

Claims

1. Use of a GPRC5DxCD3 bispecific antibody in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the GPRC5DxCD3 antibody is to be administered in combination with an anti-CD38 antibody, comprising:
 - (1) a GPRC5DxCD3 bispecific antibody to be administered to the subject at a dose of 60 $\mu\text{g/kg}$ to 1200 $\mu\text{g/kg}$ every 1-2 weeks; and
 - (2) an anti-CD38 antibody to be administered to the subject at a dose of 1200 mg to 2400 mg every 1-4 weeks.
2. The use of claim 1, comprising:
 - (1) the GPRC5DxCD3 bispecific antibody to be subcutaneously administered at a dose of 300 $\mu\text{g/kg}$ to 1200 $\mu\text{g/kg}$ every 1-2 weeks; and
 - (2) the anti-CD38 antibody to be subcutaneously administered at a dose of 1600 mg to 2000 mg every 1-4 weeks.
3. The use of claim 2, further comprising the GPRC5DxCD3 bispecific antibody to be subcutaneously administered at a dose lower than that used in step (1) prior to step (1).
4. The use of claim 2 or claim 3, wherein the GPRC5DxCD3 bispecific antibody is to be subcutaneously administered to the subject at a dose of about 300 $\mu\text{g/kg}$, 400 $\mu\text{g/kg}$, 450 $\mu\text{g/kg}$, 500 $\mu\text{g/kg}$, 550 $\mu\text{g/kg}$, 600 $\mu\text{g/kg}$, 700 $\mu\text{g/kg}$, 750 $\mu\text{g/kg}$, 800 $\mu\text{g/kg}$, 850 $\mu\text{g/kg}$, 900 $\mu\text{g/kg}$, 950 $\mu\text{g/kg}$, or 1000 $\mu\text{g/kg}$, or any dose from about 300 $\mu\text{g/kg}$ to about 1000 $\mu\text{g/kg}$, once every week or once every two weeks.
5. The use of claim 4, wherein the GPRC5DxCD3 bispecific antibody is to be subcutaneously administered to the subject at a dose of 400 $\mu\text{g/kg}$ weekly or biweekly, or 800 $\mu\text{g/kg}$ biweekly.
6. The use of claim 5, wherein the GPRC5DxCD3 bispecific antibody is to be subcutaneously administered to the subject at a dose of 400 $\mu\text{g/kg}$ weekly or 800 $\mu\text{g/kg}$ biweekly.

7. The use of any one of claims 1-6, wherein the anti-CD38 antibody is to be subcutaneously administered to the subject at the dose of 1800 mg once every week during week 1 to week 8 of the treatment, once every two weeks during week 9 to week 24 of the treatment, and once every four weeks after week 24 of the treatment.
8. The use of any one of claims 1-7, wherein the anti-CD38 antibody is to be administered or provided for administration together with rHuPH20, such as about 30,000 U of rHuPH20.
9. The use of any one of claims 1-8, wherein the GPRC5DxCD3 bispecific antibody comprises:
 - (1) a GPRC5D binding domain comprising a heavy chain variable region (VH) having heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3 of the amino acid sequences of SEQ ID NO: 27, SEQ ID NO: 28, and SEQ ID NO: 29, respectively, and a light chain variable region (VL) having light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3 of the amino acid sequences of SEQ ID NO: 30, SEQ ID NO: 31, and SEQ ID NO: 32, respectively, and
 - (2) a CD3 binding domain comprising a VH having HCDR1, HCDR2 and HCDR3 of the amino acid sequences of SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, respectively, and a VL having LCDR1, LCDR2 and LCDR3 of the amino acid sequences of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22, respectively.
10. The use of claim 9, wherein the GPRC5D binding domain comprises the VH having the amino acid sequence of SEQ ID NO: 33 and the VL having the amino acid sequence of SEQ ID NO: 34; the CD3 binding domain comprises the VH having the amino acid sequence of SEQ ID NO: 23 and the VL having the amino acid sequence of SEQ ID NO: 24.
11. The use of claim 10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having the amino acid sequence of SEQ ID NO: 35, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 36, a second heavy chain (HC2) having the

amino acid sequence of SEQ ID NO: 25, and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 26.

12. The use of any one of claims 1-11, wherein the anti-CD38 antibody comprises a VH having HCDR1, HCDR2 and HCDR3 of the amino acid sequences of SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9, respectively, and a VL having LCDR1, LCDR2 and LCDR3 of the amino acid sequences of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, respectively.
13. The use of claim 12, wherein the CD38 antibody comprises the VH having the amino acid sequence of SEQ ID NO: 5, and the VL having the amino acid sequence of SEQ ID NO: 6.
14. The use of any one of claims 1-13, wherein the cancer is multiple myeloma.
15. Use of a GPRC5DxCD3 bispecific antibody in the manufacture of a medicament for treating multiple myeloma in a subject in need thereof, wherein the GPRC5DxCD3 antibody is to be administered in combination with an anti-CD38 antibody, comprising:
 - (1) 400 µg/kg of a GPRC5DxCD3 bispecific antibody weekly; or 800 µg/kg of a GPRC5DxCD3 bispecific antibody biweekly to be subcutaneously administered to the subject, and
 - (2) 1800 mg of an anti-CD38 antibody once every week during week 1 to week 8 of the treatment, once every two weeks during week 9 to week 24 of the treatment, and once every four weeks after week 24 of the treatment to be subcutaneously administered to the subject,wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) of SEQ ID NO: 35, a first light chain (LC1) of SEQ ID NO: 36, a second heavy chain (HC2) of SEQ ID NO: 25, and a second light chain (LC2) of SEQ ID NO: 26, and the anti-CD38 antibody comprises the HC of SEQ ID NO: 13 and the LC of SEQ ID NO: 14.
16. The use of claim 15, further comprising one or more step-up doses of the GPRC5DxCD3 bispecific antibody to be subcutaneously administered to the subject, such as 10 µg/kg on day

2 of the treatment and 60 µg/kg on day 4 of the treatment, prior to the initial dose of 400 µg/kg of the GPRC5DxCD3 bispecific antibody, or one or more step-up doses of the GPRC5DxCD3 bispecific antibody to be subcutaneously administered to the subject, such as 10 µg/kg on day 2 of the treatment, 60 µg/kg on day 4 of the treatment, and 300 µg/kg on day 8 of the treatment, prior to the initial dose of 800 µg/kg of the GPRC5DxCD3 bispecific antibody.

17. The use of any one of claims 1-16, wherein the subject has received at least one prior treatment for multiple myeloma, or the subject is relapsed or refractory to the at least one prior treatment, wherein the prior treatment can comprise at least one of a proteasome inhibitor (PI) or an immunomodulatory agent (IMiD).
18. The use of claim 17, wherein the subject is refractory or relapsed to a treatment selected from the group consisting of an anti-CD38 antibody, lenalidomide, bortezomib, pomalidomide, carfilzomib, elotuzumab, ixazomib, isatuximab, melphalan and thalidomide, or any combination thereof, preferably, the subject is lenalidomide refractory.
19. The use of any one of claims 1-18, further comprising an additional therapeutic to be administered to the subject, such as pomalidomide and/or dexamethasone.
20. The use of any one of claims 1-19, wherein the treatment results in T-cell activation, such as an increase in at least one of CD25, PD-1, CD38 on CD4 and CD8 T cells, or the treatment results in an increase in frequency of at least of CD38⁺ CD8⁺ T cells, CD38⁺ CD4⁺ T cells and Tregs T cells.