

WHAT IS CLAIMED IS:

1. A method for inhibiting, delaying, or reducing malignant cell growth in a subject with cancer, comprising administering to the subject a combination therapy comprising an effective amount of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) and an effective amount of an epigenetic modulating agent.
2. The method of claim 1, wherein the antibody or fragment thereof inhibits SEMA4D interaction with its receptor.
3. The method of claim 2, wherein the receptor is Plexin-B1, Plexin-B2, or CD72.
4. The method of any one of claims 1 to 3, wherein the antibody or fragment thereof inhibits SEMA4D-mediated Plexin-B1 signal transduction.
5. The method of any one of claims 1 to 4, wherein the antibody or fragment thereof comprises a variable heavy chain (VH) comprising VH CDRs 1-3 comprising SEQ ID NOS: 2, 3, and 4, respectively, and a variable light chain (VL) comprising VL CDRs 1-3 comprising SEQ ID NOS: 6, 7, and 8, respectively.
6. The method of claim 5, wherein the VH and VL comprise, respectively, SEQ ID NO: 1 and SEQ ID NO: 5, or SEQ ID NO: 9 and SEQ ID NO: 10.
7. The method of any one of claims 1 to 6, wherein the epigenetic modulating agent comprises a histone deacetylase (HDAC) inhibitor (HDACi), a DNA methyltransferase (DNMT) inhibitor (DNMTi), or any combination thereof.
8. The method of claim 7, wherein the epigenetic modulating agent comprises a histone deacetylase (HDAC) inhibitor (HDACi).
9. The method of claim 8, wherein the HDAC comprises a Class I HDAC, a Class IIA HDAC, a Class IIB HDAC, a Class IV HDAC, or any combination thereof, or wherein the HDAC comprises a zinc-containing catalytic domain.

10. The method of claim 9, wherein the HDACi can bind to the zinc-containing catalytic domain of the HDAC.

11. The method of any one of claims 8 to 10, wherein the HDACi comprises a chemical moiety selected from the group consisting of a hydroxamic acid or a salt thereof, a cyclic tetrapeptide, a depsipeptide, a benzamide, an electrophilic ketone, an aliphatic acid or a salt thereof, or any combination thereof.

12. The method of any one of claims 8 to 11, wherein the HDACi comprises Vorinostat, Romidepsin, Chidamide, Panobinostat, Belinostat, Valproic acid or a salt thereof, Mocetinostat, Abexinostat, Entinostat, Pracinostat, Resminostat, Givinostat, Quisinostat, Kevetrin, CUDC-101, AR-42, Tefinostat (CHR-2845), CHR-3996, 4SC-202, CG200745, ACY-1215, ACY-241, any combination thereof, or any salt, crystal, amorphous structure, hydrate, derivative, metabolite, isomer, or prodrug thereof.

13. The method of claim 12, wherein the HDACi is Entinostat (Pyridin-3-ylmethyl N-[[4-[(2-aminophenyl)carbamoyl]phenyl]methyl]carbamate).

14. The method of claim 7, wherein the epigenetic modulating agent comprises a DNA methyltransferase (DNMT) inhibitor (DNMTi).

15. The method of claim 14, wherein the DNMT comprises DNMT1, DNMT-3a, DNMT-3b, or any combination thereof.

16. The method of claim 14 or claim 15, wherein the DNMTi is a nucleoside analog, an antisense oligonucleotide, a small molecule enzyme inhibitor, or any combination thereof.

17. The method of any one of claims 14 to 16, wherein the DNMTi comprises azacytidine, decitabine, zebularine, SGI-110, epigallocatechin gallate, MG98, RG108, procainamide, hydralazine, any combination thereof, or any salt, crystal, amorphous structure, hydrate, derivative, metabolite, isomer, or prodrug thereof.

18. The method of claim 17, wherein the DNMTi is azacytidine.

19. The method of any one of claims 1 to 18, wherein the antibody or antigen-binding fragment thereof and the epigenetic modulating agent are administered separately or simultaneously.

20. The method of any one of claims 1 to 19, wherein administration of the combination therapy results in enhanced therapeutic efficacy relative to administration of the antibody or fragment thereof or the epigenetic modulating agent alone.

21. The method of claim 20, wherein the enhanced therapeutic efficacy is greater than an additive effect.

22. The method of any one of claims 1 to 21, wherein the cancer comprises a solid tumor, a hematological malignancy, any metastasis thereof, or any combination thereof.

23. The method of claim 22, wherein the cancer is a solid tumor or metastasis thereof.

24. The method of claim 23, wherein the solid tumor is a sarcoma, a carcinoma, a melanoma, any metastases thereof, or any combination thereof.

25. The method of claim 24, wherein the solid tumor is squamous cell carcinoma, adenocarcinoma, basal cell carcinoma, renal cell carcinoma, ductal carcinoma of the breast, soft tissue sarcoma, osteosarcoma, melanoma, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, cancer of the peritoneum, hepatocellular carcinoma, 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, any metastases thereof, or any combination thereof.

26. The method of claim 22, wherein the cancer is a hematologic malignancy or metastasis thereof.

27. The method of claim 26, wherein the hematologic malignancy is leukemia, lymphoma, myeloma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, any metastases thereof, or any combination thereof.

28. The method of any one of claims 1 to 27, further comprising administration of an additional cancer therapy.

29. The method of claim 28, wherein the additional therapy comprises surgery, chemotherapy, radiation therapy, 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 any one of claims 1 to 13 or 19 to 29, wherein:

- (a) the isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) comprises a VH comprising the amino acid sequence SEQ ID NO: 1 and a VL comprising the amino acid sequence SEQ ID NO: 5, and
- (b) the epigenetic modulating agent comprises the HDACi Entinostat.

31. The method of any one of claims 1 to 7 or 14 to 29, wherein:

- (a) the isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) comprises a comprising the VH amino acid sequence SEQ ID NO: 1 and a VL comprising the amino acid sequence SEQ ID NO: 5, and
- (b) the epigenetic modulating agent comprises the DNMTi azacytidine.

32. A pharmaceutical composition comprising an effective amount of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D) and an effective amount of an epigenetic modulating agent.

33. The pharmaceutical composition of claim 32, further comprising a carrier, an excipient, or any combination thereof.

34. The pharmaceutical composition of claim 32 or claim 33, wherein the antibody or fragment thereof comprises a variable heavy chain (VH) comprising VH CDRs 1-3 comprising SEQ ID NOS: 2, 3, and 4, respectively, and a variable light chain (VL) comprising VL CDRs 1-3 comprising SEQ ID NOS: 6, 7, and 8, respectively.

35. The pharmaceutical composition of claim 34, wherein the VH and VL comprise, respectively, SEQ ID NO: 1 and SEQ ID NO: 5, or SEQ ID NO: 9 and SEQ ID NO: 10.

36. The pharmaceutical composition of any one of claims 32 to 35, wherein the epigenetic modulating agent comprises a histone deacetylase (HDAC) inhibitor (HDACi), a DNA methyltransferase (DNMT) inhibitor (DNMTi), or any combination thereof.

37. The pharmaceutical composition of claim 36, wherein the epigenetic modulating agent comprises a histone deacetylase (HDAC) inhibitor (HDACi).

38. The pharmaceutical composition of claim 37, wherein the HDACi comprises Vorinostat, Romidepsin, Chidamide, Panobinostat, Belinostat, Valproic acid or a salt thereof, Mocetinostat, Abexinostat, Entinostat, Pracinostat, Resminostat, Givinostat, Quisinostat, Kevetrin, CUDC-101, AR-42, Tefinostat (CHR-2845), CHR-3996, 4SC-202, CG200745, ACY-1215, ACY-241, any combination thereof, or any salt, crystal, amorphous structure, hydrate, derivative, metabolite, isomer, or prodrug thereof.

39. The pharmaceutical composition of claim 38, wherein the HDACi is Entinostat (Pyridin-3-ylmethyl N-[[4-[(2-aminophenyl)carbamoyl]phenyl]methyl]carbamate).

40. The pharmaceutical composition of claim 36, wherein the epigenetic modulating agent comprises a DNA methyltransferase (DNMT) inhibitor (DNMTi).

41. The pharmaceutical composition of claim 40, wherein the DNMTi comprises azacytidine, decitabine, zebularine, SGI-110, epigallocatechin gallate, MG98,

RG108, procainamide, hydralazine, any combination thereof, or any salt, crystal, amorphous structure, hydrate, derivative, metabolite, isomer, or prodrug thereof.

42. The pharmaceutical composition of claim 41, wherein the DNMTi is azacytidine.

43. A pharmaceutical composition comprising:

(a) an effective amount of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D), wherein the antibody or fragment thereof comprises the VH amino acid sequence SEQ ID NO: 1 and the VL amino acid sequence SEQ ID NO: 5, and

(b) an effective amount of the HDACi Entinostat.

44. A pharmaceutical composition comprising:

(a) an effective amount of an isolated antibody or antigen-binding fragment thereof that specifically binds to semaphorin-4D (SEMA4D), wherein the antibody or fragment thereof comprises the VH amino acid sequence SEQ ID NO: 1 and the VL amino acid sequence SEQ ID NO: 5, and

(b) an effective amount of the DNMTi azacytidine.