ANTI-GITR ANTIBODIES AND USES THEREOF

FIELD

[0001] The present disclosure relates to antibodies and antigen-binding fragments thereof that specifically bind glucocorticoid-induced tumor necrosis factor receptor (GITR) and methods of use thereof.

SEQUENCE LISTING

[0002] An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an ASCII formatted sequence listing with a file name of 10671WO01_Sequence_Listing_ST25.TXT, a creation date of March 5, 2021, and a size of about 60 kilobytes. The sequence listing contained in this ASCII formatted document is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND

[0003] Glucocorticoid-induced tumor necrosis factor receptor (GITR) is a member of the tumor necrosis factor receptor superfamily (TNFRSF). GITR expression is constitutively high on regulatory T-cells, low/intermediate on naïve T-cells, NK cells and granulocytes, and inducible upon activation. GITR interacts with its ligand GITRL, which is mainly expressed on antigen-presenting cells. GITR receptor activation can both augment effector T-cell proliferation and function as well as attenuate the suppression induced by regulatory T-cells. Consequently, the modulation of GITR activity can serve as a basis for cancer immunotherapy and immune disorders. Thus, there is a need for agents, *e.g.*, antibodies, that modulate the activity of GITR.

SUMMARY

[0004] The present disclosure provides antibodies and antigen-binding fragments thereof that bind glucocorticoid-induced tumor necrosis factor receptor (GITR). The antibodies provided herein are useful, *inter alia*, for targeting immune cells, *e.g.*, effector T-cells, regulatory T-cells, and natural killer (NK) cells that express GITR. The antibodies are particularly useful in that *in vivo* truncation of the antibody is minimized.

[0005] The antibodies provided herein can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, *e.g.*, to eliminate residual effector functions (Reddy *et al.*, 2000, J. Immunol. 164:1925-1933).

[0006] Exemplary anti-GITR antibodies provided herein are listed in Tables 7, 8, and 9. Table 7 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-GITR antibodies. Table 8 sets forth the nucleic acid sequence identifiers of the HCVRs, LCVRs, HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 of the exemplary anti-GITR antibodies. Table 9 provides the sequence identifiers for the full length heavy and light chain sequences of the exemplary anti-GITR antibodies.

[0007] The present disclosure provides antibodies or antigen-binding fragments thereof that specifically bind GITR, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 28, 34, and 40; and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

[0007a] In one aspect, the present disclosure refers to an isolated antibody or antigen-binding fragment thereof that binds glucocorticoid-induced tumor necrosis factor receptor (GITR), wherein the antibody or antigen-binding fragment comprises (i) three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:4, the HCDR2 comprises the amino acid sequence of SEQ ID NO:6, and the HCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO:24, SEQ ID NO:30, SEQ ID NO:36, and SEQ ID NO:42; and (ii) three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO:12, the LCDR2 comprises the amino acid sequence of SEQ ID NO:14, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:16.

[0008] The present disclosure provides antibodies or antigen-binding fragments thereof that specifically bind GITR, wherein the antibody or antigen-binding fragment thereof comprises an HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 28, 34, and 40; and an LCVR amino acid sequence of SEQ ID NO: 10.

[0009] The present disclosure provides antibodies or antigen-binding fragments thereof that specifically bind GITR, wherein the antibody comprises a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 38, and 44; and a light chain amino acid sequence of SEQ ID NO: 20.

[0010] The present disclosure provides antibodies or antigen-binding fragments thereof that specifically bind GITR, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs within an HCVR amino acid sequence of SEQ ID NO: 2 modified with N101D, N101E, N101S, or N101T mutation; and three light chain CDRs within an LCVR amino acid sequence of SEQ ID NO: 10.

[0011] The present disclosure provides antibodies or antigen-binding fragments thereof that specifically bind GITR, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs within an HCVR amino acid sequence of SEQ ID NO: 2 modified with N101A, N101F, N101G, N101H, N101I, N101K, N101L, N101M, N101P, N101Q, N101R, N101V, N101W, or N101Y mutation; and three light chain CDRs within an LCVR amino acid sequence of SEQ ID NO: 10.

[0012] The present disclosure provides antibodies or antigen-binding fragments thereof that specifically bind GITR, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs within an HCVR amino acid sequence of SEQ ID NO: 2 modified with S103A, S103D, S103E, S103F,

S103G, S103H, S103I, S103K, S103L, S103M, S103N, S103P, S103Q, S103R, S103T, S103V, S103W, or S103Y mutation; and three light chain CDRs within an LCVR amino acid sequence of SEQ ID NO: 10.

[0013] Explicitly excluded is the antibody provided in Table 1 herein and disclosed in U.S. 2017/0355774A1, wherein the antibody lacks an N101 or S103 modification or mutation in the HCVR.

[0014] The present disclosure provides antibodies or antigen-binding fragments thereof that specifically bind GITR, comprising an HCVR and an LCVR, wherein the HCVR comprises an HCDR3 amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 7. The HCVR can further comprise an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 7, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. The LCVR can comprise an LCVR amino acid sequence listed in Table 7, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0015] The present disclosure also provides antibodies or antigen-binding fragments thereof that specifically bind GITR, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising the HCVR amino acid sequences listed in Table 7 paired with the LCVR amino acid sequence listed in Table 7. According to certain examples, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-GITR antibodies listed in Table 7. In certain examples, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 22/10, 28/10, 34/10, and 40/10.

[0016] The present disclosure also provides antibodies or antigen-binding fragments thereof that specifically bind GITR, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 7.

[0017] The present disclosure also provides antibodies or antigen-binding fragments thereof that specifically bind GITR, comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 7 paired with the LCDR3 amino acid sequence provided in Table 7. According to certain examples, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-GITR antibodies listed in Table 7. In certain examples, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 24/16, 30/16, 36/16, and 42/16.

[0018] The present disclosure also provides antibodies or antigen-binding fragments thereof that

specifically bind GITR, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-GITR antibodies listed in Table 7. In certain examples, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set is selected from the group consisting of SEQ ID NOs: 4-6-24-12-14-16, 4-6-30-12-14-16, 4-6-36-12-14-16, and 4-6-42-12-14-16.

[0019] In a related example, the present disclosure provides antibodies, or antigen-binding fragments thereof that specifically bind GITR, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-GITR antibodies listed in Table 7. For example, the present disclosure includes antibodies or antigen-binding fragments thereof that specifically bind GITR, comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 24/16, 30/16, 36/16, and 42/16.

[0019a] In another aspect, the present disclosure provides an isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an HCVR of an antibody as disclosed herein.

[0020] The present disclosure also provides nucleic acid molecules encoding anti-GITR antibodies or portions thereof. For example, the present disclosure provides nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 7; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 8, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0021] The present disclosure also provides nucleic acid molecules encoding the LCVR amino acid sequence listed in Table 7; in certain examples the nucleic acid molecule comprises a polynucleotide sequence of the LCVR nucleic acid sequence listed in Table 8, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0022] The present disclosure also provides nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 7; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 8, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0023] The present disclosure also provides nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-GITR antibodies listed in Table 7.

[0024] The present disclosure also provides nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 7, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid

sequences listed in Table 7. In certain examples, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 8, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 8, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain examples provided herein, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-GITR antibody listed in Table 7.

[0024a] In another aspect, the present disclosure refers to an isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a heavy chain of an antibody as disclosed herein.

[0024b] In another aspect, the present disclosure refers to a vector comprising the polynucleotide sequence as disclosed herein.

[0025] The present disclosure also provides recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-GITR antibody. For example, the present disclosure includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 7. Also included within the scope of the present disclosure are host cells, for example, eukaryotic host cells, such as mammalian host cells, into which such vectors have been introduced. Exemplary eukaryotic host cells include yeast and mammalian cells, for example vertebrate cells such as a mouse, rat, monkey or human cell line, for example, HKB11 cells, PER.C6 cells, HEK cells or CHO cells. Also provided herein are methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced.

[0026] The present disclosure includes anti-GITR antibodies having a modified glycosylation pattern. In some examples, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al.* (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0026a] In another aspect, the present disclosure refers to an isolated host cell expressing the vector as disclosed herein.

[0027] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof as disclosed herein and a pharmaceutically acceptable carrier or diluent. In another example, the disclosure provides a pharmaceutical composition comprising a recombinant human antibody or fragment thereof which specifically binds GITR and a pharmaceutically acceptable carrier. In a related example, the disclosure features a composition which is a combination of an anti-GITR antibody and a second therapeutic agent. In one example, the second therapeutic agent is any agent that is advantageously combined with an anti-GITR antibody. The present disclosure also provides antibody-drug conjugates (ADCs) comprising an anti-GITR antibody conjugated to a cytotoxic agent. Exemplary combination therapies, co-formulations, and ADCs involving the anti-GITR

antibodies of the present disclosure are disclosed elsewhere herein.

[0027a] In another aspect, the present disclosure refers to the use of the antibody or antigen-binding fragment thereof as disclosed herein in the manufacture of a medicament for modulating anti-tumor immune response or treating cancer in a subject.

[0028] In yet another example, the disclosure provides pharmaceutical compositions comprising a recombinant human antibody or fragment thereof which specifically binds GITR for use in the manufacture of a medicament for killing tumor cells or for inhibiting or attenuating tumor cell growth, or otherwise treating a patient afflicted with cancer. In some examples, the pharmaceutical compositions are therapeutically combined with a second therapeutic agent. In some examples, the second therapeutic agent is a PD-1 inhibitor. In some examples, the PD-1 inhibitor is cemiplimab.

[0028a] In another aspect, the present disclosure refers to the use of an anti-GITR antibody or antigen-binding fragment thereof comprising an HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, an LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising an amino acid sequence of SEQ ID NO: 16, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein said medicament is to be administered in combination with cemiplimab.

[0028b] In yet another aspect, the present disclosure refers to the antibody or antigen-binding fragment thereof as disclosed herein for use in therapy.

[0029] In yet another example, the disclosure provides therapeutic methods for killing tumor cells or for inhibiting or attenuating tumor cell growth, or otherwise treating a patient afflicted with cancer, using an anti-GITR antibody or antigen-binding portion of an antibody provided herein. The therapeutic methods according to this example provided herein comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody provided herein to a subject in need thereof. The disorder treated is any disease or condition which is improved, ameliorated, inhibited, or prevented by targeting GITR and/or by increasing T-cell proliferation or function and/or inhibiting suppression activity induced by regulatory T-cells. In some examples, the methods further comprise administering a second therapeutic agent to the patient, or subject in need thereof. In some examples, the second therapeutic agent is a PD-1 inhibitor. In some examples, the PD-1 inhibitor is cemiplimab.

[0030] In yet another example, the disclosure provides the use of a recombinant human antibody or fragment thereof which specifically binds GITR, or a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, for use in the manufacture of a medicament for killing tumor cells or for inhibiting or attenuating tumor cell growth, or otherwise treating a patient afflicted with cancer.

[0031] In yet another example, the disclosure provides therapeutic methods for killing tumor cells or for inhibiting or attenuating tumor cell growth, or otherwise treating a patient afflicted with cancer, using a combination of an anti-GITR antibody or antigen-binding portion of an anti-GITR antibody and an anti-PD1 antibody or antigen-binding portion of an anti-PD1 antibody. In some examples, the anti-PD1 antibody is cemiplimab. The therapeutic methods according to this example provided herein comprise administering a therapeutically effective amount of a pharmaceutical composition comprising a combination of an anti-GITR and anti-PD1 antibody or antigen-binding fragment composition to a subject in need thereof. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by targeting both GITR and PD1.

[0032] In yet another example, the disclosure provides methods for treating cancer comprising administering, to a subject in need thereof, (i) an anti-GITR antibody or antigen-binding fragment thereof comprising a HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 16; and (ii) cemiplimab. In some examples, the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

[0033] In yet another example, the disclosure provides methods for the use of an anti-GITR antibody or antigen-binding fragment thereof comprising an HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, an LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising an amino acid sequence of SEQ ID NO: 16, in the manufacture of a medicament for use in a method of treating cancer in a subject in need thereof. The methods comprise administering to the subject the anti-GITR antibody or antigen-binding fragment thereof and cemiplimab. In some examples, the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer,

endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

[0034] In yet another example, the disclosure provides an anti-GITR antibody or antigen-binding fragment thereof for use in a method of treating cancer in a subject in need thereof, the method comprising administering to the subject: (i) the anti-GITR antibody or antigen-binding fragment thereof comprising an HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, an LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising an amino acid sequence of SEQ ID NO: 16; and (ii) cemiplimab. In some examples, the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

[0035] Other examples will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] Figure 1 depicts increase in truncation observed in CompAb1 when incubated in monkey serum or PBS. Estimated truncation rate in monkey serum was approximately 1.5%/day and in PBS was approximately 0.5%/day.

[0037] Figure 2 depicts increase in truncation observed in CompAb1 when dosed at 10 mg/kg in mice. CompAb1 was spiked into mouse serum and PBS prior to pull down (affinity purification) as a 0 day control.

[0038] Figure 3 depicts the increase in truncation observed in the CompAb1 antibody and none in variants mAb1 or mAb2 after incubation in IgG-depleted human serum. The CompAb1 antibody exhibited truncation rates of 1.9%/day at the C-terminal and 0.7%/day at the N-terminal.

[0039] Figure 4 depicts the increase in truncation observed in the CompAb1 (also referred to as CompAb1) antibody and none in variants mAb1 or mAb2 after *in vitro* incubation in mouse serum. In

What is claimed is:

1. An isolated antibody or antigen-binding fragment thereof that binds glucocorticoid-induced tumor necrosis factor receptor (GITR), wherein the antibody or antigen-binding fragment comprises (i) three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:4, the HCDR2 comprises the amino acid sequence of SEQ ID NO:6, and the HCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO:24, SEQ ID NO:30, SEQ ID NO:36, and SEQ ID NO:42; and (ii) three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO:12, the LCDR2 comprises the amino acid sequence of SEQ ID NO:14, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:16.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR3 comprising the amino acid sequence of SEQ ID NO:24.

3. The isolated antibody or antigen-binding fragment thereof of claim 2 comprising a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 22.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR3 comprising the amino acid sequence of SEQ ID NO: 30.

5. The isolated antibody or antigen-binding fragment thereof of claim 4 comprising an HCVR having an amino acid sequence of SEQ ID NO: 28.

6. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR3 comprising the amino acid sequence of SEQ ID NO: 36.

7. The isolated antibody or antigen-binding fragment thereof of claim 6 comprising an HCVR having an amino acid sequence of SEQ ID NO: 34.

8. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR3 comprising the amino acid sequence of SEQ ID NO: 42.

9. The isolated antibody or antigen-binding fragment thereof of claim 8 comprising an HCVR having an amino acid sequence of SEQ ID NO: 40.

10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-9 comprising an LCVR having an amino acid sequence of SEQ ID NO: 10.

11. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 26.

12. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 32.

13. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 38.

14. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 44.

15. The isolated antibody or antigen-binding fragment thereof of any one of claims 11-14 comprising a heavy chain and a light chain, wherein the light chain comprises an amino acid sequence of SEQ ID NO: 20.

16. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an HCVR of an antibody as set forth in any one of claims 1-15.

17. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a heavy chain of an antibody as set forth in any one of claims 1-15.

18. A vector comprising the polynucleotide sequence of claim 16 or 17.

19. An isolated host cell expressing the vector of claim 18.

20. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-15 and a pharmaceutically acceptable carrier or diluent.

21. Use of the antibody or antigen-binding fragment thereof of any of claims 1-15 in the manufacture of a medicament for modulating anti-tumor immune response or treating cancer in a subject.

22. The use according to claim 21, wherein the medicament is to be used in combination with an antibody or antigen-binding fragment thereof that binds to a second T-cell activating receptor, wherein the T-cell activating receptor is CD28, OX40, CD137, CD27, or HVEM.

23. The use according to claim 21, wherein the medicament is to be used in combination with an antibody or antigen-binding fragment thereof that binds to a T-cell inhibitory receptor, wherein the T-cell inhibitory receptor is CTLA-4, PD-1, TIM-3, BTLA, VISTA, or LAG-3.

24. The use according to claim 23, wherein the T-cell inhibitory receptor is PD1 and the antibody that binds to the T-cell inhibitory receptor is cemiplimab.

25. The use according to claim 21, wherein the medicament is to be used in combination with a radiation therapy.

26. The use according to claim 21, wherein the medicament is to be used in combination with a chemotherapeutic agent.

27. The use according to any one of claims 21 – 26, wherein the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

28. Use of an anti-GITR antibody or antigen-binding fragment thereof comprising an HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, an LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising an amino acid sequence of SEQ ID NO: 16, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein said medicament is to be administered in combination with cemiplimab.

29. The use of claim 28, wherein the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

30. The antibody or antigen-binding fragment thereof of any of claims 1-15 for use in therapy.