STATISTICAL ANALYSIS PLAN

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	Brexucabtagene Autoleucel
Protocol:	A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25) **Note: Substudies KT-US-568-0138-A and KT-US-568-0138-D were terminated early by the Sponsor (effective 21 June 2023).**
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CONFIDENTIALITY NOTICE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADaM	analysis data model
AE	adverse event
ASTCT	American Society for Transplantation and Cellular Therapy
BL	Burkitt lymphoma
BOR	best objective response
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response/remission
CRi	complete response with incomplete marrow recovery
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	data safety monitoring board
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-30	European Organization for Research and Treatment of Cancer Quality of Life Cancer Patients Questionnaire
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Scale
FAS	full analysis set
HCL	hairy cell leukemia
HLGT	high-level group term
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IRB	Institutional Review Board
KM	Kaplan-Meier
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMSE	mini-mental status exam
MRD	measurable residual disease
NCI	National Cancer Institute
NE	not evaluable

ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PK/PD	pharmacokinetics/pharmacodynamics
PET	positron emission tomography
PFS	progression-free survival
PR	partial response/remission
PRO	patient-reported outcome
RCR	replication-competent retrovirus
R/R	relapsed/refractory
RT	Richter transformation
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDTM	study data tabulation model
SMQ	standardized MedDRA query
SOA	schedule of assessments
SOC	system organ classes
SOP	standard operating procedure
SRT	safety review team
TEAE	treatment-emergent adverse event
TID	trial integrity document
TLS	tumor lysis syndrome
TTNT	time to next treatment
ULN	upper limit of normal
VAS	visual analog scale
VGPR	very good partial response
WBC	white blood cell
WM	Waldenstrom macroglobulimemia

1. INTRODUCTION

This statistical analysis plan provides the pre-specification and details of the statistical analyses outlined within the study KT-US-568-0138 (ZUMA-25), Amendment 3.0 entitled "A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25)" dated 17 August 2023. The scope of this document is to provide details on the planned interim, primary, follow-up, and final analyses.

The analyses of pharmacokinetics, pharmacodynamics, other translational exploratory analyses and patient-reported outcomes (PROs) will be described with details in separate analysis plans.

Note: Substudies KT-US-568-0138-A (WM) and KT-US-568-0138-D (HCL) were terminated early by the Sponsor (effective 21 June 2023). Therefore, the planned analyses described in this document for these 2 substudies will not be conducted.

2. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

2.1. Objectives

2.1.1. Primary Objective

The primary objective is to evaluate the efficacy of brexucabtagene autoleucel in adult subjects with rare B-cell malignancies, by determining the response rates by central assessment as defined within each respective substudy.

2.1.2. Secondary Objectives

The secondary objectives are to determine:

- Complete response (CR) by central assessment
- Durability of response
- Survival status
- Survival status without progression
- Time to next treatment
- Time to first response
- Time to best response
- Safety of brexucabtagene autoleucel by determining adverse events (AEs), AEs defined as dose-limiting toxicities (DLTs), and the incidence of anti-brexucabtagene autoleucel antibodies
- Patient reported outcomes (PROs) and quality of life.

Additional substudy-specific secondary objectives are described in each respective substudy and as detailed below:

- Relapsed/Refractory (r/r) Waldenstrom Macroglobulinemia (WM), **terminated early by Sponsor (effective 21 June 2023)**
  - To determine the Objective Response Rate (ORR) by central assessment. Defined as the proportion of subjects who achieve a best response of CR, very good partial response (VGPR), and partial response (PR)
  - To determine the combined rate of CR and VGPR by investigator assessment
  - To determine the rates of individual responses by central assessment

- r/r Richter Transformation (RT)
  - To evaluate the efficacy of brexucabtagene autoleucel in subjects by determining the ORR by investigator assessment defined as the proportion of subjects who achieve a best response of either CR or PR
  - To evaluate the efficacy of brexucabtagene autoleucel based on clonal relationship to the underlying chronic lymphocytic leukemia (CLL)
  - To evaluate the efficacy of brexucabtagene autoleucel on the underlying CLL by investigator assessment
- r/r Burkitt Lymphoma (BL)
  - To evaluate the efficacy of brexucabtagene autoleucel in subjects by ORR by investigator assessment
- r/r Hairy Cell Leukemia (HCL), **terminated early by Sponsor (effective 21 June 2023)**
  - To evaluate the efficacy of brexucabtagene autoleucel in subjects by ORR by investigator assessment

2.1.3. Exploratory Objectives

The exploratory objectives are to evaluate the pharmacokinetic and pharmacodynamic profile of brexucabtagene autoleucel in subjects with rare B-cell malignancies, and to explore the phenotypic and functional characteristics of brexucabtagene autoleucel and T-cell reactivity against brexucabtagene autoleucel in subjects with rare B-cell malignancies.

Additional substudy specific exploratory objectives are described in each respective substudy and as detailed below:

- r/r RT
  - To evaluate the CLL measurable residual disease (MRD) negative response rate in subjects who have achieved a CR. MRD will be done by local assessment.
  - To evaluate the efficacy of brexucabtagene autoleucel based on receipt of bridging therapy.
- r/r BL
  - To evaluate the efficacy of brexucabtagene autoleucel based on receipt of bridging therapy.
- r/r HCL, **terminated early by Sponsor (effective 21 June 2023)**
  - To evaluate the MRD negative response rate in subjects who have achieved a CR by central assessment.

2.2. Endpoints

2.2.1. Primary Endpoints

Primary endpoints for efficacy assessment are substudy specific and are described below:

- r/r WM, **terminated early by Sponsor (effective 21 June 2023)**
  - Combined rate of CR and VGPR, defined as the proportion of subjects who achieve a best response of either CR or VGPR by central assessment per the Sixth International Workshop in WM {Owen 2013}.
- r/r RT and r/r BL
  - ORR, defined as the proportion of subjects who achieve a best response of either CR or PR by central assessment per the Lugano Classification {Cheson 2014}.
- r/r HCL, **terminated early by Sponsor (effective 21 June 2023)**
  - ORR, defined as the proportion of subjects who achieve a best response of either CR or PR by central assessment per Grever and colleagues {Grever 2017}.

2.2.2. Secondary Endpoints

Secondary endpoints that are common across all substudies are listed below:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- CR Rate
- Time to first response
- Time to best response
- Time to next treatment (TTNT)
- Changes over time in the PRO assessment domains, EORTC-QLQ-C30 and ED-5D-5L
- Incidence of adverse events (AEs) and common terminology criteria for AE (CTCAE) grade changes in safety laboratory values
- Incidence of AEs defined as dose limiting toxicities (DLTs)
- Incidence of antibodies against brexucabtagene autoleucel (immunogenicity)
- Incidence of RCR in PBMCs at baseline and after brexucabtagene autoleucel infusion

Additional substudy specific secondary endpoints are listed in each substudy as shown below:

- r/r WM, **terminated early by Sponsor (effective 21 June 2023)**
  - ORR (the combined rate of CR, VGPR, and PR) by central assessment
  - Combined rate of CR and VGPR by investigator assessment
  - Rate of VGPR and PR, separately
- r/r RT,
  - ORR in DLBCL-RT by investigator assessment
  - ORR in DLBCL-RT based on clonal relationship to the underlying CLL by central assessment. To assess clonal relationship, the *IGHV* gene will be sequenced and compared between the CLL tumor cells (from screening bone marrow aspirate) and the DLBCL cells (from the tumor biopsy)
  - ORR (CR, CRi, or PR) in CLL by investigator assessment
- r/r BL,
  - ORR by investigator assessment
- r/r HCL, **terminated early by Sponsor (effective 21 June 2023)**
  - ORR by investigator assessment

Definitions of the secondary endpoints are provided in Section 5.

2.2.3. Exploratory Endpoints

The exploratory endpoints that are common across the substudies are detailed below:

- Levels of CAR T cells in blood and relationship with clinical outcomes (efficacy and toxicity)
- Levels of serum analytes (including cytokines and chemokines) in blood and relationship with adverse events of interest (eg, CRS and neurotoxicity)
- Levels of blood B-cells and relationship with PK profile and clinical outcome
- Product characteristics, including T-cell phenotypes and relationship with clinical outcome
- Incidence of T-cell reactivity against brexucabtagene autoleucel CAR (T cell immunogenicity)

Additional substudy-specific exploratory endpoints are listed below:

- r/r RT
  - Rate of MRD negative response among subjects who have achieved a CR
  - ORR among subjects who achieve a best response of either CR or PR, in subgroups by receipt of bridging therapy (yes/no)
- r/r BL
  - ORR among subjects who achieve a best response of either CR or PR, in subgroups by receipt of bridging therapy (yes/no)
- r/r HCL, **terminated early by Sponsor (effective 21 June 2023)**
  - Rate of MRD negative response among subjects who have achieved a CR

Definitions of the exploratory endpoints are provided in Section 5. Details of exploratory analysis will be included in a separate translational SAP.

2.3. Estimands

Note: Substudies KT-US-568-0138-A (WM) and KT-US-568-0138-D (HCL) were terminated early by the Sponsor (effective 21 June 2023).

Primary and key efficacy secondary objectives and endpoints are summarized within the following estimand framework.

2.3.1. Primary Estimand

The primary estimand is provided in Table 1.

Table 1. Primary Estimand

	Primary Estimand
Primary Objective	To evaluate the disease response rate of brexucabtagene autoleucel by central assessment in each substudy (r/r WM, r/r RT, r/r BL, and r/r HCL).
Treatment	A single infusion of brexucabtagene autoleucel administered at a target dose of either 2×10^6 CAR T cells/kg or 1×10^6 CAR T cells/kg, as recommended by the SRT, following leukapheresis, optional bridging therapy for RT and BL, optional ibrutinib therapy for WM and RT, and lymphodepleting chemotherapy consisting of cyclophosphamide and fludarabine.
Population	r/r WM: Subjects with r/r WM as defined by protocol eligibility criteria; r/r RT: Subjects r/r RT as defined by protocol eligibility criteria; r/r BL: Subjects with r/r BL as defined by protocol eligibility criteria; r/r HCL: Subjects with r/r HCL as defined by protocol eligibility criteria.

	Primary Estimand
Variable	r/r WM: Response (either CR or VGPR as best response) by central assessment per the Sixth International Workshop in WM {Owen 2013}; r/r RT and r/r BL: Objective response (either CR or PR as best response) by central assessment per the Lugano Classification {Cheson 2014}; r/r HCL: Objective response (either CR or PR as best response) by central assessment per Grever et al {Grever 2017}.
Population-level summary	Rate of CR + VGPR for WM; ORR for RT/BL/HCL
Intercurrent event	• Subsequent new anti-cancer therapies (including stem cell transplant) (while-on-treatment strategy[a]) • 2 or more consecutive missed scheduled disease assessment visits (treatment policy strategy[b])

Abbreviations: BL, Burkitt Lymphoma; CAR, chimeric antigen receptor; CR, complete response; HCL, Hairy Cell Leukemia; ORR: objective response rate; PR: partial response; r/r, relapsed/refractory; RT, Richter Transformation; VGPR, very good partial response; WM, Waldenstrom Macroglobulinemia

a. While-on-treatment means a subject is in the follow-up period after brexucabtagene autoleucel infusion until end of the study or withdrawal of consent. It is based on the assumption that the assessments prior to the occurrence of the intercurrent event is of interest. This includes assessments after the brexucabtagene autoleucel infusion up to progressive disease, the last evaluable disease assessment prior to the occurrence of the intercurrent event, the last evaluable disease assessment prior to data cutoff, or death, whichever is the earliest.

b. Treatment policy strategy is based on assumption that the assessments after the intercurrent event are still of interest while subjects are in follow up period, especially if they are still in remission (ongoing response).

2.3.2. Secondary Estimands

The secondary estimands (for DOR, PFS and OS) are provided in Table 2.

Table 2. Secondary Estimands

	Secondary Estimands		
Secondary Objective	To evaluate the efficacy of brexucabtagene autoleucel as measured by DOR by central assessment in each substudy (r/r WM, r/r RT, r/r BL, and r/r HCL)	To evaluate the efficacy of brexucabtagene autoleucel as measured by PFS by central assessment in each substudy (r/r WM, r/r RT, r/r BL, and r/r HCL)	To evaluate the efficacy of brexucabtagene autoleucel as measured by OS in each substudy (r/r WM, r/r RT, r/r BL, and r/r HCL)
Treatment	A single infusion of brexucabtagene autoleucel administered at a target dose of either 2 x 10^6 CAR T cells/kg or 1 x 10^6 CAR T cells/kg, as recommended by the SRT, following leukapheresis, optional bridging therapy for RT and BL, optional ibrutinib therapy for WM and RT, and lymphodepleting chemotherapy consisting of cyclophosphamide and fludarabine		
Population	r/r WM: Subjects with r/r WM as defined by protocol eligibility criteria; r/r RT: Subjects with r/r RT as defined by protocol eligibility criteria; r/r BL Subjects with r/r BL as defined by protocol eligibility criteria; r/r HCL: Subjects with r/r HCL as defined by protocol eligibility criteria.		

	Secondary Estimands		
Variable (Secondary Endpoint)	DOR, defined as the time from the first objective response to disease progression or death. DOR only includes subjects who achieve a response per central assessment prior to subsequent anti-cancer therapy (including stem cell transplant).	PFS, defined as the time from the date of brexucabtagene autoleucel infusion to the date of disease progression per central assessment or death from any cause.	OS, defined as the time from the date of brexucabtagene autoleucel infusion to death from any cause.
Population-level summary	Kaplan-Meier estimates		
Intercurrent event	• Subsequent new anti-cancer therapies (including stem cell transplant) (Hypothetical strategy[a] for DOR and PFS; treatment policy strategy[b] for OS) • 2 or more consecutive missed scheduled disease assessment visits (treatment policy strategy[b])		

Abbreviations: BL, Burkitt Lymphoma; CR, complete response; HCL, Hairy Cell Leukemia; DOR, duration of response; ORR: objective response rate; PFS, progression-free survival; PR: partial response; r/r, relapsed/refractory; RT, Richter Transformation; VGPR, very good partial response; WM, Waldenstrom Macroglobulinemia

a. Hypothetical strategy is utilized as if the intercurrent event would not occur; assuming the intercurrent event would not cause bias on the treatment effect assessment. Estimation was to be based on non-informative censoring, assuming that the subjects who had subsequent therapy had the same risk as those didn't have.

b. Treatment policy is based on assumption that the assessments after the intercurrent event are still of interest while subjects are in follow-up period, especially if they are still in remission (ongoing response) for DOR and PFS.

3. STUDY OVERVIEW

3.1. Study Design

Note: Substudies KT-US-568-0138-A (WM) and KT-US-568-0138-D (HCL) were terminated early by the Sponsor (effective 21 June 2023).

This Phase 2, multi-center, open-label study will use a basket study design with 4 indication-specific substudies in adult subjects diagnosed with either r/r WM, r/r RT, r/r BL or r/r HCL. Each substudy is designed to be independent of each other without data borrowing across the substudies.

Initially, 1 subject will be enrolled and infused per substudy. After the first subject is enrolled and infused, no additional subjects will be enrolled within a substudy until the first subject has been monitored for at least 28 days after the brexucabtagene autoleucel infusion. Subsequently, an additional 2 subjects in each substudy can be enrolled in parallel. After these 3 initial subjects in a substudy have undergone evaluation for at least 28 days after the brexucabtagene autoleucel infusion with the initial dose (2×10^6 CAR T cells/kg of body weight), a Safety Review team (SRT) will review the safety data and make recommendations on further study conduct, progression, and/or dose modification in each substudy. Study enrollment will be paused following treatment with brexucabtagene autoleucel of the 20th subject in substudy B (RT) and the 10th subject in substudy C (BL) and until results from the interim analysis have been assessed for substudies r/r RT and r/r BL, respectively

The screening period will have a duration of up to 28 days and begin on the date a subject signs the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF) and continues through confirmation of enrollment (ie, commencement of leukapheresis), or until a subject withdraws consent before enrollment, or it is determined that a subject is a screen failure (ie, does not meet the study eligibility criteria).

If required to reduce risk of Bruton's tyrosine kinase (BTK) inhibitor withdrawal symptoms and IgM flare, subjects in the WM and RT will be allowed to receive ibrutinib through screening and up to 30 hours (5 half-lives) prior to starting lymphodepleting chemotherapy. Moreover, after enrollment/leukapheresis, subjects in the RT and BL substudies may receive optional protocol-defined bridging therapy, at the investigator's discretion. If ibrutininb has been used through screening or bridging therapy has been administered, a new baseline disease-assessment is required prior to initiating lymphodepleting chemotherapy.

Subjects will undergo lymphodepleting chemotherapy with fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day) for 3 consecutive days from Day -5 to Day -3 followed by 2 rest days (Day -2 and Day -1).

On Day 0, subjects will receive a single infusion of brexucabtagene autoleucel administered intravenously at a target dose of either 2×10^6 CAR T cells/kg or 1×10^6 CAR T cells/kg (or a flat dose of 2×10^8 or 1×10^8, respectively, anti-CAR-T cells in subjects > 100 kg). In

combination with an initial mandatory hospitalization period of at least 7 days; this is considered as the treatment period (refer to Section 12.4 of the KT-US-568-0138 master protocol for country-specific post-infusion monitoring requirements). Subjects will be required to stay within close vicinity to the clinic, with immediate access to urgent care by the investigator until after Day 28.

After completing the treatment period, all subjects will be followed in the post-treatment follow-up period. Counting from Day 0 (the day of brexucabtagene autoleucel infusion), subjects will return to the clinic for evaluation at Day 14 and Day 28, Week 8, Month 3, and then every 3 months up to Month 12. Additional substudy-specific visits will occur as outlined below:

- r/r RT and r/r BL Month 18 and Month 24
- r/r WM and r/r HCL: every 6 months up to 36 months, and then annually up to 60 months

Thereafter, subjects will transition to a separate long-term follow-up (LTFU) study (KT-US-982-5968) to continue follow-up out to 15 years post-infusion.

The study schema is provided in Figure 1 of the KT-US-568-0138 master protocol. Disease response will be assessed as described in each substudy protocol. The schedule of assessments (SOA) for each indication is provided in respective substudy protocol.

3.2. Hypothesis

Brexucabtagene autoleucel will improve the disease response rates compared with pre-specified historical control data as described below within each substudy. The hypothesis testing will be conducted at a significance level of 0.025 (1-sided) for each substudy. No multiplicity adjustment will be made across the substudies. The responses from subjects in the study population are assumed to be independent and to follow a binomial distribution.

3.2.1. Waldenstrom Macroglobulinemia, terminated early by Sponsor (effective 21 June 2023)

An alternative hypothesis is proposed with a target 20% combined rate of CR and VGPR per central assessment against a null hypothesis that the combined rate of CR and VGPR is $\leq 6\%$. The reference rate of 6% was based on a systematic literature review and meta-analysis {Castillo 2022, Ghobadi 2016, Ghobrial I M 2014, Souchet L 2016}. The hypothesis is that the combined rate of CR and VGPR to brexucabtagene autoleucel per central assessment is greater than the response rate of 6% identified by systematic literature review of trials in similar populations.

3.2.2. Richter Transformation

An alternative hypothesis is proposed with a target 50% ORR per central assessment against a null hypothesis that the ORR is $\leq 28\%$. The reference rate of 28% was based on a systematic literature review and meta-analysis {Abrisqueta 2020, Davids 2017, Ding 2017, Faderl 2003, Thompson M C 2021, Visentin A 2017}. The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than the response rate of 28% identified by systematic literature review of trials in similar populations.

3.2.3. Burkitt Lymphoma

An alternative hypothesis is proposed with a target 70% ORR per central assessment against a null hypothesis that the ORR is ≤ 39%. The reference rate of 39% was based on Short and colleagues {Short 2017}, as an outcome of a systematic literature review. The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than the response rate of 39% identified by systematic literature review of trials in similar populations.

3.2.4. Hairy Cell Leukemia, terminated early by Sponsor (effective 21 June 2023)

An alternative hypothesis is proposed with a target 60% ORR per central assessment against a null hypothesis that the ORR is 26% or less. The reference rate of 26% was based on Nieva et al {Nieva 2003}, as an outcome of a systematic literature review. The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than the response rate of 26% identified by systematic literature review of trials in similar populations.

3.3. Sample Size Considerations

The sample size and power considerations are based on a systematic literature review of historical control response rates for each indication, and each substudy is designed to be independent of each other without data borrowing across the substudies.

The type 1 and type 2 errors are controlled for each substudy. No multiplicity adjustment is made on global type 1 error across the substudies, as the primary goal of this basket study is to determine the treatment effect of brexucabtagene autoleucel separately in each substudy rather than generalizing the treatment effect evaluation among all the studied indications.

3.3.1. Waldenstrom Macroglobulinemia, terminated early by Sponsor (effective 21 June 2023)

This substudy will enroll and treat 60 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This sample size will achieve statistical power of 88% if there is at least a 14% improvement in combined rate of CR and VGPR (brexucabtagene autoleucel: 20% vs historical control: 6%) at an alpha level of 0.025 (1-sided) under the 2-look design based on normal approximation, with variance of standardized test statistic under null hypothesis (H_0) using EAST (Version 6.5), as described in Table 4 below. The empirical power is 89% per simulation based on binomial distribution without normal approximation (Appendix 6). A statistically significant treatment effect can be claimed in this substudy if 8 or more responders (≥ 13.3%) are observed among the 60 subjects at the primary analysis.

3.3.2. Richter Transformation

This single-arm open-label substudy will enroll and treat 60 subjects at the SRT-recommended dose. The sample size will achieve a statistical power of 92% if there is at least a 22% improvement in ORR (brexucabtagene autoleucel: 50% versus historical control: 28%) with the type 1 error rate of 0.025 (1-sided) under the 2-look design based on normal approximation, with

variance of standardized test statistic under null hypothesis (H_0) using EAST (Version 6.5), as described in Table 5. The empirical power is 91% per simulation based on binomial distribution without normal approximation (Appendix 6). A statistically significant treatment effect can be claimed in this substudy if 24 or more responders (≥ 40%) are observed among the 60 subjects at the primary analysis.

3.3.3. Burkitt Lymphoma

This substudy will enroll and treat 30 subjects at the SRT-recommended dose. The sample size will achieve a statistical power of 92% if there is at least a 31% improvement in ORR (brexucabtagene autoleucel: 70% versus historical control: 39%) with the type 1 error rate of 0.025 (1-sided) under the 2-look design based on normal approximation, with variance of standardized test statistic under null hypothesis (H_0) using EAST (Version 6.5), as described in Table 6. The empirical power is 93% per simulation based on binomial distribution without normal approximation (Appendix 7). A statistically significant treatment effect can be claimed in this substudy if ≥ 17 responders (≥ 56.5%) are observed among the 30 subjects at the primary analysis.

3.3.4. Hairy Cell Leukemia, terminated early by Sponsor (effective 21 June 2023)

This substudy will enroll and treat 20 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This sample size will achieve a statistical power of 90% if there is at least a 34% improvement in ORR (brexucabtagene autoleucel: 60% vs historical control: 26%) with a type 1 error rate of 0.025 (1-sided) under the 2-look design based on normal approximation, with variance of standardized test statistic under null hypothesis (H_0) using EAST (Version 6.5), as described in Table 7. The empirical power is 87% per simulation based on binomial distribution without normal approximation (Appendix 7). A statistically significant treatment effect can be claimed in this substudy if ≥ 10 responders (≥50%) are observed among the 20 subjects at the primary analysis

3.4. Planned Analyses

An interim analysis and futility assessment will be conducted in each substudy. The interim analysis data will be reviewed by the Data Safety Monitoring Board (DSMB). The sponsor will decide if the substudies should be stopped early based on DSMB recommendation and the overall assessment of benefit and risk profile of brexucabtagene autoleucel.

If the decision, based on the interim analysis, is to continue the substudy a primary analysis will be conducted. Details regarding the primary analyses for the substudies are provided below.

All subjects receiving the brexucabtagene autoleucel infusion will be followed for survival for up to 15 years after the brexucabtagene autoleucel infusion. A follow-up analysis may be performed after all treated subjects have had the opportunity to be assessed for the pre-specified time as described below.

Additional descriptive analyses may occur after the primary analysis and follow-up analysis described above have been completed. Long-term follow-up analyses may occur as needed with data from subjects who roll over to the long-term follow-up study included.

The final analysis will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

The proposed analyses for each substudy (indication) are summarized in Table 3 below:

Table 3. Analysis Timing in Each Substudy

Indication	Study population size	Interim population size	Interim analysis (months since the last subject for interim analysis was infused)	Primary analysis (months since the last subject was infused)	Follow-up Analysis (months since the last subject was infused)
r/r WM	60	20	6	12	30
r/r RT	60	20	3	6	18
r/r BL	30	10	3	6	18
r/r HCL	20	10	3	12	30

To reduce the chance of stopping a substudy early by mistake (eg, due to the limited data available for ORR assessment and the resulting statistical power loss), while also avoiding unnecessary exposure of too many subjects to the investigational product in case it is inefficacious {Chang 2020, Xi D 2017}, we plan to conduct the interim analysis for futility in r/r WM and r/r RT substudies after 20 (out of 60) subjects have been treated and followed up for at least 6 months (for r/r WM) or 3 months (for r/r RT). Simulation results of evaluating interim analysis timing within these two substudies are included in Appendix 6. For r/r BL and r/r HCL, the interim analysis for futility will be conducted after 10 subjects have been treated and followed up for at least 3 months.

In the case that the dose is changed based on SRT recommendation, the interim analysis will be conducted after the first 20 subjects from the RT substudy and the first 10 subjects from the BL substudy have been treated at their assigned dose levels and followed up for at least 3 months.

3.4.1. Waldenstrom Macroglobulinemia, terminated early by Sponsor (effective 21 June 2023)

The statistical operating characteristics for the primary endpoint in r/r WM are summarized in Table 4.

Table 4. Statistical Operating Characteristics for the Primary Endpoint (Combined Rate of CR and VGPR) in r/r WM

Analysis	Cumulative Sample size	Cumulative Beta Spent	Futility Boundary			Cumulative Probability of Crossing Boundary Under H_0
			Z-score	Response rate (%)	p-value	
Interim	20	0.081	0.277	7.5	0.391	0.609
Primary	60	0.119	1.960	12.0	0.025	0.977

Note: EAST (Version 6.5) is used. Operating characteristics are estimated with variance of standardized test statistic under null hypothesis (H_0). Beta-spending function Rho family (parameter=0.35) is used for non-binding futility assessment.

An interim analysis will be conducted after 20 subjects (33%) have had the opportunity to be evaluated for response 6 months after treatment with brexucabtagene autoleucel. In this interim analysis, the DSMB will review investigator-reported data for both safety and efficacy (futility only). The non-binding futility boundary of a combined CR and VGPR rate of 7.5% is based on the beta spending function of rho family (parameter=0.35), with a crossing probability of 61% under the null hypothesis (combined rate of CR and VGPR $\leq$ 6%). The futility boundary is crossed if 1 or no responder is observed among the 20 subjects. If the decision is made to discontinue the substudy, then this analysis will be considered the primary analysis of this substudy.

In the case that the dose is changed based on SRT recommendation, the interim analysis will be conducted after the first 20 subjects from the RT substudy have been treated at their assigned dose levels and followed up for at least 3 months.

If the decision, based on the interim analysis, is to continue the substudy, a primary analysis will be conducted after 60 subjects have been enrolled and treated with the SRT recommended dose of brexucabtagene autoleucel and the last subject has had the opportunity to be assessed for response for at least 12 months after the brexucabtagene autoleucel infusion.

Hypothesis testing will be based on the number of responders observed among the 60 subjects, as described above. The point estimate of the combined rate of CR and VGPR will be calculated, together with its 95% confidence interval using the Clopper-Pearson method. The p-value will be calculated based on an exact test. In the event that more than 60 subjects are treated with the SRT-recommended dose in the substudy by the time of data cutoff, all treated subjects will be included in the primary analysis.

A follow-up analysis may be performed after all treated subjects have had the opportunity to be assessed for response at least 30 months after the brexucabtagene autoleucel infusion to further evaluate the risk-benefit profile of brexucabtagene autoleucel, including the durability of response. This analysis will be descriptive.

3.4.2. Richter Transformation

The statistical operating characteristics for the primary endpoint in r/r RT are summarized in Table 5.

Table 5. Statistical Operating Characteristics for the Primary Endpoint (ORR) in r/r RT

Analysis	Cumulative Sample size	Cumulative Beta Spent	Futility Boundary			Cumulative Probability of Crossing Boundary Under H_0
			Z-score	ORR (%)	p-value	
Interim	20	0.040	0.239	30.4	0.406	0.594
Primary	60	0.077	1.960	39.4	0.025	0.977

Note: EAST (Version 6.5) is used. Operating characteristics are estimated with variance of standardized test statistic under null hypothesis (H_0). Beta-spending function Rho family (parameter=0.6) is used for non-binding futility assessment.

An interim analysis will be conducted after 20 subjects (33%) have had the opportunity to be evaluated for response 3 months after treatment with brexucabtagene autoleucel. In this interim analysis, the DSMB will review investigator-reported data for both safety and efficacy (futility only). The non-binding futility boundary is ORR of 30.4% based on the beta spending function of rho family (parameter = 0.6), with a crossing probability of 59% under the null hypothesis (ORR $\leq$ 28%). The futility boundary is crossed if $\leq$ 6 responders are observed among the 20 subjects. If the decision is to discontinue the substudy, then this analysis will be considered as the primary analysis of this substudy.

If the decision, based on the interim analysis, is to continue the substudy, a primary analysis will be conducted after 60 subjects have been enrolled and treated with the SRT-recommended dose of brexucabtagene autoleucel and the last subject has had the opportunity to be assessed for response at least 6 months after the brexucabtagene autoleucel infusion. Hypothesis testing will be based on the number of objective responders observed among the 60 subjects, as described above. The point estimate of the ORR will be calculated, together with its 95% confidence interval using the Clopper-Pearson method. The p-value will be calculated based on exact test. If more than 60 subjects are treated with the SRT-recommended dose in this substudy by the time of data cutoff, all treated subjects will be included in the primary analysis.

A follow-up analysis may be performed after all treated subjects have had the opportunity to be assessed for response at least 18 months after the brexucabtagene autoleucel infusion to further evaluate the risk-benefit profile of brexucabtagene autoleucel, including the durability of response. This analysis will be descriptive.

3.4.3. Burkitt Lymphoma

The statistical operating characteristics for the primary endpoint in r/r BL are summarized in Table 6.

Table 6. Statistical Operating Characteristics for the Primary Endpoint (ORR) in r/r BL

Analysis	Cumulative Sample size	Cumulative Beta Spent	Futility Boundary			Cumulative Probability of Crossing Boundary Under H_0
			Z-score	ORR (%)	p-value	
Interim	10	0.035	0.310	43.8	0.378	0.622
Primary	30	0.076	1.960	56.5	0.025	0.978

Note: EAST (Version 6.5) is used. Operating characteristics are estimated with variance of standardized test statistic under null hypothesis (H_0). Beta-spending function Rho family (parameter=0.7) is used for non-binding futility assessment.

An interim analysis will be conducted after 10 subjects (33%) have had the opportunity to be evaluated for response 3 months after treatment with brexucabtagene autoleucel. In this interim analysis, the DSMB will review investigator-reported data for both safety and efficacy (futility only). The non-binding futility boundary is ORR of 43.8% based on the beta spending function of rho family (parameter = 0.7), with a crossing probability of 62.2% under the null hypothesis (ORR $\leq$ 39%). The futility boundary is crossed if $\leq$ 4 responders are observed among the 10 subjects. If the decision is to discontinue the substudy, then this analysis will be considered as the primary analysis of this substudy.

In the case that the dose is changed based on SRT recommendation, the interim analysis will be conducted after the first 10 subjects from the BL substudy have been treated at their assigned dose levels and followed up for at least 3 months.

If the decision based on the interim analysis is to continue the substudy, a primary analysis will be conducted after 30 subjects have been enrolled and treated with the SRT-recommended dose of brexucabtagene autoleucel and the last subject has had the opportunity to be assessed for response at least 6 months after the brexucabtagene autoleucel infusion. Hypothesis testing will be based on the number of objective responders observed among the 30 subjects. The point estimate of the ORR will be calculated, together with its 95% confidence interval using the Clopper-Pearson method. The p-value will be calculated based on exact test. If more than 20 subjects are treated with the SRT-recommended dose in this substudy by the time of data cutoff, all treated subjects will be included in the primary analysis.

A follow-up analysis may be performed after all treated subjects have had the opportunity to be assessed for response at least 18 months after the brexucabtagene autoleucel infusion to further evaluate the risk-benefit profile of brexucabtagene autoleucel, including the durability of response. This analysis will be descriptive.

3.4.4. Hairy Cell Leukemia, terminated early by Sponsor (effective 21 June 2023)

The statistical operating characteristics for the primary endpoint in r/r HCL are summarized in Table 7.

Table 7. Statistical Operating Characteristics for the Primary Endpoint (ORR) in r/r HCL

Analysis	Cumulative Sample size	Cumulative Beta Spent	Futility Boundary			Cumulative Probability of Crossing Boundary Under H_0
			Z-score	ORR (%)	p-value	
Interim	10	0.024	0.247	29.4	0.402	0.598
Primary	20	0.097	1.960	45.2	0.025	0.976

Note: EAST (Version 6.5) is used. Operating characteristics are estimated with variance of standardized test statistic under null hypothesis (H_0). Beta-spending function Rho family (parameter=2) is used for non-binding futility assessment.

An interim analysis may be conducted after 10 subjects (50%) have had the opportunity to be evaluated for response 3 months after treatment with brexucabtagene autoleucel. In this interim analysis, the DSMB will review investigator-reported data for both safety and efficacy (futility only). The non-binding futility boundary of an ORR of 29.4% is based on the beta spending function of rho family (parameter=2), with a crossing probability of 60% under the null hypothesis (ORR $\leq$ 26%). The futility boundary is crossed if $\leq$ 2 responders are observed among the 10 subjects. If the decision is made to discontinue the substudy, then this analysis will be considered the primary analysis of this substudy.

If the decision based on the interim analysis is to continue the substudy, a primary analysis will be conducted after 20 subjects have been enrolled and treated with the SRT-recommended dose of brexucabtagene autoleucel and the last subject has had the opportunity to be assessed for response at least 12 months after the brexucabtagene autoleucel infusion.

Hypothesis testing will be based on the number of objective responders observed among the 20 subjects, as described above. The point estimate of the ORR will be calculated, together with its 95% confidence interval using the Clopper-Pearson method. The p-value will be calculated based on an exact test. If more than 20 subjects are treated with the SRT recommended dose in the substudy by the time of data cutoff, all treated subjects will be included in the primary analysis.

A follow-up analysis may be performed after all treated subjects have had the opportunity to be assessed for response at least 30 months after the after the brexucabtagene autoleucel infusion to further evaluate the risk-benefit profile of brexucabtagene autoleucel, including the durability of response. This analysis will be descriptive.

4. COVARIATES

4.1. Demographic and Baseline Covariates

The following demographic and baseline disease characteristics common to the substudies may be used to examine efficacy and/or safety in subgroups or covariate analyses:

- Age (in years) at baseline (< 65, ≥ 65; 18-39, 40-64; <60, ≥60)
- Sex (Male, Female)
- Race: White, Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, other (categories may be collapsed or expanded based on accrual)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight
- Geographic region (Europe, North America)
- Country
- Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0,1)
- Number of prior regimens
- Anti-CD20 (Yes/No)
- Prior BTK inhibitors (Yes/No)
- Ibrutinib (Yes/No)
- BTK inhibitors other than ibrutinib (Yes/No)
- Prior stem cell transplant (Yes/No)
- CD19 expression by H score or % positive cells (indication specific)

The substudy specific baseline covariates are described below:

- r/r WM, **terminated early by Sponsor (effective 21 June 2023)**
  - B2-microglobulin > 3 mg/L (Yes/No)
  - LDH > 250 IU/L (Yes/No)

- Serum albumin < 3.5 g/dL (Yes/No)
- Ibrutinib during leukapheresis (Yes/No)
- Hemoglobin ≤ 110 g/L (Yes/No)
- Platelet count ≤ 100 × 10^9/L (Yes/No)
- Extramedullary Disease (Yes/No)
- Prior CNS disease (Yes/No)

- r/r RT:
  - Clonal relationship to the underlying CLL (Related vs Not related)
  - Bridging therapy (Yes/No)
  - Lactate dehydrogenase ≤ 1.5 × the upper limit of normal (ULN) (Yes/No)
  - Platelet count ≤ 100 × 10^9/L (Yes/No)
  - Tumor SPD (≤median) (Yes/No)
  - Prior therapies for CLL (1, 2, ≥ 3)
  - TP53 mutation status (Yes/No)
- r/r BL:
  - Bridging therapy (Yes/No)
  - HIV positive (Yes/No)
  - LDH > 3 × ULN (Yes/No)
  - Hgb < 11.5 g/dL (Yes/No)
  - Albumin < 3.5 g/dL (Yes/No)
  - Involvement of bone marrow (Yes/No)
  - Refractory versus early relapse (< 6 month from first remission) versus late relapse (≥ 6 months from first remission)

- r/r HCL, **terminated early by Sponsor (effective 21 June 2023)**
  - Moxetumomab pasudotox (Yes/No)
  - BRAF V600E mutation status (Yes/No)
  - Splenomegaly (<13 cm, 13 - 20 cm, > 20 cm)
  - Hairy cells in the blood (> 5×10^9/L) (Yes/No)
  - Hemoglobin < 8.5 g/dL (Yes/No)

4.2. Tocilizumab and Steroid Use

Post-baseline tocilizumab and steroid use may be used to examine efficacy in subgroups or covariate analyses.

- Tocilizumab use after brexucabtagene autoleucel infusion (Yes/No)
- Steroid use after brexucabtagene autoleucel infusion (Yes/No)
- Tocilizumab or steroid use after brexucabtagene autoleucel infusion (Yes/No)
- Tocilizumab and steroid use after brexucabtagene autoleucel infusion (Yes/No)

Covariate levels that are sparse may be collapsed for purposes of summarization and statistical analysis.

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs when a subject commences leukapheresis.

Study Day 0: Day 0 is defined as the day the subject receives the brexucabtagene autoleucel infusion. The day prior to Day 0 will be Day –1. Any days after enrollment and prior to Day –1 will be sequential and negative integer-valued.

Baseline: The baseline value is defined as the last non-missing value taken prior to lymphodepleting chemotherapy. If a subject receives an optional bridging therapy, assessments such as PET-scan must be performed after bridging therapy and before lymphodepleting chemotherapy to establish the baseline.

Study therapy: Study therapy includes lymphodepletion chemotherapy and brexucabtagene autoleucel.

On-study: Time from enrollment to the last date of contact.

End of study: Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments.

Actual follow-up time: Actual follow-up time among all subjects treated with brexucabtagene autoleucel is calculated as the time from the date of brexucabtagene autoleucel infusion to the date of death, last date known to be alive, lost to follow-up, or full withdrawal of consent, whichever is later.

Potential follow-up time: Potential follow-up time is defined as the time from the date of brexucabtagene autoleucel infusion to the data cutoff date for the analysis.

5.2. Safety

5.2.1. Treatment-emergent Adverse Event

Treatment-emergent adverse event (TEAE) is defined as any adverse event with onset on or after the brexucabtagene autoleucel infusion. All TEAEs will be summarized by preferred term and toxicity grade. AEs occurred within other study periods may be summarized as appropriate.

5.2.2. Deaths

All deaths that occur from the beginning of the lymphodepletion chemotherapy period up through the end of study will be summarized. Deaths that occur from the brexucabtagene autoleucel infusion will also be summarized.

5.2.3. Time to onset of an AE of Interest

Time to onset of an AE of interest is defined as the time from the date of the brexucabtagene autoleucel infusion until the earliest date of onset of the AE in the event class of interest, using the following equation: the start date of the first AE in the event class – the date of the brexucabtagene autoleucel infusion.

5.2.4. Resolution of an AE of Interest

An AE of interest is considered to be resolved if all AEs in the event class of interest are resolved at the time of the analysis data cutoff date. Any AE with an end date that is the same as the death date is not considered to be resolved.

5.2.5. Duration of an AE of Interest

The duration of an AE of special interest is defined as the time from the earliest onset date of the AE in the event class of interest until the resolution date of the last AE in the event class, regardless of any gaps occurring between events, using the following equation: the resolution date of the last AE in the event class – the start date of the first AE in the event class + 1. The duration of an AE of interest may only be calculated for a subject if all AEs in the event class encompassing the AE of interest have resolved by the data cutoff date.

5.2.6. Important Identified Risks

5.2.6.1. Cytokine Release Syndrome (CRS)

CRS will be identified via an eCRF that is specifically designed to collect CRS as a syndrome. Specific symptoms of CRS are collected on the AE log form and are linked to CRS. CRS severity is graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading {Lee 2019}. Neurologic AEs are not reported as part of CRS, but rather they are reported on the AE log form separately based on specific symptoms per Common Terminology Criteria for Adverse Events (CTCAE) and graded as per below.

5.2.6.2. Neurologic Events

Neurologic events will be graded as per the ASTCT Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) Consensus Grading {Lee 2019}. ICANS will be identified via an eCRF that is specifically designed to collect ICANS as a syndrome. Specific symptoms of ICANS are collected on the AE log form and are linked to ICANS.

Neurologic events, including cerebral edema, may also be identified by 2 search strategies:

- Method 1: A Medical Dictionary for Regulatory Activities (MedDRA) search term list (MST) that was developed at Kite based on a modification of the search strategy described by Topp and colleagues {Topp 2015}.

- Method 2: MedDRA System Organ Classes (SOCs) of psychiatric disorders and nervous system disorders, excluding the following 2 High-Level Group Terms (HLGTs): sleep disorders and disturbances and sleep disturbances (incl subtypes). MedDRA preferred terms may be revised based on regulatory agency feedback.

5.2.6.3. Infections

Infections are identified as AEs within the system organ class of infections and infestations that occur on or after the brexucabtagene autoleucel infusion, in MedDRA SMQ of opportunistic infections (narrow search), and in MedDRA high level group terms (HLGT) that capture events of:

- Bacterial infection, encompassing preferred terms within the MedDRA HLGTs of
  - Bacterial infectious disorders
  - Chlamydial infectious disorders
- Viral infection, encompassing preferred terms within the MedDRA HLGT of viral infectious disorders
- Other infections, encompassing preferred terms within the MedDRA HLGT of infections - pathogen unspecified.

5.2.6.4. Cytopenias (Thrombocytopenia, Neutropenia, or Anemia, Including Aplastic Anemia)

Cytopenias (thrombocytopenia, neutropenia, or anemia) will be identified as follows:

- Thrombocytopenia is identified using the SMQ for haematopoietic thrombocytopenia (narrow search)
- Neutropenia is identified using a MST search strategy defined by Kite
- Anemia (including aplastic anemia) is identified using the SMQ haematopoietic erythropenia (broad search)

5.2.6.5. Hypogammaglobulinemia

Hypogammaglobulinemia will be identified using a MST search strategy defined by Kite.

5.2.7. Important Potential Risks

5.2.7.1. Secondary Malignancies

AEs coded within the SOC of benign, malignant, and unspecified neoplasms (including cysts and polyps) and deaths will be reviewed by the Kite Safety and Pharmacovigilance Team for potential secondary malignancies.

5.2.7.2. Tumor Lysis Syndrome

Tumor lysis syndrome will be identified using the SMQ of tumor lysis syndrome. The narrow version of this SMQ will be used.

5.2.7.3. Graft-Versus-Host-Disease (GVHD)

GVHD will be identified using a MST search strategy defined by Kite that uses preferred term subsets from the HLGT of procedural related injuries and complications not elsewhere classified (NEC) and high-level term (HLT) of immune and associated conditions NEC. Aggravation of GVHD will comprise those events which are of new onset or have worsened by one or more CTCAE grades since study entry.

5.2.7.4. Immunogenicity

Subjects will be tested for the development of antibodies by testing for reactivity against FMC63, the parent murine antibody used for the development of the single-chain variable region fragment (scFv) of the anti-CD19 CAR construct. Positive samples will then be tested to confirm the presence of antibody to the extracellular portions of anti-CD19 CAR.

5.2.7.5. Replication Competent Retrovirus (RCR)

Since anti-CD19 CAR T cells comprise gamma murine retroviral vector-transduced T cells, the presence of RCR in the blood of treated subjects will be monitored.

5.2.8. Other AEs of Interest

5.2.8.1. Autoimmune Disorders

Autoimmune disorders will be identified using the SMQ of immune-mediated/autoimmune disorders. The narrow version of this SMQ will be used.

5.2.8.2. Cardiac Failure

Cardiac failure will be identified using the SMQ of cardiac failure. The narrow version of this SMQ will be used.

5.2.8.3. Cardiac Arrhythmias

Cardiac arrhythmias will be identified using the SMQ of cardiac arrhythmias. The narrow version of this SMQ with selected broad SMQ preferred terms will be used.

5.2.8.4. Prolonged Cytopenias (Thrombocytopenia, Neutropenia, or Anemia, Including Aplastic Anemia)

Prolonged cytopenias (thrombocytopenia, neutropenia, or anemia) will be identified as cytopenias present on or after Day 30 following the brexucabtagene autoleucel infusion.

5.2.9. Hy's Law

A subject meets Hy's Law laboratory criterion if AST or ALT are $\geq 3 \times$ upper limit of normal (ULN), total bilirubin is $\geq 2 \times$ ULN, and alkaline phosphatase (ALP) is $< 2 \times$ ULN at any study visit after brexucabtagene autoleucel infusion. The Kite Safety and Pharmacovigilance Team will review the cases that meet Hy's law laboratory criteria and identify those cases that also clinically meet Hy's law criteria. A case may be disregarded if a causal association with study therapy is unlikely due to timing or a more plausible alternate etiology for the laboratory abnormalities is observed.

5.2.10. Concomitant Medications of Interest

Concomitant medications are defined as the medications administered to subjects on or after the brexucabtagene autoleucel infusion.

Concomitant medication drug baskets of interest for systemic steroids, vasopressors, nonsteroidal immunosuppressants other than tocilizumab, and IV immunoglobulins are defined by Kite and are documented separately.

5.2.11. Concomitant Procedure

Concomitant procedures are defined as the procedures administered on or after the brexucabtagene autoleucel infusion.

5.3. Efficacy

5.3.1. Disease Response Rate and Best Objective Response

The disease response rate for each substudy is defined below:

- r/r WM:
  - The combined rate of CR and VGPR is defined as the proportion of subjects who achieve a best response of either CR or VGPR per the Sixth International Workshop in WM {Owen 2013}.
  - ORR is defined as the proportion of subjects who achieve a best response of CR, VGPR, or PR per the Sixth International Workshop in WM {Owen 2013}.

- r/r RT:
  - ORR is defined as the proportion of subjects who achieve a best response of either CR or PR per the Lugano Classification {Cheson 2014}.
  - In the subgroup of CLL, ORR is defined as the proportion of subjects who achieve a best response of either CR, CRi, or PR by investigator assessment per IWCLL 2018 criteria {Hallek 2018}.
- r/r BL: ORR is defined as the proportion of subjects who achieve a best response of either CR or PR per the Lugano Classification {Cheson 2014}.
- r/r HCL: ORR is defined as the proportion of subjects who achieve a best response of either CR or PR per Grever and colleagues {Grever 2017}.

The best objective response (BOR) for each substudy is defined below:

- r/r WM: BOR includes CR, VGPR, PR, MR, SD, PD, and not evaluable per the Sixth International Workshop in WM {Owen 2013}.
- r/r RT and r/r BL: BOR includes CR, PR, SD, PD, and not evaluable per the Lugano Classification {Cheson 2014}.
- r/r RT in the subgroup of CLL: BOR includes CR, CRi, PR, SD, PD, and not evaluable by investigator assessment per IWCLL 2018 criteria {Hallek 2018}.
- r/r HCL: BOR includes CR, PR, SD, PD and not evaluable per Grever and colleagues {Grever 2017}.

All subjects who do not meet the criteria for objective response by the analysis data cutoff date will be considered non-responders, including the subjects with non-evaluable assessment data and those without any assessment. The derivation of this endpoint will only include response assessments obtained prior to any other additional therapy (e.g., subsequent anti-cancer, including stem cell transplant therapy). Response may be defined per central assessment or investigator assessment.

5.3.2. Duration of Response

DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or death. Response and progression may be defined per central assessment or investigator assessment.

All 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. DOR will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (including stem cell transplant). The DOR for subjects who undergo stem cell transplant while in remission will be

censored at the last evaluable disease assessment date prior to stem cell transplant; the DOR for subjects that undergo other new anti-cancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer therapies. A supplementary analysis will be conducted in which disease assessments obtained after stem cell transplant are included in the derivation of DOR.

5.3.3. Progression-free Survival

For the modified intent-to-treat (mITT defined in Section 6.1) analysis set, PFS is defined as the time from the date of brexucabtagene autoleucel infusion to the date of disease progression or death from any cause. For the PFS with the full analysis set (FAS defined in Section 6.3) in which enrolled but not treated subjects are included, the PFS will be calculated as the time from the enrollment date to the date of disease progression or death from any cause. Progression may be defined per central assessment or investigator assessment.

All subjects alive and not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. PFS will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (including stem cell transplant). The PFS for subjects who undergo stem cell transplant while in remission will be censored at the last evaluable disease assessment date prior to stem cell transplant; the PFS for subjects that undergo other new anti-cancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer therapies. Supplementary analysis will be conducted, and the details are included on the derivation of PFS in Appendix 5.

5.3.4. Overall Survival

For the mITT analysis set, OS is defined as the time from the date of brexucabtagene autoleucel infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at the last date known to be alive or the data cutoff date, whichever is earlier. For the OS with the FAS in which enrolled but not treated subjects are included, the OS will be calculated as the time from the enrollment date to the date of death from any cause. Additional details on the derivation of overall survival and the specific data modules that will be used to derive the last date known to be alive are provided in Appendix 3.

5.3.5. Time to Next Treatment

For the mITT analysis set, Time to next anti-cancer treatment (TTNT) is defined as the time from the date of brexucabtagene autoleucel infusion to the start of new anti-cancer (including stem cell transplant) therapy or death from any cause. Subjects alive and not starting any new anti-cancer (including stem cell transplant) therapy at the analysis data cutoff date will be censored at the last contact date. For TTNT with the FAS in which enrolled but not treated subjects are included, the TTNT will be calculated as the time from the enrollment date to the date of the start of new anti-cancer (including stem cell transplant) therapy or death from any cause. Additional details on the specific data modules that will be used to derive the last date known to be alive are provided in Appendix 3, if the TTNT is also estimated using the Kaplan-Meier (KM) method.

5.3.6. Complete Response Rate

Complete response (CR) rate is defined as the proportion of subjects with a best overall response of CR per the Sixth International Workshop in WM {Owen 2013} for r/r WM, per the Lugano Classification {Cheson 2014} for r/r RT and r/r BL, and per Grever and colleagues {Grever 2017} for r/r HCL. Response may be defined per central assessment or investigator assessment. The derivation of CR rate will include response assessments obtained after the randomization up to PD, the last evaluable disease assessment prior to any subsequent anti-cancer therapy (including stem cell transplant), or the last evaluable disease assessment prior to data cutoff, whichever is the earliest.

5.3.7. Time to First Response

For the mITT analysis set, time to the first response is defined as time from the date of brexucabtagene autoleucel infusion to the date of first response per the Sixth International Workshop in WM {Owen 2013} for r/rWM, per the Lugano Classification {Cheson 2014} for r/r RT and r/r BL, and per Grever and colleagues {Grever 2017}. For the time to the first response with the FAS in which enrolled but not treated subjects are included, the time to first response will be calculated as the time from the enrollment date to the date of the first response.

5.3.8. Time to Best Response

For the mITT analysis set, time to best response is defined as time from the date of brexucabtagene autoleucel infusion to the date of best response per the Sixth International Workshop in WM {Owen 2013} for r/rWM, per the Lugano Classification {Cheson 2014} for r/r RT and r/r BL, and per Grever and colleagues {Grever 2017}. For the time to best response with the FAS in which enrolled but not treated subjects are included, the time to best response will be calculated as the time from the enrollment date to the date of best of response.

5.3.9. Rate of MRD Negative Response

For the r/r RT and r/r HCL substudies, the rate of MRD negative response is defined as the proportion of subjects achieving a CR who had an MRD negative result.

For RT, CLL MRD negative is defined as fewer than 1 CLL cell per 10,000 leukocytes (0.01%, ie, $< 10^{-4}$). The CLL MRD assessment will be done on bone marrow aspirate and/or peripheral blood at local laboratory.

For HCL, MRD is defined as fewer than 1 HCL cell per 100,000 leukocytes (0.001%, ie, $< 10^{-5}$). The HCL MRD assessment will be done on bone marrow aspirate at central laboratory.

5.4. Patient-reported Outcomes

5.4.1. EORTC QLQ-C30

This measure is a 30-item questionnaire designed to provide a multidimensional assessment of health-related quality of life (HRQoL), with a recall period of 1 week. The European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire (EORTC QLQ-C30) version (v)3.0 includes the following scales:

- 5 multi-item functional scales (assessing physical, role, emotional, cognitive, and social functioning) and 3 symptom scales (fatigue, nausea and vomiting, and pain)
- 6 single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties)
- 2 global scales (Global Health Status and HRQoL)

No items are shared between the scales. The first 28 of 30 items have 4-level ordinal responses from 1 ("not at all") to 4 ("very much"). The final 2 items, comprising the global health status and HRQoL scale, have 7-level ordinal responses from 1 ("very poor") to 7 ("excellent"). Each scale is measured from 0 to 100 after a linear transformation. Higher scores for functional scales and the Global Health Status or Global HRQoL scales indicate a higher level of functioning and a better HRQoL, respectively, whereas higher scores in symptom scales represent a higher level of symptoms.

5.4.2. EQ-5D-5L

The EuroQoL 5-Dimension 5-Level (EQ-5D-5L) is a generic measure of health status that provides a simple descriptive profile and a single index value. The EQ-5D-5L has 2 components: a questionnaire covering 5 dimensions and a tariff of values based upon direct valuations of health states using a visual analog scale (VAS).

The VAS component of the EQ-5D-5L is a 20-cm VAS for recording self-rated current HRQoL state and is used to describe the subjects' health status on the day of the assessment. This VAS score is recorded by each subject for his or her current HRQoL state and scored 0 ("the worst health you can imagine") to 100 ("the best health you can imagine").

All PRO measures will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual.

6. ANALYSIS SETS

6.1. Modified Intent-to-treat

The mITT analysis set will consist of all subjects enrolled and treated with pivotal dose of brexucabtagene autoleucel, with measurable disease at baseline (or post-bridging therapy, if applicable). This analysis set will be used for efficacy analyses.

6.2. Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of brexucabtagene autoleucel. This analysis set will be used for safety analyses.

6.3. Full Analysis Set

The full analysis set (FAS), or intent-to-treat (ITT) set, will consist of all enrolled subjects (ie, the subjects who had leukapheresis). This analysis set will also be used for summary of subject disposition, as well as analyses on the key efficacy endpoints (disease response rate, DOR, PFS, and OS).

6.4. DLT-evaluable Set

The DLT-evaluable set will consist of first 3 subjects treated. If 1 of these subjects experience a DLT within 28 days of the brexucabtagene autoleucel infusion, an additional 3 subjects will be included in the DLT-evaluable set.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

7.1. Safety Data Review by Safety Review Team

A Safety Review Team (SRT), that is internal to the study sponsor and in collaboration with at least 1 study investigator, will review safety and efficacy data and make recommendations regarding further enrollment and/or dose modification in each substudy after 3 or 6 subjects have been treated with the initial dose (2×10^6 CAR T cells/kg of body weight) and followed for 28 days. In case of dose limiting toxicities (DLTs), the SRT can recommend assessing DLTs in 3 additional subjects at the same dose level or recommend that the treating dose for the remaining patients can be reduced to 1×10^6 CAR T cells/kg. Enrollment will be paused to allow the SRT to review safety data that have been acquired for 28 days following infusion in all treated subjects in a DLT cohort, prior to providing a recommendation on the continued dose selection. Enrollment will re-start once the dose recommendation is available. Only subjects treated with the selected target dose will be included in the evaluable subject population for the primary analysis.

DLTs are defined as the following brexucabtagene autoleucel related events with onset within the first 28 days after the infusion of brexucabtagene autoleucel.

Table 8. Dose Limiting Toxicities

Dose-limiting Toxicities	Exceptions
Any brexucabtagene autoleucel related Grade 5 event	Grade 5 disease progression
Hematologic toxicity Grade 4 does not recover to Grade ≤ 2 by Day 28	Any hematologic toxicity Grade 4 attributable to underlying disease Lymphopenia
Grade 3 or 4 thrombocytopenia lasting of any duration if accompanied by Grade 2 or higher bleeding	None
All brexucabtagene autoleucel related Grade 4 nonhematologic toxicities including opportunistic infections and complications associated with HIV[a]	None
Any brexucabtagene autoleucel related Grade 3 neurotoxicity including ICANS, regardless of duration	None
All brexucabtagene autoleucel related Grade 3 nonhematological toxicities lasting ≥ 7 days including opportunistic infections and complications associated with HIV[a]	Grade 3 fever Grade 3 aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, or other liver function test elevation, provided there is resolution to Grade 2 or lower within 14 days Grade 3 nausea and/or anorexia Grade 3 febrile neutropenia returning to baseline within 2 weeks Grade 3 insomnia, fatigue, and malaise

Dose-limiting Toxicities	Exceptions
	Grade 3 infection that improves to Grade 2 or lower within 2 weeks Grade 3 TLS including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, or hyperuricemia)
All brexucabtagene autoleucel related Grade 3 cardiac and/or pulmonary events of any duration	Grade 3 cardiac and/or pulmonary events if related to CRS and improves to Grade 2 or lower within 72 hours

Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell encephalopathy; TLS, tumor lysis syndrome
Notes: Adverse events are graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. CRS and neurotoxicity is graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for CRS and immune effector cell associated neurotoxicity syndrome (ICANS) {Lee 2019}. The severity of individual signs/symptoms of CRS and neurological events will be graded according to NCI CTCAE v5.0 for those signs/symptoms that are not part of the grading scale.
a Infections associated with HIV and AIDS such as (but not exclusive to): Candidiasis of bronchi, trachea, or lungs, extrapulmonary Cryptococcosis, Cytomegalovirus disease (other than liver, spleen or nodes), Histoplasmosis, disseminated or extrapulmonary, Mycobacterium avium complex, kansasii or other species (disseminated or extrapulmonary), Pneumocystis jirovecii pneumonia or complications such as HIV-associated Encephalopathy

Table 9. Recommendations based on Dose Limiting Toxicities

Number of Subjects with a Dose Limiting Toxicity in a Cohort	Potential Recommendation
0 of 3 subjects or if 1 DLT occurred in the initial 3 subjects and no DLT occurs in the subsequent 3 subjects	If the dose is determined tolerable, then this will be the recommended dose.
1 of 3 subjects	Enroll 3 more subjects at the same dose level.
≥2 of 3 subjects or if 1 DLT occurred in the initial 3 subjects and ≥ 1 DLT occurs in the subsequent 3 subjects	The lower dose level will be established as the recommended dose (if assessed to be tolerable and recommended by the SRT).

7.2. Interim Analysis

An independent DSMB will review safety data throughout the trial duration after the target dose for each substudy is confirmed by the SRT. There will be a single interim analysis in each substudy. The DSMB will review safety and efficacy data against the non-binding futility rule and make study conduct recommendations based on an overall assessment of benefit versus risk as described in Section 3.4 above.

An interim analysis and futility assessment will be conducted in each substudy and is described below. Data from the interim analyses will be reviewed by the DSMB. The sponsor will decide if the substudies should be stopped early based on DSMB recommendation(s) and an overall assessment of benefit and risk profile. The futility boundary is described in Section 3.4.

7.3. Assessment of Criteria to Pause Enrollment

As part of its oversight of the study, the DSMB will continuously assess whether to continue, pause or stop the study. Considering the biological heterogeneity of the 4 indications under investigation, pausing enrollment to each substudy will occur independently.

In the SRT phase (that includes the treatment of the initial 3 or 6 subjects), any Grade 5 adverse event that is related to brexucabtagene autoleucel treatment will trigger a pause in enrollment.

Moreover, enrollment will be paused following the treatment of the 3 DLT-evaluable subjects, to assess the frequency of DLTs and to allow the SRT to review 28 days of data post infusion in all treated subjects prior to providing a recommendation on the target dose.

After the pivotal dose has been confirmed, enrollment within a substudy will be paused if:

1) A Grade 5 brexucabtagene autoleucel-related AE occurs

or

2) Subject incidence of the following Grade 4 brexucabtagene autoleucel-related AEs is ≥ 33%:

    a) ICANS (graded according to the ASTCT consensus grading {Lee 2019})

    b) CRS (graded according to the ASTCT consensus grading {Lee 2019})

    c) Other non-hematological Grade 4 SAEs

    d) Infection (treatment-related)

Additionally, study enrollment will be paused when the required number of subjects have been enrolled for the planned interim analyses of the r/r RT and r/r BL substudies, until the data from this interim analysis have been assessed.

7.4. Access to Aggregate and Subject-level Data and Individual Subject Treatment Assignments

This is an open-label study. Subjects, the study sponsor, and investigators will be aware that each subject is planned to be treated with Brexucabtagene Autoleucel. Data handling procedures designed to maintain the trial credibility and validity in this study are described in the Trial Integrity Document (TID).

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The database will be subject to the edit checks outlined in the Data Management Plan and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analysis and the final database lock. For interim analyses, snapshots may include data that has not passed all data cleaning procedures at the time the data are extracted.

8.2. Electronic Transfer and Archival of Data

The Medidata Rave system will be used to collect the data in this study. Raw data extracted from Medidata Rave will be archived prior to further dataset creation, maintenance, and analysis. Datasets (raw data, study data tabulation model [SDTM] data, and/or analysis data model [ADaM] data) for planned analyses will be archived. Any additional unplanned analyses that occur after the primary analysis and prior to the final analysis will also be archived. Key data external to the clinical study database (see below) will be included in the relevant SDTM and ADaM modules when the external data are available.

Data from the central pathology laboratory (including tumor pathology, tumor genetic, and molecular characteristics), the product manufacture (total T cells, CAR T cells [transduction rate], duration of manufacturing time), central laboratory assessment of subject serum samples (including CAR T cell levels in the peripheral blood, antibody assays, RCR testing), and central radiology review will be generated from contract laboratories and Kite Pharma. These data will be transferred to Kite and held in a peripheral directory and not built into the clinical trial database. At the time when analyses require these data, they may be merged with the SDTM and ADaM datasets.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy

The method for handling missing data is described in the definition for each efficacy endpoint. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date, the imputation rule and the corresponding censoring date for survival can be found in Section 13 (Appendix 1 and Appendix 2).

8.3.2. Safety

Partial AE start dates will be imputed. If dates are missing or incomplete for adverse event start dates, the algorithm defined in Appendix 1 will be used. Completely missing death dates or death dates with only a year reported will not be imputed.

8.4. Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include, but not be limited to, violations of eligibility criteria and use of exclusionary medication during the study. Lack of protocol compliance will be evaluated by summarizing the subject incidence of important protocol deviations. High rates of important protocol deviations may indicate bias.

Endpoints derived from investigator assessment of radiologic scans and disease assessments may be subject to bias; the concordance between investigator and central review of radiologic scans and disease assessments will be summarized where appropriate.

8.5. Outliers

Descriptive statistics may be used to identify potential outliers in any key variables analyzed. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6. Validation and Configuration Management

Programs for the development of the SDTM and ADaM datasets and the generation of the tables, figures, and listings will be developed and maintained according to Gilead/Kite Standard Operating Procedures (SOPs). The name and version of the software used to generate analyses will be specified in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

Summaries and statistical analyses will be performed separately for each substudy.

The goal of the primary statistical analysis is to compare the observed disease response rate per central assessment to a historical control rate prespecified in each substudy. Hypothesis testing will be one-sided, and all 95% confidence intervals will be 2-sided. At the time of the primary analysis, 95% confidence intervals for disease response rate will be presented.

A clinical study report (CSR) for each substudy will be written at the time of the primary analysis. After the primary analysis, additional follow-up analyses of efficacy and safety will be performed as needed to satisfy regulatory requirements and to perform long-term efficacy and safety follow-up. The CSR may be amended with additional subject safety and survival follow-up data after the planned primary analysis.

The final analysis will be performed after all subjects have completed a substudy, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

Subjects who receive brexucabtagene autoleucel are to be followed for up to 15 years after the brexucabtagene autoleucel infusion; part of this time will be after the subject has transitioned to a separate LTFU study of subjects who received an infusion of gene-modified cells (study KT-US-982-5968). The long-term data analysis for the current study will be performed after subjects in the brexucabtagene autoleucel treatment arm have transitioned to this separate LTFU study. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

9.2. Subject Disposition

The number of subjects screened, enrolled/leukapheresed, receiving ibrutinib during apheresis, treated with bridging therapy, treated with lymphodepleting chemotherapy, and treated with brexucabtagene autoleucel will be summarized. The reasons for discontinuing treatment and discontinuing study will be summarized.

Summaries of actual and potential follow-up time among all subjects treated with brexucabtagene autoleucel will be provided.

The number of subjects enrolled and treated by country and site will be summarized.

The number of subjects in each analysis set will be provided.

9.3. Important Protocol Deviations

The clinical study team will define important protocol deviation categories and review all potential important protocol deviations at minimum, prior to the database snapshot for the primary efficacy analysis. Important protocol deviations will be categorized by deviation type (eg, entry eligibility, use of excluded medication). The subject incidence of important protocol deviations will be summarized overall and by deviation category.

9.4. Protocol Variations due to COVID-19

The clinical study team will collect the protocol variations due to coronavirus disease (COVID-19) and define variation categories and review all protocol variations. A listing with protocol variations will be provided. In addition, the potential impact of the COVID-19 on the safety and efficacy profiles will be evaluated.

9.5. Demographic and Baseline Characteristics

Summary statistics and frequencies for the demographic and baseline characteristics as listed in Section 4.1 will be tabulated.

9.6. Efficacy Analyses

Note: Substudies KT-US-568-0138-A (WM) and KT-US-568-0138-A (HCL) were terminated early by the Sponsor (effective 21 June 2023).

9.6.1. Hypothesis Testing

The hypothesis testing of primary efficacy response rates (the combined rate of CR and VGPR for r/r WM and ORR for other substudies) per central assessment will be conducted on the mITT analysis set in the primary analysis.

The hypothesis testing for each disease indication will be conducted at a significance level of 0.025 (1-sided). The responses from subjects in the study population are assumed to be independent and follow a binomial distribution. An exact binomial test will be used to compare the observed response rates per central assessment to the historical response rate as described in each substudy.

9.6.2. Disease Response Rate and Best Response Rate

The combined rate of CR and VGPR (for r/r WM only) and ORR per central assessment will be calculated. The subject incidence rate of best response (CR, VGPR (for r/r WM only), CRi (for r/r RT only in the subgroup of CLL), PR, SD, PD, NE) per central assessment will be tabulated.

Two-sided 95% confidence intervals will be provided about the disease response rate and best response rate, calculated with the Clopper-Pearson (an exact interval) method. The analyses of disease response rate and best response rate will also be analyzed per investigator assessment.

The disease response rate and best response rate will be conducted for subjects using the mITT and FAS analysis sets. In addition, the disease response rate and best response rate will be conducted as supplementary analyses for subjects who fulfill the eligibility criteria regardless of the commencement of leukapheresis.

The concordance of objective response and best response per central assessment and investigator assessment will be evaluated. A summary table of concordance, concordance rate, a kappa statistic, and a 2-sided 95% confidence interval about the kappa statistic will be provided.

Further analyses comparing the investigator and central assessment may be performed as appropriate.

Disease response rate and 95% confidence intervals will be generated for subgroups defined by each of the categorical covariates in Section 4.1. Subgroup analysis with additional covariates may also be explored. A forest plot of the proportion of responders for each of these subgroups will be generated.

9.6.3. Duration of Response

KM estimates and 2-sided 95% CIs will be generated for the duration of response (DOR) for the subjects who responded to brexucabtagene autoleucel. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for DOR per central assessment as well as per investigator assessment. The reverse KM approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

Supplementary analyses of DOR will be conducted for subjects who undergo stem cell transplant while in remission, where the disease assessments obtained after stem cell transplant will be used in the derivation of DOR, or subsequent new anti-cancer therapies (including stem cell transplant) are considered to be events in the derivation of DOR. A sensitivity analysis may be conducted if 5% or more subjects have two or more consecutive disease assessments missed prior to receiving stem cell transplant or new anti-cancer therapy, with the DOR censored at the last evaluable disease assessment prior to the consecutive missing visits.

Analyses of DOR will be conducted in analysis sets of the mITT, FAS, and subjects who fulfill eligibility criteria regardless of the commencement of leukapheresis.

DOR may be summarized in subgroups defined by the best response attained on study.

9.6.4. Progression-free Survival

KM plots, estimates, and 2-sided 95% confidence intervals will be generated for PFS. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for PFS per central assessment and PFS per investigator assessment.

Supplementary analyses will be conducted in which disease assessments obtained after stem cell transplant (for subjects undergoing stem cell transplant while in remission) are included in the derivation of PFS, or subsequent new anti-cancer therapies (including stem cell transplant) are considered to be events in the derivation of PFS.

PFS Analyses will be conducted in analysis sets of the mITT, FAS, and subjects who fulfill eligibility criteria regardless of the commencement of leukapheresis.

Subgroup analyses of the PFS rate may be generated in subgroups defined by the covariates in Section 4.1.

PFS may be summarized in subgroups defined by the best response attained on study.

9.6.5. Overall Survival

KM estimates and 2-sided 95% CIs will be generated and estimates of the proportion of subjects alive at 3-month intervals will be provided for the mITT and FAS analysis sets.

OS may be summarized in subgroups defined by the best response attained on study.

9.6.6. Time to Next Treatment, Time to First Response, and Time to Best Response

The time to initiation of next anti-cancer treatment, time to first objective response and time to best objective response will be summarized with descriptive statistics in the mITT analysis set (time from the date of brexucabtagene autoleucel infusion) and the FAS (time from the enrollment date).

KM estimates and 2-sided 95% CIs for TTNT may be generated. The median time for TTNT and its 95% CIs may be provided.

9.6.7. Rate of MRD Negative Response

Summary of the rate of MRD negative and exact 2-sided 95% CIs will be generated.

9.7. Safety Analyses

Safety analyses will be conducted using the safety analysis set for each substudy, separately. The primary analysis of safety data will summarize TEAEs, death, and laboratory values with onset on or after the date of brexucabtagene autoleucel infusion. Sample table layouts are provided in Appendix 2.

AEs will be coded with the MedDRA at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of AEs will be graded using the National Cancer Institute CTCAE version 5.0.

CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) is graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading {Lee 2019}. The severity of individual signs/symptoms of CRS and neurological events will be graded according to NCI CTCAE v5.0 for those signs/symptoms that are not part of the grading

scale. Fatal AEs that are attributed to disease progression may be included in the death summary with a primary death reason of "disease progression" regardless of the coded CTCAE version 5.0 preferred term.

Subjects enrolled, but not dosed with brexucabtagene autoleucel, will be followed for AEs for 30 days after the last study-specific procedure. AEs reported in these subjects will be archived in the study database and available in SDTM and ADaM datasets but will not be tabulated in AE summaries.

The below safety analysis will be done for each substudy, unless specified.

9.7.1. Adverse Events

Treatment-emergent AEs (TEAEs), defined as AEs with an onset on or after the brexucabtagene autoleucel infusion.

The subject incidence of the following TEAEs will be tabulated:

- Summary of AEs (any, worst severity, serious, treatment-related)
- All AEs
- All SAEs
- All brexucabtagene autoleucel-related AEs
- All brexucabtagene autoleucel -related SAEs
- All Grade 3 or higher AEs
- All Grade 3 or higher brexucabtagene autoleucel-related AEs
- Fatal AEs
- AEs of special interest, including identified risks and potential risks
- AEs defined as dose limiting toxicities (DLTs)

The subject incidence of deaths by time periods will be provided.

A subject listing of deaths through 30 days after brexucabtagene autoleucel infusion will be provided.

Subgroup analyses of AEs may be generated for selected covariates from the list in Section 4.

The time to onset and resolution and the duration of CRS will be summarized. Cardiac arrhythmias and cardiac failure in the context of CRS may be summarized.

The time to onset and resolution and the duration of neurologic events will be summarized. Especially neurologic events will be identified using two methods. One is defined by Topp and colleagues {Topp 2015} and the other one is defined by Kite.

Cytopenias will be summarized by categories of neutropenia, anemia, and thrombocytopenia; cytopenias present after 30 days from brexucabtagene autoleucel infusion will also be summarized.

Infections will be summarized by categories (bacterial infections, viral infections, opportunistic infections, and other infections).

9.7.2. Procedures and Concomitant Medications

The incidences of procedure and concomitant medications used to manage AEs will be tabulated (see Section 9.7.7).

9.7.3. Laboratory Test Results

Laboratory results will be graded according to NCI CTCAE version 5.0. The incidence of post-infusion worst-grade lab toxicities for all analytes will be summarized. Additional summaries for the shift from baseline to the worst toxicity grade after brexucabtagene autoleucel infusion may also be generated.

9.7.4. Incidence of Antibodies Against Brexucabtagene Autoleucel CAR (Immunogenicity)

The subject incidence of any anti-CD19 CAR antibodies will be tabulated. For subjects testing positive for antibodies, the persistence of the antibody over time will be listed and summarized.

9.7.5. Replication-competent Retrovirus

The subject incidence of replication-competent retrovirus (RCR) detected in peripheral blood mononuclear cells (PBMCs) at baseline and after brexucabtagene autoleucel infusion will be tabulated overall and by assessment time. The persistence of RCR over time will be summarized.

9.7.6. Exposure to Study Treatment

Summary statistics and subject listings will be provided for the following:

- Total body surface area-adjusted dose of cyclophosphamide
- Total body surface area-adjusted dose of fludarabine
- Weight-adjusted dose of brexucabtagene autoleucel
- Total CAR T cells of the brexucabtagene autoleucel infusion

- Total T cells of the brexucabtagene autoleucel infusion
- Transduction rate
- Percentages of CD4 and CD8 T cells
- Percentages of T cell phenotypes
- Interferon (IFN)-gamma production in co-cultures of brexucabtagene autoleucel product and $CD19^+$ target cells
- Vector copy number of brexucabtagene autoleucel product

Summaries may also be provided by demographics and baseline characteristics as appropriate.

9.7.7. Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be summarized by medication category and WHO Drug coded term. The subject incidence of procedures will be tabulated. The duration and indication of concomitant medications of interest, steroids and tocilizumab for example, may be summarized.

9.7.8. Immune Effector Cell-associated Encephalopathy and Mini-Mental Status Exam

Summary statistics for the immune effector cell-associated encephalopathy score and change from baseline in the immune effector cell-associated encephalopathy score over time will be provided for all subjects in the safety analysis set.

If MMSE status exam is included in the neurologic examination, summary statistics for the Mini-Mental Status Exam (MMSE) score and change from baseline in the MMSE score over time may will be provided for all subjects in the safety analysis set and may be summarized within groups defined by the occurrence of Grade 3 or higher neurotoxicity.

9.8. Patient-reported Outcomes

9.8.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) scores

EORTC-QLQ-C30 scores will be summarized at baseline and post study treatment visits. Changes in the EORTC-QLQ-C30 scores from baseline at each post-study treatment visit will also be summarized with descriptive statistics.

9.8.2. European Quality of Life-5 Dimensions and Visual Analogue Scale Scores

EQ-5D and VAS scores will be summarized at baseline and post study treatment visits. Changes in the EQ-5D-5L and VAS scores from baseline at each post-study treatment visit will also be summarized with descriptive statistics.

9.9. Subsequent Anti-cancer Therapy

The incidence of subsequent anti-cancer therapy including stem cell transplant (by WHO Drug coded term) will be summarized.

The subject incidence of stem cell transplant post-treatment with brexucabtagene autoleucel and prior to disease progression will be tabulated among subjects who undergo stem cell transplant while in brexucabtagene autoleucel induced response.

9.10. Schedule of Study Treatment

Summary statistics will be provided for the following durations:

- Days from leukapheresis to brexucabtagene autoleucel product release
- Days from leukapheresis to receipt of brexucabtagene autoleucel at the study site
- Days from leukapheresis to the start date of lymphodepleting chemotherapy
- Days from leukapheresis to administration of brexucabtagene autoleucel
- Duration of hospitalization for the brexucabtagene autoleucel infusion

9.11. Pharmacokinetics and Pharmacodynamics

Summary statistics for the level of CAR T cells and inflammatory cytokine and chemokines in blood before (baseline) and after brexucabtagene autoleucel infusion will be provided.

The maximum CAR T cell and serum analyte levels attained, the time at which the maximum level was attained, and the time at which there were no detectable levels in blood will be summarized. The area under the concentration over time curve will be summarized from Day 0 to Day 28.

Possible association of levels of CAR T cells and serum analytes with efficacy (eg, disease response rate, CR rate and Ongoing Response Rate) and/or toxicity readouts of interest (eg, CRS and neurotoxicity) will be investigated and summarized.

Details of pharmacokinetic and pharmacodynamic analyses will be described in separate translational statistical analysis plan.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

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12. HISTORY OF REVISIONS

Version	Date	Protocol	Description of Changes
Draft	26MAY2022	Original 23MAY2022	Not Applicable The draft version has been approved by Clinical Document Review Committee.
Final 1.0	03OCT2022	Amendment 1, 20JUL2022	• Updating the power and operating characteristic of r/r BL study design due to the sample size increasing up to 30 from 20 per protocol amendment. • Adding estimands (E9R1) (as well as the sensitivity/supplementary analyses) for primary efficacy endpoint (the disease response rate), and key secondary efficacy endpoints (DOR, PFS, and OS).
Final 2.0	12JAN2023	Amendment 1.1, 12JAN2023	• Added literature used for historical control rate estimate in Richter Transformation in Section 3.2.2 and References. • Wording change to clarify the enrollment pause criteria in Section 7.3 based on Protocol Amendment 1.1. • Wording changes in Table 8 and Table 9 to clarify the DLT assessment based on Protocol Amendment 1.1. • Other minor wording changes for clarity.
Final 3.0	12SEP2023	Amendment 3.0, 17AUG2023	• Notes added: Substudies KT-US-568-0138-A (WM) and KT-US-568-0138-D (HCL) were terminated early by the Sponsor (effective 21 June 2023) per Protocol Amendment 3.0. • A sentence added in Sections 3.4, 3.4.1, and 3.4.2: 'In the case that the dose is changed based on SRT recommendation, the interim analysis will be conducted after the first 20 subjects from the RT substudy and the first 10 subjects from the BL substudy have been treated at their assigned dose levels and followed up for at least 3 months'. • Added a covariate of CD19 expression by H score or % positive cells (indication specific) in Section 4.1. • A sentence added in Section 7.3: Additionally, study enrollment will be paused when the required number of subjects have been enrolled for the planned interim analyses of the r/r RT and r/r GL substudies, until the data from this interim analysis have been assessed. • Other minor wording changes for clarity.

13. APPENDICES

Appendix 1. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates

The following data will be imputed using the following algorithm:

- Adverse event (AE) dates
- Concomitant medication dates
- Subsequent anticancer therapy dates
- Death date (using algorithm 3))

1) Start dates imputation:

Table 10. Imputation Rules for Partial or Missing Start Dates

Start Date		If end date is: Complete: *yyyymmdd* < Day 0	Complete: *yyyymmdd* ≥ Day 0	Partial: *yyyymm* < Day 0 *yyyymm*	Partial: *yyyymm* ≥ Day 0 *yyyymm*	Partial: *yyyy* < Day 0 *yyyy*	Partial: *yyyy* ≥ Day 0 *yyyy*	Missing
Partial *yyyymm*	= Day 0 *yyyymm*	2	1	2	1	n/a	1	1
	≠ day 0 *yyyymm*		2		2	2	2	2
Partial *yyyy*	= Day 0 *yyyy*	3	1	3	1	n/a	1	1
	≠ Day 0 *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

Abbreviation: n/a, not applicable.
Note: If the start date imputation leads to a start date that is after the end date, then do not impute the start date.
1 = impute the date of Day 0.
2 = impute the first of the month.
3 = impute January 1 of the year.
4 = impute January 1 of the end year.

2) End dates imputation:

- If start date is partial or missing, the start date will be imputed first.
- If year or month is missing or event is ongoing, the end date will not be imputed.
- If year and month are available, but day is missing, set the end date to the last day of the month.
- If the imputed end date is after the earliest non-missing date of data extract date, date of the end of study, and death date, set the end date to the earliest non-missing date of data extract date, date of the end of study, and death date.
- If the imputed end date is after the data cut-off date when applicable, set the end date to missing (event will then be considered as ongoing).
- The imputed end date should be no later than the start date.

3) Imputation rules for partial or missing death dates:

- If death year and month are available, but day is missing:
  - If mmyyyy for the last date known to be alive = mmyyyy for death date, set death date to the day after the last date known to be alive.
  - If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
  - If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.
- If both month and day are missing for death date or a death date is completely missing, do not impute, and censor the subject per censoring rules defined in Appendix 5.

Appendix 2. Sample Adverse Event Table Layouts

Sample Adverse Event (AE) Summary Layout 1: All AE summaries listed in Section 9.7.1 will be provided in format 1 ("Grade 1" and "Grade 2" columns are not needed for "Grade 3 or higher" summary tables). The preferred terms will be sorted by descending order of frequency of the "Any" column.

Table 11. Subject Incidence of <AE Descriptor> AEs by Preferred Term (Worst Grade)

	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any <AE descriptor> adverse event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)

Abbreviations: AE, adverse event; Gr, Grade.

Sample Adverse Event Summary Layout 2: AE summaries may also be provided in format 2 ("Grade 1" and "Grade 2" columns are not needed for "Grade 3 or higher" summary tables). The system organ classes and preferred terms will be sorted by alphabetical order of system organ class and descending incidence of preferred term within each system organ class.

Table 12. Subject Incidence of <AE Descriptor> AEs by System Organ Class and Preferred Term (Worst Grade)

	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any <AE descriptor> adverse event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
...						

Abbreviations: AE, adverse event; Gr, Grade.

Appendix 3. Last Date Known to Be Alive

Last date known to be alive with be derived by obtaining the maximum complete date among the following data modules:

- Start date of AE
- Leukapheresis dates
- Bridging therapy administration dates, if applicable
- Conditioning chemo administration dates
- anti-CD19 CAR T cells infusion dates
- Computerized tomography (CT) scan dates
- Positron emission tomography (PET) scan dates
- Clinical symptoms of lymphoma assessment dates
- Target lesion assessment
- Non-target lesion assessment
- New lesion assessment
- Other tumor assessment dates (Bone marrow and spleen assessments)
- Disease response assessment
- Long-term follow-up subject status date where status = alive
- End of treatment disposition where status is not equal to death, lost to follow-up
- End of Month 3 disposition where status is not equal to death, lost to follow-up
- End of study data where end of study reason is not equal to death, lost to follow-up
- Death date

If the last known alive date is after the cut-off date when applicable, set the last known alive date to the cut-off date.

Appendix 4. Sensitivity and Supplementary Analyses on Efficacy Endpoints

Note: Substudies KT-US-568-0138-A (WM) and KT-US-568-0138-A (HCL) were terminated early by the Sponsor (effective 21 June 2023).

The primary analysis on the primary and key secondary endpoints within the estimand framework as described in Section 2.3 will be conducted using central assessment data in the mITT population set. The additional sensitivity and supplementary analyses within the estimand framework are summarized below.

Table 13 Sensitivity and supplementary analyses on key efficacy endpoints

Endpoint	Analyses Performed	Sensitivity or Supplementary Analysis	Intercurrent Event (ICE) Handling
r/r WM: Combined rate of CR and VGPR r/r RT/BL/HCL: ORR	Investigator assessment in mITT	Sensitivity	Same as the primary estimand
	Central assessment in FAS	Supplementary	Same as primary estimand, except that the events preventing the subject(s) from being treated by brexucabtagene autoleucel were considered as terminal event and thus the subjects entered the study but not treated will be considered as non-responders.
	Investigator assessment in FAS	Supplementary	
	Central assessment in subjects who fulfill eligibility criteria regardless of the commencement of leukapheresis	Supplementary	
	Investigator assessment in subjects who fulfill eligibility criteria regardless of the commencement of leukapheresis	Supplementary	
DOR, PFS	No censoring for subsequent stem cell transplant	Supplementary	Treatment policy strategy[a]
	Subsequent new anti-cancer therapy (including stem cell transplant) considered to be events	Supplementary	Composite strategy[b]
	Censoring for 2 or more consecutive missed diseases assessment visits	Sensitivity	Two or more consecutive missing disease assessment visits will be treated as administrative termination for disease assessment, as the assessments thereafter are considered not reliable given that the subject may have relapsed/progressive disease already {Sun 2021}. DOR/PFS will be censored at the last evaluable disease assessment prior to the consecutive missing visits.

Endpoint	Analyses Performed	Sensitivity or Supplementary Analysis	Intercurrent Event (ICE) Handling
	Investigator assessment in mITT	Sensitivity	Same as DOR/PFS by central assessment in mITT
	Central assessment in FAS	Supplementary	Same as DOR/PFS by central assessment in mITT, except that the events preventing the subject(s) from being treated by brexucabtagene autoleucel were considered as terminal event and thus the subjects enrolled but not treated will be considered as non-responders and thus not included in DOR analysis; for PFS, the starting time point is enrollment date.
	Investigator assessment in FAS	Supplementary	Same as DOR/PFS by central assessment in FAS
OS	OS in FAS	Supplementary	Treatment policy strategy

Abbreviations: BL, Burkitt Lymphoma; CR, complete response; DOR, duration of response; FAS, full analysis set; HCL, Hairy Cell Leukemia; ICE, intercurrent event; mITT, modified intent-to-treat; ORR: objective response rate; OS, overall survival; PFS, progression-free survival; r/r, relapsed/refractory; RT, Richter Transformation; VGPR, very good partial response; WM, Waldenstrom Macroglobulinemia

a Treatment policy strategy is based on assumption that the assessments after the intercurrent event are still of interest while subjects are in follow up.

b Subsequent new anti-cancer therapies, including stem cell transplant, are considered to be terminal events incorporated into the endpoint definitions.

Appendix 5. Derivation of Time to Event Endpoints

Note: Substudies KT-US-568-0138-A (WM) and KT-US-568-0138-A (HCL) were terminated early by the Sponsor (effective 21 June 2023).

Additional details on the derivations of duration of response (DOR), progression-free survival (PFS), overall survival (OS), and time to the next treatment (TTNT) are provided below.

Table 14. Primary Analysis of DOR

Circumstance	Event / Censored	Date of Event / Censoring
Disease progression prior to initiation of new anti-cancer therapy (including stem cell transplant)	Event	Progression date
Death without documented disease progression and without new anti-cancer therapy (including stem cell transplant)	Event	Death date
Remain in response without new anti-cancer therapy (including stem cell transplant)	Censored	Date of last evaluable disease assessment prior to the earliest date of data cutoff, withdraw of consent, or loss to follow up
Initiated new anti-cancer therapy (including stem cell transplant) prior to documented progression or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including stem cell transplant. If no evaluable disease assessment is available, then censor at the date of brexucabtagene autoleucel infusion

Abbreviations: DOR, duration of response.

Table 15. Supplementary Analysis 1 of DOR (to include data after stem cell transplant post study treatment)

Circumstance	Event/Censored	Date of Event/Censoring
Disease progression after stem cell transplant, but prior to other new anti-cancer therapy	Event	Progression date
Death after stem cell transplant without documented progression and other new anti-cancer therapy	Event	Death date
For subjects without stem cell transplant and all other circumstances, follow the same as the "Primary Analysis of DOR."		

Abbreviations: DOR, duration of response.

Table 16. Supplementary Analysis 2 of DOR (subsequent new anti-cancer therapy (including stem cell transplant) considered to be events)

Circumstance	Event/Censored	Date of Event/Censoring
Initiated new anti-cancer therapy (including stem cell transplant) prior to documented progression or death	Event	Date of the initiation of new therapy including stem cell transplant
For subjects without stem cell transplant and all other circumstances, follow the same as the "Primary Analysis of DOR."		

Abbreviations: DOR, duration of response.

Table 17. Sensitivity Analysis of DOR (2 or more consecutive missed diseases assessment visits)

Circumstance	Event/Censored	Date of Event/Censoring
2 or more consecutive missed disease response assessment visits	Censored	The last evaluable disease assessment prior to the consecutive missing visits.
For subjects without 2 or more consecutive missing assessments and all other circumstances, follow the same as the "Primary Analysis of DOR."		

Abbreviations: DOR, duration of response.

Table 18. Primary Analysis of PFS

Circumstance	Event / Censored	Date of Event / Censoring
Disease progression prior to initiation of new anti-cancer therapy (including stem cell transplant)	Event	Progression date
Death without documented disease progression and without new anti-cancer therapy (including stem cell transplant)	Event	Death date
Remain in study and alive without new anti-cancer therapy (including stem cell transplant)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including stem cell transplant) prior to documented progression or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including stem cell transplant. If no evaluable disease assessment is available, then censor at the date of brexucabtagene autoleucel infusion
Remain in study without documented disease progression and new anti-cancer therapy (including stem cell transplant) until withdrawal of consent or loss to follow-up	Censored	Date of last evaluable disease assessment prior to the earliest date of data cutoff, withdraw of consent, or loss to follow up. If no evaluable disease assessment is available, then censor at the date of brexucabtagene autoleucel infusion

Abbreviations: PFS, progression-free survival.

Table 19. Supplementary Analysis 1 of PFS (to include data after stem cell transplant post study treatment)

Circumstance	Event/Censored	Date of Event/Censoring
Disease progression after stem cell transplant, but prior to other new anti-cancer therapy	Event	Progression date
Death after stem cell transplant without documented progression and other new anti-cancer therapy	Event	Death date
For subjects without stem cell transplant and all other circumstances, follow the same as the "Primary Analysis of PFS."		

Abbreviations: PFS, progression-free survival.

Table 20. Supplementary Analysis 2 of PFS (subsequent new anti-cancer therapy (including stem cell transplant) considered to be events)

Circumstance	Event/Censored	Date of Event/Censoring
Initiated new anti-cancer therapy (including stem cell transplant) prior to documented progression or death	Event	Date of the initiation of new therapy (including stem cell transplant)
For subjects without stem cell transplant and all other circumstances, follow the same as the "Primary Analysis of PFS."		

Abbreviations: PFS, progression-free survival.

Table 21. Sensitivity Analysis of PFS (2 or more consecutive missed diseases assessment visits)

Circumstance	Event/Censored	Date of Event/Censoring
2 or more consecutive missed disease response assessment visits	Censored	The last evaluable disease assessment prior to the consecutive missing visits.
For subjects without 2 or more consecutive missing assessments and all other circumstances, follow the same as the "Primary Analysis of PFS."		

Abbreviations: PFS, progression-free survival.

Table 22. Primary Analysis of OS

Circumstance	Event/Censored	Date of Event/Censoring
Death before data cutoff date for analysis	Event	Date of death
Death or known to be alive after data cutoff date for analysis	Censored	Data cutoff date
Alive up through data cutoff date and no further information available after data cutoff date	Censored	Last date known to be alive up through the data cutoff date
Full withdrawal of consent or lost to follow-up prior to data cutoff date	Censored	Last date known to be alive up through the data cutoff date

Abbreviation: OS, overall survival.

Table 23. Primary Analysis of TTNT

Circumstance	Event / Censored	Date of Event / Censoring
Initiate subsequent anti-cancer therapy (including stem cell transplant) prior to documented progression or death due to any cause	Event	Date of first subsequent anti-cancer therapy
Death before data cutoff date	Event	Date of death
Death or known to be alive after data cutoff date	Censored	Data cutoff date
Alive up through data cutoff date without subsequent anti-cancer therapy	Censored	Last date known to be alive through the data cutoff date
End of study due to other reason prior to data cutoff date	Censored	Last date known to be alive through the data cutoff date

Abbreviations: TTNT, Time to Next Therapy

Appendix 6. Simulation to Evaluate Futility Interim Analysis Timing in r/r WM and r/r RT

Note: Substudy KT-US-568-0138-A (WM) was terminated early by the Sponsor (effective 21 June 2023).

Simulation is conducted based on binomial distribution assumption for binary variable (Disease response=Yes/No) without normal approximation using R software (Version 4.1.2) to evaluate the futility interim analysis timing, i.e., after n1 (out of total N) subjects were treated and assessed for disease response to the investigational product (Brexucabtagene Autoleucel) within each substudy using the following criteria:

1) **prob.futilityH0**: the probability of early stop at interim analysis under the null hypothesis H_0. Estimated as the proportion of iterations early stopped at interim analysis time under H_0;

4) **prob.futilityH1**: the probability of incorrect early stop at interim analysis under the alternative hypothesis H_1. Estimated as the proportion of iterations early stopped at interim analysis time under H_1;

5) **ESSH0**: Expected sample size (ESS) under null hypothesis H_0. Estimated as the average sample size of all iterations under H_0;

6) **ESSH1**: Expected sample size (ESS) under alternative hypothesis H_1. Estimated as the average sample size of all iterations under H_1;

7) **actual.power**: the empirical statistical power. Estimated as the proportion of iterations succeeded both interim and primary boundaries under alternative H_1;

8) **power.loss**: the statistical power loss. Estimated as the proportion of iterations succeeded the primary boundary under alternative hypothesis H_1 but would have early stopped at interim analysis under alternative H_1.

An 'optimal' interim analysis timing for futility is considered as the one that leads to minimal **prob.futilityH1**, **ESSH0**, and **power.loss** (ideally <5%), and maximal **actual.power.** The **prob.futilityH0** and **ESSH1** are also included as reference.

The simulation setup and results are summarized below.

r/r WM simulation set-up: N=60, alpha=0.025 (1-sided), H_0: Response rate≤6% vs H_1: Response rate≥20%; Futility boundaries from study design shown in Section 3.4.1 Table 4: Response rate=7.5% (at Interim analysis), Response rate=12% (at Primary analysis), binomial distribution, 100,000 iterations.

	n1=10	n1=15	n1=20	n1=25	n1=30
prob.futilityH0	0.54	0.77	0.66	0.55	0.73
prob.futilityH1	0.11	0.17	0.07	0.03	0.04
ESSH0	33.10	25.27	33.68	40.72	38.08
ESSH1	54.61	52.52	57.28	59.04	58.69
actual.power	0.85	0.80	0.89	0.92	0.91
power.loss	0.09	0.13	0.05	0.02	0.02

r/r RT simulation set-up: N=60, alpha=0.025 (1-sided), H_0: ORR≤28% vs H_1: ORR≥50%; Futility boundaries from study design shown in Section 3.4.2 Table 5: ORR=30.4% (at Interim analysis), ORR=39.4% (at Primary analysis), binomial distribution, 100,000 iterations.

	n1=10	n1=15	n1=20	n1=25	n1=30
prob.futilityH0	0.70	0.58	0.68	0.60	0.68
prob.futilityH1	0.17	0.06	0.06	0.02	0.02
ESSH0	25.00	33.79	32.74	39.06	39.64
ESSH1	51.34	57.30	57.74	59.27	59.39
actual.power	0.80	0.91	0.91	0.94	0.94
power.loss	0.15	0.05	0.04	0.01	0.01

Please note that the simulation results are somewhat different from what was obtained from the multiple-look (group sequential) design using EAST software. The reason is likely because the simulation is based on binominal distribution (without normal approximation) while the latter is based on normal approximation.

Although the parameters (such as the **prob.futilityH1** and **actual.power** in R/R WM) may not show a strict monotonic pattern over the n1 due to the discrete nature of the sampling distribution (binomial distribution) for the test statistic (number of responses); However, generally speaking, conducting the futility interim analysis too early (with very small sample size) leads to higher chance to early stop the substudy by mistake (**prob.futilityH1**) due to limited data available for response rate assessment and loss of statistical power (**power.loss**), while conducting it too late would cause unnecessary exposure of more subjects to the investigational product (**ESSH0**) if it was inefficacious.

Overall, conducting the futility interim analysis at n1=20 (out of 60) subjects for each of these 2 substudies is considered a reasonable choice.

Appendix 7. Simulation of the Study Design in r/r BL and r/r HCL

Note: Substudy KT-US-568-0138-D (HCL) was terminated early by the Sponsor (effective 21 June 2023).

The simulation is conducted to evaluate the 2-look design in r/r BL and r/r HCL shown in Section 3 in the same way as described in Appendix 6 above, except for that only n1=10 is considered for these 2 substudies due to small sample size.

r/r BL simulation set-up: N=30, alpha=0.025 (1-sided), H_0: ORR≤39% vs H_1: ORR≥70%; Futility boundaries from study design shown in Section 3.4.3 Table 6: ORR=43.8% (at Interim analysis, with n1=10), ORR=56.5% (at Primary analysis), binomial distribution, 100,000 iterations.

r/r HCL simulation set-up: N=20, alpha=0.025 (1-sided), H_0: ORR≤26% vs H_1: ORR≥60%; Futility boundaries from study design shown in Section 3.4.4 Table 7: ORR=29.4% (at Interim analysis, with n1=10), ORR=45.2% (at Primary analysis), binomial distribution, 100,000 iterations.

Simulation results:

	R/R BL	R/R HCL
prob.futilityH0	0.66	0.49
prob.futilityH1	0.05	0.01
ESSH0	16.85	15.06
ESSH1	29.07	19.88
actual.power	0.93	0.87
power.loss	0.034	0.002

KT-US-568-0138-SAP_Final_V3.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical eSigned	02-Oct-2023 07:05:44