

CAR22-24	GFTFSSYAMS	166	YISSSSSTIYYADSVKG	434	DGPIRYFDHSKAFDI	473
CAR22-25	GYTFTSYMH	167	IINPSGGSTSYAQKFQG	435	EMDDSSGPDY	474
CAR22-26	GYSFTGSWIG	168	IIPGSDSTRYSPSFQG	436	GFLRGGDCCGALDI	475
CAR22-27	GGINSYYWS	169	FTSHSGNVKYNPSLTG	437	GLDPLFAYDAFEI	476
CAR22-28	GFTFSDYYMS	170	YISSSGSTIYYADSVKG	438	DDFWSGSVDY	477
CAR22-29	GYTFTSYMH	171	IINPSGGSTSYAQKFQG	439	EDDSSGYTSPFDY	478
CAR22-30	GYTFTGYMH	172	WINPNSGGTNYAQKFQG	440	EPASSSWYGYYYMDV	479
CAR22-31	GYTFTSYDIN	173	WMNPNSGNTGYAQKFQG	441	GDSNYWSYYGMDV	480
CAR22-32	GYTFTSYGIS	174	WISAYNGNTNYAQKLQG	442	FSSSDSYDY	481
CAR22-33	GFSLNTFGMSVS	175	LIDWDDDKYYSTSLRT	443	IYGGDRNTQAPYFFDL	482
CAR22-34	GASITSRHWWN	176	QIYHSGTTYNPSLGS	444	DYLELATYYGMDV	483
CAR22-35	GYTFTSYMH	177	IINPSGGSTSYAQKFQG	445	DLAAAGNYYYYGMDV	484
CAR22-36	GYTFTSYMH	178	IINPSGGSTSYAQKFQG	446	DDDFWSGSGAFDI	485
CAR22-37	GYTFTSYMH	179	IINPSGGSTSYAQKFQG	447	PEGVSYDDSSVLDY	486
CAR22-38	GYTFTSYMH	180	IINPSGGSTSYAQKFQG	448	GGYGDYLDAFDI	487

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Table 7B. Heavy Chain Variable Domain CDRs of CD22 CARs

Candidate	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CAR22-53 Kabat	SNSAAWN	488	RTYYRSKWYSDYAVSVKS	499	DPYDFWSGYPDAFDI	510
CAR22-53 Chothia	GDSVSSNSA	489	YYRSKWY	500	DPYDFWSGYPDAFDI	511
CAR22-53 Combined Kabat/Chothia	GDSVSSNSAAWN	1111	RTYYRSKWYSDYAVSVKS	1113	DPYDFWSGYPDAFDI	1115
CAR22-53	GDSVSSNSAA	1112	TYRSKWYS	1114	ARDPYDFWSGYPDAFDI	1116

IMGT						
CAR22-57 Combined	GDSVSNNNAAWN	490	RTYHRSTWYNDYVGSVKS	501	ETDYG DYGAFDI	512
CAR22-57 Kabat	NNNAAWN	1337	RTYHRSTWYNDYVGSVKS	1346	ETDYG DYGAFDI	1355
CAR22-58 Combined	GDSVSSNSAAWN	491	RTFYRSKWYNDYAVSVKG	502	GDYYYGLDV	513
CAR22-58 Kabat	SNSAAWN	1338	RTFYRSKWYNDYAVSVKG	1347	GDYYYGLDV	1356
CAR22-59 Combined	GDSVLSNSDTWN	492	RTYHRSTWYDDYASSVRG	503	DRLQDGNSWSDAFDV	514
CAR22-59 Kabat	SNSDTWN	1339	RTYHRSTWYDDYASSVRG	1348	DRLQDGNSWSDAFDV	1357
CAR22-60 Combined	GDSVLSNSDTWN	493	RTYHRSTWYDDYASSVRG	504	DRLQDGNSWSDAFDV	515
CAR22-60 Kabat	SNSDTWN	1340	RTYHRSTWYDDYASSVRG	1349	DRLQDGNSWSDAFDV	1358
CAR22-61 Combined	GDSVLSNSDTWN	494	RTYHRSTWYDDYASSVRG	505	DRLQDGNSWSDAFDV	516
CAR22-61 Kabat	SNSDTWN	1341	RTYHRSTWYDDYASSVRG	1350	DRLQDGNSWSDAFDV	1359
CAR22-62 Combined	GDSVLSNSDTWN	495	RTYHRSTWYDDYASSVRG	506	DRLQDGNSWSDAFDV	517
CAR22-62 Kabat	SNSDTWN	1342	RTYHRSTWYDDYASSVRG	1351	DRLQDGNSWSDAFDV	1360
CAR22-63 Combined	GDSVLSNSDTWN	496	RTYHRSTWYDDYASSVRG	507	DRLQDGNSWSDAFDV	518
CAR22-63 Kabat	SNSDTWN	1343	RTYHRSTWYDDYASSVRG	1352	DRLQDGNSWSDAFDV	1361
CAR22-64 Combined	GDSVLSNSDTWN	497	RTYHRSTWYDDYASSVRG	508	VRLQDGNSWSDAFDV	519
CAR22-64 Kabat	SNSDTWN	1344	RTYHRSTWYDDYASSVRG	1353	VRLQDGNSWSDAFDV	1362

CAR22-65 Combined	GDSMLSNSDTWN	498	RTYHRSTWYDDYASSVRG	509	VRLQDGNWSDAFDV	520
CAR22-65 Kabat	SNSDTWN	1343	RTYHRSTWYDDYASSVRG	1354	VRLQDGNWSDAFDV	1363

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Table 7C. Heavy Chain Variable Domain CDRs of CD22 CARs. CDRs are identified according to Kabat.

Candidate	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
m971	SNSAAWN		RTYYRSKWYNDYAVSVKS		EVTGDLEDAFDI	
CAR22-1	SNYMS		VIYSGGSTYYADSVKG		QSTPYDSSGYSGDAFDI	
CAR22-2	SNSAAWN		RTYYRSKWYNDYAVSVKS		DLGWIIVAGTFDY	
CAR22-3	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNWSDAFDV	
CAR22-4	DYAMH		GISWNSGSGYADSVKG		GLSSWHFHDALDI	
CAR22-5	DYAMH		GISWNSGSGYADSVKG		DKGGGYDFWGSDDY	
CAR22-6	SNSATWT		RTYYRSTWYNDYAVSVKS		EGSGSYAY	
CAR22-7	GYYMH		WINPNSGGTNYAQKFQG		DYWGYYGSGTLDY	
CAR22-8	SYGIS		WISAYNGNTNYAQKLQG		AGLALYSNYVPYGYGMDV	
CAR22-9	NAWMN		RIKSKTDGGTADYAAPVKG		GATDV	
CAR22-10	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNWSDAFDV	
CAR22-11	SNSAAWN		RTYYRSKWYNDYAVSVKS		EESSSGWYEGNWFDP	
CAR22-12	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNWSDAFDV	
CAR22-13	SSSYWYG		SIYYSGSTYYNPSLKS		GRMDTAMAQI	
CAR22-14	SYMH		IINPSGGSTSYAQKFQG		DLDVSLDI	
CAR22-15	SYAMH		AISSNGGSTYYANSVKD		VHSSGYYHPGPNFY	
CAR22-16	SYMH		IINPSGGSTSYAQKFQG		EAGVVAVDY	
CAR22-17	SYAMS		AISGSGGSTYYADSVKG		EPLFGVVEEDVDY	

CLAIMS

1. Use of a cell that expresses a chimeric antigen receptor (CAR) molecule that binds CD19, e.g., a CD19 CAR, in the manufacture of a medicament for the treatment of a subject having a disease associated with expression of CD19, and wherein said subject has received, ~~is receiving~~ or is about to receive an effective number of one or more cells that express a CAR molecule that binds CD22, wherein the CD22 CAR molecule comprises a CD22 binding domain comprising:

(i) a light chain complementarity determining region 1 (LC CDR1) of SEQ ID NO: 647, a light chain complementarity determining region 2 (LC CDR2) of SEQ ID NO: 658, and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 669, and

(ii) a heavy chain complementarity determining region 1 (HC CDR1) of SEQ ID NO: 497 or SEQ ID NO: 1344, a heavy chain complementarity determining region 2 (HC CDR2) of SEQ ID NO: 508 or SEQ ID NO: 1353, and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 519 or SEQ ID NO: 1362; or

(iii) a LC CDR1 of SEQ ID NO: 648, a LC CDR2 of SEQ ID NO: 659, and a LC CDR3 of SEQ ID NO: 670, and

(iv) a HC CDR1 of SEQ ID NO: 498 or SEQ ID NO: 1345, a HC CDR2 of SEQ ID NO: 509 or SEQ ID NO: 1354, and a HC CDR3 of SEQ ID NO: 520 or SEQ ID NO: 1363.

2. Use of a cell that expresses a chimeric antigen receptor (CAR) molecule that binds CD19, e.g., a CD19 CAR, in combination with a CAR molecule that binds CD22, in the manufacture of a medicament for the treatment of a disease associated with expression of CD19, wherein the CAR molecule that binds CD22 comprises an effective number of one or more cells that express a CAR molecule that binds CD22, wherein the CD22 CAR molecule comprises a CD22 binding domain comprising:

(i) a light chain complementarity determining region 1 (LC CDR1) of SEQ ID NO: 647, a light chain complementarity determining region 2 (LC CDR2) of SEQ ID NO: 658, and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 669, and

(ii) a heavy chain complementarity determining region 1 (HC CDR1) of SEQ ID NO: 497 or SEQ ID NO: 1344, a heavy chain complementarity determining region 2 (HC CDR2) of SEQ ID NO: 508 or SEQ ID NO: 1353, and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 519 or SEQ ID NO: 1362; or

(iii) a LC CDR1 of SEQ ID NO: 648, a LC CDR2 of SEQ ID NO: 659, and a LC CDR3 of SEQ ID NO: 670, and

(iv) a HC CDR1 of SEQ ID NO: 498 or SEQ ID NO: 1345, a HC CDR2 of SEQ ID NO: 509 or SEQ ID NO: 1354, and a HC CDR3 of SEQ ID NO: 520 or SEQ ID NO: 1363.

3. The use of claim 2, wherein the CD19 CAR molecule and the CD22 CAR molecule are expressed in the same cell; or the CD19 CAR molecule and the CD22 CAR molecule are expressed in different cells.

4. The use of claims 1-3, wherein the one or more cells that express a CAR molecule that binds CD19 are to be administered concurrently with the CAR molecule that binds CD22.

5. The use of any of the preceding claims, wherein the subject has relapsed or is identified as having relapsed after treatment with the one or more cells that express a CAR molecule that binds CD19, e.g., a CD19 CAR.

6. The use of claim 5, wherein the subject has relapsed or is identified as having relapsed based on one or more of:

(i) reappearance of blasts in the blood, bone marrow (e.g., reappearance of at least or more than 5% blasts in the bone marrow), or any extramedullary site, after a complete response;

(ii) detection of CD19- blasts above a predetermined threshold, e.g., over 1%, 2%, 3%, 4%, 5%, or 10%;

(iii) an increase in RNA levels of one or more of MIR199A1, MIR1203, ITM2C, or HLA-DQB1; or

(iv) a decrease in RNA levels of one or more of PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1, and EIF1AY.

7. The use of any of the preceding claims, further comprising lymphodepletion to be performed on that subject, e.g., prior to the administration of the one or more cells that express a CAR molecule that binds CD19, wherein optionally the lymphodepletion comprises one or more of melphalan, cyclophosphamide, and fludarabine to be administered.
8. The use of any of the preceding claims, wherein the CD19 CAR molecule comprises an antibody or antibody fragment which includes a CD19 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said CD19 binding domain comprises a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3) of any CD19 scFv or light chain binding domain amino acid sequence listed in **Tables 2 or 3**, and a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3) of any CD19 scFv or heavy chain binding domain amino acid sequence listed in **Tables 2 or 3**.
9. The use of any of the preceding claims, wherein the CD19 CAR molecule comprises any light chain variable region of a scFv listed in **Tables 2 or 3** and any heavy chain variable region of a scFv listed **Tables 2 or 3**.
10. The use of any of the preceding claims, wherein the CD19 CAR molecule comprises a CD19 binding domain comprising a LC CDR1 of SEQ ID NO: 25, a LC CDR2 of SEQ ID NO: 26 and a LC CDR3 of SEQ ID NO: 27; and a HC CDR1 of SEQ ID NO: 19; a HC CDR2 of SEQ ID NO: 20 and a HC CDR3 of SEQ ID NO: 24.
11. The use of any of claims 1-9, wherein the CD19 CAR molecule comprises a CD19 binding domain comprising a LC CDR1 of SEQ ID NO: 25, a LC CDR2 of SEQ ID NO: 26 and a LC CDR3 of SEQ ID NO: 27; and a HC CDR1 of SEQ ID NO: 19; a HC CDR2 of any of SEQ ID NOs: 21-23 and a HC CDR3 of SEQ ID NO: 24.
12. The use of any of claim 10 or 11, wherein:
the CD19 CAR molecule comprises a CD19 binding domain which comprises a

sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO: 4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12 or SEQ ID NO: 59, or an amino acid sequence with at least 95% identity thereto, or

the CD19 CAR comprises a polypeptide selected from the group consisting of SEQ ID NOS: 31-42 or 58, or a sequence with at least 95% identity thereto.

13. The use of any of the preceding claims, wherein the CD22 CAR molecule comprises a CD22 binding domain comprising:

- (i) a light chain variable region of SEQ ID NO: 690; or
- (ii) a light chain variable region with 95-99% identity to the light chain variable region of SEQ ID NO: 690.

14. The use of any of the preceding claims, wherein the CD22 CAR molecule comprises a CD22 binding domain comprising:

- (i) a heavy chain variable region of SEQ ID NO: 680, or
- (ii) a heavy chain variable region with 95-99% identity to the heavy chain variable region of SEQ ID NO: 680.

15. The use of any of the preceding claims, wherein the CD22 binding domain comprises a (Gly4-Ser)_n linker, wherein n=1, 2, 3 or 4 (SEQ ID NO: 53).

16. The use of any of the preceding claims, wherein the CD22 CAR molecule comprises a CD22 binding domain comprising:

- (i) a light chain variable region of SEQ ID NO: 690; and
- (ii) a heavy chain variable region of SEQ ID NO: 680.

17. The use of any of the preceding claims, wherein the CD22 CAR molecule comprises the amino acid sequence of SEQ ID NO: 140, or an amino acid sequence with 95-99% identity thereto.

18. The use of any of claims 1-12, wherein the CD22 CAR molecule comprises a CD22 binding domain comprising: a light chain variable region of SEQ ID NO: 689 or an amino acid sequence with 95-99% identity thereto.

19. The use of any of claims 1-12 or 18, wherein the CD22 CAR molecule comprises a CD22 binding domain comprising: a heavy chain variable region of SEQ ID NO: 679, or an amino acid sequence with 95-99% identity thereto.

20. The use of any of the preceding claims, wherein the CD19 CAR molecule or CD22 CAR molecule comprise a transmembrane domain that comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154.

21. The use of claim 20, wherein the CD19 CAR molecule or CD22 CAR molecule comprise an antigen binding domain which is connected to the transmembrane domain by a hinge region, wherein optionally, the hinge region comprises the amino acid sequence of SEQ ID NO:14, or an amino acid sequence with 95-99% identity thereto.

22. The use of any of the preceding claims, wherein the CD19 CAR molecule or CD22 CAR molecule comprise a costimulatory domain comprising a functional signaling domain obtained from a protein selected from the group consisting of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137), wherein optionally, the costimulatory domain comprises the amino acid sequence of SEQ ID NO:16 or SEQ ID NO:51, or an amino acid sequence with 95-99% identity thereto.

23. The use of any of the preceding claims, wherein the CD19 CAR molecule or CD22 CAR molecule comprise an intracellular signaling domain that comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta; or

wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or an amino acid sequence with 95-99% identity thereto.

24. The use of any of the preceding claims, wherein the CD19 CAR molecule or CD22 CAR molecule further comprises a leader sequence, wherein, optionally, the leader sequence comprises the amino acid sequence of SEQ ID NO: 13, or an amino acid sequence with 95-

99% identity thereto.

25. The use of any of the preceding claims, wherein the cells comprise T cells or NK cells.

26. The use of any of the preceding claims, wherein:

(a) the disease associated with CD19 expression is selected from:

(i) a proliferative disease such as a cancer, tumor, or malignancy;

(ii) a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia;

(iii) a non-cancer related indication; or

(iv) one or more of a hematologic cancer, acute leukemia, B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), small lymphocytic leukemia (SLL), acute lymphoid leukemia (ALL); chronic leukemia, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma, or myeloma; or

(b) the disease is a CD19-negative cancer, e.g., a CD19-negative relapsed cancer.

27. The use of any of the preceding claims, wherein the subject is to be administered:

an agent that increases the efficacy of a cell expressing a CAR molecule,

an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR molecule,

an agent that treats the disease associated with CD19; or

a checkpoint inhibitor.

28. The use of any of the preceding claims, wherein the subject received, has received, or is about to receive a pre-treatment, concurrent treatment, or post-CAR therapy treatment with an agent, e.g., a checkpoint inhibitor, prior to the initiation of a CAR therapy.

29. The use of any of the preceding claims, wherein the subject comprises a CD19-negative cancer cell, and a cancer cell that is positive for one or more of:

(i) CD22; or

(ii) CD10, CD20, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

30. The use of any of the preceding claims, wherein the subject is to be administered an inhibitor of one or more of the CD10, CD20, CD34, CD123, FLT-3, ROR1, CD79b,

CD179b, or CD79a for which the cancer cell is positive.

31. The use of any of the preceding claims, which further comprises a step of determining whether the subject comprises a CD19-negative cancer cell or whether the subject comprises a cancer cell that is positive for one or more of:

- (i) CD22; or
- (ii) CD10, CD20, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

32. A composition comprising, separately or admixed:

(i) one or more cells that express a CAR molecule that binds CD19, e.g., a CD19 CAR, and
(ii) a B-cell inhibitor comprising one or more cells that express a CAR molecule that binds CD22, e.g., a CD22 CAR, wherein the CD22 CAR comprises a CD22 binding domain comprising:

(i) a light chain complementarity determining region 1 (LC CDR1) of SEQ ID NO: 647, a light chain complementarity determining region 2 (LC CDR2) of SEQ ID NO: 658, and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 669, and

(ii) a heavy chain complementarity determining region 1 (HC CDR1) of SEQ ID NO: 497 or SEQ ID NO: 1344, a heavy chain complementarity determining region 2 (HC CDR2) of SEQ ID NO: 508 or SEQ ID NO: 1353, and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 519 or SEQ ID NO: 1362; or

(iii) a LC CDR1 of SEQ ID NO: 648, a LC CDR2 of SEQ ID NO: 659, and a LC CDR3 of SEQ ID NO: 670, and

(iv) a HC CDR1 of SEQ ID NO: 498 or SEQ ID NO: 1345, a HC CDR2 of SEQ ID NO: 509 or SEQ ID NO: 1354, and a HC CDR3 of SEQ ID NO: 520 or SEQ ID NO: 1363.

33. A composition comprising:

(i) a first nucleic acid encoding a CAR molecule that binds CD19, e.g., a CD19 CAR, and
(ii) a second nucleic acid encoding a CAR molecule that binds CD22, e.g., a CD22 CAR, wherein the first nucleic acid and second nucleic acid are in the same or a separate nucleic acid molecule,

wherein the CD22 CAR comprises a CD22 binding domain comprising:

- (i) a light chain complementarity determining region 1 (LC CDR1) of SEQ ID NO: 647, a light chain complementarity determining region 2 (LC CDR2) of SEQ ID NO: 658, and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 669, and
- (ii) a heavy chain complementarity determining region 1 (HC CDR1) of SEQ ID NO: 497 or SEQ ID NO: 1344, a heavy chain complementarity determining region 2 (HC CDR2) of SEQ ID NO: 508 or SEQ ID NO: 1353, and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 519 or SEQ ID NO: 1362; or
- (iii) a LC CDR1 of SEQ ID NO: 648, a LC CDR2 of SEQ ID NO: 659, and a LC CDR3 of SEQ ID NO: 670, and
- (iv) a HC CDR1 of SEQ ID NO: 498 or SEQ ID NO: 1345, a HC CDR2 of SEQ ID NO: 509 or SEQ ID NO: 1354, and a HC CDR3 of SEQ ID NO: 520 or SEQ ID NO: 1363.

34. A composition comprising one or more immune effector cells and:

- (i) a first nucleic acid encoding, or a first polypeptide comprising a CAR molecule that binds CD19, e.g., a CD19 CAR, and
- (ii) a second nucleic acid encoding, or a second polypeptide comprising, a CAR molecule that binds CD22, e.g., a CD22 CAR, wherein the CD22 CAR comprises a CD22 binding domain comprising:
 - (i) a light chain complementarity determining region 1 (LC CDR1) of SEQ ID NO: 647, a light chain complementarity determining region 2 (LC CDR2) of SEQ ID NO: 658, and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 669, and
 - (ii) a heavy chain complementarity determining region 1 (HC CDR1) of SEQ ID NO: 497 or SEQ ID NO: 1344, a heavy chain complementarity determining region 2 (HC CDR2) of SEQ ID NO: 508 or SEQ ID NO: 1353, and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 519 or SEQ ID NO: 1362; or
 - (iii) a LC CDR1 of SEQ ID NO: 648, a LC CDR2 of SEQ ID NO: 659, and a LC CDR3 of SEQ ID NO: 670, and

(iv) a HC CDR1 of SEQ ID NO:498 or SEQ ID NO: 1345, a HC CDR2 or SEQ ID NO: 509 or SEQ ID NO: 1354, and a HC CDR3 of SEQ ID NO: 520 or SEQ ID NO: 1363.

35. The composition of claim 34, wherein:

the first nucleic acid or first polypeptide and the second nucleic acid or second polypeptide are each contained within, e.g., expressed by, a first immune effector cell;

the composition comprises a first immune effector cell containing e.g., expressing, the first nucleic acid or first polypeptide and a second immune effector cell containing e.g., expressing, the second nucleic acid or second polypeptide; or

the composition does not comprise a cell containing, e.g., expressing, both of the first nucleic acid or first polypeptide and the second nucleic acid or second polypeptide.

36. A cell comprising a nucleic acid composition of claim 33, wherein the cell is a human T cell, e.g., a CD8+ T cell, or an NK cell.

37. A cell of claim 36, further expressing an inhibitory molecule that inhibits T cell function, wherein the molecule comprises:

a first polypeptide that comprises an inhibitory molecule, wherein the inhibitory molecule is chosen from PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR beta, or a fragment thereof; and;

a second polypeptide that comprises an intracellular signaling domain, wherein the intracellular signaling domain comprises a co-stimulatory intracellular signaling domain derived from 4-1BB, CD27 or CD28, or a primary signaling domain derived from CD3 zeta, or both.

38. A vector comprising a nucleic acid composition of claim 33, optionally wherein, the vector is a viral vector, e.g., a lentiviral vector, or an RNA CAR vector.

39. A method of making a cell, comprising introducing a nucleic acid composition of claim 33 into a T cell or NK cell, e.g., transducing a T cell or NK cell with a vector of claim 38, wherein the method optionally comprises:

assaying a gene signature that indicates whether a subject treated with the cell is likely to relapse, or has relapsed;

assaying the gene signature in the cell prior to infusion into the subject; or

decreasing the T_{REG} signature of a population of cells comprising the transduced cell, wherein decreasing the T_{REG} signature optionally comprises performing CD25-depletion on the population of cells.

40. The use, composition, cell, or method of any of the preceding claims, further comprising a cell, e.g., a hematopoietic stem cell, or a bone marrow cell, to be transplanted into the subject.

41. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antibody or antibody fragment which includes a CD22 binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein said CD22 binding domain comprises:

(i) a light chain complementarity determining region 1 (LC CDR1) of SEQ ID NO: 647, a light chain complementarity determining region 2 (LC CDR2) of SEQ ID NO: 658, and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 669, and

(ii) a heavy chain complementarity determining region 1 (HC CDR1) of SEQ ID NO: 497 or SEQ ID NO: 1344, a heavy chain complementarity determining region 2 (HC CDR2) of SEQ ID NO: 508 or SEQ ID NO: 1353, and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 519 or SEQ ID NO: 1362; or

(iii) a LC CDR1 of SEQ ID NO: 648, a LC CDR2 of SEQ ID NO: 659, and a LC CDR3 of SEQ ID NO: 670, and

(iv) a HC CDR1 of SEQ ID NO: 498 or SEQ ID NO: 1345, a HC CDR2 of SEQ ID NO: 509 or SEQ ID NO: 1354, and a HC CDR3 of SEQ ID NO: 520 or SEQ ID NO: 1363.

42. An isolated CAR molecule comprising a CD22 binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the CD22 binding domain comprises

(i) a light chain complementarity determining region 1 (LC CDR1) of SEQ ID

NO: 647, a light chain complementarity determining region 2 (LC CDR2) of SEQ ID NO: 658, and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 669, and

(ii) a heavy chain complementarity determining region 1 (HC CDR1) of SEQ ID NO: 497 or SEQ ID NO: 1344, a heavy chain complementarity determining region 2 (HC CDR2) of SEQ ID NO: 508 or SEQ ID NO: 1353, and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 519 or SEQ ID NO: 1362; or

(iii) a LC CDR1 of SEQ ID NO: 648, a LC CDR2 of SEQ ID NO: 659, and a LC CDR3 of SEQ ID NO: 670, and

(iv) a HC CDR1 of SEQ ID NO: 498 or SEQ ID NO: 1345, a HC CDR2 or SEQ ID NO: 509 or SEQ ID NO: 1354, and a HC CDR3 of SEQ ID NO: 520 or SEQ ID NO: 1363.

43. Use of a cell comprising the CAR molecule of claim 42, in the manufacture of a medicament for the treatment of a mammal having a disease associated with expression of CD22.

44. A pharmaceutical composition, comprising the cell of claim 36; the nucleic acid of claim 41; or the CAR molecule of claim 42.