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 and 16 November 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 with a selection of: - Bendamustine + Rituximab - Bortezomib ± Rituximab - Lenalidomide ± Rituximab - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) - VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone) - Ibrutinib - R-BAC (Rituximab, Bendamustine, Cytarabine) - Temsirolimus - R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone) - R-Cb (Rituximab, Chlorambucil) - Venetoclax

	- High-dose therapy with allogeneic stem cell transplantation - High-dose therapy with autologous stem cell transplantation 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: - Eastern Cooperative Oncology Group performance status (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
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. Interim analyses are planned at 18, 36 and 54 months from study initiation.

Approval of the Study Project Plan

Principal investigator on behalf of the EMCL Registry:

Prof. Dr. med. Georg Heß

Signature

Date (DD Month YYYY)

Kite/Gilead accountable representatives:

Dr. Dan Tovar, Senior Director Head of Medical Affairs Midsize Markets Europe

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Date (DD Month YYYY)

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

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Dr. Elande Baro, Associate Director, Biostatistics

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Date (DD Month YYYY)

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AMS Advanced Medical Services

List of Abbreviations

Abbreviation	Term/Definition
AbD	Routine Practice Data Collection *(anwendungsbegleitende Datenerhebung)*
AE	Adverse event
AESI	Adverse event of special interest
AKdÄ	Drug Commission of the German Medical Association *(Arzneimittelkommission der deutschen Ärzteschaft)*
AMG	Medicinal Products Act (*Arzneimittelgesetz*)
AMNOG	Act on the Reform of the Market for Medicinal Products *(Arzneimittelmarkt-Neuordnungsgesetz)*
AM-NutzenV	Ordinance on the Benefit Assessment of Medicinal Products *(Arzneimittel-Nutzenbewertungsverordnung)*
aRMM	Additional risk minimization measures
ATMP	Advanced therapy medicinal product *(Arzneimittel für neuartige Therapien)*
ATS	As-treated set
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-PS	Eastern Cooperative Oncology Group Performance Status
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
HCT	Hematopoietic cell transplantation
HCT-CI	HCT-specific comorbidity index
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
NCI	National Cancer Institute
NFLymSI-18	National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Lymphoma Cancer Symptom Index - 18 Item Version

Abbreviation	Term/Definition
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PEI	Paul-Ehrlich-Institute
PIC	Patient informed consent
PICO	Population, Intervention, Comparison and Outcome
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
ULN	Upper limit of normal

Abbreviation	Term/Definition
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 and SAP, 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
3.0	16 August 2023	**Implementation of G-BA resolution of 20 July 2023:** After submission on 13 April 2023, the IQWiG and G-BA reviewed the project plan and SAP (both Version 2.0, 13 April 2023). Further necessary adjustments were published in the G-BA resolution of 20 July 2023. For details on the corresponding adjustments implemented in the project plan and SAP, please see Table 1 below. **Further changes:** - **History of Project Plan Revisions, footnote to Table 1:** Inclusion of three references regarding the G-BA resolution of 20 July 2023 - **Sections 1.2 and 6.5:** Correction of the description of project plan Version 1.0 (change from "previous" to "initial") and 2.0 (change from "present" to "previous") - **Sections 2.2.2, 2.2.3 and 2.2.3.2:** Replacement of the provisional reference "Oerlemans et al, submitted" with the full and correctly formatted reference after publication - **Various sections:** Unification of variations of "activity/ies of daily life/living" to "activities of daily living" - **Appendices 1 to 4:** Appendices have been expanded from two to four and are consistently referenced in the project plan
4.0	17 February 2025	**Implementation of G-BA resolution of 16 November 2023:** After submission on 17 August 2023, the IQWiG and G-BA reviewed the project plan and SAP (both Version 3.0, 16 August 2023). Further necessary adjustments were published in the G-BA resolution of 16 November 2023. For details on the corresponding adjustments implemented in the project plan and SAP, see Table 1 below. **Further changes:** - **History of Project Plan Revisions, footnote to Table 1:** Inclusion of three references regarding the G-BA resolution of 16 November 2023 - **Section 1.1:** Inclusion of an updated version of the Onkopedia guideline for MCL

		- **Section 1.2:** Inclusion of two references regarding the G-BA amendment resolution of 16 November 2023 - **Section 1.2, Table 2; Section 2.2; Section 2.2.4:** Adaptation of PICO scheme to the current version (Geltende Fassung) of the G-BA resolution; in a footnote, inclusion of aggregated collection of specific AEs with a significant impairment of activities of daily living or CTCAE grade ≥ 3 according to the Justification associated with the G-BA resolution of 20 July 2023; in further footnotes of Table 2, inclusion of a clarification of the wording used for the operationalization of SAEs (footnote d) and a reference to a list of neurological events in Section 2.2.4.5 (footnote i) - **Section 2.1:** Inclusion of a paragraph discussing new therapy options and changes in the positioning of therapies - **Section 2.2.3.1:** Inclusion of further details regarding the PRO collection procedure (reference to national regulations, direct distribution and collection of questionnaires at Baseline and for hospitalized patients at later time points, definition of the "target day") - **Section 2.2.4.5:** Inclusion of aggregated collection of specific AEs with a significant impairment of activities of daily living or CTCAE grade ≥ 3 according to the Justification associated with the G-BA resolution of 20 July 2023 - **Section 2.2.4.6:** Inclusion of a reference to Section 2.2.4.5 for AESIs - **Sections 2.2.4.6, 3.2 (including Figure 1), 3.4, and 4.2:** Modification of the wording in the definition of the index date to focus on the date and not the decision-making process: "tumor board <u>recommendation</u> or treatment decision <u>documented by the physician"</u> - **Section 3.1:** Change of tense to reflect that the register has already carried out adjustments - **Section 3.2, Figure 1:** Replacement of "On the same day" with "As soon as possible after the decision on treatment" and deletion of the redundant statement "After consent of the patient, the patient is included in the respective arm" - **Section 3.3:** Deletion of unclear function descriptions "lymphoma tumor board coordinators" and "coordinators or respective staff" - **Sections 3.6 and 3.6.1:** Replacement of Appendix 2 with up-to-date reference 48 (List of participating centers) to facilitate redaction; Appendix 3 thus becomes Appendix 2 and Appendix 4 becomes Appendix 3 - **Section 5.3, Table 5:** Adaptations in line with SAP and data collected in the registry - **Section 5.3, Table 6:** Inclusion of a general footnote on the documentation of treatment details as induction, consolidation or maintenance treatment - **Section 6.6:** Clarification that confounders "Duration of prior BTKi therapy" and "Response to prior BTKi therapy" also include "BTKi-containing treatments" in line with changes in Table 5

		- **Section 6.7:** Specification of the time of Ann Arbor disease stage, i.e. prior to index date - **Section 6.11:** Separation of status update reports and interim analysis reports, inclusion of the respective templates as new references - **Various sections:** Uniform use of abbreviation "ECOG-PS" in line with SAP, correction of spelling mistakes All changes made in this study protocol version are listed and explained in the corresponding addendum.

Table 1. Adjustments Requested by the G-BA according to the Resolutions of 16 March 2023, 20 July 2023 and 16 November 2023

Adjustments requested by the G-BA		Implementation
G-BA Resolution of 16 March 2023		
Mandatory adjustments (G-BA Resolution of 16 March 2023)		
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.
b) Research question according to PICO: outcome;	The study protocol must define a consistent procedure regarding the transmission of the results of the respective PRO endpoints to	**Project Plan Section 2.2.3.4 Transmission of Results of Individual PROs to Treating Centers:** Definition of a procedure regarding transmission

Adjustments requested by the G-BA		Implementation
patient-reported outcomes (PRO)	the treating centers in terms of whether information is regularly not provided or is provided in full for both groups.	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 to death. **SAP Section 8.5.3.1 Adverse Events:** SAEs are defined as events that lead to hospitalization or prolongation of existing hospitalization or to 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 general criterion ”significant impairment of the activities 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 activities 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]. 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	**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 requested by the G-BA		Implementation
	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 performance status (ECOG-PS) – 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	
f) Data source: exact definition or operationalization of exposure (type and duration of drug therapy and other concomitant therapies),	[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

Adjustments requested by the G-BA		Implementation
clinical events and confounders		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 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.

Adjustments requested by the G-BA		Implementation
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 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	**SAP Section 8.1 Descriptive Analyses:** Statement regarding testing of hypotheses was deleted for consistency. The procedure regarding

Adjustments requested by the G-BA		Implementation
	collection and analysis, will be used for data analysis and interpretation of results.	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. – 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	**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. 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.

Adjustments requested by the G-BA		Implementation
	the original target population of the routine practice data collection.	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 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.	**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:** Reshaping of tolerance windows to avoid missing returns of EORTC questionnaires. Consistently adapted in **Project Plan Table 3 (Procedure for the**

Adjustments requested by the G-BA		Implementation
		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 (G-BA Justification of 16 March 2023)		
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.
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	**Project Plan Section 2.2.4 Adverse Events and Section 2.2.4.1 Serious AEs:**

Adjustments requested by the G-BA		Implementation
	not be considered. Therefore, the collection and analysis of such an AE endpoint can be omitted in the routine practice data collection.	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 autoleucel performing centers and outside the brexucabtagene autoleucel performing centers.	**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.
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	**Project Plan Section 11 Plans for Disseminating Study Results:** Deletion of the statement.

Adjustments requested by the G-BA		Implementation
	and publications have to be approved by the pharmaceutical company.	
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".
G-BA Resolution of 20 July 2023		
a) Research question according to PICO: Outcome, patient-reported endpoints	The pharmaceutical company describes in Section 2.2.3.1 of the study protocol that in order to increase the response rate of the patient-reported outcomes, it is currently being discussed whether the patient will receive a telephone call prior to submission of the questionnaire in which the process for collecting the patient-reported outcomes will be explained verbally. For the final review of the study protocol and SAP, the process of collecting patient-reported outcomes must be finalized. Therefore, it has to be defined whether the above described telephone call to the patient will be performed or not. In addition, all other necessary measures related to the process of collecting patient-reported outcomes must be finalized.	**Project Plan Section 2.2.3.1 Considerations on Patient-reported Outcomes (PRO): Symptoms and HRQoL:** Deletion of the discussed telephone call before mailing the questionnaires. Definition of the procedure for improving PRO response rates with the help of reminder letters and reminder calls, including a clear timeline. Description of follow-up with sites and local registration offices in the absence of patient response.

Adjustments requested by the G-BA		Implementation
		Statement that questionnaires of patients hospitalized at baseline will be distributed and collected at the hospital/center, because these patients cannot receive their mail at home.
b) Research question according to PICO: Outcome, patient-reported endpoints	Compared to Version 1.0 of the study protocol, the information on the tolerance window for the collection of patient-reported outcomes was changed from months to days. However, the tolerance windows were also significantly extended. For example, for the survey time point one month after study entry, the window was expanded from 1 month ± 3 days to day 31 (day 28 to day 61). The tolerance window of survey time point month 3 (now day 92) starts on day 62. In the view of the G-BA, the extended time windows are not appropriate. Therefore, the changes in the table ”Procedure for the Collection of HRQoL using Patient Questionnaires“ in Section 2.2.3.3 of the study protocol (Version 2.0) regarding the tolerance windows for the time of the respective PRO collection have to be reversed and presented according to Table 2 in Version 1.0 of the study protocol.	**Project Plan Section 2.2.3.3 Considerations on the Frequency of Patient-reported Outcomes: Symptoms and HRQoL, Table 3 Procedure for the Collection of HRQoL using Patient Questionnaires:** A minimum width of the tolerance windows for PRO collection results from the defined processes for distribution, collection and, in case of lack of response, follow-up of questionnaires. These processes include sending the uncompleted and completed questionnaires by mail as well as reminder letters and reminder calls to the patient (see issue a above). To enable these processes and to improve patient participation, the tolerance windows in Project Plan Version 2.0 had been adjusted. A detailed justification of the tolerance windows is now provided in the footnote to Table 3. The tolerance window at baseline corresponds to the operationalization of PRO collection at baseline. The end of the tolerance window at Month 6 was shifted by one day to avoid overlap with the next time point, Month 12 (corresponding adjustment also in the SAP, Table 2).
c) Research question according to PICO: Outcome, specific adverse events (AEs)	In the specific AEs defined in the study protocol (Table 6 and Section 2.2.4.5) and in the SAP (Section 8.5.3.1), the event encephalopathy is missing as part of the neurological events.	**Project Plan Section 2.2.4.5 Specific AEs (with Indication of the Respective Degree of Severity) and Table 6 Data during Treatment and Follow-up, SAP Section 8.5.3.1 Adverse Events:**

Adjustments requested by the G-BA		Implementation
		The neurological events within the list of specific AEs have been restructured: Several AEs are now listed under the umbrella term “manifestations of ICANS”, including encephalopathy and peripheral neuropathy.
	The study protocol describes that for those of the designated specific AEs for which there is a specific definition of severity in the CTCAE catalog, the specific criterion for a CTCAE grade ≥ 3 should be collected. For those of the specific AEs for which there is no such specific definition of severity, it should be recorded whether the criterion of ”significant impairment in the activities of daily living” is met. Thus, the mode of survey presented in Table 6 of the study protocol does not provide for a separate collection as to whether the event is one with CTCAE grade ≥ 3 or whether the event meets the criterion of ”significant impairment of activities of daily living.” This does not fully correspond to the need for adjustment formulated by the G-BA in the resolution of 16 March 2023, but in the context of the routine practice data collection, the aggregated collection is assessed by the G-BA as sufficient. However, in order to ensure appropriate data collection, the G-BA considers it necessary that the investigators are provided with appropriate information materials that clarify for which of the designated specific AEs specific definitions are available and how the CTCAE grades ≥ 3 are defined. This should be specified accordingly in the study protocol.	**Project Plan Appendix 1:** Insertion of a table of severity of adverse events of special interest according to NCI CTCAE version 5.0, defining grades ≥ 3.
	For the specific AEs with indication of severity, it is not clear from the table in Section 2.2.4 of the study protocol that the severity should be determined by the CTCAE grade. This has to be specified.	**Project Plan Section 2.2.4 Adverse Events:** Clarification that severity is determined by the CTCAE grade.
	The definition of severe specific AEs provided in Section 2.2.4 of the study protocol and Section 8.5.3.1 of the SAP implies that a severe specific AE is defined solely by the criterion ”significant impairment of activities of daily living”. This is not considered appropriate, as the requirement of the G-BA is ”[...] including specific AEs leading to a	**Project Plan Section 2.2.4 Adverse Events, SAP Section 8.5.3.1 Adverse Events:** Clarification that a severe specific AE is defined by significant impairment in activities of daily living or by CTCAE grade ≥ 3.

Adjustments requested by the G-BA		Implementation
	significant impairment of the activities of daily living or with CTCAE grade ≥ 3”. Therefore, a definition has to be provided that clarifies that a severe specific AE is not defined solely by the criterion ”significant impairment of activities of daily living”.	
d) Study design: Recruitment of the study population	The selection of the countries for the routine practice data collection made by the pharmaceutical company in the study protocol is not conclusively comprehensible. The study protocol does not specify which exact criteria are used to assess a sufficiently similar standard of care. This should be clarified. Therefore, it is also not comprehensible for what reasons related to the criteria for a sufficiently similar standard of care centers collaborating with the EMCL Registry are not included in the routine practice data collection. A corresponding justification must be provided in the study protocol. The pharmaceutical company describes in the study protocol that the search for suitable centers for the routine practice data collection has not yet been completed and, for example, the participation of the center in the Netherlands is still under discussion. Before the start of the routine practice data collection, the search for suitable centers must be completed. For the final review of the study protocol and statistical analysis plan, the final participating centers must therefore be presented in the study protocol.	**Project Plan Section 3.6.1 Procedure for the Inclusion of European Centers outside Germany in the Routine Practice Data Collection:** Revision of section to specify criteria to assess a sufficiently similar standard of care in European countries and to clarify the further selection process at center level **Project Plan Appendix 2:** Inclusion of a list of participating centers at the beginning of the routine practice data collection
e) Data source: Confounders	Within the study protocol, the characteristics of the confounder ”morphology“ are not consistent with the characteristics listed in Table 5 for baseline ”morphology”. For the confounder “morphology”, the pharmaceutical company defines the characteristics classical, blastoid, pleomorphic, CLL-like and unknown. At baseline, on the other hand, the characteristics classical, blastoid, pleomorphic, unknown and other are to be collected for the morphology. This needs to be aligned.	**Project Plan Section 6.6 Variables Considered for Matching, SAP Section 8.2.1 Multiple Imputation and Section 8.5.1 Descriptive Analyses for Baseline Characteristics:** Consistent adaptation of the characteristics of morphology as classical, blastoid, pleomorphic, unknown and other.

Adjustments requested by the G-BA		Implementation
f) Data analysis: Propensity score method	With regard to the criteria for sufficient balance it has to be clarified in Section 8.2.2 of the SAP in the first sentence of the second last paragraph that it is the case of a multiple imputation and that the median refers to the results of the multiple imputation per confounder and not to the median over all confounders. For the case of a complete case analysis, the description of the criteria has to be completed. Moreover, an error in Section 8.2.2 item 3 needs to be corrected. It has to read ”Sufficient balance is given by a median of <0.25 for each confounder not >0.25”.	**SAP Section 8.2.1 Multiple Imputation and Section 8.2.3 Effect Estimation and Interpretation:** Inclusion of an explanation that it is necessary to compare the complete case dataset to the original patient population. **SAP Section 8.2.2 Propensity Score Matching:** Clarification that in case of multiple imputation the statistical values including median are provided for each confounder. Correction of the error pointed out by the G-BA.
g) Data analysis: Handling missing data	There are no indications of what efforts are being made to minimize the rate of missing values in the date information. This needs to be supplemented. The restriction to ”complete case datasets” in case of too many missing values without further classification is not appropriate. It must therefore be added to the SAP that, in the case of restriction to complete case datasets, a comprehensive justification must be provided as to the extent to which the results are still transferable to the initial population when restricted to the patient population with complete confounder data.	**Project Plan Section 8.0 Management and Control of Data Quality and Section 8.2 On-site Monitoring:** Clarification that source data verification (SDV) will include dates. **SAP Section 6.3 Handling of Missing Data:** Inclusion of a reference to Project Plan Section 8.0, mentioned above. Inclusion of a statement that it cannot be excluded that dates are not properly recorded.
G-BA Resolution of 16 November 2023		
Mandatory adjustments (G-BA Resolution of 16 November 2023)		
a) Question according to PICO: Outcome, patient-reported endpoints	The 5th step of the baseline collection describes documenting the day on which the questionnaire is received by the data trustee. For the survey time points starting from month 12, this step is described as "day x + 90 days.". This information is not plausible and must be corrected. The planned procedure, including the timeline for following up patients for the collection of patient-reported endpoints who have	**Project Plan Section 2.2.3.1 Considerations on Patient-reported Outcomes (PRO): Symptoms and HRQoL:** Unification of the follow-up of patients who have not returned the questionnaires for all time points. However, this procedure does not apply at baseline because the questionnaires are then

Adjustments requested by the G-BA		Implementation
	not returned their questionnaire to the data trustee on time, must be adapted in accordance with the information on the baseline collection. The tolerance ranges for the collection of patient-reported endpoints are still too broad and inappropriate. The tolerance ranges must be recorded in accordance with Table 2 of version 1.0 of the study protocol.	distributed and collected directly at the centers and not sent by mail. Deletion of broader time intervals, including "day x + 90 days". **Project Plan Section 2.2.3.3 Considerations on Frequency of Patient-reported Outcomes: Symptoms and HRQoL:** Adaption of tolerance ranges for PRO collection in Table 3 according to Table 2 of version 1.0 of the study protocol. Further considerations are detailed in footnote b of Table 3. Importantly, the ranges at Month 12, 24 and 36 are the same length as in version 1.0, albeit asymmetrical. **SAP Section 6.8.3 Definition of Time Window for Patient-reported Outcomes: Morbidity (Symptoms) and HRQoL:** Adaption of tolerance windows in Table 2 (Assessment Schedule) in line with changes in the study protocol.
b) Data evaluation: Dealing with missing data	A comprehensive justification for the use of a complete case dataset (among others, necessity, design) must be added.	**SAP Section 8.2.1 Multiple Imputation:** Expansion of the explanations of the use of a complete case dataset. **SAP Section 8.2.3 Effect Estimation and Interpretation:** Addition of a comment on future discussion of potential influence and bias on certainty of conclusions.
c) Question according to PICO: Comparator (amended G-BA resolution of 16 November 2023)	For the comparator of routine practice data collection, the active ingredient venetoclax should be added and the therapy option R-CHOP/R-DHAP should be deleted.	**Project Plan Synopsis, Section 1.2 Rationale for this Study, Section 2.1 Main Objective, Section 4.1.2. Inclusion Criteria for the Study Population, Table 6 Data during Treatment and**

Adjustments requested by the G-BA		Implementation
		Follow-up, **and SAP Section 2 Objectives and Endpoints:** Adaption of list of comparators in line with the amended G-BA resolution of 16 November 2023.
Recommended adjustments (G-BA Justification of 16 November 2023)		
d) Study design: Recruitment of the study population	The pharmaceutical company does not provide any further justification for the assessment that there are uncertainties regarding a sufficiently similar standard of care for study sites in Croatia and Ireland compared to Germany. This is therefore not conclusively comprehensible. Since foreign centers primarily serve to recruit patients for the comparator arm, differences in the standard of care can lead to a "selection bias". However, this could be addressed by sensitivity analyses excluding study sites from individual countries. It is therefore recommended that if the study sites from Croatia and Ireland are not included in the routine practice data collection, the justification for the exclusion of these study sites should be made clear in the study documents.	**Project Plan Section 3.6.1 Procedure for the Inclusion of European Centers outside Germany in the Routine Practice Data Collection:** Categorization of Croatia and Ireland as potentially sufficiently similar to the German standard of care for the comparator arm after re-evaluation. **Project Plan Reference [48]:** Status of centers in Croatia and Ireland invited for participation in the AbD.

Source: [1-9]

Timelines and Data Reports

Milestone	Definition
Status Update 1	6 months after start of routine practice data collection (21 February 2024)
Status Update 2, Interim Analysis 1	18 months after start of routine practice data collection (21 February 2025) Data cut: 12 months after start of routine practice data collection (21 August 2024)
Status Update 3, Interim Analysis 2	36 months after start of routine practice data collection (21 August 2026) Data cut: 30 months after start of routine practice data collection (21 February 2026)
Status Update 4, Interim Analysis 3	54 months after start of routine practice data collection (21 February 2028) Data cut: 48 months after start of routine practice data collection (21 August 2027)
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.	

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1. Disease Background and Rationale

1.1. Disease Background

Mantle Cell Lymphoma (MCL) is an aggressive, generally incurable B cell malignancy, representing approximately 6% of non-Hodgkin lymphomas (NHLs). The genetic hallmark in MCL is the chromosomal translocation t(11;14) (q13;q32) present in more than 95% of MCLs and resulting in aberrant expression of cyclin D1. Overexpression of cyclin D1 can be detected by cytogenetics or fluorescence *in situ* hybridization [10, 11].

Most patients are male, and the median age of diagnosis is 68 years [12]. 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) [13].

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 [14]. 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 [15-20] 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 [19], with recent evidence confirming that post-BTKi treatments vary widely and are associated with poor median survival [21].

Despite improvements in treatment, most patients continue to develop relapse and subsequently refractory disease and finally die due to the underlying lymphoma [22-25]. 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 [26]. 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; [11]), updated in 2021 and 2023, 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 [27].

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) [28, 29]. Table 2 has been modified to reflect the modified G-BA requirements for this routine data collection (i.e., requirements included in the resolutions published on the 16 March 2023 [30, 31]) and on 16 November 2023 [32, 33], 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 [34]. 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 [35].

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] with a selection of: - Bendamustine + Rituximab - Bortezomib ± Rituximab - Lenalidomide ± Rituximab - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) - VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone) - Ibrutinib - R-BAC (Rituximab, Bendamustine, Cytarabine) - Temsirolimus - R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone) - R-Cb (Rituximab, Chlorambucil) - Venetoclax - High-dose therapy with allogeneic stem cell transplantation - High-dose therapy with autologous stem cell transplantation taking into account the response and duration of remission of previous therapies and the general condition.
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*[d]*; overall rate*[e]) - *Adverse events leading to hospitalization or prolongation of existing hospitalization (overall rate)*[f] Specific adverse events (with indication of the respective degree of severity *including specific adverse events that lead to a significant impairment of the activities of daily living or with CTCAE grade ≥ 3*[g])[h]: o Cytokine release syndrome (CRS) o Neurological events (including immune effector cell-associated neurotoxicity syndrome, encephalopathy and peripheral neuropathy)[i] o Infections o Cytopenias (anemia, leukopenia, thrombocytopenia) o Hypogammaglobulinemia o Tumor lysis syndrome (TLS) o Graft-versus-host disease (GvHD) o Subsequent neoplasms o Cardiac arrhythmias o New cardiac failure

[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] Comparator adapted, including addition of treatment option venetoclax, removal of treatment option R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) / R-DHAP (Rituximab, Dexamethasone, high-dose Cytarabine, Cisplatin) and moving the list of therapies from the footnote up into the comparator line (Version 3.0).

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

[d] In the outcome category "adverse events" of the current PICO scheme by the G-BA, "serious adverse events" are defined as: "Events leading to hospitalization or prolonging existing hospitalization **and leading to death**" ("Ereignisse, die zur Hospitalisierung führen oder eine bestehende Hospitalisierung verlängern **und die zum Tod führen"**).
To avoid the potential misinterpretation that both conditions (hospitalization/hospitalization prolongation and death) must be present, the wording in the present PICO scheme has been adjusted to: "Serious adverse events (SAEs), defined as events that lead to hospitalization, prolongation of existing hospitalization, **or to death**."
In this context, the following formulations, which can be found throughout the documents of this study intend to convey the same meaning:

- "Events leading to hospitalization or prolongation of existing hospitalization and events resulting in/leading to death"
- "Events leading to hospitalization or prolongation of existing hospitalization or to death"
- "Events leading to hospitalization or prolongation of existing hospitalization and resulting in/leading to death"

[e] Text in italics replaced "SAE; overall rate" of initial version (Version 1.0).

[f] Text in italics replaced "severe adverse events (overall rate)" of initial version (Version 1.0).

[g] Text in italics was added.

[h] In the "Justification" for the resolution of 20 July 2023 following the second review of the study documents, the G-BA clarifies that a CTCAE grade ≥ 3 or a significant impairment of the activities of daily living are regarded as criteria for severe specific AEs. However, in the context of the AbD, the G-BA considers the aggregated collection of specific AEs with a significant impairment of activities of daily living or CTCAE grade ≥ 3 to be sufficient.

[i] The neurological events, which include manifestations of immune effector cell-associated neurotoxicity syndrome (ICANS) as well as neurological events expected in the control arm, that were added to the project plan V3.0, are presented in Section 2.2.4.5.

Source: [5, 28, 30-33, 36]

The G-BA set further requirements for study design and data source for the present routine practice data collection [28] 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", 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-BAC (Rituximab, Bendamustine, Cytarabine)
- Temsirolimus
- R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone)
- R-Cb (Rituximab, Chlorambucil)
- Venetoclax
- High-dose therapy with allogeneic stem cell transplantation
- High-dose therapy with autologous stem cell transplantation

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

It must be taken into account that new therapy options may be introduced in Germany within the brexucabtagene autoleucel application area. For instance, in mid-September 2024, Pirtobrutinib was introduced for the treatment of patients with R/R MCL who have previously received a BTKi. Furthermore, the positioning of therapies may continue to evolve, as the current recommendation of the Competence Center for Oncology shows (i.e., the use of ibrutinib already in first-line therapy according to the protocol of the TRIANGLE study and the use of brexucabtagene autoleucel in second-line therapy for patients with relapse after the use of the TRIANGLE protocol in the first line who have TP-53 mutation/POD 24 [37, 38]). These developments could potentially reduce the number of patients who might be eligible for the present AbD.

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 [39, 40]. 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 [40]. 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 (overall rate)
  - Specific adverse events (=adverse events of special interest, AESIs) with indication of the respective degree of severity including specific adverse events that lead to a significant impairment of the activities of daily living or with CTCAE grade ≥ 3)

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) [41] version 3.0 and the EORTC Quality of Life

	Questionnaire Non-Hodgkin Lymphoma High Grade 29 Module (QLQ-NHL-HG29) [42, 43]. 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 [41] version 3.0 and the EORTC QLQ-NHL-HG29 [42, 43]. 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 [11]. 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 [40]. 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% [40]. 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 [44]. 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. Depending on the national regulations of the contributing countries concerning patient identifying data, IMBEI will receive and store the following data for each patient in the registry:

- Name, surname
- Postcode and address at the time of entry in the registry
- Telephone numbers, if available (landline and mobile phone)
- Date of birth

These 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. An exception is the baseline (t0) data collection, in which the questionnaires are handed out to the patients directly by the staff at the respective study center and sent to the IMBEI to a secure data platform. In order to increase the participation during the follow-up period, the following procedure will be implemented for timepoints t1-t6 (follow-up). The **target day** is the day on which the participant should ideally complete the PRO questionnaires.

1. **Target day -4d:** The IMBEI sends the questionnaires (in the local language) together with a stamped envelope via mail to the patients. The date of the postage is documented. In a letter accompanying the questionnaires (in the local language), the patients are asked to send the completed questionnaires back to the IMBEI within 7 days. It should be noted that the questionnaires may only be distributed after the patient has provided informed consent (Section 9.1).
2. **Target day +14d:** If the IMBEI does not receive the completed questionnaires by that date, a reminder letter will be sent out asking to complete/return the questionnaires now. It will also be offered to send the questionnaires again via mail. At the same time, the local investigators will be informed via secure email about the missing questionnaires and asked about any reasons they might know why the patient does not respond (e.g., complications, inpatient treatment, death, etc.).
3. **Target day +21d:** If still no letter is received, IMBEI staff will call the patient and ask whether the questionnaires have been received, and if so whether there are any problems with completion. If a

patient does not wish to complete the questionnaires at this time, the case will be closed for this occasion. These calls will be performed by trained personnel, ensuring not to put pressure on the patient but to remove potential hurdles that may hinder completion despite the patients wishing to do so. All calls will be made in the patients' local language.

4. **Target day +22d to +27d:** If the patient is not available on target day +21d, an effort will be made to contact the patient between target day +22d to +27d by phone. A maximum of two contact attempts will be conducted; if there is no response to the initial call, a second attempt will be initiated.
5. **All days:** The date of the return of the questionnaires is documented by IMBEI.

- The same procedure is followed for all time points except for 'baseline' (t0). The exact target dates for the follow-up surveys (t1-t6) and the corresponding tolerance windows can be found in Table 3.

In all letters sent to the patients, they will be given a contact number to call the IMBEI in case there are questions about completing the questionnaires.

If a letter is undeliverable, IMBEI will retrieve the current address (or potential date of death) from the local registration office (for all German patients) or from the local site (for all non-German patients). IMBEI will then resend the letter to the new address. In the rare cases when patients are hospitalized during the follow-up period (t1-t6), IMBEI contacts the study centers and asks them to distribute and collect the questionnaires. If a study center, due to country-specific legal requirements, is not allowed to transmit the person-identifying data to the IMBEI, the data collection is carried out by the study center. The completed questionnaires are sent to the IMBEI once per quarter in accordance with European data protection regulations.

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 [45] 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 [46]. 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 [43]. 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 [47].

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 [48]. 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	Target Day[a]	Tolerance Window[b]	Responsible for Administration of PRO Instruments
Baseline (t0)	Day 0	Day 0 – Day 27 (-0d / +27d)	Therapy center
Month 1 (t1)	Day 31 [Day 0 + 1m]	Day 28 – Day 61 (-3d / +30d)	Trust center (IMBEI) / Therapy center (abroad)
Month 3 (t2)	Day 92 [Day 0 + 3m]	Day 85 – Day 122 (-7d / +30d)	Trust center (IMBEI) / Therapy center (abroad)
Month 6 (t3)	Day 183 [Day 0 + 6m]	Day 176 – Day 213 (-7d / +30d)	Trust center (IMBEI) / Therapy center (abroad)
Month 12 (t4)	Day 366 [Day 0 + 12m]	Day 359 – Day 419 (-7d / +53d)	Trust center (IMBEI)/ Therapy center (abroad)
Month 24 (t5)	Day 731 [Day 0 + 24m]	Day 724 – Day 784 (-7d / +53d)	Trust center (IMBEI) / Therapy center (abroad)

Time Point	Target Day[a]	Tolerance Window[b]	Responsible for Administration of PRO Instruments
Month 36 (t6)	Day 1096 [Day 0 + 36m]	Day 1089 – Day 1149 (-7d / +53d)	Trust center (IMBEI) / Therapy center (abroad)

Day 0 is the index date, i.e., the date of tumor board recommendation or of therapy decision documented by the physician, as applicable. For detailed description of baseline see SAP chapter 6.4.

[a] Target day is the day on which the PRO questionnaires should ideally be completed.

[b] A minimum width of the tolerance windows results from the defined processes for distribution, collection and, in case of lack of response, follow-up of questionnaires. These processes require at least 28 days in total (see Section 2.2.3.1 for a detailed description of these processes). The tolerance window at baseline corresponds to the operationalization of PRO collection at baseline (Section 3.4). From Month 1 onwards the asymmetric tolerance windows are set wider than the bare minimum required in order to increase the response rates of PRO. The asymmetric tolerance windows (-3d or -7d / +30d) for Month 1, Month 3, and Month 6 take into account the return tracking process, reminder letters / phone calls to participants and logistic constraints (delays/weekends/public holidays). The asymmetric tolerance windows (-7d/ +53d) for Month 12, Month 24 and Month 36 are set wider to achieve higher response rates without compromising the validity of the data. In these later stages of treatment, it may be assumed that the quality of life will not change quickly and that the patients may be more mobile and more difficult to reach (e.g., when travelling).

As outlined above, the HRQoL questionnaires will be sent out by the trust center (except for baseline), 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 to death; overall rate) - Adverse events leading to hospitalization or prolongation of existing hospitalization (overall rate) - Specific adverse events (=adverse events of special interest, AESIs) with ”significant impairment in activities of daily living” or with CTCAE grade ≥ 3[a] AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).
[a] Only severe AESIs are to be collected based on the PICO schema defined by the G-BA (Table 2). Severe AESIs are defined as those that lead to impairment of the activities of daily living or have a CTCAE grade ≥3. In the ‘Justification’ for the resolution of 20 July 2023 following the second review of the study documents, the G-BA clarifies that a CTCAE grade ≥ 3 or a significant impairment of the activities of daily living are regarded as criteria for severe specific AEs. However, in the context of the AbD, the G-BA considers the aggregated collection of specific AEs with a significant impairment of activities of daily living or CTCAE grade ≥ 3 to be sufficient [5, 36].	

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 [30, 31] 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 [30, 31] 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 [49]: *"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 [30, 31] 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 pointed 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 [30, 31], 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 living or with a CTCAE grade ≥ 3) [1-3]. The present project plan has been adapted accordingly. In the "Justification" for the resolution of 20 July 2023 following the second review of the study documents, the G-BA states that, in the context of the AbD, the aggregated collection of specific AEs with a significant impairment of activities of daily living or CTCAE grade ≥ 3 is considered sufficient [5, 36].

Additionally, in the G-BA resolution that amends the initially established PICO schema [30, 31], 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 manifestations of immune effector cell-associated neurotoxicity syndrome [ICANS])
- Infections
- Cytopenias (anemia, leukopenia, thrombocytopenia)
- Hypogammaglobulinemia
- Tumor lysis syndrome (TLS)
- Graft-versus-host disease (GvHD)
- Subsequent neoplasms
- Cardiac arrhythmias
- New cardiac failure

In the present version of the project plan, the neurological events that will be collected are specified. It is clarified that neurological events include neurological events of interest in both arms. Events associated with administration of certain types of immunotherapies, especially immune effector cell and T cell engaging therapies, are known as immune effector cell-associated neurotoxicity syndrome (ICANS).

The following concrete neurological events will be collected (this includes manifestations of ICANS as well as neurological events expected in the control arm):

- Encephalopathy
- Tremor
- Cognitive disturbance
- Delirium
- Dysphasia
- Somnolence
- Lethargy
- Agitation

- Concentration impairment
- Seizure
- Dysarthria
- Peripheral neuropathy

The definition of CTCAE grades ≥ 3 for the above specified adverse events of special interest, where available, are listed in Appendix 1.

2.2.4.6. Considerations on the Duration of AE Assessment

The investigator is responsible for reporting all SAEs and AESIs (as defined in Section 2.2.4.5) after the index date (i.e., tumor board recommendation or treatment decision documented by the physician) 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 has undergone 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 [40] and of the G-BA, which specify the procedure in the rules of procedure of the G-BA [39] 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 [49]. 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.

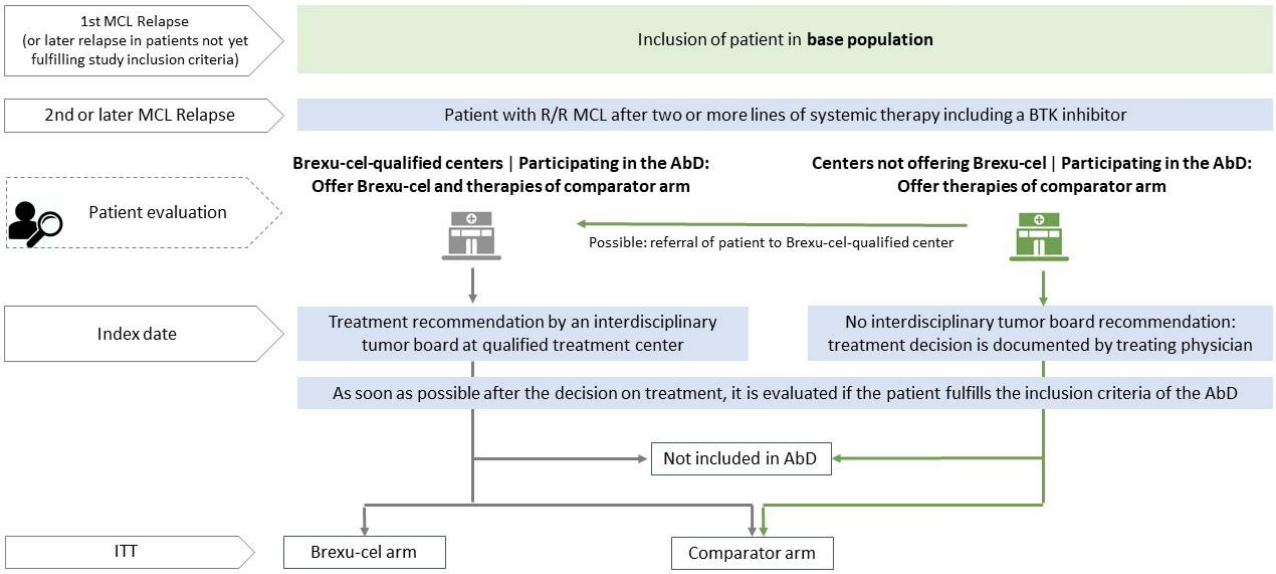
Patients are treated with brexucabtagene autoleucel in dedicated centers. There, a treatment recommendation is usually made by an interdisciplinary tumor board. Yet, the final therapy decision can be based on factors other than the tumor board recommendation, see previous paragraph. If, for example, the tumor board recommends treatment with brexucabtagene autoleucel for a patient, but the patient chooses a therapy from the comparator arm – which is expected to be very rare in this indication and line of therapy – this patient will be included in the comparative treatment arm.

A tumor board recommendation 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 recommendation by a tumor board, but by the treating physician. In this case, the date of therapy decision documented by the physician 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.

As soon as possible after the treatment decision is taken and documented, it can be 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. CAR T qualified centers as well as 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 (i.e., 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 Day 0). The baseline value will be defined as the last non-missing value prior to or until Day 0 if available. If no baseline value prior to or until Day 0 is available, the last non-missing value until date of infusion of brexucabtagene autoleucel or first administration of patient-individual therapy will be used (SAP Section 6.4). After the therapy recommendation by the tumor board (or the treatment decision documented by the treating physician), the treatment of patients may start within a short timeframe. 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 [35].

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 [35]. 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.

In accordance with the G-BA's resolution dated 21 July 2023, a list of centers participating in the routine practice data collection as to 21 August 2023 is included as reference [50]. Should any additional centers be under consideration for inclusion in the study, (e.g., due to qualification or contract completion with the EMCL-R), the proposed additions will be communicated to the G-BA. Subsequently, these inclusions will be integrated into the study after consent by the G-BA, either through an addendum to reference [50] or in accordance with specific requirements of the G-BA.

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 arm; Figure 1). Non-CAR T centers in Germany and other European countries activated for the EMCL-R are listed in reference [50]. 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 R/R 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 [11].

The main prerequisite for participation in this routine practice data collection is a standard of care in these countries that is sufficiently similar to the German standard of care. This similarity is determined by factors such as access to medicines (e.g., mirroring the options available in Germany, particularly within the control arm. Furthermore, medications like ibrutinib are accessible in earlier stages of treatment) and access to patient care (i.e., treatment by experienced hemato-oncologists and in specialized centers). For the most part, these criteria are certainly met in Austria, Italy, the Netherlands, Poland, Portugal and Spain. After re-evaluation, Croatia and Ireland were also deemed potentially comparable to the German standard of care for the comparator arm.

Further selection occurred at the center level. To enhance the study's success, the inclusion of expert centers with a strong dedication to both research and the treatment of MCL patients was sought. This dedication was evident and reflected through their active involvement in the EMCL network. The EMCL-R team in Mainz, well-versed in local conditions, reached out to these centers. Another crucial factor in the selection of the centers was the willingness and feasibility to partake in the routine practice data collection: Italian and Spanish sites refused to participate; the latter well justified by their retrospective approach to data collection. Including Austrian and Dutch centers is ongoing.

Through this process, several European centers were recruited to participate, namely in Poland, Portugal, Austria, Ireland and Croatia. In accordance with the G-BA's resolution dated 21 July 2023, the list of all the centers currently involved in the routine practice data collection can be found in reference [50].

Should any additional centers be under consideration for inclusion in the study, (e.g., due to qualification for administration of CAR T cell therapy, contract completion with EMCL-R), the proposed additions will be communicated to the G-BA. Subsequently, these inclusions will be integrated into the study following consent by the G-BA and either through an addendum to reference [50] or in accordance with specific requirements stipulated by the G-BA.

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:
    - Bendamustine + Rituximab
    - Bortezomib ± Rituximab
    - Lenalidomide ± Rituximab
    - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)
    - VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone)
    - Ibrutinib
    - R-BAC (Rituximab, Bendamustine, Cytarabine)
    - Temsirolimus
    - R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone)
    - R-Cb (Rituximab, Chlorambucil)
    - Venetoclax
    - High-dose therapy with allogeneic stem cell transplantation
    - High-dose therapy with autologous stem cell transplantation
- 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:

- Eastern Cooperative Oncology Group performance status (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

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 recommendation 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

Data 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/Other)	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, Black, Asian, Hispanic, 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[c] at primary diagnosis	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-PS[c]	Categorical (multiple choice: 0, 1, 2, unknown)	Yes
Date of ECOG-PS assessment	Quantitative -Date	Yes
Disease stage according to Ann Arbor[c] prior to index date	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

Demographic data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
Bone Marrow involvement	Categorical (Y/N)	Yes
Presence of B symptoms at baseline (Fever >38.5°C; night sweats; weight loss)	Categorical (Y/N/unknown)	Yes
Splenic involvement (spleen enlarged)	Categorical (Y/N/unknown)	Yes
Extranodal manifestation at primary diagnosis	Categorical (Y/N)	Yes
Disease morphology	Categorical (multiple choice: classical, blastoid, pleomorphic, unknown, other)	Yes
Ki-67	Quantitative [%]	Yes
MIPI (calculated based on ECOG-PS, age, leukocyte count, and LDH)	Categorical (multiple choice: MIPI risk categories: low (< 5.7), intermediate (≥ 5.7 and ≤ 6.2), high risk (> 6.2); 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)[d]	Quantitative [U/l]	Yes
Leukocyte count	Quantitative [10^9/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

Demographic data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
(Chemo)therapy regimen prior to BTKi therapy(s) / BTKi-containing treatment(s)	Categorical (multiple choice: 1-10)	Yes
(Chemo)therapy prior to BTKi therapy(s) / BTKi-containing treatment(s)	Categorical (multiple choice: name of therapies)	Yes
Use of BTKi	Categorical (Y/N)	Yes
Duration of prior BTKi therapy / BTKi-containing treatment	Quantitative [days]	Yes
Response to prior BTKi therapy / BTKi-containing treatment	Categorical (multiple choice: complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], not evaluable [n.e.])	Yes
BTKi therapy(s) / BTKi-containing treatment(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 (time from last prior therapy to study treatment)	Diverse	Yes
Symptoms[e]		
Symptoms by means of 9 symptom scales from the EORTC QLQ-C30[f]	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[e]		
HRQoL by means of EORTC QLQ-C30 function scales, global scale	Quantitative (scale scores)	Yes

Demographic data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
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 Hematopoietic Cell Transplantation-specific Comorbidity Index HCT-CI [51] and relevance for MCL patients.

[c] Classification of Ann Arbor Disease Staging and ECOG-PS is shown in Appendix 2.

[d] LDH measured by < ULN vs ≥ ULN [52].

[e] Operationalization of the PRO collection at baseline: a time window of 28 days from the index date (Day 0 – Day 27) applies in order to ensure that baseline data are available (Section 3.4).

[f] 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-BAC (Rituximab, Bendamustine, Cytarabine) - Temsirolimus - R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone) - R-Cb (Rituximab, Chlorambucil) - Venetoclax	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
Other	Categorical (Y, N)	Yes
End of Induction	Categorical (Y, N)	Yes

Data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
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 to 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 manifestations of immune effector cell-	Categorical (Y, N)	Yes

Data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
associated neurotoxicity syndrome [ICANS], for details see below this list) - Infections - Cytopenias (anemia, leukopenia, thrombocytopenia) - Hypogammaglobulinemia - Tumor lysis syndrome (TLS) - Graft-versus-host disease (GvHD) - Subsequent neoplasms - Cardiac arrhythmias - New cardiac failure The following concrete neurological events will be collected (this includes manifestations of ICANS as well as neurological events expected in the control arm): - Encephalopathy - Tremor - Cognitive disturbance - Delirium - Dysphasia - Somnolence - Lethargy - Agitation - Concentration impairment - Seizure - Dysarthria - Peripheral neuropathy		
Significant impairment of activities of daily living or CTCAE grade ≥ 3 only for Adverse Events of Special Interest (listed in row above) [d]	Categorical (Y, N)	Yes
Resolution Date	Quantitative – date (dd.mm.yyyy)	Yes

Data	Variable/Description	Collected in EMCL-R at start of routine practice data collection?[a]
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

Treatment details are documented in the registry database under the categories induction, consolidation and maintenance. Bridging therapy, which is administered as part of treatment with brexucabtagene autoleucel, is categorized as induction therapy. Leukapheresis, lymphodepletion therapy and the administration of CAR T cells are collected under consolidation therapy. None of the steps associated with treatment with brexucabtagene autoleucel are collected under maintenance therapy.

[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 (Day 0 – Day 27) 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).

[d] The definition of CTCAE grades ≥ 3 for the adverse events of special interest, where available, are listed in Appendix 1.

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 [53-56]. 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 [57]. 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 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 3.

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
	Ki-67	Substantial impact[b]	Yes (plus checkbox: Not Done)
	LDH	Substantial impact [b]	Yes

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

Grouping	Confounder	Result of Expert Review	Currently Collected in EMCL-R[a]
	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 (August 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 [51] 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 nonmelanoma skin cancer

In the initial 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 3 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, other)
- 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 [10^9/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, unknown, 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 / BTKi-containing treatment (months)
    - Response to prior BTKi therapy / BTKi-containing treatment (CR, PR, SD, PD, n.e.)

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 prior to index date (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 [58]. 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 [22-25]. Furthermore, brexucabtagene autoleucel is depicted in German Onkopedia guidelines [11] 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 [59] with the library *gsDesign* [60]. 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 enrolment, 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

Status update reports will be prepared according to the template provided by the G-BA [61]. Interim analysis reports will be prepared using module 4 of the dossier template [62], particularly Section 4.2.5. (Information synthesis and analysis) and Section 4.3.2.2 (Non-randomized comparative studies).

6.11.1. Status Update 1 (Information on the Status of Recruitment)

A first status update report 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 report 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 report and a first interim analysis report will be submitted to the G-BA 18 months after start of the routine practice data collection defined in the determination resolution. These reports will include:

- Interim analysis
    - 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
- Status update
    - 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 report and second interim analysis report will be submitted to the G-BA 36 months after start of the routine practice data collection defined in the determination resolution. These reports will include:

- Interim analysis
    - 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
- Status update
    - 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 report and third interim analysis report will be submitted to the G-BA 54 months after start of the routine practice data collection defined in the determination resolution. These reports will include:

- Interim analysis
    - 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
- Status update
    - 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; [63]). 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, including dates, 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, including dates, 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 [64].

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 [65].

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. Severity of Adverse Events of Special Interest According to NCI CTCAE Version 5.0: Definition of Grade 3, 4 and 5

Adverse Event of Special Interest	MedDRA SOC	CTCAE Term	Grade 3	Grade 4	Grade 5
Cytokine release syndrome (CRS)	Immune system disorders	Cytokine release syndrome	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated	Death
Encephalopathy	Nervous system disorders	Encephalopathy	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Peripheral neuropathy	Nervous system disorders	Peripheral motor/ sensory neuropathy	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Infections	Infections and infestations	"Various infections" [b]	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Anemia	Blood and lymphatic system disorders	Anemia	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Leukopenia	Investigations	Lymphocyte count decreased	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Neutropenia	Investigations	Neutrophil count decreased	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Thrombocytopenia	Investigations	Platelet count decreased	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Hypogammaglobulinemia [a]	-	-	-	-	-

Adverse Event of Special Interest	MedDRA SOC	CTCAE Term	Grade 3	Grade 4	Grade 5
Tumor lysis syndrome (TLS)	Metabolism and nutrition disorders	Tumor lysis syndrome	Present	Life-threatening consequences; urgent intervention indicated	Death
Graft-versus-host disease (GvHD) [a]	-	-	-	-	-
Subsequent neoplasms	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Cardiac arrhythmias	Cardiac disorders	Ventricular arrhythmia	Urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
New cardiac failure	Cardiac disorders	Heart failure	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death

ADL, Activities of daily living; CRS, Cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; GvHD, Graft-versus-host disease; ICANS, Immune effector cell-associated neurotoxicity syndrome; MedDRA, Medical dictionary for regulatory activities; NCI, National Cancer Institute; SOC, System Organ Class; TLS, Tumor lysis syndrome. A semi-colon indicates "or" within the description of the grades; a single dash (-) indicates that a grade is not available.

[a] No CTCAE term. In this case, the alternative criterion "impairment activities of daily living" will be applied.

[b] The common definitions of the grades among different types of infections are shown.

Appendix 2. Classification of ECOG Performance Status and Ann Arbor Disease Staging

A. ECOG Performance Status

Eastern Cooperative Oncology Group performance status (ECOG-PS)	
Grade	ECOG-PS
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 3. Technical Report: Confounders in the Investigation of Treatments for Relapsed/Refractory Mantle Cell Lymphoma: A Systematic Literature Review. Version 1, 08 December 2022

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 4.0
Release Date:	17 February 2025
Replaces Previous Version(s):	SAP version 3.0

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

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Signature Date (DD Month YYYY)

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

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Signature Date (DD Month YYYY)

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

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Signature Date (DD Month YYYY)

AMS accountable representative:

Silke Seemüller, Director Biostatistics

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Signature Date (DD Month YYYY)

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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
Day 0	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
HCT	Hematopoietic cell transplantation
HCT-CI	HCT-specific comorbidity index
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
ULN	Upper limit of normal
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 1 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 6.9.2 Time to (once-confirmed) clinically relevant deterioration:** Adding endpoint "once-confirmed clinically relevant deterioration" (G-BA resolution issue s). • **Section 6.9.3 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 6.10.1 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 to 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 to 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.
3.0	16 August 2023	Editorial changes to correct spelling mistakes, grammatical errors and improve readability Adjust the date and number of the SAP version After submission on 13 April 2023, the IQWiG and G-BA reviewed the Project Plan and SAP (both Version 2.0, 13 April 2023). Further necessary adjustments were published in the G-BA resolution of 20 July 2023. Implementation of G-BA resolution of 20 July 2023 (see Table 1 Adjustments Requested by the G-BA according to the Resolutions of 16 March 2023 and 20 July 2023 in the Project Plan):

		• **Section 8.5.3.1 Adverse Events:** The neurological events within the list of specific AEs have been restructured: Several AEs are now listed under the umbrella term "manifestations of ICANS", including encephalopathy and peripheral neuropathy. • **Section 8.5.3.1 Adverse Events:** Clarification that a severe specific AE is defined by significant impairment in activities of daily living or by CTCAE grade ≥ 3. • **Section 8.2.1 Multiple Imputation and Section 8.5.1 Descriptive Analyses for Baseline Characteristics:** Consistent adaptation of the characteristics of morphology as classical, blastoid, pleomorphic, unknown and other. • **Section 8.2.1 Multiple Imputation, Section 8.2.3 Effect Estimation and Interpretation and Section 8.5.1 Descriptive Analyses for Baseline Characteristics:** Inclusion of an explanation that it is necessary to compare the complete case dataset to the original patient population. • **Section 8.2.2 Propensity Score Matching:** Clarification that in case of multiple imputation the statistical values including median are provided for each confounder. Correction of the error pointed out by the G-BA. • **Section 6.3 Handling of Missing Data:** Inclusion of a reference to Section 8.0 of the Project Plan, mentioned above. Inclusion of a statement that it cannot be excluded that dates are not recorded properly.
4.0	17 February 2025	Editorial changes to correct spelling mistakes, grammatical errors and improve readability. Renumbering of Sections 6.6 to 6.10.2 due to moved and added sections. Adjust the date and number of the SAP version. After submission on 16 August 2023, the IQWiG and G-BA reviewed the Project Plan and SAP (both Version 3.0, 16 August 2023). Further necessary adjustments were published in the G-BA resolution of 16 November 2023. Implementation of G-BA resolution of 16 November 2023 (see Table 1 Adjustments Requested by the G-BA according to the Resolutions of 16 March 2023, 20 July 2023 and 16 November 2023 in the Project Plan). • **Section 2 Objectives and Endpoints:** By G-BA's resolution of 16 November 2023 the comparator of the routine practice data collection was adjusted. The active ingredient venetoclax was added to the study documents for the comparator of routine practice data collection and the therapy option R-CHOP/R-DHAP was deleted. (G-BA resolution issue c). • **Section 5 Data Review Meeting:** Process of the DRM was further specified in order to describe the procedure in detail. • **Section 6.4 Index Date and Baseline** Change of the term "tumor board decision" to "tumor board

		recommendation" to avoid the implication that the final treatment decision is made by the tumor board. • **Section 6.6 Time Derivation:** Moved section behind Section 6.4 for improved and sensible structure of the chapter. • **Section 6.8 Calculation of Duration Until Occurrence of an Event** Insert calculation of duration as an additional section for sensible structure of derivations. Content was moved from Section 6.9.3 to this new section. • **Section 6.9.3 Definition of Time Window for Patient-Reported Outcomes: Morbidity (Symptoms) and HRQoL:** Update of Table 2 according to Project Plan. By G-BA's resolution of 16 November 2023 tolerance windows were to be updated (G-BA resolution issue a). Wider tolerance windows than proposed in version 1.0 were partly necessary to ensure flow of planned process incorporating collection of questionnaires that have not been returned to the data trustee. • **Section 8.2.1 Multiple Imputation** By G-BA's resolution of 16 November 2023 justification for the use of a complete case dataset was requested. The entire process is summarized in Figure 1 and described in Section 8.2.1. Additional comment added in Section 8.2.3. Categories for response to prior BTKi therapy changed to CR, PR, SD, n.e., in line with the documentation in the registry's database. • **Section 8.5.1 Descriptive Analyses for Baseline Characteristics** Adaptations of Table 4 to data collected in the registry. All changes made in this SAP version are listed and explained in the corresponding addendum.

1. INTRODUCTION

This Statistical Analysis Plan (SAP) refers to the Project Plan, final version 4.0 dated 17 February 2025. The SAP will be in a nearly final version before any analyses will be conducted with only minor adjustments still possible. 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:

- Bendamustine + Rituximab
- Bortezomib ± Rituximab
- Lenalidomide ± Rituximab
- R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)
- VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone)
- Ibrutinib
- R-BAC (Rituximab, Bendamustine, Cytarabine)
- Temsirolimus
- R-FCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone)
- R-Cb (Rituximab, Chlorambucil)
- Venetoclax
- High-dose therapy with allogeneic stem cell transplantation
- High-dose therapy with autologous stem cell transplantation

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 and prior treatment strategies of patients in both treatment arms will be collected as soon as possible after the documented treatment decision 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 (see Section 2 and Project Plan Section 2.1)
- 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 into the study if one or more of the following criteria apply:

- 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 (21 February 2024)
Status Update 2, Interim Analysis 1	18 months after start of routine practice data collection (21 February 2025) Data cut: 12 months after start of routine practice data collection (21 August 2024)
Status Update 3, Interim Analysis 2	36 months after start of routine practice data collection (21 August 2026) Data cut: 30 months after start of routine practice data collection (21 February 2026)
Status Update 4, Interim Analysis 3	54 months after start of routine practice data collection (21 February 2028) Data cut: 48 months after start of routine practice data collection (21 August 2027)
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

If necessary, an internal DRM will be held after data cut for the interim and final analyses. Representatives of the registry, medical experts and statisticians will discuss issues that occurred during the preliminary analysis and how they should be handled.

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:

- Allocation of individual patients to the analysis populations
- Patients' treatment regimen
- Violation in time windows
- Missing data
- Data issues in general

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

Various efforts have been initiated to ensure the completeness of dates as described in Project Plan Section 8.

Nevertheless, it cannot be completely ruled out that dates are not recorded properly. 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. Index Date and Baseline

The index date (Day 0) will be defined as the date of the tumor board recommendation. For patients without tumor board recommendation, Day 0 will be defined as the date of the treatment decision documented by the treating physician. This documented date represents baseline in both treatment arms. See also Section 7 and Project Plan Sections 3.2 and 6.1.

The baseline value will be defined as the last non-missing value prior to or until Day 0 if available. If no baseline value prior to or until Day 0 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 Day 0 applies for the collection of the corresponding data.

6.5. Complete Case

A patient is considered part of the complete cases if there are no missing values for any of the patient's confounders as defined in section 8.2.1.

6.6. Time Derivations

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

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

6.7. Planned and Actual Observation Period [Months]

The planned observation period will be derived as follows:
(date of data cutoff - Day 0 + 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 - Day 0 + 1)/30.4375

6.8. Calculation of Duration Until Occurrence of an Event

For assessments occurring at/after Day 0, the study day for that assessment will be calculated as:

(Date of assessment - Date of Day 0) +1

6.9. Definitions for Assessment of Effectiveness Endpoints

6.9.1. Time to Death [Months]

Time to death [months] required for the endpoint overall survival (OS) is defined as time from Day 0 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.

6.9.2. 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.

Death is considered a clinically relevant deterioration. In case death is a patient's first clinically relevant deterioration, it is automatically counted as once-confirmed at the patient's death date.

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

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.

Tolerance windows (Table 2. Assessment Schedule) are justified in Project Plan, Section 2.2.3.3 (footnote to Table 3 of the Project Plan).

Table 2. Assessment Schedule

Terminology used in Tables and Figures	Target Day	Tolerance Window
Baseline (t0)	Day 0	Day 0 – Day 27 (-0d / +27d)
Month 1 (t1)	Day 31 [Day 0 + 1m]	Day 28 – Day 61 (-3d / +30d)
Month 3 (t2)	Day 92 [Day 0 + 3m]	Day 85 – Day 122 (-7d / +30d)
Month 6 (t3)	Day 183 [Day 0 + 6m]	Day 176 – Day 213 (-7d / +30d)
Month 12 (t4)	Day 366 [Day 0 + 12m]	Day 359 – Day 419 (-7d / +53d)
Month 24 (t5)	Day 731 [Day 0 + 24m]	Day 724 – Day 784 (-7d / +53d)
Month 36 (t6)	Day 1096 [Day 0 + 36m]	Day 1089 – Day 1149 (-7d / +53d)

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 target day (e.g., Day 31 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

6.10. Definitions for Assessment of Safety Endpoints

6.10.1. Adverse Events

AEs with onset on or after Day 0 will be considered.

6.10.2. Time to First Adverse Event [Months]

Time to first AE is defined as time from Day 0 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 based on non-missing values and number of missing observations. If not stated otherwise percentage will refer to the complete respective analysis set. The percentage can also refer to a subset of the analysis set if the parameter is a matter of further characterization, e.g., therapy details of post BTKi therapy.

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. If not stated otherwise summary of continuous variables will refer to the complete respective analysis set. The summary can also refer to a subset of the analysis set if the parameter is a matter of further characterization, e.g.

duration of post BTKi therapy. Standard deviation, median, minimum, maximum, 25% and 75% quartile will be reported if there is more than one patient in the respective treatment group.

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, quartiles 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%.

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.

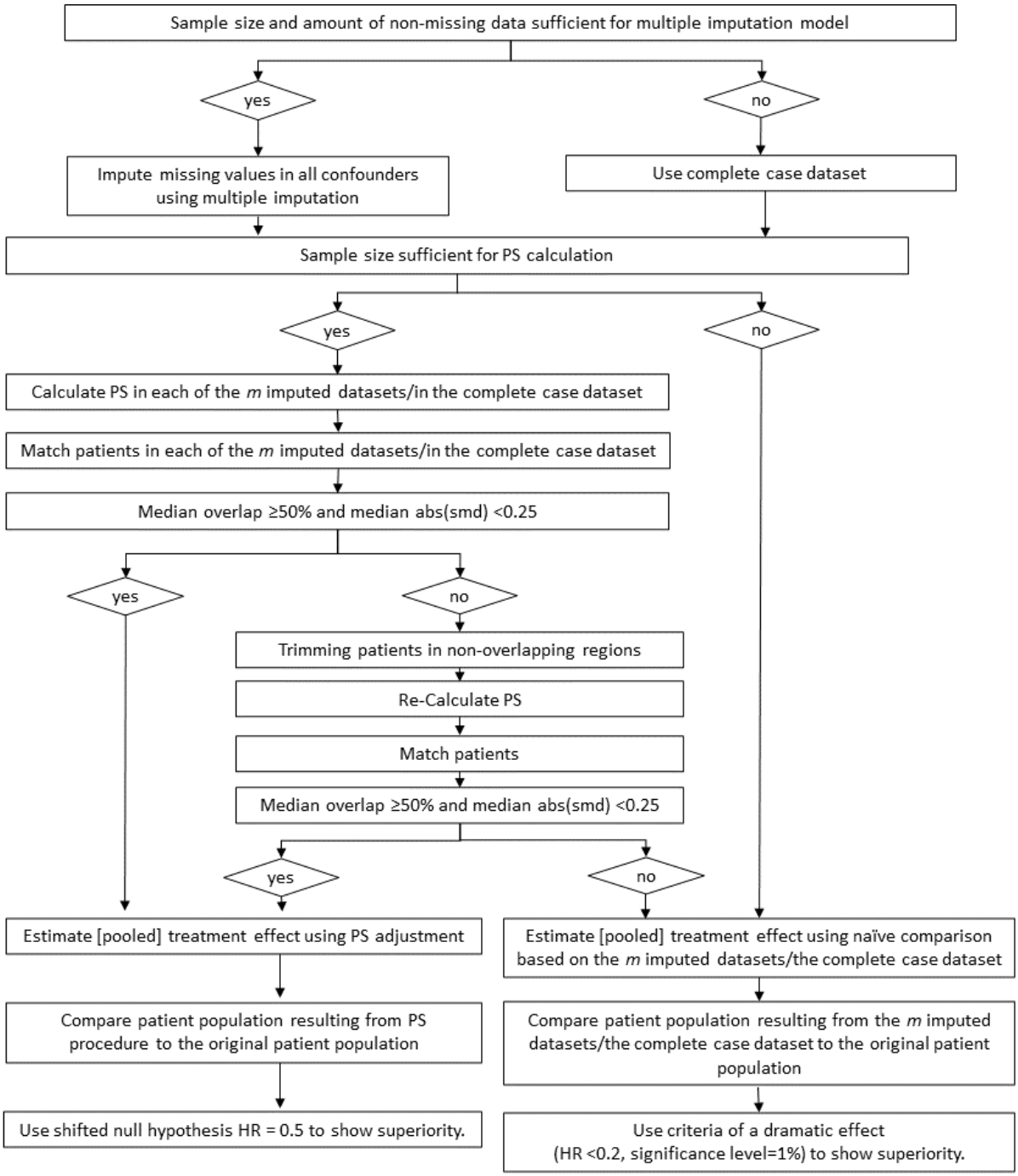

Figure 1: Overview of Multiple Imputation and Propensity Score Procedure

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 (see flowchart in Figure 1). In order to examine the certainty and transferability of results, it is necessary to compare the complete case dataset to the original patient population (see also Section 8.2.3). The level of certainty may be reduced due to the grade of missingness and reduced statistical power due to the loss of observations. The complete case analysis will be applied if MI is not possible (see flowchart in Figure 1). The number of complete cases will be summarized and discussed to evaluate and assess the pattern of missing data. Depending on the degree to which confounding factors are related to outcome and exposure, the extent of bias varies.

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, other)
    - 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 [10^9/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, unknown, 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 / BTKi-containing treatment (months)
- Response to prior BTKi therapy / BTKi-containing treatment (CR, PR, SD, PD, n.e.)

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

   In general, 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 Sheather and Jones [10], a gaussian kernel should be used.

   In case of MI, summary of the areal overlap shown in percent comprises minimum, Q1, median, Q3 and maximum for each confounder and sufficient overlap is given by a median of >50%.

   In case of a 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 and sufficient balance is given by a median of <0.25 for each confounder.

In case of complete case analysis, sufficient balance is given by an absolute standardized difference 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 7.0 [13], 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 order to correctly interpret the results of the naïve comparison, it is necessary to compare the patient population based on the *m*=30 imputed datasets / complete case dataset to the original 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. Potential influence and bias on certainty of conclusions will be discussed. The tables of baseline characteristics required are listed in Section 8.5.1.

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, 14]. 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 [15]. The hazard ratio (HR) with 95% confidence interval (CI) will be estimated based on a marginal Cox proportional hazards model with robust standard errors [16] with treatment as covariate.

If PSM is performed, a matching tuple identifier will be included as random effect.

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].

Additionally, baseline characteristics will be shown based on the complete case dataset and on the imputed datasets, if applicable. In case of MI, PROC MIANALYZE will be used to average the baseline characteristics from the *m*=30 imputed datasets.

Variables to be analyzed are listed in Table 4.

Table 4. Baseline Characteristics

Variable	Description[a]
Demographic data	
Sex	Categorical (female vs male vs other)
Age (year of index date – year of birth)	Quantitative [years]
Age categorical	Categorical (<65 vs ≥65 years)
Ethnicity	Categorical (multiple choice: Caucasian, Black, Asian, Hispanic, 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 at primary diagnosis	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 according to Ann Arbor prior to index date	Categorical (multiple choice: stages I, II, III, IV, unknown)
Bulky Disease (>7.5cm)	Categorical (yes, no)
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, unknown, other)
Ki-67	Quantitative [%]
Ki-67 categorical	Categorical (<30%, ≥30%)

Variable	Description[a]
MIPI (calculated based on ECOG-PS, age, leukocyte count, and LDH)	Categorical (multiple choice: MIPI risk categories: low (<5.7), intermediate (≥5.7 and ≤6.2), high risk (>6.2); 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)
Leukocyte count	Quantitative (10^9/l)
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), percentage refers to subset of patients with prior SCT
In case of prior SCT: time from last prior SCT to index	Categorical (multiple choice: > 12 months vs ≤ 12 months), percentage refers to subset of patients with prior SCT
(Chemo)therapy regimens prior to BTKi therapy(s) / BTKi-containing treatment(s)	Categorical (multiple choice: 1-10)
(Chemo)therapy prior to BTKi therapy(s) / BTKi-containing treatment(s)	Categorical (multiple choice: name of therapies)
Use of BTKi	Categorical (yes, no)
Duration of prior BTKi therapy / BTKi-containing treatment	Quantitative [months]
Response to prior BTKi therapy / BTKi-containing treatment	Categorical (multiple choice: complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], not evaluable [n.e.])
BTKi therapy(s) / BTKi-containing treatment(s)	Categorical (multiple choice: name of therapies)
Number of cycles (BTKi therapy / BTKi-containing treatment)	Quantitative
Response at end of prior treatment	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), percentage refers to subset of patients with post-BTKi therapy(s)
Number of cycles (post-BTKi therapy);	Quantitative, parameters refer to subset of patients with post-BTKi therapy(s)

Variable	Description[a]
Time to next treatment (time from last prior therapy to study treatment, i.e. Brexu-Cel administration or start of comparator therapy)	Quantitative [months]
a: If not stated otherwise, variables refer to non-missing observations of the complete analysis set.	

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 6.9.1. Overall survival (OS) will be estimated and plotted using the Kaplan-Meier (KM) method for up to maximum duration 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 6.9.2.

Time-to-event in each scale will be estimated and plotted using the KM method for up to maximum duration 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 6.9.3). 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 6.9.2.

Time-to-event in each scale will be estimated and plotted using the KM method for up to maximum duration 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 6.9.3). 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. For the questionnaire, completion is defined as having filled out at least one item. Percentage of every time point specific completion rate will refer to the set of patients of the ITTS still ongoing in the study.

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 to death[1]; overall rate)
- Adverse events leading to hospitalization or prolongation of existing hospitalization (overall rate)
- Adverse events of special interest (AESIs) with significant impairment of the activities of daily living or with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3, overall and separately for each AESI specified below. AESIs leading to significant impairment of the activities of daily living and AESIs with CTCAE grade ≥ 3 are collected and analyzed in aggregated form. These events are also referred to as specific adverse events in the context of the study.

All AEs may be allocated to more than one of the categories listed below. It is therefore possible for an AE to be reported in more than one analysis. All AEs may be allocated to more than one of the categories listed below and may therefore be reported more than once in the analyses. A differentiated assessment and documentation of AEs is therefore necessary to ensure a distinct

[1] In the outcome category "adverse events" of the current PICO scheme by the G-BA, "serious adverse events" are defined as: "Events leading to hospitalization or prolonging existing hospitalization **and leading to death**" ("Ereignisse, die zur Hospitalisierung führen oder eine bestehende Hospitalisierung verlängern **und die zum Tod führen"**).
To avoid the potential misinterpretation that both conditions (hospitalization/hospitalization prolongation and death) must be present, the wording in the present PICO scheme has been adjusted to: "Serious adverse events (SAEs), defined as events that lead to hospitalization, prolongation of existing hospitalization, **or to death**." In this context, the following formulations, which can be found throughout the documents of this study intend to convey the same meaning:

- "Events leading to hospitalization or prolongation of existing hospitalization and events resulting in/leading to death"
- "Events leading to hospitalization or prolongation of existing hospitalization or to death"
- "Events leading to hospitalization or prolongation of existing hospitalization and resulting in/leading to death"

allocation to the listed categories. AEs allocation to the following characteristics is required separately:

- leading to hospitalization or prolongation of existing hospitalization
- leading to death
- allocation to list of AESIs

AESIs are specified as follows:

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

The following concrete neurological events will be collected (this includes manifestations of ICANS as well as neurological events expected in the control arm):

- Encephalopathy
- Tremor
- Cognitive disturbance
- Delirium
- Dysphasia
- Somnolence
- Lethargy
- Agitation
- Concentration impairment
- Seizure
- Dysarthria
- Peripheral neuropathy

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 prior to index date (I, II, III, IV)
- Country (as applicable)

All endpoints will be evaluated as described in Sections 6.9, 6.10, 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 category 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 subgroup categories. 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. Day 0) 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		
1.1.6.1.1-2	Demographic characteristics	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.7.1.1-2	Disease characteristics	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.8.1.1-2	Treatment history	ITTS, ATS	Descriptive statistics by treatment group and overall
	Baseline Characteristics for complete case dataset		
1.1.6.2.1-2	Demographic characteristics for complete case dataset	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.7.2.1-2	Disease characteristics for complete case dataset	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.8.2.1-2	Treatment history for complete case dataset	ITTS, ATS	Descriptive statistics by treatment group and overall
	Baseline Characteristics for imputed dataset		
1.1.6.3.1-2	Demographic characteristics for imputed dataset	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.7.3.1-2	Disease characteristics for imputed dataset	ITTS, ATS	Descriptive statistics by treatment group and overall
1.1.8.3.1-2	Treatment history for imputed dataset	ITTS, ATS	Descriptive statistics by treatment group and overall
	Baseline Characteristics after PSM		
1.1.6.4.1-2	Demographic characteristics after propensity score matching	ITTS, ATS	Descriptive statistics including standardized difference by treatment group
1.1.7.4.1-2	Disease characteristics after propensity score matching	ITTS, ATS	Descriptive statistics including standardized difference by treatment group
1.1.8.4.1-2	Treatment history after propensity score matching	ITTS, ATS	Descriptive statistics including standardized difference by treatment group

Item No.	Title	Population	Content Description
	Baseline Characteristics after PSM: Subgroup Analysis		
1.1.9.1.1-x	Demographic characteristics after propensity score matching by <subgroup>	ITTS	Descriptive statistics including standardized difference by subgroup and treatment group
1.1.10.1.1-x	Baseline disease characteristics after propensity score matching by <subgroup>	ITTS	Descriptive statistics including standardized difference by subgroup and treatment group
1.1.11.1.1-4x	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 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

Item No.	Title	Population	Content Description
			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 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.

Item No.	Title	Population	Content Description
	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 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.

Item No.	Title	Population	Content Description
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 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).
1.2.2.21.1-2	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).

Item No.	Title	Population	Content Description
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 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).

Item No.	Title	Population	Content Description
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)		
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).

Item No.	Title	Population	Content Description
	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.
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

Item No.	Title	Population	Content Description
	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: 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).
1.2.3.24	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).

Item No.	Title	Population	Content Description
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 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.
1.3.1.4	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
1.3.1.5	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
1.3.1.6	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, severe AESIs
	Adverse Events: Subgroup Analysis		
1.3.1.7.1-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
1.3.1.8.1-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
1.3.1.9.1-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.

Item No.	Title	Population	Content Description
1.3.1.10.1-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
1.3.1.11.1-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
1.3.1.12.1-x	Incidence of Serious Adverse Events, Adverse Events leading to hospitalization or prolongation of existing hospitalization and Adverse Events of Special Interest by <subgroup>	ITTS	Descriptive statistics of number and percentage of patients affected and the total number of SAEs, severe AESIs
	Adverse Events: Sensitivity Analyses		
1.3.1.13	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
1.3.1.14	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
1.3.1.15	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.
1.3.1.16	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
1.3.1.17	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
1.3.1.18	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, severe AESIs
1.3.2	**Cause of death**		
1.3.2.1.1-2	Cause of death	ITTS, ATS	Descriptive statistics

Item No.	Title	Population	Content Description
1.4	**Further analyses**		
1.4.1	Planned and actual observation period	ITTS	Descriptive statistics
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	
2.2.21.1-14	Kaplan-Meier Plot: Accounting for treatment switching: EORTC QLQ-C30 <scale xxxx>: Time to clinically relevant deterioration	ITTS	

Item No.	Title	Population	Content Description
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: Severe Adverse Events of Special Interest <overall/ AESI>	ITTS	
2.3.4.1-x	Kaplan-Meier Plot: Serious Adverse Events by MedDRA SOC and PT - <SOC, PT>	ITTS	
2.3.5.1-x	Kaplan-Meier Plot: Adverse Events leading to hospitalization or prolongation of existing hospitalization by MedDRA SOC and PT - <SOC, PT>	ITTS	
	Subgroup Figures		
2.3.6.1-x	Kaplan-Meier Plot: Serious Adverse Events by <subgroup>	ITTS	
2.3.7.1-x	Kaplan-Meier Plot: Adverse Events leading to hospitalization or prolongation of existing hospitalization by <subgroup>	ITTS	
2.3.8.1-11.1-x	Kaplan-Meier Plot: Severe Adverse Events of Special Interest <overall/ AESI> by <subgroup>	ITTS	
2.3.9.1-x.1-x	Kaplan-Meier Plot: Serious Adverse Events by MedDRA SOC and PT <SOC, PT> and <subgroup>	ITTS	
2.3.10.1-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	

Item No.	Title	Population	Content Description
	Figures of Sensitivity Analyses		
2.3.11	Kaplan-Meier Plot: Serious Adverse Events	ATS	
2.3.12	Adverse Events leading to hospitalization or prolongation of existing hospitalization	ATS	
2.3.13.1-11	Kaplan-Meier Plot: Severe Adverse Events of Special Interest <overall/ AESI>	ATS	
2.3.14.1-x	Kaplan-Meier Plot: Severe Adverse Events by MedDRA SOC and PT <SOC, PT>	ATS	
2.3.15.1-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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