Kite Pharma Inc.

NON-INTERVENTIONAL DATA BASE SECONDARY DATA ANALYSIS STUDY PROTOCOL

Study Title	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL)
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
EU PAS Register No	(will be entered after EU PAS registration)
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 in terms of overall response rate. Secondary objectives: Effectiveness will be evaluated as follows: • To determine the complete remission rate after administration of Tecartus. • To determine the duration of response after administration of Tecartus. • To determine time to next treatment after administration of Tecartus. • To determine the time to relapse or progression of primary disease after administration of Tecartus. • To assess effectiveness of Tecartus by gender and age.

- To assess effectiveness of Tecartus in special populations (patients with prior allogeneic stem cell transplantation [SCT], high-risk relapse or refractory (r/r) MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status).

Safety will be evaluated as follows:

- To determine the overall survival rate and 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, and hypogammaglobulinemia.
- To assess the safety and effectiveness profile by gender, age, and in special populations (high-risk comorbidity index, patients treated with Out of Specifications [OOS] product), additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and to detect replication-competent retrovirus (RCR) in samples of patients with secondary malignancies.

CCI [redacted]

Country (-ies) Of Study

In countries where Tecartus will be authorized. At a minimum UK, Spain, Switzerland and Germany will be countries of study, further countries may be added.

Study Director / Author / Contact Person:

Name: PPD
Telephone: PPD
Email: PPD

Marketing Authorization Holder	Kite Pharma EU B.V.	
MAH Contact Person	Name:	PPD
	Address:	Kite Gilead Sciences International Ltd Director, Regulatory Affairs Flowers Building Granta Park, Abington Cambridge CB21 6GT, UK
	Telephone:	PPD
	Email:	PPD
Kite EU-Qualified Person Responsible for Pharmacovigilance:	Name:	PPD
	Telephone:	PPD
	Email:	PPD

TABLE OF CONTENTS

LIST OF ANNEXES

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

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
CRR	Complete Remission Rate
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology 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
GLPS	Global 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
OOS	Out of specifications
ORR	Overall Response Rate
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PD	Disease Progression
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
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
Marketing Authorization Holder	Kite Gilead Sciences International Ltd PPD Director, Regulatory Affairs Flowers Building Granta Park, Abington Cambridge, CB21 6GT UK	Phone: PPD Email: PPE
Study Director	PPD Sr Director, Clinical Data Science (CDS)/Real World Evidence (RWE) Gilead Sciences International Ltd 2 Roundwood Avenue Stockley Park Uxbridge, UB11 1AF UK	Phone: PPD Email: PPE
Medical Monitor	PPD Senior Director, Safety and Pharmacovigilance Kite Pharma, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: PPD Email: PPE
Biostatistics	PPD Senior Manager, Biostatistics Kite Pharma, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: PPD Email: PPE
Clinical Operations	PPD Clinical Program Manager Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany	Phone: PPD Fax: PPD Email: PPE
Pharmacovigilance	Global Patient Safety (GLPS) Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: PPD Fax: PPD Email: PPE
EU QPPV	PPD Vice President, GLPS Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany	Phone: PPD Email: PPE

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 MANTLE CELL LYMPHOMA (MCL)
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) to systematically capture information at the time of Tecartus infusion and during follow-up. The follow-up period will be 15 years for the safety part. The effectiveness part will be analyzed once 200 recipients of Tecartus have been documented in the EBMT Registry. The effectiveness part will also include safety assessments and all patients will be included in the safety part. 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}. Rationale for the effectiveness part: To determine effectiveness of treatment with Tecartus, which includes Overall Response Rate (ORR), Complete Remission Rate (CRR) and Duration Of Response (DOR), time to next treatment and time to relapse or progression. 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, risk of subsequent neoplasm and Overall Survival (OS).

Research Question and Objectives:

The primary objective of this study is as follows:

- To evaluate the effectiveness of Tecartus in terms of overall response rate.

The secondary effectiveness objectives of this study are as follows:

- To determine the complete remission rate after administration of Tecartus.
- To determine the duration of response after administration of Tecartus.
- To determine the time to next treatment after administration of Tecartus.
- To determine the time to relapse or progression of primary disease after administration of Tecartus.
- To assess effectiveness by gender and age.
- To assess effectiveness in special populations (patients with prior allogeneic stem cell transplantation [allo-SCT], high-risk relapse/refractory [r/r] MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status).

The safety objectives of this study are as follows:

- To determine the overall survival rate and causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of ADRs in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia.
- To assess the safety and effectiveness profile by gender, age, and in special populations (high-risk comorbidity index, patients treated with Out of Specifications [OOS] product), additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and to detect replication-competent retrovirus (RCR) in samples of patients with secondary malignancies.

CCI [redacted]

Study Design:	This is a long-term, non-interventional study of adult patients with r/r MCL, who have been treated with Tecartus after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor (BTKi). Patients' data might be entered into the EBMT Registry up to 1 week prior or anytime following Tecartus infusion. Patients will be followed in the EBMT Registry for both study parts. For the safety part, patients will be followed for up to 15 years; for the effectiveness part, patients will be followed until the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry (expected approximately 4 years after start of data collection). As this study will make secondary use of data collected in the EBMT Registry, expedited reporting of individual case safety reports will not occur. For the reporting of safety data, the centers will follow the standard spontaneous reporting system per local regulations and timelines.
Population:	The population comprises adult recipients of Tecartus for r/r MCL, at participating centers who consent to have data reported to the EBMT. 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, secondary use of data study makes use of the EBMT Registry and is dependent on all needed variables to be collected in the EBMT Cellular and Gene 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. • Variables utilized for analysis of the Primary Objective and Effectiveness Objectives — 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
- Date of the first relapse or progression or significant worsening of the primary disease (MCL) after the Tecartus infusion

- Variables utilized for analysis of Safety Objectives
  - Date and main cause of death, or date of the last day known being alive
  - 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, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. Date of recovery will be collected for ANC and platelets.
  - Serious infections (type, organism, treatment and date of onset of infection as well as resolution status)
  - 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
  - Type, date of onset, and resolution status of aggravated GvHD. For acute GvHD in addition: grade and relationship to cell therapy
  - In case of a secondary malignancy the sampling for RCR testing, the sample date and the test result (not collected in the current EBMT Cellular and Gene Therapy Form)

- [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 out of specification
- Demographics and Baseline Characteristics
  - Age, gender, and country
  - Height and weight at the time of Tecartus infusion
  - Disease subtype (e.g., classical MCL vs. blastoid MCL)
  - MIPI score at diagnosis
  - CD19 expression status (not collected in the current EBMT Cellular and Gene 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 cellular therapy
  - Tumor characteristics (i.e. presence of TP53 mutation and/or17p deletion; Ki-67 index)
  - 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: For this specific protocol: patient data as available within the EBMT Registry. For the EBMT Registry: the patient's medical records

Study Size: Effectiveness part:

The first 200 eligible patients who have been treated with Tecartus and documented in the EBMT Registry will be included. Approximately 4 years after the start of data collection 200 patients are expected to have been documented in the EBMT Registry. Based on the gender distribution in MCL, it is expected that 50 female and 150 male patients will be documented at this time point.

Safety part:

All eligible patients who have been treated with Tecartus and documented in the EBMT Registry within 5 years from study start will be included. 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 person-years of follow up. The available person-years of follow-up are approximated using a piecewise linear survival curve with 2-year survival rate of 65% (assumption based on the primary analysis of ZUMA-2) and an assumption of long term 15-year survival rate of 35%, indicating an average person-years of follow-up of 8.15 years. Kite also assumes 10% overall loss to follow up, resulting in approximately 2567 total person-years of follow-up. This number of person-years of follow-up will provide 97%, or 82%, or 68%, or 58%, or 50% likelihood of seeing at least one event of interest, if the true rate per 15 years of exposure is at least 1:50, or 1:100, or 1:150, or 1:200, or 1:250, respectively.

Data Analysis: Analysis of all endpoints for this study will include all patients who satisfy the eligibility criteria, are documented within the EBMT Registry 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 data. 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 will be used to model multivariate time-to-event data adjusted for predefined characteristics to estimate their prognostic effect on the outcome.

Effectiveness part:

The analysis of the effectiveness endpoints will be conducted when effectiveness data from approximately 200 eligible patients 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
- Effectiveness Endpoints
  - Complete remission rate
  - Duration of response
  - Time to next treatment of the primary disease
  - Time to relapse or progression of the primary disease
  - Effectiveness endpoints by gender and age
  - 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
  - Overall survival
  - 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 gender, 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
- Incidence rate, resolution, time to onset of aggravated GvHD by acute and chronic type; incidence rate, severity and relationship to cell therapy for acute GvHD
- Frequency of detection of RCR in samples of patients with secondary malignancies

[redacted]

Milestones:

Effectiveness part

Start of data collection:	15 January 2022
End of data collection:	14 June 2025
Study duration:	approximately 4 years
Annual Reports:	annually for 3 years
Final Report:	approximately 4.5 years after start of data collection

Safety part	
Start of data collection:	15 January 2022
End of data collection:	14 October 2041
Study duration:	20 years
Annual Reports:	annually for 5 years, then every 2 years
Final report:	Q1 2043

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

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 and the European Society for Blood and Marrow Transplantation (EBMT) prior to implementation.

4. MILESTONES

Table 3. Protocol Milestones

Milestone	Planned Date
PRAC approval of study protocol	30 September 2021
Protocol registration in the EU PAS Registry	2 weeks after PRAC approval
Start of data collection*	15 January 2022
End of data collection effectiveness part**	14 June 2025
End of data collection safety part***	14 October 2041
Analyses of published literature and databases for comparator	5 years following start of data collection
Study duration	20 years
Safety Data Reports	Quarterly reports will be generated on the basis of quarterly data transmission from EBMT. The reports will be appended to the 6 monthly PSURs, unless a quarterly report generates an urgent new safety finding, resulting in submission as a stand-alone report in between PSUR cycles. 2022 to 2026, frequency thereafter to be re-evaluated
Annual reports effectiveness part	Q3 2022 to 2024 annually
Annual reports safety part	Q1 2023 to 2027 annually, then every 2 years
Final report of study results	Q1 2043

***** 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. First data extraction for study KT-EU-472-6036 will take place 3 months after protocol registration or contract execution with the EBMT, whichever comes last.
****** When effectiveness data from approximately 200 eligible patients are documented.
******* 20 years after protocol registration, no further data will be included in the study analyses.

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 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 95 kD transmembrane protein that is uniquely expressed in normal B cells and in most B-cell malignancies {Anderson 1984, Johnson 2009, Leonard 2001, Nadler 1983, Olejniczak 2006, Rodriguez 1994, Uckun 1988}. Expression occurs beginning at the pro-B-cell stage 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 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 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).

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 postinfusion 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.

The purpose of this study is to analyze and report on the follow-up data for recipients of Tecartus captured in the EBMT Registry to address the effectiveness of this product based on ORR, CRR and DOR, and to describe the long-term safety including incidence rates and severity of adverse drug reactions (ADRs), the risk of subsequent neoplasm, OS, time to next treatment and time to relapse or progression.

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.

6. RESEARCH QUESTIONS AND OBJECTIVES

This is a long-term, non-interventional effectiveness and safety study of adult patients with r/r MCL after 2 or more lines of systemic therapy including a BTKi, who have been treated with Tecartus.

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

Therefore, the study will make secondary use of the data captured in the EBMT Registry, using the infrastructure EBMT 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. Follow-up for the effectiveness part will be stopped once the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry, 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.

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 primary objective of this study is:

- To evaluate the effectiveness of Tecartus in terms of overall response rate.

The secondary effectiveness objectives of this study are:

- To determine the complete remission rate after administration of Tecartus.
- To determine the duration of response after administration of Tecartus.
- To determine the time to next treatment after administration of Tecartus.
- To determine the time to relapse or progression of primary disease after administration of Tecartus.
- To assess effectiveness by gender and age.
- To assess effectiveness in special populations (patients with prior allogeneic stem cell transplantation [SCT], high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, CD19 expression status).

The safety objectives of this study are:

- To determine the overall survival rate and causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of ADRs in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia.
- To assess the safety and effectiveness profile by gender, age, and in special populations (high-risk comorbidity index, patients treated with Out of Specifications [OOS] product), additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and to detect of replication-competent retrovirus (RCR) in samples of patients with secondary malignancies.

CCI [redacted]

- [redacted]
- [redacted]

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 with r/r MCL after 2 or more lines of systemic therapy including a BTKi, who have been treated with Tecartus, in the post-marketing setting making secondary use of data available in the EBMT Registry. The EBMT centers enter data into the EBMT Registry following the EBMT specific procedures and requirements. According to the EBMT monitoring plan the site is responsible for completing the data collection forms within 6 weeks after a patient visit. The preferred and most common option to enter data into the EBMT Registry 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. Patients' data may be entered up to 1 week prior or anytime following administration of Tecartus infusion. 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. Patients will be followed in the EBMT Registry for both study parts. For the safety part for up to 15 years; for the effectiveness part until the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry (which is expected to be approximately 4 years after the start of data collection).

7.2. Setting

No treatments, therapy protocols, or procedures are mandated. There is no prescribed visit schedule. Data entered into the EBMT Registry will be obtained from clinical, laboratory, and diagnostic assessments conducted during the course of routine medical practice and available in the patient's medical chart, collected for the primary purpose of patient care. Data will be captured by completion of the EBMT Cellular and Gene Therapy Form for the time points described below (see 7.6), 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 (e.g. submitting data to the EBMT).

The EBMT Cellular and Gene Therapy Form was created in close cooperation with the Committee for Human Medical Products (CHMP) and other relevant Marketing Authorization Holders (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 a defined data set as specified in the EBMT Cellular and Gene Therapy Form. The EBMT Cellular and Gene Therapy Form is under the control of the EBMT, and therefore its content may change throughout the course of the study.

Available data within the EBMT Registry will be analyzed for this study at defined time points. In this registry only predefined data of interest will be collected from the medical charts.

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 be added throughout the course of the study on the EBMT Cellular and Gene Therapy Form to support structured data collection of such new relevant data during the study, if agreed by the EBMT, who owns this form.

7.2.1. Eligibility

The EBMT Registry collects data on all patients receiving cell therapy. Eligible patient data for this study is from adult patients treated with Tecartus for r/r MCL after 2 or more lines of systemic therapy including a BTKi, 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, i.e. there are no restrictions regarding the patients' performance status of any kind.

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

7.2.2. Study Centers

All centers that are qualified for the use of Tecartus and who provide their data to the EBMT Registry contribute to this study. The centers enter the data directly via the EBMT Cellular and Gene Therapy Form into the EBMT Registry following the EBMT data entry guidance documents (see Section 7.2). The centers will enter initial patient data and any subsequent follow up data.

In a commercial setting, Kite is engaging with sites at time of initial commercial center qualification process to allow the prescribing of Tecartus and when Kite delivers training on the required additional risk minimization measures (aRMMs). Kite cannot engage in EBMT Registry management related interactions with the centers.

These commercial sites are generally members of EBMT and therefore Kite has non study/registry-related contacts with sites. Nevertheless, because of the responsibilities of Kite to deliver training to qualified prescriber sites, the contact with centers that are contributing to the EBMT Registry can be used to deliver relevant reminders on the importance of spontaneous reporting and that this is not replaceable by reporting into the EBMT Registry.

7.3. Variables

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

The EBMT Cellular and Gene Therapy Form specifies the sub-set of data that are transcribed by the centers from the patients' medical charts into the EBMT Registry.

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

- 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
- Date of the first relapse or progression or significant worsening of the primary disease (MCL) after the Tecartus infusion

7.3.2. Variables utilized for analysis of Safety Objectives

The EBMT Registry will collect the variables listed and this study will utilize this data for analysis.

- Date and main cause of death, or date of the last day known being alive
- Secondary malignancy is defined as the development of any new malignancies occurring after the administration of Tecartus. The date of diagnosis, type, location and relevant details on biopsy/diagnostic results will be collected.
- 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. CRS grade (Table 6), system of grading, date of onset, treatment and resolution status will be collected.
- Neurologic toxicity is a class effect of CAR T cell therapies and most commonly includes confusion, delirium, aphasia, obtundation, myoclonus, and seizures. The 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 $\geq 500/mm^3$ for 3 consecutive values, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. The date of recovery for ANC and platelets will be collected.

- 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 EBMT Registry. The type, organism, treatment and date of onset of infection and resolution status will be collected.

- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. For hypogammaglobulinemia the date of onset, treatment, and resolution status will be collected.

- Grade, date of onset and resolution of TLS

- Type, date of onset, and resolution status of aggravated GvHD. For acute GvHD in addition: grade and relationship to cell therapy

- In case of a secondary malignancy the sampling for RCR testing, the sample date and the test result (not collected in the current EBMT Cellular and Gene Therapy Form)

Table 6. Grading of CRS

Grade[1]	Sign/Symptom/Intervention
1	Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
2	Symptoms require and respond to moderate level of intervention: Oxygen requirement < 40% FiO_2, or Hypotension responsive to intravenous fluid infusion or low dose of one vasopressor, or Grade 2 organ toxicity[2]
3	Symptoms require and respond to aggressive intervention: Oxygen requirement > 40% FiO_2, or Hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis
4	Life-threatening symptoms Requirement for mechanical ventilatory support, or Grade 4 organ toxicity (excluding transaminitis)
5	Death

1 CRS grading adapted from Lee, et al {Lee 2014}
2 Organ toxicities are defined according to National Cancer Institute (NCI) Common Terminology of Adverse Events (CTCAE).

CCI [redacted]

7.3.4. Variables for 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 out of specification.

7.3.5. Variables to Collect for Demographics and Baseline Characteristics

- Age, gender, and country
- Height and weight at the time of Tecartus infusion
- Disease subtype (e.g., classical MCL vs. blastoid MCL)
- MIPI score at diagnosis
- CD19 expression status (not collected in the current EBMT Cellular and Gene Therapy Form)
- Disease status at time of cellular therapy (e.g., sensitive or resistant to chemotherapy or radiation prior to therapy)
- Prior lines of treatment and response
- Disease stage at time of cellular therapy
- Tumor characteristics (i.e. presence of TP53 mutation and/or 17p deletion; Ki-67 index)
- Time from diagnosis of the primary disease to cellular therapy

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

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 and Gene 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 and Gene Therapy Form. Centers are instructed to electronically submit the first registration on the day of treatment (Day 0) or within a week of Day 0. 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.

7.5. Study Size

Within 4 years, Kite projects 400 patients are to have been treated with commercial Tecartus in Europe and it is anticipated that approximately 50% (200) of those patients will consent to the documentation of their data in the EBMT Registry. Based on the gender distribution in MCL, it is expected that approximately 50 female and 150 male patients will be documented at this time point. These first 200 eligible patients who have been treated with Tecartus and documented in the EBMT Registry will be evaluated in the effectiveness part of this study.

A sample size of 200 patients will allow to estimate an ORR and the according 95% confidence interval as tabulated in Table 7:

Table 7. 95% Confidence Interval of ORR by the Assumption of Observed ORR in 200 Patients

Assumed observed ORR based on 200 patients	Lower Limit of 95% CI[b]	Upper Limit of 95% CI[b]
97% (194 out of 200)	94%	99%
93% (186 out of 200)[a]	89%	96%
90% (180 out of 200)	85%	94%
85% (170 out of 200)	79%	90%
80% (160 out of 200)	74%	85%
75% (150 out of 200)	68%	81%

a 93% is the observed ORR in the ZUMA-2 study {Wang 2020}"
b 95% CI is calculated based on Clopper-Pearson exact method

For the safety part this study plans to evaluate all eligible patients who have been treated with Tecartus and documented in the EBMT Registry within 5 years from study start. In addition to the further characterization of the immediate and established toxicities of Tecartus, the study will evaluate rare and delayed safety events that occur in patients during 15 person-years of follow up. In that 5-year period, Kite projects 700 patients are to have been treated with commercial Tecartus in Europe and it is anticipated that approximately 50% (350) of those patients will consent to the documentation of their data in the EBMT Registry. The available person-years of follow-up are approximated using a piecewise linear survival curve with 2-year survival rate of 65% (assumption based on the primary analysis of ZUMA-2) and an assumption of long term 15-year survival rate of 35%, indicating an average person-years of follow-up of 8.15 years. Kite also assumes 10% overall loss to follow up, resulting in total person-years of follow-up of approximately 2567. This number of person-years of follow-up will provide 97%, or 82%, or 68%, or 58%, or 50% likelihood of seeing at least one event of interest, if the true rate per 15 years of exposure is at least 1:50, or 1:100, or 1:150, or 1:200, or 1:250, respectively. The number of 350 patients used for calculation is an assumption. The true study size for the safety part of this study will be the actual number of patients documented in the EBMT Registry within 5 years from study start.

7.6. Data Management

Data will be entered into the EBMT Registry by the centers utilizing the EBMT Cellular and Gene 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 hematopoietic cell transplantation (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. Reports will be jointly prepared as described in Section 10.1.

7.6.1. Data Transfer Procedure

EBMT will provide raw data outputs in a standard format to Kite, and these full datasets will be provided annually.

7.7. Data Analysis

7.7.1. Primary Endpoint and Effectiveness Endpoints

7.7.1.1. Primary Endpoint

- Overall response rate

7.7.1.2. Effectiveness Endpoints

- Complete remission rate
- Time to relapse or progression of the primary disease: time to relapse or progression is defined as the time from Tecartus infusion to the first relapse or progression or significant worsening of the primary disease (MCL), or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk. 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.

- Duration of response: duration of response is defined as the time from the date of the first documented response (CR or PR) to the date of the first documented progression, or first documented relapse, or death due to primary disease, whichever happens first. DOR is determined only among patients who achieve a CR or PR after the first infusion of Tecartus.

- Time to next treatment of the primary disease: time from Tecartus infusion to next treatment of the primary disease (MCL) or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk.

- Effectiveness endpoints by gender and age

- 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, CD19 expression status).

7.7.2. Safety Endpoints

- Overall survival: overall survival is the time from the date of Tecartus infusion to the date of death due to any reason.

- 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 gender, age, and in special populations (patients with prior allogeneic 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

- Incidence rate, resolution, time to onset of aggravated GvHD by acute and chronic type; incidence rate, severity and relationship to cell therapy for acute GvHD

- Frequency of detection of RCR in samples of patients with secondary malignancies

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]

[redacted]

[redacted]

7.7.4. General Considerations for Data Analysis

The study will make secondary use of the data available in the EBMT Registry. Analysis of all endpoints for this study will include all patients who satisfy the eligibility criteria, are documented within the EBMT Registry, 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, gender, and special populations (patients with prior allogeneic SCT, high-risk comorbidity index, patients treated with OOS product) 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. 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 will be used to model multivariate time-to-event data 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 effectiveness data from approximately 200 eligible patients were documented. 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 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 and in Section 7.7.5 and 7.7.6. 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. Imputation methods will be used to account for missing values in the dataset for those variables used in multivariate modeling (demographics, baseline disease assessment, medical history, treatment history) following the current ENCePP guidelines {Pharmocovigilance 2018}, {Rubin 1987}, {Moons 2006}, {Wlelch 2014}. Multiple imputation by chained equations (MICE) as sequential regression multiple imputation will be used handling of missing data {Azur 2011}. Using MICE, missing values are imputed based on the observed values for a given individual and the relationships within the data for other participants. The imputation methods will not be applied when the percentage of missing is significant (>40%), or the assumption of the imputation methods is not hold.

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. Analysis of Primary Endpoint and Effectiveness Endpoints

7.7.5.1. Analysis of Primary Endpoint

Overall response rate: The subject incidence of best overall response (BOR) including Complete remission / Normalisation of organ function / No infection present (CR), Partial remission / Partial or non normalisation of organ function (PR), no response (NR), disease progression or worsening of organ function (PD), or not evaluated will be tabulated. The objective response rate (ORR) defined as the incidence of CR or PR will be calculated. The 95% confidence intervals will be provided for ORR using exact bionomial methods.

7.7.5.2. Analysis of Effectiveness Endpoints

Complete remission rate: Complete remission rate is defined as the incidence of CR. The 95% confidence intervals will be provided using exact binomial methods.

Duration of response: The cumulative incidence of DOR and 95% CIs will be estimated using the competing risk analysis method, with death due to reasons other than primary disease considered as a competing event.

Time to next treatment of the primary disease: 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.

Time to relapse or progression of the primary disease: 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.

ORR, CRR and DOR, as well as the time to next treatment, relapse or progression of the primary disease will be analyzed on the subgroups of gender, age, and in special population (patients with prior allogeneic stem cell transplantation [SCT], high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, CD19 expression status).

Missing data in effectiveness variables will be treated as non-responders. However, this will also depend on the reason of missing data. For example, if a patient did not sign the informed consent this patient will not be considered as non-responder. In case the patient's data will be excluded clarification for exclusion will be provided.

7.7.6. Analysis of Safety Endpoints

Overall survival: Overall survival (OS) is the time from date of the first 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. The median OS along with 95% CIs will be presented if appropriate. Causes of death will also be reported.

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.

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 carried out by completing risk analysis treating death without recovery of ANC or platelets as competing risk. The point estimate and 95% CI of cumulative incidence will be reported accordingly.

Serious infections: The incidence of serious infections, 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.

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.

The above endpoints, together with ORR, CRR and DOR, will be analyzed on the subgroups of by gender, age, and in special populations (high-risk comorbidity index, 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.

Aggravated GvHD: The overall incidence of GvHD, both overall and by type, will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of GvHD after Tecartus infusion and 95% CI will be estimated using competing risk analysis. The severity and relationship to Tecartus will also be summarized.

RCR: The detection of RCR in samples of patients with secondary malignancies will be described using frequencies and percentages.

CCI [redacted]

CCI [redacted]

7.7.8. Interim Analysis

For the effectiveness part annual reports will be prepared for the first three years, in which an analysis of treated patients for the primary and the effectiveness endpoints will be included. For the safety part annual reports will be prepared for the first five years and then every two years, in which an analysis of treated patients for the safety endpoints will be included. The study objectives are not associated with formal hypothesis testing and no overall type I error control. These interim analyses are administrative interim analyses 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.

7.9. Limitations of the Research Methods

The EBMT Registry allows patient data entry any time after Tecartus infusion; therefore this study has the characteristic disadvantages of retrospective studies, and these include, information bias, history bias and recall bias. However, there will be an effort to encourage patient documentation in the EBMT Registry as promptly as possible to capture data continuously going forward. The EBMT monitoring plan further states that the site is responsible for completing the data collection forms within 6 weeks after a patient visit.

Information bias can be prevented by using standard measurement instruments, such as the 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.

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, 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 Registry to capture information about Tecartus.

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. 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.

8.2. Informed Consent

No specific informed consent will be obtained 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 consenting for input of their data into the EBMT Registry.

8.3. 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.

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 data set; and where the adverse events 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 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 and timelines. The 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 and importance to spontaneously report and that this is not substituted by reporting into the EBMT Registry.

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 clinical study subject 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 participation in the clinical study 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, prolonged cytopenia, hypogammaglobulinemia, TLS and aggravated GvHD.

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. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

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 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.

[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. 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.

10.1. Study Report and Publications

10.1.1. Safety Data Reports

After start of data collection, EBMT will provide Kite with a quarterly 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). Two quarterly reports will be submitted as appendices to the periodic safety update report (PSUR) to the Pharmacovigilance Risk Assessment Committee (PRAC). In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document. Particular attention will be paid to Adverse Events of Special Interest (AESIs) – which are considered to be the events which are the focus of 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 and aggravated GvHD
- If reported, review of any unexpected events, which do not fall under the previously recognized risks or ADRs of special interest
- Summary and conclusions

10.1.2. Annual Reports

For the effectiveness part annual reports will be prepared 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 annual reports will be prepared for the first 5 years and then every 2 years thereafter, in which an analysis of treated patients for the safety endpoints will be included. The

EBMT Cellular and Gene Therapy Form is under the control of the EBMT and its content can change throughout the course of the study (see 7.2).

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

10.1.3. Final Report

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

10.1.4. Publications, Conference Abstracts, and Manuscripts

All proposed publications and conference presentations arising from the study will be reviewed by Kite and EBMT 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.

11. REFERENCES

Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood 1984;63 (6):1424-33.

Argatoff LH, Connors JM, Klasa RJ, Horsman DE, Gascoyne RD. Mantle Cell Lymphoma: A Clinicopathologic Study of 80 Cases. Blood 1997;89 (6):2067-78.

Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 2011;20 (1):40-9.

Bear AS, Morgan RA, Cornetta K, June CH, Binder-Scholl G, Dudley ME, et al. Replication-Competent Retroviruses in Gene-Modified T Cells Used in Clinical Trials: Is It Time to Revise the Testing Requirements? Mol Ther 2012;20 (2):246-9.

BLINCYTO, Amgen Inc. BLINCYTO® (blinatumomab) for Injection, for Intravenous Use. U. S. Prescribing Information. Thousand Oaks, CA. Revised: April. 2019:

Brentjens RJ, Davila ML, Riviere I, Park J, Wang X, Cowell LG, et al. CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia. Sci Transl Med 2013;5 (177):177ra38.

Brudno JN, Kochenderfer JN. Toxicities of Chimeric Antigen Receptor T Cells: Recognition and Management. Blood 2016;127 (26):3321-30.

Cabezudo E, Carrara P, Morilla R, Matutes E. Quantitative Analysis of CD79b, CD5 and CD19 in Mature B-Cell Lymphoproliferative Disorders. Haematologica 1999;84:413-8.

Chang EC, Sensel MG, Rossi JM. Analysis of T-cell Vector Integration Sites for a Murine Gamma-Retroviral Vector Encoding the Anti-CD19 Chimeric Antigen Receptor Used in the Production of Axicabtagene Ciloleucel [Presentation]. ASGCT; 2019 29 April-02 May; Washington, D.C.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32 (27):3059-68.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25 (5):579-86.

Cooper LJ, Topp MS, Serrano LM, Gonzalez S, Chang WC, Naranjo A, et al. T-cell clones can be rendered specific for CD19: toward the selective augmentation of the graft-versus-B-lineage leukemia effect. Blood 2003;101 (4):1637-44.

Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia. Sci Transl Med 2014;6 (224):224ra25.

Finney HM, Lawson AD, Bebbington CR, Weir AN. Chimeric Receptors Providing Both Primary and Costimulatory Signaling in T Cells from a Single Gene Product. J Immunol 1998;161 (6):2791-7.

Ginaldi L, De Martinis M, Matutes E, Farahat N, Morilla R, Catovsky D. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. Journal of clinical pathology 1998;51 (5):364-9.

Gupta R, Bhaskar A, Kumar L, Sharma A, Jain P. Flow Cytometric Immunophenotyping and Minimal Residual Disease Analysis in Multiple Myeloma. Am J Clin Pathol 2009;132 (5):728-32.

Gupta S, Indelicato SR, Jethwa V, Kawabata T, Kelley M, Mire-Sluis AR, et al. Recommendations for the design, optimization, and qualification of cell-based assays used for the detection of neutralizing antibody responses elicited to biological therapeutics. J Immunol Methods 2007;321 (1-2):1-18.

Hamid O, Carvajal RD. Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. Expert opinion on biological therapy 2013;13 (6):847-61.

Johnson NA, Boyle M, Bashashati A, Leach S, Brooks-Wilson A, Sehn LH, et al. Diffuse large B-cell lymphoma: reduced CD20 expression is associated with an inferior survival. Blood 2009;113 (16):3773-80.

Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Bilhartz DL, Wyand M, et al. Overall Survival Analysis of a Phase II Randomized Controlled Trial of a Poxviral-Based PSA-Targeted Immunotherapy in Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol 2010;28 (7):1099-105.

Kershaw MH, Westwood JA, Darcy PK. Gene-engineered T cells for cancer therapy. Nat Rev Cancer 2013;13 (8):525-41.

Kochenderfer J, Somerville R, Lu T, Shi V, Yang J, Sherry R, et al. Low-dose chemotherapy followed by anti-CD19 chimeric antigen receptor (CAR) T cells induces remissions in patients with advanced lymphoma. European Hematology Association (EHA) Annual Congress 2016;Abstract #S792.

Kochenderfer JN, Dudley ME, Feldman SA, Wilson WH, Spaner DE, Maric I, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood 2012;119 (12):2709-20.

Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP, Carpenter RO, Stetler-Stevenson M, et al. Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor. J Clin Oncol 2015;33 (6):540-9.

Kochenderfer JN, Feldman SA, Zhao Y, Xu H, Black MA, Morgan RA, et al. Construction and Preclinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor. J Immunother 2009;32 (7):689-702.

Kochenderfer JN, Somerville RPT, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. J Clin Oncol 2017a;35 (16):1803-13.

Kochenderfer JN, Somerville RPT, Lu T, Yang JC, Sherry RM, Feldman SA, et al. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. Mol Ther 2017b;25 (10):2245-53.

KYMRIAH, Novartis Pharmaceuticals Corporation. KYMRIAH™ (tisagenlecleucel) suspension for intravenous infusion. U. S. Prescribing Information. East Hanover, NJ. Revised: May. 2018:

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124 (2):188-95.

Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385 (9967):517-28.

Leonard JP, Schattner EJ, Coleman M. Biology and management of mantle cell lymphoma. Curr Opin Oncol 2001;13 (5):342-7.

Lin P, Owens R, Tricot G, Wilson CS. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. Am J Clin Pathol 2004;121 (4):482-8.

Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-Term Safety and Activity of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1): A Single-Arm, Multicentre, Phase 1-2 Trial. Lancet Oncol 2019;20:31-42.

Marcondes NA, Fernandes FB, Alegretti AP, Faulhaber GAM. Expression of Bruton's Tyrosine Kinase in B-Cell Neoplasms Evaluated by Flow Cytometry. Clin Exp Med 2017;17:499-504.

Martinez A, Aymerich M, Castillo M, Colomer D, Bellosillo B, Campo E, et al. Routine Use of Immunophenotype by Flow Cytometry in Tissues With Suspected Hematological Malignancies. Cytometry B Clin Cytom 2003;56:8-15.

Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371 (16):1507-17.

Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood 2015;125 (26):4017-23.

Moons KGM, Donders RART, Stijnen T, Harrell FE. Using the outcome for imputation of missing predictor values was preferred. journal of clinical Epidemiology 2006;59:1092 - 101.

Nadler LM, Anderson KC, Marti G, Bates M, Park E, Daley JF, et al. B4, a human B lymphocyte-associated antigen expressed on normal, mitogen-activated, and malignant B lymphocytes. J Immunol 1983;131 (1):244-50.

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377 (26):2531-44.

Nicholson IC, Lenton KA, Little DJ, Decorso T, Lee FT, Scott AM, et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. Mol Immunol 1997;34 (16-17):1157-65.

Olejniczak SH, Stewart CC, Donohue K, Czuczman MS. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry. Immunol Invest 2006;35 (1):93-114.

Park JH, Geyer MB, Brentjens RJ. CD19-targeted CAR T-cell therapeutics for hematologic malignancies: interpreting clinical outcomes to date. Blood 2016;127 (26):3312-20.

ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Revision 7, dated July 2018. Accessed

Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med 2015;7 (303):303ra139.

Porter DL, Kalos M, Zheng Z, Levine B, June C. Chimeric Antigen Receptor Therapy for B-cell Malignancies. J Cancer 2011;2:331-2.

Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol 2012;12 (4):269-81.

Robbins PF, Kassim SH, Tran TL, Crystal JS, Morgan RA, Feldman SA, et al. A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1-Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response. Clin Cancer Res 2015;21 (5):1019-27.

Roberts ZJ, Better M, Bot A, Roberts MR, Ribas A. Axicabtagene ciloleucel, a first-in-class CAR T cell therapy for aggressive NHL. Leuk Lymphoma 2018;59 (8):1785-96.

Rodriguez J, Pugh WC, Romaguera JE, Cabanillas F. Primary mediastinal large cell lymphoma. Hematological Oncology 1994;12 (4):175-84.

Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy. Clin Cancer Res 2011;17 (13):4550-7.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. Multiple Imputaion 1987.

Scholler J, Brady TL, Binder-Scholl G, Hwang WT, Plesa G, Hege KM, et al. Decade-Long Safety and Function of Retroviral-Modified Chimeric Antigen Receptor T Cells. Sci Transl Med 2012;4 (132):132ra53.

Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol 2014;5:e45.

Singh N, Frey NV, Grupp SA, Maude SL. CAR T Cell Therapy in Acute Lymphoblastic Leukemia and Potential for Chronic Lymphocytic Leukemia. Curr Treat Options Oncol 2016;17 (6):28.

Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126 (6):2123-38.

Uckun FM. Regulation of Human B-Cell Ontogeny. Blood 1990;76 (10):1908-23.

Uckun FM, Jaszcz W, Ambrus JL, Fauci AS, Gajl-Peczalska K, Song CW, et al. Detailed Studies on Expression and Function of CD19 Surface Determinant by Using B43 Monoclonal Antibody and the Clinical Potential of Anti-CD19 Immunotoxins. Blood 1988;71 (1):13-29.

Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2020;382 (14):1331-42.

Wlelch CA, Peterson I, Bartlett JW, White IR, Marston L, Morris RW, et al. Evaluation of two-fold fully conditional specification multiple imputation for longitudinal electronic health record data. Statistics in Medicine 2014;Statist. Med. 2014, 33 3725–37.

Wolchok JD, Hodi FS, Weber JS, Allison JP, Urba WJ, Robert C, et al. Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma. Ann N Y Acad Sci 2013;1291 (1):1-13.

Yang W, Agrawal N, Patel J, Edinger A, Osei E, Thut D, et al. Diminished expression of CD19 in B-cell lymphomas. Cytometry Part B: Clinical Cytometry 2005;63 (1):28-35.

YESCARTA, Gilead Sciences Ltd. YESCARTA (axicabtagene ciloleucel). Summary of Product Characteristics. Holborn, London, UK. Revised: May. 2019a:

YESCARTA, Kite Pharma Inc. YESCARTA® (axicabtagene ciloleucel) Suspension for Intravenous Infusion. U. S. Prescribing Information. Santa Monica, CA. Revised: May. 2019b:

Zola H, Barclay S, Furness V, Macardle PJ, Neoh SH, Bradley J. B lymphocyte/carcinoma antigen (BLCa): Functional study in B cells. Immunol Cell Biol 1988;66 (Pt 3):199-208.

Zola H, MacArdle PJ, Bradford T, Weedon H, Yasui H, Kurosawa Y. Preparation and characterization of a chimeric CD19 monoclonal antibody. Immunol Cell Biol 1991;69 (Pt 6):411-22.

Zola H, Nikoloutsopoulos A. Effect of recombinant human tumour necrosis factor beta (TNF beta) on activation, proliferation and differentiation of human B lymphocytes. Immunology 1989;67 (2):231-6.

12. 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 MANTLE CELL LYMPHOMA (MCL)

EU PAS Register® number: tbd Study reference number (if applicable):

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

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)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[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.

Comments:

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)	☒	☐	☐	4, 9
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
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))	☐	☐	☒	9
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)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	4, 9
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	4, 9
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	4, 9
	4.2.5 Duration of follow-up	☒	☐	☐	4, 9
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	4, 9

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)	☒	☐	☐	9
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	9.7
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	9.7
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?	☒	☐	☐	4, 8, 9
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4, 9
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)	☒	☐	☐	4, 9
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)	☒	☐	☐	9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9

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)	☒	☐	☐	4, 9

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)	☒	☐	☐	4, 9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4, 9
9.1.3 Covariates and other characteristics?	☒	☐	☐	4, 9
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)	☒	☐	☐	4, 9

Section 9: Data sources	Yes	No	N/A	Section Number
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4, 9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4, 9
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates and other characteristics?	☐	☒	☐	9
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	4, 9
10.3 Are descriptive analyses included?	☒	☐	☐	4, 9
10.4 Are stratified analyses included?	☐	☒	☐	9
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	9

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)	☐	☒	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9

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?	☒	☐	☐	9
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)	☐	☒	☐	9

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?	☐	☐	☒	10

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?	☒	☐	☐	5

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: November 18, 2021 | 6:56:40 AM PST

Signature: PPD

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 (autologous anti-CD19-transduced CD3+ cells) is a gene therapy medicinal product containing autologous T cells genetically modified *ex vivo* using a retroviral vector encoding 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

Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg), with a maximum of 2 x 10^8 anti-CD19 CAR-positive viable T cells.

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

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.

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.

Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus.

Posology

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

A single dose of Tecartus contains 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.

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

Pre-treatment (lymphodepleting chemotherapy)
- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² should be administered intravenously on the 5th, 4th, and 3rd day before infusion of Tecartus.

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 intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic corticosteroids is not recommended (see section 4.5).

Monitoring after infusion
- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity (within 2 hours of travel) 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.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Tecartus should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases (see section 6.6).

Preparation for infusion
- 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 bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- 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 bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should 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 should begin within 30 minutes of thaw completion.

Administration
- For autologous single use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration.
- Verify the patient ID again to match the patient identifiers on the Tecartus 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 bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping.
- After the entire content of the 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.

For instructions on the handling, accidental exposure to and disposal of the medicinal product, 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 should be kept for a period of 30 years.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

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

Reasons to delay treatment

Due to the risks associated with Tecartus treatment, infusion should 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 should be administered again (see section 4.2)

Serological testing

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

Blood, organ, tissue and cell donation

Patients treated with Tecartus should 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 detectable cerebrospinal fluid malignant cells or brain metastases confirmed by imaging. Therefore, the benefit/risk of Tecartus has not been established in this population.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function were excluded from the study. 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 life-threatening, was very commonly observed with Tecartus with a median time to onset of 3 days (range: 1 to 13 days). Patients should 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 should 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 should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

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) should 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 should be managed by standards of critical care and measures such as echocardiography should 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) should 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

CRS Grade *(a)*	Tocilizumab	Corticosteroids
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 (encephalopathy, confusional state or delirium, decreased level of consciousness, seizures, aphasia), which could be life-threatening, were very commonly observed in patients treated with Tecartus with a median time to onset of 8 days (range: 1 to 262 days) (see section 4.8).

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines should 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 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 should be monitored for signs and symptoms of infection before, during and after infusion and treated appropriately. Prophylactic antibiotics should 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 should 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 should 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 should 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 should be taken according standard guidelines.

Hypersensitivity reactions

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

Secondary malignancies

Patients treated with Tecartus may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted 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 should 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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. 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

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 should be advised on the potential risks to the foetus. Pregnancy after Tecartus therapy should be discussed with the treating physician.

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

Breast-feeding

It is unknown whether Tecartus is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should 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 should 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

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 cytokine release syndrome (91%), infections (56%) and encephalopathy (51%).

Serious adverse reactions occurred in 57% 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 65% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (32%) 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%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Tecartus in ZUMA-2. 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 Viral infections Bacterial infections Fungal infections
Blood and lymphatic system disorders		
	Very common	Neutropenia[a] Lymphopenia[a] Leukopenia[a] Anaemia[a] Thrombocytopenia[a] Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome[b] Hypogammaglobulinaemia
Metabolism and nutrition disorders		
	Very common	Hypophosphataemia[a] Decreased appetite
	Common	Dehydration Hypoalbuminemia[a]

System Organ Class (SOC)	Frequency	Adverse reactions
Psychiatric disorders		
	Very common	Insomnia Delirium Anxiety
Nervous system disorders		
	Very common	Encephalopathy Tremor Headache Aphasia Dizziness Neuropathy
	Common	Ataxia Seizure Increased intracranial pressure
Cardiac disorders		
	Very common	Tachycardias Bradycardias
	Common	Non-ventricular arrhythmias
Vascular disorders		
	Very common	Hypotension Hypertension Thrombosis
	Common	Haemorrhage
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Pleural effusion Dyspnoea Hypoxia
	Common	Respiratory failure Pulmonary oedema
Gastrointestinal disorders		
	Very common	Constipation Nausea Diarrhoea Oral pain Abdominal pain Vomiting Dysphagia
	Common	Dry mouth
Skin and subcutaneous tissue disorders		
	Very common	Rash
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction Musculoskeletal pain
Renal and urinary disorders		
	Very common	Renal insufficiency Urine output decreased
General disorders and administration site conditions		
	Very common	Fatigue Oedema Pyrexia Pain Chills
Investigations		
	Very common	Alanine aminotransferase increased[a] Aspartate aminotransferase increased[a] Hypokalaemia[a] Hyponatraemia[a] Hypocalcaemia[a] Blood uric acid increased[a]

System Organ Class (SOC)	Frequency	Adverse reactions
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.		

Description of selected adverse reactions

Cytokine release syndrome
CRS 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.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (99%), hypotension (60%), hypoxia (37%), chills (33%), tachycardia (27%), headache (24%), fatigue (16%), nausea (13%), alanine aminotransferase increased (13%), aspartate aminotransferase increased (12%), diarrhoea (11%), and sinus tachycardia (11%). Serious adverse reactions that may be associated with CRS included hypotension, pyrexia, hypoxia, acute kidney injury, and tachycardia. See section 4.4 for monitoring and management guidance.

Neurologic events and adverse reactions
Neurologic adverse reactions 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.

The most common neurologic adverse reactions included encephalopathy (51%), tremor (38%), aphasia (20%), and delirium (18%). Serious adverse reactions including encephalopathy (26%), aphasia (6%) and seizure (2%) have been reported in patients administered with Tecartus. 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 6% of patients after Tecartus infusion. Infections occurred in 56% of patients in ZUMA-2. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 32% of patients including unspecified pathogen, bacterial, and viral infections in 26%, 6%, 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 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anaemia (17%). See section 4.4 for management guidance.

Hypogammaglobulinaemia
In ZUMA-2, hypogammaglobulinaemia occurred in 16% 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. Based on an initial screening assay, 17 patients tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients were antibody negative at all time points tested. 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, was altered in these patients.

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, ATC code: not yet assigned

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 ZUMA-2, 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 between 4 and 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 is expected 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 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, multicenter 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 central nervous system lymphoma or CNS disorders were ineligible. In total, 74 patients were enrolled (*i.e.* leukapheresed) and 68 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. ITT 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 (ITT) (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 chemotherapy 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.

An 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 ($p < 0.0001$). Results in the ITT set are shown in Table 5.

Table 5 Summary of efficacy results for ZUMA-2

Category	**All leukapheresed [a](ITT) (N = 74)**
Objective response rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]
PR n (%) [95% CI]	18 (24%) [15.1, 35.7]
Duration of response (DOR)[b]	
Median in months [95% CI]	NR [10.4, NE]
Range [c] in months	0.0+, 35.0+
Ongoing responses, CR+PR, CR, n (%) [d]	32 (43%), 30 (41%)
Progression free survival	
Median, months [95% CI]	16.2 [9.9, NE]
Overall survival	
Median, months [95% CI]	NR [24.6, NE]
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.6 [65.1, 84.8]
24 month OS (%) [95% CI]	66.5 [52.8, 77.1]
Median Follow-up in months (min, max)	16.8 [7.2, 37.6]

CI, confidence interval; CR, complete remission; ITT, intent to treat; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.

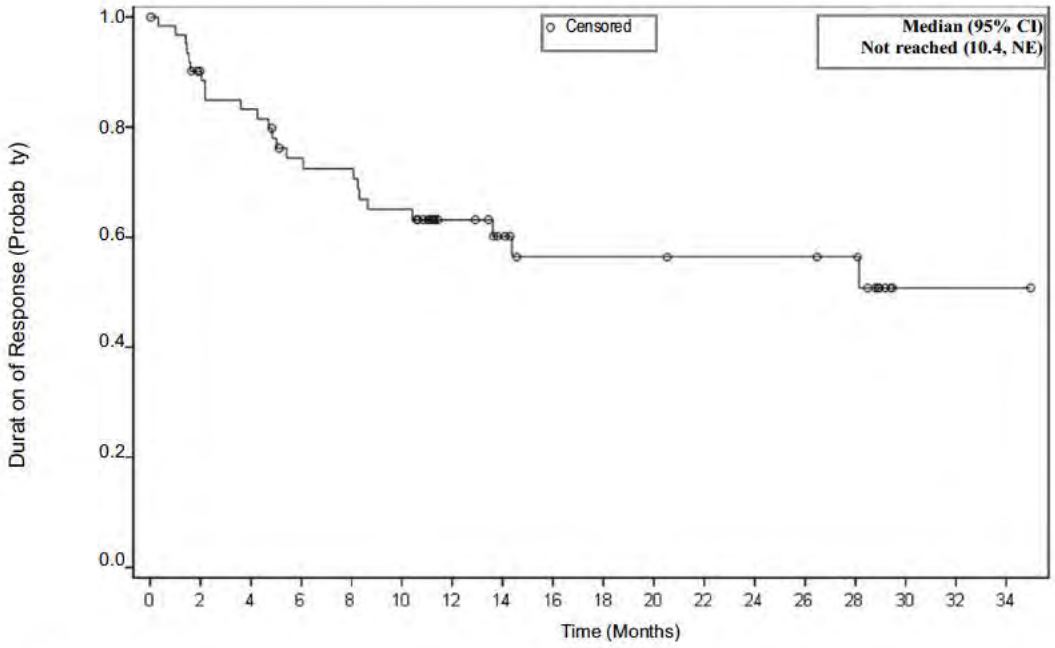
a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

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 intent to treat set



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 mantle cell lymphoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
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

Following infusion of Tecartus, 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.

The number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR) (Table 6).

Table 6 Kinetic parameters of autologous anti-CD19-transduced CD3+ cells 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, 2589.47], 62	0.39 [0.16, 22.02], 5	0.0020
AUC_{0-28} (cells/µL·days) Median [min; max], n	1386.28 [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 patients ≥65 years of age (n=39) and 112.45 cells/µL in patients <65 years of age (n=28). Median anti-CD19 CAR T-cell AUC values were 876.48 cells/µL·day in patients ≥65 years of age and 1640.21 cells/µL·day in patients <65 years of age.

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
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

Tecartus is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ − 150°C).

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

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.

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 for the transport and disposal of the medicinal product

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

Tecartus contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal products or waste material. All material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. 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(S)

EU/1/20/1492/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2020

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. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) 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. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

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

Name and address of the manufacturer(s) 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

To minimise the risks associated with the treatment of Tecartus, the MAH must ensure that hospitals and their associated centres that dispense Tecartus are specially qualified in accordance with the agreed controlled distribution program.

The MAH must ensure on-site, immediate access to at least 1 dose of tocilizumab for each patient as cytokine release syndrome (CRS) management medication prior to treating patients. Hospitals and their associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Tecartus will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals (HCP) involved in the treatment of a patient have completed the educational program.

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
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- 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

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 Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. 30 June 2042

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

This being a conditional marketing authorisation and pursuant to Article 14a(4) 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 September 2025
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.	31 March 2022

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
autologous anti-CD19-transduced CD3+ cells (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) with a target dose of 2 × 10^6 anti-CD19 CAR positive viable T cells/kg.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, 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

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

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

Keep 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

Contains genetically-modified 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:

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
autologous anti-CD19-transduced CD3+ cells (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
autologous anti-CD19-transduced CD3+ cells (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 in adults. It is used when other medicines have stopped working for you (relapsed or refractory mantle cell lymphoma). The medicine is made specially for you from your own white blood cells that have been modified and are known as autologous anti-CD19-transduced CD3+ cells.

Mantle cell lymphoma is a cancer of a part of the immune system (the body's defences). It affects a type of white blood cell called B-lymphocytes. In mantle cell lymphoma, 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 are not to 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 should only be given to you (*autologous use*).

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 will 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 and adolescents
Tecartus should not be used in children and adolescents below 18 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 should 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. 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 should stay close to the hospital where you were treated for at least 4 weeks after Tecartus treatment. Your doctor will recommend that you return to the hospital daily for at least 10 days or that you stay at the hospital as an in-patient for the first 10 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)*, alteration of the blood's ability to form clots: 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.
– Nausea, constipation, diarrhoea, abdominal pain, vomiting, difficulty swallowing.
– 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, decrease output of urine.
– High levels of uric acid seen in blood tests.
– Low levels of sodium, 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.
– Low levels of immunoglobulins seen in blood test, which may lead to infections.
– Increase in liver enzymes seen in blood tests.
– 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.
– Nerve pain.

Common: may affect up to 1 in 10 people
– Low levels of albumin seen in blood tests.
– Excessive bleeding.
– Irregular heartbeat *(arrhythmia)*.
– Loss of control of body movements.
– Dry mouth, dehydration.
– 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.

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.

Keep this medicine out of the sight and reach of children.

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.

This medicine contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal product or waste material. As this

medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product. These measures will help protect the environment.

6. Contents of the pack and other information

What Tecartus contains
The active substance is autologous anti-CD19-transduced CD3+ cells. Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "Tecartus contains sodium".

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

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

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

Ελλάδα
Gilead Sciences Ελλάς M.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

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

Κύπρος
Gilead Sciences Ελλάς M.ΕΠΕ.
Τηλ PPD

Latvija
Gilead Sciences Poland Sp. z o.o.
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

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

Sverige
Gilead Sciences Sweden AB
Tel: PPD

United Kingdom
Gilead Sciences Ltd
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.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

<--->

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 contains genetically-modified cells. Local guidelines on handling of human-derived material applicable for such products should be followed.
- Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.
- Tecartus is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Tecartus may carry a risk of transmitting infectious viruses to healthcare professionals (HCP) handling the product. Accordingly, HCP should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Tecartus to avoid potential transmission of infectious diseases.

Preparation for infusion
- 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 bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- 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 bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should 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 should 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.
- The patient's identity should be matched with the patient identifiers on the infusion bag.
- Tecartus is for autologous use only.
- Tecartus should 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 bag during infusion to prevent cell clumping. All contents of the infusion bag should be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection should 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 should 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.

Disposal of Tecartus

- Any unused medicinal product or waste material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material. Work surfaces and material which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

Accidental exposure

- Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin, removal of contaminated clothes.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.

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 MANTLE CELL LYMPHOMA (MCL)

ORIGINAL, 18 FEBRUARY 2021
VERSION 1.1, 13 JULY 2021
VERSION 1.2, 10 NOVEMBER 2021

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

PPD

Study Director (Printed)
Author

PPD

Signature

November 18, 2021 | 6:56:40 AM PST

Date

PPD

Kite Gilead EU QPPV (Printed)

PPD

Signature

November 18, 2021 | 7:06:31 AM PST

Date

Annex 5. Cellular and Gene Therapy Form

EBMT Cellular and Gene 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 10.1.2).

Advanced Cellular Therapies Form

Pre-treatment Registration

EBMT Unique Identification Code (UIC) ..... **(Please complete if the patient had a previous treatment and is already registered in the database)** ID.IDAA
(if applicable)

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): .... CENTRNR

Main indication for the therapy: INDICAT
- ☐ Primary disease including Infections with or w/o a previous HSCT
- ☐ SCT related complication: GvHD, Graft failure / Prevention, Treatment
- ☐ Both: Primary disease AND Complications

CCI

Contact person..... MEDNAME

PATIENT DATA

Date of this Report: ..... - ..... - .....
DAT1STRE *yyyy mm dd*

Hospital Unique Patient Number or Code (UPN): ..... UPN
Compulsory, registrations will not be accepted without this item. *All treatments performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.*

CCI

Initials: ....._..... (first name(s) _family name(s)) GIVNAME FAMNAME

Date of Birth: ..... - ..... - ..... DATPATBD
yyyy mm dd

Sex: ☐ Male ☐ Female PATSEX
(at birth)

ABO Group .... ABOPAT

Rh factor: ☐ Absent ☐ Present ☐ Not evaluated RHESPAT

Important:
If the patient had a previous Cellular Therapy or a stem cell transplant please make sure that this previous treatment is registered and that the latest follow up was recorded using appriopriate follow up form before proceeding. This is so we can capture relapse data and other events between the transplant/advanced cellular therapy.

INDICATION FOR ADVANCED CELLULAR THERAPY TREATMENT

SELECT ALL THAT APPLY

☐ Treatment of a Primary disease

Date of initial diagnosis: ..... - ..... - ..... IDAABB
yyyy mm dd

DISMCLFD

INDICATE THE PRIMARY DISEASE OF THE PATIENT WHO RECEIVED THIS THERAPY

☐ Primary Acute Leukaemia VACLEUK
- ☐ Acute myelogenous leukaemia (Page 8) AML
- ☐ Precursor lymphoid neoplasms (Page 12) ALLL
- ☐ Other Primary Acute Leukaemia (Page 15)

☐ Chronic Leukaemia VCHRLEUK
- ☐ Chronic Myeloid Leukaemia (CML) (Page 16)
- ☐ Chronic Lymphocytic Leukaemia (CLL) (Page 17)
- ☐ Prolymphocytic Leukaemia (PLL) (Page 18) VCPLSUBC

☐ Lymphoma WHOLYCLS (Page 19)
- ☐ Non Hodgkin
- ☐ Hodgkin Lymphoma HODGKIN (Page 22)

☐ Myelodysplastic syndrome and/or myeloproliferative neoplasm VMDSMPS
- ☐ MDS MDSSTAG (Page 24)
- ☐ MDS/MPN MDSAMPS (Page 27)
- ☐ Myeloproliferative neoplasm VMPS (Page 29)

☐ Myeloma /Plasma cell disorder VPLCEDS1 (Page 31)

☐ Aplastic Anaemia and Other Bone Marrow Failure Syndromes BMFTYPE BMFSACQ (Page 33)

☐ Haemoglobinopathy VHEMOGLO (Page 34)

☐ Solid Tumour VSOLTUMO (Page 35)

☐ Inherited disorders INHDIS (Page 37)
- ☐ Primary immune deficiencies IMMDEF
- ☐ Metabolic disorders VINBERR2
- ☐ Other (Page 38)

☐ Histiocytic disorders HISTIOCY (Page 39)

☐ Autoimmune disease VAUTOIM1
- ☐ Connective VAUTOIM2 (Page 40)
- ☐ Vasculitis VAUTOIM3 (Page 40)
- ☐ Arthritis VAUTOIM4 (Page 41)
- ☐ Neurological (MS, etc) VAUTOIM5 (Page 41)
- ☐ Haematological VAUTOIM6 (Page 41)
- ☐ Bowel disorder VAUTOIM7 (Page 42)
- ☐ Other (Diabetes, etc.) VAUTOIM8 (Page 42)

☐ Infections INFTRTAIM (Page 44)

Other primary disease (Page 43)
(check disease classification sheets for options)
☐ Specify ..... VDIAGTX

Complete and attach the relevant DISEASE CLASSIFICATION SHEET as per the page numbers indicated above, including the date of Advanced Cellular therapy and disease status at treatment, then continue from here.

☐ **Treatment or prevention of complications derived from a previous treatment including HSCT or expected from a subsequent treatment**

➡ **Please make sure that MedAB form was registered for the Transplant indicated above and that an Annual follow up form is recorded before proceeding. This is so we can capture relapse data and other events between the transplant/advanced cellular therapy.**

☐ **Other indication, specify:**_____ VDIAGTX

Please, contact the Registry helpdesk before proceeding: PPD

Date of the cell collection (apheresis) ..... - ..... - ..... IDAABC
If more than one collection use the date of the first collecition
yyyy mm dd

BASIC INFORMATION ON THE ADVANCED CELLULAR THERAPY

Clinical setting: CTCLNSETTN
(Select only one)

- ☐ As per marketing approval / Standard of care
- ☐ Institutional guidelines
- ☐ Hospital exemption
- ☐ Compassionate use / Accelerated access

PASSSTUDY
Is patient enrolled in a IV / PASS study? ☐ No ☐ Yes

☐ Investigational DP / Clinical trial (CT)

CTCLNPHASE	Phase	☐ 1	☐ 1/2	☐ 2	☐ 2/3	☐ 3
CTCLNBLIND	Blind trial	☐ No	☐ Yes			
CTCLNRAND	Randomised trial	☐ No	☐ Yes			

Eudract number…….. USA CT number…… UMIN CT number……
CTEUDRANUM CTUSANUMB CTJAPANUMB *(Japan)*

☐ Tick here if you want this registration hidden until ..... - ..... - .....
(indicate by which date the registration can be made available for research) yyyy mm dd
HIDEREG DATHIDEREG

Cell origin CETHORIG

- ☐ Autologous -> Go to page 6 *CELLULAR THERAPY INFUSION UNIT*
- ☐ Allogeneic
  - This product is manufactured from: COMMANFPRD
    - ☐ A known donor never used before to treat this patient -> Complete DONOR section on page 5
      (eg. from a Donor registry or related)
    - ☐ A donor that is already registered as part of a previous treatment -> Skip DONOR section on page 5
    - ☐ An unknown donor with not available data -> Skip DONOR section on page 5
      (eg. from a commercial product)

Donor

Donor information

Global registration identifier for donors..... ..... GRID

HLA match type DONRL

- ☐ HLA-identical sibling *(may include non-monozygotic twin)*
- ☐ Syngeneic *(monozygotic twin)*
- ☐ HLA-matched other relative
- ☐ HLA-mismatched relative: Degree of mismatch ALLMISRL ☐ 1 HLA locus mismatch ☐ ≥ 2 HLA loci mismatch

Donor ID given by the treating centre DONORID2

☐ Unrelated donor

ION code of the Donor Registry or Cord Blood Bank (*up to 4 characters*) .... IONDR

Name of donor registry or Cord Blood Bank .... DONREGID CBBANKID

Donor ID given by the Donor Registry or the Cord Blood Bank ....DONORID DONORID1

Eurocord code for the Cord Blood Bank *(complete only if applicable)* ..... EUROCID

Date of birth : .... - .... - .... DATDONBD *yyyy mm dd*

OR

Age at time of donation..... *years* ..... *months* *(if date of birth not provided)* AGEDONYR AGEDONMTH

Donor Sex ***(at birth)*** ☐ Male ☐ Female DONSEX

CELLULAR THERAPY INFUSION UNIT(S)

Was it planned to administer more than one cell infusion unit during the treatment

☐ No MNYINFUSED

☐ Yes: Indicate number of cell infusion units for this CT treatment NUMCINFUNIT

Cellular Therapy Infusion Unit – Description and collection

If more than one cell infusion unit, replicate this section for each one of them

IDENTIFICATION

Name of the manufacturer ..... ☐ N/A NAMCTIMNFCD NAMCTIMNFSP
Enter Hospital name if it isn't a commercial product

Name of the product *(if applicable)* ..... NAMCTIPKGCD NAMCTIPKGSP

TISSUE SOURCE *(check all that apply)*

☐ Bone Marrow CIUBMRRW ☐ Peripheral Blood CIUPFRBLD ☐ Umbilical cord Blood CIUUMBCBLD

☐ Tumour CIUTUMRTIS ☐ Other, specify ..... CIUOTHSRC CIUOTHRSPC

CELL TYPES

☐ CD3+ lymphocytes CIUCELCD3 ☐ CD4+ lymphocytes CIUCELCD4 ☐ CD8+ lymphocytes CIUCELCD8

☐ Gamma-Delta T-cells CIUGADETCELL ☐ Regulatory T-cells REGTCELLS ☐ Mesenchymal CIUCELMESN

☐ Dendritic cells CIUCELDNDR ☐ CD34+ CIUCELCD34 ☐ NK cells CIUCELNK

☐ Mononuclear cells (DLI) CIUCELMON ☐ Other, specify ..... CIUCELOTHR CIUCELOTSPC

COLLECTION PROCEDURE

Date of the collection ..... - ..... - ..... CIUCOLLDAT
If more than one collection use the date of the first collecition
yyyy mm dd

Number of collections ……
CIUNUMCOLL

Survival Status

VPATSTAT

☐ Alive ☐ Dead

If dead: Main Cause of Death *(check only one main cause)*: VCAUSDTH

- ☐ Relapse or Progression/Persistent disease
- ☐ Secondary malignancy
- ☐ Cellular Therapy related (indicate all toxicity related causes of death below)
- ☐ HSCT Related Cause (only if patient previously had a transplant / indicate all toxicity related causes of death below)
- ☐ Unknown
- ☐ Other: ..... DEACSBMU

Indicate toxicity related causes of death *(check as many as appropriate)*:

- ☐ GVHD VCSDTGVH
- ☐ Cytokine release syndrome VCSDTCRS
- ☐ Interstitial pneumonitis VCSDTINP
- ☐ Pulmonary toxicity VCSDTPTX
- ☐ Infection: VCSDTINF
  - ☐ bacterial VCSDTBAC
  - ☐ viral VCSDTVIR
  - ☐ fungal VCSDTFUN
  - ☐ parasitic VCSDTPAR
- ☐ Rejection/Poor graft function VCSDTREJ
- ☐ History of severe Veno occlusive disorder (VOD) VCSDTVOD
- ☐ Haemorrhage VCSDTHMR
- ☐ Cardiac toxicity VCSDTCTX
- ☐ Central nervous system (CNS) toxicity VCSDTCNS
- ☐ Gastrointestinal (GI) toxicity VCSDTGIT
- ☐ Skin toxicity VCSDTSKI
- ☐ Renal failure VCSDTREN
- ☐ Multiple organ failure VCSDTMOF

☐ Other:..... DEACSBMR

END OF PRE-TREATMENT REGISTRATION

ACUTE LEUKAEMIAS VACLEUK

Acute Myeloid Leukaemia (AML) (1 of 4)

(main disease code 1)

Disease

Classification: AML

AML with recurrent genetic abnormalities

- ☐ AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- ☐ AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- ☐ Acute promyelocytic leukaemia with t(15;17)(q22;q12); PML/RARA
- ☐ AML with t(9;11) (p22;q23); MLLT3-MLL
- ☐ AML with t(6;9) (p23;q24); DEK-NUP214
- ☐ AML with inv(3) (q21;q26.2) or t(3;3) (q21;q26.2); RPN1-EVI1
- ☐ AML (megakaryoblastic) with t(1;22) (p13;q13); RBM15-MKL1
- ☐ AML with myelodysplasia related changes (old "Acute leukaemia transformed from MDS or MDS/MPN"):

  Was there a previous diagnosis of MDS or MDS/MPN? PREVMDS

  - ☐ No → *Continue to PREDISPOSING CONDITION below*
  - ☐ Yes → *Fill in the* MYELODYPLASTIC SYNDROME (MDS) (page 24) or MDS/MPN (page 27) *until status at Cellular Therapy, then continue with PREDISPOSING CONDITION below*

- ☐ AML with 11q23 (MLL) abnormalities
- ☐ AML with BCR-ABL1
- ☐ AML with mutated NPM1
- ☐ AML with biallelic mutation of CEBPA
- ☐ AML with mutated RUNX1

AML not otherwise categorised (NOS)

- ☐ AML with minimal differentiation (FAB M0)
- ☐ AML without maturation (FAB M1)
- ☐ AML with maturation (FAB M2)
- ☐ Acute myelomonocytic leukaemia (FAB M4)
- ☐ Acute monoblastic and monocytic leukaemia (FAB M5)
- ☐ Acute erythroid leukaemia (FAB M6)
- ☐ Acute megakaryoblastic leukaemia (FAB M7)
- ☐ Acute basophilic leukaemia
- ☐ Acute panmyelosis with myelofibrosis

- ☐ Myeloid sarcoma
- ☐ Myeloid proliferations related to Down syndrome
- ☐ Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- ☐ Therapy related myeloid neoplasia *(old "Secondary Acute Leukaemia")*

  Related to prior treatment but NOT after a previous diagnosis of MDS or MPN

PREDISPOSING CONDITION?

Did the recipient have a predisposing condition prior to the diagnosis of leukaemia? VPRECOND VPREDISP

☐ No ☐ Yes:
- ☐ Aplastic anaemia
- ☐ Bloom syndrome
- ☐ Fanconi anaemia
- ☐ Unknown

Donor cell leukaemia?

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT TRANSPLANT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown RPDRGRAD

ACUTE MYELOID LEUKAEMIA (AML) (2 of 4)

Chromosome analysis at diagnosis (All methods including FISH)
Chromosome / genetic analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

☐ Normal VCHROMOS

☐ Abnormal:

Complex karyotype: ☐ No ☐ Yes ☐ Unknown MORE3AB
(3 or more abnormalities)

Monosomal karyotype: ☐ No ☐ Yes ☐ Unknown MONOSKAR
(≥ 2 autosomal monosomies or 1 autosomal monosomy + at least 1 structural abnormality)

☐ Unknown

You can transcribe the complete karyotype: .....

CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC

t(15;17) CHROPRES	☐ Absent	☐ Present	☐ Not evaluated
t(8;21)	☐ Absent	☐ Present	☐ Not evaluated
inv(16)/ t(16;16)	☐ Absent	☐ Present	☐ Not evaluated
11q23 abnormality type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if 11q23 abnormality is Present:			
t(9;11)	☐ Absent	☐ Present	☐ Not evaluated
t(11;19)	☐ Absent	☐ Present	☐ Not evaluated
t(10;11)	☐ Absent	☐ Present	☐ Not evaluated
t(6;11)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(11q23), specify: _____ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
3q26 (EVI1) abnormality type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if 3q26 (EVI1) abnormality is Present:			
inv(3) / t(3;3)	☐ Absent	☐ Present	☐ Not evaluated
t(2;3)(p21;q26)	☐ Absent	☐ Present	☐ Not evaluated
Other (3q26)/EVI1 rearrangement, specify: _____ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
t(6;9)	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if above abn 5 is Present:			
del (5q)	☐ Absent	☐ Present	☐ Not evaluated
monosomy 5	☐ Absent	☐ Present	☐ Not evaluated
Add(5q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(5q); please specify: _____ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if abn 7 is Present:			
del(7q)	☐ Absent	☐ Present	☐ Not evaluated
monosomy 7	☐ Absent	☐ Present	☐ Not evaluated
add(7q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(7q); please specify: _____ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
-17	☐ Absent	☐ Present	☐ Not evaluated
Abn(17p)	☐ Absent	☐ Present	☐ Not evaluated
t(1;22)	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Other, specify..... CHRMABND	☐ Absent	☐ Present	

ACUTE MYELOID LEUKAEMIA (AML) (3 of 4)

Molecular Markers at Diagnosis

Molecula analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

Molecular marker analysis at diagnosis MOLEBIO

☐ Absent ☐ Present ☐ Unknown

Indicate below those **markers** that have been **evaluated** and whether they were **Absent** or **Present**

IDAABECL MOLPRES

AML1-ETO (RUNX1/RUNXT1) *Molecular product of t(8;21)*	☐ Absent	☐ Present	☐ Not evaluated
CBFB-MYH11 *Molecular product of inv(16)(p13.1;q22) or (16;16)(p13.1;q22)*	☐ Absent	☐ Present	☐ Not evaluated
PML-RARα *Molecular product of t(15;17)*	☐ Absent	☐ Present	☐ Not evaluated

MLL-rearrangement/mutation: *Fill only if* 11q23 abnormality *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
MLLT3(AF9)-MLL *molecular product of t(9;11)(p22;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-PTD (partial tandem duplication)	☐ Absent	☐ Present	☐ Not evaluated
MLLT4(AF6)-MLL *molecular product of t(6;11)(q27;q23)*	☐ Absent	☐ Present	☐ Not evaluated
ELL-MLL: *molecular product of t(11;19)(q23;p13.1)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT1(ENL)-MLL: *molecular product of t(11;19)(q23;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT10(AF10)-MLL: *molecular product of t(10;11)(p12;q23)*	☐ Absent	☐ Present	☐ Not evaluated
Other MLL-rearrangement, specify: …… MOLOTHER	☐ Absent	☐ Present	☐ Not evaluated

DEK-NUP214(CAN) *molecular product of translocation t(6;9)(p23;q34)*	☐ Absent	☐ Present	☐ Not evaluated
RPN1-EVI1 *molecular product of inv(3)(q21q26.2) or t(3;3)(q21q26.2)*	☐ Absent	☐ Present	☐ Not evaluated
RBM15-MKL1 *molecular product of translocation t(1;22)(p13;q13)*	☐ Absent	☐ Present	☐ Not evaluated
NPM1 mutation	☐ Absent	☐ Present	☐ Not evaluated
CEBPA mutation	☐ Absent	☐ Present	☐ Not evaluated
FLT3-ITD *(internal tandem duplication)*	☐ Absent	☐ Present	☐ Not evaluated
DNMT3A	☐ Absent	☐ Present	☐ Not evaluated
ASXL1	☐ Absent	☐ Present	☐ Not evaluated
TP53	☐ Absent	☐ Present	☐ Not evaluated
RUNX1	☐ Absent	☐ Present	☐ Not evaluated
c-KIT	☐ Absent	☐ Present	☐ Not evaluated
Other, specify…… MOLOTHER	☐ Absent	☐ Present	☐ Not evaluated

ACUTE LEUKAEMIAS
Primary Acute Myeloid Leukaemia (AML) (4 of 4)

Involvement at Diagnosis

Was Involvement assessed ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

Involvement at diagnosis IDAABECK

Bone marrow	☐ No	☐ Yes	☐ Not evaluated	ORGANOT
CNS	☐ No	☐ Yes	☐ Not evaluated	
Testes/ovary	☐ No	☐ Yes	☐ Not evaluated	
Other	☐ No	☐ Yes, specify		ORGANOTS

Status at Cellular Therapy

STATUS VDISESTA	NUMBER	TYPE OF REMISSION	
☐ Primary induction failure	VNUMSTM		
☐ Complete haematological remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher	CYTOGENETIC REMISSION ☐ No VCYTOGRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR REMISSION ☐ No VMOLECRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Relapse	☐ 1st ☐ 2nd ☐ 3rd or higher		

* *No abnormalities detected prior to this time point*

Date of last relapse before this Cellular Therapy: ..... DATLRLPS
(If applicable) *yyyy - mm - dd*

ACUTE LEUKAEMIAS

Precursor lymphoid neoplasms *(previously ALL)* (main disease code 1)

Disease

Classification: ALLL

- ☐ B lymphoblastic leukaemia/lymphoma NOS *(old Precursor B-cell ALL)*
  - ☐ with t(9;22)(q34;q11.2); *BCR-ABL1*
  - ☐ with t(v;11q23); *MLL* rearranged
  - ☐ with t(12;21)(p13;q22); *TEL-AML1 (ETV-RUNX1)*
  - ☐ with hyperdiploidy
  - ☐ with hypodiploidy
  - ☐ with t(5;14)(q31;q32); *IL3-IGH*
  - ☐ with t(1;19)(q23;p13.3); *E2A-PBX1*
  - ☐ Not otherwise specified (NOS)
  - ☐ Other._____
- ☐ T lymphoblastic leukaemia/lymphoma *(old Precursor T-cell ALL)*

Secondary Origin?

Secondary origin

Related to prior exposure to therapeutic drugs or radiation ☐ No VSECORIG ☐ Yes ☐ Unknown

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown

RPDRGRAD

PRECURSOR LYMPHOID NEOPLASMS (previously ALL)

Chromosome Analysis at Diagnosis

Chromosome / genetic analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

Chromosome analysis at diagnosis (All methods including FISH) VCHROMOS

☐ Normal ☐ Abnormal ☐ Unknown

MORE3AB If abnormal:

Complex karyotype: ☐ No ☐ Yes ☐ Unknown
(3 or more abnormalities)

CHRMABND

You can transcribe the complete karyotype: .....

OR

Indicate below which abnormalities have been **evaluated** and whether they were **Absent** or **Present** IDAABECC CHROPRES

t(9;22)	☐ Absent	☐ Present	☐ Not evaluated
11q23 abnormalities *Fill only if* 11q23 abnormalities *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
t(4;11)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(11q23); please specify: _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
t(12;21)	☐ Absent	☐ Present	☐ Not evaluated
hyperdiploidy (>46 chromosomes) *Fill only if* hyperdiploidy *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
50 – 66 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Trisomy: Specify extra chromosome _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
Other hyperdiploid karyotype ..... number of chromosomes ..... NRCHROMS	☐ Absent	☐ Present	☐ Not evaluated
Hypodiploidy (<46 chromosomes): *Specify the number of missing chromosomes:*	☐ Absent	☐ Present	☐ Not evaluated
Low hypodiploid, 32-39 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Near haploid, 24-31 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Monosomy. Specify: ..... CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
Other. number of chromosomes ..... NRCHROMS	☐ Absent	☐ Present	☐ Not evaluated
t(5;14)(q31;q32)	☐ Absent	☐ Present	☐ Not evaluated
t(1;19)	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Other, specify..... CHRMABND	☐ Absent	☐ Present	☐ Not evaluated

PRECURSOR LYMPHOID NEOPLASMS (previously ALL)

Molecular Markers at Diagnosis

Molecula analysis done? ☐ No *(skip to WHITE BLOOD CELL COUNT)* ☐ Yes *(continue with this section)*

Marker analysis MOLEBIO
☐ Absent ☐ Present ☐ Unknown

Indicate below those **markers** that have been **evaluated** and whether they were **Absent** or **Present** IDAABECL MOLPRES

BCR-ABL *molecular product of t(9;22)(q34;q11.2)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-rearrangement/mutation	☐ Absent	☐ Present	☐ Not evaluated
Fill only if MLL-rearrangement/mutation *is Present:*			
AFF1(AF4)-MLL *molecular product of t(4;11)(q21;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT1(ENL)-MLL *molecular product of t(11;19)(q23;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT3(AF9)-MLL *molecular product of t(9;11)(p22;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MOLOTHER Other MLL-rearrangement, specify:	☐ Absent	☐ Present	☐ Not evaluated
TEL(ETV6)-AML1(RUNX1) *molecular product of t(12;21)(p13;q22)*	☐ Absent	☐ Present	☐ Not evaluated
IL3-IGH *molecular product of translocation t(5;14)(q31;q32)*	☐ Absent	☐ Present	☐ Not evaluated
TCF3-PBX1 *Molecular product of translocation (1;19)(q23 ;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
IKZF1 (IKAROS)	☐ Absent	☐ Present	☐ Not evaluated
NOTCH1 & FBXW7	☐ Absent	☐ Present	☐ Not evaluated
Other, specify..... MOLOTHER	☐ Absent	☐ Present	☐ Not evaluated

White blood cell count at diagnosis (10^9/l): .... - .... ☐ Not available / unknown WBCD

Status at Cellular Therapy

STATUS VDISESTA	NUMBER VNUMSTM	TYPE OF REMISSION	
		CYTOGENETIC REMISSION	MOLECULAR REMISSION
☐ Primary induction failure			
☐ Complete haematological remission (CR) ☐ CRi (CR with incomplete haematologic recovery)	☐ 1st ☐ 2nd ☐ 3rd or higher	☐ No VCYTOGRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	☐ No VMOLECRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Relapse	☐ 1st ☐ 2nd ☐ 3rd or higher		

* *No abnormalities detected prior to this time point*

ACUTE LEUKAEMIAS

Other Acute Leukaemias (main disease code 1)

Disease

Classification: VACLEUK

Acute Leukaemias of ambiguous lineage

- ☐ Acute undifferentiated leukaemia
- ☐ Mixed phenotype NOS
  - ☐ Mixed phenotype B/myeloid, NOS
  - ☐ Mixed phenotype T/myeloid, NOS
- ☐ Natural killer (NK)- cell lymphoblastic leukaemia/lymphoma
- ☐ Other, specify.....

Secondary Origin?

Secondary origin

Related to prior exposure to therapeutic drugs or radiation ☐ No VSECORIG ☐ Yes ☐ Unknown

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown

RPDRGRAD

Status at Cellular Therapy

STATUS VDISESTA	NUMBER VNUMSTM	TYPE OF REMISSION	
☐ Primary induction failure			
☐ Complete haematological remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher	CYTOGENETIC REMISSION ☐ No VCYTOGRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR REMISSION ☐ No VMOLECRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Relapse	☐ 1st ☐ 2nd ☐ 3rd or higher		

* *No abnormalities detected prior to this time point*

CHRONIC LEUKAEMIAS
Chronic Myelogenous Leukaemias (CML) (main disease code 2)

Disease

Classification: *(CMML is not a CML but MDS/MPN)* IDAABECC CHROPRES
At least one investigation must be positive

Translocation (9;22)	☐ Absent	☐ Present	☐ Not evaluated
bcr-abl	☐ Absent	☐ Present	☐ Not evaluated

Status at Cellular Therapy

PHASE VDISESTA	NUMBER VNUMSTM	TYPE OF REMISSION		
		HAEMATOLOGICAL	CYTOGENETIC	MOLECULAR
☐ Chronic phase (CP)	☐ 1st ☐ 2nd ☐ 3rd or higher	☐ Yes VREMTRAN ☐ No ☐ Not evaluated ☐ Unknown	☐ Yes VCYTOGRE ☐ No ☐ Not evaluated ☐ Not applicable* ☐ Unknown	☐ Yes VMOLECRE ☐ No ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Accelerated phase	☐ 1st ☐ 2nd ☐ 3rd or higher			
☐ Blast crisis	☐ 1st ☐ 2nd ☐ 3rd or higher			

* *No abnormality detected prior to this time point*

CHRONIC LEUKAEMIAS
Chronic Lymphocytic leukaemias (CLL) (main disease code 2)

Disease

Classification: VCLLSUBC

☐ Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma

☐ Richter's syndrome VCLLSUBC

Transformed from a previously known CLL VSECORIG

☐ Yes: Date of original CLL diagnosis .... - .... - .... IDAABB
yyyy mm dd

☐ No: Primary Richter *(without previous known diagnosis of CLL)*

CYTOGENETICS AT DIAGNOSIS (ALL METHODS INCLUDING FISH)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with this section)*

☐ Done: Normal ☐ Done: Abnormal ☐ Unknown VCHROMOS
IDAABECC CHROPRES

CLL and Richter			
Trisomy 12	☐ Absent	☐ Present	☐ Not evaluated
Del 13q14	☐ Absent	☐ Present	☐ Not evaluated
Del 11q22-23	☐ Absent	☐ Present	☐ Not evaluated
del(17p)	☐ Absent	☐ Present	☐ Not evaluated
Other, specify .....CHRMABND	☐ Absent	☐ Present	☐ Not evaluated

MOLECULAR MARKERS AT DIAGNOSIS MOLEBIO MOLPRES

Molecula analysis done? ☐ No *(skip next question)* ☐ Yes *(continue with the next question)*

TP53 mutations ☐ Absent ☐ Present ☐ Not evaluated ☐ unknown

Status at Cellular Therapy

STATUS VDISESTA	MINIMAL RESIDUAL DISEASE (MRD) *(by FACS or PCR)* VMFACPCR
☐ Complete remission (CR) ☐ Partial response (PR)	☐ Negative ☐ Positive ☐ Not evaluated
☐ Stable disease (SD) ☐ Relapse *(untreated)* ☐ Progression (PD) ☐ Never treated	

CHRONIC LEUKAEMIAS
Prolymphocytic and Other leukaemias (PLL & Other) (main disease code 2)

Disease

☐ Prolymphocytic Leukaemia (PLL) VCPLSUBC
- ☐ PLL, B-cell
- ☐ PLL, T-cell

☐ Hairy Cell Leukaemia VCLLSUBC

☐ Other leukaemia, specify:_____ VDIAGTX

T-CELL PLL ONLY - IMMUNOPHENOTYPING of T-cells at diagnosis

NOTE: TdT *(Terminal deoxynucleotidyl transferase)* must be negative

CD4+	☐ No	☐ Yes	☐ Not evaluated	VPIMMCD4
CD8+	☐ No	☐ Yes	☐ Not evaluated	VPIMMCD8

PLL ONLY - CYTOGENETICS AT DIAGNOSIS (ALL METHODS INCLUDING FISH) VCHROMOS

Chromosome / genetic analysis done? ☐ No *(skip to LYMPHOCYTE COUNT)* ☐ Yes *(continue with the next question)*

☐ Done: Normal ☐ Done: Abnormal ☐ Unknown VCHROMOS

IDAABECC CHROPRES

inv(14)/ t(14:14) (q11q32)	☐ Absent	☐ Present	☐ Not evaluated
del(14)(q12)	☐ Absent	☐ Present	☐ Not evaluated
t(11:14)(q23;q11)	☐ Absent	☐ Present	☐ Not evaluated
t(7:14)(q35:q32.1)	☐ Absent	☐ Present	☐ Not evaluated
t(X:14)(q35:q11)	☐ Absent	☐ Present	☐ Not evaluated
idic(8) (p11)	☐ Absent	☐ Present	☐ Not evaluated
Other, specify .....CHRMABND	☐ Absent	☐ Present	☐ Not evaluated

Lymphocyte count ..... 10^9 cells/L LYMPHOC

Status at Cellular Therapy

STATUS VDISESTA
- ☐ Complete remission (CR)
- ☐ Partial remission (PR)
- ☐ Stable disease (SD)
- ☐ Untreated Relapse
- ☐ Progression (PD)
- ☐ Never treated

LYMPHOMAS
B-Cell Non Hodgkin Lymphomas (NHL) (main disease code 3)

Disease

Mature B-cell Neoplasms WHOLYCLS	Complete only for corresponding classifications from the left side
☐ Splenic marginal zone lymphoma	
☐ Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT)	
☐ Nodal marginal zone lymphoma	
☐ Lymphoplasmacytic lymphoma (LPL)	
☐ Waldenstrom macroglobulinaemia (LPL with monoclonal IgM)	**International Prognostic Scoring System for Waldenström's Macroglobulinemia (ISSWM)** IPROSWM ☐ Low risk (0-1 score points except age >65) ☐ High risk (3-5) ☐ Intermediate risk (score 2 or age >65 alone) ☐ Not evaluated
☐ Follicular lymphoma	**Grading** DISHGRD ☐ Grade I ☐ Grade II ☐ Grade IIIa ☐ Not evaluated **Prognostic score (FLIPI)** PROSCORE ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated
☐ Primary cutaneous follicle centre lymphoma	
☐ Mantle cell lymphoma	**Grading** GRADETYP2 ☐ indolent ☐ classical ☐ pleomorphic ☐ blastoid ☐ Not evaluated **Prognostic score (MIPI)** PROSCORE ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated PRINDXKI KI-67 (Proliferation index) __ __ % Positive ☐ Not evaluated
☐ Diffuse large B-cell lymphoma (DLBCL), (NOS)	**International Prognostic Index (IPI)** IPROINDEX ☐ Low risk (0-1 score points) ☐ Low-Intermediate risk (2) ☐ High-intermediate risk (3) ☐ High risk (4 or 5) ☐ Not evaluated KI-67 (Proliferation index) __ __ % Positive ☐ Not evaluated PRINDXKI
☐ T-cell/hystiocyte rich large B cell lymphoma	
☐ Primary DLBCL of the CNS	
☐ Primary cutaneous DLBCL, leg type	
☐ EBV positive DLBCL of the elderly	
☐ DLBCL associated with chronic inflammation	
☐ Lymphomatoid granulomatosis	
☐ Primary mediastinal (thymic) large B-cell lymphoma	
☐ Intravascular large B-cell lymphoma	
☐ ALK positive large B-cell lymphoma	
☐ Plasmablastic lymphoma	
☐ Large B-cell lymphoma arising in HHV8- associated multicentric Castleman disease	
☐ Primary effusion lymphoma (PEL)	
☐ Burkitt lymphoma (BL)	
☐ High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	
☐ High-grade B-cell lymphoma, NOS	
☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Intermediate DLBCL/HD)	
☐ Other B-cell, specify:_____ VDIAGTX	

Transformed from another type of lymphoma at the event leading to this Cellular Therapy? VSECORIG

☐ No

☐ Yes: Date of original diagnosis .... - .... - .... IDAABB

yyyy mm dd

Indicate the type of the original lymphoma ..... WHOLYCLS

☐ Unknown

Selected B-Cell Non Hodgkin Lymphomas (NHL)

⇨ **Please complete this section for patients given treatment for the following types of B-cell NHL:**

- **Mantle cell lymphoma**
- **Waldenstrom macroglobulinaemia**
- **All DLBCL** (see list below)

All DLBCL, include
- Diffuse large B-cell lymphoma (DLBCL), (NOS)
- T-cell/hystiocyte rich large B cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8- associated multicentric Castleman disease
- Primary effusion lymphoma (PEL)
- Burkitt lymphoma (BL)
- High-grade B-cell lymphomas
- Intermediate DLBCL/HD

Chromosome Analysis at any time before CT

Chromosome / genetic analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

☐ Normal ☐ Abnormal ☐ Unknown VCHROMOS

If abnormal, please complete this table according to the type of lymphoma diagnosed IDAABECC CHROPRES FISHANA

	Abnormality	Absent	Present	FISH used	Not evaluated
Mantle cell lymphoma *or* Waldenstrom macroglobulinaemia	del 17p	☐	☐	☐ No ☐ Yes	☐
All DLBCL	t(2;8)	☐	☐	☐ No ☐ Yes	☐
	t(8;14)	☐	☐		☐
	t(8;22)	☐	☐		☐
	t(14;18)	☐	☐		☐
	myc rearrangement	☐	☐		☐
	BCL-2 rearrangement	☐	☐		☐
	BCL-6 rearrangement	☐	☐		☐

Molecular Markers at any time before CT

Molecular analysis done? ☐ No *(skip to the next section)* ☐ Yes *(continue with the next question)*

☐ Present ☐ Absent ☐ Unknown MOLEBIO

IDAABECL MOLPRES

Provide answers according to the type of lymphoma diagnosed

	Marker	Present	Absent	Not evaluated
Mantle cell lymphoma	TP53 mutation	☐	☐	☐
All DLBCL	*myc* rearrangement	☐	☐	☐
	BCL-2 rearrangement	☐	☐	☐
	BCL-6 rearrangement	☐	☐	☐

Immunophenotyping / immunohistochemistry at any time before CT

Immunophenotyping tested ☐ Yes ☐ No ☐ Unknown

Provide answers according to the type of lymphoma diagnosed VIMMUNOP IDAABECB IMMNDONE

	Phenotype	Present	Absent	Not evaluated
Mantle cell lymphoma	SOX11	☐	☐	☐
All DLBCL	MYC	☐	☐	☐
	BCL-2	☐	☐	☐
	BCL-6	☐	☐	☐

LYMPHOMAS
T-Cell Non Hodgkin Lymphomas (NHL) (main disease code 3)

Disease

Mature T-cell & NK-cell Neoplasms WHOLYCLS

- ☐ T-cell large granular lymphocytic leukaemia
- ☐ Aggressive NK-cell leukaemia
- ☐ Systemic EBV positive T-cell lymphoproliferative disease of childhood
- ☐ Hydroa vacciniforme-like lymphoma
- ☐ Adult T-cell leukaemia/lymphoma
- ☐ Extranodal NK/T-cell lymphoma, nasal type
- ☐ Enteropathy-associated T-cell lymphoma
- ☐ Monomorphic epitheliotropic intestinal T-cell lymphoma
- ☐ Intestinal T-cell lymphoma NOS
- ☐ Hepatosplenic T-cell lymphoma
- ☐ Subcutaneous panniculitis-like T-cell lymphoma

Complete only for corresponding classifications from the left side

- ☐ Mycosis fungoides (MF)
- ☐ Sézary syndrome

ISCL/EORTC STAGE STAGE

☐ IA ☐ IB ☐ IIA ☐ IIB ☐ IIIA ☐ IIIB ☐ IVA1 ☐ IVA2 ☐ IVB ☐ Not evaluated

- ☐ Lymphomatoid papulosis
- ☐ Primary cutaneous anaplastic large cell lymphoma
- ☐ Primary cutaneous gamma-delta T-cell lymphoma
- ☐ Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- ☐ Primary cutaneous CD4 positive small/medium T-cell lymphoma
- ☐ Peripheral T-cell lymphoma, NOS (PTCL)
- ☐ Angioimmunoblastic T-cell lymphoma
- ☐ Anaplastic large-cell lymphoma (ALCL), ALK-positive
- ☐ Anaplastic large-cell lymphoma (ALCL), ALK-negative
- ☐ Other T-cell, specify:_____ VDIAGTX

International Prognostic Index (IPI) IPROINDEX

- ☐ Low risk (0-1 score points)
- ☐ Low-Intermediate risk (2)
- ☐ High-intermediate risk (3)
- ☐ High risk (4 or 5)
- ☐ Not evaluated

LYMPHOMAS
Hodgkin Lymphomas (main disease code 3)

Classification: WHOLYCLS HODGKIN

- ☐ Nodular lymphocyte predominant
- ☐ Classical predominant
- ☐ Other, specify:_____ VDIAGTX

LYMPHOMAS
Immunodeficiency-associated lymphoproliferative disorders (including PTLD)
(main disease code 3)

Classification: WHOLYCLS

- ☐ 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:
    - Cell type: ☐ B-cell type ☐ T-/NK-cell type
  - ☐ Classical Hodgkin lymphoma PTLD
- ☐ Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

Did the disease result from a previous solid organ transplant? PREVORGTRAN

☐ No ☐ Yes:

Date of the transplant: ..... (yyy) - ..... (mm) - ..... (dd) DATEORGANT

Type of transplant: ☐ Renal ☐ Cardiac ☐ Pulmonary ☐ Other, specify…….. TYPEORGTRAN OTHORGTRAN

ALL LYMPHOMAS

Status at Cellular Therapy

Technique used for disease assessment:

CT scan done ☐ No ☐ Yes VCTSCAND

PET ☐ Negative ☐ Positive ☐ Not evaluated VPETSTAT

STATUS VDISESTA

- ☐ Never treated
- ☐ Complete remission (CR) VCRCONFI
  - ☐ Unconfirmed (CRU*) ☐ Confirmed
  - *CRU – complete response with persistent scan abnormalities of unknown significance
- ☐ Partial response (PR) – (with or without a prior CR)
- ☐ Stable disease
- ☐ Untreated relapse (from a previous CR) / untreated progression (from a previous PR) *
- ☐ Chemorefractory relapse or progression, including primary refractory disease *
- ☐ Not Evaluable
- ☐ Not Evaluated

* Answer additional Histopathological verification question below

For **Relapse** status only:
Histopathological verification of relapse? ☐ No ☐ Yes HISTPATHOLYM

Was this patient **refractory** to any line of chemotherapy before this Cellular Therapy? ☐ No ☐ Yes REFRPAST

Number of Complete remissions (CR, CRu) achieved by the patient prior to this Cellular Therapy: …….. NBRCRBG
Count all CR including this one if applicable

Number of Partial remissions (PR) achieved by the patient prior to this Cellular Therapy: …….. NCRCRUPR
Count all PR including this one if applicable

Number of prior lines of treatment ☐ 1 ☐ 2 ☐ 3 or more ☐ None ☐ unknown TOTNTHER
(since diagnosis if 1st main treatment, or since last reported main treatment)

MYELODYSPLASTIC SYNDROME (MDS) (main disease code 6)

Disease

VMDSMPS
Select only one
WHO Classification at diagnosis: MDSSTAG

- ☐ Refractory anaemia (RA) *(without ring sideroblasts)*
- ☐ RA with ring sideroblasts (RARS)
- ☐ MDS associated with isolated del(5q)
- ☐ Refractory cytopenia with multilineage dysplasia (RCMD)
- ☐ RCMD with ringed sideroblasts (RCMD-RS)
- ☐ RA with excess of blasts-1 (RAEB-1)
- ☐ RA with excess of blasts-2 (RAEB-2)
- ☐ Childhood myelodysplastic syndrome (*Refractory cytopenia of childhood (RCC)*)
- ☐ MDS Unclassifiable (MDS-U)

Secondary Origin?

Therapy related MDS:
(Secondary origin)

- ☐ Yes: Disease related to prior exposure to therapeutic drugs or radiation
- ☐ No
- ☐ Unknown VSECORIG

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT TREATMENT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown
RPDRGRAD

MYELODYSPLASTIC SYNDROME (MDS) (main disease code 6)

CYTOGENETICS DATA

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next questions)*

Chromosome analysis at diagnosis (All methods including FISH) VCHROMOS

☐ Normal

☐ Abnormal:

MORE3AB **Complex karyotype:** *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown

☐ Unknown

CHRMABND

You can transcribe the complete karyotype: .....

OR

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC

del Y *(-Y)*	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type *Fill only if* abn 5 *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
del5q *(5q-)*	☐ Absent	☐ Present	☐ Not evaluated
Other abn 5, specify	☐ Absent	☐ Present	☐ Not evaluated
del 20q *(20q-)*	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type *Fill only if* abn 7 *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
del 7q (7q-)	☐ Absent	☐ Present	☐ Not evaluated
Other abn 7, specify	☐ Absent	☐ Present	☐ Not evaluated
abn 3 type *Fill only if* abn 3 *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
inv(3)	☐ Absent	☐ Present	☐ Not evaluated
t(3q;3q)	☐ Absent	☐ Present	☐ Not evaluated
del(3q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn 3, specify	☐ Absent	☐ Present	☐ Not evaluated
del11q	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
trisomy 19	☐ Absent	☐ Present	☐ Not evaluated
i(17q)	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

MOLECULAR MARKERS AT DIAGNOSIS

Molecula analysis done? ☐ No *(skip next question)* ☐ Yes *(continue with the next question)*

Marker analysis at diagnosis

☐ Absent ☐ Present ☐ Unknown

MOLEBIO

*If you are entering an **AML with myelodyplasia related changes**, return to the Acute Leukaemia (page 8) to continue*

MYELODYSPLASTIC SYNDROME (MDS) (main disease code 6)

Status at Cellular Therapy

Select only one

WHO Classification at time of this treatment: MDSSTAG

- ☐ Refractory anaemia (without ring sideroblasts) RA
- ☐ RA with ring sideroblasts (RARS)
- ☐ MDS associated with isolated del(5q)
- ☐ Refractory cytopenia with multilineage dysplasia (RCMD)
- ☐ RCMD with ringed sideroblasts (RCMD-RS)
- ☐ RA with excess of blasts-1 (RAEB-1)
- ☐ RA with excess of blasts-2 (RAEB-2)
- ☐ Childhood myelodysplastic syndrome (*Refractory cytopenia of childhood (RCC)*)
- ☐ MDS Unclassifiable (MDS-U)

STATUS VDISESTA	NUMBER VNUMSTM
Treated with chemotherapy: ☐ Primary refractory phase (no change)	
☐ Complete remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Improvement but no CR	
☐ Relapse (after CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression/worse ☐ Never treated (Supportive care or treatment without chemotherapy)	

COMBINED MYELODYSPLASTIC SYNDROME/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN) (main disease code 6)

Disease

VMDSMPS MDSAMPS

- ☐ Chronic myelomonocytic leukaemia (CMMoL, CMML)
- ☐ Juvenile myelomonocytic leukaemia (JCMMoL, JMML, JCML, JCMML)
- ☐ Atypical CML ((t(9;22) negative and BCR-ABL1 negative)

Therapy related MDS/MPN: *(Secondary origin)*

- ☐ Yes: Disease related to prior exposure to therapeutic drugs or radiation
- ☐ No
- ☐ Unknown VSECORIG

CYTOGENETICS AND MOLECULAR MARKERS AT DIAGNOSIS

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next question)*

Chromosome analysis (All methods including FISH) VCHROMOS

- ☐ Normal
- ☐ Abnormal:

MORE3AB **Complex karyotype:** *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown

☐ Unknown

You can transcribe the complete karyotype: .....

CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC

CHROPRES

Abn 1, specify	☐ Absent	☐ Present	☐ Not evaluated
Abn 5, specify	☐ Absent	☐ Present	☐ Not evaluated
Abn 7, specify	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
Del 20	☐ Absent	☐ Present	☐ Not evaluated
Del 13	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

MOLECULAR MARKERS

Molecula analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with the next question)*

MOLEBIO

☐ Absent ☐ Present ☐ Unknown

IDAABECL MOLPRES

Indicate below those markers that have been **evaluated** and whether they were **Absent** or **Present**

BCR-ABL; *molecular product of t(9;22)(q34;q11.2)*	☐ Absent	☐ Present	☐ Not evaluated
JAK2 mutation	☐ Absent	☐ Present	☐ Not evaluated
FIP1L1-PDGFR	☐ Absent	☐ Present	☐ Not evaluated
PTPN-11	☐ Absent	☐ Present	☐ Not evaluated
K-RAS	☐ Absent	☐ Present	☐ Not evaluated
N-RAS	☐ Absent	☐ Present	☐ Not evaluated
CBL	☐ Absent	☐ Present	☐ Not evaluated
Other, specify.....	☐ Absent	☐ Present	☐ Not evaluated

COMBINED MYELODYSPLASTIC SYNDROME/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN) (main disease code 6)

Status at Cellular Therapy

WHO Classification at time of this treatment: MDMPSTAG

- ☐ Chronic myelomonocytic leukaemia (CMMoL, CMML)
- ☐ Juvenile myelomonocytic leukaemia (JCMMoL, JMML, JCML, JCMML)
- ☐ Atypical CML ((t(9;22) negative and BCR-ABL1 negative)

STATUS
CMML / Atypical CML

STATUS VDISESTA	NUMBER VNUMSTM
Treated with chemotherapy: ☐ Primary refractory phase (no change)	
☐ Complete remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Improvement but no CR	
☐ Relapse (after CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression/worse ☐ Never treated (Supportive care or treatment without chemotherapy)	

MYELOPROLIFERATIVE NEOPLASMS (MPN) (main disease code 6)

Disease

VMDSMPS VMPS

- ☐ Primary myelofibrosis *(Chronic idiopathic myelofibrosis; fibrosis with myeloid metaplasia)*
- ☐ Polycythaemia vera
- ☐ Essential or primary thrombocythaemia
- ☐ Hyper eosinophilic syndrome (HES)
- ☐ Chronic eosinophilic leukaemia (CEL)
- ☐ Chronic neutrophilic leukaemia
- ☐ Systemic mastocytosis
- ☐ Mast cell leukaemia
- ☐ Mast cell sarcoma
- ☐ MPN not otherwise specified
- ☐ Myeloid and lymphoid neoplasms with FGFR1 abnormalities *(Stem cell leukaemia-lymphoma syndrome, 8p11 syndrome)*

Secondary origin:

- ☐ Yes: Disease related to prior exposure to therapeutic drugs or radiation
- ☐ No
- ☐ Unknown VSECORIG

IPSS Risk score for Myelofibrosis IPSSRSC

☐ Low risk ☐ Intermediate-1 ☐ Intermediate-2 ☐ High risk ☐ Not evaluated

CYTOGENETICS AND MOLECULAR MARKERS AT DIAGNOSIS

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next question)*

Chromosome analysis (All methods including FISH) VCHROMOS

- ☐ Normal
- ☐ Abnormal
  - **Complex karyotype:** ☐ No ☐ Yes ☐ Unknown
- ☐ Unknown

You can transcribe the complete karyotype: .....

ARYO_YN CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC CHROPRES

Abn 1, specify	☐ Absent	☐ Present	☐ Not evaluated
Abn 5, specify.....	☐ Absent	☐ Present	☐ Not evaluated
Abn 7, specify	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
Del 20	☐ Absent	☐ Present	☐ Not evaluated
Del 13	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

Molecular markers at diagnosis MOLEBIO

Molecula analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with the next question)*

☐ Absent ☐ Present ☐ Unknown

IDAABECL MOLPRES

Indicate below those markers that have been **evaluated** and whether they were **Absent** or **Present**

BCR-ABL	☐ Absent	☐ Present	☐ Not evaluated	
JAK2 mutation	☐ Absent	☐ Present	☐ Not evaluated	If present: Allele burden % ..... MKRPERCT
cMPL mutation	☐ Absent	☐ Present	☐ Not evaluated	
Cal Reticulin mutation	☐ Absent	☐ Present	☐ Not evaluated	
FIP1L1-PDGFR	☐ Absent	☐ Present	☐ Not evaluated	
Other, specify.....	☐ Absent	☐ Present	☐ Not evaluated	

MYELOPROLIFERATIVE NEOPLASMS (MPN) (main disease code 6)

Status at Cellular Therapy

Classification at time of this treatment: VMPS

- ☐ Primary myelofibrosis *(Chronic idiopathic myelofibrosis; fibrosis with myeloid metaplasia)*
- ☐ Polycythaemia vera
- ☐ Essential or primary thrombocythaemia
- ☐ Hyper eosinophilic syndrome (HES)
- ☐ Chronic eosinophilic leukaemia (CEL)
- ☐ Chronic neutrophilic leukaemia
- ☐ Systemic mastocytosis
- ☐ Mast cell leukaemia
- ☐ Mast cell sarcoma

☐ Myeloid and lymphoid neoplasms with FGFR1 abnormalities *(Stem cell leukaemia-lymphoma syndrome, 8p11 syndrome)*

☐ Transformed to myelofibrosis from PV/ET: Date of transformation ..... - ..... - ..... DATTRAN
yyyy mm dd

- ☐ Transformed to AML
- ☐ MPN not otherwise specified

DIPSS Risk score for Myelofibrosis DIPSSRSC

☐ Low risk ☐ Intermediate-1 ☐ Intermediate-2 ☐ High risk ☐ Not evaluated

STATUS VDISESTA	NUMBER VNUMSTM
Treated with chemotherapy: ☐ Primary refractory phase (no change)	
☐ Complete remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Improvement but no CR	
☐ Relapse (after CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression/worse ☐ Never treated (Supportive care or treatment without chemotherapy)	

PLASMA CELL DISORDERS (PCD) including MULTIPLE MYELOMA (MM) (main disease code 4)

Disease

Classification VPLCEDS1

- ☐ Multiple myeloma (MM) VPLCEDS3
  - ☐ MM –heavy chain and light chain *Check light and heavy chain types →*
  - ☐ MM -light chain *Check light chain type only →*
  - ☐ MM -non-secretory
- ☐ Plasma cell leukaemia
- ☐ Solitary plasmacytoma of bone
- ☐ Primary amyloidosis
- ☐ POEMS
- ☐ Monoclonal light and heavy chain deposition disease (LCDD/HCDD)
- ☐ Other

VPLCEDS2 **IG TYPE**
- ☐ IgG
- ☐ IgA
- ☐ IgD
- ☐ IgE
- ☐ IgM *(not Waldenstrom)*

VPLCEDS4 **LIGHT CHAIN TYPE**
- ☐ Kappa
- ☐ Lambda

STAGE AT DIAGNOSIS VSTGDST
Complete both staging systems

SALMON AND DURIE (MM)

	I	II	III
A	☐	☐	☐
B	☐	☐	☐

VSALMDUR

REVISED ISS RISS

- ☐ I ISS I without high risk FISH and normal LDH
- ☐ not R-ISS I II III
- ☐ any ISS with high risk FISH and/or high LDH

***or* ISS** ISS

	β2 µglob *(mg/L)*	Albumin *(g/L)*		β2 µglob *(mg/L)*	Albumin *(g/L)*
☐ I	<3.5	≥35			
☐ II	<3.5	<35	***OR***	3.5 – ≤5.5	any
☐ III	>5.5	any			

Chromosome analysis at diagnosis (All methods including FISH) VCHROMOS
Not for Primary amyloidosis

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next question)*

- ☐ Normal
- ☐ Abnormal: VCHROMOS
  Complex karyotype: ☐ No ☐ Yes ☐ Unknown
  (3 or more abnormalities) MORE3AB
- ☐ Unknown

You can transcribe the complete karyotype: .....

CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present**

If abnormal, indicate abnormalities found: IDAABECC CHROPRES

Del 13q14	☐ Absent	☐ Present	☐ Not evaluated
t(11;14)	☐ Absent	☐ Present	☐ Not evaluated
abn 17q	☐ Absent	☐ Present	☐ Not evaluated
17p del	☐ Absent	☐ Present	☐ Not evaluated
t(4:14)	☐ Absent	☐ Present	☐ Not evaluated
t(14:16)	☐ Absent	☐ Present	☐ Not evaluated
1q amplification	☐ Absent	☐ Present	☐ Not evaluated
myc rearrangement	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

☐ Other or associated abnormalities (specify).....

PLASMA CELL DISORDERS (PCD) including MULTIPLE MYELOMA (MM) (main disease code 4)

Molecular analysis
Not for Primary amyloidosis

Molecular analysis done? ☐ No *(skip the next question)* ☐ Yes *(continue with the next question)*

MOLEBIO ☐ Absent ☐ Present (at least one) ☐ Unknown

Status at Cellular Therapy

STATUS VDISESTA	NUMBER VNUMSTM
☐ Never treated	
☐ Stringent complete remission (sCR) ☐ Complete remission (CR) ☐ Very good partial remission (VGPR) ☐ Partial remission (PR) ☐ Relapse from CR (untreated)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression ☐ No change / stable disease	

BONE MARROW FAILURE SYNDROMES (BMF) including APLASTIC ANAEMIA (AA) (main disease code 7)

Disease

Classification: BMFTYPE BMFSACQ

Acquired:

- ☐ Severe Aplastic Anaemia (SAA),
- ☐ Amegakaryocytosis, acquired (not congenital)
- ☐ Acquired Pure Red Cell Aplasia (PRCA) (not congenital)
- ☐ Paroxysmal nocturnal haemoglobinuria (PNH)
- ☐ Acquired Pure White Cell Aplasia
- ☐ Other acquired cytopenic syndrome, specify: _____ VDIAGTX

ACQBMFE Etiology:

- ☐ Secondary to hepatitis
- ☐ Secondary to toxin/other drug
- ☐ Idiopathic
- ☐ Other, specify: _____ VOTHSAEE

Congenital: BMFTYPE BMFSGEN

- ☐ Amegakaryocytosis / thrombocytopenia
- ☐ Fanconi anaemia
- ☐ Diamond-Blackfan anaemia (congenital PRCA)
- ☐ Shwachman-Diamond Syndrome
- ☐ Dyserythropoietic anaemia
- ☐ Dyskeratoris congenita
- ☐ Other congenital anaemia, specify: _____ VDIAGTX

HAEMOGLOBINOPATHY (main disease code 11)

Disease

Classification: VHEMOGLO

☐ Thalassaemia: ☐Beta 0 ☐Beta + ☐Beta E THALTYPE ☐Beta S (sickle cell + thalassaemia)
% sickle cell = ... VSICKLPC

☐ Sickle cell disease

☐ Other haemoglobinopathy, specify: _____ VDIAGTX

SOLID TUMOURS (main disease code 5)

Disease

Classification: VSOLTUMO

- ☐ Bone sarcoma (excluding Ewing sarcoma/PNET)
- ☐ Breast
- ☐ Central nervous system tumours (include CNS PNET)
- ☐ Colorectal
- ☐ Ewing sarcoma (ES)/PNET, extra-skeletal
- ☐ Ewing sarcoma(ES)/PNET, skeletal
- ☐ Germ cell tumour, extragonadal only
- ☐ Head and neck
- ☐ Hepatobiliary
- ☐ Kidney cancer excluding Wilm's tumour
- ☐ Lung cancer, non-small cell
- ☐ Lung cancer, small cell
- ☐ Medulloblastoma
- ☐ Melanoma
- ☐ Other, specify ..... VDIAGTX
- ☐ Neuroblastoma
- ☐ Ovarian (carcinoma)
- ☐ Pancreatic
- ☐ Prostate
- ☐ Renal cell
- ☐ Retinoblastoma
- ☐ Rhabdomyosarcoma
- ☐ Soft tissue sarcoma (excluding Rhabdo. and extra-skeletal ES)
- ☐ Germ cell tumour, gonadal
- ☐ Thymoma
- ☐ Wilm's tumour

TNM classification

Type: ☐ Clinical ☐ Pathological VTNMTYPE

	0	1	2	3	4	X	Not evaluated	Unknown	
Tumour	☐	☐	☐	☐	☐	☐	☐	☐	VTNMT
Nodes	☐	☐	☐	☐		☐	☐	☐	VTNMN
Metastases*	☐	☐				☐	☐	☐	VTNMM

*For metastases, 0 indicates "No metastasis", 1 indicates "Metastasis" and X indicates "Not evaluable"

Disease-specific staging I ☐ II ☐ III ☐ IV ☐ Not evaluated ☐ Unknown ☐ VSTGDST

BREAST CARCINOMA ONLY

RECEPTOR STATUS

Estrogen (ER): ☐ Negative ☐ Positive ☐ Not evaluated VESTROGR VESRCVAL if Positive, ER values …..

Progesterone (PgR): ☐ Negative ☐ Positive ☐ Not evaluated VPROGESR VPRGRCVA if Positive, PgR values …..

HER2/neu (c-erb-B2): ☐ Negative ☐ Positive HER2EUR ☐ Not evaluated

Defined by: ☐ IHC 3+ ☐ IHC 1/2+ and FISH+ HER2DEF

HISTOLOGICAL SUBCLASSIFICATION

Axillary lymph nodes at surgery: N° examined: .... / N° positive:..... .... ☐ Not evaluated VNISOBRC VNINVBRC

Sentinel Node ☐ Negative ☐ Positive ☐ Not evaluated SNTNLNDG

Carcinoma type *(tick only one)*

☐ Ductal carcinoma ☐ Lobular carcinoma VDUCTALC VLOBULAR

Proliferation index (activity by Ki67 or MiB1 immunostaining) (% of positive cells) ..... PRINDXKI

GERM CELL TUMOURS ONLY

Histological classification VHSTCLAS

☐ Seminoma ☐ Non-seminoma

Site of origin VBGFGRCT

☐ Gonadal

☐ Extragonadal: ☐ retroperitoneal ☐ mediastinal ☐ other sites (specify) ..... VBGFGRCT

Status at Cellular Therapy

GERM CELL TUMOURS

Risk category at disease recurrence (or platinum refractoriness) following first line CT GRMCLRSC

☐ Very Low ☐ Low ☐ Intermediate ☐ High ☐ Very High ☐ Not evaluated

STATUS VDISESTA

☐ Adjuvant
☐ Never treated (upfront)
☐ Stable disease/no response

☐ Complete remission (CR) VCRCONFI ☐ Confirmed ☐ Unconfirmed (CRU*) *CRU – complete response with persistent scan abnormalities of unknown significance	NUMBER VNUMSTM ☐ 1st ☐ 2nd ☐ 3rd or higher	
☐ 1st Partial response (PR1)		
☐ Relapse	NUMBER VNUMSTM ☐ 1st ☐ 2nd ☐ 3rd or higher	SENSITIVITY TO CHEMOTHERAPY ☐ Sensitive ☐ Resistant ☐ Untreated VSENSIT
☐ Progressive disease (PD)		

Organ(s) involved (*complete only if not in CR*) IDAABECK

☐ Nodes Below Diaphragm
☐ Nodes Above Diaphragm
☐ Bone
☐ CNS
☐ Lungs
☐ Liver
☐ Soft Tissue
☐ Other: ..... ORGANOTS

PRIMARY IMMUNE DEFICIENCIES (PID) (main disease code 8)

Disease

Classification: INHDIS IMMDEF

- ☐ Absence of T and B cells SCID
- ☐ Absence of T, normal B cell SCID
- ☐ ADA deficiency (Adenosine deaminase deficiency)
- ☐ Ataxia telangiectasia
- ☐ Bare lymphocyte syndrome
- ☐ Cartilage hair hypoplasia
- ☐ CD 40 Ligand deficiency
- ☐ Chediak-Higashi syndrome
- ☐ Chronic granulomatous disease
- ☐ Common variable immunodeficiency
- ☐ DiGeorge anomaly
- ☐ Immune deficiencies, not otherwise specified
- ☐ Kostmann syndrome-congenital neutropenia
- ☐ Leukocyte adhesion deficiencies
- ☐ Neutrophil actin deficiency
- ☐ Omenn syndrome
- ☐ PNP deficiency *(Purine nucleoside phosphorylase)*
- ☐ Reticular dysgenesis
- ☐ SCID other, specify: ..... VDIAGTX
- ☐ SCID, unspecified
- ☐ Wiskott Aldrich syndrome
- ☐ X-linked lymphoproliferative syndrome
- ☐ Other, specify: ..... VDIAGTX

INHERITED DISORDERS OF METABOLISM (main disease code 8)

Disease

Classification: INHDIS VINBERR2

- ☐ Adrenoleukodystrophy
- ☐ Aspartyl glucosaminuria
- ☐ B-glucuronidase deficiency (VII)
- ☐ Fucosidosis
- ☐ Gaucher disease
- ☐ Glucose storage disease
- ☐ Hunter syndrome (II)
- ☐ Hurler syndrome (IH)
- ☐ I-cell disease
- ☐ Krabbe disease (globoid leukodystrophy)
- ☐ Lesch-Nyhan (HGPRT deficiency)
- ☐ Mannosidosis
- ☐ Maroteaux-Lamy (VI)
- ☐ Metachromatic leukodystrophy
- ☐ Morquio (IV)
- ☐ Mucolipidoses, unspecified
- ☐ Mucopolysaccharidosis (V)
- ☐ Mucopolysaccharidosis, unspecified
- ☐ Niemann-Pick disease (Type A,B)
- ☐ Niemann-Pick disease (Type C,D,E)
- ☐ Neuronal ceroid – lipofuscinosis (Batten disease)
- ☐ Polysaccharide hydrolase abnormalities, unspecified
- ☐ Sanfilippo (III)
- ☐ Scheie syndrome (IS)
- ☐ Wolman disease
- ☐ Other, specify: ..... VDIAGTX
- ☐ Inherited disorders of metabolism, not otherwise specified

PLATELET and OTHER INHERITED DISORDERS (main disease code 8)

Disease

Classification: **VINBERR3**

- ☐ Glanzmann thrombasthenia
- ☐ Other inherited platelet abnormalities, unspecified

- ☐ Osteopetrosis (malignant infantile osteopetrosis)
- ☐ Other osteoclast defects, unspecified

HISTIOCYTIC DISORDERS (main disease code 9)

Disease

Classification: HISTIOCY

- ☐ Histiocytic disorders, not otherwise specified
- ☐ Familial erythro/haemophagocytic lymphohistiocytosis (FELH)
- ☐ Langerhans Cell Histiocytosis *(Histiocytosis-X)*
- ☐ Haemophagocytosis (reactive or viral associated)
- ☐ Histiocytic sarcoma *(malignant histiocytosis)*
- ☐ Other, specify:_____ VDIAGTX

AUTOIMMUNE DISORDERS (main disease code 10)

CONNECTIVE TISSUE

DISEASE

Classification:

☐ Systemic sclerosis (SS) VAUTOIM1

VAUTOIM2

Involvement/Clinical problem SSCUTEXT

- ☐ diffuse cutaneous
- ☐ limited cutaneous
- ☐ SSc sine scleroderma
- ☐ Other (MCTD: Mixed Connective Tissue Disease)
- ☐ other, specify:_____ SSCINVOT

☐ Systemic lupus erythematosus (SLE) VAUTOIM2

☐ Polymyositis- dermatomyositis VAUTOIM1

☐ Sjögren syndrome

☐ Antiphospholipid syndrome

☐ Other type of connective tisue disease, specify:_____ VDIAGTX

VAUTOIM2

VASCULITIS VAUTOIM1

DISEASE

Classification: VAUTOIM3

☐ Wegener granulomatosis

☐ Classical polyarteritis nodosa

☐ Microscopic polyarteritis nodosa

☐ Churg-Strauss

☐ Giant cell arteritis

☐ Takayasu

☐ Behçet's syndrome

☐ Overlap necrotising arteritis

☐ Other, specify:_____ VDIAGTX

AUTOIMMUNE DISORDERS cont. (main disease code 10)

ARTHRITIS VAUTOIM1

DISEASE

Classification: VAUTOIM4

- ☐ Rheumatoid arthritis
- ☐ Psoriatic arthritis/psoriasis
- ☐ Juvenile idiopathic arthritis (JIA), systemic (Stills disease)
- ☐ Juvenile idiopathic arthritis (JIA), articular: Onset ☐ Oligoarticular PRAONSET ☐ Polyarticular
- ☐ Juvenile idiopathic arthritis: other
- ☐ Other arthritis: ..... VDIAGTX

NEUROLOGICAL

DISEASE

Classification: VAUTOIM1

- ☐ MULTIPLE SCLEROSIS
- ☐ OTHER NEUROLOGICAL: VAUTOIM1 VAUTOIM5
  - ☐ Myasthenia gravis
  - ☐ Amyotrophic lateral sclerosis (ALS)
  - ☐ Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - ☐ Neuromyelitis Optica (NMO)
  - ☐ Other autoimmune neurological disorder, specify:_____ VDIAGTX

HAEMATOLOGICAL VAUTOIM1

DISEASE

Classification: VAUTOIM6

- ☐ Idiopathic thrombocytopenic purpura (ITP)
- ☐ Haemolytic anaemia
- ☐ Evan syndrome
- ☐ Autoimmune lymphoproliferative syndrome (primary diagnosis, not subsequent to transplant)
- ☐ Other haematological autoimmune disease, specify:_____ VDIAGTX

AUTOIMMUNE DISORDERS cont. (main disease code 10)

BOWEL VAUTOIM1

DISEASE

Classification: VAUTOIM7
☐ Crohn's disease
☐ Ulcerative colitis
☐ Other autoimmune bowel disease, specify:_____ VDIAGTX

OTHER AUTOIMMUNE DISORDER

DISEASE

Classification: VAUTOIM1
☐ Graves' disease
☐ Insulin dependent diabetes (IDD)
☐ Other autoimmune, specify:_____ VDIAGTX

OTHER PRIMARY DISEASE

NEUROLOGIC DISORDES (main disease code 12)

Classification:

- ☐ Duchenne Muscular Distrophy — NEURODIS
- ☐ Acute cerebral vascular ischemia
- ☐ ALS, amiotrophic lateral sclerosis
- ☐ Parkinson disease
- ☐ Spinal cord injury
- ☐ Cerebral palsy
- ☐ Congenital hydrocephalus
- ☐ Other, specify:_____ VDIAGTX

HEART (CARDIOVASCULAR) DISEASE (main disease code 13)

Classification:

- ☐ Acute myocardial infarction (AMI) — CARDIODIS
- ☐ Chronic coronary artery disease (ischemic, cardiomyopathy)
- ☐ Heart failure (non-ischemic etiology)
- ☐ Other cardiovascular disease
- ☐ Limb ischemia
- ☐ Thromboangitis obliterans
- ☐ Other peripheral vascular disease
- ☐ Other, specify:_____ VDIAGTX

MUSCULOSKELETAL (main disease code 15)

Classification:

- ☐ Avascular necrosis of femoral head — MUSCSKDIS
- ☐ Osteoarthritis
- ☐ Osteogenesis imperfecta
- ☐ Traumatic joint injury
- ☐ Other, specify:_____ VDIAGTX

INFECTIONS (main disease code 14)

☐ Prevention / prophylaxis **INFTRTAIM**
☐ Treatment:

Pathogen involved:
☐ Adenovirus ☐ BK virus ☐ Cytomegalovius (CMV) **INFTRTPATH**
☐ Epstein-Barr virus ☐ Human herpex virus
☐ Human immunodeficiency virus (HIV) ☐ Other virus, specify ……..
☐ Candida ☐ Aspergillus ☐ Other fungal, specify ……..
☐ Other, specify …….. **INFTRTPATOTH**

Advanced Cellular Therapies Form

Day 0

EBMT Unique Identification Code (UIC) ..... ID.IDAA

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): .... CENTRNR

Unit: ..... UNIT

Contact person..... MEDNAME

PATIENT DATA

Date of this Report: ..... - ..... - .....
DATLSTRE *yyyy* *mm* *dd*

Hospital Unique Patient Number or Code (UPN): ..... UPN
Compulsory, registrations will not be accepted without this item. *All treatments performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.*

CCI [redacted]

Initials: ....._..... (first name(s) _family name(s)) GIVNAME FAMNAME

Date of Birth: ..... - ..... - ..... DATPATBD
yyyy *mm* dd

Sex: ☐ Male ☐ Female PATSEX
(at birth)

Previous therapies given before transplant/advanced cellular therapy

Has the information requested in this section been submitted with a previous HSCT/Advanced Cellular Therapy registration for this patient?

☐ Yes: go to page 47, *"Status at Cellular Therapy"*
☐ No: proceed with this section

Was the patient treated before this Cellular Therapy procedure? VPRETRAT

☐ No – *Proceed to page 47, STATUS AT CELLULAR THERAPY*
☐ Yes **Date started** .... - .... IDAABC *(repeat for each line of therpy)*
yyyy mm dd

Sequential number of this treatment: ..... VSEQNUMB
(counted from diagnosis)

☐ Unknown

Chemotherapy/Drugs ☐ No ☐ Yes ☐ Unknown VCHEMOTH

If yes:

	IDAABCCD Regimen/Drugs	NUMCYCL No. of cycles	TRETSTAR Date started	VINTBTDE Date ended	TUMRSA2 Response
1st Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated
2nd Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated
3rd Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated
4th Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated

If there are more than 4 please add another copy of this page.

Enzyme replacement therapy ☐ No ☐ Yes ☐ Unknown
ENZYME

Radiotherapy ☐ No ☐ Yes ☐ Unknown
VRADIOTH

Other treatment ☐ No ☐ Yes, specify: .... ☐ Unknown VOTHERT
VOTHERTS

STATUS AT CELLULAR THERAPY

IF THE THE CELLULAR THERAPY PRODUCT WAS INFUSED REPORT:
Date of the first cell infusion ..... - ..... - ..... IDAABE / IDAABC
yyyy mm dd

OTHERWISE, IF THE TREATMENT DIDN'T GO AHEAD REPORT:
Date of the last assessment..... - ..... - ..... IDAABE / IDAABC
yyyy mm dd

WAS THE CELL PRODUCT INFUSED DURING THIS TREATMENT OR PROCEDURE? CELLPROINF

☐ No: Reason why the treatment didn't take place: …….. REASNOCT
☐ Yes

Performance score of the patient at initiation of treatment PERFSYST KARNOFSK

SYSTEM USED *(choose only one)*:

☐ Karnofsky or ☐ Lansky: Score: ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

☐ ECOG: ECOG Score: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

PATIENT WEIGHT AT CELLULAR THERAPY (kg): ..... WEIGHTB

HEIGHT AT CELLULAR THERAPY(cm): ..... HEIGHT

Was B-Cell Aplasia present at the time of treatment? ☐ No ☐ Yes ☐ Not Evaluated BCELLAPLAS

If yes, report % (percentage) of B-Cells …….. BCELLPC

COMORBIDITY INDEX

Sorror et al., Blood, 2005 Oct 15; 106(8): 2912-2919: *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1895304/*

Was there any ***clinically significant*** co-existing disease or organ impairment as listed below at time of patient assessment prior to the preparative regimen? ☐ No ☐ Yes, indicate each comorbidity below ☐ Not evaluated COMORBID

Comorbidity	Definitions	No	Yes	Not evaluated
Solid tumour, previously present MALIGN	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer Indicate type ....MALIGNTXT	☐	☐	☐
Inflammatory bowel disease INBWDIS	Crohn's disease or ulcerative colitis	☐	☐	☐
Rheumatologic RHEUMAT	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	☐	☐	☐
Infection INFECPRE	Requiring continuation of antimicrobial treatment after day 0	☐	☐	☐
Diabetes TRTDEPDB	Requiring treatment with insulin or oral hypoglycaemics but not diet alone	☐	☐	☐
Renal: moderate/severe KIDNEYCO	Serum creatinine > 2 mg/dL or >177 µmol/L, on dialysis, or prior renal transplantation	☐	☐	☐
Hepatic: mild HEPATIC	Chronic hepatitis, bilirubin between Upper Limit Normal (ULN) and 1.5 x the ULN, or AST/ALT between ULN and 2.5 × ULN	☐	☐	☐
moderate/ severe	Liver cirrhosis, bilirubin greater than 1.5 × ULN, or AST/ALT greater than 2.5 × ULN	☐	☐	☐
Arrhythmia ARRYTHBL	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	☐	☐	☐
Cardiac CARDIAC	Coronary artery disease, congestive heart failure, myocardial infarction, EF ≤ 50%, or shortening fraction in children (<28%)	☐	☐	☐
Cerebrovascular disease STROKE	Transient ischemic attack or cerebrovascular accident	☐	☐	☐
Heart valve disease VALVE	Except mitral valve prolapse	☐	☐	☐
Pulmonary: moderate PULMONC	DLco and/or FEV1 66-80% or dyspnoea on slight activity	☐	☐	☐
severe	DLco and/or FEV1 ≤ 65% or dyspnoea at rest or requiring oxygen	☐	☐	☐
Obesity OBESITY	Patients with a body mass index > 35 kg/m2	☐	☐	☐
Peptic ulcer PEPTICU	Requiring treatment	☐	☐	☐
Psychiatric disturbance PSYCH	Depression or anxiety requiring psychiatric consultation or treatment	☐	☐	☐

Specify other additional ***major*** clinical abnormalities not listed above and present prior to the preparative regimen:

.....
.....
..... OTHCLIAB

CELLULAR THERAPY INFUSION UNIT(S)

Is it planned to administer more than one cell infusion unit during this treatment

☐ No **MNYINFUSED**

☐ Yes: Number of different cell infusion units that will form part of this treatment **NUMCINFUNIT**

Cellular Therapy Infusion Unit – Description and collection

If more than one cell infusion unit, replicate this section for each one of them

IDENTIFICATION

Name of the manufacturer ..... ☐ **N/A** **NAMCTIMNFCD** **NAMCTIMNFSP**
Enter Hospital name if it isn't a commercial product

Unique ID of the product *(if applicable)* ..... **PRODUCTID**

Name of the product *(if applicable)* ..... **NAMCTIPKGCD** **NAMCTIPKGSP**

Batch number *(if applicable)* ..... **CTIPKGBAT**

Identification of the Cell Infusion Unit given by the Centre ..... **CTIUCID**
If there is only one cell infusion unit write '1'.

Is the infused Advanced Cellular Therapy product a commercial product? **COMMPROD** **CONSPECIF**

☐ Yes: Was the product use consistent with the specification? ☐ Yes ☐ No

☐ No

Cellular Therapy Infusion Unit – Manipulation

COMPLETE ONLY FOR NON-COMMERCIAL PRODUCTS

If more than one cell infusion unit, replicate this section for each one of them:

Identification of the Cell Infusion Unit given by the Centre .... CTIUCID

***EX-VIVO* MANIPULATION OF THE PRODUCTS CONTAINED IN THE CELLULAR THERAPY INFUSION UNIT** CIEXVIMANI

- ☐ No -> Skip MANIPULATION section and go straight to THERAPY AND CELL INFUSION on page 52
- ☐ Yes -> Continue with MANIPULATION section below
- ☐ Unknown

MANIPULATION

Processing/Manufacturing Facility

Onsite, by local cell processing facility	☐ No	☐ Yes MANIONSLPF
Offsite, by a non commercial facility	☐ No	☐ Yes MANIOFSNCF
Offsite, by a commercial facility	☐ No	☐ Yes MANIOFSCF

GENE MANIPULATION

☐ No MANIGENE MANIGENTRN

☐ Yes: **TYPE**

Gene transfer ☐ No ☐ Yes: ☐ Retroviral vector GENTRNRETV

GENTRNLEN ☐ Lentiviral vector

GENTRNOTH ☐ Other vector, specify ..... TRNOTHSPC

Transgene (select all that apply)

☐ CAR, specify all targets ..... TRNGENCAR GENCARSPC

☐ Suicide gene, specify..... TRNGENSUG GENSUGSPC

TRNGENTCR GENTCRSPC ☐ TCR, specify all targets ..... / specify HLA element ..... GENTCRSPCH

☐ Other, specify ..... TRNGENOTH GENOTHSPC

MANIGENEDT Gene editing ☐ No ☐ Yes: Manipulated gene ☐ CCR5 GENEDTCR5

☐ Factor IX GENEDTFIX

☐ Factor VIII GENEDTFVII

☐ Other gene, specify .....GENEDTOTH EDTOTHSPC

Other ☐ No ☐ Yes, specify ..... MANIGENOTH MANIOTHSPC

MANIPULATION AIMS

Recognition of a specific target / antigen

☐ No RECGTARANT TARANTADNV TARANTBKV TARANTCYMV TARANTEBV TARANTHHV TARANTHIV

☐ Yes: **TYPE** *(check all that apply)*

☐ Viral ☐ Adenovirus ☐ BK virus ☐ Cytomegalovirus (CMV)

VIRALANTG ☐ Epstein-Barr virus ☐ Human herpes virus 6 ☐ Human immunodeficiency virus (HIV)

☐ Other virus, specify ..... TARANTOTH TRGANTSPC

☐ Fungal ☐ Candida ☐ Aspergillus TARANTCAN TARANTASP

FUNGANTG ☐ Other fungal, specify ..... TARANTOTF TRGANTSPF

☐ Tumour / cancer antigen(s), specify all..... TUMRCANANT CANCANTSPC

☐ Other target, specify ..... RECTRGTOTH RTRGOTHSPC

Was there a cell selection process?

☐ No CTIUSELECT

☐ Yes: Positive ☐ No ☐ Yes CTIUSELPOS

If Yes, specify cell type..... CTIUSELPOSSP

Negative ☐ No ☐ Yes CTIUSELNEG

Expansion

☐ No CTIUEXPNS

☐ Yes

Cellular Therapy Infusion Unit – Manipulation cont.

Activation

☐ No CTIUACTIV

☐ Yes

Induced differentiation

☐ No CTIUINDIFF

☐ Yes

Was the generated cellular product cryopreserved prior to infusion

☐ No CTIUFREEZ

☐ Yes

THERAPY and CELL INFUSION(s)

CHRONOLOGICAL NUMBER OF CELLULAR THERAPY TREATMENT FOR THIS PATIENT ..... CELLTHNR
(please do not include any transplants the patient have had in the past)

This section to be completed only if this is the second or subsequent Cellular Therapy for this patient and the previous Cellular therapy treatment(s) cannot be registered

If number of Advanced Cellular therapy treatment >1:

Same package/product as for the previous advanced cellular therapy treatment? ☐ No ☐ Yes SAMEPACKG

If >1, date of last advanced cellular therapy treatment before this one: ..... - .....-..... DATPREVCINF
yyyy mm dd

If >1, type of last advanced cellular therapy treatment before this one: ☐ Allo ☐ Auto PASTCINFTYP

If >1 and Allograft, Was the same donor used for all prior and current advanced cellular therapy treatments?
☐ No ☐ Yes SAMECIDNR

If >1, was last advanced cellular therapy treatment performed at another institution? DIFFCTINST
☐ No ☐ Yes:

If Yes: CIC if known ..... DIFFCNTR
Name of the institution ..... DINSTNAME
City ..... DCTINSTCTY

⇨ If >1, please submit an Annual follow up form before proceeding, using the latest assessment date before this Cellular Therapy. (This is so we can capture relapse data and other events between advanced cellular therapies).

Additionally, if the patient have had a previoous HSCT please submit Med-AB Follow up form.

Reason for the cellular therapy treatment ***(tick all that apply)*** REASPRIMCT
*IF INDICATION IS THE TREATMENT OF A **PRIMARY DISEASE***

- ☐ Treatment of Primary diagnosis
- ☐ Rescue from disease relapse or progression
- ☐ Refractory disease
- ☐ Other, specify .... OTHTREASPC
- ☐ Prevention of disease relapse or progression
- ☐ Minimal residual disease reduction

Reason for the cellular therapy treatment ***(tick all that apply)***
*IF INDICATION IS THE **TREATMENT OR PREVENTION OF A COMPLICATIONS DERIVED FROM A PREVIOUS TREATMENT***

GvHD
- ☐ Unrelated to GvHD GVHDRELTRMT
- ☐ Prevention / prophylaxis of GvHD
- ☐ Treatment of GvHD

Graft function
- ☐ Unrelated to graft function GRFNCRELTRMT
- ☐ Prevention of rejection / promotion of cell engraftment
- ☐ Graft enhancement
- ☐ Graft failure treatment

Immune reconstitution
- ☐ Unrelated to Immune reconstitution IMMRCNSTRT
- ☐ Immune reconstitution

Patient preparative treatment

Preparative (lymphodepleting) **regimen given?** VCHEMOTH

☐ No (skip to the next page - CELL INFUSION EPISODES)

☐ Yes:

Specification and dose of the preparative regimen
IDAABCCD DOSE DOSEUNIT OTHECHEM

TOTAL PRESCRIBED CUMULATIVE DOSE* as per protocol:
Include any systemic drugs (chemo, growth factors, antibodies, etc.)

Name of drug (any given before day 0)	DOSE	UNITS		
.....		☐ mg/m²	☐ mg/Kg	☐ AUC**
.....		☐ mg/m²	☐ mg/Kg	☐ AUC**
.....		☐ mg/m²	☐ mg/Kg	☐ AUC**
.....		☐ mg/m²	☐ mg/Kg	☐ AUC**
.....		☐ mg/m²	☐ mg/Kg	☐ AUC**
.....		☐ mg/m²	☐ mg/Kg	☐ AUC**
.....		☐ mg/m²	☐ mg/Kg	☐ AUC**

* Report the total prescribed cumulative dose as per protocol. **Multiply daily dose in mg/kg or mg/m² by the number of days**;
eg. for Busulfan given 4mg/kg daily for 4 days, total dose to report is 16mg/kg

** AUC = Area under the curve

Other type of treatment ☐ No ☐ Yes, specify ....
VOTHERT VOTHERTS

CELL INFUSION EPISODES

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

☐ No MULTINFEPI

☐ Yes: Number of cell infusion episodes during this procedure NUMINFEPI

Cell infusion episode

If more than one cell infusion episode, replicate this section for each one of them

If more than one Unit was used, indicate the identification of the Cell Infusion Unit given by the Centre as described in the Cell Infusion Unit section

…… NAMCTIPKG2 ***This item is mandatory if more than one unit was used***

Date of cell infusion episode ..... IDAABCCQ

Reconstitution (infusion) procedure CTRECONST

Where was it done? ☐ Bedside ☐ Pharmacy ☐ Cell processing facility

☐ Other, specify…….....

Person in charge of the reconstitution …….. CTRECROLE

Route of infusion *(check all that apply)*

☐ Systemic including Intravenous RTSYSINTR

☐ Other route ..... RTINFOTH RINFOTHSPC

Dose of Cells infused *(complete either the total number of cells or actual volume infused)*

Indicate if only range of doses is available TOTALCELLSNEV

☐ Yes: skip 'Number of cells' question (it means you don't have exact number of cells infused available)

☐ No: Report number of cells infused below

Number of cells…… *(Not adjusted for cell viability)* TOTALCELLS

Units *(tick one)* ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8 TOTALCELLSUNIT

Viability……..% (in percent) VIABILITY

If number of cells infused is not available: Actual volume infused…… ☐ ml VOLINFUSED

Combined /concomitant therapies planned before this Cellular Therapy treatment to optimize efficency CIECONMTRT

☐ No ☐ Yes: specify …… CICNTRTSPC

CIESIMULT Was this treatment given:

☐ Simultaneously to the cellular therapy CIEPCLTHRP

☐ After the cellular therapy episode was finished

Survival Status

VPATSTAT

☐ Alive ☐ Dead

If dead: Main Cause of Death *(check only one main cause)*: VCAUSDTH

- ☐ Relapse or Progression/Persistent disease
- ☐ Secondary malignancy
- ☐ Cellular Therapy related
- ☐ HSCT Related Cause
- ☐ Unknown
- ☐ Other: ..... DEACSBMU

Indicate toxicity related causes of death *(check as many as appropriate)*:

- ☐ GVHD VCSDTGVH
- ☐ Cytokine release syndrome VCSDTCRS
- ☐ Interstitial pneumonitis VCSDTINP
- ☐ Pulmonary toxicity VCSDTPTX
- ☐ Infection: VCSDTINF
  - ☐ bacterial VCSDTBAC
  - ☐ viral VCSDTVIR
  - ☐ fungal VCSDTFUN
  - ☐ parasitic VCSDTPAR
- ☐ Rejection/Poor graft function VCSDTREJ
- ☐ History of severe Veno occlusive disorder (VOD) VCSDTVOD
- ☐ Haemorrhage VCSDTHMR
- ☐ Cardiac toxicity VCSDTCTX
- ☐ Central nervous system (CNS) toxicity VCSDTCNS
- ☐ Gastrointestinal (GI) toxicity VCSDTGIT
- ☐ Skin toxicity VCSDTSKI
- ☐ Renal failure VCSDTREN
- ☐ Multiple organ failure VCSDTMOF

☐ Other:..... DEACSBMR

END OF DAY 0

Advanced Cellular Therapies Form

Status at Last Assessment
(at Day 100, 6 months, Annual Follow Up)

CENTRE IDENTIFICATION

EBMT Code (CIC): .... CENTRNR

Unit: ..... UNIT

Contact person..... MEDNAME

PATIENT DATA

EBMT Unique Identification Code (UIC).....

Hospital Unique Patient Number or Code (UPN): .....UPN
Compulsory, registrations will not be accepted without this item. ***All treatments performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.***

CCI

Initials: ....._..... (first name(s) _family name(s)) GIVNAME / FAMNAME

Date of Birth: ..... - ..... - ..... DATPATBD
yyyy *mm* dd

Sex: ☐ Male ☐ Female PATSEX
(at birth)

INDICATE THE ASSESSMENT PERIOD COVERED BY THIS REPORT

☐ **Day 100** ☐ **6 months** ☐ **Annual Follow Up**

RECOVERY

Absolute neutrophil count (ANC) recovery *(Neutrophils ≥0.5X10⁹ /L)* **ENGNEUT**

☐ No: Date of last assessment: ..... - ..... - ..... **DNOENGR**
yyyy mm dd

☐ Yes: Date of ANC recovery: ..... - ..... - ..... *(first of 3 consecutive values after 7 days without transfusion containing neutrophils)* **DATCRGR2**
yyyy mm dd

☐ Never below ☐ Unknown

Platelet reconstitution

Platelets **≥20** x 10^9/l; *(first of 3 consecutive values after 7 days without platelet transfusion)* **VPLAT20A**

☐ No

☐ Yes: Date Platelets ≥ 20 x 10^9/l ..... - ..... - **DPLAT20**
yyyy mm dd

☐ Never below this level
☐ Date unknown: patient discharged before levels reached
☐ Date unknown: out-patient
☐ Unknown

Platelets **≥50** x 10^9/l; *(first of 3 consecutive values after 7 days without platelet transfusion)* **VPLAT50A**

☐ No

☐ Yes: Date Platelets ≥ 50 x 10^9/l ..... - ..... - **DPLAT50**
yyyy mm dd

☐ Never below this level
☐ Date unknown: patient discharged before levels reached
☐ Date unknown: out-patient
☐ Unknown

Date last platelet transfusion:..... - ..... - ..... ☐ Not applicable: not transfused **DLASTPLT**

RESPONSE AT THE LAST ASSESSMENT

Complete ONLY for DAY 100 and MONTH 6

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF A PRIMARY DISEASE

Best clinical/biological response after the entire Advanced Cellular therapy treatment TUMRSA2

- ☐ Complete remission / Normalisation of organ function / No infection present
- **(AML only)** ☐ CRi (CR with incomplete haematologic recovery)
- ☐ Partial remission / Partial or non normalisation of organ function
- ☐ No response
- ☐ Disease progression or worsening of organ function
- ☐ Not evaluated

Date response evaluated: ..... - ..... - .... DATRESP
yyyy mm dd

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF COMPLICATIONS DERIVED FROM A PREVIOUS TRANSPLANT/CELLULAR THERAPY

IMMRRESP RESPGRAFT RESPGVHD RESPINFECT

Complication	Response				
GvHD	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Graft failure	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Immune reconstitution	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Infection	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated

Date response evaluated: ..... - ..... - .... DATERESPCT
yyyy mm dd

LAST CONTACT DATE FOR THIS REPORT

If patient died in the period since the last report, enter the date of death, otherwise enter Date of Advanced Cellular therapy + set period (as indicated above – 100 Days, 6 months, 1 year) approximately.

Last assessment for this report: ..... - ..... - ..... ☐ Not applicable IDAABE
yyyy mm dd

Date of death: ..... - ..... - ..... ☐ Not applicable IDAABE
yyyy mm dd

Current Haematological findings

Hb (g/dL) ..... ☐ Not evaluated HBD

Platelets (10^9/L) ..... ☐ Not evaluated PLATD

Were platelets transfused within 7 days before date of the test? ☐ No ☐ Yes VTRANS2

White Blood Cells (10^9/L) ..... WBCD ☐ Not evaluated

% haematocrit ..... ☐ Not evaluated HAEMATOCRIT

Was RBC transfused within 30 days before date of the test? ☐ No ☐ Yes RBCTRANSF

% Lymphocytes ..... ☐ Not evaluated PLYPBD

% neutrophils ..... PGRPBD ☐ Not evaluated

Was B-Cell Aplasia present since the last assessment? ☐ No ☐ Yes: % (percentage) of B-Cells ..... BCELLAPLASFU BCELLPC

Performance score

(COMPLETE ONLY FOR IF PATIENT IS ALIVE)

Performance score of the patient at the last assessment PERFSYST KARNOFSK

SYSTEM USED *(choose only one)*:

☐ Karnofsky or ☐ Lansky: Score: ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

☐ ECOG: ECOG Score: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Complications since the last report

DO NOT REPORT COMPLICATIONS THAT WERE RESOLVED BEFORE THE ADVANCED CELLULAR THERAPY

DO NOT REPORT COMPLICATIONS THAT WERE PREVIOUSLY REPORTED AS RESOLVED, UNLESS THEY RECURRED

GvHD

Did GvHD occur? ☐ No
(skip to OTHER COMPLICATIONS on page 63)

☐ Yes: GVHDPRES

Type of graft versus host disease (GvHD): GVHDTYP
☐ Acute GvHD
☐ Chronic GvHD

Acute GvHD

Maximum Grade: AGVHGRMX
☐ 0 (none) ☐ I ☐ II ☐ III ☐ IV
☐ Present but grade unknown ☐ Not evaluated

Indicate type: AGVHDTYP
☐ New onset
☐ Recurrent
☐ Persistent

Onset date: ..... - ..... - ..... DATAGVH
yyyy mm dd

Stage:

Skin	☐ 0 (none)	☐ 1	☐ 2	☐ 3	☐ 4	AGVHDSKI
Liver	☐ 0 (none)	☐ 1	☐ 2	☐ 3	☐ 4	AGVHDLIV
Lower GI tract	☐ 0 (none)	☐ 1	☐ 2	☐ 3	☐ 4	AGVHDLGI
Upper GI tract	☐ 0 (none)	☐ 1				AGVHDUGI
Other site affected	☐ No	☐ Yes				AGVHOTHR

Related to Cell Therapy ☐ No ☐ Yes CTHRELATED
Resolved? ☐ No ☐ Yes VGVHDRES

aGvHD treatment

Treatment for aGvHD ☐ No VTRAGVHD
(skip to CHRONIC GVHD section below)

☐ Yes: VTRAGVH2 IDAABCCD ANIMORIG ORIGIN OTHECHEM
☐ Corticosteroids
☐ MoAB: .....
☐ ATG/ALG
☐ Extra-corporeal photopheresis (ECP) TRAGVHECP
☐ Other: specify ..... VAGVHDTO VAGVHDTR

Chronic GvHD CGVHD

Episode: GRAVHOSD
☐ First episode
☐ Recurrence
☐ Continuous since last reported episode
☐ Yes, but resolved
☐ Yes, but resolved and recurred again

DRESCGVH Resolution date: ..... - ..... - .....
yyyy mm dd

Onset date: ..... - ..... - ..... IDAABE
yyyy mm dd

GvHD cont.

Maximum extent during this period

☐ Limited ☐ Extensive ☐ Unknown VCGVHDG

Maximum NIH score during this period

☐ Mild ☐ Moderate ☐ Severe ☐ Not calculated MAXNIHSC

INFECTIOUS COMPLICATIONS WITHIN THIS REPORTING PERIOD

INFECTION RELATED COMPLICATIONS VCOMB100

☐ No -> Skip INFECTIOUS COMPLICATIONS below and go straight to SECONDARY MALIGNANCY on page 60

☐ Yes -> Continue with the INFECTIONS below INFECTIO VOTINCOM INFCPRES IDAABE/BEGINFEP PATHOGEN VOTHPATH TREATEDINF RESOLVEDINF INFSITE OTHSITE

Bacteremia (report all episodes)

☐ No ☐ Yes (report all episodes – copy this page if neccessary):
(In case of the same pathogen, report episodes occuring after 14 days)

1) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

2) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

3) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

4) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Invasive fungal disease, including candidemia

☐ No ☐ Yes (report all episodes – copy this page if neccessary):

1) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

2) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

3) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

4) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

CNS infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Pneumonia

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

C. difficile infection

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Abdominal infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: …… or specify the type of clinically documented infection, e.g. typhlitis, cholecystits, gastroenteritis, etc:
yyyy mm dd

……

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Hepatitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Retinitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Cystitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Skin infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Upper respiratory tract infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

CMV reactivation

(DNA-emia in serum/plasma/blood)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest number of copies: ……cp/ml HVALREACTIV
yyyy mm dd

Highest number of copies date: ..... - ..... - ..... HDATEREACTIV
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

EBV reactivation

(DNA-emia in serum/plasma/blood/PMN)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest number of copies: ……cp/ml
yyyy mm dd

Highest number of copies date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

HHV6 reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest number of copies: ……cp/ml
yyyy mm dd

Highest number of copies date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Adenovirus reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest number of copies: ……cp/ml
yyyy mm dd

Highest number of copies date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Other virus reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes: specify……

Onset date: ..... - ..... - ..... Highest number of copies: ……cp/ml
yyyy mm dd

Highest number of copies date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Other Infectious Complications

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest number of copies: ……cp/ml
yyyy mm dd

Highest number of copies date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Other complications or toxicities during this period VOTCO100

☐ No -> Skip TOXICITIES table below and go straight to INFECTIOUS COMPLICATIONS on page 60
☐ Yes -> Continue with the TOXICITIES below
☐ Unknown

TOXICITIES/(non-infectious) COMPLICATIONS IDAABECA / AUIMPRES / VOTCOMPS / WHOSCORE/ DBEGCOM / TREATED / ONGOING

YOU MUST REPORT AND MARK ALL THE SPECIFIC COMPLICATIONS BELOW EVEN IF THEY ARE ABSENT

Cytokine release syndrome (CRS) (Macrophage Activation Syndrome (MAS))

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd Grade:……

Scale/criteria was used to determine the Grade of CRS…….. CRSSCALE

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Neurotoxicity

☐ No ☐ Yes: Select and complete all that apply

☐ Altered mental status

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Aphasia

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Hemiparesis or other focal motor deficit

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Seizure(s)

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Tremors

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Visual hallucinations

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Encephalopathy

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Cerebral Oedema

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Other, specify ……

Onset date: ..... - ..... - ..... Grade *(if applicable)*:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Grade 3 and 4 organ toxicity as per CTCAE

☐ No ☐ Yes: Select and complete all that apply

☐ Skin

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Liver

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Lungs

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Heart

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Kidney

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Gastrointestinal

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Other organ, specify…….

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Tumor Lysis Syndrome (TLS)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Hemorrhagic stroke

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Bone marrow aplasia

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Specify……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Hypogammaglobulinemia

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd **HGGLOBIA** **HGGLOBIAW**

Was hypogammaglobulinemia present before the cellular therapy? ☐ No ☐ Yes:

If Yes, was it worsened by the cellular therapy? ☐ No ☐ Yes

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Insertional mutagenesis

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd

Exacerbation of existing neurological disorder

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify………………………………………………
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

B-Cell Aplasia (report only If there was no B-Cell Aplasia present at the time of the Cellular Therapy)

☐ No ☐ Yes:

Onset date: .... - .... - ....
yyyy mm dd

Resolved? ☐ No ☐ Yes

Other toxicity/complication

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify………………………………………………
yyyy mm dd

Grade *(if applicable)*:………

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Other toxicity/complication

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify………………………………………………
yyyy mm dd

Grade *(if applicable)*:………

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Other toxicity/complication

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify………………………………………………
yyyy mm dd

Grade *(if applicable)*:………

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Secondary malignancy

Did a secondary malignancy or autoimmune disorder occur?

☐ No ☐ Yes:

SECONDDI
DISMCLFD

Diagnosis: .....

Date of diagnosis: ..... - ..... - .....
IDAABB *yyyy* *mm* *dd*

Histologic Type:…….. **VHISTSGD**
(if applicable)

Location:…….. **LOCATION**
(if applicable)

Was sample/biopsy obtained ☐ No ☐ Yes **BIOPSYOBT**
(if applicable)

Is this secondary malignancy derived from cells that composed or were part of the infused medicinal product or advanced cellular therapy product ?

☐ No ☐ Yes ☐ Not applicable ☐ Unknown **RPDRGRAD**

POST-THERAPY TREATMENT

Additional Treatment for Complications and the Main Disease

Please include only systemic treatments

Did the patient undergo additional treatment during or immediately after the cellular therapy or since the last reported assessment? ADDTREAT

Please do not include treatment for aGvHD here, this should be reported in the GvHD section.

☐ No (skip to the last question on this page)
☐ Yes, indicate in tables below

Start date of the additional treatment since last report: .... IDAABC
yyyy mm dd

Unplanned treatment for complications

ADDPROT VCHEMOTH IDAABCCD INDICATION TRETSTARVINTBTDE

☐ No ☐ Yes, specify in the table below

Drug/Regimen (specify)	Indication (as specified in the Complications section on pages 59 to 60)	Started	Finished
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd

Unplanned treatment for Cellular Therapy failure

☐ No ☐ Yes, specify in the table below ADDPROT VCHEMOTH IDAABCCD INDICATION TRETSTARVINTBTDE

Drug/Regimen (specify)	Indication	Started	Finished
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd
		...../...../..... yyyy mm dd	...../...../..... yyyy mm dd

Other type of treatment VOTHERT ☐ No ☐ Yes, specify ..... VOTHERTS ☐ Unknown

Is patient getting any medications not related to cell therapy or its indications OTHADDTREAT
☐ No ☐ Yes

First Relapse/Progression or Significant worsening after Cellular therapy

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF A PRIMARY DISEASE INCLUDING INFECTIONS

First Relapse or Progression or Significant worsening of organ function of the primary disease
(detected by any method) VRELPROG

☐ No

☐ Yes: Date of relapse ..... - ..... - ..... IDAABE
yyyy mm dd

☐ Continuous progression since Cellular therapy

Last Disease Status

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF A PRIMARY DISEASE INCLUDING INFECTIONS

Last disease status VDISESTA

☐ Complete remission / Normalisation of organ function / No infection present

☐ Partial remission / Partial or non normalisation of organ funcition

☐ No response

☐ Disease progression or worsening of organ function

☐ Not evaluated

(LYMPHOMA only) For **Relapse** status: HISTPATHOLYM
Histopathological verification of relapse? ☐ No ☐ Yes

HAEMOGLOBINOPATHY ONLY

Transfusion status VSVSTAL

☐ No transfusion required

☐ Transfusions required: Date of the 1st transfusion ..... - ..... - ..... DATTRANSF
yyyy mm dd

Hospital admission

Was the patient transferred to the Intensive Care Unit? INTCARE ☐ No ☐ Yes

Was inpatient admission and care needed (not ICU)? INPATIENT ☐ No ☐ Yes

Quality of Life

Complete ONLY for MONTH 6 and ANNUAL FOLLOW UP

Survival Status

VPATSTAT

☐ Alive ☐ Dead ☐ Check here if patient lost to follow up

If dead: Main Cause of Death *(check only one main cause)*: VCAUSDTH

- ☐ Relapse or Progression/Persistent disease
- ☐ Secondary malignancy
- ☐ Cellular Therapy related
- ☐ HSCT Related Cause
- ☐ Unknown
- ☐ Other: ..... DEACSBMU

Indicate toxicity related causes of death *(check as many as appropriate)*:

- ☐ GVHD VCSDTGVH
- ☐ Cytokine release syndrome VCSDTCRS
- ☐ Interstitial pneumonitis VCSDTINP
- ☐ Pulmonary toxicity VCSDTPTX
- ☐ Infection: VCSDTINF
  - ☐ bacterial VCSDTBAC
  - ☐ viral VCSDTVIR
  - ☐ fungal VCSDTFUN
  - ☐ parasitic VCSDTPAR
- ☐ Rejection/Poor graft function VCSDTREJ
- ☐ History of severe Veno occlusive disorder (VOD) VCSDTVOD
- ☐ Haemorrhage VCSDTHMR
- ☐ Cardiac toxicity VCSDTCTX
- ☐ Central nervous system (CNS) toxicity VCSDTCNS
- ☐ Gastrointestinal (GI) toxicity VCSDTGIT
- ☐ Skin toxicity VCSDTSKI
- ☐ Renal failure VCSDTREN
- ☐ Multiple organ failure VCSDTMOF
- ☐ Other:..... DEACSBMR

Persistence of the Infused Cells

Were tests performed to detect the persistence of the cellular products during this period?
PRSTSTDONE

☐ No ☐ Yes: Date of the last test ..... - ..... - ..... PRSTSTDATE
yyyy *mm* *dd*

CELPRDSOUR CELPRDSOSPC

Source of cells used for the test: ☐ Bone Marrow ☐ Peripheral Blood ☐ Tumour ☐Other, specify……..

Technique used MOLPCR FLWCYTOMTR CHIMAETECH IMAGETECH IMHISTECH OTHTSTTECH / OTHTECHSPC

☐ Molecular (PCR) ☐ Flow cytometry ☐ Chimaerism ☐ Imaging ☐ Immunohistochemistry

☐ Other, specify ……..……..

Were cells detected? CELPRDTDET

☐ No

☐ Yes

END OF FOLLOW UP