KITE PHARMA, INC.

NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	Molecular profiling of tissue samples from patients who received a Kite-manufactured gene-modified cell therapy and have developed a secondary malignancy of T-cell origin
Protocol ID	KT-US-982-0910
Protocol Version/Date	Version 0.3/09 July 2025
EU PAS Register No	TBD
Clinical Trials.gov Identifier	Study not registered
Active substance	Axicabtagene ciloleucel L01XX03 Brexucabtagene autoleucel L01XL06
Medicinal Product	YESCARTA® TECARTUS®
Product reference	EMEA/H/C/004480 EMEA/H/C/005102
Last Procedure number	Not applicable
Joint PASS	No
Research Question and Objectives	This study aims to assess potential chimeric antigen receptor (CAR) transgene involvement in developing a secondary T-cell malignancy in patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel. **Primary objective** To assess potential CAR transgene involvement by performing molecular profiling of tissue samples obtained or are about to be obtained during routine clinical practice, from patients who were treated with axicabtagene ciloleucel or brexucabtagene autoleucel and developed a secondary T-cell malignancy. The molecular profiling will include the following, as applicable: ▪ The presence of the CAR transgene in the blood, tumor and/or bone marrow biopsy, as well as the CAR level, if the CAR transgene was detected. ▪ Presence of replication-competent retrovirus. CCI [redacted]

Countries of Study	European economic area (EAA) and United Kingdom (UK)	
Kite Study Director/Author/ Contact Person	Name:	PPD Gilead Sciences Switzerland Director Real-World Evidence PPD
	Phone:	PPD
	Email:	PPD
Marketing Authorization Holder	Kite Pharma. EU B.V. Tufsteen 1, 2131 NT Hoofddrop, The Netherlands	
Marketing Authorization Holder (MAH) contact person	Name:	PPD Gilead Sciences International Ltd Associate Director Regulatory Affairs Flowers Building PPD PPD
	Phone:	PPD
	Email:	PPD
Kite EU Qualified Person Responsible for Pharmacovigilance (QPPV)	Name:	PPD
	Telephone:	PPD
	Email:	PPD

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Kite Pharma, Inc., a wholly owned subsidiary of Gilead Sciences, Inc. and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Independent Ethics Committee. The information is only to be used by you. You will not disclose any of the information to others without written authorization from Kite Pharma, Inc.

Marketing authorization holder

Marketing authorization holder(s)	**Kite Pharma EU B.V.** **Tufsteen 1,** **2131 NT Hoofddorp,** **The Netherlands**
MAH Contact Person	PPD Gilead Sciences International Ltd Associate Director Regulatory Affairs Phone: PPD Email: PPD
EU QPPV	PPD PhonePPD Email: PPD

TABLE OF CONTENTS

TABLE OF CONTENTS 4
LIST OF ABBREVIATIONS 5
1. RESPONSIBLE PARTIES 6
2. ABSTRACT 7
3. AMENDMENTS AND UPDATES 9
4. MILESTONES 10
5. RATIONALE AND BACKGROUND 11
6. RESEARCH QUESTION AND OBJECTIVES 14
6.1. Primary objective 14
CCI [redacted]
7. RESEARCH METHODS 15
7.1. Study design 15
7.2. Setting 15
7.2.1. Inclusion criteria 15
7.2.2. Exclusion criteria 15
7.3. Variables 16
7.4. Data sources 16
7.4.1. Sample collection 16
7.4.2. Schedule of sample collection 18
7.4.3. Molecular profiling 19
7.4.4. Reporting of test results 20
7.5. Study size 20
7.6. Data management 20
7.7. Data analysis 20
7.8. Quality control 20
7.8.1. Inspection and auditing procedures 21
7.8.2. Source document maintenance 21
7.8.3. Record maintenance 21
7.9. Limitations of the research methods 21
7.10. Other aspects 22
8. PROTECTION OF HUMAN SUBJECTS 23
9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 24
10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 25
11. REFERENCES 26
12. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS 27
13. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS 28
14. ANNEX 3. ADDITIONAL INFORMATION 34

LIST OF ABBREVIATIONS

Abbreviation	Definition
AML	Acute myeloid leukemia
CAR	Chimeric antigen receptor
CRF	Case report form
ddPCR	Droplet digital polymerase chain reaction
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
HCP	Healthcare professional
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Institutional ethics committee
MAH	Marketing authorization holder
MDS	Myelodysplastic syndrome
NGS	Next-generation sequencing
PASS	Post-authorization safety study
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PTCL	Peripheral T-cell lymphoma
qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
RNAseq	Ribonucleic acid sequencing
SAE	Serious adverse event
SmPC	Summary of product characteristics
SSRs	Special situation reports
TCL	T-cell lymphoma

1. RESPONSIBLE PARTIES

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
MAH Contact Person	PPD Associate Director Regulatory Affairs Gilead Sciences International Ltd Flowers Building PPD	Phone: PPD Email: PPD
Study Director	PPD Director, Real-World Evidence Gilead Sciences Switzerland PPD PPD	Phone: PPD
EU QPPV	PPD Executive Director, Patient Safety Gilead Sciences GmbH Fraunhoferstr. PPD	Phone: PPD Email: PPD

2. ABSTRACT

Title	Molecular profiling of tissue samples from patients who received a Kite-manufactured gene-modified cell therapy and have developed a secondary malignancy of T-cell origin
Rationale and background	Axicabtagene ciloleucel and brexucabtagene autoleucel are genetically modified autologous cell-based products. As a result of this genomic integration, there is a theoretical risk of oncogenesis via insertional mutagenesis. In June 2024, the Pharmacovigilance Risk Assessment Committee concluded that secondary malignancies of T-cell origin may occur after treatment with chimeric antigen receptor (CAR) T-cell therapies. Due to the rarity of the cases, not many studies have explored the genetic changes of these secondary malignancies of T-cell origin and whether they result from insertional mutagenesis of the CAR transgene.
Research question and objectives	This study aims to assess potential CAR transgene involvement in developing a secondary T-cell malignancy in patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel. **Primary objective** To assess potential CAR transgene involvement by performing molecular profiling of tissue samples obtained or are about to be obtained during routine clinical practice, from patients who were treated with axicabtagene ciloleucel or brexucabtagene autoleucel and developed a secondary T-cell malignancy. The molecular profiling will include the following, as applicable: • The presence of the CAR transgene in the blood, tumor and/or bone marrow biopsy, as well as the CAR level, if the CAR transgene was detected. • Presence of replication-competent retrovirus. 
Study design	An observational study.
Population	Patients who have received a Kite-manufactured CAR T-cell therapy (axicabtagene ciloleucel or brexucabtagene autoleucel) and have reported a suspected secondary malignancy of T-cell origin.
Variables	• The presence of the CAR transgene in the blood and/or tumor and/or bone marrow biopsy. • The CAR level, if the CAR transgene was detected in the blood and/or tumor and/or bone marrow biopsy.

	• Presence of replication-competent retrovirus. • Presence of somatic mutations that are common in hematologic malignancies. • Transgene integration site analysis results. • Transcriptome/RNA analysis results.
Data sources	Communication from a healthcare professional who would like to obtain instructions on patient sample collection.
Study size	The study size cannot be estimated.
Data analysis	No statistical analysis is planned. The molecular profiling results will be described for each patient tested.
Milestones	Start of data collection: Quarter (Q)4-2025 End of data collection: N/A at this stage Study duration: N/A at this stage Final report of study results: N/A at this stage Interim reporting of cases: PSUR Interim summary reports: every 5 years

3. AMENDMENTS AND UPDATES

None

4. MILESTONES

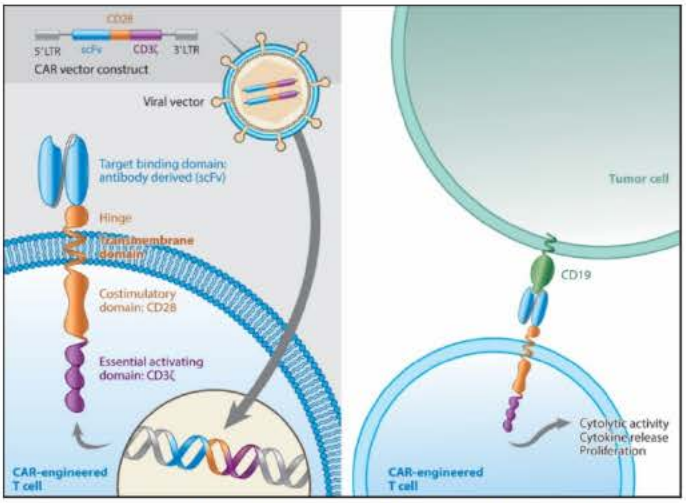
Milestone	Planned date
Start of data collection	Q4-2025
End of data collection	N/A at this stage
Study duration	N/A at this stage
Final report of study results	N/A at this stage
Interim reporting of cases	PSUR
Interim summary reports	every 5 years

Abbreviations: PSUR = periodic safety update report; Q = quarter

5. RATIONALE AND BACKGROUND

Axicabtagene ciloleucel and brexucabtagene autoleucel are genetically modified autologous cell-based products containing T cells transduced ex vivo using a retroviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment linked to CD28 co-stimulatory domain and CD3-zeta signaling domain. Axicabtagene ciloleucel and brexucabtagene autoleucel manufacturing relies on a replication-deficient murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T cell genome (see Figure 1).

Figure 1. Axicabtagene Ciloleucel and Brexucabtagene Autoleucel CAR Construct and Mechanism of Action



Abbreviations: CAR = chimeric antigen receptor; LTR = long-terminal repeat; scFv = single chain variable fragment

As a result of this genomic integration, there is a theoretical risk of oncogenesis via insertional mutagenesis (for example, by disruption of gene expression [oncogenes or tumor suppressor genes] or alteration of gene expression by the regulatory regions within the vector). Since the vector is replication-defective, this integration to the genome can only happen once per viral vector. The potential for multiple integrations in the same cell is reduced by minimizing the number of vector copies per cell during manufacturing.

The vector packaging systems used in the early days of gene therapy were not designed to completely prevent recombination events between the vector and viral genes used to assemble the virions, and thus, rarely, RCRs were generated during manufacturing. These RCRs had properties similar to those of the wild-type virus, including the ability to cause malignancies by increasing the rate of integration events and, thus, the likelihood of oncogenic events. Although the process was improved since (ie, use of split-packaging during manufacturing and reduced homology between the vector and packaging sequences to reduce the likelihood of any recombination events), these findings have been the basis for the RCR screening requirements issued by the Food and Drug Administration (FDA) and other regulatory bodies.

Therefore, when axicabtagene ciloleucel was granted marketing authorization in the European Union (EU) on 23 August 2018, the European Medicines Agency requested that secondary malignancy and RCR be included as important potential risks in the EU risk management plan. The Summary of Product Characteristics (SmPC) included instructions that patients should be monitored life-long for secondary malignancies. The same risks and SmPC language were requested for Brexucabtagene Autoleucel.

Per Kite's definition, a secondary malignancy is the development of a new malignancy suspected to be possibly related to gene-modified cell therapy (temporally associated with gene-modified cell therapy and without compelling alternate etiologies). Treatment-related malignancies due to chemotherapy (eg, acute myeloid leukemia [AML], myelodysplastic syndrome [MDS], or solid tumors) or the natural development of somatic mutations with age that may lead to clonal hematopoiesis of indeterminate potential and subsequent hematologic malignancies are not considered secondary malignancies to gene-modified cell therapy.

In November 2023, the FDA issued a notice stating that T-cell malignancies have been observed in patients receiving CAR T-cell therapy. In June 2024, the Pharmacovigilance Risk Assessment Committee concluded that secondary malignancies of T-cell origin may occur after treatment with CAR T-cell therapies. The committee evaluated data on 38 cases of secondary malignancy of T-cell origin, including T-cell lymphoma (TCL) and leukemia, reported among approximately 42,500 patients treated with all marketed CAR T-cell therapies. Tissue samples were tested in half of the cases, revealing the presence of the CAR construct in 7 cases (none were Kite's products). The secondary malignancies of T-cell origin have been reported within weeks and up to several years following the administration of CAR T-cell therapies. These findings implied that CAR T-cell therapies may have been involved in developing secondary T-cell malignancy; however, insufficient scientific evidence exists to conclude a causal relationship.

Due to the rarity of the cases, not many studies have explored the genetic changes of these secondary malignancies of T-cell origin and whether they result from insertional mutagenesis of the CAR transgene. Harrison et al. reported a case study of a 51-year-old male patient who received ciltacabtagene autoleucel (cilta-cel) and developed TCL five months post-infusion. The TCL cells showed that the CAR was inserted in the 3′ untranslated region of *PBX2*. Molecular analyses revealed the presence of genetic mutations (*TET2*, *NFkB2*, *PTPRB*, and a germline activating mutation of *JAK3*) before CAR-T manufacturing. Thus, it is unclear whether the transgene integration was associated with the development of the TCL {Harrison 2023}. Ozdemirli et al. described a 71-year-old woman who developed indolent TCL 5 months after she had received cilta-cel. The TCL harbored a CAR-vector integration in the second intron of *SSU72*; the second allele of the *SSU72* gene was undisturbed. However, the viral integration site did not appear to alter the expression level of *SSU72* mRNA. Also, no unusual splicing pattern was observed for the *SSU72* gene. Other genetic aberrations were also detected in the tumor sample and could play a role in developing the malignant phenotype {Ozdemirli 2024}. Similarly, Kobbe et al. described a case of a 60-year-old man who received tisagenlecleucel and developed peripheral TCL (PTCL) one month post-infusion. Vector integration site analysis showed that in the CAR^{+}-PTCL, only 13 integration sites were identified with substantial enrichment of 3 sites: *DPF2*, *RAB11FIP3*, and *NPLOC4*. Because these genes are not classified as cancer genes and are not involved in hematologic cancers, viral integration in these genes does

not provide a likely explanation for the onset of the lymphoma. Molecular characterization of the CAR^+-PTCL and apheresis material showed somatic *DNMT3A* and *TET2* mutations in $CD34^+$ stem cells, and their progeny were detected in the PTCL and in the apheresis specimen that was obtained for CAR T-cell production. The PTCL harbored an additional somatic *TET2* mutation, which was already detectable in the CAR T-cell apheresis product and the final CAR T-cell product at very low frequencies, providing evidence that clonal hematopoiesis had contributed to lymphomagenesis {Kobbe 2024}.

The mechanism by which transgene integration can cause clonal expansion and tumorigenesis is not completely understood. In 2018, Fraietta et al. described a patient with chronic lymphocytic leukemia treated with CTL019, who experienced clonal CAR T-cell expansion (94% T-cell clonality) in which the CAR transgene insertion was in the *TET2* gene {Fraietta 2018}. Shah et al. reported a pediatric acute lymphoblastic leukemia patient treated with CD22-directed CAR T cells that showed significant clonal expansion of the CAR T cells due to lentiviral insertion of the CAR in the *CBL-B* locus {Shah 2019}. Although the CAR T cells expanded in an abnormal and clonal pattern in both cases, they still led to disease remission without malignant transformation. Therefore, there is a gap in understanding the relationship between the CAR transgene integration and possibly prior mutations and transcriptome readouts within the malignant cell. To address the knowledge gap and better evaluate the potential role of CAR T-cell therapy in the development of secondary T-cell malignancies, molecular profiling of tissue samples from patients treated with CAR T cell therapies who developed secondary T-cell malignancies is recommended.

The challenges regarding molecular profiling in the post-marketing setting include potential lack of availability of existing tissue samples, the need to give guidance to HCPs regarding tissue collection, ethics and regulatory requirements, as well as support in the logistics of sending the tissue samples for testing. The study protocol may help to overcome these challenges by providing an appropriate framework and process guidance to support HCP in obtaining ethical approval and facilitate the collection and testing of existing tissue samples.

6. RESEARCH QUESTION AND OBJECTIVES

This study aims to assess potential CAR transgene involvement in developing a secondary T-cell malignancy in patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel.

6.1. Primary objective

To assess 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 who were treated with axicabtagene ciloleucel or brexucabtagene autoleucel and developed a secondary T-cell malignancy.

The molecular profiling will include the following, as applicable:

- The presence of the CAR transgene in the blood and/or tumor and/or bone marrow biopsy, as well as the CAR level, if the CAR transgene was detected.
- Presence of RCR.

7. RESEARCH METHODS

7.1. Study design

This observational study involves patients who have received a Kite-manufactured CAR T-cell therapy (axicabtagene ciloleucel or brexucabtagene autoleucel) and have reported a suspected secondary malignancy of T-cell origin.

The endpoint is whether there is any evidence of the CAR transgene's involvement in developing secondary malignancies of T-cell origin.

7.2. Setting

This observational study will be conducted in the EEA and UK and will enroll patients on an ongoing basis.

7.2.1. Inclusion criteria

1) Patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel who developed a suspected secondary malignancy of T-cell origin, which the health care professional (HCP) reported, and the secondary malignancy of T-cell origin diagnosis was subsequently verified by Kite's review of the pathology report.

And

2) The treating HCP obtained the tissue samples during routine clinical practice.

And

3) The HCP provided the required documentation and approvals per local regulations (i.e., institutional ethics committee [IEC] approval of the protocol and informed consent).

And

4) The physician obtained consent from the patient using the IEC-approved informed consent.

7.2.2. Exclusion criteria

1) Patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel without a confirmed diagnosis of secondary malignancy of T-cell origin.

2) Patients who were treated with axicabtagene ciloleucel or brexucabtagene autoleucel and are actively participating in other clinical trials involving other gene/cellular therapies that are not produced by Kite.

3) Patients who were treated with axicabtagene ciloleucel or brexucabtagene autoleucel and are enrolled in a Kite clinical trial that includes an existing mechanism to perform sample testing.

4) Tissue samples obtained from other secondary malignancies not of T-cell origin by the treating HCP (ie, hematologic malignancies like MDS, AML, and solid tumors); testing will not be considered for such tumors.

7.3. Variables

The following laboratory parameters will be used for molecular profiling:

- The presence of the CAR transgene in the blood and/or tumor and/or bone marrow biopsy.
- The CAR level, if the CAR transgene was detected in the blood and/or tumor and/or bone marrow biopsy.
- Presence of RCR.
- Presence of somatic mutations that are common in hematologic malignancies.
- Transgene integration site analysis results.
- Transcriptome/RNA analysis results.

7.4. Data sources

7.4.1. Sample collection

The SmPC includes instructions that in the event of a secondary malignancy of T-cell origin, Kite is to be contacted to obtain instructions for collecting patient samples for testing. If the secondary malignancy is confirmed to be of T-cell origin, Kite will contact the HCP to offer participation of the patient in this observational molecular profiling study.

Once Kite receives communication from an HCP who would like to obtain instructions on patient sample collection, Kite will contact the HCP to collect additional information (e.g., medical history, treatment outcome, prior and current molecular analyses, pathology report, cytogenetic, and/or flow cytometric reports). Following a review of the information collected from the HCP, it will be determined if the patient has a confirmed diagnosis of secondary malignancy of T-cell origin, if the patient is willing to participate in the study and has signed an informed consent, and whether adequate samples in sufficient quantity are available for testing. If the availability of patient samples is limited, prioritization of analyses should be performed.

The patient samples that can be used for molecular profiling are as follows:

- Blood (peripheral blood mononuclear cells [PBMCs])
- Formalin-fixed paraffin-embedded (FFPE) tumor biopsy

- Bone marrow aspirate
- FFPE bone marrow biopsy
- DNA extracted from blood, tumor biopsy, or bone marrow aspirate/biopsies

Available samples would be tested for the following, per the Secondary Malignancy Testing Algorithm (Figure 2):

- CAR transgene presence by droplet digital polymerase chain reaction (ddPCR)
- RCR presence by quantitative polymerase chain reaction (qPCR)
- Common hematologic mutations by next-generation sequencing (NGS)
- Transgene integration analysis by linear-amplification mediated-PCR coupled with NGS

If the availability of patient samples is limited, test prioritization will be as follows:

- CAR transgene presence
- RCR presence
- Testing for common heme mutations
- Transgene integration analysis

Kite will not ask HCPs to obtain any patient samples for the purpose of this protocol. The samples will be obtained by the treating HCP as part of their treatment and diagnostic decision-making and will not be driven by this study protocol.

Once it is determined that the patient meets the inclusion criteria (see Section 7.2.1), Kite will arrange the transfer of patient samples. If needed, Kite will provide the HCP with a link to order a sampling kit from a central laboratory vendor.

7.4.2. Schedule of sample collection

Kite will follow the below process and timelines to ensure adequate follow-up to obtain the patient samples:

Table 1. Schedule of Sample Collection

Timeline (approximate business days and per HCP local practice)	Action	Responsibility for initiating action
Day 0	HCP contacts Kite to request instructions on patient samples to collect for testing.	HCP
Day 0-1	Secondary malignancy serious adverse event reported to Patient Safety within 24 hours of awareness at Safety_FC@Gilead.com.	Kite
Day 2	Patient Safety and TM review information and determine whether additional information is required.	Kite
Day 3-7	Kite sends a request for additional information*. If necessary, Kite schedules a call with the HCP to review the information and details and prioritize the analyses to be conducted in case of limited tissue samples**. If a confirmed diagnosis of secondary malignancy cannot be obtained, no further action is needed.	Kite
Day 7-10	Kite to provide the HCP with the PASS Protocol and ICF for IEC approval.	Kite
Day 10-20	The HCP submits protocol and ICF for IEC approval.	HCP
Upon IEC approval	The HCP obtains the ICF from the patient***.	HCP
	Kite ensures the HCP has access to sampling kits(s) from the central laboratory vendor.	Kite
	TM ensures the reference laboratories conduct testing according to the Secondary Malignancy Testing Algorithm (Figure 2).	Kite
	TM receives secondary malignancy sample analysis results from the reference laboratories and reports follow-up information to Patient Safety at Safety_FC@Gilead.com.	Kite
	TM provides the HCP with the sample analysis results.	Kite

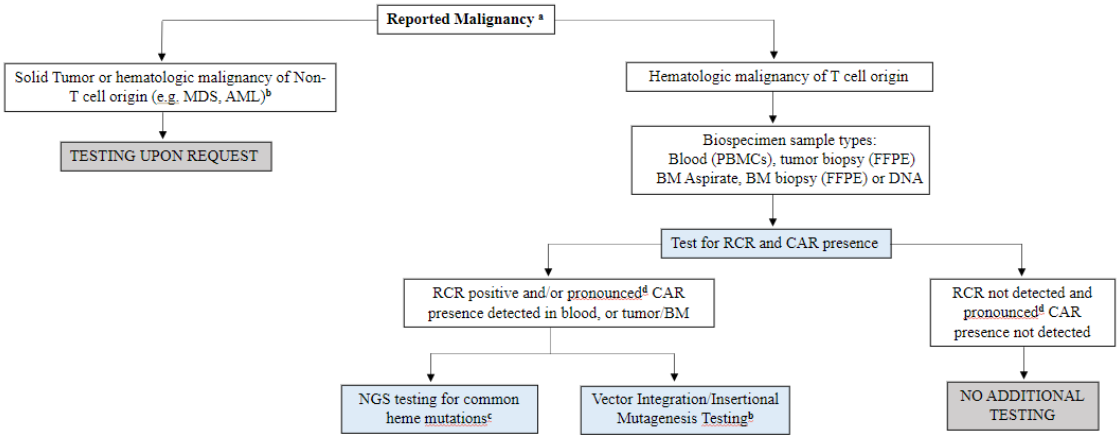
Abbreviations: HCP = healthcare professional; ICF = informed consent form; IEC = institutional ethics committee; PASS = post-authorization safety study; TM = translational medicine.
* Kite will make 3 attempts by a combination of email and phone to contact the site and will document all contacts attempts. If the site does not respond within 1 month after the third contact, the case will be closed and no additional contact with the site will be made. However, if the site recommences contact with Kite, they will resume the process as detailed in the table above.
**Adverse event information obtained regarding the event will be sent to Patient Safety post-meeting.
*** HCP will be requested to make 3 attempts by a combination of mail, email, and/or phone (as permitted by local regulations) to contact the subject. Sites must document all attempts to contact the subject. If a subject does not respond within 1 month after the third contact, the subject will be considered lost to follow-up, and no additional contact will be required.

7.4.3. Molecular profiling

7.4.3.1. Primary objectives

Patient samples will be tested for the presence of CAR and RCR using ddPCR and qPCR, respectively. If patient samples are positive for RCR or pronounced CAR (Figure 2, footnote d) is detected, samples will be tested for common hematologic mutations using NGS and undergo vector integration site analysis. Departures from this algorithm can be implemented and documented depending on the context.

Figure 2. Secondary Malignancy Testing Algorithm



Abbreviations: AE = adverse event; AML = acute myeloid leukemia; BM = bone marrow; CAR = chimeric antigen receptor; FFPE = formalin-fixed paraffin-embedded; MDS = myelodysplastic syndrome; NGS = next-generation sequencing; PBMC = peripheral blood mononuclear cells; RCR = replication-competent retrovirus.

a Ensure adverse event reporting and documentation per routine pharmacovigilance/Safety training procedures. Patient consent must be obtained prior to sample collection and testing.
b Departure from this workflow could be implemented and documented depending on the context, cross-functional discussion, and treating physician recommendation.
c Clinical evidence of pre-existing mutation from prior molecular profiling prior to CAR T treatment to be considered.
d For pronounced CAR presence, if the initial cell levels are available for the concerned patient, these should be used as reference values. No additional testing is conducted if the transgene is detected within or below the range of values observed in blood and bone marrow in clinical trials. Otherwise, additional testing may be needed.

CCI

7.4.4. Reporting of test results

Kite will provide the molecular profiling results to the patient's HCP. The results will be entered into the study and global safety databases and be reported as individual case safety report to EudraVigilance, summarized in the interim and final study reports and reported to health authorities in aggregate safety reports, where required. All results from any setting will be reported in a consistent and transparent manner across all regions in the interim and final reports for Study KT-US-982-0910, ensuring a comprehensive evaluation of all collected and analyzed cases, irrespective of geographic origin.

7.5. Study size

The incidence of T-cell malignancies following CAR T-cell therapy is very low (0.09%), and not every patient will be willing to consent; therefore, it appears likely that a small number of patients will be included in this study. Since this protocol is qualitative in nature and does not include comparisons or statistical hypothesis testing, no formal powered sample size calculation is performed.

7.6. Data management

Site name, site number, address, HCP name and email address will be entered into the study database when registering the site. Patient information (including demographics, informed consent, eligibility, disposition, sample collection, medical/disease history and survival) and the molecular profiling results will be entered into the study database, reported to Kite Patient Safety and Pharmacovigilance, and captured in the global safety database in accordance with standard pharmacovigilance practice.

7.7. Data analysis

No statistical analysis is planned. The molecular profiling results will be described for each patient tested.

7.8. Quality control

The sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles, local practices and regulations, and International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Due to the nature of this study, no on-site monitoring is planned.

7.8.1. Inspection and auditing procedures

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled. The sponsor or its representative may conduct audits at the site, including, but not limited to, the presence of required documents and the informed consent process. All medical records must be available for audit. The physician agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the site during or after the study. The physician or designee should contact Kite immediately if this occurs. He/She must cooperate fully with regulatory authorities or other audits conducted in a reasonable manner.

7.8.2. Source document maintenance

All source documents from this study will be maintained by the physician and made available for inspection by authorized personnel. The original ICF for each patient will be filed with records kept by the physician, and a copy will be given to the patients to keep.

7.8.3. Record maintenance

All data derived from this study will remain the property of Kite. Records must be retained in accordance with the current ICH Guidelines and all applicable laws including data privacy. All essential study documents, including patients' records, source documents, and case report forms (CRFs), must be kept on file.

The physician will not dispose of any records relevant to this study without written permission from the sponsor and will provide the sponsor with the opportunity to collect such records.

7.9. Limitations of the research methods

Sample collection limitations:

- Clinical feasibility
- Refusal or limited availability of the patient to consent.
- Sufficient tissue samples may not be available.
- The biopsy can contain a low proportion of tumor cells and/or be of low quality.
- Due to the invasive nature of sample collection, only a single sample is usually available, providing only a single snapshot to analyze the tumor and assess tumor heterogeneity. Thus, longitudinal tracking of cancer evolution is usually missing.
- Samples requested will only be those that have already been obtained (archival), or are about to be obtained, during clinical practice. Hence, fresh collections may be limited.

Technical limitations:

- FFPE may cause damage to the nucleic acids to be analyzed.
- PCR detected CAR transgene positivity cannot distinguish between a CAR-positive tumor cell and a non-malignant CAR T-cell that infiltrated the tumor.

Causality assessment:

The occurrence of a CAR T-positive T-cell malignancy does not necessarily mean the CAR insertion led to malignant transformation. Ozdemirli et al. showed that the TCL harbored a CAR-vector integration in the second intron of *SSU72*; however, the viral integration site did not appear to alter the expression level of *SSU72* mRNA. Also, no unusual splicing pattern was observed for the *SSU72* gene {Ozdemirli 2024}. Therefore, molecular profiling is not always sufficient in deciphering the malignant transformation and establishing causality.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

Prior to any data collection under this protocol, a written informed consent form (ICF) and possibly a privacy statement must be signed by the patient in accordance with local practice and regulations. Information about the study will be explained to the patient. A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's medical records before any data collection under this protocol. The ICF must not be altered without the prior agreement of the relevant IEC and the sponsor.

All information obtained during the study regarding the patient's state of health will be regarded as confidential. An agreement will be obtained in writing for disclosure of any such information.

To comply with government regulatory guidelines and ensure patient safety, Kite, the local research review board, or regulatory authorities may need to review the patient's medical records as they relate to this study.

Prior to collecting any study-related data, IEC approval of the protocol and ICF will be obtained in each country and for each site, as applicable. The study will be conducted per the ethical principles from the Declaration of Helsinki, applicable privacy laws, and local regulations for each participating site. This non-interventional study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This protocol is not designed to capture adverse events. Thus, adverse event collection and reporting are not required, except for reporting cases of secondary malignancy of T-cell origin. However, investigators/HCPs should follow the standard spontaneous reporting system per local regulations and timelines. The SmPC and packaging materials provide respective details and contact information. As mentioned in Table 1, safety information will be reported to Safety_FC@Gilead.com.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The MAH will register the PASS in the HMA-EMA Catalogue of real-world data studies.

The institution and physician each agree to obtain Kite's review and written consent prior to making any publication (e.g., abstracts, congress presentations, manuscripts, and posters) of the results.

Authorship of planned publications shall be aligned with the criteria of the International Committee of Medical Journal Editors (www.icmje.org).

11. REFERENCES

Fraietta JA, Nobles CL, Sammons MA, Lundh S, Carty SA, Reich TJ, et al. Disruption of TET2 Promotes the Therapeutic Efficacy of CD19-Targeted T Cells. Nature 2018;558:307-12.

Harrison SJ, Nguyen T, Rahman M, Er J, Li J, Li K, et al. CAR+ T-Cell Lymphoma Post Ciltacabtagene Autoleucel Therapy for Relapsed Refractory Multiple Myeloma. Blood 2023;142:6939.

Kobbe G, Brüggemann M, Baermann B-N, Wiegand L, Trautmann H, Yousefian S, et al. Aggressive Lymphoma after CD19 CAR T-Cell Therapy. New England Journal of Medicine 2024;391 (13):1217-26.

Ozdemirli M, Loughney TM, Deniz E, Chahine JJ, Albitar M, Pittaluga S, et al. Indolent CD4+ CAR T-Cell Lymphoma after Cilta-cel CAR T-Cell Therapy. The New England journal of medicine 2024;390 (22):2074-82.

Shah NN, Qin H, Yates B, Su L, Shalabi H, Raffeld M, et al. Clonal Expansion of CAR T Cells Harboring Lentivector Integration in the CBL Gene Following Anti-CD22 CAR T-Cell Therapy. Blood Adv 2019;3 (15):2317-22.

12. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Not applicable.

13. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Molecular profiling of tissue samples from patients who received a Kite-manufactured gene-modified cell therapy and have developed a secondary malignancy of T-cell origin

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

Comments:

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

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	x	☐	☐	
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	x	☐	☐	
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	x	
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))	☐	☐	x	
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)	x	☐	☐	

Comments:

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

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)	☐	☐	x	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	x	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	x	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	x	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	x	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	x	

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?	x	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	x	☐	☐	
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)	☐	☐	x	
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)	☐	☐	x	

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)	☐	☐	x	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	x	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	x	

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)	☐	☐	x	

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)	☐	☐	x	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	x	☐	☐	
9.1.3 Covariates and other characteristics?	☐	☐	x	
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)	☐	☐	x	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	x	☐	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	x	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	x	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	x	
9.3.3 Covariates and other characteristics?	☐	☐	x	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	x	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☐	☐	x	

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

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

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?	☐	☐	x	
12.1.2 Information bias?	☐	☐	x	
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).	☐	☐	x	
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)	x	☐	☐	

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?	x	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	x	
13.3 Have data protection requirements been described?	x	☐	☐	

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?	☐	☐	x	

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

Comments:

Name of the main author of the protocol: PPD

Date: 09/Jul/2025

Signature: _____

14. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Patient Safety eSigned	07-Jul-2025 20:31:20
PPD	Deputy QPPV eSigned	08-Jul-2025 08:16:27
PPD	Regulatory Affairs eSigned	08-Jul-2025 13:57:25
PPD	Clinical Development eSigned	08-Jul-2025 16:59:20
PPD	Real-World Evidence eSigned	08-Jul-2025 21:38:11
PPD	Clinical Pharmacology eSigned	09-Jul-2025 18:21:53