









Tisagenlecleucel (Kymriah®) and Axicabtagene ciloleucel (Yescarta®) are currently the only two approved CAR-T therapies both in the United States (US) and in the European Union (EU) for the treatment of acute lymphoblastic leukaemia (ALL), diffuse large B-cell lymphoma (DLBCL), and primary mediastinal large B-cell lymphoma (PMBCL). They both target the B-lymphocyte antigen CD19.

Cytokine release syndrome (CRS) is the main toxicity associated with CAR-T therapy and results from the overproduction of inflammatory cytokines. These cytokines, such as TNF- $\alpha$  and IL-6, are produced when CAR-T cells proliferate *in vivo*, indirectly activating macrophages and other cells of the immune system. Depending on the level of cytokine production, the clinical manifestations of CRS range from flu-like symptoms to life-threatening shock. To mitigate this risk, cytokine signaling inhibitors such as Actemra® (tocilizumab), an IL-6 receptor antagonist, have been repurposed to treat CRS when it occurs as a result of CAR-T therapy. "On-target/off-tumor" toxicity is the other main side effect, which occurs when the CAR-T cells attack non-tumor cells that express the intended target antigen. As a consequence, the patient is unable to make antibodies and becomes more susceptible to infection by microorganisms. Novel CAR constructs, such as the fourth generation which is engineered with an inducible expression unit, can effectively overcome the "on-target, off-tumor" drawbacks.

**Creative Biolabs**  
**CAR/TCR-related**  
**Products &**  
**Services**

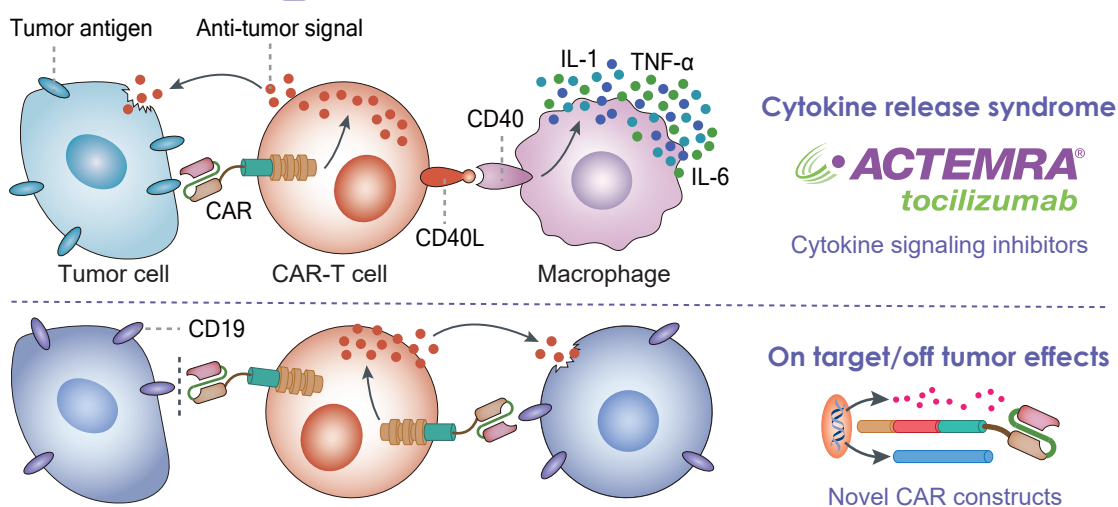
### 1 Approved CAR-T therapies

Developer	US approval	EU approval	US approval	Developer
	 August 2017	 August 2018	 October 2017	
<b>Indications</b>	 ALL DLBCL		<b>Target</b>  CD19	
			 YESCARTA® (axicabtagene ciloleucel)	
			<b>Indications</b> DLBCL PMBCL	

### 2 Representative CAR-T therapies in development

Product	Developer	Target(s)	Indication(s)
JCAR017	Juno Therapeutics/Celgene	CD19	B cell NHL (DLBCL)
UCART19	Cellectis/Pfizer	CD19	B cell ALL
bb2121	Bluebird bio	BCMA	Multiple myeloma
LCAR-B38M	Nanjing Legend Biotech	BCMA	Multiple myeloma
KITE-585	Kite Pharma/Gilead Sciences	BCMA	Multiple myeloma
AUTO2	Autolus	BCMA and TACI	Multiple myeloma
MB-102	Mustang Bio	CD123	AML and BPDCN
UCART123	Cellectis	CD123	AML and BPDCN
CD33-targeted CAR	Ziopharm Oncology (Intrexon)	CD33	AML
BPX601	Bellicum Pharmaceuticals	PSCA	Pancreatic cancer
JCAR020	Juno Therapeutics	MUC16	Ovarian cancer
CAR-EGFR/EGFRvIII T	CARsgen Therapeutics	EGFRvIII	Glioblastoma
MB-101	Mustang Bio	IL-13R $\alpha$ 2	Glioblastoma
JCAR023	Juno Therapeutics	L1CAM	Neuroblastoma
CAR CLD18 T cells	CARsgen Therapeutics	Claudin-18.1	Gastric/pancreatic adenocarcinoma
AU105	Aurora Biopharma	HER2 and CMV	Glioblastoma

### 3 Challenges and countermeasures



## WHAT WE DO:

**One-Stop CAR-T Therapy Development Services**  
**TCR Modified T Cell Development Services**  
**TCR-Like Antibody Services**  
**Dendritic Cell Vaccine Development Services**  
**Bispecific TCR Development Service**

**Products:**  
**Diseases Associated Antigen**  
**CAR Vector System**  
**Viral Particle**  
**CAR/TCR Development Kits**