CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1 Study Evaluating the Safety and Efficacy of HPV16 E7 T Cell Receptor Engineered T Cells (KITE-439) in HLA-A*02:01+ Subjects with Relapsed/Refractory HPV16+ Cancers
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SPONSOR AND INVESTIGATOR SIGNATURE PAGE

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STUDY ACKNOWLEDGMENT

A Phase 1 Study Evaluating the Safety and Efficacy of HPV16 E7 T Cell Receptor Engineered T Cells (KITE-439) in HLA-A*02:01+ Subjects with Relapsed/Refractory HPV16+ Cancers
Version: Amendment 5.0, 21 October 2021

This protocol has been approved by Kite Pharma, Inc., hereafter referred to as Kite. The following signature documents this approval.

PPD

Name (Printed)
Kite Medical Monitor

DocuSigned by:
PPD
F9D00348206949F...

Signature

October 25, 2021 | 12:25:18 PM PDT

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Sub-investigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

Principal Investigator Name (Printed)

Signature

Date

Site Number

PROTOCOL SYNOPSIS

Title:	A Phase 1 Study Evaluating the Safety and Efficacy of HPV16 E7 T Cell Receptor Engineered T Cells (KITE-439) in HLA-A*02:01$^+$ Subjects with Relapsed/Refractory HPV16$^+$ Cancers
Indication:	Treatment of human leukocyte antigen (HLA)-A*02:01$^+$ adult subjects with human papillomavirus (HPV)16$^+$ relapsed/refractory cancer.
Study Design:	This is a Phase 1 open-label, multicenter study evaluating the safety and efficacy of KITE-439 in subjects who are HLA-A*02:01$^+$ and have HPV16$^+$ relapsed/refractory cancers. The trial is separated into 2 phases: Phase 1A and Phase 1B. **PHASE 1A** Phase 1A is the single-subject, dose-escalation portion of the study. Phase 1A will enroll a minimum of 2 subjects and up to a maximum of approximately 36 subjects. **DOSE ESCALATION PERIOD** During Phase 1A, the study will employ a single-subject dose escalation scheme until Cohort 5 and 6 at which time a 3+3 design is implemented (see Section 9.7.2.1). Subjects will be monitored for the occurrence of -dose-limiting toxicities (DLTs) within the first 21 days after receiving the KITE-439 infusion (see Section 9.7.1 for DLT criteria). In Cohorts 1 through 4, if the subject does not experience a DLT during the DLT window, then the next subject will be dosed at the next higher dose cohort. If the subject does experience a DLT, then the rules as outlined in Section 9.7.2.1 will apply. **SAFETY REVIEW PERIOD** A safety review team (SRT) will make recommendations on the conduct of the study. The SRT membership includes the study sponsor and at least one Phase 1 investigator with an enrolled and dosed subject in the study. The SRT will assess overall safety and DLTs in Phase 1A as well as pausing criteria in Phase 1A and Phase 1B. See Section 9.7.2 for additional details.

	PHASE 1B After a dose has been selected based on Phase 1A, enrollment will commence in Phase 1B. At Kite's discretion, up to approximately 35 subjects will be enrolled into the following 2 cohorts. • $HPV16^+$ squamous cell carcinoma of the head and neck (n = 15) • Other $HPV16^+$ tumors (Includes all $HPV16^+$ tumors other than squamous cell carcinoma of the head and neck) (n = 20) Note: The subjects enrolled and treated in Phase 1A at the selected Phase 1B dose will contribute to the sample size for Phase 1B based on their relevant tumor type. Independent of the phase of the study (Phase 1A or Phase 1B), each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods: • Pre-screening • Screening (main study) • Enrollment/leukapheresis • CCI [redacted] • Conditioning chemotherapy • Investigational product (IP) treatment • Posttreatment assessment • Longterm follow-up (LTFU) For study requirements assigned to each study period, refer to the schedule of assessments (SOA) and Section 7.11 for details. A study schema is provided in Figure 1.
Study Objectives:	The primary objectives of Phase 1A are to evaluate the safety of KITE-439 and to determine a recommended Phase 1B dose. The primary objective of Phase 1B is to estimate the efficacy of KITE-439, as measured by objective response rate (ORR). Secondary objectives include assessing the safety of KITE-439 and additional efficacy endpoints.

Hypothesis:	Phase 1A: KITE-439 at one of the dose levels planned will be considered safe as determined by the incidence of DLTs. Phase 1B: A formal hypothesis will not be tested. The clinical hypothesis is that KITE-439 will have clinically meaningful anti-tumor activity, as measured by ORR. The Phase 1B portion of the study is designed to estimate the ORR.
Primary Endpoints:	Phase 1A: Incidence of adverse events (AEs) defined as DLTs Phase 1B: ORR (CR + PR) per modified RECIST v1.1 {Eisenhauer 2009}
Secondary Endpoint(s):	**SECONDARY ENPOINT(S) FOR PHASE 1B** • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Incidence of AEs, incidence of anti-KITE-439 antibodies, and incidence of replication-competent retrovirus (RCR) • Levels of HPV16 E7 T-cell receptor (TCR) T cells
CCI [redacted]	[redacted]
Sample Size:	Phase 1A: A minimum of 2 subjects and up to a maximum of approximately 36 subjects. The number of subjects enrolled into Phase 1A is dependent upon the number of DLTs observed in each dose cohort. Phase 1B: After a dose has been selected based on Phase 1A, enrollment will commence in Phase 1B. At Kite's discretion, up to approximately 35 subjects will be enrolled into the following 2 cohorts. • HPV16+ squamous cell cancer of the head and neck cohort (n = 15) • Other HPV16+ tumors cohort (Includes all HPV 16+ tumors other than squamous cell carcinoma of the head and neck) (n = 20) Note: The subjects enrolled and treated in Phase 1A at the selected Phase 1B dose will contribute to the sample size for Phase 1B based on their relevant tumor type.

Study Eligibility:	Refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria.
Treatment:	CCI [redacted] **CONDITIONING CHEMOTHERAPY TREATMENT** CCI [redacted] • Cyclophosphamide CCI [redacted] • Fludarabine CCI [redacted] [redacted] • See Sections 6.3 and 7.5.3.1 for details. **INVESTIGATIONAL PRODUCT** Phase 1A: KITE-439 will be administered at one of the following dose cohorts (± 20%): • Cohort 1: 1 x 10^6 E7 TCR T cells/kg • Cohort 2: 3 x 10^6 E7 TCR T cells/kg • Cohort 3: 1 x 10^7 E7 TCR T cells/kg • Cohort 4: 3 x 10^7 E7 TCR T cells/kg • Cohort 5: 1 x 10^8 E7 TCR T cells/kg • Cohort 6: 1 x 10^8 E7 TCR T cells/kg* *Dose of E7 T cells/kg is the same in Cohort 5 and 6, but maximum allowable total number of E7 T cells is higher in Cohort 6, please see Section 3.1.1. If there are ≥ 2 DLTs in Cohort 1, the study may explore a lower KITE-439 dose (Cohort –1) (see Section 9.7.2.1). Phase 1B: KITE-439 will be administered at the dose selected by Kite Pharma, Inc. The dose selected for Phase 1B will be formally communicated to participating sites in a separate communication. See Section 9.7.2 for DLT and dose escalation criteria.

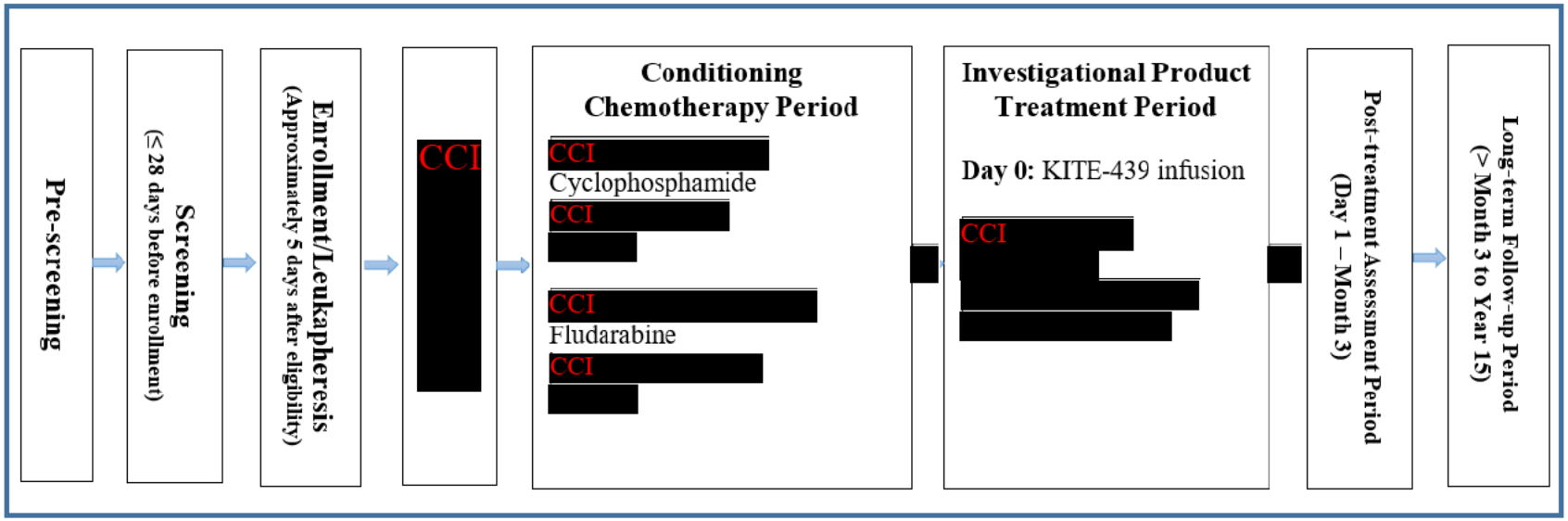
	CCI [redacted]
Procedures:	At specific time points as outlined in the SOAs (Section 7.11), subjects will undergo the following procedures. • Informed consent – Screening to determine eligibility for enrollment is a 2-step process. There is a pre-screening portion and screening portion. These are further explained in Section 7.2. Both pre-screening and screening require a separate consent. • During pre-screening, blood will be collected and analyzed locally for human leukocyte antigen (HLA) typing; archival or fresh tumor tissue will be submitted to the central laboratory for HPV16 genotyping. • During screening for the main study and on-study, the following procedures will be performed at the various time points outlined in the SOA: — Review of general medical history, including previous treatments for subject's respective cancer — Physical exam, including vital signs and performance status — Urine toxicology panel — Electrocardiogram (ECG), echocardiogram (ECHO), and computed tomography (CT) (or positron emission tomography [PET-CT]), or magnetic resonance imaging (MRI) scans

	— Neurological assessments including neurological consultation and Mini-Mental Status Exam (MMSE) — Blood will be drawn and analyzed locally for complete blood count (CBC), chemistry panels, and C-reactive protein (CRP). Women of childbearing potential will undergo a local urine or serum pregnancy test. — Blood will be drawn and submitted to the central lab for cytokines; anti-KITE-439 antibodies; peripheral blood mononuclear cells (PBMC), which includes RCR testing. — CCI [redacted] — Subjects will undergo leukapheresis to collect mononuclear cells for the manufacture of KITE-439. — Subjects will receive a CCI conditioning chemotherapy regimen of cyclophosphamide and fludarabine, treatment with KITE-439, CCI [redacted] All subjects will be hospitalized for the KITE-439 infusion and remain hospitalized for at least 7 days after the KITE-439 infusion to monitor for toxicities. — Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications, AEs, and subsequent therapy for their disease. — Subjects will also undergo routine disease assessments.
Safety Review Team (SRT):	An SRT will make recommendations on the conduct of the study. The SRT membership includes the study sponsor and at least one Phase 1 investigator with an enrolled and dosed subject in the study. The SRT will assess overall safety and DLTs in Phase 1A as well as pausing criteria in Phase 1A and Phase 1B. The SRT may also review subject-level safety and efficacy data on an ongoing basis in Phase 1B.

Statistical Considerations:	The primary endpoint for the Phase 1A portion of the study is incidence of AEs defined as DLTs. The primary endpoint for the Phase 1B portion of the study (subjects enrolled at the Phase 1B dose in the Phase 1A portion will be included) is ORR per the modified RECIST v1.1 (Appendix 1). This endpoint will be based on a modified intent to treat (mITT) population consisting of all subjects who receive Phase 1B target dose of KITE-439 and with measurable disease CCI [redacted] and prior to administration of conditioning chemotherapy. The Phase 1B uses a single-arm design to estimate response rate in each of the 2 cohorts (n = 15 in the HPV16^{+} squamous cell cancer of the head and neck cohort and n = 20 in the other HPV16+ tumors cohort that includes all HPV16+ tumors other than squamous cell carcinoma of the head and neck) and in all Phase 1B cohorts combined (n = 35). With the planned sample size in the two cohorts, the ORR can be estimated with a standard error not greater than 13% and 11%, respectively. Assuming an observed ORR of 40%, the lower bound of the 95% CI for the estimated ORR will exclude values less than 16% and 19%, respectively. With a planned total sample size of 35 for all Phase 1B cohorts combined, the ORR can be estimated with a standard error no greater than 8%. Assuming an observed ORR of 40%, the lower bound of the 95% CI for the estimated ORR will exclude values less than 24%. No formal interim analysis is planned for the Phase 1B part of the study. However, the SRT will review subject-level safety and efficacy data on an ongoing basis to monitor subject safety and ensure data quality. Informal safety and efficacy analyses may be done with accumulating data when such a need arises during the study. Within the Phase 1B HPV16^{+} squamous cell cancer of the head and neck cohort, if no response is observed in the first 7 subjects treated with the target dose after a minimum of 1 month of follow-up, the sponsor may consider stopping enrollment for this cohort. Within the other Phase 1B HPV16^{+} tumors cohort, if no response is observed in the first 10 subjects treated with the target dose after a minimum of 1 month of follow-up, the sponsor may consider stopping enrollment for this cohort.

	One primary analysis is planned for each of the cohorts in Phase 1B and will be performed after all subjects accrued for a specific cohort to the study have had the opportunity to be assessed for response 3 months after the KITE-439 infusion. If an individual cohort takes > 24 months to accrue from the initiation of Phase 1B, the primary analysis can occur with < 15 subjects accrued for the HPV16^{+} squamous cell cancer of the head and neck cohort and < 20 subjects for the other HPV16+ tumors cohort excluding squamous cell carcinoma of the head and neck. If the primary analysis for 2 cohorts is projected to occur within 3 months of each other, the cohorts may be combined and carried out at the same time.

Figure 1. STUDY SCHEMA (PHASE 1A AND PHASE 1B)



Note: After the end or termination of KITE-478-0401, subjects who received an infusion of KITE-439 will complete the remainder of the 15-year follow-up assessments in a separate Long-term Follow-up study, KT-US-982-5968.

Abbreviations: IV, intravenous; IVPB, intravenous piggyback; SC, subcutaneous.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BLAST	Basic Local Alignment Search Tool
BMI	Body mass index
CAR	Chimeric antigen receptor
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response
DVT	Deep vein thrombosis
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FDG-PET	F-flurodeoxyglucose positron emission tomography
FFPE	Formalin-fixed paraffin embedded
GCP	Good Clinical Practice
GPT	Glutamic-pyruvic transaminase
GVHD	Graft-versus-host-disease
HABA	Human anti-bovine antibodies
HEENT	Head, eyes, ears, nose, and throat
HLA	Human leukocyte antigen
HNSCC	Head and neck squamous cell carcinoma

HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation for Pharmaceuticals for Human Use
ICU	Intensive care unit
ID	Identification
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug
IP	Investigational product
IPM	Investigational Product Manual
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IV	Intravenous
IVPB	Intravenous piggyback
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin
LTFU	Long-term follow-up
LVEF	Left ventricle ejection fraction
mITT	Modified intend to treat
MMSE	Mini-Mental Status Exam
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NE	Inevaluable
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Orally
PR	Partial response

qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Stable disease
SOA	Schedule of assessment
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reactions
TCR	T-cell receptor
TIA	Transient ischemic attack
ULN	Upper limit normal
UTI	Urinary tract infection
WBC	White blood cell

1. OBJECTIVES

The primary objectives of Phase 1A are to evaluate the safety of KITE-439 and to determine a recommended Phase 1B dose.

The primary objective of Phase 1B is to estimate the efficacy of KITE-439, as measured by objective response rate (ORR). Secondary objectives include assessing the safety of KITE-439 and additional efficacy endpoints.

2. BACKGROUND AND RATIONALE

2.1. HPV-associated Cancers

Human papilloma virus (HPV) infection is considered one of the predominant causes of infection-related cancers in both men and women globally {Serrano 2018}. Over 120 HPV subtypes have been characterized, but a subset of 15 high-risk HPV subtypes are responsible for causing large proportions of cervical, head and neck, and anogenital (i.e., vulvar, vaginal, penile, anal) cancers {Arbyn 2012, Bansal 2016, Berman 2017}. The HPV16 and HPV18 subtypes have the greatest oncogenic potential and cause approximately 70% of all cervical cancers worldwide {de Sanjose 2007}. US Centers for Disease Control and Prevention (CDC) data from 1993 to 2005 show that HPV16 or HPV18 was detected in the majority of anal (79%), cervical (66%), oropharyngeal (60%), and vaginal (55%) cancers, and in nearly half of all vulvar (49%) and penile (48%) cancers {Saraiya 2015}. The analysis also showed that in the US, HPV16 was by far the most common subtype across invasive anogenital cancer, as well as head and neck cancers.

An estimated 20,000 to 30,000 HPV-associated cancers are diagnosed annually in the US {Razzaghi 2018, Viens 2016}. The American Cancer Society estimated in 2017 that over 12,000 deaths occurred due to cancers located at anatomic sites with a high frequency of HPV-associated cancers (i.e., includes oral cavity/pharynx [not tongue/mouth]; cervix; vulva; vaginal/other genital, female; penis/other genital, male; and anus, anal canal, and anorectum) {ACS 2017}. Razzaghi and colleagues recently analyzed survival of patients with HPV-associated cancers using data from 27 CDC cancer registries covering approximately 59% of the US population {Razzaghi 2018}. For this study, HPV-associated cancer were defined as invasive cancers occurring at anatomic sites where HPV DNA is frequently identified: all cervical cancers (squamous cell carcinomas [SCC] and adenocarcinomas) and SCC of the cervix, vulva, vagina, penis, oropharynx, anus, and rectum. The study showed that over 200,000 HPV-associated cancers were diagnosed from 2001 to 2011, and the 5-year, age-standardized relative survival rate was highest for cervical carcinomas, vulvar, and anal SCCs, and lowest for penile and oropharyngeal SCCs (Table 1).

Table 1. Survival Rates for Patients Diagnosed with HPV-associated Cancers in the US: 2001-2011[a]

HPV-associated Cancers[b]	Number of Patients Diagnosed	Percentage of Total	5-year Relative Survival Rate
Cervical carcinoma	79,425	36.1	64.2%
Vaginal SCC	4,871	2.2	52.8%
Vulvar SCC	19,345	8.8	66%
Penile SCC	6,248	2.8	47.4%
Anal SCC	26,026	11.8	65.9%
Rectal SCC	4,145	1.9	56.2%
Oropharyngeal SCC	80,151	36.4	51.2%
Total	220,211	100.0	-

Abbreviations: HPV, human papillomavirus; SCC, squamous cell carcinoma
Adapted from: {Razzaghi 2018}

a. Data were compiled from 27 population-based cancer registries that participate in the National Program of Cancer Registries, meet the data-quality standards for inclusion in US Cancer Statistics, and meet the criteria for inclusion in the survival data set, which covers approximately 59% of the US population. Analyses were limited to invasive cancers diagnosed 2001 through 2011 and were followed through 2011, and met specified histologic criteria for HPV-associated cancers. 5-year survival rate was calculated from diagnosis until death.

b. HPV-associated cancers were defined by Razzaghi and coauthors as invasive cancers at anatomic sites with cell types in which HPV DNA is frequently identified, which included all carcinomas of the cervix (including adenocarcinomas and SCCs), and SCCs only for the other anatomic sites. To estimate the number of cancers attributed to HPV, the number of HPV-associated cancers was multiplied by the percentage of each cancer type attributable to HPV based on the genotyping study of Saraiya and coauthors {Saraiya 2015}.

2.2. Available Therapy and Unmet Need

Depending upon the cancer type, patients with localized, early stage HPV-associated cancers may be successfully treated with surgery, radiation therapy, chemoradiotherapy, chemotherapy, or biologic therapy, but patients who relapse or are refractory to such therapies and patients with metastatic disease generally have poor prognoses {Stern 2012}. Available therapies and reported outcomes according to anatomic site of disease are summarized below. The collective data demonstrate the magnitude of this critical unmet medical need.

Head and Neck

The recurrence rate is approximately 10% to 20% in early-stage head and neck SCC (HNSCC) and 50% in locally advanced HNSCC, and patients with recurrent or metastatic HNSCC have a median overall survival (OS) less than 1 year with standard therapies {Argiris 2017, Price 2012}. Treatment for recurrent and/or metastatic HNSCC often consists of cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, plus combination chemotherapy with cisplatin or carboplatin and 5-flourouracil (5-FU), followed by maintenance with cetuximab alone. Cetuximab has been approved for HNSCC treatment using this regimen {ERBITUX 2012}. In a Phase 3 study of patients with recurrent or metastatic oropharyngeal tumors, this treatment, known as the EXTREME regimen, was compared to chemotherapy-alone; results

showed that adding cetuximab to the platinum-based chemotherapy regimen significantly increased median OS from 7.4 to 10.1 months, and improved overall response rates from 20% to 36% {Vermorken 2008}. In a subsequent retrospective analysis of this study, tissue samples were analyzed according to HPV status, and 5% of tumors were positive for HPV DNA. The analysis showed that regardless of HPV status, the addition of cetuximab to chemotherapy significantly improved survival with median OS increases from 7.1 to 13.2 months in patients with HPV^+ tumors and from 6.7 to 9.7 months in patients with HPV^- tumors {Vermorken 2014}. Patients with recurrent or metastatic HNSCC who progress during or after next-line treatment have limited treatment options, as shown by ORRs < 20% and median OS of approximately 5 to 6 months in multiple Phase 3 studies of methotrexate, docetaxel, paclitaxel, and cetuximab as monotherapies {Price 2012}.

The recent US Food and Drug Administration (FDA) approvals of the immune checkpoint inhibitors nivolumab {OPDIVO 2014} and pembrolizumab {KEYTRUDA 2016} provide an additional next-line treatment option for patients with recurrent or metastatic HNSCC. Immune checkpoint inhibitors function by altering immunosuppressive pathways normally used by cancer cells to avoid detection and elimination by the host immune system. Nivolumab and pembrolizumab are monoclonal antibodies that target the programmed cell death protein 1 (PD-1) receptor on activated T cells, thereby preventing inactivation of the T cell that could occur by interaction with PD-1 ligand-1 (PD-L1) on tumor cells. These new agents result in improved response rates compared to standard monotherapies, but the ORR is still low (13% to 32%). Nivolumab was approved in the US based on a Phase 3 trial comparing nivolumab with standard therapy in patients with platinum refractory, recurrent HNSCC {Ferris 2016}. The ORR was 13.3% with nivolumab versus 5.8% with standard therapy, and median OS with nivolumab was significantly longer than with standard therapy (7.5 vs 5.1 months). CCI [redacted]. Pembrolizumab efficacy was evaluated in an open-label Phase 1b trial in 60 patients with HNSCC tumors positive for PD-L1. Notably, results showed an ORR of 25% for patients with HPV^+ HNSCC compared with 14% in patients with HPV-negative HNSCC {Seiwert 2016}. A Phase 3 randomized trial, however, showed that the median OS was not significantly different for pembrolizumab vs standard therapy (8.4 vs. 7.1 months) {Cohen 2017}.

Cervical Cancer and Other HPV-associated Cancers

Although the incidence of invasive cervical cancer has declined substantially during the last 40 years due to screening and vaccination programs, 15% to 61% (depending on stage at diagnosis) of women develop recurrence and/or distance metastases within 2 years of completing initial treatment {Quinn 2006}. The standard treatment for recurrent/metastatic cervical cancer regardless of HPV status is platinum-based chemotherapy, but the treatment is largely palliative, and the prognosis for these patients is dismal {Boussios 2016}. In a Gynecologic Oncology Group randomized trial comparing 2-agent regimens of cisplatin plus either paclitaxel, vinorelbine, gemcitabine, or topotecan for recurrent or persistent cervical cancer, ORR ranged from 22% to 29%, with median OS rates ranging from 10 to 13 months {Monk 2009}. The addition of bevacizumab, an antibody targeting the vascular endothelial growth factor (VEGF) to

combination chemotherapy (cisplatin/paclitaxel or topotecan-paclitaxel) in patients with recurrent, persistent or metastatic cervical cancer improved median OS to 17 months versus 13.3 months with chemotherapy alone, but the majority of patients died within 2 years {Tewari 2014}. In June 2018, pembrolizumab was approved in the US for the treatment of patients with recurrent or metastatic cervical cancer whose tumors express PD-L1 (https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm610572.htm). The approval was based on results from the treatment of 98 patients with relapsed/refractory or advanced PD-L1$^+$ and PD-L1$^-$ cervical cancers in the KEYNOTE 158 open-label Phase 2 study {Chung 2018}. ORR for patients in KEYNOTE 158 was 16% in the 81 patients with PD-L1$^+$ tumors (13.3% in the overall cohort of 98 patients). Median OS was 9.4 months (range: 7.9 to 13.4 months). Given the low survival rates and overall survival, even with this new therapy, patients with recurrent, persistent, or metastatic cervical cancer represent a critical unmet need.

Although anal cancer is a rare disease and accounts for less than 1% of all new cancer diagnoses, its incidence in the US has more than doubled from 1975 to 2015. The prognosis of patients with inoperable progressive/recurrent or metastatic anal cancer is poor regardless of HPV status, with a 5-year relative survival rate of 30%. Although recommendations for therapy are debated due to a lack of evidence from large prospective studies, treatment of metastatic anal cancers or locally advanced unresectable anal cancers generally consists of a combination regimen with a platinum agent and fluoropyrimidine. Results from several retrospective studies showed ORRs ranging from 30% to 57%, with median progression-free survival (PFS) of 6 to 8 months in patients treated with a platinum agent and fluoropyrimidine {Sclafani 2018}. Next-line treatment for advanced anal cancers refractory to platinum and fluoropyrimidine has included a variety of chemotherapy agents either as monotherapy or in combinations of 2 to 4 agents, although these results were from small retrospective studies with high variability in response rates {Sclafani 2018}. Recently, the immune checkpoint inhibitors pembrolizumab and nivolumab were investigated as therapies for advanced anal cancer in 2 separate prospective studies. In a small Phase 1b single-arm study, pembrolizumab treatment of patients with PD-L1$^+$ recurrent/refractory anal cancer resulted in an ORR of 17% and median OS of 9.3 months {Ott 2017}. Similarly, in a small Phase 2 study of patients with previously treated unresectable metastatic anal cancer, treatment with nivolumab resulted in an ORR of 24% and median OS of 11.5 months {Morris 2017}. Thus, outcomes for patients with recurrent, refractory, or metastatic anal cancers remain poor even with newer agent therapies.

In conclusion, the overall poor response and survival results from these studies of available treatment options indicate that novel therapies are needed for patients with recurrent/refractory HPV-associated tumors.

2.3. Engineered T-cell Therapy

T cells play a central role in the immune system by destroying diseased cells, including tumor cells, throughout the body. Studies with tumor vaccines {Kantoff 2010}, immune checkpoint inhibitors {Hamid 2013}, and tumor infiltrating lymphocytes {Rosenberg 2011} have demonstrated the potential of T cells to treat cancer. To be effective in combating cancer, T cells must possess the appropriate specificity for a tumor, be present in sufficient numbers, and be able to overcome any local immunosuppressive factors {Kershaw 2013}.

Engineered autologous cell therapy is a process by which a subject's own T cells are collected and subsequently genetically engineered with a T-cell receptor (TCR) or a chimeric antigen receptor (CAR) specific for a target antigen expressed on the cell surface of specific malignancies {Johnson 2006, Kochenderfer 2013, Robbins 2015}. Engagement of the TCR or CAR with its target antigen induces T-cell activation, resulting in the killing of the target cancer cell, production of therapeutic cytokines, and T-cell expansion. The ability to genetically engineer human T cells and use them to mediate cancer regression in subjects has been demonstrated in a number of studies for a variety of cancers {Kochenderfer 2014, Lee 2015, Robbins 2015}.

Kite Pharma, Inc. (hereafter referred to as Kite) is developing T-cell products consisting of T cells that express a CAR or T cells that express an engineered TCR. In contrast to antibody-based targeted therapies, such as CAR T cells or monoclonal antibodies, both of which generally recognize epitopes on intact proteins, TCRs recognize short peptide fragments (8 to 18 amino acids) that are presented by class I or class II HLA molecules on the surface of tumor cells or other antigen-presenting cells. $CD8^+$ T cells require presentation of cognate peptide by a class I HLA molecule, and $CD4^+$ T cells generally recognize peptides presented in context of HLA class II molecules. Because TCRs recognize their cognate peptide only in the context of a specific HLA type, T-cell products that express engineered TCRs are of potential benefit only to patients with the corresponding HLA type. Another advantage is the ability of TCRs to recognize HLA-presented peptides derived from transmembrane or intracellular proteins, thereby providing more potential targets than CARs.

To date, available cell products engineered with TCR genes have contained both $CD4^+$ and $CD8^+$ cells {Johnson 2009, Kageyama 2015, Morgan 2006, Robbins 2015, Tawara 2017} or only $CD4^+$ cells. With both categories of product, safety profiles have been acceptable when the TCR was not affinity enhanced (i.e., genetically engineered to have higher binding affinity for HLA-peptide complexes compared with native TCRs) and when the TCR did not exhibit nonspecific binding {Linette 2013, Robbins 2015}.

2.3.1. Description of the T-cell Therapy Product: KITE-439

Kite is developing an autologous T-cell product that targets HPV16-expressing relapsed/refractory solid tumors. The HPV epitope targeted by the engineered TCR is a peptide consisting of amino acids 11 to 19 of the HPV16 E7 protein, hereafter referred to as HPV E7 peptides 11-19. HPV16 E7 is a viral protein that is constitutively expressed in, and important for the survival of, HPV-driven cancers {Honegger 2013, Longworth 2004, Sima 2008}. The E7 protein is not expressed by human tissue, making it an attractive target for anti-cancer therapy {Hinrichs 2013}.

The engineered TCR recognizes the HPV E7 peptides 11-19peptide presented by HLA-A*02:01, which is the most common class I HLA-A2 allele in humans, detected in approximately 20% to 95% of individuals across many ethnic populations {Browning 1996, Ellis 2000}. The HPV E7 peptides 11-19 9-mer peptide is a naturally processed epitope that is conserved among HPV16 strains. When presented by HLA-A*02:01 on the surface of $HPV16^+$ tumor cells, the peptide can be targeted by cytotoxic T cells, resulting in target cell killing in an in vitro assay {Riemer 2010}.

Additional details, including a risk/benefit assessment of KITE-439, are provided in the Investigator's Brochure (IB).

2.4. Nonclinical Studies

Nonclinical studies were conducted by the National Cancer Institute (NCI) to assess the binding specificity, HLA restriction, potential for cross-reactivity, cytotoxicity, effector cytokine production (IFN-γ), and in vivo efficacy of E7 TCR T cells {Jin 2018}. Details of these analyses are described in the IB.

2.5. Previous Human Experience

NCI Protocol 16-C-0154 (Investigational New Drug [IND] 16959; NCT 02858310) entitled, "A Phase I Trial of T Cell Receptor Gene Therapy Targeting HPV-16 E7 with or without PD-1 Blockade for HPV-Associated Cancers," is a first-in-human, ongoing Phase 1 study of autologous E7 TCR T cells in HLA-A*02:01^+ subjects who have metastatic or relapsed or refractory $HPV16^+$ cancers. This study uses T cells expressing the same genetically modified TCR construct and the same retroviral vector as those used in the production of KITE-439; however, the NCI manufacturing process differs from that of KITE-439. Despite these manufacturing differences, KITE-439 is anticipated to retain activity of the E7 TCR T cells and preserve the low risk of cross-reactivity observed to date in the NCI trial. Data from NCI 16-C-0154 are therefore considered to provide initial evidence of the expected efficacy and safety of KITE-439. Briefly, no off-target T-cell toxicity, cytokine release syndrome (CRS), or Grade 5 adverse events (AEs) occurred in the NCI 16-C-0154 clinical study as of the 04 May 2018 data cut-off date. One dose-limiting toxicity (DLT) occurred at dose level 3 (1×10^{11} total E7 TCR T cells). The most frequent Grade 3 or higher AEs were cytopenias. Five of nine evaluable subjects had partial responses (PRs); 2 of these PR were unconfirmed. Details are provided in the IB.

3. STUDY DESIGN

3.1. General Study Design

Study KITE-439 is a Phase 1 open-label, multicenter study evaluating the safety and efficacy of KITE-439 in subjects who are HLA-A*02:01$^+$ and have HPV16$^+$ relapsed/refractory cancers. The trial is separated into 2 phases: Phase 1A and Phase 1B.

3.1.1. Phase 1A

Phase 1A is the dose escalation portion of the study. Phase 1A will enroll a minimum of 2 subjects and up to a maximum of approximately 36 subjects.

During Phase 1A, the study will employ a single-subject dose escalation scheme until Cohort 5 and 6 at which time a 3+3 design is implemented (see Section 9.7.2.1). Subjects will be monitored for the occurrence of DLTs within the first 21 days after receiving the KITE-439 infusion (see Section 9.7.2.1 for DLT criteria). In Cohorts 1 through 4, if the subject does not experience a DLT during the DLT window, then the next subject will be dosed at the next higher dose cohort. If the subject does experience a DLT, then the rules as outlined in Section 9.7.2.1 will apply.

KITE-439 will be administered at one of the dose cohorts (± 20%) shown in Table 2.

Table 2. Phase 1A Dose Cohorts

Dose Cohort	E7 TCR T Cells/kg
1	1×10^6
2	3×10^6
3	1×10^7
4	3×10^7
5	1×10^8
6[a]	1×10^8

Abbreviations: TCR, T-cell receptor.
a Dose of E7 T cells/kg is the same in Cohort 5 and 6 but maximum allowable total number of E7 T cells is higher in Cohort 6, please see below.

If there are ≥ 2 DLTs in Cohort 1, the study may explore a lower KITE-439 dose (Cohort –1) (see Section 9.7.2.1).

For the higher dose cohorts, more than 1 bag of KITE-439 may be needed to complete the dose. CCI [redacted]

For subjects weighing greater than 100 kg, each dose of E7 TCR T cells will be calculated based on a maximum weight of 100 kg. For Cohort 5, the maximum allowable dose to be administered is 5 x 10^9 E7 TCR T cells (± 20%). For Cohort 6, the target dose is 1 x 10^8 E7 TCR T cells/kg and the total number of cells will be calculated based on weight. The minimally acceptable dose for patients above 60 kg will be 6 x 10^9 E7 TCR T cells. The maximum total number of cells in this cohort will be 1 x 10^{10} E7 TCR T cells.

A safety review team (SRT) will make recommendations on the conduct of the study. The SRT membership includes the study sponsor and at least one Phase 1 investigator with an enrolled and dosed subject in the study. The SRT will assess overall safety and DLTs in Phase 1A as well as pausing criteria in Phase 1A and Phase 1B. The dose selected for Phase 1B will be formally communicated to participating sites in a separate communication. See Section 9.7.2 for additional details.

3.1.2. Phase 1B

After a dose has been selected based on Phase 1A, enrollment will commence in Phase 1B. At Kite's discretion, up to approximately 35 subjects will be enrolled into the following 2 cohorts.

- $HPV16^+$ squamous cell cancer of the head and neck (n = 15)
- Other $HPV16^+$ tumors (Includes all $HPV16^+$ tumors other than squamous cell carcinoma of the head and neck) (n = 20)

Note: The subjects enrolled and treated in Phase 1A at the selected Phase 1B dose will contribute to the sample size for Phase 1B based on their relevant tumor type.

Conditioning chemotherapy may be given in an out-patient setting. However, all subjects will be hospitalized for the KITE-439 infusion and remain hospitalized for at least 7 days after the KITE-439 infusion to monitor for toxicities.

Refer to the Investigational Product Manual (IPM) for details and instruction on storage, preparation, and administration of KITE-439.

Independent of the phase of the study (Phase 1A or Phase 1B), each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:

- Pre-screening
- Screening (main study)
- Enrollment/leukapheresis
- CCI [redacted]

- Conditioning chemotherapy
- Investigational Product (IP) treatment
- Post -treatment assessment
- Long-term follow-up (LTFU); after the end or termination of KITE-478-0401, subjects who received an infusion of KITE-439 will complete the remainder of the 15-year follow-up assessments in a separate LTFU study, KT-US-982-5968.

For study requirements assigned to each study period, refer to the schedule of assessments (SOAs) Section 7.11 for details.

3.2. Participating Sites

Approximately 32 centers located in North America and Europe will participate in this study. Additional regions, countries, or sites may be added as necessary.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects."

Phase 1A: A minimum of 2 subjects and up to a maximum of approximately 36 subjects will participate in this study. The number of subjects enrolled into Phase 1A is dependent upon the number of DLTs observed in each dose cohort (see Section 3.1.1 for the list of dose cohorts and Section 9.7 for details regarding DLTs and dose escalation rules).

Phase 1B: After a dose has been selected based on Phase 1A, enrollment will commence in Phase 1B. At Kite's discretion, up to approximately 35 subjects will be enrolled into the following 2 cohorts.

- $HPV16^+$ squamous cell cancer of the head and neck (n = 15)
- Other $HPV16^+$ tumors (Includes all $HPV16^+$ tumors other than squamous cell carcinoma of the head and neck) (n = 20)

Note: The subjects enrolled and treated in Phase 1A at the selected Phase 1B dose will contribute to the sample size for Phase 1B based on their relevant tumor type.

It should be noted that Kite may choose to close enrollment at any time. Refer to the statistical considerations in section 10.3 for sample size estimations.

3.4. Replacement of Subjects

Subjects will continue to be enrolled in Phase 1A and Phase 1B until the specified number of subjects are attained in the DLT evaluable (Phase 1A) and modified intent-to-treat (mITT) sets (Phase 1B). See Section 10.4 for details.

If a subject is lost to follow-up or withdraws from the study prior to the 3-month assessment, the subject may be replaced.

3.5. Study Duration

The study includes a 28-day screening period, a 5-day conditioning chemotherapy treatment period, KITE-439 treatment, post-treatment assessment period (Day 1 to Month 3), and a LTFU period (> Month 3 through 15 years after the KITE-439 infusion for safety and survival surveillance).

The duration of the study for individual subjects will vary depending on their screening requirements, response to treatment, survival, and if applicable, timing of transition to the separate LTFU study, KT-US-982-5968 (discussed in Section 3.5.1).

3.5.1. End of Study

Completion of the study is defined as the time at which the last subject completes at least 3 months of assessments (the post-treatment follow-up period), or the last subject is transitioned to the LTFU study. The end-of-study for each subject is defined as the last visit on this study, or when a subject is considered lost to follow-up, withdraws consent, or dies (whichever occurs first).

3.5.2. Long-term Follow-up

If the study is terminated prior to completion of 15 years of follow-up for all subjects, those who received an infusion of KITE-439 will be transitioned to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/serious AEs (SAEs) suspected to be possibly related to KITE-439 as defined in KT-US-982-5968, presence of replication-competent retrovirus and/or insertional mutagenesis for up to 15 years from the time of KITE-439 infusion (also refer to Section 7.1.2.5).

For each subject, the final visit on this study may be combined with the subject's first visit on the LTFU study. The timing of the subject's final visit on KITE-439 protocol/first LTFU study visit will depend upon the timing of the collection of all the subject's data that are required for the planned analysis for this study. In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

4. SUBJECT IDENTIFICATION

Screening to determine eligibility for enrollment is a 2-step process. There is a pre-screening portion and screening portion. These are further explained in Section 7.2.1 and Section 7.2.2. Both pre-screening and screening require a separate consent. Each subject who enters the pre-screening period will receive a unique subject identification (ID) number.

Eligibility criteria for the main study is in Section 5.

5. SUBJECT ELIGIBILITY (MAIN STUDY)

5.1. Inclusion Criteria

101) Age ≥ 18 years

102) Advanced cancer defined as relapsed or refractory disease after at least 1 line of therapy that included systemic chemotherapy and that is not amenable to definitive locoregional therapy

103) $HPV16^+$ tumor as confirmed by the central laboratory

104) HLA type is HLA-A*02:01^+ per local assessment

105) At least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 1) per computed tomography (CT) or magnetic resonance imaging (MRI) performed after the last line of anti-cancer therapy and within 28 days before enrollment

106) No evidence of central nervous system (CNS) disease by MRI or CT (if MRI is not feasible) of the brain performed within 28 days before enrollment
Note: Subjects with prior brain metastasis, which has been treated with definitive therapy (surgical resection or radiation therapy), are eligible provided that the definitive therapy was completed more than six months prior to screening

107) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

108) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time of enrollment (i.e., leukapheresis)

109) Toxicities due to prior therapy must be recovered to baseline or ≤ Grade 1, except for clinically non-significant toxicities, such as alopecia

110) Adequate bone marrow function (in absence of transfusion or growth factor support) as evidenced by:

a) Absolute neutrophil count (ANC) ≥ $1000/mm^3$

b) Platelet ≥ $100/mm^3$

c) Hemoglobin > 8 g/dL

111) Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by:

a) Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min (24-hour urine creatinine clearance is also acceptable)

b) Alanine transaminase/Aspartate aminotransferase (ALT/AST) ≤ 2.5 x upper limit normal (ULN) or ≤ 5 x ULN if documented liver metastases

c) Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's Syndrome in whom total bilirubin must be ≤ 3.0 mg/dL

d) Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion, as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings (For ejection fraction only, MUGA scan is also acceptable)

e) No clinically significant pleural effusion

f) Baseline oxygen saturation > 92% on room air

5.2. Exclusion Criteria

201) History of malignancy other than non-melanoma skin cancer, carcinoma in situ (e.g., cervix, bladder, breast), or low-grade prostate cancer for which watch-and-wait approach is standard of care, unless disease-free for at least 3 years prior to enrollment

202) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, cardiac arrhythmia requiring antiarrhythmic or procedure, or other clinically significant cardiac disease within 12 months before enrollment

203) History of stroke or transient ischemic attack (TIA) within 12 months before enrollment

204) History of symptomatic deep vein thrombosis (DVT) or pulmonary embolism within 6 months before enrollment, catheter associated thrombosis is not included as an exclusion criterion

205) Prior T-cell therapy, including those that target HPV; vaccines are not included as an exclusion criterion

206) Live vaccine ≤ 4 weeks prior to enrollment

207) Systemic corticosteroid therapy within 7 days before enrollment
Note: Topical and inhaled corticosteroids in standard doses and physiologic replacement for subjects with adrenal insufficiency are allowed. Any new doses ≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids are not allowed

208) History of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, CCI [redacted]

209) History of severe, immediate hypersensitivity reaction attributed to aminoglycosides

210) Presence of fungal, bacterial, viral, or other infection requiring anti-microbials for management

Note: Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite medical monitor

211) Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter)
Note: Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, as well as feeding tubes such as a G-tube are permitted

212) Primary immunodeficiency

213) History of autoimmune disease (e.g., Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years prior to enrollment. Immune-mediated toxicity due to immunotherapy for treatment of cancer is not exclusionary if a healthcare professional confirms complete resolution while off systemic immunosuppressive/systemic disease modifying agents with no evidence of recurrence for at least 6 months prior to enrollment, and treatment with systemic immunosuppressive/systemic disease modifying agents, with the exception of physiologic steroid replacement, is not required during study participation

214) Known history of infection with human immunodeficiency virus (HIV), hepatitis B (HBsAg positive), or hepatitis C (anti-HCV positive). A history of treated hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative polymerase chain reaction (qPCR) and/or nucleic acid testing.

215) Females who are pregnant as confirmed by a positive serum or urine pregnancy test or are breastfeeding
Note: Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

216) Subjects of both genders of childbearing potential who are not willing to practice birth control from the time of consent through 6 months after the completion of KITE-439

217) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

218) CCI [redacted]

6. STUDY TREATMENT

6.1. Leukapheresis

Leukapheresis refers to the procedure for collecting peripheral blood mononuclear cells (PBMCs) that are used to manufacture the subject-specific KITE-439.

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of KITE-439 (see Section 7.5.1). Leukapheresed cells obtained at participating centers will be shipped to the sponsor's manufacturing facility as described in the IPM.

Leukapheresis will be performed according to institutional operating procedures.

After a subject commences leukapheresis, the subject is considered enrolled in the study.

CCI [redacted]

6.3. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of KITE-439. Subjects will receive conditioning chemotherapy from Day –7 through Day –3. Modifications to the conditioning chemotherapy dose and/or schedule may be considered when in the interest of subject safety. Any consideration for changes in the conditioning chemotherapy must be discussed with the Kite medical monitor.

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted.

Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

See Section 7.5.3 for conditioning chemotherapy procedures.

If more than 4 weeks have elapsed from the time of the screening scan to the initiation of conditioning chemotherapy (Day –7), investigator may consider repeating CT or MRI scans before conditioning chemotherapy commences to establish a new baseline.

6.3.1. Fludarabine

Fludarabine phosphate (hereafter referred to as fludarabine) is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.3.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative that acts as an alkylating agent following conversion to active metabolites in the liver and has potent immunosuppressive activity. The serum half-life after IV administration ranges from 3 to 12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

CCI [redacted]

[redacted]

[redacted]

6.3.4. Rationale for Conditioning Chemotherapy Choice and Dose

Lymphodepletion eradicates cytokine sinks for the transferred cells, eliminates T regulatory cells, and enhances antigen presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine are an effective lymphodepleting regimen. Increasing intensity of conditioning chemotherapy has been shown to correlate with clinical response to adoptive cellular therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in pre-clinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific $CD8^+$ T cells {Gattinoni 2005}.

The NCI has successfully treated subjects with cyclophosphamide 60 mg/kg/day x 2 days along with fludarabine 25 mg/m^2/day x 5 days as conditioning in several clinical trials of TCR-transduced T cells {Morgan 2013, Robbins 2015} and tumor infiltrating lymphocytes {Dudley 2008, Stevanovic 2015}. In the NCI study utilizing the identical HPV-targeting vector (IND Number 016959), this regimen as well as a dose reduced regimen using cyclophosphamide 30 mg/kg/day x 2 days along with fludarabine 25 mg/m2/day x 5 days are being used. In the phase 2 portion, NCI has primarily used the 30 mg/kg/day dose of cyclophosphamide in the lymphodepleting regimen.

6.4. KITE-439

The IP for this study is KITE-439.

KITE-439 is supplied cryopreserved in cryostorage bag(s). The cryostorage bag(s) containing KITE-439 arrives frozen in a liquid nitrogen dry shipper. To assure viable live autologous cells are administered to the subject, the bag(s) must be stored in vapor phase of liquid nitrogen, and the product must remain frozen until the subject is ready for treatment. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

In exceptional cases, a KITE-439 product lot that does not meet certain release specification criteria may be administered to the clinical study subject, when necessary to avoid an immediate significant hazard to the subject and after consideration of alternative options including the product lot remanufacture. Relevant country regulations will be followed and notifications to concerned regulatory agencies and Institutional Review Board/Independent Ethics Committee (IRBs/IECs) will be performed as necessary per local requirements, in case such out-of-specification product lot is supplied and administered to the clinical study subject.

Refer to the IPM for details and instruction on storage, thawing, and administration of KITE-439.

In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of KITE-439 or any products that support the management of KITE-439 (e.g., cryostorage bags, subject ID labels) are identified, research staff should report the problem per the instructions in the IPM.

6.4.1. Rationale for KITE-439 Dose

In the NCI Phase I study, doses up to 100 x 10^9 T cells have been administered at the NCI in a study of E7 TCR T cells using the identical HPV16 E7 TCR, which will be used in this study. One DLT was observed in subject who was treated with 1 x 10^{11} total E7 TCR T cells in the dose escalation portion of this study, and the maximum planned dose was evaluated with no maximum tolerated dose (MTD) determined. CCI [redacted]

Additional rationale for the selected starting dose includes the following:

- TCR came from a human clone, which has undergone thymic selection, minimizing the likelihood of autoimmunity
- TCR binding specificity has not been altered by mutagenesis for which reason cross-reactivity against normal human proteins has not been introduced
- Vector has been tested for cross-reactivity against peptides identified in a homology search (Basic Local Alignment Search Tool [BLAST] search) of the entire human genome and against other HPV family members, and no cross-reactivity was detected

There have been no reports of accidental overdose of subjects. In case of accidental overdose, treatment should be supportive.

Tocilizumab or corticosteroid therapy may be considered if any dose is associated with severe toxicity (see Section 7.8 for additional guidance).

CCI [redacted]

CCI

[redacted]

6.8. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study.

Investigators may prescribe any concomitant therapies deemed necessary to provide adequate supportive care except those medications listed in Section 6.9.

The investigator is responsible for reporting all concomitant medications as follows in Table 3:

Table 3. Reporting Requirements for Concomitant Medications

Subjects who are pre-screen or screen-fails	Subjects who are enrolled, but do not receive KITE-439 infusion	Subjects who are enrolled and receive KITE-439 infusion
Concomitant therapies related to serious adverse event(s) will be recorded from the date of the pre-screening informed consent or screening informed consent through 30 days after the last study-specific pre-screening or screening procedure, respectively.	Concomitant therapies will be recorded from the date of the informed consent until 30 days after the last study-specific procedure has occurred (e.g., leukapheresis, conditioning chemotherapy) or until the initiation of new anti-cancer therapy, whichever occurs first.	• Concomitant therapies including medications, intubation, dialysis, oxygen, and blood products will be recorded from the date of the informed consent until 3 months after completing treatment with KITE-439. • After this 3-month follow-up period, targeted concomitant therapies will be recorded for either 24 months after KITE-439 infusion or until disease progression, whichever occurs first. — Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

Specific concomitant therapy collection requirements and instructions are included in the case report form (CRF) completion guidelines.

See Section 9.2 and Section 9.4 for targeted AE and targeted SAE reporting requirements.

6.9. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs (with the exception of physiologic steroid replacement) must be avoided for at least 7 days before leukapheresis and at least 7 days before KITE-439 administration.

Corticosteroids and other immunosuppressive drugs (with the exception of physiologic steroid replacement) should also be avoided for at least 3 months after KITE-439 administration, unless used to manage KITE-439-related toxicities or discussed with the Kite medical monitor (see Section 7.8).

Treatment doses of anticoagulants (for example, low molecular weight heparin [LMWH] or coumadin for DVT) are not permitted until after platelet count has normalized after conditioning

chemotherapy and KITE-439 infusion, unless to treat an acute event that occurs any time after the subject has already initiated conditioning chemotherapy.

Treatment for the subject's cancer, such as chemotherapy, immunotherapy, targeted agents, radiation, and high-dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression after KITE-439 infusion. If permissibility of a specific medication/treatment is in question, contact the Kite medical monitor.

6.10. Subsequent Anti-cancer Therapy

Subsequent therapy refers to treatment administered after KITE-439 that is necessary to treat a subject's disease.

Subsequent therapy administered after KITE-439 that is necessary to treat a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, stem cell transplant, or radiation therapy, will be recorded for all subjects until one of the following happens: the subject transitions to the KT-US-982-5968 LTFU study, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled, but do not receive KITE-439 infusion, any additional anti-cancer therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow up, withdraws consent, or dies.

6.11. Neurological Assessments

A neurological consultation will be performed on the first day of conditioning chemotherapy or within 3 days prior to conditioning chemotherapy (Days –10, –9, –8, or –7). This consultation will be performed by a trained and licensed neurologist and will serve as a baseline for subsequent evaluation should the subject require additional neurological consultation due to adverse event(s).

In addition, the subject will complete a standardized assessment called the Mini-Mental Status Exam (MMSE) standard version 2.0 blue form. The (MMSE) will be completed at baseline (Day –7) during the baseline neurological consultation and then once daily from Day 0 through Day 7 and on Day 14.

For new onset of neurologic symptoms suspected to be related to KITE-439, refer to Section 7.8.

7. STUDY PROCEDURES

Research staff should refer to the SOA in Section 7.11 for an outline of the procedures required. Additional information related to a few study assessments/procedures is described below.

The visit schedule is calculated from KITE-439 infusion on Day 0.

Refer to the CRF completion guidelines for data collection requirements and best practices for documentation of study procedures.

7.1. Laboratory Assessments

7.1.1. Local and Central Lab Analysis

Assessments listed in Table 4 will be performed at the local or central laboratory at the time points indicated in the SOA.

Table 4. Clinical Laboratory Parameters

Local Lab			Central Lab[f]
Serum Chemistries	**Hematology**	**Other**	
Albumin ALT/GPT ALP AST/GOP Bicarbonate total Bilirubin total[a] BUN or urea[a] Calcium total Chloride Creatinine Glucose LDH Magnesium total Phosphorus Potassium Sodium Uric acid	CBC with differential[b]	Urine toxicology panel[c] Viral testing[d] HLA-A*02:01 typing CRP Pregnancy test (urine or serum)[e] Recommended: • Ferritin • Lactate	HPV16 genotyping Anti-KITE-439 antibodies Cytokines PBMCs Archival and fresh tumor tissue

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; GOP, serum glutamic-oxaloacetic transaminase; GPT, serum glutamic-pyruvic transaminase; LDH, lactate dehydrogenase; PBMC, peripheral blood mononuclear cell; HLA, human leukocyte antigen.

a. If BUN test cannot be analyzed by the local lab, urea should be analyzed. If total bilirubin is elevated, then direct bilirubin should be obtained.
b. Must include white blood cell (WBC), neutrophils or ANC, lymphocytes or ALC, hemoglobin, platelets, except in circumstances where institutional guideline permits for differential to not routinely be performed when ordered (e.g., WBC count is too low)
c. Standard urine toxicology panel as per institutional guidelines
d. Serology tests for European sites (serum): Serology tests (i.e., human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis) will be done per institutional guidelines and regional regulations. Testing may be done within the 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/enrollment.
e. Pregnancy test (serum or urine): For European sites, the test will be completed within 7 days before both leukapheresis and lymphodepleting chemotherapy for women of childbearing potential.
f. Refer to the central laboratory manual (provided separately) for details on collection, processing, and shipment of the central laboratory samples.

7.1.2. Central Laboratory Analyses

Clinical biospecimens which include tumor tissue, blood and blood-derived samples (see Table 4) will be sent from clinical study centers to the central laboratory for sample processing, accessioning, and distribution to specialty laboratories or the sponsor for analysis. Apheresis and product samples will be retained at Kite per sponsor guidance.

- Samples will be obtained at the times indicated in the SOA. Complete instructions regarding sample submission to central laboratories will be provided in the central laboratory manual.
- Samples to be collected by study sites include the following:
  - Tumor tissue biopsy for HPV testing and analyses of tissue biomarkers (see Section 7.6 for details)
  - Blood for pharmacokinetics (PKs; levels of transduced T cells), replication competent retrovirus (RCR testing), pharmacokinetics, and T-cell immunogenicity Serum for pharmacodynamics (cytokine levels) and B-cell immunogenicity testing (development of antibodies against KITE-439).

CCI [redacted] Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who, in turn, can contact the central laboratory. The investigator should provide the sponsor with the study and subject number so that the sample can be located and destroyed. For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor, and any data that may be generated from these samples will be entered in the study database.

Multiple specialty laboratories may be employed for specific analyses, such as baseline/archival tumor assessments, confirmation of diagnosis, pharmacokinetics, pharmacodynamics, and special safety analyses (immunogenicity and RCR testing). Refer to the central laboratory manual for instructions regarding submitting such samples to the appropriate laboratory.

CCI [redacted]

CCI [redacted]

7.1.2.2. Pharmacokinetics and Pharmacodynamics

Pharmacokinetic (PK) and pharmacodynamic analysis will be performed on blood (levels of transduced T cells) or serum (cytokines) at the intervals outlined in the SOA to evaluate predictive markers for the efficacy and safety of KITE-439.

Cerebrospinal fluid (CSF) draws and additional subject samples (e.g., pleural fluid) may be obtained from subjects who develop Grade ≥ 2 neurologic events for evaluation of inflammatory cytokine and chemokine levels and presence of transduced T cells. As applicable, lymphocyte populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of KITE-439.

7.1.2.3. Product Characteristics

Samples of apheresis material or final product will be retained and tested by the sponsor or specialty laboratory for the purpose of understanding the mechanism of action and safety profile of KITE-439.

7.1.2.4. Immunogenicity

Immunogenicity will be evaluated utilizing a flow cytometry-based assay to detect antibodies present in serum that react against the KITE-439.

Blood draws for determination of the presence of anti-KITE-439 antibodies will be performed at intervals outlined in the SOA or as clinically indicated.

The flow cytometric assay is developed and qualified to measure subject serum samples for the presence of antibodies that recognize the HPV16 E7 TCR expressed on cells transduced with the same E7 TCR transgene used to make KITE-439. Analysis of PK profiles and clinical outcomes in subjects with a positive anti-E7 TCR antibody result at baseline or after treatment with KITE-439 will also be conducted to determine the impact of anti-TCR antibodies on the efficacy and safety of KITE-439 therapy.

Immunogenicity also will be addressed by a manual review of AE terms indicative of infusion -related events and anaphylactic reactions among subjects who test positive for these antibodies.

7.1.2.5. RCR Testing

KITE-439 comprises T cells transduced with a γ-retroviral vector; hence, there is a theoretical risk for RCR developing in exposed subjects. Additional information is provided in the IB. The

timing of blood draws for determination of the presence of RCR is specified in the SOA or may be done as clinically indicated.

RCR testing will occur at baseline, Month 3 of the main study, Month 6, and Month 12 of the LTFU study. Thereafter, samples will be collected yearly and held for up to 15 years. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for up to 15 years or as clinically indicated.

If a subject dies or develops a secondary malignancy during the study or follow-up and RCR is suspected, every effort should be made to obtain a blood sample to assay for RCR and vector elements. In the case of a solid tumor new/secondary malignancy, every effort will be made to obtain a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for presence of vector elements.

Samples for RCR testing are collected as part of the blood draw for PBMCs as noted in the SOA (Section 7.11).

7.2. Informed Consent

Screening to determine eligibility for enrollment is a 2-step process. There is a pre-screening portion and a screening portion. These are further explained in Section 7.2.1 and Section 7.2.2. Both pre-screening and screening require a separate consent.

The consent process and the subject's agreement or refusal to participate are to be documented in the subject's medical records. If the subject agrees to participate, the most recent (IRB/IEC) approved informed consent form(s) (ICF) is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

The ICF should be signed prior to any study-specific activity or procedure being performed. The original signed ICF(s) will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF(s) provided to the subject.

Investigative sites will maintain a log of all pre-screened and screened subjects who were reviewed and evaluated for participation in the respective portions of the study. Information collected on the pre-screening and screening log should include limited information, such as the date of pre-screening, date the subject was enrolled, or the reason for why the subject failed pre-screening. These data will be entered into the CRF.

7.2.1. Informed Consent to Prescreen

Per the eligibility criteria, subjects are required to be HLA-A*02:01^{+} and have HPV16^{+} tumors. Because only a portion of cancer patients will meet these criteria, subjects will be pre-screened for HLA-A*02:01^{+} and HPV16 virus type. This approach to pre-screening will ensure that subjects who do not qualify based on HLA type and/or HPV virus type are not subjected to other screening procedures unnecessarily.

Before a subject consents to pre-screening, the investigator is responsible for providing an overview of the main study and the purpose for pre-screening as it relates to the main study. Subjects who are not interested in potentially participating in the main portion of the study in the future should not be pre-screened. Additionally, investigators should perform a preliminary review of the subject's medical history to ensure the subject meets the known eligibility criteria.

After the subject has consented to pre-screening, the subject will be assigned a unique subject ID number before any study-specific procedures or activities are initiated. This subject ID number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. The subject ID number must remain constant throughout the entire clinical study; it must not be changed after enrollment or if the subject is rescreened.

HLA typing will be assessed locally, and HPV typing will be assessed by the central laboratory. Subjects confirmed by the local laboratory to be HLA-A*02:01$^+$ and by the central laboratory to have HPV16$^+$ tumor may be considered for screening in the main portion of the study (see Section 7.2.2).

Subjects who are pre-screened are not obligated to participate in the main study.

Subjects will remain in the pre-screening period from the time the pre-screening ICF is signed until such time that the subject is screened (i.e., signs the ICF for the main study), withdraws consent before screening, or it is determined that the subject is a pre-screen failure (e.g., does not meet the criteria for HLA typing and/or HPV genotyping).

See the SOA for a list of pre-screening procedures.

7.2.2. Informed Consent to Participate in the Main Study

Subjects who are HLA-A*02:01$^+$ per the local laboratory and HPV16$^+$ per the central laboratory may be considered for participation in the main portion of the study.

Before a subject's participation in the study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and the potential risks. Subjects should sign the most current IRB/IEC-approved ICF prior to any study-specific activity or procedure is performed.

Subjects will remain in the screening period from the time the screening informed consent is signed until such time that the subject is considered eligible and enrolls in the trial, withdraws consent before enrollment, or it is determined that the subject is a screen failure (i.e., does not meet the eligibility criteria per Section 5).

CCI [redacted]

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC-approved ICF if relevant to their participation in the study.

See Section 7.4 for screening procedures.

7.3. Pre-screening

See Section 7.2.1 for details regarding the pre-screening informed consent process and the SOA (Section 7.11) for a list of pre-screening procedures.

7.4. Screening

See Section 7.2.2 for details regarding the screening informed consent process and the SOA (Section 7.11) for a list of screening procedures.

Unless otherwise specified, all screening procedures are to be completed within 28 days before enrollment.

Procedures that are part of routine care/practice are not considered study-specific procedures and may be performed prior to obtaining consent and used to confirm eligibility provided they are within the screening windows specified in the SOA (Section 7.11).

Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled into the study.

If, at any time prior to enrollment, the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

7.4.1. Re-screening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period, will be permitted to rescreen one time. If additional rescreens are needed, the Kite medical monitor should be contacted to discuss the options. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria need to be repeated; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs, or leukapheresis is delayed, more than 28 days from the signing of the original informed consent, subjects must be re-consented and repeat all screening procedures/assessments.

7.5. Cell Collection and Study Treatment Schedule and Administration

Dose calculation based on actual or practical body weight is as follows:

- Actual body weight is to be used for KITE-439 CCI . For subjects weighing greater than 100 kg, each dose of TCR-transduced T cells will be calculated based on a maximum weight of 100 kg. CCI
- Actual body weight is to be used for conditioning chemotherapy CCI when subject's body mass index (BMI) is ≤ 35.
- Practical body weight (see Appendix 2) is to be used for conditioning chemotherapy CCI when subjects BMI is > 35.

7.5.1. Enrollment/Leukapheresis

7.5.1.1. Requirements for Initiating Leukapheresis

Before leukapheresis commences, the following criteria must be met:

- Subjects must remain eligible per the eligibility criteria outlined in Section 5 prior to the start of leukapheresis. Expected normal variation is allowed for laboratory values (±5%).
- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and results are outside the eligibility criteria listed in Section 5, contact the medical monitor prior to proceeding with leukapheresis.
- No evidence or suspicion of an infection
- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis; physiologic replacement dose is an exception.
- If criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed more than 5 days after eligibility confirmation, baseline complete blood count (CBC) with differential and chemistry panel must be repeated. If results are outside the eligibility criteria listed in Section 5, contact the Kite medical monitor prior to proceeding with leukapheresis.

The leukapheresis visit should occur within approximately 5 days of eligibility confirmation.

Mononuclear cells will be obtained by leukapheresis CCI [redacted]. The leukapheresed cells are then packaged for expedited shipment to the cell processing facility (CPF) as described in the IPM.

After a subject commences leukapheresis, the subject is considered enrolled in the study.

Refer to the SOA (Section 7.11) for a listing of study procedures to be completed on the leukapheresis collection day.

CCI [redacted]

[redacted]

7.5.3. Conditioning Chemotherapy and KITE-439 Infusion

Administration of KITE-439 T cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion.

Signs, symptoms or abnormal laboratory results attributed to the malignancy (e.g. "tumor fever," elevated C-reactive protein [CRP]) are diagnoses of exclusion that require a documented workup to establish.

Conditioning chemotherapy and KITE-439 infusion should be initiated only once it is reasonably assured that cell infusion can safely proceed. Any consideration for changes in the dose for the conditioning chemotherapy should be discussed with the Kite medical monitor.

Refer to Section 7.5.5 for Requirements to Work-up Potential Infectious and/or Inflammatory States.

7.5.3.1. Conditioning Chemotherapy Period

7.5.3.1.1. Requirements for Initiating Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the work-up listed in Section 7.5.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours before conditioning chemotherapy
- CRP > 100 mg/L any time between enrollment to start of conditioning chemotherapy
- WBC count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy (e.g., WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- All eligibility criteria of the protocol must be met. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy. Expected normal variation is allowed for laboratory values noted in the eligibility criteria (±5%)
- Complete history and physical exam including head, eye, ear, nose, and throat (HEENT), and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of anti-microbials is allowed)
- Treatment course of any anti-microbials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials

- If a subject is confirmed to have an infectious process for which anti-microbials are not available (e.g., viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable)

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (e.g., bacterial, viral serologies, polymerase chain reaction [PCR], stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (e.g., fungal infection), adequate time must be allowed for cultures to become positive

Once the above criteria are met, then the subject can proceed with conditioning chemotherapy.

7.5.3.1.2. Conditioning Chemotherapy Administration (Day –7 through Day –3 prior to KITE-439 infusion)

The 5-day conditioning chemotherapy regimen containing cyclophosphamide and fludarabine may be administered in an out-patient setting. Following the 5-day conditioning chemotherapy regimen, subjects will have a two-day rest period prior to KITE-439 infusion. Conditioning chemotherapy can be administered as inpatient per investigator's discretion.

Before conditioning chemotherapy commences, the criteria outlined in Section 7.5.3.1.1 must be met.

Provided the criteria for conditioning chemotherapy are met, the conditioning chemotherapy regimen will be administered in accordance with the following daily dosing instructions.

Cyclophosphamide CCI [redacted]

Cyclophosphamide: CCI [redacted] IV administered on CCI [redacted] infused over 60 minutes. See Section 7.5 for practical versus actual body weight-based dose calculation.

IV hydration recommendations:

- 0.9% NaCl with 10 mEq/L of KCl recommended at 150 ml/hour to start 2 hours prior to each cyclophosphamide dose and continue for 6 hours after the completion of each dose. The fluid may continue during the cyclophosphamide infusion.

- It is recommended that urinary output and body weight be monitored starting the first hour after cyclophosphamide infusion and for at least 6 hours after cyclophosphamide. If urine output is less than 200 ml total during the first 2 hourly voids or body weight is > 2 kg over pre-cyclophosphamide value, consider furosemide CCI [redacted] IV as a one-time dose (or equivalent diuretic). If any subsequent 2 hourly voids are also less than 200 ml, consider additional diuretic administration.

- Serum potassium should be monitored and treated as indicated following administration of diuretic. Infusions may be slowed as medically indicated.

CCI [redacted]

Fludarabine (Day –7 through Day –3)

Fludarabine: CCI [redacted] IV administered on Day –7, Day –6, Day –5, Day –4, and Day –3. Each infusion is given over 30 minutes. CCI [redacted] Infusions may be slowed as medically indicated.

7.5.4. KITE-439 Treatment Period

7.5.4.1.1. Requirements for Initiating KITE-439 Infusion

If any of the following criteria are met prior to the initiation of KITE-439 infusion, then the work-up listed in Section 7.5.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of KITE-439 infusion
- CRP > 100 mg/L any time between enrollment to start of KITE-439 infusion
- WBC count or WBC differential concerning for infectious process between enrollment to start of KITE-439 infusion (e.g., WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- All eligibility criteria of the protocol must be met. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of KITE-439 infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with KITE-439 infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy). Expected normal variation is allowed for laboratory values noted in the eligibility criteria (±5%).
- Complete history and physical exam including HEENT, and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.

- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before KITE-439 (prophylactic use of anti-microbials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (e.g., viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable).

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (e.g., bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (e.g., fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with administration of KITE-439.

If the KITE-439 infusion is delayed > 2 weeks, consideration for repeat conditioning chemotherapy must be made in consultation with a Kite medical monitor.

7.5.4.1.2. Hospitalization for KITE-439 Infusion

Subjects will remain hospitalized for at least 7 days after the KITE-439 infusion, unless otherwise required by country regulatory agencies (refer to Appendix 4), for daily monitoring of signs and symptoms of CRS and neurologic events. In addition, the assessments described in Section 7.11 and the SOA (Table 5) will be performed during this period.

Subjects should not be discharged from the hospital until all KITE-439-related nonhematological toxicities resolve to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (e.g., renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing KITE-439-related fever, hypotension, hypoxia, or ongoing neurologic events > Grade 1, or if deemed necessary by the investigator.

Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following KITE-439 infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

7.5.4.1.3. KITE-439 Premedication Dosing

The following pre KITE-439 infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor.

- Acetaminophen 650 mg PO or equivalent
- Diphenhydramine 12.5 mg administered either PO or via IV or equivalent

7.5.4.1.4. KITE-439 Administration Day 0

KITE-439 will be administered at one of the dose levels as outlined in Section 3.1.1, Table 2.

Refer to the SOA (Section 7.11) for a listing of study procedures to be completed during the KITE-439 treatment period.

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of KITE-439. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of KITE-439 are outlined in the IPM. It is recommended that vital signs are recorded before KITE-439 infusion and then routinely as clinically indicated (e.g., fever ≥ 38.3°C).

The IPM must be reviewed prior to administration of KITE-439.

Research sites should follow institutional guidelines for the infusion of cell products.

7.5.5. Requirements to Work-Up Potential Infectious and/or Inflammatory States Prior to KITE-439 Infusion

In the absence of an identified source of infection (e.g., line infection, pneumonia on chest x-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or KITE-439 consists of:

- Call Kite medical monitor
- Infectious disease service consultation (if applicable)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed
- The following must be performed (prior to the initiation of anti-microbials if clinically feasible):
    - Blood cultures (aerobic and anaerobic x2 bottles each) and urinalysis and urine culture. Deep/induced sputum culture if clinically indicated

- All indwelling lines, such as central venous catheters, should be examined for any signs of infection, and additional cultures should be drawn from the line
- Nasopharyngeal-throat (NPT) swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
- Collection of fungal cultures and markers as appropriate (e.g., galactomannan, fungitell)
- Collection of appropriate serum viral studies (e.g., cytomegalovirus [CMV])

- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.
- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

Prior to proceeding with conditioning chemotherapy and/or KITE-439 infusion, the above workup must not suggest the presence of an active infection, and all requirements for conditioning chemotherapy and/or KITE-439 infusion must be satisfied. If the KITE-439 infusion is delayed > 2 weeks, consideration for repeat conditioning chemotherapy must be made in consultation with a Kite medical monitor.

If the above workup was triggered due to CRP > 100 mg/L, CRP should be repeated, and if CRP continues to increase significantly, evaluation should be performed for any other potential infectious or inflammatory condition not previously evaluated.

CCI [redacted]

7.6. Tumor Tissue Biopsy

Tumor tissue will be collected at the following time points during the course of the study:

- At the time of pre-screening, archival tumor tissue will be submitted to the central laboratory for HPV genotyping. If archival tumor tissue is not available, then the subject will have a fresh tumor tissue biopsy performed during pre-screening, and a portion of that fresh tumor tissue will be submitted to the central laboratory for HPV genotyping.

[redacted]

- Additionally, any time a tumor tissue biopsy is performed as part of standard of care, a portion of the fresh tumor tissue (e.g., formalin-fixed paraffin embedded [FFPE] block or unstained slides) should be submitted to the central laboratory. An attempt should be made to biopsy the same lesion(s) at all time points, if medically feasible.

7.7. Disease Response Assessment

Assessment of disease response will be determined by the investigator in Phase 1A and by an independent central reviewer in Phase 1B based on modified RECIST v1.1 {Eisenhauer 2009}. See Appendix 1 for additional information.

Disease assessments will be performed at baseline and after KITE-439 infusion as outlined in the SOAs (Section 7.11). CT (or positron emission tomography-computed tomography [PET-CT]) scans of the neck (if applicable), chest, abdomen, and pelvis, along with the appropriate imaging of all other sites of disease, are required. MRI can be used in subjects with contraindication to CT scan and/or CT with contrast. The same imaging modality should be used at baseline and throughout the course of the study.

[redacted]

Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA (Section 7.11).

7.8. Toxicity Management

7.8.1. KITE-439

Refer to the Guidelines for Management of Important Risks within the current KITE-439 IB for details regarding potential KITE-439 toxicity events and management guidance (e.g., CRS, tumor lysis syndrome). Administration of tocilizumab is recommended for the treatment of CRS per the IB; therefore it is recommended that sites have tocilizumab readily available as needed.

As more subjects are exposed and the safety experience with KITE-439 increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the KITE-439 IB for guidance regarding managing KITE-439 related toxicities.

CCI [redacted]

[redacted]

7.9. Post-treatment Assessment Period Procedures

After completing KITE-439 infusion, all subjects will be followed in the post-treatment follow-up visits and complete the study procedures and assessments per the SOA.

If the subject progresses before Month 3, the subject will proceed directly to the Month 3 visit, complete the Month 3 visit, and then be followed in the LTFU period of the study.

Following the initial hospitalization for the KITE-439 infusion, if the subject is hospitalized with any KITE-439 related adverse event, the following labs will be collected:

- PBMCs on day of admission, then weekly, and on day of discharge
- Cytokine levels on day of admission, then weekly, and on day of discharge

7.10. Long-term Follow-up Period Procedures

All enrolled subjects will be followed in the LTFU period for safety, survival and disease status, if applicable, for up to 15 years. Subjects will begin the LTFU period after they complete the post-treatment assessment period (whether they have responded to treatment or went straight to the Month 3 visit due to disease progression). Refer to the SOA for a listing of study procedures and disease assessments to be completed during the LTFU period.

Subjects who receive infusion of KITE-439, but who experience disease progression, will be followed in the LTFU period and undergo the following assessments at the time points outlined in the SOA:

- Survival status – subjects may be contacted by telephone to confirm survival status
- SAE reporting (see Section 9.5)
- Concomitant medications documentation (see Section 6.8)
- Subsequent therapy for disease (see Section 6.10)
- Blood draw for:
  - PBMCs
  - If applicable, anti-KITE-439 antibodies (see SOA, Section 7.11)

The following procedures/assessments will be completed for subjects who are enrolled, but do not receive KITE-439, at the time points outlined in the SOA, unless otherwise noted:

- Disease assessment per standard of care
- Survival status – subjects may be contacted by telephone to confirm survival status
- AE/SAE reporting (see Section 9.2 and Section 9.5)
- Concomitant medications documentation (see Section 6.8)
- Subsequent therapy for disease (see Section 6.10)

Subjects may also be contacted by telephone to confirm survival status and subsequent anti-cancer therapy use. If the subject fails to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts, using both the telephone and either mail or e-mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, then the subject will be considered lost to follow-up, and no additional contact will be required. However, sites will be required to continue to provide survival status as permitted by local regulations.

7.11. Schedule of Assessments

Table 5. Schedule of Assessments (Pre-screening through Post-treatment follow-up)

Procedures	Pre-screening[a]	Screening[c]	Leukapheresis /Enrollment	CCI	Conditioning Chemotherapy[i]			IP[j, v]	Post-treatment Follow-up (each visit calculated from Day 0)										
		≤ 28 days before enrollment			Day											Week (± 3 d)		Month (± 1 w)	
					D-7	D-6	D-5 to D-3	D0	D1	D2	D3	D4	D5	D6	D7	W2	W4	M2	M3[y]
Consent (pre-screen and screen)	x	x																	
Medical history[b]	x	x																	
Physical exam; height and ECOG (scr only)[d]		x			x			x								x	x	x	x
Vital signs including BP, HR, O_2, temp		x	x		x	x	x	x	x		x		x		x	x	x	x	x
Weight		x	x					x											
Neurology consultation[u]					x														
MMSE[u]					x			x	x	x	x	x	x	x	x	x			
ECG		x																	
LVEF and PE assessment by ECHO[f]		x																	
Imaging																			
Brain MRI or CT (if MRI is not feasible)		x																	
CT or MRI neck (if appl), chest, abdomen, pelvis and Disease assessment per RECIST[e]		x															x		x
Local laboratory samples																			
HLA-A*02:01 typing	x																		
Chemistry panel		x	x		x	x	*x*	x	x		x		x		x	x	x	x	x
CBC w/differential[m]		x	x		x	x	x	x	x		x		x		x	x	x	x	x

Procedures	Pre-screening[a]	Screening[c]	Leukapheresis /Enrollment	CCI	Conditioning Chemotherapy[i]			IP[j, v]	Post-treatment Follow-up (each visit calculated from Day 0)										
		≤ 28 days before enrollment			Day											Week (± 3 d)		Month (± 1 w)	
					D-7	D-6	D-5 to D-3	D0	D1	D2	D3	D4	D5	D6	D7	W2	W4	M2	M3[y]
Pregnancy test (urine or serum)[x]		x																	x
Serology for European sites (serum)[w]		x[w]	x[w]																
Urine toxicology panel		x																	
CRP[r]			x					x											
Central laboratory samples																			
Tumor biopsy[g]	x	Opt													Opt D7–D14				Opt M3-M6
Antibody[m]					x												x		x
PBMC[s]					x			x	x		x		x		x	x	x	x	x
Cytokine[s, t]					x			x	x		x		x		x	x	x		
CSF[r]								x[r]											
Study treatment																			
Leukapheresis			x																
CCI																			
Cyclophosphamide[i, l]					x	x													
Fludarabine[i, l]					x	x	x												
KITE-439 infusion[j, l, v]								x											
CCI											x								
SAE/AE reporting[n]	x	x																	
Con med and subsequent therapy reporting[o, p]		x																	

Table 6 Schedule of Assessments (LTFU)

	Long-term Follow-up Period[zz] (Each visit calculated from Day 0)												
	Month												
	6	9	12	15	18	24	30	36	42	48	54	60	Month 72, then annually through Year 15
Procedure	(± 2 weeks)					(± 1 month)							
Physical exam	x	x	x	x	x	x							
Vitals including BP, HR, O_2, temp	x	x	x	x	x	x							
CT or MRI neck (if appl), chest, abdomen, pelvis and Disease assessment per RECIST[e]	x	x	x	x	x	x	x – per SOC						
Local laboratory samples													
Chemistry	x	x	x	x	x	x							
CBC w/differential[m]	x	x	x	x	x	x							
Central laboratory samples													
CCI [redacted]	[redacted]												
Antibody[m, z]	x												
PBMC[s, z]	x		x			x		x		x		x	x
Targeted AE/SAE reporting[n]	x	x	x	x	x	x	x	x	x	x	x	x	x
Targeted concomitant medication[o]	x	x	x	x	x	x							
KITE-439-related SAEs and deaths[n]	x												
Subsequent therapy reporting[p, z]	x	x	x	x	x	x	x	x	x	x	x	x	x
Survival status telephone calls[q, z]	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: IP, investigational product, KITE-439; CCI [redacted]; ECOG, Eastern Cooperative Oncology Group; scr, screen; BP, blood pressure; HR, heart rate; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; PE, pulmonary embolism; ECHO, echocardiogram; CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors; CCI [redacted] CRP, C-reactive protein; PBMC, peripheral blood mononuclear cell; SAE, serious adverse event; AE, adverse event; Con, concomitant; CBC, complete blood count; temp, temperature; HLA, human leukocyte antigen; CCI [redacted]; CSF, cerebrospinal fluid; SOC, standard of care; M, month; D, day; MMSE, Mini-mental status exam; LTFU, Long-Term-follow-up; SAE, Significant Adverse Event

Schedule of Assessment Footnotes

a **Pre-screening for HLA typing and HPV genotyping (Section 7.2.1):** Before subjects consent to pre-screening, the investigators should perform a preliminary review of the subjects' medical history to ensure they meet the known eligibility criteria.

b **Medical history:** Demographic information (e.g., sex, year of birth, race, ethnicity, country of enrollment) about the subject will be collected as allowed per country, local regulations, and guidelines as applicable; these data will be entered into the CRF. For patients transitioning to LTFU study (KT-US-982-5968), medical history also includes AEs/SAEs that are ongoing at the time of completion of KT-US-478-0401.

c **Screening for the main study (Section 7.2.2 and Section 7.4):** All screening procedures should be performed within 28 days before enrollment (leukapheresis). Procedures that are part of routine care/practice are not considered study-specific procedures and may be performed prior to obtaining consent and used to confirm eligibility provided they are within the screening windows specified in the SOA.

d **Physical exam:** Per the Section 7.5.3.1.1 and Section 7.5.4.1.1, a complete history and physical exam including HEENT, and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation prior to the administration of conditioning chemotherapy and KITE-439 infusion. A physical exam will be performed CCI [redacted] before the start of conditioning chemotherapy, and after conditioning chemotherapy and before the start of KITE-439 infusion to confirm no evidence of infection/inflammation.

e **CT/MRI scans (Section 7.7 and Appendix 1):** A CT or MRI scan (with contrast and appropriate slice thickness) of the neck (if applicable), chest, abdomen, pelvis, and all other sites of disease should be performed per the SOA. The baseline scans should be performed: 1) as close to enrollment as possible, 2) must be performed after the last line of therapy and ≤ 28 days before enrollment, 3) If the subject receives any anti-cancer therapy between screening and conditioning chemotherapy, then the CT or MRI scans must be repeated after the anti-cancer therapy and before commencing conditioning chemotherapy to establish a new baseline. Lastly, CT or MRI scans may be repeated to establish a new baseline if conditioning chemotherapy (Day –7) does not commence within 4 weeks of the screening scans. After Month 24, CT or MRI scans will be performed per standard of care until progressive disease is confirmed per RECIST. The same modality used at screening should be used for all subsequent assessments, **RECIST (Appendix 1):** Disease assessments will be performed by the investigator based on modified RECIST v1.1 guidelines. For a subject to be assigned an overall best response of stable disease (SD) or better, the response must be documented ≥ 28 days after the KITE-439 infusion. A response of complete response (CR) or partial response (PR) must be confirmed with repeat scans performed no less than 28 days after the criteria for response were first met.

f **ECHO:** If the last chemotherapy regimen the subject received is not considered cardiotoxic, then an ECHO performed within 28 days prior to signing the consent may be used for eligibility. If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO performed within 28 days prior to enrollment must be used for confirmation of eligibility

g **Tumor tissue biopsy (Section 7.6):** Tumor tissue will be collected at the following time points: 1) At the time of pre-screening, archival tumor tissue will be submitted to the central laboratory for HPV genotyping. If archival tumor tissue is not available, then the subject will have a tumor tissue biopsy performed during pre-screening, and a portion of that fresh tumor tissue will be submitted to the central laboratory for HPV genotyping. CCI [redacted] 3) Additionally, any time a tumor tissue biopsy is performed as part of standard of care, a portion of the fresh tumor tissue should be submitted to the central laboratory. CCI [redacted]. Please refer to the central laboratory manual for details.

[redacted]

i **Conditioning chemotherapy requirements (Section 7.5.3.1.1):** Subjects must meet the requirements listed in section 7.5.3.1.1 before conditioning chemotherapy commences.

j **KITE-439 infusion requirements (Section 7.5.4.1.1):** Subjects must meet the requirements listed in section 7.5.4.1.1 before KITE-439 infusion commences. During the hospitalization for KITE-439, it is recommended that vital signs are recorded before KTE-439 infusion and then routinely as clinically indicated (e.g., fever ≥ 38.3°C).

[redacted]

l **Weight based dose calculation:** See Section 7.5 for practical versus actual body weight-based dose calculation. See Appendix 2 for practical body weight formula.

m **CBC w/differentials and antibody:** CBC: 5-part is preferred, but 3-part is acceptable. At Months 15, 18, and 24, CBC w/differential should be collected if standard of care. Antibody: For serum samples that demonstrate anti-KITE-439 or HABA antibodies at the Month 3 visit over baseline values, attempts will be made to obtain and test

additional serum samples approximately every 3 months until the antibody levels return to baseline, become negative, or up to 1 year after the KITE-439 treatment, whichever occurs first. Site will be notified if the Month 3 antibody sample tests positive.

n **AE/SAE reporting (Section 9.2 and Section 9.5):** Procedure related SAE reporting for pre-screened subjects will begin at the time the pre-screening consent form is signed and will continue until 30 days after the last pre-screening procedure is completed. If the subject is screened for the main study within 30 days after signing the pre-screening consent, then SAE reporting will continue (Section 9.4).For enrolled subjects, after 3 months, only serious targeted adverse events observed by the investigator or reported by the subject will be reported for 15 years after KITE-439 infusion or until enrollment into the LTFU study. SAEs are reported within 24 hours using the SAE Report Form and in the CRF. Targeted adverse events include serious neurological, serious hematological, serious Kite product-related infections, GVHD, serious autoimmune disorders, and new/secondary malignancies. In addition to the above SAE reporting requirements, anytime a KITE-439 related SAE occurs it will be reported within 24 hours using the SAE report form and in the CRF. All deaths that occur from ICF through end of study will be reported in the CRF.

o **Concomitant medications reporting (Section 6.8):** After 3 months of follow-up, only targeted concomitant medications will be collected for 24 months after KITE-439 infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

p **Subsequent therapy for disease (Section 6.10):** Documentation of subsequent therapy for the subject's disease will continue to be documented while the subject remains on study. Subjects may be contacted by telephone.

q **Survival Status (Section 7.10):** Subjects may be contacted by telephone to confirm survival status. Publicly available data (death records) can be included after withdrawal of consent or if lost to follow-up if local regulations permit.

r **Recommended labs related to CRS:**

- Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regards to CRS. It is, therefore, recommended that CRP, ferritin, and LDH (if LDH is elevated at baseline) be monitored daily starting at Day 0. Daily CRP should be monitored for at least 7 days after KITE-439 infusion or until resolution of any CRS, whichever is later. In addition, lactate should be monitored as clinically indicated. Reference Table 4 for required local lab assessments.
- CSF central lab draws and additional subject samples (e.g., pleural fluid) may be obtained from subjects who develop Grade ≥ 2 neurologic events

s **Additional AE related blood draws for PBMCs and cytokines:**

- Following the initial hospitalization for the KITE-439 infusion, if the subject is hospitalized with any KITE-439 related adverse events, blood samples for PBMCs and cytokines will be collected on day of admission, then weekly, and on day of discharge.
- If the subject experiences a Grade ≥ 3 KITE-439-related toxicity, such as Grade 3 CRS or neurologic event, one additional blood draw for cytokines will be taken at the time of the Grade ≥ 3 KITE-439-related toxicity and upon resolution of the event.

t **If the subject experiences a Grade ≥ 2 CRS (per Lee 2014 criteria),** an additional cytokine sample should be drawn at the first onset and first reoccurrence of any ≥ Grade 2 CRS if not already collected on that day.

u **See neurological assessments section 6.11.** Note: baseline neurological consultation will include baseline MMSE. Baseline neurological consultation and MMSE may occur on Days -10, -9, -8, or -7. In the event of a ≥ Grade 1 neurological toxicity please refer to IB Section 6.5.2 for management guidelines.

v **Subjects will be hospitalized to receive KITE-439 infusion** and will remain in the hospital for at least 7 days to monitor for signs and symptoms of CRS and neurologic events, unless otherwise required by country regulatory agencies (refer to Appendix 4). See Section 7.5.4.1.2. Hospitalization for KITE-439 infusion.

w **Serology tests for European sites (serum):** Serology tests (i.e., human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis) will be done per institutional guidelines and regional regulations. Testing may be done within the 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/enrollment.

x **Pregnancy test (serum or urine):** For European sites, the test will be completed within 7 days before both leukapheresis and lymphodepleting chemotherapy for women of childbearing potential.

y **If the subject progresses before Month 3:** The subject will proceed directly to the Month 3 visit, complete the Month 3 visit, and then be followed in the long-term follow-up (LTFU) period of the study.

z **If the subject progresses in the LTFU phase:** The subject will be followed in the LTFU phase for survival status and subsequent therapy for his or her cancer, and then have blood drawn for PBMCs and, if applicable, anti-KITE-439 antibodies.

[zz] **If this study is terminated prior to the completion of the 15-year follow-up**, all subjects who received an infusion of KITE-439 will be provided the opportunity to transition to a LTFU study (KT-US-982-5968) after providing signed informed consent. For each subject, the final on-study visit may be combined with the subject's first visit on the LTFU study. The timing of the final on-study visit/first LTFU study visit will depend on the timing of the collection of all the subject's data that are required for the planned analysis for this study.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study-required treatment and/or other protocol-required procedures at any time during the study while continuing to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from the investigational product, study treatment, or other protocol-required therapies and must also discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol-required therapy, undergo procedures, and continue participating in study follow-up. Subject data collected up until withdrawal of consent will be retained and included in the analysis of the study. Publicly available data (death records) can be included after withdrawal of consent if local regulations permit. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may also be asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol-required IPs or procedures include any of the following:

- AE
- Subject request
- Product not available
- Lost to follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from additional follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record. The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (e.g., more frequent headaches for a subject with pre-existing headaches or blood pressure is now more increased in a subject with pre-existing hypertension).

A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered AEs. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered AEs.

The term "disease progression," as assessed by measurement of malignant lesions on radiographs or other methods, should not be reported as AEs. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g., B-cell lymphoma).

When an AE or SAE is due to the disease under investigation, it is necessary to report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. If a subject requests to withdraw from protocol-required therapies or the study because of an AE, then the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.1.1. Diagnosis Versus Signs and Symptoms

For AEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and signs and symptoms will be captured on the CRF AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

9.1.2. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an adverse event. A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an adverse event. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the CRF.

9.1.3. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Associated with clinical symptoms
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

9.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject as follows in Table 7:

Table 7. Reporting Requirements for Adverse Events

Subjects who are enrolled, but do not receive KITE-439 infusion	Subjects who are enrolled and receive KITE-439 infusion
Adverse events that occur from enrollment (i.e., commencement of leukapheresis) through 30 days after the last study specific procedure (e.g., leukapheresis, bridging chemotherapy, conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be reported	• AEs that occur from enrollment (i.e., commencement of leukapheresis through 3 months after treatment with KITE-439 infusion will be reported • After 3 months, only serious targeted AEs will be reported for 15 years after KITE-439 infusion or until enrollment into the LTFU study — Targeted adverse events include serious neurological events, serious hematological events, serious Kite product-related infections, GVHD, serious autoimmune disorders, and new/secondary malignancies.

Abbreviations: GVHD, graft-versus-host-disease.
See Section 6.8 for concomitant medication and Section 9.5 for SAE reporting requirements.

The investigator must provide the information listed below regarding the AEs being reported:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, conditioning chemotherapy, or study procedures
- Action taken

The AE grading scale used will be the NCI CTCAE version 5.0. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov).

Individual CRS symptoms will be graded according to NCI CTCAE v5.0. CRS syndrome will be reported using the modified grading scale by Lee and colleagues {Lee 2014} outlined in the KITE-439 IB. AEs attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) KITE-439, CCI [redacted], 3) conditioning chemotherapy, 4) any protocol-required study procedure (including leukapheresis) or treatment, 5) disease progression, 6) concurrent disease, 7) concomitant medication, or 8) other. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

The investigator is expected to follow reported AEs until stabilization or resolution. If a subject begins a new anti-cancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

9.3. Definition of Serious Adverse Events

An SAE is defined as an AE (as defined in Section 9.2) that meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
  - An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (e.g., overnight stay).
  - Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event
  - If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event"

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each adverse event recorded on the CRF.

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and indicated as being due to disease progression with the CRF. If the malignancy has a fatal outcome before the end of the SAE reporting period, then the event leading to the death must be recorded as a SAE with the outcome being fatal.

9.3.1. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE as described in Section 9.5.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (e.g., for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

9.4. Reporting Deaths

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment.

Any death occurring after signing of the main study informed consent and within 3 months of KITE-439 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the 3-month SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment.

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of underlying malignancy should be recorded as SAEs with the preferred term being the subject's underlying cancer and must be reported immediately to the sponsor.

Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. Every effort should be made to capture the established cause of death, which may become available later on (e.g., after autopsy).

9.5. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject. Unless otherwise indicated in Table 8 below, all SAEs will be reported within 24 hours and recorded in the CRF.

Table 8. Reporting Requirements for Serious Adverse Events

Subjects who are pre-screen fails, screen-fails or who are enrolled, but do not receive KITE-439 infusion	Subjects who are enrolled and receive KITE-439 infusion
For subjects who are pre-screen failures, only SAEs related to a pre-screening procedure that occurs from signing of the pre-screening informed consent form through 30 days after the last study-specific pre-screening procedure will be recorded in the CRF and reported. For subjects who are screen failures or are enrolled but do not receive KITE-439 infusion, all SAEs that occur from signing of the screening informed consent form through 30 days after the last study specific procedure (e.g., screening procedure, leukapheresis, CCI [redacted] conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be recorded in the CRF and reported.	• All SAEs that occur from signing of the screening informed consent form through 3 months after the KITE-439 infusion or until initiation of another anti-cancer therapy, whichever occurs first, will be recorded in the CRF and reported • After 3 months, only targeted SAEs will be reported for 15 years after KITE-439 infusion until enrollment into the LTFU study — Targeted SAEs include serious neurological events, serious hematological events, serious Kite product-related infections, GVHD, serious autoimmune disorders, and new/secondary malignancies. • All SAEs deemed related to KITE-439 infusion regardless of time period • All deaths that occur from signing of the ICF through the end of study will be recorded in the CRF

Abbreviations: SAE, serious adverse event; GVHD, graft-versus-host-disease; CRF, case report form; ICF, informed consent form.
See Section 6.8 for concomitant medication and Section 9.5 for targeted AE reporting requirements.

The following must be submitted to Kite via the eSAE system within 24 hours following the Investigators' knowledge of the event:

- All serious adverse events
- CRS (cytokine release syndrome) events grade ≥ 3 per {Lee 2014}
- Neurologic events grade ≥ 3
- All events of cerebral edema
- Pregnancy or lactation exposure

If the eSAE system is unavailable (e.g., system outage), then the SAE must be submitted using the SAE Report Form and sent via email to the SAE Reporting mailbox: PPD

Following completion of KT-US-478-0401, any relevant information on ongoing SAEs must be submitted to the Kite Pharma within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox:
PPD

Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines.

For reporting of targeted concomitant medications and AEs, see Section 6.8 and Section 9.2.

9.6. Pregnancy and Lactation

There is no relevant clinical experience with KITE-439 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations**.** Refer to Appendix 3 for the definition of childbearing potential. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after conditioning chemotherapy dosing**.** Male subjects are recommended to not father a child for 6 months after the conditioning chemotherapy dosing. Please refer to main study informed consent form for recommended methods of highly-effective contraception.

Any pregnancy in a female subject enrolled into the study must be reported, regardless of the time after KITE-439 infusion. If the pregnancy occurs in a female partner of a male subject within 6 months after completing lymphodepleting chemotherapy or the administration of KITE-439, whichever is longer, the pregnancy must be reported. All such pregnancies must be reported to Kite Pharmacovigilance and Epidemiology using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. The outcome should be reported to Kite Pharmacovigilance and Epidemiology using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Pharmacovigilance and Epidemiology. Pregnancy report forms should be reported to Kite Pharmacovigilance and Epidemiology at PPD or fax: PPD

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome post study must be reported to Kite Pharmacovigilance and Epidemiology.

If a lactation case occurs in a female subject in the study, the lactation case must be reported to Kite Pharmacovigilance and Epidemiology within 24 hours after the investigator's awareness of the event using the Special Situations Reporting Form. Report the lactation case and Special Situations report forms to Kite Pharmacovigilance and Epidemiology at PPD or fax: PPD

Sponsor Reporting Requirement (Includes Reporting of SAEs and Deaths)

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Kite may be required to expedite to worldwide regulatory agencies reports of serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Kite or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Kite using reference safety information specified in the current IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

9.7. Dose-limiting Toxicity and Safety Review Team

9.7.1. Dose-limiting Toxicity

DLTs are defined in Table 9.

9.7.2. Safety Review Team

A SRT will make recommendations on the conduct of the study. The SRT membership includes the study sponsor and at least one Phase 1 investigator with an enrolled and dosed subject in the study. The SRT will assess overall safety and DLTs in Phase 1A as well as pausing criteria in Phase 1A and Phase 1B. The SRT will also review subject-level safety and efficacy data on an ongoing basis in Phase 1B.

The SRT, which is internal to the study sponsor and in collaboration with at least one study investigator with an enrolled and dosed subject, will be specifically chartered to review safety data during the Phase 1 component of the study and make recommendations on further study conduct and progression of the study based on the incidence of KITE-439 related DLTs and review of serious adverse events. The SRT safety review outcome will be communicated to the active clinical study sites after the SRT safety review meeting.

9.7.2.1. Dose Escalation Criteria

During Phase 1A, the study will employ a single-subject dose escalation scheme for the first 4 of the planned 6 dose cohorts (see Section 3.1.1). Subjects will be monitored for the occurrence of DLTs within the first 21 days after receiving the KITE-439 infusion (see Section 9.7.1 for DLT criteria). If the subject does not experience a DLT during the DLT window, then the next subject will be dosed at the next higher dose cohort for the first 4 of the planned 6 dose cohorts. Once the highest dose cohort is reached, it will follow a 3+3 design, (noted as Cohort 5 and 6 (n=3+3) below). If the subject does experience a DLT, then the rules as outlined below will apply. Enrollment in the dose cohorts will proceed as follows based on the incidence of DLTs:

- If there are no DLTs in any dose cohort from Cohort 1 to Cohort 6, enrollment will proceed as follows:

  — Cohort 1 (n = 1): 1 x 10^6 E7 TCR T cells/kg

  — Cohort 2 (n = 1): 3 x 10^6 E7 TCR T cells/kg

  — Cohort 3 (n = 1): 1 x 10^7 E7 TCR T cells/kg

  — Cohort 4 (n = 1): 3 x 10^7 E7 TCR T cells/kg

  — Cohort 5 (n = 3 + 3): 1 x 10^8 E7 TCR T cells/kg

  — Cohort 6* (n = 3+3): 1 x 10^8 E7 TCR T cells/kg

  * For Cohort 6, the target dose is 1 x 10^8 E7 TCR T cells/kg and the total number of cells will be calculated based on weight. The minimally acceptable dose for patients above 60 kg will be 6 x 10^9 E7 TCR T cells. The maximum total number of cells in this cohort will be 1 x 10^{10} E7 TCR T cells.

In single-subject dose escalation/de-escalation design,

- If the initial subject had DLT in Cohort 1, Cohort 1 will be expanded to 6 subjects. If the incidence of DLT is < 33% after the expansion, then enrollment will continue to the next dose cohort with all subsequent cohorts being expanded to 3 + 3. If there are ≥ 2 DLTs in Cohort 1, the study may explore a lower KITE-439 dose (Cohort –1).

- If the first subject in dose cohort 2, 3 or 4 experiences a DLT, enrollment will proceed as follows:

  — The previous dose cohort will be expanded to 3 + 3. If there are < 33% DLTs in the previous dose cohort after the expansion or if the previous dose cohort had already been expanded, then the current dose cohort will be expanded to 6 subjects.

    ■ If there are < 33% DLTs in the expanded cohort, then enrollment will continue to the next dose cohort.

    ■ All subsequent dose cohorts will be expanded to 3 + 3.

    ■ If the incidence of DLTs remains < 33%, then enrollment will continue with this approach until the highest dose cohort is reached.

  The highest dose cohort in which the incidence of DLTs is < 33% will be designated the MTD.

- If there are ≥ 2 DLTs in any dose cohort after the first dose cohort, enrollment will proceed as follows:

  — The previous dose cohort will be expanded to 3 + 3, unless it was already expanded in which case the dose tested in the previous cohort will be designated the MTD.

    ■ If there is 0 or 1 DLT (i.e., 0 DLT in 3 subjects or 1 DLT in 6 subjects) in the previous cohort, then that dose cohort will be designated the MTD.

    ■ If there are ≥ 2 DLTs (i.e., ≥ 2 DLTs in 6 subjects) in the previous cohort, then the cohort before the previous cohort will be expanded to 3 + 3 and so on.

  The highest dose cohort in which the incidence of DLTs is < 33% will be designated the MTD.

At any time, when ≥ 2 DLTs have been observed prior to completing dosing of the planned number of subjects in a cohort, enrollment and dosing of additional subjects in that cohort will be stopped, and the cohort will be deemed unsafe.

In 3+3 study design,

- If there is no DLT observed among the first 3 subjects of Cohort 5, then the enrollment will continue to Cohort 6.

- If there is a DLT observed among the first 3 subjects, then an additional 3 subjects will be enrolled into the same cohort.

- If there is no DLT among the additional 3 subjects in Cohort 5, then the enrollment will continue to Cohort 6.

- If there are ≥ 2 DLTs among the first 3 subjects or at least 1 DLT among the additional 3 subjects in Cohort 5, then follow the single-subject dose escalation/de-escalation process described in the "If there are ≥ 2 DLTs in any dose cohort after the first dose cohort" above.

- Cohort 6 will follow the same process as Cohort 5, except

  — If there is no DLT in the first 3 subjects or 1 DLT in the first 6 subjects, Cohort 6 may be designated as MTD.

  — Otherwise Cohort 5 may be designated as MTD.

Based on the incidence of DLTs and other accumulating data, such as AEs and objective response outcomes, each disease type will be evaluated to proceed to the Phase 1B portion of the study. Kite/sponsor reserves the right to recommend one or more doses to be evaluated in Phase 1B, provided that each dose is at or below the MTD.

The decision to proceed with a specific dose or doses of KITE-439 to Phase 1B will be made by Kite and formally communicated to participating sites in a separate communication.

9.7.2.2. Criteria to Pause Enrollment

As part of its oversight of the study, the SRT will assess criteria to pause enrollment during the study.

Enrollment will be paused if the following KITE-439-related AEs are observed:

- After 15 and 30 subjects enrolled in the study (including both Phase 1A and Phase 1B, respectively) have been treated with KITE-439 and have had the opportunity to be followed for 21 days, the incidence of Grade 4 CRS is greater than 25%

- Any Grade 4 infusion reaction/hypersensitivity

- Any Grade 4 cardiac event

- Any Grade 4 neurologic toxicity

- Any Grade 5 SAE after KITE-439 infusion at least possibly related to KITE-439

Applicable Regulatory Agencies will be notified within applicable safety reporting timelines if any of these pausing rules occur.

In the event that the enrollment is paused after the pausing criteria have been met, overall assessment of the benefit/risk ratio will be conducted. If the overall assessment of the benefit/risk

ratio is favorable, the study can resume enrollment. Restart of the study may require prior approval if required by applicable regulatory requirements or mandated by country specific Regulatory Agency.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

Phase 1A: KITE-439 at one of the dose levels planned will be considered safe as determined by the incidence of DLTs.

Phase 1B: A formal hypothesis will not be tested. The clinical hypothesis is that KITE-439 will have clinically meaningful anti-tumor activity, as measured by ORR, in adult subjects with relapsed/refractory HPV16^{+} cancers. The Phase 1B portion of the study is designed to estimate the ORR.

10.2. Study Endpoints

10.2.1. Primary

Phase 1A: Incidence of AEs defined as DLTs

Phase 1B: ORR (complete response [CR] + partial response [PR]) per modified RECIST v1.1 (Appendix 1)

10.2.2. Secondary

- Duration of response (DOR): For subjects who experience an objective response, DOR is defined as the time from the date of their first objective response to the date of disease progression per modified RECIST v1.1 (Appendix 1) or death regardless of cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date, and their response will be noted as ongoing.

- PFS is defined as the time from the KITE-439 infusion date to the date of disease progression per modified RECIST v1.1 (Appendix 1) or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

- OS is defined as the time from KITE-439 infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

- Incidence of AEs

- Incidence of anti-KITE-439 antibodies, and incidence of RCR

- Levels of E7 TCR T cells

CCI [redacted]

[redacted]

10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 2 to 71 subjects.

Approximately 2 to 36 subjects will be enrolled into the Phase 1A portion of this study.

If the study proceeds to Phase 1B, including subjects from Phase 1A, subjects will enroll into 1 of 2 Phase 1B cohorts (n = 15 subjects total for the HPV16$^+$ squamous cell cancer of the head and neck cohort and n = 20 subjects total for the HPV16$^+$ tumors other than squamous cell carcinoma of the head and neck cohort).

The primary efficacy endpoint and all analyses based on the objective response (objective response, DOR, PFS) of the study will be based on a mITT population consisting of all subjects who receive any dose of KITE-439 and with measurable disease after completion of bridging chemotherapy (if applicable) and prior to administration of conditioning chemotherapy.

The Phase 1B uses a single-arm design to estimate response rate in each of the 2 cohorts (n = 15 for the HPV16$^+$ squamous cell carcinoma of the head and neck cohort, n = 20 for the HPV16$^+$ tumors other than squamous cell carcinoma of the head and neck cohort) and in all Phase 1B cohorts combined (n = 35). With the planned sample size in the two cohorts, the ORR can be estimated with a standard error not greater than 13% (HPV16$^+$ squamous cell cancer of the head and neck cohort) and 11% (other HPV16$^+$ tumors cohort). Assuming an observed ORR of 40%, the lower bound of the 95% CI for the estimated ORR will exclude values less than 16% (HPV16$^+$ squamous cell cancer of the head and neck cohort) and 19% (other HPV16$^+$ tumors cohort). With a planned total sample size of 35 for all Phase 1B cohorts combined, the ORR can be estimated with a standard error no greater than 8%. Assuming an observed ORR of 40%, the lower bound of the 95% CI for the estimated ORR will exclude values less than 24%.

One primary analysis is planned for each of the Phase 1B cohorts and will be performed after all subjects accrued for a specific cohort to the study have had the opportunity to be assessed for response 3 months after the KITE-439 infusion. If an individual cohort takes > 24 months to accrue from the initiation of Phase 1B, the primary analysis would occur with < 15 subjects accrued for the HPV16$^+$ squamous cell carcinoma of the head and neck cohort and < 20 subjects accrued for the other HPV16$^+$ tumors cohort. If the primary analysis for 2 cohorts is projected to occur within 3 months of each other, the cohorts may be combined and carried out at the same time. No formal hypothesis testing will be performed. However, within the HPV16$^+$ squamous cell carcinoma of the head and neck cohort and compared to a control of 20% ORR, 5 or more responses would indicate an improvement in response with p-value of 0.164 or smaller; 6 or more responses would indicate a significant improvement in response with p-value of 0.061 or smaller. Within the other HPV16+ cohort excluding squamous cell carcinoma of the head and neck and compared to a control of 20% ORR, 7 or more responses would indicate an improvement in response with p-value of 0.087 or smaller; 8 or more responses would indicate a

significant improvement in response with p-value of 0.032 or smaller, by exact binomial test. The CIs of the objective response and p-values will be presented for descriptive purpose. These may be used as guidance for decision of further development of KITE-439.

Statistical software R version 3.2.0 and EAST version 6.3 were used to calculate the sample sizes and evaluate the operational characteristics of this design.

10.4. Analysis Subsets

- The DLT evaluable set (Phase 1A only) will include subjects treated in the Phase 1A portion who:
  - Received the target dose (± 20%) and had the opportunity to be followed for at least 21 days after the KITE-439 infusion; or
  - Received a dose of KITE-439 lower than the target dose and experienced a DLT within 21 days after the KITE-439 infusion
- mITT: The mITT set will consist of all subjects enrolled and treated with Phase 1B target dose of KITE-439 and with measurable disease after completion of bridging chemotherapy (if applicable) and prior to administration of conditioning chemotherapy. This analysis set will be used for all analyses of objective response and endpoints based on objective response (objective response, DOR, PFS).
- Safety analysis set: The safety analysis set is defined as all subjects treated with any dose of KITE-439.
- Full analysis set (FAS): The full analysis set will consist of all enrolled subjects and will be used for the summary of subject disposition.

10.5. Access to Individual Subject Treatment Assignments

This is a single-arm, open-label study, and subjects and investigators will be aware of treatment received.

10.6. Safety Review and Interim Analysis

10.6.1. Phase 1A Safety Review

The SRT will be chartered to review safety during Phase 1A of the study only and make recommendations on further study conduct in Phase 1A (see details in Section 9.7).

10.6.2. Efficacy Interim Analysis

No formal interim analysis is planned for the Phase 1B part of the study. However, the SRT will review subject-level safety and efficacy data on an ongoing basis to monitor subject safety and ensure data quality. Informal safety and efficacy analyses may be done with accumulating data when such a need arises during the study. Within the Phase 1B HPV16^{+} squamous cell cancer of the head and neck cohort, if no response is observed in the first 7 subjects treated with the target dose after a minimum of 1 month of follow-up, the sponsor may consider stopping enrollment for this cohort. Within the other Phase 1B HPV16^{+} tumors cohort, if no response is observed in the first 10 subjects treated with the target dose after a minimum of 1 month of follow-up, the sponsor may consider stopping enrollment for this cohort.

10.7. Planned Method of Analysis

The primary efficacy analysis of each cohort in Phase 1B will be performed when all enrolled subjects in each cohort have had the opportunity to be evaluated for response 3 months after the KITE-439 infusion. Additional analyses may occur after the primary analysis has been completed. The final analysis will occur when all subjects have completed the study.

Analyses of efficacy endpoints will be summarized by cohort and overall. Analyses of safety endpoints will be evaluated by cohort and overall.

10.7.1. Objective Response Rate

The incidence of objective response and exact 2-sided 95% CIs will be generated. An exact binomial test will be used to compare the observed response rate to a response rate of 20%. The p-values from such tests will be for descriptive purposes only.

10.7.2. Duration of Response

Kaplan-Meier estimates and 2-sided 95% CIs will be generated for DOR.

10.7.3. Progression-free Survival

Kaplan-Meier estimates and 2-sided 95% CIs will be generated for PFS time.

10.7.4. Overall Survival

Kaplan-Meier estimates and 2-sided 95% CIs will be generated for OS.

10.7.5. Safety

Subject incidence rates of AEs, including all, serious, fatal, CTCAE Grade 3 or higher, and treatment -related AEs reported throughout the conduct of the study, will be tabulated by system organ class and preferred terms. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths through the LTFU and treatment-related SAEs will be provided.

MMSE at baseline and change from baseline will be summarized.

10.7.6. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject is enrolled. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

11. REGULATORY OBLIGATIONS

11.1. Independent Review Board/Independent Ethics Committee

A copy of the protocol, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each site's respective IRB/IEC for approval. After approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (i.e., annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site-specific and study SAEs (provided to the site by the key sponsor contact), along with any protocol deviations, to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be contained for all material submitted to the key sponsor contact. The following rules are to be applied:

- Subjects will be identified by a unique ID number.
- Year of birth will be reported according to local laws and regulations.
- Age at the time of enrollment

For reporting of SAEs, subjects will be identified by their respective subject ID number, initials, and year of birth (as per their local reporting requirements for both initials and year of birth).

Per federal regulations and International Conference on Harmonization/Good Clinical Practice (ICH/GCP) guidelines, investigators and institutions are required to permit authorization to the sponsor, Contract Research Organization (CRO), IRB/IEC, and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which includes access to personal information.

11.2.1. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participated in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigator's agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties is to be submitted to the key sponsor contact.

Kite reserves the right to terminate the study at any time. Both Kite and the investigator reserve the right to terminate the investigator's participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite reserves the unilateral right, at its sole discretion, to determine whether to manufacture KITE-439 T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities are outlined and included in the Delegation of Authority Form.

Source documents are original documents, data, and records for which the study data are collected and verified. Examples of such source documents may include, but are not limited to, hospital records and subject charts; laboratory, pharmacy, radiology, and records; subject diaries; microfiches; correspondence; and death registries. CRF entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities, and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject ID lists
- Protocols and protocol amendments, IB, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite and the investigator. If storage is no longer available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping of the documents.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject ID
- Documentation that subject meets eligibility criteria (i.e., medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number/name)
- Study discussed and date of informed consent

- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of IP, including start and stop times of KITE-439 administration
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end date, dose if relevant, and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

Traceability records for the product, from procurement through manufacture to the administration of the product, should be kept by each relevant party (e.g., the sponsor and the investigator/institution) for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by agreement with the sponsor. Before, during, and after completion or termination of the trial, each party should hold the necessary information available at all times to ensure bidirectional traceability, linking the subject information at the procurement site to the product and the subject information at the clinical trial site to the product, whilst ensuring the data protection legally required for the subject.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kite to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

If a subject transfers to another study site, the investigator must notify Kite in advance before assigning the subject's study records to another party or moving them to another location.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors, or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records, assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy, and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility(ies), review of subject and study-related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English, and concomitant medications should be identified by trade names. For additional details surrounding the completion of CRFs, refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in this study will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013), which states authorship should be based on:

- Substantial contributions to the conception or design of the work; acquisition of data, analysis, or interpretation of data for the work; and
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individual who accepts direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data, or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite for review and approval. The study contract among the institution, principal investigator, and Kite or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite will provide compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

17. REFERENCES

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18. APPENDICES

Appendix 1. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines Version 1.1 with Modifications
Appendix 2. Practical Body Weight Calculation for Subjects Whose BMI is > 35
Appendix 3. Childbearing Potential and Birth Control
Appendix 4. Country-specific Regulatory Agency Requirements

Appendix 1. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines Version 1.1 with Modifications

These guidelines provide a standard approach to solid tumor measurement and definitions for objective assessments of change in tumor size and are based on guidelines developed and published by {Eisenhauer 2009}. Modifications to the guidelines are listed in Table 13.

Eligibility

Per protocol, subjects must have at least 1 measurable lesion per modified RECIST v1.1 (see Table 13) on the most recent computed tomography (CT) or magnetic resonance imaging (MRI) staging evaluation.

Method

CT scans (or MRI scans) of the neck (if applicable), chest, abdomen, pelvis, and all other sites of disease will be performed to evaluate tumor response. Lesions identified on chest x-ray should be imaged by CT or MRI scan. Ultrasound (US) and F-flurodeoxyglucose positron emission tomographic (FDG-PET) alone cannot be used to measure objective tumor response or progressive disease (PD).

Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be the greater of either at least 10 mm or twice the slice thickness.

MRI is acceptable to assess disease extent if used throughout the study.

At baseline and throughout the study, images should be performed using the same method of assessment, and the same technique should be used to characterize each identified and reported lesion. A switch from CT to MRI (or vice versa) is considered the only acceptable change in modality. It should not preclude response assessment if, in the judgement of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to intravenous (IV) contrast for CT scans while on trial. If this happens, contact the Kite medical monitor to discuss the change in modality on a per subject basis.

For this protocol, a response of complete response (CR), partial response (PR), or stable disease (SD) will be determined as assessed by cross-sectional imaging techniques (CT or MRI).

FDG-PET will not contribute to the assessment of response. It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression. For the determination of PD, FDG-PET could be used to identify new lesions as follows:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD if a new lesion is identified.

- No FDG-PET at baseline and a positive FDG-PET at follow-up:

  — If the positive FDG-PET at follow-up corresponds to a new location of disease, confirm by CT (or MRI) this is the PD.

  — If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT (or MRI), additional follow-up CT (or MRI) scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

  — If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT (or MRI) that is not progressing on the basis of the anatomic images, this is not PD.

If a combined FDG-PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol for Response Evaluation Criteria in Solid Tumor (RECIST) measurements unless the site can document that the CT performed as part of the FDG PET-CT is of identical diagnostic quality to a diagnostic CT. Tumor markers alone cannot be used to assess objective tumor response.

Physical exam cannot be used to quantify tumor measurements other than in the case of cutaneous or palpable subcutaneous lesions.

Definitions of "Measurable" and "Non-measurable"

All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded unidimensionally.

At baseline, tumor lesions/pathologic lymph nodes are categorized as measurable or non-measurable according to the following definitions:

- Measurable or target lesions:

  — Measurable target lesions are defined at baselines as lesions that can be accurately measured in at least 1 dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

  — To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis diameter when assessed by CT scan.

- Non-measurable or non-target lesions:

  — All other lesions that were not chosen as target lesions, including lesions too small to measure (longest diameter < 10 mm, lymph nodes with ≥ 10 or < 15 mm short axis diameter), and other truly non-measurable lesions are considered non-measurable and characterized as non-target lesions.

- Other examples of non-measurable lesions include:
  - Some bone lesions
  - Inflammatory breast disease

The following examples should not be followed as lesions for assessment of disease:

- Nodes that have short axis < 10 mm are considered non-pathological and should not be recorded or followed.
- Ascites or pleural effusions are not considered non-measurable for this study.

Baseline Documentation of "Target" and "Non-target" Lesions

Baseline images will be used to prospectively identify all sites of disease present as close as possible to the start of treatment and never more than 35 days before enrollment/leukapheresis.

Site of disease will be characterized as either target or non-target lesions.

- Target lesions
  - Up to 5 target lesions (a maximum of 2 per organ) meeting the target lesion definition above will be chosen to measure at baseline and over the course of the study.
  - Target lesions should be selected on the basis of their size and suitability for accurate repeated measurements by imaging techniques.
  - Target lesions must not be chosen from a previously irradiated field unless there has been documented tumor progression in that field prior to enrollment.
  - The distribution of these target lesions should be representative of the subject's overall disease status.
  - A sum of the diameters (longest for non-nodal lesions, short axis diameter for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

- Non-target lesions

  — All other lesions (or sites of disease) meeting the non-target lesion definition above should be identified as non-target lesions.

  — Non-target lesions should be recorded and assessed qualitatively over the course of therapy. These lesions should be followed as "present," "absent," or, in rare cases, "unequivocal progression."

  — It is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (CRF) (e.g., multiple enlarged pelvic lymph nodes or multiple liver metastases).

Response Criteria

The subject's overall tumor response will be assessed based on the response of the target lesions (Table 10), the response of the non-target lesions (Table 11), and the presence or absence of new lesions.

Evaluation of Target Lesions

Table 10. Evaluation of Target Lesions at Each Assessment Point

Response	Criteria
Complete response (CR):	Disappearance of all target lesions Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial response (PR):	At least a 30% decrease in the sum of diameters[a] of all target lesions, taking as a reference the baseline sum diameters[a]
Progressive disease (PD):	At least a 20% increase in the sum of diameters[a] of all target lesions, taking as a reference the nadir (i.e., smallest sum of the diameters[a] since receiving KITE-439) The sum must also demonstrate an absolute increase of at least 5 mm above the same reference (i.e., nadir).
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the nadir (i.e., smallest sum of diameters[a] since receiving KITE-439)
Inevaluable (NE):	Scans were not performed, were incomplete, or were inevaluable due to poor scan quality at this time point and did not permit the measurement of all or some target lesions.

a Diameters used:
For nodal disease, shortest axis.
For non-nodal disease, sum of longest diameters.

While on study, all target lesions (nodal and non-nodal) recorded at baselines should have their actual measurements recorded at each subsequent evaluation. The conventions will be used that if a lesion being measured is faintly seen and/or too small to measure, a value of 5 mm will be assigned. If a lesion disappears, a measurement of "0" mm should be recorded.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the "sum" of target lesions may not be 0 even if CR criteria are met because a normal lymph node is defined as having a short axis < 10 mm. For CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Evaluation of Non-target Lesions

Table 11. Evaluation of Non-target Lesions at Each Assessment Point

Response	Criteria
Complete response (CR)	Disappearance of all non-target lesions All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of 1 or more non-target lesions
Progressive disease (PD):	Unequivocal progression of existing non-target lesions, or Appearance of 1 or more new lesions
Not applicable (NA):	No non-target lesions identified at baseline
Inevaluable (NE):	Scans were not performed, were incomplete, or were inevaluable due to poor scan quality at this time point and did not permit the assessment of all or some non-target lesions.

When the subject also has measurable disease, to achieve an unequivocal progression, there must be an overall level of substantial worsening in non-target disease such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the subject has only non-measurable disease, the increase of non-measurable disease should be comparable in magnitude to the increase required to declare PD for measurable disease (e.g., equivalent to a 20% increase in sum of diameters of all measurable lesions).

Evaluation of Best Overall Response

Table 12 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease.

Table 12. Time Point Response in Subjects with Target (± non-target) Disease

Target Lesions (response)	Non-target Lesions (response)	New Lesions (Yes or No)	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
PR	NA*	No	PR
CR	NA*	No	CR
SD	NA*	No	SD
NE	NA*	No	NE

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable; NA*, no non-target lesions identified at baseline.

Non-CR/non-PD is preferred over "stable disease" for non-target disease because SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured, is not advised.

For equivocal findings (e.g., very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), if progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Response Confirmation

For a subject to be assigned an overall best response of PR or CR, the responses of PR or CR must be confirmed by performing additional radiological exams no less than 28 days after the initial criteria for response are first met.

For a subject to be assigned an overall best response of SD or better, the response must be documented ≥ 28 days after the KITE-439 infusion; otherwise the overall response will be inevaluable (NE).

Table 13. Modifications from RECIST 1.1

Original Content of RECIST 1.1	Modifications Made in this Protocol	Rationale
Measurable lesions may be assessed by: • Chest x-ray if the lesion has ≥ 20 mm diameter, is clearly defined, and is surrounded by aerated lung • Clinical exam if the lesion is superficial and has ≥ 10 mm diameter using calipers	Measurable lesions must be assessed by CT scan or MRI.	CT or MRI are the preferred methods of measurable lesion assessment per Eisenhauer 2009. Lesions identified on chest x-ray should be imaged by CT or MRI scan. If the chest CT scan performed at baseline is found to be normal, repeat imaging with CT scan for tumor assessment is preferred. Note a chest x-ray can be performed at each subsequent tumor imaging.
Tumor markers alone cannot be used to assess objective tumor response. If tumor markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease-specific, instructions for their measurement are incorporated into the protocol.	Tumor markers will not contribute to the assessment of disease response and progression in this study.	Tumor markers are not in standard use for cervical, head, neck, and genitourinary malignancies.
In some situations, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.	Confirmation of CR status via histology will not be required to confirm CR status.	CCI [redacted] It is not deemed appropriate to perform fine needled aspirate/biopsies given that CR is not a primary objective.

Abbreviations: CR, complete response; CT, computed tomography; MRI, magnetic resonance imaging.

Appendix 2. Practical Body Weight Calculation for Subjects Whose BMI is > 35

Dose calculation based on actual or practical body weight is as follows:

- Actual body weight is to be used for KITE-439 CCI . For subjects weighing greater than 100 kg, each dose of TCR-transduced T cells will be calculated based on a maximum weight of 100 kg. CCI
- Actual body weight is to be used for conditioning chemotherapy CCI when subjects body mass index (BMI) is ≤ 35.
- Practical body weight is to be used for conditioning chemotherapy CCI when subjects BMI is > 35. See formula below.

BMI determination:

- BMI = weight (kg)/[height (m)]^2 or
- BMI = 703 x weight (lb)/[height (in)]^2

Calculation of ideal body weight:

- Male = 50 kg + 2.3 (number of inches over 60 inches)
  - Example: ideal body weight of 5'10" male
  - 50 + 2.3 (10) = 73 kg
- Female = 45.5 kg + 2.3 (number of inches over 60 inches)
  - Example: ideal body weight of a 5'3" female
  - 45.5 + 2.3 (3) = 52.4 kg

Calculation of "practical weight": Calculate the average of the actual and the ideal body weights.

Appendix 3. Childbearing Potential and Birth Control

This study will follow the recommendations from the Clinical Trial Facilitation Group (CTFG) {Clinical Trials Facilitation Group (CTFG) 2014}, as described below.

A. Definition of Childbearing Potential

A woman is considered of childbearing potential (i.e., fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this study, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

B. Birth Control Methods That May Be Considered as Highly Effective

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device (IUD) [2]

[1] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

- Intrauterine hormone-releasing system (IUS) [2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

C. Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM). A female condom and a male condom should not be used together.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Appendix 4. Country-specific Regulatory Agency Requirements

A. France, Italy, and Germany

The post-infusion monitoring of subjects, described in Section 7.5.4 of this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in the Schedule of Assessments (Table 5), "Post-treatment Follow-up" column. The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator. The daily monitoring will include vital signs (refer to Table 5), blood draw for chemistry panel with C-reactive protein, blood draw for complete blood count with differential, and neurological assessment (refer to Section 6.11). Any observed toxicity will be managed according to Section 7.8 of this protocol.