

APPROVED*By M. Serabian at 4:23 pm, Sep 19, 2017*

I concur with this review. M. Serabian 9/05/17

**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**

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PRODUCT: Axicabtagene ciloleucel (YESCARTA™; KTE-C19)

APPLICANT: Kite Pharma, Inc.

PROPOSED INDICATION: 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).

PHARM/TOX REVIEWER: Jinhua Lu

PHARM/TOX TEAM LEADER: Iwen Wu

PHARM/TOX BRANCH CHIEF: Mercedes Serabian

PRODUCT (CMC) REVIEWERS: Don Fink, Anna Kwilas, Graeme Price, Jakob Reiser, Hyesuk Kong

CLINICAL REVIEWERS: Najat Bouchkouj, Bindu George, Yvette Kasamon, R. Angelo de Claro

PROJECT MANAGER: Mark Davidson

DIVISION DIRECTOR: Tejashri Purohit-Sheth

OFFICE DIRECTOR: Wilson Bryan

APPROVED*By Tejashri Purohit-Sheth, M.D. at 4:32 pm, Sep 19, 20***EXECUTIVE SUMMARY:**

YESCARTA™ (axicabtagene ciloleucel, KTE-C19) is a cell suspension consisting of autologous human T cells transduced with a retroviral vector encoding an anti-CD19 CD28/CD3-ζ chimeric antigen receptor (CAR).

In vitro pharmacology studies were conducted to evaluate the specificity and activity of anti-

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). A subsequent co-culture study of anti-CD19 CAR T cells derived from peripheral blood mononuclear cells obtained from patients with NHL demonstrated CD19-specific induction of multiple cytokines, chemokines, and effector molecules.

To evaluate CD19-specific anti-tumor activity *in vivo*, an analogous murine CAR construct recognizing the murine CD19 molecule was evaluated in a lymphodepleted syngeneic mouse model of CD19+ B cell lymphoma. Following intravenous injection of murine T cells expressing the anti-murine CD19 CAR into the mice, tumors were eliminated (i.e., lymphoma cells were undetectable) and animal survival was extended. However, depletion of normal B cells (i.e., B cell aplasia) also occurred, but no effect on overall animal health was observed.

No *in vitro* and *in vivo* genotoxicity and carcinogenicity assessments for KTE-C19 were conducted. To address the risk of retroviral vector insertional mutagenesis and potential carcinogenicity/tumorigenicity the applicant performed a review of published nonclinical and clinical information reported for T cells transduced with retroviral vectors. The data suggest that T cells are relatively resistant to malignant transformation by retroviral vectors.

No animal developmental and reproductive toxicity (DART) studies were conducted with KTE-C19 to assess whether the product can cause embryo or fetal harm when administered to women of childbearing potential.

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-C19. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry

Axicabtagene ciloleucel (KTE-C19) consists of autologous T cells that have been genetically modified *ex vivo* to express a chimeric antigen receptor (CAR) that targets CD19, which is expressed on the cell surface of malignant and normal B cells. The active substance of axicabtagene ciloleucel is composed of a patient's T cells that have undergone *ex vivo* T cell activation, followed by gene transfer using a replication-deficient retroviral vector (b) (4) (Vector), and expansion. Refer to the CMC review memos for details of these processes. The anti-CD19 CAR vector ((b) (4)) encodes: 1) a single chain variable fragment (scFv) derived from the murine FMC63 monoclonal antibody directed against human CD19, 2) the extracellular, transmembrane, and intracellular signaling domains of CD28, and 3) the intracellular CD3- ζ signaling domain.

Axicabtagene ciloleucel is supplied cryopreserved at a temperature less than or equal to -150°C in cryostorage bags. Each cryostorage bag contains: 1) a nominal 68 mL of axicabtagene ciloleucel (target dose level of 2.0×10^6 CAR T cells/kg), 2) (b) (4) 3) (b) (4) and 4) albumin (human) (b) (4)

Abbreviations

ALL	Acute lymphoblastic leukemia
ASCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CLL	Chronic lymphocytic leukemia
DLBCL	Diffuse large B-cell lymphoma
ELISA	Enzyme-linked immunosorbent assay
FACS	Fluorescence-activated cell sorting
FL	Follicular lymphoma
HCL	Hairy cell leukemia
ICH	International Conference on Harmonisation
IFN	Interferon
IL	Interleukin
ITAM	Immunoreceptor tyrosine-based activation motif
IV	Intravenous
LTFU	Long term follow-up
MCL	Mantle cell lymphoma
NCI	National Cancer Institute
NGFR	Nerve growth factor receptor
NHL	Non-Hodgkin lymphoma
PBMC	Peripheral blood mononuclear cell
qPCR	Quantitative polymerase chain reaction
SC	Subcutaneous
scFv	Single chain variable fragment
SLL	Small lymphocytic lymphoma
TCR	T cell receptor
TBI	Total body irradiation
TNF	Tumor necrosis factor

Related File(s)

IND #16278 [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.; Active]

IND (b) (4)

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a hematologic malignancy that can originate from B or T lymphocytes. The most common types of NHL involve B cells and include diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). Patients with relapsed or refractory aggressive B cell NHL have limited options, and outcomes are generally poor. Only about 10% of relapsed or refractory patients who are eligible for high dose therapy and autologous stem cell transplantation (ASCT) experience long-term survival. No curative options currently exist for those patients that are not eligible for ASCT.¹ Immunotherapy is an approach that utilizes the body's immune system to target cancer. Studies with tumor vaccines,² immune checkpoint inhibitors,³ and tumor infiltrating lymphocytes⁴ have demonstrated the potential utility of T cells in cancer treatment.

T cells that are genetically-modified to express a CAR can redirect their specificity to target tumor antigens and become activated upon antigen stimulation through intracellular signaling transduction processes. Activated CAR-expressing T cells can elicit anti-tumor responses by: 1) direct killing of tumor cells with effector molecules such as granzymes and perforin and 2) secretion of various cytokines that potentiate and sustain the cytotoxic response and promote T cell survival. CD19 is a 95 kD transmembrane protein expressed only in the B cell lineage. It is

¹ Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2011; 2011:498-505.

² Kantoff PW, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-422.

³ Wolchok JD, et al. Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma. Ann NY Acad Sci. 2013; 1291:1-13. doi: 10.1111/nyas.12180.

⁴ Rosenberg SA, Durable complete responses in heavily pretreated patients with metastatic melanoma using T cells transfer immunotherapy. Clin Cancer Res. 2011; Jul 1;17(13):4550-7.

expressed in all normal B cells, beginning at the pre-B cell stage until the final differentiation stage. This protein is not expressed in pluripotent hematopoietic stem cells or in most plasma cells. This pattern of CD19 expression is maintained in B cell malignancies, including all subtypes of B-cell NHL, CLL, and non-T cell acute lymphoblastic leukemia (ALL).⁵ Administration of CAR T cells directed to the CD19 antigen has resulted in durable objective responses in patients with lymphoma and leukemia.^{5,6,7}

Axicabtagene ciloleucel (KTE-C19) is a genetically-modified autologous T cell product that can target CD19-expressing B cell malignancies. A lymphodepletion regimen consisting of cyclophosphamide (500 mg/m²/infusion) and fludarabine (30 mg/m²/infusion) is indicated prior to infusion of axicabtagene ciloleucel.

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NONCLINICALSTUDIES

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted and public available information was used to support the rationale for the administration of KTE-C19 to treat the proposed clinical indication.

In vitro Studies

Study Number	Study/Publication Description
1	CD19 Expression on Normal and Malignant B-lineage Cells ^{9,10,11}

⁵ Kochenderfer JN, et al. Chemotherapy-refractory diffuse large-cell and indolent B-cell malignancies can be effectively treated with autologous T cells expressing anti-CD19 chimeric antigen receptor. J Clin Oncol. 2014; pii: JCO.2014.56.2025.

⁶ Davila ML, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci. Transl. Med. 2014; 6, 224ra25.

⁷ Maude SL, et al. Chimeric antigen receptor T cells for sustained remission in leukemia. N Engl J Med. 2014; 371:1507-17.

⁸ Kochenderfer JN, et al. Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. Blood. 2010a; 116(19):3875-86.

⁹ Uckun FM, et al. Detailed studies on expression and function of CD19 surface determinant by using B43 monoclonal antibody and the clinical potential of anti-CD19 immunotoxins. Blood. 1988; 71(1):13-29.

¹⁰ Olejniczak SH, et al. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry. Immunological Investigations. 2006; 35(1):93-114.

Study Number	Study/Publication Description
2	Development of a Gamma-Retroviral Vector Encoding an Anti-CD19 CAR ¹²
3	Product Characterization Conducted at Kite Pharma Using Patient-Derived Anti-CD19 CAR T cells from Subjects on (b) (4)

Note: The designation of ‘study’ is an arbitrary identification made by this reviewer. Each ‘study’ represents a cluster of studies conducted by the applicant or reported in the scientific literature to evaluate a specific nonclinical aspect of KTE-C19. Summaries of the data submitted in individual modules were reviewed in this review.

In vivo Studies

Study Number	Publication Description
4	Anti-Murine CD19 CAR T-Cell Activity in a Syngeneic Mouse Lymphoma Model ⁸

Overview of Pharmacology Studies

Overview of In vitro Studies

Study #1: CD19 expression on normal and malignant B-lineage cells

The applicant provided a review of three publications to demonstrate that CD19 expression was restricted to normal and malignant B cells.

Primary neoplastic cells were obtained from 151 patients with malignant lymphoma and from 340 patients with leukemia, and non-neoplastic cells (normal bone marrow, lymph nodes, spleen, and nonhematopoietic tissues) obtained from six healthy volunteer donors. CD19 expression was detected on all B-lineage lymphoid cells, which included the pro-B-cell maturation stage, naïve B cells, and differentiated B cells. Additionally, CD19 was detected in 88% of all B-cell lymphoma sub-types evaluated. Erythroid, myeloid, megakaryocytoid, and multi-lineage normal bone marrow progenitor cells did not express CD19.⁸

The expression pattern and levels of CD19 was determined in the peripheral blood, bone marrow, and lymph nodes obtained from patients with six different common B-cell malignancies (CLL, small lymphocytic lymphoma, B-lineage ALL, hairy cell leukemia, DLBCL, and FL). Although the levels were variable across the different malignancies, all had measurable levels of CD19 expression above the control reference CD3+ T cells.⁹

Analysis of biopsies obtained from 80 patients with DLBCL showed that all samples had detectable cell surface expression of CD19, with 88.8% of samples displaying high expression levels that were at least 51-fold higher than the level of expression of the control CD3+ T cells.¹⁰

¹¹ Johnson NA, et al. Diffuse large B-cell lymphoma: reduced CD20 expression is associated with an inferior survival. *Blood*. 2009; 113(16):3773-80.

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In summary, data reported in these publications demonstrate that CD19 is expressed on the surface of normal B lineage cells and B cell malignancies, including DLBCL and FL, which are two subtypes of NHL.

Study #2: Development of a Gamma-Retroviral Vector Encoding an Anti-CD19 CAR¹¹

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

¹³ Nicholson IC, et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. *Molecular Immunology*. 1997; 34(16-17):1157- 65.

2 Pages Determined to be Non-Releaseable: (b)(4)

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Overview of In vivo Studies

Study #4: 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 safety. A study report for the multiple experiments that constituted this study was not submitted to IND #16278 or to this BLA. Instead the experiments and results were submitted as a publication.⁸ Relevant information from this publication is 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.¹⁴

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. Nontransduced T cells served as an additional negative control. The transduced cells produced high levels of IFN- γ when cultured with CD19+ target cells (Table 3). Both of the anti-murine CD19 CAR constructs showed low, but detectable, production of IFN- γ in the absence of the CD19 antigen.

¹⁴ Zhao Y, et al. A Herceptin-Based Chimeric Antigen Receptor with Modified Signaling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity. *J. Immunology*. 2009; 183(9):5563-74.

Table 3: Anti-murine CD19 CAR T cells produced IFN- γ in response to CD19 stimulation
(Reproduced from Kochenderfer et al., 2010)

Transduced T cells	CD19 ⁺ targets			CD19 ⁻ targets			No Target Cells
	38c13	CD19-K562	Splenocytes	Sol8	CCL12	NGFR-K562	
1D3-28Z.1-3	286,480	234,252	16,378	1224	969	1531	1126
1D3-28Z	294,150	297,100	18,085	5892	4480	6055	6267
Not transduced	211	123	292	178	129	124	122

Abbreviations: CCL, chronic lymphocytic leukemia; CD, cluster of differentiation; IFN, interferon; NGFR, nerve growth factor receptor.

Notes: Values are means of duplicate wells in an IFN- γ ELISA. 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 ITAMs of the CD3- ζ molecule were inactivated.

Source: Table 1 Kochenderfer et al, 2010a.

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 1×10^5 38c13 murine lymphoma cells. 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:

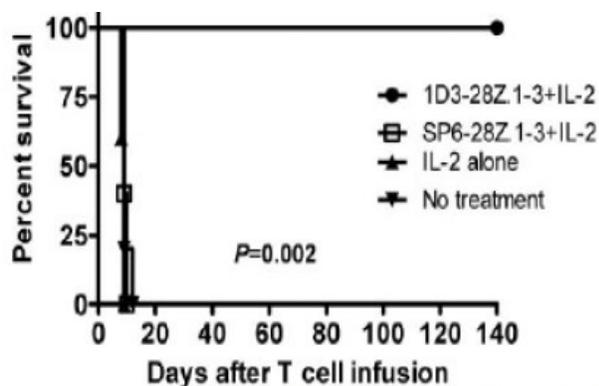
- **B.1** - Groups of C3H/HeN mice (5/group) were conditioned and i. p. injected with 38c13 murine lymphoma cells in the same manner as in Experiment A. Mice were then i.v. injected with each of the two CAR T cells as in Experiment A. Splens were collected, and splenocytes were stained for the expression 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 1 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 1. Anti-lymphoma activity of anti-murine CD19 CAR T cells
(Reproduced from Kochenderfer et al., 2010)



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 ITAMs of the CD3- ζ molecule were inactivated. 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: Figure 5 in Kochenderfer et al, 2010a.

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:

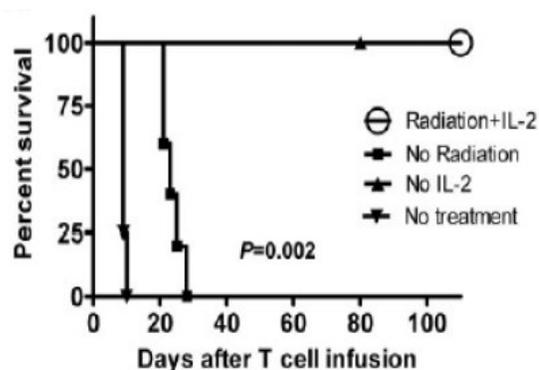
1. 'Radiation + IL-2' group - TBI (5 Gy) followed by i.p. injection of 38c13 cells the same day, and i.v. injection of anti-murine CD19 CAR T cells transduced with 1D3-28Z1-3 on the following day. IL-2 was administered immediately after the T cell injection, and again one day later.
2. 'No Radiation' 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 2 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 2: Effect of radiation-induced lymphodepletion and IL-2 on the anti-lymphoma efficacy of anti-murine CD19 CAR T cells

(Reproduced from Kochenderfer et al., 2010)



The p-value refers to the comparison of the 'Radiation + IL-2' group to the 'No Radiation' group. Note, 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 ITAMs of the CD3- ζ molecule were inactivated. Each treatment group comprised 5 mice, except for the 'No treatment' group, which had 4 mice.

Source: Figure 5 in Kochenderfer et al, 2010a.

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

later, when the tumor was no larger than 7 mm in diameter, mice (5 /group) received the following:

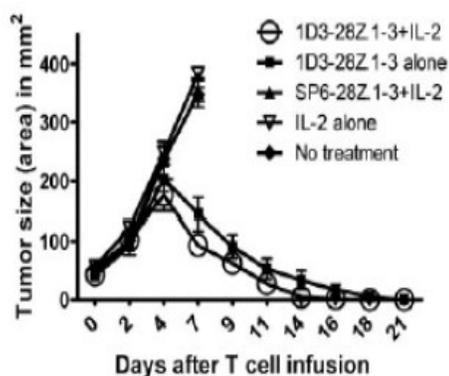
- Group 1 - 1D3-28Z1-3 transduced anti-murine CD19 CAR T cells + IL-2
- Group 2 - the same CAR T cells alone
- Group 3 - control (SP6-28Z1-3) CAR T cells + IL-2
- Group 4 - IL-2 alone
- Group 5 - no treatment

Tumor growth and survival were assessed over time.

Results: As shown in Figure 3, 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 4).

Figure 3: Effect of anti-murine CD19 CAR T cells on established lymphoma tumors in mice

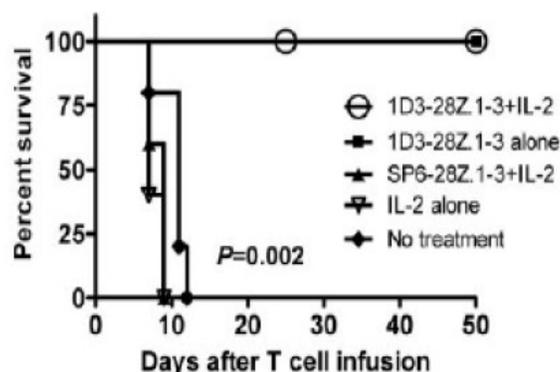
(Reproduced from Kochenderfer et al., 2010)



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 killed. 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 ITAMs of the CD3- ζ molecule were inactivated. 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: Figure 6 in [Kochenderfer et al, 2010a](#).

Figure 4: Effect of anti-murine CD19 CAR T cells on survival
(Reproduced from Kochenderfer et al., 2010)



The survival of the groups of mice described in the figure above is shown. The p-value refers to the comparison of the 1D3-28Z.1-3 + IL-2 group and the "No treatment" group. The 1D3-28Z.1-3 + IL-2 group and the 1D3-28Z.1-3 alone group both had 100% survival. 1D3-28Z.1-3 refers to the anti-murine CD19 CAR in which the first and third ITAMs of the CD3- ζ molecule were inactivated. 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.

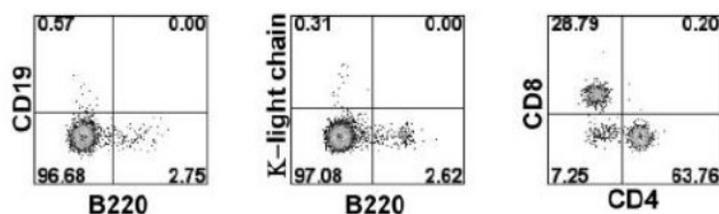
Source: Figure 6 in Kochenderfer et al, 2010a.

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.

Figure 5: Persistent B cell aplasia observed in mice administered 1D3-CD28Z1-3 transduced anti-murine CD19 CAR T cells
(Reproduced from Kochenderfer et al., 2010)



Mice were irradiated and then injected intraperitoneally with 38c13 lymphoma. The next day, the mice received 1D3-28Z.1-3-transduced T cells. The mice received IL-2 on the day of T-cell transfer and the next day. One hundred forty-three days later, the mice were killed and splenocytes were analyzed for B cells and T cells by flow cytometry. A representative example of 5 mice tested is shown. The CD19 versus B220 plot and the kappa light chain versus B220 plot are gated on live lymphocytes. The CD8 versus CD4 plot is gated on live CD3⁺ cells. The numbers on the plots are the percentages of cells in each quadrant.

Source: Figure 4 in Kochenderfer et al, 2010a.

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); 3) B cell aplasia was observed, but no overt toxicity was exhibited (Experiment E). The nonclinical findings are consistent with results obtained in clinical trials of KTE-C19.

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies were conducted.

PHARMACOKINETIC STUDIES (Biodistribution)**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 #4), 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**

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 #4), 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). This finding is consistent with the clinical trial data for KTE-C19.

Developmental and Reproductive Toxicology Studies (DART)

No DART studies were conducted.

Genotoxicity Studies

No genotoxicity studies were conducted.

Carcinogenicity/Tumorigenicity Studies:

Nonclinical: Assessment of potential oncogenicity of KTE-C19 due to transformation and clonal expansion was based on published *in vivo* studies in mice cited by the applicant. Hematopoietic stem cells or T cells were transduced with a retrovirus vector encoding an oncogene, followed by administration into non-tumor bearing immune deficient mice. Only mice transplanted with the transduced stem cells, displayed hematological malignancies.¹⁵ Other published studies reported that multiple events are likely required to induce leukemogenesis of retrovirus-transduced T cells.¹⁶ Furthermore, polyclonal T cells may suppress the outgrowth of oncogene-expressing clonal T cells.¹⁷ Taken together, these data suggest that T cells are relatively resistant to malignant transformation by γ -retroviral vectors.

Clinical: In the published literature on γ -retroviral-mediated gene transfer in HSC, a total of 19 malignancies were reported among 99 subjects with severe combined immune-deficiency (SCID), chronic granulomatous disease (CGD), or Wiskott-Aldrich syndrome (WAS).¹⁸ To further assess the oncogenic risk for KTE-C19, the applicant examined published assessments of genotoxicity and carcinogenicity outcomes in subjects administered γ -retroviral vector transduced T cells. The resulting data in subjects with hematologic malignancies are summarized in Table 4 below. These data further support a reduced risk of malignancy following administration of KTE-C19.

Table 4: Clinical experience following administration of γ -retroviral vector transduced T cells in subjects with hematologic malignancies
(Contents obtained from Table 1 in Module 4.2.3.3.2)

Publication	Findings	Notes
Kochenderfer, et al. ¹⁹ cells	<ul style="list-style-type: none"> • 8 subjects: 3 FL; 4 CLL; 1 SMZL – • Up to 2 years follow-up • No persistent expansion of CAR T cells • Long-term depletion of normal polyclonal 	<ul style="list-style-type: none"> • Administered retrovirus-transduced T cells, utilizing the same CAR as in KTE-C19

¹⁵ Newrzela S, et al. Resistance of mature T cells to oncogene transformation. *Blood*. 2008; 112(6):2278-86.

¹⁶ Newrzela S, et al. Retroviral insertional mutagenesis can contribute to immortalization of mature T lymphocytes. *Mol Med*. 2011; 17(11-12):1223-32.

¹⁷ Newrzela S, et al. T-cell receptor diversity prevents T-cell lymphoma development. *Leukemia*. 2012; 26(12):2499-507.

¹⁸ Mukherjee S, Thrasher AJ. Gene therapy for PIDs: progress, pitfalls and prospects. *Gene*. 2013;525(2):174-81.

¹⁹ Kochenderfer JN., et al. B-cell depletion and remission of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric antigen receptor transduced T cells. *Blood*. 2012; 119 (12):2709-20.

	<p>CD19+ B-lineage cells in most subjects; induction of IFN-γ and TNF-α in 4/8 subjects</p> <ul style="list-style-type: none"> No additional malignancies reported at 7-18 months 	
Brentjens R, et al. ²⁰	<ul style="list-style-type: none"> 5 subjects with relapsed B-lineage ALL No additional malignancies reported at a follow up period of 5 weeks to 34 months. 	
Kochenderfer J et al. ²¹	<ul style="list-style-type: none"> 15 subjects: 4 CLL1; 1 SMZL1; 4 PMBCL; 5 DLBCL; 1 low-grade NHL No additional malignancies reported at 6-23 months 	<ul style="list-style-type: none"> Administered the retroviral-based anti-CD19 CAR utilizing the same CAR as in KTE-C19
Robbins PF et al. ²²	<ul style="list-style-type: none"> 18 subjects with synovial cell sarcoma No additional malignancies reported at 3-58 months 	<ul style="list-style-type: none"> Genetically redirected T cells expressing NY-ESO-1 specific T cell receptor
Kochenderfer J, et al. ²³	<ul style="list-style-type: none"> 22 subjects: 19 with DLBCL, 1 with MCL, 2 with FL No additional malignancies reported up to 20 months 	

Comment:

- This reviewer appraised each publication cited in Table 3 and confirmed that the contents of Table 4 reflect the respective publication. Note that Kochenderfer et al., 2016, is Abstract #S792 that was presented at the 2016 European Hematology Association (EHA) Annual Congress, thus does not contain detailed information.

Other Safety/Toxicology Studies

KTE-C19 is administered intravenously, thus the applicant did not conduct local tolerance studies. The incidence, severity, and nature of local and systemic hypersensitivity reactions were examined in the clinical trials (refer to the clinical review memos for detail).

APPLICANT'S PROPOSED LABEL

- Subsections 8.1-8.3 of Section 8 ('Use in Specific Populations') should be revised to comply with 21 CFR 201.56(d)(1), 201.57(c)(9), and 201.57(c)(14).²⁴

²⁰ Brentjens RJ, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med.* 2013;5(177):177ra38.

²¹ Kochenderfer JN, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol.* 2015;33(6):540-9.

²² Robbins PF, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. *Clin Cancer Res.* 2015;21(5):1019-27.

²³ Kochenderfer JN, et al. Low-dose chemotherapy followed by anti-CD19 chimeric antigen receptor (CAR) T cells induces remissions in patients with advanced lymphoma. *European Hematology Association (EHA) Annual Congress.* 2016;Abstract #S792.

- Section 12 ('Mechanism of Action') should be supported by appropriate references.
- Section 13 ('Nonclinical Toxicology') should be revised to accurately reflect the available nonclinical data.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

Axicabtagene ciloleucel, YESCARTA™, KTE-C19, anti-CD19 CAR T cells, chimeric antigen receptor, CAR, B cell aplasia, B cell malignancy, retroviral vector, T cells

²⁴ *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* at:
<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm450636.pdf>