A matching-adjusted indirect comparison of acalabrutinib with and without obinutuzumab versus zanubrutinib in treatment-naive chronic lymphocytic leukemia

Abstract number: 1550098

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Introduction

- The second-generation Bruton tyrosine kinase inhibitors acalabrutinib and zanubrutinib have not been compared with each other in a head-to-head randomized controlled trial (RCT).
  - Acalabrutinib plus obinutuzumab and acalabrutinib monotherapy were evaluated against chlorambucil plus obinutuzumab in treatment-naive patients with chronic lymphocytic leukemia (CLL) in the ELEVATE-TN RCT.[1]
  - Zanubrutinib monotherapy was evaluated against bendamustine plus rituximab in treatment-naive patients with CLL/small lymphocytic lymphoma (SLL) in cohort 1 of the SEQUOIA RCT, which only included patients without del(17p).[2,3]
- To compare the efficacy and safety of acalabrutinib plus obinutuzumab and acalabrutinib monotherapy versus zanubrutinib in patients with treatment-naive CLL/SLL without del(17p), we conducted an unanchored matching-adjusted indirect comparison (MAIC)[4] using individual patient data (IPD) from ELEVATE-TN and published aggregate data from SEQUOIA cohort 1.

Methods

- A summary of the methodology is shown in **Figure 1**.

Matching variables

- In the unanchored MAIC, IPD for patients without del(17p) receiving acalabrutinib with or without obinutuzumab in ELEVATE-TN were weighted to match baseline data for patients without del(17p) receiving zanubrutinib in cohort 1 of SEQUOIA.
- Patients were matched based on variables considered prognostic and/or predictive of investigator-assessed progression-free survival (INV-PFS) in an exploratory multivariable Cox regression analysis of ELEVATE-TN.

Efficacy analysis

- INV-PFS was assessed in all randomized patients without del(17p) (acalabrutinib + obinutuzumab, n = 162; acalabrutinib monotherapy, n = 163; zanubrutinib, n = 241) using the most recent data cut-offs (DCOs) for ELEVATE-TN (October 2021) and SEQUOIA (October 2022), which report the most mature data (median follow-up: 58 vs 44 months).
  - Pseudo-IPD for INV-PFS for zanubrutinib were obtained from Kaplan–Meier curves using the algorithm by Guyot *et al*.[5]
- A sensitivity analysis assessed if adding all possible variables that could be matched on, regardless of whether they were found to be predictive or prognostic of INV-PFS, impacted INV-PFS.

Safety analysis

- The safety analysis assessed the incidence of adverse events (AEs) and reported the odds ratios (ORs) of AEs in treated patients (acalabrutinib + obinutuzumab, n = 162; acalabrutinib monotherapy, n = 162; zanubrutinib, n = 240).
  - To compare the incidence of AEs, the ELEVATE-TN September 2020 DCO was used because this aligned most closely with the median follow-up from the SEQUOIA October 2022 DCO (47 vs 44 months).
- A sensitivity analysis assessed the impact of matching on only characteristics considered relevant for safety by clinical experts, which were age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and cytopenia.

Results

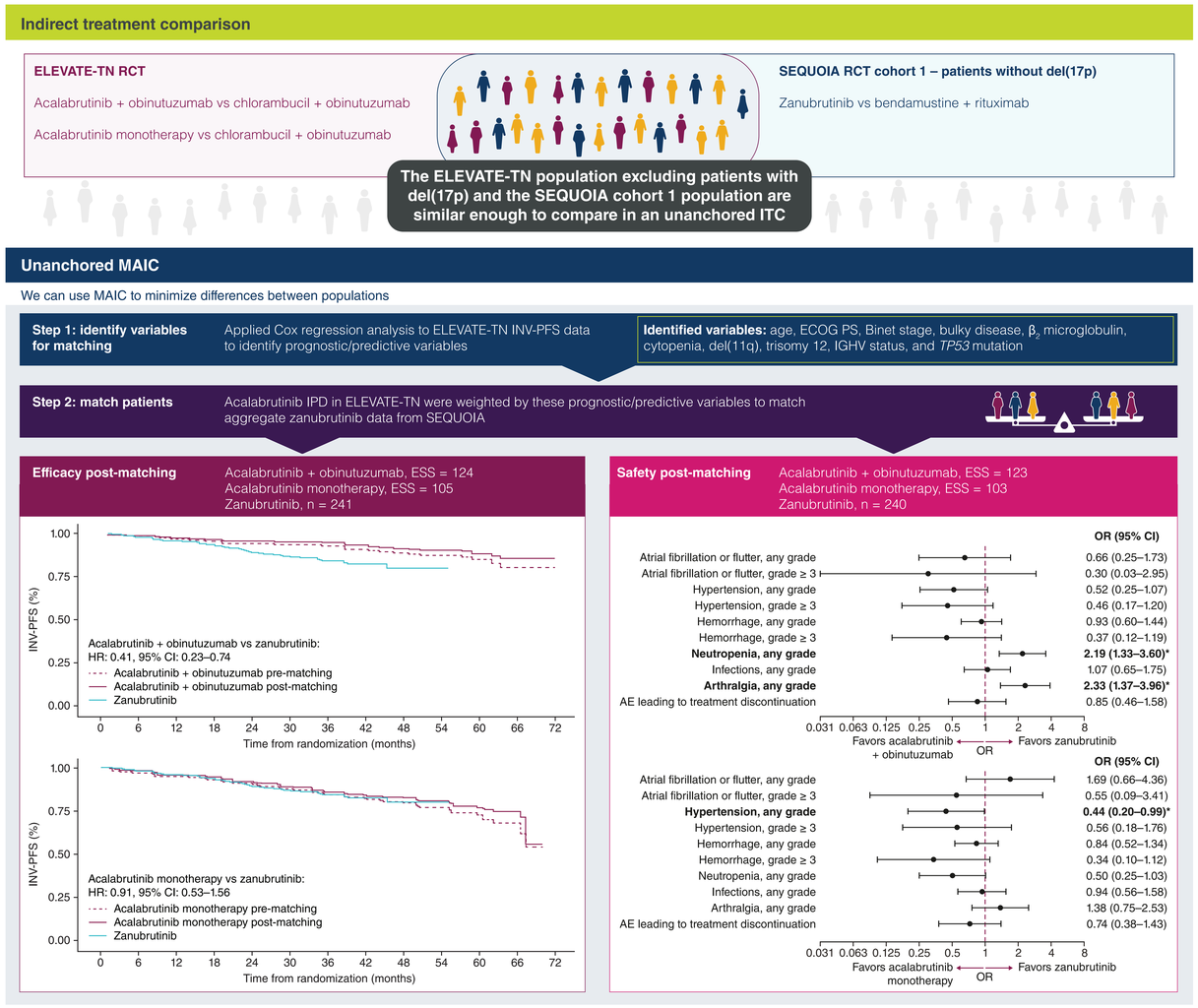
Matching variables

- Variables identified as prognostic and/or predictive of INV-PFS in the Cox regression analyses can be found in **Figure 1**.

Efficacy analysis

- After matching, the acalabrutinib plus obinutuzumab and acalabrutinib monotherapy effective sample sizes (ESSs) were 124 and 105, respectively (77% and 64% of the original efficacy sample size, respectively).
  - After matching, there were no differences between treatment arms for matched variables, and the differences between treatment arms for non-matched variables were mostly small (**Supplementary Table 1**).

Figure 1. Unanchored MAIC methodology and results



Note: ORs in bold with an asterisk are statistically significant.
AE, adverse event; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable; INV-PFS, investigator-assessed progression-free survival; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; OR, odds ratio; RCT, randomized controlled trial; *TP53*, tumor protein 53.

- Matching had little impact on acalabrutinib plus obinutuzumab or acalabrutinib monotherapy INV-PFS (**Figure 1**) and post-matching:
  - 36-month INV-PFS was higher with acalabrutinib plus obinutuzumab (95%, 95% confidence interval [CI]: 90–97) than with zanubrutinib (84%, 95% CI: 79–88).
  - there was no evidence of a difference between acalabrutinib monotherapy and zanubrutinib when looking at 36-month INV-PFS (86%, 95% CI: 78–91 vs 84%, 95% CI: 79–88).
- The results of the sensitivity analysis that used all possible matching variables were consistent with the results from the primary analysis (**Supplementary Figure 1**).

Safety analysis

- In the safety analysis, the acalabrutinib plus obinutuzumab and acalabrutinib monotherapy ESSs post-matching were 123 and 103, respectively (76% and 64% of the original safety sample size, respectively).
  - Some AEs only occurred in a few patients, resulting in wide CIs.
  - Some of the results in either direction were only marginally significant or non-significant.
- There were no significant differences in the odds of acalabrutinib plus obinutuzumab compared with zanubrutinib in the occurrence of most types of AEs, except for higher odds of having any grade neutropenia with acalabrutinib plus obinutuzumab (OR: 2.19, 95% CI: 1.33–3.60) and arthralgia (OR: 2.33, 95% CI: 1.37–3.96; **Figure 1**).
- The odds of hypertension of any grade were significantly lower with acalabrutinib monotherapy (OR: 0.44, 95% CI: 0.20–0.99) than with zanubrutinib, whereas there were no significant differences in the odds of other AEs (**Figure 1**).
- There were no significant differences in the odds of atrial fibrillation or flutter between acalabrutinib plus obinutuzumab and zanubrutinib (OR: 0.66, 95% CI: 0.25–1.73) or between acalabrutinib monotherapy and zanubrutinib (OR: 1.69, 95% CI: 0.66–4.36).
- The results of the sensitivity analysis that matched only on variables thought to impact safety outcomes were consistent with the results from the primary analysis (**Supplementary Figure 2**).

Conclusions

- In this indirect treatment comparison of ELEVATE-TN and SEQUOIA that evaluated patients with treatment-naive CLL/SLL without del(17p), when looking at INV-PFS:
  - acalabrutinib plus obinutuzumab had improved efficacy compared with zanubrutinib.
  - there was no significant difference in the efficacy of acalabrutinib monotherapy compared with zanubrutinib.
- The safety profiles of acalabrutinib with or without obinutuzumab and zanubrutinib were largely similar, with a few notable exceptions:
  - acalabrutinib plus obinutuzumab was associated with higher odds of neutropenia and any grade arthralgia than zanubrutinib.
  - the odds of hypertension of any grade were lower with acalabrutinib monotherapy than with zanubrutinib.
- Limitations of indirect treatment comparison analyses mean that the results should be viewed as hypothesis-generating.
- Despite these limitations, our results systematically compare commonly used regimens for which randomized, prospective data are not available.

Acknowledgments

This study was funded by AstraZeneca, USA. The authors thank Barbara Xella PhD and Helen Fishpool BSc of PharmaGenesis Oxford Central, Oxford, UK, for medical writing support, which has been funded by AstraZeneca, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (www.ismpp.org/gpp-2022).
ASK is a recipient of the Conquer Cancer, the ASCO Foundation, Career Development Award.

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Supported by: AstraZeneca

Presented at the International Workshop on Chronic Lymphocytic Leukemia, October 6–9, 2023, Boston, MA, USA