~~What is claimed is:~~CLAIMS

1. An anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, wherein the monoclonal antibody, or antigen-binding fragment thereof comprises:

a) a VH CDR1 amino acid sequence of SEQ ID NO: 206, a VH CDR2 amino acid sequence of SEQ ID NO: 210, and a VH CDR3 amino acid sequence of SEQ ID NO: 214; and

b) a VL CDR1 amino acid sequence of SEQ ID NO: 224, a VL CDR2 amino acid sequence of SEQ ID NO: 228, and a VL CDR3 amino acid sequence of SEQ ID NO: 232.

2. The anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof of claim 1, wherein the monoclonal antibody, or antigen-binding fragment thereof comprises:

a) a heavy chain variable domain comprising an amino acid sequence with at least 95% identity to SEQ ID NO: 199; and

b) a light chain variable domain comprising an amino acid sequence with at least 95% identity to SEQ ID NO: 217.

3. The anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof of claim 1, wherein the monoclonal antibody, or antigen-binding fragment thereof comprises:

a) a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 199; and

b) a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 217.

~~1. A monoclonal antibody, or antigen-binding fragment thereof, wherein the monoclonal antibody comprises:~~

~~a) a heavy chain sequence with at least about 95% identity to a heavy chain sequence selected from the group consisting of the sequences listed in Table 2; and/or~~

~~b) a light chain sequence with at least about 95% identity to a light chain sequence selected from the group consisting of the sequences listed in Table 2.~~

~~2~~4. An anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, wherein the monoclonal antibody comprises:

a) a heavy chain CDR sequence ~~with at least about 95% identity to a heavy chain CDR sequence~~ selected from the group consisting of the sequences listed in Table 2; ~~and/or~~

b) a light chain CDR sequence ~~with at least about 95% identity to a light chain CDR sequence~~ selected from the group consisting of the sequences listed in Table 2~~.~~;

~~3. A monoclonal antibody, or antigen-binding fragment thereof, wherein the monoclonal antibody comprises:~~

~~a~~c) a heavy chain sequence selected from the group consisting of the sequences listed in Table 2; and/or

~~b~~d) a light chain sequence selected from the group consisting of the sequences listed in Table 2.

~~4. A monoclonal antibody, or antigen-binding fragment thereof, wherein the monoclonal antibody comprises:~~

~~a) a heavy chain CDR sequence selected from the group consisting of the sequences listed in Table 2; and/or~~

~~b) a light chain CDR sequence selected from the group consisting the sequences listed in Table 2.~~

5. The anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-4, wherein the anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof,

a) is chimeric, humanized, composite, murine, or human~~.~~

~~6. The monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-5, wherein the monoclonal antibody, or antigen-binding fragment thereof,~~;

b) is detectably labeled, comprises an effector domain, comprises an Fc domain, and/or is selected from the group consisting of Fv, Fav, F(ab')$_2$~~)~~, Fab', dsFv, scFv, sc(Fv)$_2$, and diabodies fragments~~.~~; or

~~7. The monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-6, wherein said monoclonal antibody, or antigen-binding fragment thereof, is obtainable from hybridoma _____ deposited under deposit accession number _____.~~

~~8. The monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-7, wherein the monoclonal antibody, or antigen-binding fragment thereof,~~

c) inhibits ~~a~~i) the binding of HHLA2 to TMIGD2, ~~b~~ii) the binding of HHLA2 to KIR3DL3, or ~~c~~iii) the binding of HHLA2 to TMIGD2 and the binding of HHLA2 to KIR3DL3.

~~9. The monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-8, wherein the monoclonal antibody, or antigen-binding fragment thereof, specifically binds HHLA2.~~

~~10. An immunoglobulin heavy and/or light chain selected from the group consisting of immunoglobulin heavy and light chain sequences listed in Table 2.~~

~~11~~6. An isolated nucleic acid molecule that hybridizes, under stringent conditions, with the complement of a nucleic acid encoding a polypeptide selected from the group consisting of polypeptide sequences of SEQ ID NO: 199, 202, 204, 206, 208, 210, 212, 214, 216, 217, 220, 222, 224, 226, 228, 230, 232, and 234~~listed in Table 2~~, or a sequence with at least about 95% homology to a nucleic acid encoding a polypeptide selected from the group consisting of the polypeptide sequences of SEQ ID NO: 199, 202, 204, 206, 208, 210, 212, 214, 216, 217, 220, 222, 224, 226, 228, 230, 232, and 234~~listed in Table 2~~.

~~12~~7. A vector comprising the isolated nucleic acid of claim ~~11~~6.

~~13~~8. A host cell which comprises the isolated nucleic acid of claim ~~11~~6, comprises the vector of claim ~~12~~7, expresses the anti-HHLA2 antibody, or antigen-binding fragment thereof, of any one of claims 1-~~9~~5~~, or is accessible under deposit accession number _____~~.

~~14~~9. A device or kit comprising at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5, said device or kit ~~optionally~~ comprising a label to detect the at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, or a complex comprising the anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof.

~~15~~10. A method of producing at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5, 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-HHLA2 monoclonal antibody according to any one of claims 1-~~9~~ 5 under conditions suitable to allow expression of said anti-

HHLA2 monoclonal antibody, or antigen-binding fragment thereof; and (ii) recovering the expressed monoclonal antibody, or antigen-binding fragment thereof.

~~16~~11. A method of detecting the presence or level of an HHLA2 polypeptide comprising obtaining a sample and detecting said polypeptide in the sample by use of at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5.

~~17. The method of claim 16~~, optionally wherein the at least one monoclonal antibody, or antigen-binding fragment thereof, forms a complex with an HHLA2 polypeptide and the complex is detected in the form of an enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or using an intracellular flow assay.

~~18~~12. A method for monitoring the progression of a disorder associated with aberrant HHLA2 expression in a subject, the method comprising:

a) detecting in a subject sample at a first point in time the level of HHLA2 using at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5;

b) repeating step a) at a subsequent point in time; and

c) comparing the level of HHLA2 detected in steps a) and b) to monitor the progression of the disorder in the subject.

~~19. The method of claim 18~~, optionally wherein between the first point in time and the subsequent point in time, the subject has undergone treatment to ameliorate the disorder.

~~20~~13. A method for predicting the clinical outcome of a subject afflicted with a disorder associated with aberrant HHLA2 expression, the method comprising:

a) determining the level of HHLA2 in a subject sample using at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5;

b) determining the level of HHLA2 in a sample from a control subject having a good clinical outcome using the at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof; and

c) comparing the level of HHLA2 in the subject sample and in the sample from the control subject;

wherein a significantly higher level of HHLA2 in the subject sample as compared to the level in the sample from the control subject is an indication that the subject has a poor clinical outcome, optionally wherein said significantly higher level of HHLA2 comprises an at least twenty percent increase between the level of HHLA2 in the subject sample relative to the normal level of HHLA2 in the sample from the control subject.

~~21~~14. A method of assessing the efficacy of a therapy for a disorder associated with aberrant HHLA2 expression in a subject, the method comprising:

a) determining the level of HHLA2 using at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5, in a first sample obtained from the subject prior to providing at least a portion of the therapy to the subject, and

b) determining the level of HHLA2 in a second sample obtained from the subject following provision of the portion of the therapy,

wherein a significantly lower level of HHLA2 in the second sample, relative to the first sample, is an indication that the therapy is efficacious for inhibiting the disorder in the subject, optionally wherein said significantly lower level of HHLA2 comprises an at least twenty percent decrease of the level of HHLA2.

~~22~~15. A method of assessing the efficacy of a test compound for inhibiting a disorder associated with aberrant HHLA2 expression in a subject, the method comprising:

a) determining the level of HHLA2 using at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5, in a first sample obtained from the subject and exposed to the test compound; and

b) determining the level of HHLA2 in a second sample obtained from the subject, wherein i) the second sample is not exposed to the test compound, and a significantly lower level of HHLA2, relative to the second sample, is an indication that the test compound is efficacious for inhibiting the disorder in the subject, optionally wherein said significantly

lower level of HHLA2 comprises an at least twenty percent decrease of the level of HHLA2.; and/ or

~~23. The method of claim 22, wherein~~ ii) the first and second samples are portions of a single sample obtained from the subject or portions of pooled samples obtained from the subject.

~~24~~16. The method of any one of claims ~~18~~12-~~23~~15, wherein the disorder is a cancer~~.~~

~~25. The method of claim 24,~~ optionally wherein the cancer is selected from the group consisting of lung cancer, renal cancer, pancreatic cancer, colorectal cancer, Acute myeloid leukemia, head and neck carcinoma, liver cancer, ovarian cancer, prostate cancer, uterine cancer, gliomas, glioblastoma, neuroblastoma, breast cancer, pancreatic ductal carcinoma, thymoma, B-CLL, leukemia, B cell lymphoma, and a cancer infiltrated with immune cells expressing a receptor to HHLA2.

~~26~~17. The method of any one of claims ~~16~~11-~~25~~16, wherein the sample comprises cells, serum, peritumoral tissue, and/or intratumoral tissue obtained from the subject, optionally~~.~~

~~27. The method of claim 20, wherein said significantly higher level of HHLA2 comprises an at least twenty percent increase between the level of HHLA2 in the subject sample relative to the normal level of HHLA2 in the sample from the control subject.~~

~~28. The method of any one of claims 21-26, wherein said significantly lower level of HHLA2 comprises an at least twenty percent decrease of the level of HHLA2.~~

~~29. The method of any one of claims 18-28~~, wherein the subject is a human.

~~30~~18. ~~A method of treating a subject afflicted with cancer comprising administering to the subject~~Use of at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof, according to any one of claims 1-~~9~~5, in the manufacture of a pharmaceutical composition for the treatment of cancer in a subject afflicted with cancer.

~~31~~19. The ~~method~~ use of claim ~~30~~18, wherein the at least one anti-HHLA2 monoclonal antibody, or antigen-binding fragment thereof,

a) is conjugated to a cytotoxic agent.

32. The method of claim 31, optionally wherein the cytotoxic agent is selected from the group consisting of a chemotherapeutic agent, a biologic agent, a toxin, and a radioactive isotope;.

33. The method of any one of claims 30-32, wherein the at least one monoclonal antibody, or antigen-binding fragment thereof,
b) reduces the number of proliferating cells in the cancer and/or reduces the volume or size of a tumor of the cancer.;

34. The method of any one of claims 30-33, wherein the at least one monoclonal antibody, or antigen-binding fragment thereof, c) is to be administered in a pharmaceutically acceptable formulation.;

35. The method of any one of claims 30-34, d) further comprising administering to the subject a therapeutic agent or regimen for treating cancer to be administered.; or

36. The method of any one of claims 30-35, e) further comprising administering to the subject an additional therapy to be administered, the additional therapy is selected from the group consisting of immunotherapy, checkpoint blockade, cancer vaccines, chimeric antigen receptors, chemotherapy, radiation, target therapy, and surgery.

3720. The method use of any one of claims 3018 or 19-36, wherein a) cancer cells and/or tumor immune infiltrating cells in the subject express HHLA2.

38. The method of any one of claims 30-37, optionally wherein the cancer is selected from the group consisting of lung cancer, renal cancer, pancreatic cancer, colorectal cancer, Acute myeloid leukemia, head and neck carcinoma, liver cancer, ovarian cancer, prostate cancer, uterine cancer, gliomas, glioblastoma, neuroblastoma, breast cancer, pancreatic ductal carcinoma, thymoma, B-CLL, leukemia, B cell lymphoma, and a cancer infiltrated with immune cells expressing a receptor to HHLA2 or .

39. The method of claim 38, wherein the cancer is selected from the group consisting of lung cancer, renal cancer, pancreatic cancer, colorectal cancer, acute myeloid leukemia

(AML), head and neck carcinoma, liver cancer, ovarian cancer, prostate cancer, and uterine cancer~~.~~;

~~40. The method of any one of claims 30-39, wherein~~ b) the subject is an animal model of cancer~~.~~

~~41. The method of claim 40, wherein the animal model is,~~ a mouse model, ~~optionally wherein the mouse model is~~ or a humanized mouse model~~.~~; or

~~42. The method of any one of claims 30-41, wherein~~ c) the subject is a mammal~~.~~,

~~43. The method of claim 42, wherein the mammal is~~ a humanized mouse or a human.

~~44. The method of claim 43, wherein the mammal is a human.~~

~~45. A method of modulating an immune response by inhibiting the interaction between HHLA2 and its binding inhibitor recept, KIRDL3.~~

~~46. The method of claim 45, wherein the interaction between HHLA2 and KIRDL3 is blocked for use in checkpoint blockade cancer immunotherapy.~~

~~47. The method of claim 45 or 46, wherein the interaction between HHLA2 and KIRDL3 is inhibited or blocked using an anti-HHLA2 antibody.~~

~~48. The method of claim 47, wherein the anti-HHLA2 antibody is a checkpoint inhibitor of T cell activation for cancer immunotherapy.~~

~~49. A method of modulating an immune response by selectively inhibiting the interaction between HHLA2 and its binding inhibitor receptor, KIR3DL3, without blocking or significantly inhibiting the interaction between HHLA2 and its binding stimulatory receptor, TMIGD2.~~