I concur with this review memo. I Wu 7/27/20

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch

BLA NUMBER:	STN #125703.000
DATE RECEIVED BY CBER:	12/11/2019
DATE REVIEW COMPLETED:	4/30/2020; amended 5/29/2020; amended 6/4/2020
PRODUCT:	KTE-X19 (brexucabtagene autoleucel; TECARTUS™)
APPLICANT:	Kite Pharma Inc
PROPOSED INDICATION:	KTE-X19 is proposed for the treatment of adults with relapsed or refractory (r/r) mantle cell lymphoma (MCL)
PHARM/TOX REVIEWER:	Gaya Hettiarachchi
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EXECUTIVE SUMMARY:

KTE-X19 is an autologous chimeric antigen receptor (CAR) T-cell product engineered with a retroviral vector to express an anti-CD19 single-chain antibody fragment that is linked to CD3ζ and CD28 T-cell activating domains. This product uses the same retroviral vector and anti-CD19 CAR transgene as the applicant's approved product, axicabtagene ciloleucel (YESCARTA™; BLA #125643).

In vitro characterization of KTE-X19 included demonstration of CD19-dependent cytotoxicity, cytokine release and proliferation when co-cultured with tumor cell lines expressing CD19. Additionally, an in vivo study conducted using an analogous murine CAR construct recognizing the murine CD19 molecule demonstrated anti-tumor activity and increased survival in a lymphodepleted syngeneic adoptive transfer mouse model of CD19+ B cell lymphoma. These studies indicated that the CAR T cells could target normal B cells, however, no other effects on the overall health of the animals was observed.

Traditional in vitro and in vivo genotoxicity and carcinogenicity/tumorigenicity assessments of KTE-X19 were not conducted. Published clinical and nonclinical data derived from different CAR T products supports a relatively low risk for malignant transformation of T cells by retroviral vectors. Additionally, vector integration analysis conducted using axicabtagene ciloleucel found the integration profile consistent with published data for similar vectors.

No animal reproductive and developmental toxicity studies were conducted with KTE-X19 which is acceptable based on the product characteristics and safety profile.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:
There were no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of KTE-X19. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry:
The active substance of KTE-X19 consists of autologous T cells that have been genetically modified *ex vivo* to express a CAR that targets CD19. The active substance of KTE-X19 is produced using the (b) (4) manufacturing process which involves the use of the patient's T cells that have undergone *ex vivo* (b) (4) activation via anti-CD3 and anti-CD28 antibodies followed by gene transfer using a replication-deficient retroviral vector (b) (4) Vector) and T cell expansion. The engineered, autologous T cell product is formulated in a cryopreservation medium suitable for infusion and is supplied cryopreserved at a temperature of ≤ -150°C. Each cryostorage bag contains (b) (4) anti-CD19 CAR T cells/kg, (b) (4) of CryoStor (b) (4) of Sodium Chloride (b) (4) and (b) (4) of human Albumin (b) (4).

Abbreviations

ALL	Acute lymphoblastic leukemia
ASCT	Autologous stem cell transplant
BLA	Biologics license application
CAR	Chimeric antigen receptor
CBL	Casitas B-lineage lymphoma
CLL	Chronic lymphocytic leukemia
DART	Developmental and reproductive toxicity
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
E:T	Effector:target
(b) (4)	(b) (4)
FL	Follicular lymphoma
Gy	Grays
HCL	Hairy cell leukemia
HIV	Human immunodeficiency virus
ICH	International conference on harmonisation
IFNγ	Interferon gamma
IL	Interleukin
ITAM	Immunoreceptor tyrosine-based activation motif
IP	intraperitoneal
IV	Intravenous
KD	KiloDalton
KG	Kilogram
KO	Knockout
LLOQ	Lower limit of quantitation
LTFU	Long term follow-up
MCL	Mantle cell lymphoma
mL	Milliliters
NCI	National cancer institute
NGFR	Nerve growth factor receptor
NGS	Next generation sequencing
NHL	Non-Hodgkin lymphoma
NTD	Non-transduced T cells
PBMC	Peripheral blood mononuclear cell
P/T	Pharmacology/toxicology
(b) (4)	(b) (4)
r/r	relapsed or refractory
SC	Subcutaneous
scFv	Single chain variable fragment
SLL	Small lymphocytic lymphoma
TBI	Total body irradiation

TCR	T cell receptor
TET2	Tet methylcytosine dioxygenase 2
TNFα	Tumor necrosis factor alpha
TSS	Transcription start site
ULOQ	Upper limit of quantitation
VIS	Vector integration site
(b) (4)	Kite CAR T-cell manufacturing process that uses (b) (4)

Related File(s)

BLA 125643 [APPROVED] YESCARTA™, an engineered autologous T cell immunotherapy, is indicated for the treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT) held by Kite Pharma Inc.

IND 16675 [ACTIVE] Autologous Peripheral Blood T Cells (b) (4) Selected (b) (4) and IL-2, CD3, and CD28 Activated Transduced with Retroviral Vector (b) (4) Expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor (KTE-C19 CAR); and Cultured with Cytokines; Following CSF Prophylaxis, Bridging Chemotherapy as needed, Fludarabine, and Cyclophosphamide, held by Kite Pharma Inc.

IND #16278 [ACTIVE] KTE-C19; Autologous Peripheral Blood T Cells Transduced with Retroviral Vector (b) (4) Expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor (CAR); and Cultured with Cytokines; Following Fludarabine and Cyclophosphamide, held by Kite Pharma, Inc.

IND (b) (4)

Table of Contents

INTRODUCTION

KTE-X19 is an autologous CAR T cell product indicated for the treatment of relapsed or refractory (r/r) MCL in adult patients.

T cells that are genetically modified to express a CAR can target specific tumor antigens and elicit an anti-tumor response. Potential mechanisms of anti-tumor activity include direct killing of tumor cells with effector molecules and secretion of various cytokines that potentiate and sustain the cytotoxic response in addition to promoting T cell survival.

KTE-X19 was designed to target CD19-expressing B cell malignancies. CD19 is a 95 kD transmembrane protein that is expressed in all normal B cells and in B cell malignancies including all subtypes of B-cell non-hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and non-T cell acute lymphoblastic leukemia (ALL). CD19 is not found in pluripotent hematopoietic stem cells or in most plasma cells.

CD19 expression has been observed in MCL across a number of studies[1-7]. This subtype of NHL affects the lymphatic system resulting in cancerous B-cells and represents approximately 7% of adults with NHLs[8]. A hallmark of this life-threatening disease is the overexpression of Cyclin D1 due to a specific chromosomal translocation (t(11;14)(q13;q32))[9]. Standard treatment approaches for MCL include chemotherapy with or without autologous hematopoietic stem cell transplant[10]. Many of these therapies are associated with considerable toxicities and limited therapeutic benefits.

NONCLINICAL STUDIES

Note: The KTE-X19 manufacturing process is based on the axicabtagene ciloleucel manufacturing process. Both products use the same anti-CD19 CAR construct, (b) (4) vector, final composition and cryopreservation method. As described by the applicant, the following major changes in manufacturing were aimed at accommodating differences in apheresis material obtained from patients based on the indications for KTE-X19 and axicabtagene ciloleucel (Module 3.2.S.2.6 Manufacturing Process development):

- (b) (4)

Given the similarities between axicabtagene ciloleucel (KTE-C19) and KTE-X19 and the applicability of nonclinical studies originally submitted and reviewed under BLA #125643, several of these studies were also submitted to support BLA #125703. The review from these studies is reproduced from the Pharmacology/Toxicology (P/T) review memo under BLA #125643. Reference to KTE-C19 or axicabtagene ciloleucel was retained in the duplicated reviews and are used interchangeably. Modifications were made, as needed, for 508 Compliance and numerical consistency with other tables and figures included in this memo. Nonclinical studies specifically evaluating KTE-X19 are comprehensively evaluated here.

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

Note:

- Studies that were originally conducted and submitted under BLA #125643 that were also submitted under BLA #125703 are indicated in the table below.

- Supporting studies #4-6 were not reviewed comprehensively in this memo because these studies were product development and characterization studies which are not relevant for assessing the Pharmacology of the final product.

- The designation of ‘study’ is an arbitrary identification made by this reviewer. Each ‘study’ represents a group of studies conducted by the applicant or reported in the scientific literature to evaluate a specific nonclinical aspect of the product. Summaries of the data submitted in individual modules are provided in this review.

Study Number	Study Title / Publication Citation	Report Number	BLA#
1	Characterization of the Activation, Transduction, and Expansion of Anti-CD19 CAR T-cell Products Manufactured Using Isolated (b) (4) T Cells as Starting Material (b) (4)	No. PC-472-2001	125703
2	Functional Characterization of Anti-CD19 CAR T-cell Products Manufactured Using the (b) (4) Manufacturing Process	No. PC-472-2002	125703
3	Anti-Murine CD19 CAR T-Cell Activity in a Syngeneic Mouse Lymphoma Model	N/A; cited publications[11]	125643
4	Development of a Gamma-retroviral Vector Encoding an Anti-CD19 CAR	N/A; cited publication[12]	125643
5	(b) (4)	DR-00201	125643
6	(b) (4)	DR-00204	125643

Overview of Pharmacology Studies

Overview of In Vitro Studies

Study #1: Characterization of the Activation, Transduction, and Expansion of Anti-CD19 CAR T-cell Products Manufactured Using Isolated (b) (4) T Cells as Starting Material (b) (4)

Objective: Determine the feasibility of using selected (b) (4) autologous T cells as starting material for KTE-X19.

Methods: (b) (4)

Results: Viability was found to range between (b) (4) with variable levels of expansion for each donor. High, stable surface expression of anti-CD19 CAR was observed over the course of (b) (4)

Comment: While this was a small-scale study, the data supports the feasibility of producing CAR T cells with high viability and stable CAR expression via the proposed (b) (4) manufacturing process.

Study #2: Functional Characterization of Anti-CD19 CAR T-cell Products Manufactured Using the (b) (4) Manufacturing Process

Objective: Evaluate the in vitro functionality of product manufactured using the (b) (4) process.

Methods: (b) (4)

Results: CD19-specific 1) cytotoxicity on day (b) (4) 2) increased (b) (4) cytokine production on day (b) (4) increased T cell proliferation up to (b) (4) on day (b) (4) were observed in all (b) (4) donor samples.

Comment: CD19-specific cytotoxicity, cytokine release, and T cell proliferation supported both the specificity and functionality of the product produced via the (b) (4) manufacturing process.

Overview of In Vivo Studies

Note: The following review was reproduced from the P/T review memo for BLA #125643. Unless otherwise noted, conclusions and interpretations from these studies are consistent with this reviewer's conclusions and interpretations of the data and apply to KTE-X19.

Study #3: Anti-Murine CD19 CAR T-Cell Activity in a Syngeneic Mouse Lymphoma Model

Comment: The scFv construct used to manufacture KTE-C19 recognizes human, but not murine CD19. Therefore, the NCI investigators developed an anti-murine CD19 CAR construct to administer in a syngeneic mouse model of B cell lymphoma in proof-of-concept experiments that also evaluated general but limited safety. A study report for the multiple experiments that constituted this study was not submitted to IND #16278 or to BLA #125643. Instead the experiments and results were submitted as a publication[11]. Relevant information from this publication are summarized below.

In vitro Characterization of an Anti-Murine CD19 CAR Construct Analogous to KTE-C19

This anti-murine CD19 CAR construct, designated as 1D3-28Z, consisted of the 1D3 scFv domain of a rat antibody that binds to murine CD19. The elements in 1D3-28Z were arranged similarly to FMC63-28Z, but with the murine CD28 and CD3-ζ domains. A second anti-murine CD19 CAR construct, 1D3-28Z.1-3, was designed such that the first and third immunoreceptor tyrosine-based activation motif (ITAMs) of the CD3-ζ molecule were inactivated so that apoptosis of T cells would be decreased[13].

The *in vitro* activity of murine T cells transduced with the retrovirus vector encoding 1D3-28Z or 1D3-28Z.1-3 was investigated by measuring IFN-γ expression after co-culturing the cells with CD19+ target cells, CD19- target cells, or without target cells. Non-transduced T cells served as an additional negative control. The transduced cells produced high levels of IFN-γ when cultured with CD19+ target cells (Table 1). Both of the anti-murine CD19 CAR constructs showed low, but detectable, production of IFN-γ in the absence of the CD19 antigen.

Table 1 Anti-murine CD19 CAR T Cells Produced IFN-γ Specifically in Response to CD19 Stimulation

Transduced T Cells	$CD19^+$ Targets			$CD19^-$ Targets			No Target Cells
	38c13	mCD19-K562	Splenocytes	Sol8	CCL12	NGFR-K562	
1D3-28Z.1-3	286,480	234,252	16,378	1,224	969	1,531	1,126
1D3-28Z	294,150	297,100	18,085	5,892	4,480	6,055	6,267
Not transduced	211	123	292	178	129	124	122

Abbreviations: CAR, chimeric antigen receptor; CCL, chronic lymphocytic leukemia; CD, cluster of differentiation; IFN, interferon; mCD19-K562, mouse CD19-K562; NGFR, nerve growth factor receptor.
Notes: Values are means of duplicate wells in an IFN-γ enzyme-linked immunosorbent assay. The units are in pg per mL of IFN-γ. All target cells cultured alone produced undetectable levels of IFN-γ. 1D3-28Z refers to the anti-murine CD19 CAR construct. 1D3-28Z.1-3 refers to the anti-murine CD19 CAR in which the first and third immunoreceptor tyrosine-based activation motifs of the CD3-ζ molecule were inactivated

Source: BLA 125703; Module 4.2.1.1; pg 15

Comment:

- The low levels of IFN-γ that were detected in the absence of the CD19 target cells may be due to experimental background or may suggest that some anti-murine CD19 CAR T cells were activated without CD19.

In vivo Experiments:

Note: The delineation of 'Experiments A-E' was made by this reviewer.

A. Characterization of T Cells Expressing Different Anti-murine CD19 CAR Constructs After Injection Into Mice

Design: C3H/HeN mice underwent total body irradiation (TBI) at 5 Grays (Gy). The same day, the mice were injected intraperitoneally (i.p.) with 1 x 105 38c13 murine lymphoma cells, a CD19-expressing B-cell lymphoma of C3H/HeN origin. The next day, CAR T cells transduced with 1D3-28Z.1-3 (3.9×10^6 T cells) or 1D3-28Z (3.3×10^6 T cells) were administered by intravenous (i.v.) injection. A control group did not receive cells. Splenocytes from animals sacrificed on Day 8 post-T cell injection were stained for CAR expressing cells.

Results: CAR expressing CD4+ and CD8+ T cells were detected in the spleens of mice administered T cells transduced with either anti-murine CD19 CAR construct. The T cells produced IFN-γ, as assessed via intracellular cytokine staining, in a CD19-specific manner.

Comment:

- The number of animals in each group for this experiment was not provided.

B. Effects of Anti-murine CD19 CAR T Cell in Mice Challenged with 38c13 Murine Lymphoma Cells

Design:

- B.1 - Groups of C3H/HeN mice (5/group) were conditioned and i. p. injected with 38c13 murine lymphoma cells in the same manner as in Experiment A. Mice were then i.v. injected with each of the two CAR T cells as in Experiment A. Spleens were collected, and splenocytes were stained for the expression of kappa light chain for lymphoma cells and B220 for normal B cells.

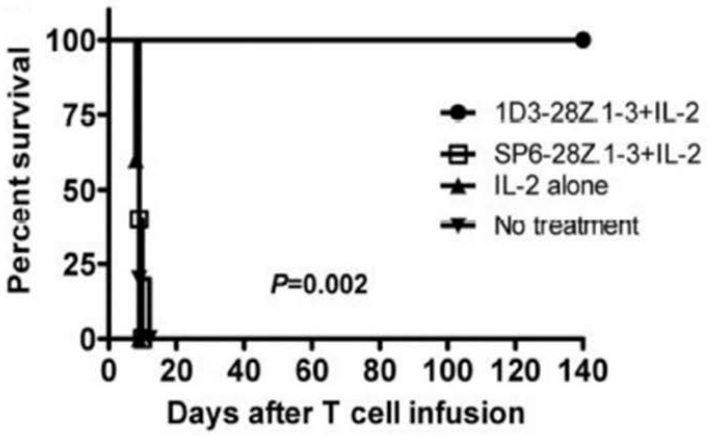
- B.2 - Groups of the lymphoma-bearing mice (5/group) were also administered 1) T cells transduced with 1D3-28Z.1-3 + IL-2 (, 2) T cells transduced with negative control SP6-28Z.1-3 + IL-2, 3) IL-2 alone, or 4) no treatment. Mice were monitored for survival over time.

Results:

- B.1 - Lymphoma and normal B cells were absent from the spleens of mice injected with anti-murine CD19 CAR T cells, while control mice had many lymphoma cells. According to the publication, all mice injected with anti-murine CD19 CAR T cells were alive, without signs of lymphoma or toxicity, at 8 to 9 days after T cell infusion.

- B.2 - As shown in Figure 4 below, mice injected with anti-murine CD19 CAR T cells survived and remained healthy long-term, while mice administered IL-2 alone or no treatment became moribund due to lymphoma and were sacrificed.

Figure 4 **Anti-lymphoma Activity of Anti-murine CD19 CAR T Cells**



Abbreviations: CAR, chimeric antigen receptor; IL, interleukin.
Notes: The p-value refers to the comparison of the 1D3-28Z.1-3 plus IL-2 group to the SP6-28Z.1-3 plus IL-2 group. 1D3-28Z.1-3 refers to the anti-murine CD19 CAR in which the first and third immunoreceptor tyrosine-based activation motifs of the CD3-ζ molecule were inactivated (refer to Section 2.3). SP6-28Z.1-3 refers to the hapten-specific control CAR construct with the same modified CD3-ζ regions as 1D3-28Z.1-3. Each treatment group comprised 5 mice.

Source: BLA 125703; Module 4.2.1.1; pg 22

C. Effect of Radiation-Induced Lymphodepletion and Supplemental IL-2 on the Efficacy of Anti-murine CD19 CAR T Cells

Design: Groups of C3H/HeN mice (4-5/group) consisted of:

1. 'Radiation + IL-2' group - TBI (5 Gy) followed by i.p. injection of 38c13 cells the same day, and i.v. injection of anti-murine CD19 CAR T cells transduced with 1D3-28Z1-3 on the following day. IL-2 was administered immediately after the T cell injection, and again one day later.

2. 'No Radiation' group - treated the same as the 'Radiation + IL-2' group, except that TBI was not administered.

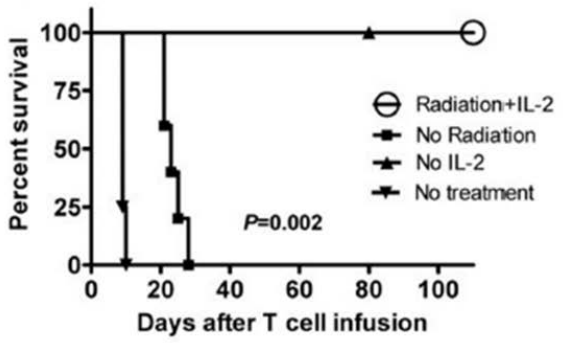
3. 'No IL-2' group - treated the same as the 'Radiation + IL-2' group, except that phosphate-buffered saline was administered in place of IL-2.

4. 'No Treatment' group - i.p. injected with lymphoma cells, but otherwise untreated.

Mice were monitored for survival over time.

Results: As shown in Figure 5 below, the 'Radiation + IL-2' group exhibited survival longer than 100 days. The anti-tumor activity of CAR T cells was significantly reduced in the 'No Radiation' group.

Figure 5 **Effect of Radiation-induced Lymphodepletion and IL-2 on the Anti-lymphoma Efficacy of Anti-murine CD19 CAR T Cells**



Abbreviations: CAR, chimeric antigen receptor; IL, interleukin.
Notes: The p-value refers to the comparison of the "Radiation + IL-2" group to the "No Radiation" group. Mice in each group other than the "No treatment" group received T cells transduced with 1D3-28Z.1-3, the anti-murine CD19 CAR construct in which the first and third immunoreceptor tyrosine-based activation motifs of the CD3-ζ molecule were inactivated (refer to Section 2.3). Each treatment group comprised 5 mice, except for the "No treatment" group, which had 4 mice.

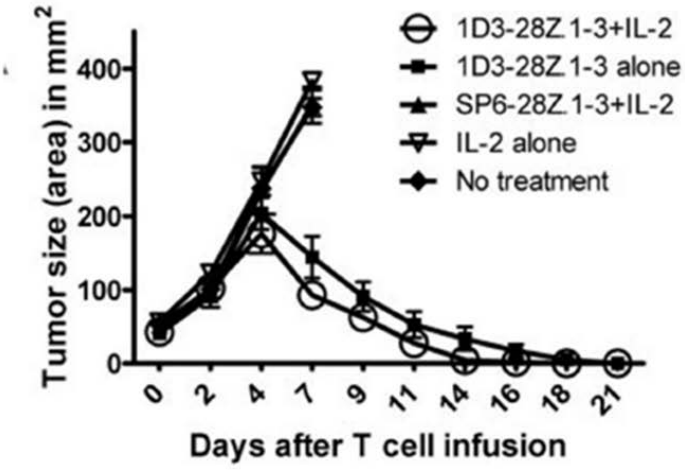
Source: BLA 125703; Module 4.2.1.1; pg 23

D. Effect of Anti-murine CD19 CAR T Cells on Established Subcutaneous Lymphoma Masses

Design: Mice underwent TBI and were subcutaneously (s.c.) injected with 0.5×10^6 38c13 cells later the same day, with or without daily s.c. injections of IL-2 for 3 days. Four days following:
Group 1 - 1D3-28Z1-3 transduced anti-murine CD19 CAR T cells + IL-2
Group 2 - the same CAR T cells alone
Group 3 - control (SP6-28Z1-3) CAR T cells + IL-2
Group 4 - IL-2 alone
Group 5 - no treatment
Tumor growth and survival were assessed over time.

Results: As shown in Figure 6, mice injected with the anti-murine CD19 CAR T cells with or without IL-2, displayed inhibition of tumor growth, while the control groups displayed progressive tumor growth. In addition, the Groups 1 and 2 mice (anti-murine CD19 CAR T cells with or without IL-2) exhibited 100% survival out to the Day 50 time point, compared to the control groups.

Figure 6 **Effect of Anti-murine CD19 CAR T Cells on Established Lymphoma Tumors in Mice**



Abbreviations: CAR, chimeric antigen receptor; IL, interleukin.
Notes: The mean tumor sizes of each group are shown. The tumor size curves of the control groups end when the first mouse from a group was euthanized. There were 5 mice in each group, and these results are representative of 2 experiments with nearly identical results. 1D3-28Z.1-3 refers to the anti-murine CD19 CAR in which the first and third immunoreceptor tyrosine-based activation motifs s of the CD3-ζ molecule were inactivated (refer to Section 2.3). SP6-28Z.1-3 refers to the hapten-specific control CAR construct with the same modified CD3-ζ regions as 1D3-28Z.1-3. Each treatment group had 5 mice.

Source: BLA 125703; Module 4.2.1.1; pg 24

E. On-target, Off-tumor Effect of Anti-murine CD19 CAR T Cells on Normal B Cells

Design: In experiments A-D, following injection of anti-murine CD19 CAR T cells in the mice the levels of normal B cells in different tissues (spleen, bone marrow, lymph nodes) were determined by staining for the B cell surface marker B220.

Results: No splenic B cells were detected on Days 8, 63, or 143. On Days 143 and 209, no B cells were detected in the lymph nodes and bone marrow. According to the publication, the mice appeared normal.

Comment:

- These series of experiments reported by Kochenderfer et al., 2010, demonstrated that following intravenous administration of anti-murine CD19 CAR T cells into lymphodepleted syngeneic tumor bearing mice: 1) CD19 antigen stimulation resulted in production of IFN-γ (Experiment A); 2) tumors were eliminated (i.e., lymphoma cells were not detected) and animal survival was extended (Experiments B-D); and 3) B cell aplasia was observed but no overt toxicity was exhibited (Experiment E).

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies were conducted.

PHARMACOKINETIC STUDIES (biodistribution)

Note: This information was reproduced from the P/T review memo for BLA #125643.

In vivo Studies

No biodistribution studies with KTE-C19 were conducted. However, the publication by Kochenderfer et al., 2010a, which is summarized in the Pharmacology section of this review memo (Study #3), examined the persistence of anti-murine CD19 CAR T cells following administration into immune competent tumor-bearing mice. Resulting data (Experiment A) showed detection of CD8+ and CD4+ anti-murine CD19 CAR T cells in the spleen at 8 days after T cell infusion. However, this experiment provided limited information because evaluation included examination of the spleen only, and did not investigate time points beyond 8 days following T cell administration.

Comment: Per the applicant, the ability of KTE-C19 to circulate and home to specific tissues and organs requires interactions of various molecules on KTE-C19 and human tissues/organs, which cannot be replicated in animal models. Thus, the extent to which the data reported using anti-murine CD19 CAR T cells in syngeneic mice translates to the distribution profile of KTE-C19 following in vivo administration in human is not known.

TOXICOLOGY STUDIES

Toxicology Studies

Note: This information was reproduced from the P/T review memo for BLA #125643.

No toxicology studies with KTE-C19 were conducted. However, the publication by Kochenderfer et al., 2010a, which is summarized in the Pharmacology section of this review memo (Study #3), also evaluated overall safety following administration of the anti-murine CD19 CAR T cells into immune competent tumor-bearing mice. Some mice were followed out to Day 209. The publication reported no overt toxicity, but normal B cells were decreased (i.e., B cell aplasia).

Developmental and Reproductive Toxicology Studies (DART)

No DART studies were conducted.

Genotoxicity Studies

Traditional genotoxicity studies were not conducted using KTE-X19, however, given the use of a murine γ-retroviral vector to stably integrate the anti-CD19 CAR into the T cell genome, a risk associated with insertional mutagenesis exists. In addition to a discussion of published literature, the applicant provided brief data from integration analyses conducted using axicabtagene ciloleucel (Module 4.2.3.3.2).

Integration Site Analysis

Methods: T cells from 3 healthy donors with (b) (4) for Donor 1, 2 and 3 respectively were used. Five cell aliquots per donor product were analyzed, each containing approximately 500,000 T cells (analysis was performed using transduced and non-transduced T cells present in the product). Genomic DNA (100 ng) extracted from each aliquot was subjected to next generation sequencing (NGS). Vector integration sites (VIS) were identified using (b) (4) Basic Local Alignment Search Tool (BLAST®) analysis was used to identify the retroviral long-terminal repeat sequences and genomic coordinates. Each VIS was quantified by the sequence tag. Functional tests were not performed to identify clones with proliferative advantage.

Results: There was no indication of dominant VIS that would suggest an advantage for clonal expansion, however, there was a low frequency of integration events in exons that may suggest a potential for gene disruption. Preferential integration was noted within close proximity to TSS and transcriptionally active T cell genes consistent with published data. Similar results were observed previously using other retrovirally transduced T-cell products[14,15].

Carcinogenicity/Tumorigenicity Studies

No carcinogencity/tumorigenicity studies were conducted. However, the applicant provided a review of the literature regarding the potential for oncogenicity due to transformation and clonal expansion. Based on published data derived from other CAR T products, the risk of malignant transformation of transduced T cells is considered to be low. Additionally, the applicant performed the integration site analysis reviewed above.

APPLICANT'S PROPOSED LABEL

No P/T changes were made to the sponsor's proposed labeling for Sections 8 and 13. This labeling is consistent with that of axicabtagene ciloleucel under BLA #125643.

CONCLUSION OF NONCLINICAL STUDIES

No significant safety concerns were identified during the review of nonclinical studies. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

KTE-X19, anti-CD19 CAR T cells, chimeric antigen receptor, CAR, B cell aplasia, B cell malignancy, retroviral vector, T cells, axicabtagene ciloleucel, YESCARTA™, TECARTUS™

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