

CLAIMS

1. An antibody or fragment thereof binding to CLDN18.2, wherein the antibody or fragment thereof exhibits increased binding to tumor tissue expressing CLDN18.2 over healthy tissue expressing CLDN18.2.
- 5 2. An antibody or fragment thereof binding to CLDN18.2 comprising the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 21, SEQ ID NO: 22, and SEQ ID NO: 23, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, respectively.
3. The antibody or fragment thereof of claim 1 or 2, comprising:
 - 10 a. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 15 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;
 - b. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;
 - 15 c. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 17, SEQ ID NO: 14 and SEQ ID NO: 11, respectively;
 - 20 d. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 11, respectively;
 - e. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO: 15 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;
 - 25 f. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 20 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;
 - 30 g. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 20 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3

sequences of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 11,
respectively;

- h. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO:
20 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3
sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;
or

- i. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO:
20 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3
sequences of SEQ ID NO: 17, SEQ ID NO: 14 and SEQ ID NO: 11,
respectively.

4. The antibody or fragment thereof of claim 1 or 2, comprising:

- a. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 2
and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3
sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;
b. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 7
and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3
sequences of SEQ ID NO: 9, SEQ ID NO: 10 and SEQ ID NO: 11,
respectively; or
c. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO:
2 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3
sequences of SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 11,
respectively,

preferably comprising:

- d. a VH sequence of SEQ ID NO: 27 and a VL sequence of SEQ ID NO: 28;
e. a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 30; or
f. a VH sequence of SEQ ID NO: 31 and a VL sequence of SEQ ID NO: 32.

5. The antibody or fragment thereof of any one of claims 1-3, comprising:

- a. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at
least 98% sequence identity with the amino acid sequence of SEQ ID NO: 33;
b. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at
least 98% sequence identity with the amino acid sequence of SEQ ID NO: 34;

- 5 c. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 35;
- d. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 36; or
- 5 e. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 37;
- and
- f. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 38;
- 10 g. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 39;
- h. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 40; or
- i. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 41,
- 15

preferably comprising:

- a. a VH sequence of: SEQ ID NO: 33;
- b. a VH sequence of SEQ ID NO: 34;
- c. a VH sequence of SEQ ID NO: 35;
- 20 d. a VH sequence of SEQ ID NO: 36; or
- e. a VH sequence of SEQ ID NO: 37;
- and
- f. a VL sequence of SEQ ID NO: 38;
- g. a VL sequence of SEQ ID NO: 39;
- 25 h. a VL sequence of SEQ ID NO: 40; or
- i. a VL sequence of SEQ ID NO: 41.

6. The antibody or fragment thereof of claim 1 or 2, comprising:
- a. a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 38;
- b. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 38;
- 30 c. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 39;

- d. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 40;
 - e. a VH sequence of SEQ ID NO: 35 and a VL sequence of SEQ ID NO: 38;
 - f. a VH sequence of SEQ ID NO: 36 and a VL sequence of SEQ ID NO: 41;
 - g. a VH sequence of SEQ ID NO: 36 and a VL sequence of SEQ ID NO: 40;
 - 5 h. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 41;
 - i. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 38; or
 - j. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 39.
7. The antibody of any one of claims 1-3, comprising:
- a. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least
10 95% or at least 98% sequence identity with the amino acid sequence of the heavy
chain sequence of SEQ ID NO: 46 and a light chain sequence having at least 80%,
at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the
amino acid sequence of the light chain sequence of SEQ ID NO: 51;
 - b. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least
15 95% or at least 98% sequence identity with the amino acid sequence of the heavy
chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%,
at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the
amino acid sequence of the light chain sequence of SEQ ID NO: 51;
 - c. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least
20 95% or at least 98% sequence identity with the amino acid sequence of the heavy
chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%,
at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the
amino acid sequence of the light chain sequence of SEQ ID NO: 52;
 - d. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least
25 95% or at least 98% sequence identity with the amino acid sequence of the heavy
chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%,
at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the
amino acid sequence of the light chain sequence of SEQ ID NO: 53;
 - e. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least
30 95% or at least 98% sequence identity with the amino acid sequence of the heavy
chain sequence of SEQ ID NO: 48 and a light chain sequence having at least 80%,

at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 51;

- 5 f. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 54;
- 10 g. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 49 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 53;
- 15 h. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 50 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 54;
- 20 i. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 50 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 51;
- 25 j. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 50 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 52

preferably comprising:

- 30 k. the heavy chain sequence of SEQ ID NO: 46 and light chain sequence of SEQ ID NO: 51;
- l. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 51;

- m. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 52;
- n. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 53;
- 5 o. the heavy chain sequence of SEQ ID NO: 48 and light chain sequence of SEQ ID NO: 51;
- p. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 54;
- 10 q. the heavy chain sequence of SEQ ID NO: 49 and light chain sequence of SEQ ID NO: 53;
- r. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 54;
- s. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 51;
- 15 t. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 52,
or versions thereof with an engineered Fc domain.

- 8. An antibody or fragment thereof binding to CLDN18.2, wherein the antibody or
20 fragment thereof
 - (i) binds to the same epitope as an antibody comprising a heavy chain sequence of SEQ ID NO: 46 and a light chain sequence of SEQ ID NO: 51;
 - (ii) competes for binding with an antibody comprising a heavy chain sequence of SEQ ID NO: 46 and a light chain sequence of SEQ ID NO: 51; and/or
 - 25 (iii) competitively inhibits binding of an antibody comprising a heavy chain sequence of SEQ ID NO: 46 and a light chain sequence of SEQ ID NO: 51 to CLDN18.2.
- 9. The antibody or fragment thereof of any one of claims 1 to 8, wherein the antibody or
fragment thereof
 - 30 a. is IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, synthetic IgG, IgM, F(ab)₂, Fv, scFv, IgGACH2, F(ab')₂, scFvCH3, Fab, VL, VH, scFv4, scFv3, scFv2, dsFv, Fv,

- scFv-Fc, (scFv)₂, a non-depleting IgG, a diabody, a bivalent antibody or Fc-engineered versions thereof;
- b. is humanized;
- c. does not bind to CLDN18.1;
- 5 d. is isolated; and/or
- e. is less susceptible to posttranslational deamidation than IMAB362.
10. The antibody or fragment thereof of any one of claims 1 to 9, wherein the increased binding to tumor tissue expressing CLDN18.2 over healthy tissue expressing CLDN18.2 is measured by flow cytometry or by immunohistochemistry.
- 10 11. The antibody or fragment thereof of any one of claims 1 to 9 wherein the antibody or fragment thereof binds to CLDN18.2 expressed in HEK293T cells or PA-TU-8988-High cells with an EC50 value that is at least 1.1 times higher, at least 1.2 times higher, at least 1.5 times higher, at least 2 times higher or at least 2.5 times higher but not more than 3 times higher than the EC50 value of IMAB362 binding to CLDN18.2 expressed in
- 15 HEK293T cells or PA-TU-8988-High cells, optionally wherein binding is measured by flow cytometry (FC) titration.
12. A nucleic acid encoding the antibody or fragment thereof of any of claims 1 to 11.
13. A vector comprising the nucleic acid of claim 12.
14. A host cell comprising the nucleic acid of claim 12 or the vector of claim 13.
- 20 15. The antibody or fragment thereof of any one of claims 1 to 11, the nucleic acid of claim 12, the vector of claim 13 or the host cell of claim 14 for use in the treatment of a subject
- a. suffering from,
- b. at risk of developing, and/or
- c. being diagnosed for
- 25 a neoplastic disease; optionally wherein the neoplastic disease is selected from the group consisting of pancreatic, gastric, esophageal, ovarian and lung cancer.