CLAIMS

WHAT IS CLAIMED IS:

1. An isolated antibody or antigen-binding fragment thereof that binds to human GITR comprising:

a) a light chain variable domain comprising three complementarity determining sequences (CDRs) comprising amino acid sequences selected from the group consisting of SEQ ID NOs: 56-88, optionally, wherein one residue of any of said CDRs are substituted with another residue; and

b) a heavy chain variable domain comprising three complementarity determining sequences (CDRs) comprising amino acid sequences selected from the group consisting of SEQ ID NOs: 23-55, optionally, wherein one residue of any of said CDRs are substituted with another residue.

2. The antibody or fragment of claim 1 wherein the CDRs comprise:

a) a CDRL1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 56-66, wherein one CDR-L1 residue is substituted with another residue; a CDRL2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 67-77, wherein one CDR-L2 residue is substituted with another residue; and a CDRL3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 78-88; and

b) a CDRH1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23-33; a CDRH2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-44; and a CDRH3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 45-55.

3. A antibody or fragment of claim 1 wherein:

a) the amino acid sequence of the heavy chain variable domain is selected from the group consisting of SEQ ID NOs: 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, and 110; and

b) the amino acid sequence of the light chain variable domain is selected from the group consisting of 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, and 111.

4. The antibody or fragment of claim 3, wherein:

a) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 90, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 91;

b) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 92, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 93;

c) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 94, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 95;

d) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 96, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 97;

e) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 98, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 99;

f) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 100, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 101;

g) the amino acid sequence of the heavy chain domain is SEQ ID NO: 102, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 103;

h) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 104, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 105;

i) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 106, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 107;

j) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 108, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 109; or

k) the amino acid sequence of the heavy chain variable domain is SEQ ID NO: 110, and the amino acid sequence of the light chain variable domain is SEQ ID NO: 111.

5. An antibody or antigen-binding fragment thereof that blocks binding of the antibody or fragment of Claim 4 to human GITR in a cross-blocking assay.

6. An isolated nucleic acid encoding at least one of the light chain variable domain or heavy chain variable domain of the antibody or fragment of Claim 4.

7. An expression vector comprising the nucleic acid of Claim 6 operably linked to control sequences that are recognized by a host cell when the host cell is transfected with the vector.

8. A host cell comprising the expression vector of Claim 7.

9. A method of producing a polypeptide comprising:

culturing the host cell of Claim 8 in culture medium under conditions wherein the nucleic acid sequence is expressed, thereby producing polypeptides comprising the light and heavy chain variable domains; and

recovering the polypeptides from the host cell or culture medium.

10. The antibody or fragment of Claim 4, further comprising a heavy chain constant region comprising a γ1 human heavy chain constant region or a variant thereof, wherein the constant region variant comprises up to 20 conservatively modified amino acid substitutions.

11. The antibody or fragment of Claim 4, further comprising a heavy chain constant region comprising a γ4 human heavy chain constant region or a variant thereof, wherein the constant region variant comprises up to 20 conservatively modified amino acid substitutions.

12. The antibody or fragment of Claim 4, wherein the antibody or fragment is an antigen-binding fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv, $F(ab')_2$, and a diabody.

13. Use of an antibody or antigen-binding fragment thereof of claim 5 that specifically binds to human GITR, in the manufacture of a medicament for enhancing an immune response in a human subject.

14. The use of claim 13, wherein the antibody or antigen-binding fragment thereof is to be co-administered with an anti-TGFβ antibody.

15. The use of claim 13, wherein the antibody or antigen-binding fragment thereof is to be co-administered with local radiation.

16. The use of claim 13, wherein the immune response is against a proliferative disorder.

17. The use of claim 13, wherein the immune response is against a viral infection.

18. A pharmaceutical composition comprising the antibody or fragment of claim 4 and a pharmaceutically acceptable carrier.

19. An antibody or antigen binding fragment thereof, produced by a hybridoma deposited at the American Type Culture Collection (ATCC), wherein the hybridoma is selected from the group consisting of PTA-9889, PTA-9890, PTA-9891, PTA-9892, PTA-9893, PTA-10286, PTA-10287, PTA-10288, PTA-10289, PTA-10290, and PTA-10291.

20. An antibody or antigen binding fragment that binds to human GITR protein, wherein the antibody or antigen binding fragment recognizes an epitope spanning module 3 and module 4 of human GITR protein (SEQ ID NO: 89).

21. The antibody or antigen binding fragment of claim 20, wherein the epitope comprises Gly^{57}, Arg^{65}, His^{67}, Lys^{80}, Phe^{81}, Ser^{82}, and Gln^{86}.

22. The antibody or fragment of claim 20 that cross-blocks at least one of the antibodies or fragments produced by a hybridoma selected from group consisting of PTA-9889, PTA-9890, PTA-9891, PTA-9892, PTA-9893, PTA-10286, PTA-10287, PTA-10288, PTA-10289, PTA-10290, and PTA-10291.

23. An isolated heavy chain variable domain polypeptide comprising three complementarity determining sequences (CDRs) comprising the amino acid sequences set forth in SEQ ID NOs: 23, 34 and 45.

24. The polypeptide of claim 23 which is fused to a γ1 human heavy chain constant domain.

25. A method of producing the polypeptide of claim 23 comprising:
culturing a host cell comprising a nucleic acid that encodes the polypeptide in culture medium under conditions wherein the nucleic acid sequence is expressed, and
recovering the polypeptide from the host cell or culture medium.

26. An isolated antibody or antigen-binding fragment thereof comprising:
CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO: 23;
CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: 34;
CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO: 45;
CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 56, wherein one CDR-L1 residue is substituted with another residue;
CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO: 67, wherein one CDR-L1 residue is substituted with another residue;
and
CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO: 78.

27. The antibody or fragment of claim 26 comprising a γ1 human heavy chain constant domain.

28. Use of the antibody or fragment of claim 26 in the manufacture of a medicament for enhancing an immune response in a human subject.

29. The use of claim 28, wherein the antibody or fragment is co-administered with an anti-TGF antibody.

30. The use of claim 28, wherein the antibody or fragment is co-administered with local radiation.

31. The use of claim 28, wherein the immune response is against a proliferative disorder.

32. The use of claim 28, wherein the immune response is against a viral infection.

33. A pharmaceutical composition comprising the antibody or fragment of claim 26 and a pharmaceutically acceptable carrier.

34. The use of claim 13 wherein the immune response is against adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, hepatic carcinoma, hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, multiple myeloma, salivary gland carcinoma, kidney cancer, renal cell carcinoma, Wilms' tumors, basal cell carcinoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and head and neck cancer.

35. The use of claim 34 wherein the immune response is against colorectal cancer, non-small cell lung cancer or melanoma.

36. The use of claim 28 wherein the immune response is against adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, hepatic carcinoma, hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, multiple myeloma, salivary gland carcinoma, kidney cancer, renal cell carcinoma, Wilms' tumors, basal cell carcinoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and head and neck cancer.

37. The use of claim 36 wherein the immune response is against colorectal cancer, non-small cell lung cancer or melanoma.

CLAIMS

WHAT IS CLAIMED IS:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to human GITR protein comprising:
CDR-L1, CDR-L2 and CDR-L3 of the light immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 105; and
CDR-H1, CDR-H2 and CDR-H3 of the heavy immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 104.

2. An isolated antibody or antigen-binding fragment thereof that binds specifically to human GITR protein comprising a light chain immunoglobulin variable domain comprising an amino acid sequence which is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 105; and a heavy chain immunoglobulin variable domain comprising an amino acid sequence which is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 104.

3. The antibody or antigen-binding fragment of claim 2 comprising a light chain immunoglobulin variable domain comprising the amino acid sequence set forth in SEQ ID NO: 105; and a heavy chain immunoglobulin variable domain comprising an amino acid sequence which is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 104 wherein the heavy chain immunoglobulin variable domain comprises the CDR-H1, CDR-H2 and CDR-H3 of the heavy immunoglobulin chain comprising the amino acid sequence set forth in SEQ ID NO: 104.

4. An isolated antibody or antigen-binding fragment thereof that specifically binds to human GITR comprising:
a CDR-L1 that comprises the amino acid sequence set forth in SEQ ID NO: 56 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO:56;
A CDR-L2 that comprises the amino acid sequence set forth in SEQ ID NO: 67 or variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 67;
a CDR-L3 that comprises the amino acid sequence set forth in SEQ ID NO: 78 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 78;

a CDR-H1 that comprises the amino acid sequence set forth in SEQ ID NO: 23 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 23;
CDR-H2 that comprises the amino acid sequence set forth in SEQ ID NO: 34 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO: 34; and
CDR-H3 that comprises the amino acid sequence set forth in SEQ ID NO: 45 or a variant thereof, wherein the variant comprises one conservative amino acid substitution relative to SEQ ID NO:45.

5. The antibody or antigen-binding fragment of claim 4 comprising:
CDR-L1 that comprises the amino acid sequence set forth in SEQ ID NO: 56, wherein one residue of said CDR-L1 is conservatively substituted with another residue;
CDR-L2 that comprises the amino acid sequence set forth in SEQ ID NO: 67, wherein one residue of said CDR-L2 is conservatively substituted with another residue;
CDR-L3 that comprises the amino acid sequence set forth in SEQ ID NO: 78;
CDR-H1 that comprises the amino acid sequence set forth in SEQ ID NO: 23;
CDR-H2 that comprises the amino acid sequence set forth in SEQ ID NO: 34; and
CDR-H3 that comprises the amino acid sequence set forth in SEQ ID NO: 45.

6. The antibody or antigen-binding fragment thereof of claim 5 comprising:
CDR-L1 that comprises the amino acid sequence set forth in SEQ ID NO: 56, wherein one asparagine of said CDR-L1 is substituted with a glutamine;
CDR-L2 that comprises the amino acid sequence set forth in SEQ ID NO: 67, wherein one asparagine of said CDR-L2 is substituted with a glutamine;
CDR-L3 that comprises the amino acid sequence set forth in SEQ ID NO: 78;
CDR-H1 that comprises the amino acid sequence set forth in SEQ ID NO: 23;
CDR-H2 that comprises the amino acid sequence set forth in SEQ ID NO: 34; and
CDR-H3 that comprises the amino acid sequence set forth in SEQ ID NO: 45.

7. The antibody or antigen-binding fragment of any one of claims 1-6, which is an antigen-binding fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv, $F(ab')_2$, and a diabody.

8. An isolated antibody or antigen-binding fragment thereof, produced by a hybridoma deposited at the American Type Culture Collection (ATCC), wherein the hybridoma is PTA-9890.

9. An isolated antibody or antigen-binding thereof that binds to human GITR protein, wherein the antibody or antigen-binding fragment recognizes an epitope spanning module 3 and module 4 of human GITR protein (SEQ ID NO: 89).

10. The antibody or antigen-binding fragment of claim 9, wherein the epitope comprises Gly57, Arg65, His67, Lys80, Phe81, Ser82, and Gln86.

11. An isolated antibody or antigen-binding fragment thereof that is able to block binding of the antibody or antigen-binding fragment of any one of claims 1-10 to human GITR protein.

12. The antibody or antigen-binding fragment of any one of claims 1-11 which is an antibody.

13. The antibody or antigen-binding fragment of any one of claims 1-11 which is a monoclonal antibody.

14. The antibody or antigen-binding fragment of any one of claims 1-11 which is a humanized antibody.

15. The antibody or antigen-binding fragment of any one of claims 1-14 wherein the heavy immunoglobulin chain is fused to a γ1 human immunoglobulin constant domain.

16. The antibody or antigen-binding fragment of any one of claims 1-14, comprising a γ1 human heavy chain constant region or a variant thereof, wherein the constant region variant comprises up to 20 conservatively modified amino acid substitutions.

17. The antibody or antigen-binding fragment of any one of claims 1-14, comprising a γ4 human heavy chain constant region or a variant thereof, wherein the constant region variant comprises up to 20 conservatively modified amino acid substitutions.

18. A pharmaceutical composition comprising the antibody or antigen-binding of any one of claims 1-17 and a pharmaceutically acceptable carrier.

19. An isolated immunoglobulin polypeptide comprising:
CDR-H1 that comprises the amino acid sequence set forth in SEQ ID NO: 23;
CDR-H2 that comprises the amino acid sequence set forth in SEQ ID NO: 34; and
CDR-H3 that comprises the amino acid sequence set forth in SEQ ID NO: 45;
fused to a γ1 human immunoglobulin constant domain.

20. An isolated nucleic acid encoding at least one of the light immunoglobulin chain or the heavy immunoglobulin chain of the antibody or antigen-binding fragment or polypeptide of any one of claims 1-19.

21. An expression vector comprising the nucleic acid of claim 20 operably linked to an expression control sequence that is recognized by a host cell when the host cell is transformed with the vector.

22. An isolated host cell comprising the expression vector of claim 21.

23. The host cell of claim 22 which is a Chinese Hamster Ovary cell or a *Pichia pastoris* cell.

24. A composition comprising the antibody or antigen-binding fragment of any one of claims 1-17 and a second therapeutic agent.

25. The composition of claim 24 wherein the second therapeutic agent is an antibody.

26. A composition comprising the antibody or antigen-binding fragment of any one of claims 1-17 and a member selected from the group consisting of thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, KW-2189, CB 1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimnustine, calicheamicin, calicheamicin gamma II, calicheamicin omega II, dynemicin, dynemicin A, clodronate, neocarzinostatin chromophore, aclacinomysins, actinomycin,

authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, 5-fluorouracil (5-FU), denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, sizofuran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine, T-2 toxin, verracurin A, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside, cyclophosphamide, paclitaxel, a cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel, docetaxel, chloranbucil, gemcitabine, 6-thioguanine, mercaptopurine, methotrexate, cisplatin, carboplatin, vinblastine, platinum, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, capecitabine, ibandronate, CPT-11, RFS2000, difluoromethylornithine (DMFO), retinoic acid, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, toremifene, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestanie, fadrozole, vorozole, letrozole, anastrozole, flutamide, nilutamide, bicalutamide, leuprolide, goserelin, troxacitabine, angiozyme, allovectin, leuvectin, vaxid, recombinant IL-2, lurtotecan and abarelix.

27. A composition comprising the antibody or antigen-binding fragment of any one of claims 1-17 and a member selected from the group consisting of an alkylating agent, an ethylenimine, a methylamelamine, an acetogenin, a camptothecin, a cryptophycin, a sarcodictyin, an antibiotic, a bisphosphonate, a mitomycin, an anti-metabolite, a folic acid analogue, a purine analog, an androgen, an anti-adrenal, a folic acid replenisher, an epothilone, a trichothecene, a taxoid, a retinoid, an anti-

hormonal agent, an aromatase inhibitor, an anti-androgen, an antisense oligonucleotide, a ribozyme, a HER2 expression inhibitor and a vaccine.

28. A method of producing a polypeptide comprising: culturing the host cell of claim 22 in culture medium under conditions wherein the nucleic acid sequence is expressed; and recovering the polypeptides from the host cell or culture medium or both.

29. Use of an antibody or antigen-binding fragment of any one of claims 1-17 in the manufacture of a medicament for enhancing an immune response in a human subject.

30. The use of claim 29, wherein the antibody or antigen-binding fragment is co-administered with a second therapeutic agent.

31. The use of claim 30 wherein the second therapeutic agent is an antibody.

32. The use of claim 29, wherein the antibody or antigen-binding fragment is co-administered with an anti-TGFβ antibody.

32. The use of claim 29, wherein the antibody or antigen-binding fragment is co-administered with local radiation.

33. The use of claim 29, wherein the antibody or antigen-binding fragment is co-administered with a member selected from the group consisting of thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, KW-2189, CB 1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimnustine, calicheamicin, calicheamicin gamma II, calicheamicin omega II, dynemicin, dynemicin A, clodronate, neocarzinostatin chromophore, aclacinomysins, actinomycin,

authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, 5-fluorouracil (5-FU), denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, sizofuran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine, T-2 toxin, verracurin A, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside, cyclophosphamide, paclitaxel, a cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel, docetaxel, chloranbucil, gemcitabine, 6-thioguanine, mercaptopurine, methotrexate, cisplatin, carboplatin, vinblastine, platinum, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, capecitabine, ibandronate, CPT-11, RFS2000, difluoromethylornithine (DMFO), retinoic acid, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, toremifene, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestanie, fadrozole, vorozole, letrozole, anastrozole, flutamide, nilutamide, bicalutamide, leuprolide, goserelin, troxacitabine, angiozyme, allovectin, leuvectin, vaxid, recombinant IL-2, lurtotecan and abarelix.

34. The use of claim 29, wherein the antibody or antigen-binding fragment is co-administered with a member selected from the group consisting of an alkylating agent, an ethylenimine, a methylamelamine, an acetogenin, a camptothecin, a cryptophycin, a sarcodictyin, an antibiotic, a bisphosphonate, a mitomycin, an anti-metabolite, a folic acid analogue, a purine analog, an androgen, an anti-adrenal, a folic acid replenisher, an epothilone, a trichothecene, a taxoid, a retinoid, an anti-

hormonal agent, an aromatase inhibitor, an anti-androgen, an antisense oligonucleotide, a ribozyme, a HER2 expression inhibitor and a vaccine.

35. The use of claim 29, wherein the immune response is against a proliferative disorder.

36. The use of claim 29 wherein the immune response is against cancer.

37. The use of claim 36 wherein the cancer is a member selected from the group consisting of adenocarcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, salivary gland carcinoma, kidney cancer, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and head and neck cancer.

38. The use of claim 29, wherein the immune response is against a viral infection.

39. The use of claim 38 wherein viral infection is caused by a virus which is a member selected from the group consisting of human papilloma viruses (HPV), herpes simplex virus, hepatitis B virus, hepatitis C virus, measles virus, human immunodeficiency virus (HIV) and Epstein Barr virus (EBV).