CLAIMS

1. Use of a population of cells that expresses a CAR molecule that binds CD19 ("CAR19-expressing cells") in the manufacture of a medicament for treating a mammal having a disease associated with expression of CD19, wherein the mammal has previously received a kinase inhibitor chosen from a BTK inhibitor, a CDK4 inhibitor, an mTOR inhibitor, or a MNK inhibitor.

2. The use of claim 1, wherein the CAR19-expressing cells are formulated for administration at least 2 weeks, 3 weeks, 1 month, 1.5 months, 2 months, 3 months, 4 months, 6 months, 9 months, 12 months, 15 months, or 18 months after the mammal received the kinase inhibitor.

3. The use of claim 1 or 2, wherein the CAR19-expressing cells are formulated for administration in combination with continued administration of the previously received kinase inhibitor.

4. A method of making a CAR19-expressing cell or a population of CAR19-expressing cells, comprising:

(i) providing a cell or a population of cells isolated from a mammal that has previously received a kinase inhibitor chosen from a BTK inhibitor, a CDK4 inhibitor, an mTOR inhibitor, or a MNK inhibitor; and

(ii) introducing or transducing a nucleic acid encoding a CAR molecule that binds CD19 into the cell or population of cells under conditions such that the CAR molecule that binds CD19 is expressed.

5. The method of claim 4, wherein:

(a) the cell or population of cells was isolated from the mammal at least 2 weeks, 3 weeks, 1 month, 1.5 months, 2 months, 3 months, 4 months, 6 months, 9 months, 12 months, 15 months, or 18 months after the mammal received the kinase inhibitor;

(b) the cell is a T cell or NK cell, or the population of cells comprises T cells, NK cells, or both;

(c) the population of cells comprises cancer cells; or

(d) the method further comprises depleting T regulatory cells or CD25+ cells from the population of cells.

6. Use of the CAR19-expressing cell or population of CAR19-expressing cells made by the method of claim 4 or 5 in the manufacture of a medicament for treating a mammal having a disease associated with expression of CD19.

7. The use of claim 6, wherein the CAR19-expressing cell or population of CAR19-expressing cells are formulated for administration in combination with a kinase inhibitor chosen from a BTK inhibitor, a CDK4 inhibitor, an mTOR inhibitor, or a MNK inhibitor.

8. The method of claim 4 or 5, or the use of any one of claims 1-3, 6, and 7, wherein:

(a) the BTK inhibitor is chosen from ibrutinib, GDC-0834, RN-486, CGI-560, CGI-1764, HM-71224, CC-292, ONO-4059, CNX-774, or LFM-A13;

(b) the CDK4 inhibitor is chosen from palbociclib, aloisine A, flavopiridol, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone, crizotinib (PF-02341066), P276-00, RAF265, indisulam, roscovitine, dinaciclib, BMS 387032, MLN8054, AG-024322, AT7519, AZD5438, BMS908662, or ribociclib;

(c) the mTOR inhibitor is chosen from rapamycin or a rapamycin analog chosen from everolimus, temsirolimus, ridaforolimus, semapimod, AZD8055, PF04691502, SF1126, XL765, or OSI-027; or

(d) the MNK inhibitor is chosen from CGP052088, CGP57380, cercosporamide, ETC-1780445-2, or 4-amino-5-(4-fluoroanilino)-pyrazolo [3,4-d] pyrimidine.

9. The method of claim 4 or 5, or the use of any one of claims 1-3 and 6-8, wherein the previously received kinase inhibitor is ibrutinib.

10. The method or use of claim 9, wherein the ibrutinib has a dose of about 250 mg, 300 mg, 350 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, or 600 mg daily.

11. The method of claim 4 or 5, or the use of any one of claims 1-3 and 6-10, wherein the CAR molecule that binds CD19 comprises an anti-CD19 binding domain, a transmembrane domain, and an intracellular signaling domain.

12. The method or use of claim 11, wherein the anti-CD19 binding domain comprises a light chain complementarity determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25, a light chain complementarity determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26, a light chain complementarity determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27, a heavy chain complementarity determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19, a heavy chain complementarity determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 20, and a heavy chain complementarity determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

13. The method or use of claim 11 or 12, wherein the anti-CD19 binding domain is connected to the transmembrane domain by a hinge region.

14. The method or use of claim 13, wherein the hinge region comprises the amino acid sequence of SEQ ID NO:14.

15. The method or use of any one of claims 11-14, wherein the anti-CD19 binding domain comprises the amino acid sequence of SEQ ID NO:59, or an amino acid sequence with 95-99% identify thereto.

16. The method or use of any one of claims 11-15, wherein the anti-CD19 binding domain is an scFv that comprises a light chain variable region attached to a heavy chain variable region via a linker.

17. The method or use of claim 16, wherein the linker comprises the amino acid sequence of SEQ ID NO: 53.

18. The method or use of any one of claims 11-17, wherein the transmembrane domain comprises a transmembrane domain of a protein chosen from: 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 or CD154.

19. The method or use of any one of claims 11-18, wherein the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 15.

20. The method or use of any one of claims 11-19, wherein the intracellular signaling domain comprises a costimulatory domain and a primary signaling domain.

21. The method or use of claim 20, wherein the costimulatory domain comprises a functional signaling domain of a protein chosen from: OX40, CD2, CD27, CD28, ICAM-1, LFA-1 (CD11a/CD18) or 4-1BB (CD137).

22. The method or use of claim 20 or 21, wherein the costimulatory domain comprises the amino acid sequence of SEQ ID NO: 16.

23. The method or use of any one of claims 11-22, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB, a functional signaling domain of CD3 zeta, or both.

24. The method or use of any one of claims 11-23, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO:17.

25. The method or use of any one of claims 11-24, wherein the CAR molecule further comprises a leader sequence.

26. The method or use of claim 25, wherein the leader sequence comprises the amino acid sequence of SEQ ID NO: 13.

27. The method or use of any one of claims 11-26, wherein the CAR molecule comprises the amino acid sequence of SEQ ID NO:58.

28. The use of any one of claims 1-3 and 6-27, wherein an agent which inhibits an immune inhibitory molecule chosen from: PD1, PD-L1, CTLA4, TIM3, CEACAM, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR beta is to be further administered to the mammal.

29. The use of any one of claims 1-3 and 6-28, wherein:

(a) the population of cells comprises 1-5 x 10^8 CAR19-expressing cells;

(b) the population of cells comprises about 5 x 10^6, 1 x 10^7, 2 x 10^7, or 5 x 10^7 CAR19-expressing cells; or

(c) the CAR19-expressing cells are formulated for administration at a dosage of 10^4 to 10^9 CAR19-expressing cells/kg body weight.

30. The use of any one of claims 1-3 and 6-29, wherein the disease associated with expression of CD19 is a hematological cancer.

31. The use of any one of claims 1-3 and 6-30, wherein the disease associated with expression of CD19 is chosen from a leukemia or lymphoma.

32. The use of any one of claims 1-3 and 6-30, wherein the disease associated with expression of CD19 is chosen from: chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), multiple myeloma, acute lymphoblastic leukemia (ALL), Hodgkin lymphoma, B-cell acute lymphoblastic leukemia (BALL), T-cell acute lymphoblastic leukemia (TALL), small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma (DLBCL), DLBCL associated with chronic inflammation, follicular lymphoma, pediatric follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue), Marginal zone lymphoma, myelodysplasia and myelodysplastic syndrome,

non-Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, splenic lymphoma/leukemia, splenic diffuse red pulp small B-cell lymphoma, hairy cell leukemia-variant, lymphoplasmacytic lymphoma, a heavy chain disease, plasma cell myeloma, solitary plasmocytoma of bone, extraosseous plasmocytoma, nodal marginal zone lymphoma, pediatric nodal marginal zone lymphoma, primary cutaneous follicle center lymphoma, lymphomatoid granulomatosis, primary mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, primary effusion lymphoma, B-cell lymphoma, or unclassifiable lymphoma.

33. The use of any one of claims 1-3 and 6-30, wherein the disease associated with expression of CD19 is chosen from MCL, CLL, ALL, Hodgkin lymphoma, or multiple myeloma.

34. The use of any one of claims 1-3 and 6-33, wherein the CAR19-expressing cells are formulated for administration in combination with a cytokine chosen from IL-7, IL-15, or IL-21.

35. The method of claim 4 or 5, or the use of any one of claims 1-3 and 6-34, wherein the CAR molecule is a regulatable CAR (RCAR) comprising:

(a) an intracellular signaling member comprising an intracellular signaling domain and a first switch domain,

(b) an antigen binding member comprising an antigen binding domain that binds CD19 and a second switch domain; and

(c) a transmembrane domain.

36. The method of claim 4 or 5, or the use of any one of claims 1-3 and 6-35, wherein the mammal is identified as having a BTK mutation.

37. The method of claim 4 or 5, or the use of any one of claims 1-3 and 6-36, wherein the mammal has undergone lymphodepletion.

38. The use of any one of claims 1-3 and 6-37, wherein a low, immune enhancing dose of an mTOR inhibitor is to be further administered to the mammal.

39. The use of claim 38, wherein the mTOR inhibitor is everolimus or rapamycin.

40. The method of claim 4 or 5, or the use of any one of claims 1-3 and 6-39, wherein the CAR19-expressing cells comprise human immune effector cells.

41. The method or use of claim 40, wherein the human immune effector cells comprise human T cells or human NK cells.