

CLAIMS

1. Use of a therapeutically effective amount of GREM1 antagonist in the manufacture of a medicament for the treatment of a GREM1-expressing cancer in a subject, wherein the cancer is characterized in reduced androgen receptor (AR) signaling.
2. The use of claim 1, wherein the cancer is a) an AR-expressing cancer or is an AR negative cancer, and/or b) selected from the group consisting of prostate cancer, breast cancer, lung cancer, head and neck cancer, testis cancer, endometrial cancer, ovarian cancer, and skin cancer, and/or c) metastatic, optionally, the cancer is metastatic prostate cancer, further optionally, the cancer is lung metastasis of prostate cancer, and/or d) characterized in GREM1 overexpression.
3. The use of claim 1 or 2, wherein the subject is receiving or has received an androgen deprivation therapy, or is resistant to an androgen deprivation therapy.
4. Use of a therapeutically effective amount of GREM1 antagonist in the manufacture of a medicament for increasing sensitivity of an AR-expressing cancer to an androgen deprivation therapy in a subject.
5. Use of a therapeutically effective amount of GREM1 antagonist in the manufacture of a medicament for the treatment of a GREM1-related disease or condition characterized in deficiency in PTEN and/or p53 in a subject in need thereof, or inhibiting FGFR1 activation in a subject in need thereof, or inhibiting MAPK signaling in a subject in need thereof.
6. The use of claim 5, wherein the deficiency in PTEN and/or p53 is characterized in absence of functional PTEN and/or p53, or in absence of PTEN and/or p53 expression.
7. The use of claim 6, wherein the deficiency in PTEN and/or p53 is characterized in the presence of inactivating mutation in PTEN and/or p53.
8. The use of any one of claims 5-7, wherein the GREM1-related disease or condition is characterized in GREM1 expression or overexpression.

9. The use of any one of claims 5-7, wherein the GREM1-related disease or condition is selected from the group consisting of cancer, fibrotic disease, angiogenesis, glaucoma or retinal disease, kidney disease, pulmonary arterial hypertension, and osteoarthritis (OA).

10. The use of any one of claims 1-9, wherein the cancer is prostate cancer, breast cancer, glioma, liposarcoma, hepatocellular carcinoma, lung cancer, cervical cancer, endometrial carcinoma, uterine leiomyosarcoma, squamous cell carcinoma of the head and neck, thyroid cancer, liver cancer, pancreatic cancer, bladder cancer, colon cancer, esophageal cancer, bile duct cancer, osteosarcoma, glioblastoma, ovarian cancer, gastric cancer, triple negative breast cancer (TNBC), small cell lung cancer or melanoma.

11. The use of claim 2 or 10, wherein the prostate cancer is:

- a) negative in androgen receptor (AR) expression,
- b) negative in both androgen receptor (AR) expression and neuroendocrine (NE) differentiation;
- c) resistant to an androgen deprivation therapy, optionally castration-resistant,
- d) showing a level of Prostate Specific Antigen (PSA) lower than a reference level, or
- e) any combinations of a) to d).

12. The use of claim 2 or 10, wherein the breast cancer is triple negative breast cancer.

13. The use of claim 9, wherein the fibrotic disease is lung fibrosis, skin fibrosis, diabetic nephropathy, or ischaemic renal injury.

14. The use of any one of claims 1-13, wherein the GREM1 antagonist comprises an anti-GREM1 antibody or antigen-binding fragment thereof, an inhibitory GREM1 mimetic peptide, an inhibitory nucleic acid targeting GREM1 RNA or DNA, a polynucleotide encoding the inhibitory nucleic acid, a compound inhibiting interaction between gremlin and BMP or a compound inhibiting the GREM1 activity.

15. The use of any one of claims 1-14, wherein the GREM1 antagonist comprises a GREM1-FGFR1 axis inhibitor.

16. The use of claim 15, wherein the GREM1-FGFR1 axis inhibitor comprises an FGFR1-binding inhibitor.

17. The use of claim 15, wherein the GREM1 antagonist or GREM1-FGFR1 axis inhibitor comprises an antibody against hGREM1 or an antigen-binding fragment thereof.

18. The use of claim 17, wherein the antibody against hGREM1 or antigen-binding fragment thereof comprises:

- a) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 2, and a HCDR3 comprising the sequence of SEQ ID NO: 3; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 4, a LCDR2 comprising the sequence of SEQ ID NO: 5, and a LCDR3 comprising the sequence of SEQ ID NO: 6;
- b) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 11, a HCDR2 comprising the sequence of SEQ ID NO: 12, and a HCDR3 comprising the sequence of SEQ ID NO: 13; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 14, a LCDR2 comprising the sequence of SEQ ID NO: 15, and a LCDR3 comprising the sequence of SEQ ID NO: 16;
- c) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 21, a HCDR2 comprising the sequence of SEQ ID NO: 22, and a HCDR3 comprising the sequence of SEQ ID NO: 23; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 24, a LCDR2 comprising the sequence of SEQ ID NO: 25, and a LCDR3 comprising the sequence of SEQ ID NO: 26; or

- d) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 31, a HCDR2 comprising the sequence of SEQ ID NO: 32, and a HCDR3 comprising the sequence of SEQ ID NO: 33; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 34, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 36.

19. The use of claim 17 or 18, wherein the antibody against hGREM1 or antigen-binding fragment thereof comprises:

- a) a heavy chain variable region comprising the sequence of SEQ ID NO: 7 and a light chain variable region comprising the sequence of SEQ ID NO: 8; or
- b) a heavy chain variable region comprising a sequence of SEQ ID NO: 17 and a light chain variable region comprising a sequence of SEQ ID NO: 18; or
- c) a heavy chain variable region comprising a sequence of SEQ ID NO: 27 and a light chain variable region comprising a sequence of SEQ ID NO: 28; or
- d) a heavy chain variable region comprising a sequence of SEQ ID NO: 37 and a light chain variable region comprising a sequence of SEQ ID NO: 38; or
- e) a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 43 and SEQ ID NO: 45, and a light chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 47 and SEQ ID NO: 49; or
- f) a pair of heavy chain variable region and light chain variable region sequences selected from the group consisting of: SEQ ID NOs: 41/47, 41/49, 43/47, 43/49, 45/47, and 45/49; or
- g) a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55 and SEQ ID NO: 57, and a light chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 59 and SEQ ID NO: 61; or

- h) a pair of heavy chain variable region and light chain variable region sequences selected from the group consisting of: SEQ ID NOs: 51/59, 51/61, 53/59, 53/61, 55/59, 55/61, 57/59, and 57/61.

20. The use of any one of claims 17-19, wherein the antibody against hGREM1 or antigen-binding fragment thereof comprises an immunoglobulin constant region, optionally a constant region of human IgG, or optionally a constant region of human IgG1, IgG2, IgG3, or IgG4.

21. The use of any one of claims 17-20, wherein the antibody against hGREM1 or antigen-binding fragment thereof is humanized and/or bispecific.

22. The use of any one of claims 17-21, wherein the antibody against hGREM1 or antigen-binding fragment thereof is capable of specifically binding to a first and a second epitope of gremlin, or capable of specifically binding to both hGREM1 and a second antigen.

23. The use of claim 22, wherein the second antigen comprises an immune related target or a tumor antigen, wherein the immune related target is selected from the group consisting of: PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG3, A2AR, CD160, 2B4, TGF β , VISTA, BTLA, TIGIT, LAIR1, OX40, CD2, CD27, CD28, CD30, CD40, CD47, CD122, ICAM-1, IDO, NKG2C, SLAMF7, SIGLEC7, NKp80, CD160, B7-H3, LFA-1, 1COS, 4-1BB, GITR, BAFFR, HVEM, CD7, LIGHT, IL-2, IL-7, IL-15, IL-21, CD3, CD16 or CD83; wherein the tumor antigen is selected from the group consisting of: prostate specific antigen (PSA), CA-125, gangliosides G(D2), G(M2) and G(D3), CD20, CD52, CD33, Ep-CAM, CEA, bombesin-like peptides, HER2/neu, epidermal growth factor receptor (EGFR), erbB2, erbB3/HER3, erbB4, CD44v6, Ki-67, cancer-associated mucin, VEGF, VEGFRs (e.g., VEGFR-1, VEGFR-2, VEGFR-3), estrogen receptors, Lewis-Y antigen, TGF β 1, IGF-1 receptor, EGF α , c-Kit receptor, transferrin receptor, Claudin 18.2, GPC-3, Nectin-4, ROR1, methothelin, PCMA, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15, BCR-ABL, E2APRL, H4-RET, IGH-IGK, MYL-RAR, IL-2R, CO17-1A, TROP2,

and LIV-1.

24. The use of any one of the preceding claims, further comprising administering a therapeutically effective amount of a second therapeutic agent, wherein the second therapeutic agent comprises an anti-cancer therapy, or wherein the anti-cancer therapy is selected from a chemotherapeutic agent, radiation therapy, an immunotherapy agent, anti-angiogenesis agent (e.g. antagonist of a VEGFR such as VEGFR-1, VEGFR-2, and VEGFR-3), a targeted therapy agent, a cellular therapy agent, a gene therapy agent, a hormonal therapy agent, cytokines, palliative care, surgery for the treatment of cancer (e.g., tumorectomy), one or more anti-emetics, treatments for complications arising from chemotherapy, or a diet supplement for cancer patients (e.g. indole-3-carbinol).

25. The use of claim 24, wherein the anti-cancer therapy comprises an anti-prostate cancer drug selected from the group consisting of: androgen deprivation therapy; androgen axis inhibitor; an androgen synthesis inhibitor; a PARP inhibitor; Abiraterone Acetate, Apalutamide, Bicalutamide, Cabazitaxel, Casodex (Bicalutamide), Darolutamide, Degarelix, Docetaxel, Eligard (Leuprolide Acetate), Enzalutamide, Erleada (Apalutamide), Firmagon (Degarelix), Flutamide, Goserelin Acetate, Histrelin (Vantas), Jevtana (Cabazitaxel), Leuprolide Acetate, Lupron (Leuprolide Acetate), Lupron Depot (Leuprolide Acetate), Lynparza (Olaparib), Ketoconazole (Nizoral), Mitoxantrone Hydrochloride, Nilandron (Nilutamide), Nilutamide, Nubeqa (Darolutamide), Olaparib, Provenge (Sipuleucel-T), Radium 223 Dichloride, Relugolix (Orgovyx), Rubraca (Rucaparib Camsylate), Rucaparib Camsylate, Sipuleucel-T, Taxotere (Docetaxel), Triptorelin (Trelstar), Xofigo (Radium 223 Dichloride), Xtandi (Enzalutamide), Zoladex (Goserelin Acetate) and Zytiga (Abiraterone Acetate) or any combination thereof .

26. The use of claim 25, wherein the androgen axis inhibitor is degarelix, bicalutamide, flutamide, nilutamide, apalutamide, darolutamide, enzalutamide, or abiraterone.