

CLAIMS

1. Use of a therapeutically effective amount of a CLDN18.2 antagonist in combination with a therapeutically effective amount of PD-1/PD-L1 axis inhibitor in the manufacture of a medicament for the treatment of a CLDN18.2-associated disease or condition in a subject in need,

wherein the subject is determined to have CLDN18.2 expression in a diseased tissue.

2. The use of claim 1, wherein a therapeutically effective amount of a chemotherapeutic agent is further to be administered to the subject.

3. The use of claim 1, wherein the CLDN18.2 expression in the diseased tissue is higher than or comparable to expression in healthy or noncancerous stomach cells or stomach tissue.

4. The use of claim 1, wherein the CLDN18.2 expression in the diseased tissue is lower than expression in healthy or noncancerous stomach cells or stomach tissue but higher than expression in a healthy or noncancerous tissue or organ other than stomach.

5. The use of claim 1, wherein the CLDN18.2 expression in the diseased tissue is comparable to expression in a healthy or noncancerous tissue or organ other than stomach, and is detectable by an anti-CLDN18.2 diagnostic antibody.

6. The use of claim 1, wherein the subject is determined to have PD-L1 expression in the diseased tissue.

7. The use of claim 1, wherein the subject is determined to have low or no PD-L1 expression in the diseased tissue.

8. The use of claim 7, wherein the PD-L1 expression in the diseased tissue is lower than a reference level.

9. The use of claim 7, wherein no more than 20% of the cells of the diseased tissue are

positive for PD-L1 expression.

10. The use of claim 9, wherein the cells of a diseased tissue comprise disease cells and immune cells in the diseased tissue.

11. The use of claim 7, wherein the PD-L1 expression in the diseased tissue is comparable to that in a healthy or noncancerous tissue, or the PD-L1 expression in the diseased tissue is low or non-detectable by an anti-PD-L1 diagnostic antibody.

12. Use of a therapeutically effective amount of a CLDN18.2 antagonist, optionally in combination with a therapeutically effective amount of a PD-1/PD-L1 axis inhibitor in the manufacture of a medicament for sensitizing a disease or condition to a treatment with PD-1/PD-L1 axis inhibitor in a subject in need,

wherein the subject is determined to have low or no expression of PD-L1 in a diseased tissue.

13. The use of claim 12, wherein a chemotherapeutic agent is further to be administered to the subject.

14. Use of a therapeutically effective amount of a CLDN18.2 antagonist, and optionally in combination with a therapeutically effective amount of a PD-1/PD-L1 axis inhibitor in the manufacture of a medicament for increasing responsiveness of a tumor to a treatment with PD-1/PD-L1 axis inhibitor in a subject, wherein the subject is determined to have a tumor resistant or refractory to the treatment with a PD-1/PD-L1 axis inhibitor.

15. The use of claim 14, wherein a chemotherapeutic agent is further to be administered to the subject.

16. The use of claim 1, wherein the CLDN18.2 antagonist comprises an anti-CLDN18.2 antibody, such as a monoclonal anti-CLDN18.2 antibody, a bi-specific antibody targeting CLDN18.2 and a second antigen (e.g., CD3, 4-1BB, TGF β , SIRP α , and IL15), or immune cells expressing chimeric antigen receptors (CARs) or genetically modified TCRs comprising an anti-CLDN18.2 antigen binding domain.

17. The use of claim 16, wherein the anti-CLDN18.2 antibody comprises heavy chain HCDR1, HCDR2 and HCDR3 and/or light chain LCDR1, LCDR2 and LCDR3 sequences, wherein:

the HCDR1 sequence comprises **GYNMN** (SEQ ID NO: 1), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR2 sequence comprises **NIDPYYGGTSYNQKFKG** (SEQ ID NO: 2), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR3 sequence comprises **MYHGNAFDY** (SEQ ID NO: 3), or a homologue sequence of at least 80% sequence identity thereof;

the LCDR1 sequence comprises **KSSQSLLNSGNLKNYLT** (SEQ ID NO: 4) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR2 sequence comprises **WASTRKS** (SEQ ID NO: 5) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR3 sequence comprises **QNDYSYPLT** (SEQ ID NO: 6) or a homologue sequence of at least 80% sequence identity thereof.

18. The use of claim 17, wherein the anti-CLDN18.2 antibody comprises a heavy chain variable region and a light chain variable region, wherein

the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 7, and the light chain variable region comprises an amino acid sequence of SEQ ID NO: 8.

19. The use of claim 16, wherein the anti-CLDN18.2 antibody further comprises an immunoglobulin constant region, and wherein the constant region comprises one or more amino acid residue substitutions relative to SEQ ID NO: 9, selected from the group consisting of: L235V, F243L, R292P, Y300L, P396L, or any combination thereof.

20. The use of claim 19, wherein the constant region comprises the sequence of SEQ ID NO: 11, optionally the constant region further comprises the sequence of SEQ ID

NO: 10.

21. The use of claim 19, wherein the anti-CLDN18.2 antibody comprises a heavy chain variable region and a light chain variable region, wherein

the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14, and

the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 15 and SEQ ID NO: 16.

22. The use of claim 16, wherein the anti-CLDN18.2 antibody comprises a heavy chain and a light chain, wherein

the heavy chain comprises an amino acid sequence of SEQ ID NO: 39, and

the light chain comprises an amino acid sequence of SEQ ID NO: 40.

23. The use of claim 16, wherein the anti-CLDN18.2 antibody is capable of inducing the expression of PD-L1 in the diseased tissue of the subject.

24. The use of claim 1, wherein the PD-1/PD-L1 axis inhibitor comprises PD-1 inhibitor selected from the group consisting of antibody, small molecule, and combination thereof, or the PD-1/PD-L1 axis inhibitor comprises PD-L1 inhibitor selected from the group consisting of antibody, small molecule, and combination thereof.

25. The use of claim 24, wherein

(i) the PD-1 inhibitor comprises an anti-PD-1 antibody selected from the group consisting of: Nivolumab (OPDIVO; BMS-936558), Dostarlimab (TSR-042), Pembrolizumab (KEYTRUDA; MK-3475), MEDI0680 (AMP-514), MEDI4736, BI 754091, Pidilizumab (CT-011), Cemiplimab (LIBTAYO, REGN2810), Spartalizumab (PDR001), Cetrelimab (JNJ 63723283), Toripalimab (JS001), PF-06801591, Tislelizumab (BGB-A317), AMP-224 (GSK-2661380), ABBV-181, Lambrolizumab, Camrelizumab (SHR-1210), Sintilimab (Tyvyt, IBI308), Penpulimab (AK105),

Zimberelimab, Retifanlimab, Serplulimab, Balstilimab, Geptanolimab, Prolgolimab, Ezabenlimab, Sasanlimab, Pimivalimab, Budigalimab, Nofazinlimab, Sindelizumab, MGA404, Sym021, BAT1306, HX008; or

(ii) the PD-L1 inhibitor comprises an anti-PD-L1 antibody selected from the group consisting of: Atezolizumab (TECENTRIQ; R05541267; MPDL3280A; RG7446), BMS-936559, Avelumab (bavencio), lodapolimab (LY3300054), Durvalumab (MEDI4736), CX-072 (Proclaim-CX-072), FAZ053, Envafolimab (KN035), MDX-1105, STI-1040, CS1001, Adebrelimab (SHR-1316), SHR-1701, TOB2450, Bintrafusp, LP002, STI-3031, Cosibelimab, Pacmilimab, NM01, LDP, AMP-224, Garivulimab (BGB-A333), A167, SCD-135, Opucolimab, GR1405; optionally the PD-L1 inhibitor is Atezolizumab (TECENTRIQ; R05541267; MPDL3280A; RG7446); or the PD-L1 inhibitor comprises a bispecific antibody targeting both PD-L1 and another checkpoint molecule selected from the group consisting of PD-1, PD-L1, PD-L2, CLTA-4, SIRP, TIM-3, LAG3, A2AR, CD160, 2B4, TGF β , VISTA, BTLA, TIGIT, LAIR1, OX40, CD2, CD27, CD28, CD30, CD40, CD122, ICAM-1, IDO, NKG2C, SLAMF7, SIGLEC7, NKp80, CD160, B7-H3, LFA-1, ICOS, 4-1BB, GITR, BAFR, HVEM, CD7, LIGHT, IL-2, IL-15, CD3, CD16 or CD83.

26. The use of claim 1, wherein the PD-L1 inhibitor comprises an anti-PD-L1 antibody comprising heavy chain HCDR1, HCDR2 and HCDR3 and/or light chain LCDR1, LCDR2 and LCDR3 sequences, wherein:

(a) the HCDR1 sequence comprises DYYMN (SEQ ID NO: 22), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR2 sequence comprises DINPNAETLYNHKFKG (SEQ ID NO: 23), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR3 sequence comprises WGDGPFAY (SEQ ID NO: 24), or a homologue sequence of at least 80% sequence identity thereof;

the LCDR1 sequence comprises KASQNVGAAVA (SEQ ID NO: 25) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR2 sequence comprises SVSDRYT (SEQ ID NO: 26) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR3 sequence comprises QQYSNYPT (SEQ ID NO: 27) or a homologue sequence of at least 80% sequence identity thereof; or

(b) the HCDR1 sequence comprises TYWMH (SEQ ID NO: 32), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR2 sequence comprises MIQPNSGGTKYNEKFKK (SEQ ID NO: 33), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR3 sequence comprises GAGTVDYFDY (SEQ ID NO: 34), or a homologue sequence of at least 80% sequence identity thereof;

the LCDR1 sequence comprises RASESVDIYGNSFMH (SEQ ID NO: 35) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR2 sequence comprises RASNLES (SEQ ID NO: 36) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR3 sequence comprises QQSTEDPYT (SEQ ID NO: 37) or a homologue sequence of at least 80% sequence identity thereof.

27. The use of claim 26, wherein the PD-L1 inhibitor comprises an anti-PD-L1 antibody comprising a heavy chain variable region and a light chain variable region, wherein

(a) the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 17, and

the light chain variable region comprises an amino acid sequence of SEQ ID NO: 18; or

(b) the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 28, and

the light chain variable region comprises an amino acid sequence of SEQ ID NO: 29.

28. The use of claim 27, wherein the PD-L1 inhibitor comprises an anti-PD-L1 antibody comprising a heavy chain and a light chain, wherein

(a) the heavy chain comprises an amino acid sequence of SEQ ID NO: 19 or SEQ ID NO: 20, and

the light chain comprises an amino acid sequence of SEQ ID NO: 21; or

(b) the heavy chain comprises an amino acid sequence of SEQ ID NO: 30, and

the light chain comprises an amino acid sequence of SEQ ID NO: 31.

29. The use of claim 1, wherein the disease or condition is cancer, or the diseased tissue comprises a cancer cell.

30. The use of claim 29, wherein the cancer is selected from the group consisting of gastric cancer, lung cancer, bronchial cancer, bone cancer, liver and bile duct cancer, pancreatic cancer, breast cancer, liver cancer, ovarian cancer, testicle cancer, kidney cancer, bladder cancer, head and neck cancer, spine cancer, brain cancer, cervix cancer, uterine cancer, endometrial cancer, colon cancer, colorectal cancer, rectal cancer, anal cancer, esophageal cancer, gastrointestinal cancer, skin cancer, prostate cancer, pituitary cancer, stomach cancer, vagina cancer, thyroid cancer, glioblastoma, astrocytoma, melanoma, myelodysplastic syndrome, sarcoma, teratoma, and adenocarcinoma.

31. The use of claim 1, wherein the disease or condition is resistant or refractory to a treatment with a PD-1/PD-L1 axis inhibitor, optionally the resistance is de novo or acquired.

32. The use of claim 31, wherein the disease or condition is resistant or refractory to a combinatory therapy with a PD-1/PD-L1 axis inhibitor and a chemotherapeutic agent.

33. The use of claim 32, wherein the chemotherapeutic agent is selected from the group consisting of: antimetabolites such as methotrexate and 5-fluorouracil (5-FU), Oxaliplatin, alkylating agents (e.g., thiotepa and cyclophosphamide (CytosanTM), alkyl sulfonates (e.g., busulfan, improsulfan and piposulfan), aziridines (e.g., benzodopa, carboquone, meturedopa, and uredopa), emylerumines and memylamelamines (e.g., altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, and trimethylolomelamine), acetogenins, a camptothecin (e.g., synthetic analogue topotecan), bryostatin, calystatin, CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues), cryptophycins (particularly cryptophycin and cryptophycin), dolastatin, duocarmycin (including the synthetic analogues, KW-2 189 and CBI-TMI), eleutherobin, pancratistatin, a sarcodictyin, spongistatin, cisplatin, nitrogen mustards (e.g., chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard), nitrosoureas (e.g., carmustine, chlorozotocin, foremostine, lomustine, nimustine, ranimustine, folic acid analogues (e.g., demopterin, methotrexate, pteropterin, trimetrexate, purine analogs (e.g., fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, pyrimidine analogues (e.g., ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine), androgens (e.g., calusterone, dromostanolone propionate, epitostanol, mepitostane, testolactone), anti-adrenals (e.g., aminoglutethimide, mitotane, trilostane), folic acid replinisher (e.g., frolic acid), aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, hestrabucil, bi santrene, edatrexate, defofamine, demecolcine, diaziquone, elformthine, elliptinium acetate, an epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, maytansinoids (e.g., maytansine and ansamitocins), mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, P SKTM, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2,2"-tricUorotriemylamine, trichothecenes, urethane, vindesine, dacarbazine, mannomustine, mitobronitol,

mitolactol.

34. A kit useful in treating a disease or condition in a subject in need thereof, comprising a first container that comprises a CLDN18.2 antagonist and a second container that comprises a PD-1/PD-L1 axis inhibitor, and optionally instructions for use of the kit,

wherein the disease or condition is characterized in having: a) CLDN18.2 expression in a diseased tissue, and/or b) low or no expression of PD-L1 in the diseased tissue.

35. A kit, comprising a CLDN18.2 antagonist and a package insert comprising instructions for using the CLDN18.2 antagonist in combination with a PD-1/PD-L1 axis inhibitor to treat a disease or condition in a subject in need thereof,

wherein the disease or condition is characterized in having: a) CLDN18.2 expression in a diseased tissue, and/or b) low or no expression of PD-L1 in the diseased tissue.