

the need for multiple separate intravenous infusions of the anti-PD-1 or anti-PD-L1 mAbs by engineering the CAR T or NK cell to secrete the anti-PD-1 or anti-PD-L1 mAbs once the CAR T or NK cells are infused inside the body. In one aspect, the present disclosure refers to an isolated nucleic acid or a vector comprising: a. a polynucleotide encoding a chimeric antigen receptor (CAR) comprising: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; and (d) an intracellular domain; and b. a polynucleotide encoding a bispecific antibody or fragment thereof that recognizes, binds and antagonizes PD-1 and PD-L1. In another aspect, the present disclosure refers to an isolated cell comprising the isolated nucleic acid as described herein, the vector as described herein, optionally wherein the cell is a prokaryotic cell or wherein the cell is a eukaryotic cell, further optionally wherein the eukaryotic cell is selected from an animal cell, a mammalian cell, a bovine cell, a feline cell, a canine cell, a murine cell, an equine cell or a human cell, yet further optionally wherein the eukaryotic cell is an immune cell, optionally a T-cell, a B-cell, a NK-cell, a dendritic cell, a myeloid cell, a monocyte, or a macrophage, and optionally an activated cell.

[0007a] In yet another aspect, the present disclosure refers to an expanded population, optionally a substantially homogenous population, of cells as described herein.

[0007b] In yet another aspect, the present disclosure refers to a composition or a kit comprising one or more of: the isolated nucleic acid as described herein, the vector as described herein, the isolated cell as described herein, or the population of cells as described herein; optionally a pharmaceutically acceptable carrier; further optionally an effective amount of an FLT3 inhibitor, optionally selected from the group consisting of gilteritinib, quizartinib, midostaurin, FF-10101, sorafenib, sunitinib, lestauritinib, or dovitinib; and yet further optionally instructions for use. In a further aspect, the present disclosure refers to a method of producing a CAR expressing cell comprising transducing an isolated cell with the isolated nucleic acid as described herein or the vector as described herein, optionally wherein the isolated cells are selected from a group consisting of T-cells, Bcells, NK-cells, dendritic cells, myeloid cells, monocytes, or macrophages. In a further aspect, the present disclosure refers to the isolated cell as described herein, or the composition as described herein for use in inhibiting the growth of a cancer or tumor expressing FLT3, optionally acute myeloid leukemia (AML) in a subject, by contacting with the cancer or tumor, optionally wherein expression of PD-1 or PD-L1 or both is measured in the subject and the subject expressing PD-1 or PD-L1 or both is to be administered with one or more of

the isolated cell as described herein, the antibody or the antigen binding fragment as described herein, or the composition as described herein to, optionally wherein the contacting is to be in vivo; optionally wherein the contacting is to be in vivo and the isolated cells are autologous to the subject being treated; optionally wherein the contacting is to be in vivo and the isolated cells are allogeneic to the subject being treated; optionally wherein the subject is to be further administered with an effective amount of a cytoreductive therapy, optionally comprising chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy; and optionally wherein the subject is a human patient. Accordingly, the CAR T or NK cell of this disclosure eliminates the need for large pharmacologic loading doses of the anti-PD-1 and/or anti-PD-L1 mAbs to be infused into the blood stream by separate, repeated administration. Based on the pharmacology and toxicity data published to date, it is reasonable to assume that this disclosure will avoid all PD-1(+) T or NK cells from becoming immediately saturated with anti-PD-1 mAb, very likely reducing some or all of the adverse events noted above. In addition, (1) the release of the antibody would only come from the CAR T or NK cells as they expand, so release of the anti-PD-1 or anti-PD-L1 mAbs into the bloodstream would be gradual; (2) given that the CAR homes the CAR T or NK cell to the tumor, the release of the anti-PD-1 or anti-PD-L1 mAbs would be more confined to the tumor microenvironment versus multiple massive intravenous systemic administrations as is currently FDA approved, and would therefore localize its anti-tumor effect more to the relevant T or NK cells in the tumor microenvironment. Additionally, this approach would result in huge cost savings (approximately six figure cost savings) to the patient as there would be no need for anti-PD-1 or anti-PD-L1 mAb infusions.

[0008] Unexpectedly, it has recently been reported that human natural killer cells from cancer patients express PD-L1 and that anti-PD-L1 antibody bound to NK cells was unexpectedly found to increase the NK cell killing of the tumor cell. Thus, this disclosure, whereby infected NK cells express both a CAR and a secreted anti-PD-L1 could significantly enhance NK killing of the tumor cell locally at the tumor microenvironment.

[0009] To that end, disclosed herein is/are one or more vectors or isolated polynucleotides comprising, or alternatively consisting essentially of, or further consisting of, a polynucleotide encoding a nucleic acid sequence of a chimeric antigen receptor (CAR) comprising: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; (d) and an intracellular domain; and a polynucleotide encoding a nucleic acid sequence of an antibody comprising an antigen binding domain that recognizes

and binds PD-1 and/or PD-L1. In some examples, a contiguous polynucleotide or a single vector further comprises, or further consists essentially of, or yet further consists, of both the polynucleotide encoding the nucleic acid sequence of a CAR comprising: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; (d) and an intracellular domain; and the polynucleotide encoding the nucleic acid sequence of an antibody comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1. In other examples, provided herein is an isolated nucleic acid or a vector comprising, or alternatively consisting essentially of, or yet further consisting of:

- a. a polynucleotide encoding a chimeric antigen receptor (CAR) comprising, or alternatively consisting essentially of, or yet further consisting of: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; (d) and an intracellular domain; and
- b. a polynucleotide encoding an antibody or antigen binding fragment thereof comprising, or alternatively consisting essentially of, or yet further consisting of an antigen binding domain that recognizes and binds PD-1 and/or PD-L1.

[0010] In further examples, the vector may be polycistronic, optionally bicistronic, and/or each of the polynucleotides may be operatively linked to regulatory polynucleotide sequences, such as enhancer elements and/or promoter elements.

[0011] An example of a contiguous polynucleotide of this disclosure is shown in **FIG. 1**. In some examples, the disclosure provides that each of the polynucleotides encoding the nucleic acid sequence of a CAR as disclosed above and within, and in one example, the CAR comprising: (1) (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; (d) and an intracellular domain; and (2) the polynucleotide encoding the nucleic acid sequence of an antibody or antigen binding fragment thereof comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1, the polynucleotides of (1) and (2) are comprised on separate independent polynucleotides or within separate vectors.

[0012] In any of the above examples, the vector or vectors is/are a plasmid or a viral vector, optionally selected from the group of a retroviral vector, a lentiviral vector, an adenoviral vector, and an adeno-associated viral vector.

[0013] In any of the above examples, the polynucleotides and/or vector or vectors may optionally comprise, or alternatively consist essentially of, or further consist, of a detectable label and/or a polynucleotide conferring antibiotic resistance and/or regulatory elements for

the transcription and translation for the CAR and the antigen binding domain that recognizes and binds PD-1 and/or PD-L1. In a further example, the therapeutic methods are combined with diagnostic methods that identify the subject or patient suitable for therapy by analyzing a suitable sample isolated from the patient of subject for expression of FLT3 and/or PD-1 and/or PD-L1, and determining that the patient or subject expresses one, two or three of FLT3, PD-1 and/or PD-L1, is suitable for the therapy. In a further example, the therapy is then administered to the subject or patient. Suitable samples include those that comprise cancer and/or tumor cells.

[0014] The isolated nucleic acid or vector disclosed above encoding the CAR can comprise, or alternatively consist essentially of, or yet further consist of any CAR disclosed herein. In one example, the isolated nucleic acid or the vector of this disclosure encoding the CAR further comprises, or alternatively consists essentially of, or yet further consists of a signaling domain. In another example, the isolated nucleic acid or the vector encoding the CAR further comprises an inducible or a constitutively active element. In one example, the inducible or the constitutively active element controls the expression of a polynucleotide encoding an immunoregulatory molecule or a cytokine. The immunoregulatory molecule or cytokine can comprise, or alternatively consist essentially of, or yet further consist of one or more of B7.1, CCL19, CCL21, CD40L, CD137L, GITRL, GM-CSF, IL-12, IL-2, low-toxicity IL-2, IL-15, IL-18, IL-21, LEC, and/or OX40L. In another example, the immunoregulatory molecule or cytokine can comprise, or alternatively consist essentially of, or yet further consist of IL-12 and/or GM-CSF; and/or IL-12 and/or one or more of IL-2 and low-toxicity IL-2; and/or IL-12 and/or IL-15; and/or IL-12 and/or IL-21; IL-12 and/or B7.1; and/or IL-12 and/or OX40L; and/or IL-12 and/or CD40L; and/or IL-12 and/or GITRL; and/or IL-12 and/or IL-18; and/or one or more of IL-2 and low-toxicity IL-2 and one or more of CCL19, CCL21, and LEC; and/or IL-15 and one or more of CCL19, CCL21, and LEC; and/or IL-21 and one or more of CCL19, CCL21, and LEC; and/or GM-CSF and one or more of CCL19, CCL21, and LEC; and/or OX40L and one or more of CCL19, CCL21, and LEC; and/or CD137L and one or more of CCL19, CCL21, and LEC; and/or comprises B7.1 and one or more of CCL19, CCL21, and LEC; and/or CD40L and one or more of CCL19, CCL21, and LEC; and/or GITRL and one or more of CCL19, CCL21, and LEC.

[0015] In any of the above examples, each of the polynucleotides may be operatively linked to a regulatory polynucleotide, optionally a promoter and/or enhancer. In some examples, the

polynucleotide encoding an antibody or antigen binding fragment thereof comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1 is

operatively linked to a promoter and/or enhancer which allows for low, moderate or high expression, or yet further overexpression of the antibody or antigen binding fragment thereof.

[0016] In any of the above examples, the polynucleotide encoding the CAR may comprise, or alternatively consist essentially of, or further consist of a polynucleotide encoding: (a) an antigen binding domain of a FLT3 antibody; (b) a CD8 α hinge domain; (c) a CD8 α transmembrane domain; (d) a CD28 costimulatory signaling region and/or a 4-1BB costimulatory signaling region; and (e) a CD3 zeta (ξ) signaling domain. Non-limiting examples of the FLT3 antibody comprise, or alternatively consist essentially of, or further consist of a heavy chain variable region comprising: a CDHR1 having the amino acid sequence (SYWMH) or (NYGLH) or an equivalent of each thereof, a CDHR2 having the amino acid sequence (EIDPSDSYKDYNQKFKD) or (VIWSGGSTDYNAAFIS) or an equivalent of each thereof, and a CDHR3 having the amino acid sequence (AITTTPFDF) or (GGIYYANHYYAMDY) or an equivalent of each thereof, and/or a light chain variable region comprising: a CDLR1 having the amino acid sequence (RASQSISSNNLH) or (KSSQSLLNSGNQKNYM) or an equivalent of each thereof, a CDLR2 having the amino acid sequence (YASQSISS) or (GASTRES) or an equivalent of each thereof, and a CDLR3 having the amino acid sequence (QQSNTWPYT) or (QNDHSYPLT) or an equivalent of each thereof.

[0017] Non-limiting examples of the antibody comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1 or antigen binding fragment thereof include a PD-1 antagonist or agonist and/or a PD-L1 antagonist or agonist. In certain examples, the antibody or antigen binding fragment thereof comprises, or alternatively consists essentially thereof, or further consists of the relevant CDR regions of an antibody to PD-1 and/or an antibody to PD-L1, or an equivalent of each thereof. In some examples, the antibody or antigen binding fragment thereof comprises, or alternatively consists essentially thereof, or further consists of the heavy chain and/or light chain variable region of an antibody to PD-1 and/or PD-L1, and/or an equivalent of each thereof. In some examples, the antibody or antigen binding fragment thereof comprises, or consists essentially of, or yet further consists of a single chain variable fragment (scFv) comprising an antigen binding domain of a PD-1 antibody and/or a single chain variable fragment (scFv) comprising an antigen binding domain of a PD-L1

antibody, and/or an equivalent each thereof. In some examples, the antibody comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1 or antigen binding fragment thereof comprises, or consists essentially of, or yet further consists of a single chain variable fragment (scFv) comprising an antigen binding domain of a PD-L1 antibody.

[0018] In some examples, the antibody or antigen binding fragment is a bispecific antibody. Non-limiting examples of the bispecific antibody include the relevant CDR regions of an antibody to PD-1 and an antibody to PD-L1, or an equivalent of each thereof, and, optionally a linker. Additional non-limiting examples include the relevant CDR regions of an antibody to PD-1 and an antibody to PD-L1, or an equivalent of each thereof and, optionally a linker. An additional example includes the heavy chain and/or light chain variable region of an antibody to PD-1 and/or PD-L1, and an equivalent of each thereof and, optionally a linker. A yet further example includes a single chain variable fragment (scFv) comprising, or alternatively consisting essentially of, or yet further consisting of, an antigen binding domain of a PD-1 antibody and a single chain variable fragment (scFv) comprising, or alternatively consisting essentially of, or yet further consisting of, an antigen binding domain of a PD-L1 antibody, and/or an equivalent each thereof and, optionally a linker.

[0019] Also provided herein is an isolated cell comprising, or alternatively consisting essentially of, or consisting of any one or more of the antibodies, the vectors and/or isolated polynucleotides of any one of the above examples, alone or in combination with each other. The cell can be a prokaryotic or a eukaryotic cell, and is optionally selected from an animal cell, a mammalian cell, a bovine cell, a feline cell, a canine cell, a murine cell, an equine cell or a human cell. In some examples, the eukaryotic cell is an immune cell, optionally a T-cell, a B-cell, a NK-cell, a dendritic cell, a myeloid cell, a monocyte, or a macrophage. In further examples, the immune cell is a T-cell, which may be optionally modified to suppress endogenous TCR expression, using any appropriate system, e.g., a CRISPR system. In any of the above examples relating to an isolated cell, the isolated cell expresses the CAR on the cell surface and secretes the antibody comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1 or antigen binding fragment thereof, optionally the bispecific antibody.

[0020] Still further examples relate to a composition comprising any one or more of the vectors and/or isolated nucleic acids and/or isolated cells as disclosed herein and, optionally, a carrier that is optionally a pharmaceutically acceptable carrier. Also provided herein is a

composition comprising, or alternatively consisting essentially of, or yet further consisting of the isolated nucleic acid or vector, the antibody, the antigen binding fragment, the polypeptide, the isolated cell and/or the population of cells disclosed herein, and, optionally, a pharmaceutically acceptable carrier. In further examples, the composition comprises, or alternatively consisting essentially of, or yet further consisting of, an effective amount of a FLT3 inhibitor. In some examples, the effective amount is an amount effective to increase FLT3 surface expression on cancer or tumor cells.

[0021] This disclosure also provides an isolated complex comprising any of the isolated cells expressing the CAR bound to: (i) a cell expressing FLT3 and/or PD-1 and/or PD-L1 and/or a fragment thereof and/or, (ii) FLT3 and/or PD-1 and/or PD-L1 and/or a fragment thereof.

[0022] Methods to produce a CAR expressing cell is also disclosed. The methods comprise transducing an isolated cell with a polynucleotide or a vector as disclosed herein. In some examples, the isolated cells are selected from a group consisting of T-cells, B-cells, NK-cells, dendritic cells, myeloid cells, monocytes, or macrophages. In some examples, the isolated cells are selected from a group consisting of T-cells, B-cells, NK-cells, dendritic cells, myeloid cells, monocytes, or macrophages. In further examples, the isolated cells are T-cells, which are optionally modified to suppress endogenous TCR expression. In further examples, the isolated cells are NK cells. The cells can be isolated from any appropriate species, e.g., mammalian such as a human cell.

[0023] The CAR expressing cells are useful diagnostically and therapeutically. In one example, the cells are useful in a method of inhibiting the growth of a cancer cell or tumor each expressing FLT3, optionally wherein the cell is a FLT3 acute myeloid leukemia (AML) cell. This disclosure also relates to methods of inhibiting the growth of a cancer or tumor expressing FLT3, optionally acute myeloid leukemia (AML) in a subject, comprising, or alternatively consisting essentially of, or yet further consisting of contacting the cancer or tumor with the isolated cell of or the composition of this disclosure. In one example, the method of inhibiting the growth of a cancer or tumor expressing FLT3 in a subject, optionally AML, comprises, or alternatively consists essentially of, or yet further consists of measuring expression of PD-1 and/or PD-L1 in the subject and administering the isolated cell, the antibody, the antigen binding fragment and/or the composition of this disclosure to a subject expressing PD-1 and/or PD-L1. Further disclosed herein are methods of inhibiting the

growth of a cancer or tumor in a subject, optionally AML, comprising, or alternatively consisting essentially of, or yet further consisting of measuring expression of PD-1 and/or PD-L1 in the subject and administering the antibody, the antigen binding fragment and/or the composition to a subject expressing PD-1 and/or PD-L1. The methods may comprise, or alternatively consist essentially of, or yet further consist of contacting the cancer cell or tumor with any of the isolated cells or compositions disclosed herein above. The contacting may be in vitro or in vivo. In some examples, the contacting is in vivo and the isolated cells are autologous and/or allogeneic to a subject being treated. In further examples, the method further comprises, or consists essentially of, or yet further consists of, administering to the subject an effective amount of cytoreductive therapy, optionally comprising or selected from the group consisting of chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy. In some examples, the subject being treated is a human patient.

[0024] Further provided herein are antibodies comprising, or alternatively consisting essentially of, or yet further consisting of a single chain variable fragment sequence (scFv) comprising, or alternatively consisting essentially of, or yet further consisting of an amino acid sequence of (Q V Q L V Q S G V E V K K P G A S V K V S C K A S G Y T F T N Y Y M Y W V R Q A P G Q G L E W M G G I N P S N G G T N F N E K F K N R V T L T T D S S T T T A Y M E L K S L Q F D D T A V Y Y C A R R D Y R F D M G F D Y W G Q G T T V T V S S G G G G S G G G G S G G G G S D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y C Q Q Y L Y H P A T F G Q G T K V E I K R) or an equivalent thereof. In one example, the antibody comprising, or alternatively consisting essentially of, or yet further consisting of a single chain variable fragment sequence (scFv) is encoded by the nucleotide sequence comprising, or alternatively consisting essentially of, or yet further consisting of a nucleic acid sequence of:

(CAGGTCCAATTGGTACAGAGCGGCGTCGAAGTAAAGAAGCCTGGAGCCAGCGT
TAAAGTTTCTTGCAAGGCTTCAGGATATACTTTCACTAACTACTATATGTACTGG
GTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCT
AACGGCGGCACTAACTTTAACGAAAAATTTAAAAATAGGGTGACCCTCACAAC
TCAAGTACGACTACAGCATACTGGAACCTCAAATCTCTCCAATTCGATGACA
CGGCTGTCTATTATTGCGCGAGAAGAGACTATCGCTTCGATATGGGGTTTGATTA
TTGGGGGCAAGGTACTACGGTTACCGTCAGCTCCGGGGGTGGCGGCTCCGGCGG
CGGTGGGTCAGGTGGAGGAGGGTCTGACATTCAGATGACGCAATCCCCAAGCTC

TCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGAT
GTGTCAACCGCTGTGCGCTGGTACCAACAGAAGCCTGGGAAGGCCCTAAGCTTC
TCATCTACTCAGCTTCTTTTCTGTACTCAGGGGTACCGTCTAGATTCTCAGGATCC
GGTAGTGGGACGGACTTCACATTGACCATAAGTTCCTTGCAGCCTGAGGATTTTCG
CTACATATTATTGCCAACAGTACCTTTACCATCCTGCCACTTTTGGCCAGGGTACT
AAGGTCGAGATCAAACGG) or an equivalent thereof.

[0025] Also described herein are antibodies comprising, or alternatively consisting essentially of, or yet further consisting of a single chain variable fragment sequence (scFv) comprising, or alternatively consisting essentially of, or yet further consisting of an amino acid sequence of:

(EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAVISPYG
GSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQ
GTLVTVSAGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGYS
YLHWYQQKPGEAPRLLIYLAASYLESGVPARFSGSGSGTDFTLTISSELPEDFAVYYCQ
HSRDLPLTFGGGTKVEIK) or an equivalent thereof.

[0026] In one example, the antibody comprises, or alternatively consists essentially of, or yet further consists of a single chain variable fragment sequence (scFv) encoded by the nucleotide sequence comprising, or alternatively consisting essentially of, or yet further consisting of a nucleic acid sequence of:

(GAAGTTCAGTTGGTCGAGTCAGGAGGAGGCCTGGTGCAACCCGGGGGCTCACTC
CGGTTGTCCTGTGCTGCTTCAGGATTTACGTTTTCTGACTCATGGATACATTGGGT
GCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGG
GGGTTCCACCTACTATGCTGATTACAGTAAAAGGACGGTTCCTATAAGCGCGGAT
ACAAGTAAGAATACTGCCTATCTTCAAATGAATTCTCTTCGCGCCGAGGATACAG
CGGTATATTATTGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGCA
GGGTACTCTTGTGACCGTTAGTGCGGGAGGTGGTGGCAGCGGTGGAGGCGGCTC
CGGGGGTGGTGGTTCAGAAATTGTCCTGACTCAATCCCCTGCCACATTGAGTTTG
AGCCCAGGAGAGAGAGCAACTCTGTGTCATGCCGGGCGTCAAAAGGTGTCAGTACG
TCAGGCTACTCCTATCTTCATTGGTATCAGCAGAAACCGGGAGAAGCGCCGCGCC
TTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTAGTGG
GAGTGGGTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGA
CTTCGCGGTTTACTATTGCCAACATTACGCGATTTGCCCCTCACCTTCGGCGGTG
GAACGAAGGTTGAAATAAAA) or an equivalent thereof.

[0027] Also described herein is a bispecific antibody comprising, or alternatively consisting essentially of, or yet further consisting of a single chain variable fragment sequence (scFv) comprising, or alternatively consisting essentially of, or yet further consisting of an amino acid sequence of: (Q V Q L V Q S G V E V K K P G A S V K V S C K A S G Y T F T N Y Y M Y W V R Q A P G Q G L E W M G G I N P S N G G T N F N E K F K N R V T L T T D S S T T T A Y M E L K S L Q F D D T A V Y Y C A R R D Y R F D M G F D Y W G Q G T T V T V S S G G G G S G G G G S G G G G S D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y C Q Q Y L Y H P A T F G Q G T K V E I K R) and/or

(EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAVWISPYG GSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQ GTLVTVSAGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGYS YLHWYQQKPGEAPRLLIYLA SYLESGV PARFSGSGSGTDFTLTISSELPEDFAVYYCQ HSRDLPLTFGGGTKVEIK) or an equivalent of each thereof.

[0028] In one example, the bispecific antibody comprises, or alternatively consists essentially of, or yet further consists of a single chain variable fragment sequence (scFv) encoded by the nucleotide sequence comprising, or alternatively consisting essentially of, or yet further consisting of a nucleic acid sequence of:

(CAGGTCCAATTGGTACAGAGCGGCGTCTGAAGTAAAGAAGCCTGGAGCCAGCGT TAAAGTTTCTTGCAAGGCTTCAGGATATACTTTCACTAACTACTATATGTACTGG GTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCT AACGGCGGCACTAACTTTAACGAAAAATTTAAAAATAGGGTGACCCTCACAACT GACTCAAGTACGACTACAGCATAACATGGAAC TCAAATCTCTCCAATTCGATGACA CGGCTGTCTATTATTGCGCGAGAAGAGACTATCGCTTCGATATGGGGTTTGATTA TTGGGGGCAAGGTACTACGGTTACCGTCAGCTCCGGGGGTGGCGGCTCCGGCGG CGGTGGGTCAGGTGGAGGAGGGTCTGACATTCAGATGACGCAATCCCCAAGCTC TCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGAT GTGTCAACCGCTGTGCGCTGGTACCAACAGAAGCCTGGGAAGGCCCTAAGCTTC TCATCTACTCAGCTTCTTTTCTGTACTCAGGGGTACCGTCTAGATTCTCAGGATCC GGTAGTGGGACGGACTTCACATTGACCATAAGTTCCTTGCAGCCTGAGGATTTCG CTACATATTATTGCCAACAGTACCTTTACCATCCTGCCACTTTTGGCCAGGGTACT AAGGTCGAGATCAAACGG) and/or

(GAAGTTCAGTTGGTCGAGTCAGGAGGAGGCCTGGTGCAACCCGGGGGCTCACTC
CGGTTGTCCTGTGCTGCTTCAGGATTTACGTTTTCTGACTCATGGATACATTGGGT
GCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGG
GGGTTCCACCTACTATGCTGATTCAGTAAAAGGACGGTTCCTATAAGCGCGGAT
ACAAGTAAGAATACTGCCTATCTTCAAATGAATTCTCTTCGCGCCGAGGATACAG
CGGTATATTATTGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGCA
GGGTACTCTTGTGACCGTTAGTGCGGGAGGTGGTGGCAGCGGTGGAGGCGGCTC
CGGGGGTGGTGGTTCAGAAATTGTCCTGACTCAATCCCCTGCCACATTGAGTTTG
AGCCCAGGAGAGAGAGCAACTCTGTCATGCCGGGCGTCAAAGGTGTCAGTACG
TCAGGCTACTCCTATCTTCATTGGTATCAGCAGAAACCGGGAGAAGCGCCGCGCC
TTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTAGTGG
GAGTGGGTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGA
CTTCGCGGTTTACTATTGCCAACATTCACGCGATTTGCCCTCACCTTCGGCGGTG
GAACGAAGGTTGAAATAAAA) or an equivalent thereof.

[0029] The antibody can be an IgA, an IgD, an IgE, an IgG or an IgM antibody. In one particular example, the antibody comprises, or alternatively consists essentially of, or yet further consists of a constant region. The constant region may comprise, or alternatively consist essentially of, or yet further consist of an IgA, an IgD, an IgE, an IgG or an IgM constant region. In some examples, the constant region is an IgG1 constant region or an Ig kappa constant region.

[0030] This disclosure also relates to antibodies that competes for binding with the antibodies described herein. The antibody of this disclosure may be a polyclonal, a monoclonal or a humanized antibody. Also provided herein are the antigen binding fragments of the antibodies of this disclosure. The antigen binding fragment may be selected from the group consisting of Fab, F(ab')₂, Fab', scFv, and Fv. In one example, the antigen binding fragment may comprise, or alternatively consist essentially of, or yet further consist of an amino acid sequence of: (Q V Q L V Q S G V E V K K P G A S V K V S C K A S G Y T F T N Y Y M Y W V R Q A P G Q G L E W M G G I N P S N G G T N F N E K F K N R V T L T T D S S T T T A Y M E L K S L Q F D D T A V Y Y C A R R D Y R F D M G F D Y W G Q G T T V T V S S G G G G S G G G G S G G G G S D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y C Q Q Y L Y H P A T F G Q G T K V E I K R) or an equivalent of each thereof. The antigen binding fragment can be encoded by

the nucleotide sequence comprising, or alternatively consisting essentially of, or yet further consisting of a nucleic acid sequence of:

(CAGGTCCAATTGGTACAGAGCGGCGTCGAAGTAAAGAAGCCTGGAGCCAGCGT
TAAAGTTTCTTGCAAGGCTTCAGGATATACTTTCACTAACTACTATATGTACTGG
GTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCT
AACGGCGGCACTAACTTTAACGAAAAATTTAAAAATAGGGTGACCCTCACAACT
GACTCAAGTACGACTACAGCATAACATGGAACCTCAAATCTCTCCAATTCGATGACA
CGGCTGTCTATTATTGCGCGAGAAGAGACTATCGCTTCGATATGGGGTTTGATTA
TTGGGGGCAAGGTACTACGGTTACCGTCAGCTCCGGGGGTGGCGGCTCCGGCGG
CGGTGGGTGAGGTGGAGGAGGGTCTGACATTCAGATGACGCAATCCCCAAGCTC
TCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGAT
GTGTCAACCGCTGTGCGCTGGTACCAACAGAAGCCTGGGAAGGCCCTAAGCTTC
TCATCTACTCAGCTTCTTTTCTGTACTCAGGGGTACCGTCTAGATTCTCAGGATCC
GGTAGTGGGACGGACTTCACATTGACCATAAGTTCCTTGCAGCCTGAGGATTTTCG
CTACATATTATTGCCAACAGTACCTTTACCATCCTGCCACTTTTGGCCAGGGTACT
AAGGTGAGATCAAACGG) or an equivalent of each thereof.

[0031] In another example, the antigen binding fragment may comprise, or alternatively consist essentially of, or yet further consist of an amino acid sequence of:

(EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAVISPYG
GSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWQG
GTLVTVSAGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGYS
YLHWYQQKPGEAPRLLIYLA SYLESVGPARGSGSGTDFTLTISLEPEDFAVYYCQ
HSRDLPLTFGGGTKVEIK) or an equivalent of each thereof. The antigen binding fragment can be encoded by the nucleotide sequence comprising, or alternatively consisting essentially of, or yet further consisting of:

(GAAGTTCAGTTGGTCGAGTCAGGAGGAGGCCTGGTGCAACCCGGGGGCTCACTC
CGGTTGTCCTGTGCTGCTTCAGGATTTACGTTTTCTGACTCATGGATACATTGGGT
GCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGG
GGGTTCCACCTACTATGCTGATTCAGTAAAAGGACGGTTCCTATAAGCGCGGAT
ACAAGTAAGAATACTGCCTATCTTCAAATGAATTCTCTTCGCGCCGAGGATACAG
CGGTATATTATTGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGCA
GGGTACTCTTGTGACCGTTAGTGCGGGAGGTGGTGGCAGCGGTGGAGGCGGCTC
CGGGGGTGGTGGTTCAGAAATTGTCCTGACTCAATCCCCTGCCACATTGAGTTTG

AGCCCAGGAGAGAGAGCAACTCTGTCATGCCGGGCGTCAAAAGGTGTCAGTACG
TCAGGCTACTCCTATCTTCATTGGTATCAGCAGAAACCGGGAGAAGCGCCGCGCC
TTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTAGTGG
GAGTGGGTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGA
CTTCGCGGTTTACTATTGCCAACATTCACGCGATTTGCCCTCACCTTCGGCGGTG
GAACGAAGGTTGAAATAAAA) or an equivalent of each thereof.

[0032] Also described herein are polypeptides comprising, or alternatively consisting essentially of, or yet further consisting of an amino acid sequence of any one of: (Q V Q L V Q S G V E V K K P G A S V K V S C K A S G Y T F T N Y Y M Y W V R Q A P G Q G L E W M G G I N P S N G G T N F N E K F K N R V T L T T D S S T T T A Y M E L K S L Q F D D T A V Y Y C A R R D Y R F D M G F D Y W G Q G T T V T V S S G G G G S G G G S G G G G S D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y C Q Q Y L Y H P A T F G Q G T K V E I K R) or (EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYG GSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQ GTLVTVSAGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGYS YLHWYQQKPGEAPRLLIYLA SYLES GVPARFSGSGSGTDFTLTIS SLEPEDFAVYYCQ HSRDLPLTFGGGTKVEIK) or an equivalent of each thereof.

[0033] This disclosure further relates to isolated nucleic acids comprising, or alternatively consisting essentially of, or yet further consisting of a nucleic acid sequence of: (CAGGTCCAATTGGTACAGAGCGGCGTCGAAGTAAAGAAGCCTGGAGCCAGCGT TAAAGTTTCTTGCAAGGCTTCAGGATATACTTTCACTAACTACTATATGTACTGG GTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCT AACGGCGGCACTAACTTTAACGAAAAATTTAAAAATAGGGTGACCCTCACA ACT GACTCAAGTACGACTACAGCATA CATGGA ACTCAAATCTCTCCAATTCGATGACA CGGCTGTCTATTATTGCGCGAGAAGAGACTATCGCTTCGATATGGGGTTTGATTA TTGGGGGCAAGGTACTACGGTTACCGTCAGCTCCGGGGGTGGCGGCTCCGGCGG CGGTGGGTCAGGTGGAGGAGGGTCTGACATTCAGATGACGCAATCCCCAAGCTC TCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGAT GTGTCAACCGCTGTGCGCTGGTACCAACAGAAGCCTGGGAAGGCCCTAAGCTTC TCATCTACTCAGCTTCTTTTCTGTACTCAGGGGTACCGTCTAGATTCTCAGGATCC

GGTAGTGGGACGGACTTCACATTGACCATAAGTTCCTTGCAGCCTGAGGATTTCTG
CTACATATTATTGCCAACAGTACCTTTACCATCCTGCCACTTTTGGCCAGGGTACT
AAGGTCGAGATCAAACGG) or
(GAAGTTCAGTTGGTCGAGTCAGGAGGAGGCCTGGTGCAACCCGGGGGCTCACTC
CGGTTGTCCTGTGCTGCTTCAGGATTTACGTTTTCTGACTCATGGATACATTGGGT
GCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGG
GGGTTCCACCTACTATGCTGATTCAAGTAAAAGGACGGTTCCTATAAGCGCGGAT
ACAAGTAAGAATACTGCCTATCTTCAAATGAATTCTCTTCGCGCCGAGGATACAG
CGGTATATTATTGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGCA
GGGTACTCTTGTGACCGTTAGTGCGGGAGGTGGTGGCAGCGGTGGAGGCGGCTC
CGGGGGTGGTGGTTCAGAAATTGTCCTGACTCAATCCCCTGCCACATTGAGTTTG
AGCCAGGAGAGAGAGCAACTCTGTCATGCCGGGCGTCAAAAGGTGTCAGTACG
TCAGGCTACTCCTATCTTCATTGGTATCAGCAGAAACCGGGAGAAGCGCCGCGCC
TTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTAGTGG
GAGTGGGTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGA
CTTCGCGGTTTACTATTGCCAACATTCACGCGATTTGCCCCTCACCTTCGGCGGTG
GAACGAAGGTTGAAATAAAA) or an equivalent of each thereof.

[0034] Further disclosed herein are methods of preparing the antibodies of this disclosure.

[0035] Also provided herein are the antigen binding fragments of the antibodies of this disclosure. Further described herein are polypeptides comprising, or alternatively consisting essentially of, or yet further consisting of an amino acid sequence of: (Q V Q L V Q S G V E V K K P G A S V K V S C K A S G Y T F T N Y Y M Y W V R Q A P G Q G L E W M G G I N P S N G G T N F N E K F K N R V T L T T D S S T T T A Y M E L K S L Q F D D T A V Y Y C A R R D Y R F D M G F D Y W G Q G T T V T V S S G G G G S G G G G S G G G S D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y C Q Q Y L Y H P A T F G Q G T K V E I K R) or
(EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAVWISPYG GSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWQG GTLVTVSAGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGYS YLHWYQQKPGEAPRLLIYLA SYLES GVPARFSGSGSGTDFTLTISSELPEDFAVYYCQ HSRDLPLTFGGGTKVEIK) or an equivalent of each thereof.

[0036] This disclosure further relates to isolated nucleic acids comprising, or alternatively consisting essentially of, or yet further consisting of a nucleic acid sequence of:

(CAGGTCCAATTGGTACAGAGCGGCGTCGAAGTAAAGAAGCCTGGAGCCAGCGT
TAAAGTTTCTTGCAAGGCTTCAGGATATACTTTCACTAACTACTATATGTACTGG
GTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCT
AACGGCGGCACTAACTTTAACGAAAAATTTAAAAATAGGGTGACCCTCACAAC
GACTCAAGTACGACTACAGCATAACATGGAAC TCAAATCTCTCCAATTCGATGACA
CGGCTGTCTATTATTGCGCGAGAAGAGACTATCGCTTCGATATGGGGTTTGATTA
TTGGGGGCAAGGTACTACGGTTACCGTCAGCTCCGGGGGTGGCGGCTCCGGCGG
CGGTGGGTGTCAGGTGGAGGAGGGTCTGACATTCAGATGACGCAATCCCCAAGCTC
TCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGAT
GTGTCAACCGCTGTGCGCTGGTACCAACAGAAGCCTGGGAAGGCCCTAAGCTTC
TCATCTACTCAGCTTCTTTTCTGTACTCAGGGGTACCGTCTAGATTCTCAGGATCC
GGTAGTGGGACGGACTTCACATTGACCATAAGTTCCTTGCAGCCTGAGGATTTTCG
CTACATATTATTGCCAACAGTACCTTTACCATCCTGCCACTTTTGGCCAGGGTACT
AAGGTCGAGATCAAACGG) or

(GAAGTTCAGTTGGTCGAGTCAGGAGGAGGCCTGGTGCAACCCGGGGGCTCACTC
CGGTTGTCCTGTGCTGCTTCAGGATTTACGTTTTCTGACTCATGGATACATTGGGT
GCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGG
GGGTTCCACCTACTATGCTGATTCAGTAAAAGGACGGTTCCTATAAGCGCGGAT
ACAAGTAAGAATACTGCCTATCTTCAAATGAATTCTCTTCGCGCCGAGGATACAG
CGGTATATTATTGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGCA
GGGTACTCTTGTGACCGTTAGTGCGGGAGGTGGTGGCAGCGGTGGAGGCGGCTC
CGGGGGTGGTGGTTCAGAAATTGTCCTGACTCAATCCCCTGCCACATTGAGTTTG
AGCCCAGGAGAGAGAGCAACTCTGTCATGCCGGGCGTCAAAGGTGTCAGTACG
TCAGGCTACTCCTATCTTCATTGGTATCAGCAGAAACCGGGAGAAGCGCCGCGCC
TTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTAGTGG
GAGTGGGTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGA
CTTCGCGGTTTACTATTGCCAACATTCACGCGATTTGCCCCTCACCTTCGGCGGTG
GAACGAAGGTTGAAATAAAA) or an equivalent of each thereof.

[0037] Also disclosed herein are kits comprising, or alternatively consisting essentially of, or consisting of one or more of the above noted compositions and instructions for their use in the methods as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] **FIG. 1** shows the design of bicistronic FLT3 CAR with secretory PD-1-PD-L1 bispecific antibody (biAb). FLT3 CAR was driven by EF1 α promoter. PD-1-PD-L1 biAb was linked with CAR by T2A and led by a secretory signal peptide (SS). The whole cassette was flanked with long terminal repeats in a safe lentiviral construct.

[0039] **FIGS. 2A-2C** show enhanced cytotoxicity upon recognizing FLT3(+) AML cell lines. Cytotoxic activity of unmodified NK-92 cells, EV NK-92 cells, and FLT3 CAR NK-92 cells against: (**FIG. 2A**) FLT3(+) MOLM-13 (FLT3(+) EOL-1 or (FLT3(-) U937 cells; (**FIG. 2B**) FLT3(+) AML blasts from each of two patients using a ⁵¹Cr release assay. Target leukemic cells were labeled with ⁵¹Cr and co-cultured with NK-cells at the indicated effector/target ratios (E/T) in the wells of 96-well V-bottom plate at 37°C for 4 hours. Supernatants were harvested and the release of ⁵¹Cr was measured on TopCount counter (Canberra Packard). (**FIG. 2C**) Cytotoxicity of primary FLT3 CAR NK-cells against normal hematopoietic stem cells (HSCs) defined as CD34(+) and dendritic cells defined as CD123(+) from bone marrow of healthy donors. Topro3(+) cells were considered dead.

[0040] **FIGS. 3A-3C** show FLT3 CAR T and FLT3 NK-cells suppress *in vivo* growth of human AML and prolong the survival of AML-bearing mice. NSG mice were injected with FLT3(+) MOLM-13 cells (**FIG. 3A**) or FLT3(+) AML patient blasts (**FIG. 3B**). A week later T-cells, T-cells with empty vector or FLT3 CAR T-cells were intravenously injected. (**FIG. 3C**) For FLT3(+) CAR NK-cells, NSG mice were injected with FLT3(+) MOLM-13 cells and NK, NK with empty vector or FLT3 CAR NK (shown here as “FLT3 CAR”, or PBS were infused. Kaplan-Meier curves were plotted. Δ = continuous CR.

[0041] **FIGS. 4A-4D** show FLT-3 CAR NK-cells and expanded primary NK-cells expressed high level of PD-1. (**FIGS. 4A**) CAR NK-cells were in culture after transduction and stained for anti-PD-1 antibody. (**FIGS. 4B**) Primary NK-cells (without CAR

WHAT IS CLAIMED IS:

1. An isolated nucleic acid or a vector comprising:
 - a. a polynucleotide encoding a chimeric antigen receptor (CAR) comprising: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; and (d) an intracellular domain; and
 - b. a polynucleotide encoding a bispecific antibody or fragment thereof that recognizes, binds and antagonizes PD-1 and PD-L1.
2. The isolated nucleic acid or the vector of claim 1, wherein the CAR further comprises an inducible or a constitutively active element, optionally wherein the inducible or the constitutively active element controls the expression of a polynucleotide encoding an immunoregulatory molecule or a cytokine, further optionally wherein the immunoregulatory molecule or cytokine comprises one or more of B7.1, CCL19, CCL21, CD40L, CD137L, GITRL, GM-CSF, IL-12, IL-2, low-toxicity IL-2, IL-15, IL-18, IL-21, LEC, and/or OX40L, and yet further optionally wherein the immunoregulatory molecule or cytokine comprises IL-12 and/or GM-CSF; and/or IL-12 and/or one or more of IL-2 and low-toxicity IL-2; and/or IL-12 and/or IL-15; and/or IL-12 and/or IL-21; IL-12 and/or B7.1; and/or IL-12 and/or OX40L; and/or IL-12 and/or CD40L; and/or IL-12 and/or GITRL; and/or IL-12 and/or IL-18; and/or one or more of IL-2 and low-toxicity IL-2 and one or more of CCL19, CCL21, and LEC; and/or IL-15 and one or more of CCL19, CCL21, and LEC; and/or IL-21 and one or more of CCL19, CCL21, and LEC; and/or GM-CSF and one or more of CCL19, CCL21, and LEC; and/or OX40L and one or more of CCL19, CCL21, and LEC; and/or CD137L and one or more of CCL19, CCL21, and LEC; and/or comprises B7.1 and one or more of CCL19, CCL21, and LEC; and/or CD40L and one or more of CCL19, CCL21, and LEC; and/or GITRL and one or more of CCL19, CCL21, and LEC.
3. The isolated nucleic acid or vector of claim 1 or claim 2, wherein the CAR comprises one or more of:
 - (b1) a CD8 α hinge domain;
 - (c1) a CD8 α transmembrane domain;

(d1) the intracellular domain comprising a signaling domain that optionally comprises a CD3 zeta signaling domain;

(d2) the intracellular domain further comprising a costimulatory signaling region that optionally comprises a CD28 costimulatory signaling region or a 4-1BB costimulatory signaling region or both; or

(a1) the antigen binding domain of the FLT3 antibody that comprises

a heavy chain variable region comprising:

a CDHR1 comprising the amino acid sequence (SYWMH) or (NYGLH),

a CDHR2 comprising the amino acid sequence (EIDPSDSYKDYNQKFKD) or (VIWSGGSTDYNAAFIS), and

a CDHR3 comprising the amino acid sequence (AITTTPFDF) or (GGIYYANHYYAMDY), and/or

a light chain variable region comprising:

a CDLR1 comprising the amino acid sequence (RASQISNNLH) or (KSSQSLLNSGNQKNYM) ,

a CDLR2 comprising the amino acid sequence (YASQIS) or (GASTRES), and

a CDLR3 comprising the amino acid sequence (QQSNTWPYT) or (QNDHSYPLT) .

4. The isolated nucleic acid or vector of any one of claims 1 to 3, wherein the bispecific antibody or the antigen binding fragment thereof comprises one or more of:

(a) a PD-1 antagonist and a PD-L1 antagonist,

(b) CDR regions of an antibody to PD-1 and PD-L1, and/or,

(c) a heavy chain and a light chain variable region of an antibody to PD-1 and PD-L1,

or

(d) a single chain variable fragment (scFv) comprising the antigen binding domain of a PD-1 antibody and a single chain variable fragment (scFv) comprising an antigen binding domain of a PD-L1 antibody;

further optionally comprises a linker,

further optionally wherein the bispecific antibody thereof comprises CDR regions of an antibody to PD-1 and PD-L1, and, optionally, further comprises a linker,

further optionally wherein the bispecific antibody comprises a heavy chain and light chain variable region of an antibody to PD-1 and PD-L1 and, optionally, further comprises a linker, or

further optionally wherein the bispecific antibody comprises a single chain variable fragment (scFv) comprising an antigen binding domain of a PD-1 antibody and a single chain variable fragment (scFv) comprising an antigen binding domain of a PD-L1 antibody and, optionally, further comprises a linker.

5. The isolated nucleic acid or vector of any one of claims 1 to 4, further comprising a promoter or enhancer or both operatively linked to the polynucleotide encoding the antibody or the antigen binding fragment that recognizes and binds PD-1 and/or PD-L1.

6. The vector of any one of claims 1 to 5, wherein the vector is a plasmid or wherein the vector is a viral vector optionally selected from a retroviral vector, a lentiviral vector, an adenoviral vector, or an adeno-associated viral vector, and further optionally wherein the vector is bicistronic.

7. An isolated cell comprising the isolated nucleic acid of any one of claims 1 to 5, the vector of any one of claims 1 to 6, optionally wherein the cell is a prokaryotic cell or wherein the cell is a eukaryotic cell, further optionally wherein the eukaryotic cell is selected from an animal cell, a mammalian cell, a bovine cell, a feline cell, a canine cell, a murine cell, an equine cell or a human cell, yet further optionally wherein the eukaryotic cell is an immune cell, optionally a T-cell, a B-cell, a NK-cell, a dendritic cell, a myeloid cell, a monocyte, or a macrophage, and optionally an activated cell.

8. The isolated cell of claim 7, expressing the CAR and secreting the antibody.

9. An expanded population, optionally a substantially homogenous population, of cells of claim 7 or 8.

10. A composition or a kit comprising one or more of: the isolated nucleic acid of any one of claims 1 to 5 or 11, the vector of any one of claims 1 to 6, the isolated cell of claim 7 or claim 8, or the population of cells of claim 9; optionally a pharmaceutically acceptable carrier; further optionally an effective amount of an FLT3 inhibitor, optionally selected from the group consisting of gilteritinib, quizartinib, midostaurin, FF-10101, sorafenib, sunitinib, lestauritinib, or dovitinib; and yet further optionally instructions for use.

11. A method of producing a CAR expressing cell comprising transducing an isolated cell with the isolated nucleic acid of any one of claims 1 to 5 or the vector of any one of claims 1 to 6, optionally wherein the isolated cells are selected from a group consisting of T-cells, B-cells, NK-cells, dendritic cells, myeloid cells, monocytes, or macrophages.

12. The isolated cell of claim 7 or claim 8, or the composition of claim 10 for use in inhibiting the growth of a cancer or tumor expressing FLT3, optionally acute myeloid leukemia (AML) in a subject, by contacting with the cancer or tumor, optionally wherein expression of PD-1 or PD-L1 or both is measured in the subject and the subject expressing PD-1 or PD-L1 or both is to be administered with one or more of the isolated cell of claim 7 or 8, the antibody or the antigen binding fragment of claim 10, or the composition of claim 12 to,

optionally wherein the contacting is to be in vivo;

optionally wherein the contacting is to be in vivo and the isolated cells are autologous to the subject being treated;

optionally wherein the contacting is to be in vivo and the isolated cells are allogeneic to the subject being treated;

optionally wherein the subject is to be further administered with an effective amount of a cytoreductive therapy, optionally comprising chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy; and

optionally wherein the subject is a human patient.

13. The isolated cell, the antibody or the antigen binding fragment or the composition for use of claim 12, wherein the subject is to be further administered with an effective amount of an FLT3 inhibitor, optionally selected from the group consisting of gilteritinib, quizartinib, midostaurin, FF-10101, sorafenib, sunitinib, lestauritinib, or dovitinib.