Kite Pharma Inc.

NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA, PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA AND FOLLICULAR, LYMPHOMA
Protocol ID	KT-EU-471-0117
Protocol Version/Date:	Original: 07 February 2019 Version 1.1: 03 July 2019 Version 1.2: 09 October 2019 Version 1.3: 06 November 2019 Version 2.0: 01 July 2021 Version 2.1: 03 August 2022
EU PAS Register No	EUPAS32539
Clinical Trials.gov Identifier	Study not registered
Active substance	Axicabtagene ciloleucel
Medicinal Product	YESCARTA®
Product reference	EMEA/H/C/004480
Procedure number	EMEA/H/C/PSP/S/0079
Joint PASS	No
Research Question and Objectives	Primary objective: To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential.

	Secondary objectives: To determine the overall survival rate and causes of death after administration of YESCARTA. To determine the time to next treatment after administration of YESCARTA. To determine the time to relapse or progression of primary disease after administration of YESCARTA. To assess the safety and effectiveness profile by gender, age, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored. To assess the risk of tumor lysis syndrome (TLS) and aggravation of Graft Versus Host Disease (GvHD), and the detection of replication competent retrovirus (RCR) in samples of patients with secondary malignancies. CCI [redacted]
Country (-ies) of study	In countries where YESCARTA will be authorized. At a minimum UK, Spain and Germany will be countries of study, further countries might be added.
Kite Study Director / Author / Contact Person:	Name: PPD Telephone: PPD Email: PPD
Marketing Authorization Holder	Kite Pharma EU B.V.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
aRMMs	additional Risk Minimization Measures
auto-SCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CHMP	Committee for Human Medical Products
CI	Confidence interval
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology of Adverse Events
DLBCL	Diffuse large B-cell lymphoma
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
FL	Follicular Lymphoma
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
LBCL	Large B-Cell Lymphoma
mAb	Monoclonal antibody
MAH	Marketing Authorization Holder
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
OOS	Out of specifications
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PMBCL	Primary Mediastinal B-cell Lymphoma

PVE	Pharmacovigilance & Epidemiology
QPPV	Qualified Person for Pharmacovigilance
RCR	Replication-competent retrovirus
RWE	Real World Evidence
SAE	Serious adverse event
SADR	Serious adverse drug reaction
scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SSR	Special situation report
TCR	T-cell receptor
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 (MAH) contact person	PPD Director Regulatory Affairs Kite Gilead Sciences International Ltd Flowers Building Granta Park, Abington Cambridge CB21 6GT, UK	Phone: PPD Email: PPD
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2. PROTOCOL SYNOPSIS/ABSTRACT

Kite Pharma Inc.

Study Title:	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA, PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA, AND FOLLICULAR LYMPHOMA
Rationale and Background:	To capture long-term follow-up data for recipients of YESCARTA to evaluate the safety, specifically incidence rates and severity of ADRs including long term safety, the risk of subsequent neoplasm as well as the known and potential risks associated with this product. 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 YESCARTA infusion and for 15 years of follow-up.
Research Question and Objectives:	The primary objective of this study is as follows: • To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. The secondary objectives of this study are as follows: • To determine the overall survival rate and causes of death after administration of YESCARTA. • To determine the time to next treatment after administration of YESCARTA. • To determine the time to relapse or progression of primary disease after administration of YESCARTA. • To assess the safety and effectiveness profile by gender, age, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored.

- To assess the risk of tumor lysis syndrome (TLS) and aggravation of Graft Versus Host Disease (GvHD), and the detection of replication competent retrovirus (RCR) in samples of patients with secondary malignancies.

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Study Design: This is a long-term, non-interventional study of patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of therapy, or with relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy, who have been treated with YESCARTA.
Patients' data might be entered into the EBMT Registry up to 1 week prior or anytime following YESCARTA infusion and patients will be followed for 15 years in the EBMT registry.

Population: Recipients of YESCARTA for relapsed/refractory diffuse large B-cell lymphomas (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of therapy, or with relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy, at participating centers who consent to have data reported to the European Society for Blood and Marrow Transplantation (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, ECOG and Karnofsky score are allowed.

Patients participating in interventional clinical trials 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 Primary Objectives
  - Secondary malignancy (date of diagnosis, type, location and relevant details on biopsy/diagnostic results)
  - CRS (grade, date of onset, treatment and resolution status)

- Neurologic toxicity (type, grade, 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 100 days after the administration of YESCARTA. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive days, 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.
- Pregnancy that occurs after administration of YESCARTA and additional information related to the outcome of the pregnancy and the newborn's health

- Variables utilized for analysis of Secondary Objectives
  - Date and main cause of death, and date of last assessment
  - Additional treatment and date of treatment received for primary disease (DLBCL, PMBCL or FL) after YESCARTA administration
  - Date of the first relapse or progression or significant worsening of the primary disease (DLBCL, PMBCL or FL) after the YESCARTA infusion
  - Grade, date of onset and resolution of TLS
  - Type, resolution status, onset date of aggravation of GvHD. For acute GvHD: 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]

CCI [redacted]

- Variables utilized for analysis of exposure to YESCARTA
  - Name and dose level of lymphodepleting chemotherapy received prior to YESCARTA infusion
  - YESCARTA infusion: date, and whether YESCARTA 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 YESCARTA infusion
  - Indication for treatment with YESCARTA
  - Disease subtype (eg, NHL histologies)
  - Disease status at time of cellular therapy (eg, sensitive or resistant to chemotherapy or radiation prior to therapy)
  - Prior lines of treatment and response
  - Disease stage at time of cellular therapy
  - Prognostic information: double/triple hit, international prognostic index, cytogenetics (GCB-DLBCL, ABC-DLBCL)
  - 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

Data Sources:

For this specific protocol: patient data as available within the EBMT Registry for this study. For the EBMT Registry: the patient's medical records

Study Size:

All eligible patients who have been treated with YESCARTA and documented in the EBMT Registry within five years from study start for patients with DLBCL and PMBCL, or for all patients with FL treated with Yescarta within five years from time of approval of FL indication and approval of the protocol for this study to include FL patients.

In addition to the further characterisation of the immediate and established toxicities of YESCARTA, the study is designed to detect rare and delayed safety events occurring in patients during 15 person-years of follow up.

For Large B-Cell Lymphoma (LBCL), the available person-years of follow-up are estimated using a piecewise linear survival curve with 50% survival at 2 years and 30% survival long-term. A 10% overall loss to follow-up is assumed. The targeted accrual will provide 95%, or 83%, or 70% likelihood of detecting one event of interest if the true rate is 1 in 100, or 1 in 150, or 1 in 250 over a 15-year period.

For FL, the available person-years of follow-up are estimated using a piecewise linear survival curve with 72% survival at 2 years and 35% survival long-term. A 10% overall loss to follow-up is assumed. The targeted accrual will provide >99%, 98%, 79%, 54%, 41%, 32%, 27% likelihood of detecting one event of interest if the true rate is 1 in 10, or 1 in 20, or 1 in 50, or 1 in 100, or 1 in 150, or 1 in 200, or 1 in 250 over a 15-year period.

Data Analysis:

- Primary Endpoints
  - — Incidence rates, time to onset, type and location of secondary malignancy
  - — Incidence rates, severity, time to onset, management and resolution of CRS
  - — Incidence rates, severity, time to onset, management and resolution, and type of neurologic events
  - — Incidence rates of prolonged cytopenias
  - — 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

  - Incidence rates of pregnancy, and pregnancy outcome among women with childbearing potential

- Secondary Endpoints
  - Overall survival
  - Time to next treatment of the primary disease
  - Time to relapse or progression of the primary disease
  - Primary and secondary endpoints on subgroups by gender, age, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (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 aggravation of 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]

Analysis of all endpoints for this study will include all patients satisfying the eligibility criteria who are documented within the EBMT Registry and treated with YESCARTA.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 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 follow-up period, specified subgroups and other potential confounders (demographics and baseline characteristics, see Section 7.3.5).

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 and time to next treatment, 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 subgroups and other potential confounders (demographics and baseline characteristics; see Section 7.3.5).

Milestones:

DLBCL and PMBCL

Start of data collection:	21 August 2020
End of data collection:	22 May 2040
Study duration:	20 years
Annual Reports:	Annually for 5 years, then every 2 years
Final Study report:	14 November 2040

FL

Start of data collection:	01 March 2023
End of data collection:	01 December 2042
Study duration:	20 years
Annual Reports:	Annually for 5 years, then every 2 years
Final report:	01 June 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	03 July 2019	Various	Update	To address the comments of the PRAC Request for a Revised PASS protocol in the PRAC PASS protocol assessment report and to implement the respective changes
1.2	09 October 2019	Various	Update	To address the comments of the 2nd PRAC Request for a Revised PASS protocol in the PRAC PASS protocol assessment report and to implement the respective changes
1.3	06 November 2019	Various	Update	To address comments of the 3rd PRAC Request for revisions of the PASS protocol and to implement the respective changes
2.0	01 July 2021	Various	Amendment	To add new indication FL
2.1	03 August 2022	Various	Amendment	To address comments of the PRAC Request for revisions of the PASS protocol to update the milestone dates for FL indication and specify that the EBMT quarterly and annual reports will include both DLBCL and FL indications (not prepared separately)

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 EBMT prior to implementation.

4. MILESTONES

Table 3. Protocol Milestones

Milestone	Planned Date
PRAC approval of study protocol*	31 October 2019
Protocol registration in the EU PAS Registry	10 December 2019
DLBCL and PMBCL:	
Start of data collection**	21 August 2020
End of data collection***	22 May 2040
Study duration	20 years
Safety Data Reports****	2020 to 2024, frequency thereafter to be re-evaluated
Annual reports	2021 to 2025 annually, then every 2 years
Final report of study results	14 November 2040
FL:	
Start of data collection**	01 March 2023
End of data collection***	01 December 2042
Study duration	20 years
Safety Data Reports****	2023 to 2028, frequency thereafter to be re-evaluated
Annual reports	2024 to 2028 annually, then every 2 years
Final report of study results	01 June 2043

***** Date when EMA/PRAC endorsed protocol version 1.2 and acknowledged Kite's commitments for future protocol edits that resulted in protocol version 1.3, dated 06 November 2019. Per EMA recommendation no formal submission of version 1.3 occurred.
****** 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-471-0117 will take place three months after protocol registration or contract execution with the EBMT, whichever comes last.
******* 20 years after PRAC approval of protocol or contract execution with the EBMT, whichever comes last, no further data will be included in the study analyses.
******** 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 - when it will be submitted stand-alone in between PSUR cycles.

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

Engineered autologous T-cell immunotherapy, which uses a patient's own immune cells, offers a promising approach to treating many types of cancer. To be effective, such T cells must possess the appropriate specificity for a tumor, be present in sufficient numbers, and be able to overcome any local immunosuppressive factors. Selecting an appropriate target antigen for T-cell therapy is critical to the potency and safety of the therapy. 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 cell therapies have demonstrated promising antitumor activity across numerous B-cell malignancies, including non-Hodgkin lymphoma (NHL) {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a, Kochenderfer 2017b, KYMRIAH 2020, KYMRIAH™ 2018, Locke 2019, Schuster 2019, Turtle 2016, Wang 2020, YESCARTA 2020, YESCARTA 2019} chronic lymphocytic leukemia (CLL) {Kochenderfer 2015, Porter 2015, Porter 2011}, and acute lymphoblastic leukemia (ALL) {Davila 2014, Gupta 2007, Lee 2015, Maude 2014, Maude 2015, Michea 2018, Singh 2016}.

Anti-CD19 Chimeric Antigen Receptor T-cell Product: Axicabtagene Ciloleucel Axicabtagene ciloleucel is an anti CD19 CAR T cell product manufactured by Kite Pharma, Inc. (hereafter referred to as Kite) that is currently approved for the treatment of r/r large B-cell lymphomas {Locke 2019, Neelapu 2017, YESCARTA 2019}. In the US axicabtagene ciloleucel is also approved for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

CD19 is a 95 kD transmembrane protein expressed only in the B-cell lineage. Expression begins at the pro-B-cell stage and continues throughout B-cell differentiation {Anderson 1984, Nadler 1983, Uckun 1990, Uckun 1988}; expression is downregulated in plasma cells {Gupta 2009, Lin 2004}. CD19 expression is maintained in most B-cell malignancies, including all subtypes of B-cell non-Hodgkin lymphoma (NHL, CLL, non-T-cell ALL, and on a subset of multiple myeloma plasma cells) {Anderson 1984, Garfall 2015, Hajek 2013, Johnson 2009, Leonard 2001, Nadler 1983, Olejniczak 2006, Rodriguez 1994, Uckun 1988}.

Axicabtagene ciloleucel is an autologous CAR T-cell product in which a subject's T cells are engineered to express receptors consisting of a single-chain antibody fragment (ScFv) against CD19 linked to CD3ζ and CD28 T cell activating domains that result in elimination of CD19-expressing cells {Jackson 2016}. 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 (IL)-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct 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}. A schematic of the anti-CD19 CAR construct is shown in Figure 1.

Figure 1. Axicabtagene Ciloleucel Anti-CD19 CAR Construct

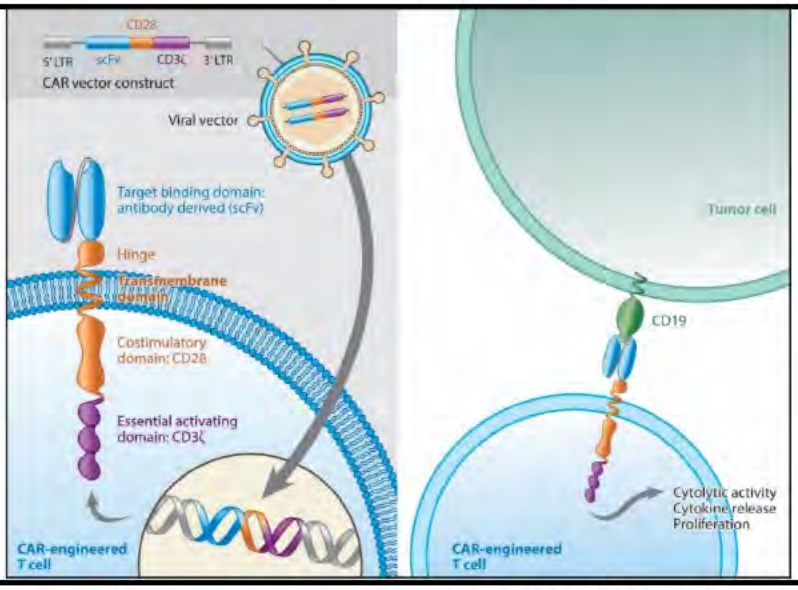

Figure 1: Left panel demonstrates axicabtagene ciloleucel construct with scFv/CD28/CD3ζ, which is inserted in a replication-incompetent gamma-retroviral vector and, upon transfection of T-cells, expresses the chimeric transmembrane protein. The right panel demonstrates the anti-CD19 CAR T-cell binding to its target CD19 on the tumor cell surface.

Treatment of relapsed or refractory large B-cell lymphomas with anti-CD19 CAR T cells results in a high response rate with durable remissions. In the primary analysis based on the modified intent-to-treat (mITT) population (minimum follow up of 6 months) in the pivotal multicenter trial (ZUMA-1) by Kite Pharma, Inc. (hereafter referred to as Kite), the ORR was 72% and complete response (CR) rate was 51%, as determined by an independent review committee. Administration of CAR T cells carries a number of risks independent of target because the immune reaction against tumor cells can elicit a generalized reaction that includes fever, hypotension, respiratory failure, and death {Brudno 2016}. These toxicities are defined as Cytokine Release Syndrome (CRS) and generally occur within the first week from treatment (Table 4). A revised grading system was proposed by Lee and colleagues based on the number of affected organs, severity, and therapeutic approaches needed, ie, vasopressors or ventilatory support {Lee 2014}. Secondly, neurologic events are also observed, which can occur either in the presence or absence of CRS with symptoms ranging from fine tremors to aphasia and seizures (Table 4) {Brudno 2016, Lee 2014, Park 2016}. In the ZUMA-1 pivotal trial, the overall rates of CRS and neurologic events were 93% and 64%, respectively. The rates of Grade 3 or higher CRS and neurologic events were 12% and 31%, respectively. The rate of Grade 5 CRS was 1% (2 subjects). While no Grade 5 neurologic events were reported in the pivotal cohort, Grade 5 events of intracranial hemorrhage (not related to axicabtagene ciloleucel) and cerebral edema (related to axicabtagene ciloleucel) have been reported in the non-pivotal cohorts of ZUMA-1. The median time to onset of first CRS symptoms was 2 days (range: 1 to 12 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median duration of CRS symptoms was 7 days (range: 2 to 29 days, excluding 1 outlying subject with a duration of 58 days). The median time to onset of first neurologic events was 5 days (range: 1 to 17 days). Among the subjects whose neurologic events resolved, the median

duration of neurologic events was 13 days (range: 1 to 191 days, excluding 1 outlying subject with a duration of 451 days).

Table 4. Selected Signs and Symptoms of CRS and Neurologic Events after Infusion of CAR T Cells

Cytokine Release Syndrome Symptoms
Fever
Fatigue
Cardiac failure
Tachycardia
Other cardiac arrhythmias
Dyspnea
Hypoxia
Capillary leak syndrome
Chills
Renal function impairment
Headache
Malaise
Liver function abnormalities
Nausea
Diarrhea
Hypotension
Coagulation impairment
Neurologic Symptoms
Seizures
Somnolence
Headache
Confusion
Agitation
Speech impairment
Tremor
Encephalopathy
Ataxia
Memory impairment
Mental status changes
Hallucinations
Depressed level of consciousness
Delirium
Dysmetria
Brain oedema

Target-specific toxicities are related to direct cytotoxicity against the tumor and normal B cells expressing the antigens. CD19-specific CAR T cells have a direct effect on B cells, which leads to B-cell aplasia and, consequently, hypogammaglobulinemia {Frey 2016, Grupp 2013, Lee 2015, Maude 2014, Maus 2016}.

Patients with lymphoproliferative disorders, such as B-cell lymphomas, have a higher risk of developing other cancers (subsequent neoplasms) compared to the general population (standardized incidence ratio of 1.25 to 1.43) {Bilmon 2014, Chien 2015, Rossi 2015}. This higher risk results primarily from exposure to prior chemotherapy and radiation either as initial or subsequent treatment or as part of an autologous stem cell transplant (auto-SCT). The probability of developing a secondary malignancy 10 years after auto-SCT in patients with lymphoma ranges from 7.9% to 12.9% {Metayer 2003, Seshadri 2009, Smeland 2016}. The types of subsequent neoplasms most commonly observed are acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and melanoma {Bilmon 2014, Metayer 2003, Vaxman 2015}. Cumulative incidence of subsequent neoplasm 10 years after HDT and auto-SCT ranges from 5% to 21% {Bilmon 2014, El-Najjar 2014, Forrest 2005, Pirani 2011, Seshadri 2009, Tarella 2011}.

Axicabtagene ciloleucel manufacturing relies on a replication defective murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T-cell genome, which presents a theoretical risk of oncogenesis via insertional mutagenesis or replication-competent retrovirus (RCR). However, numerous nonclinical {Heinrich 1998 Newrzela 2008} and clinical studies of patients with hematologic malignancies or solid tumors and in patients infected with human immunodeficiency virus (HIV) showed no overt genotoxic effects of γ-retroviral vector-mediated gene transfer of T cells. A review of previous observations of genotoxic events in early clinical trials of γ-retroviral vector-mediated gene transfer into hematopoietic stem cells (HSCs) by Bushman and colleagues indicated that genotoxic events were attributable to activation of oncogenes by retroviral insertion and that the use of HSCs and introduction of cellular growth factors aimed to restore immune competency were facilitating factors {Bushman 2007}.

Among 86 unique patients who exhibited clinical benefit and had follow-up times ranging from 3 months to >5 years across 5 clinical studies of hematologic malignancies and solid tumors, no malignancies secondary to axicabtagene ciloleucel have been reported {Brentjens 2013, Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015, Robbins 2015}.

One of these studies has shown no evidence of subsequent neoplasms over a period of up to 23 months in a total of 43 patients with advanced B-cell malignancies treated with retrovirally transduced T cells expressing the same CAR as utilized in axicabtagene ciloleucel {Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015}. Long term results from 3 studies to evaluate gamma retroviral vector engineered T-cells for the treatment of HIV showed no treatment-related malignancies 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 samples tested for at least 11 years post-infusion. This analysis represented over 540 patient-years and showed no clinical evidence of viral vector integration-mediated toxicity.

In addition, a retrospective analysis of subjects treated with replication defective γ-retrovirus-transduced T cells across 29 clinical trials spanning from 2001 to 2009, covering 297 individual products and 629 follow-up samples ranging from 1 month to 8 years after infusion, showed no evidence of RCR or insertional mutagenesis {Bear 2012}. In summary, more than a decade of follow-up of patients treated with T cells engineered to express a TCR or CAR encoded by a γ-retroviral vector has not revealed any cases of genotoxicity or RCR that have translated to a subsequent neoplasm.

A theoretical risk remains, however, that genetic modification of T cells with γ-retroviral vectors could result in subsequent neoplasms manifested through insertional mutagenesis introduced during the manufacturing process or by the development of RCR. Although the manufacturing of CAR T cells using vectors similar to the one used in the manufacture of axicabtagene ciloleucel includes provisions to ensure that the virus is replication- defective and the likelihood of insertional mutagenesis in mature polyclonal T cells is low, there is a potential risk of insertional mutagenesis and emergence of RCR after these cell products are more broadly used. Monitoring the presence of γ-retroviral vector sequences and RCR in the development of subsequent neoplasms is an important step to understand the long-term safety profile of this product.

5.1.1. Diffuse Large B-cell Lymphoma (DLBCL)

Treatment of relapsed or refractory DLBCLs with anti-CD19 CAR T cells results in a high response rate with durable remissions. The overall response rate (defined as the sum of complete and partial responses) in the Kite pivotal multicenter trial (ZUMA-1) was 82%, with a complete response rate of 54% {Neelapu 2017}. Due to responses that occurred between the 6- and 12-month data cuts, the overall response rate and the complete response rate (ORR) improved to 83% and 58% respectively in the 12-month analysis {Locke 2019, Neelapu 2017}.

In the ZUMA-1 pivotal trial, the overall rates of CRS and neurologic toxicities were 93% and 64%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 13% and 28%, respectively. The rate of Grade 5 CRS was 1%. While no Grade 5 neurologic toxicities were reported in the pivotal cohort, Grade 5 events of intracranial hemorrhage and cerebral edema have been reported in the non-pivotal cohorts of ZUMA-1. The median time to onset of first CRS symptoms was 2 days (range: 1 to 12 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median time to resolution of CRS symptoms was 8 days. The median time to onset of first neurologic toxicities was 5 days (range: 1 to 17 days). Among the subjects whose neurologic toxicities resolved, the median time to resolution of neurologic toxicities was 17 days.

The rates of CRS and neurologic toxicities in the 24-month analysis were similar to those from the primary analysis. In the 24-month analysis, the overall rates of CRS and neurologic toxicities were 93% and 67%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 11% and 32%, respectively. The rate of Grade 5 CRS was 1%. No new Grade 5 CRS or neurologic events were reported. The median time to onset of first CRS symptoms was 2 days (range: 1 to 12 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median time to resolution of CRS symptoms was 7 days. The median time to onset of first neurologic toxicities was 5 days (range: 1 to 17 days). Among the subjects whose neurologic toxicities resolved, the median time to resolution of neurologic toxicities was 13 days (range: 1 to 191 days) {Locke 2019}.

5.1.2. Follicular Lymphoma (FL)

In the primary analysis of ZUMA-5 with 12 month follow-up, the rates of any grade CRS and neurologic toxicities were 78% and 56%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 6% and 15%, respectively. The rate of Grade 5 CRS was 1%. No Grade 5 neurologic toxicities were observed. The median time to onset of first CRS symptoms was 4 days (range: 1 to 15 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median duration of CRS was 6 days. The median time to onset of first neurologic toxicities was 7 days (range: 1 to 177 days). Among the subjects whose neurologic toxicities resolved, the median duration of neurologic toxicities was 14 days. The rates of CRS and neurologic toxicities, median onset and duration of both CRS and neurologic toxicities in the 18-month analysis were consistent with data observed in the primary analysis.

5.1.3. Purpose of the Current Study

The purpose of this study is to analyze and report on the long-term follow-up data for recipients of axicabtagene ciloleucel captured in the EBMT Registry to address the long-term safety of this product, including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. The purpose of the study therefore includes the further characterisation of the immediate and recognised toxicities of YESCARTA, as well as the long-term and delayed onset ADRs.

The EBMT is a non-profit organisation that was established in 1974 to allow scientists and physicians involved in clinical bone marrow transplantation to share their experiences and develop co-operative studies. More recently, the scope of the organisation 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 stem cell transplant registry to systematically capture data on all cell therapies. This study will use the data accrued on YESCARTA in the EBMT Registry to systematically evaluate information on patients receiving YESCARTA and for 15 years of follow-up.

6. RESEARCH QUESTIONS AND OBJECTIVES

This is a long-term safety study of recipients of YESCARTA for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy, or of relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

The study will utilize long-term follow-up data for recipients of YESCARTA to evaluate the safety including long term safety, specifically incidence rates and severity of ADRs, the risk of subsequent neoplasm, known and potential risks associated with this product, as well as rare and delayed safety events occurring in patients.

Therefore, the study will make secondary use of the data captured in the EBMT Registry, using the infrastructure EBMT created for the stem cell transplant registry, to systematically capture information at the time of YESCARTA infusion and for 15 years of follow-up.

The primary objective of this study is:

To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential.

The secondary objectives of this study are:

- To determine the overall survival rate and causes of death after administration of YESCARTA.
- To determine the time to next treatment after administration of YESCARTA.
- To determine the time to relapse or progression of primary disease after administration of YESCARTA.
- To assess the safety and effectiveness profile by gender, age, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravation of GvHD, and the detection of RCR in samples of patients with secondary malignancies.

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7. RESEARCH METHODS

7.1. Study Design

This study is a long-term, non-interventional study planned to evaluate outcomes of recipients of YESCARTA for treatment of relapsed or refractory DLBCL and PMBCL after two or more lines of systemic therapy, or of relapsed or refractory FL after three or more lines of systemic therapy, 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. 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 YESCARTA infusion and patients will be followed for 15 years. 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.

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 in 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 (currently dated 21/12/2020)).

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 in their registry 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 its content can 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 also 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 patients treated with YESCARTA for relapsed/refractory diffuse large B-cell lymphomas (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of therapy, or relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy, irrespective of whether the YESCARTA 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 will not be included in the study analyses.

7.2.2. Study Centers

All centers that are qualified for the use of YESCARTA 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 YESCARTA 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 both initial as well as refresher training to qualified prescriber sites, the contact with centers that are contributing to the EBMT Registry can 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 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 Objectives

- Secondary malignancy is defined as the development of any new malignancies, with the exception of relapsed large B-cell lymphomas, occurring after the administration of YESCARTA. The EBMT Registry will collect the date of diagnosis, type, location and, if a biopsy occurred, information whether secondary malignancy was derived from cells that composed or were part of the infused medicinal product or cell/gene therapy product, and this study will utilize this data for analysis.

- CRS is a class effect of CAR T-cell therapies, which may occur at different grades of severity, characterized by fever; rigors; nausea; emesis; headache; hypotension; and pulmonary, hepatic, and renal dysfunction. The EBMT Registry will collect CRS grade, system of grading, date of onset, treatment and resolution status and this study will utilize this data for analysis.

- Neurologic toxicity is a class effect of CAR T-cell therapies and most commonly includes confusion, delirium, aphasia, obtundation, myoclonus, and seizures. The EBMT Registry will collect the type, grade (according to the Common Terminology of Adverse Events [CTCAE] or ICANS score), treatment, date of onset and resolution status of all neurologic toxicities, and this study will utilize this data for analysis.

- Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 100 days after the administration of YESCARTA. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive days, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. The EBMT Registry will collect the date of recovery for ANC and platelets, and this study will utilize this data for analysis.

- 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 EBMT Registry will collect the type, organism, treatment and date of onset of infection as well as resolution, and this study will utilize this data for analysis.

- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. The EBMT Registry will collect for hypogammaglobulinemia the date of onset, treatment, and resolution status, and this study will utilize this data for analysis.

- The EBMT Registry will collect data on any pregnancy that occurs after administration of YESCARTA and additional information related to the outcome of the pregnancy and the newborn's health, and this study will utilize this data for analysis.

Table 5. 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).

7.3.2. Variables utilized for analysis of Secondary Objectives

- Date and main cause of death, and date of last assessment
- Additional treatment and date of treatment received for primary disease (DLBCL, PMBCL or FL) after YESCARTA administration
- Date of the first relapse or progression or significant worsening of the primary disease (DLBCL, PMBCL or FL) after the YESCARTA infusion
- Grade, date of onset and resolution of Tumor lysis syndrome (TLS)
- Type, resolution status, onset date of GvHD. For acute GvHD: grade, and relationship to YESCARTA
- 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)

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7.3.4. Variables for exposure to YESCARTA

- Name and dose level of lymphodepleting chemotherapy received prior to YESCARTA infusion.
- YESCARTA infusion: date, and whether YESCARTA 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 YESCARTA infusion
- Indication for treatment with YESCARTA
- Disease subtype (eg, NHL histologies)
- Disease status at time of cellular therapy (eg, sensitive or resistant to chemotherapy or radiation prior to therapy)
- Prior lines of treatment and response
- Disease stage at time of cellular therapy
- Prognostic information: double/triple hit, international prognostic index, cytogenetics (GCB-DLBCL, ABC-DLBCL)
- 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 (Appendix 5). The data on patients receiving YESCARTA 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 MED-A and/or 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

This study plans to evaluate all eligible patients who have been treated with YESCARTA and documented in the EBMT Registry within five years from study start for patients with DLBCL and PMBCL, or for all patients with FL treated with Yescarta within five years from time of approval of FL indication and approval of the protocol for this study to include FL patients and to follow these patients for 15 years. In addition to the further characterisation of the immediate toxicities of YESCARTA, the study is designed to detect rare or late onset safety events occurring in patients. Therefore, the primary analysis will consist of estimation of the rate of endpoint events per 15 person-years of follow up and the cumulative incidence of the event by 15 years, along with 95% confidence intervals (CIs). The events of interest (i.e., those described in Section 7.3.1) are subject to competing risks of death, which decrease the available person-years of follow-up.

For DLBCL and PMBCL, the available person-years of follow-up are estimated using a piecewise linear survival curve with 50% survival at 2 years and 30% survival long-term, indicating an average person-years of follow-up of 6.7 years. A 10% overall loss to follow-up is further assumed, resulting in total person-years of follow-up of approximately 4522. For FL, the available person-years of follow-up are estimated using a piecewise linear survival curve with 72% survival at 2 years and 35% survival long-term, indicating an average person-years of follow-up of 8.7 years. A 10% overall loss to follow-up is further assumed, resulting in total person-years of follow-up of approximately 1171. The assumed person-years of follow-up will provide the likelihood of seeing at least one event of interest as shown in Table 6, if the true event rate per 15 years of follow up is 1:250 through 1:10, respectively.

Table 6. Likelihood of Observing ≥ 1 Event of Interest for Patients with LBCL, FL Followed for Up to 15 Years

	True Event Rate						
Disease Type	**1:10**	**1:20**	**1:50**	**1:100**	**1:150**	**1:200**	**1:250**
LBCL	> 99%	> 99%	> 99%	95%	87%	78%	70%
FL	> 99%	98%	79%	54%	41%	32%	27%

a 2-year survival rate used in the calculation for LBCL and FL are based on the observed 2-year survival rate from ZUMA-1 study primary analysis for LBCL and from ZUMA-5 study primary analysis for FL.

b The likelihood calculation is based on projection that 1500 LBCL and 300 FL patients will be commercially treated in EU, and 50% of them will consent to participate in the study, ie, 750 and 150 commercially treated subjects in EU are assumed to be enrolled into the study. The true number of patients required to be enrolled to the study is depending on the number of patients enrolled according to the 5-year accrual period since the study starts implementing for the corresponding indication.

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 have 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 Day 100, 6 and 12 months and then annually for 15 years after infusion. 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 time lines as described in Section 9.

The center that administers YESCARTA 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 YESCARTA 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 provides raw data outputs in a standard format to Kite. Safety datasets are provided quarterly and full datasets annually.

7.7. Data Analysis

7.7.1. Primary Endpoints

- Incidence rates, time to onset, type and location of secondary malignancy
- Incidence rates, severity, time to onset, management and resolution of CRS
- Incidence rates, severity, time to onset, management and resolution, and type of neurologic events
- Incidence rates of prolonged cytopenias
- 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
- Incidence rates of pregnancy, and pregnancy outcome among women with childbearing potential

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 YESCARTA 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 YESCARTA infusion + 1. Deaths before experiencing the event will be taken as a competing risk.

7.7.2. Secondary Endpoints

- Overall survival: overall survival is the time from the date of YESCARTA infusion to the date of death due to any reason.
- Time to next treatment of the primary disease: time from YESCARTA infusion to next treatment of the primary disease (DLBCL, PMBCL or FL) or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk.
- Time to relapse or progression of the primary disease: time to relapse or progression is defined as the time from YESCARTA infusion to the first relapse or progression or significant worsening of the primary disease (DLBCL, PMBCL or FL), 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.

- Primary and secondary endpoints on subgroups by gender, age, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (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 aggravation of 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.

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[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 satisfying the eligibility criteria who are documented within the EBMT Registry and treated with YESCARTA. Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

Incidence rates of endpoint events will be provided, except where indicated. Multivariate Poisson regression analyses will be used to estimate incidence rates, adjusted for follow-up period, specified subgroups and other potential confounders (demographics and baseline characteristics; see Section 7.3.5).

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 and time to next treatment, 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 subgroups and other potential confounders (demographics and baseline characteristics; see Section 7.3.5).

The analysis will be firstly based on complete case analysis when the percentage of missing is around 5-10%. However, the potential impact of the missing values on the analysis will be also 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 describe 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 as sensitivity analyses 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).

7.7.5. Analysis of Primary Endpoint

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 YESCARTA 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 YESCARTA infusion. Treatment and resolution of neurologic toxicities will be described.

Prolonged cytopenias: The proportion of patients who fail to recover neutrophil and platelet counts, as previously specified, by Day 100 after the administration of YESCARTA will be described along with 95% CI using exact binomial methods.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 YESCARTA 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 YESCARTA 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 therapy will also be described as part of this endpoint.

Pregnancy and pregnancy outcome: Both the proportion of women who become pregnant and the pregnancy outcome and the newborn's health will be described as part of this outcome.

7.7.6. Analysis of Secondary Endpoints

Overall survival: Overall survival (OS) is the time from date of YESCARTA 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.

Time to next treatment: 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 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.

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 YESCARTA infusion and 95% CI will be estimated using competing risk analysis.

Aggravation of 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 YESCARTA infusion and 95% CI will be estimated using competing risk analysis. The severity and relationship to YESCARTA 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]

[redacted]

[redacted]

7.7.8. Interim Analysis

Annual reports will be prepared for the first five years and then every 2 years, in which an analysis of treated patients for the primary and secondary endpoints will be included. The study objective is 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 YESCARTA.

After start of data collection and until the patients at the EBMT centers have signed the revised version of the informed consent for data entry into the EBMT Registry, EBMT will provide data to Kite in anonymized form as aggregated reports. Only the revised informed consent form allows the EBMT to share pseudonymized data with Kite. Once the majority of patients signed this revised informed consent form, EBMT will provide Kite with a quarterly raw data output. Based on the data transferred, Kite performs an aggregate data analysis for YESCARTA within 30 days (45 days for the first report). Two quarterly reports will be submitted as appendices to the PSUR to the PRAC. In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document.

Interim analysis and annual reports will include both LBCL and FL indications.

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 4.000 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 are done, including the analyses of outliers, additional data requests and if needed statistic adjustments for missing data.

Apart from remote monitoring activities, on-site monitoring of data for 10% of the included YESCARTA 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 or 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 was not submitted for a patient during the 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 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 study monitoring plan.

7.9. Limitations of the Research Methods

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

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

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 YESCARTA 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 reduces to unacceptable levels because of low exposure rates, extremely slow patient accrual, or loss of the ability to follow-up

In the event that 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 YESCARTA.

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, 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 will be benefiting future patients. The only risk to patients is the risk of loss of privacy and confidentiality. This is a well-mitigated risk in relationship to the potential benefit to future recipients from 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) Modules VI and VIII – Post-Authorisation Safety Studies, 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 secondary analysis of existing data. 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 be consenting to provide 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 safety study protocol qualifies as non-interventional research with a design based on secondary use of data (i.e. utilizing data from patients 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. By 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, health authorities or to the EMA. The SmPC and packaging materials provide respective details and contact information. Kite further gives 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 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 YESCARTA 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 primary objective: secondary malignancies, CRS, neurologic toxicities, prolonged cytopenia, serious infections, and hypogammaglobulinemia. As part of the primary objective, pregnancy outcomes in female patients of childbearing potential are also of special interest.

9.2.3. Adverse Drug Reactions

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

9.2.4. Serious Adverse Events

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

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

This study has a primary endpoint to investigate pregnancy outcomes in female patients of childbearing potential reported to Kite. 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 examples are provided below:

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

- Pregnancy reports (maternal pregnancy and partner pregnancy): Reports of pregnancy following maternal or paternal exposure to the product.
- 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

10.1. Study Report and Publications

Reports listed below will be inclusive of both LBCL and FL patients'data.

10.1.1. Safety Data Reports

After start of data collection and until the patients at the EBMT centers have signed the revised version of the informed consent for data entry into the EBMT Registry, EBMT will provide data to Kite in anonymized form as aggregated reports. Only the revised informed consent form allows the EBMT to share pseudonymized data with Kite. Once the majority of patients signed this revised informed consent form, EBMT will provide Kite with a quarterly raw data output. Based on the data transferred, Kite performs an aggregate data analysis for YESCARTA within 30 days (45 days for the first report). Two quarterly reports will be submitted as appendices to the PSUR to the PRAC. In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document. A particular focus are the Adverse Events of Special Interest (AESIs) – which are considered to be the events which are the focus of the primary objective (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 primary objectives of the PASS study:
  secondary malignancies, CRS, neurologic toxicities, prolonged cytopenia, serious infections, hypogammaglobulinemia
- If reported, review of any unexpected events, which do not fall under the previously recognized risks or ADRs of special interest
- Review of pregnancies and outcomes
- Summary and conclusions

10.1.2. Annual Reports

Annual reports will be prepared for the first five years and then every 2 years, in which an analysis of treated patients for the primary and secondary endpoints will be included. The versions of the EBMT Cellular and Gene Therapy Form utilized in the EBMT Registry during the respective time period will be provided as appendices to these reports. 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, review and approve 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, and 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 to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

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

12. APPENDICES

Appendix 1. List of Stand-Alone Documents
Appendix 2. ENCePP Checklist for Study Protocols
Appendix 3. Reference Safety Information
Appendix 4. Kite Signature Page
Appendix 5. Cellular and Gene Therapy Form

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	None		

Appendix 2. ENCePP Checklist for Study Protocols

Study title:
LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND PRIMARY MEDIASTINAL B-CELL LYMPHOMA

EU PAS Register® number: EUPAS32539 **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))	☐	☐	☒	
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)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	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)	☐	☒	☐	
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
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)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 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?	☐	☒	☐	
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?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

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)	☐	☒	☐	
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)	☐	☒	☐	

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?	☐	☐	☒	

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: Meng Wang

Date:

Signature:

amd-5-KT-EU-471-0117_Annex 2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Epidemiology eSigned	05-Aug-2022 09:43:15

Appendix 3. Reference Safety Information

Current version of the EU SmPC for YESCARTA®.

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

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Yescarta (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare Yescarta, patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment linked to CD28 co-stimulatory domain and CD3-zeta signalling domain. The anti-CD19 CAR-positive viable T cells are expanded and infused back into the patient, where they can recognise and eliminate CD19-expressing target cells.

2.2 Qualitative and quantitative composition

Each patient specific single infusion bag of Yescarta 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 T cells.

Excipients with known effect

Each bag of Yescarta contains 300 mg sodium.

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

Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

4.2 Posology and method of administration

Yescarta 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 Yescarta. 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 treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

Posology

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

A single dose of Yescarta contains 2 x 10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.

The availability of Yescarta must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous must be administered prior to infusing Yescarta. The recommended days are on the 5^{th}, 4^{th}, and 3^{rd} day before infusion of Yescarta.

Pre-medication

- Paracetamol 500-1 000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour before Yescarta infusion is recommended.
- Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of Yescarta.

Monitoring

- Patients must 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 or symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion.
- Patients must be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Special populations

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection
There is no clinical experience in patients with active HIV, HBV or HCV infection.

Paediatric population
The safety and efficacy of Yescarta in children and adolescents below 18 years of age have not yet been established. No data are available.

Elderly
No dose adjustment is required in patients ≥ 65 years of age. Efficacy was consistent with the overall treated patient population.

Method of administration

Yescarta is to be administered via intravenous infusion.

Yescarta 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 Yescarta must take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation for infusion
- Verify that the patient's identity (ID) matches the patient identifiers on the Yescarta cassette.
- The Yescarta 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 Yescarta bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for the handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Yescarta 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. Yescarta must not be washed, spun down, and/or re-suspended in new medium prior to infusion. Thawing takes approximately 3 to 5 minutes.
- Once thawed, Yescarta is stable at room temperature (20 °C-25 °C) for up to 3 hours. However, Yescarta infusion must begin within 30 minutes of thaw completion.

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

For instructions on the handling, accidental exposure to and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

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

General

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

Patients must 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 is to 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 function must be considered depending on the severity of the reaction.

Reasons to delay treatment

Due to the risks associated with Yescarta treatment, infusion must be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection.
- Active graft-versus-host disease (GVHD).

Serological testing

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

Blood, organ, tissue and cell donation

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

Concomitant disease

Patients with active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Primary central nervous system (CNS) lymphoma

There is no experience of use of Yescarta in patients with primary CNS lymphoma. Therefore, the risk/benefit of Yescarta has not been established in this population.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, including life-threatening and fatal reactions, was very commonly observed with Yescarta with a time to onset of 1 to 12 days in ZUMA-1 and 1 to 11 days in ZUMA-5 (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. Interleukin-6 (IL-6) receptor inhibitor based therapy such as tocilizumab has been administered for moderate or severe CRS associated with Yescarta.

At least 1 dose of tocilizumab per patient must be on site and available for administration prior to Yescarta infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicine Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

Monitor patients daily for signs and symptoms of CRS for at least 10 days following infusion at the qualified clinical facility. After the first 10 days following infusion, the patient is to be monitored at the physician's discretion.

Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Yescarta. These include the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) must be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening- CRS, consider intensive-care supportive therapy.

Yescarta must not be administered to patients with active infections or inflammatory disease until these conditions have resolved.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction must be managed by standards of critical care and measures such as echocardiography are to be considered.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

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

Yescarta continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Yescarta-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, manage as Grade 2.	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity[b].	Administer tocilizumab[c] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternate measures for treatment of CRS.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
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). Continue corticosteroids use until the event is Grade 1 or less, then taper. If not improving, manage as Grade 4 (below).
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 1 000 mg intravenously per day for 3 days; if improves, then manage as above. Consider alternate immunosuppressants if no improvement or if condition worsens.

N/A = not available/not applicable

a. Lee et al 2014.

b. Refer to Table 2 for management of neurologic adverse reactions.

c. Refer to tocilizumab summary of product characteristics for details.

Neurologic adverse reactions

Severe neurologic adverse reactions, also known as immune effector cell-associated neurotoxicity syndrome (ICANS) have been very commonly observed in patients treated with Yescarta, which could be life-threatening or fatal (see section 4.8). Patients with a history of CNS disorders such as seizures or cerebrovascular ischaemia may be at increased risk. Fatal and serious cases of cerebral oedema have been reported in patients treated with Yescarta. Patients must be monitored for signs and symptoms of neurologic adverse reactions (Table 2). Patients must be monitored at least daily for 10 days at the qualified healthcare facility following infusion for signs and symptoms of neurologic toxicity/ICANS. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion. Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of

neurologic toxicity/ICANS occur. Monitoring of vital signs and organ functions must be considered depending on the severity of the reaction.

Patients who experience Grade 2 or higher neurologic toxicities /ICANS must 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 are to be considered for seizure prophylaxis 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 Yescarta. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2: Neurologic adverse reaction/ICANS grading and management guidance

Grading assessment	**Concurrent CRS**	**No concurrent CRS**
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab 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.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1 000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1 000 mg intravenously per day for 2 more days; if improves, then manage as above. If not improving, consider 1 000 mg of methylprednisolone intravenously 3 times a day or alternate therapy[a]	Administer methylprednisolone 1 000 mg intravenously per day for 3 days; if improves, then manage as above. If not improving, consider 1 000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.[a]
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

a. Alternate therapy includes (but is not limited to) anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

Infections and febrile neutropenia

Serious infections have been very commonly observed with Yescarta (see section 4.8). Patients must be monitored for signs and symptoms of infection before, during, and after Yescarta infusion and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Yescarta 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.

HBV reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B-cells. Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Yescarta infusion. Grade 3 or higher prolonged cytopenias following Yescarta infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia. Monitor blood counts after Yescarta infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Yescarta. Hypogammaglobulinaemia has been very commonly observed in patients treated with Yescarta. Immunoglobulin levels should be monitored after treatment with Yescarta and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of Yescarta. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in Yescarta.

Secondary malignancies

Patients treated with Yescarta may develop secondary malignancies. Monitor patients life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

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

Prior treatment with anti-CD19 therapy

There is limited experience with Yescarta in patients exposed to prior CD19-directed therapy. Yescarta is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Excipients

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

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 Yescarta.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Yescarta.

Live vaccines

The safety of immunisation with live viral vaccines during or following Yescarta 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 Yescarta treatment, and until immune recovery following treatment with Yescarta.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of child bearing potential must be verified before starting Yescarta 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 Yescarta.

Pregnancy

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

It is not known if Yescarta 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, Yescarta is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women must be advised on the potential risks to the foetus. Pregnancy after Yescarta therapy must be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborns of mothers treated with Yescarta must be considered.

Breast-feeding

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

Fertility

No clinical data on the effect of Yescarta 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

Yescarta has major influence on the ability to drive and use machines. Due to the potential for neurologic events, including altered mental status or seizures, patients must refrain from driving or operating 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 are from a total of 227 adult patients treated with Yescarta in two multi-centre pivotal clinical studies (ZUMA-1 and ZUMA-5, which treated 108 patients with DLBCL or PMBCL and 119 patients with FL).

Diffuse Large B-cell Lymphoma and Primary Mediastinal Large B-cell Lymphoma
The safety data described in this section reflect exposure to Yescarta in ZUMA-1, a Phase 1/2 study in which 108 patients with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) received CAR-positive T cells based on a recommended dose which was weight-based. The data described are from the 54-month follow-up analysis where median actual duration of follow-up was 23.5 months (range: 0.3 to 67.8 months).

The most significant and frequently occurring adverse reactions were CRS (93%), encephalopathy (60%), and infections (40%).

Serious adverse reactions occurred in 51% of patients. The most common serious adverse reactions included encephalopathy (22%), unspecified pathogen infections (15%), bacterial infections (6%), viral infections (6%), febrile neutropenia (5%) and fever (5%).

The most common (≥5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (31%), unspecified pathogen infections (19%), CRS (11%), bacterial infection (9%), viral infection (6%), delirium (6%), hypotension (6%), transaminases increased (6%) and hypertension (6%).

Follicular Lymphoma
The safety data described in this section reflect exposure to Yescarta in ZUMA-5, a Phase 2 study in which 119 patients with relapsed/refractory FL, received CAR-positive T cells based on a recommended dose which was weight-based. The data described are from the 24-month follow-up analysis where median actual duration of follow-up was 25.9 months (range: 0.3 to 44.3 months).

The most significant and frequently occurring adverse reactions were CRS (77%), infections (59%) and encephalopathy (47%).

Serious adverse reactions occurred in 45% of patients. The most common serious adverse reactions included encephalopathy (16%), unspecified pathogen infections (12%), CRS (12%), bacterial infections (5%), fever (4%), viral infection (4%) and thrombosis (3%).

The most common (≥5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (14%), unspecified pathogen infections (11%) and CRS (6%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Yescarta in ZUMA-1 (n=108) and ZUMA-5 (n=119) and from post-marketing reports. 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); uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse drug reactions identified with Yescarta

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections Viral infections Bacterial infections
	Common	Fungal infections
Blood and lymphatic system disorders		
	Very common	Febrile neutropenia[#] Neutropenia[#] Lymphopenia[#] Leukopenia[#] Anaemia[#] Thrombocytopenia[#]
	Common	Coagulopathy[a]
Immune system disorders		
	Very common	Cytokine Release Syndrome Hypogammaglobulinaemia[n]
	Common	Hypersensitivity
	Uncommon	Haemophagocytic Lymphohistiocytosis
Metabolism and nutrition disorders		
	Very common	Hyponatraemia[#] Hypophosphatemia[#] Hyperuricemia[#] Decreased appetite[o] Weight decrease
	Common	Hypokalemia[#] Hypocalcaemia[#] Hypoalbuminaemia[#] Dehydration[p]
Psychiatric disorders		
	Very common	Delirium[y] Insomnia
	Common	Affective disorder[z]
Nervous system disorders		
	Very common	Encephalopathy[s] Tremor[u] Headache[t] Dizziness[v]
	Common	Seizure Hemiparesis Ataxia[x] Neuropathy peripheral[w]
	Uncommon	Quadriplegia Spinal cord oedema Myelitis Dyscalculia Myoclonus
Cardiac disorders		
	Very common	Tachycardia[b] Arrhythmia[c]
	Common	Cardiac arrest Cardiac failure[d]
Vascular disorders		
	Very common	Hypotension[hh] Hypertension
	Common	Thrombosis[ii]

System Organ Class (SOC)	Frequency	Adverse reactions
Respiratory, thoracic and mediastinal disorders		
	Very common	Dyspnoea[cc] Cough[bb]
	Common	Hypoxia[dd] Pleural effusion Nasal inflammation[ee]
	Uncommon	Respiratory failure[ff]
Gastrointestinal disorders		
	Very common	Vomiting Diarrhoea[f] Constipation Abdominal pain[g] Nausea
	Common	Dysphagia* Dry mouth[h]
Skin and subcutaneous tissue disorders		
	Very common	Rash[gg]
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction[r] Musculoskeletal pain[q]
	Uncommon	Rhabdomyolysis
Renal and urinary disorders		
	Common	Renal impairment[aa]
General disorders and administration site conditions		
	Very common	Fever[j] Oedema[k] Fatigue[i] Chills
	Common	Pain
	Uncommon	Multiple organ dysfunction syndrome
Eye Disorders		
	Common	Visual impairment[e]

System Organ Class (SOC)	Frequency	Adverse reactions
Investigations		
	Very common	Transaminases increased[#l]
	Common	Hyperbilirubinemia[#m]

* Dysphagia has been reported in the setting of neurologic toxicity and encephalopathy.

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

a. Coagulopathy includes Coagulopathy, Blood fibrinogen decreased, Disseminated intravascular coagulation, International normalised ratio increased, Prothrombin time prolonged

b. Tachycardia includes Tachycardia, Sinus tachycardia

c. Arrhythmia includes Arrhythmia, Atrial fibrillation, Atrial flutter, Atrioventricular block, Atrioventricular block first degree, Bradycardia, Bundle branch block right, Electrocardiogram QT prolonged, Electrocardiogram T wave inversion, Extrasystoles, Heart rate irregular, Sinus bradycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular tachycardia

d. Cardiac failure includes Cardiac failure, Acute left ventricular failure, Ejection fraction decreased, Stress cardiomyopathy

e. Visual impairment includes Vision blurred, Visual acuity reduced

f. Diarrhoea includes Diarrhoea, Colitis, Enteritis

g. Abdominal pain includes Abdominal pain, Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort

h. Dry mouth includes Dry mouth, Lip dry

i. Fatigue includes Fatigue, Asthenia, Decreased activity, Malaise

j. Fever includes Hyperthermia, Pyrexia

k. Edema includes Oedema, Conjunctival oedema, Face oedema, Generalized oedema, Localized oedema, Oedema genital, Oedema peripheral, Periorbital oedema, Peripheral swelling, Scrotal oedema, Swelling, Swelling face

l. Transaminases increased includes Transaminases increased, Hepatic enzyme increased, Alanine aminotransferase increased, Aspartate aminotransferase increased

m. Hyperbilirubinemia increased includes Hyperbilirubinemia, Blood bilirubin increased

n. Immunoglobulins decreased includes Hypogammaglobulinemia, Blood immunoglobulin G decreased

o. Decreased appetite includes Decreased appetite, Hypophagia

p. Dehydration includes Dehydration, Hypovolaemia

q. Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Flank pain, Groin pain, Musculoskeletal chest pain, Myalgia, Neck pain, Osteoarthritis, Pain in extremity

r. Motor dysfunction includes Motor dysfunction, Muscle rigidity, Muscle spasms, Muscle spasticity, Muscle strain, Muscular weakness

s. Encephalopathy includes Encephalopathy, Agraphia, Amnesia, Aphasia, Aphonia, Apraxia, Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Dysarthria, Dysgraphia, Dyskinesia, Hypersomnia, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Leukoencephalopathy, Loss of consciousness, Memory impairment, Mental status changes, Neurotoxicity, Somnolence, Speech disorder, Stupor

t. Headache includes Headache, Head discomfort

u. Tremor includes Tremor, Head titubation

v. Dizziness includes Dizziness, Presyncope, Syncope, Vertigo

w. Neuropathy peripheral includes, Neuropathy peripheral, Allodynia, Cervical radiculopathy, Hyperaesthesia, Hypoaesthesia, Paraesthesia, Parosmia, Peripheral motor neuropathy, Peripheral sensory neuropathy

x. Ataxia includes Ataxia, Balance disorder, Gait disturbance, Vestibular disorder

y. Delirium includes Delirium, Agitation, Delusion, Disorientation, Hallucination, Restlessness

z. Affective disorder includes Impulsive behavior, Mania, Mood altered, Panic attack

aa. Renal impairment includes Acute kidney injury, Blood creatinine increased, Renal failure

bb. Cough includes Cough, Productive cough, Upper-airway cough syndrome

cc. Dyspnea includes Dyspnoea, Dyspnoea exertional

dd. Hypoxia includes Hypoxia, Oxygen saturation decreased

ee. Nasal inflammation includes Rhinitis allergic, Rhinorrhoea

ff. Respiratory failure includes Respiratory failure, Acute respiratory failure

gg. Rash includes Rash, Dermatitis bullous, Erythema, Pruritus, Rash erythematous, Rash macular, Rash maculo-papular, Rash pustular, Stevens-Johnson syndrome, Urticaria

hh. Hypotension includes Hypotension, Capillary leak syndrome, Diastolic hypotension, Hypoperfusion, Orthostatic hypotension

ii. Thrombosis includes Thrombosis, Deep vein thrombosis, Device occlusion, Embolism, Jugular vein thrombosis, Peripheral embolism, Peripheral ischaemia, Pulmonary embolism, Splenic vein thrombosis, Subclavian vein thrombosis, Thrombosis in device, Vascular occlusion

Description of selected adverse reactions from ZUMA-1 and ZUMA-5

Cytokine release syndrome

CRS occurred in 93% of patients in ZUMA-1 and 77% of patients in ZUMA-5. Eleven percent (11%) of patients in ZUMA-1 and 6% of patients in ZUMA-5 experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 2 days (range: 1 to 12 days) for patients in ZUMA-1 and 4 days (range: 1 to 11 days) for patients in ZUMA-5, and the median duration was 7.5 days (range: 2 to 29 days, with the exception of one outlying observation of 58 days) for patients

in ZUMA-1 and 6 days (range: 1 to 27 days) for patients in ZUMA-5. Ninety-eight percent (98%) of patients in ZUMA-1 and 99% of patients in ZUMA-5 recovered from CRS.

The most common signs or symptoms associated with CRS included pyrexia (90%), hypotension (42%), hypoxia (23%), chills (23%), tachycardia (17%) and sinus tachycardia (17%). Serious adverse reactions that may be associated with CRS included pyrexia (5%), hypoxia (3%), hypotension (1%), acute kidney injury (1%), atrial fibrillation (1%), atrial flutter (1%) and ejection fraction decrease (1%). See section 4.4 for monitoring and management guidance.

Neurologic adverse reactions
Neurologic adverse reactions occurred in 66% of patients in ZUMA-1 and 57% of patients in ZUMA-5. Thirty-one percent (31%) of patients in ZUMA-1 and 16% of patients in ZUMA-5 experienced Grade 3 or higher (severe or life-threatening) adverse reactions. Neurologic toxicities occurred within the first 7 days of infusion for 93% of patients in ZUMA-1 and 65% of patients in ZUMA-5. The median time to onset was 5 days (range: 1 to 17 days) for patients in ZUMA-1 and 7 days (range: 1 to 177 days) for patients in ZUMA-5. The median duration was 13 days in ZUMA-1 and 14 days in ZUMA-5, with resolution occurring within 3 weeks for 61% and 60% of patients respectively, following infusion.

The most common signs or symptoms associated with neurologic adverse reactions included tremors (30%), encephalopathy (28%), confusional state (25%), aphasia (15%), and somnolence (12%). Serious neurologic adverse reactions reported in patients who were administered Yescarta included encephalopathy (12%), confusional state (5%), aphasia (3%), agitation (2%), somnolence (2%) and delirium (1%).

Other neurologic adverse reactions have been reported less frequently in clinical trials and included dysphagia (5%), myelitis (0.2%), and quadriplegia (0.2%).

Spinal cord oedema and ICANS have been reported in the context of neurologic toxicity in the post-marketing setting.

See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 16% of patients after Yescarta infusion. Infections occurred in 50% of patients. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 22% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 15%, 7%, and 5% of patients respectively. The most common site of infection was in the respiratory tract. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Grade 3 or higher neutropenia , anaemia, and thrombocytopenia occurred in 60%, 32%, and 29% of patients, respectively. Prolonged (still present at Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher neutropenia, thrombocytopenia, and anaemia occurred in 26%, 16%, and 8% of patients, respectively. In ZUMA-1, Grade 3 or higher neutropenia, thrombocytopenia, and anaemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively. See section 4.4 for management guidance.

Hypogammaglobulinaemia
Hypogammaglobulinaemia was reported in 16% of patients treated with Yescarta. Cumulatively, 36 (33%) of 108 subjects in ZUMA-1 received intravenous immunoglobulin therapy at the time of the 54-month analysis, and 32 (27%) of 119 subjects in ZUMA-5 received intravenous immunoglobulin therapy at the time of the 24-month follow-up analysis. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Yescarta 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. Three out of 106 patients in ZUMA-1 preliminary tested positive via an ELISA screen for anti-FMC63 antibodies prior to being treated with Yescarta. In ZUMA-5, 13 out of 116 patients preliminary tested positive for antibodies in the ELISA screen prior to being treated with Yescarta, and 2 subjects who had negative results prior to treatment had positive test results after treatment. Results of a confirmatory cell-based assay demonstrated that all patients treated with Yescarta and had an ELISA positive result were antibody negative by the confirmatory assay, before, during and after treatment. An impact of these antibodies on efficacy or safety was not discernible.

Special population

There is limited experience with Yescarta in patients ≥ 75 years of age. Generally, safety and efficacy were similar between patients ≥ 65 years and patients < 65 years of age treated with Yescarta. Outcomes were consistent between patients with Eastern Cooperative Oncology Group (ECOG) of 0 and 1 and by sex.

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 Yescarta.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX70

Mechanism of action

Yescarta, an engineered autologous T-cell immunotherapy product, binds to CD19 expressing cancer cells and normal B-cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains 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 apoptosis and necrosis of CD19-expressing target cells.

Pharmacodynamic effects

In phase 2 of ZUMA-1 and ZUMA-5, after Yescarta 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, IFN-γ, and IL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target, off-tumour effect of Yescarta, a period of B-cell aplasia is expected following treatment. Among 73 DLBCL and PMBCL patients with evaluable samples at baseline, 40% had

detectable B-cells; the B-cell aplasia observed in the majority of patients at baseline was attributed to prior therapies. Following Yescarta treatment, the proportion of patients with detectable B-cells decreased: 20% had detectable B-cells at Month 3, and 22% had detectable B-cells at Month 6. The initiation of B-cell recovery was first noted at Month 9, when 56% of patients had detectable B-cells. This trend of B-cell recovery continued over time, as 64% of patients had detectable B-cells at Month 18, and 77% of patients had detectable B-cells at Month 24. Patients were not required to be followed after they progressed; thus, the majority of patients with evaluable samples were responders. Among 113 FL patients with evaluable samples at baseline, 75% of patients had detectable B-cells. Following Yescarta treatment, the proportion of patients with detectable B-cells decreased: 40% of patients had detectable B-cells at Month 3. B-cell recovery was observed over time, with 61% of patients had detectable B-cells at Month 24.

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 inflammatory serum analytes including IL-6, were correlated with Grade 3 or higher neurologic events and Grade 3 or higher CRS. Higher levels of multiple serum analytes including IL-15 were associated with Grade 3 or higher neurologic events and Grade 3 or higher CRS in ZUMA-1 and were associated with Grade 3 or higher CRS in ZUMA-5.

Clinical efficacy and safety

DLBCL, PMBCL and DLBCL arising from follicular lymphoma (ZUMA-1)
A total of 108 patients were treated with Yescarta in a phase 1/2 open-label, multicentre, single-arm study in patients with relapsed or refractory aggressive B-cell NHL. Efficacy was based on 101 patients in phase 2, including histologically confirmed DLBCL (N = 77), PMBCL (N = 8), or DLBCL arising from follicular lymphoma, (N = 16) based on the 2008 WHO-classification. DLBCL in ZUMA-1 included patients with DLBCL NOS, other DLBCL subtypes, and high-grade B-cell lymphoma (HGBCL) based on the 2016 WHO-classification. Forty-seven patients were evaluable for MYC, BCL-2, and BCL-6 status. Thirty were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 5 were found to have HGBCL with MYC, BCL-2 or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBCL not otherwise specified. Sixty-six patients were evaluable for cell-of-origin classifications (germinal center B-cell type [GCB] or activated B-cell type [ABC]). Of these, 49 patients had GCB-type and 17 patients had ABC-type.

Eligible patients were ≥ 18 years of age with refractory disease defined as progressive disease (PD) or stable disease (SD) as best response to last line of therapy, or disease progression within 12 months after autologous stem cell transplant (ASCT). Patients who were refractory to chemotherapy or who relapsed after two or more lines of systemic therapy were generally ineligible for haematopoietic stem cell transplantation. Patients must have received at least prior anti-CD20 antibody therapy and an anthracycline containing regimen. Patients with CNS lymphoma, a history of allogeneic stem cell transplantation (SCT) or prior anti-CD19 CAR or other genetically modified T-cell therapy were excluded. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia), cardiac ejection fraction of less than 50% or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow-up was 63.1 months (still ongoing). A summary of the patient demographics is provided in Table 4.

Table 4: Summary of demographics for ZUMA-1 phase 2 (12 month analysis)

Category	All leukapheresed (ITT) Cohort 1 + 2 (N = 111)	All treated (mITT) Cohort 1 + 2 (N = 101)
Age (years)		
Median (min, max)	58 (23, 76)	58 (23, 76)
≥ 65	23%	24%
Male gender	69%	67%
Race		
White	85%	86%
Asian	4%	3%
Black	4%	4%
ECOG status		
ECOG 0	41%	42%
ECOG 1	59%	58%
Median number of prior therapies (min, max)	3 (1, 10)	3 (1, 10)
Patients with refractory disease to ≥ 2 prior lines of therapy	77%	76%
Patients relapsed within 1 year of ASCT	20%	21%
Patients with International Prognostic Index 3/4	46%	46%
Patients with disease stage III/IV	85%	85%

Yescarta was administered as a single infusion at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of 500 mg/m^2 intravenous cyclophosphamide and 30 mg/m^2 intravenous fludarabine on the 5th, 4th, and 3rd day before Yescarta. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for observation for a minimum of 7 days after Yescarta infusion.

Of 111 patients who underwent leukapheresis, 101 received Yescarta. Nine patients were not treated, primarily due to progressive disease or serious adverse events after enrolment and prior to cell delivery. One out of 111 patients did not receive the product due to manufacturing failure. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0 x 10^6 anti-CD19 CAR T cells/kg. ITT was defined as all patients who underwent leukapheresis; mITT was defined as all patients who received Yescarta.

The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DOR), overall survival (OS), and severity of adverse events. The ORR was prespecified to be tested in the first 92 treated patients and was significantly higher than the prespecified rate of 20% ($P < 0.0001$).

In the primary analysis, based on the mITT population (minimum follow-up of 6 months) the ORR was 72% and the complete response (CR) rate was 51%, as determined by an independent review committee. In the 12 month followup analysis (Table 5), the ORR was 72% and the CR rate was 51%. The median time to response was 1.0 months (range: 0.8 to 6.3 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of partial response (PR). Of the 52 patients who achieved CR, 7 patients had SD and 9 had PR at their initial tumour assessment and converted to CR as late as 6.5 months. The ORR results within PMBCL and DLBCL arising from follicular lymphoma were both 88%. CR rates were 75% and 56%, respectively. Of the 111 patients in the ITT population, the ORR was 66% and the CR was 47%. Other outcomes were consistent with those of the mITT population.

In the 24-month follow-up analysis, based on the mITT population (results from an independent review committee), the ORR and the CR rate were 74% and 54%, respectively. The median time to response was 1.0 months (range: 0.8 to 12.2 months). The DOR was longer in patients who achieved CR compared to patients with a best response of PR (Table 5). Of the 55 patients who achieved CR, 7 patients had SD and 10 had PR at their initial tumour assessment and converted to CR as late as 12

months after Yescarta infusion. Median duration of response and median overall survival had not been reached (Table 5). In a 36-month analysis (median study follow-up of 39.1 months) the median overall survival was 25.8 months with 47 patients (47%*) still alive. In a 48-month analysis (median study follow-up of 51.1 months) the median overall survival was 25.8 months with 43 patients (44%*) still alive. In a 60-month analysis (median study follow-up of 63.1 months) the median overall survival was 25.8 months with 42 patients (43%*) still alive.
*The Kaplan-Meier estimates of the 3-year,4-year and 5-year OS rates were 47%, 44% and 43% respectively.

In the phase 1 part of ZUMA-1, 7 patients were treated. Five patients responded, including 4 CRs. At the 12-month follow-up analysis, 3 patients remained in CR 24 months after Yescarta infusion. At the 24-month follow-up analysis, these 3 patients remained in CR at 30 to 35 months after Yescarta infusion.

Table 5. Summary of efficacy results for ZUMA-1 phase 2

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**		**All treated (mITT) Cohort 1 + 2 (N = 101)**	
	12-month analysis	**24-month analysis**	**12-month analysis**	**24-month analysis**
ORR (%) [95% CI]	66 (56, 75)	68 (58, 76)	72 (62, 81)	74 (65, 82)
CR (%)	47	50	51	54
Duration of Response[a], median (range) in months	14.0 (0.0, 17.3)	NE (0.0, 29.5)	14.0 (0.0, 17.3)	NE (0.0, 29.5)
Duration of Response[a], CR, median (range) in months	NE (0.4, 17.3)	NE (0.4, 29.5)	NE (0.4, 17.3)	NE (0.4, 29.5)
Overall Survival, median (months) [95% CI]	17.4 (11.6, NE)	17.4 (11.6, NE)	NE (12.8, NE)	NE (12.8, NE)
6 month OS (%) [95% CI]	81.1 (72.5, 87.2)	81.1 (72.5, 87.2)	79.2 (69.9, 85.9)	79.2 (69.9, 85.9)
9 month OS (%) [95% CI]	69.4 (59.9, 77.0)	69.4 (59.9, 77.0)	69.3 (59.3, 77.3)	69.3 (59.3, 77.3)
12 month OS (%) [95% CI]	59.3 (49.6, 67.8)	59.5 (49.7, 67.9)	60.4 (50.2, 69.2)	60.4 (50.2, 69.2)
24 month OS (%) [95% CI]	Not applicable	47.7 (38.2, 56.7)	Not applicable	50.5 (40.4, 59.7)

NE= Not estimable (not reached)
a. Duration of response was censored at the time of SCT for subjects who received SCT while in response.
Note: The 12-month analysis had a median follow-up of 15.1 months. The 24-month analysis had a median follow-up of 27.1 months. OS relates to the time from the leukapheresis date (ITT) or Yescarta infusion (mITT) to death from any cause.

SCHOLAR-1
A retrospective, patient-level, pooled analysis of outcomes in refractory aggressive NHL (N = 636) was conducted (Crump et al., 2017) to provide confirmation of the prespecified control response rate of 20% and historical context for interpreting the ZUMA-1 results. The analysis included patients who had not responded (SD or PD) to their last line of therapy, or had relapsed within 12 months after ASCT. Response and survival after treatment with available standard-of-care therapy was evaluated. The ORR was 26% [95% CI (21, 31)] and the CR rate was 7% [95% CI (3, 15)], with a median OS of 6.3 months.

Relapsed or refractory FL (ZUMA-5)
The efficacy and safety of Yescarta in adult patients with FL, who were treated with Yescarta, were evaluated in a phase 2 single-arm, open-label, multicentre study in patients with relapsed or refractory FL based on 2016 WHO-classification.

Eligible patients were ≥ 18 years of age with refractory disease after 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent (single-agent anti-CD20 antibody did not count as line of therapy for eligibility). Patients with stable disease (SD) (without relapse) > 1 year from completion of last therapy were not considered eligible. Patients with CNS lymphoma, a history of allogeneic stem cell transplantation (SCT) or prior anti-CD19 CAR or other genetically modified T-cell therapy were excluded. Patients with a history of

CNS disorders (such as seizures or cerebrovascular ischemia), left ventricular ejection fraction of less than 50% or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were ineligible. The study excluded patients with active or serious infections and patients with FL Grade 3b. The actual duration of follow-up was 25.9 months (range: 0.3 to 44.3 months, still ongoing). A summary of the patient demographics is provided in Table 6.

At the time of the primary analysis, a total of 122 FL patients were enrolled (i.e. *leukapheresed*), including 75 patients who had received 3 or more lines of previous therapy. In the period between the primary analysis data cut-off date and the 24-month follow-up analysis data cut-off date, no additional subjects with FL were enrolled or treated with Yescarta.

Table 6: Summary of demographics for ZUMA-5 FL patients (24-month analysis)

Category	**All leukapheresed (N = 122)**	**All leukapheresed with ≥ 3 lines of therapy (N = 75*)**
Age (years)		
Median (min, max)	60 (34, 79)	60 (34, 79)
≥ 65	30%	31%
Male gender	60%	63%
Race		
White	93%	93%
Asian	2%	4%
Black	2%	1%
ECOG status		
0	63%	59%
1	37%	41%
High tumour bulk as defined by GELF criteria	52%	57%
Median number of prior therapies (min, max)	3 (1, 10)	4 (3, 10)
Patients with refractory disease to ≥ 2 prior lines of therapy	30%	24%
Patients with disease stage III/IV	86%	86%
Patients with prior autologous stem cell transplant	25%	29%
Prior PI3K inhibitor	26%	40%
Time to relapse from first anti-CD20 chemotherapy combination therapy < 24 months	54%	51%

* All subjects with locally confirmed diagnosis, including 60 subjects with centralised confirmed diagnosis. Number of leukapheresed (n=75) and treated (n=73) subjects.

Yescarta was administered as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the 5th, 4th, and 3rd day before Yescarta. All patients were hospitalized for observation for a minimum of 7 days after Yescarta infusion. The administration and monitoring of Yescarta is consistent between ZUMA-5 and ZUMA-1.

The primary analysis was performed, when at least 80 consecutively enrolled FL patients had a minimum follow-up of 12 months from first response assessment. The primary endpoint was ORR. Secondary endpoints included CR rate, ORR and CR in subjects who received 3 or more lines of prior therapy, DOR, OS and progression free survival (PFS) and incidence of adverse events. Three out of the 122 FL patients enrolled at the time of the primary analysis were not treated, primarily due to ineligibility, experiencing CR prior or death prior to the treatment.
A 24-month follow-up analysis was performed, when at least 80 FL patients had a minimum follow-up of 24 months after infusion.

As of the 24-month follow-up analysis, no additional patients underwent leukapheresis nor were treated with Yescarta. No manufacturing failures occurred. The median time from leukapheresis to product release was 12 days (range: 10 to 37 days), leukapheresis to product delivery was 17 days (range: 13 to 72 days) and leukapheresis to Yescarta infusion was 27 days (range: 19 to 330 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg.
At the time of the primary analysis data cut, 122 FL patients were enrolled. Among the 75 enrolled FL patients who had 3 or more lines of prior therapy, the ORR was 91% and the CR rate was 77%.

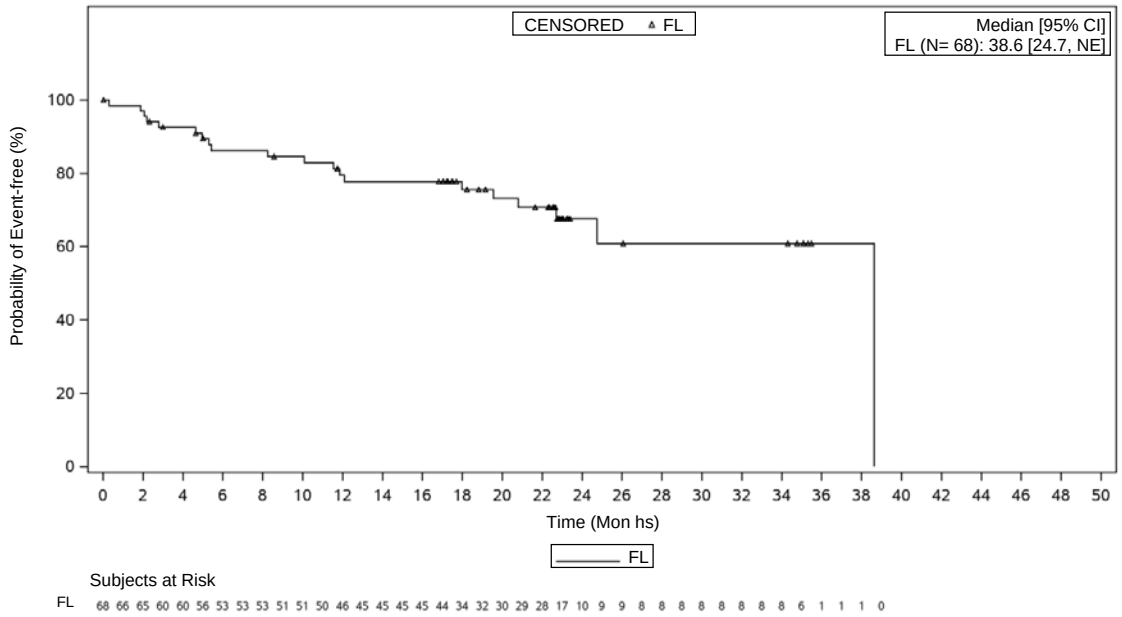
The 24-month follow-up analysis was performed on the 122 enrolled FL patients, and 119 of these patients were treated with Yescarta. Among the 122 enrolled FL patients, 75 had 3 or more lines of prior therapy, resulting in an ORR of 91% and CR rate of 77%. The median time to response was 1 month (range: 0.8 to 3.1 months), the median DOR was 38.6 months and the proportion of responders who remained in response was 56% at Month 24. Twenty nine out of 75 FL patients who had 3 or more prior lines of therapy initially achieved a PR, 19 of whom later achieved CR. Subgroup analysis included ORR in patients who were refractory (88%), FLIPI score ≥3 (94%), high tumour burden (91%), progression of disease within 24 months of first immunotherapy (89%) and prior treatment with PI3K inhibitor (90%). Key efficacy results for FL patients with 3 or more prior lines of therapy are summarized in Table 7.

Table 7. Summary of Efficacy Results for all enrolled ZUMA-5 FL patients with 3 or more prior lines of therapy (24-month analysis)

Category	**All leukapheresed (ITT)** **N = 75***
ORR[a], (%) [95% CI]	91% (82, 96)
CR, (%)	77%
PR, (%)	13%
Duration of Response[b], median in months [95% CI] (range)	38.6 (24.7, NE) (0.0, 38.6)
Ongoing Response (n)	42
Rate of Continued Remission[b] % [95% CI] 12 Month 18 Month 24 Month	 79.5(67.2, 87.6) 75.5 (62.5, 84.6) 67.6 (52.7, 78.7)

CI, confidence interval; NE, not estimable; ORR, objective response; CR, complete response; PR, partial response.
a. Per the International Working Group Lugano Classification (Cheson 2014), as assessed by the Independent Radiology Review Committee.
b. Measured from the date of first objective response to the date of progression or death.
* All subjects with locally confirmed diagnosis, including 60 subjects with centralized confirmed diagnosis. Number of leukapheresed (n=75) and treated (n=73) subjects.

Figure 1 Kaplan Meier DOR in the all leukapheresed set, subjects with objective response (FL patients with 3 or more lines of prior therapy, 24-month analysis, independent review committee)



5.2 Pharmacokinetic properties

Peak levels of anti-CD19 CAR T cells occurred within the first 8 to 15 days after Yescarta infusion. Among patients with DLBCL, the median peak level of anti-CD19 CAR T cells in the blood (C_{max}) was 38.3 cells/µL (range: 0.8 to 1513.7 cells/µL), which decreased to a median of 2.1 cells/µL by 1 month (range: 0 to 167.4 cells/µL) and to a median of 0.4 cells/µL by 3 months (range: 0 to 28.4 cells/µL) after Yescarta infusion. Among patients with FL, the median peak level of anti-CD19 CAR T cells in the blood (C_{max}) was 37.6 cells/µL (range: 0.5 to 1415.4 cells/µL). The median time to peak of anti-CD19 CAR T cells in the blood was 8 days after infusion (range: 8 to 371 days). By 3 months, anti-CD19 CAR T cell levels decreased to near baseline levels to a median of 0.3 cells/µL (range: 0 to 15.8 cells/µL).

Age (range: 23 to 76 years) and sex had no significant impact on AUC and C_{max} of Yescarta.

Among patients with DLBCL and PMBCL,the number of anti-CD19 CAR T cells in the blood was positively associated with objective response (CR or PR). The median anti-CD19 CAR T cell C_{max} level in responders (N = 71) was 216% higher compared to the corresponding level in nonresponders (N = 25) (43.6 cells/µL *versus* 20.2 cells/µL). Median $AUC_{Day\ 0\text{-}28}$ in responding patients (N = 71) was 253% of the corresponding level in nonresponders (N = 25) (562.0 days x cells/µL *versus* 222.0 days x cells/µL).

Among patients with FL, the median peak anti-CD19 CAR T-cell levels in responders (n=112) versus nonresponders (n=5) were 38.0 cells/µL and 31.3 cells/µL, respectively. The median $AUC_{0\text{-}28}$ in responders versus nonresponders were 454.8 cells/µL•days and 247.1 cells/µL•days, respectively.

Yescarta comprises human autologous T cells. The anticipated metabolic products are typical cellular degradation products resulting from normal cellular clearance mechanisms. Thus, the infused CAR T cells are expected to be cleared over time.

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

5.3 Preclinical safety data

Yescarta 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 drug development were not performed.

No carcinogenicity or genotoxicity studies have been conducted with Yescarta.

No studies have been conducted to evaluate the effects of Yescarta 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

Yescarta is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ -150 ˚C).

The stability of Yescarta upon completion of thawing is up to 3 hours at room temperature (20 ˚C to 25 °C). However, Yescarta infusion must begin within 30 minutes of thaw completion and the total Yescarta infusion time should not exceed 30 minutes. Thawed product must not be refrozen.

6.4 Special precautions for storage

The Yescarta bag must be stored in the vapour phase of liquid nitrogen (≤ -150 ˚C) and Yescarta must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are administered to the patient.

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

6.5 Nature and contents of container

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 cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

<u>Precautions to be taken for transport and disposal of the medicinal product</u>

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

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

Accidental exposure to Yescarta must be avoided. Local guidelines on handling of waste of human derived-materials mustbe 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 Yescarta 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/1/18/1299/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2018

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturers of the biological active substance

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

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

Name and address of the manufacturer responsible for batch release

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSUR)**

The requirements for submission of PSUR 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

The MAH will ensure that hospitals and their associated centres that dispense Yescarta are qualified in accordance with the agreed controlled distribution programme by:
- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Yescarta infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- ensuring healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.

Educational program – Prior to the launch of Yescarta 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 Yescarta is marketed, all HCPs who are expected to prescribe, dispense, and administer Yescarta shall be provided with a guidance document to:
- 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; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicine Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site

Patient Educational program

To inform and explain to patients
- the risks of CRS and serious neurologic adverse reactions, associated with Yescarta
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where Yescarta was received for at least 4 weeks following Yescarta 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**
Non-interventional post-authorisation safety study (PASS): In order to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting, the applicant should conduct and submit a study based on a registry.	•Update reports: Annual safety reports and 5-yearly interim reports •Final report of study results: December 2038

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CONTAINER (CASSETTE)

1. NAME OF THE MEDICINAL PRODUCT

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (CAR) with a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, human albumin, sodium chloride. See leaflet for further information.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1299/001

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

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (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

One sterile infusion bag.
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

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (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 Yescarta is and what it is used for
2. What you need to know before you are given Yescarta
3. How Yescarta is given
4. Possible side effects
5. How to store Yescarta
6. Contents of the pack and other information

1. What Yescarta is and what it is used for

Yescarta is a gene therapy medicine used for treating adults with aggressive diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma (FL) affecting your lymph tissue (part of the immune system) that affects a type of white blood cell called B lymphocytes and other organs in your body. Too many of these abnormal white blood cells accumulate in your tissue and this is the cause of the symptoms you may have. It is used to treat these conditions when other available medicines have stopped working for you.

The medicine is made specially for you as a single administration of your own modified white blood cells. It is given by a drip (*infusion*) into a vein (*intravenously*).

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

You must not be given Yescarta 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.

Warnings and precautions

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

Before you are given Yescarta you must tell your doctor if you:

- have problems with your nervous system (such as fits, stroke, or memory loss).
- have kidney problems.
- have low blood cell levels (blood counts).

- have had a stem cell transplant in the last 4 months.
- have any lung, heart or blood pressure (low or raised) problems.
- have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- notice the symptoms of your cancer are getting worse. If you have lymphoma this might include fever, feeling weak, night sweats, sudden weight loss.
- have an infection. The infection will be treated before the Yescarta infusion.
- have had hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

If any of the above apply to you (or you are not sure), talk to your doctor before being given Yescarta.

Tests and checks

Before you are given Yescarta your doctor will:
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you are given Yescarta.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant.
- 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.

After you have been given Yescarta

Tell your doctor or nurse immediately if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, or rapid heartbeat, which may be symptoms of a condition known as cytokine release syndrome. Take your temperature twice a day for 3-4 weeks after treatment with Yescarta. 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, 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.

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

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

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you are given Yescarta. Your doctor may need to take special care of you during your treatment with Yescarta.

In some cases, it might not be possible to go ahead with the planned treatment with Yescarta. For example:

- If Yescarta infusion is delayed for more than 2 weeks after you have received preparatory chemotherapy you may have to receive more preparative chemotherapy.

Children and adolescents

Yescarta must not be used in children and adolescents below 18 years of age.

Other medicines and Yescarta

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

Before you are given Yescarta 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 Yescarta.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for the Yescarta cells.
- During Yescarta 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 Yescarta 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 Yescarta, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Yescarta can only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Yescarta.

Driving and using machines

Some people may feel tired, dizzy or have some shaking after being given Yescarta. If this happens to you, do not drive or use heavy machines until at least 8 weeks after infusion or until your doctor tells you that you have completely recovered.

Yescarta contains sodium

This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion bag. This is the equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Yescarta is given

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

- Since Yescarta 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 make Yescarta. It usually takes about 3 to 4 weeks to receive your Yescarta therapy but the time may vary.

Medicines given before Yescarta treatment

During the 30 to 60 minutes before you are given Yescarta 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.

Prior to receiving Yescarta, you will be given other medicines such as preparative chemotherapy, which will allow your modified white blood cells in Yescarta to multiply in your body when the medicine is given to you.

Your doctor or nurse will check carefully that this medicine is yours.

How you are given Yescarta

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

- Yescarta is given in a single dose.
- Your doctor or nurse will give you a single infusion of Yescarta through a catheter placed into your vein (*intravenous* infusion) over about 30 minutes.
- Yescarta 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.

You must receive Yescarta infusion in a qualified clinical facility and be discharged only when your doctor thinks it is safe for you to go home.
Your doctor may do blood tests to check for side effects.

After you are given Yescarta

- Plan to stay within proximity from the hospital where you were treated for at least 4 weeks after you have been given Yescarta. Your doctor will recommend that you return to the hospital daily for at least 10 days and will consider whether you need to stay at the hospital as an in-patient for the first 10 days after infusion. 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 the qualified clinical facility 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.

Yescarta can cause side effects to your immune system that may be serious or life-threatening, and can lead to death.

The following side effects have been reported with Yescarta.

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*).
- Abnormally low number of white blood cells, which may increase your risk of infection.

- Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, involuntary shaking (*tremor*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
- Decrease in the number of red blood cells (*cells that carry oxygen*): symptoms can include extreme tiredness with a loss of energy.
- Extreme tiredness.
- Low number of cells that help clot the blood (*thrombocytopenia*): symptoms can include excessive or prolonged bleeding or bruising.
- Muscle and joint pain, back pain.
- Fever or chills, which may be signs of an infection.
- Headache.
- High levels of uric acid, or magnesium seen in blood tests. Low levels of sodium or phosphate, seen in blood tests.
- Nausea, constipation, diarrhoea, abdominal pain, vomiting.
- Decreased appetite, weight loss.
- Low blood pressure, dizziness.
- Shortness of breath, cough.
- Fast or slow heartbeat.
- Irregular heartbeat (*arrhythmia*).
- Low levels of immunoglobulins seen in blood test, which may lead to infections.
- 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, decreased output of urine.
- Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
- Skin rash or skin problems.
- Difficulty sleeping
- High blood pressure.
- 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.
- Increase in liver enzymes seen in blood tests.

Common (may affect up to 1 in 10 people)
- Dry mouth, dehydration, difficulty swallowing.
- Pain in the hands or feet.
- High levels of bilirubin seen in blood tests. Low levels of albumin, potassium or calcium seen in blood tests.
- Low oxygen level in blood.
- Failure of the kidneys causing your body to hold onto fluid which can be serious or life threatening.
- Swelling in the limbs, fluid around the lungs (*pleural effusion*).
- Lung infection.
- Alteration of the blood ability to form clots (*coagulopathy*): symptoms can include excessive or prolonged bleeding or bruising.
- Changes in vision which makes it difficult to see things (*visual impairment*).
- Pain.
- Sudden, unexpected stopping of the heart (cardiac arrest); this is serious and life-threatening.
- Heart failure.
- Fits (*seizures*),
- Inability to move one side of the body
- Hypersensitivity: symptoms such as rash, hives, itching, swelling and anaphylaxis.
- Mood disorders.
- Nasal inflammation.
- Weakness or inability to move on one side of the body, making it hard to perform everyday activities like eating or dressing.
- Loss of control of body movements.

Uncommon (may affect up to 1 in 100 people)

- Difficulty understanding numbers, memory loss, fits.
- Breakdown of muscle tissue that leads to the release of muscle fibre into the blood.
- Improper functioning of at least 2 organs (eg, liver, lungs and kidneys) that requires medical treatment and/or procedures to restore normal organ function.
- Inflammation and swelling of spinal cord which may cause partial or total paralysis of limbs and torso.
- Paralysis of all four limbs.
- Condition of severe systemic inflammation.
- Inability to breathe on one's own.

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

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 Yescarta

The following information is intented 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.

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 must 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 Yescarta contains

The active substance is axicabtagene ciloleucel. 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.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "Yescarta contains sodium".

What Yescarta looks like and contents of the pack

Yescarta 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 and Manufacturer
Kite Pharma EU B.V.
Tufsteen 1

2132 NT Hoofddorp
The Netherlands

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

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

България
Gilead Sciences Ireland UC
Тел.: PPD

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

Danmark
Gilead Sciences Sweden AB
Tlf: PPD

Deutschland
Gilead Sciences GmbH
Tel: PPD

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

Ελλάδα
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: PPD

España
Gilead Sciences, S.L.
Tel: PPD

France
Gilead Sciences
Tél: PPD

Hrvatska
Gilead Sciences Ireland UC
Tel PPD

Ireland
Gilead Sciences Ireland UC
Tel: PPD

Ísland
Gilead Sciences Sweden AB
Sími: PPD

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

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

Magyarország
Gilead Sciences Ireland UC
Tel: PPD

Malta
Gilead Sciences Ireland UC
Tel: PPD

Nederland
Gilead Sciences Netherlands B.V.
Tel: PPD

Norge
Gilead Sciences Sweden AB
Tlf: PPD

Österreich
Gilead Sciences GesmbH
Tel: PPD

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

Portugal
Gilead Sciences, Lda.
Tel: PPD

România
Gilead Sciences Ireland UC
Tel: PPD

Slovenija
Gilead Sciences Ireland UC
Tel: PPD

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

Italia
Gilead Sciences S r.l.
Tel: PPD

Κύπρος
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: PPD

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

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

Sverige
Gilead Sciences Sweden AB
Tel PPD

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

This leaflet was last revised in

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 Yescarta.

Precautions to be taken before handling or administering the medicinal product

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

Preparation for infusion

- Verify that the patient's identity (ID) matches the patient identifiers on the Yescarta cassette.
- The Yescarta product 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 Yescarta product bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label. Inspect the product 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 Yescarta 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. Yescarta must not be washed, spun down, and/or re-suspended in new medium prior to infusion. Thawing takes approximately 3 to 5 minutes.
- Once thawed, Yescarta is stable at room temperature (20˚C - 25˚C) for up to 3 hours.
- However, Yescarta infusion must begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration

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

volume of Yescarta has been infused, the infusion bag must be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

Disposal of Yescarta

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

Accidental exposure

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

Appendix 4. Kite Signature Page

KITE PHARMA INC.

LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA, PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA AND FOLLICULAR LYMPHOMA

ORIGINAL, 07 FEBRUARY 2019
VERSION 1.1, 03 JULY 2019
VERSION 1.2, 09 OCTOBER 2019
VERSION 1.3, 06 NOVEMBER 2019
VERSION 2.0, 01 JULY 2021
VERSION 2.1, 03 AUGUST 2022

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

Meng Wang

Kite Study Director (Printed)
Author

Signature

Date

Dr. Anne-Ruth van Troostenburg de Bruyn

Kite Gilead EU QPPV (Printed)

Signature

Date

amd-5-KT-EU-471-0117_Annex 4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Epidemiology eSigned	05-Aug-2022 09:41:51
PPD	QPPV eSigned	05-Aug-2022 09:51:05

Appendix 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).

CELLULAR THERAPIES FORM
-- Pre-Infusion Registration --

INFORMED CONSENT

Was the patient asked to consent to data submission?	☐ **No**	☐ **Yes**	
Date of informed consent: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*			
Is your centre using the EBMT consent form?	☐ **No**	☐ **Yes**	
Did the patient consent to data sharing with health authorities and/or researchers?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to data sharing with Health Technology Assessment bodies (HTA)?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to data sharing with Market Authorisation Holders (MAH)?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to their medical records being reviewed?	☐ **No**	☐ **Yes**	☐ **Unknown**

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): _____

Hospital: _____

Unit: _____

Type of unit or team responsible for this cellular therapy:
(Optional; this is a coded replication of the above unit field and can be used by centres that have more than one department/unit reporting to the EBMT)

- ☐ Adults
- ☐ Allograft
- ☐ Autograft
- ☐ BMT unit
- ☐ Dept. Medicine
- ☐ Haematology
- ☐ Oncology
- ☐ Paediatrics
- ☐ Paediatric haematology
- ☐ Paediatric oncology

Contact person: _____

PATIENT DATA

EBMT Unique Identification Code (UIC): _____
(Patient number in EBMT database; complete if patient had a previous treatment and is already registered in the database)

Date of this report: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Hospital Unique Patient Number or code (UPN): _____
(Compulsory; registrations will not be accepted without this item. All treatments (transplants and CAR T-cell) 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.)

Other type of patient identification code(s): _____
(Optional; to be used by the centre to register a patient code for internal use as necessary)

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Sex *(at birth)*:
☐ Male
☐ Female

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

ABO group:
☐ A
☐ B
☐ AB
☐ O

Rh factor:
☐ Absent
☐ Present
☐ Not evaluated

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 has been recorded using the appropriate follow-up form before proceeding; this is so relapse data and other events between transplants/advanced cellular therapies can be captured.

INDICATION FOR CELLULAR THERAPY

☐ **Treatment of a primary disease:**

Indicate below for which disease this cellular therapy has been received.

☐ Primary Acute Leukaemia	
Acute Myelogenous Leukaemia (AML)	*(page 8)*
Precursor Lymphoid Neoplasms (previously ALL)	*(page 12)*
Other Primary Acute Leukaemia	*(page 15)*
☐ Chronic Leukaemia	
Chronic Myeloid Leukaemia (CML)	*(page 16)*
Chronic Lymphocytic Leukaemia (CLL)	*(page 16)*
Prolymphocytic Leukaemias (PLL) and Other Chronic Leukaemias	*(page 17)*
☐ Lymphoma	
Non-Hodgkin Lymphoma (NHL)	*(page 19)*
Hodgkin's Lymphoma (HL)	*(page 23)*
Immunodeficiency-associated lymphoproliferative disorders (including PTLD)	*(page 23)*
☐ Myelodysplastic Syndromes (MDS) and/or Myeloproliferative Neoplasm (MPN)	
MDS	*(page 24)*
MDS/MPN	*(page 26)*
MPN	*(page 28)*
☐ Plasma Cell Disorders (PCD including Multiple Myeloma (MM)	*(page 31)*
☐ Bone Marrow Failure Syndromes including Aplastic Anaemia	*(page 33)*
☐ Haemoglobinopathy	*(page 34)*
☐ Solid Tumour	*(page 35)*
☐ Inherited Disorders	
Primary immune deficiencies (PID)	*(page 37)*
Metabolic disorders	*(page 38)*
Platelet and other inherited disorder	*(page 39)*
☐ Histiocytic disorders	*(page 40)*
☐ Autoimmune disease	
Connective tissue	*(page 41)*
Vasculitis	*(page 41)*
Arthritis	*(page 41)*
Neurological	*(page 42)*
Haematological	*(page 42)*
Bowel disorder	*(page 42)*
Other autoimmune disease (Diabetes, etc.)	*(page 42)*
☐ Infections	*(page 43)*
☐ Other primary disease; specify: _____	*(page 44)*

Complete and attach the relevant disease classification sheet as per page numbers indicated above.

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

INDICATION FOR CELLULAR THERAPY continued

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

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

☐ **Both, treatment of primary disease and complication**
Complete and attach the relevant disease classification sheet as per page numbers indicated above.

BASIC INFORMATION ON THE PLANNED CELLULAR THERAPY

Clinical setting:
(select only one)

☐ As per marketing approval / Standard of care / Institutional guidelines

☐ Hospital exemption

☐ Compassionate use / Accelerated access

☐ Investigational drug product (IDP)/ Clinical trial (CT)

Phase: ☐ 1 ☐ 1/2 ☐ 2 ☐ 2/3 ☐ 3
Blind trial: ☐ No ☐ Yes
Randomised trial: ☐ No ☐ Yes

Eudract number: _____

USA NCT number: _____

UMIN CT number: _____

☐ Unknown

Cell origin:

☐ Autologous --> *Continue with 'Planned Cellular Therapy Product' on page 5*

☐ Allogeneic

This product is manufactured from:

☐ A known donor never used to treat this patient *(e.g. from a donor registry or related)*
--> *Complete 'Donor' section on page 5*

☐ A donor that is already registered as part of a previous treatment
--> *Skip 'Donor' section and continue with 'Planned Cellular Therapy Product' on page 5*

☐ An unknown donor with no data available *(e.g. from a commercial product)*
--> *Skip 'Donor' section and continue with 'Planned Cellular Therapy Product' on page 5*

DONOR INFORMATION

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* *OR* **Age at time of donation :** _____ *(years)* _____ *(months)*
(only if date of birth not provided)

Sex ***(at birth)*****:**
☐ Male
☐ Female

Donor Identification:

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

Global registration identifier for donors: _____

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

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

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

Name of Donor Registry or Cord Blood Bank: _____

PLANNED CELLULAR THERAPY PRODUCT
Description

If more than one planned cellular therapy product please replicate this section for each one of them.

Is the planned cellular therapy product a commercial product?
☐ No
☐ Yes

Will the planned cellular therapy product consist of more than one cell infusion unit?
☐ No
☐ Yes: Number of different cell infusion units: _____

PLANNED CELLULAR THERAPY INFUSION PRODUCT
Description continued

If more than one planned cellular therapy product please replicate this section for each one of them.

Identification:

Name of manufacturer:

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

Name of product *(if applicable)*:

- ☐ Abecma
- ☐ Breyanzi
- ☐ Cilta-cel
- ☐ Eli-cel
- ☐ Kymriah
- ☐ Tecartus
- ☐ Yescarta
- ☐ Other; specify: _____

Tissue source:

- ☐ Bone Marrow
- ☐ Peripheral Blood
- ☐ Umbilical Cord Blood
- ☐ Tumour
- ☐ Other; specify: _____

Collection procedure:

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

Number of collections: _____

END OF GENERAL PRE-INFUSION REGISTRATION

To complete PRE-INFUSION REGISTRATION please fill in the applicable disease classification.

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

DISEASE

Classification:

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 (previously "Acute Leukaemia transformed from MDS or MDS/MPN"):
  Was there a previous diagnosis of MDS or MDS/MPN?
  - ☐ No *(continue with 'Predisposing Condition'* below)
  - ☐ Yes *(fill in the MDS (page 24) or MDS/MPN (page 26); 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)
- ☐ AML (megakaryoblastic) with t(1;22) (p13;q13); RBM15-MKL1
- ☐ 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 (previously "Secondary Acute Leukaemia"; related to prior treatment but NOT after a previous diagnosis of MDS or MDS/MPN .)

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

DISEASE continued

Did the patient have a predisposing condition prior to the diagnosis of leukaemia?

☐ No

☐ Yes:
- ☐ Aplastic Anaemia
- ☐ Bloom Syndrome
- ☐ Fanconi Anaemia
- ☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of acute leukaemia.)

☐ No

☐ Yes

☐ Not evaluated

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
	Monosomal karyotype: *(≥2 autosomal monosomies or 1 autosomal monosomie + at least 1 structural abnormality)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

CHROMOSOME ANALYSIS continued

Transcribe the complete karyotype:

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

t(15;17)	☐ Absent	☐ Present	☐ Not evaluated
t(8;21)	☐ Absent	☐ Present	☐ Not evaluated
inv(16)/ t(16;16)	☐ Absent	☐ Present	☐ Not evaluated
11q23 abnormality type *(fill in only if a 11q23 abnormality is present)*:	☐ Absent	☐ Present	☐ Not evaluated
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: __________	☐ Absent	☐ Present	
3q26 (EVI1) abnormality type *(fill in only if a 3q26 abnormality is present)*:	☐ Absent	☐ Present	☐ Not evaluated
inv(3) / t(3;3)	☐ Absent	☐ Present	☐ Not evaluated
t(2;3)(p21;q26)	☐ Absent	☐ Present	☐ Not evaluated
Other (3q26)/EVI1 rearrangement; specify: __________	☐ Absent	☐ Present	
t(6;9)	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type *(fill in only if an abn 5 is present)*:	☐ Absent	☐ Present	☐ Not evaluated
del (5q)	☐ Absent	☐ Present	☐ Not evaluated
monosomy 5	☐ Absent	☐ Present	☐ Not evaluated
Add(5q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(5q); specify: __________	☐ Absent	☐ Present	
abn 7 type *(fill in only if an abn 7 is present)*:	☐ Absent	☐ Present	☐ Not evaluated
del(7q)	☐ Absent	☐ Present	☐ Not evaluated
monosomy 7	☐ Absent	☐ Present	☐ Not evaluated
add(7q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(7q); specify: __________	☐ Absent	☐ Present	
-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: __________	☐ Absent	☐ Present	

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

Indicate below whether the markers were absent, present or not evaluated.

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 in 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: _____	☐ 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: _____	☐ Absent	☐ Present	☐ Not evaluated

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

INVOLVEMENT AT DIAGNOSIS

Involvement at diagnosis:

Bone Marrow:	☐ No	☐ Yes	☐ Not evaluated
CNS:	☐ No	☐ Yes	☐ Not evaluated
Testes/Ovary:	☐ No	☐ Yes	☐ Not evaluated
Other:	☐ No	☐ Yes; specify: _____	

ACUTE LEUKAEMIAS
Precursor Lymphoid Neoplasms (previously ALL) - *main disease code 1*

DISEASE

Classification:

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

Secondary origin: Is this PLN related to prior exposure of therapeutic drugs or radiation?

☐ No
☐ Yes
☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of acute leukaemia.)

☐ No
☐ Yes
☐ Not evaluated

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

- ☐ Normal
- ☐ Abnormal: Complex karyotype: *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown
- ☐ Not done or failed
- ☐ Unknown

ACUTE LEUKAEMIAS
Precursor Lymphoid Neoplasms (previously ALL) - *main disease code 1*

CHROMOSOME ANALYSIS continued

Transcribe the complete karyotype: ______________________________________

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

t(9;22)	☐ Absent	☐ Present	☐ Not evaluated
11q23 abnormalities *(fill in only if 11q23 abnormalities is present)*	☐ Absent	☐ Present	☐ Not evaluated
t(4;11)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(11q23); specify: ________________	☐ Absent	☐ Present	
t(12;21)	☐ Absent	☐ Present	☐ Not evaluated
Hyperdiploidy (>46 chromosomes) *(fill in only if hyperdiploidy is present)*:	☐ Absent	☐ Present	☐ Not evaluated
50 – 66 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Trisomy; specify extra chromosome: _____	☐ Absent	☐ Present	☐ Not evaluated
Other hyperdiploid karyotype; number of chromosomes: _____	☐ Absent	☐ Present	
Hypodiploidy (<46 chromosomes): *(fill in only if hypodiploidy is present)*:	☐ Absent	☐ Present	☐ Not evaluated
Low hypodiploid; 32 - 39 chromosomes;	☐ Absent	☐ Present	☐ Not evaluated
Near haploid, 24-31 chromosomes;	☐ Absent	☐ Present	☐ Not evaluated
Monosomy; specify: __________________	☐ Absent	☐ Present	☐ Not evaluated
Other; number of chromosomes: _____	☐ Absent	☐ Present	
t(5;14)(q31;q32)	☐ Absent	☐ Present	☐ Not evaluated
t(1;19)	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: __________________	☐ Absent	☐ Present	

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

ACUTE LEUKAEMIAS
Precursor Lymphoid Neoplasms (previously ALL) - *main disease code 1*

MOLECULAR MARKER ANALYSIS continued

Indicate below whether the abnormalities were absent, present or not evaluated.

BCR-ABL *Molecular product of t(9;22)(q34;q11.2)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-rearrangement/mutation *(fill in only if a MLL-rearrangement abnormality is present)*:	☐ Absent	☐ Present	☐ Not evaluated
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
Other MLL-rearrangement; specify: _____	☐ Absent	☐ Present	
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 & FBWX7	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _____	☐ Absent	☐ Present	

White blood cell count at diagnosis: _____ 10^9 cells/L ☐ Not available/Unknown

ACUTE LEUKAEMIAS
Other Acute Leukaemias - *main disease code 1*

DISEASE

Classification:

Acute leukaemia 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: Is this other acute leukaemia related to prior exposure of therapeutic drugs or radiation?

☐ No
☐ Yes
☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of acute leukaemia.)

☐ No
☐ Yes
☐ Not evaluated

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

DISEASE

Classification:
(At least one investigation must be positive; note: CMML is not a CML but MDS/MPN.)

t(9;22) *(Chromosome analysis)*	☐ Absent	☐ Present	☐ Not evaluated
bcr-abl *(Molecular marker analysis)*	☐ Absent	☐ Present	☐ Not evaluated

CHRONIC LEUKAEMIAS
Chronic Lymphocytic Leukaemias (CLL) - *main disease code 2*

DISEASE

Classification:

☐ Chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma

☐ Richter's syndrom:

Transformed from a previous known CLL? ☐ Yes: Date of original CLL diagnosis: _ _ _ _/_ _/_ _ *(YYYY/MM/DD)*
☐ No: Primary Richter *(without previously known diagnosis of CLL)*

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)***:**
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal
☐ Abnormal
☐ Not done or failed
☐ Unknown

Transcribe the complete karyotype:

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

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: ______________	☐ Absent	☐ Present	

CHRONIC LEUKAEMIAS
Chronic Lymphocytic Leukaemias (CLL) - *main disease code 2*

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done of failed
☐ Unknown

Indicate below whether the markers were absent, present or not evaluated.

TP53 mutations	☐ Absent ☐ Present ☐ Not evaluated
Other; specify:	☐ Absent ☐ Present

CHRONIC LEUKAEMIAS
Prolymphocytic Leukaemias (PLL) and Others - *main disease code 2*

DISEASE

Classification:

☐ Prolymphocytic Leukaemia (PLL)
☐ PLL; B-cell
☐ PLL; T-cell
☐ Hairy Cell Leukaemia
☐ Other chronic leukaemia; specify: _____

CHROMOSOME ANALYSIS
only applicable for PLL

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal
☐ Abnormal
☐ Not done or failed
☐ Unknown

CHRONIC LEUKAEMIAS
Prolymphocytic Leukaemias (PLL) and Others - *main disease code 2*

CHROMOSOME ANALYSIS continued
only applicable for PLL

Transcribe the complete karyotype: __

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

inv(14)/ t(14;14)(q11;q32)	☐ 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: ______________	☐ Absent	☐ Present	

IMMUNOPHENOTYPING
only applicable for T-cell PLL

Immunophenotype of T-cells at diagnosis:
Note: Terminal desoxynucleotidyl transferase (TdT) must be negative.

Indicate below whether the phenotypes were absent, present or not evaluated.

CD4+	☐ Absent	☐ Present	☐ Not evaluated
CD8+	☐ Absent	☐ Present	☐ Not evaluated

Lymphocyte count at diagnosis: 10^9 cells/L

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

DISEASE

Classification: Mature B-cell Neoplasms

☐ 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):** ☐ Low risk *(0-1 score points except age >65)* ☐ Intermediate risk *(2 score points or age >65 alone)* ☐ High risk *(3-5 score points)* ☐ Not evaluated
☐ Follicular lymphoma	**Grading:** ☐ Grade I ☐ Grade II ☐ Grade III ☐ Not evaluated **Prognostic score (FLIPI):** ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated
☐ Primary cutaneous follicle centre lymphoma	
☐ Mantle cell lymphoma	**Grading:** ☐ Indolent ☐ Classical ☐ Pleomorphic ☐ Blastoid ☐ Not evaluated **Prognostic score (MIPI):** ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated **KI-67 *(proliferation index)*:** **% positive** ☐ Not evaluated

☐ Diffuse large B-cell lymphoma (DLBCL), (NOS)	
☐ T-cell/histiocyte rich large B cell lymphoma	
☐ Primary DLBCL of the CNS	
☐ Primary cutaneous DLBCL, leg type	
☐ EBV positive DLBCL of the elderly	
☐ Germinal centre B-cell type (GCB) DLBCL	
☐ Activated B-cell type (ABC or non-GCB) DLBCL	
☐ 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	
☐ HHV8-positive DLBCL,NOS	
☐ Primary effusion lymphoma (PEL)	
☐ Burkitt lymphoma (BL)	
☐ High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements	
☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (Intermediate DLCBL/BL)	
☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Gray zone lymphoma)	
☐ Other B-cell lymphoma; specify: _____	

International prognostic score (IPI):
☐ Low risk *(0-1 score points)*
☐ Low-intermediate risk *(2 score points)*
☐ High-intermediate risk *(3 score points)*
☐ High risk *(4-5 score points)*
☐ Not evaluated

KI-67: % positive *(proliferation index)* ☐ Not evaluated

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

DISEASE continued

Transformed from another type of lymphoma at the event leading to this cellular therapy?

☐ No

☐ Yes: Date of original diagnosis: ____/__/__ *(YYYY/MM/DD)*

Indicate the type of the original lymphoma: _____

☐ Unknown

Please complete Chromosome Analysis, Molecular Marker Analysis and Immunophenotyping sections only for patients receiving cellular therapy for the followin types of B-cell NHL:

- *Mantle cell lymphoma*
- *Waldenstrom macroglobulinaemia*
- *Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma*

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal

☐ Abnormal

☐ Not done or failed

☐ Unknown

If abnormal, complete this table according to the type of lymphoma diagnosed.

Mantle cell lymphoma or Waldenstrom macro- globulinaemia	**del(17p)**	☐ Absent ☐ Present ☐ Not evaluated FISH used: ☐ No ☐ Yes
Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma	**t(2;8)**	☐ Absent ☐ Present ☐ Not evaluated
	t(8;14)	☐ Absent ☐ Present ☐ Not evaluated
	t(8;22)	☐ Absent ☐ Present ☐ Not evaluated
	t(14;18)	☐ Absent ☐ Present ☐ Not evaluated
	myc rearrangement	☐ Absent ☐ Present ☐ Not evaluated
	BCL2 rearrangement	☐ Absent ☐ Present ☐ Not evaluated
	BCL6 rearrangement	☐ Absent ☐ Present ☐ Not evaluated

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

Please complete Chromosome Analysis, Molecular Marker Analysis and Immunophenotyping sections only for patients receiving cellular therapy for the followin types of B-cell NHL:

- *Mantle cell lymphoma*
- *Waldenstrom macroglobulinaemia*
- *Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma*

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done of failed
☐ Unknown

If abnormal, complete this table according to the type of lymphoma diagnosed.

Mantle cell lymphoma	**TP53 mutation**	☐ Absent ☐ Present ☐ Not evaluated
Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma	**myc rearrangment**	☐ Absent ☐ Present ☐ Not evaluated
Intermediate DLBCL/ Burkitt lymphoma	**BCL2 rearrangement**	☐ Absent ☐ Present ☐ Not evaluated
	BCL6 rearrangement	☐ Absent ☐ Present ☐ Not evaluated

IMMUNOPHENOTYPING

Immunophenotyping at diagnosis:

☐ Absent
☐ Present
☐ Not done of failed
☐ Unknown

If abnormal, complete this table according to the type of lymphoma diagnosed.

Mantle cell lymphoma	**SOX 11**	☐ Absent ☐ Present ☐ Not evaluated
Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma	**MYC**	☐ Absent ☐ Present ☐ Not evaluated
Intermediate DLBCL/ Burkitt lymphoma	**BCL2/IgH**	☐ Absent ☐ Present ☐ Not evaluated
	BCL6	☐ Absent ☐ Present ☐ Not evaluated

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

DISEASE

Classification: Mature T-cell & NK-cell Neoplasms

☐ 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	
☐ Hepatosplenic T-cell lymphoma	
☐ Subcutaneous panniculitis-like T-cell lymphoma	
☐ Mycosis fungoides (MF)	**ISCL/EORT staging:** ☐ IA ☐ IIIA ☐ IVB ☐ IB ☐ IIIB ☐ Not evaluated ☐ IIA ☐ IVA1 ☐ IIB ☐ IVA2
☐ Sézary syndrome	
☐ 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)	**International prognostic score (IPI):** ☐ Low risk *(0-1 score points)* ☐ Low-intermediate risk *(2 score points)* ☐ High-intermediate risk *(3 score points)* ☐ High risk *(4-5 score points)* ☐ Not evaluated
☐ Angioimmunoblastic T-cell lymphoma	
☐ Anaplastic large-cell lymphoma (ALCL), ALK-positive	
☐ Anaplastic large-cell lymphoma (ALCL), ALK-negative	
☐ Other T-cell: specify: _____	

LYMPHOMAS
Hodgkin Lymphomas - *main disease code 3*

DISEASE

Classification:

- ☐ Nodular lymphocyte predominant
- ☐ Classical predominant; lymphocyte-rich
- ☐ Classical predominant; nodular sclerosis
- ☐ Classical predominant; mixed cellularity
- ☐ Classical predominant; lymphocyte-depleted
- ☐ Classical predominant; NOS
- ☐ Other; specify: _____

LYMPHOMAS
Immunodeficiency-associated lymphoproliferative disorders (incl. PTLD) - *main disease code 3*

DISEASE

Classification:

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

Did the disease result from a previous solid organ transplant?

☐ No

☐ Yes: Date of transplant: ____/__/__ *(YYYY/MM/DD)*

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

☐ Unknown

MYELODYSPLASTIC SYNDROMES (MDS)
main disease code 6

DISEASE

Classification:

- ☐ Refractory anaemia without ring sideroblasts (RA)
- ☐ Refractory anaemia with ring sideroblasts (RARS)
- ☐ Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
- ☐ Refractory cytopenia with multi-lineage dysplasia (RCMD)
- ☐ Refractory cytopenia with multi-lineage dysplasia with ringed sideroblasts (RCMD-RS)
- ☐ Refractory anaemia with excess of blasts-1 (RAEB-1)
- ☐ Refractory anaemia with excess of blasts-2 (RAEB-2)
- ☐ Childhood myelodysplastic syndrome (Refractory cytopenia of childhood; RCC)
- ☐ Myelodysplastic syndrome, unclassifiable (MDS-U)

Therapy-related MDS?
(Secondary origin)

- ☐ No
- ☐ Yes, disease related to prior exposure to therapeutic drugs or radiation
- ☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of MDS.)

- ☐ No
- ☐ Yes
- ☐ Not evaluated

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

- ☐ Normal
- ☐ Abnormal: Complex karyotype: *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown
- ☐ Not done or failed
- ☐ Unknown

MYELODYSPLASTIC SYNDROMES (MDS)

main disease code 6

CHROMOSOME ANALYSIS continued

Transcribe the complete karyotype: __

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

del(Y)	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type *(fill in only if an abn 5 is present)*:	☐ Absent	☐ Present	☐ Not evaluated
del(5q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(5q); specify: __________	☐ Absent	☐ Present	
del(20q)	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type *(Ffll in only if an abn 7 is present)*:	☐ Absent	☐ Present	☐ Not evaluated
del(7q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(7q); specify: __________	☐ Absent	☐ Present	
abn 3 type *(Ffll in only if an 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(3q); specify: _________	☐ Absent	☐ Present	
del(11q)	☐ 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	

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or fialed
☐ Unknown

If an AML with myelodysplasia-related changes is entered, return to Acute Leukaemias on page 8 to continue.

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

DISEASE

Classification:

☐ 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/MPD?
(Secondary origin)

☐ No

☐ Yes, disease related to prior exposure to therapeutic drugs or radiation

☐ Unknown

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

Transcribe the complete karyotype: __

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

abn 1 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
del(20q)	☐ Absent	☐ Present	☐ Not evaluated
del(13q)	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _______________	☐ Absent	☐ Present	

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

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

Indicate below whether the markers were absent, present or not evaluated.

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	

MYELOPROLIFERATIVE NEOPLASM (MPN)

main disease code 6

DISEASE

Classification:

☐ 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)
☐ Other; specify: _____

Therapy-related MDS/MPD?
(Secondary origin)

☐ No

☐ Yes, disease related to prior exposure to therapeutic drugs or radiation

☐ Unknown

IPPS risk score for myelofibrosis:

☐ Low risk

☐ Intermediate-1

☐ Intermediate-2

☐ High risk

☐ Not evaluated

MYELOPROLIFERATIVE NEOPLASM (MPN)
main disease code 6

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)***:**
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

Transcribe the complete karyotype:

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

abn 1 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
del(20q)	☐ Absent	☐ Present	☐ Not evaluated
del(13q)	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _______________	☐ Absent	☐ Present	

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

MYELOPROLIFERATIVE NEOPLASM (MPN)

main disease code 6

MOLECULAR MARKER ANALYSIS continued

Indicate below whether the markers were absent, present or not evaluated.

BCR-ABL; *Molecular product of t(9;22)(q34;q11.2)*	☐ Absent ☐ Present ☐ Not evaluated
JAK2 mutation	☐ Absent ☐ Present ☐ Not evaluated **If present: allele burden _____ %**
cMPL mutation	☐ Absent ☐ Present ☐ Not evaluated
Calreticulin (CALR) mutation	☐ Absent ☐ Present ☐ Not evaluated
FIP1L1-PDGFR	☐ Absent ☐ Present ☐ Not evaluated
Other; specify: _____	☐ Absent ☐ Present

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

DISEASE

Classification:

☐ Multiple myeloma (MM)		Heavy chain type:	Light chain type:
☐ MM; heavy chain and light chain	→ *Check light and/or heavy chain types as applicable*	☐ IgG ☐ IgA ☐ IgD ☐ IgE ☐ IgM (not Waldenstrom)	☐ Kappa ☐ Lambda
☐ MM; light chain	→		
☐ MM; non-secretory			
☐ Plasma cell leukaemia			
☐ Solitary plasmacytoma of bone			
☐ Primary amyloidosis			
☐ POEMS			
☐ Monoclonal light and heavy chain deposition disease (LCDD/HCDD)			
☐ Other; specify: _____			

Staging at diagnosis:

Salmon & Durie staging for multiple myeloma:
(Please tick both columns.)

Stage	Symptoms
☐ I	☐ A
☐ II	☐ B
☐ II	

Revised ISS:

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

OR

ISS STAGE:

Stage	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

PLASMA CELL DISORDERS (PCD) incl. MULTIPLE MYELOMA (MM)

main disease code 4

CHROMOSOME ANALYSIS

Not applicable for Primary amyloidosis.

Chromosome analysis at diagnosis *(all methods including FISH)***:**
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

Transcribe the complete karyotype:

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

del(13q14)	☐ Absent	☐ Present	☐ Not evaluated
t(11;14)	☐ Absent	☐ Present	☐ Not evaluated
abn(17q)	☐ Absent	☐ Present	☐ Not evaluated
del(17p)	☐ 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	

MOLECULAR MARKER ANALYSIS

Not applicable for Primary amyloidosis.

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

BONE MARROW FAILURE SYNDROMES (BMF) incl. APLASTIC ANAEMIA (AA)

main disease code 7

DISEASE

Classification:

Aquired:

☐ Severe Aplastic Anaemia (SAA)	Etiology:
☐ Amegakaryocytosis, acquired (not congenital)	☐ Secondary to hepatitis
☐ Acquired Pure Red Cell Aplasia (PRCA) (not congenital)	☐ Secondary to toxin/other drug
☐ Paroxysmal nocturnal haemoglobinuria (PNH)	☐ Idiopathic
☐ Acquired Pure White Cell Aplasia	☐ Other; specify: _____
☐ Other acquired cytopenic syndrome; specify: _____	

Congenital:

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

HAEMOGLOBINOPATHY
main disease code 1

DISEASE

Classification:

- ☐ Thalassaemia
  - ☐ Beta 0
  - ☐ Beta+
  - ☐ Beta E
  - ☐ Beta S (sickle cell + thalassaemia): **Percentage sickle cell:** _____ %
- ☐ Sickle Cell Disease
- ☐ Other haemoglobinopathy; specify: _____

SOLID TUMOURS
main disease code 5

DISEASE

Classification:

☐ 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
☐ Germ cell tumour, gonadal
☐ Head and neck
☐ Hepatobiliary
☐ Kidney cancer excluding Wilm's tumour
☐ Lung cancer, non-small cell
☐ Lung cancer, small cell
☐ Medulloblastoma
☐ Melanoma
☐ Neuroblastoma
☐ Ovarian (carcinoma)
☐ Pancreatic
☐ Prostate
☐ Renal cell
☐ Retinoblastoma
☐ Rhabdomyosarcoma
☐ Soft tissue sarcoma (excluding Rhabdo. and extra-skeletal ES)
☐ Thymoma
☐ Wilm's tumour
☐ Other; specify: _____

TNM classification:

Type:
- ☐ Clinical
- ☐ Pathological

Tumour:
- ☐ TX
- ☐ T0
- ☐ T1
- ☐ T2
- ☐ T3
- ☐ T4
- ☐ Not evaluated
- ☐ Unknown

Nodes:
- ☐ NX
- ☐ N0
- ☐ N1
- ☐ N2
- ☐ N3
- ☐ Not evaluated
- ☐ Unknown

Metastases:
- ☐ MX
- ☐ M0
- ☐ M1
- ☐ Not evaluated
- ☐ Unknown

SOLID TUMOURS
main disease code 5

DISEASE continued

Disease-specific staging:

- ☐ I
- ☐ II
- ☐ III
- ☐ IV
- ☐ Not evaluated
- ☐ Unknown

Breast carcinoma risk factors and staging at diagnosis *(Breast carcinoma only)*:

Receptor status:

Estrogen (ER):	☐ Negative	☐ Positive: ER values: _____	☐ Not evaluated
Progesteron (PgR):	☐ Negative	☐ Positive: PgR values: _____	☐ Not evaluated
HER2/neu (c-erb-B2):	☐ Negative	☐ Positive	☐ Not evaluated

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

Axillary lymph nodes at surgery: Nº positive / Nº examined = _____ / _____ ☐ Not evaluated

Sentinel Node: ☐ Negative ☐ Positive ☐ Not evaluated

Carcinoma type *(tick only one)*: ☐ Ductal carcinoma ☐ Lobular carcinoma

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

Germ cell tumour risk factors and staging at diagnosis *(Germ cell tumours only)*:

Histological classification: ☐ Seminoma ☐ Non-seminoma

Site of origin: ☐ Gonadal

☐ Extra-gonadal: ☐ retroperitoneal ☐ mediastinal ☐ Other sites; specify: _____

INHERITED DISORDERS
Primary Immune Deficiencies (PID) - *main disease code 8*

DISEASE

Classification:

☐ 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 deficiency)
☐ Reticular dysgenesis
☐ SCID, other; specify: _____
☐ SCID, unspecified
☐ Wiskott Aldrich syndrome
☐ X-linked lymphoproliferative syndrome
☐ Other; specify: _____

INHERITED DISORDERS
Inherited Disorders of Metabolism - *main disease code 8*

DISEASE

Classification:

☐ 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)
☐ Inherited disorders of metabolism, not otherwise specified
☐ 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: _____

INHERITED DISORDERS
Platelet and Other Inherited Disorders - *main disease code 8*

DISEASE

Classification:

☐ Glanzmann thrombasthenia
☐ Other inherited platelet abnormalities: specify: _____
☐ Osteopetrosis (malignant infantile osteopetrosis)
☐ Other osteoclast defects: specify: _____

HISTIOCYTIC DISORDERS
main disease code 9

DISEASE

Classification:

☐ 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: _____

AUTOIMMUNE DISORDERS
main disease code 10

DISEASE

Classification:

Connective tissue:

☐ Systemic sclerosis (SS)

Involvement/clinical problem:
- ☐ diffuse cutaneous
- ☐ limited cutaneous
- ☐ SSc sine scleroderma
- ☐ Mixed Connective Tissue Disease (MCTD)
- ☐ Other; specify: _____

☐ Systemic lupus erythematosus (SLE)
☐ Polymyositis dermatomyositis
☐ Sjögren syndrome
☐ Antiphospholipid syndrome
☐ Other type of connective tissue disease; specify: _____

Vasculitis:

☐ Wegener granulomatosis
☐ Classical polyarteritis nodosa
☐ Microscopic polyarteritis nodosa
☐ Churg-Strauss
☐ Giant cell arteritis
☐ Takayasu
☐ Behçet syndrome
☐ Overlap necrotising arteritis
☐ Other; specify: _____

Arthritis:

☐ Rheumatoid arthritis
☐ Psoriatic arthritis/psoriasis
☐ Juvenile idiopathic arthritis (JIA), systemic (Still's disease)
☐ Juvenile idiopathic arthritis (JIA), articular
- ☐ oligoarticular onset
- ☐ polyarticular onset

☐ Other Juvenile idiopathic arthritis; specify: _____
☐ Other arthritis; specify: _____

AUTOIMMUNE DISORDERS
main disease code 10

DISEASE continued

Classification:

Neurological diseases:

- ☐ Multiple Sclerosis
- ☐ Myasthenia gravis
- ☐ Amyotrophic lateral sclerosis (ALS)
- ☐ Chronic inflammatory demyelinating polyneuropathy (CIDP)
- ☐ Neuromyelitis Optica (NMO)
- ☐ Other autoimmune neurological disorder; specify: _____

Haematological diseases:

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

Bowel diseases:

- ☐ Crohn's disease
- ☐ Ulcerative colitis
- ☐ Other autoimmune bowel disease; specify: _____

Other autoimmune diseases:

- ☐ Grave's disease
- ☐ Insuline-dependent diabetes (IDD)
- ☐ Other autoimmune disease; specify: _____

OTHER PRIMARY DISEASES
Infections - *main disease code 14*

DISEASE

Classification:

☐ Prevention/Prophylaxis

☐ Treatment:

Pathogen involved:

- ☐ Adenovirus
- ☐ BK virus
- ☐ Cytomegalovirus (CMV)
- ☐ Epstein-Barr virus
- ☐ Human herpes virus
- ☐ Human immunodeficiency virus (HIV)
- ☐ Other virus; specify: _____
- ☐ Candida
- ☐ Aspergillus
- ☐ Other fungus; specify: _____
- ☐ Other infection; specify: _____

OTHER PRIMARY DISEASES
Neurological Disorders - *main disease code 12*

DISEASE

Classification:

- ☐ Duchenne muscular dystrophy
- ☐ Acute cerebral vascular ischemia
- ☐ Amyotrophic lateral sclerosis (ALS)
- ☐ Parkinson's disease
- ☐ Spinal cord injury
- ☐ Cerebral palsy
- ☐ Congenital hydrocephalus
- ☐ Other; specify: _____

OTHER PRIMARY DISEASES
Cardiovascular (Heart) Diseases - *main disease code 13*

DISEASE

Classification:

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

OTHER PRIMARY DISEASES
Musculoskeletal Disorders - *main disease code 15*

DISEASE

Classification:

☐ Avascular necrosis of femoral head
☐ Osteoarthritis
☐ Osteogenesis imperfecta
☐ Traumatic joint injury
☐ Other; specify: _____

END OF PRE-INFUSION REGISTRATION & DISEASE CLASSIFICATION SHEETS

Change history:

Version	Date	Description
v1.0	9-Feb-2022	First final version

CELLULAR THERAPIES FORM
-- Day 0 --

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): _____

Hospital: _____

Unit: _____

Contact person: ___

Centre in which the treatment is given (CIC): _____

PATIENT DATA

EBMT Unique Identification Code (UIC): _____
(Patient number in EBMT database; complete if patient had a previous treatment and is already registered in the database)

Date of this report: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Hospital Unique Patient Number or code (UPN): _____
(Compulsory; registrations will not be accepted without this item. All treatments (transplants or CAR T-cell) 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.)

Other type of patient identification code(s): _____
(Optional; to be used by the centre to register a patient code for internal use as necessary.)

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

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Sex *(at birth)*:

☐ Male

☐ Female

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

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

☐ No *(continue with this section)*

☐ Yes *(proceed to 'Patient Status at Cellular Therapy' on page 5)*

Was the patient treated before this cellular therapy procedure?

☐ No *(proceed to 'Patient Status at Cellular Therapy' on page 5)*

☐ Yes: Date started: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Copy and repeat the whole 'Previous Therapies' section for each line of treatment. Do not include preparative/lymphodepleting regimen.

Sequential number of this treatment *(counted from diagnosis)*: __________

☐ Unknown

Chemotherapy/Drugs given?

☐ No *(proceed to "Radiotherapy' on page 3)*

☐ Yes *(report below)*

☐ Unknown

List all chemotherapy/drugs given during one line of treatment:

Drug/ Regimen:	**Nº of cycles:**	**Date started:** *(YYYY/MM/DD)*	**Date ended:** *(YYYY/MM/DD)*
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _

PREVIOUS THERAPIES GIVEN BEFORE TRANSPLANT/CELLULAR THERAPY (inlcuding bridging therapies) continued

Copy and repeat the whole 'Previous Therapies' section for each line of treatment. Do not include preparative/lymphodepleting regimen.

List all chemotherapy/drugs given during one line of treatment:

Drug/ Regimen:	**Nº of cycles:**	**Date started:** *(YYYY/MM/DD)*	**Date ended:** *(YYYY/MM/DD)*
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _
		_ _ _ _/_ _/_ _	_ _ _ _/_ _/_ _

If there were more drugs given during one line of treatment add more copies of this page.

Radiotherapy:

☐ No

☐ Yes: Date started: _ _ _ _/_ _/_ _ *(YYYY/MM/DD)*

Date ended: _ _ _ _/_ _/_ _ *(YYYY/MM/DD)*

☐ Unknown

Other treatment:

☐ No

☐ Yes; specify: ____________________

☐ Unknown

PREVIOUS THERAPIES GIVEN BEFORE TRANSPLANT/CELLULAR THERAPY (inlcuding bridging therapies) continued

Copy and repeat the whole 'Previous Therapies' section for each line of treatment. Do not include preparative/lymphodepleting regimen.

Response to this line of treatment:
(complete only the section that is relevant to the main diagnosis for which this cellular treatment is given)

Acute Leukaemias:
- ☐ Complete remission (CR); maintained or achieved
- ☐ Relapse/Progression
- ☐ Not evaluable

MDS and MPN:
- ☐ Complete remission (CR); maintained or achieved
- ☐ Relapse/Progression
- ☐ Improvement but no CR
- ☐ Not evaluable

Plasma cell disorders incl. Multiple Myeloma:
- ☐ Stringent complete remission (sCR)
- ☐ Complete remission (CR)
  - Number of this sCR or CR:
    - ☐ 1st
    - ☐ 2nd
    - ☐ 3rd or higher
- ☐ Very good partial remission (VGPR)
- ☐ Partial remission (PR)
  - Number of this VGPR or PR:
    - ☐ 1st
    - ☐ 2nd
    - ☐ 3rd or higher
- ☐ Stable disease *(no change; includes old MR)*
- ☐ Progression
- ☐ Not evaluable

Haemoglobinopathy:
- ☐ No transfusion required *(in Promise select 'Complete remission'.)*
- ☐ Transfusions required *(in Promise select 'Never in CR'.)*

Lymphomas:
- ☐ Complete remission (CR); maintained or achieved
  - ☐ Unconfirmed
  - ☐ Confirmed, by: ☐ CT scan ☐ PET
- ☐ Partial remission (>50%)
- ☐ No response (<50%)
- ☐ Progression
- ☐ Not evaluable

Bone marrow failure syndrome (incl. Aplastic Anaemia)
- ☐ Complete remission (CR)
- ☐ Partial remission (transfusion and growth factor independent)
- ☐ No response
- ☐ Progression
- ☐ Not evaluable
- ☐ Other

Solid tumours:
- ☐ Complete remission (CR)
- ☐ Stable disease
- ☐ Very good partial remission
- ☐ Progressive disease
- ☐ Partial remission (>50)
- ☐ Minor response (>25% and <50%)
- ☐ Not evaluable

Other diagnoses:
- ☐ Cured *(in Promise select 'Complete remission'.)*
- ☐ Improved *(in Promise select 'Partial remission'.)*
- ☐ Worse *(in Promise select 'Progression'.)*
- ☐ No response
- ☐ Not evaluable

PATIENT STATUS AT CELLULAR THERAPY
(All Diagnoses)

Performance score at initiation of treatment *(choose only one)*:

Type of score used:	Score:									
☐ Karnofsky ☐ Lansky	☐ 10	☐ 20	☐ 30	☐ 40	☐ 50	☐ 60	☐ 70	☐ 80	☐ 90	☐ 100
☐ ECOG	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4					

Patient weight at time of cellular therapy: _____ kg

Patient height at time of cellular therapy: _____ cm

B-cell aplasia at time of cellular therapy?

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

DISEASE STATUS AT CELLULAR THERAPY

Status at cellular therapy:
(complete only the section that is relevant to the main diagnosis for which this cellular treatment is given)

Acute Leukaemias:
- ☐ Primary induction failure
- ☐ Complete remission (CR)
- ☐ Relapse

Lymphomas:
- ☐ Never treated
- ☐ Complete remission (CR)
- ☐ Partial remission (PR)
- ☐ Stable disease (no change/no response)
- ☐ Untreated relapse (from a previous CR) or progression from a previous PR
- ☐ Chemorefractory relapse or progression, including primary refractory disease

MDS, MPN and MDS/MPN:
- ☐ Primary refractory
- ☐ Complete remission (CR)
- ☐ Improvement but no CR
- ☐ Relapse
- ☐ Progression
- ☐ Never treated

Plasma cell disorders incl. Multiple Myeloma:
- ☐ Stringent complete remission (sCR)
- ☐ Complete remission (CR)
- ☐ Very good partial remission (VGPR)
- ☐ Partial remission (PR)
- ☐ Relapse
- ☐ Progression
- ☐ Stable disease (no change/no response)
- ☐ Never treated

Chronic Leukaemias:

CML:
- ☐ Chronic phase
- ☐ Accelerated phase
- ☐ Blast crisis

CLL/ PLL:
- ☐ Complete remission (CR)
- ☐ Partial remission (PR)
- ☐ Stable disease (no change/no response)
- ☐ Relapse
- ☐ Progression
- ☐ Never treated

Solid tumours:
- ☐ Adjuvant
- ☐ Never treated
- ☐ Stable disease (no change/no response)
- ☐ Complete remission (CR)
- ☐ First partial response (PR1)
- ☐ Relapse
- ☐ Progression

Other diagnoses:
- ☐ Cured *(select 'Complete remission'.)*
- ☐ Improved *(select 'Partial remission'.)*
- ☐ Worse *(select 'Progression'.)*
- ☐ No response
- ☐ Not evaluable

COMORBIDITY INDEX

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)*

☐ Unknown

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

Were there any additional major clinical abnormalities not listed above and present prior to the preparative regimen?

Specify: _____

CELLULAR THERAPY TREATMENT

Was the cellular product infused during this treatment/procedure?

☐ Yes

☐ No; Reason why the treatment did not take place:
- ☐ Production failure
- ☐ Out-of-specification product refused by physician
- ☐ Disease progresion
- ☐ Patient condition worsened (ineligible for treatment) or patient died
- ☐ Other; specify: _

Date of the first cell infusion: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(if the cellular therapy product was infused)

OR

Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(only applicable if the cellular therapy product was not infused)

CELLULAR THERAPY INFUSION UNIT(S)

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

☐ No

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

CELLULAR THERAPY INFUSION UNIT(S)
Description

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

Identification:

Name of manufacturer:

- ☐ Autolus
- ☐ Bluebird Bio
- ☐ Celgene/ Bristol Myer Squibb
- ☐ Celyad
- ☐ GlaxoSmithKline (GSK)
- ☐ Janssen (Johnson & Johnson)
- ☐ Kite Gilead
- ☐ Miltenyi
- ☐ Novartis
- ☐ Orchard
- ☐ Vertex
- ☐ Local hospital or university
- ☐ Other

CELLULAR THERAPY INFUSION UNIT(S)
Description continued

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

Identification continued:

Name of product *(if applicable)*:

- ☐ Abecma
- ☐ Breyanzi
- ☐ Cilta-cel
- ☐ Eli-cel
- ☐ Kymriah
- ☐ Tecartus
- ☐ Yescarta
- ☐ Other

Unique ID of the product: _____
(If applicable; enter only if the CT product was infused.)

Batch number: _____
(If applicable; enter only if the CT product was infused.)

Identification of the cell infusion unit given by the centre: _____
(If there is only one cell infusion unit enter "1"; enter only if the CT product was infused)

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

Was the infused cellular product consistent with the specifications?

- ☐ No
- ☐ Yes

Was the cellular therapy product cryopreserved prior to infusion?

- ☐ No
- ☐ Yes

CELLULAR THERAPY INFUSION UNIT(S)
Manipulation

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

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

***Ex-vivo* manipulation of the product contained in the cellular therapy infusion unit:**

☐ No (*proceed to 'Therapy and Cell Infusion' on page 11*)
☐ Yes (*continue with 'Manipulation' section below.*)
☐ Unknown

Manipulation:

Processing/Manufacturing facility:

☐ Onsite, by local cell processing facility
☐ Offsite, by a non-commercial facility
☐ Offsite, by a commercial facility

Gene manipulation:

☐ No

☐ Yes: Type *(check all that apply)*:

☐ Gene transfer: Vector: ☐ Retroviral vector
☐ Lentiviral vector
☐ Other vector; specify: _____

Transgene: ☐ CAR; specify all targets: _____
☐ TCR; specify all targets: _____
specify HLA element: _____
☐ Suicide gene; specify: _____
☐ Other: specify: _____

☐ Gene editing: ☐ No
☐ Yes: Manipulated gene: ☐ CCR5
☐ Factor IX
☐ Factor VIII
☐ Other gene; specify: __ ___

☐ Other: ☐ No
☐ Yes: specify: _____

CELLULAR THERAPY INFUSION UNIT(S)
Manipulation continued

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

Manipulation aims:

Recognition of a specific target/antigen:

☐ No

☐ Yes: Type *(check all that apply)*:

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

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

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

☐ Other target; specify: _____

Cell types *(check all that apply)*:

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

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

THERAPY & CELL INFUSION(S)

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

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

If > 1:

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

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

Type of last cellular therapy before this one:
☐ Auto
☐ Allo: Was the same donor used for all prior and current cellular therapy? ☐ No ☐ Yes

Was the last cellular therapy performed at another institution?
☐ No
☐ Yes:
CIC (if known): _____
Name of institution: _____
City: _____

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

Reason for this cellular therapy (check all that apply):

If indication is the <u>treatment of a primary disease:</u>
☐ Treatment of primary diagnosis
☐ Prevention of disease relapse or progression
☐ Rescue from disease relapse or progression
☐ Minimal residual disease reduction
☐ Refractory disease
☐ Other; specify: _____

If indication is the <u>treatment or prevention of a complication derived from a previous treatment:</u>

GvHD
☐ Unrelated to GvHD
☐ Prevention/Prophylaxis of GvHD
☐ Treatment of GvHD

Graft function
☐ Unrelated to graft function
☐ Preventionof rejection/Promotion of cell engraftment
☐ Graft enhancement
☐ Graft failure treatment

Immune reconstitution
☐ Unrelated to immune reconstitution
☐ Immune reconstitution

THERAPY & CELL INFUSION(S)
Preparative Treatment

Did the patient receive preparative (lymphodepleting) treatment?

☐ No

☐ Yes: Specification and dose of the preparative regimen:

Include any systemic drugs (chemotherapy, growth factors, antibodies, etc.

Name of drug *(any given before day 0)*	**Total prescribed cumulative dose*** *(as per protocol)*	**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**

** 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 preparative treatment:

☐ No

☐ Yes; specify: _____

CELL INFUSION EPISODE(S)

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

☐ No

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

CELL INFUSION EPISODE(S)
Description

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

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

Route of infusion:

☐ Intravenous

☐ Intrathecal

☐ Intratumour injection

☐ Other route; specify: __ ___

Combined/concomitant therapies planned before this cellular therapy to optimize efficiency?

☐ No

☐ Yes; specify: _____

Treatment given: ☐ Simultaneously to the cellular therapy

☐ After the cellular therapy episode was finished

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

Is the exact number of cells infused available?

☐ No, only a range is available

☐ Yes: Number of cells: _____ Unit *(tick only one)*: ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8
(not adjusted for cell viability)

Cell viability: **%**

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

Is the exact number of cells infused available?

☐ No, only a range is available

☐ Yes: Number of cells: _____ Unit *(tick only one)*: ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8
(not adjusted for cell viability)

Cell viability: **%**

SURVIVAL STATUS

Survival status:

☐ Alive

☐ Dead: Date of death *(if death happened around time of cellular therapy)*: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD)

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

☐ Relapse or progression/persistent disease
☐ Secondary malignancy
☐ Cellular therapy-related
☐ HSCT-related *(only if patient previously had a transplant)*
☐ Unknown
☐ Other; specify: __ __

Contributory causes of death:
(check all that apply)

☐ GvHD
☐ Cytokine release syndrome
☐ Interstitial pneumonitis
☐ Pulmonary toxicity
☐ Infection: ☐ bacterial
☐ viral
☐ fungal
☐ parasitic
☐ unknown
☐ Rejection/Poor graft function
☐ History of severe veno occlusive disorder (VOD)
☐ Haemorrhage
☐ Cardiac toxicity
☐ Central nervous system (CNS) toxicity
☐ Gastrointestinal (GI) toxicity
☐ Skin toxicity
☐ Renal failure
☐ Multiple organ failure
☐ Other; specify: _____

END OF DAY 0 REGISTRATION

Change history:

Version	Date	Description
v1.0	9-Feb-2022	First final version
v2.0	23-May-2022	Typos corrected Disease status at time of CT: label sets for MDS, MPN and MDS/MPN; Solid Tumors and Plasma cell disorders incl. Multiple Myeloma updated

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

EBMT Unique Identification Code (UIC): _____
(Patient number in EBMT database)

Date of this report: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): _____

Unit: _____

Contact person: _____

PATIENT DATA

Hospital Unique Patient Number or code (UPN): _____
(Compulsory; registrations will not be accepted without this item. All treatments (transplants or CAR T-cell) 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.)

Other type of patient identification code(s): _____
(Optional; to be used by the centre to register a patient code for internal use as necessary.)

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

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Sex *(at birth)*:
☐ Male
☐ Female

Assessment period covered by this report:
☐ Day 100
☐ 6 Months
☐ Annual Follow-Up

RECOVERY

Absolute neutrophil count (ANC) recovery *(Neutrophils ≥ 0.5x10⁶ cells/L)*:

☐ No: Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Yes: Date of ANC recovery: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(first of 3 consecutive values after 7 days without transfusion containing neutrophils)

☐ Never below

☐ Unknown

Platelet reconstitution:

Platelets **≥ 20x10⁹ cells/L**:

☐ No: Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Yes: Date of platelet reconstitution: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(first of 3 consecutive values after 7 days without platelet transfusion)

☐ Date unknown; patient discharged before levels reached

☐ Date unknown; out-patient

☐ Never below

☐ Unknown

Platelets **≥ 50x10⁹ cells/L**:

☐ No: Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Yes: Date of platelet reconstitution: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(first of 3 consecutive values after 7 days without platelet transfusion)

☐ Date unknown; patient discharged before levels reached

☐ Date unknown; out-patient

☐ Never below

☐ Unknown

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

RESPONSE TO CELLULAR THERAPY

Complete only for Day 100 and 6 Months.

Best clinical/biological response after the entire cellular therapy treatment:

If the indication was the treatment of a primary disease:

☐ Complete remission (CR) / Normalisation of organ function / No infection present

☐ *for AML only:* Complete remission with incomplete haematological recovery (CRi)

☐ Partial remission / Partial or non-normalisation of organ function

☐ No response

☐ Disease progression or worsening of organ function

☐ Not evaluated

Date response evaluated: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

LAST CONTACT DATE FOR THIS REPORT

Date of last assessment for this report: ____/__/__ *(YYYY/MM/DD)*
(enter date of advanced cellular therapy plus the set period - Day 100, 6 Months, Annual Follow-Up - approximately)

CURRENT HAEMATOLOGICAL FINDINGS

Was a haematological investigation performed?

☐ No

☐ Yes:

Hb	_____ g/dl
Platelets	_____ 10^9 cells/L
Were platelets transfused within 7 days before date of test?	☐ No ☐ Yes
White blood cells	_____ 10^9 cells/L
Haematocrit	_____ %
Were RBC transfused within 30 days before date of test?	☐ No ☐ Yes
Percentage Lymphocytes	_____ %
Percentage Neutrophils	_____ %

B-cell aplasia since last assessment:

☐ Absent

☐ Present: Percentage of B-cells: _____ % *(If the patient received tretament for B-cell aplasia, add details in "Post-Therapy Treatment' on page 16)*

☐ Unknown

PERFORMANCE SCORE

Performance score at the last assessment *(choose only one)*:

Type of score used:	Score:
☐ Karnofsky ☐ Lansky	☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100
☐ ECOG	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

COMPLICATIONS SINCE THE LAST REPORT
-- GvHD --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Did graft versus host disease (GvHD) occur?

☐ No *(proceed to 'Complications since last report - Toxicities (non-infectious)' on page 5)*

☐ Yes: Type of GvHD *(check all that apply)*:

☐ **Acute GvHD:** Maximum grade: ☐ I ☐ II ☐ III ☐ IV ☐ Present but grade unknown ☐ Not evaluated

Type: ☐ New onset ☐ Recurrent ☐ Persistent

Date of onset: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Stage:

Skin:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4
Liver:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4
Lower GI tract:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4
Upper GI tract:	☐ 0 *(none)*	☐ 1			
Other site affected:	☐ No	☐ Yes			

Related to cell terapy: ☐ No ☐ Yes

Resolved: ☐ No ☐ Yes

Treatment for acute GvHD:
☐ No
☐ Yes: ☐ Corticosteroids ☐ Monoclonal Antibodies (MoAB) ☐ ATG/ALG ☐ Extra-corporeal photopheresis (ECP) ☐ Other; specify: _

☐ **Chronic GvHD:** Episode: ☐ First episode ☐ Recurrence ☐ Continuous since last reported episode ☐ Yes, but resolved ☐ Yes, but resolved and reccured again

Date of onset: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Maximum extent during this period: ☐ Limited ☐ Extensive ☐ Unknown

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

COMPLICATIONS SINCE THE LAST REPORT
Toxicities (non infectious)

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Toxicities/Non-infectious complications:

☐ No *(proceed to "Complications since last report - Infections' on page 10)*

☐ Yes *(report all non-infectious complications below)*

☐ Unknown *(proceed to "Complications since last report - Infections' on page 10)*

Cytokine release syndrome (CRS): ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Maximum grade: _____ Scale/Criteria used to determine CRS grade:
- ☐ ASBMT/ASTCT
- ☐ Penn
- ☐ CTCAE
- ☐ Lee 2014
- ☐ MDACC
- ☐ CARTOX
- ☐ Other; specify: _____
- ☐ Unknown

Treatment given?
- ☐ No
- ☐ Yes *(If patient was treated for CRS add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Neurotoxicity: ☐ **No** ☐ **Yes**

☐ Altered mental status: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Aphasia: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Toxicities (non-infectious) --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Neurotoxicity *continued*:

☐ Hemiparesis or other focal motor deficit: Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Seizures: Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Tremors: Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Visual hallucinations: Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Encephalopathy: Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Cerebral oedema: Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Other; specify: Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
Toxicities (non infectious)

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Grade 3 and 4 organ toxicities as per CTCAE: ☐ **No** ☐ **Yes** *(select and complete all that apply)*

☐ Skin: Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Liver: Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Lung: Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Heart: Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Kidney: Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Gastrointestinal: Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Other organ; specify: _____ Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Toxicities (non-infectious) --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Tumor lysis syndrome (TLS): ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Bone marrow aplasia: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Specify: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Hypogammaglobulinemia: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD)

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

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Insertional mutagenesis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD)

Resolved: ☐ No ☐ Yes ☐ Unknown

Exacerbation of existing neurological disorder: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Specify: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Hemorrhagic stroke: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT

-- Toxicities (non-infectious) --

Do not report complications that were resolved __before__ the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Other toxicity/complication: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: ______________________

Grade *(if applicable)*: ________

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Other toxicity/complication: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: ______________________

Grade *(if applicable)*: ________

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Other toxicity/complication: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: ______________________

Grade *(if applicable)*: ________

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Infections --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Infection-related complications:
(Report only grade 3 and 4 infections as per CTCAE)

☐ No *(proceed to 'Secondary Malignancies' on page 15)*

☐ Yes *(report all infection-related complications below)*

☐ Unknown *(proceed to 'Secondary Malignancies' on page 15)*

Bacteremia: ☐ **No** ☐ **Yes** *(report all episodes below; in case of the same pathogen report episodes occuring after 14 days)*

1) Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

2) Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

3) Onset date: / / (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

4) Onset date: / / (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

5) Onset date: / / (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

If more than 5 episodes copy this page as necessary.

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Invasive fungal disease including candidemia: ☐ **No** ☐ **Yes**

1) Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

2) Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

3) Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in "Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

4) Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

5) Onset date: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

If more than 5 episodes copy this page as necessary.

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

CNS infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Pneumonia ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

C. difficile infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Abdominal infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Hepatitis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Retinitis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD) Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Cystitis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Skin infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Upper respiratory tract iunfection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

CMV reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma/blood)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

EBV reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma/blood/PMN)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

HHV6 reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Adenovirus reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Other virus reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Other infectious complication: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

SECONDARY MALIGNANCIES

Did a secondary malignancy or autoimmune disorder occur?

☐ No

☐ Yes: Diagnosis: _____

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

Histologic type *(if applicable)*: _____

Location *(if applicable)*: _____

Secondary malignancy material preserved:

☐ No

☐ Yes

POST-THERAPY TREATMENT

Include only systemic treatments; do not include treatment for acute GvHD as this should be reported in the GvHD section.

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

☐ No
☐ Yes: Date started: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
☐ Unknown

List all chemotherapy/drugs given during one line of treatment:

Drug/ Regimen:	**Indication:** *(as specified in 'Complications' section)*	**Date started:** *(YYYY/MM/DD)*	**Treatment ongoing?**	**Date ended:** *(YYYY/MM/DD)*
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _

Did the patient receive any other type of additional treatment?

☐ No
☐ Yes; specify: ____________________
☐ Unknown

Is the patient receiving any medication not related to cell therapy or its indications?

☐ No
☐ Yes
☐ Unknown

FIRST RELAPSE/PROGRESSION OR SIGNIFICANT WORSENING AFTER ADVANCED CELLULAR THERAPY

Only applicable when indication was the treatment of a primary disease including infections.

First relapse/progression or significant worsening of organ function of the primary disease:
(detected by any method)

☐ No
☐ Yes: Date of relapse: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
☐ Continuous progression since advanced cellular therapy

LAST DISEASE STATUS

Only applicable when indication was the treatment of a primary disease including infections.

Last disease status:

☐ Complete remission/Normalisation of organ function/No infection present
☐ Partial remission
☐ No response
☐ Disease progression or worsening of organ function
☐ Not evaluated

Histological verification of relapse *(only applicable to lymphoma with status relapse)*:

☐ No
☐ Yes

Transfusion status *(only applicable to haemoglobinopathies)*:

☐ No transfusion required
☐ Transfusion required

Disease burden:

LDH level:
☐ Normal
☐ Elevated
☐ Not evaluated

Inflammatory state (C-reactive protein [CPR] concentration):
☐ Normal
☐ Elevated: Maximum CRP concentration: _____ Unit *(check only one)*: ☐ mg/dL ☐ mg/L
☐ Not evaluated

Date of C-reactive protein level assessment: _ _ _ _/ _ _/ _ _ *(YYYY/MM/DD)*

HOSPITAL ADMISSION

Complete only for Day 100 and 6 Months.

Was inpatient admission and care needed?

☐ No
☐ Yes
☐ Unknown

Was the patient transferred to the intensive care unit (ICU)?

☐ No
☐ Yes
☐ Unknown

PREGNANCY AFTER CELLULAR THERAPY

Complete only for 6 Months and Annual Follow-Up.

Has the patient or partner become pregnant after this cellular therapy?

☐ No

☐ Yes: Did the pregnancy result in a live birth?

- ☐ No: Pregnancy outcome:
  - ☐ Abortion (elective, therapeutic, spontaneous)
  - ☐ Stillbirth
- ☐ Yes: Newborn status:
  - ☐ Healthy
  - ☐ Affected by a disease
  - ☐ Information not provided
- Length of term:
  - ☐ Full-term
  - ☐ Premature
  - ☐ Information not provided
- ☐ Unknown

☐ Unknown

PERSISTENCE OF THE INFUSED CELLS

Were tests performed to assess persistence of the infused cellular products during this period?

☐ No

☐ Yes: Date of the last test: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Source of cells used for testing:
- ☐ Bone Marrow
- ☐ Peripheral blood
- ☐ Tumour
- ☐ Other; specify: _

Technique used for testing:
- ☐ Molecular (PCR)
- ☐ Flow cytometry
- ☐ Chimaerism
- ☐ Imaging
- ☐ Immunohistochemistry
- ☐ Other; specify: _____

Were cells detected:
- ☐ No
- ☐ Yes

SURVIVAL STATUS

Survival status:

☐ Alive

☐ Dead: Date of death *(if death happened since last report)*: _ _ _ _/ _ _/ _ _ (YYYY/MM/DD)

☐ Lost to follow-up

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

☐ Relapse or progression/persistent disease

☐ Secondary malignancy

☐ Cellular therapy-related

☐ HSCT-related *(only if patient previously had a transplant)*

☐ Unknown

☐ Other; specify: __ __

Contributory causes of death:
(check all that apply)

☐ GvHD

☐ Cytokine release syndrome

☐ Interstitial pneumonitis

☐ Pulmonary toxicity

☐ Infection: ☐ bacterial
☐ viral
☐ fungal
☐ parasitic
☐ unknown

☐ Rejection/Poor graft function

☐ History of severe veno occlusive disorder (VOD)

☐ Haemorrhage

☐ Cardiac toxicity

☐ Central nervous system (CNS) toxicity

☐ Gastrointestinal (GI) toxicity

☐ Skin toxicity

☐ Renal failure

☐ Multiple organ failure

☐ Other; specify: _____

END OF FOLLOW-UP REGISTRATION

Change history:

Version	Date	Description
v1.0	9-Feb-2022	First final version