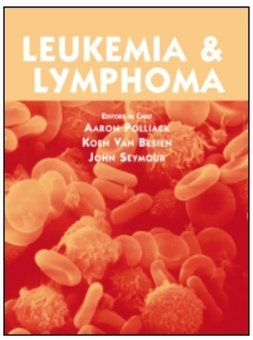

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ORIGINAL ARTICLE

Matching-adjusted indirect comparisons of safety and efficacy of acalabrutinib versus other targeted therapies in patients with treatment-naïve chronic lymphocytic leukemia

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ABSTRACT

Acalabrutinib is a highly selective, potent, next-generation, covalent Bruton tyrosine kinase inhibitor with minimal off-target activity. Matching-adjusted indirect comparisons (MAICs) were performed to estimate the safety and efficacy of acalabrutinib compared to other targeted therapies for treatment-naïve patients with chronic lymphocytic leukemia (CLL). Individual patient data for acalabrutinib (ELEVATE-TN trial) were matched to aggregate baseline characteristics for comparators. After matching, acalabrutinib (with or without obinutuzumab) showed improved safety outcomes, except for increased risk of neutropenia ($p < 0.001$) for acalabrutinib plus obinutuzumab versus ibrutinib and increased risk of leukopenia ($p < 0.05$) for acalabrutinib (with or without obinutuzumab) versus venetoclax plus obinutuzumab. There was no statistically significant difference in progression-free survival between acalabrutinib (with or without obinutuzumab) and any of the comparators. This MAIC demonstrated a favorable safety profile for acalabrutinib-based therapy compared with other targeted therapies in treatment-naïve patients with CLL, without compromising efficacy.

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KEYWORDS
Acalabrutinib; Bruton tyrosine kinase inhibitor; chronic lymphocytic leukemia; matching-adjusted indirect comparison; targeted therapy

Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in Western countries, with an annual incidence of 4.2 cases per 100,000 population [1]. The majority of patients with CLL have early-stage asymptomatic disease at diagnosis [2]. Active disease includes manifestation of significant B symptoms, cytopenias, bulky lymphadenopathy, splenomegaly, or hepatomegaly [3,4]. Treatment of CLL is generally initiated for patients with active disease who meet established criteria for treatment [5]. The median age at diagnosis is 72 years [6], presenting a challenge for clinicians because the frailty of many patients precludes them from intensive chemoimmunotherapy. Treatment decisions are based on patient fitness, including the presence of comorbidities, as well as molecular and cytogenetic determinants, such as del(13q), del(17p), and mutated *TP53* or immunoglobulin heavy-chain variable (*IGHV*).

Over the past two decades, treatment for CLL has shifted from cytotoxic chemotherapy (e.g. fludarabine, cyclophosphamide, bendamustine, chlorambucil) to more targeted therapies, including: anti-CD20 monoclonal antibodies (rituximab, obinutuzumab, ofatumumab); Bruton tyrosine kinase inhibitors (ibrutinib and acalabrutinib); phosphoinositide 3-kinase inhibitors (idelalisib and duvelisib); and a B-cell lymphoma 2 inhibitor (venetoclax) [1,4,7,8]. Targeted agents can provide a suitable treatment option for most patients with CLL, including older patients who have multiple comorbidities or high-risk cytogenetic abnormalities, including del(11q), del(17p), and complex karyotype [9]. However, clinical guidelines vary in their recommendations for the use of targeted therapies.

Acalabrutinib is a highly selective, potent, next-generation, covalent Bruton tyrosine kinase inhibitor with minimal off-target activity *in vitro* [10,11]. It has been studied for use in patients with treatment-naïve CLL who are not eligible for fludarabine-containing

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chemoimmunotherapy, including those with del(17p) or mutated *TP53* [12,13]. Acalabrutinib received approval from the US Food and Drug Administration, the Australian Therapeutic Goods Administration, and Health Canada in November 2019, and from the European Medicines Agency in November 2020, for the treatment of adults with CLL or small lymphocytic lymphoma in either the first-line or relapsed/refractory setting [14,15]. Interim results for the phase 3 ELEVATE-TN trial (ACE-CL-007, NCT02475681) in patients with treatment-naïve CLL showed that acalabrutinib (with or without obinutuzumab) significantly improved progression-free survival (PFS) compared with obinutuzumab plus chlorambucil chemoimmunotherapy, providing a chemotherapy-free treatment option with an acceptable side-effect profile that was consistent with previous studies [13].

Timely and reliable comparative evidence regarding the safety and effectiveness of new therapeutic entities can help clinicians, patients, and health care payers to make informed treatment and reimbursement decisions [16]. To date, there have been no published head-to-head randomized controlled trials (RCTs) comparing the safety and efficacy of targeted therapies for previously untreated patients with CLL. Network meta-analysis (NMA) relying solely on aggregate study data can facilitate indirect treatment comparisons between RCTs. However, even though it is highly informative, this approach may be limited by cross-trial heterogeneity and requires a common comparator (e.g. placebo) [16]. Matching-adjusted indirect comparisons (MAICs) adjust for differences in baseline patient characteristics between trials and provide an alternative method for comparing the relative treatment effects of different therapies. Using patient-level data, baseline characteristics from the clinical trial of one treatment are weighted to match aggregate data reported from a comparator trial [16,17]. After matching, treatment outcomes can be compared between the balanced study populations, in a well-defined clinical context. The present analysis used MAIC to assess the safety and efficacy of acalabrutinib (with or without obinutuzumab) versus other approved targeted therapies in previously untreated patients with CLL.

Materials and methods

Source data

Individual patient-level data for acalabrutinib were available only from the ELEVATE-TN trial [13]. A systematic literature review was conducted through August 2019 to identify clinical trials for relevant comparator treatments for previously untreated patients with CLL (Supplemental Figure S1). The following data sources were used in the literature search: EMBASE, PubMed, and the Cochrane Library (Supplemental Tables S1–S3). Bibliographic and conference searches were also performed. Following full-text screening, 68 studies were suitable for inclusion according to pre-determined eligibility criteria (Supplemental Table S4). According to 2019 National Comprehensive Cancer Network guidance [7], five of these trials were deemed relevant as a source of comparator data for ELEVATE-TN within a MAIC-based comparative assessment (i.e. the pivotal phase 3 RCTs of targeted therapies for CLL/small lymphocytic leukemia): RESONATE-2 (ibrutinib versus chlorambucil) [18,19], iLLUMINATE (ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab) [20], CLL-14 (venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab) [21], ALLIANCE (ibrutinib or ibrutinib plus rituximab versus bendamustine plus rituximab) [22], and CLL-11 (chlorambucil plus obinutuzumab versus chlorambucil plus rituximab or chlorambucil monotherapy) [23]. Here, we present the results of the MAICs comparing the safety and efficacy of acalabrutinib with targeted comparators (ibrutinib and venetoclax) using data from the RESONATE-2, iLLUMINATE, and CLL-14 trials. The ALLIANCE trial was excluded from further analysis because the follow-up period (38 months) was longer than that reported for the other trials (range, 28.1–31.3 months). This would have been considered a modifier of the treatment effect, leading to potential bias in the indirect treatment comparison. Similarity between trials is a determinant of the validity of the analysis, hence the importance of consistency in the duration of the follow-up [24].

MAICs and data preparation

This study used MAIC methodology that was internally and externally validated by biostatisticians and was in accordance with guidance issued by the United Kingdom's National Institute for Health and Care Excellence (NICE) [25]. The feasibility of each MAIC was assessed by evaluating cross-trial similarities and differences in study design, sample sizes, inclusion and exclusion criteria, baseline characteristics, and outcomes of interest (relevance, availability, and definitions) between ELEVATE-TN and each comparator trial (Supplemental Table S5). The following baseline characteristics were selected to be matched in the MAICs on the basis of the preliminary feasibility assessment

and discussions with clinical experts: age, sex, bulky disease (≥5 cm), presence of chromosome 17p13.1 or 11q22.3 deletions, *TP53* mutation, Eastern Cooperative Oncology Group Performance Score, β2 microglobulin at baseline (>3.5 mg/L), Rai or Binet stage, complex karyotype, *IGHV* gene mutation status, creatinine clearance, and Cumulative Illness Rating Scale-Geriatric score (CIRS). Patients who were less than 65 years old or who had chromosome del(17p) were not included in the MAICs of acalabrutinib (with or without obinutuzumab) with ibrutinib monotherapy because these patients were excluded from the RESONATE-2 trial.

Matching trial populations

Individual patient-level data were extracted from the ELEVATE-TN trial and adjusted to match the average baseline characteristics for each comparator. Individual patients in the ELEVATE-TN trial were assigned weights such that: (a) the weighted mean (± standard deviation) baseline characteristics in ELEVATE-TN exactly matched those reported for patients in each of the comparator trials; and (b) each individual patient's weight was equal to their estimated odds (relative propensity) of being in the comparator trial versus ELEVATE-TN. After matching, the baseline characteristics were compared between acalabrutinib and comparator treatment trial populations to ensure exact matching of the baseline means (± standard deviations). The distribution of weights was visually inspected to identify potential sensitivity to extreme weightings. The weights were used to calculate the effective sample size (ESS) achieved after matching patients $(\sum w_i)^2/(\sum w_i^2)$. A low ESS indicates high variability in the weights due to a lack of overlap between the study populations, meaning that only a small proportion of patients may be utilized to drive the treatment effect. Patients with missing values in the baseline characteristics to be matched were excluded from the analysis.

Comparison of efficacy and safety outcomes

Comparative analyses of PFS (Independent Review Committee-assessed) and selected safety outcomes (grades 3/4 adverse events [AEs] and serious AEs; deemed to be of clinical relevance in this indirect comparison) were conducted before and after weighting. Outcomes were compared at similar follow-up durations to reduce heterogeneity (median follow-up, ELEVATE-TN: acalabrutinib plus obinutuzumab, 28.5 months; acalabrutinib, 28.4 months; RESONATE-2: 29 months; iLLUMINATE: 31.3 months; CLL-14: 28.1 months) (Supplemental Table S5). PFS and OS medians were not reached in any of the trials, with data being relatively immature: RESONATE-2 ($N = 136$), 24-month PFS: 89%, 24-month OS: 98%; iLLUMINATE ($N = 113$), 31-month PFS: 79%, 30-month OS: 86%; CLL-14 ($N = 216$), 24-month PFS: 88.2%, 24-month OS: 91.8%; ELEVATE-TN ($N = 179$), 30 month-PFS: 90%, 82%, 30-month OS: 95%, 94% (both acalabrutinib plus obinutuzumab and acalabrutinib, respectively). Overall survival (OS) data in the same trials were insufficiently mature, and therefore were not included in the present analysis [13,18–21,26].

PFS outcomes were estimated individually for each of the comparator therapies using published Kaplan–Meier curves, applying the method recommended by NICE [27,28]. PFS Kaplan–Meier data were subsequently digitized, and a published reconstruction algorithm used to create pseudo-individual patient-level data.

Before matching, safety outcomes were summarized in proportions and compared using a chi-squared test. Risk differences and odds ratios with 95% confidence intervals (CI) and *p*-values were reported. PFS was summarized using Kaplan–Meier curves and compared using the log-rank test and hazard ratios (HRs) estimated from a Cox proportional hazards model. After matching, PFS and selected safety outcomes were compared between the balanced trial populations using the weights generated in the MAIC. Safety outcomes were compared using a weighted chi-squared test. Risk differences comparing acalabrutinib with comparator treatment were reported for safety outcomes. The 95% confidence intervals and *p*-values for the indirect comparisons were based on a robust estimate of the variance and on a sandwich estimator, which accounted for the variability in the propensity score weights. For PFS, weighted survival curves based on the Nelson–Aalen estimator were generated. PFS was compared using a weighted log-rank test, and HRs were estimated from a weighted Cox proportional hazards model.

Results

Baseline characteristics

After matching, the baseline characteristics of the trial populations were well-balanced for each of the MAICs (Tables 1–4, Supplemental Tables S6–7). The effective sample size after weighting varied in each of the MAICs (Tables 1–4, Supplemental Tables

Table 1. Baseline characteristics before and after matching in MAIC of acalabrutinib plus obinutuzumab versus ibrutinib.

	Before matching			After matching	
Characteristic	Acalabrutinib + obinutuzumab, *n* (%) (*n* = 126)[a] [A]	Ibrutinib, *n* (%) (*n* = 136) [B]	*p*-value [A] vs [B]	Acalabrutinib + obinutuzumab, % (ESS = 59)	Ibrutinib, % (*n* = 136)
Age ≥73 years	48 (38.1)	68 (50.0)	0.07	50.0	50.0
Sex, male	85 (67.5)	88 (65.0)	0.77	65.0	65.0
Bulky disease ≥5 cm	34 (27.0)	54 (40.0)	<0.05	40.0	40.0
Chromosome 11q22.3 deletion	22 (17.5)	30 (22.0)	<0.05	22.0	22.0
ECOG PS = 0	65 (51.6)	60 (44.0)	0.27	44.0	44.0
ECOG PS = 1	55 (43.7)	65 (48.0)	0.56	48.0	48.0
β2 microglobulin	102 (81.0)	84 (62.0)	<0.01	62.0	62.0
Rai stage 3 or 4	62 (49.2)	60 (44.0)	0.47	44.0	44.0
Unmutated *IGHV*[b]	76 (60.3)	65 (48.0)	0.06	48.0	48.0
CrCl <60 mL/min	38 (30.2)	60 (44.0)	<0.05	44.0	44.0

Baseline characteristics for acalabrutinib and obinutuzumab were derived by using patient-level data from the ELEVATE-TN trial. Baseline characteristics for ibrutinib were derived from the RESONATE-2 trial.
[a]Pre-match *n* does not necessarily match *n* of ELEVATE-TN owing to incomplete baseline data recording for some patients in some outcomes.
[b]Baseline *IGHV* mutation status was available for *n* = 121 of patients receiving ibrutinib in the RESONATE-2 trial [17].
CrCl: creatine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESS: effective sample size; *IGHV*: immunoglobulin heavy-chain variable; MAIC: matching-adjusted indirect comparison.

Table 2. Baseline characteristics before and after matching in MAIC of acalabrutinib versus ibrutinib.

	Before matching			After matching	
Characteristic	Acalabrutinib, *n* (%) (*n* = 136)[a] [A]	Ibrutinib, *n* (%) (*n* = 136) [B]	*p*-value [A] vs [B]	Acalabrutinib, % (ESS = 79) [A]	Ibrutinib, % (*n* = 136) [B]
Age ≥73 years	47 (34.6)	68 (50.0)	<0.05	50.0	50.0
Sex, male	86 (63.2)	88 (65.0)	0.86	65.0	65.0
Bulky disease ≥5 cm	53 (39.0)	54 (40.0)	0.96	40.0	40.0
Chromosome 11q22.3 deletion	24 (17.6)	30 (22.0)	0.45	22.0	22.0
ECOG PS = 0	73 (53.7)	60 (44.0)	0.14	44.0	44.0
ECOG PS = 1	53 (39.0)	65 (48.0)	0.17	48.0	48.0
β2 microglobulin >3.5 mg/L	111 (81.6)	84 (62.0)	<0.001	62.0	62.0
Rai stage 3 or 4	68 (50.0)	60 (44.0)	0.38	44.0	44.0
Unmutated *IGHV*[b]	86 (63.2)	65 (48.0)	<0.05	48.0	48.0
CrCl <60 mL/min	44 (32.4)	60 (44.0)	0.06	44.0	44.0

Baseline characteristics for acalabrutinib were derived by using patient-level data from the ELEVATE-TN trial. Baseline characteristics for ibrutinib were extracted from the RESONATE-2 trial. CrCl: creatine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESS: effective sample size; *IGHV*: immunoglobulin heavy-chain variable; MAIC: matching-adjusted indirect comparison.
[a]Pre-match *n* does not necessarily match *n* of ELEVATE-TN owing to incomplete baseline data recording for some patients in some outcomes.
[b]Baseline *IGHV* mutation status was available for *n* = 121 of patients receiving ibrutinib in the RESONATE-2 trial [17].

S6–7); it was greatest for the comparisons to iLLUMINATE (ESS = 97 for both acalabrutinib plus obinutuzumab and acalabrutinib, respectively) while lowest for the comparisons to CLL-14 (ESS = 43 and 51 for acalabrutinib plus obinutuzumab and acalabrutinib, respectively).

Efficacy outcomes

After matching the summary baseline characteristics between ELEVATE-TN and the trials of comparator treatment regimens, acalabrutinib plus obinutuzumab was associated with increased PFS (HR, range: 0.55–0.78; Figure 1 and Supplemental Figure S2) in all comparisons. Acalabrutinib monotherapy was also associated with increased PFS in all comparisons, except versus venetoclax plus obinutuzumab (Figure 1 and Supplemental Figure S3). These differences in PFS were not statistically significant.

Safety outcomes

Safety outcomes after matching baseline characteristics are shown in Table 5. Treatment with acalabrutinib plus obinutuzumab, after matching, was associated with significantly lower rates of peripheral edema ($p < 0.001$) and febrile neutropenia ($p < 0.05$) compared with ibrutinib plus obinutuzumab, and lower rates of infusion reactions ($p < 0.01$) and neutropenia ($p < 0.001$) compared with venetoclax plus obinutuzumab. Conversely, acalabrutinib plus obinutuzumab was associated with significantly higher rates of neutropenia ($p < 0.001$) compared with ibrutinib monotherapy, and leukopenia ($p < 0.001$) versus venetoclax plus obinutuzumab. Acalabrutinib monotherapy was associated with significantly lower rates of atrial fibrillation ($p < 0.05$) and infections ($p < 0.05$) compared with ibrutinib monotherapy. Rates of the following grade 3/4 AEs

Table 3. Baseline characteristics before and after matching in MAIC of acalabrutinib plus obinutuzumab versus ibrutinib plus obinutuzumab.

	Before matching			After matching	
Characteristic	Acalabrutinib + obinutuzumab, *n* (%) (*n* = 113)[a] [A]	Ibrutinib + obinutuzumab, *n* (%) (*n* = 113) [B]	*p*-value [A] vs [B]	Acalabrutinib + obinutuzumab, % (ESS = 97) [A]	Ibrutinib + obinutuzumab, % (*n* = 113) [B]
Age ≥70 years	48 (42.5)	57 (50.0)	0.32	50.0	50.0
Sex, male	65 (57.5)	67 (59.0)	0.93	59.0	59.0
Bulky disease ≥5cm	31 (27.4)	31 (27.0)	1.00	27.0	27.0
Chromosome 11q22.3 deletion	23 (20.4)	14 (12.0)	0.13	12.0	12.0
TP53 mutation	17 (15.0)	14 (12.0)	0.64	12.0	12.0
Chromosome 17p13.1 deletion	14 (12.4)	14 (12.0)	1.00	12.0	12.0
ECOG PS = 0	53 (46.9)	57 (50.0)	0.74	50.0	50.0
ECOG PS = 1	56 (49.6)	52 (46.0)	0.69	46.0	46.0
Rai stage 3 or 4	58 (51.3)	60 (53.0)	0.91	53.0	53.0
Unmutated *IGHV*	68 (60.2)	70 (62.0)	0.89	62.0	62.0
CrCl <60 mL/min	21 (18.6)	26 (23.0)	0.51	23.0	23.0
CIRS-G score >6	52 (46.0)	37 (33.0)	0.06	33.0	33.0

Baseline characteristics for acalabrutinib and obinutuzumab were derived by using patient-level data from the ELEVATE-TN trial. Baseline characteristics for ibrutinib and obinutuzumab were extracted from the iLLUMINATE trial. CIRS-G: Cumulative Illness Rating Scale for Geriatrics; CrCl: creatine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESS: effective sample size; *IGHV*: immunoglobulin heavy-chain variable; MAIC: matching-adjusted indirect comparison.

[a]Pre-match *n* does not necessarily match *n* of ELEVATE-TN owing to incomplete baseline data recording for some patients in some outcomes.

Table 4. Baseline characteristics before and after matching in MAIC of acalabrutinib versus ibrutinib and obinutuzumab.

	Before matching			After matching	
Characteristic	Acalabrutinib, *n* (%) (*n* = 114)[a] [A]	Ibrutinib + obinutuzumab, *n* (%) (*n* = 113) [B]	*p*-value [A] vs [B]	Acalabrutinib, % (ESS = 97) [A]	Ibrutinib + obinutuzumab, % (*n* = 113) [B]
Age ≥70 years	46 (43.5)	57 (50.0)	0.18	50.0	50.0
Sex, male	70 (61.4)	67 (59.0)	0.81	59.0	59.0
Bulky disease ≥ 5 cm	38 (33.3)	31 (27.0)	0.37	27.0	27.0
Chromosome 11q22.3 deletion	19 (16.7)	14 (12.0)	0.42	12.0	12.0
TP53 mutation	12 (15.3)	14 (12.0)	0.89	12.0	12.0
Chromosome 17p13.1 deletion	11 (9.7)	14 (12.0)	0.72	12.0	12.0
ECOG PS = 0	55 (48.2)	57 (50.0)	0.90	50.0	50.0
ECOG PS = 1	49 (43.0)	52 (46.0)	0.75	46.0	46.0
Rai stage 3 or 4	55 (48.2)	60 (53.0)	0.56	53.0	53.0
Unmutated *IGHV*	80 (71.8)	70 (62.0)	0.25	62.0	62.0
CrCl <60 mL/min	27 (23.7)	26 (23.0)	1.00	23.0	23.0
CIRS-G score >6	50 (43.9)	37 (33.0)	0.12	33.0	33.0

Baseline characteristics for acalabrutinib were derived by using patient-level data from the ELEVATE-TN trial. Baseline characteristics for ibrutinib and obinutuzumab were extracted from the iLLUMINATE trial. CIRS-G: Cumulative Illness Rating Scale for Geriatrics; CrCl: creatine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESS: effective sample size; *IGHV*: immunoglobulin heavy-chain variable; MAIC: matching-adjusted indirect comparison.

[a]Pre-match *n* does not necessarily match *n* of ELEVATE-TN owing to incomplete baseline data recording for some patients in some outcomes.

were significantly lower for acalabrutinib monotherapy compared with ibrutinib plus obinutuzumab: any grade 3/4 AE ($p < 0.001$), peripheral edema ($p < 0.001$), atrial fibrillation ($p < 0.05$), neutropenia ($p < 0.001$), thrombocytopenia ($p < 0.001$), and pneumonia ($p < 0.05$). Rates of the following grade 3/4 AEs were significantly lower for acalabrutinib monotherapy compared with venetoclax plus obinutuzumab: any grade 3/4 AE ($p < 0.001$), infusion-related reaction ($p < 0.001$), neutropenia ($p < 0.001$), diarrhea ($p < 0.01$), thrombocytopenia ($p < 0.001$), and infections ($p < 0.05$). There was an increased rate of leukopenia ($p < 0.05$) with acalabrutinib monotherapy versus venetoclax plus obinutuzumab.

Discussion

To our knowledge, this retrospective study is the first to assess the comparative effectiveness and tolerability of targeted therapies in treatment-naïve patients with CLL using MAIC methodology. After adjusting for baseline population characteristics, the PFS HRs for all

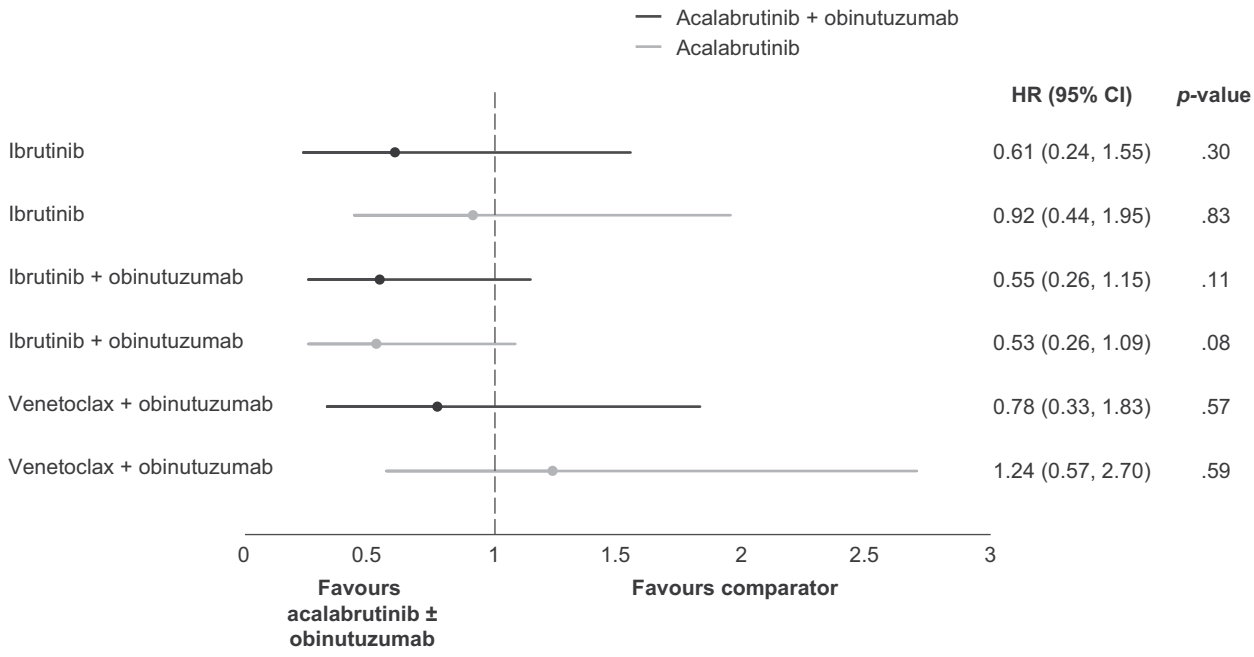

Figure 1. Progression-free survival for acalabrutinib monotherapy or acalabrutinib plus obinutuzumab versus comparators. CI: confidence interval; HR: hazard ratio.

comparisons, except acalabrutinib monotherapy versus venetoclax plus obinutuzumab, numerically favored acalabrutinib; however, none of these differences were statistically significant. Acalabrutinib plus obinutuzumab showed a stronger PFS benefit than acalabrutinib monotherapy, with HRs ranging from 0.55 to 0.78 and 0.53 to 1.24, respectively.

After matching, acalabrutinib monotherapy was associated with significantly lower rates atrial fibrillation and infections compared with ibrutinib monotherapy. In addition, acalabrutinib monotherapy was associated with lower rates of any grade 3/4 AE, infusion-related reactions, neutropenia, diarrhea, thrombocytopenia, and infections compared with venetoclax plus obinutuzumab. The rate of grade 3/4 AEs was lower with acalabrutinib monotherapy versus ibrutinib plus obinutuzumab and venetoclax plus obinutuzumab, suggesting that overall acalabrutinib has a better safety profile. Acalabrutinib plus obinutuzumab generally showed lower rates of AEs compared with ibrutinib plus obinutuzumab and venetoclax plus obinutuzumab. The only exception to this was a higher rate of leukopenia versus that reported with venetoclax plus obinutuzumab treatment. Acalabrutinib plus obinutuzumab was also associated with a higher rate of neutropenia versus ibrutinib monotherapy. These safety findings are consistent with *in vitro* studies showing the improved selectivity and reduced off-target activity of acalabrutinib compared with ibrutinib [10]. Furthermore, a previous MAIC in patients with relapsed/refractory mantle cell lymphoma also showed an improved
tolerability profile for acalabrutinib versus ibrutinib, with a significant decrease in the risk of grade 3/4 atrial fibrillation and thrombocytopenia [29].

We compared the MAIC results to two published NMAs evaluating the efficacy and safety of acalabrutinib against other frontline treatments for CLL [30,31]. One advantage of conducting indirect comparisons using NMA methodology is that the relative treatment effects can be compared across multiple RCTs can be evaluated without breaking randomization. As a result, differences in prognostic factors across clinical trials will not introduce confounding unless the prognostic factors are also effect modifiers [24]. An NMA by Sheng et al. compared the efficacy and safety of acalabrutinib plus obinutuzumab with ibrutinib plus obinutuzumab, and venetoclax plus obinutuzumab. Sheng et al. found that acalabrutinib plus obinutuzumab demonstrated a statistically significant improvement in investigator-assessed PFS versus both comparators (PFS HR versus ibrutinib plus obinutuzumab: 0.46 [95% CI: 0.22, 0.96]; versus venetoclax plus obinutuzumab: 0.34 [95% CI: 0.17, 0.68]. These findings are in line with the direction of the PFS HRs in our MAIC analysis, which may have lacked power after matching to reach the threshold of statistical significance. As with the MAIC, the NMA found no difference in the risk of grade 3/4 AEs between acalabrutinib plus obinutuzumab and ibrutinib plus obinutuzumab (risk ratio versus ibrutinib

Table 5. Safety outcomes after matching in MAIC of acalabrutinib monotherapy or acalabrutinib plus obinutuzumab versus comparators.

	Acalabrutinib + obinutuzumab vs ibrutinib				Acalabrutinib vs ibrutinib			
	Acalabrutinib + obinutuzumab (ESS = 59)	Ibrutinib (n = 136)	Rate difference (%)		Acalabrutinib (ESS = 79)	Ibrutinib (n = 136)	Rate difference (%)	
AE	[A], %	[B], %	Mean (95% CI) [A] – [B]	p-value	[A], %	[B], %	Mean (95% CI) [A] – [B]	p-value
Grade 3/4								
Arthralgia	1.4	2.0	−0.6 (−3.6, 2.5)	0.72	0.0	2.0	−2 (−4.4, 0.0)	0.1
Peripheral edema	0	1.0	−1 (−2.7, 0.7)	0.24	0.0	1.0	−1 (−2.7, 0.0)	0.24
Nausea	0	1.0	−1 (−2.7, 0.7)	0.24	0.0	1.0	−1 (−2.7, 0.0)	0.24
Cough	0	0	0 (0.0, 0.0)	0.00	1.5	0.0	+1.5 (−1.2, 4.0)	0.31
Fatigue	0	1.0	−1 (−2.7, 0.7)	0.24	0.1	1.0	−0.9 (−2.6, 0.0)	0.26
Pyrexia	0	0	0 (0.0, 0.0)	–	0.0	0.0	0 (0.0, 0.0)	–
Vomiting	1.2	0	+1.2 (−1.0, 3.4)	0.3	0.5	0.0	0.5 (−0.5, 1.0)	0.32
Atrial fibrillation	0.9	4.0	−3.1 (−6.8, 0.6)	0.1	0.0	4.0	−4.0 (−7.3, 0.0)	<0.05
Anemia	11.7	7.0	+4.7 (−4.0, 13.3)	0.29	6.9	7.0	−0.1 (−6.8, 6.0)	0.98
Neutropenia	32.7	12.0	+20.7 (10.7, 30.7)	<0.001	12.8	12.0	0.8 (−7.5, 9.0)	0.85
Diarrhea	4.3	4.0	+0.3 (−4.6, 5.2)	0.9	2.0	4.0	−2 (−6.8, 2.0)	0.41
Hypertension	2	5.0	−3 (−7.1, 1.1)	0.15	3.1	5.0	−1.9 (−7.3, 3.0)	0.5
Hemorrhage	2.4	6.0	−3.6 (−8.6, 1.4)	0.16	1.8	6.0	−4.2 (−9.0, 0.0)	0.08
Infections	20.6	24.0	−3.4 (−15.3, 8.5)	0.57	12.4	24.0	−11.6 (−21.9, −1.0)	<0.05
	Acalabrutinib + obinutuzumab vs ibrutinib + obinutuzumab				Acalabrutinib vs ibrutinib + obinutuzumab			
	Acalabrutinib + obinutuzumab	Ibrutinib + obinutuzumab	Rate difference (%)		Acalabrutinib	Ibrutinib + obinutuzumab	Rate difference (%)	
	(ESS = 97) [A], %	(n = 113) [B], %	Mean (95% CI) [A] – [B]	p-value	(ESS = 97) [A], %	(n = 113) [B], %	Mean (95% CI) [A] – [B]	p-value
Grade 3/4								
Any	69.4	68.0	+1.4 (−10.4, 13.3)	0.81	44.1	68.0	−23.9 (−36.6, −11.2)	<0.001
Peripheral edema	0.6	12.0	−11.4 (−17.5, −5.3)	<0.001	0.0	12.0	−12 (−18.0, −6.0)	<0.001
Febrile neutropenia	0.5	5.0	−4.5 (−8.6, −0.4)	<0.05	0.8	5.0	−4.2 (−8.5, 0.1)	0.05
Dyspnea	0.0	2.0	−2.0 (−4.6, 0.6)	0.13	0.6	2.0	−1.4 (−4.2, 1.5)	0.35
Nausea	0.0	0.0	0.0 (0.0, 0.0)	–	0.0	0.0	0 (0, 0)	–
Cough	0.0	1.0	−1.0 (−2.8, 0.8)	0.29	0.0	1.0	−1 (−2.8, 0.8)	0.29
Fatigue	1.2	0.0	+1.2 (−0.5, 2.9)	0.17	1.6	0.0	+1.6 (−0.6, 3.8)	0.16
Pyrexia	0.0	2.0	−2.0 (−4.6, 0.6)	0.13	0.4	2.0	−1.6 (−4.3, 1.1)	0.25
Arthralgia	1.0	1.0	0.0 (−2.6, 2.7)	0.99	0.0	1.0	−1 (−2.8, 0.8)	0.29
Vomiting	0.5	0.0	+0.5 (−0.4, 1.4)	0.31	1.5	0.0	+1.5 (−1.1, 4.1)	0.26
Atrial fibrillation	1.2	−5.2	−3.8 (−8.4, 0.8)	0.11	0.0	5.0	−5 (−9.0, −1.0)	<0.05
Anemia	8.3	4.0	+4.3 (−2.2, 10.8)	0.2	7.0	4.0	3 (−3.0, 9.0)	0.33
Neutropenia	35.0	37.0	−2 (−14.1, 10.2)	0.75	10.2	37.0	−26.8 (−37.3, −16.4)	<0.001
Diarrhea	3.7	3.0	+0.7 (−3.8, 5.1)	0.77	0.0	3.0	−3 (−6.1, 0.1)	0.06
Hypertension	1.2	4.0	−2.8 (−6.8, 1.2)	0.17	3.9	4.0	−0.1 (−5.6, 5.3)	0.96
Thrombocytopenia	14.4	19.0	−4.6 (−14.4, 5.2)	0.35	1.7	19.0	−17.3 (−24.9, −9.8)	<0.001
Pneumonia	5.8	7.0	−1.2 (−7.5, 5.1)	0.72	1.3	7.0	−5.7 (−10.6, −0.8)	<0.05
Constipation	0.0	0.0	0 (0.0, 0.0)	–	0.0	0.0	0 (0, 0)	–
Headache	1.4	0.0	+1.4 (−0.6, 3.5)	0.17	0.0	0.0	0 (0, 0)	–

(*continued*).

Table 5. Continued.

	Acalabrutinib + obinutuzumab vs venetoclax + obinutuzumab				Acalabrutinib vs venetoclax + obinutuzumab			
	Acalabrutinib + obinutuzumab (ESS = 83) [A], %	Venetoclax + obinutuzumab (*n* = 216) [B], %	Rate difference (%) Mean (95% CI) [A] – [B]	*p*-value	Acalabrutinib (ESS = 51) [A], %	Venetoclax + obinutuzumab (*n* = 216) [B], %	Rate difference (%) Mean (95% CI) [A] – [B]	*p*-value
Serious AE	54.3	49.1	+5.2 (–6.0, 16.4)	0.36	39.6	49.1	–9.5 (–21.1, 2.1)	0.11
Grade 3/4								
Any	69.6	78.8	–9.2 (–19.6, 1.2)	0.08	55.1	78.8	–23.7 (–34.4, –13.0)	<0.001
Febrile neutropenia	3.8	5.2	–1.4 (–6.4, 3.5)	0.56	1.9	5.2	–3.3 (–7.7, 1.0)	0.13
Infusion-related reaction	1.7	9.0	–7.3 (–11.8, –2.8)	<0.01	0.0	9.0	–9 (–12.8, –5.2)	<0.001
Leukopenia	27.5	2.4	+25.1 (16.2, 34.1)	<0.001	11.0	2.4	+8.6 (1.8, 15.5)	<0.05
Anemia	9.8	8.0	+1.8 (–5.3, 9.0)	0.61	4.0	8.0	–4 (–9.0, 1.1)	0.12
Neutropenia	27.5	52.8	–25.3 (–36.3, –14.3)	<0.001	11.0	52.8	–41.8 (–51.1, –32.4)	<0.001
Diarrhea	2.6	4.2	–1.6 (–6.1, 2.9)	0.49	0.0	4.2	–4.2 (–6.9, –1.5)	<0.01
Thrombocytopenia	7.5	13.7	–6.2 (–12.9, 0.5)	0.07	2.6	13.7	–11.1 (–16.4, –5.7)	<0.001
Pneumonia	5.4	4.2	+1.2 (–4.4, 6.7)	0.68	2.0	4.2	–2.2 (–5.6, 1.3)	0.22
Infections	15.5	17.5	–2 (–10.6, 6.6)	0.65	9.3	17.5	–8.2 (–15.5, –1.0)	<0.05

AE: adverse event; CI: confidence interval; ESS: effective sample size; MAIC: matching-adjusted indirect comparisons.

plus obinutuzumab: 1.10 [95% CI: 0.52, 2.32]; or versus venetoclax plus obinutuzumab: 0.89 [95% CI: 0.45, 1.77] [30]. Similar findings were reported by Davids et al. in an NMA comparing acalabrutinib both as monotherapy and in combination with obinutuzumab with 10 frontline CLL treatment regimens. In concordance with the present MAIC, the NMA found a non-statistically significant improvement in the risk of PFS (investigator assessed) for acalabrutinib versus ibrutinib plus obinutuzumab: PFS HR 0.63 (95% CI: 0.32, 1.27); but unlike the MAIC, there was a significant PFS improvement compared with venetoclax plus obinutuzumab: PFS HR 0.47 (95% CI: 0.24, 0.89) [31].

The overall approach of this MAIC was consistent with methodological guidance issued by NICE [25]. It provided a comprehensive evaluation of cross-trial heterogeneity and potential sources of bias. Moreover, the use of individual patient-level data for acalabrutinib plus obinutuzumab and acalabrutinib monotherapy adjusted for observed cross-trial differences in multiple patient characteristics versus the comparator trials. However, several limitations of the MAIC need to be taken into consideration when interpreting the results of this analysis. Firstly, there were some differences in trial characteristics including follow-up length, a factor important to the maturity of time-to-event outcomes. For the MAIC between acalabrutinib (with or without obinutuzumab) and venetoclax plus obinutuzumab, it should be noted that the ELEVATE-TN trial utilized a treat to progression approach, while the CLL-14 trial investigated fixed-duration treatment. The median duration of treatment exposure also differed between these two trials. Overall, these differences could not have been fully adjusted for in the MAIC and, therefore, may have confounded the comparison of outcomes. While this unanchored MAIC adjusted for observed baseline differences between acalabrutinib and comparator trial(s), it was a comparison of non-randomized treatment groups and may have been biased by residual, unobserved cross-trial differences. In this study, the reduction in sample size that occurred after matching varied across comparisons. While the resulting effective sample sizes were considered acceptable for the MAICs, they were not powered to detect statistical differences in outcomes between therapies and the possibility of type 2 errors cannot be excluded [25]. The findings presented here are based on relatively immature data and, while they provide an indication of early comparisons of safety and efficacy outcomes, further analyses should be undertaken as longer-term trial data become available to establish the durability of the estimated differences in treatment outcomes. However,

only prospective head-to-head comparative studies can definitively answer such questions.

Overall, first-line treatment of patients with CLL has dramatically improved in recent years through the development of targeted therapies that can provide deep and sustained hematological responses, particularly when used in combination, alongside an acceptable tolerability profile. Acalabrutinib is a new addition to the clinician's armamentarium and, compared with prior novel agent-based regimens, it may have a lower risk of AEs without compromising efficacy. This MAIC analysis provides an initial insight into potential differences between acalabrutinib and ibrutinib for treatment-naïve patients as we await the first prospective data to emerge from the ongoing, head-to-head, randomized trial in the relapsed/refractory CLL population (ELEVATE R/R: NCT02477696).

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Disclosure statement

Dr. Waweru is an employee and stockholder of AstraZeneca LP. At the time of the study, Dr. Telford was an employee and stockholder of AstraZeneca LP, but is now an employee and stockholder of GlaxoSmithKline. At the time of the study, Dr. Abhyankar was an employee and stockholder of Acerta Pharma, a member of the AstraZeneca Group, but is now an employee of Genentech. Dr. Davids has received institutional research grants from AstraZeneca, BMS, Genentech, MEI Pharma, Pharmacyclics, Surface Oncology, TG Therapeutics, and Verastem, and consulting fees from AbbVie, Adaptive Biotechnologies, Ascentage Pharma, AstraZeneca, BeiGene, Celgene, Genentech, Gilead Sciences, Janssen, MEI Pharma, Merck, Pharmacyclics, Syros Pharmaceuticals, TG Therapeutics, Verastem, and Zentalis. Dr Ringshausen has received institutional research grants from Acerta/AstraZeneca. The authors have indicated that they have no other conflicts of interest regarding the content of this article. The sponsor was involved in the study design, analysis, data interpretation, writing of the manuscript, and the decision to submit the article for publication.

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