Kite Pharma Inc.

NON-INTERVENTIONAL POST AUTHORIZATION EFFECTIVENESS AND SAFETY STUDY PROTOCOL

Study Title	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL) OR ADULT PATIENTS WITH R/R B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Protocol ID	KT-EU-472-6036
Protocol Version/Date:	Original: 18 February 2021 Version 1.1: 13 July 2021 Version 1.2: 10 November 2021 Version 2.0: 15 March 2024 Version 2.1: 06 August 2024 Version 2.2: 17 December 2024
EU PAS Register No	EUPAS45813
Clinical Trials.gov Identifier	Study not registered
Active Substance	KTE-X19
Medicinal Product	Tecartus®
Product Reference	EMEA/H/C/005102
Procedure Number	EMEA/H/C/005102
Research Question and Objectives	Primary objective: To evaluate the effectiveness of Tecartus by indication in terms of overall response rate [ORR] (complete remission [CR] + partial response [PR]) for MCL and overall complete remission rate [OCR] (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]) for ALL. Secondary objectives: Effectiveness will be evaluated by indication as follows:

- To determine the overall survival (OS) rate after administration of Tecartus.
- To determine the duration of response (MCL) or duration of remission (ALL) after administration of Tecartus.
- To determine the complete remission rate after administration of Tecartus (MCL only).
- To determine time to next treatment after administration of Tecartus.
- To determine the time to relapse or progression of primary disease (MCL) or time to relapse (ALL) after administration of Tecartus.
- To assess effectiveness of Tecartus by sex, age, country and region.
- To assess effectiveness of Tecartus in special populations
  - For MCL, patients with prior stem cell transplantation, high risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status.
  - For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT (EBMT and CIBMTR) and patients treated with Out of Specifications (OOS) product (EBMT only).

Safety will be evaluated (pooled and by indication) as follows:

- To determine causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, non-relapse mortality (NRM) and hypogammaglobulinemia.
- To assess the safety profile by sex, age, country and region, and in special populations; additional subgroups may also be explored.
  - For MCL, high-risk comorbidity index, patients treated with OOS product.

— For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with OOS product.

- To assess the risk of tumor lysis syndrome (TLS).

CCI [redacted] of childbearing potential or partners of male patients.

Country (-ies) Of Study	In countries where Tecartus will be authorized. At a minimum UK, Spain, Switzerland, Germany, Canada and US will be countries of study, further countries may be added.
Study Director / Author / Contact Person:	Name: PPD Telephone: PPD Email: PPD
Marketing Authorization Holder **MAH Contact Person**	Kite Pharma EU B.V. Name: PPD Address: Kite Gilead Sciences International Ltd Senior Manager, Regulatory Affairs Flowers Building Granta Park, Abington Cambridge CB21 6GT, UK Telephone: PPD Email: PPD

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
allo-SCT	allogeneic stem cell transplantation
ANC	Absolute neutrophil count
aRMMs	additional Risk Minimization Measures
ASCT	Autologous stem cell transplant
BOR	Best Overall Response
BTKi	Bruton's tyrosine kinase inhibitor
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CDS	Clinical Data Science
CHMP	Committee for Human Medical Products
CI	Confidence interval
CR	Complete Remission
CRi	Complete remission with incomplete hematologic recovery
CRR	Complete Remission Rate
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria of Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of Response
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
PS	Patient Safety
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GvHD	Graft Versus Host Disease
GVP	European Medicines Agency Guidelines on Good Pharmacovigilance Practices
HCP	Health Care Professional
HCT	Hematopoietic cell transplantation
HDT	High dose chemotherapy
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HMA	Heads of Medicines Agencies
IL	Interleukin
KM	Kaplan-Meier
mAb	Monoclonal antibody
MAH	Marketing Authorization Holder

MCL	Mantle cell lymphoma
MICE	Multiple imputation by chained equations
MIPI	Mantle Cell Lymphoma International Prognostic Index
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
MCL	Mantle Cell Lymphoma
MRD	Minimal residual disease
OCR	Overall complete remission
OOS	Out of specifications
ORR	Overall Response Rate
OS	Overall survival
PAES	Post-Authorization Effectiveness Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PD	Disease Progression
PLD	Patient-Level Data
PMBCL	Primary Mediastinal B-cell Lymphoma
PR	Partial Remission
PSUR	periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
RCR	Replication-competent retrovirus
r/r	relapsed/refractory
SAE	Serious adverse event
SADR	Serious adverse drug reaction
scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SD	stable disease
SSR	Special situation report
TCR	T-cell receptor
TLS	Tumour lysis syndrome
TTNT	Time to next treatment
US, USA	United States, United States of America

1. RESPONSIBLE PARTIES

Table 1. Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
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2. PROTOCOL SYNOPSIS/ABSTRACT

Kite Pharma Inc.

Study Title:	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL) OR ADULT PATIENTS WITH R/R B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Rationale and Background:	This study will make secondary use of data collected within the infrastructure created by the European Society for Blood and Marrow Transplantation (EBMT) (i.e., the EBMT Registry) and the Center for International Blood and Marrow Transplant Research (i.e., CIBMTR) to systematically capture information at the time of Tecartus infusion and during follow-ups. The follow-up period will be 15 years for the safety part. The effectiveness part will be analyzed once: • For MCL: 200 recipients of Tecartus with MCL have been documented in the EBMT Registry and 500 recipients of Tecartus with MCL have been documented in the CIBMTR registry, with patient-level data (PLD) available to the MAH. • For ALL: 200 recipients of Tecartus with ALL have been documented in the EBMT Registry and 500 recipients of Tecartus with ALL have been documented in the CIBMTR registry, with patient-level data available to the MAH. The effectiveness part will also include safety assessments and all patients will be included in the safety part. The safety part will continue recruitment for each indication until the earliest of 300 recipients with PLD for each indication or 5 years of recruitment, whichever comes first. As this study will make secondary use of data collected under 'real-world' conditions, effectiveness - and not efficacy - will be evaluated. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under 'real-world' conditions {Singal 2014}. The CIBMTR cohort captures both effectiveness and safety outcomes in recipients of Tecartus for the treatment of r/r MCL or r/r ALL at participating centers who consent to have data reported to the

CIBMTR and has a target accrual of 500 patients for each indication (n=1000 patients in total). CIBMTR includes BTKi naive patients in the MCL cohort, as there are no BTKi restrictions in the US label.

Rationale for the effectiveness part:

To determine effectiveness of treatment with Tecartus, which includes Overall Response Rate (ORR) - MCL, Overall Complete Remission (OCR) rate - ALL, Complete Remission Rate (CRR) - MCL, Overall Survival (OS), Duration of Response (DOR), time to next treatment (TTNT), time to relapse, time to progression -MCL.

Rationale for the safety part:

To capture long-term follow-up data for recipients of Tecartus to evaluate the safety, as well as the known and potential risks associated with this product, including incidence rates and severity of adverse drug reactions (ADRs), long term safety, and risk of secondary malignancy.

Research Question and Objectives:

Primary objective:

To evaluate the effectiveness of Tecartus by indication in terms of overall response rate [ORR] (complete remission [CR] + partial response [PR]) for MCL and overall complete remission rate [OCR] (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]) for ALL.

Secondary objectives:

- Effectiveness will be evaluated by indication as follows:
- To determine the overall survival (OS) rate after administration of Tecartus.
- To determine the duration of response (MCL) or duration of remission (ALL) after administration of Tecartus.
- To determine the complete remission rate after administration of Tecartus (MCL only).
- To determine time to next treatment after administration of Tecartus.
- To determine the time to relapse or progression of primary disease (MCL) or time to relapse (ALL) after administration of Tecartus.
- To assess effectiveness of Tecartus by sex, age, country and region.
- To assess effectiveness of Tecartus in special populations

- For MCL, patients with prior stem cell transplantation, high risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status.
- For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT (EBMT and CIBMTR) and patients treated with Out of Specifications (OOS) product (EBMT only).

Safety will be evaluated (pooled and by indication) as follows:

- To determine causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, non-relapse mortality (NRM) and hypogammaglobulinemia.
- To assess the safety profile by sex, age, country and region, and in special populations; additional subgroups may also be explored.
  - For MCL, high-risk comorbidity index, patients treated with OOS product.
  - For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with OOS product.
- To assess the risk of tumor lysis syndrome (TLS).

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Study Design: This is a long-term, non-interventional study of adult patients with:

- r/r MCL, who have been treated with Tecartus.
- r/r B-cell precursor ALL who have been treated with Tecartus.

This study will make secondary use of data collected in the EBMT and CIBMTR Registries. For the safety analysis, patients will be followed for up to 15 years.

Population: The population comprises adult recipients of Tecartus for r/r MCL or ALL, at participating centers who consent to have data reported to the EBMT or CIBMTR and share their patient-level data with the MAH. Patients with underlying organ impairments (e.g. hepatic, renal, cardiac, pulmonary, etc.) will be included in the study analyses. There are no restrictions regarding the patients' performance status of any kind; patients with any grade for Sorror score, Eastern Cooperative Oncology Group (ECOG), and Karnofsky score are allowed.

Patients participating in interventional clinical trials at the same time will not be included in the study analyses.

Variables: This non-interventional study makes secondary use of data from the EBMT Registry and CIBMTR Registry.

- Variables utilized for analysis of the Primary Objective and Effectiveness Objectives:
  - MCL:
    - Overall response in terms of complete remission (CR) or partial remission (PR) and date response evaluated
    - Date of first response (CR or PR) and date of first relapse, progression or death due to any cause
    - Additional treatment and date of treatment received for primary disease (MCL) after Tecartus administration
  - ALL:
    - OCR and date remission evaluated
    - Additional treatment and date of treatment received for primary disease (r/r ALL) after Tecartus administration
  - Date of the first relapse or significant worsening of the primary disease after the Tecartus infusion
  - Date of the first progression of the primary disease (MCL) after the Tecartus infusion

- Date and main cause of death, or date of the last day known being alive
- Region defined by geography and database (EBMT and CIBMTR)

- Variables utilized for analysis of Safety Objectives:
  - Secondary malignancy (date of diagnosis, type, location and relevant details on biopsy/diagnostic results)
  - CRS (grade, grade system, date of onset, treatment and resolution status)
  - Neurologic toxicity (type, grade, grade system, management including treatment, date of onset and resolution status of all neurologic toxicities)
  - Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 30 days after the administration of Tecartus. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive values, platelet recovery is defined as platelet count $\geq 20 \times 10^9/L$ for 3 consecutive values after 7 days without platelet transfusion. Time to recovery of ANC and platelets are defined as time from infusion to the first date of recovery among those who had deficient ANC or platelets.
  - Serious infections (type, organism, treatment and date of onset of infection as well as resolution status). Note: Not defined as per serious adverse event (SAE) definition, please see Section 7.3.2 and Section 9.2.4.
  - Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. Date of onset, treatment, and resolution status will be collected.
  - Grade, date of onset, treatment and resolution of TLS
  - Use of OOS product (EBMT only)

- [redacted]

CCI [redacted]

- Variables utilized for analysis of exposure to Tecartus:
  - Name and dose level of lymphodepleting chemotherapy received prior to Tecartus infusion
  - Tecartus infusion: date, and whether Tecartus was released at physician's request, because the manufactured product was OOS

Demographics and Baseline Characteristics:

- Age, sex, and country
- Height and weight at the time of Tecartus infusion
- Disease subtype (e.g., classical MCL vs. blastoid MCL)
- MIPI score at diagnosis (for MCL)
- CD19 expression status (not collected in the current CIBMTR or EBMT Cellular Therapy Form)
- Disease status at time of cellular therapy (e.g., sensitive or resistant to chemotherapy or radiation prior to therapy, nodal vs extranodal)
- Prior lines of treatment and response
- Disease stage at time of diagnosis (MCL)
- Tumor characteristics (i.e., presence of TP53 mutation (in EBMT), TP53 deletion (in CIBMTR) and/or17p deletion; Ki-67 index) (for MCL)
- Time from diagnosis of the primary disease to cellular therapy
- Prior hematopoietic SCT: autologous or allogeneic, donor human leukocyte antigen (HLA) match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (umbilical cord blood, bone marrow, peripheral blood), immunosuppressants (type and duration), prior GvHD
- Prior cellular therapy (other than autologous SCT or allo-SCT)

- — Performance score (ECOG or Karnofsky)
- — Comorbidities index (Sorror score)
- — Active autoimmune, neurologic and hematological disease; infection related complications

For Data Sources: Secondary patient-level data as available within the EBMT for this study and secondary patient-level data as available with the CIBMTR Registries collected under the US post marketing requirement (PMR) protocol.

Study Size: Patients with PLD will be followed in the EBMT Registry for both effectiveness and safety.

For the effectiveness part, patients will be recruited until the first 200 eligible patients with MCL and 200 with ALL treated with Tecartus have been documented in the EBMT Registry and have agreed to share their patient-level data (PLD) with the MAH (expected approximately 4 years after start of data collection).

The safety part will continue recruitment for each indication until the earliest of 300 recipients with PLD for each indication or 5 years of recruitment, whichever comes first. For the safety part, patients will be followed for up to 15 years.

The CIBMTR cohort includes both effectiveness and safety outcome assessments in recipients of Tecartus for the treatment of r/r MCL or r/r ALL at participating centers who consent to have data reported to the CIBMTR and has a target accrual of 500 patients per indication (n = 1000 patients total). The 500 patients in each indication will be included in both the safety and effectiveness analyses. In addition to the further characterization of the immediate and established toxicities of Tecartus, the study will evaluate rare and delayed safety events occurring in patients during 15 years of follow-up.

Data Analysis: Analysis of all endpoints for this study will include all patients who satisfy the eligibility criteria, are documented within the EBMT Registry or CIBMTR Registries and are treated with Tecartus.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition with 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

Patient incidence of endpoint events will be provided. Multivariate Poisson regression analyses will be used to estimate cumulative incidence rates adjusted for the follow-up period and predefined characteristics, to estimate their prognostic effect on the outcome.

Kaplan-Meier (KM) curves will be used to illustrate all time-to-event endpoints without competing risks. Cumulative incidence function will be used for time-to-event endpoints with competing risks. The competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression of primary disease and time to next treatment of primary disease, and the cumulative incidence at specified time points will be provided. Cox -proportional hazard models and cause-specific Cox model will be used to model multivariate time-to-event data without and with competing risks respectively, adjusted for predefined characteristics, to estimate their prognostic effect on the outcome.

Effectiveness part:

The analysis of the effectiveness endpoints will be conducted by indication when effectiveness data from approximately 200 eligible patients in EBMT Registry and 500 in CIBMTR Registry for each indication has been documented. Time-to-event endpoints will be analyzed using the KM method (median, 1st quartile, and 3rd quartile along with their 95% CI will be provided as applicable). Cumulative incidence for relapse or progression of primary disease will also be provided using the competing risk method.

- Primary Endpoint
  - Overall response rate (for MCL)
  - Overall Complete Remission rate (for ALL)
- Effectiveness Endpoints
  - Complete remission rate (MCL only)
  - Overall survival
  - Duration of response
  - Time to next treatment of the primary disease
  - Time to relapse/progression of the primary disease (MCL only)
  - Time to relapse of the primary disease (ALL only)
  - Effectiveness endpoints by sex and age
  - Effectiveness endpoints by country and region
  - Effectiveness endpoints in special populations (patients with prior stem cell transplantation, high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status)

- Safety Endpoints
  - — Incidence rates, time to onset, type and location of secondary malignancy
  - — Incidence rates, severity, time to onset, management and resolution of CRS
  - — Incidence rates, severity, time to onset, management and resolution, and type of neurologic events
  - — Incidence rates of prolonged cytopenias and time to recovery of ANC and platelets
  - — Incidence rates, type, organism, resolution, and time to onset of serious infections
  - — Incidence rates, time to onset of hypogammaglobulinemia, and use of replacement immunoglobulin therapy
  - — Safety and effectiveness endpoints on subgroups by sex, age, and in special populations (patients with prior allo-SCT, high-risk comorbidity index, patients treated with OOS product), and additional subgroups may also be explored
  - — Incidence rate, severity, resolution, and time to onset of TLS
- [redacted]

Milestones:

MCL Effectiveness part	
Start of data collection:	24 July 2020 (CIBMTR) 18 April 2023 (EBMT)
End of data collection:	Q2 2027
Study duration:	approximately 4 years
Interim Reports:	annually for 3 years
Final Report:	Q4 2027
MCL Safety part	
Start of data collection:	24 July 2020 (CIBMTR) 18 April 2023 (EBMT)
End of data collection:	approximately Q2 2043
Study duration:	20 years
Interim Reports:	annually for 4 years, then every 2 years
Final report:	approximately Q4 2043
ALL Effectiveness part	
Start of data collection:	01 Oct 2021 (CIBMTR) *pending* (EBMT)
End of data collection:	*pending*
Study duration:	approximately 4 years
Interim Reports:	annually for 3 years
Final Report:	approximately 4.5 years after start of data collection for ALL
ALL Safety part	
Start of data collection:	01 Oct 2021 (CIBMTR) *pending* (EBMT)
End of data collection:	*pending*
Study duration:	approximately 20 years
Interim Reports:	annually for 4 years, then every 2 years
Final Report:	approximately 20.5 years after start of data collection for ALL

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPP) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

3. AMENDMENTS AND UPDATES

Table 2. Protocol Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.1	13 July 2021	various	Update	To address the protocol related comments in the PRAC Assessment Report for the Post-Authorisation Measure ANX 002 and to implement the respective changes
1.2	10 November 2021	various	Update	To address the protocol related comment in the PRAC Assessment Report for the Post Authorisation Measure ANX 002 and to implement the respective changes
2.0	15 March 2024	various	Amendment	To address the protocol related comments in the PRAC Assessment Report, combine the MCL and ALL studies and include CIBMTR as a data source
2.1	06 August 2024	various	Amendment	To address the protocol related comment in the PRAC Assessment Report for the Post Authorisation Measure ANX 11.2 and to implement the respective changes
2.2	17 December 2024	Section 7.7.2	Amendment	To address the protocol related comment in the PRAC assessment report for the Post Authorisation Measure ANX 002.5 and to implement the respective changes

Protocol Modifications

Protocol modifications may only be made by Kite Pharma Inc., a wholly owned subsidiary of Gilead Sciences, Inc. Any planned amendments will be discussed with the regulatory authority, the European Society for Blood and Marrow Transplantation (EBMT), and CIBMTR prior to implementation.

4. MILESTONES

Table 3. Protocol Milestones

Milestone	Planned Date
MCL	
PRAC approval of study protocol	30 September 2021
Protocol registration in the EU PAS Registry	01 March 2022
Start of data collection*	24 July 2020 (CIBMTR) 18 April 2023 (EBMT)
End of data collection effectiveness part**	Q2 2027
End of data collection safety part***	Q2 2043
Analyses of published literature and databases for comparator	Q2 2025
Study duration	20 years
Safety Data Reports****	Quarterly reports from 2023 to 2026
Interim reports effectiveness part	Q1 2024 to Q1 2026 annually
Final Report for Effectiveness part	Q4 2027
Interim reports safety part****	Q2 2024 to Q2 2027 annually, then every 2 years
Final report of study results	Q4 2043
ALL	
Approval (EC Decision) of study protocol	To be determined
Protocol registration in the EU PAS Registry	2 weeks after EC decision
Start of data collection*	01 Oct 2021 (CIBMTR) Pending (EBMT)
End of data collection effectiveness part**	Approx. 4 years after start of data collection
End of data collection safety part***	Approx. 20 years after start of data collection
Study duration	Approx. 20 years
Safety Data Reports****	Quarterly reports for 4 years after start of data collection
Interim reports effectiveness part	Annually for 3 years after start of data collection for effectiveness assessment
Final Report for Effectiveness part	Approx. 4.5 years after start of data collection
Interim reports safety part****	Annually for 4 years after start of data collection, then every 2 years for safety assessment
Final Report of Study Results	Approx. 20.5 years after start of data collection

* As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection is the date from which data extraction starts.
** When effectiveness data from approximately 200 eligible patients are documented.
*** 15 years after the last patient enrollment in the study, no further data will be included in the study analyses.
**** Safety Data Reports will be appended to the Tecartus PSURs, unless a Safety Data Report generates an urgent new safety finding that will be submitted as a stand-alone report in between PSUR cycles. Safety data in the Safety Data Reports are included the Interim Reports safety part; after quarterly Safety Data Reports are completed, safety data will be reported through the Interim Reports safety part and a separate Safety Data Report will not be generated.

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

T cells play a central role in the immune system by destroying diseased cells, including tumor cells, throughout the body {Kershaw 2013}. Studies with tumor vaccines {Kantoff 2010}, immune checkpoint inhibitors {Hamid 2013, Wolchok 2013}, tumor infiltrating lymphocytes {Rosenberg 2011}, the bispecific cluster of differentiation 19 (CD19)-directed CD3 T-cell engager blinatumomab {BLINCYTO 2019}, and chimeric antigen receptor (CAR) T-cells {KYMRIAH 2018, YESCARTA 2019a, YESCARTA 2019b} have demonstrated the potential of T cells to treat cancer.

Engineered autologous T cell immunotherapy, which uses a patient's own immune cells, offers a promising approach for treating many types of cancer. One type of engineered autologous T cell therapy comprises T cells that have been engineered ex vivo to express a CAR directed toward a tumor surface antigen. These CARs are fusion proteins with CD-19 antigen-binding, transmembrane, and T cell activation domains that, when expressed in T cells, can target tumor antigens for T cell-mediated killing {Kershaw 2013}. CAR T cells have demonstrated promising antitumor activity across numerous B-cell malignancies, including non-Hodgkin lymphoma {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a, Kochenderfer 2017b, Locke 2019, Neelapu 2017, Turtle 2016}, chronic lymphocytic leukemia {Kochenderfer 2015, Porter 2015, Porter 2011}, and acute lymphoblastic leukemia {Davila 2014, Gupta 2007, Lee 2015, Maude 2014, Maude 2015, Singh 2016}.

5.1.1. Anti-CD19 CAR T-cell Product: Tecartus

Tecartus is an autologous CAR T-cell therapy that targets CD19, a cell surface antigen that is expressed in normal B-cells and in most malignant B-cells {Anderson 1984, Johnson 2009, Leonard 2001, Nadler 1983, Olejniczak 2006, Rodriguez 1994, Uckun 1988}. Expression occurs beginning at the normal B-cell precursors - and continues throughout B-cell differentiation {Anderson 1984, Nadler 1983, Uckun 1990, Uckun 1988}, but is down regulated in plasma cells {Gupta 2009, Lin 2004}. Specifically, CD19 expression is maintained in MCL {Argatoff 1997, Cabezudo 1999, Ginaldi 1998, Leonard 2001, Marcondes 2017, Martinez 2003, Yang 2005}.

Kite Pharma, Inc. has developed manufacturing processes that harness the power of a patient's own immune system, to selectively target and eradicate cancer cells to meet the needs of patients with different types of B-cell malignancies. Tecartus has been developed for the treatment of diseases with circulating $CD19^{+}$ tumor cells such as leukemias and MCL. Tecartus is currently approved in the United States (US) for the treatment of adult patients with relapsed/refractory (r/r) MCL or r/r B-cell precursor ALL and in the European Union (EU) for the treatment of adult patients with r/r MCL after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor (BTKi), as well as adult patients 26 years of age or older with r/r B-cell precursor ALL.

The structure of the anti-CD19 CAR construct used for production of Tecartus and the product's mechanism of action are shown in Figure 1. Briefly, the construct comprises the following domains: an anti-human CD19 single-chain variable region fragment (scFv) region; the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor (TCR) complex {Kochenderfer 2009}.

The CAR antigen-binding domain is a scFv derived from the FMC63 murine monoclonal antibody (mAb) directed against human CD19{Nicholson 1997}. This antigen-binding domain extends from the engineered T-cell membrane into the extracellular space, where it can recognize CD19, its target antigen. CCI

Extensive comparative analyses {Nicholson 1997} demonstrated that the specificity of the scFv was equivalent to that of the original FMC63 mAb {Zola 1988, Zola 1991, Zola 1989}. Kinetic studies with radiolabeled material showed that the scFv binds target cells with a dissociation constant of 2.3×10^{-9}, which is comparable to the dissociation constant of 4.2×10^{-9} for the parent mAb {Nicholson 1997}.

Following CAR engagement with CD19+ target cells, the CD3ζ domain activates the downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity {Roberts 2018}. The intracellular signaling domain of CD28 provides a costimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct the killing of target cells. In addition, activated T cells secrete cytokines, chemokines, and other molecules that can recruit and activate additional antitumor immune cells {Restifo 2012}.

Kite is conducting a Phase 2, multicenter, open-label study (hereafter referred to as ZUMA-2) to evaluate the safety and efficacy of Tecartus in subjects with r/r MCL.

Eligible patients had disease progression after last regimen or refractory disease to the most recent therapy. All subjects had to have received up to 5 prior lines of therapy, which included a regimen with anthracycline or bendamustine, an anti-CD20 mAb, and a Bruton's tyrosine kinase inhibitor (BTKi) treatment. The study excluded patients who had previously undergone allogeneic stem cell transplantation (allo-SCT), detectable malignant cells in the cerebrospinal fluid or brain metastases, any history of central nervous system lymphoma or central nervous system disorders, and active or serious infections.

5.1.2. Outcome of Patients Treated With Tecartus in ZUMA-2

Treatment of r/r MCL with anti-CD19 CAR T cells results in a high response rate with durable remissions. The primary endpoint of the ZUMA-2 study was to evaluate the efficacy of Tecartus, as measured by the ORR. Based on a central assessment per Lugano Classification {Cheson 2014} in the inferential analysis set (n=68), the ORR was 93% with a CR rate of 67%, demonstrating that the primary endpoint of ZUMA-2 was met {Wang 2020}. Among 42 subjects who initially had a PR or stable disease (SD), 24 subjects (57%) went on to achieve a CR after a median of 2.2 months (range: 1.8 to 8.3 months). Of the 24 subjects whose responses improved over time, 21 subjects converted from PR to CR, and 3 subjects converted from SD to CR.

Administration of CAR T cells carries a number of risks independent from the type of target because the immune reaction against tumor cells can elicit a generalized reaction that include fever, hypotension, respiratory failure, and death {Brudno 2016}. These toxicities are defined as CRS and generally occur within the first week from treatment (Table 4). Lee, et al, proposed a grading system based on the number of affected organs, severity, and therapeutic approaches needed, ie, vasopressors or ventilatory support {Lee 2014}. In the modified grading scale, neurologic toxicities were not reported as part of CRS. Individual symptoms of CRS were graded for severity using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and linked to the corresponding CRS episode. Neurologic toxicities can occur in the absence of CRS, concurrently with CRS, or after CRS has resolved, and the symptoms include fine tremors, aphasia, and seizures (Table 5) {Brudno 2016, Lee 2014, Park 2016}. Prolonged cytopenias, infections, and hypogammaglobulinemia were also observed in ZUMA-2.

CRS following treatment with Tecartus infusion occurred in 91% of patients. Fifteen percent (15%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 10 days (range: 1 to 50 days). All patients (100%) recovered from CRS.

Neurologic adverse reactions following treatment with Tecartus infusion occurred in 68% of patients. Thirty-three percent (33%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 8 days (range: 1 to 262 days). Neurologic events resolved for 47 out of 56 patients with a median duration of 13 days (range: 1 to 567 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Eighty-five percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

Table 4. Selected Signs and Symptoms of Cytokine Release Syndrome

Signs and Symptoms of Cytokine Release Syndrome
Pyrexia
Hypotension
Hypoxia
Chills
Tachycardia
Headache
Alanine aminotransferase increased
Aspartate aminotransferase increased
Fatigue
Nausea
Diarrhea

Table 5. Selected Signs and Symptoms of Neurologic Events

Signs and Symptoms of Neurologic Events
Encephalopathy
Tremor
Confusional State
Aphasia
Somnolence
Lethargy
Agitation
Disturbance in attention
Memory impairment
Seizure
Delirium
Dysarthrias

Tecartus manufacturing relies on a replication incompetent murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T-cell genome, thus creating a theoretical risk of oncogenesis via insertional mutagenesis or replication-competent retrovirus (RCR). However, numerous clinical studies in patients with hematologic malignancies or solid tumors and in patients infected with human immunodeficiency virus (HIV) showed no overt genotoxic effects manifested by development of subsequent neoplasms following infusion of T cells that had been transduced with replication incompetent γ-retroviruses encoding a therapeutic TCR or CAR. These findings represent data from 86 unique patients with hematologic malignancies or solid tumors who exhibited clinical benefit and have follow-up ranging from 3 months to 4.8 years {Brentjens 2013, Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a, Robbins 2015}. One of these studies (Study NCI 09-C-0082) is ongoing and has shown no evidence of secondary malignancy over a period of up to 24 months of follow-up in a total of 43 patients with advanced B-cell malignancies {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a}. Further analysis of Study NCI 09-C-0082 by Kite showed no evidence of secondary malignancies resulting from the infusion of the anti-CD19 CAR T cells at a median follow-up of 36 months (range: 13 to 78 months) (Kite, data on file). These patients were treated with retrovirally transduced T cells expressing the same CAR as utilized in Tecartus. Data from Study KTE-C19-101 (ZUMA-1) in 101 patients with r/r large-cell lymphomas and using Kite's first approved CAR T-cell therapy, Yescarta, which uses the same retroviral vector, producer clone, and anti-CD19 CAR construct as used for Tecartus, showed no reports of malignancies related to the anti-CD19 CAR T-cell after a median follow-up of 27.7 months {Locke 2019}.

In the HIV clinical studies, no treatment-related malignancies have been observed among more than 40 patients with HIV who were treated and followed for a period of 1 to 11 years {Scholler 2012}. Notably, Scholler and colleagues have shown that CAR T cells were detected in 98% of post-infusion samples over this period. This analysis represented over 540 patient-years of accumulated follow-up and showed no clinical evidence of viral vector integration-mediated toxicity.

Additionally, a comprehensive summary of RCR data derived from patients treated with T cells transduced ex vivo with murine γ-retroviral vectors was performed on 629 follow-up samples obtained 1 month to 8 years after infusion {Bear 2012}. The data demonstrated a lack of RCR events in patient samples, including samples from HIV-infected patients, across 29 clinical studies. Due to a lack of detectable RCR in patients, the authors further concluded that infectious and replication-competent γ-retroviral vector particles used to modify the patient's own T cells are not shed via saliva, urine, or feces into the environment and, therefore, do not represent any risk to organisms present in the environment. Additional vector integration site analyses conducted by the sponsor support the low risk of insertional mutagenesis in patients treated with engineered T-cell products {Chang 2019}.

Taken together, the clinical studies described above suggest that T-cell transformation due to γ––retroviral or lentiviral insertional mutagenesis is an extremely rare event that likely requires the contribution of multiple additional factors beyond the integration site of the viral vector.

5.1.3. Outcome of Patients Treated With Tecartus in ZUMA-3

Evaluation of the efficacy and safety of Tecartus in adult patients with r/r B-ALL is based on the pivotal Phase 1/2, multicenter, open label study KTE-C19-103, hereafter referred to as ZUMA-3. In ZUMA-3 Phase 2, a total of 71 patients were enrolled (ie leukapheresed) and 55 patients were treated with Tecartus. ZUMA-3 enrolment is complete.

The ZUMA-3 study demonstrated high response rates and durable remissions in subjects with r/r ALL. In the 55 patients treated with Tecartus, the overall complete remission (OCR) rate was 70.9% with a CR rate of 56.4%, which was significantly greater than the prespecified control rate of 40%. Among the 39 patients who achieved a CR or complete remission with incomplete hematologic recovery (CRi), the median time to response was 1.1 months (range: 0.85 to 2.99 months).

As of the 23 July 2021 data cut-off, all treated patients had potential follow-up for ≥ 18 months with a median follow-up time of 20.5 months (95% CI: 0.3, 32.6 months) and a median follow-up time for OS of 24.0 months (95% CI: 23.3, 24.6).

In the primary analysis of ZUMA-3, the rates of any grade Cytokine release syndrome (CRS) and neurologic toxicities in the Phase 2 safety set were 89% and 60%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 24% and 25%, respectively. No subject experienced Grade 5 CRS. One subject experienced a Grade 5 neurologic event of brain herniation. The median time to onset of first CRS symptoms was 5 days (range:1 to 12 days) after infusion of Tecartus. Among the subjects whose CRS symptoms resolved, the median time to resolution of CRS symptoms was 7.5 days (range: 2 to 48 days). The median time to onset of first neurologic toxicities was 9 days (range: 2 to 16 days) after infusion of Tecartus. Among the subjects whose neurologic toxicities resolved, the median time to resolution of neurologic toxicities was 7 days (range: 1 to 75 days).

Selected signs and symptoms of CRS and neurologic events are presented in Table 6 and Table 7, respectively.

Table 6. Selected signs and symptoms of Cytokine Release Syndrome

Signs and Symptoms of Cytokine Release Syndrome
Pyrexia
Hypotension
Hypoxia
Chills
Tachycardia
Headache
Alanine aminotransferase increased
Aspartate aminotransferase increased
Fatigue
Nausea
Diarrhea

Table 7. Selected Signs and Symptoms of Neurologic Events

Signs and Symptoms of Neurologic Events
Encephalopathy
Tremor
Confusional State
Aphasia
Somnolence
Lethargy
Agitation
Disturbance in attention
Memory impairment
Seizure
Delirium
Dysarthrias

Tecartus manufacturing relies on a replication incompetent murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T-cell genome, thus creating a theoretical risk of oncogenesis via insertional mutagenesis or replication competent retrovirus (RCR). However, numerous clinical studies in patients with hematologic malignancies or solid tumors and in patients infected with human immunodeficiency virus showed no overt genotoxic effects manifested by development of subsequent neoplasms following infusion of T cells that had been transduced with replication incompetent γ-retroviruses encoding a therapeutic TCR or CAR. These findings represent data from 86 unique patients with hematologic malignancies or solid tumors who exhibited clinical benefit and have follow-up ranging from 3 months to 4.8 years. One of these studies (Study NCI 09C0082) is ongoing and has shown no evidence of secondary

malignancy over a period of up to 24 months of follow-up in a total of 43 patients with advanced B-cell malignancies.

In the HIV clinical studies, no treatment-related malignancies have been observed among more than 40 patients with HIV who were treated and followed for a period of 1 to 11 years. Notably, Scholler and colleagues have shown that CAR T cells were detected in 98% of post-infusion samples over this period. This analysis represented over 540 patient-years of accumulated follow-up and showed no clinical evidence of viral vector integration mediated toxicity.

Additionally, a comprehensive summary of RCR data derived from patients treated with T cells transduced ex vivo with murine γ-retroviral vectors was performed on 629 follow-up samples obtained 1 month to 8 years after infusion. The data demonstrated a lack of RCR events in patient samples, including samples from HIV-infected patients, across 29 clinical studies. Due to a lack of detectable RCR in patients, the authors further concluded that infectious and replication competent γ-retroviral vector particles used to modify the patient's own T cells are not shed via saliva, urine, or feces into the environment and, therefore, do not represent any risk to organisms present in the environment. Additional vector integration site analyses conducted by the sponsor support the low risk of insertional mutagenesis in patients treated with engineered T-cell products{Chang 2019}.

Taken together, the clinical studies described above suggest that T-cell transformation due to γ–retroviral or lentiviral insertional mutagenesis is an extremely rare event that likely requires the contribution of multiple additional factors beyond the integration site of the viral vector.

5.1.4. Purpose of Current Study

The purpose of this study is to analyze and report on the follow-up data for recipients of Tecartus captured in the EBMT and CIBMTR Registries to address the effectiveness of this product for r/r MCL and r/r ALL patients based on ORR, OCR rate, CRR, OS, DOR, time to next treatment (TTNT) and time to relapse or progression as well as further characterization of the short- and long-term known and hypothetical ADRs.

The EBMT is a non-profit organization that was established in 1974 to allow scientists and physicians involved in clinical bone marrow transplantation to share their experiences and develop cooperative studies. More recently, the scope of the organization has broadened to include work in cellular therapy as well. The EBMT has created a specific cell therapy module of its registry and utilizes the infrastructure created for the SCT registry to systematically capture data on all cell therapies. This study will use the data accrued on Tecartus in the EBMT Registry to systematically evaluate information on patients who receive Tecartus.

The CIBMTR is a research collaboration between Medical College of Wisconsin (MCW) and the National Marrow Donor Program (NMDP) in the US. CIBMTR collaborates with a network of more than 500 international centers to collect clinical information from allogeneic transplants, autologous transplants, and other cellular therapies. The CIBMTR Research Database contains detailed information on patient characteristics, demographics, clinical variables, and outcomes contributed by centers worldwide and followed-up by frequent clinical updates. The CIBMTR infrastructure was used to develop prospective observational post approval studies in collaboration with Kite Pharma to fulfill regulatory requirements for evaluation of long-term safety and efficacy of Kite products in the US. This study will use the data accrued on Tecartus in the EBMT Registry and CIBMTR Registry to systematically evaluate information on patients receiving Tecartus and for 15 years of follow-up.

6. RESEARCH QUESTIONS AND OBJECTIVES

This is a long-term, non-interventional effectiveness and safety study of adult (18 years and above) patients with r/r MCL, who have been treated with Tecartus and of adult patients ([aged 26 years of age and above in the EU and GB)], and aged 18 years of age above in US, Canada and Switzerland) treated with Tecartus for r/r B-cell precursor ALL.

The study will utilize follow-up data for recipients of Tecartus to determine the effectiveness including ORR, OCR rate, CRR, OS and DOR, and to evaluate the long-term safety including incidence rates and severity of ADRs, the risk of subsequent neoplasm, time to next treatment and time to relapse or progression.

Therefore, the study will make secondary use of the data captured in the EBMT and CIBMTR Registries, using the infrastructure EBMT and CIBMTR created for the SCT registry, to systematically capture information at the time of Tecartus infusion and for up to 15 years of follow-up in the safety part. Enrollment for the effectiveness part will be stopped once the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry for each indication, and this timepoint is expected to occur approximately 4 years after start of data collection. The effectiveness part will also include safety assessments and all patients will be included in the safety part.

The CIBMTR cohort collected under the US PMR protocol includes assessments of both effectiveness and safety in recipients of Tecartus for the treatment of r/r MCL and r/r ALL at participating centers who consent to have data reported to the CIBMTR and has a target accrual of 500 patients per indication.

As this study will make secondary use of data collected under ‘real-world' conditions, effectiveness - and not efficacy - will be evaluated. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under ‘real-world' conditions {Singal 2014}.

Primary objective:

To evaluate the effectiveness of Tecartus by indication in terms of overall response rate [ORR] (complete remission [CR] + partial response [PR]) for MCL and overall complete remission rate [OCR] (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]) for ALL.

Secondary objectives:

Effectiveness will be evaluated by indication as follows:

- To determine the overall survival (OS) rate after administration of Tecartus.
- To determine the duration of response (MCL) or duration of remission (ALL) after administration of Tecartus.

- To determine the complete remission rate after administration of Tecartus (MCL only).
- To determine time to next treatment after administration of Tecartus.
- To determine the time to relapse or progression of primary disease (MCL) or time to relapse (ALL) after administration of Tecartus.
- To assess effectiveness of Tecartus by sex, age, country and region.
- To assess effectiveness of Tecartus in special populations
  - For MCL, patients with prior stem cell transplantation, high risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status.
  - For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT (EBMT and CIBMTR) and patients treated with Out of Specifications (OOS) product (EBMT only).

Safety will be evaluated (pooled and by indication) as follows:

- To determine causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, non-relapse mortality (NRM) and hypogammaglobulinemia.
- To assess the safety profile by sex, age, country and region, and in special populations; additional subgroups may also be explored.
  - For MCL, high-risk comorbidity index, patients treated with OOS product.
  - For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with OOS product.
- To assess the risk of tumor lysis syndrome (TLS).

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7. RESEARCH METHODS

7.1. Study Design

This study is a long-term, non-interventional effectiveness and safety study planned to evaluate outcomes of adult patients (18 years of age and above) with r/r MCL after 2 or more lines of systemic therapy including a BTKi, and of adult patients (26 years of age and above in the EU and GB; and 18 years of age and above in the US, Canada and Switzerland) treated with Tecartus for r/r B-cell precursor ALL who have been treated with Tecartus, in the post-marketing setting making secondary use of data available in the EBMT and CIBMTR Registries.

Participating centers enter data into the EBMT or CIBMTR Registry following the EBMT or CIBMTR specific procedures and requirements according to each registry.

According to the EBMT monitoring plan, the site is responsible for completing the data collection forms within 6 weeks after a patient visit. For EBMT, the preferred and most common option to enter data is direct electronic data entry by a trained and authorized staff member from the center. This option ensures immediate access of the center's data by the EBMT and authorized users. Alternatively, direct data entry by a national registry on behalf of specific centers that submit paper forms to this national registry is possible. Data entry into the EBMT Registry requires signed informed consent by the patient or a legal guardian to allow data to be provided to the EBMT and patient-level data to the MAH. Patients' data may be entered up to 1 week prior or anytime following administration of Tecartus infusion. Patients will be followed in the EBMT Registry for both the safety part, for up to 15 years, and the effectiveness part, until and including the first 200 eligible patients treated with Tecartus for each indication have been documented in the EBMT Registry (which is expected to be approximately 4 years after the start of data collection).

For CIBMTR, participating centers register patients and submit data through FormsNet, the CIBMTR electronic data capture system. The FormsNet application is compliant with US database security requirement as established by the Health Resource & Service Administration (HRSA) Office of Information Technology. Patients may enroll up to 1 week prior or up to 3 months following receipt of Tecartus. Enrollment requires signed informed consent by the patient or a legal guardian to allow data to be provided to the CIBMTR. The informed consent document will include information of sharing data with the CIBMTR and also the possible need to provide blood and/or tissue samples if the patient develops a subsequent neoplasm after receiving Tecartus. The first 500 enrolled patients will be followed for both safety and effectiveness.

Enrolled patients will be followed for up to 15 years in both the EBMT Registry and CIBMTR Registry.

7.2. Setting

No treatments, therapy protocols, or procedures are mandated except for CIBMTR patients who develop subsequent neoplasm will be consented for sample collection.

All study data will be obtained from clinical, laboratory, and diagnostic assessments conducted in the course of routine medical practice and available in the patient's medical chart, collected for the primary purpose of patient care, except for CIBMTR laboratory assays will be performed in patients who develop subsequent neoplasms.

For EBMT, data will be captured by completion of the EBMT Cellular Therapy Forms, using the most current data available. Data entry into the EBMT Registry will be done by the EBMT centers irrespective of this study according to EBMT guidance documents in its most current versions (eg, submitting data to the EBMT (currently dated 21/12/2020)). The EBMT Cellular Therapy Forms were created in close cooperation with the Committee for Human Medical Products (CHMP) and other relevant MAHs. The aim is not to collect all possible information from the medical charts, but to collect the essential information in the EBMT Registry. For safety data, the forms specifically collect data on events of special interest. There is also an option to add other complications/toxicities in the EBMT Registry. The EBMT therefore collects in their registry a defined data set as specified in the EBMT Cellular Therapy Forms. The EBMT Cellular Therapy Forms are under the control of the EBMT and its content can change throughout the course of the study.

Spontaneous ADR reporting independent from this study is the primary source for detecting new safety concerns/signals. New emerging safety concerns and respective data/variables might also be added throughout the course of the study on the EBMT Cellular Therapy Forms to support structured data collection of such new relevant data during the study if agreed by the EBMT, who owns this form.

In the CIBMTR, data collection for this study will utilize the CIBMTR Cellular Therapy Essential Data (CTED) suite of forms and disease-specific forms that are captured by CIBMTR proprietary FormsNet web-based software. Participating sites will be responsible for completing a data collection form at the time points described below (see 7.6), using the most current data available. This data collection schedule is designed to align with the likely pattern of routine medical care for these patients. Integrity and quality of data are monitored at different levels, including onsite audits and computers checks for discrepancies.

Available data within the EBMT Registry and secondary data available with the CIBMTR Registry collected under the US PMR protocol will be analyzed for this study at defined time points.

7.2.1. Eligibility

The EBMT and CIBMTR Registries collect data on all patients receiving cell therapy. Eligible patient data for this study is from adult (18 years of age and above) patients treated with Tecartus for r/r MCL, or adult patients (26 years of age and above in the EU and GB, and 18 years of age and above in the US, Canada and Switzerland) treated with Tecartus for r/r B-cell precursor ALL, irrespective of whether the Tecartus product was within approved product specifications or out of specifications, but released at physician's request. Eligible patient data includes data of patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary, etc.) and with any grade for Sorror score, ECOG and Karnofsky score.

Patients participating in interventional clinical trials at the same time will not be included in this study's analyses.

Patients must consent to share clinical data with EBMT or CIBMTR and their pseudonymized patient-level data with the MAH.

7.3. Variables

7.3.1. Variables utilized for analysis of Primary Objective and Effectiveness Objectives

- For MCL, overall response in terms of complete remission (CR) or partial remission (PR) and date of response evaluated; for ALL, OCR in terms of complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) and date of remission evaluated
- Date of the first relapse, progression, or significant worsening of the primary disease after Tecartus infusion
- Date of death due to any cause, or the last day known being alive
- Additional treatment and date of treatment received for primary disease after Tecartus administration
- Region defined by geography and database (EBMT and CIBMTR)

7.3.2. Variables utilized for analysis of Safety Objectives

- The main cause of death
- Secondary malignancy is defined as the development of any new malignancies, with the exception of relapse, progression, or transformation of the primary disease occurring after the administration of Tecartus. The Registries will collect the date of diagnosis for EBMT and time from diagnosis from CIBMTR, type, location and, if a biopsy occurred, information whether secondary malignancy was derived from cells that composed or were part of the infused medicinal product or cell/gene therapy product, and this study will utilize this data for analysis.

- CRS is a class effect of CAR-T -cell therapies, which may occur at different grades of severity, characterized by fever, rigors, nausea, emesis, headache, hypotension, and pulmonary, hepatic, and renal dysfunction. The Registries will collect CRS grade (Table 8), system of grading, date of onset, treatment and resolution status will be collected.
- ICANS and other neurologic toxicity is a class effect of CAR T cell therapies and most commonly includes confusion, delirium, aphasia, obtundation, myoclonus, and seizures. The Registry holders will collect type, grade, system of grading (Common Terminology of Adverse Events [CTCAE] or ICANS score), treatment, date of onset and resolution status of all neurologic toxicities will be collected.
- Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 30 days after the administration of Tecartus. ANC recovery is defined as neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive values after 7 days without transfusion containing neutrophils, and platelet recovery is defined as platelet count $\geq 20 \times 109$/L for 3 consecutive values after 7 days without platelet transfusion. Time to recovery of ANC and platelets are defined as time from infusion to the first date of recovery among those who had deficient ANC or platelets.
- Serious infections are defined as viral, bacterial or fungal infections that require intervention or have led to a negative outcome for the patient (including death) as determined by the treating physician and reported to the Registries. Serious infections in this study is not defined as per SAE definition (Section 9.2.4), but the definition is outlined in Section 7.7.2. The Registries will collect the type, organism, treatment and date of onset of infection as well as resolution (treatment and resolution only applicable to EBMT data), and this study will utilize this data for analysis.
- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. The Registries will collect for hypogammaglobulinemia the date of onset, treatment, and resolution status will be collected.
- Grade, date of onset and resolution of TLS

Table 8. Grading of CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula ‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/minute

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7.3.4. Variables for exposure to Tecartus

- Name and dose level of lymphodepleting chemotherapy received prior to Tecartus infusion (dose level is applicable to EBMT Registry cases only).
- Tecartus infusion: date, and whether Tecartus was released at physician's request, because the manufactured product was out of specification (OOS; applicable to EBMT Registry cases only).

7.3.5. Variables to Collect for Demographics and Baseline Characteristics

- Age, sex, country, and treatment center
- Height and weight at the time of Tecartus infusion
- Performance score (ECOG or Karnofsky)
- Comorbidities index (Sorror score)
- Disease status at time of cellular therapy (e.g., sensitive or resistant to chemotherapy or radiation prior to therapy)
- Time from diagnosis of the primary disease to cellular therapy
- Prior lines of treatment and response
- Prior hematopoietic cell transplantation: autologous or allogeneic, donor HLA match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (umbilical cord blood, bone marrow, peripheral blood), immunosuppressants (type and duration), prior GvHD
- Prior cellular therapy (other than autologous or allogeneic SCT)
- MCL-specific variables
  - Disease subtype (e.g., classical MCL vs. blastoid MCL)
  - MIPI score at diagnosis
  - CD19 expression status where available
  - Disease stage at time of diagnosis
  - Tumor characteristics (i.e. presence of TP53 mutation in the EBMT Registry, TP53 deletion in the CIBMTR Registry and/or 17p deletion; Ki-67 index)
- ALL-specific variables
  - Bone marrow burden (% blasts) at infusion: 0-5%, 5-25%, 25-50%, 50-75% and 75%-100%
  - Cytogenetic abnormalities at diagnosis where available
  - Active CNS disease at infusion
  - Extra-medullary involvement at infusion
  - Minimal residual disease (MRD) status at infusion

7.4. Data Sources

The source data for the EBMT Registry will be the data presented in the patients' medical records. A sub-set of these data from patients' medical records will be transcribed by the centers in the EBMT Registry utilizing the EBMT Cellular Therapy Form (Annex 5). The data on patients receiving Tecartus available in the EBMT Registry will be the data source for this study.

The EBMT maintains a registry which encompasses all haematopoietic stem cell transplant (HSCT) procedures for all indications. It also stores immunosuppressive treatments for bone marrow failure syndromes (i.e., aplastic anaemias), cell therapy treatments other than HSCT and donor information pertaining to collection and donor follow-up.

All EBMT centers are asked to submit the minimum essential data as recorded through the EBMT Cellular e Therapy Form. An update should be submitted 100 days, and 6 months after the date of transplant or cell therapy infusion for non-transplanted patients, or when the patient dies, whichever comes first. Yearly follow-up data should be submitted for all patients from then onwards.

The CIBMTR collects more than 99% of data electronically via FormsNet3, a comprehensive electronic data submission system containing greater than 250 forms related to the capturing of hematopoietic cell transplantation (HCT) outcomes for donors and recipients of hematopoietic stem cell transplants as well as cellular therapy.

The data source for the CIBMTR will be the respective database for the registry, FormsNet3. Other data sources will be substantiated from a combination of patient medical records, possible analysis of tumor samples from patients reporting the development of a second malignancy, and spontaneously reported events such as pregnancy, a subsequent malignancy, or death.

Patient-level data for patients who meet the selection criteria will be extracted from the registry on a regular basis and provided to Kite and in turn as part of a regularly required submission to an applicable health authority or in response to the request of a health authority. Patient data will be handled in accordance with all applicable privacy laws.

7.5. Study Size

Patients will be followed in the EBMT Registry for both effectiveness and safety.

For the effectiveness part, patients will be followed until the first 200 eligible patients with MCL and 200 with ALL treated with Tecartus have been documented in the EBMT Registry and have agreed to share their patient-level data (PLD) with the MAH (expected approximately 4 years after start of data collection).

The safety part will continue recruitment for each indication until the earliest of 300 recipients for each indication or 5 years of recruitment, whichever comes first. For the safety part, patients will be followed for up to 15 years.

The CIBMTR cohort includes both effectiveness and safety outcome assessments in recipients of Tecartus for the treatment of r/r MCL or r/r ALL at participating centers who consent to have data reported to the CIBMTR and has a target accrual of 500 patients per indication (n = 1000 patients total).

The sample size for this study is not based on statistical consideration but on Health Authority's recommendation.

7.6. Data Management

7.6.1. EBMT

Data will be entered into the EBMT Registry by the centers utilizing the EBMT Cellular Therapy Form. EBMT will liaise with individual centers and will provide standard training on how to enter the data and how to use the data management system. Trained personnel will enter data directly into the EBMT Registry database, users will have user accounts with password in order to gain access to the EBMT Registry database. EBMT will cooperate with centers to reduce the amount of missing/erroneous data in the registry.

An imperative need for clear understanding of the secondary nature of the data is appreciated, wherein data are transcribed into the EBMT Registry from the medical record. To fully ensure the secondary categorization of the data is not disrupted, personnel at the centers will be trained and instructed by the EBMT to enter only information available in the medical record, and to make no inferences outside of this practice.

Data will be collected at the center's standard follow-up time points, including at least time points during the first year at approximately Day 100, 6 and 12 months and then annually thereafter. Expedited reporting of individual case safety reports to EBMT or by EBMT will not occur. Reporting of adverse events by centers or clinicians will follow the standard spontaneous reporting system per local regulations and timelines as described in Section 9.

The center that administers Tecartus is responsible for reporting follow-up unless the responsibilities are formally transferred to and accepted by a healthcare provider at another center. Patients who receive a HCT or other cellular therapy or any other treatment for the primary disease after Tecartus will continue to be followed.

EBMT will conduct the study specific analyses and provide overviews to update Kite Inc. regarding the progress of the data entry into the EBMT Registry.

7.6.2. CIBMTR

Data collection from CIBMTR will utilize the Cellular Therapy Essential Data (CTED) suite of forms and disease-specific forms that are captured by CIBMTR proprietary FormsNet web-based software. Centers initiate the report through the generation of a CIBMTR Recipient Identification (CRID) number and Therapy Indication Form, which will trigger a series of forms due. Baseline CTED forms include the pre-CTED product, infusion, and baseline lymphoma disease-specific forms. Follow-up forms include the post-CTED and follow-up lymphoma forms. Forms will be completed on a calendar-driven basis, except for forms for subsequent neoplasm and death, which will require expedited completion. Additionally, centers will be instructed that in the event of the development of subsequent neoplasms, reporting to the CIBMTR using the specific form for subsequent neoplasms will be required. Data will be collected at 3, 6, and 12 months and then yearly for 15 years after infusion. The center that administers Tecartus is responsible for reporting follow-up unless the responsibilities are formally transferred to and accepted by a healthcare provider at another center. Patients who receive a HCT or other cellular therapy after Tecartus will continue to be followed, although the follow-up schedule may be modified to reflect appropriate milestones after this subsequent therapy. However, the schedule will not be modified to include fewer time points than those outlined above.

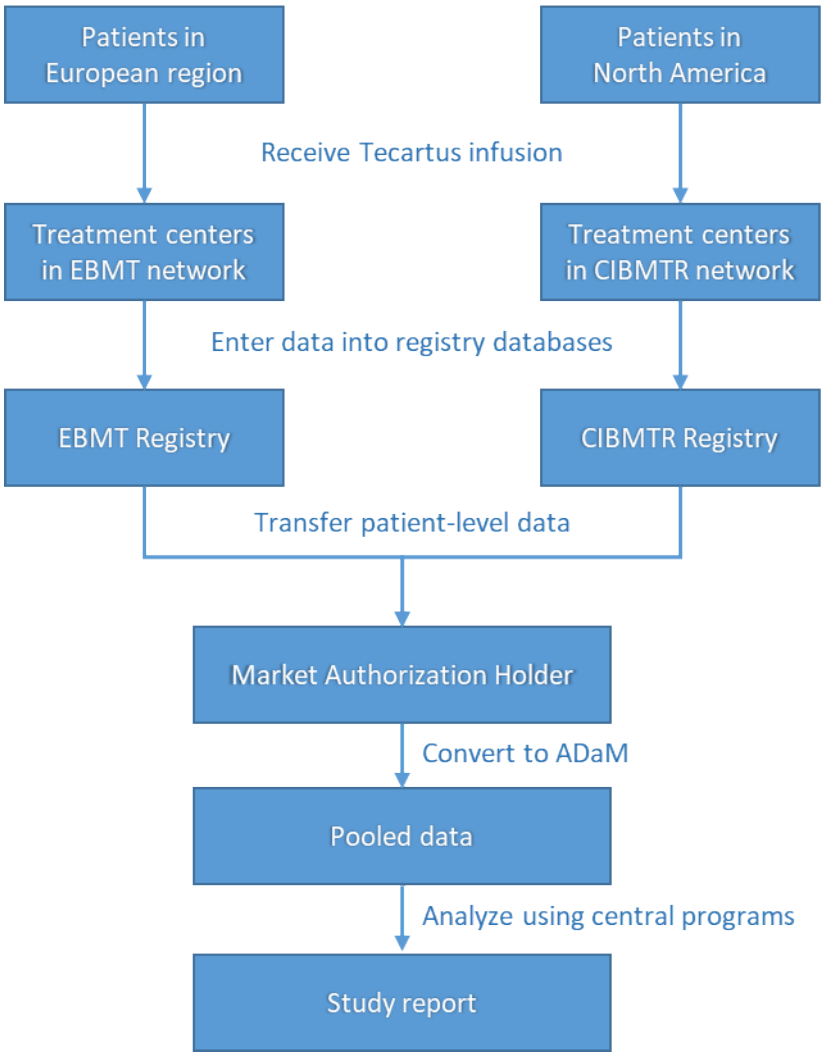
7.6.3. Data Transfer Procedure

At regular intervals (quarterly for EBMT and bi-annually for CIBMTR), the registries will provide pseudonymized patient-level datasets to the MAH through a secure file transfer protocol. These datasets will include the baseline characteristics, outcome variables, and other covariates. Data dictionaries will also be prepared to describe all variables included in the datasets.

7.6.4. Data Integration Procedure

Since the two registry databases are very similar in content, the patient-level data will be integrated into one CDISC Analysis Dataset Model (ADaM) to allow consistent and periodic reporting where possible based on the “sharing of data” model defined by the ENCePP guidelines {(EMA) 2018}. The central analysis removes variability linked to the statistical programming and analysis. A diagram of data collection, transfer and integration is provided in Figure 2.

Figure 2. Flow Diagram of Data Collection, Transfer, and Integration



7.7. Data Analysis

The study population in the primary analysis will consist of a combined patient population of CIBMTR and EBMT-enrolled patients. For primary, secondary effectiveness and CCI [redacted]. For secondary safety endpoints, patients will be analyzed as both a pooled population and separately by indication. The pooled analyses will follow the CHMP guideline on registry-based studies. The Statistical Analysis Plan (SAP) will describe the specifics regarding the integration of the CIBMTR and EBMT data. To inform the comparability of the two populations (EBMT and CIBMTR), stratified analysis will be performed to provide a descriptive comparison of the patient populations in terms of demographic and clinical characteristics, treatment received before, peri- and post-CAR-T, and outcomes.

7.7.1. Primary Endpoint and Effectiveness Endpoints

Missing data in effectiveness variables will be treated as non-responders. However, this will also depend on the reason for missing data. Clarification for exclusion will be provided if patient data is excluded.

7.7.1.1. Primary Endpoint

- For MCL, the ORR, defined as the incidence of CR or PR, will be calculated. The 95% confidence intervals will be provided for ORR using exact binomial methods.
- For ALL, the OCR, defined as the incidence of CR + CRi, will be calculated. The 95% confidence intervals will be provided for OCR using exact binomial methods.

7.7.1.2. Effectiveness Endpoints

- Complete remission rate (CRR): defined as the incidence of CR, will be calculated. The 95% confidence intervals will be provided using exact binomial methods (for MCL only).
- Duration of response (DOR): For MCL, duration of response is defined as the time from the first objective response (CR/PR) to the first progression or death due to MCL, among subjects who experience an objective response. For ALL, duration of remission is defined as the time from the first OCR (CR/CRi) to the first relapse or death due to ALL, among subjects who experience an OCR. The cumulative incidence of DOR and 95% Cis will be estimated at 6, 12, 24 and 36 months using the competing risk analysis method, with death due to reasons other than primary disease considered as a competing event.
- Overall survival (OS): overall survival is the time from the date of Tecartus infusion to the date of death due to any reason. All patients will be followed up for survival information regardless of whether they received additional treatment post infusion. Patients who are alive at last contact will be censored at that time, but no censoring will be done for additional treatment. OS will be summarized using the Kaplan-Meier (KM) estimate and 95% CI at 1, 2, 5, 10 and 15 years. The median OS along with 95% CIs will be presented if appropriate. Causes of death will also be reported.
- Time to next treatment of the primary disease (TTNT): time from Tecartus infusion to next treatment of the primary disease or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk. The cumulative incidence of time to next treatment and 95% CI will be estimated using competing risk analysis method, with death without relapse or progression or without subsequent treatment of primary disease considered as a competing risk. Pointwise estimates and 95% CIs at 6, 12, 24, and 36 months will be calculated.
- For MCL patients, time to REL/PD is defined as the time from Tecartus infusion to the first relapse, progression, significant worsening of the primary disease, or death due to the primary disease. Death due to reasons other than primary disease will be taken as a competing risk. Patients who are alive without REL/PD will be censored. Relapse of the primary disease is defined as reappearance of the primary tumor among patients who achieved a remission as the best response. Progression of the primary disease is defined by at

least a 50% increase in the size of an existent mass or lymph node or increase in the number of lymph nodes or new sites of disease. Refer to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma {Cheson 2007} and Lugano Classification {Cheson 2014} for more details. The cumulative incidence of relapse or disease progression and 95% CI will be estimated using competing risk analysis method, with death without relapse or progression considered as a competing risk. Pointwise estimates and 95% CIs at 6, 12, 24, and 36 months will be calculated.

- For ALL patients, time to relapse is defined as the time from Tecartus infusion to the earliest documented relapse through clinical/hematologic assessment (including pathology and laboratory assessment as well as physical examination) or death due to the primary disease. Subjects who have not achieved a complete remission (CR or CRi) at the analysis data cutoff will be evaluated as having the event at Day 0. Death due to reasons other than primary disease will be taken as a competing risk. Patients who are alive without relapse will be censored. The cumulative incidence of relapse or disease progression and 95% CI will be estimated using competing risk analysis method, with death without relapse or progression considered as a competing risk. Pointwise estimates and 95% CIs at 6, 12, 24, and 36 months will be calculated.

- Effectiveness endpoints by sex, age (including stratified analyses for CIBMTR in the group of 18–25-year-old patients of ALL indication), country, and region

- Effectiveness endpoints in special populations

- For MCL, patients with prior stem cell transplantation, high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, CD19 expression status.

- For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with Out of Specifications (OOS) product.

7.7.2. Safety Endpoints

- Secondary malignancy: the overall incidence of secondary malignancies, and secondary malignancy by type and location will be summarized using frequencies and percentages, as well as follow-up adjusted rates. Cumulative incidence curve of time to onset of secondary malignancy shown out to 15 years, treating death prior to secondary malignancy as a competing event. Estimates and 95% CIs for the cumulative incidence of secondary malignancy will be provided at 1, 2, 5, 10, and 15 years.

- CRS: the overall incidence and grade of CRS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of CRS and 95% CI will also be estimated using competing risk analysis method, with death before experiencing CRS treated as a competing event for the onset of CRS up through 30 days after Tecartus infusion. Management and resolution of CRS will also be described.

- ICANS and other neurologic events: the overall incidence and grade of neurologic events, both overall and by type, will be described using frequencies and percentages, as well as

follow-up adjusted rates. The incidence of neurologic events and 95% CI will also be estimated using competing risk analysis method, with death before experiencing neurologic events treated as a competing event for the onset of neurologic event up through 90 days after Tecartus infusion. Treatment and resolution of neurologic toxicities will be described.

- Prolonged cytopenias: the proportion of patients who fail to recover ANC and platelet counts, as previously specified, by Day 30 after the administration of Tecartus will be described along with 95% CI using exact binomial methods. Time to event analysis for absolute neutrophil and platelets recovery will be summarized as continuous values among those who had deficient ANC or platelets.
- Serious infections: the incidence of serious infections (not defined as SAE definition), type and organism will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of serious infections after Tecartus infusion and 95% CI will be estimated using competing risk analysis method, with death before experiencing serious infections treated as a competing event. Resolution of serious infections will be described.
- Hypogammaglobulinemia: the incidence of hypogammaglobulinemia will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of hypogammaglobulinemia after Tecartus infusion and 95% CI will be estimated using competing risk analysis method, with death before experiencing hypogammaglobulinemia treated as a competing event for the onset of hypogammaglobulinemia. Use of replacement immunoglobulin therapy will also be described as part of this endpoint.
- Safety endpoints by sex, age (including stratified analyses for CIBMTR in the group of 18-25-year-old patients of ALL indication), country, region and indication
- Safety endpoints in special populations
- For MCL, patients with high-risk comorbidity index, patients treated with OOS product, and additional subgroups may also be explored.
- For ALL, patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with OOS product, and additional subgroups may also be explored.
- TLS: the overall incidence and grade of TLS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of TLS after Tecartus infusion and 95% CI will be estimated using competing risk analysis. Resolution of TLS will be described.

Time to onset of event of interest (secondary malignancy, or CRS, or neurologic events, or serious infections, or hypogammaglobulinemia) is defined as the time from the first Tecartus infusion to the date of onset of the first event of interest, i.e., the date of the first onset of the event or censoring – the date of the first Tecartus infusion + 1. Deaths before experiencing the event will be taken as a competing risk.

CCI [redacted]

[redacted]

7.7.4. General Considerations for Data Analysis

The study will make secondary use of the data available in the EBMT and CIBMTR Registries. Analysis of all endpoints for this study will include all patients with PLD who satisfy the eligibility criteria, are documented within the Registries, and are treated with Tecartus.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition and will include 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

This study will evaluate the risk of age, sex, country and region, and in special populations (patients with prior SCT, high risk comorbidity index, patients treated with OOS product for MCL; patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with OOS product for ALL) on the effectiveness and safety endpoints using multivariable regression analyses. Depending on the data, additional baseline characteristics may also be explored.

Patient incidence of endpoint events will be provided. Multivariate Poisson regression analyses will be used to estimate cumulative incidence rates adjusted for follow-up period and specified characteristics (as mentioned in the prior paragraph) to estimate their prognostic effect on the outcome.

Kaplan-Meier curves will be used to illustrate all time-to-event data without competing risk. Competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression of primary disease and time to next treatment of primary disease, and the cumulative incidence at specified time points will be provided. Cox -proportional hazard models and cause-specific Cox model will be used to model multivariate time-to-event data without and with competing risk respectively adjusted for specified characteristics (as mentioned in the prior paragraph) to estimate their prognostic effect on the outcome.

For the effectiveness part, the analysis of the effectiveness endpoints will be conducted when the first 200 eligible patients were documented in EBMT Registry and 500 in CIBMTR Registry for each indication. Time-to-event endpoints will be analyzed through Kaplan-Meier method (median, 1st quartile, 3rd quartile along with their 95% confidence interval will be provided if applicable). Cumulative incidence for relapse or progression of primary disease will also be provided through the competing risk method.

The potential impact of the missing values on the analysis will be evaluated and possible patterns of relationship between missing values and both influential characteristics and outcomes will be investigated. Results of the analysis of the type of missing data will be described in the results to support the appropriateness of the statistical analysis performed.

Missing events due to deaths will be adjusted through competing risk analysis method for time-to-event subjects described above. The extent of missing data in the study will be described and tabulated. When possible, the number of missing data will be reduced by retrieving the data or imputing the correct value if it can be derived from other information already collected in this protocol.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by Preferred Term (PT) and primary System Organ Class (SOC).

Published literature and relevant databases will be reviewed during the five years from start of data collection to identify a suitable comparator. If an appropriate comparator is forthcoming a meta-analysis or a patient-level data specific analysis to compare the effectiveness and safety between Tecartus and the selected comparator will be conducted, subject to data availability.

7.7.5. Interim Analysis

For the effectiveness part interim reports will be prepared annually for the first three years, in which an analysis of treated patients for the primary and the effectiveness endpoints will be included. The effectiveness interim analyses will include both pooled as well as stratified analyses by data source (CIBMTR and EBMT) as detailed in the SAP. For the safety part interim reports will be prepared annually for the first four years and then every two years, in which an

analysis of treated patients for the safety endpoints will be included. The safety interim analyses will include both pooled as well as stratified analyses by indication (MCL and ALL) and data source (CIBMTR and EBMT) as detailed in the SAP. Safety interim reports will include a discussion on the background risk of the safety endpoints, in particular for secondary malignancies. The study objectives are not associated with formal hypothesis testing and no overall type I error control. These interim analyses are administrative for the purpose of monitoring the progress of the study enrollment, safety and effectiveness profile of Tecartus.

7.8. Quality Control

The data collected will be entered in the EBMT database according to standard operating procedures, work instructions, manuals and guidelines that are in place and maintained by EBMT.

At a registry level EBMT has built in more than four thousand control triggers, which promote consistency of the data. In addition, EBMT personnel and registry users can run data quality reports, which predominantly focus on missing data. For all studies (both retrospective and prospective) based on registry data additional data cleaning efforts, including the analyses of outliers, additional data requests and if needed statistic adjustments for missing data, are performed.

Apart from remote monitoring activities, on-site monitoring of data for 10% of the included Tecartus patients will be performed by the EBMT. Centers will be selected for on-site monitoring based on a risk-based approach using quality indicators as described in the monitoring plan.

Additional quality control measures supported by EBMT include:

- Automatic data validation checks verify the accuracy and internal consistency of entries in the database at the point of entry.
- Data quality control reports can be run by users (or by registry personnel) to check for missing, inconsistent or incorrect data.
- Follow-up requests on missing or incorrect data are issued by the registry/Study Office, this also applies, if yearly follow-up data were not submitted for a patient during the up to 15-year follow-up period.
- Education and training sessions (face to face and on-line) are available for data entry staff.
- Remote manual data quality review is performed in accordance with the study data quality and monitoring documents. In addition, monitors will engage centers with regard to data quality and completeness via telephone calls and may perform onsite visits, as documented in the EBMT monitoring plan.

For the CIBMTR Registry, the data collected by the mechanisms outlined above (see 7.6) will be entered in the CIBMTR Research Database according to standard operating procedures.

Computerized error checks identify outliers and inconsistent values and generate requests to the reporting centers for clarification. Centers are additionally audited by statistical center personnel for data quality one time every 4 years.

CIBMTR's data quality efforts are continuous and cyclical. They are under constant refinement to ensure that any new data concerns that arise can be prevented or identified as far upstream as possible. CIBMTR's clinical data quality team coordinates several aspects of the post-collection data validation process. This team coordinates requests from various areas of CIBMTR to participating centers to ensure consistency in messaging and prioritization guidelines.

As new issues are identified, the clinical data quality team evaluates existing resources, including instruction manuals, available training videos, and FormsNet3 validation, and the team coordinates enhancements to the relevant systems and materials. FormsNet validation happens in real-time as data are entered. Users are prompted and can resolve errors immediately in the application. Forms will not be considered "complete" by the application until any and all errors are addressed.

The FormsNet Query Management Tool allows CIBMTR to place a query on a field directly within FormsNet so all system validation happens normally, preventing the user from generating additional errors. This enhances efficiency and protects privacy by reducing manual processes, such as emails and phone calls. The tool also requires action from CIBMTR staff members to "approve" the response before the form can go back to a complete status, ensuring the response truly resolves the data issue. Resolution of these queries is traced within the CPI compliance program. Centers must address a target percentage of queries within a trimester to remain in good standing.

The CIBMTR also maintains a series of ongoing data audits performed at all CIBMTR participating centers as part of the CIBMTR's overall data quality assurance program. The audit compares data in source documents maintained by the center with data contained in the CIBMTR outcomes registry. The audits identify errors that otherwise would go undetected by the online validations built into the data entry program.

The goals of the audit program are to ensure the quality and accuracy of the research database by:

- Ensuring the accuracy and completeness of data reported to the CIBMTR
- Identifying system and non-systemic errors
- Requesting corrective action for errors identified during the audit
- Providing training to center data management staff

As part of the ongoing data quality program, the CIBMTR conducts data quality audits at regular intervals to ensure the accuracy of data submitted to the CIBMTR's observational database. CIBMTR Clinical Research Associates serve as auditors. They compare submitted data with source documentation, provide training to data management staff, and identify any systemic data reporting issues at transplant centers qualifying for audit.

All data elements on all forms are subject to audit. However, the audit concentrates on "critical" data, i.e., data most likely to be included in a research study. Data elements considered "non-critical" are randomly audited to increase the validity of the audit error rates. Auditors also review consent forms for completeness. Following the audit, the CIBMTR generates a report and may require the center to complete corrective action.

7.9. Limitations of the Research Methods

This non-interventional secondary use of data study makes use of the EBMT Registry and the CIBMTR Registry and is dependent on all needed variables to be collected in the respective registries in the EBMT Cellular Therapy Form. Furthermore, certain variables may not be generated as part of routine medical practice or local regulations limit the ability to collect the information.

The EBMT Registry allows patient data entry any time after Tecartus infusion and the CIBMTR Registry up to 3 months after; therefore, this study has the characteristic disadvantages of retrospective studies, for example, information bias, history bias and recall bias. However, there will be an effort to encourage patient documentation in the registries as promptly as possible to capture data continuously going forward.

Information bias can be prevented by using standard measurement instruments, like electronic data collection form and appropriate training of personnel entering the data. Appropriate training of personnel entering data is also important to avoid missing values when checking the patients' medical records.

Merging CIBMTR and EBMT Registry data into a single pooled analysis presents methodological difficulties. One of the challenges includes the chronology bias due to the difference in time of start of data collection of the EBMT and CIBMTR cohorts.

Patient selection, clinical practices and management of AEs may differ between registries and might have evolved over time, thus introducing potential biases. Kite anticipates that this would mainly affect early safety events including CRS and ICANS (neurologic events) but not effectiveness and long-term safety outcomes. The incidences and severity of CRS and ICANS may be decreased by more frequent and effective use of prophylactic medications in more recent time {Oluwole 2024}. However, this will unlikely affect the validity of the incidence estimates for CRS and ICANS. Kite will assess whether there are potential chronology trends in each outcome by comparing results from the stratified analysis by cohorts using descriptive statistics as treatment periods are mainly sequential with minimal overlap (ie, the CIBMTR subjects were treated earlier than the EBMT subjects). For other safety outcomes, especially secondary malignancies, chronology bias is unlikely to be an issue. The pooled data from the EBMT Registry and CIBMTR cohorts can be used to obtain a more reliable effect estimate on the incidence of secondary malignancies overall in patients receiving brexucabtagene autoleucel.

In addition, there are differences in the way outcomes are described in the CIBMTR cohort versus the EBMT cohort.

7.10. Other Aspects

7.10.1. Study Discontinuation

No patient's treatment will be dictated by the protocol of this long-term observational study or by EBMT, CIBMTR, or Kite. Consequently, continuing or discontinuing this study will not impact patient care. Therefore, identification of adverse effects of Tecartus will not constitute sufficient reason to terminate the study. However, early termination of the study will be considered if:

- Sufficient information is accumulated to meet the scientific objectives of the study.
- The feasibility of collecting sufficient information is reduced to unacceptable levels because of low exposure rates, extremely slow patient accrual, or loss of the ability to follow-up.

In case such conditions are met, any consideration for termination of the study will be discussed and agreed with the European Medicines Agency (EMA) beforehand.

8. PROTECTION OF HUMAN SUBJECTS

Because this is a non-interventional study with no pre-specified interventions and no interaction with patients, no potential physical or psychological risks to patients exist. This study will make secondary use of data collected within the EBMT and CIBMTR Registries to capture information about Tecartus.

8.1. EBMT

EBMT will use standard processes for ensuring the protection of human subjects for patients whose cellular therapy data are reported to the EBMT Registry. Participating centers are responsible for obtaining informed consent for patient data entry into the EBMT Registry, registering patients, and submitting baseline and follow-up data on participating patients into the EBMT Registry following EBMT's procedures and requirements.

There is no potential benefit to those who agree to have their data entered into the EBMT Registry. All benefits of long-term follow-up data collection will assist in understanding late effects that occur after treatment with CAR T cells, and thus may benefit future patients. The only risk to patients is the risk of loss of privacy and confidentiality. This is a well-mitigated risk with respect to the potential benefit of knowledge gained through these research studies.

8.1.1. Informed Consent

No specific informed consent will be obtained by Kite to participate in this study, as this study will involve secondary analysis of data already existing in the EBMT Registry. According to established practices of the EBMT and country requirements, at each of the centers an informed consent document will be obtained from each participating patient and maintained at the center. With this informed consent document patients will provide consent for input of their data into the EBMT Registry and sharing of data with Kite and health authorities.

8.1.2. Confidentiality

All data evaluated for this study will be collected in an EBMT data collection form with a unique identifier for each patient by each participating center. The patient identifiers will be removed, and the data will contain no patient identifiable fields when analyzed data is shared with Kite by the EBMT.

8.2. CIBMTR

The CIBMTR will use standard processes for ensuring the protection of human subjects for patients whose cellular therapy data are reported to the CIBMTR Research Database and Research Sample Repository. The National Marrow Donor Program Institutional Review Board has primary oversight for the CIBMTR Research Database Protocol and Protocol for Research Sample Repository. All US centers are required to have a Federal Wide Assurance with the Office for Human Research Protection and, as part of their Data Transmission Agreement with the CIBMTR, agree to obtain local IRB approval for the CIBMTR Research Database Protocol

(http://www.ClinicalTrials.gov Identifier: NCT01166009). Participating centers are responsible for recruiting patients, obtaining informed consent, registering subjects, and submitting baseline and follow-up data on participating patients. Centers register patients and submit data through FormsNet, the CIBMTR electronic data capture system. The FormsNet application is compliant with US database security requirements as established by the Health Resources & Services Administration (HRSA) Office of Information Technology. HRSA security audits are performed annually; the most recent audit was in September 2017. With this vigilant surveillance and systems security, there is minimal risk that a subject's privacy or confidentiality would be breached.

Patients will be identified to participate in the US CIBMTR registry by personnel at the participating centers when they receive their therapy. According to established practices at each of the centers, a study database IRB-approved informed consent document which allows for sharing of data with other registries will be obtained from each participating patient. Documentation of assent, of parent legal guardian permission of minor participants, and consent for adult participants must be maintained at the center where the participant or their parent or legal guardian provided consent to participate. Centers are required to enter the date that informed consent was obtained from the patient on the data collection form submitted to the CIBMTR. Patients are provided information regarding the types of data collected from their medical record, the time intervals at which data will be submitted, the types of studies in which their data may be included, and the research sample to be collected in the event of a subsequent neoplasm. The research sample to be provided in the event of a subsequent neoplasm may consist of peripheral blood and/or a tumor biopsy, depending on the diagnosis and if tumor collection is applicable. Samples will be evaluated for presence of γ-retroviral vector sequences and RCR.

8.3. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the European Medicines Agency – Guideline on Good Pharmacovigilance Practices (GVP), following the requirements for studies making secondary use of data, and including the archiving of essential documents. The study will further be conducted in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), by enclosing the ENCePP Checklist in the submission and registering the study in the EU PAS Registry.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The operational model for this post-authorization study protocol 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 EBMT Registry or CIBMTR data set; and where the AEs have already occurred and will not be reported in expedited manner) as outlined in GVP Module VI. According to this guidance, reporting of safety information in the form of individual case safety reports (ICSRs) is not required and all adverse event and safety data are only required to be recorded and summarized in the interim safety analysis and in the final study report. All adverse events will be summarized in aggregate during all reporting efforts, including in the interim and final study reports.

Reporting of individual adverse events and adverse reactions will follow the standard spontaneous reporting system per local regulations, agreements and timelines. EBMT centers will report any suspected adverse reactions directly to Kite or respective health authorities. The SmPC and packaging materials provide respective details and contact information. Kite further provides clear guidance to HCPs in the aRMMs of the need for and importance of spontaneously report and that this is not substituted by reporting into the EBMT or CIBMTR Registries.

9.1. Kite Reporting Requirements to Regulatory Authorities

Kite is responsible for analyzing spontaneous reports of all safety information received independently from this study and for reporting to regulatory agencies as determined by country-specific legislation or regulations.

9.2. Definitions

9.2.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of treatment will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the Tecartus treatment cycle was initiated. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

9.2.2. Adverse Events of Special Interest

An Adverse Events of Special Interest (AESI) for this study is considered to be an event in the focus of the safety objectives: secondary malignancies, CRS, neurologic events, serious infections (not defined as per SAE definition), prolonged cytopenia, hypogammaglobulinemia, TLS and aggravated GvHD. Pregnancy outcomes in female patients of childbearing potential or partners of male patients are also of special interest.

9.2.3. Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

9.2.4. Serious Adverse Events

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life -threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

9.2.5. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

9.2.6. Special Situations Reports

CCI [redacted] Other Special situation reports (SSRs) are not within the objectives of the study, but if reported spontaneously, Kite will accept these reports and handle them as appropriate.

Special situation reports include reports of abuse, drug interactions, counterfeit or falsified medicine, exposure via breastfeeding, lack of effect, medication error, misuse, occupational exposure, off-label use, overdose, pregnancy, product complaints, transmission of infectious agents via the product, and unexpected benefit. Definitions and examples are provided below.

- Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient.
- Drug interactions: Any reports of drug/drug, drug/food, or drug/device interactions.
- Counterfeit or falsified medicine: Any medicinal product with a false representation of a) its identity, b) its source, or c) its history.
- Exposure via breastfeeding: Reports of any exposure to a medicinal product during breastfeeding.
- Lack of effect: A report of a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.
- Medication error: Any unintentional error in the prescribing, dispensing, preparation for administration or administration of a medicinal product while the medication is in the control of a healthcare professional, patient or consumer.
- Misuse: Use of a medicinal product that is intentional and inappropriate not in accordance with its authorized product information.
- Occupational exposure: Exposure to a medicinal product as a result of one's professional or non-professional occupation.
- Off-label use: Where a medicinal product is intentionally used by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population.
- Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose in the product labelling.

- CCI [redacted]
- Product complaint: Complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.
- Unexpected benefits: An unintended therapeutic effect where the results are judged to be desirable and beneficial.
- Transmission of infectious agents via the product: Any suspected transmission of an infected agent through a Kite medicinal product.

10. DATA FROM ADDITIONAL REGISTRIES

Aggregated patient data from the DESCAR-T registry will be provided, when available, together with the interim report of the KT-EU-472-6036 PAES/PASS. The results will be incorporated in the results section of the report and discussed in this context. While DESCAR-T data cannot be integrated into the analysis of the PAES/PASS, the results from the PAES/PASS will be contextualized with data from DESCAR-T as an external data source. The contextualization of results from the KT-EU-472-6036 PAES/PASS with the data from the DESCAR-T Registry will be conducted based on the data accessible to Kite either as part of pre-agreed data sharing agreements or published data.

In addition, where patient-level data is not possible to obtain within the EBMT registry, Kite will reasonably endeavour to obtain patient-level data from EU national registries. A status report will be provided with the 2025 annual interim report.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Kite will include updates on the progress of the study as well as updates on the published literature and relevant databases to identify a suitable comparator in the PSURs at appropriate intervals.

11.1. Study Report and Publications

11.1.1. Safety Data Reports

After start of data collection, EBMT will provide Kite with a raw data output. Based on the data transferred, Kite performs an aggregate data analysis for Tecartus within 30 days (45 days for the first report). Safety Data Reports will be submitted as appendices in accordance with the applicable periodic safety update report (PSUR) to the Pharmacovigilance Risk Assessment Committee (PRAC). In case an intervening Safety Data Report identifies a major new safety finding or there is an unfavourable change in the risk/benefit profile, the respective report will be submitted promptly as stand-alone document to the Safety Data Reports will focus on Adverse Events of Special Interest (AESIs) – which are considered to be the events related to the safety objectives (please see below and in Section 9.2.2) – where information is available for patient-level presentation and causality assessment, this will be included.

The Safety Data Reports will contain the following information, as available:

- Patient enrollment in registry
- Baseline characteristics
- Aggregate numbers of reported fatal adverse events
- Aggregate numbers of all reported adverse events
- Review of events considered AESIs via the safety objectives of this study: secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenia, hypogammaglobulinemia, TLS, aggravated GvHD, and pregnancies and their outcomes.
- If reported, review of any unexpected events, which do not fall under the previously recognized risks or AEs of special interest
- Summary and conclusions

11.1.2. Interim Reports

For the effectiveness part, interim reports will be prepared annually for the first 3 years, in which an analysis of treated patients for the primary and the effectiveness endpoints will be included. For the safety part, interim reports will be prepared annually for the first 4 years and then every 2 years thereafter, in which an analysis of treated patients in both EBMT and CIBMTR for the safety endpoints will be included. Safety interim reports will include a discussion on the

background risk of the safety endpoints, in particular for secondary malignancies. The versions of the EBMT Cellular Therapy Forms utilized in the EBMT Registry and the relevant forms in the CIBMTR Registry during the respective time period will be provided as appendices to these reports. The data collection forms are under the control of the EBMT and CIBMTR registries, and their content can change throughout the course of the study (see Section 7.2). Based on the data transferred from EBMT and CIBMTR, Kite performs an aggregate data analysis for Tecartus within 90 days to generate interim reports (120 days for the first report).

Based upon the approved reports, Kite will submit information to regulatory agencies in accordance with any agreements/commitments.

11.1.3. Final Report

Following the final data analysis, Kite, EBMT, and CIBMTR will cooperate to prepare the final report. The final report will be submitted to the Regulatory authorities as applicable by Kite as the study sponsor.

11.1.4. Publications, Conference Abstracts, and Manuscripts

All proposed publications and conference presentations arising from the study will be reviewed by Kite, EBMT, and CIBMTR representatives prior to submission. Both EBMT and Kite will share responsibilities in the development of the statistical analysis plan, data analysis, abstracts and manuscripts. The EBMT investigators and Kite staff may share authorship. The study contract between EBMT and Kite will outline the requirements for publication.

Kite shall communicate the final manuscript to the EMA and the competent authorities of the Member States in which the product is authorized within 2 weeks after first acceptance for publication.

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13. ANNEXES

Annex 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	None		

Annex 2. ENCePP Checklist for Study Protocols

Study title:

LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL) OR ADULT PATIENTS WITH R/R B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

EU PAS Register® number: EUPAS45813

Study reference number (if applicable): KT EU 472 6036

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☒	☐	☐	4
1.1.4 Interim report(s)	☒	☐	☐	4
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	5, 6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	5, 7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	5, 7
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	6, 7
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9, 11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	5, 7
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	5, 7
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	5, 7
	4.2.5 Duration of follow-up	☒	☐	☐	5, 7
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	5, 7

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	

5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	5, 7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	5, 7
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	5, 7
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	7
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	5,7

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	5,7
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	5,7
	9.1.3 Covariates and other characteristics?	☒	☐	☐	5,7
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	5,7
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	5,7
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	5,7
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	7
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7
	9.3.3 Covariates and other characteristics?	☐	☒	☐	7
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	7

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	5, 7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	5, 7
10.3	Are descriptive analyses included?	☒	☐	☐	5, 7
10.4	Are stratified analyses included?	☒	☐	☐	7
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	7
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	7
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	7
10.8	Are relevant sensitivity analyses described?	☐	☒	☐	7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	8, 9
11.2 Are methods of quality assurance described?	☒	☐	☐	7
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	7

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	7
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	7

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	8, 9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: PPD

Date: 17/December/2024

Signature: _____

Annex 2_ENCePP Checklist for Study Protocols_PA05

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Real-World Evidence eSigned	09-Dec-2024 14:43:59

Annex 3. Reference Safety Information

Current version of the EU SmPC for Tecartus®.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Tecartus (brexucabtagene autoleucel) is a genetically modified autologous cell-based product containing T cells transduced *ex vivo* using a retroviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Mantle cell lymphoma

Each patient-specific infusion bag of Tecartus contains brexucabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 2 × 10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 × 10^6 – 2 × 10^6 cells/kg), with a maximum of 2 × 10^8 anti-CD19 CAR-positive viable T cells suspended in a Cryostor CS10 solution.

Each infusion bag contains approximately 68 mL of dispersion for infusion.

Acute lymphoblastic leukaemia

Each patient-specific infusion bag of Tecartus contains brexucabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 1 × 10^6 anti CD19 CAR positive viable T cells/kg body weight, with a maximum of 1 × 10^8 anti CD19 CAR positive viable T cells suspended in a Cryostor CS10 solution.

Each infusion bag contains approximately 68 mL of dispersion for infusion.

Excipient(s) with known effect

This medicinal product contains 300 mg sodium.
Each dose contains 0.05 mL of dimethyl sulfoxide (DMSO) per mL of Tecartus.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to opaque, white to red dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mantle cell lymphoma

Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

Acute lymphoblastic leukaemia

Tecartus is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

4.2 Posology and method of administration

Tecartus must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

Posology

Tecartus is intended for autologous use only (see section 4.4).

Mantle cell lymphoma
Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one infusion bag. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above.

Tecartus is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy for MCL patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy) for MCL patients
- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously must be administered prior to infusing Tecartus. The recommended days are on the 5th, 4th, and 3rd day before infusion of Tecartus.

Acute lymphoblastic leukaemia
Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one infusion bag. The target dose is 1×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 1×10^8 CAR-positive viable T cells for patients 100 kg and above.

Tecartus is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy for ALL patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy) for ALL patients
A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m^2 intravenously over 60 minutes must be administered prior to infusing Tecartus. This is recommended on the 2nd day before infusion of Tecartus. Fludarabine 25 mg/m^2 intravenously over 30 minutes must be administered prior to infusing Tecartus. The recommended days are on the 4th, 3rd, and 2nd day before infusion of Tecartus.

Mantle cell lymphoma and acute lymphoblastic leukaemia

Pre-medication
- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenously or orally (or equivalent medicinal products) approximately 1 hour before the infusion of Tecartus.
- Prophylactic use of systemic corticosteroids is not recommended (see section 4.5).

Monitoring prior to infusion
- In some patient groups at risk, a delay of the Tecartus infusion may be indicated (see section 4.4- Reasons to delay treatment).

Monitoring after infusion
- Patients must be monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians can consider hospitalisation for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events.
- After the first 7 days following the infusion, the patient is to be monitored at the physician's discretion.
- Patients must remain within proximity of a qualified treatment centre for at least 4 weeks following infusion.

Special populations

Elderly
No dose adjustment is required in patients ≥65 years of age.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)
There is no experience with manufacturing Tecartus for patients with a positive test for HIV, active HBV, or active HCV infection. Therefore, the benefit/risk has not yet been established in this population.

Paediatric population
The safety and efficacy of Tecartus in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

Tecartus is for intravenous use only.

Tecartus must not be irradiated. Do NOT use a leukodepleting filter.

Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Tecartus infusion bag and cassette.

Administration
- A leukodepleting filter must not be used.
- Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period. In the exceptional case where tocilizumab is not available due to a shortage

that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- For autologous use only, verify the patient ID to match the patient identifiers on the Tecartus infusion bag.
- Once tubing has been primed, infuse the entire content of the Tecartus infusion bag within 30 minutes by either gravity or a peristaltic pump.

For detailed instructions on preparation, administration, accidental exposure and disposal of Tecartus, see section 6.6.

CCI [redacted]

[redacted]

[redacted]

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years.

Autologous use

Tecartus is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Tecartus infusion bag and cassette. Do not infuse Tecartus if the information on the patient-specific cassette label does not match the intended patient's identity.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Reasons to delay treatment

Due to the risks associated with Tecartus treatment, infusion must be delayed if a patient has any of the following conditions:
- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active graft-versus-host disease (GvHD).

In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen must be administered again (see section 4.2)

Monitoring after infusion

Patients must be monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians can consider hospitalisation for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events. After the first 7 days following infusion, the patient is to be monitored at the physician's discretion.

Patients must remain within proximity of a qualified treatment centre for at least 4 weeks following infusion and seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions must be considered depending on the severity of the reaction.

Serological testing

Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Tecartus (see section 4.2).

Blood, organ, tissue and cell donation

Patients treated with Tecartus must not donate blood, organs, tissues, or cells for transplantation.

Active central nervous system (CNS) lymphoma

There is no experience of use of this medicinal product in patients with active CNS lymphoma defined as brain metastases confirmed by imaging. In ALL, asymptomatic patients with a maximum of CNS-2 disease (defined as white blood cells <5/µL in cerebral spinal fluid with presence of lymphoblasts) without clinically evident neurological changes were treated with Tecartus, however, data is limited in this population. Therefore, the benefit/risk of Tecartus has not been established in these populations.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function were excluded from the studies. These patients are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, which can be fatal, was observed with Tecartus with a median time to onset of 3 days (range: 1 to 13 days). Patients must be closely monitored for signs or symptoms of these events, such as high fever, hypotension, hypoxia, chills, tachycardia and headache (see section 4.8). CRS is to be managed at the physician's discretion, based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 1.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection.

Management of cytokine release syndrome associated with Tecartus
At least 1 dose per patient of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, must be on site and available for administration prior to Tecartus infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Tecartus. These include the use of tocilizumab or tocilizumab and corticosteroids, as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) must be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction must be managed by standards of critical care and measures such as echocardiography is to be considered. In some cases, macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) is to be considered in patients with severe or unresponsive CRS.

Tecartus continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Tecartus-associated CRS.

Table 1 CRS grading and management guidance

CRS Grade *(a)*	**Tocilizumab**	**Corticosteroids**
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternative measures for treatment of CRS. If improving, discontinue tocilizumab.	If no improvement within 24 hours after starting tocilizumab, manage as per Grade 3. If improving, taper corticosteroids, and manage as Grade 1.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids. If improving, manage as Grade 2. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, taper corticosteroids, and manage as Grade 3. If not improving, consider alternate immunosuppressants.

N/A = not available/not applicable
(a) Lee et al 2014.
(b) Refer to Table 2 for management of neurologic adverse reactions.
(c) Refer to tocilizumab summary of product characteristics for details.

Neurologic adverse reactions

Severe neurologic adverse reactions, also known as immune effector cell-associated neurotoxicity syndrome (ICANS), have been observed in patients treated with Tecartus, which could be life-threatening or fatal. The median time to onset was 7 days (range: 1 to 262 days) following Tecartus infusion (see section 4.8).

Patients who experience Grade 2 or higher neurologic toxicity/ICANS must be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicity/ICANS. Non-sedating, anti-seizure medicines are to be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on Tecartus. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2 Neurologic adverse reaction/ICANS grading and management guidance

Grading assessment	**Concurrent CRS**	**No concurrent CRS**
Grade 2	Administer tocilizumab as per Table 1 for management Grade 2 CRS. If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab. If still not improving, manage as Grade 3.	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less. If improving, taper corticosteroids
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2. If still not improving, manage as Grade 4.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Severe infections, which could be life-threatening, were very commonly observed with Tecartus (see section 4.8).

Patients must be monitored for signs and symptoms of infection before, during and after infusion and treated appropriately. Prophylactic antibiotics must be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Tecartus infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6 and progressive multifocal leukoencephalopathy) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations must be performed.

Viral reactivation

Viral reactivation, e.g. Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus infusion and must be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following Tecartus infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia (see section 4.8). Patient blood counts must be monitored after Tecartus infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Tecartus. Hypogammaglobulinaemia was very commonly observed in patients treated with Tecartus (see section 4.8). Hypogammaglobulinaemia predisposes patients to have infections. Immunoglobulin levels should be monitored after treatment with Tecartus and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement in case of recurrent infections and must be taken according to standard guidelines.

Hypersensitivity reactions

Serious hypersensitivity reactions including anaphylaxis, may occur due to DMSO or residual gentamicin in Tecartus.

Secondary malignancies including of T cell origin

Patients treated with Tecartus may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-directed CAR T-cell therapy. There have been fatal outcomes. Patients must be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus infusion. Signs and symptoms of TLS must be monitored, and events managed according to standard guidelines.

Prior stem cell transplantation (GvHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of Tecartus worsening GvHD.

Prior treatment with anti-CD19 therapy

Tecartus is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Sodium content

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Long-term follow up
Patients are expected to enrol in a registry in order to better understand the long-term safety and efficacy of Tecartus.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Tecartus.

Prophylactic use of systemic corticosteroids may interfere with the activity of Tecartus. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section 4.2).

Administration of corticosteroids as per the toxicity management guidelines does not impact the expansion and persistence of CAR T cells.

Live vaccines

The safety of immunisation with live viral vaccines during or following Tecartus treatment has not been studied. As a precautionary measure, vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Tecartus treatment, and until immune recovery following treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

The pregnancy status of women of childbearing potential must be verified before starting Tecartus treatment.

See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Tecartus.

Pregnancy

There are no available data with Tecartus use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with Tecartus to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if Tecartus has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Tecartus is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women must be advised on the potential risks to the foetus. Pregnancy after Tecartus therapy must be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborn infants of mothers treated with Tecartus must be considered.

Breast-feeding

It is unknown whether Tecartus is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women must be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of Tecartus on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Tecartus has major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures, patients must not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

Mantle cell lymphoma
The safety data described in this section reflect exposure to Tecartus in ZUMA-2, a Phase 2 study in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight-based.

The most significant and frequently occurring adverse reactions were CRS (91%), infections (55%) and encephalopathy (51%).

Serious adverse reactions occurred in 56% of patients. The most common serious adverse reactions included encephalopathy (26%), infections (28%) and cytokine release syndrome (15%).

Grade 3 or higher adverse reactions were reported in 67% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (34%) and encephalopathy (24%). The most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%).

Acute lymphoblastic leukaemia
The safety data described in this section reflect exposure to Tecartus in ZUMA-3, a Phase 1/2 study in which a total of 100 patients with relapsed/refractory B-cell precursor ALL received a single dose of CAR-positive viable T cells (0.5×10^6, 1×10^6, or 2×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight based.

The most significant and frequently occurring adverse reactions were CRS (91%), encephalopathy (57%), and infections (41%).

Serious adverse reactions occurred in 70% of patients. The most common serious adverse reactions included CRS (25%), infections (22%) and encephalopathy (21%).

Grade 3 or higher adverse reactions were reported in 76% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (27%), CRS (25%) and encephalopathy (22%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in a total of 182 patients exposed to Tecartus in two multi-centre pivotal clinical studies, ZUMA-2 (n=82) and ZUMA-3 (n=100). These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse drug reactions identified with Tecartus

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections Bacterial infections Fungal infections Viral Infections
Blood and lymphatic system disorders		
	Very common	Leukopenia[a] Neutropenia[a] Lymphopenia[a] Thrombocytopenia[a] Anaemia[a] Febrile neutropenia
	Common	Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome[b] Hypogammaglobulinaemia
	Common	Hypersensitivity Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders		
	Very common	Hypophosphataemia[a] Decreased appetite Hypomagnesaemia Hyperglycaemia[a]
	Common	Hypoalbuminemia[a] Dehydration
Psychiatric disorders		
	Very common	Delirium Anxiety Insomnia
Nervous system disorders		
	Very common	Encephalopathy Tremor Headache Immune effector cell-associated neurotoxicity syndrome (ICANS[b, c]) Aphasia Dizziness Neuropathy

System Organ Class (SOC)	Frequency	Adverse reactions
	Common	Seizure Ataxia Increased intracranial pressure
Cardiac disorders		
	Very common	Tachycardias Bradycardias
	Common	Non-ventricular arrhythmias
Vascular disorders		
	Very common	Hypotension Hypertension Haemorrhage
	Common	Thrombosis
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Dyspnoea Pleural effusion Hypoxia
	Common	Respiratory failure Pulmonary oedema
Gastrointestinal disorders		
	Very common	Nausea Diarrhoea Constipation Abdominal pain Vomiting Oral pain
	Common	Dry mouth Dysphagia
Skin and subcutaneous tissue disorders		
	Very common	Rash Skin disorder
Musculoskeletal and connective tissue disorders		
	Very common	Musculoskeletal pain Motor dysfunction
Renal and urinary disorders		
	Very common	Renal insufficiency
	Common	Urine output decreased
General disorders and administration site conditions		
	Very common	Oedema Fatigue Pyrexia Pain Chills
	Common	Infusion related reaction
Eye Disorders		
	Common	Visual impairment
Investigations		
	Very common	Alanine aminotransferase increased[a] Blood uric acid increased[a] Aspartate aminotransferase increased[a] Hypocalcaemia[a] Hyponatraemia[a] Direct bilirubin increased[a] Hypokalaemia[a]
	Common	Bilirubin increased[a]

Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3.

[a] Frequency based on Grade 3 or higher laboratory parameter.

[b] See section Description of selected adverse reactions.

[c] The frequency of ICANS has been estimated from events reported in the post-marketing setting.

ZUMA-2 data cutoff: 24 July 2021; ZUMA-3 data cutoff: 23 July 2021

Description of selected adverse reactions from ZUMA-2 and ZUMA-3 (n=182), and from post marketing reporting

Cytokine release syndrome
CRS occurred in 91% of patients. Twenty percent (20%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 9 days (range: 1 to 63 days). Ninety-seven percent (97%) of patients recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (94%), hypotension (64%), hypoxia (32%), chills (31%), tachycardia (27%), sinus tachycardia (23%), headache (22%), fatigue (16%), and nausea (13%). Serious adverse reactions that may be associated with CRS included hypotension (22%), pyrexia (15%), hypoxia (9%), tachycardia (3%), dyspnoea (2%) and sinus tachycardia (2%). See section 4.4 for monitoring and management guidance.

Neurologic events and adverse reactions
Neurologic adverse reactions occurred in 69% of patients. Thirty-two percent (32%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 7 days (range: 1 to 262 days). Neurologic events resolved for 113 out of 125 patients (90.4%) with a median duration of 12 days (range: 1 to 708 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Ninety-three percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

The most common neurologic adverse reactions including ICANS represented tremor (32%), confusional state (27%), encephalopathy (27%), aphasia (21%), and agitation (11%). Serious adverse reactions including encephalopathy (15%), aphasia (6%), confusional state (5%) and serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus. See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 12% of patients after Tecartus infusion. Infections occurred in 87 of the 182 patients treated with Tecartus in ZUMA-2 and ZUMA-3. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 30% of patients including unspecified pathogen, bacterial, fungal and viral infections in 23%, 8%, 2% and 4% of patients respectively. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy.

Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 48% of patients and included neutropenia (34%), thrombocytopenia (27%) and anaemia (15%). See section 4.4 for management guidance.

Hypogammaglobulinaemia
Hypogammaglobulinaemia occurred in 12% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Tecartus has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. To date, no anti-CD19 CAR T-cell antibody immunogenicity has been observed in MCL patients. Based on an initial screening assay, 17 patients in ZUMA-2 at any time point tested

positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients in ZUMA-2 were antibody negative at all time points tested. Based on an initial screening assay, 16 patients in ZUMA-3 tested positive for antibodies at any timepoint. Among patients with evaluable samples for confirmatory testing, two patients were confirmed to be antibody-positive after treatment. One of the two patients had a confirmed positive antibody result at Month 6. The second patient had a confirmed positive antibody result at retreatment Day 28 and Month 3. There is no evidence that the kinetics of initial expansion, CAR T-cell function and persistence of Tecartus, or the safety or effectiveness of Tecartus, were altered in these patients.

Secondary malignancies

There have been cases of the following adverse effect(s) reported after treatment with other CAR T-cell products, which might also occur after treatment with Tecartus: secondary malignancy of T-cell origin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are no data regarding the signs of overdose with Tecartus.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, antineoplastic cell and gene therapy, ATC code: L01XL06.

Mechanism of action

Tecartus, a CD19-directed genetically modified autologous T-cell immunotherapy, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacodynamic effects

In both ZUMA-2 and ZUMA-3, after Tecartus infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, interferon-gamma (IFN-γ) and IL-2 receptor alpha were analysed. Peak elevation was generally observed within the first 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on target, off-tumour effect of Tecartus a period of B-cell aplasia may occur following treatment.

Translational analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of multiple serum analytes, including IL-6, IL-10 and TNF-α, were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

Relapsed or refractory MCL: ZUMA-2
The efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti CD20 antibody, and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib), was evaluated in a phase 2 single-arm, open-label, multi-centre trial. Eligible patients also had disease progression after last regimen or refractory disease to the most recent therapy. Patients with active or serious infections, prior allogeneic haematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid malignant cells or brain metastases, and any history of CNS lymphoma or CNS disorders were ineligible. In ZUMA-2, a total of 74 patients were enrolled (*i.e.* leukapheresed) and 68 of these patients were treated with Tecartus. Three patients did not receive Tecartus due to manufacturing failure. Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with Tecartus after receiving lymphodepleting chemotherapy due to ongoing active atrial fibrillation. The full analysis set (FAS) was defined as all patients who underwent leukapheresis. A summary of the patient baseline characteristics is provided in Table 4.

Table 4 Summary of baseline characteristics for ZUMA-2

Category	**All leukapheresed (FAS) (N=74)**
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%
Male gender	84%
Median number of prior therapies (min, max)	3 (1; 5)
Relapsed/refractory subgroup	
Relapsed after auto-SCT	42%
Refractory to last MCL therapy	39%
Relapsed after last MCL therapy	19%
Patients with disease stage IV	86%
Patients with bone marrow involvement	51%
Morphological characteristic	
Classical MCL	54%
Blastoid MCL	26%
Other	1%
Unknown	19%
Received bridging therapy	
Yes	38%
No	62%
Ki-67 IHC by central laboratory	
N	49
Median	65%

Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum.

Tecartus was administered to patients as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells) after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the 5th, 4th, and 3rd day before treatment. Bridging therapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

For patients treated with Tecartus, the median time from leukapheresis to product release was 13 days (range: 9 to 20 days) and the median time from leukapheresis to Tecartus infusion was 27 days (range: 19 to 74 days, with the exception of one outlier of 134 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), progression free survival (PFS) and severity of adverse events.

For the primary analysis, the analysis set was defined a priori which consisted of the first 60 patients treated with Tecartus who were evaluated for response 6 months after the Week 4 disease assessment after Tecartus infusion. In this analysis set of 60 patients the ORR was 93% with a CR rate of 67%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$).

The updated 24-month follow-up analyses of efficacy were conducted using the modified intent to treat (mITT) analysis set, which consisted of 68 patients treated with Tecartus. In the 24-month follow up analysis, the ORR and CR rates in the 68 patients in the mITT analysis set were 91% and 68% respectively.

Results in the FAS from both the primary analysis and 24-month follow-up analysis are shown in Table 5.

Table 5 Summary of efficacy results for ZUMA-2

Category	**All leukapheresed [a](FAS) (N = 74)**	
	Primary Analysis	**24-month Follow-Up**
Objective response rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]	46 (62%) [50.1, 73.2]
PR n (%) [95% CI]	18 (24%) [15.1, 35.7]	16 (22%)[12.9, 32.7]
Duration of response (DOR)[b]		
Median in months [95% CI]	NR [10.4, NE]	28.2 (13.5, 47.1)
Range [c] in months	0.0+, 35.0+	0.0+, 53.0+
Ongoing responses, CR+PR, CR, n (%) [d]	32 (43%), 30 (41%)	25 (34%), 25 (34%)
Progression free survival		
Median, months [95% CI]	16.2 [9.9, NE]	24.0 (10.1, 48.2)
Overall survival		
Median, months [95% CI]	NR [24.6, NE]	47.4 (24.6, NE)
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.6 [65.1, 84.8]	76.7 [65.3, 84.8]
24 month OS (%) [95% CI]	66.5 [52.8, 77.1]	63.0 [50.9, 70.3]
30 month OS (%) [95% CI]	Not applicable	56.2 (44.1, 66.7)
36 month OS (%) [95% CI]	Not applicable	53.9 (41.5, 64.8)
54 month OS (%) [95% CI]	Not applicable	38.7 (24.8, 52.4)
Median Follow-up in months (min, max)	16.8 [7.2, 37.6]	36.6 (27.3, 57.0)

CI, confidence interval; CR, complete remission; FAS, full analysis set;; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.

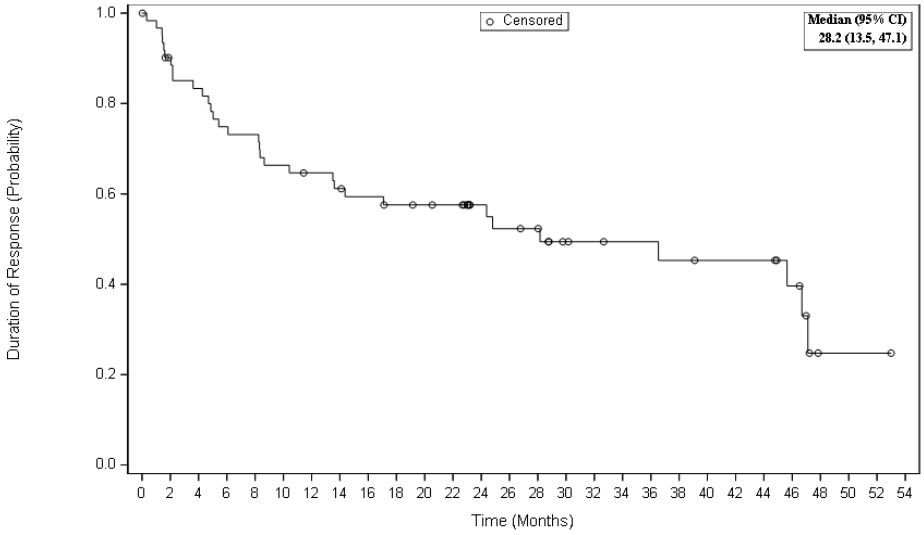
a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

b Among all responders. DOR is measured from the date of first objective response to the date of progression or death.

c A + sign indicates a censored value.

d At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.

Figure 1 Kaplan Meier DOR in the FAS



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tecartus in all subsets of the paediatric population in treatment of MCL (see section 4.2 for information on paediatric use).

Relapsed or refractory B-cell precursor ALL: ZUMA-3
A Phase 2, open-label, multicenter trial evaluated the efficacy and safety of Tecartus in adult patients with relapsed or refractory B-precursor ALL. Relapsed or refractory was defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogeneic stem cell transplant (allo-SCT) (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment). The study excluded patients with active or serious infections, active graft-vs-host disease, and any history of CNS disorders. Patients with CNS-2 disease without clinically evident neurologic changes were eligible. In ZUMA-3 Phase 2, a total of 71 patients were enrolled (i.e. leukapheresed) and 55 patients were treated with Tecartus. Six patients did not receive Tecartus due to manufacturing failure. Eight other patients were not treated, primarily due to AEs following leukapheresis. Two patients who underwent leukapheresis and received lymphodepleting chemotherapy were not treated with Tecartus; one patient experienced bacteremia and neutropenic fever and the other patient did not meet eligibility criteria after lymphodepleting chemotherapy. The FAS included all patients who underwent leukapheresis and the modified intent to treat (mITT) analysis set includes all patients leukapheresed and treated with Tecartus in Phase 2. A summary of patient baseline characteristics is provided in Table 6.

Table 6 Summary of baseline characteristics for ZUMA-3 Phase 2

Category	**All leukapheresed (FAS) (N=71)**	**All treated (mITT) (N=55)**
Age (years)		
Median (min, max)	44 (19 to 84)	40 (19 to 84)
Male gender	58%	60%
White ethnicity	72%	67%
Primary refractory disease	30%	33%
Relapsed/refractory disease after ≥ 2 lines of therapy	76%	78%

Category	All leukapheresed (FAS) (N=71)	All treated (mITT) (N=55)
First relapse if first remission ≤ 12 months	28%	29%
Number of Lines of Prior Therapy		
Median (min, max)	2 (1 to 8)	2 (1 to 8)
≥ 3	48%	47%
Prior Therapies		
Allo-SCT	39%	42%
Blinatumomab	46%	45%
Inotuzumab	23%	22%
Philadelphia chromosome (Ph^+)	27%	27%
Allo-SCT, allogenic stem cell transplant; Max, maximum; Min, minimum		

Following lymphodepleting chemotherapy, Tecartus was administered to patients as a single intravenous infusion at a target dose of 1×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 1×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 900 mg/m^2 intravenously over 60 mins on the 2nd day before Tecartus infusion and fludarabine 25 mg/m^2 intravenously over 30 mins on the 4th, 3rd, and 2nd day before Tecartus infusion. Of the 55 patients who recived Tecartus, 51 patients received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden.

The median time from leukapheresis to product delivery was 16 days (range: 11 to 42 days) and the median time from leukapheresis to Tecartus infusion was 29 days (range: 20 to 60 days). The median dose was 1.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was overall complete remission rate (OCR) (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]) in patients treated with Tecartus as determined by an independent review. In the 55 patients treated with Tecatrus (mITT), the OCR rate was 70.9% with a CR rate of 56.4% (Table 7), which was significantly greater than the prespecified control rate of 40%. Among the 39 patients who achieved a CR or CRi, the median time to response was 1.1 months (range: 0.85 to 2.99 months).

All treated patients had potential follow-up for ≥ 18 months with a median follow-up time of 20.5 months (95% CI: 0.3, 32.6 months) and a median follow-up time for OS of 24.0 months (95% CI: 23.3, 24.6).

Table 7 Summary of efficacy results for ZUMA3 Phase 2

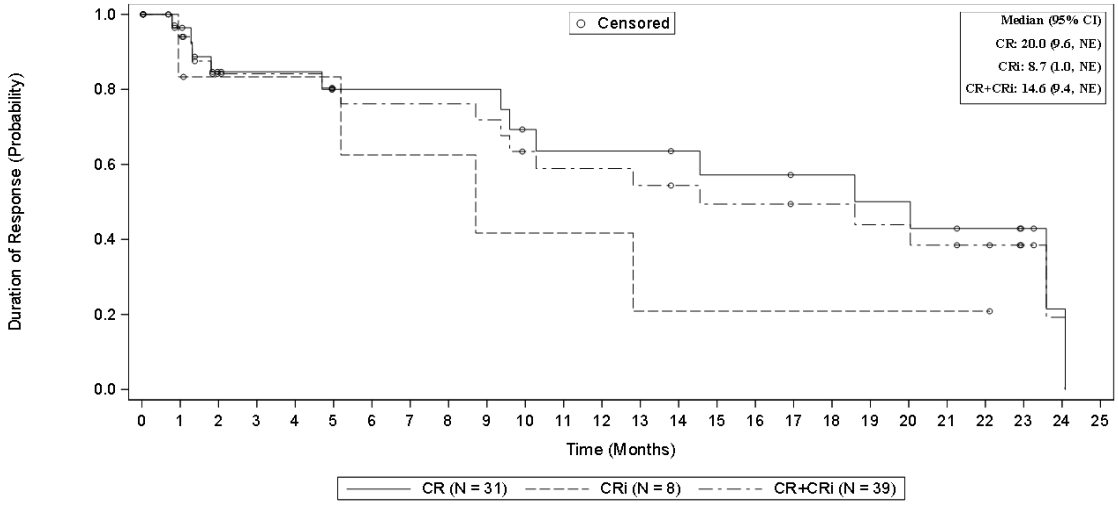
	FAS N = 71	mITT[a] N = 55
OCR rate (CR + CRi) n (%) [95% CI]	39 (54.9) [43, 67]	39 (70.9) [57.0, 82.0]
CR rate, n (%) [95% CI]	31 (43.7) [32, 56]	31 (56.4) [42.0, 70.0]
Minimal Residual Disease (MRD) negative rate among OCR (CR or CRi) patients, n (%)	n = 39 38 (97%)	n = 39 38 (97%)
Duration of Remission, median in months [95% CI] [b] Median range in months	14.6 [9.4, NE][c] (0.03+, 24.08+)	14.6 [9.4, NE][c] (0.03+, 24.08+)
CI, confidence interval; CR, complete remission; NE, not estimable a. Of the 71 patients that were enrolled (and leukapheresed), 57 patients received conditioning chemotherapy, and 55		

patients received Tecartus.

b. Subjects were censored at their last evaluable disease assessment before initiation of a new anticancer therapy (excluding resumption of a tyrosine kinase inhibitor) or allo-SCT to exclude any contribution that the new therapy might have on DOR that could confound the contribution of KTE-X19. The results of the analyses that did not censor for subsequent allo-SCT or the initiation of new anti-cancer therapy were consistent with the analyses that did censor the events.

c. The duration of remission was defined only for subjects achieving an OCR, therefore the results of the analysis in the FAS and mITT were identical.

Figure 2 Kaplan Meier DOR in the mITT Analysis Set[a]



a. The DOR was defined only for subjects achieving an OCR, therefore the results of the analysis in the FAS and mITT were identical.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Tecartus in one or more subsets of the B-cell ALL paediatric population and waived the obligation to submit the results of studies with Tecartus for the treatment of ALL in the paediatric population weighing less than 6kg. See section 4.2 for information on paediatric use.

Conditional Approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited in both the MCL and ALL patient population.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Cellular kinetics

Mantle cell lymphoma
Following infusion of 2×10^6 anti-CD19 CAR T cells/kg of Tecartus in ZUMA-2, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 15 days after the infusion.

Among patients with MCL, the number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR) (Table 8).

Table 8 Summary of brexucabtagene autoleucel pharmacokinetics in ZUMA-2

Number of anti-CD19 CAR T cell	Responding patients (CR or PR) (N=63)	Non-responding patients (N=5)	P-Value
Peak (cells/µL) Median [min; max], n	97.52 [0.24, 2 589.47], 62	0.39 [0.16, 22.02], 5	0.0020
$AUC_{0–28}$ (cells/µL·day) Median [min; max], n	1 386.28 [3.83 to 2.77×10^4], 62	5.51 [1.81, 293.86], 5	0.0013

P-value is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 74.08 cells/µL in MCL patients ≥65 years of age (n=39) and 112.45 cells/µL in MCL patients <65 years of age (n=28). Median anti-CD19 CAR T-cell AUC values were 876.48 cells/µL·day in MCL patients ≥65 years of age and 1 640.21 cells/µL·day in MCL patients <65 years of age.

Acute lymphoblastic leukaemia
Following infusion of a target dose of 1×10^6 anti-CD19 CAR T cells/kg of Tecartus in ZUMA-3 (Phase 2), anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Median time to peak levels of anti-CD19 CAR T cells was within the first 15 days after Tecartus infusion.

A summary of the Tecartus pharmacokinetics over time, based on central assessment by overall response, is provided in Table 9.

Table 9 Summary of brexucabtagene autoleucel pharmacokinetics in ZUMA-3 Phase 2

Number of anti-CD19 CAR T cell	Patients with overall complete remission (CR/CRi) (N=39)	Patients with non-complete remission[a] (N=16)	P-Value
Peak (cells/µL) Median [min; max], n	38.35 [1.31, 1 533.4], 36[b]	0.49 [0.00, 183.50], 14[b]	0.0001[c]
$AUC_{0–28}$ (cells/µL·day) Median [min; max], n	424.03 [14.12 to 19 390.42], 36[b]	4.12 [0.00, 642.25], 14[b]	0.0001[c]

a. Three of 39 subjects who achieved CR or CRi and 2 of 16 subjects who were non-CR/CRi had no anti-CD19 CAR T-cell data at any postinfusion visit.
b. Noncomplete remission includes all non-CR/CRi subjects whose response is classified incomplete remission response with partial hematologic recovery, blast-free hypoplastic or aplastic bone marrow (N = 4), partial response (N = 0), no response (N = 9), or not evaluable (N = 3).
c. .Pvalue is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 34.8 cells/µL in ALL patients ≥65 years of age (n=8) and 17.4 cells/µL in ALL patients <65 years of age (n=47). Median anti-CD19 CAR T-cell AUC values were 425.0 cells/µL·day in ALL patients ≥65 years of age and 137.7 cells/µL·day in ALL patients <65 years of age.

In MCL and ALL patients, gender had no significant impact on $AUC_{Day\ 0–28}$ and C_{max} of Tecartus.

Studies of Tecartus in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

Tecartus comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

No carcinogenicity or genotoxicity studies have been conducted.

No studies have been conducted to evaluate the effects of this treatment on fertility, reproduction, and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10 (contains DMSO)
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

1 year.

Tecartus is stable at room temperature (20 °C to 25 °C) for up to 3 hours after thawing. However, Tecartus infusion must begin within 30 minutes of thaw completion and the total infusion time should not exceed 30 minutes.

6.4 Special precautions for storage

Tecartus must be stored in the vapour phase of liquid nitrogen (≤ − 150 °C) and must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration. Thawed product must not be refrozen.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene-vinyl acetate cryostorage bag with sealed addition tube and two available spike ports, containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping metal cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken before handling or administering the medicinal product

Tecartus must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling Tecartus must take appropriate precautions (wearing gloves and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.

- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the infusion bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the infusion bag is compromised, follow the local guidelines for handling of waste of human derived material (and immediately contact Kite).

Thawing

- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the infusion bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the infusion bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus must not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, Tecartus infusion must begin within 30 minutes of thaw completion.

Administration

- For autologous single use only.
- Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration of Tecartus.
- Verify the patient ID again to match the patient identifiers on the Tecartus infusion bag.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the Tecartus infusion bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the infusion bag during infusion to prevent cell clumping.
- After the entire content of the infusion bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Tecartus (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on the handling of waste of human-derived material.

Accidental exposure
In case of accidental exposure to Tecartus local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/20/1492/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2020
Date of latest renewal: 07 December 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Kite Pharma, Inc.
2355 Utah Avenue
El Segundo
California
CA 90245
United States

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

Name and address of the manufacturer responsible for batch release

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification

The MAH will ensure that hospitals and their associated centres that dispense Tecartus are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Tecartus infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- ensuring healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.
- as part of site qualification training, ensuring HCPs are made aware of the need to contact the MAH to obtain recommendations for tumour sample collection and testing following the development of a secondary malignancy.

Educational program – Prior to the launch of Tecartus in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where Tecartus is marketed, all HCPs who are expected to prescribe, dispense, and administer Tecartus shall be provided with a guidance document to:

- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study
- facilitate identification of CRS and serious neurologic adverse reactions, including ICANS.
- facilitate management of the CRS and serious neurologic adverse reactions, including ICANS.
- ensure adequate monitoring of CRS and serious neurologic adverse reactions, including ICANS.
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site. The qualified treatment centre must have access to additional doses of tocilizumab within 8 hours; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site
- inform on the risk of secondary malignancy of T-cell origin

Patient Educational program

To inform and explain to patients:

- the risks of CRS and serious neurologic adverse reactions, associated with Tecartus
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where Tecartus was received for at least 4 weeks following Tecartus infusion
- the need to carry the patient alert card at all times

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory (r/r) mantle cell Lymphoma (MCL) and adult patients with r/r acute lymphoblastic leukaemia (ALL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	MCL: 31 March 2043 ALL: 31 December 2042

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.	30 April 2027
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2).	31 March 2025
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry, according to an agreed protocol.	31 December 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

METAL CASSETTE

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
brexucabtagene autoleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells transduced with retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR).
This medicine contains cells of human origin.

Contains: 0.4 to 2 × 10^8 CAR+ viable T cells.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10 (contains DMSO), human albumin, sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not irradiate.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
STOP confirm patient ID prior to infusion.
Read the package leaflet before use.
For intravenous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:
SEC:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
brexucabtagene autoleucel (CAR+ viable T cells)
For intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contents: approximately 68 mL of cell dispersion.

6. OTHER

For autologous use only.
Verify patient ID.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
brexucabtagene autoleucel (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecartus is and what it is used for

Tecartus is a gene therapy medicine used for treating mantle cell lymphoma and B-cell acute lymphoblastic leukaemia in adults. It is used when other medicines have stopped working for you (relapsed or refractory disease). The medicine is made specially for you from your own white blood cells that have been modified and is known as brexucabtagene autoleucel.

Mantle cell lymphoma and B-cell acute lymphoblastic leukaemia are cancers of a part of the immune system (the body's defences). They affect a type of white blood cell called B-lymphocytes. In both mantle cell lymphoma and B-cell acute lymphoblastic leukaemia, B-lymphocytes grow in an uncontrolled way and build up in the lymph tissue, bone marrow or blood.

How Tecartus works

The white blood cells are taken from your blood and are genetically modified so that they can target the cancer cells in your body. When Tecartus is infused into your blood, the modified white blood cells will kill the cancer cells.

2. What you need to know before you are given Tecartus

You must not be given Tecartus
- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you can't receive the medicine to reduce the number of white blood cells in your blood (*lymphodepleting chemotherapy*) (see also section 3, How Tecartus is given).

Warnings and precautions

Tecartus is made from your own white blood cells and must only be given to you (*autologous use*).

Patients treated with Tecartus may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with other similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

Tests and checks

Before you are given Tecartus your doctor will:
- Check your lungs, heart, kidney and blood pressure.
- Look for signs of infection or inflammation; and decide whether you need to be treated before you are given Tecartus.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called *tumour lysis syndrome.* You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.
- Check if you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- Check if you have previously received a treatment that attaches to the protein called CD19.

In some cases, it might not be possible to go ahead with the planned treatment with Tecartus. If Tecartus infusion is delayed for more than 2 weeks after you have received lymphodepleting chemotherapy you may have to receive more chemotherapy (see also section 3, How Tecartus is given).

After you have been given Tecartus

Tell your doctor or nurse immediately or get emergency help right away if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, rapid or irregular heartbeat, severe nausea, vomiting, or diarrhoea which may be symptoms of a condition known as *cytokine release syndrome.* Take your temperature twice a day for 3 to 4 weeks after treatment with Tecartus. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech, loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever (e.g. temperature above 38°C), which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

You may be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Tecartus.

Do not donate blood, organs, tissues, or cells for transplants.

Children, adolescents and young adults

Tecartus must not be used in children and adolescents below 18 years of age or young adults below 26 years of age.

Other medicines and Tecartus

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given Tecartus tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Tecartus.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of lymphodepleting chemotherapy to prepare your body for the Tecartus cells.
- During Tecartus treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Tecartus in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with Tecartus, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Tecartus can only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Tecartus.

Driving and using machines

Tecartus can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks after it is given.

Do not drive, use machines, or take part in activities that need you to be alert for at least 8 weeks after your Tecartus treatment or until your doctor tells you that you have completely recovered.

Tecartus contains sodium, dimethylsulfoxide (DMSO) and gentamicin

This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion bag. This is equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult. It also contains DMSO and gentamicin which may cause severe hypersensitivity reactions.

3. How Tecartus is given

Tecartus will always be given to you by a healthcare professional.

- Since Tecartus is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in

your vein (a procedure call *leukapheresis*). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent away to a manufacturing center to make your Tecartus. It usually takes about 2 to 3 weeks to make Tecartus but the time may vary.

Medicines given before Tecartus treatment

A few days before you receive Tecartus, you will be given lymphodepleting chemotherapy, which will allow the modified white blood cells in Tecartus to multiply in your body when the medicine is given to you.

During the 30 to 60 minutes before you are given Tecartus you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol.
- An antihistamine such as diphenhydramine.

How you are given Tecartus

Tecartus will always be given to you by a doctor in a qualified treatment centre.

- Tecartus is given in a single dose.
- Your doctor or nurse will give you a single infusion of Tecartus through a catheter placed into your vein (*intravenous infusion*) over about 30 minutes.
- Tecartus is the genetically modified version of your white blood cells. Your healthcare professional handling the treatment will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local guidelines on handling of waste of human-derived material to clean up or dispose of any material that has been in contact with it.

After you are given Tecartus

- You must stay within proximity of a hospital as discussed with your doctor for at least 4 weeks after you have been given Tecartus. Your doctor will recommend that you return to the hospital daily for at least 7 days or that you stay at the hospital as an in-patient for the first 7 days after Tecartus treatment. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or your treatment centre as soon as possible to reschedule your appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Do not try to treat your side effects on your own.

Tecartus can cause side effects that may be serious or life-threatening. **Get urgent medical attention** if you get any of the following side effects after the Tecartus infusion.

Very common: may affect more than 1 in 10 people

– Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called *cytokine release syndrome*).
– Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, difficulty speaking or slurred speech, involuntary shaking

(*tremor*), fits (*seizures*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
– Fever, chills, which may be signs of an infection.

Other possible side effects

Other side effects are listed below. If these side effects become severe or serious, tell your doctor immediately.

Very common: may affect more than 1 in 10 people

– Abnormally low number of white blood cells, which may increase your risk of infection.
– Low number of cells that help clot the blood *(thrombocytopenia)*: symptoms can include excessive or prolonged bleeding or bruising.
– High blood pressure.
– Decrease in the number of red blood cells (cells that carry oxygen): symptoms can include extreme tiredness with a loss of energy.
– Extreme tiredness.
– Fast or slow heartbeat.
– Decrease of oxygen reaching body tissues: symptoms can include changes to the colour of your skin, confusion, rapid breathing.
– Shortness of breath, cough.
– Excessive bleeding.
– Nausea, constipation, diarrhoea, abdominal pain, vomiting.
– Muscle pain, joint pain, bone pain, pain in the extremities of the body.
– Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
– Headache.
– Kidney problems causing your body to hold onto fluid, build-up of fluids in tissue *(oedema)* which can lead to weight gain and difficulty in breathing.
– High levels of uric acid and sugar *(glucose)*seen in blood tests.
– Low levels of sodium, magnesium, phosphate, potassium or calcium seen in blood tests.
– Decreased appetite, sore mouth.
– Difficulty sleeping, anxiety.
– Swelling in the limbs, fluid around the lungs *(pleural effusion)*.
– Skin rash or skin problems.
– Low levels of immunoglobulins seen in blood test, which may lead to infections.
– Increase in liver enzymes seen in blood tests.
– Nerve pain.

Common: may affect up to 1 in 10 people

– Low levels of albumin seen in blood tests.
– High levels of bilirubin seen in blood tests.
– Irregular heartbeat *(arrhythmia)*.
– Loss of control of body movements.
– Dry mouth, dehydration, difficulty swallowing.
– Decreased output of urine (due to kidney problems described above).
– Breathlessness *(respiratory failure)*.
– Difficulty breathing which makes you unable to speak in full sentence, cough due to fluid in the lungs.
– Increase of the pressure inside your skull.
– Blood clots: symptoms can include pain in the chest or upper back, difficulty breathing, coughing up blood or cramping pain, swelling in a single leg, warm and darkened skin around the painful area.
– Alteration of the blood ability to form clots (*coagulopathy*): symptoms can include excessive or prolonged bleeding or bruising.
– Changes in vision which makes it difficult to see things *(visual impairment)*.

– Infusion related reactions: symptoms including dizziness or fainting, flushing, rash, itching, fever, shortness of breath or vomiting, abdominal pain, and diarrhoea.
– Hypersensitivity: symptoms such as rash, hives, itching, swelling and anaphylaxis.

A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin) has been reported for other similar medicines.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Tecartus

The following information is intended for doctors only.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag after EXP.

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C until thawed for use.
Do not refreeze.

6. Contents of the pack and other information

What Tecartus contains

The active substance is brexucabtagene autoleucel ($0.4 – 2 \times 10^8$ cells dispersion for infusion). Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR-positive viable T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg for mantle cell lymphoma patients and a target dose of 1×10^6 anti-CD19 CAR-positive viable T cells/kg for B-cell acute lymphoblastic leukaemia patients.
The other ingredients (excipients) are: Cryostor CS10 (contains DMSO), sodium chloride, human albumin. See section 2 “Tecartus contains sodium, dimethyl sulphoxide (DMSO), and residual gentamicin”.

This medicine contains genetically modified human blood cells.

What Tecartus looks like and contents of the pack

Tecartus is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

Marketing Authorisation Holder
Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

Manufacturer
Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Gilead Sciences Belgium SRL-BV
Tél/Tel: PPD

България
Gilead Sciences Ireland UC
Тел.: PPD

Česká republika
Gilead Sciences s.r.o.
Tel: PPD

Danmark
Gilead Sciences Sweden AB
Tlf: PPD

Deutschland
Gilead Sciences GmbH
Tel: PPD

Eesti
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Ελλάδα
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: PPD

España
Gilead Sciences, S.L.
Tel: PPD

France
Gilead Sciences
Tél : PPD

Hrvatska
Gilead Sciences Ireland UC
Tel: PPD

Ireland
Gilead Sciences Ireland UC
Tel: PPD

Ísland
Gilead Sciences Sweden AB
Sími: PPD

Lietuva
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Luxembourg/Luxemburg
Gilead Sciences Belgium SRL-BV
Tél/Tel: PPD

Magyarország
Gilead Sciences Ireland UC
Tel: PPD

Malta
Gilead Sciences Ireland UC
Tel: PPD

Nederland
Gilead Sciences Netherlands B.V.
Tel: PPD

Norge
Gilead Sciences Sweden AB
Tlf: PPD

Österreich
Gilead Sciences GesmbH
Tel: PPD

Polska
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Portugal
Gilead Sciences, Lda.
Tel: PPD

România
Gilead Sciences Ireland UC
Tel: PPD

Slovenija
Gilead Sciences Ireland UC
Tel: PPD

Slovenská republika
Gilead Sciences Slovakia s.r.o.
Tel: PPD

Italia
Gilead Sciences S.r.l.
Tel: PPD

Κύπρος
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: PPD

Latvija
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Suomi/Finland
Gilead Sciences Sweden AB
Puh/Tel: PPD

Sverige
Gilead Sciences Sweden AB
Tel: PPD

United Kingdom (Northern Ireland)
Gilead Sciences Ireland UC
Tel: PPD

This leaflet was last revised in

This medicine has been given 'conditional approval'.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

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The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Tecartus.

Precautions to be taken before handling or administering the medicinal product

Tecartus must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling Tecartus must take appropriate precautions (wearing gloves and eye protection) to avoid potential transmission of infectious diseases.

Work surfaces and materials that have potentially been in contact with Tecartus must be decontaminated according to local guidelines on the handling of waste of human-derived materials.

Preparation prior to administration

- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the infusion bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the infusion bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).

Thawing

- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the infusion bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the infusion bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus must not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, the infusion must begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration

- The medicine must be administered in a qualified treatment centre by a physician(s) with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus.
- Ensure that at least 1 dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals and associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- The patient's identity must be matched with the patient identifiers on the infusion bag.
- Tecartus is for autologous use only.
- Tecartus must be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the infusion bag during infusion to prevent cell clumping. All contents of the infusion bag must be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection must be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Tecartus has been infused, the infusion bag must be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

<u>Precations to be taken for the disposal of the medicinal product</u>
Unused medicinal product and any waste material that has been in contact with Tecartus (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure
In case of accidental exposure, local guidelines on handling of human-derived material must be followed which may include washing of the contaminated skin, removal of contaminated clothes. Work surfaces and material which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

Annex 4. Kite Signature Page

KITE PHARMA INC.

LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL) OR ADULT PATIENTS WITH R/R B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

ORIGINAL, 18 FEBRUARY 2021
VERSION 1.1, 13 JULY 2021
VERSION 1.2, 10 NOVEMBER 2021
VERSION 2.0, 15 MARCH 2024

VERSION 2.1, 06 AUGUST 2024

VERSION 2.2, 17 DECEMBER 2024

This protocol has been approved by Kite Pharma Inc. The following signatures document this approval.

PPD	*See appended electronic signature*
Study Director (Printed) Author	Signature
See appended electronic signature	
Date	
PPD	*See appended electronic signature*
Kite Gilead EU QPPV (Printed)	Signature
See appended electronic signature	
Date	

Annex 5. Cellular Therapy Form

EBMT Cellular Therapy Form provided for entries in the EBMT Registry at the time point of this protocol version. During the course of the study, updated versions of this form will be provided as appendices of annual reports (see Section 11.1.2).

PATIENT REGISTRATION

INFORMED CONSENT

Did the patient consent to having their data submitted to EBMT?	☐ **No**	☐ **Yes**	
First informed consent date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*			
Most recent consent date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*			
Is your centre using the EBMT consent form?	☐ **No**	☐ **Yes**	
Did the patient consent to data sharing with health authorities and/or researchers?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to data sharing with HTA bodies/reimbursement agencies?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to data sharing with Market Authorisation Holders (MAH)?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to their medical records being reviewed?	☐ **No**	☐ **Yes**	☐ **Unknown**

PATIENT DATA

Hospital Unique Patient Number or code (UPN): _____
(Compulsory; registration will not be accepted without this item. All treatments (HCT/CT/IST) of the patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.)

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(Year of birth is compulsory; month and date are strongly recommended)

Sex *(at birth)*:

☐ Male

☐ Female

Initials: _____ / _____ *(first name / family name)*

PATIENT DATA continued

Blood group:

☐ A
☐ B
☐ AB
☐ O

Rhesus factor:

☐ Negative
☐ Positive

Participation in non-EBMT national/international study/trial:

☐ No
☐ Yes: Name/identifier of study/trial: _____

Can the patient be included in EBMT studies? ☐ No ☐ Yes

APPENDIX
For relevant centres only

Area or postal code where patient was living during the HCT/CT/IST: _____
(Optional; to be used by the centre to register this data if required by the country legislation)

Ethnicity:

- ☐ White - British
- ☐ White - Irish
- ☐ White - Any other White background
- ☐ Mixed - White and Black Caribbean
- ☐ Mixed - White and Black African
- ☐ Mixed - White and Asian
- ☐ Mixed - Any other mixed background
- ☐ Asian or Asian British - Indian
- ☐ Asian or Asian British - Pakistani
- ☐ Asian or Asian British - Bangladeshi
- ☐ Asian or Asian British - Any other Asian background
- ☐ Black or Black British - Caribbean
- ☐ Black or Black British - African
- ☐ Black or Black British - Any other Black background
- ☐ Other Ethnic Groups - Chinese
- ☐ Other Ethnic Groups - Any other ethnic group
- ☐ Not stated
- ☐ Unknown

LYMPHOMAS

DISEASE

Note: complete this form only if this diagnosis was the indication for the HCT/CT or if it was specifically requested. Consult the manual for further information.

Date of diagnosis: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD)

Classification:

☐ B-cell lymphoma (including Hodgkin and Non-Hodgkin lymphoma)
☐ T-cell non-Hodgkin lymphoma (NHL)
☐ Immunodeficiency-associated lymphoproliferative disorder (incl. PTLD)
☐ Other; specify _____

LYMPHOMAS
B-cell lymphoma (including Hodkin and Non-Hodkin lymphoma)

DISEASE

Sub-Classification: Mature B-cell neoplasms

- ☐ Splenic B-cell lymphomas and leukaemias
  - ☐ Splenic marginal zone lymphoma
  - ☐ Splenic diffuse red pulp small B-cell lymphoma
- ☐ Lymphoplasmacytic lymphoma
  - ☐ IgM-LPL/ Waldenström Macroglobulinaemia (WM) type
  - ☐ Non-WM type LPL
- ☐ Marginal zone lymphoma
  - ☐ Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
  - ☐ Primary cutaneous marginal zone lymphoma
  - ☐ Nodal marginal zone lymphoma
  - ☐ Paediatric marginal zone lymphoma
- ☐ Follicular lymphoma
  - ☐ Classical follicular lymphoma (cFL)
  - ☐ Follicular large B-cell lymphoma (FLBL)
  - ☐ FL with uncommon features (uFL)
- ☐ Paediatric-type follicular lymphoma
- ☐ Duodenal-type follicular lymphoma
- ☐ Cutaneous follicle centre lymphoma
- ☐ Mantle cell lymphoma
  - ☐ Mantle cell lymphoma
  - ☐ Leukaemic non-nodal mantle cell lymphoma

LYMPHOMAS
B-cell lymphoma (including Hodkin and Non-Hodkin lymphoma)

DISEASE continued

Sub-Classification: Mature B-cell neoplasms

- ☐ Large B-cell lymphomas
  - ☐ Diffuse large B-cell lymphoma (DLBCL), NOS
    - ☐ Germinal centre B- cell-like subtype (GCB)
    - ☐ Activated B-cell-like subtype (ABC)
  - ☐ T-cell/histiocyte-rich large B-cell lymphoma
  - ☐ Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with MYC and BCL2 rearrangements
  - ☐ ALK-positive large B-cell lymphoma
  - ☐ Large B-cell lymphoma with IRF4 rearrangement
  - ☐ High-grade B-cell lymphoma with 11q aberrations
  - ☐ Lymphomatoid granulomatosis
  - ☐ EBV-positive diffuse large B-cell lymphoma
  - ☐ Diffuse large B-cell lymphoma associated with chronic inflammation
  - ☐ Fibrin-associated large B-cell lymphoma
  - ☐ Fluid overload-associated large B-cell lymphoma
  - ☐ Plasmablastic lymphoma
  - ☐ Primary large B-cell lymphoma of immune-privileged sites
    - ☐ Primary large B-cell lymphoma of the CNS
    - ☐ Primary large B-cell lymphoma of the vitreoretina
    - ☐ Primary large B-cell lymphoma of the testis
  - ☐ Primary cutaneous diffuse large B-cell lymphoma, leg type
  - ☐ Intravascular large B-cell lymphoma
  - ☐ Primary mediastinal large B-cell lymphoma
  - ☐ Mediastinal grey zone lymphoma
  - ☐ High-grade B-cell lymphoma, NOS
- ☐ Burkitt lymphoma
  - ☐ EBV-positive BL
  - ☐ EBV-negative BL
- ☐ KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas
  - ☐ Primary effusion lymphoma
  - ☐ KSHV/HHV8-positive diffuse large B-cell lymphoma
  - ☐ KSHV/HHV8-positive germinotropic lymphoproliferative disorder
- ☐ Hodgkin lymphoma
  - ☐ Classic Hodgkin lymphoma
  - ☐ Nodular lymphocyte predominant Hodgkin lymphoma

DISEASE continued

Transformation of indolent B-cell lymphoma:

☐ No
☐ Yes (If not reported yet, complete respective non-indication diagnosis form in addition to the current form)
☐ Unknown

Parameters for international prognostic indices:

Age at diagnosis:	_____ years (*this is calculated automatically in the database)*
LDH levels elevated:	☐ No ☐ Yes ☐ Not evaluated ☐ Unknown
Ann Arbor staging:	☐ I ☐ II ☐ III ☐ IV ☐ Not evaluated ☐ Unknown
ECOG performance status:	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Not evaluated ☐ Unknown
> 1 extranodal site involved:	☐ No ☐ Yes ☐ Not evaluated ☐ Unknown
> 4 nodal sites involved:	☐ No ☐ Yes ☐ Not evaluated ☐ Unknown
Haemoglobin < 120g/L:	☐ No ☐ Yes ☐ Not evaluated ☐ Unknown
White Blood Cell count:	_____ x 10^9/L ☐ Not evaluated ☐ Unknown
CNS Involvement:	☐ No ☐ Yes ☐ Not evaluated ☐ Unknown

Final score:

(only for patients with LBCL (except Primary large B-cell lymphoma of immune-privileged sites), Mantle cell lymphoma, Follicular lymphoma, Waldenstrom macroglobulinaemia)

IPI: *(for LBCL (except Primary large B-cell lymphoma of immune-privileged sites) and FLBL)*	**MIPI:** *(for Mantle cell lymphoma)*	**FLIPI:** *(for Follicular lymphoma (except FLBL))*	**ISSWM:** *(for Waldenstrom macroglobulinaemia)*
☐ Low risk (0-1 score points) ☐ Low-intermediate risk (2 score points) ☐ High-intermediate risk (3 score points) ☐ High risk (4-5 score points) ☐ Not evaluated	☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated	☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated	☐ Low risk (0-1 score points except age > 65) ☐ Intermediate risk (2 score points OR age > 65) ☐ High risk (3-5 score points) ☐ Not evaluated

CHROMOSOME ANALYSIS

Please complete chromosome analysis section only for patients with the following types of B-cell NHL:
- *Mantle cell lymphoma*
- *Waldenstrom macroglobulinaemia (LPL with monoclonal IgM)*
- *Burkitt lymphoma or Intermediate DLBCL/BL and all LBCL)*

Chromosome analysis done before HCT/CT treatment:
(Describe results of the most recent complete analysis)

☐ No
☐ Yes: **Output of analysis:** ☐ Separate abnormalities ☐ Full karyotype
☐ Unknown

Extended dataset

Chromosome analysis method used: ☐ Karyotyping
(select all that apply) ☐ FISH

If chromosome analysis was done:
What were the results?

☐ Normal
☐ Abnormal: number of abnormalities present: _____
☐ Failed

Date of chromosome analysis:: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) ☐ Unknown

For abnormal results, indicate below whether the abnormalities were absent, present or not evaluated *(according to the type of lymphoma diagnosed).*

Mantle cell lymphoma or Waldenstrom macro-globulinaemia	**del(17p)**	☐ Absent	☐ Present	☐ Not evaluated
	FISH used:	☐ No	☐ Yes	
Burkitt lymphoma or all LBCL	**t(2;8)**	☐ Absent	☐ Present	☐ Not evaluated
	t(8;14)	☐ Absent	☐ Present	☐ Not evaluated
	t(8;22)	☐ Absent	☐ Present	☐ Not evaluated
	t(14;18)	☐ Absent	☐ Present	☐ Not evaluated
All above mentioned B-cell lymphomas	**Other chromosome abnormalities; specify:** _______	☐ Absent	☐ Present	

OR

Transcribe the complete karyotype: ____

MOLECULAR MARKER ANALYSIS

Please complete molecular marker analysis section only for patients with the following types of B-cell NHL:
- *Mantle cell lymphoma*
- *Burkitt lymphoma (BL) or Intermediate DLBCL/BL and all LBCL*

Molecular marker analysis done before HCT/CT treatment:
(Describe results of the most recent complete analysis)

☐ No
☐ Yes
☐ Unknown

Date of molecular marker analysis *(if tested)*:: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

Indicate below whether the markers were absent, present or not evaluated, according to the type of lymphoma diagnosed.

Mantle cell lymphoma	**TP53 mutation**	☐ Absent ☐ Present ☐ Not evaluated
Burkitt lymphoma or all LBCL	**MYC rearrangement**	☐ Absent ☐ Present ☐ Not evaluated
All LBCL	**BCL2 rearrangement**	☐ Absent ☐ Present ☐ Not evaluated
	BCL6 rearrangement	☐ Absent ☐ Present ☐ Not evaluated
All above mentioned B-cell lymphomas	**Other molecular markers; specify:** _____	☐ Absent ☐ Present

IMMUNOPHENOTYPING

Please complete immunophenotyping section only for patients with the following types of B-cell NHL:
- *Mantle cell lymphoma*
- *Burkitt lymphoma (BL) or Intermediate DLBCL/BL and all LBCL*

Immunophenotyping done before HCT/CT treatment:
(Describe results of the most recent complete analysis)

☐ No
☐ Yes
☐ Unknown

Date of immunophenotyping (if tested): _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Indicate below whether the immunophenotypes were absent, present or not evaluated, according to the type of lymphoma diagnosed.

Mantle cell lymphoma	**SOX 11**	☐ Absent ☐ Present ☐ Not evaluated
Burkitt lymphoma or all LBCL	**MYC**	☐ Absent ☐ Present ☐ Not evaluated
LBCL	**BCL2/IgH**	☐ Absent ☐ Present ☐ Not evaluated
	BCL6	☐ Absent ☐ Present ☐ Not evaluated
All above mentioned B-cell lymphomas	**Other immunophenotype; specify:** _____	☐ Absent ☐ Present

LYMPHOMAS
T-cell non-Hodgkin lymphoma (NHL)

DISEASE

Sub-Classification: Mature T-cell & NK-cell neoplasms

☐ **Mature T-cell and NK-cell leukaemias**
- ☐ T-large granular lymphocytic leukaemia
- ☐ NK-large granular lymphocytic leukaemia
- ☐ Adult T-cell leukaemia/lymphoma
- ☐ Sezary syndrome
- ☐ Aggressive NK-cell leukaemia

☐ **Primary cutaneous T-cell lymphomas**
- ☐ Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder
- ☐ Primary cutaneous acral CD8-positive lymphoproliferative disorder
- ☐ Mycosis fungoides
- ☐ Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: lymphomatoid papulosis
- ☐ Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: primary cutaneous anaplastic large cell lymphoma
- ☐ Subcutaneous panniculitis-like T-cell lymphoma
- ☐ Primary cutaneous gamma/delta T-cell lymphoma
- ☐ Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
- ☐ Primary cutaneous peripheral T-cell lymphoma, not otherwise specified

☐ **Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas**
- ☐ Indolent T-cell lymphoma of the gastrointestinal tract
- ☐ Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
- ☐ Enteropathy-associated T-cell lymphoma
- ☐ Monomorphic epitheliotropic intestinal T-cell lymphoma
- ☐ Intestinal T-cell lymphoma not otherwise specified

☐ **Hepatosplenic T-cell lymphoma**

☐ **Anaplastic large cell lymphomas**
- ☐ ALK-positive anaplastic large cell lymphoma
- ☐ ALK-negative anaplastic large cell lymphoma
- ☐ Breast implant-associated anaplastic large cell lymphoma

LYMPHOMAS
T-cell non-Hodgkin lymphoma (NHL)

DISEASE continued

Sub-Classification: Mature T-cell & NK-cell Neoplasms

- ☐ **Nodal T-follicular helper (TFH) lymphomas**
  - ☐ Nodal TFH cell lymphoma, angioimmunoblastic-type
  - ☐ Nodal TFH cell lymphoma, follicular type
  - ☐ Nodal TFH cell lymphoma, not otherwise specified
- ☐ **Peripheral T-cell lymphoma, not otherwise specified**
- ☐ **EBV-positive NK/T-cell lymphomas**
  - ☐ EBV-positive nodal T- and NK-cell lymphoma
  - ☐ Extranodal NK/T-cell lymphoma
- ☐ **EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood**
  - ☐ Severe mosquito bite allergy
  - ☐ Hydroa vacciniforme lymphoproliferative disorder
  - ☐ Systemic chronic active EBV disease
  - ☐ Systemic EBV-positive T-cell lymphoma of childhood

LYMPHOMAS
Immunodeficiency-associated lymphoproliferative disorders (incl. PTLD)

DISEASE

Sub-Classification: Immunodeficiency-associated lymphoproliferative disorders (incl. PTLD)

- ☐ Lymphoproliferative disease associated with primary immune disorder
- ☐ Lymphoma associated with HIV infection
- ☐ Post-transplant lymphoproliferative disorder (PTLD)
  - ☐ Non-destructive PTLD
    - ☐ Plasmacytic hyperplasia PTLD
    - ☐ Infectious mononucleosis PTLD
    - ☐ Florid follicular hyperplasia PTLD
  - ☐ Polymorphic PTLD
  - ☐ Monomorphic PTLD
    - ☐ B-cell type
    - ☐ T-/NK-cell type
  - ☐ Classical Hodgkin lymphoma PTLD
- ☐ Other immunodeficiency-associated lymphoproliferative disorder

Did the disease result from a previous solid organ transplant?

☐ No

☐ Yes: **Date of transplant:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown

Type of transplant: ☐ Renal
☐ Cardiac
☐ Pulmonary
☐ Other; specify: _____

☐ Unknown

LYMPHOMAS

PREVIOUS THERAPIES
(between diagnosis and HCT/CT)

Previous therapy lines before the HCT/CT:

☐ No

☐ Yes: **complete the "Treatment — non-HCT/CT/GT/IST" form**

☐ Unknown

CELLULAR THERAPY
Day 0

PRE-INFUSION

Cell collection procedure - Apheresis:

Date of collection: _ _ _ _ / _ _ /_ _ (YYYY/MM/DD)
(If more than one collection enter the date of the first collection.)

☐ Date unknown
(e.g. allogeneic product from unknown donor)

Number of collections: _____

INDICATION FOR PLANNED CELLULAR THERAPY

☐ **Treatment of a primary disease:**

Indication diagnosis for this cellular therapy:_____
(make sure the indication diagnosis has been registered first, using the relevant diagnosis form)

Reason for cellular therapy: (select all that apply)

- ☐ Induction therapy
- ☐ Prevention of disease relapse or progression
- ☐ Rescue from disease relapse or progression
- ☐ Minimal residual disease reduction
- ☐ Refractory disease
- ☐ Other; specify: _____

☐ **Treatment or prevention of complications:**
(derived from a previous treatment or expected from a subsequent treatment)

Date of the last treatment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Before continuing please make sure that the above mentioned treatment has been registered and that relevant follow-up form has been submitted; this is so relapse data and other events between transplants and/or cellular therapies can be captured.

Reason for cellular therapy:

- ☐ GvHD
  - ☐ Treatment of GvHD
  - ☐ Preventive treatment for GvHD
- ☐ Graft function
  - ☐ Graft failure treatment
  - ☐ Prevention of rejection/Promotion of cell engraftment
  - ☐ Graft enhancement
- ☐ Immune reconstitution

☐ **Other indication;** specify: _____

BASIC INFORMATION ON THE PLANNED CELLULAR THERAPY

Clinical setting:
(check only one)

☐ As per marketing approval / Standard of care / Institutional guidelines	
☐ Hospital exemption	
☐ Compassionate use / Accelerated access	
☐ Investigational drug product (IDP)/ Clinical trial	Phase: ☐ 1 ☐ 1/2 ☐ 2 ☐ 2/3 ☐ 3 Blind trial: ☐ No ☐ Yes Randomised trial: ☐ No ☐ Yes EudraCT number: _____ USA NCT number: _____ UMIN CT number: _____ ☐ Tick here if this registration should be hidden. Date by which the registration can be made available for research: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Cell origin:

☐ Autologous *(Proceed to 'Planned cellular therapy infusion product(s)' section on page 3)*

☐ Allogeneic:

This product is manufactured from:

☐ A known donor never used to treat this patient *(e.g. from a donor registry or related)*
(Proceed to 'Donor information' section on page 3.)

☐ A donor that is already registered as part of a previous treatment
(Proceed to 'Planned cellular therapy infusion product(s)' section on page 3.)

☐ An unknown donor with no data available *(e.g. from a commercial product)*
(Proceed to 'Planned cellular therapy infusion product(s)' section on page 3.)

DONOR INFORMATION

Complete only if cell source was allogeneic

Did the donor consent to having their data in the EBMT registry?

☐ No (complete only fields marked with '*' in this section)

☐ Yes

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* **OR:** ***Age at time of donation: _____ years**

If the donor was younger than 2 years:
***Age in months:** ____

Sex** ***(at birth)**:**

☐ Male

☐ Female

Donor Identification:

Donor ID given by the treating centre *(mandatory)*: _____

Global registration identifier for donors (GRID): _____

ION code of the Donor Registry or Cord Blood Bank *(mandatory)*: _____

EuroCord code for the Cord Blood Bank *(if applicable)*: _____

Name of Donor Registry or Cord Blood Bank: _____

Donor ID given by the Donor Registry or Cord Blood Bank: _____

Patient ID given by the Donor Registry or Cord Blood Bank: _____

PLANNED CELLULAR INFUSION PRODUCT(S)

Will the planned cellular infusion product consist of more than one infusion unit?

☐ No

☐ Yes: Number of infusion units: _____

☐ Unknown

Tissue source ***(check all that apply)*****:**

☐ Bone marrow

☐ Peripheral blood

☐ Cord blood

☐ Tumour

☐ Other; specify: _____

PLANNED CELLULAR INFUSION PRODUCT(S)

Is the planned cell infusion product a commercial product?

☐ No
☐ Yes

Identification:

Name of manufacturer:

☐ Autolus
☐ Celgene/ Bristol-Myers Squibb
☐ Celyad
☐ GlaxoSmithKline (GSK)
☐ Janssen (Johnson & Johnson)
☐ Kite Gilead
☐ Miltenyi
☐ Novartis
☐ Local hospital or university
☐ Other; specify: _____

Name of product:

☐ Abecma
☐ Breyanzi
☐ Carvykti
☐ Kymriah
☐ Tecartus
☐ Yescarta
☐ No product name available
☐ Other; specify: _____

END OF PRE-INFUSION SECTION

PLEASE PROCEED WITH THE CELLULAR THERAPY SECTION TO COMPLETE

THE CELLULAR THERAPY DAY 0 REPORT

CELLULAR THERAPY

Date of (planned) cell infusion: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*

Centre where infusion took place (CIC): ____
(if the product was not infused, report the centre where the infusion was planned to take place)

Patient UPN for this treatment: _____

Team or unit where treatment took place *(select all that apply):*

☐ Adults ☐ Pediatrics ☐ Haematology ☐ Oncology ☐ Allograft ☐ Autograft ☐ Other; specify: _____

Unit number: _____ ☐ Not applicable

Was the cellular therapy product infused during this treatment/procedure?

☐ No: Reason why the treatment did not take place:
Select all reasons that apply

- ☐ Production failure
- ☐ Out of specification product rejected by physician
- ☐ Disease progression or patient condition worsening
- ☐ Patient became ineligible for treatment
- ☐ Patient died
- ☐ Other reason; specify: _____

☐ Yes: **B-cell aplasia at time of cellular therapy?**

- ☐ Absent
- ☐ Present: Percentage of B-cells: _____ %
- ☐ Not evaluated

THERAPY & CELL INFUSION(S)

Chronological number of cellular therapy treatment for this patient: _____
(Please do not include any transplants the patient has had in the past)

Complete this section only if this is the second or a subsequent cellular therapy for this patient and the previous cellular treatments cannot be registered.

If > 1:

Same product as for the previous cellular therapy?

☐ No

☐ Yes

Date of the last cellular therapy before this one: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Type of the last cellular therapy before this one:

☐ Autologous

☐ Allogeneic: Was the same donor used both for prior and current cellular therapy? ☐ No
☐ Yes

Was the last cellular therapy performed at another institution?

☐ No

☐ Yes: CIC (if known): _____

Name of institution: _____

City: _____

If > 1 submit an annual follow-up form before proceeding using the latest assessment date before this cellular therapy; this is so relapse data and other events between transplants/cellular therapies can be captured.

Did the patient receive a previous HCT?

☐ No

☐ Yes: Date of the last HCT before this CT: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Type of the last HCT before this CT: ☐ Autologous
☐ Allogeneic

For same indication as the cellular therapy? ☐ No
☐ Yes

PREVIOUS THERAPIES incl. BRIDGING
(before transplant/cellular therapy)

Was the patient treated before this cellular therapy procedure?

☐ No (*proceed to 'Cellular therapy infusion unit(s)' on page 8)*

☐ Yes — **complete the "Treatment — non-HCT/CT/GT/IST" form**

☐ Unknown (*proceed to 'Cellular therapy infusion unit(s)' on page 8)*

CELLULAR THERAPY INFUSION UNIT(S)

Was there more than one cell infusion unit administered during this treatment?

☐ No

☐ Yes: Number of different cell infusion units that were part of this treatment: _____

CELLULAR THERAPY INFUSION UNIT(S) DESCRIPTION

If the CT product was not infused proceed to 'Survival status' section on page 14.

If more than one cell infusion unit please copy and fill-in this section for each one of them.

Unique ID of the product: _____
(If applicable)

Batch number: _____
(If applicable)

Identification of the cell infusion unit given by the centre: _____
(If there is only one cell infusion unit enter "1")

Was the infused cellular product consistent with the specifications?

☐ No: specify the difference from specifications: _____

☐ Yes

☐ Unknown

Was the cellular therapy product cryopreserved prior to infusion?

☐ No

☐ Yes: **Date of cryopreservation:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown

☐ Unknown

CELLULAR THERAPY INFUSION UNIT(S) MANIPULATION

Complete only for non-commercial products. If more than one cell infusion unit please copy and fill-in this section for each one of them.

Identification of the cell infusion unit (given by the centre)**:** _____

Manipulation:

Processing/Manufacturing facility:

☐ Onsite, by local cell processing facility

☐ Offsite, by a non-commercial facility

Gene manipulation:

☐ No

☐ Yes: Type

Gene transfer: ☐ No

☐ Yes: Vector: ☐ Retroviral vector

☐ Lentiviral vector

☐ Other vector; specify: _____

Transgene: ☐ CAR; specify all targets: _____ *See appendix 1 for a list of target antigens*

☐ TCR; specify all targets: _____

specify HLA element: _____

☐ Suicide gene; specify: _____

☐ Other: specify: _____

Other: ☐ No

☐ Yes: specify: _____

CELLULAR THERAPY INFUSION UNIT(S)
MANIPULATION continued

Complete only for non-commercial products. If more than one cell infusion unit please copy and fill-in this section for each one of them.

Manipulation aims:

Recognition of a specific target/antigen:

☐ No

☐ Yes: Type *(check all that apply)*:

☐ Viral:
- ☐ Adenovirus
- ☐ BK Virus
- ☐ Covid-19 (SARS-CoV-2)
- ☐ Cytomegalovirus (CMV)
- ☐ Epstein-Barr virus
- ☐ Human herpes virus 6
- ☐ Human immunodeficiency virus (HIV)
- ☐ RSV-CTL
- ☐ Other virus; specify: _____

☐ Fungal:
- ☐ Candida
- ☐ Aspergillus
- ☐ Other fungus; specify: _____

☐ Tumour/cancer antigen(s); specify all: _____

☐ Other target; specify: _____

Cell types administered *(check all that apply)*:

- ☐ CD3+ lymphocytes
- ☐ CD4+ lymphocytes
- ☐ CD8+ lymphocytes
- ☐ CD34+
- ☐ Dendritic cells
- ☐ Gamma-Delta cells
- ☐ Mesenchymal cells
- ☐ NK cells
- ☐ Regulatory T-cells
- ☐ Other; specify: _____

Expansion:	**Activation:**	**Induced differentiation:**
☐ No	☐ No	☐ No
☐ Yes	☐ Yes	☐ Yes
☐ Unknown	☐ Unknown	☐ Unknown

PREPARATIVE REGIMEN

Do not include lines of therapy given for disease treatment, bridging therapy or maintenance, these should be reported in other form.

Preparative conditioning / lymphodepletion regimen given?

☐ No

☐ Yes: **Drugs given?** *(any active agent, including chemotherapy, monoclonal antibody, polyclonal antibody, serotherapy, etc.)*

- ☐ No
- ☐ Yes (provide details in the table on pages 12-13)
- ☐ Unknown

PREPARATIVE REGIMEN continued

Specification and dose of the preparative regimen:

(Report the total prescribed cumulative dose as per protocol. Multiply daily dose in mg/kg or mg/m² by the number of days; e.g. for Busulfan given 4mg/kg daily for 4days, total dose to report is 16mg/kg.
Report dosages and units only for individual drugs.)

Chemotherapy	Dose	Units
☐ Alemtuzumab	_____	☐ mg/m² ☐ mg/kg
☐ Anti-Thymocyte Globulin|Anti-Lymphocyte Globulin Product name: _____ Origin: ☐ Rabbit ☐ Horse ☐ Other; specify: _____	_____	☐ mg/m² ☐ mg/kg
☐ Bendamustine	_____	☐ mg/m² ☐ mg/kg
☐ Bleomycin	_____	☐ mg/m² ☐ mg/kg
☐ Busulfan Route of administration: ☐ Oral ☐ IV ☐ Both Drug monitoring performed: ☐ No ☐ Yes; total AUC: _____ ☐ mg x hr/L ☐ micromol x min/L ☐ mg x min/mL	_____	☐ mg/m² ☐ mg/kg
☐ Carboplatin Drug monitoring performed: ☐ No ☐ Yes; total AUC: _____ ☐ mg x hr/L ☐ micromol x min/L ☐ mg x min/mL	_____	☐ mg/m² ☐ mg/kg
☐ Carmustine	_____	☐ mg/m² ☐ mg/kg
☐ Cisplatin	_____	☐ mg/m² ☐ mg/kg
☐ Clofarabine	_____	☐ mg/m² ☐ mg/kg
Corticosteroids:		
☐ Beclometasone	_____	☐ mg/m² ☐ mg/kg
☐ Budesonide	_____	☐ mg/m² ☐ mg/kg
☐ Dexamethasone	_____	☐ mg/m² ☐ mg/kg
☐ Methylprednisolone	_____	☐ mg/m² ☐ mg/kg
☐ Prednisolone	_____	☐ mg/m² ☐ mg/kg
☐ Cyclophosphamide	_____	☐ mg/m² ☐ mg/kg

PREPARATIVE REGIMEN continued

Specification and dose of the preparative regimen:
(Report the total prescribed cumulative dose as per protocol. Multiply daily dose in mg/kg or mg/m² by the number of days; e.g. for Busulfan given 4mg/kg daily for 4days, total dose to report is 16mg/kg.)

Chemotherapy	Dose	Unit
☐ Cytarabine	_____	☐ mg/m² ☐ mg/kg
☐ Daunorubicin	_____	☐ mg/m² ☐ mg/kg
☐ Doxorubicin	_____	☐ mg/m² ☐ mg/kg
☐ Epirubicin	_____	☐ mg/m² ☐ mg/kg
☐ Etoposide	_____	☐ mg/m² ☐ mg/kg
☐ Fludarabine	_____	☐ mg/m² ☐ mg/kg
☐ Gemtuzumab ozogamicin	_____	☐ mg/m² ☐ mg/kg
☐ Ibritumomab tiuxetan	_____	☐ mCi ☐ MBq
☐ Idarubicin	_____	☐ mg/m² ☐ mg/kg
☐ Ifosfamide	_____	☐ mg/m² ☐ mg/kg
☐ Imatinib	_____	☐ mg/m² ☐ mg/kg
☐ Lomustine	_____	☐ mg/m² ☐ mg/kg
☐ Melphalan	_____	☐ mg/m² ☐ mg/kg
☐ Mitoxantrone	_____	☐ mg/m² ☐ mg/kg
☐ Paclitaxel	_____	☐ mg/m² ☐ mg/kg
☐ Anti-CD20 antibodies	_____	☐ mg/m² ☐ mg/kg
☐ Teniposide	_____	☐ mg/m² ☐ mg/kg
☐ Thiotepa	_____	☐ mg/m² ☐ mg/kg
☐ Tositumomab	_____	☐ mCi ☐ MBq
☐ Treosulfan	_____	☐ mg/m² ☐ mg/kg
☐ Other; specify*: _____	_____	☐ mg/m² ☐ mg/kg ☐ mCi ☐ MBq

*Please consult the **LIST OF CHEMOTHERAPY DRUGS/AGENTS AND REGIMENS** on the EBMT website for drugs/regimens names

Total body irradiation (TBI):

☐ No

☐ Yes; total prescribed radiation dose as per protocol: _____ Gy

number of fractions: _____

number of radiation days: _____

CELL INFUSION EPISODE(S)

Was there more than one cell infusion episodes during this treatment or procedure?

☐ No

☐ Yes: Number of cell infusion episodes during this treatment/procedure: _____

CELL INFUSION EPISODE(S) DESCRIPTION

If more than one cell infusion unit please copy and fill-in this section for each one of them.

Date of cell infusion episode: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*

Route of infusion:
(check all that apply)

☐ Intraveneous

☐ Intrathecal

☐ Intratumour injection

☐ Other route; specify: _____

Did the patient receive concomitant therapy?

☐ No

☐ Yes; specify: _____

Treatment given: ☐ Simultaneously to the cellular therapy
☐ After the cellular therapy episode was finished

If more than one unit was used, indicate the identification of the cell infusion given by the centre as described in the 'Cell Infusion Unit' section *(This item is mandatory if more than one cell infusion unit was used.)*: _____

Is the exact number of cells infused available?

☐ No

☐ Yes: Number of cells: _____ *(not adjusted for cell viability)*

Unit *(check only one)*: ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8

Cell viability: _____ **%**

If more than one cell infusion unit was administered please copy and fill-in this section for each one of them.

END OF THE CELLULAR THERAPY DAY 0 REPORT

proceed to form DISEASE STATUS AT HCT/CT/GT/IST

Appendix 1
-- List of transgene CAR targets --

AFP (alpha fetoprotein)
BAFF-R
BCMA
B7H3
CD11
CD16
CD19
CD20
CD22
CD30
CD33
CD38
CD56
CD123
CD138
CD171
CD229
CLL1
CS-1 (SLAMF7)
EGFR
GD2
GPRC5D
HER2
HPV-16E6
Integrinβ7
Lewis-Y
MAGE-A4
MAGE-A10
Mesothelin (MSLN)
MUC16
NKG2D
NY-ESO-1
PRAME
PSCA
SSX
Survivin
TACI
WT-1
Other (specify)

CELLULAR THERAPIES
--- Day 100, 6 Months, Annual & Unscheduled Follow-Up ---

SURVIVAL STATUS

Date of follow-up _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*
(if died: date of death, if lost to follow up: date last seen)

Survival status:

☐ Alive
☐ Dead
☐ Lost to follow-up

Assessment period covered by this report:

☐ Day 100
☐ 6 Months
☐ Annual or unscheduled follow-up

Main cause of death:
(check only one main cause)

☐ Relapse or progression/persistent disease	
☐ Secondary malignancy	
☐ CT-related	**Select treatment related cause:** *(select all that apply)* ☐ Graft versus Host Disease ☐ Non-infectious complication ☐ Infectious complication: *(select all that apply)* ☐ Bacterial infection ☐ Viral infection ☐ Fungal infection ☐ Parasitic infection ☐ Infection with unknown pathogen
☐ HCT-related	
☐ GT-related	
☐ IST-related	
☐ Unknown	
☐ Other; specify: _____	

Was an autopsy performed?

☐ No
☐ Yes
☐ Unknown

BEST RESPONSE

Complete only for Day 100 and 6 Months Follow-Up.
Not applicable for Inborn Errors

Best clinical/biological response after this CT* *(observed before any subsequent treatment)*: _____

Date best response first observed: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown

* Indicate the best clinical/biological response after CT corresponding to indication diagnosis for CT was given by selecting from the list provided in Appendix 1

BEST RESPONSE continued

If the indication was the treatment of complication derived from a previous transplant/cellular therapy:

GvHD	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Graft failure	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Immune reconsitution	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Infection	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated

RECOVERY

Complete only for Day 100 Follow-Up and 6 Months Follow-up.

If the recovery occurred before 100 days and was reported at Day 100 Follow-up the section can be skipped at 6 Months Follow-up.

Absolute neutrophil count (ANC) recovery *(neutrophils ≥ 0.5x10⁹ /L)*:

- ☐ No: **Date of the last assessment:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*
- ☐ Yes: **Date of ANC recovery:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*
  (first of 3 consecutive values after 7 days without transfusion containing neutrophils)
- ☐ Never below
- ☐ Not evaluated
- ☐ Unknown

Platelet reconstitution *(platelets ≥ 20x10⁹ /L:)*:

- ☐ No: **Date of the last assessment:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*
- ☐ Yes: **Date of platelet reconstitution:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown
  (first of 3 consecutive values after 7 days without platelet transfusion)
- ☐ Never below
- ☐ Not evaluated
- ☐ Unknown

Date of the last platelet transfusion: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Not applicable *(not transfused)* ☐ Unknown

Was B-cell count monitored during this follow-up period ?

- ☐ No
- ☐ Yes: **Was there a B-cell recovery?**
  - ☐ No: **Date of the last assessment**: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*
  - ☐ Yes: **Date of the first B-cell recovery**: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* *(If the recovery was reported on the last follow-up , this question can be skipped.)*
  - ☐ Unknown
- ☐ Unknown

CURRENT HAEMATOLOGICAL FINDINGS

Hb	_____ g/dL	☐ Not evaluated	☐ Unknown
Platelets	_____ 10^9 /L	☐ Not evaluated	☐ Unknown
Were platelets transfused within 7 days before assessment?		☐ No ☐ Yes	☐ Unknown
White blood cells	_____ 10^9 /L	☐ Not evaluated	☐ Unknown
Lymphocytes	_____ %	☐ Not evaluated	☐ Unknown
Neutrophils	_____ %	☐ Not evaluated	☐ Unknown

Extended dataset

Antimicrobial prophylaxis

Did the patient receive antimicrobial prophylaxis during this follow-up period? ☐ No ☐ Yes

If yes, what type of prophylaxis? ☐ Antibacterial ☐ Antifungal ☐ Antiviral
(select all that apply and complete the relevant section)

Antibacterial

Antibiotic *(select all that were administered)*	**Phase** *Day 100 0nly*	**Responses for > 100 days only**
☐ Ciprofloxacin	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Levofloxacin	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Moxifloxacin	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Penicillin	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown

Extended dataset

Antibacterial

Antibiotic *(select all that were administered)*	**Phase** *Day 100 only*	**Responses for > 100 days only**
☐ Non-absorbable antibiotic	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown

Final date antibacterial prophylaxis was discontinued: _ _ _ _/ _ _ / _ _ *(YYYY/MM/DD)* ☐ Ongoing ☐ Unknown

Extended dataset

Antiviral

Did the patient receive cytomegalovirus (CMV) prophylaxis during this follow-up period?

☐ No

☐ Yes: **Which drugs were used?** *(select all that apply)*
- ☐ High-dose acyclovir
- ☐ High-dose valacyclovir
- ☐ Gancyclovir intravenous
- ☐ Valgancyclovir
- ☐ Foscarnet
- ☐ Other drug

Final date CMV prophylaxis was discontinued: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Ongoing ☐ Unknown

Did the patient receive prophylaxis for varicella-zoster virus (VZV) or herpes simplex virus (HSV) with either acyclovir or valacyclovir during this follow-up period?

☐ No

☐ Yes: **Final date VZV or HSV prophylaxis was discontinued:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Ongoing ☐ Unknown

Did the patient receive rituximab or another anti-CD20 monoclonal drug as prophylaxis for Epstein-Barr virus post-transplant lymphoproliferative disorder (EBV-PTLD) during this follow-up period?

☐ No

☐ Yes

Did the patient receive prophylaxis for hepatitis B virus (HBV) during this follow-up period?

☐ No

☐ Yes: **Which drugs were used?** *(select all that apply)*
- ☐ Lamivudine
- ☐ Entecavir
- ☐ Tenofovir
- ☐ Other drug

Final date HBV prophylaxis was discontinued: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Ongoing ☐ Unknown

Extended dataset

Antifungal

Antifungal *(select all that were administered)*	**Phase** *Day 100 Only*	**Responses for > 100 days only**
☐ Fluconazole	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Voriconazole	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Posaconazole	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Itraconazole	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown

Extended dataset

Antifungal

Antifungal *(select all that were administered)*	**Phase** *Day 100 Only*	**Responses for > 100 days only**
☐ Caspofungin	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Micafungin	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown
☐ Anidulafungin	☐ Pre-engraftment ☐ Post-engraftment; specify: ☐ Only post-engraftment ☐ Started pre-engraftment and continued into post-engraftment ☐ Started and stopped in pre-engraftment phase and restarted in post-engraftment phase ☐ Unknown	☐ Started in this follow-up period; **Start date:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown ☐ Ongoing since previous follow-up ☐ Unknown

Final date antifungal prophylaxis was discontinued: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Ongoing ☐ Unknown

Did the patient receive prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) during this follow-up period?

☐ No

☐ Yes: **Which drugs were used?** *(select all that apply)*

- ☐ Trimethoprim-sulfamethoxazole
- ☐ Dapsone
- ☐ Atovaquone
- ☐ Pentamidine inhaled
- ☐ Pentamidine intravenous
- ☐ Other drug

Final date prophylaxis was discontinued: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Ongoing ☐ Unknown

☐ Unknown

Extended dataset

Pre-emptive viral therapy

Did the patient receive pre-emptive therapy for a viral infection during this follow-up period? ☐ No ☐ Yes

If yes, for what virus? ☐ CMV ☐ EBV
(select all that apply)

Specify the pre-emptive therapy for each CMV episode that occurred during this follow-up period

CMV treatment start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

Antiviral(s) used:
(Select all that apply)

- ☐ Valgancyclovir
- ☐ Gancyclovir intravenous
- ☐ Foscarnet
- ☐ Cidofovir
- ☐ Maribavir
- ☐ Specific CMV T-cell
- ☐ Other drug

Was this episode of CMV infection due to a resistant CMV strain?
☐ No ☐ Yes ☐ Unknown

Copy as often as necessary to reflect all episodes that occurred

Specify the pre-emptive therapy for each EBV episode that occurred during this follow-up period

EBV treatment start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

Antiviral(s) used:
(Select all that apply)

- ☐ Rituximab
- ☐ Specific EBV T-cells
- ☐ Other drug

Copy as often as necessary to reflect all episodes that occurred

COMPLICATIONS SINCE THE LAST REPORT
-- GvHD --

Do not report complications that were resolved before this cellular therapy.
Do not report complications that were previously reported as resolved, unless they recurred.

Did graft versus host disease (GvHD) occur during this follow-up period?

☐ No *(proceed to 'Complications since the last report - Non-infectious complications')*

☐ Yes: **Did the patient receive a systemic/immunosuppressive treatment for GvHD during this follow-up period?**
- ☐ No
- ☐ Yes: ☐ Started in this follow-up period; **Date treatment started:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

Treatment stopped:
- ☐ No
- ☐ Yes; **Stop date of treatment:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown
- ☐ Unknown

☐ Unknown

☐ Unknown *(proceed to 'Complications since the last report - Non-infectious complications')*

Did acute GvHD occur during this follow-up period?

☐ No

☐ Yes: ☐ Started in this follow-up period; **Date of onset:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

aGvHD resolved:
- ☐ No
- ☐ Yes; **Date of resolution:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown
- ☐ Unknown

Maximum observed organ severity score during this period:

Skin:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated ☐ Unknown
Liver:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated ☐ Unknown
Lower GI tract:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated ☐ Unknown
Upper GI tract:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated ☐ Unknown
Other site affected:	☐ No	☐ Yes; specify: _____				

Overall maximum grade observed during this period: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Not evaluated ☐ Unknown

Steroid-refractory acute GvHD: ☐ No
- ☐ Yes: ☐ Started in this follow-up period; **Date of onset:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

aGvHD resolved:
- ☐ No
- ☐ Yes; **Date of resolution:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown
- ☐ Unknown

☐ Unknown

aGvHD resolved:
- ☐ No
- ☐ Yes; **Date of aGvHD resolution:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown
- ☐ Unknown

☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT continued
-- GvHD --

Did chronic GvHD occur during this follow-up period?

☐ No

☐ Yes: ☐ Started in this follow-up period; **Date of onset:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown

cGvHD resolved:
☐ No
☐ Yes; **Date of resolution:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown
☐ Unknown

Maximum NIH score during this period: ☐ Mild ☐ Moderate ☐ Severe ☐ Unknown ☐ Not evaluated

Date of maximum NIH score: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown

Maximum observed organ severity score during this period:

Skin:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Oral:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Gastrointestinal:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Eyes:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Liver:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Joints and fascia:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Lungs:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Genitalia:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ Not evaluated	☐ Unknown
Other site affected:	☐ No	☐ Yes; specify: _____					

Steroid-refractory chronic GvHD: ☐ No
☐ Yes: ☐ Started in this follow-up period; **Date of onset:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown
☐ Ongoing since previous follow-up
☐ Unknown

cGvHD resolved: ☐ No
☐ Yes; **Date of cGvHD resolution:** _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown
☐ Unknown

Was overlap syndrome observed: ☐ No ☐ Yes ☐ Unknown
(features of both chronic and acute GvHD)

☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Non-infectious complications --

Do not report complications that were resolved before this cellular therapy.
Do not report complications that were previously reported as resolved, unless they recurred.

Did non-infectious complications occur during the follow-up period?

☐ No (*proceed to 'Complications since the last report - Infectious complications')*
☐ Yes (report in the table below)

Cytokine release syndrome (CRS)

Complication observed during this follow-up period? ☐ No
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum grade observed during this period: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Grading system:
☐ ASTCT consensus (Lee 2019)
☐ Penn
☐ CTCAE
☐ Lee 2014
☐ MDACC
☐ Other; specify: _____

Onset date (*YYYY/MM/DD*): _ _ _ _/ _ _/ _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _/ _ _/ _ _ ☐ Unknown
☐ Unknown

IEC-associated neurotoxicity syndrome (ICANS)

Complication observed during this follow-up period? ☐ No
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum grade observed during this period: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Grading system:
☐ ASTCT consensus (Lee 2019)
☐ CTCAE
☐ Lee 2014
☐ MDACC
☐ Other; specify: _____

Onset date (*YYYY/MM/DD*): _ _ _ _/ _ _/ _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _/ _ _/ _ _ ☐ Unknown
☐ Unknown

* Grade 0-2

COMPLICATIONS SINCE THE LAST REPORT
-- Non-infectious complications --

Other neurotoxicity observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessm
☐ Unknown

Specify:_____

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown
☐ Unknown

Macrophage activation syndrome (MAS)

[redacted] t

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown
☐ Unknown

Secondary haemophagocytic lymphohistiocytosis

Complication observed during this follow-up period? ☐ No
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown
☐ Unknown

Organ toxicity: skin

Complication observed during this follow-up period? ☐ No
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _/ _ _/ _ _ ☐ Unknown
☐ Unknown

*Grade 0-2

COMPLICATIONS SINCE THE LAST REPORT
-- Non-infectious complications --

Organ toxicity: liver

Complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Organ toxicity: lung

Complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Organ toxicity: heart

Complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Organ toxicity: kidney

Complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** *(YYYY/MM/DD)*: _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

* Grade 0-2

COMPLICATIONS SINCE THE LAST REPORT
-- Non-infectious complications --

Organ toxicity: gastrointestinal

Complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Other organ toxicity observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Organ specify:_____

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Tumour lysis syndrome

Complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

B-cell aplasia

Complication observed during this follow-up period? ☐ No
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

% B-cells: ____ ☐ Not evaluated

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

* Grade 0-2

COMPLICATIONS SINCE THE LAST REPORT
-- Non-infectious complications --

Bone marrow aplasia

Complication observed during this follow-up period? ☐ No
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Hypogammaglobulinemia

Complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Was it also present at time of the cellular therapy? ☐ No, occurred after the cellular therapy
☐ Yes: **Was it worsened by the cellular therapy?** ☐ No ☐ Yes

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Exacerbation of existing neurological disorder observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Specify:_____
(Indicate CTCAE term)

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

Other complication observed during this follow-up period? ☐ No*
☐ Yes: ☐ Newly developed ☐ Ongoing since previous assessment
☐ Unknown

Specify: _____ *Consult appendix 4 for a list of complications that should not be reported*
(Indicate CTCAE term)

Maximum CTCAE grade observed during this period: ☐ 3 ☐ 4 ☐ 5 (fatal) ☐ Unknown

Onset date (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown *Only if newly developed*

Resolved: ☐ No
☐ Yes; **Stop date** (*YYYY/MM/DD*): _ _ _ _ / _ _ / _ _ ☐ Unknown
☐ Unknown

*Grade 0-2

If more other complications occurred, copy and fill-in this table as many times as necessary.

COMPLICATIONS SINCE THE LAST REPORT
-- Infectious complications --

Do not report infections that were already reported as resolved on the previous assessment and did not reoccur.

Did infectious complications occur during the follow-up period?

☐ No *Consult appendix 4 for a list of complications that should not be reported*

☐ Yes (*report all infection-related complications below*)

Bacterial infection: ☐ No ☐ Yes

1) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

☐ Gram-positive ☐ Gram-negative ☐ Other

Pathogen*: _____

Infection with clinical implications: ☐ No ☐ Yes: *(select all that apply during this period)*

☐ Symptoms/signs of disease

☐ Administration of pathogen-directed therapy

☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)**: _____

Localisation 2 (CTCAE term)**: _____

Localisation 3 (CTCAE term)**: _____

Intravascular catheter-related infection: ☐ No ☐ Yes; specify***: _____ ☐ Unknown

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)

Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

2) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

☐ Gram-positive ☐ Gram-negative ☐ Other

Pathogen*: _____

Infection with clinical implications: ☐ No ☐ Yes: *(select all that apply during this period)*

☐ Symptoms/signs of disease

☐ Administration of pathogen-directed therapy

☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)**: _____

Localisation 2 (CTCAE term)**: _____

Localisation 3 (CTCAE term)**: _____

Intravascular catheter-related infection: ☐ No ☐ Yes; specify***: _____ ☐ Unknown

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)

Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

If more than 2 bacterial infections, copy and fill-in this table as many times as necessary.

* Indicate the pathogen and sub-type (if applicable) by choosing from the list of pathogens provided in Appendix 2

** Indicate CTCAE term by choosing from the list provided in Appendix 3

*** If intravascular catheter-related infection, specify it by choosing from the list provided in Appendix 5

COMPLICATIONS SINCE THE LAST REPORT
-- Infectious complications -- continued

Viral infection: ☐ No ☐ Yes

1) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

Pathogen*: _____

If the pathogen was CMV/EBV: **Was this infection a reactivation?** ☐ No ☐ Yes

Infection with clinical implications: ☐ No ☐ Yes: *(select all that apply during this period)*
- ☐ Symptoms/signs of disease
- ☐ Administration of pathogen-directed therapy
- ☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)**: _____

Localisation 2 (CTCAE term)**: _____

Localisation 3 (CTCAE term)**: _____

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)
Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

2) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

Pathogen*: _____

If the pathogen was CMV/EBV: **Was this infection a reactivation?** ☐ No ☐ Yes

Infection with clinical implications: ☐ No ☐ Yes: *(select all that apply during this period)*
- ☐ Symptoms/signs of disease
- ☐ Administration of pathogen-directed therapy
- ☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)**: _____

Localisation 2 (CTCAE term)**: _____

Localisation 3 (CTCAE term)**: _____

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)
Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

If more than 2 viral infections, copy and fill-in this table as many times as necessary.

* Indicate the pathogen and sub-type (if applicable) by choosing from the list of pathogens provided in Appendix 2
** Indicate CTCAE term by choosing from the list provided in Appendix 3
*** If intravascular catheter-related infection, specify it by choosing from the list provided in Appendix 5

COMPLICATIONS SINCE THE LAST REPORT
-- Infectious complications -- continued

Fungal infection: ☐ No ☐ Yes

1) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD) only if newly developed*

☐ Yeasts ☐ Moulds

Pathogen*: _____

Infection with clinical implications: ☐ No
☐ Yes: *(select all that apply during this period)*
☐ Symptoms/signs of disease
☐ Administration of pathogen-directed therapy
☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term):** _____

Localisation 2 (CTCAE term):** _____

Localisation 3 (CTCAE term):** _____

Intravascular catheter-related infection: ☐ No
☐ Yes; specify***: _____
☐ Unknown

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)
Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

2) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD) only if newly developed*

☐ Yeasts ☐ Moulds

Pathogen*: _____

Infection with clinical implications: ☐ No
☐ Yes: *(select all that apply during this period)*
☐ Symptoms/signs or disease
☐ Administration of pathogen-directed therapy
☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term):** _____

Localisation 2 (CTCAE term):** _____

Localisation 3 (CTCAE term):** _____

Intravascular catheter-related infection: ☐ No
☐ Yes; specify***: _____
☐ Unknown

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)
Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

If more than 2 fungal infections, copy and fill-in this table as many times as necessary.

* Indicate the pathogen and sub-type (if applicable) by choosing from the list of pathogens provided in Appendix 2
** Indicate CTCAE term by choosing from the list provided in Appendix 3
*** If intravascular catheter-related infection, specify it by choosing from the list provided in Appendix 5

COMPLICATIONS SINCE THE LAST REPORT
-- Infectious complications -- continued

Parasitic infection: ☐ No ☐ Yes

1) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

☐ Protozoa ☐ Helminths

Pathogen*: _____

Infection with clinical implications: ☐ No
☐ Yes: *(select all that apply during this period)*
☐ Symptoms/signs or disease
☐ Administration of pathogen-directed therapy
☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)**: _____

Localisation 2 (CTCAE term)**: _____

Localisation 3 (CTCAE term)**: _____

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)

Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

---

2) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

☐ Protozoa ☐ Helminths

Pathogen*: _____

Infection with clinical implications: ☐ No
☐ Yes: *(select all that apply during this period)*
☐ Symptoms/signs or disease
☐ Administration of pathogen-directed therapy
☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)**: _____

Localisation 2 (CTCAE term)**: _____

Localisation 3 (CTCAE term)**: _____

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)

Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

If more than 2 parasitic infections, copy and fill-in this table as many times as necessary.

* Indicate the pathogen and sub-type (if applicable) by choosing from the list of pathogens provided in Appendix 2
** Indicate CTCAE term by choosing from the list provided in Appendix 3
*** If intravascular catheter-related infection, specify it by choosing from the list provided in Appendix 5

COMPLICATIONS SINCE THE LAST REPORT
-- Infectious complications -- continued

Infection with unknown pathogen: ☐ No ☐ Yes:
(for clinical infections without microbiological documentation, like pneumonia, cellulitis, etc.)

1) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

Infection with clinical implications: ☐ No
☐ Yes: *(select all that apply during this period)*
☐ Symptoms/signs or disease
☐ Administration of pathogen-directed therapy
☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)*: _____

Localisation 2 (CTCAE term)*: _____

Localisation 3 (CTCAE term)*: _____

Intravascular catheter-related infection: ☐ No
☐ Yes; specify**: _____
☐ Unknown

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)
Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

2) **New or ongoing:** ☐ Newly developed ☐ Ongoing since previous assessment

Start date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD) only if newly developed*

Infection with clinical implications: ☐ No
☐ Yes: *(select all that apply during this period)*
☐ Symptoms/signs or disease
☐ Administration of pathogen-directed therapy
☐ Unknown

Indicate at least 1 location involved during this period:

Localisation 1 (CTCAE term)*: _____

Localisation 2 (CTCAE term)*: _____

Localisation 3 (CTCAE term)*: _____

Intravascular catheter-related infection: ☐ No
☐ Yes; specify**: _____
☐ Unknown

Resolved: ☐ No ☐ Yes ☐ Unknown

(if patient died)
Contributory cause of death: ☐ No ☐ Yes ☐ Unknown

If more than 2 infections with unknown pathogen, copy and fill-in this table as many times as necessary.

* Indicate CTCAE term by choosing from the list provided in Appendix 3
** If intravascular catheter-related infection, specify it by choosing from the list provided in Appendix 5

Extended dataset

SARS-CoV-2 RELATED QUESTION

Did the patient receive a vaccination against SARS-CoV-2 during this follow-up period?

☐ No

☐ Yes: **Number of doses during this follow-up period:** _____ ☐ Unknown

Date of the last dose: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

☐ Unknown

SECONDARY MALIGNANCIES AND AUTOIMMUNE DISORDERS

Did a secondary malignancy or autoimmune disorder occur during this follow-up period?

☐ No

☐ Yes:

☐ Iatrogenic disease in relation with treatments administered prior to cellular therapy cells indication and administration (i.e. cytotoxic agents, targeted therapies, immunotherapies, radiation therapy, etc. Please provide more details below)

☐ Transformation of engineered immune effector cells through insertional mutagenesis or other mechanisms (please provide more details below)

Further details on secondary malignancy or autoimmune disorder: _____

Date of diagnosis: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Histologic type *(if applicable)*: _____

Location *(if applicable)*: _____

Secondary malignancy material preserved:	Concomitant PBMCs preserved:
☐ No	☐ No
☐ Yes	☐ Yes
☐ Unknown	☐ Unknown

Was this disease an indication for a subsequent HCT/CT/IST/GT?

☐ No (*complete the relevant non-indication diagnosis form*)

☐ Yes (*complete the relevant indication diagnosis form*)

☐ Unknown

PERSISTENCE OF THE INFUSED CELLS

Was persistence of the infused cellular products assessed since the last follow-up?

☐ No

☐ Yes: **Date of the last assessment:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

Source of cells used for testing:
- ☐ Bone marrow
- ☐ Peripheral blood
- ☐ Tumour
- ☐ Other; specify: _____

Technique used for testing:
- ☐ Molecular (PCR)
- ☐ Flow cytometry
- ☐ Chimaerism
- ☐ Imaging
- ☐ Immunohistochemistry
- ☐ Other; specify: _____

Were immune effector cells (IEC) detected: ☐ No ☐ Yes

☐ Unknown

LAST DISEASE STATUS
Additional Assessments

Disease burden:

LDH level:

☐ Normal

☐ Elevated

☐ Not evaluated

☐ Unknown

Inflammatory state (C-reactive protein [CRP] concentration):

☐ Normal

☐ Elevated: **Maximum CRP concentration**: _____ Unit *(check only one)*: ☐ mg/dL ☐ mg/L

☐ Not evaluated

☐ Unknown

Date of C-reactive protein level assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

ADDITIONAL TREATMENTS

Include only systemic treatments designed to consolidate the anti-tumour activity of CT cells, prevent relapse (i.e. administration of immune checkpoint inhibitors). Indicate only treatments that have not been reported at previous follow-up(s).

Did the patient undergo additional treatment during this follow-up period?

☐ No

☐ Yes; **complete the "Treatment — non-HCT/CT/GT/IST" form**

☐ Unknown

ADDITIONAL CELL INFUSIONS

Did the patient receive additional cell infusions *(excluding a new HCT and CT)* **during this follow-up period?**

☐ No

☐ Yes: **Is this cell infusion an allogeneic boost* ?** ☐ No ☐ Yes

** An allogeneic boost is an infusion of cells from the same donor without conditioning, with no evidence of graft rejection.*

Date of the allogeneic boost: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*

Is this cell infusion an autologous boost? ☐ No ☐ Yes

Date of the autologous boost: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*

If this cell infusion is not a boost, attach the Cell Infusion (CI) sheet available in Appendix 6, completing as many sheets as episodes of cell infusion that took place during this interval; then continue below.

Did the patient receive subsequent HCT *(either at your or another centre)***?**

☐ No

☐ Yes

Did the patient receive subsequent cellular therapy *(either at your or another centre)***?**

☐ No

☐ Yes; **Reason for subsequent CT:** ☐ Primary failure
☐ Consolidation
☐ Mitigation of side effects

If the patient had a subsequent HCT/CT, please, make sure that this subsequent treatment is registered using the appropriate treatment form before proceeding.

HOSPITAL ADMISSION

Complete only for Day 100 and 6 Months Follow-Up.

Was inpatient admission and care needed since the last follow-up?

☐ No

☐ Yes; **Number of days in hospital**: _____

☐ Unknown

Was the patient transferred to the intensive care unit (ICU) since the last follow-up?

☐ No

☐ Yes; **Number of days in ICU**: _____

☐ Unknown

RELAPSE/PROGRESSION, RECURRENCE OF DISEASE OR SIGNIFICANT WORSENING

(not relevant for Inborn Errors)

Was there a relapse, progression, recurrence of disease or significant worsening of organ function related to the primary disease since last follow-up? *(detected by any method)*

☐ No

☐ Yes; *for every relapse, progression, recurrence, significant worsening complete the questions below*

Type: ☐ Relapse / Recurrence of disease

☐ (Continuous) progression / Significant worsening

Date of relapse/progression/recurrence/worsening: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown

Malignant disorders only:

Type of relapse/progression:

Medullary: ☐ No ☐ Yes ☐ Unknown

Extramedullary: ☐ No ☐ Yes ☐ Unknown

If the relapse/progression was extramedullary or both medullary and extramedullary:

Involvement at time of relapse/progression:

Skin: ☐ No ☐ Yes ☐ Not evaluated

CNS: ☐ No ☐ Yes ☐ Not evaluated

Testes/Ovaries: ☐ No ☐ Yes ☐ Not evaluated

Other: ☐ No ☐ Yes; specify: _____

copy and fill-in this table as many times as necessary.

CD19 expression at relapse after CT *(only for Precursor lymphoid neoplasms)*:

☐ Absent

☐ Present

☐ Unknown

PATIENT STATUS

Performance status at the last assessment *(check only one)*:

Type of scale used: Score:

☐ Karnofsky ☐ Lansky	☐ 10	☐ 20	☐ 30	☐ 40	☐ 50	☐ 60	☐ 70	☐ 80	☐ 90	☐ 100
☐ ECOG	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4					

PREGNANCY AFTER CELLULAR THERAPY

Complete only after 6 Months

Has patient become pregnant or impregnated another person since last follow-up?

☐ No;

Extended dataset
Was there an attempted pregnancy since last follow-up? ☐ No ☐ Yes ☐ Unknown

☐ Yes: **Did the pregnancy result in a live birth?**

☐ No; **Date of spontaneous or induced termination:** _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) ☐ Unknown

☐ Yes; **Year of birth:** _ _ _ _ (YYYY) **Month of birth:** _ _ (MM) ☐ Unknown

☐ Still pregnant at time of follow-up

☐ Unknown

Extended dataset
Conception method: ☐ Natural ☐ Assisted ☐ Unknown

☐ Unknown

DISEASE STATUS

Disease specific

Not applicable for Inborn Errors

Disease status at this follow-up or at time of death*: _____

* Indicate the disease status at this follow-up or at time of death corresponding to indication diagnosis by selecting from the list provided in Appendix 1

Appendix 1
Best Response and Disease Status (Disease Specific)

Complete only one section with the main indication diagnosis for which CT was given.

Appendix 1
Best Response and Disease Status (Disease Specific)

Acute leukaemias (AML, PLN, Other)

☐ Complete remission (CR)
☐ Not in complete remission
☐ Not evaluated
☐ Unknown

Proceed to next page for Diseases Status section

Chronic leukaemias (CML, CLL, PLL, Other)

Chronic Myeloid Leukaemia (CML):

☐ Chronic phase (CP); **Number**: ☐ 1st ☐ 2nd ☐ 3rd or higher ☐ Unknown **Haematological remission:** ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown **Cytogenetic remission:** ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown **Molecular remission:** ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown
☐ Accelerated phase; **Number**: ☐ 1st ☐ 2nd ☐ 3rd or higher ☐ Unknown
☐ Blast crisis; **Number**: ☐ 1st ☐ 2nd ☐ 3rd or higher ☐ Unknown
☐ Not evaluated
☐ Unknown

Proceed to next page for Diseases Status section

Chronic Lymphocytic Leukaemia (CLL), Prolymphocytic Leukaemia (PLL) and other chronic leukaemias:

☐ Complete remission (CR)
☐ Partial remission (PR)
☐ Progression: ☐ Resistant to last regimen ☐ Sensitive to last regimen ☐ Unknown
☐ Stable disease (no change, no response/loss of response)
☐ Not evaluated
☐ Unknown

Proceed to next page for Diseases Status section

Plasma cell neoplasms (PCN)

☐ Complete remission (CR)	**Number:** ☐ 1st ☐ 2nd ☐ 3rd or higher ☐ Unknown
☐ Stringent complete remission (sCR)	
☐ Very good partial remission (VGPR)	
☐ Partial remission (PR)	
☐ Relapse	
☐ Progression	
☐ Stable disease (no change, no response/loss of response)	
☐ Not evaluated	
☐ Unknown	

Proceed to next page for Diseases Status section

Appendix 1
Best Response and Disease Status (Disease Specific)
continued

Complete only for PCN Disease Status

Was the patient on dialysis during this follow-up period?

☐ Yes; ☐ Started in this follow-up period: **Start date:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown

☐ Ongoing since previous follow-up

Did dialysis stop? ☐ No
☐ Yes; **End date:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown
☐ Unknown

☐ No

☐ Unknown

Complete only for AL, CLL and PCN Disease Status

Leukaemias (AL, CLL) and PCN (complete only for patient in CR or sCR)

Minimal residual disease (MRD):

☐ Positive;

☐ Increasing (>1log10 change) ☐ Stable (<1log10 change) ☐ Decreasing (>1log10 change) ☐ Unknown

☐ Negative

☐ Not evaluated

☐ Unknown

Date MRD status evaluated: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown

Sensitivity of MRD assay:

☐ $\leq 10^{-6}$
☐ $\leq 10^{-5}$
☐ $\leq 10^{-4}$
☐ $\leq 10^{-3}$
☐ Other; specify: _____
☐ Unknown

Method used:
(select all that apply)

☐ PCR
☐ Flow cytometry
☐ NGS
☐ Other; specify: _____
☐ Unknown

Myeloproliferative neoplasms (MPN), Myelodysplastic neoplasms (MDS), MDS/MPN overlap syndromes

☐ Complete remission (CR)	Number:	☐ 1st ☐ 2nd ☐ 3rd or higher ☐ Unknown
☐ Improvement but no CR		
☐ Primary refractory phase (no change)		
☐ Relapse	Number:	☐ 1st ☐ 2nd ☐ 3rd or higher ☐ Unknown
☐ Progression/Worsening		
☐ Not evaluated		
☐ Unknown		

Appendix 1
Best Response and Disease Status (Disease Specific)
continued

Lymphomas

☐ Chemorefractory relapse or progression, including primary refractory disease
☐ Complete remission (CR): ☐ Confirmed ☐ Unconfirmed (CRU*) ☐ Unknown
☐ Partial remission (PR)
☐ Stable disease (no change, no response/loss of response)
☐ Untreated relapse (from a previous CR) or progression (from a previous PR)
☐ Not evaluated
☐ Unknown

** CRU: Complete response with persistent scan abnormalities of unknown significance*

Solid tumours

☐ Complete remission (CR): ☐ Confirmed ☐ Unconfirmed ☐ Unknown
☐ First partial remission
☐ Partial remission (PR)
☐ Progressive disease
☐ Relapse: ☐ Resistant ☐ Sensitive ☐ Unknown
☐ Stable disease (no change, no response/loss of response)
☐ Not evaluated
☐ Unknown

Bone marrow failures (incl. AA)

☐ Complete remission (CR)
☐ Partial remission (PR)
☐ Haematological improvement (HI); *NIH partial response*
☐ Stable disease (no change, no response/loss of response)
☐ Relapse / Progression
☐ Not evaluated
☐ Unknown

Complete only for Bone marrow failures (incl. AA) Disease Status

Did transfusions stop during the follow-up period?

☐ Patient was never transfusion dependent
☐ No
☐ Yes; **Did the patient return to transfusion dependency afterwards?**
  ☐ No
  ☐ Yes; **First transfusion date**: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* ☐ Unknown
  (after transfusion free period)
  ☐ Unknown
☐ Ongoing transfusion independence since last follow-up
☐ Unknown

Appendix 1
Best Response and Disease Status (Disease Specific)
continued

Autoimmune disorders

☐ No evidence of disease
☐ Improved
☐ Unchanged
☐ Worse
☐ Not evaluated
☐ Unknown

Haemoglobinopathies

Thalassaemia:

Complete only for Thalassemia Best Response

☐ Transfusion independent;	**Date of last transfusion:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown *(after cellular therapy)*
☐ Transfusions required;	**Date of first transfusion:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown *(after cellular therapy)*
☐ Not evaluated	
☐ Unknown	

Complete only for Thalassemia Disease Status

Patient requires transfusions during follow-up period:

☐ No

☐ Yes; ☐ Return to transfusion dependence after cellular therapy or transfusion free period; **Date of first transfusion:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown (after cellular therapy or transfusion free period)

☐ Ongoing transfusion dependence since previous assessment

Number of units: ____ ☐ Unknown
(during follow-up period)

Did transfusions stop? ☐ No
☐ Yes; **Date of last transfusion:** _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) ☐ Unknown
☐ Unknown

☐ Unknown

Appendix 1
Best Response and Disease Status (Disease Specific)
continued

Haemoglobinopathies

Sickle cell disease:

Complete only for Sickle cell disease Best Response

☐ No return of sickling episodes
☐ Return of sickling episodes; **Date of first episode:** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown *(after cellular therapy)*
☐ Not evaluated
☐ Unknown

Complete only for Sickle cell disease Disease Status

Sickling episodes occur during follow-up period:

☐ No
☐ Yes; ☐ First return of sickling episodes after cellular therapy **Date of first episode :** _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Unknown (after cellular therapy) ☐ Ongoing presence of sickling episodes **Number of SCD episodes**: ____ ☐ Unknown (during follow-up)
☐ Unknown

Other diagnosis

☐ No evidence of disease
☐ Improved
☐ No response
☐ Worse
☐ Not evaluated
☐ Unknown

Appendix 2
-- Pathogens as per EBMT Registry database --

**As defined by the IDSA (Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45)*

Bacterial infections

Gram-positive:
- Clostridioides difficile
- Enterococcus faecalis (vancomycin-susceptible)
- Enterococcus faecalis (vancomycin-resistant)
- Enterococcus faecium (vancomycin-susceptible)
- Enterococcus faecium (vancomycin-resistant)
- Listeria monocytogenes
- Nocardia spp (specify)
- Staphylococcus aureus MSSA (methicillin-susceptible)
- Staphylococcus aureus MRSA (methicillin-resistant) vancomycin-susceptible
- Staphylococcus aureus MRSA (methicillin-resistant) vancomycin not tested
- Staphylococcus aureus MRSA and VISA (vancomycin-intermediate, MIC 4-8 µg/ml)
- Staphylococcus aureus MRSA and VRSA (vancomycin-resistant, MIC ≥ 16 µg/ml)
- Staphylococcus coagulase-negative spp (at least two positive blood cultures)
- Streptococcus pneumoniae
- Streptococcus viridans
- Streptococcus other spp (specify)
- Gram-positive bacteria other spp (specify)

Gram-negative:
- Acinetobacter baumannii
- Campylobacter jejuni
- Citrobacter freundii
- Enterobacter cloacae
- Enterobacter other spp (specify)
- Escherichia coli
- Haemophilus influenzae
- Helicobacter pylori
- Klebsiella aerogenes (carbapenem-susceptible)
- Klebsiella pneumoniae (carbapenem-susceptible)
- Klebsiella other spp (carbapenem-resistant) (specify)
- Legionella pneumophila
- Morganella morganii
- Neisseria gonorrhoeae
- Neisseria meningitidis
- Proteus vulgaris
- Providencia spp
- Pseudomonas aeruginosa (carbapenem-susceptible)
- Pseudomonas aeruginosa (carbapenem-resistant)
- Salmonella spp (specify)
- Serratia marcescens
- Shigella spp
- Stenotrophomonas maltophilia
- Treponema pallidum
- Gram-negative bacteria other spp (specify)

Other bacteria:
- Chlamydia spp
- Chlamydophila
- Mycobacterium other spp (specify)
- Mycobacterium tuberculosis
- Mycoplasma pneumoniae
- Rickettsia spp
- Bacteria other (specify)

Viral infections:
- Adenovirus
- Gastrointestinal viruses:
  - o Norovirus
  - o Rotavirus
- Hepatotropic viruses:
  - o HAV
  - o HBV
  - o HCV
  - o HEV
- Herpes group:
  - o CMV
  - o EBV
  - o HHV6
  - o HHV7
  - o HHV8
  - o HS
  - o VZ
- HIV
- Human papilloma viruses (HPV)
- Parvovirus
- Polyomaviruses:
  - o BK
  - o JC
  - o Merkel cell
  - o Other polyomavirus (specify)
- Respiratory viruses:
  - o Enterovirus
  - o Human coronavirus
  - o Influenza A
  - o Influenza B
  - o Metapneumovirus
  - o Parainfluenza
  - o Rhinovirus
  - o RSV
  - o SARS-CoV-2
  - o Respiratory virus other (specify)
- Viruses other (specify)

Appendix 2
-- Pathogens as per EBMT Registry database -- continued

**As defined by the IDSA (Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45)*

Fungal infections:

Yeasts:
- Candida albicans
- Candida auris
- Candida other (specify)
- Cryptococcus neoformans
- Trichosporon (specify)
- Pneumocytis jiroveci
- Yeasts other (specify)

Moulds:
- Aspergillus flavus
- Aspergillus fumigatus
- Aspergillus other spp (specify)
- Aspergillus terreus
- Fusarium other spp (specify)
- Fusarium solani
- Lomentospora prolificans (formerly Scedosporium prolificans)
- Order Mucorales (specify)
- Dematiaceous fungi (Phaeohyphomycosis) (specify)
- Scedosporium spp (specify)
- Moulds other spp (specify)
- Mould infection diagnosed based on positive galactomannan only, without microbiological confirmation
- Blastomyces spp
- Histoplasma spp (specify)
- Coccidioides spp
- Paracoccidioides spp

Parasitic infections:

Protozoa:
- Babesia spp (specify)
- Cryptosporidium
- Giardia spp
- Leishmania spp (specify)
- Plasmodium spp (specify)
- Toxoplasma gondii
- Trypanosoma cruzi
- Protozoa other spp (specify)

Helminths:
- Strongyloides stercoralis
- Other helminths

Appendix 3
-- CTCAE term --

CTCAE terms related to infections and infestations (version 5.0.)
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

Respiratory tract
- Bronchial infection
- Lung infection
- Laryngitis infective
- Pleural infection
- Tracheitis infective
- Upper respiratory infection

Intra-abdominal infections
- Anorectal infection
- Appendicitis infective
- Appendicitis with perforation infective
- Biliary tract infection
- Cecal infection
- Duodenal infection
- Enterocolitis infective
- Esophageal infection
- Gallbladder infection
- Gastritis infective
- Hepatic infection
- Pancreas infection
- Pelvic infection
- Peritoneal infection
- Splenic infection
- Stoma site infection
- Small intestine infection
- Typhlitis infective

Blood
- Bacteremia
- Fungemia
- Viremia

Uro-genital tract infections
- Cystitis infective
- Cervicitis infective
- Kidney infection
- Ovarian infection
- Scrotal infection
- Penile infection
- Prostate infection
- Urethral infection
- Urinary tract infection
- Uterine infection
- Vaginal infection
- Vulval infection

Muscles and bones
- Bone infection
- Myositis infective
- Joint infection

Nervous system infection
- Cranial nerve infection
- Encephalitis infective
- Encephalomyelitis infective
- Meningitis infective
- Myelitis infective
- Peripheral nerve infection

Cardiovascular infections
- Arteritis infective
- Endocarditis infective
- Mediastinal infection
- Phlebitis infective

Skin, soft tissue and mucosal surfaces
- Breast infection
- Folliculitis infective
- Lymph gland infection
- Nail infection
- Mucosal infection
- Papulo/pustular rash
- Paronychia
- Skin infection
- Soft tissue infection
- Wound infection

Head and neck
- Conjunctivitis infective
- Corneal infection
- Endophthalmitis infective
- Retinitis
- Gum infection
- Lip infection
- Oral cavity infection
- Otitis externa infective
- Otitis media infective
- Periorbital infection
- Salivary gland infection
- Sinusitis infective
- Tooth infection

Others
- Device related infection (other than Intravascular catheter)
- Febrile Neutropenia
- Fever of unknown origin (FUO)
- Sepsis

Appendix 4
-- Non-infectious Complications CTCAE term -- No Reporting Required

Non-infectious complications
- Allergic reaction
- All laboratory abnormalities
- All types of pain
- Alopecia
- Blurred vision
- Diarrhoea (enteropathy)
- Dry mouth
- Dyspepsia
- Dysphagia
- Edema
- Esophageal stenosis
- Fatigue
- Flashes
- Gastritis
- Hematologic toxicities
- Hematoma
- Hypertension
- Injection site reaction
- Malaise
- Mucositis
- Sore throat
- Tinnitus
- Vertigo
- Weight loss

Infectious complications
- Minor ophthalmologic bacterial infections
- External otitis treated topically
- Otitis media treated with oral antibiotics
- Isolated lip herpes simplex
- Bacterial tonsillitis or pharyngitis treated orally
- Laryngitis without viral identification managed at home by inhalations or without any intervention
- URTI without viral/bacterial identification managed at home
- Bilateral cervical lymph node enlargement concurrent with URTI that resolved without specific treatment, together with the resolution of URTI
- Local superficial wound infection resolved under topical antibiotics (incl. impetigo)
- Minor skin bacterial infections
- Minor fungal skin infection
- Diaper rash treated with local antifungals
- Candidal balanitis treated topically
- Vaginal candidiasis treated topically or with a single oral dose
- Asymptomatic bacteriuria due to a pathogen not multi-resistant
- Single low urinary tract infection treated orally without need for hospitalisation
- Phlebitis following peripheral intravascular infusion that resolved after intravascular removal without treatment with antibiotics
- Any isolate that is considered part of the normal flora of the place (oral cavity, vagina, skin, stools) except if it carries an antimicrobial resistance that has clinical implications (induce isolation precautions or a pathogen-directed therapy)
- Positive culture without clinical implications

Appendix 5
-- Intravascular catheter-related infections --

CVC infections:
- Catheter colonization
- Phlebitis
- Exit site infection
- Tunnel infection
- Pocket infection
- Bloodstream infection

Appendix 6
Cell Infusion Sheet

Chronological number of CI episode for this patient: _____

Date of the first infusion *(within this episode)*: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD)

Number of infusions within this episode (10 weeks): _____
(Count only infusions that are part of the same regimen and given for the same indication.)

Source of cells:
(check all that apply)
- ☐ Allogeneic
- ☐ Autologous

Type of cells:
(check all that apply)
- ☐ Lymphocytes (DLI)
- ☐ Mesenchymal
- ☐ Fibroblasts
- ☐ Dendritic cells
- ☐ NK cells
- ☐ Regulatory T-cells
- ☐ Gamma/delta cells
- ☐ Virus-specifc T-cells; specify virus: _____
- ☐ Other; specify: _____

Not applicable for Inborn Errors

Disease status at time of this cell infusion*: _____

* Indicate the disease status corresponding to indication diagnosis by selecting from the list provided in Appendix 1

Indication:
(check all that apply)
- ☐ Planned/protocol
- ☐ Prophylactic
- ☐ Treatment of acute GvHD
- ☐ Treatment of chronic GvHD
- ☐ Treatment PTLD, EBV lymphoma
- ☐ Treatment for primary disease
- ☐ Mixed chimaerism
- ☐ Loss/decreased donor chimaerism
- ☐ Treatment of viral infection other than EBV
- ☐ Poor graft function
- ☐ Infection prophylaxis
- ☐ Other; specify: _____

Acute GvHD – maximum grade *(after this infusion episode but before any subsequent cell infusion/HCT/CT)*:
- ☐ 0 (none)
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ Present but grade unknown

Date Acute GvHD onset after cell infusion: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD)

☐ Unknown

KT-EU-472-6036_Protocol V2.2_Amendment 5.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Real-World Evidence eSigned	09-Dec-2024 14:17:09
PPD	QPPV eSigned	09-Dec-2024 15:35:32