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
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	Version 1.2:	09 October 2019
	Version 1.3:	06 November 2019
	Version 2.0:	01 July 2021
	Version 2.1:	03 August 2022
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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	
Last Procedure number	EMEA/H/C/PSP/S/102	
Joint PASS	No	

Research Question and Objectives	Primary objective: (EBMT [European Society for Blood and Marrow Transplantation] and CIBMTR [Center for International Blood and Marrow Transplant Research] data): • To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Yescarta (pooled and by indication), including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential or partners of male patients. Secondary objectives by indication (EBMT and CIBMTR data): • 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 sex, age, country, region, and in special populations (patients with prior allogeneic stem-cell transplant [SCT] and high-risk comorbidity index). • To assess the risk of tumor lysis syndrome (TLS). Exploratory objectives (EBMT and CIBMTR data): • To assess the detection of replication-competent retrovirus (RCR) in samples of patients with secondary malignancies of T-cell origin. Exploratory objectives (EBMT data only): • To assess the safety and effectiveness profile of patients treated with an out-of-specification (OOS) product. • To assess the risk of aggravation of graft-versus-host disease (GvHD). • To determine the occurrence of loss of target antigen and of functional chimeric antigen receptor T-cell (CAR-T) persistence in patients relapsing after Yescarta therapy and those with progressive disease.

Countries of study	In countries where Yescarta will be authorized. At a minimum Belgium, Canada, Czech Republic, France, Germany, Greece, Italy, Poland, Portugal, Spain, Switzerland, the Netherlands, the United Kingdom, and the United States will be countries of study; further countries might be added.
Kite Study Director/Author/ Contact Person:	Name: PPD Telephone: Email:
Marketing Authorization Holder	Kite Pharma. EU B.V.
MAH contact person	Name: PPD Kite Gilead Sciences International Ltd Associate Director Regulatory Affairs Flowers Building Granta Park, Abington Cambridge CB21 6GT, UK Telephone: PPD Email:
Kite-Qualified Person Responsible for Pharmacovigilance:	Name: Telephone: Email:

CONFIDENTIALITY STATEMENT

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADaM	Analysis dataset model
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
ASTCT	American Society for Transplantation and Cellular Therapy
auto-SCT	Autologous stem-cell transplant
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T-cell
CDISC	Clinical Data Interchange Standards Consortium
CDM	Common data model
CHMP	Committee for Human Medical Products
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL	Chronic lymphocytic leukemia
CRF	Case report form
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTED	Cellular Therapy Essential Data
DESCAR-T	Dispositif d'Enregistrement et Suivi des patients traités par CAR-T
DLBCL	Diffuse large B-cell lymphoma
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FL	Follicular lymphoma
GvHD	Graft-versus-host disease
GVP	Good Pharmacovigilance Practices
HCT	Hematopoietic cell transplantation
HRSA	Health Resource & Service Administration
HSC	Hematopoietic stem cells
ICANS	Immune-effector cell-associated neurotoxicity syndrome
IRB	Institutional Review Board
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
MAH	Marketing authorization holder
MICE	Multiple imputation by chained equations

NGS	Next-generation sequencing
NHL	Non-Hodgkin lymphoma
OOS	Out of specification
ORR	Overall response rate
OS	Overall survival
PASS	Post-authorization safety study
PLD	Patient-level data
PMBCL	Primary mediastinal large B-cell lymphoma
PRAC	Pharmacovigilance risk assessment committee
PSUR	Periodic safety update report
QPPV	Qualified person for pharmacovigilance
r/r	Relapsed/refractory
RCR	Replication-competent retrovirus
SAE	Serious adverse event
SCT	Stem-cell transplant
SSR	Special situation report
TLS	Tumor lysis syndrome

1. RESPONSIBLE PARTIES

Table 1. Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing authorization holder (MAH) contact person	PPD Associate Director Regulatory Affairs Kite Gilead Sciences International Ltd Flowers Building Granta Park, Abington Cambridge CB21 6GT, UK	Phone: Email: PPD
Study Director	PPD Director, Real World Evidence Kite, a Gilead company General -Guisan-Strasse 8 6300 Zug CH Switzerland	Phone: Email: PPD
Medical Monitor	PPD Associate Director, Safety and Pharmacovigilance Kite, a Gilead Company 2400 Broadway Santa Monica, CA 90404 USA	Phone: Email: PPD
Clinical Operations	PPD Clinical Trial Manager Gilead Sciences Europe Ltd 2 Roundwood Avenue Stockley Park Uxbridge, UB11 1AF United Kingdom	Phone: Email: PPD
Pharmacovigilance	Patient Safety (PS) Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: Fax: Email: PPD
EU QPPV	PPD Executive Director, PS Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany	Phone: Email: PPD

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 the long-term follow-up data for recipients of Yescarta to evaluate the safety, specifically incidence rates and severity of adverse drug reactions (ADRs), 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) and the Center for International Blood and Marrow Transplant Research (CIBMTR) to systematically capture information at the time of Yescarta infusion and for 15 years of follow-up.
Research Question and Objectives:	Primary objective (EBMT and CIBMTR data): • To evaluate the incidence rate and severity of ADRs in patients treated with Yescarta (pooled and by indication), including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential or partners of male patients. Secondary objectives by indication (EBMT and CIBMTR data): • 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 sex, age, country, region, and in special populations (patients with prior allogeneic stem-cell transplant [SCT], high-risk comorbidity index).

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

Exploratory objectives (EBMT and CIBMTR)

- To assess the detection of replication-competent retrovirus (RCR) in samples of patients with secondary malignancies of T-cell origin.

Exploratory objectives (EBMT data only)

- To assess the safety and effectiveness profile of patients treated with an out of specifications (OOS) product.
- To assess the risk of aggravation of graft-versus-host disease (GvHD).
- To determine the occurrence of loss of target antigen and of functional chimeric antigen receptor T-cell (CAR-T) persistence in patients relapsing after Yescarta therapy and those with progressive disease.

Study Design:

This is a long-term, non-interventional study of patients with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) or with relapsed/refractory follicular lymphoma (FL), who have been treated with Yescarta.

Data for this study will be retrieved from ongoing Registry holders EBMT and CIBMTR. EBMT and CIBMTR will be responsible and accountable for the accuracy and completeness of the data entered in their databases.

Population:

Recipients of Yescarta for r/r DLBCL, PMBCL at participating centers who consent to have data reported to EBMT, and recipients of Yescarta for relapsed/refractory DLBCL, PMBCL or with relapsed/refractory FL who consent to have data reported to the CIBMTR are included in this study. Patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary) will be included in the study analyses.

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

Variables:

This non-interventional, secondary use of data study utilizes both the EBMT Registry and the CIBMTR Registry.

- Variables utilized for analysis of Primary Objectives:
  - Secondary malignancy (date of diagnosis [EBMT] or time from infusion to diagnosis [CIBMTR], type, location and relevant details on biopsy results).
  - CRS (grade, date of onset, treatment and resolution status).
  - Neurologic events (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 $\geq 0.5 \times 10^9$/L for 3 consecutive values, and platelet recovery is defined as platelet count $\geq 20 \times 10^9$/L without transfusion support within 7 days in both EBMT and CIBMTR. 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), not defined as per severe adverse event definition.
  - Hypogammaglobulinemia is defined as serum IgG (Immunoglobulin G) 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.
- Variables utilized for analysis of Secondary Objectives:
  - Date and main cause of death, and date of last assessment.
  - Sex, age, country, and region.
  - 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.

- Variables utilized for analysis of Other Exploratory Objectives:
  - Product received OOS.
  - Type, resolution status, onset date of aggravation of GvHD.
  - In case of a secondary malignancy of T-cell origin, the bio-specimen sampling for RCR testing, the sample date, and the test result (not collected in the current EBMT Cellular Therapy Forms).
  - Date of sampling for loss of target antigen and result (not collected in the current EBMT Cellular Therapy Forms).
  - Data of B-cell recovery as an indirect measure of functional CAR-T persistence: date, whether immune effector cells were detected, and detection method.
- Variables for exposure to Yescarta:
  - Name and dose level (EBMT only) 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 OOS.
- Variables for demographics and baseline characteristics:
  - Age, sex, treatment center, and country.
  - Height and weight at the time of Yescarta infusion.
  - Indication for treatment with Yescarta.
  - Disease subtype (e.g., non-Hodgkin lymphoma histologies).
  - Disease status at the time of cellular therapy (e.g., sensitive or resistant to chemotherapy or radiation prior to therapy).
  - Prior lines of treatment and response.
  - Disease stage at the 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.

- — 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 or other comorbidities collected in the Sorror comorbidity index.

Data Sources: Patient data, as available within the EBMT and CIBMTR Registries will be utilized for this study.

Study Size: Recruitment will go on until patient-level data on at least 750 LBCL (Large B-Cell Lymphoma) patients from EBMT are available, and patient-level data on 1500 LBCL patients and 300 FL patients from CIBMTR are available.

The sample size for this study is not only based on statistical considerations, as it is not a hypothesis-testing study, but also on Health Authority recommendations.

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 female patients of childbearing potential and partners of male patients
- 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 sex, age, indication, country, region, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with OOS product)
  - Incidence rate, severity, resolution, and time to onset of TLS
- Other Exploratory Endpoints:
  - Incidence rate, resolution, time to onset of aggravation of GvHD by acute and chronic type
  - Frequency of detection of RCR in samples of patients with secondary malignancies of T-cell origin
  - Safety and effectiveness endpoints described in primary and secondary endpoints for OOS products
  - Occurrence of loss of target antigen in patients relapsing after Yescarta therapy
  - Occurrence of functional CAR-T persistence in patients relapsing after Yescarta therapy and those with progressive disease

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

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

Incidence rates of events will be provided. 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).

Kaplan-Meier curves will be used to illustrate time-to-event variables without competing risk. Competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression and time to next treatment, and the cumulative incidences at specified time points will be provided. Cause-specific Cox models and Cox proportional hazards models will be used to model multivariate time-to-event data adjusted for subgroups and other potential confounders with and without competing risk, respectively (demographics and baseline characteristics).

Milestones:	DLBCL and PMBCL	
	Start of data collection:	21 August 2020
	End of data collection:	31 December 2038
	Study duration:	18 years
	Interim reports:	Annually 2021-2025, then every 2 years
	Final report:	30 June 2039
	FL	
	Start of data collection:	05 March 2021
	End of data collection:	31 December 2037
	Study duration:	17 years
	Interim Reports:	Annually in 2024 and 2025, then every 2 years
	Final report:	30 June 2039

This study will be conducted in accordance with the European Medicines Agency – Guideline on Good Pharmacovigilance Practices 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)
3.0	29 September 2023	Various	Amendment	To address the PRAC Request for revisions of the PASS protocol and include the CIBMTR dataset into the PASS
3.1	21 February 2024	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
3.2	19 November 2025	Various	Update	To address the comments of the PRAC request for a revised PASS protocol in the 4th interim assessment report and the integrated SAP assessment report, and to implement the respective changes

Protocol Modifications

Protocol modifications may only be made by Kite Pharma, Inc., a wholly owned subsidiary of Gilead Sciences, Inc. Any planned amendments will be discussed with the regulatory authority, EBMT (European Society for Blood and Marrow Transplantation) and CIBMTR (Center for International Blood and Marrow Transplant Research) 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	6 December 2019
DLBCL and PMBCL:	
Start of data collection**	1 April 2025 (CIBMTR) 21 August 2020 (EBMT)
End of data collection***	31 December 2038
Study duration	18 years
Safety data reports****	Quarterly reports from Q3 2020 to Q4 2023
Interim reports	2021 to 2025 annually, then every 2 years
Final report of study results	30 June 2039
FL:	
Start of data collection*****	05 March 2021(CIBMTR)
End of data collection***	31 December 2037
Study duration	17 years
Interim reports	Annually in 2024 and 2025, then every 2 years
Final report of study results	30 June 2039

* 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 3 months after protocol registration or contract execution with the EBMT, whichever comes last.
*** Fifteen years after the last patient enrollment in the study, no further data will be included in the study analyses.
**** Safety Data Reports will be appended to the Yescarta PSURs, unless a Safety Data Report generates an urgent new safety finding or there is an unfavorable change in the risk/benefit profile that will be submitted stand-alone in between PSUR cycles. Safety data in the Safety Data Reports are included in the Interim Reports; after quarterly Safety Data Reports are completed, safety data will be reported through the Interim Reports and a separate Safety Data Report will not be generated.
***** First enrollment in the CIBMTR Registry.

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 chimeric antigen receptor (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 2018, KYMRIAH 2020, 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 CAR T-cell product: 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 relapsed/refractory (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 follicular lymphoma (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 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 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**

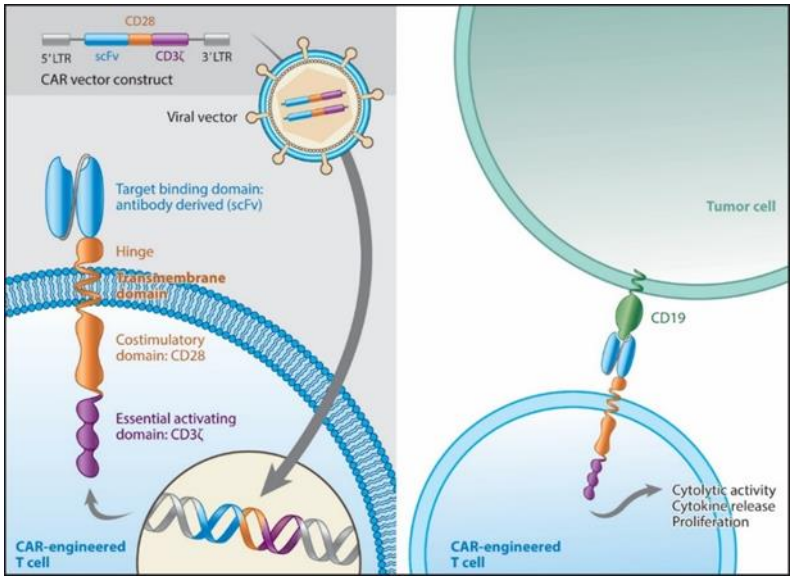

Figure 1: Left panel demonstrates axicabtagene ciloleucel construct with scFv/CD28/CD3ζ, which is inserted in a replication-incompetent gamma-retroviral vector and, upon transfection of T cells, expresses the chimeric transmembrane protein. The right panel demonstrates the anti-CD19 CAR T-cell binding 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, the overall response rate (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, i.e., 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}.

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

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

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 high-dose chemotherapy 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 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 up to 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 ORR (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 ORR and the complete response rate 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 66%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 11% and 31%, 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 66%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 11% and 31%, 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}.

ZUMA-7 included patients with large B-cell lymphoma that was refractory to or had relapsed no more than 12 months after first-line chemoimmunotherapy, to receive axicabtagene ciloleucel (or standard care [two or three cycles of investigator-selected, protocol-defined chemoimmunotherapy, followed by high-dose chemotherapy with auto-SCT in patients with a response to the chemoimmunotherapy]). The primary endpoint was event-free survival according to blinded central review. Safety was also assessed.

A total of 180 patients were randomly assigned to receive axicabtagene ciloleucel and 179 to receive standard care. The primary endpoint analysis of event-free survival showed that axi-cel therapy was superior to standard care. At a median follow-up of 24.9 months, the median event-free survival was 8.3 months in the axi-cel group and 2.0 months in the standard-care group, and the 24-month event-free survival was 41% and 16%, respectively (hazard ratio for event or death, 0.40; 95% confidence interval [CI], 0.31 to 0.51; $p < 0.001$). Adverse events (AEs) of Grade 3 or higher occurred in 91% of the patients who received axi-cel and in 83% of those who received standard care. Among patients who received axi-cel, Grade 3 or higher CRS occurred in 6%, and Grade 3 or higher neurologic events in 21%. No deaths related to CRS or neurologic events occurred. Axi-cel therapy led to significant improvements as compared with

standard care in event-free survival and response, with the expected level of high-grade toxic effects.

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 82% and 57%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 7% and 18%, 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 and CIBMTR Registries 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 or partners of male patients. The purpose of the study therefore includes the further characterization of the short- and long-term ADRs and known and hypothetical ADRs.

The EBMT is a non-profit organization that was established in 1974 to allow scientists and physicians involved in clinical bone marrow transplantation to share their experiences and develop cooperative studies. More recently, the scope of the organization has broadened to include work in cellular therapy as well. The EBMT has created a specific cell therapy module of its registry and utilizes the infrastructure created for the stem-cell transplant (SCT) registry to systematically capture data on all cell therapies.

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

This study will use the data accrued on Yescarta in the EBMT and CIBMTR Registries to systematically evaluate the 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) or of relapsed/refractory follicular lymphoma (FL).

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 neoplasms, 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 and the CIBMTR Registry, using the infrastructure EBMT and CIBMTR created for the stem-cell transplant registry, to systematically capture information at the time of Yescarta infusion and for 15 years of follow-up.

Primary objective (EBMT and CIBMTR data):

- To evaluate the incidence rate and severity of ADRs in patients treated with Yescarta (pooled and by indication), including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential or partners of male patients.

Secondary objectives by indication (EBMT and CIBMTR data):

- To determine the overall survival (OS) 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 sex, age, country, region, and in special populations (patients with prior allogeneic SCT, high-risk comorbidity index).
- To assess the risk of tumor lysis syndrome (TLS).

Exploratory objectives (EBMT and CIBMTR data):

- To assess the detection of RCR in samples of patients with secondary malignancies of T-cell origin.

Exploratory objectives (EBMT data only):

- To assess the safety and effectiveness profile of patients treated with Out-of-Specification (OOS) product.
- To assess the risk of aggravation of graft-versus-host disease (GvHD).
- To determine the occurrence of loss of target antigen in patients relapsing after Yescarta therapy
- To determine the functional CAR-T persistence in patients relapsing after Yescarta therapy and those with progressive disease.

7. RESEARCH METHODS

7.1. Study Design

This study is a long-term, non-interventional cohort study with up to 15 years of follow-up planned to evaluate outcomes of recipients of Yescarta for treatment of relapsed or refractory DLBCL and PMBCL, or of relapsed or refractory FL, in the post-marketing setting, making secondary use of data available in the EBMT Registry and the CIBMTR Registry.

Participating centers enter data into the EBMT and CIBMTR Registries following the standard procedures and requirements according to each registry. CIBMTR and EBMT will be responsible and accountable for the accuracy and completeness of the data entered in their databases.

For the EBMT Registry, the preferred and most common option to enter data is direct electronic data entry by a trained and authorized staff member from the center. This option ensures immediate access of the center's data by the EBMT and authorized users. Alternatively, direct data entry by a national registry on behalf of specific centers that submit paper forms to this national registry is possible. Data entry into the EBMT Registry requires signed informed consent by the patient or a legal guardian to allow data to be provided to the EBMT. Patients' data may be entered up to 1 week prior or anytime following administration of Yescarta infusion.

For CIBMTR, participating centers register patients and submit data through FormsNet, the CIBMTR electronic data capture system. The FormsNet application is compliant with US database security requirements as established by the Health Resource & Service Administration (HRSA) Office of Information Technology. Patients may enroll up to 1 week prior or up to 3 months following receipt of Yescarta. Enrollment requires signed informed consent by the patient or a legal guardian to allow data to be provided to the CIBMTR. The informed consent document will include information on sharing data with the CIBMTR and also the possible need to provide blood and/or tissue samples if the patient develops a subsequent neoplasm after receiving Yescarta. Enrollment for the CIBMTR Registry cohort has been completed (n = 1500 for r/r LBCL, n = 300 for r/r FL).

Enrolled patients will be followed for 15 years in respectively the EBMT Registry and CIBMTR Registry.

7.2. Setting

This study is a non-interventional study with a design based on secondary use of data (i.e., use of existing data). No treatments, therapy protocols, or procedures are mandated for the conduct of this study, and the EBMT and CIBMTR data are collected as part of their respective initiatives. All study data will be obtained from clinical, laboratory, and diagnostic assessments conducted in the course of routine medical practice and available in the patient's medical chart, collected for the primary purpose of patient care. This study makes secondary use of data from the US CIBMTR PMR study laboratory assays, which are performed in patients who develop subsequent neoplasms. The US CIBMTR PMR study continues to collect samples as secondary malignancies arise. The collection of the sample data is not added in the context or for the purposes of this study but is an already existing process in the US CIBMTR Registry.

For EBMT, data will be captured by completion of the EBMT Cellular Therapy Forms for the time points described below (see Section 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 December 21, 2020]). The EBMT Cellular Therapy Forms were 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 dataset as specified in the EBMT Cellular Therapy Forms. The EBMT Cellular Therapy Forms are under the control of the EBMT, and their content can change throughout the course of the study. Spontaneous ADR reporting independent from this study is the primary source for detecting new safety concerns/signals. New emerging safety concerns and respective data/variables might also be added throughout the course of the study on the EBMT Cellular Therapy Forms to support structured data collection of such new relevant data during the study if agreed by the EBMT, who owns this form.

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

Available data within the EBMT Registry and CIBMTR Registry will be analyzed for this study at defined time points.

7.2.1. Eligibility

The EBMT and CIBMTR Registries collect data on all patients receiving cellular therapy. Eligible patient data for this study is from patients treated with Yescarta for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) or relapsed/refractory follicular lymphoma (FL). Specific eligibility criteria include the receipt of Yescarta for LBCL or FL indications and the collection of patient consent.

Eligible patient data includes data of patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary) and with any grade for Sorror score, ECOG (Eastern Cooperative Oncology Group) score and Karnofsky score.

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 and the CIBMTR contribute to this study. The centers enter the data directly via the EBMT Cellular Therapy Forms 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. Participating CIBMTR centers register patients and submit data through FormsNet, the CIBMTR electronic data capture system.

In a commercial setting, Kite is engaging with sites at the 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 or CIBMTR Registry management-related interactions with the centers.

These commercial sites are generally members of EBMT or CIBMTR, 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 or CIBMTR Registry can deliver relevant reminders on the importance of spontaneous reporting and that this is not replaceable by reporting into the EBMT and CIBMTR Registries.

7.3. Variables

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 relapse, progression or transformation of the primary disease occurring after the administration of Yescarta. The Registries will collect the date of diagnosis for EBMT and time from infusion to diagnosis for CIBMTR, type, location and, if a biopsy occurred, information on whether secondary malignancy was derived from cells that composed or were part of the infused medicinal product or cell/gene therapy product, and this study will utilize this data for analysis.

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

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

- Prolonged cytopenias within 30 days are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 30 days and 100 days after the administration of Yescarta. ANC recovery is defined as neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive values, and platelet recovery is defined as platelet count $\geq 20 \times 10^9$/L without transfusion support within 7 days in both CIBMTR and EBMT. The Registries 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 Registries. The Registries will collect the type, organism, treatment and date of onset of infection as well as resolution (EBMT only), and this study will utilize this data for analysis. Serious infections are not defined as per the serious adverse event (SAE) definition. Neither registries collects infection grading information.

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

- The Registries will collect data on any pregnancy that occurs after administration of Yescarta and additional information related to the outcome of the pregnancy, and this study will utilize this data for analysis.

Table 5. ASTCT Grading of CRS Adapted From Lee, et al {Lee 2018}

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

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

7.3.2. Variables Utilized for Analysis of Secondary Objectives

- Date and main cause of death and date of last assessment
- Sex, age, country, and region
- 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

7.3.3. Variables utilized for analysis of Exploratory Objectives

- Product received was OOS
- In case of secondary malignancies of T-cell origin, the bio-specimen sampling for RCR testing, type, data collected, the sample date and the test result for the CIBMTR cohort (not collected in the current EBMT Cellular Therapy Forms)
- Type, resolution status, onset date of GvHD
- Date of sampling for loss of target antigen and result for the CIBMTR cohort (not collected in the current EBMT Cellular Therapy Forms)
- Data on B-cell recovery as an indirect measure of functional CAR-T persistence: date, whether immune effector cells were detected, detection method, and time to earliest and latest positive test

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 OOS

7.3.5. Variables to Collect for Demographics and Baseline Characteristics

- Age, sex, country, and treatment center
- Height and weight at the time of Yescarta infusion
- Indication for treatment with Yescarta
- Disease subtype (e.g., NHL histologies)

- Disease status at the time of cellular therapy (e.g., sensitive or resistant to chemotherapy or radiation prior to therapy)
- Prior lines of treatment and response
- Disease stage at the time of cellular therapy
- Prognostic information: double/triple hit, international prognostic index, follicular lymphoma international prognostic index, cytogenetics (GCB-DLBCL, ABC-DLBCL)
- Time from diagnosis of the primary disease to cellular therapy
- Prior hematopoietic cell transplantation (HCT): autologous or allogeneic
- 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 or other comorbidities collected in the Sorror comorbidity index

7.4. Data Sources

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

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

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

The source data for the EBMT Registry will be the data presented in the patients' medical records. A subset of these data from patients' medical records will be transcribed by the centers in the EBMT Registry utilizing the EBMT Cellular Therapy Forms (Appendix 6). The data on patients receiving Yescarta available in the EBMT Registry will be the data source for this study.

The EBMT maintains a registry that encompasses all HCT procedures for all indications. It also stores immunosuppressive treatments for bone marrow failure syndromes (i.e., aplastic anemias), cell therapy treatments other than hematopoietic SCT 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 core dataset and/or EBMT Cellular Therapy Forms. 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.

Assessment of potential CAR transgene involvement by performing molecular profiling of tissue samples obtained or are about to be obtained in the course of routine clinical practice from patients treated with axicabtagene ciloleucel in the post-marketing setting who developed a secondary T-cell malignancy is not part of this current study protocol (KT-EU-471-0117). These procedures are conducted under a separate study protocol (KT-US-982-0910).

7.5. Study Size

Since this is a non-interventional cohort study, a target number of about 2,550 eligible patients who are treated with Yescarta and documented in the EBMT and CIBMTR Registries will be enrolled, which is considered feasible within a 5-year accrual period since the study starts implementing for the corresponding indication. The 2,550 patients will include approximately 750 and 1500 patients with DLBCL and PMBCL documented in EBMT and CIBMTR registries, respectively, and 300 patients with FL documented in the CIBMTR.

In addition to the further characterization 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 an 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% 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.

The sample size for this study is not only based on statistical considerations as it is not a hypothesis-testing study, but also on Health Authority recommendations.

7.6. Data Management

Data will be extracted from the EBMT and CIBMTR electronic data collection forms managed by the two registry holders.

7.6.1. Data Transfer Procedure

7.6.2. Data Integration Procedure

7.7. Data Analysis

7.7.1. Analysis Sets

The study population in the primary analysis will consist of a combined patient population of CIBMTR- and EBMT-enrolled patients. The pooled analyses will follow the CHMP guideline on registry-based studies and include analyses of heterogeneity. The statistical analysis plan will describe the specifics regarding the integration of the CIBMTR and EBMT data. To inform the comparability of the two populations, stratified analysis will be performed to provide a descriptive comparison of the patient populations in terms of demographic and clinical characteristics, treatment received pre-, peri-, and post-CAR-T, and outcomes.

Due to the non-interventional nature of the study, it is not possible to define formal analysis populations such as intent-to-treat or per-protocol populations. We define instead the analysis sets as follows:

- Infused set: all patients who met the eligibility criteria mentioned above and were registered on Day 0
- Safety and effectiveness set: all patients from the infused set with information on safety outcomes during follow-up

7.7.2. Analysis Sets for Subgroup Analyses

Subgroup analyses will be performed in patients who were enrolled in EBMT and in CIBMTR, and in EBMT-enrolled patients who consented to share patient-level data. Safety and effectiveness profiles will be assessed by sex, age, country, region, and in special populations (patients with prior allogeneic SCT, high-risk comorbidity index).

7.7.3. 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 outcomes among women with childbearing potential and partners of male patients

Time to onset of event of interest (secondary malignancy, CRS, neurologic events, serious infections, hypogammaglobulinemia) is defined as the time from Yescarta infusion to the date of onset of the first event of interest, ie the time interval (in days) between infusion and event for the j^{th} patient is calculated as:

$$\text{Interval}^{j}_{\text{event}} = (\text{Date}^{j}_{\text{event}} - \text{Date}^{j}_{\text{infusion}}) + 1$$

Deaths before experiencing the event will be taken as a competing risk.

7.7.4. Secondary Endpoints

- Overall survival (OS): OS is the time from the date of Yescarta infusion to the date of death due to any cause.
- 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 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 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 as 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 sex, age, indication, country, region, and in special populations (patients with prior allogeneic SCT and high-risk comorbidity index).

- Incidence rate, severity, resolution, and time to onset of TLS.

7.7.5. Exploratory Endpoints

- Safety and effectiveness endpoints in primary and secondary endpoints for patients treated with OOS product.

- Frequency of detection of RCR in samples of patients with secondary malignancies of T-cell origin.

- Incidence rate, resolution, and time to onset of aggravation of GvHD by acute and chronic type.

- Occurrence of loss of target antigen in patients relapsing after Yescarta therapy.

- Occurrence of functional CAR-T persistence in patients relapsing after Yescarta therapy and those with progressive disease, including time to earliest and latest positive test.

7.7.6. General Considerations for Data Analysis

The study will make secondary use of the data available in the EBMT Registry and CIBMTR Registry. Analysis of all endpoints for this study will include all patients satisfying the eligibility criteria who are documented within the Registries and treated with Yescarta. Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 95% 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 the follow-up period, specified subgroups, and other potential confounders (demographics and baseline characteristics; see Section 7.3.5).

Kaplan-Meier (KM) curves will be used to illustrate time-to-event variables without competing risk. The competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression and time to next treatment, and the cumulative incidences at specified time points will be provided. Cause-specific Cox models and Cox proportional hazards models will be used to model multivariate time-to-event data adjusted for subgroups and other potential confounders with and without competing risk, respectively (demographics and baseline characteristics; see Section 7.3.5).

The analysis will be firstly based on complete case analysis when the percentage missing is less than 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 described above and in Sections 7.7.7 and 7.7.8. 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 inputting 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 {Moons 2006, Pharmocovigilance 2018, Rubin 1987, Wlelch 2014}. Multiple imputation by chained equations (MICE) as sequential regression multiple imputation will be used for 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 missing is greater than 40% or the assumption of the imputation methods is not met.

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).

Subgroup analyses, including those by country/region, will only be conducted when the sample size is sufficient (more than 20) to protect the privacy of the patients. Additional details are provided in the statistical analysis plan.

Where possible, subpopulation analyses will be performed comparing patients who consented to share PLD versus patients who did not. Additionally, differences in results obtained from PLD versus aggregated report data will be investigated. Details for the different scenarios of data analysis will be specified in the statistical analysis plan.

For efficacy outcomes and high-frequency safety outcomes (CRS, neurologic events, prolonged cytopenias, infections), the main findings are based on the results in each individual cohort (EBMT, CIBMTR). For rare safety outcomes (secondary malignancies and non-relapse mortality), the main findings will be based on the pooled cohort for more reliable incidence estimates.

For secondary malignancies, the incidence estimates (secondary malignancies overall and by type) will be based on the pooled cohort (EBMT + CIBMTR). For RCR detection, the incidence rates of RCR or the presence of CAR vector sequences in secondary T-cell malignancies will be reported among all patients with valid data on RCR/vector testing, along with a detailed description of any cases with RCR in secondary T-cell malignancies (country, primary cancer, secondary cancer diagnosis, RCR, vector sequence result).

7.7.7. Analysis of Primary Endpoints

The primary endpoints will be analyzed first on integrated EBMT and CIBMTR data, then separately within each registry.

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. A cumulative incidence curve of time to onset of secondary malignancy up to 15 years will be provided, treating death without previously documented 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% CIs will also be estimated using the competing risk analysis method, with death without previously documented 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% CIs will also be estimated using the competing risk analysis method, with death without previously documented 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% CIs using exact binomial methods.

Serious infections: The incidence of serious infections, the 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% CIs will be estimated using the competing risk analysis method, with death without previously documented 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% CIs will be estimated using the competing risk analysis method, with death without previously documented hypogammaglobulinemia treated as a competing event for the onset of hypogammaglobulinemia. The use of replacement therapy will also be described as part of this endpoint.

Pregnancy and pregnancy outcome: Both the proportion of female patients or partners of male patients who become pregnant and the pregnancy outcome will be described as part of this outcome.

7.7.8. Analysis of Secondary Endpoints

The secondary endpoints will be analyzed first on integrated EBMT and CIBMTR data, then separately within each registry.

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 KM estimator. 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% CIs will be estimated using the 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% CIs will be estimated using the competing risk analysis method, with death without relapse or progression considered 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 a competing risk analysis, with death without previously documented TLS considered a competing risk.

7.7.9. Analysis of Exploratory Endpoints

The exploratory endpoints will only be analyzed using EBMT Registry data, except for RCR, for which data from both the EBMT and CIBMTR Registries will be analyzed separately.

RCR: The detection of RCR in samples of patients with secondary T-cell malignancies will be described using frequencies and percentages. In the EBMT-derived cohort, upon diagnosis of a secondary malignancy of T-cell origin, collection of bio-samples for RCR testing may be requested at the discretion of the treating physician and should be guided by the Yescarta product information, risk minimization measures approved in the country, and institutional guidelines. However, these data will not be directly captured in the EU PASS (data not collected in the current EBMT Cellular Therapy Forms). Patients will be offered participation in a separate study, KT-US-982-0910, aiming to assess the potential CAR transgene involvement in the development of secondary T-cell malignancies in patients treated with axicabtagene ciloleucel. In the CIBMTR-derived cohort, testing for RCR in the blood (peripheral blood mononuclear cell) or tumor samples of CIBMTR subjects is performed only if the subject tested positive for anti-CD19 CAR transgene and only as required by the US CIBMTR PMR study protocol.

Aggravation of GvHD among EBMT patients with allogeneic SCT prior to Yescarta infusion: The 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% CIs will be estimated using competing risk analysis, with death without GvHD as a competing risk.

Loss of target antigen: Occurrence of loss of target antigen in patients relapsing after Yescarta therapy will be described using frequencies and percentages.

Functional CAR-T persistence: Occurrence of functional CAR-T persistence in patients relapsing after Yescarta therapy and those with progressive disease will be described using frequencies and percentages. Time from infusion to the earliest and latest positive test will also be summarized.

7.7.10. Interim Analysis

For DLBCL/PMBCL, interim reports will be prepared annually from 2021 to 2025 and then every 2 years thereafter. Starting from 2025, data from the CIBMTR Registry will be integrated into the study and an analysis of treated patients in both the EBMT and CIBMTR Registries for the primary and secondary endpoints will be included in the interim reports for DLBCL/PMBCL. For FL, interim reports using CIBMTR data will be prepared annually for 2024 and 2025 and then every 2 years thereafter. The study objective is not associated with formal hypothesis testing, and thus no overall type I error control. These interim analyses are administrative interim analyses for the purpose of monitoring the progress of study enrollment and the safety and effectiveness profile of Yescarta.

After the start of data collection and until the patients at the EBMT centers have signed the revised version of the informed consent form for data entry into the EBMT Registry, the EBMT will provide data to Kite in an anonymized form as aggregate reports. Only the revised informed consent form allows the EBMT to share pseudonymized data with Kite. Once the majority of patients have signed this revised informed consent form, EBMT will provide Kite with raw data outputs. Based on the data transferred from the EBMT and CIBMTR Registries, EBMT (2021-2024) or Kite (2025-) will perform an annual aggregate/integrated data analysis for Yescarta within 60 days (for EBMT aggregate analysis) or 90 days (for Kite integrated analysis) to generate interim reports (90 days for the first EBMT aggregate analysis; 120 days for the first Kite integrated analysis). Interim reports will be submitted to the PRAC annually for the first 5 years, then every two years for assessment of the PASS interim data. Starting from 2024, interim reports will include the FL indication and starting from 2025, interim analyses and reports will include both LBCL and FL indications.

7.8. Quality Control

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7.9. Limitations of the Research Methods

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

The EBMT Registry allows patient data entry any time after Yescarta infusion and the CIBMTR Registry up to 3 months after; therefore, this study has the characteristic disadvantages of retrospective studies, for example, information bias, history bias, and recall bias. However, there will be an effort to encourage patient documentation in the registries as promptly as possible to capture data continuously going forward. Following a patient's enrollment, subsequent data collection/capturing is prospective in nature in the registries.

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

Merging CIBMTR and EBMT Registry data into a single pooled analysis presents some methodological difficulties. One of the challenges includes the possibility of a chronology bias due to the difference in time of enrollment of patients into the CIBMTR Registry and the EBMT Registry. For instance, the enrollment of LBCL patients into the CIBMTR Registry subgroup of this PASS was completed in August 2020. However, data collection for the DLBCL/PMBCL patients who enrolled into the EBMT Registry subgroup of this PASS started in August 2020, and thus, there is minimal overlapping period in the time of enrollment of patients into the CIBMTR Registry and the EBMT Registry. Patient selection, clinical practices and management of AEs may differ between registries and might have evolved over the years, thus introducing potential biases. Kite anticipates that this would mainly affect early safety events including CRS and ICANS (neurologic events) but not effectiveness and long-term safety outcomes. The incidences and severity of CRS and ICANS may be decreased by more frequent and effective use of prophylactic medications in more recent years {Oluwole 2021, Oluwole 2024}. However, this will unlikely affect the validity of the incidence estimates for CRS and ICANS. Kite will assess whether there are potential chronology trends in each outcome by comparing results from the stratified analysis by cohorts using descriptive statistics as treatment period are sequential and not overlapping (i.e., the CIBMTR subjects were treated earlier than the EBMT subjects). For other safety outcomes, especially secondary malignancies, the main safety concern for CAR-T, chronology bias is unlikely to be an issue. The pooled data from the EBMT and CIBMTR cohorts can be used to obtain a more reliable effect estimate on the incidence of secondary cancers overall in patients receiving axicabtagene ciloleucel.

7.9.1. Study Discontinuation

No patient's treatment will be dictated by the protocol of this long-term observational study or by EBMT, CIBMTR, or Kite. Consequently, continuing or discontinuing this study will not impact patient care. Therefore, identification of adverse effects of 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 upon with the EMA beforehand.

8. PROTECTION OF HUMAN SUBJECTS

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

8.1. EBMT

EBMT will use standard processes for ensuring the protection of subjects 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 considering the potential benefit to future recipients from knowledge gained through this research study.

8.1.1. Informed Consent

No specific informed consent will be obtained by Kite 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 and sharing of data with Kite and health authorities.

8.1.2. Confidentiality

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

8.2. CIBMTR

The CIBMTR will use standard processes for ensuring the protection of patients whose cellular therapy data are reported to the CIBMTR Research Database and Research Sample Repository. The National Marrow Donor Program Institutional Review Board (IRB) has primary oversight for the CIBMTR Research Database Protocol and Protocol for Research Sample Repository. All US centers are required to have a Federal Wide Assurance with the Office for Human Research Protection and, as part of their Data Transmission Agreement with the CIBMTR, agree to obtain local IRB approval for the CIBMTR Research Database Protocol (http://www.ClinicalTrials.gov; identifier: NCT01166009). Participating centers are responsible for recruiting patients, obtaining

informed consent, registering subjects, and submitting baseline and follow-up data on participating patients. Centers will register patients and submit data through FormsNet, the CIBMTR electronic data capture system. The FormsNet application is compliant with the US database security requirements as established by the HRSA Office of Information Technology. HRSA security audits are performed annually; the most recent audit was in September 2017. With this vigilant surveillance and systems security, there is minimal risk that a subject's privacy or confidentiality would be breached.

Patients will be identified to participate in the study by personnel at the participating centers when they receive their therapy. According to established practices at each of the centers, a study database IRB-approved informed consent document will be obtained from each participating patient. Documentation of assent, of parent legal guardian permission of minor participants, and consent for adult participants must be maintained at the center where the participant or their parent or legal guardian provided consent to participate. Centers are required to enter the date that informed consent was obtained from the patient on the data collection form submitted to the CIBMTR. Patients are provided information regarding the types of data collected from their medical record, the time intervals at which data will be submitted, the types of studies in which their data may be included, and the research sample to be collected in the event of a subsequent neoplasm for testing.

8.3. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the European Medicines Agency – Guideline on Good Pharmacovigilance Practices (GVP) Modules VI and VIII – PASS, 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 ENCePP, by enclosing the ENCePP Checklist in the submission and registering the study in the ENCePP Registry.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The operational model for this PASS protocol qualifies as non-interventional research with a design based on the secondary use of data (i.e., utilizing data from patients' medical records that were previously collected for another purpose and included in the EBMT Registry or CIBMTR dataset; and where the AEs have already occurred and will not be reported in an expedited manner) as outlined in GVP Module VI. According to this guidance, reporting of safety information in the form of individual case safety reports is not required, and all AEs 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.

The 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 summary of product characteristics (SmPC) and packaging materials provide respective details and contact information. Kite further gives clear guidance to healthcare practitioners in the aRMMs regarding the need for and importance of spontaneous reports, which are 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. An exception will be for reports to the CIBMTR Registry of subsequent neoplasms and death, and reports secondary malignancies of T-cell origin, which require expedited reporting.

9.2. Definitions

9.2.1. Adverse Events

An 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 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 event of special interest** (AESI) for this study is considered to be an event in the focus of the primary objective: secondary malignancies, CRS, neurologic events, prolonged cytopenia, serious infections (not defined as per the SAE definition), and hypogammaglobulinemia. As part of the primary objective, pregnancy outcomes in female patients of childbearing potential and partners of male patients are also of special interest.

9.2.3. Adverse Drug Reactions

An 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

An SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening event (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.)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

- 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, an infection resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

9.2.5. Serious Adverse Drug Reaction

A serious ADR is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

9.2.6. Special Situation Reports

This study has a primary endpoint to investigate pregnancy outcomes in female patients of childbearing potential and partners of male patients 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.

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

- Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient.

- Drug interactions: Any reports of drug/drug, drug/food, or drug/device interactions.

- Counterfeit or falsified medicine: Any medicinal product with a false representation of its identity, source, or 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, inappropriate, and 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 healthcare 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 that 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. DATA FROM ADDITIONAL REGISTRIES

Aggregated patient data from the DESCAR-T registry will be provided, when available, together with the interim report of the KT-EU-471-0117 PASS. The results will be incorporated in the results section of the report and discussed in this context. While DESCAR-T data cannot be integrated into the analysis of the PASS, the results from the PASS will be contextualized with data from DESCAR-T as an external data source. The contextualization of results from the KT EU-471-0117 PASS with the data from the DESCAR-T Registry will be conducted based on the data accessible to Kite either as part of pre-agreed data sharing agreement or published data.

In addition, where patient-level data is not possible to obtain within the EBMT registry, Kite will reasonably endeavour to obtain patient-level data from EU national registries. A status report will be provided with the 2024 annual interim report.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Study Report and Publications

Reports listed below will be inclusive of both LBCL and FL patients' data and according to the milestones outlined in Table 3.

11.1.1. Safety Data Reports

After the start of data collection and until the patients at the EBMT centers have signed the revised version of the informed consent form for data entry into the EBMT Registry, the EBMT will provide data to Kite in an anonymized form as aggregate reports. Only the revised informed consent form allows the EBMT to share pseudonymized data with Kite. Once the majority of patients have signed this revised informed consent form, the EBMT will provide Kite with a quarterly raw data output. Based on the data transferred, the EBMT will perform an aggregate data analysis for Yescarta within 30 days to generate safety data reports (45 days for the first report) from Q3 2020 until Q4 2023. Safety data reports will be submitted as appendices to the PSUR to the PRAC in accordance with the applicable PSUR reporting period until the end of 2023. During the time period in which these reports will be generated, in the event that a safety data report identifies a major new safety finding or there is an unfavorable change in the risk/benefit profile, the respective report will be submitted promptly as a stand-alone document. The safety data reports will focus on the AESIs – which are considered to be the events related to the primary objective (please see below and in Section 9.2.2). Information on patient-level presentation and causality assessment will be included when available.

The safety data reports will contain the following information, as available:

- Patient enrollment in the registry
- Baseline characteristics
- Aggregate numbers of reported fatal AEs
- Aggregate numbers of all reported AEs
- Review of events considered primary objectives of the PASS study: secondary malignancies, CRS, neurologic events, prolonged cytopenia, serious infections, hypogammaglobulinemia, and pregnancies and their outcomes
- If reported, review of any unexpected events that do not fall under the previously recognized risks or AESI
- Summary and conclusions

11.1.2. Interim Reports

For DLBCL/PMBCL, interim reports will be prepared annually from 2021 to 2025 and then every 2 years thereafter. Starting from 2025, data from the CIBMTR Registry will be integrated into the study and an analysis of treated patients in both the EBMT and CIBMTR Registries for the primary and secondary endpoints will be included in the interim reports for DLBCL/PMBCL. For FL, interim reports will be prepared from the CIBMTR data annually for 2024 and 2025, and then every 2 years thereafter. The versions of the EBMT Cellular Therapy Forms utilized in the EBMT Registry and the relevant CTED forms in the CIBMTR Registry during the respective time period will be provided as appendices to these reports. The data collection forms are under the control of the EBMT and CIBMTR. Registries and their content can change throughout the course of the study (see Section 7.2). Based on the data transferred from the EBMT and CIBMTR Registries, EBMT (2021-2024) or Kite (2025-) will perform an aggregate/integrated data analysis for Yescarta within 60 days (for EBMT aggregate report) or 90 days (for Kite integrated report) to generate interim reports (90 days for the first EBMT aggregate analysis; 120 days for the first Kite integrated analysis). Interim reports will include FL starting in 2024 and FL + LBCL/PMBCL starting in 2025.

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

11.1.3. Final Report

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

11.1.4. Publications, Conference Abstracts, and Manuscripts

All proposed publications and conference presentations arising from the study will be reviewed by Kite, EBMT, and CIBMTR representatives prior to submission. Both the 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.

12. REFERENCES

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

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

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

Bilmon IA, Ashton LJ, Le Marsney RE, Dodds AJ, O'Brien TA, Wilcox L, et al. Second Cancer Risk in Adults Receiving Autologous Haematopoietic SCT for Cancer: A Population-Based Cohort Study. Bone Marrow Transplant 2014;49 (5):691-8.

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

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

Bushman FD. Retroviral integration and human gene therapy. J Clin Invest 2007;117 (8):2083-6.

Chien SH, Liu CJ, Hong YC, Teng CJ, Hu YW, Ku FC, et al. Development of second primary malignancy in patients with non-Hodgkin lymphoma: a nationwide population-based study. J Cancer Res Clin Oncol 2015;141 (11):1995-2004.

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

El-Najjar I, Boumendil A, Luan JJ, Bouabdallah R, Thomson K, Mohty M, et al. The Impact of Total Body Irradiation on the Outcome of Patients with Follicular Lymphoma Treated with Autologous Stem-cell Transplantation in the Modern Era: a Retrospective Study of the EBMT Lymphoma Working Party. Ann Oncol 2014;25 (11):2224-9.

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

Forrest DL, Hogge DE, Nevill TJ, Nantel SH, Barnett MJ, Shepherd JD, et al. High-dose therapy and autologous hematopoietic stem-cell transplantation does not increase the risk of second neoplasms for patients with Hodgkin's lymphoma: a comparison of conventional therapy alone versus conventional therapy followed by autologous hematopoietic stem-cell transplantation. J Clin Oncol 2005;23 (31):7994-8002.

Frey NV, Porter DL. CAR T-cells merge into the fast lane of cancer care. Am J Hematol 2016;91 (1):146-50.

Garfall AL, Maus MV, Hwang WT, Lacey SF, Mahnke YD, Melenhorst JJ, et al. Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma. N Engl J Med 2015;373 (11):1040-7.

Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia. N Eng J Med 2013;368 (16):1509-18.

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

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

Hajek R, Okubote SA, Svachova H. Myeloma Stem Cell Concepts, Heterogeneity and Plasticity of Multiple Myeloma. Br J Haematol 2013;163:551-64.

Heinrich PC, Behrmann I, Muller-Newen G, Schaper F, Graeve L. Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. The Biochemical journal 1998;334 (Pt 2):297-314.

Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. Nat Rev Clin Oncol 2016;13 (6):370-83.

Johnson LA, Morgan RA, Dudley ME, Cassard L, Yang JC, Hughes MS, et al. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood 2009;114 (3):535-46.

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

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

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

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

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

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

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

KYMRIAH, Novartis Pharmaceuticals Corporation. KYMRIAH® (tisagenlecleucel) suspension for intravenous infusion. U.S. Prescribing Information. East Hanover, NJ. Revised December. 2020:

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

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

Lee SY, Olsen P, Lee DH, Kenoyer AL, Budde LE, O'Steen S, et al. Preclinical Optimization of a CD20-specific Chimeric Antigen Receptor Vector and Culture Conditions [Author Manuscript]. J Immunother 2018;41 (1):19-31.

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

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

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

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

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

Maus MV, Levine BL. Chimeric Antigen Receptor T-Cell Therapy for the Community Oncologist. The oncologist 2016;21 (5):608-17.

Metayer C, Curtis RE, Vose J, Sobocinski KA, Horowitz MM, Bhatia S, et al. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multicenter case-control study. Blood 2003;101 (5):2015-23.

Michea P, Noel F, Zakine E, Czerwinska U, Sirven P, Abouzid O, et al. Adjustment of dendritic cells to the breast-cancer microenvironment is subset specific. Nat Immunol 2018;19 (8):885-97.

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

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

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

Newrzela S, Cornils K, Li Z, Baum C, Brugman MH, Hartmann M, et al. Resistance of mature T cells to oncogene transformation. Blood 2008;112 (6):2278-86.

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

Oluwole OO, Bouabdallah K, Munoz J, De Guibert S, Vose JM, Bartlett NL, et al. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol 2021.

Oluwole OO, Forcade E, Munoz J, de Guibert S, Vose JM, Bartlett NL, et al. Long-term outcomes of patients with large B-cell lymphoma treated with axicabtagene ciloleucel and prophylactic corticosteroids. Bone Marrow Transplant 2024.

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

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

Pirani M, Marcheselli R, Marcheselli L, Bari A, Federico M, Sacchi S. Risk for second malignancies in non-Hodgkin's lymphoma survivors: a meta-analysis. Ann Oncol 2011;22 (8):1845-58.

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

Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med 2011;365 (8):725-33.

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

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

Roberts KG. Genetics and Prognosis of ALL in Children vs Adults. Am Soc Hematol 2018;2018 (1):137-45.

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

Rossi C, Jegu J, Mounier M, Dandoit M, Colonna M, Daubisse-Marliac L, et al. Risk assessment of second primary cancer according to histological subtype of non-Hodgkin lymphoma. Leuk Lymphoma 2015;56 (10):2876-82.

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

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

Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019;380 (1):45-56.

Seshadri T, Pintilie M, Kuruvilla J, Keating A, Tsang R, Zadeh S, et al. Incidence and risk factors for second cancers after autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. Leuk Lymphoma 2009;50 (3):380-6.

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

Smeland KB, Kiserud CE, Lauritzsen GF, Blystad AK, Fagerli UM, Falk RS, et al. A national study on conditional survival, excess mortality and second cancer after high dose therapy with autologous stem cell transplantation for non-Hodgkin lymphoma. Br J Haematol 2016;173 (3):432-43.

Tarella C, Passera R, Magni M, Benedetti F, Rossi A, Gueli A, et al. Risk factors for the development of secondary malignancy after high-dose chemotherapy and autograft, with or without rituximab: a 20-year retrospective follow-up study in patients with lymphoma. J Clin Oncol 2011;29 (7):814-24.

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

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

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

Vaxman I, Ram R, Gafter-Gvili A, Vidal L, Yeshurun M, Lahav M, et al. Secondary malignancies following high dose therapy and autologous hematopoietic cell transplantation-systematic review and meta-analysis. Bone Marrow Transplant 2015;50 (5):706-14.

Wang N, Hu X, Cao W, Li C, Xiao Y, Cao Y, et al. Efficacy and Safety of CAR19/22 T-Cell Cocktail Therapy in Patients with Refractory/Relapsed B-Cell Malignancies. Blood 2020;135 (1):17-27.

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

YESCARTA, Kite Pharma Inc. YESCARTA® (axicabtagene ciloleucel) suspension for intravenous infusion. U.S. Prescribing Information. Santa Monica, CA. Revised July. 2020:

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

13. APPENDICES

Appendix 1. List of Stand-Alone Documents
Appendix 2. Amendments and Updates
Appendix 3. ENCePP Checklist for Study Protocols
Appendix 4. Reference Safety Information
Appendix 5. Kite Signature Page
Appendix 6. Cellular Therapy Forms

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	None		

Appendix 2. Amendments and Updates

A high-level summary of this amendment is provided in tabular form in the subsection below. All modifications are deemed non-substantial, with the majority initiated at the request of the European Medicines Agency.

Minor changes such as edits to clarify language or the correction of typographic errors, grammar, or formatting are not detailed.

Earlier separate summaries of changes for previous protocol amendments are available upon request.

A separate tracked change (redlined) document comparing the previous version(s) of the protocol to this amendment will be made available.

Amendment 8 (Non-substantial): 19-Nov 2025

Amendment Rationale for Key Changes Included in Amendment 7	Affected Sections
Updated the protocol version, date and QPPV personnel change update.	Section: PROTOCOL COVER PAGE Protocol Version/Date, Kite-Qualified Person Responsible for Pharmacovigilance,
Revision of the writing style of Yescarta throughout the document.	Section: PROTOCOL COVER PAGE Yescarta
Updated the change in Study Management Team	Section 1: Responsible Parties Table 1. Table of Responsible Parties
Added more clarification on Variables and Other Exploratory Endpoints.	Section 2: PROTOCOL SYNOPSIS/ABSTRACT Variables
Provided the scientific rationale to justify the change as provided in the Amendment History section of the protocol amendment	Section 3: AMENDMENTS AND UPDATES. Table 2: Protocol Amendments and Updates.
Provided more detail on timelines of data collection from CIBMTR and EBMT	Section 4: MILESTONES. Table 3. Protocol Milestones
Added language to address PRAC's Request to explain why the study is considered as non-interventional.	Section 7: RESEARCH METHODS. Section 7.2: Setting

Amendment Rationale for Key Changes Included in Amendment 7	Affected Sections
Added day 30 as an additional endpoint for cytopenias and clarification on registries not collecting infections grading information more general: clarification on variables.	Section 7: RESEARCH METHODS. Section 7.3: Variables Section 7.3.1: Variables Utilized for Analysis of Primary Objectives
Added more general clarification on the definition of analysis set.	Section 7.7: Data Analysis 7.7.1. Analysis Sets
Added more general: clarification on the definition of endpoints	Section 7.7.4: Secondary Endpoints
Added more clarity on exploratory endpoints	Section 7.7.5: Exploratory Endpoints
Clarified the potential CAR transgene involvement in the development of secondary T-cell malignancies in a different study	Section 7.7.9. Analysis of Exploratory Endpoints
Replaced neurotoxicity with neurologic events throughout the protocol	Throughout the protocol

Appendix 3. 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, PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA, AND FOLLICULAR 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]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☒	☐	☐	4
1.1.4 Interim report(s)	☒	☐	☐	4
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

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

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

Comments:

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)	☒	☐	☐	6, 7
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
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?	☒	☐	☐	7
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	5, 6, 7
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	5, 7
	4.2.5 Duration of follow-up	☒	☐	☐	6,7
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	6, 7

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	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)	☒	☐	☐	6, 7
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	6, 7
9.1.3 Covariates and other characteristics?	☒	☐	☐	6, 7
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	6, 7
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	6, 7
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	6, 7
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))	☒	☐	☐	7
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)	☒	☐	☐	7

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7
10.3 Are descriptive analyses included?	☒	☐	☐	7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7
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?	☒	☐	☐	7
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	7

Comments:

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

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?	☒	☐	☐	3

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11.1.4

Comments:

Name of the main author of the protocol: PPD

Date: *[See appended electronic signature]*

Signature: *[See appended electronic signature]*

Appendix 4. Reference Safety Information

Current version of the EU SmPC (Summary of product characteristics) for Yescarta®.

Appendix 5. 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
VERSION 3.0, 29 SEPTEMBER 2023
VERSION 3.1, 21 FEBRUARY 2024
VERSION 3.2, 19 NOVEMBER 2025

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

PPD

Kite Study Director (Printed)
Author

[See appended electronic signature]

Signature

[See appended electronic signature]

Date

PPD

Kite Gilead EU QPPV (Printed)

[See appended electronic signature]

Signature

[See appended electronic signature]

Date

Appendix 6. Cellular Therapy Forms

EBMT Cellular Therapy Forms 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 interim reports (see Section 11.1.2).

Signature Page for VV-CLIN-865835 v1.0

eSignature Approval Task Verdict: Approved (eSigned)	PPD QPPV eSigned 19-Nov-2025 19:39:42 GMT+0000

eSignature Approval Task Verdict: Approved (eSigned)	PPD vidence eSigned 19-Nov-2025 20:51:53 GMT+0000

Signature Page for VV-CLIN-865835 v1.0