

CLAIMS

1. An antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 (NTPDase1) protein, for use in treating a human individual, the treatment comprising administering to the patient an effective amount of each of: (a) an antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 (NTPDase1) protein, and (b) an agent that neutralizes the 5'-ectonucleotidase activity of human CD73.

2. An agent that neutralizes the 5'-ectonucleotidase activity of human CD73, for use in treating a human individual, the treatment comprising administering to the patient an effective amount of each of: (a) an antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 (NTPDase1) protein, and (b) an agent that neutralizes the 5'-ectonucleotidase activity of human CD73.

3. An antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 (NTPDase1) protein, for use in the treatment of an individual having a CD73-positive cancer.

4. The use of claim 3, wherein the method further comprises administering to the individual an agent, optionally an antibody, that neutralizes the 5'-ectonucleotidase activity of human CD73.

5. The compound for use of any one of claims 1, 2 or 4, wherein the agent that neutralizes the ATPase activity of human CD39 is administered prior to the administration of the agent that neutralizes the 5'-ectonucleotidase activity of human CD73.

6. The compound for use of any one of the above claims, wherein the antibody that neutralizes the ATPase activity of human CD39 is capable of causing a decrease in the ATPase activity of human extracellular domain CD39 protein in solution by more than 50%, optionally more than 60%, optionally more than 70% or optionally more than 80%.

7. The compound for use of any one of the above claims, wherein the agent that neutralizes the 5'-ectonucleotidase activity of human CD73 is an antibody.

8. The compound for use of any one of the above claims, wherein the antibody that neutralizes the ATPase activity of human CD39 and the agent that neutralizes the 5'-ectonucleotidase activity of CD73 are formulated for separate administration and are administered concurrently or sequentially.

9. The compound for use of any one of claims 1-8, wherein the individual has a CD73-positive cancer.

10. The compound for use of any of the above claims, wherein the antibody that neutralizes the ATPase activity of CD39 comprises the heavy chain CDR1, CDR2 and CDR3 domains of a heavy chain variable domain having the sequence set forth in SEQ ID NOS: 6, and the light chain CDR1, CDR2 and CDR3 domains of a light chain variable domain having the sequence set forth in SEQ ID NO: 7.

11. The compound for use of any of the above claims, wherein an agent that neutralizes the 5'-ectonucleotidase activity of CD73 is an antibody that binds a CD73 polypeptide and induces or increases the intracellular internalization of CD73.

12. The compound for use of any of claims 1-10, wherein the agent that neutralizes the 5'-ectonucleotidase activity of CD73 is an antibody that binds a CD73 polypeptide and neutralizes the 5'-ectonucleotidase activity of CD73 without substantially increasing the intracellular internalization of CD73.

13. The compound for use of any of claims 1-12, wherein an antibody that neutralizes the ATPase activity of CD39 substantially lacks binding to human CD16, CD32a, CD32b and/or CD64 polypeptides.

14. The compound for use of any of the above claims, wherein said anti-CD39 and/or anti-CD73 antibody is a chimeric, human or humanized antibody.

15. The compound for use of any of the above claims, wherein the anti-CD39 and/or anti-CD73 antibody lacks an Fc domain or comprises an Fc domain that is modified to reduce binding between the Fc domain and an Fcγ receptor.

16. The compound for use of any of the above claims, wherein said antibody is an antibody fragment.

17. The compound for use of claim 16, wherein said antibody fragment is selected from Fab, Fab', Fab'-SH, F(ab')₂, Fv, a diabody, a single-chain antibody fragment, or a multispecific antibody comprising multiple different antibody fragments.

18. An antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein, for use in the treatment of cancer in an individual who has a poor prognosis for response to treatment with an agent that neutralizes the 5'-ectonucleotidase activity of CD73, and/or who has a solid tumor that is resistant to treatment with an agent that inhibits a human CD73 polypeptide.

19. The compound for use of any of the above claims, wherein the individual comprises immune effector cells characterized by one or markers of immune suppression and/or exhaustion.

20. The compound for use of any of the above claims, wherein the individual comprises tumor tissue and/or tumor adjacent tissue characterized by a high level of CD73-expressing cells.

21. An antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein, for use in the treatment or prevention of a cancer in an individual, the treatment comprising:

a) determining whether the individual has a poor prognosis for response to treatment with an agent that neutralizes the 5'-ectonucleotidase activity of CD73, and

b) upon a determination that the individual has a poor prognosis for response to treatment with an agent that neutralizes the 5'-ectonucleotidase activity of CD73, administering to the individual an antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein.

22. The use of claim 21, wherein determining the individual has a poor prognosis for response to treatment with an agent that neutralizes the inhibitory activity of CD73 comprises assessing whether immune effector cells in a biological sample from the individual are characterized by one or more markers of immune suppression and/or exhaustion, wherein the presence or and/or elevated levels of immune effector cells characterized by one or more markers of immune suppression and/or exhaustion indicates a poor prognosis for response to treatment with an agent that neutralizes the 5'-ectonucleotidase activity of CD73.

23. The use of claims 21 or 22, wherein determining the individual has a poor prognosis for response to treatment with an agent that neutralizes the inhibitory activity of CD73 comprises assessing whether tumor tissue and/or tumor adjacent tissue from the individual is characterized by CD73 expression, optionally high levels of CD73 expression, wherein CD73 expression, optionally high levels of CD73 expression indicates a poor prognosis for response to treatment with an agent that neutralizes the inhibitory activity of CD73.

24. The use of any of the above claims, wherein the individual has a cancer that has progressed or relapsed following prior treatment with an agent that inhibits a human CD73 polypeptide.

25. The use of claims 18-24, wherein the treatment further comprises administering to the individual an agent that inhibits a human CD73 polypeptide.

26. The use of any of the above claims, wherein the individual has a solid tumor.

27. The use of any of the above claims, wherein the individual has an ovarian cancer.

28. The use of any of claims 1-26, wherein the individual has a gastric cancer.

29. The use of any of claims 1-26, wherein the individual has a lung cancer.

30. The use of any of claims 1-26, wherein the individual has a colon cancer.

31. The use of any of claims 1-26, wherein the individual has an esophageal cancer.

32. A pharmaceutical composition comprising an antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein, an agent, optionally an antibody, that neutralizes the 5'-ectonucleotidase activity of CD73, and a pharmaceutically acceptable carrier.

33. A kit comprising: (a) a dose of an antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein, and (b) a dose of an agent, optionally an antibody, that neutralizes the 5'-ectonucleotidase activity of CD73.

34. A kit comprising: (a) multiple packages of single-dose pharmaceutical compositions containing an effective amount of an antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein, and (b) multiple packages of single-dose pharmaceutical compositions containing an effective amount of an antibody that neutralizes the 5'-ectonucleotidase activity of CD73.

35. The composition or use of any one of the above claims, wherein the antibody comprises a HCDR1 comprising an amino acid sequence DYNMH (SEQ ID NO: 8); a HCDR2 comprising an amino acid sequence YIVPLNGGSTFNQKFKG (SEQ ID NO: 9); a HCDR3 comprising an amino acid sequence GGTRFAY (SEQ ID NO: 10); a LCDR1 comprising an amino acid sequence RASESVDNFGVSFMY (SEQ ID NO: 11); a LCDR2 region comprising an amino acid sequence GASNQGS (SEQ ID NO: 12); and a LCDR3 region comprising an amino acid sequence QQTKEVPYT (SEQ ID NO: 13).

36. The composition or use of any one of the above claims, wherein the antibody comprises a heavy chain comprising CDR 1, 2 and 3 of the heavy chain variable region of SEQ ID NO: 6 and (ii) a light chain comprising CDR 1, 2 and 3 of the light chain variable region of SEQ ID NO: 7.

37. The composition or use of any one of the above claims, wherein the antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein comprises a heavy chain comprising CDR 1, 2 and 3 of the heavy chain variable region of I-395, I-396, I-397, I-398 or I-399 and (ii) a light chain comprising CDR 1, 2 and 3 of the light chain variable region of I-395, I-396, I-397, I-398 or I-399.

38. The composition or use of any one of the above claims, wherein the antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein comprises a heavy chain variable region that is a function-conservative variant of the heavy chain variable region of antibody I-394, I-395, I-

396, I-397, I-398 or I-399, and a light chain variable region that is a function-conservative variant of the light chain variable region of the respective I-394, I-395, I-396, I-397, I-398 or I-399 antibody.

39. The composition or use of any one of the above claims, wherein the antibody that is capable of binding and inhibiting the ATPase activity of a soluble extracellular domain human CD39 protein comprises a heavy chain that is a function-conservative variant of the heavy chain variable region of antibody I-394, I-395, I-396, I-397, I-398 or I-399 fused to a human heavy chain constant region of any of SEQ ID NOS: 59-62, and a light chain that is a function-conservative variant of the light chain variable region of the respective I-394, I-395, I-396, I-397, I-398 or I-399 antibody fused to a human CK light chain constant region.

40. The composition or use of any one of the above claims, wherein the antibody has reduced binding to:

(a) a mutant CD39 polypeptide comprising a mutation at 1, 2, 3 or 4 residues selected from the group consisting of Q96, N99, E143 and R147 (with reference to SEQ ID NO: 1), relative to binding between the antibody and a wild-type CD39 polypeptide comprising the amino acid sequence of SEQ ID NO: 1;

(b) a mutant CD39 polypeptide comprising the mutations R138A, M139A and E142K (with reference to SEQ ID NO: 1), relative to binding between the antibody and a wild-type CD39 polypeptide comprising the amino acid sequence of SEQ ID NO: 1;

(c) a mutant CD39 polypeptide comprising the mutations K87A, E100A and D107A (with reference to SEQ ID NO: 1), relative to binding between the antibody and a wild-type CD39 polypeptide comprising the amino acid sequence of SEQ ID NO: 1; and/or

(d) a mutant CD39 polypeptide comprising the mutations N371K, L372K, E375A, K376G and V377S, and an insertion of a valine between residues 376 and 377 (with reference to SEQ ID NO: 1), relative to binding between the antibody and a wild-type CD39 polypeptide comprising the amino acid sequence of SEQ ID NO: 1.

41. The composition or use of any one of the above claims, wherein the antibody comprises a modified human IgG1 Fc domain comprising N-linked glycosylation at Kabat residue N297 and comprising an amino acid substitution at Kabat residue(s) 234 and 235, optionally further at Kabat residue 331, optionally at Kabat residues 234, 235, 237 and at Kabat residues 330 and/or 331, optionally wherein the Fc domain comprises L234A/L235E/P331S substitutions, L234F/L235E/P331S substitutions, L234A/L235E/G237A/P331S substitutions, or L234A/L235E/G237A/A330S/P331S substitutions.