Adoptive immunotherapy with CAR modified T cells in cancer: current landscape and future perspectives

Table of content

1. Abstract

2. Introduction

domain, an intracellular CD3ζ chain as the

to phosphorylation of CD3ζ and additional signaling cascades

3. Anti-CD19 CAR T cells

3.1. Currently approved anti-CD19 CAR T cells

3.1.1. Tisagenlecleucel (CTL019, Kymriah®)

a CD3ζ

in vivo

Children's Hospital of Philadelphia and

's

% of patients developed grade ≥3

investigator’s discretion

grade ≥3 encephalopathy.

3.1.2. Axicabtagene Ciloleucel (KTE-C19, Yescarta®)

CD3ζ.

+ fludarabine 30 mg/m

120 or 60 mg/kg + fludarabine 25 mg/m

s −5, −4, and −3 before the CAR T cell

with a ≥ 1

five% of patients developed grade ≥3 adverse events, including grade ≥3 neutropenia in 78%, grade ≥3 anemia in 43%, and grade ≥3 thrombocytopenia in 38%. C

grade (grade 1 37%, grade 2 44%, grade ≥3 13%, including one death related to

patients, 28% being grade ≥3. Tocilizumab was given to 43% of patients and glucocorticoids to 27%.

xperienced a grade 5 event of CRS. Grade ≥3 CRS

3.2. Other anti-CD19 CAR T cell products under development

3.2.1. Lisocabtagene Maraleucel (JCAR017)

a CD3ζ activation domain, and a 4

detected in 13% of patients, and 28% had grade ≥3

3.2.2. UCART19

CD3ζ mol

“safety switch” (allowing tar

4. Alternative targets for CAR T cells

4.1. Novel T-cell targets for B-cell malignancies

1BB/CD3ζ CAR and transient responses were obs

–

4.2. T-cell targets for multiple myeloma

and the CD3ζ T

β

4.3. T-cell targets for non-B-cell lymphoproliferative disorders

β chain

ex vivo

positive T cells transfected with a CD28/OX40/CD3ζ anti

in vitro

30 cell infusion was well tolerated, with grade ≥3 toxicities occurring only in

4.4. CAR T cells for myeloid diseases

s a “bridge to transplant”.

.

in vitro *in vivo*

in vivo

4.5. CAR T cells for solid tumors

in vivo

α –

5. CAR-T cells related toxicities

5.1. Cytokine release syndrome

in vivo

5.2. Neurotoxicity

CD19

to predict a higher risk of developing grade ≥4 neurotoxicity

grade ≥2 CRS but the physio

6. Alternative sources and *off-the-shelf* carriers for CARs

off-the-shelf

6.1. Post-allogeneic stem cell transplant CAR T cells

ex vivo–

each patient's allo

6.2. *Off-the-shelf* allogeneic CAR T cells

α and β

α β

off-the-shelf

killing by the patient's own T cells that recognize non

from rejection included the knockout of the β2 microglobulin gene combined with TCR knockout. In the absence of β2 microglobulin (β chain), class

due to "missing self" recognition. To prevent activation of recipient's NK cells through this mechanism, different way

6.3. Alternative *off-the-shelf* CAR carriers

off-the-shelf

off-the-shelf

delta T cells (γδ

Immunotherapy with γδ

cells. Aminobisphosphonates are the most efficient reagents to grow γδ

ex vivo

setting γδ

. For this reason, γδ

alloreactivity the combination of γδ

clinical trial with CAR γδ

αβTC

in vitro

off-the-shelf

7. Conclusion and Perspectives

8. Acknowledgement

9. References

Science

Nature

Sci Transl Med

Contemp Oncol (Pozn)

Proc Natl Acad Sci U S A

Biochem Biophys Res Commun

Blood

N Engl J Med

N Engl J Med

Nat Med

Leukemia

Nat Biotechnol

Sci Transl Med

N Engl J Med

N Engl J Med

N Engl J Med

Blood

Sci Transl Med

JCI Insight

J Clin Oncol

Mol Ther

Mol Ther

N Engl J Med

Blood

Leukemia

Sci Transl Med

J Clin Invest

Blood

Sci Transl Med

Blood

Cytometry B Clin Cytom

Nat Med

Blood

Blood

Nat Med

J Clin Invest

Clin Cancer Res

Int J Cancer

Blood

Cancer Res

Blood

Oncoimmunology

Leukemia

Cancer Immunol Res

Haematologica

Clin Lymphoma Myeloma Leuk

Haematologica

Blood

J Clin Oncol

Blood

Blood

Hum Gene Ther

Journal of Clinical Oncology

Blood

Gene Ther

Blood

Blood

Nat Med

Leukemia

Blood

Nat Med

N Engl J Med

Semin Hematol

Clin Cancer Res

J Clin Invest

Lancet

Ther Adv Hematol

Seminars in Hematology

Leuk Lymphoma

Blood

Blood

PLoS One

Blood Cancer J

Cell

Cancer Cell

Blood

Leuk Lymphoma

Leukemia

Leukemia

Blood

Leukemia

Mol Ther

Hum Gene Ther

Mol Ther

Blood

Blood

Blood

Clin Cancer Res

Cytotherapy

Haematologica

EHA

Blood

Blood

Clin Transl Immunology

Int J Mol Sci

Leukemia

Mol Ther

Front Immunol

Mol Ther

Mol Ther

Cancer Immunol Immunother

J Hematol Oncol

Hum Gene Ther

Cell Death Dis

Gastroenterology

Cancer Gene Ther

Clin Cancer Res

Clin Cancer Res

Clin Cancer Res

J Clin Immunol

J Clin Invest

Neuro Oncol

J Hematol Oncol

Cancer Immunol Res

Sci Transl Med

Gene Ther

Oncoimmunology

Clin Cancer Res

Cell Rep

Nat Biotechnol

Mol Ther

Nat Med

Biochem Soc Trans

Front Immunol

Clin Cancer Res

J Clin Invest

Mol Ther

Int J Mol Sci

Clin Cancer Res

Nat Biotechnol

Cancer Res

Hum Gene Ther

J Hematol Oncol

J Clin Oncol

Journal of Clinical Oncology

Blood

Mol Ther

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Journal of Clinical Oncology

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JAMA Oncol

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Clin Cancer Res

Nat Med

Clin Cancer Res

N Engl J Med

Nat Med

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Journal of Clinical Oncology

Cancer Discov

Cancer Discov

OncLive

Nat Rev Clin Oncol

Blood

Biol Blood Marrow Transplant

Expert Opin Biol Ther

Blood

Oncoimmunology

J Clin Oncol

J Clin Invest

Lancet

Blood

Blood

Lancet

Nat Med

Blood

Blood

Blood

Tissue Antigens

Nat Biotechnol

Nat Biotechnol

Sci Transl Med

Mol Ther

Science

Blood

Protein Cell

Curr Hematol Malig Rep

Nature

Blood

Oncotarget

Nat Biotechnol

J Clin Invest

Cell Stem Cell

Nat Immunol

Front Immunol

Front Immunol

Semin Immunopathol

Cancer J

J Cell Mol Med

Cancer Res

Oncoimmunology

Pathol Res Pract

Blood Rev

Bone Marrow Transplant

Mol Ther

Mol Ther

J Immunol

Blood

Oncoimmunology

10. Key words

11. Send correspondence to:

Figure legend

Figure 1. Schematic structure of chimeric antigen receptor (CAR).

Running title

Figure 1.

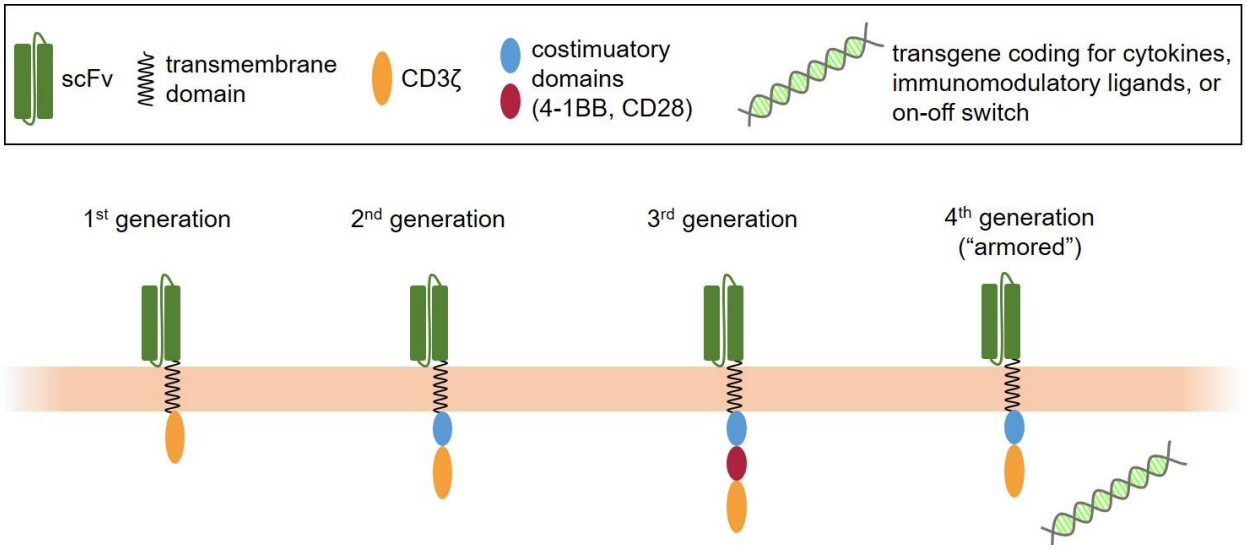
scFv
transmembrane domain
CD3ζ
costimuatory domains (4-1BB, CD28)
transgene coding for cytokines, immunomodulatory ligands, or on-off switch
1st generation
2nd generation
3rd generation
4th generation ("armored")

Table 1.

	Tisagenlecleucel	**Axicabtagene Ciloleucel**	**Lisocabtagene Maraleucel**	**UCART19**
	CD3ζ	CD3ζ	CD3ζ	CD3ζ “safety switch”
	(≤ ≥2	≥2		

Table 2.

Target	Construct details	Patient population	Results	Location	NCT identifier	Reference
	1BB/CD3ζ					
	1BB/CD3ζ					
	1BB/CD3ζ					
	CD28/CD3ζ			Texas Children's Hospital,		
	ζ					
	1BB/CD3ζ, lentiviral					
	1BB/CD3ζ					
	1BB/CD3ζ					
	CD28/CD3ζ					
	ζ					

	CD3ζ					
	CD3ζ					
	CD3ζ plus DAP10 signal					
	CD3ζ plus DAP10 signal					
	CD3ζ (intra					
	CD3ζ					
	CD3ζ					
	CD3ζ					
	ζ					
	ζ					
	CD3ζ					
	CD3ζ,					
	CD3ζ					

	CD3ζ					
	CD3ζ					
13Rα2	CD3ζ (intra					