CLINICAL STUDY SUBPROTOCOL

Protocol Title:	A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25) – *Substudy C – Relapsed/Refractory Burkitt Lymphoma*
Note:	This subprotocol should be used in conjunction with the KT-US-568-0138 master protocol
Protocol Number:	KT-US-568-0138-C (ZUMA-25C)
Indication:	Relapsed/refractory Burkitt lymphoma
Kite Investigational Product:	Brexucabtagene autoleucel
Kite IND Number:	028542
EU CT Number:	2022-501261-46-00
Clinical Trials.gov Identifier:	NCT05537766
Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Contact Information:	The medical monitor name and contact information is provided on the Key Study Team Contact List
Protocol Version/Date:	Original: 23 May 2022 Amendment 1.0: 20 July 2022 Amendment 1.1: 12 January 2023 Amendment 2.0: 01 March 2023 Amendment 3.0: 17 August 2023

This study will be conducted under United States (US) Food and Drug Administration (FDA) Investigational New Drug (IND) application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, and Switzerland are not included under the IND application and are not considered to be IND application sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory and local requirements.

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PROTOCOL SYNOPSIS

Kite Pharma, Inc.
2400 Broadway
Santa Monica, CA 90404

Protocol Title: A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25)

Substudy C – Relapsed/Refractory Burkitt Lymphoma

Indication: Adult subjects with relapsed/refractory (r/r) Burkitt lymphoma (BL)

Kite IND Number: 028542

EU CT Number: 2022-501261-46-00

Clinical Trials.gov Identifier: NCT05537766

Kite Investigational Product: Brexucabtagene autoleucel

Other Investigational Product/IND Number: Not applicable

IDE Number: Not applicable

Number of Study Sites Planned: Approximately 25

Objectives and Endpoints: Objectives and endpoints that are common to all indications are detailed in the KT-US-568-0138 master protocol.

Additional objectives and endpoints that are specific to this substudy are detailed below.

Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with BL, by determining the objective response rate (ORR) by central assessment	• ORR, defined as the proportion of subjects who achieve a best response of either complete response (CR) or partial response (PR). Response will be determined by central assessment per the Lugano Classification {Cheson 2014}
Secondary Objective	**Secondary Endpoint**
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with BL, by determining the ORR by investigator assessment	• ORR, defined as the proportion of subjects who achieve a best response of either CR or PR. Response will be determined by investigator assessment per the Lugano Classification {Cheson 2014}
Exploratory Objective	**Exploratory Endpoint**
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with BL based on receipt of bridging therapy	• ORR, defined as the proportion of subjects who achieve a best response of either CR or PR, in subgroups by receipt of bridging therapy (yes/no)

Study Design: This substudy protocol contains details regarding all elements of the study that are unique to subjects with BL. In contrast, the KT-US-568-0138 master protocol contains additional information that is common for all indications in this basket study. Both the KT-US-568-0138 master protocol and this substudy protocol should be referenced in parallel.

This is a Phase 2, open-label, multicenter study evaluating the efficacy of brexucabtagene autoleucel in subjects with r/r BL.

Initially, 1 subject will be enrolled and infused. No additional subjects will be enrolled until the subject has been monitored for at least 28 days post-infusion. Subsequently, an additional 2 subjects can be enrolled in parallel. After these initial 3 subjects have been evaluated for at least 28 days, the safety review team (SRT) will make recommendations on the further conduct of this substudy.

Following enrollment, eligible subjects will be treated with cyclophosphamide and fludarabine lymphodepleting chemotherapy, followed by an initial dose of 2×10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg body weight. Following review by the SRT, the dose may be lowered to 1×10^6 anti-CD19 CAR T cells/kg body weight.

Disease response will be assessed at Day 28, Month 3, and then every 3 months up to Month 12, followed by every 6 months up to Month 24.

Additional study details are provided in the KT-US-568-0138 master protocol.

Subjects enrolled in this substudy may receive optional bridging therapy as described in Section 7.1.

The study schema is detailed in Figure 1 of the KT-US-568-0138 master protocol.

Number of Subjects Anticipated to be Enrolled and Treated: Approximately 30 subjects with r/r BL will be enrolled and treated in this substudy. Three to 6 additional subjects may be enrolled if the SRT recommends proceeding at the lower dose level.

Target Population: Male or female adults ≥ 18 years of age diagnosed with r/r BL

Duration of Treatment and of Study Participation: The treatment period will be 1 week following infusion, and the duration of the study is 24 months.

Eligibility Criteria Unique to the BL Substudy:

In addition to the common eligibility criteria specified in the KT-US-568-0138 master protocol, all of the following additional substudy-specific eligibility criteria must also be met.

BL Substudy-specific Inclusion Criteria:

1) Histologically confirmed mature B-cell non-Hodgkin lymphoma Burkitt lymphoma/leukemia
2) Relapsed or refractory disease after any first-line chemoimmunotherapy, defined as 1 of the following:
   a) Refractory disease, defined as progressive disease or stable disease as best response to first-line therapy; subjects who are intolerant to first-line therapy are excluded

b) Relapsed disease, defined as complete remission to first-line therapy followed by biopsy-proven disease relapse. Subjects will be eligible regardless of the duration of remission prior to relapse.

At least 1 measurable lesion based on the Lugano Classification {Cheson 2014}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

BL Substudy-specific Exclusion Criteria:

1) Burkitt-like lymphoma with 11q aberration, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement, or high-grade B-cell lymphoma not otherwise specified
2) Prior allogeneic stem cell transplant < 3 months prior to screening and/or < 4 months prior to planned infusion of brexucabtagene autoleucel
3) Presence of active graft-versus-host disease following prior allogeneic stem cell transplant
4) Presence of central nervous system (CNS) involvement. Subjects with a prior history of CNS involvement are eligible if they show a negative cerebrospinal fluid (CSF) and no involvement by imaging

Study Procedures: Subjects will undergo procedures and assessments as detailed in the schedule of assessments (see Section 12.2).

Investigational Product and Study Treatments, Dose, and Mode of Administration:

Treatment consists of a lymphodepleting chemotherapy regimen, followed by a single infusion of brexucabtagene autoleucel. Additional details are provided in the KT-US-568-0138 master protocol.

Safety Review Team and Data Safety Monitoring Board: An SRT, comprising the study sponsor and at least 1 study investigator, will be specifically chartered to review the safety data and make recommendations on further study conduct, progression, and/or dose modification after 3 or 6 subjects in this substudy have been treated with the initial dose (2×10^6 anti-CD19 CAR T cells/kg of body weight) and followed for 28 days, as detailed in the KT-US-568-0138 master protocol.

An independent Data Safety Monitoring Board (DSMB) will be chartered to review safety and efficacy data to make study conduct recommendations based on an analysis of risk versus benefit. The DSMB will review serious adverse event (SAE) information (listings or narratives) and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout subject treatment in the study and per the DSMB charter or DSMB discretion. The DSMB may request additional safety or efficacy data or recommend modifying the study conduct. The sponsor may request additional reviews by the DSMB. Data submitted to the DSMB may or may not be source data verified to facilitate timely DSMB review.

SUSARs and SAE listings or narratives may be submitted to the DSMB chair as described in the DSMB charter.

Additional details regarding the SRT, DSMB, and dose-limiting toxicities are provided in the KT-US-568-0138 master protocol.

Statistical Methods:

Hypothesis: An alternative hypothesis is proposed with a target 70% ORR per central assessment against a null hypothesis that the ORR is ≤ 39%. The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than 39%.

Sample Size Calculation: This single-arm, open-label substudy will enroll and treat 30 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This 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 a type 1 error rate of 0.025 (1-sided).

Analyses: 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 2 purposes:

- Futility (efficacy): 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 ≤ 39%). A decision on futility will be made by the sponsor based on DSMB recommendation, with the complete benefit/risk profile of brexucabtagene autoleucel being taken into account. The futility boundary is crossed if ≤ 4 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. Study enrollment will be paused following treatment of the 10th subject with brexucabtagene autoleucel and until results from the interim analysis have been assessed.
- 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, 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 30 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.

Additional descriptive analyses may occur after the primary analysis and follow-up analysis described above have been completed.

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.

This study will be conducted in compliance with this protocol; the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines of Good Clinical Practice, including archiving of essential documents; and all applicable regulatory and local requirements.

This study will be conducted under United States Code of Federal Regulations Title 21 Part 312 or equivalent.

LIST OF ABBREVIATIONS

ASCO	American Society of Clinical Oncology
BL	Burkitt lymphoma
CAR	chimeric antigen receptor
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
FDG	fluorodeoxyglucose
ICANS	immune effector cell-associated neurotoxicity syndrome
IHC	immunohistochemistry
IV	intravenous
MRI	magnetic resonance imaging
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PR	partial response
r/r	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SOA	schedule of assessments
SOC	standard of care
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction

1. INTRODUCTION

Refer to the KT-US-568-0138 master protocol for information related to brexucabtagene autoleucel (KT-US-568-0138 master protocol – Section 1.1), previous clinical studies (KT-US-568-0138 master protocol – Section 1.2.2), and the study rationale (KT-US-568-0138 master protocol – Section 1.4).

1.1. Disease Background

1.1.1. Epidemiology

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma (NHL) which manifests in the subtypes of sporadic, endemic (Epstein-Barr virus [EBV]-associated), and immunodeficiency-associated BL. The sporadic subtype of BL is the most frequent outside of Africa and is EBV-associated in 10% to 20% of patients. BL is observed in the United States and Europe with an overall incidence of 3 cases per million persons per year in the general population, and thus accounts for < 1% of adult NHLs {Morton 2006}. BL is more common in children, where it represents 30% of NHLs and has a peak incidence at 11 years of age, whereas the peak incidence is at 30 years in adults. Whites have a higher incidence of the disease, and the incidence in males is 3 to 4 times that observed in females {Jacobson 2014}.

1.1.2. Diagnosis

Due to the aggressive nature of BL, patients often present with rapidly enlarging masses and evidence of spontaneous tumor lysis and high serum lactate dehydrogenase levels. Moreover, sporadic BL has a propensity for involving the abdomen and involves the bone marrow and central nervous system (CNS) {Jacobson 2014}.

BL is of germinal center B-cell origin with tumor cells expressing CD10, BCL6, CD19, CD20, CD79a, and CD45 and is characterized by a chromosomal translocation most commonly involving the *MYC* gene locus on chromosome 8 and the immunoglobulin heavy chain locus on chromosome 14 (t(8;14)). Furthermore, up to 70% of patients harbor *TCF3* or *ID3* mutations {Dunleavy 2018a, Jacobson 2014, Schmitz 2012}.

1.1.3. Frontline Treatment

BL is currently treated with high-intensity, multi-drug chemotherapy regimens including doxorubicin, alkylators, vincristine, and etoposide (CODOX-M/IVAC, HyperCVAD, and DA-REPOCH). Due to the significant tumor burden in BL, many regimens include a steroid preface with a focus on avoiding tumor lysis syndrome. Therapy directed at the eradication and/or prevention of CNS disease is also applied. Survival outcomes using such frontline approaches generally exceed 70% {Jacobson 2014}.

1.1.4. Second-line Treatment

Treatment options for patients with relapsed/refractory (r/r) BL are limited and outcomes are poor {Dunleavy 2018a}. Second-line therapies include chemotherapy such as etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and regular- or double-dose rituximab (DA-EPOCH-R or -RR), as well as hematopoietic stem cell transplant. Recently, Short and colleagues evaluated such regimens in a retrospective cohort of 35 r/r patients with Burkitt leukemia (n = 21), BL (n = 7), high-grade B-cell leukemia (n = 6), and high-grade B-cell lymphoma (n = 1) treated with varying chemotherapeutic regimens and found an objective response rate (ORR) of 39% {Short 2017}. Meanwhile, Pineda and colleagues found a median overall survival (OS) after relapse between 3 and 4 months in a Spanish population including BL patients across 40 sites from 1997 to 2014 {Pineda 2015}. Accordingly, patients with chemotherapy-sensitive disease can obtain deep remissions, while the overall outcome for patients with r/r disease remains dismal {Short 2017, Sweetenham 1996}.

Recently, chimeric antigen receptor (CAR) T-cell therapy has been investigated in subjects with r/r BL. In a study of 6 adults who received a CAR19/22 T-cell therapy, 3 achieved an objective response, including 2 partial responses (PRs) and 1 complete response (CR). The subject who achieved a CR subsequently received allogeneic stem cell transplant, and 1 subject who achieved a PR had received CAR19/22 T cells following autologous stem cell transplant; both were in remission at 37 and 22 months of follow-up, respectively {Zhou 2021}.

Nonetheless, r/r BL remains a largely incurable disease, and patients have very poor outcomes, with an ORR to salvage therapy of 39% and a median OS of 2.8 months {Short 2017}. Thus, new treatment options are needed to achieve durable responses in a significant fraction of patients.

2. OBJECTIVES AND ENDPOINTS

Refer to Section 2 of the KT-US-568-0138 master protocol for a summary of common objectives and endpoints for this study.

Additional objectives and endpoints that are specific for this substudy are detailed in Table 1.

Table 1. Substudy-specific Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with BL, by determining the ORR by central assessment	• ORR, defined as the proportion of subjects who achieve a best response of either CR or PR. Response will be determined by central assessment per the Lugano Classification {Cheson 2014}
Secondary Objective	**Secondary Endpoint**
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with BL, by determining the ORR by investigator assessment	• ORR, defined as the proportion of subjects who achieve a best response of either CR or PR. Response will be determined by investigator assessment per the Lugano Classification {Cheson 2014}
Exploratory Objective	**Exploratory Endpoint**
• To evaluate the efficacy of brexucabtagene autoleucel in subjects with BL based on receipt of bridging therapy	• ORR, defined as the proportion of subjects who achieve a best response of either CR or PR, in subgroups by receipt of bridging therapy (yes/no)

Abbreviations: BL, Burkitt lymphoma; CR, complete response; ORR, objective response rate; PR, partial response.

3. STUDY DESIGN

3.1. Study Design

This substudy protocol contains details regarding all elements of the study that are unique to subjects with BL. In contrast, the KT-US-568-0138 master protocol contains additional information that is common for all indications in this basket study. Both the KT-US-568-0138 master protocol and this substudy protocol should be referenced in parallel.

This is a Phase 2, open-label, multicenter study evaluating the efficacy of brexucabtagene autoleucel in subjects with r/r BL.

Initially, 1 subject will be enrolled and infused. No additional subjects will be enrolled until the subject has been monitored for at least 28 days post-infusion. Subsequently, an additional 2 subjects can be enrolled in parallel. After these initial 3 subjects have been evaluated for at least 28 days, the safety review team (SRT) will make recommendations on the further conduct of this substudy.

Following enrollment, eligible subjects will be treated with cyclophosphamide and fludarabine lymphodepleting chemotherapy, followed by an initial dose of 2×10^6 anti-CD19 CAR T cells/kg body weight. Following review by the SRT, the dose may be lowered to 1×10^6 CAR T cells/kg body weight.

Disease response will be assessed at Day 28, Month 3, and then every 3 months up to Month 12, followed by every 6 months up to Month 24.

Additional details of the study design are provided in Section 3 of the KT-US-568-0138 master protocol.

Subjects enrolled in this substudy may receive optional bridging therapy as described in Section 7.1.

The study schema is detailed in Figure 1 of the KT-US-568-0138 master protocol.

An SRT, comprising the study sponsor and at least 1 study investigator, will be specifically chartered to review the safety data and make recommendations on further study conduct, progression, and/or dose modification. Additional details of the SRT are provided in Section 8.1.

An independent Data Safety Monitoring Board (DSMB) will be chartered to review safety and efficacy data to make study conduct recommendations based on an analysis of risk versus benefit. The DSMB will review investigator-reported safety and efficacy data against the futility rules after 10 subjects (50%) in this substudy have been treated with the SRT-recommended dose of brexucabtagene autoleucel and have had the opportunity to be followed for 3 months after the brexucabtagene autoleucel infusion. Study enrollment will be paused following treatment of the 10^{th} subject with brexucabtagene autoleucel and until results from the interim analysis have been assessed. Additional details of the DSMB are provided in Section 8.1.

The end-of-study is defined in the Master protocol (refer to Section 3.4 of the Master protocol).

3.1.1. Rationale for Study Design Elements

3.1.1.1. Rationale for Bridging Therapy

Due to the aggressive nature of BL, bridging therapy may be administered at the discretion of the investigator, if deemed necessary for disease control between leukapheresis and availability of brexucabtagene autoleucel. Bridging therapy regimens and timing requirements are described in Section 7.1.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 30 subjects with r/r BL who have received at least 1 line of prior therapy will be enrolled and treated. Three to 6 additional subjects may be enrolled if the SRT recommends proceeding at the lower dose level (refer to Section 8.10.1 of the KT-US-568-0138 master protocol for additional details).

4.2. Eligibility Criteria

To be enrolled in the study, subjects must meet the common eligibility criteria detailed in Section 4.2 of the KT-US-568-0138 master protocol. In addition, subjects must also meet all of the additional substudy-specific eligibility criteria detailed in Section 4.2.1 and Section 4.2.2.

4.2.1. BL Substudy-specific Inclusion Criteria

1) Histologically confirmed mature B-cell NHL Burkitt lymphoma/leukemia

Relapsed or refractory disease after any first-line chemoimmunotherapy, defined as 1 of the following:

a) Refractory disease, defined as progressive disease or stable disease as best response to first-line therapy; subjects who are intolerant to first-line therapy are excluded

b) Relapsed disease, defined as complete remission to first-line therapy followed by biopsy-proven disease relapse. Subjects will be eligible regardless of the duration of remission prior to relapse.

At least 1 measurable lesion based on the Lugano Classification {Cheson 2014}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

4.2.2. BL Substudy-specific Exclusion Criteria

1) Burkitt-like lymphoma with 11q aberration, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement, or high-grade B-cell lymphoma not otherwise specified
2) Prior allogeneic stem cell transplant < 3 months prior to screening and/or < 4 months prior to planned infusion of brexucabtagene autoleucel
3) Presence of active graft-versus-host disease following prior allogeneic stem cell transplant
4) Presence of central nervous system (CNS) involvement. Subjects with a prior history of CNS involvement are eligible if they show a negative cerebrospinal fluid (CSF) and no involvement by imaging.

5. STUDY TREATMENT

Study treatment consists of lymphodepleting chemotherapy and a single infusion of brexucabtagene autoleucel, as described in Section 3.2 of the KT-US-568-0138 master protocol.

Subjects enrolled in this substudy may receive optional bridging therapy as described in Section 7.1. Permitted bridging therapy regimens are detailed in Table 2.

Refer to Section 5 of the KT-US-568-0138 master protocol for additional details of the brexucabtagene autoleucel treatment, prior and concomitant medications, and excluded medications.

6. STUDY ASSESSMENTS UNIQUE TO BURKITT LYMPHOMA

The study assessments that are either unique to BL or that are managed differently for subjects with BL are described here. Please refer to Section 6 of the KT-US-568-0138 master protocol for details of all other study assessments. Study assessments described in the KT-US-568-0138 master protocol and herein are to be performed according to the schedule of assessments (SOA) presented in Section 12.2 (Table 5 and Table 6) of this substudy protocol.

6.1. Brain Magnetic Resonance Imaging

Brain magnetic resonance imaging (MRI) will be performed with contrast whenever possible or without contrast in case of contraindication.

Screening:

- All subjects are required to have a brain MRI at screening to confirm the absence of CNS involvement and study eligibility.
- The MRI should be performed as close to enrollment/leukapheresis as possible and within 28 days before leukapheresis for eligibility. An MRI collected as standard of care (SOC) within this timeframe is acceptable.
- After the initial screening and eligibility confirmation, if the subject presents with new-onset symptoms or clinical signs of CNS malignancy/disease, a repeat MRI is required to reassess eligibility prior to the start of lymphodepleting chemotherapy.
- CNS involvement will be assessed by local review, and images will not be sent for central review.

Post-infusion:

- Subjects are recommended to have a brain MRI if presenting with new-onset symptoms or clinical signs of CNS malignancy/disease, such as severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurological findings on physical examination.
- In addition, in the case of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), refer to the American Society of Clinical Oncology (ASCO) management guidelines for guidance of requirements for brain imaging {Santomasso 2021}. In summary: i) brain MRI can be considered for all grades of CRS; ii) brain MRI or other neuroimaging can be considered for ICANS Grade 2 or higher, as supported by the ASCO management guidelines.
- A brain MRI only needs to be submitted to the independent central reviewer when there is evidence of disease progression.

6.1.1. Lumbar Puncture

Opening pressures should be measured with each lumbar puncture when possible and recorded in the subject's site chart.

Screening:

- All subjects are required to have a new lumbar puncture performed at screening and as close as possible to leukapheresis to assess cerebrospinal fluid (CSF) for possible CNS involvement and to determine the presence of CNS malignancy.

- After the initial screening and eligibility confirmation, if the subject presents with new-onset symptoms or clinical signs of CNS malignancy/disease, a repeat lumbar puncture is required to reassess eligibility prior to the start of lymphodepleting chemotherapy.

Post-infusion:

- Subjects with symptoms or clinical signs of CNS malignancy, such as new-onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical examination, will have a lumbar puncture for examination of CSF (and brain MRI as described in Section 6.1).

- In the case of CRS and ICANS, refer to the ASCO management guidelines for guidance for requirements for lumbar puncture examination {Santomasso 2021}. In summary: i) lumbar puncture is recommended for consideration in cases of CRS; ii) for ICANS, a lumbar puncture is recommended for Grade 3 or higher neurotoxicity and may be considered for Grade 2.

CSF samples will be analyzed at the local laboratory. An aliquot will be sent to the central laboratory for assessment of analytes (including cytokines) and immune cell subsets.

6.2. Disease Assessments

Disease assessments will be performed according to the schedule presented in the SOA (Table 5 and Table 6) and as described below. In addition, subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.

6.2.1. Imaging Requirements

Positron emission tomography (PET)-diagnostic computed tomography (CT) scans are required in all subjects at screening, after bridging therapy (if applicable), and at the disease response assessment time points specified in the SOA (Table 5 and Table 6).

For all PET-CT scans, the following requirements should be met:

- The CT must be of diagnostic quality with intravenous (IV)-iodinated contrast, performed by either of the following modalities, depending on the site's capability:
  - as part of a combined PET-diagnostic CT; or
  - as a separate diagnostic-quality CT (with IV-iodinated contrast)
- The PET-diagnostic CT scan must include the neck, chest, abdomen, and pelvis, along with appropriate imaging of all other sites of disease.
- If IV-iodinated contrast is contraindicated per the investigator, then the diagnostic CT scan can use non-iodinated contrast. If non-iodinated contrast is not available or not recommended by the investigator, then the diagnostic CT can be nonenhanced.
- In cases where CT with contrast is contraindicated, MRI of the abdomen and pelvis and CT of the chest without contrast is an acceptable alternative.
- All screening/baseline and disease assessment PET-diagnostic CT scans will be submitted to and reviewed by an independent central reviewer.
- Technical and shipping requirements for the PET-diagnostic CT scans will be outlined in the study imaging manual.
- On-study images will be performed with the same imaging modality and anatomical location as imaged at baseline.
- The PET portion of the PET-diagnostic CT scan will be scored per the Deauville 5-point scale. Both the PET and CT portions of the scan will be interpreted according to the Lugano Classification {Cheson 2014}. Refer to Section 12.3.1 for additional details.

Screening/Baseline:

- To confirm eligibility and/or to establish baseline (if bridging therapy is administered), PET-diagnostic CT scans are required at screening.
- PET-diagnostic CT scans should be performed as close to enrollment/leukapheresis as possible and within 28 days before leukapheresis for eligibility (unless imaging is available from SOC assessment within 28 days before enrollment), with the following clarifications:
  - A PET-diagnostic CT scan performed at the study site after the subject's last line of therapy and before signing of the informed consent form may be used for confirmation of eligibility, if relevant requirements described above are fulfilled and if it was performed within 28 days before enrollment/leukapheresis and no other anticancer treatment has been administered. (For subjects who are referred, a screening image is required.)

— If a PET-diagnostic CT scan is performed > 28 days before the initiation of lymphodepleting chemotherapy or if the subject receives any anticancer therapy (bridging therapy) between the last PET-diagnostic CT scan and initiation of lymphodepleting chemotherapy, the PET-diagnostic CT scan must be repeated before lymphodepleting chemotherapy to establish a new baseline.

Disease Assessment:

- The PET-diagnostic CT scans will be performed at the time points outlined in the SOA (Table 5 and Table 6) through Month 24 or until disease progression, whichever comes first.
- A PET-diagnostic CT scan can be performed at any time disease progression is suspected.
- To limit radiation exposure, investigators are encouraged to leave at least 4 weeks between consecutive scans

6.2.2. Bone Marrow Aspirate/Biopsy

Refer to Section 12.3.1 for treatment response assessment requirements per the Lugano Classification {Cheson 2014}. Bone marrow aspirate and biopsies will be analyzed by the investigator at the local laboratory.

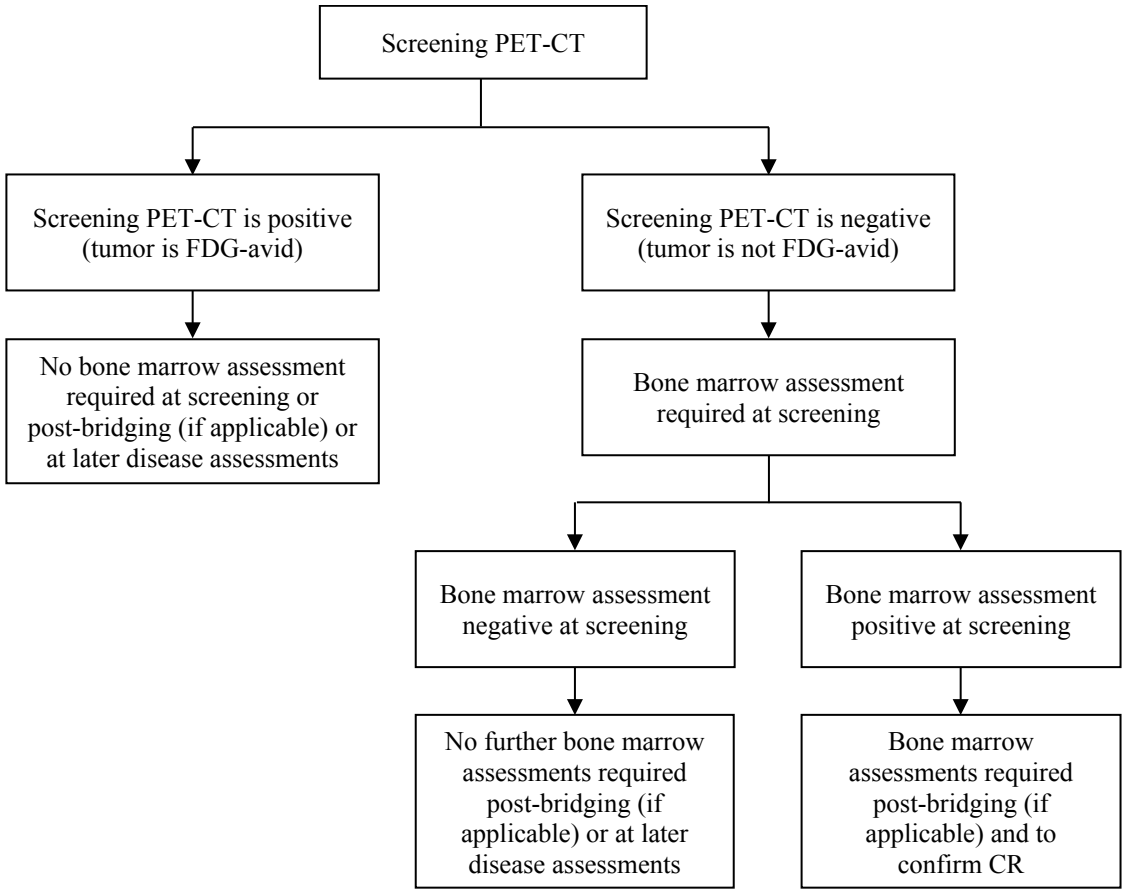
Screening/Baseline:

- For fluorodeoxyglucose (FDG)-avid lymphoma, a subject's bone marrow involvement should be assessed by PET-diagnostic CT (refer to Section 6.2.1).
- If the lymphoma is not FDG-avid, a bone marrow aspirate and biopsy is required at screening. If the screening bone marrow assessment shows infiltration, bone marrow aspirate and biopsy will be required after bridging therapy (if applicable) (Figure 1).

Disease/Response Assessment:

- If there is evidence of baseline bone marrow involvement, the PET-diagnostic CT is not available, the lymphoma is not FDG-avid, or there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm CR {Cheson 2014} (also refer to Figure 1).
- To confirm a CR, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or, if indeterminate by morphology, must be negative by immunohistochemistry (IHC).

Figure 1. Bone Marrow Assessment Schema



Abbreviations: CR, complete response; FDG, fluorodeoxyglucose; PET-CT, positron emission tomography-computed tomography.

6.3. Tumor Biopsy

Screening:

To retrospectively confirm the BL diagnosis, the most recently available archived or newly acquired tumor biopsy sample will be collected and submitted to the central laboratory. A new biopsy is only to be acquired if the location is easily accessible, and if appropriate taking into account subject safety. Archived tumor biopsy samples will consist of either 1 formalin-fixed paraffin-embedded tumor block or at least 20 unstained slides. Should an archived tumor sample be unavailable or insufficient, a fresh tumor sample is required to be obtained before initiation of lymphodepleting chemotherapy.

Disease Progression:

If a tumor biopsy that is clinically indicated in the management of a study-treated subject is acquired, a portion of the biopsy should be sent to the central laboratory for additional exploratory analyses.

6.4. Disease-specific Exploratory Assessments

Tumor biopsy at screening will be collected for central laboratory assessment in order to perform genetic testing for the evaluation of somatic mutations of *MYC* by fluorescence in situ hybridization (FISH) analysis and IHC staining with a B-cell lymphoma panel to confirm the BL diagnosis and for investigation of prognostic markers in exploratory analyses.

7. STUDY PROCEDURES UNIQUE TO BURKITT LYMPHOMA

Refer to Section 7 of the KT-US-568-0138 master protocol for the list of procedures for this study. Additional procedures for this BL subprotocol are listed below.

For short-term disease control, optional bridging therapy is allowed per investigator discretion. To exclude any impact of bridging therapy, a new baseline for subjects receiving bridging therapy is required as outlined in the SOA.

7.1. Optional Bridging Therapy

Bridging therapy will be permitted at the discretion of the investigator, if deemed required to control disease after leukapheresis. Bridging therapy is recommended for subjects with high disease burden. Bridging therapy may be administered after leukapheresis, and the last dose of any bridging therapy regimen must be completed at least 7 days or 5 half-lives, whichever is shorter, before initiating lymphodepleting chemotherapy.

If a subject receives any bridging therapy between leukapheresis and lymphodepleting chemotherapy, then the baseline imaging and any additional assessments to confirm measurable disease must be repeated after the bridging therapy and before lymphodepleting chemotherapy commences to establish a new baseline. For subjects who receive irradiation as bridging therapy, irradiated lesions can no longer serve as target lesions, and other target lesions must be present to allow for response assessment.

Permitted bridging therapy regimens are outlined in Table 2. Doses listed are recommendations only and should be adjusted for age, comorbidities, or per local or institutional guidelines.

Table 2. Bridging Therapy Regimens

Type	Therapy Regimen	Timing and Washout Requirements
R-ICE {Kewalramani 2004}	Rituximab 375 mg/m^2 IV on Day 1 Ifosfamide 5,000 mg/m^2 IV on Day 4 Carboplatin area under the curve 5, dose = 5 × (25 + CrCl), capped at 800 mg, IV on Day 4 Etoposide 100 mg/m^2/day IV on Days 3 to 5	May be administered after leukapheresis/enrollment Last dose must be completed at least 7 days or 5 half-lives, whichever is shorter, before the start of lymphodepleting chemotherapy
DA-EPOCH-R {Dunleavy 2018b}	Etoposide 50 mg/m^2/day IV on Days 1 to 4 Doxorubicin 10 mg/m^2/day IV on Days 1 to 4 Vincristine 0.4 mg/m^2/day IV on Days 1 to 4 Cyclophosphamide 750 mg/m^2/day IV on Day 5 Prednisone 60 mg/m^2/BID PO on Days 1 to 5 Rituximab 375 mg/m^2 IV on Day 1	
R-GEMOX {Collignon 2019}	Rituximab 375 mg/m^2 IV on Days 1 and 15 Gemcitabine 1,000 mg/m^2 IV on Day 1 Oxaliplatin 100 mg/m^2 IV on Day 1	
Hyper-CVAD {Thomas 2006}	Hyperfractionated cyclophosphamide 300 mg/m^2 IV every 12 hours for 6 doses on Days 1 to 3, with sodium mercaptoethanesulfonate 600 mg/m^2 daily via continuous infusion on Days 1 to 3 Vincristine 2 mg IV on Days 4 and 11 Doxorubicin 50 mg/m^2 IV over 24 hours on Day 4 Dexamethasone 40 mg PO or IV daily on Days 1 to 4 and Days 11 to 14	
Dexamethasone	40 mg daily for 4 days	
Irradiation	As per local guidelines	May be administered after leukapheresis/enrollment Last irradiation dose must be completed at least 7 days before the start of lymphodepleting chemotherapy

Abbreviations: BID, twice a day; CrCl, creatinine clearance; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IV, intravenous; PO, oral; R-GEMOX, rituximab with gemcitabine and oxaliplatin; R-ICE, rituximab with ifosfamide, carboplatin, and etoposide.

Bridging therapy will be supplied by the study site. Sites should refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management of bridging therapy.

Regardless of the choice of bridging regimen, all organ and marrow functional parameters listed in the KT-US-568-0138 master protocol common inclusion criteria must be met before initiation of lymphodepleting chemotherapy, and all toxicities related to bridging therapy must return to Grade 1 or lower or baseline levels before initiation of lymphodepleting chemotherapy.

The procedures to be performed during the period in which bridging therapy is administered are detailed in the SOA (Section 12.2).

8. ADVERSE EVENTS AND TOXICITY MANAGEMENT

Refer to Section 8 of the KT-US-568-0138 master protocol for adverse events and toxicity management. The SRT and independent DSMB for this subprotocol are described below.

8.1. Safety Review Team and Data Safety Monitoring Board

An SRT, comprising the study sponsor and at least 1 study investigator, will be specifically chartered to review the safety data and make recommendations on further study conduct, progression, and/or dose modification after 3 to 6 subjects in this substudy have been treated with the initial dose (2 x 10^6 anti-CD19 CAR T cells/kg of body weight) and followed for 28 days, as detailed in the KT-US-568-0138 master protocol.

An independent DSMB will be chartered to review safety and efficacy data to make study conduct recommendations based on an analysis of risk versus benefit. The DSMB will review investigator-reported safety and efficacy data against the futility rules after 10 subjects (50%) in this substudy have been treated with the SRT-recommended dose of brexucabtagene autoleucel and have had the opportunity to be followed for 3 months after the brexucabtagene autoleucel infusion. Study enrollment will be paused following treatment of the 10^{th} subject with brexucabtagene autoleucel and until results from this interim analysis have been assessed. The DSMB will also review serious adverse event (SAE) information (listings or narratives) and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout subject treatment in the study and per the DSMB charter or DSMB discretion. The DSMB may request additional safety or efficacy data or recommend modifying the study conduct. The sponsor may request additional reviews by the DSMB. Data submitted to the DSMB may or may not be source data verified to facilitate timely DSMB review.

SUSARs and SAE listings or narratives may be submitted to the DSMB chair as described in the DSMB charter.

Additional details regarding the SRT, DSMB, and dose-limiting toxicities are provided in Section 8.10.1, Section 8.10.2, and Section 8.1.2 of the KT-US-568-0138 master protocol, respectively.

9. STATISTICAL CONSIDERATIONS

An overview of the statistical considerations that are specific to this subprotocol are provided below. Refer to Section 9 of the KT-US-568-0138 master protocol for an overview of the statistical considerations that are common across indications.

Details of the statistical analysis plan (SAP) will be provided in the SAP document.

9.1. Hypothesis

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 systemic literature review. The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is greater than 39%.

The hypothesis testing 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.

9.2. Definition of Substudy Endpoints

In addition to the secondary and exploratory endpoints outlined in the KT-US-568-0138 master protocol, the endpoints outlined below also apply to this substudy.

9.2.1. Definition of Substudy Primary Endpoints

The primary endpoint for this substudy is the 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}.

9.2.2. Definition of Substudy Secondary Endpoints

The secondary endpoint for this substudy is defined in Table 3.

Table 3. Definition of Substudy Secondary Endpoint

Secondary Endpoint	Definition
ORR by investigator assessment	Proportion of subjects who achieve a best response of either CR or PR by investigator assessment per the Lugano Classification {Cheson 2014}

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response.

9.2.3. Definition of Other Substudy Endpoints of Interest

The exploratory endpoint for this substudy is defined in Table 4.

Table 4. Definition of Substudy Exploratory Endpoint

Exploratory Endpoint	Definition
ORR based on receipt of bridging therapy	Proportion of subjects who achieve a best response of either CR or PR, in subgroups by receipt of bridging therapy (yes/no)

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response.

9.3. Determination of Sample Size

This single-arm, open-label substudy will enroll and treat 30 subjects with the SRT-recommended dose of brexucabtagene autoleucel. This 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 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). The empirical power is 93% per simulation based on binomial distribution without normal approximation. 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.

9.4. Planned Analyses

9.4.1. Interim Analysis and Early Stopping Guidelines

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. Study enrollment will be paused following treatment of the 10th subject with brexucabtagene autoleucel and until results from this interim analysis have been assessed. 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 ≤ 39%). The futility boundary is crossed if ≤ 4 responders are observed among the 10 subjects. A decision on futility will be made by the sponsor based on DSMB recommendation, with the complete benefit/risk profile of brexucabtagene autoleucel being taken into account. If the decision is made to discontinue the substudy, then this analysis will be considered the primary analysis of this substudy.

9.4.2. Primary Analysis

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 (modified intent-to-treat [mITT] analysis set) 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, 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 30 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.

9.4.3. Follow-Up 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.

Additional descriptive analyses may occur after the primary analysis and follow-up analysis described above have been completed.

9.4.4. Final Analysis

The duration of the study is 24 months. 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.

10. RESPONSIBILITIES

Please refer to Section 10 of the KT-US-568-0138 master protocol for details regarding investigator and sponsor responsibilities.

11. REFERENCES

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12. APPENDICES

Section 12.1. Sponsor and Investigator Signature Page

Section 12.2. Schedule of Assessments

Section 12.3. Disease Response Criteria

Section 12.4. Protocol Amendment History

12.1. Sponsor and Investigator Signature Page

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25) – *Substudy C – Relapsed/Refractory Burkitt Lymphoma*

Amendment 3.0, 17 AUGUST 2023

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

See appended signature page	See appended signature page
Kite Medical Monitor Name (Printed)	Signature
See appended signature page	
Date	

INVESTIGATOR STATEMENT

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

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

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

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

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

Principal Investigator Name (Printed)	Signature
Date	Study Site Number

12.2. Schedule of Assessments

Table 5. Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Periods

Timeframe:	Screening	Pretreatment Period						Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression[b]
		Enrollment/ Leukapheresis	Optional Bridging Therapy Note: bridging therapy is optional, and these procedures only apply if bridging therapy has been administered		Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
Procedure	Within 28 days before enrollment	Within approx. 5 days after eligibility confirmation	Dosing of bridging therapy and monitoring	Post-bridging therapy disease assessment	D−5	D−4	D−3	D0	D1 to D7[a]	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
Informed consent	X													
Demographic data	X													
Medical history	X													
Previous cancer treatment history	X													
Physical examination[c]	X	X		X	X	X	X	X	Daily	X	X	X	X	X
Weight (height at screening only)	X	X												
Vital signs[d]	X	X	X	X	X	X	X	X	Daily	X	X	X	X	X
Neurologic examination[e]	X							X	QOD	X	X	X	X	
ECOG performance status	X				X									
LVEF (ECHO or MUGA)	X													
ECG	X													
Brain MRI[f]	X													
Lumbar puncture[g]	X													

Timeframe:	Screening	Pretreatment Period						Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression[b]
		Enrollment/ Leukapheresis	Optional Bridging Therapy Note: bridging therapy is optional, and these procedures only apply if bridging therapy has been administered		Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
Procedure	Within 28 days before enrollment	Within approx. 5 days after eligibility confirmation	Dosing of bridging therapy and monitoring	Post-bridging therapy disease assessment	D−5	D−4	D−3	D0	D1 to D7[a]	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
PROs: EORTC-QLQ-C30 and EQ-5D-5L[h]	X				X			X			X		X	
Disease response assessments (please refer to the imaging manual and central laboratory manual for guidance)														
PET-diagnostic CT[i]	X			X							X		X	X
Bone marrow aspirate and biopsy[j]	X			X							X		X	X
Archived/fresh tumor sample[k]	X													X
Overall response assessment											X		X	X
Local laboratory assessments														
Chemistry panel (CrCl at screening) (serum)	X	X	X		X	X	X	X[l]	Daily	X	X	X	X	X
CBC with differential (blood)	X	X	X		X	X	X	X[l]	Daily	X	X	X	X	X
LDH[m], CRP, ferritin (serum)		X			X			X[l]	Daily	X	X			X
β-hCG pregnancy test ([WOCBP] serum or urine)	X	X[n]			X[n]						X		X	X
Serology for EU/CH sites (serum)[o]	X[o]	X[o]												

Timeframe:	Screening	Pretreatment Period						Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression[b]
		Enrollment/ Leukapheresis	Optional Bridging Therapy Note: bridging therapy is optional, and these procedures only apply if bridging therapy has been administered		Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
Procedure	Within 28 days before enrollment	Within approx. 5 days after eligibility confirmation	Dosing of bridging therapy and monitoring	Post-bridging therapy disease assessment	D−5	D−4	D−3	D0	D1 to D7[a]	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
HIV positive subjects only: HIV viral load and CD4 count	X[p]							X			X		X	
Central laboratory assessments (please refer to the central laboratory manual for guidance)														
CBC with differential (blood)[q]		X			X[r]			X[l]	D3, D7	X	X	X	X	X
Anti-brexucabtagene autoleucel antibodies (serum)		X									X		X	X
Analytes, including cytokines (serum/plasma)[s]		X[r]			X[r]			X[l]	D1, D2, D3, D5, D7	X	X	X	X	X
Brexucabtagene autoleucel CAR T-cell levels and exploratory analyses (PBMCs)[s]		X[r]			X[r]			X[l]	D3, D7	X	X	X	X	X
RCR (PBMCs)[t]								X[l]					X	
Leukapheresis		X												
Bridging therapy (optional)[u]			X											
Fludarabine/ cyclophosphamide[v]					X	X	X							

Timeframe:	Screening	Pretreatment Period						Treatment Period		Post-treatment Follow-up Period				Suspected Disease Progression[b]
		Enrollment/ Leukapheresis	Optional Bridging Therapy Note: bridging therapy is optional, and these procedures only apply if bridging therapy has been administered		Lymphodepleting Chemotherapy			Infusion of Brexucabtagene Autoleucel and Monitoring		(Each visit calculated from D0)				
Procedure	Within 28 days before enrollment	Within approx. 5 days after eligibility confirmation	Dosing of bridging therapy and monitoring	Post-bridging therapy disease assessment	D−5	D−4	D−3	D0	D1 to D7[a]	D14 (±2 d)	D28 (±3 d)	W8 (±1 w)	M3 (±2 w)	
Brexucabtagene autoleucel infusion (IV) and premedications								X						
Concomitant medications	X	X	X	X	X	X	X	X	Daily	X	X	X	X	X
Adverse events and serious adverse events[w]	X	X	X	X	X	X	X	X	Daily	X	X	X	X	X

Abbreviations: approx., approximately; ASCO, American Society of Clinical Oncology; CAR, chimeric antigen receptor; CBC, complete blood count; CNS, central nervous system; CR, complete response; CrCl, creatinine clearance; CRP, C-reactive protein; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; CT, computed tomography; D/d, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level scale; EU, European Union; FDG, fluorodeoxyglucose; hCG, human chorionic gonadotropin; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICF, informed consent form; IV, intravenous; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; M, month; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PBMC, peripheral blood mononuclear cell; PET, positron emission tomography; PRO, patient-reported outcome; QOD, every other day; RCR, replication-competent retrovirus; SOA, schedule of assessments; SOC, standard of care; W/w, week; WOCBP, women of childbearing potential.

Note: Please refer to the footnotes listed below in parallel with Section 6 of this protocol and the KT-US-568-0138 master protocol.

a For EU and CH, post-infusion monitoring extended by monitoring on Days 8, 9, and 10 (vital signs, blood draw for chemistry panel with CRP and CBC and neurological examination). For EU, the subject may remain hospitalized or return to the clinic daily for this extended monitoring, at the discretion of the investigator. For CH, patients must remain hospitalized.

b Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.

c Physical examination will include assessment of splenomegaly and lymphadenopathy. Subjects with symptoms or clinical signs related to CRS should undergo physical examination at least daily until symptoms resolve to baseline.

d Vital signs will include blood pressure, heart rate, respiration rate, oxygen saturation, and temperature. It is recommended that vital signs are monitored during and after study treatment and then routinely per institutional guidelines. Vital signs may be monitored more frequently as clinically indicated.

e Neurologic examination: A neurologic examination, including an ICE cognition assessment, should be performed on Day 0 before the brexucabtagene autoleucel infusion and should be performed every other day during the hospitalization period. If a subject hospitalization is extended beyond Day 7, a neurologic examination including a cognition assessment will continue to be performed as clinically indicated.

f Brain MRI:
- Screening through start of lymphodepletion: All subjects are required to have a brain MRI at screening to confirm the absence of CNS involvement and study eligibility. After the initial screening and eligibility confirmation, if the subject presents with new-onset symptoms or clinical signs of CNS malignancy/disease, a repeat MRI is required to reassess eligibility prior to the start of lymphodepleting chemotherapy (see Section 6.1).
- Post-infusion: Subjects are recommended to have a brain MRI if presenting with new-onset symptoms or clinical signs of CNS malignancy/disease, such as severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurological findings on physical examination. In addition, in the case of CRS and ICANS, refer to the ASCO management guidelines for guidance of requirements for brain imaging {Santomasso 2021}. In summary: i) brain MRI can be considered for all grades of CRS; ii) brain MRI or other neuroimaging can be considered for ICANS Grade 2 or higher, as supported by the ASCO management guidelines.

g Lumbar puncture: Opening pressures should be measured with each lumbar puncture when possible and recorded in the subject's site chart.
- Screening: All subjects will undergo a new lumbar puncture at screening as close as possible to leukapheresis to assess for CNS disease. After the initial screening and eligibility confirmation, if the subject presents with new-onset symptoms or clinical signs of CNS malignancy/disease, a repeat lumbar puncture is required to reassess eligibility prior to the start of lymphodepleting chemotherapy. Subjects with a prior history of CNS involvement are eligible if they show a negative cerebrospinal fluid (CSF) at screening and no involvement by imaging.
- Post-infusion: Subjects with symptoms or clinical signs of CNS malignancy, such as new-onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical examination, will have a lumbar puncture for examination of CSF, including sending a sample to the central laboratory. In the case of CRS and ICANS, refer to the ASCO management guidelines for guidance for requirements for lumbar puncture examination {Santomasso 2021}. In summary: i) lumbar puncture is recommended for consideration in cases of CRS; ii) for ICANS, a lumbar puncture is recommended for Grade 3 or higher neurotoxicity and may be considered for Grade 2 (see Section 6.1.1).

h PROs are to be completed by the subject before any study-specific assessments or procedures are performed (excluding blood draws) and before the subject receives any disease status information or the brexucabtagene autoleucel infusion on Day 0.

i PET-diagnostic CT:
- Screening/baseline: PET-CT scan should be performed as close to enrollment/leukapheresis as possible and within 28 days before leukapheresis for eligibility (unless imaging is available from SOC assessment within 28 days before enrollment). If a PET-CT scan is performed > 28 days before the initiation of lymphodepleting chemotherapy or if the subject receives any anticancer therapy (bridging therapy) between the last PET-CT scan and initiation of lymphodepleting chemotherapy, a new baseline PET-CT scan must be performed before lymphodepleting chemotherapy.
- Disease assessment: PET-CT is required for each disease response assessment per the SOA and at any time disease progression is suspected.To limit radiation exposure, investigators are encouraged to leave at least 4 weeks between consecutive scans

j Bone marrow aspirate and biopsy (only relevant for non-FDG-avid lymphoma):
- Screening/baseline: For FDG-avid lymphoma, a subject's bone marrow involvement should be assessed by PET-diagnostic CT. If the lymphoma is not FDG-avid, a bone marrow aspirate and biopsy is required at screening. If the screening bone marrow assessment shows infiltration, bone marrow aspirate and biopsy will be required after bridging therapy (if applicable).
- Disease/response assessment: If there is evidence of baseline bone marrow involvement, the PET-diagnostic CT is not available, the lymphoma is not FDG-avid, or there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm CR (see Section 6.2.2). To confirm a CR, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or, if indeterminate by morphology, must be negative by immunohistochemistry.

k Archived/fresh tumor sample(s):
- Screening: The most recently available archived or newly acquired tumor biopsy sample will be collected and submitted to the central laboratory. Archived tumor biopsy samples will consist of either 1 formalin-fixed paraffin-embedded tumor block or at least 20 unstained slides. Should an archived tumor sample be unavailable or insufficient, a fresh tumor sample is required to be obtained before initiation of lymphodepleting chemotherapy.
- Disease progression: If a tumor biopsy that is clinically indicated in the management of a study-treated subject is acquired, a portion of the biopsy should be sent to the central laboratory for additional exploratory analyses.

l Assessments may be performed on the day before administration of brexucabtagene autoleucel (ie, on Day −1). For tests performed at the central laboratory, this decision will be driven by the availability of the central laboratory to process samples on the day they are collected from the subject (refer to the laboratory manual for holidays). For samples collected on Day 0, collection will occur before the start of the brexucabtagene autoleucel infusion.

m LDH should continue to be monitored after the baseline assessment as clinically indicated.

n Pregnancy test (serum or urine): For EU/CH study sites, the test will be completed within 7 days before both leukapheresis and lymphodepleting chemotherapy for females of childbearing potential.

o Serology tests for EU/CH study sites (serum): Serology tests (ie, HIV, hepatitis B virus, hepatitis C virus, and syphilis) will be done per institutional guidelines and EU/CH regulations. Testing may be done within the 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/enrollment.

p Hepatitis B and C testing is also required at screening.

q CBC with differential (blood): At the time points at which PBMC samples are collected for analysis of brexucabtagene autoleucel CAR T-cell levels, blood samples will also be collected and sent to the central laboratory for assessment of CBC with differential (these samples are in addition to samples collected at the specified time points and that are sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation).

r Baseline for assessments of brexucabtagene autoleucel CAR T cells and analytes: A sample will be collected at enrollment/before the leukapheresis procedure. Subjects who receive bridging therapy will also have a blood sample collected before receiving the first dose of lymphodepleting chemotherapy.

s Analytes (including cytokines) (serum/plasma) and brexucabtagene autoleucel CAR T cells (PBMCs):

- Samples on Day 3 may be collected ± 1 day.
- If a subject is re-admitted to the hospital after the initial hospitalization observation period with any brexucabtagene autoleucel-related adverse events, blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes will be collected on the day of hospital re-admission and then weekly through, and including, the day of discharge, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- If the subject experiences a Grade 3 or higher brexucabtagene autoleucel-related toxicity, such as Grade 3 CRS or neurologic event, 1 additional blood draw for brexucabtagene autoleucel CAR T cells (PBMCs) and serum analytes will be collected at the time of the Grade 3 or higher brexucabtagene autoleucel-related toxicity and upon resolution of the event, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- Blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes should be collected at the time of disease progression prior to starting subsequent anticancer therapy.
- Exploratory T-cell immunogenicity will be performed with PBMCs at leukapheresis and Month 3. Extra blood collection is required for such testing.
- Exploratory analyses will include lymphocyte subsets.

t RCR (PBMCs):

- Samples will be collected at baseline (before CAR T-cell infusion) and at Month 3.
- If a subject develops a secondary malignancy during the study, every effort should be made to obtain a blood sample to assay for RCR and vector elements. In the case of a secondary malignancy, every effort will be made to obtain a blood sample (PBMC) and biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a testing workflow, including tests such as transgene elements, RCR, presence of common cancer-drivers/mutations and insertional mutagenesis (see Section 6.3.15.3 of the KT-US-568-0138 master protocol).

u Bridging therapy may be administered per investigator discretion if deemed required for disease control. Refer to Section 7.1 for details.

v Mesna will be administered around the time of the cyclophosphamide dose according to institutional standards (refer to Section 5.1.2.3 and Section 7.5.3 of the KT-US-568-0138 master protocol).

w Collection of serious adverse events starts from signing of the screening ICF, and collection of adverse events starts from commencement of the leukapheresis procedure.

Table 6. Schedule of Assessments: Post-treatment Follow-up Period

Timeframe:	Long-term Follow-up Period (Each visit calculated from Day 0)					Suspected Disease Progression[a]
Procedure	**M6 (± 2 w)**	**M9 (± 2 w)**	**M12 (± 2 w)**	**M18 (± 1 M)**	**M24 (± 1 M)**	
Physical examination[b]	X	X	X	X	X	X
Vital signs						X
Lumbar puncture						
PROs: EORTC-QLQ-C30 and EQ-5D-5L[c]	X	X	X	X	X	
Disease response assessments (please refer to the imaging manual and central laboratory manual for guidance)						
PET-diagnostic CT[d]	X	X	X	X	X	X
Bone marrow aspirate and biopsy[e]			X[e]			X
Overall response assessment	X	X	X	X	X	X
Local/central laboratory assessments						
CBC with differential (blood)[f]	X	X	X	X	X	X
Local laboratory assessments						
Chemistry panel (serum)						X
LDH[g]			X			X
β-hCG pregnancy test ([WOCBP] serum or urine)						X
HIV positive subjects only: HIV viral load and CD4 count	X	X	X	X	X	
Central laboratory assessments (please refer to the central laboratory manual for guidance)						
Analytes, including cytokines (serum/plasma)[h]						X
Anti-brexucabtagene autoleucel antibodies (serum)	X	X	X			X
Brexucabtagene autoleucel CAR T-cell levels and exploratory analyses (PBMCs)[h]	X	X	X	X	X	X

Timeframe:	Long-term Follow-up Period (Each visit calculated from Day 0)					Suspected Disease Progression[a]
Procedure	**M6 (± 2 w)**	**M9 (± 2 w)**	**M12 (± 2 w)**	**M18 (± 1 M)**	**M24 (± 1 M)**	
RCR (PBMCs)[i]	X		X			
Tumor biopsy[j]						X
All brexucabtagene autoleucel-related SAEs and any deaths regardless of causality	X	X	X	X	X	X
Targeted AE/SAEs[k]	X	X	X	X	X[k]	X
Targeted concomitant medications[l]	X	X	X	X	X	X
Subsequent therapy for BL[m]	X	X	X	X	X	X
Survival status[n]	X	X	X	X	X	X

Abbreviations: AE, adverse event; BL, Burkitt lymphoma; CAR, chimeric antigen receptor; CBC, complete blood count; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level scale; FDG, fluorodeoxyglucose; GP, general practitioner; hCG, human chorionic gonadotropin; HCP, healthcare provider; LDH, lactate dehydrogenase; LTFU, long-term follow-up; M, month; PBMC, peripheral blood mononuclear cell; PET, positron emission tomography; PRO, patient-reported outcome; RCR, replication-competent retrovirus; SAE, serious adverse event; SOA, schedule of assessments; w, week; WOCBP, women of childbearing potential.

Note: Please refer to the footnotes listed below in parallel with Section 6 of this protocol and the KT-US-568-0138 master protocol.

a Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.

b Physical examination will include assessment of splenomegaly and lymphadenopathy.

c PROs are to be completed before any assessments or procedures are performed (excluding blood draws) and before the subject receives any disease status information.

d PET-diagnostic CT: PET-CT is required for each disease response assessment per the SOAs and at any time disease progression is suspected. To limit radiation exposure, investigators are encouraged to leave at least 4 weeks between consecutive scans.

e If there is evidence of baseline bone marrow involvement, the PET-diagnostic CT is not available, the lymphoma is not FDG-avid, or there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm CR (see Section 6.2.2). To confirm a CR, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or, if indeterminate by morphology, must be negative by immunohistochemistry.

f CBC with differential (blood):

- Local laboratory assessments: Blood will be collected at the time points specified through Month 24 or until disease progression, whichever occurs first, and sent to the local laboratory for clinical/safety evaluation.
- Central laboratory assessments: Blood will be collected at the time points specified through Month 24 and sent to the central laboratory for assessment of CBC with differential (these samples are in addition to samples collected at the specified time points that are sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation).

g LDH should continue to be monitored after the baseline assessment as clinically indicated.

h Analytes (including cytokines) (serum/plasma) and brexucabtagene autoleucel CAR T cells (PBMCs):
- If a subject is re-admitted to the hospital after the initial hospitalization observation period with any brexucabtagene autoleucel-related AEs, blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes will be collected on the day of hospital re-admission and then weekly through, and including, the day of discharge, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- If the subject experiences a Grade 3 or higher brexucabtagene autoleucel-related toxicity, such as Grade 3 CRS or neurologic event, 1 additional blood draw for brexucabtagene autoleucel CAR T cells (PBMCs) and serum analytes will be collected at the time of the Grade 3 or higher brexucabtagene autoleucel-related toxicity and upon resolution of the event, if the samples were not already collected on the same days as per the SOA (ie, 2 identical collections on the same day are not needed).
- Blood samples for assessment of brexucabtagene autoleucel CAR T cells and serum analytes should be collected at the time of disease progression prior to starting subsequent anticancer therapy.
- Exploratory analyses will include lymphocyte subsets.

i RCR (PBMCs):
- Samples will be collected at Month 6 and Month 12 and analyzed. Additional samples will be collected and analyzed only if an RCR event is clinically suspected and/or a subject's PBMC sample tests positive for RCR at any time point within the first 12 months following brexucabtagene autoleucel infusion.
- If a subject develops a secondary malignancy during the study or follow-up and RCR is suspected, every effort should be made to obtain a blood sample to assay for RCR and vector elements. In the case of a secondary malignancy, every effort will be made to obtain a blood sample (PBMC) and biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a testing workflow, including tests such as transgene elements, RCR, presence of common cancer-drivers/mutations and insertional mutagenesis (see Section 6.3.15.3 of the KT-US-568-0138 master protocol).

j If a tumor biopsy that is clinically indicated in the management of a study-treated subject is acquired, a portion of the biopsy should be sent to the central laboratory for additional exploratory analyses.

k Targeted AEs/SAEs include neurologic events, hematologic events, serious infections, autoimmune disorders, and secondary malignancies. From 3 months after the brexucabtagene autoleucel infusion, targeted AEs/SAEs will be reported through Month 24 after the initial brexucabtagene autoleucel infusion or until disease progression and/or the start of subsequent anticancer therapy, whichever occurs first. After Month 24, the subject will transition to the LTFU study where targeted AEs/SAEs will be reported through 15 years. All new malignancies (defined as the development of any new malignancies occurring after the administration of brexucabtagene autoleucel) are to be reported; however, only secondary malignancies (defined as the development of any new malignancy suspected to be possibly related to brexucabtagene autoleucel) are considered to be targeted AEs/SAEs.

l Targeted concomitant medications will be collected up to 24 months after the brexucabtagene autoleucel infusion or until disease progression or the start of subsequent anticancer therapy, whichever occurs first. (Reporting will continue through 60 months as part of the LTFU study.)

m Subsequent anticancer therapy administered after brexucabtagene autoleucel infusion for a subject's disease will be collected until 1 of the following occurs: subject completes the post-treatment follow-up period, is considered lost to follow-up, withdraws consent, or dies. The subject and/or the referring HCP and/or GP may be contacted directly by telephone or email to collect information about subsequent therapy.

n Subject and/or referring HCP and/or GP may be contacted directly by telephone or email to assess survival status.

12.3. Disease Response Criteria

12.3.1. International Working Group Lugano Classification

Disease assessments are to be performed according to the International Working Group Lugano Response Criteria for Malignant Lymphoma {Cheson 2014}; refer also to instructions provided in the study imaging manual.

The Deauville 5-point scale (5PS) is used for positron emission tomography (PET) scoring; the scores and their descriptions are presented in Table 7.

Table 7. Deauville 5-point Scale for Positron Emission Tomography Scoring

Score	Description
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Source: {Cheson 2014}.

12.3.1.1. Complete Remission

12.3.1.1.1. Complete Metabolic Response for PET−Computed Tomography-based Response

The designation of complete metabolic response requires all of the following:

- A 5PS score of 1, 2, or 3, with or without a residual mass:
  - In Waldeyer's ring or extranodal sites with high physiologic uptake or activation within the spleen or marrow, uptake may be greater than normal in the mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- No new sites of disease should be observed
- No evidence of fluorodeoxyglucose (FDG)-avid disease in bone marrow

12.3.1.1.2. Complete Radiologic Response for Computed Tomography-based Response

The designation of complete radiologic response requires all of the following:

- Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter (LDi) of a lesion
- No extra lymphatic sites of disease
- Absent nonmeasured lesion
- Organ enlargement regress to normal
- No new sites of disease should be observed
- Bone marrow normal by morphology; if indeterminate, immunohistochemistry negative

12.3.1.2. Partial Remission

12.3.1.2.1. Partial Metabolic Response for PET–Computed Tomography-based Response

The designation of partial metabolic response requires all of the following:

- A 5PS score of 4 or 5, with reduced uptake compared to baseline (screening), and residual mass(es) of any size.

  Note:

  — At the interim, these findings suggest responding disease

  — At the end of treatment, these findings suggest residual disease

- No new sites of disease should be observed
- Residual uptake is higher than uptake in normal bone marrow but reduced compared with baseline (diffuse uptake is compatible with reactive changes from chemotherapy allowed)

If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with magnetic resonance imaging or biopsy or an interval scan.

12.3.1.2.2. Partial Radiologic Response for Computed Tomography-based Response

The designation of partial radiologic response requires all of the following:

- ≥ 50% decrease in the sum of the product of the perpendicular diameters of up to 6 target measurable nodes and extranodal sites.
  - When a lesion is too small to measure on a computed tomography (CT) scan, assign 5 mm × 5 mm as the default value
  - When the lesion is no longer visible, assign 0 x 0 mm
  - For a node > 5 mm × 5 mm, but smaller than normal, use the actual measurement for calculation
- Absent/normal, regressed, but no increase of nonmeasured lesions
- Spleen must have regressed by > 50% in length beyond normal
- No new sites of disease should be observed

12.3.1.3. Stable Disease

12.3.1.3.1. No Metabolic Response for PET–CT-based Response

The designation of no metabolic response requires all of the following:

- A 5PS score of 4 or 5, with no significant change in FDG uptake compared with baseline (screening) at an interim time point or the end of treatment
- No new sites of disease should be observed
- No change from baseline in bone marrow

12.3.1.3.2. Stable Radiologic Disease for CT-based Response

The designation of stable radiologic disease requires all of the following:

- < 50% decrease from baseline in the sum of the product of the perpendicular diameters of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease (PD) are met
- No increase consistent with progression in nonmeasured lesion and organ enlargement
- No new sites of disease should be observed

12.3.1.4. Progressive Disease

12.3.1.4.1. Progressive Metabolic Disease for PET–CT-based Response

The designation of progressive metabolic disease requires at least 1 of the following:

- A 5PS score 4 or 5 with an increase in intensity of uptake from baseline nadir and/or
- New FDG-avid foci consistent with lymphoma at an interim time point or the end of treatment assessment
- New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection or inflammation). If uncertain regarding the etiology of new lesions, a biopsy or interval scan may be considered
- New or recurrent FDG-avid foci in bone marrow

12.3.1.4.2. Progressive Radiologic Disease for CT-based Response

The designation of progressive radiologic disease requires at least 1 of the following:

- An individual node/lesion must be abnormal with:
  - LDi > 1.5 cm, and
  - An increase by ≥ 50% from the cross product of LDi and perpendicular diameter nadir, and
  - An increase in LDi or shortest transverse diameter, shortest axis perpendicular to the LDi, (shortest transverse diameter) from nadir
    - 0.5 cm for lesions ≤ 2 cm
    - 1.0 cm for lesions > 2 cm
  - In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If there is no prior splenomegaly, the spleen must increase by ≥ 2 cm from baseline
  - New or recurrent splenomegaly
- New or clear progression of preexisting nonmeasured lesions

- New lesion:
  - Regrowth of previously resolved lesions
  - A new node > 1.5 cm in any axis
  - A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and attributable to lymphoma
  - Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent bone marrow involvement

12.4. Protocol Amendment History

12.4.1. Amendment 1.0 (dated 20 July 2022)

Changes from the original protocol (dated 23 May 2022) to Amendment 1.0 (dated 20 July 2022) are detailed below.

Section Number and Name	High-level Description of Change	Brief Rationale
Synopsis Number of study sites planned	Number of study sites increased from approximately 40 to 50	Increased the number of study sites to optimize enrolment
Synopsis Number of subjects enrolled and treated and Section 4.1 Number of subjects and subject selection	Updated sample size of Burkitt Lymphoma to 30 subjects.	BL sample size increased in consideration of EMA Scientific Advice recommendations
Synopsis Statistical methods	Updated statistical methods to reflect the updated number of BL subjects that will be enrolled in substudy C.	Updates to statistical methods due to increase in number of subjects planned to be treated in Burkitt Lymphoma substudy.
Section 6.4 Tumor biopsy	Disease Progression: If a tumor biopsy that is clinically indicated in the management **of a study-treated subject** is acquired, a portion of the biopsy should be sent to the central laboratory for additional exploratory analyses.	Addition to clarify samples are applicable only for study treated subjects
Section 9.3 Determination of sample size	Updates to indicate this single-arm, open-label substudy will enroll and **treat 30 subjects** with the SRT recommended dose of brexucabtagene autoleucel. Additional edits to indicate this sample size will achieve a statistical power of **92%** and that 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.	Updated statistical rationale for increased sample size calculations
Section 9.4.1 Interim analysis and early stopping guidelines	Updates to indicate that 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 ≤ 39%).	Updates to statistical methods for planned analyses due to increase in number of subjects planned to be treated in Burkitt Lymphoma substudy following EMA scientific feedback
Section 9.4.2 Primary analysis	Subject number for primary analysis increased from 20 to **30**. In addition, text is amended to indicate that hypothesis testing will be based on the number of objective responders observed among the **30** subjects	Updates to statistical methods for planned analyses due to increase in number of subjects planned to be treated in Burkitt Lymphoma substudy following EMA scientific feedback

Section Number and Name	High-level Description of Change	Brief Rationale
Section 12.2 Schedule of assessments, Table 5 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Periods	Added schedule of PROs: EORTC-QLQ-C30 and EQ-5D-5L at Post-bridging therapy assessment (if applicable)	Correction. Added an applicable PROs assessment timepoint
Section 12.2 Schedule of assessments, Table 5 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-treatment Periods	Footnote k Disease progression: If a tumor biopsy that is clinically indicated in the management of a **study-treated** subject is acquired, a portion of the biopsy should be sent to the central laboratory for additional exploratory analyses	Addition to clarify samples are applicable only for study treated subjects
Section 12.2 Schedule of assessments, Table 6 Schedule of Assessments: Post-treatment Follow-up Period	Footnote j: If a tumor biopsy that is clinically indicated in the management of a **study-treated** subject is acquired, a portion of the biopsy should be sent to the central laboratory for additional exploratory analyses	Addition to clarify samples are applicable only for study treated subjects

12.4.2. Amendment 1.1 EU-specific Amendment (dated 12 January 2023)

A high-level summary of this amendment is provided in tabular form in the subsection below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

For changes from Amendment 1 to Amendment 2, please refer to Section 12.4.2 and Section 12.4.3. Amendment 2 incorporates all changes in Amendment 1.1 together with the changes outlined in Section 12.4.3.

Protocol changes that are common across all substudies are detailed in the Master protocol (Appendix 12.10).

Section Number and Name	High-level Description of Change	Brief Rationale
Title page and Synopsis	Added EU CT and NCT numbers	EU CT and NCT numbers not previously available
Section 3.1 Study Design	Add text to detail that the end of study is defined in the Master protocol (Section 3.4). (Defined as the LPLV within each specific substudy)	For clarity
Synopsis Statistical Methods and Sections 9.1 Hypothesis and 9.4.2 Primary Analysis	• "significantly" removed from statement that "The hypothesis is that the ORR to brexucabtagene autoleucel per central assessment is significantly greater than 39%."	For clarity

Section Number and Name	High-level Description of Change	Brief Rationale
	• Text edited to now state that the p-value 'will be' calculated based on an exact test, rather than 'may be' tested.	
Synopsis Eligibility Criteria Unique to the BL Substudy and Section 4.2.1 BL Substudy-Specific Inclusion Criteria	Inclusion criterion 2 updated to (i) allow any first line chemoimmunotherapy, and (ii) Subjects will be eligible regardless of the duration of remission prior to relapse	For clarity
Section 6.4 Tumor Biopsy	Added text to detail that a new biopsy will be acquired only if the location is easily accessible, and if appropriate taking into account subject safety	Self-explanatory
Section 12.2 Schedule of Assessments Table 5	Pregnancy test added at Day 28	Alignment with CTFG guidelines for pregnancy testing following administration of fludarabine and cyclophosphamide

12.4.3. Amendment 2.0 (dated 01 March 2023)

Changes from Amendment 1.1 (dated 12 January 2023) to Amendment 2 (dated 01 March 2023) are detailed below

Section Number and Name	High-level Description of Change	Brief Rationale
Entire document	Correction of minor typographical errors	Self-explanatory
Title Page	Study title updated to read "A Phase 2, Open-Label, Multicenter, Basket Study Evaluating the Efficacy of Brexucabtagene Autoleucel in Adults with Rare B-cell Malignancies (ZUMA-25) – *Substudy C – Relapsed/Refractory Burkitt Lymphoma"*. The evaluation of safety (secondary endpoint) removed from the study title.	Request during Part 1 EU-CTR application to update the trial title to focus on the primary endpoint only
Title Page	Amendment history added	Self-explanatory
Synopsis and Section 4.2.2 Exclusion Criteria	Exclusion criterion # 4 added "presence of central nervous system (CNS) involvement. Subjects with a prior history of CNS involvement are eligible if they show a negative cerebrospinal fluid (CSF) and no involvement by imaging"	Self-explanatory
Section 6.1 Brain Magnetic Resonance Imaging	At screening, CNS involvement will be assessed by local review, and images will not be sent for central review.	For clarification

Section Number and Name	High-level Description of Change	Brief Rationale
Section 12.2 Schedule of Assessments, Table 5 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Requirement for PRO assessment at post-bridging therapy disease assessment removed	Typo. PRO assessments will be done at Day -5 in all subjects, regardless of whether the subject received bridging therapy
Section 12.2 Schedule of assessments, Table 5 Schedule of Assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Added text to Footnote 'a': "For EU and UK, the subject may remain hospitalized or return to the clinic daily for this extended monitoring, at the discretion of the investigator. For CH, patients must remain hospitalized for 10 days after brexucabtagene autoleucel"	Request by Swiss Regulatory Authority
Section 12.2 Schedule of Assessments, Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Added text to Footnote 'g': "Subjects with a prior history of CNS involvement are eligible if they show a negative cerebrospinal fluid (CSF) at screening and no involvement by imaging".	Self-explanatory
Section 12.2 Schedule of assessments, Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Footnotes 'n' pregnancy testing and 'o' serology testing updated to include Switzerland (CH)	Request by Swiss Regulatory Authority and alignment with Master protocol Section 6
Section 12.2 Schedule of assessments, Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Footnote 's': Samples on Day 3 may be collected ± 1 day	Provides flexibility regarding central laboratory sample collection when the Day 3 visit falls over a weekend
Section 12.2 Schedule of Assessments, Table 6 Schedule of Assessments: Post-Treatment period	Visit window for M18 changed from ± 2 weeks to ± 1 month	Provides added flexibility

12.4.4. Amendment 3.0 (dated 17 August 2023)

Changes from Amendment 2.0 (dated 01 March 2023) to Amendment 3 (dated 17 August 2023) are detailed below

Section Number and Name	High-level Description of Change	Brief Rationale
General	Correction of typographical errors Removed references to study sites in the UK as UK is no longer participating.	Self-explanatory
Synopsis- Study Design	Removed to indicate that the study will focus on efficacy and not safety	Request from EMA reviewer during Part 1 EU-CTR application to update the trial title to focus on the primary endpoint only
Synopsis - Number of Study Sites Planned	Number of participating sites amended to approximately 25	Number of sites reduced due to early termination of substudies A and D
Synopsis- Statistical Methods	Added language to indicate study enrollment will be paused following treatment of the 10th subject with brexucabtagene autoleucel and until results from the interim analysis have been assessed	To allow the Sponsor to review for futility prior to exposing additional subjects to study treatment
Section 3.1 Study Design	Text removed to indicate that the study will focus on efficacy and not safety	Request during Part 1 EU-CTR application to update the trial title to focus on the primary endpoint only
Section 3.1 Study Design	Added language to indicate study enrollment will be paused following treatment of the 10th subject with brexucabtagene autoleucel and until results from the interim analysis have been assessed	To allow the Sponsor to review for futility prior to exposing additional subjects to study treatment
Study 6.1.1 Lumbar Puncture	Added text to indicate a screening lumbar puncture should be performed as close as possible to leukapheresis	To specify timing of the lumbar puncture
Section 6.2.1 Imaging Requirements	Added language to indicate that to limit radiation exposure, investigators are encouraged to leave at least 4 weeks between consecutive scans	To limit radiation exposure of subjects
Section 8.1 SRT and DSMB	Added language to indicate study enrollment will be paused following treatment of the 10th subject with brexucabtagene autoleucel and until results from the interim analysis have been assessed	To allow the Sponsor to review for futility prior to exposing additional subjects to study treatment

Section Number and Name	High-level Description of Change	Brief Rationale
Section 9.4.1 Interim Analysis and Early Stopping Guidelines	Added language to indicate study enrollment will be paused following treatment of the 10th subject with brexucabtagene autoleucel and until results from the interim analysis have been assessed	To allow the Sponsor to review for futility prior to exposing additional subjects to study treatment
Section 12.2 Schedule of assessments, Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Footnote e- added clarifying text that neurological should be performed every other day during the hospitalization period	To clarify requirements for neurological assessments
Section 12.2 Schedule of assessments, Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Added text to indicate a screening lumbar puncture should be performed as close as possible to leukapheresis	To specify timing of the lumbar puncture
Section 12.2 Schedule of assessments, Table 5 Schedule of assessments: Screening, Pretreatment, Treatment, and Post-Treatment Periods	Footnote i: added that “To limit radiation exposure, investigators are encouraged to leave at least 4 weeks between consecutive scans”	To limit radiation exposure of subjects
Section 12.2 Schedule of Assessments, Table 6 Schedule of Assessments: Post-Treatment period	Footnote d: added that “To limit radiation exposure, investigators are encouraged to leave at least 4 weeks between consecutive scans”	To limit radiation exposure of subjects

ZUMA-25_BL Amendment 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	31-Aug-2023 14:20:52