Claims

1. Use of an anti-GREM1 antagonist in the manufacture of a medicament for treating or preventing a cancer, wherein the medicament is to be further administered with a cytidine analogue or deoxycytidine analogue.

2. Use according to claim 1, wherein:

(a) the cancer is a solid cancer;

(b) the cancer has stromal GREM1 overexpression;

(c) the cancer is a metastatic cancer;

(d) the cancer comprises dormant cancer cells, optionally dormant stem-like cancer cells;

(e) the cancer is a recurring cancer and/or wherein said method is for preventing relapse of a cancer;

(f) the cancer is a cancer that is poorly responsive, non-responsive or refractory to treatment with a cytidine analogue or deoxycytidine analogue; optionally wherein the cancer is a cancer that is poorly responsive, non-responsive or refractory to treatment with gemcitabine, or a derivative thereof; and/or

(g) the cancer is selected from colorectal cancer, multiple myeloma, pancreatic cancer, bladder cancer, breast cancer, lung cancer, stomach cancer, duodenal cancer, oesophageal cancer, head and neck cancer, prostate cancer, glioma, endometrial cancer, ovarian cancer, liver cancer, spleen cancer, bone-resident cancer, and osteosarcoma.

3. Use according to claim 2 (g), wherein:

(a) the cancer is pancreatic cancer; optionally wherein:

(i) the pancreatic cancer is an exocrine pancreatic cancer; and/or

(ii) the pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC);

(b) the cancer is lung cancer; optionally wherein the cancer is non-small cell lung cancer;

(c) the cancer is bladder cancer;

(d) the cancer is breast cancer; or

(e) the cancer is ovarian cancer.

4. Use according to any one of the preceding claims, wherein:

(a) (i) the cancer has epithelial GREM1 overexpression; optionally wherein the cancer is a GREM1-initiated cancer;
(ii) the cancer is a disseminated cancer; and/or
(iii) the cancer is an established cancer; and/or

(b) (i) the cytidine analogue or deoxycytidine analogue is gemcitabine, or a derivative thereof;
(ii) the cytidine analogue or deoxycytidine analogue is azacitidine, or a derivative thereof;
(iii) the cytidine analogue or deoxycytidine analogue is cytarabine, or a derivative thereof;
(iv) the cytidine analogue or deoxycytidine analogue is decitabine, or a derivative thereof; or
(v) the cytidine analogue or deoxycytidine analogue is troxacitabine, or a derivative thereof.

5. Use of an anti-GREM1 antagonist in the manufacture of a medicament for treating or preventing pancreatic cancer, wherein the medicament is to be further administered with a proliferation-dependent cytotoxic agent.

6. Use according to claim 5, wherein:

(a) the pancreatic cancer is an exocrine pancreatic cancer;

(b) the pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC);

(c) the pancreatic cancer is metastatic pancreatic cancer;

(d) the pancreatic cancer is recurrent pancreatic cancer; and/or

(e) the pancreatic cancer is a pancreatic cancer that is poorly responsive, non-responsive or refractory to treatment with a proliferation-dependent cytotoxic agent.

7. Use according to claim 5 or claim 6, wherein:

(a) the proliferation-dependent cytotoxic agent is a nucleoside inhibitor or an antimetabolite;

(b) the proliferation-dependent cytotoxic agent is a cytidine analogue or deoxycytidine analogue;

(c) the proliferation-dependent cytotoxic agent is a mitotic inhibitor; optionally wherein:

(i) the mitotic inhibitor is a microtubule-stabilizing drug; and/or

(ii) the mitotic inhibitor and/or microtubule stabilizing drug is selected from abraxane and paclitaxel;

(d) the proliferation-dependent cytotoxic agent comprises one or more of oxaliplatin, folinic acid, irinotecan and fluorouracil; optionally wherein the proliferation-dependent cytotoxic agent is FOLFIRINOX or FOLFOX; or

(e) the proliferation-dependent cytotoxic agent is:

(i) gemcitabine or a derivative thereof;

(ii) azacitidine or a derivative thereof;

(iii) cytarabine or a derivative thereof;

(iv) decitabine or a derivative thereof;

(v) troxacitabine or a derivative thereof; or

(vi) capecitabine.

8. Use according to any one of the preceding claims, wherein the antagonist is a peptide, a protein, an antibody, a polynucleotide, an oligonucleotide, an antisense RNA, a small interfering RNA (siRNA), a small molecule inhibitor or a small hairpin RNA (shRNA).

9. Use according to claim 8, wherein:

(a) the antagonist is an antibody which binds to an epitope on Gremlin-1 comprising at least one residue selected from Ile131, Lys147, Lys148, Phe149, Thr150, Thr151, Arg169, Lys174 and Gln175, wherein the residue numbering is according to SEQ ID NO: 1; optionally wherein:

(i) the antibody binds an epitope comprising all of Ile131, Lys147, Lys148, Phe149, Thr150, Thr151, Arg169, Lys174 and Gln175; and/or

(ii) Lys147, Lys148, Phe149, Thr150, Thr151, Arg169, Lys174 and Gln175 are located on the same Gremlin-1 monomer and Ile131 is located on the second Gremlin-1 monomer;

(b) the antagonist is an anti-Gremlin-1 antibody which comprises heavy chain complementarity determining region (HCDR) sequences contained within a heavy chain variable region (HCVR) of SEQ ID NO: 10 or 12 and/or light chain complementarity determining region (LCDR) sequences contained within a light chain variable region (LCVR) of SEQ ID NO: 11 or 13; or

(c) the antagonist is an anti-Gremlin-1 antibody which comprises at least one HCDR sequence selected from SEQ ID NOs: 3, 4, 5 and 6 and/or at least one LCDR sequence selected from SEQ ID NOs: 7, 8 and 9; optionally wherein:

(i) the anti-Gremlin-1 antibody comprises a HCDR3 sequence of SEQ ID NO: 6;

(ii) the anti-Gremlin-1 antibody comprises an HCDR1/HCDR2/HCDR3 sequence combination selected from SEQ ID NOs: 4/5/6 or from SEQ ID NOs:3/5/6 and/or an LCDR1/LCDR2/LCDR3 sequence combination selected from SEQ ID NOs: 7/8/9;

(iii) the anti-Gremlin-1 antibody comprises a HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3 sequence combination of SEQ ID NOs: 4/5/6/7/8/9 or SEQ ID NOs: 3/5/6/7/8/9; and/or

(iv) the anti-Gremlin-1 antibody comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 10 or 12 and/or a light chain variable region (LCVR) sequence of SEQ ID NO: 11 or 13, or sequences which are at least 95% identical thereto.

10. Use according to claim 9 (c)(iv), wherein:

(a) the anti-Gremlin-1 antibody comprises a HCVR and LCVR sequence pair of SEQ ID NOs: 10/11 or 12/13 or sequences which are at least 95% identical thereto; optionally wherein the anti-Gremlin-1 antibody comprises HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3 sequences consisting of SEQ ID NOs: 4/5/6/7/8/9 or SEQ ID NOs: 3/5/6/7/8/9 and the remainder of the HCVR and LCVR comprise at least 95% identity to SEQ ID NOs: 10, 11, 12 and/or 13 respectively; and/or

(b) the anti-Gremlin-1 antibody comprises a heavy chain of SEQ ID NO: 14, 16, 18, 22, 28, 30, 32 or 34 and/or a light chain of SEQ ID NO: 15, 17, 19, 23, 29, 31, 33 or 35, or sequences which are at least 95% identical thereto, optionally wherein the anti-Gremlin-1 antibody comprises a heavy and light chain pair of SEQ ID NOs: 14/15, 16/17, 18/19, 22/23, 28/29 or 30/31, 32/33, 34/35, or sequences which are at least 95% identical thereto; further optionally wherein the HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3 sequences of the

antibody consist of SEQ ID NOs: 4/5/6/7/8/9 or SEQ ID NOs: 3/5/6/7/8/9 and the remainder of the heavy and light chains comprise at least 95% identity to SEQ ID NOs: 14, 15, 16 and/or 17 respectively.

11. Use according to claim 8, wherein:

(a) the antagonist is an antibody which competes for binding to Gremlin-1 with an antibody as defined in any one of claims 9(a)(i)-10; or

(b) the antagonist is an antibody which binds the same epitope on Gremlin-1 as an antibody defined in any one of claims 9(a)(i)-10.

12. Use according to any one of claims 8-11, wherein:

(a) the antagonist antibody is a chimeric, human or humanised antibody; and/or

(b) the antagonist antibody is a Fab, modified Fab, Fab', modified Fab', $F(ab')_2$, Fv, single domain antibody or an scFv.

13. Use according to claim 8, wherein the antagonist is a polynucleotide encoding an antibody as defined in any one of claims 9-12, or an expression vector carrying said polynucleotide.

14. Use according to any one of claims 8-12, wherein the antagonist antibody is comprised in pharmaceutical composition further comprising a pharmaceutically acceptable adjuvant and/or carrier.

15. Use according to any one of the preceding claims, wherein the medicament is to be further administered with an additional anti-cancer agent; optionally wherein:

(a) the medicament is to be administered with gemcitabine in combination with a further cytidine analogue or deoxycytidine analogue; and/or

(b) the medicament is to be administered with gemcitabine in combination with troxacitabine

16. Use of a cytidine analogue or deoxycytidine analogue in the manufacture of a medicament for treating or preventing cancer wherein the medicament is to be further administered with an anti-GREM1 antagonist; optionally wherein said cancer, said antagonist, said cytidine analogue or deoxycytidine analogue and/or said medicaments are as defined in any one of claims 1-4 and 8 to 15.

17. Use of a proliferation-dependent cytotoxic agent in the manufacture of a medicament for treating or preventing pancreatic cancer, wherein the medicament is to be further administered with an anti-GREM1 antagonist; optionally wherein said proliferation-dependent cytotoxic agent, said pancreatic cancer, said antagonist and/or said medicaments are as defined in any one of claims 5 to 15.

18. A composition or kit comprising an anti-GREM1 antagonist and a cytidine analogue or deoxycytidine analogue; optionally wherein the cytidine analogue or deoxycytidine analogue is as defined in claim 4(b) .

19. A composition or kit comprising:

    an anti-GREM1 antagonist and a mitotic inhibitor, optionally wherein the mitotic inhibitor is as defined in any one of claims 7(c)(i) or 7(c)(ii).

20. The composition or kit according to any one of claims 18 and 19, wherein the anti-GREM1 antagonist is as defined in any one of claims 8 to 13.

21. A method for determining:

    (a) whether or not a patient having or suspected of having or being at risk of developing cancer is likely to respond to a combination treatment with a GREM1 antagonist and a cytidine analogue or deoxycytidine analogue, which method comprises measuring stromal and/or epithelial expression of GREM1 in a sample obtained from the patient, and thereby predicting whether or not the patient is likely to respond to treatment with the combination; or

    (b) whether or not a patient having or suspected of having or being at risk of developing pancreatic cancer is likely to respond to a combination treatment with a

GREM1 antagonist and a proliferation-dependent cytotoxic agent, which method comprises measuring stromal and/or epithelial expression of GREM1 in a sample obtained from the patient, and thereby predicting whether or not the patient is likely to respond to treatment with the combination.