Medicinrådet

Bilag til Medicinrådets vurdering af acalabrutinib til behandling af voksne patienter med recidiverende eller refraktær mantle celle lymfom (MCL), som ikke tidligere har modtaget behandling med BTK-inhibitor

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. acalabrutinib
2. Amgros' forhandlingsnotat vedr. acalabrutinib
3. Ansøgning vedr. acalabrutinib

Medicinrådet
Dampfærgevej 21-23, 3. Sal
2100 København Ø

Notat til Medicinrådets evalueringsrapport på Calquence (acalabrutinib) til behandling af voksne patienter med recidiverende eller refraktær mantle celle lymfom (MCL), som ikke tidligere har modtaget behandling med BTK-inhibitor.
AstraZeneca vil gerne takke Medicinrådets for deres vurdering af Calquence og muligheden for at kommentere på evalueringsrapporten. AstraZeneca deler Medicinrådets vurdering af, at acalabrutinib og ibrutinib ikke adskiller sig markant i effekt, og at acalabrutinib kan have en mere favorabel bivirkningsprofil for visse patienter med specifikke risikofaktorer sammenlignet med ibrutinib.

I evalueringsrapporten henvises der til, at der ikke er indsendt en analyse mod kemoterapi, i samme afsnit beskrives der at kemoterapi ikke er en relevant komparator for patienter der er kandidater til BTKi.
AstraZeneca enig med Medicinrådet, i at kemoterapi ikke er en relevant komparator,da Ibrutinib er nuværende behandlingspraksis for de relevante patienter,
Derudover har andre virksomheder indsendt sammenligninger mod ibrutinib for indikationer, som ikke tidligere er vurderet af Medicinrådet. Medicinrådet har eksempelvis vurderet zanubrutinib til Waldenströms makroglobulinæmi; her var det, selv om ibrutinib ikke tidligere var vurderet af Medicinrådet, stadig muligt at sammenligne zanubrutinib med ibrutinib og anbefale zanubrutinib uden yderligere sammenligninger.(1) Dette forhold er også beskrevet i denne evaluering.

Slutteligt, vil vi gerne takke Medicinrådet for en god proces.

Referencer

1. https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/z/zanubrutinib-brukinsa-lymfekraeft

Venlig Hilsen

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22.12.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	AstraZeneca
Lægemiddel	Calquence (acalabrutinib)
Ansøgt indikation	Monoterapi til voksne patienter med recidiverende eller refraktær mantle celle lymfom (MCL), som ikke tidligere har været behandlet med en Bruton's tyrosin kinase inhibitor (BTKi).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Calquence (acalabrutinib):

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Calquence	100 mg /(60 stk. Tabletter)	40.994,30	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Calquence	100 mg, (60 stk.)	200 mg daglig, oral	[redacted]	[redacted]
Imbruvica	560 mg, (28 stk.)	560 mg daglig, oral	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Anbefalet		Link til anbefaling
England	Under vurdering		Link til status

Sverige	Anbefalet	Anbefalet til CLL samt MCL i anden linje	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Acalabrutinib for the treatment of adult patients with MCL who have received at least one prior therapy

Contact information

Contact information	
Name	**[Name / company]**
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E-mail	Jannick Burmester
Name (External representation)	**[Name / company]**
Title	
Phone number	[Include country code]
E-mail	

[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to medicinraadet@medicinraadet.dk.]

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Tables and Figures

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Abbreviations

Abbreviation	Definition
AE	Adverse event
ASCT	Autologous stem cell transplant
BCR	B-cell receptor
BI	Budget impact
BID	Twice daily
BIM	Budget impact model
BLNK	B-cell linker
BNF	British National Formulary
BR	Bendamustine plus rituximab
BTK	Bruton tyrosine kinase
Ca2+	Calcium ion
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CMA	Cost-minimization analysis
CMM	Cost-minimization model
CNS	Central nervous system
CR	Complete response
Cru	Unconfirmed complete response
CT	Computed tomography
CVAD	Cyclophosphamide, vincristine, doxorubicin, dexamethasone
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQoL 5-dimension questionnaire
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	Europe
EU5	European Union 5 (France, Germany, Italy, Spain, and United Kingdom)
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration

FDG-PET	[18F]fluorodeoxyglucose-positron emission tomography
GI	Gastrointestinal
HCRU	Healthcare resource-use
HDT	High-dose therapy
HDAC	High-dose cytarabine
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
ICER	Incremental cost-effectiveness ratio
ICT	Investigator's choice of therapy
IHP	International Harmonization Project
IKK	Inhibitor of kappa-B kinase
INV	Investigator assessment
IQR	Interquartile range
IRC	Independent Review Committee
IV	Intravenous
IWG	International Working Group
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LY	Life year
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MCL	Mantle cell lymphoma
MIPI	Mantle Cell Lymphoma Prognostic Index
MoA	Mechanism of action
mTOR	Mammalian target of rapamycin
N/A	Not available
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NFAT	Nuclear factor of activated T-cells
NFκB	Nuclear factor kappa-light-chain enhancer of activated B cells
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PEPC	Prednisone, etoposide, procarbazine, and cyclophosphamide
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
PI	Prescribing information
PK	Pharmacokinetics
PKCβ	Protein kinase C beta
PLCɣ2	Phospholipase-gamma-2

PMPM Per member per month
PO Orally
PPS Post-progression survival
PR Partial response
PSA Probabilistic sensitivity analysis
PSM Partitioned survival model
PSS Personal Social Services
PTMPM Per treated member per month
QALY Quality-adjusted life year
QD Daily
QLQ-C30 Quality of life questionnaire cancer-30
QTc Corrected QT interval
QW Weekly
RB Rituximab plus bendamustine
R-BAC Rituximab, bendamustine, cytarabine
R-CHOP Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
R-DHAP Rituximab, dexamethasone, high-dose cytarabine, cisplatin
RCC Renal cell carcinoma
RCT Randomized controlled trial
RD Risk difference
RI Rituximab plus ibrutinib
RL Rituximab plus lenalidomide
R/R Relapsed/refractory
SC Subcutaneous
SCT Stem cell transplant
SD Stable disease
SEER Surveillance, Epidemiology and End Results Program
SEM Standard error of the mean
SoC Standard of care
SYK Spleen tyrosine kinase
TEAE Treatment-emergent adverse event
TRAE Treatment-related adverse event
UK United Kingdom
US United States
USA United States of America
VcR-CVAD Rituximab, bortezomib, modified hyper-cyclophosphamide, doxorubicin, vincristine, dexamethasone
VTE Venous thromboembolism

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Calquence
Generic name	Acalabrutinib
Therapeutic indication as defined by EMA	Acalabrutinib is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	L01EL02
Combination therapy and/or co-medication	Monotherapy
(Expected) Date of EC approval	2 June 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	• Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). • Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. • Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT). • Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Overview of the medicine		
	• Calquence as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) not previously treated with a BTK inhibitor.	
Other indications that have been evaluated by the DMC (yes/no)	• Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). • Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.	
Joint Nordic assessment (JNHB)	No	
Dispensing group	BEGR	
Packaging – types, sizes/number of units and concentrations	Drug name	Calquence
	Unit number	099916
	Strength	100 mg
	Package	60 stk. tablets

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Indication relevant for the assessment	Calquence as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) not previously treated with a BTK inhibitor.
Dosage regiment and administration	Acalabrutinib (100 mg) is administered orally twice daily in repeated 30-day cycles until progression or unacceptable side effects
Choice of comparator	Given their similar mechanisms of action and overlapping regulatory labels patients eligible for ibrutinib therapy are also expected to be eligible candidates for treatment with acalabrutinib. Ibrutinib is widely utilized for the treatment of

Summary	
	relapsed MCL in Denmark and internationally and will serve as the relevant comparator for acalabrutinib.
Prognosis with current treatment (comparator)	According to findings from a Danish real-world, population-based study, the median PFS and OS after initiating ibrutinib therapy for R/R MCL are 6 months and 12 months, respectively (1).
Type of evidence for the clinical evaluation	ITC (MAIC)
Most important efficacy endpoints (Difference/gain compared to comparator)	Safety PFS OS
Most important serious adverse events for the intervention and comparator	Adverse events grade 3 and above included in the analysis are (frequency in %): • Neutropenia (intervention: 15%, comparator 17%) • Thrombocytopenia (intervention: 5.3%, comparator 12.4%) • Pneumonia (intervention 8.7%, comparator 12.7%) • Anemia (intervention 14.8%, comparator 10.0%) • Atrial fibrillation (intervention 0%, comparator 6.2%)
Impact on health-related quality of life	Clinical documentation: EORTC QLQ-C30 HRQOL is not extensively reported in the pivotal studies on ibrutinib, making it challenging to draw meaningful comparisons between acalabrutinib and ibrutinib in the context of RR MCL. However, a direct comparison between acalabrutinib and ibrutinib has been conducted in RR CLL through the ELEVATE RR study, a Phase 3 trial evaluating acalabrutinib versus ibrutinib in high-risk RR CLL. Although there are differences in pathology and dosing of ibrutinib between MCL and CLL, the patients in these studies are of a similar age group. Despite its limitations, this method may offer the most solid basis for comparing the HRQOL of the two treatments The difference in mean change from baseline between arms across all timepoints was + 1.32 (95% CI [- 2.75; 5.38]; p=0.523) in favor of acalabrutinib, but the difference was not statistically significant.

Summary	
	Health economic model: HRQoL not used in the cost-minimization analysis, but acalabrutinib is expected to have equal efficacy with fewer adverse events.
Type of economic analysis that is submitted	Type of analysis: Cost-minimizing
Data sources used to model the clinical effects	LY-004 clinical trial (NCT02213926) PCYC-1104 clinical trial (NCT01236391) SPARK clinical trial (NCT01599949) RAY clinical trial (NCT01646021)
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	-796 831 DKK
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Incidence: 26 every year Prevalence: N/A
Budget impact (in year 5)	-22 087 852 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL) with complex pathophysiology. In Denmark, the median age at diagnosis is 65, and MCL represents about 6–9% of NHL cases in Western Europe (2). Primarily affecting older patients, MCL poses significant treatment challenges and is generally considered incurable (2, 3). This section outlines the disease's pathophysiology, clinical presentation, prognosis, and impact on quality of life, providing context for MCL management and unmet clinical needs.

Pathophysiology

MCL features abnormal B lymphocytes in the mantle zone of lymph nodes (3). Most cases are CD5 and SOX11 positive, with the genetic abnormality involving the t(11;14)(q13;q32) translocation being the most common driver of MCL pathogenesis. This translocation is present in more than 95% of patients and leads to the overexpression of cyclin D1, promoting cell division and proliferation resulting in the accumulation of abnormal cells (2, 4, 5).

Per the International Consensus Classification (ICC)/WHO 2022, MCL can be divided into nodal and non-nodal subgroups. Nodal MCL, constituting 80%-90% of cases, has a more aggressive course, characterized by unmutated IGHV and SOX11 overexpression. Non-nodal leukemic MCL, typically presents with a more indolent course and mutated IGHV and SOX11 negativity. Additionally, blastoid and pleomorphic variants are distinguishable and represent high-risk MCL subtypes (6, 7). Other predictors for unfavorable outcomes include high Ki-67 (≥30%), and TP53 abnormalities (8, 9).

Clinical Presentation

Many MCL patients do not experience any symptoms during early stages of the disease, however, patients may eventually seek medical help due to persistent swelling of lymph nodes. Some patients may also develop non-specific symptoms such as lack of appetite, nausea, abdominal swelling and/or pain (3). At advanced stages, when the disease has spread to extra-nodal sites, patients may present with widespread systemic symptoms, such as fever, night sweats, unexplained weight loss and fatigue (10).

Due to the aggressive nature of MCL and often asymptomatic early stages, over 80% of patients present with advanced-stage disease (stage III or IV), typically characterized by lymphadenopathy and involvement of the liver, spleen, bone marrow, and

gastrointestinal tract (11). Diagnosis follows WHO guidelines and involves histological examination of surgical biopsies, immunophenotyping, and genetic testing. Diagnostic imaging assesses lymph node enlargement and potential extra-nodal involvement, along with a complete blood test (2, 12). Most patients require treatment at diagnosis, while a minority may be managed initially with a "watch and wait" (W&W) approach (13, 14).

Staging of MCL is performed using the Lugano staging system for MCL which is based on the Ann Arbor system for NHLs (15).

Patient Prognoses

Despite the availability of effective treatments, MCL remains largely incurable. According to a leading Danish expert in MCL, approximately 80% of newly diagnosed patients start systemic treatment, with the choice of therapy being guided by the patient's ability to tolerate intensive regimens. For young and fit patients in Denmark, chemoimmunotherapy followed by autologous stem-cell transplantation represents the standard of care, offering high response rates and extended progression-free survival (2). Conversely, older or more frail patients often experience increased toxicity with dose-intensive therapies, making treatment with bendamustine-rituximab the preferred standard of care for this population (2, 16).

While there is a lack of Danish studies detailing the prognosis of MCL patients, the Swedish nationwide real-world evidence project, MCL*complete,* examining MCL patients diagnosed between 2006 and 2018, provides valuable insights. The majority of patients identified in the Swedish Lymphoma Registry received chemoimmunotherapy in front line, with the most common regimens being BR (28.9%), the Nordic MCL2 protocol (27.7%), and R-CHOP (13.4%). The median PFS was 2.7, 5.1, and 1.5 years, while the median OS was 4.1, 11.7, and 2.9 years for BR, Nordic MCL2, and R-CHOP, respectively. During a median follow-up of 3.9 years from primary diagnosis, 46% experienced at least 1 relapse, with 86.7% of these receiving second-line treatment (13).

In Denmark, the BTKi, ibrutinib, is the standard of care for patients with relapsed/refractory (R/R) MCL (2). To assess the treatment outcomes of ibrutinib in an R/R setting, a real-world, population-based study has been conducted. This study included 146 Danish patients diagnosed between 2010 and 2022 who received ibrutinib as a second-line or later therapy. The findings revealed that the median PFS and OS after initiating ibrutinib therapy were 6 months and 12 months, respectively. Adverse events resulted in the discontinuation of ibrutinib in 15% of patients, dose reduction in 16%, and were assessed as directly related to death in 8% of cases (1).

In addition to treatment regimens, several clinical and biological characteristics are recognized as prognostic factors for MCL. Higher age, poorer ECOG performance status, elevated lactate dehydrogenase (LDH), and a higher white blood cell count (WBC) are independently associated with shorter overall survival among MCL patients. These factors are part of the simplified Mantle Cell International Prognostic Index (MIPI), which stratifies risk into low, intermediate, and high categories based on assigned points(17).

Other prognostic factors that correlate negatively to OS include TP53 aberrations, Ki-67 (≥30%), and blastoid and pleomorphic histology (9, 17, 18).

Impact on Quality of Life

MCL significantly impacts the health-related quality of life (HRQoL) due to its aggressive nature and the side effects of treatment regimens. Patients often experience a decline in physical, cognitive, and role functioning following induction chemotherapy, with HRQoL potentially stabilizing or modestly improving after maintenance therapy (19).

3.2 Patient population

Mantle cell lymphoma is a rare form of B-cell neoplasm, accounting for 6%-9% of non-Hodgkin's lymphomas in Western Europe. MCL occurs more frequently in men than in women, with a ratio of 3:1. The median age at the time of diagnosis in Denmark is 65 years (2). The annual incidence rate of MCL in Denmark has shown an upward trend over the years, currently estimated at approximately 1.5 per 100,000, compared to 0.9 per 100,000 reported in a Danish population-based study from 1992 to 2000 (20, 21). Table 1 describes the annual incidence of MCL in Denmark from 2020 to 2024. Data from 2020 to 2023 were obtained from the Danish Lymphoma Database (LYFO), and the incidence rates per 100,000 has been calculated using the respective annual population sizes, reported by *Danmarks Statistik* (20, 22). The incidence of MCL for 2024 has not yet been published and was, therefore, projected by calculating the average from the preceding four years. To our knowledge, the prevalence of MCL has not been documented either in Denmark or globally. However, a Danish MCL expert estimates the prevalence to be around 4 per 100,000 in Denmark. Based on this estimate, the annual population sizes were used to calculate the predicted number of patients living with MCL in Denmark between 2020 and 2024 (22). The results are described in Table 1.

Table 1 Incidence and prevalence of MCL in Denmark in the past 5 years.

Year	2020	2021	2022	2023	2024
Incidence in Denmark (per 100, 000) (20)	84 (1.44)	86 (1.47)	92 (1.57)	90 (1.52)	88 (1.48)
Prevalence in Denmark (per 100,000)	233 (4)	234 (4)	236 (4)	238 (4)	239 (4)
Global prevalence *	N/A	N/A	N/A	N/A	N/A

* For small patient groups, also describe the worldwide prevalence.

Treatment with acalabrutinib as monotherapy is intended for adult patients with relapsed or refractory MCL who have not previously been treated with a BTK inhibitor (23). In Denmark, there is currently no difference in how patients in the R/R setting are treated; therefore, acalabrutinib monotherapy is relevant for patients irrespective of their first-line treatment (2).

According to Danish MCL experts, approximately 80% of newly diagnosed patients start systemic therapy at diagnosis. The remaining 20% of patients include those with asymptomatic indolent disease managed through a watch and wait strategy, patients in stages I-IIA who are suitable for radiation therapy, and those who are compromised and receiving palliative care (2).

As detailed in *Section 3.1*, the Swedish real-world evidence project, *MCLcomplete*, observed that 46% of patients initiating MCL treatment experienced at least one relapse during follow-up. Given that the majority of patients in this study received chemotherapy regimens comparable to the standard-of-care treatments for first-line MCL in Denmark, it is reasonable to assume that the observed relapse rate is also representative of Danish patients (2, 13). According to a leading Danish MCL expert, approximately 80% of patients who relapse or exhibit refractory disease after first-line therapy are candidates for treatment with BTK inhibitors.

Based on the above data and assumptions, the estimated annual number of patients eligible for acalabrutinib monotherapy was calculated and is presented in Table 2.

Table 2 Estimated annual number of MCL patients eligible for treatment with acalabrutinib monotherapy in Denmark.

	Proportion	Number of patients per year
Incidence of MCL in Denmark (20)	100%	88 (average from 2020-2023)
Proportion of patients starting systemic front-line therapy	80%	70
Proportion of patients who relapse or are refractory to 1.L therapy (13)	46%	32
Proportion of R/R patients suitable for acalabrutinib monotherapy	80%	26

Table 3 describes the estimated number of MCL patients eligible for treatment with acalabrutinib monotherapy in the coming years, assuming stable incidence (20). Population growth has not been accounted for due to the small numbers.

Table 3 Estimated number of patients eligible for treatment in the coming years.

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	26	26	26	26	26

3.3 Current treatment options

The current Danish treatment guideline for MCL is closely aligned with the 2017 ESMO guidelines. Detailed flowcharts illustrating both first-line and subsequent treatment approaches can be found in the Danish mantel cell lymphoma guideline(2, 24).

Current 1L treatment options

MCL is often diagnosed at an advanced stage. However, a small subset of patients presents with either indolent or localized forms of the disease. These patients may be managed with a "watch and wait" approach or localized radiotherapy, respectively. Additionally, compromised patients receive palliative care (2).

For the majority of MCL patients, initiating systemic therapy at diagnosis is critical. The choice of systemic treatment is determined by the patient's ability to tolerate the therapy. Young and fit patients typically receive an intensive frontline induction regimen consisting of immunochemotherapy, which is followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT). Post-ASCT, patients receive rituximab maintenance every two months for a duration of three years (2).

For patients who are ineligible for ASCT due to age or comorbidities, treatment with R-Bendamustine is recommended. In some cases, R-Bendamustine in combination with cytarabine (R-BAC) is utilized. Both treatment regimens are followed by rituximab maintenance therapy (2).

Current treatment options following relapse

Although some patients obtain prolonged remission after 1L chemoimmunotherapy, many will need several lines of treatment (13). Following relapse on front-line therapy, current treatment options include both immunochemotherapy and targeted approaches. When considering treatment with immunochemotherapy at relapse, the choice of treatment depends on the outcome of the previously administered therapy. In cases of early relapse (within 12-24 months), a non-cross-resistant regimen should be preferred (e.g., bendamustine following CHOP and vice versa). The addition of rituximab may be considered if the prior immunochemotherapy resulted in a remission duration greater than 6-12 months (2).

In the landscape of treatment options for R/R disease, targeted therapies have become increasingly significant. According to a leading Danish MCL expert, most patients in this setting are now treated with a targeted approach. The current Danish treatment guidelines for R/R disease include ibrutinib and lenalidomide, both with and without rituximab (25-28). In the R/R setting, monotherapy with BTK inhibitors has become the preferred salvage treatment, based on superior efficacy compared with conventional chemotherapy or other targeted therapies. BTKis are also generally well tolerated and can be administered to most patients irrespective of age (29-31). At the time of the publication of the Danish MCL treatment guidelines, ibrutinib was the only approved BTKi for R/R MCL in Europe. It is administered once daily at a dose 560 mg until disease progression or tolerability issues (2, 29). According to a Danish MCL expert, approximately 80% of patients who relapse following front-line immunochemotherapy in Denmark today, are treated with ibrutinib.

For detailed prognostic expectations related to current MCL treatments, please refer to Section 3.1, "Patient Prognoses."

Given the similar target and mechanisms of action of ibrutinib and acalabrutinib, patients eligible for ibrutinib are also expected to be suitable candidates for treatment with acalabrutinib. As mentioned, ibrutinib is extensively used for treating relapsed MCL both in Denmark and internationally and will serve as the relevant comparator for acalabrutinib.

3.4 The intervention

Overview of intervention	
Indication relevant for the assessment	Calquence as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) not previously treated with a BTK inhibitor.
ATMP	NA
Method of administration	Acalabrutinib is administered orally twice daily
Dosing	100 mg twice daily
Dosing in the health economic model (including relative dose intensity)	100 mg twice daily, RDI 100%. The assumption of 100% relative dose intensity is based on no reported differences in the median RDI of LY004 (98.6%) and the pooled ibrutinib results (98.4%)
Should the medicine be administered with other medicines?	Acalabrutinib is used as monotherapy in relapsed MCL
Treatment duration / criteria for end of treatment	Progressive disease or unacceptable toxicities

Overview of intervention		
Necessary monitoring, both during administration and during the treatment period	Full blood test should be performed during the treatment period	
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	NA	
Package size(s)	Strength	100 mg
	Package	60 stk. tablets

3.4.1 Description of ATMP

NA

3.4.2 The intervention in relation to Danish clinical practice

Acalabrutinib is expected to replace ibrutinib in relapsed mantle cell lymphoma patients as treatment with acalabrutinib is associated with better tolerance and a lower occurrence of safety events, especially cardiovascular events, see comparative results in section 7.1.3 and MAIC publication (32). The mean doses in clinical practice are expected to be similar to the dose in the ACE-LY-004 trial.

3.5 Choice of comparator(s)

An assessment of acalabrutinb versus placebo, as suggested in the methods guide, is not possible and could not accurately depict the current clinical practice for the relevant patients, and therefore, would not provide value to the assessment.

According to a leading Danish MCL expert and the DMC expert committee that was consulted during a dialogue meeting, the only relevant comparator for this assessment is ibrutinib. If acalabrutinib is reimbursed it is expected to displace ibrutinib. Both treatments have similar mechanisms of action and are expected to be used in a similar way.

Ibrutinib has not been evaluated by the DMC specifically for relapsed MCL however, it was recommended by KRIS on 10 December 2014 (33). A similar scenario occurred when the DMC assessed zanubrutinib for Waldenström's macroglobulinemia. In that instance, despite the fact that ibrutinib had not previously been reviewed by the DMC, it was still possible to compare zanubrutinib to ibrutinib and recommend zanubrutinib for Waldenström's macroglobulinemia without other comparisons. (34)

[redacted]

xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Overview of comparator	
Generic name	Ibrutinib
ATC code	L01EL01
Mechanism of action	BTKi
Method of administration	Oral
Dosing	560 mg once daily
Dosing in the health economic model (including relative dose intensity)	560 mg once daily RDI=100% The assumption of 100% relative dose intensity is based on no reported differences in the median RDI of LY004 (98.6%) and the pooled ibrutinib results (98.4%)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Until progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	560 mg x 28 tablets

3.6 Cost-effectiveness of the comparator(s)

Ibrutinib has not been assessed by the DMC in the context of relapsed MCL. However, as ibrutinib is a well-established SOC in Denmark and internationally, including Norway, Finland and Sweden, we are considering it a cost-effective treatment option. Furthermore, the cost-minimization analysis will show cost savings by using acalabrutinib instead of ibrutinib. Both ibrutinib and acalabrutinib have been reimbursed for relapsed MCL in Norway and Sweden:

- Links to assessments in Norway:
  - Ibrutinib: https://www.nyemetoder.no/metoder/ibrutinib-imbruvica-indikasjon-ii/
  - Acalabrutinib: https://www.nyemetoder.no/metoder/id2025_042/
- Links to TLV assessments in Sweden:
  - Ibrutinib:
    - https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2022-09-23-imbruvica-ingar-i-hogkostnadsskyddet-med-

begransning-for-ytterligare-en-patientgrupp.html?query=imbruvica%20mcl

- https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2023-06-19-imbruvica-ingar-i-hogkostnadsskyddet-med-forandrad-formansbegransning.html?query=imbruvica%20mcl

- Acalabrutinib: https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2025-07-14-calquence-ingar-i-hogkostnadsskyddet-med-begransning-for-ytterligare-en-patientgrupp.html?query=calquence

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 4 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall response rate (ORR) (as per Cheson 2014 and Cheson 2007)	**LY-004: (35)** Cheson 2007 and Cheson 2014 DCO: 4 December 2020 Median 38.1 months of follow-up **Pooled Ibrutinib(36-38):** Cheson 2007, DCO: 28 February 2017 Median 15.2 months of follow-up	ORR was defined as the proportion of subjects who achieved either a CR or PR at any time during the treatment period based on investigator assessment according to the 2014 Lugano classification for non-Hodgkin lymphoma	CT and PET-CT based on investigator assessment according to the Lugano classification for non-Hodgkin lymphoma The rate of response is classified according to the Cheson 2014 and 2007 clinical guidelines based on CT and PET-CT.
Progression-free survival (PFS)	**LY-004: (35)** Median 38.1 months of follow-up **Pooled Ibrutinib (36-38) trials**:	PFS was defined as the interval from the start of study treatment to the first documentation of objective MCL disease progression	Investigator and BICR assessed.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	Median 41.4 months of follow-up	per investigator assessment or death from any cause.	
Overall survival (OS)	**LY-004: (35)** Median 38.1 months of follow-up **Pooled Ibrutinib (36-38) trials:** Median 41.4 months of follow-up	OS is defined as the time from randomization to death from any cause. OS is defined as time from first treatment registered in registry X to date of death from any cause.	The duration of OS was measured from the time of first study treatment administration until the date of death from any cause. Subjects who were known to be alive as of their last known status were censored at their last date known to be alive.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

The most persuasive outcome to demonstrate efficacy in anticancer trials is OS and other possible efficacy endpoints include PFS and patient-reported outcomes (39). Data on ORR, DoR, time to progression (TTP)/PFS and confirmed ORR are considered suitable markers of anti-tumor activity.

Additionally, in DMC´s treatment guideline for the treatment of chronic lymphocytic leukemia for another hematologic malignancy, the DMC pre-specified OS, PFS, and QoL (assessed via the EORTC QLQ-C30) as critical or important efficacy measures. All of these outcome measures were defined as endpoints in the LY-004 trial and ibrutinib trials. Further, the conclusion that acalabrutinib and ibrutinib are sufficiently similar to justify a cost-minimization analysis was based on outcomes which directly represent treatment goals for MCL patients in Denmark: OS, PFS and adverse events.

4. Health economic analysis

4.1 Model structure

A cost-minimization analysis between acalabrutinib monotherapy and ibrutinib monotherapy was performed. This model choice was confirmed in a dialogue meeting with the DMC.

4.2 Model features

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	R/R MCL patients	Trial population relevant for clinical practice
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Five years	Both treatments are assumed to have to equal efficacy and are to be used to progression or unacceptable toxicity. Five year time horizon chosen to align with budget impact calculations.
Cycle length	Annual costs summed for five years	Cost-minimization analysis
Half-cycle correction	No	Cost-minimization analysis
Discount rate	3.5 % for costs	According to DMC guidelines. Discounting for effects not relevant since the analysis is a cost-minimization analysis.
Intervention	Acalabrutinib 200 mg daily (100 mg twice daily)	Intervention in scope for application
Comparator(s)	Ibrutinib 560 mg daily	According to national treatment guideline. Validated by Danish clinical expert
Outcomes	Drug acquisition costs Adverse event costs	Cost-minimization analysis

4.3 Model choice rationale

We propose a cost-minimization analysis limited to treatment costs for acalabrutinib versus ibrutinib in R/R MCL. This approach is justified because the indirect treatment comparison (ITC, presented in Section 7) demonstrates no statistically significant differences in progression-free survival or overall survival, and available data indicate comparable treatment duration and discontinuation patterns across BTK inhibitors. Previous DMC assessments for CLL R/R (authorised 15 June 2022 (40)) concluded time to progression and overall survival for acalabrutinib and ibrutinib are similar with no documented differences. The DMC has also placed zanubrutinib (another BTKi) directly into the CLL guidelines (21 February 2024 (41)), affirming that BTKis are considered

equivalent in efficacy and safety. In a treat-to-progression setting, where patients remain on therapy until progression or intolerable toxicity, equivalent time-to-event outcomes mean additional modeling of progression or survival would not change the relative comparison. Therefore, a cost-only framework captures the relevant differences between these therapies without introducing uninformative complexity.

Previous simple cost minimization analyses submitted to the DMC, such as the assessments for upadacitinib (Rinvoq) and acoramidis (Beyonttra), have been accepted without modeling of progression data. For atopic eczema in the upadacitinib assessment (authorized 25 Jan 2023 (42), the Medicines Council chose to conduct a cost-minimzation analysis instead of a cost-utility analysis (which was originally submitted by the company) as it accepted the ITC showing equivalence to the comparator. The DMC did not include differences in efficacy in the health economic assessment as they did not consider there to be a significant difference in the relevant endpoints between the intervention and the comparator. In the acoramidis assessment for transthyretin amyloidosis with cardiomyopathy (authorised 21 May 2025(43), only drug costs over a time horizon of one year were compared, with a relative dose intensity of 100%. Acoramidis is taken daily until death (event) or unacceptable toxicity, this is similar to the BTKis that are taken daily until progression (event), death (event) or unacceptable toxicity. No time-to-event data were included in the cost-comparison.

In summary, the evidence presented in this documtent and DMC precedents indicate equivalence in efficacy, treatment duration, and discontinuation for BTK inhibitors, including acalabrutinib and ibrutinib. Under these conditions, a cost-only cost-minimization analysis is the methodologically appropriate and consistent approach.

5. Overview of literature

5.1 Literature used for the clinical assessment

AstraZeneca, clinical experts, and the DMC Secretariat at the dialogue meeting agreed that the most appropriate comparator for acalabrutinib monotherapy in R/R MCL is ibrutinib monotherapy.

As no randomized, head-to-head trial comparing acalabrutinib and ibrutinib in this setting exists, the pivotal trials serve as the primary sources of evidence: LY-004 for acalabrutinib, and PCYC-1104, SPARK, and RAY for ibrutinib A pooled analysis of individual patient data (IPD) from the ibrutinib trials—PCYC-1104 (n=111), SPARK (n=120), and RAY (n=139), totalling 370 patients—has been published, incorporating data from multiple follow-up time points (23, 44-47). This pooled dataset was used in a published MAIC, conducted by AstraZeneca, which compared patient-level data from LY-004 with the pooled ibrutinib population (37, 38, 48, 49).

The initial MAIC was published in 2019 based on the data available at the time. For this clinical assessment, the most recent MAIC published in 2024 is used(32). This analysis

includes updated data with median follow-up times of 38.1 months for LY-004 and 41.4 months for the pooled ibrutinib trials (49). The 2024 MAIC is considered the most relevant and robust comparison currently available between acalabrutinib and ibrutinib monotherapy in R/R MCL. As such, we do not report an SLR. The SLR can be shared upon request.

As mentioned, acalabrutinib and ibrutinib have not been compared in any head-to-head Phase 3 studies in MCL, which is a limitation when evaluating these treatments for this indication. However, head-to-head Phase 3 studies of acalabrutinib vs ibrutinib exist in other hematologic malignancies. Notably, acalabrutinib and ibrutinib were compared directly in the ELEVATE-RR study, a Phase 3 randomized controlled trial conducted in patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL) (50). Efficacy and safety data from ELEVATE-RR are provided in **Appendix K.**

Table 6 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
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. (51)	LY-004	NCT02213926	Start: 02/03/2015 Completion: 04/12/2020 Data cut-off: 04/12/2020 Future data cut-offs: NA	Acalabrutinib vs ibrutinib
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;387:770e778 (31)	MCL3001 (RAY)	NCT01646021	Start: 10/12/2012 Completion: 05/06/2015 Data cut-off: 15/12/2016 Future data cut-offs: NA	Included in pooled ibrutinib population
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;126:739e745 (52)	PCYC-1104	NCT01236391	Start: 02/2011 Completion: 01/2014 Data cut-off: 01/2014 Future data cut-offs: NA	Included in pooled ibrutinib population
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, 4471e4471.(53)	MCL2001 (SPARK)	NCT01599949	Study Start: 2012-08 Completion: 2015-05 Data cut-off: 2015-05	Included in pooled ibrutinib population

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Rule, S., et al. (2017). "Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies", https://doi.org/10.1111/bjh.14870	MCL3001 (RAY) PCYC-1104 MCL2001 (SPARK)	NCT01646021 NCT01236391 NCT01599949	See above	Acalabrutinib vs ibrutinib
Rule S., et al. (2019) "Long-Term Outcomes with Ibrutinib Versus the Prior Regimen: A Pooled Analysis in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) with up to 7.5 Years of Extended Follow-up" https://doi.org/10.1182/blood-2019-124691	MCL3001 (RAY) PCYC-1104 MCL2001 (SPARK)	NCT01646021 NCT01236391 NCT01599949	See above	Acalabrutinib vs ibrutinib
Dreyling M., et al (2022) " Long-term Outcomes With Ibrutinib Treatment for Patients With Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis of 3 Clinical Trials With Nearly 10 Years of Follow-up" 2022 Apr 13;6(5):e712. doi: 10.1097/HS9.0000000000000712	MCL3001 (RAY) PCYC-1104 MCL2001 (SPARK)	NCT01646021 NCT01236391 NCT01599949	See above	Acalabrutinib vs ibrutinib

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
L. Cai,. Et al (2024) “Matching-adjusted indirect comparison of acalabrutinib versus ibrutinib in relapsed/refractory mantle cell lymphoma” Accession Number: 39461001 DOI: 10.1080/13696998.2024.2422227	LY-004 MCL3001 (RAY) PCYC-1104 MCL2001 (SPARK)	NCT02213926 NCT01646021 NCT01236391 NCT01599949	See above	Acalabrutinib vs ibrutinib
J. C. Byrd,.Et al (2021) “ Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial Accession Number: 34310172 PMCID: PMC8547923 DOI: 10.1200/JCO.21.01210	ELEVATE-RR	NCT02477696	Study Start (Actual) 2015-07-28 Primary Completion (Actual) 2020-09-15 Study Completion (Estimated) 2028-01-03 Enrollment (Actual) 533	H2H comparison of acalabrutinib and ibrutinib in CLL to support the indirect comparison of acalabrutinib and ibrutinib in MCL.

5.2 Literature used for the assessment of health-related quality of life

No health-related quality of life data was used in the cost minimization analysis of acalabrutinib vs ibrutinib.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
NA	NA	NA

5.3 Literature used for inputs for the health economic model

No systematic literature search was carried out for inputs included in the cost-minimization analysis (CMA). Costs included in the analysis were sourced according to DMC guidelines and a more detailed description can be found in section 11

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NA	NA	NA	NA

6. Efficacy

Acalabrutinib and ibrutinib have not been compared in any head-to-head Phase 3 studies in R/R MCL, which is a limitation when evaluating these treatments for this indication. However, head-to-head Phase 3 studies of acalabrutinib vs ibrutinib exist in other hematologic malignancies. Notably, acalabrutinib and ibrutinib were compared directly in the ELEVATE-RR study, a Phase 3 randomized controlled trial conducted in patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL) (50). Efficacy and safety data from ELEVATE-RR are provided in **Appendix K.**

ELEVATE-RR showed similar efficacy between acalabrutinib and ibrutinib for PFS, with a trend in OS favouring acalabrutinib. Overall, patients treated with acalabrutinib were less likely to experience grade 3 or higher AEs than those receiving ibrutinib. Additionally, a pooled safety analysis of randomized controlled trials evaluating acalabrutinib across various indications is available in **Appendix L**

6.1 Efficacy of acalabrutinib compared to ibrutinib for R/R MCL

In the absence of head-to-head clinical trials, a peer-reviewed MAIC was used to compare the two BTKi's in the R/R MCL population (49).

The MAIC presented in Section 7.1.2.1, compared acalabrutinib with ibrutinib using individual patient-level data (IPD) from the LY-004 trial involving 124 patients (23) and data from a pooled analysis of ibrutinib pivotal trials. The pooled analysis was conducted by Rule et al (44). The pooled analysis used ibrutinib data from three separate ibrutinib trials: PCYC-1104 with 111 patients, SPARK with 120 patients, and RAY with 139 patients, totalling 370 patients (45-47). The is detailed in Table 9.

As the MAIC is based on the pooled analysis of ibrutinib pivotal trials, only the results from the pooled analysis are presented in the section below, rather than from the individual studies (54)

6.1.1 Relevant studies

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma (LY-004) NCT02213926 (55).	LY004 is a Phase 2, single-arm, multicenter, open-label study in subjects with histologically documented MCL, who had relapsed after at least 1 prior treatment regimen. Patients were enrolled at 40 sites in ten countries (56).	**Study Start Date:** 02 Mar 2015 **Primary Completion Date:** 04 Dec 2020 (cutoff date for the 54-month close-out analysis) **Estimated Study Completion Date:** 06	Included patients Men and women aged ≥ 18 years Pathologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1. Disease has relapsed after or been refractory to ≥ 1 prior therapy for MCL and now requires further treatment. Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy. At least 1, but no more than 5, prior treatment regimens for MCL.	Acalabrutinib (100 mg) was given orally twice per day in 28-day cycles until progressive disease or unacceptable toxicity. All 124 patients enrolled in the study received treatment (35).	This was a single-arm study with no comparator (35).	**The primary endpoint** of the study is overall response rate (ORR), defined as the proportion of subjects achieving either partial remission (PR) or complete response (CR) according to the Lugano Classification for NHL as assessed by investigators **(55)**. Median follow-up: 38.1 months (range: 0.3 to 68.8) (at the 54-month close-out analysis) (57). The follow-up period was predefined (55). **Secondary endpoints (55):** Efficacy: Investigator-assessed Duration of Response (DOR). Median follow-up: 38.1 months (range: 0.3 to 68.8) (57). The follow-up period was predefined (55). IRC-assessed DOR. Median follow-up of 15.2 months (range 14.2–17.0) (35). The follow-up period was predefined (55).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
		Sept 2026 (57).	Eastern Cooperative Oncology Group performance status of ≤ 2 (55).			Investigator assessed progression-free survival (PFS) per Lugano Classification. Median follow-up: 38.1 months (range: 0.3 to 68.8) (57). The follow-up period was predefined (55). IRC-assessed Progression-free survival (PFS) per Lugano Classification. Median follow-up of 15.2 months (range 14.2–17.0) ((35). The follow-up period was predefined (55). Overall survival (OS). Median follow-up: 38.1 months (range: 0.3 to 68.8) (57). The follow-up period was predefined (55). IRC-assessed ORR. Median follow-up of 15.2 months (range 14.2–17.0) (35). The follow-up period was predefined (55). Safety: Frequency, severity, and relatedness of adverse events (AEs). Median follow-up: 38.1 months

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						(range: 0.3 to 68.8) (57). The follow-up period was predefined (55). Frequency of AEs requiring discontinuation of study drug or dose reductions. Median follow-up: 38.1 months (range: 0.3 to 68.8) (57). The follow-up period was predefined (55). Effect of acalabrutinib on peripheral T/B/natural killer (NK) cell counts. Median follow-up: 38.1 months (range: 0.3 to 68.8) (57). The follow-up period was predefined (55). Effect of acalabrutinib on serum immunoglobulin levels. Median follow-up: 38.1 months (range: 0.3 to 68.8) (57). The follow-up period was predefined (55). Exploratory endpoints: Time to Response Based on Investigator Assessment According the Lugano Classification. The median time to best response was 2.1 months (range: 1.6 to 52.5). Complete response (CR) was achieved in 59 (47.6%) subjects. The

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						median time to CR was 3.7 months (range: 1.7 to 52.5). EORTC Core Quality of Life Questionnaire (QLQ-C30). Numerical improvement in global health status/HRQoL of the EORTC QLQ C 30 scale in patients at treatment month 2 (equivalent to 2 x 28-day cycles of treatment), compared with scores recorded at screening. Patients also demonstrated a sustained benefit over the remainder of the 15-month follow-up period Pharmacokinetics: Plasma pharmacokinetics of acalabrutinib (55). Median follow-up: 26.7 months (58).
Multicenter, phase 2 study of Bruton's tyrosine kinase (BTK) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma (PCYC-1104), NCT number: 01236391 (29, 52, 59, 60).	This is a Phase 2, open-label, nonrandomized, multicenter, monotherapy study in subjects with histologically	**Study Start:** Feb 2011 **Study Completion:** Jan 2014 (61).	Included patients: Men and women ≥ 18 years of age. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.	Patients received single-agent ibrutinib administered orally at a daily dose of 560 mg until progression of disease or until	This study did not have a comparator arm (59).	**Primary endpoint:** ORR defined as a subject achieving either a partial remission (PR) or complete remission (CR) according to the revised International Working Group Criteria for non-Hodgkin lymphoma (NHL) as assessed by investigators (59). Median follow-up: 26.7 months (52). The follow-up period was predefined (59).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
	documented MCL who have relapsed after ≥ 1 (but not > 5) prior treatment regimens. The study design followed a two-stage procedure with two treatment groups in parallel. Patients were stratified into 2 groups based on prior bortezomib exposure (59).		Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or t(11;14), and measurable disease on cross sectional imaging that is ≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions per computed tomography (CT). Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen. At least 1, but no more than 5, prior treatment regimens for MCL (59).	unacceptable levels of adverse events occurred. 111 patients received at least one dose of ibrutinib (29).		**Secondary endpoints** <u>Efficacy (59):</u> Investigator assessed duration of response (DOR) Investigator assessed progression-free survival (PFS) Overall survival (OS) For all the defined efficacy endpoints the median follow-up was 26.7 months (52), and the follow-up period was predefined (59). <u>Safety (59):</u> Frequency, severity, and relatedness of AEs Frequency of AEs requiring discontinuation of study drug or dose reductions Effect of PCI-32765 on peripheral B/T/natural killer (NK) cell counts Effect of PCI-32765 on serum immunoglobulin levels For all the defined safety endpoints the median follow-up was 26.7 months (52), and the follow-up period was predefined (59). <u>Pharmacokinetics (59):</u>

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						Plasma pharmacokinetics (PK) of PCI-32765 and a major metabolite, PCI-45227. The last PK sample was taken on cycle 1 day 22 as predefined in the protocol (59). <u>Patient Reported Outcomes (59):</u> Health-related quality of life. Median follow-up: 26.7 months (52). The follow-up period was predefined (59).
A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy (RAY), NCT01646021 (31, 62).	This is a randomized, controlled, open-label, multicentre, phase 3 study comparing the efficacy and safety of ibrutinib with temsirolimus in patients with R/R MCL. Patients were randomly	**Study Start:** 2012-12-10 **Primary Completion:** 2015-06-05 **Study Completion:** 2016-12-15 (63).	**Included patients (64):** Aged ≥18 years Diagnosis of MCL including morphology and expression of either cyclin D1 in association with one B-cell marker (eg, CD19, CD20, or PAX5) and CD5 or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridisation, or polymerase chain reaction Received at least one prior rituximab-containing chemotherapy regimen	Patients in the ibrutinib group received 560 mg ibrutinib orally once per day until disease progression or unacceptable toxic effects. 139 patients were randomized to the ibrutinib group, and all patients received treatment (31).	Patients in the temsirolimus group received 175 mg temsirolimus intravenously on days 1, 8, and 15 of the first cycle, followed by 75 mg on days 1, 8, and 15 of each	**Primary endpoint:** Progression-Free Survival (PFS) assessed by the independent review committee (IRC). Median follow-up: 20.0 months (31). **Secondary endpoints:** IRC assessed Overall Response Rate (ORR). Median follow-up: 20.0 months (31). Investigator assessed ORR. Median follow-up: 38.7 months (62). Overall Survival (OS). Median follow-up: 38.7 months (62). PFS assessed by the investigator. Median follow-up: 38.7 months (62).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
	assigned 1:1 to oral ibrutinib or intravenous temsirolimus. Randomization was balanced by using randomly permuted blocks and stratified by number of previous lines of therapy (one, two, or three or more) and sMIPI score (low risk [0–3] vs intermediate risk [4–5] vs high risk [6–11]). On July 30, 2014, the protocol was amended to		Documented relapse or disease progression following the last anti-MCL treatment ECOG performance status 0 or 1 Hematology values within the following limits: - Absolute neutrophil count ≥ 1000/mm3 independent of growth factor support - Platelet count ≥ 75 000/mm3 or ≥ 50 000/mm3 if bone marrow involvement independent of transfusion support - Hemoglobin level ≥8 g/dL, independent of transfusion support Biochemical values within the following limits:		subsequent 21-day cycle. The patients were treated until disease progression or unacceptable toxic effects. 141 patients were assigned to temsirolimus, and 139 patients received treatment (31).	1-Year Survival Rate. 1 year follow-up (31). Duration of Response (DOR). Median follow-up: 38.7 months (62). Time to Next Treatment. Median follow-up: 38.7 months (62). Safety. Median follow-up: 38.7 months (62). Prespecified Patient-Reported Outcomes. Median follow-up: 20.0 months (31). Biomarkers and Pharmacokinetics. Median follow-up: 20.0 months (31). Medical Resource Use Rate. Median follow-up: 20.0 months (31).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
	include formal crossover of patients on the temsirolimus group to ibrutinib who have independent review committee-confirmed progression of disease (31).		- Alanine aminotransferase and aspartate aminotransferase ≤3 × upper limit of normal (ULN) - Total bilirubin ≤1·5 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) - Serum creatinine ≤2 × ULN - Fasting serum cholesterol level ≤350 mg/dL - Fasting serum triglyceride level ≤400 mg/dL			
A Phase 2, Multicenter, Single-Arm, Study to Evaluate the Efficacy and Safety of Single-Agent	This is a Phase 2, open-label, single-arm, international	**Study Start:** 2012-08	**Included patients:** Diagnosis of confirmed mantle cell lymphoma (MCL) with at least 1	Patients were treated with 560 mg/day oral ibrutinib	This was a single-arm study with no	**Primary endpoint (46):**

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy (SPARK), NCT01599949 (46).	multicenter, monotherapy study in subjects with MCL who had received a rituximab-containing regimen and had progressed after at least 2 cycles of bortezomib therapy (46). The study has been completed.	**Study Completion:** 2015-05 (65)	measurable site of disease according to Revised Response Criteria for Malignant Lymphoma Must have received at least 1 prior rituximab-containing chemotherapy regimen, but no more than 5 prior regimens Must have received at least 2 cycles of bortezomib therapy (single-agent or in combination) and have documented progressive disease during or after bortezomib therapy Eastern Cooperative Oncology Group performance status score 0, 1, or 2 Hematology and biochemical values within protocol-defined parameters (65).	continuously until progressive disease or unacceptable toxicity. 120 patients were treated (46).	comparator (46).	Overall response rate (ORR) in response-evaluable patients, as assessed by an Independent Review Committee (IRC). Median follow-up: 14.9 months. **Secondary Endpoints (46):** IRC assessed duration of response (DoR). Median follow-up: 14.9 months. IRC assessed progression-free survival (PFS). Median follow-up: 14.9 months. Overall survival (OS). Median follow-up: 14.9 months. Safety. Median follow-up: 14.9 months.

6.1.2 Comparability of studies

The four studies, LY-004, PCYC-1104, SPARK, and RAY, focus on treatments for MCL and share several inclusion criteria, although there are some differences in their specifics:

All studies required patients to have been previously treated with at least one prior therapy. Both LY-004 and PCYC-1104 specify that patients must have received between one and five prior treatments, while SPARK and RAY details the necessity for prior rituximab-containing chemotherapy.

All four studies require participants to have an ECOG performance status within a range of 0 to 2, although RAY restricts further to scores of 0 or 1. All studies require participants to be adults.

Despite these differences, the inclusion criteria of these studies are largely comparable. The studies uniformly require previous treatment history, confirmation of MCL with measurable disease, and similar performance status level.

6.1.2.1 Comparability of patients across studies

Baseline characteristics of patients included in the studies used in the comparative analysis is presented in Table 10.

Table 10 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	Acalabrutinib	Ibrutinib			
	LY-004 (n=124)	PCYC-1104 (n=111)	SPARK (n=120)	RAY (n=139)	Pooled (n=370)
Age, median (range)	68 (42-90)	68 (NR)	67,5 (NR)	67 (NR)	67,5 (NR)
ECOG performance status, %					
0–1, %	93*	89	91	99	94
2, %	7	10	9	1	6
>2, %	NR	1	0	0	1
sMIPI, %					
Low risk (1–3), %	39	14	24	32	24
Intermediate risk (4–5), %	44	38	48	47	45
High risk (6–11), %	17	49	28	22	32
Missing	1	NR	NR	NR	NR
Bulky disease (≥5 cm), %	37	39	53	54	49
Extranodal disease, %	72	54	60	60	58

	Acalabrutinib	Ibrutinib			
	LY-004 (n=124)	PCYC-1104 (n=111)	SPARK (n=120)	RAY (n=139)	Pooled (n=370)
Median number of previous therapies, n (range)	2 (1-5)	3 (1–5)	2 (1–8)	2 (1–9)	2 (1–9)
Previous therapy, %					
Rituximab-based regimen %	95	NR	NR	NR	NR
CHOP-based regimen%	52	NR	NR	NR	NR
BR-based regimen%	22	NR	NR	NR	NR
Hyper-CVAD%	21	NR	NR	NR	NR
Bortezomib or carfilzomib%	19	43	100	22	54
SCT%	22	11	33	24	23
Lenalidomide%	9	24	19	6	16
Lactate dehydrogenase, %	NR	80	43	42	54

* One patient who had an ECOG PS of 1 at screening had an ECOG PS of 3 at the baseline assessment (cycle 1, day 1)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

To the best of our knowledge, detailed characteristics of MCL patients in Denmark have not been extensively reported. To ascertain whether the demographic and clinical characteristics of the LY-004 study population align with those of Danish patients with relapsed/refractory MCL, we consulted a Danish MCL expert. Upon reviewing and discussing baseline characteristics of patients in the LY-004 study, the expert confirmed that the characteristics generally are comparable to those of the relevant Danish patient population. See Table 10.

Table 11 Comparability of the study population with Danish patients

	Value in Danish population (35)	Value used in health economic model (reference if relevant)
Age, median (range)	68 (42-90)	NA

6.1.4 Efficacy – results per LY-004

6.1.4.1 ORR

At the primary data analysis, with a median follow-up of 15.2 months, 70 patients (56%) were still continuing to receive study treatment. Acalabrutinib demonstrated high ORRs in patients with R/R MCL, with 100 patients (81%) achieving a response and 49 patients (40%) achieving a CR, by investigator assessment according to the 2014 Lugano classification (Table 12). ORR was also evaluated by an IRC using the same criteria; with high concordance observed between investigator-assessed and IRC-assessed ORR and CR (91% and 94% concordance, respectively).

At the final data analysis, with a median follow-up of 38.1 months, 18 patients (14.5%) were still continuing to receive the study treatment. Acalabrutinib increased ORR to 81.5% (101/124) according to the 2014 Lugano classification by investigator assessment. Six patients improved in status from a PR to CR, thus increasing the CR rate to 47.6% (59 patients) (Table 12).

Table 12 ORR based on investigator assessment according to the 2014 Lugano classification

	All patients (n=124)			
	Primary data analysis (66)		Final data analysis(67)	
	n (%)	95% CI	n (%)	95% CI
ORR (CR + PR)	100 (80.6%)	72.6%, 87.2%	101 (81.5%)	73.5%, 87.9%
CR	49 (39.5%)	30.9%, 48.7%	59 (47.6%)	38.5%, 56.7%
PR	51 (41.1%)	32.4%, 50.3%	42 (33.9%)	25.6%, 42.9%
SD	11 (8.9%)	4.5%, 15.3%	10 (8.1%)	3.9%, 14.3%
PD	10 (8.1%)	3.9%, 14.3%	10 (8.1%)	3.9%, 14.3%
NE	3 (2.4%)	0.5%, 6.9%	3 (2.4%)	0.5%, 6.9%

CI: Confidence interval; CR: Complete response; NE: Not estimable; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease

IRC-assessed response rates were analyzed only for the primary data analysis because the IRC and investigator data were highly concordant and additional confirmation was not required.

6.1.4.2 ORR by IRC assessment based on the 2007 IHP criteria

At a median follow-up of 15.2 months, response rates based on IRC assessment according to the 2007 IHP criteria demonstrated a similar ORR, but slightly lower CR rate compared with the responses based on the 2014 Lugano classification (24). Based on the 2007 IHP criteria, treatment with acalabrutinib resulted in an ORR of 75% (95% CI: 66%, 82%) and CR rate of 30% (95% CI: 22%, 39%) (Table 13). Given the differences between the two criteria, the differences in the ORR and CR rate were as expected.

Table 13 ORR based on IRC assessment according to the 2007 IHP classification – Primary data analysis

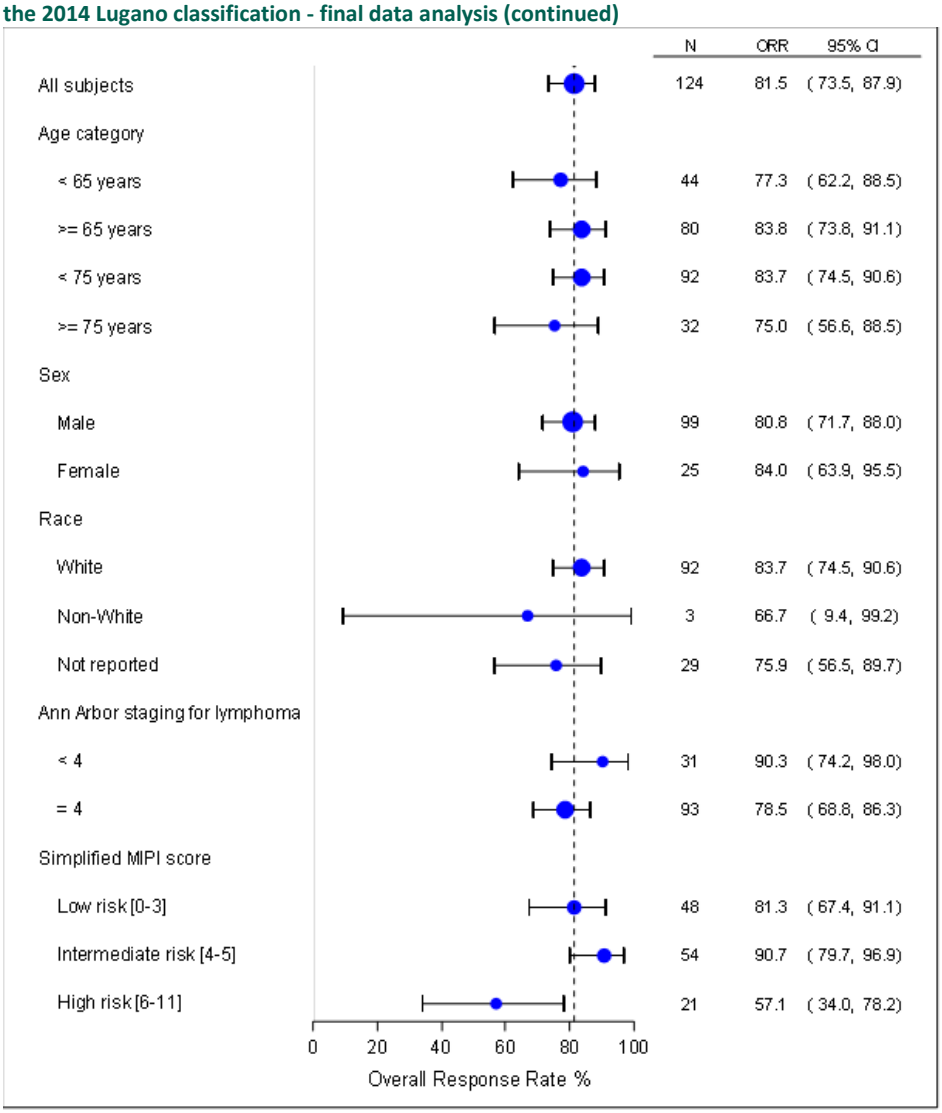
	All patients (n=124)	
	n (%)	95% CI
ORR (CR + PR)	93 (75.0%)	(66.4%, 82.3%)
CR	37 (29.8%)	(22.0%, 38.7%)
PR	56 (45.2%)	(36.2%, 54.3%)
SD	14 (11.3%)	(6.3%, 18.2%)
PD	10 (8.1%)	(3.9%, 14.3%)
NE	5 (4.0%)	(1.3%, 9.2%)
No evidence of disease	1 (0.8%)	(0.0%, 4.4%)
Unknown	1 (0.8%)	(0.0%, 4.4%)

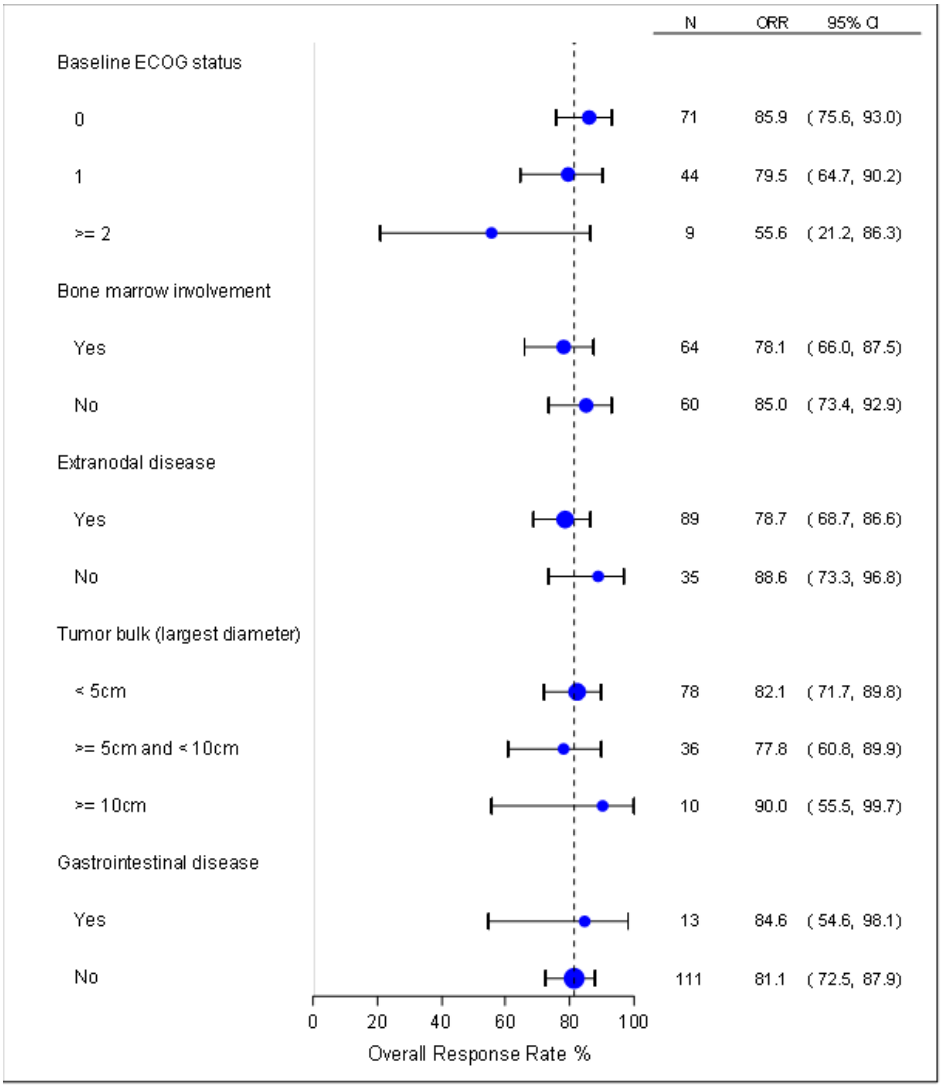
CI: Confidence interval; CR: Complete response; IHP: International Harmonization Project; IRC: Independent Review Committee; NE: Not estimable; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease

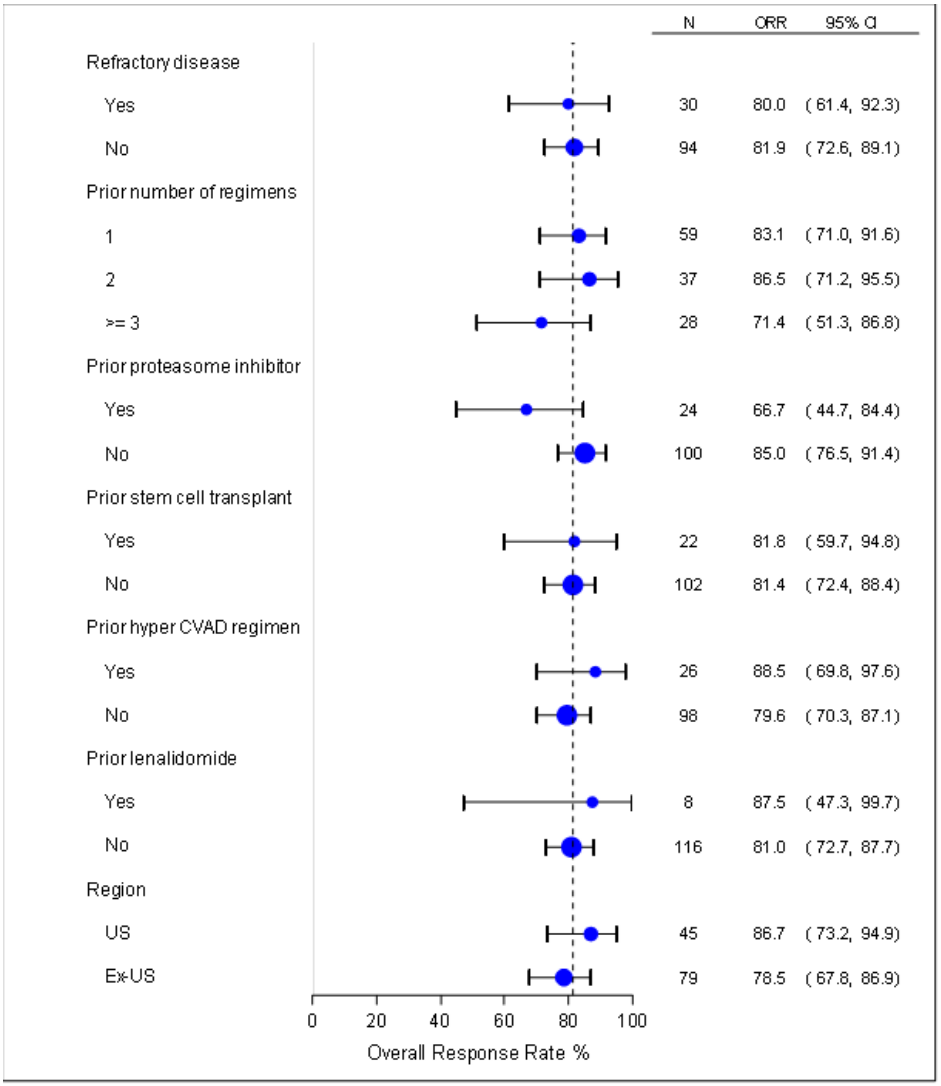
6.1.4.3 Subgroup analysis of ORR

In the final data analysis, investigator-assessed ORR was consistent across pre-specified baseline and disease characteristic variables, including subgroups with varying numbers of previous therapies. These results suggest that acalabrutinib can be used broadly for R/R MCL patients.

Figure 1 Pre-specified subgroup analysis of ORR based on investigator assessment according to the 2014 Lugano classification - final data analysis (continued)




N
ORR
95% CI
Baseline ECOG status
0
71
85.9
(75.6, 93.0)
1
44
79.5
(64.7, 90.2)
>= 2
9
55.6
(21.2, 86.3)
Bone marrow involvement
Yes
64
78.1
(66.0, 87.5)
No
60
85.0
(73.4, 92.9)
Extranodal disease
Yes
89
78.7
(68.7, 86.6)
No
35
88.6
(73.3, 96.8)
Tumor bulk (largest diameter)
< 5cm
78
82.1
(71.7, 89.8)
>= 5cm and < 10cm
36
77.8
(60.8, 89.9)
>= 10cm
10
90.0
(55.5, 99.7)
Gastrointestinal disease
Yes
13
84.6
(54.6, 98.1)
No
111
81.1
(72.5, 87.9)
0
20
40
60
80
100
Overall Response Rate %



CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; Hyper-CVAD: Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MIPI: Mantle Cell Lymphoma International Prognostic Index; ORR: Overall response rate; US: United States

6.1.4.4 PFS

Based on the final data analysis, 85 (68.5%) subjects had either progressed or died as of the data cutoff date (04 December 2020). Median PFS was 22.0 months (95% CI: 16.6, 33.3). PFS at different landmarks can be seen inTable 14

Results of a sensitivity analysis of PFS based on investigator assessment according to the Lugano classification, which included events after the start of subsequent therapy, were consistent with the primary analysis results for PFS.

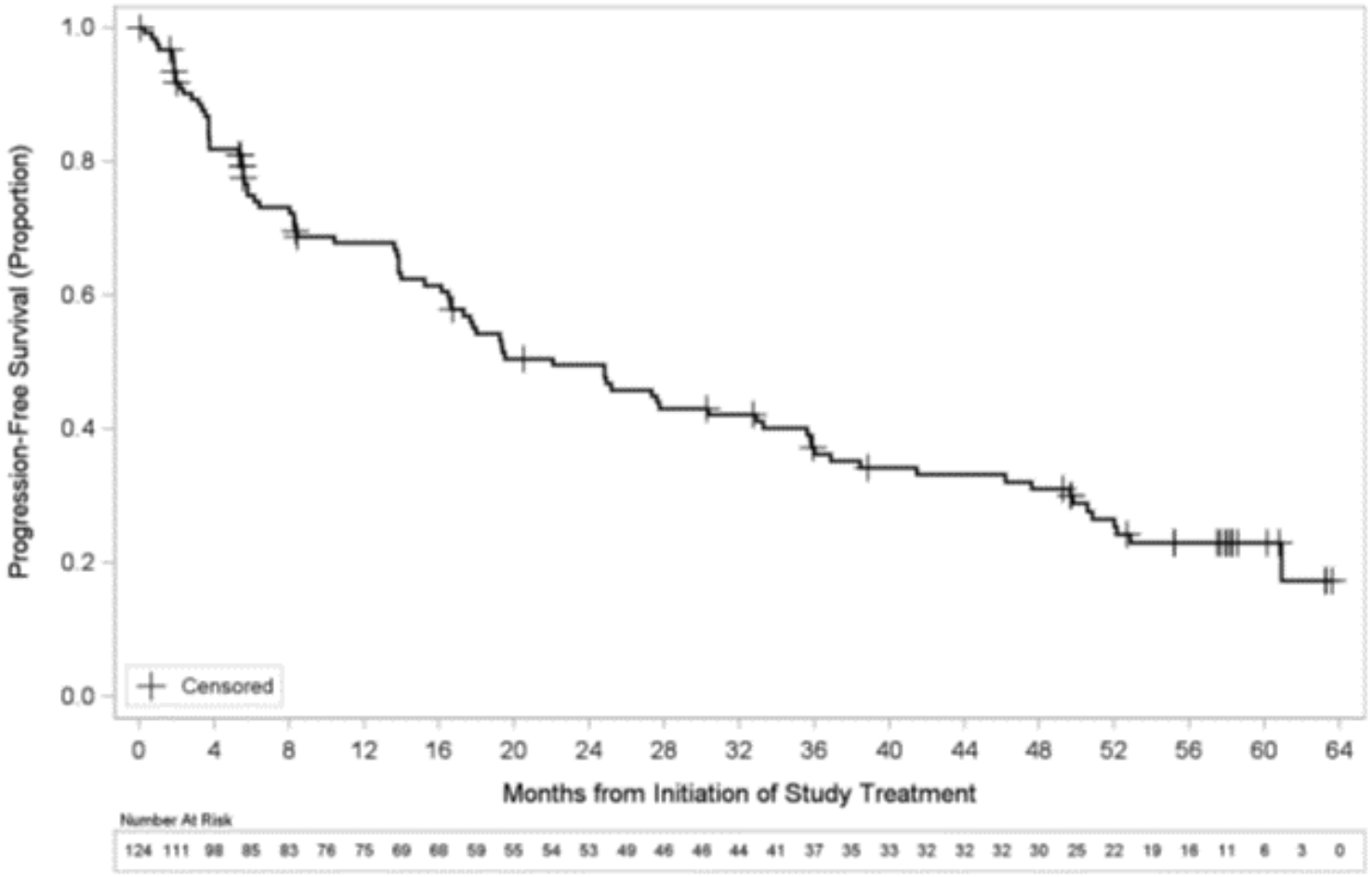
Table 14 PFS based on investigator assessment according to the 2014 Lugano classification

	All patients (n=124)

	Primary data analysis	Final data analysis
Median PFS, months (95% CI)	NE (15, NE)	22.0 (16.6, 33.3)
PFS rate at 12 months, % (95% CI)	67 (58, 75)	67.8 (58.5, 75.4)
PFS rate at 24 months, % (95% CI)	NA	49.6 (40.1, 58.4)
PFS rate at 36 months, % (95% CI)	NA	37.2 (28.2, 46.1)
PFS rate at 60 months, % (95% CI)	NA	23.0 (15.3, 31.7)

CI: Confidence interval; NA: Not available; NE: Not estimable; PFS: Progression-free survival

Figure 2 KM curve for PFS according to investigator assessment based on the 2014 Lugano classification – Final data analysis


Progression-Free Survival (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Censored
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64
Months from Initiation of Study Treatment
Number At Risk
124 111 98 85 83 76 75 69 68 59 55 54 53 49 46 46 44 41 37 35 33 32 32 32 30 25 22 19 16 11 6 3 0

KM: Kaplan-Meier; PFS: Progression-free survival

6.1.4.5 OS

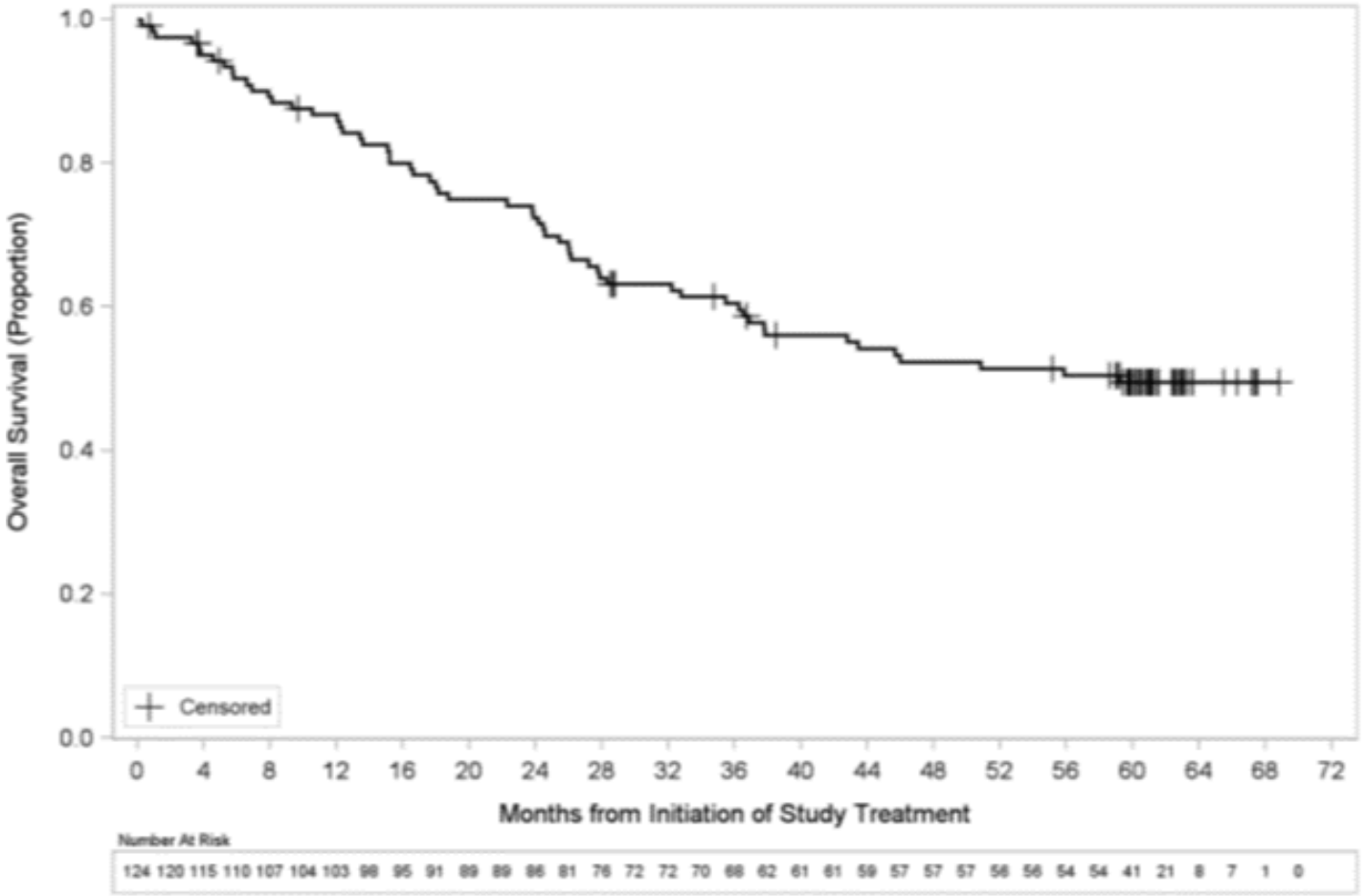
Based on the final data analysis, 47.6% of subjects had died as of the data cutoff date (04 December 2020). Median OS was 59.2 months (95% CI: 36.5, not estimable [NE]).OS at different landmarks can be seen in Table 15.

Table 15 OS for the primary analysis and the final data analysis

	All patients (n=124)	
	Primary data analysis	**Final data analysis**
Median OS, months (95% CI)	NE (18, NE)	59.2 (36.5, NE)
OS rate at 12 months, % (95% CI)	87 (79, 92)	86.8 (79.3, 91.7)
OS rate at 24 months, % (95% CI)	NA	72.4 (63.5, 79.5)
OS rate at 36 months, % (95% CI)	NA	60.5 (51.1, 68.7)
OS rate at 66 months, % (95% CI)	NA	49.5 (40.1, 58.2)

CI: Confidence interval; NA: Not available; NE: Not estimable; OS: Overall survival

Figure 3 KM curve for OS – Final data analysis


Overall Survival (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Censored
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72
Months from Initiation of Study Treatment
Number At Risk
124 120 115 110 107 104 103 98 95 91 89 89 86 81 76 72 72 70 68 62 61 61 59 57 57 57 56 56 54 54 41 21 8 7 1 0

KM: Kaplan-Meier; OS: Overall survival

6.1.5 Efficacy – results per ibrutinib studies

Efficacy results from the pooled analysis are presented in this section. The pooled analysis used data from three separate ibrutinib trials: PCYC-1104 with 111 patients(45), SPARK with 120 patients (46), and RAY with 139 patients(47), totalling 370 patients.

The pooled analysis has been updated with longer follow-up data since the first publication in 2017 by Rule et al (44). It was updated in 2019 by Rule et al (48) and recently in 2022 by Dreyling et al (68). ORR, PFS and OS data from Dreyling 2022 will be presented below and safety from Dreyling et al. is presented in section 0 (68).

6.1.5.1 ORR

The median (range) follow-up were 41 months (0.2-92.4**).** Patients treated with ibrutinib had an ORR of 69.7% (27.6% complete response; 42.2% partial response) (68).

6.1.5.2 PFS

The median (range) follow-up were 41 months (0.2-92.4**).** The median investigator assessed PFS for the overall MCL population was 12.5 (95%: CI: 9.8-16.6)(68).

6.1.5.3 OS

The median (range) follow-up were 41 months (0.2-92.4**).** The median OS for the overall MCL population was 26.7 (95%: CI: 22.5-38.4) (68).

7. Comparative analyses of efficacy

The LY-004 trial, being a single-arm study, does not allow for traditional indirect comparisons (e.g., Bucher analyses or network meta-analyses, NMAs). Instead, a naïve comparison of clinical results and an unanchored matching-adjusted indirect comparison (MAIC) were utilized to evaluate the relative efficacy and safety of acalabrutinib versus ibrutinib in treating R/R MCL. Complementing this, data from the phase 3 ELEVATE-RR trial, which directly compared acalabrutinib and ibrutinib in R/R CLL is included as reference in Appendix K.

7.1.1 Differences in definitions of outcomes between studies

For the response rates in the naïve comparison, 15-month follow-up data using the 2007 IHP criteria as assessed by an IRC were used for both acalabrutinib and ibrutinib (29, 35). In addition, the naïve comparison will show response rates using the Lugano 2014 criteria for acalabrutinib which will be different from the criteria used in the ibrutinib trial.

7.1.2 Method of synthesis

7.1.2.1 Naïve comparison

For the naïve comparison, the PCYC-1104 phase II study of ibrutinib as a single agent in R/R MCL was selected (NCT01236391). The trial was an open-label, nonrandomized, multicenter, monotherapy study in subjects with histologically documented MCL who have relapsed after ≥ 1 (but not > 5) prior treatment regimens. All subjects meeting eligibility criteria received ibrutinib capsules at a dosage of 560 mg/day once daily for a 28-day cycle until disease progression, unacceptable toxicity, or enrollment in a long-term extension study, whichever occurred earlier. The primary endpoint was ORR, with DoR, PFS, OS and safety as secondary endpoints.(29) This trial was selected for the naïve comparison due to the similar trial design, inclusion criteria, and trial participants as LY-004.

7.1.2.2 MAIC

The MAIC analysis of acalabrutinib and ibrutinib compared individual patient-level data from LY-004 (n=124) and a pooled population (n=370) from three the ibrutinib trials, PCYC-1104 (n=111) SPARK (n=120), and RAY (n=139)(23, 44-47).

The MAIC was first published in 2019 using the data available at that time, namely the 26.3-month follow-up LY-004 dataset and the 24-month follow-up ibrutinib pooled dataset (69). Since then, further data cuts have been published. Below the updated MAIC is reported utilizing median follow-up time of 38.1 months and 41.4 months for LY-004 and the pooled ibrutinib datasets, respectively (49).

After cross-trial similarities and differences were assessed, the baseline characteristics to be matched were selected based on data availability and inputs from clinical experts. The trial populations were then balanced and efficacy and safety outcomes compared. To conserve the effective sample size (ESS), only the most relevant prognostic variables were used for matching in this MAIC. Selection of prognostic variables for matching was based on literature, clinical judgment, or statistically significant association with PFS in univariate and multivariate regression analyses of acalabrutinib data. The following prognostic variables were matched in the updated analysis: ECOG PS, simplified MIPI score, tumor bulk, LDH, blastoid histology, and number of prior lines of therapy (LoT), see Table 16. Matching on these six variables resulted in an effective sample size (ESS) of 73 (60% of the total LY-004 population (n=122, 2 individuals were dropped due to missing values)). Distribution of weights was slightly left-skewed with a mean of 0.8 , indicating a reasonably good overlap between matched acalabrutinib arm and comparator arm, see **Figure 4**

Table 16 Baseline characteristics of prognostic variables before and after matching

Baseline characteristic	Pre-match	Post-match Acalabrutinib, %,	Ibrutinib, %, (N=370)

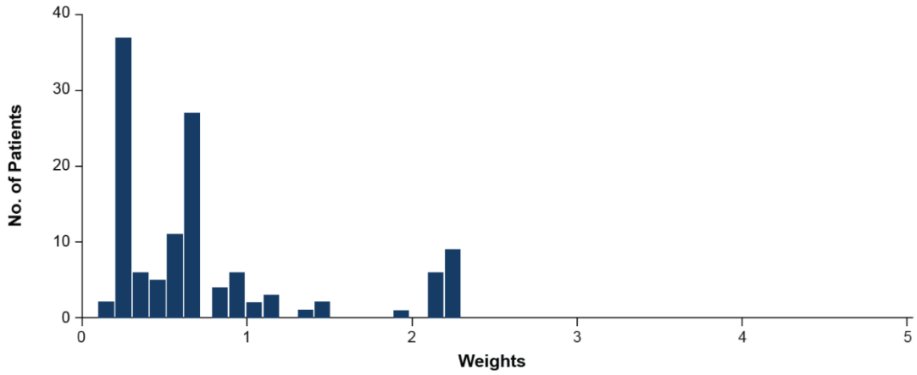
	Acalabrutinib, n (%), (N=122)	(ESS=73)	
Matched variables			
ECOG PS ≤1	113 (92.6)	94.0	94
Low sMIPI	48 (39.3)	24.0	24
Bulky disease ≥5 cm	46 (37.7)	49.0	49
High LDH[a]	32 (26.2)	55.0	55[b]
2 Prior LoT	37 (30.3)	40.4	29
Prior LoT ≥ 3	26 (21.3)	32.6	44
Blastoid histology	14 (11.5)	11.9	12
Unmatched variables			
Age <65 y	44 (36.1)	33.3	38
Male	98 (80.3)	81.0	78
White race	90 (96.8)[c]	94.5	89
ECOG PS 2	8 (6.6)	4.7	6
ECOG PS 3	1 (0.8)	1.3	1
Intermediate sMIPI	54 (44.3)	49.9	45
High sMIPI	20 (16.4)	26.1	32
1 Prior LoT	59 (48.4)	27.0	27
Extranodal disease	87 (71.3)	75.7	58
Bone marrow involvement	60 (49.2)	56.0	46
Categorical variables	**Pre-match Acalabrutinib, median (range), (N=122)**	**Post-match Acalabrutinib, median, (ESS=73)**	**Ibrutinib, median (range), (N=370)**
Age	68 (42-90)	70	67.5
Number of prior LoT	2 (1-5)	2	2 (1-9)

[a]High defined as greater than the upper limit of normal of 234 units/L.

[b]Number of evaluable patients is 363.

[c]Number of evaluable patients is 93.
ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; LDH, lactate dehydrogenase; LoT, lines of therapy; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; y, years.

Figure 4 Histogram of distribution of weights of individual patient data after matching



7.1.3 Results from the comparative analysis

7.1.3.1 Naïve comparison of clinical data

Naïve side-by-side comparisons of the response rates reported in the pivotal clinical trials for acalabrutinib (based on both the Lugano 2014 and IHP 2007 criteria) and ibrutinib (based on the IHP 2007 criteria alone) suggest superior outcomes associated with acalabrutinib treatment Table 17. Furthermore, the naïve comparison suggests lower incidences of AEs of clinical interest with acalabrutinib compared with ibrutinib, see Table 17. As this comparison is naïve, with no adjustment for any heterogeneity within the populations assessed and trial design, these results may be subject to bias. See section 7.1.3.2 for results from the MAIC that was conducted between the single-arm data from the acalabrutinib and ibrutinib pivotal trials in MCL to provide a more robust comparison of the treatments.

Table 17 Naïve comparison of clinical data for acalabrutinib versus ibrutinib

Response rates	Acalabrutinib (n=124)			Ibrutinib (n=111)	
	Lugano 2014		IHP 2007	IHP 2007	
	IRC	INV	IRC	INV	IRC
ORR, % (95% CI)	79.8* (71.7, 86.5)	80.6* 72.6, 87.2)	75.0 (66.0, 82.0)	65.8* (56.2, 74.5)	69.0* (N/A, N/A)
CR, % (95% CI)	39.5* (30.9, 48.7)	39.5* (30.9, 48.7)	30.0 (22.0, 39.0)	17.1* (N/A, N/A)	20.7* (N/A, N/A)
PR, % (95% CI)	40.3* (31.6, 49.5)	41.1* (32.4, 50.3)	45.0 (26.0, 54.0)	48.6* (N/A, N/A)	47.4* (N/A, N/A)

Safety	Acalabrutinib (n=124)	Ibrutinib (n=111)
Atrial fibrillation (Grade 3-4), n (%)	0	7 (6)
Hemorrhage (Grade 3-4), n (%)	1 (1)	7 (6)
Infection (Grade 3-4), n (%)	16 (13)	20 (18)

SOURCE: ((70) *Data presented in the treatment PI, CI: Confidence interval; CR: Complete response; IHP: International Harmonization Project; INV: Investigator assessment; IRC: Independent Review Committee; N/A: Not available; ORR: Overall response rate; PI: Prescribing information; PR: Partial response

7.1.3.2 MAIC results

Results from the MAIC analysis of acalabrutinib and ibrutinib is presented in Table 18.

It should be noted that there is a discrepancy between the PFS and OS reported for ibrutinib in Table 18 compared to what is reported in Dreyling et al. (68).The discrepancy is caused by the digitizing tool. The data in the MAIC slightly overestimates the effect of ibrutinib, but does not change the outcome of the comparison. In Dreyling et al., PFS is 12.5 months and OS is 26.7 months (68).how

Table 18 Results from the comparative analysis of acalabrutinib vs. ibrutinib for patients with R/R MCL

Outcome measure	Acalabrutinib pre-match (n=122)	Acalabrutinib post-match (n=73)	Ibrutinib (n=370)	Result from matched populations (HR (95% CI)
OS, median median follow-up time of acalabrutinib: 38.1 months and ibrutinib: 41.4 months	NR	36.5	27.9	0.87 (0.64, 1.17)
PFS, median median follow-up time of acalabrutinib: 38.1 months and ibrutinib: 41.4 months	22.0 (16.6, 33.3)	17.8	12.8	0.92 (0.74, 1.15)
Grade ≥ 3 adverse events median follow-up time of acalabrutinib: 38.1 months and ibrutinib: 41.4 months				**% of risk difference (95% CI) and p-value for the difference between post-match**

Outcome measure	Acalabrutinib pre-match (n=122)	Acalabrutinib post-match (n=73)	Ibrutinib (n=370)	Result from matched populations (HR (95% CI)
				acalabrutinib and ibrutinib
Neutropenia,%,	11.5	15	17	-2 (-11.4, 7.4) P=0.67
Thrombocytopenia,%	4.1	5.3	12.4	-7.1 (-13.3,-0.8) P=0.05
Pneumonia, %	6.6	8.7	12.7	-4 (-11.7,3.7) P=0.31
Anemia, %	10.7	14.8	10.0	4.8 (-4.3, 14.0) P=0.3
Atrial Fibrillation, %	0	0	6.2	-6.2 (-8.7, -3.7) P=0.001
Hypertension, %	1.6	2.6	5.1	-2.5 (-7.4, 2.4) P=0.32

7.1.4 Efficacy – results per OS

Before matching, the risk of death was statistically significantly lower (p = 0.01) for acalabrutinib compared with ibrutinib (HR = 0.67; 95% CI = 0.49–0.90) see Figure 5.

After matching, the difference was not statistically significant (HR = 0.87; 95% CI = 0.64–1.17, p=0.35) see Figure 6 Figure 6.

Figure 5 OS before matching

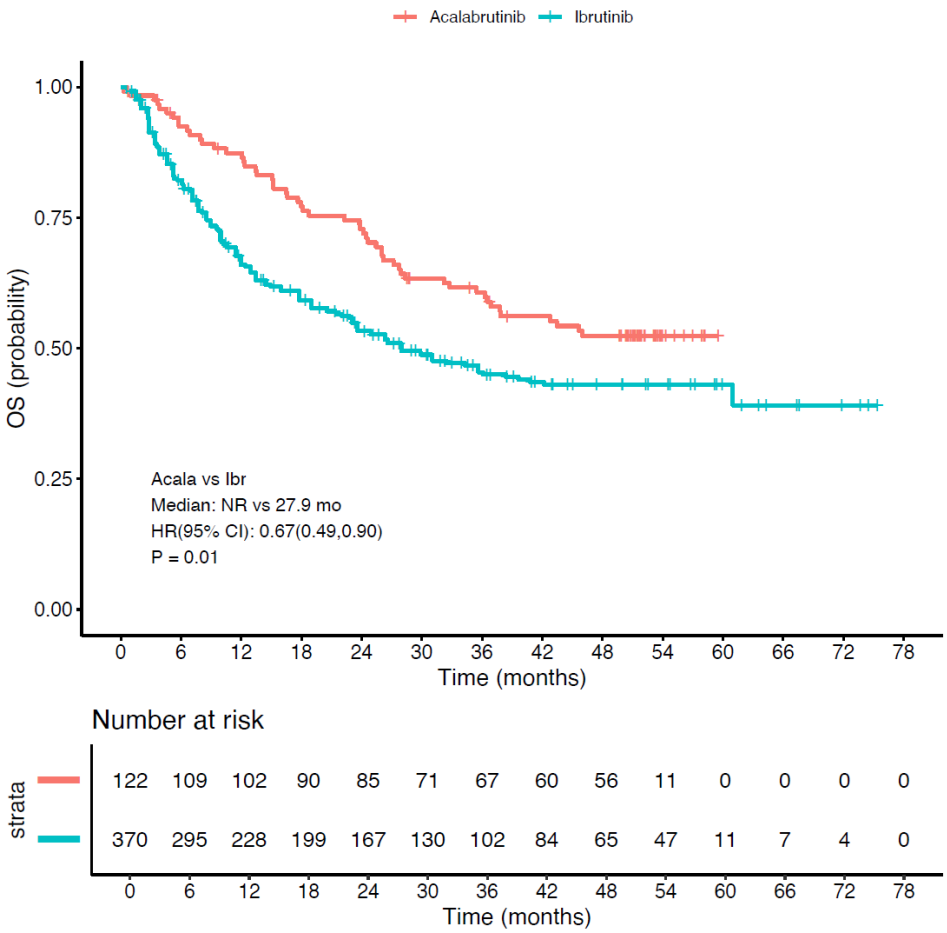
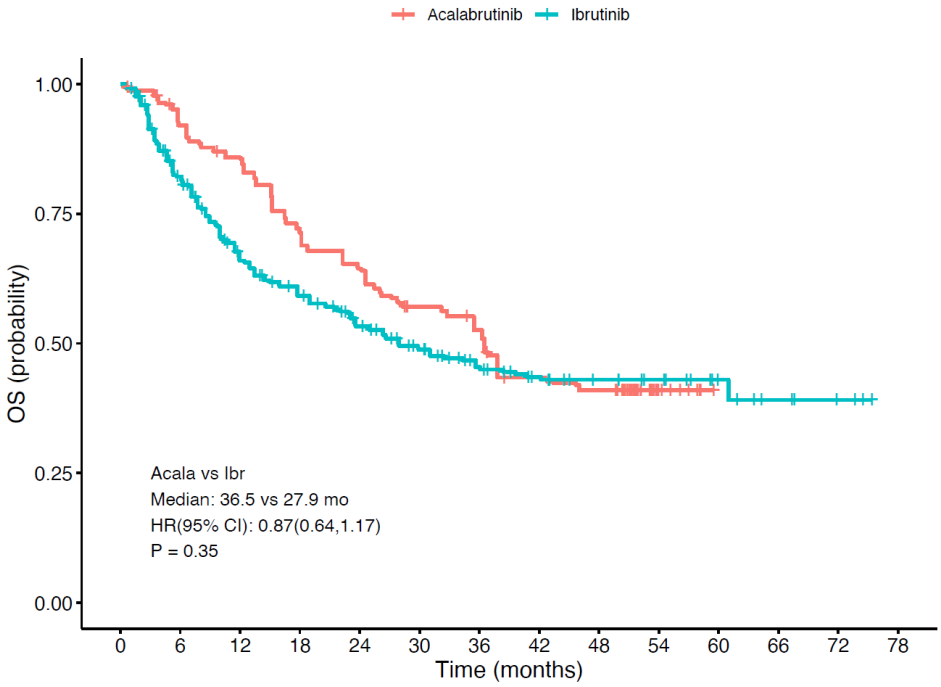


Figure 6 OS after matching



7.1.5 Efficacy – results per PFS

Before matching, the risk of progression or death was statistically significantly lower (p = 0.02) in the acalabrutinib group compared with the ibrutinib group (hazard ratio [HR] = 0.75; 95% CI = 0.58–0.96), see Figure 7

After matching, the difference was not statistically significant (HR = 0.92; 95% CI = 0.74–1.15, p=0.48) Figure 8

Figure 7 PFS before matching

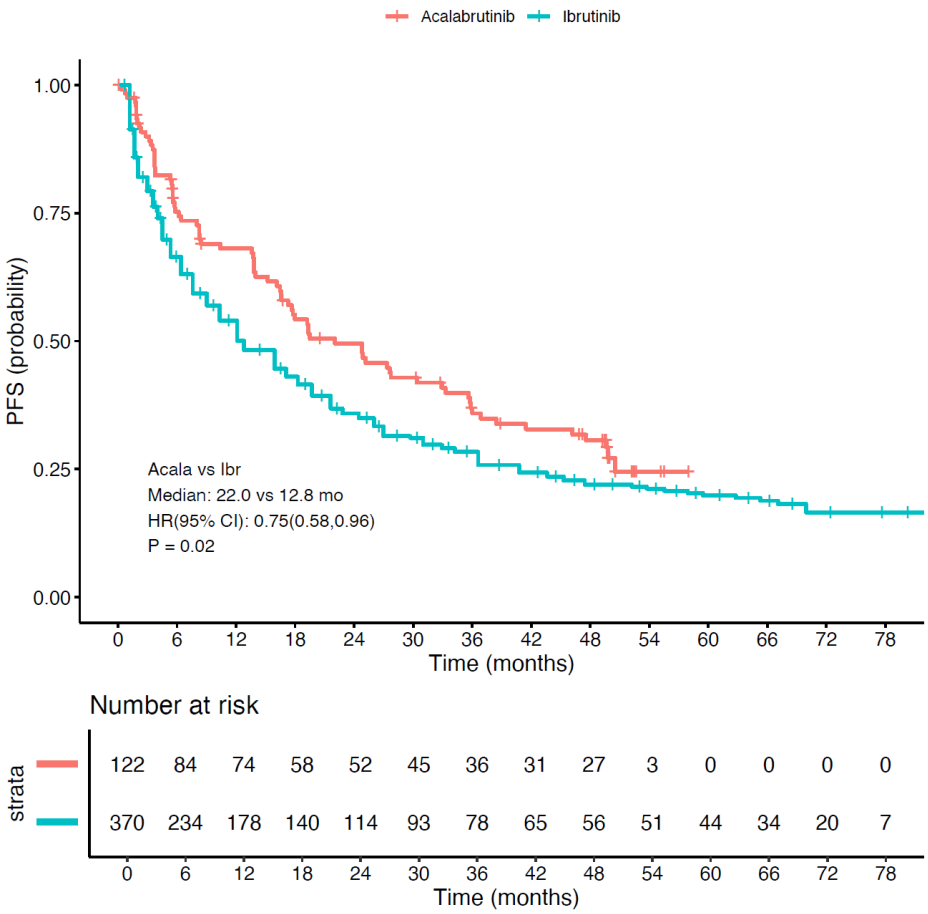
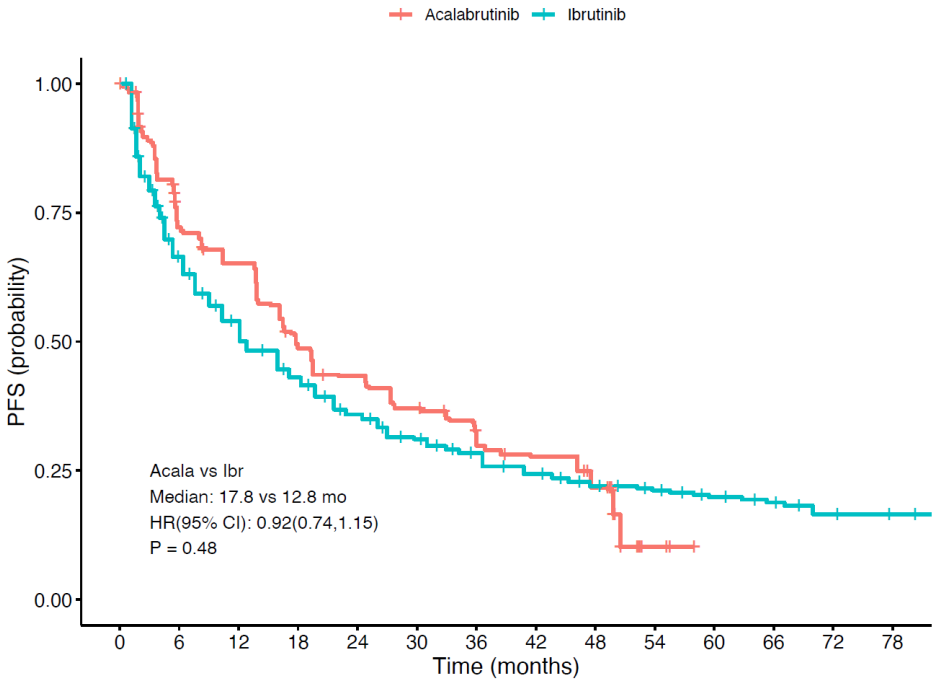


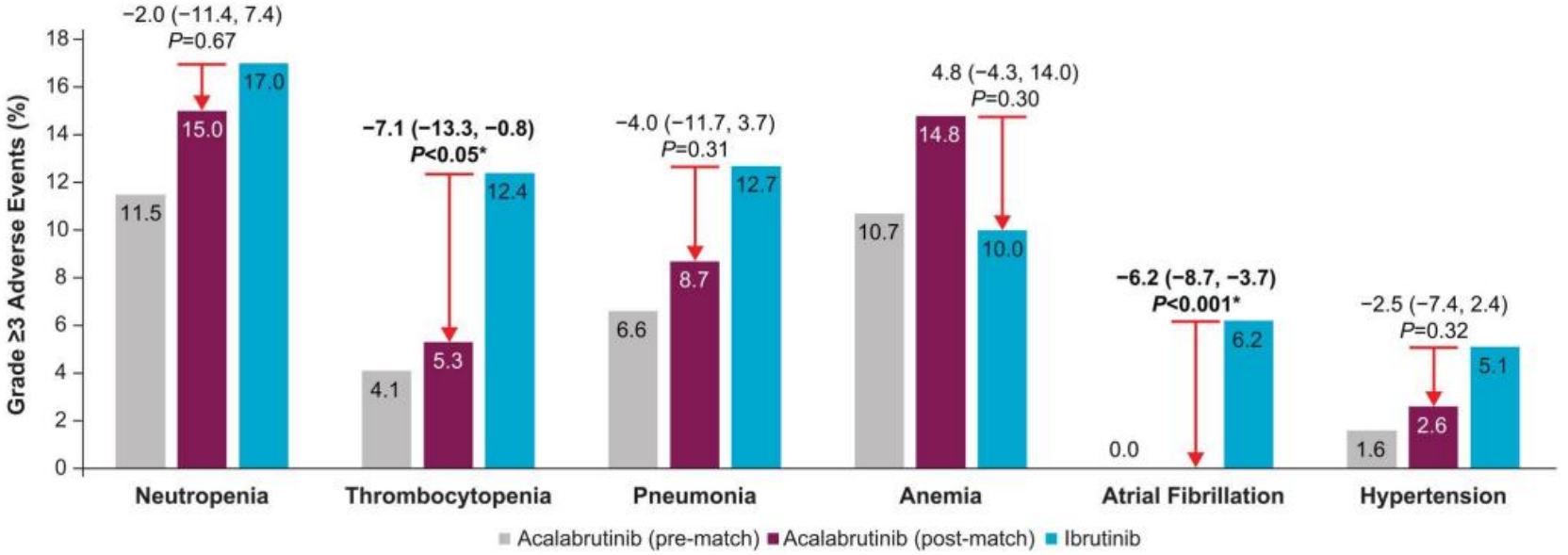
Figure 8 PFS after matching



7.1.6 Efficacy – results per Grade ≥ 3 adverse events

Rates of grade ≥ 3 adverse events of neutropenia, thrombocytopenia, pneumonia, anemia, atrial fibrillation (AF), and hypertension were compared for acalabrutinib and ibrutinib. After matching, rates of grade ≥ 3 AF and thrombocytopenia were statistically significantly lower with acalabrutinib compared with ibrutinib see Figure 9. Grade ≥ 3 adverse events of neutropenia, pneumonia, hypertension, and anemia were not statistically significantly different between acalabrutinib and ibrutinib both pre- and post-matching.

Figure 9 Grade ≥ 3 adverse events (%): % of risk difference (95% CI) and p-value for the difference between post-match acalabrutinib and ibrutinib. * Statistically significant



8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

NA

8.1.1 Extrapolation of efficacy data

NA

8.1.1.1 Extrapolation of [effect measure 1]

Table 19 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	NA
Model	NA
Assumption of proportional hazards between intervention and comparator	NA
Function with best AIC fit	NA
Function with best BIC fit	NA
Function with best visual fit	NA
Function with best fit according to evaluation of smoothed hazard assumptions	NA
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	NA
Adjustment of background mortality with data from Statistics Denmark	NA

Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	NA
Assumptions of waning effect	NA
Assumptions of cure point	NA

NA

8.1.1.2 Extrapolation of [effect measure 2]

NA

8.1.2 Calculation of transition probabilities

NA

Table 20 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	NA	NA	NA
	NA	NA	NA
Recurrence	NA	NA	NA
Health state/Transition	NA	NA	NA

NA

8.2 Presentation of efficacy data from [additional documentation]

NA

8.3 Modelling effects of subsequent treatments

NA

8.4 Other assumptions regarding efficacy in the model

Both acalabrutinib and ibrutinib are assumed to have equal efficacy on R/R MCL based on the MAIC reported in Section 7.

8.5 Overview of modelled average treatment length and time in model health state

NA

Table 21 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	NA	NA	NA
[Name of comparator]	NA	NA	NA

Table 22 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

[Intervention]	**NA**	**NA**	**NA**
[Comparator]	**NA**	**NA**	**NA**

9. Safety

This section presents the unadjusted safety data from LY-004 and the pooled ibrutinib analysis used in the ITC (See section 7.1.3.2 MAIC results for adjusted comparison). However, documentation on safety is not extensively reported in the pivotal studies on ibrutinib, making it challenging to draw meaningful comparisons between acalabrutinib and ibrutinib in the context of RR MCL using the DMC template.

To supplement the comparison, we also report safety data in separate tables in section 9.3 from ELEVATE RR. ELEVATE RR was a phase 3 trial evaluating acalabrutinib versus ibrutinib in CLL. Although there are differences in pathology and dosing of ibrutinib between MCL and CLL, the patients in these studies are of a similar age group and predominantly received chemo-immune therapy in previous lines. It should be noted that ibrutinib is administered at 420 mg in CLL, which is lower than the 560 mg that is used for MCL while acalabrutinib is dosed the same across indications. Efficacy and safety of the ELEVATE RR study is reported in **Appendix K**. Additionally, a pooled safety

analysis of randomized controlled trials evaluating acalabrutinib across various indications is available in **Appendix L**

9.1 Safety data LY-004 and pooled ibrutinib trials

The safety population consisted of all subjects who received at least 1 dose of study drug.

Acalabrutinib:

All 124 subjects were intended to receive 100 mg bid of study treatment in uninterrupted 28-day cycles. At the median follow-up of 38,1 months, the median duration of treatment was 17.5 months (range: 0.1 to 65.3). A total of 59.7% of subjects received acalabrutinib for > 12 months, and 43.5% received acalabrutinib for > 24 months. The median relative dose intensity was 98.6%.

Ibrutinib:

The 370 subjects on ibrutinib were intended to receive 560 mg of study treatment in uninterrupted 28-day cycles. Safety data from a median 41.4 months of follow up is reported in the tables below. The duration of treatment was not reported for the pooled analysis.

The following tables present an overview of the safety events in the studies, including the adverse events used in the cost-minimization analysis.

Table 23 Overview of safety events.

	Acalabrutinib (N=124) (70) Median follow-up: 38,1 months	Ibrutinib (N=370) (44, 68, 71)) Median follow-up: 41,4 months	Difference, % (95 % CI)
Number of adverse events, n (%)	NR	NR	
Number and proportion of patients with ≥1 adverse events, n (%)	123 (99,2)	NR	NA
Number of serious adverse events*, n	NR	NR	
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	62 (50,0)	241 (65,1)	-15% (-25%;-5%)
Number of CTCAE grade ≥ 3 events, n	NR	NR	
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	78 (62,9)	302 (81,6))	-32% (-41%;-22%)

	Acalabrutinib (N=124) (70) Median follow-up: 38,1 months	Ibrutinib (N=370) (44, 68, 71)) Median follow-up: 41,4 months	Difference, % (95 % CI)
Number of adverse reactions, n	NR	NR	
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	99 (79,8)	NR	NA
Number and proportion of patients who had a dose reduction, n (%)	13 (10.5)	NR	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	124 (100)**	346 (93,5)	6% (4%;9%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	15 (12.1)	45 (12,2)	0% (-7%;7%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

** At study termination 18 (14,5%) of patients was still on treatment

§ CTCAE v. 5.0 must be used if available.

Table 24 Serious adverse events in ≥ 5% recorded in the studies

Adverse events	Acalabrutinib (N=124) Median follow-up: 38,1 months		Ibrutinib (N=370) Median follow-up: 41,4 months	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Pneumonia	8 (6.5)	NR	NR	NR
Major Hemorrhage	0	NR	27 (7.3)	NR
Atrial fibrillation	0	NR	22 (5.9)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Table 25 Adverse events used in the health economic model

Adverse events	Acalabrutinib	Ibrutinib		
	Frequency used in economic model (%)	Frequency used in economic model (%)	Source	Justification

Adverse events	Acalabrutinib	Ibrutinib		
Neutropenia	15.0	17.0	MAIC	Grade ≥ 3 adverse events result in treatment costs
Thrombocytopenia *	5.3	12.4	MAIC	Grade ≥ 3 adverse events result in treatment costs
Pneumonia	8.7	12.7	MAIC	Grade ≥ 3 adverse events result in treatment costs
Anemia	14.8	10.0	MAIC	Grade ≥ 3 adverse events result in treatment costs
Atrial fibrillation*	0.0	6.2	MAIC	Grade ≥ 3 adverse events result in treatment costs

* indicates, after matching, rates of grade ≥ 3 AF and thrombocytopenia were statistically significantly lower with acalabrutinib compared with ibrutinib

9.2 Safety data from external literature applied in the health economic model

NA

Table 26 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	NA							

9.3 Safety data from ELEVATE RR in CLL

The safety population consisted of all subjects who received at least 1 dose of study drug. The safety population was used for the safety analyses and subjects were analyzed

as treated. If a subject incorrectly received both acalabrutinib and ibrutinib in any amount, the subject was analyzed under the acalabrutinib arm.
The median follow-up was 41.1 months (range: 0.0 to 58.2) in the acalabrutinib arm and 40.7 months (range: 0.2 to 59.1) in the ibrutinib arm.

Acalabrutinib

All but 3 subjects randomized to the acalabrutinib arm received acalabrutinib, and 1 additional subject randomized to ibrutinib received both acalabrutinib and ibrutinib and was therefore included in the acalabrutinib arm of the safety population. The median duration of acalabrutinib treatment was 38.3 months (range: 0.3 to 55.9), with 86.5% of subjects receiving ≥ 1 year of therapy. Median relative acalabrutinib dose intensity was 99.0%.

Ibrutinib

All but 1 subject randomized to ibrutinib received ibrutinib, and 1 subject randomized to ibrutinib received both acalabrutinib and ibrutinib and was therefore analyzed in the acalabrutinib safety population as described above. The median duration of ibrutinib treatment was 35.5 months (range: 0.2 to 57.7), with 76.4% of subjects receiving ≥ 1 year of therapy.

Table 27 Overview of safety events. Data cutoff: September 15, 2020.

	Acalabrutinib (N=266) (50)	Ibrutinib (N=263) (50)	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NR
Number and proportion of patients with ≥1 adverse events, n (%)	260 (97,7)	256 (97,3)	0,4% (-2%;3%)
Number of serious adverse events*, n	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	143 (53,8)	154 (58,6)	-5% (-13%;4%)
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	183 (68,7)	197 (74,9)	-6% (-14%;2%)
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	203 (76,3)	223 (84,8)	-8% (-15%;-2%)
Number and proportion of patients who had a dose reduction, n (%)	17 (6,4)	15 (5,7)	1% (-3%;5%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	141 (52,6)	155 (58)	-6% (-14%;3%)

	Acalabrutinib (N=266) (50)	Ibrutinib (N=263) (50)	Difference, % (95 % CI)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	39 (14,7)	56 (21,3)	-7% (-13%;0%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Table 28 Serious Treatment-Emergent Adverse Events Reported in ≥ 2 Subjects with frequency of ≥ 5% in either Treatment Arm

Adverse events	Acalabrutinib (N=266) (50)		Ibrutinib (N=263) (50)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Subjects with at least 1 serious TEAE	143 (53.8%)	126 (47.4%)	154 (58.6%)	138 (52.5%)
Pneumonia	27 (10.2%)	25 (9.4%)	26 (9.9%)	22 (8.4%)
Anaemia	14 (5.3%)	11 (4.1%)	13 (4.9%)	11 (4.2%)
Pyrexia	10 (3.8%)	6 (2.3%)	5 (1.9%)	1 (0.4%)
Atrial fibrillation	6 (2.3%)	6 (2.3%)	14 (5.3%)	7 (2.7%)

10. Documentation of health-related quality of life (HRQoL)

HRQoL is not extensively reported in the pivotal studies on ibrutinib, making it challenging to draw meaningful comparisons between acalabrutinib and ibrutinib in the context of RR MCL. However, a direct comparison between acalabrutinib and ibrutinib has been conducted in RR CLL through the ELEVATE RR study, a Phase 3 trial evaluating acalabrutinib versus ibrutinib in high-risk RR CLL. Although there are differences in pathology and dosing of ibrutinib between MCL and CLL, the patients in these studies are of a similar age group. Despite its limitations, this method may offer the most solid basis for comparing the HRQoL of the two treatments. In CLL, ibrutinib is administered at 420 mg, which is lower than the 560 mg that is used for MCL. As such, this comparison should be considered as a conservative estimate for ibrutinib. Efficacy and safety of the ELEVATE RR study is reported in Appendix K. Due to these limitations this section reports the EORTC QLQ-C30 results from LY-004 and EORTC QLQ-C30 from ELEVATE RR that compared acalabrutinib and ibrutinib.

The assessment of EORTC QLQ-C30 data is conducted for comparative purposes. HRQoL data is not relevant for model due to the cost-minimization approach.

Table 29 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	LY-004	Clinical effectiveness
EORTC QLQ-C30	ELEVATE RR	Comparative analysis
EORTC QLQ-C30	PCYC	Naive comparison
FACT-Lym	RAY	Naive comparison
EQ-5D-5L	RAY	Naive comparison

10.1 Presentation of the health-related quality of life of LY004

10.1.1 Study design and measuring instrument

EORTC QLQ C-30 from LY-004

The European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) Version 3.0 was used to assess health-related quality of life. Data collections occurred at Screening and at the end of Cycle 2, Cycle 4, and Cycle 6; and then every 3 cycles (12 weeks) thereafter until PD or use of subsequent anticancer therapy. To determine the scheduled timepoints, all scores were to be assigned to a particular time window for a scheduled timepoint.
The instrument was scored, missing values handled, and standardized scores derived (ranging from 0 to 100) as recommended in the EORTC user manual. At each assessment point, summary statistics of absolute scores and changes from baseline were calculated for each subscale.

10.1.2 Data collection

Table 30 Pattern of missing data and completion

Time point	HRQoL population N	Missing N	Expected to complete N	Completion %
	Number of patients at randomization	Number of patients for whom data is missing	Number of patients "at risk" at time point X	% of patients expected to complete
BASELINE	124	0	124	94.4%
CYCLE 2 DAY 28	124	8	116	82.8%
CYCLE 4 DAY 28	124	22	102	90.2%

Time point	HRQoL population N	Missing N	Expected to complete N	Completion %
CYCLE 6 DAY 28	124	28	96	86.5%
CYCLE 9 DAY 28	124	42	82	89.0%
CYCLE 12 DAY 28	124	49	75	86.7%
CYCLE 15 DAY 28	124	50	74	91.9%
CYCLE 18 DAY 28	124	58	66	98.5%
CYCLE 21 DAY 28	124	66	58	86.2%
CYCLE 24 DAY 28	124	70	54	100.0%
CYCLE 27 DAY 28	124	72	52	98.1%
CYCLE 30 DAY 28	124	76	48	97.9%
CYCLE 33 DAY 28	124	78	46	95.7%
CYCLE 36 DAY 28	124	80	44	95.5%
CYCLE 39 DAY 28	124	83	41	95.1%
CYCLE 42 DAY 28	124	90	34	97.1%
CYCLE 45 DAY 28	124	90	34	91.2%
CYCLE 48 DAY 28	124	91	33	97.0%
CYCLE 51 DAY 28	124	92	32	90.6%
CYCLE 54 DAY 28	124	95	29	96.6%
CYCLE 57 DAY 28	124	107	17	100.0%
CYCLE 60 DAY 28	124	100	24	66.7%
CYCLE 63 DAY 28	124	111	13	100.0%
CYCLE 66 DAY 28	124	116	8	100.0%
CYCLE 69 DAY 28	124	121	3	100.0%

N= subjects include those who were on study without PD or initiation of subsequent anticancer therapy at each scheduled visit before data cutoff

10.1.3 HRQoL results

Acalabrutinib demonstrated a numerical improvement in global health status/HRQoL of the EORTC QLQ C-30 scale in patients at treatment month 2 (equivalent to 2 x 28-day cycles of treatment), compared with scores recorded at screening (23, 58). Patients also demonstrated a sustained benefit over the remainder of the 15-month follow-up period (23, 58).

Patients treated with acalabrutinib maintained high mean functional scores (>80 out of 100) on EORTC QLQ C-30 scales for physical, role, emotional, cognitive, and social functioning (72).

Patients also demonstrated low mean symptom scores on EORTC QLQ C-30 scales (out of 100): fatigue <30, nausea and vomiting <5, pain < 20, dyspnea <20, insomnia <25, appetite loss <15, constipation <10, and diarrhea <15 (72).

The numerical improvement from baseline in global health status/HRQoL of the EORTC QLQ C-30 scale demonstrated with acalabrutinib after a 15-month follow-up was also sustained throughout the entire trial period((72).

Figure 10) (72).

Figure 10 Mean Plot of EORTC QLQ-C30 Over Time: Global Health Status/Quality of Life; Final data analysis

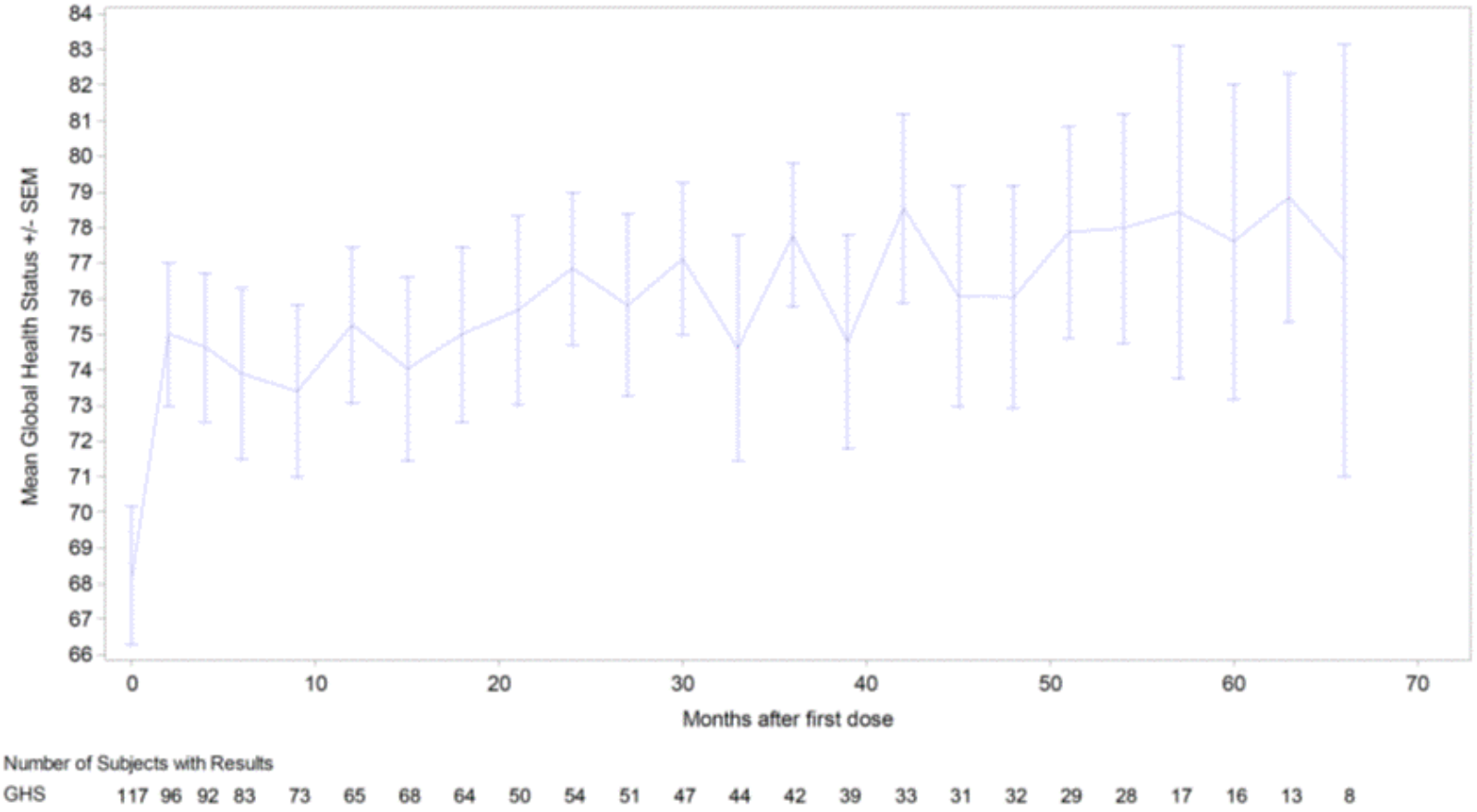


Table 31 HRQoL EORTC QLQ-C30 summary statistics Global Health Status/Quality of Life

	Observed		Change from baseline
Visit	N	Mean (SD)	Mean (SD)
BASELINE	117	68.2 (20.87)	
CYCLE 2 DAY 28	92	74.5 (19.84)	3.2 (20.29)
CYCLE 4 DAY 28	88	74.8 (20.18)	3.5 (24.36)
CYCLE 6 DAY 28	82	73.7 (21.85)	3.4 (23.57)
CYCLE 9 DAY 28	72	73.3 (20.84)	1.7 (21.07)
CYCLE 12 DAY 28	65	75.3 (17.55)	5.8 (20.93)
CYCLE 15 DAY 28	67	73.9 (21.41)	4.2 (18.99)
CYCLE 18 DAY 28	63	74.9 (19.83)	3.6 (20.83)
CYCLE 21 DAY 28	50	75.7 (18.66)	5.0 (20.55)
CYCLE 24 DAY 28	54	76.9 (15.75)	4.6 (19.80)
CYCLE 27 DAY 28	51	75.8 (18.35)	3.1 (16.99)
CYCLE 30 DAY 28	47	77.1 (14.59)	2.8 (17.49)
CYCLE 33 DAY 28	44	74.6 (20.96)	-0.8 (23.14)
CYCLE 36 DAY 28	42	77.8 (13.10)	1.2 (13.47)
CYCLE 39 DAY 28	39	74.8 (18.78)	-2.6 (19.42)
CYCLE 42 DAY 28	33	78.5 (15.31)	-0.3 (15.52)
CYCLE 45 DAY 28	31	76.1 (17.31)	-1.3 (16.82)
CYCLE 48 DAY 28	32	76.0 (17.68)	-2.1 (17.07)
CYCLE 51 DAY 28	29	77.9 (15.95)	-1.7 (16.72)
CYCLE 54 DAY 28	28	78.0 (17.00)	-0.3 (17.49)
CYCLE 57 DAY 28	17	78.4 (19.33)	0.5 (19.43)
CYCLE 60 DAY 28	16	77.6 (17.67)	2.6 (17.67)
CYCLE 63 DAY 28	13	78.8 (12.55)	1.9 (17.40)
CYCLE 66 DAY 28	8	77.1 (17.11)	2.1 (16.52)
CYCLE 69 DAY 28	3	72.2 (26.79)	-11.1 (26.79)

N= "subjects with baseline and at least 1 post-baseline record in the analysis population"

10.1.4 Study design and measuring instrument

EORTC QLQ C-30 from ELEVATE RR

As mentioned, documentation on HRQOL is not extensively reported in the pivotal studies on ibrutinib, making it challenging to draw meaningful comparisons of QOL between acalabrutinib and ibrutinib in the context of RR MCL. However, a direct comparison between acalabrutinib and ibrutinib has been conducted in RR CLL through the ELEVATE RR study, a Phase 3 trial evaluating acalabrutinib versus ibrutinib in this patient population (50). Results are reported below.

The European Organization for Research and Treatment of Cancer EORTC QLQ-C30 was used to assess health-related quality of life. PROs were administered the first week of the treatment phase (first visit following randomization), at Week 12 of treatment, every 4 weeks thereafter until Week 24, and then every 12 weeks thereafter. PRO administration ceased once study drug had been discontinued (e.g., treatment phase ended due to progression or unacceptable toxicity). The instrument was scored, missing values handled, and standardized scores derived (ranging from 0 to 100) as recommended in the EORTC user manual. At each assessment point, summary statistics of absolute scores and changes from baseline were calculated for each subscale.

10.1.5 Data collection

Table 32 Pattern of missing data and completion

Time point	HRQoL population N	Missing N	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	A=268, I=265	A=3, I=1	A=265, I=264	A=244 (92%), I=237 (89%)
Week 12	A=268, I=265	A=14, I=19	A=254, I=246	A=223 (88%), I=216 (82%)
Week 16	A=268, I=265	A=20, I=25	A=248, I=240	A=209 (84%), I=196 (74%)
Week 20	A=268, I=265	A=22, I=27	A=246, I=238	A=210 (85%), I=197 (74%)
Week 24	A=268, I=265	A=26, I=33	A=242, I=232	A=216 (89%), I=201 (76%)
Week 36	A=268, I=265	A=33, I=46	A=235, I=219	A=210 (89%), I=191 (72%)
Week 48	A=268, I=265	A=36, I=53	A=232, I=212	A=199 (86%), I=181 (68%)
Week 60	A=268, I=265	A=42, I=69	A=226, I=196	A=198 (88%), I=167 (63%)

Time point	HRQoL population N	Missing N	Expected to complete N	Completion N (%)
Week 72	A=268, I=265	A=51, I=77	A=217, I=188	A=192 (88%), I=165 (62%)
Week 84	A=268, I=265	A=60, I=85	A=208, I=180	A=183 (88%), I=159 (60%)
Week 96	A=268, I=265	A=68, I=91	A=200, I=174	A=174 (87%), I=152 (57%)
Week 108	A=268, I=265	A=74, I=102	A=194, I=163	A=180 (93%), I=140 (53%)
Week 120	A=268, I=265	A=79, I=109	A=189, I=156	A=167 (88%), I=140 (53%)
Week 132	A=268, I=265	A=94, I=117	A=174, I=148	A=156 (90%), I=129 (49%)
Week 144	A=268, I=265	A=96, I=122	A=172, I=143	A=146 (85%), I=122 (46%)
Week 156	A=268, I=265	A=117, I=134	A=151, I=131	A=129 (85%), I=114 (43%)
Week 168	A=268, I=265	A=133, I=150	A=135, I=115	A=101 (75%), I=87 (33%)
Week 180	A=268, I=265	A=165, I=175	A=103, I=90	A=78 (76%), I=68 (26%)
Week 192	A=268, I=265	A=190, I=194	A=78, I=71	A=52 (67%), I=53 (20%)
Week 204	A=268, I=265	A=218, I=215	A=50, I=50	A=30 (60%), I=29 (11%)
Week 216	A=268, I=265	A=236, I=231	A=32, I=34	A=19 (59%), I=23 (09%)
Week 228	A=268, I=265	A=252, I=254	A=16, I=11	A=12 (75%), I=5 (02%)
Week 240	A=268, I=265	A=265, I=260	A=3, I=5	A=3 (100%), I=4 (02%)
Week 252	A=268, I=265		A=-, I=1	

N= subjects include those who were on study without PD or initiation of subsequent anticancer therapy at each scheduled visit before data cutoff

10.1.6 HRQoL results

The change from baseline in the EORTC QLQ-C30 scores over the treatment phase was analyzed using a MMRM methodology, with the model parametrized to include random effects for subject and study week and a residual covariance structure.

The model includes data through the last timepoint at which at least 25% of subjects in each arm (relative to baseline data) have non-missing data. Model covariance structures were compared using information criteria (AIC and BIC). For all domains except Physical Functioning, Autoregressive was selected for all models; for Physical Functioning Banded Toeplitz was selected for all models.

For Global Health Status, the full model did not yield a significant time x arm interaction (B [SE]: - 0.032 [0.018]; p=0.082) indicating that (the lack of) difference between arms in change from baseline did not differ by timepoint.
An increase (i.e., improvement) in mean score from baseline was observed at the first timepoint assessment (i.e., Week 12) in both arms with this increase stabilizing thereafter.

The increase observed at Week 12 was comparable between arms and was considered clinically meaningful (i.e., ≥8). The mean increase from baseline was + 12.48 (SE: 2.46) and + 11.17 (SE: 2.53) in the acalabrutinib and ibrutinib arms, respectively.

The difference in mean change from baseline between arms across all timepoints was + 1.32 (95% CI [- 2.75; 5.38]; p=0.523) in favor of acalabrutinib, but the difference was not statistically significant.

Figure 11 LS mean change from baseline in EORTC QLQ-C30 GHS

A. Global Health Status

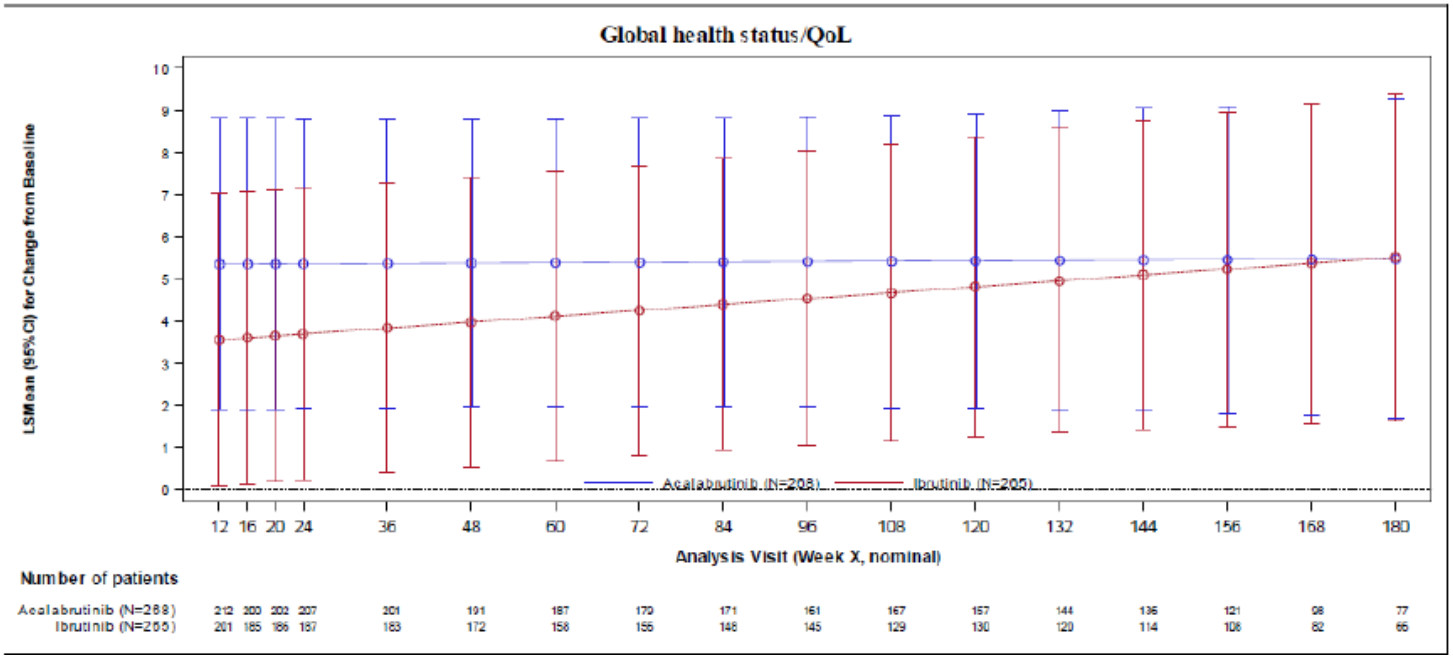


Figure is hard to read, higher resolution can't be obtained, please refer to Table 33 for number of patients at each timepoint.

Y-axis = LSMean (95% CI) for Change from baseline, X-axis=Analysis visit (Week x, nominal)

Table 33 HRQoL change from baseline in the EORTC QLQ-C30 ITT population

	Acalabrutinib		Ibrutinib		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Average	-	5.39 (1.74)	-	4.26 (1.75)	1.12 ([-1.26; 3.51]) 0.356
Week 12	212	5.35 (1.76)	201	3.55 (1.77)	1.79 ([-0.77; 4.36]) 0.170
Week 16	200	5.35 (1.76)	185	3.60 (1.77)	1.75 ([-0.79; 4.29]) 0.176
Week 20	202	5.35 (1.75)	186	3.65 (1.76)	1.71 ([-0.81; 4.22]) 0.182
Week 24	207	5.36 (1.75)	187	3.69 (1.76)	1.66 ([-0.82; 4.15]) 0.189
Week 36	201	5.37 (1.74)	183	3.83 (1.75)	1.53 ([-0.90; 3.96]) 0.216
Week 48	191	5.37 (1.74)	172	3.97 (1.75)	1.40 ([-0.99; 3.79]) 0.250
Week 60	187	5.38 (1.74)	158	4.11 (1.75)	1.27 ([-1.11; 3.65]) 0.294
Week 72	179	5.39 (1.74)	156	4.25 (1.75)	1.14 ([-1.24; 3.52]) 0.348
Week 84	171	5.40 (1.74)	148	4.39 (1.76)	1.01 ([-1.41; 3.43]) 0.412
Week 96	161	5.41 (1.75)	145	4.53 (1.77)	0.88 ([-1.59; 3.35]) 0.485
Week 108	167	5.42 (1.77)	129	4.67 (1.79)	0.75 ([-1.80; 3.29]) 0.564
Week 120	157	5.43 (1.79)	130	4.81 (1.81)	0.62 ([-2.02; 3.25]) 0.646
Week 132	144	5.44 (1.81)	120	4.95 (1.84)	0.49 ([-2.26; 3.23]) 0.729
Week 144	136	5.45 (1.83)	114	5.09 (1.87)	0.35 ([-2.52; 3.23]) 0.808
Week 156	121	5.46 (1.86)	108	5.23 (1.90)	0.22 ([-2.79; 3.24]) 0.884
Week 168	98	5.46 (1.89)	82	5.37 (1.94)	0.09 ([-3.07; 3.26]) 0.954
Week 180	77	5.47 (1.92)	66	5.51 (1.98)	-0.04 ([-3.36; 3.29]) 0.982

N= "subjects with baseline and at least 1 post-baseline record in the analysis population"

10.2 Naïve comparison of ibrutinib studies

As part of the assessment the DMC secretariate has asked for the inclusion of available HRQoL to enable a naïve comparison of HRQoL between acalabrutinib and ibrutinib. The available HRQoL data is presented below and is added to Table 29. The naïve comparisons are presented in the HRQoL sections in section 10.2.3, section 10.2.6 and 10.2.7. Please note that these naïve comparisons entail a high amount of uncertainty due to not adjusting for different patient populations, and AstraZeneca does not support comparisons across different HRQoL instruments.

10.2.1 EORTC QLQ-C30 from PCYC

EORTC QLQ-C30 was measured at pre-dose and at cycle 5, the results are only available on clinicaltrials.gov. The authors only report number of patients analysed and a single mean value with standard deviation.

https://clinicaltrials.gov/study/NCT01236391?tab=results

10.2.2 Data collection

Participants received PCI-32765 560 mg daily and completed the EORTC QLQ-C30 questionnaire at Pre-Dose and at Cycle 5 (week 20).

10.2.3 HRQoL results

A total of 69 out of 115 eligible patients was analysed.

The mean change from pre-dose to cycle 5 in EORTC QLQ-C30 was 0.6 (SD: 22.4).

Naïve comparison with LY004

In Table 31 mean changes from baseline in EORTC QLQ-C30 scores were shown for the LY004 study. At Cycle 4, 88 of the 124 eligible patients were included in the analysis, yielding a mean change from baseline of 3.5 (SD: 24.36). For Cycle 6, 82 of the 124 eligible patients were analysed, with a mean change from pre-dose to Cycle 6 of 3.4 (SD: 23.57).

In comparison, for the PCYC study, the mean change from pre-dose to Cycle 5 in EORTC QLQ-C30 was 0.6. Over a comparable treatment period in LY004 (Cycles 4–6), mean changes ranged from 3.5 to 3.4.

These results indicate that acalabrutinib was associated with a numerically greater improvement in EORTC QLQ-C30 scores compared to ibrutinib. The greater improvement seen with acalabrutinib is in line with the improved safety profile of acalabrutinib.

10.2.4 FACT-LYM from RAY

FACT-LYM is available in 3-year follow-up publication of RAY (62).

Time to worsening in the Lymphoma subscale of the FACT-Lym, defined as the interval from the date of randomization to the start date of worsening. Worsening was defined by a 5-point decrease from baseline. FACT-Lym Lymphoma subscale contains 15 questions, scores from 0 to 4 for each question (higher the worse). Lymphoma subscale score is the total of reverse scores, range 0 to 60. Higher scores indicate a better quality of life.

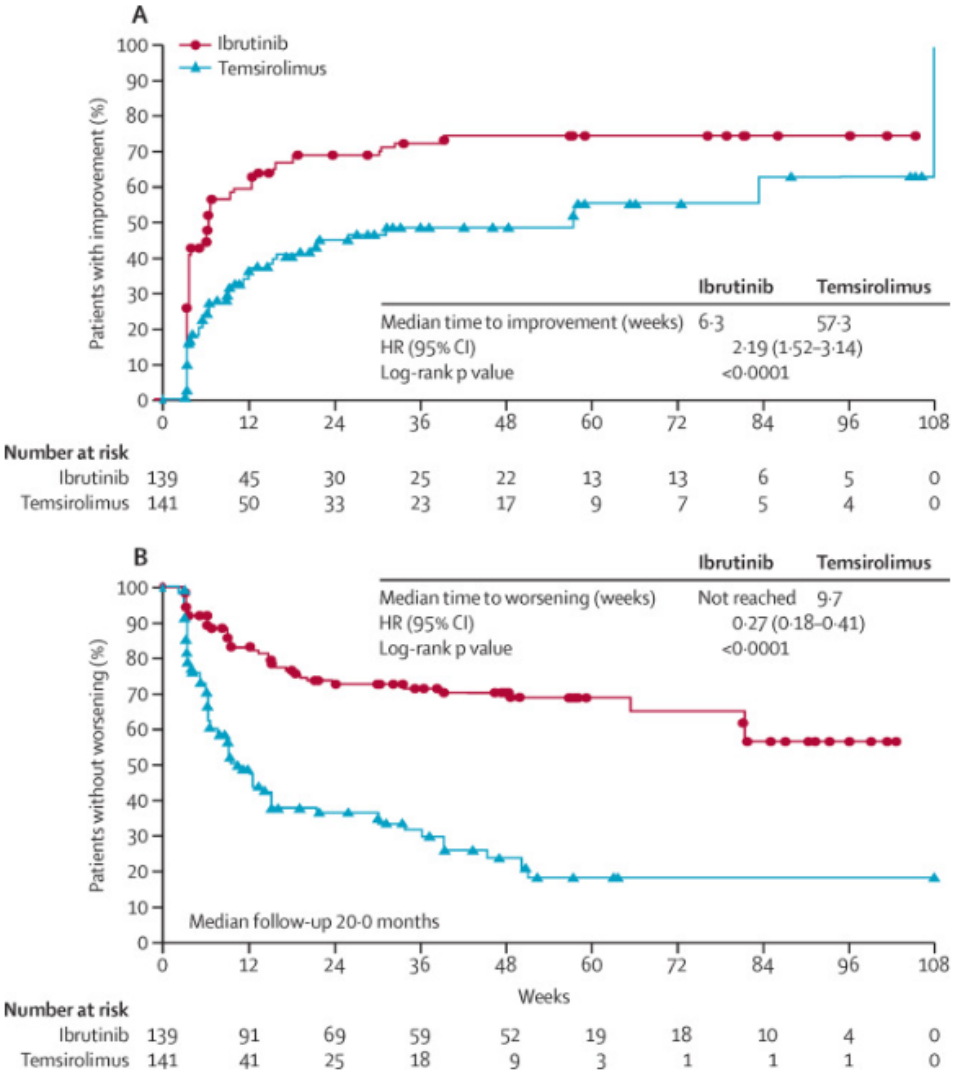
10.2.5 Data collection

NA

10.2.6 HRQoL results

A greater proportion of patients treated with ibrutinib had a clinically meaningful improvement in lymphoma symptoms versus those treated with temsirolimus (86 [62%] *vs* 50 [35%]). Improvement in symptoms occurred more quickly with ibrutinib versus temsirolimus, with a median time to clinically meaningful improvement of 6·3 (IQR not estimable) weeks versus 57·3 (101·4) weeks, respectively (p<0·0001; figure 12). Similarly, a smaller proportion of patients treated with ibrutinib experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (37 [27%] *vs* 73 [52%]) and worsening of symptoms occurred later with ibrutinib versus temsirolimus (HR 0·27 [95% CI 0·18–0·41]; p<0·0001).

Figure 12 Time to clinically meaningful improvement and time to worsening on the FACT-Lym lymphoma subscale in the intention-to-treat population



(A) Time to clinically meaningful improvement on the FACT-Lym lymphoma subscale. (B) Time to worsening on the FACT-Lym lymphoma subscale. HR=hazard ratio.

Naïve comparison with LY004

LY004 did not measure FACT-LYM, therefore making even a naïve comparison between two different HRQoL instruments not recommendable. However, when comparing Figure 10 and **Error! Reference source not found.**Figure 11, it is evident that both acalabrutinib and ibrutinib lead to improvements in health-related quality of life for patients receiving either treatment when compared with their baseline values.

10.2.7 EQ-5D-5L from RAY

The EQ-5D-5L results are only available on clinicaltrials.gov.

https://www.clinicaltrials.gov/study/NCT01646021?tab=results

10.2.8 Data collection

Baseline, Cycle 2, 3, 4, 5, 6, 7, 8, 11, 14, 17, 20, 28, 36 and End of treatment (approximately up to 23 months).

10.2.9 HRQoL results

Table 34 was made using EQ-5D-5L data available on:

https://www.clinicaltrials.gov/study/NCT01646021?tab=results

The table show mean change from baseline in EQ-5D-5L and was kept stable from baseline.

Table 34 Comparative Table: Ibrutinib vs Temsirolimus from Clinicaltrials

Time Point	Ibrutinib (Mean (SD), N Analyzed)	Temsirolimus (Mean (SD), N Analyzed)
Overall Participants Analyzed	138	130
Baseline	0.7 (0.2), 130	0.7 (0.2), 120
Change at Cycle 2	0.0 (0.2), 113	0.0 (0.2), 95
Change at Cycle 3	0.1 (0.2), 115	-0.1 (0.2), 85
Change at Cycle 4	0.0 (0.2), 103	0.0 (0.3), 70

Time Point	Ibrutinib (Mean (SD), N Analyzed)	Temsirolimus (Mean (SD), N Analyzed)
Change at Cycle 5	0.0 (0.2), 102	0.0 (0.2), 57
Change at Cycle 6	0.1 (0.2), 99	0.0 (0.2), 49
Change at Cycle 7	0.0 (0.2), 98	0.0 (0.2), 39
Change at Cycle 8	0.0 (0.2), 90	0.0 (0.2), 37
Change at Cycle 11	0.0 (0.2), 88	0.0 (0.2), 33
Change at Cycle 14	0.0 (0.2), 72	0.0 (0.1), 26
Change at Cycle 17	0.0 (0.2), 69	0.0 (0.2), 19
Change at Cycle 20	0.0 (0.2), 64	0.0 (0.2), 16
Change at Cycle 28	-0.1 (0.2), 22	0.1 (0.2), 6
Change at Cycle 36	0.0 (0.3), 10	-0.1 (0.2), 4
Change at End of Treatment	0.0 (0.2), 23	-0.1 (0.3), 65

Naïve comparison with LY004

LY004 did not measure EQ-5D, and making a naïve comparison between two different HRQoL instruments not recommendable. However, when comparing Table 31 and Table 34, it is evident that acalabrutinib lead to improvements in HRQol measured with EORTC QLQ-C30 for patients throughout the study period, while ibrutinib did not worsen or improve HRQol from baseline measured with EQ-5D-5L across the study period.

10.3 Health state utility values (HSUVs) used in the health economic model

NA

10.3.1 HSUV calculation

NA

10.3.1.1 Mapping

NA

10.3.2 Disutility calculation

NA

10.3.3 HSUV results

NA

Table 35 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

10.4 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

NA

10.4.1 Study design

NA

10.4.2 Data collection

NA

10.4.3 HRQoL Results

NA

10.4.4 HSUV and disutility results

NA

Table 36 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

Table 37 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

The medicines and dosing used in the analysis can be found in Table 38, while the costs of the medicines can be found in Table 39. The costs of medicines are based on prices from medicinpriser.dk (AIP). It is assumed that patients will incur the full annual cost of treatment each year in the 5-year analysis, without discontinuation. The assumption of 100% relative dose intensity (RDI) is based on no reported differences in the median RDI of LY004 (98.6%) and the pooled ibrutinib results (98.4%) (71). The resulting daily costs are DKK 1 366.48 for acalabrutinib and DKK 1 817.96 for ibrutinib, corresponding to an annual cost of DKK 499 106 and DKK 664 011 respectively, DKK 164 905 higher for ibrutinib than for acalabrutinib.

Table 38 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Acalabrutinib	200 mg	100 %	100 mg twice daily	No
Ibrutinib	560 mg	100 %	560 mg daily	No

The medicine costs used for the analysis can be found in Table 39. Medicine costs used in the model

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Cost per mg	Cost per day
Acalabrutinib	100 mg	60	40 994.30	6.83	1 366.48
Ibrutinib	560 mg	28	50 902.94	3.25	1 817.96

11.2 Medicines– co-administration

NA

11.3 Administration costs

The cost-minimization analysis assumes no administration costs as both treatments are oral treatments, any instructions to the patient on administration of acalabrutinib and ibrutinib is expected to be the same and is as such not modelled.

Table 40 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	Every day	0	NA	Assumption

11.4 Disease management costs

As the cost-minimization analysis assumes equal efficacy it is assumed that disease management costs will be the same between the two treatments, and disease management costs are not included in the calculations.

Table 41 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
NA	NA	NA	NA	NA

11.5 Costs associated with management of adverse events

The cost minimization analysis includes costs for grade 3+ AEs that were included in the MAIC shown in 7.1.3. The included AEs were neutropenia, thrombocytopenia, pneumonia, anemia, atrial fibrillation and hypertension.

The total cost was calculated as the product of the percentage of patients experiencing the adverse event and its respective unit cost. The percentage was taken from the results of the MAIC, shown in Table 18 in section 7.1.3. The adverse event costs only incur the first year of the analysis.

It is assumed that AEs will require a hospital stay for more than 12 hours, and a stay above 12 hours was used in the Danish Health Data Authority's Interactive DRG tool when estimating costs. The unit costs for AE management used in the model are presented in Table 42.

Table 42 Cost associated with management of adverse events

	DRG code	Unit cost (DKK)/DRG tariff
Neutropenia	16MA03 Granulo- og trombocytopeni. Diagnosis code: DD709 Neutropeni UNS	37 482
Thrombocytopenia	16MA03 Granulo- og trombocytopeni. Diagnosis code: DD696 Trombocytopeni UNS	37 482
Pneumonia	04MA13 Lungebetændelse og pleuritis, pat. mindst 60 år Diagnosis code: DJ189 Pneumoni UNS	44 614
Anemia	16MA10, øvrige sygdomme i blod og bloddannende organer. Diagnosis code: DD649, Anæmi UNS	28 342
Atrial fibrillation	05MA07 Hjertearytmi og synkope. Diagnosis code: DI489, Atrieflagren eller atrieflimren UNS	21 047
Hypertension	05MA11 Hypertension Diagnosis code: DI159 Sekundær hypertension UNS	18 807

11.6 Subsequent treatment costs

NA

Table 43 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
NA				
NA				

11.7 Patient costs

The cost-minimization analysis assumes equal efficacy between acalabrutinib and ibrutinib, and both drugs are oral drugs. Patient costs for disease management and administration are therefore not included in the analysis. There may be some difference in patient costs due to adverse events, but these are expected to have a small impact on the results, and a conservative approach was taken where these costs are not included.

Table 44 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
NA	

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

NA

12. Results

12.1 Base case overview

Table 45 Base case overview

Feature	Description
Comparator	Ibrutinib
Type of model	Cost minimization
Time horizon	5 years
Treatment line	2nd line. Subsequent treatment lines not included.
Measurement and valuation of health effects	NA
Costs included	Medicine costs Costs of adverse events
Dosage of medicine	Fixed dosage according to SmPC
Average time on treatment	Acalabrutinib: 5 years Ibrutinib: 5 years
Parametric function for PFS	NA
Parametric function for OS	NA
Inclusion of waste	NA
Average time in model health state Health state 1 Health state 2 Health state 3 Death	NA

12.1.1 Base case results

The results show cost savings for acalabrutinib at around DKK 776 000.

Table 46 Base case results, discounted estimates

	Acalabrutinib	Ibrutinib	Difference
Medicine costs	2 332 360	3 102 974	-770 614
Medicine costs – co-administration	NA	NA	NA
Administration	0	0	0
Disease management costs	NA	NA	NA
Costs associated with management of adverse events	16 174	21 784	-5 610
Subsequent treatment costs	NA	NA	NA
Patient costs	NA	NA	NA
Palliative care costs	NA	NA	NA

	Acalabrutinib	Ibrutinib	Difference
Total costs	**2 348 534**	**3 124 758**	**-776 225**
Life years gained (health state A)	NA	NA	NA
Life years gained (health state B)	NA	NA	NA
Total life years	**NA**	**NA**	**NA**
QALYs (state A)	NA	NA	NA
QALYs (state B)	NA	NA	NA
QALYs (adverse reactions)	NA	NA	NA
Total QALYs	**NA**	**NA**	**NA**
Incremental costs per life year gained		**NA**	
Incremental cost per QALY gained (ICER)		**NA**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Sensitivity analyses were conducted by changing the drug prices of acalabrutinib and ibrutinib in 10 % increments up to ±100 %. The results of the two way sensitivity analyses where both were changed simultaneously can be found in Table 48, while a one way analysis changing only the drug price of acalabrutinib upwards can be found in Table 47. Additionally, adverse events have a very low impact on results, where excluding them from the calculations only reduces the cost difference by approximately DKK 5 600, see Table 46.

Table 47 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	-776 225	-	-
Change in drug price for acalabrutinib	+10%	Assumption	-542 989	-	-
Change in drug price for acalabrutinib	+20%	Assumption	-309 753	-	-
Change in drug price for acalabrutinib	+30%	Assumption	-76 517	-	-
Change in drug price for acalabrutinib	+40%	Assumption	156 719	-	-

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Change in drug price for acalabrutinib	+50%	Assumption	389 955	-	-
Change in drug price for acalabrutinib	+60%	Assumption	623 191	-	-
Change in drug price for acalabrutinib	+70%	Assumption	856 427	-	-
Change in drug price for acalabrutinib	+80%	Assumption	1 089 663	-	-
Change in drug price for acalabrutinib	+90%	Assumption	1 322 899	-	-
Change in drug price for acalabrutinib	+100%	Assumption	1 556 135	-	-

Table 48 Two-way sensitivity analysis, results of cost minimization with changes in drug prices of acalabrutinib or ibrutinib (in thousands, DKK). Green=Acalabrutinib has lower costs. Red=Ibrutinib has lower costs.

Price change acala-brutinib	Price change ibrutinib																				
	-100 %	-90 %	-80 %	-70 %	-60 %	-50 %	-40 %	-30 %	-20 %	-10 %	**0 %**	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100 %
-100 %	-6	-316	-626	-937	-1 247	-1 557	-1 867	-2 178	-2 488	-2 798	***-3 109***	-3 419	-3 729	-4 039	-4 350	-4 660	-4 970	-5 281	-5 591	-5 901	-6 212
-90 %	228	-83	-393	-703	-1 014	-1 324	-1 634	-1 944	-2 255	-2 565	***-2 875***	-3 186	-3 496	-3 806	-4 117	-4 427	-4 737	-5 047	-5 358	-5 668	-5 978
-80 %	461	151	-160	-470	-780	-1 091	-1 401	-1 711	-2 022	-2 332	***-2 642***	-2 952	-3 263	-3 573	-3 883	-4 194	-4 504	-4 814	-5 124	-5 435	-5 745
-70 %	694	384	74	-237	-547	-857	-1 168	-1 478	-1 788	-2 099	***-2 409***	-2 719	-3 029	-3 340	-3 650	-3 960	-4 271	-4 581	-4 891	-5 202	-5 512
-60 %	927	617	307	-4	-314	-624	-934	-1 245	-1 555	-1 865	***-2 176***	-2 486	-2 796	-3 107	-3 417	-3 727	-4 037	-4 348	-4 658	-4 968	-5 279
-50 %	1 161	850	540	230	-81	-391	-701	-1 012	-1 322	-1 632	***-1 942***	-2 253	-2 563	-2 873	-3 184	-3 494	-3 804	-4 114	-4 425	-4 735	-5 045
-40 %	1 394	1 084	773	463	153	-158	-468	-778	-1 089	-1 399	***-1 709***	-2 019	-2 330	-2 640	-2 950	-3 261	-3 571	-3 881	-4 192	-4 502	-4 812
-30 %	1 627	1 317	1 006	696	386	76	-235	-545	-855	-1 166	***-1 476***	-1 786	-2 097	-2 407	-2 717	-3 027	-3 338	-3 648	-3 958	-4 269	-4 579
-20 %	1 860	1 550	1 240	929	619	309	-2	-312	-622	-932	***-1 243***	-1 553	-1 863	-2 174	-2 484	-2 794	-3 104	-3 415	-3 725	-4 035	-4 346
-10 %	2 094	1 783	1 473	1 163	852	542	232	-79	-389	-699	***-1 009***	-1 320	-1 630	-1 940	-2 251	-2 561	-2 871	-3 182	-3 492	-3 802	-4 112
0 %	***2 327***	***2 016***	***1 706***	***1 396***	***1 086***	***775***	***465***	***155***	***-156***	***-466***	***-776***	***-1 087***	***-1 397***	***-1 707***	***-2 017***	***-2 328***	***-2 638***	***-2 948***	***-3 259***	***-3 569***	***-3 879***
10 %	2 560	2 250	1 939	1 629	1 319	1 008	698	388	78	-233	***-543***	-853	-1 164	-1 474	-1 784	-2 094	-2 405	-2 715	-3 025	-3 336	-3 646
20 %	2 793	2 483	2 173	1 862	1 552	1 242	931	621	311	1	***-310***	-620	-930	-1 241	-1 551	-1 861	-2 172	-2 482	-2 792	-3 102	-3 413
30 %	3 026	2 716	2 406	2 096	1 785	1 475	1 165	854	544	234	***-77***	-387	-697	-1 007	-1 318	-1 628	-1 938	-2 249	-2 559	-2 869	-3 179
40 %	3 260	2 949	2 639	2 329	2 019	1 708	1 398	1 088	777	467	***157***	-154	-464	-774	-1 084	-1 395	-1 705	-2 015	-2 326	-2 636	-2 946
50 %	3 493	3 183	2 872	2 562	2 252	1 941	1 631	1 321	1 011	700	***390***	80	-231	-541	-851	-1 162	-1 472	-1 782	-2 092	-2 403	-2 713
60 %	3 726	3 416	3 106	2 795	2 485	2 175	1 864	1 554	1 244	933	***623***	313	3	-308	-618	-928	-1 239	-1 549	-1 859	-2 169	-2 480
70 %	3 959	3 649	3 339	3 029	2 718	2 408	2 098	1 787	1 477	1 167	***856***	546	236	-74	-385	-695	-1 005	-1 316	-1 626	-1 936	-2 247
80 %	4 193	3 882	3 572	3 262	2 951	2 641	2 331	2 021	1 710	1 400	***1 090***	779	469	159	-152	-462	-772	-1 082	-1 393	-1 703	-2 013
90 %	4 426	4 116	3 805	3 495	3 185	2 874	2 564	2 254	1 943	1 633	***1 323***	1 013	702	392	82	-229	-539	-849	-1 159	-1 470	-1 780
100 %	4 659	4 349	4 039	3 728	3 418	3 108	2 797	2 487	2 177	1 866	***1 556***	1 246	936	625	315	5	-306	-616	-926	-1 237	-1 547

12.2.2 Probabilistic sensitivity analyses

NA

13. Budget impact analysis

Assumptions on patient numbers are explained in section 3.2. The same patient numbers are used in the budget impact analysis. 80% of newly diagnosed patients start systemic therapy at diagnosis, with 46 % having a relapse. Of these, 80 % are assumed to be eligible for treatment with acalabrutinib, resulting in 26 patients yearly. In the budget impact analysis, it is assumed that all these eligible patients will receive acalabrutinib if acalabrutinib is implemented (100 % market share). If acalabrutinib is not implemented, it is assumed that 0 % of these 26 patients will receive acalabrutinib.

Costs for the budget impact analysis are taken from the cost-minimization model, without discounting. The resulting annual cost is DKK 499 106 for acalabrutinib and DKK 664 011 for ibrutinib, DKK 164 905 higher for ibrutinib than for acalabrutinib. The analysis uses a simplified approach where it is assumed that patients are treated throughout the time horizon of the budget impact analysis. Adverse events are assumed to only incur the first year of treatment.

The expected budget impact at AIP prices is around DKK -22 million in the fifth year, making acalabrutinib cost saving at the AIP list price level.

Number of patients (including assumptions of market share)

Table 49 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Acalabrutinib	26	26	26	26	26
Ibrutinib	0	0	0	0	0
			Non-recommendation		
Acalabrutinib	0	0	0	0	0
Ibrutinib	26	26	26	26	26

Budget impact

Table 50 Expected budget impact of recommending the medicine for the indication (in million DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	13,3	26,3	39,2	52,1	65,1

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is NOT recommended	17,8	35,0	52,2	69,4	86,6
Budget impact of the recommendation	**-4,4**	**-8,7**	**-13,0**	**-17,2**	**-21,5**

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

[Complete Table 51 for each study included. Comply with section 3 of the methods guide.]

Table 51 Main characteristic of studies included

Trial name: An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma **(LY-004)**	**NCT number: 02213926**
Objective	The primary objective in this study was to determine the activity of acalabrutinib in subjects with relapsed/refractory MCL as measured primarily by response rate. In addition, the activity of acalabrutinib was evaluated using duration of response, progression-free survival, and overall survival. Secondary objectives included the characterization of the safety profile and PK profile of acalabrutinib, as well as the evaluation of PD effects of acalabrutinib (55).

Trial name: An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma **(LY-004)**	**NCT number: 02213926**
Publications – title, author, journal, year	Wang, Michael, et al. "Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial." *The Lancet* 391.10121 (2018): 659-667 (35). Furman RR, Byrd JC, Owen RG, et al. Safety of acalabrutinib (Acala) monotherapy in hematologic malignancies: Pooled analysis from clinical trials. J Clin Oncol 2020;38(15_suppl):8064 (73). Furman RR, Byrd JC, Owen RG, et al. Safety of acalabrutinib monotherapy in mature B cell malignancies: pooled analysis from clinical trials. Abstract EP698. Presented at the European Hematology Association (EHA) Annual Meeting, June 11-21, 2020 (virtual meeting) (74). Wang M, Rule S, Zinzani PL, et al. Acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a Phase 2 study. Blood 2020;136 (supplement):38-9 (75). Wang M, Rule S, Zinzani PL, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma [letter]. Leukemia 2019;33:2762–6 (76). 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 (Supplement 1):2876 (51).
Study type and design	LY004 was a Phase 2, single-arm, multicenter, open-label study in subjects with histologically documented MCL, who had relapsed after at least 1 prior treatment regimens. The primary completion date of the study was 04 Dec. 2020 (57).
Sample size (n)	124 patients were enrolled and all patients received treatment (35).
Main inclusion criteria	Men and women aged ≥ 18 years Pathologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1. Disease has relapsed after or been refractory to ≥ 1 prior therapy for MCL and now requires further treatment. Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy. At least 1, but no more than 5, prior treatment regimens for MCL. Eastern Cooperative Oncology Group performance status of ≤ 2 (55).

Trial name: An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma **(LY-004)**	**NCT number: 02213926**
Main exclusion criteria	Patients with significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction) within 6 months of screening, any class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval more than 480 msec. Concomitant treatment with warfarin or equivalent vitamin K antagonists Previous treatment with BCR inhibitors (BTK, PI3K, or SYK inhibitors) or BCL-2 inhibitors. Any immunotherapy within 4 weeks of first dose of study drug. History of prior malignancy (with some exclusions) Absolute neutrophil count less than 0.75 × 10^9 /L or platelet count less than 50 × 10^9 /L (or neutrophil count <0.50 × 10^9/ L or platelet count <30 × 10^9/L for patients with bone marrow involvement) Creatinine level more than 2.5-times the upper limit of normal (55).
Intervention	Acalabrutinib (100 mg) was given orally twice per day in 28-day cycles until progressive disease or unacceptable toxicity. All 124 patients enrolled in the study received treatment (35).
Comparator(s)	This was a single-arm study with no comparator (35).
Follow-up time	As of the data cutoff date for the 54-month close-out analysis (04 December 2020), the median follow-up was 38.1 months (range: 0.3 to 68.8) (57).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**<u>All study endpoints (55):</u>** **The primary endpoint** of the study is overall response rate (ORR), defined as the proportion of subjects achieving either a partial remission (PR) or complete response (CR) according to the Lugano Classification for NHL as assessed by investigators. **Secondary endpoints:** Efficacy: Investigator assessed duration of response (DOR) Investigator assessed progression-free survival (PFS) Overall survival (OS) Independent Review Committee (IRC)-assessed ORR, DOR, and PFS per Lugano Classification Safety:

Frequency, severity, and relatedness of adverse events (AEs)

Frequency of AEs requiring discontinuation of study drug or dose reductions

Effect of acalabrutinib on peripheral T/B/natural killer (NK) cell counts

Effect of acalabrutinib on serum immunoglobulin levels

Pharmacokinetics:

Plasma pharmacokinetics of acalabrutinib

Exploratory endpoints:

Patient-reported outcomes (PRO): Health-related quality of life

Time to response (TTR) per Lugano Classification as assessed by investigators and IRC

Time to initial response

Time to best response

Time to complete response

IRC-assessed ORR, DOR, TTR, and PFS per Revised Response Criteria for Malignant Lymphoma

[State all primary, secondary * MERGEFORMAT and exploratory endpoints of the study, regardless of whether results are provided in this application.

Endpoints included in this application:

- ORR
- TTR
- PFS
- OS
- SAFETY
- HRQOL: EORTC QLQ-C30

Method of analysis

The safety analyses and primary efficacy analyses for all efficacy endpoints (except for DOR and TTR) was performed on the All-treated population, defined as all enrolled subjects who receive ≥ 1 dose of study drug. The analysis of DOR and TTR was conducted on the subset of the All-treated population who achieve CR or PR as their best overall response.

Duration of response, progression-free survival, and overall survival was estimated using the Kaplan-Meier method.

Trial name: An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma **(LY-004)**	**NCT number: 02213926**
	Non-compartmental pharmacokinetic analysis of individual plasma acalabrutinib concentration-time data was done using Phoenix WinNonlin (version 6.4). The European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) was used to assess health-related quality of life (55).
Subgroup analyses	A prespecified subgroup analyses were performed for the proportion of patients achieving an overall response and complete response using prespecified baseline and disease characteristic variables. The analysis was performed to evaluate the consistency of investigator-assessed ORR and CR rates. The prespecified baseline and disease characteristic variables included in the subgroup analysis are listed below: Sex (male vs. female) Age category (year) (< 65 vs. ≥ 65; < 75 vs. ≥ 75) Race (White vs. Non-White vs. Not Reported) Ann Arbor staging for lymphoma (< 4 vs. 4) Simplified MIPI score (Low risk [0-3], Intermediate risk [4-5] or High risk [6-11]) Baseline ECOC performance status (0 vs. 1 vs. ≥ 2) Bone marrow involvement (Yes vs. No) Extranodal disease (Yes vs. No) Tumor bulk (largest diameter, cm): (< 5 cm vs. ≥ 5 cm and < 10 cm versus ≥ 10 cm) Gastrointestinal disease (Yes. vs. No) Refractory disease (Yes vs. No) Prior number of regimens (1 vs. 2 vs. ≥3) Prior proteasome inhibitor (Yes vs. No) Prior stem cell transplant (Yes vs. No) Prior hyper CVAD regimen (Yes vs. No) Prior lenalidomide (Yes vs. No) Region (US vs. Ex-US) The overall response rate and complete response rate in the subgroup analysis were assessed by the investigator according to the Lugano classification (all treated subjects). The results were presented in Forest plots with 95% CIs based on exact binomial distribution (58).
Other relevant information	Summary of prior therapies for MCL, n (%) Rituximab as single agent or part of a regimen: 118 (95.2%) CHOP based regimen: 64 (51.6%) ARA-C based regimen: 42 (33.9%) Bendamustine and Rituximab based regimen: 27 (21.8%) Hyper-CVAD: 26 (21.0%)

Trial name: An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma **(LY-004)**	**NCT number: 02213926**
	Bortezomib/Carfilzomib: 24 (19.4%) DHAP: 24 (19.4%) Stem Cell Transplant: 22 (17.7%) Other chemotherapy: 12 (9.7%) BEAM: 9 (7.3%) FC: 8 (6.5%) Lenalidomide: 8 (6.5%) mTOR: 6 (4.8%) Other": 3 (2.4%)

Trial name: Multicenter, phase 2 study of Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma (PCYC-1104)	**NCT number: 01236391**
Objective	The primary objective of this trial is to evaluate the efficacy of PCI-32765 (Ibrutinib) in relapsed/refractory subjects with mantle cell lymphoma (MCL) (59).
Publications – title, author, journal, year	Wang, Michael, et al. "Interim results of an international, multicenter, phase 2 study of Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), in relapsed or refractory mantle cell lymphoma (MCL): durable efficacy and tolerability with longer follow-up." *Blood* 120.21 (2012): 904 (60). Wang, Michael L., et al. "Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma." *New England Journal of Medicine* 369.6 (2013): 507-516 (29). Wang, Michael L., et al. "Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results." *Blood, The Journal of the American Society of Hematology* 126.6 (2015): 739-745 (52). Rule, Simon, et al. "Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies." *British journal of haematology* 179.3 (2017): 430-438 (37). Rule, Simon, et al. "Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis." *Haematologica* 104.5 (2019): e211 (36). Dreyling, Martin, et al. "Long-term outcomes with ibrutinib treatment for patients with relapsed/refractory mantle cell

Trial name: Multicenter, phase 2 study of Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma (PCYC-1104)	NCT number: 01236391

lymphoma: a pooled analysis of 3 clinical trials with nearly 10 years of follow-up." *Hemasphere* 6.5 (2022): e712 (38).

Study type and design	This is a Phase 2, open-label, nonrandomized, multicenter, monotherapy study in subjects with histologically documented MCL who have relapsed after ≥ 1 (but not > 5) prior treatment regimens. The study design followed a two-stage procedure with two treatment groups in parallel. Patients were stratified into 2 groups based on prior bortezomib exposure (29).
Sample size (n)	A total of 115 patients were enrolled. 111 patients received at least one dose of ibrutinib (29).
Main inclusion criteria	Men and women ≥ 18 years of age. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or t(11;14), and measurable disease on cross sectional imaging that is ≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions per computed tomography (CT).

Trial name: Multicenter, phase 2 study of Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma (PCYC-1104)	NCT number: 01236391
	Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen. At least 1, but no more than 5, prior treatment regimens for MCL (59).
Main exclusion criteria	Prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of study drug. History of other malignancies within the past year except for treated basal cell or squamous cell skin cancer or in situ cervical cancer. Known central nervous system lymphoma. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 (moderate) or 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, or corrected QT interval (QTc) ≥ 500 msec. Any of the following laboratory abnormalities: - Absolute neutrophil count < 750 cells/mm3 (0.75×10^9 /L) unless there is documented bone marrow involvement. - Platelet count < 50,000 cells/mm3 (50×10^9 /L) independent of transfusion support unless there is documented bone marrow involvement. - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 × upper limit of normal (ULN). - Creatinine > 2.0 × ULN (59).
Intervention	Patients received single-agent ibrutinib administered orally at a daily dose of 560 mg until progression of disease or until unacceptable levels of adverse events occurred. 111 patients received at least one dose of ibrutinib (29).
Comparator(s)	This study did not have a comparator arm (59).
Follow-up time	Median follow-up of 26.7 months (52).
Is the study used in the health economic model?	Yes, in a pooled analysis with three open-label ibrutinib studies.

Trial name: Multicenter, phase 2 study of Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma (PCYC-1104)	NCT number: 01236391
Primary, secondary and exploratory endpoints	The **Primary endpoint** of the study is the ORR defined as a subject achieving either a partial remission (PR) or complete remission (CR) according to the revised International Working Group Criteria for non-Hodgkin lymphoma (NHL) as assessed by investigators (59). **Secondary endpoints** <u>Efficacy:</u> Investigator assessed duration of response (DOR) Investigator assessed progression-free survival (PFS) Overall survival (OS) <u>Safety</u>: Frequency, severity, and relatedness of AEs Frequency of AEs requiring discontinuation of study drug or dose reductions Effect of PCI-32765 on peripheral B/T/natural killer (NK) cell counts Effect of PCI-32765 on serum immunoglobulin levels <u>Pharmacokinetics:</u> Plasma pharmacokinetics (PK) of PCI-32765 and a major metabolite, PCI-45227 <u>Patient Reported Outcomes:</u> Health-related quality of life (59). **Endpoints included in this application:** Endpoints included from the pooled analysis of three ibrutinib studies (including this study) used in the MAIC analysis include: ORR PFS OS TEAE
Method of analysis	The per-protocol (PP) and intent-to-treat populations were used for analyzing the efficacy endpoints. The safety population (all enrolled subjects who received at least 1 dose of study drug) was used for analyzing the safety endpoints. ORR was calculated for the PP analysis set. The corresponding 95% two-sided confidence interval was derived. DOR, PFS, and OS were estimated with the use of the Kaplan–Meier method. All statistical tests were based on a two-sided alpha level of 0.05.

Trial name: Multicenter, phase 2 study of Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma (PCYC-1104)	NCT number: 01236391
	The EORTC QLQ-30 was used to assess health-related quality of life (59).
Subgroup analyses	A predefined subgroup analysis was performed to evaluate ORR according to predefined subgroups, including (59): Age (< 65 years vs. ≥ 65 years) Bortezomib-naive vs bortezomib-exposed Sex (male vs. female) Race: (Caucasian vs. non-Caucasian) Prior number of regimens (< 3 vs. ≥ 3) Simplified MCL international prognostic index (MIPIb) (low risk [0-3]; versus intermediate risk [4-5]; versus high risk [6-11]) Baseline ECOG performance status (0 vs. 1 vs. 2) Advanced disease at baseline (extra nodal site and/or bone marrow involvement) (yes/no) Tumor bulk (largest diameter): ≥ 5 cm vs. ≥ 10 cm 10. Blastoid history: (Yes/No) Refractory disease: (Yes/No) Prior high intensity therapy: (Yes/No) Prior lenalidomide: (Yes/No) Region (US vs. Europe) The subgroup analysis was presented in a forest plot for all treated patients showing the overall response rate according to demographic and clinical characteristics and risk factors. The 95% confidence intervals (CIs) were based on normal approximation to the binomial distribution (29).
Other relevant information	*N/A*

Trial name: A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy (RAY)	**NCT number:** 01646021
Objective	The objective of this study was to evaluate the efficacy and safety of ibrutinib versus temsirolimus in patients with relapsed or refractory mantle cell lymphoma who received at least 1 prior rituximab containing chemotherapy regimen (31).
Publications – title, author, journal, year	Dreyling, Martin, et al. "Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study." *The Lancet* 387.10020 (2016): 770-778 (31). Rule, Simon, et al. "Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study." *Leukemia* 32.8 (2018): 1799-1803 (62). Rule, Simon, et al. "Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies." *British journal of haematology* 179.3 (2017): 430-438 (37). Rule, Simon, et al. "Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis." *Haematologica* 104.5 (2019): e211 (36). Dreyling, Martin, et al. "Long-term outcomes with ibrutinib treatment for patients with relapsed/refractory mantle cell lymphoma: a pooled analysis of 3 clinical trials with nearly 10 years of follow-up." *Hemasphere* 6.5 (2022): e712 (38). Freeman, Ciara L., et al. "Molecular determinants of outcomes in relapsed or refractory mantle cell lymphoma treated with ibrutinib or temsirolimus in the MCL3001 (RAY) trial." *Leukemia* 36.10 (2022): 2479-2487 (77).
Study type and design	This is a randomized, controlled, open-label, multicentre, phase 3 study comparing the efficacy and safety of ibrutinib with temsirolimus in patients with relapsed or refractory mantle-cell lymphoma confirmed by central pathology. Enrolled patients were randomly assigned 1:1 to oral ibrutinib or intravenous temsirolimus based on a computer-generated randomization schedule. Randomization was balanced by using randomly permuted blocks and stratified by number of previous lines of therapy (one, two, or three or more) and simplified mantle-cell lymphoma international

Trial name: A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy (RAY)	**NCT number:** 01646021
	prognostic index (sMIPI) score (low risk [0–3] vs intermediate risk [4–5] vs high risk [6–11]). On July 30, 2014, the protocol was amended to include formal crossover of patients on the temsirolimus group to ibrutinib who have independent review committee-confirmed progression of disease (31).
Sample size (n)	280 patients were randomly assigned to ibrutinib (n=139) or temsirolimus (n=141). All patients in the ibrutinib arm received the allocated intervention, while 139 out of 141 patients assigned to the temsirolimus arm received the allocated intervention (31).
Main inclusion criteria	Aged ≥18 years Diagnosis of MCL including morphology and expression of either cyclin D1 in association with one B-cell marker (eg, CD19, CD20, or PAX5) and CD5 or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridisation, or polymerase chain reaction Received at least one prior rituximab-containing chemotherapy regimen Documented relapse or disease progression following the last anti-MCL treatment ECOG performance status 0 or 1 Hematology values within the following limits: - Absolute neutrophil count ≥ 1000/mm3 independent of growth factor support - Platelet count ≥ 75 000/mm3 or ≥ 50 000/mm3 if bone marrow involvement independent of transfusion support - Hemoglobin level ≥8 g/dL, independent of transfusion support Biochemical values within the following limits: - Alanine aminotransferase and aspartate aminotransferase ≤3 × upper limit of normal (ULN) - Total bilirubin ≤1·5 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) - Serum creatinine ≤2 × ULN - Fasting serum cholesterol level ≤350 mg/dL - Fasting serum triglyceride level ≤400 mg/dL (64).
Main exclusion criteria	Received prior nitrosoureas within 6 weeks, chemotherapy within 3 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy or other

Trial name: A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy (RAY)	NCT number: 01646021
	investigational agents within 3 weeks, or major surgery within 4 weeks of randomization Received prior treatment with temsirolimus, other mTOR inhibitors, ibrutinib, or other BTK inhibitors Had central nervous system lymphoma Had a history of stroke or intracranial haemorrhage within 6 months prior to first dose of study drug Required anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with a strong CYP3A4/5 inhibitor (64).
Intervention	Patients in the ibrutinib group received 560 mg ibrutinib orally once per day until disease progression or unacceptable toxic effects. 139 patients were randomized to the ibrutinib group, and all patients received treatment (31).
Comparator(s)	Patients in the temsirolimus group received 175 mg temsirolimus intravenously 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. The patients were treated until disease progression or unacceptable toxic effects. 141 patients were assigned to temsirolimus, and 139 patients received treatment (31).
Follow-up time	Median follow-up time: 38.7 months (62).
Is the study used in the health economic model?	Yes, in a pooled analysis with three open-label ibrutinib studies.
Primary, secondary and exploratory endpoints	**Primary Endpoint (31):** Progression-Free Survival (PFS) assessed by the independent review committee. Complete response, partial response, and progressive disease were assessed by an independent review committee per revised Cheson criteria. **Secondary Endpoints (31):** Overall Response Rate (ORR) assessed by both the independent review committee and the investigator Overall Survival (OS)

Trial name:	NCT number:
A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy (RAY)	01646021

	PFS assessed by the investigator 1-Year Survival Rate Duration of Response (DOR) Time to Next Treatment Safety Prespecified Patient-Reported Outcomes Biomarkers and Pharmacokinetics Medical Resource Use Rate **Endpoints included in this application:** Endpoints included from the pooled analysis of three ibrutinib studies (including this study) used in the MAIC analysis include: ORR PFS OS TEAE
Method of analysis	The primary efficacy analysis was done on the intention-to-treat population. The Kaplan-Meier method was used to estimate the distribution of PFS for each treatment group. The treatment effect of ibrutinib compared with temsirolimus based on PFS was tested with a stratified two-sided log-rank test stratified by sMIPI and previous lines of therapy. The HR for ibrutinib relative to temsirolimus and its associated 95% CI were calculated based on the stratified Cox proportional hazards model by the stratification factors at randomisation. All time-to-event endpoints, including OS, were analysed using the same methods as PFS. ORR was analysed using the Cochran-Mantel-Haenszel χ^2 test adjusted for stratification. For patient-related outcomes, the proportions of patients improving and declining were calculated, and median time to clinically meaningful improvement and time to worsening were estimated. Clinically meaningful improvement was defined as a 5-point or greater increase from baseline, and worsening was defined as a 5-point or greater decrease from baseline. Safety was analysed in patients who received at least one dose of study drug (31).

Trial name:	NCT number:
A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy (RAY)	01646021

Subgroup analyses	A predefined subgroup analysis was performed to evaluate the effect of baseline factors on PFS. A multivariate Cox regression analysis was done to assess the effects of these factors on the study outcome. A sensitivity analysis using PFS by investigator was also performed. The predefined subgroups included: Sex (male vs female) Age group (≥65 vs < 65 years) Race (Caucasian vs non-Caucasian) Baseline ECOG PS (1 vs 0) Region (Europe vs non-Europe) Baseline extranodal disease (yes vs no) MIPI score (low vs intermediate vs high) Prior lines of therapy (≥3 vs <3) Stage of disease (IV vs I-III) Prior bortezomib (yes vs no) Tumour bulk (≥5 vs <5 cm) Histology (blastoid vs non-blastoid) Refractory disease (yes vs no) Bone marrow involvement (yes vs no) The subgroup analysis for PFS by IRC assessment was presented in a forest plot, including the 95% confidence intervals (CIs) (31, 64).
Other relevant information	*N/A*

A Phase 2, Multicenter, Single-Arm, Study to Evaluate the Efficacy and Safety of Single-Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy (SPARK)	NCT number: 01599949
Objective	The objective of this study was to evaluate the efficacy and safety of single-agent ibrutinib specifically in patients with MCL who had received a rituximab-containing regimen and had progressed after at least 2 cycles of bortezomib therapy (46).
Publications – title, author, journal, year	Wang, Michael, et al. "Efficacy and safety of single-agent ibrutinib in patients with mantle cell lymphoma who progressed after bortezomib therapy." *Blood* 124.21 (2014): 4471 (46). Rule, Simon, et al. "Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies." *British journal of haematology* 179.3 (2017): 430-438 (37). Rule, Simon, et al. "Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis." *Haematologica* 104.5 (2019): e211 (36). Dreyling, Martin, et al. "Long-term outcomes with ibrutinib treatment for patients with relapsed/refractory mantle cell lymphoma: a pooled analysis of 3 clinical trials with nearly 10 years of follow-up." *Hemasphere* 6.5 (2022): e712 (38).
Study type and design	This is a Phase 2, open-label, single-arm, international multicenter, monotherapy study in subjects with MCL who had received a rituximab-containing regimen and had progressed after at least 2 cycles of bortezomib therapy (46). The study is completed.
Sample size (n)	120 patients (46).
Main inclusion criteria	Diagnosis of confirmed mantle cell lymphoma (MCL) with at least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma Must have received at least 1 prior rituximab-containing chemotherapy regimen, but no more than 5 prior regimens Must have received at least 2 cycles of bortezomib therapy (single-agent or in combination) and have documented progressive disease during or after bortezomib therapy Eastern Cooperative Oncology Group performance status score 0, 1, or 2 Hematology and biochemical values within protocol-defined parameters (65).

A Phase 2, Multicenter, Single-Arm, Study to Evaluate the Efficacy and Safety of Single-Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy (SPARK)	NCT number: 01599949

Main exclusion criteria	Prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy or other investigational agents within 3 weeks, or major surgery within 4 weeks of the first dose of study drug Prior treatment with ibrutinib or other Bruton's tyrosine kinase inhibitors More than 5 prior lines of therapy Known central nervous system lymphoma Diagnosed or treated for malignancy other than MCL, with some exceptions History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug Requires anticoagulation with warfarin or equivalent vitamin K antagonists Requires treatment with strong CYP3A4/5 inhibitors Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification (65).

A Phase 2, Multicenter, Single-Arm, Study to Evaluate the Efficacy and Safety of Single-Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy (SPARK)	NCT number: 01599949
Intervention	Patients were treated with 560 mg/day oral ibrutinib continuously until progressive disease or unacceptable toxicity. 120 patients were treated (46).
Comparator(s)	This was a single-arm study with no comparator (46).
Follow-up time	Median follow-up of 14.9 months (46).
Is the study used in the health economic model?	Yes, in a pooled analysis with three open-label ibrutinib studies.
Primary, secondary and exploratory endpoints	**Primary endpoint (46):** Overall response rate (ORR) in response evaluable patients, as assessed by an Independent Review Committee (IRC). **Secondary Endpoints (46):** Duration of response (DoR) Progression-free survival (PFS) Overall survival (OS) Safety All secondary endpoints were also assessed by the IRC. **Endpoints included in this application:** Endpoints included from the pooled analysis of three ibrutinib studies (including this study) used in the MAIC analysis include: ORR PFS OS TEAE
Method of analysis	Efficacy endpoints, including overall response rate, duration of response, progression-free survival, and overall survival, were assessed by an Independent Review Committee in response-evaluable patients. To the best of our knowledge, information regarding the analytical population and specific statistical methods used is not available (46).

A Phase 2, Multicenter, Single-Arm, Study to Evaluate the Efficacy and Safety of Single-Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy (SPARK)	NCT number: 01599949
Subgroup analyses	A subgroup analysis was performed to evaluate the effect of predefined baseline characteristics on ORR. The baseline factors included was (46): Age Gender Geographic region Number of prior lines of therapies Baseline extranodal disease Simplified MIPI score Bulky disease Stage of MCL
Other relevant information	*N/A*

Appendix B. Efficacy results per study

B.1 Results per study

[Complete the table for all studies included, regardless of whether they have been used in the health economic model. Explain how all estimates, such as CIs and p-values, have been estimated, this includes the method used, adjustment variables, stratification variables, weights, corrections (in cases with 0 counts), correlation structure (mixed effects model for repeated measurements) and methods used for imputation. Specify how assumptions were checked. Survival rates: state at which time point these are reported for.]

Table 52 Results per LY-004

Results of [LY-004 (NCT 02213926)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Overall Response Rate	Acalabrutinib	124	101 (73.5%, 87.9%)	NA	NA	NA	NA	NA	NA	Overall response rate (ORR) and best overall response based on investigator assessment according to the Lugano classification	LY004 CSR
	NA	NA	NA								
Progression-Free Survival by Investigator Assessment According to	Acalabrutinib	124	22.0 (16.6, 33.3)	NA	NA	NA	NA	NA	NA	PFS based on investigator assessment according to the Lugano classification is presented	LY004 CSR
	NA	NA	NA								

Results of [LY-004 (NCT 02213926)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
the Lugano Classificatio n											
KM point estimate for progression-free survival 12 month	Acalabruti nib	124	67.8% (58.5%, 75.4%)	NA	NA	NA	NA	NA	NA	PFS based on investigator assessment according to the Lugano classification is presented	LY004 CSR
	NA	NA	NA								
KM point estimate for progression-free survival 24 month	Acalabruti nib	124	49.6% (40.1%, 58.4%)	NA	NA	NA	NA	NA	NA	PFS based on investigator assessment according to the Lugano classification is presented	LY004 CSR
	NA	NA	NA								
KM point estimate for progression-free survival 36 month	Acalabruti nib	124	37.2% (28.2%, 46.1%)	NA	NA	NA	NA	NA	NA	PFS based on investigator assessment according to the Lugano classification is presented	LY004 CSR
KM point estimate for progression-	Acalabruti nib	124	31.1% (22.5%, 39.9%)	NA	NA	NA	NA	NA	NA	PFS based on investigator assessment according to the	LY004 CSR

Results of [LY-004 (NCT 02213926)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
free survival 48 month										Lugano classification is presented	
KM point estimate for progression-free survival 60 month	Acalabrutinib	124	23.0% (15.3%, 31.7%)	NA	NA	NA	NA	NA	NA	PFS based on investigator assessment according to the Lugano classification is presented	LY004 CSR
Overall survival	Acalabrutinib	124	59.2 (36.5, NE)	NA	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	LY004 CSR
KM point estimate for OS 12 month	Acalabrutinib	124	86.8% (79.3%, 91.7%)	NA	NA	NA	NA	NA	NA		LY004 CSR
KM point estimate for	Acalabrutinib	124	72.4 (63.5%, 79.5%)	NA	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	LY004 CSR

Results of [LY-004 (NCT 02213926)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS 24 month											
KM point estimate for OS 36 month	Acalabrutinib	124	60.5% (51.1%, 68.7%)	NA	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	LY004 CSR
KM point estimate for OS 48 month	Acalabrutinib	124	52.4% (42.9%, 61.0%)	NA	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	LY004 CSR
KM point estimate for OS 60 month	Acalabrutinib	124	49.5% (40.1%, 58.2%)	NA	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	LY004 CSR

Results of Pooled ibrutinib trials, SPARK (NCT 01599949), RAY (NCT 01646021) PCYC (NCT 01236391) latest data cut											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Overall Response Rate	Ibrutinib	370	258	NA	NA	NA	NA	NA	NA		(37, 48, 68, 71)
Median PFS	Ibrutinib	370	12,5 (9,8-16,6)	NA	NA	NA	NA	NA	NA		(37, 48, 68, 71)
Median OS	Ibrutinib	370	26,7 (22,5-38,4)	NA	NA	NA	NA	NA	NA		(37, 48, 68, 71)

Appendix C. Comparative analysis of efficacy

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Table 53 Comparative analysis of studies comparing acalabrutinib to ibrutinib for patients with 2 L MCL.

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
ORR %, Cheson 2007 Acala vs Ibru, unadjusted comparison.	LY004: 75.0% Pooled Ibrutinib: 69%	6%	NA	NA	NA	NA	NA		No, cost minimization analysis conducted
CR %, Cheson 2007 Acala vs Ibru, unadjusted comparison.	LY004: 30% Pooled Ibrutinib: 20.7%	9.3%	NA	NA	NA	NA	NA		No, cost minimization analysis conducted

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
PR %, Cheson 2007 Acala vs Ibru, unadjusted comparison.	LY004: 45.2% Pooled Ibrutinib: 47.4%	-2.4%	NA	NA	NA	NA	NA		No, cost minimization analysis conducted
PFS, Acala vs Ibru, Unadjusted. Median	LY004: 22.0 Pooled Ibrutinib: 12.8	9,2	NA	NA	0.75	0.58 – 0.96	0.02		No, cost minimization analysis conducted
OS, Acala vs Ibru, Unadjusted. Median	LY004: NR Pooled Ibrutinib: 27.9	NR vs 27.9			0.67	0.49 - 0.90	0.01		No, cost minimization analysis conducted

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
PFS, Acala vs Ibru, Adjusted Median	LY004: 17.8 Pooled Ibrutinib: 12.8	5	NA	NA	HR: 0.92	0.74 – 1.15	0.48	Unanchored MAIC	No, cost minimization analysis conducted
OS, Acala vs Ibru, Adjusted Median	LY004: 36.5 Pooled Ibrutinib: 27.9	8.6	NA	NA	0.87	0.64 – 1.17	0.35	Unanchored MAIC	No, cost minimization analysis conducted

Appendix D. Extrapolation

NA

[Describe in detail how extrapolation is performed in accordance with sections 6.4.2 and 6.4.3 of the methods guide and the online appendix "Anvendelse af forløbsdata i sundhedsøkonomiske analyser".

- Specify which parametric function was selected for the intervention and comparator, respectively. All standard parametric models (exponential, Weibull, Gompertz, gamma, log normal, log logistic and generalized gamma) and other considered extrapolations must be available in the Excel model.
- Specify if the extrapolation models for the intervention and comparator are fitted in a joint model or independently.
- The section must include a discussion about using the same or different parametric function to extrapolate data for the intervention and comparator.
- A graphical representation of the time-to-event data curves where both the Kaplan-Meier (KM) estimate and the parametric distributions are shown in the same figure must be presented in this section (for both intervention and comparator). The figure must include a graph with the general population's mortality rate and must display the entire time horizon of the model.
- Describe whether (and how) adjustments have been made for treatment switching/cross-over (intervention and/or comparator).
- Describe and explain how the extrapolations have been validated and present the results. When relevant, present a graphical representation of the validation.]

NA

D.1 Extrapolation of [effect measure 1]

NA

D.1.1 Data input

NA

D.1.2 Model

NA

D.1.3 Proportional hazards

NA

[If the extrapolation model relies on proportional hazards, provide a plot with Schoenfeld residuals and a log-cumulative hazard plot.]

D.1.4 Evaluation of statistical fit (AIC and BIC)

NA

[Provide a table with the AIC and BIC and discuss the statistical fit.]

D.1.5 Evaluation of visual fit

NA

D.1.6 Evaluation of hazard functions

NA

[Provide a plot of the hazard function of the effect measure. The plots must be presented in separate figures for the intervention and comparator, respectively, and must include the estimated hazard for the observed data (if applicable). The plot must be discussed in the context of chosen the distribution for extrapolating the data of the effect measure.]

D.1.7 Validation and discussion of extrapolated curves

NA

D.1.8 Adjustment of background mortality

NA

D.1.9 Adjustment for treatment switching/cross-over

NA

D.1.10 Waning effect

NA

D.1.11 Cure-point

NA

D.2 Extrapolation of [effect measure 2]

NA

[For each effect measure please, fill in this section using the same template as stated in section D.1]

Appendix E. Serious adverse events

All treatment-emergent serious adverse events observed in the LY-004 study are listed in Table 54 (by preferred term and grade). As of data cut-off on the 4th of December 2020, the median follow-up was 38.1 months. The median treatment duration was 17.5 months (range: 0.1 to 65.3) (*AstraZeneca Data on File: LY-004 CSR-tables-Dec20_DOC, Table 14.3.4.1* (72).

Table 54 Subject Incidence of Treatment-Emergent Serious Adverse Events reported in LY-004

	All (N=124)					
Preferred term	**Any Grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Number of Subjects Reporting Treatment-Emergent Serious Adverse Events - n (%)	62 (50.0%)	0	1 (0.8%)	43 (34.7%)	14 (11.3%)	4 (3.2%)
Pneumonia	8 (6.5%)	0	0	8 (6.5%)	0	0
Anaemia	6 (4.8%)	0	0	5 (4.0%)	1 (0.8%)	0
General physical health deterioration	4 (3.2%)	0	0	3 (2.4%)	1 (0.8%)	0
Colitis	2 (1.6%)	0	0	2 (1.6%)	0	0
Gastrointestinal haemorrhage	2 (1.6%)	0	0	2 (1.6%)	0	0
Pyrexia	2 (1.6%)	1 (0.8%)	1 (0.8%)	0	0	0
Sepsis	2 (1.6%)	0	0	0	2 (1.6%)	0
Tumour lysis syndrome	2 (1.6%)	0	0	1 (0.8%)	1 (0.8%)	0
Upper respiratory tract infection	2 (1.6%)	0	0	2 (1.6%)	0	0
Vomiting	2 (1.6%)	0	1 (0.8%)	1 (0.8%)	0	0

Abdominal pain	1 (0.8%)	0	0	1 (0.8%)	0	0
Acute coronary syndrome	1 (0.8%)	0	0	1 (0.8%)	0	0
Acute febrile neutrophilic dermatosis	1 (0.8%)	0	0	1 (0.8%)	0	0
Acute myocardial infarction	1 (0.8%)	0	0	1 (0.8%)	0	0
Ankle fracture	1 (0.8%)	0	0	1 (0.8%)	0	0
Aortic stenosis	1 (0.8%)	0	0	0	0	1 (0.8%)
Arthralgia	1 (0.8%)	0	1 (0.8%)	0	0	0
Arthritis bacterial	1 (0.8%)	0	0	1 (0.8%)	0	0
Autoimmune encephalopathy	1 (0.8%)	0	0	1 (0.8%)	0	0
Bacteraemia	1 (0.8%)	0	0	1 (0.8%)	0	0
Basal cell carcinoma	1 (0.8%)	0	1 (0.8%)	0	0	0
Cardiac failure	1 (0.8%)	0	0	1 (0.8%)	0	0
Cardio-respiratory arrest	1 (0.8%)	0	0	0	1 (0.8 %)	0
Catheter site infection	1 (0.8%)	0	0	1 (0.8%)	0	0
Chest pain	1 (0.8%)	0	0	1 (0.8%)	0	0
Cholecystitis	1 (0.8%)	0	1 (0.8%)	0	0	0
Cholelithiasis	1 (0.8%)	0	0	1 (0.8%)	0	0
Clostridium difficile infection	1 (0.8%)	0	0	1 (0.8%)	0	0
Coronary artery disease	1 (0.8%)	0	0	1 (0.8%)	0	0
Decreased appetite	1 (0.8%)	0	0	1 (0.8%)	0	0
Diarrhoea	1 (0.8%)	0	0	1 (0.8%)	0	0
Diffuse large B-cell lymphoma	1 (0.8%)	0	0	1 (0.8%)	0	0

Dyspnoea	1 (0.8%)	0	0	0	1 (0.8 %)	0
Escherichia infection	1 (0.8%)	0	0	1 (0.8%)	0	0
Fall	1 (0.8%)	0	0	1 (0.8%)	0	0
Febrile neutropenia	1 (0.8%)	0	0	1 (0.8%)	0	0
Gastroenteritis viral	1 (0.8%)	0	0	1 (0.8%)	0	0
General physical condition abnormal	1 (0.8%)	0	0	1 (0.8%)	0	0
Haematuria	1 (0.8%)	0	0	1 (0.8%)	0	0
Haemolytic anaemia	1 (0.8%)	0	0	1 (0.8%)	0	0
Headache	1 (0.8%)	0	0	1 (0.8%)	0	0
Hodgkin's disease	1 (0.8%)	0	0	1 (0.8%)	0	0
Humerus fracture	1 (0.8%)	0	0	1 (0.8%)	0	0
Hydronephrosis	1 (0.8%)	0	0	0	1 (0.8 %)	0
Hypotension	1 (0.8%)	0	0	1 (0.8%)	0	0
Incisional hernia	1 (0.8%)	0	0	1 (0.8%)	0	0
Inguinal hernia	1 (0.8%)	0	0	1 (0.8%)	0	0
Inguinal hernia strangulated	1 (0.8%)	0	0	1 (0.8%)	0	0
Interstitial lung disease	1 (0.8%)	0	0	0	1 (0.8 %)	0
Intestinal obstruction	1 (0.8%)	0	0	1 (0.8%)	0	0
Invasive ductal breast carcinoma	1 (0.8%)	0	0	1 (0.8%)	0	0
Ischaemic stroke	1 (0.8%)	0	0	1 (0.8%)	0	0

Jaundice extrahepatic obstructive	1 (0.8%)	0	0	0	1 (0.8 %)	0
Lactic acidosis	1 (0.8%)	0	0	1 (0.8%)	0	0
Leukostasis syndrome	1 (0.8%)	0	0	0	1 (0.8 %)	0
Lower respiratory tract infection	1 (0.8%)	0	0	1 (0.8%)	0	0
Lower respiratory tract infection bacterial	1 (0.8%)	0	0	1 (0.8%)	0	0
Metastases to meninges	1 (0.8%)	0	0	1 (0.8%)	0	0
Myelodysplastic syndrome	1 (0.8%)	0	0	0	1 (0.8 %)	0
Nausea	1 (0.8%)	0	1 (0.8%)	0	0	0
Non-cardiac chest pain	1 (0.8%)	0	0	1 (0.8%)	0	0
Non-small cell lung cancer	1 (0.8%)	0	0	0	0	1 (0.8%)
Pancreatitis acute	1 (0.8%)	0	0	0	1 (0.8 %)	0
Paronychia	1 (0.8%)	0	0	1 (0.8%)	0	0
Peripheral ischaemia	1 (0.8%)	0	0	0	1 (0.8 %)	0
Peripheral swelling	1 (0.8%)	0	0	1 (0.8%)	0	0
Pharyngitis	1 (0.8%)	0	0	0	1 (0.8 %)	0
Pleural effusion	1 (0.8%)	0	0	1 (0.8%)	0	0
Prostatitis	1 (0.8%)	0	0	1 (0.8%)	0	0
Pseudomonal bacteraemia	1 (0.8%)	0	0	1 (0.8%)	0	0

Psychotic disorder	1 (0.8%)	0	0	0	1 (0.8 %)	0
Pulmonary embolism	1 (0.8%)	0	0	0	0	1 (0.8%)
Pulmonary fibrosis	1 (0.8%)	0	1 (0.8%)	0	0	0
Radius fracture	1 (0.8%)	0	0	1 (0.8%)	0	0
Respiratory syncytial virus infection	1 (0.8%)	0	0	1 (0.8%)	0	0
Respiratory tract infection	1 (0.8%)	0	0	1 (0.8%)	0	0
Squamous cell carcinoma of skin	1 (0.8%)	0	0	1 (0.8%)	0	0
Streptococcal bacteraemia	1 (0.8%)	0	0	1 (0.8%)	0	0
Subdural haematoma	1 (0.8%)	0	0	0	1 (0.8 %)	0
Suicide attempt	1 (0.8%)	0	0	0	0	1 (0.8%)
Tibia fracture	1 (0.8%)	0	0	1 (0.8%)	0	0
Transfusion reaction	1 (0.8%)	0	0	1 (0.8%)	0	0
Umbilical hernia	1 (0.8%)	0	0	1 (0.8%)	0	0
Urinary tract infection	1 (0.8%)	0	0	1 (0.8%)	0	0
Urinary tract infection bacterial	1 (0.8%)	0	0	1 (0.8%)	0	0
Urosepsis	1 (.8%)	0	0	0	1 (0.8 %)	0

Due to limitations in publicly available data, it is not possible to report serious adverse events from the included ibrutinib studies (please refer to Table 51 in Appendix A) with the same level of detail as for Ly-004 study. Comprehensive listings of individual serious adverse events for these ibrutinib studies have, to our knowledge, not been published. Therefore, in the tables below, we have provided an overview of the serious adverse events reported in the three ibrutinib studies, based on the information that is currently accessible.

Serious adverse events observed in at least 2% of patients in the *Multicenter, phase 2 study of BTK inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma (PCYC-1104)* at a median follow-up of 15.3 months (range 1.9-22.3) are listed in Table 55 (29, 78). An updated safety and efficacy analysis on this study was subsequently performed at a median follow-up of 26.7-month (52). Serious adverse events observed in ≥2% of patients, regardless of attribution, as reported in this updated analysis, are summarized in

Table 56.

Table 55 Serious Adverse Events in at Least 2% of Patients in PCYC-1104 (median follow-up: 15.3 mo) (78).

	All patients (N=111)
Total no. of patients with treatment-emergent serious adverse events	62 (55.9%)
System organ class	
Preferred term	
Infections and infestations	22 (19.8%)
Pneumonia	6 (5.4%)
Urinary tract infection	4 (3.6%)
General disorders and administration site conditions	11 (9.9%)
Oedema peripheral	3 (2.7%)
Pyrexia	3 (2.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (9.0%)
Mantle cell lymphoma	8 (7.2%)
Blood and lymphatic system disorders	9 (8.1%)
Febrile neutropenia	3 (2.7%)
Cardiac disorders	8 (7.2%)
Atrial fibrillation	5 (4.5%)
Gastrointestinal disorders	8 (7.2%)
Abdominal pain	3 (2.7%)
Renal and urinary disorders	6 (5.4%)
Renal failure acute	3 (2.7%)
Injury, poisoning and procedural complications	5 (4.5%)
Subdural haematoma	3 (2.7%)

Table 56 **Summary of serious adverse events (≥2% of patients) in PCYC-1104 regardless of attribution (median follow-up: 26.7 mo) (52).**

	Total (N = 111)		
SAE*, n (%)	**Any grade**	**Grade 3-4**	**Grade 5**
Disease progression†	11 (10%)	3 (3%)	8 (7%)
Pneumonia	8 (7%)	7 (6%)	1 (1%)
Atrial fibrillation	7 (6%)	6 (5%)‡	0
Urinary tract infection	4 (4%)	3 (3%)	0
Febrile neutropenia	3 (3%)	3 (3%)	0
Abdominal pain	3 (3%)	3 (3%)	0
Acute renal failure	3 (3%)	2 (2%)	1 (1%)
Subdural hematoma	3 (3%)	2 (2%)	0
Pyrexia	3 (3%)	1 (1%)	0
Confusional state	3 (3%)	1 (1%)	0

* SAEs were updated with an estimated median follow-up of 26.7 months.
† Mantle cell lymphoma reported as a SAE by investigators.
‡ One additional patient had a grade 3 atrial fibrillation that was not considered an SAE.

A list of the serious adverse events reported in patients in the Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the BTK Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy (RAY), cannot be provided, as relevant publications does not detail SAE (31). However, in the 3-year follow-up analysis of the study (median follow-up: 38.7 months), it is reported that serious adverse events were observed in 57% of patients treated with ibrutinib (62).

A summary of serious adverse events observed in patients in the *Phase 2*, *Multicenter, Single-Arm, Study to Evaluate the Efficacy and Safety of Single-Agent BTK Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy (SPARK),* cannot be listed as these data have not previously been reported (46).

E.1 Most commonly reported AE's in LY004

Final data anaylsis

In the final data analysis, the most frequently reported AEs (in ≥15% of subjects) included headache (39%), diarrhea (38%), and fatigue (30%) (*Table 57***).**

Table 57: Most common AEs reported in ≥15% of patients in LY-004

AEs	All patients (n=124), n (%)
Headache	48 (38.7%)
Diarrhea	47 (37.9%)
Fatigue*	37 (29.8%)
Cough	29 (23.4%)
Myalgia	27 (21.8%)
Nausea	27 (21.8%)
Asthenia	22 (17.7%)
Constipation	20 (16.1%)
Upper respiratory tract infection	20 (16.1%)
Dyspnoea	19 (15.3%)
Pyrexia	19 (15.3%)
Vomiting	19 (15.3%)

*Includes one case of fatigue without grading. AE: Adverse event

Grade ≥3 AEs were low and were mostly hematologic in nature. The most common Grade ≥3 AEs (occurring in ≥5% of patients) included neutropenia and anaemia (11% each), and pneumonia (7%) (**Table 58**).

Table 58: Most commonly reported Grade ≥3 AEs in ≥5% patients in LY-004

AEs	All patients (n=124), n (%)
Anemia	14 (11.3%)
Neutropenia	14 (11.3%)
Pneumonia	9 (7.3%)

AE: Adverse event

E.2 Treatment-emergent adverse event in ibrutinib trials

Rule 2019 data cut (36)

Treatment-emergent AEs were reported in 364 (98.4%) patients in the MCL pooled population. Grade ≥3 AEs were reported in 265 (71.6%) patients. The most frequently reported AEs (any grade) were diarrhoea (*n* = 146, 39.5%), fatigue (*n* = 129, 34.9%), cough (*n* = 81, 21.9%), nausea (*n* = 80, 21.6%), peripheral oedema and thrombocytopenia (both *n* = 74, 20.0%) see Table 15. Other AEs of clinical interest occurred in a minority of patients, including grade ≥3 atrial fibrillation in 17 (4.6%) patients, and grade ≥3 major bleeding in 18 (4.9%) patients. Rash occurred in 57 (15.4%) patients. The incidence of other malignancies was 5.7% in the overall population, the majority of which (67%) were non-melanoma skin cancers.

Table 59 Common treatment-emergent adverse events (≥10% of patients)

Safety population (*N* = 370)	Any grade	Grade ≥3
Any adverse event, *n* (%)	364 (98·4)	265 (71·6)
Non-haematological adverse event, n (%)		
Diarrhoea	146 (39·5)	13 (3·5)
Fatigue	129 (34·9)	16 (4·3)
Cough	81 (21·9)	0
Nausea	80 (21·6)	1 (0·3)
Peripheral oedema	74 (20·0)	6 (1·6)
Upper respiratory tract infection	73 (19·7)	3 (0·8)
Dyspnoea	69 (18·6)	12 (3·2)

Pyrexia	68 (18·4)	3 (0·8)
Muscle spasms	67 (18·1)	0
Vomiting	62 (16·8)	1 (0·3)
Decreased appetite	62 (16·8)	3 (0·8)
Constipation	57 (15·4)	0
Rash	57 (15·4)	4 (1·1)
Contusion	46 (12·4)	0
Pneumonia	44 (11·9)	33 (8·9)
Back pain	44 (11·9)	6 (1·6)
Abdominal pain	42 (11·4)	13 (3·5)
Sinusitis	39 (10·5)	1 (0·3)
Urinary tract infection	38 (10·3)	6 (1·6)
Arthralgia	38 (10·3)	2 (0·5)
Headache	37 (10·0)	0
Haematological adverse event, *n* (%)		
Thrombocytopenia	74 (20·0)	41 (11·1)
Neutropenia	70 (18·9)	61 (16·5)
Anaemia	63 (17·0)	30 (8·1)

Dreyling 2022 data cut (38)

There was no late unexpected toxicity with ibrutinib during extended follow-up. The incidence of grade ≥3 treatment-emergent AEs (TEAEs) and SAEs was highest during the first year of treatment and generally decreased over time, see Table 60. With up to 9.7 years of follow-up, the most frequent grade ≥3 TEAEs (in ≥5% of patients) included neutropenia (17.0%), pneumonia (13.5%), thrombocytopenia (12.4%), anemia (10.5%), atrial fibrillation (6.8%), and hypertension (5.1%). During the 2 additional years of follow-up since the last reported 2019 data cut. The most common type of secondary malignancy was nonmelanoma skin cancer. Since the 2019 report, 1 additional patient experienced a grade 5 TEAE of prostate cancer, which was considered unrelated to ibrutinib by the investigator.

Table 60 AE's of Ibrutinib over time

	Years on Ibrutinib

	AEs Over Time (Years)								
AE, n (%)	**<1 n = 370**	**1 – <2 n= 180**	**2 – <3 n = 115**	**3 – <4 n = 83**	**4 – <5 n = 62**	**5 – <6 n = 45**	**6 – <7 n = 32**	**≥7 n = 27**	**Overall N = 370**
Grade ≥3	251 (67.8)	86 (47.8)	39 (33.9)	31 (37.3)	22 (35.5)	17 (37.8)	9 (28.1)	7 (25.9)	302 (81.6)
SAEs	175 (47.3)	61 (33.9)	34 (29.6)	23 (27.7)	19 (30.6)	15 (33.3)	8 (25.0)	6 (22.2)	241 (65.1)
Major hemorrhage	18 (4.9)	4 (2.2)	3 (2.6)	2 (2.4)	0	1 (2.2)	0	0	27 (7.3)
Atrial fibrillation									
Grade ≥3	16 (4.3)	5 (2.8)	4 (3.5)	0	1 (1.6)	1 (2.2)	1 (3.1)	0	25 (6.8)
SAE	15 (4.1)	2 (1.1)	2 (1.7)	0	1 (1.6)	1 (2.2)	1 (3.1)	0	22 (5.9)
Diarrhea									
Grade ≥3	11 (3.0)	3 (1.7)	1 (0.9)	0	1 (1.6)	0	0	0	15 (4.1)
SAE	4 (1.1)	0	1 (0.9)	0	1 (1.6)	0	0	0	6 (1.6)
Hypertension									
Grade ≥3	10 (2.7)	6 (3.3)	3 (2.6)	2 (2.4)	0	0	0	1 (3.7)	19 (5.1)
SAE	0	0	0	0	0	0	0	0	0
Rash									
Grade ≥3	4 (1.1)	0	0	0	0	0	0	0	4 (1.1)
SAE	1 (0.3)	0	0	0	0	0	0	0	1 (0.3)
Arthralgia									
Grade ≥3	2 (0.5)	1 (0.6)	1 (0.9)	1 (1.2)	0	0	0	0	4 (1.1)
SAE	1 (0.3)	0	0	1 (1.2)	0	0	0	0	2 (0.5)

Appendix F. Health-related quality of life

NA

Appendix G. Probabilistic sensitivity analyses

NA

Table 61. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
NA				
NA	NA	NA		Beta
NA	NA	NA		
NA				
NA	NA	NA		Beta
NA	NA	NA		
NA				
NA	NA	NA		Gamma
NA	NA	NA		

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

NA

[Follow section 3 of the methods guide. Describe how the literature search was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced.
Literature searches that are more than one year old are generally not accepted. If this is the case, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

If an existing/global systematic literature review (SLR) is (re)used the appendix must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted in/as the appendix. Please find an editable PRISMA flowchart at the end of this document. This diagram is to be used when existing SLRs are (re)used, so it is clear how it has been locally adapted, i.e. how many references are included and excluded from the original SLR. As mentioned above, if the literature search is more than a year old, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

Objective of the literature search: What questions is the literature search expected to answer?

Databases/other sources: Fill in the databases and other sources, e.g. conference material used in the literature search.]

Table 62 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	NA	NA	NA
Medline	NA	NA	NA
CENTRAL	NA	NA	NA

Abbreviations:

Table 63 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	NA
e.g. EMA website	NA	NA	NA

Abbreviations:

Table 64 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	NA	NA	NA	NA
	NA	NA	NA	NA

H.1.1 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Table 65 of search strategy table for [name of database]

No.	Query	Results
#1	NA	NA
#2	NA	NA
#3	NA	NA
#4	NA	NA
#5	NA	NA
#6	NA	NA
#7	NA	NA
#8	NA	NA
#9	NA	NA

No.	Query	Results
#10	NA	NA

H.1.2 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion. If the table relates to an existing SLR broader in scope, please indicate which criteria are relevant for the current application.]

Table 66 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	NA	NA	NA
Intervention	NA	NA	NA
Comparators	NA	NA	NA
Outcomes	NA	NA	NA
Study design/publication type	NA	NA	NA
Language restrictions	NA	NA	NA

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document. If an existing SLR is used, the editable diagram is to be used, so it is clear how many references have been included and excluded from the original SLR.]

Table 67 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	NA	NA	NA	NA	NA	NA
Study 2	NA	NA	NA	NA	NA	NA

H.1.3 Excluded fulltext references

NA

[Please provide in a list or table the references that were excluded during fulltext screening along with a short reason. If using an existing, locally adapted SLR, please fill in the references originally included in the SLR but excluded in the current application.]

H.1.4 Quality assessment

NA

[Describe strengths and weaknesses of the literature search performed.]

H.1.5 Unpublished data

NA

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

NA

[Follow sections 3 and 7.1.2 of the methods guide.
Describe how the literature search for the health-related quality of life data was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced. Literature searches that are more than one year old are generally not accepted. If this is the case, a new search (e.g. in PubMed) should be carried out for more recent literature.

If existing/global systematic literature review (SLR) is (re)used, Appendix I must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted in/as the appendix. Please find an editable PRISMA flowchart at the end of this document. This diagram is to be used when existing SLRs are (re)used, so it is clear how it has been locally adapted, i.e. how many references are included and excluded from the original SLR. As mentioned above, if the literature search is more than a year old, a new search (e.g. in PubMed) should be carried out for more recent literature.

If targeted literature searches have been carried out, e.g. to identify reduction of health related quality of life associated with adverse events (disutilities), these should be documented. In separate sections (for each individual search), account for the sources used, the choice of search criteria and terms, and explain the process of inclusion and exclusion. Sufficient information must be provided to enable the results to be reproduced where possible.

Objective of literature search: What questions is the literature search expected to answer?

Sources: Describe briefly which databases, and other sources were used in the literature search.]

Table 68 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	NA	NA	NA
Medline	NA	NA	NA
Specific health economics databases[1]	NA	NA	NA

Abbreviations:

Table 69 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	NA	NA	NA
CEA Registry	NA	NA	NA

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Table 70 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	NA	NA	NA	NA
	NA	NA	NA	NA

I.1.1 Search strategies

NA

[Describe the development of the search strategy and search string. Enter the inclusion and exclusion criteria for the search and justify (e.g. patient population, outcomes, study design, language, time frame, etc.).

The search must be documented for each database or resource incl. terms and syntax used, number of results retrieved in the table below.

Describe which criteria have been used to reject irrelevant studies (for example of a table to record exclusions, see Table 5 in NICE DSU Technical Support Document 9) and how the final selection has been made. Use PRISMA charts if appropriate (see example here) or use the editable table at the end of this document].

Table 71 Search strategy for [name of database]

No.	Query	Results
#1	NA	NA
#2	NA	NA
#3	NA	NA
#4	NA	NA
#5	NA	NA
#6	NA	NA
#7	NA	NA
#8	NA	NA
#9	NA	NA
#10	NA	NA

Literature search results included in the model/analysis:

[Insert results in a table]

I.1.2 Quality assessment and generalizability of estimates

NA

[Provide a complete quality assessment for each relevant study identified. When non-Danish estimates are used, generalizability must be addressed.]

I.1.3 Unpublished data

NA

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted.]

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

NA

[Describe and document how the literature for the model was identified and selected. This may be a combination of systematic database searches, targeted searches etc. Explain in separate sections (for each type of search) the sources used, the selection of the search criteria and terms used, and explain the process for inclusion and exclusion. Sufficient details should be provided so that the results may be reproduced where possible.]

J.1.1 Example: Systematic search for […]

[Objective of the literature search: What questions is the literature search expected to answer?]

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	NA	NA	NA
Medline	NA	NA	NA
CENTRAL	NA	NA	NA

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion. For systematic searches, the requirements from the literature search for clinical evidence apply, see Appendix H].

J.1.2 Example: Targeted literature search for [estimates]

[Objective of the literature search: What questions is the literature search expected to answer?] NA

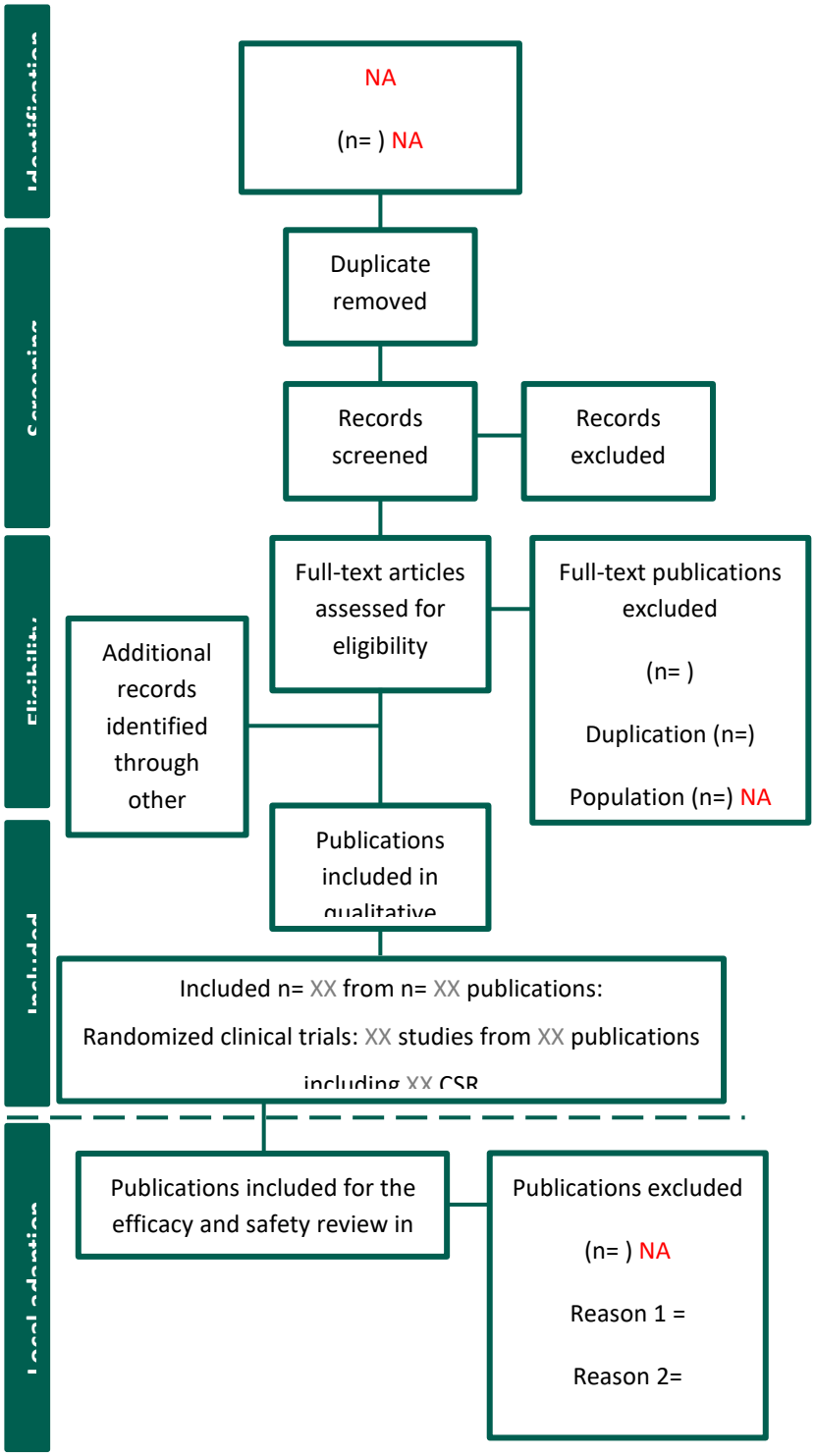
Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NA	NA	NA	NA
NA	NA	NA	NA

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion.]

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Appendix K. Efficacy and safety of acalabrutinib vs ibrutinib in Phase 3 head-head study in CLL

Key points
• ELEVATE-RR met the primary endpoint of non-inferiority and demonstrated that the efficacy of acalabrutinib is similar to that of ibrutinib, with a median IRC-assessed PFS of 38.4 months in both arms • The incidence of atrial fibrillation or atrial flutter of any grade was lower with acalabrutinib than with ibrutinib (9.4% vs 16.0%; *p* = 0.02) • There was no difference in the incidence of grade 3 or higher infections or Richter's transformation between the acalabrutinib and ibrutinib arms • Median OS was not reached in either treatment arm, with 63 deaths (23.5%) with acalabrutinib and 73 (27.5%) with ibrutinib (HR: 0.82) • Median IRC-assessed EFS was similar between the acalabrutinib and ibrutinib arms (33.2 months vs 33.0 months) • Investigator-assessed PFS was consistent with the primary analysis (HR: 0.90; 95% CI: 0.69–1.16) • A similar proportion of patients responded to treatment with acalabrutinib and ibrutinib, according to IRC assessment (81.0% vs 77.0%)

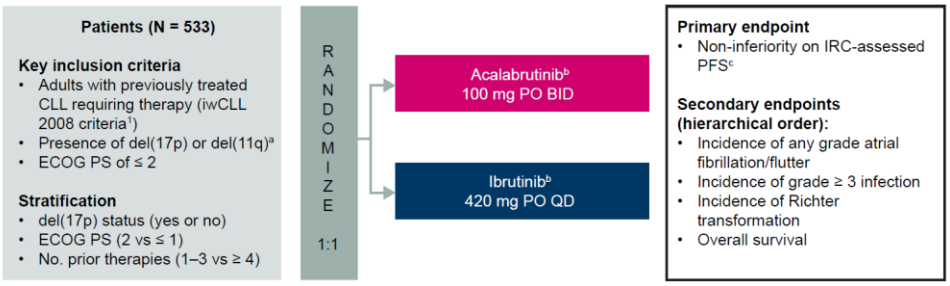
K.1 Design, interventions and dosing

Patients in ELEVATE-RR were randomized to one of two treatment arms: acalabrutinib or ibrutinib (Figure 13). Crossover between treatment groups was not permitted.[134]

Acalabrutinib and ibrutinib have a similar mechanism of action and have shown a similar efficacy in indirect treatment comparisons. As a result, a very large sample would be required to identify statistically and clinically significant differences in efficacy between acalabrutinib and ibrutinib. Therefore, in order to avoid a large recruitment burden, a non-inferiority design was chosen to investigate the efficacy of acalabrutinib compared with ibrutinib, and to evaluate their risk–benefit outcomes.

Study participants were drawn from 124 centres in 15 countries.[134] Participants were randomized and stratified according to del(17p) status (yes or no) , ECOG Performance Status (2 vs < 1) and number of previous treatment regimens (1–3 vs ≥ 4).[134]

Figure 13 ELEVATE-RR study design



[a]By central laboratory testing.
[b]Continued until disease progression or unacceptable toxicity.
[c]Conducted after enrolment completion and accrual of ~250 IRC-assessed PFS events.

BID, twice daily; CLL, chronic lymphocytic leukaemia; del(11q), deletion of chromosome 11q region; del(17p), deletion of chromosome 17p region; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IRC, Independent Review Committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PFS, progression-free survival; PO, oral; QD, once daily.

Source: ELEVATE-RR Supplement, Slide 3.[134]

Baseline characteristics and patient disposition

K.1.1 Characteristics

In total, 533 patients were randomized: 268 to acalabrutinib and 265 to ibrutinib. Demographic and baseline characteristics were generally well balanced and there were no notable differences between treatment arms (Table 72). Overall, patients had a median age of 66 years, the median number of previous therapies was two in both the acalabrutinib and ibrutinib arms, and 241 patients (45.2%) had del(17p) and 342 (64.2%) had del(11q) [31,134]

Table 72 Baseline demographics, disease characteristics and treatment history

	Number of patients (%)	
	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Age, years		
Median (range)	66 (41–89)	65 (28–88)

≥ 75	44 (16.4)	43 (16.2)
Sex (male)	185 (69.0)	194 (73.2)
ECOG PS		
0–1	247 (92.2)	243 (91.7)
2	20 (7.5)	22 (8.3)
Bulky disease (≥ 5 cm)	128 (47.8)	136 (51.3)
Rai stage 3 or 4	131 (48.9)	134 (50.6)
Cytogenic subgroup		
Del(17p)	121 (45.1)	120 (45.3)
Del(11q)	167 (62.3)	175 (66.0)
Complex karyotype[a]	124 (46.3)	125 (47.2)
***TP53* mutational status**		
Mutated	100 (37.3)	112 (42.3)
Unmutated	167 (62.3)	153 (57.7)
***IGHV* mutational status**		
Mutated	44 (16.4)	28 (10.6)
Unmutated	220 (82.1)	237 (89.4)
Cytopenia at baseline		
Haemoglobin ≤ 11.0 g/dL	100 (37.3)	96 (36.2)
Platelet count ≤ 100 x 10^9/L	96 (35.8)	92 (34.7)
Absolute neutrophil count ≤ 1.5 x 10^9/L	25 (9.3)	18 (6.8)
Number of previous therapies		
Median (range)	2 (1–9)	2 (1–12)
1–3	234 (87.3)	237 (89.4)
≥ 4	33 (12.3)	28 (10.6)

Most common previous therapies[b]		
Alkylators	242 (90.3)	240 (90.6)
Anti-CD20 monoclonal antibodies	227 (84.7)	229 (86.4)
Purine analogues	172 (64.2)	158 (59.6)
Steroids	62 (23.1)	62 (23.4)
Chemotherapy[c]	39 (14.6)	37 (14.0)
Alemtuzumab	16 (6.0)	11 (4.2)
Lenalidomide (monotherapy and in combination)	5 (1.9)	13 (4.9)

Data are n (%) unless otherwise stated. [a]Patients with three or more chromosomal abnormalities and one or more structural abnormalities. [b]A patient was only counted once for each category. [c]Includes doxorubicin, bleomycin, vinca/alkaloids, etoposide and platinum-based regimens. del(11q), deletion of chromosome 11q region; del(17p), deletion of chromosome 17p region; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *IGHV*, immunoglobulin heavy chain variable gene; *TP53*, tumour protein 53 gene. Source: ELEVATE-RR, Table 1.[134]

K.1.2 Disposition

Patient disposition and flow through the study are shown in Table 68. In total, 533 patients were randomized and 529 were treated. Overall, the median duration of follow-up was 40.9 months.

As of the data cut-off date (15 September 2020), 141 patients (52.6%) in the acalabrutinib arm and 155 patients (58.5%) in the ibrutinib arm had discontinued treatment. The primary reason for discontinuing acalabrutinib and ibrutinib was disease progression (82 patients [30.6%] and 68 patients [25.7%], respectively[134]

Table 73 Patient disposition at data cut-off date

	Acalabrutinib (n = 268)	**Ibrutinib** (n = 265)
Patients who were randomized (ITT population)	268 (100)	265 (100)
Patients who were randomized and did not receive study treatment	3 (1.1)	1 (0.4)
Patients who were treated with study drug (safety population)	266 (99.3)	263 (99.2)

Patients who discontinued all study treatment	141 (52.6)	155 (58.5)
Death	5 (1.9)	6 (2.3)
Lost to follow-up	0	0
Withdrawal of consent	7 (2.6)	7 (2.6)
AE/SAE	40 (14.9)	59 (22.3)
CLL progressive disease	82 (30.6)	68 (25.7)
Investigator discretion	5 (1.9)	5 (1.9)
Pregnancy	0	0
Othera	2 (0.7)	10 (3.8)

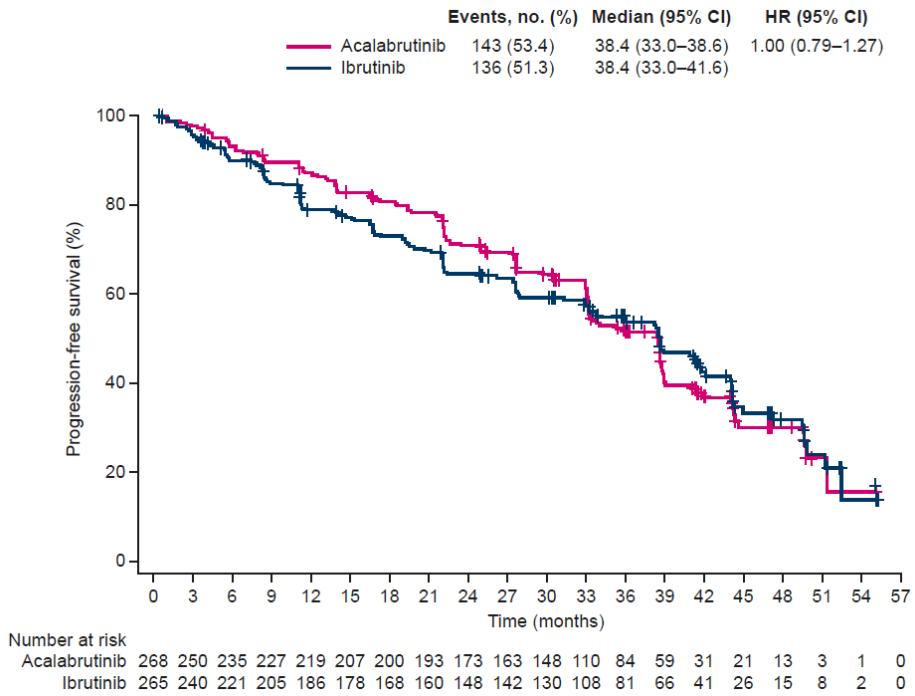
Data presented are n (%). [a]Includes patients who discontinued treatment but agreed to remain on the study for follow-up. Source: ELEVATE-RR CSR, Table 9.[47]

K.1.3 Primary outcome – IRC-assessed PFS

After a median follow-up of 40.9 months, the pre-specified criterion for non-inferiority was met, and the median IRC-assessed PFS was 38.4 months for both the acalabrutinib (95% CI: 33.0–38.6) and ibrutinib (95% CI: 33.0–41.6) arms (HR: 1.00; 95% CI: 0.79–1.27; Figure 14 and Table 74). IRC-assessed PFS was generally comparable across pre-specified subgroups including patients with del(17p) and del(11q) and regardless of the number of prior therapies.

At the data cut-off, 143 patients (53.4%) had either progressed or died while receiving acalabrutinib compared with 136 patients (51.3%) receiving ibrutinib.

Figure 14 Kaplan–Meier plot for PFS (IRC assessment)



CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; PFS, progression-free survival. Source: ELEVATE-RR CSR.

Table 74 PFS landmark analysis (IRC assessment)

	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Events, n (%)		
Death	22 (8.2)	28 (10.6)
Disease progression	121 (45.1)	108 (40.8)
KM-estimated PFS, % (95% CI)[a]		
6-month PFS	92.2 (88.1–94.9)	90.0 (85.6–93.1)
12-month PFS	86.7 (81.8–90.3)	78.8 (73.1–83.4)
18-month PFS	80.7 (75.3–85.0)	72.8 (66.7–77.9)
24-month PFS	70.9 (64.8–76.1)	64.5 (58.1–70.2)
30-month PFS	64.5 (58.2–70.1)	59.2 (52.6–65.1)
36-month PFS	51.4 (44.7–57.8)	53.8 (47.0–60.1)

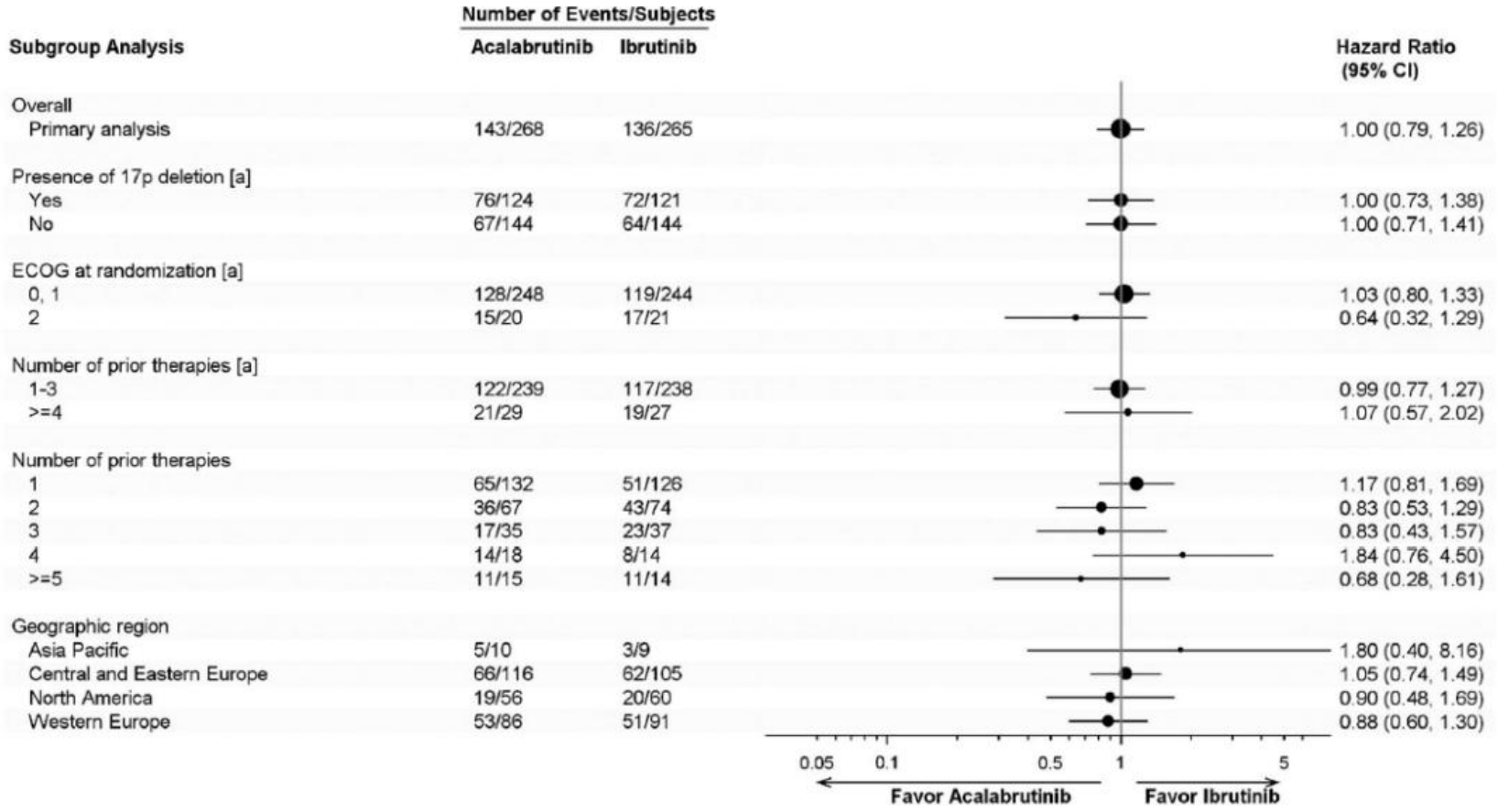
42-month PFS	36.9 (29.8–44.0)	41.6 (34.2–48.9)
48-month PFS	30.2 (22.5–38.2)	31.7 (23.6–40.1)
54-month PFS	15.7 (4.8–32.2)	14.1 (4.2–29.6)

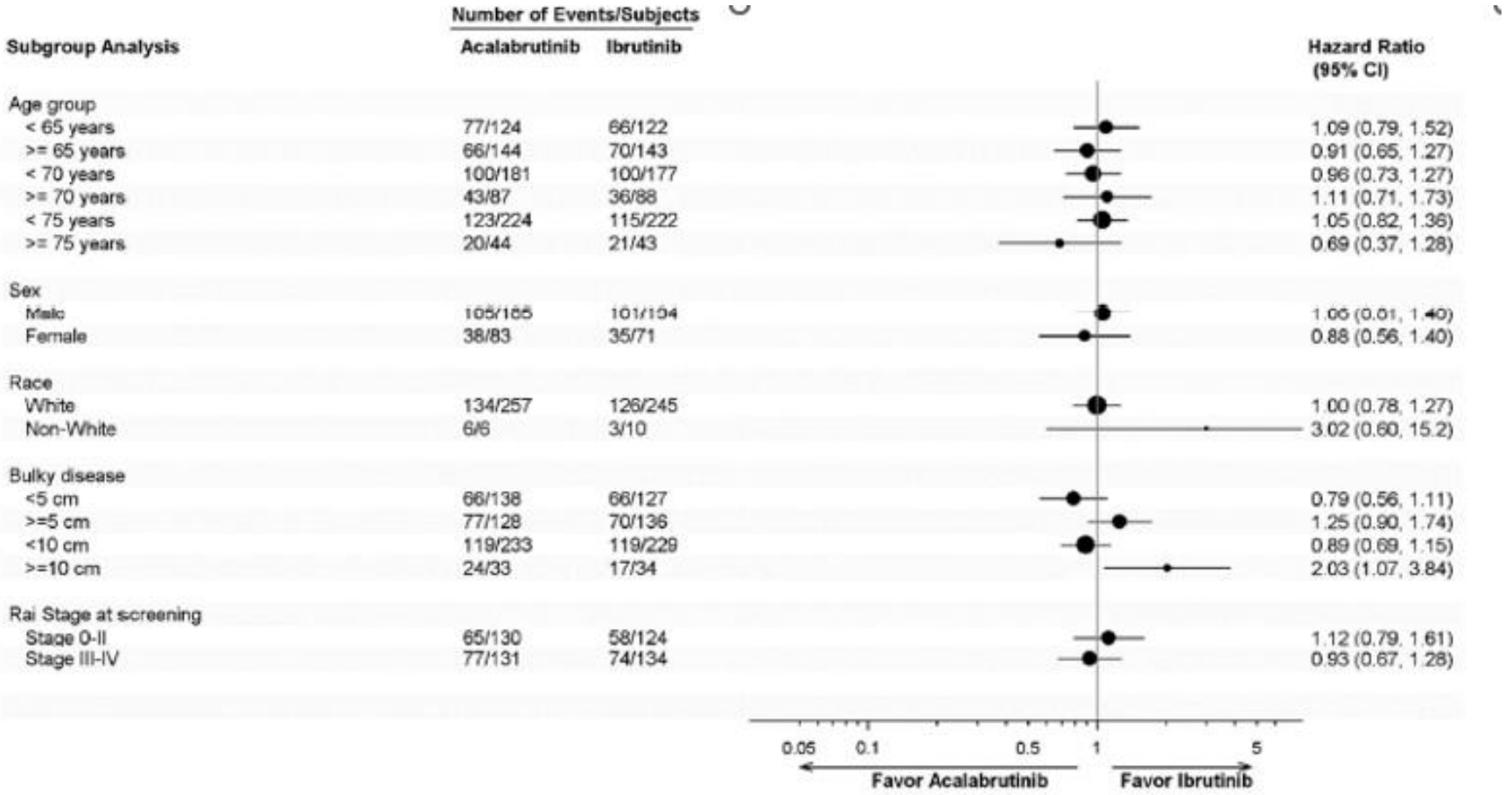
[a]Assessed by IRC. CI, confidence interval; IRC, Independent Review Committee; KM, Kaplan–Meier; PFS, progression-free survival. Source: ELEVATE-RR CSR, Table 18.[47]

K.1.4 Patient subgroups

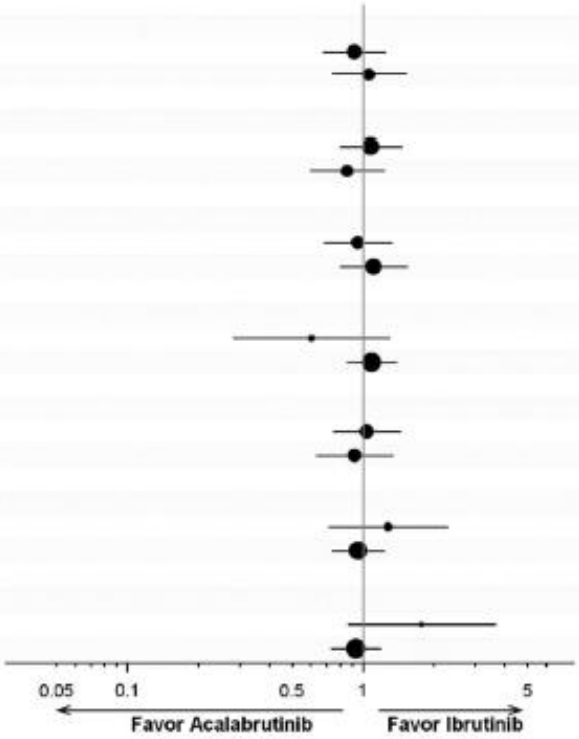
The benefit of acalabrutinib on IRC-assessed PFS was comparable across pre-specified subgroups. This included patients with chromosomal characteristics (del[17p], *TP53* mutation, del[11q] or unmutated *IGHV*) and non-chromosomal risk factors (advanced stage disease [Rai stage III or IV], age ≥ 65 years or bulky disease ≥ 5 cm) associated with poor prognosis (Figure 15).[134]

Figure 15 PFS subgroup analysis (IRC assessment)

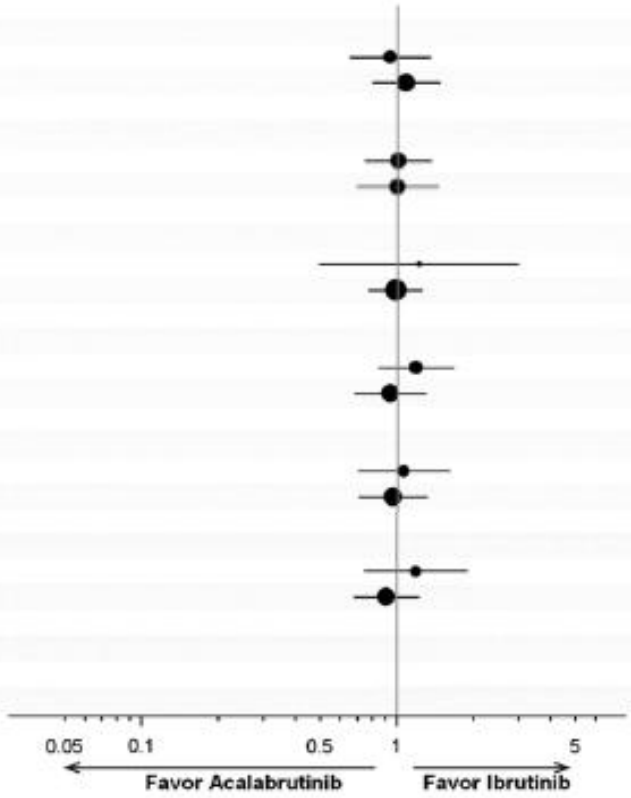



Number of Events/Subjects
Subgroup Analysis
Acalabrutinib
Ibrutinib
Hazard Ratio (95% CI)
Age group
< 65 years 77/124 66/122 1.09 (0.79, 1.52)
>= 65 years 66/144 70/143 0.91 (0.65, 1.27)
< 70 years 100/181 100/177 0.96 (0.73, 1.27)
>= 70 years 43/87 36/88 1.11 (0.71, 1.73)
< 75 years 123/224 115/222 1.05 (0.82, 1.36)
>= 75 years 20/44 21/43 0.69 (0.37, 1.28)
Sex
Male 105/165 101/134 1.06 (0.81, 1.40)
Female 38/83 35/71 0.88 (0.56, 1.40)
Race
White 134/257 126/245 1.00 (0.78, 1.27)
Non-White 6/6 3/10 3.02 (0.60, 15.2)
Bulky disease
<5 cm 66/138 66/127 0.79 (0.56, 1.11)
>=5 cm 77/128 70/136 1.25 (0.90, 1.74)
<10 cm 119/233 119/229 0.89 (0.69, 1.15)
>=10 cm 24/33 17/34 2.03 (1.07, 3.84)
Rai Stage at screening
Stage 0-II 65/130 58/124 1.12 (0.79, 1.61)
Stage III-IV 77/131 74/134 0.93 (0.67, 1.28)
0.05
0.1
0.5
1
5
Favor Acalabrutinib
Favor Ibrutinib

Subgroup Analysis	Number of Events/Subjects Acalabrutinib	Ibrutinib	Hazard Ratio (95% CI)
Cytopenias at baseline			
Yes	84/148	78/137	0.92 (0.68, 1.25)
No	58/117	58/127	1.06 (0.74, 1.53)
Presence of 11q del			
Yes	85/167	79/175	1.08 (0.80, 1.47)
No	58/100	57/90	0.86 (0.59, 1.24)
TP53 mutation			
Yes	64/100	73/112	0.95 (0.68, 1.33)
No	79/167	63/153	1.11 (0.80, 1.55)
IGHV			
Mutated	13/44	13/28	0.60 (0.28, 1.31)
Unmutated	130/220	123/237	1.09 (0.85, 1.40)
Complex Karyotype			
Yes	74/124	66/125	1.04 (0.74, 1.44)
No	52/116	56/116	0.92 (0.63, 1.35)
Beta2-microglobulin at baseline			
<=3.5 mg/L	28/58	19/51	1.28 (0.71, 2.30)
>3.5 mg/L	113/207	117/214	0.95 (0.74, 1.24)
17p del and 11q del			
Yes	17/21	13/30	1.78 (0.86, 3.67)
No	126/246	123/235	0.93 (0.73, 1.20)



Subgroup Analysis	Number of Events/Subjects		Hazard Ratio (95% CI)
	Acalabrutinib	Ibrutinib	
17p del and TP53 mutation			
Yes	54/85	62/97	0.94 (0.65, 1.35)
No	89/182	74/168	1.08 (0.79, 1.47)
17p del and/or TP53 mutation			
Yes	85/136	81/135	1.01 (0.74, 1.37)
No	58/131	55/130	1.00 (0.69, 1.45)
17p del and 11q del and TP53 mutation			
Yes	9/12	10/20	1.22 (0.49, 3.00)
No	134/255	126/245	0.98 (0.77, 1.26)
17p del and unmutated IGHV			
Yes	68/92	65/105	1.18 (0.84, 1.67)
No	75/172	71/160	0.94 (0.68, 1.30)
17p del and complex karyotype			
Yes	46/67	42/68	1.06 (0.70, 1.62)
No	80/173	80/173	0.96 (0.70, 1.31)
11q del and complex karyotype			
Yes	39/70	32/74	1.19 (0.74, 1.89)
No	87/170	90/167	0.91 (0.68, 1.22)



11q del, deletion of chromosome 11q region; 17p del, deletion of chromosome 17p region; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *IGHV*, immunoglobulin heavy chain variable gene; IRC, Independent Review Committee; PFS, progression-free survival; *TP53*, tumour protein 53 gene.

Source: ELEVATE-RR CSR, Figure 3.[47]

K.1.5 Sensitivity analyses

The results of all sensitivity analyses for the primary outcome, including the key analysis of PFS without censoring for subsequent anti-cancer therapy, were similar to those of the primary analysis, with HRs ranging from 0.99 to 1.01, confirming the robustness of the primary analysis.

K.2 Overall survival

The OS data are not mature and median OS was not reached in either treatment arm; however, the OS trend favoured acalabrutinib with an HR of 0.82 (95% CI: 0.59–1.15; *p* = 0.2517). After a median follow-up of 40.9 months, 63 patients (23.5%) in the acalabrutinib arm and 73 (27.5%) in the ibrutinib arm had died (Table 75; Figure 16). The KM estimate of OS at 36 months for acalabrutinib and ibrutinib was 80.7% (95% CI: 75.2–85.0) and 75.8% (95% CI: 70.0–80.7), respectively.

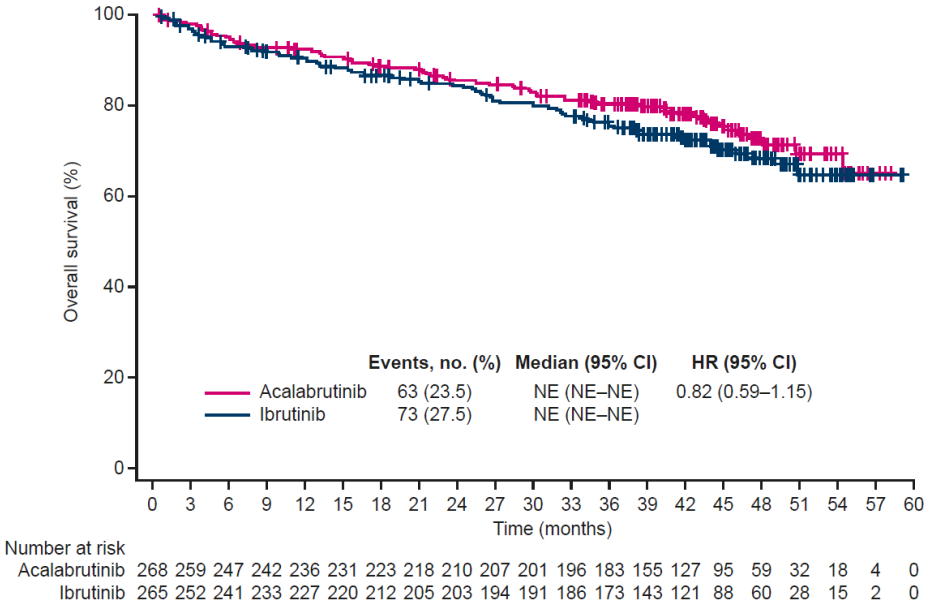
Table 75 Analysis of overall survival (ITT population)

	Acalabrutinib (N = 268)	Ibrutinib (N = 265)
Events, n (%)		
Death	63 (23.5)	73 (27.5)
Median OS, months (95% CI)	NE (NE–NE)	NE (NE–NE)
HR (95% CI)[a,b]	0.82 (0.59–1.15)	
***p* value[c]**	0.2517	
KM-estimated OS,[d] % (95% CI)		
6 months	94.3 (90.7–96.5)	93.1 (89.3–95.6)
12 months	92.4 (88.5–95.0)	90.0 (85.6–93.1)
18 months	88.9 (84.4–92.1)	86.8 (82.0–90.4)
24 months	85.6 (80.7–89.4)	84.7 (79.7–88.6)
30 months	82.8 (77.5–86.9)	80.1 (74.6–84.5)
36 months	80.7 (75.2–85.0)	75.8 (70.0–80.7)
42 months	78.5 (72.8–83.2)	72.8 (66.7–78.0)

48 months	73.0 (66.2–78.7)	68.8 (61.9–74.7)
54 months	69.8 (61.6–76.6)	65.3 (56.9–72.4)

[a]Stratified by del(17p) status (yes vs no) and number of prior therapies (1–3 vs ≥ 4). [b]Estimated based on stratified Cox proportional hazards model for HR (95% CI). [c]Estimated based on stratified log rank test for *p* value. [d]Kaplan–Meier estimate of the proportion of patients who were alive at the time point. CI, confidence interval; ITT, intent-to-treat; HR, hazard ratio; KM, Kaplan–Meier; NE, not estimable; OS, overall survival. Source: ELEVATE-RR CSR, Table 23.[47]

Figure 16 Kaplan–Meier plot for OS



CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Source: ELEVATE-RR,

K.2.1 Investigator-assessed PFS

After a median follow-up of 40.9 months, investigator-assessed PFS was consistent with IRC-assessed PFS in both the acalabrutinib and ibrutinib arms (46.9 vs 44.1 months; HR: 0.90; 95% CI: 0.69–1.16).

K.2.2 Treatment response

The IRC-assessed ORR was 81.0% (95% CI: 75.8–85.2) with acalabrutinib and 77.0% (95% CI: 71.5–81.6) with ibrutinib. Response rates from the investigator assessment were consistent with those from the IRC assessment (Table 76).

Table 76 Best overall response as assessed by investigator and IRC (ITT population)

	IRC assessment		Investigator assessment	
	Acalabrutinib (N = 268)	Ibrutinib (N = 265)	Acalabrutinib (N = 268)	Ibrutinib (N = 265)
Best overall response, n (%)				
CR	5 (1.9)	8 (3.0)	25 (9.3)	26 (9.8)
CRi	0	0	2 (0.7)	0
nPR	2 (0.7)	3 (1.1)	0	0
PR	210 (78.4)	193 (72.8)	205 (76.5)	186 (70.2)
PRL	6 (2.2)	8 (3.0)	16 (6.0)	25 (9.4)
Overall response rates				
ORR (CR + CRi + nPR + PR), n (%) [95% CI][a]	217 (81.0) [75.8–85.2]	204 (77.0) [71.5–81.6]	232 (86.6) [82.0–90.1]	212 (80.0) [74.8–84.4]
***p* value[b]**	0.2503		0.0408	
ORR + PRL (CR + CRi + nPR + PR + PRL), n (%) [95% CI][a]	223 (83.2) [78.3–87.2]	212 (80.0) [74.8–84.4]	248 (92.5) [88.8–95.1]	237 (89.4) [85.2–92.6]
***p* value[b]**	0.3298		0.2113	

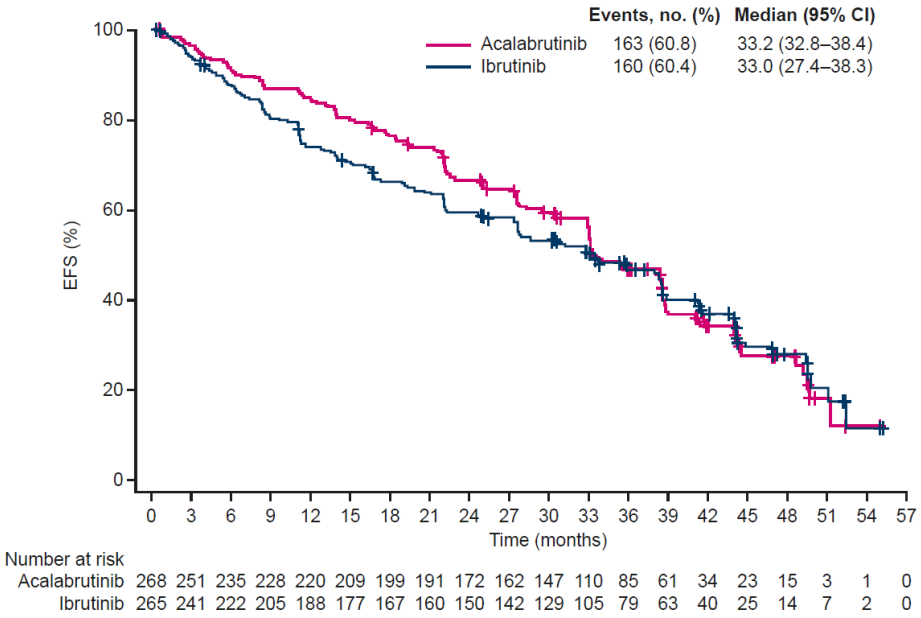
[a]95% CI based on Normal approximation (with use of Wilson's score). [b]Based on Cochran–Mantel–Haenszel test with adjustment for randomization stratification factors. CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; IRC, Independent Review Committee; ITT, intent-to-treat; nPR, nodular partial response; ORR, overall response rate; PR, partial response; PRL, partial response with lymphocytosis.

Source: ELEVATE-RR CSR, Table 26.[47]

K.3 Event-free survival

Median IRC-assessed EFS was similar between the acalabrutinib and ibrutinib arms (33.2 vs 33.0 months; HR: 0.95; 95% CI: 0.76–1.18; Figure 17). Similar results were seen for the median investigator-assessed EFS (HR: 0.84; 95% CI: 0.66–1.06).

Figure 17 Kaplan–Meier plot for IRC-assessed EFS



CI, confidence interval; EFS, event-free survival; IRC, Independent Review Committee.

Source: ELEVATE-RR, Figure 2.[134]

K.4 Duration of response

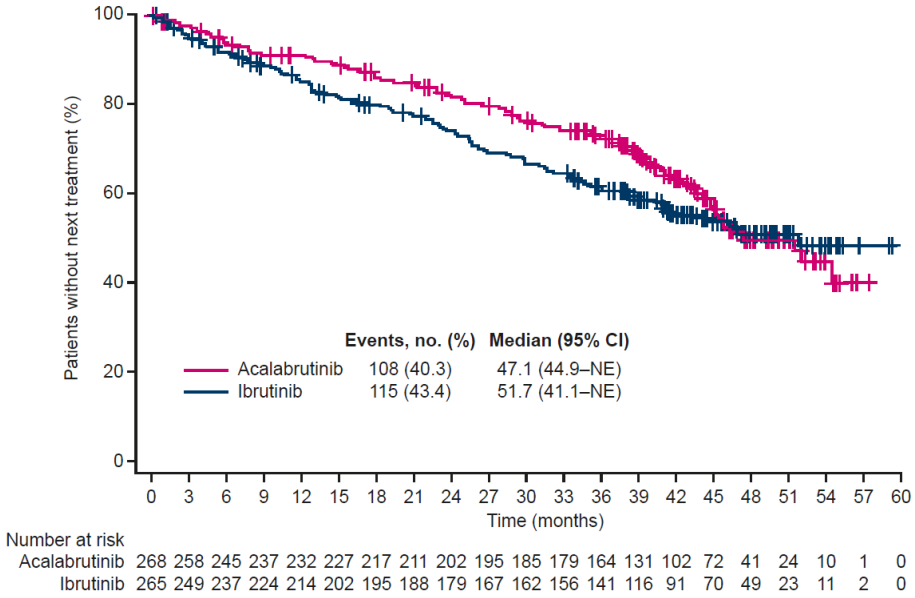
Based on IRC assessment, no differences were observed between the acalabrutinib and ibrutinib arms for the median DOR (33.1 vs 35.9 months; HR: 1.10; 95% CI: 0.83–1.45). The KM estimate of the proportion of responders without a PFS event at 36 months with acalabrutinib and ibrutinib were 40.4% and 48.6%, respectively.

Similar results were seen with the investigator assessment, with a median DOR of 46.9 months (95% CI: 35.7–NE) and 41.8 months (95% CI: 38.4–NE) for acalabrutinib and ibrutinib, respectively. (HR: 1.04; 95% CI: 0.77–1.41). The KM estimate of the proportion of responders without a PFS event at 36 months with acalabrutinib and ibrutinib were 56.3% and 60.1%, respectively.

K.5 Time to next treatment

Subsequent anti-cancer therapy for CLL was initiated by 60 patients (23.3%) in the acalabrutinib arm and 56 patients (22.2%) in the ibrutinib arm. Median investigator-assessed TTNT was similar between the acalabrutinib and ibrutinib arms (47.1 [95% CI: 44.9–NE] months vs 51.7 [95% CI: 41.1–NE] months; Figure 18).[134]

Figure 18 Investigator-assessed time to next treatment



CI, confidence interval; NE, not estimable.

Source: ELEVATE-RR, Figure S3.[134]

K.6 Medical resource utilization (ITT population)

Healthcare resource utilization in the ELEVATE-RR trial is shown in Table 77. Compared with ibrutinib, acalabrutinib was associated with fewer hospital admissions but slightly more platelet transfusions, and emergency department visits and plasma, whole blood and packed red blood cell transfusions were similar between treatment arms.

Table 77 Healthcare resource utilization

Resource utilization, number of events per person-year	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Hospitalizations	0.299	0.386
Emergency department visits	0.076	0.081
Plasma, whole blood and packed RBC transfusions	0.188	0.204
Platelet transfusions	0.046	0.021
Use of haematopoietic growth factors	0.188	0.172

RBC, red blood cell.

Source: ELEVATE-RR CSR, Table 31.[47]

K.7 Relapsed or refractory CLL – safety and tolerability (ELEVATE-RR)

Key points
• In total, 97.7% of patients receiving acalabrutinib and 97.3% receiving ibrutinib experienced AEs of any grade • Overall, patients treated with acalabrutinib were less likely to experience grade 3 or higher AEs than those receiving ibrutinib (68.8% vs 74.9%;) • Atrial fibrillation or atrial flutter of any grade was less frequent with acalabrutinib than with ibrutinib (9.4% vs 16.0%; *p* = 0.02) • Serious AEs (SAEs) occurred in 53.8% and 58.6% of patients who received acalabrutinib and ibrutinib, respectively • At the time of this analysis, 17 patients (6.4%) in the acalabrutinib arm and 25 patients (9.5%) in the ibrutinib arm had died as of the data cut-off date owing to AEs

K.8 Overview of safety

Acalabrutinib demonstrated a safety and tolerability profile in this study that was consistent with those previously observed in other acalabrutinib monotherapy haematological malignancy clinical trials, including in CLL. Compared with ibrutinib, acalabrutinib was associated with a lower incidence of grade 3 or higher TEAEs (68.8% for acalabrutinib vs 74.9% for ibrutinib), as well as a lower incidence of SAEs (53.8% vs 58.6%) and AEs (14.7% vs 21.3%) that led to treatment discontinuation.

K.8.1 Exposure

The median treatment exposure in the acalabrutinib arm (38.3 months) was similar to the ibrutinib arm (35.5 months).[134]

K.8.2 Adverse events

In total, 97.7% of patients receiving acalabrutinib and 97.3% receiving ibrutinib experienced AEs of any grade. Overall, patients with acalabrutinib were less likely to experience grade 3 or higher AEs than those receiving ibrutinib (68.8% vs 74.9%).[26]

The most common AEs among patients treated with acalabrutinib were diarrhoea (34.6%), headache (34.6%) and cough (28.9%). In patients treated with ibrutinib, the most common AEs were diarrhoea (46.0%), neutropenia (24.7%) and upper respiratory tract infection (24.7%). Most AEs were grade 1 or 2; the most common grade 3 or higher TEAE in both treatment arms was neutropenia (acalabrutinib: 19.5%; ibrutinib: 22.8%), followed by anaemia (11.7% and 12.9%) and pneumonia (10.5% and 8.7%; Table 78).[134]

AEs led to fewer treatment discontinuations in the acalabrutinib (14.7%) than the ibrutinib (21.3%) arm.[134] AEs leading to dose interruption or dose reduction occurred at similar frequencies in both arms.[134]

Table 78 Most common adverse events reported in at least 10% (any grade) or 5% (grade ≥ 3) of patients in either arm

Events, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Diarrhoea[a,b]	92 (34.6)	3 (1.1)	121 (46.0)	13 (4.9)
Headache[a,b]	92 (34.6)	4 (1.5)	53 (20.2)	0
Cough[a]	77 (28.9)	2 (0.8)	56 (21.3)	1 (0.4)
Upper respiratory tract infection	71 (26.7)	5 (1.9)	65 (24.7)	1 (0.4)
Pyrexia	62 (23.3)	8 (3.0)	50 (19.0)	2 (0.8)
Anaemia	58 (21.8)	31 (11.7)	49 (18.6)	34 (12.9)
Neutropenia	56 (21.1)	52 (19.5)	65 (24.7)	60 (22.8)
Fatigue[b]	54 (20.3)	**9 (3.4)**	44 (16.7)	0
Arthralgia[a]	42 (15.8)	0	**60 (22.8)**	2 (0.8)
Hypertension[a,b]	23 (8.6)	11 (4.1)	**60 (22.8)**	**23 (8.7)**
Nausea	47 (17.7)	0	49 (18.6)	1 (0.4)
Pneumonia	47 (17.7)	28 (10.5)	43 (16.3)	23 (8.7)
Thrombocytopenia	40 (15.0)	26 (9.8)	35 (13.3)	18 (6.8)
Dyspnoea	37 (13.9)	6 (2.3)	23 (8.7)	1 (0.4)
Bronchitis	34 (12.8)	3 (1.1)	23 (8.7)	2 (0.8)

Constipation	31 (11.7)	0	37 (14.1)	2 (0.8)
Contusion[a]	31 (11.7)	0	**48 (18.3)**	1 (0.4)
Nasopharyngitis	29 (10.9)	0	27 (10.3)	0
Dizziness	28 (10.5)	0	26 (9.9)	0
Vomiting	28 (10.5)	1 (0.4)	36 (13.7)	3 (1.1)
Peripheral oedema	26 (9.8)	0	38 (14.4)	1 (0.4)
Rash	26 (9.8)	2 (0.8)	33 (12.5)	0
Myalgia	25 (9.4)	2 (0.8)	27 (10.3)	1 (0.4)
Atrial fibrillation[a]	24 (9.0)	12 (4.5)	**41 (15.6)**	9 (3.4)
Urinary tract infection[a]	22 (8.3)	3 (1.1)	**36 (13.7)**	6 (2.3)
Back pain[a]	20 (7.5)	0	**34 (12.9)**	2 (0.8)
Epistaxis	19 (7.1)	1 (0.4)	28 (10.6)	1 (0.4)
Muscle spasms[a]	16 (6.0)	0	**35 (13.3)**	2 (0.8)
Dyspepsia[a]	10 (3.8)	0	**32 (12.2)**	0

Higher incidences with statistical differences are shown in bold text.

[a]Descriptive two-sided $p < 0.05$ on the basis of Barnard's exact test without multiplicity adjustment for all-grade adverse events.

[b]Descriptive two-sided $p < 0.05$ on the basis of Barnard's exact test without multiplicity adjustment for grade ≥ 3 adverse events.

Source: ELEVATE-RR, Table 2.[134]

K.8.3 Incidence of atrial fibrillation

Atrial fibrillation or atrial flutter of any grade was significantly less frequent with acalabrutinib than with ibrutinib (9.4% vs 16.0%; $p = 0.02$; Table 79; Figure 19). Additionally, the median time to any-grade (28.8 vs 16.0 months) and grade 3 or higher (22.3 vs 4.8 months) atrial fibrillation/flutter events was longer with acalabrutinib than with ibrutinib. No patients discontinued acalabrutinib owing to atrial fibrillation, whereas seven patients (2.7%) discontinued ibrutinib owing to atrial fibrillations. The incidence of treatment-emergent atrial fibrillation was reduced with acalabrutinib compared with ibrutinib across almost all pre-specified subgroups.

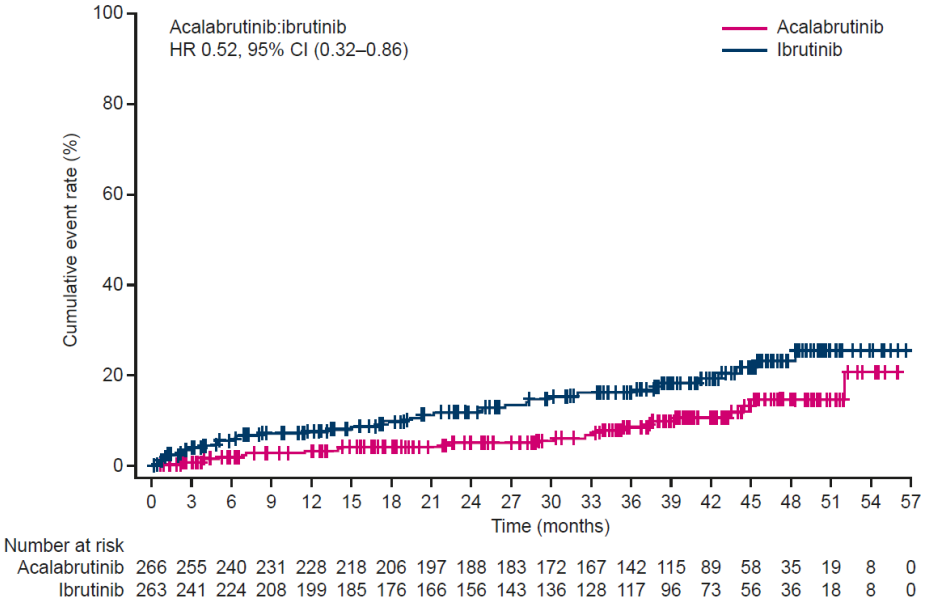
Table 79 Incidence of atrial fibrillation/flutter

	Any grade			
	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Atrial fibrillation/flutter, n (%)[a]	25 (9.4)[b]	13 (4.9)	42 (16.0)[a]	10 (3.8)
Events/100 person-months	0.366	0.155	0.721	0.124
Time to atrial fibrillation onset, median (range), months	28.8 (0.4–52.0)	22.3 (0.4–45.1)	16.0 (0.5–48.3)	4.8 (0.5–28.2)
Leading to treatment discontinuation[b]	0	0	7 (16.7)	2 (20.0)
Interventional procedures for atrial fibrillation, n (%)	4 (16.0)	3 (23.1)	6 (14.3)	1 (10.0)
Cardioversion	4 (16.0)	2 (15.4)	5 (11.9)	1 (10.0)
Cardiac pacemaker insertion	1 (4.0)	1 (7.8)	0	0
Cardiac ablation	0	0	1 (2.4)	0
Implantable defibrillator insertion	0	0	1 (2.4)	0

[a]Includes events with the preferred terms of atrial fibrillation and atrial flutter (a patient was only counted once if he or she experienced both types of events); atrial flutter was reported in one patient in the acalabrutinib arm and two patients in the ibrutinib arm (one of the two ibrutinib patients also had an atrial fibrillation event and was counted only once for the combined atrial fibrillation or flutter term).
[b]Part of the multiple testing procedure; difference in any-grade incidence was –6.6% (95% CI: –12.2, –0.9; $p = 0.02$).

Source: ELEVATE-RR, Figure 4.[134]

Figure 19 Cumulative incidence of atrial fibrillation



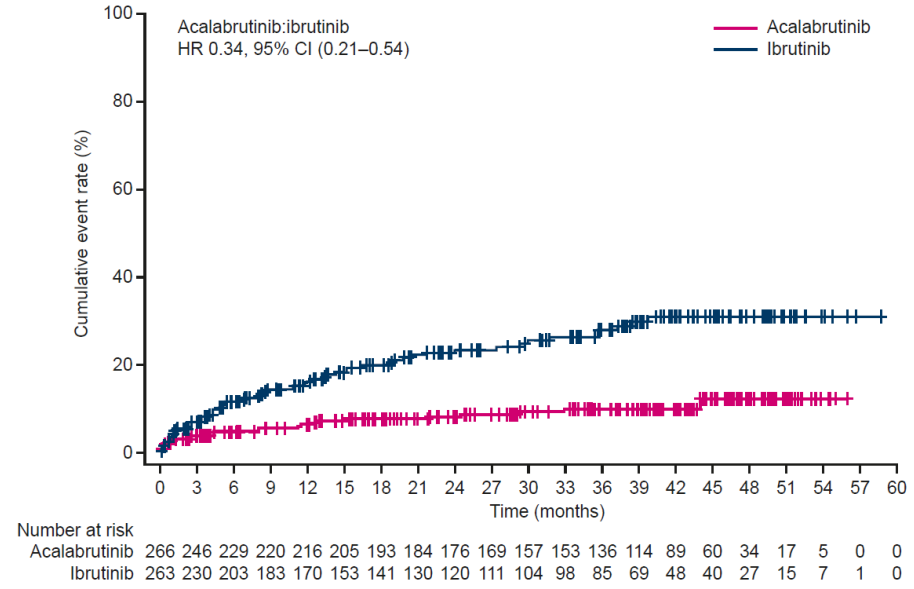
CI, confidence interval; HR, hazard ratio.

Source: ELEVATE-RR, Figure 4.[134]

K.8.4 Incidence of hypertension and selected cardiac events

The rate of hypertension was lower in patients receiving acalabrutinib than in those receiving ibrutinib (any grade: 0.444 vs 1.243 events per 100 person-months; $p < 0.001$; grade ≥ 3: 0.133 vs 0.435 events per 100 person-months; $p = 0.0214$; Figure 20and Table 80).

Figure 20 Cumulative incidence of hypertension



CI, confidence interval; HR, hazard ratio.

Source: ELEVATE-RR, Figure 4.[134]

Table 80 Incidence of hypertension and selected cardiac events

	Any grade			
	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hypertension events[a], n (%)	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Events/100 person-months	0.444	0.133	1.243	0.435
Patients with a history of hypertension, n (%)	16 (64.0)	9 (81.8)	30 (49.2)	16 (66.7)
Cardiac events, n (%)	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Ventricular arrhythmia or cardiac arrest	1 (0.4)	1 (0.4)	5 (1.9)	3 (1.1)
Cardiorespiratory arrest	1 (0.4)	1 (0.4)	0	0
Cardiac arrest	0	0	2 (0.8)	2 (0.8)
Ventricular arrhythmia	0	0	1 (0.4)	0
Ventricular extrasystoles	0	0	1 (0.4)	0
Ventricular fibrillation	0	0	1 (0.4)	1 (0.4)

[a]Includes events with the preferred terms of hypertension, blood pressure increased and blood pressure systolic increased.

Source: ELEVATE-RR, Figure 4.[134]

K.8.5 Incidence of grade 3 or higher infection

The incidence of grade 3 or higher infections was comparable between the treatment arms with 82 (30.8%) and 79 (30.0%) events in the acalabrutinib and ibrutinib arms, respectively (Table 81). The most common (occurred in ≥ 2% of patients) infections in either arm that were grade 3 or higher were pneumonia, sepsis and urinary tract

infection. Analysis of treatment-emergent grade 3 or higher infections across pre-specified subgroups showed no specific trends.

Table 81 Analysis of treatment-emergent grade 3 or higher infections (safety population)

	Acalabrutinib (N = 266)	Ibrutinib (N = 263)
Patients with treatment-emergent grade ≥ 3 infections, n (%) [95% CI[a]]	82 (30.8) [25.6–36.6]	79 (30.0) [24.8–35.8]
***p* value[b]**	0.8777	

[a]95% CI based on Normal approximation (with use of Wilson's score).

[b]Based on Cochran–Mantel–Haenszel test stratified by randomization factors.

CI, confidence interval.

Source: ELEVATE-RR CSR, Table 21.[47]

K.8.6 Richter's transformation

Richter's transformation, which most commonly manifested as diffuse large B-cell lymphoma, occurred in 10 patients (3.8%) receiving acalabrutinib and 13 patients (4.9%) receiving ibrutinib. The median (range) time to onset was 7.1 (2.0–44.7) months and 11.5 (2.2–43.6) months with acalabrutinib and ibrutinib, respectively.[134] Analysis of the incidence of treatment-emergent Richter's transformation across pre-specified subgroups showed no specific trends.

Table 82 Analysis of Richter's transformation (safety population

	Acalabrutinib (N = 266)	Ibrutinib (N = 263)
Patients with Richter's transformation, n (%) [95% CI[a]]	10 (3.8) [2.1–6.8]	13 (4.9) [2.9–8.3]
***p* value[b]**	0.5131	

[a]95% CI based on Normal approximation (with use of Wilson's score).

[b]Based on Cochran–Mantel–Haenszel test stratified by randomization factors.

CI, confidence interval.

Source: ELEVATE-RR CSR, Table 22.[47]

K.8.7 Serious adverse events

SAEs occurred in 53.8% and 58.6% of patients who received acalabrutinib and ibrutinib, respectively. The most common serious adverse events in at least 5% of patients in either arm (acalabrutinib vs ibrutinib) were pneumonia (10.2% vs 9.9%), anaemia (5.3% vs 4.9%) and atrial fibrillation (2.3% vs 5.3%).[134]

K.8.8 Deaths

Deaths due to AEs within the treatment-emergent period were reported in 17 (6.4%) acalabrutinib and 25 (9.5%) ibrutinib patients. These deaths include those occurring within 30 days of the last dose; deaths occurring after the start of subsequent anti-cancer therapy were not included in the assessment of deaths within 30 days of last dose, regardless of time after last dose.

Appendix L. Pooled safety analysis of RCT's evaluating acalabrutinib across indications

L.1 Pooled analysis of safety data from 1040 patients

A pooled analysis of safety data from 1040 patients treated with at least one dose of acalabrutinib in nine phase 1, 2 and 3 studies, including ELEVATE-TN and ASCEND, was conducted. (available at: https://pubmed.ncbi.nlm.nih.gov/33907299/) A large proportion of patients had CLL, but patients with small lymphocytic lymphoma, mantle cell lymphoma, prolymphocytic leukaemia, Richter transformation, relapsed or refractory (R/R) activated B-cell like subtype of diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma and waldenström macroglobulinemia were also included. A larger proportion of patients with CLL had R/R disease (65%) than received acalabrutinib first-line (35%). The median duration of follow-up was 24.6 months (range, 0.0–58.5) and at data cut off, 65% of patients remained on acalabrutinib. The most frequent dose of acalabrutinib was 100 mg twice per day (83%) and the median relative dose intensity was 98.7% (total dose received/total planned dose).

AEs of any grade occurred in 1001 patients (96%) and the most common AEs were mostly grade 1 or 2 in severity (Table 83). The most common AEs were headache, which occurred in 393 patients (37.8%), and diarrhoea, which occurred in 382 patients (36.7%); the majority of headache (366 patients; 35%) and diarrhoea (273 patients; 26%) events occurred in the first 6 months. Most headache events occurred early, resolved and did not recur; the median duration was 20 days and only one patient (0.1%) discontinued

treatment due to headache. Grade ≥ 3 AEs occurred in 563 patients (54%) and the most frequent grade ≥ 3 AEs (occurred in ≥ 5% of patients) were neutropenia (116 patients; 11.2%), anaemia (81 patients; 7.8%) and pneumonia (53 patients; 5.1%). SAEs of any grade occurred in 405 patients (39%) and the only SAE that occurred in ≥ 2% of patients was pneumonia (5%; grade ≥ 3, 5%). The most frequent causes of death were disease progression (62 patients, 6%), following by AEs (52 patients, 5%), with pneumonia being the most frequent fatal AE (8 patients, 1%). All other fatal AEs occurred in ≤ 3 patients each. AEs led to treatment discontinuation in 97 patients (9%) and of these events, the majority occurred within 6 months of treatment initiation. Among events of clinical interest, haemorrhage was experienced by 482 patients (46%; grade ≥ 3, 3%). Other events of clinical interest, including atrial fibrillation, secondary primary malignancy and hypertension were infrequent.

Table 83 Most common AEs (reported in ≥ 10% of patients)

AE preferred term	All patients (N = 1040, n (%)					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Headache	393 (37.8)	286 (27.5)	96 (9.2)	11 (1.1)	0	0
Diarrhoea	382 (36.7)	247 (23.8)	108 (10.4)	27 (2.6)	0	0
URTI	229 (22.0)	56 (5.4)	165 (15.9)	8 (0.8)	0	0
Contusion	226 (21.7)	202 (19.4)	24 (2.3)	0	0	0
Nausea	226 (21.7)	162 (15.6)	52 (5.0)	12 (1.2)	0	0
Fatigue	222 (21.3)	133 (12.8)	70 (6.7)	18 (1.7)	0	0
Cough	218 (21.0)	152 (14.6)	65 (6.3)	1 (0.1)	0	0
Arthralgia	199 (19.1)	127 (12.2)	65 (6.3)	7 (0.7)	0	0
Constipation	151 (14.5)	127 (12.2)	23 (2.2)	1 (0.1)	0	0
Pyrexia	149 (14.3)	102 (9.8)	37 (3.6)	10 (1.0)	0	0
Dizziness	139 (13.4)	124 (11.9)	13 (1.3)	2 (0.2)	0	0
Anaemia	138 (13.3)	18 (1.7)	39 (3.8)	75 (7.2)	6 (0.6)	0
Vomiting	138 (13.3)	96 (9.2)	33 (3.2)	9 (0.9)	0	0
Neutropenia	128 (12.3)	2 (0.2)	10 (1.0)	49 (4.7)	67 (6.4)	0
Rash	126 (12.1)	94 (9.0)	28 (2.7)	4 (0.4)	0	0

Back pain	123 (11.8)	69 (6.6)	46 (4.4)	8 (0.8)	0	0
Myalgia	113 (10.9)	88 (8.5)	23 (2.2)	2 (0.2)	0	0
Dyspnoea	111 (10.7)	65 (6.3)	28 (2.7)	13 (1.3)	5 (0.5)	0
Oedema peripheral	111 (10.7)	87 (8.4)	20 (1.9)	4 (0.4)	0	0
Petechiae	111 (10.7)	104 (10.0)	7 (0.7)	0	0	0
Sinusitis	111 (10.7)	19 (1.8)	89 (8.6)	3 (0.3)	0	0

AE, adverse event; URTI, upper respiratory tract infection.

Source: Furman *et al.* 2019[40]

L.2 Pooled analysis of cardiovascular adverse events with acalabrutinib

Key points
• A pooled analysis of four acalabrutinib clinical trials in CLL (phase 1/2, phase 2 and phase 3) demonstrated that the incidence of CV AEs and treatment discontinuation was low with acalabrutinib

L.2.1 Introduction

Acalabrutinib is a more selective BTK inhibitor than ibrutinib and is therefore expected to have better tolerability and lower incidence of cardiovascular (CV) events. To explore the incidence of CV events in patients with CLL receiving acalabrutinib, a retrospective pooled analysis of CV AEs from four clinical trials of acalabrutinib was conducted.[41] The included studies were ELEVATE-TN (and ASCEND, the phase 1/2 ACE-CL-001 trial (NCT02029443,) and the phase 2 15-H-0016 trial (NCT02337829).

L.2.2 Methods

Data from a pooled population of patients with CLL who were treated with at least one dose of acalabrutinib monotherapy until progressive disease or an AE of clinical interest were used in this analysis. In total, 166 patients (22%) initially received acalabrutinib at a different dose to 100 mg twice daily (which is the recommended dose for acalabrutinib), with 55 patients receiving doses greater than 100 mg twice daily (200 mg twice daily, 250 mg daily once daily, and 400 mg once daily). AEs were coded using the Medical Dictionary for Regulatory Activities v21.1 and were defined as those occurring or

worsening on or after the first dose, during the treatment phase and within 30 days of the last dose. Severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. For this analysis, cardiac AEs were those categorized under the system organ class 'cardiac disorders'. Hypertension AEs, which were considered AEs of clinical interest, included the following preferred terms: hypertension, blood pressure increase, essential hypertension, hypertensive crisis, malignant hypertension, hypertensive heart disease and orthostatic hypertension.

L.2.3 Results

This analysis included data from 762 patients, 352 of whom received first-line therapy and 410 of whom had R/R CLL. The median duration of follow-up was 25.9 months (range, 0.0–58.5) and at the data cut-off, 553 patients (73%) were still receiving acalabrutinib and 208 patients (27%) had discontinued treatment. The most common reasons for treatment discontinuation were progressive disease (82 patients [11%]) and AEs (70 patients [9%]). In the population receiving first-line therapy, 68 patients (19%) discontinued treatment compared with 140 patients (34%) in the R/R population (19 [5%] versus 63 [15%] patients because of progressive disease and 27 [8%] versus 43 [10%] patients because of AEs, respectively).

L.2.4 Cardiac AEs

A total of 199 cardiac AEs of any grade were experienced by 129 patients (17%) (Table 84). Of the patients who had experienced cardiac AEs, 58 had received first-line acalabrutinib and 71 had R/R CLL. Overall, 51 grade ≥ 3 AEs were reported by 37 patients (5%) and 7 patients (1%) discontinued treatment owing to cardiac AEs. The median time to onset of cardiac AEs was 10.1 months (range: 0.1–49.7; Figure 21 Time to onset of (A) cardiac adverse events and (B) atrial fibrillation/flutter and hypertension adverse events). The most common any-grade cardiac AEs (incidence ≥ 2%) were atrial fibrillation/flutter (38 patients [5%]), palpitations (23 patients [3%]) and tachycardia (17 patients [2%]). Most patients who experienced a cardiac AE had CV risk factors before acalabrutinib treatment (91%). Throughout the study period, no patients experienced sudden cardiac death.

Table 84 Incidence of cardiac adverse events

AE, n (%)	All patients (N = 762)	
	Any grade	Grade ≥ 3
Any cardiac AE[a,b]	129 (17)	37 (5)
Most common cardiac AEs (occurring in ≥ 4 patients)		
Atrial fibrillation/flutter	38 (5)	11 (1.4)

Atrial fibrillation[c]	34 (4)	10 (1)
Atrial flutter	4 (0.5)	1 (0.1)
Palpitations	23 (3)	0
Tachycardia	17 (2)	0
Sinus tachycardia	11 (1)	1 (0.1)
Angina pectoris	10 (1)	2 (0.3)
Bradycardia	9 (1)	2 (0.3)
Cardiac failure	6 (0.8)	3 (0.4)
Acute myocardial infarction	5 (0.7)	5 (0.7)
Supraventricular tachycardia	4 (0.5)	1 (0.1)

[a]AEs categorized under the system organ class cardiac disorders. [b]199 AEs were reported in 129 patients (17%). No events under the preferred terms 'sudden death' or 'sudden cardiac death' were reported. [c]There was no overlap between patients with atrial fibrillation and atrial flutter events. [c]Patients with atrial fibrillation or atrial flutter preferred terms combined. There was no overlap between patients with atrial fibrillation and atrial flutter events.

L.2.5 Adverse events

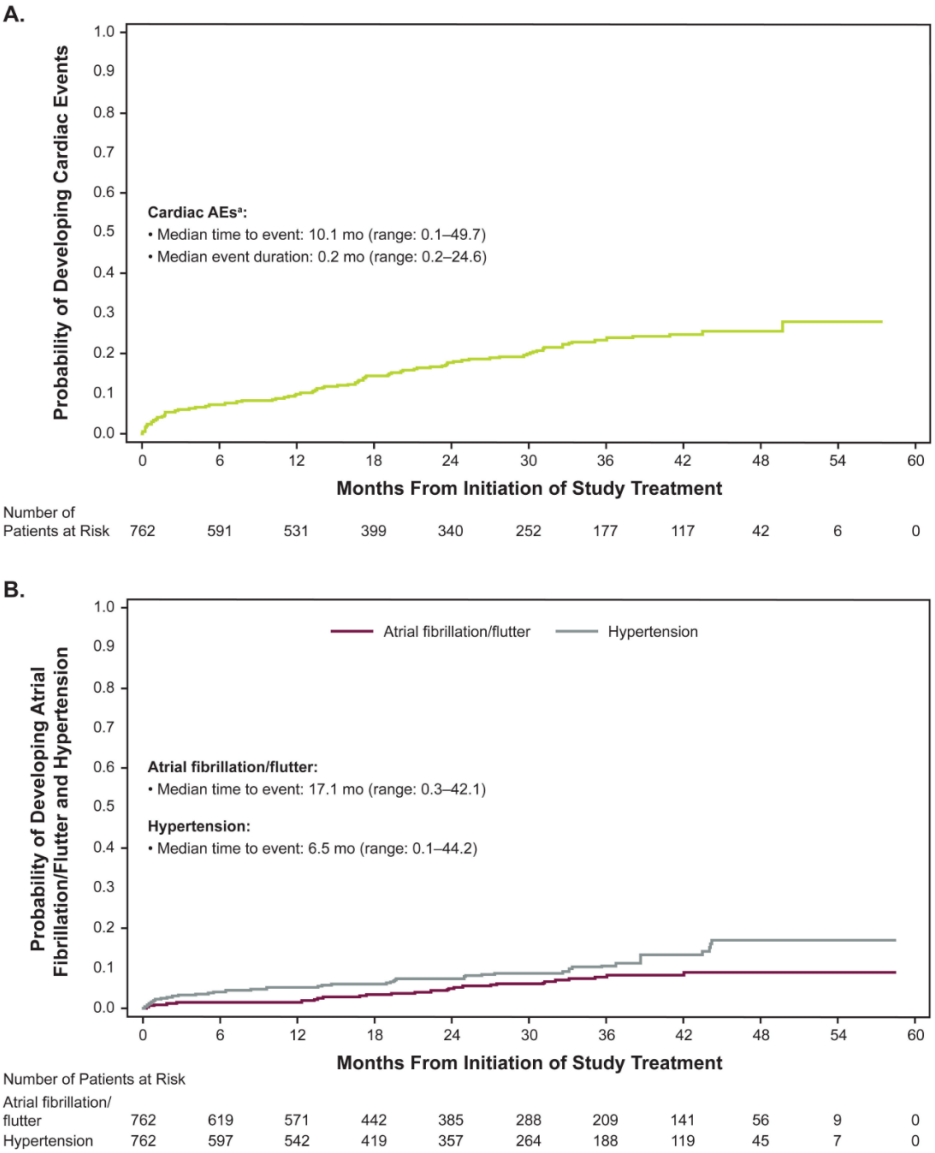
L.2.5.1 Atrial fibrillation/flutter AEs

Atrial fibrillation/flutter AEs of any grade were reported by 38 patients (5%),15 of whom were receiving first-line acalabrutinib and 23 of whom had R/R CLL. Atrial fibrillation was the most common cardiac AE and occurred in 34 patients (4%). Median time to onset of an event of atrial fibrillation/flutter was 17.1 months (Figure 9B) and the events had a median duration of 0.1 month (range: 0.0–12.4). Among the 38 patients with atrial fibrillation/flutter events, 7 (18%) had prior history of arrhythmia or atrial fibrillation/flutter.

L.2.5.2 Hypertension AEs

Hypertension AEs of any grade were reported by 67 patients (9%), 28 of whom were receiving first-line acalabrutinib and 39 of whom had R/R CLL. Median time to onset of a hypertension event was 6.5 months (Figure 21). More patients who experienced hypertension AEs had risk factors for hypertension (79%) compared with patients who did not experience a hypertension AE (59%). In addition, most patients who experienced a hypertension AE had pre-existing hypertension (43 patients [64%]). A total of 35 grade ≥ 3 hypertension AEs were reported in 30 patients, 24 of whom (80%) had prior history of hypertension. No patients discontinued treatment owing to hypertension.

Figure 21 Time to onset of (A) cardiac adverse events and (B) atrial fibrillation/flutter and hypertension adverse events



[a]AEs categorized under the system organ class cardiac disorders.

AE, adverse event.

L.2.5.3 Conclusions

These data demonstrate that the incidence of CV AEs and treatment discontinuation in patients with CLL receiving acalabrutinib is low, in line with the findings from the ELEVATE-RR study.

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