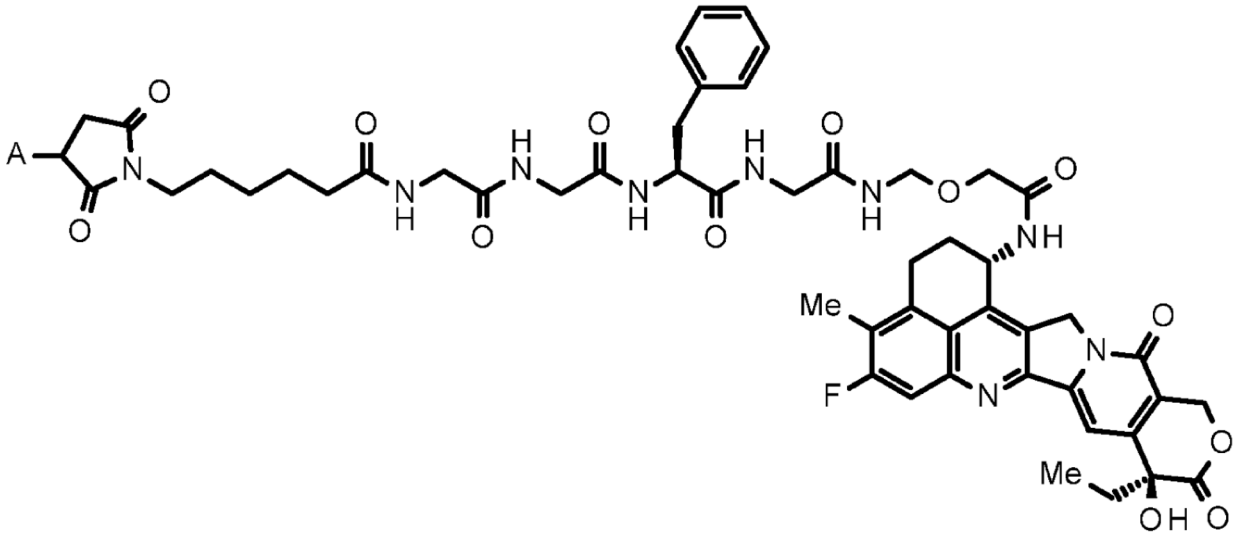
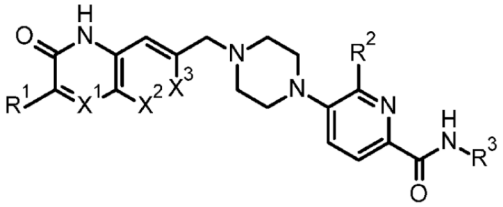
CLAIMS

1. ~~A pharmaceutical product comprising~~ Use of an anti-HER2 antibody-drug conjugate in the preparation of a medicament for treating cancer, wherein the anti-HER2 antibody-drug conjugate is to be administered in combination with ~~and~~ a PARP1 selective inhibitor ~~for administration in combination~~, and wherein the anti-HER2 antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:



wherein A represents the connecting position to an antibody, is conjugated to an anti-HER2 antibody via a thioether bond.

2. The ~~pharmaceutical product~~ use according to claim 1, wherein the PARP1 selective inhibitor is a compound represented by the following formula (I):



(I)

wherein:

X^1 and X^2 are each independently selected from N and C(H),

X^3 is independently selected from N and $C(R^4)$, wherein R^4 is H or fluoro,

R^1 is C_{1-4} alkyl or C_{1-4} fluoroalkyl,

R^2 is independently selected from H, halo, C_{1-4} alkyl, and C_{1-4} fluoroalkyl, and

R^3 is H or C_{1-4} alkyl,

or a pharmaceutically acceptable salt thereof

provided that:

when X^1 is N, then X^2 is C(H), and X^3 is $C(R^4)$,

when X^2 is N, then X^1 ~~=~~ is C(H), and X^3 is $C(R^4)$, and

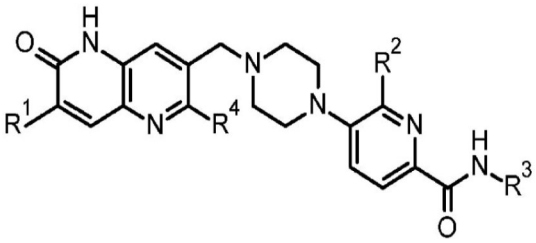
when X^3 is N, then X^1 and X^2 are both C(H).

3. The ~~pharmaceutical product~~ use according to claim 2 wherein, in formula (I), R^3 is C_{1-4} alkyl.

4. The ~~pharmaceutical product~~ use according to claim 2 wherein, in formula (I), R^3 is methyl.

5. The ~~pharmaceutical product~~ use according to any one of claims 2 to 4 wherein, in formula (I), R^1 is ethyl.

6. The ~~pharmaceutical product~~ use according to claim 1, wherein the PARP1 selective inhibitor is a compound represented by the following formula (Ia):



(Ia)

wherein

R^1 is C_{1-4} alkyl,

R^2 is selected from H, halo, C_{1-4} alkyl, and C_{1-4} fluoroalkyl,

R^3 is H or C_{1-4} alkyl, and

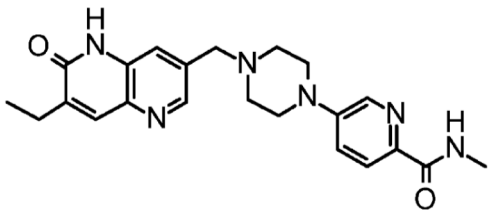
R^4 is H,

or a pharmaceutically acceptable salt thereof.

7. The ~~pharmaceutical product~~ use according to claim 6 wherein, in formula (Ia), R^2 is H or halo.

8. The ~~pharmaceutical product~~ use according to claim 6 wherein, in formula (Ia), R^1 is ethyl, R^2 is selected from H, chloro and fluoro, and R^3 is methyl.

9. The ~~pharmaceutical product~~ use according to claim 1, wherein the PARP1 selective inhibitor is AZD5305 represented by the following formula:



or a pharmaceutically acceptable salt thereof.

10. The ~~pharmaceutical product~~ use according to any one of claims 1 to 9, wherein the anti-HER2 antibody is an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence represented by SEQ ID NO: 3, CDRH2 consisting of an amino acid sequence represented by SEQ ID NO: 4 and CDRH3 consisting of an amino acid sequence represented by SEQ ID NO: 5, and a light chain comprising CDRL1 consisting of an amino acid sequence represented by SEQ ID NO: 6, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 1 to 3 of SEQ ID NO: 7 and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 8.

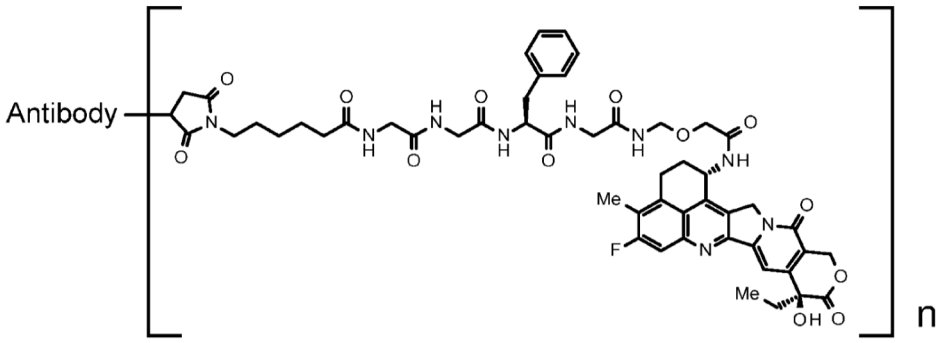
11. The ~~pharmaceutical product~~ use according to any one of claims 1 to 9, wherein the anti-HER2 antibody is an antibody comprising a heavy chain comprising a heavy chain variable region consisting of an amino acid sequence represented by SEQ ID NO: 9 and a light chain comprising a light chain variable region consisting of an amino acid sequence represented by SEQ ID NO: 10.

12. The ~~pharmaceutical product~~ use according to any one of claims 1 to 9, wherein the anti-HER2 antibody is an antibody comprising a

heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 1 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 2.

13. The ~~pharmaceutical product~~ use according to any one of claims 1 to 9, wherein the anti-HER2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 11 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 2.

14. The ~~pharmaceutical product~~ use according to any one of claims 1 to 13, wherein the anti-HER2 antibody-drug conjugate is represented by the following formula:



wherein 'Antibody' indicates the anti-HER2 antibody conjugated to the drug-linker via a thioether bond, and n indicates an average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate, wherein n is in the range of from 7 to 8.

15. The ~~pharmaceutical product~~ use according to any one of claims 1 to 14, wherein the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan (DS-8201).

16. The ~~pharmaceutical product~~use according to any one of claims 1 to 15, wherein ~~the product is a composition comprising~~ the anti-HER2 antibody-drug conjugate and the PARP1 selective inhibitor~~,~~ ~~for~~are to be simultaneously ~~administration~~administered.

17. The ~~pharmaceutical product~~ use according to any one of claims 1 to 15, wherein ~~the product is a combined preparation comprising~~ the anti-HER2 antibody-drug conjugate and the PARP1 selective inhibitor~~, for~~are ~~—~~to be sequentially administered ~~or simultaneous administration~~.

~~18. The pharmaceutical product according to any one of claims 1 to 17, wherein the product is for treating cancer.~~

~~19~~18. The ~~pharmaceutical product~~use according to claim ~~18~~1, wherein the cancer is at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, head-and-neck cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, digestive tract stromal tumor, uterine cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma.

~~20~~19. The ~~pharmaceutical product~~ use according to claim ~~19~~ 18, wherein the cancer is breast cancer.

~~21~~20. The ~~pharmaceutical product~~ use according to claim ~~20~~ 19, wherein the breast cancer has a HER2 status score of IHC 3+.

~~22~~21. The ~~pharmaceutical product~~ use according to claim ~~20~~ 19, wherein the breast cancer is HER2 low-expressing breast cancer.

~~23~~22. The ~~pharmaceutical product~~ use according to claim ~~20~~ 19, wherein the breast cancer has a HER2 status score of IHC 2+.

~~24~~23. The ~~pharmaceutical product~~ use according to claim ~~20~~ 19, wherein the breast cancer has a HER2 status score of IHC 1+.

~~25~~24. The ~~pharmaceutical product~~ use according to claim ~~20~~ 19, wherein the breast cancer has a HER2 status score of IHC >0 and <1+.

~~26~~25. The ~~pharmaceutical product~~ use according to claim ~~20~~ 19, wherein the breast cancer is triple-negative breast cancer.

~~27~~26. The ~~pharmaceutical product~~ use according to claim ~~18~~19, wherein the cancer is gastric cancer.

~~28~~27. The ~~pharmaceutical product~~ use according to claim ~~18~~19, wherein the cancer is colorectal cancer.

~~29~~28. The ~~pharmaceutical product~~ use according to claim ~~18~~19, wherein the cancer is lung cancer.

~~30~~29. The ~~pharmaceutical product~~ use according to claim ~~29~~ 28, wherein the lung cancer is non-small cell lung cancer.

~~31~~30. The ~~pharmaceutical product~~ use according to claim ~~18~~19, wherein the cancer is pancreatic cancer.

~~32~~31. The ~~pharmaceutical product~~ use according to claim ~~18~~19, wherein the cancer is ovarian cancer.

~~33~~32. The ~~pharmaceutical product~~ use according to claim ~~18~~19, wherein the cancer is prostate cancer.

~~34~~33. The ~~pharmaceutical product~~ use according to claim ~~18~~19, wherein the cancer is kidney cancer.

~~35. A pharmaceutical product as defined in any one of claims 1 to 17, for use in treating cancer.~~

~~36. The pharmaceutical product for the use according to claim 35, wherein the cancer is at least one selected from the group~~

~~consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, head-and-neck cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, digestive tract stromal tumor, uterine cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma.~~

~~37. The pharmaceutical product for the use according to claim 35, wherein the cancer is breast cancer.~~

~~38. The pharmaceutical product for the use according to claim 37, wherein the breast cancer has a HER2 status score of IHC 3+.~~

~~39. The pharmaceutical product for the use according to claim 37, wherein the breast cancer is HER2 low-expressing breast cancer.~~

~~40. The pharmaceutical product for the use according to claim 37, wherein the breast cancer has a HER2 status score of IHC 2+.~~

~~41. The pharmaceutical product for the use according to claim 37, wherein the breast cancer has a HER2 status score of IHC 1+.~~

~~42. The pharmaceutical product for the use according to claim 37, wherein the breast cancer has a HER2 status score of IHC >0 and <1+.~~

~~43. The pharmaceutical product for the use according to claim 37, wherein the breast cancer is triple-negative breast cancer.~~

~~44. The pharmaceutical product for the use according to claim 35, wherein the cancer is gastric cancer.~~

~~45. The pharmaceutical product for the use according to claim 35, wherein the cancer is colorectal cancer.~~

~~46. The pharmaceutical product for the use according to claim 35, wherein the cancer is lung cancer.~~

~~47. The pharmaceutical product for the use according to claim 46, wherein the lung cancer is non-small cell lung cancer.~~

~~48. The pharmaceutical product for the use according to claim 35, wherein the cancer is pancreatic cancer.~~

~~49. The pharmaceutical product for the use according to claim 35, wherein the cancer is ovarian cancer.~~

~~50. The pharmaceutical product for the use according to claim 35, wherein the cancer is prostate cancer.~~

~~51. The pharmaceutical product for the use according to claim 35, wherein the cancer is kidney cancer.~~

~~52. Use of an anti-HER2 antibody-drug conjugate or a PARP1 selective inhibitor in the manufacture of a medicament for administration of the anti-HER2 antibody-drug~~

~~conjugate and the PARP1 selective inhibitor in combination, wherein the anti-HER2 antibody-drug conjugate and the PARP1 selective inhibitor are as defined in any one of claims 1 to 15, for treating cancer.~~

~~53. The use according to claim 52, wherein the cancer is at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, head-and-neck cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, digestive tract stromal tumor, uterine cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma.~~

~~54. The use according to claim 52, wherein the cancer is breast cancer.~~

~~55. The use according to claim 54, wherein the breast cancer has a HER2 status score of IHC 3+.~~

~~56. The use according to claim 54, wherein the breast cancer is HER2 low-expressing breast cancer.~~

~~57. The use according to claim 54, wherein the breast cancer has a HER2 status score of IHC 2+.~~

~~58. The use according to claim 54, wherein the breast cancer has a HER2 status score of IHC 1+.~~

~~59. The use according to claim 54, wherein the breast cancer has a HER2 status score of IHC >0 and <1+.~~

~~60. The use according to claim 54, wherein the breast cancer is triple-negative breast cancer.~~

~~61. The use according to claim 52, wherein the cancer is gastric cancer.~~

~~62. The use according to claim 52, wherein the cancer is colorectal cancer.~~

~~63. The use according to claim 52, wherein the cancer is lung cancer.~~

~~64. The use according to claim 63, wherein the lung cancer is non-small cell lung cancer.~~

~~65. The use according to claim 52, wherein the cancer is pancreatic cancer.~~

~~66. The use according to claim 52, wherein the cancer is ovarian cancer.~~

~~67. The use according to claim 52, wherein the cancer is prostate cancer.~~

~~68. The use according to claim 52, wherein the cancer is kidney cancer.~~

~~69. The use according to any one of claims 52 to 68 wherein the medicament is a composition comprising the anti-HER2 antibody-drug conjugate and the PARP1 selective inhibitor, for simultaneous administration.~~

~~70. The use according to any one of claims 52 to 68 wherein the medicament is a combined preparation comprising the anti-HER2 antibody-drug conjugate and the PARP1 selective inhibitor, for sequential or simultaneous administration.~~

~~71. A method of treating cancer comprising administering an anti-HER2 antibody-drug conjugate and a PARP1 selective inhibitor as~~

~~defined in any one of claims 1 to 15 in combination to a subject in need thereof.~~

~~72. The method according to claim 71, wherein the cancer is at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, head-and-neck cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, digestive tract stromal tumor, uterine cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma.~~

~~73. The method according to claim 71, wherein the cancer is breast cancer.~~

~~74. The method according to claim 73, wherein the breast cancer has a HER2 status score of IHC 3+.~~

~~75. The method according to claim 73, wherein the breast cancer is HER2 low-expressing breast cancer.~~

~~76. The method according to claim 73, wherein the breast cancer has a HER2 status score of IHC 2+.~~

~~77. The method according to claim 73, wherein the breast cancer has a HER2 status score of IHC 1+.~~

~~78. The method according to claim 73, wherein the breast cancer has a HER2 status score of IHC >0 and <1+.~~

~~79. The method according to claim 73, wherein the breast cancer is triple-negative breast cancer.~~

~~80. The method according to claim 71, wherein the cancer is gastric cancer.~~

~~81. The method according to claim 71, wherein the cancer is colorectal cancer.~~

~~82. The method according to claim 71, wherein the cancer is lung cancer.~~

~~83. The method according to claim 82, wherein the lung cancer is non-small cell lung cancer.~~

~~84. The method according to claim 71, wherein the cancer is pancreatic cancer.~~

~~85. The method according to claim 71, wherein the cancer is ovarian cancer.~~

~~86. The method according to claim 71, wherein the cancer is prostate cancer.~~

~~87. The method according to claim 71, wherein the cancer is kidney cancer.~~

~~88. The method according to any one of claims 71 to 87, wherein the method comprises administering the anti-HER2 antibody-drug conjugate and the PARP1 selective inhibitor sequentially.~~

~~89. The method according to any one of claims 71 to 87, wherein the method comprises administering the anti-HER2 antibody-drug conjugate and the PARP1 selective inhibitor simultaneously.~~