to the tumor microenvironment, the question of what role SEMA4D can play in migration, survival, differentiation and organization of the different cell types that constitute the tumor stroma remains to be addressed.

BRIEF SUMMARY

[0004] This application addresses the need for safe and effective cancer treatments that serve either as a single agent that inhibits, reduces, suppresses, prevents, slows or delays the progression of, shrinks, or directly attacks tumor cells or that can act in combination with other immune modulating therapies to enhance their therapeutic benefit. In particular, SEMA4D was shown to play a role in the infiltration, maturation and organization of immune cells and macrophage that either promote or inhibit tumor growth, which can contribute to development of effective methods for reducing tumor growth and metastases in a subject with cancer.

[0004a] In one aspect, there is provided use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for increasing the density of Tumor Infiltrating Lymphocytes (TIL) in tumor microenvironment (TME) of a subject with a tumor, wherein the anti-SEMA4D antibody or fragment thereof (a) can bind to the same SEMA4D epitope as a reference monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17; or (b) can competitively inhibit a references monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17 from binding to SEMA4D.

[0004b] In another aspect, there is provided use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) and at least one other immune modulating therapy in the preparation of a medicament for inhibiting, delaying, or reducing tumor growth in a subject with a solid tumor; wherein the anti-SEMA4D antibody or fragment thereof (a) can bind to the same SEMA4D epitope as a reference monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17; or (b) can competitively inhibit a references monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17 from binding to SEMA4D; wherein the medicament can provide enhanced therapeutic efficacy relative to anti-SEMA4D antibody or fragment thereof alone or the at least one other immune modulating therapy alone.

[0005] Certain ~~aspects~~ examples of the application are directed to a method for inhibiting, delaying, or reducing tumor growth or metastases or both tumor growth and metastases in a subject with cancer comprising administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy.

[0006] In some ~~embodiments~~examples, the binding molecule inhibits SEMA4D interaction with its receptor (e.g., Plexin-B1). In some ~~embodiments~~examples, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In some ~~embodiments~~examples, the inhibition, delay, or reduction of metastases occurs independently of primary tumor growth inhibition, delay, or reduction. In some ~~embodiments~~examples, the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof. In some ~~embodiments~~examples, the subject has elevated levels of either B cells, T cells or both B cells and T cells when compared to other cancer subjects.

[0007] In some ~~embodiments~~ examples, the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody selected from the group consisting of VX15/2503 and 67. In some examples~~embodiments~~, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In some ~~embodiments~~examples, the antibody or antigen-binding fragment thereof comprises the six complementarity determining regions (CDRs) of monoclonal antibody VX15/2503 or 67.

[0008] In some examples~~embodiments~~, the immune modulating therapy is selected from the group consisting of a cancer vaccine, an immunostimulatory agent, adoptive T cell or antibody therapy, immune checkpoint blockade and a combination thereof. In some examples~~embodiments~~, the immune modulating agent is selected from the group consisting of interleukins, cytokines, chemokines, antagonists of immune checkpoint blockades and a combination thereof. In some examples~~embodiments~~, the immune modulating therapy can be a cancer therapy. In some examples~~embodiments~~, the cancer therapy is selected from the group consisting of surgery or surgical procedures, radiation therapy, chemotherapy or a combination thereof. In some examples~~embodiments~~, the isolated binding molecule and the immune modulating agent or immune modulating therapy are administered separately or concurrently.

[0009] In some examples~~embodiments~~, methods for inhibiting, delaying, or reducing tumor growth in a subject with cancer are provided that comprise administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy. In some examples~~embodiments~~, the binding molecule inhibits SEMA4D interaction with its receptor. In some embodiments, the receptor is Plexin-B1. In some examples~~embodiments~~, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In some examples~~embodiments~~, the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof. In some examples~~embodiments~~, the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody VX15/2503 or 67. In some examples~~embodiments~~, the isolated binding

molecule competitively inhibits a reference monoclonal antibody VX15/2503 or 67 from specifically binding to SEMA4D. In some examplesembodiments, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In some examplesembodiments, the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively. In some examplesembodiments, the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18. In some examplesembodiments, the immune modulating therapy is selected from the group consisting of administration of a cancer vaccine, administration of an immunostimulatory agent, adoptive T cell or antibody therapy, administration of an immune checkpoint blockade inhibitor, administration of a regulatory T cell (Treg) modulator, and a combination thereof. In some examplesembodiments, the immune modulating therapy comprises an immune checkpoint blockade inhibitor. In some embodimentsexamples, wherein the immune checkpoint blockade inhibitor is an anti-CTLA4 antibody, an anti-PD-1 antibody, or a combination thereof. In some examplesembodiments, the immune modulating therapy comprises administration of a cancer vaccine. In some examples embodiments, the Treg modulator is cyclophosphamide. In some examplesembodiments, the isolated binding molecule and the immune modulating therapy are administered separately or concurrently. In some examplesembodiments, administration of the combination of the isolated binding molecule and the immune modulating therapy results in enhanced therapeutic efficacy relative to administration of the isolated binding molecule or the immune modulating therapy alone. In some examplesembodiments, the subject has an elevated level of B cells, T cells or both B cells and T cells when compared to other cancer subjects. In some examplesembodiments, the level of B cells and/or T cells per microliter of blood in the subject is about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5 times the mean number of B cells and/or T cells in circulation in other cancer patients. In some examplesembodiments, the level of B cells and/or T cells per microliter of blood in the subject ranges from about 147 to about 588 and from about 1173 to about 3910, respectively, e.g., ,when compared to other cancer patients. In some examplesembodiments, the subject has B cell and/or T cell levels that fall within or above the range of B cells and/or T cells of healthy, non-cancer patients. In some examplesembodiments, the B cell and/or T cell levels per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650 or more, respectively, e.g., ,when compared to healthy, non-cancer patients.

[0010] In some examplesembodiments, methods for treating a subject having cancer with immunotherapy are provided that comprise: (a) determining the number of B cells and/or T cells in a subject with cancer; and (b) administering to the subject an effective amount of an isolated binding

molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy if the number of B cells and/or T cells in the subject exceeds a predetermined threshold level. In some examplesembodiments, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject is about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5 times the mean number of B cells and/or T cells in circulation in other cancer patients. In some examplesembodiments, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject range from about 147 to about 588 and from about 1173 to about 3910, respectively, e.g., when compared to other cancer patients. In some examplesembodiments, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject fall within or above the range of B cells and/or T cells of healthy, non-cancer patients. In some examplesembodiments, the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650, or more, respectively, e.g., when compared to healthy, non-cancer patients.

[0011] In some examplesembodiments, methods of treating a subject having cancer with immunotherapy are provided that comprise: administering a combination of an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy to a subject with cancer, wherein administration of the combination results in enhanced therapeutic efficacy relative to administration of the isolated binding molecule or the other immune modulating therapy alone. In some examplesembodiments, the immune modulating therapy is selected from the group consisting of administration of a cancer vaccine, administration of an immunostimulatory agent, adoptive T cell or antibody therapy, administration of an immune checkpoint blockade inhibitor, administration of a regulatory T cell (Treg) modulator, and a combination thereof. In some examplesembodiments, the immune modulating therapy comprises an immune checkpoint blockade inhibitor. In some examplesembodiments, the immune checkpoint blockade inhibitor is an anti-CTLA4 antibody, an anti-PD-1 antibody, or a combination thereof. In some examplesembodiments, the immune modulating therapy comprises administration of a cancer vaccine. In some embodiments, the Treg modulator is cyclophosphamide. In some examplesembodiments, the isolated binding molecule and the immune modulating therapy are administered separately or concurrently. In some examplesembodiments, the subject has elevated levels of either B cells, T cells or both B cells and T cells when compared to other cancer subjects. In some examplesembodiments, the levels of B cells and/or T cells per microliter of blood in the subject is about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5 times the mean number of B cells and/or T cells in circulation in other cancer

patients. In some examplesembodiments, the levels of B cells and/or T cells per microliter of blood in the subject range from about 147 to about 588 and from about 1173 to about 3910, respectively, e.g., when compared to other cancer patients. In some examplesembodiments, the subject has levels of B cells and/or T cells that fall within or above the range of B cells and/or T cells of healthy, non-cancer patients. In some examplesembodiments, the levels of B cells and/or T cells per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650, or more, respectively, e.g., when compared to healthy, non-cancer patients. In some examplesembodiments, the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof. In some examplesembodiments of any of the aforementioned methods, the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody selected from the group consisting of VX15/2503 or 67. In some embodimentsexamples of any of the aforementioned methods, the isolated binding molecule competitively inhibits a reference monoclonal antibody selected from the group consisting of VX15/2503 or 67 from specifically binding to SEMA4D. In some examplesembodiments, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In some examplesembodiments, the antibody or antigen-binding fragment thereof comprises the six complementarity determining regions (CDRs) of monoclonal antibody VX15/2503 or 67. In some examplesembodiments, the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67.

[0012] Also provided are methods for inhibiting, delaying, or reducing growth of tumor cells expressing Her2 and Plexin B1, Plexin B2, or a combination thereof, comprising contacting the tumor cells with an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D), wherein growth of the tumor cells is inhibited, delayed, or reduced. In some embodiments, the contacting comprises administration of the SEMA4D binding molecule to a subject with cancer, wherein the subject's cancer cells express Her2 and Plexin B1, Plexin B2, or a combination thereof. In some examplesembodiments, the cancer is breast cancer, ovarian cancer, lung cancer, or prostate cancer.

[0013] Also ~~provided~~ disclosed are methods for treating a subject having cancer comprising: (a) assaying the subject's cancer cells for expression of Her2 and Plexin B1, Plexin B2, or a combination thereof; and (b) administering to the subject an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D) if the subject's cancer cells express Her2 and Plexin B1, Plexin B2, or a combination thereof. The method of claim 48 or claim 49, further comprising the administration of an effective amount of an anti-HER2/neu binding molecule. The method of claim 48 or claim 49, wherein the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody VX15/2503 or 67. The method of claim 48 or claim 49, wherein the isolated binding molecule competitively inhibits a reference monoclonal antibody VX15/2503 or 67 from specifically binding to SEMA4D. The method of claim 48 or claim 49, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. The method of claim 53, wherein the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively. The method of claim 54, wherein the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0014] **FIGURES 1A-1B:** Measurement of tumor volume in mice implanted with syngeneic Colon26 tumor cells. FIG. 1A shows measurement of Colon26 tumor volume in Balb/c and SCID mice treated twice weekly with either 1 mg (50mg/kg) of anti-SEMA4D antibody (Ab) 67 or 2B8 isotype control immunoglobulin (2B8 Control Ig). FIG. 1B shows survival time, as defined in Example 1 below, of Balb/c and SCID mice treated with either anti-SEMA4D Ab 67 or 2B8 Control Ig.

[0015] **FIGURE 2:** Shows measurement of Colon26 tumor volume in Balb/c mice implanted with tumor cells and treated first with anti-CD8 depleting antibody (Clone 2.43, BioXCell) or control Rat Ig (150 mg/kg) and then treated as in FIG 1A with either 2B8 Control Ig or anti-SEMA4D Ab 67.

[0016] **FIGURES 3A-3B:** Measurement of immune cell density in Colon26 tumor of grafted mice. FIG. 3A shows density of CD8+ T cells as determined by % tumor area stained with anti-CD8

WHAT IS CLAIMED IS:

1. A method for inhibiting, delaying, or reducing tumor growth in a subject with cancer, comprising administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy.

2. The method of claim 1, wherein the binding molecule inhibits SEMA4D interaction with its receptor.

3. The method of claim 2, wherein the receptor is Plexin-B1.

4. The method of claim 1, wherein the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction.

5. The method of claim 1, wherein the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof.

6. The method of claim 1, wherein the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody VX15/2503 or 67.

7. The method of claim 1, wherein the isolated binding molecule competitively inhibits a reference monoclonal antibody VX15/2503 or 67 from specifically binding to SEMA4D.

8. The method of claim 1, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof.

9. The method of claim 8, wherein the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively.

10. The method of claim 9, wherein the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18.

11. The method of claim 1, wherein the immune modulating therapy is selected from the group consisting of administration of a cancer vaccine, administration of an immunostimulatory

agent, adoptive T cell or antibody therapy, administration of an immune checkpoint blockade inhibitor, administration of a regulatory T cell (Treg) modulator, and a combination thereof.

12. The method of claim 11, wherein the immune modulating therapy comprises an immune checkpoint blockade inhibitor.

13. The method of claim 12, wherein the immune checkpoint blockade inhibitor is an anti-CTLA4 antibody, an anti-PD-1 antibody, or a combination thereof.

14. The method of claim 11, wherein the immune modulating therapy comprises administration of a cancer vaccine.

15. The method of claim 11, wherein the Treg modulator is cyclophosphamide.

16. The method of claim 1, wherein the isolated binding molecule and the immune modulating therapy are administered separately or concurrently.

17. The method of claim 1, wherein administration of the combination of the isolated binding molecule and the immune modulating therapy results in enhanced therapeutic efficacy relative to administration of the isolated binding molecule or the immune modulating therapy alone.

18. The method of claim 1, wherein the subject has an elevated level of B cells, T cells or both B cells and T cells when compared to other cancer subjects.

19. The method of claim 18, wherein the level of B cells and/or T cells per microliter of blood in the subject is about 1.5 to about 5 times the mean number of B cells and/or T cells in circulation in other cancer patients.

20. The method of claim 18, wherein the level of B cells and/or T cells per microliter of blood in the subject ranges from about 147 to about 588 and from about 1173 to about 3910, respectively.

21. The method of claim 1, wherein the subject has B cell and/or T cell levels that fall within or above the range of B cells and/or T cells of healthy, non-cancer patients.

22. The method of claim 21, wherein the B cell and/or T cell levels per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650 or more, respectively.

23. A method for treating a subject having cancer with immunotherapy, comprising:

(a) determining the number of B cells and/or T cells in a subject with cancer; and

(b) administering to the subject an effective amount of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other

immune modulating therapy if the number of B cells and/or T cells in the subject exceeds a predetermined threshold level, thereby treating the subject with cancer.

24. The method of claim 23, wherein the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject is about 1.5 to about 5 times the mean number of B cells and/or T cells in circulation in other cancer patients.

25. The method of claim 24, wherein the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject range from about 147 to about 588 and from about 1173 to about 3910, respectively.

26. The method of claim 23, wherein the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject fall within or above the range of B cells and/or T cells of healthy, non-cancer patients.

27. The method of claim 26, wherein the predetermined threshold levels of B cells and/or T cells per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650 and more, respectively.

28. A method of treating a subject having cancer with immunotherapy comprising: administering a combination of an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D) and an effective amount of at least one other immune modulating therapy to a subject with cancer, wherein administration of the combination results in enhanced therapeutic efficacy relative to administration of the isolated binding molecule or the other immune modulating therapy alone.

29. The method of claim 28, wherein the immune modulating therapy is selected from the group consisting of administration of a cancer vaccine, administration of an immunostimulatory agent, adoptive T cell or antibody therapy, administration of an immune checkpoint blockade inhibitor, administration of a regulatory T cell (Treg) modulator, and a combination thereof.

30. The method of claim 29, wherein the immune modulating therapy comprises an immune checkpoint blockade inhibitor.

31. The method of claim 30, wherein the immune checkpoint blockade inhibitor is an anti-CTLA4 antibody, an anti-PD-1 antibody, or a combination thereof.

32. The method of claim 29, wherein the immune modulating therapy comprises administration of a cancer vaccine.

33. The method of claim 32, wherein the Treg modulator is cyclophosphamide.

34. The method of claim 28, wherein the isolated binding molecule and the immune modulating therapy are administered separately or concurrently.

35. The method of claim 28, wherein the subject has elevated levels of either B cells, T cells or both B cells and T cells when compared to other cancer subjects.

36. The method of claim 35, wherein the levels of B cells and/or T cells per microliter of blood in the subject is about 1.5 to about 5 times the mean number of B cells and/or T cells in circulation in other cancer patients.

37. The method of claim 36, wherein the levels of B cells and/or T cells per microliter of blood in the subject range from about 147 to about 588 and from about 1173 to about 3910, respectively.

38. The method of claim 28, wherein the subject has levels of B cells and/or T cells that fall within or above the range of B cells and/or T cells of healthy, non-cancer patients.

39. The method of claim 38, wherein the levels of B cells and/or T cells per microliter of blood in the subject range from about 225 to about 275 or more and from about 1350 to about 1650 or more, respectively.

40. The method of claim 28, wherein the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, and a combination thereof.

41. The method of any one of claims 28-40, wherein the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody selected from the group consisting of VX15/2503 or 67.

42. The method of any one of claims 28-40, wherein the isolated binding molecule competitively inhibits a reference monoclonal antibody selected from the group consisting of VX15/2503 or 67 from specifically binding to SEMA4D.

43. The method of claim 42, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof.

44. The method of claim 43, wherein the antibody or antigen-binding fragment thereof comprises the six complementarity determining regions (CDRs) of monoclonal antibody VX15/2503 or 67.

45. The method of claim 44, wherein the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or 67.

46. A method for inhibiting, delaying, or reducing growth of tumor cells expressing Her2 and Plexin B1, Plexin B2, or a combination thereof, comprising contacting the tumor cells with an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D), wherein growth of the tumor cells is inhibited, delayed, or reduced.

47. The method of claim 46, wherein the contacting comprises administration of the SEMA4D binding molecule to a subject with cancer, wherein the subject's cancer cells express Her2 and Plexin B1, Plexin B2, or a combination thereof.

48. The method of claim 47, wherein the cancer is breast cancer, ovarian cancer, lung cancer, or prostate cancer.

49. A method for treating a subject having cancer comprising:

(a) assaying the subject's cancer cells for expression of Her2 and Plexin B1, Plexin B2, or a combination thereof; and

(b) administering to the subject an effective amount of an isolated binding molecule that specifically binds to semaphorin-4D (SEMA4D) if the subject's cancer cells express Her2 and Plexin B1, Plexin B2, or a combination thereof.

50. The method of claim 48 or claim 49, further comprising the administration of an effective amount of an anti-HER2/neu binding molecule.

51. The method of claim 48 or claim 49, wherein the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody VX15/2503 or 67.

52. The method of claim 48 or claim 49, wherein the isolated binding molecule competitively inhibits a reference monoclonal antibody VX15/2503 or 67 from specifically binding to SEMA4D.

53. The method of claim 48 or claim 49, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof.

54. The method of claim 53, wherein the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 6, 7, and

8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 14, 15, and 16, respectively.

55. The method of claim 54, wherein the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17 or SEQ ID NO: 10 and SEQ ID NO: 18.

WHAT IS CLAIMED IS:

1. Use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) in the preparation of a medicament for increasing the density of Tumor Infiltrating Lymphocytes (TIL) in tumor microenvironment (TME) of a subject with a tumor, wherein the anti-SEMA4D antibody or fragment thereof

(a) can bind to the same SEMA4D epitope as a reference monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17; or

(b) can competitively inhibit a references monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17 from binding to SEMA4D.

2. The use of claim 1, wherein the anti-SEMA4D antibody or fragment thereof can increase the density of CD8+ T lymphocytes, CD20+ B lymphocytes, M1+ macrophages, or a combination thereof in the TME of the subject.

3. The use of claim 2, wherein the CD8+ T lymphocytes comprise tumor-specific CD8+ T lymphocytes.

4. The use of claim 3, wherein administration of the anti-SEMA4D antibody or fragment thereof improves the tumor-specific CD8+ T cell activity in the TME.

5. The use of any one of claims 1 to 4, wherein the anti-SEMA4D antibody or fragment thereof can increase secretion of interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNFα), or a combination thereof in the TME of the subject.

6. The use of any one of claims 1 to 5, wherein the anti-SEMA4D antibody or fragment thereof can decrease the frequency of M2+ macrophages in the TME of the subject.

7. The use of any one of claims 1 to 6, further comprising the use of at least one other immune modulating therapy in the preparation of the medicament, wherein the medicament can provide enhanced therapeutic efficacy relative to anti-SEMA4D antibody or fragment thereof alone or the at least one immune modulating therapy alone.

8. Use of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) and at least one other immune modulating therapy in the preparation of a medicament for inhibiting, delaying, or reducing tumor growth in a subject with a solid tumor; wherein the anti-SEMA4D antibody or fragment thereof

(a) can bind to the same SEMA4D epitope as a reference monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17; or

(b) can competitively inhibit a references monoclonal antibody comprising the variable heavy chain (VH) amino acid sequence SEQ ID NO: 9 and the variable light chain (VL) amino acid sequence SEQ ID NO: 17 from binding to SEMA4D;

wherein the medicament can provide enhanced therapeutic efficacy relative to anti-SEMA4D antibody or fragment thereof alone or the at least one other immune modulating therapy alone.

9. The use of claim 7 or claim 8, wherein the at least one other immune modulating therapy comprises a cancer vaccine, an immunostimulatory agent, adoptive T cell or antibody therapy, an immune checkpoint blockade inhibitor, a regulatory T cell (Treg) modulator, or a combination thereof.

10. The use of claim 9, wherein the immune checkpoint blockade inhibitor comprises an anti-Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA4) antibody, an anti-Programmed Cell Death 1 (PD-1) antibody, an anti-Programmed Death-Ligand 1 (PD-L1) antibody, an anti-

Lymphocyte Activation Gene 3 (LAG3) antibody, an anti-B7-H3 antibody, an antigen-binding fragment thereof, or a combination thereof.

11. The use of claim 9, wherein the Treg modulator comprises cyclophosphamide.

12. The use of claim 9, wherein the adoptive T cell therapy comprises TIL recovered from the TME of the subject with a tumor.

13. The use of claim 12, wherein the recovered TIL have been expanded *in vitro*.

14. The use of claim 13, wherein the *in vitro* expansion comprises incubating the recovered TIL with allo-reactive feeder cells, interleukin-2 (IL-2), anti-CD3 antibody, or any combination thereof.

15. The use of claim 13 or claim 14, wherein the *in vitro* expansion enriches for cytotoxic CD8+ T cells.

16. The use of claim 9, wherein the adoptive T cell therapy comprises T cells transduced with a chimeric antigen receptor.

17. The use of claim 16, wherein the chimeric antigen receptor is reactive to a targeted tumor antigen.

18. The use of any one of claims 7 to 17, wherein the anti-SEMA4D antibody or fragment thereof and the at least one immune modulating therapy are formulated for separate administration.

19. The use of any one of claims 7 to 17, wherein the anti-SEMA4D antibody or fragment thereof and the at least one immune modulating therapy are formulated for concurrent administration.

20. The use of any one of claims 1 to 19, wherein the subject has elevated levels of B cells, T cells or both B cells and T cells in circulation when compared to other patients with solid tumors.

21. The use of claim 20, wherein the level of B cells and/or T cells per microliter of blood in the subject is about 1.5 to about 5 times the mean number of B cells and/or T cells in circulation in other patients with solid tumors.

22. The use of claim 20, wherein the subject has B cell and/or T cell levels that fall within or above the range of B cells and/or T cells of healthy individuals.

23. The use of any one of claims 1 to 21, wherein the anti-SEMA4D antibody or fragment thereof inhibits SEMA4D interaction with its receptor.

24. The use of claim 23, wherein the receptor is Plexin-B1.

25. The use of any one of claims 1 to 21, wherein the anti-SEMA4D antibody or fragment thereof inhibits SEMA4D-mediated Plexin-B1 signal transduction.

26. The use of any one of claims 1 to 25, wherein the anti-SEMA4D antibody or fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOS: 6, 7, and 8, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOS: 14, 15, and 16, respectively.

27. The use of claim 26, wherein the VH and VL comprise, respectively, SEQ ID NO: 9 and SEQ ID NO: 17, or SEQ ID NO: 10 and SEQ ID NO: 18.

28. The use of any one of claims 1 to 27, wherein the solid tumor is carcinoma, lymphoma, blastoma, sarcoma, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, gastric cancer, pancreatic cancer, neuroendocrine

cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, brain cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, esophageal cancer, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, head and neck cancer, or a combination thereof.

29. The use of claim 28, wherein the solid tumor expresses Her2 and either Plexin B1 or Plexin B2.