of at least 1000 mg/m$^2$. Furthermore, the data presented herein demonstrate that the antibody is fully functional in these patients to execute anti-tumor cell effects and evidence for antitumoral activity was obtained.

## SUMMARY

In one aspect, the present disclosure refers to an *in vitro* method of determining the responsiveness of a cancer patient to treatment of a cancer disease with an antibody binding to an epitope of CLDN18.2, said method comprising the step of determining the blood level of one or more markers, wherein the one or more markers are selected from the group consisting of CA 125, CA 15-3, CA 19-9, CEA, IL-2, IL-15, IL-6, IFNγ, and TNFα, wherein the antibody comprises either an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein a patient is responsive to treatment of the cancer (i) when the administration of the antibody induces a decrease in the level of a marker selected from the group of CA 125, CA 15-3, CA 19-9, CEA, IL-2, IL-15, IFNγ, and TNFα, or (ii) when the administration of the antibody induces an increase in the level of IL-6.

In another aspect, the present disclosure refers to an *in vitro* method of determining whether a cancer patient is amenable to treatment of a cancer disease, said method comprising the step of determining the percentage of CLDN18.2 positive cancer cells, wherein the antibody either comprises an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein a level of at least 50% CLDN18.2 positive cancer cells indicates that the patient is amenable to treatment of the cancer disease.

In yet another aspect, the present disclosure refers to a use of an antibody having the ability of binding to CLDN18.2 and inducing killing of cells expressing CLDN18.2 in the manufacture of a medicament for treating a cancer disease of a patient, wherein the treatment comprises that an antibody to provide a serum level of at least 50 µg/ml is to be administered to the patient, wherein the antibody comprises either an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid

sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein the cancer is gastric cancer, gastroesophageal cancer, advanced gastroesophageal cancer, advanced adenocarcinoma of the stomach or the lower oesophagus, or metastatic, refractory or recurrent advanced gastroesophageal cancer.

In yet another aspect, the present disclosure refers to a use of an antibody having the ability of binding to CLDN18.2 and inducing killing of cells expressing CLDN18.2 in the manufacture of

a medicament for treating a cancer disease of a patient, wherein the treatment comprises that an antibody to provide a serum level of at least 50 µg/ml is to be administered to the patient, wherein at least 50% of the cancer cells of the patient are CLDN18.2 positive and/or at least 40% of the cancer cells of the patient are positive for surface expression of CLDN18.2, wherein the antibody either comprises an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein the cancer is gastric cancer, gastroesophageal cancer, advanced gastroesophageal cancer, advanced adenocarcinoma of the stomach or the lower oesophagus, or metastatic, refractory or recurrent advanced gastroesophageal cancer.

In yet another aspect, the present disclosure refers to a use of an antibody having the ability of binding to CLDN18.2 and inducing killing of cells expressing CLDN18.2 in the manufacture of a medicament for treating a cancer disease of a patient, wherein the treatment comprises a combination therapy of the antibody with one or more selected from the group consisting of antiemetics, antispasmodics, parasympatholytics and agents which protect gastric mucosa, wherein the antibody is to be administered to provide a serum level at 50 µg/ml and wherein the antibody comprises either an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein the cancer is gastric cancer, gastroesophageal cancer, advanced gastroesophageal cancer, advanced adenocarcinoma of the stomach or the lower oesophagus, or metastatic, refractory or recurrent advanced gastroesophageal cancer.

In a first example, the present disclosure refers to the use of an antibody having the ability of binding to CLDN18.2 in the manufacture of a medicament for treating or preventing a cancer disease in a patient, wherein the antibody is to be administered so as to provide a serum level of at least 40 µg/ml. In another example, the present disclosure refers to the use of an antibody having the ability of binding to CLDN18.2 in the manufacture of a medicament for treating or preventing a cancer disease in a patient, wherein the antibody is to be administered at a dose of at least 300 mg/m$^2$. In still another example, the present disclosure refers to the use of an antibody having the ability of binding to CLDN18.2 in the manufacture of a medicament for treating or preventing a cancer disease in a patient, wherein at least 50% of the cancer cells of the patient are CLDN18.2 positive and/or at least 40% of the cancer cells of the patient are positive for surface expression of CLDN18.2. In still another example, the present disclosure refers to the use of an antibody having the ability of binding to CLDN18.2 in the manufacture of a medicament for achieving stable disease in a cancer patient. In a further example, the present disclosure

**Claims**

1. An *in vitro* method of determining the responsiveness of a cancer patient to treatment of a cancer disease with an antibody binding to an epitope of CLDN18.2, said method comprising the step of determining the blood level of one or more markers, wherein the one or more markers are selected from the group consisting of CA 125, CA 15-3, CA 19-9, CEA, IL-2, IL-15, IL-6, IFNγ, and TNFα, wherein the antibody comprises either an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein a patient is responsive to treatment of the cancer
(i) when the administration of the antibody induces a decrease in the level of a marker selected from the group of CA 125, CA 15-3, CA 19-9, CEA, IL-2, IL-15, IFNγ, and TNFα, or
(ii) when the administration of the antibody induces an increase in the level of IL-6.

2. The method of claim 1 wherein the level is determined in blood, plasma or serum.

3. An *in vitro* method of determining whether a cancer patient is amenable to treatment of a cancer disease, said method comprising the step of determining the percentage of CLDN18.2 positive cancer cells, wherein the antibody either comprises an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein a level of at least 50% CLDN18.2 positive cancer cells indicates that the patient is amenable to treatment of the cancer disease.

4. The method of claim 3 wherein a level of at least 50% cancer cells which are positive for surface expression of CLDN18.2 indicates that the patient is amenable to treatment of a cancer disease.

5. The method of any one of claims 1 to 4, wherein the antibody 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.

6. The method of any one of claims 1 to 5 wherein the cancer is gastroesophageal cancer.

7. The method of any one of claims 1 to 6 wherein the cancer is metastatic, refractory or recurrent advanced gastroesophageal cancer.

8. The method of any one of claims 1 to 7 wherein the patient had prior therapy with at least one drug selected from the group consisting of pyrimidine analogs, platinum compounds, epirubicine, docetaxel and detoxifying agents for antineoplastic treatment.

9. The method of any one of claims 1 to 7 wherein the patient is to be treated in a combination therapy with an agent stabilizing or increasing expression of CLDN18.2, which agent is selected from the group consisting of (i) oxaliplatin and 5-fluorouracil, (ii) epirubicin, oxaliplatin and 5-fluorouracil, (iii) 5-fluorouracil, folinic acid and oxaliplatin, (iv) irinotecan, (v) docetaxel and (vi) cisplatin, and prodrugs thereof.

10. The method of any one of claims 1 to 9 wherein CLDN18.2 has the amino acid sequence according to SEQ ID NO: 1.

11. Use of an antibody having the ability of binding to CLDN18.2 and inducing killing of cells expressing CLDN18.2 in the manufacture of a medicament for treating a cancer disease of a patient, wherein the treatment comprises that an antibody to provide a serum level of at least 50 µg/ml is to be administered to the patient, wherein the antibody comprises either an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein the cancer is gastric cancer, gastroesophageal cancer, advanced gastroesophageal cancer, advanced adenocarcinoma of the stomach or the lower oesophagus, or metastatic, refractory or recurrent advanced gastroesophageal cancer.

12. The use of claim 11 wherein the antibody is to be administered to provide a serum level of between 50 µg/ml and 700 µg/ml.

13. The use of claim 11 or 12 wherein the serum level is provided for at least 7 days.

14. The use of any one of claims 11 to 13 wherein the treatment comprises that a dose of the antibody of 300 mg/m$^2$ is to be administered.

15. Use of an antibody having the ability of binding to CLDN18.2 and inducing killing of cells expressing CLDN18.2 in the manufacture of a medicament for treating a cancer disease of a patient, wherein the treatment comprises that an antibody to provide a serum level of at least 50 µg/ml is to be administered to the patient, wherein at least 50% of the cancer cells of the patient are CLDN18.2 positive and/or at least 40% of the cancer cells of the patient are positive for surface expression of CLDN18.2, wherein the antibody either comprises an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein the cancer is gastric cancer, gastroesophageal cancer, advanced gastroesophageal cancer, advanced adenocarcinoma of the stomach or the lower oesophagus, or metastatic, refractory or recurrent advanced gastroesophageal cancer.

16. The use of any one of claims 11 to 15 wherein treatment of the cancer disease results in achieving stable disease for at least 2 months.

17. The use of any one of claims 11 to 16 wherein the antibody is to be administered in a single dose or in multiple doses.

18. The use of claim 17 wherein the antibody is to be administered in at least 3 doses.

19. The use of claims 17 or 18 wherein the doses of the antibody are to be administered in time intervals of at least 7 days.

20. Use of an antibody having the ability of binding to CLDN18.2 and inducing killing of cells expressing CLDN18.2 in the manufacture of a medicament for treating a cancer disease

of a patient, wherein the treatment comprises a combination therapy of the antibody with one or more selected from the group consisting of antiemetics, antispasmodics, parasympatholytics and agents which protect gastric mucosa, wherein the antibody is to be administered to provide a serum level at 50 µg/ml and wherein the antibody comprises either an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 32 and an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 39, or wherein the antibody is a functional variant of said antibody which binds to the same epitope of CLDN18.2, wherein the cancer is gastric cancer, gastroesophageal cancer, advanced gastroesophageal cancer, advanced adenocarcinoma of the stomach or the lower oesophagus, or metastatic, refractory or recurrent advanced gastroesophageal cancer.

21. The use of any one of claims 11 to 20 wherein the antibody is to be administered by i.v. infusion over a time period of between 1 and 4 hours.

22. The use of any one of claims 15 to 21, wherein the antibody is to be administered to provide a serum level of between 50 µg/ml and 700 µg/ml.

23. The use of any one of claims 15 to 22, wherein the treatment comprises that a dose of the antibody of 300 mg/m$^2$ is to be administered.