

examples, the epitope is determined by hydrogen deuterium exchange mass spectrometry (HDX-MS) analysis.

The present disclosure further provides an antibody or antigen binding fragment that binds human ILT3 comprising a heavy chain (HC) wherein the heavy chain variable domain (V_H) comprises a heavy chain complementarity determining region (HC-CDR) 3 having an amino acid sequence selected from the group consisting of SEQ ID NO: 22, 49, 57, 65, 73, 81, 89, 97, and 105, or having an amino acid sequence that has 3, 2, or 1 differences with an amino acid sequence selected from the group consisting of SEQ ID NO: 22, 49, 57, 65, 73, 81, 89, 97, and 105. In some examples the amino acid sequence differences are conservative changes/substitutions. In particular examples, the antibody or antigen binding fragment that binds human ILT3 comprises a heavy chain (HC) wherein the heavy chain variable domain (V_H) comprises a heavy chain complementarity determining region (HC-CDR) 3 having an amino acid sequence selected from the group consisting of SEQ ID NO: 23, 49, 57, 65, 73, 81, 89, 97, and 105, or having an amino acid sequence that has 3, 2, or 1 differences with an amino acid sequence selected from the group consisting of SEQ ID NO: 23, 49, 57, 65, 73, 81, 89, 97, and 105. In particular examples the amino acid sequence differences are conservative changes/substitutions.

In a further example, the antibody or antigen binding fragment binds to an epitope on the human ILT3 or competes with an antibody disclosed for binding to an epitope on the human ILT3, wherein the epitope comprises at least one amino acid from one or more of the amino acid sequences set forth in the group consisting of SEQ ID NO: 3, 4, 5, 6, 7, and 8. In further examples, the antibody or antigen binding fragment binds to an epitope on the human ILT3 or competes with an antibody disclosed for binding to an epitope on the human ILT3, wherein the epitope comprises one or more of the amino acid sequences set forth in SEQ ID NOs: 3, 4, 5, 6, 7, and 8. In further examples, the antibody or antigen binding fragment binds to an epitope on the human ILT3 or competes with an antibody disclosed for binding to an epitope on the human ILT3, wherein the epitope comprises the amino acid sequences set forth in SEQ ID NOs: 3, 4, 5, 6, 7, and 8. In particular examples, the epitope is determined by hydrogen deuterium exchange mass spectrometry (HDX-MS) analysis.

The present disclosure provides an antibody or antigen binding fragment that binds to human immunoglobulin-like transcript 3 (ILT3) comprising (a) an HC having a variable domain (V_H) comprising a variable domain complementarity determining region (HC-CDR) 1 having the amino acid sequence set forth in SEQ ID NO: 17, 47, 55, 63, 71, 79, 87, 95, or 103; an HC-CDR2 having the

amino acid sequence set forth in SEQ ID NO: 18, 48, 56, 64, 72, 80, 88, 96, or 104; and an HC-CDR3 having the amino acid sequence set forth in SEQ ID NO: 23, 49, 57, 65, 73, 81, 89, 97, or 105; and, variants thereof wherein one or more of the HC-CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations thereof; and (b) a light chain (LC) having variable domain (V_L) comprising a variable domain complementarity determining region (LC-CDR) 1 having the amino acid sequence set forth in SEQ ID NO: 27, 50, 58, 66, 74, 82, 90, 98, or 106; an LC-CDR2 having the amino acid sequence set forth in SEQ ID NO: 43, 51, 59, 67, 75, 83, 91, 99, or 107; and an LC-CDR3 having the amino acid sequence set forth in SEQ ID NO: 44, 60, 68, 76, 84, 92, 100, or 108; and, variants thereof wherein one or more of the LC-CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations thereof. The present disclosure, in one aspect, provides an antibody or antigen binding fragment that binds to human immunoglobulin-like transcript 3 (ILT3), comprising: (a) heavy chain complementarity determining region 1 (HC-CDR1) having the amino acid sequence set forth in SEQ ID NO: 17; an HC-CDR2 having the amino acid sequence set forth in SEQ ID NO: 19, 20 or 21; and an HC-CDR3 having the amino acid sequence set forth in SEQ ID NO: 23; and (b) a light chain complementarity determining region 1 (LC-CDR1) having the amino acid sequence set forth in SEQ ID NO: 34, 35, 36, 37, 38, 39, 40, 41, or 42; an LC-CDR2 having the amino acid sequence set forth in SEQ ID NO: 43; and an LC-CDR3 having the amino acid sequence set forth in SEQ ID NO: 44. In particular examples the amino acid sequence differences are conservative changes/substitutions.

In a further examples of the antibody or antigen binding fragment, HC-CDR1 has the amino acid sequence set forth in SEQ ID NO:17; HC-CDR2 has the amino acid sequence set forth in SEQ ID NO: 19, 20, or 21; HC-CDR3 has the amino acid sequence set forth in SEQ ID NO: 23; and LC-CDR1 has the amino acid sequence set forth in SEQ ID NO: 34, 35, 36, 37, 38, 39, 40, 41, or 42; LC-CDR2 has the amino acid sequence set forth in SEQ ID NO: 43; and, LC-CDR3 has the amino acid sequence set forth in SEQ ID NO:44; and, variants thereof wherein one or more of the HC-CDRs and LC-CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations thereof. In particular examples the amino acid sequence differences are conservative changes/substitutions.

In a further example of the antibody or antigen binding fragment, HC-CDR1 has the amino acid sequence set forth in SEQ ID NO: 17; HC-CDR2 has the amino acid sequence set forth in SEQ ID NO: 20; and HC-CDR3 has the amino acid sequence set forth in SEQ ID NO: 23; and LC-CDR1 having the amino acid sequence set forth in SEQ ID NO: 41; LC-CDR2

having the amino acid sequence set forth in SEQ ID NO: 43; and, LC-CDR3 having the amino acid sequence set forth in SEQ ID NO: 44; and, variants thereof wherein one or more of the HC-CDRs and LC-CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations thereof. In particular examples the amino acid sequence differences are

5 conservative changes/substitutions.

In a further example of the antibody or antigen binding fragment, the antibody or antigen binding fragment comprises (a) a V_H having a framework selected from the group consisting of human V_H1, V_H2, V_H3, V_H4, V_H5, and V_H6 family and variants thereof having

glycine-lysine dipeptide. In particular examples, the HC comprises the amino acid sequence set forth in SEQ ID NO: 143 or 177. In particular examples, the HC set forth in SEQ ID NO: 177 further lacks a C-terminal glycine.

In a further example of the antibody, the antibody comprises an LC comprising the amino acid sequence set forth in SEQ ID NO: 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, or 166. In particular examples, the LC comprises the amino acid set forth in SEQ ID NO: 165.

In a further example of the antibody, the antibody comprises an HC having the amino acid sequence set forth in SEQ ID NO:143 and an LC comprising the amino acid sequence set forth in SEQ ID NO:165. In particular examples, the HC comprising the amino acid sequence set forth in SEQ ID NO: 143 lacks a C-terminal lysine or a C-terminal glycine-lysine dipeptide.

The present disclosure provides a chimeric, humanized, or recombinant human antibody or antigen binding fragment that binds to an epitope on a human immunoglobulin-like transcript 3 (ILT3), wherein the epitope comprises at least one amino acid from one or more of the amino acid sequences set forth in the group consisting of SEQ ID NOs:3, 4, 5, 6, 7, and 8. In a further example, the chimeric, humanized, or recombinant human antibody or antigen binding fragment binds to an epitope on a human ILT3 comprising the amino acid sequences set forth in SEQ ID NOs: 3, 4, 5, 6, 7, and 8. In these examples, the epitope is determined by hydrogen deuterium exchange mass spectrometry (HDX-MS) analysis.

The present disclosure further provides a chimeric, humanized, or recombinant human antibody or antigen binding fragment that binds ILT3 wherein the binding cross-blocks or competes with the binding of an antibody comprising a heavy chain having the amino acid sequence set forth in SEQ ID NO: 15 and a light chain having the amino acid sequence shown in SEQ ID NO: 16. In a further example, the chimeric, humanized, or recombinant human antibody or antigen binding fragment that cross-blocks or competes with an antibody comprising a heavy chain having the amino acid sequence set forth in SEQ ID NO: 15 and a light chain having the amino acid sequence shown in SEQ ID NO: 16 binds an epitope on ILT3 that comprises the amino acid sequences set forth in SEQ ID NOS: 3, 4, 5, 6, 7, and 8.

The present disclosure, in another aspect, provides a composition comprising one or more of any one of the antibody or antigen binding fragment disclosed or claimed herein and a pharmaceutically acceptable carrier.

The present disclosure further provides an antibody or antigen binding fragment disclosed or claimed herein for treatment of a cancer in a subject wherein the treatment further comprises one or more inhibitors or antagonists of PD-1, PD-L1 and/or PD-L2. The present disclosure, in another aspect, provides the antibody or antigen binding fragment disclosed or claimed herein in combination with one or more inhibitors or antagonists of PD-1, PD-L1 and/or PD-L2 for use in combination therapy of cancer.

In one example, the antagonist of PD-1 is an antibody or antigen binding fragment thereof that binds to human PD-1 and blocks the binding of PD1 to PD-L1 and PD-L2.

In one example, the antagonist of PD-L1 or PD-L2 is an antibody or antigen binding fragment thereof that binds to human PD-L1 or PD-L2 and blocks the binding of human PD-L1 or PD-L2 PD1.

In a further example, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or pidilizumab and the PD-L1 inhibitor is durvalumab, atezolizumab, avelumab, YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105.

The present disclosure further provides for use of an antibody or antigen binding fragment disclosed or claimed herein for the treatment of a cancer.

The present disclosure further provides for use of an antibody or antigen binding fragment disclosed or claimed herein for the manufacture of a medicament for the treatment of a cancer. The present disclosure, in another aspect, provides use of an antibody or antigen binding fragment disclosed or claimed herein in the manufacture of a medicament for treatment of a cancer.

In a further example, the cancer is pancreatic cancer, melanomas, breast cancer, lung cancer, head and neck cancer, bronchus cancer, colorectal cancer, prostate cancer, pancreatic cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

WHAT IS CLAIMED:

1. An antibody or antigen binding fragment that binds to human immunoglobulin-like transcript 3 (ILT3), comprising:

(a) a heavy chain complementarity determining region 1 (HC-CDR1) having the amino acid sequence set forth in SEQ ID NO: 17; an HC-CDR2 having the amino acid sequence set forth in SEQ ID NO: 19, 20 or 21; and an HC-CDR3 having the amino acid sequence set forth in SEQ ID NO: 23; and

(b) a light chain complementarity determining region 1(LC-CDR1) having the amino acid sequence set forth in SEQ ID NO: 34, 35, 36, 37, 38, 39, 40, 41, or 42; an LC-CDR2 having the amino acid sequence set forth in SEQ ID NO: 43; and an LC-CDR3 having the amino acid sequence set forth in SEQ ID NO: 44.

2. The antibody or antigen binding fragment of claim 1, wherein

(a) the HC-CDR1 has the amino acid sequence set forth in SEQ ID NO: 17; the HC-CDR2 has the amino acid sequence set forth in SEQ ID NO:20; and the HC-CDR3 has the amino acid sequence set forth in SEQ ID NO: 23; and

(b) the LC-CDR1 has the amino acid sequence set forth in SEQ ID NO: 41; the LC-CDR2 has the amino acid sequence set forth in SEQ ID NO:43; and, the LC-CDR3 has the amino acid sequence set forth in SEQ ID NO: 44.

3. The antibody or antigen binding fragment of claim 1 or 2, wherein the V_H comprises a framework selected from the group consisting of human V_H1 , V_H2 , V_H3 , V_H4 , V_H5 , and V_H6 , and variants thereof having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof; and, the V_L comprises a framework selected from the group consisting of human V_K1 , V_K2 , V_K3 , V_K4 , V_K5 , V_K6 , $V_\lambda1$, $V_\lambda2$, $V_\lambda3$, $V_\lambda4$, $V_\lambda5$, $V_\lambda6$, $V_\lambda7$, $V_\lambda8$, $V_\lambda9$, and $V_\lambda10$, and variants thereof having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

4. The antibody or antigen binding fragment of claim 1 or 2, wherein the antibody comprises an HC having a human IgG1, IgG2, IgG3, or IgG4 HC constant domain or variant thereof having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions,

or combinations thereof compared to the amino acid sequence of the native IgG1, IgG2, IgG3, or IgG4 isotype constant domain.

5 5. The antibody or antigen binding fragment of claim 3 or 4, wherein the antibody comprises an LC having a human kappa or lambda LC constant domain or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof compared to the amino acid sequence of the native human kappa or lambda light chain constant domain.

10 6. The antibody or antigen binding fragment of claim 2, wherein the antibody comprises:

 (i) a V_H having a framework selected from human V_H1 , V_H2 , V_H3 , V_H4 , V_H5 , and V_H6 and a human IgG1 or IgG4 HC constant domain or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof compared to the amino acid sequence of the native IgG1 or IgG4 isotype HC constant domain; and,

 (ii) a V_L having a framework selected from human V_K1 , V_K2 , V_K3 , V_K4 , V_K5 , V_K6 , $V_\lambda1$, $V_\lambda2$, $V_\lambda3$, $V_\lambda4$, $V_\lambda5$, $V_\lambda6$, $V_\lambda7$, $V_\lambda8$, $V_\lambda9$, and $V_\lambda10$ and a human kappa or lambda LC constant domain or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof compared to the amino acid sequence of the native human kappa or lambda LC constant domain.

 7. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment comprises a V_H and a V_L having the amino acid sequences set forth in SEQ ID NO: 15 and SEQ ID NO: 16, respectively.

 8. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment comprises a V_H having the amino acid sequence set forth in SEQ ID NO: 117, 118, 119, 123, 124, or 125 and a V_L having the amino acid sequence set forth in SEQ ID NO: 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, or 141.

9. The antibody or antigen binding fragment of claim 8, wherein the antibody or antigen binding fragment comprises a V_H having the amino acid sequence set forth in SEQ ID NO: 118 and a V_L having the amino acid sequence set forth in SEQ ID NO: 140.

5 10. The antibody or antigen binding fragment of claim 8, wherein the antibody comprises a heavy chain (HC) comprising the amino acid sequence set forth in SEQ ID NO: 143 and a light chain (LC) comprising the amino acid sequence set forth in SEQ ID NO: 165, and variants thereof wherein the HC lacks a C-terminal Lysine residue or a C-terminal glycine-lysine.

10 11. A composition comprising:
an antibody or antigen binding fragment of any one of claims 1-10 and a pharmaceutically acceptable carrier.

15 12. An antibody or antigen binding fragment of any one of claims 1-10 for use in the treatment of a cancer in a subject.

20 13. The antibody or antigen binding fragment of claim 12 in combination with one or more inhibitors or antagonists of PD-1, PD-L1 and/or PD-L2 for use in combination therapy of cancer.

25 14. The antibody or antigen binding fragment for use of claim 13, wherein the one or more inhibitors or antagonists of PD-1, PD-L1 and/or PD-L2 is an anti-PD-1 antibody selected from the group consisting of pembrolizumab, nivolumab, cemiplimab, and pidilizumab.

30 15. The antibody or antigen binding fragment for use of claim 14, wherein the one or more inhibitors or antagonists of PD-1, PD-L1 and/or PD-L2 is a PD-L1 inhibitor selected from the group consisting of durvalumab, atezolizumab, avelumab, YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, and MDX-1105.

16. The antibody or antigen binding fragment for use of claim 12 or 13, wherein the cancer is pancreatic cancer, melanomas, breast cancer, lung cancer, head and neck cancer, bronchus cancer, colorectal cancer, prostate cancer, pancreatic cancer, stomach cancer,

ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

17. Use of an antibody or antigen binding fragment of any one of claims 1-10 in the manufacture of a medicament for treatment of a cancer.

18. The use of an antibody or antigen binding fragment of any one of claims 1-10 in the manufacture of a medicament for treatment of a cancer, wherein the cancer is pancreatic cancer, melanomas, breast cancer, lung cancer, head and neck cancer, bronchus cancer, colorectal cancer, prostate cancer, pancreatic cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

19. A nucleic acid molecule encoding an anti-ILT3 antibody or antigen binding fragment of any one of claims 1-10.

20. A vector comprising the nucleic acid molecule of claim 19.

21. A host cell comprising the vector of claim 20.

22. A method for producing an antibody or antigen binding fragment of any one of claims 1-10 comprising:

- (a) providing a host cell comprising the vector of claim 20;
- (b) culturing the host cell in culture medium under conditions to enable expression of the antibody or antigen binding fragment encoded by the vector; and,
- (c) obtaining the antibody or antigen binding fragment from the culture medium to provide the antibody or antigen binding fragment.