Matching-adjusted Indirect Comparisons of the Efficacy and Safety of Acalabrutinib Versus Other Targeted Therapies in Relapsed/Refractory Mantle Cell Lymphoma

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ABSTRACT

Purpose: Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma that can be either aggressive or indolent. Although MCL usually responds well to initial treatment with chemotherapy-based regimens, the disease often relapses or becomes refractory within a few years. Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase inhibitor with minimal off-target activity. WIthout head-to-head clinical trial data, estimation of the comparative efficacy and safety of new therapeutic entities provides valuable information for patients, clinicians, and health care payers. The objective of this analysis was to compare the efficacy and safety of acalabrutinib versus other targeted therapies employed for the treatment of relapsed/refractory MCL by using matching-adjusted indirect comparisons.

Methods: Individual data from 124 patients treated with acalabrutinib in the Phase II ACE-LY-004 trial were adjusted to match average baseline characteristics of populations from studies using alternative targeted treatment regimens for relapsed/refractory MCL (for monotherapy: ibrutinib, bortezomib, lenalidomide, and temsirolimus; for combination therapies: ibrutinib + rituximab, bendamustine + rituximab, and lenalidomide + rituximab). Patient populations were matched on age, sex, race, Eastern Cooperative Oncology Group performance status, Simplified MCL International Prognostic Index score, tumor bulk, lactate dehydrogenase concentration, extranodal disease, bone marrow involvement, and number of previous treatment regimens. Outcomes assessed included overall response rate (ORR), complete response (CR) rate, overall survival (OS), progression-free survival (PFS), and adverse events.

Findings: After matching, acalabrutinib was associated with significant increases in ORR and CR rate (estimated treatment difference [95% CI]) versus ibrutinib (ORR, 9.3% [0.3−18.3]; CR, 14.9% [5.4−24.3]), bortezomib (ORR, 50.6% [40.2−61.0]; CR, 18.8% [9.1−28.5]), lenalidomide (ORR, 38.1% [27.1−49.1]; CR, 43.5% [34.8−52.3]), and temsirolimus (ORR, 40.7% [31.0−50.4]; CR, 27.1% [19.2−35.0]). PFS (hazard ratio [95% CI]) with acalabrutinib was significantly increased versus bortezomib (0.36 [0.26−0.51]), lenalidomide (0.65 [0.48−0.89]), lenalidomide + rituximab (0.57 [0.35−0.93]), and temsirolimus (0.33 [0.24−0.45]). Acalabrutinib was associated with significantly increased OS (hazard ratio) versus bortezomib (0.36 [0.22−0.61]) and temsirolimus (0.32 [0.23−0.44]). The overall safety profile of acalabrutinib was similar or better compared with the monotherapies; however, infection risk increased versus bendamustine + rituximab, and anemia increased risk versus lenalidomide + rituximab and ibrutinib + rituximab.

Implications: This comparison of targeted therapies used in the treatment of relapsed/refractory MCL

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showed that acalabrutinib has the potential to provide increased response rates, with trends for increased PFS and OS, and an improved safety profile. (*Clin Ther.* 2019;41:2357–2379)

Key words: mantle cell lymphoma, acalabrutinib, pooled analysis, matching-adjusted indirect comparison.

INTRODUCTION

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma (NHL), caused by chromosomal translocation t(11; 14) (q13; q32), that can be either aggressive or indolent.[1,2] It is usually diagnosed in people aged >50 years (median age at diagnosis, 68 years) and is more prevalent among white and male subjects, representing ~6.0% of all new cases of NHL, with an incidence rate of ~1 per 100,000 in Europe and the United States.[3–7] MCL is usually diagnosed as a late-stage disease that has typically spread to the gastrointestinal tract and bone marrow, which results in a poor prognosis with median overall survival (OS) reported to be 4–5 years.[8]

Although MCL usually responds well to initial treatment with chemotherapy-based regimens, patients often relapse or become refractory within a few years.[9–11] As with other forms of NHL, there is no consensus on the best treatment for relapsed/refractory MCL. The type of treatment recommended for relapsed/refractory MCL depends on multiple factors, namely time to the relapse, extent of disease, previous regimens, candidacy for allogeneic stem cell transplantation, and the patient's overall health.[12] The targeted therapies that have been approved for the treatment of relapsed/refractory MCL are acalabrutinib, bortezomib, ibrutinib, lenalidomide, and temsirolimus.[13–19]

Acalabrutinib was approved in October 2017 by the US Food and Drug Administration, based on data from the ACE-LY-004 (NCT02213926) trial, for the treatment of adult patients with MCL who have received at least 1 previous therapy; it also received orphan drug designation from the European Medicines Agency for MCL in March 2016.[19,20] Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase (BTK) inhibitor with minimal off–target activity.[21] In the ACE-LY-004, single-arm, multicenter, Phase II trial, at a median follow-up of 26.3 months, 81% of patients achieved an overall response (ORR), and 43% achieved a complete response (CR). The median duration of response was 25.7 months (95% CI, 17.5 months–not reached). Median progression-free survival (PFS) was 19.5 months (95% CI, 16.5–27.7). Median OS was not reached; however, the 24-month OS rate was 72% (95% CI, 64–80). Adverse events (AEs) were mostly grade 1 or 2; there were no cases of new-onset atrial fibrillation (there was 1 episode in a patient with a history of paroxysmal atrial fibrillation) and only 3 cases of grade 3 or higher bleeding.[22,23]

The highly selective and potent BTK inhibition provided by acalabrutinib may translate into an improved safety profile compared with other targeted therapies.[21] Improvements in the safety profile could have a long-term impact on outcomes for patients due to lower rates of discontinuation and an increase in treatment duration. Estimation of comparative efficacy and safety of new therapeutic entities provides valuable information for clinicians and health care payers in the absence of head-to-head data. The objective of the present analysis was to compare the efficacy and safety of acalabrutinib versus other targeted therapies employed for the treatment of relapsed/refractory MCL by using matching-adjusted indirect comparisons (MAICs).

MATERIALS AND METHODS

Evidence Base

Individual patient-level data (IPD) for acalabrutinib were drawn from the ACE-LY-004 trial (data cut, February 12, 2018; median follow-up, 26.3 months). A systematic literature review of published data spanning from 1996 to December 2017 was conducted in December 2017. The goal was to identify relevant trials that would be used to evaluate the efficacy and safety of acalabrutinib (as reported in the ACE-LY-004 trial) compared with alternative targeted therapies approved by the US Food and Drug Administration and European Medicines Agency for which comparative evidence was available, or bendamustine + rituximab, in the treatment of patients with relapsed/refractory MCL.

The following data sources were used in the literature search: EMBASE, MEDLINE, MEDLINE

In-Process, and the Cochrane Library. Abstract databases from the American Society of Clinical Oncology, the European Society for Medical Oncology, the American Society of Hematology, the International Conference on Malignant Oncology, and the Academy of Managed Care Pharmacy congresses were also searched. A prespecified search strategy was employed, using terms applicable to the population of interest (relapsed/refractory MCL in adults), outcomes (all efficacy and safety), study design (randomized controlled trials, nonrandomized controlled trials, and single-arm trials), and the interventions of interest (for monotherapy: ibrutinib, bortezomib, lenalidomide, and temsirolimus; for combination therapies: ibrutinib + rituximab, bendamustine + rituximab, and lenalidomide + rituximab). The studies that were considered eligible for inclusion in the MAICs reported on one or more of the interventions of interest in the relapsed/refractory setting. The review was limited to articles written in English. The systematic review was conducted according to the National Institute for Health and Care Excellence (NICE) guidelines.[24] Citations were screened by 2 independent reviewers, and full-text copies of citations matching eligibility criteria were obtained. Full-text versions were then screened by 2 independent reviewers, with discrepancies reconciled by a third reviewer. Data were subsequently extracted for the included trials by 2 independent reviewers, and discrepancies were reconciled by a third reviewer.

A feasibility assessment for each of the MAICs was conducted to evaluate the overall relevance, availabilities, and definitions of baseline characteristics and outcomes across all trials and comparators.

Efficacy and Safety Parameters

The following efficacy and safety outcomes, which were selected by 2 independent hematologists based on clinical importance, were evaluated: ORR, CR rate, PFS, and OS. Also evaluated, depending on data availability, were anemia, atrial fibrillation, headache, infection, leukopenia, neutropenia, thrombocytopenia (grade 3/4), diarrhea (grade 3/4 or any grade), and bleeding (grade 3/4).

The Independent Review Committee assessment of the ORR and the CR rate from the ACE-LY-004 trial used in this analysis was based on the 2007 criteria of Cheson et al,[25] because these are the response criteria most commonly used in comparator trials; thus, heterogeneity between outcomes was minimized. Although these criteria were collected in ACE-LY-004 at the first data cut (February 28, 2017; median follow-up, 15.2 months), they were not collected at subsequent follow-up. To reduce heterogeneity further, response rates at a comparable time period were used for comparators. The most recent data cut (February 12, 2018; median follow-up, 26.3 months) was used in this analysis for PFS, OS, and safety comparisons.

PFS and OS outcomes were estimated individually for each of the comparator therapies by using published Kaplan–Meier curves, applying the method recommended by NICE.[26,27] PFS and OS Kaplan–Meier data were subsequently digitized, and a published algorithm was used to create pseudo-IPD.[28]

Statistical Methods: MAICs

The MAIC approach used IPD from the ACE-LY-004 trial and adjusted the trial population to match average baseline characteristics reported for the comparator trials. Patients from the ACE-LY-004 trial were selected based on the inclusion/exclusion criteria of the comparator trials. In each comparison, patients with missing values in the baseline characteristics to be matched were excluded from the analysis. The following baseline characteristics were considered to be matched in MAICs based on the preliminary feasibility assessment and discussions with clinical experts: age, sex, race, Eastern Cooperative Oncology Group (ECOG) performance status, simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI), tumor bulk, Ann Arbor staging, refractory disease, lactate dehydrogenase concentration, extranodal disease, bone marrow involvement, and number of previous treatment regimens. After matching these characteristics, efficacy and safety outcomes were compared across balanced trial populations. Detailed methodology for MAIC has been published previously.[29]

Individual patients in the acalabrutinib ACE-LY-004 trial were assigned weights such that: (1) weighted average (SD) baseline characteristics in the acalabrutinib ACE-LY-004 trial exactly match all of those reported for patients in the comparator trials; and (2) each individual patient's weight (w_i) is equal to his or her estimated odds (relative propensity) of being in the comparator trials versus the

acalabrutinib ACE-LY-004 trial. The weights were used to calculate the effective sample size (ESS). The ESS was calculated as $(\Sigma w_i)^2/(\sum w_i^2)$. A low ESS indicates greater differences in baseline characteristics between populations. The uncertainty in the comparative estimates is reflected in the 95% CIs. Response rates from ACE-LY-004, based on nonresponder imputation (ie, impute patients with missing response as nonresponders), were used in the analyses, thus ensuring a conservative approach.

Comparison of Efficacy and Safety Outcomes Before and After Matching

Comparative analyses were conducted both before and after matching. Before matching, binary outcomes (ie, proportion with ORR, CR, and safety outcomes) were summarized and compared by using the χ^2 test. Risk differences with their 95% CIs and *P* values were reported. Population weights generated in the MAICs were applied to the ACE-LY-004 trial data, allowing for similar postmatching comparisons of efficacy and safety outcomes between balanced trial populations. The 95% CIs and *P* values for the indirect comparisons were based on a robust estimate of the variance, based on a sandwich estimator, consistent with Signorovitch et al.[30] PFS and OS were summarized by using Kaplan–Meier curves and were compared by using weighted log-rank tests. Hazard ratios were estimated from a weighted Cox proportional hazards model. The proportional hazards assumption was tested both before and after matching.

RESULTS

The systematic literature review identified 14 unique studies split across 12 publications for the respective comparators (see the Supplemental Figure S1 in the Appendix A): ibrutinib, bortezomib, lenalidomide, temsirolimus, bendamustine + rituximab, ibrutinib + rituximab, and lenalidomide + rituximab.[31–40] Two studies were excluded because there was insufficient data reported to allow the study population to be matched with the ACE-LY-004 population.[22]

In the ibrutinib comparison, IPD from 3 separate trials were pooled.[31] Inclusion and exclusion criteria were similar across the trials; however, patients in SPARK (MCL2001) had received previous treatment with rituximab and bortezomib, whereas in RAY (MCL3001), patients were required to have received previous treatment with rituximab.[31]

Study Characteristics

An overview of the study designs and patient populations of the included studies is presented in Table I. The criteria for response differed from ACE-LY-004 for the following comparisons (based on criteria of Cheson et al[41]): bortezomib, lenalidomide, lenalidomide + rituximab, and temsirolimus.[32–35,37,40]

Baseline Characteristics

After matching, the baseline characteristics of the trial populations were well matched for each of the comparisons. Although the ESS of the acalabrutinib population was reasonable for most comparisons, it was low for the ibrutinib + rituximab (ESS = 16) and lenalidomide (ESS = 28) MAICs. Baseline characteristics before and after matching are presented in Tables II–VIII.

Efficacy Outcomes

The results of this analysis suggest that after matching the summary baseline characteristics between ACE-LY-004 and trials of comparator treatment regimens, acalabrutinib is associated with significant increases in ORR and CR rate (rate difference [CI_{95}]) compared with ibrutinib (ORR, 9.3% [0.3–18.3]; CR, 14.9% [5.4–24.3]), bortezomib (ORR, 50.6% [40.2–61.0]; CR, 18.8% [9.1–28.5]), lenalidomide (ORR, 38.1% [27.1–49.1]; CR, 43.5% [34.8–52.3]), and temsirolimus (ORR, 40.7% [31.0–50.4]; CR, 27.1% [19.2–35.0]). For the rituximab combinations (bendamustine + rituximab, ibrutinib + rituximab, and lenalidomide + rituximab) there was no significant difference in the ORR or the CR rate (Tables IX and X).

Comparisons in PFS trended in favor of acalabrutinib except for bendamustine + rituximab (Figure 1) and were mostly statistically significant. Similarly, OS hazard ratios trended in favor of acalabrutinib, but these were accompanied by wide CIs in most instances, suggesting a high level of uncertainty (Figure 2). Median PFS and OS for acalabrutinib versus comparators are shown in Table XI.

Safety Outcomes

Compared with ibrutinib, acalabrutinib was associated with a significant decrease in the risk of grade 3/4 atrial fibrillation (rate difference

Table I. Overview of ACE-LY-004 and comparator trial designs and patient populations.

Comparator	Study	Author and Year	Phase	Study Design	n	Patient Population	Treatment	Primary End Point	IWG Criteria Version	Median Duration of Follow-up
Acalabrutinib	ACE-LY-004	Wang 2018[23]	2	Single-arm, open-label, international multicenter	124	Histologically documented patients with MCL, who have relapsed after ≥1 (but not >5) previous treatment regimens	Acalabrutinib 100 mg BID continuously, in repeated 28-day cycles until PD or an unacceptable drug-related toxicity occurred	ORR	2014 (primary) and 2007 (exploratory)	26.3 mo
Ibrutinib	MCL3001 (RAY)*	Dreyling 2016[36]	3	Randomized, open-label, international multicenter	139	Relapsed or refractory MCL	Ibrutinib 560 mg orally once per day until PD or unacceptable toxic effects	PFS	2007	20 mo (24-month pooled population)[29]
Ibrutinib	PCYC-1104*	Wang 2015[51]	2	Single-arm, open-label, international multicenter	111	Relapsed or refractory MCL	Ibrutinib 560 mg/d orally until PD or unacceptable toxicity	ORR	2007	26.7 mo (24-month pooled population)[29]
Ibrutinib	MCL2001 (SPARK)*	Wang 2014[52]	2	Single-arm, open-label, international multicenter	120	Patients with MCL who had received a rituximab-containing regimen and had progressed after at least 2 cycles of bortezomib therapy	Ibrutinib 560 mg/d orally until PD or unacceptable toxicity	ORR	NR	14.9 mo (24-month pooled population)[29]
Bortezomib	PINNACLE	Goy 2009[32]	2	Single-arm, international multicenter	155	Relapsed or refractory MCL	Bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle, for up to 17 cycles or 4 cycles beyond initial reporting of CR/CRu, discontinuing for PD or unacceptable toxicity, or by patient/investigator decision	ORR [CR/CRu + PR], DOR, TTP, and OS	1999	26.4 mo
Lenalidomide	MCL-002 SPRINT	Trněný 2016[33]	2	Randomized, controlled, open-label, international multicenter	170	Patients with relapsed/refractory MCL, who are ineligible for intensive chemotherapy or stem cell transplantation	Lenalidomide 25 mg (10 mg for patients with creatinine clearance between ≥30 mL/min and <60 mL/min) orally on days 1–21 of each	PFS	1999	15.9 mo

(continued on next page)

Table I. (*Continued*)

Comparator	Study	Author and Year	Phase	Study Design	n	Patient Population	Treatment	Primary End Point	IWG Criteria Version	Median Duration of Follow-up
							28-day cycle until PD or unacceptable toxic effects			
Lenalidomide	MCL-001/EMERGE study	Goy 2015[45]	2	Single-arm, open-label, international multicenter	134	Patients with confirmed MCL diagnosis, who had documented relapsed, refractory, or PD after bortezomib treatment (alone or in combination)	Lenalidomide 25 mg orally on days 1–21 every 28 days until PD or intolerance	ORR and DOR	NR	13.2 mo
Temsirolimus	MCL3001 (RAY)	Dreyling 2016[36]	3	Randomized, 2-arm, open-label, international multicenter	141	Confirmed diagnosis of MCL, who have documented relapse or disease progression after the last anti-MCL treatment	Temsirolimus 175 mg IV on days 1, 8, and 15 of the first cycle, followed by 75 mg on days 1, 8, and 15 of each subsequent 21-day cycle until PD or unacceptable toxic effects	PFS	2007	20 mo
Temsirolimus	OPTIMAL	Hess 2009[37]	3	Randomized, multi-arm, open-label, international multicenter	54	Refractory and/or relapsed MCL after 2–7 previous therapies	Temsirolimus 175 mg IV per week for 3 weeks followed by weekly dose of 75 mg IV	PFS	1999	NR
Temsirolimus	Jurczak 2018	Jurczak 2018[35]	4	Randomized, multi-arm, open-label, multicenter	47	Patients with relapsed/refractory MCL previously treated with 2–7 previous therapies	Temsirolimus 175 mg IV once a week for first 3 weeks, followed by 75 mg IV once a week until PD	PFS	1999	NR
Ibrutinib + rituximab	Wang 2016	Wang 2016[39]	2	Single-arm, open-label, single-center	50	Patients with a confirmed MCL diagnosis, no upper limit on the number of previous treatments received	Ibrutinib 560 mg orally, daily until PD or unacceptable toxic effects + rituximab 375 mg/m^2 IV once per week for 4 weeks during cycle 1, then on day 1 of cycles 3–8, and thereafter once every other cycle up to 2 years (1 cycle was 28 days)	ORR	2007	16.5 mo

Bendamustine + rituximab	Czuczman 2015	Czuczman 2015[38]	2	Single-arm, open-label, multicenter	45	Relapsed/refractory MCL who had received ≤3 previous standard chemotherapy regimens	Bendamustine 90 mg/m^2 IV on days 1 and 2 of a 28-day cycle, and rituximab was administered as an intravenous infusion of 375 mg/m^2 on day 1. The treatment period consisted of 6 cycles; however, patients could receive up to 8 cycles if they had not achieved CR and did not have PD	ORR	2007	19.2 mo (from date of last treatment)
Lenalidomide + rituximab	Wang 2012	Wang 2012[40]	1/2	Single-arm, open-label, multicenter	44	Patients with relapsed or refractory MCL who had received 1–4 previous lines of treatment	Lenalidomide 20 mg orally daily on days 1–21 of each 28-day cycle and 375 mg/m^2 of IV rituximab once per week for 4 weeks only during cycle 1, beginning on day 1 until PD, stem cell transplantation, or withdrawal for toxicity. Median (range) dose for lenalidomide was 15 mg (5–20 mg)	ORR	1999	23.1 mo

BID = twice a day; CR = complete response; CRu = complete response unconfirmed; DOR = duration of response; IWG = International Working Group; MCL = mantle cell lymphoma; NR = not reported; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SPRINT = Analyses of Revlimid® MCL-002; TTP = thrombotic thrombocytopenic purpura.

* Pooled analysis of 3 trials used in acalabrutinib versus ibrutinib MAIC.[31]

Table II. Baseline characteristics before and after matching for acalabrutinib versus ibrutinib.

Characteristic	Before Matching			After Matching	
	Acalabrutinib, No. (%) (n = 123) [A]	Ibrutinib, No. (%) (n = 370) [B]	*P* [A] vs [B]	Acalabrutinib, % (ESS = 45) [A]	Ibrutinib, % (n = 370) [B]
Age ≥65 y	79 (64.2)	231 (62.4)	0.80	62.4	62.4
Male sex	99 (80.5)	289 (78.1)	0.67	78.1	78.1
White	91 (74.0)	329 (88.9)	<0.001*	88.9	88.9
ECOG 0−1	114 (92.7)	346 (93.5)	0.91	93.5	93.5
ECOG = 2	8 (6.5)	23 (6.2)	0.99	6.2	6.2
ECOG = 3	1 (0.8)	1 (0.3)	0.44	0.3	0.3
Low risk (sMIPI)	48 (39.0)	88 (23.8)	<0.01*	23.8	23.8
Intermediate risk (sMIPI)	54 (43.9)	164 (44.3)	1.00	44.3	44.3
High risk (sMIPI)	21 (17.1)	118 (31.9)	<0.01*	31.9	31.9
Tumor bulk <5 cm	77 (62.6)	189 (51.1)	<0.05*	51.1	51.1
High LDH concentration	33 (26.8)	199 (53.8)	<0.001*	53.8	53.8
Extranodal disease	89 (72.4)	215 (58.1)	<0.01*	58.1	58.1
Bone marrow involvement	62 (50.4)	169 (45.7)	0.42	45.7	45.7
1 Previous cancer regimen	59 (48.0)	99 (26.8)	<0.001*	26.8	26.8
2 Previous cancer regimens	37 (30.1)	109 (29.5)	0.99	29.5	29.5
≥3 Previous cancer regimens	27 (22.0)	162 (43.8)	<0.001*	43.8	43.8

ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; LDH = lactate dehydrogenase; sMIPI = simplified Mantle Cell Lymphoma International Prognostic Index.

Note: The baseline characteristics for acalabrutinib were derived by using individual patient-level data from the ACE-LY-004 trial.[22,23] The baseline characteristics for ibrutinib were extracted from a pooled population of 3 ibrutinib trials.[31] One patient in the ACE-LY-004 trial with missing values in the sMIPI was excluded from the analysis. Baseline characteristics were compared by using the χ^2 test before matching and a weighted χ^2 test after matching.

*$P < 0.05$.

Table III. Baseline characteristics before and after matching for acalabrutinib versus bortezomib. Values are no. (%) unless otherwise indicated.

Characteristic	Before Matching			After Matching	
	Acalabrutinib (n = 124) [A]	Bortezomib (n = 155) [B]	*P* [A] vs [B]	Acalabrutinib (ESS = 61) [A]	Bortezomib (n = 155) [B]
Age, mean (SD), y	67.1 (10.5)	64.9 (9.3)	0.07	64.9 (9.3)	64.9 (9.3)
Male sex	99 (79.8)	125 (80.6)	0.99	80.6	80.6
White	92 (74.2)	142 (91.6)	<0.001*	91.6	91.6
ECOG = 0	71 (57.3)	110 (71.2)	<0.05*	71.2	71.2
ECOG = 1	44 (35.5)	37 (24.2)	<0.05*	24.2	24.2
ECOG = 2	8 (6.5)	7 (4.6)	0.66	4.6	4.6
ECOG = 3	1 (0.8)	0 (0.0)	0.44	0.0	0.0
Ann Arbor stage I	2 (1.6)	5 (3.2)	0.47	3.2	3.2
Ann Arbor stage II	7 (5.6)	7 (4.5)	0.88	4.5	4.5
Ann Arbor stage III	22 (17.7)	24 (15.5)	0.73	15.5	15.5
Ann Arbor stage IV	93 (75.0)	119 (76.8)	0.84	76.8	76.8
High LDH concentration	33 (26.6)	56 (36.2)	0.12	36.2	36.2
Extranodal disease	90 (72.6)	117 (75.5)	0.68	75.5	75.5
Bone marrow involvement	63 (50.8)	84 (54.2)	0.66	54.2	54.2
1−2 Previous cancer regimens	96 (77.4)	149 (96.1)	<0.001*	96.1	96.1
≥3 Previous cancer regimens	28 (22.6)	6 (3.9)	<0.001*	3.9	3.9

ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; LDH = lactate dehydrogenase.
Note: The baseline characteristics for acalabrutinib were derived by using individual patient-level data from the ACE-LY-004 trial.[22,23] The baseline characteristics for bortezomib were extracted from the PINNACLE trial.[32] Previous bortezomib use was not allowed in the PINNACLE study; 24 patients (19%) had previous use of bortezomib/carfilzomib in the ACE-LY-004 trial. Baseline characteristics were compared by using the χ^2 test before matching and the weighted χ^2 test after matching.
*$P < 0.05$.

[CI_{95}], −4.6% [−6.7 to −2.5]) and grade 3/4 thrombocytopenia (−7.1% [−12.4 to −1.7]) (Table IX). Compared with bortezomib, acalabrutinib was associated with a significant decrease in the risk of grade 3/4 thrombocytopenia (−8.6% [−14.2 to −2.9]). Compared with lenalidomide, acalabrutinib was associated with a significant decrease in the risk of grade 3/4 diarrhea (−3.9% [−6.5 to −1.4]), grade 3/4 leukopenia (−7.3% [−10.2 to −4.4]), grade 3/4 neutropenia (−27.4% [−36.3 to −18.5]), and grade 3/4 thrombocytopenia (−20.0% [−25.6 to −14.4]). Compared with temsirolimus, acalabrutinib was associated with a significant decrease in the risk of grade 3/4 thrombocytopenia (−42.9% [−50.1 to −35.6]) (Table IX).

Compared with ibrutinib + rituximab, acalabrutinib was associated with a significant decrease in the risk of grade 3/4 atrial fibrillation (−12.0% [−21.0 to −3.0]) and any-grade diarrhea (−55.0% [−70.0 to −39.8]), and a significant increase in the risk of grade 3/4 anemia (9.7% [3.2 to 16.2]) (Table X). Compared with bendamustine + rituximab, acalabrutinib was associated with a significant decrease in the risk of grade 3/4 leukopenia (−43.8% [−58.4 to −29.2]) and grade 3/4 neutropenia (−33.1% [−49.4 to −16.8]), and a significant increase in the risk of grade 3/4

Table IV. Baseline characteristics before and after matching for acalabrutinib versus lenalidomide.

Characteristic	Before Matching			After Matching	
	Acalabrutinib, No. (%) (n = 122) [A]	Lenalidomide, No. (%) (n = 304) [B]	*P* [A] vs [B]	Acalabrutinib, % (ESS = 28) [A]	Lenalidomide, % (n = 304) [B]
Age ≥65 y	78 (63.9)	200 (65.8)	0.80	65.8	65.8
Male sex	98 (80.3)	231 (76.0)	0.40	76.0	76.0
ECOG 0−1	114 (93.4)	259 (85.1)	<0.05*	85.1	85.1
ECOG = 2	8 (6.6)	45 (14.9)	<0.05*	14.9	14.9
Low risk (sMIPI/MIPI)	48 (39.3)	87 (28.5)	<0.05*	28.5	28.5
Intermediate risk (sMIPI/MIPI)	54 (44.3)	118 (38.7)	0.35	38.7	38.7
High risk (sMIPI/MIPI)	20 (16.4)	100 (32.8)	<0.001*	32.8	32.8
Ann Arbor stage I−II	9 (7.4)	23 (7.7)	1.00	7.7	7.7
Ann Arbor stage III−IV	113 (92.6)	281 (92.3)	1.00	92.3	92.3
Refractory disease	30 (24.6)	144 (47.4)	<0.001*	47.4	47.4
High LDH concentration	32 (26.2)	120 (39.5)	<0.05*	39.5	39.5
Bone marrow involvement	62 (50.8)	76 (25.0)	<0.001*	25.0	25.0
1−2 Previous cancer regimens	96 (78.7)	154 (50.7)	<0.001*	50.7	50.7
≥3 Previous cancer regimens	26 (21.3)	150 (49.3)	<0.001*	49.3	49.3
Previous bortezomib/carfilzomib	23 (18.9)	155 (51.0)	<0.001*	36.4	51.0
Previous stem cell transplantation	22 (18.0)	69 (22.7)	0.35	16.0	22.7
Previous ARA-C-based regimen	40 (32.8)	121 (39.8)	0.22	37.4	39.8

ARA-C = cytosine arabinoside; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; LDH = lactate dehydrogenase; MIPI = Mantle Cell Lymphoma International Prognostic Index; sMIPI = simplified Mantle Cell Lymphoma International Prognostic Index.

Note: The baseline characteristics for acalabrutinib were derived by using individual patient-level data from the ACE-LY-004 trial.[20] The baseline characteristics for lenalidomide were extracted from 2 lenalidomide trials (MCL-002 and MCL-001).[31,32]

*$P < 0.05$.

Table V. Baseline characteristics before and after matching for acalabrutinib versus temsirolimus.

Characteristic	Before Matching			After Matching	
	Acalabrutinib, No. (%)	Temsirolimus, No. (%)	*P*	Acalabrutinib, %	Temsirolimus, %
	(n = 123)	(n = 242)		(ESS = 120)	(n = 242)
	[A]	[B]	[A] vs [B]	[A]	[B]
Male sex	98 (79.7)	188 (77.7)	0.76	77.7	77.7
ECOG 0–1	115 (93.5)	225 (93.0)	1.00	93.0	93.0
ECOG = 2	8 (6.5)	17 (7.0)	1.00	7.0	7.0
Ann Arbor stage I	2 (1.6)	4 (1.7)	1.00	1.7	1.7
Ann Arbor stage II	7 (5.7)	6 (2.5)	0.21	2.5	2.5
Ann Arbor stage III–IV	114 (92.7)	232 (95.8)	0.30	95.8	95.8

ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size.
Note: The baseline characteristics for acalabrutinib were derived by using individual patient-level data from the ACE-LY-004 trial.[22,23] The baseline characteristics for temsirolimus were extracted from 3 temsirolimus trials (MCL3001/RAY, OPTIMAL, and Jurczak et al.[35]).[35–37] One patient with an ECOG performance status of 3 in the ACE-LY-004 trial was excluded from the analysis. Baseline characteristics before matching were compared by using the χ^2 test.

infections (14.7 [3.1 to 26.3]) (Table X). Compared with lenalidomide + rituximab, acalabrutinib was associated with a significant decrease in the risk of any-grade diarrhea (–24.4% [–42.8 to –6.0]), grade 3/4 leukopenia (–27.9% [–41.7 to –14.0]), grade 3/4 neutropenia (–53.7% [–69.7, –37.8]), and grade 3/4 thrombocytopenia (–19.0% [–32.0 to –6.0]), and a significant increase in the risk of grade 3/4 anemia (9.3% [1.3 to 17.4]) (Table X).

In summary, the overall safety profile of acalabrutinib was similar to or better than that of the monotherapies; however, there was an increased risk of grade 3/4 infections versus the combination bendamustine + rituximab, and an increased risk of anemia compared with lenalidomide + rituximab and ibrutinib + rituximab.

DISCUSSION

To our knowledge, in the absence of head-to-head randomized controlled trials, the present analysis is the first to assess the efficacy and safety of acalabrutinib versus other targeted therapies in the treatment of relapsed/refractory MCL. Based on the results of the ACE-LY-004 trial, these MAICs suggest that acalabrutinib is associated with increased response rates compared with other targeted monotherapies. The increased response rate with acalabrutinib was associated with increased PFS versus temsirolimus, bortezomib, and lenalidomide, and increased OS versus temsirolimus and bortezomib. OS and PFS were numerically but not statistically significantly increased for acalabrutinib versus ibrutinib. However, statistical significance can be difficult to achieve, especially with a relatively small ESS.[42] Acalabrutinib was associated with similar or decreased rates of AEs compared with other targeted monotherapies. When compared with combination therapies, similar or decreased rates of AEs were observed for acalabrutinib except for grade 3/4 anemia versus lenalidomide + rituximab and ibrutinib + rituximab, and grade 3/4 infections versus bendamustine + rituximab.

The improved safety profile of acalabrutinib versus the other targeted monotherapies, and within the

Table VI. Baseline characteristics before and after matching for acalabrutinib vs ibrutinib + rituximab.

Characteristic	Before Matching			After Matching	
	Acalabrutinib, No. (%)	Ibrutinib + Rituximab, No. (%)	*P*	Acalabrutinib, %	Ibrutinib + Rituximab, %
	(n = 84)	(n = 50)		(ESS = 16)	(n = 50)
	[A]	[B]	[A] vs [B]	[A]	[B]
Age ≥67 y	49 (58.3)	25 (50.0)	0.45	50.0	50.0
Male sex	66 (78.6)	38 (76.0)	0.90	76.0	76.0
Refractory disease	21 (25.0)	35 (70.0)	<0.001*	70.0	70.0
ECOG = 0−1	84 (100.0)	50 (100.0)	1.00	100.0	100.0
Low risk (sMIPI/MIPI)	28 (33.3)	22 (44.0)	0.29	44.0	44.0
Intermediate risk (sMIPI/MIPI)	43 (51.2)	22 (44.0)	0.53	44.0	44.0
High risk (sMIPI/MIPI)	13 (15.5)	6 (12.0)	0.76	12.0	12.0
Ann Arbor stage IV	84 (100.0)	50 (100.0)	1.00	100.0	100.0
Bone marrow involvement	55 (65.5)	15 (30.0)	<0.05*	30.0	30.0
1−2 Previous cancer regimens	64 (76.2)	23 (46.0)	<0.001*	46.0	46.0
≥3 Previous cancer regimens	20 (23.8)	27 (54.0)	<0.001*	54.0	54.0

ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; MIPI = Mantle Cell Lymphoma International Prognostic Index; sMIPI = simplified Mantle Cell Lymphoma International Prognostic Index.
Note: The baseline characteristics for acalabrutinib were derived by using individual patient-level data from the ACE-LY-004 trial.[22,23] The baseline characteristics for ibrutinib and rituximab were derived by using data from the ibrutinib + rituximab trial.[39] The median age of patients receiving ibrutinib and rituximab-based therapy was 67 years in the Wang 2016 trial. The prognostic index score was evaluated by using sMIPI in the ACE-LY-004 trial and MIPI in the ibrutinib + rituximab trial. Nine patients with an ECOG performance status ≥2 and one patient with a missing sMIPI in the LY-004 trial were excluded from the analysis. Baseline characteristics were compared by using the χ^2 test before matching and the weighted χ^2 test after matching.
*$P < 0.05$.

BTK inhibitor class in particular, may translate into a reduced treatment burden on patients and possibly contribute to lower rates of treatment discontinuation. Furthermore, the differences in the profile of AEs between acalabrutinib and combination therapies should be considered by physicians when assessing patients' individual risk factors before commencing treatment.

The primary considerations when treating patients with relapsed/refractory MCL are time to relapse, depth of response to the first-line regimen, high-risk features, and existing comorbidities. In patients with early relapse (<12−24 months) a non-cross-resistant chemotherapy-based regimen is recommended, and this therapy should be combined with rituximab if the previous regimen contained a CD20 antibody and the period of remission was >6 months.[7,43] Targeted therapies (either as monotherapy or in combination with rituximab) are also strongly recommended for cases of early relapse or refractory disease, or in

Table VII. Baseline characteristics before and after matching for acalabrutinib versus bendamustine + rituximab.

Characteristic	Before Matching			After Matching	
	Acalabrutinib, No. (%)	Bendamustine + Rituximab, No. (%)	*P*	Acalabrutinib, %	Bendamustine + Rituximab, %
	(n = 121)	(n = 45)		(ESS = 56)	(n = 45)
	[A]	[B]	[A] vs [B]	[A]	[B]
Age ≥70 y	55 (45.5)	22 (50.0)	0.83	50.0	50.0
Male sex	97 (80.2)	32 (71.1)	0.30	71.1	71.1
Low risk (sMIPI/MIPI)	47 (38.8)	24 (53.3)	0.13	53.3	53.3
Intermediate risk (sMIPI/MIPI)	53 (43.8)	12 (26.7)	0.07	26.7	26.7
High risk (sMIPI/MIPI)	21 (17.4)	9 (20.0)	0.87	20.0	20.0
Ann Arbor stage I	0 (0.0)	0 (0.0)	1.00	0.0	0.0
Ann Arbor stage II	7 (5.8)	4 (8.9)	0.49	8.9	8.9
Ann Arbor stage III	22 (18.2)	4 (8.9)	0.23	8.9	8.9
Ann Arbor stage IV	92 (76.0)	37 (82.2)	0.52	82.2	82.2
Refractory disease	30 (24.8)	24 (53.3)	<0.001*	53.3	53.3

ESS = effective sample size; MIPI = Mantle Cell Lymphoma International Prognostic Index; sMIPI = Simplified Mantle Cell Lymphoma International Prognostic Index.
Note: The baseline characteristics for acalabrutinib were derived by using individual patient-level data from the ACE-LY-004 trial.[22,23] The baseline characteristics for bendamustine and rituximab combination therapy were extracted from the bendamustine and rituximab combination therapy trial.[38] The prognostic index score was evaluated by using sMIPI in the ACE-LY-004 trial and MIPI in the bendamustine and rituximab combination therapy trial. One patient with missing values in the sMIPI and 2 patients with Ann Arbor stage I in the ACE-LY-004 trial were excluded from the analysis. Baseline characteristics were compared by using the χ^2 test before matching and the weighted χ^2 test after matching.
*$P < 0.05$.

patients who are older, frail, or have multiple comorbidities.[7,43]

In recent years, several targeted therapies have been approved for the treatment of relapsed/refractory MCL. Ibrutinib has been shown to achieve high response rates and extended periods of remission.[36,44] Lenalidomide has also shown long periods of remission, particularly when used in combination with rituximab.[33,40,45,46] Temsirolimus and bortezomib used as adjuncts to chemotherapy are both effective treatment options but have less deep and enduring responses when used as monotherapy.[32,47–49] All therapeutic agents carry the risk of AEs, including cytopenia, diarrhea, venous thromboembolism, bleeding, and atrial fibrillation. Determining the suitability of a targeted therapy depends on the therapeutic profile of the drug and the health status of the patient.[7,43] Although guidelines for the management of relapsed/refractory MCL have been published, there is no consensus on the best treatment options in the second- and subsequent-line settings.[7,43] Ibrutinib is emerging as the preferred treatment option; it is not reimbursed in all markets, however.

Ibrutinib and acalabrutinib are currently the only BTK inhibitors approved for the treatment of relapsed/refractory MCL.[16,19] Within the BTK inhibitor class, acalabrutinib is associated with a

Table VIII. Baseline characteristics before and after matching for acalabrutinib versus lenalidomide + rituximab.

Characteristic	Before Matching			After Matching	
	Acalabrutinib, No. (%)	Lenalidomide + Rituximab, No. (%)	*P*	Acalabrutinib, %	Lenalidomide + Rituximab, %
	(n = 124)	(n = 44)		(ESS = 64)	(n = 44)
	[A]	[B]	[A] vs [B]	[A]	[B]
Age ≥66 y	76 (61.3)	22 (50.0)	0.26	50.0	50.0
Male sex	99 (79.8)	40 (90.9)	0.11	90.9	90.9
Bone marrow involvement	63 (50.8)	22 (50.0)	1.00	50.0	50.0
1−2 Previous cancer regimens	96 (77.4)	32 (72.7)	0.67	72.7	72.7
≥3 Previous cancer regimens	28 (22.6)	12 (27.3)	0.67	27.3	27.3
Ann Arbor stage I	2 (1.6)	0 (0.0)	1.00	0.0	0.0
Ann Arbor stage II	7 (5.6)	0 (0.0)	0.19	0.0	0.0
Ann Arbor stage III	22 (17.7)	0 (0.0)	<0.01*	0.0	0.0
Ann Arbor stage IV	93 (75.0)	44 (100.0)	<0.001*	100.0	100.0
Previous rituximab as single agent or part of a regimen	118 (95.2)	44 (100.0)	0.34	95.8	100.0
Previous bortezomib/carfilzomib	24 (19.4)	12 (27.3)	0.38	21.3	27.3

ESS = effective sample size.
Note: The baseline characteristics for acalabrutinib were derived by using individual patient-level data from the ACE-LY-004 trial.[22,23] The baseline characteristics for lenalidomide + rituximab were derived by using data from the lenalidomide + rituximab trial.[40] The following baseline characteristics were matched between the ACE-LY-004 and lenalidomide + rituximab combination therapy trials: age, sex, bone marrow involvement, and number of previous cancer regimens. Baseline characteristics after matching were compared by using the weighted χ^2 test.
*$P < 0.05$.

higher ORR and CR rate, and a reduced risk of atrial fibrillation and thrombocytopenia, compared with ibrutinib monotherapy. These findings may be due to the improved selectivity and reduced off-target activity of acalabrutinib compared with ibrutinib.[21] The comparative effectiveness of ibrutinib versus other treatments for relapsed/refractory MCL has previously been assessed by using the MAIC method.[50] That study found that ibrutinib provided significantly better odds of achieving an ORR compared with bortezomib.[50] The present analysis suggests that acalabrutinib may offer further incremental improvements in response rates compared with other targeted therapies. In the absence of head-to-head data, the findings of this study may help to inform the decisions of clinicians when treating patients with relapsed/refractory MCL.

Table IX. Overall response rate (ORR), complete response (CR) rate, and safety outcomes before and after matching in matching-adjusted indirect comparisons of acalabrutinib versus single-agent regimens.

Variable	Before Matching				After Matching			
	Acalabrutinib (n = 123) [A], %	Ibrutinib (n = 370) [B], %	Rate Difference (%) Mean (95% CI) [A–B]	*P*	Acalabrutinib (ESS = 45) [A], %	Ibrutinib (n = 370) [B], %	Rate Difference (%) Mean (95% CI) [A–B]	*P*
ORR	74.8	64.6	10.2 (1.1 to 19.3)	<0.05*	73.9	64.6	9.3 (0.3 to 18.3)	<0.05*
CR	30.1	18.9	11.2 (2.1 to 20.2)	<0.05*	33.8	18.9	14.9 (5.4 to 24.3)	<0.01*
Diarrhea (any grade)	35.8	39.5	−3.7 (−13.6 to 6.1)	0.46	31.0	39.5	−8.5 (−19.8 to 2.8)	0.14
Atrial fibrillation (grade 3/4)	0	4.6	−4.6 (−6.7 to −2.5)	<0.001*	0	4.6	−4.6 (−6.7 to −2.5)	<0.001*
Anemia (grade 3/4)	10.6	8.1	2.5 (−3.7 to 8.6)	0.43	14.7	8.1	6.6 (−3.7 to 8.6)	0.43
Diarrhea (grade 3/4)	3.3	3.5	−0.2 (−3.9 to 3.4)	0.89	1.7	3.5	−1.8 (−4.5 to 0.9)	0.19
Neutropenia (grade 3/4)	10.6	16.5	−5.9 (−1.26 to 0.7)	0.08	18.4	16.5	1.9 (−9.7 to 13.6)	0.74
Thrombocytopenia (grade 3/4)	4.1	11.1	−7 (−11.8 to −2.3)	<0.01*	4	11.1	−7.1 (−12.4 to −1.7)	<0.01*
Bleeding (grade 3/4)	2.4	4.9	−2.5 (−6.0 to 1.1)	0.17	2.3	4.9	−2.6 (−6.8 to 1.6)	0.22
Headache (grade 3/4)	0.8	0	0.8 (−0.8 to 2.4)	0.32	0.7	0	0.7 (−0.6 to 2.0)	0.31
	Acalabrutinib (n = 124) [A], %	Bortezomib (n = 155) [B], %	Rate Difference (%) Mean (95% CI) [A–B]	*P*	Acalabrutinib (ESS = 61) [A], %	Bortezomib (n = 155) [B], %	Rate Difference (%) Mean (95% CI) [A–B]	*P*
ORR	75.0	29.0	46.0 (35.5 to 56.4)	<0.001*	79.6	29.0	50.6 (40.2 to 61.0)	<0.001*
CR	29.8	7.1	22.7 (13.7 to 31.8)	<0.001*	25.9	7.1	18.8 (9.1 to 28.5)	<0.001*
Diarrhea (any grade)	36.3	47.1	−10.8 (−22.4 to 0.8)	0.07	38.6	47.1	−8.5 (−22.6 to 5.5)	0.23
Diarrhea (grade 3/4)	3.2	7.1	−3.9 (−9.0 to 1.2)	0.14	3.8	7.1	−3.3 (−9.6 to 3.0)	0.31
Thrombocytopenia (grade 3/4)	4.0	11.0	−6.9 (−13.0 to −0.9)	<0.05*	2.4	11.0	−8.6 (−14.2 to −2.9)	<0.01*

(*continued on next page*)

	Acalabrutinib (n = 122) [A], %	Lenalidomide (n = 304) [B], %	Rate Difference (%) Mean (95% CI) [A−B]	P	Acalabrutinib (ESS = 28) [A], %	Lenalidomide (n = 304) [B], %	Rate Difference (%) Mean (95% CI) [A−B]	P
ORR	74.6	34.9	39.7 (30.3 to 49.1)	<0.001*	73	34.9	38.1 (27.1 to 49.1)	<0.001*
CR	30.3	6.2	24.1 (15.4 to 32.7)	<0.001*	49.8	6.2	43.5 (34.8 to 52.3)	<0.001*
Diarrhea (any grade)	36.1	26.5	9.5 (−0.4 to 19.4)	0.06	23.1	26.5	−3.4 (−13.7 to 6.9)	0.51
Anemia (grade 3/4)	10.7	9.6	1.0 (−5.4 to 7.5)	0.75	13.0	9.6	3.3 (−5.2 to 11.9)	0.44
Diarrhea (grade 3/4)	3.3	4.6	−1.4 (−5.3 to 2.6)	0.50	0.7	4.6	−3.9 (−6.5 to −1.4)	<0.01*
Leukopenia (grade 3/4)	0.8	7.3	−6.5 (−9.8 to −3.2)	<0.001*	0.0	7.3	−7.3 (−10.2 to −4.4)	<0.001*
Neutropenia (grade 3/4)	10.7	43.5	−32.9 (−40.7 to −25.0)	<0.001*	16.1	43.5	−27.4 (−36.3 to −18.5)	<0.001*
Thrombocytopenia (grade 3/4)	4.1	22.2	−18.1 (−24.0 to −12.3)	<0.001*	2.2	22.2	−20.0 (−25.6 to −14.4)	<0.001*
	Acalabrutinib (n = 123) [A], %	Temsirolimus (n = 242) [B], %	Rate Difference (%) Mean (95% CI) [A−B]	P	Acalabrutinib (ESS = 120) [A], %	Temsirolimus (n = 242) [B], %	Rate Difference (%) Mean (95% CI) [A−B]	P
ORR	74.8	33.9	40.9 (31.2 to 50.7)	<0.001*	74.6	33.9	40.7 (31.0 to 50.4)	<0.001*
CR	30.1	2.1	28 (19.7 to 36.3)	<0.001*	29.2	2.1	27.1 (19.2 to 35.0)	<0.001*
Diarrhea (any grade)	36.6	35.0	1.6 (−8.8 to 12.1)	0.76	36.3	35.0	1.3 (−9.0 to 11.7)	0.80
Anemia (grade 3/4)	10.6	17.5	−7.0 (−14.2 to 0.3)	0.06	11.2	17.5	−6.3 (−13.7 to 1.1)	0.10
Diarrhea (grade 3/4)	3.3	4.6	−1.3 (−5.4 to 2.8)	0.53	3.4	4.6	−1.2 (−5.4 to 3.0)	0.57
Bleeding (grade 3/4)	2.4	4.2	−1.7 (−5.5 to 0.2)	0.36	2.6	4.2	−1.6 (−5.4 to 2.2)	0.40
Neutropenia (grade 3/4)	10.6	13.4	−2.8 (−9.7 to 4.1)	0.43	11.1	13.4	−2.3 (−9.1 to 4.5)	0.51
Thrombocytopenia (grade 3/4)	4.1	47.0	−43.0 (−50.2 to −35.8)	<0.001*	4.2	47.0	−42.9 (−50.1 to −35.6)	<0.001*

ESS = effective sample size.

Note: ORR and CR based on Independent Review Committee assessment according to the 2007 criteria of Cheson were used for the ACE-LY-004 trial.[20,23] Adverse events for acalabrutinib were defined by preferred terms. Patients with missing response data were considered to be non-responders.

*$P < 0.05$.

Table X. Overall response rate (ORR), complete response (CR) rate, and safety outcomes before and after matching in matching-adjusted indirect comparisons of acalabrutinib versus combination regimens.

Variable	Before Matching				After Matching			
	Acalabrutinib	Ibrutinib + Rituximab	Rate Difference (%)		Acalabrutinib	Ibrutinib + Rituximab	Rate Difference (%)	
	(n = 84)	(n = 50)	Mean (95% CI)	*P*	(ESS = 16)	(n = 50)	Mean (95% CI)	*P*
	[A], %	[B], %	[A−B]		[A], %	[B], %	[A−B]	
ORR	73.8	88	−14.2 (−27.3 to −1.1)	<0.05*	77.4	88	−10.6 (−22.8 to 1.5)	0.09
CR	25.0	44	−19.0 (−35.6 to −2.4)	<0.05*	52.3	44	8.3 (−8.3 to 24.8)	0.33
Diarrhea (any grade)	40.5	82.0	−41.5 (−56.5 to −26.5)	<0.001*	27.0	82.0	−55.0 (−70.0 to −39.8)	<0.001*
Anemia (grade 3/4)	13.1	0.0	13.1 (5.8 to 20.4)	<0.001*	9.7	0.0	9.7 (3.2 to 16.2)	<0.01*
Atrial fibrillation (grade 3/4)	0.0	12.0	−12.0 (−21.0 to −3.0)	<0.01*	0.0	12.0	−12.0 (−21.0 to −3.0)	<0.01*
Diarrhea (grade 3/4)	4.8	4.0	0.8 (−6.3 to 7.9)	0.83	2.3	4.0	−1.7 (−7.8 to 4.4)	0.58
Bleeding (grade 3/4)	3.6	6.0	−2.4 (−10.1 to 5.3)	0.54	1.6	6.0	−4.4 (−11.4 to 2.6)	0.22
Neutropenia (grade 3/4)	9.5	4.0	5.5 (−2.8 to 13.9)	0.19	6.0	4.0	2.0 (−5.5 to 9.5)	0.60
Thrombocytopenia (grade 3/4)	4.8	4.0	0.8 (−6.3 to 7.9)	0.83	3.6	4.0	−0.4 (−7.4 to 6.6)	0.91
	Acalabrutinib	Bendamustine + Rituximab	Rate Difference (%)		Acalabrutinib	Bendamustine + Rituximab	Rate Difference (%)	
	(n = 121)	(n = 45)	Mean (95% CI)	*P*	(ESS = 56)	(n = 45)	Mean (95% CI)	*P*
	[A], %	[B], %	[A−B]		[A], %	[B], %	[A−B]	
ORR	75.2	82.2	−7.0 (−20.6 to 6.6)	0.31	72.4	82.2	−9.8 (−25.6 to 5.9)	0.22
CR	29.8	40	−10.2 (−26.7 to 6.2)	0.22	28.7	40	−11.3 (−28.5 to 5.9)	0.20
Diarrhea (any grade)	36.4	35.6	0.8 (−15.6 to 17.2)	0.92	29.6	35.6	−5.9 (−23.0 to 11.1)	0.49
Anemia (grade 3/4)	10.7	4.4	6.3 (−1.9 to 14.5)	0.13	11.9	4.4	7.4 (−1.4 to 16.3)	0.10
Leukopenia (grade 3/4)	0.8	44.4	−43.6 (−58.2 to −29.0)	<0.001*	0.6	44.4	−43.8 (−58.4 to −29.2)	<0.001*
Neutropenia (grade 3/4)	10.7	44.4	−33.7 (−49.2 to −18.2)	<0.001*	11.4	44.4	−33.1 (−49.4 to −16.8)	<0.001*
Thrombocytopenia (grade 3/4)	4.1	6.7	−2.5 (−10.6 to 5.6)	0.54	7.0	6.7	0.3 (−9.8 to 10.4)	0.95
Infections (grade 3/4)	14.9	4.4	10.4 (1.7 to 19.2)	<0.05*	19.1	4.4	14.7 (3.1 to 26.3)	<0.05*

(*continued on next page*)

	Acalabrutinib	Lenalidomide + Rituximab	Rate Difference (%)		Acalabrutinib	Lenalidomide + Rituximab	Rate Difference (%)	
	(n = 93)	(n = 44)	Mean (95% CI)	P	(ESS = 64)	(n = 44)	Mean (95% CI)	P
	[A], %	[B], %	[A−B]		[A], %	[B], %	[A−B]	
ORR	73.1	56.8	16.3 (−0.9 to 33.5)	0.06	70.9	56.8	14.1 (−4.2 to 32.3)	0.13
CR	22.6	36.4	−13.8 (−30.4 to 2.8)	0.10	25	36.4	−11.4 (−29.0 to 6.3)	0.21
Diarrhea (any grade)	38.7	65.9	−27.2 (−44.4 to −10.0)	<0.01*	41.5	65.9	−24.4 (−42.8 to −6.0)	<0.01*
Anemia (grade 3/4)	14.0	2.3	11.7 (3.4 to 20.0)	<0.01*	11.6	2.3	9.3 (1.3 to 17.4)	<0.05*
Diarrhea (grade 3/4)	4.3	0.0	4.3 (0.2 to 8.4)	<0.05*	5.6	0.0	5.6 (−0.5 to 11.6)	0.07
Infections (grade 3/4)	6.5	2.3	4.2 (−2.5 to 10.9)	0.22	6.9	2.3	4.6 (−3.2 to 12.4)	0.25
Leukopenia (grade 3/4)	1.1	29.5	−28.5 (−42.1 to −14.8)	<0.001*	1.7	29.5	−27.9 (−41.7 to −14.0)	<0.001*
Neutropenia (grade 3/4)	11.8	65.9	−54.1 (−69.6 to −38.6)	<0.001*	12.2	65.9	−53.7 (−69.7 to −37.8)	<0.001*
Thrombocytopenia (grade 3/4)	4.3	22.7	−18.4 (−31.5 to −5.4)	<0.01*	3.7	22.7	−19.0 (−32.0 to −6.0)	<0.01*

ESS = effective sample size.
Note: ORR and CR based on Independent Review Committee assessment according to the 2007 criteria of Cheson et al were used for the ACE-LY-004 trial.[20,23] Adverse events for acalabrutinib were defined by preferred terms. Patients with missing response data were considered to be nonresponders.
*$P < 0.05$.

The main strengths of this analysis are the comprehensive evaluation of cross-trial heterogeneity and potential sources of bias, the use of IPD for acalabrutinib to adjust for observed cross-trial differences in multiple patient characteristics versus the comparator trials using MAICs, and its consistency with methodological guidance issued by NICE (Decision Support Unit, Technical Support Document 18).[42] The estimates from this analysis could potentially be used to link the single-arm trial of acalabrutinib into a network meta-analysis and as the basis of cost-effectiveness analyses for health care payers and clinicians.

This analysis has several limitations. These limitations include differences in trial characteristics and follow-up durations, which were not fully adjusted for due to a paucity of data (not all trial characteristics were available for all studies). The definition of response was similar across comparators except in the following, which used the older (1999) criteria of Cheson et al[41]: bortezomib, lenalidomide, lenalidomide + rituximab, and temsirolimus.[32–35,37,40] Although these MAICs adjust for observed baseline differences between acalabrutinib and comparator trials, they are comparisons of nonrandomized treatment groups and may therefore be biased by potential unobserved cross-trial differences. The data used in this study come from clinical trial populations with specific patient selection criteria, which may not be representative of a broader relapsed/refractory MCL population. The small initial sample size in ACE-LY-004 (N = 124) contributed to the small ESS in some of the comparisons, which may have obscured real differences in outcomes between therapies that did not reach statistical significance in this analysis. In addition, this analysis is limited in that OS data for acalabrutinib were still relatively immature (33%), whereas PFS had reached the median (53%). Longer duration follow-up data for OS and PFS have become available for several comparators (ibrutinib, lenalidomide, temsirolimus, and ibrutinib + rituximab) since the systematic review supporting this analysis was undertaken. In the present analysis, follow-up durations were similar, and it is recommended that a further analysis comparing PFS and OS is undertaken as longer-term follow-up data also become available for acalabrutinib.

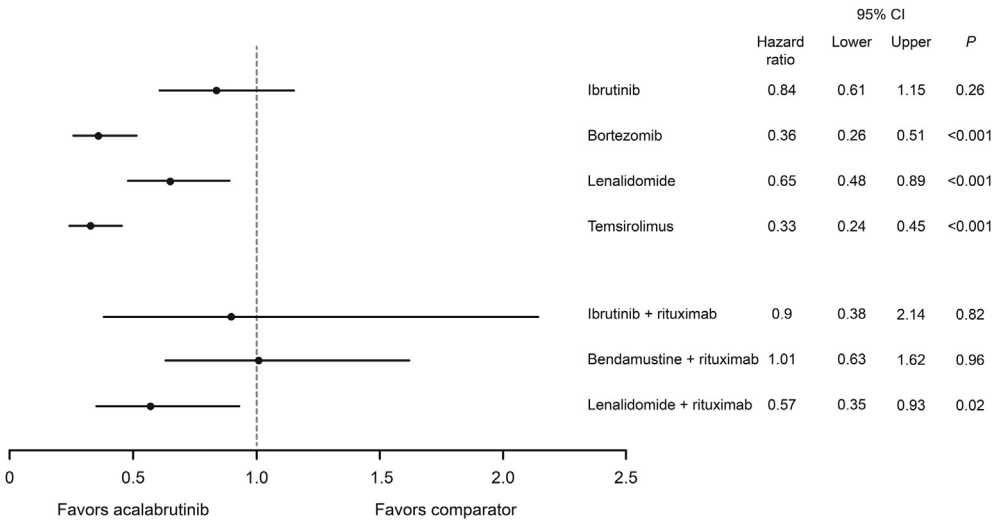

Figure 1. Progression-free survival hazard ratios after matching for acalabrutinib versus comparators.

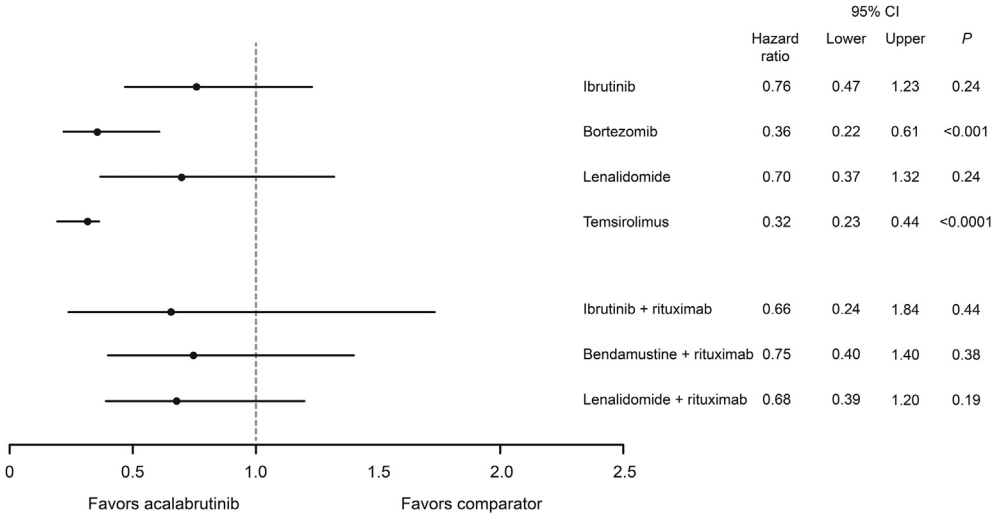

Figure 2. Overall survival hazard ratios after matching for acalabrutinib versus comparators.

Table XI. Progression-free survival (PFS) and overall survival (OS) before and after matching in matching-adjusted indirect comparisons of acalabrutinib versus combination regimens.

Variable	Before Matching, Median, mo		After Matching, Weighted Median, mo	
	Acalabrutinib	Ibrutinib	Acalabrutinib	Ibrutinib
PFS	19.5	12.8	18.0	12.8
OS	NR	25.1	NR	25.1
	Acalabrutinib	Bortezomib	Acalabrutinib	Bortezomib
PFS	19.5	6.7	18.0	6.7
OS	NR	24.0	NR	24.0
	Acalabrutinib	Lenalidomide	Acalabrutinib	Lenalidomide
PFS	19.5	6.3	19.5	6.3
OS	NR	24.9	NR	25.0
	Acalabrutinib	Temsirolimus	Acalabrutinib	Temsirolimus
PFS	22.1	5.4	22.1	5.4
OS	NR	18.0	NR	18.0
	Acalabrutinib	Ibrutinib + Rituximab	Acalabrutinib	Ibrutinib + Rituximab
PFS	19.4	NR	27.7	NR
OS	32.2	NR	32.2	NR
	Acalabrutinib	Bendamustine + Rituximab	Acalabrutinib	Bendamustine + Rituximab
PFS	19.4	17.2	24.8	17.2
OS	NR	38.4	NR	38.4
	Acalabrutinib	Lenalidomide + Rituximab	Acalabrutinib	Lenalidomide + Rituximab
PFS	19.3	11.1	19.21	11.1
OS	NR	24.2	NR	24.2

NR = not reached.

CONCLUSIONS

MCL is a B-cell lymphoma that, while often initially responsive to treatment, has a high rate of relapse. This comparison of targeted therapies used in the treatment of relapsed/refractory MCL has shown that acalabrutinib has the potential to provide higher response rates, with trends for longer PFS and OS, and an improved safety profile.

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Drs. Telford, Song, Signorovitch, and Zhao and Mr. Yao were responsible for designing and conducting the analyses. All authors contributed to the data interpretation, writing and review of the manuscript, and provided final approval of the submitted version.

DISCLOSURES

Drs. Telford and Kabadi are employees and stockholders of AstraZeneca LP. Dr. Abhyankar is an employee and stockholder of Acerta Pharma, a member of the AstraZeneca Group. Drs. Song, Signorovitch, and Zhao and Mr. Yao have acted in a consulting/advisory capacity for AstraZeneca PLC. 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.

REFERENCES

1. Sandoval-Sus JD, Sotomayor EM, Shah BD. Mantle cell lymphoma: contemporary diagnostic and treatment perspectives in the age of personalized medicine. *Hematol Oncol Stem Cell Ther*. 2017;10:99–115.
2. Li J-Y, Gaillard F, Moreau A, et al. Detection of translocation t(11;14)(q13;q32) in mantle cell lymphoma by fluorescence in situ hybridization. *Am J Pathol*. 1999;154:1449–1452.
3. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood*. 1997;89:3909–3918.
4. Smith A, Crouch S, Lax S, et al. Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer*. 2015;112:1575–1584.
5. Wang Y, Ma S. Risk factors for etiology and prognosis of mantle cell lymphoma. *Expert Rev Hematol*. 2014;7:233–243.
6. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006;107:265–276.
7. Dreyling M, Campo E, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv62–iv71.
8. Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol*. 2017;92:806–813.
9. Fisher R, Dahlberg S, Nathwani B, Banks P, Miller T, Grogan T. A clinical analysis of two indolent lymphoma entities: mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): a Southwest Oncology Group study. *Blood*. 1995;85:1075–1082.
10. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. *J Clin Oncol*. 2002;20:1288–1294.
11. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol*. 2005;23:1984–1992.
12. Maddocks K. Update on mantle cell lymphoma. *Blood*. 2018;132:1647–1656.
13. US Food and Drug Administration. TREANDA® (Bendamustine Hydrochloride) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022303lbl.pdf (Accessed October 2019).
14. US Food and Drug Administration. VELCADE (Bortezomib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021602s044lbl.pdf (Accessed October 2019).
15. US Food and Drug Administration. REVLIMID (Lenalidomide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021880s057lbl.pdf (Accessed October 2019).
16. US Food and Drug Administration. IMBRUVICA® (Ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205552s028,210563s003lbl.pdf (Accessed October 2019).
17. US Food and Drug Administration. Rituxan (Rituximab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103705s5457lbl.pdf (Accessed October 2019).
18. European Medicines Agency. Torisel 30 mg (Temsirolimus) Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/torisel-epar-product-information_en.pdf (Accessed October 2019)
19. US Food and Drug Administration. CALQUENCE® (Acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf (Accessed October 2019)
20. European Medicines Agency. Acalabrutinib for the treatment of mantle cell lymphoma: public summary of opinion on orphan designation. https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/16/1625-public-summary-opinion-orphan-designation-acalabrutinib-treatment-mantle-cell-lymphoma_en.pdf (Accessed October 2019)
21. Wu J, Zhang M, Liu D. Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor. *J Hematol Oncol*. 2016;9:21.
22. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391:659–667.
23. Wang M, Rule S, Zinzani PL, et al. Long-term follow-up of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma. *Blood*. 2018;132:2876.
24. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal 2013 Process and Methods Guides No. 92013.

25. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579–586.
26. Latimer N. *NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data*. Sheffield: Report by the Decision Support Unit; 2011. http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf (Accessed October 2019).
27. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12:9.
28. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. *Res Synth Methods*. 2010;1:258–271.
29. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health*. 2012;15:940–947.
30. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics*. 2010;28:935–945.
31. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *Br J Haematol*. 2017;179:430–438.
32. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Ann Oncol*. 2009;20:520–525.
33. Trněný M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. *Lancet Oncol*. 2016;17:319–331.
34. Goy A, Kalayoglu Besisik S, Drach J, et al. Longer-term follow-up and outcome by tumour cell proliferation rate (Ki-67) in patients with relapsed/refractory mantle cell lymphoma treated with lenalidomide on MCL-001(EMERGE) pivotal trial. *Br J Haematol*. 2015;170:496–503.
35. Jurczak W, Ramanathan S, Giri P, et al. Comparison of two doses of intravenous temsirolimus in patients with relapsed/refractory mantle cell lymphoma. *Leuk Lymphoma*. 2018;59:670–678.
36. Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet*. 2016;387:770–778.
37. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2009;27:3822–3829.
38. Czuczman MS, Goy A, Lamonica D, Graf DA, Munteanu MC, van der Jagt RH. Phase II study of bendamustine combined with rituximab in relapsed/refractory mantle cell lymphoma: efficacy, tolerability, and safety findings. *Ann Hematol*. 2015;94:2025–2032.
39. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:48–56.
40. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. *Lancet Oncol*. 2012;13:716–723.
41. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol*. 1999;17:1244.
42. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. *Med Decis Making*. 2018;38:200–211.
43. NCCN. Clinical. *Guidelines in Oncology (NCCN Guidelines) B-Cell Lymphomas Version 4.2018*. May 15, 2018.
44. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369:507–516.
45. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) Study. *J Clin Oncol*. 2013;31:3688–3695.
46. Zinzani PL, Vose JM, Czuczman MS, et al. Long-term follow-up of lenalidomide in relapsed/refractory mantle cell lymphoma: subset analysis of the NHL-003 study. *Ann Oncol*. 2013;24:2892–2897.
47. Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *N Engl J Med*. 2015;372:944–953.
48. Ansell SM, Tang H, Kurtin PJ, et al. Temsirolimus and rituximab in patients with relapsed or refractory mantle cell lymphoma: a phase 2 study. *Lancet Oncol*. 2011;12:361–368.
49. Hess G, Karola W, LaRosee P, et al. Temsirolimus in combination with bendamustine and rituximab (BeRT) for the treatment of relapsed mantle cell and follicular lymphoma: final Phase I/II results. *Blood*. 2016;128:2977.
50. Tongbram V, Sengupta N, Gaudig M, et al. Comparative effectiveness of treatments for relapsed or refractory

mantle cell lymphoma (R/R MCL), using matching adjusted indirect comparison. *Value Health*. 2014;17: A614–A615.
51. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126:739–745.
52. Wang M, Goy A, Martin P, et al. Efficacy and Safety of Single-Agent Ibrutinib in Patients with Mantle Cell Lymphoma Who Progressed after Bortezomib Therapy. *Blood*. 2014;124, 4471–4471.

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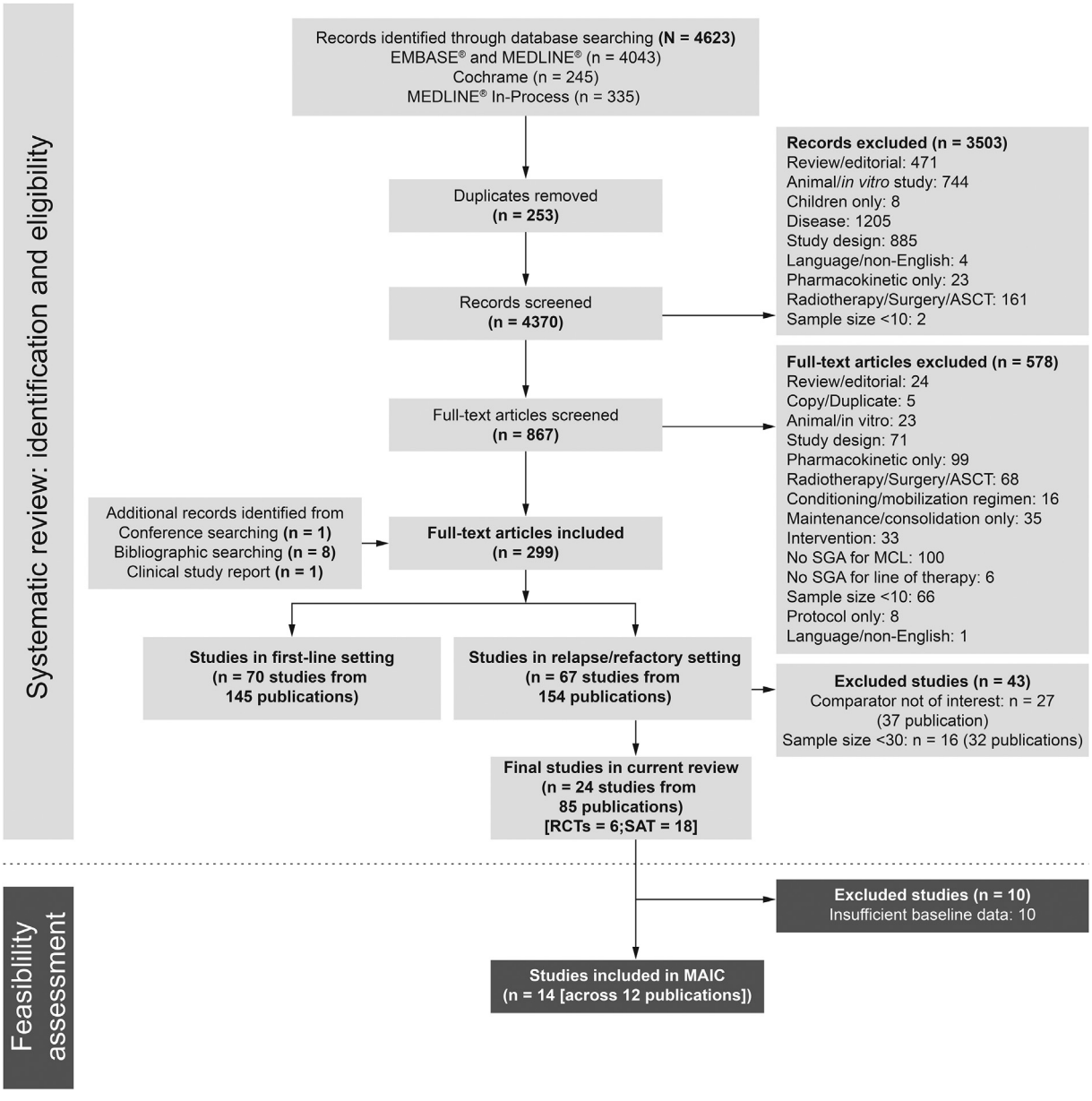
APPENDIX A



ASCT: autologous stem cell transplant, EMBASE: Excerpta Medica Database; MAIC: matching-adjusted indirect comparison, MEDLINE: Medical Literature Analysis and Retrieval System Online, RCT: randomized controlled trial, SAT: single-arm trial

Figure S1. Flow of trials through the systematic review process and feasibility assessment.