

European Union to treat diseases such as unresectable or metastatic melanoma and metastatic non-small cell lung cancer. Treatment of patients with these agents has resulted in anti-tumor responses as measured by improvement in either progression free survival and/or overall survival.

[0008] The recent failure of OPDIVO® to slow progression of advanced lung cancer in a treatment-naïve patient population in a clinical trial comparing OPDIVO® with conventional chemotherapy highlights the need for alternative approaches and additional cancer treatments to complement existing therapeutic standards of care.

5. SUMMARY

[0009] The present disclosure provides anti-OX40 antibodies that specifically bind to and activate OX40. The amino acid sequences of exemplary complementarity determining regions (CDRs), the heavy chain variable domain (V_H) and light chain variable domain (V_L) regions (*i.e.*, the V_H and V_L chains, respectively), and the heavy and light chains of exemplary anti-OX40 antibodies are provided in the Detailed Description below. Anti-OX40 antibodies provided herein result in activation of the adaptive immune response.

[0009a] In one aspect, there is provided an anti-OX40 antibody which comprises (i) a V_H chain comprising three CDRs; and (ii) a V_L chain comprising three CDRs, wherein:

V _H CDR#1 is selected from:	GFTFSRYGMS	(SEQ ID NO:101),
	GYSIASGYWN	(SEQ ID NO:111),
	GFNIKDTYMH	(SEQ ID NO:121),
	GFSLTSYGVH	(SEQ ID NO:131);
V _H CDR#2 is selected from:	TINSNGGRTYYPDSVKG	(SEQ ID NO:102),
	YISYDGSNNYNPSLG	(SEQ ID NO:112),
	RIDPANGNTKYDPKFQG	(SEQ ID NO:122),
	VIWSGGSTDYNAAFIS	(SEQ ID NO:132);
V _H CDR#3 is selected from:	EGITTAYAMDY	(SEQ ID NO:103),
	TLPYYFDY	(SEQ ID NO:113),
	GGPAWVY	(SEQ ID NO:123),
	EEFDY	(SEQ ID NO:133);
V _L CDR#1 is selected from:	KASQSVDYDGD SYMH	(SEQ ID NO:104),
	RASQDISNYLN	(SEQ ID NO:114);
V _L CDR#2 is selected from:	AASILES	(SEQ ID NO:105),
	YTSRLHS	(SEQ ID NO:115),
	YTSRLRS	(SEQ ID NO:125);
V _L CDR#3 is selected from:	QQSNEDPRT	(SEQ ID NO:106),
	QQGNTLPLT	(SEQ ID NO:116),
	QQGNTLPWT	(SEQ ID NO:126),
	QQGYTLPPT	(SEQ ID NO:136).

[0010] The anti-OX40 antibodies may include modifications and/or mutations that alter the properties of the antibodies, such as increase half-life, increase or decrease antigen-dependent cellular cytotoxicity (ADCC), as is known in the art.

[0010a] In another aspect, there is provided a nucleic acid comprising a nucleotide sequence encoding the anti-OX40 antibody disclosed herein. In another aspect, there is provided a vector comprising the nucleic acid disclosed herein. In another aspect, there is provided a prokaryotic host cell transformed with the vector disclosed herein. In another aspect, there is provided a eukaryotic host cell transformed with the vector disclosed herein. In another aspect, there is provided a eukaryotic host cell engineered to express the nucleic acid disclosed herein. In another aspect, there is provided a method of producing an anti-OX40 antibody, comprising: (a) culturing the host cell disclosed herein and (b) recovering the anti-OX40 antibody.

[0011] Nucleic acids comprising nucleotide sequences encoding the anti-OX40 antibodies of the disclosure are provided herein, as are vectors comprising nucleic acids. Additionally, prokaryotic and eukaryotic host cells transformed with a vector comprising a nucleotide sequence encoding a disclosed anti-OX40 antibody are provided herein, as well as eukaryotic (such as mammalian) host cells engineered to express the nucleotide sequences. Methods of producing antibodies, by culturing host cells and recovering the antibodies are also provided, and discussed further in the Detailed Description below.

[0011a] In another aspect, there is provided a pharmaceutical composition comprising the anti-OX40 antibody disclosed herein, and a pharmaceutically acceptable carrier.

[0012] In another example, the present disclosure provides compositions including the anti-OX40 antibodies described herein. The compositions generally comprise one or more anti-OX40 antibodies as described herein, and one or more excipients, carriers or diluents.

[0012a] In another aspect, there is provided use of the anti-OX40 antibody disclosed herein, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for activating the immune system in a patient in need thereof. In another aspect, there is provided use of the anti-OX40 antibody disclosed herein, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0013] The present disclosure provides methods of treating subjects, such as human subjects, diagnosed with a solid tumor with an anti-OX40 antibody. The method generally involves administering to the subject an amount of an anti-OX40 antibody described herein effective to

WHAT IS CLAIMED IS:

1. An anti-OX40 antibody which comprises (i) a V_H chain comprising three CDRs; and (ii) a V_L chain comprising three CDRs, wherein:

V _H CDR#1 is selected from:	GFTFSRYGMS	(SEQ ID NO:101),
	GYSIASGYAWN	(SEQ ID NO:111),
	GFNIKDTYMH	(SEQ ID NO:121),
	GFSLTSGVH	(SEQ ID NO:131);
V _H CDR#2 is selected from:	TINSNGGRTYYPDVK	(SEQ ID NO:102),
	YISYDGSNNYNPSLG	(SEQ ID NO:112),
	RIDPANGNTKYDPKFQG	(SEQ ID NO:122),
	VIWSGGSTDYNAAFIS	(SEQ ID NO:132);
V _H CDR#3 is selected from:	EGITTAYAMDY	(SEQ ID NO:103),
	TLPYFDY	(SEQ ID NO:113),
	GGPAWFVY	(SEQ ID NO:123),
	EEFDY	(SEQ ID NO:133);
V _L CDR#1 is selected from:	KASQSVDDYDGDSYMH	(SEQ ID NO:104),
	RASQDISNYLN	(SEQ ID NO:114);
V _L CDR#2 is selected from:	AASILES	(SEQ ID NO:105),
	YTSRLHS	(SEQ ID NO:115),
	YTSRLRS	(SEQ ID NO:125);
V _L CDR#3 is selected from:	QQSNEDPRT	(SEQ ID NO:106),
	QQGNTLPLT	(SEQ ID NO:116),
	QQGNTLPWT	(SEQ ID NO:126),
	QQGYTLPT	(SEQ ID NO:136).

2. The anti-OX40 antibody of **claim 1**, having a V_H chain comprising three CDRs of SEQ ID NOS: 101, 102, and 103; and a V_L chain comprising three CDRs of SEQ ID NOS: 104, 105, and 106.
3. The anti-OX40 antibody of **claim 1**, which comprises a V_H chain having an amino acid sequence according to:

EVQLVESGGGLVQPGGSLKLSCAASGFTFSRYGMSWVRQTPDKRLELVATINSNGG
RTYYPD SVKGRFTISRDN AKNTLYLQMSSLKSEDTAMYYCAREGITTAYAMDYWG
QGTSVTVSS (SEQ ID NO:21);

NVQLQESGPGLVKPSQSLSLTCSVTGYSIASGYWNWIRQFPGNKLEWMGYISYDGS
NNYNPSLGNRISITRDTSKNQVFLKLNSVTTEDTATYYCVKTLPPYFDYWGQGTTLT
VSS (SEQ ID NO:23);

EVQLQQSGAELVKPGASVKLSCTASGFNIKDTYMHVVKQRPEQGLEWIGRIDPANG
NTKYDPKFQ GKATITADTSSNTAYLQLSSLTSED TDVYYCARGGPAW FVYWGQGT
LVTVSA (SEQ ID NO:25); or

QVQLKQSGPGLVQPSQSL SITCTVSGFSLTSYGVHWVRQSPGKGLEWLGVIWSSGGST
DYNAAFISRLSISKDNSKSQVFFKMNSLQADDTAIYCCAREEFDYWGQGTTLT VSS
(SEQ ID NO:27);

and a V_L chain having an amino acid sequence according to:

DIVLTQSPASLA VSLGQRATISCKASQSV DYGDSYMHWYQQKPGQPPKLLIYAASI
LES GIPARFSGSGSGTDFTLN IHPVEEEDAATYYCQQSNE DPRTFGGGTKLEIK (SEQ
ID NO:31);

DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIFYTSRLHSGV
PSRFSGGGSGTDYSLTISNLEQEDIATYFCQQGNTLPLTFGAGTKLELK (SEQ ID
NO:33);

DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIYYTSRLRSGL
PSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPWTFGGG TKLEIK (SEQ ID
NO:35); or

DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWFQQKPDGTVKLLIYYTSRLHSGV
PSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGYTLPTFGGGTKLEIK (SEQ ID
NO:37).

4. The anti-OX40 antibody of **claim 1, 2, or 3**, which is monoclonal.
5. The anti-OX40 antibody of **claim 1**, which is humanized.

6. The anti-OX40 antibody of **claim 5**, which comprises a V_H chain having an amino acid sequence according to:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMSWVRQAPGKGLELVATINSNGG
RTYYPD SVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCAREGITTAYAMDYWG
QGTTVT VSS (SEQ ID NO:22);

EVQLQESGPGLVKPSDTLSLTCAVSGYSIASGYWNWIRQPPGKGLEWMGYISYDGS
NNYNPSLGNRITISRDTSKNQVSLKLSSVTAVDTAVYYCVKTL PYYFDYWGQGTTVT
VSS (SEQ ID NO:24);

EVQLVQSGAEVKKPGSSVKVSCKASGFNIKDTYMHWVRQAPGQGLEWIGRIDPANG
NTKYDPKFQGRATITADTSTNTAYMELSSLRSED TAVYYCARGGPAWFVYWGQGT
LVT VSS (SEQ ID NO:26); or

EVQLVESGGGLVQPGGSLRLSCAVSGFSLTSYGVHWVRQAPGKGLEWLGVWSGG
TDYNAAFISRLTISKDNSKSTVYLQMNSLRAEDTAVYYCAREEFDYWGQGTTVT VSS
(SEQ ID NO:28);

and a V_L chain having an amino acid sequence according to:

DIVMTQSPDSLAVSLGERATINCKASQSV D YDGDSYMHWYQQKPGQP PKLLIYAASI
LES GVPDRFSGSGSGTDFTLTIS SLQAEDVAVYYCQQSNEDPRTFGGGTKVEIK (SEQ
ID NO:32);

DIQMTQTPSSLSASVGDRV TITCRASQDISNYLNWYQQKPGKAPKLLIFYTSRLHSGV
PSRFSGSGSGTDYTLTIS SLQPEDFATYYCQQGNTLPLTFGGGTKLEIK (SEQ ID
NO:34);

DIQMTQSPSSLSASVGDRV TITCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLRSG
PSRFSGSGSGTDYTLTIS SLQPEDFATYYCQQGNTLPWTFGGGTKVEIK (SEQ ID
NO:36); or

DIQMTQSPSSLSASVGDRV TITCRASQDISNYLNWFQQKPGKAPKLLIYYTSRLHSGV
PSRFSGSGSGTDYTLTIS SLQPEDFATYYCQQGYTLPTFGGGTKVEIK (SEQ ID
NO:38).

7. The anti-OX40 antibody of **claim 5**, which comprises a V_H chain having an amino acid sequence according to SEQ ID NO:22; and a V_L chain having an amino acid sequence according to SEQ ID NO:32.
8. The anti-OX40 antibody of **claim 5**, which comprises a V_H chain having an amino acid sequence according to SEQ ID NO:24; and a V_L chain having an amino acid sequence according to SEQ ID NO:34.
9. The anti-OX40 antibody of **claim 5**, which comprises a V_H chain having an amino acid sequence according to SEQ ID NO:26; and a V_L chain having an amino acid sequence according to SEQ ID NO:36.
10. The anti-OX40 antibody of **claim 5**, which comprises a V_H chain having an amino acid sequence according to SEQ ID NO:28; and a V_L chain having an amino acid sequence according to SEQ ID NO:38.
11. The anti-OX40 antibody of any one of **claims 1 to 10**, which is an IgG.
12. The anti-OX40 antibody of **claim 11**, which is an IgG₁.
13. The anti-OX40 antibody of **claim 11** which comprises a heavy chain having an amino acid sequence according to any one of SEQ ID NOS: 41-48; and a light chain having an amino acid sequence according to any one of SEQ ID NOS: 51-54.
14. The anti-OX40 antibody of **claim 13** which comprises a heavy chain having an amino acid sequence according to SEQ ID NOS: 41 or 42; and a light chain having an amino acid sequence according to SEQ ID NO: 51.
15. The anti-OX40 antibody of **claim 13** which comprises a heavy chain having an amino acid sequence according to SEQ ID NOS: 43 or 44; and a light chain having an amino acid sequence according to SEQ ID NO: 52.
16. The anti-OX40 antibody of **claim 13** which comprises a heavy chain having an amino acid sequence according to SEQ ID NOS: 45 or 46; and a light chain having an amino acid sequence according to SEQ ID NO: 53.

17. The anti-OX40 antibody of **claim 13** which comprises a heavy chain having an amino acid sequence according to SEQ ID NOS: 47 or 48; and a light chain having an amino acid sequence according to SEQ ID NO: 54.
18. The anti-OX40 antibody of any one of **claims 1 to 17** which has a K_D against human OX40 (SEQ ID NO:1) of less than about 100 nM.
19. A pharmaceutical composition comprising the anti-OX40 antibody of any one of **claims 1 to 18**, and a pharmaceutically acceptable carrier.
20. A nucleic acid comprising a nucleotide sequence encoding the anti-OX40 antibody of any one of **claims 1 to 18**.
21. A vector comprising the nucleic acid of **claim 20**.
22. A prokaryotic host cell transformed with the vector of **claim 21**.
23. A eukaryotic host cell transformed with the vector of **claim 21**.
24. A eukaryotic host cell engineered to express the nucleic acid of **claim 20**.
25. The eukaryotic host cell of **claim 23 or 24** which is a mammalian host cell.
26. A method of producing an anti-OX40 antibody, comprising: (a) culturing the host cell of **claim 23 or claim 24** and (b) recovering the anti-OX40 antibody.
27. Use of the anti-OX40 antibody of any one of **claims 1 to 18**, or the pharmaceutical composition according to **claim 18** in the manufacture of a medicament for activating the immune system in a patient in need thereof.
28. Use of the anti-OX40 antibody of any one of **claims 1 to 18**, or the pharmaceutical composition according to **claim 19** in the manufacture of a medicament for treating cancer in a patient in need thereof.

29. The use of **claim 28**, wherein the cancer is selected from bladder cancer, breast cancer, head and neck cancer, gastric cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, skin cancer, and a tumor with evidence of DNA mismatch repair deficiency.
30. The use of **claim 29**, wherein the lung cancer is small cell lung cancer, non-small cell lung cancer, or mesothelioma.
31. The use of **claim 28**, in which the medicament is to be administered as a monotherapy.
32. The use of **claim 28**, in which the medicament is to be administered adjunctive to or with another agent commonly used to treat the cancer.
33. The use of **claim 32**, in which the medicament is to be administered adjunctive to or with an anti-PD-1 antibody.