

CLAIMS

1. A monoclonal antibody or antigen binding fragment comprising three heavy chain CDRs (CDR-H) and three light chain CDRs (CDR-L), wherein:
 - a) CDR-H1, CDR-H2, and CDR-H3 comprise SEQ ID NOs: 13, 14, and 15, respectively, wherein X in SEQ ID NO: 15 is selected from A, C and S, and CDR-L1, CDR-L2, and CDR-L3 comprise SEQ ID NOs: 16, 17, and 18, respectively;
 - b) CDR-H1, CDR-H2, and CDR-H3 comprise SEQ ID NOs: 1, 2, and 3, respectively, and CDR-L1, CDR-L2, and CDR-L3 comprise SEQ ID NOs: 4, 5, and 6, respectively; or
 - c) CDR-H1, CDR-H2, and CDR-H3 comprise SEQ ID NOs: 7, 8, and 9, respectively, and CDR-L1, CDR-L2, and CDR-L3 comprise SEQ ID NOs: 10, 11, and 12, respectively.
2. The antibody or antigen binding fragment of claim 1, comprising:
 - a) a heavy chain comprising SEQ ID NO: 19, 21, or 23, wherein X in SEQ ID NO: 23 is selected from A, C and S;
 - b) a light chain comprising SEQ ID NO: 20, 22, 24, or 45; or
 - c) both a) and b).
3. The antibody or antigen binding fragment of claim 1, wherein said antibody or antigen binding fragment is humanized and said X is A or S.
4. The antibody or antigen binding fragment of claim 3, wherein said X is A, SEQ ID NO: 15 is identical to SEQ ID NO: 25, and SEQ ID NO: 23 is identical to SEQ ID NO: 28.
5. A monoclonal antibody or antigen-binding fragment comprising a heavy chain that comprises SEQ ID NO: 28 and a light chain that comprises SEQ ID NO: 24.

6. A monoclonal antibody comprising a heavy chain that comprises SEQ ID NO: 28 and a light chain that comprises SEQ ID NO: 24, wherein said antibody is of a human IgG4 isotype.
7. A monoclonal antibody or antigen binding fragment that:
 - a) binds a human leukocyte immunoglobulin-like receptor subfamily B member 1 (ILT2) epitope within a sequence of human ILT2 selected from SEQ ID NOs: 41, 42, 43, and 44, optionally wherein said epitope is a three-dimensional epitope comprising residues within SEQ ID NOs: 41, 42, 43 and 44;
 - b) binds ILT2 and inhibits direct interaction between said ILT2 and beta-2-microglobulin (B2M), optionally wherein said antibody or antigen binding fragment inhibits interaction of said ILT2 and an HLA protein or MHC-I protein via said inhibition of ILT2 direct interaction with B2M, optionally wherein said HLA is HLA-G; or
 - c) both a) and b).
8. The monoclonal antibody or antigen binding fragment of any one claims 1 to 7, wherein said antibody or antigen-binding fragment binds ILT2 and induces in a subject suffering from cancer at least three of:
 - a) increased natural killer (NK) cell cytotoxicity;
 - b) increased T cell cytotoxicity, proliferation, or both;
 - c) increased macrophage phagocytosis, increased generation of M1 inflammatory macrophages, decreased generation of M2 suppressor macrophages or a combination thereof; and
 - d) increased dendritic cell homing to a tumor of said cancer, increased dendritic cell activation or a combination thereof;optionally wherein said cancer is an HLA-G or MHC-I expressing cancer.
9. An antibody or antigen binding fragment of any one of claims 1 to 8, for use in
inducing/enhancing an anti-tumor T-cell response,
increasing T-cell proliferation,
reducing cancer-induced suppressor myeloid activity,

increasing natural killer cell cytotoxicity,
increasing macrophage phagocytosis,
increasing generation of M1 inflammatory macrophages,
decreasing generation of M2 suppressor macrophages,
increasing dendritic cell number in a tumor microenvironment,
increasing dendritic cell activation,
treating an HLA-G expressing cancer, or
treating an MHC-I expressing cancer
in a patient in need thereof.

10. An antibody or antigen binding fragment of any one of claims 1 to 8, for use in treating an HLA-G or MHC-I expressing cancer in a subject in need thereof.
11. The antibody or antigen binding fragment for use of claim 10, wherein said treatment further comprises administering to said subject an opsonizing agent.
12. The antibody or antigen binding fragment for use of claim 11, wherein said opsonizing agent is an EGFR inhibitor, optionally wherein said EGFR inhibitor is cetuximab.
13. The antibody or antigen binding fragment for use of claim 11 or 12, wherein said treatment further comprises administering to said subject an anti-PD-L1/PD-1 based immunotherapy.
14. The antibody or antigen binding fragment for use of claim 10, wherein said treatment comprises:
 - a) confirming that expression of ILT2 or soluble HLA-G in said subject is above a predetermined threshold; and
 - b) administering to said subject said antibody or antigen binding fragment.
15. The antibody or antigen binding fragment for use of claim 14, wherein said confirming comprises measuring expression of ILT2 or soluble HLA-G in said subject before said administering.

16. The antibody or antigen binding fragment for use of claim 14 or 15, wherein said treatment comprises confirming expression of ILT2 and wherein said expression of ILT2 is in an immune cell of said subject.
17. The antibody or antigen binding fragment for use of claim 16, wherein said immune cell is a peripheral blood immune cell or an intratumor immune cell.
18. The antibody or antigen binding fragment for use of claim 16 or 17, wherein said immune cell is selected from a CD8 positive T cell, a macrophage, an NK cell and a TEMRA cell, optionally wherein said immune cell is a peripheral blood CD8 positive T cell.
19. The antibody or antigen binding fragment for use of claim 14 or 15, wherein said treatment comprises confirming expression of soluble HLA-G.
20. An antibody or antigen binding fragment of any one of claims 1 to 8, for use in increasing the efficacy of an anti-PD-L1/PD-1 based therapy against a cancer cell expressing HLA-G, MHC-I, or both.
21. The antibody or antigen binding fragment for use of claim 13, wherein said anti-PD-L1/PD-1 based immunotherapy is an anti-PD-1 blocking antibody.
22. The antibody or antigen binding fragment for use of any one of claims 9 to 21, wherein said cancer is refractory to anti-PD-L1/PD-1 based therapy.
23. A pharmaceutical composition comprising an antibody or antigen binding fragment of any one of claims 1 to 8.
24. A method for producing an agent, the method comprising:
 - a) obtaining an agent that binds to an ILT2 extracellular domain or fragment thereof, testing an ability of said agent to induce at least two of: increased phagocytosis of a cancer cell by macrophages, increased T cell activity against a

cancer cell, increased generation of M1 macrophages, reduced generation of M2 macrophages, increased recruitment of dendritic cells to a tumor microenvironment, increased dendritic cell activation and increased natural killer (NK) cell cytotoxicity against a cancer cell and selecting at least one agent that induces at least two of said increased phagocytosis, said increased activity, said increased generation, said reduced generation, said recruitment, said increased activation, said decreased activity and said increased cytotoxicity; or

culturing a host cell comprising one or more vectors comprising a nucleic acid sequence encoding an agent, wherein the nucleic acid sequence is that of an agent that was selected by:

- i) obtaining an agent that binds to an ILT2 extracellular domain or fragment thereof;
 - ii) testing an ability of said agent to induce at least two of: increased phagocytosis of a cancer cell by macrophages, increased T cell activity against a cancer cell, increased generation of M1 macrophages, reduced generation of M2 macrophages, increased recruitment of dendritic cells to a tumor microenvironment, increased dendritic cell activation and increased natural killer (NK) cell cytotoxicity against a cancer cell; and
 - iii) selecting at least one agent that increases at least two of said increased phagocytosis, said increased activity, said increased generation, said reduced generation, said recruitment, said increased activation, said decreased activity and said increased cytotoxicity;
- thereby producing an agent.

25. A method for producing an agent, the method comprising:

obtaining an agent that binds to an ILT2 extracellular domain or fragment thereof, testing an ability of said agent to increase efficacy of an anti-PD-L1/PD-1 based therapy against a cancer cell and selecting at least one agent that increases the efficacy of an anti-PD-L1/PD-1 based therapy; or culturing a host cell comprising one or more vectors comprising a nucleic acid sequence encoding an agent, wherein the nucleic acid sequence is that of an agent that was selected by:

- i) obtaining an agent that binds to an ILT2 extracellular domain or fragment thereof;
 - ii) testing an ability of said agent to increase efficacy of an anti-PD-L1/PD-1 based therapy against a cancer cell; and
 - iii) selecting at least one agent that increases efficacy of an anti-PD-L1/PD-1 based therapy against a cancer cell;
 thereby producing an agent.

- 26. A method for producing an agent, the method comprising:
 - obtaining an agent that binds to an ILT2 extracellular domain or fragment thereof, testing an ability of said agent to inhibit interaction between ILT2 and B2M and selecting at least one agent that inhibits interaction between ILT2 and B2M; or culturing a host cell comprising one or more vectors comprising a nucleic acid sequence encoding an agent, wherein the nucleic acid sequence is that of an agent that was selected by:
 - i) obtaining an agent that binds to an ILT2 extracellular domain or fragment thereof;
 - ii) testing an ability of said agent to inhibit interaction between ILT2 and B2M;
 and
 - iii) selecting at least one agent that inhibits interaction between ILT2 and B2M;
 thereby producing an agent.

- 27. A method for producing an agent, the method comprising:
 - obtaining an agent that binds to an ILT2 epitope within a sequence of human ILT2 selected from SEQ ID NO: 41, 42, 43 and 44, or
 - culturing a host cell comprising one or more vectors comprising a nucleic acid sequence encoding an agent, wherein the nucleic acid sequence is that of an agent that was selected by obtaining an agent that binds to an ILT2 epitope within a sequence of human ILT2 selected from SEQ ID NO: 41, 42, 43 and 44; thereby producing an agent.

- 28. A nucleic acid molecule encoding an antibody or antigen binding fragment of any one of claims 1 to 8.

29. The nucleic acid molecule of claim 28, wherein said nucleic acid molecule is an expression vector.