Acalabrutinib (AKA) versus venetoclax with obinutuzumab (VEN+OBI) in patients with untreated chronic lymphocytic leukemia (CLL) and unmutated IGHV genes – indirect comparison

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INTRODUCTION

Disease Background

- Chronic lymphocytic leukemia is a B-cell malignancy that is most common in older patients and has a variable course. The unmutated status of the IGHV genes is a well-known and common predictor of a poorer prognosis.

Evaluated Technology

- From November 1, 2021, combined therapy with venetoclax and obinutuzumab is included in the Polish drug program "TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA WITH VENETOCLAX (ICD-10: C.91.1)" and covered by reimbursement in the 1st line of treatment for patients with CLL (CrCl >30 i <70 ml/min or CIRS > 6, ECOG = 1).
- VEN+OBI therapy in a mentioned drug program (CrCl >30 and <70 ml/min or CIRS > 6, ECOG = 1) will be a comparator for AKA in the group of patients with high genetic risk (del17p/TP53 mutation or non-mutated IgHV genes).

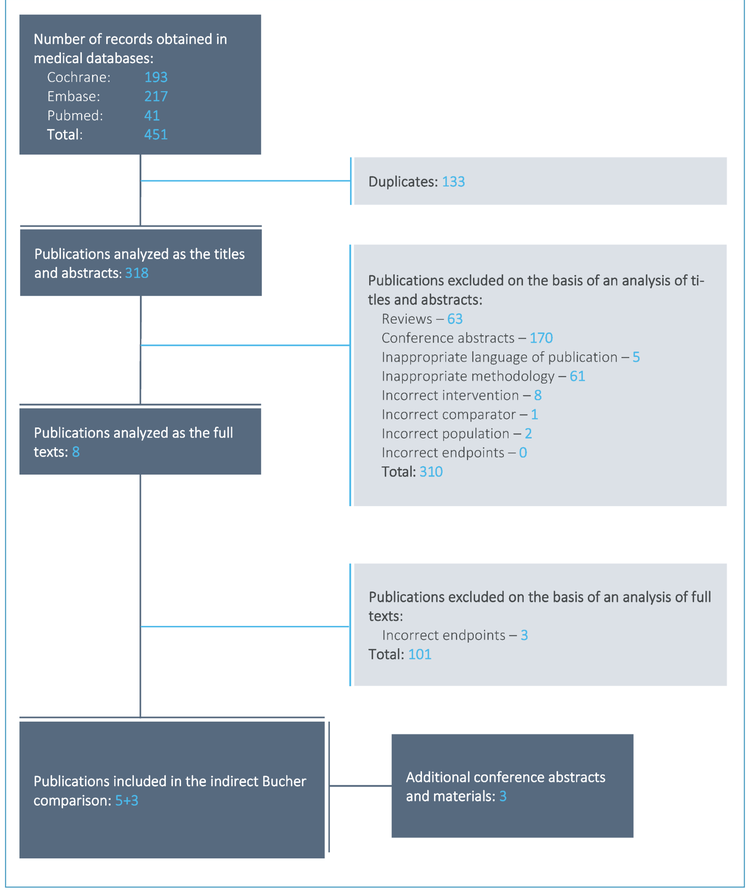
OBJECTIVES

- The objective of this study was to compare the efficacy of AKA, a selective covalent BTK inhibitor, and VEN+OBI in previously untreated patients with chronic lymphocytic leukemia (CLL) and unmutated IGHV genes.

METHODS

- A systematic review was conducted on June 13, 2023, using PubMed, Embase, and Cochrane databases, following the Polish Health Technology Assessment (HTA) guidelines (Figure 1).
- Due to the absence of direct head-to-head trials, an indirect Bucher comparison was performed using a common comparator (OBI + chlorambucil) (Figure 2).
- The analysis included 4 publications from the ELEVATE study (*Sharman 2020*, *Sharman 2022*, *Sharman 2022a* and *EHA 2022*) and 4 publications from the CLL14 study (Fisher 2019, *Al-Sawaf 2020*, *Al-Sawaf 2023* and *Al-Sawaf 2023a*).

Figure 1. Systematic Review Flowchart.

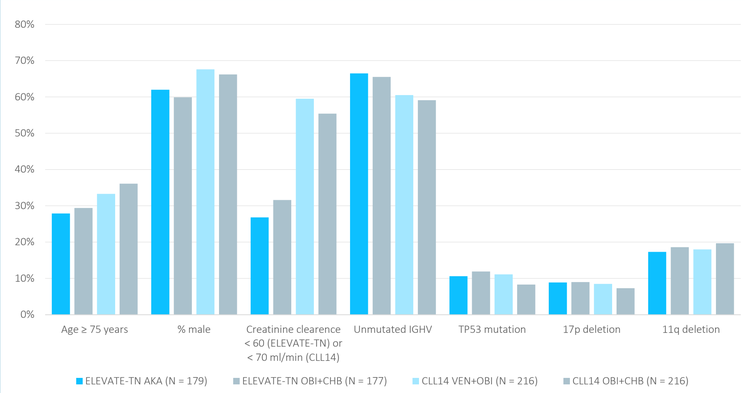


RESULTS

Characteristics of included studies

- Two RCTs were included: *ELEVATE-TN* (AKA vs OBI+CHB, N = 356) and *CLL14* (VEN+OBI vs OBI+CHB, N = 432).
- These trials presented results for patients with unmutated IGHV genes, accounting for 66.0% and 59,8% of the respective study population.
- Most baseline characteristics were similar between groups (Figure 3).

Figure 3. Baseline characteristics of cohorts in the ELEVATE-TN and CLL14.



Follow-up

- The longest available follow-up periods were selected for analysis, yielding 58.2 vs. 76.4 months overall and 58.2 vs. 65.4 months for high-risk subgroups.

PFS

- Comparison of AKA vs. VEN+OBI demonstrated a significant improvement in favour of AKA in terms of progression-free survival (PFS) in both the overall population (hazard ratio [HR] = 0.53, 95% CI: 0.34-0.81) and the unmutated IGHV subgroup (HR = 0.44, 95% CI: 0.26-0.76), with a consistent trend observed in the TP53mut/del17p subgroup (HR = 0.44, 95% CI: 0.15-1.31; data for medians follow-up: 58.2 vs 65.4 months) (Table 1, Figure 4).

OS

- Overall survival did not differ significantly between the two interventions (HR = 1.42, 95% CI: 0.75-2.69) (Table 1, Figure 4).

Table 1. ITC results: AKA vs VEN+OBI in the 1st line of treatment, ELEVATE-TN vs CLL14 trials.

Endpoint/population	AKA vs OBI+CHB HR (95% CI)	VEN+OBI vs OBI+CHB HR (95% CI)	AKA vs VEN+OBI HR (95% CI)
Follow-up medians: 28.3 vs 28.1 months; *ELEVATE-TN* (*Sharman 2020*) vs *CLL14* (*Fisher 2019*)			
PFS. ITT population, IV assessment	**0.16 (0.10-0.27)**	**0.35 (0.23-0.53)**	**0.46 (0.24-0.87)**
PFS, unmutated IGHV, ICR assessment *ELEVATE-TN*, IV assessment w *CLL14*	**0.11 (0.07-0.19)**	**0.22 (0.12-0.38)**	0.50 (0.23-1.07)
PFS, 17p deletion/TP53 mutation, ICR assessment	**0.23 (0.09-0.61)**	**0.31 (0.13-0.76)**	0.74 (0.20-2.73)
OS	0.60 (0.28-1.27)	1.24 (0.64-2.40)	0.48 (0.18-1.32)
Follow-up medians: 46.9 vs 39.6 months; *ELEVATE-TN* (*Sharman 2022*) vs *CLL14* (*Al-Sawaf 2020*)			
PFS, ITT population, IV assessment	**0.19 (0.13-0.28)**	**0.31 (0.22-0.44)**	0.61 (0.37-1.03)
PFS, unmutated IGHV, IV assessment	**0.10 (0.06-0.16)**	**0.23 (0.15-0.35)**	**0.43 (0.23-0.83)**
PFS: 17p deletion/TP53 mutation, IV assessment	**0.18 (0.07-0.46)**	0.48 (0.22-1.08)	0.38 (0.11-1.29)
OS	0.95 (0.52-1.74)	1.03 (0.60-1.75)	0.92 (0.41-2.07)
Follow-up medians: 46.9 vs 65.4 months; *ELEVATE-TN* (*Sharman 2022*) vs *CLL14* (*Al-Sawaf 2023*)			
PFS, ITT population, IV assessment	**0.19 (0.13-0.28)**	**0.35 (0.26-0.46)**	**0.54 (0.34-0.88)**
PFS. unmutated IGHV, IV assessment	**0.10 (0.06-0.16)**	**0.27 (0.19-0.38)**	**0.37 (0.20-0.68)**
PFS: 17p deletion/TP53 mutation, IV assessment	**0.18 (0,07-0,46)**	**0.48 (0.24-0.94)**	0.38 (0.12-1.20)
OS	0.95 (0.52-1.74)	0.72 (0.48-1.09)	1.36 (0.70-2.64)
Follow-up medians: 58.2 vs 65.4 months; *ELEVATE-TN* (*Sharman 2022a*) vs *CLL14* (*Al-Sawaf 2023*)			
PFS, ITT population, IV assessment	**0.21 (0.15-0.30)**	**0.35 (0.26-0.46)**	**0.60 (0.38-0.94)**
PFS, unmutated IGHV, IV assessment	**0.12 (0.08-0.18)***	**0.27 (0.19-0.38)**	**0.44 (0.26-0.76)**
PFS: 17p deletion/TP53 mutation, IV assessment	**0.21 (0.09-0.50)**	**0.48 (0.24-0.94)**	0.44 (0.15-1.31)
OS	0.98 (0.58-1.64)	0.72 (0.48-1.09)	1.32 (0.64-2.74)
Follow-up medians: 58.2 vs 76.4 months; *ELEVATE-TN* (*Sharman 2022a*) vs *CLL14* (*Al-Sawaf 2023a*)			
PFS, ITT population, IV assessment	**0.21 (0.15-0.30)**	**0.40 (0.31-0.52)**	**0.53 (0.34-0.81)**
OS	0.98 (0.58-1.64)	0.69 (0.48-1.01)	1.42 (0.75-2.69)

IV – investigator; ICR – independent review committee; OS – overall survival; PFS progression-free survival, CI – confidence intervals; **bold** – statistically significant
* data from *EHA 2023* presentation (data on file).

Figure 2. Indirect comparison network.

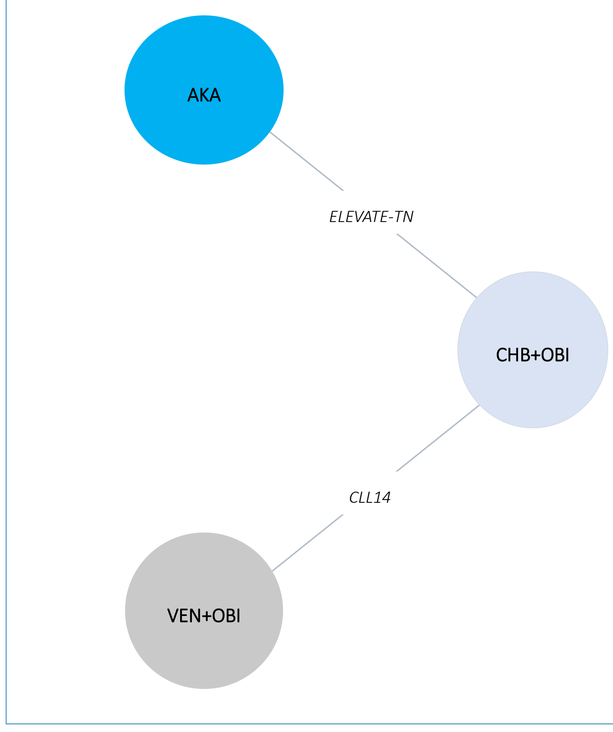
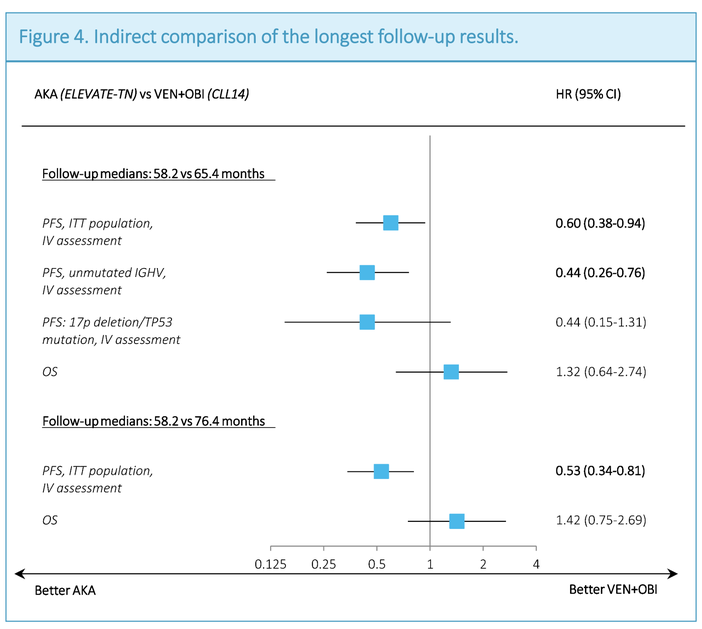


Figure 4. Indirect comparison of the longest follow-up results.



CONCLUSIONS

Compared to previously published evaluations, the use of longer follow-up periods with a larger number of events in the calculations demonstrates that AKA compared to VEN+OBI significantly reduces the risk of progression or death by 47% in the overall population and by 56% in the subgroup of patients with unmutated IGHV genes.

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8. EHA 2023 presentation (data on file).

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DISCLOSURES

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