STUDY PROJECT PLAN

Real world effectiveness and safety of brexucabtagene autoleucel versus patient-individual therapy in relapsed/refractory mantle cell lymphoma: A European Mantle Cell Lymphoma Network (EMCL) registry study mandated by the G-BA

Project Plan Number: RW-X19-2206

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Project Plan Synopsis

Title	Real world effectiveness and safety of brexucabtagene autoleucel versus patient-individual therapy in relapsed/refractory mantle cell lymphoma: A European Mantle Cell Lymphoma Network (EMCL) registry study mandated by the G-BA
Study Design	Non-interventional, prospective cohort study within the European Mantle Cell Lymphoma Network Registry (EMCL-R)
Sponsor	University Medical Center of the Johannes Gutenberg-University Mainz
Sponsor Delegate and Coordinator / Principal Investigator	Prof. Dr. med. Georg Heß Department of Hematology and Medical Oncology University Medical Center of the Johannes Gutenberg-University Mainz Langenbeckstr. 1 55131 Mainz Germany
Project Management	Department of Hematology and Medical Oncology & Interdisciplinary Center for Clinical Trials (IZKS) University Medical Center of the Johannes Gutenberg-University Mainz Langenbeckstr. 1 55131 Mainz Germany
Rationale and Background	With the resolution published on 21 July 2022, the Federal Joint Committee (G-BA) requested Gilead, as the local representative of Kite Pharma EU BV in Germany, to conduct a prospective routine practice data collection (AbD) and evaluations comparing brexucabtagene autoleucel (Tecartus®) to patient-individual therapy in patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) after two or more lines of therapy including a Bruton's tyrosine kinase inhibitor (BTKi). The present study aims to fulfill this requirement.
Study Type	Secondary use of data collected within the infrastructure of the registry of the European Mantle Cell Lymphoma Network (EMCL-R) for the purpose of benefit assessment in accordance with the Act on the Reform of the Market for Medicinal Products (AMNOG).
Objectives and Endpoints	The objective of this study is to evaluate the effectiveness and safety of brexucabtagene autoleucel (Tecartus®) versus a patient-individual therapy, **if possible, including allogeneic or autologous stem cell transplantation (SCT)**. The following therapies are considered suitable comparators by the G-BA in the context of routine practice data collection and evaluations: - Bendamustine + Rituximab - Bortezomib ± Rituximab - Lenalidomide ± Rituximab - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) - VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone) - Ibrutinib - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) / R-DHAP (Dexamethasone, high-dose Cytarabine, Cisplatin) - R-BAC (Rituximab + Bendamustine + Cytarabine) - Temsirolimus - R-FCM (Fludarabine + Cyclophosphamide + Mitoxantron + Rituximab)

	- R-Cb (Rituximab + Chlorambucil) The effectiveness and safety will be assessed based on patient-relevant endpoints resulting from the G-BA's resolution requiring this study. The endpoints are as follows: - Mortality: Overall Survival - Morbidity: Symptoms, collected using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire Non-Hodgkin Lymphoma High Grade 29 Module (QLQ-NHL-HG29) - Health-related Quality of Life, collected using the EORTC QLQ-C30 and the EORTC QLQ-NHL-HG29 - Safety: Adverse Events
Inclusion Criteria	Patients have to meet all of the following criteria to be included in the study: - Adult patients with R/R MCL after 2 or more prior lines of systemic therapy including a BTKi - Patient must be considered suitable for treatment with brexucabtagene autoleucel and at least one of the comparative treatment options by treating physician (fulfillment of positivity) - Intention of treatment with either brexucabtagene autoleucel or one of the comparative treatment options (fulfillment of positivity) - Informed consent by the patient for participation in the EMCL-R
Exclusion Criterion	Patients who are part of an investigational study at the time of index will be excluded from this study.
Sample Size	The estimated sample size for analysis is 257 in a 2:1 ratio allocation (i.e., 171 in the brexucabtagene autoleucel arm and 86 in the comparator arm).
Follow-up Time	At least 36 months follow-up from time of study inclusion per study participant
Duration of Study / Timelines	The study is planned to read out in July 2028 with interim analyses planned at 18, 36 and 54 months from study initiation (assuming patient recruitment starts in early 2023).

Approval of the Study Project Plan

Principal investigator on behalf of the EMCL registry:

Prof. Dr. med. Georg Heß

Signature	Date (DD Month YYYY)

Kite/Gilead accountable representatives:

Medical Affairs

Signature	Date (DD Month YYYY)

Market Access

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AMS Advanced Medical Services

List of Abbreviations

Abbreviation	Term/Definition
AbD	Routine Practice Data Collection (*anwendungsbegleitende Datenerhebung*)
AE	Adverse event
AESI	Adverse event of special interest
AKdÄ	Drug Commission of the German Medical Association (*Arzneimittelkommission der deutschen Ärzteschaft*)
AMG	Medicinal Products Act (*Arzneimittelgesetz*)
AMNOG	Act on the Reform of the Market for Medicinal Products (*Arzneimittelmarkt-Neuordnungsgesetz*)
AM-NutzenV	Ordinance on the Benefit Assessment of Medicinal Products (*Arzneimittel-Nutzenbewertungsverordnung*)
aRMM	Additional risk minimization measures
ATS	As-treated set
ATMP	Advanced therapy medicinal product (*Arzneimittel für neuartige Therapien*)
autoSCT	Autologous stem cell transplantation
BfArM	Federal Institute for Drugs and Medicinal Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*)
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CAR	Chimeric antigen receptor
CAR T	Chimeric antigen receptor T cells
CD	Cluster of differentiation
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	central nervous system
CR	Complete response
CRR	Complete remission rate
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	German Society for Hematology and Medical Oncology (*Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e. V.*)
DRST	German registry for stem cell transplantation (*Deutsches Register für Stammzelltransplantation*)
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EMCL	European Mantle Cell Lymphoma Network
EMCL-R	European Mantle Cell Lymphoma Network Registry

Abbreviation	Term/Definition
EORTC	European Organization for Research and Treatment of Cancer
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
G-BA	Federal Joint Committee (*Gemeinsamer Bundesausschuss*)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (*Datenschutz-Grundverordnung*)
GvHD	Graft-versus-host disease
GVP	Good Pharmacovigilance Practices
HG	High grade
HL	Hodgkin lymphoma
HCP	Health care professional
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health technology assessment
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation
ID	Identity
IPW	Inverse probability weighting
IMBEI	Institute for Medical Biostatistics, Epidemiology and Informatics (*Institut für Medizinische Biometrie, Epidemiologie und Informatik, Universitätsmedizin Mainz*)
IQWiG	Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*)
IT	Information technology
ITT	Intention-to-treat
ITTS	Intention-to-treat Set
IZKS	Interdisciplinary Center for Clinical Trials (*Interdisziplinäres Zentrum Klinische Studien, Universitätsmedizin Mainz*)
LDH	Lactate dehydrogenase
LG	Low grade
MAH	Marketing authorization holder
MCL	Mantle cell lymphoma
MedDRA	Medical dictionary for regulatory activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
NFLymSI-18	National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Lymphoma Cancer Symptom Index - 18 Item Version
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PEI	Paul-Ehrlich-Institute
PIC	Patient informed consent
PICO	Population, Intervention, Comparison and Outcome

Abbreviation	Term/Definition
PR	Partial response
PRO	Patient-reported outcome
PS	Propensity score
PT	Preferred term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-NHL-HG29	Quality of Life Questionnaire Non-Hodgkin Lymphoma High Grade 29 Module
QLQ-NHL-LG20	Quality of Life Questionnaire Non-Hodgkin Lymphoma Low Grade 20 Module
QoL	Quality of life
QTC	Kite qualified treatment center
RR	Relative risk
R/R	Relapsed/refractory
R-BAC	Rituximab/Bendamustine/Cytarabine
R-Cb	Rituximab/Chlorambucil
R-CHOP	Rituximab/Cyclophosphamide/Doxorubicin/Vincristine/Prednisone
R-DHAP	Rituximab/Dexamethasone/high-dose Cytarabine/Cisplatin
R-FCM	Rituximab/Fludarabine/Cyclophosphamide/Mitoxantron
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCT	Stem cell transplantation
SD	Stable disease
SDV	Source data verification
SGB V	German Social Code, Fifth Book (*Sozialgesetzbuch, Fünftes Buch*)
SIC	Site initiation contact
SmPC	Summary of Product Characteristics
SoC	Standard of care
SOC	System Organ Class
SOP	Standard Operating Procedure
TLS	Tumor lysis syndrome
UMM	University Medical Center of the Johannes Gutenberg-University, Mainz (*Universitätsmedizin der Johannes Gutenberg-Universität, Mainz*)
VR-CAP	Bortezomib/Rituximab/Cyclophosphamide/Doxorubicin/Prednisone
vs	Versus

History of Project Plan Revisions

Version	Date	Feedback from IQWiG/G-BA received on	Changes made and reasons for change
1.0	21 December 2022		

Timelines and Data Reports

Milestone	Definition
Status Update 1	6 months after start of routine practice data collection
Status Update 2, Interim Analysis 1	18 months after start of routine practice data collection Data cut: 12 months after start of routine practice data collection
Status Update 3, Interim Analysis 2	36 months after start of routine practice data collection Data cut: 30 months after start of routine practice data collection
Status Update 4, Interim Analysis 3	54 months after start of routine practice data collection Data cut: 48 months after start of routine practice data collection
Final Report	21 July 2028 (expected, subject to patient recruitment) Data cut: when a minimum of 171 patients in the brexucabtagene autoleucel arm have completed at least 36 months follow-up **and** a minimum of 86 patients in the comparator arm have completed at least 36 months of follow-up
For further details, see Section 6.10.	

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1. Disease Background and Rationale

1.1. Disease Background

Mantle Cell Lymphoma (MCL) is an aggressive, generally incurable B-cell malignancy, representing approximately 6% of non-Hodgkin lymphomas (NHLs). The genetic hallmark in MCL is the chromosomal translocation t(11;14) (q13;q32) present in more than 95% of MCLs and resulting in aberrant expression of cyclin D1. Overexpression of cyclin D1 can be detected by cytogenetics or fluorescence *in situ* hybridization [1, 2].

Most patients are male, and the median age of diagnosis is 68 years [3]. Prognosis varies based on clinical and laboratory parameters and can be estimated using the mantle cell international prognostic index (MIPI). The MIPI uses the four independent prognostic factors of age, performance status, lactate dehydrogenase (LDH), and leukocyte count to classify patients as low (60% to 83% 5-year overall survival [OS]), intermediate (35% to 63% 5-year OS), or high risk (20% to 34% 5-year OS) [4].

The advent of autologous stem cell transplantation (autoSCT) in combination with rituximab and a high-dose ARA-C containing induction regimen as front-line treatment improved the poor prognosis of only 3-5 years significantly. There are some patients who have benefitted from autoSCT for more than 10 years whereas others have relapsed within the first year after autoSCT [5]. Ultimately, most of the patients relapse even after receiving such intensive treatment.

The improved understanding of the pathophysiology of MCL has led to the identification of a variety of potential molecular treatment targets [6-11] and development of specific drugs, which have improved current treatment results, especially at relapse. However, there is no established standard of care (SoC) for the treatment of relapsed/refractory (R/R) MCL. Treatment options include cytotoxic chemotherapy, proteasome inhibitors, immunomodulatory drugs, Bruton's tyrosine kinase inhibitors, and stem cell transplant (SCT). The choice of regimen is influenced by prior therapy, comorbidities, and tumor chemosensitivity. Ibrutinib, an oral inhibitor of Bruton's tyrosine kinase (BTKi), has very good activity in R/R MCL, and has been extensively used for patients who have received at least one prior line of therapy and can be considered the most relevant treatment choice currently. Approximately 70% of patients responded to ibrutinib, but relapses occur continuously [10], with recent evidence confirming that post-BTKi treatments vary widely and are associated with poor median survival [12].

Despite improvements in treatment, most patients continue to develop relapse and subsequently refractory disease and finally die due to the underlying lymphoma [13-16]. Therefore, there remains a high need for improved understanding of the reason for treatment failure, optimal treatment sequencing and the value of rescue strategies.

In Europe, the chimeric antigen receptor T cell (CAR T) therapy brexucabtagene autoleucel was conditionally approved in December 2020 for R/R MCL patients who received two or more prior systemic therapies that included a BTKi. The approval was based on the primary safety and efficacy analysis of the multicenter trial ZUMA-2, which included 60 adults with R/R MCL who were followed for at least 6 months after their first objective disease response. The complete remission rate (CRR) after treatment was 67%, and the objective response rate (ORR) was 93%. In an intention-to-treat (ITT) analysis, 68 out of 74 patients received the CAR T cell therapy. The CRR and ORR of the ITT study population was 59% and 85%, respectively. Many of the patients in this study had high risk disease [17]. With the approval, brexucabtagene autoleucel has become a relevant clinical standard for patients in Germany. The relevance of brexucabtagene autoleucel is reflected

in the Onkopedia guideline of the German Society for Hematology and Medical Oncology (DGHO; [2]), updated in 2021, in which brexucabtagene autoleucel was included as new treatment standard for MCL patients with relapses after a BTKi.

1.2. Rationale for this Study

Brexucabtagene autoleucel received conditional marketing authorization (Article 14-a of Regulation (EC) No. 726/2004) for the treatment of R/R MCL after two or more lines of systemic therapy including a BTKi from the European Commission (EC) on 14 December 2020. Considering ongoing and completed studies on brexucabtagene autoleucel that were taken into account for the marketing authorization, the Federal Joint Committee (G-BA) in Germany identified evidence gaps related to long-term additional benefit and safety of brexucabtagene autoleucel as well as the lack of data comparing brexucabtagene autoleucel with the existing therapy alternatives for the patient population covered by the approval. According to the G-BA, the indirect comparison (i.e., SCHOLAR-2 vs. ZUMA-2) presented as part of the benefit assessment according to section 35a SGB V (German Social Code, Fifth Book) was not suitable for deriving conclusions about the extent of the additional benefit. This was due to deficiencies associated with retrospective data, such as lack of collection of endpoints including morbidity, Health-related Quality of Life, side effects as well as the collection of relevant confounders and the implementation of the ITT-principle [18].

For the aforementioned reasons, on 21 July 2022 the G-BA requested a non-randomized, prospective comparative registry study (routine practice data collection, AbD) comparing brexucabtagene autoleucel with appropriate comparator treatments, preferably in the EMCL indication registry (EMCL-R). The G-BA noted that the registry would need to undergo extensive adjustments to fulfill the quality criteria specified by the G-BA and the Institute for Quality and Efficiency in Health Care (IQWiG). The adjustments are essential for the EMCL-R to be considered an appropriate data source for the routine practice data collection. The specific requirements for the study by the G-BA are based on the IQWiG concept, which uses the “Population, Intervention, Comparison and Outcome” (PICO) scheme as a basis (Table 1) [19, 20].

Additionally, the G-BA has taken measures to ensure that the use of brexucabtagene autoleucel is only possible if documented: In order to obtain complete, non-fragmented, valid and meaningful data of the insured patients treated with brexucabtagene autoleucel, the supply and therefore reimbursement of brexucabtagene autoleucel will be restricted to service providers that participate in the study. This measure has been introduced in another resolution published on 21 July 2022 and will be valid from the time of study start [21]. At the moment, the use of CAR T cell therapy is restricted to centers that comply with the G-BA´s quality assurance directive for the use of medicinal products for advanced therapies in accordance with § 136a paragraph 5 SGB V [22].

Table 1. Requirements of the G-BA for the Routine Practice Data Collection in a PICO Scheme

Population	Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor[a]
Intervention	Autologous anti-CD19-transduced CD3+ cells (brexucabtagene autoleucel) The marketing authorization and the dosage information in the product information for brexucabtagene autoleucel (Tecartus®) must be taken into account
Comparator	Patient-individual therapy [b] taking into account the response and duration of remission of the prior therapies and the general condition, if possible, including allogeneic or autologous stem cell transplant (SCT)
Outcome	**Mortality** - Overall survival **Morbidity** - Symptoms **Health-related Quality of Life** **Side effects** - Serious adverse events (SAE; overall rate) - Severe adverse events (overall rate) - Discontinuation due to adverse events (overall rate) - Specific adverse events (with indication of the respective severity)

[a] For the inclusion and exclusion criteria of the routine practice data collection and evaluations, the criteria for the suitability of treatment with brexucabtagene autoleucel are to be applied [to fulfill positivity (Section 4.1)].

[b] In the context of routine practice data collection and evaluations, the following therapies are considered suitable comparators:

- Bendamustine + Rituximab
- Bortezomib ± Rituximab
- Lenalidomide ± Rituximab
- R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)
- VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone)
- Ibrutinib
- R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) / R-DHAP (Dexamethasone, high-dose Cytarabine, Cisplatin)
- R-BAC (Rituximab + Bendamustine + Cytarabine)
- Temsirolimus
- R-FCM (Fludarabine + Cyclophosphamide + Mitoxantron + Rituximab)
- R-Cb (Rituximab + Chlorambucil)

Source: [19]

The G-BA set further requirements for study design and data source for the present routine practice data collection [19] including:

- **Duration of data collection:** According to the G-BA, the results of the pivotal phase II study ZUMA-2 show a possible plateauing of overall survival at the earliest 36 months after patient inclusion. Therefore, routine practice data collection should include an observation period of at least 36 months.

- **Approximation of the appropriate sample size:** According to the G-BA, the results of an orienting sample size estimate based on the endpoint of overall survival indicate a sample size of approx. 190 patients necessary for the evaluation, assuming an equal distribution between intervention and comparator groups. The G-BA, however, points out that if the recruitment possibilities for the comparator arm are limited, a different distribution between intervention and control arms (e.g., 2:1) for the sample size estimate can also be assumed.

The requirements as stated by the G-BA and the fulfillment/implementation thereof will be discussed in the following sections.

2. Objectives and Endpoints

2.1. Main Objective

The objective of this study is to evaluate the effectiveness and safety of brexucabtagene autoleucel (Tecartus®) versus a "patient-individual therapy, **if possible, including allogeneic or autologous stem cell transplantation (SCT)**", as defined by G-BA, in patients with R/R MCL after two or more lines of therapies including a BTKi. The following therapies are considered suitable comparators by the G-BA in the context of the routine practice data collection:

- Bendamustine + Rituximab
- Bortezomib ± Rituximab
- Lenalidomide ± Rituximab
- R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)
- VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone)
- Ibrutinib
- R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) / R-DHAP (Dexamethasone, high-dose Cytarabine, Cisplatin)
- R-BAC (Rituximab + Bendamustine + Cytarabine)
- Temsirolimus
- R-FCM (Fludarabine + Cyclophosphamide + Mitoxantron + Rituximab)
- R-Cb (Rituximab + Chlorambucil)

This project plan does not recommend the use of any specific treatments. Patients are treated in accordance with local prescribing regulations.

2.2. Endpoints

The effectiveness and safety will be assessed based on patient-relevant endpoints resulting from the G-BA's resolution requiring this study. The definition of endpoints as primary or secondary is omitted due to the non-interventional character of this real world data collection. This is consistent with the general methodology of the German benefit assessment according to § 35a SGB V, which requires the assessment of patient-relevant endpoints regardless of their classification as primary or secondary in a specific study [23, 24]. An endpoint is considered patient-relevant if it reflects how a patient feels, if he or she can carry out his or her functions and activities, or if he or she survives [24]. The outcomes defined by the G-BA are the following (Table 1):

- **Mortality:** Overall survival
- **Morbidity:** Symptoms
- **Health-related Quality of Life**
- **Adverse Events**
    - Serious adverse events (SAE; overall rate)
    - Severe adverse events (overall rate)
    - Discontinuation due to adverse events (overall rate)
    - Treatment-specific adverse events (with indication of the respective severity)

In the following sections, the endpoints are defined. Additionally, some considerations are given to the implementation and feasibility of collecting such endpoints.

2.2.1. Mortality: Overall Survival

Endpoint as requested by the G-BA	Overall survival
Currently collected in EMCL-R*	Yes
Operationalization in present study	OS is defined as time from the index date to death due to any cause. Patients who have not died by the analysis data cutoff date or for whom no information is available (e.g., lost-to-follow-up, withdrawal of consent, inclusion in a clinical trial) will be censored at the data cutoff date or the last date known alive, whichever occurs first. For full details on the statistical methods please refer to the Statistical Analysis Plan.

*As of 21 December 2022.

2.2.2.Morbidity: Symptoms

Endpoint as requested by the G-BA	Symptoms
Currently collected in EMCL-R*	No. Adjustment in EMCL-R needed.
Operationalization in present study	In the present study, symptoms will be assessed using the symptom scales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) [25] version 3.0 and the EORTC Quality of Life Questionnaire Non-Hodgkin Lymphoma High Grade 29 Module (QLQ-NHL-HG29) [26] (Oerlemans et al, submitted). The EORTC QLQ-C30 is a 30-item instrument with 15 scales in total: nine symptom scales, five functional scales (physical, emotional, cognitive, role, and social functioning), and a global quality of life score. Scales are scored according to the manual if at least half the items are complete. Scores range from 0 to 100, with higher scores on symptom scales indicating worse symptom burden, higher scores on functional scales indicating better function, and higher scores on the global quality of life scale indicating better quality of life. **The symptom scales will be used for the morbidity (symptoms) endpoint and include the following**: **1.** Fatigue **2.** Nausea and vomiting **3.** Pain **4.** Dyspnea **5.** Insomnia **6.** Appetite loss **7.** Obstipation **8.** Diarrhea

	9. Financial difficulties The following analyses are planned to be conducted: - Time to deterioration, defined as a decrease in score of at least 10 points (scale range 0-100) - Time to deterioration by 15 points (corresponds to 15% of the scale range) - Questionnaire completion rate The EORTC QLQ-NHL-HG29 is a module to be used in conjunction with the EORTC QLQ-C30 to capture symptoms and quality of life in high grade non-Hodgkin lymphomas. It consists of 29 items. **For the morbidity (symptoms) endpoint, the following scales will be used:** **10.** Symptom burden **11.** Neuropathy **12.** Physical condition/Fatigue The planned analyses of QLQ-NHL-HG29 correspond to the QLQ-C30. For full details on the statistical methods, please refer to the Statistical Analysis Plan.

*As of 21 December 2022.

2.2.3. Health-related Quality of Life (HRQoL)

Endpoint as requested by the G-BA	Health-related Quality of Life
Currently collected in EMCL-R*	No. Adjustment in EMCL-R needed
Operationalization in present study	In the present study, the Health-related Quality of Life will be assessed using the EORTC QLQ-C30 [25] version 3.0 and the EORTC QLQ-NHL-HG29 [26] (Oerlemans et al., submitted). For a description of the EORTC QLQ-C30 and the EORTC QLQ-NHL-HG29, see Section 2.2.2. **The EORTC QLQ-C30 includes five functional scales that will be used to assess Health-related Quality of Live:** **1.** Physical functioning **2.** Emotional functioning **3.** Cognitive functioning **4.** Role functioning **5.** Social functioning and a global quality of life score. The EORTC QLQ-NHL-HG29 is a module to be used in conjunction with the EORTC QLQ-C30. **Those scales not used for**

	morbidity (symptoms) are used for health-related quality of life, i.e: **6.** Emotional impact **7.** Worries/fears about health and functioning For full details on the statistical methods please refer to the Statistical Analysis Plan.

*As of 21 December 2022.

Considerations on patient-reported outcomes (PRO): Symptoms and HRQoL

In the Onkopedia guideline for MCL of the German Society for Hematology and Medical Oncology (DGHO), the frequency of medical checks after completion of therapy is recommended every 3 months during the first three years and then every six to twelve months [2]. A guideline, however, can only describe how the evidence suggests that clinical practice should be undertaken. It usually does not reflect the complexity of the real world or the reality of medical practice. In the present study, there are uncertainties regarding the frequencies of medical checks among the study arms during the study period. An additional uncertainty is whether the patients will continue to be evaluated at the center in which the treatment took place, or if they will be followed up in small clinical practices whose data are not collected in the registry.

The previous consideration is also related to the level of response rates that can be achieved in the context of everyday clinical care. According to the General Methods of IQWiG, results on patient-reported endpoints usually are not considered in the benefit assessment if they are based on fewer than 70% of the study participants included in the data collection [24].

Another consideration is the difference in response rates between the two arms: the results are usually not considered in the benefit assessment if the difference in the proportion of study participants who were not taken into account between the groups is greater than 15% [24]. This has proven challenging even in large, randomized phase III clinical trials. One example of this is depicted in the G-BA justification for the active substance blinatumomab, which was evaluated in a phase III clinical trial against chemotherapy [27].

To improve the likelihood of successfully collecting symptoms (morbidity) and HRQoL, the collection procedure described below will be implemented.

A third party (the Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), part of the sponsoring institution) will act as a trust center. IMBEI will receive and store the following data for each patient in the registry:

- Name, surname
- Post code and address as at the time of entry in the registry
- Date of birth

This data will be linked to the patient pseudonym (patient identity [ID]) and stored separately from the medical data on a secured server.

The Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI) will contact patients participating in the study based on their informed consent and send the EORTC questionnaires directly to them. If a letter is

undeliverable, IMBEI will retrieve the current address (or potential date of death) from the local registration office ("Einwohnermeldeamt") and resend the letter. If the patient does not return the completed questionnaires within 2 weeks, up to two reminder letters will be sent by IMBEI.

Rationale for selection of instruments for patient-reported outcomes: symptoms and HRQoL

Several instruments have been taken into account to best suit R/R MCL patients: EORTC QLQ-C30, EORTC QLQ-NHL-HG29, EORTC QLQ-NHL-LG20 (Quality of Life Questionnaire Non-Hodgkin Lymphoma Low Grade 20 Module), FACT-Lym (Functional Assessment of Cancer Therapy – Lymphoma), and NFLymSI-18 (National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Lymphoma Cancer Symptom Index - 18 Item Version).

Only limited published literature exists regarding the HRQoL instrument best suited for R/R MCL patients. Based on a recent systematic review [28] only five studies have so far reported HRQoL for MCL. Three of these five studies used FACT-Lym and the other two used the EORTC QLQ-C30. The two instruments generally cover the same aspects of HRQoL (physical, social, emotional, functional, and role/family), but the FACT-Lym also has 15 additional items specific to lymphoma [29]. Although some of these are questions specific to lymphomas (e.g., bothered by lumps or swelling, bothered by itching, bothered by fevers, worry about infections), a lot of the additional items overlap with questions from the QLQ-C30 (e.g., trouble sleeping, trouble concentrating, loss of appetite). On the other hand, using EORTC QLQ-C30 alone is not specific enough, as it does not contain lymphoma-specific items.

According to experts from EMCL-R and IMBEI, using several instruments capturing the same or overlapping constructs is not advisable because patients will then get frustrated more easily and the missing values increase. HRQoL instruments should be as short as possible. These rules out the use of both EORTC QLQ-C30 and FACT-Lym questionnaires for this study.

EORTC has developed and validated several disease-specific HRQoL questionnaires to supplement the QLQ-C30, for several types of B-cell lymphomas, including patients with Hodgkin lymphoma (HL), high- or low-grade non-Hodgkin lymphoma (HG/LG-NHL), and chronic lymphocytic leukemia (CLL). Patients included in this study suffer from MCL in an R/R setting that often resembles high grade lymphoma. Therefore, the combination of EORTC QLQ-C30 and QLQ-NHL-HG29 will provide a short enough but comprehensive picture of the symptom burden of these patients. The QLQ-NHL-HG29 was developed also for MCL patients and is internationally validated (Oerlemans et al., submitted). By using a general and a disease-specific questionnaire that have been developed, standardized and validated to be used in conjunction, the goal is to comprehensively assess symptoms and HRQoL of R/R MCL patients in the context of this study.

Considerations on the frequency of patient-reported outcomes: symptoms and HRQoL

Measuring symptoms / quality of life by means of questionnaires is not part of routine medical practice. This is due to several reasons including, among others, time and budget constraints but also the fact that the measurement of quality of life in the clinical setting (outside a study) may generate the expectation that the clinician might be able to influence it, which is not always possible considering that usually these instruments quantify the broader context of a patient's life [30].

Concerning the measurement of quality of life, specifically in the brexucabtagene autoleucel arm, there are uncertainties regarding the frequency that would be considered as appropriate by the G-BA/IQWiG. In a recent evaluation of tisagenlecleucel for the treatment of follicular lymphoma by the G-BA, it was stated that the time

interval between the first survey at the time of screening and the next 3 months after the infusion was very long and that the direct and possibly only short-term effect of the administration of this CAR T infusion were not reflected by the survey times chosen [31]. According to expert opinion, if HRQoL is assessed too often, it increases the risk of non-completion and missing values. Therefore, based on experiences from several similar studies where this worked well, the following procedure is considered to be the most appropriate (Table 2):

Table 2. Procedure for the Collection of HRQoL using Patient Questionnaires

Time point	Schedule (time window)	Responsible for administration of patient-reported (PRO) instrument
t0	At screening	Study nurse at center
t1	1 month after t0 (± 3 days)	Trust center (IMBEI)
t2	3 months after t0 (± 7 days)	Trust center (IMBEI)
t3	6 months after t0 (± 7 days)	Trust center (IMBEI)
t4	12 months after t0 (± 1 months)	Trust center (IMBEI)
t5	24 months after t0 (± 1 months)	Trust center (IMBEI)
t6	36 months after t0 (± 1 months)	Trust center (IMBEI)

As outlined above, the HRQoL questionnaires will be sent out by the trust center, based on a clear time schedule, independent of the patient visiting the center. This ensures better monitoring of questionnaire completion and reduces the workload for the centers. The recall period of the instruments (patients are asked about their experience with their condition during the past week) should not be changed because they are validated with this recall period. The one week recall period has been proven to be optimal in terms of covering important HRQoL issues and at the same time reducing hindsight bias.

2.2.4. Adverse Events

Endpoint as requested by the G-BA	Adverse events (AE)
Currently collected in EMCL-R*	No. Adjustment in EMCL-R needed.
Operationalization in present study	In the present study, the following adverse events will be documented: - AEs that require inpatient hospitalization or lead to prolongation of existing hospitalization - AEs that require inpatient hospitalization or lead to prolongation of existing hospitalization - related to treatment - AEs that result in death - Specific adverse events (= adverse events of special interest) that require inpatient hospitalization or lead to prolongation of existing hospitalization as defined below AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

*As of 21 December 2022.

Considerations

In the G-BA resolution published on 21 July 2021 the following adverse events (AEs) are mandated:

- Serious AEs (overall rate)
- Severe AEs (overall rate)
- Therapy discontinuation due to AEs (overall rate)
- Specific adverse events (with indication of the respective degree of severity)

The operationalization of this endpoint in the present study will deviate from the G-BA requirements. The reasons are explained below.

Serious AEs

A serious AE is defined as any untoward medical occurrence that 1) results in death, 2) is life threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly / birth defect.

After discussing this with clinical experts, it was concluded that AEs that are life threatening, result in persistent or significant disability/incapacity or result in death, will be covered by AEs that require inpatient hospitalization or lead to prolongation of existing hospitalization. Development of a congenital anomaly or birth defect is not expected to play a role in the study population.

AEs that result in death will be also documented as cause of death. If a patient has died, it should be clarified if the cause of death was due to an AE and if the AE was related to treatment for R/R MCL.

Severe AEs

In the context of clinical trials, AE severity is graded according to Common Terminology Criteria for Adverse Events (CTCAE). This grading, however, is not performed in routine medical practice.
Grade 3 AEs refers to AEs that are severe or medically significant but not immediately life threatening or in which hospitalization or prolongation of hospitalization is indicated or disabling or limiting selfcare / activities of daily living. After consulting with clinical experts, it was concluded that severe AEs will be covered by AEs that require inpatient hospitalization or lead to prolongation of existing hospitalization.

Therapy discontinuation due to AEs

Brexucabtagene autoleucel is a one-time treatment and therefore discontinuation due to AEs is not possible after application. Discontinuation due to AE can occur before the infusion (i.e., leukapheresis, bridge therapy). As part of the consultation request to the G-BA this aspect was mentioned and discussed by the company as well as by the registry lead. In the context of the consultation request the G-BA stated the following [32]:
"The proportion of people that discontinue the treatment prior to treatment due to AEs would be also shown in relation to the overall rate of people who did not *receive the cell infusion. Therefore, taking into account the defined interventions and study design required for the application-accompanying data collection, it appears appropriate in principle to refrain from collecting the endpoint 'discontinuation due to AEs'."*

Relation to treatment

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. The relation to the treatment received will be documented: Was the AE related to treatment? Yes/possibly/no.

Specific AEs (with indication of the respective degree of severity)

Specific AEs are interpreted here as adverse events of special interest (AESIs). Regarding the grading of AESIs, various aspects should be considered: as discussed previously, grading of AEs according to CTCAE does not take place in routine medical practice. On the other hand, due to the study design (non-interventional, routine practice data collection) a specification on when or how often the patients should be evaluated for AEs cannot take place. As a result, the study is dependent on the information that can be collected during hospitalization of the patients. An additional uncertainty is whether the patients will continue to be evaluated at the center in which the treatment took place or if they will be followed up in small clinical practices whose data are not collected in the registry.

Patients who are hospitalized in order to receive treatment and/or to be closely monitored during the first days after treatment will be under an increased surveillance of AEs even when these do not cause a symptomatology: e.g., a complete blood count is performed, and an anemia is diagnosed by means of a hemoglobin of 10.8 gr/dl but there are no symptoms. Patients who are in the ambulatory setting would only visit a medical center (and be hospitalized) if they develop symptoms that make them seek medical attention and which require inpatient management. To overcome this limitation, it is considered that only AESIs that require inpatient hospitalization or lead to prolongation of existing hospitalization should be documented/considered.

The G-BA did not specify which AESIs should be included. Following AEs are considered to be of special interest based on the therapies included in the brexucabtagene autoleucel and comparator arm:

- Cytokine release syndrome (CRS)
- Neurological events (including Immune effector cell-associated neurotoxicity syndrome [ICANS] [peripheral neuropathy])
- Infections
- Cytopenias (anemia, leukopenia, thrombocytopenia)
- Hypogammaglobulinemia
- Tumor lysis syndrome (TLS)
- Graft-versus-host disease (GvHD)
- Subsequent neoplasms
- Cardiac arrhythmias
- New cardiac failure

Considerations on the duration of AE assessment

The investigator is responsible for reporting all AEs (including AESIs) that lead to hospitalization or prolongation of hospitalization after the treatment decision until the initiation of new lymphoma therapy. The rationale for discontinuing AE reporting when a therapy switch occurs is that observation beyond a therapy switch may result in a misleading estimate of benefit:

If patients in the brexucabtagene autoleucel group switch to the comparator treatment (patient-individual therapy) from which they benefit less, an ITT analysis will underestimate the "true" benefit associated with brexucabtagene autoleucel treatment - that is, the benefit that would have been observed if the treatment switch had not been included in the analyses. Conversely, if patients in the comparison group (patient-individual therapy) switch to and benefit from brexucabtagene autoleucel treatment, an ITT analysis will overestimate the "true" benefit associated with the treatment offered in the comparison group (patient-individual therapy) - that is, the benefit that would have been observed if the treatment switch had not been included in the analyses. Further, in case the benefit is higher in the comparison group, an ITT analysis will overestimate the “true” benefit associated with brexucabtagene autoleucel treatment when therapy switches take place.

3. Study Design

3.1. General Study Design

This is a non-interventional, prospective, comparative registry study without randomization. This study has a design based on secondary use of data generated in the EMCL indication registry (EMCL-R). This registry will undergo extensive adjustments in order to fulfill the G-BA/IQWiG specified quality criteria in order to be considered as a suitable data source for the routine practice data collection. Please refer to Section 5.1 (Data Source: EMCL-R) for additional details.

The study does not examine an investigational medicinal product. Patients will be observed as they receive their physician-prescribed treatment with no advice given for the treatment of an individual patient by the study sponsor. The recommendations of the IQWiG with its general methods [24] and of the G-BA, which specify the procedure in the rules of procedure of the G-BA [23] and define procedural steps on the basis of the Ordinance on the Benefit Assessment of Medicinal Products (AM-NutzenV) according to § 35a SGB V, will be followed, whenever possible.

3.2. Study Scheme and Patient Flow

Currently, the goal of the EMCL-R is to include all patients with MCL in the study, regardless of therapy or lines of therapy received. In this context, there will be patients included in the EMCL-R that should be closely followed up, as they could, at any time point, fulfill the inclusion criteria of the present study. These patients are those with R/R MCL after one line of systemic therapy (that is, before they are fully eligible for brexucabtagene autoleucel treatment), patients who have not received a BTKi, or patients with R/R MCL after ≥2 lines of systemic therapy who had not yet received brexucabtagene autoleucel. These patients will be classified as “base population”. Patients fulfilling the inclusion criteria for the study will be analyzed in the “study population” (Figure 1).

Patients in the study population will be divided into two groups based on the treatment decision for their next line of therapy (Figure 1). The treatment decision can be based on different factors such as tumor board recommendation, availability of therapy, physician’s choice, and patient’s choice [32]. Due to the need to implement the ITT principle, it is relevant to clarify the concept of therapy availability. For the purpose of this study, therapy availability includes the possible situation in which the health insurance refuses the reimbursement of the treatment and therefore this cannot be ordered/ administered to the patient. Manufacturing failures will, however, not be considered as therapy unavailability as the patients (who fulfill

the inclusion criteria) are in the ITT population starting the moment in which the decision is made in favor of brexucabtagene autoleucel.

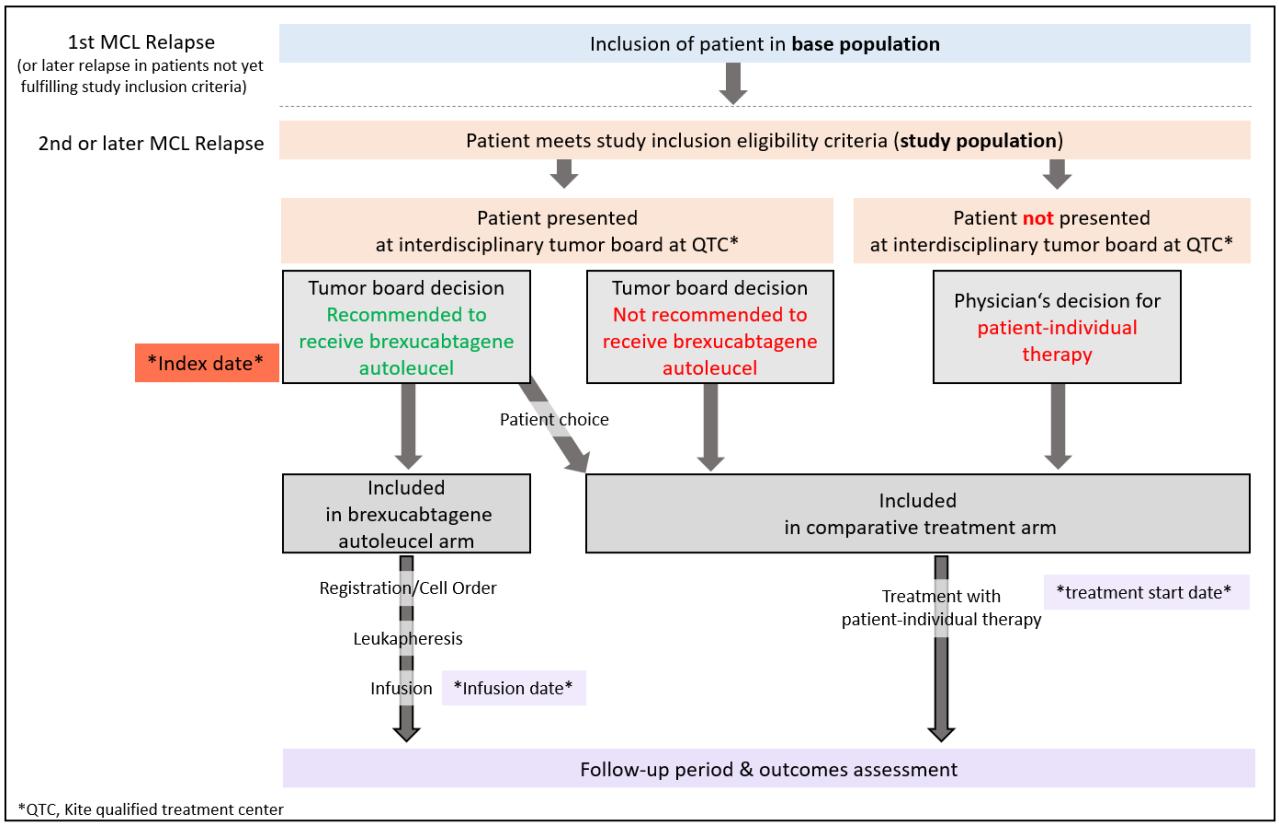
Patients are treated with brexucabtagene autoleucel in dedicated centers. There, the treatment decision is usually made by an interdisciplinary tumor board. Yet, the final therapy decision can also be made by the patient, e.g., if the tumor board advises him or her to treat with brexucabtagene autoleucel, but the patient chooses a patient-individual therapy, which in this indication (and line of therapy) is expected to be very rare. These patients will be included in the comparative treatment arm.

A tumor board decision against brexucabtagene autoleucel for patients who are considered suitable for brexucabtagene autoleucel as defined in the inclusion criteria is expected to occur scarcely.

To overcome recruitment challenges, particularly in the comparative treatment arm, study enrolment of other patients from the EMCL-R with MCL relapse after 2 prior lines of systemic therapy including a BTKi, who receive comparative treatments (e.g., who are not treated at qualified CAR T centers) is possible. These other patients may not have a therapy decision by a tumor board, but by the treating physician. In this case, the date of physician's therapy decision is taken as the index date, applying the intention-to-treat principle (Figure 1).

Furthermore, in order to reach the recruitment target, it is planned to include centers participating in the EMCL-R in other European countries with a comparable care structure to Germany. The selection of further countries remains to be determined, depending on their fulfillment of requirements specifically defined for the purpose of data collection for this study. This is further specified in Section 3.6.

Figure 1. Patient Flow in the Routine Practice Data Collection



3.3. Screening Procedure

Every patient in the registry with R/R MCL after one line of systemic therapy - or after ≥2 lines of systemic therapy if brexucabtagene autoleucel has not yet been administered - should be included in the "base population" (Figure 1). Once the next relapse occurs, inclusion criteria are met and patients may be considered suitable for treatment with brexucabtagene autoleucel and one of the therapy options in the comparator arm, these patients are enrolled into the study. In order to allow for data collection at the time of eligibility for study inclusion, a "tumor board alert system" is being implemented. Lymphoma tumor board coordinators at CAR T qualified centers will be contacted weekly via MCL patient alert/ email list server to screen for potential MCL patients that are R/R after 2 or more lines of systemic therapy including a BTKi, and thus may qualify for study inclusion. In addition, Kite/Gilead will inform the EMCL-R about any brexucabtagene autoleucel cell therapy order for R/R MCL that is received via Kite connect®. The respective sites will then be contacted by EMCL-R staff, to allow for collection of baseline data.

3.4. Baseline Data

These will include disease characteristics and measurements that were assessed at baseline (i.e., the index date). After the therapy decision by the tumor board (or the treating physician), the treatment of patients often starts immediately. This may not leave enough time to measure the required endpoints at the beginning of treatment as baseline values. This will especially be the case for the patient questionnaires EORTC QLQ-C30 and EORTC QLQ-NHL-HG29. To ensure that these baseline data are nevertheless available, a time window of 28 days after the index date applies for the collection of the corresponding data.

3.5. Study Period

According to the IQWiG concept, recruitment should be able to be completed within 2 years and patients must have a follow up of at least 36 months. The duration of recruitment provided by IQWiG is based on the estimation that approximately 130 patients can be recruited by year. This estimation, however, as mentioned before is uncertain. This leads to the possibility that recruitment duration might be longer than 2 years and that therefore the study end will take place at a later time point.
The therapy, which was decided upon at the index date, will be considered the relevant therapy for all analyses. For instance, if a patient switches to another therapy during the study period, the treatment arm assigned to at index date will be retained for the outcome analyses. Patients will be followed up until death, study end or loss to follow-up, whichever event occurs first. While treatment switches from brexucabtagene autoleucel to a patient-individual therapy or from a patient-individual therapy to brexucabtagene autoleucel are not considered for the main analysis of treatment effects, for sensitivity analysis of OS and patient questionnaires, patients with treatment switches will be censored at the date of treatment switching.

3.6. Study Sites

All sites included in this study need to be part of the EMCL-R, either in Germany or in other European member countries. Centers, which are already part of the EMCL-R will be approached and invited to participate. If not already included in the registry yet considered for this study, sites will be contacted and initiated by the EMCL-R.

For the brexucabtagene autoleucel arm, centers that are qualified for brexucabtagene autoleucel administration in Germany (according to the quality criteria for Advanced Therapy Medicinal Products (ATMPs)) are invited to participate in this study. These sites will be approached and asked to provide the relevant information. Data of patients treated with brexucabtagene autoleucel are additionally entered into to the German registry for stem cell transplantation (DRST) / European Society for Blood and Marrow Transplantation (EBMT) registry as per G-BA's resolution on quality requirements for the use of medicinal products for advanced therapies in accordance with § 136a paragraph 5 SGB V [22].

In order to offer treatment with CAR-T cell therapy, centers need to fulfill structural requirements as described in the quality assurance guidelines for ATMPs § 6 to participate in the study [22]. These requirements include sufficient training of healthcare personal regarding CAR-T therapy, application of Standard Operating Procedures (SOPs) to apply safety measures and monitoring of patients, as well as the execution of daily patient visits. Furthermore, eligible centers need to supply diagnostic and treatment options across specialties including an intensive care unit with specified equipment, sufficient doses of potentially required medication as well as SOPs in place for sufficient out-patient care of patients before and after CAR T therapy.

At present (20 December 2022), a total of 37 centers are qualified to prescribe brexucabtagene autoleucel and further centers are expected to be added within the study period. At this point, it should be considered that there could be qualified treatment centers, which may not participate in this study. Thus, the final number of included treatment centers for the purpose of this study may differ from the total number of certified centers eligible for brexucabtagene autoleucel treatment.

In addition, centers that are not qualified to prescribe brexucabtagene autoleucel but are part of the EMCL-R are invited to participate in the study (inclusion of patients in comparative treatment arm; Figure 1).

The inclusion of centers mainly in Germany is intended to ensure that routine care practice for MCL patients in Germany is optimally reflected in the study. However, it is assumed that routine care in other European countries participating in the EMCL-R is sufficiently similar to that in Germany. Therefore, the possibility/feasibility to recruit patients from other European EMCL-R sites and collect data as required by the present protocol is being studied. This may help to overcome low recruitment in the comparator arm, which is expected due to the fact that in German guidelines brexucabtagene autoleucel appears as the preferred therapy in the target population of this study [2].

Based on EMCL-R experience, inclusion of centers in other European countries might be feasible in general. However, at present, uncertainties exist regarding their active participation in this study as well as regarding the feasibility of collecting data as requested by the G-BA. Activation will be made via regular participation within the EMCL-R.

Eligible treatment centers in European countries other than Germany will be identified by the EMCL-R/IZKS.

3.7. Number of Study Subjects

The estimated sample size for analysis is 257 in a 2:1 ratio allocation (i.e., 171 in the brexucabtagene autoleucel arm and 86 in the comparator arm).

Please refer to the statistical consideration section of the project plan (Section 6.8) for sample size estimations.

4. Study Population

The study population consists of adult patients with R/R mantle cell lymphoma (MCL) after 2 or more systemic therapies that include a Bruton's tyrosine kinase (BTK) inhibitor. Following the G-BA recommendation, the EMCL-R will be the primary data source for this study (Section 5.1). Therefore, patients will be included in the study primarily from this registry.

4.1. Inclusion Criteria

Inclusion Criteria for base population (Section 3.2)

- Inclusion in the EMCL-R
- R/R MCL after 1 line of systemic therapy - or after ≥2 lines of systemic therapy if brexucabtagene autoleucel has not yet been administered
- Informed consent by the patient for participation in the EMCL-R

Inclusion Criteria for the study population

Patients have to meet all of the following criteria to be included in the study:

- Adult patients with R/R MCL after 2 or more lines of systemic therapy including a BTKi
- Patient must be considered suitable for treatment with brexucabtagene autoleucel and at least one of the comparative treatment options by treating physician (fulfillment of positivity). A possibility that is currently under discussion (feasibility of implementation by EMCL-R not clear) is for the treating physicians to answer the following question: Was the patient at the time point of treatment decision eligible for treatment with both, brexucabtagene autoleucel and one of the patient individual therapies?
- Intention of treatment with either brexucabtagene autoleucel or patient-individual therapy from the following list of eligible treatments, if possible, including allogeneic or autologous stem cell transplant (SCT):
  - Bendamustine + Rituximab
  - Bortezomib ± Rituximab
  - Lenalidomide ± Rituximab
  - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)
  - VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone)
  - Ibrutinib
  - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) / R-DHAP (Dexamethasone/high-dose Cytarabine/Cisplatin)
  - R-BAC (Rituximab + Bendamustine + Cytarabine)
  - Temsirolimus
  - R-FCM (Fludarabine + Cyclophosphamide + Mitoxantron + Rituximab)
  - R-Cb (Rituximab + Chlorambucil)
- Informed consent by the patient for participation in the EMCL-R if patient is not already included in the base population

4.2. Exclusion Criterion

Patients who are part of an investigational study at the index date will be excluded from this study.

5. Data Collection

5.1. Data Source: EMCL-R

The G-BA commissioned the IQWiG to develop a concept for the routine practice data collection of brexucabtagene autoleucel for treatment of patients with R/R MCL after 2 or more systemic therapies that include a Bruton´s tyrosine kinase (BTK) inhibitor. In this concept, the IQWiG identified the EMCL-R as a potential data source for this study. This, however, according to IQWiG, is only possible after several adjustments have been made to meet the minimal quality criteria. These minimal criteria and their fulfillment by the registry are shown in Table 3.

Table 3. Minimal Quality Criteria and Fulfillment by the EMCL-R

Number	Minimal Quality Criteria As Depicted In G-BA's Resolution (21 July 2022)	Fulfillment by Registry
1	Detailed registry description (protocol)	yes
2	Exact definition or operationalization of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints, and confounders	project-specific
3	Use of standard classifications and terminologies	yes
4	Use of validated standard survey instruments (questionnaires, scales, tests)	yes
5	Training on data collection and recording	yes
6	Implementation of an approved disease-specific core data set	yes
7	Use of exact dates for the patient, the disease, important examinations, and treatments/interventions	limited (dates of primary diagnosis/relapses, start/end of therapies, but no exact dates of assessments)
8	Clearly defined inclusion and exclusion criteria for registry patients	yes
9	Strategies to avoid unwanted selections during patient inclusion in order to achieve representativeness	N/A (all patients who fulfill the inclusion criteria can be documented)
10	Specifications to ensure completeness of data per survey date and completeness of survey dates	eCRF: mandatory fields, medical review, queries; completeness of paper-based PRO checked on a regular basis
11	Source data verification for 100% of patients per survey center for the primary endpoint and for at least 10% of randomly selected patients per survey center for all other endpoints over the period since the start of data collection	project-specific
12	Assurance of scientific independence and transparency of the registry	yes
Number	**Additional adjustments to be implemented in the EMCL-R as depicted in G-BA´s Justification (21 July 2022)**	**Fulfillment by Registry**
13	Significant increase in the documentation goal and with this achieving completeness	yes

14	Implementation of the collection of patient-reported endpoints on symptoms	yes
15	Implementation of the collection of patient-reported endpoints on health-related quality of life	yes
16	Implementation of the collection of adverse events	yes
17	Expansion of the data set to include relevant confounders that have not yet been recorded	yes
Number	**Additional adjustments to be implemented in the EMCL-R as depicted in IQWiG´s concept for brexucabtagene autoleucel (31 March 2022)**	**Fulfillment by Registry**
18	Collection structure (fixed collection time points)	project-specific in alignment with the non-interventional nature of the study
19	Information technology (IT)-supported checks and a query system (systematic clarification of abnormalities)	yes

In general, the EMCL-R includes patients with MCL regardless of disease stage or line of treatment. Data on epidemiological distribution and therapies are collected both prospectively and retrospectively. Patients can be included in the registry at any time during the MCL treatment journey.

The study may be supported by the integration of centers outside Germany. The prerequisite for this is that data are collected in accordance with the requirements. A further prerequisite is that the medical care in the country in which the data are collected is sufficiently similar to the care in Germany. We assume that this requirement is met in European countries participating in the EMCL-R.

5.2. Database and Data Management

Patients will be recruited from the EMCL-R using sites in Germany. In the event of recruitment challenges, especially for the comparator cohort, there is the possibility to allow recruitment from other European sites. The registry utilizes a web-based database solution that is provided to the study centers with a modular system with various access options. The system is operated by using an electronic Case Report Form (eCRF) through which data are collected. The existing data from the eCRF is automatically pseudonymized when it is entered into the central system. All participating sites will use the same clinical database, which will be hosted by the Interdisciplinary Center for Clinical Trials (IZKS) at the sponsoring institution, University Medical Center of the Johannes Gutenberg-University, Mainz (UMM), Germany.

The system allows to repeatedly access individual patient cases to expand the information available.

Data on the patient's history and certain baseline characteristics can be added retrospectively given the quality of data is assured.

Data from the paper based EORTC questionnaires that are completed by patients directly will be entered into the database of the IMBEI by the IMBEI team. Data entry is validated by a separate member of staff. According to EORTC guidelines, the score is only computed if at least 50% of the items per scale are completed. Otherwise, the score will be considered as missing. The scale scores will be computed using a syntax with statistical software.

The individual scores per patient and time point will be transferred to the EMCL-R from IMBEI, using the patient ID as the key to link it to the medical data.

Study nurses will be instructed how to hand out and collect the questionnaires at t0 (Table 2). No further training is required.

5.3. Baseline Data

Date collected at baseline for all enrolled patients are presented in Table 4. Some of the data will be collected based on the most recent assessment that occurred within 4 weeks prior to treatment decision (R/R MCL after two or more lines of therapies including a BTKi).

Table 4. Baseline Data

Demographic data	**Variable/Description**	**Currently collected in EMCL-R?***
Site	Categorical (multiple choice)	Yes
Sex	Categorical (Female/Male)	Yes
Date of birth	Quantitative – date (dd.mm.yyyy)	Yes
Age (year of index date – year of birth)**	Quantitative [years]	Yes
Ethnicity	Categorical (multiple choice: Caucasian, Asian, African, other)	Yes
Informed consent signed?	Categorical (Y, N, n/a)	Yes
Disease information including diagnostic and prognostic factors		
Disease stage according to Ann Arbor	Categorical (multiple choice: Stages I, II, III, IV, unknown)	Yes
Age at diagnosis or Date of MCL diagnosis (TBD)**	Primary diagnosis date, quantitative – date ((dd).mm.yyyy); can be calculated based on date of birth and date of diagnosis	Yes
ECOG performance status	Categorical (multiple choice: 0, 1, 2, 3, 4, unknown)	Yes
Date of ECOG assessment**	Quantitative -Date	Yes
Disease stage prior to index	Categorical (multiple choice: Stages I, II, III, IV, unknown)	Yes
Bulky Disease (>7.5cm)	Categorical (Y/N)	Yes
Central Nervous System (CNS) involvement (CNS lymphoma)	Categorical (Y/N)	Yes
Bone Marrow involvement	Categorical (Y/N)	Yes
Presence of B symptoms at baseline (Fever >38.5°C; night sweats; weight loss)	Categorical (Y/N/unknown)	Yes
Splenic involvement (spleen enlarged)	Categorical (Y/N/unknown)	Yes
Extranodal manifestation at primary diagnosis	Categorical (Y/N)	Yes
Histology	Categorical (multiple choice: classical, CLL-like, blastoid, unknown, other)	Yes
Ki-67	Quantitative [%]	Yes
MIPI (calculated based on ECOG, age, leukocyte count, and LDH)	Categorical (multiple choice: MIPI risk categories, low, intermediate, high risk; missing)	Yes
t(11; 14)	Categorical (Y/N)	Yes
Cyclin D1 overexpression	Categorical (Y/N)	Yes
TP53 mutation / 17p deletion	Categorical (Y/N)	Yes

Demographic data	Variable/Description	Currently collected in EMCL-R?*
SOX-11 expression	Categorical (positive/negative/unknown)	Yes
LDH level	Quantitative [U/l]	Yes
Prior therapy for MCL and outcomes		
Number of prior lines of therapy**	Categorical (multiple choice: 2, 3, 4, 5+)	Yes
Bendamustine-containing therapy prior to index**	Categorical (Y/N)	Yes
Prior SCT **	Categorical (Y/N)	Yes
Type(s) of prior SCT(s) (not mutually exclusive)**	Categorical (multiple choice: autologous vs. allogeneic)	Yes
In case of prior SCT: time from last prior SCT to index **	Categorical (multiple choice: > 12 months vs. ≤ 12 months)	Yes
(Chemo)therapy regimen prior to BTKi therapy(s)**	Categorical (multiple choice: 1-10)	Yes
(Chemo)therapy prior to BTKi therapy(s)**	Categorical (multiple choice: name of therapies)	Yes
Use of BTKi**	Categorical (Y/N)	Yes
BTKi therapy status**	Categorical (multiple choice: refractory vs relapsed vs intolerant)	Yes
BTKi therapy(s)**	Categorical (multiple choice: name of therapies)	Yes
Start and end date; Number of cycles; Best response (CR, PR, SD, PD, n.e.) and date of response; Date of discontinuation	Diverse	Yes
Post-BTKi therapy(s)**	Categorical (Y/N)	Yes
Which post-BTKi therapy(s) have been used**	Categorical (multiple choice: name of therapies)	Yes
Start and end date; Number of cycles; Date of progression, discontinuation, and time to next treatment or death	Diverse	Yes
Symptoms		
Symptoms by means of 9 symptom scales from the EORTC QLQ-C30**	TBD	No
Symptoms by means of 3 symptom scales from the EORTC QLQ-NHL-HG29**	TBD	No
Health-related quality of life		
HRQoL by means of EORTC QLQ-C30 function scales, global scale**	TBD	No
HRQoL by means of EORTC QLQ-NHL-HG29**	TBD	No

* Only data items collected in clinical routine are collected in this registry in line with its non-interventional nature.

**As of 21st December 2022, not included in EMCL-R. Adjustments will be performed by registry.

6. Statistical Considerations

This section presents the key analyses planned for the study. A detailed Statistical Analysis Plan (SAP) is presented separately.

6.1. Definition of Analysis Sets

The following analysis sets will be used in this study:

- **Intent-to-treat Set (ITTS):** This group includes eligible patients with treatment decision for their next line of therapy, based on which patients will be assigned to either treatment arm.
- **As-treated Set (ATS):** This group includes patients that received therapy with brexucabtagene autoleucel or a patient-individual therapy. Patients will be assigned to treatment arms based on the initial treatment they received after treatment decision.

6.2. Operationalization of Endpoints in the Study

Please refer to Section 2.2 for additional information on the operationalization of endpoints.

6.3. Descriptive Data Analyses

Continuous variables and scales will be summarized descriptively by number of patients, number of missings, mean, standard deviation, median, 25% quartile, 75% quartile, minimum, and maximum. Categorical variables will be summarized by number and percentage of patients in each categorical definition.

For binary and continuous variables, the odds ratio, relative risk, and absolute risk reduction will be reported with 2-sided 95% confidence intervals (CIs). A responder analysis will be used for continuous variables to determine these risk measures. Scores will be evaluated using mean differences and Hedges' g.

Time-to-event analysis will be conducted using Kaplan-Meier methods including Kaplan-Meier curves. The median time-to-event will be estimated with the 2-sided 95% CI. The proportion of patients without occurrence of an event over time with the corresponding 2-sided 95% CIs will be presented.

6.4. Methods for Comparative Research

Different approaches have been proposed to account for differences between study arms for the purpose of estimating treatment effects [33-36]. For this study, propensity scores (PS) will be used to balance the baseline characteristics of the two study arms and to allow assessment of overlap and balance [37]. The PS will be defined as the probability of patients being treated with brexucabtagene autoleucel as a function of the selected prognostic factors. It will be derived using a multivariable model with a logit link function. Further details about the matching approach will be provided in the SAP.

6.5. Identification and Evaluation of Confounding Factors

For this routine practice data collection, a systematic literature review for confounders in the investigation of treatments for R/R MCL in the post-BTKi setting was carried out by [redacted] on 15 November 2022. As evidence in the post-BTKi setting is limited in the published literature, the scope of the literature review has been expanded to the R/R MCL setting. A systematic search syntax was used to search the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Cochrane Database of Systematic Reviews (CENTRAL) for published systematic literature reviews and treatment guidelines on R/R MCL. Reports and manuscripts based on this literature were also eligible for inclusion, extending the

inclusion criteria to treatment guideline highlights and summaries of health technology assessment (HTA) reports. Additional manual searches were conducted on various conferences. The search yielded an evidence base of 20 publications (including 14 guideline-related publications, 4 systematic literature reviews and 2 HTA-related reports). The comprehensive technical report describing the systematic literature review, including methodology and results, is provided in Appendix 2.

A total of 32 potential confounders were identified. They are presented in Table 5, broadly arranged into categories based on whether they represent biomarkers; clinical status, tumor characteristics and assessment scales; demographics; or treatment history. The categorization or the order of presentation is not supposed to imply weighting or suggestion of relative importance.

The list of identified potential confounders was then evaluated by clinical consultation under the guidance of Prof. Dr. med. Georg Heß who is the sponsor delegated and coordinator/principal investigator of the present study. Clinical evaluation was based on two categories (Table 5):

- **Substantial impact:** These confounders have a substantial impact on the results and are essential for adjusting the statistical analyses in a non-randomized study (*green color* in Table 5)
- **No substantial impact:** These confounders have a minor influence on the results or are not considered relevant to this study (*beige*), e.g., due to being captured as endpoints or due to the specific study setting. Variables for which the evidence concerned MCL in general and not R/R MCL (*blue*), as well as variables that are not routinely assessed in the real-world setting (*grey*), were also assigned to this group

Table 5. Confounding Factors: Identification in a Systematic Literature Review and Clinical Evaluation

Grouping	Confounder	Result of Expert Review	Currently collected in EMCL-R*
Biomarkers	ATM gene	Not routinely assessed in real world setting	No
	Beta 2 microglobulin levels	References to these potential confounders were for MCL more broadly rather than in the context of R/R MCL	No
	Hemoglobin level	References to these potential confounders were for MCL more broadly rather than in the context of R/R MCL	No
	Ki-67	Substantial impact**	Yes (plus checkbox: Not Done)
	LDH	Substantial impact**	Yes
	Secondary chromosomal aberration	Not routinely assessed in real world setting	No
	TP53 mutation	Substantial impact	Yes

Grouping	Confounder	Result of Expert Review	Currently collected in EMCL-R*
Clinical status, tumor characteristics, and assessment scales	Bulky disease	No substantial impact (not considered relevant by clinical expert review)	Yes
	Comorbidities	No substantial impact (assessed in context of inclusion criteria, positivity)	No
	ECOG performance score	No substantial impact (assessed in context of inclusion criteria, positivity)**	Yes
	Extranodal disease	No substantial impact (not considered relevant by clinical expert review)	Yes (Primarily extranodal)
	Minimal residual disease	Not routinely assessed in real world setting	No
	MIPI	No substantial impact	Yes
	MIPI-c	No substantial impact (MIPI is captured)	No
	Simplified MIPI	No substantial impact (MIPI is captured)	No
	Tumor stage	No substantial impact (will be assessed in subgroup analysis)	Yes (Ann Arbor classification)
	Disease morphology (pleomorphic or blastoid)	Substantial impact	Yes (Histology)
	Bone marrow reserve	No substantial impact (not considered relevant by clinical expert review)	No (but bone marrow involvement)
	Peripheral blood involvement	References to these potential confounders were for MCL more broadly rather than in the context of R/R MCL	Yes (Leukemic Disease, monoclonal B-cells detected in peripheral blood)
Demographics	Age	No substantial impact (will be assessed in subgroup analysis)	Yes (Date of birth)
	Race	No substantial impact (in Europe)	Yes (Ethnicity)
	Sex	References to these potential confounders were for MCL more broadly rather than in the context of R/R MCL	Yes (Gender)

Grouping	Confounder	Result of Expert Review	Currently collected in EMCL-R*
Treatment history	Choice of initial therapy	No substantial impact (not considered relevant by clinical expert review)	No
	Prior treatment(s) received	No substantial impact (not considered relevant by clinical expert review)	Generally, treatments are recorded
	Number of lines of prior therapy	Substantial impact	Not directly
	Response to prior therapy	No substantial impact	Not directly
	Duration of response to prior therapy	No substantial impact	Not directly
	Combination therapy with rituximab	No substantial impact (not considered relevant by clinical expert review)	As antibody in induction treatment
	Prior bendamustine exposure	No substantial impact (not considered relevant by clinical expert review)	As chemotherapy in induction treatment
	Prior bortezomib exposure	No substantial impact (not considered relevant by clinical expert review)	As novel agent in induction treatment
	Early treatment failure after first-line therapy (POD12)	No substantial impact (not considered relevant by clinical expert review)	Not directly
	POD24	No substantial impact (evidence identified outside of the formal systematic literature review process)	No

*As of 21 December 2022

**Included in MIPI

Only confounders rated as having a substantial impact will be considered for propensity score matching. Please refer to Section 6.6.

6.6. Variables Considered for Matching

Confounders have been assessed via a systemic literature review followed by ranking of these under the guidance of Prof. Dr. med. Georg Heß, who is the sponsor delegate and coordinator/principal investigator of the present study. Based on the outcome, the following list of confounders will be considered for PS matching (closest to index date):

- Number of prior lines of therapy (2, 3, 4, 5+)
- Ki-67 (%)
- TP53 mutation (Yes, No)
- Disease morphology (Classical, Blastoid, Pleomorphic, Other, Unknown)

- Lactate dehydrogenase (LDH) [U/l]

6.7. Subgroups

Based on the G-BA consultation, the following subgroups have been defined:

- Age (≥ 65, < 65 years)
- Sex (Male, Female)
- Disease stage according to Ann Arbor (I, II, III, IV)
- Country (as applicable)

Descriptive analyses as defined in Section 6.3 are planned for all endpoints and subgroups. Homogeneity or interaction tests or using interaction terms from regression analyses (stating the relevant standard errors) will test for potential effect modification.

Subgroup analyses are only conducted if each subgroup comprises at least 10 people and, in the event of binary and time-to-event data, at least 10 events occurred in one of the subgroups.

Further details will be provided in the SAP.

6.8. Sample Size Calculation

Background information on G-BA request and considerations

For the benefit assessment of brexucabtagene autoleucel in MCL, Gilead as local representative of Kite submitted a dossier on 15 February 2021 to the G-BA [38]. As part of this dossier, an estimation on annual number of patients in the approved population (adult patients with R/R MCL after two or more systemic therapies that include a BTKi) was to be submitted. In this case, an analysis by the market research institute Oncology Information service in Germany was used as basis and this led to an estimation of 105-150 patients per year in the approved indication for brexucabtagene autoleucel. The average of this estimation (i.e., 130) has been used by the G-BA and IQWiG as the assumption on the expected number of patients that could be recruited by year. This estimation, however, is uncertain, as also stated by the IQWiG in its evaluation of the dossier.

During the elaboration of the concept for the AbD (routine practice data collection) by the IQWiG, the EMCL-R stated that 76 R/R MCL patients after two or more lines of systemic therapies including a BTKi had been documented from 2017 to 2021. This means approximately 20 patients per year. While this was attributed to a low documentation, it cannot be excluded that the actual number of patients in the target population is lower than the estimated number.

According to the concept of the IQWiG developed for brexucabtagene autoleucel in MCL - assuming an event rate (patients who die after 36 months) of 64% (for the comparison group based on SCHOLAR-2) vs. 42% (for the brexucabtagene autoleucel arm based on ZUMA-2) - a hazard ratio (HR) of 0.53 would be obtained. This HR would not be enough for showing (in context of the AbD) a favorable effect in favor of brexucabtagene autoleucel. IQWiG states that larger effect sizes for the AbD will be required as compared to a randomized controlled trial.

Therefore, IQWiG argues that it would be possible to have better outcomes in favor of brexucabtagene autoleucel and the following rates are assumed: 74% vs 32%. Based on these numbers, the resulting HR would be of 0.29 which would allow to show a favorable effect in favor of brexucabtagene autoleucel. Based

on this and additional assumptions (significance level 5%, two tailed, power: 80% and a Cox regression with a shifted null hypothesis HR=0.5) the sample size proposed by IQWIG results in 95 patients per arm in a 1:1 distribution.

Based on the information submitted in the Tecartus benefit dossier, IQWiG assumes that 130 patients could be recruited per year and therefore recruitment would be completed within two years. As mentioned before, this estimation is, however, uncertain.

In addition to the aforementioned limitations, there is also uncertainty as to whether enough patients with R/R MCL after two or more lines of systemic therapies including a BTKi will be treated with therapies other than brexucabtagene autoleucel. With brexucabtagene autoleucel, patients are offered a therapy option with better survival outcomes in comparison to other available therapies, with survival outcomes of 2.5 to 12.5 months [13-16]. Furthermore, brexucabtagene autoleucel is depicted in German Onkopedia guidelines [2] as the preferred treatment for this patient population.

After careful consideration of IQWiG´s approach it is considered that a deviation from this is necessary. The reasons thereof will be depicted in the following section.

Proposed approach for this study

For the sample size calculation, it is assumed that censoring occurs at the end of study. As a result, HRs for OS will be taken as relative risks. The sample size is based on a shifted null hypothesis. The hypothesis is:

$$H_0: RR \geq RR0 \; vs \; H_1: RR < RR0$$

A statement on benefit can be made if the upper limit of the two-sided 95% confidence interval for the relative risk is below the threshold $RR0$ where $RR0 \leq 1$.

The following threshold value for all-cause mortality outcome per [24] will be used:

$$RR0 = 0.85 \text{ (major added benefit)}$$

Additional assumptions are:

- Significance level 5%, two tailed
- Power: 80%
- Control event rate = 64%
- Brexucabtagene autoleucel event rate = 42%
- Expected HR = 0.5
- 2:1 ratio allocation

Applying the above-mentioned shifted null hypothesis approach, the patient sample size would be 257 in a 2:1 ratio allocation (i.e., 171 in the brexucabtagene autoleucel arm and 86 in the comparator arm).

Considerations

The assumed control rate of 74% mentioned in the final sample size calculation in the IQWiG concept document is unlikely to be seen. At the moment no sources could be identified supporting such assumption.

The expected HR of 0.29 outlined in the IQWiG concept is deemed improbable given the results seen in SCHOLAR-2. Additionally, it needs to be taken into account that patients in the comparator arm may switch

to the brexucabtagene autoleucel arm after treatment failure which might further attenuate the HR toward the null.

In the absence of specific thresholds for routine data collection studies, a shifted null hypothesis of 0.85 will be used to show a major benefit of brexucabtagene autoleucel over the comparator arm. A control event rate of 64% at 36 months of follow-up based on the OS rate in SCHOLAR-2 using the inverse probability weighting (IPW) adjustment method is applied (aligned with the initial suggestion in the IQWiG concept document). For brexucabtagene autoleucel an event rate of 42% (according to ZUMA-2 results) is applied.

An approximated HR of 0.5 was used based on the OS Hazard ratio for the ITT analysis set that has previously been reported in the context of SCHOLAR-2 [39]. Here, an HR on 0.46 was seen in naive comparison and an HR of 0.49 under multivariate regression.

To increase the probability of successfully recruiting the required sample size in two years, particularly in the comparator arm, an allocation ratio of 2:1 in favor of brexucabtagene autoleucel has been used. If patient numbers are too low compared to the required sample size, statistically insignificant results are to be expected irrespective of the true treatment effect.

6.9. Study Limitations

As this is a non-interventional study relying on the observation of real-world practice, assessments will not be mandatory. The type, frequency, method, and a potential confirmation of a finding will be solely based on routine medical care. Nevertheless, data reporting/collection will be conducted in a consistent way to avoid bias in the data collection process.

Despite this study is using a prospective cohort design, the risk of misclassification bias cannot be discounted. To mitigate for this, plausibility checks will be carried out on all the data and the EMCL study team will have the ability to verify the source data in case of discrepancies. Although all the study sites will be using the same eCRF, there could be certain variations in the data entry. The study team will provide proper site initiation trainings and arrange for adequate resources to carry out the study. While every effort will be taken to reduce missing data for this study, its elimination is not a certainty. As missing data can introduce a myriad of biases into a study, appropriate methods will be used to account for it. These will be detailed in the SAP.

6.10. Planned Analyses in Status Updates and Reports

Status Update 1 (Information on the status of recruitment)

A first status update will be submitted to the G-BA 6 months after start of the routine practice data collection defined in the determination resolution.

This status update will include:

- Number of patients and the respective medicinal treatment of the patients included in the study population so far
- Patient-related observation times
- Possible deviations regarding the expected enrolment number at this time point: Assuming 130 patients per year, 65 patients are expected to have been enrolled at 6 months (in total). Assuming a 2:1 ratio, the expectation would be 22 patients in the comparator arm and 43 in the brexucabtagene autoleucel arm.

Status Update 2 & interim analysis 1

A second status update will be submitted to the G-BA 18 months after start of the routine practice data collection defined in the determination resolution.

This status update will include:

- Interim analysis submitted using module 4 of the dossier template chapters 4.2.5. (Information synthesis and analysis) and 4.3.2.2 (non-randomized comparative studies)
    - Description of the design and methods of the study
    - Baseline characteristics for study population prior and after propensity score matching including number of eligible patients and observation times (status of recruitment)
    - Risk of bias at study level
    - Operationalization of endpoints including a risk of bias assessment for each endpoint
    - Results of main and sensitivity analyses for all endpoints
    - Results of subgroup analyses
- Possible deviations regarding the expected number of recruits: Assuming 130 patients per year and data cutoff 12 months after study start, 130 patients are expected to have been enrolled. Assuming a 2:1 ratio, the expectation would be 43 patients in the comparator arm and 87 in the brexucabtagene autoleucel arm.

The data cutoff will be 12 months after start of routine practice data collection, as the extensive documentation of the study characteristics and results for G-BA submission requires data cleaning, statistical analyses, and document preparation.

Status Update 3 & interim analysis 2

A third status update will be submitted to the G-BA 36 months after start of the routine practice data collection defined in the determination resolution.

This status update will include:

- Interim analysis submitted using module 4 of the dossier template chapters 4.2.5. (Information synthesis and analysis) and 4.3.2.2 (non-randomized comparative studies)
    - Description of the design and methods of the study
    - Baseline characteristics for study population prior and after propensity score matching including number of eligible patients and observation times (status of recruitment)
    - Risk of bias at study level
    - Operationalization of endpoints including a risk of bias assessment for each endpoint
    - Results of main and sensitivity analyses for all endpoints
    - Results of subgroup analyses
- Possible deviations regarding the expected number of recruits: Assuming 130 patients per year it is expected that the sample size may have been completed after 24 months. Assuming a 2:1 ratio, the expectation would be 86 patients in the comparator arm and 171 patients in the brexucabtagene autoleucel arm.

The data cutoff will be 30 months after start of routine practice data collection, as the extensive documentation of the study characteristics and results for G-BA submission requires data cleaning, statistical

analyses, and document preparation.

Status Update 4 & interim analysis 3

A fourth status update will be submitted to the G-BA 54 months after start of the routine practice data collection defined in the determination resolution.

This status update will include:

- Interim analysis submitted using module 4 of the dossier template chapters 4.2.5. (Information synthesis and analysis) and 4.3.2.2 (non-randomized comparative studies)
    - Description of the design and methods of the study
    - Baseline characteristics for study population prior and after propensity score matching including number of eligible patients and observation times (status of recruitment)
    - Risk of bias at study level
    - Operationalization of endpoints including a risk of bias assessment for each endpoint
    - Results of main and sensitivity analyses for all endpoints
    - Results of subgroup analyses
- Possible deviations regarding the expected number of recruits: For this interim analysis deviations would not be expected if assumptions are correct. I.e., minimal target sample size would have been completed after 24 months.

The data cutoff will be 48 months after start of routine practice data collection, as the extensive documentation of the study characteristics and results for G-BA submission requires data cleaning, statistical analyses, and document preparation.

Final Report (Final analyses)

The final report for benefit assessment of medicinal Products with new active ingredients according to § 35a SGB V will be submitted by 21 July 2028. The duration of recruitment provided by IQWiG is based on the estimation that approximately 130 patients can be recruited by year. This estimation, however, as mentioned before is uncertain. This leads to the possibility that recruitment duration might be longer than 2 years and that therefore the study end will take place at a later time point.

The final data cutoff will be when a minimum of 171 patients in the brexucabtagene autoleucel arm have completed at least 36 months follow-up **and** a minimum of 86 patients in the comparator arm have completed at least 36 months of follow-up.

7. Management and Reporting of Safety Information

The registry, in contrast to interventional therapy studies, is not subject to the regulations of the current amendment of the Medicinal Products Act (AMG) on the obligation to report. However, physicians in Germany are obliged to report adverse events according to § 6 of the professional code of conduct for physicians working in Germany. Reports are to be addressed alternatively to the Drug Commission of the German Medical Association (AKdÄ), the Federal Institute for Drugs and Medicinal Devices (BfArM), the Paul-Ehrlich-Institute (PEI) or to the marketing authorization holder (MAH) by the participating site.

Required reporting to the AKdÄ or federal authorities must be carried out by the participating sites and is not within the obligations of the EMCL-R.

The operational model for this post-authorization project qualifies as non-interventional research with a design based on secondary use of data (i.e., utilizing data from patient's medical records that was previously collected for another purpose and included into the EMCL-R data set; and where the adverse events have already occurred and will not be reported in expedited manner) as outlined in Good Pharmacovigilance Practices (GVP) Module VI by the European Medicines Agency (EMA) (VI.C.1.2.1.2. Non-interventional post-authorization studies with a design based on secondary use of data; [40]). According to this guidance, reporting of safety information in the form of individual case safety reports is not required and all adverse event and safety data are only required to be recorded and summarized in the interim analyses and in the final study report. Reporting of individual adverse events and adverse reactions will follow the standard spontaneous reporting system per local regulations and timelines. The centers will report any suspected adverse reactions directly to Kite or respective health authorities. The Summary of Product Characteristics (SmPC) and packaging materials provide respective details and contact information. Regarding the application of brexucabtagene autoleucel, the MAH further provides clear guidance to health care professionals (HCPs) in the additional risk minimization measures (aRMMs) regarding the need for and importance of spontaneously report AEs. This obligation is not substituted by reporting into a registry.

8. Management and Control of Data Quality

It is required to ensure completeness of the data for each collection time and to perform source data verification (SDV) on 100% of patients for the primary endpoint, i.e., OS. In addition, SDV needs to be performed on at least 10% randomly selected patients per center for all other endpoints over the period since data collection began. All clinical data for this project are collected and stored exclusively in the EMCL-R. Study site staff is responsible for patient clinical data collection and data entry into the EMCL-R. Data are entered into electronic case report forms (eCRFs) of the EMCL-R. Data from the paper-based EORTC questionnaires that are completed by patients directly will be entered into the database of the IMBEI by the IMBEI team. Data entry is validated by a separate member of staff. The scale scores will be computed using a syntax with support of a statistical software and individual scores per patient and time point will be transferred to the EMCL-R eCRF from IMBEI, using the patient ID as the key to link it to the medical data.

8.1. Central Monitoring

Personalized reminders for data entry (phone calls or emails) are sent to study sites regularly and in due time before each data cut for the required interim analyses. Initial validation of entered patient clinical data is carried out via automated edit checks (plausibility checks), programmed checks for completeness of entered data and a full medical review. EMCL-R personnel will also run regular data quality reports, which predominantly focus on missing data. Queries are generated from these checks, the resolution of which including corrective measures are followed up by phone or email by the EMCL-R team. A site initiation contact (SIC) is conducted at each center within 2 weeks after the first patient is enrolled to provide data entry training if needed.

8.2. On-site Monitoring

On-site monitoring for SDV is performed by an IZKS representative (personnel different from the site staff who perform entry) on the basis of all available patient records. The frequency of on-site monitoring visits is determined based on the number of enrolled patients and the quality of the site's data documentation: for each study site, a site visit is planned after the inclusion of five patients or one year after inclusion of the first patent and at the data cut for the final analysis. Patient informed consent (PIC) will be verified for each patient. SDV for 100% of patients per center for the mortality/OS endpoint and for at least 10% of randomly selected patients per center for all other endpoints over the period since the start of data collection for this study will be performed. 100% SDV of the mortality/OS endpoint is to be performed before data cut at each interim analysis. This can be performed by phone/ email by EMCL-R. On average, 2.5 on-site visits per site are expected to be conducted per center.

SDV will be possible for each patient with PIC. However, the centralized nature of the application of CAR T cell therapy makes a change of treating site/physician likely in the course of the study. This needs to be accounted for patients in the brexucabtagene autoleucel arm and may bring some uncertainties regarding the possibilities and limitations of performing SDV as part of this study. Based on the assessments of clinical experts as well as those responsible for the EMCL-R, the extent to which independent documentation is carried out in electronic patient records is also currently unclear and probably varies between individual centers. If necessary, changes to the possible extent of SDV will be depicted in an amendment to the study project plan.

9. Regulatory Obligations

9.1. Informed Consent

Patient informed consent for this study will be covered by the consent for the EMCL-R. Patients will be asked to provide consent so that their clinical data can be entered into the database and be used for analyses of the EMCL network. Specifically, patients will have the chance to opt in for the following:

- Use of their data in co-operations with academic research groups (anonymous)
- Use of their data in co-operations with other entities incl. pharmaceutical companies (anonymous, cumulative, single data set level)
- Use of available biological materials for research projects, which are documented in the registry (e.g., samples from biopsies etc.). In any case this analysis will have to be approved separately
- Provision of additional information on specific quality of life projects
- Provision of additional information on long term sequelae of treatment

Participation in this project is voluntary. There is no direct impact on the treatment of the individual patient. The informed consent form will be distributed to patients eligible for this study by the treatment centers. In addition, patients will receive all relevant information on data protection in its latest version and the potential use of their data for the different analyses, including shared analyses with network and commercial cooperation partners. Patients may opt out according to national and local ethics requirements for the different project types, if required.

9.2. Ethical Conduct of the Study

The study will be conducted according to the ethical considerations stipulated in the EMCL Registry master protocol [41].

10. Data Protection

Within the registry, the applicable data protection is respected. The EU Regulation 2016/679 of the European Parliament and the Council General Data Protection Regulation (GDPR), which has been in force in Germany since May 2018, defines various legal aspects of data protection [42].

According to Article 6(1) (a), the processing of personal data is permitted if "the data subject has given his or her consent to the processing of personal data for one or more purposes". Article 5(1) (b) also states that "personal data may be used only for specified, explicit and legitimate purposes and may not be used for other purposes not agreed upon; the further use of data intended for archives in the public interest, for scientific or historical research projects or for statistical purposes is not incompatible with the original purposes pursuant to Article 89(1)". Article 7(1) further states that "if the use of the data is based on consent, the person responsible must prove that the individual concerned has given consent to the use of personal data".

In order to comply with the provisions of the GDPR, the collection of data in the registry is only possible if written consent has been obtained from the patient, if not addressed in special regulations (e.g., deceased patients).

In case of given consent, participating centers will receive an individual access code and the collected data can be entered into the access-protected database. This database does not contain any information that allows clinical data to be assigned to an individual person. Instead, all data are assigned to a clearly defined alphanumeric pseudonym that contains neither parts of the name nor the date of birth.

The trust center (IMBEI) will receive the person-identifying information as mentioned in Section 2.2.3 along with the patient ID. These data are stored on a secure server independent from the medical and PRO data.

A data protection risk assessment according to GDPR will be performed before starting data collection.

11. Plans for Disseminating Study Results

The data collected in this study will primarily be used in order to fulfill the G-BA requirements regarding this study. These include the status reports and interim analyses as well as the final benefit dossier. For these purposes, EMCL-R will provide Kite/Gilead with aggregated data. In addition, results of these analyses will be presented at national and/or international conferences as well as in a peer-reviewed journal. All data presentations and publications will be developed jointly and will be co-authored by investigators and Kite responsible employees. All data presentations in form of abstracts, posters and publications must be reviewed and approved by the contributing investigators and Kite/Gilead.

12. References

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APPENDICES

Appendix 1. Classification of ECOG Performance Status and Ann Arbor Disease Staging

A. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% or waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

B. Ann Arbor Classification

Ann Arbor Disease Staging for Lymphomas	
Stage	Criteria
I	Involvement of a single node region, or a single extralymphatic organ or site (Stage IE)
II	Two or more involved lymph node regions on the same side of diaphragm, or with localized involvement of an extralymphatic organ or site (IIE)
III	Lymph node involvement on both sides of the diaphragm, or with localized involvement of an extralymphatic organ or site (IIE), or spleen (IIIS), or both (IIIES)
IV	Presence of diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement.

[redacted]

Appendix 2. Technical Report: Confounders in the investigation of treatments for relapsed/refractory mantle cell lymphoma: A systematic literature review. Version 1, 08 December 2022[redacted]

Confounders in the investigation of treatments for relapsed/refractory mantle cell lymphoma: A systematic literature review

Technical Report

Prepared for:

[redacted]

[redacted]

Version 1
December 8, 2022

[redacted]

Study team

Project Lead:	[redacted] Project lead
	[redacted]
Project Team:	[redacted] Reviewer
	[redacted] Reviewer
	[redacted] Senior technical advisor

[redacted]

Version history

Version	Changes	Date issued
1	--	8 December 2022

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[redacted]

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Abbreviations

ALSG	Asian Lymphoma Study Group
ASCO	American Society of Clinical Oncology
ASTCT	American Society for Transplantation and Cellular Therapy
AWMF	Association of the Scientific Medical Societies in Germany
BCSH	British Committee for Standards in Haematology
Bexu-cel	Brexucabtagene autoleucel
BSH	British Society of Haemotology
BTKi	Bruton's tyrosine kinase inhibitors
CADTH	Canadian Agency for Drugs and Technology in Health
CAR T-cell therapy	Chimeric antigen receptor T-cell therapy
CENTRAL	Cochrane Database of Systematic Reviews
CIBMTR	Center for International Blood and Marrow Transplant Research
CR	Complete response
EBMT	European Group for Blood & Marrow Transplantation
ESMO	European Society for Medical Oncology
GGPO	German Guideline Program in Oncology
HTA	Health technology assessment
JSH	Japan Society of Hepatology
LDH	Lactate dehydrogenase
MCL	Mantle cell lymphoma
MEDLINE	Medical Literature Analysis and Retrieval System Online
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
PFS	Progression-free survival
POD12	Progression of disease within 12 months
POD24	Progression of disease within 24 months
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
r/r	Relapsed or refractory

1 Introduction

1.1 Mantle cell lymphoma

Mantle cell lymphoma (MCL) is an aggressive subtype of B-cell non-Hodgkin's lymphoma (NHL) named after its location on the outer edge of the lymph node, the so-called mantle zone. It is associated with a poor prognosis.[43, 44] Overall, MCL accounts for fewer than 10% of all lymphomas across the US and Europe, and, consequently, has limited evidence in the literature relative to other forms of NHL.[45]

The prognosis for patients with MCL treated with conventional chemotherapy is poor, with historical evidence suggesting median overall survivals of three to five years. More recent advances, such as the introduction of intensified cytarabine-containing induction therapies followed by consolidation treatment with high-dose chemotherapy and autologous stem cell transplantation (autoSCT) have improved outcomes.[46, 47] Yet, the clinical course remains heterogenous, with some patients benefitting from treatment for decades and others relapsing within months.[5] Other patients with indolent MCL may be managed through watch and wait strategies which last years.[48]

The advent of Bruton's tyrosine kinase inhibitors (BTKi), with ibrutinib being the first to be granted marketing authorization by the European Medicines Agency in October 2014, has improved prognosis for patients with r/r MCL. However, many patients continue to progress and novel therapeutic options are needed.[14] Advances in chimeric antigen receptor (CAR) T-cell therapy have yielded promising findings in this regard.[17, 49] Based on the findings of the ZUMA-2 trial (NCT02601313), an open-label, multicenter, single-arm phase II trial with an objective response rate of 93% (N = 60),[17, 50] brexucabtagene autoleucel (brexu-cel; TECARTUS) received marketing authorization from the European Medicines Association for the treatment of adult patients with MCL whose cancer has returned following two or more previous treatments. These previous treatments should include a BTKi. Brexu-cel was designated an orphan medicine for MCL in November 2019 and received a conditional marketing authorization in December 2020. Presently, brexu-cel is the only CAR T-cell therapy approved in Europe for use in the post-BTKi r/r MCL setting.

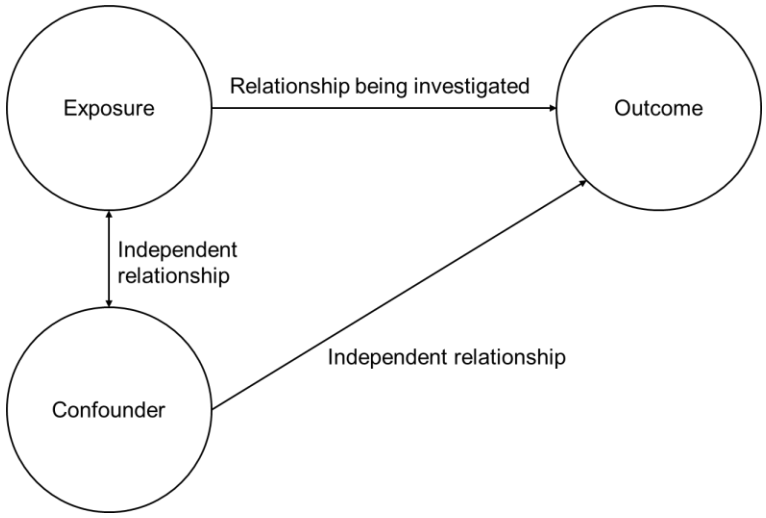
1.2 Considerations for clinical research programs and the impact of confounders

Clinical research, whether prospective or retrospective, should formally incorporate some analysis of measures and characteristics proven to be associated with the outcomes under investigation. These may be implemented in several ways, such as through subgroup stratification of patients or through statistical analyses which adjust for the level or presence of a characteristic. The appropriate methodology chosen will depend on several factors, such as the availability of data, the anticipated influence of the characteristic or measure, and the purpose of the analysis.

Confounders are 'third variables' which have an independent association or relationship with both the exposure and the outcome and therefore distort the exposure-outcome relationship (**Figure 2**). For example, an investigator evaluating the impact of stem cell transplantation on overall survival should

consider the impact of patient age, which is independently associated with both the intervention's effectiveness as well as with the patient's overall survival from the time of receiving the intervention.

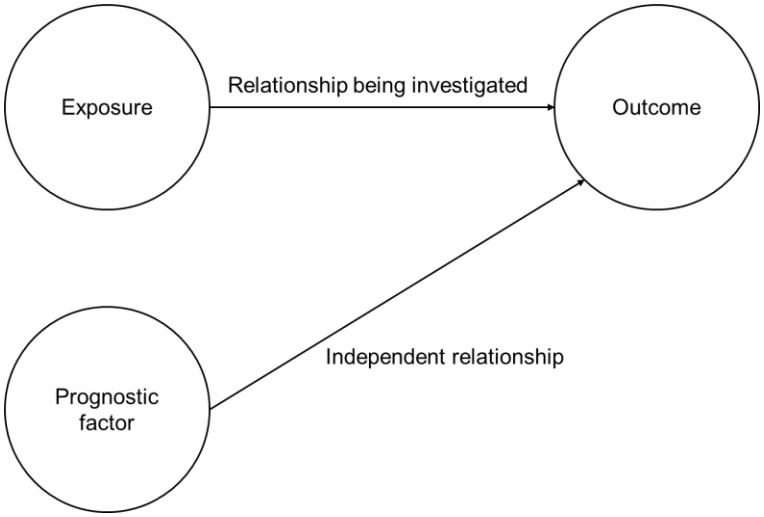
Figure 2: Illustration of the impact of a confounder on investigations of an exposure-outcome relationship



There are independent relationships between both the exposure and the confounder and the confounder and the outcome. These relationships may not be easily disentangled, therefore there is a risk of the presence or level of the confounder distorting the exposure-outcome relationship.

Prognostic factors are another important category of measures for investigators to consider in study designs (**Figure 3**). These are commonly referenced as measures of the natural history of the disease as they are associated with clinical outcomes in the absence of therapy or in the context of a standard of care. That is, these measures are associated with the patient's prognosis largely irrespective of the treatment context. In the example of stem cell transplantation, an investigator should consider the impact of patient sex on overall survival. However, if there is no direct, independent relationship between the effectiveness of stem cell therapy and sex, then sex is not a confounder for this investigation. Importantly, though not of direct consequence for this report, a measure may be both a confounder and a prognostic factor.

Figure 3: Illustration of the impact of a prognostic factor on investigations of an exposure-outcome relationship



There is an independent relationship between the prognostic factor and the outcome under investigation. However, the prognostic factor is not related to the exposure.

While the terms 'confounder', 'prognostic factor', and 'risk factor' have distinct and significant meanings, the term 'confounder' will be used in this report to refer to these terms collectively.

Kite is conducting a comparative effectiveness research study in the post-BTKi setting. To support the development of the research protocol, Kite requires an understanding of the evidence landscape with respect to known confounders in this treatment context. However, the post-BTKi literature is relatively immature and limited evidence is anticipated to be described for the topics of interest in this setting. As it is reasonable to expect evidence in the broader r/r MCL setting to be applicable to the study of patients post-BTKi, the focus of this report is on confounders in this body of literature.

1.3 Confounders in mantle cell lymphoma

The first prognostic score for aggressive B-cell lymphomas, the international prognostic index (IPI), was developed in 1993 as a model for predicting the outcomes of patients with aggressive NHL prior to the initiation of treatment.[51] Through consideration of a collection of clinical features, five prognostic predictors were selected to be included: Ann Arbor stage; Age; Performance status; Lactate dehydrogenase (LDH); and the Presence of more than two extranodal sites. Hoster and colleagues (2008) evaluated whether the IPI and the subsequently developed Follicular Lymphoma International Prognostic Index (FLIPI) could reliably differentiate patients in different risk groups with MCL.[52] Based on data from 455 patients drawn from the prospective GLSG1996, GLSG2000, and European MCL Trial 1 trials, both the IPI and the FLIPI poorly differentiated survival curves. However, three IPI risk factors (Age; Performance status; LDH) retained independent prognostic factor significance through a multivariate Cox regression analysis. Leukocyte count was also found to be a significant prognostic factor in MCL. Therefore, the MCL-specific score (MIPI) was published to formally incorporate these four measures to stratify patients into low-, intermediate-, or high-risk groups. The prognostic value of the MIPI was subsequently validated by Hoster and colleagues (2014) using data from the MCL Younger and MCL Elderly trial (N = 958) where the MIPI was prognostic for overall survival and time-to-treatment

failure.[53] In this study, the five-year overall survival for patients in the low-, intermediate-, and high-risk MIPI groups were 83%, 63%, and 34%, respectively.

To further the discriminatory power and, therefore, the prognostic value of the MIPI, Hoster and colleagues (2016) later considered the independent value of other measures.[54] Among these was the percentage of Ki-67 positive cells, where this percentage was found to be a strong biologic prognostic parameter. It was operationalized as a dichotomized measure (<30% or ≥30%) to create the MIPI-c. Based on data from the MCL Younger or MCL Younger trial, patients labelled as low risk, low-intermediate risk, high-intermediate risk, or high risk had five-year overall survival rates of 85%, 72%, 43%, and 17% ($p < 0.001$), respectively. Similar results were observed for PFS.

In addition to these measures and characteristics, investigators have also evaluated the value of genetic markers. For instance, tissue analyses conducted by the European Mantle Cell Lymphoma Network (N = 365) found that high TP53 expression (>50%) was strongly prognostic for both inferior time-to-treatment failure (HR: 2.0; $p = 0.0054$) and OS (HR: 2.1; $p = 0.0068$) compared to low TP53 expression (1-10%) in both a univariate and multivariable analyses.[55] This was further supported by evidence from the pooled Nordic MCL2 and MCL3 clinical trials of front-line therapy (N = 183) where TP53 retained independent prognostic significance for OS (HR: 6.2, $p <0.0001$) in a multivariable analysis.[56] As stated by Kumar and colleagues (2022), TP53 mutation is the single strongest negative prognostic marker and the widespread adoption of mutation testing is encouraged.[57]

Despite a relative wealth of research on the topic of MCL, most parameters used for risk stratification in MCL have been validated for patients in the first-line setting. A prominent example of this is the MIPI, which is not formally intended for use in patients in the context of relapsed or refractory disease.[58] Indeed, prognostic parameters for relapsed patients remain scarce.[47] This is complicated by the biologic heterogeneity of MCL which is present not only at diagnosis but also at relapse. A systematic literature review was undertaken to identify confounders, prognostic factors, and risk factors (collectively referenced here as “confounders”) to be considered in a clinical investigation initiated by Kite in the r/r MCL setting.

[redacted]

Objective

To support the development of a prospective comparative effectiveness research study protocol for submission to Germany's Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA), Kite requires a systematic evaluation of the literature to identify and describe potential confounders. These potential confounders will be validated through clinical consultation. While literature in the post-BTKi setting is preferable, given its specific relevance to the context of Kite's proposed research program, the scope of this literature review will be extended to patients with r/r MCL given the limited evidence base of the post-BTKi setting. Thus, the objectives of this review are to:

- To systematically identify and describe confounders in the r/r MCL setting; and
- To highlight, where possible, confounders of importance in the post-BTKi setting.

2 Methodology

2.1 Scope of the literature review

The design of the systematic literature review, including the search strategy and screening eligibility criteria, was guided by the PICOS (Population, Interventions, Controls, Outcomes, and Study Designs) criteria outlined in **Table 6**. Briefly, published systematic literature review and clinical guidelines or recommendations, including publications which are intended to accompany or summarize those guidelines, were eligible for inclusion if the topic of r/r MCL was addressed and some discussion or reference to potential or known confounders was included. A formal statistical evaluation of a suspected confounder was not a requirement for inclusion in this literature review.

Table 6: Eligibility criteria for the systematic literature review

Criteria	Description
Population	Patients with a diagnosis of relapsed/refractory mantle cell lymphoma
Interventions	No restrictions
Comparators	No restrictions
Outcomes	Confounders, risk factors, and prognostic factors
Study design	• Clinical guidelines and recommendations • Systematic literature reviews and meta-analyses
Language	• English • German

2.2 Study identification

Relevant studies were identified by searching Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Cochrane Database of Systematic Reviews (CENTRAL) via Ovid on 15 November 2022. Separate search strategies were used to identify each systematic literature reviews and clinical guidelines or recommendations from MEDLINE, with a sensitive, population-focused search strategy executed in CENTRAL (**Appendix A**). Validated search syntax was adapted from the Canadian Agency for Drugs and Technology in Health (CADTH) website.[59]

In addition to running the searches, further manual searches were conducted on the following conferences:

- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- American Society of Clinical Oncology (ASCO)

- German Guideline Program in Oncology (GGPO), jointly launched by the Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society and the German Cancer Aid
- Google (free-hand search)
- Google-Scholar (free-hand search)
- PubMed (free-hand search)

2.3 Study selection

Two reviewers, working independently and in duplicate, reviewed all abstracts and proceedings identified by the search against the review's high-level selection criteria. This screening did not exclude publications on the outcome criteria. The full-text publications identified as eligible during abstract screening were then screened at a full-text stage by the same two reviewers against the review's complete eligibility criteria. The full-text publications identified at this stage were included for data extraction. Following initial reconciliation between the two reviewers, a third reviewer provided arbitration to resolve any remaining discrepancies. The process of study identification and selection was summarized with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[60]

2.4 Data extraction

Two reviewers, working independently and in duplicate, extracted the characteristics of included systematic literature review or clinical guidelines or recommendations as well as the list of potential or known confounders as reported in the included publications. Data were extracted into piloted data extraction templates. Following extraction, confounders were grouped into common categories and confounder labels were standardized across publications for a streamlined dissemination of findings. The specific nuances of each publication were retained in a separate, detailed data extraction element. Where discrepancies in data extraction could not be resolved through discussion, a third, senior reviewer provided arbitration.

2.5 Data synthesis

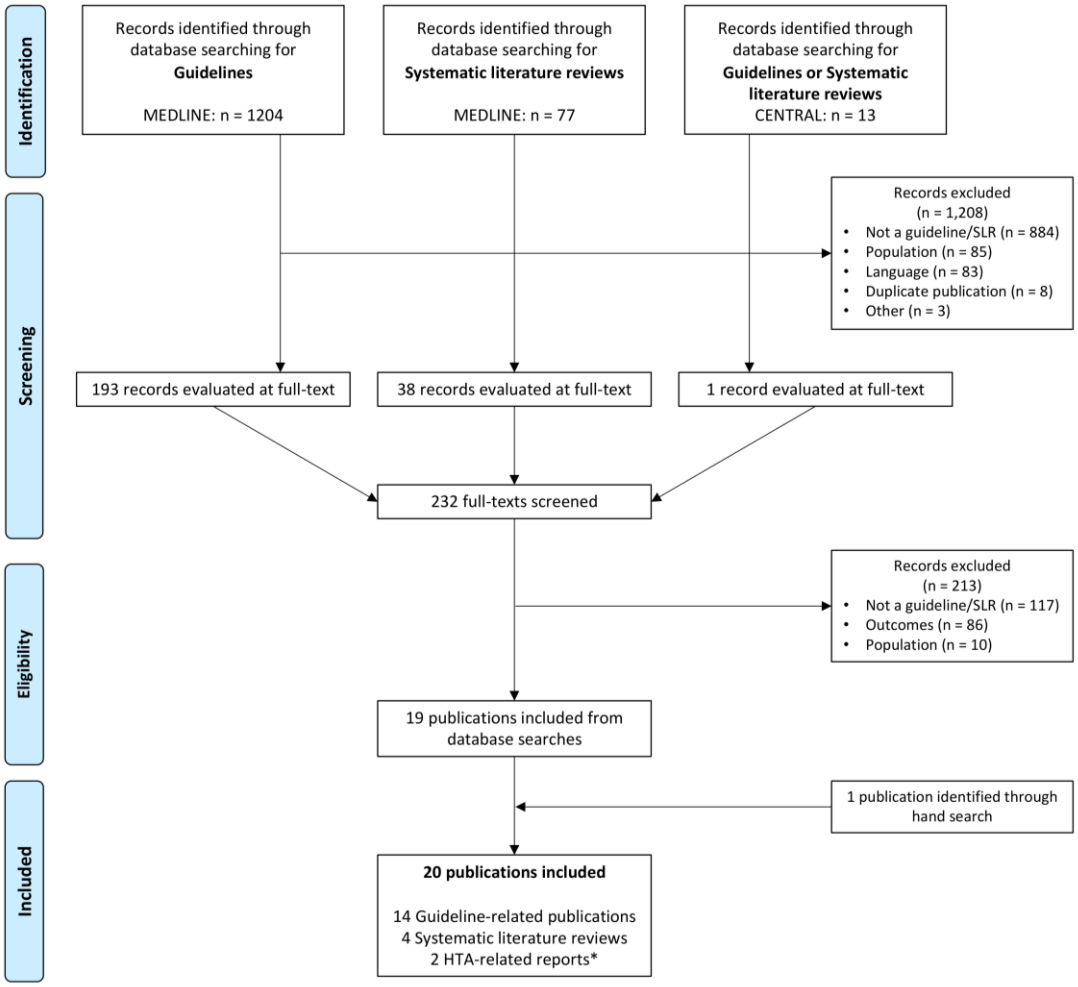
The findings of the literature review were summarized through a narrative synthesis. No formal statistical analysis was planned or anticipated.

3 Results

3.1 Evidence base

From the 1294 publications identified through searches of MEDLINE (1204 publications through the 'Guidelines' search; 77 publications through the 'Systematic literature reviews' search) and CENTRAL (13 publications for either topic), 232 publications satisfied high-level eligibility criteria and were evaluated through full-text screening. From these, 20 publications satisfied all inclusion criteria, with 8 publications related to clinical guidelines or recommendations, four systematic literature reviews, and two publications directly or indirectly referencing the findings of a health technology assessment.[61-80] A decision was made to include health technology assessment-related publications that these evaluations draw from systematic evaluations of the literature. The literature review process is illustrated in **Figure 4**.

Figure 4: Study selection flow diagram



**Two publications relating to a health technology assessment (HTA) were identified and considered eligible for inclusion*

The majority of publications identified through the literature review process were clinical guidelines or recommendations, 14 guidelines from eight distinct bodies included (**Table 11**).[61, 62, 64-68, 71-74, 78-80] Four publications were based on guidance published by the European Society of Medical Oncology (ESMO), with additional representation of organizations in the United States, the United Kingdom, Spain, and Asia. The guidance documents included in this review were not limited to r/r MCL, and included publications scoped to MCL more broadly if specific recommendations were made to the r/r setting. The outcomes described, with respect to the impact of confounders, were generally broad and often were directed towards considerations of risk factors or prognostic factors in clinical decision making. The details of statistical analyses were not reported in these publications.

Two of the four systematic literature reviews identified in our review were directed towards outcomes of patients managed with ibrutinib compared to other interventions.[63, 70, 75, 76] One review, published by Monga and colleagues (2020), was an epidemiology-focused study describing the global burden of illness.[70] The number of publications included in each review was limited, varying from 7-12 publications specific to r/r MCL. However, none of these reported statistical evaluations, such as meta-analyses, of confounders for patients in the r/r MCL setting. The outcomes described in these literature reviews were all related to efficacy, which were either defined broadly or with specific references to overall response rate, overall survival, and progression-free survival. More details on the included guidelines are available in **Appendix B** (**Table 11**).

A National Institute for Health and Care Excellence (NICE) single technology appraisal publication was also identified through the literature search and considered eligible for inclusion in this review. This document describes the health technology assessment (HTA) for ibrutinib in the treatment of patients with r/r MCL based on clinical effectiveness and cost effectiveness evidence for ibrutinib submitted by the manufacturer (Janssen). A systematic literature review of economic literature, which made specific reference to this NICE appraisal, was also identified and included.

3.2 Confounders in relapsed/refractory mantle cell lymphoma

Thirty-three potential confounders, organized into four categories, were identified in the included systematic literature reviews and clinical guidelines or recommendations (**Table 7**). Within each category, confounders have been listed alphabetically. The order of presentation has no weighting on their relative importance.

These categories represented each confounder's relevance to biomarkers (n = 6), clinical status, tumour characteristics, and assessment scales (n = 14), demographics (n = 2), or treatment history (n = 11). The scope and scale of each confounder varied, with some overlap within each category. For example, 'prior treatment(s) received' was a broadly defined confounder which includes other, more specific potential confounders such as 'prior bendamustine exposure' and 'prior bortezomib use'. These more narrowly defined confounders were captured when publications made these specific references and were often recorded in addition to the higher-level, more sensitive characteristic.

[redacted]

The number of publications referring to each confounder varied from single observations (e.g., ‘ATM gene’, ‘LDH’, and ‘Bone marrow reserve’) to several citations across both systematic literature reviews and clinical guidelines or recommendations (e.g., ‘Ki-67’, ‘TP53 mutation’, ‘Age’, and ‘MIPI’).

The outcomes anticipated or demonstrated to be impacted by each confounder varied to include broadly defined efficacy, prognosis, survival, or safety/tolerability outcomes to more specific references to overall survival, PFS, or various response rates.

[redacted]

Table 7: Potential confounders in r/r MCL

Category	Confounder	Outcomes referenced	Referenced by
Biomarker	ATM gene	OS, PFS, ORR	Roufarshbaf 2022 (SLR)[76]
	Genetic Mutation	Efficacy (broadly)	Roufarshbaf 2022 (SLR)[76]
	Ki-67	Efficacy outcomes (broadly), Prognosis (broadly), OS, PFS, ORR	Cao 2021 (SLR)[63] Dreyling 2014 (Guideline from ESMO)[66] Dreyling 2017 (Guideline from ESMO)[65] O'Reilly 2022 (Guideline from BSH)[73] Parrott 2018 (SLR) [75] Roufarshbaf 2022 (SLR)[76] Zelenetz 2021 (Guideline from NCCN)[79]
	LDH	OS, PFS	O'Reilly 2022 (Guideline from BSH)[73]
	P53 overexpression	Survival (broadly)	Caballero 2013 (Guideline from GEL/TAMO)[62]
	TP53 mutation	Prognosis, OS, PFS, ORR	Munshi 2021a (Guideline from ASTCT, CIBMTR, and EBMT)[71] Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)[72] O'Reilly 2022 (Guideline from BSH)[73] Parrott 2018 (SLR)[75] Roufarshbaf 2022 (SLR)[76]

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Category	Confounder	Outcomes referenced	Referenced by
			Yoon 2020 (Guideline from ALSG)[78] Zelenetz 2021 (Guideline from NCCN)[79]
Clinical status, tumour characteristics, and assessment scales	Bone marrow reserve	Prognosis (broadly)	McKay 2012 (Guideline from BCSH)[68]
	Bulky disease	Prognosis (broadly), Drop-out rate	O'Reilly 2022 (Guideline from BSH)[73]
	Co-morbidities	Prognosis (broadly)	McKay 2018 (Guideline from BSH)[67]
	Disease morphology	Prognosis (broadly), Survival (broadly), OS, PFS, ORR	Caballero 2013 (Guideline from GEL/TAMO)[62] O'Reilly 2022 (Guideline from BSH)[73] Parrott 2018 (SLR)[75] Roufarshbaf 2022 (SLR)[76] Zelenetz 2021 (Guideline from NCCN)[79]
	ECOG performance score	Prognosis (broadly), PFS	Buske 2017 (Guideline from ESMO)[61] Caballero 2013 (Guideline from GEL/TAMO)[62] McKay 2012 (Guideline from BCSH)[68] McKay 2018 (Guideline from BSH)[67] O'Reilly 2022 (Guideline from BSH)[73]

Category	Confounder	Outcomes referenced	Referenced by
			Okamoto & Kusumoto 2020 (Guideline from JSH)[74]
	Extra-nodal disease	PFS	Yoon 2020 (Guideline from ALSG)[78]
	Minimal residual disease	Prognosis (broadly)	Dreyling 2014 (Guideline from ESMO)[66]
	MIPI	Efficacy outcomes (broadly), Prognosis (broadly), OS, PFS	Cao 2021 (SLR)[63] O'Reilly 2022 (Guideline from BSH)[73] Roufarshbaf 2022 (SLR)[76] Yoon 2020 (Guideline from ALSG)[78]
	MIPI-c	Prognosis (broadly)	Dreyling 2017 (Guideline from ESMO)[65]
	Organ function	Prognosis (broadly)	Okamoto & Kusumoto 2020 (Guideline from JSH)[74]
	POD24	Prognosis (broadly), OS, PFS	O'Reilly 2022 (Guideline from BSH)[73] Zelenetz 2021 (Guideline from NCCN)[79]
	Simplified MIPI	Prognosis (broadly)	O'Reilly 2022 (Guideline from BSH)[73] Parrott 2018 (SLR)
	Tumour load	Prognosis (broadly)	Dreyling 2014 (Guideline from ESMO)[66]
	Tumour stage		Caballero 2013 (Guideline from GEL/TAMO)[62]

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Category	Confounder	Outcomes referenced	Referenced by
		Prognosis (broadly), Survival (broadly)	Monga 2020 (SLR)[70] O'Reilly 2022 (Guideline from BSH)[73]
Demographics	Age	Efficacy outcomes (broadly), Prognosis (broadly), Survival (broadly), PFS	Buske 2018 (Guideline from ESMO)[61] Caballero 2013 (Guideline from GEL/TAMO)[62] Cao 2021 (SLR)[63] Dreyling 2014 (Guideline from ESMO)[66] Dreyling 2017 (Guideline from ESMO)[65] McKay 2012 (Guideline from BCSH)[68] McKay 2018 (Guideline from BSH)[67] Monga 2020 (SLR)[70] O'Reilly 2022 (Guideline from BSH)[73] Okamoto & Kusumoto 2020 (Guideline from JSH)[74]
	Race	Safety/Tolerability (broadly)	Yoon 2020 (Guideline from ALSG)[78]
Treatment history	Chemosensitive disease	Survival (broadly)	Caballero 2013 (Guideline from GEL/TAMO)[62]
	Choice of initial therapy	Prognosis (broadly)	McKay 2012 (Guideline from BCSH)[68]
	Combination therapy with rituximab	ORR, CR, PFS	Yoon 2020 (Guideline from ALSG)[78]

Category	Confounder	Outcomes referenced	Referenced by
	Duration of response to prior therapy	Prognosis (broadly)	Yoon 2020 (Guideline from ALSG)[78]
	Ibrutinib resistance	Prognosis (broadly)	Dreyling 2018 (Guideline)[64]
	Number of prior lines of therapy	Survival (broadly), Prognosis (broadly), OS, PFS, ORR, CR, DOR	Caballero 2013 (Guideline from GEL/TAMO)[62] Roufarshbaf 2022 (SLR)[76] Tappenden 2019 (NICE HTA)[77] Yoon 2020 (Guideline from ALSG)[78]
	POD12	Prognosis (broadly)	Zelenetz 2021 (Guideline from NCCN)[79]
	Prior bendamustine exposure	Prognosis (broadly)	Yoon 2020 (Guideline from ALSG)[78]
	Prior bortezomib use	DOR, PFS	Dreyling 2018 (Guideline)[64]
	Prior treatment(s) received	Prognosis (broadly), Survival (broadly), PFS	Caballero 2013 (Guideline from GEL/TAMO)[62] Dreyling 2014 (Guideline from ESMO)[66] Dreyling 2018 (Guideline)[64] McKay 2018 (Guideline from BSH)[67] Okamoto & Kusumoto 2020 (Guideline from JSH)[74]
	Response to prior treatment	Prognosis (broadly), OS, PFS	Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)[72] Okamoto & Kusumoto 2020 (Guideline from JSH)[74] Yoon 2020 (Guideline from ALSG)[78]

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Outcome acronyms and notes: The term broadly is used when publications referenced a general category of outcomes with reference specific outcome; OS: Overall survival; PFS: Progression-free survival; ORR: Objective response rate; CR: Complete response; DOR: Duration of response

Issuing body acronyms: ALSG: Asian Lymphoma Study Group; ASTCT, CIBMTR, and EBMT: American Society for Transplantation and Cellular Therapy, Center for International Blood and Marrow Transplant Research, and European Group for Blood & Marrow Transplantation; BCSH: British Committee for Standards in Haematology; BSH: British Society of Haemotology; ESMO: European Society of Medical Oncology; GEL/TAMO: GEL/TAMO Spanish Cooperative Group; JSH: Japan Society of Hepatology; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence

4 Discussion

4.1 Summary of the literature review

A systematic literature review was undertaken to identify confounders, prognostic factors, and risk factors (collectively referenced here as "confounders") to be considered in a clinical investigation of the r/r MCL setting. Owing to feasibility considerations, a pragmatic approach was adopted to only consider published systematic literature reviews and clinical guidelines as eligible for inclusion. It is anticipated that these publications represent thorough investigations and summaries of the literature and, therefore, when consolidated through a review of reviews, provide a sufficiently complete overview of the existing literature. However, few systematic literature reviews were identified through our searches. Indeed, the majority of includes were clinical guidelines or guideline-adjacent publications intended to support readers in interpreting clinical direction and justification. It is typical for these publications to provide limited statistical exploration or justification of confounders and to instead provide more succinct direction to a clinical audience. Furthermore, clinical guidance is directed not only towards achieving clinical effectiveness, but also to considerations of safety and lowering the risk of adverse events. While these dual purposes are significant for our intentions, they are often not clearly delineated in the published texts. Finally, most publications were broadly scoped to the topic of lymphoma or MCL more generally, with sub-sections of text targeted to the r/r MCL setting of interest for this review.

Despite these considerations, several confounders of interest were identified for consideration in the design of novel investigations in the post-BTKi setting. These were broadly categorized as relating to (i) biomarkers, (ii) clinical status, tumour characteristics, and assessment scales, (iii) demographics, or (iv) treatment history. Some overlap between confounder labels within each category was observed, reflecting the level of detail which with references were made to these characteristics in the literature. All confounders described here were reported in the context of r/r MCL and no literature to support discussions in the post-BTKi setting was identified.

4.2 Secondary supporting searches

In the absence of robust statistical evidence to support the identification of confounders identified through the systematic literature review, a supplementary, cursory hand search was undertaken to identify publications which provide such validation. Many of the studies described here were referenced in the publications included through the systematic literature review, though they were often cited without specific details on statistical findings. Supporting evidence was identified for:

- Duration of response to prior therapy
    - A 2014 study by Dietrich and colleagues of patients with r/r MCL found that time to relapse post-autoSCT (<12 months vs. >12 months; HR 0.62) was prognostically significant for overall survival.[5]

- Ki-67 positive cells

    - As suggested by a retrospective study of 118 patients who had undergone autoSCT, the percentage of Ki-67 positive cells may have some prognostic significance.[81] Four patients lived beyond five years post-relapse without intensive salvage treatment. These patients had a long recurrence-free period following autoSCT and, in one patient, the percentage of Ki-67 cells was 5%. However, this finding should be interpreted with caution given the limited number of observations.

    - Further evidence to support Ki-67 as a proliferation index has been drawn from a study of ibrutinib plus rituximab therapy in r/r MCL.[82, 83] In the overall study cohort, 88% and 58% of patients had an objective response and a complete response, respectively. However, among patients with a Ki-67 proliferation index of 50% of higher, objective response and complete response rates diminished to 50% and 17%, respectively. The 3-year progression-free survival in these patients was 1%.

    - Investigators for the multicenter, retrospective Spanish IBRORS-MCL study, which evaluated outcomes in r/r MCL patients treated with ibrutinib in routine clinical practice across 24 centers, evaluated the prognostic value of several measures against clinical outcomes.[84] The prognostic value of several of the measures considered varied depending on whether they were considered in a univariate or multivariate analysis. For instance, Ki-67 levels (>30%) were significantly associated with several outcomes: PFS, significant in both a univariate and multivariate model; Overall survival, significant in a univariate model only; and ORR, only Ki-67 levels were independently associated with this outcome.

- Prior treatment(s) received

    - A 2014 study by Dietrich and colleagues of patients with r/r MCL found that previous treatment with high-dose ARA-C (HR: 1.43) was prognostically significant for overall survival.[5]

- MIPI and simplified MIPI (s-MIPI)

    - A retrospective analysis was conducted using data from a pivotal multicenter phase III trial (NCT00117598) where 162 patients with r/r MCL were randomized to one of two temsirolimus regimens or investigator's choice.[7, 58] The simplified MIPI, retroactively applied to patients at baseline, successfully differentiated patients as those with high s-MIPI scores had less favourable outcomes. The investigators noted, however, that MIPI parameters and, therefore, s-MIPI scores, were not available for all patients.

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Additionally, classification into risk categories decreased the statistical power for evaluations of efficacy in each treatment arm.

- In a study of ibrutinib plus rituximab therapy in r/r MCL, patients with high scores on the MIPI had worse outcomes.[82, 83]

- Investigators for the multicenter, retrospective Spanish IBRORS-MCL study, which evaluated outcomes in r/r MCL patients treated with ibrutinib in routine clinical practice across 24 centers, valuated the prognostic value of several measures against clinical outcomes.[84] The prognostic value of several of the measures considered varied depending on whether they were considered in a univariate or multivariate analysis. A high simplified MIPI score was a risk factor for both PFS and overall survival in a univariate analyses, though the relationship was not statistically significant in a multivariate model.

- Number of prior lines of therapy

  - Based on 3.5 years of follow-up from a pooled analysis of 370 patients with r/r MCL treated with ibrutinib in three studies (PCYC-1104, SPARK, RAY), patients who received ibrutinib in second line, compared to in later lines of therapy, had more favourable outcomes on overall survival, PFS, ORR, complete response rate, and duration of response. In multivariate analyses of PFS and overall survival, the number of prior lines of therapy remained an independent predictor of PFS (HR 1.64, 95% CI: 1.197 – 2.248, $p = 0.002$).[85]

- Disease morphology (blastoid morphology)

  - In a study of ibrutinib plus rituximab therapy in r/r MCL, patients with blastoid morphologic features had worse outcomes.[82, 83]

- POD24

  - Investigators for the multicenter, retrospective Spanish IBRORS-MCL study, which evaluated outcomes in r/r MCL patients treated with ibrutinib in routine clinical practice across 24 centers, evaluated the prognostic value of several measures against clinical outcomes.[84] POD24 was a risk factor for overall survival in a univariate analyses, though lost its statistical significance in a multivariate model.

- TP53

[redacted]

- Investigators for the multicenter, retrospective Spanish IBRORS-MCL study, which evaluated outcomes in r/r MCL patients treated with ibrutinib in routine clinical practice across 24 centers, evaluated the prognostic value of several measures against clinical outcomes.[84] The presence of a TP53 mutation at diagnosis was a risk factor for PFS in a univariate analysis, though it was not statistically significant in predicting PFS in a multivariate model. Interestingly, however, TP53 mutation status was a risk factor in both a univariate and multivariate analysis for overall survival.

- Evidence from 3.5 years of follow-up from a pooled analysis of 370 patients with r/r MCL treated with ibrutinib in three studies (PCYC-1104, SPARK, RAY) suggests less favourable outcomes in patients with a known TP53 mutation. This was based on the observation that patients with mutated and wild-type TP53, respectively, median PFS of 4.0 (95% CI: 2.1 – 8.3) months and 12.0 (95% CI: 7.1 – 15.6) months were observed. Similarly, the median overall survival was 10.3 (95% CO: 2.5 – 12.6) months and 33.6 (95% CI: 18.3 – Not evaluable) months in these subgroups. There was also a marked difference in the percentage of patients achieving ORR across the TP53-mutated (55.0%) and TP53-wild-type (70.2%) stratifications.[85]

- Tumour stage

  - Advanced stage IV disease at diagnosis may also be associated with overall survival, as suggested by a retrospective trial of 69 patients with r/r MCL treated with ibrutinib across 10 centers conducted on behalf of the regional Tuscan lymphoma network.[86] However, this trend was not statistically significant.

- Serum lactate dehydrogenase (LDH)

  - As described in a retrospective analysis of patients with MCL treated with ibrutinib at MD Anderson Cancer Center between January 2011 and January 2014, elevated serum LDH at the time of disease progression was "adversely prognostic" for overall survival in a univariate analysis (n = 31).[87]

- Minimal residual disease

  - The prognostic value of minimal residual disease (MRD) burden has been demonstrated on progression-free survival and overall survival. This includes a study by Pott and colleagues (2006) of patients treated with high dose chemotherapy and autoSCT where PFS estimates of 92 months and 21 months were observed in the MRD-negative and MRD-positive groups, respectively. Median overall survival (44 months in the MRD-positive group; Not reached in the MRD-negative group) further supported this

prognostic indicator.[88] Further evidence from the MCL Younger and MCL Elderly trial of the European MCL network supported these findings.[89]

- Response to prior treatment

    - A 2014 study by Dietrich and colleagues of patients with r/r MCL found that having primary refractory disease (HR 1.92) was prognostically significant for overall survival.[5]

4.3 Strengths and limitations

The scope of searches for this systematic literature review was restricted to published systematic literature reviews and clinical guidelines or recommendations. These criteria were extended to include guideline-adjacent publications, which expand upon the literature or nuances contained in clinical guidelines, typically for a clinical audience, and health technology assessments which draw from and stratify evaluations based on evidence curated through literature reviews. Publications which referenced confounders without statistical explorations, such as in making recommendations for future research, were also eligible for inclusion.

Despite this flexible approach to the literature review's eligibility criteria, a relatively small evidence base, dominated by clinical guideline- or recommendation-related publications, was identified. While this literature highlights many confounders of interest, such as through references to subgroups or patient characteristics to be considered in clinical decision making, these discussions are often unaccompanied with specific statistical rationalizations and justifications. The relative absence of systematic literature reviews in our evidence base, specifically with respect to evaluations or discussions of confounders, is reflective of the immaturity of this clinical context. Indeed, several of the included publications referenced confounders as intended subgroups of interest which were not feasible for analysis given a lack of data. To address this limitation, a hand search was conducted to identify primary publications which supported the statements of the included literature. This returned several studies which described the results of statistical evaluations to support recommendations and conclusions.

5 Conclusion

This systematic literature review was designed to support a novel research program being proposed by Kite in the post-BTKi clinical space by generating a list of potential confounders for consideration and validation. Given the limited evidence in the post-BTKi setting, the scope of this review was extended to the broader r/r MCL patient population. For feasibility considerations, the scope of eligible publications was restricted to published systematic literature reviews and clinical guidelines or recommendations which referenced r/r MCL. Several confounders of interest were identified through the included publications, though they often lacked formal statistical analyses and rationalizations for their inclusion. Importantly, most of the included systematic literature reviews called for additional research to facilitate the conduct of subgroup analyses on particular covariates of interest. To supplement the literature review, a hand search of primary publications was conducted (presented in Section 4.2) to

[redacted]

describe primary studies which referenced confounders, often with statistical backing. Overall, while no literature on confounders in the post-BTKi r/r MCL setting was found, a comprehensive list of confounders was identified in the broader context of r/r MCL. Thus, this systematic literature review satisfies Kite's objectives of engaging clinical experts in a validation exercise to discuss and rationalize the appropriateness the inclusion of these confounders in future research.

[redacted]

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[redacted]

Appendix A: Search Strategy

MEDLINE was searched (via Ovid) to identify clinical guidelines and recommendations (**Table 8**) and systematic literature reviews

[redacted]

Table 9). A sensitive, population-focused search strategy was applied to CENTRAL (via Ovid) to identify both types of publications (

[redacted]

Table 10).

Table 8: MEDLINE search for treatment guidelines and recommendations, 1946 to November 14, 2022

Search	Query	Hits
1	exp Lymphoma, Mantle-Cell/	3627
2	mantle.mp.	15368
3	lymphom*.mp.	273601
4	2 and 3	6883
5	1 or 4	6883
6	exp clinical pathway/	7624
7	exp clinical protocol/	186977
8	clinical protocols/	29782
9	exp consensus/	19506
10	exp consensus development conference/	12628
11	exp consensus development conferences as topic/	2998
12	critical pathways/	7624
13	exp guideline/	37344
14	guidelines as topic/	42028
15	exp practice guideline/	30114
16	practice guidelines as topic/	127423
17	health planning guidelines/	4165
18	Clinical Decision Rules/	889
19	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.	47213
20	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf.	43498
21	(standards or guideline or guidelines).ti,kf.	130575
22	((practice or treatment* or clinical) adj guideline*).ab.	50105
23	(CPG or CPGs).ti.	6304
24	consensus*.ti,kf.	33050
25	consensus*.ab. /freq=2	32264
26	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf.	25288
27	recommendat*.ti,kf. or guideline recommendation*.ab.	55700

[redacted]

Search	Query	Hits
28	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf.	78439
29	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf.	9634
30	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf.	12252
31	(guideline* or standards or consensus* or recommendat*).au.	564
32	(guideline* or standards or consensus* or recommendat*).ca.	1290
33	or/6-32	725504
34	5 and 33	1204

Search executed on 15 November 2022

[redacted]

Table 9: MEDLINE search for systemic literature reviews and meta-analyses, 1946 to November 14, 2022

Search	Query	Hits
1	exp Lymphoma, Mantle-Cell/	3627
2	mantle.mp.	15368
3	lymphom*.mp.	273601
4	2 and 3	6883
5	1 or 4	6883
6	Meta-Analysis as Topic/	21844
7	meta analy$.tw.	249308
8	metaanaly$.tw.	2481
9	Meta-Analysis/	170562
10	(systematic adj (review$1 or overview$1)).tw.	264003
11	exp Review Literature as Topic/	21050
12	or/6-11	421953
13	cochrane.ab.	122794
14	embase.ab.	139920
15	(psychlit or psyclit).ab.	917
16	(psychinfo or psycinfo).ab.	53750
17	(cinahl or cinhal).ab.	41887
18	science citation index.ab.	3621
19	bids.ab.	640
20	cancerlit.ab.	638
21	or/13-20	224328
22	reference list$.ab.	21293
23	bibliograph$.ab.	21554
24	hand-search$.ab.	8250
25	relevant journals.ab.	1318
26	manual search$.ab.	5693
27	or/22-26	52177
28	selection criteria.ab.	34838
29	data extraction.ab.	29893
30	28 or 29	62139
31	Review/	3072390
32	30 and 31	33278
33	Comment/	985895
34	Letter/	1198833
35	Editorial/	625805
36	animal/	7192798
37	human/	20865227
38	36 not (36 and 37)	5029857
39	or/33-35,38	7065026
40	12 or 21 or 27 or 32	504474
41	40 not 39	479802
42	5 and 41	77

Search executed on 15 November 2022

[redacted]

[redacted]

Table 10: EBM Reviews – Cochrane Database of systemic reviews <2005 to November 9, 2022>

Search	Query	Hits
1	mantle.mp.	18
2	lymphom*.mp.	342
3	1 and 2	13

Search executed on 15 November 2022

[redacted]

Appendix B: List of included

The complete list included publications, arranged by systematic literature review or clinical guideline, is presented in **Table 11**.

Table 11: Study mapping of the systematic literature review evidence base

Guideline issuing body, if applicable	Author Year	Title
American Society for Transplantation and Cellular Therapy, Center for International Blood and Marrow Transplant Research, and European Group for Blood & Marrow Transplantation (ASTCT, CIBMTR, and EBMT)	Munshi 2021a[71]	ASTCT, CIBMTR, and EBMT clinical practice recommendations for transplant and cellular therapies in mantle cell lymphoma
	Munshi 2021b[72]	American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and European Society for Blood and Marrow Transplantation clinical practice recommendations for transplantation and cellular therapies in mantle cell lymphoma
British Committee for Standards in Haematology (BCSH)	McKay 2012[68]	Guidelines for the investigation and management of mantle cell lymphoma
British Society of Haemotology (BSH)	O'Reilly 2022[73]	Addendum to British society for haematology guideline for the management of mantle cell lymphoma, 2018 (br. J. Haematol. 2018; 182: 46-62): Risk assessment of potential car t candidates receiving a covalent Bruton tyrosine kinase inhibitor for relapsed/refractory disease
	McKay 2018[67]	Guideline for the management of mantle cell lymphoma
--	Cao 2021[63]	Meta-Analysis of the Efficacy and Adverse Reactions of Ibrutinib in the Treatment of Refractory/Relapsed Mantle Cell Lymphoma
European Society of Medical Oncology (ESMO)	Buske 2018[61]	ESMO consensus conference on malignant lymphoma: General perspectives and recommendations for the clinical management of the elderly patient with malignant lymphoma
	Dreyling 2018[64]	Treatment for patients with relapsed/refractory mantle cell lymphoma: European-based recommendations
	Dreyling 2017[65]	Newly diagnosed and relapsed mantle cell lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up
	Dreyling 2014[66]	Newly diagnosed and relapsed mantle cell lymphoma: EMSO clinical practice guidelines for diagnosis, treatment and follow-up
GEL/TAMO Spanish Cooperative Group (GEL/TAMO)	Caballero 2013[62]	Clinical practice guidelines for diagnosis, treatment, and follow-up of patients with mantle cell lymphoma. Recommendations from the GEL/TAMO Spanish Cooperative Group

[redacted]

Guideline issuing body, if applicable	Author Year	Title
--	Monga 2020[70]	Systematic literature review of the global burden of illness of mantle cell lymphoma
--	Monga 2021[69]	Systematic literature review of economic evaluations, costs/resource use, and quality of life in patients with mantle cell lymphoma
National Comprehensive Cancer Network (NCCN)	Zelenetz 2021[79]	NCCN guidelines insights: B-cell lymphomas, version 5.2021
	Zelenetz 2012[80]	Non-Hodgkin's lymphomas, version 3.2012
Japanese Society of Hepatology (JSH)	Okamoto & Kusumoto 2020[74]	JSH practical guidelines for hematological malignancies, 2018: II. Lymphoma-4. Mantle cell lymphoma (MCL)
--	Parrott 2018[75]	A systematic review of treatments of relapsed/refractory mantle cell lymphoma
--	Roufarshbaf 2022[76]	Efficacy and safety of ibrutinib in mantle cell lymphoma: A systematic review and meta-analysis
National Institute for Health and Care Excellence (NICE)	Tappenden 2019[77]	Ibrutinib for treating relapsed or refractory mantle cell lymphoma: An evidence review group perspective of a nice single technology appraisal
Asian Lymphoma Study Group (ALSG)	Yoon 2020[78]	Treatment of mantle cell lymphoma in Asia: A consensus paper from the Asian lymphoma study group

Appendix C: Context of references to confounders in relapsed/refractory MCL

This Appendix presents the context of references to confounders in the publications included in the systematic literature review, including relevant in-text quotations (**Table 12**) and the context of the in-text references (

Table 13).

Table 12: In-text references to confounders in the included publications

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
Biomarker	ATM gene	Roufarshbaf 2022 (SLR)[76]	"Based on subgroup analyses in a trial studying ibrutinib and venetoclax combination...the highest ORRs were seen in patients with...ATM (90%) genetic aberrations, respectively."	Handunnetti 2019
	Genetic Mutation	Roufarshbaf 2022 (SLR)[76]	"Based on subgroup analyses in a trial studying ibrutinib and venetoclax combination, the lowest and the highest ORRs were seen in patients with TP53 (50%) and ATM (90%) genetic aberrations, respectively. Along with ibrutinib-containing regimens for the treatment of R/R MCL patients."	Handunnetti 2019
	Ki-67	Cao 2021 (SLR)[63]	"Nevertheless, the present study had some limitations: ... 2) Presently, only a few studies have studies this new drug for R/R MCL, but the sample size was small. Thus, expand the sample size to conduct a subgroup analysis of the influence of Ki-67 index, MIPI score, and age on the efficacy, is an urgent requirement to obtain accurate results"	--
		Dreyling 2014 (Guideline from ESMO)[66]	Referenced in a figure	--
		Dreyling 2017 (Guideline from ESMO)[65]	"The evaluation of the cell proliferation antigen Ki-67 is the most applicable method to evaluate cell proliferation, and is considered the most established biological risk factor in MCL. As the reproducibility of quantitative scores among pathologists may vary, a standardised method has been suggested."	--
		O'Reilly 2022 (Guideline from BSH)[73]	"Overall initial responses in high-risk disease such as pleomorphic/blastoid morphology, TP53 mutations or Ki-67 proliferation index ≥50% appeared comparable but small numbers preclude valid conclusions...Real-world reporting, enriched for patients with poor prognostic features, has demonstrated similar initial rates of response and toxicity."	Iacoboni 2022, Jain 2022
		Parrott 2018 (SLR)[75]	"Additional factors that should be considered when comparing trials are...the proportion of patients with high Ki-67 scores, indicating more aggressive disease…which will affect the outcomes"	--
		Roufarshbaf 2022 (SLR)[76]	"In a trial, Jain et al...studied the ibrutinib and rituximab combination in R/R MCL patients; they suggested that patients with a low Ki-67% index (< 50%) benefited more from therapy by achieving longer PFS and OS significantly compared with those with a high Ki-67% index."	Jain 2018
		Zelenetz 2021 (Guideline from NCCN)[79]	"The ORRs were consistently higher among patients with poor prognostic features, including pleomorphic or blastoid morphology, TP53 mutation, or Ki-67 index ≥50%."	Wang 2020
	LDH	O'Reilly 2022 (Guideline from BSH)[73]	"An additional pooled trial analysis and extended follow-up of 370 patients receiving ibrutinib monotherapy at relapse established that disease bulk of 5 cm or larger, raised lactate dehydrogenase (LDH), high- risk Mantle Cell Lymphoma International Prognostic Index (MIPI)	Rule 2017, Dreyling 2022

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
			score, progression of disease within 24months of front-line therapy (POD24) and blastoid histology predict for shorter PFS and OS."	
	P53 overexpression	Caballero 2013 (Guideline from GEL/TAMO)[62]	"Blastoid variants of MCL and P53 overexpression have also been associated with a trend towards worse prognosis."	Milpied 1998
	TP53 mutation	Munshi 2021a (Guideline from ASTCT, CIBMTR, and EBMT)[71]	"The panel recommends both CAR T cell therapy or allogeneic transplant consolidation as acceptable options, in relapsed MCL patients with TP53 mutation (or biallelic deletion) in a complete or partial remission after second or subsequent lines of therapy."	--
		Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)[72]	"The panel acknowledges that in the modern era of novel immunotherapies, auto-HCT will likely play a limited role in the management of R/R MCL, particularly in the presence of TP53 aberrations where the panel does not recommend auto-HCT"	--
		O'Reilly 2022 (Guideline from BSH)[73]	"Patients from this same cohort harbouring a TP53 mutation also demonstrate poor out- comes, with a median PFS of only 4.0 months."	Rule 2019
		Parrott 2018 (SLR)[75]	"Additional factors that should be considered when comparing trials are the differences in...other biologic factors such as TP53 mutation...which will affect the outcomes."	--
		Roufarshbaf 2022 (SLR)[76]	"Based on subgroup analyses in a trial studying ibrutinib and venetoclax combination, the lowest and the highest ORRs were seen in patients with TP53 (50%) and ATM (90%) genetic aberrations, respectively. Along with ibrutinib-containing regimens for the treatment of R/R MCL patients."	Handunnetti 2019
		Yoon 2020 (Guideline from ALSG)[78]	"Clinical trial enrollment is strongly suggested where possible, especially for patients with TP53 mutation associated with poor prognosis."	--
		Zelenetz 2021 (Guideline from NCCN)[79]	"The ORRs were consistently higher among patients with poor prognostic features, including pleomorphic or blastoid morphology, TP53 mutation, or Ki-67 index ≥50%."	Wang 2020
Clinical status, tumour characteristics, and assessment scales	Bone marrow reserve	McKay 2012 (Guideline from BCSH)[68]	"It is acknowledged that there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient age, performance status, initial therapy, bone marrow reserve and history of infections."	--
	Bulky disease	O'Reilly 2022 (Guideline from BSH)[73]	"An additional pooled trial analysis and extended follow-up of 370 patients receiving ibrutinib monotherapy at relapse established that disease bulk of 5 cm or larger, raised lactate dehydrogenase (LDH), high- risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score, progression of disease within 24months of front-line therapy (POD24) and blastoid histology predict for shorter PFS and OS."	Rule 2017, Dreyling 2022
	Co-morbidities	McKay 2018 (Guideline from BSH)[67]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--
	Disease morphology	Caballero 2013 (Guideline from GEL/TAMO)[62]	"When selecting the type of salvage regimen to be adminis- tered, several factors have to be taken into consideration, including patient age, performance status, histology at relapse, previous treatment, and whether the patient has received a prior SCT."	--
		Caballero 2013 (Guideline from GEL/TAMO)[62]	"Blastoid variants of MCL and P53 overexpression have also been associated with a trend towards worse prognosis."	Milpied 1998

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
		O'Reilly 2022 (Guideline from BSH)[73]	"A predominance of older patients, inferior Eastern Cooperative Oncology Group (ECOG) performance status (PS) and blastoid histology (32%), had achieved a median PFS of only 3.4 months with ibrutinib, highlighting a subset with resistant and rapidly progressive disease."; "An additional pooled trial analysis and extended follow-up of 370 patients receiving ibrutinib monotherapy at relapse established that disease bulk of 5 cm or larger, raised lactate dehydrogenase (LDH), high- risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score, progression of disease within 24months of front-line therapy (POD24) and blastoid histology predict for shorter PFS and OS."	McCulloch 2021
		O'Reilly 2022 (Guideline from BSH)[73]	Referenced in a figure	--
		O'Reilly 2022 (Guideline from BSH)[73]	"Overall initial responses in high-risk disease such as pleomorphic/blastoid morphology, TP53 mutations or Ki-67 proliferation index ≥50% appeared comparable but small numbers preclude valid conclusions...Real-world reporting, enriched for patients with poor prognostic features, has demonstrated similar initial rates of response and toxicity."	Iacoboni 2022, Jain 2022
		Parrott 2018 (SLR)[75]	"The blastoid histologic type represents a small proportion of the total MCL population; it is important that patients with this subtype are included in trials to collect data on how they respond to various treatments. It would not be feasible to perform a trial of this subtype alone; therefore, imbalances in the baseline characteristics of this nature between treatment arms should be tolerated, acknowledging that they could affect the results"; "Although prognostic indicators such as the simplified MCL international prognostic index score or blastoid variant were reported in some of the studies, none of the trials reported outcomes according to these important factors owing to the small numbers of patients in these groups. The original protocol intended to undertake a subgroup analysis for these prognostic indicators; however, owing to the lack of data, such an analysis was not possible"	--
		Roufarshbaf 2022 (SLR)[76]	"R/R MCL patients with non-blastoid morphology, low-risk MIPI score, and low Ki-67% index (< 50%) benefited more from the combination therapy, demonstrating longer PFS and OS; also, the CR rate with ibrutinib plus rituximab (58%) was superior to the CR rate of patients receiving single-agent ibrutinib (23%)."	Wang 2015, Rule 2018
		Zelenetz 2021 (Guideline from NCCN)[75]	"The ORRs were consistently higher among patients with poor prognostic features, including pleomorphic or blastoid morphology, TP53 mutation, or Ki-67 index ≥50%."	Wang 2020
	ECOG performance score	Buske 2017 (Guideline from ESMO)[61]	"As with first-line treatment, the choice of second-line and subsequent treatment should be adapted to the age and PS of the patient with relapsed or refractory disease."	--
		Caballero 2013 (Guideline from GEL/TAMO)[62]	"When selecting the type of salvage regimen to be adminis- tered, several factors have to be taken into consideration, including patient age, performance status, histology at relapse, previous treatment, and whether the patient has received a prior SCT."	--
		McKay 2012 (Guideline from BCSH)[68]	"It is acknowledged that there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient age, performance status, initial therapy, bone marrow reserve and history of infections."	--
		McKay 2018 (Guideline from BSH)[67]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
		O'Reilly 2022 (Guideline from BSH)[73]	"A predominance of older patients, inferior Eastern Cooperative Oncology Group (ECOG) performance status (PS) and blastoid histology (32%), had achieved a median PFS of only 3.4 months with ibrutinib, highlighting a subset with resistant and rapidly progressive disease."; "An additional pooled trial analysis and extended follow-up of 370 patients receiving ibrutinib monotherapy at relapse established that disease bulk of 5 cm or larger, raised lactate dehydrogenase (LDH), high- risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score, progression of disease within 24months of front-line therapy (POD24) and blastoid histology predict for shorter PFS and OS."	McCulloch 2021
		Okamoto & Kusumoto 2020 (Guideline from JSH)[74]	"The appropriate salvage therapy should be selected with consideration to the patient's performance status and organ function as well as the properties of each salvage therapy and previous treatments and responsiveness."	--
	Extra-nodal disease	Yoon 2020 (Guideline from ALSG)[78]	"A subsequent analysis of factors affecting response in this study suggested that the ORR is higher in rituximab-treated patients receiving one versus two or more prior lines of chemotherapy, and PFS was shorter in patients with extra-nodal disease and those receiving two or more prior lines of chemo- therapy."	Igarashi 2002
	Minimal residual disease	Dreyling 2014 (Guideline from ESMO)[66]	"The independent prognostic role of minimal residual disease (MRD) applying patient-specific primers has been confirmed in numerous studies."	--
	MIPI	Cao 2021 (SLR)[63]	"Nevertheless, the present study had some limitations: ... 2) Presently, only a few studies have studies this new drug for R/R MCL, but the sample size was small. Thus, expand the sample size to conduct a subgroup analysis of the influence of Ki-67 index, MIPI score, and age on the efficacy, is an urgent requirement to obtain accurate results"	--
		O'Reilly 2022 (Guideline from BSH)[73]	"An additional pooled trial analysis and extended follow-up of 370 patients receiving ibrutinib monotherapy at relapse established that disease bulk of 5 cm or larger, raised lactate dehydrogenase (LDH), high- risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score, progression of disease within 24months of front-line therapy (POD24) and blastoid histology predict for shorter PFS and OS."	Rule 2017, Dreyling 2022
		Roufarshbaf 2022 (SLR)[76]	"R/R MCL patients with non-blastoid morphology, low-risk MIPI score, and low Ki-67% index (< 50%) benefited more from the combination therapy, demonstrating longer PFS and OS; also, the CR rate with ibrutinib plus rituximab (58%) was superior to the CR rate of patients receiving single-agent ibrutinib (23%)."	Wang 2015, Rule 2018
		Yoon 2020 (Guideline from ALSG)[78]	"however, higher MIPI and/or prior benda- mustine exposure was associated with ibrutinib treat- ment failure and poorer outcomes"	Jeon 2019
	MIPI-c	Dreyling 2017 (Guideline from ESMO)[65]	"The evaluation of the cell proliferation antigen Ki-67 is the most applicable method to evaluate cell proliferation, and is considered the most established biological risk factor in MCL. As the reproducibility of quantitative scores among pathologists may vary, a standardised method has been suggested."	--
	Organ function	Okamoto & Kusumoto 2020 (Guideline from JSH)[74]	"The appropriate salvage therapy should be selected with consideration to the patient's performance status and organ function as well as the properties of each salvage therapy and previous treatments and responsiveness."	--
	POD24	O'Reilly 2022 (Guideline from BSH)[73]	"An additional pooled trial analysis and extended follow-up of 370 patients receiving ibrutinib monotherapy at relapse established that disease bulk of 5 cm or larger, raised lactate dehydrogenase (LDH), high- risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score, progression of disease within 24months of front-line therapy (POD24) and blastoid histology predict for shorter PFS and OS."	Rule 2017, Dreyling 2022

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
	POD24	Zelenetz 2021 (Guideline from NCCN)[79]	"Early treatment failure after first-line therapy (disease relapse and initiation of second-line therapy within 12 months after up-front autologous HCT) and POD24 are associated with a poor prognosis."	Dietrich 2014, Kumar 2019, Visco 2019
	Simplified MIPI	O'Reilly 2022 (Guideline from BSH)[73]	"Risk assessment pre-cBTKi should include up-to-date imaging and Simplified MIPI (sMIPI) status."	--
		Parrott 2018 (SLR)[75]	"Additional factors that should be considered when comparing trials are the differences in the MCL international prognostic index scores...which will affect the outcomes"; "Although prognostic indicators such as the simplified MCL international prognostic index score or blastoid variant were reported in some of the studies, none of the trials reported outcomes according to these important factors owing to the small numbers of patients in these groups. The original protocol intended to undertake a subgroup analysis for these prognostic indicators; however, owing to the lack of data, such an analysis was not possible"	--
	Tumour load	Dreyling 2014 (Guideline from ESMO)[66]	"The selection of optimal treatment is mainly based on clinical references and biological risk factors, symptoms and tumour load."	--
	Tumour stage	Caballero 2013 (Guideline from GEL/TAMO)[62]	"Some studies have indicated that the factors that most influence the extent of survival benefit achieved with autotransplantation are the number of prior chemotherapy lines and disease status at transplant."	Freedman 1998, Milpied 1998
		Monga 2020 (SLR)[70]	"In a Dutch study that stratified survival data according to year of diagnosis and treatment received during the study period, 5-year net survival… Five-year net survival was poorer for patients with more advanced disease (stage III/IV)"	Issa 2015
		O'Reilly 2022 (Guideline from BSH)[73]	Referenced in a figure	--
Demographics	Age	Buske 2018 (Guideline from ESMO)[61]	"As with first-line treatment, the choice of second-line and subsequent treatment should be adapted to the age and PS of the patient with relapsed or refractory disease."	--
		Caballero 2013 (Guideline from GEL/TAMO)[62]	"Factors that influence the risk of relapse and patient survival after allotransplantation include presence of chemosensitive disease… age at transplantation, and number of prior chemotherapy lines "; "When selecting the type of salvage regimen to be adminis- tered, several factors have to be taken into consideration, including patient age, performance status, histology at relapse, previous treatment, and whether the patient has received a prior SCT."	Cook 2010, Corradini 2007, Robinson 2002
		Cao 2021 (SLR)[63]	"Nevertheless, the present study had some limitations: ... 2) Presently, only a few studies have studies this new drug for R/R MCL, but the sample size was small. Thus, expand the sample size to conduct a subgroup analysis of the influence of Ki-67 index, MIPI score, and age on the efficacy, is an urgent requirement to obtain accurate results"	--
		Dreyling 2014 (Guideline from ESMO)[66]	Referenced in a figure	--
		Dreyling 2017 (Guideline from ESMO)[65]	Referenced in a figure	--
		McKay 2012 (Guideline from BCSH)[68]	"It is acknowledged that there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient	--

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
			age, performance status, initial therapy, bone marrow reserve and history of infections."	
		McKay 2018 (Guideline from BSH)[67]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--
		Monga 2020 (SLR)[70]	"In a Dutch study that stratified survival data according to year of diagnosis and treatment received during the study period, 5-year net survival (an epidemiological measure of excess cancer-related mortality compared with the general population matched by age, sex, race and calendar year) ranged from 17% (95% CI, 11–23) in patients >75 years old diagnosed during 2001–2004 to 72% (95% CI, 66–77) in patients <65 years old diagnosed during 2005–2010."	Issa 2015
		O'Reilly 2022 (Guideline from BSH)[73]	"A predominance of older patients, inferior Eastern Cooperative Oncology Group (ECOG) performance status (PS) and blastoid histology (32%), had achieved a median PFS of only 3.4 months with ibrutinib, highlighting a subset with resistant and rapidly progressive disease."; "An additional pooled trial analysis and extended follow-up of 370 patients receiving ibrutinib monotherapy at relapse established that disease bulk of 5 cm or larger, raised lactate dehydrogenase (LDH), high- risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score, progression of disease within 24months of front-line therapy (POD24) and blastoid histology predict for shorter PFS and OS."	McCulloch 2021
		Okamoto & Kusumoto 2020 (Guideline from JSH)[74]	Referenced in a figure	--
		Zelenetz 2012 (Guideline from NCCN)[80]	Referenced in a figure	--
	Race	Yoon 2020 (Guideline from ALSG)[78]	"Limited data on the epidemiology of MCL within Asian populations were found, emphasizing the importance of comprehensive and contemporary registry data. It is recognized that ethnic characteristics can affect treatment efficacy and side effect profiles."	Nazha 2019
Treatment history	Chemosensitive disease	Caballero 2013 (Guideline from GEL/TAMO)[62]	"Factors that influence the risk of relapse and patient survival after allotransplantation include presence of chemosensitive disease…"	Cook 2010, Corradini 2007, Robinson 2002
	Choice of initial therapy	McKay 2012 (Guideline from BCSH)[68]	"It is acknowledged that there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient age, performance status, initial therapy, bone marrow reserve and history of infections."	--
	Combination therapy with rituximab	Yoon 2020 (Guideline from ALSG)[78]	"A subsequent analysis of factors affecting response in this study suggested that the ORR is higher in rituximab-treated patients receiving one versus two or more prior lines of chemotherapy, and PFS was shorter in patients with extra-nodal disease and those receiving two or more prior lines of chemo- therapy."	Igarashi 2002
	Duration of response to prior therapy	Yoon 2020 (Guideline from ALSG)[78]	"Guidelines agree that the choice of salvage therapy is influenced by the prior lines of therapy used and duration of response to prior therapy."	--
	Ibrutinib resistance	Dreyling 2018 (Guideline)[64]	"Two separate retrospective reviews reported poor outcomes for patients with ibrutinib-resistant MCL after subsequent salvage therapy, with a median OS of 5.8 and 8.4 months after ibrutinib cessation."	Martin 2016, Cheah 2015

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
	Number of prior lines of therapy	Caballero 2013 (Guideline from GEL/TAMO)[62]	"Some studies have indicated that the factors that most influence the extent of survival benefit achieved with autotransplantation are the number of prior chemotherapy lines."; "Factors that influence the risk of relapse and patient survival after allotransplantation include presence of chemosensitive disease… age at transplantation, and number of prior chemotherapy lines "	Vose 2000, Cook 2010, Corradini 2007, Robinson 2002
		Roufarshbaf 2022 (SLR)[76]	"R/R MCL patients with non-blastoid morphology, low-risk MIPI score, and low Ki-67% index (< 50%) benefited more from the combination therapy, demonstrating longer PFS and OS; also, the CR rate with ibrutinib plus rituximab (58%) was superior to the CR rate of patients receiving single-agent ibrutinib (23%)."	Wang 2015, Rule 2018
		Tappenden 2019 (NICE HTA)[77]	"The cost-effectiveness profile of ibrutinib appears to be improved in the one prior LOT subgroup, but may be subject to confounding due to the post hoc definition of the subgroup and bias due to the poor fit of the Weibull function used to model PFS"; "The committee concluded that the most plausible ICER for the one prior LOT subgroup is likely to be lower than the company's estimate of £49,848 per QALY gained"; "Noting its conclusion that trial evidence and clinical experience suggest that ibrutinib is most effective in people who have had only one prior LOT..."	--
		Yoon 2020 (Guideline from ALSG)[78]	"In addition, in a pooled ana- lysis after an extended 3.5-year follow-up of phase II and III clinical trials of patients with relapsed/refractory MCL, those who received second-line therapy and those achieving a CR derived the greatest benefit from ibruti- nib treatment; median PFS and OS were 12.5 and 26.7 months, respectively."	Rule 2018
		Yoon 2020 (Guideline from ALSG)[78]	"In the 3-year follow-up of the RAY study, ibrutinib showed a favorable OS trend versus temsirolimus (median OS 30.3 versus 23.5 months; hazard ratio [HR] 0.74 [95% CI 0.54–1.02], P = 0.0621), with the most benefit seen in patients receiving only one prior line of therapy."	Rule 2018
		Yoon 2020 (Guideline from ALSG)[78]	"A subsequent analysis of factors affecting response in this study suggested that the ORR is higher in rituximab-treated patients receiving one versus two or more prior lines of chemotherapy, and PFS was shorter in patients with extra-nodal disease and those receiving two or more prior lines of chemo- therapy."	Igarashi 2002
	POD12	Zelenetz 2021 (Guideline from NCCN)[79]	"Early treatment failure after first-line therapy (disease relapse and initiation of second-line therapy within 12 months after up-front autologous HCT) and POD24 are associated with a poor prognosis."	Dietrich 2014, Kumar 2019, Visco 2019
	Prior bendamustine exposure	Yoon 2020 (Guideline from ALSG)[78]	"however, higher MIPI and/or prior bendamustine exposure was associated with ibrutinib treatment failure and poorer outcomes"; "Real-world data of ibrutinib monotherapy in a salvage setting in Korea showed a favorable ORR and duration of response; however, higher MIPI and/or prior bendamustine exposure was associated with ibrutinib treatment failure and poorer outcomes."	Jeon 2019
	Prior bortezomib use	Dreyling 2018 (Guideline)[64]	"Response rates did not differ between bortezomib-naïve versus pre-treated patients, although trends toward longer DOR and PFS were observed in patients who had received prior bortezomib."	Wang 2014
	Prior treatment(s) received	Caballero 2013 (Guideline from GEL/TAMO)[62]	"When selecting the type of salvage regimen to be adminis- tered, several factors have to be taken into consideration, including patient age, performance status, histology at relapse, previous treatment, and whether the patient has received a prior SCT."	--
		Dreyling 2014 (Guideline from ESMO)[66]	"Selection of salvage treatment depends on efficacy of prior regimens."	--

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
		Dreyling 2018 (Guideline)[64]	"Analysis of subgroups and regression analyzes associated superior PFS with lenali- domide over IC therapy irrespective of prior treatment history."	Trneny 2015
		McKay 2018 (Guideline from BSH)[67]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--
		Okamoto & Kusumoto 2020 (Guideline from JSH)[74]	"The appropriate salvage therapy should be selected with consideration to the patient's performance status and organ function as well as the properties of each salvage therapy and previous treatments and responsiveness."	--
	Response to prior treatment	Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)[72]	"The panel recommends allogeneic transplantation in eligible MCL patients relapsing/progressing after CAR T-cell therapy, if they achieve a complete or partial remission or if they have stable disease with subsequent anti-lymphoma therapies."	--
		Okamoto & Kusumoto 2020 (Guideline from JSH)[74]	"The appropriate salvage therapy should be selected with consideration to the patient's performance status and organ function as well as the properties of each salvage therapy and previous treatments and responsiveness."	--
		Yoon 2020 (Guideline from ALSG)[78]	"In addition, in a pooled analysis after an extended 3.5-year follow-up of phase II and III clinical trials of patients with relapsed/refractory MCL, those who received second-line therapy and those achieving a CR derived the greatest benefit from ibrutinib treatment; median PFS and OS were 12.5 and 26.7 months, respectively."	Rule 2018

**Citations as referenced in the systematic literature review or clinical guideline/recommendation, as applicable*

Issuing body acronyms: ALSG: Asian Lymphoma Study Group; ASTCT, CIBMTR, and EBMT: American Society for Transplantation and Cellular Therapy, Center for International Blood and Marrow Transplant Research, and European Group for Blood & Marrow Transplantation; BCSH: British Committee for Standards in Haematology; BSH: British Society of Haemotology; ESMO: European Society of Medical Oncology; GEL/TAMO: GEL/TAMO Spanish Cooperative Group; JSH: Japan Society of Hepatology; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence

Table 13: Context of references to confounders in the included publications

Category	Confounder	Publication	Systematic literature review			Guidelines		
			Evaluated or referenced as a subgroup	Referenced in narrative summary	Intended but infeasible analysis; Direction for future research	Described in a figure for decision-making?	Referenced as a consideration in treatment selection	Referenced in a narrative summary
Biomarker	ATM gene	Roufarshbaf 2022 (SLR)[76]	Yes	--	--	--	--	--
	Genetic Mutation	Roufarshbaf 2022 (SLR)[76]	--	--	--	--	--	--
	Ki-67	Cao 2021 (SLR)[63]	--	--	Yes	--	--	--
		Dreyling 2014 (Guideline from ESMO)[66]	--	--	--	--	--	--

Category	Confounder	Publication	Systematic literature review			Guidelines		
			Evaluated or referenced as a subgroup	Referenced in narrative summary	Intended but infeasible analysis; Direction for future research	Described in a figure for decision-making?	Referenced as a consideration in treatment selection	Referenced in a narrative summary
		Dreyling 2017 (Guideline from ESMO)[65]	--	--	--	Yes	--	--
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--		Yes
		Parrott 2018 (SLR)[75]	--	--	Yes	--	--	--
		Roufarshbaf 2022 (SLR)[76]	--	Yes	--	--	--	--
		Zelenetz 2021 (Guideline from NCCN)[79]	--	--	--	--	--	Yes
	LDH	O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
	P53 overexpression	Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	--	Yes
	TP53 mutation	Munshi 2021a (Guideline from ASTCT, CIBMTR, and EBMT)	--	--	--	Yes	Yes	--
		Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)	--	--	--	Yes	Yes	--
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		Parrott 2018 (SLR)	--	--	Yes	--	--	--
		Roufarshbaf 2022 (SLR)[76]	--	--	--	--	--	--
		Yoon 2020 (Guideline from ALSG)	--	--	--	Yes	Yes	--
		Zelenetz 2021 (Guideline from NCCN)	--	--	--	--	--	Yes
Clinical status, tumour characteristics, and	Bone marrow reserve	McKay 2012 (Guideline from BCSH)	--	--	--	--	Yes	Yes

Category	Confounder	Publication	Systematic literature review			Guidelines		
			Evaluated or referenced as a subgroup	Referenced in narrative summary	Intended but infeasible analysis; Direction for future research	Described in a figure for decision-making?	Referenced as a consideration in treatment selection	Referenced in a narrative summary
assessment scales	Bulky disease	O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
	Co-morbidities	McKay 2018 (Guideline from BSH)	--	--	--	--	Yes	--
	Disease morphology	Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	Yes	Yes
		Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	--	Yes
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	Yes	--	--
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		Parrott 2018 (SLR)	--	--	Yes	--	--	--
		Roufarshbaf 2022 (SLR)	Yes	--	--	--	--	--
		Zelenetz 2021 (Guideline from NCCN)	--	--	--	--	--	Yes
	ECOG performance score	Buske 2017 (Guideline from ESMO)	--	--	--	--	Yes	--
		Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	Yes	Yes
		McKay 2012 (Guideline from BCSH)	--	--	--	--	Yes	Yes
		McKay 2018 (Guideline from BSH)	--	--	--	--	Yes	--
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		Okamoto & Kusumoto 2020	--	--	--	--	Yes	--

Category	Confounder	Publication	Systematic literature review			Guidelines		
			Evaluated or referenced as a subgroup	Referenced in narrative summary	Intended but infeasible analysis; Direction for future research	Described in a figure for decision-making?	Referenced as a consideration in treatment selection	Referenced in a narrative summary
		(Guideline from JSH)						
	Extra-nodal disease	Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
	Minimal residual disease	Dreyling 2014 (Guideline from ESMO)	--	--	--	--	Yes	Yes
	MIPI	Cao 2021 (SLR)	--	--	Yes	--	--	--
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		Roufarshbaf 2022 (SLR)		Yes	--	--	--	--
		Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
	MIPI-c	Dreyling 2017 (Guideline from ESMO)	--	--	--	Yes	--	--
	Organ function	Okamoto & Kusumoto 2020 (Guideline from JSH)	--	--	--	--	Yes	--
	POD24	O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		Zelenetz 2021 (Guideline from NCCN)	--	--	--			Yes
	Simplified MIPI	O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		Parrott 2018 (SLR)	--	--	Yes	--	--	--
	Tumour load	Dreyling 2014 (Guideline from ESMO)	--	--	--	--	Yes	Yes
	Tumour stage	Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	--	Yes
		Monga 2020 (SLR)	Yes	Yes	--	--	--	--

Category	Confounder	Publication	Systematic literature review			Guidelines		
			Evaluated or referenced as a subgroup	Referenced in narrative summary	Intended but infeasible analysis; Direction for future research	Described in a figure for decision-making?	Referenced as a consideration in treatment selection	Referenced in a narrative summary
		O'Reilly 2022 (Guideline from BSH)	--	--	--	Yes	--	--
Demographics	Age	Buske 2018 (Guideline from ESMO)	--	--	--	--	Yes	--
		Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	--	Yes
		Cao 2021 (SLR)	--	--	Yes	--	--	--
		Dreyling 2014 (Guideline from ESMO)	--	--	--	--	--	--
		Dreyling 2017 (Guideline from ESMO)	--	--	--	Yes	--	--
		McKay 2012 (Guideline from BCSH)	--	--	--	--	Yes	Yes
		McKay 2018 (Guideline from BSH)	--	--	--	--	Yes	--
		Monga 2020 (SLR)	Yes	Yes	--	--	--	--
		O'Reilly 2022 (Guideline from BSH)[73]	--	--	--	--	--	Yes
		Okamoto & Kusumoto 2020 (Guideline from JSH)	--	--	--	Yes	Yes	--
		Zelenetz 2012 (Guideline from NCCN)	--	--	--	Yes	Yes	--
	Race	Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
Treatment history	Chemosensitive disease	Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	--	Yes
	Choice of initial therapy	McKay 2012 (Guideline from BCSH)	--	--	--	--	Yes	Yes

Category	Confounder	Publication	Systematic literature review			Guidelines		
			Evaluated or referenced as a subgroup	Referenced in narrative summary	Intended but infeasible analysis; Direction for future research	Described in a figure for decision-making?	Referenced as a consideration in treatment selection	Referenced in a narrative summary
	Combination therapy with rituximab	Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
	Duration of response to prior therapy	Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
	Ibrutinib resistance	Dreyling 2018 (Guideline)	--	--	--	--	--	Yes
	Number of prior lines of therapy	Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	--	Yes
		Roufarshbaf 2022 (SLR)	--	Yes	--	--	--	--
		Tappenden 2019 (NICE HTA)	--	--	--	--	--	--
		Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
		Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
		Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
	POD12	Zelenetz 2021 (Guideline from NCCN)	--	--	--	--	--	Yes
	Prior bendamustine exposure	Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
	Prior bortezomib use	Dreyling 2018 (Guideline)	--	--	--	--	--	Yes
	Prior treatment(s) received	Caballero 2013 (Guideline from GEL/TAMO)	--	--	--	--	Yes	Yes
		Dreyling 2014 (Guideline from ESMO)	--	--	--	--	Yes	Yes
		Dreyling 2018 (Guideline)	--	--	--	--	Yes	Yes
		McKay 2018 (Guideline from BSH)	--	--	--	--	Yes	--

Category	Confounder	Publication	Systematic literature review			Guidelines		
			Evaluated or referenced as a subgroup	Referenced in narrative summary	Intended but infeasible analysis; Direction for future research	Described in a figure for decision-making?	Referenced as a consideration in treatment selection	Referenced in a narrative summary
		Okamoto & Kusumoto 2020 (Guideline from JSH)	--	--	--	--	Yes	--
	Response to prior treatment	Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)	--	--	--	Yes	Yes	--
	Response to prior treatment	Okamoto & Kusumoto 2020 (Guideline from JSH)	--	--	--	--	Yes	--
		Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes

The two publications describing or referencing the NICE single technology appraisal are not included in this table

**In cases where a publication described different levels of a confounder but in different contexts, these data were extracted under separate confounder lines which were later grouped into a common category and label. Therefore, the same publication may be referenced multiple times under a single confounder name and with different context columns indicated.*

Issuing body acronyms: ALSG: Asian Lymphoma Study Group; ASTCT, CIBMTR, and EBMT: American Society for Transplantation and Cellular Therapy, Center for International Blood and Marrow Transplant Research, and European Group for Blood & Marrow Transplantation; BCSH: British Committee for Standards in Haematology; BSH: British Society of Haemotology; ESMO: European Society of Medical Oncology; GEL/TAMO: GEL/TAMO Spanish Cooperative Group; JSH: Japan Society of Hepatology; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence