

human antibody agents, multi-specific binding agents (e.g., bi-specific antibodies) and chimeric antigen receptors effectively mediate killing of cancer cells characterized by CD19 expression (e.g., lymphomas and/or leukemias).

[004a] In one aspect, provided herein is an antibody or antibody fragment that specifically binds human cluster of differentiation 19 (CD19), the antibody or antibody fragment comprising:

heavy chain-complementarity determining region 1 (HC-CDR1) of SEQ ID NO: 151, heavy chain-complementarity determining region 2 (HC-CDR2) of SEQ ID NO: 152, and heavy chain-complementarity determining region 3 (HC-CDR3) of SEQ ID NO: 153, and

light chain-complementarity determining region 1 (LC-CDR 1) of SEQ ID NO: 259,

light chain-complementarity determining region 2 (LC-CDR2) of SEQ ID NO: 260, and

light chain-complementarity determining region 3 (LC-CDR3) of SEQ ID NO: 261,

wherein the antibody or antibody fragment may have one of the following substitutions (i) to (vi):

(i) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3;

(ii) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of E residue for the D residue at the 8th from the N-terminus of the amino acid sequence of SEQ ID NO:261 of LC-CDR3;

(iii) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of G residue for the D residue at the 8th from the N-terminus of the amino acid sequence of SEQ ID NO:261 of LC-CDR3;

(iv) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of T residue for the S residue at in the 6th from the N-terminus of the amino acid sequence of SEQ ID NO:261 of LC-CDR3;

(v) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of N residue for the Y residue at the 12th from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3; and

(vi) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3,

substitution of F residue for the Y residue at the 7th from the N-terminus of the amino acid sequence of SEQ ID NO: 151 of HC-CDR1, and

substitution of V residue for the A residue at the 1st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3.

[004b] In one aspect, provided herein is a bi-specific antibody comprising a first antigen-binding site and a second antigen-binding site, wherein the first antigen-binding site is from an antibody or antibody fragment as described herein, and the bi-specific antibody specifically binds human cluster of differentiation 19 (CD19) by the first antigen-binding site.

[004c] In one aspect, provided herein is a chimeric antigen receptor comprising an antigen-binding site of an antibody or antibody fragment as described herein and specifically binding human cluster of differentiation 19 (CD19).

[004d] In one aspect, provided herein is a nucleic acid molecule encoding, in whole, the antibody or antibody fragment as described herein, the bi-specific antibody of as described herein, or the chimeric antigen receptor as described herein.

[004e] In one aspect, provided herein is a vector comprising the nucleic acid molecule as described herein.

[004f] In one aspect, provided herein is cell comprising the nucleic acid molecule as described herein or the vector as described herein or expressing the antibody or antibody fragment as described herein, the bi-specific antibody as described herein, or the chimeric antigen receptor as described herein.

[004g] In one aspect, provided herein is an effector cell expressing the antibody or antibody fragment as described herein, the bi-specific antibody as described herein, or the chimeric antigen receptor as described herein.

[004h] In one aspect, provided herein is a pharmaceutical composition comprising the antibody or antibody fragment as described herein, the bi-specific antibody as described herein, the chimeric antigen receptor as described herein, the nucleic acid molecule as described herein, the vector as described herein, or the effector cell as described herein, and a pharmaceutically acceptable carrier or diluent.

[004i] In one aspect, provided herein is a use of a composition comprising the antibody or antibody fragment as described herein, the bi-specific antibody as described herein, the chimeric antigen receptor as described herein, the nucleic acid molecule as described herein, the vector as described herein, the effector cell as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a medical condition characterized by CD19 expression in a subject.

[004j] In one aspect, provided herein is a use of a composition comprising the antibody or antibody fragment as described herein, the bi-specific antibody as described herein, the chimeric antigen receptor as described herein, the nucleic acid molecule of as described herein, the vector as described herein, the effector cell as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer.

[004k] In one aspect, provided herein is a use of a medical composition comprising the antibody or antibody fragment as described herein, the bi-specific antibody as described herein, the chimeric antigen receptor as described herein, the nucleic acid molecule as described herein, the vector as described herein, the effector cell as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for inhibiting tumor growth or killing tumor cells.

[004l] In one aspect, provided herein is the antibody or antibody fragment as described herein, the bi-specific antibody as described herein, the chimeric antigen receptor as described herein, the nucleic acid molecule as described herein, the vector as described herein, the effector cell as described herein, or the pharmaceutical composition as described herein for use in therapy.

[005] Although embodiments employing antibody agents that contain human sequences (i.e., human heavy and light chain variable region sequences including human CDR sequences) are extensively discussed herein, the present invention also provides non-human antibody agents. In some embodiments, non-human antibody agents comprise human CDR sequences from an antibody agent as described herein and non-human framework sequences. Non-human framework sequences include, in some embodiments, any sequence that can be used for generating synthetic heavy and/or light chain variable regions using one or more human CDR sequences as described herein, including, e.g., mammals, e.g., mouse, rat, rabbit, pig, bovine (e.g., cow, bull, buffalo), deer, sheep, goat, chicken, cat, dog, ferret, primate (e.g., marmoset, rhesus monkey), etc. In some embodiments, a provided antibody agent includes an antibody agent generated by grafting one or more human CDR sequences as described herein onto a non-human framework sequence (e.g., a mouse or chicken framework sequence). In many embodiments, provided antibody agents are human antibody agents (e.g., a human monoclonal

antibody or fragment thereof, human antigen-binding protein or polypeptide, human multi-specific binding agent [e.g., a human bi-specific antibody], a human polypeptide having one or more structural components of a human immunoglobulin polypeptide).

[006] In some embodiments, the present invention provides an antibody agent that specifically binds human CD19, wherein the antibody agent comprises a heavy chain CDR1 (HC-CDR1), heavy chain CDR2 (HC-CDR2) and a heavy chain CDR3 (HC-CDR3), and a light chain CDR1 (LC-CDR1), light chain CDR2 (LC-CDR2) and a light chain CDR3 (LC-CDR3),

wherein the HC-CDR1 comprises G-X₁-X₂-F-X₃-S-X₄-X₅ (SEQ ID NO:291), and wherein X₁ is F, G, Y or V, X₂ is S or T, X₃ is S or T, X₄ is N or Y, and X₅ is A, W or Y;

wherein the HC-CDR2 comprises I-X₆-P-X₇-X₈-X₉-X₁₀-T (SEQ ID NO:292), and wherein X₆ is S, D or Y, X₇ is E, S, G or I, X₈ is D, F or V, X₉ is G or S, and X₁₀ is K, E, Y, D or T;

wherein the LC-CDR1 comprises S-S-N-X₁₁-G-X₁₂-X₁₃-X₁₄ (SEQ ID NO:293) or N-I-G-S-X₁₅-S (SEQ ID NO:294), and wherein X₁₁ is I or V, X₁₂ is N, S or T, X₁₃ is N, H or K, X₁₄ is Y, A or T, and X₁₅ is K or E; and/or

wherein the LC-CDR2 comprises X₁₆-X₁₇-X₁₈ (SEQ ID NO:295), and wherein X₁₆ is D, E, S, R or Y, X₁₇ is N or D, and X₁₈ is N, Y, S or D.

[007] In some embodiments, the present invention provides a human antibody agent that specifically binds human CD19, wherein the human antibody agent comprises one or more

CLAIMS

1. An antibody ~~agent~~ or antibody fragment that specifically binds human cluster of differentiation 19 (CD19₊), the antibody or antibody fragment comprising:
- heavy chain-complementarity determining region 1 (HC-CDR1) of SEQ ID NO: 151,
heavy chain-complementarity determining region 2 (HC-CDR2) of SEQ ID NO: 152,
and heavy chain-complementarity determining region 3 (HC-CDR3) of SEQ ID NO: 153, and
light chain-complementarity determining region 1 (LC-CDR 1) of SEQ ID NO: 259,
light chain-complementarity determining region 2 (LC-CDR2) of SEQ ID NO: 260, and
light chain-complementarity determining region 3 (LC-CDR3) of SEQ ID NO: 261,

wherein the antibody ~~agent comprises a heavy chain CDR1 (HC-CDR1), heavy chain CDR2 (HC-CDR2) and a heavy chain CDR3 (HC-CDR3), and a light chain CDR1 (LC-CDR1), light chain CDR2 (LC-CDR2) and a light chain~~ or antibody fragment may have one of the following substitutions (i) to (vi):

- (i) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3 ~~(LC-CDR3);~~

~~wherein the HC-CDR1 comprises G-X₁-X₂-F-X₃-S-X₄-X₅ (SEQ ID NO:291), and wherein X₁ is F, G, Y or V, X₂ is S or T, X₃ is S or T, X₄ is N or Y, and X₅ is A, W or Y;~~

~~wherein the HC-CDR2 comprises I-X₆-P-X₇-X₈-X₉-X₁₀-T (SEQ ID NO:292), and wherein X₆ is S, D or Y, X₇ is E, S, G or I, X₈ is D, F or V, X₉ is G or S, and X₁₀ is K, E, Y, D or T;~~

~~wherein the LC-CDR1 comprises S-S-N-X₁₁-G-X₁₂-X₁₃-X₁₄ (SEQ ID NO:293) or N-I-G-S-X₁₅-S (SEQ ID NO:294), and wherein X₁₁ is I or V, X₁₂ is N, S or T, X₁₃ is N, H or K, X₁₄ is Y, A or T, and X₁₅ is K or E; and/or~~

~~wherein the LC-CDR2 comprises X₁₆-X₁₇-X₁₈ (SEQ ID NO:295), and wherein X₁₆ is D, E, S, R or Y, X₁₇ is N or D, and X₁₈ is N, Y, S or D.~~

2. ~~An antibody agent that specifically binds human CD19, wherein the antibody agent comprises~~

~~at least one heavy chain CDR (HC-CDR) comprising a sequence that is at least 95% identical to any one of SEQ ID NOs:73-123, and/or~~

~~at least one light chain CDR (LC-CDR)~~ (ii) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of E residue for the D residue at the 8th from the N-terminus of the amino acid sequence of SEQ ID NO:261 of LC-CDR3;

(iii) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of G residue for the D residue at the 8th from the N-terminus of the amino acid sequence of SEQ ID NO:261 of LC-CDR3;

(iv) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of T residue for the S residue at in the 6th from the N-terminus of the amino acid sequence of SEQ ID NO:261 of LC-CDR3;

(v) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3, and

substitution of N residue for the Y residue at the 12th from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3; and

(vi) substitution of M residue for the L residue at the 21st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3,

substitution of F residue for the Y residue at the 7th from the N-terminus of the amino acid sequence of SEQ ID NO: 151 of HC-CDR1, and

substitution of V residue for the A residue at the 1st from the N-terminus of the amino acid sequence of SEQ ID NO: 153 of HC-CDR3.

2. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment may comprise the substitution (i), the substitution (ii), the substitution (iii) or the substitution (vi).

3. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment does not have the substitutions (i) to (vi).

4. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises the sequence of SEQ ID NO: 42 as an amino acid sequence comprising a sequence that is at least 95% identical to any one of SEQ ID NOs:181-231.

~~3. The antibody agent of claim 2, wherein the antibody agent comprises~~

~~(a) a HC-CDR1, HC-CDR2 and HC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:73, SEQ ID NO:74 and SEQ ID NO:75, respectively, and a LC-CDR1, LC-CDR2 and LC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:181, SEQ ID NO:182 and SEQ ID NO:183, respectively;~~

~~(b) a HC-CDR1, HC-CDR2 and HC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:76, SEQ ID NO:77 and SEQ ID NO:78, respectively, and a LC-CDR1, LC-CDR2 and LC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:184, SEQ ID NO:185 and SEQ ID NO:186, respectively;~~

~~(c) a HC-CDR1, HC-CDR2 and HC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:79, SEQ ID NO:80 and SEQ ID NO:81, respectively, and a LC-CDR1, LC-CDR2 and LC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:187, SEQ ID NO:188 and SEQ ID NO:189, respectively;~~

~~(d) a HC-CDR1, HC-CDR2 and HC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:82, SEQ ID NO:83 and SEQ ID NO:84, respectively, and a LC-CDR1, LC-CDR2 and LC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:190, SEQ ID NO:191 and SEQ ID NO:192, respectively;~~

~~(e) a HC-CDR1, HC-CDR2 and HC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:85, SEQ ID NO:86 and SEQ ID NO:87, respectively, and a LC-CDR1, LC-CDR2 and LC-CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:193, SEQ ID NO:194 and SEQ ID NO:195, respectively;~~

~~(f) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:196, SEQ ID NO:197 and SEQ ID NO:198, respectively;~~

~~(g) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:91, SEQ ID NO:92 and SEQ ID NO:93, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:199, SEQ ID NO:200 and SEQ ID NO:201, respectively;~~

~~(h) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:94, SEQ ID NO:95 and SEQ ID NO:96, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:202, SEQ ID NO:203 and SEQ ID NO:204, respectively;~~

~~(i) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:97, SEQ ID NO:98 and SEQ ID NO:99, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:205, SEQ ID NO:206 and SEQ ID NO:207, respectively;~~

~~(j) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:100, SEQ ID NO:101 and SEQ ID NO:102, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:208, SEQ ID NO:209 and SEQ ID NO:210, respectively;~~

~~(k) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:103, SEQ ID NO:104 and SEQ ID NO:105, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:211, SEQ ID NO:212 and SEQ ID NO:213, respectively;~~

~~(l) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that~~

is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:214, SEQ ID NO:215 and SEQ ID NO:216, respectively;

(m) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:109, SEQ ID NO:110 and SEQ ID NO:111, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:217, SEQ ID NO:218 and SEQ ID NO:219, respectively;

(n) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:112, SEQ ID NO:113 and SEQ ID NO:114, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:220, SEQ ID NO:221 and SEQ ID NO:222, respectively;

(o) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:115, SEQ ID NO:116 and SEQ ID NO:117, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:223, SEQ ID NO:224 and SEQ ID NO:225, respectively;

(p) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:118, SEQ ID NO:119 and SEQ ID NO:120, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:226, SEQ ID NO:227 and SEQ ID NO:228, respectively; or

(q) a HC CDR1, HC CDR2 and HC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:121, SEQ ID NO:122 and SEQ ID NO:123, respectively, and a LC CDR1, LC CDR2 and LC CDR3 that each have a sequence that is at least 95% identical to the amino acid sequences set forth in SEQ ID NO:229, SEQ ID NO:230 and SEQ ID NO:231, respectively.

4. — The antibody agent of claim 3, wherein the antibody agent comprises

(a) the HC CDRs of SEQ ID NO:73, SEQ ID NO:74 and SEQ ID NO:75, and the LC CDRs of SEQ ID NO:181, SEQ ID NO:182 and SEQ ID NO:183;

(b) the HC CDRs of SEQ ID NO:76, SEQ ID NO:77 and SEQ ID NO:78, and the LC CDRs of SEQ ID NO:184, SEQ ID NO:185 and SEQ ID NO:186;

~~(c) the HC CDRs of SEQ ID NO:79, SEQ ID NO:80 and SEQ ID NO:81 and the LC CDRs of SEQ ID NO:187, SEQ ID NO:188 and SEQ ID NO:189;~~

~~(d) the HC CDRs of SEQ ID NO:82, SEQ ID NO:83 and SEQ ID NO:84, and the LC CDRs of SEQ ID NO:190, SEQ ID NO:191 and SEQ ID NO:192;~~

~~(e) the HC CDRs of SEQ ID NO:85, SEQ ID NO:86 and SEQ ID NO:87, and the LC CDRs of SEQ ID NO:193, SEQ ID NO:194 and SEQ ID NO:195;~~

~~(f) the HC CDRs of SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90 and the LC CDRs of SEQ ID NO:196, SEQ ID NO:197 and SEQ ID NO:198;~~

~~(g) the HC CDRs of SEQ ID NO:91, SEQ ID NO:92 and SEQ ID NO:93, and the LC CDRs of SEQ ID NO:199, SEQ ID NO:200 and SEQ ID NO:201;~~

~~(h) the HC CDRs of SEQ ID NO:94, SEQ ID NO:95 and SEQ ID NO:96, and the LC CDRs of SEQ ID NO:202, SEQ ID NO:203 and SEQ ID NO:204;~~

~~(i) the HC CDRs of SEQ ID NO:97, SEQ ID NO:98 and SEQ ID NO:99, and the LC CDRs of SEQ ID NO:205, SEQ ID NO:206 and SEQ ID NO:207;~~

~~(j) the HC CDRs of SEQ ID NO:100, SEQ ID NO:101 and SEQ ID NO:102, and the LC CDRs of SEQ ID NO:208, SEQ ID NO:209 and SEQ ID NO:210;~~

~~(k) the HC CDRs of SEQ ID NO:103, SEQ ID NO:104 and SEQ ID NO:105, and the LC CDRs of SEQ ID NO:211, SEQ ID NO:212 and SEQ ID NO:213;~~

~~(l) the HC CDRs of SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108, and the LC CDRs of SEQ ID NO:214, SEQ ID NO:215 and SEQ ID NO:216;~~

~~(m) the HC CDRs of SEQ ID NO:109, SEQ ID NO:110 and SEQ ID NO:111, and the LC CDRs of SEQ ID NO:217, SEQ ID NO:218 and SEQ ID NO:219;~~

~~(n) the HC CDRs of SEQ ID NO:112, SEQ ID NO:113 and SEQ ID NO:114, and the LC CDRs of SEQ ID NO:220, SEQ ID NO:221 and SEQ ID NO:222;~~

~~(o) the HC CDRs of SEQ ID NO:115, SEQ ID NO:116 and SEQ ID NO:117, and the LC CDRs of SEQ ID NO:223, SEQ ID NO:224 and SEQ ID NO:225;~~

~~(p) the HC CDRs of SEQ ID NO:118, SEQ ID NO:119 and SEQ ID NO:120, and the LC CDRs of SEQ ID NO:226, SEQ ID NO:227 and SEQ ID NO:228; or~~

~~(q) the HC CDRs of SEQ ID NO:121, SEQ ID NO:122 and SEQ ID NO:123, and the LC CDRs of SEQ ID NO:229, SEQ ID NO:230 and SEQ ID NO:231.~~

5. An antibody agent that competes for binding CD19 with an antibody agent that comprises

~~(a) the HC CDRs of SEQ ID NO:73, SEQ ID NO:74 and SEQ ID NO:75, and the LC CDRs of SEQ ID NO:181, SEQ ID NO:182 and SEQ ID NO:183;~~

~~(b) the HC CDRs of SEQ ID NO:76, SEQ ID NO:77 and SEQ ID NO:78, and the LC CDRs of SEQ ID NO:184, SEQ ID NO:185 and SEQ ID NO:186;~~

~~(c) the HC CDRs of SEQ ID NO:79, SEQ ID NO:80 and SEQ ID NO:81 and the LC CDRs of SEQ ID NO:187, SEQ ID NO:188 and SEQ ID NO:189;~~

~~(d) the HC CDRs of SEQ ID NO:82, SEQ ID NO:83 and SEQ ID NO:84, and the LC CDRs of SEQ ID NO:190, SEQ ID NO:191 and SEQ ID NO:192;~~

~~(e) the HC CDRs of SEQ ID NO:85, SEQ ID NO:86 and SEQ ID NO:87, and the LC CDRs of SEQ ID NO:193, SEQ ID NO:194 and SEQ ID NO:195;~~

~~(f) the HC CDRs of SEQ ID NO:88, SEQ ID NO:89 and SEQ ID NO:90 and the LC CDRs of SEQ ID NO:196, SEQ ID NO:197 and SEQ ID NO:198;~~

~~(g) the HC CDRs of SEQ ID NO:91, SEQ ID NO:92 and SEQ ID NO:93, and the LC CDRs of SEQ ID NO:199, SEQ ID NO:200 and SEQ ID NO:201;~~

~~(h) the HC CDRs of SEQ ID NO:94, SEQ ID NO:95 and SEQ ID NO:96, and the LC CDRs of SEQ ID NO:202, SEQ ID NO:203 and SEQ ID NO:204;~~

~~(i) the HC CDRs of SEQ ID NO:97, SEQ ID NO:98 and SEQ ID NO:99, and the LC CDRs of SEQ ID NO:205, SEQ ID NO:206 and SEQ ID NO:207;~~

~~(j) the HC CDRs of SEQ ID NO:100, SEQ ID NO:101 and SEQ ID NO:102, and the LC CDRs of SEQ ID NO:208, SEQ ID NO:209 and SEQ ID NO:210;~~

~~(k) the HC CDRs of SEQ ID NO:103, SEQ ID NO:104 and SEQ ID NO:105, and the LC CDRs of SEQ ID NO:211, SEQ ID NO:212 and SEQ ID NO:213;~~

~~(l) the HC CDRs of SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108, and the LC CDRs of SEQ ID NO:214, SEQ ID NO:215 and SEQ ID NO:216;~~

~~(m) the HC CDRs of SEQ ID NO:109, SEQ ID NO:110 and SEQ ID NO:111, and the LC CDRs of SEQ ID NO:217, SEQ ID NO:218 and SEQ ID NO:219;~~

~~(n) the HC CDRs of SEQ ID NO:112, SEQ ID NO:113 and SEQ ID NO:114, and the LC CDRs of SEQ ID NO:220, SEQ ID NO:221 and SEQ ID NO:222;~~

~~(o) the HC CDRs of SEQ ID NO:115, SEQ ID NO:116 and SEQ ID NO:117, and the LC CDRs of SEQ ID NO:223, SEQ ID NO:224 and SEQ ID NO:225;~~

~~(p) the HC CDRs of SEQ ID NO:118, SEQ ID NO:119 and SEQ ID NO:120, and the LC CDRs of SEQ ID NO:226, SEQ ID NO:227 and SEQ ID NO:228; or~~

~~(q) the HC CDRs of SEQ ID NO:121, SEQ ID NO:122 and SEQ ID NO:123, and the LC CDRs of SEQ ID NO:229, SEQ ID NO:230 and SEQ ID NO:231.~~

~~6. An antibody agent that specifically binds human CD19, wherein the antibody agent comprises~~

~~a heavy chain variable region (HCVR) having a sequence that is at least 95% identical to the HCVR of any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34, and~~

~~a light chain variable region (LCVR) having a sequence that is at least 95% identical to the LCVR of any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34.~~

~~7. The antibody agent of claim 6, wherein the antibody agent comprises~~

~~(a) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:2, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:2;~~

~~(b) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:4, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:4;~~

~~(c) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:6, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:6;~~

~~(d) a HCVR region having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:8, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:8;~~

~~(e) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:10, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:10;~~

~~(f) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:12, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:12;~~

~~(g) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:14, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:14;~~

~~(h) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:16, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:16;~~

~~(i) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:18, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:18;~~

~~(j) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:20, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:20;~~

~~(k) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:22, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:22;~~

~~(l) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:24, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:24;~~

~~(m) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:26, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:26;~~

~~(n) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:28, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:28;~~

~~(o) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:30, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:30;~~

~~(p) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:32, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:32; or~~

~~(q) a HCVR having a sequence that is at least 95% identical to the HCVR of SEQ ID NO:34, and a LCVR having a sequence that is at least 95% identical to the LCVR of SEQ ID NO:34.~~

8. ~~The antibody agent of claim 6 or 7, wherein the antibody agent comprises the HCVR and LCVR sequences of any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32 and SEQ ID NO:34.~~

9. ~~An antibody agent that specifically binds human CD19, wherein the antibody agent comprises one or more amino acid substitutions as compared to a parental or antibody agent, and wherein the parental antibody agent comprises any one set of HC CDR and LC CDR sequences recited in claim 2.~~

10. ~~The antibody agent fragment of any one of claims 1-9 to 4, wherein the antibody agent further comprises one to five amino acid substitutions in a HC CDR, HC framework, LC CDR, LC framework or combinations thereof.~~

11. ~~The antibody agent of claim 10, wherein the antibody agent comprises
a light chain variable region with amino acid substitutions D52N and D95E,
a heavy chain variable region with amino acid substitution S63F,
a heavy chain variable region with amino acid substitutions Q3R, Y32F and A97V,
a heavy chain variable region with amino acid substitution M117L, or
a light chain variable region with amino acid substitutions S25N and V34I, and a heavy chain variable region with amino acid substitutions K12E and D109E.~~

12. ~~The antibody agent of claim 10, wherein the antibody agent comprises
(a) the HC CDRs of SEQ ID NO:124, SEQ ID NO:125 and SEQ ID NO:126, and the LC CDRs of SEQ ID NO:232, SEQ ID NO:233 and SEQ ID NO:234;
(b) the HC CDRs of SEQ ID NO:127, SEQ ID NO:128 and SEQ ID NO:129, and the LC CDRs of SEQ ID NO:235, SEQ ID NO:236 and SEQ ID NO:237;
(c) the HC CDRs of SEQ ID NO:130, SEQ ID NO:131 and SEQ ID NO:132, and the LC CDRs of SEQ ID NO:238, SEQ ID NO:239 and SEQ ID NO:240;
(d) the HC CDRs of SEQ ID NO:133, SEQ ID NO:134 and SEQ ID NO:135, and the LC CDRs of SEQ ID NO:241, SEQ ID NO:242 and SEQ ID NO:243;~~

~~(e) the HC CDRs of SEQ ID NO:136, SEQ ID NO:137 and SEQ ID NO:138, and the LC CDRs of SEQ ID NO:244, SEQ ID NO:245 and SEQ ID NO:246;~~

~~(f) the HC CDRs of SEQ ID NO:139, SEQ ID NO:140 and SEQ ID NO:141, and the LC CDRs of SEQ ID NO:247, SEQ ID NO:248 and SEQ ID NO:249;~~

~~(g) the HC CDRs of SEQ ID NO:142, SEQ ID NO:143 and SEQ ID NO:144, and the LC CDRs of SEQ ID NO:250, SEQ ID NO:251 and SEQ ID NO:252;~~

~~(h) the HC CDRs of SEQ ID NO:145, SEQ ID NO:146 and SEQ ID NO:147, and the LC CDRs of SEQ ID NO:253, SEQ ID NO:254 and SEQ ID NO:255;~~

~~(i) the HC CDRs of SEQ ID NO:148, SEQ ID NO:149 and SEQ ID NO:150, and the LC CDRs of SEQ ID NO:256, SEQ ID NO:257 and SEQ ID NO:258;~~

~~(j) the HC CDRs of SEQ ID NO:151, SEQ ID NO:152 and SEQ ID NO:153, and the LC CDRs of SEQ ID NO:259, SEQ ID NO:260 and SEQ ID NO:261;~~

~~(k) the HC CDRs of SEQ ID NO:154, SEQ ID NO:155 and SEQ ID NO:156, and the LC CDRs of SEQ ID NO:262, SEQ ID NO:263 and SEQ ID NO:264;~~

~~(l) the HC CDRs of SEQ ID NO:157, SEQ ID NO:158 and SEQ ID NO:159, and the LC CDRs of SEQ ID NO:265, SEQ ID NO:266 and SEQ ID NO:267;~~

~~(m) the HC CDRs of SEQ ID NO:160, SEQ ID NO:161 and SEQ ID NO:163, and the LC CDRs of SEQ ID NO:268, SEQ ID NO:269 and SEQ ID NO:270;~~

~~(n) the HC CDRs of SEQ ID NO:163, SEQ ID NO:164 and SEQ ID NO:165, and the LC CDRs of SEQ ID NO:271, SEQ ID NO:272 and SEQ ID NO:273;~~

~~(o) the HC CDRs of SEQ ID NO:166, SEQ ID NO:167 and SEQ ID NO:168, and the LC CDRs of SEQ ID NO:274, SEQ ID NO:275 and SEQ ID NO:276;~~

~~(p) the HC CDRs of SEQ ID NO:169, SEQ ID NO:170 and SEQ ID NO:171, and the LC CDRs of SEQ ID NO:277, SEQ ID NO:278 and SEQ ID NO:279;~~

~~(q) the HC CDRs of SEQ ID NO:172, SEQ ID NO:173 and SEQ ID NO:174, and the LC CDRs of SEQ ID NO:280, SEQ ID NO:281 and SEQ ID NO:282;~~

~~(r) the HC CDRs of SEQ ID NO:175, SEQ ID NO:176 and SEQ ID NO:177, and the LC CDRs of SEQ ID NO:283, SEQ ID NO:284 and SEQ ID NO:285; or~~

~~(s) the HC CDRs of SEQ ID NO:178, SEQ ID NO:179 and SEQ ID NO:180, and the LC CDRs of SEQ ID NO:286, SEQ ID NO:287 and SEQ ID NO:288.~~

13. —The antibody agent of claim 10, wherein the antibody agent comprises the HCVR and LCVR sequences of any one of SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID

~~NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70 and SEQ ID NO:72.~~

~~14. — An antibody agent that specifically binds human CD19 whose sequence includes 1-5 amino acid substitutions as compared to a reference antibody agent having the HCVR and LCVR of SEQ ID NO:30 or SEQ ID NO:32.~~

~~15. — The antibody agent of claim 14, wherein the 1-5 amino acid substitutions are within a framework region and/or a CDR.~~

~~16. — The antibody agent of any one of claims 1-15, wherein the antibody agent fragment is or comprises an immunoglobulin, Fab, F(ab')₂, Fd, Fv, single chain Fv (scFv), or a dAb.~~

~~17.~~ The antibody agent or antibody fragment of any one of claims 1-~~16~~ to 5, wherein the antibody agent or antibody fragment is conjugated to a therapeutic agent, a detection agent, a cytotoxic agent or moiety, or a radio-isotope.

~~18.~~ The antibody agent or antibody fragment of any one of claims 1-~~17~~ to 6, wherein the antibody agent or antibody fragment is a human antibody agent or antibody fragment.

~~19.~~ A bi-specific antibody comprising a first antigen-binding site and a second antigen-binding site, wherein the first antigen-binding site is from ~~or based on~~ an antibody agent or antibody fragment of any one of claims 1-~~18~~ to 7, and the bi-specific antibody specifically binds human cluster of differentiation 19 (CD19) by the first antigen-binding site.

~~20.~~ The bi-specific antibody of claim ~~19~~, wherein the second antigen-binding site binds an immune cell selected from the group consisting of a T cell, NK cell, B cell, dendritic cell, monocyte, macrophage, neutrophil, mesenchymal stem cell and neural stem cell.

~~24~~10. A chimeric antigen receptor comprising an antigen-binding site of an antibody ~~agent~~or antibody fragment of any one of claims 1-~~18~~to 7 and specifically binding human cluster of differentiation 19 (CD19).

~~22~~11. The chimeric antigen receptor of claim ~~21~~10, further comprising a transmembrane domain and an intracellular signaling domain, ~~which~~wherein the intracellular signaling domain comprises a CD3 ζ intracellular signaling sequence and a CD28 intracellular signaling sequence.

~~23. The chimeric antigen receptor of claim 21, further comprising a transmembrane domain and/or an intracellular signaling domain of a native cell receptor.~~

~~24. The chimeric antigen receptor of claim 23, wherein the native cell receptor is a T cell receptor (TCR).~~

~~25~~12. A nucleic acid molecule encoding, in whole ~~or in part~~,
the antibody ~~agent~~or antibody fragment of any one of claims 1-~~18~~,

7, the bi-specific antibody of claim ~~19~~8 or 9, or ~~20~~the chimeric antigen receptor of claim 10 or 11.

~~the chimeric antigen receptor of any one of claims 21-24.~~

~~26~~13. A vector comprising the nucleic acid molecule of claim ~~25~~12.

~~27~~14. A cell comprising the nucleic acid molecule of claim ~~25~~12 or the vector of claim ~~26~~13 or expressing the antibody ~~agent~~or antibody fragment of any one of claims 1-~~18~~7, the bi-specific antibody of claim ~~19~~8 or 209, or the chimeric antigen receptor of ~~any one of claims 21-24~~claim 10 or 11.

~~28~~15. An effector cell expressing the antibody ~~agent~~or antibody fragment of any one of claims 1-~~18~~7, the bi-specific antibody of claim ~~19~~8 or ~~20~~9, or the chimeric antigen receptor of ~~any one of claims 21-24~~claim 10 or 11.

~~29~~16. The effector cell of claim ~~28~~15, wherein the effector cell is a T cell.

~~30. A kit comprising the antibody agent of any one of claims 1-18, the nucleic acid molecule of claim 25, the vector of claim 26, or the cell of claim 27.~~

~~31~~17. A pharmaceutical composition comprising the antibody ~~agent~~or antibody fragment of any one of claims 1-~~18~~7, the bi-specific antibody of claim ~~19~~8 or ~~20~~9, the chimeric antigen receptor of ~~any one of claims 21-24~~claim 10 or 11, the nucleic acid molecule of claim ~~25~~12, the vector of claim ~~26~~13, or the effector cell of claim ~~28~~15 or ~~29~~16, and ~~further comprising~~ a pharmaceutically acceptable carrier or diluent.

~~32. A method of 18. Use of a composition treating a medical condition characterized by CD19 expression in a subject, comprising a step of administering the antibody agent~~or antibody fragment of any one of claims 1-~~18~~7, the bi-specific antibody of claim ~~19~~8 or ~~20~~9, the chimeric antigen receptor of ~~any one of claims 21-24~~claim 10 or 11, the nucleic acid molecule of claim ~~25~~12, the vector of claim ~~26~~13, the effector cell of claim ~~28~~15 or ~~29~~16, or the pharmaceutical composition of claim ~~31 to said subject~~17 in the manufacture of a medicament for treating a medical condition characterized by CD19 expression in a subject.

~~33. The method of claim 32, wherein the medical condition characterized by CD19 expression is rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), diabetes or scleroderma.~~

~~34. The method of claim 32~~19. The use of claim 18, wherein the medical condition characterized by CD19 expression is B cell lymphoma, acute lymphoblastic leukemia, chronic

lymphocytic leukemia, Burkitt lymphoma, non-~~Hodgkin's~~Hodgkin's lymphoma, or acute myeloid leukemia.

~~35.—A method~~20. Use of a composition treating cancer, the method comprising ~~a step of administering to a subject the~~ the antibody ~~agent~~or antibody fragment of any one of claims 1-~~18~~7, the bi-specific antibody of claim ~~19~~8 or ~~20~~9, the chimeric antigen receptor of ~~any one of claims 21-24~~claim 10 or 11, the nucleic acid molecule of claim ~~25~~12, the vector of claim ~~26~~13, the effector cell of claim ~~28~~15 or ~~29~~16, or the pharmaceutical composition of claim ~~31 to said subject~~17 in the manufacture of a medicament for treating cancer.

~~36.—A method of~~21. Use of a medical composition inhibiting tumor growth or killing tumor cells, the method comprising ~~a step of contacting tumor cells with~~ the antibody ~~agent~~or antibody fragment of any one of claims 1-~~18~~7, the bi-specific antibody of claim ~~19~~8 or ~~20~~9, the chimeric antigen receptor of ~~any one of claims 21-24~~claim 10 or 11, the nucleic acid molecule of claim ~~25~~12, the vector of claim ~~26~~13, the effector cell of claim ~~28 or 29~~,
~~the contacting being performed under conditions and for a time sufficient so that inhibition of tumor growth or tumor cell killing is observed.~~

~~37.—A method of directing T cells to kill target cells expressing CD19, the method comprising a step of~~
~~—contacting one or more target cells expressing CD19 with one~~15 or more T cells and16,
~~or the pharmaceutical composition of claim 17 in the manufacture of a medicament for inhibiting tumor growth or killing tumor cells.~~

22. The antibody ~~agent~~or antibody fragment of any one of claims 1-~~18 or~~7, the bi-specific antibody of claim ~~19 or 20~~8 or

~~contacting one~~9, the chimeric antigen receptor of claim 10 or more target cells expressing CD19 with11, the nucleic acid molecule of claim 12, the vector of claim 13, the effector cell of claim ~~28~~15 or ~~29, wherein the effector cell is a T cell,~~

~~the contacting being performed under conditions and for a time sufficient so that T cells to which the antibody agent~~16, or the bi-specific antibody has bound mediate killing of the target cells or that the effector cell mediate killing of the target cells.

~~38. — A kit pharmaceutical composition of claim 17 for diagnosing a subject suffering from a CD19-related disease, or a pre-disposition thereto, or for providing a prognosis of the subject's condition, the kit comprising detection means for detecting the concentration of CD19 present in a sample from a test subject, wherein the detection means comprises an antigen-binding site of the antibody agent of any one of claims 1-18, which is optionally derivatized, wherein presence of CD19 in the sample indicates that the subject suffers from a CD19-related disease.~~

~~39. — A method of diagnosing a medical condition characterized by CD19 expression use in a subject, the method comprising a step of therapy.~~

~~administering the antibody agent of any one of claims 1-18, the bi-specific antibody of claim 19 or 20, or the chimeric antigen receptor of any one of claims 21-24, and
measuring binding of said antibody agent, bi-specific antibody or chimeric antigen receptor to a cell expressing CD19 in said subject.~~

~~40. — The method of claim 39, wherein the method further comprises a step of measuring one or more activities of one or more cells of said subject.~~

~~41. — The method of claim 40, wherein one or more activities include cell growth or apoptosis.~~