

CLAIMS

1. A monoclonal anti-immunoglobulin-like transcript 2 (ILT2) antibody or an antigen binding fragment thereof, wherein said antibody or antigen-binding fragment comprises 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, wherein said antibody or antigen binding fragment is humanized and said X in SEQ ID NO: 15 is A or S.
3. The antibody or antigen binding fragment of claim 1, comprising a heavy chain and a light chain comprising the amino acid sequences of:
 - a) SEQ ID NOs: 23 and 24, respectively, wherein X in SEQ ID NO: 23 is selected from A, C, and S;
 - b) SEQ ID NOs: 23 and 45, respectively, wherein X in SEQ ID NO: 23 is selected from A, C, and S;
 - c) SEQ ID NOs: 28 and 24, respectively;
 - d) SEQ ID NOs: 29 and 24, respectively;
 - e) SEQ ID NOs: 30 and 45, respectively;
 - f) SEQ ID NOs: 19 and 20, respectively; or
 - g) SEQ ID NOs: 21 and 22, respectively.

4. The antibody or antigen binding fragment of claim 2 or 3, wherein said X in SEQ ID NO: 15 or 23 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. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises
a CDR-H1 amino acid sequence of SEQ ID NO: 13,
a CDR-H2 amino acid sequence of SEQ ID NO: 14,
a CDR-H3 amino acid sequence of SEQ ID NO: 25,
a CDR-L1 amino acid sequence of SEQ ID NO: 16,
a CDR-L2 amino acid sequence of SEQ ID NO: 17, and
a CDR-L3 amino acid sequence of SEQ ID NO: 18.
6. A monoclonal anti-ILT2 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.
7. A monoclonal anti-ILT2 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.
8. The antibody or antigen binding fragment of any one of claims 1-7, wherein said antibody or antigen-binding fragment inhibits direct interaction between ILT2 and beta-2-microglobulin (B2M).
9. The antibody or antigen-binding fragment of claim 8, wherein said antibody or antigen binding fragment inhibits interaction of ILT2 and an HLA protein or MHC-I protein via said inhibition of ILT2 direct interaction with B2M.
10. The monoclonal antibody or antigen binding fragment of any one claims 1 to 9, wherein said antibody or antigen-binding fragment is capable of inducing in a human subject with 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.
11. The antibody or antigen binding fragment of any one of claims 1 to 10, 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, or increasing dendritic cell activation in a human subject with cancer, optionally wherein said cancer is an HLA-G or MHC-I expressing cancer.
12. The antibody or antigen binding fragment of any one of claims 1 to 11, for use in treating an HLA-G or MHC-I expressing cancer in a human subject in need thereof.
13. The antibody or antigen binding fragment for use of claim 12, wherein said treatment further comprises an opsonizing agent.
14. The antibody or antigen binding fragment for use of claim 13, wherein said opsonizing agent is an EGFR inhibitor, optionally wherein said EGFR inhibitor is cetuximab.

15. The antibody or antigen binding fragment for use of any one of claims 9 to 14, wherein said treatment further comprises an anti-PD-L1 and/or anti-PD-1 based therapy.
16. The antibody or antigen binding fragment for use of any one of claims 9 to 15, wherein expression of ILT2 or soluble HLA-G in a sample from said subject has been confirmed to be greater than expression of said molecule in a sample from a healthy control subject.
17. The antibody or antigen binding fragment for use of claim 16, wherein said confirmation comprises measuring expression of ILT2 or soluble HLA-G in a sample from said subject before said treatment.
18. The antibody or antigen binding fragment for use of claim 16 or 17, wherein said confirmation comprises measuring expression of ILT2 in an immune cell of said subject.
19. The antibody or antigen binding fragment for use of claim 18, wherein said immune cell is a peripheral blood immune cell or an intratumor immune cell.
20. The antibody or antigen binding fragment for use of claim 18 or 19, 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.
21. The antibody or antigen binding fragment for use of claim 16 or 17, wherein said confirmation comprises measuring expression of soluble HLA-G.
22. The antibody or antigen binding fragment of any one of claims 1 to 11, for use in increasing the efficacy of an anti-PD-L1 and/or anti-PD-1 based therapy against a cancer expressing HLA-G, MHC-I, or both.

23. The antibody or antigen binding fragment for use of any one of claims 15 to 21, wherein said anti-PD-L1 and/or anti-PD-1 based therapy is an anti-PD-1 blocking antibody.
24. The antibody or antigen binding fragment for use of any one of claims 11 to 23, wherein said cancer is refractory to anti-PD-L1 and/or anti-PD-1 based therapy.
25. A pharmaceutical composition comprising the antibody or antigen binding fragment of any one of claims 1 to 11.
26. Nucleic acid molecule(s) encoding the antibody or antigen binding fragment of any one of claims 1 to 11.
27. The nucleic acid molecule(s) of claim 24, wherein said nucleic acid molecule(s) are expression vector(s).