An overview of CAR T-cell clinical trial activity to 2021

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Abbreviations

1G  First generation
2G  Second generation
3G  Third generation
4G  fourth generation
ALCL  anaplastic large cell lymphoma
allo  allogeneic
AML  acute myeloid leukaemia
auto  autologous
B-ALL  B-cell acute lymphoblastic leukaemia
B-CLL  B-cell chronic lymphocytic leukaemia
BCMA  B-cell maturation antigen
B-NHL  B-cell non-Hodgkin’s lymphoma
CAR  chimeric antigen receptors
CEA  carcinoembryonic antigen
CM central memory
CR complete response
CRh CR with partial haematological recovery
CRi CR with incomplete count recovery
CRS cytokine release syndrome
Cy cyclophosphamide
DFS disease-free survival
DLBCL diffuse large B-cell lymphoma
DLT dose-limiting toxicity
EFS event-free survival
FHCRC Fred Hutchinson Cancer Research Center
FL follicular lymphoma
Flu fludarabine
GBM glioblastoma multiforme
GD2 ganglioside D2
HD Hodgkin’s disease
ICANs immune effector cell-associated neurotoxicity
LBCL large B-cell lymphoma
LD lymphodepletion
| Abbreviation | Full Form |
|--------------|-----------|
| MDACC        | MD Anderson Cancer Center |
| MDS          | myelodysplastic syndrome |
| Med          | median |
| MGH          | Massachusetts General Hospital |
| MM           | multiple myeloma |
| MSKCC        | Memorial Sloan Kettering Cancer Center |
| MZL          | marginal zone lymphoma |
| N/A          | not available |
| NCI          | National Cancer Institute |
| NK           | natural killer |
| ORR          | overall response rate |
| OS           | overall survival |
| Pembro       | pembrolizumab |
| PFS          | progression-free survival |
| PI3K         | phosphatidylinositol 3-kinase |
| PLA          | People’s Liberation Army |
| PR           | partial response |
| PSCA         | prostate stem cell antigen |
| PSMA         | prostate-specific membrane antigen |
| Abbreviation | Definition |
|--------------|------------|
| scFv | single chain variable fragment |
| sCR | stringent CR |
| SD | stable disease |
| SLL | small cell lymphocytic lymphoma |
| TACI | transmembrane activator and CAML interactor |
| TCR | T-cell receptor |
| tFL | transformed follicular lymphoma |
| TRAC | TCRα locus |
| UPenn | University of Pennsylvania |
| VGPR | very good partial response |
In recent years, we have witnessed a paradigm shift in cancer treatment with the advent of effective immunotherapies for both haematological and solid cancers. Alongside traditional therapeutic modalities, immune checkpoint inhibitors, and cell-based therapies are increasingly being used in mainstream clinical practice. In what would have been an unthinkable development some 20 years ago, cell-based immunotherapies have now become the largest area of drug development in immuno-oncology. Moreover, it is particularly noteworthy that the largest year on year increase in this activity has involved the CAR T-cell sector (1).

Chimeric antigen receptors (CAR) T-cells are synthetic receptors that bind one or more native cell surface target(s), obviating the need for HLA-dependent antigen presentation or restriction. While this limits targeting potential to the subset of proteins found on the cell surface, CAR specificity can also be directed against non-proteinaceous antigens (e.g. tumour-associated gangliosides) or peptide/HLA complexes. The first CAR was described over 30 years ago and entailed the substitution of the variable domains of an antibody heavy and light chain for the corresponding regions within an \( \alpha\beta \) T-cell receptor (TCR) heterodimer (2). Eshhar simplified this design to create a homodimeric fusion receptor, cleverly using a single chain antibody fragment (scFv) to confer target specificity (3). This antigen recognition element was fused to a spacer, transmembrane domain and TCR-like activating domain, thereby coupling tumour engagement to the delivery of a cytotoxic T-cell signal. However, these early “first generation” designs failed to achieve clinical impact and CAR T-cell research remained a niche and somewhat dismissed academic activity for many years. This situation was dramatically reversed through the introduction of a co-stimulatory domain within the linear CAR framework, a platform that was conceived and first evaluated by Finney and colleagues in the Jurkat leukaemic T-cell model (4). Two clinically active second generation CAR systems have been developed in which either CD28 or 4-1BB are used to provide co-stimulation, while the \( \zeta \) chain of the TCR-associated CD3 complex is most commonly employed to deliver an activating signal.
Clinical development of CAR T-cell immunotherapy was pioneered in the US, at a speed reminiscent of the space race. Intense clinical trial activity at multiple centres was initiated on the back of encouraging early case reports which demonstrated the therapeutic promise of CD19-specific second generation CAR T-cells against B-cell malignancy (5, 6). The fruit of these collective efforts was the attainment of unprecedented response rates in patients with relapsed/ refractory B-cell leukaemias and a range of lymphomas. Commercialisation soon followed as major academic centres partnered with the pharmaceutical industry, or established successful new companies. Ultimately, this led to marketing approval in the US of three CD19-specific CAR T-cell products for the treatment of relapsed/ refractory B-cell malignancy, namely Tisagenlecleucel (Kymriah), Axicabtagene Ciloleucel (Yescarta) and Brexucabtagene autoleucel (Tecartus). Both Kymriah and Yescarta have also secured regulatory approval in many other territories worldwide, including the UK. Further approvals are highly likely in the near future.

Given the ever-increasing number of clinical trials involving CAR T-cell immunotherapy of cancer, we set out here to capture published studies in a simple tabular format. Had this task been undertaken 10 years ago, a very short list indeed would have been generated. In total, we identified more than 150 CAR T-cell clinical trials that involved a minimum of 6 patients (published in abstract or full manuscript format) and these are presented chronologically in Table 1. Our overview is designed to complement a presentation of the therapeutic landscape in this area, published last year (7). Wherever possible, data has been selected from peer previewed publications rather than entries made on other sites. We also sought to extract information from the newest articles pertaining to each trial and have employed commonly used abbreviations for diseases, as detailed at the foot of the Table. Pivotal (registrational) trials are highlighted as grey rows to distinguish these from earlier phase studies. While the table is dominated by trials involving B-cell malignancy, there are an increasing number of studies focussed on multiple myeloma, in which B-cell maturation antigen (BCMA) has proved to be a highly tractable target. We have presented response and survival data in addition to the two common acute toxicities that are associated with this intervention, namely
cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANs). In reviewing the list, readers may wish to review the original trial data since there is considerable variability across studies in the use of ancillary or bridging therapies. Patient conditioning with lymphodepleting chemotherapy was undertaken in the majority of trials and there is a clear preference for the use of fludarabine and cyclophosphamide in this role (8).

Solid tumours represent the bulk of human cancers and represented the primary focus of early CAR T-cell clinical trial activity. However, even with the advent of second generation CAR systems, we have only seen sporadic responses in a small number of patients. While the list of targets under study in B-cell and plasma cell malignancy is limited, there is much greater diversity in target selection in solid tumour-based clinical trials. This sub-optimal efficacy justifies the need for additional innovation around CAR design, the nature and fitness of the cellular host, and complementary use of additional interventions that may help to render the tumour microenvironment more favourable.

An important enabling attribute of CAR T-cell technology is the tremendous potential for innovation around this highly modular framework. Illustrating this, we are seeing the emergence of many switchable systems in which a universal CAR-engineered cell is utilised in combination with a bridging molecule that confers the desired tumour antigen specificity. A range of drug controllable, logic-gated and split-signalling CAR systems are also in development that offer the potential to improve therapeutic specificity and control. A further key point is the compatibility of CAR technology with other cutting-edge innovations. These include genome editing technologies, systems to precisely modulate host cell gene expression, cytokine armouring approaches and potential for metabolic manipulation and modulation of epigenetic properties of host cells.

The landscape of clinical CAR T-cell immunotherapy continues to evolve rapidly. Recently, there has been a tremendous expansion of clinical CAR T-cell activity in China, which overtook the US in 2017 as the country with the greatest number of registered CAR T-cell clinical trials (9). A
cursory inspection of the accompanying table emphasises this evolving trend. Alternative cell hosts other than αβ T-cells are increasingly being studied and are now beginning to emerge as viable alternatives for clinical use. Examples include natural killer (NK) cells, γδ T-cells, invariant NK T-cells and macrophages. In an increasing number of cases, these cells are being used as the basis to develop an allogeneic or off-the-shelf CAR therapy. A further exciting example involves the use of induced pluripotent stem cells, a technology that offers the promise of unprecedented scalable manufacture, although safety will need to be strictly ensured.

Immunotherapy using CAR-engineered immune cells has emerged as a transformative therapeutic intervention for human cancer and is now increasingly under study in other disease arenas, such as autoimmunity and transplantation. We look forward to the increasing clinical translation of these flexible and transformative therapies in the coming years.
DATA AVAILABILITY STATEMENT

Data derived from public domain sources.

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DECLARATION OF INTERESTS

J.M. is CSO, scientific founder and shareholder of Leucid Bio.

AUTHOR CONTRIBUTION

A.A. and J.M collected data and wrote the manuscript.

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References

1. Yu JX, Upadhaya S, Tatake R, Barkalow F, Hubbard-Lucey VM. Cancer cell therapies: the clinical trial landscape. Nat Rev Drug Discov. 2020;19(9):583-4.
2. Kuwana Y, Asakura Y, Utsunomiya N, Nakanishi M, Arata Y, Itoh S, et al. Expression of chimeric receptor composed of immunoglobulin-derived V regions and T-cell receptor-derived C regions. Biochem Biophys Res Commun. 1987;149(3):960-8.
3. Eshhar Z, Waks T, Gross G, Schindler DG. Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the gamma or zeta subunits of the immunoglobulin and T-cell receptors. Proc Natl Acad Sci U S A. 1993;90(2):720-4.
4. Finney HM, Lawson AD, Bebbington CR, Weir AN. Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. J Immunol. 1998;161(6):2791-7.
5. Kochenderfer JN, Wilson WH, Janik JE, Dudley ME, Stetler-Stevenson M, Feldman SA, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood. 2010;116(20):4099-102.
6. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011;365(8):725-33.
7. MacKay M, Afshinnekoo E, Rub J, Hassan C, Khunte M, Baskaran N, et al. The therapeutic landscape for cells engineered with chimeric antigen receptors. Nat Biotechnol. 2020;38(2):233-44.
8. Bechman N, Maher J. Lymphodepletion strategies to potentiate adoptive T-cell immunotherapy - what are we doing; where are we going? Expert Opin Biol Ther. 2020.
9. Wei J, Guo Y, Wang Y, Wu Z, Bo J, Zhang B, et al. Clinical development of CAR T cell therapy in China: 2020 update. Cell Mol Immunol. 2020.
| Ref | Year | Institution/Sponsor | Clinical Trial register | Target | CAR Gen. | Disease | No. treated | Conditionin g | Cell product & dose | Clinical outcome | Toxicity (>grade 3) | Survival |
|-----|------|----------------------|------------------------|--------|----------|---------|------------|-------------|------------------|----------------|------------------|----------|
| (1) | 2011 | MSKCC | NCT00466531 NCT01044069 | CD19 | 2G: CD28 | B-CLL B-ALL | 9 | Nil or Cy | 1.2 - 3x10^7/Kg (B-CLL) 3x10^7, 1-3x10^7/Kg (B-ALL) | 33% SD | 0% CRS 0% ICANS 1 fatality - presumed sepsis | N/A |
| (2) | 2011 | Baylor | N/A | CD19 | 2G: CD28 | B-NHL | 6 | Nil | 2x10^7/m^2 1x10^7/m^2 2x10^7/m^2 | 33% SD | 0% CRS 0% ICANS | SD n=2 for 3 and 10m |
| (3) | 2012 | NCI | NCT00924326 | CD19 | 2G: CD28 | B-NHL B-CLL | 8 | Flu/Cy | 0.3-3x10^7/Kg | 13% CR 75% PR | ≥Grade 3 toxicity in all patients | 1 ongoing CR at 15m |
| (4) | 2014 | MSKCC | NCT01044069 | CD19 | 2G: CD28 | B-ALL | 16 | Cy | 3x10^6/Kg | 88% CR/CRI | 44% CRS 6% ICANS | 44% in remission post allo HSCT |
| (5) | 2014 | Novartis | NCT01626495 NCT01029366 | CD19 | 2G: 41BB | B-ALL Children/young adults | 30 | Flu/Cy | 0.76x10^6 to 20.6x10^6/Kg | 90% CR | 27% CRS 0% ICANS | At 6m, EFS 67% |
| (6) | 2015 | UPenn | NCT01029366 | CD19 | 2G: 41BB | B-CLL | 14 | Flu/Cy/other s | 0.14x10^6 to 11x10^5/Kg | 57% ORR 29% CR 29% PR | 35% CRS 7% ICANS | 100% PFS for CR pts - median duration 40m |
| (7) | 2015 | NCI | NCT00924326 (update of (3)) | CD19 | 2G: CD28 | B-NHL B-CLL | 15 | Flu/Cy | 1x10^6/Kg | 53% CR 27% PR | Seen in 13, including sepsis, CRS and ICANS | At 7m, all CRs ongoing |
| Year | Institution | Trial ID | CD | 2G: CD28/CD28 | Disease | Dose | ORR | CR | CRS | ICANS | OS | Follow-up |
|------|-------------|----------|----|----------------|---------|------|-----|----|-----|-------|----|-----------|
| 2015 | NCI         | NCT01593696 | CD19 | 2G: CD28 | B-ALL (children/young adults) | Flu/Cy | 1-3 x10^6/Kg | 70% | 60% | 5% | 51.6% OS med 10m follow-up |
| 2016 | Baylor      | NCT00881920 | CD19 | 2G: CD28 | B-NHL | Cy unless lymphopenic | 1.7 x10^7 to 1.9 x10^7/m^3 | 2 CR and 1 PR | 0% | 0% | 1 durable CR at 3y |
| 2016 | Chinese PLA General Hospital | NCT01735604 | CD20 | 2G: 41BB | B-NHL | Cytoreductive chemotherapy, including Cy | 0.41 x10^7 to 1.46 x10^7/Kg | 82% ORR | 55% CR | 0% | 0% | Med PFS >6m |
| 2016 | UPenn       | NCT01747488 | CD19 | 2G: 41BB | B-CLL | Flu/Cy | 5 x10^7 to 1 x10^8 cells | 24% CR at higher dose | 20% CR | Med follow-up 26m - 12% CR |
| 2016 | UPenn       | NCT01626495 | CD19 | 2G: 41BB | B-ALL (children) | Flu/Cy | 1 x10^7 to 1 x10^8/Kg | 93% CR | 27% CRS | Med follow-up 12m - 57% CR |
| 2016 | City of Hope | NCT01318317 | CD19 | 1G | B-NHL | Administered post auto HSCT | 25 to 200 x10^6 (CD8^+) CM | 38% CR | 25% PR | 0% | 50% PFS at 1y |
| 2016 | City of Hope | NCT01815749 | CD19 | 2G: CD28 | B-NHL | Administered post auto HSCT | 50 to 800 x10^6 (CD4^+ and CD8^+ CM) | 75% CR | 25% PR | 0% | 75% PFS at 1y |
| 2016 | FHCRC       | NCT018665617 | CD19 | 2G: 41BB | B-ALL | Cy ± Flu | 2 x10^7/Kg | 23% CRS | 93% ORR | 10% CR | 400d post CAR-T |
| 2016 | FHCRC       | NCT01865617 | CD19 | 2G: 41BB | B-NHL | Cy ± Flu | 2 x10^7/Kg | 13% CRS | 28% ICANS | Cy/Flu: 72% CR | Med OS - No Flu 6.3m; Cy/Flu 25m Med PFS - No Flu 1.5m |
| Study | Year | Institution | Trial ID | CD19 | Product | CD | Disease | Dose | Treatment | CR | ORR | PFS | Follow-up |
|-------|------|-------------|---------|------|---------|----|---------|------|-----------|-----|------|------|------------|
| (16)  | 2016 | MDACC       | NCT00968760 | CD19 | 2G: CD28 | B-ALL, B-NHL | 7 | Auto HSCT | 10^7 to 5x10^9/m^2 Sleeping beauty | 0% CRS | 86% CR | 83.3% PFS | 30m |
|       |      |             |         |      |          |       |       |       | N/A       |      |      |      |            |
| (17)  | 2017 | UPenn       | NCT02640209 | CD19 | 2G: 41BB | B-CLL | 10 | Flu/Cy | N/A       | 89% CR (marrow) | 10% CRS | Med follow-up 6m |
| (18)  | 2017 | UPenn       | NCT02030834 | CD19 | 2G: 41BB | DLBCL, FL | 28 | Flu/Cy | 5x10^5/Kg | 64% ORR (DLBCL) | 18% CRS | 11% ICANS |
|       |      |             |         |      |          |       |       |       | 43% CR (FL) |      |      |      |            |
| (19)  | 2017 | FHCRC       | NCT02028455 | CD19 | 2G: 41BB | B-ALL (paediatric/young adults) B-CLL | 43 | Various, including Flu/Cy | 0.5-10x10^6, 0.5-5x10^6/Kg | CR 93% | 93% CRS | 51% EFS | 12m |
|       |      |             |         |      |          |       |       |       | 50% CRS (DLBCL) |      |      |      |            |
| (20)  | 2017 | FHCRC       | NCT01865617 | CD19 | 2G: 41BB | B-ALL | 24 | Flu/Cy | 2x10^6/Kg, 2x10^6/Kg (1:1 CD4:CD8) | 71% ORR | 83% CRS | 33% ICANS | Med OS | 6.6m |
|       |      |             |         |      |          |       |       |       | 50% CRS (DLBCL) |      |      |      |            |
| (21)  | 2017 | Zhejiang University/ Innovative Cellular Therapeutics | ChiCTR-OCC-15007008 | CD19 | 2G: 41BB | B-ALL | 15 | Flu/Cy | 1.1x10^6 to 9.8x10^6/Kg | 80% CR | 40% CRS | OS 65.5% and DFS 37.8% at 150d |
|       |      |             |         |      |          |       |       |       | 33% ICANS |      |      |      |            |
| (22)  | 2017 | NCI         | NCT00924326 | CD19 | 2G: CD28 | DLBCL | 22 | Flu/Cy | 1x10^6 to 6x10^6/Kg | 73% ORR | 0% CRS | Duration of response 7- |
| Year | Institution | Study ID | CART Construction | Disease Type | N or Age | Control | Flu/Cy | CR/CRi | CRS % | ICANS % | Follow-up | OS | EFS |
|------|-------------|----------|--------------------|--------------|----------|---------|--------|--------|-------|---------|-----------|----|-----|
| 2017 | Hebei Yanda Lu Daopei Hospital / Shanghai Pulmonary Hospital | N/A | CD19 2G:41BB | B-ALL | 51 | Flu/Cy | 0.05-14x10^5 /Kg 1x10^6/Kg | 18% PR | 90% CR/CRi | 16% CRS | 4% ICANS | ongoing 23/27 bridged to allo HSCT remained in CR at med follow up of 206d |
| 2018 | MSKCC | NCT0144069 | CD19 2G: CD28 | B-ALL | 53 | Flu/Cy | 1x10^6 to 3x10^6/Kg | 83% CR | 26% CRS | 43% ICANS | Med EFS 6.1m Med OS 12.9m |
| 2018 | NCI/Stanford University | NCT02315612 | CD22 2G: 41BB | B-ALL children/young adults | 21 (17 prior CD19 CAR-T) | Flu/Cy | 3x10^5 to 3x10^6/Kg | 73% CR | 0% CRS | 28% ICANS (?grade) | Med response duration 6m |
| 2018 | Uppsala University | NCT02132624 | CD19 3G: CD28/41BB | CD19+ leukaemia or lymphoma | 15 | Flu/Cy | 2x10^7 to 2x10^8 cells/m^2 | 36% CR (B-NHL) 50% CR (B-ALL) | 20% CRS | 13% ICANS | Med response duration 5m |
| 2018 | Sheba Medical Center | NCT02772198 | CD19 2G: CD28 | B-ALL | 20 | Flu/Cy | 1x10^6/Kg | 90% CR | 20% CRS | 30% ICANS (?grade) | 73% EFS and 90% OS at 1y |
| 2018 | Third Military Medical University | NCT02349698 | CD19 2G: CD28 2G: 41BB | B-ALL | 10 (5-CD28) (5-41BB) | Flu/Cy | 1x10^6 to 1x10^7/Kg | CD28: 60% CR 41BB: 60% CR | 0% CRS | 0% ICANS | Med PFS 6m |
| 2018 | Xuzhou Medical | N/A | CD19 2G: 41BB | B-ALL | 14 | Flu/Cy | 1x10^6/Kg | 92.9% CR/CRi | 29% CRS | 7% ICANS (?grade) | At 180d OS 65.8% DFS 71.4% |
| (30, 31) 2018 | Novartis | NCT02435849 (ELIANA) | CD19 | 2G: 41BB (Kymriah; Tisagenlecleucel) | B-ALL (paediatric/young adults) | 79 | Flu/Cy in 76/79 | 0.2−5 × 10^8 | 0.1−2×10^9/Kg | 60% CR | 21% CRi | 48% CRS | 13% ICANS | 66% DFS at 18m | Med OS not reached |
| (32) 2018 | Third Military Medical University | NCT02685670 | CD19 | 2G: CD28 | 2G: 41BB | B-ALL (6) and B-CLL (1) | 7 | Flu/Cy | 1x10^6/Kg | 2G CAR T-cells mixed 1:1 | 71% CR | 0% CRS | 0% ICANS | Med OS | 12m | Med PFS 5m |
| (33) 2018 | Novartis-UPenn | NCT02445248 (JULIET) | CD19 | 2G: 41BB (Kymriah; Tisagenlecleucel) | DLBCL | 93 | Flu/Cy | Med dose 3×10^8 | | 52% ORR | 40% CR | 12% PR | 22% CRS | 12% ICANS | DFS 65% at 12m |
| (34) 2018 | MSKCC | NCT01416974 | CD19 | 2G: CD28 | B-CLL | 8 | Cy | 3×10^6 to 3×10^7/Kg | 25% CR | 13% PR | 0% CRS | 0% ICANS | Med PFS 13.6m | Med OS not reached |
| (35) 2018 | Stanford University | NCT03233854 | CD19 & CD22 | 2G: 41BB Bispecific CAR | B-ALL | DLBCL | 6 | Flu/Cy | 1x10^6/Kg | 3x10^6/Kg | 1x10^7/Kg | 33% CR | 33% CRS | 0% ICANS | N/A |
| (36) 2018 | Eureka Therapeutics | NCT02658929 (ARTEMIS) | CD19 | 2G: 41BB | B-NHL | 21 | Flu/Cy | 1x10^6/Kg | 3x10^6/Kg | 6x10^6/Kg | 52% ORR | 29% CR | 0% CRS | 0% ICANS | 24% CR at 6m |
| (37) 2019 | Kite/Gilead | NCT02348216 (ZUMA-1) | CD19 | 2G: CD28 (Yescarta; Axicabtagene Ciloleucel) | B-NHL | 108 treated | Flu/Cy | 2x10^6/Kg | | 83% ORR | 58% CR | 11% CRS | 32% ICANS | Med duration of response 11.1m | Med PFS 5.9m |
| (38) 2019 | MSKCC | NCT01840566 | CD19 | 2G: | B-NHL | 15 | Auto HSCT | 5x10^6/Kg | | 53% CR | 40% CRS | 30% PFS at |
| Study Year | Institution | Trial ID | CD19 or CD19+CAR | Disease | CD28 | CD4:CD8 | Flu/Cy | CD4:CD8 | CR Rate | ORR Rate | CRS Rate | ICANS Rate | Follow-up | EFS | OS | CR Rate | ORR Rate | CRS Rate | ICANS Rate | Median PFS | CR Patients | OS Rates at 6m | OS Rates at 12m | CR Patients at 6m |
|------------|-------------|---------|------------------|---------|-------|---------|--------|---------|---------|---------|----------|-----------|------------|------------|---------|----|---------|---------|-----------|-----------|-------------|--------------|----------------|----------------|------------------|
| 2019       | FHCRC       | NCT01865617 | CD19 2G:41BB B-ALL | 57 treated | Flu/Cy | 2x10^6/Kg 1:1 | 85% CR | N/A | Med follow-up 30.9m EFS 61% OS 72% |
| 2019       | FHCRC       | NCT01865617 | CD19 2G:41BB B-NHL | 65 treated | Flu/Cy | 2x10^6/Kg 1:1 | 51% ORR 40% CR | N/A | Med PFS 20m in CR patients |
| 2019       | UCL         | NCT02443831 (CARPALL) | CD19 2G:41BB AUTO1 B-ALL Burkitt NHL (paediatric/young adults) | 14 | Flu/Cy | 1x10^6 cells/Kg | 86% CR | 0% CRS 7% ICANS | OS 84% at 6m OS 63% at 12m |
| 2019       | Shanghai Institute of Hematology | NCT03355859 | CD19 2G:41BB B-NHL | 10 treated | Flu/Cy | 2x10^7, 5 x10^7 and 1x10^6 cells | 67% CR 33% PR | 0% CRS 11% ICANS | 56% still in CR at 6m |
| 2019       | FHCRC       | NCT01865617 | CD19 2G:41BB B-NHL: FL (38%)/ tFL(62%) | 21 | Flu/Cy | 2x10^6 cells/Kg 1:1 | 88% CR (FL) 46% CR (tFL) | 0% CRS 0% ICANS | All FL CR patients still in CR at 24m; Med PFS 10.2m in tFL group |
| Year | Institution | NCT Number | Treatment | Disease | Dose 1 | Dose 2 | CR/CRI | CRS | ICANS | Consolidation | Outcome |
|------|-------------|------------|-----------|---------|--------|--------|--------|-----|-------|--------------|---------|
| 2019 | MSKCC       | NCT01860937| CD19/2G: CD28 | B-ALL (paediatric/young adults) | 25 treated | 24 evaluable | 1x10^7/Kg | CR/CRI | 75% | 16% CRS | 28% ICANS | Most consolidated by allo HSCT. 44% alive at time of publication. |
| 2019 | The Second Hospital of Hebei Medical University | NCT02963038 | CD19/2G: 41BB | B-ALL | 10 | Flu/Cy | Average dose 0.71x10^6/Kg | 80% | CR | 40% CRS | 30% ICANS (all grades) | 57% | CR |
| 2019 | MGH         | N/A        | CD19/2G: 41BB | CNS Lymphoma | 8 | Flu/Cy | 0.6x10^6 to 6x10^6/Kg | 25% | CR | 25% PR | 0% CRS | 0% ICANS | 38% ongoing response at >180d |
| 2019 | Peking Univ Cancer Hospital; Norris Comp Cancer Center | NCT02842138 | CD19/2G: 41BB | B-NHL | 25 | Flu/Cy | 3x10^6 to 3.6x10^6/Kg | 28% | CR | (55% at highest dose level); 32% PR | 0% CRS | 0% ICANS |
| 2019 | Huazhong University of Science and Technology | NCT02965092 and NCT03366350 | CD19/2G: 41BB | B-ALL | 58 | Flu/Cy | 0.89x10^6 to 4.01x10^6/Kg | 87.9% | CR | 38% CRS | 15% ICANS | Med response >181d for 6 patients show achieved CR at highest dose level. Consolidation by allo HSCT in 21 patients. |
| 2019 | Tianjin Medical University | ChiCTR-ONN-16009862 and ChiCTR1800019288 | CD19/2G: 41BB | B-NHL | 11 | Flu/Cy and nivolumab | 8x10^6/Kg | 82% | ORR | 45% CR | 0% CRS | 0% ICANS | Med PFS 6m | 27% ongoing CR |
| 2019 | Peking Univ | NCT03528421 | CD19/2G: CD28 | B-NHL | 9 (CD28) | Flu/Cy | 0.75-5x10^6/Kg | 78% | CR | 1/3 grade 5 CRS (CD28) | 67% response |
| Cancer Hospital | Year | ID | CD19 | CAR Modification | CD28/CD27 | CD19 treated | CD28/CD27 treated | Flu/Cy | Med dose | ORR | CR | CRS | ICANS | OS | Follow up | CRs | Remarks |
|----------------|------|----|------|-----------------|-----------|--------------|------------------|--------|----------|-----|----|-----|-------|-----|------------|------|---------|
| (51) 2019 MSKCC | 2G: 41BB | CD19 | Nil or Cy | 0.4-3x10^7/Kg | 25% CR | 10% CRS | 10% ICANS | 1/3 grade 3 ICANS (CD28) | ongoing at 3m |
| (52) 2019 Multicentre China | CD22 | 2G: 41BB | Flu/Cy | ≤1x10^7/kg to ≤4x10^6 per kg | 80% CR/Cri | 3% CRS | 0% ICANS | 1-year LFS 71.6% (11 bridged to allo HSCT) |
| (53) 2019 Multicentre China | CD19 | 4G: CD28 +CD27 | Flu/Cy | Med dose 7.133x10^7/Kg | 92% ORR | 80% CR | 0% ICANS | Med OS 267 |
| (54) 2019 Autolus (Amelia) | CD19 & CD22 | 2x2G: OX40 (CD19) & 4-1BB (CD22) (AUTO3) | Flu/Cy | 1.3 or 5x10^6/Kg | 100% CR/Cri | 0% CRS | 0% ICANS | Med follow-up 8m 57% CR/Cri |
| (55) 2020 NCI | CD19 | 2G: CD28 | Flu/Cy | 1-30x10^6/Kg | 81% ORR | 58% CR | N/A | Med follow up 42m Med EFS 55m Med OS 20.3m |
| (56) 2020 Medical College of Wisconsin | CD19 & CD20 | 2G: 41BB Bispecific CAR | Flu/Cy | 2.5x10^5 to 2.5x10^6/Kg | 82% ORR | 64% CR | 5% CRS | 14% ICANS |
| (57) 2020 NCI | CD19 | 2G: CD28 | Flu/Cy | 0.66 x 10^6, 2 x 10^6 or 6 x 10^6 cells/Kg (some received 2 doses) | 70% OR | 55% CR | 10% CRS | 5% ICANS | 40% ongoing CRs ranging from 17-35m |
| Study (Ref) | Year | Institution | NCT Number | Disease | CAR Design | CAR Target(s) | CD38 Dose (cells/Kg) | CR | PR | CRS | ICANS | PFS | OS |
|-------------|------|-------------|------------|---------|------------|---------------|-------------------|----|----|-----|-------|-----|----|
| (58) 2020 Kite/ Gilead | NCT02601313 (ZUMA-2) | 2 | 2G: CD28 (Tecartus; Brexucabtagene autoleuce) | Mantle cell lymphoma | 68 treated 60 evaluable for efficacy | Flu/Cy | 2x10^6 cells/Kg | 67% CR 27% PR | 15% CRS 31% ICANS | At 12m PFS 61% and OS 81% |
| (59) 2020 Lu Daopei Hospital | NCT03173417 | 1/2 | 2G: CD28 2G: 41BB | B-ALL 65% children 35% adult | CD28 21 4-1BB 89 | Flu/Cy | 1-10x10^6/Kg | 93% CR | 16% CRS 14% ICANS (grade 2-3) | 58% DFS and 64% OS at 1y |
| (60) 2020 Autolus (Alexander) | NCT03287817 | CD19 & CD22 | 2 x 2G: OX40 (CD19) 4-1BB (CD22) (AUTO3) | DLBCL 19 treated 18 evaluable for efficacy | Flu/Cy & Pembrolizumab | 50,150 or 450x10^6 cells | dose > 50 x 10^6 64% ORR 55% CR | 0% CRS 5% ICANS | All CRs ongoing at 1-12m |
| (61) 2020 Chinese PLA General Hospital | NCT03185494 | CD19 & CD22 | 2G: 41BB Bispecific CAR | B-ALL 6 | Flu/Cy | 1.7x10^6 To 3x10^6/Kg | 100% CR | 0% CRS 0% ICANS | DFS 3-11m |
| (62) 2020 UPenn and NCT01029366 | NCT02030847 | CD19 | 2G: 41BB (adult) | 35 | Flu/Cy | 5x10^7 cells (9) 5x10^8 cells (26) (single dose or fractionated) | 33% CR low dose 90% CR high dose | 3 CRS deaths in high single dose group; High dose fractionated safest and most effective with 5% CRS | High dose fractionated 2y OS 73% EFS 49.5% |
| (63) 2020 Multicentre China | ChiCTR- OOC-16007779. | CD19 | 4G: CD28 +CD27 | B-NHL 21 | Flu/Cy | 8.9x10^6/Kg | 67% OR 43% CR 24% PR | 0% CRS 5% ICANS | Med OS 23.8m |
| (64) 2020 | FHCRC | NCT01865617 | CD19 | 2G: 41BB (outcome of second infusion) | B-ALL 14 | B-CLL 9 | B-NHL 21 | Flu/Cy | 2 doses CART1&2 ALL 2x10^6 to 2x10^6/Kg | B-ALL 21% CR | B-CLL 22% CR | 9% CRS 11% ICANS | Med duration response B-CLL, B-NHL, B-ALL was 33.6 and 4m respectively |
| (65) 2020 | JW Therapeutics | NCT04089215 | CD19 | 2G: 41BB Relmacab b-tagene autoleucel | B-NHL | 59 treated | Flu/Cy | 100x10^6 | 76% ORR 52% CR | 5.1% CRS 5.1% ICANS | ORR 60.3% at 3m |
| (66) 2020 | Multicentre China | ChiCTR-OIB-17013670 | CD19 & CD22 | 2G: 41BB Sequential CAR T-cell infusions | B-ALL (paediatric) | 20 | Flu/Cy | Median dose for both CAR T-cells 10x10^6/Kg | 100% CR | 5% CRS 5% ICANS | DFS and OS 79.5% and 92.3% respectively at 1y (no HSCT consolidation) |
| (67) 2020 | Second Hospital of Anhui Medical University | NCT02735291 | CD19 | 2G: 41BB (paediatric/adult) | B-ALL | 51 treated | Flu/Cy/others | 1–5x10^6/Kg | 80.9% CR/CRi | 23.4% CRS 6.4% ICANS | OS and DFS 53% and 45% respectively at 1y |
| (68) 2020 | Sheba Medical Center | NCT00287131 | CD19 | 2G: CD28 | B-ALL B-NHL | 90 | Flu/Cy | 1x10^6/Kg | ALL: 84.4% ORR (67% MRD neg); NHL: 62% ORR and 31% CR | N/A | N/A |
| No. | Year | Institution | Location | Study ID | CD19 & CD20 CAR | CD28 Type | CD28 CAR | CD28 CAR | CD28 CAR | CD28 CAR | CD28 CAR |
|-----|------|-------------|----------|----------|-----------------|------------|----------|----------|----------|----------|----------|
| (69) | 2020 | Lyon Sud Hospital | N/A | CD19 | 2G: CD28 (Yescarta; Axicabtagene Ciloleucel) | 61 | Flu/Cy (98%) | Bendamustine (2%) | As per EMA approval | Yescarta: 40% CR | 8% CRS | 0% ICANS | At med follow-up 5.7m |
| (70) | 2020 | Multicentre China | NCT03097770 | CD19 & CD20 | 2G: 41BB (Kymriah; Tisagenlecleucel) | Flu/Cy | 0.5-6×10⁶/Kg | 79% ORR | 71% CR | 14% CRS | 0% ICANS | PFS 64% at 12m |
| (71) | 2020 | Tongji Medical College | ChiCTR-OPN-16008526 | CD19 & CD22 | 3G: CD28 & 41BB (Bispecific CAR) | Flu/Cy | B-ALL 2.6×10⁶/Kg | CAR19 & 2.7×10⁶/Kg CAR22 | B-ALL 96% CR | 50% CR | 23.52% CRS | 0% ICANS | B-ALL med OS and PFS 31 and 13.6m respectively |
| (72) | 2020 | US Lymphoma CAR T Consortium | N/A | CD19 | 2G: CD28 (Axicabtagene Ciloleucel as standard of care) | 275 | Flu/Cy | As per FDA approval | 82% ORR | 64% CR | 7% CRS | 31% ICANS | at med follow-up 12.9m |
| (73) | 2020 | Xuzhou Medical University | NCT03207178 | CD19 & CD20 | 2G: 41BB co-infusion | Flu/Cy (19) or Ifosfamide (2) | CD19 CAR T-cell dose 0.2- | 81% ORR | 52.4% CR | 28.5% CRS | 9.5% ICANS | med PFS 5.0m |

**Notes:**
- LBCL = Lymphoblastic Lymphoma
- B-NHL = B-Non-Hodgkin Lymphoma
| Year | Sponsor | Trial ID | CARs | CAR T-cell dose | Objective | CD4:CD8 | ORR | CR | PR | SD | CRS | ICANS | PFS | OS at 1y | OS at 21m |
|------|---------|----------|------|-----------------|-----------|---------|-----|----|----|----|-----|--------|-----|---------|-----------|
| 2020 | Juno | NCT02631044 (TRANSCEND NHL-001) | CD19 | 4x10⁶/Kg | 269 treated, 256 evaluable for efficacy | Flu/Cy | 50x10⁶ | 73% ORR | 53% CR | 20% PR | 13% SD | 2% CRS | 44% PFS and 58% OS at 1y med OS | 8.1m |
| 2020 | Kite/Gilead | NCT03105336 (ZUMA-5) | CD19 | 2G: CD28 (Yescarta; Axicabtagene Ciloleucel) | 146 treated (124 FL; 22MZL) | Flu/Cy | 2x10⁶/Kg | 92% ORR | 76% CR | 7% CRS | 19% ICANS | Med follow up 17.5m | 92% ORR 76% CR |
| 2020 | First Affiliated Hospital of Zhengzhou University | N/A (Abstract only available) | CD19 | 2G: 41BB | N/A (Abstract only available) | Flu/Cy | 2x10⁶/Kg | N/A | N/A | N/A | N/A | N/A (Abstract only available) |
| 2020 | Kite/Gilead | NCT02926833 (ZUMA-6) | CD19 | 2G: CD28 | Flu/Cy + atezolizumab | 2x10⁶/Kg | 75% ORR | 46% CR | 4% CRS | 29% ICANS | Med follow up 10.2m, 46% ongoing responders |
| 2020 | Autolus | NCT04404660 (ALLCAR) | CD19 | 2G: 41BB AUTO1 | Flu/Cy | 410 x 10⁶ cells as split dose d1 and 10 | 84% CR | 0% CRS | 15% ICANS | EFS at 6m 69% EFS at 12m 52% |
(80) 2020 Kite/ Gilead NCT03761056 (ZUMA-12) CD19 2G: CD28 (Yescarta; Axicabtagene Ciloleucel) High risk LBCL 31 Flu/Cy 2x10⁶/Kg 92% ORR 75% CR 20% CRS 27% ICANS 75% CRs persisted at data cut-off

Other haematological malignancies

| Year | Institution | Study Identify | Target | Combination | Dose | ORR | CR | PR | SD | CRS | ICANS | PFS |
|------|-------------|----------------|--------|-------------|------|-----|----|----|----|-----|-------|-----|
| (9)  | 2016        | Baylor         | NCT00881920 | Light chain | MM | 7 | Cy unless lymphopenic | 4 SD 1.7x10⁷ to 1.9x10⁷/m² | 0% CRS 0% ICANS | SD for 117m and 24m
| (81) | 2016        | NIH            | NCT02215967 | MM | 12 | Flu/Cy | 0.5x10⁶ to 9x10⁶/Kg | 8% CR 8% ICANS (both at highest dose level) | 33% CRS 8% ICANS (grades) 8% ongoing response at 26w
| (82) | 2017        | Chinese PLA General Hospital | NCT02259556 | CD30 | 2G: 41BB HD | 18 | Flu/Cy or two others | 1x10⁶ to 3x10⁶/Kg | 39% PR 0% CRS 0% ICANS | med PFS 6 mo
| (83) | 2017        | Baylor         | NCT01316146 | CD30 | 2G: CD28 HD/ALCL | 9 | Nil | 2x10⁶/m² 1x10⁶/m² 2x10⁶/m² | 33% CR 0% CRS 0% ICANS | 2 CRs for 9 & 30 months
| (84) | 2018        | Juno           | NCT03430011 (EVOLVE) | BCMA | 2G: 41BB MM | 13 treated 8 evaluable | Flu/Cy | 50x10⁶ 150x10⁶ cells | 100% ORR 38% CR 12% ICANS | At data cut, no patients had progressed
| Year | Institution | Study ID | CAR T Cells | Dose | ORR | CRS | ICANS | Duration |
|------|-------------|----------|-------------|------|-----|-----|-------|----------|
| 2018 | MSKCC       | NCT03070327 | BCMA 2G:41BB MM | 11 Cy or Flu/Cy cells | 72-818x10^6 | 64% | 20% | 0% | med response 106d |
| 2018 | UPenn       | NCT02135406 | CD19 2G:41BB MM | 10 High dose melphalan and auto HSCT | 1x10^7 to 5x10^7 | 80% | 0% | 0% | med PFS 200d |
| 2018 | Celyad Oncology | NCT03018405 (Think study) | NKG2D ligands 1G plus endog. DAP10 AML MDS MM | 16 treated Nil | 3x10^6 1x10^6 3x10^6 (multiple infusions) | 46% | 42% | 0% | One AML CR patient bridged to allo HSCT and in CR for >1y |
| 2018 | The Second Affiliated Hospital of Henan University of Traditional Chinese Medicine | NCT03093168 | BCMA 2G:41BB MM | 17 Flu/Cy | 9x10^6/Kg | 79% | 7% | 7% | Two responses sustained at 15m |
| 2018 | FHCRC       | NCT03338972 | BCMA 2G:41BB MM | 7 Flu/Cy | 5 to 15x10^7 cells 1:1 CD4:CD8 | 100% | 0% | 0% | All surviving at a median of 16w follow up |
| 2018 | Huazhong University of Science and Technology | ChiCTR-OPC-16009113 | BCMA 2G:CD28 MM | 28 Flu/Cy | 5.4-25x10^6/Kg | 93% | 14% | 0% | Med PFS 296d and 64d based on BCMA expression |
| Year | Institution/Company | Study ID | CD19 & BCMA | Cell Type | CD28 | OX40 | T-cell infusions | Dosage | Route | Response | Toxicity | PFS/Med Duration | Notes |
|------|---------------------|---------|-------------|-----------|-------|------|-----------------|--------|-------|----------|----------|-----------------|-------|
| 2018 | Jiangsu Institute of Hematology | NCT03455972 | CD19 & BCMA | 3G: CD28 + OX40 | Sequential CAR | MM | 9 | Cy/Bu and auto HSCT | 1x10^6/Kg CD19 1x10^5/Kg BCMA | 100% ORR 33% CR 0% CRS 0% ICANS | Not available as pts had further treatments |
| 2019 | Celgene/Bluebird Bio | NCT02658929 | BCMA | 2G: 41BB (BB2121; idecabtagene vicleucel) | MM | 33 | Flu/Cy | 50x10^6 to 800x10^6 cells | 85% ORR 45% CR 6% CRS 3% ICANS | Med PFS 11.8m |
| 2019 | Xuzhou Medical University | ChiCTR-OIC-17011272 | CD19 & BCMA | Both 2G: 41BB and infused on the same day | MM | 21 | Flu/Cy | 1x10^6/Kg CD19 + 1x10^5/Kg BCMA | 95% ORR 57% CR 4% CRS 0% ICANS | Med PFS for responders 243d |
| 2019 | Celyad Oncology | NCT02203825 | NKG2D ligands | 1G plus endog. DAP10 (CYAD-01) | AML | 7 | AML | Nil | 1x10^9 to 3x10^7 cells | No responses 0% CRS 0% ICANS | Med OS 4.7m |
| 2019 | Celyad Oncology (Deplethink) | NCT03466320 | NKG2D ligands | 1G plus endog. DAP10 (CYAD-01) | AML | 9 | Flu/Cy | 1x10^5 3x10^6 1x10^7 cells | 0% ORR first 2 dose levels 22% CRS 11% ICANS 33% did not progress after 1m | |
| 2019 | Tongji Medical College | ChiCTR1800018143 | BCMA & CD38 | 2G: 41BB Bispecific CAR | MM | 16 | Flu/Cy | 0.5-4x10^9/Kg | 85% ORR 50% sCR 12.5% VGPR 25% PR 25% CRS 0% ICANS | Med duration of PFS not reached 75% PFS at 9m |
| Year | Source | Clinical ID | Therapy | Disease | N | Dose | ORR | CR | CRS | ICANS | Duration of response | Other |
|------|--------|-------------|---------|---------|-----|-------|-----|----|-----|-------|----------------------|--------|
| 2019 | UPenn  | NCT02546167| BCMA 2G: 41BB | MM | 25 | Cy (cohorts 2&3) | 1x10^8 to 5x10^8, 1x10^7 to 5x10^7, 1x10^6 to 5x10^6 cells | 48% | 8% | 12% | 100% | 1×10^8 to 5x10^8 to 5x10^7 | N/A |
| 2019 | Tongji Medical College | ChiCTR18000181 | BCMA 2G: 41BB | MM | 9 | Flu/Cy | 1x10^6 to 6x10^6/Kg x 3 doses | 100% | 44% | 0% | N/A | 1 DLT at highest dose level | N/A |
| 2019-101 | Nanjing Legend Biotech Co | NCT03090659 | BCMA 2G: 41BB | MM | 57 | Cy or Flu/Cy | 0.2 to 1.5 x 10^6/Kg | 88% | 82% | 6% | 41% | Med OS not reached | Med OS not reached |
| 2019 | The First Affiliated Hospital of Soochow University | NCT03196414 | CD19 & BCMA 3G: CD28 + OX40 | MM | 28 | Flu/Cy | CART-19, 1x10^7/Kg, CART-BCMA 2-6.8x10^7/kg | 92.6% | 40.7% | 32% | 3% | Med PFS 8m | Med OS 16m |
| 2019 | FHCRC | NCT03502577 | BCMA 2G: 41BB | MM | 7 | Flu/Cy + JSMD194 (γ-secretase inhibitor) | 5x10^7 cells 1:1 CD4:CD8 | 100% | 16% | 16% | 70% | No relapses at median follow-up 5 months | No relapses at median follow-up 5 months |
| 2019 | Multicentre China | NCT03716856 NCT03302403 NCT03380039 | BCMA 2G: 41BB | MM | 24 | Flu/Cy | 0.5-1.8x10^8 cells | 87.5% | 79.2% | 33% | 12.5% | 54% ongoing CR at med follow-up of 383d | N/A |
| 2019 | UCL | NCT03287804 | BCMA 3G: MM | MM | 12 | Flu/Cy | 15 to | 43% | 0% | 0% | N/A | 54% ongoing CR at med follow-up of 383d | N/A |
| Reference | Year | Sponsor | Study ID | Target | Dose | Dose | % ORR | % CR | % ICANS | Best duration of response | Other Details |
|-----------|------|---------|----------|--------|------|------|-------|------|---------|--------------------------|--------------|
| (106)     | 2019 | NCI     | NCT03602612 | BCMA 2G: 41BB MM | 12 Flu/Cy | 900x10^6 cells | 28% PR | 0% ICANS |                      |              |
| (107)     | 2019 | Bluebird Bio | NCT03274219 | BCMA 2G: 41BB MM | 22 Flu/Cy 150, 450, 800, 1200x10^6 cells | 83% ORR | 41% CR & VGPR | 8% CRS | 9% ICANS | 50% ongoing response at ≥2m follow-up (including 2 pts at 15&18m) |              |
| (108)     | 2020 | Poseida Therapeutics | NCT03288493 | BCMA 2G: 41BB MM | 43 Flu/Cy treated | 0.75-15x10^6 cells/Kg 57% ORR | 3% CRS | 0% ICANS | Median OS not reached |              |
| (109, 110)| 2020 | Celyad Oncology | NCT04167696 (CYCLE-1) | NKG2D ligands 1G plus endog. DAP10 (CYAD-02; includes shRNA targeting MICA/B) 2G: 41BB AML MDS | 9 Flu/Cy 1x10^6 3x10^6 1x10^9 cells | 14% CR | 14% CRS | 0% ICANS | Ongoing responses at 4 & 6m |              |
| (111)     | 2020 | CARsgen Therapeutics | NCT03975907 (Lummicar-1) | BCMA 2G: 41BB MM | 14 Flu/Cy treated 12 evaluable for efficacy | 1.0-1.5x10^5 CAR+ T-cells 100% ORR | 42% CR | 0% ICANS | N/A |              |
| (112) | 2020 | CARsgen Therapeutics | NCT03915184 (Lummicar-2) | BCMA | 2G: 41BB | MM | 14 treated 10 evaluable for efficacy | Flu/Cy | 0.5–1.8×10⁸ | 100% ORR | 40% CR | 0% CRS | 0% ICANS | N/A |
| (113) | 2020 | Celgene | NCT03361748 (KarMMa) | BCMA | 2G: 41BB (BB2121; idecamab-gene vicleucel) | MM | 128 | Flu/Cy | 150×10⁶ to 450×10⁶ CAR+ T-cells | 73% ORR | 31% CR | 5.5% CRS (1 fatal) | 3% ICANS | Med PFS 8.6m | Med duration of response 10.6m | Med OS 19.4m |
| (114, 115) | 2020 | Janssen Research & Dvpt | NCT03548207 CARTITUDE-1 | BCMA | 2G: 41BB (JNJ-68284528; LCAR-B38M; Ciltacabt a-gene autoleucel) | MM | 97 | Flu/Cy | Target dose 0.75×10⁹/Kg (range 0.5-1.0×10⁹/Kg) | 94.8% ORR | 55.7% sCR | 4.1% CRS (1 fatal) | 10.3% ICANS (1 fatal) | Med PFS 87.4% at 6m | Med OS 93.8% at 6m | Med duration of response not reached (med follow up 8.8m) |

**Solid Tumours**

| (116-118) | 1998 | Cell Genesys | N/A | TAG-72 | 1G | Colorectal cancer | 16 | Nil | Up to 10¹⁰ cells by IV (10) or intrahepatic artery infusion (6) | No responses | Hyperbilirubinemia n=2 | N/A |
| (117) | 2002 | N/A | N/A | CEA | 1G | Colorectal cancer and breast cancer | 7 | Nil | Up to 10¹¹ cells + IL-2 (n=2) | Two “minor responses” | Tolerance “adequate” | N/A |
| (119) | 2006 | NCI | N/A | FR-α | 1G | Ovarian | 14 | Nil | 3-216×10⁹ in | No | Toxicity | N/A |
| Study | Year | Institution | Trial ID | Receptor | CD80 | Cancer Type | Dose | Effect | Toxicity | Follow-up |
|-------|------|-------------|----------|----------|------|-------------|------|--------|----------|-----------|
| (120) | 2007 | Children's Hospital Seattle | N/A | L1-CAM | 1G | Neuroblastoma | 6 | Nil | 1-2 doses + IL-2 (n=8) | 1-11 x 10^9/m^2 in 1-2 doses + IL-2 in some cases | 0% CRS | 0% ICANS | Died of disease d162-1670 |
| (121-123) | 2006 - 2013 | Erasmus University Medical Center | N/A | CAIX | 1G | Renal cell carcinoma | 12 | Nil | Cannot assess owing to additional therapies | 0.2-2.1 x 10^9 cells | 33% hepatotoxicity due to on-target off-tumour toxicity | Med OS 9.5m (12.5m in 4 patients who received a CAIX blocking antibody prior to CAR T-cells) |
| (124, 125) | 2008 - 2011 | Baylor | NCT00085930 | GD2 | 1G | Neuroblastoma | 19 | Treated | 2-20 x 10^7 cells | 27% CR | 0% CRS | 0% ICANS | Two CR durable for >60m and >21m |
| (126) | 2013 | MSKCC | NCT01140373 | PSMA | 2G: CD28 | Prostate cancer | 7 | Cy | 1 to 3 x 10^7/kg | 29% SD | Pyrexia up to 39°C | SD for 6 and 16m |
| (127) | 2015 | Baylor | NCT00902044 | HER2 | 2G: CD28 | Sarcoma | 19 | Nil | 1 x 10^4 to 1 x 10^8 cells/m^2 | 24% SD for 12w to 14m | 0% CRS | 0% ICANS | Med OS 10.3m |
| (128) | 2015 | Roger Williams Medical Center | NCT01373047 | CEA | 2G: CD28 | CEA+ metastatic liver disease | 6 | Nil | 1 x 10^8 to 1 x 10^10 cells by 3 sequential intrahepatic artery infusions + IL-2 in 3 | 17% SD | 0% CRS | 0% ICANS | Med OS 15w |
| Study ID  | Year  | Institution                                      | Target | CAR Type | Number of Patients | Treatment Details                                                                 | Cases | Responses | Toxicity | Follow-up |
|----------|-------|--------------------------------------------------|--------|----------|-------------------|----------------------------------------------------------------------------------|-------|-----------|----------|-----------|
| (129)    | 2016  | Chinese PLA General Hospital                     | EGFR   | 2G: 41BB | Lung              | Non-small cell lung cancer Nil, Cy alone or Cy with additional cytotoxic drugs | 11    | 18% PR    | 0% CRS   | 2-8m      |
| (130)    | 2017  | Chinese PLA General Hospital                     | EGFR   | 2G: 41BB | Biliary tract cancer | Cy/ nab-paclitaxel Median 2.65 x10^5/kg x 1-3 cycles | 19    | 6% CR     | 15% CRS (grade 3 acute fever/chill) | Med PFS 4m |
| (131)    | 2017  | The Christie NHS                                 | CEA    | 1G       | CEA+ malignancy   | Fludarabine alone or Flu/Cy + IL-2 Up to 5x10^5 cells | 14    | No responses | 50% SD | No long term sustained responses |
| (132)    | 2017  | Third Military Medical University                | CEA    | 2G: CD28 | Colorectal cancer  | Cy 1 x10^5 to 1 x10^6/kg | 10    | 70% SD    | 0% CRS   | 20% SD at 30w follow up |
| (133)    | 2017  | UPenn                                           | MET    | 2G: 41BB | Breast cancer     | Nil 3x10^7 3x10^8 cells mRNA transfected CAR T-cells administered directly to tumour | 6     | No responses | 0% CRS   | 1SD at med follow up 10m |
| (134)    | 2017  | Baylor                                          | GD2    | 3G: CD28/ | Neuroblastoma     | Nil or Flu/Cy 1-17x10^7/m^2 | 11    | 45% SD    | 0% CRS   | Med OS 506d |
| Study ID   | Year | Institution        | Trial Identifier | Cancer Type | Tumor Location | CAR+ Cell Type | CAR+ Cell Dose | Antigen Loss | CRS | ICANS | Med OS/Med PFS/Other |
|-----------|------|--------------------|------------------|-------------|---------------|----------------|----------------|--------------|-----|-------|---------------------|
| (135)     | 2017 | UPenn              | NCT02209376      | GBM         | Nil           | 1x10^8 to 5x10^8 CAR+ cells | 90% SD | (Antigen loss noted in 5/7 tumours) | 0% | 0% ICANS | Med OS 8m |
| (136)     | 2017 | Baylor             | NCT01109095      | GBM         | Nil           | 1x10^6 to 1x10^8/m^2 virus-specific T-cells (CMV, EBV, adenovirus) | 6% PR | 41% SD | 0% CRS | 0% ICANS | Med OS 11.1m |
| (137)     | 2018 | Chinese PLA       | NCT01935843      | GBM         | Nil           | Median dose 2.1x10^6/Kg x 1-2 cycles | 9% PR | 45% SD | 0% CRS | 0% ICANS | Med PFS 4.8m |
| (138)     | 2018 | UPenn              | NCT01897415      | GBM         | Nil           | mRNA transfected CAR T-cells x 9 infusions of 1-3x10^6/m^2 cells over 3 weeks | 33% SD | Reduction in FDG uptake seen by PET in one patient | 0% CRS | 0% ICANS | PFS 3.8 and 5.4m in 2 patients |
| (139)     | 2018 | King’s College     | NCT01818323      | GBM         | Nil           | 1x10^6 to 1x10^7 CAR+ cells by intratumoral injection | 69% SD | 0% CRS | 0% ICANS | N/A |
| (140)     | 2019 | UPenn              | NCT02159716      | GBM         | Nil or Cy     | 1-3x10^6 or 1-3x10^6/m^2 | 73% SD | 0% CRS | 0% ICANS | Med PFS 2.1m |
| Study Year | Institute | Study ID | Target | Cancer Type | CAR + Cell Line | Treatment | Dose | CR | SD | Adverse Events |
|------------|-----------|----------|--------|-------------|----------------|-----------|------|----|----|----------------|
| 2019       | Bellicum Pharmaceuticals | NCT02744287 | PSCA | Ovarian cancer, Pancreatic cancer | Nil, Cy or Flu/Cy | 1.25x10^6 | 53% SD | 0% CRS | 0% ICANS | N/A |
| 2019       | Baylor    | NCT00902044 | HER2 | Sarcoma (paediatric) | Fludarabine alone or Flu/Cy | 1x10^9/m^2 | 20% CR | 0% CRS | 0% ICANS | Two survivors at 32 and 33m |
| 2019       | UPenn     | NCT03089203 | PSMA | Prostate cancer | Nil or Flu/Cy (cohort 3) | 1.3-10^7/m^3, 1.3-10^7/m^3 | Med 33.2% PSA decline | 40% CRS DLT cohort 3 | N/A |
| 2019       | Changhai Hospital | NCT03159819 | Claudin 18.2 | Gastric or pancreatic cancer | Flu/Cy alone or with nab-paclitaxel | 0.5-55x10^6 CAR+ cells administered over 1-5 cycles | 9% CR 27% PR 45% SD | 0% CRS 0% ICANS | Med PFS 130d |
| Study ID   | Year | Institution/Center | Study Code | Tumor Type | Targeting Strategy | Cohort Size | Dose | Efficacy Parameters | Toxicity Parameters | Progression-Free Survival | Overall Survival |
|-----------|------|--------------------|------------|------------|--------------------|-------------|------|---------------------|----------------------|------------------------|------------------|
| (147)     | 2019 | MSKCC              | NCT02414269 | Mesothelin | 2G: CD28 Pleural cancers | 20          | Nil (3), Cy (3) Cy + anti-PD-1 (14) | 3x10^6 - 1x10^9/Kg | 14% CR, 36% PR, 29% SD | 0% CRS, 0% ICANS         | N/A              |
| (148)     | 2019 | NCI                | NCT01454596 | EGFR vIII  | 3G: CD28 & 41BB GBM | 18          | Flu/Cy + IL-2 6.3 x10^6 to 2.6x10^10 CAR+ cells | No responders | 1 fatal pulmonary event at highest dose level (?)CRS, 1 grade 3 neurological event | Med PFS 1.3m, Med OS 6.9m |                |
| (149)     | 2019 | Beijing Sanbo Brain Hospital | NCT02937844 | PD-L1/2 PD1-CD28 switch receptor GBM | 14          | Cy up to 1x10^8 cells over three IV infusions. One patient received IV & intracavitary cells | Transient response | 0% CRS, 0% ICANS | Med OS 4.4 months |                |
| (150)     | 2020 | Roger Williams Medical Centre | NCT02416466 (HITM-SIR) | CEA | 2G: CD28 CEA+ metastatic liver disease | 6            | Selective intra-arterial radiation with SIR spheres 1x10^14 cells by 3 sequential intrahepatic artery infusions & IL-2 | 16% SD prior to SIR sphere administration | 0% CRS, 0% ICANS | Med OS 8m |                |
| (151)     | 2020 | RenJi Hospital | NCT02395250 | GLP-3 | 2G: CD28 HCC | 13          | Cy alone or Flu/Cy 7-40.77x10^8 CAR+ cells administrated over 2-9 cycles | 15% PR (case proved fatal) 0% ICANS | OS at 3y 10.5% |                |
| (152)     | 2020 | UCL/ | NCT02761915 | GD2 | 2G: Neurobl | 12          | Nil 1x10^6 - 1x10^9 | No | 8% CRS |                |                |


| (153) 2020 MSKCC NCT02498912 | MUC1 6 | Ovarian cancer 16 | Nil or Flu/Cy | 3x10^6 - 1x10^7/Kg | No responses (best response stable disease) | 2/3 developed macrophage activation-like syndrome in Flu/Cy cohort |
|---|---|---|---|---|---|---|
| (154) 2013 Baylor NCT00840853 | CD19 2G: CD28 B-ALL B-CLL 8 treated 6 evaluable | 3m-13y post allo HSCT | 1.5x10^7/m^2 | 1.2x10^7/m^2 donor-derived virus-specific T-cells | 38% CR (2/3 patients in CR at time of treatment) 12% PR | 0% CRS 0% ICANS 0% GvHD | Follow-up still ongoing in 2 CR patients at 2 and 8 months. Third CR lasted 3m |
| (155) 2013 NCI | CD19 2G: CD28 B-cell malignancy | 20 | No conditioning | 1x10^6 to 10x10^6/Kg donor derived T-cells | 30% CR 10% PR | 50% CRS (inferred from information provided) 0% ICANS 0% GvHD | CR sustained for 3-30m at time of writing |
| (156) 2013 NCI | CD19 2G: CD28 B-cell malignancy | 20 | No conditioning | 1x10^6 to 10x10^6/Kg donor derived T-cells | 30% CR 10% PR | 50% CRS (inferred from information provided) 0% ICANS 0% GvHD | CR sustained for 3-30m at time of writing |
| (16) 2016 MDACC | CD19 2G: CD28 B-ALL B-NHL 19 | Allogeneic HSCT | 10^6 to 10^7/m^2 | 58% CR | 0% CRS 0% ICANS | 53% PFS at 12 mo |
| Study ID   | Year  | Institution                  | Study ID   | Year  | Institution                  | Study ID   | Year  |
|------------|-------|------------------------------|------------|-------|------------------------------|------------|-------|
| NCT01195480 | 2017  | Multicentre UK & Germany     | NCT01195480 | 2017  | Multicentre UK & Germany     |              |       |
| CD19 1G    |       |                              | CD19 1G    |       |                              |            |       |
| 6 B-ALL (paediatric) relapsed post HSCT or at high risk of relapse post second allo HSCT | 6 Fludarabine | 4x10^7 - 2x10^8/m^2 donor-derived EBV-specific T-cells | 15% CR (2/2 were in CR at time of infusion) | No exacerbation of GvHD |

| Study ID   | Year  | Institution                  | Study ID   | Year  | Institution                  | Study ID   | Year  |
|------------|-------|------------------------------|------------|-------|------------------------------|------------|-------|
| NCT03692429 | 2019  | Celyad Oncology              | NCT03692429 | 2019  | Celyad Oncology              | NCT03692429 | 2019  |
| ALLOSHRINK |       |                              | ALLOSHRINK |       |                              | ALLOSHRINK |       |
| NKG2D ligand | 1G plus endog. DAP10 (CYAD-101, also comprising truncated CD3ζ) to reduce | CRC 15 | Concurrent FOLFOX chemotherapy x 3 cycles | 1x10^6 cells x 3 infusions with concurrent FOLFOX | 13% PR 60% SD |

| Study ID   | Year  | Institution                  | Study ID   | Year  | Institution                  | Study ID   | Year  |
|------------|-------|------------------------------|------------|-------|------------------------------|------------|-------|
| NCT03692429 | 2019  | Celyad Oncology              | NCT03692429 | 2019  | Celyad Oncology              | NCT03692429 | 2019  |
| ALLOSHRINK |       |                              | ALLOSHRINK |       |                              | ALLOSHRINK |       |
| NKG2D ligand | 1G plus endog. DAP10 (CYAD-101, also comprising truncated CD3ζ) to reduce | CRC 15 | Concurrent FOLFOX chemotherapy x 3 cycles | 1x10^6 cells x 3 infusions with concurrent FOLFOX | 13% PR 60% SD |

| Study ID   | Year  | Institution                  | Study ID   | Year  | Institution                  | Study ID   | Year  |
|------------|-------|------------------------------|------------|-------|------------------------------|------------|-------|
| NCT03692429 | 2019  | Celyad Oncology              | NCT03692429 | 2019  | Celyad Oncology              | NCT03692429 | 2019  |
| ALLOSHRINK |       |                              | ALLOSHRINK |       |                              | ALLOSHRINK |       |
| NKG2D ligand | 1G plus endog. DAP10 (CYAD-101, also comprising truncated CD3ζ) to reduce | CRC 15 | Concurrent FOLFOX chemotherapy x 3 cycles | 1x10^6 cells x 3 infusions with concurrent FOLFOX | 13% PR 60% SD |

### Conclusions

- **Sleeping beauty transposon**
- **No exacerbation of GvHD**
- **One survivor at 3y**
| Study (160) (161) | Year | Company | Study ID | Target | Indication | CD19 | Subset | Treatment | Dose (cells) | Response | GvHD | ICANS | CRS | Other |
|------------------|------|---------|----------|--------|------------|------|--------|------------|-------------|----------|------|-------|-----|-------|
| Allogene Therapeutics | 2020 | NCT03939026 (ALPHA) | CD19 | B-NHL | 2G: 41BB (ALLO-501) | 22 treated | Flu/Cy/ Allo-647 (two dose levels Allo-647) | 40x10^6 | 160x10^6 | 360x10^6 | 63% ORR | 5% CRS | 0% ICANS | 0% GvHD | 9 of 12 patients remain in response at med follow up of 3.8m |
| Allogene Therapeutics | 2020 | NCT04093596 (UNIVERSAL) | BCMA | MM | 2G: 41BB (ALLO-715) | 31 treated | Flu/Cy/ Allo-647 (two dose levels Allo-647) or Cy/Allo-647 | 40x10^6 | 160x10^6 | 320x10^6 | 480x10^6 | 60% ORR | 0% CRS | 0% ICANS | 0% GvHD | Med follow-up 3.2m 6/9 treated at DL3 or DL4 still in response |
| CRISPR Therapeutics | 2020 | NCT04035434 (CARBON) | CD19 | B-NHL | 2G: CD28 (CTX110) | 11 Flu/Cy | 30x10^5 | 100x10^5 | 300x10^5 | 600x10^5 | 36% CR | 30% CRS | 10% ICANS | 0% GvHD | Death of only patient treated at highest dose level (herpes viral reactivation) CR still ongoing at 1 month |
| MDACC | 2020 | NCT03056339 | CD19 | B-NHL | 2G: | 11 Flu/Cy | 1x10^7 to | 64% CR | 0% CRS | Other |
| Study | Year | Collaborators | Study ID | Disease | Cell Source | Treatment | Toxicity | Response | Toxicity | Toxicity | Toxicity |
|-------|------|---------------|----------|---------|-------------|-----------|----------|----------|----------|----------|----------|
| CD28 + IL-15 + inducible caspase 9 suicide gene | 2020 | Multicentre | NCT02808442 & NCT02746952 (UCART19) | B-CLL | Umbilical cord blood derived NK cells | 1x10^7/Kg | 9% PR | 0% ICANS | 0% GvHD | Therapies administered >30d after CAR-NK |
| 2G: 41BB | B-ALL | 21 | Flu/Cy with or without alemtuzumab | 1.1-2.3 × 10^6 kg (paediatrics) | 67% CR or CRi | 14% CRS | 0% ICANS | 55% OS | 27% PFS at 6m |
References

1. Brentjens RJ, Riviere I, Park JH, Davila ML, Wang X, Stefanski J, et al. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. Blood. 2011;118(18):4817-28.
2. Savoldo B, Ramos CA, Liu E, Mims MP, Keating MJ, Carrum G, et al. CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients. J Clin Invest. 2011;121(5):1822-6.
3. Kochenderfer JN, Dudley ME, Feldman SA, Wilson WH, Spaner DE, Marie I, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood. 2012;119(12):2709-20.
4. Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014;6(224):224ra25.
5. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-17.
6. Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med. 2015;7(303):303ra139.
7. Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP, Carpenter RO, Stetler-Stevenson M, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol. 2015;33(6):540-9.
8. Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385(9967):517-28.
9. Ramos CA, Savoldo B, Torrano V, Ballard B, Zhang H, Dakhova O, et al. Clinical responses with T lymphocytes targeting malignancy-associated χ light chains. J Clin Invest. 2016;126(7):2588-96.
10. Zhang WY, Wang Y, Guo YL, Dai HR, Yang QM, Zhang YJ, et al. Treatment of CD20-directed Chimeric Antigen Receptor-modified T cells in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an early phase IIa trial report. Signal Transduct Target Ther. 2016;1:16002.
11. Porter DL, Frey NV, Melenhorst JJ, Hwang W-T, Lacey SF, Shaw PA, et al. Randomized, phase II dose optimization study of chimeric antigen receptor (CAR) modified T cells directed against CD19 in patients (pts) with relapsed, refractory (R/R) CLL. Journal of Clinical Oncology. 2016;34(15_suppl):3009-.
12. Maude SL, Teachey DT, Rheingold SR, Shaw PA, Aplenc R, Barrett DM, et al. Sustained remissions with CD19-specific chimeric antigen receptor (CAR)-modified T cells in children with relapsed/refractory ALL. Journal of Clinical Oncology. 2016;34(15_suppl):3011-.
13. Wang X, Popplewell LL, Wagner JR, Naranjo A, Blanchard MS, Mott MR, et al. Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL. Blood. 2016;127(24):2980-90.
14. Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123-38.
15. Turtle CJ, Hanafi LA, Berger C, Hudecek M, Pender B, Robinson E, et al. Immunotherapy of non-Hodgkin’s lymphoma with a defined ratio of CD8<sup>+</sup>:CD4<sup>+</sup> CD19-specific chimeric antigen receptor–modified T cells. Science Translational Medicine. 2016;8(355):355ra116-355ra116.
16. Kebriaei P, Singh H, Huls MH, Figliola MJ, Bassett R, Oliwares S, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. J Clin Invest. 2016;126(9):3363-76.
17. Gill S, Frey NV, Hexner EO, Lacey SF, Melenhorst JJ, Byrd JC, et al. CD19 CAR-T cells combined with ibrutinib to induce complete remission in CLL. Journal of Clinical Oncology. 2017;35(15_suppl):7509-.
18. Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129(25):3322-31.
19. Pan J, Yang JF, Deng BP, Zhao XJ, Zhan X, et al. High efficacy and safety of low-dose CD19-directed CAR-T cell therapy in 51 refractory or relapsed B acute lymphoblastic leukemia patients. Leukemia. 2017;31(12):2587-93.
20. Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):449-59.
21. Enblad G, Karlsson H, Gammelgård G, Wenthe J, Lövgren T, Amini RM, et al. A Phase I/IIa Trial Using CD19-Targeted Third-Generation CAR T Cells for Lymphoma and Leukemia. Clin Cancer Res. 2018;24(24):6185-94.
22. Jacoby E, Bielorai B, Avigdor A, Itzhaki O, Hutt D, Nussboim V, 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):1485-92.
29. Cao J, Wang G, Cheng H, Wei C, Qi K, Sang W, et al. Potent anti-leukemia activities of humanized CD19-targeted Chimeric antigen receptor T (CAR-T) cells in patients with relapsed/refractory acute lymphoblastic leukemia. Am J Hematol. 2018;93(7):851-8.

30. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-48.

31. Grupp SA, Maude SL, Rives S, Baruchel A, Boyer MW, Bittencourt H, et al. Updated Analysis of the Efficacy and Safety of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed/Refractory (r/r) Acute Lymphoblastic Leukemia. Blood. 2018;132:895.

32. Cheng Z, Wei R, Ma Q, Shi L, He F, Shi Z, et al. In Vivo Expansion and Antitumor Activity of Coinfused CD28- and 4-1BB-Engineered CAR-T Cells in Patients with B Cell Leukemia. Mol Ther. 2018;26(4):976-85.

33. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. New England Journal of Medicine. 2018;380(1):45-56.

34. Geyer MB, Rivièrè I, Sénéchal B, Wang X, Wang Y, Purdon TJ, et al. Autologous CD19-Targeted CAR T Cells in Patients with Residual CLL following Initial Purine Analog-Based Therapy. Mol Ther. 2018;26(8):1896-905.

35. Hossain N, Sahaf B, Abramian M, Spiegel JY, Kong K, Kim S, et al. Phase I Experience with a Bi-Specific CAR Targeting CD19 and CD22 in Adults with B-Cell Malignancies. Blood. 2018;132(Supplement 1):490-.

36. Ying Z, Long L, Liu H, Song Y, Rizziere DA, Nejadnik B, et al. ET190L1-ArtemisTM T Cell Therapy Results in Durable Disease Remissions with No Cytokine Release Syndrome or Neurotoxicity in Patients with Relapsed and Refractory B-Cell Lymphoma. Blood. 2018;132(Supplement 1):1689-

37. Locke FL, Ghabadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, 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):31-42.

38. Sauter CS, Senechal B, Riviere I, Ni A, Bernal Y, Wang X, et al. CD19 CAR T cells following autologous transplantation in poor-risk relapsed and refractory B-cell non-Hodgkin lymphoma. Blood. 2019;134(7):626-35.

39. Hay KA, Gauthier J, Hirayama AV, Voutsinas JM, Wu Q, Li D, et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood. 2019;133(15):1652-63.

40. Hirayama AV, Gauthier J, Hay KA, Voutsinas JM, Wu Q, Gooley T, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. Blood. 2019;133(17):1876-87.

41. Ghorashian S, Kramer AM, Onuoha S, Wright G, Bartram J, Richardson R, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. Nat Med. 2019;25(9):1408-14.

42. Yan ZX, Li L, Wang W, OuYang BS, Cheng S, Wang L, et al. Clinical Efficacy and Tumor Microenvironment Influence in a Dose-Escalation Study of Anti-CD19 Chimeric Antigen Receptor T Cells in Refractory B-Cell Non-Hodgkin's Lymphoma. Clin Cancer Res. 2019;25(23):6995-7003.

43. Hirayama AV, Gauthier J, Hay KA, Voutsinas JM, Wu Q, Pender BS, et al. High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. Blood. 2019;134(7):636-40.
44. Curran KJ, Margossian SP, Kernan NA, Silverman LB, Williams DA, Shukla N, et al. Toxicity and response after CD19-specific CAR T-cell therapy in pediatric/young adult relapsed/refractory B-ALL. Blood. 2019;134(26):2361-8.

45. Ma F, Ho JY, Du H, Xuan F, Wu X, Wang Q, et al. Evidence of long-lasting anti-CD19 activity of engrafted CD19 chimeric antigen receptor-modified T cells in a phase I study targeting pediatrics with acute lymphoblastic leukemia. Hematol Oncol. 2019;37(5):601-8.

46. Frigault MJ, Dietrich J, Martinez-Lage M, Leick M, Choi BD, DeFilipp Z, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood. 2019;134(11):860-6.

47. Ying Z, Huang XF, Xiang X, Liu Y, Kang X, Song Y, et al. A safe and potent anti-CD19 CAR T cell therapy. Nat Med. 2019;25(6):947-53.

48. Jiang H, Li C, Yin P, Guo T, Liu L, Xia L, et al. Anti-CD19 chimeric antigen receptor-modified T-cell therapy bridging to allogeneic hematopoietic stem cell transplantation for relapsed/refractory B-cell acute lymphoblastic leukemia: An open-label pragmatic clinical trial. American Journal of Hematology. 2019;94(10):1113-22.

49. Cao Y, Lu W, Sun R, Jin X, Cheng L, He X, et al. Anti-CD19 Chimeric Antigen Receptor T Cells in Combination With Nivolumab Are Safe and Effective Against Relapsed/Refractory B-Cell Non-hodgkin Lymphoma. Frontiers in Oncology. 2019;9(767).

50. Ying Z, He T, Wang X, Zheng W, Lin N, Tu M, et al. Parallel Comparison of 4-1BB or CD28 Co-stimulated CD19-Targeted CAR-T Cells for B Cell Non-Hodgkin's Lymphoma. Mol Ther Oncolytics. 2019;15:60-8.

51. Geyer MB, Rivièrè I, Sénéchal B, Wang X, Wang Y, Purdon TJ, et al. Safety and tolerability of conditioning chemotherapy followed by CD19-targeted CAR T cells for relapsed/refractory CLL. JCI Insight. 2019;5(9).

52. Pan J, Niu Q, Deng B, Liu S, Wu T, Gao Z, et al. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. Leukemia. 2019;33(12):2854-66.

53. Tu S, Huang R, Guo Z, Deng L, Song C, Zhou X, et al. Shortening the ex vivo culture of CD19-specific CAR T-cells retains potent efficacy against acute lymphoblastic leukemia without CAR T-cell-related encephalopathy syndrome or severe cytokine release syndrome. Am J Hematol. 2019;94(12):E322-e5.

54. Amrolia PJ, Wynn R, Hough RE, Vora A, Bonney D, Veys P, et al. 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 (ttr B-ALL): Amelia Study. Blood. 2019;134(Supplement_1):2620-.

55. Cappell KM, Sherry RM, Yang JC, Goff SL, Vanasse DA, McIntyre L, et al. Long-Term Follow-Up of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. J Clin Oncol. 2020;38(32):3805-15.

56. Shah NN, Johnson BD, Schneider D, Zhu F, Szabo A, Keever-Taylor CA, et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase I dose escalation and expansion trial. Nat Med. 2020;26(10):1569-75.

57. Brudno JN, Lam N, Vanasse D, Shen YW, Rose JJ, Rossi J, et al. Safety and feasibility of anti-CD19 CAR T cells with fully human binding domains in patients with B-cell lymphoma. Nat Med. 2020;26(2):270-80.

58. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020;382(14):1331-42.

59. Zhang X, Lu XA, Yang J, Zhang G, Li J, Song L, et al. Efficacy and safety of anti-CD19 CAR T-cell therapy in 110 patients with B-cell acute lymphoblastic leukemia with high-risk features. Blood Adv. 2020;4(10):2325-38.
60. Osborne W, Marzolini M, Tholouli E, Ramakrishnan A, Bachier CR, McSweeney PA, et al. Phase I Alexander study of AUTO3, the first CD19/22 dual targeting CAR T cell therapy, with pembrolizumab in patients with relapsed/refractory (r/r) DLBCL. Journal of Clinical Oncology. 2020;38(15_suppl):8001-.

61. Dai H, Wu Z, Jia H, Tong C, Guo Y, Ti D, et al. Bispecific CAR-T cells targeting both CD19 and CD22 for therapy of adults with relapsed or refractory B cell acute lymphoblastic leukemia. J Hematol Oncol. 2020;13(1):30.

62. Frey NV, Shaw PA, Hexner EO, Pequignot E, Gill S, Luger SM, et al. Optimizing Chimeric Antigen Receptor T-Cell Therapy for Adults With Acute Lymphoblastic Leukemia. J Clin Oncol. 2020;38(5):415-22.

63. Zhou X, Tu S, Wang C, Huang R, Deng L, Song C, et al. Phase I Trial of Fourth-Generation Anti-CD19 Chimeric Antigen Receptor T Cells Against Relapsed or Refractory B Cell Non-Hodgkin Lymphomas. Front Immunol. 2020;11:564099.

64. Gauthier J, Bezerra ED, Hirayama AV, Fiorenza S, Sheih A, Chou CK, et al. Factors associated with outcomes after a second CD19-targeted CAR T-cell infusion for refractory B cell malignancies. Blood. 2020.

65. Ying Z, Yang H, Guo Y, Li W, Zou D, Zhou D, et al. Relmacabtagene autoleucel (relma-cel) CD19 CAR-T therapy for adults with heavily pretreated relapsed/refractory large B-cell lymphoma in China. Cancer Med. 2020.

66. Pan J, Zuo S, Deng B, Xu X, Li C, Zheng Q, et al. Sequential CD19-22 CAR T therapy induces sustained remission in children with r/r B-ALL. Blood. 2020;135(5):387-91.

67. An F, Wang H, Liu Z, Wu F, Zhang J, Tao Q, et al. Influence of patient characteristics on chimeric antigen receptor T cell therapy in B-cell acute lymphoblastic leukemia. Nat Commun. 2020;11(1):5928.

68. Itzhaki O, Jacoby E, Nissani A, Levi M, Nagler A, Kubi A, et al. Head-to-head comparison of in-house produced CD19 CAR-T cell in ALL and NHL patients. J Immunother Cancer. 2020;8(1).

69. Sesques P, Ferrant E, Safar V, Wallet F, Tordo J, Dhomps A, et al. Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. Am J Hematol. 2020;95(11):1324-33.

70. Tong C, Zhang Y, Liu Y, Ji X, Zhang W, Guo Y, et al. Optimized tandem CD19/CD20 CAR-engineered T cells in refractory/relapsed B-cell lymphoma. Blood. 2020;136(14):1632-44.

71. Wang N, Hu X, Cao W, Li C, Xiao Y, Cao Y, et al. Efficacy and safety of CAR19/22 T-cell cocktail therapy in patients with refractory/relapsed B-cell malignancies. Blood. 2020;135(1):17-27.

72. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Gholbadi A, Lin Y, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. Journal of Clinical Oncology. 2020;38(27):3119-28.

73. Sang W, Shi M, Yang J, Cao J, Xu L, Yan D, et al. Phase II trial of co-administration of CD19- and CD20-targeted chimeric antigen receptor T cells for relapsed and refractory diffuse large B cell lymphoma. Cancer Med. 2020;9(16):5827-38.

74. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-52.

75. Jacobson C, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Primary Analysis of Zuma-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL). Blood.
2020: https://ashpublications.org/blood/article/136/Supplement%201/40/470462/Primary-
Analysis-of-Zuma-5-A-Phase-2-Study-of , accessed 15/1/2021.
76. Chen X, Li X, Liu Y, Zhang Z, Zhang X, Huang J, et al. A Phase I clinical trial of chimeric antigen receptor-modified T cells in patients with relapsed and refractory lymphoma. Immunotherapy. 2020;12(10):681-96.
77. Jacobson CA, Locke FL, Miklos DB, Herrera AF, Westin JR, Lee J, et al. End of Phase 1 Results from Zuma-6: Axicabtagene Ciloleucel (Axi-Cel) in Combination with Atezolizumab for the Treatment of Patients with Refractory Diffuse Large B Cell Lymphoma. Blood. 2018;132(Supplement 1):1492-. 
78. Jacobson CA, Westin JR, Miklos DB, Herrera AF, Lee J, Seng J, et al. Phase 1/2 primary analysis of ZUMA-6: Axicabtagene ciloleucel (Axi-Cel) in combination With atezolizumab (Atezo) for the treatment of patients (Pts) with refractory diffuse large B cell lymphoma (DLBCL). Cancer Res. 2020;80:Abstract nr CT055.
79. https://www.globenewswire.com/news-release/2020/12/05/2140158/0/en/Autolus-Therapeutics-presents-compelling-AUTO1-data-from-ALLCAR-Phase-1-study-in-Adult-Acute-Lymphoblastic-Leukemia-ALL-during-the-62nd-ASH-Annual-Meeting.html , accessed 8.1.21.
80. Neelapu SS, Dickinson M, Ulrickson ML, Oluwole OO, Herrera AF, Thieblemont C, et al. Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) as First-Line Therapy in Patients (Pts) With High-Risk Large B Cell Lymphoma (LBCL). Blood. 2020: https://ash.confex.com/ash/2020/webprogram/Paper134449.html , accessed 16/01/2021.
81. Ali SA, Shi V, Marie I, Wang M, Stroncek DF, Rose JJ, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood. 2016;128(13):1688-700.
82. Wang CM, Wu ZQ, Wang Y, Guo YL, Dai HR, Wang XH, et al. Autologous T Cells Expressing CD30 Chimeric Antigen Receptors for Relapsed or Refractory Hodgkin Lymphoma: An Open-Label Phase I Trial. Clin Cancer Res. 2017;23(5):1156-66.
83. Ramos CA, Ballard B, Zhang H, Dakhova O, Gee AP, Mei Z, et al. Clinical and immunological responses after CD30-specific chimeric antigen receptor-directed lymphocytes. J Clin Invest. 2017;127(9):3462-71.
84. Mailankody S, Htut M, Lee K, Bensinger W, Devries T, Piasceki J, et al. JCARH125, Anti-BCMA CAR T-cell Therapy for Relapsed/Refractory Multiple Myeloma: Initial Proof of Concept Results from a Phase 1/2 Multicenter Study (EOLVE). Blood. 2018;132:957-.
85. Mailankody S, Ghosh A, Staehr M, Purdon TJ, Roshal M, Halton E, et al. Clinical Responses and Pharmacokinetics of MCARH171, a Human-Derived Bcma Targeted CAR T Cell Therapy in Relapsed/Refractory Multiple Myeloma: Final Results of a Phase I Clinical Trial. Blood. 2018;132(Supplement 1):959-.
86. Garfall AL, Stadtmauer EA, Hwang W-T, Lacey SF, Melenhorst JJ, Krevvata M, et al. Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. JCI Insight. 2019;3(8).
87. Sallman DA, Kerre T, Poire X, Havelange V, Lewalle P, Davila ML, et al. Remissions in Relapse/Refractory Acute Myeloid Leukemia Patients Following Treatment with NKG2D CAR-T Therapy without a Prior Preconditioning Chemotherapy. Blood. 2018;132(Supplement 1):902-.
88. Liu Y, Chen Z, Fang H, Wei R, Yu K, Jiang S, et al. Durable Remission Achieved from Bcma-Directed CAR-T Therapy Against Relapsed or Refractory Multiple Myeloma. Blood. 2018;132(Supplement 1):956-.
89. Green DJ, Pont M, Sather BD, Cowan AJ, Turtle CJ, Till BG, et al. Fully Human Bcma Targeted Chimeric Antigen Receptor T Cells Administered in a Defined Composition Demonstrate Potency at Low Doses in Advanced Stage High Risk Multiple Myeloma. Blood. 2018;132(Supplement 1):1011-.

90. Li C, Wang Q, Zhu H, Mao X, Wang Y, Zhang Y, et al. T Cells Expressing Anti B-Cell Maturation Antigen Chimeric Antigen Receptors for Plasma Cell Malignancies. Blood. 2018;132:1013-.

91. Shi X, Yan L, Shang J, Qu S, Kang L, Zhou J, et al. Tandem Autologous Transplantation and Combined Infusion of CD19 and Bcma-Specific Chimeric Antigen Receptor T Cells for High Risk MM: Initial Safety and Efficacy Report from a Clinical Pilot Study. Blood. 2018;132(Supplement 1):1009-.

92. Raje N, Berdeja J, Lin Y, Siegel D, Jagannath S, Madduri D, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2019;380(18):1726-37.

93. Yan Z, Cao J, Cheng H, Qiao J, Zhang H, Wang Y, et al. A combination of humanised anti-CD19 and anti-BCMA CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, phase 2 trial. Lancet Haematol. 2019;6(10):e521-e9.

94. Baumeister SH, Murad J, Werner L, Daley H, Trebeden-Negre H, Gicobi JK, et al. Phase I Trial of Autologous CAR T Cells Targeting NKG2D Ligands in Patients with AML/MDS and Multiple Myeloma. Cancer Immunol Res. 2019;7(1):100-12.

95. https://celyad.com/wp-content/uploads/2020/06/191209-Interim-Results-DEPLETHINK-%C2%B0POSTER.pdf. (accessed Dec 21st 2020)

96. Li C, Mei H, Hu Y, Guo T, Liu L, Jiang H, et al. A Bispecific CAR-T Cell Therapy Targeting Bcma and CD38 for Relapsed/Refractory Multiple Myeloma: Updated Results from a Phase 1 Dose-Climbing Trial. Blood. 2019; https://ashpublications.org/blood/article/134/Supplement_1/930/427103/A-Bispecific-CAR-T-Cell-Therapy-Targeting-Bcma-and , accessed 16/1/2021.

97. Cohen AD, Garfall AL, Stadtmauer EA, Melenhorst JJ, Lacey SF, Lancaster E, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. J Clin Invest. 2019;129(6):2210-21.

98. Li C, Zhou J, Wang J, Hu G, Du A, Zhou X, et al. Clinical responses and pharmacokinetics of fully human BCMA targeting CAR T-cell therapy in relapsed/refractory multiple myeloma. Journal of Clinical Oncology. 2019; https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.8013 , accessed 16/01/2021.

99. Chen L, Xu J, Fu W, Jin S, Yang S, Yan S, et al. Updated Phase 1 Results of a First-in-Human Open-Label Study of Lcar-B38M, a Structurally Differentiated Chimeric Antigen Receptor T (CAR-T) Cell Therapy Targeting B-Cell Maturation Antigen (Bcma). Blood. 2019;134:1858-.

100. Xu J, Chen LJ, Yang SS, Sun Y, Wu W, Liu YF, et al. Exploratory trial of a biepitopic CAR T-targeting B cell maturation antigen in relapsed/refractory multiple myeloma. Proc Natl Acad Sci U S A. 2019;116(19):9543-51.

101. Zhao WH, Liu J, Wang BY, Chen YX, Cao XM, Yang Y, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. J Hematol Oncol. 2018;11(1):141.

102. Yan L, Yan Z, Shang J, Shi X, Jin S, Kang L, et al. Sequential CD19- and Bcma-Specific Chimeric Antigen Receptor T Cell Treatment for RRMM: Report from a Single Center Study. Blood. 2019;134(Supplement_1):578-. 
103. Cowan AJ, Pont M, Sather BD, Turtle CJ, Till BG, Nagengast AM, et al. Efficacy and Safety of Fully Human Bcma CAR T Cells in Combination with a Gamma Secretase Inhibitor to Increase Bcma Surface Expression in Patients with Relapsed or Refractory Multiple Myeloma. Blood. 2019;134(Supplement_1):204-.

104. Jie J, Hao S, Jiang S, Li Z, Yang M, Zhang W, et al. Phase 1 Trial of the Safety and Efficacy of Fully Human Anti-Bcma CAR T Cells in Relapsed/Refractory Multiple Myeloma. Blood. 2019;134(Supplement_1):4435-.

105. Popat R, Zweegman S, Cavet J, Yong K, Lee L, Faulkner J, et al. Phase 1 First-in-Human Study of AUTO2, the First Chimeric Antigen Receptor (CAR) T Cell Targeting APRIL for Patients with Relapsed/Refractory Multiple Myeloma (RRMM). Blood. 2019;134(Supplement_1):3112-.

106. Mikkilineni L, Manasanch EE, Lam N, Vanasse D, Brudno JN, Maric I, et al. T Cells Expressing an Anti-B-Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor with a Fully-Human Heavy-Chain-Only Antigen Recognition Domain Induce Remissions in Patients with Relapsed Multiple Myeloma. Blood. 2019;134(Supplement_1):3230-.

107. Berdeja JG, Alsina M, Shah ND, Siegel DS, Jagannath S, Madduri D, et al. Updated Results from an Ongoing Phase 1 Clinical Study of bb21217 Anti-Bcma CAR T Cell Therapy. Blood. 2019;134(Supplement_1):927-.

108. Costello CL, Cohen AD, Patel KK, Ali SS, Berdeja JG, Sha h N, et al. Phase 1/2 Study of the Safety and Response of P-BCMA-101 CAR-T Cells in Patients with Relapsed/Refractory (r/r) Multiple Myeloma (MM) (PRIME) with Novel Therapeutic Strategies. Blood. 2020:https://ash.confex.com/ash/2020/webprogram/Paper142695.html, accessed 9/1/21.

109. Deeren D, Maertens JA, Lin T, Beguin Y, Demoulin B, Fontaine M, et al. First Results from the Dose Escalation Segment of the Phase I Clinical Study Evaluating Cyad-02, an Optimized Non Gene-Edited Engineered NKG2D CAR T-Cell Product, in Relapsed or Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients. Blood. 2020;136(Supplement 1):36-.

110. https://www.globenewswire.com/news-release/2020/12/07/2140208/0/en/Celyad-Oncology-Provides-Updates-on-Allogeneic-and-Autologous-CAR-T-Programs-at-62nd-ASH-Annual-Meeting-and-Exposition.html, analysed 11/1/2021.

111. Chen W, Fu C, Cai Z, Li Z, Wang H, Yan L, et al. Results from Lummicar-1: A Phase 1 Study of Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT053) in Chinese Subjects with Relapsed and/or Refractory Multiple Myeloma. Blood. 2020:https://ash.confex.com/ash/2020/webprogram/Paper140727.html, accessed 9/1/2021.

112. Kumar SK, Baz RC, Orlowski RZ, Anderson LD, Ma H, Shrewsbury A, et al. Results from Lummicar-2: A Phase 1b/2 Study of Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT053) in Patients with Relapsed and/or Refractory Multiple Myeloma. Blood. 2020:https://ash.confex.com/ash/2020/webprogram/Paper139802.html, accessed 9/1/2021.

113. Munshi NC, Anderson LD, Shah N, Jagannath S, Berdeja JG, Lonial S, et al. Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T-cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): Initial KarMMa results. Journal of Clinical Oncology. 2020:https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8503, accessed 16/01/2021.

114. Berdeja JG, Madduri D, Usmani SZ, Singh I, Zudaire E, Yeh T-M, et al. Update of CARTITUDE-1: A phase Ib/II study of NJJ-4528, a B-cell maturation antigen (BCMA)-directed CAR-T-cell therapy, in relapsed/refractory multiple myeloma. Journal of Clinical Oncology. 2020;38(15_suppl):8505-.

115. Madduri D, Berdeja JG, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation
Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma. Blood. 2020: https://ash.confex.com/ash/2020/webprogram/Paper136307.html, accessed 11/1/2021.

116. Warren RS FG, Bergsland EK, Pennathur-Das R, Nemunaitis J, Venook AP, Hege KM. Clinical studies of regional and systemic gene therapy with autologous CC49-z modified T cells in colorectal cancer metastatic to the liver. Cancer Gene Therapy. 1998;5:S1-S2.

117. Ma Q, Gonzalo-Daganzo RM, Junghans RP. Genetically engineered T cells as adoptive immunotherapy of cancer. Cancer Chemother Biol Response Modif. 2002;20:315-41.

118. Hege KM, Bergsland EK, Fisher GA, Nemunaitis JJ, Warren RS, McArthur JG, et al. Safety, tumor trafficking and immunogenicity of chimeric antigen receptor (CAR) T cells specific for TAG-72 in colorectal cancer. J Immunother Cancer. 2017;5:22.

119. Kershaw MH, Westwood JA, Parker LL, Wang G, Eshhar Z, Mavroukakis SA, et al. A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer. Clin Cancer Res. 2006;12(20 Pt 1):6106-15.

120. Park JR, Digiusto DL, Slovak M, Wright C, Naranjo A, Wagner J, et al. Adoptive transfer of chimeric antigen receptor re-directed cytolytic T lymphocyte clones in patients with neuroblastoma. Mol Ther. 2007;15(4):825-33.

121. Lamers CH, Sleijfer S, Vulto AG, Kruit WH, Kliffen M, Debets R, et al. Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase IX: first clinical experience. J Clin Oncol. 2006;24(13):e20-2.

122. Lamers CH, Willemsen R, van Elzakker P, van Steenbergen-Langeveld S, Broertjes M, Oosterwijk-Wakka J, et al. Immune responses to transgene and retroviral vector in patients treated with ex vivo-engineered T cells. Blood. 2011;117(1):72-82.

123. Lamers CH, Sleijfer S, van Steenbergen S, van Elzakker P, van Krimpen B, Groot C, et al. Treatment of metastatic renal cell carcinoma with CAIX CAR-engineered T cells: clinical evaluation and management of on-target toxicity. Mol Ther. 2013;21(4):904-12.

124. Pule MA, Savoldo B, Myers GD, Rossig C, Russell HV, Dotti G, et al. Virus-specific T cells engineered to coexpress tumor-specific receptors: persistence and antitumor activity in individuals with neuroblastoma. Nat Med. 2008;14(11):1264-70.

125. Louis CU, Savoldo B, Dotti G, Pule M, Yvon E, Myers GD, et al. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma. Blood. 2011;118(23):6050-6.

126. Slovin SF, Wang X, Hullings M, Arauz G, Bartido S, Lewis JS, et al. Chimeric antigen receptor (CAR+) modified T cells targeting prostate-specific membrane antigen (PSMA) in patients (pts) with castrate metastatic prostate cancer (CMPC). Journal of Clinical Oncology. 2013: https://ascopubs.org/doi/10.1200/jco.2013.31.6_suppl.72, accessed 16/01/21.

127. Ahmed N, Brawley VS, Hegde M, Robertson C, Ghazi A, Gerken C, et al. Human Epidermal Growth Factor Receptor 2 (HER2) -Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma. J Clin Oncol. 2015;33(15):1688-96.

128. Katz SC, Burga RA, McCormack E, Wang LJ, Mooring W, Point GR, et al. Phase I Hepatic Immunotherapy for Metastases Study of Intra-Arterial Chimeric Antigen Receptor-Modified T-cell Therapy for CEA+ Liver Metastases. Clin Cancer Res. 2015;21(14):3149-59.

129. Feng K, Guo Y, Dai H, Wang Y, Li X, Jia H, et al. Chimeric antigen receptor-modified T cells for the immunotherapy of patients with EGFR-expressing advanced relapsed/refractory non-small cell lung cancer. Sci China Life Sci. 2016;59(5):468-79.
130. Guo Y, Feng K, Liu Y, Wu Z, Dai H, Yang Q, et al. Phase I Study of Chimeric Antigen Receptor-Modified T Cells in Patients with EGFR-Positive Advanced Biliary Tract Cancers. Clin Cancer Res. 2018;24(6):1277-86.

131. Thistlethwaite FC, Gilham DE, Guest RD, Rothwell DG, Pillai M, Burt DJ, et al. The clinical efficacy of first-generation carcinoembryonic antigen (CEACAM5)-specific CAR T cells is limited by poor persistence and transient pre-conditioning-dependent respiratory toxicity. Cancer Immunol Immunother. 2017;66(11):1425-36.

132. Zhang C, Wang Z, Yang Z, Wang M, Li S, Li Y, et al. Phase I Escalating-Dose Trial of CAR-T Therapy Targeting CEA(+) Metastatic Colorectal Cancers. Mol Ther. 2017;25(5):1248-58.

133. Tchou J, Zhao Y, Levine BL, Zhang PJ, Davis MM, Melenhorst JJ, et al. Safety and Efficacy of Intratumoral Injections of Chimeric Antigen Receptor (CAR) T Cells in Metastatic Breast Cancer. Cancer Immunol Res. 2017;5(12):1152-61.

134. Hecezey A, Louis CU, Savolbo B, Dakhova O, Durett A, Grilley B, et al. CAR T Cells Administered in Combination with Lymphodepletion and PD-1 Inhibition to Patients with Neuroblastoma. Mol Ther. 2017;25(9):2214-24.

135. O’Rourke DM, Nasrallah MP, Desai A, Melenhorst JJ, Mansfield K, Morrissette JJD, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. Sci Transl Med. 2017;9(399).

136. Ahmed N, Brawley V, Hegde M, Bielamowicz K, Krala M, Landi D, et al. HER2-Specific Chimeric Antigen Receptor-Modified Virus-Specific T Cells for Progressive Glioblastoma: A Phase 1 Dose-Escalation Trial. JAMA Oncol. 2017;3(8):1094-101.

137. Feng K, Liu Y, Guo Y, Qiu J, Wu Z, Dai H, et al. Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. Protein Cell. 2018;9(10):838-47.

138. Beatty GL, O’Hara MH, Lacey SF, Torigian DA, Nazimuddin F, Chen F, et al. Activity of Mesothelin-Specific Chimeric Antigen Receptor T Cells Against Pancreatic Carcinoma Metastases in a Phase I Trial. Gastroenterology. 2018;155(1):29-32.

139. Papa S, Adami A, Metoudi M, Achkova D, van Schalkwyk M, Parente-Pereira A, et al. A phase I trial of T4 CAR T-cell immunotherapy in head and neck squamous cancer (HNSCC). J Clin Oncol. 2018;https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.3046.

140. Haas AR, Tanyi JL, O’Hara MH, Gladney WL, Lacey SF, Torigian DA, et al. Phase I Study of Lentiviral-Transduced Chimeric Antigen Receptor-Modified T Cells Recognizing Mesothelin in Advanced Solid Cancers. Mol Ther. 2019;27(11):1919-29.

141. Becerra CR, Hoof P, Paulson AS, Manji GA, Gardner O, Malankar A, et al. Ligand-inducible, prostate stem cell antigen (PSCA)-directed GoCAR-T cells in advanced solid tumors: Preliminary results from a dose escalation. Journal of Clinical Oncology. 2019;37(4_suppl):283-.

142. Navai S, Derenzo C, Joseph S, Sanber K, Byrd T, Zhang H, et al. Administration of HER2-CAR T cells after lymphodepletion safely improves T cell expansion and induces clinical responses in patients with advanced sarcomas. 2019;https://www.abstractsonline.com/pp8/#/1/6812/presentation/9413 accessed 13/1/2021.

143. Hegde M, Joseph SK, Pashankar F, DeRenzo C, Sanber K, Navai S, et al. Tumor response and endogenous immune reactivity after administration of HER2 CAR T cells in a child with metastatic rhabdomyosarcoma. Nat Commun. 2020;11(1):3549.
144. Narayan V, Gladney W, Plesa G, Vapiwala N, Carpenter E, Maude SL, et al. A phase I clinical trial of PSMA-directed/TGFβ-insensitive CAR-T cells in metastatic castration-resistant prostate cancer. Journal of Clinical Oncology. 2019;37(7_suppl):TPS347-TPS.

145. https://www.morressier.com/article/phase-1-clinical-trial-psmadirectedtgfinsensitive-cart-cells-metastatic-castrationresistant-prostate-cancer/5f69edd69b74b699bf38c603? a.

146. Zhan X, Wang B, Li Z, Li J, Wang H, Chen L, et al. Phase I trial of Claudin 18.2-specific chimeric antigen receptor T cells for advanced gastric and pancreatic adenocarcinoma. J Clin Oncol. 2019;24:1158-66.

147. Katz SC, Hardaway J, Prince E, Guha P, Cunetta M, Moody A, et al. HITM-SIR: phase Ib trial of intraarterial chimeric antigen receptor T-cell therapy and selective internal radiation therapy for CEA(+) liver metastases. Cancer Gene Ther. 2020;27(5):3979-89.

148. Shaat K, Flutter B, Wallace R, Jain N, Loka T, Depani S, et al. Antitumor activity without on-target off-tumor toxicity of GD2-chimeric antigen receptor T cells in patients with neuroblastoma. Sci Transl Med. 2020;12(571).

149. Guo JX, Wu CX, Wang PF, Li ZJ, Han S, Jin W, et al. Bioactivity and safety of chimeric switch receptor T cells in glioblastoma patients. Front Biosci (Landmark Ed). 2019;24:31854-0.

150. Rossig C, Pule M, Altvater B, Saiagh S, Wright G, Ghorashian S, et al. Vaccination to improve the persistence of CD19CAR gene-modified T cells in relapsed pediatric acute lymphoblastic leukemia. Leukemia. 2017;31(5):1087-95.
159. https://www.businesswire.com/news/home/20210117005022/en/Celyad-Oncology-Presents-Data-Update-from-Phase-1-alloSHRINK-Trial-for-CYAD-101-in-mCRC-at-ASCO-GI-Symposium

160. https://www.globenewswire.com/news-release/2020/05/29/2040891/0/en/Allogene-Therapeutics-with-Collaborator-Servier-Reports-Positive-Results-from-its-Phase-1-ALPHA-Study-of-ALLO-501-in-Relapsed-Refractory-Non-Hodgkin-Lymphoma-at-the-American-Society

161. Neelapu SS, Munoz J, Locke FL, Miklos DB, Brown R, McDevitt JT, et al. First-in-human data of ALLO-501 and ALLO-647 in relapsed/refractory large B-cell or follicular lymphoma (R/R LBCL/FL): ALPHA study. J Clin Oncol. 2020; https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8002, accessed 11/1/2021.

162. https://ir.allogene.com/news-releases/news-release-details/allogene-therapeutics-reports-positive-initial-results-phase-1. (accessed Dec 21st 2020)

163. Mailankody S, Matous JV, Liedtke M, Sidana S, Malik S, Nath R, et al. Universal: An Allogeneic First-in-Human Study of the Anti-Bcma ALLO-715 and the Anti-CD52 ALLO-647 in Relapsed/Refractory Multiple Myeloma. Blood. 2020; https://ash.confex.com/ash/2020/webprogram/Paper140641.html, accessed 11/1/2021.

164. https://ir.allogene.com/news-releases/news-release-details/allogene-therapeutics-reports-positive-top-line-results-from-its-phase-1-CARBON-Trial-of-CTX110-in-Relapsed-or-Refractory-CD19-B-cell-Malignancies.html. (accessed Dec 21st 2020)

165. Liu E, Marin D, Banerjee P, Macapinlac HA, Thompson P, Basar R, et al. Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. N Engl J Med. 2020;382(6):545-53.

166. Benjamin R, Graham C, Yallop D, Jozwik A, Mirci-Danicar OC, Lucchini G, et al. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies. Lancet. 2020;396(10266):1885-94.