

CLAIMS

What is claimed is:

1. A method of treating a cancer in a subject in need thereof, comprising:
determining a DKK1 expression H-score in a sample of the subject's cancer;
and
administering a first amount of a DKK1 inhibitor to the subject determined to have the DKK1 expression H-score above a predetermined value.
2. The method of Claim 1, wherein the predetermined value is an optimal DKK1 expression H-score.
3. The method of Claim 1, wherein the predetermined value is the lower boundary of the upper tertile of DKK1 expression H-scores in a sample of subjects suffering from cancer.
4. The method of any one of Claims 1-3, wherein the cancer is selected from an esophagogastric cancer, a gynecological cancer, or a cholangiocarcinoma.
5. The method of Claim 4, wherein the cancer is selected from an esophageal cancer, a gastro-esophageal junction cancer, a gastric cancer, an epithelial endometrial cancer, an epithelial ovarian cancer, or a cholangiocarcinoma.
6. The method of Claim 4, wherein the patient is immunotherapy-naïve and is suffering from an esophagogastric cancer.
7. The method of Claim 4, wherein the patient is suffering from a gastroesophageal cancer or a gastric cancer.
8. The method of Claim 5, wherein the cancer is esophagogastric cancer and is refractory to one or more immunotherapeutic agents.

9. The method of any one of Claims 1-4, wherein:
 - the cancer is the esophagogastric cancer and the predetermined value is the lower boundary of the upper tertile of DKK1 expression H-scores in a sample of subjects suffering from esophagogastric cancer, or
 - the cancer is the gynecological cancer and the predetermined value is the lower boundary of the upper tertile of DKK1 expression H-scores in a sample of subjects suffering from the gynecological cancer.
10. The method of any one of Claims 1-4, wherein:
 - the cancer is the esophagogastric cancer and the predetermined value is an optimal cutoff value of 38,
 - the cancer is the gynecological cancer and the predetermined value is an optimal cutoff value of 38, or
 - the cancer is cholangiocarcinoma, and the predetermined value is an optimal cutoff value of 38.
11. The method of any one of Claims 1-4, wherein the cancer is the gastric/GEJ cancer, and the predetermined value is 35.
12. The method of Claim 11, wherein the subject is IO-naïve.
13. The method of any one of Claims 1-12, wherein the DKK1 inhibitor is a DKK1 antibody or antigen binding-fragment thereof.
14. The method of any one of claims 1-13, wherein the DKK1 antibody, or antigen binding-fragment thereof, comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3, wherein LCDR1 has the amino sequence of SEQ ID NO:1, LCDR2 has the amino sequence of SEQ ID NO:2, LCDR3 has the amino sequence of SEQ ID NO:3, HCDR1 has the amino sequence of SEQ ID NO:4, HCDR2 has the amino sequence of SEQ ID NO:5, and an HCDR3 has the amino sequence of SEQ ID NO:6.

15. The method of claim 14, wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 7 and the HCVR comprises the amino acid sequence of SEQ ID NO: 8.
16. The method of claim 14 or 15, wherein the LCVR and HCVR comprise amino acid sequences selected from the group consisting of: (i) a LCVR comprising the amino acid sequence of SEQ ID NO: 9 and a HCVR comprising the amino acid sequence of SEQ ID NO: 10; (ii) a LCVR comprising the amino acid sequence of SEQ ID NO: 11 and a HCVR comprising the amino acid sequence of SEQ ID NO: 12; (iii) a LCVR comprising the amino acid sequence of SEQ ID NO: 13 and a HCVR comprising the amino acid sequence of SEQ ID NO: 10; (iv) a LCVR comprising the amino acid sequence of SEQ ID NO: 14 and a HCVR comprising the amino acid sequence of SEQ ID NO: 10.
17. The method of claim 16, wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 11 and the HCVR comprises the amino acid sequence of SEQ ID NO: 12.
18. The method of claim 17, wherein the DKK1 antibody comprises a heavy chain and a light chain amino acid sequence selected from the group consisting of a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and light chain comprising the amino acid sequence of SEQ ID NO: 16, b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 and a light chain comprising the amino acid sequence of SEQ ID NO: 18, c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20, and d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 21.
19. The method of Claim 18, wherein the DKK1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 and a light chain comprising the amino acid sequence of SEQ ID NO: 18.
20. The method of any one of claims 1-19, wherein the subject is a human.

21. The method of any one of Claims 1-20, further comprising administering to the subject a second amount of a second therapeutic agent.
22. The method of Claim 21, wherein the second therapeutic agent is a taxane.
23. The method of Claim 22, wherein the second agent is a paclitaxel.
24. The method of Claim 21, wherein the cancer is the gynecological cancer and the second therapeutic agent is paclitaxel.
25. The method of Claim 24, wherein the cancer is the epithelial endometrial cancer or the epithelial ovarian cancer, the DKK1 antagonist is the DKN-01 antibody, and the second therapeutic agent is paclitaxel.
26. The method of Claim 21, further comprising administering to the subject a third amount of a third therapeutic agent.
27. The method of Claim 26, wherein the second therapeutic agent is gemcitabine and the third therapeutic agent is a cisplatin.
28. The method of Claims 27, wherein the cancer is a biliary tract cancer.
29. A method of treating a cancer in a subject in need thereof, comprising:
 - determining a DKK1 expression % positive value in a sample of the subject's cancer; and
 - administering a first amount of a DKK1 inhibitor to the subject determined to have the DKK1 expression % positive value at or above a predetermined value.
30. The method of Claim 29, wherein the predetermined value is an optimal value of the DKK1 expression % positive values.

31. The method of Claim 29, wherein the predetermined value is the lower boundary of the upper tertile of DKK1 expression % positive values in a sample of subjects suffering from cancer.
32. The method of any one of Claims 29-31, wherein the cancer is selected from an esophagogastric cancer, a gynecological cancer, or a cholangiocarcinoma.
33. The method of Claim 32, wherein the cancer is selected from an esophageal cancer, a gastro-esophageal junction cancer, a gastric cancer, an epithelial endometrial cancer, an epithelial ovarian cancer, or a cholangiocarcinoma.
34. The method of Claim 32, wherein the patient is immunotherapy-naïve and is suffering from an esophagogastric cancer.
35. The method of Claim 32, wherein the patient is suffering from a gastroesophageal cancer or a gastric cancer.
36. The method of Claim 32, wherein the cancer is esophagogastric cancer and is refractory to one or more immunotherapeutic agents.
37. The method of any one of Claims 29-32, wherein:
 - the cancer is the esophagogastric cancer and the predetermined value is the lower boundary of the upper tertile of DKK1 expression % positive values in a sample of subjects suffering from esophagogastric cancer, or
 - the cancer is the gynecological cancer and the predetermined value is the lower boundary of the upper tertile of DKK1 expression % positive values in a sample of subjects suffering from the gynecological cancer.
38. The method of any one of Claims 29-32, wherein:
 - the cancer is the esophagogastric cancer and the predetermined value is 26%.
39. The method of any one of Claims 29-32, wherein:
 - the cancer is GC/GEJ and the predetermined value is 20%.

40. The method of Claim 39, wherein the subject is IO-naïve.
41. The method of any one of Claims 29-40, wherein the DKK1 inhibitor is a DKK1 antibody or antigen binding-fragment thereof.
42. The method of any one of claims 29-41, wherein the DKK1 antibody, or antigen binding-fragment thereof, comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3, wherein LCDR1 has the amino sequence of SEQ ID NO:1, LCDR2 has the amino sequence of SEQ ID NO:2, LCDR3 has the amino sequence of SEQ ID NO:3, HCDR1 has the amino sequence of SEQ ID NO:4, HCDR2 has the amino sequence of SEQ ID NO:5, and an HCDR3 has the amino sequence of SEQ ID NO:6.
43. The method of claim 42, wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 7 and the HCVR comprises the amino acid sequence of SEQ ID NO: 8.
44. The method of claim 42 or 43, wherein the LCVR and HCVR comprise amino acid sequences selected from the group consisting of: (i) a LCVR comprising the amino acid sequence of SEQ ID NO: 9 and a HCVR comprising the amino acid sequence of SEQ ID NO: 10; (ii) a LCVR comprising the amino acid sequence of SEQ ID NO: 11 and a HCVR comprising the amino acid sequence of SEQ ID NO: 12; (iii) a LCVR comprising the amino acid sequence of SEQ ID NO: 13 and a HCVR comprising the amino acid sequence of SEQ ID NO: 10; (iv) a LCVR comprising the amino acid sequence of SEQ ID NO: 14 and a HCVR comprising the amino acid sequence of SEQ ID NO: 10.
45. The method of claim 44, wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 11 and the HCVR comprises the amino acid sequence of SEQ ID NO: 12.

46. The method of claim 45, wherein the DKK1 antibody comprises a heavy chain and a light chain amino acid sequence selected from the group consisting of a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and light chain comprising the amino acid sequence of SEQ ID NO: 16, b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 and a light chain comprising the amino acid sequence of SEQ ID NO: 18, c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20, and d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 21.
47. The method of Claim 46, wherein the DKK1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 and a light chain comprising the amino acid sequence of SEQ ID NO: 18.
48. The method of any one of claims 29-47, wherein the subject is a human.
49. The method of any one of Claims 29-48, further comprising administering to the subject a second amount of a second therapeutic agent.
50. The method of Claim 49, wherein the second therapeutic agent is a taxane.
51. The method of Claim 50, wherein the second agent is a paclitaxel.
52. The method of Claim 49, wherein the cancer is the gynecological cancer and the second therapeutic agent is paclitaxel.
53. The method of Claim 52, wherein the cancer is the epithelial endometrial cancer or the epithelial ovarian cancer, the DKK1 antagonist is the DKN-01 antibody, and the second therapeutic agent is paclitaxel.
54. The method of Claim 50, further comprising administering to the subject a third amount of a third therapeutic agent.

55. The method of Claim 54, wherein the second therapeutic agent is gemcitabine and the third therapeutic agent is a cisplatin.
56. The method of Claims 55, wherein the cancer is a biliary tract cancer.
57. The method of Claim 4, wherein the cancer is gastric/GEJ cancer and is refractory to one or more immunotherapeutic agents.
58. The method of Claim 4, wherein the cancer is gastric cancer and is refractory to one or more immunotherapeutic agents.
59. The method of Claim 4, wherein the cancer is GEJ cancer and is refractory to one or more immunotherapeutic agents.
60. The method of any one of Claims 57-59, wherein the predetermined value is 59.
61. The method of Claim 32, wherein the cancer is gastric/GEJ cancer and is refractory to one or more immunotherapeutic agents.
62. The method of Claim 32, wherein the cancer is gastric cancer and is refractory to one or more immunotherapeutic agents.
63. The method of Claim 32, wherein the cancer is GEJ cancer and is refractory to one or more immunotherapeutic agents.
64. The method of any one of Claims 61-63, wherein the predetermined value is 33%.
65. The method of Claim 30, wherein the cancer is the esophagogastric cancer (EGC) and the predetermined value is an optimal cutoff value of 23%.
66. A method of treating a cancer in a subject in need thereof, comprising:
 - determining a DKK1 expression H-score in a sample of the subject's cancer;
 - and

administering a first amount of a DKK1 inhibitor to the subject determined to have the DKK1 expression H-score at or above 30.

67. The method of Claim 66, wherein the subject is determined to have the DKK-1 H-score at or above 35.
68. The method of any one of Claims 66 or 67, wherein the cancer is GEJ/GC.