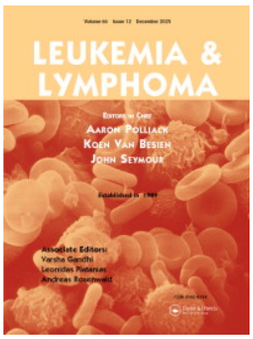

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Zanubrutinib versus acalabrutinib indirect treatment comparison in relapsed or refractory mantle cell lymphoma

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ABSTRACT

Zanubrutinib and acalabrutinib have demonstrated efficacy in separate single-arm clinical trials in patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL). Given these single-arm trials lacked a common comparator, an unanchored indirect treatment comparison was conducted to assess the comparative efficacy of zanubrutinib versus acalabrutinib using a simulated treatment comparison (STC) method. In the base case analysis (adjusted for all covariates), zanubrutinib treatment was associated with significantly improved progression-free survival (hazard ratio [HR], 0.57 [95% confidence interval [CI], 0.35–0.94]; $p=0.0272$) and overall survival (HR, 0.43 [95% CI, 0.23–0.82]; $p=0.0105$) versus acalabrutinib. Overall response rate was numerically higher with zanubrutinib versus acalabrutinib (odds ratio [OR], 2.05 [95% CI, 0.72–5.84]; $p=0.1798$). Sensitivity analyses, including a subset of covariates, provided consistent results. In the absence of a head-to-head trial, these results provide important insights into the comparative efficacy of zanubrutinib and acalabrutinib for physicians managing patients with R/R MCL.

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KEYWORDS
Zanubrutinib; acalabrutinib; MCL; indirect treatment comparison

Introduction

Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin lymphoma. MCL comprises approximately 5% of all non-Hodgkin lymphomas and is a rare B-cell malignancy [1]. The prevalence of MCL has been estimated at 20,000 patients in the United States (US) [2]. Most patients with MCL are diagnosed with advanced stage disease, involving lymphadenopathy of several sites. The median age at diagnosis ranges from 60 to 70 years. Most patients have extranodal manifestations, including bone marrow, blood, liver, and the gastrointestinal tract. MCL has a poor prognosis, with a median overall survival (OS) of 3–5 years [1,3–5]. The economic burden of MCL is considerable, with average monthly all-cause costs of $5,131 to $16,117 per patient month [6].

Despite the availability of several treatment options, MCL is an incurable disease. The biggest challenge is that patients with relapsed or refractory (R/R) MCL generally experience repeated relapses and can acquire resistance to therapy. The treatment landscape of R/R MCL has evolved significantly with the introduction of targeted therapies and chimeric antigen receptor (CAR) T-cell therapy, offering new hope for patients [7–9]. Zanubrutinib and acalabrutinib are second-generation covalent Bruton tyrosine kinase inhibitors (BTKis) with improved safety profiles compared to the first-generation BTKi ibrutinib in clinical trials of hematological malignancies [10,11]. Both zanubrutinib and acalabrutinib are approved in the US by the Food and Drug Administration (FDA) and are available for patients with MCL who received at least one prior line of therapy [12,13]. Notably, the FDA approval of ibrutinib for MCL in the US has been withdrawn since April 2023 [14].

Zanubrutinib is a highly potent, selective, and irreversible BTKi that has demonstrated efficacy and safety in a single-arm, open-label study in patients with R/R MCL, with an overall response rate (ORR) of 84% (complete response [CR] 78%) over a median follow-up of 35.3 months [15,16]. Acalabrutinib was efficacious in a single-arm study with a median follow-up of 38.1 months, where 81.5% of patients with R/R MCL achieved ORR (CR 47.6%) [17,18]. Although zanubrutinib and acalabrutinib have demonstrated clinical

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benefits in separate single-arm trials in patients with R/R MCL [15–19], evidence on the comparative effectiveness of zanubrutinib and acalabrutinib is lacking.

Population-adjusted indirect treatment comparison (ITC) methods such as matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) present a robust statistical approach to estimate the comparative effectiveness of treatments in the absence of head-to-head comparison trials [20,21]. These methods adjust for cross-trial differences in patient characteristics to provide a useful comparison between treatments, thereby offering valuable insights into their relative efficacy and safety profiles. A key advantage of STC is that it retains the entire patient population in the analysis, even when the characteristics of the trial populations do not overlap well. Unlike STC, MAIC may down-weight or exclude individuals, effectively reducing the sample size. This makes STC particularly well-suited for settings with limited patient data, such as MCL. The objective of the present study was to assess the comparative efficacy of zanubrutinib versus acalabrutinib in patients with R/R MCL, in the absence of head-to-head clinical trials, using an STC approach.

Methods

Study identification and selection

Clinical trials of zanubrutinib and acalabrutinib in the MCL indication were identified through a targeted literature review, conducted in the PubMed database and clinical trials identifier: clinicaltrials.gov (searched on December 07, 2023). The targeted review followed the PICOS criteria (i.e. Population, Intervention, Comparator, Outcomes, and Study design). We included clinical trials conducted in patients with R/R MCL (population) and assessing zanubrutinib (intervention), or acalabrutinib (comparator) as monotherapies. Studies of all phases of clinical development were considered for inclusion, if reporting the efficacy data. Outcomes that are commonly assessed in cancer trials, e.g. progression-free survival (PFS), OS, and ORR, were the targeted outcomes of interest. There were no restrictions on the time frame of searches. However, conference abstracts were not included as they tend to report limited information on outcomes' assessment methods and baseline characteristics.

Before conducting the quantitative analysis as a STC, a qualitative feasibility assessment was carried out to compare the included trials of zanubrutinib and acalabrutinib, in terms of population inclusion/exclusion criteria, study design, outcomes assessed, and definition of outcomes. This exercise helped clarify the similarities or differences across trials that were considered for the quantitative synthesis of the evidence.

Statistical analysis (indirect treatment comparison)

The relative efficacy of zanubrutinib versus acalabrutinib in the present ITC was estimated following guidance reported by the Decision Support Unit (DSU) in the National Institute for Health and Care Excellence (NICE) DSU Technical Support Document 18 [22]. An STC approach was adopted, which could be conducted either as an anchored comparison (with a common comparator between treatments compared) or as an unanchored comparison (in the absence of a common comparator). We selected STC over MAIC methodology to avoid substantial reduction in effective sample size (ESS) after balancing for the potential differences between studies.

STC is based on outcome regression adjustment to balance cross-trial population differences and provide an estimate of relative treatment effect that reflects the effect in the trial population with aggregate data (i.e. the comparator study). An STC approach consists of 3 steps (Figure 1): (a) fitting a regression model to the individual patient-level data (IPD) including all potential prognostic variables and effect modifiers, (b) predicting the outcome according to the comparator study population, and (c) deriving an estimate of the ITC using the predicted estimate from step (b) and the reported estimate from the comparator study [21,23].

For time-to-event outcomes, such as PFS and OS, a Cox proportional hazard model with selected baseline covariates was fitted using IPD of zanubrutinib. The survival probability of zanubrutinib for individuals from the acalabrutinib trial was predicted based on the fitted Cox model. Kaplan-Meier (KM) curves for each individual were generated given the survival time (x-axis) and predicted survival probability (y-axis). The predicted average KM was obtained by marginalization of the predicted conditional estimates for the sampled individuals in the acalabrutinib trial. IPD were reconstructed from the predicted average KM and the published KM curves in the acalabrutinib trial, using methodology described by Guyot et al. [24]. The hazard ratio (HR) was estimated from another Cox model with reconstructed IPD.

For binary outcomes, such as ORR, a logistic regression model with selected baseline covariates was fitted using zanubrutinib IPD. The probability of achieving ORR of zanubrutinib for individuals from the acalabrutinib trial was predicted based on the fitted logistic

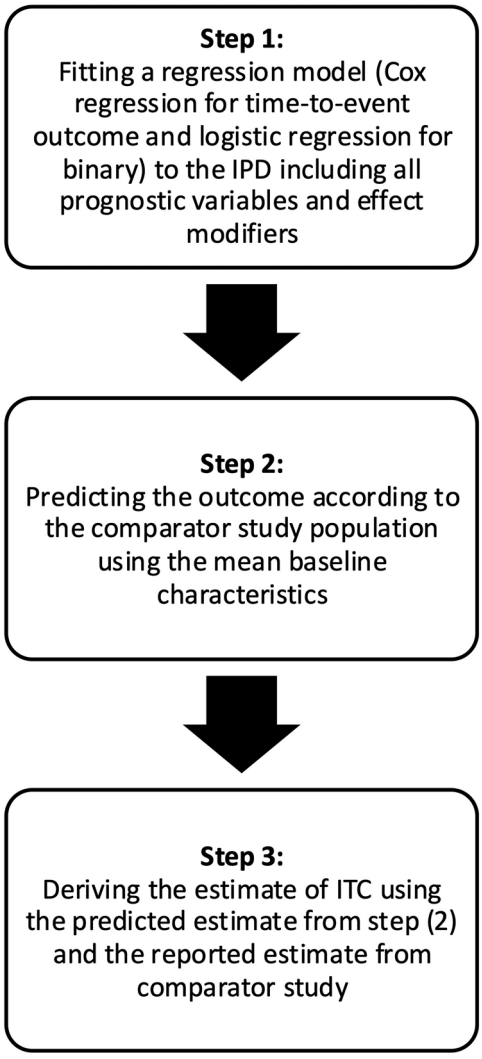

Figure 1. Three-step approach for STC methodology.
Note: IPD, individual patient-level data; ITC, indirect treatment comparison; STC, simulated treatment comparison.

regression. The predicted average effect was obtained by marginalization of the predicted conditional estimates for the sampled individuals in the acalabrutinib trial. The odds ratio (OR) of the ORR between zanubrutinib and acalabrutinib was estimated by the reported ORR in the acalabrutinib trial, and the predicted ORR of zanubrutinib.

Per the STC approach, a Cox proportional hazard model (for PFS and OS) and logistic regression (for ORR) was used in step (a). Covariates were sampled using a Gaussian copula approach in the prediction step (b) to avoid aggregation bias. Standardization or marginalization was used to obtain the relative treatment effect (e.g. HR for PFS and OS, and OR for ORR) [25–27]. The 95% confidence intervals (CIs) and *p*-values were estimated using bootstrapping with 1,000 replications. Two-sided $p < 0.05$ indicated statistical significance.

Covariates selection

All potential prognostic variables and effect modifiers were adjusted for in this STC approach. The covariates for population adjustment in the current study were identified through a literature review. A list of the prognostic variables or effect modifiers from previously published ITCs in MCL was prepared and validated with clinical experts. These covariates were age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI), tumor bulk, disease stage, lactate dehydrogenase (LDH) concentration, extranodal disease, bone marrow involvement, number of previous treatment regimens, prior autologous stem cell transplantation (ASCT), response to prior BTKi therapy, and duration on prior BTKi therapy.

Covariates for which the data were available in the included trials of zanubrutinib and acalabrutinib were considered for adjustment in the base case analysis. Sensitivity analyses were conducted by excluding the covariates that were imbalanced largely across trials of zanubrutinib and acalabrutinib to assess robustness of the results.

Results

The targeted literature review identified 10 clinical trials in MCL, including 7 of zanubrutinib and 3 of acalabrutinib. However, only 2 clinical trials of zanubrutinib (BGB-3111-206 [15,16] and BGB-3111-AU-003 [19]) and 1 of acalabrutinib (ACE-LY-004) [17,18] were considered eligible for the present STC study. The other trials were excluded for several reasons, including difference in populations (untreated MCL), zanubrutinib or acalabrutinib not assessed as monotherapy, or ongoing studies with no reported data.

Table 1 presents the comparison of study designs, inclusion/exclusion criteria, endpoints, and outcomes definition in both trials of zanubrutinib and acalabrutinib. Overall, except for a few differences, all 3 studies had sufficient similarities to allow for comparison. The differences that were anticipated to influence the results were adjusted in the analyses where feasible.

Both trials of zanubrutinib (BGB-3111-206 and BGB-3111-AU-003) and the ACE-LY-004 trial of acalabrutinib differed in the countries of patients' enrollment. While BGB-3111-AU-003 was a global study with most patients from Australia and New Zealand, BGB-3111-206 had patients only from China [15,16,19]. ACE-LY-004 was conducted globally, with nearly 40% of patients from the US [17,18]. Despite noticeable differences in patient baseline characteristics in BGB-3111-AU-003

Table 1. Study design characteristics and inclusion criteria in zanubrutinib (BGB-3111-206 and BGB-3111-AU-003) and acalabrutinib (ACE-LY-004) trials.

Characteristics	BGB-3111-206 (NCT03206970) [15,16]	BGB-3111-AU-003 (NCT02343120) [19]	ACE-LY-004 (NCT02213926) [17,18]
Study design			
	N = 86	*N* = 37	*N* = 124
Phase	2	1/2	2
Design	Single arm	Single arm	Single arm
Blinding	Open-label	Open label	Open label
Center	Multicenter	Multicenter	Multicenter
Country	China	Australia, Italy, New Zealand, South Korea, the UK, and the USA	Australia, Belgium, Czech Republic, France, Italy, the Netherlands, Poland, Spain, the UK, and the USA
Enrollment period	March 2017 – September 2017	September 2014 – March 2018	March 2015 – January 2016
Key population eligibility criteria			
Patients	• Patients had confirmed MCL with cyclin D1 overexpression, translocation t(11;14)(q13;q32), or both as confirmed by central pathological review of archival or fresh tumor biopsy tissue • Measurable disease (≥1 lymph node >1.5 cm in the longest diameter and measurable in 2 perpendicular dimensions of CT or MRI scan) • Had received ≥1 prior line of therapy and had relapsed or were refractory • Refractory disease defined as achieving neither PR nor CR to their last regimen	• Patients with B-cell malignancies, including patients with confirmed diagnosis of MCL • Refractory disease defined as best overall response of stable disease or PD from last prior anticancer regimen	• Patients had confirmed MCL with translocation t(11;14)(q13;q32), overexpressed cyclin D1, or both confirmed by pathology • Measurable disease (≥1 lesions measuring ≥2 cm in the longest diameter) • Had relapsed after, or were refractory to, one to five previous therapies • Refractory disease defined as achieving less than PR with the most recent treatment before study entry
Age	18–75 years	≥18 years	≥18 years
ECOG PS	0–2	0–2	0–2
Previous lines of treatment	≥1 and <5	≥1	≥1
Absolute neutrophil count	≥1 × 10^9/L	≥1 × 10^9/L	≥0.75 × 10^9/L (≥0.50 × 10^9/L for BM involvement)
Platelet count	≥75 × 10^9/L (≥50 × 10^9/L for BM involvement)	≥50 × 10^9/L	≥50 × 10^9/L (≥30 × 10^9/L for BM involvement)
Aspartate aminotransferase	≤2.5 x upper limit of normal	≤3 x upper limit of normal	Not reported
Alanine aminotransferase	≤2.5 x upper limit of normal	≤3 x upper limit of normal	Not reported
Total bilirubin	≤2 x upper limit of normal	≤1.5 x upper limit of normal	Not reported
Disease history (Exclusion)	• CNS lymphoma • Other active malignancies within 2 years of study entry • Cardiovascular disease • Uncontrolled (systemic) infection requiring parenteral anti-microbial therapy • HIV, or active hepatitis B/C • QT interval corrected with Fridericia's formula >450 msec or other significant electrocardiogram abnormalities	• CNS lymphoma • Histologically transformed disease • Cardiovascular disease (NYHA function status of ≥3) • Uncontrolled systemic infection requiring parenteral anti-microbial therapy • HIV, or active hepatitis B/C • Active renal, neurologic, psychiatric, hepatic, or endocrinologic disease (investigator's opinion)	• A life-threatening illness, medical condition or organ system dysfunction • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive HF, or MI within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by NYHA Functional Classification, or corrected QT interval (QTc) >480 msec • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
Prior treatment (Exclusion)	• Prior exposure to a BTKi • Corticosteroids with anti-neoplastic intent within a week • Major surgery within a month of screening	• Prior exposure to a BTKi • Prior allogenic SCT within 6 months of study entry • Corticosteroids with anti-neoplastic intent within a week, chemotherapy/ radiotherapy within 2 weeks, or monoclonal antibody within 4 weeks • Major surgery within a month of screening	• Prior exposure to a BTKi
Efficacy endpoints			
Primary	ORR • Assessed by IRC per 2014 Lugano classification • PET-CT, bone marrow biopsies, and gastrointestinal endoscopy based evaluations	ORR • Assessed by IRC per 2014 Lugano classification • CT-based evaluation	ORR • Assessed by Investigator per 2014 Lugano classification • PET-CT based evaluation

(*Continued*)

Table 1. Continued.

Characteristics	BGB-3111-206 (NCT03206970) [15,16]	BGB-3111-AU-003 (NCT02343120) [19]	ACE-LY-004 (NCT02213926) [17,18]
Secondary	• PFS, DoR, TTR, and safety • ORR (assessed by Investigator per 2014 modification of the IWG on non-Hodgkin Lymphoma Criteria)	• ORR, DoR, TTR (assessed by Investigator) • PFS, OS (assessed by IRC)	• PFS, OS, DoR, safety, pharmacokinetics, and pharmacodynamics (assessed by Investigator) • ORR, PFS, DoR (assessed by IRC per 2014 Lugano classification)
Exploratory	OS	–	• ORR, PFS, DoR (assessed by IRC per 2007 International Harmonization project) • Patient-reported outcomes
Outcomes definitions			
ORR	• Proportion of patients achieving a CR or PR from the start of zanubrutinib until data cutoff or start of new antineoplastic treatment	• Proportion of patients with PR or CR	• Proportion of patients achieving either a PR or a CR at any time during the treatment period
PFS	• Time from the starting date of zanubrutinib to the date of first documentation of disease progression or death, whichever occurred first	• Time from the first dose of zanubrutinib to disease progression or death from any cause	Not reported
OS	Not reported	• Time from the first dose of zanubrutinib until death from any cause	Not reported
DOR	• Time from the date that the response criteria are first met to the date that progressive disease was objectively documented or death (whichever occurs first)	• Time from the first qualifying response until disease progression or death from any cause	Not reported

Note: The data source for the efficacy of zanubrutinib was informed by the pooled IPD from BGB-3111-206 (NCT03206970) and BGB-3111-AU-003 (NCT02343120) trials; acalabrutinib was informed by the published aggregated data of the ACE-LY-004 (NCT02213926) trial.
BM, bone marrow; BTKi, Bruton tyrosine kinase inhibitor; CNS, central nervous system; CR, complete response; CT, computed tomography; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HF, heart failure; HIV, human immunodeficiency virus; IRC, independent review committee; IWG, International Working Group; MCL, mantle cell lymphoma; MI, myocardial infarction; MRI, magnetic resonance imaging; msec, microseconds; NYHA, New York Heart Association; ORR, overall response rate; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; PS, performance status; SCT, stem cell transplantation; TTR, time to response; UK, United Kingdom; USA, United States of America.

and BGB-3111-206, the nature of the two trials was sufficiently similar to allow for pooling of the data. A pooled analysis of BGB-3111-AU-003 and BGB-3111-206 has been published previously [28,29]. Patient enrollment criteria were fairly similar across zanubrutinib and acalabrutinib clinical trials. The ACE-LY-004 and BGB-3111-206 trials included patients with a documented diagnosis of MCL with cyclin D1 overexpression, translocation t(11;14)(q13;q32), or both as confirmed by pathology or fresh tumor biopsy tissue. In BGB-3111-AU-003, patients with B-cell malignancies including those with a confirmed diagnosis of MCL were eligible. Patients with a history of central nervous system (CNS) lymphoma and significant cardiovascular diseases were excluded. Patients had received ≥1 prior line of therapy (zanubrutinib trial) or 1–5 previous therapies (acalabrutinib trial) and had relapsed or were refractory to treatment. Refractory disease was defined as achieving neither partial response (PR) nor CR to their last regimen or as best overall response of stable disease or progressive disease from last prior anticancer regimen in the zanubrutinib trials and as achieving less than PR with the most recent treatment before study entry in the acalabrutinib trial. The previous therapies were consistent, with most patients having exposure to rituximab alone or as part of a combination regimen, although slightly more patients had ASCT in the ACE-LY-004 trial (Table 2) [15,18,19]. The IRC-assessed ORR was the primary outcome in both trials of zanubrutinib, evaluated using computed tomography (CT) scans in BGB-3111-AU-003 and positron emission tomography (PET)-CT scans in BGB-3111-206. The primary outcome of ORR was investigator-assessed in ACE-LY-004, and the responses were evaluated using CT scans or PET-CT scans. Definitions of the outcomes are provided in Table 1.

Baseline characteristics

Fourteen prognostic variables or effect modifiers were listed from the previously published ITCs in MCL [30–32] and confirmed with clinical experts. However, only those covariates available in BGB-3111-206 or BGB-3111-AU-003 and ACE-LY-004 were considered for adjustment. These covariates are shown in Table 2, and comprise prior lines of therapy and prior ASCT,

Table 2. Summary of key baseline patient characteristics identified as prognostic variables and effect modifiers.

Baseline characteristics (proportion of patients)	ACE-LY-004 ($N=124$)	BGB-3111-206 + AU003 ($N=123$)
Age ≥65 years	64.5%	39.8%
Race: White	74.2%	24.4%
Sex: Male	79.8%	74.8%
ECOG PS 1–2 (vs. 0)	42.7%	35.8%
sMIPI intermediate risk (vs. low)	43.9%	37.4%
sMIPI high risk (vs. low)	17.1%	15.4%
Bulky disease (LD ≥5 cm)	37.1%	38.8%
Ann Arbor stage III–IV	75.0%	90.2%
Extranodal disease	72.6%	57.7%
Lactate dehydrogenase, high	26.6%	38.2%
Prior lines of treatment >2	22.6%	32.5%
Bone marrow involvement	50.8%	49.6%
Prior autologous SCT	17.7%	8.9%

ECOG PS, Eastern Cooperative Oncology Group Performance Scale; LD, largest dimension; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; SCT, stem cell transplantation.

LDH concentration, ECOG performance status, sMIPI, age and sex, tumor bulk, race, bone marrow involvement, disease stage, and extranodal disease. All these covariates were adjusted in the base case analysis.

Covariates of baseline ECOG performance status 1–2, sMIPI intermediate and high risk, bulky disease (≥5 cm), prior therapies >2, bone marrow involvement, and prior ASCT were similar between trials of zanubrutinib and acalabrutinib. Noticeable differences were observed for the proportions of patients aged ≥65 years (65% vs. 40%), patients who identified as White (74% vs. 24%), or who had extranodal disease (73% vs. 58%), which were higher in the ACE-LY-004 trial (versus the zanubrutinib trials), whereas patients with Ann Arbor disease stage III–IV were lower (75% vs. 90%) (Table 2). Sensitivity analyses were conducted by: (i) excluding race, and (ii) excluding age, as there were noticeable differences in these covariates at baseline in the pooled data of zanubrutinib and published data of acalabrutinib.

Indirect treatment comparisons

Base case

In the base case analysis (adjusted for all covariates), the results of the unanchored STC showed that zanubrutinib treatment was associated with a beneficial treatment effect in PFS, with the KM curve indicating a favorable trend for zanubrutinib versus acalabrutinib (Figure 2(a)). Zanubrutinib was associated with a statistically significant improvement in PFS versus acalabrutinib (HR, 0.57 [95% CI, 0.35–0.94]; $p=0.0272$; Figure 3). Similarly, zanubrutinib treatment was associated with a statistically significantly longer OS versus acalabrutinib (0.43 [95% CI, 0.23–0.82]; $p=0.0105$; Figures 2(b),3).

Regarding the ORR, the results of the STC showed that odds of achieving ORR were higher for patients treated with zanubrutinib versus acalabrutinib (OR, 2.05 [95% CI, 0.72–5.84]; $p=0.1798$), but the difference did not reach statistical significance.

Sensitivity analysis

The sensitivity analyses were conducted without race or age as covariates. The results of the sensitivity analyses were consistent with base case analysis, with the HR (95% CI) for PFS (without race, 0.62 [0.39–0.98]; without age, 0.58 [0.35–0.97]) and OS (without race, 0.42 [0.25–0.70]; without age, 0.48 [0.25–0.94]) being in favor of zanubrutinib versus acalabrutinib (Table 3). These results demonstrate the robustness of the ITC analysis using a STC and support the conclusion that zanubrutinib is more beneficial than acalabrutinib in treating patients with R/R MCL.

Discussion

In this study, we utilized pooled IPD from the BGB-3111-206 and BGB-3111-AU-003 clinical trials and published aggregated data of the ACE-LY-004 trial to compare the efficacy of zanubrutinib versus acalabrutinib in patients with MCL who had received at least 1 prior line of therapy and had relapsed or were refractory to the most recent treatment. The results of this population-adjusted STC revealed that zanubrutinib treatment was associated with a significantly improved PFS and OS versus acalabrutinib. Patients treated with zanubrutinib were also shown to achieve a numerically higher ORR than patients treated with acalabrutinib. To the best of our knowledge, this is the first study comparing the efficacy of zanubrutinib and acalabrutinib in R/R MCL, providing insights that could facilitate clinical decision making for the better treatment of patients with R/R MCL.

MAIC and STC are population-adjusted ITC methods. MAIC is based on propensity score weighting, whereas STC is based on outcome regression adjustment. MAIC is more frequently used in health technology assessments due to the use of a pseudo-population after reweighting. While MAIC is intuitively easy to understand and implement, it can lead to a large reduction in the ESS after weighting and a less robust estimate. BGB-3111-AU-003 [19] was a global study of zanubrutinib in patients with B-cell malignancies and the sample size of patients with R/R MCL was small (37 patients), whereas BGB-3111-206 [15,16] with a large sample size (86 patients) was conducted in China only. Matching zanubrutinib study populations with patients

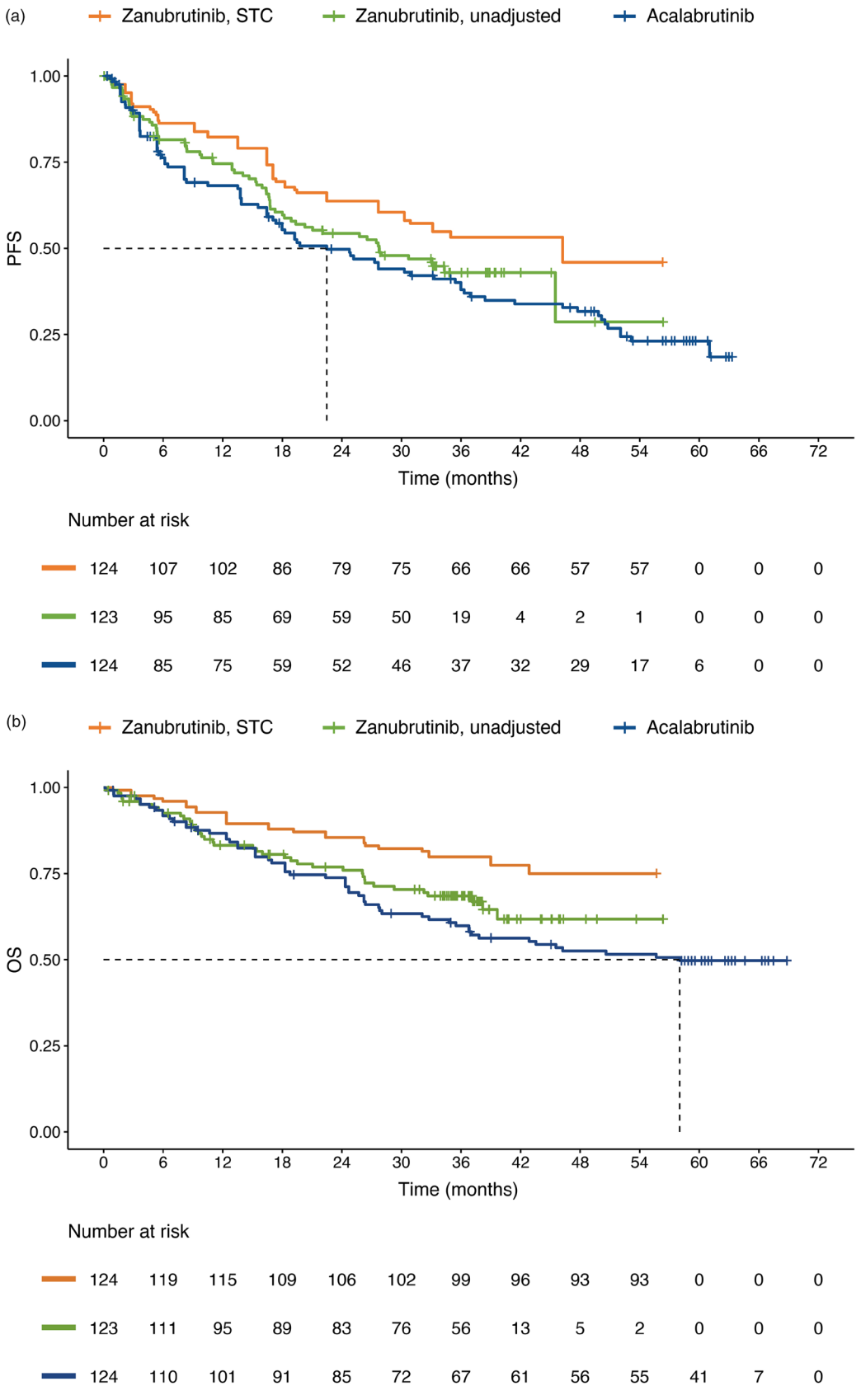

Figure 2. Kaplan–Meier curve for survival outcomes. (a) Progression-free survival, and (b) overall survival.
Population adjusted for covariates including age, sex, race, ECOG performance status, sMIPI, LDH concentration, tumor bulk, bone marrow involvement, disease stage, extranodal disease, prior lines of therapy and prior ASCT.
ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; STC, simulated treatment comparison.

Table 3. Sensitivity analyses results of STC comparing zanubrutinib vs. acalabrutinib for efficacy outcomes.

Sensitivity analyses	PFS HR (95% CI, *p* value)	OS HR (95% CI, *p* value)	ORR OR (95% CI, *p* value)
Sensitivity analysis 1 (base case without race)	**0.62** (0.39–0.98, $p=0.0418$)	**0.42** (0.25–0.70, $p=0.0009$)	1.48 (0.57–3.82, $p=0.4165$)
Sensitivity analysis 2 (base case without age)	**0.58** (0.35–0.97, $p=0.0388$)	**0.48** (0.25–0.94, $p=0.0335$)	2.19 (0.73–6.52, $p=0.1606$)

*Population adjusted for covariates including age, sex, race, ECOG performance status, sMIPI, LDH concentration, tumor bulk, bone marrow involvement, disease stage, extranodal disease, prior lines of therapy and prior autologous SCT.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; SCT, stem cell transplantation; STC, simulated treatment comparison.

in the acalabrutinib global study (ACE-LY-004) [17,18] would lead to a very small ESS, which would be considered inadequate to provide a robust estimate or conclusions. Thus, an STC-based approach was adopted. STC also has the advantage that model assumptions can be checked explicitly. The concordance index (C-index) is the most frequently used metric for model fit assessment on prognostic models in survival analysis, with higher values indicating better models [33]. The C-index in our STC was 0.687 (standard error [SE] 0.034) for PFS and 0.754 (SE 0.038) for OS, indicating reasonable model fit.

The current STC was adjusted for a large set of covariates, identified from published ITCs in R/R MCL [30–32,34,35], and validated in consultation with clinical experts. Most baseline characteristics were well balanced. Some differences in the covariates of age, race, proportion of patients with high LDH, prior lines of treatment, bone marrow involvement, ASCT, *TP53* gene mutation, Ki-67 index, and method of ORR assessment were observed. The patients in the zanubrutinib trials appeared to be younger (i.e. proportion of patients aged ≥65 years being 40% vs. 65% in the acalabrutinib trial). One of the two trials of zanubrutinib was conducted in China only and another had most patients from Australia and New Zealand. Sensitivity analyses conducted by excluding the covariates of age and race indicated no impact of these covariates on outcomes (i.e. HRs for PFS and OS, and OR for ORR were not altered significantly). Sensitivity analyses excluding the covariates of age and race demonstrated that these variables did not influence the treatment outcomes. Specifically, HRs for PFS and OS, and OR for ORR remained consistent with the primary analysis. This suggests that the observed outcomes are robust and not confounded by differences in age or race between the study populations, reinforcing the validity and robustness of the findings. The proportion of patients with high LDH and >2 prior lines of treatment was slightly higher in zanubrutinib pooled data than the acalabrutinib trial, and these covariates were found to be significantly predictive of survival outcomes in the regression models. Given the trials of zanubrutinib and acalabrutinib were conducted in countries with differences in practice, the type and the number of prior lines of treatment appeared to be slightly different. These might have had an impact on the estimates but were not investigated. Bone marrow involvement and prior ASCT were not considered clinically meaningful in the opinion of experts. With regards to ASCT, there were fewer prior ASCT in the zanubrutinib trials given that the population was younger. As a large sample of patients in the acalabrutinib trial was from the US, the higher proportion of patients with prior ASCT appeared to be in line with US practice. Several studies have shown the poor prognostic impact of tumor protein p53 (*TP53*) gene mutation [36–38] and Ki-67 index [39–41] in patients with MCL. Due to the unavailability of baseline data on the covariates of *TP53* mutation and Ki-67 index in the acalabrutinib trial, these prognostic variables were not adjusted for in our analysis. In terms of method of ORR assessment, CT-based responses are likely to underestimate ORR compared to PET-based. The sizable number of patients in the zanubrutinib trials that had CT-based assessment compared to acalabrutinib gives acalabrutinib an advantage over zanubrutinib in ORR assessment. Nonetheless, our results showed that odds of achieving ORR were higher for patients treated with zanubrutinib versus acalabrutinib.

Several ITCs have been published previously in R/R MCL or B-cell malignancies comparing BTKis. Telford et al. [32] conducted MAICs comparing acalabrutinib using IPD data from ACE-LY-004 with ibrutinib as well as other targeted therapies in R/R MCL. Findings from this MAIC indicated that PFS and OS with acalabrutinib were comparable to ibrutinib, with no statistically significant differences observed; however, acalabrutinib demonstrated superiority over therapies such as bortezomib and temsirolimus [32]. A recently published MAIC by Salles et al. demonstrated clinically and statistically significant benefits of gene therapy (brexu-cel) in ORR, CR, and PFS versus pirtobrutinib in patients with R/R MCL pretreated with a BTKi [42]. In another MAIC, Song et al. showed that zanubrutinib (IPD from BGB-3111-206) had significantly longer PFS compared with orelabrutinib (HR, 0.54; 95% CI: 0.34–0.86;

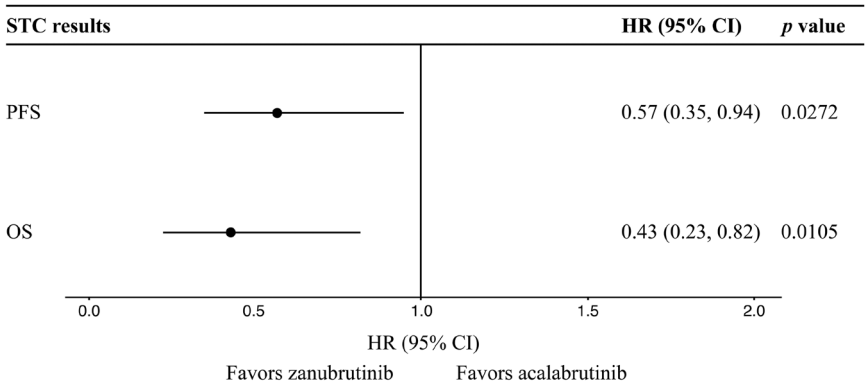

Figure 3. Results of the STC comparing zanubrutinib vs. acalabrutinib for efficacy outcomes in the base case analysis.
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparison.

$p = 0.009$) in the treatment of patients with R/R MCL based on the ICP-CL-00102 trial [31]. The findings of the present STC provide evidence to support the superiority of zanubrutinib over acalabrutinib in R/R MCL.

This study did not include an indirect comparison of the safety profiles of zanubrutinib and acalabrutinib. Evaluating safety outcomes is often more robustly achieved through meta-analyses that synthesize data across multiple trials and indications, providing a broader and more reliable assessment of adverse event (AE) patterns. A recent meta-analysis encompassing 61 clinical trials and 6,959 patients treated with ibrutinib (± anti-CD20 antibody), acalabrutinib, or zanubrutinib offered a comprehensive evaluation of safety outcomes across various B-cell malignancies. This analysis revealed notable differences in the AE profiles of zanubrutinib and acalabrutinib, highlighting the importance of considering safety alongside efficacy when selecting a treatment. These findings can help inform clinical decision-making, particularly in patient populations where tolerability is a key concern [43].

The strength of the present STC study lies in the fact it was conducted per standards documented in the NICE DSU Technical Support Document 18 [22], with rigorous statistical methods to provide reliable estimates after adjusting for a large set of covariates. Nevertheless, the population-adjusted ITC brings certain inherent limitations that warrant discussion. First, the reliance on the aggregated data for comparator(s) in the absence of IPD limits the granularity and specificity of the analysis. The differences in designs, patient populations, or treatment regimens across the studies being compared can introduce heterogeneity, potentially affecting the validity of indirect comparisons. A key limitation of ITCs such as MAIC/STC is the potential for residual confounding. Despite adjusting for observed baseline characteristics, unmeasured or unreported confounders may still influence the treatment outcomes, limiting the ability to draw definitive conclusions. In the current study, a large set of covariates, which in the opinion of clinical experts could influence treatment outcomes, were adjusted in the analysis. The results of the ITC may be sensitive to the choice of statistical methods and the selection of covariates. However, our sensitivity analyses demonstrated the robustness of the results regarding selection of covariates. The generalizability of study findings to broader or different patient populations than the acalabrutinib trial may be limited.

ITCs are not a substitute for direct head-to-head comparison clinical trials, which are still regarded as the gold standard of data in the hierarchical pyramid of evidence. Therefore, the conclusions drawn from ITCs should be interpreted in the context of this inherent limitation. However, the significance of the current study in providing much needed evidence on the comparative efficacy of zanubrutinib and acalabrutinib in R/R MCL in the absence of head-to-head trials should not be undermined.

In conclusion, this ITC demonstrated that zanubrutinib had significantly better PFS and OS versus acalabrutinib in the treatment of patients with R/R MCL after adjusting for a large set of covariates. In the absence of head-to-head trials, this study offers clinically meaningful insights into the comparative efficacy of zanubrutinib and acalabrutinib, which may support evidence-based treatment decisions and optimize care for patients with relapsed/refractory mantle cell lymphoma (R/R MCL)

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Authorship contributions

Contribution to conception/design: BS, SC, RW, KY; Analysis of data: SX; Interpretation of data: BS, SC, SX, RW, SR, TS, RG,

KY, NS, CT; Writing - Original draft: BS, SC, SX, RW, SR, TS, RG, KY, NS, CT; Writing - Review & editing: BS, SC, SX, RW, SR, TS, RG, KY, NS, CT

Disclosure statement

BS reports employment with Moffitt Cancer Center; research funding from Jazz Pharmaceuticals, Servier, Kite; travel accommodations for Kite; other relationships with DSMB, Pepromene Bio.

SC is an employee of BeOne Medicines and owns stock in BeOne Medicines.

SX is an employee of BeOne Medicines and owns stock in BeOne Medicines.

RW is an employee of BeOne Medicines and owns stock in BeOne Medicines.

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KY is an employee of BeOne Medicines and owns stock in BeOne Medicines.

NS reports research funding from Seagen, Eli Lilly, Incyte, Genentech, BeOne Medicines, Merck, Morphosys, Acerta, Karyopharm, AstraZeneca, Amgen; consulting fees from Seagen, AbbVie, ADC therapeutics, Eli Lilly, Incyte, Genentech, BeOne Medicines; payment for expert testimony from Hollingsworth; receipt of equipment, materials, drugs, medical writing, gifts or other services from AbbVie.

CT reports receiving funding from Janssen-Cilag (Inst), AbbVie (Inst), BeOne Medicines (Inst); consulting or advisory roles with Janssen, Loxo, Roche, BeOne Medicines, and AbbVie; and honoraria from Janssen-Cilag, AbbVie, Novartis, BeOne Medicines, Pharmacyclics, Roche/Genentech, and Loxo/Lilly.

Data availability statement

On request, and subject to certain criteria, conditions, and exceptions, BeOne Medicines Ltd, will provide access to individual de-identified participant data from BeOne Medicines-sponsored global interventional clinical studies conducted (1) for indications that have been approved based on the BeOne Medicines data sharing policy or (2) in programs that have been terminated. BeOne Medicines shares data only when permitted by applicable data privacy and security laws and regulations, shares when it is feasible to do so without compromising the privacy of the study participants and other considerations. Data requests may be submitted to ClinicalTrials@BeOneMed.com.

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