Description

Title of Invention: COMBINATION OF ANTIBODY-DRUG CONJUGATE AND TUBULIN INHIBITOR

Technical Field

[0001]

The present invention relates to a pharmaceutical composition wherein a specific antibody-drug conjugate and a tubulin inhibitor are administrated in combination, and/or a method of treatment wherein a specific antibody-drug conjugate and a tubulin inhibitor are administrated in combination to a subject.

Background Art

[0002]

Tubulin inhibitors are drugs that affect microtubule dynamics, and thus arrest cell division at the G_2 phase (pre-mitotic gap phase) and/or M phase (mitotic phase) of the cell cycle and induce cell death by apoptosis, thereby suppressing growth of cancer cells (Non-Patent References 1, 2).

[0003]

Tubulin inhibitors include agents that promote tubulin polymerization, thereby affecting microtubule dynamics (tubulin polymerization accelerator); and agents

that inhibit tubulin polymerization, thereby affecting microtubule dynamics (tubulin polymerization inhibitor).

[0004]

Known tubulin polymerization accelerators include paclitaxel, docetaxel, and cabazitaxel. Meanwhile, known tubulin polymerization inhibitors include eribulin; vincristine; vinblastine; vinorelbine; vindesine; brentuximab vedotin, which is an antibody-drug conjugate containing monomethyl auristatin E (MMAE) as a component; and trastuzumab emtansine, which is an antibody-drug conjugate containing DM1 as a component.

[0005]

An antibody-drug conjugate (ADC) having a drug with cytotoxicity conjugated to an antibody capable of binding to an antigen expressed on the surface of cancer cells and cellular internalization, can deliver the drug selectively to cancer cells and can thus be expected to cause accumulation of the drug within cancer cells and to kill the cancer cells (Non-Patent References 3 to 7).

[0006]

As one such antibody-drug conjugate, an antibody-drug conjugate comprising an antibody and a derivative of exatecan, which is a topoisomerase I inhibitor, as its components is known (Patent References 1 to 7, Non-Patent References 8 to 11).

[0007]

Furthermore, Patent References 1 to 7 disclose that the foregoing antibody-drug conjugate can be administered with a variety of cancer therapeutic agents.

[0008]

However, none of the references describes any test result showing an excellent combined effect when the foregoing antibody-drug conjugate and a tubulin inhibitor are used in combination, or any scientific basis for suggesting such a test result.

Citation List

Patent Literature

[0009]

Patent Reference 1: International Publication No. WO 2014/057687

Patent Reference 2: International Publication No. WO 2014/061277

Patent Reference 3: International Publication No. WO 2015/098099

Patent Reference 4: International Publication No. WO 2015/115091

Patent Reference 5: International Publication No. WO 2015/146132

Patent Reference 6: International Publication No. WO 2015/155976

Patent Reference 7: International Publication No. WO 2015/155998

Non-Patent Literature

[0010]

Non-Patent Reference 1: Dumontet C, et al., Nat Rev Drug Discov. 2010 Oct; 9 (10): 790-803.

Non-Patent Reference 2: Mukhtar E, et al., Mol Cancer Ther. 2014 Feb: 13(2): 275-284.

Non-Patent Reference 3: Ducry, L., et al., Bioconjugate Chem. (2010) 21, 5-13.

Non-Patent Reference 4: Alley, S. C., et al., Current Opinion in Chemical Biology (2010) 14, 529-537.

Non-Patent Reference 5: Damle N. K. Expert Opin. Biol. Ther. (2004) 4, 1445-1452.

Non-Patent Reference 6: Senter P. D., et al., Nature Biotechnology (2012) 30, 631-637.

Non-Patent Reference 7: Howard A. et al., J Clin Oncol 29: 398-405.

Non-Patent Reference 8: Ogitani Y. et al., Clinical Cancer Research (2016) 22 (20), 5097-5108.

Non-Patent Reference 9: Ogitani Y. et al., Cancer Science (2016) 107, 1039-1046.

Non-Patent Reference 10: Doi T, et al., Lancet Oncol 2017; 18: 1512-22.

Non-Patent Reference 11: Takegawa N, et al., Int. J. Cancer: 141, 1682-1689 (2017)

Summary of Invention

Technical Problem

[0011]

The antibody-drug conjugates used in the present invention (antibody-drug conjugates containing an exatecan derivative as a component) have been confirmed to exert a superior antitumor effect even as a single agent. However, there has been a need for obtaining a method of treatment which can suppress growth of cancer cells in multiple manners and exert a further superior antitumor effect by using the antibody-drug conjugate in combination with another anticancer agent having a different mechanism of action.

[0012]

An object of the present invention is to provide a pharmaceutical composition wherein a specific antibody-drug conjugate and a tubulin inhibitor are administrated in combination, and/or a method of treatment wherein a specific antibody-drug conjugate and a tubulin inhibitor are administrated in combination to a subject.

Solution to Problem

[0013]

As a result of diligent studies in order to solve the above problems, the present inventors have found that combined administration of a specific antibody-drug conjugate and a tubulin inhibitor exhibits a superior combined effect, and thereby completed the present invention.

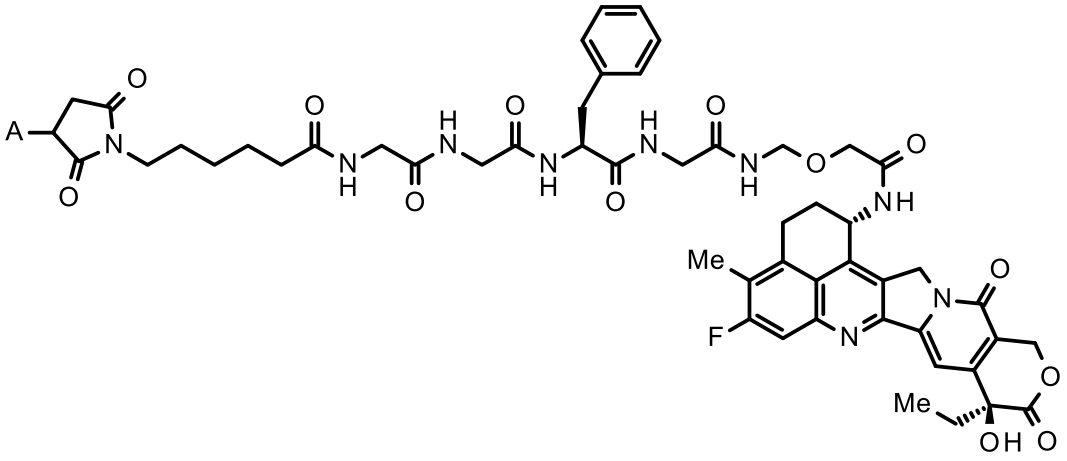
[0014]

Thus, the present invention provides the following [1] to [344].

[1] A pharmaceutical composition, wherein an antibody-drug conjugate and a tubulin inhibitor are administered in combination, and the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0015]

[Formula 1]



[0016]

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

[2] The pharmaceutical composition according to [1], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[3] The pharmaceutical composition according to [2], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[4] The pharmaceutical composition according to [3], wherein the anti-HER2 antibody 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.

[5] The pharmaceutical composition according to [3], 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.

[6] The pharmaceutical composition according to any one of [3] to [5], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[7] The pharmaceutical composition according to [2], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[8] The pharmaceutical composition according to [7], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.

[9] The pharmaceutical composition according to [8], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[10] The pharmaceutical composition according to any one of [7] to [9], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0017]

[11] The pharmaceutical composition according to [2], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[12] The pharmaceutical composition according to [11], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.

[13] The pharmaceutical composition according to [12], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[14] The pharmaceutical composition according to any one of [11] to [13], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[15] The pharmaceutical composition according to [2], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[16] The pharmaceutical composition according to [15], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.

[17] The pharmaceutical composition according to [16], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[18] The pharmaceutical composition according to any one of [15] to [17], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[19] The pharmaceutical composition according to [2], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[20] The pharmaceutical composition according to [19], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence

consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0018]

[21] The pharmaceutical composition according to [20], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[22] The pharmaceutical composition according to any one of [19] to [21], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[23] The pharmaceutical composition according to [2], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.

[24] The pharmaceutical composition according to [23], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.

[25] The pharmaceutical composition according to [24], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[26] The pharmaceutical composition according to any one of [23] to [25], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[27] The pharmaceutical composition according to any one of [1] to [26], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[28] The pharmaceutical composition according to [27], wherein the tubulin inhibitor is paclitaxel.

[29] The pharmaceutical composition according to any one of [1] to [26], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[30] The pharmaceutical composition according to [29], wherein the tubulin inhibitor is eribulin mesylate.

[0019]

[31] The pharmaceutical composition according to any one of [1] to [30], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times.

[32] The pharmaceutical composition according to any one of [1] to [31], wherein the pharmaceutical composition is for use in treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian

cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[33] The pharmaceutical composition according to [32], wherein the pharmaceutical composition is for use in treating breast cancer.

[34] The pharmaceutical composition according to [32], wherein the pharmaceutical composition is for use in treating gastric cancer.

[35] The pharmaceutical composition according to [32], wherein the pharmaceutical composition is for use in treating lung cancer.

[36] The pharmaceutical composition according to [32], wherein the pharmaceutical composition is for use in treating ovarian cancer.

[37] The pharmaceutical composition according to any one of [1] to [36], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[38] The pharmaceutical composition according to [37], wherein the drug sensitivity factor is SLFN11.

[39] The pharmaceutical composition according to any one of [1] to [36], wherein the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[40] The pharmaceutical composition according to [39], wherein the drug resistance factor is ABCG2.

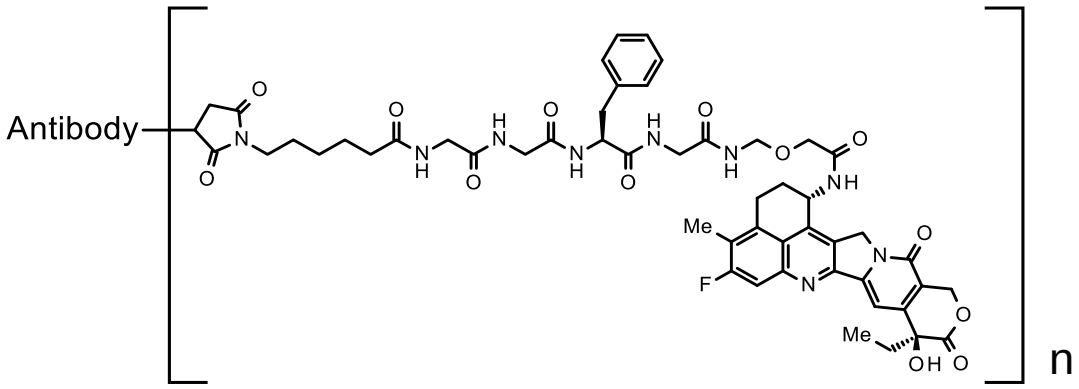
[41] A pharmaceutical composition, wherein

an antibody-drug conjugate and a tubulin inhibitor are administered in combination, and

the antibody-drug conjugate is an antibody-drug conjugate represented by the following formula:

[0020]

[Formula 2]



[0021]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

[42] The pharmaceutical composition according to [41], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[43] The pharmaceutical composition according to [42], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[44] The pharmaceutical composition according to [43], wherein the anti-HER2 antibody 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.

[45] The pharmaceutical composition according to [43], 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.

[46] The pharmaceutical composition according to any one of [43] to [45], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[47] The pharmaceutical composition according to [42], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[48] The pharmaceutical composition according to [47], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.

[49] The pharmaceutical composition according to [48], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[50] The pharmaceutical composition according to any one of [47] to [49], wherein the average number of units of

the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0022]

[51] The pharmaceutical composition according to [42], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[52] The pharmaceutical composition according to [51], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.

[53] The pharmaceutical composition according to [52], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[54] The pharmaceutical composition according to any one of [51] to [53], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[55] The pharmaceutical composition according to [42], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[56] The pharmaceutical composition according to [55], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence

consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.

[57] The pharmaceutical composition according to [56], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[58] The pharmaceutical composition according to any one of [55] to [57], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[59] The pharmaceutical composition according to [42], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[60] The pharmaceutical composition according to [59], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0023]

[61] The pharmaceutical composition according to [60], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[62] The pharmaceutical composition according to any one of [59] to [61], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.
[63] The pharmaceutical composition according to [42], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.
[64] The pharmaceutical composition according to [63], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.
[65] The pharmaceutical composition according to [64], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.
[66] The pharmaceutical composition according to any one of [63] to [65], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.
[67] The pharmaceutical composition according to any one of [41] to [66], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[68] The pharmaceutical composition according to [67], wherein the tubulin inhibitor is paclitaxel.

[69] The pharmaceutical composition according to any one of [41] to [66], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[70] The pharmaceutical composition according to [69], wherein the tubulin inhibitor is eribulin mesylate.

[0024]

[71] The pharmaceutical composition according to any one of [41] to [70], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times.

[72] The pharmaceutical composition according to any one of [41] to [71], wherein the pharmaceutical composition is for use in treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[73] The pharmaceutical composition according to [72], wherein the pharmaceutical composition is for use in treating breast cancer.

[74] The pharmaceutical composition according to [72], wherein the pharmaceutical composition is for use in treating gastric cancer.

[75] The pharmaceutical composition according to [72], wherein the pharmaceutical composition is for use in treating lung cancer.

[76] The pharmaceutical composition according to [72], wherein the pharmaceutical composition is for use in treating ovarian cancer.

[77] The pharmaceutical composition according to any one of [41] to [76], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[78] The pharmaceutical composition according to [77], wherein the drug sensitivity factor is SLFN11.

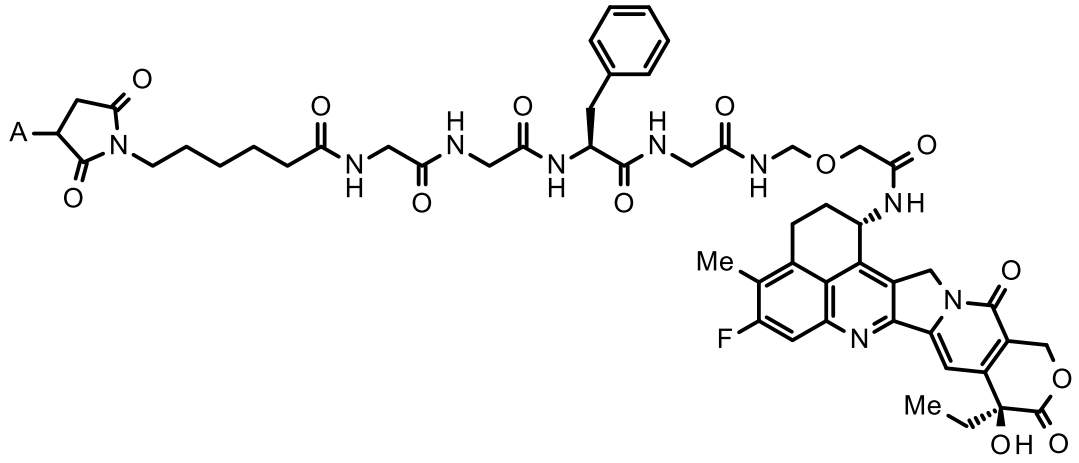
[79] The pharmaceutical composition according to any one of [41] to [76], wherein the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[80] The pharmaceutical composition according to [79], wherein the drug resistance factor is ABCG2.

[81] A method of treatment, comprising administering an antibody-drug conjugate and a tubulin inhibitor in combination to a subject in need of treatment, wherein the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0025]

[Formula 3]



[0026]

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

[82] The method of treatment according to [81], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[83] The method of treatment according to [82], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[84] The method of treatment according to [83], wherein the anti-HER2 antibody 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.

[85] The method of treatment according to [83], 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.

[86] The method of treatment according to any one of [83] to [85], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[87] The method of treatment according to [82], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[88] The method of treatment according to [87], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.

[89] The method of treatment according to [88], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[90] The method of treatment according to any one of [87] to [89], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0027]

[91] The method of treatment according to [82], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[92] The method of treatment according to [91], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.

[93] The method of treatment according to [92], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[94] The method of treatment according to any one of [91] to [93], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[95] The method of treatment according to [82], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[96] The method of treatment according to [95], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.

[97] The method of treatment according to [96], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[98] The method of treatment according to any one of [95] to [97], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[99] The method of treatment according to [82], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[100] The method of treatment according to [99], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0028]

[101] The method of treatment according to [100], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[102] The method of treatment according to any one of [99] to [101], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[103] The method of treatment according to [82], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.

[104] The method of treatment according to [103], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.

[105] The method of treatment according to [104], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[106] The method of treatment according to any one of [103] to [105], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[107] The method of treatment according to any one of [81] to [106], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[108] The method of treatment according to [107], wherein the tubulin inhibitor is paclitaxel.

[109] The method of treatment according to any one of [81] to [106], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[110] The method of treatment according to [109], wherein the tubulin inhibitor is eribulin mesylate.

[0029]

[111] The method of treatment according to any one of [81] to [110], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times.

[112] The method of treatment according to any one of [81] to [111], wherein the method of treatment is for treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[113] The method of treatment according to [112], wherein the method of treatment is for treating breast cancer.

[114] The method of treatment according to [112], wherein the method of treatment is for treating gastric cancer.

[115] The method of treatment according to [112], wherein the method of treatment is for treating lung cancer.

[116] The method of treatment according to [112], wherein the method of treatment is for treating ovarian cancer.

[117] The method of treatment according to any one of [81] to [116], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[118] The method of treatment according to [117], wherein the drug sensitivity factor is SLFN11.

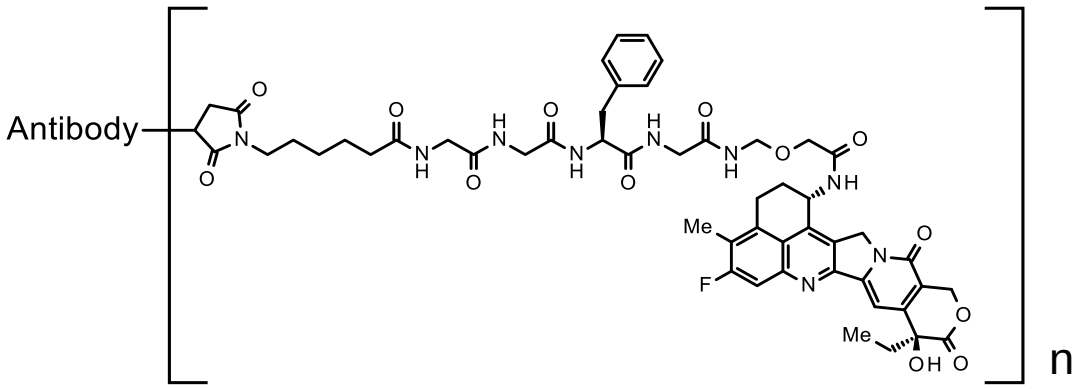
[119] The method of treatment according to any one of [81] to [116], wherein the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[120] The method of treatment according to [119], wherein the drug resistance factor is ABCG2.

[121] A method of treatment, comprising administering an antibody-drug conjugate and a tubulin inhibitor in combination to a subject in need of treatment, wherein the antibody-drug conjugate is an antibody-drug conjugate represented by the following formula:

[0030]

[Formula 4]



[0031]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

[122] The method of treatment according to [121], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[123] The method of treatment according to [122], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[124] The method of treatment according to [123]. wherein the anti-HER2 antibody 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.

[125] The method of treatment according to [123], 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.

[126] The method of treatment according to any one of [123] to [125], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[127] The method of treatment according to [122], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[128] The method of treatment according to [127], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.

[129] The method of treatment according to [128], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[130] The method of treatment according to any one of [127] to [129], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0032]

[131] The method of treatment according to [122], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[132] The method of treatment according to [131], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.

[133] The method of treatment according to [132], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[134] The method of treatment according to any one of [131] to [133], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[135] The method of treatment according to [122], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[136] The method of treatment according to [135], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence

consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.

[137] The method of treatment according to [136], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[138] The method of treatment according to any one of [135] to [137], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[139] The method of treatment according to [122], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[140] The method of treatment according to [139], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0033]

[141] The method of treatment according to [140], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[142] The method of treatment according to any one of [139] to [141], wherein the average number of units of

the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[143] The method of treatment according to [122], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.

[144] The method of treatment according to [143], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.

[145] The method of treatment according to [144], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[146] The method of treatment according to any one of [143] to [145], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[147] The method of treatment according to any one of [121] to [146], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[148] The method of treatment according to [147], wherein the tubulin inhibitor is paclitaxel.

[149] The method of treatment according to any one of [121] to [146], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[150] The method of treatment according to [149], wherein the tubulin inhibitor is eribulin mesylate.

[0034]

[151] The method of treatment according to any one of [121] to [150], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times.

[152] The method of treatment according to any one of [121] to [151], wherein the method of treatment is for treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[153] The method of treatment according to [152], wherein the method of treatment is for treating breast cancer.

[154] The method of treatment according to [152], wherein the method of treatment is for treating gastric cancer.

[155] The method of treatment according to [152], wherein the method of treatment is for treating lung cancer.

[156] The method of treatment according to [152], wherein the method of treatment is for treating ovarian cancer.

[157] The method of treatment according to any one of [121] to [156], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[158] The method of treatment according to [157], wherein the drug sensitivity factor is SLFN11.

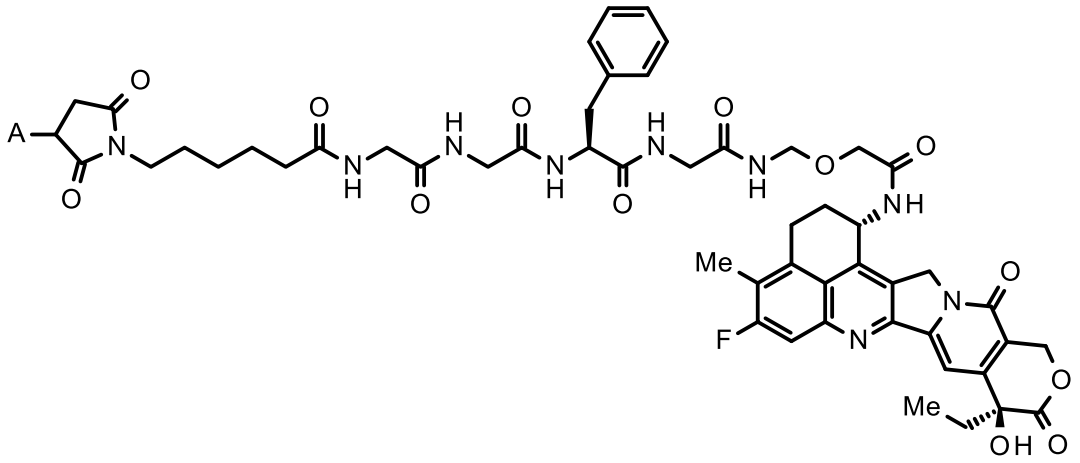
[159] The method of treatment according to any one of [121] to [156], wherein the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[160] The method of treatment according to [159], wherein the drug resistance factor is ABCG2.

[161] An antibody-drug conjugate for use in treating a disease through being administered in combination with a tubulin inhibitor, wherein a drug-linker represented by the following formula:

[0035]

[Formula 5]



[0036]

wherein A represents a connecting position to an antibody,

is conjugated to the antibody via a thioether bond in the antibody-drug conjugate.

[162] The antibody-drug conjugate according to [161], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[163] The antibody-drug conjugate according to [162], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[164] The antibody-drug conjugate according to [163], wherein the anti-HER2 antibody 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.

[165] The antibody-drug conjugate according to [163], 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.

[166] The antibody-drug conjugate according to any one of [163] to [165], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[167] The antibody-drug conjugate according to [162], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[168] The antibody-drug conjugate according to [167], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.

[169] The antibody-drug conjugate according to [168], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[170] The antibody-drug conjugate according to any one of [167] to [169], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0037]

[171] The antibody-drug conjugate according to [162], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[172] The antibody-drug conjugate according to [171], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.

[173] The antibody-drug conjugate according to [172], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[174] The antibody-drug conjugate according to any one of [171] to [173], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[175] The antibody-drug conjugate according to [162], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[176] The antibody-drug conjugate according to [175], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence

consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.

[177] The antibody-drug conjugate according to [176], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[178] The antibody-drug conjugate according to any one of [175] to [177], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[179] The antibody-drug conjugate according to [162], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[180] The antibody-drug conjugate according to [179], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0038]

[181] The antibody-drug conjugate according to [180], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[182] The antibody-drug conjugate according to any one of [179] to [181], wherein the average number of units of

the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[183] The antibody-drug conjugate according to [162], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.

[184] The antibody-drug conjugate according to [183], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.

[185] The antibody-drug conjugate according to [184], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[186] The antibody-drug conjugate according to any one of [183] to [185], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[187] The antibody-drug conjugate according to any one of [161] to [186], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[188] The antibody-drug conjugate according to [187], wherein the tubulin inhibitor is paclitaxel.

[189] The antibody-drug conjugate according to any one of [161] to [186], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[190] The antibody-drug conjugate according to [189], wherein the tubulin inhibitor is eribulin mesylate.

[0039]

[191] The antibody-drug conjugate according to any one of [161] to [190], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times.

[192] The antibody-drug conjugate according to any one of [161] to [191], wherein the antibody-drug conjugate is for use in treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[193] The antibody-drug conjugate according to [192], wherein the antibody-drug conjugate is for use in treating breast cancer.

[194] The antibody-drug conjugate according to [192], wherein the antibody-drug conjugate is for use in treating gastric cancer.

[195] The antibody-drug conjugate according to [192], wherein the antibody-drug conjugate is for use in treating lung cancer.

[196] The antibody-drug conjugate according to [192], wherein the antibody-drug conjugate is for use in treating ovarian cancer.

[197] The antibody-drug conjugate according to any one of [161] to [196], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[198] The antibody-drug conjugate according to [197], wherein the drug sensitivity factor is SLFN11.

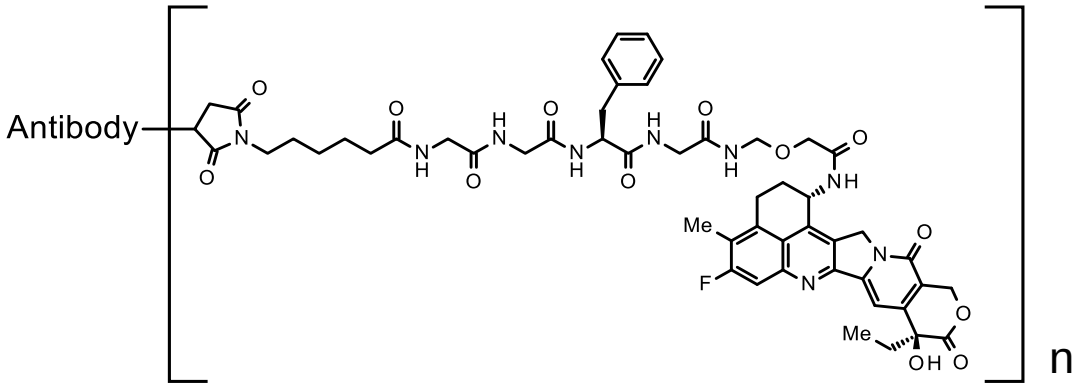
[199] The antibody-drug conjugate according to any one of [161] to [196], wherein the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[200] The antibody-drug conjugate according to [199], wherein the drug resistance factor is ABCG2.

[201] An antibody-drug conjugate for use in treating a disease through being administered in combination with a tubulin inhibitor, wherein the antibody-drug conjugate is represented by the following formula:

[0040]

[Formula 6]



[0041]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

[202] The antibody-drug conjugate according to [201], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[203] The antibody-drug conjugate according to [202], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[204] The antibody-drug conjugate according to [203], wherein the anti-HER2 antibody 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.

[205] The antibody-drug conjugate according to [203], 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.

[206] The antibody-drug conjugate according to any one of [203] to [205], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[207] The antibody-drug conjugate according to [202], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[208] The antibody-drug conjugate according to [207], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.

[209] The antibody-drug conjugate according to [208], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[210] The antibody-drug conjugate according to any one of [207] to [209], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0042]

[211] The antibody-drug conjugate according to [202], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[212] The antibody-drug conjugate according to [211], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.

[213] The antibody-drug conjugate according to [212], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[214] The antibody-drug conjugate according to any one of [211] to [213], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[215] The antibody-drug conjugate according to [202], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[216] The antibody-drug conjugate according to [215], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence

consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.

[217] The antibody-drug conjugate according to [216], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[218] The antibody-drug conjugate according to any one of [215] to [217], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[219] The antibody-drug conjugate according to [202], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[220] The antibody-drug conjugate according to [219], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0043]

[221] The antibody-drug conjugate according to [220], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[222] The antibody-drug conjugate according to any one of [219] to [221], wherein the average number of units of

the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[223] The antibody-drug conjugate according to [202], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.

[224] The antibody-drug conjugate according to [223], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.

[225] The antibody-drug conjugate according to [224], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[226] The antibody-drug conjugate according to any one of [223] to [225], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[227] The antibody-drug conjugate according to any one of [201] to [226], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[228] The antibody-drug conjugate according to [227], wherein the tubulin inhibitor is paclitaxel.

[229]

The antibody-drug conjugate according to any one of [201] to [226], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[230] The antibody-drug conjugate according to [229], wherein the tubulin inhibitor is eribulin mesylate.

[0044]

[231] The antibody-drug conjugate according to any one of [201] to [230], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times.

[232] The antibody-drug conjugate according to any one of [201] to [231], wherein the antibody-drug conjugate is for use in treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[233] The antibody-drug conjugate according to [232], wherein the antibody-drug conjugate is for use in treating breast cancer.

[234] The antibody-drug conjugate according to [232], wherein the antibody-drug conjugate is for use in treating gastric cancer.

[235] The antibody-drug conjugate according to [232], wherein the antibody-drug conjugate is for use in treating lung cancer.

[236] The antibody-drug conjugate according to [232], wherein the antibody-drug conjugate is for use in treating ovarian cancer.

[237] The antibody-drug conjugate according to any one of [201] to [236], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[238] The antibody-drug conjugate according to [237], wherein the drug sensitivity factor is SLFN11.

[239] The antibody-drug conjugate according to any one of [201] to [236], wherein the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

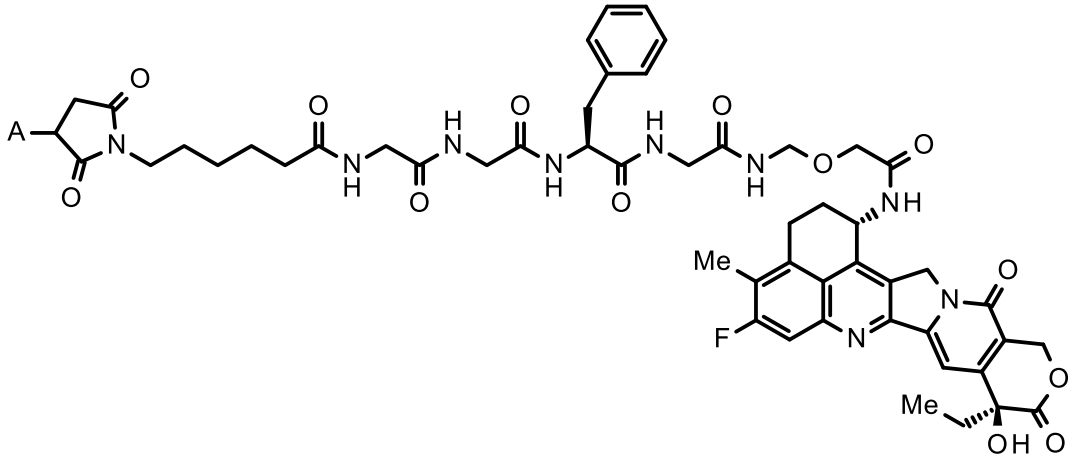
[240] The antibody-drug conjugate according to [239], wherein the drug resistance factor is ABCG2.

[241] Use of an antibody-drug conjugate for the manufacture of a medicament for treating a disease through being administered in combination with a tubulin

inhibitor, wherein a drug-linker represented by the following formula:

[0045]

[Formula 7]



[0046]

wherein A represents a connecting position to an antibody,

is conjugated to the antibody via a thioether bond in the antibody-drug conjugate.

[242] The use according to [241], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[243] The use according to [242], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[244] The use according to [243], wherein the anti-HER2 antibody 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.

[245] The use according to [243], 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.

[246] The use according to any one of [243] to [245], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[247] The use according to [242], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[248] The use according to [247], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.

[249] The use according to [248], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[250] The use according to any one of [247] to [249], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0047]

[251] The use according to [242], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.
[252] The use according to [251], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.
[253] The use according to [252], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.
[254] The use according to any one of [251] to [253], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.
[255] The use according to [242], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.
[256] The use according to [255], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.
[257] The use according to [256], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[258] The use according to any one of [255] to [257], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[259] The use according to [242], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[260] The use according to [259], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0048]

[261] The use according to [260], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[262] The use according to any one of [259] to [261], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[263] The use according to [242], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.

[264] The use according to [263], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light

chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.

[265] The use according to [264], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[266] The use according to any one of [263] to [265], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[267] The use according to any one of [241] to [266], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[268] The use according to [267], wherein the tubulin inhibitor is paclitaxel.

[269] The use according to any one of [241] to [266], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[270] The use according to [269], wherein the tubulin inhibitor is eribulin mesylate.

[0049]

[271] The use according to any one of [241] to [270], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components

in different formulations, and are administered simultaneously or at different times.

[272] The use according to any one of [241] to [271], wherein the use is for treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[273] The use according to [272], wherein the use is for treating breast cancer.

[274] The use according to [272], wherein the use is for treating gastric cancer.

[275] The use according to [272], wherein the use is for treating lung cancer.

[276] The use according to [272], wherein the use is for treating ovarian cancer.

[277] The use according to any one of [241] to [276], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[278] The use according to [277], wherein the drug sensitivity factor is SLFN11.

[279] The use according to any one of [241] to [276], wherein the tubulin inhibitor suppresses increased

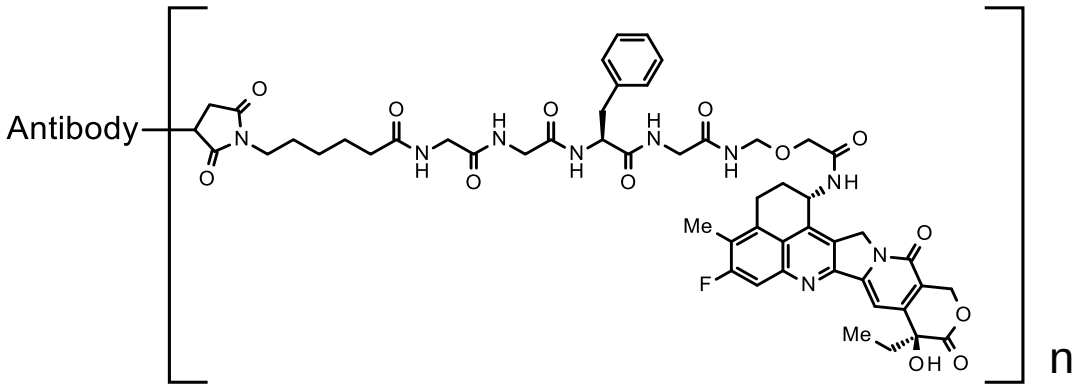
expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[280] The use according to [279], wherein the drug resistance factor is ABCG2.

[281] Use of an antibody-drug conjugate for the manufacture of a medicament for treating a disease through being administered in combination with a tubulin inhibitor, wherein the antibody-drug conjugate is represented by the following formula:

[0050]

[Formula 8]



[0051]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

[282] The use according to [281], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, or an anti-CDH6 antibody.

[283] The use according to [282], wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.
[284] The use according to [283], wherein the anti-HER2 antibody 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.
[285] The use according to [283], 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.
[286] The use according to any one of [283] to [285], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.
[287] The use according to [282], wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.
[288] The use according to [287], wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4.
[289] The use according to [288], wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[290] The use according to any one of [287] to [289], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[0052]

[291] The use according to [282], wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[292] The use according to [291], wherein the anti-TROP2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6.

[293] The use according to [292], wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[294] The use according to any one of [291] to [293], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[295] The use according to [282], wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[296] The use according to [295], wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain

consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8.

[297] The use according to [296], wherein the anti-B7-H3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[298] The use according to any one of [295] to [297], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3.5 to 4.5.

[299] The use according to [282], wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[300] The use according to [299], wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10.

[0053]

[301] The use according to [300], wherein the anti-GPR20 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[302] The use according to any one of [299] to [301], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[303] The use according to [282], wherein the antibody in the antibody-drug conjugate is an anti-CDH6 antibody.

[304] The use according to [303], wherein the anti-CDH6 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12.

[305] The use according to [304], wherein the anti-CDH6 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[306] The use according to any one of [303] to [305], wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[307] The use according to any one of [281] to [306], wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

[308] The use according to [307], wherein the tubulin inhibitor is paclitaxel.

[309] The use according to any one of [281] to [306], wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

[310] The use according to [309], wherein the tubulin inhibitor is eribulin mesylate.

[0054]

[311] The use according to any one of [281] to [310], wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times.

[312] The use according to any one of [281] to [311], wherein the use is for treating at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

[313] The use according to [312], wherein the use is for treating breast cancer.

[314] The use according to [312], wherein the use is for treating gastric cancer.

[315] The use according to [312], wherein the use is for treating lung cancer.

[316] The use according to [312], wherein the use is for treating ovarian cancer.

[317] The use according to any one of [281] to [316], wherein the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate.

[318] The use according to [317], wherein the drug sensitivity factor is SLFN11.

[319] The use according to any one of [281] to [316], wherein the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[320] The use according to [319], wherein the drug resistance factor is ABCG2.

[0055]

[321] A pharmaceutical composition, wherein an antibody-drug conjugate and a tubulin inhibitor are administered in combination, and

1) the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate, and/or

2) the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[322] The pharmaceutical composition according to [321], wherein the drug sensitivity factor is SLFN11.

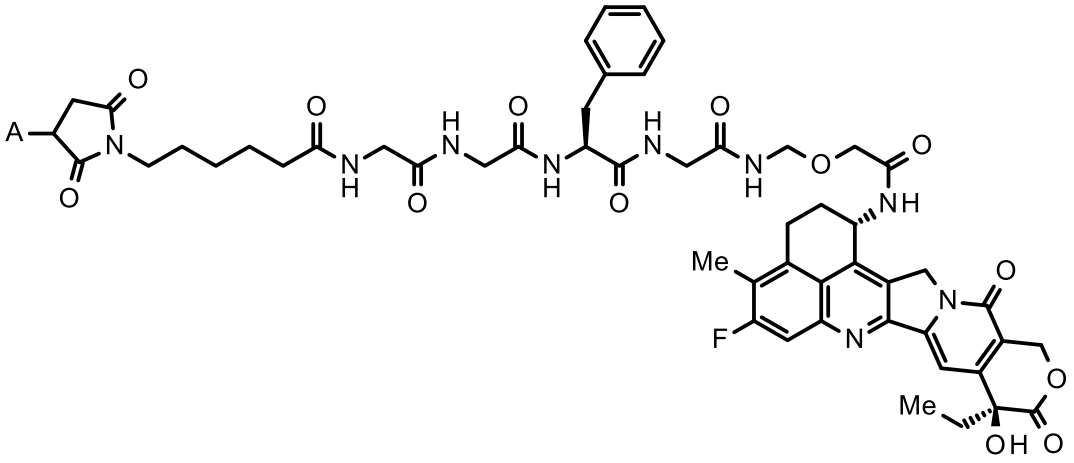
[323] The pharmaceutical composition according to [321] or [322], wherein the drug resistance factor is ABCG2.

[324] The pharmaceutical composition according to any one of [321] to [323], wherein the drug in the antibody-drug conjugate has a topoisomerase I inhibitory effect.

[325] The pharmaceutical composition according to any one of [321] to [323], wherein the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0056]

[Formula 9]



[0057]

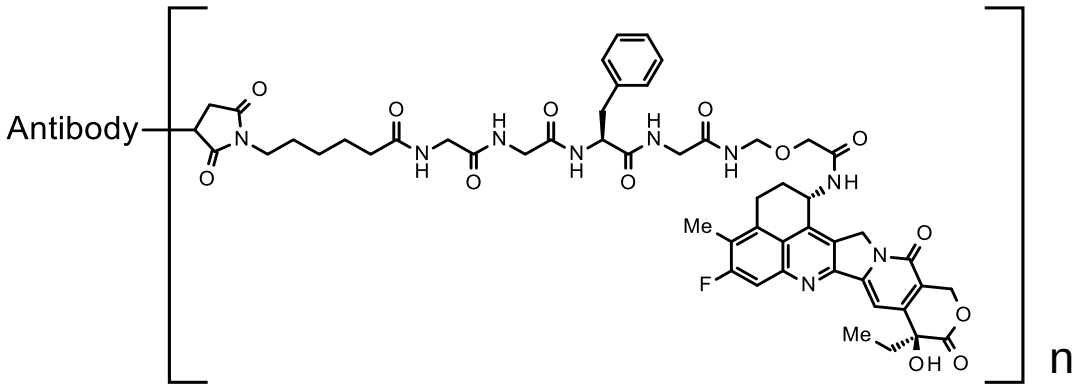
wherein A represents a connecting position to an antibody, is conjugated to the antibody via a thioether bond.

[326] The pharmaceutical composition according to any one of [321] to [323], wherein

the antibody-drug conjugate is an antibody-drug conjugate represented by the following formula:

[0058]

[Formula 10]



[0059]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

[327] A method of treatment, comprising administering an antibody-drug conjugate and a tubulin inhibitor in combination to a subject in need of treatment, wherein

1) the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate, and/or

2) the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[328] The method of treatment according to [327], wherein the drug sensitivity factor is SLFN11.

[329] The method of treatment according to [327] or [328], wherein the drug resistance factor is ABCG2.

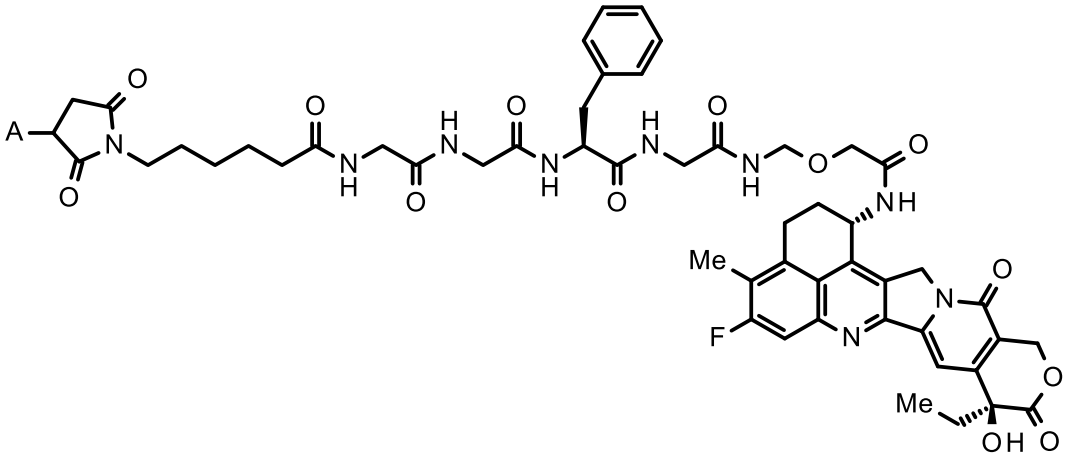
[330] The method of treatment according to any one of [327] to [329], wherein the drug in the antibody-drug conjugate has a topoisomerase I inhibitory effect.

[331] The method of treatment according to any one of [327] to [329], wherein

the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0060]

[Formula 11]



[0061]

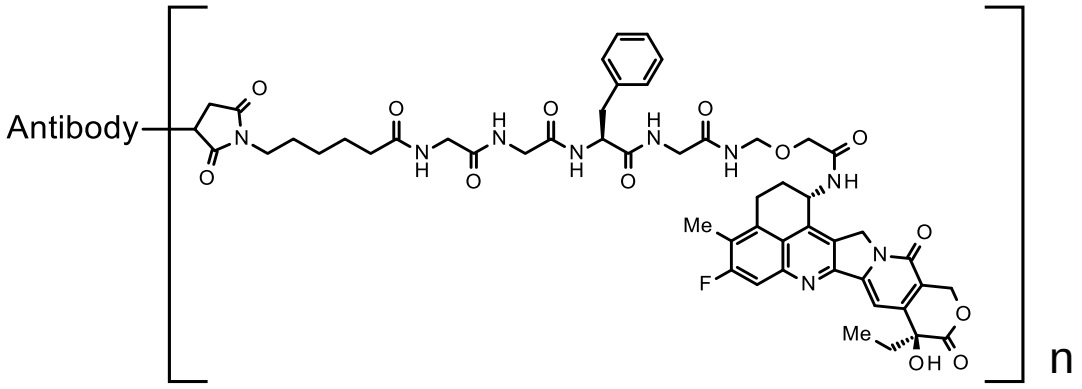
wherein A represents a connecting position to an antibody, is conjugated to the antibody via a thioether bond.

[332] The method of treatment according to any one of [327] to [329], wherein

the antibody-drug conjugate is an antibody-drug conjugate represented by the following formula:

[0062]

[Formula 12]



[0063]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

[333] An antibody-drug conjugate for use in treating a disease through being administered in combination with a tubulin inhibitor, wherein

1) the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate, and/or

2) the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[334] The antibody-drug conjugate according to [333], wherein the drug sensitivity factor is SLFN11.

[335] The antibody-drug conjugate according to [333] or [334], wherein the drug resistance factor is ABCG2.

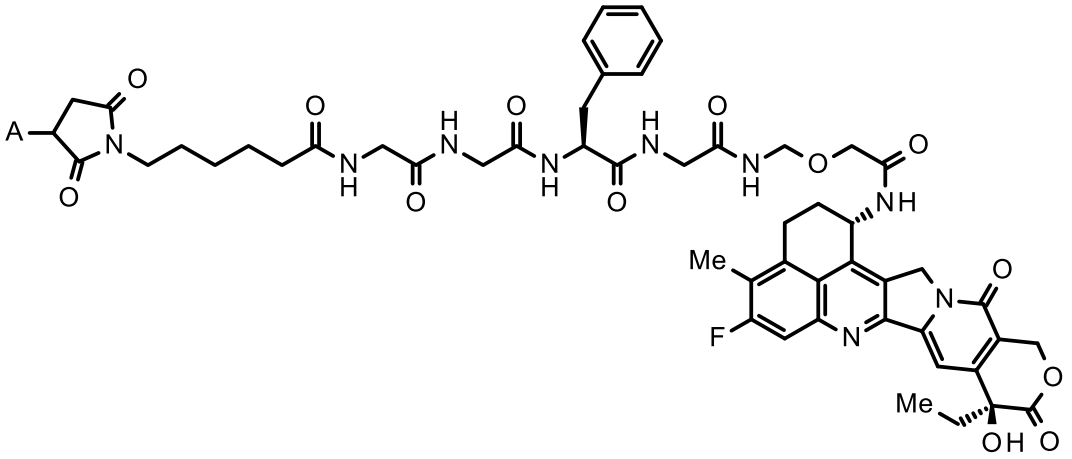
[336] The antibody-drug conjugate according to any one of [333] to [335], wherein the drug in the antibody-drug conjugate has a topoisomerase I inhibitory effect.

[337] The antibody-drug conjugate according to any one of [333] to [335], wherein

the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0064]

[Formula 13]



[0065]

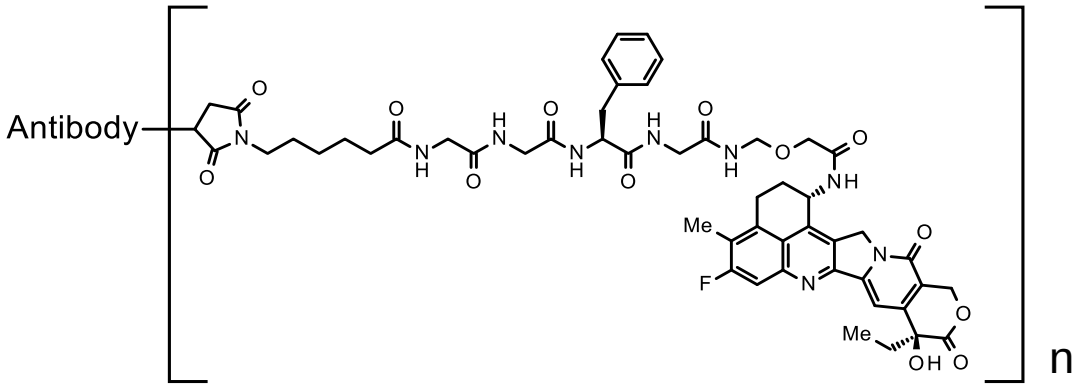
wherein A represents a connecting position to an antibody, is conjugated to the antibody via a thioether bond.

[338] The antibody-drug conjugate according to any one of [333] to [335], wherein

the antibody-drug conjugate is an antibody-drug conjugate represented by the following formula:

[0066]

[Formula 14]



[0067]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

[339] Use of an antibody-drug conjugate for the manufacture of a medicament for treating a disease through being administered in combination with a tubulin inhibitor, wherein

1) the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate, and/or

2) the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate.

[340] The use according to [339], wherein the drug sensitivity factor is SLFN11.

[341] The use according to [339] or [340], wherein the drug resistance factor is ABCG2.

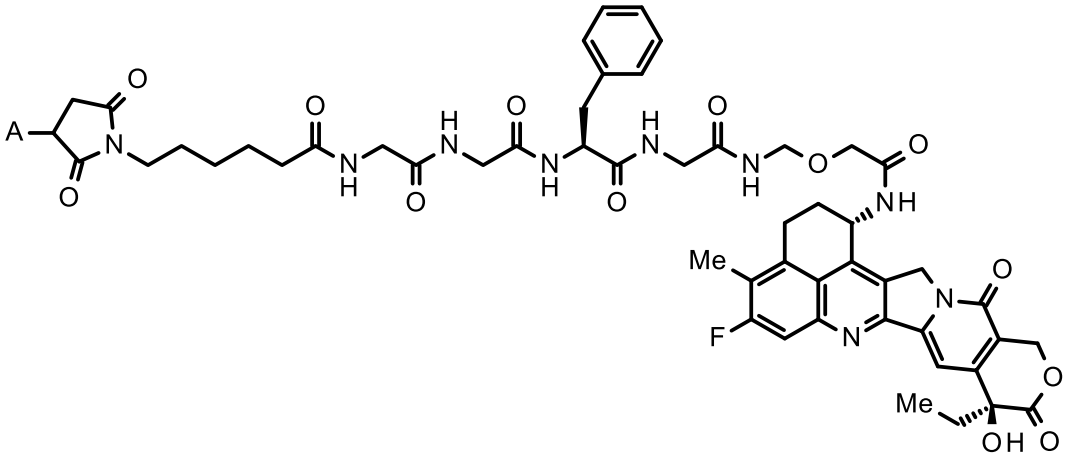
[342] The use according to any one of [339] to [341], wherein the drug in the antibody-drug conjugate has a topoisomerase I inhibitory effect.

[343] The use according to any one of [339] to [341], wherein

the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0068]

[Formula 15]



[0069]

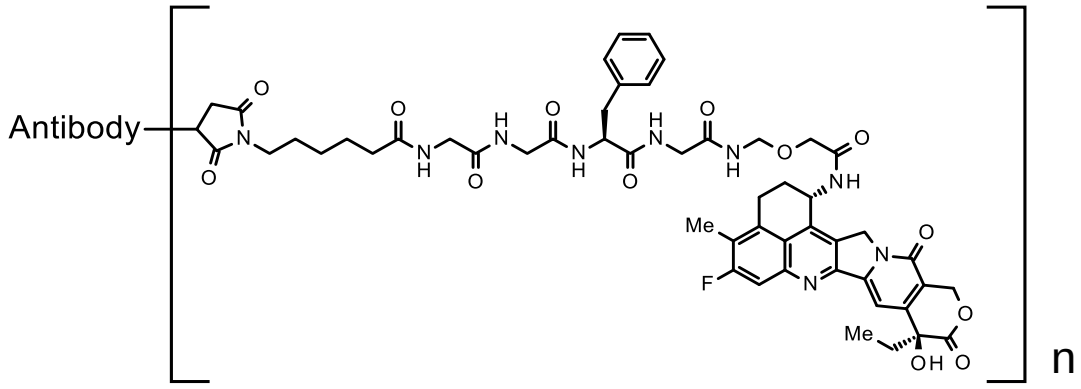
wherein A represents a connecting position to an antibody, is conjugated to the antibody via a thioether bond.

[344] The use according to any one of [339] to [341], wherein

the antibody-drug conjugate is an antibody-drug conjugate represented by the following formula:

[0070]

[Formula 16]



[0071]

wherein the drug-linker is conjugated to the antibody via a thioether bond, and n is the average number of units of the drug-linker conjugated per antibody molecule.

Advantageous Effects of Invention

[0072]

The present invention provides a pharmaceutical composition wherein a specific antibody-drug conjugate and a tubulin inhibitor are administered in combination, and/or a method of treatment wherein a specific antibody-drug conjugate and a tubulin inhibitor are administered in combination to a subject.

Brief Description of Drawings

[0073]

[Figure 1] Figure 1 is a diagram showing the amino acid sequence of a heavy chain of an anti-HER2 antibody (SEQ ID NO: 1).

[Figure 2] Figure 2 is a diagram showing the amino acid sequence of a light chain of an anti-HER2 antibody (SEQ ID NO: 2).

[Figure 3] Figure 3 is a diagram showing the amino acid sequence of a heavy chain of an anti-HER3 antibody (SEQ ID NO: 3).

[Figure 4] Figure 4 is a diagram showing the amino acid sequence of a light chain of an anti-HER3 antibody (SEQ ID NO: 4).

[Figure 5] Figure 5 is a diagram showing the amino acid sequence of a heavy chain of an anti-TROP2 antibody (SEQ ID NO: 5).

[Figure 6] Figure 6 is a diagram showing the amino acid sequence of a light chain of an anti-TROP2 antibody (SEQ ID NO: 6).

[Figure 7] Figure 7 is a diagram showing the amino acid sequence of a heavy chain of an anti-B7-H3 antibody (SEQ ID NO: 7).

[Figure 8] Figure 8 is a diagram showing the amino acid sequence of a light chain of an anti-B7-H3 antibody (SEQ ID NO: 8).

[Figure 9] Figure 9 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted KPL-4 cells in single administration groups of an antibody-drug conjugate (1) and paclitaxel respectively, and a combined administration group of the antibody-drug conjugate (1) and paclitaxel.

[Figure 10] Figure 10 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted KPL-4 cells in single administration groups of an antibody-drug conjugate (1) and eribulin mesylate respectively, and a combined administration group of the antibody-drug conjugate (1) and eribulin mesylate.

[Figure 11] Figure 11 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted JIMT-1 cells in single administration groups

of an antibody-drug conjugate (1) and paclitaxel respectively, and a combined administration group of the antibody-drug conjugate (1) and paclitaxel.

[Figure 12] Figure 12 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted JIMT-1 cells in single administration groups of an antibody-drug conjugate (1) and eribulin mesylate respectively, and a combined administration group of the antibody-drug conjugate (1) and eribulin mesylate.

[Figure 13] Figure 13 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted NCI-N87 cells in single administration groups of an antibody-drug conjugate (1) and paclitaxel respectively, and a combined administration group of the antibody-drug conjugate (1) and paclitaxel.

[Figure 14] Figure 14 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted NCI-N87 cells in single administration groups of an antibody-drug conjugate (1) and eribulin mesylate respectively, and a combined administration group of the antibody-drug conjugate (1) and eribulin mesylate.

[Figure 15] Figure 15 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted MDA-MB-453 cells in single administration groups of an antibody-drug conjugate (1) and paclitaxel

respectively, and a combined administration group of the antibody-drug conjugate (1) and paclitaxel.

[Figure 16] Figure 16 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted SNU-1 cells in single administration groups of an antibody-drug conjugate (1) and paclitaxel respectively, and a combined administration group of the antibody-drug conjugate (1) and paclitaxel.

[Figure 17] Figure 17 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted NCI-H441 cells in single administration groups of an antibody-drug conjugate (1) and paclitaxel respectively, and a combined administration group of the antibody-drug conjugate (1) and paclitaxel.

[Figure 18] Figure 18 is a diagram showing the amino acid sequence of a heavy chain of an anti-GPR20 antibody (SEQ ID NO: 9).

[Figure 19] Figure 19 is a diagram showing the amino acid sequence of a light chain of an anti-GPR20 antibody (SEQ ID NO: 10).

[Figure 20] Figure 20 is a diagram showing the amino acid sequence of a heavy chain of an anti-CDH6 antibody (SEQ ID NO: 11).

[Figure 21] Figure 21 is a diagram showing the amino acid sequence of a light chain of an anti-CDH6 antibody (SEQ ID NO: 12).

[Figure 22] Figure 22 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted JIMT-1 cells in single administration groups of an antibody-drug conjugate (2) and paclitaxel respectively, and a combined administration group of the antibody-drug conjugate (2) and paclitaxel.
[Figure 23] Figure 23 is a diagram showing the tumor growth suppressing effect in mice with subcutaneously transplanted OV-90 cells in single administration groups of an antibody-drug conjugate (3) and paclitaxel respectively, and a combined administration group of the antibody-drug conjugate (3) and paclitaxel.

Description of Embodiments

[0074]

Hereinafter, preferred modes for carrying out the present invention are described. The embodiments described below are given merely for illustrating one example of a typical embodiment of the present invention and are not intended to limit the scope of the present invention.

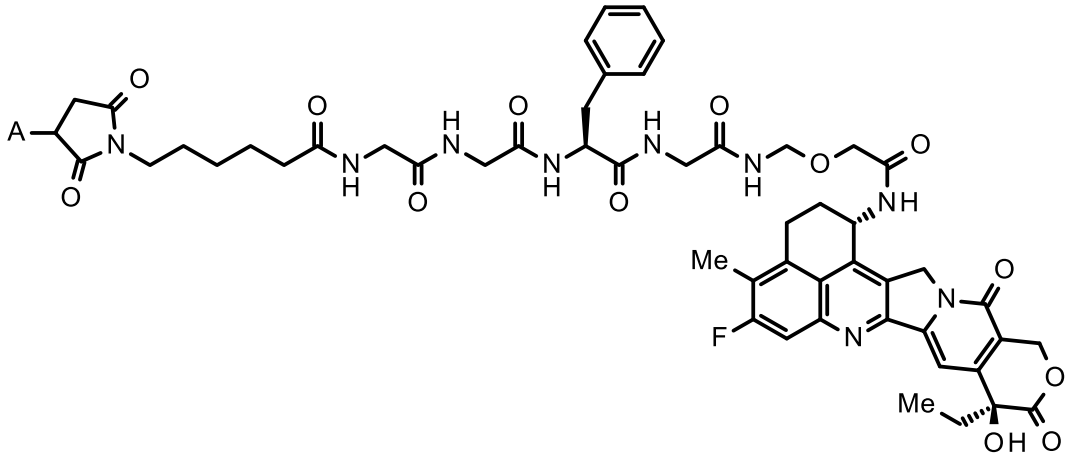
[0075]

1. Antibody-drug conjugate

The antibody-drug conjugate used in the present invention is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0076]

[Formula 17]



[0077]

wherein A represents a connecting position to an antibody,

is conjugated to the antibody via a thioether bond.

[0078]

In the present invention, the partial structure consisting of a linker and a drug in the antibody-drug conjugate is referred to as a "drug-linker". The drug-linker is connected to a thiol group (in other words, the sulfur atom of a cysteine residue) formed at an interchain disulfide bond site (two sites between heavy chains, and two sites between a heavy chain and a light chain) in the antibody.

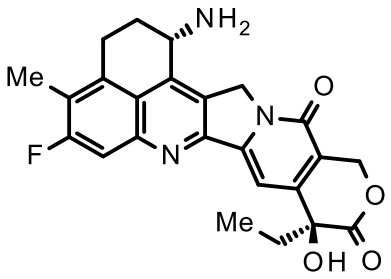
[0079]

The drug-linker of the present invention includes exatecan (IUPAC name: (1S,9S)-1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-

10,13-dione, (also expressed as chemical name: (1S,9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-10,13(9H,15H)-dione)), which is a topoisomerase I inhibitor, as a component. Exatecan is a camptothecin derivative having an antitumor effect, represented by the following formula:

[0080]

[Formula 18]



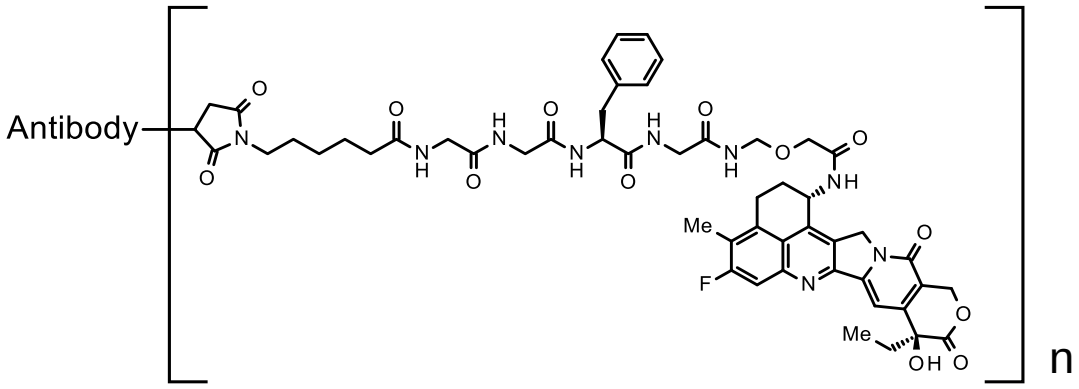
[0081]

[0082]

The antibody-drug conjugate used in the present invention can also be represented by the following formula:

[0083]

[Formula 19]



[0084]

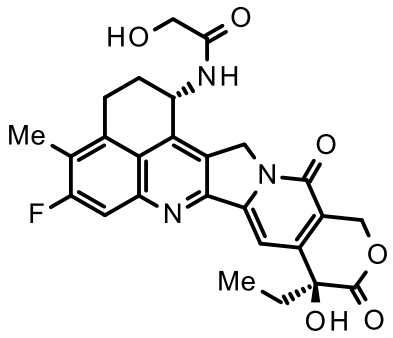
wherein, the drug-linker is conjugated to an antibody via a thioether bond. The meaning of n is the same as that of what is called the average number of conjugated drug molecules (DAR; Drug-to-Antibody Ratio), and indicates the average number of units of the drug-linker conjugated per antibody molecule.

[0085]

After migrating into cancer cells, the antibody-drug conjugate used in the present invention is cleaved at the linker portion to release the compound represented by the following formula:

[0086]

[Formula 20]



[0087]

[0088]

The aforementioned compound is inferred to be the original source of the antitumor activity of the antibody-drug conjugate used in the present invention, and has been confirmed to have a topoisomerase I inhibitory effect (Ogitani Y. et al., Clinical Cancer

Research, 2016, Oct 15;22 (20) :5097-5108, Epub 2016 Mar 29.)

[0089]

Topoisomerase I is an enzyme that cleaves and rejoins single strands of DNA, thereby transforming the conformation of the DNA for participation in DNA synthesis. Therefore, agents with a topoisomerase I inhibitory effect can inhibit DNA synthesis, and thus arrest cell division at the S phase (DNA synthesis phase) of the cell cycle and induce cell death by apoptosis, thereby suppressing growth of cancer cells.

[0090]

On the other hand, tubulin inhibitors affect microtubule dynamics, and thus arrest cell division at the G_2 phase (pre-mitotic gap phase) and/or M phase (mitotic phase) of the cell cycle and induce cell death via apoptosis, thereby suppressing growth of cancer cells (Dumontet C, et al., Nat Rev Drug Discov. 2010 Oct; 9 (10): 790-803.) (Mukhtar E, et al., Mol Cancer Ther. 2014 Feb: 13 (2): 275-284.)

[0091]

Accordingly, the antibody-drug conjugate used in the present invention (which has an agent with topoisomerase I inhibitory effect as the original source of the antitumor activity) is administered in combination with a tubulin inhibitor, thereby arresting cell division at the S phase and G_2 phase and/or M phase of the cell cycle in

multiple manners, thus enabling it to exert an excellent combined effect (antitumor effect).

[0092]

The antibody-drug conjugate used in the present invention is also known to have a bystander effect (Ogitani Y. et al., Cancer Science (2016) 107, 1039-1046).

[0093]

The bystander effect is exerted through a process such that the antibody-drug conjugate used in the present invention is internalized in cancer cells expressing the target and the aforementioned compound is released and then exerts an antitumor effect also on cancer cells which are present therearound and not expressing the target.

[0094]

The bystander effect is also exerted as an excellent antitumor effect when the antibody-drug conjugate according to the present invention is used in combination with a tubulin inhibitor.

[0095]

2. Antibody in the antibody-drug conjugate

The antibody in the antibody-drug conjugate used in the present invention may be derived from any species, and is preferably an antibody derived from a human, a rat, a mouse, or a rabbit. In cases when the antibody is derived from species other than human species, it is preferably chimerized or humanized using a well-known

technique. The antibody of the present invention may be a polyclonal antibody or a monoclonal antibody and is preferably a monoclonal antibody.

[0096]

The antibody in the antibody-drug conjugate used in the present invention is an antibody preferably having the characteristic of being able to target cancer cells, and is preferably an antibody possessing, for example, the property of being able to recognize a cancer cell, the property of being able to bind to a cancer cell, the property of being internalized in a cancer cell, and/or cytocidal activity against cancer cells.

[0097]

The binding activity of the antibody against cancer cells can be confirmed using flow cytometry. The internalization of the antibody into tumor cells can be confirmed using (1) an assay of visualizing an antibody incorporated in cells under a fluorescence microscope using a secondary antibody (fluorescently labeled) binding to the therapeutic antibody (Cell Death and Differentiation (2008) 15, 751-761), (2) an assay of measuring a fluorescence intensity incorporated in cells using a secondary antibody (fluorescently labeled) binding to the therapeutic antibody (Molecular Biology of the Cell, Vol. 15, 5268-5282, December 2004), or (3) a Mab-ZAP assay using an immunotoxin binding to the therapeutic antibody wherein the toxin is released upon

incorporation into cells to inhibit cell growth (Bio Techniques 28: 162-165, January 2000). As the immunotoxin, a recombinant complex protein of a diphtheria toxin catalytic domain and protein G may be used.

[0098]

The antitumor activity of the antibody can be confirmed in vitro by determining inhibitory activity against cell growth. For example, a cancer cell line overexpressing a target protein for the antibody is cultured, and the antibody is added at varying concentrations into the culture system to determine inhibitory activity against focus formation, colony formation, and spheroid growth. The antitumor activity can be confirmed in vivo, for example, by administering the antibody to a nude mouse with a transplanted cancer cell line highly expressing the target protein, and determining changes in the cancer cells.

[0099]

Since the compound conjugated in the antibody-drug conjugate exerts an antitumor effect, it is preferred but not essential that the antibody itself should have an antitumor effect. For the purpose of specifically and selectively exerting the cytotoxic activity of the antitumor compound against cancer cells, it is important and also preferred that the antibody should have the

property of being internalized to migrate into cancer cells.

[0100]

The antibody in the antibody-drug conjugate used in the present invention can be obtained by a procedure known in the art. For example, the antibody of the present invention can be obtained using a method usually carried out in the art, which involves immunizing animals with an antigenic polypeptide and collecting and purifying antibodies produced in vivo. The origin of the antigen is not limited to humans, and the animals may be immunized with an antigen derived from a non-human animal such as a mouse, a rat and the like. In this case, the cross-reactivity of antibodies binding to the obtained heterologous antigen with human antigens can be tested to screen for an antibody applicable to a human disease.

[0101]

Alternatively, antibody-producing cells which produce antibodies against the antigen can be fused with myeloma cells according to a method known in the art (for example, Kohler and Milstein, Nature (1975) 256, p.495-497; Kennet, R. ed., Monoclonal Antibodies, p.365-367, Plenum Press, N.Y. (1980)), to establish hybridomas, from which monoclonal antibodies can in turn be obtained.

[0102]

The antigen can be obtained by genetically engineering host cells to produce a gene encoding the

antigenic protein. Specifically, vectors that permit expression of the antigen gene are prepared and transferred to host cells so that the gene is expressed. The antigen thus expressed can be purified. The antibody can also be obtained by a method of immunizing animals with the above-described genetically engineered antigen-expressing cells or a cell line expressing the antigen.

[0103]

The antibody in the antibody-drug conjugate used in the present invention is preferably a recombinant antibody obtained by artificial modification for the purpose of decreasing heterologous antigenicity to humans such as a chimeric antibody or a humanized antibody, or is preferably an antibody having only the gene sequence of an antibody derived from a human, that is, a human antibody. These antibodies can be produced using a known method.

[0104]

As the chimeric antibody, an antibody in which antibody variable and constant regions are derived from different species, for example, a chimeric antibody in which a mouse- or rat-derived antibody variable region is connected to a human-derived antibody constant region can be exemplified (Proc. Natl. Acad. Sci. USA, 81, 6851-6855, (1984)).

[0105]

As the humanized antibody, an antibody obtained by integrating only the complementarity determining region (CDR) of a heterologous antibody into a human-derived antibody (Nature (1986) 321, pp. 522-525), an antibody obtained by grafting a part of the amino acid residues of the framework of a heterologous antibody as well as the CDR sequence of the heterologous antibody to a human antibody by a CDR-grafting method (WO 90/07861), and an antibody humanized using a gene conversion mutagenesis strategy (U.S. Patent No. 5821337) can be exemplified.
[0106]

As the human antibody, an antibody generated by using a human antibody-producing mouse having a human chromosome fragment including genes of a heavy chain and a light chain of a human antibody (see Tomizuka, K. et al., Nature Genetics (1997) 16, p.133-143; Kuroiwa, Y. et. al., Nucl. Acids Res. (1998) 26, p.3447-3448; Yoshida, H. et. al., Animal Cell Technology: Basic and Applied Aspects vol.10, p.69-73 (Kitagawa, Y., Matsuda, T. and Iijima, S. eds.), Kluwer Academic Publishers, 1999; Tomizuka, K. et. al., Proc. Natl. Acad. Sci. USA (2000) 97, p.722-727, etc.) can be exemplified. As an alternative, an antibody obtained by phage display, the antibody being selected from a human antibody library (see Wormstone, I. M. et. al, Investigative Ophthalmology & Visual Science. (2002) 43 (7), p.2301-2308; Carmen, S. et. al., Briefings in Functional Genomics and Proteomics

(2002), 1 (2), p.189-203; Siriwardena, D. et. al., Ophthalmology (2002) 109 (3), p.427-431, etc.) can be exemplified.

[0107]

In the antibody in the antibody-drug conjugate used in present invention, modified variants of the antibody are also included. The modified variant refers to a variant obtained by subjecting the antibody according to the present invention to chemical or biological modification. Examples of the chemically modified variant include variants including a linkage of a chemical moiety to an amino acid skeleton, variants including a linkage of a chemical moiety to an N-linked or O-linked carbohydrate chain, etc. Examples of the biologically modified variant include variants obtained by post-translational modification (such as N-linked or O-linked glycosylation, N- or C-terminal processing, deamidation, isomerization of aspartic acid, or oxidation of methionine), and variants in which a methionine residue has been added to the N terminus by being expressed in a prokaryotic host cell. Further, an antibody labeled so as to enable the detection or isolation of the antibody or an antigen according to the present invention, for example, an enzyme-labeled antibody, a fluorescence-labeled antibody, and an affinity-labeled antibody are also included in the meaning of the modified variant. Such a modified variant

of the antibody according to the present invention is useful for improving the stability and blood retention of the antibody, reducing the antigenicity thereof, detecting or isolating an antibody or an antigen, and so on.

[0108]

Further, by regulating the modification of a glycan which is linked to the antibody according to the present invention (glycosylation, defucosylation, etc.), it is possible to enhance antibody-dependent cellular cytotoxic activity. As the technique for regulating the modification of a glycan of antibodies, WO 99/54342, WO 00/61739, WO 02/31140, WO 2007/133855, WO 2013/120066, etc. are known. However, the technique is not limited thereto. In the antibody according to the present invention, antibodies in which the modification of a glycan is regulated are also included.

[0109]

It is known that a lysine residue at the carboxyl terminus of the heavy chain of an antibody produced in a cultured mammalian cell is deleted (Journal of Chromatography A, 705: 129-134 (1995)), and it is also known that two amino acid residues (glycine and lysine) at the carboxyl terminus of the heavy chain of an antibody produced in a cultured mammalian cell are deleted and a proline residue newly located at the carboxyl terminus is amidated (Analytical Biochemistry,

360: 75-83 (2007)). However, such deletion and modification of the heavy chain sequence do not affect the antigen-binding affinity and the effector function (complement activation, antibody-dependent cellular cytotoxicity, etc.) of the antibody. Therefore, in the antibody according to the present invention, antibodies subjected to such modification and functional fragments of the antibody are also included, and deletion variants in which one or two amino acids have been deleted at the carboxyl terminus of the heavy chain, variants obtained by amidation of the deletion variants (for example, a heavy chain in which the carboxyl terminal proline residue has been amidated), and the like are also included. The type of deletion variant having a deletion at the carboxyl terminus of the heavy chain of the antibody according to the present invention is not limited to the above variants as long as the antigen-binding affinity and the effector function are conserved. The two heavy chains constituting the antibody according to the present invention may be of one type selected from the group consisting of a full-length heavy chain and the above-described deletion variant, or may be of two types in combination selected therefrom. The ratio of the amount of each deletion variant can be affected by the type of cultured mammalian cells which produce the antibody according to the present invention and the culture conditions; however, an antibody in which one

amino acid residue at the carboxyl terminus has been deleted in both of the two heavy chains in the antibody according to the present invention can be preferably exemplified.

[0110]

As isotypes of the antibody according to the present invention, for example, IgG (IgG1, IgG2, IgG3, IgG4) can be exemplified. Preferably, IgG1 or IgG2 can be exemplified.

[0111]

Examples of antibodies in the antibody-drug conjugate used in the present invention can include, but are not particularly limited to, an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-CD3 antibody, an anti-CD30 antibody, an anti-CD33 antibody, an anti-CD37 antibody, an anti-CD56 antibody, an anti-CD98 antibody, an anti-DR5 antibody, an anti-EGFR antibody, an anti-EPHA2 antibody, an anti-FGFR2 antibody, an anti-FGFR4 antibody, an anti-FOLR1 antibody, an anti-VEGF antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD70 antibody, an anti-PSMA antibody, an anti-CEA antibody, an anti-Mesothelin antibody, an anti-A33 antibody, an anti-CanAg antibody, an anti-Cripto antibody, an anti-G250 antibody, an anti-MUC1 antibody, an anti-GPNMB antibody, an anti-Integrin antibody, an anti-Tenascin-C antibody, an anti-SLC44A4 antibody, an anti-GPR20 antibody, and an anti-

CDH6 antibody. Further, an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, an anti-GPR20 antibody, and an anti-CDH6 antibody can be preferably exemplified.

[0112]

In the present invention, the term "anti-HER2 antibody" refers to an antibody which binds specifically to HER2 (Human Epidermal Growth Factor Receptor Type 2; ErbB-2), and preferably has an activity of internalization in HER2-expressing cells by binding to HER2.

[0113]

Examples of the anti-HER2 antibody include trastuzumab (U.S. Patent No. 5821337) and pertuzumab (International Publication No. WO 01/00245). Preferably, trastuzumab can be exemplified.

[0114]

In the present invention, the term "anti-HER3 antibody" refers to an antibody which binds specifically to HER3 (Human Epidermal Growth Factor Receptor Type 3; ErbB-3), and preferably has an activity of internalization in HER3-expressing cells by binding to HER3.

[0115]

Examples of the anti-HER3 antibody include patritumab (U3-1287), U1-59 (International Publication No. WO 2007/077028), MM-121 (seribantumab), an anti-ERBB3

antibody described in International Publication No. WO 2008/100624, RG-7116 (lumretuzumab), and LJM-716 (elgemtumab). Preferably, patritumab and U1-59 can be exemplified.

[0116]

In the present invention, the term "anti-TROP2 antibody" refers to an antibody which binds specifically to TROP2 (TACSTD2: Tumor-associated calcium signal transducer 2; EGP-1), and preferably has an activity of internalization in TROP2-expressing cells by binding to TROP2.

[0117]

Examples of the anti-TROP2 antibody include hTINA1-H1L1 (International Publication No. WO 2015/098099).

[0118]

In the present invention, the term "anti-B7-H3 antibody" refers to an antibody which binds specifically to B7-H3 (B cell antigen #7 homolog 3; PD-L3; CD276), and preferably has an activity of internalization in B7-H3-expressing cells by binding to B7-H3.

[0119]

Examples of the anti-B7-H3 antibody include M30-H1-L4 (International Publication No. WO 2014/057687).

[0120]

In the present invention, the term "anti-GPR20 antibody" refers to an antibody which binds specifically to GPR20 (G Protein-coupled receptor 20), and preferably

has an activity of internalization in GPR20-expressing cells by binding to GPR20.

[0121]

Examples of the anti-GPR20 antibody include h046-H4e/L7 (International Publication No. WO 2018/135501).

[0122]

In the present invention, the term "anti-CDH6 antibody" refers to an antibody which binds specifically to CDH6 (Cadherin-6), and preferably has an activity of internalization in CDH6-expressing cells by binding to CDH6.

[0123]

Examples of the anti-CDH6 antibody include H01L02 (International Publication No. WO 2018/212136).

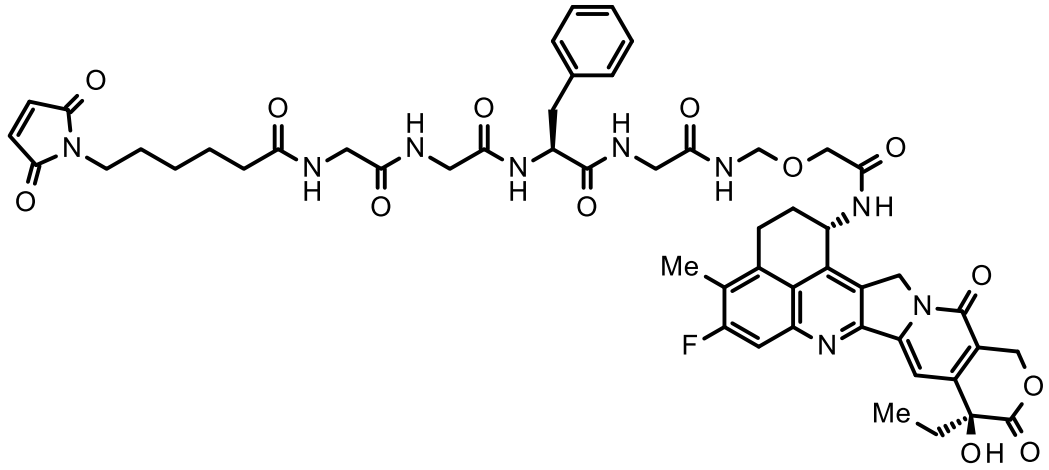
[0124]

3. Production of the antibody-drug conjugate

A drug-linker intermediate for use in the production of the antibody-drug conjugate used in to the present invention is represented by the following formula.

[0125]

[Formula 21]



[0126]

The drug-linker intermediate can be expressed as the chemical name N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]glycylglycyl-L-phenylalanyl-N-[(2-{[(1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl]amino}-2-oxoethoxy)methyl]glycinamide, and can be produced with reference to descriptions in International Publication No. WO 2014/057687, International Publication No. WO 2015/098099, International Publication No. WO 2015/115091, International Publication No. WO 2015/155998, International Publication No. WO 2019/044947, and so on.

[0127]

The antibody-drug conjugate used in the present invention can be produced by reacting the above-described drug-linker intermediate and an antibody having a thiol group (alternatively referred to as a sulfhydryl group).

[0128]

The antibody having a sulfhydryl group can be obtained by a method well known in the art (Hermanson, G. T, Bioconjugate Techniques, pp. 56-136, pp. 456-493, Academic Press (1996)). For example, by using 0.3 to 3 molar equivalents of a reducing agent such as tris(2-carboxyethyl)phosphine hydrochloride (TCEP) per interchain disulfide within the antibody and reacting with the antibody in a buffer solution containing a chelating agent such as ethylenediamine tetraacetic acid (EDTA), an antibody having a sulfhydryl group with partially or completely reduced interchain disulfides within the antibody can be obtained.

[0129]

Further, by using 2 to 20 molar equivalents of the drug-linker intermediate per the antibody having a sulfhydryl group, an antibody-drug conjugate in which 2 to 8 drug molecules are conjugated per antibody molecule can be produced.

[0130]

The average number of conjugated drug molecules per antibody molecule of the antibody-drug conjugate produced can be determined, for example, by a method of calculation based on measurement of UV absorbance for the antibody-drug conjugate and the conjugation precursor thereof at two wavelengths of 280 nm and 370 nm (UV method), or a method of calculation based on

quantification through HPLC measurement for fragments obtained by treating the antibody-drug conjugate with a reducing agent (HPLC method).

[0131]

Conjugation between the antibody and the drug-linker intermediate and calculation of the average number of conjugated drug molecules per antibody molecule of the antibody-drug conjugate can be performed with reference to descriptions in International Publication No. WO 2014/057687, International Publication No. WO 2015/098099, International Publication No. WO 2015/115091, International Publication No. WO 2015/155998, International Publication No. WO 2018/135501, International Publication No. WO 2018/212136, and so on.

[0132]

In the present invention, the term "anti-HER2 antibody-drug conjugate" refers to an antibody-drug conjugate such that the antibody in the antibody-drug conjugate according to the invention is an anti-HER2 antibody.

[0133]

The anti-HER2 antibody is preferably 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; or 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.

[0134]

The average number of units of the drug-linker conjugated per antibody molecule in the anti-HER2 antibody-drug conjugate is preferably 2 to 8, more preferably 3 to 8, even more preferably 7 to 8, even more preferably 7.5 to 8, and even more preferably about 8.

[0135]

The anti-HER2 antibody-drug conjugate can be produced with reference to descriptions in International Publication No. WO 2015/115091 and so on.

[0136]

In the present invention, the term "anti-HER3 antibody-drug conjugate" refers to an antibody-drug conjugate such that the antibody in the antibody-drug conjugate according to the invention is an anti-HER3 antibody.

[0137]

The anti-HER3 antibody is preferably an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence consisting of amino acid residues 26 to 35 of SEQ ID NO: 3, CDRH2 consisting of an amino acid sequence consisting of amino acid residues 50 to 65 of SEQ ID NO: 3, and CDRH3 consisting of an amino acid sequence consisting of amino acid residues 98 to 106 of

SEQ ID NO: 3, and a light chain comprising CDRL1 consisting of an amino acid sequence consisting of amino acid residues 24 to 39 of SEQ ID NO: 4, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 56 to 62 of SEQ ID NO: 4, and CDRL3 consisting of an amino acid sequence consisting of amino acid residues 95 to 103 of SEQ ID NO: 4,

more preferably an antibody comprising a heavy chain comprising a heavy chain variable region consisting of an amino acid sequence consisting of amino acid residues 1 to 117 of SEQ ID NO: 3, and a light chain comprising a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 1 to 113 of SEQ ID NO: 4, and

even more preferably an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[0138]

The average number of units of the drug-linker conjugated per antibody molecule in the anti-HER3 antibody-drug conjugate is preferably 2 to 8, more preferably 3 to 8, even more preferably 7 to 8, even more preferably 7.5 to 8, and even more preferably about 8.

[0139]

The anti-HER3 antibody-drug conjugate can be produced with reference to descriptions in International Publication No. WO 2015/155998 and so on.

[0140]

In the present invention, the term "anti-TROP2 antibody-drug conjugate" refers to an antibody-drug conjugate such that the antibody in the antibody-drug conjugate according to the invention is an anti-TROP2 antibody.

[0141]

The anti-TROP2 antibody is preferably an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence consisting of amino acid residues 50 to 54 of SEQ ID NO: 5, CDRH2 consisting of an amino acid sequence consisting of amino acid residues 69 to 85 of SEQ ID NO: 5, and CDRH3 consisting of an amino acid sequence consisting of amino acid residues 118 to 129 of SEQ ID NO: 5, and a light chain comprising CDRL1 consisting of an amino acid sequence consisting of amino acid residues 44 to 54 of SEQ ID NO: 6, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 70 to 76 of SEQ ID NO: 6, and CDRL3 consisting of an amino acid sequence consisting of amino acid residues 109 to 117 of SEQ ID NO: 6,

more preferably an antibody comprising a heavy chain comprising a heavy chain variable region consisting of an amino acid sequence consisting of amino acid residues 20

to 140 of SEQ ID NO: 5, and a light chain comprising a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 21 to 129 of SEQ ID NO: 6, and

even more preferably an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[0142]

The average number of units of the drug-linker conjugated per antibody molecule in the anti-TROP2 antibody-drug conjugate is preferably 2 to 8, more preferably 3 to 5, even more preferably 3.5 to 4.5, and even more preferably about 4.

[0143]

The anti-TROP2 antibody-drug conjugate can be produced with reference to descriptions in International Publication No. WO 2015/098099 and so on.

[0144]

In the present invention, the term "anti-B7-H3 antibody-drug conjugate" refers to an antibody-drug conjugate such that the antibody in the antibody-drug conjugate according to the invention is an anti-B7-H3 antibody.

[0145]

The anti-B7-H3 antibody is preferably an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence consisting of amino acid residues 50 to 54 of SEQ ID NO: 7, CDRH2 consisting of an amino acid sequence consisting of amino acid residues 69 to 85 of SEQ ID NO: 7, and CDRH3 consisting of an amino acid sequence consisting of amino acid residues 118 to 130 of SEQ ID NO: 7, and a light chain comprising CDRL1 consisting of an amino acid sequence consisting of amino acid residues 44 to 53 of SEQ ID NO: 8, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 69 to 75 of SEQ ID NO: 8, and CDRL3 consisting of an amino acid sequence consisting of amino acid residues 108 to 116 of SEQ ID NO: 8,

more preferably an antibody comprising a heavy chain comprising a heavy chain variable region consisting of an amino acid sequence consisting of amino acid residues 20 to 141 of SEQ ID NO: 7, and a light chain comprising a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 21 to 128 of SEQ ID NO: 8, and

even more preferably an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8, or a

variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[0146]

The average number of units of the drug-linker conjugated per antibody molecule in the anti-B7-H3 antibody-drug conjugate is preferably 2 to 8, more preferably 3 to 5, even more preferably 3.5 to 4.5, and even more preferably about 4.

[0147]

The anti-B7-H3 antibody-drug conjugate used in the present invention can be produced with reference to descriptions in International Publication No. WO 2014/057687 and so on.

[0148]

In the present invention, the term "anti-GPR20 antibody-drug conjugate" refers to an antibody-drug conjugate such that the antibody in the antibody-drug conjugate according to the invention is an anti-GPR20 antibody.

[0149]

The anti-GPR20 antibody is preferably an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence consisting of amino acid residues 45 to 54 of SEQ ID NO: 9, CDRH2 consisting of an amino acid sequence consisting of amino acid residues 69 to 78 of SEQ ID NO: 9, and CDRH3 consisting of an amino acid sequence consisting of amino acid residues 118 to 131 of

SEQ ID NO: 9, and a light chain comprising CDRL1 consisting of an amino acid sequence consisting of amino acid residues 44 to 54 of SEQ ID NO: 10, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 70 to 76 of SEQ ID NO: 10, and CDRL3 consisting of an amino acid sequence consisting of amino acid residues 109 to 117 of SEQ ID NO: 10,

more preferably an antibody comprising a heavy chain comprising a heavy chain variable region consisting of an amino acid sequence consisting of amino acid residues 20 to 142 of SEQ ID NO: 9, and a light chain comprising a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 21 to 129 of SEQ ID NO: 10, and

even more preferably an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[0150]

The average number of units of the drug-linker conjugated per antibody molecule in the anti-GPR20 antibody-drug conjugate is preferably 2 to 8, more preferably 3 to 8, even more preferably 7 to 8, even more preferably 7.5 to 8, and even more preferably about 8.

[0151]

The anti-GPR20 antibody-drug conjugate can be produced with reference to descriptions in International Publication No. WO 2018/135501 and so on.

[0152]

In the present invention, the term "anti-CDH6 antibody-drug conjugate" refers to an antibody-drug conjugate such that the antibody in the antibody-drug conjugate according to the invention is an anti-CDH6 antibody.

[0153]

The anti-CDH6 antibody is preferably an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence consisting of amino acid residues 45 to 54 of SEQ ID NO: 11, CDRH2 consisting of an amino acid sequence consisting of amino acid residues 69 to 78 of SEQ ID NO: 11, and CDRH3 consisting of an amino acid sequence consisting of amino acid residues 118 to 130 of SEQ ID NO: 11, and a light chain comprising CDRL1 consisting of an amino acid sequence consisting of amino acid residues 44 to 54 of SEQ ID NO: 12, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 70 to 76 of SEQ ID NO: 12, and CDRL3 consisting of an amino acid sequence consisting of amino acid residues 109 to 116 of SEQ ID NO: 12,

more preferably an antibody comprising a heavy chain comprising a heavy chain variable region consisting of an

amino acid sequence consisting of amino acid residues 20 to 141 of SEQ ID NO: 11, and a light chain comprising a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 21 to 128 of SEQ ID NO: 12, and

even more preferably an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[0154]

The average number of units of the drug-linker conjugated per antibody molecule in the anti-CDH6 antibody-drug conjugate is preferably 2 to 8, more preferably 3 to 8, even more preferably 7 to 8, even more preferably 7.5 to 8, and even more preferably about 8.

[0155]

The anti-CDH6 antibody-drug conjugate can be produced with reference to descriptions in International Publication No. WO 2018/212136 and so on.

[0156]

4. Tubulin inhibitor

In the present invention, the term "tubulin inhibitor" refers to an agent that affects microtubule

dynamics, and thus arrests cell division at the G_2 phase (pre-mitotic gap phase) and/or M phase (mitotic phase) of the cell cycle and induces cell death by apoptosis, thereby suppressing growth of cancer cells (Dumontet C, et al., Nat Rev Drug Discov. 2010 Oct; 9 (10): 790-803.)(Mukhtar E, et al., Mol Cancer Ther. 2014 Feb: 13 (2): 275-284.).

[0157]

Tubulin inhibitors include agents that promote tubulin polymerization, thereby affecting microtubule dynamics (referred to as "tubulin polymerization accelerator" in the present invention); and agents that inhibit tubulin polymerization, thereby affecting microtubule dynamics (referred to as "tubulin polymerization inhibitor" in the present invention).

[0158]

Known tubulin polymerization accelerators include taxanes (such as paclitaxel, docetaxel, and cabazitaxel). Known tubulin polymerization inhibitors include halichondrins (such as eribulin), vinca alkaloids (such as vincristine, vinblastine, vinorelbine, and vindesine), dolastatins (such as MMAE and MMAF), and maytansinoids (such as DM1 and DM4). These agents and pharmacologically acceptable salts thereof can be used as the tubulin inhibitors in the present invention. Furthermore, a conjugate of any of these drugs to albumin (e.g., nab-paclitaxel, which is a conjugate of paclitaxel

with albumin), and an antibody-drug conjugate in which any of these drugs is conjugated to an antibody via a linker (e.g., brentuximab vedotin, which is an antibody-drug conjugate in which MMAE is conjugated to an anti-CD30 antibody via a linker; trastuzumab emtansine, which is an antibody-drug conjugate in which DM1 is conjugated to an anti-HER2 antibody via a linker; CDX-011, which is an antibody-drug conjugate in which MMAE is conjugated to an anti-GPMNB antibody via a linker [International Publication No. WO 2006/071441 and the like]; IMGN-853, which is an antibody-drug conjugate in which DM4 is conjugated to an anti-FOLR1 antibody via a linker [International Publication No. WO 2017/049149 and the like]; RG-7596, which is an antibody-drug conjugate in which MMAE is conjugated to an anti-CD79b antibody via a linker [U.S. Patent Application Publication No. 2017/304438 and the like]; SAR-3419, which is an antibody-drug conjugate in which DM4 is conjugated to an anti-CD19 antibody via a linker [U.S. Patent Application Publication No. 2015/071949 and the like]; PSMA-ADC, which is an antibody-drug conjugate in which MMAE is conjugated to an anti-PSMA antibody via a linker [International Publication No. WO 2007/002222 and the like]; BT-062, which is an antibody-drug conjugate in which DM4 is conjugated to an anti-CD138 antibody via a linker [U.S. Patent Application Publication No. 2007/183971 and the like]; BAY-94-9343, which is an

antibody-drug conjugate in which DM4 is conjugated to an anti-mesothelin antibody via a linker [International Publication No. WO 2010/124797 and the like]; SGN-CD19A, which is an antibody-drug conjugate in which MMAF is conjugated to an anti-CD19 antibody via a linker [International Publication No. WO 2009/052431 and the like]; AGS-16C3F, which is an antibody-drug conjugate in which MMAF is conjugated to an anti-ENPP3 antibody via a linker); and the like can also be used as the tubulin inhibitor in the present invention.

[0159]

Among the tubulin inhibitors preferably used in the present invention, tubulin polymerization accelerators can be exemplified by taxanes or pharmacologically acceptable salts thereof, or a conjugate of taxanes to albumin; can be more preferably exemplified by paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel; can be even more preferably exemplified by paclitaxel, docetaxel trihydrate, or cabazitaxel acetonate, or nab-paclitaxel; and can be even more preferably exemplified by paclitaxel.

[0160]

Among the tubulin inhibitors preferably used in the present invention, tubulin polymerization inhibitors can be exemplified by halichondrins, or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which halichondrins is conjugated to an antibody via a

linker; can be more preferably exemplified by eribulin, or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to an antibody via a linker (e.g., MORAb-202, which is an antibody-drug conjugate in which eribulin is conjugated to an anti-FOLR1 antibody via a linker [U.S. Patent Application Publication No. 2017/252458 and the like]); and can be even more preferably exemplified by eribulin mesylate.

[0161]

In the present invention, the term "pharmacologically acceptable salt" may be any of acid addition salts and base addition salts. Examples of the acid addition salts include lower alkanesulfonates such as camsylate (camphorsulfonate), mesylate (methanesulfonate), trifluoromethanesulfonate, and ethanesulfonate; arylsulfonates such as tosylate (p-toluenesulfonate) and benzenesulfonate; inorganic acid salts such as phosphate, nitrate, perchlorate, and sulfate; hydrohalides such as hydrochloride, hydrobromide, hydroiodide, and hydrofluoride; organic acid salts such as acetate, malate, fumarate, succinate, citrate, tartrate, oxalate, and maleate; and amino acid salts such as an ornithine salt, glutamate, and aspartate. Examples of the base addition salts include alkali metal salts such as a sodium salt, a potassium salt, and a lithium salt; alkaline earth metal salts such as a calcium salt

and a magnesium salt; inorganic salts such as an ammonium salt; organic amine salts such as a dibenzylamine salt, a morpholine salt, a phenylglycine alkyl ester salt, ethylenediamine salt, an N-methylglucamine salt, a diethylamine salt, a triethylamine salt, a cyclohexylamine salt, a dicyclohexylamine salt, an N,N'-dibenzylethylenediamine salt, a diethanolamine salt, an N-benzyl-N-(2-phenylethoxy)amine salt, a piperazine salt, a tetramethylammonium salt, and a tris(hydroxymethyl)aminomethane salt; and amino acid salts such as an arginine salt.

[0162]

Further, pharmacologically acceptable salts may exist as solvates, and these solvates are also included in the term "pharmacologically acceptable salt" according to the present invention. Examples of such solvates can include hydrates (for example, hemihydrate, monohydrate, dihydrate, trihydrate), ethanolate, and acetonate.

[0163]

5. Medicament

Described in the following are a pharmaceutical composition and a method of treatment according to the present invention, wherein an antibody-drug conjugate and a tubulin inhibitor are administered in combination.

[0164]

The pharmaceutical composition and method of treatment of the present invention may be those in which

the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations and are administered simultaneously or at different times, or may be those in which the antibody-drug conjugate and the tubulin inhibitor are contained as active components in a single formulation and administered.

[0165]

The pharmaceutical composition and method of treatment of the present invention can be used for treating cancer, and can be preferably used for treating at least one disease selected from the group consisting of breast cancer, gastric cancer (also called gastric adenocarcinoma), colorectal cancer (also called colon and rectal cancer, and including colon cancer and rectal cancer), lung cancer (including small cell lung cancer and non-small cell lung cancer), esophageal cancer, head-and-neck cancer (including salivary gland cancer and pharyngeal cancer), esophagogastric junction cancer, biliary tract cancer (including bile duct cancer), Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, uterine cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, endometrial cancer, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma,

plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, and melanoma; can be more preferably used for treating at least one cancer selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma; and can be even more preferably used for treating at least one cancer selected from the group consisting of breast cancer, gastric cancer, lung cancer, and ovarian cancer.

[0166]

Among the antibody-drug conjugates used in the present invention, the kind of antibody preferably used in the antibody-drug conjugate can be determined by examining the type of cancer and tumor markers. For example, if HER2 expression is found in the cancer, an anti-HER2 antibody-drug conjugate can be preferably used; if HER3 expression is found in the cancer, an anti-HER3 antibody-drug conjugate can be preferably used; if TROP2 expression is found in the cancer, an anti-TROP2 antibody-drug conjugate can be preferably used; if B7-H3 expression is found in the cancer, an anti-B7-H3 antibody-drug conjugate can be preferably used; if GPR20 expression is found in the cancer, an anti-GPR20 antibody-drug conjugate can be preferably used; and if

CDH6 expression is found in the cancer, an anti-CDH6 antibody-drug conjugate can be preferably used.

[0167]

The presence or absence of HER2, HER3, TROP2, B7-H3, GPR20, and CDH6, and other tumor markers can be checked by, for example, collecting tumor tissue from a cancer patient, and subjecting the formalin-fixed paraffin-embedded specimen (FFPE) to an examination at a gene product (protein) level, such as an immunohistochemistry (IHC) method, a flow cytometry, a western blot method, or an examination at a gene transcription level such as an in situ hybridization method (ISH), a quantitative PCR method (q-PCR), or a microarray analysis; alternatively, it can also be checked by collecting cell-free blood circulating tumor DNA (ctDNA) from a cancer patient and subjecting to an examination which uses a method such as next generation sequencing (NGS).

[0168]

The pharmaceutical composition and method of treatment of the present invention can be preferably used for mammals, and can be more preferably used for humans.

[0169]

The antitumor effect of the pharmaceutical composition and method of treatment of the present invention can be confirmed by, for example, generating a model in which cancer cells are transplanted to a test animal, and measuring reduction in tumor volume, life-

prolonging effects due to applying the pharmaceutical composition and method of treatment of the present invention. Furthermore, comparison with the antitumor effect of single administration of each of the antibody-drug conjugate and the tubulin inhibitor used in the present invention can provide confirmation of the combined effect of the antibody-drug conjugate and the tubulin inhibitor used in the present invention.

[0170]

In addition, the antitumor effect of the pharmaceutical composition and method of treatment of the present invention can be confirmed, in a clinical study, with the Response Evaluation Criteria in Solid Tumors (RECIST) evaluation method, WHO's evaluation method, Macdonald's evaluation method, measurement of body weight, and other methods; and can be determined by indicators such as Complete response (CR), Partial response (PR), Progressive disease (PD), Objective response rate (ORR), Duration of response (DoR), Progression-free survival (PFS), and Overall survival (OS).

[0171]

Further, the combined effect of the pharmaceutical composition and method of treatment of the present invention can also be determined based on variations in the expression level of a drug sensitivity factor and/or a drug resistance factor. For example, the expression level of the drug sensitivity factor and/or drug

resistance factor is compared among respective single administrations of the antibody-drug conjugate used in the present invention and the tubulin inhibitor, combined administration thereof, and non-administration (control) to a test subject. Then, when it can be confirmed that the tubulin inhibitor suppresses decreased expression of a drug sensitivity factor caused by the administration of the antibody-drug conjugate used in the present invention, it can be determined that there is a combined effect of the antibody-drug conjugate and the tubulin inhibitor. Examples of such drug sensitivity factors include SLFN11. SLFN11 is known to be a sensitivity factor of a topoisomerase I inhibitor (Zoppoli G. et al., Proc Natl Acad Sci U S A. 2012; 109 (39): 15030-5). Alternatively, when it can be confirmed that the tubulin inhibitor suppresses increased expression of a drug resistance factor caused by the administration of the antibody-drug conjugate used in the present invention, it can be determined that there is a combined effect of the antibody-drug conjugate and the tubulin inhibitor. Examples of such drug resistance factors include ABCG2. ABCG2 is known to be a resistance factor (transporter) of the drug which is released from the antibody-drug conjugate according to the present invention (Nagai Y. et al., Xenobiotica. 2019; 49 (9): 1086-96). The expression level of the drug sensitivity factor and/or drug resistance factor can be compared at the gene (RNA, etc.)

level, and the expression level can also be compared at the protein level.

[0172]

The foregoing methods can provide confirmation of superiority in terms of the antitumor effect of the pharmaceutical composition and method of treatment of the present invention compared to existing pharmaceutical compositions and methods of treatment for cancer therapy.

[0173]

The pharmaceutical composition and method of treatment of the present invention can retard growth of cancer cells, suppress their proliferation, and further can kill cancer cells. These effects can allow cancer patients to be free from symptoms caused by cancer or can achieve an improvement in the QOL of cancer patients and attain a therapeutic effect by sustaining the lives of the cancer patients. Even if the pharmaceutical composition and method of treatment of the present invention do not accomplish the killing of cancer cells, they can achieve higher QOL of cancer patients while achieving longer-term survival, by inhibiting or controlling the growth of cancer cells.

[0174]

The pharmaceutical composition of the present invention can be expected to exert a therapeutic effect by application as systemic therapy to patients, and additionally, by local application to cancer tissues.

[0175]

The pharmaceutical composition of the present invention may be administered as a pharmaceutical composition containing at least one pharmaceutically suitable ingredient. The pharmaceutically suitable ingredient can be suitably selected and applied from formulation additives or the like that are generally used in the art, in view of the dosage, administration concentration or the like of the antibody-drug conjugate and the tubulin inhibitor used in the present invention. For example, the antibody-drug conjugate used in the present invention may be administered as a pharmaceutical composition containing a buffer such as a histidine buffer, an excipient such as sucrose or trehalose, and a surfactant such as polysorbate 80 or 20. The pharmaceutical composition containing the antibody-drug conjugate used in the present invention can be preferably used as an injection, can be more preferably used as an aqueous injection or a lyophilized injection, and can be even more preferably used as a lyophilized injection.

[0176]

In the case that the pharmaceutical composition containing the antibody-drug conjugate used in the present invention is an aqueous injection, it can be preferably diluted with a suitable diluent and then given as an intravenous infusion. For the diluent, a dextrose solution, physiological saline, and the like, can be

exemplified, and a dextrose solution can be preferably exemplified, and a 5% dextrose solution can be more preferably exemplified.

[0177]

In the case that the pharmaceutical composition containing the antibody-drug conjugate used in the present invention is a lyophilized injection, it can be preferably dissolved in water for injection, subsequently a required amount can be diluted with a suitable diluent and then given as an intravenous infusion. For the diluent, a dextrose solution, physiological saline, and the like, can be exemplified, and a dextrose solution can be preferably exemplified, and a 5% dextrose solution can be more preferably exemplified.

[0178]

Examples of the administration route which may be used to administer the pharmaceutical composition of the present invention include intravenous, intradermal, subcutaneous, intramuscular, and intraperitoneal routes; and preferably include an intravenous route.

[0179]

The antibody-drug conjugate used in the present invention can be administered to a human once at intervals of 1 to 180 days, and can be preferably administered once a week, once every 2 weeks, once every 3 weeks, or once every 4 weeks, and can be even more preferably administered once every 3 weeks. Also, the

antibody-drug conjugate used in the present invention can be administered at a dose of about 0.001 to 100 mg/kg, and can be preferably administered at a dose of 0.8 to 12.4 mg/kg. In the case that the antibody-drug conjugate used in the present invention is an anti-ER2 antibody-drug conjugate, it can be preferably administered once every 3 weeks at a dose of 0.8 mg/kg, 1.6 mg/kg, 3.2 mg/kg, 5.4 mg/kg, 6.4 mg/kg, 7.4 mg/kg, or 8 mg/kg. In the case that the antibody-drug conjugate used in the present invention is an anti-HER3 antibody-drug conjugate, it can be preferably administered once every 3 weeks at a dose of 1.6 mg/kg, 3.2 mg/kg, 4.8 mg/kg, 5.6 mg/kg, 6.4 mg/kg, 8.0 mg/kg, 9.6 mg/kg, or 12.8 mg/kg. In the case that the antibody-drug conjugate used in the present invention is an anti-TROP2 antibody-drug conjugate, it can be preferably administered once every 3 weeks at a dose of 0.27 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg, 6.0 mg/kg, or 8.0 mg/kg.

[0180]

The tubulin inhibitor according to the present invention can be administered to a human once at intervals of 1 to 180 days, and can be preferably administered once a week, once every 2 weeks, once every 3 weeks, or once every 4 weeks. Also, the tubulin inhibitor according to the present invention can be administered at a dose of about 0.001 to 100 mg/kg. In the case that the tubulin inhibitor according to the

present invention is paclitaxel, it can be preferably intravenously administered (by infusion) once a week or once every 3 weeks at a dose of 100, 125, 135, 175, or 260 mg/m^2 (body surface area). If it is administered once a week, the fourth week after 3-weeks of continuous administration is a drug holiday. In the case that the tubulin inhibitor according to the present invention is eribulin mesylate, it can be preferably intravenously administered once a week at a dose of 1.4 mg/m^2 (body surface area), and the third week after 2-weeks of continuous administration is a drug holiday.

[0181]

The pharmaceutical composition and method of treatment of the present invention may further contain a cancer therapeutic agent other than the antibody-drug conjugate and the tubulin inhibitor according to the present invention. The pharmaceutical composition and method of treatment of the present invention can also be administered in combination with another cancer therapeutic agent, thereby enhancing the antitumor effect. Other cancer therapeutic agents to be used for such purpose may be administered to a subject simultaneously with, separately from, or sequentially with the pharmaceutical composition of the present invention, or may be administered while varying the dosage interval for each. Such cancer therapeutic agents are not limited as long as they are agents having antitumor activity, and

can be exemplified by at least one selected from the group consisting of irinotecan (CPT-11), cisplatin, carboplatin, oxaliplatin, fluorouracil (5-FU), gemcitabine, capecitabine, doxorubicin, epirubicin, cyclophosphamide, mitomycin C, tegafur-gimeracil-oteracil combination, cetuximab, panitumumab, bevacizumab, ramucirumab, regorafenib, trifluridine-tipiracil combination, gefitinib, erlotinib, afatinib, methotrexate, pemetrexed, tamoxifen, toremifene, fulvestrant, leuprorelin, goserelin, letrozole, anastrozole, progesterone formulation, trastuzumab, pertuzumab, and lapatinib.

[0182]

The pharmaceutical composition and method of treatment of the present invention can also be used in combination with radiotherapy. For example, a cancer patient may receive radiotherapy before and/or after or simultaneously with receiving therapy with the pharmaceutical composition of the present invention.

[0183]

The pharmaceutical composition and method of treatment of the present invention can also be used as an adjuvant chemotherapy in combination with a surgical procedure. The pharmaceutical composition of the present invention may be administered for the purpose of diminishing the size of a tumor before a surgical procedure (referred to as pre-operative adjuvant

chemotherapy or neoadjuvant therapy), or may be administered after a surgical procedure for the purpose of preventing the recurrence of a tumor (referred to as post-operative adjuvant chemotherapy or adjuvant therapy).

Examples

[0184]

The present invention is specifically described in view of the examples shown below. However, the present invention is not limited to these. Further, it is by no means to be interpreted in a limited way.

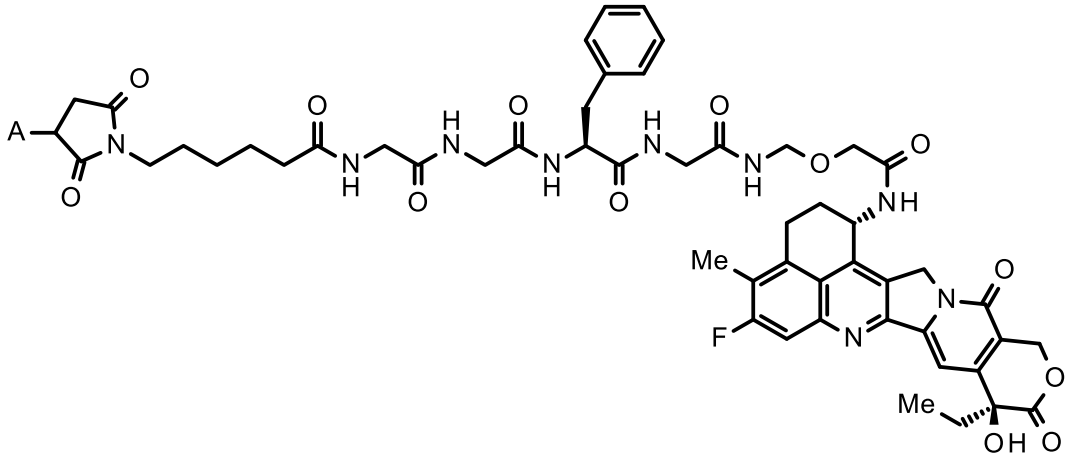
[0185]

Example 1: Production of the antibody-drug conjugate

In accordance with a production method described in International Publication No. WO 2015/115091 with use of a humanized anti-HER2 antibody (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), an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0186]

[Formula 22]



[0187]

wherein A represents a connecting position to an antibody,

is conjugated to the anti-HER2 antibody via a thioether bond (hereinafter referred to as the "antibody-drug conjugate (1)") was produced. The DAR of the antibody-drug conjugate (1) is 7.7 or 7.8.

[0188]

Example 2: Antitumor study (1)

Mouse: Female 5-6-week-old BALB/c nude mice (CHARLES RIVER LABORATORIES JAPAN, INC.) were subjected to the experiments.

[0189]

Measurement and calculation formula: In all studies, the major axis and minor axis of tumors were measured twice a week with an electronic digital caliper (CD15-CX, Mitutoyo Corp.), and the tumor volume (mm^3) was calculated. The calculation formula is as shown below.

Tumor volume (mm^3) = 1/2 × Major axis (mm) × [Minor axis (mm)]^2

The antibody-drug conjugate (1) was diluted with ABS buffer (10 mM acetate buffer [pH 5.5], 5% sorbitol), and intravenously administered in a fluid volume of 10 mL/kg to the tail vein. Paclitaxel was dissolved with cremophor and ethanol (1:1), diluted with physiological saline, and then intravenously administered to the tail vein in a fluid volume of 10 or 20 mL/kg. Eribulin mesylate was diluted with physiological saline, and intravenously administered to the tail vein in a fluid volume of 10 mL/kg.

[0190]

Human breast cancer cell line KPL-4, which was obtained from Dr. Junichi Kurebayashi in Kawasaki Medical School [British Journal of Cancer, (1999) 79 (5/6). 707-717], was suspended into physiological saline, subcutaneously transplanted at 1.5×10^7 cells into the right side of female nude mice, and the mice were randomly grouped 17 days after the transplantation (Day 0). The antibody-drug conjugate (1) (DAR: 7.8) was intravenously administered to the tail vein at a dose of 7.5 mg/kg on Day 0. Paclitaxel was intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0 and Day 7, and eribulin mesylate was intravenously administered to the tail vein at a dose of 0.8 mg/kg on Day 0 and Day 4. Single administration groups of each

drug, a combined administration group, and a solvent administration group as a control group were set up. [0191]

Results of a combination of the antibody-drug conjugate (1) and paclitaxel are shown in Figure 9. Single administration of paclitaxel showed a tumor growth inhibition (TGI) of 48% in the last day of the study. Single administration of the antibody-drug conjugate (1) showed TGI of 87%. On the other hand, combined administration of the antibody-drug conjugate (1) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of paclitaxel ($P < 0.01$ [calculated by Dunnett's test; the same applies hereinafter]), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.05$); the combined effect was so strong that all cases exhibited disappearance of tumor (TGI, 100%). Here, in the Figure, the abscissa axis represents days after cell transplantation, and the longitudinal axis represents tumor volume. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss. Incidentally, in the following evaluation examples relating to antitumor studies, unless otherwise described, the studies are performed by the procedure used in this evaluation example.

[0192]

Results of a combination of the antibody-drug conjugate (1) and eribulin mesylate are shown in Figure 10. Single administration of eribulin mesylate showed TGI of 91%. Single administration of the antibody-drug conjugate (1) showed TGI of 87%. On the other hand, combined administration of the antibody-drug conjugate (1) and eribulin mesylate exhibited a significantly superior tumor growth suppression effect than single administration of eribulin mesylate ($P < 0.05$), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.05$); the combined effect was so strong that all cases exhibited disappearance of tumor (TGI, 100%). Here, in the Figure, the abscissa axis represents days after cell transplantation, and the longitudinal axis represents tumor volume. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0193]

Example 3: Antitumor study (2)

Human breast cancer cell line JIMT-1, which was purchased from DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH), was suspended into physiological saline, subcutaneously transplanted at 5×10^6 cells into the right side of female nude mice, and

the mice were randomly grouped 13 days after the transplantation (Day 0). The antibody-drug conjugate (1) (DAR: 7.7) was intravenously administered to the tail vein at a dose of 10 mg/kg on Day 0. Paclitaxel was intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0, Day 7 and Day 14. Eribulin mesylate was intravenously administered to the tail vein at a dose of 0.8 mg/kg on Day 0 and Day 3. Single administration groups of each drug, a combined administration group, and a solvent administration group as a control group were set up.

[0194]

Results of a combination of the antibody-drug conjugate (1) and paclitaxel are shown in Figure 11. Single administration of paclitaxel showed TGI of 30%. Single administration of the antibody-drug conjugate (1) showed TGI of 73%. On the other hand, combined administration of the antibody-drug conjugate (1) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of paclitaxel ($P < 0.001$), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.001$); TGI was 97%. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0195]

Results of a combination of the antibody-drug conjugate (1) and eribulin mesylate are shown in Figure 12. Single administration of eribulin mesylate showed TGI of 73%. Single administration of the antibody-drug conjugate (1) showed TGI of 73%. On the other hand, combined administration of the antibody-drug conjugate (1) and eribulin mesylate exhibited a significantly superior tumor growth suppression effect than single administration of eribulin mesylate ($P < 0.05$), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.001$); TGI was 97%. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0196]

Example 4: Antitumor study (3)

Human gastric cancer cell line NCI-N87, which was purchased from ATCC (American Type Culture Collection), was suspended into physiological saline, subcutaneously transplanted at 1×10^7 cells into the right side of female nude mice, and the mice were randomly grouped 6 days after the transplantation (Day 0). The antibody-drug conjugate (1) (DAR: 7.8) was intravenously administered to the tail vein at a dose of 1 mg/kg on Day 0. Paclitaxel was intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0 and Day 7. Eribulin

mesylate was intravenously administered to the tail vein at a dose of 0.4 mg/kg on Day 0 and Day 4. Single administration groups of each drug, a combined administration group, and a solvent administration group as a control group were set up.

[0197]

Results of a combination of the antibody-drug conjugate (1) and paclitaxel are shown in Figure 13. Single administration of paclitaxel showed TGI of 50%. Single administration of the antibody-drug conjugate (1) showed TGI of 45%. On the other hand, combined administration of the antibody-drug conjugate (1) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of paclitaxel ($P < 0.001$), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.001$); TGI was 82%. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0198]

Results of a combination of the antibody-drug conjugate (1) and eribulin mesylate are shown in Figure 14. Single administration of eribulin mesylate showed TGI of 64%. Single administration of the antibody-drug conjugate (1) showed TGI of 45%. On the other hand, combined administration of the antibody-drug conjugate

(1) and eribulin mesylate exhibited a significantly superior tumor growth suppression effect than single administration of eribulin mesylate ($P < 0.01$), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.001$); TGI was 77%. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0199]

Example 5: Antitumor study (4)

Human breast cancer cell line MDA-MB-453, which was purchased from ATCC, was suspended into Matrigel basal membrane matrix (Matrigel), subcutaneously transplanted at 1×10^7 cells into the right side of female nude mice, and the mice were randomly grouped 7 days after the transplantation (Day 0). The antibody-drug conjugate (1) (DAR: 7.8) was intravenously administered to the tail vein at a dose of 0.5 mg/kg on Day 0. Paclitaxel was intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0 and Day 7. Single administration groups of each drug, a combined administration group, and a solvent administration group as a control group were set up.

[0200]

Results of a combination of the antibody-drug conjugate (1) and paclitaxel are shown in Figure 15.

Single administration of paclitaxel showed TGI of 96%. Single administration of the antibody-drug conjugate (1) showed TGI of 75%. On the other hand, combined administration of the antibody-drug conjugate (1) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.01$); TGI was 100%. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0201]

Example 6: Antitumor study (5)

Human gastric cancer cell line SNU-1, which was purchased from ATCC, was suspended into Matrigel, subcutaneously transplanted at 1×10^7 cells into the right side of female nude mice, and the mice were randomly grouped 28 days after the transplantation (Day 0). The antibody-drug conjugate (1) (DAR: 7.8) was intravenously administered to the tail vein at a dose of 10 mg/kg on Day 0. Paclitaxel was intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0 and Day 7. Single administration groups of each drug, a combined administration group, and a solvent administration group as a control group were set up.

[0202]

Results of a combination of the antibody-drug conjugate (1) and paclitaxel are shown in Figure 16.

Single administration of paclitaxel showed TGI of 58%. Single administration of the antibody-drug conjugate (1) showed TGI of 79%. On the other hand, combined administration of the antibody-drug conjugate (1) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of paclitaxel ($P < 0.01$); TGI was 87%. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0203]

Example 7: Antitumor study (6)

Human lung cancer cell line NCI-H441, which was purchased from ATCC, was suspended into Matrigel, subcutaneously transplanted at 5×10^6 cells into the right side of female nude mice, and the mice were randomly grouped 7 days after the transplantation (Day 0). The antibody-drug conjugate (1) (DAR: 7.8) was intravenously administered to the tail vein at a dose of 10 mg/kg on Day 0. Paclitaxel was intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0 and Day 7. Single administration groups of each drug, a combined administration group, and a solvent administration group as a control group were set up.

[0204]

Results of a combination of the antibody-drug conjugate (1) and paclitaxel are shown in Figure 17. Single administration of paclitaxel showed TGI of 55%.

Single administration of the antibody-drug conjugate (1) showed TGI of 92%. On the other hand, combined administration of the antibody-drug conjugate (1) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of paclitaxel ($P < 0.001$), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (1) ($P < 0.01$); TGI was 99%. None of the single and combined administration groups exhibited any particular notable finding such as weight loss.

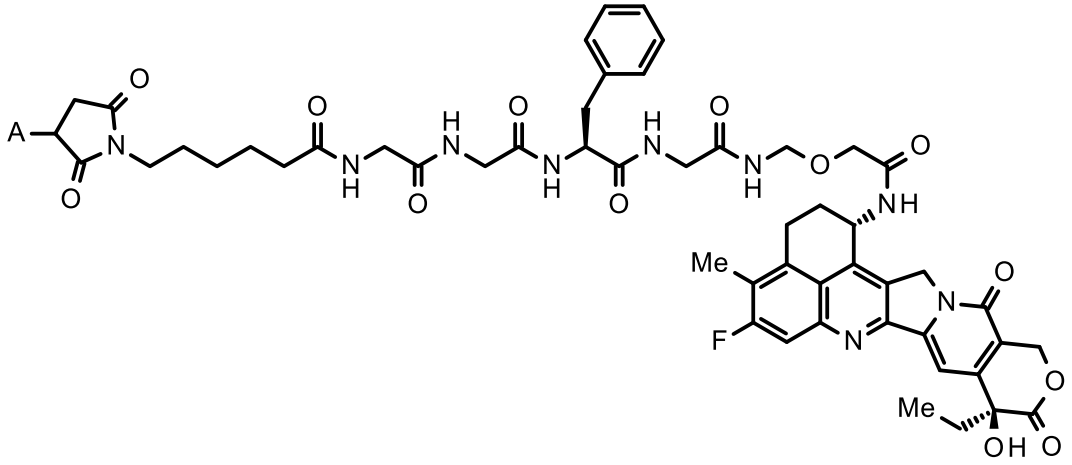
[0205]

Example 8: Production of the antibody-drug conjugate (2)

In accordance with a production method described in International Publication No. WO 2015/155998 with use of an anti-HER3 antibody (an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4), an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0206]

[Formula 23]



[0207]

wherein A represents a connecting position to an antibody,

is conjugated to the anti-HER3 antibody via a thioether bond (hereinafter referred to as "antibody-drug conjugate (2)") was produced. The DAR of the antibody-drug conjugate (2) is 7.6.

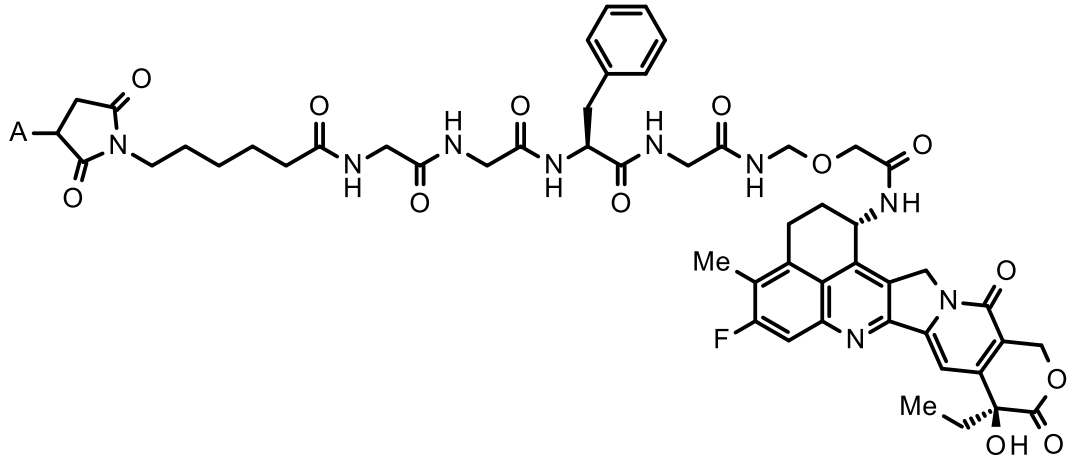
[0208]

Example 9: Production of the antibody-drug conjugate (3)

In accordance with a production method described in International Publication No. WO 2018/212136 with use of an anti-CDH6 antibody (an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 11 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 12), an antibody-drug conjugate in which a drug-linker represented by the following formula:

[0209]

[Formula 24]



[0210]

wherein A represents a connecting position to an antibody,

is conjugated to the anti-CDH6 antibody via a thioether bond (hereinafter referred to as "antibody-drug conjugate (3)") was produced. The DAR of the antibody-drug conjugate (3) is 7.8.

[0211]

Example 10: Antitumor study (7)

Human breast cancer cell line JIMT-1, which was purchased from DSMZ, was suspended into physiological saline, subcutaneously transplanted at 5×10^6 cells into the right side of female nude mice, and the mice were randomly grouped 10 days after the transplantation (Day 0). The antibody-drug conjugate (2) (DAR: 7.6) was intravenously administered to the tail vein at a dose of 10 mg/kg on Day 0, Day 7, and Day 14. Paclitaxel was

intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0 and Day 7. Single administration groups of each drug, a combined administration group, and a solvent administration group as a control group were set up.

[0212]

Results of a combination of the antibody-drug conjugate (2) and paclitaxel are shown in Figure 22. Single administration of paclitaxel showed TGI of 36%. Single administration of the antibody-drug conjugate (2) showed TGI of 69%. On the other hand, combined administration of the antibody-drug conjugate (2) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of paclitaxel ($P < 0.001$), and also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (2) ($P < 0.001$); TGI was 97%. None of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0213]

Example 11: Antitumor study (8)

Human ovarian cancer cell line OV-90, which was purchased from ATCC, was suspended into Matrigel, subcutaneously transplanted at 2.5×10^6 cells into the right side of female nude mice, and the mice were randomly grouped 15 days after the transplantation (Day

0). The antibody-drug conjugate (3) (DAR: 7.8) was intravenously administered to the tail vein at a dose of 10 mg/kg on Day 0. Paclitaxel was intravenously administered to the tail vein at a dose of 15 mg/kg on Day 0, Day 7, and Day 14. Single administration groups of each drug, a combined administration group, and a solvent administration group as a control group were set up.

[0214]

Results of a combination of the antibody-drug conjugate (3) and paclitaxel are shown in Figure 23. Single administration of paclitaxel on Day 17 showed TGI of 80%; single administration of the antibody-drug conjugate (3) showed TGI of 97%; and combined administration of the antibody-drug conjugate (3) and paclitaxel showed TGI of 99%. Further, combined administration of the antibody-drug conjugate (3) and paclitaxel exhibited a significantly superior tumor growth suppression effect than single administration of paclitaxel ($P < 0.001$) on Day 27. It also exhibited a significantly superior tumor growth suppression effect than single administration of the antibody-drug conjugate (3) ($P < 0.01$ (calculated by the Student's t-test)) on Day 38. In addition, none of the single and combined administration groups exhibited any particular notable finding such as weight loss.

[0215]

Example 12: RNA expression analysis

Human breast cancer cell line JIMT-1 is transplanted into nude mice, and single administration groups of the antibody-drug conjugate (1), paclitaxel, or eribulin mesylate, combined administration groups of the antibody-drug conjugate (1) and paclitaxel or the antibody-drug conjugate (1) and eribulin mesylate, and a control group are set up. Tumors are sampled before and after drug administration, and used in RNA expression analysis. After weight measurement, the tumors are incubated overnight in RNAlater RNA Stabilization Reagent, and stored at -80°C after RNAlater removal. RNA is extracted through QIACube using RNeasy Mini Kit (Qiagen N.V.), and a library is prepared from the obtained RNA using NEBNext Poly(A) mRNA Magnetic Module and NEBNext Ultra RNA Library Prep Kit for Illumina. The library is analyzed in Illumina NextSeq 500 or 550 sequencer using Illumina NextSeq 500/550 High Output Kit v2.5 to output base call files. The obtained base call files are converted to fastq files using bcl2fastq ver. 2.20.0.422. The reads of the fastq files are aligned against the reference sequences of transcripts based on human reference genome GRCh37 assembly using STAR ver. 2.5.3a15, and the number of reads of each gene is estimated with RSEM ver. 1.3.016. Gene expression levels are indicated by normalized Transcripts Per Kilobase Million (TPM) values by the

inter-sample median ratio normalization method using EBSeq ver. 1.22.0.

[0216]

It is confirmed that the average TPM value of the SLFN11 gene after single administration of the antibody-drug conjugate (1) shows a lower value than that in the tumors of the control group. Further, it is confirmed that the average TPM value of the SLFN11 gene after combined administration of the antibody-drug conjugate (1) and paclitaxel or after combined administration of the antibody-drug conjugate (1) and eribulin mesylate shows a higher value than that after single administration of the antibody-drug conjugate (1).

[0217]

Further, it is confirmed that the average TPM value of the ABCG2 gene after single administration of the antibody-drug conjugate (1) shows a higher value than that in the tumors of the control group. Further, it is confirmed that the average TPM value of the ABCG2 gene after combined administration of the antibody-drug conjugate (1) and paclitaxel or after combined administration of the antibody-drug conjugate (1) and eribulin mesylate shows a lower value than that after single administration of the antibody-drug conjugate (1).

[0218]

Example 13: Protein expression analysis

Human breast cancer cell line JIMT-1 is transplanted into nude mice, and single administration groups of the antibody-drug conjugate (1), paclitaxel, or eribulin mesylate, combined administration groups of the antibody-drug conjugate (1) and paclitaxel or the antibody-drug conjugate (1) and eribulin mesylate, and a control group are set up. Tumors are sampled before and after drug administration, and used in protein expression analysis. The tumors excised from the mice are homogenized and lysed in RIPA buffer, and supernatants after centrifugation are recovered as tumor lysates. SLFN11 protein expression and β-Actin expression in the obtained tumor lysates are detected using Simple Western Systems (Wes or Peggy Sue), and peak area values are calculated using Compass for SW ver. 4.0.0. The SLFN11 protein expression level ratio of each tumor lysate is calculated according to the following expression.

[0219]

SLFN11 protein expression level ratio = (Peak area value of the SLFN11 protein at each point in time / Peak area value of β-Actin at each point in time) / (Peak area value of the SLFN11 protein on Day 0 / Peak area value of β-Actin on Day 0)

It is confirmed that the SLFN11 protein expression level in the combined administration group of the antibody-drug conjugate (1) and paclitaxel or the combined administration group of the antibody-drug

conjugate (1) and eribulin mesylate shows a higher value than that in the single administration group of the antibody-drug conjugate (1).

Free Text of Sequence Listing

[0220]

SEQ ID NO: 1 - Amino acid sequence of a heavy chain of the anti-HER2 antibody

SEQ ID NO: 2 - Amino acid sequence of a light chain of the anti-HER2 antibody

SEQ ID NO: 3 - Amino acid sequence of a heavy chain of the anti-HER3 antibody

SEQ ID NO: 4 - Amino acid sequence of a light chain of the anti-HER3 antibody

SEQ ID NO: 5 - Amino acid sequence of a heavy chain of the anti-TROP2 antibody

SEQ ID NO: 6 - Amino acid sequence of a light chain of the anti-TROP2 antibody

SEQ ID NO: 7 - Amino acid sequence of a heavy chain of the anti-B7-H3 antibody

SEQ ID NO: 8 - Amino acid sequence of a light chain of the anti-B7-H3 antibody

SEQ ID NO: 9 - Amino acid sequence of a heavy chain of the anti-GPR20 antibody

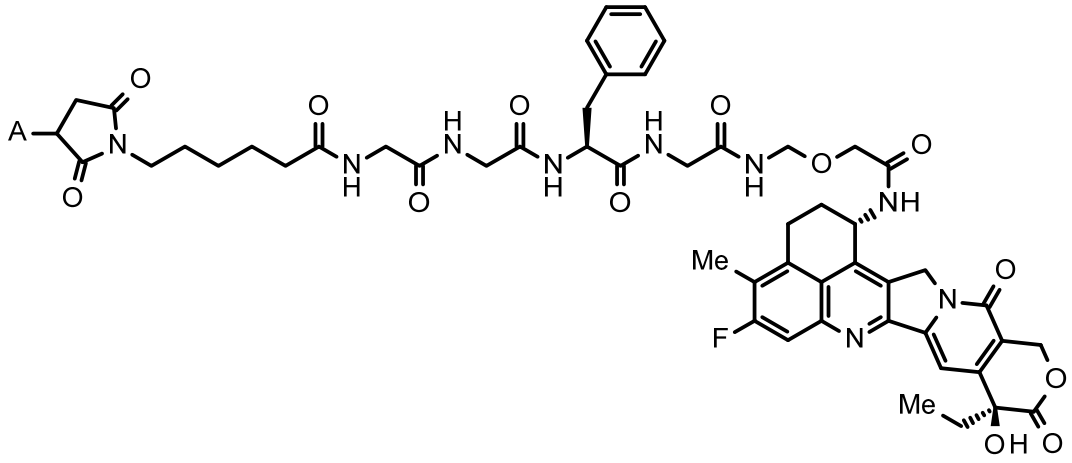
SEQ ID NO: 10 - Amino acid sequence of a light chain of the anti-GPR20 antibody

SEQ ID NO: 11 - Amino acid sequence of a heavy chain of the anti-CDH6 antibody

SEQ ID NO: 12 - Amino acid sequence of a light chain of the anti-CDH6 antibody

Claims

1. Use of an antibody-drug conjugate in the manufacture of a medicament for treating cancer, wherein
the antibody-drug conjugate and a tubulin inhibitor are to be administered in combination, and
the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula is conjugated to the antibody via a thioether bond:



wherein A represents a connecting position to an antibody;

wherein the antibody is an anti-HER2 antibody comprising a heavy chain consisting of amino acid residues 1 to 449 of SEQ ID NO: 1 and a light chain consisting of amino acid residues 1 to 214 of SEQ ID NO: 2, or wherein the antibody is an anti-HER2 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; and

wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof; nab-paclitaxel; eribulin or a pharmacologically acceptable salt thereof; or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

2. Use according to claim 1, wherein the anti-HER2 antibody comprises a heavy chain consisting of amino acid residues 1 to 449 of SEQ ID NO: 1 and a light chain consisting of amino acid residues 1 to 214 of SEQ ID NO: 2.

3. Use according to claim 1, wherein the anti-HER2 antibody comprises 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.

4. Use according to any one of claims 1 to 3, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

5. Use according to any one of claims 1 to 4, wherein the tubulin inhibitor is paclitaxel, docetaxel, cabazitaxel, or a pharmacologically acceptable salt thereof, or nab-paclitaxel.

6. Use according to claim 5, wherein the tubulin inhibitor is paclitaxel.

7. Use according to any one of claims 1 to 4, wherein the tubulin inhibitor is eribulin or a pharmacologically acceptable salt thereof, or an antibody-drug conjugate in which eribulin is conjugated to the antibody via a linker.

8. Use according to claim 7, wherein the tubulin inhibitor is eribulin mesylate.

9. Use according to any one of claims 1 to 8, wherein the antibody-drug conjugate and the tubulin inhibitor are separately contained as active components in different formulations, and are to be administered simultaneously or at different times.

10. Use according to any one of claims 1 to 9, wherein the cancer is at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, salivary gland

cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, bladder cancer, prostate cancer, and uterine carcinosarcoma.

11. Use according to claim 10, wherein the cancer is breast cancer.

12. Use according to claim 10, wherein the cancer is gastric cancer.

13. Use according to claim 10, wherein the cancer is lung cancer.

14. Use according to claim 10, wherein the cancer is ovarian cancer.