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]

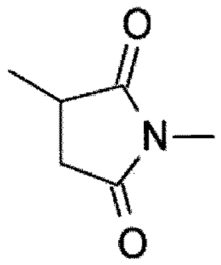
In one aspect, the invention refers to the use of an antibody-drug conjugate in which a linker and a drug represented by the following formula are conjugated to an anti-HER2 antibody, for the production of a medicine for treating a human subject with HER2-expressing cancer having resistance or refractoriness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

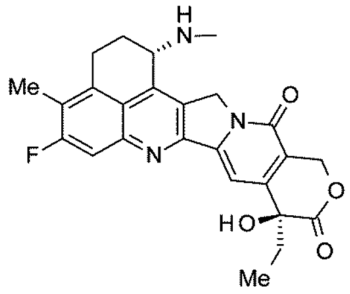


which is connected to the anti-HER2 antibody at position 3 thereof via a thioether bond and is

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-,

wherein the existing anti-HER2 drug is at least one selected from the group consisting of trastuzumab emtansine, trastuzumab, pertuzumab, and lapatinib, wherein a dose per administration of the antibody-drug conjugate is in a range of 5.4 mg/kg to 8 mg/kg, wherein the antibody-drug conjugate is to be administered once every 3 weeks.

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

Claims

[Claim 1]

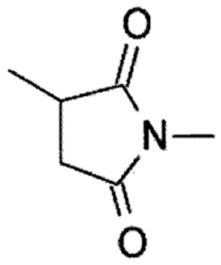
Use of an antibody-drug conjugate in which a linker and a drug represented by the following formula are conjugated to an anti-HER2 antibody, for the production of a medicine for treating a human subject with HER2-expressing cancer having resistance or refractoriness to an existing anti-HER2 drug:

-(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:

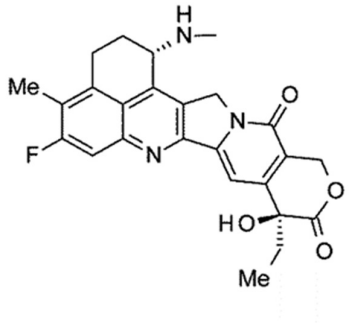
[Formula 1]



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-,

wherein the existing anti-HER2 drug is at least one selected from the group consisting of trastuzumab emtansine, trastuzumab, pertuzumab, and lapatinib,

wherein a dose per administration of the antibody-drug conjugate is in a range of 5.4 mg/kg to 8 mg/kg,

wherein the antibody-drug conjugate is to be administered once every 3 weeks.

[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~~4]

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

[Claim ~~6~~5]

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

[Claim ~~7~~6]

The use according to any of claims 1 to ~~6~~5, wherein the medicine is to be administered to a patient having a history of treatment with an existing anticancer drug.

[Claim ~~8~~7]

The use according to claim ~~7~~6, 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~~8]

The use according to claim ~~7~~6, wherein the existing anticancer drug comprises trastuzumab emtansine.

[Claim ~~10~~9]

The use according to claim ~~7~~6, wherein the existing anticancer drug comprises trastuzumab.

[Claim ~~11~~10]

The use according to claim ~~7~~6, wherein the existing anticancer drug comprises irinotecan.

[Claim ~~12~~11]

The use according to any of claims 1 to ~~11~~10, 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~~12]

The use according to any of claims 1 to ~~11~~10, 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~~13]

The use according to any of claims 1 to ~~13~~12, 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~~14]

The use according to any of claims 1 to ~~13~~12, 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~~15]

The use according to any of claims 1 to ~~15~~14, wherein a dose per administration of the antibody-drug conjugate is 5.4 mg/kg.

[Claim ~~17~~16]

The use according to any of claims 1 to ~~15~~14, wherein a dose per administration of the antibody-drug conjugate is 6.4 mg/kg.

[Claim ~~18~~17]

The use according to any of claims 1 to ~~15~~14, wherein a dose per administration of the antibody-drug conjugate is 7.4 mg/kg.

[Claim ~~19~~18]

The use according to any of claims 1 to ~~15~~14, wherein a dose per administration of the antibody-drug conjugate is 8 mg/kg.

~~[Claim 20]~~

~~The use according to any of claims 1 to 19, wherein the antibody-drug conjugate is to be administered once every 3 weeks.~~

[Claim ~~21~~19]

The use according to any of claims 1 to ~~20~~18, 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 ~~22~~20]

The use according to any of claims 1 to ~~20~~18, wherein the cancer is breast cancer.

[Claim ~~23~~21]

The use according to any of claims 1 to ~~20~~18, wherein the cancer is gastric cancer.

[Claim ~~24~~22]

The use according to any of claims 1 to ~~20~~18, wherein the cancer is gastric cancer or esophagogastric junction adenocarcinoma.

[Claim ~~25~~23]

The use according to any of claims 1 to ~~20~~18, wherein the cancer is colorectal cancer.

[Claim ~~26~~24]

The use according to any of claims 1 to ~~20~~18, wherein the cancer is non-small cell lung cancer.

[Claim ~~27~~25]

The use according to any of claims 1 to ~~20~~18, wherein the cancer is salivary gland cancer.

[Claim ~~28~~26]

The use according to any of claims 1 to ~~27~~25, wherein the HER2-expressing cancer is HER2-overexpressing cancer.

[Claim ~~29~~27]

The use according to claim ~~28~~26, wherein the HER2-overexpressing cancer is cancer given a score of 3+ for the expression of HER2 in an immunohistochemical method.

[Claim ~~30~~28]

The use according to claim ~~28~~26, 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 ~~31~~29]

The use according to any of claims 1 to ~~27~~25, wherein the HER2-expressing cancer is HER2 low-expressing cancer.

[Claim ~~32~~30]

The use according to claim ~~31~~29, 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 ~~33~~31]

The use according to claim ~~31~~29, wherein the HER2 low-expressing cancer is cancer given a score of 1+ for the expression of HER2 in an immunohistochemical method.

[Claim ~~34~~32]

The use according to any of claims 1 to ~~33~~31, wherein the cancer is inoperable or recurrent cancer.

[Claim ~~35~~33]

The use according to any of claims 1 to ~~34~~32, comprising a pharmaceutically acceptable formulation component.