Claims

1. An isolated antibody, which specifically binds to Fms-like tyrosine kinase 3 (FLT3), wherein the antibody comprises

(a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 90, 91, or 92; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 93 or 94; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 95; and

(b) a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 171; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 172; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 173.

2. An isolated antibody which specifically binds to Fms-like tyrosine kinase 3 (FLT3), wherein the antibody comprises:

a VH region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 20; and

a VL region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 19.

3. A bispecific antibody wherein the bispecific antibody is a full-length antibody, comprising a first antibody variable domain of the bispecific antibody specifically binding to a target antigen, and comprising a second antibody variable domain of the bispecific antibody capable of recruiting the activity of a human immune effector cell by specifically binding to an effector antigen located on the human immune effector cell, wherein the first antibody variable domain comprises a heavy chain variable (VH) region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 20; and a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 19.

4. A bispecific antibody wherein the bispecific antibody is a full-length antibody, comprising a first antibody variable domain of the bispecific antibody specifically binding to a target antigen, and comprising a second antibody variable domain of the bispecific antibody capable of recruiting the activity of a human immune effector cell by specifically binding to an effector antigen located on the human immune effector cell, wherein the first antibody variable domain comprises

a. a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID

NO: 90, 91, or 92; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 93 or 94; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 95; and

b. a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 171; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 172; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 173.

5. The bispecific antibody of claim 4, wherein the second antibody variable domain specifically binds to the effector antigen CD3.

6. The bispecific antibody of claim 5, wherein the second antibody variable domain comprises

a. a heavy chain variable (VH) region comprising (i) a VH complementary determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 285, 286, or 287; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 288 or 289; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 290; and/or

b. a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 291; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 292; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 234.

7. The bispecific antibody of claim 3, wherein both the first and the second antibody variable domains of the heterodimeric protein comprise amino acid modifications at positions 223, 225, and 228 in the hinge region and at position 409 or 368 (EU numbering scheme) in the CH3 region of a human IgG2 (SEQ ID NO: 290).

8. The bispecific antibody of claim 7, further comprising an amino acid modification at one or more of positions 265, 330 and 331 of the human IgG2.

9. A nucleic acid encoding the antibody of any one of claims 1-8.

10. A vector comprising the nucleic acid of claim 9.

11. A host cell comprising the nucleic acid of claim 9.

12. The antibody of any one of claims 1-8 for use as a medicament.

13. The antibody of claim 12, wherein the medicament is for use in treatment of an FLT3 related cancer selecting from the group consisting of multiple myeloma, malignant plasma cell neoplasm, Hodgkin’s lymphoma, nodular lymphocyte predominant Hodgkin’s

lymphoma, Kahler's disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulienemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmactyic lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, and other hematopoietic cells related cancer.

14. A pharmaceutical composition comprising the antibody of any one of claims 1-8.

15. Use of the antibody of any one of claims 1-8 or the pharmaceutical composition of claim 14 in the manufacture of a medicament for the treatment of a condition associated with malignant cells expressing FLT3.

16. The use of claim 15, wherein the condition is a cancer.

17. The use of claim 16, wherein the cancer is an FLT3 related cancer selected from the group consisting of multiple myeloma, malignant plasma cell neoplasm, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, Kahler's disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulienemia, diffuse large B cell lymphoma, follicular lymphoma,

marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmactyic lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, and other hematopoietic cells related cancer.

18. Use of the pharmaceutical composition of claim 14 in the manufacture of a medicament for inhibiting tumor growth or progression in a subject who has malignant cells expressing FLT3.

19. Use of the pharmaceutical composition of claim 14 in the manufacture of a medicament for inhibiting metastasis of malignant cells expressing FLT3 in a subject.

20. Use of the pharmaceutical composition of claim 14 in the manufacture of a medicament for inducing tumor regression in a subject who has malignant cells expressing FLT3.

21. A combination therapy, wherein the combination therapy comprises either:

the use of an effective amount of a first therapeutic agent and an effective amount of a second therapeutic agent in the manufacture of a combination medicament, wherein the first therapeutic agent is the antibody of any one of claims 1-8 or the pharmaceutical composition of claim 14,

or

the use of an effective amount of a first therapeutic agent in the manufacture of a first medicament in combination with the use of an effective amount of a second therapeutic agent in the manufacture of a second medicament, wherein the first therapeutic agent is the antibody of any one of claims 1-8 or the pharmaceutical composition of claim 14,

wherein either the combination medicament or the combination of the use of the first medicament and the use of the second medicament are for:

(a) the treatment of a condition associated with malignant cells expressing FLT3,

(b) inhibiting tumor growth or progression in a subject who has malignant cells expressing FLT3,

(c) inhibiting metastasis of malignant cells expressing FLT3 in a subject, or

(d) inducing tumor regression in a subject who has malignant cells expressing FLT3.

22. The combination therapy of claim 21, wherein the second therapeutic agent is a cytokine, TNFα (Tumor Necrosis Factor alpha), a PAP (phosphatidic acid phosphatase) inhibitor, an oncolytic virus, a kinase inhibitor, an IDO (Indoleamine-pyrrole 2,3-dioxygenase) inhibitor, a glutaminase GLS1 inhibitor, a CAR (Chimeric Antigen Receptor)-T cell or T cell therapy, a TLR (Toll-Like Receptor) Agonist, or a tumor vaccine.

23. The combination therapy of claim 22, wherein the second therapeutic agent is a cytokine and the cytokine is IL-15.

24. The combination therapy of claim 22, wherein the second therapeutic agent is a kinase inhibitor and the kinase inhibitor is midostaurin, lestaurtinib, sorafenib, sunitinib, quizartinib, ponatinib, crenolanib, palbociclib, or gilteritinib.

25. A method of producing an antibody encoded by the nucleic acid of claim 9, comprising culturing the host cell of claim 11 under conditions that result in production of the antibody, and isolating the antibody from the host cell or culture.

26. The combination therapy of claim 21, wherein either the combination medicament or the combination of the use of the first medicament and the use of the second medicament are for:

(a) the treatment of a condition associated with malignant cells expressing FLT3,

wherein the condition is a cancer.

27. The combination therapy of claim 26, wherein the cancer is an FLT3 related cancer selected from the group consisting of multiple myeloma, malignant plasma cell neoplasm, Hodgkin’s lymphoma, nodular lymphocyte predominant Hodgkin’s lymphoma, Kahler’s disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin’s lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute

lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulienemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmactyic lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, and other hematopoietic cells related cancer.