

CLAIMS

We claim:

1. An antibody that specifically binds human CD38, wherein the antibody comprises
 - a) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 2 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - b) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 3 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - c) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 4 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - d) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
 - e) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9, or
 - f) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
 - g) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9.

2. A pharmaceutical composition comprising a formulated antibody, wherein the formulated antibody comprises an antibody, sucrose, L-histidine, and polysorbate 80 (PS80), wherein the antibody specifically binds human CD38 and is present at a concentration of 50 mg/mL, the sucrose is present at a concentration of 8 % (w/v), the L-histidine is present at a concentration of 10 mM, and the PS80 is present at a concentration of 0.05 % (v/v), wherein the formulation has a pH of 6.2, and wherein the antibody comprises
 - a) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 2 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - b) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 3 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - c) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 4 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - d) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
 - e) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9, or

- f) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
 - g) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9.
3. A unit dosage form of a formulated antibody that specifically binds human CD38, wherein the formulated antibody comprises 215 mg of the antibody, 6.21 mg L-histidine, 344 mg sucrose, and 2.15 mg polysorbate 80, wherein the formulated antibody is lyophilized, and wherein the antibody comprises
- a) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 2 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - b) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 3 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - c) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 4 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - d) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
 - e) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9, or
 - f) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
 - g) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9.
4. The pharmaceutical composition of claim 2 or unit dosage form of claim 3, wherein the formulated antibody is lyophilized.
5. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 1-4, wherein amino acid at position 1 of the HC amino acid sequence is pyroglutamine.
6. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 1-5 wherein the antibody has an isoelectric point (pI) of 5.8 to 9.0 when measured by capillary isoelectric focusing (cIEF).

7. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 1-6, wherein the antibody comprises a main charge variant and at least one acidic charge variant and wherein the antibody has at least one of
- a) the HC of the at least one charge variant comprises at least one deamidated asparagine selected from the group consisting of N289, N318, N387, and N392 as numbered according to SEQ ID NO: 1, or
 - b) the antibody comprises a main charge variant and least one acidic charge variant, wherein the main charge variant comprises at least 71% of the antibody and the acidic charge variant comprises no more than 30% of the antibody, or
 - c) the main charge variant has an isoelectric point (pI) of 7.5 and wherein the one or more acidic charge variant has pI of 5.8 when measured by capillary isoelectric focusing (cIEF).
8. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 1-7, wherein the antibody comprises at least one basic charge variant, and wherein the antibody has at least one of
- a) the basic charge variant comprises no more than 4% of the antibody, or
 - b) the one or more basic charge variants has a pI of 9.0 when measured by capillary isoelectric focusing (cIEF).
9. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 1-8, wherein the antibody
- a) is capable of killing a CD38-expressing cell by Antibody Dependent Cellular Cytotoxicity (ADCC), wherein the cell has a CD38 receptor density of $\leq 13,000$ CD38 sites on the surface of the cell in the presence of Natural Killer cells expressing the 158F, 158V, or both 158F and 158V variants CD16a (Fc γ RIIIa), and/or
 - b) binds CD16a (Fc γ RIIIa) having phenylalanine at amino acid position 158 (158F) with a K_D of 59 nM as measured by Surface Plasmon Resonance (SPR) and wherein the antibody binds CD16a having valine at amino acid position 158 (158V) with a K_D of 75 nM as measured by SPR, and/or
 - c) binds CD16a (Fc γ RIIIa) having phenylalanine at amino acid position 158 (158F) with a K_D of 96 nM as measured by binding to Fc γ RIIIa 158F-expressing HEK cells and wherein the antibody binds Fc γ RIIIa having valine at amino acid position 158 (158V) with a K_D of 40 nM as measured by binding to Fc γ RIIIa 158V-expressing HEK cells, and/or

d) binds CD32a (FcγRIIa) having arginine at amino acid position 131 (131R) with a K_D of 94 nM as measured by binding to FcγRIIa 131R-expressing HEK cells and wherein the antibody binds FcγRIIa having histidine at amino acid position 131 (131H) with a K_D of 222 nM as measured by binding to FcγRIIa 131H-expressing HEK cells.

10. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 1-8, wherein

a) the antibody is capable of killing a CD38-expressing cell by ADCC wherein the cell has a CD38 receptor density of $>400,000$ on the surface of the cell, and is capable of killing a CD38-expressing cell by ADCC wherein the cell has a CD38 receptor density of $\geq 100,000$ on the surface of the cell, and is capable of killing a CD38-expressing cell by ADCC wherein the cell has a CD38 receptor density of $\leq 13,000$ on the surface of the cell, in the presence of Natural Killer cells expressing the 158F, 158V, or both 158F and 158V variants of CD16a (FcγRIIIa) and/or

b) the antibody is capable of killing a CD38-expressing cell by Antibody Dependent Cellular Phagocytosis (ADCP) in the presence of human peripheral blood mononuclear cells (PMBCs), wherein the cell has a CD38 receptor density of $>400,000$ on the surface of the cell.

11. The antibody, pharmaceutical composition, or unit dosage form of claim 9 or 10, wherein

a) in the presence of Natural Killer cells expressing the higher affinity variant (158V) of CD16a (FcγRIIIa), the antibody is capable of killing KMS-12BM cells by ADCC with an EC₅₀ of about 0.6 ng/mL and/or

b) in the presence of Natural Killer cells expressing the lower affinity variant (158F) of CD16a (FcγRIIIa), the antibody is capable of killing KMS-12BM cells by ADCC with an EC₅₀ of about 0.65 ng/mL and/or

c) in the presence of Natural Killer cells expressing the higher affinity variant (158V) of CD16a (FcγRIIIa), the antibody is capable of killing RPMI-8226 cells by ADCC with an EC₅₀ of about 0.09 ng/mL and/or

d) in the presence of Natural Killer cells expressing the lower affinity variant (158F) of CD16a (FcγRIIIa), the antibody is capable of killing RPMI-8226 cells by ADCC with an EC₅₀ of about 0.09 ng/mL and/or

e) in the presence of Natural Killer cells expressing the higher affinity variant (158V) of CD16a (FcγRIIIa), the antibody is capable of killing MOLP-8 cells by ADCC with an EC 50 of about 0.14 ng/mL and/or

f) in the presence of Natural Killer cells expressing the lower affinity variant (158F) of CD16a (FcγRIIIa), the antibody is capable of killing MOLP-8 cells by ADCC with an EC 50 of about 0.28 ng/mL.

12. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 9-11, wherein in the presence of human PMBCs expressing the higher affinity variant (158V) of CD16a (FcγRIIIa), the antibody is capable of killing MOLP-8 cells by ADCP with an EC 50 of about 31.87 ng/mL.

13. The antibody, pharmaceutical composition, or unit dosage form of any one of claims 1-12, wherein the antibody is capable of improving survival of mice in a murine tumor model, wherein mice in the model express human CD16a (158F), and wherein the mice have been injected with 500,000 EL4 cells expressing human CD38.

14. A process for preparing pharmaceutical composition comprising an antibody that specifically binds human CD38, wherein the antibody comprises

- a) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 2 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
- b) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 3 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
- c) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 4 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
- d) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
- e) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9, or
- f) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
- g) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9,

the method comprising the steps of:

- i) expressing the antibody in a cell culture;
 - ii) subjecting the antibody to at least one purification step selected from the group consisting of chromatography and ultrafiltration to produce a purified antibody solution; and
 - iii) adjusting the purified antibody solution to produce a formulated antibody comprising
 - the purified antibody at a concentration of 50 mg/mL,
 - sucrose at a concentration of 8 % w/v,
 - L-histidine at a concentration of 10 mM, and
 - polysorbate 80 at a concentration of 0.05 % v/v,wherein the formulated antibody has a pH of 6.2; and
 - iv) lyophilizing the formulated antibody,
- thereby preparing the pharmaceutical composition.

15. A method for preparing a reconstituted formulated antibody, comprising
- a) providing a lyophilized antibody formulation comprising sucrose, L-histidine, polysorbate 80, and an antibody that specifically binds human CD38; and
 - b) reconstituting the lyophilized antibody formulation in a diluent, wherein the reconstituted antibody formulation comprises
 - the antibody at a concentration of 50 mg/mL,
 - sucrose at a concentration of 8 % w/v,
 - L-Histidine at a concentration of 10 mM, and
 - polysorbate 80 at a concentration of 0.05 % v/v,wherein the reconstituted antibody formulation has a pH of 6.2;
- wherein the antibody comprises
- i) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 2 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - ii) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 3 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
 - iii) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 4 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or

- iv) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
- v) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9, or
- vi) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
- vii) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9.

16. An antibody for use in treating a disease that comprises CD38-expressing cells, wherein the antibody specifically binds human CD38, wherein the antibody comprises

- a) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 2 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
- b) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 3 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
- c) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 4 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 7, or
- d) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
- e) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 5 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9, or
- f) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 8, or
- g) a heavy chain (HC) having an amino acid sequence of SEQ ID NO: 6 and a light chain (LC) having an amino acid sequence of SEQ ID NO: 9.

17. The antibody for use of claim 16, wherein the disease is of hematological origin.