CLAIMS

1. A cell that expresses a chimeric antigen receptor (CAR) molecule that binds CD19, e.g., a CD19 CAR, for use in 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 one or more B-cell inhibitors, wherein the B-cell inhibitor comprises an inhibitor of one or more of CD22, CD10, CD20, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

2. Use of a cell that expresses a chimeric antigen receptor (CAR) molecule that binds CD19, e.g., a CD19 CAR, in combination with one or more B-cell inhibitors, in the manufacture of a medicament for the treatment of a disease associated with expression of CD19, wherein the B-cell inhibitor comprises an inhibitor of one or more of CD22, CD10, CD20, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

3. A B-cell inhibitor, e.g., an inhibitor of one or more of CD22, CD10, CD20, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a, for use in the treatment of a subject who is, or is identified as being, a non-responder, partial responder, or relapser to a CD19 inhibitor, e.g., a CD19 chimeric antigen receptor (CAR) therapy.

4. Use of a B-cell inhibitor, e.g., an inhibitor of one or more of CD22, CD10, CD20, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a, in the manufacture of a medicament for the treatment of a subject who is, or is identified as being, a non-responder, partial responder, or relapser to a CD19 inhibitor, e.g., a CD19 chimeric antigen receptor (CAR) therapy.

5. The use of any of the preceding claims, wherein the B-cell inhibitor comprises an inhibitor of one or more of CD10, CD20, CD22, CD34, CD123, FLT-3, or ROR1.

6. The use of any of the preceding claims, wherein the B-cell inhibitor comprises an effective number of one or more cells that express a CAR molecule that binds one or more of CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

7. The use of any of the preceding claims, wherein the one or more cells that express a CAR molecule that binds CD19 are administered concurrently with, before, or after the one or more B-cell inhibitors.

8. 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.

9. The use of claim 8, wherein the subject has relapsed or is identified as having relapsed based on one or more of reappearance of blasts in the blood, bone marrow (> 5%), or any extramedullary site, after a complete response; or

wherein the subject has relapsed or is identified as having relapsed based on detection of CD19- blasts above a predetermined threshold, e.g., over 1%, 2%, 3%, 4%, 5%, or 10%; or

wherein the subject has relapsed or is identified as having relapsed based on an increase in RNA levels of one or more of MIR199A1, MIR1203, uc021ovp, ITM2C, or HLA-DQB1; or

wherein the subject has relapsed or is identified as having relapsed based on a decrease in RNA levels of one or more of PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1, and EIF1AY.

10. The use of any of the preceding claims, further comprising performing lymphodepletion on that subject, e.g., prior to administering the one or more cells that express a CAR molecule that binds CD19, wherein optionally the lymphodepletion comprises administering one or more of melphalan, cytoxan, cyclophosphamide, and fludarabine.

11. The use of any of the preceding claims, wherein the B-cell inhibitor comprises an effective number of one or more cells that express: a CAR molecule that binds CD10; a CAR molecule that binds CD20; a CAR molecule that binds CD22; a CAR molecule that binds CD34; a CAR molecule that binds CD123; a CAR molecule that binds FLT-3; or a CAR molecule that binds ROR1.

12. The use of any of the preceding claims, wherein the CD19 CAR 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 one or more of (e.g., all three of) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD19 scFv or light chain binding domain amino acid sequence listed in **Tables 2 or 3**, and one or more of (e.g., all three of) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD19 scFv or heavy chain binding domain amino acid sequence listed in **Tables 2 or 3**.

13. The use of any of the preceding claims, wherein the CD19 CAR 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.

14. The use of any of the preceding claims, wherein the CD19 CAR comprises a CD19 binding domain which comprises a sequence selected from a 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 and SEQ ID NO:12, or an amino acid sequence with at least 95% identity thereof, or a polypeptide of SEQ ID NO:59, or a sequence with at least 95% identity thereof, or

wherein 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 thereof.

15. The use of any of the preceding claims, wherein the B-cell inhibitor comprises a CD20 CAR which comprises an antibody or antibody fragment which includes a CD20 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said CD20 binding domain comprises one or more of light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD20 light chain binding domain amino acid sequence listed in **Table 13**, and one or more of heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD20 heavy chain binding domain amino acid sequence listed in **Table 12A or 12B**.

16. The use of any of the preceding claims, wherein the B-cell inhibitor comprises a CD22 CAR which comprises an antibody or antibody fragment which includes a CD22 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said CD22 binding domain comprises one or more of light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD22 light chain binding domain amino acid sequence listed in **Table 8A or 8B**, and one or more of heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD22 heavy chain binding domain amino acid sequence listed in **Table 7A, 7B, or 7C**.

17. The use of claim 16, wherein the CD22 CAR comprises any light chain variable region listed in **Table 10A or 10B**, any heavy chain variable region listed in **Table 9A or 9B**, or any light chain variable region listed in **Table 10A or 10B** and any heavy chain variable region listed **Table 9A or**

9B.

18. The use of any of the preceding claims, wherein the B-cell inhibitor comprises a CD123 CAR which comprises an antibody or antibody fragment which includes a CD123 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said CD123 binding domain comprises one or more of light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD123 light chain binding domain amino acid sequence listed in **Table 18**, and one or more of heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD123 heavy chain binding domain amino acid sequence listed in **Table 17**.

19. The use of claim 18, wherein the CD123 CAR comprises any light chain variable region listed in **Table 16**, any heavy chain variable region listed in **Table 16**, or any light chain variable region listed in **Table 16** and any heavy chain variable region listed **Table 16**.

20. The use of any of the preceding claims, wherein the B-cell inhibitor comprises a CD123 CAR which comprises an antibody or antibody fragment which includes a CD123 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said CD123 binding domain comprises one or more of light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD123 light chain binding domain amino acid sequence listed in **Table 27**, and one or more of heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD123 heavy chain binding domain amino acid sequence listed in **Table 26**.

21. The use of claim 20, wherein the CD123 CAR comprises any light chain variable region listed in **Table 25**, any heavy chain variable region listed in **Table 25**, or any light chain variable region listed in **Table 25** and any heavy chain variable region listed **Table 25**.

22. The use of any of the preceding claims, wherein the B-cell inhibitor comprises a CAR (a "B-cell inhibitor CAR") which comprises an antibody or antibody fragment which includes an antigen binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and optionally wherein, said antigen binding domain comprises one or more of

(e.g., all of) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3), and one or more of (e.g., all of) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3).

23. The use of any of the preceding claims, wherein the B-cell inhibitor comprises a CAR which comprises a scFv.

24. The use of any of the preceding claims, wherein the B-cell inhibitor CAR or CAR molecule that binds CD19 comprises 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.

25. The use of claim 22, wherein the B-cell inhibitor CAR or CAR molecule that binds CD19 comprises an antigen binding domain 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 thereof.

26. The use of claim 22, wherein the B-cell inhibitor CAR or CAR molecule that binds CD19 comprises a costimulatory domain which is 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 thereof.

27. The use of claim 22, wherein the B-cell inhibitor CAR or CAR molecule that binds CD19 comprises 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 thereof.

28. The use of claim 22, wherein the B-cell inhibitor CAR or CAR molecule that binds CD19 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 thereof.

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

30. The use of any of the preceding claims, wherein the disease associated with CD19 expression is selected from a proliferative disease such as a cancer, tumor, or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or is a non-cancer related indication associated with expression of CD19, or

wherein the disease is 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

wherein the disease is a CD19-negative cancer, e.g., a CD19-negative relapsed cancer.

31. The use of any of the preceding claims, further comprising administering:

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

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

an agent that treats the disease associated with CD19; or

a checkpoint inhibitor.

32. The use of any of the preceding claims, wherein the subject receives 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.

33. The use of any of the preceding claims, wherein the patient comprises a CD19-negative cancer cell, and a cancer cell that is positive for one or more of CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

34. The use of any of the preceding claims, further comprising administering to the patient an inhibitor of one or more of the CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a for which the cancer cell is positive.

35. The use of any of the preceding claims, which further comprises a step of determining whether the patient comprises a CD19-negative cancer cell or whether the patient comprises a cancer cell that is positive for one or more of CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or

CD79a.

36. 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) one or more B-cell inhibitors chosen from inhibitors of one or more of CD10, CD20,CD22, CD34, CD123, FLT-3, or ROR1.

37. 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 a B-cell antigen chosen from one or more of CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a, wherein the first nucleic acid and second nucleic acid are in the same or a separate nucleic acid molecule.

38. 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 a B-cell antigen chosen from one or more of CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

39. The composition of claim 38, 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.

40. A cell comprising a nucleic acid composition of claim 37, wherein the cell is optionally a human T cell, e.g., a CD8+ T cell, or an NK cell.

41. A cell of claim 40, 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.

42. A vector comprising a nucleic acid composition of claim 37, optionally wherein, the vector is a viral vector, e.g., a lentiviral vector, or an RNA CAR vector.

43. A method of making a cell, comprising introducing a nucleic acid composition of claim 37 into a T cell or NK cell, e.g., transducing a T cell or NK cell with a vector of claim 42, 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.

44. The use of, composition, cell, or method of any of the preceding claims, wherein the CD19 inhibitor comprises a CD19 CAR and the B-cell inhibitor comprises a CD123 CAR, wherein optionally the CD19 CAR or CD123 CAR comprises a split intracellular signaling domain such that full activation of the cell, e.g., the population of immune effector cells, occurs when both the CD19 CAR and CD123 CAR bind to a target cell, e.g., a target CD19+CD123+ cell (e.g., a B-ALL blast cell), compared to activation when the CD19 CAR and CD123 CAR bind to a target cell that expresses one of CD19 or CD123 (e.g., a hematopoietic stem cell).

45. The use of, composition, cell, or the method of any of the preceding claims, further comprising transplanting a cell, e.g., a hematopoietic stem cell, or a bone marrow, into the mammal.

46. A composition comprising one or more cells that express a CAR molecule that binds CD19, e.g., a CD19 CAR, in combination with a PD1 inhibitor, for use in the treatment of a subject having DLBCL, e.g. primary DLBCL, ,wherein optionally the subject has, or is identified as having, at least 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of DLBCL cells which are CD3+/PD1+.

47. A composition comprising one or more cells that express a CAR molecule that binds CD19, e.g., a CD19 CAR, for use in the treatment of a subject having DLBCL, e.g. primary DLBCL, wherein optionally the subject has, or is identified as having, at least 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of DLBCL cells which are CD3+/PD1+.

48. A composition comprising one or more cells that express a CAR molecule that binds CD19, e.g., a CD19 CAR, in combination with a PD-L1 inhibitor, for use in the treatment of a subject having DLBCL, wherein optionally the subject has, or is identified as having, less than 20%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% of cells in the cancer, e.g., cancer microenvironment, are double positive for CD19 and PD-L1.

49. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antibody or antibody fragment which includes a CD20 binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein said CD20 binding domain comprises one or more of light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD20 light chain binding domain amino acid sequence listed in **Table 13, 15A, or 15B**, and one or more of heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD20 heavy chain binding domain amino acid sequence listed in **Table 12A, 12B, 14A, or 14B**.

50. An isolated CAR molecule comprising a CD20 binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the CD20 binding domain comprises one or more light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD20 binding domain listed in **Table 13, 15A, or 15B**, and one or more heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD20 binding domain listed in **Table 12A, 12B, 14A, or 14B**.

51. A cell comprising the CAR molecule of claim 50, for use in the treatment of a mammal having a disease associated with expression of CD20, comprising administering to the mammal an effective amount of the cell comprising a CAR molecule of claim 50.

52. 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 one or more of light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD22 light chain binding domain amino acid sequence listed in **Table 8A, 8B, 10A or 10B**, and one or more of heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD22 heavy chain binding domain amino acid sequence listed in **Table 7A, 7B, 7C, 9A, or 9B**.

53. An isolated CAR molecule comprising a CD22 binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the CD22 binding domain comprises one or more light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of any CD22 binding domain listed in **Table 8A, 8B, 10A or 10B**, and one or more heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of any CD22 binding domain listed in **Table 7A, 7B, 7C, 9A, or 9B**.

54. A cell comprising the CAR molecule of claim 53, for use in the treatment of a mammal having a disease associated with expression of CD22 comprising administering to the mammal an effective amount of the cell comprising a CAR molecule of claim 53.

55. A pharmaceutical composition, comprising the cell of claim 38-40, 41, 51 or 54; the nucleic acid of claim 37; or the CAR molecule of claims 50 or 53.