

Claims

1. ~~A method of treating a hematological malignancy, preferably a multiple myeloma, in a subject in need thereof, comprising administering to the subject~~ Use of a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof ~~for the manufacture of a medicament for use in the treatment of a hematological malignancy, preferably a multiple myeloma, in a subject in need thereof,~~ wherein the subject is relapsed or refractory to treatment with a prior anti-cancer treatment.
2. The ~~method-use~~ of claim 1, wherein the GPRC5DxCD3 bispecific antibody is administered intravenously or subcutaneously at a dose of about 0.2 µg/kg to about 2400 µg/kg.
3. The ~~method-use~~ of claim 2, comprising:
 - (1) administering to the subject the GPRC5DxCD3 bispecific antibody intravenously or subcutaneously at a first priming dose of 0.5 µg/kg to 10 µg/kg, such as 0.5 µg/kg, 1.0 µg/kg, 1.5 µg/kg, 2.25 µg/kg, 2.5 µg/kg, 2.75 µg/kg, 3.0 µg/kg, 3.25 µg/kg, 3.38 µg/kg, 3.5 µg/kg, 3.75 µg/kg, 4 µg/kg, 4.5 µg/kg, 5 µg/kg, 6 µg/kg, 7 µg/kg, 8 µg/kg, 9 µg/kg, 10 µg/kg, or any value in between, preferably every 2 to 4 days, and
 - (2) subsequently administering to the subject the GPRC5DxCD3 bispecific antibody subcutaneously at a treatment dose higher than the first priming dose, in the range of 1.5 µg/kg to 2400 µg/kg or 1.5 µg/kg to 1000 µg/kg, such as 1.5 µg/kg, 5 µg/kg, 10 µg/kg, 15 µg/kg, 30 µg/kg, 45 µg/kg, 100 µg/kg, 135 µg/kg, 200 µg/kg, 300 µg/kg, 400 µg/kg, 405 µg/kg, 500 µg/kg, 600 µg/kg, 700 µg/kg, 800 µg/kg, 900 µg/kg, 1000 µg/kg, 1200 µg/kg, 1600 µg/kg, 2000 µg/kg, 2400 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly or twice a week,optionally, the method further comprising administering to the subject the GPRC5DxCD3 bispecific antibody subcutaneously at one or more additional priming doses higher than the first priming dose but lower than the treatment dose, wherein the one or more additional priming doses are administered after the first priming dose but before the administration of the treatment dose.
4. The ~~method-use~~ of claim 2, wherein the GPRC5DxCD3 bispecific antibody is administered intravenously at a dose of about 0.2 µg/kg to about 500 µg/kg,

preferably about 1 µg/kg to about 300 µg/kg, most preferably about 10 µg/kg to about 200 µg/kg, such as about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly, or twice a week.

5. The ~~method~~-use of claim 4, comprising:

(1) administering to the subject the GPRC5DxCD3 bispecific antibody intravenously at a first priming dose of 0.5 µg/kg to 5 µg/kg, such as 0.5 µg/kg, 1.0 µg/kg, 1.5 µg/kg, 2.25 µg/kg, 2.5 µg/kg, 2.75 µg/kg, 3.0 µg/kg, 3.25 µg/kg, 3.38 µg/kg, 3.5 µg/kg, 3.75 µg/kg, 4 µg/kg, 4.5 µg/kg, 5 µg/kg, or any value in between preferably every 2 to 4 days, and

(2) subsequently administering to the subject the GPRC5DxCD3 bispecific antibody intravenously at a treatment dose higher than the first priming dose, in the range of 1.5 µg/kg to 200 µg/kg, such as 1.5 µg/kg, 2.25 µg/kg, 3.38 µg/kg, 5 µg/kg, 7.5 µg/kg, 11.25 µg/kg, 20 µg/kg, 40 µg/kg, 60 µg/kg, 80 µg/kg, 100 µg/kg, 120 µg/kg, 140 µg/kg, 160 µg/kg, 180 µg/kg, 200 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly or twice a week,

optionally, the method further comprising administering to the subject the GPRC5DxCD3 bispecific antibody intravenously at one or more additional priming doses higher than the first priming dose but lower than the treatment dose, wherein the one or more additional priming doses are administered after the first priming dose but before the administration of the treatment dose.

6. The ~~method~~-use of claim 2, wherein the GPRC5DxCD3 bispecific antibody is administered subcutaneously at a dose of about 0.5 µg/kg to about 2400 µg/kg, or about 1 µg/kg to about 2400 µg/kg, or about 10 µg/kg to about 2400 µg/kg, such as about 10, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1600, 2000, 2400 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly, or twice a week.

7. The ~~method~~-use of claim 6, comprising:

(1) administering to the subject the GPRC5DxCD3 bispecific antibody at one or more priming doses of 0.3 µg/kg to 400 µg/kg, preferably every 2 to 4 days, and

(2) subsequently administering to the subject the GPRC5DxCD3 bispecific antibody at a treatment dose higher than the priming doses, such as 1 µg/kg to 2400 µg/kg, preferably monthly, tri-weekly, bi-weekly, weekly or twice a week.

8. ~~A method of treating a multiple myeloma in a subject in need thereof, comprising subcutaneously administering to the subject~~Use of 405 µg/kg of a GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof for the manufacture of a medicament for use in the treatment of multiple myeloma in a subject in need thereof, wherein 405 µg/kg of the GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof is subcutaneously administered to the subject weekly or biweekly, wherein the subject is relapsed or refractory to treatment with a prior anti-cancer treatment, preferably the initial administration of the 405 µg/kg GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof occurs after the subject is administered with one or more priming doses of the antibody or antigen binding fragment thereof, such as one or more priming doses of 10, 60, and 300 µg/kg administered subcutaneously weekly or biweekly.
9. ~~A method of treating a multiple myeloma in a subject in need thereof, comprising subcutaneously administering to the subject~~800 µg/kg-Use of a GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof for the manufacture of a medicament for use in the treatment of multiple myeloma in a subject in need thereof, wherein 800 µg/kg of the GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof is subcutaneously administered to the subject weekly or biweekly, wherein the subject is relapsed or refractory to treatment with a prior anti-cancer treatment, preferably the initial administration of the 800 µg/kg GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof occurs after the subject is administered with one or more priming doses of the antibody or antigen binding fragment thereof, such as one or more priming doses of 10, 60, and 300 µg/kg administered subcutaneously weekly or biweekly.
10. The ~~method-use~~ of any one of claims 1 to 9, wherein the GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.

11. The ~~method~~-use of any one of claims 1 to 10, wherein the GPRC5D binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a VH having the amino acid sequence of SEQ ID NO: 20 and a VL having the amino acid sequence of SEQ ID NO: 21.
12. The ~~method~~-use of any one of claims 1 to 11, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises phenylalanine at position 405 and arginine at position 409 in a first heavy chain (HC1) and leucine at position 405 and lysine at position 409 in a second heavy chain (HC2), wherein residue numbering is according to the EU Index.
13. The ~~method~~-use of any one of claims 1 to 12, wherein the GPRC5DxCD3 bispecific antibody further comprises proline at position 228, alanine at position 234 and alanine at position 235 in both the HC1 and the HC2.
14. The ~~method~~-use of any one of claims 1 to 13, wherein the GPRC5DxCD3 bispecific antibody comprises the HC1 having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, the HC2 having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.
15. The ~~method~~-use of any one of claims 1 to 14, wherein the GPRC5DxCD3 bispecific antibody is talquetamab.
16. The ~~method~~-use of any one of claims 1 to 15, wherein the treatment achieves a complete response, stringent complete response, very good partial response, partial response, minimal response or stable disease status, and can be continued until disease progression or lack of patient benefit.
17. The ~~method~~-use of claim 16, wherein the treatment achieves the complete response that is characterized by negative minimal residual disease (MRD) status, preferably negative MRD status at 10^{-6} cells, as determined by next generation sequencing (NGS), or an overall response rate of at least 20%, such as at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or any value in between.
18. The ~~method~~-use of any one of claims 1 to 17, wherein the treatment results in an exposure of GPRC5DxCD3 bispecific antibody at a steady state mean C_{max} of 10 to

25,000 ng/ml, such as 100 to 20,000 ng/ml or 1000-10,000 ng/ml, and a steady state mean AUC_{0-14d} of 1000 to 1,500,000 ng h/ml, such as 5000 to 1,000,000 ng h/ml or 10,000 to 1,000,000 ng h/mL.

19. The ~~method~~-use of any one of claims 1 to 18, wherein the prior anti-cancer treatment is selected from the group consisting of thalidomide, lenalidomide, pomalidomide, bortezomib, ixazomib, carfilzomib, panobinostat, pamidronate, zoledronic acid, daratumumab, elotuzumab, melphalan, selinexor, belantamab mafodotin-blmf, Venetoclax, CC-92480, CAR-T therapies, other BCMA-directed therapies, other CD38-directed therapies, and combinations of two or more thereof.
20. The ~~method~~-use of any one of claims 1 to 19, wherein the subject is a human in need of a treatment of multiple myeloma and is relapsed or refractory to treatment with the prior treatment of the multiple myeloma.
21. The ~~method~~-use of any one of claims 1 to 20, further comprising administering to the subject one or more additional anti-cancer therapies.
22. The ~~method~~-use of claim 21, wherein the one or more additional anti-cancer therapies are selected from the group consisting of autologous stem cell transplants (ASCT), radiation, surgery, chemotherapeutic agents, CAR-T therapies, cellular therapies, immunomodulatory agents, targeted cancer therapies, a therapy that reduces or depletes Treg, and combinations of two or more thereof.
23. The ~~method~~-use of claim 21, wherein the one or more additional anti-cancer therapies are selected from the group consisting of selinexor, belantamab mafodotin-blmf, isatuximab, venetoclax, lenalidomide, thalidomide, pomalidomide, bortezomib, carfilzomib, elotuzumab, ixazomib, melphalan, dexamethasone, vincristine, cyclophosphamide, hydroxydaunorubicin, prednisone, rituximab, imatinib, dasatinib, CC-92480, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib, danusertib, cytarabine, daunorubicin, idarubicin, mitoxantrone, hydroxyurea, decitabine, cladribine, fludarabine, topotecan, etoposide 6-thioguanine, corticosteroid, methotrexate, 6-mercaptopurine, azacitidine, arsenic trioxide and all-trans retinoic acid, and combinations of two or more thereof.