

CLAIMS:

1. An anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, comprising:
 - a) a HC CDR1 comprising an amino acid sequence GFTFSNY,
 - b) a HC CDR2 comprising an amino acid sequence RLKSNNYA,
 - c) a HC CDR3 comprising an amino acid sequence FYGSSFPY,
 - d) a LC CDR1 comprising an amino acid sequence RASQDISNYLN,
 - e) a LC CDR2 comprising an amino acid sequence YTSILQL, and
 - f) a LC CDR3 comprising an amino acid sequence QQGNTLPFT.
2. The anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof of claim 1, comprising:
 - a) a heavy chain variable sequence with at least 95% identity to a heavy chain variable amino acid sequence
ELKLEESGGGLVQPGGSMKLSCVASGFTFSNYWMNWVRQSPEKGLEWIAEIRLKSNNY
ATHYAESVKGRFTISRDDSKSSVYLQMNNLRAEDTGIFYCTPFYGSFPYWGQGTLVTV
SA; and
 - b) a light chain variable sequence with at least 95% identity to a light chain variable amino acid sequence
DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIYYTSILQLGVPP
RFGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPFTFGAGTKVELK.
3. The anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, of claim 1 or 2, wherein the anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, is chimeric, humanized, composite, or murine.
4. The anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-3, wherein the anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, is (a) detectably labeled, (b) conjugated to a cytotoxic agent, optionally a chemotherapeutic agent, a biologic agent, a toxin, and/or a radioactive isotope, (c) comprises an

effector domain, (d) comprises an Fc domain, and/or (e) is selected from the group consisting of Fv, Fav, F(ab')₂, Fab', dsFv, scFv, sc(Fv)₂, and diabodies fragments.

5. The anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-4, wherein the anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, inhibits the binding of HHLA2 to KIR3DL3.

6. The anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-5, wherein the anti-KIR3DL3 monoclonal antibody, or antigen-binding fragment thereof, specifically binds KIR3DL3.

7. An anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, comprising:
a) a HC CDR1 comprising an amino acid sequence GFTFSNY,
b) a HC CDR2 comprising an amino acid sequence RLKSNNYA,
c) a HC CDR3 comprising an amino acid sequence FYGSSFPY,
d) a LC CDR1 comprising an amino acid sequence RASQDISNYLN,
e) a LC CDR2 comprising an amino acid sequence YTSILQL, and
f) a LC CDR3 comprising an amino acid sequence QQGNTLPFT.

8. The anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof of claim 7, comprising:

a) a heavy chain variable sequence with at least 95% identity to a heavy chain variable amino acid sequence

ELKLEESGGGLVQPGGSMKLSCVASGFTFSNYWMNWVRQSPEKGLEWIAEIRLKSNNY
ATHYAESVKGRFTISRDDSKSSVYLQMNNLRAEDTGIFYCTPFYGSSFPYWGQGTLVTV
SA; and

b) a light chain variable sequence with at least 95% identity to a light chain variable amino acid sequence

DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIYYTSILQLGVPP
RFGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPFTFGAGTKVELK.

9. The anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, of claim 7 or 8, wherein the anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, is chimeric, humanized, composite, murine, or human.

10. The anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, of any one of claims 7-9, wherein the anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, is (a) detectably labeled, (b) conjugated to a cytotoxic agent, optionally a chemotherapeutic agent, a biologic agent, a toxin, and/or a radioactive isotope, (c) comprises an effector domain, (d) comprises an Fc domain, and/or (e) is selected from the group consisting of Fv, Fav, F(ab')₂, Fab', dsFv, scFv, sc(Fv)₂, and diabodies fragments.

11. The anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, of any one of claims 7-10, wherein the anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, inhibits the binding of (a) HHLA2 to KIR3DL3, and (b) PD-1 to PD-L1 and/or PD-L2.

12. The anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, of any one of claims 7-11, wherein the anti-KIR3DL3 bispecific antibody, or antigen-binding fragment thereof, specifically binds KIR3DL3 and PD-1.

13. An isolated nucleic acid molecule that (a) encodes the anti-KIR3DL3 antibody, or antigen-binding fragment thereof, of any one of claims 1-12; and/or (b) hybridizes, under stringent conditions, with the complement of a nucleic acid encoding a polypeptide sequence(s)
ELKLEESGGGLVQPGGSMKLSCVASGFTFSNYWMNWVRQSPEKGLEWIAEIRLKSNNY
ATHYAESVKGRFTISRDDSKSSVYLQMNNLRAEDTGIFYCTPFYGSSFPYWGQGTLVTV
SA and/or
DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIYYTSILQLGVPP
RFGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPFTFGAGTKVELK, or a sequence with at least 95% homology to a nucleic acid encoding a polypeptide sequence(s)
ELKLEESGGGLVQPGGSMKLSCVASGFTFSNYWMNWVRQSPEKGLEWIAEIRLKSNNY
ATHYAESVKGRFTISRDDSKSSVYLQMNNLRAEDTGIFYCTPFYGSSFPYWGQGTLVTV
SA and/or

DIQMTQTTSSLASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIYYTSILQLGVPP
RFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPFTFGAGTKVELK.

14. A vector comprising the isolated nucleic acid of claim 13.
15. A host cell which comprises the isolated nucleic acid of claim 13, comprises the vector of claim 14, or expresses the anti-KIR3DL3 antibody, or antigen-binding fragment thereof, of any one of claims 1-12.
16. A device or kit comprising at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, according to any one of claims 1-12, said device or kit optionally comprising a label to detect the at least one antibody, or antigen-binding fragment thereof, or a complex comprising the antibody, or antigen-binding fragment thereof.
17. A method of producing at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, according to any one of claims 1-12, which method comprises the steps of:
 - (i) culturing a transformed host cell which has been transformed by a nucleic acid comprising a sequence encoding the least one anti-KIR3DL3 antibody or antigen-binding fragment under conditions suitable to allow expression of said antibody, or antigen-binding fragment thereof; and
 - (ii) recovering the expressed antibody, or antigen-binding fragment thereof.
18. A method of detecting the presence or level of an KIR3DL3 polypeptide comprising detecting said polypeptide in a sample by use of at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, according to any one of claims 1-12,
 - optionally wherein the at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, forms a complex with an KIR3DL3 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.
19. A method of predicting the responsiveness to a therapy targeting KIR3DL3, the method comprising:

a) determining the level of KIR3DL3 in a subject sample using at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, according to any one of claims 1-12;

b) determining the level of KIR3DL3 in a sample from at least one control subject having good responsiveness to a therapy targeting KIR3DL3, using the at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof; and

c) comparing the level of KIR3DL3 in the subject sample and in the sample from the control subject;

wherein

the same or higher level of KIR3DL3 in the subject sample as compared to the level in the sample from the at least one control subject is an indication that the subject will be responsive to the therapy,

optionally wherein the therapy targets KIR3DL3 using at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, according to any one of claims 1-12.

20. A method of predicting the responsiveness to a therapy targeting KIR3DL3 using at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, according to any one of claims 1-12, the method comprising:

a) determining the level of KIR3DL3 in a subject sample;

b) determining the level of KIR3DL3 in a sample from at least one control subject having good responsiveness to a therapy targeting KIR3DL3; and

c) comparing the level of KIR3DL3 in the subject sample and in the sample from the control subject;

wherein

the same or higher level of KIR3DL3 in the subject sample as compared to the level in the sample from the at least one control subject is an indication that the subject will be responsive to the therapy; optionally wherein the sample is a portion of a single sample obtained from at least one subject or portions of pooled samples obtained from at least one subject;

the therapy blocks the interaction and/or signaling between (a) HHLA2 and KIR3DL3; and/or (b) PD-1 and PD-L1 and/or PD-L2;

optionally wherein the sample comprises cells, serum, peritumoral tissue, and/or intratumoral tissue obtained from the subject; and/or

optionally wherein the cells are T cells or natural killer (NK) cells.

21. A composition comprising at least one anti-KIR3DL3 antibody or antigen-binding fragment thereof according to any one of claims 1-12 for use in therapy.

22. Use of at least one anti-KIR3DL3 antibody or antigen-binding fragment thereof according to any one of claims 1-12 in the manufacture of a medicament for treating cancer in a subject.

23. The use of claim 22, wherein

the at least anti-KIR3DL3 one antibody, or antigen-binding fragment thereof, (a) reduces the number of proliferating cancer cells in the cancer; (b) reduces the volume or size of a tumor of the cancer; and/or (c) activates a T cell and/or an NK cell;

the at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, is to be administered in a pharmaceutically acceptable formulation;

the subject is to be further administered a therapeutic agent or regimen for treating cancer;

the subject is to be further subjected to an additional therapy selected from the group consisting of immunotherapy, checkpoint blockade, cancer vaccines, chimeric antigen receptors, chemotherapy, radiation, target therapy, and surgery;

the chimeric antigen receptors target CD19;

cancer cells and/or tumor immune infiltrating cells in the subject express HHLA2;

the cancer is selected from the group consisting of adenocarcinoma, chronic myelogenous leukemia (CML), 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;

the subject is an animal model of cancer;

the animal model is optionally a mouse model;

the mouse model is optionally a humanized mouse model;

the subject is optionally a mammal; and/or

the mammal is optionally a humanized mouse or a human.

24. Use of at least one anti-KIR3DL3 antibody or antigen-binding fragment thereof according to any one of claims 1-12, in the manufacture of a medicament for modulating an immune response.

25. The use of claim 24, wherein

the at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, inhibits or disrupts the interaction between HHLA2 and its binding inhibitor receptor, KIR3DL3;

at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxic agent;

the cytotoxic agent is selected from the group consisting of a chemotherapeutic agent, a biologic agent, a toxin, and a radioactive isotope;

the immune response is downregulated or upregulated;

the at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, is according to any one of claims 1-12;

the interaction between (a) HHLA2 and KIR3DL3; and/or (b) PD-1 and PD-L1 and/or PD-L2 is blocked;

the at least one anti-KIR3DL3 antibody, or antigen-binding fragment thereof, is a checkpoint inhibitor of T cell activation for cancer immunotherapy;

the modulating an immune response comprises modulating a T cell function or NK cell function, optionally wherein the T cell function or NK cell function comprises a cytotoxic activity, optionally wherein the cytotoxic activity is against cancer cells;

the cancer cells express HHLA2;

the cancer is selected from the group consisting of adenocarcinoma, chronic myelogenous leukemia (CML), 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;

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;

an additional therapy selected from the group consisting of immunotherapy, checkpoint blockade, cancer vaccines, chimeric antigen receptors, chemotherapy, radiation, target therapy, and surgery;

the chimeric antigen receptors target CD19;

the immune response is modulated in an animal model of cancer;

the animal model is a mouse model, optionally wherein the mouse model is a humanized mouse model;

the immune response is modulated in a mammal; and/or

the mammal is optionally a humanized mouse or a human.