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 of the EMCL Registry	University Medical Center of the Johannes Gutenberg-University Mainz
Sponsor Delegate and Coordinator of the EMCL Registry/ 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 and amended on 16 March 2023, 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 (Rituximab, Dexamethasone, high-dose Cytarabine, Cisplatin)

	- R-BAC (Rituximab, Bendamustine, Cytarabine) - Temsirolimus - R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone) - 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 lines of systemic therapy including a BTKi - Intention of treatment with either brexucabtagene autoleucel or patient-individual therapy from a list of eligible treatments provided by the G-BA (see Objectives and Endpoints, above) - Informed consent by the patient for participation in the EMCL-R if patient is not already included in the base population
Exclusion Criteria	Patients will not be included in the study if one or more of the following criteria apply: - ECOG > 2 - Absolute contraindication to fludarabine and cyclophosphamide, including history of severe hypersensitivity reaction to these - Acute impaired organ function (cardiac, pulmonary, renal, hepatic) - Active uncontrolled infection
Sample Size	The estimated preliminary sample size for analysis is 261 patients in a 2:1 ratio allocation (i.e., 174 in the brexucabtagene autoleucel arm and 87 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

[redacted] [redacted]

Signature Date (DD Month YYYY)

Kite/Gilead accountable representatives:

Dr. med. Christel Zeisse, Sr. Director Medical Affairs, Kite Country Medical Lead Germany

[redacted] [redacted]

Signature Date (DD Month YYYY)

Dr. Robert Welte, Sr. Director Market Access and Reimbursement Germany

[redacted] [redacted]

Signature Date (DD Month YYYY)

Dr. Taha Itani, Director Medical Affairs, Real World Evidence

[redacted] [redacted]

Signature Date (DD Month YYYY)

Dr. Elande Baro, Associate Director, Biostatistics

[redacted] [redacted]

Signature Date (DD Month YYYY)

Key administrative information

Project coordination & development

Johanna Flach, PhD
Associate Director, Medical Affairs

Katharina Schmidt, PhD
Senior Manager, Medical Affairs

Laura Reimeir, MD, MSc
Senior Manager, Market Access

Statistical considerations

Francis Nissen, MD, PhD
Director, Medical Affairs, Real World Evidence

Agency support

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.*)
DRM	Data review meeting
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

Abbreviation	Term/Definition
EMCL-R	European Mantle Cell Lymphoma Network Registry
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
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
HCP	Health care professionals
HG	High grade
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
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
MI	Multiple imputation
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

Abbreviation	Term/Definition
PD	Progressive disease
PEI	Paul-Ehrlich-Institute
PIC	Patient informed consent
PICO	Population, Intervention, Comparison and Outcome
PR	Partial response
PRO	Patient-reported outcome
PS	Propensity score
PSM	Propensity score matching
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/Mitoxantrone
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	Changes made and reasons for change
1.0	21 December 2022	N/A, first version
2.0	13 April 2023	**Implementation of G-BA resolution of 16 March 2023:** After submission on 21 December 2022, the IQWiG and G-BA reviewed the project plan and SAP. Mandatory and recommended adjustments were published in the G-BA resolution of 16 March 2023. For details on the corresponding adjustments implemented in the project plan, please see Table 1 below. **Further changes:** - **Project Plan Synopsis:** Specification of "Sponsor" and "Sponsor Delegate and Coordinator" by adding "of the EMCL Registry"; update of sample size estimate after recalculation - **Timelines and Data Reports:** Adjustment of preliminary sample size estimates after recalculation - **Section 1.2:** Modification of Table 2 (Requirements of the G-BA for the Routine Practice Data Collection in a PICO Scheme) based on the G-BA resolution published on 16 March 2023 - **Section 2.2:** Modification of outcomes based on the G-BA resolution published on 16 March 2023; inclusion of a statement that all mandatory and most recommended adjustments required by the G-BA are implemented in the subsequent sections - **Sections 2.2.1-4:** Deletion of row "currently collected in EMCL-R" because at start of data collection, all variables will be collected - **Section 2.2.3.1:** Inclusion of possible phone calls to patients by IMBEI as appropriate in order to increase questionnaire response rates. - **Section 2.2.4:** Deletion of redundant and obsolete considerations - **Sections 2.2.4.1-5:** Implementation of changes based on the G-BA resolution published on 16 March 2023 - **Section 2.2.4.3:** Correction of the English translation of the transcript of the G-BA consultation - **Section 3.6:** Expanded description of CAR T cell qualified vs. not qualified centers and German vs. European centers; update of the number of qualified and not qualified centers in the EMCL-R - **Section 5.2:** Deletion of obsolete procedure regarding handing-out of patient questionnaires at t0. - **Section 5.3:** Update of Table 5 (Baseline Data) regarding collection of variables at start of routine practice data collection - **Section 6:** Various adaptions to SAP - **Section 6.5:** Specification of comorbidities collected in the EMCL-R (footnote to Table 7)

		- **Section 6.11.2:** Update of sample size estimate after recalculation - **Section 7:** Reference to similar regulations in other European countries - **Section 8:** Inclusion of data entry checks to avoid data entry errors - **Section 12:** Update of references - Numbering of all headings, including headings of the third hierarchy level and below in all relevant sections - Consistent naming of comparator therapies throughout project plan - Correction of typos throughout project plan

Table 1. Mandatory and Recommended Adjustments Requested by the G-BA according to the Resolution of 16 March 2023

Adjustments		Implementation
Mandatory adjustments		
a) Research question according to PICO: patient population; inclusion criteria	The study protocol must specifically define how the requirement "Information on the operationalization of the criteria for the suitability of treatment with brexucabtagene autoleucel" is implemented within the inclusion criteria. It is not appropriate to assign patients to the comparison group who, according to the tumor board's decision, are not suitable for treatment with brexucabtagene autoleucel due to disease-related characteristics. Specific exclusion criteria for therapy with brexucabtagene autoleucel must be stated when implementing the above requirement. This includes at least a contraindication to cyclophosphamide and fludarabine due to the mandatory lymph depletion prior to therapy with brexucabtagene autoleucel.	**Project Plan Synopsis, Section 4.1.2 Inclusion Criteria for the Study Population, Section 4.2 Exclusion criteria:** Adjustment of inclusion and exclusion criteria to ensure positivity. **Project Plan Section 3.2 Study Scheme and Patient Flow:** Revision of Figure 1 (Patient Flow in Routine Practice Data Collection) deleting the group without recommendation to receive brexucabtagene autoleucel but assigned to the comparison group, to ensure positivity. **SAP Section 3.1 Eligibility Criteria:** Adjustment of inclusion and exclusion criteria to ensure positivity.

Adjustments		Implementation
b) Research question according to PICO: outcome; patient-reported outcomes (PRO)	The study protocol must define a consistent procedure regarding the transmission of the results of the respective PRO endpoints to the treating centers in terms of whether information is regularly not provided or is provided in full for both groups.	**Project Plan Section 2.2.3.4 Transmission of Results of Individual PROs to Treating Centers:** Definition of a procedure regarding transmission of PRO results to centers consistent for both treatment groups.
c) Research question according to PICO: outcome; adverse events (AEs) that result in hospitalization or prolong existing hospitalization or lead to death	The study protocol must define a joint evaluation of adverse events (AEs) leading to death and AEs leading to hospitalization or prolonging an existing hospitalization.	**Project Plan Section 2.2.4 Adverse Events:** Operationalization of serious adverse events (SAEs) as events leading to hospitalization or prolongation of hospitalization or death. **SAP Section 8.5.3.1 Adverse Events:** SAEs are defined as events that lead to hospitalization or prolongation of existing hospitalization or death so that a pooled assessment of these events is specified.
d) Research question according to PICO: outcome; specific AEs with CTCAE grade ≥ 3	For the specific adverse events mentioned in the study protocol, in addition to the indication of the respective severity, the respective criterion for a CTCAE grade 3 or higher stated in the CTCAE classification or the or the general criterion "significant impairment of the activity of daily living" must be recorded and these events must be evaluated separately.	**Project Plan Section 2.2.4 Adverse Events:** Insertion of recording and separate evaluation of specific AEs that significantly impair activities of daily living (CTCAE grade ≥ 3). **SAP Section 8.5.3.1 Adverse Events:** Adding analyses of AESI separated by severity with severe AESI defined as AESI with significant impairment of activity of daily living (according to CTCAE grade ≥3).
e) Data source: confounders	Confounders must be identified by a systematic literature search and complemented by expert interviews. The procedure for confounder selection carried out by the pharmaceutical company is not considered appropriate by the G-BA. The section on the identification and definition of the confounders in the study protocol therefore requires revision, taking into account the aspects outlined in the supporting reasons [1].	**Project Plan Section 6.6 Variables Considered for Matching:** Adoption of the extended list of confounders deemed as relevant by the G-BA. **SAP Section 8.2.1 Multiple Imputation:** Updated List of Confounders.

Adjustments		Implementation
	In the present case, the G-BA considers it possible to implement the requirements of the G-BA by defining the following factors as relevant confounders for the routine practice data collection - taking into account the benefit assessment performed on brexucabtagene autoleucel in the present indication in accordance with Section 35a of the German Social Code, Book V, the advice provided on the preparation of the study protocol and statistical analysis plan (SAP) for the present routine practice data collection, and the confounders already named in the study protocol: – Age – Sex – Eastern Cooperative Oncology Group (ECOG) performance status – Comorbidities – Disease stage – Extranodal disease – Bone marrow involvement – Lactate dehydrogenase (LDH) – Leukocyte count – Disease morphology – Presence of B symptoms – Mantle Cell Lymphoma International Prognostic Index (MIPI) – Number of prior lines of therapy – Prior autologous stem cell transplantation – Duration of prior BTK inhibitor therapy – Response to prior BTK inhibitor therapy – Ki-67 – TP53 mutation	

Adjustments		Implementation
f) Data source: exact definition or operationalization of exposure (type and duration of drug therapy and other concomitant therapies), clinical events and confounders	[The degree of fulfillment of this quality criterion is described in the study protocol as "project-specific", but the concrete meaning of this classification remains unclear.] A distinct list of variables of follow-up data for the routine practice data collection must be added. Moreover, the list of variables for the baseline data must be completed [the operationalization of the PRO collection at baseline is missing].	**Project Plan Section 5.1 Data Source: EMCL-R, Table 4 (Minimal Quality Criteria and Fulfillment by the EMCL-R):** Clarification of the meaning of “project-specific”. **Project Plan Section 5.3 Data Collected at Baseline and during the Course of the Study:** Insertion of the operationalization of PRO collection at baseline in a footnote of Table 5 (Baseline Data); insertion of Table 6 (Data during Treatment and Follow-up).
g) Data source: use of exact dates for the patient, the disease, important examinations and treatments / interventions	It must be clarified which specific data or examinations are subsumed under the term "assessments". For non-anamnestic data, exact dates are required. When revising the study documents, the pharmaceutical company must check whether there is a need for further adjustments to this quality criterion.	**Project Plan Section 5.1 Data Source: EMCL-R, Table 4 (Minimal Quality Criteria and Fulfillment by the EMCL-R):** Changing “Fulfillment” from “limited” to “yes” and insertion of further details on the use of exact dates.
h) Data source: strategies to avoid unintended selections during patient inclusion in order to achieve representativeness	The recruitment measures for the treatment groups defined in the study protocol must be adjusted to avoid selection effects. In this regard, measures must be defined for both treatment groups that lead to active recruitment at both national and international level.	**Project Plan Section 3.3 Screening Procedure:** Definition of recruitment measures to minimize selection effects with regard to the two treatment groups. **Project Plan Section 5.1 Data Source: EMCL-R, Table 4 (Minimal Quality Criteria and Fulfillment by the EMCL-R):** Insertion of a reference to the above-mentioned recruitment measures in a footnote.
i) Study design: recruitment of the study population	The involvement of countries or centers outside Germany must be clarified before the start of data collection and described in the study protocol.	**Project Plan Section 3.2 Study Scheme and Patient Flow:** Statement that European centers will be included in the routine practice data collection. **Project Plan Section 3.6.1 Procedure for the Inclusion of European Centers outside Germany**

Adjustments		Implementation
		in the Routine Practice Data Collection: Explanation of the inclusion of European centers in the routine practice data collection. **SAP Section 6.1 Data Source:** Adaption regarding the recruitment of other European countries. Further European centers will be included.
j) Study design or data analysis: information on the adaptation of routine practice data collection	In the study protocol and SAP, information must be added to implement the requirement to review the sample size estimate as part of the first interim analysis on the basis of the mortality endpoint and a shifted hypothesis boundary. In addition, information on discontinuation criteria due to futility must be added to the study protocol and SAP. The study documents must also specify that any changes to the implementation of the routine practice data collection and its analysis must be agreed on with the G-BA. This applies in particular to a possible change in the sample size estimate, the possible discontinuation of the routine practice data collection and the data review meeting (DRM) before database closure described in the study documents.	**Project Plan Section 1.2 Rationale for this Study:** Insertion of the G-BA requirement to calculate an updated sample size estimate based on the first and second interim analysis. **Project Plan Section 6.8.3 Updated Sample Size Calculation:** Insertion of an updated sample size calculation based on interim analyses after preliminary sample size calculation in this project plan. **Project Plan Section 6.9 Futility Assessment:** Insertion of a section on futility assessment. **SAP Section 4 Sample Size:** Section 4.1 Preliminary Sample Size and Section 4.2 Updated Sample Size was introduced in order to comply with G-BA's requirement to reassess the sample size calculation after the interim analyses. **SAP Section 3.2 Planned Analyses in Status Updates and Reports**: Futility assessment added. **SAP Section 1 (Introduction) and Section 5 (Data Review Meeting):** Clarification, that any additions or changes discussed in the DRM that affect the analyses prespecified in the SAP will have to be agreed by

Adjustments		Implementation
		the G-BA. Deletion of statement that decisions in the DRM minutes may potentially amend/overrule methodology planned in the SAP.
k) Data analysis: shifted hypothesis boundary	In the study protocol and SAP, taking into account the non-randomized study design, it should be specified that a shifted hypothesis boundary of 0.2 to 0.5, depending on the quality of data collection and analysis, will be used for data analysis and interpretation of results.	**SAP Section 8.1 Descriptive Analyses:** Statement regarding testing of hypotheses was deleted for consistency. The procedure regarding testing of hypotheses is described in detail in section 8.2.3 Effect Estimation and Interpretation. **SAP Section 8.2 Multiple Imputation and Propensity Score Matching:** A flow chart to give an overview of multiple imputation, propensity score procedure and interpretation of effect measures was added. Section 8.2.3 Effect Estimation and Interpretation, Adapting the assessment of the treatment effect after propensity score matching (PSM) taking into account a shifted null-hypothesis. **Project Plan Section 6 Statistical Considerations:** Reference to the detailed SAP.
l) Data analysis: propensity score procedure	The following aspects regarding the propensity score procedure must be added in the SAP: − Criteria for when visual examination of the propensity score histograms results in sufficient overlap and when it does not. − A decision algorithm to adjust the propensity score analysis when there is a lack of overlap and balance after applying the first procedure. Here, it must be specifically determined which alternative method is selected under which conditions for each case.	**SAP Section 8.2 Multiple Imputation and Propensity Score Matching:** Adding a flow chart to give an overview of multiple imputation, propensity score procedure and interpretation of effect measures. Adding Section 8.2.2 Propensity Score Matching Adapting matching method from Optimal matching with 2:1 ratio to balanced pairwise sequential nearest neighbor matching with variable 2:1 matching to improve precision and reduce potential bias. Adding calculation of areal overlap.

Adjustments		Implementation
	− What the consequences will be if no propensity score procedure can be found with which sufficient overlap and balance of the groups to be compared can be achieved. − Explanations on the necessity of a detailed description of the patient population resulting from the application of the respective propensity score procedure, including the necessity of a comparison of this patient population with the original target population of the routine practice data collection.	Adding the possibility of trimming if sufficient overlap and balance cannot be achieved with the initially defined procedure. Clarification that a detailed and comparative description of the patient populations prior and after PSM will be conducted in the course of reporting the results. Adding naïve comparisons as an alternative if sufficient overlap and balance cannot be reached or if the logistic regression model for PS does not converge. Adapting the assessment of the treatment effect using the criteria of a dramatic effect. **SAP Section 8.5.1 Descriptive analyses for baseline characteristics:** Clarification that the analysis of baseline characteristics will be conducted based on the original patient population (prior PSM) and after PSM, if applicable. Descriptive analyses after PSM will include the standardized mean difference compared to the original patient population.
m) Data analysis: handling of missing values	The definition that a confounder with more than 30% missing data is not to be considered in the adjustment is not appropriate and must be deleted from the SAP. Instead, the pharmaceutical company must describe in the SAP the effects of missing data on confounders and how the loss of information will be dealt with during the analysis. In addition, it must be described under which conditions the attempt to adjust for confounders is meaningful at all. The planned replacement of the month potentially leads to considerable distortions and is not appropriate. This definition must therefore be deleted. Instead, the	**SAP Section 6.3 Handling of Missing Data:** Summarizing efforts to avoid missing values Deletion of the restriction that confounders with more than 30% missing values will be discarded from the PS model. Deletion of imputation strategy for missing data for month. Adding section imputation of endpoint data. Adding statement on patients lost-to-follow-up. **SAP Section 6.7.3 Definitions of time windows for patient-reported outcomes:**

Adjustments		Implementation
	pharmaceutical company must state what efforts are being made to minimize the rate of missing values in the dates. Moreover, reasonable replacement strategies for missing data on endpoints must be defined in the SAP and corresponding measures must be described to minimize the proportion of missing values on endpoints.	Reshaping of tolerance windows to avoid missing returns of EORTC questionnaires. Consistently adapted in **Project Plan Table 3 (Procedure for the Collection of HRQoL using Patient Questionnaires)**. **SAP Section 8.2 Multiple Imputation and Propensity Score Matching:** Adding a flow chart to give an overview of multiple imputation, propensity score procedure and interpretation of effect measures. **SAP Section 8.2.1 Multiple Imputation:** Adding Section 8.2.1 Multiple Imputation for details on multiple imputation (MI).
n) Data analysis: EORTC QLQ-C30 and EORTC QLQ-NHL-HG29	For the analysis of the EORTC questionnaires, only a response threshold of 10 points is to be considered with regard to the responder analysis. The analysis of the response criterion of 15 points must therefore be deleted from the SAP.	**SAP Section 8.5.2.2 Morbidity and Section 8.5.2.3 Health-related Quality of Life:** Deletion of time to clinically relevant deterioration of 15 points as only a response threshold of 10 points is to be considered in the benefit assessment. (Consistently adapted in **Project Plan Section 2.2.2 Morbidity: Symptoms**.)
Recommended adjustments		
o) Research question according to PICO: EORTC-QLQ-C30	The scale "Financial difficulties" does not represent a symptom in the proper sense and is usually not used for benefit assessment. Therefore, collection of this scale can be omitted in the context of the routine practice data collection.	**Project Plan Section 2.2.2 Morbidity: Symptoms:** Clarification in a footnote that for technical reasons, the scale “Financial difficulties” will be collected (as part of the standard questionnaire), but not evaluated. **SAP Section 8.5.2.2 Morbidity:** Deletion of EORTC QLQ-C30 scale “financial difficulties” as this scale will not be considered in the benefit assessment.

Adjustments		Implementation
p) Research question according to PICO: further AE endpoints	In the context of benefit assessment, AEs which, according to the assessment of the study physician, are related to the treatment will not be considered. Therefore, the collection and analysis of such an AE endpoint can be omitted in the routine practice data collection.	**Project Plan Section 2.2.4 Adverse Events and Section 2.2.4.1 Serious AEs:** Omission of the documentation of AEs/SAEs related to treatment. **SAP Section 8.5.3.1 Adverse Events:** The assessment of AEs which, according to the assessment of the study physician, are related to the treatment were deleted as they will not be considered in the benefit assessment.
q) Data source: completeness of data	In the study protocol, the pharmaceutical company qualifies the completeness of the data collection in several places. In the study protocol, this is mainly related to the data collection, which takes place outside of the centers performing brexucabtagene autoleucel. In this regard, it should be noted that for brexucabtagene autoleucel in the present indication, the restriction of the authority to supply care was resolved on 21 July 2022. As clarified in the supporting reasons for the corresponding resolution, the authorized care providers must work towards the most complete data transfer possible. In addition, it is the responsibility of the pharmaceutical company to take appropriate measures to implement a valid routine practice data collection as well as the evaluation of the collected data and to enable a corresponding quantification of the additional benefit in the context of the new benefit assessment. Therefore, the G-BA recommends to revise the corresponding statements in the study protocol. If indicated, the pharmaceutical company should define and describe further measures that are necessary to ensure the completeness and quality of the data collection both in the brexucabtagene	**Project Plan Section 2.2.3.1 Consideration on Patient-reported Outcomes (PROs): Symptoms and HRQoL:** Revision of qualifying statements, insertion of / reference to measures to ensure completeness and quality of data collection.

Adjustments		Implementation
	autoleucel performing centers and outside the brexucabtagene autoleucel performing centers.	
r) Data source: ensuring scientific independence and transparency	To ensure scientific independence and transparency, it is recommended to delete the requirement that all abstracts, posters and publications have to be approved by the pharmaceutical company.	**Project Plan Section 11 Plans for Disseminating Study Results:** Deletion of the statement.
s) Data analysis: evaluation of PRO endpoints	Currently, the pharmaceutical company plans to evaluate the time to first worsening of the PRO endpoints. With relevantly different observation durations between the treatment arms, the time to first change is the only responder evaluation that can be meaningfully interpreted for the benefit assessment. However, according to the study protocol, no early end of observation is planned in the context of the routine practice data collection. The pharmaceutical company could therefore also consider additionally defining an operationalization that takes into account the follow-up observations even after the initial deterioration, for example in the form of a once- or twice-confirmed deterioration. As sensitivity analyses, comparisons of the mean change from baseline are provided for each observation time point. The G-BA also recommends defining responder analyses with a response threshold of 10 points for each observation time point as part of the sensitivity analyses.	**Project Plan Section 2.2.2 Morbidity: Symptoms:** Insertion and definition of endpoint “once-confirmed clinically relevant deterioration”. **SAP Section 6.7.2 Time to (once-confirmed) clinically relevant deterioration:** Adding endpoint “once-confirmed clinically relevant deterioration”. **SAP Section 8.5.2.2 Morbidity and Section 8.5.2.3 Health-related Quality of Life:** Adding endpoint “once-confirmed clinically relevant deterioration”.

Source: [1-3]

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 174 patients in the brexucabtagene autoleucel arm have completed at least 36 months follow-up **and** a minimum of 87 patients in the comparator arm have completed at least 36 months of follow-up
For further details, see Section 6.11.	

Table of Contents

List of Tables

List of Figures

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 [4, 5].

Most patients are male, and the median age of diagnosis is 68 years [6]. 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) [7].

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 [8]. 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 [9-14] 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 [13], with recent evidence confirming that post-BTKi treatments vary widely and are associated with poor median survival [15].

Despite improvements in treatment, most patients continue to develop relapse and subsequently refractory disease and finally die due to the underlying lymphoma [16-19]. 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 [20]. 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; [5]), 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 [21].

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 2) [22, 23]. In the present version of this document (version 2.0), Table 2 has been modified to reflect the modified G-BA requirements for this routine data collection (i.e., requirements included in the resolution published on the 16 March 2023 [24, 25]), which were published after the IQWiG and G-BA evaluated the study documents that were initially submitted by the company on the 21 December 2022.

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 [26]. 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 [27].

Table 2. 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**[c] - Serious adverse events (*operationalized as events leading to hospitalization or prolongation of existing hospitalization or to death; overall rate*[d]) - *Adverse events leading to hospitalization or prolongation of existing hospitalization*[e] - Specific adverse events (with indication of the respective degree of severity *including specific adverse events that lead to a significant impairment of the activity of daily life or with CTCAE grade ≥ 3*[f])

[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 (Rituximab, Dexamethasone, high-dose Cytarabine, Cisplatin)
- R-BAC (Rituximab, Bendamustine, Cytarabine)
- Temsirolimus
- R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone)
- R-Cb (Rituximab, Chlorambucil)

[c] Discontinuation due to adverse events (overall rate) was removed.

[d] Text in italics replaced "SAE; overall rate" of previous version (version 1.0).

[e] Text in italics replaced "severe adverse events" of previous version (version 1.0).

[f] Text in italics was added.

Source: [22, 24, 25]

The G-BA set further requirements for study design and data source for the present routine practice data collection [22] 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. An updated sample size estimate is expected to be calculated on the basis of the first interim analysis using the endpoint overall survival.

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 (Rituximab, Dexamethasone, high-dose Cytarabine, Cisplatin)
- R-BAC (Rituximab, Bendamustine, Cytarabine)
- Temsirolimus
- R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone)
- 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 [28, 29]. 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 [29]. The outcomes defined by the G-BA are the following (Table 2):

- **Mortality:** Overall survival
- **Morbidity:** Symptoms
- **Health-related Quality of Life**
- **Adverse Events**
    - Serious adverse events (operationalized as events leading to hospitalization or prolongation of existing hospitalization or to death; overall rate)
    - Adverse events leading to hospitalization or prolongation of existing hospitalization
    - Specific adverse events (with indication of the respective degree of severity including specific adverse events that lead to a significant impairment of the activity of daily life or with CTCAE grade ≥ 3); including serious specific adverse events

In the following sections, the endpoints are defined. Additionally, some considerations are given to the implementation and feasibility of collecting such endpoints. Furthermore, all mandatory and most of the recommended adjustments required by the G-BA as published in the resolution of 16 March 2023 are implemented.

2.2.1. Mortality: Overall Survival

Endpoint as requested by the G-BA	Overall survival
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.

2.2.2. Morbidity: Symptoms

Endpoint as requested by the G-BA	Symptoms
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) [30] version 3.0 and the EORTC Quality of Life Questionnaire Non-Hodgkin Lymphoma High Grade 29 Module (QLQ-NHL-HG29) [31] (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.** Constipation **8.** Diarrhea

	9. Financial difficulties[a] The following analyses are planned to be conducted: - Time to clinically relevant deterioration, defined as a decrease in score of at least 10 points (scale range 0-100) - Time to once-confirmed clinical relevant deterioration, defined as a decrease in score of at least 10 points (scale range 0-100) at 2 consecutive assessments - 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:** **1.** Symptom burden **2.** Neuropathy **3.** 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.

[a] According to the G-BA, the scale "Financial difficulties" does not represent a symptom in the proper sense and is usually not used for benefit assessment [1]. For technical reasons, this scale will nevertheless be collected (as part of the standard questionnaire), but not evaluated.

2.2.3. Health-related Quality of Life (HRQoL)

Endpoint as requested by the G-BA	Health-related Quality of Life
Operationalization in present study	In the present study, the Health-related Quality of Life will be assessed using the EORTC QLQ-C30 [30] version 3.0 and the EORTC QLQ-NHL-HG29 [31] (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: **1.** Emotional impact **2.** Worries/fears about health and functioning For full details on the statistical methods please refer to the Statistical Analysis Plan.

2.2.3.1. 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 [5]. 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. General appropriate measures to ensure completeness of data collection are included below (implementation of a trust center), in Section 3.3 (recruitment measures) and in Section 8 (control of data quality).

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 [29]. The implementation of a trust center to improve the likelihood of successfully collecting patient-reported outcome data are described below in this section.

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% [29]. 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 [32]. The trust center described below will handle all patients equally regardless of their treatment arm, and thereby help minimize differences in response rates between the two arms.

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
- Telephone number
- 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. In order to increase the response rates, it is currently being discussed that before the submission of the questionnaire, the patient will receive a phone call in which the procedure for collecting the PROs will be explained verbally. The patient will also be given a contact number to call in case there are questions about completing the questionnaire. 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, the patient will be contacted by telephone twice and up to two reminder letters will be sent by IMBEI.

2.2.3.2. 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 [33] 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 [34]. 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.

2.2.3.3. 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 [35].

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 cell infusion were not reflected by the survey times chosen [36]. 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 3):

Table 3. Procedure for the Collection of HRQoL using Patient Questionnaires

Time Point	Theoretical Day (Tolerance Window)	Responsible for Administration of PRO Instruments
Baseline	Day 0 (Day 0 – Day 27)	Trust center (IMBEI)
Month 1	Day 31 (Day 28 – Day 61)	Trust center (IMBEI)
Month 3	Day 92 (Day 62 – Day 137)	Trust center (IMBEI)
Month 6	Day 183 (Day 138 – Day 274)	Trust center (IMBEI)
Month 12	Day 366 (Day 274 – Day 458)	Trust center (IMBEI)
Month 24	Day 731 (Day 639 – Day 823)	Trust center (IMBEI)
Month 36	Day 1096 (Day 1004 – Day 1188)	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.

2.2.3.4. Transmission of Results of Individual PROs to Treating Centers

In the resolution of 16 March 2023, the G-BA required the specification of a consistent procedure regarding the transmission of PRO information to the treating centers [1-3]. In order to fulfill this requirement, the project plan specifies the following: to ensure consistency, patient-specific PRO information will not be made available to physicians or centers in either treatment group. The reasons for this decision include the following:

- Sharing the results of the PROs without a concrete guidance as to how modify treatment or offer supportive measures does not seem adequate.

- The decision on sharing the PRO results with the physician has to be taken individually by the patient, while incorporating PRO results in the treatment decisions must be individually taken by the treating physicians. Neither the registry nor the pharmaceutical company has any influence on these two mentioned individual decisions. This could lead to an imbalance where it is not clear how the availability of this additional information would lead to modifications in treatment decisions and, therefore, HRQoL outcomes.
- The goal of the routine practice data collection is to compare the outcomes between the intervention and the comparator. The development or incorporation of tailored treatment of QoL deficits such as counseling or other measures (that have been mentioned in the literature cited in the addendum of the IQWiG) is not an objective of the study.

2.2.4. Adverse Events

Endpoint as requested by the G-BA	Adverse events (AE)
Operationalization in present study	In the present study, the following adverse events will be documented: - Serious adverse events (SAEs; operationalized as events that lead to hospitalization or prolongation of hospitalization or death; overall rate) - Adverse events leading to hospitalization or prolongation of existing hospitalization (overall rate) - Specific adverse events (= adverse events of special interest, AESI) with indication of the respective severity - Severe AESIs with "significant impairment in activities of daily living" (CTCAE grade ≥ 3) - Serious AESIs (defined as AESIs that lead to hospitalization or prolongation of hospitalization or death) (not required by the resolution but added to meet the G-BA requirements in reporting [module 4]) AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

2.2.4.1. 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.

In the G-BA resolution of 16 March 2023 [24, 25] the G-BA modified the wording on the operationalization of serious AEs as follows: “operationalized as events leading to hospitalization or prolongation of existing hospitalization or to death; overall rate”.

2.2.4.2. Severe AEs (replaced in G-BA resolution by adverse events leading to hospitalization or prolongation of existing hospitalization)

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.

In the G-BA resolution of 16 March 2023 [24, 25] the G-BA replaced “severe AEs” by the definition used in the previous paragraph: “Adverse events leading to hospitalization or prolongation of existing hospitalization”. In this context, events that lead to hospitalization or prolongation of existing hospitalization would be collected in the category serious AEs (Section 2.2.4.1) and in the present category (adverse events leading to hospitalization or prolongation of existing hospitalization). The difference between these two categories would be the inclusion of adverse events leading to death (which is to be included under the category “serious AEs”).

2.2.4.3. Therapy Discontinuation Due to AEs

Brexucabtagene autoleucel is a one-time treatment and therefore discontinuation due to AE 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 [37]: *“The proportion of subjects who discontinue treatment due to AEs before CAR T cell infusion would be also reflected in* the overall rate of subjects who did not *receive CAR T cell infusion. Therefore, taking into account the interventions and study design defined in the present requirement for the routine practice data collection, it appears appropriate in principle to refrain from collecting the endpoint ‘*discontinuation *due to AE’.”*

In the G-BA resolution of 16 March 2023 [24, 25] the G-BA agreed to remove this category (therapy discontinuation due to AEs) from the routine data collection requirements.

2.2.4.4. 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. In the G-BA resolution of 16 March 2023 [1], it is points out that in the context of benefit assessment, treatment-related AEs as judged by the physician will not be considered. Therefore, the collection and analysis of treatment-related AEs will be omitted in the present routine practice data collection.

2.2.4.5. 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.

However, in the G-BA resolution of 16 March 2023 [24, 25], it is stated that it is necessary to collect and evaluate the below listed AESIs as well as their severity grade (as specific AEs leading to significant impairment of the activities of daily life / with a CTCAE grade ≥ 3) [1-3]. The present project plan has been adapted accordingly.

Additionally, in the G-BA resolution that amends the initially established PICO schema [24, 25], the following specific AEs (interpreted here as adverse events of special interest) that had been proposed in Version 1.0 of the project plan, are agreed on and formally incorporated in the PICO schema:

- 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

2.2.4.6. Considerations on the Duration of AE Assessment

The investigator is responsible for reporting all SAEs and AESIs 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 [29] and of the G-BA, which specify the procedure in the rules of procedure of the G-BA [28] 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 who 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 [37]. 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.

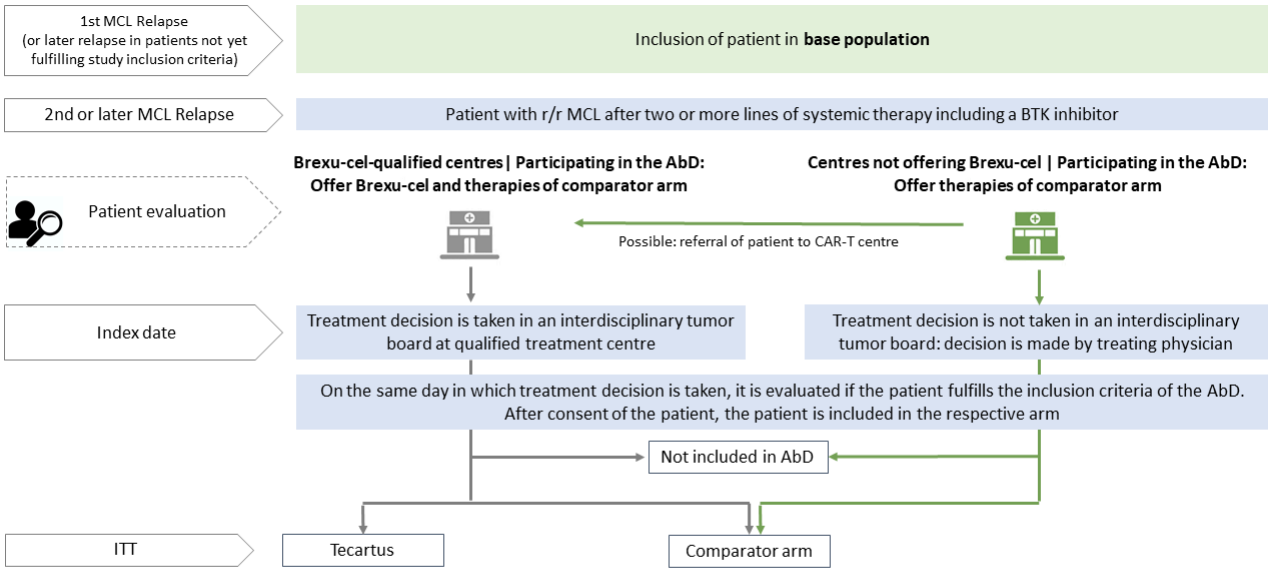
Patients are treated with brexucabtagene autoleucel in dedicated centers. There, the treatment decision is usually made by an interdisciplinary tumor board. Yet, the final therapy decision can also be made by the patient, e.g., if the tumor board advises him or her to be treated with brexucabtagene autoleucel, but the patient chooses a therapy from the comparator arm, 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, centers participating in the EMCL-R in other European countries with a comparable care structure to Germany will be included. The ongoing selection of further centers depends on the fulfillment of requirements specifically defined for the purpose of the present study. Involvement of centers or countries outside Germany 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, patients will be assessed by their treating physicians at either a brexucabtagene autoleucel qualified center or at a center/practice that is not qualified for administration of brexucabtagene autoleucel. Centers that are qualified for the administration of brexucabtagene autoleucel can offer both, brexucabtagene autoleucel and the therapies of the comparator arm. Centers/practices not qualified for the administration of brexucabtagene autoleucel can only offer the

therapies that are part of the comparator arm. Physicians at centers not qualified for CAR T can refer the patient to brexucabtagene autoleucel qualified centers in case this is the preferred therapy.

On the same day on which the treatment decision is taken, it is evaluated if the patient fulfills the inclusion criteria of the routine practice data collection (AbD). After consent of the patient, the patient is included in the respective arm.

In order to allow for data collection at the time of eligibility for study inclusion, an "alert system" is being implemented. Lymphoma tumor board coordinators at CAR T qualified centers as well as coordinators or respective staff at non-CAR T centers will be contacted at the same frequency, i.e. 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.

To avoid selection effects during recruitment into the two treatment groups as much as possible, the following recruitment measures are defined:

- **Active regular approach to the centers:** Contact of CAR T qualified and not qualified centers to screen for MCL patients who may qualify for study inclusion (via MCL patient alert / email list server) will be carried out equally and at the same frequency (weekly) at both types of centers and for both treatment arms. All patients in first relapse will be followed up and regular calls will be extended to non-CAR T sites to ask for patients in their second relapse. Although these may be referred to CAR T centers, they will not be lost for the comparator arm in case they are not referred (e.g., due to patient wish).
- **Information letter:** All EMCL-R sites will continuously and uniformly be updated via information letters (sent by email).
- **Training:** All EMCL-R sites will be trained consistently and uniformly at study start and new staff will also be trained during the course of the present study. Re-training of sites will be initiated if data review reveals relevant deficiencies.
- **Hotline:** A hotline will be available uniformly for all EMCL-R centers during business hours to support the sites with any questions that arise.

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 (Day 0 – Day 27) from 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.

Centers that offer brexucabtagene autoleucel („qualified centers“) as well as centers that do not offer brexucabtagene autoleucel will be included in the routine practice data collection. **The procedure for including these types of centers is identical: all centers are contacted both in writing and by telephone with the same frequency.**

Patients receiving brexucabtagene autoleucel therapy can only be treated at CAR-T cell therapy-qualified centers, and all such centers will be contacted by the EMCL-R. Patients receiving comparator therapies may be treated at both CAR-T cell therapy-qualified centers and non-qualified centers/facilities.

German centers not qualified for CAR T are already included in the EMCL-R. The German centers in the EMCL-R, basically both CAR T qualified and not qualified, are distributed across all of Germany. The German centers included in the EMCL-R have a certain focus on the treatment of patients with MCL, because MCL is a rare disease. In particular, the treatment of advanced patients with R/R MCL requires experience with these patients, which can only be guaranteed at centers with a certain degree of specialization. For these reasons, the EMCL-R includes, by its own estimate, about 95% of the MCL treatment centers in Germany.

The choice of European centers outside Germany is based on their specialization in the treatment of patients with R/R MCL, in addition to no regular availability of brexucabtagene autoleucel (e.g., due to lack of reimbursement) to allow the recruitment of sufficient patients for the comparator arm, and willingness to participate in the routine practice data collection.

For the brexucabtagene autoleucel arm, qualified centers 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 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 [27].

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 [27]. These requirements include sufficient training of healthcare personal regarding CAR-T cell 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 cell therapy.

At present (01 April 2023), a total of 40 centers are qualified in Germany 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 qualified centers.

In addition, centers in Germany as well as selected other European member countries 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). Currently (01 April 2023), 26 non-CAR T centers are active in the EMCL-R and will be invited to contribute eligible patients to this study. The procedure for including not qualified centers is identical to the inclusion of qualified centers: all centers will be contacted both in writing and by telephone with the same frequency.

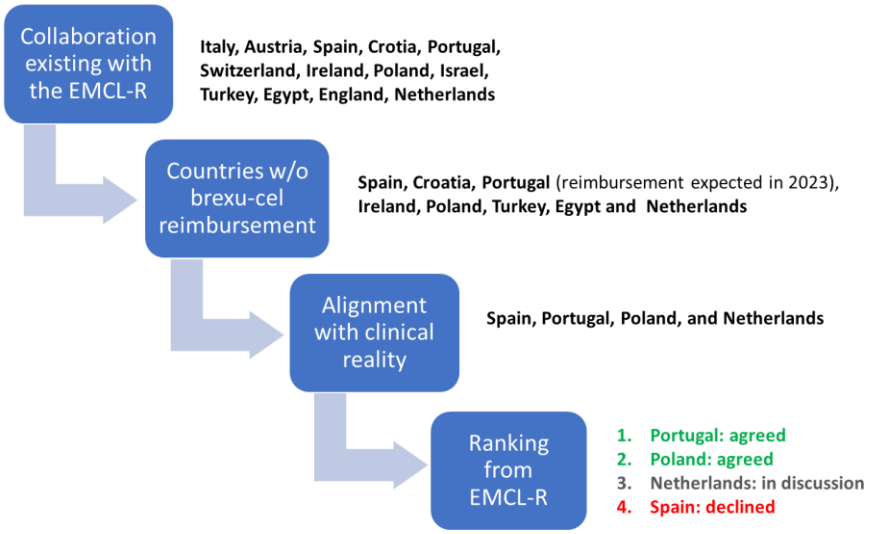
3.6.1. Procedure for the Inclusion of European Centers outside Germany in the Routine Practice Data Collection

On the one hand, the inclusion of German centers ensures that routine care practice for MCL patients in Germany is optimally reflected in the study. On the other hand, it is assumed that routine care in several other European countries participating in the EMCL-R is sufficiently similar to that in Germany. Therefore, recruitment of patients from other European EMCL-R sites is explicitly intended. 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 [5].

Based on the G-BA request, a plan was developed to include further selected European centers in this study (as depicted below). The selection of the specific centers in other European countries is based on scientific interest in the treatment of MCL patients and reflects the centers' activity in the EMCL network. Each country within the EMCL-R is represented by a country lead investigator. As the main goal of including patients that are treated in centers outside Germany is to recruit enough patients for the comparator arm, the centers of those countries in which brexucabtagene autoleucel is available (i.e., can be prescribed and will be reimbursed) were excluded. Countries without enough similarity to German clinical care (as based on physician judgement) were also excluded (see Figure 2). Based on the previous criteria, four centers (one in each country, representing the respective countries' lead investigator site) were identified in the following countries: Portugal, Poland, Spain and the Netherlands. These centers were contacted by the EMCL-R team in Mainz: The contacted center in Spain was unable to agree to participate in the data collection due to their retrospective data collection set-up. The participation of the center in the Netherlands is still under discussion. The center in Portugal and the center in Poland have agreed to participate in the routine data collection, which was re-confirmed on 11 April 2023. Reimbursement for brexucabtagene autoleucel in Portugal is expected for Q2 2023; nevertheless, currently there are only two qualified treatment centers for brexucabtagene autoleucel. Therefore, it is anticipated that a considerable number of patients with R/R MCL may not be treated with brexucabtagene autoleucel and thus, represent potential candidates for the comparator arm of this study.

With the aim to further increase the number of patients that could receive therapies in the comparator arm, the sponsor of the EMCL-R remains vigilant regarding additional centers that could be included in the present routine data collection. Potential additional candidates are further centers in Portugal, Poland, and the Netherlands, as well as in Austria and Italy. The main reason for considering centers in Austria and Italy is the similarity with the German clinical care practice. Nevertheless, centers in Austria and Italy have access (and reimbursement) to brexucabtagene autoleucel and therefore, the number of patients eligible for the comparator arm might remain low.

Figure 2. Selection Criteria for European Centers to be Included in the Routine Data Collection



3.7. Number of Study Subjects

The estimated preliminary sample size for analysis is 261 patients in a 2:1 ratio allocation (i.e., 174 in the brexucabtagene autoleucel arm and 87 in the comparator arm).

Please refer to the statistical consideration section of the project plan (Section 6.8.2) for preliminary 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

4.1.1. 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

4.1.2. 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
- 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 (Rituximab, Dexamethasone, high-dose Cytarabine, Cisplatin)
    - R-BAC (Rituximab, Bendamustine, Cytarabine)
    - Temsirolimus
    - R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone)
    - 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 Criteria for the Study Population

Patients will not be included in the study if one or more of the following criteria apply:

- ECOG > 2
- Absolute contraindication to fludarabine and cyclophosphamide, including history of severe hypersensitivity reaction to these
- Acute impaired organ function (cardiac, pulmonary, renal, hepatic)
- Active uncontrolled infection

Exclusion criteria have been revised based on the requirements of the G-BA Resolution of 16 March 2023 and adapted based on feedback from five clinical experts from five different hospitals in Germany. The selected clinical experts not only regularly assess and treat patients with R/R MCL but are also involved in tumor board discussions, in which the indication for the treatment of a patient with brexucabtagene autoleucel is determined.

On top of the aforementioned inclusion and exclusion criteria, which ensure the fulfillment of positivity, the physician will answer the following question which will reiterate the suitability of the patients in the study: "Was the patient at the time point of treatment decision eligible for treatment with both, brexucabtagene autoleucel and at least one of the therapies in the comparator arm? "

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 4.

Table 4. 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 (i.e., only relevant concomitant therapies will be collected as part of routine practice data collection; data collection will be prospective only)
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	yes (all exact dates required for the routine practice data collection will be recorded, including index date, date of baseline visit, PROs, start dates of AEs and AESIs, treatment [brexucabtagene autoleucel, patient-individual therapy, follow-up therapy / treatment switch], end of observation)
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)[a]
10	Specifications to ensure completeness of data per survey date and completeness of survey dates	eCRF: mandatory fields, medical review, queries;

Number	Minimal Quality Criteria As Depicted In G-BA's Resolution (21 July 2022)	Fulfillment by Registry
		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

[a] Measures to avoid selection effects during recruitment into the two treatment groups are defined in Section 3.3.

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.

5.2. Database and Data Management

Patients will be recruited from the EMCL-R using sites in Germany and selected European countries outside Germany (Section 3.6). 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.

5.3. Data Collected at Baseline and during the Course of the Study

Date collected at baseline for all enrolled patients are presented in Table 5. 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). Data collected during the course of the study are presented in Table 6.

Table 5. Baseline Data

Demographic data	**Variable/Description**	**Collected in EMCL-R at start of routine practice data collection?[a]**
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
Age categorical	Categorical (< 65, ≥ 65 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		
Comorbidities (Cardiac disease; Diabetes; Cerebrovascular disease; Depression/anxiety requiring psychiatric consultation or treatment; Known infection with Hepatitis B/C or HIV; Renal dysfunction; Pulmonary dysfunction; Prior solid tumor or nonmelanoma skin cancer)[b]	Categorical (Y/N for each comorbidity)	Yes
Disease stage according to Ann Arbor	Categorical (multiple choice: Stages I, II, III, IV, unknown)	Yes
Age at diagnosis or Date of MCL diagnosis (year of diagnosis – year of birth)	Quantitative [years]	Yes
ECOG performance status	Categorical (multiple choice: 0, 1, 2, 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

Demographic data	**Variable/Description**	**Collected in EMCL-R at start of routine practice data collection?[a]**
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
Disease morphology	Categorical (multiple choice: classical, blastoid, pleomorphic, 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
SOX-11 expression	Categorical (positive/negative/unknown)	Yes
LDH level	Quantitative [U/l]	Yes
LDH upper limit of normal (ULN)[c]	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 of prior SCT (not mutually exclusive)	Categorical (multiple choice: autologous, allogeneic, unknown)	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
Duration of prior BTKi therapy	Quantitative [days]	Yes

Demographic data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
Response to prior BTKi therapy	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, not evaluable [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[d]		
Symptoms by means of 9 symptom scales from the EORTC QLQ-C30[e]	Quantitative (scale scores)	Yes
Symptoms by means of 3 symptom scales from the EORTC QLQ-NHL-HG29	Quantitative (scale scores)	Yes
Health-related quality of life[d]		
HRQoL by means of EORTC QLQ-C30 function scales, global scale	Quantitative (scale scores)	Yes
HRQoL by means of EORTC QLQ-NHL-HG29	Quantitative (scale scores)	Yes

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

[b] The specific comorbidities collected in the registry have been selected by EMCL-R experts based on the HCT-CI [38] and relevance for MCL patients.

[c] LDH measured by < ULN vs ≥ ULN [39].

[d] Operationalization of the PRO collection at baseline: a time window of 28 days from the index date (D0 – D27) applies in order to ensure that baseline data are available (Section 3.4).

[e] The scale “Financial difficulties” will be collected, but not evaluated (Section 2.2.2).

Table 6 Data during Treatment and Follow-up

Data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
Induction Treatment		
Induction Treatment	Categorical (Started, Not Started yet, No Induction Treatment)	Yes
Treatment within Clinical Trial?	Categorical (Y, N)	Yes
Start of Induction Treatment	Quantitative – date (dd.mm.yyyy)	Yes
Therapy Scheme	- 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 (Rituximab, Dexamethasone, high-dose Cytarabine, Cisplatin) - R-BAC (Rituximab, Bendamustine, Cytarabine) - Temsirolimus - R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone) - R-Cb (Rituximab, Chlorambucil)	Yes
Number of cycles	Quantitative	Yes
Other treatment	Categorical (Y, N)	Yes
Radiotherapy	Categorical (Y, N)	Yes
Dose	Quantitative	Yes
CNS Prophylaxis	Categorical (Y, N)	Yes
Type of CNS Prophylaxis	Categorical (HD-MTX, MTX-AraC)	Yes

Data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
Other	Categorical (Y, N)	Yes
End of Induction	Categorical (Y, N)	Yes
End Date of Induction	Quantitative – date (dd.mm.yyyy)	Yes
Reason for End of Induction	Categorical (Completion of treatment, Failure of response/, Intolerance/Toxicity, Patient will/ Physician's decision/ Progression)	Yes
Consolidation Treatment		
Consolidation Treatment	Categorical (Started, Not Started yet, No Consolidation Treatment)	Yes
Start of Consolidation Treatment	Quantitative – date (dd.mm.yyyy)	Yes
Type of Consolidation	Categorical (Autologous Transplantation (High Dose Therapy), Allogenic Transplantation, Radiation, Received CAR therapy or other genetically modified T-cell therapy, Other)	Yes
Autologous Transplantation: Conditioning Regimen	Categorical (TBI, BEAM, Other)	Yes
Allogenic Transplantation	Categorical (Mini, Full)	Yes
End of Consolidation	Categorical (Y, N)	Yes
End Date	Quantitative – date (dd.mm.yyyy)	Yes
Reason for End of Consolidation	Categorical (Completion of treatment, Failure of response/, Intolerance/Toxicity, Patient will/ Physician's decision/ Progression)	Yes
Maintenance Treatment		
Maintenance Treatment	Categorical (Started, Not Started yet, No Maintenance Treatment)	Yes
Start of Maintenance Treatment	Quantitative – date (dd.mm.yyyy)	Yes
Type of Maintenance Treatment	Categorical (multiple choice: Rituximab, Lenalidomid, Ibrutinib, Other)	Yes
End of Maintenance	Categorical (Y, N)	Yes
End Date	Quantitative – date (dd.mm.yyyy)	Yes

Data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
Reason for End of Maintenance	Categorical (Completion of treatment, Failure of response/, Intolerance/Toxicity, Patient will/ Physician's decision/ Progression)	Yes
Symptoms[b]		
EORTC QLQ-C30 symptom scales and items (fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties[c])	Quantitative (scale scores)	Yes
EORTC QLQ-NHL-HG29 scales symptom burden, neuropathy, and physical condition/fatigue	Quantitative (scale scores)	Yes
Health-related quality of life[b]		
EORTC QLQ-C30 functional scales (physical, emotional, cognitive, role, and social functioning) and the global QoL score	Quantitative (scale scores)	Yes
EORTC QLQ-NHL-HG29 scales emotional impact and worries/fears about health and functioning	Quantitative (scale scores)	Yes
Adverse Events		
Event term	Text	Yes
Seriousness	Categorical (Serious AE [i.e., AE leads to hospitalization, prolongation of hospitalization, or death], Non-serious AE)	Yes
Serious Criteria	Categorical (Hospitalization, Prolongation of hospitalization, Death)	Yes
AE Onset Date	Quantitative – date (dd.mm.yyyy)	Yes
Adverse Events of Special Interest - Cytokine release syndrome (CRS) - Neurological events (including Immune effector cell-associated neurotoxicity	Categorical (Y, N)	Yes

Data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
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		
Significant impairment of activity of daily living / CTCAE grade ≥ 3 only for Adverse Events of Special Interest (listed in row above)	Categorical (Y, N)	Yes
Resolution Date	Quantitative – date (dd.mm.yyyy)	Yes
End of Observation		
Date of End of Observation (incl. date of death)	Quantitative – date (dd.mm.yyyy)	Yes
Reason for End of Observation	Categorical (Withdrawal of informed consent, Lost-to-follow-up, Death due to any cause, Other)	Yes
Reason of Death	Categorical (Primary disease, Toxicity, Secondary Cancer, Other)	Yes

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

[b] Operationalization of the PRO collection at baseline: a time window of 28 days from the index date (D0 – D27) applies in order to ensure that baseline data are available (Section 3.4).

[c] The scale “Financial difficulties” will be collected, but not evaluated (Section 2.2.2).

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 a treatment decision for their next line of therapy, based on which patients will be assigned to either treatment arm. The treatment decision will be based on different factors such as tumor board recommendation, availability of therapy, physician's choice, and patient's choice.
- **As-treated Set (ATS):** This group includes eligible patients who received therapy with brexucabtagene autoleucel or a patient-individual therapy. Patients will be assigned to treatment groups based on their initial treatment.

6.2. Operationalization of Endpoints in the Study

Please refer to Section 2.2 for 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 category and number of missing values.

For binary 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.

Time-to-event analysis will be conducted using the Kaplan-Meier method 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. Estimation of Hazard Ratio will be derived from a Cox proportional hazard model.

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 [40-43]. For this study, propensity score (PS) matching will be used to balance the confounders of the two study arms and to allow assessment of overlap and balance [44]. If possible, multiple imputation will be used to replace missing values in confounders.

If the assumptions for PS matching cannot be confirmed or the logistic model for PS calculation does not converge, naïve comparisons will be conducted.

Further details about multiple imputation and methods to calculate and interpret the treatment effect 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 7, 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 7):

- **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 7)
- **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 7. Confounding Factors: Identification in a Systematic Literature Review and Clinical Evaluation

Grouping	Confounder	Result of Expert Review	Currently Collected in EMCL-R[a]
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

Grouping	Confounder	Result of Expert Review	Currently Collected in EMCL-R[a]
	Ki-67	Substantial impact[b]	Yes (plus checkbox: Not Done)
	LDH	Substantial impact [b]	Yes
	Secondary chromosomal aberration	Not routinely assessed in real world setting	No
	TP53 mutation	Substantial impact	Yes
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)	Yes[c]
	ECOG performance score	No substantial impact (assessed in context of inclusion criteria, positivity)[b]	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)

Grouping	Confounder	Result of Expert Review	Currently Collected in EMCL-R[a]
	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)
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

[a] As of 21 December 2022.

[b] Included in MIPI.

[c] The following comorbidities are currently (March 2023) collected in the EMCL-R. The specific comorbidities collected in the registry have been selected by EMCL-R experts based on the HCT-CI [38] and relevance for MCL patients:

- Cardiac disease
- Diabetes
- Cerebrovascular disease
- Depression/anxiety requiring psychiatric consultation or treatment

- Known infection with Hepatitis B/C or HIV
- Renal dysfunction
- Pulmonary dysfunction
- Prior solid tumor or non-melanoma skin cancer

In the previous version of the present document (Version1.0) it was stated that only confounders rated as having a substantial impact would be considered for propensity score matching. Nevertheless, due to the observations contained in the G-BA resolution of 16 March 2023, this procedure has been modified (see Section 6.6).

6.6. Variables Considered for Matching

In the resolution of 16 March 2023, the G-BA states that the procedure for confounder selection described in Section 6.5 and Appendix 2 of this project plan was not considered appropriate [1-3]. In the case at hand, however, taking into account the benefit assessment performed on brexucabtagene autoleucel in MCL in accordance with § 35a SGB V, the advice provided on the preparation of the study plan and SAP for the present routine practice data collection and the confounders already identified in the study protocol, the G-BA considers it possible to implement the G-BA's requirements by defining the following factors as relevant confounders for the routine practice data collection:

- Age (years) (< 65, ≥ 65)
- Sex (female, male)
- ECOG-PS (0, 1, 2)
- Number of comorbidities (0, 1, 2+) (based on modified HCT-CI)
- Mantle Cell Lymphoma International Prognostic Index (MIPI) score: (low risk, intermediate risk, high risk, unknown)
- Lactate dehydrogenase (LDH) [U/l] (< ULN vs. ≥ ULN)
- Leukocyte count [µl/l]
- Disease state according to Ann Arbor (I, II, III, IV, unknown)
- Extranodal manifestation at primary diagnosis (yes, no, unknown)
- Bone marrow involvement (yes, no, unknown)
- Disease morphology (classical, blastoid, pleomorphic, CLL-like, other)
- Presence of B symptoms (yes, no, unknown)
- Ki-67 (< 30% vs. ≥ 30%)
- TP53 mutation (yes, no, unknown)
- Prior therapies:
    - Number of prior lines of therapy (2, > 2)
    - Type of prior SCT (allogeneic, autologous, none)
    - Duration of prior BTKi therapy (months)
    - Response to prior BTKi therapy (refractory, relapsed, intolerant)

Although in the G-BA resolution of 16 March 2023 the confounders that are considered as relevant are listed, there is no information regarding the operationalization that should be implemented for these. Regarding

the confounder “comorbidities” the number of comorbidities (0, 1, ≥2) has now been specified. Nevertheless, it is uncertain if the number thereof or only specific types of comorbidities play a role as confounder.

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

6.8.1. 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 [45]. 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 [16-19]. Furthermore, brexucabtagene autoleucel is depicted in German Onkopedia guidelines [5] as the preferred treatment for this patient population.

Despite these limitations, the sample size calculation for the present study was conducted based on the assumptions described by IQWiG in their sample size calculation.

6.8.2. Preliminary Sample Size Calculation

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 was applied. 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.

Based on the assumptions described above, the sample size calculation was performed using the software R [46] with the library *gsDesign* [47]. The total number of patients was derived from the necessary number of events (calculated with *nEvents*) and the allocation ratio, assuming a study duration of 36 months, using the following formula:

$$total\ number\ of\ patients = \frac{(allocation\ ratio + 1) \times number\ of\ events}{0.32\ \times allocation\ ratio + 0.74}$$

The approach for the sample size calculation was chosen in an attempt to reproduce the sample size calculation reported by IQWiG for a 1:1 allocation ratio. Applying this approach to a 1:1 allocation ratio resulted in an estimated sample size of 200 patients (106 events), which approximates the results reported by IQWiG (190 patients [100 events]). For a 2:1 allocation ratio, the calculation yielded an estimated sample size of 261 patients (174 in the brexucabtagene autoleucel arm and 87 in the comparator arm).

6.8.3. Updated Sample Size Calculation

Due to a high degree of uncertainty regarding patient enrollment, effect measures and event rates, a re-evaluation of the sample size calculation will be conducted in collaboration with G-BA after the first and second interim analysis, 18 and 36 months after start of the routine practice data collection, respectively. The sample size will be re-calculated using the same method and assumptions as described above, applying effect estimates and event rates generated for OS in the respective interim analyses. Based on these results, which will be included in the submission of module 4 of the dossier template to G-BA, and upon consultation with the G-BA, the sample size may be adjusted if necessary.

6.9. Futility Assessment

Due to uncertainties regarding the actual number of patients included in the study, and particularly the allocation ratio of the included patients, study feasibility cannot be assessed a priori. As requested by G-BA, a futility assessment will be performed with each interim analysis at 18, 36 and 54 months.

In cooperation with G-BA, a qualitative assessment will be made regarding the feasibility of the study. The assessment will be based on the number of enrolled patients fulfilling the inclusion and exclusion criteria and their allocation between the brexucabtagene autoleucel arm and comparator arm until the time of the interim analysis. Due to the high number of patient-relevant endpoints assessed in this study, effect sizes of endpoints as observed in the interim analyses will not be considered in the futility assessment. Setting termination criteria based on a single endpoint, e.g., OS, would undermine the importance of the other patient-relevant endpoints, such as symptoms, health-related quality of life and AEs. As a result, a futility assessment based on effect sizes cannot be considered as an appropriate approach in the context of the German benefit assessment according to § 35a SGB V, which requires the assessment of patient-relevant endpoints regardless of their classification in a specific study (see Section 2.2).

At the time of the first interim analysis, the futility assessment will be performed, but there will be no discontinuation due to futility, as the uncertainty regarding the updated sample size is very high, especially regarding the recruitment of patients in other European countries outside Germany, which could be delayed. The feasibility of the study in relation to the number of patients enrolled in the study will still be subject of discussion in the report of results from the first interim analysis.

6.10. 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-R 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.

6.11. Planned Analyses in Status Updates and Reports

6.11.1. 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.

6.11.2. Status Update 2 and 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.

6.11.3. Status Update 3 and 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 87 patients in the comparator arm and 174 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.

6.11.4. Status Update 4 and 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.

6.11.5. 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 174 patients in the brexucabtagene autoleucel arm have completed at least 36 months follow-up **and** a minimum of 87 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. Similar regulations and reporting requirements apply to other European countries.

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; [48]). 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/Gilead 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 entry checks will be implemented to avoid data entry errors directly during documentation. 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 [49].

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 all European Union member states since May 2018, defines various legal aspects of data protection [50].

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/Gilead responsible employees.

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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.

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]

[redacted]

[redacted]

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

Technical Report

Prepared for:

[redacted]
Kite, A Gilead Company
[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

[redacted]

Table of Contents

[redacted]

Tables

Figures

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.[1,2] 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.[3]

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.[4,5] Yet, the clinical course remains heterogenous, with some patients benefitting from treatment for decades and others relapsing within months.[6] Other patients with indolent MCL may be managed through watch and wait strategies which last years.[7]

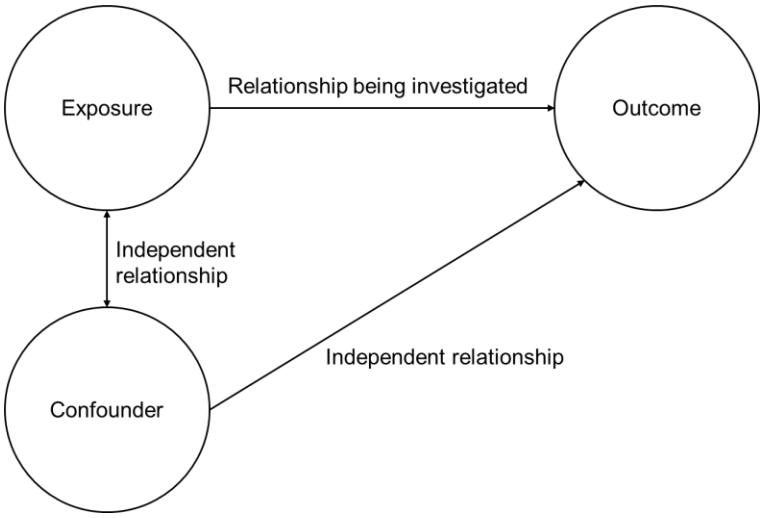
The advent of Bruton's tyrosine kinase inhibitors (BTKi), with ibrutinib being the first to be granted marketing authorization by the European Medicines Agency in October 2014, has improved prognosis for patients with r/r MCL. However, many patients continue to progress and novel therapeutic options are needed.[8] Advances in chimeric antigen receptor (CAR) T-cell therapy have yielded promising findings in this regard.[9,10] 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),[9,11] 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 1**). 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.

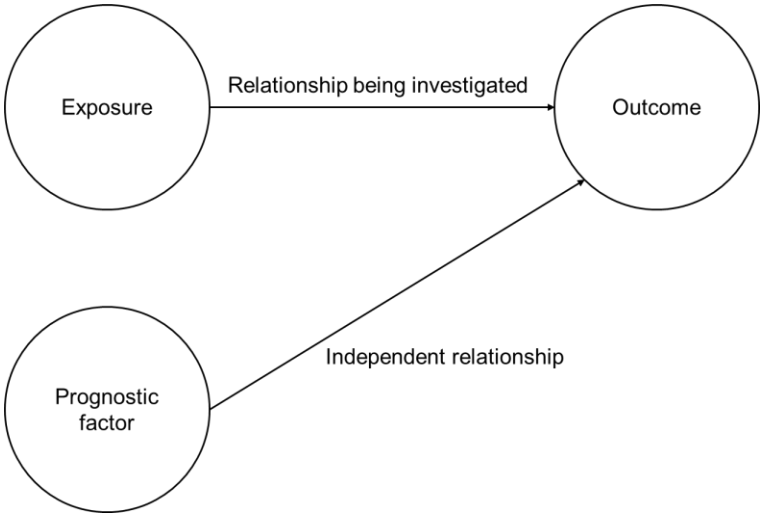
Figure 1: Illustration of the impact of a confounder on investigations of an exposure-outcome relationship



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 2**). 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 2: 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.[12] 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.[13] 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.

[redacted]

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.[14] 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.[15] 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.[16] 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.[17] 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.[18]

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.[19] Indeed, prognostic parameters for relapsed patients remain scarce.[5] 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 1**. 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 1: 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.[20]

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.21

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

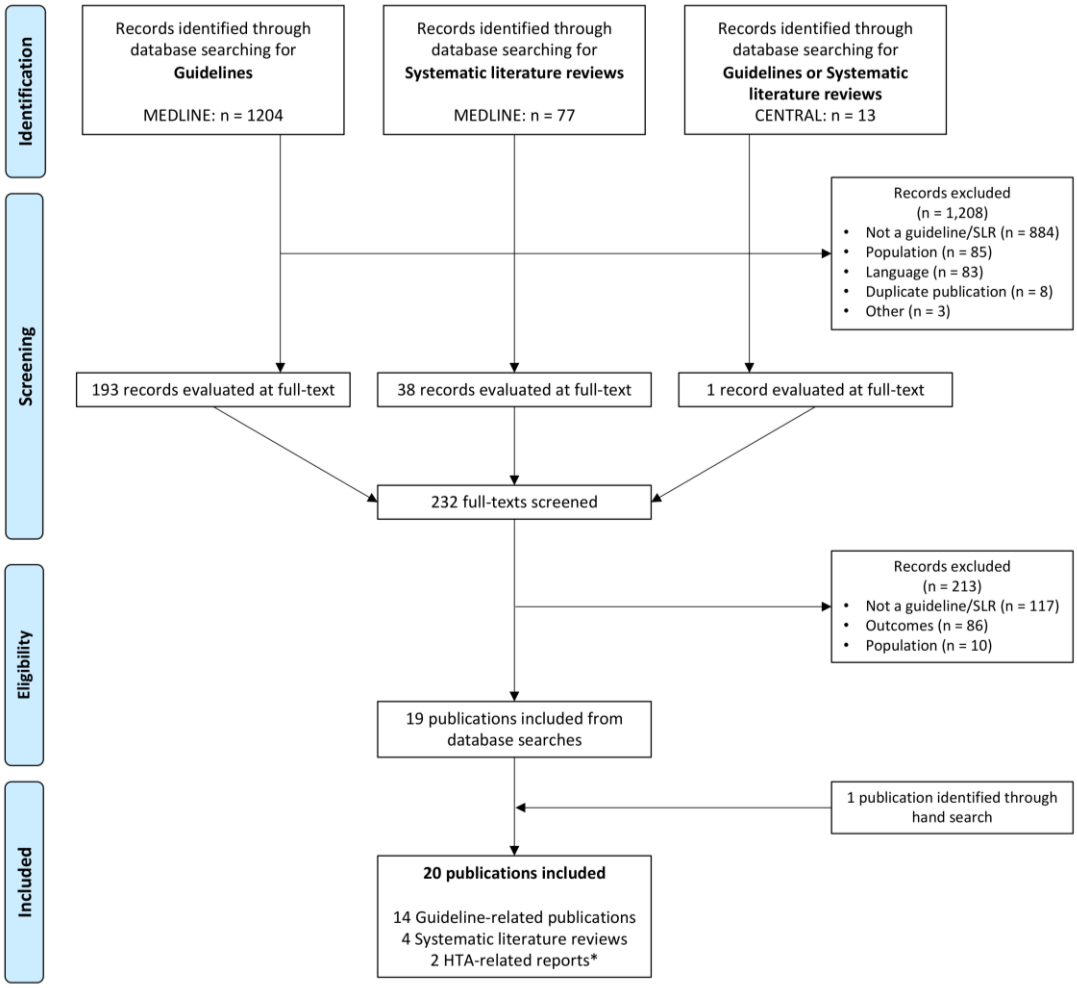
The findings of the literature review were summarized through a narrative synthesis. No formal statistical analysis was planned or anticipated.

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.[22-41] 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 3**.

Figure 3: Study selection flow diagram



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

[redacted]

The majority of publications identified through the literature review process were clinical guidelines or recommendations, 14 guidelines from eight distinct bodies included (**Table 6**).[22,23,25-29,32-35,39-41] 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.[24,31,36,37] One review, published by Monga and colleagues (2020), was an epidemiology-focused study describing the global burden of illness.[31] 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 6**).

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 2**). 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

[redacted]

defined confounders were captured when publications made these specific references and were often recorded in addition to the higher-level, more sensitive characteristic.

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 2: Potential confounders in r/r MCL

Category	Confounder	Outcomes referenced	Referenced by
Biomarker	ATM gene	OS, PFS, ORR	Roufarshbaf 2022 (SLR)[37]
	Genetic Mutation	Efficacy (broadly)	Roufarshbaf 2022 (SLR)[37]
	Ki-67	Efficacy outcomes (broadly), Prognosis (broadly), OS, PFS, ORR	Cao 2021 (SLR)[24] Dreyling 2014 (Guideline from ESMO)[27] Dreyling 2017 (Guideline from ESMO)[26] O'Reilly 2022 (Guideline from BSH)[34] Parrott 2018 (SLR) [36] Roufarshbaf 2022 (SLR)[37] Zelenetz 2021 (Guideline from NCCN)[40]
	LDH	OS, PFS	O'Reilly 2022 (Guideline from BSH)[34]
	P53 overexpression	Survival (broadly)	Caballero 2013 (Guideline from GEL/TAMO)[23]
	TP53 mutation	Prognosis, OS, PFS, ORR	Munshi 2021a (Guideline from ASTCT, CIBMTR, and EBMT)[32] Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)[33] O'Reilly 2022 (Guideline from BSH)[34] Parrott 2018 (SLR)[36] Roufarshbaf 2022 (SLR)[37] Yoon 2020 (Guideline from ALSG)[39] Zelenetz 2021 (Guideline from NCCN)[40]
Clinical status, tumour characteristics, and assessment scales	Bone marrow reserve	Prognosis (broadly)	McKay 2012 (Guideline from BCSH)[29]
	Bulky disease	Prognosis (broadly), Drop-out rate	O'Reilly 2022 (Guideline from BSH)[34]
	Co-morbidities	Prognosis (broadly)	McKay 2018 (Guideline from BSH)[28]
	Disease morphology	Prognosis (broadly), Survival (broadly), OS, PFS, ORR	Caballero 2013 (Guideline from GEL/TAMO)[23] O'Reilly 2022 (Guideline from BSH)[34] Parrott 2018 (SLR)[36] Roufarshbaf 2022 (SLR)[37] Zelenetz 2021 (Guideline from NCCN)[40]

Category	Confounder	Outcomes referenced	Referenced by
	ECOG performance score	Prognosis (broadly), PFS	Buske 2017 (Guideline from ESMO)[22] Caballero 2013 (Guideline from GEL/TAMO)[23] McKay 2012 (Guideline from BCSH)[29] McKay 2018 (Guideline from BSH)[28] O'Reilly 2022 (Guideline from BSH)[34] Okamoto & Kusumoto 2020 (Guideline from JSH)[35]
	Extra-nodal disease	PFS	Yoon 2020 (Guideline from ALSG)[39]
	Minimal residual disease	Prognosis (broadly)	Dreyling 2014 (Guideline from ESMO)[27]
	MIPI	Efficacy outcomes (broadly), Prognosis (broadly), OS, PFS	Cao 2021 (SLR)[24] O'Reilly 2022 (Guideline from BSH)[34] Roufarshbaf 2022 (SLR)[37] Yoon 2020 (Guideline from ALSG)[39]
	MIPI-c	Prognosis (broadly)	Dreyling 2017 (Guideline from ESMO)[26]
	Organ function	Prognosis (broadly)	Okamoto & Kusumoto 2020 (Guideline from JSH)[35]
	POD24	Prognosis (broadly), OS, PFS	O'Reilly 2022 (Guideline from BSH)[34] Zelenetz 2021 (Guideline from NCCN)[40]
	Simplified MIPI	Prognosis (broadly)	O'Reilly 2022 (Guideline from BSH)[34] Parrott 2018 (SLR)
	Tumour load	Prognosis (broadly)	Dreyling 2014 (Guideline from ESMO)[27]
	Tumour stage	Prognosis (broadly), Survival (broadly)	Caballero 2013 (Guideline from GEL/TAMO)[23] Monga 2020 (SLR)[31] O'Reilly 2022 (Guideline from BSH)[34]

[redacted]

Category	Confounder	Outcomes referenced	Referenced by
Demographics	Age	Efficacy outcomes (broadly), Prognosis (broadly), Survival (broadly), PFS	Buske 2018 (Guideline from ESMO)[22] Caballero 2013 (Guideline from GEL/TAMO)[23] Cao 2021 (SLR)[24] Dreyling 2014 (Guideline from ESMO)[27] Dreyling 2017 (Guideline from ESMO)[26] McKay 2012 (Guideline from BCSH)[29] McKay 2018 (Guideline from BSH)[28] Monga 2020 (SLR)[31] O'Reilly 2022 (Guideline from BSH)[34] Okamoto & Kusumoto 2020 (Guideline from JSH)[35]
	Race	Safety/Tolerability (broadly)	Yoon 2020 (Guideline from ALSG)[39]
Treatment history	Chemosensitive disease	Survival (broadly)	Caballero 2013 (Guideline from GEL/TAMO)[23]
	Choice of initial therapy	Prognosis (broadly)	McKay 2012 (Guideline from BCSH)[29]
	Combination therapy with rituximab	ORR, CR, PFS	Yoon 2020 (Guideline from ALSG)[39]
	Duration of response to prior therapy	Prognosis (broadly)	Yoon 2020 (Guideline from ALSG)[39]
	Ibrutinib resistance	Prognosis (broadly)	Dreyling 2018 (Guideline)[25]
	Number of prior lines of therapy	Survival (broadly), Prognosis (broadly), OS, PFS, ORR, CR, DOR	Caballero 2013 (Guideline from GEL/TAMO)[23] Roufarshbaf 2022 (SLR)[37] Tappenden 2019 (NICE HTA)[38] Yoon 2020 (Guideline from ALSG)[39]
	POD12	Prognosis (broadly)	Zelenetz 2021 (Guideline from NCCN)[40]
	Prior bendamustine exposure	Prognosis (broadly)	Yoon 2020 (Guideline from ALSG)[39]
	Prior bortezomib use	DOR, PFS	Dreyling 2018 (Guideline)[25]
	Prior treatment(s) received	Prognosis (broadly), Survival (broadly), PFS	Caballero 2013 (Guideline from GEL/TAMO)[23] Dreyling 2014 (Guideline from ESMO)[27] Dreyling 2018 (Guideline)[25] McKay 2018 (Guideline from BSH)[28] Okamoto & Kusumoto 2020 (Guideline from JSH)[35]

[redacted]

Category	Confounder	Outcomes referenced	Referenced by
	Response to prior treatment	Prognosis (broadly), OS, PFS	Munshi 2021b (Guideline from ASTCT, CIBMTR, and EBMT)[33] Okamoto & Kusumoto 2020 (Guideline from JSH)[35] Yoon 2020 (Guideline from ALSG)[39]

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

[redacted]

- 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.[6]

- 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.[42] 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.[43,44] 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.[45] 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.[6]

- 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.[19,46] 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. 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.[43,44]

- 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.[45] 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, $p = 0.002$).[47]

- Disease morphology (blastoid morphology)

  - In a study of ibrutinib plus rituximab therapy in r/r MCL, patients with blastoid morphologic features had worse outcomes.[43,44]

- 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.[45] POD24 was a risk factor for overall survival in a univariate analyses, though lost its statistical significance in a multivariate model.

- TP53

  - 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.[45] 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.[47]

- 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.[48] 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).[49]
- 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.[50] Further evidence from the MCL Younger and MCL Elderly trial of the European MCL network supported these findings.[51]
- 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.[6]

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 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.

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Appendix A: Search Strategy

MEDLINE was searched (via Ovid) to identify clinical guidelines and recommendations (**Table 3**) and systematic literature reviews

[redacted]

Table 4). A sensitive, population-focused search strategy was applied to CENTRAL (via Ovid) to identify both types of publications (

[redacted]

Table 5).

Table 3: 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
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 4: 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]

Table 5: 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

Appendix B: List of included

The complete list included publications, arranged by systematic literature review or clinical guideline, is presented in **Table 6**.

Table 6: 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[32]	ASTCT, CIBMTR, and EBMT clinical practice recommendations for transplant and cellular therapies in mantle cell lymphoma
	Munshi 2021b[33]	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[29]	Guidelines for the investigation and management of mantle cell lymphoma
British Society of Haemotology (BSH)	O'Reilly 2022[34]	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[28]	Guideline for the management of mantle cell lymphoma
--	Cao 2021[24]	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[22]	ESMO consensus conference on malignant lymphoma: General perspectives and recommendations for the clinical management of the elderly patient with malignant lymphoma
	Dreyling 2018[25]	Treatment for patients with relapsed/refractory mantle cell lymphoma: European-based recommendations
	Dreyling 2017[26]	Newly diagnosed and relapsed mantle cell lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up
	Dreyling 2014[27]	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[23]	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[31]	Systematic literature review of the global burden of illness of mantle cell lymphoma
--	Monga 2021[30]	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[40]	NCCN guidelines insights: B-cell lymphomas, version 5.2021
	Zelenetz 2012[41]	Non-Hodgkin's lymphomas, version 3.2012
Japanese Society of Hepatology (JSH)	Okamoto & Kusumoto 2020[35]	JSH practical guidelines for hematological malignancies, 2018: II. Lymphoma-4. Mantle cell lymphoma (MCL)
--	Parrott 2018[36]	A systematic review of treatments of relapsed/refractory mantle cell lymphoma
--	Roufarshbaf 2022[37]	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[38]	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[39]	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 7**) and the context of the in-text references (

Table 8).

Table 7: In-text references to confounders in the included publications

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
Biomarker	ATM gene	Roufarshbaf 2022 (SLR)[37]	"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)[37]	"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)[24]	"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)[27]	Referenced in a figure	--
		Dreyling 2017 (Guideline from ESMO)[26]	"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)[34]	"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)[36]	"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)[37]	"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)[40]	"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

[redacted]

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
	LDH	O'Reilly 2022 (Guideline from BSH)[34]	"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
	P53 overexpression	Caballero 2013 (Guideline from GEL/TAMO)[23]	"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)[32]	"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)[33]	"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)[34]	"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)[36]	"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)[37]	"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)[39]	"Clinical trial enrollment is strongly suggested where possible, especially for patients with TP53 mutation associated with poor prognosis."	--
		Zelenetz 2021 (Guideline from NCCN)[40]	"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)[29]	"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)[34]	"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)[28]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--
	Disease morphology	Caballero 2013 (Guideline from GEL/TAMO)[23]	"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)[23]	"Blastoid variants of MCL and P53 overexpression have also been associated with a trend towards worse prognosis."	Milpied 1998
		O'Reilly 2022 (Guideline from BSH)[34]	"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	McCulloch 2021

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
			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."	
		O'Reilly 2022 (Guideline from BSH)[34]	Referenced in a figure	--
		O'Reilly 2022 (Guideline from BSH)[34]	"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)[36]	"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)[37]	"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)[36]	"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)[22]	"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)[23]	"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)[29]	"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)[28]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--
		O'Reilly 2022 (Guideline from BSH)[34]	"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)[35]	"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."	--

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
	Extra-nodal disease	Yoon 2020 (Guideline from ALSG)[39]	"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)[27]	"The independent prognostic role of minimal residual disease (MRD) applying patient-specific primers has been confirmed in numerous studies."	--
	MIPI	Cao 2021 (SLR)[24]	"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)[34]	"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)[37]	"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)[39]	"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)[26]	"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)[35]	"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)[34]	"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
	POD24	Zelenetz 2021 (Guideline from NCCN)[40]	"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)[34]	"Risk assessment pre-cBTKi should include up-to-date imaging and Simplified MIPI (sMIPI) status."	--
		Parrott 2018 (SLR)[36]	"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"	--

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Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
	Tumour load	Dreyling 2014 (Guideline from ESMO)[27]	"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)[23]	"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)[31]	"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)[34]	Referenced in a figure	--
Demographics	Age	Buske 2018 (Guideline from ESMO)[22]	"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)[23]	"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)[24]	"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)[27]	Referenced in a figure	--
		Dreyling 2017 (Guideline from ESMO)[26]	Referenced in a figure	--
		McKay 2012 (Guideline from BCSH)[29]	"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)[28]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--
		Monga 2020 (SLR)[31]	"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)[34]	"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)[35]	Referenced in a figure	--

[redacted]

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
		Zelenetz 2012 (Guideline from NCCN)[41]	Referenced in a figure	--
	Race	Yoon 2020 (Guideline from ALSG)[39]	"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)[23]	"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)[29]	"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)[39]	"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)[39]	"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)[25]	"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
	Number of prior lines of therapy	Caballero 2013 (Guideline from GEL/TAMO)[23]	"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)[37]	"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)[38]	"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)[39]	"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)[39]	"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

Category	Confounder	Publication and type	Quotation(s)	Supporting citations*
		Yoon 2020 (Guideline from ALSG)[39]	"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)[40]	"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)[39]	"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)[25]	"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)[23]	"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)[27]	"Selection of salvage treatment depends on efficacy of prior regimens."	--
		Dreyling 2018 (Guideline)[25]	"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)[28]	"Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy."	--
		Okamoto & Kusumoto 2020 (Guideline from JSH)[35]	"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)[33]	"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)[35]	"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)[39]	"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

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Table 8: 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)[37]	Yes	--	--	--	--	--
	Genetic Mutation	Roufarshbaf 2022 (SLR)[37]	--	--	--	--	--	--
	Ki-67	Cao 2021 (SLR)[24]	--	--	Yes	--	--	--
		Dreyling 2014 (Guideline from ESMO)[27]	--	--	--	--	--	--
		Dreyling 2017 (Guideline from ESMO)[26]	--	--	--	Yes	--	--
		O'Reilly 2022 (Guideline from BSH)[34]	--	--	--	--		Yes
		Parrott 2018 (SLR)[36]	--	--	Yes	--	--	--
		Roufarshbaf 2022 (SLR)[37]	--	Yes	--	--	--	--
		Zelenetz 2021 (Guideline from NCCN)[40]	--	--	--	--	--	Yes
	LDH	O'Reilly 2022 (Guideline from BSH)[34]	--	--	--	--	--	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)[34]	--	--	--	--	--	Yes
		Parrott 2018 (SLR)	--	--	Yes	--	--	--
		Roufarshbaf 2022 (SLR)[37]	--	--	--	--	--	--
		Yoon 2020 (Guideline from ALSG)	--	--	--	Yes	Yes	--
		Zelenetz 2021 (Guideline from NCCN)	--	--	--	--	--	Yes
Clinical status, tumour characteristics,	Bone marrow reserve	McKay 2012 (Guideline from BCSH)	--	--	--	--	Yes	Yes
	Bulky disease	O'Reilly 2022 (Guideline from BSH)[34]	--	--	--	--	--	Yes

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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
and assessment scales	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)[34]	--	--	--	--	--	Yes
		O'Reilly 2022 (Guideline from BSH)[34]	--	--	--	Yes	--	--
		O'Reilly 2022 (Guideline from BSH)[34]	--	--	--	--	--	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)[34]	--	--	--	--	--	Yes
		Okamoto & Kusumoto 2020 (Guideline from JSH)	--	--	--	--	Yes	--
	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)[34]	--	--	--	--	--	Yes
		Roufarshbaf 2022 (SLR)		Yes	--	--	--	--
		Yoon 2020 (Guideline from ALSG)	--	--	--	--	--	Yes
	MIPI-c	Dreyling 2017 (Guideline from ESMO)	--	--	--	Yes	--	--

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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
	Organ function	Okamoto & Kusumoto 2020 (Guideline from JSH)	--	--	--	--	Yes	--
	POD24	O'Reilly 2022 (Guideline from BSH)[34]	--	--	--	--	--	Yes
		Zelenetz 2021 (Guideline from NCCN)	--	--	--			Yes
	Simplified MIPI	O'Reilly 2022 (Guideline from BSH)[34]	--	--	--	--	--	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	--	--	--	--
		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)[34]	--	--	--	--	--	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

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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
	Choice of initial therapy	McKay 2012 (Guideline from BCSH)	--	--	--	--	Yes	Yes
	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	--
		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	--

[redacted]

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
		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

STATISTICAL ANALYSIS PLAN

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
Study 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
Product Name:	Brexucabtagene autoleucel (TECARTUS®)
Version Number:	SAP version 2.0
Release Date:	13 April 2023
Replaces Previous Version(s):	SAP version 1.0

APPROVAL OF THE STATISTICAL ANALYSIS PLAN

Principal investigator on behalf of the EMCL registry:

Prof. Dr. med. Georg Heß

[redacted] [redacted]

Signature Date (DD Month YYYY)

Kite/Gilead accountable representatives:

Dr. Elande Baro, Associate Director, Biostatistics

[redacted] [redacted]

Signature Date (DD Month YYYY)

Dr. Robert Welte, Sr. Director Market Access and Reimbursement Germany

[redacted] [redacted]

Signature Date (DD Month YYYY)

Dr. Taha Itani, Director Medical Affairs, Real World Evidence

[redacted] [redacted]

Signature Date (DD Month YYYY)

AMS accountable representative:

Hannah Schmidt, Biostatistician

[redacted] [redacted]

Signature Date (DD Month YYYY)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ATS	As-treated set
Brexu-cel	Brexucabtagene autoleucel
BTKi	Bruton's tyrosine kinase inhibitor
CI	Confidence interval
CNS	Central nervous system
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DRM	Data Review Meeting
D0	Index date
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
eCRF	Electronic Case Report Form
EM	Expectation-maximization
EMCL	European Mantle Cell Lymphoma Network
EMCL-R	European Mantle Cell Lymphoma Network Registry
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-NHL-HG29	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Non-Hodgkin Lymphoma - High Grade 29 Module
G-BA	Federal Joint Committee (*Gemeinsamer Bundesausschuss*)
GvHD	Graft-versus-host disease
HR	Hazard ratio
HRQoL	Health-related Quality of Life
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation

ID	Identity
IMBEI	Institute for Medical Biostatistics, Epidemiology and Informatics
IQWiG	Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*)
ITTS	Intent-to-treat set
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
MCL	Mantle cell lymphoma
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MIPI	Mantle Cell Lymphoma International Prognostic Index
MMRM	Mixed effect Model Repeat Measurement
OR	Odds ratio
OS	Overall survival
PS	Propensity score
PSM	Propensity score matching
PT	Preferred term
QoL	Quality of Life
RD	Risk difference
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, Mitoxantrone
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCT	Stem cell transplantation
SMD	Standardized mean difference
SOC	System organ class
TLS	Tumor lysis syndrome
VR-CAP	Bortezomib/Rituximab/Cyclophosphamide/Doxorubicin/Prednisone
vs	Versus

WHO INN	World Health Organization International Nonproprietary Names

HISTORY OF SAP REVISIONS

Version	Date	Changes made and reasons for change
1.0	21 December 2022	N/A, first version
2.0	13 April 2023	Editorial changes to correct spelling mistakes, grammatical errors and improve readability Adjust the date and number of the SAP version Implementation of G-BA resolution of 16 March 2023 (see Table 2 in the Project Plan): • **Section 1 Introduction:** Clarification, that any additions or changes discussed in the DRM that affect the analyses prespecified in this SAP will have to be agreed by the G-BA (G-BA resolution issue j). • **Section 3.1 Eligibility Criteria:** Adjustment of inclusion and exclusion criteria to ensure positivity (G-BA resolution issue a) • **Section 3.2 Planned Analyses in Status Updates and Reports:** Adding futility assessment (G-BA resolution issue j) • **Section 4 Sample Size:** Section 4.1 Preliminary Sample Size and Section 4.2 Updated Sample Size were introduced in order to comply with G-BA's requirement to reassess the sample size calculation after the interim analyses (G-BA resolution issue j) • **Section 5 Data Review Meeting:** Clarification that a DRM will be held prior to database hard lock for the interim and the final analyses. Deletion of statement that decisions in the DRM minutes may potentially amend/overrule methodology planned in this SAP. Clarification, that any changes to the routine practice data collection and its analyses will have to be agreed by the G-BA (G-BA resolution issue j). • **Section 6.1 Data Source:** Adaption regarding the recruitment from other European Countries. Further European centers will be included (G-BA resolution issue i). Deletion of statement regarding handling of missing items in EORTC questionnaires due to consistency as handling of missing data of EORTC questionnaires are described in detail in section 6.3 Handling of Missing Data. • **Section 6.3 Handling of Missing Data:** Summarizing efforts to avoid missing values (G-BA resolution issue m). Adding section imputation of endpoint data (G-BA resolution issue m). Deletion of the restriction that confounders with more than 30% missing values will be discarded from the PS model (G-BA resolution issue m). Deletion of imputation strategy for missing data for month (G-BA resolution issue m). Adding statement on patients lost-to-follow-up.

		• **Section 6.7.2 Time to (once-confirmed) clinically relevant deterioration:** Adding endpoint "once-confirmed clinically relevant deterioration" (G-BA resolution issue s) • **Section 6.7.3 Definition of time window for patient-reported outcomes:** Rewording from "screening" to "baseline" Reshaping of tolerance windows to avoid missing returns of EORTC questionnaires (G-BA resolution issue m). • **Section 6.8.1 Adverse Events:** Removing definitions of AEs as the operationalizations of AEs are described in detail in Section 8.5.3.1. • **Section 7 Analysis Sets:** Statement regarding treatment switches was deleted for consistency. Handling of treatment switches is described in detail in section 8.4 Censoring to address Treatment Switch. • **Section 8.1 Descriptive Analyses:** Statement regarding testing of hypotheses was deleted for consistency. The procedure regarding testing of hypotheses is described in detail in section 8.2.3 Effect Estimation and Interpretation (G-BA resolution issue k) • **Section 8.2 Multiple Imputation and Propensity Score Matching:** The section regarding propensity score matching was comprehensively revised to address G-BA's issues on the previous version 1.0 of the SAP. o Adding a flow chart to give an overview of multiple imputation, propensity score procedure and interpretation of effect measures (G-BA resolution issues k, l, m) o Adding Section 8.2.1 Multiple Imputation: Adding details on MI (G-BA resolution issue m) o Updating list of confounders (G-BA resolution issue e) o Adding Section 8.2.2 Propensity Score Matching: Adapting matching method from optimal matching with 2:1 ratio to balanced pairwise sequential nearest neighbor matching with variable 2:1 matching to improve precision and reduce potential bias. Adding calculation of areal overlap (G-BA resolution issue l). Adding the possibility of trimming if sufficient overlap and balance cannot be achieved with the initially defined procedure (G-BA resolution issue l). o Adding Section 8.2.3 Effect Estimation and Interpretation: Adapting the assessment of the treatment effect after PSM taking into account shifted a null-hypothesis (G-BA resolution issue k) Clarification that a detailed and comparative description of the patient populations prior and after PSM will be conducted in the course of reporting the results (G-BA resolution issue l) Adding naïve comparisons as an alternative if sufficient overlap and balance cannot be reached or if the logistic regression model for PS does not converge. Adapting the assessment of the treatment effect using the criteria of a dramatic effect (G-BA resolution issue l). • **Section 8.5.1 Descriptive analyses for baseline characteristics:** Clarification that the analysis of baseline characteristics will be conducted based on the original patient population (prior PSM) and after PSM, if applicable. Descriptive analyses after PSM will include the standardized mean difference compared to the original patient population (G-BA resolution issue l). Deletion of statement that analysis of baseline characteristics by subgroup

		will be performed, as it is normally not necessary for benefit assessment. Adaption of the table presenting baseline characteristics to be analyzed to show baseline characteristics that will be actually assessed instead of baseline data that is generally collected in the register. • **Section 8.5.2.1 Mortality, Section 8.5.2.2 Morbidity and Section 8.5.2.3** Health-related Quality of Life: Deletion of sensitivity analyses taking into account treatment switches by censoring based on the ATS to streamline the analyses. Sensitivity analyses taking into account treatment switches by censoring will only be based on the ITTS. • **Section 8.5.2.2 Morbidity:** Deletion of EORTC QLQ-C30 scale "financial difficulties" as this scale will not be considered in the benefit assessment (G-BA resolution issue o). • **Section 8.5.2.2 Morbidity and Section 8.5.2.3 Health-related Quality of Life:** Adding endpoint "once-confirmed clinically relevant deterioration" (G-BA resolution issue s). Deletion of time to clinically relevant deterioration of 15 points as only a response threshold of 10 points is to be considered in the benefit assessment (G-BA resolution issue n). Adding responder analyses with a response threshold of a decrease of 10 points for each scale at each time point of assessment as sensitivity analysis instead of assessment of hedges' g and MMRM (G-BA resolution issue s). • **Section 8.5.3.1 Adverse Events:** SAEs are defined as events that lead to hospitalization or prolongation of existing hospitalization or death so that a pooled assessment of these events is specified (G-BA resolution issue c). The assessment of AEs which, according to the assessment of the study physician, are related to the treatment were deleted as they will not be considered in the benefit assessment (G-BA resolution issue p). Adding analyses of AESI separated by severity with severe AESI defined as AESI with significant impairment of activity of daily living (according to CTCAE grade ≥3) (G-BA resolution issue d). Adding analyses of serious AESI defined as AESIs that lead to hospitalization or prolongation of hospitalization or death to fulfil requirements of dossier template module 4. • **Section 8.5.5.2 Patient Disposition and Withdrawals:** Deletion of patient listing as no patient individual data will be reported.

1. INTRODUCTION

This Statistical Analysis Plan (SAP) refers to the Project Plan, version final 2.0 dated 13 April 2023. The SAP will be finalized latest before any analysis will be conducted. The specifications included in this SAP provide more detail to the analysis descriptions in the Project Plan and are focused on statistical methodologies for interim and final analyses.

Additions or changes to the analyses planned in this SAP may be defined during the Data Review Meetings (DRMs) and documented in the DRM minutes, which will be approved by the DRM participants prior to database hard lock. Any additions or changes discussed in the DRM that affect the analyses prespecified in this SAP will have to be agreed by the Federal Joint Committee (G-BA).

The document is written in compliance with the International Council of Harmonisation (ICH) Guidelines E9.

2. OBJECTIVES AND ENDPOINTS

The objective of this study is to evaluate the effectiveness and safety of brexucabtagene autoleucel (Tecartus®) versus patient-individual therapy as defined by the G-BA, in adult patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor (BTKi). The following therapies are considered suitable comparators by the G-BA in the context of routine practice data collection and evaluations, if possible, including **allogeneic or autologous stem cell transplantation (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 (Rituximab, Dexamethasone, high-dose Cytarabine, Cisplatin)
- R-BAC (Rituximab, Bendamustine, Cytarabine)
- Temsirolimus
- R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone)
- 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 (HRQoL), collected using the EORTC QLQ-C30 and the EORTC QLQ-NHL-HG29
- Safety: Adverse events (AEs)

Patient baseline characteristics prior treatment strategies of patients in the brexucabtagene autoleucel cohort and comparative therapies cohort will be collected and summarized.

3. 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 European Mantle Cell Lymphoma Network (EMCL) indication registry. 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. For further information please refer to the study Project Plan section 3.

3.1. Eligibility Criteria

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 lines of systemic therapy including a BTKi
- Intention of treatment with either brexucabtagene autoleucel or patient-individual therapy from the list of eligible treatments above, if possible, including allogeneic or autologous stem cell transplantation (SCT)
- Informed consent by the patient for participation in the EMCL-R if patient is not already included in the base population

Exclusion criteria

- ECOG-PS>2
- Absolute contraindication to fludarabine and cyclophosphamide, including history of severe hypersensitivity reaction to these
- Acute impaired organ function (cardiac, pulmonary, renal, hepatic)
- Active uncontrolled infection

For further information on the inclusion and exclusion criteria please refer to Project Plan section 4.1 and 4.2.

3.2. Planned Analyses in Status Updates and Reports

Table 1. Timelines of Status Updates and Final Report

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 174 patients in the brexucabtagene autoleucel arm have completed at least 36 months follow-up and a minimum of 87 patients in the comparator arm have completed at least 36 months of follow-up

For detailed information on planned analyses in status updates and reports please refer to Project Plan section 6.11.

As requested by G-BA, a futility assessment will be performed with each interim analysis at 18, 36 and 54 months. In cooperation with G-BA, a qualitative assessment will be made regarding the feasibility of the study. The assessment will be based on the number of enrolled patients fulfilling the inclusion and exclusion criteria and their allocation between the brexucabtagene autoleucel arm and comparator arm until the time of the interim analysis.

At the time of the first interim analysis, the futility assessment will be performed, but there will be no discontinuation due to futility, as the uncertainty regarding the updated sample size is very high, especially regarding the recruitment of patients in other European countries outside Germany, which could be delayed. The feasibility of the study in relation to the number of patients enrolled in the study will still be subject of discussion in the report of results from the first interim analysis. For a detailed justification of this approach please refer to Project Plan section 6.9.

4. SAMPLE SIZE

4.1. Preliminary Sample Size

The estimated preliminary sample size for analysis is 261 patients in a 2:1 ratio allocation (174 in the brexucabtagene autoleucel arm and 87 in the comparator arm). Please refer to Project Plan section 6.8.2 for information on the sample size calculation.

4.2. Updated Sample Size

Due to a high degree of uncertainty regarding patient enrollment, effect measures and event rates, a re-evaluation of the sample size calculation will be conducted in collaboration with G-BA after the first and second interim analysis, 18 and 36 months after start of the routine practice data collection, respectively. Please refer to Project Plan section 6.8.3 for details on the calculation.

5. DATA REVIEW MEETING

A DRM will be held prior to database hard lock for the interim analyses and final report. Deviations from the Project Plan will be determined in order to be able to define the analysis populations.

In general, inconsistent data shall be queried and resolved. If the problem is not resolved sufficiently then the inconsistent data will be set to missing in the statistical analysis unless otherwise agreed upon prior to or within the DRM.

Listings relating to the following topics will be prepared for the discussion in the DRM, the exact set of listings will be defined upfront the meeting:

- Informed consent available
- Violation of inclusion criteria
- Violation of exclusion criteria
- Allocation of individual patients to the analysis populations

Full details on the reviews performed and the decisions made in the DRM will be documented in writing in the DRM minutes and will be approved by signature of the main attendees. The DRM minutes will be handled as an addendum to the SAP. Any changes to the routine practice data collection and its analyses have to be agreed by the G-BA.

6. DEFINITIONS AND DERIVATIONS

6.1. Data Source

Patients will be recruited from the EMCL registry using sites in Germany and further European centers as outlined in Section 3.6 of the Project Plan. 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.

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 Institute for Medical Biostatistics, Epidemiology and Informatics (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 statistical software.

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

6.2. Coding

The process of coding is performed according to relevant coding guidelines.

AEs will be coded using the English version of the Medical Dictionary for Regulatory Activities (MedDRA). For the analysis, the most recent MedDRA version will be taken.

Therapies will be coded using World Health Organization International Nonproprietary Names (WHO INN).

6.3. Handling of Missing Data

Various efforts have been initiated to increase the awareness of centers, treating physicians and patients about the importance of complete data collection. These efforts include site trainings, source data verification, central monitoring (including plausibility checks, programmed checks for completeness, full medical review) and on-site monitoring. Additional details on these measures can be found in Section 8 of the Project Plan.

To improve the likelihood of successfully collecting data from patient reported outcomes (EORTC QLQ-C30 and EORTC QLQ-NHL-HG29) a third party will act as a trust center and e. g. contact patients if they do not return the completed questionnaires within 2 weeks (see Project Plan Section 2.2.3.1). For these EORTC questionnaires, data entry is validated by a separate member of staff (see Project Plan Section 8).

Missing endpoint data

Missing values in EORTC items will be replaced according to the EORTC manual [1]: If at least half of the items from the scale have been answered, it is assumed that the missing items have values equal to the average of those items which are present for that respondent in the respective scale. Single-item scores will be set to missing.

Missing scales of the EORTC scales will be imputed with the last observation carried forward.

Missing data in covariates of the propensity score (PS) model

Multiple imputation (MI) will be performed to impute missing baseline values of confounders used for propensity score matching (PSM) based on the observed data

Missing data in dates

In general, if the day of a date is unknown, missing day information will be assumed as the 1st. For end dates (e.g., of treatment or of observation), missing day information will be imputed as the last of the month.

However, if the start date of an AE is missing and it is not sure whether this AE happened prior to, at, or after the infusion of brexucabtagene autoleucel or first study treatment administration, the day of the infusion or first study treatment administration is used to impute the start date of this AE.

Patients lost-to-follow-up

Values for patients known as lost-to-follow-up will be set to missing after the date of end of observation.

6.4. Time Derivations

Years will be derived from days as follows: [days]/365.25

Months will be derived from days as follows: [days]/(30.4375)

6.5. Index Date and Baseline

The index date (D0) will be defined as the date of the tumor board decision. For patients without tumor board decision, D0 will be defined as the date of the physician's therapy decision.

The baseline value will be defined as the last non-missing value prior to or until D0 if available. If no baseline value prior to or until D0 is available, the last non-missing value until date of infusion of brexucabtagene autoleucel or first administration of patient-individual therapy will be used. In addition, to ensure that baseline data of EORTC questionnaires is available, a time window of 28 days after D0 applies for the collection of the corresponding data.

6.6. Planned and Actual Observation Period [Months]

The planned observation period will be derived as follows: (date of data cutoff –D0 + 1)/30.4375

The actual observation period will be derived as follows: (date of end of observation or date of data cutoff, whatever occurs first –D0 +1)/30.4375

6.7. Definitions for Assessment of Effectiveness Endpoints

6.7.1. Time to Death [Months]

Time to death [months] required for the endpoint overall survival (OS) is defined as time from D0 to death due to any cause. If death event dates are not recorded (e.g., individuals who survived until study end, patients lost-to-follow-up), patients will be censored at the data cutoff date or the end date of the observation depending on which date is earlier.

6.7.2. Time to (once-confirmed) Clinically Relevant Deterioration [Months]

Time to clinically relevant deterioration of 10 points [months] is relevant for patient reported outcomes, i.e., morbidity (symptoms) and HRQoL. This is defined as the time from baseline to deterioration of at least 10 points for the patient questionnaire score (date of first confirmed deterioration minus first date of assessment). Patients without deterioration of at least 10 points will be censored at the last documented assessment of the patient questionnaire.

Once-confirmed clinically relevant deterioration of 10 points is defined as a decrease by at least 10 points on 2 consecutive assessments, i. e. deterioration of at least 10 points has been observed and at the next evaluation the score is still at least 10 points below baseline. This second time point then constitutes the event time.

6.7.3. Definition of Time Window for Patient-Reported Outcomes: Morbidity (Symptoms) and HRQoL

For assessments occurring at/after D0, the study day for that assessment will be calculated as:

(Date of assessment –Date of D0) +1

Patients should complete the EORTC QLQ-C30 and EORTC QLQ-NHL-HG29 at the following time points: at baseline, month 1, month 3, month 6, month 12, month 24, and month 36.

For the statistical analysis, assessments will be allocated to the time windows defined below. Unless otherwise stated, patient questionnaire results will be presented following these predefined time schedules.

Table 2. Assessment Schedule

Terminology used in Tables and Figures	Theoretical Day	Tolerance Window
Baseline	Day 0	Day 0 – Day 27
Month 1	Day 31	Day 28 – Day 61
Month 3	Day 92	Day 62 – Day 137
Month 6	Day 183	Day 138 – Day 274
Month 12	Day 366	Day 274 – Day 458

Terminology used in Tables and Figures	Theoretical Day	Tolerance Window
Month 24	Day 731	Day 639 – Day 823
Month 36	Day 1096	Day 1004 – Day 1188

Due to the assignment to the time windows specified above, a patient may have more than one non-missing value within one time window. The "Nearest value" strategy will be applied to select one value per patient for summaries by the predefined time schedules:

Table 3. "Nearest Value" Strategy

Filter	Description
"Nearest value"	Non-missing value with minimum study day difference to the scheduled study day (e.g., Day 30 for the Month 1 visit) will be selected. If several values qualify (e.g., a value at Day 30 and a value at Day 32) then the chronologically first one will be selected

6.8. Definitions for Assessment of Safety Endpoints

6.8.1. Adverse Events

AEs with onset on or after D0 will be considered.

6.8.2. Time to First Adverse Event [Months]

Time to first AE is defined as time from D0 to first onset date of an AE. Patients without AE will be censored at the data cutoff date, end date of the observation or treatment switch as defined in section 8.4 depending on which date is earlier.

7. ANALYSIS SETS

The following analysis sets will be used in this study:

- **Intent-to-treat set (ITTS):** This group includes eligible patients with a treatment decision for their next line of therapy, based on which patients will be assigned to either treatment arm. The treatment decision will be based on different factors such as tumor board recommendation, availability of therapy, physician's choice, and patient's choice.
- **As-treated set (ATS):** This group includes eligible patients who received therapy with brexucabtagene autoleucel or a patient-individual therapy. Patients will be assigned to treatment groups based on their initial treatment.

8. STATISTICAL METHODS FOR PLANNED ANALYSES

Tables and figures to be produced as the output of the statistical analyses described in this SAP are summarized in section 9.

8.1. Descriptive Analyses

Categorical variables will be summarized with absolute and relative frequencies (percentages) per category and number of missing observations.

Continuous variables and scales will be summarized descriptively by number of observations, number of missing observations, mean, standard deviation, median, minimum, maximum, 25% quartile and 75% quartile derived from all non-missing values.

The results will be rounded to the following number of decimal points: for min and max, the decimals will be used as captured in the database; arithmetic mean, median and standard deviation will be depicted with one more decimal than captured in the database. Percentages will be rounded to one decimal place; therefore, there may be occasions when the total of the percentages does not exactly equal 100%. Where not mentioned otherwise, percentages are counted relative to the number of patients with non-missing data.

If not mentioned otherwise, descriptive analyses will be stratified by treatment group displaying the following groups (in this order): “Brexu-cel”, “Patient-individual therapy” and “Total”.

8.2. Multiple Imputation and Propensity Score Matching

There are different approaches that have been proposed to adequately adjust analyses for confounders [2-5]. For this study, PSM will be used to balance the confounders of the two treatment groups and to allow assessment of overlap and balance [6]. If possible, MI will be used to replace missing values in confounders.

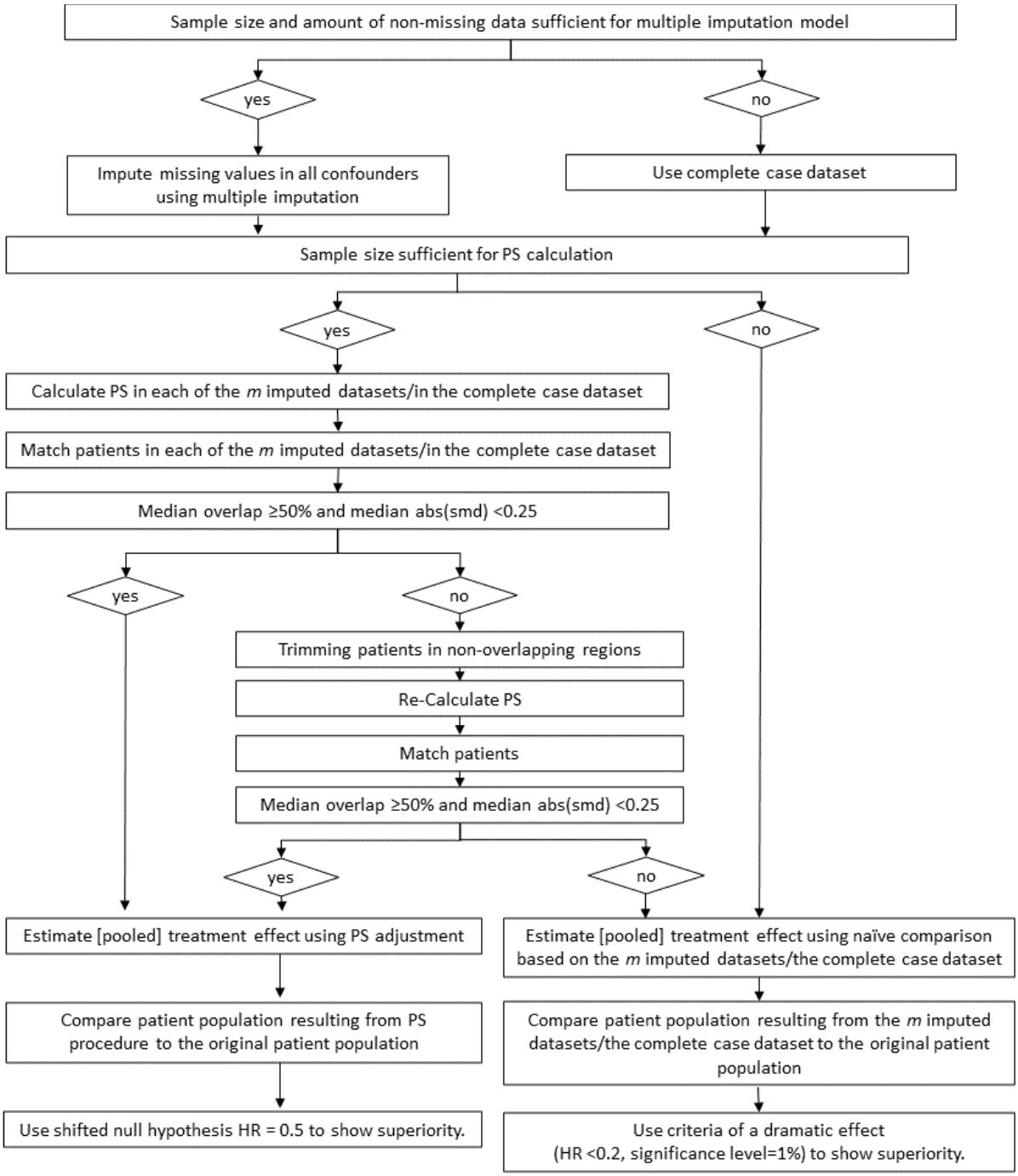

Figure 1: Overview of Multiple Imputation and Propensity Score Procedure

Figure 1 gives an overview of MI and PS procedures, which will be described in more detail below.

8.2.1. Multiple Imputation

MI should be performed to impute missing baseline values of confounders used for PSM based on the observed data.

If the amount of non-missing data and the sample size are sufficient for the MI model, the SAS software procedure PROC MI will be applied to create m=30 datasets with fully imputed confounders. The imputation model uses the Markov chain Monte Carlo (MCMC)-algorithm, initial mean and covariance estimates are derived from the Expectation-maximization (EM)-algorithm and non-informative priors are assumed. The amount of missing data in confounders is too high or sample size is not sufficient if there is no convergence within 1000 iterations.

If the amount of missing data in confounders is too high or sample size is not sufficient for the MI models, i. e. there is no convergence within 1000 iterations, it is not possible to conduct MI and PS calculation will be based on the complete case dataset.

The following variables will be included in the imputation model:

- OS
- Overall AEs requiring unplanned inpatient hospitalization or prolongation of existing hospitalization or death
- Treatment
- Confounders, as specified in Project Plan section 6.6:
    - Age (<65, ≥ 65 years)
    - Sex (female, male)
    - ECOG-PS (0, 1, 2)
    - Number of Comorbidities (0 ,1 ,2+) (based on modified HCT-CI)
    - Mantle Cell Lymphoma International Prognostic Index (MIPI) score (low risk, intermediate risk, high risk, unknown)
    - Lactate dehydrogenase (LDH) (<ULN vs. ≥ULN)
    - Leukocyte count [µl/l]
    - Disease state According to Ann Arbor (I, II, III, IV, unknown)
    - Extranodal manifestation at primary diagnosis (yes, no, unknown)
    - Bone marrow involvement (yes, no, unknown)
    - Disease morphology (Classical, Blastoid, Pleomorphic, CLL-like, Other)
    - Presence of B symptoms (yes, no, unknown)
    - Ki-67 (<30% vs. ≥30%)
    - TP53 mutation (yes, no, unknown)
    - Number of prior lines of therapy (2, >2)
    - Type of prior SCT (allogeneic, autologous, none)
    - Duration of prior BTKi therapy (months)
    - Response to prior BTKi therapy (refractory, relapsed, intolerant)

Although the relevant confounders are listed in the G-BA resolution of 16 March 2023, there is no information regarding the operationalization, which should be applied to these. Regarding the confounding comorbidities the number of comorbidities (0, 1, ≥2) has been considered as

relevant and specified for the purpose of this study. Nevertheless, it is uncertain if the number thereof or the specific types of comorbidities play a role as a confounder in the therapy outcome for MCL.

8.2.2. Propensity Score Matching

PSM will be performed incorporating the following steps:

1. Calculation of PS

   PS is calculated as the probability of patients being treated with brexucabtagene autoleucel as a function of the selected confounders. It will be derived using a multivariable model with a logit link function.

   In case of multiple imputations, PS is calculated separately in each of the 30 imputed data sets. In case of complete case analysis, PS is calculated in the complete case dataset.

   If a sufficient sample size cannot be reached for PS calculation as described above, a Firth-Regression should be carried out using the FIRTH option in the MODEL statement in PROC LOGISTIC [7]. If this is also not calculable it is only possible to conduct naïve comparisons. The sample size is not sufficient for the PS calculation if the respective model for PS does not converge.

2. PSM

   PSM will be conducted using balanced pairwise sequential nearest neighbor matching with variable 2:1 matching ratio without replacement within a caliper distance equal to 0.25 [8, 9].

3. Assessment of overlap and balance

   Overlap is assessed by the areal overlap of the propensity score densities given in percent. For the kernel density estimation, the bandwidth should be obtained by the method of Shealther and Jones [10], a gaussian kernel should be used. In case of MI, summary of the areal overlap given in percent comprises minimum, Q1, median, Q3 and maximum. Sufficient overlap is given by a median of >50%. In case of complete case analysis, sufficient overlap is given by an areal overlap of at least 50%.

   A criterion for balance (<0.25 median of the standardized difference of all confounders between treatment groups) will be applied [11]. For continuous confounders the standardized mean difference will be considered and for categorical confounders the multivariate Mahalanobis distance method will be used to calculate the standardized difference [12]. In case of MI, summary of this absolute standardized difference comprises minimum, Q1, median, Q3 and maximum for each confounder. Sufficient balance is given by a median of >0.25 for each confounder.

If sufficient overlap and balance cannot be reached, patients in non-overlapping regions will be trimmed, the PSM will be re-calculated and the overlap and balanced will be reassessed.

8.2.3. Effect Estimation and Interpretation

If sufficient overlap and balance can be reached, the calculation of effect estimates will be estimated using PS adjustment. To show superiority of brexucabtagene autoleucel, a shifted null hypothesis of HR=0.5 is assumed. To properly interpret the results of this analysis, it is necessary to compare the patient population resulting from the PS procedure to the original patient population. The detailed and comparative description of the patient populations based on the baseline characteristics will be conducted in the course of reporting the results. The tables of baseline characteristics required are listed in section 8.5.1.

If sufficient balance cannot be reached after trimming either or if the logistic regression model for PS calculation does not converge, a naïve comparison will be conducted. To account for the high uncertainty of this analysis, the criteria of a dramatic effect will be applied to show superiority. According to IQWiG General Methods Version 6.1 [14], an effect significant at a level of 1% and an observed risk of 5 to 10 respectively can no longer be plausibly explained only by confounding. Based on these statements, an HR<0.2 significant on a level of 1% is considered to show superiority of brexucabtagene autoleucel.

In case of MI, effects will be estimated in each imputed dataset. The SAS software procedure PROC MIANALYZE will be used to pool the resulting m=30 effect estimates by averaging [11, 15]. To provide baseline characteristics from the patient population resulting from the PS procedure, PROC MIANALYZE will be used to average the baseline characteristics from the m=30 imputed datasets.

8.3. Time-to-Event Analyses

For time-to-event analyses, comparison of treatment groups will be performed using a two-sided stratified log-rank test [16]. The hazard ratio (HR) with 95% confidence interval (CI) will be estimated based on a marginal Cox proportional hazards model with robust standard errors [17] with treatment as covariate.

8.4. Censoring to Address Treatment Switch

To assess the uncertainty arising from treatment switch, sensitivity analyses for mortality and morbidity, and HRQoL will be conducted. Patients with treatment switch prior to the event of interest, data cutoff date or end date of observation (whichever comes earlier) will be censored at the date of infusion of brexucabtagene autoleucel (patients with initial patient-individual treatment) or start date of one of the patient-individual therapies defined in section 2 (patients with initial brexucabtagene autoleucel therapy).

8.5. Details on Statistical Analyses

The following section summarizes all analyses planned for the data collected within this study. Milestones of planned analyses in status updates and final analysis are outlined in section 3.2.

For detailed information on planned analyses in status updates and final analysis, refer to Project Plan section 6.11.

8.5.1. Descriptive Analyses for Baseline Characteristics

The analysis of baseline characteristics will be performed as described in section 8.1 with the ITTS and the ATS. Analyses will be conducted based on the original patient population (prior PSM) and after PSM, if applicable. Descriptive analyses after PSM, after trimming if applicable, will include the standardized difference compared to the original patient population to show balance of confounders after matching instead of the column "Total". For continuous confounders the standardized mean difference will be considered and for categorical confounders the multivariate Mahalanobis distance method will be used to calculate the standardized difference [12].

Variables to be analyzed are listed in Table 4.

Table 4. Baseline Characteristics

Variable	Description
Demographic data	
Sex	Categorical (female vs male)
Age (year of index date – year of birth)	Quantitative [years]
Age categorical	Categorical (<65 vs ≥65 years)
Ethnicity	Categorical (multiple choice: Caucasian, Asian, African, other)
Disease information including diagnostic and prognostic factors (disease characteristics)	
Comorbidities Cardiac disease Diabetes Cerebrovascular disease Depression/anxiety requiring psychiatric consultation or treatment Known infection with Hepatitis B/C or HIV Renal dysfunction Pulmonary dysfunction Prior solid tumor or nonmelanoma skin cancer ties	Categorical (yes, no) for each listed comorbidity
Number of comorbidities	Categorical (0, 1, 2+)
Disease stage according to Ann Arbor	Categorical (multiple choice: Stages I, II, III, IV, unknown)
Age at diagnosis or Date of MCL diagnosis (year of diagnosis – year of birth)	Quantitative [years]
ECOG-PS	Categorical (multiple choice: 0, 1, 2, unknown)
Disease stage prior to index	Categorical (multiple choice: stages I, II, III, IV, unknown)
Bulky Disease (>7.5cm)	Categorical (yes, no)

Variable	Description
Central Nervous System (CNS) involvement (CNS lymphoma)	Categorical (yes, no)
Bone marrow involvement	Categorical (yes, no)
Presence of B symptoms at baseline (Fever >38.5°C; night sweats; weight loss)	Categorical (yes, no, unknown)
Splenic involvement (spleen enlarged)	Categorical (yes, no, unknown)
Extranodal manifestation at primary diagnosis	Categorical (yes, no)
Disease morphology	Categorical (multiple choice: classical, blastoid, pleomorphic, CLL-like, unknown, other)
Ki-67	Quantitative [%]
Ki-67 categorical	Categorical (<30%, ≥30%)
MIPI (calculated based on ECOG-PS, age, leukocyte count, and LDH)	Categorical (multiple choice: MIPI risk categories, low, intermediate, high risk; missing)
t(11; 14)	Categorical (yes, no)
Cyclin D1 overexpression	Categorical (yes, no)
TP53 mutation/ 17p deletion	Categorical (yes, no)
SOX-11 expression	Categorical (positive, negative, unknown)
LDH level	Quantitative [U/l]
LDH categorical	Categorical (<ULN, ≥ULN)
Prior therapy for MCL and outcomes (treatment history)	
Number of prior lines of therapy	Categorical (2, >2)
Bendamustine-containing therapy prior to index	Categorical (yes, no)
Prior SCT	Categorical (yes, no)
Type of prior SCT (not mutually exclusive)	Categorical (multiple choice: autologous, allogeneic, unknown)
In case of prior SCT: time from last prior SCT to index	Categorical (multiple choice: > 12 months vs ≤ 12 months)
(Chemo)therapy regimen prior to BTKi therapy(s)	Categorical (multiple choice: 1-10)
(Chemo)therapy prior to BTKi therapy(s)	Categorical (multiple choice: name of therapies)
Use of BTKi	Categorical (yes, no)
Duration of prior BTKi therapy	Quantitative [months]
Response to prior BTKi therapy	Categorical (multiple choice: refractory vs relapsed vs intolerant)
BTKi therapy(s)	Categorical (multiple choice: name of therapies)
Number of cycles (BTKi therapy)	Quantitative

Variable	Description
Best response	Categorical (CR, PR, SD, PD, not evaluable)
Post-BTKi therapy(s)	Categorical (yes, no)
Which post-BTKi therapy(s) have been used	Categorical (multiple choice: name of therapies)
Number of cycles (post-BTKi therapy);	Quantitative
Time to next treatment or death	Quantitative [months]

8.5.2. Analyses for Effectiveness Endpoints

Effectiveness analyses will be performed after PSM if criteria of sufficient overlap and balance as defined in section 8.2 are met. Otherwise, analyses will be performed without PSM.

8.5.2.1. Mortality

The algorithm to calculate time to death [months] can be found in section 6.7.1.

Overall survival (OS) will be estimated and plotted using the Kaplan-Meier (KM) method for up to 36 months of follow-up (including the number of patients at risk) separately for each treatment group.

Median OS and its two-sided 95% CI based on the log-log transformation will be tabulated along with the total number and percentage of deaths due to any cause.

The proportion of patients surviving specific time points (6 months, 12 months, 18 months, 24 months, 36 months) will be estimated using the KM method and reported along with the corresponding two-sided 95% CIs based on the log-log transformation.

Estimation of HR and comparison of treatment groups will be performed as described in section 8.3

The primary analysis will be performed with the ITTS.

Sensitivity analyses:

- The analyses described above will additionally be conducted with the ATS.
- If applicable, the analyses described above will additionally be performed after complete case PSM (without MI) with the ITTS and ATS.
- The analyses described above will additionally be performed with the ITTS, taking into account treatment switch by censoring according to section 8.4.

8.5.2.2. Morbidity

Morbidity will be assessed using the EORTC QLQ-C30 symptom scales and items (fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea) and the EORTC QLQ-NHL-HG29 scales symptom burden, neuropathy, and physical condition/fatigue.

For each of these scales, time-to-event analyses will be performed for

- time to clinically relevant deterioration of 10 points [months], and
- time to once-confirmed clinically relevant deterioration of 10 points [months]

The algorithms used to calculate the time to respective event can be found in section 6.7.2.

Time-to-event in each scale will be estimated and plotted using the KM method for up to 36 months of follow-up (including the number of persons at risk) separately for each treatment group.

Median time-to-event and its two-sided 95% CI based on the log-log transformation will be tabulated along with the total number and percentage of events.

The proportion of patients without an event at specific time points (1 month, 3 months, 6 months, 12 months, 24 months, 36 months) will be estimated using the KM method and reported along with the corresponding two-sided 95% CIs based on the log-log transformation.

Estimation of HR and comparison of treatment groups will be performed as described in section 8.3.

The primary analysis will be conducted with the ITTS and presented in separate tables for EORTC QLQ-C30 and EORTC QLQ-NHL-HG29. Patients without assessment of the EORTC QLQ-C30 questionnaire at baseline and at least one assessment post-baseline will be excluded from the analysis of the EORTC QLQ-C30. Patients without assessment of the EORTC QLQ-NHL-HG29 questionnaire at baseline and at least one assessment post-baseline will be excluded from the analysis of the EORTC QLQ-NHL-HG29.

For each scale and treatment group, the questionnaire completion rate will be provided by assessment time point (see section 6.7.3). The completion rate will be defined as the proportion of patients who completed the questionnaire at that time point using the number of patients in the ITTS alive and not withdrawn from the study at the particular time point as the denominator.

Sensitivity analyses:

- The analyses described above will additionally be conducted with the ATS. Questionnaire completion rates will not be calculated with the ATS.
- If applicable, the time-to-event analyses described above will additionally be performed after complete case PSM (without MI) with the ITTS and ATS.
- The time-to-event analyses described above will additionally be performed with the ITTS, taking into account treatment switch by censoring according to section 8.4.
- Descriptive analyses of absolute values and change from baseline as described in section 8.1 of each scale over time (months 1, 3, 6, 12, 24, and 36) will be performed with

the ITTS. Additionally, mean and standard deviation will be visualized graphically via line plots over time for each scale.

- Responder analyses with a response threshold of a decrease of 10 points for each scale at each time point of assessment (months 1, 3, 6, 12, 24, and 36) will be performed with the ITTS. Odds ratio (OR), relative risk (RR) and risk difference (RD) with 95% confidence intervals will be calculated to assess the effect size of the difference between treatment groups.

8.5.2.3. Health-related Quality of Life

HRQoL will be assessed using the EORTC QLQ-C30 functional scales (physical, emotional, cognitive, role, and social functioning) and the global Quality of Life (QoL) score as well as the EORTC QLQ-NHL-HG29 scales emotional impact and worries/fears about health and functioning.

For each of these scales and the global QoL score, time-to-event analyses will be performed for

- time to clinically relevant deterioration of 10 points [months], and
- time to once-confirmed clinically relevant deterioration of 10 points [months],

The algorithms used to calculate the time to respective event can be found in section 6.7.2.

Time-to-event in each scale and the global QoL score will be estimated and plotted using the KM method for up to 36 months of follow-up (including the number of persons at risk) separately for each treatment group.

Median time-to-event and its two-sided 95% CI based on the log-log transformation will be tabulated along with the total number and percentage of events.

The proportion of patients without event at specific time points (1 month, 3 months, 6 months, 12 months, 24 months, 36 months) will be estimated using the KM method and reported along with the corresponding two-sided 95% CIs based on the log-log transformation.

Estimation of HR and comparison of treatment groups will be performed as described in section 8.3.

The primary analysis will be conducted with the ITTS and presented in separate tables for EORTC QLQ-C30 and EORTC QLQ-NHL-HG29. Patients without assessment of the EORTC QLQ-C30 questionnaire at baseline and at least one assessment post-baseline will be excluded from the analysis of the EORTC QLQ-C30. Patients without assessment of the EORTC QLQ-NHL-HG29 questionnaire at baseline and at least one assessment post-baseline will be excluded from the analysis of the EORTC QLQ-NHL-HG29.

For each questionnaire, scale and treatment group, the questionnaire completion rate will be provided by assessment time point (see section 6.7.3). The completion rate will be defined as the proportion of patients who completed the questionnaire at that time point using the number of patients in the ITTS alive and not withdrawn from the study at the particular time point as the denominator.

Sensitivity analyses:

- The analyses described above will additionally be conducted with the ATS. Questionnaire completion rates will not be calculated with the ATS.
- If applicable, the time-to-event analyses described above will additionally be performed after complete case PSM (without MI) with the ITTS and ATS.
- The time-to-event analyses described above will additionally be performed with the ITTS, taking into account treatment switching by censoring treatment switches according to section 8.4.
- Descriptive analyses of absolute values and change from baseline as described in section 8.1 of each scale and the global QoL score over time (months 1, 3, 6, 12, 24, and 36) will be performed with the ITTS. Additionally, mean and standard deviation will be visualized graphically via line plots over time for each scale and the global QoL score.
- Responder analyses with a response threshold of a decrease of 10 points for each scale and the global QoL score at each observation time point (months 1, 3, 6, 12, 24, and 36) will be performed with the ITTS. OR, RR and RD with 95% confidence intervals will be calculated to assess the effect size of the difference between treatment groups.

8.5.3. Analyses for Safety Endpoints

Safety analyses will be performed after PSM if criteria of sufficient overlap and balance as defined in section 8.2 are met. Otherwise, analyses will be performed without PSM.

8.5.3.1. Adverse Events

The analysis of AEs will be based on the ITTS and will be conducted for the following categories:

- Serious adverse events (SAEs, defined as events that lead to hospitalization or prolongation of existing hospitalization or death)
- Adverse events leading to hospitalization or prolongation of existing hospitalization
- Adverse events of special interest (AESIs) all grades, overall and separately for each AESI specified below
- Severe AESIs with significant impairment of activity of daily living (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3), overall and separately for each AESI specified below
- Serious AESIs (defined as AESIs that lead to hospitalization or prolongation of existing hospitalization or death), overall and separately for each AESI specified below

AESIs are specified as follows:

- Cytokine release syndrome (CRS)
- Neurological events (including immune effector cell-associated neurotoxicity syndrome [ICANS]) [peripheral neuropathy])
- Infections
- Cytopenia (anemia, leukopenia, thrombocytopenia)
- Hypogammaglobulinemia

- Tumor lysis syndrome (TLS)
- Graft-versus-host disease (GvHD)
- Subsequent neoplasms
- Cardiac arrhythmias
- New cardiac failure

Time to first AE will be estimated and plotted separately for the AE categories defined above, using the KM method (including the number of patients at risk) separately for each treatment group. The algorithms to calculate the time to first AE can be found in section 6.8.2. Median time to first corresponding AE and its two-sided 95% CI based on the log-log transformation will be tabulated along with the total number and percentage of patients with at least one corresponding AE.

Estimation of HR and comparison of treatment groups will be performed as described in section 8.3.

Time-to-event analysis of SAEs and AEs leading to hospitalization or prolongation of existing hospitalization will be additionally performed and plotted by system organ class (SOC) and preferred term (PT) using the following criteria: Events occurring in at least 5% of patients in any treatment group. Tables will be ordered by most frequent SOC and corresponding PTs in descending order.

Furthermore, the incidence of the AE categories defined above will be displayed as the number and percentage of patients affected, as well as the total number of the respective events.

Sensitivity analysis:

The analysis described above will additionally be conducted with the ATS.

8.5.3.2. Cause of Death

Number and percentage of patients who died during the study will be analyzed with the ITTS and ATS. Cause of death (primary disease, toxicity, secondary cancer, other, not reported) will be analyzed as defined in section 8.1.

8.5.4. Subgroup Analysis

The following subgroups with respect to baseline will be defined:

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

All endpoints will be evaluated as described in sections 6.7, 6.8, 8.5.2 and 8.5.3.1 based on ITTS. Subgroup analyses will not include sensitivity analyses. KM curves will only be presented for

subgroup analyses with a statistically significant interaction term ($p<0.05$). In other instances where there is no statistical interaction between the treatment and the subgroup, the results will be presented in tables without showing the KM curves.

Potentially varying effects between the different subgroups of a subgroup variable will be assessed using interaction tests. MI and PSM as described in section 8.2 will be performed for all subjects. Subgroup variables will be removed from the list of confounders for the respective analyses. For time-to-event analyses, a Wald test-based p-value from a Cox regression model as defined in section 8.3 with the covariates treatment and subgroup variable and the interaction of treatment and subgroup variable will be used to identify effect modification.

Subgroup analyses are only conducted if each subgroup comprises at least 10 subjects and, in the event of binary and time-to-event data, at least 10 events occurred in one of the subgroups. If the criteria are not met in one or more of the subgroup categories, subgroups will be combined if medically appropriate.

8.5.5. Further Analyses

8.5.5.1. Planned and Actual Observation Period

The planned and the actual observation period (defined in section 6.6) will be analyzed descriptively as defined in section 8.1 with the ITTS.

8.5.5.2. Patient Disposition and Withdrawals

The date of first patient in the study (resp. D0) and last patient out of the study (resp. data cutoff date) will be given for the ITTS.

The number of patients in each analysis set will be summarized by country, center and overall.

The incidence and reason for exclusion from the ATS will be summarized using the ITTS.

The incidence of premature study termination and its reason (withdrawal of informed consent, lost-to-follow-up, death due to any cause, other) will be analyzed descriptively for the ITTS.

The incidence of not receiving an infusion of brexucabtagene autoleucel or the discontinuation of patient-individual treatment and its reason (completion of treatment, failure of response, intolerance/toxicity, patient will/physician’s decision, progression, death) will be analyzed for the ITTS.

9. TABLES AND FIGURES

Item No.	Title	Population	Content Description
1	**Tables**		
1.1	**Patient Disposition and Baseline Characteristics**		
1.1.1	Incidence and reason of premature study termination	ITTS	Descriptive statistics of incidences and reason for premature study termination by treatment group and overall
1.1.2	Duration of study	ITTS	Date of first patient in and last patient out
1.1.3	Number of patients in analysis sets by country, center and overall	ITTS	Descriptive statistics by treatment group and overall
1.1.4	Incidence and reason for exclusion from the as-treated-set	ITTS	Descriptive statistics by treatment group and overall
1.1.5	Incidence and reason for discontinuation of study treatment	ITTS	Descriptive statistics by treatment group and overall
	Baseline Characteristics		
1.1.6.1-2	Demographic characteristics	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.7.1-2	Disease characteristics	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.8.1-2	Treatment history	ITTS, ATS	Descriptive statistics by treatment group and overall
	Baseline Characteristics after PSM		
1.1.9.1-2	Demographic characteristics after propensity score matching	ITTS, ATS	Descriptive statistics including standardized difference by treatment group
1.1.10.1-2	Disease characteristics after propensity score matching	ITTS, ATS	Descriptive statistics including standardized difference by treatment group
1.1.11.1-2	Treatment history after propensity score matching	ITTS, ATS	Descriptive statistics including standardized difference by treatment group
	Baseline Characteristics after PSM: Subgroup Analysis		
1.1.12.1.1-x	Demographic characteristics after propensity score matching by <subgroup>	ITTS	Descriptive statistics including standardized difference by subgroup and treatment group
1.1.13.1.1-x	Baseline disease characteristics after propensity score matching by <subgroup>	ITTS	Descriptive statistics including standardized difference by subgroup and treatment group
1.1.14.1.1-4x	Treatment history after propensity score matching by <subgroup>	ITTS	Descriptive statistics including standardized difference by subgroup and treatment group
1.2	**Effectiveness**		
1.2.1	**Mortality**		
1.2.1.1	Summary of overall survival	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by

Item No.	Title	Population	Content Description
			treatment group, and hazard ratio with 95% CI and log-rank p-value
	Mortality: Subgroup Analysis		
1.2.1.2.1-x	Summary of overall survival by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
	Mortality: Sensitivity Analyses		
1.2.1.3	Summary of overall survival	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.2.1.4.1-2	Summary of overall survival: complete case analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.2.1.5	Summary of overall survival: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, descriptive statistics for proportions at specific time points, number and percentage of events and censored patients by treatment group hazard ratio with 95% CI and log-rank p-value
1.2.2	**Morbidity**		
	EORTC QLQ-C30 symptom scales and items (fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea)		
1.2.2.1	Summary of EORTC QLQ-C30 symptom scores – Time to clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.2	Summary of EORTC QLQ-C30 symptom scores - Time to once-confirmed clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.3	EORTC QLQ-C30 symptom scores - completion rate	ITTS	Number and percentage of patients completing EORTC QLQ-C30 symptom scores over time by treatment group and overall
	EORTC QLQ-NHL-HG29 scales (symptom burden, neuropathy, and physical condition/fatigue)		
1.2.2.4	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value

Item No.	Title	Population	Content Description
			Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.5	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.6	EORTC QLQ-NHL-HG29 - completion rate	ITTS	Number and percentage of patients completing EORTC QLQ-NHL-HG29 scores over time by treatment group and overall
	Morbidity: Subgroup Analysis		
	EORTC QLQ-C30 symptom scales and items (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)		
1.2.2.7.1-x	Summary of EORTC QLQ-C30 symptom scores – Time to clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.8.1-x	Summary of EORTC QLQ-C30 symptom scores - Time to once-confirmed clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
	EORTC QLQ-NHL-HG29 scales (symptom burden, neuropathy, and physical condition/fatigue)		
1.2.2.9.1-x	Summary of EORTC QLQ-C30 symptom scores – Time to clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.10.1-x	Summary of EORTC QLQ-C30 symptom scores - Time to once-confirmed clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
	Morbidity: Sensitivity Analyses		
	EORTC QLQ-C30 symptom scales and items (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)		
1.2.2.11	Summary of EORTC QLQ-C30 symptom scores – Time to clinically relevant deterioration	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value

Item No.	Title	Population	Content Description
			Note: Analysis for each symptom scale.
1.2.2.12	Summary of EORTC QLQ-C30 symptom scores - Time to once-confirmed clinically relevant deterioration	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.13.1-2	Summary of EORTC QLQ-C30 symptom scores – Time to clinically relevant deterioration: complete case analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.14.1-2	Summary of EORTC QLQ-C30 symptom scores - Time to once-confirmed clinically relevant deterioration: complete case analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.15	Summary of EORTC QLQ-C30 symptom scores – Time to clinically relevant deterioration: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.16	Summary of EORTC QLQ-C30 symptom scores - Time to once-confirmed clinically relevant deterioration: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.2.17	EORTC QLQ-C30 symptom scores over time	ITTS	Descriptive statistics of absolute values and change from baseline by treatment group and overall
1.2.2.18	Responder analysis of EORTC QLQ-C30 symptom scores over time	ITTS	Descriptive statistics incl. OR, RR and RD with 95% confidence intervals
	EORTC QLQ-NHL-HG29 scales (symptom burden, neuropathy, and physical condition/fatigue)		
1.2.2.19	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration: complete case analysis	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.20	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by

Item No.	Title	Population	Content Description
	deterioration: complete case analysis		treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.21.1-2	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration: Complete Case Analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.22.1-2	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration: Complete Case Analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.23	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.24	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (symptom burden, neuropathy, and physical condition/fatigue).
1.2.2.25	EORTC QLQ-NHL-HG29 scores over time	ITTS	Descriptive statistics of absolute values and change from baseline by treatment group and overall
1.2.2.26	Responder analysis of EORTC QLQ-NHL-HG29 scores over time	ITTS	Descriptive statistics incl. OR, RR and RD with 95% confidence intervals
1.2.3	**Health-related Quality of Life**		
	EORTC QLQ-C30 functional scales (physical, emotional, cognitive, role, and social functioning) and global QoL score		
1.2.3.1	Summary of EORTC QLQ-C30 functional scores and global QoL score – Time to clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by

Item No.	Title	Population	Content Description
			treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.2	Summary of EORTC QLQ-C30 functional scores and global QoL score - Time to once-confirmed clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.3	EORTC QLQ-C30 functional scores and global QoL score - completion rate	ITTS	Number and percentage of patients completing EORTC QLQ-C30 symptom scores over time by treatment group and overall
	EORTC QLQ-NHL-HG29 scales (emotional impact and worries/fears about health and functioning)		
1.2.3.4	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.5	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.6	EORTC QLQ-NHL-HG29 - completion rate	ITTS	Number and percentage of patients completing EORTC QLQ-NHL-HG29 scores over time by treatment group and overall
	Health-related Quality of Life: Subgroup Analysis		
	EORTC QLQ-C30 functional scales and global QoL score		
1.2.3.7.1-x	Summary of EORTC QLQ-C30 functional scores and global QoL score – Time to clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.8.1-x	Summary of EORTC QLQ-C30 functional scores and global QoL score - Time to once-confirmed clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
	EORTC QLQ-NHL-HG29 scales (emotional impact and worries/fears about health and functioning)		

Item No.	Title	Population	Content Description
1.2.3.9.1-x	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.10.1-x	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration by <subgroup>	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
	Health-related Quality of Life: Sensitivity Analyses		
	EORTC QLQ-C30 functional scales (physical, emotional, cognitive, role, and social functioning) and global QoL score		
1.2.3.11	Summary of EORTC QLQ-C30 functional scores and global QoL score – Time to clinically relevant deterioration	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.12	Summary of EORTC QLQ-C30 functional scores and global QoL score - Time to once-confirmed clinically relevant deterioration	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.13.1-2	Summary of EORTC QLQ-C30 functional scores and global QoL score – Time to clinically relevant deterioration: complete case analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.14.1-2	Summary of EORTC QLQ-C30 functional scores and global QoL score - Time to once-confirmed clinically relevant deterioration: complete case analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.15	Summary of EORTC QLQ-C30 functional scores and global QoL score – Time to clinically relevant deterioration: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.

Item No.	Title	Population	Content Description
1.2.3.16	Summary of EORTC QLQ-C30 functional scores and global QoL score - Time to once-confirmed clinically relevant deterioration: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each symptom scale.
1.2.3.17	EORTC QLQ-C30 functional scores and global QoL score over time	ITTS	Descriptive statistics of absolute values and change from baseline by treatment group and overall
1.2.3.18	Responder analysis of EORTC QLQ-C30 functional scores and global QoL score over time	ITTS	Descriptive statistics incl. OR, RR and RD with 95% confidence intervals
	EORTC QLQ-NHL-HG29 scales (emotional impact and worries/fears about health and functioning)		
1.2.3.19	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.20	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration	ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.21.1-2	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration: complete case analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.22.1-2	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration: complete case analysis	ITTS, ATS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.23	Summary of EORTC QLQ-NHL-HG29 – Time to clinically relevant deterioration:	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by

Item No.	Title	Population	Content Description
	Accounting for treatment switching		treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.24	Summary of EORTC QLQ-NHL-HG29 - Time to once-confirmed clinically relevant deterioration: Accounting for treatment switching	ITTS	Kaplan-Meier estimates, proportions at specific time points, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each scale (emotional impact and worries/fears about health and functioning).
1.2.3.25	EORTC QLQ-NHL-HG29 scales over time	ITTS	Descriptive statistics of absolute values and change from baseline by treatment group and overall
1.2.3.26	Responder analysis of EORTC QLQ-NHL-HG29 scales over time	ITTS	Descriptive statistics incl. OR, RR and RD with 95% confidence intervals
1.3	**Safety**		
1.3.1	**Adverse Events**		
1.3.1.1	Summary of Serious Adverse Events	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value.
1.3.1.2	Summary of Adverse Events leading to hospitalization or prolongation of existing hospitalization	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value.
1.3.1.3	Summary of Adverse Events of Special Interest all grades	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value. Note: Analysis overall and for each AES
1.3.1.4	Summary of Severe Adverse Events of Special Interest	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis overall and for each AESI.
1.3.1.5	Summary of Serious Adverse Events of Special Interest	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis overall and for each AESI.
1.3.1.6	Summary of Serious Adverse Events by System Organ Class and Preferred Term	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value

Item No.	Title	Population	Content Description
1.3.1.7	Summary of Adverse Events leading to hospitalization or prolongation of existing hospitalization by System Organ Class and Preferred Term	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.8	Incidence of Serious Adverse Events, Adverse Events leading to hospitalization or prolongation of existing hospitalization and Adverse Events of Special Interest	ITTS	Descriptive statistics of number and percentage of patients affected and the total number of SAEs, AEs leading to hospitalization or prolongation of existing hospitalization, AESIs, severe AESIs and serious AESIs
	Adverse Events: Subgroup Analysis		
1.3.1.9.1-x	Summary of Serious Adverse Events by <subgroup>	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.10.1-x	Summary of Adverse Events leading to hospitalization or prolongation of existing hospitalization by <subgroup>	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.11.1-x	Summary of Adverse Events of Special Interest all grades by <subgroup>	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each AESI.
1.3.1.12.1-x	Summary of Severe Adverse Events of Special Interest by <subgroup>	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each AESI.
1.3.1.13.1-x	Summary of Serious Adverse Events of Special Interest by <subgroup>	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis for each AESI.
1.3.1.14.1-x	Summary of Serious Adverse Events by System Organ Class and Preferred Term by <subgroup>	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.15.1-x	Summary of Adverse Events leading to hospitalization or prolongation of existing hospitalization by System Organ Class and Preferred Term by <subgroup>	ITTS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.16.1-x	Incidence of Serious Adverse Events, Adverse Events leading to hospitalization or prolongation of existing	ITTS	Descriptive statistics of number and percentage of patients affected and the total number of SAEs, AESIs, severe AESIs and serious AESIs

Item No.	Title	Population	Content Description
	hospitalization and Adverse Events of Special Interest by <subgroup>		
	Adverse Events: Sensitivity Analyses		
1.3.1.17	Summary of Serious Adverse Events	ATS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.18	Summary of Adverse Events leading to hospitalization or prolongation of existing hospitalization	ATS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.19	Summary of Adverse Events of Special Interest all grades	ATS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis overall and for each AESI.
1.3.1.20	Summary of Severe Adverse Events of Special Interest	ATS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis overall and for each AESI.
1.3.1.21	Summary of Serious Adverse Events of Special Interest	ATS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value Note: Analysis overall and for each AESI
1.3.1.22	Summary of Serious Adverse Events by System Organ Class and Preferred Term	ATS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.23	Summary of Adverse Events leading to hospitalization or prolongation of existing hospitalization by System Organ Class and Preferred Term	ATS	Kaplan-Meier estimates, number and percentage of events and censored patients by treatment group, and hazard ratio with 95% CI and log-rank p-value
1.3.1.24	Incidence of Serious Adverse Events, Adverse Events leading to hospitalization or prolongation of existing hospitalization and Adverse Events of Special Interest	ATS	Descriptive statistics of number and percentage of patients affected and the total number of SAEs, AESIs, severe AESIs and serious AESIs
1.3.2	**Cause of death**		
1.3.2.1.1-2	Cause of death	ITTS, ATS	Descriptive statistics
1.4	**Further analyses**		
1.4.1	Planned and actual observation period	ITTS	Descriptive statistics

Item No.	Title	Population	Content Description
2	**Figures**		
2.1	**Mortality**		
2.1.1	Kaplan-Meier Plot: overall survival	ITTS	
	Subgroup Figures		
2.1.2.1-x	Kaplan-Meier Plot: overall survival by <subgroup>	ITTS	
	Figures of Sensitivity Analyses		
2.1.3	Kaplan-Meier Plot: overall survival	ATS	
2.1.4.1-2	Kaplan-Meier Plot: complete case analysis: overall survival	ITTS, ATS	
2.1.5	Kaplan-Meier Plot: Accounting for treatment switching: overall survival	ITTS	
2.2	**Morbidity and Health-related Quality of Life**		
2.2.1.1-14	Kaplan-Meier Plot: EORTC-QLQ-C30 <scale xxxx>: Time to clinically relevant deterioration	ITTS	
2.2.2.1-14	Kaplan-Meier Plot: EORTC-QLQ-C30 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ITTS	
2.2.3.1-6	Kaplan-Meier Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to clinically relevant deterioration	ITTS	
2.2.4.1-6	Kaplan-Meier Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ITT	
2.2.5.1-14	Line Plot: EORTC-QLQ-C30 <scale xxxx>: mean and standard deviation over time	ITTS	
2.2.6.1-6	Line Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: mean and standard deviation over time	ITTS	
	Subgroup Figures		
2.2.7.1-14.1-x	Kaplan-Meier Plot: EORTC-QLQ-C30 <scale xxxx>: Time to clinically relevant deterioration by <subgroup>	ITTS	
2.2.8.1-14.1-x	Kaplan-Meier Plot: EORTC-QLQ-C30 <scale xxxx>: Time to once-confirmed clinically relevant deterioration by <subgroup>	ITTS	

Item No.	Title	Population	Content Description
2.2.9.1-6.1-x	Kaplan-Meier Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to clinically relevant deterioration by <subgroup>	ITTS	
2.2.10.1-6.1-x	Kaplan-Meier Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to once-confirmed clinically relevant deterioration by <subgroup>	ITTS	
	Figures of Sensitivity Analyses		
2.2.11.1-14	Kaplan-Meier Plot: EORTC-QLQ-C30 <scale xxxx>: Time to clinically relevant deterioration	ATS	
2.2.12.1-14	Kaplan-Meier Plot: EORTC-QLQ-C30 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ATS	
2.2.13.1-6	Kaplan-Meier Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to clinically relevant deterioration	ATS	
2.2.14.1-6	Kaplan-Meier Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ATS	
2.2.15.1-14	Line Plot: EORTC-QLQ-C30 <scale xxxx>: mean and standard deviation over time	ATS	
2.2.16.1-6	Line Plot: EORTC QLQ-NHL-HG29 <scale xxxx>: mean and standard deviation over time	ATS	
2.2.17.1-14.1-2	Kaplan-Meier Plot: Complete Case Analysis: EORTC-QLQ-C30 <scale xxxx>: Time to clinically relevant deterioration	ITTS, ATS	
2.2.18.1-14.1-2	Kaplan-Meier Plot: Complete Case Analysis: EORTC-QLQ-C30 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ITTS, ATS	
2.2.19.1-6.1-2	Kaplan-Meier Plot: Complete Case Analysis: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to clinically relevant deterioration	ITTS, ATS	
2.2.20.1-6.1-2	Kaplan-Meier Plot: Complete Case Analysis: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ITTS, ATS	

Item No.	Title	Population	Content Description
2.2.21.1-14	Kaplan-Meier Plot: Accounting for treatment switching: EORTC-QLQ-C30 <scale xxxx>: Time to clinically relevant deterioration	ITTS	
2.2.22.1-14	Kaplan-Meier Plot: Accounting for treatment switching: EORTC-QLQ-C30 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ITTS	
2.2.23.1-6	Kaplan-Meier Plot: Accounting for treatment switching: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to clinically relevant deterioration	ITTS	
2.2.24.1-6	Kaplan-Meier Plot: Accounting for treatment switching: EORTC QLQ-NHL-HG29 <scale xxxx>: Time to once-confirmed clinically relevant deterioration	ITTS	
2.3	**Adverse Events**		
2.3.1	Kaplan-Meier Plot: Serious Adverse Events	ITTS	
2.3.2	Kaplan-Meier Plot: Adverse Events leading to hospitalization or prolongation of existing hospitalization	ITTS	
2.3.3.1-11	Kaplan-Meier Plot: Adverse Events of Special Interest <overall/ AESI>	ITTS	
2.3.4.1-11	Kaplan-Meier Plot: Severe Adverse Events of Special Interest <overall/ AESI>	ITTS	
2.3.5.1-11	Kaplan-Meier Plot: Serious Adverse Events of Special Interest <overall/ AESI>	ITTS	
2.3.6.1-x	Kaplan-Meier Plot: Serious Adverse Events by MedDRA SOC and PT - <SOC, PT>	ITTS	
2.3.7.1-x	Kaplan-Meier Plot: Adverse Events leading to hospitalization or prolongation of existing hospitalization by MedDRA SOC and PT - <SOC, PT>	ITTS	
	Subgroup Figures		
2.3.8.1-x	Kaplan-Meier Plot: Serious Adverse Events by <subgroup>	ITTS	
2.3.9.1-x	Kaplan-Meier Plot: Adverse Events leading to	ITTS	

Item No.	Title	Population	Content Description
	hospitalization or prolongation of existing hospitalization by <subgroup>		
2.3.10.1-11.1-x	Kaplan-Meier Plot: Adverse Events of Special Interest <overall/ AESI> by <subgroup>	ITTS	
2.3.11.1-11.1-x	Kaplan-Meier Plot: Severe Adverse Events of Special Interest <overall/ AESI> by <subgroup>	ITTS	
2.3.12.1-11.1-x	Kaplan-Meier Plot: Serious Adverse Events of Special Interest <overall/ AESI> by <subgroup>	ITTS	
2.3.13.1-x.1-x	Kaplan-Meier Plot: Serious Adverse Events by MedDRA SOC and PT <SOC, PT> and <subgroup>	ITTS	
2.3.14.1-x.1-x	Kaplan-Meier Plot: Adverse Events leading to hospitalization or prolongation of existing hospitalization by MedDRA SOC and PT <SOC, PT> and <subgroup>	ITTS	
	Figures of Sensitivity Analyses		
2.3.15	Kaplan-Meier Plot: Serious Adverse Events	ATS	
2.3.16	Adverse Events leading to hospitalization or prolongation of existing hospitalization	ATS	
2.3.17.1-11	Kaplan-Meier Plot: Adverse Events of Special Interest <overall/ AESI>	ATS	
2.3.18.1-11	Kaplan-Meier Plot: Severe Adverse Events of Special Interest <overall/ AESI>	ATS	
2.3.19.1-11	Kaplan-Meier Plot: Serious Adverse Events of Special Interest <overall/ AESI>	ATS	
2.3.20.1-x	Kaplan-Meier Plot: Serious Adverse Events by MedDRA SOC and PT <SOC, PT>	ATS	
2.3.21.1-x	Kaplan-Meier Plot: Adverse Events leading to hospitalization or prolongation of existing hospitalization by MedDRA SOC and PT <SOC, PT>	ATS	

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