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GmbH

CAR T-Cell Therapy

Horizon Scanning

EBEU Report No. 11/2020
AIHTA Policy Brief No. 006a

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List of Abbreviations

AIHTA	Austrian Institute for Health Technology Assessment GmbH
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ASH	American Society of Haematology
ATMP	Advanced Therapy Medicinal Products
BCMA	B-Cell Maturation Antigen
BLA	Biologics License Application
BPDCN	Blastic Plasmacytoid Dendritic Cell Neoplasm
CAR	Chimeric Antigen Receptor
CEA	Carcinoembryonic Antigen
CLL	Chronic Lymphocytic Leukaemia
CMC	Chemistry, Manufacturing and Control
CPIs	Checkpoint Inhibitors
CRS	Cytokine Release Syndrome
DLBCL	Diffuse-Large B-Cell Lymphoma
EGFRvIII	Epidermal Growth Factor Receptor Variant III
EMA	European Medicines Agency
EAAS	Early Awareness and Alert System
EU	European Union
EWS	Early Warning System
4SCART	4th Generation Chimeric Antigen Receptor gene-modified T-cells
FDA	Food and Drug Administration
FL	Follicular Lymphoma
GMP	Good Manufacturing Practice
GTMP	Gene Therapy Medicinal Products

GvHD	Graft-versus-Host Disease
HL	Hodgkin's Lymphoma
HSS	Horizon Scanning System
ICC	Intrahepatic Cholangiocarcinoma
IND	Investigational New Drug
iNHL	indolent Non-Hodgkin Lymphoma
ITCRP	International Clinical Trials Registry Platform
MAA	Market Authorization Application
MCL	Mantle Cell Lymphoma
MDS	Myelodysplastic Syndrome
MHC	Major Histocompatibility Complex
MM	Multiple Myeloma
NHL	Non-Hodgkin Lymphoma
NMPA	National Medical Products Administration
PDUFA	Prescription Drug User Fee Act
PMBCL	Primary Mediastinal B-cell Lymphoma
PSCA	Prostate Stem Cell Antigen
PRIME	Priority Medicines Designation
PSMA	Prostate-specific Membrane Antigen
PTCL	Peripheral T-cell Lymphoma
RCT	Randomized Controlled Trial
RMAT	Regenerative Medicine Advanced Therapy
R/R	Relapsed/Refractory
TALEN	Transcription Activator-like Effector Nuclease
TLBL	T-cell Lymphoblastic Lymphoma
US	United States
ZFN	Zinc Finger Nuclease

Deutsche Zusammenfassung

Hintergrund

Die Immuntherapie hat die Krebsbehandlung bedeutend verändert und stellt aktuell eines der intensivsten Forschungsgebiete in der Onkologie dar. Zu den beiden wichtigsten Ansätzen hinter dieser Entwicklung gehören die sogenannten Immun-Checkpoint-Inhibitoren, die auf Checkpoint-Proteine wie PD-L1 und PD-1 abzielen, und die Chimäre Antigenrezeptor (CAR) T-Zell-Therapie. Die CAR T-Zell-Therapie basiert auf gentechnisch veränderten T-zellen mit synthetischen antigenspezifischen Rezeptoren und ist eine neue Art von personalisierter, zellulärer Immuntherapie.

Derzeit sind drei CD19-spezifische CAR T-Zell-Produkte bereits durch die amerikanische FDA zugelassen, Tisagenlecleucel (Kymriah®), Axicabtagen Ciloleucel (Yescarta®) und seit Juli 2020 auch Brexucabtagene Autoleucel (Tecartus®). Eine Zulassung durch die EMA gibt es aktuelle nur für Tisagenlecleucel und Axicabtagen Ciloleucel. Beide Produkte sind für das relapsiert/refraktäre diffuse großzellige B-Zell-Lymphom (DLBCL) zugelassen, Tisagenlecleucel zusätzlich noch für die r/r B-ALL (bis zum 25. Lebensjahr) und Axicabtagen Ciloleucel zusätzlich noch für das primär mediastinale B-Zell-Lymphom (PMBCL) und das transformierte follikuläre Lymphom. Brexucabtagene Autoleucel hat die FDA Zulassung zur Behandlung des relapsiert/refraktären Mantelzelllymphoms (MCL) erhalten.

CAR-T-Zellen fallen unter den Begriff „advanced therapeutic medicinal product“(ATMP) und sind per Definition ein Arzneimittel, welches unter GMP (good manufacturing practice) Bedingungen hergestellt werden muss. Der komplexe Herstellungsprozess umfasst die Aufreinigung der T-Zellen, die Transduktion dieser Zellen mit einem die CAR-Kassette enthaltenden lentiviralen Vektor oder retroviralen Vektor und die anschließende Expansion der transduzierten Zellen in Kultur. Der Weg bis zur fertigen Arzneispezialität ist derzeit noch sehr kompliziert und setzt eine gute und enge Zusammenarbeit zwischen Behandlungszentrum, Apheresezentrum und pharmazeutischem Hersteller voraus.

Trotz vielversprechende Ergebnisse v.a. bei einigen hämatologischen Krebserkrankungen, beschäftigen sich zahlreiche Forschungsvorhaben mit der Verbesserung der Wirksamkeit, Erhöhung der Sicherheit und Indikationsausdehnung auf andere onkologische Erkrankungen z.B. solide Tumore. Zudem soll der Herstellungsprozess verbessert/verkürzt und die Verfügbarkeit der CAR T-Zell-Therapie mittels allogener CAR T-Zellprodukte erhöht werden.

Die intensive Forschung auf dem Gebiet der CAR-T-Zelltherapie bringt neue Technologien hervor, die vor besonderen regulatorischen, ethischen und finanziellen Herausforderungen stehen. Daher besteht ein großes Interesse an Horizon Scanning Systemen (HSS), um neue und in Entwicklung befindliche CAR-T-Zelltherapien mit relevanten Auswirkungen auf das Gesundheitssystem zu identifizieren.

Methode

Folgende zwei primäre Fragestellungen wurden bearbeitet:

1. Welche CAR T-Zell-Therapien werden derzeit entwickelt und für welche onkologischen Indikationen?
2. Wie ist der Entwicklungsstand dieser Technologien und bis wann kann mit einer Zulassung gerechnet werden?

Es wurde eine systematische Suche in folgenden Studienregistern im Juni 2020 durchgeführt:

- ClinicalTrials.gov https://clinicaltrials.gov/
- WHO International Clinical Trials Registry Platform (ICTRP) http://apps.who.int/trialsearch/
- EU Clinical Trials Register https://www.clinicaltrialsregister.eu/ctr-search/search

Die Suche wurde auf klinische Studien der Phase 2, 3 und 4 eingeschränkt. Zu den identifizierten laufenden klinischen Studien wurden Daten aus diesen Studienregistern extrahiert, insbesondere zum Status der Studien, zur beabsichtigten onkologischen Indikation und zur betroffenen CAR T-Zell-Technologie. Um jene CAR T-Zell-Therapien, welche am weitesten in der Entwicklung oder kurz vor der Beantragung einer Zulassung sind, zu identifizieren, wurden die Daten aus Studienregistern, weiters durch Informationen von Herstellerwebsites, von öffentlich zugänglich medizinischen Publikationen und durch gezielte Internetsuche ergänzt.

Ergebnisse

Die Suchen in den Studienregistern ergab 521 laufende Studien zu CAR T-Zellprodukten. Nach Entfernung von Duplikaten und Studien zu nicht-onkologischen Indikationen konnten schließlich 289 Studien weiter ausgewertet werden. Die Analyse dieser Studien ergab 66 CAR T-Zell-Technologien, wovon nach weiterer Literatursuche 13 CAR T-Zell-Therapien in einem fortgeschrittenen Entwicklungsstatus identifiziert wurden. Für drei dieser Technologien ist mit einer Zulassung in den nächsten Monaten durch die FDA und EMA zu rechnen:

- **Brexucabtagene Autoleucel (KTE-X19)** zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem Mantelzelllymphom (von Kite, einem Unternehmen von Gilead): Die FDA erteilte am 24. Juli 2020 bereits eine beschleunigte Zulassung; das Medikament wird derzeit in der Europäischen Union geprüft und hat von der EMA den PRIME-Status erhalten;
- **Idecabtagene vicleucel (ide-cel; bb2121)** für Patienten mit vorbehandeltem rezidiviertem oder refraktärem multiplem Myelom (von Bristol-Myers Squibb): Im März 2020 wurde bei der FDA ein BLA-Antrag eingereicht, allerdings müssen dazu von BMS noch Informationen zur Herstellung und Kontrolle nachgeliefert werden. Das Unternehmen plant, den Antrag bis Ende Juli 2020 erneut einzureichen; Ide-cel wurde im März 2020 von der EMA der "Accelerated Assessment" Status vergeben;
- **Lisocabtagene maraleucel (liso-cel; JCAR017)** für erwachsene Patienten mit rezidiviertem oder refraktärem großzelligem B-Zell-Lymphom nach mindestens zwei vorherigen Therapien (von Bristol-Myers Squibb): Von der FDA wurde das Aktionsdatum des Prescription Drug User Fee Act mit 16. November 2020 festgelegt; im Juli 2020 startete die EMA den Überprüfungsprozess für Liso-cel zur Behandlung von Erwachsenen mit rezidiviertem oder

refraktärem diffusem großzelligem B-Zell-Lymphom, primärem mediastinalem B-Zell-Lymphom und follikulärem Lymphom Grad 3B nach mindestens zwei vorherigen Therapien.

Weiters konnten Studien zu den bereits zugelassenen CAR T-Zell-Therapien Tisagenlecleucel, Axicabtagen-ciloleucel und Brexucabtagene Autoleucel in neuen Indikationen wie follikuläres Lymphom oder CLL identifiziert werden.

Zusätzliche relevanten Entwicklungen im Bereich der CAR T-Zell-Therapie umfassen die allogene CAR T-Zell-Therapie und die dezentrale Herstellung von CAR T-Zellen im Krankenhaus unter Anwendung eines halbautomatischen Herstellungsprozesses mittels z.B. CliniMACS Prodigy von Miltenyi Biotec™. Zahlreiche Studien dazu sind bereits im Laufen.

Schlussfolgerungen & Empfehlungen

Die Anzahl an klinischen Studien mit CAR-T-Zell-Technologien zur Krebsbehandlung hat in den letzten Jahren stark zugenommen, die Ergebnisse dieser Studien bleiben jedenfalls abzuwarten und sollten zu einer verbesserten Evidenzbasis beitragen. In den derzeit laufenden Studien werden eine Vielzahl an Ansätzen verfolgt (u.a. neue Zielstrukturen ("Targets"), Kombination mit anderen Immuntherapien und die Anwendung bei anderen Krebserkrankungen z.B. solide Tumore), diese können aber noch einem frühen Entwicklungsstadium zugeordnet werden. Der Großteil der identifizierten CAR-T-Zelltherapie befindet sich noch im experimentellem Stadium und nur wenige Kandidaten befinden sich zum Zeitpunkt der Berichterstellung in einem fortgeschrittenen Entwicklungsprozess oder kurz vor der Zulassung. Es wird geschätzt, dass drei bis fünf Pipeline-CAR-T-Zell-Technologien voraussichtlich innerhalb der nächsten 2 bis 5 Jahre die Zulassung zur Behandlung von Krebspatienten erhalten werden. Neben ALL und B-Zell Lymphomen werden auch neue Indikationen für eine CAR T-Zell-Therapie dazu kommen, darunter v.a. das Multiples Myelom. Eine genaue Prognose ist schwierig, da viele dieser Studien noch nicht abgeschlossen sind und daher keine Ergebnisse vorliegen, die eine Einschätzung des Nutzen-Risiko-Profils bereits jetzt ermöglichen würden. Weiters ist eine Ausdehnung der bereits zugelassenen CD-19-gerichteten CAR-T-Zelltherapien (Kymriah, Yescarta, Tecartus) auf weitere Indikationen wie follikuläres Lymphom oder CLL sowie in früheren Therapielinien zu erwarten. Ebenfalls noch als experimentell einzustufen aber zukünftig (abhängig von den Ergebnissen der klinischen Studien) relevant, sind jene Aktivitäten, die unternommen werden, um Einschränkungen wie Verfügbarkeit und hohe Kosten durch die Entwicklung allogener (universeller) CAR-T-Zellen oder dezentraler (stationärer) Herstellungsprozesse zu überwinden.

Basierend auf diesen Erkenntnissen aus der Analyse laufender klinischer Studien, können folgende Empfehlungen abgeleitet werden:

- Trotz vielversprechender Ergebnisse müssen der langfristigen Nutzen und das Risiko der CAR-T-Zelltherapie zur Behandlung von Krebserkrankungen aufgrund der z. T. kurzen medianen Nachbeobachtungszeit der Studien noch belegt werden. Die Durchführung von klinischen Studien sollte hier jedenfalls unterstützt werden.
- CAR T-Zell-Technologien werden als ATMP eingestuft und ihre Herstellung und Anwendung werfen auch ethische, rechtliche und wirtschaftliche Fragen auf. Diese neuen

Herausforderungen sollten durch einen offenen Dialog zwischen allen relevanten Interessensgruppen angegangen werden.

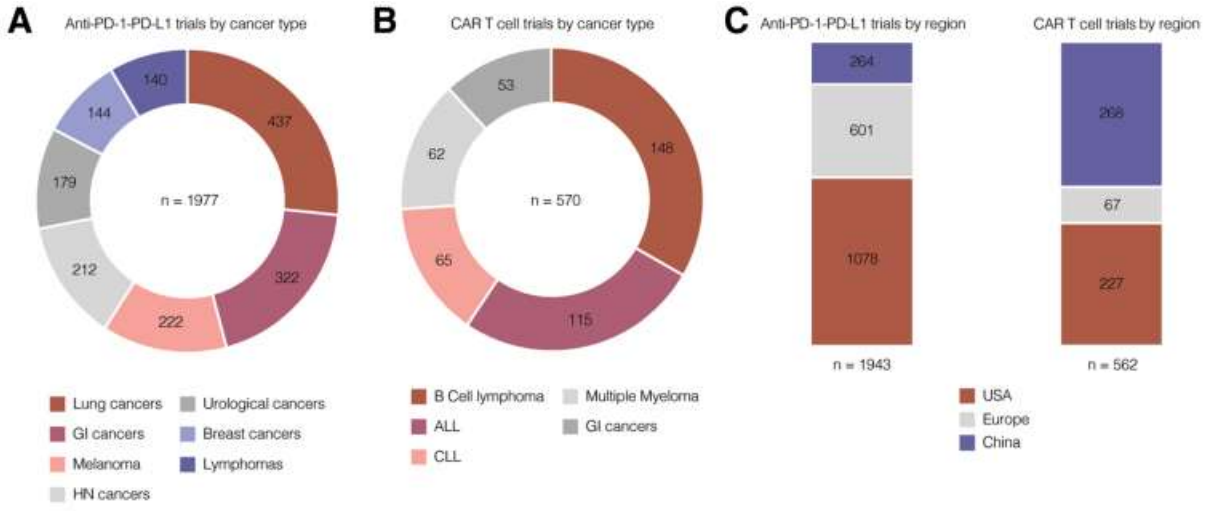
- Spezialisierte und qualifizierte CAR T-Zell-Zentren sind von entscheidender Bedeutung, um die Zugänglichkeit und Qualität der Versorgung sicherzustellen und die nationalen Forschungsaktivitäten auf diesem Gebiet zu konzentrieren. In Bezug auf Österreich sollte diesbezüglich ein enger und kontinuierlicher Austausch zwischen (politischen) Entscheidungsträgern und der österreichischen CAR T-Zell Plattform (https://innere-med-1.meduniwien.ac.at/haematology/car-t-cell-network/) stattfinden.
- Die schnelle Zulassung von CAR-T-Zelltherapien durch FDA und EMA macht es erforderlich, die klinische Wirksamkeit und Sicherheit dieser Technologien kontinuierlich zu überwachen und Rahmenbedingungen für ihre Bewertung zu entwickeln, um Entscheidungsträger zu unterstützen (vgl. CADTH "Life-Cycle Approach to Health Technology Assessment").
- Aufgrund der zunehmenden Forschungsaktivitäten auf dem Gebiet der Krebsimmuntherapie ist es erforderlich, die Entwicklung der CAR-T-Zelltherapie im Laufe der Zeit durch Horizon Scanning-Aktivitäten zu verfolgen. Da HSS als einmalige Aktivität zeitaufwändig und ineffizient ist, wird empfohlen, sich internationalen Initiativen mit ihren systematischen und dauerhaften Aktivitäten anzuschließen, z.B. die BeNeLuxA-Initiative zum Horizon Scanning: https://beneluxa.org/horizonscanning.

1 Introduction

Cancer Immunotherapy & CAR T-cells

Immunotherapy of cancer has already improved the prognosis of many patients with a broad variety of haematological and solid malignancies, but it is still a rapidly evolving field. The two main approaches behind this development are checkpoint inhibitors (CPIs), targeting checkpoint proteins like PD-L1 and PD-1, and chimeric antigen receptor (CAR) T-cells. A lot of studies are currently registered on clinicaltrials.gov for these two approaches (see Figure 1), and clinical trials especially of CAR T-cell therapy are growing fast in recent years. Most of these CAR T-cell trials are initiated by sponsors from the United States and China. A recent comparative analysis of 289 clinical trials from the two countries found that overall subject sample size and study centre numbers are still larger in China, while the design of the clinical trials is more cautious in the United States. In addition, they found differences between the two countries in CAR-targeted antigens in solid tumours and genetic modifications besides CARs for enhancing the potency of CAR T-cells [1].

Figure 1: Cancer Immunotherapy: Checkpoint inhibitors (anti-PD-1 / anti-PD-L1) and CAR T-cell trials in 2019 (ClinicalTrials.gov)



Checkpoint inhibitors (anti-PD-1 / anti-PD-L1) and CAR T-cell trials in 2019: (a, b) included tumour types, (c) regional distribution; Source: [2]

CAR T-cells are genetically modified T cells, where a patient's own (autologous) T cells are manipulated ex vivo to express an antibody derived antigen-recognizing domain (scFv-domain) that is fused to the intracellular domain of a CD3 TCR (CD3-zeta). As a result, recognition of a specific cell surface antigen activates T cell response independently of MHC recognition [3]. Chimeric antigen receptors consist of an extracellular antigen-recognition domain, which is usually an antibody single-chain variable fragment (scFv), but can also be a peptide or another protein, linked to intracellular signalling domains (e.g. usually two or three co-stimulatory domains like 4-1BB + CD3 zeta or CD28 + CD3zeta (2nd generation CARs) or CD28+4-1BB or OX40 + CD3zeta (3rd generation CARs). The extracellular portion of the CAR permits the recognition of a specific antigen by a transduced T cell and, subsequently, the

signalling domains stimulate T-cell proliferation, cytolysis and cytokine secretion to eliminate the target cell. The patients' own T cells (or those from an allogeneic donor) are isolated, activated and genetically modified to generate CAR T-cells, which are then given back to the patient [4].

Two cellular cancer immunotherapies, i.e. CAR T-cell therapies, have already received approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2017 and 2018, respectively. **Tisagenlecleucel (Kymriah®)** and **axicabtagen-ciloleucel (Yescarta®)** are approved to treat patients with acute lymphoblastic leukaemia (ALL, tisagenlecleucel) and diffuse-large B cell lymphoma (DLBCL, tisagenlecleucel and axicabtagen-ciloleucel) [5, 6]. Recently in **July 2020**, the FDA approved the third CAR T-cell therapy **brexucabtagene autoleucel (Tecartus®),** formerly known as KTE-X19, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) [7].

CAR T-cells have been studied most extensively in hematologic malignancies in clinical trials targeting CD19, the pan-B cell marker [3]. Novel CAR targets are required to improve response rates and to reduce the selection pressure caused by a one-directed therapy approach. The primary aim is to prevent the generation of resistance phenomena and to increase the valid number of responding patients like supposed to happen in dual-targeting concepts. In addition, the search for new targets should widen the indication of CAR T-cell therapy. Examples of the most-promising CAR T-cell targets for the treatment of haematological malignancies include [4]:

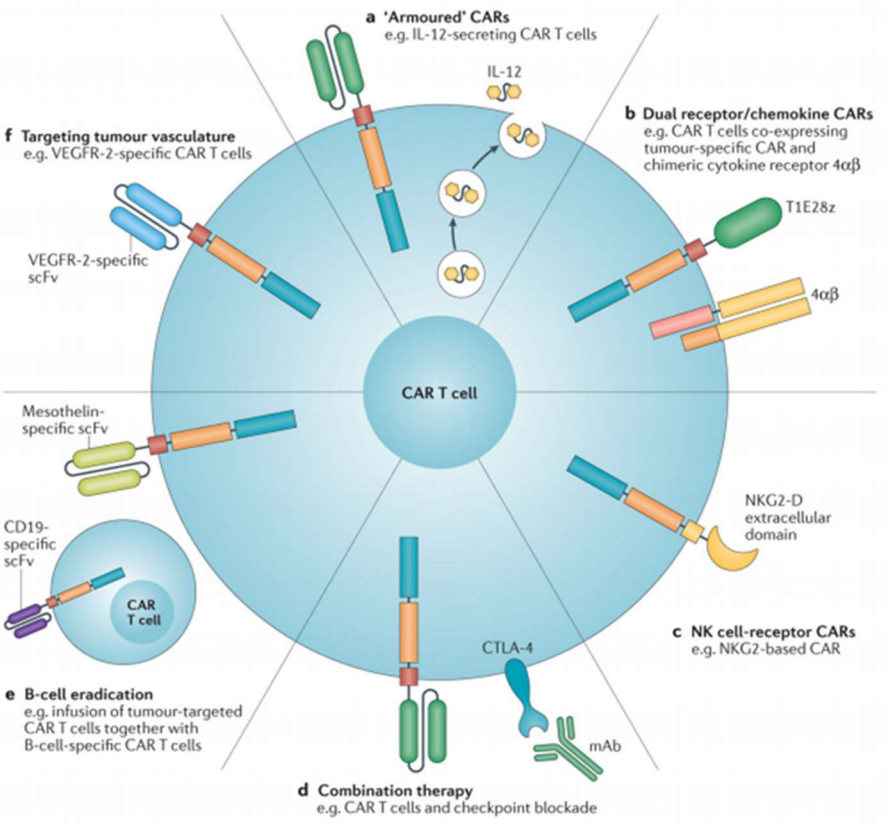
- CD22, and CD20,
- inactive tyrosine-protein kinase transmembrane receptor ROR1 (ROR1),
- immunoglobulin kappa chain (Igκ),
- B-cell maturation antigen (BCMA),
- CD30, CD138, CD33, and CD123,
- Lewis Y antigen (LeY)

Several researchers are investigating the use of CAR T-cell therapy for the treatment of solid tumours. Examples of CAR targets for the treatment of solid malignancies [4] include:

- PSMA (prostate-specific membrane antigen)
- Mesothelin
- EGFRvIII (epidermal growth factor receptor variant III)
- CEA (carcinoembryonic antigen)
- CD171
- GD2
- Glypican-3
- HER2
- IL-13

In addition, several strategies are under development to improve CAR-T-cell-mediated antitumor responses (e.g. 'armoured' CAR T-cells, dual receptor/cytokine-based CARs, CARs based on natural-killer-cell receptors and other cell receptors, Figure 2) and several strategies to improve the safety of CAR T-cell therapy (e.g. management of cytokine-release syndrome, as well as engineered CAR T-cells that are easier to eradicate in case of adverse events) [4, 8, 9].

Figure 2: Approaches to improve CAR T-cell therapy



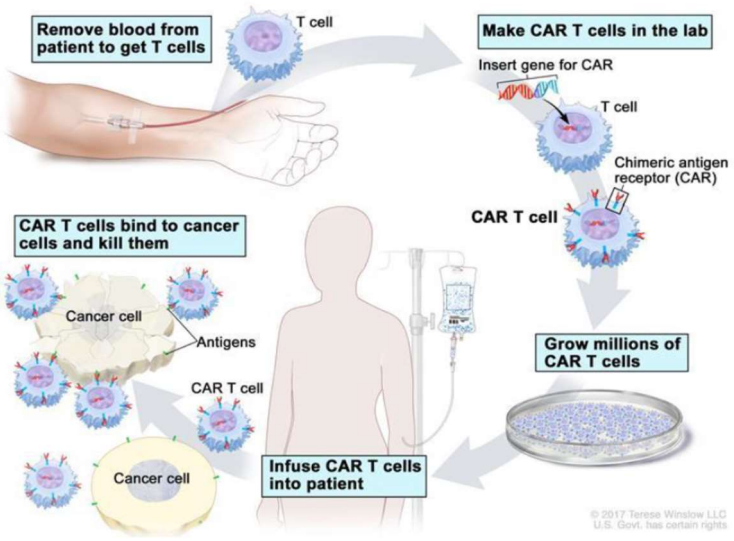
Overview of the improvements to CAR T-cell therapy and clinical trials testing those strategies: a | Engineered CAR T-cells that secrete pro-inflammatory cytokines (armoured CAR T-cells; NCT02498912). b | Dual receptor expression to target tumour cells and convert tumour derived cytokines into T-cell activators (NCT01818323). c | Using natural killer (NK)-cell-based recognition domains, such as NKG2-D, in CARs (NCT02203825). d | Combination therapy with monoclonal antibodies (mAb) targeting immune-checkpoint inhibitory receptors to relieve immunosuppression (NCT00586391). e | Infusion of two populations of CAR T-cells to eradicate B cells and enable increased persistence of tumour specific CAR T-cells by preventing antibody responses against their foreign antigen components (NCT02465983). f | Targeting the tumour vasculature with CAR T-cells, such as VEGFR-2-specific CAR T-cells NCT01218867160. 4αβ, 4αβ chimeric cytokine receptor; CTLA-4, cytotoxic T-lymphocyte-associate antigen-4; T1E28z, T1E28z chimeric antigen receptor; VEGFR-2, vascular endothelial growth factor receptor 2. Source: [3]

CAR T-cell production for clinical application

In general, T cells from each individual patient are ex vivo genetically engineered with the CAR, amplified to clinically relevant numbers and re-infused to the patient after nonmyeloablative pre-conditioning (see Figure 3)[10]. In particular, the procedure includes collecting the cells by leukapheresis, genetic transduction by retro- or lentivirus infection or by RNA electroporation, T cell amplification, and quality control of the final cell product, all processes in accordance to good manufacturing procedure (GMP) guidelines [11]. The manufacturing process from leukapheresis to the release of the final T cell product requires about 12 to 14 days. The manufacturing process is currently an entirely hands-on manufacturing procedure and for Kymriah, Yescarta and Tecartus provided by the pharmaceutical company [12, 13]. The process includes [14]:

- **Cell Collection (at the hospital):** Leukapheresis, when a patient's own T cells are collected from the blood, occurs over 3 to 6 hours. Within 24 hours, the leukapheresis material is cryopreserved.
- **Manufacturing (by pharmaceutical company):** The patient's cryopreserved cells are shipped via specialized courier to the approved manufacturing facility, where the patient's cells are genetically reprogrammed into KYMRIAH, YESCARTA or TECARTUS CAR-T cells.
- **Infusion**: The patient will receive lymphodepleting chemotherapy to prepare the body for CAR T-cells. The patient receives their reprogrammed KYMRIAH, YESCARTA or TECARTUS CAR T-cells during an infusion (the administration of CAR T-cells comprises at least one but even up to three bags). CAR T-cell therapies are administered in an inpatient setting (at a certified CAR T center).
- **Monitoring**: The patient is monitored 2 times per week during the first 2-3 weeks following infusion. The patient should stay within proximity of the treatment centre for at least 4 weeks after CAR T-cell infusion to monitor and be treated for potential side effects.

Figure 3: Schematic representation of CAR T cell therapy (Source: National Cancer Institute)



Manufacturing of commercially available CAR T-cells occurs at a central facility and must be coordinated closely with the treatment centre to ensure timely management of each patient leading up to infusion. Currently for Kymriah, Yescarta and Tecartus, patient's T cells are engineered and amplified on the individual basis by these facilities which demands an individualized and cost-intensive manufacturing and time-consuming delivery process (e.g. cryopreservation and shipping). Therefore, research also focuses on in-hospital manufacturing processes by automated and entirely controlled procedures with a high degree of standardization (e.g. CliniMACS Prodigy from Miltenyi Biotech [15]), and on the production in advance of ideally "universal" allogeneic T cells for the "off-the-shelf" administration [16].

Regulatory requirements

CAR T-cell therapies are classified as gene therapy medicinal products (GTMP), a subgroup of advanced therapy medicinal products (ATMPs) in the European Union (EU) and therefore the production and marketing authorisation comes along with comprehensive regulatory requirements provided by the European Medicines Agency [12, 17]. On 30 December 2008, the Regulation 1394/2007 amending Directive 2001/83/EC on Advanced Therapy Medicinal Products entered into force and the first European Union wide regulatory framework for ATMPs was established (the criteria for ATMPs are set out in Article 17 of Regulation (EC) No 1394/2007) [18]. The EMA is responsible for the scientific evaluation of marketing authorisation applications for all ATMPs in the European Economic Area, as they fall under the mandatory scope of the centralised procedure [17].

The intensive research in the field of ATMPs/CAR T-cell therapy brings up new technologies facing especially regulatory, ethical and financial challenges. Thus, there is great interest in Horizon Scanning Systems (HSS) [19, 20] to identify new and emerging ATMPs/CAR T-cell therapies with a potential impact on the health care system. Several countries have already addressed this issue to inform national decision makers [18, 21-23].

2 Scope

As CAR T-cell therapies are an evolving field in the management of haematological malignancies as well as solid tumours, numerous clinical trials with emerging CAR T-cell technologies for various forms of cancer are under way. The aim of the present report is to use the horizon scanning approach [19, 20] to give an overview and forecast on CAR T-cell products in clinical research for cancer treatment.

This report aimed to address the following two main questions:

1. Which CAR T-cell therapies are under development and for which oncological indications?
2. What is the stage of development and by when can an approval be expected?

This report was commissioned by the management board of Tirol Kliniken GmbH and carried out in collaboration with the Austrian Institute for Health technology Assessment (AIHTA) in response to increasing interest and activity in the area of CAR T-cell therapies. The report provides an in-depth horizon scan of clinical trials and an overview of CAR T-cell therapies that are currently at an advanced stage of development and are therefore most likely to appear on the market within the next few years.

The report is not a systematic review of the literature and does not involve a detailed critical appraisal of identified studies or information. It is not intended to provide recommendations for or against a particular technology. General aspects of emerging CAR T-cell technologies are considered, but clinical and cost-effectiveness of individual therapies are not reviewed. Moreover, details on mechanisms, processes related to manufacturing and administration, and regulatory aspects are not within the scope of this report and therefore are only mentioned generally.

A complete list of ongoing clinical trials on CAR T-cell therapies around the world is also not within the scope of this report, but an extensive search in various clinical trial registries was performed to identify and list relevant CAR T-cell technologies.

3 Methods

We conducted a systematic database search and extracted relevant clinical trial data to identify new CAR T-cell technologies in the field of cancer treatment or new uses of existing (approved) CAR T-cell interventions (i.e., Kymriah, Yescarta, Tecartus) that have the potential to effect health and health services.

Approach

A Horizon Scanning approach [19, 20] was used and the following methods were applied to answer the research questions:

1. A systematic search in trial registries was conducted to identify CAR T-cell therapies under development.
2. Data on the identified ongoing clinical trials was extracted from the trial registries, especially on status of trials, intended oncological indication and responsible sponsor.
3. Additional information was sought in published information from sponsors and information from medical articles and complemented by a focused Internet search to identify those therapies closest to approval.

Search strategy

A search in the following clinical trials registries was conducted on June 15, June 24 and June 25, 2020 to identify potential CAR T-cell therapy products and relevant oncological indications:

- ClinicalTrials.gov https://clinicaltrials.gov/
- WHO International Clinical Trials Registry Platform (ICTRP) http://apps.who.int/trialsearch/
- EU Clinical Trials Register https://www.clinicaltrialsregister.eu/ctr-search/search

We limited the search to phase 2, 3 and 4 clinical trials. Results from each database were crossed check with findings from the other databases and duplicates with the same trial-ID were removed. The following key words were used within the search: CAR-T cells, chimeric antigen receptor T Cells, and CAR-T cell therapy. The specific search strategy employed for each database can be found in the Appendix.

Secondly, a targeted literature search in Medline (via Pubmed) and other search engines like Google or Google Scholar was conducted to find publicly available information for identified new and emerging CAR T-cell technologies on their current role in cancer treatment. The search in Pubmed was limited to articles published in English and German between 2015 and 2020 and restricted to the following publication types „Clinical Trial; Comparative Study; Controlled Clinical Trial; Randomized Controlled Trial; Systematic Reviews; Reviews; Practice Guideline“.

Additional information was gathered from the homepage of the European Medicines Agency [24] as well as from the webpages of the pharmaceutical industry (sponsors) that have CAR T-cell technologies in their pipeline.

Eligibility Criteria

The inclusion and exclusion criteria for relevant literature are summarized in Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Application human medicine	Publications on basic research or animal experiments without direct clinical application
Therapeutic indication in oncology (haematological malignancies, solid tumors)	Pre-clinical, phase 1 studies, observational studies
Clinical trial phase 2, 3, 4 or approved technologies in new indications	Articles in languages other than English or German
Interventional studies	Articles not publicly available
	Interventions not for oncology indications

Data extraction

The following relevant clinical trial data were extracted: Trial-ID, title, status (e.g. recruiting, active not recruiting etc.), condition, intervention, name of sponsor, phase, number of patients enrolled, start date, completion date. The detailed extraction tables from relevant clinical trials are presented in the Appendix.

Moreover, the results from the search in clinical trials registries were analysed by CAR T-cell technology and complemented by relevant literature retrieved from Pubmed, EMA [24], the companies' websites or other search engines to identify those CAR T-cell technologies closest to approval.

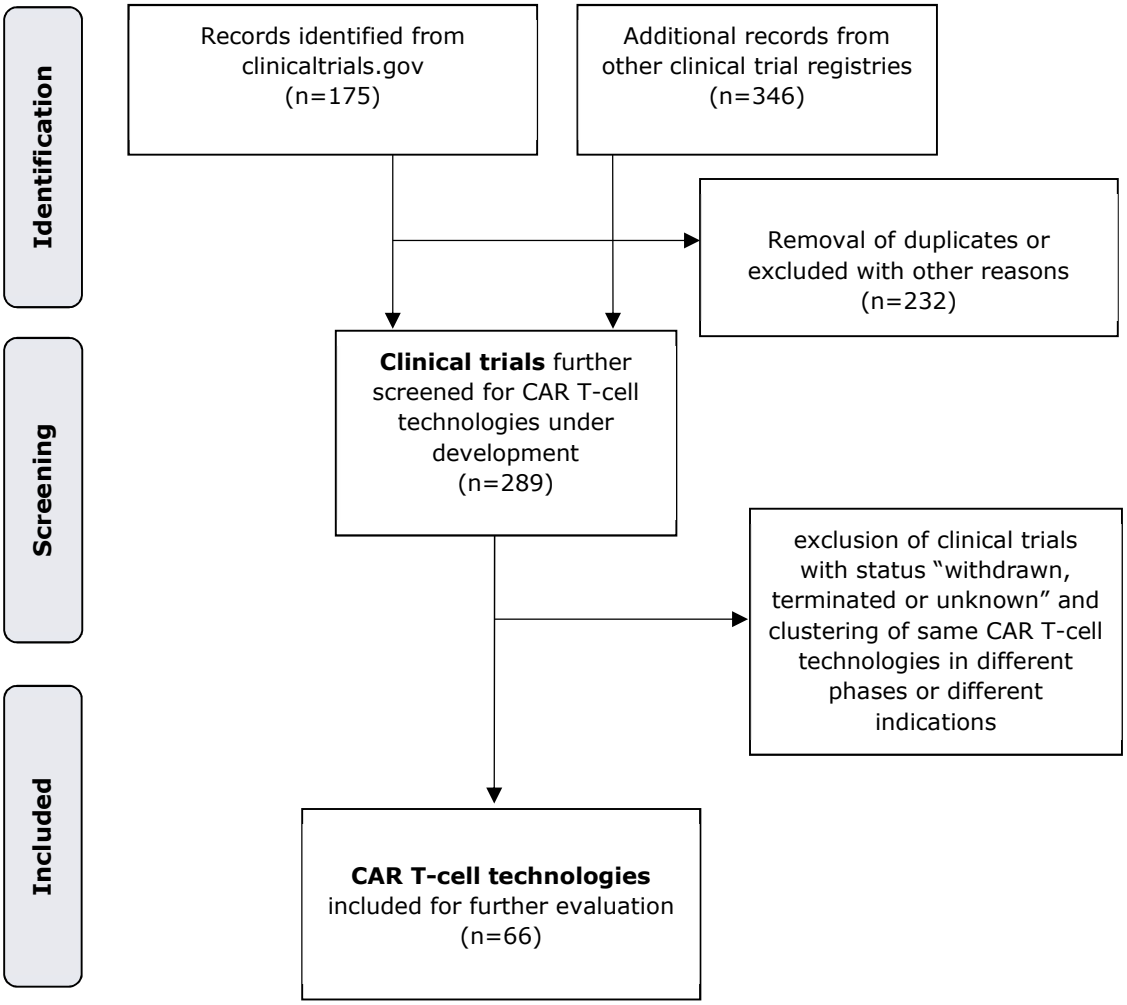
4 Results

Search results

The search in trial registries yielded 521 hits for CAR T-cell therapies under investigation. After deduplication and removal of clinical trials with other interventions or in non-oncological indications 289 trials remained. For CAR T-cell therapies phase 1 and phase 2 trials are often combined and if therapies show substantial benefit, they may be approved on the basis of these phase 1/2 data alone. Therefore, we included these combination trials within our results. The clustering of same CAR T-cell technologies in different phases or same CAR T-cell technologies in different indication and the exclusion of CAR T-cell technologies from clinical trials with status "terminated, withdrawn or unknown" resulted in 66 CAR T-cell technologies currently under advanced stage development.

The selection process is displayed in Figure 4. Detailed clinical trials results (n=289) are presented in the Appendix.

Figure 4: Flow chart of clinical trial identification and CAR T-cell technologies inclusion



CAR T-cell technologies under advanced stage development

The analysis of the 289 identified clinical trials resulted in 66 CAR T-cell technologies currently under development in minimum phase 1/2 clinical trials. The identified CAR T-cell technologies are listed in Table 2.

Table 2: Overview of identified CAR T-cell technologies (sorted by target)

	CAR T-cell technology	**Target**	**Oncological indication**	**Pharmaceutical company or institution**	**Phase of clinical trial**	**Study-ID*: primary completion date, location(s)**
1	P-BCMA-101	BCMA	Multiple myeloma	Poseida Therapeutics	2 (regist-rational)**	NCT03288493: 12/2021, US
2	Idecaptagene Cicleucel (Ide-Cel; bb2121)	BCMA	Multiple myeloma	Celgene (BMS), Bluebird Bio	2 (3)	NCT03361748: 11/2024
3	JCARH125 Orvacabtagene autoleucel (orva-cel)	BCMA	Multiple myeloma	Celgene/ Juno Therapeutics	1/2	NCT03430011: 03/2023, US
4	Descartes-11	BCMA	Multiple myeloma	Cartesian Therapeutics	2	NCT04436029: 04/2022, US
5	LCAR-B38M CAR T-cells JNJ-68284528 (JNJ-4528)	BCMA	Multiple myeloma	Janssen-Cilag (Johnson-Johnson)	2b 3	NCT03758417: 09/2020, China NCT04181827: 04/2026; US, EU
6	BCMA CAR-T (CT053)	BCMA	Multiple myeloma	Carsgen Therapeutics	1/2	NCT03975907: 12/2022, China
7	BCMA CAR T (CT103A)	BCMA	Multiple myeloma	IASO Biotherapeutics (IASO BIO), Innovent Biologics, Inc.	1/2	ChiCTR1800018137: 12/2020, China
8	CARTBCMA (ARI0002h)	BCMA	Multiple myeloma	Sara V. Latorre	1/2	NCT04309981: 04/2023, Spain
9	BCMA CAR-NK 92 cells	BCMA	Multiple myeloma	Asclepius Technology company	1/2	NCT03940833: 05/2021, China
10	Descartes-08	BCMA	Multiple myeloma	Cartesian Therapeutics	1/2	NCT03448978: 07/2020, US
11	BCMA-CAR-T\CD138-CAR-T	BCMA CD138 (dual Specificity)	Multiple myeloma	Chinese PLA General Hospital	1/2	NCT03767751: 05/2022, China
12	CD123/CLL1 CAR-T Cells	CD123 CLL1	AML	Fujian Medical University	2/3	NCT03631576: 08/2021, China
13	CD123-targeted CART (MB-102)	CD123	AML	Mustang Bio	1/2	NCT04109482: 03/2023, US

14	CART133	CD133	solid tumours	Chinese PLA General Hospital	1/2	NCT02541370: 06/2019, China
15	Sarcoma specific CAR-T cells	CD133, GD2, Muc1, CD117	sarcoma	Shenzhen Geno-Immune Medical Institute	1/2	NCT03356782: 11/2023, China NCT04433221: 05/2023, China
16	CART-138 T Cells Targeting CD138/BCMA/CD19/ More Antigens (CART-138/ BCMA/19/More)	CD138 BCMA CD19	Multiple Myeloma	The First Affiliated Hospital of Soochow University	1/2	NCT03196414: 09/2026, China
17	AUTO1	CD19	adult ALL paediatric ALL	Autolus Therapeutics	1b/2	NCT04404660: 03/2023, US
18	AUTO3	CD19 CD22	DBCL Paediatric ALL	Autolus Therapeutics	1/2	NCT03287817: 03/2021, UK NCT03289455: 12/2021, US
19	ssCART-19 cell therapy	CD19	ALL	The First Affiliated Hospital of Soochow University	1/2	NCT03919240: 12/2020, China
20	Lisocabtagene Maraleucel (JCAR017, liso-cel)	CD19	NHL B-cell lymphoma	Celgene/BMS	2/3	NCT03484702: 08/2021, EU NCT04245839: 10/2022 NCT03575351: 09/2023, US NCT03744676: 11/2022, US
21	CD19-PD1-CART Cells	CD19	B-Cell Lymphoma	Chinese PLA General Hospital	2	NCT04163302: 07/2021, China
22	SCRI-huCAR19v1	CD19	Leukaemia lymphoma	Seattle Children's Hospital	1/2	NCT03684889: 12/2021, US
23	MB-CART19.1	CD19	ALL, CLL B-cell lymphoma	Miltenyi Biomedicine GmbH	1/2	NCT03853616: 07/2020, Germany
24	CLIC-1901	CD19	ALL NHL	Ottawa Hospital Research Institute	1/2	NCT03765177: 10/2022, Canada
25	IM19 CAR-T	CD19	NHL	Immunochina Pharmaceuticals	1(2)	NCT04440436: 06/2022, China
26	CT032	CD19	NHL	Carsgen Therapeutics	1/2	NCT03994913: 06/2022, China
27	TBI-1501	CD19	ALL	Takara Bio Inc Otsuka Pharmaceutical Co.	1/2	NCT03155191: 03/2020, Japan

28	BinD19	CD19	ALL	Shenzhen BinDeBio Ltd	1/2	NCT03265106: 06/2020, China
29	IM19 CAR-T	CD19	NHL	Beijing Immuno-china Medical Science & Technology Co., Ltd.	1/2	NCT04440436: 06/2022, China
30	KTE-X19 (brexucabtagene autoleucel)	CD19	Mantel cell lymphoma ALL CLL	KITE pharma	2	ZUMA-2 NCT02601313: 07/2019, US/EU FDA approval 07/2020
31	Anti-CD19, Dual Co-stimulatory (4-1BB, CD3ζ) Chimeric Antigen Receptor T-cells	CD19	NHL ALL	University of Alberta	1/2	NCT03938987: 12/2022, Canada
32	iC9-CAR19 cells	CD19 cells with the safety switch are referred to as iC9-CAR19 cells	ALL	Bellicum Pharmaceuticals	1/2	NCT03016377: 11/2021, US
33	CD20-targeted CAR-T cells	CD20	Lymphoma NHL	Fred Hutchinson Cancer Research Centre	1/2	NCT03277729: 11/2022, US
34	Anti-CD22-CAR	CD22	Lymphoma ALL, CLL	Kecellitics Biotech Co.	1/2	NCT04163575: 07/2021 NCT02935153: 10/2019, China NCT03262298: 08/2019, China NCT04340167: 05/2020, China
35	CD30 CAR-T cells (TT11) CART30	CD30	Hodgkin Lymphoma	Tessa Therapeutics	2	NCT02259556: 10/2018, China
36	ATLCAR.CD30 T cells	CD30	Peripheral T Cell Lymphoma (PTCL)	UNC Lineberger Comprehensive Cancer Centre	2	NCT04083495: 09/2021, US
37	multi-CAR T-cell therapy (Muc1/CLL1/CD33/CD38/CD56/CD123-specific gene-engineered T cells)	CD33, CD38, CD123, CD56, Muc1, and CLL1	AML	Shenzhen Geno-Immune Medical Institute	1 (2)	NCT03222674: 12/2019, China
38	CD38 CART CART-38	CD38	ALL Multiple myeloma AML	e.g. Sorrento Therapeutics	1/2	NCT03754764: 11/2022, China NCT03464916: 04/2020, US NCT04351022: 12/2021, China

39	CAR-T CD44v6 MLM-CAR44.1	CD44	various types of CD44v6 positive cancers (e.g. stomach cancer, breast cancer, prostate cancer, multiple myeloma and lymphoma) AML	MolMed S.p.A. (Italy) EU-funded project (Horizon 2020 - European Commission EURE-CART)	1/2	NCT04427449: 05/2023, China NCT04097301: 06/2023, Italy
40	CD7-CART	CD7	ALL TLBL, PTCL	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	1 (2)	NCT04004637: 06/2021, China
41	GC197	CD7 CD19	B-cell leukaemia B-cell lymphoma	Gracell Biotechnologies Co.	1/2	ISRCTN11885863: 10/2022, China
42	Anti-hCD70 CAR	CD70	Pancreatic cancer Renal cell cancer Breast cancer Melanoma Ovarian cancer (CD70 expressing cancers)	National Cancer Institute (NCI)	1/2	NCT02830724: 01/2027
43	CD99 CAR T	CD99	recurrent/ refractory CD99+ lymphoproliferative diseases	Affiliated Hospital of Xuzhou Medical University	1/2	ChiCTR2000033989, China
44	Anti-CEA CAR-T	CEA	pancreatic adenocarcinoma with liver metastases	Sorrento Therapeutics	2/3	NCT04037241: 01/2022
45	IL-7 & CCL19 CAR-T Cells (7x19 CAR-T)	Co-expressing cytokines and chemokines	B-cell Lymphoma	Second Affiliated Hospital, School of Medicine, Zhejiang University	1 (2)	NCT04381741: 09/2023, China
46	CTX110 (previously called as CTX 101)	CD19	Relapsed or Refractory B-Cell Malignancies	CRISPR Therapeutics	1/2	NCT04035434: 07/2026, US
47	CLL-1.CAR	C-type lectin 1 (CLL-1, CD371)	AML	Baylor College of Medicine	1 (2)	NCT04219163: 07/2024, US
48	Epidermal growth factor receptor (EGFRv)III Chimeric antigen receptor (CAR) transduced PBL	EGFR	Glioma Brain cancer	National Cancer Institute (NCI)	1/2	NCT01454596: completed 08/2019, US
49	GD2-CART01	GD2	Neuroblastoma	Bambino Gesù Hospital and Research Institute	1/2	NCT03373097: 12/2024, Italy

50	4SCAR-GD2	GD2	Solid tumours	Shenzhen Geno-Immune Medical Institute	1/2	NCT02992210: 06/2019, China
51	Cervical cancer-specific CAR-T cells	GD2, PSMA, Muc1, Mesothelin	cervical cancer	Shenzhen Geno-Immune Medical Institute	1/2	NCT03356795: 12/2020, China
52	GPC3-CART cells	GPC3	Hepatocellular carcinoma	Shanghai GeneChem Co.	1/2	NCT02395250: completed 11/2018, China
53	HER2 CAR-T	HER2	Brain tumours	Baylor College of Medicine	1/2	NCT02442297: 02/2021, US
54	Multi-4SCAR-T	Her2-, GD2- and CD44v6-specific CAR-T	Breast cancer	Shenzhen Geno-Immune Medical Institute	1/2	NCT04430595: 05/2023, China
55	Anti-Lewis Y Chimeric Antigen Receptor-T Cells (LeY-CAR-T)	Lewis Y antigen	myeloid malignancies advanced solid cancer	Southwest Hospital, China Peter MacCallum Cancer Centre, Australia	1/2	NCT02958384: 10/2020, China NCT03851146: 12/2019, Australia
56	anti-MESO CAR-T cells	mesothelin	Ovarian cancer	Second Affiliated Hospital, Zhejiang University	1/2	NCT03916679: 04/2022, China
57	PD-1 antibody expressing mesoCAR.T cells	mesothelin	advanced solid tumours	Shanghai Cell Therapy Research Institute	1/2	NCT03615313: 10/2020; China
58	iCasp9M28z T cell	mesothelin	Lung cancer Breast cancer	Atara Biotherapeutics Bellicum Pharmaceuticals	1/2	NCT02414269: 04/2021, US
59	anti-MUC1 CAR T	MUC1	Lung cancer Oesophageal cancer ICC	PersonGen Bio Therapeutics	1/2	NCT03525782: 01/2021, China NCT03706326: 09/2021, China NCT03633773: 08/2023, China
60	CAR-T/TCR-T cell immunotherapy (EGFRvIII/DR5/NY-ESO-1/Mesothelin CAR-T/TCR-T Cells Immunotherapy)	Multi target: anti-NY-ESO-1 antibody for oesophagus cancer; anti-DR5 antibody for hepatoma; anti-EGFRvIII antibody for hepatoma and glioma; anti-Mesothelin antibody for gastric cancer	Oesophagus Cancer Hepatoma Glioma Gastric Cancer ALL lymphoma	Shenzhen BinDeBio Ltd	1/2	NCT03941626: 12/2020, China NCT03638206: 03/2023, China

61	PSCA-CAR-T	PSCA	Castration resistant prostate cancer	City of Hope Medical Centre	1 (2)	NCT03873805: 02/2021, US
62	4SCAR-PSMA T cells 4SCAR-Fra	PSMA	Bladder cancer PSMA Positive Tumours	Shenzhen Geno-Immune Medical Institute	1/2	NCT03185468: 12/2020, China NCT04429451: 10/2023, China
63	BiCAR NK cells (ROBO1 CAR-NK cells)	ROBO1	Pancreatic cancer Other solid tumours	Asclepius Technology company	1/2	NCT03940820: 05/2022, China NCT03941457: 05/2022, China NCT03931720: 05/2022, China
64	SLAMF7 CAR-T***	SLAMF7	Multiple myeloma	National Cancer Institute (NCI)	1 (2)	NCT03958656: 05/2023, US
65	B7-H3-CAR-T	Tandem CAR-T cells targeting CD70 and B7-H3	glioblastoma	BoYuan RunSheng Pharma (Hangzhou) Co., Ltd.	1/2	NCT04077866: 06/2024, China
66	AUTO4	TRBC1	T-cell lymphoma	Autolus Ltd.	1 (2)	NCT03590574: 07/2021, UK

4SCART=4th generation chimeric antigen receptor gene-modified T cells; BCMA= B-cell maturation antigen; MM=multiple myeloma; AML=acute myeloid leukaemia; ALL=acute lymphoblastic leukaemia; DBCL=diffuse-large B cell lymphoma; NHL=Non-Hodgkin Lymphoma; CLL=Chronic lymphocytic leukaemia; PTCL= Peripheral T Cell Lymphoma; TLBL=T-cell lymphoblastic lymphoma; ICC= Intrahepatic cholangiocarcinoma; PSMA=prostate-specific membrane antigen; PSCA= Prostate stem cell antigen

* no comprehensive list of clinical trials;
** Phase 3 may not be required if Phase 2 is registrational; Registrational Trial means one or more controlled, multi-centre clinical trials in human patients, whether a Phase 2 trial or a Phase 3 trial, that is designed in consultation with the JSC to obtain sufficient efficacy and safety data to support Marketing Approval and labelling of the Product;
*** EU-funded project CARAMBA (Horizon 2020) https://www.caramba-cart.eu/

An additional literature search for these 66 identified new and emerging CAR T-cell technologies on their actual stage of development and their potential relevance in cancer treatment resulted in the exclusion of those CAR T-cell technologies which are still in an early development phase. A shorter list of CAR T-cell technologies that are at the most advanced development stage or considered most relevant is presented in Table 3.

Table 3: Overview of CAR T technologies at the most advanced development stage

	CAR T-cell technology	Target	Oncological indication	Pharma-ceutical company	Phase; Study-ID: primary completion date, location(s)	EMA/FDA status/ others
1	P-BCMA-101	BCMA	Multiple myeloma	Poseida Thera-peutics	phase 2 (registrational) NCT03288493: 12/2021, US	EMA: - FDA: 05/2019 orphan designation
2	**Idecaptagene Vicleucel** **(Ide-Cel; bb2121)**	**BCMA**	**Multiple myeloma**	**Celgene (BMS), Bluebird Bio**	**phase 2** **NCT03361748: 11/2024** **phase 3** **NCT03651128: 06/2025, US/EU**	**EMA: 03/2020 granted accelerated assessment** **FDA: 2017 granted a break-through therapy designation, 04/2020 license application**
3	JCARH125 Orvacabtagene autoleucel (orva-cel)	BCMA	Multiple myeloma	Celgene/ Juno Therapeutics	phase 1/2 NCT03430011: 03/2023, US	-
4	Descartes-11	BCMA	Multiple myeloma	Cartesian Therapeutics	phase 2 NCT04436029: 04/2022, US	-
5	LCAR-B38M CAR T-cells JNJ-68284528 (JNJ-4528)	BCMA	Multiple myeloma	Janssen-Cilag (Johnson-Johnson)	phase 2b NCT03758417: 09/2020, China phase 3 NCT04181827: 04/2026; US, EU	EMA: 04/2019 granted PRIME (PRIority MEdicines) designation FDA: 02/2019 granted Orphan Drug Designation
6	BCMA CAR-T (CT053)	BCMA	Multiple myeloma	Carsgen Thera-peutics	phase 1/2 NCT03975907: 12/2022, China	EMA: 04/2020 positive opinion on orphan designation FDA: 10/2019 granted Regenerative Medicine Advanced Therapy (RMAT) designation
7	BCMA CAR T (CT103A)	BCMA	Multiple myeloma	IASO Biotherapeutics (IASO BIO), Innovent Biologics, Inc.	Phase 1/2 ChiCTR1800018137: 12/2020, China	EMA/FDA: - China: The National Medical Products Administration (NMPA) in China has granted approval to the investigational new drug (IND)* application for CT103A
8	CD123-targeted CART (MB-102)	CD123	AML	Mustang Bio	phase 1/2 NCT04109482: 03/2023, US	EMA: - FDA: 07/2017 granted orphan drug designation

9	AUTO3	CD19 CD22 (bi-cistronic CAR)	DBCL Paediatric ALL	Autolus Therapeutics	phase 1/2 NCT03287817: 03/2021, UK NCT03289455: 12/2021, US	EMA: - FDA: 04/2019 orphan drug status for ALL
10	**Lisocabtagene Maraleucel (JCAR017, liso-cel)**	**CD19**	**NHL** **B-cell lymphoma**	**Celgene/ BMS**	**phase 2/3** **NCT03484702: 08/2021, EU** **NCT04245839: 10/2022** **NCT03575351: 09/2023, US** **NCT03744676: 11/2022, US**	**EMA: 11/2018 granted orphan designation** **FDA: 12/2020 U.S. FDA approval of liso-cel expected**
11	CD19-PD1-CART Cells (CD19CART cells secreting mutant PD-1Fc fusion protein)	CD19	B-Cell Lymphoma	Chinese PLA General Hospital	phase 2 NCT04163302: 07/2021, China	-
12	**KTE-X19** **(Brexucabtagene Autoleucel)**	**CD19**	**Mantel cell lymphoma** **ALL** **CLL**	**KITE pharma**	**phase 2 (ZUMA-2)** **NCT02601313: 07/2019, US/EU**	**EMA: 01/2020 under evaluation** **FDA: 02/2020 U.S. FDA Grants Priority Review for Kite's KTE-X19 Biologics License Application (BLA)** in Relapsed or Refractory Mantle Cell Lymphoma** **FDA approval 07/2020**
13	CD30 CAR-T cells (TT11) CART30	CD30	CD30 + Hodgkin Lymphoma	Tessa Therapeutics	phase 2 NCT02259556: 10/2018, China	FDA: 02/2020 Regenerative Medicine Advanced Therapy (RMAT) Designation Granted

EMA; European Medicines Agency, FDA: US Food & Drug Administration, PRIME; priority medicines designation, RMAT; regenerative medicine advanced therapy, U.S.; United States; BCMA= B-cell maturation antigen; MM=multiple myeloma; AML=acute myeloid leukaemia; ALL=acute lymphoblastic leukaemia; DBCL=diffuse-large B cell lymphoma; NHL=Non-Hodgkin Lymphoma; CLL=Chronic lymphocytic leukaemia

* IND application: investigational new drug (before phase 1 trial)

** BLA/MAA means a Biologics License Application ("BLA") submitted to the FDA or a Market Authorization Application ("MAA") submitted to the EMA or MHLW, or any supplemental filing to a BLA or MAA

- **P-BCMA-101**

  P-BCMA-101 is a CAR-T cell product targeting B Cell Maturation Antigen (BCMA). P-BCMA-101 is produced using the piggyBac® DNA Modification System instead of the viral vector that is used with most CAR-T cells, requiring only plasmid DNA and mRNA. P-BCMA-101 is developed by Poseida Therapeutics Inc. which received FDA orphan drug designation for P-BCMA-101 for the treatment of multiple myeloma in May 2019. A pivotal Phase 2 study has recently been

designed and initiated (PRIME; NCT03288493) in r/r multiple myeloma (MM) patients who have received at least 3 prior lines of therapy [25].

- **Idecaptagene Vicleucel (Ide-Cel; bb2121)**

  Idecabtagene vicleucel (ide-cel; previously bb2121) is a cancer immunotherapy candidate that Celgene (now part of Bristol-Myer Squibb) is developing in collaboration with Bluebird Bio to treat people with multiple myeloma. Ide-cel is a CAR T-cell therapy and recognizes the protein called BCMA, which is present in high numbers on the surface of myeloma cells.

  In addition to the pivotal KarMMa trial (NCT03361748) evaluating ide-cel in patients with relapsed and refractory multiple myeloma, Bristol Myers Squibb and bluebird bio's broad clinical development program for ide-cel includes clinical studies (KarMMa-2, KarMMa-3, KarMMa-4) in earlier lines of treatment for patients with multiple myeloma, including newly diagnosed multiple myeloma.

  Ide-cel was granted accelerated assessment by the European Medicines Agency on March 26, 2020 [26]. In May 2020, Bristol Myers Squibb and bluebird bio, Inc. announced that they received a Refusal to File letter from the U.S. Food and Drug Administration regarding the Biologics License Application for idecabtagene vicleucel (ide-cel; bb2121) for patients with heavily pre-treated relapsed and refractory multiple myeloma, which was submitted in March 2020 (based on data from the Phase II KarMMa trial). Upon preliminary review, the FDA determined that the Chemistry, Manufacturing and Control (CMC) module of the BLA requires further detail to complete the review. No additional clinical or non-clinical data have been requested or are required. Bristol Myers Squibb is planning to resubmit the BLA no later than the end of July 2020 [27].

- **JCARH125 (Orvacabtagene autoleucel, orva-cel)**

  JCARH125 is a human-derived single-chain variable fragment (scFv) product with a lentiviral vector and 4-1BB costimulatory domain developed by Juno Therapeutics, a subsidiary of Celgene.

  There is an ongoing phase 1/2 EVOLVE study (NCT03430011) in adult patients with relapsed and/or refractory multiple myeloma. Initial Proof of Concept results were presented at the American Society of Haematology (ASH) Meeting in 2018: At data cut off, 44 patients have been infused with JCARH125 in three dose escalation cohorts. These patients were heavily pre-treated, with a median of seven prior lines of therapies (range, 3-23), and 77% had high-risk cytogenetics. Seventy-one percent of patients experienced grade 1 and 2 cytokine release syndrome (CRS) with 9% of patients experiencing grade 3/4 CRS. In addition, 18% of patients experienced grade 1 and 2 neurological events with 7% of patients experiencing a grade 3/4 event. Other frequent grade 3/4 adverse events included neutropenia (86%), anaemia (50%), thrombocytopenia (43%) and infection (14%). The median follow up was only 11 weeks [28].

- **Descartes-11**

  Descartes-11 s an autologous CD8+ anti-BCMA CAR T-cell therapy being developed by Cartesian Therapeutics.

In June 2020, Cartesian Therapeutics initiated phase 2 trial (NCT04436029) to evaluate efficacy of Descartes-11 in patients with high-risk multiple myeloma who have residual disease following induction therapy.

- **JNJ-68284528 (JNJ-4528, LCAR-B38M)**

  JNJ-68284528 (LCAR-B38M) is an investigational CAR-T therapy for the treatment of patients with relapsed or refractory multiple myeloma developed by Janssen Pharmaceutical Companies of Johnson & Johnson [29]. The design comprises a structurally differentiated CAR-T with two BCMA-targeting single domain antibodies. In December 2017, Janssen entered into an exclusive worldwide license and collaboration agreement with Legend Biotech to develop and commercialize JNJ-68284528 (LCAR-B38M). In May 2018, Janssen initiated a Phase 1b/2 trial (NCT03548207, CARTITUDE-1) to evaluate the efficacy and safety of JNJ-68284528 in adults with relapsed or refractory multiple myeloma, informed by the LEGEND-2 study results. The primary completion date for this study is September 14, 2021. In February 2019, the FDA granted Janssen an Orphan Drug Designation for JNJ-4528. In April 2019, JNJ-68284528 was granted PRIME designation by the EMA. In December 2019, Janssen announced receipt of a Breakthrough Therapy Designation from the FDA, which is granted to expedite the development and regulatory review of an investigational medicine that is intended to treat a serious or life-threatening condition.

  In addition, a phase 3 randomized study comparing JNJ-68284528 versus pomalidomide, bortezomib and dexamethasone or daratumumab, pomalidomide and dexamethasone in subjects with relapsed and lenalidomide-refractory multiple myeloma was initiated in June 2020 by Janssen Research & Development, LLC (NCT04181827).

- **BCMA CAR-T (CT053)**

  CT053 are fully human anti-BCMA autologous chimeric antigen receptor T-cells for the treatment of multiple myeloma developed by CARsgen Therapeutics. CT053 recently received positive EMA opinion on orphan drug designation in April 2020. In October 2019, the U.S. Food and Drug Administration has granted its Regenerative Medicine Advanced Therapy (RMAT) designation to the investigational therapy CT053 for the treatment of relapsed or refractory multiple myeloma. The designation follows a recently granted orphan drug designation by the FDA and priority medicines (PRIME) eligibility from the European Medicines Agency. It was based on data from an ongoing Phase 1 clinical trial (NCT03975907) in people with heavily pre-treated multiple myeloma [30].

- **BCMA CAR T (CT103A)**

  CT103A is a novel BCMA-targeting CAR-T with a lentiviral vector containing a CAR structure with a fully human scFv, CD8a hinger, and transmembrane, 4-1BB co-stimulatory and CD3z activation domains developed by Iaso Biotherapeutics Co. Ltd and investigated in patients with relapsed/refractory multiple myeloma (ChiCTR1800018137) [31].

  The National Medical Products Administration (NMPA) in China has granted approval to the investigational new drug (IND) application for CT103A, for the treatment of relapsed/refractory multiple myeloma in October 2019.

- **CD123-targeted CART (MB-102)**

  MB-102 is a CAR T-cell therapy that is produced by engineering patient T cells to recognize and eliminate CD123-expressing tumours and is developed by Mustang Bio Inc. CD123 is widely expressed on bone marrow cells of patients with myelodysplastic syndrome and hematologic malignancies, including in 75-89% of AML patients and over 90% in blastic plasmacytoid dendritic cell neoplasm (BPDCN) patients. MB-102 has shown promising response rates in early small populations of these patients in an investigator-sponsored Phase 1 clinical trial (NCT02159495).

  On July 24, 2019, Mustang announced that the FDA granted Orphan Drug Designation to MB-102 for the treatment of AML. The FDA also previously granted Orphan Drug Designation to MB-102 for the treatment of BPDCN. In August 2019, the U.S. Food and Drug Administration (FDA) has approved the Company's IND application to initiate a multi-centre Phase 1/2 clinical trial of MB-102 (CD123 CAR T) in acute myeloid leukaemia (AML), blastic plasmacytoid dendritic cell neoplasm (BPDCN) and high-risk myelodysplastic syndrome (MDS) [32].

- **AUTO3**

  AUTO3 is a CAR T-cell therapy designed to target CD19 and CD22 simultaneously and developed by Autolus Therapeutics. First results of a phase 1 study (Amelia Study) in paediatric patients with relapsed/refractory B-cell acute lymphoblastic leukaemia [33] and a phase 1/2 study in patients with relapsed/refractory DLBCL (Alexander Study) [34] were presented at the ASH Meeting in November 2019. The FDA has granted orphan drug designation for AUTO3 in ALL in April 2019.

- **Lisocabtagene Maraleucel (JCAR017, liso-cel):**

  Lisocabtagene maraleucel aims to target CD19-expressing cells through a CAR construct that includes an anti-CD19 single-chain variable fragment (scFv) targeting domain for antigen specificity, a transmembrane domain, a 4-1BB costimulatory domain hypothesized to increase T-cell proliferation and persistence, and a CD3-ζ (zeta) T-cell activation domain. Lisocabtagene maraleucel (liso-cel; JCAR017; Anti-CD19 CAR T-Cells) was originally developed by Juno Therapeutics, at the time a wholly-owned subsidiary of Celgene, before both companies were taken over by being Bristol-Myers Squibb. Liso-cel is an immunotherapy for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after at least two prior therapies and the FDA has accepted priority review in February 2020. The FDA has set a Prescription Drug User Fee Act (PDUFA) goal date of August 17, 2020 [35].

  In July 2020, the EMA has agreed to review a request to approve the investigational CAR T-cell therapy, lisocabtagene maraleucel (liso-cel), for people with pre-treated lymphomas. The marketing authorization application, submitted by Bristol Myers Squibb, is specific to patients with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma grade 3B (FL3B), who have tried at least two prior therapies. Bristol-Myers filed similar request with the FDA, and a decision is expected by mid-November [36].

  The recent application was based on data from the Phase 1 TRANSCEND-NHL-001 trial (NCT02631044), and the Phase 2 TRANSCEND WORLD trial (NCT03484702), which is investigating the safety and efficacy of liso-cel in people with aggressive forms of NHL. This

study is recruiting participants at sites across Europe and Japan, with top-line findings expected in August 2021.

- **CD19-PD1-CART Cells**

  CD19-PD1-CART cells are CD19CART which secretes the mutant PD-1Fc fusion protein. Preclinical studies have shown that CD19CART cells secreting mutant PD-1Fc fusion protein have a superior killing effect to CD19CART cells which does not express PD-1 fusion protein. CD19-PD1-CART cells are investigated in a single centre, non-randomized, open-label, phase 2 study in patients with relapsed/refractory B Cell Lymphoma initiated by the Chinese PLA General Hospital (NCT04163302).

- **KTE-X19 (Brexucabtagene Autoleucel)**

  KTE-X19 is an autologous, anti-CD19 CAR T-cell therapy developed by Kite, a Gilead Company. KTE-X19 uses the XLP™ manufacturing process that includes T-cell selection and lymphocyte enrichment. Lymphocyte enrichment is a necessary step in certain B-cell malignancies with evidence of circulating lymphoblasts. KTE-X19 is currently in Phase 1/2 trials in acute lymphoblastic leukaemia, mantle cell lymphoma (MCL) and chronic lymphocytic leukaemia. The company has submitted a Biologics License Application to the FDA for KTE-X19 for the treatment of adult patients with relapsed or refractory MCL [37]. The BLA submission is based on data from the Phase 2 ZUMA-2 trial which was published by Wang et al. in April 2020 [38]: "*In an intention-to-treat analysis involving all 74 patients, 85% had an objective response; 59% had a complete response. At a median follow-up of 12.3 months (range, 7.0 to 32.3), 57% of the 60 patients in the primary efficacy analysis were in remission. At 12 months, the estimated progression-free survival and overall survival were 61% and 83%, respectively. Common adverse events of grade 3 or higher were cytopenias (in 94% of the patients) and infections (in 32%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 15% and 31% of patients, respectively; none were fatal. Two grade 5 infectious adverse events occurred.*"

  Based on the results from this ongoing, single-arm, open-label ZUMA-2 pivotal trial, the FDA granted accelerated approval to KTE-X19 (brexucabtagene autoleucel (Tecartus) in July 2020 [39].

  In January 2020, Kite announced that KTE-X19 is under evaluation by the EMA.

- **CD30 CAR-T cells (TT11, CART30)**

  CD30.CAR-T are CD30-Directed Genetically Modified Autologous T cells developed by Tessa Therapeutics and investigated in adult and paediatric patients with relapsed or refractory CD30 Positive Classical Hodgkin Lymphoma. In February 2020, the FDA granted Regenerative Medicine Advanced Therapy designation for CD30.CAR-T [40]. The RMAT designation is supported by clinical data from two independent CD30 CAR-T Phase 1/2 studies in patients with relapsed or refractory CD30-positive classical Hodgkin lymphoma conducted by Baylor College of Medicine (NCT02917083) and University of North Carolina Lineberger Comprehensive Cancer Centre (NCT02690545). Both studies demonstrated objective response rates of more than 70%, with 18 patients achieving complete response out of 27 patients treated with CD 30 CAR- T with lymphodepleting chemotherapy as of November 2019. The

company is now initiating a pivotal Phase 2 clinical study to investigate their autologous CD30.CAR-T cell therapy program.

Finally, based on a target-oriented literature search, the following candidates of CAR T-cell therapies closest to approval by the FDA and EMA could be identified:

- **Brexucabtagene Autoleucel (KTE-X19)** for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (by Kite, a Gilead Company): **FDA granted accelerated approval on July 24, 2020; the drug is currently under review in the European Union and has been granted PRIME designation by the EMA for relapsed or refractory MCL**

- **Idecabtagene vicleucel (ide-cel; bb2121)** for patients with pre-treated relapsed and refractory multiple myeloma (by Bristol-Myers Squibb): **A Biologics License Application was submitted in March 2020 to the FDA, which concluded that additional information was needed for the Chemistry, Manufacturing and Control module of the BLA – the company plans to resubmit the application by the end of July 2020; Ide-cel was granted Accelerated Assessment status by the EMA in March 2020**

- **Lisocabtagene maraleucel (liso-cel; JCAR017)** for adult patients with relapsed or refractory large B-cell lymphoma after at least two prior therapies (by Bristol-Myers Squibb): **In May 2020, the FDA has extended the action date by three months for the BLA for liso-cel, the new Prescription Drug User Fee Act action date set by the FDA is November 16, 2020; In July 2020, the EMA validated the marketing authorization application for liso-cel, for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma Grade 3B after at least two prior therapies and the EMA started the centralized review process**

Extension of indications for Kymriah, Yescarta and Tecartus

Kymriah® and Yescarta® were the first two FDA- and EMA-approved CAR-T cell therapy products available on the market. Kymriah (CTL019, Tisagenlecleucel; Novartis) was approved in August 2017 by the FDA for the treatment of ALL and DLBCL, whereas Yescarta (KTE-C19, Axicabtagen-ciloleucel; Kite/Gilead) was approved on October 2017 by the FDA for the treatment of DLBCL and Non-Hodgkin's lymphoma. Both CAR T-cell therapies are approved by the EMA as well. The third CD19-directed CAR T-cell therapy, brexucabtagene autoleucel (Tecartus; KTE-X19; Kite/Gilead), has been granted accelerated approval at present only by the FDA for the treatment of adult patients with relapsed or refractory mantle cell lymphoma in July 2020.

Our search in clinicaltrials.gov resulted in several ongoing clinical trials for these CD-19 directed CAR T-cell therapies in either additional indications or in their use in earlier lines (see Tables 4 to 6).

Table 4: List of ongoing clinical trials for Tisagenlecleucel (Novartis)

	NCT Number	Conditions	Phase	Start Date	Primary Completion Date	Locations
1	NCT04456023	relapsed or refractory DLBCL	Phase 2	May 27, 2021	March 30, 2027	NA
2	NCT04156659	relapsed or refractory B-cell ALL	Phase 2	September 22, 2020	January 17, 2022	NA
3	NCT04225676	reinfusion of tisagenlecleucel in paediatric and young adult patients with ALL who were treated with tisagenlecleucel and experience B cell recovery	Phase 2	May 29, 2020	February 28, 2022	NA
4	NCT04094311	B-cell ALL Diffuse Large B-cell Lymphoma	Phase 3	November 21, 2019	March 31, 2022	Japan
5	NCT04234061	relapsed or refractory Mantle Cell Lymphoma	Phase 2	April, 2020	September, 2027	Australia
6	NCT03876769	First-line High-risk Paediatric and Young Adult Patients With B-cell Acute Lymphoblastic Leukaemia (B-ALL) Who Are Minimal Residual Disease Positive at the End of Consolidation Therapy	Phase 2	June 24, 2019	November 26, 2026	US
7	NCT03568461	relapsed or refractory Follicular Lymphoma	Phase 2	November 12, 2018	February 22, 2021	US
8	NCT04161118	First-Relapsed or Primary Refractory Aggressive B-cell Non-Hodgkin Lymphoma	Phase 2	August 2020	August 2023	Germany
9	NCT03610724	children and adolescents with relapsed/refractory B-cell non-Hodgkin lymphoma	Phase 2	February 15, 2019	March 31, 2022	US
10	NCT03570892	patients with aggressive B-cell Non-Hodgkin Lymphoma after failure of rituximab and	Phase 3	May 7, 2019	December 30, 2025	US

		anthracycline containing frontline immune-chemotherapy				
11	NCT03123939	Relapsed/Refractory Paediatric/Young Adult ALL	Phase 3	April 24, 2017	August 21, 2020	EU, Japan, Canada
12	NCT02435849	paediatric patients with r/r B-cell ALL and high risk B-cell ALL at first relapse	Phase 2	April 8, 2015	November 28, 2022	US
13	NCT02445248	Relapsed or Refractory Diffuse Large B-cell Lymphoma	Phase 2	July 29, 2015	February 20, 2023	US

NA=not available; DLBCL= diffuse-large B cell lymphoma; ALL= acute lymphoblastic leukaemia

In addition to ALL and DLBCL, tisagenlecleucel is also currently under development in earlier lines (e.g. first-line High-risk B-cell Acute Lymphoblastic Leukaemia or First-Relapsed or Primary Refractory Aggressive B-cell Non-Hodgkin Lymphoma) and in relapsed or refractory Mantle Cell Lymphoma and relapsed or refractory Follicular Lymphoma (see Table 4).

Table 5: List of ongoing clinical trials for Axicabtagen-ciloleucel (Kite/Gilead)

	NCT Number	Conditions	Phases	Start Date	Primary Completion Date	Locations
1	NCT02926833 (ZUMA-6)	KTE-C19 in Combination With Atezolizumab in Subjects With Refractory DLBCL	1/2	September 29, 2016	February 21, 2019	US
2	NCT02348216	Adults With Refractory Aggressive Non-Hodgkin Lymphoma	1/2	January 2015	August 2020	US
3	NCT03391466	Axicabtagene-ciloleucel versus standard of care therapy in subjects with relapsed/refractory DLBCL (second-line)	Phase 3	December 14, 2017	January 15, 2022	US
5	NCT03105336	Relapsed/ Refractory iNHL	Phase 2	June 20, 2017	February 2022	US
6	NCT03761056 (ZUMA-12)	First-Line Therapy in Subjects With High-Risk Large B-Cell Lymphoma	Phase 2	January 29, 2019	April 2021	US
8	NCT03704298	Axicabtagene-Ciloleucel in Combination With Utomilumab in Subjects With Refractory Large B-Cell Lymphoma	1/2	November 20, 2018	February 2022	US

DLBCL=Diffuse Large B-Cell Lymphoma; iNHL=Indolent Non-Hodgkin Lymphoma

In addition to DLBCL and NHL, axicabtagene-ciloleucel is also currently under clinical development in earlier lines (e.g. first-line therapy in High-Risk Large B-Cell Lymphoma) or in combination with other immunotherapy like atezolizumab or utomilumab (see Table 5).

Table 6: List of ongoing clinical trials for brexucabtagene autoleucel (Kite/Gilead)

	NCT Number	Conditions	Phases	Start Date	Primary Completion Date	Locations
1	NCT03624036	Relapsed/Refractory CLL Relapsed/Refractory SLL	1	11/2018	03/2021	US
2	NCT02625480	ALL Relapsed Non Hodgkin Lymphoma Refractory Non-Hodgkin Lymphoma	1/2	02/2016	08/2023	US
3	NCT02614066	ALL	1/2	03/2016	08/2020	US

CLL= Chronic lymphocytic leukaemia; SLL= Small Lymphocytic Lymphoma; ALL= Acute Lymphoblastic Leukaemia;

In addition to MCL, brexucabtagene autoleucel is also currently in Phase 1/2 trials in acute lymphoblastic leukaemia and chronic lymphocytic leukaemia (see Table 6).

Allogeneic CAR T-cell therapy

Allogeneic CAR T-cell therapies are generated from healthy donor T-cells, as opposed to traditional CAR T-cell therapy which uses the patient's own T-cells (autologous). This approach is hypothesized to overcome some of the challenges experienced with traditional CAR T-cell therapy such as the potentially long time between apheresis and product manufacturing, during which time a patient's condition can deteriorate.

Our search in clinicaltrials.gov resulted in several allogeneic CAR T-cell therapies under development in phase 1/2 clinical trials (see Table 7).

Table 7: Allogeneic CAR T-cell therapies under development

	CAR- T technology	Conditions	Sponsor	Phases	NCT Number, location(s)	Start Date	Primary Completion Date
1	ALLO-501A	Relapsed/ Refractory Large B Cell Lymphoma	Allogene Therapeutics	1/2	NCT04416984, US	May 21, 2020	December 2022
2	PBCAR20A	Relapsed/ Refractory (r/r) Non-Hodgkin Lymphoma r/r Chronic Lymphocytic Leukaemia Small Lymphocytic Lymphoma	Precision BioSciences, Inc.	1/2	NCT04030195, US	March 24, 2020	July 2021
3	PBCAR0191	Relapsed/ Refractory (r/r) Non-Hodgkin Lymphoma r/r B-cell Acute Lymphoblastic Leukaemia	Precision BioSciences, Inc.	1/2	NCT03666000; US	March 11, 2019	July 2020
4	CARCIK-CD19	Adult and Paediatric Patients With Relapsed or Refractory B-cell Acute Lymphoblastic Leukaemia, After Hematopoietic Stem Cell Transplantation	Fondazione Matilde Tettamanti Menotti De Marchi Onlus	1/2	NCT03389035, Italy	December 20, 2017	December 31, 2020
5	UCART019*	Relapsed or Refractory CD19+ Leukaemia and Lymphoma	Chinese PLA General Hospital	1/2	NCT03166878, China	June 2017	May 2022
6	CTX110	Relapsed or Refractory B-Cell Malignancies	CRISPR Therapeutics AG	1/2	NCT04035434, US & EU	July 22, 2019	July 2026
7	PBCAR269A	Relapsed/ Refractory Multiple Myeloma	Precision BioSciences, Inc.	1/2	NCT04171843, US	April 30, 2020	May 2021

* UCART=Universal Chimeric Antigen Receptor T-cells ("off-the-shelf" allogeneic products) by Cellectics biopharmaceutical company

In-hospital production of CAR T-cell therapies

In contrast to the industrially manufactured CAR T-cell therapies, there are alternative systems for the CAR T-cell production in the hospital setting ("in-house production, in-hospital production or point-of-care production" of CAR T-cell therapies) under development. One of these systems is using CliniMACS Prodigy (Miltenyi Biotec™) [41] which allows cell preparation, enrichment, activation, transduction, expansion, final formulation, and sampling in a single device. Miltenyi Biotec™ has established a semi-automated manufacturing process that can be made available to academic settings for the systematic exploration of CAR strategies in advanced clinical studies.

Several ongoing clinical trials try to demonstrate the feasibility of manufacturing CAR T-cell products in the hospital-/academic setting. Table 8 presents an overview of identified clinical trials from clinicaltrials.gov using the point-of-care CAR T-cell production approach.

Table 8: Examples of clinical trials with point-of-care CAR T-cell production

	CAR- T technology	**Conditions**	**Sponsor/ Collaborators**	**Phase**	**NCT Number**	**Start Date**	**Primary Completion Date**
1	MB-CART20.1	Patients With Metastatic Melanoma	Miltenyi Biomedicine GmbH	1	NCT03893019	March 8, 2019	July 2021
2	MB-CART20.1	Relapsed or Resistant CD20 Positive B-NHL	Miltenyi Biomedicine GmbH	1/2	NCT03664635	September 25, 2018	February 10, 2022
3	MB-CART19.1	Relapsed or Refractory CD19 Positive B Cell Malignancies	Miltenyi Biomedicine GmbH	1/2	NCT03853616	November 26, 2018	July 2021
4	MB-CART2019.1	Relapsed or Resistant CD20 and CD19 Positive B-NHL	Miltenyi Biotec B.V. & Co. KG	1/2	NCT03870945	February 25, 2019	December 3, 2020
5	GD2 CAR T-cells	Diffuse Intrinsic Pontine Gliomas (DIPG) and Spinal Diffuse Midline Glioma	Crystal Mackall, MD| CureSearch (using Miltenyi CliniMACS Prodigy® system)	1	NCT04196413	June 4, 2020	December 2023
6	CLIC-1901 CAR-T cell (Canadian-Led Immuno-therapies)	Relapsed/ Refractory CD19 Positive Hematologic Malignancies	Ottawa Hospital Research Institute	1/2	NCT03765177	10/2019	10/2022
7	ARI-0001	CD19+ Leukaemia or Lymphoma Refractory to Therapy	Sara V. Latorre (In-hospital CAR-T cell production)	1	NCT03144583	06/2017	05/2021

8	SJCAR19	Paediatric and Young Adult Patients ≤ 21 Years of Age With Relapsed or Refractory CD19+ Acute Lymphoblastic Leukaemia	St. Jude Children's Research Hospital (using CliniMacs device)	1/2	NCT03573700	07/2018	07/2023
9	CAR-20/19-T	Relapsed and/or Refractory CD19 or CD20 Positive B Cell Malignancies	Medical College of Wisconsin (using the CliniMACS Prodigy device)	1	NCT03019055	10/2019	10/2022

5 Discussion

Currently, the US Food and Drug Administration has approved 3 chimeric antigen receptor (CAR) T-cell therapies: axicabtagene ciloleucel (Yescarta, Kite), tisagenlecleucel (Kymriah, Novartis) and brexucabtagene autoleucel (Tecartus, Kite). The European Medicines Agency by now has approved only axicabtagene ciloleucel and tisagenlecleucel. The third CAR T-cell therapy is still under review in the European Union. CAR T-cell therapies are a rapidly progressing field in oncology since promising results have been shown in the management of haematological malignancies [42-44], especially in relapsed/refractory patients. Although CAR T-cell technologies offer new treatment opportunities for cancer patients, these therapies will also raise new challenges to the health care system like uncertainty in efficacy and safety as they reach the market on the basis of early evidence, high costs for individual treatments due to an expensive manufacturing and delivery process, complex procedural requirements and specialized patient care before, during and after treatment as well as legal and ethical issues as these therapies are classified as gene therapy medicinal products, a subgroup of advanced therapy medicinal products. Therefore, we used a Horizon Scanning approach to identify new and emerging CAR T-cell therapies with a potential impact on the health care system in order to enable proactive planning and/or decision-making by policymakers and health care providers regarding the access, use and reimbursement of these therapies. This report was part of a project collaboration with the Austrian Institute for Health Technology Assessment and focused on CAR T-cell therapies for cancer treatment, whereas ATMPs in non-oncological indications and gene therapies under development are covered in a separate report [45].

Our search in clinical trial registries in June 2020 yielded more than 280 ongoing clinical trials investigating CAR T-cell therapies in phase 1/2 or later (see Appendix). The further analysis of these trials resulted in more than 60 different CAR T-cell technologies under development. The majority of these technologies (47/66) are examined in combined phase 1 and phase 2 clinical trials. If therapies show substantial benefit, they may be approved on the basis of these phase 1/2 data alone. Despite this impressive number of CAR T-cell candidates, only 13 technologies could be assigned a more advanced development stage and only three out of these are expected to reach the European market within the next two years:

- **Brexucabtagene Autoleucel (KTE-X19)** for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (by Kite, a Gilead Company)
- **Idecabtagene vicleucel (ide-cel; bb2121)** for patients with pre-treated relapsed and refractory multiple myeloma (by Bristol-Myers Squibb)
- **Lisocabtagene maraleucel (liso-cel; JCAR017)** for adult patients with relapsed or refractory large B-cell lymphoma after at least two prior therapies (by Bristol-Myers Squibb)

Moreover, the analysis of the identified clinical trials also posed the following three relevant issues regarding CAR T-cell technologies:

- Additional oncological indications for CAR T-cell therapies
- Off-the-shelf immunotherapies based on allogeneic gene-edited CAR T-cells

- In-hospital production of CAR T-cell therapies to overcome the time-consuming manufacturing and delivering process

Additional oncological indications

Promising results have been seen for CAR T-cell therapy as a treatment for leukaemia and lymphoma which has led to rapid proliferation of trials developing CAR T-cell therapies for a range of other cancers. Leukaemia and lymphoma are still two of the most commonly investigated indications of CAR T-cell clinical trials but the treatment approach is expanding to other malignancies.

- **Acute Lymphoblastic Leukaemia**
  Tisagenlecleucel was the first CAR T-cell therapy approved by the FDA and the EMA for therapy of children and young adults under 25 years with relapsed/refractory B-cell ALL. Despite the high initial response rate, the therapy is limited by life-threatening toxicities and the occurrence of relapses in a significant fraction of patients [46]. To overcome these limitations and to improve CAR T-cell therapy in patients with ALL novel developments like CD19/CD22 dual-target CAR T-cells, CAR T-cells targeting CD7 or CD38 or universal CAR T-cells are in phase 1 (2) clinical trials [47-49].

- **Chronic lymphocytic leukaemia**
  The efficacy of CAR T-cell therapy in CLL is currently lower than seen in ALL or DLBCL. Future improvements e.g. using alternatives to the currently preferred antigenic target in B lymphoid hemopathies, CD19, like CD23 or ROR1, could improve the results [50]. Although promising in the management of CLL, CAR T-cell technologies are still in early phase 1/2 clinical trials.

- **Acute Myeloid Leukaemia**
  AML has not shown the same successful outcomes with CAR T-cell therapy as ALL. An early focus of CAR-T cells for AML has been on CD123 and CD33 as targets. Two recently published articles conclude that CAR-T cell therapies in AML are limited by the insufficient selectivity of the currently approached CAR T targets and that identifying leukaemia-specific target antigens in AML remains the major challenge [51, 52].

- **Non-Hodgkin's lymphoma** including
  - diffuse large B cell lymphoma
  - transformed follicular lymphoma
  - primary mediastinal large B cell lymphoma
  - mantle cell lymphoma
  - indolent B cell lymphoma

  There are CAR T-cell therapies approved for the treatment of patients with DLBCL, PMBCL and since July 2020 for MCL. Although CD19 CAR T-cells showed promising results in these indications, some patients fail CAR T-cell therapy. Several mechanisms of relapse are described in literature including CD19 antigen loss, lack of CAR-T persistence, expression of immune checkpoint proteins on tumours cells, and phenotypic switch. To address these limitations,

several novel constructs are currently under clinical development like dual targeting CAR T-cells (CD19/CD22), armored CAR-T cell therapies or the combination of PD-1 inhibition with CAR-T cell therapy [42, 53]. CAR T-cell therapies for FL and indolent B cell lymphoma are still in clinical trials and the efficacy of CAR-T cell therapies in these indications has to be determined. Tisagenlecleucel is currently investigated in a phase 2, single arm, and multicentre, open label trial sponsored by Novartis in adult patients with refractory or relapsed follicular lymphoma. According to the company, regulatory filing for tisagenlecleucel in relapsed or refractory follicular lymphoma is anticipated in 2021.

- **Hodgkin's lymphoma**

  CD30 is an ideal target for CAR T-cell therapy of Hodgkin's lymphoma (HL), because HL cells express CD30 to a high degree. CD30 is also expressed on several activated T cells, making it more challenging to develop CD30 CAR T-cell therapy. Studies with CD30 CAR T-cell therapy have demonstrated great potential and may be relevant in patients with HL [43]. In February 2020, the FDA granted RMAT designation for CD30.CAR-T for patients with relapsed or refractory CD30-positive classical Hodgkin lymphoma. A pivotal Phase 2 clinical study to investigate this autologous CD30.CAR-T cell therapy program will be initiated in 2020. The results have to be awaited.

- **Multiple myeloma**

  Whilst no CAR T-cell therapy is currently approved by either the U.S. FDA or the EMA for use in patients with MM, several significant regulatory designations have been granted, making an approval of a CAR T-cell product in MM likely in the coming years. One potential candidate is idecabtagene vicleucel (ide-cel; bb2121) for patients with pre-treated relapsed and refractory MM. Bristol-Myers Squibb has already submitted a BLA to the FDA in March 2020 and the EMA has already granted Accelerated Assessment status to Ide-cel. Several other CAR T-cell technologies, mainly targeting the BCMA, have demonstrated promising clinical results in mostly heavily pre-treated patients with MM. These results are limited by potentially life-threatening complications and not durable responses. Therefore, phase 2/3 trials (bb2121 – NCT03651128; JNJ-4528 – NCT04181827) will further determine the suitability of anti-BCMA CAR T-cell therapy as a potential new treatment paradigm for MM [54, 55]. In addition to anti-BCMA CAR T-cell therapy, CAR T products targeting other cell surface antigens like CD138, SLAMF7, CD44v6 and CD38 are also in development [56-58].

In addition to indications like DLBCL, PMBCL, MCL and ALL, CAR T-cell therapies will be commercially available for patients with relapsed and refractory multiple myeloma in the near future, most likely followed by indications like FL and CLL. Currently the role of CAR-T cell therapy in these indications is limited to a refractory/relapsed setting but ongoing clinical trials already incorporate CAR T-cell therapies in treatment paradigms at multiple points.

For other indications like AML or HL (see above) as well as brain tumours [59] or solid tumours CAR T-cell therapies are still in an early stage of development. A large number of solid tumour CAR T-cells trials are currently ongoing, and additional clinical data is being generated rapidly. CAR T-cell therapy for solid tumours has shown promising results in early phases of clinical trials, but final results of most

of the trials are awaited. A review by Bagley et al. provides an overview on completed and ongoing clinical trials of CAR T-cells for solid tumours, as well as an overview of strategies to improve CAR T cell efficacy in non-hematologic malignancies and concluded that challenges related to CAR T cell trafficking to the tumour, expansion and persistence in a severely immunosuppressive tumour microenvironment, and antigen heterogeneity are among the main barriers to success identified in solid tumour studies thus far [60]. To date, despite a few interesting results, there is little evidence that CAR-T therapy can advance as a standard treatment option for patients with solid tumours [61-63].

Allogeneic CAR T-cell therapy

Manufacturing a personalized CAR T product takes time and is not always successful. To address that issue, the design of off-the-shelf CAR T strategies is being pursued by multiple groups [64, 65]. Genome-editing technologies including ZFN (zinc finger nuclease), TALEN (transcription activator-like effector nuclease), and CRISPR-Cas9 are being used to generate the universal third-party T-cells. In addition, split, universal, and programmable (SUPRA) CARs are being developed to enhance the flexibility and controllability of CAR T-cells [66]. CAR T-cells engineered from allogeneic donor T cells present an alternative to autologous CAR T cells and could circumvent the manufacturing issues of inadequate cell numbers, suboptimal T cell states and delays in treatment [67]. In addition, the development of universal CAR T cells will provide opportunities for upscaling of manufacturing and banking of the product. These improvements in manufacturing could potentially expand the access of patients with cancer to CAR T-cell therapies and might also lead to decreases in the substantial costs of CAR T-cell therapies [8]. Depil et al. [68] analysed the different sources of T cells for optimal allogeneic CAR-T cell therapy and describe the different technological approaches (mainly based on gene editing) to produce allogeneic CAR T-cells with limited potential for graft- versus-host disease. In their review they additionally give a comparison between autologous and allogeneic CAR T-cells (see Table 9) and provide an overview of the main programmes of allogeneic CAR-T cell development (preclinical and clinical development phase).

Our search in clinicaltrials.gov resulted in several allogeneic CAR T-cell therapies under development in early phase 1/2 clinical trials (see Table 7) but there are still key issues (e.g. risk of graft-versus-host disease (GvHD)) that need to be resolved before an application of universal CAR T cells outside of clinical trials is possible [16].

Table 9: Comparison between autologous and allogeneic CAR T-cells (by Depil et al.)

Characteristic	Autologous CAR T-cells	Allogeneic CAR T-cells
Origin of the donor	Patient	Healthy donor
Production and manufacturing process	Complex logistics; delay from leukapheresis to CAR T-cell administration; variations of T-cell characteristics according to the patient's immune characteristics and influence of previous treatments	Scaled-up industrialized process in which a high number of CAR T-cells can be produced and cryopreserved from a single donor; batches immediately available for patient treatment; possible standardization of T-cell characteristics

Clinical indications	Haematological malignancies (demonstrated activity); solid tumours	Haematological malignancies (ongoing trials); solid tumours
Main issues/risks	Cytokine release syndrome; CAR-related gene modifications; potential long-term side effects (B-cell aplasia for anti-CD19 CAR T-cells)	Cytokine release syndrome; CAR and/or gene editing-related gene modifications; GvHD; rejection of allogeneic cells; toxicity in the case of intense lymphodepletion
Persistence	Intermediate to long (months to years)	Short to intermediate (weeks to months)
Redosing	Limited by the number of cells	Not limited by the number of cells but risk of alloimmunization
Cost	Currently high (may decrease in the future)	Expected to be moderate

In-hospital production of CAR T-cell therapy

The manufacturing process of approved CAR T-cell therapies is currently an entirely hands-on manufacturing procedure and for Kymriah, Yescarta and Tecartus provided by the pharmaceutical company. Several limitations exist with this off-site commercial CAR-T cell production: (1) manufacturing can take several weeks, requires cryopreservation and shipping patient cells; (2) off-site manufacturing limits treatment options for patients with rapidly progressive disease; (3) high cost of the products may limit their availability. To address these challenges and to develop new CAR T-cell products, including phase 1 and 2 clinical trials, for many different targets and diseases in academic research centres, several countries are exploring an alternative decentralized CAR T-cell production mode ("in-house/point-of-care CAR T-cell production") e.g. based on the use of CliniMACS Prodigy, a semi-automated closed system by Miltenyi Biotech [41]. Several clinical trials are currently underway to investigate this manufacturing process (see Table 8) [69-71].

In-house CAR T-cell production (or non-industrially manufactured CAR T-cell therapies), must meet strict European requirements and the production must be authorized by the competent authorities at the national level (member state authorization for in-house manufacturing of CAR T-cells). In addition, in-house manufacturing requires a cell therapy department or a GMP facility on site and the production must follow current GMP regulations [72, 73].

The cost of CAR T cell immunotherapy is very high, the available CAR T-cell therapies currently cost approximately between € 300,000 to 400,000 and it takes about one month to make a specific CAR T-cell product for use in patients. Thus, many enterprises and institutions are now studying more efficient production strategies [74]. A decentralized (in-hospital) CAR T-cell production might be one less costly alternative to the current centralized production mode by pharmaceutical companies. Ran et al. recently examined the cost of an alternative method of T-cell production in Germany [75]. They estimated the "on-site" production costs of CAR T-cells in an academic non-profit setting based on data collected at a single site in Germany and using the CliniMACS Prodigy device for calculation. The authors found that for a clean room with one machine for closed and automated manufacturing installed, annual fixed costs summed up to approximately € 438,098 and the variable cost per production was roughly € 34,798. At the maximum capacity of one machine, total cost per product would be close to € 60,000 [75].

Outlook

Following almost three decades of development, CAR T-cell therapies have nowadays changed the landscape of cancer treatment. Although these concepts show promising efficacy results, several challenges remain and ongoing efforts therefore aim to

- improve CAR T-cell efficacy and safety [76-78]
- investigate the use of combination therapies (e.g. with anti-PD-1) [79-81]
- investigate a broader clinical application/new indications [62, 82, 83]
- find new targets/ multi-antigen targets [4, 84-86]
- investigate allogeneic (universal) CAR T-cells [87, 88]
- set up a decentralized CAR T-cell production process [69]

Limitation of the report

The search in clinical trial registries was based on the search terms “CAR-T cells, chimeric antigen receptor T Cells, and CAR-T cell therapy” with the cut-off date June 25, 2020. The search, data extraction and analysis of clinical trials were conducted by one person and not checked by a second author. We therefore might have missed studies or CAR T-cell technologies currently under development. However, the scope of this report was not a complete list of ongoing clinical trials on CAR T-cell therapies around the world but the identification of CAR T-cell therapies at a late stage of development and which are expected to reach the market within the next few years. Since our findings were supported by an additional intensive internet search in various sources, the possibility of missed technologies is estimated to be very low.

6 Conclusion & Recommendation

HSS has become an activity in many countries, meaning “keeping an eye on the future for upcoming change; understanding future medicines, devices and diagnostics, helping to shape policy, regulation, approvals and stimulating research activity” [89]. The present report was carried out in collaboration with the Austrian Institute for Health Technology Assessment and presents a “snapshot in time” of new and emerging CAR T-cell therapies in an advanced stage of development or close to approval.

This horizon scanning report found

- an increasing number of clinical trials investigating CAR T-cell technologies underway or planned which will lead to a rapidly evolving evidence base over the next few years;
- a significant expansion of CAR T-cell therapy research in terms of targets and cancers involved (e.g. new targets, multi-targets, expansion to solid tumours);
- that CAR T-cell therapy developments are largely in the research stage and only a few candidates are in a more advanced stage of clinical research or close to approval (not all clinical trials conducted so far have shown promising results);
- that three to five pipeline CAR T-cell technologies are likely to gain approval within the next 2 to 5 years to treat patients (since many studies have not yet been completed and therefore results are not available, a more precise forecast is not possible at present);
- that additional indications or the use in earlier lines of approved CD-19 directed CAR T-cell therapies (Kymriah, Yescarta, Tecartus) are most likely;
- that follicular lymphoma and multiple myeloma are the next new indications for which CAR T-cell therapy will be approved;
- that efforts are made to overcome limitations like availability and high costs by developing allogeneic (Universal) CAR T-cells or decentralized (in-hospital) manufacturing processes.

Based on this in-depth horizon scan and literature search the following remarks and recommendations can be made:

- There are still challenges of CAR T-cell therapy regarding long-term benefits (e.g. some patients fail to response or relapse early, unclear durability of response) and harms due to limited median follow-up of most studies. Therefore, clinical trials should be supported to generate further evidence.
- CAR T-cell technologies are classified as ATMP and their manufacturing and application furthermore raise ethical, legal and economic (cost and reimbursement) issues. These new challenges should be addressed by an open dialogue among all relevant stakeholders.
- Specialized and qualified CAR T-cell centres are vital to ensure accessibility and quality of care and to concentrate national research activities in this field. Regarding Austria, a close and ongoing exchange between policymakers and the Austrian CAR-T Cell Network (https://innere-med-1.meduniwien.ac.at/haematology/car-t-cell-network/) should be supported to address the challenges coming up with CAR T-cell therapies.
- Fast-track approval of CAR T-cell therapies by FDA and EMA make it necessary to continuously monitor clinical efficacy and safety of these technologies and to development frameworks for

their health technology assessment to support decision makers (e.g. CADTH: Life-Cycle Approach to Health Technology Assessment [90].

- Due to increasing research activities in the field of cancer immunotherapy, it is necessary to follow CAR T-cell therapy development over time by Horizon Scanning activities. As the present small scale HSS is time-consuming and inefficient as a one-time activity, it is recommended to join international initiatives with their systematic and permanent activities e.g. the BeNeLuxA initiative on Horizon Scanning: https://beneluxa.org/horizonscanning.

7 References

1. Gou, L., et al., *The landscape of CAR T-cell therapy in the United States and China: A comparative analysis.* Int J Cancer, 2019. **144**(8): p. 2043-2050.
2. Kruger, S., et al., *Advances in cancer immunotherapy 2019 - latest trends.* J Exp Clin Cancer Res, 2019. **38**(1): p. 268.
3. *Principles of cancer immunotherapy (available: https://www.uptodate.com/contents/principles-of-cancer-immunotherapy, cited: June 18, 2020)*.
4. Jackson, H.J., S. Rafiq, and R.J. Brentjens, *Driving CAR T-cells forward.* Nat Rev Clin Oncol, 2016. **13**(6): p. 370-83.
5. *Kymriah - European Medicines Agency (available: https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah, cited: June 18, 2020)*.
6. *Yescarta - European Medicines Agency (available: https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta, cited: June 18, 2020)*.
7. *FDA approves brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma (available: https://www.fda.gov/drugs/fda-approves-brexucabtagene-autoleucel-relapsed-or-refractory-mantle-cell-lymphoma, cited: July 28, 2020)*.
8. Rafiq, S., C.S. Hackett, and R.J. Brentjens, *Engineering strategies to overcome the current roadblocks in CAR T cell therapy.* Nat Rev Clin Oncol, 2020. **17**(3): p. 147-167.
9. Yu, S., et al., *Next generation chimeric antigen receptor T cells: safety strategies to overcome toxicity.* Mol Cancer, 2019. **18**(1): p. 125.
10. *CAR T-cell therapy. NIH - National Cancer Institute (available: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy, cited: July 27, 2020)*.
11. Holzinger, A. and H. Abken, *CAR T Cells: A Snapshot on the Growing Options to Design a CAR.* Hemasphere, 2019. **3**(1): p. e172.
12. Buechner, J., et al., *Chimeric Antigen Receptor-T Cell Therapy: Practical Considerations for Implementation in Europe.* Hemasphere, 2018. **2**(1): p. e18.
13. *Tecartus - Package Insert (available: https://www.fda.gov/media/140409/download, cited: July 28, 2020)*.
14. *KYMRIAH® (tisagenlecleucel) - Treatment Process (available: https://www.hcp.novartis.com/products/kymriah/acute-lymphoblastic-leukemia-children/treatment-process/, cited: July 27, 2020)*.
15. *CliniMACS Prodigy®- Cell production in a functionally closed and automated system (available: https://www.miltenyibiotec.com/US-en/products/cell-manufacturing-platform/clinimacs-prodigy.html#gref, cited: July 27, 2020)*.
16. Reuben, B., *Advances in Off-the-Shelf CAR T-Cell Therapy.* Clinical Advances in Hematology & Oncology, 2019. **17**(3 March 2019): p. 155-157.
17. *EMA - Human regulatory: Advanced therapies: marketing authorisation (ATMP) (available: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies-marketing-authorisation, cited: july 27, 2020)*.
18. Eder, C. and C. Wild, *Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption.* J Mark Access Health Policy, 2019. **7**(1): p. 1600939.
19. Geiger-Gritsch, S., *Horizon Scanning in Oncology – Concept Development for the Preparation of a Horizon Scanning System in Austria. HTA Project Report 2008; 14.* 2008.

20. Lepage-Nefkens, I., et al., *Horizon scanning for pharmaceuticals: proposal for the BeNeLuxA collaboration. .* Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2017. KCE Reports 283. D/2017/10.273/15., 2017.
21. Sinclair, A., S. Islam, and S. Jones, *Gene Therapy: An Overview of Approved and Pipeline Technologies*, in *CADTH Issues in Emerging Health Technologies*. 2016, Canadian Agency for Drugs and Technologies in Health Copyright © CADTH 2018.
22. *PCORI Issue Brief - Gene Therapy in 2019: Milestones and Challenges (available: https://www.pcori.org/sites/default/files/PCORI-Issue-Brief-Gene-Therapy-2019-Milestones-and-Challenges.pdf, cited: July 30, 2020)*. 2019.
23. Kew K, et al. *CAR T-cell therapy: a summary of evidence: an Evidence Check rapid review brokered by the Sax Institute (www.saxinstitute.org.au) for the NSW Ministry of Health, 2018 (available: https://www.saxinstitute.org.au/publications/car-t-cell-therapy-summary-evidence/, cited: July 30, 2020)*. 2018.
24. *EMA - Medicines under evaluation (available: https://www.ema.europa.eu/en/medicines/medicines-under-evaluation#2020, cited: July 27, 2020)*.
25. *Phase 2 Study of the Response and Safety of P-Bcma-101 CAR-T Cells in Patients with Relapsed/Refractory (r/r) Multiple Myeloma (MM) (PRIME) - ASH Publications 11/2019 (available: https://ashpublications.org/blood/article/134/Supplement_1/3184/423869/Phase-2-Study-of-the-Response-and-Safety-of-P-Bcma, cited: July 27, 2020)*.
26. *European Medicines Agency Validates Bristol Myers Squibb's Applications for Idecabtagene Vicleucel (Ide-cel, bb2121) and CC-486 (available: https://news.bms.com/press-release/corporatefinancial-news/european-medicines-agency-validates-bristol-myers-squibbs-ap-0, cited: July 27, 2020)*.
27. *Bristol Myers Squibb and bluebird bio Provide Regulatory Update on Idecabtagene Vicleucel (ide-cel, bb2121) for the Treatment of Patients with Multiple Myeloma (available: https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-and-bluebird-bio-provide-regulatory-updat, cited: July 27, 2020)*.
28. *Celgene Corporation Announces Initial Clinical Data from Ongoing Phase 1/2 Evolve Trial with Anti-BCMA CAR T Therapy JCARH125 in Relapsed/Refractory Multiple Myeloma at ASH 2018 (available: https://ir.celgene.com/press-releases-archive/press-release-details/2018/Celgene-Corporation-Announces-Initial-Clinical-Data-from-Ongoing-Phase-12-Evolve-Trial-with-Anti-BCMA-CAR-T-Therapy-JCARH125-in-RelapsedRefractory-Multiple-Myeloma-at-ASH-2018/default.aspx, cited: July 27, 2020)*.
29. *Janssen Presents Initial Results for BCMA CAR-T Therapy JNJ-4528 Showing Early, Deep and High Responses in the Treatment of Relapsed or Refractory Multiple Myeloma (available: https://www.jnj.com/janssen-presents-initial-results-for-bcma-car-t-therapy-jnj-4528-showing-early-deep-and-high-responses-in-the-treatment-of-relapsed-or-refractory-multiple-myeloma, cited: July 27, 2020)*.
30. *CARsgen's CT053 Receives RMAT Status from FDA for Multiple Myeloma Treatment (available: https://myelomaresearchnews.com/2019/10/30/carsgens-ct053-receives-rmat-status-from-fda-for-multiple-myeloma-treatment/, cited: July 27, 2020).*
31. *ASH 2019 - Efficacy and Safety of Fully Human Bcma Targeting CAR T Cell Therapy in Relapsed/Refractory Multiple Myeloma (available: https://ashpublications.org/blood/article/134/Supplement_1/929/426483/Efficacy-and-Safety-of-Fully-Human-Bcma-Targeting, cited: July 27, 2020)*.

32. *FDA Clears IND for Mustang Bio's MB-102 (CD123 CAR T) (available: https://pipelinereview.com/index.php/2019080671960/DNA-RNA-and-Cells/FDA-Clears-IND-for-Mustang-Bios-MB-102-CD123-CAR-T.html, cited: July 27, 2020)*.
33. *ASH 2019 - Phase I Study of AUTO3, a Bicistronic Chimeric Antigen Receptor (CAR) T-Cell Therapy Targeting CD19 and CD22, in Pediatric Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia (r/r B-ALL): Amelia Study (available: https://ashpublications.org/blood/article/134/Supplement_1/2620/423305/Phase-I-Study-of-AUTO3-a-Bicistronic-Chimeric, cited: July 27, 2020)*.
34. *Autolus Therapeutics Announces New Data Showcasing Clinical Progress of AUTO3 in B Cell Malignancies (available: https://www.globenewswire.com/news-release/2019/12/08/1957575/0/en/Autolus-Therapeutics-Announces-New-Data-Showcasing-Clinical-Progress-of-AUTO3-in-B-Cell-Malignancies.html, cited: July 27, 2020)*.
35. *U.S. FDA Accepts Priority Review for Lisocabtagene Maraleucel R/R Large B-Cell Lymphoma (available: https://www.oncozine.com/u-s-fda-accepts-priority-review-for-lisocabtagene-maraleucel-r-r-large-b-cell-lymphoma/, cited: July 27, 2020)*.
36. *EMA to Review Liso-cel as CAR T-cell Therapy for Advanced Lymphomas (available: https://immuno-oncologynews.com/2020/07/22/ema-reviewing-liso-cell-car-t-cell-therapy-for-relapsed-refractory-lymphomas/, cited: July 27, 2020)*.
37. *Kite Submits Biologics License Application to U.S. Food and Drug Administration for Company's Second CAR T Cell Therapy (available: https://www.gilead.com/news-and-press/press-room/press-releases/2019/12/kite-submits-biologics-license-application-to-us-food-and-drug-administration-for-companys-second-car-t-cell-therapy, cited: July 27, 2020)*.
38. Wang, M., et al., *KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma.* N Engl J Med, 2020. **382**(14): p. 1331-1342.
39. *FDA Approves Brexucabtagene Autoleucel for Relapsed/Refractory Mantle Cell Lymphoma (availabel: https://www.cancernetwork.com/view/fda-approves-brexucabtagene-autoleucel-for-relapsed-refractory-mantle-cell-lymphoma, cited: July 27, 2020)*.
40. *Tessa Therapeutics Announces U.S. FDA Regenerative Medicine Advanced Therapy (RMAT) Designation Granted to its CD30 CAR-T Cell Therapy for the Treatment of Relapsed or Refractory CD30-positive Classical Hodgkin Lymphoma (available: https://www.tessatherapeutics.com/2020/02/27/tessa-therapeutics-announces-u-s-fda-regenerative-medicine-advanced-therapy-rmat-designation-granted-to-its-cd30-car-t-cell-therapy-for-the-treatment-of-relapsed-or-refractory-cd30-positive-classic/, cited: July27, 2020)*.
41. *CliniMACS Prodigy®- Cell production in a functionally closed and automated system (Miltenyi Biotec) (available: https://www.miltenyibiotec.com/US-en/products/cell-manufacturing-platform/clinimacs-prodigy.html#gref, cited: July 27, 2020)*.
42. Abramson, J.S., *Anti-CD19 CAR T-Cell Therapy for B-Cell Non-Hodgkin Lymphoma.* Transfus Med Rev, 2020. **34**(1): p. 29-33.
43. Yang, X., G.X. Wang, and J.F. Zhou, *CAR T Cell Therapy for Hematological Malignancies*. Curr Med Sci, 2019. **39**(6): p. 874-882.
44. Locke, F.L., et al., *Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial.* Lancet Oncol, 2019. **20**(1): p. 31-42.
45. Wild C, Wohlhöfner K, and Grössmann N, *ATMP and Gene Therapies in Development, Horizon Scanning. AIHTA Policy Brief Nr.: 006b; 2020. Wien: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.*
46. Greinix, H., *Role of CAR-T cell therapy in B-cell acute lymphoblastic leukemia.* memo, 2020. **13**: p. 36-42.

47. Malard, F. and M. Mohty, *Acute lymphoblastic leukaemia.* Lancet, 2020. **395**(10230): p. 1146-1162.
48. Simioni, C., et al., *New biomarkers and therapeutic strategies in acute lymphoblastic leukemias: Recent advances.* Hematol Oncol, 2020. **38**(1): p. 22-33.
49. Zhao, J., Y. Song, and D. Liu, *Clinical trials of dual-target CAR T cells, donor-derived CAR T cells, and universal CAR T cells for acute lymphoid leukemia.* J Hematol Oncol, 2019. **12**(1): p. 17.
50. Lemal, R. and O. Tournilhac, *State-of-the-art for CAR T-cell therapy for chronic lymphocytic leukemia in 2019.* J Immunother Cancer, 2019. **7**(1): p. 202.
51. Rudzki, J. and D. Wolf, *AML—is it time to drive a CAR(-T)?* memo, 2020. **13**: p. 50-54.
52. Sauer, T. and C.M. Rooney, *Current challenges for CAR T-cell therapy of acute myeloid leukemia.* Transfusion, 2019. **59**(4): p. 1171-1173.
53. Levin, A. and N.N. Shah, *Chimeric antigen receptor modified T cell therapy in B cell non-Hodgkin lymphomas.* Am J Hematol, 2019. **94**(S1): p. S18-s23.
54. Cho, S.F., et al., *BCMA-Targeting Therapy: Driving a New Era of Immunotherapy in Multiple Myeloma.* Cancers (Basel), 2020. **12**(6).
55. D'Agostino, M. and N. Raje, *Anti-BCMA CAR T-cell therapy in multiple myeloma: can we do better?* Leukemia, 2020. **34**(1): p. 21-34.
56. Steiner, N. and E. Gunsilius, *CAR-T cells in multiple myeloma: current status.* memo, 2020. **13**: p. 43-49.
57. Martin, T. and C.A. Huff, *Multiple Myeloma: Current Advances and Future Directions.* Clin Lymphoma Myeloma Leuk, 2019. **19**(5): p. 255-263.
58. Wu, C., et al., *Chimeric antigen receptor T cell therapies for multiple myeloma.* J Hematol Oncol, 2019. **12**(1): p. 120.
59. Akhavan, D., et al., *CAR T cells for brain tumors: Lessons learned and road ahead.* Immunol Rev, 2019. **290**(1): p. 60-84.
60. Bagley, S.J. and D.M. O'Rourke, *Clinical investigation of CAR T cells for solid tumors: Lessons learned and future directions.* Pharmacol Ther, 2020. **205**: p. 107419.
61. Ma, S., et al., *Current Progress in CAR-T Cell Therapy for Solid Tumors.* Int J Biol Sci, 2019. **15**(12): p. 2548-2560.
62. Metzinger, M.N., et al., *Chimeric Antigen Receptor T-Cell Therapy: Reach to Solid Tumor Experience.* Oncology, 2019. **97**(2): p. 59-74.
63. Springuel, L., et al., *Chimeric Antigen Receptor-T Cells for Targeting Solid Tumors: Current Challenges and Existing Strategies.* BioDrugs, 2019. **33**(5): p. 515-537.
64. McCreedy, B.J., V.V. Senyukov, and K.T. Nguyen, *Off the shelf T cell therapies for hematologic malignancies.* Best Pract Res Clin Haematol, 2018. **31**(2): p. 166-175.
65. Harrison, R.P., et al., *Chimeric antigen receptor-T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods.* Cytotherapy, 2019. **21**(2): p. 224-233.
66. Zhao, J., et al., *Universal CARs, universal T cells, and universal CAR T cells.* J Hematol Oncol, 2018. **11**(1): p. 132.
67. Qasim, W., *Allogeneic CAR T cell therapies for leukemia.* Am J Hematol, 2019. **94**(S1): p. S50-s54.
68. Depil, S., et al., *'Off-the-shelf' allogeneic CAR T cells: development and challenges.* Nat Rev Drug Discov, 2020. **19**(3): p. 185-199.
69. Castella, M., et al., *Point-Of-Care CAR T-Cell Production (ARI-0001) Using a Closed Semi-automatic Bioreactor: Experience From an Academic Phase I Clinical Trial.* Front Immunol, 2020. **11**: p. 482.

70. Jacoby, E., et al., *Locally produced CD19 CAR T cells leading to clinical remissions in medullary and extramedullary relapsed acute lymphoblastic leukemia.* Am J Hematol, 2018. **93**(12): p. 1485-1492.
71. Zhu, F., N. Shah, and D. Schneider, *Automated Manufacturing of CD20.19 Bi-Specific Chimeric Antigen Receptor T (CAR-T) Cells at an Academic Center for a Phase I Clinical Trial in Relapsed, Refractory NHL.* Biology of Blood and Marrow Transplantation, 2019. **25**(3): p. S62.
72. Gee, A.P., *GMP CAR-T cell production.* Best Pract Res Clin Haematol, 2018. **31**(2): p. 126-134.
73. *EHA Guidance Document The process of CAR-T cell therapy in Europe.* Hemasphere, 2019. **3**(4): p. e280.
74. Zhao, L. and Y.J. Cao, *Engineered T Cell Therapy for Cancer in the Clinic.* Front Immunol, 2019. **10**: p. 2250.
75. Ran, T., et al., *Cost of decentralized CAR T-cell production in an academic nonprofit setting.* Int J Cancer, 2020.
76. Grigor, E.J.M., et al., *Risks and Benefits of Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Cancer: A Systematic Review and Meta-Analysis.* Transfus Med Rev, 2019. **33**(2): p. 98-110.
77. Yadav, R.K., et al., *CAR T cell therapy: newer approaches to counter resistance and cost.* Heliyon, 2020. **6**(4): p. e03779.
78. Hartmann, J., et al., *Clinical development of CAR T cells-challenges and opportunities in translating innovative treatment concepts.* EMBO Mol Med, 2017. **9**(9): p. 1183-1197.
79. Wang, H., et al., *Immune checkpoint blockade and CAR-T cell therapy in hematologic malignancies.* J Hematol Oncol, 2019. **12**(1): p. 59.
80. Grosser, R., et al., *Combination Immunotherapy with CAR T Cells and Checkpoint Blockade for the Treatment of Solid Tumors.* Cancer Cell, 2019. **36**(5): p. 471-482.
81. Yoon, D.H., et al., *Incorporation of Immune Checkpoint Blockade into Chimeric Antigen Receptor T Cells (CAR-Ts): Combination or Built-In CAR-T.* Int J Mol Sci, 2018. **19**(2).
82. Charrot, S. and S. Hakllam. *CAR-T Cells: Future Perspectives HemaSphere: April 2019 - Volume 3 - Issue 2 - p e188 (available: https://journals.lww.com/hemasphere/Fulltext/2019/04000/CAR_T_Cells__Future_Perspectives.2.aspx, cited: July 30, 2020)*. 2019.
83. Mohanty, R., et al., *CAR T cell therapy: A new era for cancer treatment (Review).* Oncol Rep, 2019. **42**(6): p. 2183-2195.
84. Wei, J., et al., *Target selection for CAR-T therapy.* J Hematol Oncol, 2019. **12**(1): p. 62.
85. Han, X., et al., *Multi-antigen-targeted chimeric antigen receptor T cells for cancer therapy.* J Hematol Oncol, 2019. **12**(1): p. 128.
86. Sermer, D. and R. Brentjens, *CAR T-cell therapy: Full speed ahead.* Hematol Oncol, 2019. **37 Suppl 1**: p. 95-100.
87. Daniyan, A.F. and R.J. Brentjens, *CARs of the future.* Am J Hematol, 2019. **94**(S1): p. S55-s58.
88. Calmels, B., B. Mfarrej, and C. Chabannon, *From clinical proof-of-concept to commercialization of CAR T cells.* Drug Discov Today, 2018. **23**(4): p. 758-762.
89. *National Institute for Health Research (NIHR) Innovation Observatory "What is 'horizon scanning?' And what does the Innovation Observatory do?" (available: http://www.io.nihr.ac.uk/what-we-do/, cited: July 30, 2020)*.
90. *CADTH 2018–2021 STRATEGIC PLAN - Life-Cycle Approach to Health Technology Assessment (available: https://cadth.ca/sites/default/files/corporate/planning_documents/CADTH_2018-2021_Strategic_Plan.pdf, cited: August 3, 2020)*.

8 Appendix

Search strategy for clinical trial registries

1) **ClinicalTrials.gov (https://clinicaltrials.gov/) - June 16, 2020:**

Search: 175 Studies found for the following terms:

Chimeric Antigen Receptor T Cells AND CAR-T cells AND CAR-T cell therapy | Phase 2, 3, 4 (applied filters: study phase)

https://clinicaltrials.gov/ct2/results?term=Chimeric+Antigen+Receptor+T+Cells+AND+CAR-T+cells+AND+CAR-T+cell+therapy&phase=123

2) **WHO International Clinical Trials Registry Platform (ICTRP) http://apps.who.int/trialsearch/ - June 24, 2020**

Search: chimeric antigen receptor OR CAR T (applied filter: Phase 2/3/4)

288 trials found for: chimeric antigen receptor OR CAR T

3) **EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search) – June 25, 2020**

58 result(s) found for: "CAR T" OR "chimeric antigen receptor" (Trials with EudraCT protocol)

https://www.clinicaltrialsregister.eu/ctr-search/search?query=%22CAR+T%22+OR+%22chimeric+antigen+receptor%22

Search results from clinical trial registries

*Table 10: Overview of CAR-T Cell products in clinical trials: results from clinicaltrials.gov**

	NCT Number	Title	Status	Conditions	Interventions	Sponsor/ Collaborators	Phase	Number of patients	Start Date	Completion Date
1	NCT03628612	Long-term Follow-up of Patients Treated With Autologous T Cells Genetically Modified	Enrolling by invitation	Multiple Myeloma|DLBCL|ALL, Pediatric|T Cell Lymphoma	Biological: AUTO CAR T cell therapy	Autolus Limited	2	500	August 3, 2018	December 2032
2	NCT04271644	BCMA-Targeted CAR-T Cell Therapy for Relapsed/Refractory Multiple Myeloma	Recruiting	Multiple Myeloma|Neoplasm, Plasma Cell|Multiple Myeloma in Relapse	Biological: BCMA CAR-T cells	Chongqing Precision Biotech Co., Ltd	1/2	80	April 1, 2019	July 1, 2023
3	NCT03919240	CAR-T Cell Therapy Targeting to CD19 for R/R ALL	Recruiting	Acute Lymphoblastic Leukaemia With Failed Remission	Biological: CAR T-cell therapy	The First Affiliated Hospital of Soochow University|Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd	1/2	50	December 1, 2015	December 31, 2023
4	NCT04271410	CD19-Targeted CAR-T Cell Therapy for Relapsed/Refractory CD19+ B Cell Leukaemia and Lymphoma	Recruiting	Leukemia|Lymphoma, Large B-Cell, Diffuse|Leukemia, B-cell|Lymphoma, B-Cell|Leukemia, Lymphocytic, Chronic, B-Cell	Biological: CD19 CAR-T cells	Chongqing Precision Biotech Co., Ltd	1/2	80	June 1, 2019	July 1, 2022
5	NCT03631576	CD123/CLL1 CAR-T Cells for R/R AML (STPHI_0001)	Recruiting	Relapsed/Refractory AML	Biological: CD123/CLL1 CAR-T Cells	Fujian Medical University	2/3	20	August 10, 2018	August 10, 2021
6	NCT04265963	CD123-Targeted CAR-T Cell Therapy for Relapsed/Refractory Acute Myeloid Leukemia	Recruiting	Leukemia|Leukemia Myeloid|Leukemia, Myeloid, Acute	Biological: CD123 CAR-T cells	Chongqing Precision Biotech Co., Ltd	1/2	45	September 1, 2019	July 1, 2022
7	NCT02737085	the Sequential Therapy of CD19-targeted and CD20-targeted CAR-T Cell Therapy for Diffuse Large B Cell Lymphoma(DLBCL)	Unknown status	Lymphoma, Large B-Cell, Diffuse	Biological: Anti-CD19 CAR-T cells and Anti-CD20 CAR-T cells	Southwest Hospital, China	1/2	40	March 2016	December 2019

8	NCT04272151	Safety and Efficacy of BCMA-Targeted CAR-T Therapy for Relapsed/Refractory Multiple Myeloma	Recruiting	Multiple Myeloma|Multiple Myeloma in Relapse|Neoplasm, Plasma Cell	Biological: BCMA CAR-T cells	Chongqing Precision Biotech Co., Ltd	1/2	40	December 1, 2019	July 1, 2023
9	NCT02537977	CD19-directed CAR T Cells Therapy in Relapsed/Refractory B Cell Malignancy	Recruiting	Leukemia| Lymphoma	Biological: CD19-directed CAR-T cells	Shanghai Tongji Hospital, Tongji University School of Medicine	1/2	60	July 2015	June 2020
10	NCT04271800	Safety and Efficacy of CD19-Targeted CAR-T Therapy for Relapsed/Refractory CD19+ B Cell Leukemia and Lymphoma	Recruiting	Leukemia|Lymphoma|Leukemia, B-Cell|Leukemia, Lymphocytic, Chronic, B-Cell	Biological: CD19 CAR-T cells	Chongqing Precision Biotech Co., Ltd	1/2	40	December 1, 2019	July 1, 2023
11	NCT04272125	Safety and Efficacy of CD123-Targeted CAR-T Therapy for Relapsed/Refractory Acute Myeloid Leukemia	Recruiting	Leukemia|Leukemia Myeloid|Leukemia, Myeloid, Acute	Biological: CD123 CAR-T cells	Chongqing Precision Biotech Co., Ltd	1/2	40	December 1, 2019	July 1, 2023
12	NCT04287660	Study of BiRd Regimen Combined With BCMA CAR T-cell Therapy in Newly Diagnosed Multiple Myeloma (MM) Patients	Recruiting	Multiple Myeloma	Drug: clarithromycin, lenalidomide, dexamethasone and autologous BCMA-directed CAR T-cells	The First Affiliated Hospital of Soochow University| Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd	3	30	October 19, 2017	January 31, 2024
13	NCT04010877	Multiple CAR-T Cell Therapy Targeting AML	Recruiting	Acute Myeloid Leukemia	Biological: CLL-1, CD33 and/or CD123-specific CAR gene-engineered T cells	Shenzhen Geno-Immune Medical Institute	1/2	10	August 1, 2019	December 31, 2023
14	NCT03916679	MESO-CAR T Cells Therapy for Relapsed and Refractory Epithelial Ovarian Cancer	Recruiting	Ovarian Cancer	Biological: anti-MESO CAR-T cells	Second Affiliated Hospital, School of Medicine, Zhejiang University	1/2	20	April 20, 2019	April 20, 2023
15	NCT03222674	Multi-CAR T Cell Therapy for Acute Myeloid Leukemia	Recruiting	Acute Myeloid Leukemia	Biological: Muc1/CLL1/CD33/CD38/CD56/CD123-specific gene-engineered T cells	Shenzhen Geno-Immune Medical Institute| Zhujiang Hospital, China	1/2	10	July 15, 2017	December 31, 2020
16	NCT04163302	Safety and Efficiency Study of CD19-PD1-CART Cell in	Recruiting	Lymphoma, B-Cell	Biological: CD19-PD1-CART Cell	Chinese PLA General Hospital	2	30	July 7, 2019	July 1, 2022

		Relapsed/Refractory B Cell Lymphoma								
17	NCT04162119	Safety and Efficiency Study of BCMA-PD1-CART Cells in Relapsed/Refractory Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: BCMA-PD1-CART Cell	Chinese PLA General Hospital	2	30	July 7, 2019	October 10, 2022
18	NCT04033302	Multi-CAR T Cell Therapy Targeting CD7-positive Malignancies	Recruiting	T-cell Acute Lymphoblastic Leukemia|T-cell Acute Lymphoblastic Lymphoma|Acute Myeloid Leukemia|NK Cell Lymphoma	Biological: CD7-specific CAR gene-engineered T cells	Shenzhen Geno-Immune Medical Institute	1/2	30	September 1, 2019	December 31, 2023
19	NCT03271632	Multi-CAR T Cell Therapy in the Treatment of Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: CAR T cells	Shenzhen Geno-Immune Medical Institute	1/2	20	July 15, 2017	December 31, 2020
20	NCT04206943	Study of CD19 Specific Chimeric Antigen Receptor Positive T Cells (CAR-T) in ALL and NHL	Recruiting	Acute Lymphoblastic Leukemia|Non Hodgkin Lymphoma	Biological: Car-T Cell Therapy	Acibadem University| |The Scientific and Technological Research Council of Turkey|	1/2	24	October 12, 2019	January 1, 2021
21	NCT04348643	Safety and Efficacy of CEA-Targeted CAR-T Therapy for Relapsed/Refractory CEA+ Cancer	Recruiting	Solid Tumor|Lung Cancer|Colorectal Cancer|Liver Cancer|Pancreatic Cancer|Gastric Cancer|Breast Cancer	Biological: CEA CAR-T cells	Chongqing Precision Biotech Co., Ltd	1/2	40	April 20, 2020	April 30, 2023
22	NCT04429438	Multi-CAR-T Cells Targeting B Cell Lymphomas	Recruiting	B Cell Lymphoma (BCL)	Biological: 4SCAR19 and 4SCAR20/22/70/PSMA/13/79b/GD2	Shenzhen Geno-Immune Medical Institute|The Seventh Affilliated Hospital, Sun Yat-Sen University|Shenzhen Children's Hospital	1/2	11	June 1, 2020	December 31, 2023
23	NCT03125577	Combination CAR-T Cell Therapy Targeting Hematological Malignancies	Recruiting	B-cell Malignancies	Biological: 4SCAR19 and 4SCAR22|Biological: 4SCAR19 and 4SCAR38|Biological:	Shenzhen Geno-Immune Medical Institute	1/2	100	July 15, 2017	December 2021

					4SCAR19 and 4SCAR20|Biological: 4SCAR19 and 4SCAR123|Biological: 4SCAR19 and 4SCAR70|Biological: 4SCAR19 and 4SCAR30					
24	NCT04097301	Study of CAR T-cell Therapy in Acute Myeloid Leukemia and Multiple Myeloma	Recruiting	Acute Myeloid Leukemia|Multiple Myeloma	Drug: MLM-CAR44.1 T-cells, cyclophosphamide and fludarabine from -5 to -3	MolMed S.p.A.|Horizon 2020 - European Commission	1/2	58	August 27, 2019	June 28, 2023
25	NCT03468153	Dual Specificity CD19 and CD22 CAR-T Cell Immunotherapy for CD19+CD22+ Relapsed and Refractory Lymphoma	Unknown status	Lymphoma	Biological: Dual Specificity CD19 and CD22 CAR-T Cell Immunotherapy	Ruijin Hospital|Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd	1/2	10	January 1, 2018	January 1, 2020
26	NCT02782351	Humanized CAR-T Therapy for Treatment of B Cell Malignancy	Unknown status	Leukemia, Lymphocytic, Chronic, B-Cell	Biological: CAR-T	Kai Lin Xu	1/2	50	May 2016	December 2018
27	NCT03767751	A Feasibility and Safety Study of Dual Specificity CD38 and BCMA CAR-T Cell Immunotherapy for Relapsed or Refractory Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: Dual Specificity CD38 and bcma CAR-T Cells	Chinese PLA General Hospital	1/2	80	December 5, 2018	December 5, 2022
28	NCT04429451	PSMA-specific CAR-T Cell Therapy	Recruiting	PSMA Positive Tumors or Tumor Tissues	Biological: 4SCAR-PSMA T cells	Shenzhen Geno-Immune Medical Institute|Shenzhen Children's Hospital|The Seventh Affilliated Hospital, Sun Yat-Sen University|Shenzhen Hospital of Southern Medical University	1/2	100	January 1, 2020	December 31, 2024
29	NCT03754764	A Feasibility and Safety Study of CD38 CAR-T Cell Immunotherapy for Relapsed B-cell Acute Lymphoblastic Leukemia After CD19 CAR-T Adoptive Cellular Immunotherapy	Recruiting	Relapsed B-cell Acute Lymphoblastic Leukemia After CD19 CAR-T ACI	Biological: Specificity CD38 CAR-T Cells	Chinese PLA General Hospital	1/2	80	November 23, 2018	November 23, 2022

30	NCT03398967	A Feasibility and Safety Study of Universal Dual Specificity CD19 and CD20 or CD22 CAR-T Cell Immunotherapy for Relapsed or Refractory Leukemia and Lymphoma	Recruiting	B Cell Leukemia|B Cell Lymphoma	Biological: Universal Dual Specificity CD19 and CD20 or CD22 CAR-T Cells	Chinese PLA General Hospital	1/2	80	January 2, 2018	May 20, 2022
31	NCT03366324	Anti-CD19 CAR-T Therapy Combine With HSCT to Treat MRD+ B-cell Malignancies	Recruiting	Acute Lymphoblastic Leukemia|B Cell Lymphoma	Genetic: Second generation CAR-T cells|Procedure: Hematological stem cell transplantation	Wuhan Sian Medical Technology Co., Ltd|Wuhan Union Hospital, China|Jingzhou Central Hospital|Xiangyang Central Hospital|The First People's Hospital of Yuhang District	1/2	20	May 1, 2016	June 1, 2021
32	NCT04257578	Acalabrutinib and Anti-CD19 CAR T-cell Therapy for the Treatment of B-cell Lymphoma	Not yet recruiting	B-Cell Non-Hodgkin Lymphoma|Diffuse Large B-Cell Lymphoma, Not Otherwise Specified|High Grade B-Cell Lymphoma|Primary Mediastinal (Thymic) Large B-Cell Lymphoma|Transformed Follicular Lymphoma to Diffuse Large B-Cell Lymphoma	Drug: Acalabrutinib|Biological: Axicabtagene Ciloleucel	University of Washington|National Cancer Institute (NCI)|AstraZeneca	1/2	20	July 6, 2020	March 1, 2029
33	NCT03262298	Anti-CD22 CAR-T Cell Therapy Targeting B Cell Malignancies	Recruiting	Leukemia| Lymphoma	Biological: Anti-CD22-CAR-transduced T cells	Affiliated Hospital to Academy of Military Medical Sciences	1/2	20	August 20, 2017	August 20, 2021
34	NCT04404660	A Study of CD19 Targeted CAR T Cell Therapy in Adult Patients With Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia (ALL)	Recruiting	Relapsed or Refractory B Cell Acute Lymphoblastic Leukemia	Biological: AUTO1	Autolus Limited	1/2	145	March 4, 2020	Apr.24

35	NCT03684889	CD19-specific CAR T Cells With a Fully Human Binding Domain for CD19+ Leukemia or Lymphoma	Active, not recruiting	Leukemia|Lymphoma	Biological: SCRI-huCAR19v1	Seattle Children's Hospital	1/2	112	November 28, 2018	December 2036
36	NCT03013712	A Clinical Research of CAR T Cells Targeting EpCAM Positive Cancer	Recruiting	Colon Cancer|Esophageal Carcinoma|Pancreatic Cancer|Prostate Cancer|Gastric Cancer|Hepatic Carcinoma	Biological: CAR-T cell immunotherapy	First Affiliated Hospital of Chengdu Medical College	1/2	60	January 2017	December 2020
37	NCT04416984	Safety and Efficacy of ALLO-501A Anti-CD19 Allogeneic CAR T Cells in Adults With Relapsed/Refractory Large B Cell Lymphoma (ALPHA-2)	Recruiting	Relapsed/Refractory Large B Cell Lymphoma	Genetic: ALLO-501A|Biological: ALLO-647|Drug: Fludarabine|Drug: Cyclophosphamide	Allogene Therapeutics	1/2	120	May 21, 2020	December 2022
38	NCT03984968	CD19 CAR-T Consolidation Therapy for Acute Lymphoblastic Leukemia	Enrolling by invitation	Acute Lymphoblastic Leukemia, Adult B-Cell	Biological: CAR-T infusion	The First Affiliated Hospital of Soochow University	2	10	January 1, 2018	June 30, 2022
39	NCT03525782	Anti-MUC1 CAR T Cells and PD-1 Knockout Engineered T Cells for NSCLC	Recruiting	Lung Neoplasm Malignant|Non-small Cell Lung Cancer	Biological: CAR-T Cells|Combination Product: CAR-T combining PD-1 Knockout|Biological: PD-1 knockout|Drug: PD-1 mAb|Other: Sham control	The First Affiliated Hospital of Guangdong Pharmaceutical University|Guangzhou Anjie Biomedical Technology Co., Ltd.|University of Technology, Sydney	1/2	60	February 1, 2018	January 31, 2022
40	NCT02965092	CD19 Chimeric Antigen Receptor (CAR)-Modified T Cell Therapy in Treating Patients With B-cell Malignancies	Recruiting	Acute Lymphoblastic Leukemia|B Cell Lymphoma	Genetic: Second generation CAR-T cells	Wuhan Sian Medical Technology Co., Ltd|Wuhan Union Hospital, China|Jingzhou Central Hospital|Xiangyang Central Hospital|People Hospital Of Yichang	1/2	80	December 2, 2015	December 2021

41	NCT04406610	CAR-T Cell Immunotherapy for GD2 Positive Glioma Patients	Terminated	Glioma of Brain|CAR-T Cell Immunotherapy	Biological: GD2 CAR-T immunotherapy	Fuda Cancer Hospital, Guangzhou	1/2	2	September 1, 2015	August 15, 2017
42	NCT03929107	Interleukin-7 and Chemokine (C-C Motif) Ligand 19-expressing CD19-CAR-T for Refractory/Relapsed B Cell Lymphoma.	Recruiting	B Cell Lymphoma	Biological: Interleukin-7 and Chemokine (C-C Motif) Ligand 19-expressing CD19-CAR-T cells	Wenbin Qian|Zhejiang Provincial Tongde Hospital|First Affiliated Hospital of Zhejiang University	2	80	March 28, 2019	April 30, 2022
43	NCT02903810	Combination Transfer of αCD19-TCRz-41BB and αCD22-TCRz-41BB CAR-T Cells for B-cell Hematologic Malignancy	Unknown status	Hematopoietic/ Lymphoid Cancer	Biological: Mixed CAR-T Transfer	Xuzhou Medical University	1/2	20	Sep.16	December 2019
44	NCT03179007	CTLA-4 and PD-1 Antibodies Expressing MUC1-CAR-T Cells for MUC1 Positive Advanced Solid Tumor	Unknown status	Advanced Solid Tumor	Biological: Anti-CTLA-4/PD-1 expressing MUC1-CAR-T	Shanghai Cell Therapy Research Institute	1/2	40	June 7, 2017	April 20, 2019
45	NCT03971799	Study of Anti-CD33 Chimeric Antigen Receptor-Expressing T Cells (CD33CART) in Children and Young Adults With Relapsed/Refractory Acute Myeloid Leukemia	Recruiting	Acute Myelogenous Leukemia	Biological: CD33CART	Center for International Blood and Marrow Transplant Research|National Marrow Donor Program|St. Baldrick's Foundation	1/2	34	January 8, 2020	December 2039
46	NCT03182816	CTLA-4 and PD-1 Antibodies Expressing EGFR-CAR-T Cells for EGFR Positive Advanced Solid Tumor	Unknown status	Advanced Solid Tumor	Biological: anti-CTLA-4/PD-1 expressing EGFR-CAR-T	Shanghai Cell Therapy Research Institute	1/2	40	June 7, 2017	April 20, 2019
47	NCT03166878	A Study Evaluating UCART019 in Patients With Relapsed or Refractory CD19+ Leukemia and Lymphoma	Recruiting	B Cell Leukemia|B Cell Lymphoma	Biological: UCART019	Chinese PLA General Hospital	1/2	80	June 2017	May 2022
48	NCT03467256	CD19 T-CAR for Treatment of Children and Young Adults With r/r B-ALL	Recruiting	B-cell Acute Lymphoblastic Leukemia|Acute Lymphocytic Leukemia, Pediatric	Biological: Chimeric Antigen Receptor T-Cell Therapy|Drug: Fludarabine|Drug:	Federal Research Institute of Pediatric Hematology,	1/2	18	May 14, 2018	March 2023

					Cyclophosphamide|Drug: Tocilizumab	Oncology and Immunology				
49	NCT04181827 (JPRN-JapicCTI-205280)	A Study Comparing JNJ-68284528, a CAR-T Therapy Directed Against B-cell Maturation Antigen (BCMA), Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Participants With Relapsed and Lenalidomide-Refractory Multiple Myeloma	Not yet recruiting	Multiple Myeloma	Drug: JNJ-68284528|Drug: Pomalidomide|Drug: Bortezomib|Drug: Dexamethasone|Drug: Daratumumab	Janssen Research & Development, LLC	3	400	May 31, 2020	April 10, 2026
50	NCT03182803	CTLA-4 and PD-1 Antibodies Expressing Mesothelin-CAR-T Cells for Mesothelin Positive Advanced Solid Tumor	Unknown status	Advanced Solid Tumor	Biological: CTLA-4/PD-1 antibodies expressing mesoCAR-T	Shanghai Cell Therapy Research Institute	1/2	40	June 7, 2017	April 20, 2019
51	NCT02713984	A Clinical Research of CAR T Cells Targeting HER2 Positive Cancer	Withdrawn	Breast Cancer| Ovarian Cancer| Lung Cancer| Gastric Cancer| Colorectal Cancer| Glioma| Pancreatic Cancer	Biological: Anti-HER2 CAR-T	Zhi Yang|Southwest Hospital, China	Phase 1|Phase 2	0	March 2016	July 2019
52	NCT03258047	Novel Autologou CAR-T Therapy for Relapsed/Refractory B Cell Lymphoma	Active, not recruiting	B Cell Lymphoma	Combination Product: CAR-T	First Affiliated Hospital of Zhejiang University	2	60	September 15, 2017	July 30, 2019
53	NCT03277729	A Phase I/II Study to Evaluate the Safety of Cellular Immunotherapy Using Autologous T Cells Engineered to Express a CD20-Specific Chimeric Antigen Receptor for Patients With Relapsed or Refractory B Cell Non-Hodgkin Lymphomas	Recruiting	CD20 Positive|Recurrent B-Cell Non-Hodgkin Lymphoma|Recurrent Chronic Lymphocytic Leukemia|Recurrent Diffuse Large B-Cell Lymphoma| Recurrent Follicular Lymphoma| Recurrent Lymphoplasmacytic	Biological: Chimeric Antigen Receptor T-Cell Therapy|Drug: Cyclophosphamide|Drug: Fludarabine|Other: Laboratory Biomarker Analysis|Procedure: Leukapheresis|Drug: Fludarabine Phosphate	Fred Hutchinson Cancer Research Center|National Cancer Institute (NCI)	1/2	30	December 5, 2017	November 16, 2037

				Lymphoma| Recurrent Mantle Cell Lymphoma| Recurrent Marginal Zone Lymphoma| Refractory B-Cell Non-Hodgkin						
54	NCT02959151	A Study of Chimeric Antigen Receptor T Cells Combined With Interventional Therapy in Advanced Liver Malignancy	Unknown status	Carcinoma, Hepatocellular| Pancreatic Cancer Metastatic| Colorectal Cancer Metastatic	Drug: CAR-T cell	Shanghai GeneChem Co., Ltd.|Shanghai Cancer Hospital, China	1/2	20	July 2016	July 2018
55	NCT03758417	A Study of LCAR-B38M CAR-T Cells, a Chimeric Antigen Receptor T-cell (CAR-T) Therapy Directed Against B-cell Maturation Antigen (BCMA) in Chinese Participants With Relapsed or Refractory Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: LCAR-B38M CAR-T Cell	Nanjing Legend Biotech Co.|Janssen Research & Development, LLC	2	60	January 23, 2019	June 23, 2022
56	NCT03288493	P-BCMA-101 Tscm CAR-T Cells in the Treatment of Patients With Multiple Myeloma (MM)	Recruiting	Multiple Myeloma	Biological: P-BCMA-101 CAR-T cells|Drug: Rimiducid	Poseida Therapeutics, Inc.|California Institute for Regenerative Medicine (CIRM)	1/2	220	September 20, 2017	June 30, 2022
57	NCT02873390	PD-1 Antibody Expressing CAR-T Cells for EGFR Family Member Positive Advanced Solid Tumor	Unknown status	PD-1 Antibody|CAR-T Cells|Advanced Malignancies	Biological: HerinCAR-PD1 cells	Ningbo Cancer Hospital	1/2	20	Aug.16	July 2018
58	NCT03275493	Humanized CD19 CAR-T Cells With CRS Suppression Technology for r/r CD19+ Acute Lymphoblastic Leukemia	Recruiting	Acute Lymphoblastic Leukemia| CD19 Positive| Relapse|Refractory	Biological: Humanized CD19 CAR-T cells|Biological: Humanized CD19 CAR-T cells with CRS suppression technology	Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd|The First Affiliated Hospital of Soochow University	1/2	40	July 1, 2017	September 18, 2020
59	NCT02846584	a Clinical Research of Sequential CAR-T Bridging HSCT in the Treatment of Relapse/Refractory B-cell Malignancies	Unknown status	Lymphoma, Large B-Cell, Diffuse|Leukemia, Lymphocytic, Chronic, B-	Biological: CD19 or CD20 CAR T cells briging HSCT	Southwest Hospital, China	2	100	July 2016	December 2019

				Cell|Lymphomaï¼Œ Malignant						
60	NCT03030001	PD-1 Antibody Expressing CAR T Cells for Mesothelin Positive Advanced Malignancies	Unknown status	Solid Tumor, Adult|Advanced Cancer	Biological: PD-1 antibody expressing mesothelin specific CAR-T cells	Ningbo Cancer Hospital	1/2	40	February 15, 2017	February 1, 2019
61	NCT02247609	Evaluation of 4th Generation Safety-designed CAR T Cells Targeting High-risk and Refractory B Cell Lymphomas	Unknown status	B-cell Lymphomas	Genetic: Anti-CD19 CAR T cells	Peking University|University of Florida	1/2	20	January 2014	October 2017
62	NCT02274584	CAR T Cells Targeting CD30 Positive Lymphomas (4SCAR30273)	Unknown status	Lymphomas	Genetic: Anti-CD30 CAR T cells	Peking University|University of Florida	1/2	20	March 2014	October 2017
63	NCT03435796	Long-Term Follow-up Protocol for Subjects Treated With Gene-Modified T Cells	Recruiting	Neoplasms	Genetic: Gene-modified (GM) T cell therapy	Celgene	2/3	191	June 19, 2018	November 30, 2032
64	NCT02794961	CD22 Targeting CAR-T Therapy Against B Cell Hematological Malignancies	Unknown status	Recurrent or Refractory B Cell Malignancy	Biological: CD22 CAR-T	Kai Lin Xu	1/2	10	June 2016	June 2019
65	NCT03931421	B Cell Maturation Antigen (BMCA)-Targeted CAR-T for Refractory/Relapsed Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: CAR-T treatment	First Affiliated Hospital of Zhejiang University	2	30	July 31, 2019	December 31, 2022
66	NCT02862028	PD-1 Antibody Expressing CAR-T Cells for EGFR Family Member Positive Advanced Solid Tumor (Lung, Liver and Stomach)	Unknown status	PD-1 Antibody|CAR-T Cells|Advanced Solid Tumor	Biological: HerinCAR-PD1 cells	Shanghai International Medical Center	1/2	20	Aug.16	July 2018
67	NCT03706326	CAR T and PD-1 Knockout Engineered T Cells for Esophageal Cancer	Recruiting	Advanced Esophageal Cancer	Biological: Anti-MUC1 CAR-T cells|Biological: PD-1 knockout Engineered T cells|Combination Product: CAR-T combined with PD-1 Knockout T cells	The First Affiliated Hospital of Guangdong Pharmaceutical University|Guangzhou Anjie Biomedical Technology Co., Ltd.	1/2	20	September 28, 2018	September 28, 2021
68	NCT03185494	Treatment of Relapsed and/or Chemotherapy Refractory B-cell Malignancy by Tandem	Active, not recruiting	Hematopoietic/Lymphoid Cancer| Adult Acute Lymphoblastic	Biological: anti-CD19/22-CAR vector-transduced T cells	Chinese PLA General Hospital	1/2	30	August 1, 2017	August 1, 2020

		CAR T Cells Targeting CD19 and CD22		Leukemia in Remission|B-cell Adult Acute Lymphoblastic Leukemia|B-Cell Chronic Lymphocytic Leukemia in Relapse (Diagnosis)| Prolymphocytic Leukemia| Recurrent Grade 1,2,3 Follicular Lymphoma| Mantle Cell Lymphoma| Refractory Chronic Lymphocytic Leukemia| Stage III Adult Diffuse Large Cell Lymphoma| Stage III Grade 1,2,3 Follicular Lymphoma| Mantle Cell Lymphoma| Stage IV Adult Diffuse Large Cell Lymphoma| Stage IV Chronic Lymphocytic Leukemia|						
69	NCT03321123	MB-CART19.1 in Patients With R/R ALL	Unknown status	Precursor B-Lymphoblastic Lymphoma/Leukaemia Refractory	Drug: MB-CART19.1	Shanghai Children's Medical Center|Miltenyi Biotec B.V. & Co. KG	2	10	December 1, 2017	December 31, 2019
70	NCT04340154	Study of Sequential CAR-T Cell Treating Leukemia Children	Recruiting	Acute Lymphoblastic Leukemia|Acute Lymphoblastic Leukemia, in Relapse|Refractory Acute Lymphoid Leukemia	Biological: chimeric antigen receptor T cell	Beijing Boren Hospital	2	100	May 1, 2020	November 1, 2022
71	NCT02715362	A Study of GPC3 Redirected Autologous T Cells for Advanced HCC	Unknown status	Carcinoma, Hepatocellular	Drug: TAI-GPC3-CART cells	Shanghai GeneChem Co., Ltd.	1/2	30	March 2016	March 2019

72	NCT03765177	CLIC-1901 for the Treatment of Patients With Relapsed/Refractory CD19 Positive Hematologic Malignancies	Recruiting	Acute Lymphoblastic Leukemia|Non-Hodgkin's Lymphoma	Biological: CLIC-1901	Ottawa Hospital Research Institute	1/2	60	October 16, 2019	October 31, 2022
73	NCT04340167	Study of Anti-CD22 CAR-T Cells Treating Leukemia Children	Recruiting	Acute Lymphoblastic Leukemia|Acute Lymphoblastic Leukemia, in Relapse|Refractory Acute Lymphoblastic Leukemia	Biological: Autologous humanized anti-CD22 chimeric antigen receptor T cells	Beijing Boren Hospital	2	100	May 1, 2020	October 1, 2022
74	NCT04325841	Phase II Study of Anti-CD19 CAR-T Cells Treating Leukemia Children	Recruiting	Acute Lymphoblastic Leukemia, Pediatric| Acute Lymphoblastic Leukemia, in Relapse| Refractory Acute Lymphoblastic Leukemia	Biological: Murine autologous anti-CD19 chimeric antigen receptor T cells	Beijing Boren Hospital	2	100	May 1, 2020	November 1, 2022
75	NCT02535364	Study Evaluating the Efficacy and Safety of JCAR015 in Adult B-cell Acute Lymphoblastic Leukemia (B-ALL)	Terminated	Acute Lymphoblastic Leukemia	Biological: JCAR015 (CD19-targeted CAR T cells)	Juno Therapeutics, a Subsidiary of Celgene	2	82	August 21, 2015	September 1, 2017
76	NCT03050190	A Phase I/II Multiple Center Trial of 4SCAR19 Cells in the Treatment of Relapsed and Refractory B Cell Malignancies	Recruiting	B-cell Malignancies	Genetic: Therapeutic 4SCAR19 cells	Shenzhen Geno-Immune Medical Institute	1/2	200	July 2013	December 2020
77	NCT03289455	CD19 /22 CAR T Cells (AUTO3) for the Treatment of B Cell ALL	Active, not recruiting	B Acute Lymphoblastic Leukemia| Recurrent Childhood Acute Lymphoblastic Leukemia| Refractory Childhood Acute Lymphoblastic Leukemia| B-cell Acute	Biological: AUTO3 (CD19/22 CAR T cells	Autolus Limited	1/2	23	June 26, 2017	December 2021

				Lymphoblastic Leukemia						
78	NCT04430595	Multi-4SCAR-T Therapy Targeting Breast Cancer	Recruiting	Breast Cancer	Biological: 4SCAR T cells	Shenzhen Geno-Immune Medical Institute|The Seventh Affilliated Hospital, Sun Yat-Sen University	1/2	100	June 1, 2020	December 31, 2023
79	NCT03196830	CAR-T for R/R B-NHL	Recruiting	Relapsed Non Hodgkin Lymphoma| Refractory Non-Hodgkin Lymphoma| CAR - T CD19/CD20/CD22/CD30	Biological: CAR-T	The First Affiliated Hospital of Soochow University|Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd	2	10	June 1, 2017	May 31, 2021
80	NCT04257175	CAR-T CD19 for Acute Myelogenous Leukemia With t 8:21 and CD19 Expression	Not yet recruiting	Acute Myeloid Leukemia	Biological: CAR-T CD19	Sheba Medical Center	2/3	10	March 1, 2020	December 1, 2023
81	NCT02992834	Anti-CD19:TCRÎ Chimeric Antigen Receptor-T Cells in the Treatment for CD19+ B Cell Lymphoma	Not yet recruiting	Lymphoma, B Cell	Biological: IL-2 pre-treated CD19 cells|Biological: IL-7/IL-15 pre-treated CD19 cells	jiangjingting|The First People's Hospital of Changzhou	1	10	December 2016	January 2022
82	NCT02259556	CD30-directed Chimeric Antigen Receptor T (CART30) Therapy in Relapsed and Refractory CD30 Positive Lymphomas	Recruiting	Hodgkin's Lymphoma|Non-Hodgkin's Lymphoma	Biological: CART30	Chinese PLA General Hospital	1/2	30	October 2014	October 2029
83	NCT04029038	Modified Immune Cells (CD19-CD22 CAR T Cells) in Treating Patients With Recurrent or Refractory CD19 Positive, CD22 Positive Leukemia or Lymphoma	Not yet recruiting	CD19 Positive|CD22 Positive| Minimal Residual Disease| Progressive Disease| Recurrent B Acute Lymphoblastic Leukemia| Recurrent Chronic Lymphocytic Leukemia| Recurrent Non-Hodgkin Lymphoma| Refractory B Acute	Biological: Autologous CD19/CD22 Chimeric Antigen Receptor T-cells|Drug: Cyclophosphamide|Drug: Fludarabine	M.D. Anderson Cancer Center|National Cancer Institute (NCI)	1/2	30	November 30, 2019	August 31, 2023

				Lymphoblastic Leukemia| Refractory Chronic Lymphocytic Leukemia| Refractory Non-Hodgkin Lymphoma						
84	NCT04037241	Study of Anti-CEA CAR-T + Chemotherapy VS Chemotherapy Alone in Patients With CEA+Pancreatic Cancer & Liver Metastases	Not yet recruiting	Malignant Tumor of Pancreas Metastatic to Liver	Biological: Anti-CEA CAR-T cells|Drug: gemcitabine/nab paclitaxel|Drug: NLIR+FU/FA|Drug: Capecitabine	Sorrento Therapeutics, Inc.	2/3	167	November 1, 2021	January 1, 2022
85	NCT03068416	CD19-targeting, 3rd Generation CAR T Cells for Refractory B Cells Malignancy	Active, not recruiting	B-cell Leukemia|B-Cell Lymphoma	Biological: CAR T cells	Uppsala University|Uppsala University Hospital|AFA Insurance	2	25	September 18, 2017	Apr.22
86	NCT03548207	A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-Cell Maturation Antigen (BCMA) in Participants With Relapsed or Refractory Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: JNJ-68284528	Janssen Research & Development, LLC	1/2	118	June 29, 2018	April 30, 2022
87	NCT03287804	APRIL CAR T Cells (AUTO2) Targeting BCMA and TACI for the Treatment of Multiple Myeloma	Terminated	Multiple Myeloma	Biological: AUTO2	Autolus Limited	1/2	12	May 5, 2017	September 5, 2019
88	NCT04133636	A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-cell Maturation Antigen (BCMA) in Participants With Multiple Myeloma	Recruiting	Multiple Myeloma	Drug: JNJ-68284528|Drug: Lenalidomide	Janssen Research & Development, LLC	2	80	November 7, 2019	August 13, 2023
89	NCT03448978	Autologous CD8+ T-cells Expressing an Anti-BCMA CAR in Patients With Myeloma	Recruiting	Multiple Myeloma	Biological: Descartes-08|Drug: Fludarabine|Drug: Cyclophosphamide	Cartesian Therapeutics	1/2	30	February 26, 2018	September 1, 2020
90	NCT02710149	A Clinical Research of CD20-Targeted CAR-T in B Cell Malignancies	Recruiting	Leukemia| Lymphoma	Biological: Anti-CD20-CAR-transduced T cells	Southwest Hospital, China	1/2	45	March 2016	March 2021

91	NCT02954445	A Clinical Research of BCMA-Targeted CAR-T in B Cell Malignancies	Recruiting	Leukemia| Lymphoma| Multiple Myeloma	Biological: Anti-BCMA-CAR-transduced T cells	Southwest Hospital, China	1/2	45	October 2016	October 2020
92	NCT02935153	A Clinical Research of CD22-Targeted CAR-T in B Cell Malignancies	Recruiting	Leukemia| Lymphoma	Biological: Anti-CD22-CAR-transduced T cells	Southwest Hospital, China	1/2	45	October 2016	October 2020
93	NCT02958384	A Clinical Research of LeY-Targeted CAR-T in Myeloid Malignancies	Recruiting	Myeloid Malignancies	Biological: Anti-LeY-CAR-transduced T cells	Southwest Hospital, China	1/2	45	October 2016	October 2020
94	NCT03598179	XLCART001 Treatment in Relapsed/Refractory/ High-risk B-cell Malignancy Subjects	Active, not recruiting	Lymphoma, B-Cell| Leukemia, B-cell	Biological: chimeric antigen receptor T cells	The First Affiliated Hospital with Nanjing Medical University	2	10	June 1, 2018	July 1, 2020
95	NCT02958397	A Clinical Research of CD33-Targeted CAR-T in Myeloid Malignancies	Recruiting	Myeloid Malignancies	Biological: Anti-CD33-CAR-transduced T cells	Southwest Hospital, China	1/2	45	October 2016	October 2020
96	NCT02958410	A Clinical Research of CD30-Targeted CAR-T in Lymphocyte Malignancies	Recruiting	Leukemia| Lymphoma	Biological: Anti-CD30-CAR-transduced T cells	Southwest Hospital, China	1/2	45	October 2016	October 2020
97	NCT03287817	CD19/22 CAR T Cells (AUTO3) for the Treatment of Diffuse Large B Cell Lymphoma	Recruiting	Diffuse Large B Cell Lymphoma| Relapsed Diffuse Large B-Cell Lymphoma| Refractory Diffuse Large B-Cell Lymphoma|DLBCL	Biological: AUTO3	Autolus Limited	1/2	171	September 5, 2017	March 2021
98	NCT02937103	A Clinical Research of CD123-Targeted CAR-T in Myeloid Malignancies	Recruiting	Leukemia	Biological: Anti-CD123-CAR-transduced T cells	Southwest Hospital, China	1/2	45	October 2016	October 2020
99	NCT03356795	Intervention of CAR-T Against Cervical Cancer	Recruiting	Cervical Cancer	Biological: Cervical cancer-specific CAR-T cells	Shenzhen Geno-Immune Medical Institute	1/2	20	November 15, 2017	December 2020
100	NCT03633773	Safety and Efficacy Evaluation of MUC-1 CART in the Treatment of Intrahepatic Cholangiocarcinoma	Recruiting	Intrahepatic Cholangiocarcinoma	Biological: MUC-1 CART cell immunotherapy	Second Affiliated Hospital, School of Medicine, Zhejiang University	1/2	9	July 1, 2018	December 31, 2024
101	NCT01886976	Treatment of Chemotherapy Refractory Multiple Myeloma by CART-138	Unknown status	Multiple Myeloma	Biological: CART-138 cells	Chinese PLA General Hospital	1/2	10	June 2013	June 2016
102	NCT03937544	Intravenous Autologous CD19 CAR-T Cells for R/R B-ALL	Recruiting	Relapsed B Acute Lymphoblastic Leukaemia|	Biological: CD19 CAR-T CELLS|Drug:	National University of	2/3	10	March 19, 2019	March 18, 2024

				Refractory B Acute Lymphoblastic Leukaemia	Cyclophosphamide|Drug: Fludarabine	Malaysia|Gaia Science				
103	NCT01864902	Treatment of Relapsed and/or Chemotherapy Refractory CD33 Positive Acute Myeloid Leukemia by CART-33	Unknown status	Relapsed Adult Myeloid Leukemia|Chemotherapy Refractory Adult Myeloid Leukemia	Biological: CART33 cells|Biological: anti-CD33 CART|Biological: anti-CD33 CAR T cells	Chinese PLA General Hospital	1/2	10	Apr.13	Apr.17
104	NCT03118180	CD19 Targeted Chimeric Antigen Receptor T Cells for B Cell Lymphoma	Recruiting	Lymphoma	Biological: CD19 targeted chimeric antigen receptor T cells	Zhejiang University|Innovative Cellular Therapeutics Co., Ltd.	1/2	50	April 5, 2017	December 31, 2020
105	NCT03090659	LCAR-B38M-02 Cells in Treating Relapsed/Refractory (R/R) Multiple Myeloma	Enrolling by invitation	Refractory or Relapsed Multiple Myeloma	Biological: LCAR-B38M CAR-T cell injection	Nanjing Legend Biotech Co.|Second Affiliated Hospital of Xi'an Jiaotong University|Ruijin Hospital|Jiangsu Provincial People's Hospital|Shanghai Changzheng Hospital	1/2	100	October 2, 2015	December 31, 2021
106	NCT03373071	Anti-CD19 CAR T Cells in Pediatric Patients Affected by Relapsed/Refractory CD19+ ALL and NHL	Recruiting	CD19-ALL| CD19-LNH	Biological: CD19-CAR T cell	Bambino GesÃ¹ Hospital and Research Institute	1/2	32	December 2017	December 2027
107	NCT04268706	Phase 2 Study Evaluating Autologous CD30.CAR-T Cells in Adult and Pediatric Patients With Relapsed/Refractory HL	Not yet recruiting	Hodgkin Lymphoma, Adult|Hodgkin Disease Recurrent|Hodgkin Disease Refractory|Hodgkin Disease, Pediatric	Drug: CD30.CAR-T	Tessa Therapeutics	2	90	May 1, 2020	Aug.24
108	NCT03097770	Treatment of Relapsed and/or Chemotherapy Refractory B-cell Malignancy by Tandem CAR T Cells Targeting CD19 and CD20	Recruiting	Hematopoietic/Lymphoid Cancer| Adult Acute Lymphoblastic Leukemia in Remission| B-cell Adult Acute Lymphoblastic Leukemia| B-cell Chronic Lymphocytic	Biological: anti-CD19/20-CAR vector-transduced T cells	Chinese PLA General Hospital	1/2	100	April 1, 2017	April 30, 2020

				Leukemia| Prolymphocytic Leukemia| Recurrent Adult Diffuse Large Cell Lymphoma| Recurrent Grade 1 Follicular Lymphoma| Recurrent Mantle Cell Lymphoma| Refractory Chronic Lymphocytic Leukemia| Stage III Adult Diffuse Large Cell Lymphoma| Stage III Chronic Lymphocytic Leukemia|						
109	NCT03615313	PD-1 Antibody Expressing mesoCAR-T Cells for Mesothelin Positive Advanced Solid Tumor	Recruiting	Advanced Solid Tumor	Biological: PD-1 antibody expressing mesoCAR-T cells	Shanghai Cell Therapy Research Institute	1/2	50	August 6, 2018	December 3, 2020
110	NCT03356782	Safety and Efficacy Evaluation of 4th Generation Safety-engineered CAR T Cells Targeting Sarcomas	Recruiting	Sarcoma|Osteoid Sarcoma|Ewing Sarcoma	Biological: Sarcoma-specific CAR-T cells	Shenzhen Geno-Immune Medical Institute	1/2	20	December 1, 2017	December 31, 2023
111	NCT02723942	CAR-T Cell Immunotherapy for HCC Targeting GPC3	Completed	GPC3 Positive Hepatocellular Carcinoma|CAR-T Cell Immunotherapy	Biological: CAR-T cell immunotherapy	Fuda Cancer Hospital, Guangzhou	1/2	60	June 2015	August 15, 2017
112	NCT03322735	Study of BCMA CAR-T in Multiple Myeloma	Unknown status	Multiple Myeloma	Drug: Fludarabine|Drug: Cyclophosphamide|Biological: BCMA CAR-T	Henan Cancer Hospital|The Pregene (ShenZhen) Biotechnology Company, Ltd.	1/2	10	December 8, 2017	December 2019
113	NCT03312205	CAR-T Cells for Relapsed or Refractory Haematopoietic and Lymphoid Malignancies	Recruiting	Leukemia| Lymphoma| Multiple Myeloma of Bone (Diagnosis)	Biological: Autologous CAR-T cells	Hebei Senlang Biotechnology Inc., Ltd.|Hebei Yanda Ludaopei Hospital|Beijing Ludaopei Hospital	1/2	50	August 29, 2017	August 29, 2023
114	NCT04196205	Anti-CD19 CAR-T Cells for Relapsed or Refractory	Recruiting	Acute Lymphoblastic	Biological: Anti-CD19 CAR-T	The First Affiliated Hospital of	1/2	20	December 1, 2019	August 1, 2021

		Acute Lymphoblastic Leukemia and Lymphomas		Leukemia Lymphomas		Nanchang University				
115	NCT03373097	Anti-GD2 CAR T Cells in Pediatric Patients Affected by High Risk and/or Relapsed/Refractory Neuroblastoma	Recruiting	Neuroblastoma|Neuroblastoma Recurrent	Biological: GD2-CART01	Bambino GesÃ¹ Hospital and Research Institute	1/2	42	December 2017	December 2027
116	NCT01475058	CD19 CAR T Cells for B Cell Malignancies After Allogeneic Transplant	Completed	Philadelphia Chromosome Negative Adult Precursor Acute Lymphoblastic Leukemia|Philadelphia Chromosome Positive Adult Precursor Acute Lymphoblastic Leukemia| Recurrent Adult Acute Lymphoblastic Leukemia| Recurrent Adult Diffuse Large Cell Lymphoma| Recurrent Adult Immunoblastic Large Cell Lymphoma| Recurrent Mantle Cell Lymphoma|Refractory Chronic Lymphocytic Leukemia	Biological: allogeneic cytomegalovirus-specific cytotoxic T lymphocytes	Fred Hutchinson Cancer Research Center|National Cancer Institute (NCI)	1/2	1	Apr.12	July 2014
117	NCT02132624	CD19-targeting 3rd Generation CAR T Cells for Refractory B Cell Malignancy - a Phase I/IIa Trial.	Completed	B Cell Lymphoma| B Cell Leukemia	Biological: Autologous 3rd generation CD19-targeting CAR T cells	Uppsala University|Uppsala University Hospital|Karolinska University Hospital|AFA Insurance|Swedish Cancer Society	1/2	15	Apr.14	May 31, 2017
118	NCT02652910	Memory-enriched CAR-T Cells Immunotherapy for B Cell Lymphoma	Unknown status	Recurrent Adult Diffuse Large Cell Lymphoma|	Drug: CD19.CAR-T cells	Xinqiao Hospital of Chongqing|Xuzho	1/2	20	December 2015	December 2019

				Recurrent Follicular Lymphoma| Recurrent Mantle Cell Lymphoma| Stage III Adult Diffuse Large Cell Lymphoma| Stage III Follicular Lymphoma| Stage III Mantle Cell Lymphoma| Stage IV Adult Diffuse Large Cell Lymphoma| Stage IV Follicular Lymphoma|Stage IV Mantle Cell Lymphoma		u Medical University|Hrain Biotechnology Co., Ltd.|Shanghai Changzheng Hospital				
119	NCT04430530	4SCAR-T Therapy Post CD19-targeted Immunotherapy	Recruiting	CD19 Negative B-cell Malignancies	Biological: Infusion of 4SCAR-T specific to CD22/CD123/CD38/ CD10/CD20	Shenzhen Geno-Immune Medical Institute|ShiJiaZhuang Zhongxi Children Hospital|Shenzhen Children's Hospital|The Seventh Affilliated Hospital, Sun Yat-Sen University	1/2	100	June 1, 2020	December 31, 2023
120	NCT02028455	A Pediatric and Young Adult Trial of Genetically Modified T Cells Directed Against CD19 for Relapsed/Refractory CD19+ Leukemia	Recruiting	CD19+ Acute Leukemia	Biological: Patient Derived CD19 specific CAR T cells also expressing an EGFRt	Seattle Children's Hospital	1/2	80	February 11, 2014	Sep.35
121	NCT03191773	A Study of Anti-CD19 CAR-T Cell Immunotherapy for Refractory /Relapsed B Cell Malignancies	Recruiting	Acute Lymphocytic Leukemia| Chronic Lymphocytic Leukemia| Lymphoma	Combination Product: Drugs and anti-CD19 CAR transduced T cells	Second Affiliated Hospital of Guangzhou Medical University|Shenzhen Institute for Innovation and Translational Medicine|Guangzhou First People's Hospital|First	1/2	100	June 30, 2017	December 31, 2020

						People's Hospital of Foshan|Dongguan People's Hospital|The First Affiliated Hospital of Guangdong Pharmaceutical University				
122	NCT03207178	Sequential Infusion of Anti-CD19 and Anti-CD20 CAR-T Cells Against Relapsed and Refractory B-cell Lymphoma	Unknown status	Recurrent or Refractory B Cell Malignancy	Biological: Mixed CD19/CD20 CAR-T Transfer	Shanghai Longyao Biotechnology Inc., Ltd.|Xuzhou Medical University|Shanghai Jiao Tong University School of Medicine	1/2	20	March 1, 2017	February 28, 2020
123	NCT03676504	Treatment of Patients With Relapsed or Refractory CD19+ Lymphoid Disease With T Cells Expressing a Third-generation CAR	Recruiting	Acute Lymphoblastic Leukemia, Adult|Acute Lymphoblastic Leukemia, Pediatric|Chronic Lymphocytic Leukemia|Diffuse Large B Cell Lymphoma| Follicular Lymphoma| Mantle Cell Lymphoma	Biological: CD19.CAR T Cells|Drug: Fludarabine|Drug: Cyclophosphamide	University Hospital Heidelberg	1/2	48	September 7, 2018	October 1, 2020
124	NCT01218867	CAR T Cell Receptor Immunotherapy Targeting VEGFR2 for Patients With Metastatic Cancer	Terminated	Metastatic Cancer| Metastatic Melanoma| Renal Cancer	Biological: Anti-VEGFR2 CAR CD8 plus PBL|Drug: Cyclophosphamide|Biological: Aldesleukin|Drug: Fludarabine	National Cancer Institute (NCI)|National Institutes of Health Clinical Center (CC)	1/2	24	November 10, 2010	December 15, 2015
125	NCT02672501	A Study to Assess CD19-targeted Immunotherapy T Cells in Patients With Relapsed or Refractory CD19+ B Cell Leukemia	Unknown status	Leukemia, B-Cell	Drug: anti-CD19-CAR-T cells	Shanghai GeneChem Co., Ltd.	1/2	30	January 2016	December 2019
126	NCT03142646	Safety and Efficacy Evaluation of IM19 CAR-T Cells	Unknown status	Leukemia	Biological: IM19 CAR-T	Beijing Immunochina Medical Science &	1/2	60	August 30, 2016	October 1, 2018

						Technology Co., Ltd.				
127	NCT02980315	A New EBV Related Technologies of T Cells in Treating Malignant Tumors and Clinical Application	Unknown status	Nasopharyngeal Neoplasms	Other: CAR-T cells	The Second Hospital of Nanjing Medical University	1/2	20	Nov.16	December 2017
128	NCT03590574	Phase I/II Study Evaluating AUTO4 in Patients With TRBC1 Positive T Cell Lymphoma	Recruiting	T Cell Non-Hodgkin Lymphoma| Peripheral T-Cell Lymphoma, Not Otherwise Specified| Angioimmunoblastic T-cell Lymphoma| Anaplastic Large Cell Lymphoma	Biological: AUTO4	Autolus Limited	1/2	55	August 30, 2018	December 2022
129	NCT01454596	CAR T Cell Receptor Immunotherapy Targeting EGFRvIII for Patients With Malignant Gliomas Expressing EGFRvIII	Completed	Malignant Glioma| Glioblastoma|Brain Cancer|Gliosarcoma	Biological: Epidermal growth factor receptor(EGFRv)III Chimeric antigen receptor (CAR) transduced PBL|Drug: Aldesleukin|Drug: Fludarabine|Drug: Cyclophosphamide	National Cancer Institute (NCI)|National Institutes of Health Clinical Center (CC)	1/2	18	May 16, 2012	January 17, 2019
130	NCT02081937	CART-19 Immunotherapy in Mantle Cell Lymphoma	Unknown status	Hematopoietic/ Lymphoid Cancer| Non-hodgkin Lymphoma,B Cell|Mantle Cell Lymphoma	Biological: anti-CD19-CAR vector-transduced T cells	Chinese PLA General Hospital	1/2	2	March 2014	December 2019
131	NCT02685670	Competitive Transfer of Î±CD19-TCRz-CD28 and Î±CD19-TCRz-CD137 CAR-T Cells for B-cell Leukemia/Lymphoma	Unknown status	Hematopoietic/ Lymphoid Cancer| Adult Acute Lymphoblastic Leukemia in Remission|B-cell Adult Acute Lymphoblastic Leukemia|B-cell Chronic Lymphocytic Leukemia| Recurrent Adult Diffuse Large Cell Lymphoma|	Biological: anti-CD19 CAR-T|Drug: Fludarabine|Drug: Cyclophosphamide	The Second Affiliated Hospital of Henan University of Traditional Chinese Medicine|Xinqiao Hospital of Chongqing|Xuzhou Medical University	1/2	20	February 2016	December 2019

				Follicular Lymphoma| Recurrent Mantle Cell Lymphoma| Refractory Chronic Lymphocytic Leukemia|						
132	NCT03173417	Safety and Efficacy Evaluation of IM19 CAR-T Cells (IM19CAR-T)	Completed	Leukemia	Biological: IM19 CAR-T|Drug: fludarabine and cyclophosphamide	Beijing Immunochina Medical Science & Technology Co., Ltd.	1/2	177	May 23, 2017	May 1, 2019
133	NCT04186520	CAR-20/19-T Cells in Patients With Relapsed Refractory B Cell Malignancies	Recruiting	Non Hodgkin Lymphoma (NHL)| Mantle Cell Lymphoma (MCL)	Biological: 8-Day Production of Car-T Cells|Biological: 12-Day Production of Car-T Cells	Medical College of Wisconsin	1/2	32	May 18, 2020	May 1, 2025
134	NCT02772198	T-cells Expressing Anti-CD19 CAR in Pediatric and Young Adults With B-cell Malignancies	Unknown status	Acute Lymphoblastic Leukemia, B-precursor| Non-Hodgkin Lymphoma, B-cell	Biological: CD19 CAR T cells	Sheba Medical Center	1/2	80	Nov.16	Nov.19
135	NCT03098355	Interleukin-2 Following 4SCAR19/22 T Cells Targeting Refractory and/or Recurrent B Cell Malignancies	Unknown status	B-Cell Leukemia| B-Cell Lymphoma	Biological: 4SCAR19/22 T cells|Drug: Interleukin-2	Zhujiang Hospital|Shenzhen Geno-Immune Medical Institute	1/2	30	December 30, 2017	December 31, 2019
136	NCT04053062	PSMA-CART in Treating Patients With Refractory Castrate-Resistant Prostate Cancer	Recruiting	Castrate-Resistant Prostate Cancer	Biological: PSMA-CART cells	Shanghai Bioray Laboratory Inc.|Changhai Hospital	1/2	12	August 8, 2019	Aug.22
137	NCT02765243	Anti-GD2 4th Generation CART Cells Targeting Refractory and/or Recurrent Neuroblastoma	Recruiting	Neuroblastoma| Effects of Immunotherapy	Biological: Anti-GD2 CART	Zhujiang Hospital	2	30	March 23, 2016	December 30, 2019
138	NCT02030847	Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR and 4-1BB Signaling Domains in Patients With Chemotherapy Resistant or Refractory Acute Lymphoblastic Leukemia	Completed	Patients With B Cell ALL, Relapsed or Refractory, With no Available Curative Treatment Options	Biological: CART-19	University of Pennsylvania	2	42	February 27, 2014	April 26, 2018

139	NCT04089215	CD19-targeted CAR T Cells for Relapsed and Refractory (R/R) Non-Hodgkins Lymphoma	Recruiting	Lymphoma, Non-Hodgkin| Diffuse Large B Cell Lymphoma| Follicular Lymphoma	Biological: CD19-targeted Chimeric Antigen Receptor (CAR) T Cells	Shanghai Ming Ju Biotechnology Co., Ltd.	2	82	June 11, 2019	January 31, 2022
140	NCT03366350	Anti-CD19 CAR-T Therapy Bridging to HSCT for CD19+ B-Cell Malignancies	Recruiting	Acute Lymphoblastic Leukemia| B Cell Lymphoma	Procedure: Allogeneic hematological stem cell transplantation	Wuhan Sian Medical Technology Co., Ltd|Wuhan Union Hospital, China|Jingzhou Central Hospital|Xiangyang Central Hospital|People Hospital Of Yichang	1/2	50	April 15, 2016	June 1, 2021
141	NCT03994913	Clinical Trial to Evaluate CD19 CAR T (CT032) in Patients With Relapsed and/or Refractory Non-Hodgkin's B Cell Lymphoma	Recruiting	Refractory B-Cell Non-Hodgkin Lymphoma| Relapsed B-cell Non-Hodgkin Lymphoma	Biological: CAR-CD19 T Cells	Carsgen Therapeutics, Ltd.|First Affiliated Hospital of Zhejiang University|RenJi Hospital	1/2	78	September 27, 2019	September 30, 2022
142	NCT01865617	Laboratory Treated T Cells in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphoma, or Acute Lymphoblastic Leukemia	Active, not recruiting	CD19-Positive Neoplastic Cells Present| Recurrent Adult Acute Lymphoblastic Leukemia| Recurrent Chronic Lymphocytic Leukemia| Recurrent Diffuse Large B-Cell Lymphoma| Recurrent Mantle Cell Lymphoma| Recurrent Non-Hodgkin Lymphoma| Recurrent Small Lymphocytic Lymphoma| Refractory Acute	Biological: Autologous Anti-CD19CAR-4-1BB-CD3zeta-EGFRt-expressing T Lymphocytes|Other: Laboratory Biomarker Analysis	Fred Hutchinson Cancer Research Center|National Cancer Institute (NCI)	1/2	203	May 22, 2013	April 2, 2034

				Lymphoblastic Leukemia| Refractory Chronic Lymphocytic Leukemia| Refractory Diffuse Large B-Cell Lymphoma| Refractory Mantle Cell Lymphoma| Refractory Non-Hodgkin Lymphoma| Refractory Small Lymphocytic Lymphoma						
143	NCT04427449	4SCAR-CD44v6 T Cell Therapy Targeting Cancer	Recruiting	Cancers Which Are CD44v6 Positive	Biological: CD44v6-specific CAR gene-engineered T cells	Shenzhen Geno-Immune Medical Institute|Shenzhen Hospital of Southern Medical University|The Seventh Affilliated Hospital, Sun Yat-Sen University|Shenzhen Children's Hospital	1/2	100	June 1, 2020	December 31, 2023
144	NCT03016377	Administration of Autologous CAR-T CD19 Antigen With Inducible Safety Switch in Patients With Relapsed/Refractory ALL	Recruiting	Acute Lymphoblastic Leukemia| Immune System Diseases| Immunoproliferative Disorders	Biological: iC9-CAR19 cells|Drug: Rimiducid|Drug: Cyclophosphamide|Drug: Fludarabine	UNC Lineberger Comprehensive Cancer Center|Bellicum Pharmaceuticals	1/2	54	March 22, 2018	October 2036
145	NCT04351022	CD38-targeted Chimeric Antigen Receptor T Cell (CART) in Relapesd or Refractory Acute Myeloid Leukemia	Recruiting	Acute Myeloid Leukemia	Biological: CART-38	The First Affiliated Hospital of Soochow University	1/2	20	July 1, 2017	December 31, 2023
146	NCT00924326	CAR T Cell Receptor Immunotherapy for Patients With B-cell Lymphoma	Active, not recruiting	Primary Mediastinal B-cell Lymphoma| Diffuse, Large B-cell Lymphoma| Diffuse Large B-Cell Lymphoma Transformed From	Drug: Fludarabine|Drug: Cyclophosphamide|Biological: Anti-cluster of differentiation 19 (CD19)-CAR PBL|Drug: Aldesleukin	National Cancer Institute (NCI)|National Institutes of Health Clinical Center (CC)	1/2	43	February 17, 2009	December 31, 2020

				Follicular Lymphoma|Mantle Cell						
147	NCT01583686	CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer	Terminated	Cervical Cancer| Pancreatic Cancer| Ovarian Cancer| Mesothelioma| Lung Cancer	Drug: Fludarabine|Biological: Anti-mesothelin chimeric T cell receptor (CAR) transduced peripheral blood lymphocytes (PBL)|Drug: Cyclophosphamide|Drug: Aldesleukin	National Cancer Institute (NCI)|National Institutes of Health Clinical Center (CC)	1/2	15	May 4, 2012	December 17, 2018
148	NCT03430011	Study Evaluating the Safety and Efficacy of JCARH125 in Subjects With Relapsed and/or Refractory Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: JCARH125|Biological: JCARH125 + anakinra	Juno Therapeutics, a Subsidiary of Celgene	1/2	245	February 1, 2018	March 2023
149	NCT02414269	Malignant Pleural Disease Treated With Autologous T Cells Genetically Engineered to Target the Cancer-Cell Surface Antigen Mesothelin	Recruiting	Malignant Pleural Disease| Mesothelioma| Metastases| Lung Cancer| Breast Cancer	Genetic: iCasp9M28z T cell infusions|Drug: cyclophosphamide|Drug: pembrolizumab	Memorial Sloan Kettering Cancer Center|Atara Biotherapeutics|Bellicum Pharmaceuticals	1/2	179	May 2015	Apr. 2021
150	NCT01735604	Genetically Engineered Lymphocyte Therapy in Treating Patients With Lymphoma That is Resistant or Refractory to Chemotherapy	Unknown status	Hematopoietic/ Lymphoid Cancer| Adult Acute Lymphoblastic Leukemia in Remission| B-cell Adult Acute Lymphoblastic Leukemia| B-cell Chronic Lymphocytic Leukemia| Prolymphocytic Leukemia| Recurrent Adult Diffuse Large Cell Lymphoma| Recurrent Follicular Lymphoma| Recurrent Mantle Cell Lymphoma|	Biological: anti-CD20-CAR vector-transduced autologous T cells|Other: genetically engineered lymphocyte therapy	Chinese PLA General Hospital	1/2	50	January 2013	October 2018

				Refractory Chronic Lymphocytic Leukemia|Stage III Adult Diffuse Large Cell Lymphoma| Stage III Chronic Lymphocytic Leukemia| Mantle Cell Lymphoma						
151	NCT03155191	Study of TBI-1501 for Relapsed or Refractory Acute Lymphoblastic Leukemia	Recruiting	Lymphoblastic Leukemia, Acute Adult	Biological: TBI-1501	Takara Bio Inc.	1/2	21	June 1, 2017	March 31, 2020
152	NCT02541370	Treatment of Relapsed and/or Chemotherapy Refractory Advanced Malignancies by CART133	Completed	Liver Cancer| Pancreatic Cancer| Brain Tumor| Breast Cancer| Ovarian Tumor| Colorectal Cancer| Acute Myeloid and Lymphoid Leukemias	Biological: anti-CD133-CAR vector-transduced T cells	Chinese PLA General Hospital	1/2	20	June 2015	June 2019
153	NCT02935543	CART19 in Adult Patients With Minimal Residual Disease During Upfront Treatment for ALL	Terminated	Leukemia, Acute Lymphoblastic	Biological: CART 19	University of Pennsylvania	2	1	October 2016	December 12, 2018
154	NCT03084380	Anti-GPC3 CAR-T for Treating GPC3-positive Advanced Hepatocellular Carcinoma (HCC)	Unknown status	Hepatocellular Carcinoma	Biological: Retroviral vector-transduced autologous T cells to express anti-GPC3 CARs|Drug: Fludarabine|Drug: Cyclophosphamide	Xinqiao Hospital of Chongqing	1/2	20	June 1, 2017	May 31, 2020
155	NCT03994705	Descartes-11 in Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: Descartes-11|Drug: Fludarabine|Drug: Cyclophosphamide	Cartesian Therapeutics	1/2	18	August 6, 2019	December 2021
156	NCT03265106	A Clinical Study Evaluating the Safety and Efficacy of BinD19 Treatment in Childhood R/R ALL and Lymphoma Subjects	Recruiting	Relapsed B-cell Acute Lymphoblastic Leukemia, Childhood| Refractory B-cell Acute Lymphoblastic Leukemia,	Biological: BinD19	Shenzhen BinDeBio Ltd.|Children's Hospital of Fudan University	1/2	20	November 1, 2016	December 30, 2020

				Childhood| Relapsed/Refractory B-cell Lymphoma, Childhood						
157	NCT03232619	CD19-CART Treatment for ALL	Recruiting	Acute Leukemia	Biological: CD19 CART	Shanghai Bioray Laboratory Inc.|Second Xiangya Hospital of Central South University	1/2	20	August 1, 2018	December 2021
158	NCT04083495	CD30 CAR for Relapsed/Refractory CD30+ T Cell Lymphoma	Recruiting	Peripheral T Cell Lymphoma	Biological: ATLCAR.CD30 T cells	UNC Lineberger Comprehensive Cancer Center	2	20	September 17, 2019	Sep.34
159	NCT02830724	Administering Peripheral Blood Lymphocytes Transduced With a CD70-Binding Chimeric Antigen Receptor to People With CD70 Expressing Cancers	Recruiting	Pancreatic Cancer| Renal Cell Cancer| Breast Cancer|Melanoma| Ovarian Cancer	Drug: Cyclophosphamide|Drug: Fludarabine|Drug: Aldesleukin|Biological: Anti-hCD70 CAR transduced PBL	National Cancer Institute (NCI)|National Institutes of Health Clinical Center (CC)	1/2	124	April 6, 2017	January 1, 2028
160	NCT02134262	Gene Therapy for B-Cell Non-Hodgkin Lymphoma Using CD19 CAR Gene Transduced T Lymphocytes	Unknown status	Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma	Drug: Cyclophosphamide or Bendamustine|Genetic: Dose Level -1|Genetic: Dose Level 1|Genetic: Dose Level 2|Genetic: Dose Level 3	Jichi Medical University|Takara Bio Inc.	1/2	18	May 2014	March 2017
161	NCT03614858	CD19/CD22-targeted Chimeric Antigen Receptor Engineered T Cell (CART) in B-Cell Acute Lymphoblastic Leukemia.	Recruiting	Leukemia, B-cell	Biological: CART-19/22	Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd|The First Affiliated Hospital of Soochow University	1/2	20	September 1, 2017	January 1, 2021
162	NCT03975907	Clinical Trial to Evaluate BCMA Car-T (CT053) in Patients With Relapsed and/or Refractory Multiple Myeloma	Recruiting	Multiple Myeloma	Biological: CAR-BCMA T Cells	Carsgen Therapeutics, Ltd.|Beijing Chao Yang Hospital|The First Affiliated Hospital of Soochow University|Xinhua Hospital, Shanghai Jiao Tong University	1/2	62	June 10, 2019	December 1, 2022

						School of Medicine|Tianjin Medical University General Hospital|				
163	NCT03573700	Evaluation of CD19-Specific CAR Engineered Autologous T-Cells for Treatment of Relapsed/Refractory CD19+ Acute Lymphoblastic Leukemia	Recruiting	Acute Lymphoblastic Leukemia, in Relapse| Acute Lymphoblastic Leukemia, Refractory	Drug: Cyclophosphamide|Drug: Fludarabine|Drug: Mesna|Device: CliniMACS|Biological: CD19- specific CAR engineered autologous T-cells (SJCAR19 product)	St. Jude Children's Research Hospital	1/2	35	July 24, 2018	July 1, 2024
164	NCT03483103	Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-PILOT-017006)	Recruiting	Lymphoma, Non-Hodgkin| Lymphoma, Nonhodgkin| Lymphoma, B-Cell| Lymphoma, Large B-Cell, Diffuse	Biological: lisocabtagene maraleucel	Juno Therapeutics, a Subsidiary of Celgene	2	56	July 26, 2018	July 31, 2022

* 164/175 clinical trials extracted (11 trials excluded due to non-cancer indications)

*Table 11: Overview of CAR-T Cell products in clinical trials: results from https://apps.who.int/trialsearch/**

	Trial ID	Title	Status	Conditions	Interventions	Sponsor/ Collaborators	Phase	Number of patients	Start Date	Completion Date
1	ChiCTR2000033989	Single-center, open, single-arm clinical study of the safety and efficacy of anti-CD99 Car-T infusion in the treatment of recurrent/refractory CD99+ lymphoproliferative diseases	recruiting	Patients with CD99 + lymphoproliferative diseases	Infusion Anti - CD99 CAR - T	Affiliated Hospital of Xuzhou Medical University	1/2	20	07/2020	06/2022
2	NCT04440436	Phase I/II Clinical Study to Evaluate the Safety and Efficacy of IM19 Chimeric Antigen Receptor T Cells(CAR-T) in the Treatment of Recurrent or Refractory (R/R) CD19 Positive Aggressive Non-Hodgkin's Lymphoma	recruiting	Recurrent or Refractory (R/R) CD19 Positive Aggressive Non-Hodgkin's Lymphoma	IM19 CAR-T Cells	Beijing Immunochina Medical Science & Technology Co., Ltd. China	1/2	52	06/2020	06/2022
3	ChiCTR2000033946	Phase I/II Clinical Study on Fully Human BCMA Chimeric Antigen Receptor Autologous T Cell Injection (CT103A) in the Treatment of Patients with Relapsed/refractory Multiple Myeloma	recruiting	Relapsed/refractory Multiple Myeloma	Fully Human BCMA Chimeric Antigen Receptor Autologous T Cell Injection	Huazhong University of Science Tongji Hospital, Tongji Medical College	1/2	50	09/2019	09/2022
4	NCT04433221	Safety and Efficacy Evaluation of a Combination Immunotherapy Targeting Sarcomas	recruiting	sarcoma	Multiple sarcoma-specific CAR-T cells and sarcoma vaccines	Shenzhen Geno-Immune Medical Institute	1/2	20	07/2020	05/2023
5	NCT04309981	Clinical Trial Using Humanized CART Directed Against BCMA (ARI0002h) in Patients With Relapsed/Refractory Multiple Myeloma to Proteasome Inhibitors, Immunomodulators and Anti-CD38 Antibody.	recruiting	Relapsed/ Refractory Multiple Myeloma	CARTBCMA ARI0002h	Sara V. Latorre	1/2	36	05/2020	04/2023
6	NCT04276870	Phase 2 Trial of CD19-Directed Chimeric Antigen Receptor CD19 Redirected Autologous T Cells (CART19) for Orphan Indications of Pediatric B Cell Acute Lymphoblastic Leukemia (B ALL)	recruiting	CD19+ B-ALL	Murine CART19	University of Pennsylvania	2	81	03/2020	03/2035
7	NCT02349698	A Clinical Research of CAR T Cells Targeting CD19 Positive	recruiting	Relapsed or refractory B cell	Chimeric Antigen Receptor Modified	Southwest Hospital, China	1/2	45	12/2014	12/2023

		Malignant B-cell Derived Leukemia and Lymphoma		derived acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and non-hodgkin lymphoma	T cells Targeting CD19					
8	ISRCTN11885863	Investigating the safety and efficacy of a Universal CAR-T cell immunotherapy in patients with relapse and refractory B-cell acute lymphoblastic leukemia and B lymphoblastic lymphoma	ongoing	Relapse and refractory B cell malignancies, Malignant neoplasms, B cell malignancy, B cell lymphoma, B cell leukaemia	GC197 injection	Gracell Biotechnologies Co., Ltd	1/2	15	02/2020	-
9	ISRCTN19144142	A single-arm, open-label, single-center study of GC027 injection in relapse and refractory T-ALL or relapse and refractory T-LBL	ongoing	Relapse and Refractory T cell acute lymphoblastic leukaemia (T-ALL), Relapse and Refractory T cell lymphoblastic lymphoma (T-LBL)	GC027 injection	Gracell Biotechnologies Co., Ltd	1/2	15	01/2020	-
10	ChiCTR2000028781	Evaluation of the safety and efficacy of CD19 CAR-T cells therapy for Refractory/Relapse Central Nervous System Diffuse Large B-cell Lymphoma	recruiting	Hematological malignancy	CAR-T cells	The Third Affiliated Hospital of Kunming Medical University	-	8	10/2019	-
11	NCT04163575	Immunotherapy With CD22 CAR T-cells for B-Cell Lymphoma, ALL and CLL	Not yet recruiting	Relapsed or refractory B cell derived acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL) and non-hodgkin lymphoma.	Anti-CD22-CAR	Kecellitics Biotech Company Ltd	1/2	100	02/2020	07/2022
12	NCT04077866	B7-H3-Targeted Chimeric Antigen Receptor (CAR) T Cells in Treating Patients With	recruiting	Recurrent Glioblastoma	Biological: B7-H3 CAR-T	Second Affiliated Hospital, School of Medicine, Zhejiang University; BoYuan	1/2	40	05/2022	07/2024

		Recurrent or Refractory Glioblastoma				RunSheng Pharma (Hangzhou) Co., Ltd.				
13	ChiCTR1900024824	A phase I/II study for the tolerance, safety, cell kinetics and efficiency of immunotherapy in patients With stage III/IV colorectal cancer	recruiting	Colorectal cancer	CAR-T cells	Peking University Shougang Hospital	1/2	30	07/2019	-
14	NCT04016129	CART Immunotherapy Targeting CD19 Negative Acute Lymphoblastic Leukemia	recruiting	B-cell Leukemia	Biological: 4SCAR-CD22/CD123/CD38 /CD10/CD20/TSLPR	Shenzhen Geno-Immune Medical Institute	1/2	100	07/2019	12/2023
15	NCT04008524	A Clinical Study of CAR-T Cells in the Treatment of Relapsed and Refractory Hematological Malignancies	available	Relapsed and Refractory Hematological Malignancies	Biological: CAR-T cells	Institute of Hematology & Blood Diseases Hospital; Juventas Cell Therapy Ltd.	Expanded access	-	-	-
16	ChiCTR1900023624	BCMA-CAR-T\CD138-CAR-T cell sequential therapy for relapse refractory Multiple Myeloma clinical study	pending	relapse refractory Multiple Myeloma	BCMA-CAR-T\CD138-CAR-T cell therapy	He'nan Provincial People's Hospital	-	20	06/2019	-
17	NCT03941626	EGFRvIII/DR5/NY-ESO-1/Mesothelin CAR-T/TCR-T Cells Immunotherapy for Solid Malignancies	recruiting	anti-NY-ESO-1 antibody for esophagus cancer;anti-DR5 antibody for hepatoma; anti-EGFR vIII antibody for hepatoma and glioma; anti-Mesothelin antibody for gastric cancer.	Biological: CAR-T/TCR-T cells immunotherapy	Shenzhen BinDeBio Ltd.	1/2	50	09/2019	12/2020
18	NCT03941457	Clinical Research of ROBO1 Specific BiCAR-NK Cells on Patients With Pancreatic Cancer	recruiting	Pancreatic cancer	Biological: BiCAR-NK cells (ROBO1 CAR-NK cells)	Asclepius Technology Company Group (Suzhou) Co., Ltd.	1/2	9	05/2019	05/2022
19	NCT03940820	Clinical Research of ROBO1 Specific CAR-NK Cells on Patients With Solid Tumors	recruiting	Solid tumors	Biological: ROBO1 CAR-NK cells	Asclepius Technology Company Group (Suzhou) Co., Ltd.	1/2	20	05/2019	05/2022

20	NCT03940833	Clinical Research of Adoptive BCMA CAR-NK Cells on Relapse/Refractory MM	recruiting	Multiple Myeloma	Biological: BCMA CAR-NK 92 cells	Asclepius Technology Company Group (Suzhou) Co., Ltd.	1/2	20	05/2019	05/2022
21	NCT03938987	Anti-CD19, Dual Co-stimulatory (4-1BB, CD3ζ) Chimeric Antigen Receptor T-cells in Patients With Relapsed/Refractory Aggressive Lymphoma or Acute Lymphoblastic Leukemia (ALL) (ACIT001/EXC002)	Not yet recruiting	Relapsed Non Hodgkin Lymphoma Relapsed Adult ALL Relapsed Pediatric ALL	autologous CD19-directed chimeric antigen receptor (CAR) T-cells	University of Alberta	1/2	63	09/2020	12/2024
22	NCT03931720	Clinical Research of ROBO1 Specific BiCAR-NK/T Cells on Patients With Malignant Tumor	recruiting	Advanced solid tumors	Biological: BiCAR-NK/T cells (ROBO1 CAR-NK/T cells)	Asclepius Technology Company Group (Suzhou) Co., Ltd.	1/2	20	05/2019	05/2022
23	NCT03937544	Intravenous Autologous CD19 CAR-T Cells for R/R B-ALL	recruiting	Relapsed B Acute Lymphoblastic Leukaemia	CD19 CAR-T CELLS	National University of Malaysia, Gaia Science	2/3	10	03/2019	03/2024
24	NCT03896854	CART-19 T Cell in CD19 Positive Relapsed or Refractory Acute Myeloid Leukemia (AML)	recruiting	Acute Myeloid Leukemia (AML)	CART-19	Shanghai Unicar-Therapy Bio-medicine Technology Co.,Ltd	1/2	15	10/2017	01/2022
25	NCT03792633	Study of huCART19 for Very High-Risk (VHR) Subsets of Pediatric B-ALL	recruiting	Acute Lymphoid Leukemia	huCART19 (huCTL019)	University of Pennsylvania	2	85	01/2019	08/2021
26	ChiCTR1800020306	A single arm study for PD1 Gene knock-down anti-CD19 CAR-T Cell Immunotherapy for Relapsed/ Refractory/High risk B Cell Malignancies	recruiting	B Cell Malignancies	PD1 Gene knock-down anti-CD19 CAR-T Cell Immunotherapy	The Affiliated Tumor Hospital of Guangxi Medical University	2	20	12/2018	-
27	ChiCTR1800020064	A single-center, single-arm, open-label, dose escalation study for evaluating the safety & preliminary anti-tumor activity of CD19 allogeneic chimeric antigen receptor T cells (CD19 Allo-CAR-T) in the treatment of patients with relapsed / refractory B cell malignancies	recruiting	CD19-positive B cell malignancy	CD19 Allo-CAR-T	Tianjin First Central Hospital	1/2	15	12/2018	-
28	ChiCTR1800018277	Safety and efficacy of autologous PSCA-CAR-T cells immunotherapy for castration	recruiting	castration resistant prostate cancer	PSCA-CAR-T infusion	Hebei General Hospital	1/2	-	09/2018	-

		resistant prostate cancer: a A phase I & phase II study								
29	ChiCTR1800018142	Treatment of Relapsed or Refractory B-Cell Lymphoma by PD-1 Antibody Coexpression CD19-Targeted Chimeric Antigen Receptor (CAR)-Modified T Cells	recruiting	Relapsed or Refractory B-Cell Lymphoma	PD-1 Antibody Coexpression CD19-Targeted Chimeric Antigen Receptor (CAR)-Modified T Cells	Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	1/2	20	09/2018	-
30	ChiCTR1800018111	Treatment of Relapsed or Refractory B-Cell Lymphoma by CD19-Targeted Chimeric Antigen Receptor (CAR)-Modified T Cells	recruiting	Relapsed or Refractory B-Cell Lymphoma	CD19-Targeted Chimeric Antigen Receptor (CAR)-Modified T Cells	Istitute of Hematology, Union Hospital,Tongji Medical College,Huazhong University of Science and Technology	1/2	20	09/2018	-
31	ChiCTR1800017892	Safety and efficacy research of Chimeric Antigen Receptor T-Cell targeting CD19 in the treatment of CD19 positive malignant b-cell leukemia or lymphoma	recruiting	malignant b-cell leukemia or lymphoma	CAR-T cells	Affiliated Hospital of Jining Medical College	1/2	20	06/2018	-
32	NCT03638206	Autologous CAR-T/TCR-T Cell Immunotherapy for Malignancies	recruiting	B-cell Acute Lymphoblastic Leukemia Lymphoma Myeloid Leukemia Multiple Myeloma Hepatoma Gastric Cancer Pancreatic Cancer Mesothelioma Colorectal Cancer Esophagus Cancer Lung Cancer Glioma Melanoma Synovial Sarcoma	CAR-T cell immunotherapy	Shenzhen BinDeBio Ltd.	1/2	73	03/2018	03/2023

				Ovarian Cancer Renal Carcinoma						
33	NCT03651128	Efficacy and Safety Study of bb2121 Versus Standard Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)	recruiting	Multiple Myeloma	Biological: bb2121	Celgene	3	381	10/2018	06/2025
34	NCT02644655	Immunotherapy Using Autologous T Cell-Engineered With CD19-specific Chimeric Antigen Receptor for the Treatment of Recurrent /Refractory B Cell Leukemia	unknown	Recurrent B-Cell Tumor	CD19-specific chimeric antigen receptor	Second Military Medical University	1/2	20	09/2015	09/2017
35	NCT02742727	CAR-pNK Cell Immunotherapy in CD7 Positive Leukemia and Lymphoma	unknown	CD7 positive relapsed or refractory Leukemia and Lymphoma	anti-CD7 CAR-pNK cells	PersonGen BioTherapeutics (Suzhou) Co., Ltd	1/2	10	03/2016	03/2018
36	NCT02839954	CAR-pNK Cell Immunotherapy in MUC1 Positive Relapsed or Refractory Solid Tumor	unknown	MUC1 positive relapsed or refractory solid tumor.	anti-MUC1 CAR-pNK cells	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	1/2	10	07/2016	07/2018
37	ChiCTR-OIC-16008291	A clinical study of chimeric antigen receptor T-cell immunotherapy in the treatment of CD19+ B-cell hematologic malignancies	recruiting	B-cell hematologic malignancies	CAR-T cells	The Affiliated Hospital of Xuzhou Medical College	2	60	04/2016	-
38	ChiCTR-OIN-16007723	A clinical trial of anti-CD19 chimeric antigen receptor–modified T cells (Anti-CD19 CAR-T) therapy for relapsed, refractory and high-risk CD19+ B cell malignancies	recruiting	1.B cell Acute lymphoblastic leukemia. 2.Indolent B cell lymphoma (CLL, FL, MZL, LPL, HCL). 3.Aggressive B cell lymphoma (DLBCL, BL, MCL). 4.Multiple myeloma (MM).	autologous Car-T cells	Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	1/2	20	01/2016	-
39	ChiCTR-OIC-17012374	Clinical study on the safety and efficacy of allogeneic hematopoietic stem cell transplantation combined with	recruiting	B-cell hematologic malignancies	CAR-T cells	The Affiliated Hospital of Xuzhou Medical University	2	20	08/2017	-

		CD19 CAR-T in the treatment of B-cell hematologic malignancies								
40	ChiCTR-OIC-17013633	Anti-CD19 Chimeric Antigen Receptor (CAR)-Transduced T Cell Therapy for Patients With B Cell Malignancies	recruiting	B-Cell Malignancies	Anti-CD19-CAR transduced T cells	Shenzhen Innovation Immunotechnology Co., Ltd	1/2	20	12/2017	-
41	NCT02851589	Study Evaluating the Efficacy and Safety of PCAR-019 in CD19 Positive Relapsed or Refractory Leukemia and Lymphoma	unknown	CD19 positive relapsed or refractory Leukemia and Lymphoma	PCAR-019 (anti-CD19 CAR-T cells)	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	1/2	10	11/2018	11/2019
42	NCT02862704	A Study of MG7 Redirected Autologous T Cells for Advanced MG7 Positive Liver Metastases(MG7-CART)	unknown	liver metastases expressing MG7 positively	Biological: MG7-CART	Shanghai GeneChem Co., Ltd.	1/2	20	06/2016	12/2017
43	NCT02965157	Pilot Study of Anti-CD20-CAR-engineered T Cells in Patients With Chemotherapy Resistant or Refractory CD20+ Lymphoma	unknown	B-Cell Lymphoma	CART20	Beijing Biohealthcare Biotechnology Co.,Ltd	1/2	15	08/2016	01/2018
44	NCT02587689	Phase I/II Study of Anti-Mucin1 (MUC1) CAR T Cells for Patients With MUC1+ Advanced Refractory Solid Tumor	unknown	Hepatocellular Carcinoma Non-small Cell Lung Cancer Pancreatic Carcinoma Triple-Negative Invasive Breast Carcinoma	anti-MUC1 CAR T Cells	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	1/2	20	10/2015	10/2018
45	ChiCTR-OIC-17011272	An open single center single arm clinical study of through infusion of anti-BCMA CAR-T and anti-CD19 CAR-T therapy for relapsed and refractory multiply myeloma	recruiting	Multiple Myeloma	CAR-T cells	The Affiliated Hospital of Xuzhou Medical University	2	20	05/2017	-
46	ChiCTR-OIC-17011271	An open single center single arm clinical study of t fully human anti-CD19 CAR-T therapy for CD19+ B-cell hematologic malignancies	recruiting	B-cell hematologic malignancies	CAR-T cells	The Affiliated Hospital of Xuzhou Medical University	2	20	05/2017	-
47	ChiCTR-OIC-16009259	Phase II study of autologous anti-CD19 chimeric antigen receptor T cells treating	recruiting	refractory or relapsed B acute lymphoblastic leukemia	Chimeric Antigen Receptor T-Cell Immunotherapy	Hebei Yanda Ludaopei Hospital	2	30	09/2016	-

		refractory and relapsed B acute lymphoblastic leukemia								
48	ChiCTR-OIN-17011414	Clinical trials on immune targeting bladder cancer gene with modified T cell interventional therapy	recruiting	Bladder cancer	4S-PSMA-CART	Shenzhen Geno-immune Medical Institute	1/2	10	05/2017	-
49	ChiCTR1800014936	Clinical Study on Safety and Efficacy of TSHR CART Cell in the Treatment of Refractory Thyroid Cancer	recruiting	Relapsed / refractory thyroid cancer	Relapsed / refractory thyroid cancer	Henan Province Cancer Hospita	1/2	10	02/2018	-
50	NCT02575261	CAR-T Cell Immunotherapy for EphA2 Positive Malignant Glioma Patients	completed	EphA2 positive malignant glioma patients	CAR-T cell immunotherapy	Fuda Cancer Hospital, Guangzhou	1/2	60	09/2015	08/2017
51	NCT02819583	CAR-T Cell Immunotherapy in CD19 Positive Relapsed or Refractory Leukemia and Lymphoma	unknown	CD19 positive relapsed or refractory Leukemia and Lymphoma.	PCAR-019 (anti-CD19 CAR-T cells)	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	1/2	10	10/2016	09/2019
52	NCT02617134	CAR-T Cell Immunotherapy in MUC1 Positive Solid Tumor	unknown	Malignant Glioma of Brain Colorectal Carcinoma Gastric Carcinoma	anti-MUC1 CAR-T cells	PersonGen BioTherapeutics (Suzhou) Co., Ltd	1/2	20	11/2015	11/2018
53	NCT02892695	PCAR-119 Bridge Immunotherapy Prior to Stem Cell Transplant in Treating Patients With CD19 Positive Leukemia and Lymphoma	unknown	Acute Lymphocytic Leukemia Chronic Lymphocytic Leukemia Follicular Lymphoma Mantle Cell Lymphoma B-cell Prolymphocytic Leukemia Diffuse Large Cell Lymphoma	Biological: anti-CD19 CAR-NK cells	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	1/2	10	09/2016	09/2019
54	NCT02944162	CAR-pNK Cell Immunotherapy for Relapsed/Refractory CD33+ AML	unknown	AML	anti-CD33 CAR-NK cells	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	1/2	10	10/2016	09/2018
55	NCT03263208	CD19 CAR-T Cells for Patients With Relapse and Refractory CD19+ B-ALL	unknown	B-cell Acute Lymphocytic Leukemia	CD19 CAR-T	The Pregene (ShenZhen)	1/2	20	08/2017	07/2019

						Biotechnology Company, Ltd				
56	NCT03076437	Anti-CD19 Chimeric Antigen Receptor (CAR)-Transduced T Cell Therapy for Patients With B Cell Malignancies	unknown	Acute Lymphocytic Leukemia Chronic Lymphocytic Leukemia Lymphoma	Anti-CD19-CAR transduced T cells	Shenzhen Institute for Innovation and Translational Medicine	1/2	36	01/2016	12/2019
57	NCT00924287	Gene Therapy Using Anti-Her-2 Cells to Treat Metastatic Cancer	terminated (This study was terminated after the first patient treated on study died as a result of the treatment.)	Metastatic cancer	chimeric T cell receptor (CAR) gene-transduced PBL	National Cancer Institute (NCI)	1/2	1	11/2008	12/2010
58	NCT02547948	CD19-targeting CAR T Cells for Refractory B Cell Lymphoma	completed	B Cell lymphoma	CD19-targeting CAR T Cells	Fuda Cancer Hospital, Guangzhou	1/1	60	09/2015	08/2017
59	NCT02547961	Chimeric Antigen Receptor-Modified T Cells for Breast Cancer	completed	Breast cancer	Biological: HER-2-targeting CAR T Cells infusion	Fuda Cancer Hospital, Guangzhou	1/2	60	09/2015	08/2017
60	NCT03130712	A Study of GPC3-targeted T Cells by Intratumor Injection for Advanced HCC (GPC3-CART)	unknown	Hepatocellular carcinoma	Drug: GPC3-CART cells	Shanghai GeneChem Co., Ltd.	1/2	10	04/2017	03/2018
61	NCT02963038	CAR T Cells for Refractory B Cell Malignancy	recruiting	B-Cell Leukemia B-Cell Lymphoma	Biological: Autologous CD19-targeting CAR T cells	Hebei Senlang Biotechnology Inc., Ltd.	1/2	10	06/2016	06/2021
62	NCT03252171	CAR-T Cell Immunotherapy for GD2 Positive Glioma Patients	completed	GD2 Positive Glioma	CAR-T cell immunotherapy	Fuda Cancer Hospital, Guangzhou	1/2	60	10/2015	08/2017
63	ChiCTR1800014927	MUC-1 targeted Chimeric Antigen Receptor T Cells (CART) Therapy in Pancreatic Cancer	recruiting	Pancreatic cancer	MUC-1 CAR Tcell	Henan Province Cancer Hospital	1/2	10	02/2018	-
64	ChiCTR1800015817	CD19 targeted Chimeric Antigen Receptor T Cells (CART) Therapy in	recruiting	Refractory Aggressive Non-Hodgkin	CD19 CART cell	The First Affiliated Hospital of Medical School of Zhejiang University	1/2	10	04/2017	-

		Refractory/Relapsed non - Hodgkin's lymphoma		Lymphoma (NHL)						
65	ChiCTR1800015855	Clinical study of GPC3-targeted Autologous T cells in patients with advanced hepatocellular carcinoma	recruiting	Liver tumor	CAR-GPC3 T-cell	the Affiliated Drum Tower Hospital, School of Medicine, Nanjing University	2	20	06/2018	-
66	NCT03556982	CART-123 FOR Relapsed/Refractory Acute Myelocytic Leukemia（AML）	unknown	AML	CART-123 cells	The Affiliated Hospital of the Chinese Academy of Military Medical Sciences	1/2	10	03/2018	03/2020
67	NCT03544021	CART-19 FOR Relapsed/Refractory Acute Lymphoblastic Leukemia （ALL ）	unknown	ALL	CART-19 cells	The Affiliated Hospital of the Chinese Academy of Military Medical Sciences	1/2	10	03/2018	03/2020
68	JPRN-UMIN000015617	Clinical Research of gene therapy for relapsed or refractory B-cell Non-Hodgkin Lymphoma using autologous T cells expressing a chimeric antigen receptor specific to the CD19 antigen	recruiting	Relapsed/ Refractory CD19+ B-NHL	CD19-CAR-T cells	Jichi Medical University	1/2	18	11/2014	-
69	JPRN-JapicCTI-183914	A Phase 2 Multicenter, Open-label, Single-arm Study of KTE-C19 in Japanese Patients with Refractory or Relapsed Large B Cell Lymphoma	completed	Refractory or relapsed (relapse after transplant or relapse after medication in patients ineligible for transplant) diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), transformed follicular lymphoma (TFL) or High-grade B cell lymphoma	axicabtagene ciloleucel (Anti-CD19 CAR T cells, KTE-C19)	DAIICHI SANKYO Co.,Ltd.	2	10	10/2018	-
70	TCTR20160921001	Phase I/II Pilot Study of Maximum Tolerated Dose of Chimeric Antigen Receptor	Enrolling by invitation	B-cell leukemia	CAR-CD19 T cells	TCELS	1/2	15	09/2016	-

		(CAR) - modified T-cell lymphocytes against CD19 antigen in patients with relapsed/refractory B cell leukemia								
71	NCT03579927	CAR.CD19-CD28-zeta-2A-iCasp9-IL15-Transduced Cord Blood NK Cells, High-Dose Chemotherapy, and Stem Cell Transplant in Treating Participants With B-cell Lymphoma	Withdrawn (lack of funding)	CD19 Positive Mantle Cell Lymphoma Recurrent Diffuse Large B-Cell Lymphoma Recurrent Follicular Lymphoma Refractory B-Cell Non-Hodgkin Lymphoma Refractory Diffuse Large B-Cell Lymphoma Refractory Follicular Lymphoma	CAR.CD19-CD28-zeta-2A-iCasp9-IL15-transduced cord blood natural killer (CB-NK) cells	M.D. Anderson Cancer Center	1/2	0	03/2019	-
72	NCT02794246	CART-19 Post-ASCT for Multiple Myeloma	Terminated (Study was terminated due to administrative reasons.)	Multiple myeloma	CART-19 cells	University of Pennsylvania	2	6	06/2016	05/2019
73	NCT01747486	Dose Optimization Trial of CD19 Redirected Autologous T Cells	completed	Relapsed or Refractory CLL (3rd Line) or SLL	CART-19 Tisagenlecleucel-T	University of Pennsylvania	2	42	01/2013	04/2018
74	NCT03185468	Intervention of Bladder Cancer by CAR-T	recruiting	Bladder Cancer Urothelial Carcinoma Bladder	4SCAR-PSMA 4SCAR-FRa	Shenzhen Geno-Immune Medical Institute	1/2	20	05/2017	12/2020
75	NCT03594162	Compassionate Use of CAR T Cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch	No longer available	ALL	iC9-CAR19 cells	Bellicum Pharmaceuticals	-	-	07/2018	-
76	NCT02744287	Use of Ligand-Inducible Autologous T Cells Engineered to Target PSCA on Tumor Cells in Selected Advanced Solid Tumors	recruiting	Pancreatic Adeno-carcinoma Gastric Adeno-carcinoma	Biological: BPX-601	Bellicum Pharmaceuticals	1/2	151	11/2016	02/2024

				Prostate Adeno-carcinoma						
77	NCT03601078	An Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma and in Subjects With High-Risk Multiple Myeloma (KarMMa-2)	Recruiting	Multiple myeloma	bb2121	Celgene	2	181	12/2018	03/2025
78	NCT03391466	Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7)	Active, not recruiting	Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL)	Axicabtagene Ciloleucel	Kite, A Gilead Company	3	359	12/2017	01/2035
79	NCT02690545	Study of CD30 CAR for Relapsed/Refractory CD30+ HL and CD30+ NHL	Recruiting	Lymphoma Lymphoma, Non-Hodgkin	ATLCAR.CD30 cells	UNC Lineberger Comprehensive Cancer Center	1/2	40	08/2016	02/2022

* Note: clinical trials already identified from clinicaltrials.gov are excluded; 79/288 trials extracted (209 trials for non-cancer conditions, with other interventions, or duplicates)

*Table 12: Overview of CAR-T Cell products in clinical trials: results from EU Clinical Trials Register (Trials with EudraCT Protocol)**

	EudraCT number	Title	Status	Conditions	Interventions	Sponsor/ Collaborators	Phase	Number of patients	Start Date	Completion Date
1	2016-004043-36	CD19-TARGETING 3RD GENERATION CAR T CELLS FOR REFRACTORY B CELL MALIGNANCY – A PHASE II TRIAL	ongoing	CD19+ B cell lymphoma or leukemia	3rd generation anti-CD19 CAR T cells	Uppsala University	2	25	04/2017	-
2	2016-004867-38	Long-term follow-up of patients previously treated with autologous T cells genetically modified with viral vectors.	ongoing	Potential malignancy in patients who received treatment with Autolus' CAR T cell therapy	AUTO3 (CD19/22-CAR POSITIVE T CELLS)	Autolus Limited	-	500	05/2018	-
3	2014-001673-14 (NCT02445222)	Long Term Follow-Up of Patients Exposed to Lentiviral-Based CAR T-Cell Therapy	ongoing	B-cell type acute leukaemia B-cell lymphoma	tisagenlecleucel-T	Novartis Pharma Services AG	-	700	06/2015	-
4	2019-001937-16	An Open-Label, Multi-Centre, Phase Ib/II Study Evaluating The Safety and Efficacy Of AUTO1, A CAR T Cell Treatment Targeting CD19, In Adult Patients With Relapsed Or Refractory B Cell Acute Lymphoblastic Leukaemia	ongoing	Relapsed or refractory B cell acute lymphoblastic leukaemia	AUTO1 (Autologous enriched T-cells transduced with a lentiviral vector to express anti-CD19 chimeric antigen receptor)	Autolus Limited	1b/2	145	02/2020	-
5	2019-001413-16	A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma	ongoing	Multiple myeloma	JNJ-68284528	Janssen-Cilag International NV	3	400	05/2020	-
6	2016-004808-60	Treatment of patients with relapsed or refractory CD19+ lymphoid disease with T lymphocytes transduced by RV-SFG.CD19.CD28.4-1BBzeta retroviral vector - A unicenter Phase I /II clinical trial	ongoing	Acute lymphoblastic leukemia recurrent Non-Hodgkin's lymphoma NOS refractory	3G. CD19 CAR T Cells	University Hospital Heidelberg	1/2	48	07/2017	-
7	2018-004124-10	A Phase 2, Multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T)	ongoing	Multiple Myeloma	JNJ-68284528	Janssen-Cilag International NV	2	80	12/2019	-

		Therapy Directed Against BCMA in Subjects with Multiple Myeloma								
8	2018-000264-28	A Phase 2, Multi-cohort, Open-label, Multi-center Study to Determine the Efficacy and Safety of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma and in Subjects With High-Risk Multiple Myeloma Having Progressed Within One Year of Initial Treatment (KarMMa-2)	restarted	Relapsed and Refractory Multiple Myeloma and High-Risk Multiple Myeloma Having Progressed Within One Year of Initial Treatment	Autologous CD3+ T Cells Expressing BCMA Chimeric Antigen Receptor (bb2121)	Celgene Corporation	2	122	08/2018	-
9	2018-000121-32	A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma	Pre-maturely Ended	Relapsed or Refractory Multiple Myeloma	JNJ-68284528	Janssen-Cilag International NV	1b/2	110	09/2019	-
10	2017-002245-29 (NCT03361748)	A phase 2, multicenter study to determine the efficacy and safety of bb2121 in subjects with relapsed and refractory multiple myeloma	ongoing	Multiple myeloma	Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector (bb2121)	Celgene Corporation	2	140	05/2018	-
11	2017-002849-30 (NCT01626495)	A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCRzeta and 4-1BB Signaling Domains in Patients With Chemotherapy Resistant Or Refractory CD19+ Leukemia and Lymphoma	ongoing	Chemotherapy resistant or refractory CD19+ B-cell Leukemia and Lymphoma	tisagenlecleucel	University of Pennsylvania/Novartis Pharma	1/2a	86	11/2017	-
12	2015-005007-86 (NCT02348216)	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL) (ZUMA-1)	ongoing	Diffuse Large B-cell Lymphoma (DLBCL), Primary Mediastinal B cell lymphoma (PMBCL) and Transformed Follicular Lymphoma (TFL).	axicabtagene ciloleucel	Kite Pharma, Inc	1/2	286	07/2017	-
13	2018-003916-38	A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Efficacy of Allogeneic CRISPR-Cas9–Engineered T Cells (CTX110) in Subjects with Relapsed or Refractory B-Cell Malignancies	ongoing	diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) - high grade B-cell lymphoma with MYC	CTX110	CRISPR Therapeutics AG	1/2	95	12/2019	-

				and BCL2 and/or BCL6 re-arrangements - transformed follicular lymphoma (FL) - grade 3b FL - Richter's transformation of chronic lymphocytic leukemia (CLL)						
14	2014-003060-20 (NCT02445248)	A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	ongoing	relapsed or refractory DLBCL, having failed 2 or more lines of therapy and not eligible for HSCT	tisagenlecleucel-T	Novartis Pharma Services AG	2	100	10/2015	-
15	2016-001706-42	A Phase 2, Open-Label, Multiple Cohort, Single-Arm, Multi-Center Trial To Determine The Safety, Feasibility, And Efficacy Of JCAR015 In Adult Subjects With B-Cell Acute Lymphoblastic Leukemia	Pre-maturely Ended	B-cell Acute Lymphoblastic Leukemia (ALL)	Autologous CD3+ T Cells Expressing CD19 Chimeric Antigen Receptor (JCAR015)	Celgene Corporation	2	105	11/2016	03/2017
16	2015-005008-27 (NCT02601313)	Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (r/r MCL) (ZUMA-2)	Ongoing	Relapsed/Refractory Mantle Cell Lymphoma (MCL)	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (KTE-X19)	Kite Pharma, Inc	2	130	08/2018	-
17	2018-001023-38	A Phase 3, Multicenter, Randomized, Open Label Study to Compare the Efficacy and Safety of BB2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)	ongoing	Multiple myeloma (MM) with at least 2 prior therapies including an immunomodulatory (IMiD) compound and a proteasome inhibitor (PI) and demonstrated disease progression on or within 60 days of completion of the last therapy.	Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector - bb2121 (ide-cel) idecabtagene vicleucel	Celgene Corporation	3	381	08/2019	-
18	2018-000929-32 (NCT03575351)	A global randomized multicenter Phase 3 trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-	ongoing	Transplant-eligible relapsed or refractory (R/R) aggressive B-cell Non Hodgkin Lymphoma (B-NHL)	JCAR017	Celgene Corporation	3	182	08/2018	-

		cell non-Hodgkin lymphomas (TRANSFORM)								
19	2017-002475-26	Phase I/II study of anti-GD2 Chimeric Antigen Receptor-Expressing T cells in pediatric patients affected by High Risk and/or relapsed/refractory Neuroblastoma	Ongoing	High Risk and/or relapsed/refractory Neuroblastoma	GD2-CART01	IRCCS Ospedale Pediatrico Bambino Gesù, Italy	1/2	42	12/2017	-
20	2017-001912-13 (NCT03105336)	A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL) (ZUMA-5	Ongoing	Relapsed or Refractory Indolent Non-Hodgkin Lymphoma (r/r) iNHL.	axicabtagene ciloleucel (KTE-C19)	Kite Pharma, Inc.	2	50	04/2018	-
21	2017-002088-16	Phase I/II study of anti-CD19 Chimeric Antigen Receptor-Expressing T cells in pediatric patients affected by relapsed/refractory CD19+ Acute Lymphoblastic Leukemia and Non Hodgkin Lymphoma	Su-spended by CA	Acute Lymphoblastic Leukemia and Non Hodgkin Lymphoma	CD19-CART01	Bambino Gesù Children's Hospital, Italy	1/2	32	12/2017	-
22	2017-000106-38	A Phase 2, Single-arm, Multi-cohort, Multi-center Trial to Determine the Efficacy and Safety of JCAR017 in Adult Subjects with Aggressive B-Cell Non-Hodgkin Lymphoma (TRANSCEND WORLD)	restarted	Aggressive B-cell Non Hodgkin Lymphoma (B-NHL)	Lisocabtagene maraleucel (JCAR017)	Celgene Corporation	2	116	07/2018	-
23	2018-001246-34 (NCT03743246)	A phase 1/2, open-label, single arm, multicohort, multicenter trial to evaluate the safety and efficacy of JCAR017 in pediatric subjects with relapsed/refractory B-ALL and B-NHL (TRANSCEND PEDALL)	Tempo-rarily Halted	Relapsed or refractory (r/r) CD19+ B-Cell Acute Lymphoblastic Leukemia (B-ALL) and B-Cell Non-Hodgkin Lymphoma (B-NHL).	Lisocabtagene maraleucel (JCAR017)	Celgene Corporation	1/2	121	07/2019	-
24	2013-001393-19	CD19-targeting 3rd generation CAR T cells for refractory B cell malignancy - a phase I/IIa trial.	completed	CD19+ B cell lymphoma or leukemia	3rd generation CAR T cells	Uppsala university, Sweden	1/2a	30	04/2014	05/2017
25	2019-001264-30	A phase I/IIa clinical trial to assess feasibility, safety and antitumor activity of autologous SLAMF7 CAR-T cells in multiple myeloma	ongoing	Multiple myeloma (MM)	SLAMF7 CAR-T	Universitätsklinikum Würzburg, Germany	1/2a	38	03/2020	-
26	2019-001263-70	Immunotherapy with differential, adult, autologous, peripheral blood cells, expanded and transduced (genetically modified) using a lentiviral vector to express a chimeric receptor with anti-CD30	Ongoing	Classic Hodgkin lymphoma and T-cell lymphoma with CD30 expression	Linfocitos HSP-CAR30	Institut de Recerca H. de la Santa Creu i Sant Pau, Spain	-	30	03/2020	-

		specificity associated with costimulatory sequences 4-1-BB and CD3z in patients with Classical Hodgkin's lymphoma and non-Hodgkin's lymphoma T with CD30 expression								
27	2015-005009-35 (NCT02614066)	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)	Ongoing	Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL)	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor. (KTE-X19)	Kite Pharma Inc	1/2	100	09/2018	-
28	2016-002972-29	Pilot study on the infusion of differentiated autologous T-cells from peripheral blood, expanded and transduced with a lentivirus to express a chimeric antigen receptor with anti-CD19 specificity (A3B1) conjugated with the co-stimulatory regions 4-1BB and CD3z (ARI-0001 cells) in patients with CD19+ leukemia or lymphoma refractory to therapy	Ongoing	Patients with leukemia or lymphoma refractory to therapy	Adult differentiated autologous T-cells from peripheral blood, expanded and transduced with a lentivirus to express a chimeric antigen receptor ARI-0001	IDIBAPS, Spain	-	10	05/2017	-
29	2018-000813-19	A Phase I-IIa trial to assess the safety and antitumor activity of autologous CD44v6 CAR T-cells in acute myeloid leukemia and multiple myeloma expressing CD44v6.	-	Acute myeloid leukemia and Multiple myeloma	MolMed S.p.A.	MolMed S.p.A., Italy	1/2	68	09/2019	-
30	2016-000296-24 (NCT02746952)	Phase I, open label, dose-escalation study followed by a safety expansion part to evaluate the safety, expansion and persistence of a single dose of UCART19 (allogeneic engineered T-cells expressing anti-CD19 chimeric antigen receptor), administered intravenously in patients with relapsed or refractory CD19 positive B-cell acute lymphoblastic leukaemia (B-ALL)).	ongoing	Patients with relapsed or refractory CD19 positive B-cell acute lymphoblastic leukaemia (B-ALL).	CD19CAR/RQR8+_ TCRαβ-_T-cells (UCART19)	Institut de Recherches Internationales Servier (I.R.I.S), France	1	30	05/2016	-

31	2018-001018-14	Phase I, open label dose-escalation study to evaluate the safety, expansion, persistence and clinical activity of multiple infusions of UCART123 (allogeneic engineered T-cells expressing anti-CD123 chimeric antigen receptor) in patients with adverse genetic risk Acute Myeloid Leukaemia	Pre-maturely Ended	Adverse genetic Acute Myeloid Leukaemia	CD123-CAR+_TCRαβ–_T-cells (UCART123)	CELLECTIS SA, France	1	18	11/2018	12/2019
32	2016-000297-38 (NCT02735083)	Long-term follow-up study of patients who have previously been exposed to UCART19 / ALLO-501 (allogeneic engineered T-cells expressing a lentiviral-based anti-CD19 chimeric antigen receptor)	ongoing	Advanced lymphoid malignancies	CD19CAR/RQR8+_TCRαβ-_T-cells (UCART19)	Institut de Recherches Internationales Servier (I.R.I.S), France	-	200	06/2016	-
33	2015-005010-30 (NCT02625480)	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Pediatric and Adolescent Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia or Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma (ZUMA-4)	ongoing	Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) Relapsed/Refractory B-cell non-Hodgkin lymphoma (r/r NHL	autologous peripheral blood T cells CD4 and CD8 selected, and CD3 and CD28 activated transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured KTE-X19	Kite Pharma, Inc	1/2	116	04/2020	-
34	2017-002261-22	A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/ Refractory Diffuse Large B Cell Lymphoma (ZUMA-7)	ongoing	Relapsed/Refractory Diffuse Large B cell Lymphoma (r/r DLBCL).	axicabtagene ciloleucel	Kite Pharma, Inc.	3	350	08/2018	-
35	2016-001991-31	Phase IIIb study for relapsed/refractory pediatric/young adult acute lymphoblastic leukemia patients to be treated with CTL019	completed	Paediatric/young adult patients with B-cell acute lymphoblastic leukaemia who are chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT	Tisagenlecleucel (CTL019)	Novartis Pharma AG	3b	80	03/2017	-

36	2017-005019-15	A Phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in pediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL) (BIANCA)	Ongoing	pediatric and adolescents patients with CD19positive r/r mature B-cell NHL who have relapsed after one or more prior therapies or are primary refractory	Tisagenlecleucel	Novartis Pharma AG	2	35	03/2019	-
37	2016-002966-29	Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial (BELINDA)	Ongoing	adult patients with aggressive B-cell NHL after failure of rituximab and anthracycline containing first line immunochemotherapy	Tisagenlecleucel	Novartis Pharma AG	3	318	03/2019	-
38	2017-002116-14 (NCT03876769)	A phase II trial of tisagenlecleucel in first-line high-risk (HR) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (B-ALL) who are minimal residual disease (MRD) positive at the end of consolidation (EOC) therapy	Ongoing	Pediatric and young adult patients aged 1 to 25 years with first-line NCI high-risk (HR) B-cell acute lymphoblastic leukemia (B-ALL) who are in CR1 with minimal residual disease (MRD) positive (MRD ≥ 0.01%) at the end of consolidation (EOC) therapy by central laboratory assessment	Tisagenlecleucel	Novartis Pharma AG	2	140	07/2019	-
39	2013-003205-25 (NCT02435849)	A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia	ongoing	Paediatric patients with B-cell acute lymphoblastic leukaemia who are chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT	tisagenlecleucel-T	Novartis Pharma Services AG	2	65	01/2016	-
40	2007-007612-29 (NCT01195480)	Immunotherapy with CD19ζ chimeric antigen receptor gene-modified EBV-specific CTLs after stem cell transplant in children with high-risk acute lymphoblastic leukaemia	ongoing	childhood precursor B acute lymphoblastic leukaemia (ALL).	CD19 T Cell Receptor (TCR) gene modified donor EBV-specific Cytotoxic T Lymphocytes (EBV-CTL) - CD19 transduced EBV-CTL	University College London, UK	-	30	09/2011	-
41	2017-001965-26	Phase I/II study evaluating AUTO4 (an experimental drug derived from the patient's own blood) in patients	Ongoing	Relapsed or refractory T cell Non-Hodgkin Lymphoma (T-NHL)	AUTO4	Autolus Ltd, UK	1/2	200	02/2018	-

		with T Cell Lymphoma (a type of blood cancer								
42	2016-004680-39	A Single Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 in Paediatric and Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia.	Ongoing	Acute lymphoblastic leukaemia (ALL)	CD19/CD22-CAR POSITIVE T CELLS – AUTO3	Autolus Limited, UK	1/2	100	06/2017	-
43	2016-004682-11	A Single Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD-1 Antibody in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma.	Ongoing	Relapsed or refractory Diffuse Large B Cell Lymphoma (DLBCL) and large B cell lymphoma subsets	CD19/CD22-CAR POSITIVE T CELLS (AUTO3)	Autolus Limited, UK	1/2	171	07/2017	-
44	2016-003893-42	A Single Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO2, a CAR T Cell Treatment Targeting BCMA and TACI, in Patients with Relapsed or Refractory Multiple Myeloma.	Ongoing (NL) Pre-maturely ended (GB)	Relapsed or Refractory Multiple Myeloma	AUTO2	Autolus Limited, UK	1/2	60	09/2017	-
45	2018-001923-38 (NCT03624036)	Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia	Pre-maturely Ended (ongoing GB)	Relapsed/Refractory Chronic Lymphocytic Leukemia	KTE-X19	Kite Pharma, Inc	1/2	108	05/2019	-
46	2015-004293-15 (NCT02808442)	A phase 1, open label, non-comparative, study to evaluate the safety and the ability of UCART19 to induce molecular remission in paediatric patients with relapsed /refractory B-cell acute lymphoblastic leukaemia	ongoing	Paediatric relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia	CD19CAR/RQR8+_ TCRαβ–_T-cells (UCART19)	Institut de Recherches Internationales Servier (I.R.I.S), France	1	18	05/2016	-

* 46/58 clinical trials (12 clinical trials with other intervention/non-cancer disease were excluded)

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