

CLAIMS

1. An anti-CD38 antibody or antigen-binding fragment thereof, in which the antibody or antigen-binding fragment thereof specifically binds to an epitope of human CD38, in which the epitope comprises amino acids 65-79 of SEQ ID NO: 47, and in which the antibody or
 5 fragment thereof:

exhibits antibody-dependent cell-mediated cytotoxicity (ADCC) activity against CD38+ target cells;

exhibits no complement dependent cytotoxicity (CDC) or reduced CDC activity against a CD38+ target cell as compared to daratumumab under the same conditions; and

10 induces immune effector cell activation.

2. An anti-CD38 antibody or antigen-binding fragment thereof according to Claim 1, in which the antibody or antigen-binding fragment thereof:

(i) exhibits either no CDC or exhibits CDC:

15 (a) with an EC50 that is at least 0.5-fold higher or at least 1-fold higher than daratumumab; or

(b) with a maximum % lysis as measured in Raji and/or Daudi cells in the presence of 10% complement that is no more than half that exhibited by daratumumab;

20 (ii) induces CDC with an EC50 value of more than 0.05 µg/mL against Daudi cells and/or Raji cells in the presence of 10% complement;

(iii) the reduction in CDC activity is such that the EC50 of the antibody or antibody binding fragment thereof is at least 0.5-fold or at least 1-fold greater than that of Daratumumab under the same conditions;

25 (iv) in which reduction in CDC activity compared to daratumumab is such that the maximum % lysis of cells is no more than half that exhibited by daratumumab under the same conditions;

(v) exhibits antibody-dependent cellular phagocytosis (ADCP) against CD38-expressing cells;

(vi) increases T cell proliferation in CD4⁺ and/or CD8⁺ cells by at least 20% as compared to untreated cells; and/or

(vii) induces the secretion of a cytokine selected from the group consisting of IL-2, TNF- α , IFN- γ , IL-10 and/or GM-CSF in CD4⁺ and/or CD8⁺ cells in an amount greater than is induced by daratumumab under the same conditions.

3. An anti-CD38 antibody or antigen-binding fragment thereof according to Claim 1 or 2, in which the antibody or antigen-binding fragment thereof induces T cell activation.

4. An anti-CD38 antibody or antigen-binding fragment thereof according to Claim 3, in which when T cell activation is determined by measuring NFAT signalling in luc_reporter Jurkat cells, the NFAT signalling of the antibody or antigen-binding fragment thereof is at least 20% higher than that of daratumumab.

5. An anti-CD38 antibody or antigen-binding fragment thereof according to Claim 3 or 4, in which T cell activation is characterised by an increase in T cell proliferation, and/or an increase in cytokine secretion, in which the cytokines are selected from the group consisting of IL-2, TNF- α , IFN- γ , IL-10 and GM-CSF.

6. An anti-CD38 antibody or antigen-binding fragment thereof according to any preceding claim, in which the antibody or antigen-binding fragment thereof induces NK cell activation.

7. An anti-CD38 antibody or antigen-binding fragment thereof according to Claim 6, in which NK cell activation is characterised by an increase in NK cell proliferation, an increase in intra-cellular IFN γ , and/or an increase in expression of CD107a.

8. An anti-CD38 antibody or antigen-binding fragment thereof according to any of Claims 1 to 7, in which the antibody has an inhibitory effect on CD38 cyclase activity.

9. An anti-CD38 antibody or antigen-binding fragment thereof according to Claim 8, in which the CD38 cyclase activity is at least 10% lower compared to the CD38 cyclase activity in the presence of an IgG non-binding control antibody as measured by the conversion of NGD⁺ into cGDPR in Jurkat cells.

10. An anti-CD38 antibody or antigen-binding fragment thereof according to Claim 8 or 9, in which the anti-CD38 antibody or antigen-binding fragment thereof reduces the CD38

cyclase activity to no less than 25% of the CD38 cyclase activity in the presence of an IgG non-binding control antibody as measured by the conversion of NGD⁺ into cGDPR in Jurkat cells.

11. An anti-CD38 antibody or antigen-binding fragment thereof according to any preceding claim, in which the antibody or antigen-binding fragment thereof is a monoclonal antibody, a Fab fragment, a F(ab')₂ fragment, a single chain variable fragment (scFv), a scFv-Fc fragment or a single chain antibody (scAb).
12. An anti-CD38 antibody or antigen-binding fragment thereof according to any preceding claim, in which the antibody or antigen-binding fragment thereof is a rabbit, mouse, chimeric, humanized or fully human antigen-binding antibody.
13. An anti-CD38 antibody or antigen-binding fragment thereof according to any preceding claim, in which the antibody or antigen binding fragment thereof:
 - (i) is selected from the group consisting of IgG1, IgG2, IgG3, and IgG4 isotype antibodies;
 - (ii) is comprised in a bispecific antibody, a multispecific antibody, or an immunoconjugate further comprising a therapeutic or diagnostic agent; or
 - (iii) binds the extracellular domain of human CD38.
14. An antibody or an antigen-binding fragment thereof according to any preceding claim, in which the antibody or antigen-binding fragment thereof is afucosylated.
15. A nucleic acid molecule encoding an antibody or antigen-binding fragment thereof according to any preceding claim.
16. A nucleic acid vector comprising the nucleic acid molecule according to Claim 15.
17. A host cell comprising the nucleic acid vector according to Claim 16.
18. A method of producing an antibody or antigen binding fragment thereof according to any of Claims 1 to 14 comprising culturing a host cell according to Claim 17.

19. A composition comprising an antibody or antigen-binding fragment thereof according to any of Claims 1 to 14 and a pharmaceutically acceptable carrier or excipient.
20. Use of an antibody according to any of Claims 1 to 14, or of a composition according to Claim 19 in the manufacture of a medicament for treating a cancer.
- 5 21. Use according to Claim 20, in which the antibody is for administration, simultaneously or sequentially in any order, with a second agent.
22. Use according to Claim 20 or 21, in which the subject has a solid tumour or a haematological cancer.