metastasis such as Krukenberg tumors, peritoneal metastasis and lymph node metastasis. Particularly preferred cancer diseases are pancreatic cancer and the metastases thereof.

In one aspect, the present disclosure provides use of an antibody having the ability to bind to CLDN18.2 in the preparation of a medicament for use in combinatorial therapy for treating ~~or preventing~~ a cancer disease, wherein said medicament is to be administered in combination with an agent stabilizing or increasing expression of CLDN18.2, wherein the cancer is CLDN18.2 positive, and wherein (a) the antibody binds to CLDN18.2 and mediates killing of cells expressing CLDN18.2, and (b) the agent stabilizing or increasing expression of CLDN18.2 comprises an agent selected from the group consisting of gemcitabine and a salt, ester or conjugate thereof.

In another aspect, the present disclosure provides use of an agent for stabilizing or increasing expression of CLDN18.2 in the preparation of a medicament for use in combinatorial therapy for treating ~~or preventing~~ a cancer disease, wherein said medicament is to be administered in combination with an antibody having the ability of binding to CLDN18.2, wherein the cancer is CLDN18.2 positive, and wherein (a) the antibody binds to CLDN18.2 and mediates killing of cells expressing CLDN18.2 and (b) the agent stabilizing or increasing expression of CLDN18.2 comprises an agent selected from the group consisting of gemcitabine and a salt, ester or conjugate thereof.

In one example, the present disclosure provides a method of treating or preventing pancreatic cancer in a patient comprising administering to the patient (i) an antibody having the ability of binding to CLDN18.2 and (ii) an agent stabilizing or increasing expression, i.e. the level, of CLDN18.2. Expression of CLDN18.2 is preferably at the cell surface of a cancer cell. The agent stabilizing or increasing expression of CLDN18.2 may be administered prior to, simultanously with or following administration of the antibody having the ability of binding to CLDN18.2, or a combination thereof.

The agent stabilizing or increasing expression of CLDN18.2 may be a cytotoxic and/or cytostatic agent. In one example, the agent stabilizing or increasing expression of CLDN18.2 comprises an agent which induces a cell cycle arrest or an accumulation of cells in one or more phases of the cell cycle, preferably in one or more phases of the cell cycle other than the G1-phase such as the S-phase, G2-phase, or a combination thereof or a combination of the S-

Claims:

1. Use of an antibody having the ability to bind to CLDN18.2 in the preparation of a medicament for use in combinatorial therapy for treating ~~or preventing~~ a cancer disease, wherein said medicament is to be administered in combination with an agent stabilizing or increasing expression of CLDN18.2, wherein the cancer is CLDN18.2 positive, and wherein

(a) the antibody binds to CLDN18.2 and mediates killing of cells expressing CLDN18.2, and

(b) the agent stabilizing or increasing expression of CLDN18.2 comprises an agent selected from the group consisting of gemcitabine and a salt, ester or conjugate thereof.

2. Use of an agent for stabilizing or increasing expression of CLDN18.2 in the preparation of a medicament for use in combinatorial therapy for treating ~~or preventing~~ a cancer disease, wherein said medicament is to be administered in combination with an antibody having the ability of binding to CLDN18.2, wherein the cancer is CLDN18.2 positive, and
wherein

(a) the antibody binds to CLDN18.2 and mediates killing of cells expressing CLDN18.2 and

(b) the agent stabilizing or increasing expression of CLDN18.2 comprises an agent selected from the group consisting of gemcitabine and a salt, ester or conjugate thereof.

3. The use of claim 1 or 2, wherein the antibody comprises an antibody heavy chain amino acid sequence and an antibody light chain amino acid sequence, wherein the antibody heavy chain comprises a heavy chain variable region comprising the set of complementarity-determining regions CDR1, CDR2 and CDR3 of SEQ ID NO: 32 ~~or a variant thereof~~ and the antibody light chain comprises a light chain variable region comprising the set of complementarity-determining regions CDR1, CDR2 and CDR3 of SEQ ID NO: 39~~ or a variant thereof, wherein said variant comprises up to 5 amino acid substitutions in said CDR region~~.

4. The use of any one of claims 1 to 3, wherein the antibody heavy chain amino acid sequence of said antibody comprises the amino acid sequence shown in SEQ ID NO: 17

and the antibody light chain amino acid sequence comprises the amino acid sequence shown in SEQ ID NO: 24.

5. The use of any one of claims 1 to 4, wherein expression of CLDN18.2 is at the cell surface of a cancer cell.

6. The use of any one of claims 1 to 5, wherein the agent stabilizing or increasing expression of CLDN18.2 comprises an agent which induces a cell cycle arrest or an accumulation of cells in one or more phases of the cell cycle.

7. The use of any one of claims 1 to 6, wherein the agent stabilizing or increasing expression of CLDN18.2 comprises an agent selected from the group consisting of nucleoside analogs, platinum compounds, camptothecin analogs, taxanes, salts thereof, and combinations thereof.

8. The use of any one of claims 1 to 7, wherein the agent stabilizing or increasing expression of CLDN18.2 comprises an agent selected from the group consisting of gemcitabine, 5-fluorouracil, oxaliplatin, irinotecan, paclitaxel, albumin-bound paclitaxel, salts thereof, and combinations thereof.

9. The use of any one of claims 1 to 8, wherein the agent stabilizing or increasing expression of CLDN18.2 comprises an agent inducing immunogenic cell death.

10. The use of claim 9, wherein the agent inducing immunogenic cell death comprises oxaliplatin.

11. The use of any one of claims 1 to 10, wherein the therapy comprises that a combination of gemcitabine and oxaliplatin, a combination of gemcitabine and cisplatin, a combination of gemcitabine and carboplatin or a combination of oxaliplatin, 5-fluorouracil or capecitabine and irinotecan is to be administered.

12. The use of any one of claims 1 to 11, wherein the therapy comprises that folinic acid, oxaliplatin, 5-fluorouracil or capecitabine and irinotecan are to be administered.

13. The use of any one of claims 1 to 12, wherein the therapy further comprises that an agent stimulating γδ T cells is to be administered, wherein said agent is a bisphosphonate.

14. The use of claim 13, wherein the γδ T cells are Vγ9Vδ2 T cells.

15. The use of claim 13 or 14, wherein the agent stimulating γδ T cells is a nitrogen-containing bisphosphonate.

16. The use of any one of claims 13 to 15, wherein the agent stimulating γδ T cells is selected from the group consisting of zoledronic acid, clodronic acid, ibandronic acid, pamidronic acid, risedronic acid, minodronic acid, olpadronic acid, alendronic acid, incadronic acid and salts thereof.

17. The use of any one of claims 13 to 16, wherein the agent stimulating γδ T cells is to be administered in combination with interleukin-2.

18. The use of any one of claims 1 to 17, wherein the antibody having the ability of binding to CLDN18.2 binds to the first extracellular loop of CLDN18.2.

19. The use of any one of claims 1 to 18, wherein the antibody having the ability of binding to CLDN18.2 mediates cell killing by one or more of complement dependent cytotoxicity (CDC) mediated lysis, antibody dependent cellular cytotoxicity (ADCC) mediated lysis, induction of apoptosis and inhibition of proliferation.

20. The use of any one of claims 1 to 19, wherein the therapy comprises that the antibody having the ability of binding to CLDN18.2 at a dose of up to 1000 mg/m^2 is to be administered.

21. The use of any one of claims 1 to 20, wherein the therapy comprises that the antibody having the ability of binding to CLDN18.2 repeatedly at a dose of 300 to 600 mg/m^2 is to be administered.

22. The use of any one of claims 1 to 21, wherein CLDN18.2 has the amino acid sequence according to SEQ ID NO: 1.

23. The use of any one of claims 1 to 22, wherein the cancer is a pancreatic cancer.

24. The use of claim 23, wherein the pancreatic cancer comprises primary cancer, advanced cancer or metastatic cancer, or a combination thereof such as a combination of pancreatic primary cancer and metastatic cancer.

25. The use of claim 24, wherein the metastatic cancer comprises metastasis to the lymph nodes, ovary, liver or lung, or a combination thereof.

26. The use of any one of claims 23 to 25, wherein the pancreatic cancer comprises a cancer of the pancreatic duct.

27. The use of any one of claims 23 to 26, wherein the pancreatic cancer comprises an adenocarcinoma or carcinoma, or a combination thereof.

28. The use of any one of claims 1 to 27, wherein the pancreatic cancer comprises a ductal adenocarcinoma, a mucinous adenocarcinoma, a neuroendocrine carcinoma or an acinic cell carcinoma, or a combination thereof.

29. The use of any one of claims 1 to 28, wherein the cancer is partially or completely refractory to gemcitabine treatment such as gemcitabine monotherapy.

~~30. The use of any one of claims 23 to 29, wherein preventing pancreatic cancer comprises preventing a recurrence of pancreatic cancer.~~

~~31~~30. The use of any one of claims 1 to ~~30~~29, wherein the patient had a surgery for pancreatic cancer.

~~32~~31. The use of any one of claims 1 to ~~31~~30, wherein the patient has a precancerous pancreatic lesion, or a precancerous pancreatic lesion comprising a beginning malignant histological change in the pancreatic ducts.