

indefinitely self-renew and produce plenty of daughter blast cells with a specific phenotype of CD371, acting as one of most important reasons of leukemia relapse (Siveen et al., *Mol Cancer* (2017);16:13; Yoshida et al., *Cancer Sci* (2016);107:5–11). Given the significant role for CD371 in diseases, antibodies that bind to CD371 and methods of using such agents, are desired.

3. SUMMARY ~~OF THE INVENTION~~

In one aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising

(a) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11; and

(b) a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region and the light chain variable region are selected from the group consisting of:

(a) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO:1, and a light chain variable region

comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO:2;

5 (b) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 3, and a light chain variable region
10 comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 4;

15 (c) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 5, and a light chain variable region
20 comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO:6;

25 (d) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 7, and a light chain variable region
30 comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 8;

35 (e) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 9, and a light chain variable region
40 comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 10; and

(f) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 11, and a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 12.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising

(a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11; and

(b) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising a heavy chain variable region that comprises CDR1, CDR2, and CDR3 domains; and a light chain variable region that comprises CDR1, CDR2, and CDR3 domains, wherein the heavy chain variable region and light chain variable region CDR3 domains are selected from:

(a) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 33 and a conservative modification thereof;

(b) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 36 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 39 and a conservative modification thereof;

(c) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 42 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 45 and a conservative modification thereof;

5 (d) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 48 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 51 and a conservative modification thereof;

10 (e) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 54 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57 and a conservative modification thereof; and

15 (f) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63 and a conservative modification thereof.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising:

20 (a) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30;

25 (b) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 34; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 35; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 36;

30 (c) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 40; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 41; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 42;

(d) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 46; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 47; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 48;

35 (e) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 52; a heavy chain variable region CDR2 comprising the amino acid sequence set

forth in SEQ ID NO: 53; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 54, or

(f) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 58; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising:

(a) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 31; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 32; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 33;

(b) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 37; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 38; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 38;

(c) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 43; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 44; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 45;

(d) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 49; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 50; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 51;

(e) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 55; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 56; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57, or

(f) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 61; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 62; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63.

In another aspect, provided herein is an anti-CD371 antibody or an antigen-binding fragment thereof, comprising:

(a) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29; a heavy chain variable region CDR3 comprising the amino acid

sequence set forth in SEQ ID NO: 30; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 31; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 32; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 33;

5 (b) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 34; a heavy chain variable region CDR2 comprising an amino acid sequence set forth in SEQ ID NO: 35; a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 36; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 37; a light chain variable region CDR2 comprising the
10 amino acid sequence set forth in SEQ ID NO: 38; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 39;

(c) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 40; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 41; a heavy chain variable region CDR3 comprising the amino acid
15 sequence set forth in SEQ ID NO: 42; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 43; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 44; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 45;

(d) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 46; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 47; a heavy chain variable region CDR3 comprising the amino acid
20 sequence set forth in SEQ ID NO: 48; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 49; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 50; and a light chain variable region CDR3
25 comprising the amino acid sequence set forth in SEQ ID NO: 51;

(e) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 52; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 53; a heavy chain variable region CDR3 comprising the amino acid
30 sequence set forth in SEQ ID NO: 54; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 55; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 56; and a light chain variable region CDR3
comprising the amino acid sequence set forth in SEQ ID NO: 57; or

(f) heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 58; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59; a heavy chain variable region CDR3 comprising the amino acid
35 sequence set forth in SEQ ID NO: 60; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 61; a light chain variable region CDR2 comprising the

amino acid sequence set forth in SEQ ID NO: 62; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63.

In another aspect, provided herein is an antibody or an antigen-binding fragment thereof, which cross-competes for binding to CD371 with an antibody or an antigen-binding fragment thereof as described herein.

In another aspect, provided herein is an antibody or an antigen-binding fragment thereof, which binds to the same epitope on CD371 with an antibody or an antigen-binding fragment thereof as described herein.

In another aspect, provided herein is an antibody or an antigen-binding fragment thereof, comprising the amino acid sequence set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, or SEQ ID NO: 21.

In another aspect, provided herein is a composition comprising the antibody or antigen-binding fragment thereof of as described herein.

In another aspect, provided herein is an immunoconjugate comprising the antibody or antigen-binding fragment thereof as described herein, linked to a therapeutic agent.

In another aspect, provided herein is a composition comprising the immunoconjugate as described herein.

In another aspect, provided herein is a bispecific molecule comprising the antibody or antigen-binding fragment thereof as described herein, linked to a second functional moiety.

In another aspect, provided herein is a composition comprising the bispecific molecule as described herein.

In another aspect, provided herein is a nucleic acid that encodes an antibody or antigen-binding fragment thereof as described herein.

In another aspect, provided herein is an expression vector comprising the nucleic acid molecule as described herein.

In another aspect, provided herein is a host cell comprising the expression vector as described herein.

In another aspect, provided herein is a method for detecting CD371 in a whole cell or tissue, comprising:

_____ contacting a cell or tissue with the antibody or antigen-binding fragment thereof as described herein, wherein said antibody or antigen-binding fragment thereof comprises a detectable label; and

_____ determining the amount of the labeled antibody or antigen-binding fragment thereof bound to said cell or tissue by measuring the amount of detectable label associated with said cell or tissue, wherein the amount of bound antibody or antigen-binding fragment thereof indicates the amount of CD371 in said cell or tissue.

In another aspect, provided herein is use of an antibody or antigen-binding fragment thereof as described herein, the immunoconjugate as described herein, the bispecific molecule as described herein, or the composition as described herein in the manufacture of a medicament for reducing tumor burden in a subject, wherein the antibody or antigen-binding fragment thereof as described herein, the immunoconjugate as described herein, the bispecific molecule as described herein, or the composition as described herein is to be administered to the subject.

In another aspect, provided herein is use of an antibody or antigen-binding fragment thereof as described herein, the immunoconjugate as described herein, the bispecific molecule as described herein, or the composition of as described herein in the manufacture of a medicament for treating and/or preventing a tumor or neoplasm in a subject, wherein the antibody or antigen-binding fragment thereof as described herein, the immunoconjugate as described herein, the bispecific molecule as described herein, or the composition as described herein is to be administered to the subject.

In another aspect, provided herein is use of an antibody or antigen-binding fragment thereof as described herein, the immunoconjugate as described herein, the bispecific molecule as described herein, or the composition as described herein in the manufacture of a medicament for increasing or lengthening survival of a subject having a tumor or neoplasm, wherein an antibody or antigen-binding fragment thereof as described herein, the immunoconjugate as described herein, the bispecific molecule as described herein, or the composition as described herein is to be administered to the subject.

In yet another aspect, provided herein is a kit for reducing tumor burden in a subject, treating and/or preventing a tumor or neoplasm in a subject, and/or increasing or lengthening survival of a subject having a tumor or neoplasm, comprising the antibody or antigen-binding fragment thereof as described herein.

In yet another aspect, provided herein is an antibody or antigen-binding fragment thereof as described herein, the immunoconjugate as described herein, the bispecific molecule as described herein, or the composition as described herein for use in therapy.

The presently disclosed subject matter provides antibodies or antigen-binding fragments thereof that specifically bind to CD371, and methods of using the antibodies or antigen-binding fragments thereof.

In certain ~~embodiment~~examples, the anti-CD371 antibody or an antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11.

In certain embodiment examples, the anti-CD371 antibody or an antigen-binding fragment thereof comprises a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In certain embodiment examples, the anti-CD371 antibody or an antigen-binding fragment thereof comprises (a) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11; and (b) a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In certain embodiment examples, the heavy chain variable region and the light chain variable region of the anti-CD371 antibody or antigen-binding fragment thereof are selected from the group consisting of:

5 (a) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 2;

15 (b) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 3, and a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 4;

20 (c) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 5, and a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 6;

30 (d) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 7, and a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least

about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 8;

(e) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 9, and a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ

ID NO: 10; and

(f) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 11, and a light chain variable region comprising an amino acid sequence that is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 100% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 12.

In certain embodiment examples, the anti-CD371 antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11. In certain embodiment examples, the anti-CD371 antibody or antigen-binding fragment thereof, comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In certain embodiment examples, the anti-CD371 antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 11; and light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or SEQ ID NO: 12.

In certain embodiment examples, the anti-CD371 antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region,

wherein the heavy chain variable region and the light chain variable region are selected from the group consisting of:

- 5 (a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2;
- (b) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 4;
- 10 (c) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 5, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 6;
- (d) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 7, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 8;
- 15 (e) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:9, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:10; and
- (f) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 11, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 12.
- 20

In certain ~~embodiment~~examples, the anti-CD371 antibody or antigen-binding fragment thereof comprises a heavy chain variable region that comprises CDR1, CDR2, and CDR3 domains; and a light chain variable region that comprises CDR1, CDR2, and CDR3 domains, wherein the heavy chain variable region and light chain variable region CDR3 domains are
25 selected from the group consisting of:

- (a) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 33 and a conservative modification thereof;
- 30 (b) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 36 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 39 and a conservative modification thereof;

(c) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 42 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 45 and a conservative modification thereof;

5 (d) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 48 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 51 and a conservative modification thereof;

10 (e) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 54 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57 and a conservative modification thereof; and

15 (f) a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60 and a conservative modification thereof; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63 and a conservative modification thereof.

In certain ~~embodiment~~examples, the heavy chain variable region and light chain variable region CDR2 domains of the antibody or antigen-binding portion thereof are selected from the group consisting of:

20 (a) a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29 and a conservative modification thereof; and a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 32 and a conservative modification thereof;

25 (b) a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 35 and a conservative modification thereof; and a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 38 and a conservative modification thereof;

30 (c) a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 41 and a conservative modification thereof; and a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 44 and a conservative modification thereof;

(d) a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 47 and a conservative modification thereof; and a light chain

variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 50 and a conservative modification thereof;

(e) a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 53 and a conservative modification thereof; and a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 56 and a conservative modification thereof; and

(f) a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59 and a conservative modification thereof; and a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 62 and a conservative modification thereof.

In certain ~~embodiment~~examples, the anti-CD371 heavy chain variable region and light chain variable region CDR1 domains of the antibody or antigen-binding portion thereof are selected from the group consisting of:

(a) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28 and a conservative modification thereof; and a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 31 and a conservative modification thereof;

(b) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 34 and a conservative modification thereof; and a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 37 and a conservative modification thereof;

(c) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 40 and a conservative modification thereof; and a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 43 and a conservative modification thereof;

(d) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 46 and a conservative modification thereof; and a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 49 and a conservative modification thereof;

(e) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 52 and a conservative modification thereof; and a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 55 and a conservative modification thereof; and

(f) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 58 and a conservative modification thereof; and a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 61 and a conservative modification thereof.

5 In certain embodiment examples, one or more of the CDR sequences have up to about 5 amino acid substitutions. In certain embodiment examples, one or more of the CDR sequences have up to about 3 amino acid substitutions.

 In certain embodiment examples, the anti-CD371 antibody or antigen-binding fragment thereof comprises:

10 (a) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30;

 (b) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in
15 SEQ ID NO: 34; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 35; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 36;

 (c) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in
20 SEQ ID NO: 40; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 41; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 42;

 (d) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in
25 SEQ ID NO: 46; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 47; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 48;

 (e) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in
SEQ ID NO: 52; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 53; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 54, or

30 (f) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 58; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59; and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60.

In certain ~~embodiment~~examples, the anti-CD371 antibody or antigen-binding fragment thereof comprises:

5 (a) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 31; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 32; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 33;

10 (b) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 37; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 38; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 39;

(c) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 43; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 44; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 45;

15 (d) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 49; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 50; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 51;

20 (e) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 55; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 56; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57, or

25 (f) a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 61; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 62; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63.

In certain ~~embodiment~~examples, the anti-CD371 antibody or antigen-binding fragment thereof comprises:

30 (a) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29; a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 31; a light chain variable

region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 32; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 33;

5 (b) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 34; a heavy chain variable region CDR2 comprising an amino acid sequence set forth in SEQ ID NO: 35; a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 36; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 37; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 38; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 39;

10 (c) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 40; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 41; a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 42; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 43; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 44; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 45;

15 (d) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 46; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 47; a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 48; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 49; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 50; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 51;

20 (e) a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 52; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 53; a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 54; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 55; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 56; and a

light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57; or

(f) heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 58; a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59; a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60; a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 61; a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 62; and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63.

The presently disclosed subject matter provides an antibody or an antigen-binding fragment thereof, which cross-competes for binding to CD371 with any of the above-described antibody or an antigen-binding fragment thereof.

The presently disclosed subject matter provides an antibody or an antigen-binding fragment thereof, which binds to the same epitope on CD371 with any of the above-described antibody or an antigen-binding fragment thereof.

In certain embodimentexamples, the sequence of the antibody is in a light-heavy variable chain orientation (V_L - V_H). In certain embodimentexamples, the antibody or antigen-binding fragment thereof binds to human CD371 with a dissociation constant (K_D) of between about 1×10^{-7} M and about 1×10^{-8} M or between about 1×10^{-9} M and about 1×10^{-8} M.

In certain embodimentexamples, the antibody or antigen-binding fragment thereof comprises the amino acid sequence set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, or SEQ ID NO: 21.

In certain embodimentexamples, the antibody or antigen-binding fragment thereof comprises a human variable region framework region. In certain embodimentexamples, the antibody or antigen-binding fragment thereof is a fully human or an antigen-binding fragment thereof. In certain embodimentexamples, the antibody or antigen-binding fragment thereof is a chimeric antibody or an antigen-binding fragment thereof. In certain embodimentexamples, the antibody or antigen-binding portion thereof is a humanized antibody or an antigen-binding fragment thereof. In certain embodimentexamples, the antigen-binding fragment of the antibody is a Fab, Fab', F(ab')₂, variable fragment (Fv) or a single chain variable fragment (scFv).

The presently disclosed subject matter also provides an immunoconjugate comprising the antibody or antigen-binding fragment thereof disclosed herein, linked to a therapeutic agent. In certain ~~embodiment~~examples, the therapeutic agent is a drug, a cytotoxin, or a radioactive isotope.

5 Furthermore, the presently disclosed subject matter provides a bispecific molecule comprising the antibody or antigen-binding fragment thereof disclosed herein, linked to a second functional moiety. In certain ~~embodiment~~examples, the second functional moiety has a different binding specificity than the antibody or antigen binding fragment thereof.

10 The presently disclosed subject matter also provides a composition comprising the antibody or antigen-binding fragment thereof disclosed herein, the immunoconjugate disclosed herein, or the bispecific antibody disclosed herein. In certain ~~embodiment~~examples, the composition is a pharmaceutical composition that further comprises a pharmaceutically acceptable carrier.

15 In addition, the presently disclosed subject matter provides a nucleic acid that encodes the antibody or antigen-binding fragment thereof disclosed herein, an expression vector comprising such nucleic acid molecule, and a host cell comprising such expression vector.

20 The presently disclosed subject matter provides a method for detecting CD371 in a whole cell or tissue. In certain ~~embodiment~~examples, the method comprises: contacting a cell or tissue with the antibody or antigen-binding fragment thereof disclosed herein, wherein said antibody or antigen-binding fragment thereof comprises a detectable label; and determining the amount of the labeled antibody or antigen-binding fragment thereof bound to said cell or tissue by measuring the amount of detectable label associated with said cell or tissue, wherein the amount of bound antibody or antigen-binding fragment thereof indicates the amount of CD371 in said cell or tissue.

25 Furthermore, the presently disclosed subject matter provides methods of treating a tumor burden in a subject. In certain ~~embodiment~~examples, the method comprises administering to the subject an antibody or antigen-binding fragment thereof, the immunoconjugate thereof, the bispecific molecule thereof, or the composition disclosed herein. In certain ~~embodiment~~examples, the method reduces the number of the tumor cells. In certain ~~embodiment~~examples, the method reduces the tumor size. In certain ~~embodiment~~examples, the

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method eradicates the tumor in the subject. In certain embodimentexamples, the subject is a human.

Furthermore, the presently disclosed subject matter provides methods of treating and/or preventing a tumor or neoplasm in a subject. In certain embodimentexamples, the method comprises administering to the subject an antibody or antigen-binding fragment thereof, the immunoconjugate thereof, the bispecific molecule thereof, or the composition thereof disclosed herein. In certain embodimentexamples, the method eradicates the tumor in the subject. In certain embodimentexamples, the subject is a human.

In addition, the presently disclosed subject matter provides a method of increasing or lengthening survival of a subject having a tumor or neoplasm. In certain embodimentexamples, the method comprises administering to the subject an antibody or antigen-binding fragment thereof, the immunoconjugate thereof, the bispecific molecule thereof, or the composition thereof disclosed herein. In certain embodimentexamples, the method eradicates the tumor in the subject. In certain embodimentexamples, the subject is a human.

In addition, the presently disclosed subject matter provides a method of preventing and/or treating a tumor or neoplasm. In certain embodimentexamples, the method comprises administering to the subject an antibody or antigen-binding fragment thereof, the immunoconjugate thereof, the bispecific molecule thereof, or the composition thereof disclosed herein. In certain embodimentexamples, the subject is a human.

In certain embodimentexamples, the tumor or neoplasm is selected from the group consisting of acute myeloid leukemia (AML), multiple myeloma, Non-Hodgkin's Lymphoma, Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia (CLL), glioblastoma, myelodysplastic syndrome (MDS), and chronic myelogenous leukemia (CML). In certain embodimentexamples, the tumor is AML.

Furthermore, the presently disclosed subject matter provides a kit for treating a tumor burden in a subject, treating and/or preventing a tumor or neoplasm, and/or increasing or lengthening survival of a subject having a tumor or neoplasm, comprising the antibody or antigen-binding fragment thereof, the immunoconjugate thereof, the bispecific molecule thereof, or the composition thereof disclosed herein. In certain embodimentexamples, the kit further comprises written instructions for using the antibody or antigen-binding fragment thereof, the immunoconjugate thereof, the bispecific molecule thereof, or the composition thereof disclosed herein for treating a tumor burden in a