CLAIMS

1) An *in vitro* method for selecting a cancer patient susceptible to responding to treatment with an immune checkpoint inhibitor, said method comprising the steps of:

a) contacting a biological sample from said subject with at least one progastrin-binding ~~molecule~~antibody, chosen in the group consisting of

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30,

respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively,

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39, respectively, and
- A monoclonal antibody produced by the hybridoma deposited at the CNCM, Institut Pasteur, 25-28 rue du Docteur Roux, 75724 Paris CEDEX 15, France, on 27 December 2016, under reference I-5158

and

~~a)~~b) detecting the binding of said progastrin-binding ~~molecule~~ antibody to progastrin in said sample, wherein a concentration of progastrin of at least 3 pM, at least 5 pM, at least 10 pM, at least 20 pM, at least 30 pM, in said biological sample is indicative of the presence of a cancer which is not responsive to treatment with an immune checkpoint inhibitor in said subject~~wherein said binding indicates the patient is not responsive to treatment with an immune checkpoint inhibitor~~.

~~2) The method of claim 1, wherein a concentration of progastrin of at least 3 pM, at least 5 pM, at least 10 pM, at least 20 pM, at least 30 pM, in said biological sample is indicative of the presence of a cancer which is not responsive to treatment with an immune checkpoint inhibitor in said subject.~~

~~3)~~2) The method of ~~any one of~~ claim~~s~~ 1~~ or 2~~, wherein the method comprises the further steps of:

~~b)~~c) determining a reference concentration of progastrin in a reference sample,

~~c)~~d) comparing the concentration of progastrin in said biological sample with said reference concentration of progastrin,

~~d)~~e) determining, from the comparison of step d), whether said patient is responsive or not to treatment with an immune checkpoint inhibitor.

~~4) The method of any one of claims 1 to 3, wherein said progastrin-binding molecule is wherein said progastrin-binding molecule is an antibody, or an antigen-binding fragment thereof.~~

~~5) The method of any of claims 1 to 4, wherein said antibody, or antigen-binding fragment thereof, is selected among N-terminal anti-progastrin monoclonal antibodies and C-terminal anti-progastrin monoclonal antibodies.~~

~~6) The method of any of claims 1 to 5, wherein said antibody binding to progastrin is a monoclonal antibody chosen in the group consisting of:~~

~~- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9, respectively,~~

~~- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively,~~

~~- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively,~~

~~- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, and~~

~~a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively,~~

~~- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively,~~

~~- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39, respectively, and~~

~~- A monoclonal antibody produced by the hybridoma deposited at the CNCM, Institut Pasteur, 25-28 rue du Docteur Roux, 75724 Paris CEDEX 15, France, on 27 December 2016, under reference I-5158.~~

~~7)~~3) The method of any one of claim 1 ~~to 6~~or 2, wherein the determination of step a) includes:

(i) contacting said sample with a first progastrin-binding ~~molecule~~ antibody which binds to a first ~~part~~ epitope of progastrin, and

(ii) contacting said sample with a second progastrin-binding ~~molecule~~ antibody which binds to a second ~~part~~ epitope of progastrin.

~~8)~~4) The method of claim ~~7~~3, wherein the first progastrin-binding ~~molecule~~ antibody binds an epitope within the C-terminus of progastrin.

~~9)~~5) The method of ~~any one of~~ claim~~s 7 or 8~~4, wherein said first progastrin-binding ~~molecule~~ antibody is a monoclonal antibody produced by the hybridoma deposited at the CNCM, Institut Pasteur, 25-28 rue du Docteur Roux, 75724 Paris CEDEX 15, France, on 27 December 2016, under reference I-5158.

~~10)~~6) The method of any one of claims ~~7~~ 3 to ~~9~~5, wherein the second progastrin-binding ~~molecule~~ antibody binds an epitope within the N-terminus of progastrin.

~~11)~~7) The method of any one of claims ~~7~~ 3 to ~~10~~6, wherein said second progastrin-binding ~~molecule~~ antibody is: ~~a polyclonal antibody binding an epitope within the N-terminus of progastrin or~~ a monoclonal antibody comprising a heavy chain comprising the following three CDRs, CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising the following three CDRs, CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively.

~~12)~~8) The method of any one of claims 1 to ~~11~~7, wherein the level of progastrin is determined in step a) with an ELISA.

~~13) The method of any one of claims 1 to 6, wherein said biological sample is contacted with a first molecule, which binds to a first part of progastrin, and with a second molecule, which binds to a second part of progastrin.~~

~~14)~~9) The method of any one of claims 1 to ~~13~~8, wherein said biological sample is chosen among: blood, serum and plasma.

~~15)~~10) The method of any one of claims 1 to ~~14~~9, wherein said cancer is oesophageal cancer, liver cancer, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer and gastrointestinal stromal cancer, pancreatic cancer, Hodgkin lymphoma, colon cancer, rectal cancer, colorectal cancer, hepatoma, hepatic carcinoma, anal carcinoma, non-melanoma skin cancer, skin melanoma, cervical cancer, uterine cancer, endometrial cancer, ovarian cancer, or breast cancer.

~~16)~~11) Use of a~~A~~n immune checkpoint inhibitor ~~for~~in the manufacture of a medicament for the treatment of ~~use in treating~~ cancer, ~~said use~~ comprising a prior ~~step~~ selection of:

~~a)selecting~~ a patient responsive to immune checkpoint inhibitors using a method according any one of claims 1 to 10~~15~~.

~~17)~~12) Use of a~~A~~n immune checkpoint inhibitor in the manufacture of a medicament for ~~use~~ the treatment of ~~in treating~~ cancer, ~~said use~~ comprising:

a) contacting a biological sample from said subject with at least one progastrin-binding ~~molecule~~antibody chosen in the group consisting of:

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-

H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39, respectively, and

- A monoclonal antibody produced by the hybridoma deposited at the CNCM, Institut Pasteur, 25-28 rue du Docteur Roux, 75724 Paris CEDEX 15, France, on 27 December 2016, under reference I-5158,

~~a)~~b) detecting the binding of said progastrin-binding ~~molecule~~ antibody to progastrin in said sample, wherein a concentration of progastrin of at least 3 pM, at least 5 pM, at least 10 pM, at least 20 pM, at least 30 pM, in said biological sample is indicative of the presence of a cancer which is not responsive to treatment with an immune checkpoint inhibitor in said subject~~wherein said binding indicates the patient is not responsive to treatment with an immune checkpoint inhibitor~~, and

~~b)~~c) ~~adapting~~ the immune checkpoint inhibitor treatment is to be adapted in function of the result of step b).

~~18)~~13) An *in vitro* method for prognosing a cancer treatment with an immune checkpoint inhibitor in a subject, said method comprising the steps of:

a) contacting a biological sample from said subject with at least one progastrin-binding ~~molecule~~antibody chosen in the group consisting of

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively,

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39, respectively, and
- A monoclonal antibody produced by the hybridoma deposited at the CNCM, Institut Pasteur, 25-28 rue du Docteur Roux, 75724 Paris CEDEX 15, France, on 27 December 2016, under reference I-5158, and

~~a)~~b) detecting the binding of said progastrin-binding ~~molecule~~ antibody to progastrin in said sample, wherein a concentration of progastrin of at least 3 pM, at least 5 pM, at least 10 pM, at least 20 pM, at least 30 pM, in said biological sample indicates the prognosis is negative ~~wherein said binding indicates the prognosis is negative~~.

~~19) The method of claim 18, wherein a concentration of progastrin of at least 3 pM, at least 5 pM, at least 10 pM, at least 20 pM, at least 30 pM, in said biological sample is indicative of a negative prognosis.~~

~~20)~~14) The method of ~~any one of~~ claim~~s 18 and 19~~ 13 wherein the method comprises the further steps of:

~~b)~~a) determining a reference concentration of progastrin in a reference sample,

~~c)~~b) comparing the concentration of progastrin in said biological sample with said reference concentration of progastrin,

~~b)~~c) prognosing, from the comparison of step ~~d~~b), said cancer treatment with an immune checkpoint inhibitor.