including laboratory abnormalities, in patients who received BRUKINSA (N=1729) are decreased neutrophil count (51%), decreased platelet count (41%), upper respiratory tract infection (38%), hemorrhage (32%), and musculoskeletal pain (31%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

Please see accompanying full Prescribing Information including Patient Information.

References: 1. Shadman M, Brown JR, Williams R, et al. Efficacy of zanubrutinib versus acalabrutinib in the treatment of relapsed or refractory chronic lymphocytic leukemia (R/R CLL): A matching-adjusted indirect comparison (MAIC). Presented at: 28th International Congress on Hematologic Malignancies; February 29-March 3, 2024. **2.** Kittai AS, Skarbnik A, Miranda M, et al. A matching-adjusted indirect comparison of acalabrutinib versus zanubrutinib in relapsed or refractory chronic lymphocytic leukemia. Poster presented at: American Society of Clinical Oncology (ASCO) 2023 Annual Meeting; June 2-6, 2023. Abstract 7540. **3.** Ter Veer E, van Oijen MGH, van Laarhoven HWM. The use of (network) meta-analysis in clinical oncology. *Front Oncol*. 2019;9:822. **4.** *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry.* US Department of Health and Human Services, Food and Drug Administration; 2018. Accessed March 5, 2024. https://www.fda.gov/media/71195/download **5.** Kittai AS, Skarbnik A, Miranda M, et al. A matching-adjusted indirect comparison of acalabrutinib versus zanubrutinib in relapsed or refractory chronic lymphocytic leukemia. *Am J Hematol*. 2023;88(12)(suppl):E387-E390. **6.** Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-332. **7.** CALQUENCE. Package insert. AstraZeneca Pharmaceuticals LP; 2022. **8.** BRUKINSA. Package insert. BeiGene USA, Inc; 2024.

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Efficacy of Zanubrutinib Versus Acalabrutinib in the Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia (R/R CLL): A Matching-Adjusted Indirect Comparison (MAIC)

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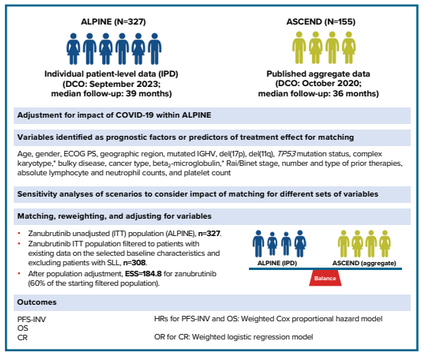
BACKGROUND AND OBJECTIVE

- Zanubrutinib, a next-generation covalent Bruton tyrosine kinase inhibitor (BTKi), is the only BTKi that demonstrated progression-free survival (PFS) superiority vs ibrutinib (first-generation BTKi) in relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) in the ALPINE trial.[1]
- Acalabrutinib, a second-generation BTKi, showed improved PFS vs rituximab-idelalisib/bendamustine in R/R CLL in the ASCEND trial,[2,3] but PFS noninferiority vs ibrutinib in patients with R/R CLL with chromosome 17p or 11q deletions in the ELEVATE-RR trial.[4]
- As no head-to-head clinical trial of zanubrutinib and acalabrutinib in R/R CLL exists, an indirect treatment comparison was performed to evaluate the relative efficacy of these two treatments.
- The objective of this study was to compare the efficacy of zanubrutinib in ALPINE and acalabrutinib in ASCEND using matching-adjusted indirect comparison (MAIC) methodology.

METHODOLOGY

- Individual patient-level data (IPD) from ALPINE was matched against the aggregate data from ASCEND.[1,3]
- An unanchored MAIC was used due to the lack of a common comparator arm between the ALPINE and ASCEND trials.
- Given the timing of the study in relation to the COVID-19 pandemic for ASCEND vs ALPINE, adjustments on ALPINE were made for the impact of COVID-19.
- Population adjustment in the base case analysis considered all variables identified as prognostic factors or predictors of treatment effect **(Fig. 1; Table 1)**.
- Pseudo IPD for PFS and overall survival (OS) in the acalabrutinib arm of ASCEND were reconstructed from the digitized Kaplan-Meier curves reported in the ASCEND publication using the algorithm by Guyot et al.[5]
- A weighted Cox proportional hazard model was used to compare investigator-assessed PFS (PFS-INV) and OS and a weighted logistic regression model to compare complete response (CR).

Figure 1. Details of the overall methodology



*Covariates not matched in the base case.
CR, complete response; DCO, data cut-off; del(11q), chromosome 11q deletion; del(17p), chromosome 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable; IPD, individual patient-level data; ITT, intent to treat; OR, odds ratio; OS, overall survival; PFS-INV, investigator-assessed progression-free survival; SLL, small lymphocytic lymphoma.

METHODOLOGY

Table 1. Covariates matched in the base case and sensitivity analyses

Covariates	Main analysis		Sensitivity analyses					
	Unadjusted population	Base case adjusted population	S1	S2	S3	S4	S5	S6
Age ≥75, %		✓	✓	✓	✓	✓	✓	✓
Male, %		✓	✓	✓	✓	✓	✓	✓
ECOG PS score=0 (vs. ≥1), %		✓	✓		✓	✓	✓	✓
Geographic region								
United States and Canada, %		✓	✓	✓	✓	✓	✓	✓
Australia and New Zealand, %		✓	✓	✓	✓	✓	✓	✓
Asia, %		✓	✓	✓	✓	✓	✓	✓
Europe, %		✓	✓	✓	✓	✓	✓	✓
Genomic status								
Mutated IGHV, %		✓	✓	✓	✓	✓	✓	✓
Del(17p), %		✓	✓	✓	✓	✓	✓	✓
Del(11q), %		✓	✓	✓	✓	✓	✓	✓
TP53 mutation, %		✓	✓	✓	✓	✓	✓	✓
Complex karyotype ≥3, %*								✓
Bulky disease, LDi in cm, ≥5, %		✓	✓	✓	✓	✓	✓	✓
Cancer type, CLL, %		✓	✓	✓	✓	✓	✓	✓
$Beta_2$-microglobulin >3.5 mg/L, %*								✓
Rai stage 0-II or Binet A/B, %		✓	✓	✓	✓	✓	✓	✓
Number of prior therapies								
2, %		✓	✓	✓	✓			✓
3, %		✓	✓	✓	✓			✓
≥4, %		✓	✓	✓	✓		✓	✓
Prior therapy								
Anti-CD20 antibody, %		✓	✓			✓	✓	✓
Alkylators other than bendamustine, %		✓	✓			✓	✓	✓
Bendamustine, %		✓	✓			✓	✓	✓
Purine analog, %		✓	✓			✓	✓	✓
Absolute lymphocyte count, 10^9 cells/L, median		✓				✓	✓	✓
Absolute neutrophil count, 10^9 cells/L, median		✓				✓	✓	✓
Platelet count, 10^9 cells/L, median		✓				✓	✓	✓

*Covariates not matched in the base case.
Del (11q), chromosome 11q deletion; del (17p), chromosome 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable; LDi, longest diameter.

RESULTS

Table 2. Baseline characteristics of the zanubrutinib and acalabrutinib populations

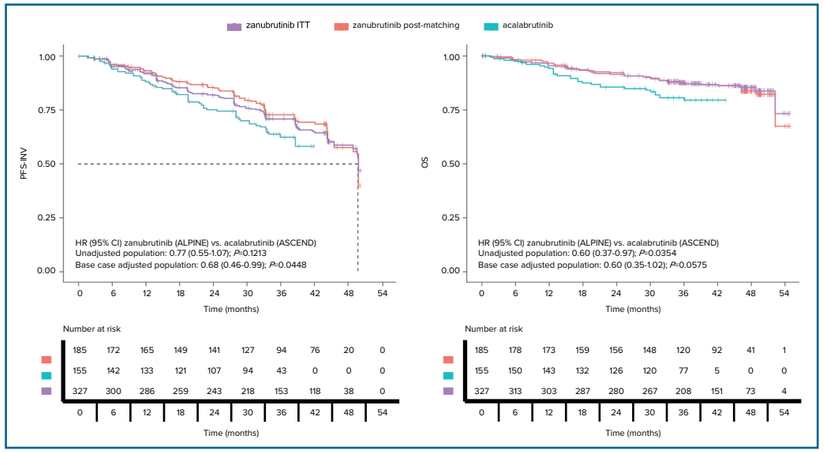
Covariates	Acalabrutinib ASCEND (N=155)	Zanubrutinib ALPINE (N=327)	Zanubrutinib ALPINE post-matching (ESS=184.8)
Age ≥75, %	21.9	22.6	21.9
Male, %	69.7	65.1	69.7
ECOG PS score=0 (vs. ≥1), %	37.4	39.9	37.4
Geographic region			
United States and Canada, %	**5.2**	**15.9**	5.2
Australia and New Zealand, %	5.8	8.6	5.8
Asia, %	**4.5**	**15.0**	4.5
Europe, %	**84.5**	**60.6**	84.5
Genomic status			
Mutated IGHV, %	**16.2**	**25.0**	16.2
Del(17p), %	17.4	13.8	17.4
Del(11q), %	25.2	27.8	25.2
***TP53* mutation, %**	**25.2**	**15.3**	25.2
Complex karyotype ≥3, %*	32.4	26.8	28.6
Bulky disease, LDi in cm, ≥5, %	49.0	44.3	49.0
Cancer type, CLL, %	100	96	100
$Beta_2$-microglobulin >3.5 mg/L, %*	77.4	62.6	62.8
Rai stage 0-II or Binet A/B, %	58.1	58.0	58.1
Number of prior therapies			
2, %	25.8	26.3	25.8
3, %	11.0	7.6	11.0
≥4, %	10.3	7.3	10.3
Prior therapy			
Anti-CD20 antibody, %	83.9	83.8	83.9
Alkylators other than bendamustine, %	85.8	83.8	85.8
Bendamustine, %	30.3	25.7	30.3
Purine analog, %	**70.3**	**54.4**	70.3
Absolute lymphocyte count, 10^9 cells/L, median	48.9	36.0	49
Absolute neutrophil count, 10^9 cells/L, median	3.8	4.0	4
Platelet count, 10^9 cells/L, median	119.5	126.0	119.0

Bold values imply a statistically significant difference between zanubrutinib and acalabrutinib pre- matching.
*Covariates not matched in the base case.
del(11q), chromosome 11q deletion; del(17p), chromosome 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, Immunoglobulin heavy chain variable; LDi, longest diameter.

Efficacy outcomes

- PFS-INV was significantly improved for zanubrutinib post-matching **(Fig 2A)**; OS was potentially improved for zanubrutinib post-matching **(Fig 2B)**.
- CR favored zanubrutinib in the unadjusted and base case adjusted populations **(Table 3)**.
- Results for the sensitivity analyses were consistent with the base case **(Table 3)**.

Figure 2. (A) PFS-INV and (B) OS for zanubrutinib ITT and post-matching, and acalabrutinib



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS-INV, investigator-assessed progression-free survival.

Table 3. Relative treatment effects for base case and sensitivity analyses

	Main analysis		Sensitivity analyses					
	Unadjusted population	Base case adjusted population	S1	S2	S3	S4	S5	S6
Sample size for ALPINE zanubrutinib	N=327	ESS=184.8	ESS=188.9	ESS=210.3	ESS=208.1	ESS=188.2	ESS=187.4	ESS=78.2
HR PFS-INV zanubrutinib vs. acalabrutinib (95% CI, *P* value)	0.77 (0.55-1.07, *P*=0.1213)	**0.68 (0.46-0.99, *P*=0.0448)**	**0.68 (0.47-1.00, *P*=0.0483)**	0.72 (0.5-1.04, *P*=0.0842)	0.73 (0.51-1.05, *P*=0.0921)	**0.67 (0.46-0.98, *P*=0.0410)**	**0.67 (0.46-0.98, *P*=0.0386)**	0.71 (0.43- 1.17, *P*=0.1822)
HR OS zanubrutinib vs. acalabrutinib (95% CI, *P* value)	**0.6 (0.37-0.97, *P*=0.0354)**	0.6 (0.35-1.02, *P*=0.0575)	**0.59 (0.35-1.00, *P*=0.0481)**	0.63 (0.38-1.04, *P*=0.0720)	0.66 (0.40-1.09, *P*=0.1030)	0.61 (0.36-1.03, *P*=0.0627)	0.61 (0.36-1.03, *P*=0.0667)	0.68 (0.33-1.39, *P*=0.2872)
OR CR zanubrutinib vs. acalabrutinib (95% CI, *P* value)	**2.88 (1.18-7.02, *P*=0.0198)**	**2.90 (1.13-7.43, *P*=0.0270)**	**2.88 (1.13-7.38, *P*=0.0273)**	**2.69 (1.06-6.85, *P*=0.0377)**	**2.78 (1.09-7.07, *P*=0.0316)**	**2.85 (1.11-7.31, *P*=0.0294)**	**2.80 (1.09-7.19, *P*=0.0326)**	**3.34 (1.15-9.71, *P*=0.0264)**

Bold values indicate P<0.05.
CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS-INV, investigator-assessed progression-free survival.

CONCLUSIONS

- This comprehensive MAIC demonstrated a significant PFS and CR advantage, and potentially improved OS for zanubrutinib compared with acalabrutinib.
  - Results were robust across multiple sensitivity analyses.
- In a previous publication, Kittai et al. presented a MAIC to compare the efficacy and safety of zanubrutinib (ALPINE, aggregate) vs. acalabrutinib (ASCEND, IPD) in R/R CLL. Findings showed similar efficacy for zanubrutinib and acalabrutinib (PFS-INV) and different adverse event profiles.[7]
  - The efficacy results differ from those presented here because the analysis by Kittai et al. had several important limitations, including different follow-ups between ALPINE and ASCEND, lack of any adjustment for COVID-19, and incomplete matching variables (e.g., no granularity in geographic regions and number and types of prior therapies).
- While MAICs provide a scientific basis for evaluating hypotheses with regards to treatment efficacy across trials, the gold standard for evaluating evidence of relative efficacy remains randomized controlled trials.

LIMITATIONS

- There is a potential for bias resulting from the strong assumption that cross-trial differences can be entirely explained by variables selected for matching.
- Independent review committee-assessed PFS was not analyzed in the current MAIC due to unavailability of data in ASCEND and the latest ALPINE data cutoff.
- The study did not compare safety for zanubrutinib vs acalabrutinib, given different treatment exposure times across the two trials.
  - Safety of a drug is best evaluated via meta-analyses that use all available evidence across all indications.
  - A recent meta-analysis of 61 trials involving 6,959 patients who received ibrutinib, ibrutinib ± anti-CD20 antibody, acalabrutinib, and zanubrutinib extensively analyzed the AE profiles of zanubrutinib and acalabrutinib across several indications and reported differences between the two treatments.[6]

DISCLOSURES

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REFERENCES

1. Brown JR, et al. *N Engl J Med.* 2023; 388: 319-332.
2. Ghia P, et al. *J Clin Oncol.* 2020; 38: 2849-2861.
3. Ghia P, et al. *Hemasphere.* 2022; 6(12):e801.
4. Byrd JC, et al. *J Clin Oncol.* 2021; 39: 3441–3452.
5. Guyot P, et al. *BMC Med Res Methodol.* 2012; 12: 9.
6. Hwang S, et al. *Hemasphere.* 2023;7(S3):1134.
7. Kittai AS, et al. *Am J Hematol.* 2023;98(12):E387-E390.