

[0006] It is clear that there continues to be a need for diagnostic, prognostic, and predictive methods to identify patients that are more likely to benefit from anti-tumor treatments that modulate OX40 activity. The invention described herein meets these needs and provides other benefits.

[0007] All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

BRIEF SUMMARY

[0008] The present disclosure describes methods and biomarkers for predicting efficacy and evaluation of an OX40 agonist treatment, including methods for predicting responsiveness, monitoring pharmacodynamic activity or responsiveness, and methods of treating or delaying progression of cancer.

[0009] The present disclosure provides a method for predicting responsiveness of a subject having cancer to an OX40 agonist treatment, comprising: (a) measuring the expression level of one or more marker genes in a sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CD8a, CD8b, H2-d, CTLA4, CD64, CXCL9, IFN γ , IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R; and (b) classifying the subject as a responsive or non-responsive subject based on the expression level of said one or more marker genes in the sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates the subject may be responsive to an OX40 agonist treatment.

[0009a] In certain aspects, there is provided a method for predicting responsiveness of a subject having cancer to an anti-OX40 agonist antibody treatment, comprising:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CD8a, CD8b, HLA-B, CTLA4, CD64, CXCL9, IFN γ , IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R; and

(b) classifying the subject as a responsive or non-responsive subject based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates the subject may be responsive to an anti-OX40 agonist antibody treatment.

[0010] The present disclosure also provides a method for treating or delaying progression of cancer in a subject, comprising: (a) measuring the expression level of one or more marker genes in a sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CD8a, CD8b, H2-d, CTLA4, CD64, CXCL9, IFN γ , IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R; and (b) if the expression level of said one or more marker genes in the sample obtained from the subject is higher than a reference, administering to the subject an effective amount of an OX40 agonist.

[0010a] In certain aspects, the present disclosure provides a use of an anti-OX40 agonist antibody in the manufacture of a medicament for a method for treating or delaying progression of cancer in a subject, wherein said method comprises:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CD8a, CD8b, HLA-B, CTLA4, CD64, CXCL9, IFNg, IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R; and

(b) wherein the anti-OX40 agonist antibody is to be administered to the subject if the expression level of said one or more marker genes in the tumor sample obtained from the subject is higher than a reference.

[0011] The present disclosure also provides a method for treating or delaying progression of cancer in a subject, comprising administering to the subject an effective amount of an OX40 agonist, wherein a sample comprising leukocytes obtained from the subject has increased expression of one or more marker genes are selected from the group consisting of CD8a, CD8b, H2-d, CTLA4, CD64, CXCL9, IFNg, IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R, as compared with a reference.

[0011a] In certain aspects, the present disclosure provides a use of an anti-OX40 agonist antibody in the manufacture of a medicament for treating or delaying progression of cancer in a subject, wherein the anti-OX40 agonist antibody is to be administered to the subject, and wherein a tumor sample comprising leukocytes obtained from the subject has been detected to possess increased expression of one or more marker genes are selected from the group consisting of CD8a, CD8b, HLA-B, CTLA4, CD64, CXCL9, IFNg, IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R, as compared with a reference.

[0012] In some embodiments, said one or more marker genes are selected from the group consisting of CD8a, CD8b, IFNg, GZMA, GZMB, PRF1, and PDCA1. In some embodiments, said one or more marker genes are selected from the group consisting of H2-d, CTLA4, CXCL9, PTPRC, IL7R, KLRK1, and CXCL1. In some embodiments, said one or more marker genes are selected from the group consisting of CD64, IDO1, and ITGAM.

[0013] The present disclosure also provides a method for predicting responsiveness of a subject having cancer to an OX40 agonist treatment, comprising: (a) measuring the expression level of one or more marker genes in a sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1; and (b)

classifying the subject as a responsive or non-responsive subject based on the expression level of said one or more marker genes in the sample obtained from the subject, as compared with a reference, wherein a decreased expression level of the one or more marker genes as compared with the reference indicates the subject may be responsive to an OX40 agonist treatment.

[0013a] In certain aspects, the present disclosure provides a method for predicting responsiveness of a subject having cancer to an anti-OX40 agonist antibody treatment, comprising:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1; and

(b) classifying the subject as a responsive or non-responsive subject based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein a decreased expression level of the one or more marker genes as compared with the reference indicates the subject may be responsive to an anti-OX40 agonist antibody treatment.

[0014] The present disclosure also provides a method for treating or delaying progression of cancer in a subject, comprising: (a) measuring the expression level of one or more marker genes in a sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1; and (b) if the expression level of said one or more marker genes in the sample obtained from the subject is lower than a reference, administering to the subject an effective amount of an OX40 agonist.

[0014a] In certain aspects, the present disclosure provides a use of an anti-OX40 agonist antibody in the manufacture of a medicament for a method for treating or delaying progression of cancer in a subject, wherein said method comprises:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1; and

(b) wherein the anti-OX40 agonist antibody is to be administered to the subject if the expression level of said one or more marker genes in the tumor sample obtained from the subject is lower than a reference.

[0015] The present disclosure also provides a method for treating or delaying progression of cancer in a subject, comprising administering to the subject an effective amount of an OX40 agonist, wherein a sample comprising leukocytes obtained from the subject has decreased expression of one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1, as compared with a reference.

[0015a] In certain aspects, the present disclosure provides a use of an anti-OX40 agonist antibody in the manufacture of a medicament for treating or delaying progression of cancer in a subject, wherein the anti-OX40 agonist antibody is to be administered to the subject, and wherein a tumor sample comprising leukocytes obtained from the subject has been detected to possess decreased expression of one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1, as compared with a reference.

[0016] The present disclosure also provides a method for monitoring pharmacodynamic activity of an OX40 agonist treatment, comprising: (a) measuring the expression level of one or more marker genes in a sample comprising leukocytes obtained from the subject, wherein the subject has been treated with an OX40 agonist, and wherein said one or more marker genes are selected from the group consisting of ARG1, CCL2, CCL22, CCL5, CCR5, CD226, CD27, CD274, CD28, CD3E, CD40, CD8A, CD8b, CXCL10, CXCL9, EOMES, FasL, Fcgr1/CD64, FOXP3, GZMA, GZMB, HAVCR2, ICAM1, IDO1, IFNg, IL10, IL12A (TDO2), IL13, IL2, IL7R, ITGAM, KLRK1, LAG3, MAP4K1, MS4A1, PDCD1, PDCD1LG2, PRF1, PTPRC, TNF, TNFRSF14, TNFRSF9, and TNFSF4; and (b) determining the treatment as demonstrating pharmacodynamic activity based on the expression level of said one or more marker genes in the sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates pharmacodynamic activity to the OX40 agonist treatment. In some embodiments, said one or more marker genes are selected from the group consisting of CD3, CD8, IFNg, GZMA, GZMB, PRF1, TNFa, PDCD1, and CD274.

[0016a] In certain aspects, the present disclosure provides a method for monitoring pharmacodynamic activity of an anti-OX40 agonist antibody treatment, comprising:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein the subject has been treated with an anti-OX40 agonist antibody, wherein the subject has cancer, and wherein said one or more marker genes are selected from the group consisting of ARG1, CCL2, CCL22, CCL5, CCR5, CD226, CD27, CD274, CD28, CD3E, CD40, CD8A, CD8b, CXCL10, CXCL9, EOMES, FasL, Fcgr1/CD64, FOXP3, GZMA, GZMB, HAVCR2, ICAM1, IDO1, IFNg, IL10, IL12A (TDO2), IL13, IL2, IL7R, ITGAM, KLRK1, LAG3, MAP4K1, MS4A1, PDCD1,

PDCD1LG2, PRF1, PTPRC, TNF, TNFRSF14, TNFRSF9, and TNFSF4; and

(b) determining the treatment as demonstrating pharmacodynamic activity based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates pharmacodynamic activity to the anti-OX40 agonist antibody treatment.

[0017] The present disclosure also provides a method for monitoring responsiveness of a subject to an OX40 agonist treatment, comprising: (a) measuring the expression level of one or more marker genes in a sample comprising leukocytes obtained from the subject, wherein the subject has been treated with an OX40 agonist, and wherein said one or more marker genes are selected from the group consisting of BTLA, CD4, CD69, CD80, CD83, CD86, CSF2, CTLA4, CXCR3, Fcgr2b/CD32, Fcgr3/CD16, H2-aa, H2-d, H2-k, ICOS, IL10, PDCA1, and TNFRSF18; and (b) classifying the subject as responsive or non-responsive to said treatment based on the expression level of said one or more marker genes in the sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates a responsive subject. In some embodiments, said one or more marker genes are selected from

the group consisting of CD80, CD86, ICOS, H2-aa, and CXCR3. In some embodiments, responsiveness comprises immune activation and/or treatment efficacy.

[0017a] In certain aspects, the present disclosure provides a method for monitoring responsiveness of a subject to an anti-OX40 agonist antibody treatment, comprising:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein the subject has been treated with an anti-OX40 agonist antibody, wherein the subject has cancer, and wherein said one or more marker genes are selected from the group consisting of BTLA, CD4, CD69, CD80, CD83, CD86, CSF2, CTLA4, CXCR3, Fcgr2b/CD32, Fcgr3/CD16, HLA-DQA1, HLA-B, HLA-A, ICOS, IL10, PDCA1, and TNFRSF18; and

(b) classifying the subject as responsive or non-responsive to said treatment based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates a responsive subject. In some embodiments, said one or more marker genes are selected from the group consisting of CD80, CD86, ICOS, H2-aa, and CXCR3. In some embodiments, responsiveness comprises immune activation and/or treatment efficacy.

[0018] In some embodiments, the sample comprising leukocytes is from a tumor sample obtained from the subject. In some embodiments, the sample comprising leukocytes is from a peripheral blood sample obtained from the subject. In some embodiments, the expression level of said one or more marker genes is normalized to the expression level of a reference gene in the sample. In some embodiments, the reference gene is a housekeeping gene. In

CLAIMS

What is claimed is:

1. A method for predicting responsiveness of a subject having cancer to an anti-OX40 agonist antibody treatment, comprising:
 - (a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CD8a, CD8b, HLA-B, CTLA4, CD64, CXCL9, IFNg, IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R; and
 - (b) classifying the subject as a responsive or non-responsive subject based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates the subject may be responsive to an anti-OX40 agonist antibody treatment.
2. Use of an anti-OX40 agonist antibody in the manufacture of a medicament for a method for treating or delaying progression of cancer in a subject, wherein said method comprises:
 - (a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CD8a, CD8b, HLA-B, CTLA4, CD64, CXCL9, IFNg, IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R; and
 - (b) wherein the anti-OX40 agonist antibody is to be administered to the subject if the expression level of said one or more marker genes in the tumor sample obtained from the subject is higher than a reference.
3. Use of an anti-OX40 agonist antibody in the manufacture of a medicament for treating or delaying progression of cancer in a subject, wherein the anti-OX40 agonist antibody is to be administered to the subject, and wherein a tumor sample comprising leukocytes obtained from the subject has been detected to possess increased expression of one or more marker genes are selected from the group consisting of CD8a, CD8b, HLA-B, CTLA4, CD64, CXCL9, IFNg, IDO1, GZMA, GZMB, PRF1, PDCA1, KLRK1, PTPRC, CXCL1, ITGAM, and IL7R, as compared with a reference.
4. The method or use of any one of claims 1-3, wherein said one or more marker genes are selected from the group consisting of CD8a, CD8b, IFNg, GZMA, GZMB, PRF1, and PDCA1.

5. The method or use of any one of claims 1-3, wherein said one or more marker genes are selected from the group consisting of HLA-B, CTLA4, CXCL9, PTPRC, IL7R, KLRK1, and CXCL1.
6. The method or use of any one of claims 1-3, wherein said one or more marker genes are selected from the group consisting of CD64, IDO1, and ITGAM.
7. A method for predicting responsiveness of a subject having cancer to an anti-OX40 agonist antibody treatment, comprising:
 - (a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1; and
 - (b) classifying the subject as a responsive or non-responsive subject based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein a decreased expression level of the one or more marker genes as compared with the reference indicates the subject may be responsive to an anti-OX40 agonist antibody treatment.
8. Use of an anti-OX40 agonist antibody in the manufacture of a medicament for a method for treating or delaying progression of cancer in a subject, wherein said method comprises:
 - (a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein said one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1; and
 - (b) wherein the anti-OX40 agonist antibody is to be administered to the subject if the expression level of said one or more marker genes in the tumor sample obtained from the subject is lower than a reference.
9. Use of an anti-OX40 agonist antibody in the manufacture of a medicament for treating or delaying progression of cancer in a subject, wherein the anti-OX40 agonist antibody is to be administered to the subject, and wherein a tumor sample comprising leukocytes obtained from the subject has been detected to possess decreased expression of one or more marker genes are selected from the group consisting of CSF2, CCL22, EPCAM, GATA3, IL13, and VTCN1, as compared with a reference.
10. A method for monitoring pharmacodynamic activity of an anti-OX40 agonist antibody treatment, comprising:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein the subject has been treated with an anti-OX40 agonist antibody, wherein the subject has cancer, and wherein said one or more marker genes are selected from the group consisting of ARG1, CCL2, CCL22, CCL5, CCR5, CD226, CD27, CD274, CD28, CD3E, CD40, CD8A, CD8b, CXCL10, CXCL9, EOMES, FasL, Fcgr1/CD64, FOXP3, GZMA, GZMB, HAVCR2, ICAM1, IDO1, IFNg, IL10, IL12A (TDO2), IL13, IL2, IL7R, ITGAM, KLRK1, LAG3, MAP4K1, MS4A1, PDCD1, PDCD1LG2, PRF1, PTPRC, TNF, TNFRSF14, TNFRSF9, and TNFSF4; and

(b) determining the treatment as demonstrating pharmacodynamic activity based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates pharmacodynamic activity to the anti-OX40 agonist antibody treatment.

11. The method of claim 10, wherein said one or more marker genes are selected from the group consisting of CD3, CD8, IFNg, GZMA, GZMB, PRF1, TNFa, PDCD1, and CD274.

12. A method for monitoring responsiveness of a subject to an anti-OX40 agonist antibody treatment, comprising:

(a) measuring the expression level of one or more marker genes in a tumor sample comprising leukocytes obtained from the subject, wherein the subject has been treated with an anti-OX40 agonist antibody, wherein the subject has cancer, and wherein said one or more marker genes are selected from the group consisting of BTLA, CD4, CD69, CD80, CD83, CD86, CSF2, CTLA4, CXCR3, Fcgr2b/CD32, Fcgr3/CD16, HLA-DQA1, HLA-B, HLA-A, ICOS, IL10, PDCA1, and TNFRSF18; and

(b) classifying the subject as responsive or non-responsive to said treatment based on the expression level of said one or more marker genes in the tumor sample obtained from the subject, as compared with a reference, wherein an increased expression level of the one or more marker genes as compared with the reference indicates a responsive subject.

13. The method of claim 12, wherein said one or more marker genes are selected from the group consisting of CD80, CD86, ICOS, HLA-DQA1, and CXCR3.

14. The method of claim 12 or claim 13, wherein responsiveness comprises immune activation and/or treatment efficacy.

15. The method or use of any one of claims 1-14, wherein the expression level of said one or more marker genes is normalized to the expression level of a reference gene in the sample.
16. The method or use of claim 15, wherein the reference gene is a housekeeping gene.
17. The method or use of any one of claims 1-16, wherein the expression level of said one or more marker genes is mRNA expression level.
18. The method or use of claim 17, wherein the mRNA expression level is measured by an assay selected from the group consisting of quantitative PCR, semi-quantitative PCR, nucleotide microarray, RNA-seq, in situ hybridization, and Northern blotting.
19. The method or use of any one of claims 1-16, wherein the expression level of said one or more marker genes is protein expression level.
20. The method or use of claim 19, wherein the protein expression level is measured by Western blotting, peptide microarray, immunohistochemistry, flow cytometry, or mass spectrometry.
21. The method or use of any one of claims 1-20, wherein the cancer is selected from the group consisting of colorectal cancer, non-small cell lung cancer, renal cell carcinoma, bladder cancer, ovarian cancer, glioblastoma, neuroblastoma, melanoma, breast carcinoma, gastric cancer, and hepatocellular carcinoma.
22. The method or use of claim 21, wherein the breast carcinoma is triple-negative breast carcinoma.
23. The method or use of any one of claims 1-22, wherein the antibody is a monoclonal antibody.
24. The method or use of any one of claims 1-22, wherein the antibody is a humanized or human antibody.
25. The method or use of any one of claims 1-22, wherein the antibody comprises an IgG1 Fc region.
26. The method or use of any one of claims 1-22, wherein the antibody comprises an IgG4 Fc region.
27. The method or use of any one of claims 1-22, wherein the antibody comprises an Fc region comprising a mutation that decreases binding to an Fc receptor.
28. The method or use of any one of claims 1-22, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, 8 or 9; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, 10, 11, 12, 13, or 14; (c) HVR-H3 comprising the amino acid

sequence of SEQ ID NO:4, 15 or 19; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:7, 22, 23, 24, 25, 26, 27 or 28.

29. The method or use of any one of claims 1-22, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:7.

30. The method or use of any one of claims 1-22, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:26.

31. The method or use of any one of claims 1-22, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:27.

32. The method or use of any one of claims 1-22, wherein the antibody is MEDI6469 or MEDI0562.