

CLAIMS

~~What is claimed is:~~

1. Use of a DKK1 inhibitor in the manufacture of a medicament for ~~A method of treating a~~ cancer in a subject in need thereof, ~~comprising~~wherein:

~~determining~~ a DKK1 expression H-score is determined in a sample of the subject's cancer; and

~~administering~~ a first amount of a DKK1 inhibitor is to be administered to the subject determined to have the DKK1 expression H-score above a predetermined value.

2. The ~~method-use~~ of Claim 1, wherein the predetermined value is an optimal DKK1 expression H-score.

3. The ~~method-use~~ 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-use~~ 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-use~~ 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-use~~ of Claim 4, wherein the patient-subject is immunotherapy-naïve and is suffering from an esophagogastric cancer.

7. The ~~method-use~~ of Claim 4, wherein the patient-subject is suffering from a gastroesophageal cancer or a gastric cancer.

8. The ~~method~~-use of Claim 5, wherein the cancer is esophagogastric cancer and is refractory to one or more immunotherapeutic agents.
9. The ~~method~~-use 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~~-use 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~~-use of any one of Claims 1-4, wherein the cancer is the gastric/GEJ cancer, and the predetermined value is 35.
12. The ~~method~~-use of Claim 11, wherein the subject is IO-naïve.
13. The ~~method~~-use of any one of Claims 1-12, wherein the DKK1 inhibitor is a DKK1 antibody or antigen binding-fragment thereof.
14. The ~~method~~-use 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-use~~ 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-use~~ 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-use~~ 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-use~~ 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-use~~ 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-use~~ of any one of claims 1-19, wherein the subject is a human.
21. The ~~method-use~~ of any one of Claims 1-20, ~~wherein further comprising administering to the subject~~ a second amount of a second therapeutic agent is to be conjointly administered to the subject.
22. The ~~method-use~~ of Claim 21, wherein the second therapeutic agent is a taxane.
23. The ~~method-use~~ of Claim 22, wherein the second agent is a paclitaxel.
24. The ~~method-use~~ of Claim 21, wherein the cancer is the gynecological cancer and the second therapeutic agent is paclitaxel.
25. The ~~method-use~~ 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-use~~ of Claim 21, ~~wherein further comprising administering to the subject a~~ third amount of a third therapeutic agent is to be conjointly administered to the subject.
27. The ~~method-use~~ of Claim 26, wherein the second therapeutic agent is gemcitabine and the third therapeutic agent is a cisplatin.
28. The ~~method-use~~ of Claims 27, wherein the cancer is a biliary tract cancer.

29. Use of a DKK1 inhibitor in the manufacture of a medicament for ~~A method of treating a~~ cancer in a subject in need thereof, ~~comprising~~ wherein:
- ~~determining~~ a DKK1 expression % positive value is determined in a sample of the subject's cancer; and
- ~~administering~~ a first amount of a DKK1 inhibitor is to be administered to the subject determined to have the DKK1 expression % positive value at or above a predetermined value.
30. The ~~method-use~~ of Claim 29, wherein the predetermined value is an optimal value of the DKK1 expression % positive values.
31. The ~~method-use~~ 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-use~~ 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-use~~ 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-use~~ of Claim 32, wherein the ~~patient-subject~~ is immunotherapy-naïve and is suffering from an esophagogastric cancer.
35. The ~~method-use~~ of Claim 32, wherein the ~~patient-subject~~ is suffering from a gastroesophageal cancer or a gastric cancer.
36. The ~~method-use~~ of Claim 32, wherein the cancer is esophagogastric cancer and is refractory to one or more immunotherapeutic agents.

37. The ~~method~~-use 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~~-use of any one of Claims 29-32, wherein:
- the cancer is the esophagogastric cancer and the predetermined value is 26%.
39. The ~~method~~-use of any one of Claims 29-32, wherein:
- the cancer is GC/GEJ and the predetermined value is 20%.
40. The ~~method~~-use of Claim 39, wherein the subject is IO-naïve.
41. The ~~method~~-use of any one of Claims 29-40, wherein the DKK1 inhibitor is a DKK1 antibody or antigen binding-fragment thereof.
42. The ~~method~~-use 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~~-use 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~~-use 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~~-use 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~~-use 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~~-use 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~~-use of any one of claims 29-47, wherein the subject is a human.

49. The ~~method-use~~ of any one of Claims 29-48, ~~wherein further comprising administering to the subject~~ a second amount of a second therapeutic agent is to be conjointly administered to the subject.
50. The ~~method-use~~ of Claim 49, wherein the second therapeutic agent is a taxane.
51. The ~~method-use~~ of Claim 50, wherein the second agent is a paclitaxel.
52. The ~~method-use~~ of Claim 49, wherein the cancer is the gynecological cancer and the second therapeutic agent is paclitaxel.
53. The ~~method-use~~ 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-use~~ of Claim 50, ~~wherein further comprising administering to the subject a~~ third amount of a third therapeutic agent is to be conjointly administered to the subject.
55. The ~~method-use~~ of Claim 54, wherein the second therapeutic agent is gemcitabine and the third therapeutic agent is a cisplatin.
56. The ~~method-use~~ of Claims 55, wherein the cancer is a biliary tract cancer.
57. The ~~method-use~~ of Claim 4, wherein the cancer is gastric/GEJ cancer and is refractory to one or more immunotherapeutic agents.
58. The ~~method-use~~ of Claim 4, wherein the cancer is gastric cancer and is refractory to one or more immunotherapeutic agents.
59. The ~~method-use~~ of Claim 4, wherein the cancer is GEJ cancer and is refractory to one or more immunotherapeutic agents.

60. The ~~method~~use of any one of Claims 57-59, wherein the predetermined value is 59.
61. The ~~method~~use of Claim 32, wherein the cancer is gastric/GEJ cancer and is refractory to one or more immunotherapeutic agents.
62. The ~~method~~use of Claim 32, wherein the cancer is gastric cancer and is refractory to one or more immunotherapeutic agents.
63. The ~~method~~use of Claim 32, wherein the cancer is GEJ cancer and is refractory to one or more immunotherapeutic agents.
64. The ~~method~~use of any one of Claims 61-63, wherein the predetermined value is 33%.
65. The ~~method~~use of Claim 30, wherein the cancer is the esophagogastric cancer (EGC) and the predetermined value is an optimal cutoff value of 23%.
66. Use of a DKK1 inhibitor in the manufacture of a medicament for ~~A method of treating a~~ cancer in a subject in need thereof, ~~comprising wherein:~~
 ~~determining~~ a DKK1 expression H-score is determined in a sample of the subject's cancer; and
 ~~administering~~ a first amount of a DKK1 inhibitor is to be administered to the subject determined to have the DKK1 expression H-score at or above 30.
67. The ~~method~~use of Claim 66, wherein the subject is determined to have the DKK-1 H-score at or above 35.
68. The ~~method~~use of any one of Claims 66 or 67, wherein the cancer is GEJ/GC.