mg/kg) and cynomolgus monkeys (up to 5 weekly applications of up to 100 mg/kg) repeated doses of IMAB362 i.v. are well tolerated. No signs of systemic or local toxicity are induced. Specifically, no gastric toxicity has been observed in any toxicity study. IMAB362 does not induce immune activation and cytokine release. No adverse effects on male or female reproductive organs were recorded. IMAB362 does not bind to tissues lacking the target. Biodistribution studies in mice indicate that the reason for lack of gastric toxicity is most likely compartimentalization of tight junctions at the luminal site in healthy gastric epithelia, which appears to impair accessibility of the IMAB362 epitope profoundly.

IMAB362 is in early clinical testing. A phase I clinical study has been conducted in human. 5 dose cohorts (33 mg/m^2, 100 mg/m^2, 300 mg/m^2, 600 mg/m^2, 1000 mg/m^2) of 3 patients each have received a single intravenous administration of IMAB362 and have been observed for 28 days. IMAB362 was very well tolerated, with no relevant safety observation in the patients. In one patient all measured tumor markers decreased significantly within 4 weeks after treatment. In an ongoing phase IIa clinical study IMAB362 is given repetitively.

Here we present data demonstrating that chemotherapeutic agents can stabilize or increase expression of CLDN18.2 on the surface of pancreatic cancer cells resulting in an enhanced drugability of CLDN18.2 by an anti-CLDN18.2 antibody such as IMAB362. A synergistic effect of an anti-CLDN18.2 antibody such as IMAB362 with particular chemotherapeutic regimens, in particular chemotherapeutic regimens used for pancreatic cancer treatment was observed. Human cancer cells pre-treated with chemotherapy are more susceptible to antibody-induced target-specific killing. In mouse tumor models, tumor control with an anti-CLDN18.2 antibody plus chemotherapy is superior to that with an anti-CLDN18.2 antibody as single agent.

SUMMARY

The present disclosure generally provides a combination therapy for effectively treating and/or preventing diseases associated with cells expressing CLDN18.2, including cancer diseases such as gastric cancer, esophageal cancer, pancreatic cancer, lung cancer such as non small cell lung cancer (NSCLC), ovarian cancer, colon cancer, hepatic cancer, head-neck cancer, and cancer of the gallbladder and metastases thereof, in particular gastric cancer

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-

phase or the G2-phase with the G1-phase. The agent stabilizing or increasing expression of CLDN18.2 may comprise an agent selected from the group consisting of nucleoside analogs, platinum compounds, camptothecin analogs and taxanes, prodrugs thereof, salts thereof, and combinations thereof. The nucleoside analog may be selected from the group consisting of gemcitabine, 5-fluorouracil, prodrugs thereof and salts thereof. The platinum compound may selected from the group consisting of oxaliplatin, cisplatin, prodrugs thereof and salts thereof. The camptothecin analog may be selected from the group consisting of irinotecan, topotecan, prodrugs thereof and salts thereof. The taxane may be selected from the group consisting of paclitaxel, docetaxel, prodrugs thereof and salts thereof. The agent stabilizing or increasing expression of CLDN18.2 may comprise an agent selected from the group consisting of gemcitabine, 5-fluorouracil, oxaliplatin, irinotecan, paclitaxel, prodrugs thereof, salts thereof and combinations thereof. The agent stabilizing or increasing expression of CLDN18.2 may comprise a combination of oxaliplatin and 5-fluorouracil or prodrugs thereof, a combination of cisplatin and 5-fluorouracil or prodrugs thereof, a combination of at least one taxane and oxaliplatin, a combination of at least one taxane and cisplatin, a combination of at least one taxane and 5-fluorouracil or prodrugs thereof, or a combination of at least one camptothecin analog and 5-fluorouracil or prodrugs thereof. The agent stabilizing or increasing expression of CLDN18.2 may comprise 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 prodrugs thereof and irinotecan. Accordingly, the method of the disclosure may comprise administering 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 prodrugs thereof and irinotecan. In one example, the method of the disclosure comprises administering folinic acid, 5-fluorouracil or prodrugs thereof, irinotecan and oxaliplatin. The agent stabilizing or increasing expression of CLDN18.2 may comprise an agent inducing immunogenic cell death. The agent inducing immunogenic cell death may comprise oxaliplatin.

In a further example, the present disclosure provides a method of treating or preventing cancer in a patient comprising administering to the patient (i) an antibody having the ability of binding to CLDN18.2 and (ii) gemcitabine. In one example, the cancer is selected from the group consisting of gastric cancer, esophageal cancer, pancreatic cancer, lung cancer, ovarian cancer, colon cancer, hepatic cancer, head-neck cancer, cancer of the gallbladder and the metastasis thereof. The cancer disease may be a Krukenberg tumor, peritoneal metastasis

and/or lymph node metastasis. In one example, the cancer is an adenocarcinoma, in particular an advanced adenocarcinoma. In one example, the cancer is pancreatic cancer.

In one example, the method of the disclosure further comprises administering an agent stimulating γδ T cells. In one example, the γδ T cells are Vγ9Vδ2 T cells. In one example, the agent stimulating γδ T cells is a bisphosphonate such as a nitrogen-containing bisphosphonate (aminobisphosphonate). In one example, 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. In one example, the agent stimulating γδ T cells is administered in combination with interleukin-2.

The method of the disclosure may further comprise administering at least one further chemotherapeutic agent which may be a cytotoxic agent.

The antibody having the ability of binding to CLDN18.2 may bind to native epitopes of CLDN18.2 present on the surface of living cells. In one example, the antibody having the ability of binding to CLDN18.2 binds to the first extracellular loop of CLDN18.2. In one example, 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. In one example, the antibody having the ability of binding to CLDN18.2 is a monoclonal, chimeric or humanized antibody, or a fragment of an antibody. In one example, the antibody mediates cell killing when bound to cellular CLDN18.2, in particular to CLDN18.2 expressed by cells on their cell surface, wherein the cells are preferably cancer cells, such as cells of the cancers described herein. In one example, the antibody having the ability of binding to CLDN18.2 is an antibody selected from the group consisting of (i) an antibody produced by and/or obtainable from a clone deposited under the accession no. DSM ACC2737, DSM ACC2738, DSM ACC2739, DSM ACC2740, DSM ACC2741, DSM ACC2742, DSM ACC2743, DSM ACC2745, DSM ACC2746, DSM ACC2747, DSM ACC2748, DSM ACC2808, DSM ACC2809, or DSM ACC2810, (ii) an antibody which is a chimerized or humanized form of the antibody under (i), (iii) an antibody having the specificity of the antibody under (i) and (iv) an antibody comprising the antigen binding portion or antigen binding site, in particular the variable region, of the antibody under (i) and

preferably having the specificity of the antibody under (i). In one example, the antibody is coupled to a therapeutic agent such as a toxin, a radioisotope, a drug or a cytotoxic agent.

In one example, the method of the disclosure comprises administering the antibody having the ability of binding to CLDN18.2 at a dose of up to 1000 mg/m^2. In one example, the method of the disclosure comprises administering the antibody having the ability of binding to CLDN18.2 repeatedly at a dose of 300 to 600 mg/m^2.

According to the disclosure, CLDN18.2 preferably has the amino acid sequence according to SEQ ID NO: 1.

In one example, the cancer described herein is CLDN18.2 positive. In one example, cancer cells of the cancer described herein are CLDN18.2 positive. In one example, cancer cells of the cancer described herein express CLDN18.2 on their cell surface.

In one example, the pancreatic cancer described herein comprises primary cancer, advanced cancer or metastatic cancer, or a combination thereof such as a combination of pancreatic primary cancer and metastatic cancer. In one example, the methods of the disclosure are for the simultanous treatment of primary cancer and metastatic cancer such as pancreatic primary cancer and pancreatic metastatic cancer. In one example, the metastatic cancer comprises metastasis to the lymph nodes, ovary, liver or lung, or a combination thereof. In one example, the pancreatic cancer comprises cancer of the pancreatic duct. In one example, the pancreatic cancer comprises an adenocarcinoma or carcinoma, or a combination thereof. In one example, the pancreatic cancer comprises a ductal adenocarcinoma, a mucinous adenocarcinoma, a neuroendocrine carcinoma or an acinic cell carcinoma, or a combination thereof. In one example, the pancreatic cancer is partially or completely refractory to gemcitabine treatment such as gemcitabine monotherapy. In one example, preventing pancreatic cancer comprises preventing a recurrence of pancreatic cancer.

In one example, the patient to be treated according to the disclosure had a surgery for pancreatic cancer. In one example, the patient has a precancerous pancreatic lesion, in particular a precancerous pancreatic lesion comprising a beginning malignant histological change in the pancreatic ducts. In these examples, the methods of the disclosure preferably aim at preventing the development of malignant pancreatic cancer.

In a further example, the present disclosure provides a medical preparation for treating or preventing pancreatic cancer comprising (i) an antibody having the ability of binding to CLDN18.2 and (ii) an agent stabilizing or increasing expression of CLDN18.2. The medical preparation of the present disclosure may further comprise an agent stimulating γδ T cells. The antibody having the ability of binding to CLDN18.2 and the agent stabilizing or increasing expression of CLDN18.2, and optionally the agent stimulating γδ T cells, may be present in the medical preparation in a mixture or separate from each other. The medical preparation may be present in the form of a kit comprising a first container including the antibody having the ability of binding to CLDN18.2 and a second container including the agent stabilizing or increasing expression of CLDN18.2, and optionally a container including the agent stimulating γδ T cells. The medical preparation may further include printed instructions for use of the preparation for treatment or prevention of pancreatic cancer, in particular for use of the preparation in a method of the disclosure. Different examples of the medical preparation, and, in particular, of the antibody having the ability of binding to CLDN18.2, the agent stabilizing or increasing expression of CLDN18.2 and the agent stimulating γδ T cells are as described above for the methods of the disclosure.

In a particular example, the present disclosure provides a medical preparation comprising (i) an antibody having the ability of binding to CLDN18.2, and (ii) gemcitabine. The medical preparation of the present disclosure may further comprise an agent stimulating γδ T cells. The antibody having the ability of binding to CLDN18.2 and gemcitabine, and optionally the agent stimulating γδ T cells, may be present in the medical preparation in a mixture or separate from each other. The medical preparation may be for treating or preventing cancer such as pancreatic cancer. The medical preparation may be present in the form of a kit comprising a first container including the antibody having the ability of binding to CLDN18.2 and a second container including gemcitabine, and optionally a container including the agent stimulating γδ T cells. The medical preparation may further include printed instructions for use of the preparation for treatment or prevention of cancer such as pancreatic cancer, in particular for use of the preparation in a method of the disclosure. Different examples of the medical preparation, and, in particular, of the antibody having the ability of binding to CLDN18.2, the agent stabilizing or increasing expression of CLDN18.2 and the agent stimulating γδ T cells are as described above for the methods of the disclosure.

The present disclosure also provides the agents described herein such as the antibody having the ability of binding to CLDN18.2 and/or the agent stabilizing or increasing expression of CLDN18.2 for use in the methods described herein. For example, the present disclosure also provides the antibody having the ability of binding to CLDN18.2 for administration in conjunction with an agent stabilizing or increasing expression of CLDN18.2 such as gemcitabine, and optionally an agent stimulating γδ T cells.

Other features and advantages of the instant disclosure will be apparent from the following detailed description and claims.

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

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