

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 intended 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

(i) the CD19 CAR-expressing cells and the PD-1 inhibitor, ~~e.g., an anti-PD-1 antibody molecule,~~ are to be administered sequentially, wherein the medicament is administered 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, at least 20 days, ~~or 25-40 days (e.g., about 25-30 days, about 30-35 days, or about 35-40 days, or e.g., about 35 days)~~ before the PD-1 inhibitor is administered; or

(ii) the CD19 CAR-expressing cells and the PD-1 inhibitor, ~~e.g., an anti-PD-1 antibody molecule,~~ are to be administered sequentially, wherein administration of the PD-1 inhibitor is to be initiated 20 days or less after administration of the medicament,

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 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.

3. The use of claim 1 or 2, wherein administration of the PD-1 inhibitor is to be initiated after the subject ~~has, or is~~ to be 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.

4. The use of any one of claims 1-3, 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.

~~5. The use of any one of claims 1-4, further comprising evaluating the presence or absence of cytokine release syndrome (CRS) in the subject.~~

65. The use of any one of claims 1-54, wherein the subject does not have, or is to be 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.

76. The use of claim 65, wherein administration of the PD-1 inhibitor is to be initiated:
(i) after the subject is to be identified as not having CRS, ~~e.g., severe CRS (e.g., CRS grade 3 or grade 4)~~, after administration of the CD19 CAR-expressing cells; or
(ii) after treatment of CRS, ~~e.g., after CRS resolution~~, after the administration of the medicament.

87. The use of any one of claims 1-76, 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.

98. The use of claim 87, wherein:
(i) ~~one or more subsequent doses, e.g., 1, 2, 3, 4, or 5 or more~~ subsequent 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.

~~109.~~ The use of claim ~~87~~, wherein the medicament comprises an RNA encoding a CD19 CAR, ~~e.g., an in vitro transcribed (IVT) RNA~~, and wherein:

(i) ~~one or more, e.g., 1, 2, 3, 4, or 5, or more~~ subsequent doses of the medicament is to be administered to the subject after the initial dose of the CD19 CAR-expressing cells ; 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.

~~110.~~ The use of claim ~~9-8~~ or ~~109~~, 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.

~~1211.~~ The use of any one of claims 1-~~1110~~, wherein the medicament comprises a dose of CD19 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.

~~13~~12. The use of any one of claims 1-~~12~~11, 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 200 mg 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 CD19 CAR-expressing cells are 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.

~~14. The use of any one of claims 1-13, 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).~~

~~15~~13. The use of any one of claims 1-~~14~~12, wherein the PD-1 inhibitor is:

(i) an antibody molecule chosen from: Nivolumab, Pembrolizumab, PDR001, AMP 514, or an anti-PD-1 antibody molecule provided in Table 6; ~~or~~

(ii) ~~the anti-PD-1 fusion protein AMP 224.~~

~~16~~14. The use of any one of claims 1-~~15~~13, 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); 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;

(ii) a HC CDR1 amino acid sequence chosen from SEQ ID NO: 137, a HC CDR2 amino acid

sequence of SEQ ID NO: 138, and a HC CDR3 amino acid sequence of SEQ ID NO: 139; and a LC CDR1 amino acid sequence of SEQ ID NO: 146, a LC CDR2 amino acid sequence of SEQ ID NO: 147, and a LC CDR3 amino acid sequence of SEQ ID NO: 166, according to Kabat; or

(iii) a HC CDR1 amino acid sequence chosen from SEQ ID NO: 140, a HC CDR2 amino acid sequence of SEQ ID NO: 141, and a HC CDR3 amino acid sequence of SEQ ID NO: 139; and a LC CDR1 amino acid sequence of SEQ ID NO: 149, a LC CDR2 amino acid sequence of SEQ ID NO: 150, and a LC CDR3 amino acid sequence of SEQ ID NO: 167, according to Chothia.

~~1715~~. The use of claim ~~1614~~, 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., or~~ 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., or~~ SEQ ID NOs: 142, 144, 154, 158, 172, 184, 216, or 220; and

(b) a light chain variable region comprising:

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

~~1816~~. The use of claim ~~1614~~ or ~~1715~~, 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.

1917. The use of claim ~~1513~~, 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.

2018. The use of any one of claims 1-~~1917~~, 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.

2119. The use of claim ~~2018~~, 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., 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;

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., 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.

~~2220~~. The use of claim ~~20-18~~ or ~~24-19~~, 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., 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.

~~2321~~. The use of any one of claims 1-~~2220~~, 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.

2422. The use of any one of claims 1-2321, 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 (KLRF1), 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.

2523. The use of any one of claims 1-2422, 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.

2624. The use of any one of claims 1-2523, 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.

27. — The use of any one of claims 1-26, wherein the population of immune effector cells comprises T cells or NK cells.

2825. The use of any one of claims 1-2724, wherein the cancer is a hematological cancer, a lymphoma, or a leukemia chosen from one or more of B-cell acute lymphoid lymphoblastic leukemia (BALL), T-cell acute lymphoid lymphoblastic leukemia (TALL), small lymphocytic leukemia-lymphoma (SLL), acute lymphoid 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.

2926. The use of any one of claims 1-2825, wherein the subject:

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

30. — ~~A combination of a population of immune effector cells expressing a CAR that binds to CD19 (“CD19 CAR-expressing cells”) and a PD-1 inhibitor, for use in the treatment of cancer, wherein the PD-1 inhibitor binds to PD-1 or reduces PD-1 expression, and wherein the CAR comprises an antigen-binding domain, a transmembrane domain and an intracellular signaling domain; and wherein~~

~~(i) the CD19 CAR-expressing cells and the PD-1 inhibitor, e.g., anti-PD-1 antibody molecule are to be administered sequentially, wherein the CD19 CAR-expressing cells are administered 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, at least 20 days, or 25-40 days (e.g., about 25-30, 30-35, or 35-40 days, e.g., about 35 days) before the PD-1 inhibitor is administered; or~~

~~(ii) the CD19 CAR-expressing cells and the PD-1 inhibitor, e.g., an anti-PD-1 antibody molecule, are administered sequentially, wherein administration of the PD-1 inhibitor is to be initiated 20 days or less after administration of the CD19 CAR-expressing cells.~~

31. — ~~The combination for use of claim 30, wherein:~~

~~— (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 CD19 CAR-expressing cells;~~

- ~~—— (b) a relapsed cancer after the CD19 CAR-expressing cells;~~
- ~~—— (c) a cancer refractory to the CD19 CAR-expressing cells;~~
- ~~—— (d) a progressive form of the cancer after the CD19 CAR-expressing cells; or~~
- ~~—— (e) B cell recovery, e.g., less than 3 months, after the CD19 CAR-expressing cells.~~