RUNNING TITLE: Publication landscape in CAR-modified immune cell research

Effects of the COVID-19 pandemic on publication landscape in chimeric antigen receptor-modified immune cell research

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Abstract

Chimeric antigen receptors (CARs) are artificial receptors introduced mainly into T cells. CAR-induced immune cell (CARi) products have achieved impressive success rates in treating some difficult-to-treat hematological malignancies. Here, we describe effects of the global COVID-19 pandemic on CARi publication landscape. Due to the pandemic, the total number of publications decreased in 2020 compared to 2019 in all fields of cancer immunotherapy except CARi. Nearly exponential increases in the number of CARi publications slowed-down in 2020 for the first time in the past 11 years. There were more CARi than coronavirus publications until 2020 when coronavirus publications increased over 5,000% compared to 2019 (575 publications in 2019 vs. 30,390 in 2020). Unlike cancer immunotherapy where the majority of the publications consist of conference abstracts and review articles, majority of the coronavirus publications are original research articles. There are more coronavirus publications in Pubmed than Embase. The opposite is true for CARi publications. Our analysis of the data from the FDA Adverse Event Reporting System (FAERS) show significantly higher death rate in patients treated with Kymirah than Yescarta (28.14% vs. 16.02%). Kymirah and Yescarta are the two main CAR T cell products for treatment of DLBCL and/or B-ALL. However, despite being highly significant, this result is not easily interpretable due to multiple confounding variables in the FAERS data. Our analysis additionally suggest that the significant effects of co-stimulatory domains (4-1BB vs. CD28) consistently reported in preclinical studies do not translate into clinical results. Our manual curation of the CARi publications in PubMed shows that only 5.2% of the publications report results from CARi clinical trials, although we found 663 clinical trials listed on ClinicalTrials.gov database. In conclusion, publication landscape in CARi as well as other fields

of cancer immunotherapy has changed due to the global COVID-19 pandemic. This trend will likely continue in the near future. CARi research is now in need of increased measures by publishers to reduce repetitive and/or duplicate publications and more stringent criteria for data entry into public databases including PubMed, Embase, ClinicalTrials.gov, and FAERS to advance this important field of medical research.

Keywords: Chimeric antigen receptor, T cells, NK cells, Cancer immunotherapy, Coronavirus

The COVID-19 pandemic has re-shaped the publication landscape in chimeric antigen receptor-modified immune cell research

The global COVID-19 pandemic is probably one of the most significant natural disasters in modern times with major biological, economical, and social impacts on the society at large. Effects of the pandemic on publication landscape in cancer immunotherapy research have not been thoroughly investigated in the literature. Here, we provide a comprehensive overview of the changes in the field due to the pandemic with a focus on chimeric antigen receptor (CAR)-modified immune cell (CARi) research.

CARs are artificial receptors introduced mainly into T cells¹. We and others have shown that CAR-induced natural killer (CAR NK) cells are likely as effective and offer additional advantages compared to the CAR-induced T (CAR T) cells²⁻⁶. CARs are composed of an extracellular single-chain variable fragment (scFv) domain derived from the heavy and light chains of monoclonal antibodies raised against tumor-associated antigens (TAA) attached to intracellular activating domain(s) such as CD3 ζ and/or co-stimulatory domain(s) such as CD28 or 4-1BB⁶. The binding of the extracellular domain to the TAA, which may be as specific as in binding by monoclonal antibodies, activates the intracellular domain(s), which in turn activates the immune cell, resulting in the killing of tumor cells.

CARi research has been one of the most exciting fields in immunotherapy. Anti-CD19 CAR T cells have achieved unprecedented success rates as high as 90% in treating relapsed or refractory acute lymphoblastic leukemia (ALL) and other B cell leukemia and lymphomas, bringing fresh

hope to cancer patients and prompting the FDA to issue breakthrough designations⁷. CARi therapy is one of the costliest types of immunotherapy, but it is covered by The Centers for Medicare and Medicaid Services in the U.S. The CARi technology is projected to create a market in the range of billions of U.S. dollars in the near future⁸. Along with this huge clinical success has come a boom in the number of publications.

Publications containing the terms “chimeric antigen receptor” in the title or abstract have ballooned from a single publication in 1989 to 1,391 in 2020 in PubMed (Medline) and 1,629 in Embase (Excerpta Medica dataBASE) (Fig. 1A). As of January 2021, there are 4,192 and 7,140 CARi publications in PubMed and Embase, respectively. Moreover, 2,725 publications are shared between the two databases whereas 348 and 4,035 publications are unique to the Medline and Embase, respectively (Fig. 1B). Each year since 2010 has seen a nearly exponential increase in the number of CARi publications except that in 2020, a year heavily affected by COVID-19, where the total number of publications in Embase seemed to reach a plateau (Fig. 1A); the publication growth rate was only 4.78% compared to 2019 (1,555 vs. 1,632), the lowest in the past 11 years. This slow-down in CARi publications was not seen in PubMed likely because PubMed includes no conference abstracts and more review manuscripts than Embase.

Plotting CARi publication types in Embase by year revealed a sharp decrease in the number of conference abstracts (746 in 2019 vs. 374 in 2020) and a clear slow-down in the number of review articles (351 in 2019 vs. 404 in 2020), although original research articles grew at a rate similar to the previous years (411 in 2019 vs. 771 in 2020, Fig. 1C). We manually curated 500 CARi publications in PubMed and compared the types of publications in PubMed and Embase (Figs. 1D

and 1E). Despite the similar percent research articles (30.8% vs. 29.72%), there is nearly twice in number more review articles (41.8% vs. 19.25%) and significantly less “other” (i.e., publications that are neither original research articles nor reviews) type of manuscripts in PubMed than Embase (27.4% vs. 51.03%, Fig. 1D).

Interestingly, only 5.2% of the publications (26 of the 500 representative publications corresponding to 205 of the 3,937 publications in total) in PubMed report results from CARi clinical trials, although we found 663 clinical trials listed on *ClinicalTrials.gov* when we searched the terms "chimeric antigen receptor, chimeric antigen receptor T, chimeric antigen receptor NK, chimeric antigen receptor natural killer, CAR, CAR T, CAR NK, and CAR natural killer" and removed duplicates and trials missing critical information such as targets or disease types (Figs. 1F and 1G, Supp. Figs. 1-2, Supp. Table 1). Unlike preclinical studies that focused on B cell markers as well as solid tumors, the clinical trials mostly targeted B cell markers alone or in combination with antibodies or modified or multiple CARs (Supp. Tables 2-5).

The largest number of clinical trials has been registered by (with number of trials conducted in parentheses) Zhejiang University (30) and People’s Liberation Army General Hospitals (25) in China and University of Pennsylvania (22), City of Hope National Medical Center, and National Institutes of Health (19 each) in the U.S. (Fig. 1H, Supp. Table 6). These five institutions conduct 17.4% of all clinical trials worldwide. In total, 56.2% and 36.8% of all clinical trials are being conducted in China and U.S., respectively; only 7% of the clinical trials are being conducted in the rest of the world.

Although the top three Chinese institutions conduct more trials than the top three U.S. institutions (68 vs. 60, Fig. 1H), the latter institutions published 2.2-fold (772 vs. 348) more total manuscripts including 2.4-fold (220 vs. 92) more review articles than their Chinese counterparts as revealed by searching the terms “Zhejiang”, “Beijing”, “Hebei”, “Pennsylvania”, “City of Hope”, or “National Institutes of Health” in PubMed along with the terms "chimeric antigen receptor". Interestingly, Zhejiang University Hospitals, a Chinese institution conducting the largest number of clinical trials, conducted more trials (30 vs. 22) but published 4.1-fold less (599 vs. 140) manuscripts than its American counterpart, University of Pennsylvania. Although limited by possible language barriers, these results suggest that Chinese institutions conduct more clinical trials but publish fewer manuscripts than U.S. institutions.

In order to investigate if the slow-down in CARi publications in Embase was associated with the global COVID-19 pandemic or changes in other types of cancer immunotherapy, we compared the number of publications in CARi, coronavirus, antibody-drug conjugates (ADC), anti-PD-1 (pembrolizumab), and anti-CTLA4 (ipilimumab) monoclonal antibody research (Figs. 2-5). Inhibitors of PD-1 and CTLA-4, the two checkpoint blockers, along with ADC represent the two other major fields of research in cancer immunotherapy in addition to CARi. There was a higher percent of review articles in CARi than in the other cancer immunotherapy fields. The total number of publications decreased in 2020, compared to 2019, in all fields of immunotherapy except CARi. In contrast, coronavirus publications spiked at unprecedented proportions (5,185% increase, 575 in 2019 vs. 30,390 in 2020).

Unlike cancer immunotherapy where majority of the publications consist of conference abstracts and review articles, most of the coronavirus publications were original research articles. In 2020, there was a higher percent of review articles (24.75% vs 15.71%) and conference abstracts (22.92% vs. 3.4%) but less original research articles (47.24% vs. 70.3%) published in CARi than coronavirus research. Conference abstracts decreased in all immunotherapy fields in 2020 but spiked in coronavirus research. These results suggest an overall slow-down or decrease in the number of publications in cancer immunotherapy research publications coinciding with the global COVID-19 pandemic.

Our manual curation of the CARi publications in PubMed revealed that some potentially high-impact CARi research questions have yet to be satisfactorily answered in the literature. For example, studies investigating CARi target selection, the first critical step in creating novel CARi cell products, through search of gene expression databases such as Gene Expression Omnibus by The National Center for Biotechnology Information (NCBI), The Cancer Genome Atlas (TCGA), or the Expression Atlas by European Molecular Biology Laboratory (EMBL) to discover highly and uniformly expressed genes in cancer subtypes or research focusing on CARi signaling, have rarely been explored. On the contrary, redundant, duplicate, or minimally relevant publications have increased at an alarming rate. The most frequent objective in original research articles involves trying to optimize CAR T cell design.

Safety of CAR T cell products is investigated in 12.5% of the sampled publications in PubMed. The four CAR T cell products already approved by the U.S. FDA include Kymirah (tisagenlecleucel) by Novartis, Breyanzi (lisocabtagene maraleucel) by Juno Therapeutics (now a

part of Celgene), and Yescarta (axicabtagene ciloleucel) and Tecartus (brexucabtagene autoleucel) by Kite Pharma (now a part of Gilead Sciences) (Supp. Table 7). Kymirah and Yescarta were approved for B-ALL and diffuse large B-cell lymphoma (DLBCL), respectively, in 2017. Kymirah and Brenyazi were approved for DLBCL in 2018 and 2021, respectively. Tecartus was approved for mantle cell lymphoma in 2020.

FDA has created a public database, FDA Adverse Event Reporting System (FAERS) where adverse events (AEs) can be entered by consumers, manufacturers, or health care professionals mainly for post-marketing surveillance. As of January 2021, only three AEs including one death in patients treated with Tecartus have been entered into the database (Supp. Table 7), likely due to its recent approval. Further, 2,072 AEs in patients treated with Yescarta have been reported; 1,972 of these events were serious, and 332 (16.02%) resulted in death. As for Kymirah, 1,546 AEs have been reported, where 1,461 of which were serious and 435 (28.14%) resulted in death. Although 50 AEs, all of which were serious, including 9 deaths (18%), have been reported in patients treated with Breyanzi, all 50 events occurred before the approval of Breyanzi by the FDA in February 2021. Therefore, they may not be considered as “post-marketing” events.

Although limited by multiple confounding variables, the higher death rate reported in patients with AEs treated with Kymirah (28%) than Yescarta (16.02%) and Breyanzi (18%) is still intriguing. Disease type could be important in these differences because Yescarta and Breyanzi are only indicated for DLBCL, whereas Kymirah is indicated for both DLBCL and B-ALL. An interesting observation can be made regarding the role of co-stimulatory domains in these death rates. Preclinical studies have consistently shown that 4-1BB is safer than CD28⁹. However, the death

rate is higher in Kymirah, which contains 4-1BB, than Yescarta, which contains CD28. In addition, death rates in Breyanzi and Yescarta, which have different co-stimulatory domains but indicated for the same disease, are similar. These observations suggest that the significant effects of co-stimulatory domains reported in preclinical studies do not necessarily translate into real-world scenarios.

These data from FAERS, an official database, are difficult to interpret due to many confounding variables. Reporting AEs to FAERS is currently voluntary. Therefore, some severe AEs may not have been reported. It is unknown how many patients were treated successfully and, thus, were not reported. Additionally, the number of AEs in patients treated with CARi products in FAERS has an unusually wide range (1 to 35), suggesting that some institutions may have entered only the partial AE profile of patients. Several variables such as event date, age, or weight have been entered for some patients but not for others. It is not clear whether FDA has any oversight at all on data entry. In addition, these drugs are administered to different patient populations, likely following different protocols. Considering that the patients are heavily pre-treated before starting the CAR T therapy, most patients likely suffer from multiple conditions. It is not clear if or how many of these AEs are due to secondary conditions, or other drugs used to treat them, rather than the CAR T therapy itself.

All of the anti-CD19 CAR T products including Kymirah, Yescarta, Tecartus, and Breyanzi were granted “fast-track” approval by the FDA based on the JULIET (Phase II), ZUMA-1 (Phase I/II), ZUMA-2 (Phase II), and TRANSCEND-NHL-001 (Phase I) clinical trials, respectively. We are not aware of any Phase III clinical trials reported to evaluate these products. Well-controlled,

randomized clinical trials are needed to assess the efficacy and safety profiles of these CAR-modified T cell products. Until then, the pivotal trials that led to the FDA approval, and were recently reviewed by us¹⁰ and others, are perhaps the best sources of information to evaluate the efficacy and safety of these CAR T products.

The number of CARi and coronavirus publications obtained through the “results by year” function of the new version of PubMed released in November 2019 differs from those obtained through the classical “search” method. To create a representative database allowing a detailed analysis, we entered the terms "dabrafenib lung" in PubMed in February, 2021. The search returned 130 publications. However, there were 151 publications in the timeline obtained through the "results by year" function. In order to investigate the reason for this discrepancy, we downloaded the raw Medline files directly from the NCBI databases through Entrez using scripts executed in PERL, an open source programming language, in a Unix shell using the same search terms. This strategy returned 130 publications. A detailed analysis of the 151 publications retrieved through the "results by year" approach revealed that 26 publications had different online and actual publication dates, suggesting that these 26 publications were likely entered twice in databases used to obtain the "results by year" timeline although it is unknown why the search produced 151 rather than 156 publications. We included only data obtained through the “search” function of the PubMed in this manuscript as the "results by year" timeline does not seem reliable.

In conclusion, publication landscape in CARi as well as other fields of cancer immunotherapy has changed due to the global COVID-19 pandemic. This trend will likely continue in the near future as scientists try to contain the pandemic. CARi research is now in need of increased measures by

publishers to reduce non-peer-reviewed, repetitive and/or duplicate publications, at least in high-impact journals, and more stringent criteria for data entry into public databases including *PubMed*, *Embase*, *ClinicalTrials.gov*, and FAERS. These measures have the potential to significantly ease the burden on scientists trying to obtain reliable data that they urgently need to advance this important field of medical research.

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The authors regret that it was not possible to include many interesting studies in the field due to limited space.

Authors' contributions

All authors wrote the initial draft, revised the review, finalized the last version of the article, and approved the final version.

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Competing interests

Dr. Jianhua Yu is the co-founder of the Cytoimmune, Inc.

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Fig. 1. *A* CAR-modified immune cell (CARI) publications in Embase and PubMed by year of publication. *B* Total CARI publications from 1989 to 2021 shared between PubMed and Embase. *C* CARI publication types in Embase. *D* Percent publication types in Embase vs. PubMed. *E* Types of CARI publications in PubMed. *F* Status of CARI clinical trials as of 2021. *G* CARI clinical trials conducted per year. Trials without a clear start date or those that are projected to start in the future are not included, *H* Notable institutions conducting CARI clinical trials.

Fig. 2. Publications in coronavirus and cancer immunotherapy research plotted by year. Total number of publications decreased in all cancer immunotherapy fields examined except CARi (A - D). When all publications are considered, there are nearly twice more research articles and less review articles and conference abstracts in coronavirus than CARi research (E - F). X axis = year of publication, Y axis = number of publications. The legend in A applies to A – D, and the legend in E applies to E and F. Data are current as of February, 2021. Conf. Abs. = conference abstracts, All publications = all publication types combined.

Figure 3. A comparison of cancer immunotherapy and coronavirus publications in Embase vs. PubMed from 2010 to 2020. When all publication types are considered, there are more cancer immunotherapy publications in Embase than PubMed (A - D). There is an opposite trend in coronavirus research where there are more publications in PubMed than Embase (E - F). Reviews as a percentage of all publications is lower in coronavirus than CARi research in both PubMed and Embase. X axis = year of publication, Y axis = number of publications. The legend in A applies to the Figures A - D, and the legend in E applies to Figures E and F. All = all publication types, including reviews, original research articles, conference abstracts, etc.

Figure 4. A comparison of publication types in cancer immunotherapy and coronavirus research from 2010 to 2020. Historically, there have been significantly more research articles published in coronavirus than cancer immunotherapy research. Unlike coronavirus publications with a steady growth rate over the years, cancer immunotherapy publications quickly grew and surpassed the coronavirus publications beginning in 2018. However, in the year 2020 when the pandemic took over, there were nearly 10 times more coronavirus publications than all other cancer immunotherapy fields combined. Growth in the number of conference abstracts is especially striking in pembrolizumab (PEM) research. The number of PEM conference abstracts was the largest among all fields only two years after its first publication in 2014 and have remained the largest ever since. The number of conference abstracts was lowest in coronavirus than in any other field but, in 2020, they dramatically increased and reached a level slightly less than PEM (1,034 vs. 1,066). The Y axis is drawn to the $\log_{10}$ scale. All = all publication types including original research articles, reviews, conference abstracts, etc; X axis = year of publication; Y axis = number of publications. The legend in Figure D applies to all graphs. CAR = chimeric antigen receptor modified immune cells, PEM = pembrolizumab, CORONA = coronavirus, IPI = ipilimumab, ADC = antibody drug conjugate.

Figure 5. Total cancer immunotherapy and coronavirus publications from 1989 to 2020 in PubMed vs. Embase. PubMed contains fewer total but more review articles than Embase in all cancer immunotherapy fields. In coronavirus research, however, there are more both overall and review manuscripts in PubMed than Embase. All = all publication types including original research articles, reviews, conference abstracts, etc; reviews = review manuscripts; CARi = chimeric antigen receptor-modified immune cells; ADC = antibody drug conjugate.

Supplementary Figure 1. Search of the terms “chimeric antigen receptor, chimeric antigen receptor T, chimeric antigen receptor NK, chimeric antigen receptor natural killer, CAR, CAR T, CAR NK, and CAR natural killer” on *ClinicalTrials.gov* returned 2,240 clinical trials. Only 663 clinical trials remained after removal of duplicates or trials lacking critical information such as target or cell type.

Supplementary Figure 2. Percent clinical trials conducted by country from 2003 to 2020^a

^a6, 7, 231 and 353 clinical trials are registered in Germany, England, US, and China, respectively. Twelve clinical trials are registered in other countries.

Supplementary Table 1. Clinical trials retrieved when the terms below were searched on *ClinicalTrials.gov* in January, 2021.

Search term entered	Clinical trials found, <i>N</i>
Chimeric antigen receptor	358
Chimeric antigen receptor T	313
Chimeric antigen receptor NK	6
Chimeric antigen receptor natural killer	6
CAR	810
CAR T	723
CAR NK	16
CAR natural killer	8
TOTAL	2,240

1 **Supplementary Table 2.** Tumor-associated antigens targeted in chimeric antigen receptor-modified immune cell (CARi) clinical
2 trials. % = percent of all clinical trials; *N* = number of clinical trials.

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Clinical trials		Target	Alias	Function of the target
<i>N</i>	%			
208	31.42	CD19 ^a	B-lymphocyte antigen	B cell development and function ¹
69	10.42	BCMA ^b	B-cell maturation antigen	Implicated in development of multiple myeloma ² , important in survival and maturation of B cells ^{2,3} , important in autoimmunity ⁴
26	3.93	Mesothelin ^c	Mesothelin	A tumor differentiation antigen present on the mesothelial cells ⁵
25	3.78	CD19/CD22	CD22 (SIGLEC2)	CD22 is an inhibitory co-receptor in signaling through B cell receptor ⁶ , it is highly expressed in ALL ⁷ and inhibits autoimmune disease, along with FcγIIb, by silencing B cells ⁸ . Anti-CD22 CAR T cells induce remission in B-ALL resistant to CD19 CAR T therapy ⁹
23	3.47	CD19/CD20	CD20 (MS4A1)	A pan B cell marker along with CD19, CD20 is important in B cell signaling and development ¹⁰ ; its expression is lost upon differentiation into plasma cells, suggesting that it may be important in differentiation of B-cells into plasma cells ¹¹ . In addition, it mediates T-cell independent antibody responses ¹² . Anti-CD20 antibodies are used for treating B cell malignancies
20	3.02	GD2 ^d	Disialoganglioside-2	Highly and specifically expressed in neuronal tumors ¹³

18	2.72	CD22	SIGLEC-2	See above
17	2.57	CD30	TNFRSF8	A Type 2 T cell marker ¹⁴
16	2.42	CD123	IL-3R	Highly expressed in AML subtypes; it is a marker of leukemic stem cells ¹⁵
16	2.42	GP3	Glypican 3	Implicated in bone and skeletal muscle cell proliferation and differentiation ¹⁶
13	1.96	HER2	Receptor tyrosine-protein kinase ErbB-2	An oncogene in the EGFR family important especially in breast cancer ¹⁷
10	1.51	EGFR ^e	ErbB-1	Along with HER2, Her 3, and Her 4, EGFR is a member of receptor tyrosine kinases important in oncogenesis and signal transduction ¹⁸
9	1.36	BCMA	B-cell maturation antigen	See above
9	1.36	MUC1 ^f	Mucin 1, epithelial membrane antigen	MUC1, overexpressed in cancerous epithelial cells lining epithelial surfaces in the lungs, intestine, etc. is a marker for solid tumors ¹⁹
9	1.36	PSCA/PMSA	PSCA, prostate stem cell antigen / PSMA, prostate-specific membrane antigen	Increased PSCA expression is a marker for bladder, pancreatic, and prostate cancers ²⁰ ; PSMA, a glutamate carboxypeptidase that cleaves N-acetylaspartylglutamate, is important in diagnosis of prostate cancer ²¹
8	1.21	CD7	GP40	Important in lymphocyte development and T and B-cell trafficking. It is targeted in T cell-acute lymphoblastic leukemia ²² due to its role in apoptosis in activated T lymphocytes ²³

7	1.06	CEA	Carcinoembryonic antigen	Important in signaling, cell adhesion, and metastasis ²⁴
6	0.91	CD33	SIGLEC3	Anti-CD33 monoclonal antibody conjugated with calicheamicin (gemtuzumab ozogamicin) has been approved by FDA for newly diagnosed and relapsed or refractory acute myeloid leukemia ²⁵
6	0.91	EFGRvIII ^g	ErbB-1	A deletion mutant version of EGFR frequently found in brain tumors ²⁶
6	0.91	EpCAM	Epithelial cell adhesion molecule	Important in epithelial cell to cell adhesion, proliferation, and differentiation ²⁷
6	0.91	NKG2D	NKG2D	Recognizes stress-induced surface ligands ²⁸
5	0.76	B7-H3	CD276, B7 Homolog 3	B7-H3 is a pro-tumorigenic immune checkpoint protein and a strong inhibitor of T cell proliferation and activation ^{29,30}
5	0.76	CD20	MS4A1	See above
4	0.6	Claudin18.2	Claudin18.2	Claudin 18.2 (CLDN18.2) is an important component of the tight junctions in epithelial cells; it is highly expressed in gastric tumors ^{31,32}
4	0.6	ROR1/ROR2	NTRKR1 / NTRKR2	ROR1, important in cell migration, is a prognostic factor for triple negative breast cancer ³³ ; ROR2, important in cartilage and growth plate development ³⁴ , has prognostic value in colorectal cancers ³⁵

3	0.45	CD38	cyclic ADP ribose hydrolase	Anti-CD38 antibodies daratumumab and isatuximab are established treatment options for multiple myeloma ²²
3	0.45	CD70	TNFSF7	CD70 is a marker for T and B cell activation (i.e., absent in resting T cells but induced upon activation), and mediates suppressor functions of TGF-beta especially on effector memory T cells ³⁶
3	0.45	CS1	SLAMF7	Marker for malignant plasma cells, highly expressed in multiple myeloma ^{37,38}
3	0.45	IL13R α 2	CD213A2	Plays a role in binding and internalization of IL13, overexpressed in brain tumors ³⁹
3	0.45	Lewis Y	Lewis Y	Lewis Y is a carbohydrate antigen highly expressed in a range of solid tumors ⁴⁰
3	0.45	NKG2DL	NKG2DL	Ligand for the activating immunoreceptor NKG2D, important in activation of cytotoxic lymphocytes through recognition of MHC class I-related glycoproteins on virally infected or malignant cells ⁴¹
2	0.3	CD138	Syndecan 1	Syndecan 1 is a transmembrane protein important in tumor cell proliferation, angiogenesis, matrix remodeling and migration ⁴²
2	0.3	CD147	Basigin	Basigin is a transmembrane glycoprotein receptor important in tumor metastasis and virus entry into cells especially during SARS-CoV-2 infection ⁴³
1	0.15	CD171	L1CAM	Important in cell adhesion, development of the nervous system, and prognosis in several cancers ⁴⁴

85	12.84	Others	Not applicable	Not applicable
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^aCD19 alone or in combination with IL-7, CCL19, IL-15, IL-13R α 2, iCasp9, or acalabrutinib

^bBCMA alone or in combination with CD19, BiRD, lenalidomide, CD29, CD38, CS1, or PD-1

^cMesothelin alone or in combination with PD-1 or CTLA-4

^dGD2 alone or in combination with IL-7R, IL-15, iCasp9, CD276, or PSMA

^eEGFR alone or in combination with PD-1, CXCR5, or IL-12

^fMUC1 alone or in combination with PD-1 or CTLA-4

^gEFGRvIII alone or in combination with pembrolizumab

Supplementary Table 3. Additional modifications or compounds used to improve CARi efficacy in clinical trials.

NCT number	Name of trial	Cancer type	Target	Additional modification or combination	Name of modification or combination	Rationale for the additional modification or combination
NCT04194931	Humanized CAR-T Cells of Anti-BCMA and Anti-CD19 Against Relapsed and Refractory Multiple Myeloma	Multiple myeloma	BCMA	CD19	B-Lymphocyte Surface Antigen B4	CD19 is important in B cell development ¹ , highly expressed in all stages of B cell development but not in hematopoietic stem cells ⁴⁵
NCT04287660	Study of BiRD Regimen Combined With BCMA CAR T-cell Therapy in Newly Diagnosed Multiple Myeloma (MM) Patients	Multiple myeloma	“	BiRD	Biaxin (Clarithromycin)-Lenalidomide-Reduced-Dose-Dexamethasone	A regimen used in treatment of multiple myeloma ⁴⁶
NCT03070327	BCMA Targeted CAR T Cells With or Without Lenalidomide for the Treatment of Multiple Myeloma	Multiple myeloma	“	Lenalidomide	Revlimid	Inhibits plasma cell-induced angiogenesis and metastasis, reduces expression of proteins involved in angiogenesis and tumor-secreted cytokine secretion in multiple myeloma ⁴⁷

NCT03767751	A Feasibility and Safety Study of Dual Specificity CD38 and BCMA CAR-T Cell Immunotherapy for Relapsed or Refractory Multiple Myeloma	Multiple myeloma	“	CD38	Cyclic ADP ribose hydrolase	Important in cell adhesion, signal transduction and calcium signaling; daratumumab, an anti-CD38 monoclonal antibody is highly effective in treatment of multiple myeloma as well as other hematologic malignancies ⁴⁸
NCT04156269	BCMA-CS1 Compound CAR (cCAR) T Cells for Relapsed/Refractory Multiple Myeloma	Multiple myeloma	“	CS1	SLAMF7	Induces antigen-specific memory T lymphocyte production in multiple myeloma ⁴⁹
NCT04162119	Safety and Efficiency Study of BCMA-PD1-CART Cells in Relapsed/Refractory Multiple Myeloma	Multiple myeloma	“	PD-1	Programmed cell death protein 1, CD279	Cell surface immune checkpoint protein, promotes immune suppression through inhibiting autoreactive T cells and suppressing apoptosis ⁵⁰ and promoting proliferations in Tregs ⁵¹ . Pembrolizumab, an anti-PD-1 antibody has been approved by FDA for treatment of multiple solid tumors ⁵²

NCT03631576	CD123/CLL1 CAR-T Cells for R/R AML	AML	CD123	CLL1	C-type lectin-like molecule-1	Highly expressed in acute myeloid leukemia and leukemic stem cells but not present in normal hematopoietic stem cells ⁵³
NCT04381741	CD19 CAR-T Expressing IL7 and CCL19 Combined With PD1 mAb for Relapsed or Refractory Diffuse Large B Cell Lymphoma (CICPD)	DLBCL	CD19	IL-7	Interleukin-7	Promotes T-acute lymphoblastic leukemia by downregulating p27 ⁵⁴ and permits Th1/Tc1 maturation ⁵⁵
NCT04381741	See above	See above	“	CCL19	Chemokine (C-C motif) ligand 19	Binds CCR7 ⁵⁶ , attracts dendritic, B and T cells ⁵⁷ and improves CAR T cell persistence and function ⁵⁸
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	B-cell Lymphoma	“	IL-15	Interleukin-15	IL-15 activates Jak3 / STAT3 signaling and mediates glucose uptake ⁵⁹ ; it inhibits IL-2-induced apoptosis ⁶⁰ , IL-15 is anti-tumorigenic as it stimulates proliferation of CD8+ T and NK cells ⁶¹

NCT03579927	See above	See above	“	iCasp9	Inducible caspase-9	Inducible form of Caspase-9, an initiator caspase required for apoptosis signaling through mitochondrial pathway ⁶²
NCT04510051	CAR T Cells After Lymphodepletion for the Treatment of IL13Rα2 Positive Recurrent or Refractory Brain Tumors in Children	Brain tumors	“	IL13Rα2	CD213A2	Along with FAM120A, IL13Rα2 plays a key role in colon cancer metastasis via PI3K pathway and IL13R signaling ⁶³
NCT04257578	Acalabrutinib and Anti-CD19 CAR T-cell Therapy for the Treatment of B-cell Lymphoma	B-cell Lymphoma	“	Acalabrutinib	Calquence	A covalent inhibitor of Bruton's tyrosine kinase ⁶⁴ , effective in treating B cell malignancies and autoimmune disease through a reduction in B cell proliferation ⁶⁵
NCT04007029	Modified Immune Cells (CD19/CD20 CAR-T Cells) in Treating Patients With Recurrent or Refractory B-Cell Lymphoma or Chronic Lymphocytic Leukemia	B-Cell Lymphoma or Chronic Lymphocytic Leukemia	“	CD20	B-lymphocyte antigen CD20	Same as in Supplementary Table 2

NCT04539444	A Study of CD19/22 CART Cells Combined With PD-1 Inhibitor in Relapsed/Refractory B-cell Lymphoma	B-Cell Lymphoma	“	CD22	SIGLEC2	Same as in Supplementary Table 2
NCT04163302	Safety and Efficiency Study of CD19-PD1-CART Cell in Relapsed/Refractory B Cell Lymphoma	B-Cell Lymphoma	“	PD-1	See above	See above
NCT04556669	Anti-PD-L1 Armored Anti-CD22 CAR-T/CAR-TILs Targeting Patients With Solid Tumors	Solid Tumors	CD22	PD-L1	B7-H1, programmed death-ligand 1	Ligand for PD-1, binding of PD-1 to PD-L1 suppresses immunity during pregnancy or autoimmunity by reducing T cell proliferation and inducing Treg proliferation. PD-L1 expression protects the tumor against attacks by CD8+ T cells ⁵²
NCT03602157	Study of CAR-T Cells Expressing CD30 and CCR4 for r/r CD30+ HL and CTCL	Hodgkin Lymphoma, Cutaneous T-cell Lymphoma	CD30	CCR4	C-C motif chemokine receptor 4	CCR4 is being targeted for treatment of cutaneous T-cell lymphoma where it is highly expressed ⁶⁶ ; it is required for recruitment of FoxP3+ Tregs that mediate allograft tolerance ⁶⁷

NCT03182816	CTLA-4 and PD-1 Antibodies Expressing EGFR-CAR-T Cells for EGFR Positive Advanced Solid Tumors	EGFR Positive Solid Tumors	EGFR	CTLA-4	Cytotoxic T-lymphocyte-associated protein 4	Immunosuppressive checkpoint protein expressed on Tregs and activated T cells, its loss results in massive lymphocyte proliferation and tissue destruction ⁶⁸ ; ipilimumab, an anti-CTLA-4 monoclonal antibody has been approved by FDA for treatment of metastatic melanoma ⁶⁹
NCT04153799	Study of CXCR5 Modified EGFR Chimeric Antigen Receptor Autologous T Cells in EGFR- Positive Patients With Advanced Non-small Cell Lung Cancer	Non-small Cell Lung Cancer	“	CXCR5	Burkitt lymphoma receptor 1 (BLR1), CD185	Vgamma9Vdelta2 T cell subsets expressing CXCR5 also secrete IL-4 and IL-10 and help B cells in antibody production ⁷⁰
NCT03542799	EGFR-IL12-CART Cells for Patients With Metastatic Colorectal Cancer (EGFRCART)	Colorectal Cancer	“	IL-12	p70	IL-12 produced by dendritic cells converts naïve CD4+ T cell into the Th1 cells ⁷¹ , activates CD8+ T cells ⁷² , and inhibits IL-4 producing Th cells ⁷³ , induces interferon gamma release from NK ⁷⁴ and T cells; anti-IL-12 treatment

						prevents autoimmune encephalomyelitis ⁷⁵
NCT03726515	CART-EGFRvIII + Pembrolizumab in GBM	Glioblastoma	EGFRvIII	Pembrolizumab	Keytruda	A humanized antibody, pembrolizumab allows immune system to destroy tumor cells by blocking PD-1 that enables tumors to escape immune surveillance ⁵²
NCT04099797	C7R-GD2.CAR T Cells for Patients With GD2-expressing Brain Tumors (GAIL-B)	Brain Tumors	GD2	IL-7R	CD127	IL-7R mediates effects of IL-7, a hematopoietic growth factor, that regulates B and T cell progenitor activity ⁷⁶ , and lymphocyte growth, maturation, and survival
NCT03721068	Study of CAR T-Cells Targeting the GD2 With IL-15+iCaspase9 for Relapsed/Refractory Neuroblastoma	Neuroblastoma	“	IL-15	Interleukin-15	See above
NCT01822652	3rd Generation GD-2 Chimeric Antigen Receptor and iCaspase Suicide Safety Switch,	Neuroblastoma	“	iCasp9	Inducible caspase-9	See above

Neuroblastoma, GRAIN
(GRAIN)

NCT04637503	4SCAR-T Therapy Targeting GD2, PSMA and CD276 for Treating Neuroblastoma	Neuroblastoma	“	PSMA	Prostate-specific membrane antigen	Same as in Supplementary Table 2
NCT04637503	See above	Neuroblastoma	“	CD276	B7 Homolog 3	Pro-tumorigenic immune checkpoint protein ⁷⁷ that inhibits T cell activation ³⁰ and proliferation ⁷⁸
NCT04377932	Interleukin-15 Armored Glypican 3-specific Chimeric Antigen Receptor Expressed in T Cells for Pediatric Solid Tumors	Pediatric Solid Tumors	GP3	IL-15	Interleukin-15	See above
NCT04093648	T Cells co-expressing a Second Generation Glypican 3-specific Chimeric Antigen Receptor With Cytokines Interleukin-21 and 15 as	Liver Cancer	“	IL-21	CVID11	IL-21 induces differentiation of naïve B cells into plasma cells ⁷⁹ , stimulates T cell activation and cytokine secretion ⁸⁰ , and promotes NK cell proliferation ⁸¹ . It is

Immunotherapy for
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required to control chronic
viral infections⁸²

NCT04684459	Dual-targeting HER2 and PD-L1 CAR-T for Cancers With Pleural or Peritoneal Metastasis	Cancers With Pleural or Peritoneal Metastasis	HER2	PD-L1	See above	See above
NCT02414269	Malignant Pleural Disease Treated With Autologous T Cells Genetically Engineered to Target the Cancer-Cell Surface Antigen Mesothelin	Malignant Pleural Disease	Mesothelin	iCasp9	See above	See above
NCT03179007	CTLA-4 and PD-1 Antibodies Expressing MUC1-CAR-T Cells for MUC1 Positive Advanced Solid Tumor	Solid Tumor	MUC1	CTLA-4	Cytotoxic T-lymphocyte-associated protein 4	See above

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Supplementary Table 4. Clinical trials targeting multiple CARs.

NCT number	Year	Targets	Condition
NCT04430530	2020	CD22/CD123/CD38/CD10/CD20	CD19 negative B-cell Malignancies
NCT04429438	2020	CD19/CD20/CD22/CD70/PSMA/CD13/CD79b/GD2	B Cell Lymphoma
NCT04010877	2019	CLL-1/CD33/CD123	Acute Myeloid Leukemia
NCT03778346	2018	Integrin β 7/BCMA/CS1/CD38/CD138	Multiple Myeloma
NCT03125577	2017	CD19/CD20/CD22/CD30/CD38/CD70/CD123	B-cell Malignancies
NCT03198052	2017	HER2/Mesothelin/Lewis-Y/PSCA/MUC1/GPC3/AXL /EGFR/B7-H3/Claudin18.2	Lung Cancer
NCT03222674	2017	Muc1/CLL1/CD33/CD38/CD56/CD123	Acute Myeloid Leukemia
NCT03196414	2016	CD138/BCMA/CD19	Multiple Myeloma

Supplementary Table 5. Representative preclinical studies of CAR T and CAR NK cell-based cancer immunotherapy.

<i>Disease</i>	<i>Target(s)</i>	<i>Signaling Domain(s)</i>	<i>Types of cells</i>	<i>Methods</i>	<i>References</i>
Multiple myeloma	BCMA	CD28	T cells	γ -retroviruses	83
Glioblastoma multiforme	HER2	CD28	T cells	Retrovirus	84
Melanoma	CD19	CD28	T cells	Vaccinia virus	85
Solid tumors	CSPG-4 ^a	CD28	T cells	γ -retroviruses	86
T cell malignancies	CD7	CD28	T cells	γ -retroviruses	87
Glioblastoma	EGFRvIII	CD28, 4-1BB	T cells	γ -retroviruses	88
Mesothelioma	Mesothelin	4-1BB	T cells	Lentivirus	89
Lymphoid malignancies	CD 19	4-1BB, CD3 ζ	PB NK	Electroporation	90
Lymphoid malignancies	CD 19	4-1BB, CD3 ζ	NK-92	Retrovirus	91
Lymphoid malignancies	CD 19	DAP10, 4-1BB, CD3 ζ	PB NK	Retrovirus	92
Lymphoid malignancies	CD 19	4-1BB, CD3 ζ	PB NK	Electroporation	93
Lymphoid malignancies	CD 20	4-1BB, CD3 ζ	PB NK	Electroporation	94
Lymphoid malignancies	CD19/CD20	CD3 ζ	NK-92	Lentivirus	95
Lymphoid malignancies	CD20	CD3 ζ	NK-92	Retrovirus	96
Myeloid leukemia	CD33	CD28, 4-1BB, CD3 ζ	NK-92	Lentivirus	97
Multiple myeloma	CD138	CD3 ζ	PB NK	Lentivirus	98

Multiple myeloma	CS1	CD28, CD3 ζ	NK-92, NKL	Lentivirus	99
Melanoma	GPA7	CD3 ζ	NK-92	Electroporation	100
Neuroblastoma	GD2	CD3 ζ	NK-92	Retrovirus	101,102
Neuroblastoma	EGFR, EGFRvIII	CD28, CD3 ζ	NK-92, NKL	Lentivirus	103
Glioblastoma	HER-2	CD28, CD3 ζ	PB NK	Lentivirus	104
Lymphoid malignancies, ovarian carcinoma	HER-2	CD28, CD3 ζ	PB NK	Retrovirus	105
Leukemia, neuroblastoma	CD19/GD2	CD244, 4-1BB, CD3 ζ	PB NK	Retrovirus	106
Breast and ovarian carcinoma	HER-2	CD3 ζ	NK-92	Retrovirus	107
Breast and ovarian carcinoma	HER-2	CD28, 4-1BB, CD3 ζ	NK-92	Lentivirus	108
Ovarian carcinoma	HER-2	CD28, CD3 ζ	PB NK	Retrovirus	109
Breast carcinoma	EPCAM	CD28, CD3 ζ	NK-92	Lentivirus	110
Breast carcinoma	EGFR	CD28, CD3 ζ	NK-92, PB NK	Lentivirus	111
Prostate cancer	PSCA	CD28, CD3 ζ , DAP12	NK-92, PB NK	Lentivirus	112
Ovarian carcinoma	Mesothelin	Combinations of CD3 ζ , CD28, 4- 1BB, CD16, 2B4, NKp44, DAP10, NKp46,	NK cells derived from iPSC	Lentivirus	113

		NKG2D, DAP12, and DAP10			
Ovarian cancer	α FR (folate receptor α)	CD28, 4-1BB, CD3 ζ	NK-92	Lentivirus	114
Ovarian cancer	Mesothelin	CD28, 4-1BB, CD3 ζ	NK-92	Lentivirus	115
Glioblastoma	EGFR and EGFRvIII	CD28, CD3 ζ	NK-92	Lentivirus	116
Triple negative breast cancer	Tissue factor	CD28, 4-1BB, CD3 ζ	NK92MI	Lentivirus	117
Ewing sarcoma	GD2	CD28, 4-1BB, t2B4 (CD244), CD3 ζ	PB NK	Retrovirus	118
Ovarian cancer	CD24	CD28, 4-1BB, CD3 ζ	NK-92	Lentivirus	119
Ovarian cancer	CD24	CD28, 4-1BB, CD3 ζ	NK-92	Lentivirus	120
Liver cancer	c-MET	4-1BB, DAP12	PB NK	Lentivirus	121
Breast cancer	ErbB2	CD28, CD3 ζ	NK-92	Electroporation	122
Glioblastoma	EGFRvIII	DAP12	YTS	Lentivirus	123
Acute lymphoblastic leukemia	CD19	CD28, CD3 ζ	PB NK	Lentivirus, retrovirus	124
Glioblastoma	EGFRvIII	CD28, 4-1BB, CD3 ζ	Human NK cell line KHYG-1	Lentivirus	125

B-cell leukemia and lymphoma	CD19	CD28, CD3ζ	NK-92	Lentivirus	126
B-ALL	FLT3	CD28, CD3ζ	NK-92	Lentivirus	127
Leukemia	CD19	CD28, 4-1BB, CD3ζ	Primary NK cells	Alpharetrovirus	128
Solid tumors	CD73	DAP10, CD3ζ	NK cells	Piggyback	129
Hepatocellular carcinoma	GPC-3	CD28, CD3ζ	NK-92, primary NK cells	Lentivirus	130
Glioblastoma	ErbB2/HER2	CD28, CD3ζ	NK-92	Lentivirus	131
Renal cell carcinoma	EGFR	CD28, 4-1BB, CD3ζ	NK-92	Lentivirus	132
Colorectal cancer	EpCAM	4-1BB, CD3ζ	NK-92	Lentivirus	133

^aCSPG-4: Chondroitin sulfate proteoglycan 4

Supplementary Table 6. Notable institutions performing CARi clinical trials^a

Institution	<i>N</i>
Zhejiang University Hospitals, Zhejiang, China	30
People's Liberation Army General Hospitals, Beijing, China	25
University of Pennsylvania	22
City of Hope National Medical Center	19
National Institutes of Health	19
Houston Methodist Hospital	17
University of Washington	13
Yanda Ludaopei Hospital, Hebei, China	13
University of North Carolina	13
3rd Military Medical University, Chongqing, China	12
Memorial Sloan Kettering Cancer Center	10
Seattle Children's Hospital	10
Texas Children's Hospital	8
Tongji Medical College, Wuhan, Hubei, China	8
Xinqiao Hospital, Chongqing, China	7
PersonGen Biomedicine, Jiangsu, China	7
Soochow university, Jiangsu, China	7
University of Alabama at Birmingham	7
University of California, San Francisco	5

^aOnly the lead institution is included whenever multiple institutions were involved. Closely related institutions such as Abramson Cancer Center and University of Pennsylvania are combined. *N* = number of clinical trials performed by the institution.

Supplementary Table 7. An overall comparison of the anti-CD19 CAR T cell products approved by the FDA^a

	Tisagenlecleucel	Axicabtagene ciloleucel	Brexucabtagene autoleucel	Lisocabtagene maraleucel
Brand name	Kymriah ¹³⁴	Yescarta ¹³⁴	Tecartus ¹³⁵	Breyanzi
Approval date	August, 2017 ¹³⁵ : FDA-approved for B-ALL, May, 2018 ¹³⁶ : FDA-approved for adult DLBCL	October, 2017: FDA-approved for DLBCL ^{137,138}	July, 2020 ¹³⁹ : FDA-approved for MCL	February, 2021: FDA-approved for DLBCL
The firsts	The first FDA-approved gene therapy ¹⁴⁰ (along with Luxturna)	The first FDA-approved CAR-T cell product for large B cell lymphoma ¹³⁹	The first cell-based therapy for MCL, an aggressive type of B cell non-Hodgkin's lymphoma seen mostly in adults over 60 years of age with no proven therapy regimen ¹⁴¹	The first CAR T cell therapy with the regenerative medicine advanced therapy designation
Patients	Adults with r/r DLBCL and young adults or children under 25 years of age ¹⁴² with r/r B-cell precursor ALL	Adults	Adults	Adults
Developer	Developed at the University of Pennsylvania and Children's Hospital of Pennsylvania; further developed and marketed by Novartis ¹⁴³	Kite Pharma ¹⁴⁴ (acquired by Gilead in 2017)	Kite Pharma	Juno therapeutics (acquired by Celgene in 2018)

Pivotal trial	JULIET phase II trial (NCT02445248)	ZUMA-1 (Phase I/II)	ZUMA-2 (Phase II) ¹⁴⁵ (NCT02601313)	TRANSCEND-NHL-001 (Phase I) ¹⁴⁶ (NCT02631044)
Co-stimulatory domain ¹⁴⁷	4-1BB	CD28	CD28	4-1BB
Patients reported to the FDA Adverse Event Reporting System				
Patients with AEs	1,546	2,072	3	50
Patients with serious AEs	1,461 (94.50%)	1,972 (95.17%)	2	50
Death rate^b	435 (28.14%)	332 (16.02%)	1 (50%)	9 (18%)

^ar/r = relapsed/refractory; nos = not otherwise specified; MCL = mantle cell lymphoma, AE = adverse event.

^bDeath rate as a percentage of serious adverse events.

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