pathological conditions involve aberrant cell proliferation and/or regulation. Solid cancers and exudative macular degeneration depend upon the recruitment of a new blood supply for continued growth as well as metastasis.

SUMMARY OF THE INVENTION

[0009] Provided herein are new formulations of anti-CD105 antibodies, pre-filled syringes containing the formulations, and the use of such formulations for treating angiogenesis-related disorders. The present application provides formulations that may be used for intravenous or intraocular administration of, for example, treatment of cancers associated with CD105 and ophthalmologic conditions.

[0010] In one aspect, provided herein is a formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 4.0 to 5.5; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

[0011] In one aspect, the formulation is stable following preparation, which can be tested according to conventional means. With respect to stability of the formulation over time, at least 95% of the anti-CD105 antibody, or antigen-binding fragment thereof, may be present as a monomer following storage at about 2 to 8°C for at least about 12 months as measured by size exclusion chromatography (SEC). In some embodiments, the buffering agent of such formulations is histidine or phosphate buffered saline. With respect to the stability of the formulation over time, at least 90% of the anti-CD105 antibody, or antigen-binding fragment thereof, may be present as a monomer following storage at about 25° C for at least about 6 months as measured by size exclusion chromatography (SEC). In some embodiments, the buffering agent of such formulations is acetate.

[0012] Further, the anti-CD105 antibody, or antigen-binding fragment thereof, may display from about 50 to about 150% binding by a CD105 ELISA binding assay after storage at about 2 to 8°C for at least about 12 months.

[0013] The average isoelectric point (pI) of the anti-CD105 antibody may be from about 8.7 to about 9.2 after storage at 2 to 8°C for at least about 12 months, as measured by, for example, capillary electrophoresis-isoelectric focusing.

[0014] One would understand that the anti-CD105 antibody, or antigen-binding fragment thereof, may be stable for at least about 12 months, at least about 18 months, at least about 24 months, at least about 30 months, at least about 36 months, or more.

[0015] A formulation may contain at least 95% of the anti-CD105 antibody present as monomer as measured by SEC following freezing and thawing cycles of the formulation. Alternatively, or

about 80%, about 90%, about 95%, or about 100% following administration of one or more doses of the formulation to the patient.

[0044] In another embodiment, one or more signs or symptoms are reduced in severity or duration by about 2-fold, about 5-fold, about 10-fold, about 15-fold, about 20-fold, about 25-fold, about 30-fold, about 35-fold, about 40-fold, about 45-fold, about 50-fold, about 55-fold, about 60-fold, about 65-fold, about 70-fold, about 75-fold, about 80-fold, about 90-fold, about 95-fold, about 100-fold, or more, following administration of one or more doses of the formulation to the patient.

[0045] Provided herein is a method of treating an ophthalmologic condition in a patient in need thereof, comprising administering to said patient a formulation described herein, whereby one or more signs or symptoms of said ophthalmologic condition are ameliorated by the treatment. Administration of the formulation may be intravitreal administration.

[0046] Also provided herein is a method of preventing or treating a cancer or metastasis in a subject in need thereof, comprising administering to said patient a formulation described herein, whereby one or more signs or symptoms of said cancer or metastasis are ameliorated. Administration of the formulation may be intravenous administration.

[0047] In the methods provided herein, a subject to be treated can be a human or a non-human subject. Formulations provided herein can be administered once or multiple times depending on the health of the patient, the progression of the disease or condition, and the efficacy of the treatment. Adjustments to therapy and treatments can be made throughout the course of treatment (*e.g.*, the dosage of an antibody in a composition).

[0047a] In one embodiment, there is provided a pre-filled syringe suitable for intravenous administration comprising the formulation as described herein.

[0047b] In one embodiment, there is provided a pre-filled syringe suitable for intravitreal administration comprising a formulation as described herein.

[0048] In one embodiment, there is provided the use of a formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 4.0 to 5.5, in the manufacture of a medicament for treating an angiogenesis-related disease in a subject in need thereof; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

[0048a] In one embodiment, there is provided the use of a formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, a pH of from 4.0 to 5.5, and optionally a surfactant, in the manufacture of a medicament for treating an ophthalmologic condition in a patient in need thereof, wherein the ophthalmologic condition is age-related macular degeneration, diabetic retinopathy, or choroidal neovascularization; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

[0048b] In one embodiment, there is provided the use of a formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 4.0 to 5.5, in the manufacture of a medicament for preventing or treating a cancer or a metastasis thereof in a subject in need thereof; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

[0048c] Provided herein is a method of monitoring the efficacy of one or more of any of the methods provided herein. Levels of soluble CD105 have been correlated with survival in cancer patients and can be monitored prior to and during therapy. Levels of soluble CD105 can, therefore, be one indication that a therapeutic regimen is effective in treating the patient. Treatments described herein may include one or more additional treatments.

INCORPORATION BY REFERENCE

[0049] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] The novel features of the embodiments are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present embodiments may be obtained by reference to the following detailed description that sets forth illustrative

CLAIMS

WHAT IS CLAIMED IS:

1. A formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 4.0 to 5.5; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

2. The formulation of claim 1, wherein at least 95% of the anti-CD105 antibody is present as a monomer following storage at 2 to 8° C for at least 12 months as measured by size exclusion chromatography (SEC).

3. The formulation of claim 1, wherein at least 95% of the anti-CD105 antibody is present as a monomer following storage at 25° C for at least 6 months as measured by size exclusion chromatography (SEC).

4. The formulation of claim 1, wherein at least 90% of the anti-CD105 antibody is present as a monomer following storage at 25° C for at least 6 months as measured by size exclusion chromatography (SEC).

5. The formulation of claim 1, wherein the buffering agent is citrate.

6. The formulation of claim 1, wherein the buffering agent is acetate and the pH is 4.

7. The formulation of claim 1, wherein the buffering agent is histidine and the pH is 5.5.

8. The formulation of claim 1, wherein the anti-CD105 antibody displays 50 to 150% binding by a CD105 ELISA binding assay after storage at 2 to 8 °C for at least 12 months.

9. The formulation of claim 1, wherein the average isoelectric point (pI) of the anti-CD105 antibody is from 8.7 to 9.2 after storage at 2 to 8° C for at least 12 months, as measured by capillary electrophoresis-isoelectric focusing.

10. The formulation of claim 1, wherein the anti-CD105 antibody comprises a light chain variable region (V_L) having an amino acid sequence set forth as SEQ ID NO: 1; a light chain constant region (C_L) having an amino acid sequence set forth as SEQ ID NO: 2; a heavy chain variable region (V_H) having an amino acid sequence set forth as SEQ ID NO: 3; and a constant region (Fc) having an amino acid sequence set forth as SEQ ID NO: 4.

11. The formulation of claim 1, wherein the anti-CD105 antibody comprises a V_L CDR1 having an amino acid sequence set forth as SEQ ID NO: 5; a V_L CDR2 having an

amino acid sequence set forth as SEQ ID NO: 6; a V_L CDR3 having an amino acid sequence set forth as SEQ ID NO: 7; a V_H CDR1 having an amino acid sequence set forth as SEQ ID NO: 8; a V_H CDR2 having an amino acid sequence set forth as SEQ ID NO: 9; and a V_H CDR3 having an amino acid sequence set forth as SEQ ID NO: 10.

12. The formulation of claim 1, comprising 25 mg/ml of the anti-CD105 antibody.

13. The formulation of claim 1, comprising 50 mg/ml of the anti-CD105 antibody.

14. The formulation of claim 1, comprising 100 mg/ml of the anti-CD105 antibody.

15. The formulation of claim 1, wherein the buffering agent is histidine or acetate.

16. The formulation of claim 15, comprising 20 mM histidine or acetate.

17. The formulation of claim 1, wherein the formulation is formulated for intravitreal administration.

18. The formulation of claim 1, wherein the formulation is formulated for intravenous administration.

19. The formulation of claim 1, further comprising an acceptable carrier or excipient.

20. The formulation of claim 19, wherein the carrier or excipient is a pharmaceutically acceptable carrier or excipient.

21. The formulation of claim 1, which is isotonic or hypertonic.

22. The formulation of claim 1, wherein the formulation is made isotonic with a salt.

23. The formulation of claim 1, wherein at least 95% of the anti-CD105 antibody is present as monomer as measured by SEC following freezing and thawing cycles of the formulation.

24. The formulation of claim 1, wherein at least 95% of the anti-CD105 antibody is present as monomer as measured by SEC when subjected to agitation stress.

25. The formulation of claim 1, comprising 240 mM trehalose.

26. The formulation of claim 1, comprising 240 mM sorbitol.

27. The formulation of claim 1, further comprising a surfactant.

28. The formulation of claim 27, wherein the surfactant is polysorbate 20, polysorbate 80 or Pluronic® F68.

29. A pre-filled syringe suitable for intravenous administration comprising the formulation of any of the preceding claims.

30. A pre-filled syringe suitable for intravitreal administration comprising a formulation of any one of claims 1-28.

31. Use of a formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 4.0 to 5.5, in the manufacture of a medicament for treating an angiogenesis-related disease in a subject in need thereof; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

32. The use of claim 31, wherein the anti-CD105 antibody comprises a light chain variable region (V_L) having an amino acid sequence set forth as SEQ ID NO: 1; a light chain constant region (C_L) having an amino acid sequence set forth as SEQ ID NO: 2; a heavy chain variable region (V_H) having an amino acid sequence set forth as SEQ ID NO: 3; and a constant region (Fc) having an amino acid sequence set forth as SEQ ID NO: 4.

33. The use of claim 31, wherein the anti-CD105 antibody comprises a V_L CDR1 having an amino acid sequence set forth as SEQ ID NO: 5; a V_L CDR2 having an amino acid sequence set forth as SEQ ID NO: 6; a V_L CDR3 having an amino acid sequence set forth as SEQ ID NO: 7; a V_H CDR1 having an amino acid sequence set forth as SEQ ID NO: 8; a V_H CDR2 having an amino acid sequence set forth as SEQ ID NO: 9; and a V_H CDR3 having an amino acid sequence set forth as SEQ ID NO: 10.

34. The use of claim 31, comprising 25 mg/ml of the anti-CD105 antibody.

35. The use of claim 31, comprising 50 mg/ml of the anti-CD105 antibody.

36. The use of claim 31, comprising 100 mg/ml of the anti-CD105 antibody.

37. The use of claim 31, wherein the formulation is made isotonic with a salt.

38. The use of claim 31, wherein the buffering agent is histidine or acetate.

39. The use of claim 38, comprising 20 mM histidine or acetate.

40. The use of claim 31, comprising 240 mM trehalose.

41. The use of claim 31, comprising 240 mM sorbitol.

42. The use of claim 31, wherein the formulation is to be administered intravitreally.

43. The use of claim 31, wherein the formulation is to be administered intravenously.

44. The use of claim 31, wherein the formulation further comprises a surfactant.

45. The use of claim 44, wherein the surfactant is polysorbate 20, polysorbate 80 or Pluronic® F68.

46. The use of claim 31, wherein the angiogenesis-related disease is a cancer, or a metastasis thereof.

47. The use of claim 46, wherein the cancer is a solid tumor.

48. The use of claim 46, wherein the cancer is an epithelial based tumor.

49. The use of claim 46, wherein the cancer is a lung cancer, a melanoma, a breast cancer, a pancreatic cancer, an ovarian cancer, a colorectal cancer, a prostate cancer, a kidney cancer, a liver cancer, a uterine cancer, a neck cancer, a sarcoma, a myeloma, a brain cancer, or a lymphoma.

50. The use of claim 31, wherein the angiogenesis-related disease is an ophthalmologic condition.

51. The use of claim 50, wherein the ophthalmologic condition is age-related macular degeneration, diabetic retinopathy, or choroidal neovascularization.

52. The use of claim 51, wherein the age related macular degeneration (AMD) is wet AMD or dry AMD.

53. The use of claim 31, wherein the formulation is to be administered to the subject one or more times.

54. The use of claim 31, wherein the formulation is to be administered to the subject once per day, once per week, once per month, once bi-monthly, once every two months, once every three months, once every four months, once every 5 months, or once every 6 months.

55. The use of claim 31, wherein the formulation is to be administered to the subject until one or more signs or symptoms of the angiogenesis-related disease are reduced, wherein the one or more signs or symptoms are shrinking blood vessels, inhibiting endothelial cell proliferation associated with ocular disease, clearing signs or symptoms of bleeding, treating cloudy vision, providing stasis of vision loss, improving vision, preventing leakage of blood vessels, or a combination thereof.

56. The use of claim 31, wherein administration of the medicament results in improvement of the subject's condition and improvement is assessed by determining if one or more of the following factors has occurred: decreased cell proliferation, decreased numbers of cells, increased apoptosis, or decreased survival of at least a portion of the cells comprising the cell proliferative disorder.

57. The use of claim 46, wherein administration of the medicament results in partial or total elimination of the cancer, or metastasis thereof, and/or prolongation of survival of the subject.

58. Use of a formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, a pH of from 4.0 to 5.5, and optionally a surfactant, in the manufacture of a medicament for treating an ophthalmologic condition in a patient in need thereof, wherein the ophthalmologic condition is age-related macular degeneration, diabetic retinopathy, or choroidal neovascularization; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

59. The use of claim 58, wherein the age-related macular degeneration (AMD) is wet AMD or dry AMD.

60. The use of claim 58, wherein the anti-CD105 antibody comprises a light chain variable region (V_L) having an amino acid sequence set forth as SEQ ID NO: 1; a light chain constant region (C_L) having an amino acid sequence set forth as SEQ ID NO: 2; a heavy chain variable region (V_H) having an amino acid sequence set forth as SEQ ID NO: 3; and a constant region (Fc) having an amino acid sequence set forth as SEQ ID NO: 4.

61. The use of claim 58, wherein the anti-CD105 antibody comprises a V_L CDR1 having an amino acid sequence set forth as SEQ ID NO: 5; a V_L CDR2 having an amino acid sequence set forth as SEQ ID NO: 6; a V_L CDR3 having an amino acid sequence set forth as SEQ ID NO: 7; a V_H CDR1 having an amino acid sequence set forth as SEQ ID NO: 8; a V_H CDR2 having an amino acid sequence set forth as SEQ ID NO: 9; and a V_H CDR3 having an amino acid sequence set forth as SEQ ID NO: 10.

62. The use of claim 58, wherein the one or more signs or symptoms of the ophthalmologic condition are shrinking blood vessels, inhibiting endothelial cell proliferation associated with ocular disease, clearing signs or symptoms of bleeding, treating cloudy vision, providing stasis of vision loss, improving vision, preventing leakage of blood vessels, or a combination thereof.

63. The use of claim 58, wherein the formulation is made isotonic with a salt.

64. Use of a formulation comprising from 25 mg/ml to 100 mg/ml of an anti-CD105 antibody, from 10 mM to 20 mM of a buffering agent, up to 240 mM of a polyol, and a pH of from 4.0 to 5.5, in the manufacture of a medicament for preventing or treating a cancer or a metastasis thereof in a subject in need thereof; wherein the buffering agent is histidine, acetate or citrate; and wherein the polyol is trehalose or sorbitol.

65. The use of claim 64, wherein the anti-CD105 antibody comprises a light chain variable region (V_L) having an amino acid sequence set forth as SEQ ID NO: 1; a light chain constant region (C_L) having an amino acid sequence set forth as SEQ ID NO: 2; a heavy

chain variable region (V_H) having an amino acid sequence set forth as SEQ ID NO: 3; and a constant region (Fc) having an amino acid sequence set forth as SEQ ID NO: 4.

66. The use of claim 64, wherein the anti-CD105 antibody comprises a VL CDR1 having an amino acid sequence set forth as SEQ ID NO: 5; a VL CDR2 having an amino acid sequence set forth as SEQ ID NO: 6; a VL CDR3 having an amino acid sequence set forth as SEQ ID NO: 7; a VH CDR1 having an amino acid sequence set forth as SEQ ID NO: 8; a VH CDR2 having an amino acid sequence set forth as SEQ ID NO: 9; and a VH CDR3 having an amino acid sequence set forth as SEQ ID NO: 10.

67. The use of claim 64, wherein administration of the formulation prolongs the life of the subject.

68. The use of claim 64, wherein the cancer is a primary tumor or a metastatic tumor.

69. The use of claim 64, wherein the cancer is a solid tumor.

70. The use of claim 69, wherein the solid tumor is of a tissue or organ selected from the group consisting of skin, melanoma, lung, pancreas, breast, ovary, colon, rectum, stomach, thyroid, larynx, prostate, neck, eye, mouth, throat, esophagus, chest, bone, testis, lymphoid, marrow, bone, sarcoma, sweat gland, liver, kidney and brain.

71. The use of claim 69, wherein the solid tumor is a colon tumor, a breast tumor, a kidney tumor, a lung tumor, a prostate tumor, an ovarian tumor, or a metastasis of any of such tumors.

72. The use of claim 64, wherein administration of the medicament results in improving the subject's condition and can be assessed by determining if one or more of the following factors has occurred: decreased cell proliferation, decreased numbers of cells, increased apoptosis, or decreased survival of at least a portion of the cells comprising the cell proliferative disorder.

73. The use of claim 68, wherein administration of the medicament results in partial or total elimination of a tumor or a metastasic tumor, and/or prolongation of survival of the patient.

74. The use of claim 64, comprising 25 mg/ml of the anti-CD105 antibody.

75. The use of claim 64, comprising 50 mg/ml of the anti-CD105 antibody.

76. The use of claim 64, comprising 100 mg/ml of the anti-CD105 antibody.

77. The use of claim 64, wherein the buffering agent is histidine or acetate.

78. The use of claim 77, comprising 20 mM histidine or acetate.

79. The use of claim 64, comprising 240 mM trehalose.

80. The use of claim 64, comprising 240 mM sorbitol.

81. The use of claim 64, wherein the formulation is made isotonic with a salt.

82. The use of claim 64, comprising a surfactant.

83. The use of claim 82, wherein the surfactant is polysorbate 20, polysorbate 80 or Pluronic® F68.

84. The use of claim 64, wherein the formulation is to be administered intravenously.

85. The use of claim 49, wherein the brain cancer is a glioblastoma multiforme or a glioma.

86. The use of claim 69, wherein the solid tumor is a brain cancer that is a glioblastoma multiforme or a glioma.