[Non-patent Literature 32] Vogel CL, et al., J Clin Oncol. 2002;20(3):719-726.

[Non-patent Literature 33] Baselga et al., J. Clin. Oncol. 14:737-744 (1996).

[Non-patent Literature 34] Howard A. et al., J Clin Oncol 2011;29:398-405.

[Non-patent Literature 35] Adams CW, et al., Cancer Immunol Immunother. 2006;6:717-727.

[Non-patent Literature 36] Ogitani Y. et al., Clinical Cancer Research, 2016, Oct 15;22(20):5097-5108, Epub 2016 Mar 29.

[Summary]

[Technical Problem]

[0014]

It is known that when administration for treatment is continued, an anticancer drug is confirmed to temporarily have an effect, but loses its therapeutic effect due to the acquired resistance (hereinafter, also referred to as "secondary resistance" in the present disclosure) of cancer cells. For example, it is known that as a result of treating HER2-expressing cancer with trastuzumab emtansine, cancer that has acquired resistance or refractoriness to trastuzumab emtansine occurs newly. Thus, there is a demand for a medicine that can provide a novel treatment method effective for cancer that has acquired such resistance (hereinafter, also referred to as "secondary resistant cancer" in the present disclosure). A main object of

the present disclosure is to provide a therapeutic agent and a treatment method having a sufficient therapeutic effect even on HER2-expressing cancer that has acquired resistance or refractoriness by treatment with an existing anti-HER2 drug.

Furthermore, Cancer originally having resistance or refractoriness to existing anti-HER2 drug, albeit expressing HER2 (in other words, HER2-expressing cancer having resistance or refractoriness intrinsic to the cancer to an existing anti-HER2 drug independently of treatment with the existing anti-HER2 drug) is known. Examples of such HER2-expressing cancer can include HER2 low-expressing cancer and solid cancer other than breast cancer and gastric cancer (e.g., colorectal cancer and non-small cell lung cancer). Another main object of the present disclosure is to provide a therapeutic agent and a treatment method having a sufficient therapeutic effect even on such HER2-expressing cancer.

[Solution to Problem]

[0015]

The present inventors found in preclinical and clinical trials that an antibody-drug conjugate in which a linker and a drug represented by the following formula:

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

are conjugated to an anti-HER2 antibody exhibits an excellent antitumor effect on HER2-expressing cancer having resistance or refractoriness to an existing anti-HER2 drug and has also favorable safety profile. This antibody-drug conjugate can be expected to offer effective treatment even for secondary resistant cancer.

[0016]

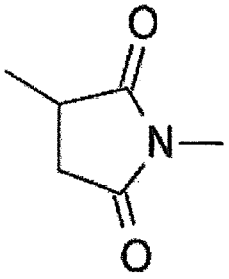
In one aspect, the invention refers to the use of an antibody-drug conjugate in which a linker and a drug represented by the following formula are conjugated to an anti-HER2 antibody, for the production of a medicine for treating HER2-expressing cancer having resistance or refractoriness to an existing anti-HER2 drug:

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

wherein

-(Succinimid-3-yl-N)- has a structure represented by the following formula:

[Formula 1]

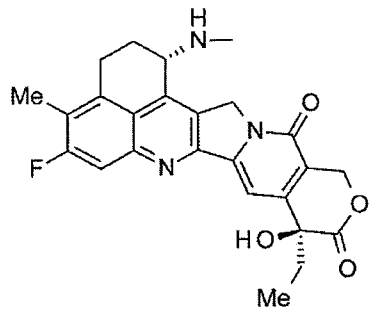


which is connected to the anti-HER2 antibody at position 3 thereof via a thioether bond and is

connected to the methylene group in the linker structure containing this structure on the nitrogen atom at position 1,

-(NH-DX) represents a group represented by the following formula:

[Formula 2]



wherein the nitrogen atom of the amino group at position 1 is the connecting position, and

-GGFG- represents the tetrapeptide residue of -Gly-Gly-Phe-Gly-.

Specifically, the present disclosure provides the following [1] to [144].

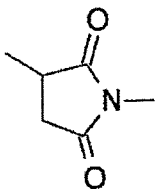
[1] A therapeutic agent for HER2-expressing cancer having resistance or refractoriness to an existing anti-HER2 drug, comprising an antibody-drug conjugate in which a linker and a drug represented by the following formula are conjugated to an anti-HER2 antibody:

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

wherein

-(Succinimid-3-yl-N)- has a structure represented by the following formula:

[Formula 4]



which is connected to the anti-HER2 antibody at position 3 thereof via a thioether bond and is

Claims

[Claim 1]

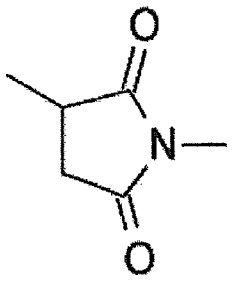
Use of an antibody-drug conjugate in which a linker and a drug represented by the following formula are conjugated to an anti-HER2 antibody, for the production of a medicine for treating HER2-expressing cancer having resistance or refractoriness to an existing anti-HER2 drug:

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

wherein

-(Succinimid-3-yl-N)- has a structure represented by the following formula:

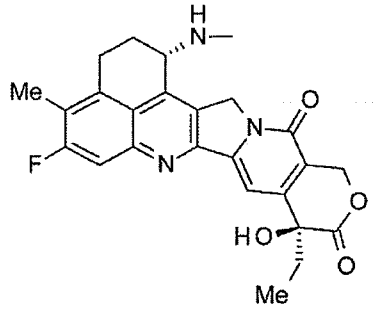
[Formula 1]



which is connected to the anti-HER2 antibody at position 3 thereof via a thioether bond and is connected to the methylene group in the linker structure containing this structure on the nitrogen atom at position 1,

-(NH-DX) represents a group represented by the following formula:

[Formula 2]



wherein the nitrogen atom of the amino group at position 1 is the connecting position, and

-GGFG- represents the tetrapeptide residue of -Gly-Gly-Phe-Gly-.

[Claim 2]

The use according to claim 1, wherein the resistance or refractoriness is resistance or refractoriness acquired by the cancer due to treatment with the existing anti-HER2 drug.

[Claim 3]

The use according to claim 1, wherein the resistance or refractoriness is resistance or refractoriness intrinsic to the cancer independently of treatment with the existing anti-HER2 drug.

[Claim 4]

The use according to any of claims 1 to 3, wherein the existing anti-HER2 drug is at least one selected

from the group consisting of trastuzumab emtansine, trastuzumab, pertuzumab, and lapatinib.

[Claim 5]

The use according to any of claims 1 to 3, wherein the existing anti-HER2 drug is trastuzumab emtansine.

[Claim 6]

The use according to any of claims 1 to 3, wherein the existing anti-HER2 drug is trastuzumab.

[Claim 7]

The use according to any of claims 1 to 6, wherein the medicine is to be administered to a patient having a history of treatment with an existing anticancer drug.

[Claim 8]

The use according to claim 7, wherein the existing anticancer drug comprises at least one selected from the group consisting of trastuzumab emtansine, trastuzumab, pertuzumab, lapatinib, irinotecan, cisplatin, carboplatin, oxaliplatin, fluorouracil, gemcitabine, capecitabine, paclitaxel, docetaxel, doxorubicin, epirubicin, cyclophosphamide, mitomycin C, a tegafur-gimeracil-oteracil combination drug, cetuximab, panitumumab, bevacizumab, ramucirumab, regorafenib, a trifluridine-tipiracil combination drug, gefitinib, erlotinib, afatinib, methotrexate, and pemetrexed.

[Claim 9]

The use according to claim 7, wherein the existing anticancer drug comprises trastuzumab emtansine.

[Claim 10]

The use according to claim 7, wherein the existing anticancer drug comprises trastuzumab.

[Claim 11]

The use according to claim 7, wherein the existing anticancer drug comprises irinotecan.

[Claim 12]

The use according to any of claims 1 to 11, wherein an average number of units of the drug-linker structure conjugated per antibody molecule of the antibody-drug conjugate is in a range of 7 to 8.

[Claim 13]

The use according to any of claims 1 to 11, wherein an average number of units of the drug-linker structure conjugated per antibody molecule of the antibody-drug conjugate is in a range of 7.5 to 8.

[Claim 14]

The use according to any of claims 1 to 13, wherein the anti-HER2 antibody in the antibody-drug conjugate is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 1 to 449 of SEQ ID NO: 1 and a light chain consisting of an amino acid sequence consisting of amino acid residues 1 to 214 of SEQ ID NO: 2.

[Claim 15]

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

[Claim 16]

The use according to any of claims 1 to 15, wherein a dose per administration of the antibody-drug conjugate is in a range of 5.4 mg/kg to 8 mg/kg.

[Claim 17]

The use according to any of claims 1 to 15, wherein a dose per administration of the antibody-drug conjugate is 5.4 mg/kg.

[Claim 18]

The use according to any of claims 1 to 15, wherein a dose per administration of the antibody-drug conjugate is 6.4 mg/kg.

[Claim 19]

The use according to any of claims 1 to 15, wherein a dose per administration of the antibody-drug conjugate is 7.4 mg/kg.

[Claim 20]

The use according to any of claims 1 to 15, wherein a dose per administration of the antibody-drug conjugate is 8 mg/kg.

[Claim 21]

The use according to any of claims 1 to 20, wherein the antibody-drug conjugate is to be administered once every 3 weeks.

[Claim 22]

The use according to any of claims 1 to 21, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, non-small cell lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, bile duct cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine cancer and sarcoma.

[Claim 23]

The use according to any of claims 1 to 21, wherein the cancer is breast cancer.

[Claim 24]

The use according to any of claims 1 to 21, wherein the cancer is gastric cancer.

[Claim 25]

The use according to any of claims 1 to 21, wherein the cancer is gastric cancer and esophagogastric junction adenocarcinoma.

[Claim 26]

The use according to any of claims 1 to 21, wherein the cancer is colorectal cancer.

[Claim 27]

The use according to any of claims 1 to 21, wherein the cancer is non-small cell lung cancer.

[Claim 28]

The use according to any of claims 1 to 21, wherein the cancer is salivary gland cancer.

[Claim 29]

The use according to any of claims 1 to 28, wherein the HER2-expressing cancer is HER2-overexpressing cancer.

[Claim 30]

The use according to claim 29, wherein the HER2-overexpressing cancer is cancer given a score of 3+ for the expression of HER2 in an immunohistochemical method.

[Claim 31]

The use according to claim 29, wherein the HER2-overexpressing cancer is cancer given a score of 2+ for the expression of HER2 in an immunohistochemical method and determined as positive for the expression of HER2 in an in situ hybridization method.

[Claim 32]

The use according to any of claims 1 to 28, wherein the HER2-expressing cancer is HER2 low-expressing cancer.

[Claim 33]

The use according to claim 32, wherein the HER2 low-expressing cancer is cancer given a score of 2+ for the expression of HER2 in an immunohistochemical method

and determined as negative for the expression of HER2 in an in situ hybridization method.

[Claim 34]

The use according to claim 32, wherein the HER2 low-expressing cancer is cancer given a score of 1+ for the expression of HER2 in an immunohistochemical method.

[Claim 35]

The use according to any of claims 1 to 34, wherein the cancer is inoperable or recurrent cancer.

[Claim 36]

The use according to any of claims 1 to 35, comprising a pharmaceutically acceptable formulation component.