

small cell lung cancer. Efforts to inhibit immunosuppressive proteins such as CTLA-4 have led to the development and clinical evaluation of anti-CTLA-4 antibodies, such as tremelimumab and ipilimumab (Yervoy®).

[0007] There remains a need for alternative approaches and additional cancer treatments to complement existing therapeutic standards of care.

5. SUMMARY

[0008] Human CD40 (SEQ ID NO:40) is a tumor necrosis factor (TNF) receptor superfamily member (TNF superfamily member 5) expressed on antigen-presenting cells such as B cells, dendritic cells (DC), and monocytes, and nonimmune cells, including certain types of tumor cells. When activated by human CD40 ligand (SEQ ID NO:41), human CD40 activates antigen-presenting cells and induces responses from both innate and adaptive immune systems. Agonistic CD40 agents can be used to induce the immune system to prevent proliferation of and/or kill tumor cells, and thus provide effective therapeutic treatment of solid tumors.

[0009] The present disclosure provides anti-CD40 antibodies and binding fragments thereof that specifically bind to human CD40 (SEQ ID NO:40). The amino acid sequences of exemplary CDRs, as well as the amino acid sequence of the V_H and V_L regions of the heavy and light chains of exemplary anti-CD40 antibodies are provided in the Detailed Description below.

[0009a] In one aspect, the present disclosure provides an anti-CD40 antibody or binding fragment 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 GYSITSNYYWN (SEQ ID NO:8); V_H CDR#2 is YIRYDGSNNYNPSLKN (SEQ ID NO:18); V_H CDR#3 is LDY (SEQ ID NO:35); V_L CDR#1 is RSSQSLENTNGNTFLN (SEQ ID NO:58); V_L CDR#2 is RVSNRFS (SEQ ID NO:68); and V_L CDR#3 is LQVTHVPFT (SEQ ID NO:88).

[0009b] In another aspect, the present disclosure provides a pharmaceutical composition comprising an anti-CD40 antibody or binding fragment as described herein, and a pharmaceutically acceptable carrier.

[0010] The V_H and V_L chains of the anti-CD40 antibodies described herein afford an allosteric agonistic receptor response that can activate human CD40 in the presence or absence of CD40 ligand (CD40L), without competing with the CD40L-CD40 binding interaction. Moreover, the present anti-CD40 antibodies, by interacting with CD40, can enhance CD40L binding to CD40.

[0011] The anti-CD40 antibodies may include modifications and/or mutations that alter the properties of the antibodies, such as increase half-life, increase or decrease ADCC, or increase agonistic activity, as is known in the art.

[0012] Nucleic acids comprising nucleotide sequences encoding the anti-CD40 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-CD40 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.

[0013] In another example, the present disclosure provides compositions including the anti-CD40 antibodies described herein. The compositions generally comprise one or more anti-CD40 antibody as described herein, and/or salts thereof, and one or more excipients, carriers or diluents.

[0014] The present disclosure provides methods of treating subjects, such as human subjects, diagnosed with a solid tumor with an anti-CD40 antibody. The method generally involves administering to the subject an amount of an anti-CD40 antibody described herein effective to provide therapeutic benefit. The subject may be diagnosed with any one of a number of solid tumors that may be newly diagnosed, relapsed, or relapsed and refractory. An anti-CD40 antibody is typically administered as an intravenous infusion or intratumoral injection at doses ranging from about 0.001 mg/kg to about 4 mg/kg. An anti-CD40 antibody is typically administered as an intravenous infusion or intratumoral injection twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

[0015] The anti-CD40 antibodies may be administered as single therapeutic agents (monotherapy) or adjunctive to or with other therapeutic agents typically, but not necessarily, those used for the treatment of a solid tumor. Therapeutic agents typically will be used at their approved dose, route of administration, and frequency of administration, but may be used at lower dosages.

[0016] The anti-CD40 antibodies may be administered via a variety of routes or modes of administration, including but not limited to, intravenous infusion and/or injection, subcutaneous injection, and intratumoral injection. The amount administered will depend upon the route of administration, the dosing schedule, the type of cancer being treated, the stage of the cancer being treated, and other parameters such as the age and weight of the patient, as is well known in the art. Specific exemplary dosing schedules expected to provide therapeutic benefit are provided in the Detailed Description.

[0017] Based on data presented herein, it is expected that the anti-CD40 antibodies described herein will provide therapeutic benefit to subjects diagnosed with a solid tumor.

WHAT IS CLAIMED IS:

1. An anti-CD40 antibody or binding fragment 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 GYSITSNYYWN (SEQ ID NO:8);
V_H CDR#2 is YIRYDGSNNYNPSLKN (SEQ ID NO:18);
V_H CDR#3 is LDY (SEQ ID NO:35);
V_L CDR#1 is RSSQSLENTNGNTFLN (SEQ ID NO:58);
V_L CDR#2 is RVSNRFS (SEQ ID NO:68); and
V_L CDR#3 is LQVTHVPFT (SEQ ID NO:88).
2. The anti-CD40 antibody or binding fragment of **claim 1** which is human or humanized.
3. The anti-CD40 antibody or binding fragment of **claim 1** which comprises a V_H chain corresponding to the sequence of SEQ ID NO:117 and a V_L chain corresponding to the sequence of SEQ ID NO:170.
4. The anti-CD40 antibody or binding fragment of **claim 1**, which is an IgG.
5. The anti-CD40 antibody of **claim 4**, which is an IgG₁ and comprises a variant CH2 region comprising the amino acid substitution V273E or V273Y.
6. The anti-CD40 antibody of **claim 4**, which is an IgG₁ and comprises a variant Fc region comprising the amino acid substitutions D356E and L358M.
7. The anti-CD40 antibody of **claim 4** comprising a kappa light chain constant region.
8. The anti-CD40 antibody of **claim 1** having a heavy chain sequence according to SEQ ID NOS:130 or 131, and a light chain sequence according to SEQ ID NO:140.
9. The anti-CD40 antibody of **claim 1** having a heavy chain sequence according to SEQ ID NOS:132 or 133, and a light chain sequence according to SEQ ID NO:141.
10. The anti-CD40 antibody of **claim 1** having a heavy chain sequence according to SEQ ID NO: 132 and a light chain sequence according to SEQ ID NO: 141.
11. The anti-CD40 antibody of **claim 1** having a heavy chain sequence according to SEQ ID NO: 133 and a light chain sequence according to SEQ ID NO: 141.

12. The anti-CD40 antibody of **claim 1** having a heavy chain sequence according to SEQ ID NOS:132 or 133, and a light chain sequence according to SEQ ID NO:142.
13. A pharmaceutical composition comprising an anti-CD40 antibody or binding fragment of **claim 1**, and a pharmaceutically acceptable carrier.