

Claims

1. An anti-CD39 antibody, or antigen-binding fragment thereof, comprising
 - (i) at least one antigen binding domain that binds ectonucleoside triphosphate diphosphohydrolase-1 (CD39) at a site such that the anti-CD39 antibody forms a stable immune complex, and
 - (ii) an FcγRIIIa binding moiety that binds FcγRIIIa receptor and confers antibody-dependent cellular cytotoxicity (ADCC) activity against CD39+ cells to the anti-CD39 antibody.
 2. The anti-CD39 antibody, or antigen-binding fragment thereof, of claim 1, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, promotes:
 - (i) stable immune complex formation when incubated with HCC1739BL cells as characterized by loss of less than 30% of the immune complex after 24 hours, optionally wherein the immune complex formation is detected by fluorescent intensity using a fluorescently labeled secondary antibody;
 - (ii) complement dependent cytotoxicity (CDC) activity against CD39+ cells;
 - (iii) antibody-mediated target cytolysis of CD39 on CD45+ immune cells;
 - (iv) antibody-mediated target cytolysis of CD39 from tumor vascular endothelium disruption or vasculature network collapse in a tumor;
 - (v) (optionally) binding to a CD39 epitope having a sequence selected from the group of CD39 amino acid epitope sequences listed in Figure 33; and/or
 - (vi) (optionally) binding to CD39 in a manner that is non-competitive or only partially competitive with monoclonal antibody clone A1 binding to CD39.
 3. The anti-CD39 antibody, or antigen-binding fragment thereof, of claim 1 or 2, wherein the FcγRIIIa binding moiety is selected from the group consisting of an Fc domain, an antibody or fragment thereof that binds to FcγRIIIa, and an FcγRIIIa binding peptide.
 4. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-3, wherein the antigen binding domain is selected from the group consisting of a Fab, Fab', F(ab')₂, Fv or single chain Fv (scFv), Fav, dsFv, sc(Fv)₂, Fde, sdFv, single domain antibody (dAb), and diabodies fragments and/or wherein the anti-CD39 antibody, or antigen-binding fragment, is monoclonal.
 5. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-4, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is conjugated to an agent, optionally wherein the agent is selected from the group consisting of a binding protein, an enzyme, a drug, a chemotherapeutic agent, a biologic agent, a toxin, a radionuclide, an immunomodulatory agent, a detectable moiety, and a tag.
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6. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-5, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, has a VH domain with an amino acid sequence that can be encoded by a nucleic acid that hybridizes under stringent conditions to the nucleic acid of SEQ ID No. 1 and a VL domain with an amino acid sequence that can be encoded by a nucleic acid that hybridizes under stringent conditions to the nucleic acid of SEQ ID No. 3.
7. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-6, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, comprises a heavy chain having CDRs at least 60% identical to the CDRs of SEQ ID No. 2, 6, 10, 14, 18, 22, 26, 42, 46, 50, or 54, and a light chain having CDRs at least 60% identical to the CDRs of SEQ ID No. 4, 8, 12, 16, 20, 24, 28, 44, 48, 52, or 56.
8. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-7, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, comprises a variable heavy (VH) chain at least 60% identical to SEQ ID No. 2, 6, 10, 14, 18, 22, 26, 42, 46, 50, or 54, and a variable light (VL) chain at least 60% identical to SEQ ID No. 4, 8, 12, 16, 20, 24, 28, 44, 48, 52, or 56.
9. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-8, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, comprises:
 - (i) a heavy chain having a CDR1 amino acid sequence at least 80% identical to SEQ ID No. 29, a CDR2 amino acid sequence at least 80% identical to SEQ ID No. 30, and a CDR3 amino acid sequence at least 80% identical to SEQ ID No. 31; and
 - (ii) a light chain having a CDR1 amino acid sequence at least 80% identical to SEQ ID No. 32, a CDR2 amino acid sequence at least 80% identical to SEQ ID No. 33, and a CDR3 amino acid sequence at least 80% identical to SEQ ID No. 34.
10. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-8, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, comprises a heavy chain having CDRs selected from the group consisting of CDRs of SEQ ID No. 6, 10, 14, 18, 22, 26, 42, 46, 50, and 54, and a light chain having CDRs selected from the group consisting of CDRs of SEQ ID No. 8, 12, 16, 20, 24, 28, 44, 48, 52, and 56, and human framework sequences to form humanized heavy and light chains with an antigen binding site able to specifically bind human CD39.
11. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-10, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, comprises an Fc domain of an IgG1 or IgG3 isotype, optionally wherein the Fc domain is human.

12. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-11, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is hypo-fucosylated or afucosylated.
13. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-12, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is human or is humanized.
14. The anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-13, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is a bispecific including at least one additional antigen binding site for a tumor antigen, immune checkpoint, or costimulatory receptor, wherein if the additional antigen binding site is for an immune checkpoint it functions as a checkpoint inhibitor and wherein if the additional antigen binding site is for a costimulatory receptor it functions as a costimulatory agonist.
15. The anti-CD39 antibody, or antigen-binding fragment thereof, of claim 14, wherein the additional antigen binding site binds to a checkpoint protein selected from the group consisting of PD-1, PD-L1, CTLA-4/B7-1/B7-2, PD-L2, NKG2A, KIR, LAG-3, TIM-3, CD96, VISTA, TIGIT and Siglec-15.
16. The anti-CD39 antibody, or antigen-binding fragment thereof, of claim 14 or 15, wherein the additional antigen binding site binds a checkpoint protein upregulated on T-cells and associated with T-cell exhaustion.
17. The anti-CD39 antibody, or antigen-binding fragment thereof, of claim 14, wherein the additional antigen binding site binds to an immune costimulatory receptors selected from the group consisting of MHCII molecules, BTLA receptor, OX40, CD27, CD28, CD3, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278) and 4-1BB (CD137).
18. The anti-CD39 antibody, or antigen-binding fragment thereof, of claim 14, wherein the additional antigen binding site binds to CD47, SIRP α , CD24 or Siglec-10.
19. A pharmaceutical preparation comprising a therapeutically effective amount of at least one anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18, and one or more pharmaceutically acceptable excipients, buffers or solutions.
20. The pharmaceutical preparation of claim 19 for improving anti-tumor T cell immunity and suitable for administration to a subject having a tumor, comprising an effective amount of the anti-CD39 antibody, or antigen-binding fragment thereof, and one or more pharmaceutically acceptable excipients, buffers or solutions, wherein administration of the anti-CD39 antibody to the subject results in a reduction in numbers of intratumoral CD39^{high} cells and enhances T-cell infiltration into the tumor or decreases T-cell exhaustion in the tumor or both.
21. An isolated nucleic acid molecule that

- i) hybridizes, under stringent conditions, with the complement of a nucleic acid encoding an immunoglobulin heavy and/or light chain polypeptide of the anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18;
 - ii) has a sequence with at least about 90% identity across its full length to a nucleic acid encoding an immunoglobulin heavy and/or light chain polypeptide of the anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18; or
 - iii) encodes an immunoglobulin heavy and/or light chain polypeptide of the anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18.
22. An isolated immunoglobulin heavy and/or light chain polypeptide encoded by the nucleic acid of claim 21.
23. A vector comprising the isolated nucleic acid of claim 21, optionally wherein the vector is an expression vector.
24. A host cell which comprises the isolated nucleic acid of claim 21, that:
- a) expresses the anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18;
 - b) comprises the immunoglobulin heavy and/or light chain polypeptide of claim 22; and/or
 - c) comprises the vector of claim 23.
25. A device or kit comprising at least one anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18, said device or kit optionally comprising a label to detect at least one anti-CD39 antibody, or antigen-binding fragment thereof, or a complex comprising the anti-CD39 antibody, or antigen-binding fragment thereof.
26. A device or kit comprising the pharmaceutical composition, isolated nucleic acid molecule, isolated immunoglobulin heavy and/or light chain polypeptide, vector, and/or host cell of any one of claims 19-24.
27. A method of producing at least one anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18, which method comprises the steps of: (i) culturing a transformed host cell which has been transformed by a nucleic acid comprising a sequence encoding at least one anti-CD39 antibody, or antigen-binding fragment thereof, under conditions suitable to allow expression of said anti-CD39 antibody, or antigen-binding fragment thereof; and (ii) recovering the expressed anti-CD39 antibody, or antigen-binding fragment thereof.
28. A method of detecting the presence or level of CD39 polypeptide comprising obtaining a sample and detecting said polypeptide in the sample by use of at least one anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18.

29. The method of claim 28, wherein at least one anti-CD39 antibody, or antigen-binding fragment thereof, forms a complex with the CD39 polypeptide and the complex is detected in the form of an enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemical assay, Western blot, mass spectrometry assay, nuclear magnetic resonance assay, or using an intracellular flow assay.
30. A method for improving anti-tumor T cell immunity by depleting intratumoral CD39^{high} cells, comprising administering to a subject having a tumor an effective amount of a pharmaceutical composition of an anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18, wherein administration of the anti-CD39 antibody, or antigen-binding fragment thereof, results in a reduction in numbers of intratumoral CD39^{high} cells and enhances T-cell infiltration into the tumor or decreases T-cell exhaustion in the tumor or both.
31. A method for promoting immune cell infiltration into tumors, comprising administering to a subject having a tumor an effective amount of a pharmaceutical composition of an anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18, wherein administration of the anti-CD39 antibody, or antigen-binding fragment thereof, results in ablation and reduction of CD39+ CD45- SCA-1+ stromal cells in the tumor and increased infiltration of the tumor with cytotoxic T-cells.
32. A method for reducing type II NKT cells suppression of intratumoral immune cell function, comprising administering to a subject having a tumor an effective amount of a pharmaceutical composition of an anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18,
wherein administration of the anti-CD39 antibody, or antigen-binding fragment thereof, results in ablation and reduction of type II NKT cells cell in the tumor.
33. A method for reducing regulatory T cells (Treg) suppression of intratumoral immune cell function, comprising administering to a subject having a tumor an effective amount of a pharmaceutical composition of an anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18,
wherein administration of the anti-CD39 antibody, or antigen-binding fragment thereof, results in ablation and reduction of CD39^{high} Tregs in the tumor.
34. A method for reducing tumor-associated macrophages (TAMs) suppression of intratumoral immune cell function, comprising administering to a subject having a tumor an effective amount of a pharmaceutical composition of an anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18, wherein administration of the anti-CD39 antibody, or antigen-binding fragment thereof, results in ablation and reduction of CD39^{high} macrophages in the tumor.

35. A method for promoting an anti-tumor immune response comprising administering to a subject having a tumor an anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18, in an amount sufficient to result in a reduction of CD39 expressing cells in the tumor.
36. A method for promoting T-cell mediated immune function in a tumor of a subject, comprising
- (i) identifying a cancer subject having a degree of tumor infiltrated tumor-reactive lymphocytes that is below a predetermined threshold so as to be characterized as being a non-infiltrated or under-infiltrated tumor phenotype; and
 - (ii) administering to the subject an anti-CD39 antibody, or antigen-binding fragment thereof, of any one of claims 1-18 in an amount that increases tumor infiltration by tumor-reactive T-cells.
37. The method of claim 30, 31 or 34, wherein the intratumoral CD39^{high} cells are selected from hematopoietic stem or progenitor cells (CD45-Sca-1+), CD39+ NKT cells, CD39+ macrophages, CD39+ cancer cells, CD39+ endothelial cells or a combination thereof.
38. The method of claim 30, 31 or 34, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, reduces levels of CD39^{high} cells occurring within one or more hematopoietic compartments, optionally wherein the one or more hematopoietic compartments is selected from the group consisting of blood, spleen and liver.
39. The method of any one of claims 30-38, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is administered as part of an antitumor therapy.
40. The method of any one of claims 30-39, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is administered as part of an anti-infective therapy, optionally wherein the anti-infect therapy is antiviral therapy (including treatment of HIV and HBV infection as well as COVID-19 infection), treatment for *Mycobacterium tuberculosis*, and treatment for visceral leishmaniasis.
41. The method of any one of claims 30-40, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is administered as part of an antitumor therapy for treating a solid tumor, optionally wherein the solid tumor is pancreatic cancer, liver cancer, lung cancer, stomach cancer, esophageal cancer, head and neck squamous cell carcinoma, prostate cancer, colon cancer, breast cancer, lymphoma, gallbladder cancer, renal cancer, multiple myeloma, ovarian cancer, cervical cancer or glioma.
42. The method of any one of claims 30-41, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is administered as part of an antitumor therapy for treating a liquid tumor, optionally wherein the liquid tumor is a leukemia.

43. The method of any one of claims 30-42, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is administered as part of a therapy involving one or more chemotherapeutic agents, anti-angiogenetic agents, immuno-oncology agents and/or radiation.
44. The method of any one of claims 30-43, wherein the therapy includes administering one or more inhibitors (antagonists) of one or more checkpoint molecules, optionally wherein the one or more checkpoint molecules is selected from the group consisting of a PD-1 antagonists, a CTLA-4 antagonist, a LAG-3 antagonist, a TIM-3 antagonist, a TIGIT antagonist and a Siglec-15 antagonist.
45. The method of any one of claims 30-44, wherein the therapy includes administering one or more activators (agonists) of one or more costimulatory molecules, optionally wherein the one or more costimulatory molecules is selected from the group consisting of a GITR agonist, a CD27 agonist, a 4-1BB agonist, an OX40 agonist, a CD137 agonist, an ICOS agonist and a CD28 agonist.
46. The method of any one of claims 30-45, wherein the therapy includes administering one or more of a VEGFR or VEGF antagonist, an EGFR or EGF antagonist, an IDO inhibitor, an IDO1 inhibitor, an HDAC inhibitor, a PI3K delta inhibitor, an IL-15 agonist, a CXCR4 antagonist, a CXCL12 antagonist, a DNMT inhibitor, interleukin-21, an anti-KIR antibody, an anti-CSF-1R antibody, an anti-CCR4 antibody, GM-CSF, an anti-PS antibody, an anti-CD30 antibody-aurostatin E conjugate, an anti-CD19 antibody, an anti-CEA IL-2 antibody, an anti-NY-ESO-1 antibody, an anti-NKG2A antibody, a STING agonist, a TLR7/8 agonist, a RIG-1 agonist and/or NLRP3 inhibitor, an anti-CD73 antibody (such as MEDI9447), a P2X7 antagonist or an adenosine A2A receptor antagonist.
47. The method of any one of claims 30-46, wherein the therapy includes administering one or more innate immune inducers, optionally wherein the one or more innate immune inducers is selected from the group consisting of an inhibitor of the CD47-SIRP α axis, an inhibitor of the CD24-Siglec-10 axis, an NGK2A checkpoint inhibitor that blocks HLA-E driven inhibition of NK and CD8+ cells, a STING agonist, a TLR7/8 agonist and an RIG-I agonist.
48. The method of any one of claims 30-46, wherein the anti-CD39 antibody, or antigen-binding fragment thereof, is administered as a part of therapy including a tumor vaccine, adoptive cell therapy, antitumor gene therapy, inhibitory nucleic acid therapy and/or oncolytic viral therapy.
49. The pharmaceutical composition or method of any one of claims 20 or 30-48, wherein the subject is an animal model of cancer.
50. The pharmaceutical composition or method of any one of claims 20 or 30-49, wherein the subject is a mammal, optionally wherein the mammal is a human or a rodent.