KYMRIAH® VS. YESCARTA®

	KYMRIAH® (tisagenlecleucel) Suspension for IV infusion	YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion
Company	Novartis	Kite/Gilead
Generic Name	CTL019 Tisagenlecleucel	KTE-C19 Axicabtagen ciloleucel
FDA Breakthrough Therapy Designation	Yes	Yes
Date of Initial FDA Approval	August 2017	October 2017
FDA Approved Indications	Acute lymphoblastic leukemia (ALL) Diffuse large B-cell lymphoma (DLBCL)	DLBCL Non-Hodgkins lymphoma
Approx. Cost Per Treatment	$475,000 USD for ALL $373,000 USD for DLBCL	$373,000 USD
Approx. Response Time	1 month	1 month
Side Effects	Cytokine release syndrome Neurotoxicity	Cytokine release syndrome Neurotoxicity
Disease Free Survival/Remission Rate	62% for ALL 64% for DLBCL	51%
Manufacturing Time	22 days	17 days
Gene Editing Vector	Lentivirus	Retrovirus
Promoter	EF1a	MSCV
ScFv (CD19)	FMC63	FMC63
Signaling Domain	4-1BB zeta	CD28 zeta
Hinge and TM	CD8 alpha	CD28
Cell Culture	Frozen CD8/28 beads	Fresh PBMC/CD3
CAR-T Persistence	Atleast 1 - 7 weeks	< 6 weeks
Treatment Type	Autologous	Autologous

SIDE EFFECTS

Cytokine release syndrome (CRS): occurs post CAR-T cell treatment due to rapid release cytokines from immune cells, manifests as flu-like symptoms but can be potentially life-threatening, may require corticosteroids, tocilizumab or siltuximab.

Tocilizumab: also known as Actemra, immunosuppressive drug; humanized monoclonal antibody against the IL-6 receptor.

Siltuximab: anti-IL-6 chimeric monoclonal antibody, direct IL-6 blocker.

Neurotoxicity: damage to the nervous system, associated with CRS, symptoms: confusion; delirium; aphasia; seizure; limb weakness or numbness; loss of memory, vision or intellect; headache; cognitive and behavioral problems.

B-cell aplasia: result of "on-target, off-tumor" toxicity; depletion B cells - including healthy cells that occurs when anti-CD19 CAR-T cells kill normal lymphocytes that express CD19; puts patient at high risk of infection, requires chronic treatment with gamma globulin replacement.

PROMOTERS

Promoters: DNA sequences located upstream of a gene that define where transcription by RNA polymerase begins.

EF1alpha: human elongation factor-1 alpha; a promoter of human origin, drives robust, constitutive, long-term gene expression in cell types where other promoters have diminished activity or have been silenced (e.g. stem cells).

MSCV: murine stem cell virus; a retroviral expression system that contains vectors that are optimized for introducing and expressing target genes in pluripotent cell lines.

VIRAL VECTORS

Retrovirus: retroviruses are a family of RNA viruses that produce reverse transcriptase, which copies the viral RNA into DNA to insert into the host cell's genome.

Lentiviruses: subtype of retroviruses that can infect both quiescent and mitotically active cell types, while other retroviruses are only capable of infecting actively dividing cell types.

CANCER TYPES

Acute lymphoblastic leukemia (ALL): quickly progressing cancer of the blood and bone marrow; leads to creation of immature white blood cells, most common type of cancer in children.

Diffuse large B-cell lymphoma (DLBCL): most common type of non-Hodgkin lymphoma in adults, affects B cells, usually occurs with age.

Non-Hodgkin's lymphoma: usually develops in the lymph nodes and lymphatic tissue though in some cases, can affect bone marrow and blood, can begin in C or T cells but ~90% of cases start in B cells.

Leukemia vs. Lymphoma: both are blood cell cancers but leukemias begin in the bone marrow while lymphomas tend to affect lymph nodes.

TREATMENT BASICS

PBMC: peripheral blood mononuclear cell; any peripheral blood cell with a round nucleus - lymphocytes (T cells, B cells, NK cells) and monocytes.

CAR-T Persistence: promotion of long-term anti-tumor effects, T cells persist in vivo to ensure long-term therapeutic effects of treatment and prevent tumor relapse.

Autologous vs. Allogeneic: autologous treatments use a person's own cells, while allogeneic treatments use cells from a donor whose human leukocyte antigens (HLA) are acceptable matches to the patient's.

COMPONENTS OF CARS

ScFv (CD19): Single-chain variable fragment; extracellular antigen recognition domain, a fusion protein of the variable regions of the heavy and light chains of immunoglobulins, connected by a short linker peptide; CD19 is expressed at normal to high levels in B cell malignancies.

FMC63: antibody that specifically binds to human CD19, which is a B-lymphocyte antigen used as a biomarker in CAR-T cell therapy.

Signaling Domain: transduces extracellular binding signal into CAR T cells to initiate activation of downstream signaling cascades.

4-1BB zeta: activation-induced costimulatory molecule, regulator of immune response; induced when T cells receive antigen-specific signals and subsequently triggers cytokine release.

CD28 zeta: T-cell co-stimulatory receptor; recognizes CD19 and enhances activation and signaling; inclusion of CD28 may increase proliferation of T cells and antitumor activity compared to inclusion of the CD3-zeta chain alone.

Hinge and TM: hinge domain and transmembrane spacer; hinge domain is a structure between the targeting moiety and the T cell plasma membrane, enhances CAR T cells migratory capacity, contributes to CAR T cell expansion, and can increase anti-tumor efficacy; the length and composition of the extracellular spacer domain is crucial in optimizing the design for CAR-T.

CD3/28: cluster of differentiation 3; cell co-receptor helps activate both the cytotoxic T cell and T helper cells.

Nucleus Biologics