# The net clinical benefit of targeted agents in the upfront treatment of elderly/unfit Chronic Lymphocytic Leukaemia (CLL) patients: Results of Network Meta-Analysis

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- Studies of indirect comparison of targeted agents in the upfront therapy of chronic lymphocytic leukemia (CLL) mainly focused on progression-free survival (PFS)
- This network meta-analysis (NMA) evaluated for the first time an array of efficacy and safety outcomes.
- Results allow the assessment of net clinical benefit of targeted agents in the upfront therapy of elderly with CLL.

To the Editor:

The current shift in the treatment paradigm from chemoimmunotherapy (CIT) to targeted agent (TA) therapy has rapidly changed the therapeutic landscape of chronic lymphocytic leukaemia (CLL)(1). Current European and US guidelines recommend continuous first- or second-generation Bruton tyrosine kinase inhibitors (BTKis) and time-limited venetoclax-based therapy in the setting of previously untreated or relapsed-refractory CLL (2-3). However, the lack of head-to-head randomized clinical trials, especially in the upfront setting, limits the potential of guidelines to address questions related to the choice of TA. Published studies of indirect comparisons of TA therapies across separate trials have appraised available evidence in favor of any given TA (4-8). Such cross-trial analyses of upfront CLL therapy mainly utilize progression-free survival (PSF) as the primary efficacy outcome (4-8). Therefore, these results may have limited applicability in clinical practice as other relevant endpoints that complement efficacy outcomes are not included in such analyses. In addition, safety outcomes are often overlooked, thus preventing the assessment of the net clinical benefit of different TAs. Treatment with TAs necessitates patients to remain on therapy for many years, therefore, the long-term tolerability of such therapies is a critical factor to assess (1).

To increase the understanding of these clinical questions, we conducted a systematic review and network meta-analysis (NMA) under the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement, which includes all published randomized controlled trials (RCTs) assessing the efficacy and safety of BTKis and venetoclax-based regimens in treatment-naïve CLL patients (*Suppl Figure 1)*.

The literature search employed PubMed, EMBASE, and the Cochrane databases to identify original full-text articles and research letters published in English. The search strategy used Medical Subject Headings terms and free text words to increase the sensitivity. Abstract evaluation and data extraction were independently performed by two reviewers (S.M. and D.G.). The analysis included distinct efficacy and safety endpoints to predict the net benefit of TAs in treatment-naïve CLL patients. For each trial, we evaluated hazard ratios (HRs) of outcomes of efficacy (PFS, overall survival [OS], time to next treatment [TTNT], overall response rate [ORR], complete remission [CR], minimal residual disease [MRD]), and toxicity (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or above for

atrial fibrillation, infections, neutropenia, and diarrhoea). Since information about bleeding is reported only for the ELEVATE-TN this toxicity was not assessed in the NMA.

According to the Cochrane Handbook for Systematic Reviews of Interventions, the quality of selected studies was assessed by the allocation of 1 point for each of the following 5 criteria: method of randomization, allocation concealment, blindness, withdrawal or dropout, and adequate follow-up. Studies were given a grade of A, B, or C depending on how many of the five points were met: 4 to 5, 2 to 3, or 0 to 1.

NMA results were presented in the form of the surface under the cumulative ranking curve (SUCRA). SUCRA offers a numeric representation (range from 0 to 1.0) of each treatment, allowing for an overall ranking. The closer the SUCRA value to 1.0, the higher the likelihood that therapy is in the top rank, whereas the closer to 0 the SUCRA value, the more likely treatment is in the bottom rank (9). A high ranking would indicate that treatment would be more preferred for the endpoint under consideration, whilst a low ranking would denote a less preferred approach.

Nine RCTs met the low risk for bias criteria according to the Cochrane Handbook for Systematic Reviews of Interventions *(Supplementary Table 1)*(10-18). Five were excluded because of the lack of a common comparator (RESONATE2, ALLIANCE, ECOG-ACRIN, FLAIR, SEQUOIA)(10-14). Four trials were suitable for the network analysis (ILLUMINATE, ELEVATE-TN, CLL14, GLOW)(15-18) *(Supplementary Table 2)*. Chlorambucil-obinutuzumab (CO) was the control arm across these four studies (n=610). In aggregate, the four studies included 1547 patients and evaluated ibrutinib-obinutuzumab (IO) (ILLUMINATE; n=113), venetoclax-obinutuzumab (VO) (CLL14; n=216), acalabrutinib (A) monotherapy (ELEVATE-TN; n=179), A plus obinutuzumab (AO)(ELEVATE-TN; n=179) and ibrutinib-venetoclax (IV)(GLOW , n=195). In this NMA, we used the longest published follow-up for each trial (GLOW 27.7 months, CLL14 52,4 months, ILLUMINATE 45 months, ELEVATE-TN 46.9 months) (15-18). Patients with *TP53* disruption were excluded from the GLOW study; hence this subset was excluded from our analysis.

Efficacy outcomes of different regimens scored according to the SUCRA are presented in table 1. Acalabrutinib-based regimens had the highest efficacy in terms of PFS (SUCRA for AO and A were, respectively, 0.9923 and 0.7250). Of note, the AO combination also had the highest probability of prolonged OS (SUCRA OS, 0.9010) and increased ORR (SUCRA ORR,0.8670). When the quality of clinical and MRD responses was analyzed, venetoclax-based regimens received the highest ranking. IV ranked first in terms of CR (SUCRA 0.9208) and VO in terms of undetectable MRD (SUCRA,0.9020). Since the ELEVATE-TN trial

TTNT results were unavailable, the TTNT analysis did not include acalabrutinib-based regimens. The ranking demonstrated that IO was associated with the longest TTNT (SUCRA,0.9810).

We next developed a ranking chart for efficacy outcomes. An efficacy rankogram (k ranks ranged from 1 to 6) was generated using the average (Av) SUCRA for PFS, OS, ORR, and CR. MRD and TTNT outcomes were not included because this information was not available for all RCTs studied. In the aggregate efficacy rankogram, AO ranked first and CO last (Fig 1a). The full Av SUCRA ranking order was AO, IV, VO, IO, A, CO (Av SUCRA, 0.8544, 0.5793,0.5747,0.4456,0.3864, 0.0575) (Table 2a).

When we analyzed safety outcomes, reduced toxicity was associated with increased SUCRA values. As expected, ibrutinib-based regimens were more frequently associated with a higher likelihood of developing atrial fibrillation (AF) assessed as CTCAE grade 3 or above (SUCRA IO and IV, respectively, 0.2322 and 0.2122). Such risk declined with acalabrutinib-based regimens (SUCRA A and AO, respectively, 0.4146 and 0.4940). Of note, VO was the combination associated with the lowest risk of AF(SUCRA,0.9156)(Table 2b). Patients treated with a BTKI in association with an anti-CD20 monoclonal antibody had a higher likelihood of CTCAE grade 3 infections (SUCRA IO,0.2240; AO, 0.1784). Such risk was lower with venetoclax-based regimens (SUCRA IV, 0.6774; VO, 0.5370). Finally, the lowest risk of developing neutropenia (SUCRA,1.000) or diarrhea (SUCRA,0.9446) was observed with A (Table 2b).

The CTCAE grade 3 Av SUCRA values for neutropenia, infections, diarrhea, and AF allowed the development of an aggregate safety rankogram. In this aggregate safety rankogram, A ranked first and IO last (Fig 1b). The full safety Av SUCRA ranking order was A, CO, AO, IV VO, and IO (Av SUCRA; 0.7016, 0.6650,0.4390,0.4377, 0.4325, and 0.3242)(Table 2b).

To our knowledge, this is the first NMA evaluating a comprehensive array of efficacy and safety outcomes across RCTs of TA therapy for previously untreated CLL. Our results indicate that clinical decisions around the choice of TA therapy should carefully consider the net risk-benefit profile for each treatment option. Of note, adverse events lead to lower adherence to therapy, compromising the chosen treatment's clinical efficacy and need to be considered in treatment selection(19).

This study has some limitations. Firstly, the patient population across RCTs was heterogeneous regarding the comorbidity load. Notably, patients with CIRS score > 6 were more frequently found in the GLOW and CLL14 studies than in the ELEVATE-TN or

ILLUMINATE trials. (15-18). In addition, the analysis of the safety profile of different TAs is only based on the crude rate of adverse events without any adjustment for the duration of exposure to TA treatment (20). Finally, the health economic value of TA for the frontline treatment of CLL was not assessed in this NMA. A recent probabilistic cost-effectiveness analysis of first-line therapy of CLL in Canada suggests that VO is a cost-effective treatment option for unfit frontline CLL patients and provides value for money to healthcare payers (21). However, cost studies of TAs in CLL are limited by short follow-up times that did not capture the full impact of treatment costs. When more robust cost-effectiveness analyses will be available they will provide further insights into the choice of best TAs for personalized upfront therapy in CLL.

Nonetheless, this NMA can aid the selection of upfront therapy in CLL patients with intact *TP53*. In those patients who are physically fit, a model based solely upon efficacy may be able to inform treatment decisions. In contrast, a model based exclusively on toxicity outcomes may guide therapy selection in unfit patients.

## CONFLICT OF INTEREST

SM received honoraria from Janssen, Abbvie, and AstraZeneca, advisory board for Janssen, Abbvie, and AstraZeneca. DA, AP, and DG have nothing to disclose.

## AUTHOR CONTRIBUTIONS

S.M. designed the study, interpreted data and wrote the paper. D.G. was responsible for statistical analysis. D.A. and A.P. interpreted data and revised the manuscript. All authors approved the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**Legend Figure 1**

**Ranking of treatments based on network meta-analysis (NMA) results.**

**Tab 2a** - SUCRA value for each regimen with respect to efficacy outcomes [progression-free survival (PFS) , overall survival (OS), overall response rate (ORR), complete remission (CR)].

**Tab 2b -** SUCRA value for each regimen with respect to toxicity outcomes [Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or above for atrial fibrillation (AF), infections, neutropenia and diarrhea] Of note, in the case of toxicity, the higher the SUCRA, the safer the regimen is for patients.

**Fig 1 a** – Average SUCRA for efficacy outcomes. Rankogram (k) ranks ranged from 1 to 6
**Fig 1b -** Average SUCRA for toxicity outcomes. Rankogram (k) ranks ranged from 1 to 6