

CLAIMS

1. Use of a population of immune effector cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of cancer, wherein the medicament is intended for use in combination with a PD-1 inhibitor, and wherein:

(i) the CAR comprises an antigen (e.g., a CD19) binding domain, a transmembrane domain and an intracellular signaling domain; and

(ii) the PD-1 inhibitor, e.g., anti-PD-1 antibody molecule, is to be administered at a dose of about 200 mg to about 450 mg, e.g., about 300 mg to about 400 mg, e.g., optionally wherein the PD-1 inhibitor is to be administered every 2 weeks, 3 weeks, 4 weeks, or 5 weeks.

2. Use of a population of immune effector cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of cancer, wherein the medicament is intended for use in combination with a PD-1 inhibitor, and wherein;

(i) the CAR comprises an antigen (e.g., a CD19) binding domain, a transmembrane domain and an intracellular signaling domain; and

(ii) administration of the PD-1 inhibitor is to be initiated 20 days or less after administration of the medicament.

3. The use of claim 1 or 2, wherein administration of the PD-1 inhibitor is to be initiated 16 days or less, 15 days or less, 14 days or less, 13 days or less, 12 days or less, 11 days or less, 10 days or less, 9 days or less, 8 days or less, 7 days or less, 6 days or less, 5 days or less, 4 days or less, 3 days or less, 2 days or less, after administration of the medicament.

4. Use of a population of immune effector cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of cancer, wherein the medicament is intended for use in combination with a PD-1 inhibitor, and wherein:

(i) the CAR comprises an antigen (e.g., a CD19) binding domain, a transmembrane domain and an intracellular signaling domain; and

(ii) administration of the PD-1 inhibitor is to be initiated after the subject has, or is identified as having, one or more of the following:

(a) a partial or no detectable response to the medicament;

(b) a relapsed cancer after the medicament;

(c) a cancer refractory to the medicament;

(d) a progressive form of the cancer after the medicament; or

(e) B cell recovery, e.g., less than 3 months, after the medicament.

5. The use of any one of claims 1 to 4, further comprising the administration of one or more, e.g., 1, 2, 3, 4, or 5 or more, subsequent doses of the PD-1 inhibitor.
6. The use of any one of claims 1 to 5, further comprising evaluating the presence or absence of cytokine release syndrome (CRS) in the subject.
7. The use of any one of claims 1 to 6, wherein the subject does not have, or is identified, as not having cytokine release syndrome (CRS), e.g., severe CRS (e.g., CRS grade 3 or grade 4) after the administration of the medicament.
8. The use of claim 7, wherein administration of the PD-1 inhibitor is to be initiated:
 - (i) after the subject is identified as not having CRS, e.g., severe CRS (e.g., CRS grade 3 or grade 4), after the CAR therapy; or
 - (ii) after treatment of CRS, e.g., after CRS resolution, after the administration of the medicament.
9. The use of any one of claims 1 to 8, wherein the medicament and the PD-1 inhibitor are to be administered for a treatment interval, and wherein the treatment interval:
 - (i) comprises a single dose of the PD-1 inhibitor and a single dose of the medicament;
 - (ii) is to be initiated upon administration of the dose of the medicament and completed upon administration of the dose of the PD-1 inhibitor;
 - (iii) further comprises the administration of one or more subsequent doses of the PD-1 inhibitor;
 - (iv) is repeated; or
 - (v) is followed by one or more subsequent treatment intervals, wherein the one or more subsequent treatment interval is different from the first or previous treatment interval.
10. The use of any one of claims 1 to 2 or 4 to 9, wherein a dose of the medicament is to be administered:
 - (i) at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11, days, at least 12, at least 13, at least 14 days, at least 15 days, at least 16 days, at least 17 days, at least 18 days, at least 19 days, or at least 20 days before the dose of PD-1 inhibitor is to be administered; or
 - (ii) 25-40 days (e.g., about 25-30, 30-35, or 35-40 days, e.g., about 35 days) before the dose of the PD-1 inhibitor is to be administered.

11. The use of any one of claims 1, or 6 to 8, wherein the medicament and the PD-1 inhibitor are to be administered for a treatment interval, wherein the treatment interval:

(i) comprises a first and second dose of the PD-1 inhibitor and a dose of the medicament, and wherein the dose of the medicament is to be administered after the administration of the first dose of the PD-1 inhibitor but before the administration of the second dose of the PD-1 inhibitor; or

(ii) is to be initiated upon administration of the first dose of the PD-1 inhibitor and completed upon administration of the second dose of the PD-1 inhibitor.

12. The use of claim 11, wherein:

(i) the second dose of the PD-1 inhibitor is to be administered at least 5 days, 7 days, 1 week, 2 weeks, or 3 weeks after the administration of the first dose of the PD-1 inhibitor;

(ii) the dose of the medicament is to be administered at least 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or 2 weeks after the administration of the first dose of the PD-1 inhibitor;

(iii) the second dose of the medicament is to be administered at least 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or 2 weeks after the administration of the dose of the CAR-therapy;

(iv) the treatment interval is repeated, e.g., one or more times, e.g., 1, 2, 3, 4, or 5 more times; or

(v) the treatment interval is followed by one or more, e.g., 1, 2, 3, 4, or 5, subsequent treatment intervals, optionally wherein, the one or more subsequent treatment intervals is different from the first or previous treatment interval.

13. The use of any one of claims 9 to 12, wherein:

(i) one or more subsequent doses, e.g., 1, 2, 3, 4, or 5 or more doses, of the PD-1 inhibitor is to be administered after the completion of one or more treatment intervals;

(ii) a dose of the PD-1 inhibitor is to be administered every 5 days, 6 days, 7 days, 10 days, 2 weeks, 3 weeks, or 4 weeks after the completion of one or more treatment intervals;

(iii) the treatment interval comprises a dose of medicament which is to be administered 2-20 days, 5-17 days, 7-16 days, 8-16 days, 10-15 days, 14-21 days or 2-3 weeks before the dose of the PD-1 inhibitor is to be administered;

(iv) the treatment interval is repeated 0-52 times;

(v) the treatment intervals are to be initiated at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 2 weeks, at least 1 month, at least 3 months, at least 6 months, or at least 1 year after the completion of the previous treatment interval; or

(vi) one or more subsequent doses of the PD-1 inhibitor is to be administered every 5 days, 7 days, 2 weeks, 3 weeks, or 4 weeks, after the second treatment interval.

14. The use of claim 9, wherein the medicament comprises an RNA encoding a CAR, e.g., an in vitro transcribed (IVT) RNA, and wherein:
- (i) one or more, e.g., 1, 2, 3, 4, or 5, subsequent doses of the medicament is to be administered to the subject after the initial dose of the CAR-therapy; or
 - (ii) one or more subsequent doses of the medicament is to be administered at least 2 days, e.g., 2, 3, 4, 5, 6, 7 days, 2 weeks, or 3 weeks, after the previous dose of the medicament.
15. The use of any one of claims 12 to 14, wherein:
- (i) one or more, e.g., 1, 2, 3, 4, or 5 or more, subsequent doses of PD-1 inhibitor are to be administered after administration of the single dose of the PD-1 inhibitor;
 - (ii) one or more subsequent doses of the PD-1 inhibitor are to be administered at least 5 days, 7 days, 2 weeks, 3 weeks or 4 weeks, after the previous dose of PD-1 inhibitor;
 - (iii) one or more subsequent doses of the PD-1 inhibitor are to be administered at least 1, 2, 3, 4, 5, 6, or 7 days, or 2 weeks or 3 weeks, after a dose of the medicament, e.g., the initial dose of the CAR-therapy; or
 - (iv) administration of the one or more doses of the medicament and the one or more doses of PD-1 inhibitor is repeated.
16. The use of any one of claims 1 to 15, wherein the medicament comprises a dose of CAR-expressing cells comprising:
- (i) about 10^4 to about 10^9 cells/kg, e.g., about 10^4 to about 10^5 cells/kg, about 10^5 to about 10^6 cells/kg, about 10^6 to about 10^7 cells/kg, about 10^7 to about 10^8 cells/kg, about 10^8 to about 10^9 cells/kg, or about $1-5 \times 10^7$ cells/kg to about $1-5 \times 10^8$ cells/kg;
 - (ii) about $1-5 \times 10^7$ cells/kg; or
 - (iii) about $1-5 \times 10^8$ cells/kg.
17. The use of any one of claims 1 to 16, wherein:
- (i) the dose of the PD-1 inhibitor, e.g., anti-PD-1 antibody molecule, is about 200 mg to about 450 mg, e.g., about 200 mg to about 400 mg, optionally wherein, the PD-1 inhibitor is to be administered every 2 weeks, 3 weeks, 4 weeks, or 5 weeks;
 - (ii) the dose of the PD-1 inhibitor is about 200mg or about 300 mg, optionally wherein, the PD-1 inhibitor is to be administered every 3 weeks;
 - (iii) the dose of the PD-1 inhibitor is about 400 mg, optionally wherein, the PD-1 inhibitor is to be administered every 4 weeks; or
 - (iv) the PD-1 inhibitor, e.g., PD-1 antibody molecule, is to be administered at a dose of about 300 mg every 2 weeks, 3 weeks, or 4 weeks, and the CAR therapy is to be administered at a dose of $1-5 \times 10^8$ cells,

optionally wherein, the PD-1 inhibitor is to be administered via intravenous infusion.

18. The use of any one of claims 1 to 17, wherein the PD-1 inhibitor comprises: an antibody molecule; a small molecule; a polypeptide (e.g., a fusion protein); or an inhibitory nucleic acid (e.g., a siRNA or shRNA).

19. The use of any one of claims 1 to 18, wherein the PD-1 inhibitor is an antibody molecule chosen from: Nivolumab, Pembrolizumab, PDR001, Pidilizumab, AMP 514, AMP-224, or an anti-PD-1 antibody molecule provided in Table 6.

20. The use of any one of claims 1 to 19, wherein the PD-1 inhibitor comprises an anti-PD-1 antibody molecule comprising:

(i) 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 an PD-1 antibody molecule amino acid sequence listed in Table 6; and 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 an PD-1 antibody molecule amino acid sequence listed in Table 6; or

(ii) a HC CDR1 amino acid sequence chosen from SEQ ID NO: 137 or 140, a HC CDR2 amino acid sequence of SEQ ID NO: 138 or 141, and a HC CDR3 amino acid sequence of SEQ ID NO: 139; and a LC CDR1 amino acid sequence of SEQ ID NO: 146 or 149, a LC CDR2 amino acid sequence of SEQ ID NO: 147 or 150, and a LC CDR3 amino acid sequence of SEQ ID NO: 166, or 167.

21. The use of claim 20, wherein the anti-PD-1 antibody molecule comprises:

(a) a heavy chain variable region comprising:

(i) the amino acid sequence of any heavy chain variable region listed in Table 6, e.g., SEQ ID NOs: 142, 144, 154, 158, 172, 184, 216, or 220;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to the amino acid sequence of any heavy chain variable region provided in Table 6, e.g., SEQ ID NOs: 142, 144, 154, 158, 172, 184, 216, or 220; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of any heavy chain variable region provided in Table 6, e.g., SEQ ID NOs: 142, 144, 154, 158, 172, 184, 216, or 220; and/or

(b) a light chain variable region comprising:

(i) the amino acid sequence of any light chain variable region listed in Table 6, e.g., SEQ ID NOs: 152, 162, 168, 176, 180, 188, 192, 196, 200, 204, 208, or 212;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to the amino acid sequence of any light chain variable region provided in Table 6, e.g., SEQ ID NOs: 152, 162, 168, 176, 180, 188, 192, 196, 200, 204, 208, or 212; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of any light chain variable region provided in Table 6, e.g., SEQ ID NOs: 152, 162, 168, 176, 180, 188, 192, 196, 200, 204, 208, or 212.

22. The use of claim 20 or 21, wherein the anti-PD-1 antibody molecule comprises:

i) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 204;

ii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 142 or 144 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 152;

iii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 154 or 158 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 162;

iv) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 154 or 158 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 168;

v) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 176;

vi) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 180;

vii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 184 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 180;

viii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 184 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 188;

ix) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 188;

x) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 192;

xi) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 196;

xii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 184 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 200;

xiii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 200;

- xiv) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 184 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 204;
- xv) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 204;
- xvi) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 208;
- xvii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 212;
- xviii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 216 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 204;
- xix) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 216 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 200;
- xx) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 220 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 200;
- xxi) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 176;
- xxii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 188;
- xxiii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 200; or
- xxiv) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 184 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 204.

23. The use of claim 19, wherein the anti-PD1 antibody molecule comprises:

(i) a heavy chain variable (VH) region comprising the VHCDR1 amino acid sequence of SEQ ID NO: 530; the VHCDR2 amino acid sequence of SEQ ID NO: 531; and the VHCDR3 amino acid sequence of SEQ ID NO: 532; and

(ii) a light chain variable (VL) region comprising the VLCDR1 amino acid sequence of SEQ ID NO: 527; the VLCDR2 amino acid sequence of SEQ ID NO: 528; and the VLCDR3 amino acid sequence of SEQ ID NO: 529,

or an amino acid sequence at least 85%, 90%, 95% identical or higher.

24. The use of any one of claims 1 to 23, wherein the CD19 binding domain comprises 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) according to the HC CDR amino acid sequences in Table 4; and 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) according to the LC CDR amino acid sequences in Table 5.

25. The use of any one of claims 1 to 24, 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;
- b. an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to the amino acid sequence of any heavy chain variable region of a CD19 binding domain provided in Table 2 or 3; or
- c. an amino acid sequence at least 95% identical, e.g., 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/or

(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;
- b. an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to the amino acid sequence of any light chain variable region of a CD19 binding domain provided in Table 2 or 3; or
- c. an amino acid sequence at least 95% identical, e.g., 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.

26. The use of any one of claims 1 to 25, 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;
- b. an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to 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
- c. an amino acid sequence at least 95% identical, e.g., 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.

27. The use of any one of claims 1 to 26, wherein the transmembrane domain comprises:

- (i) 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;
- (ii) the amino acid sequence of SEQ ID NO: 6;
- (iii) an amino acid sequence comprising at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:6; or
- (iv) a sequence at least 95% identical to the amino acid sequence of SEQ ID NO:6.

28. The use of any one of claims 1 to 27, wherein the intracellular signaling domain comprises:

- (i) 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, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRP1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, 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;

- (ii) the amino acid sequence of SEQ ID NO:7; an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7; or an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:7;

- (iii) a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta;

- (iv) the amino acid sequence of SEQ ID NO: 7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or an amino acid sequence at least 95%

identical to the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or

(v) the amino acid sequence of SEQ ID NO:7 and the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the amino acid sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

29. The use of any one of claims 1 to 28, 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;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications 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; or

(iii) 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.

30. The use of any one of claims 1 to 29, wherein the population of immune effector cells comprising the medicament comprises a nucleic acid encoding the medicament, optionally wherein the nucleic acid encoding the medicament: (i) is introduced into the cells by lentiviral transduction; or (ii) is an in vitro transcribed RNA.

31. The use of any one of claims 1 to 30, wherein the population of immune effector cells comprises T cells or NK cells.

32. The use of any one of claims 1 to 31, wherein the cancer is a hematological cancer, a lymphoma or a leukemia chosen from one or more of B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), small lymphocytic leukemia (SLL), acute lymphoid 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.

33. The use of any one of claims 1 to 32, wherein the subject:

- (i) is a mammal, e.g., a human;
- (ii) expresses PD-1, PD-L1 and/or PD-L2; or
- (iii) has, or is 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.

34. A composition (e.g., one or more compositions or dosage forms), comprising:

- (i) a cell, e.g., a population of immune effector cells, comprising a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and
- (ii) a PD-1 inhibitor chosen from Table 6, e.g., comprising the variable light chain amino acid sequence of SEQ ID NO: 204, and the variable heavy chain amino acid sequence of SEQ ID NO: 172.

35. The use of any one of claims 1 to 33, or the composition of claim 34, wherein:

- (i) the CAR or medicament comprises a CD19 binding domain comprising the amino acid sequence of SEQ ID NO: 109; or
- (ii) the CAR or medicament comprises the amino acid sequence of SEQ ID NO: 108.

36. A chimeric antigen receptor (CAR) therapy comprising a population of immune effector cells expressing the CAR, for use in the treatment of cancer, in combination with a PD-1 inhibitor, wherein:

- (i) the CAR comprises an antigen (e.g., a CD19) binding domain, a transmembrane domain and an intracellular signaling domain; and
- (ii) the PD-1 inhibitor, e.g., anti-PD-1 antibody molecule, is to be administered at a dose of about 200 mg to about 450 mg, e.g., about 300 mg to about 400 mg, optionally wherein the PD-1 inhibitor is to be administered every 2 weeks, 3 weeks, 4 weeks, or 5 weeks.

37. A chimeric antigen receptor (CAR) therapy comprising a population of immune effector cells expressing the CAR for use in the treatment of cancer, in combination with a PD-1 inhibitor, and wherein;

- (i) the CAR comprises an antigen (e.g., a CD19) binding domain, a transmembrane domain and an intracellular signaling domain; and

(ii) administration of the PD-1 inhibitor is to be initiated 20 days or less after the administration of the CAR.

38. A chimeric antigen receptor (CAR) therapy comprising a population of immune effector cells expressing the CAR, for use in combination with a PD-1 inhibitor for treating a subject having a cancer, wherein:

(i) the CAR comprises an antigen (e.g., a CD19) binding domain, a transmembrane domain and an intracellular signaling domain; and

(ii) administration of the PD-1 inhibitor is to be initiated after the subject has, or is identified as having, one or more of the following:

- (a) a partial or no detectable response to the CAR therapy;
- (b) a relapsed cancer after the CAR therapy;
- (c) a cancer refractory to the CAR therapy;
- (d) a progressive form of the cancer after the CAR therapy; or
- (e) B cell recovery, e.g., less than 3 months, after the CAR therapy.