

Claims

1. Use of a population of immune effector cells expressing a chimeric antigen receptor (CAR) that binds to CD19 (“CD19 CAR-expressing cells”) in the manufacture of a medicament for the treatment of cancer in a subject, wherein the medicament is for use in combination with a PD-1 inhibitor, wherein the PD-1 inhibitor binds to PD-1 or reduces PD-1 expression, wherein the CAR comprises an antigen binding domain, a transmembrane domain and an intracellular signaling domain; and wherein:
the CD19 CAR-expressing cells and the PD-1 inhibitor are to be administered sequentially, wherein the medicament is administered at least 2 days before the PD-1 inhibitor is administered;
and wherein the population of immune effector cells comprises T cells or NK cells, wherein the PD-1 inhibitor is an anti-PD-1 antibody molecule, and wherein the cancer is a hematological cancer.
2. The use of claim 1, wherein administration of the PD-1 inhibitor is to be initiated 2-40 days after administration of the medicament.
3. The use of claim 1 or 2, further comprising the administration of one or more subsequent doses of the PD-1 inhibitor.
4. The use of any one of claims 1-3, wherein the subject is to be identified as not having cytokine release syndrome (CRS) after the administration of the medicament.
5. The use of any one of claims 1-4, wherein the medicament and the PD-1 inhibitor are to be administered for a treatment interval, and wherein the treatment interval comprises a single dose of the PD-1 inhibitor and a single dose of the medicament.
6. The use of any one of claims 1-5, wherein the medicament comprises a dose of CD19 CAR-expressing cells comprising:
 - (i) 10^4 to 10^9 cells/kg;
 - (ii) $1-5 \times 10^7$ cells/kg; or
 - (iii) $1-5 \times 10^8$ cells/kg.
7. The use of any one of claims 1-6, wherein the dose of the PD-1 inhibitor is 200 mg to 450 mg to be administered every 2 weeks, 3 weeks, 4 weeks, 5 weeks, or 6 weeks.
8. The use of any one of claims 1-7, wherein the dose of the PD-1 inhibitor is 200 mg or 300 mg to be administered every 3 weeks.

9. The use of any one of claims 1-7, wherein the dose of the PD-1 inhibitor is 400 mg to be administered every 6 weeks.

10. The use of any one of claims 1-9, wherein the PD-1 inhibitor is to be administered via intravenous infusion.

11. The use of any one of claims 1-10, wherein the PD-1 inhibitor is an antibody molecule chosen from: Pembrolizumab, Nivolumab, PDR001, Pidilizumab, REGN-2810, PF-06801591, BGB-108, INCSHR1210, TSR-042, AMP 514, and BGB-A317.

12. The use of any one of claims 1-11, wherein the CD19 binding domain comprises:

(i) an HC CDR1 of SEQ ID NO: 117; an HC CDR2 of SEQ ID NO: 118; an HC CDR3 of SEQ ID NO: 122; a LC CDR1 of SEQ ID NO: 123; a LC CDR2 of SEQ ID NO: 124; and a LC CDR3 of SEQ ID NO: 125;

(ii) an HC CDR1 of SEQ ID NO: 117; an HC CDR2 of SEQ ID NO: 119; an HC CDR3 of SEQ ID NO: 122; a LC CDR1 of SEQ ID NO: 123; a LC CDR2 of SEQ ID NO: 124; and a LC CDR3 of SEQ ID NO: 125;

(iii) an HC CDR1 of SEQ ID NO: 117; an HC CDR2 of SEQ ID NO: 120; an HC CDR3 of SEQ ID NO: 122; a LC CDR1 of SEQ ID NO: 123; a LC CDR2 of SEQ ID NO: 124; and a LC CDR3 of SEQ ID NO: 125; or

(iv) an HC CDR1 of SEQ ID NO: 117; an HC CDR2 of SEQ ID NO: 121; an HC CDR3 of SEQ ID NO: 122; a LC CDR1 of SEQ ID NO: 123; a LC CDR2 of SEQ ID NO: 124; and a LC CDR3 of SEQ ID NO: 125.

13. The use of claim 12, wherein the CD19 binding domain comprises:

(i) a heavy chain variable region comprising:

a. the amino acid sequence of any heavy chain variable region of a CD19 binding domain listed in Table 2 or 3; or

b. an amino acid sequence at least 95% identical, or with 95-99% identity, to the amino acid sequence of any heavy chain variable region of a CD19 binding domain provided in Table 2 or 3; and

(ii) a light chain variable region comprising:

a. the amino acid sequence of any light chain variable region of a CD19 binding domain listed in Table 2 or 3; or

b. an amino acid sequence at least 95% identical, or with 95-99% identity, to the amino acid sequence of any light chain variable region of a CD19 binding domain provided in Table 2 or 3.

14. The use of claim 12 or 13, wherein the CD19 binding domain comprises:

a. an amino acid sequence chosen from SEQ ID NO: 109, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51,

SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 110, SEQ ID NO: 112, or SEQ ID NO: 115; or

b. an amino acid sequence at least 95% identical, or with 95-99% identity, to the amino acid sequence of SEQ ID NO: 109, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 110, SEQ ID NO: 112, or SEQ ID NO: 115.

15. The use of any one of claims 1-14, wherein the transmembrane domain comprises a transmembrane domain 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, or CD154.

16. The use of any one of claims 1-14, wherein the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6 or a sequence at least 95% identical thereto.

17. The use of any one of claims 1-16, wherein the intracellular signaling domain comprises a costimulatory signaling domain of a MHC class I molecule, a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, or a ligand that specifically binds with CD83.

18. The use of any one of claims 1-17, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

19. The use of any one of claims 1-18, wherein the intracellular signaling domain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 7 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 9.

20. The use of claim 19, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 9.

21. The use of any one of claims 1-18, wherein the intracellular signaling domain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:7 and an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 10.

22. The use of claim 21, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 10.

23. The use of any one of claims 12-22, wherein the medicament comprises:

(i) the amino acid sequence of any of SEQ ID NO: 108; SEQ ID NO: 93; SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 111, SEQ ID NO: 114, or SEQ ID NO: 116; or

(ii) an amino acid sequence at least 95% identical to any of SEQ ID NO: 108; SEQ ID NO: 93; SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 111, SEQ ID NO: 114, or SEQ ID NO: 116.

24. The use of any one of claims 1-23, wherein the cancer is a lymphoma, or a leukemia chosen from one or more of B-cell acute lymphoblastic leukemia (BALL), T-cell acute lymphoblastic leukemia (TALL), small lymphocytic lymphoma (SLL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin lymphoma, Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, or Waldenstrom macroglobulinemia.

25. The use of any one of claims 1-24, wherein the subject is a human.

26. The use of any one of claims 1-25, wherein the subject:

(i) expresses PD-1, PD-L1, and/or PD-L2; or

(ii) is to be identified as having a higher number or percentage of immune effector cells expressing one, two, three, or all of PD-1, LAG-3, or TIM-3, compared to a reference value.

27. The use of any one of claims 1-26, wherein the CD19 CAR of the CD19 CAR-expressing cells comprises:

(a) a CD19 binding domain which comprises an HC CDR1 of SEQ ID NO: 117; an HC CDR2 of SEQ ID NO: 118; an HC CDR3 of SEQ ID NO: 122; a LC CDR1 of SEQ ID NO: 123; a LC CDR2 of SEQ ID NO: 124; and a LC CDR3 of SEQ ID NO: 125;

(b) a CD19 binding domain which comprises the amino acid sequence of SEQ ID NO: 109; and/or

(c) the amino acid sequence of SEQ ID NO: 108.