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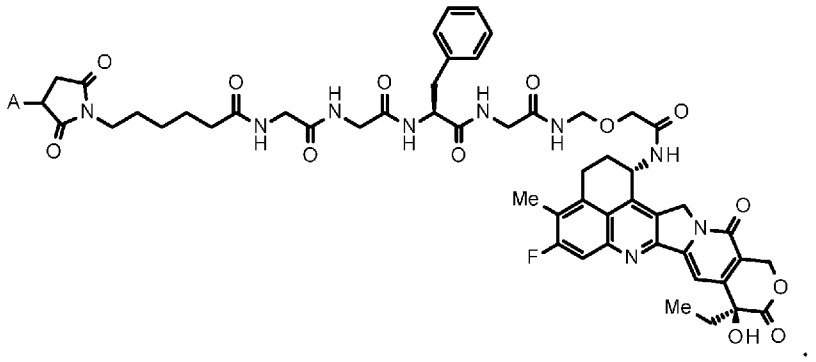
(54) Title: COMBINATION OF ANTIBODY-DRUG CONJUGATE AND DNA-PK INHIBITOR



(57) Abstract: A pharmaceutical product for administration of an anti HER2 antibody-drug conjugate in combination with a DNA-PK inhibitor is provided. The ant1-HER2 antibody-drug conjugate is an antibody-drug conjugate in which a drug linker represented by the following formula (wherein A represents the connecting position to an antibody) is conjugated to an ant1-HER2 antibody via a thioether bond. Also provided is a therapeutic use and method wherein the antibody-drug conjugate and the DNA-PK inhibitor are administered in combination to a subject:

WO 2021/260583 A1

COMBINATION OF ANTIBODY-DRUG CONJUGATE AND DNA-PK INHIBITOR

[Technical Field]

The present disclosure relates to a pharmaceutical product for administration of a specific antibody-drug conjugate, having an antitumor drug conjugated to an anti-HER2 antibody via a linker structure, in combination with a DNA-PK inhibitor, and to a therapeutic use and method wherein the specific antibody-drug conjugate and the DNA-PK inhibitor are administered in combination to a subject.

[Background]

DNA-PK is a nuclear serine/threonine protein kinase complex composed of the catalytic subunit DNA-PKcs and a heterodimer of Ku proteins (Ku70/Ku80) and is a member of the phosphatidylinositol 3-kinase-related kinase (PIKK) family of protein kinases. DNA-PK plays a crucial role in the repair of DNA double strand breaks (DSBs), serving to maintain genomic integrity, and in the process of V(D)J recombination, resulting in the highly diverse repertoire of antibodies/immunoglobulins and T cell receptors found on B- and T-cells respectively. DNA-PK has also been implicated in a range of other biological processes, including modulation of chromatin structure, telomere maintenance, transcriptional regulation, and the response to replication stress (Smith and Jackson, Genes

and Development 1999; 13: 916-934; Goodwin and Knudsen, Cancer Discovery 2014; 4: 1126-1139).

DNA-PK inhibitors such as NU7026, NU7441, KU-0060648 and CC-115 have demonstrated the therapeutic potential of targeting DNA-PK consistent with the known mechanisms of action of the DNA-PK protein. DNA-PK inhibitors are disclosed, for example, in WO2018/114999 and WO2019/238929.

Antibody-drug conjugates (ADCs) which are composed of a cytotoxic drug conjugated to an antibody, can deliver the drug selectively to cancer cells, and are therefore expected to cause accumulation of the drug within cancer cells and to kill the cancer cells (Ducry, L., et al., Bioconjugate Chem. (2010) 21, 5-13; Alley, S. C., et al., Current Opinion in Chemical Biology (2010) 14, 529-537; Damle N. K. Expert Opin. Biol. Ther. (2004) 4, 1445-1452; Senter P. D., et al., Nature Biotechnology (2012) 30, 631-637; Burris HA., et al., J. Clin. Oncol. (2011) 29(4): 398-405).

One such antibody-drug conjugate is trastuzumab deruxtecan, which is composed of a HER2-targeting antibody and a derivative of exatecan (Ogitani Y. et al., Clinical Cancer Research (2016) 22(20), 5097-5108; Ogitani Y. et al., Cancer Science (2016) 107, 1039-1046).

Despite the therapeutic potential of antibody-drug conjugates and DNA-PK inhibitors, no literature is published that describes a test result demonstrating an excellent effect of combined use of the antibody-drug

conjugate and a DNA-PK inhibitor or any scientific basis suggesting such a test result. To the contrary, the literature demonstrates that deleting non-homologous end joining (NHEJ) core components including DNA-PKcs does not sensitise cells to topoisomerase I inhibitors (such as exatecan), but only sensitized chicken DT40 cells to topoisomerase II inhibitors (Maede Y. et al., Mol Cancer Ther (2014) 13(1), 214-220). Similarly, data from mouse embryonic stem cells shows that deleting NHEJ core components does not cause increased sensitivity of ATM deficient cells to the topoisomerase I inhibitor topotecan (Balmus G. et al., Nat Commun (2019) 10(1), 87), and that DNA-PK inhibition does not sensitise cells to the topoisomerase I inhibitor camptothecin (Chanut P. et al., Nat Commun (2016) 7, 12889). Moreover, in the absence of test results, a possibility exists that combined administration of the antibody-drug conjugate together with another cancer treating agent such as a DNA-PK inhibitor could lead to negative interactions and/or sub-additive therapeutic outcomes, and thus an excellent or superior effect obtained by such combination treatment could not be expected.

Accordingly, a need remains for improved therapeutic compositions and methods, that can enhance efficacy of existing cancer treating agents, increase durability of therapeutic response and/or reduce dose-dependent toxicity.

[Summary of Disclosure]

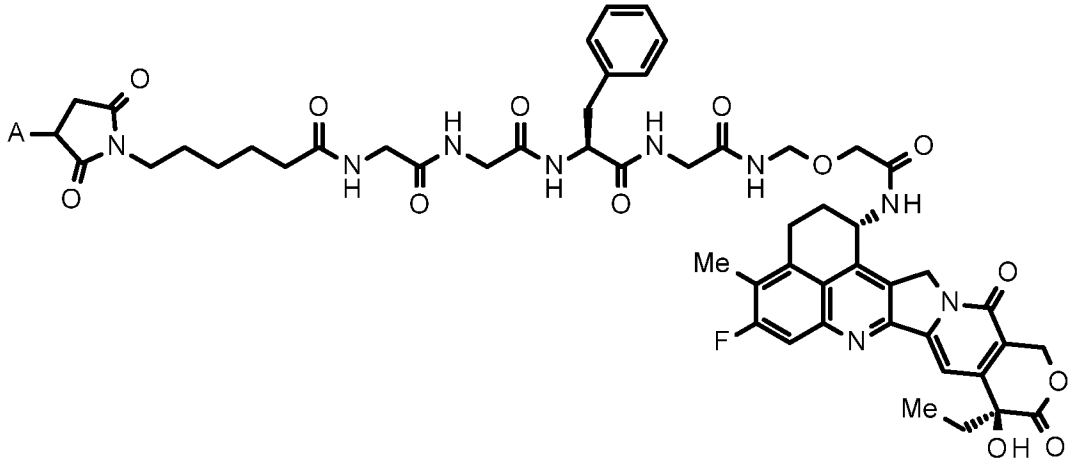
The antibody-drug conjugate used in the present disclosure (an anti-HER2 antibody-drug conjugate that includes a derivative of the topoisomerase I inhibitor exatecan, as a component) has been confirmed to exhibit an excellent antitumor effect in the treatment of certain cancers such as breast cancer and gastric cancer, when administered singly. Furthermore, a DNA-PK inhibitor has been confirmed to exhibit an antitumor effect in the treatment of certain cancers. However, it is desired to provide a medicine and treatment which can obtain a superior antitumor effect in the treatment of cancers, such as enhanced efficacy, increased durability of therapeutic response and/or reduced dose-dependent toxicity.

The present disclosure provides a pharmaceutical product which can exhibit an excellent antitumor effect in the treatment of cancers, through administration of an anti-HER2 antibody-drug conjugate in combination with a DNA-PK inhibitor. The present disclosure also provides a therapeutic use and method wherein the anti-HER2 antibody-drug conjugate and DNA-PK inhibitor are administered in combination to a subject.

Specifically, the present disclosure relates to the following [1] to [52]:

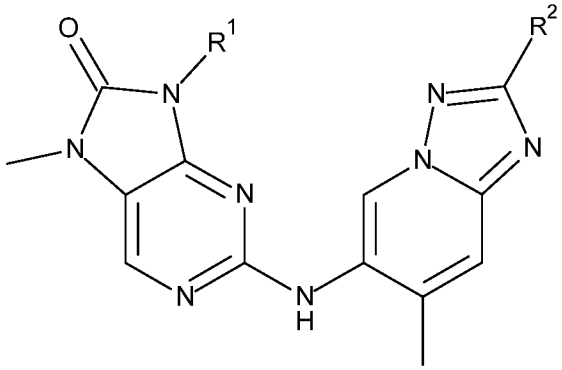
[1] a pharmaceutical product comprising an anti-HER2 antibody-drug conjugate and a DNA-PK inhibitor for administration in combination, wherein the anti-HER2

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



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

[2] the pharmaceutical product according to [1], wherein the DNA-PK inhibitor is a compound represented by the following formula (I):



(I)

wherein:

$\mathbf{R^1}$ is a cyclohexyl, tetrahydrofuranyl or oxanyl ring, each of which is optionally substituted by one or

more groups slected from hydroxyl, methoxy and methyl; and

R^2 is hydrogen or methyl,

or a pharmaceutically acceptable salt thereof;

[3] the pharmaceutical product according to [2] wherein, in formula (I), R^1 is oxanyl;

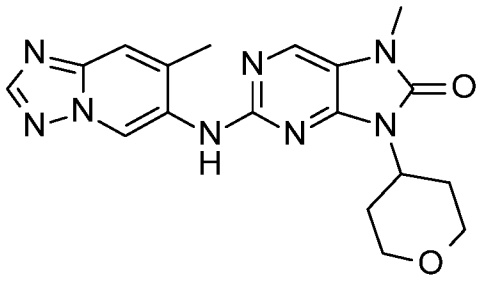
[4] the pharmaceutical product according to [3] wherein, in formula (I), R^1 is oxan-4-yl;

[5] the pharmaceutical product according to [2] wherein, in formula (I), R^1 is cyclohexyl;

[6] the pharmaceutical product according to [5] wherein, in formula (I), R^1 is 1-hydroxy-1-methyl-cyclohex-4-yl;

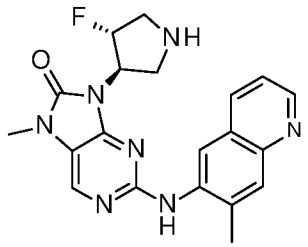
[7] the pharmaceutical product according to any one of [2] to [6] wherein, in formula (I), R^2 is hydrogen;

[8] the pharmaceutical product according to [2], wherein the DNA-PK inhibitor is AZD7648, also known as AZ13880164, represented by the following formula:



or a pharmaceutically acceptable salt thereof;

[9] the pharmaceutical product according to [1], wherein the DNA-PK inhibitor is the compound represented by the following formula:



or a pharmaceutically acceptable salt thereof;

[10] the pharmaceutical product according to any one of [1] to [9], wherein the anti-HER2 antibody is an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence represented by SEQ ID NO: 3 [= amino acid residues 26 to 33 of SEQ ID NO: 1], CDRH2 consisting of an amino acid sequence represented by SEQ ID NO: 4 [= amino acid residues 51 to 58 of SEQ ID NO: 1] and CDRH3 consisting of an amino acid sequence represented by SEQ ID NO: 5 [= amino acid residues 97 to 109 of SEQ ID NO: 1], and a light chain comprising CDRL1 consisting of an amino acid sequence represented by SEQ ID NO: 6 [= amino acid residues 27 to 32 of SEQ ID NO: 2], CDRL2 consisting of an amino acid sequence consisting of amino acid residues 1 to 3 of SEQ ID NO: 7 [= amino acid residues 50 to 52 of SEQ ID NO: 2] and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 8 [=amino acid residues 89 to 97 of SEQ ID NO: 2];

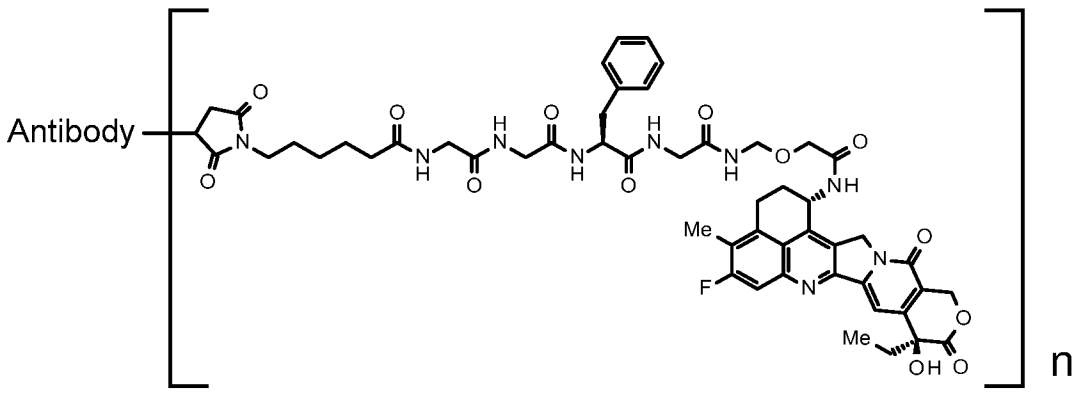
[11] the pharmaceutical product according to any one of [1] to [9], wherein the anti-HER2 antibody is an antibody comprising a heavy chain comprising a heavy chain variable region consisting of an amino acid sequence represented by SEQ ID NO: 9 [= amino acid residues 1 to

120 of SEQ ID NO: 1] and a light chain comprising a light chain variable region consisting of an amino acid sequence represented by SEQ ID NO: 10 [= amino acid residues 1 to 107 of SEQ ID NO: 2];

[12] the pharmaceutical product according to any one of [1] to [9], wherein the anti-HER2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 1 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 2;

[13] the pharmaceutical product according to any one of [1] to [9], wherein the anti-HER2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 11 [= amino acid residues 1 to 449 of SEQ ID NO: 1] and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 2;

[14] the pharmaceutical product according to any one of [1] to [13], wherein the anti-HER2 antibody-drug conjugate is represented by the following formula:



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

[15] the pharmaceutical product according to any one of [1] to [14], wherein the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan (DS-8201);

[16] the pharmaceutical product according to any one of [1] to [15] wherein the product is a composition comprising the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor, for simultaneous administration;

[17] the pharmaceutical product according to any one of [1] to [15] wherein the product is a combined preparation comprising the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor, for sequential or simultaneous administration;

[18] the pharmaceutical product according to any one of [1] to [17], wherein the product is for treating cancer;

[19] the pharmaceutical product according to [18], wherein the cancer is at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, head-and-neck cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, digestive tract stromal tumor, uterine

cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma;

[20] the pharmaceutical product according to [19], wherein the cancer is breast cancer;

[21] the pharmaceutical product according to [20], wherein the breast cancer has a HER2 status score of IHC 3+;

[22] the pharmaceutical product according to [20], wherein the breast cancer is HER2 low-expressing breast cancer;

[23] the pharmaceutical product according to [20], wherein the breast cancer has a HER2 status score of IHC 2+;

[24] the pharmaceutical product according to [20], wherein the breast cancer has a HER2 status score of IHC 1+;

[25] the pharmaceutical product according to [20], wherein the breast cancer has a HER2 status score of IHC >0 and <1+;

[26] the pharmaceutical product according to [20], wherein the breast cancer is triple-negative breast cancer;

[27] the pharmaceutical product according to [18], wherein the cancer is gastric cancer;

[28] the pharmaceutical product according to [18], wherein the cancer is colorectal cancer;

[29] the pharmaceutical product according to [18], wherein the cancer is lung cancer;

[30] the pharmaceutical product according to [29], wherein the lung cancer is non-small cell lung cancer;

[31] the pharmaceutical product according to [18], wherein the cancer is pancreatic cancer;

[32] the pharmaceutical product according to [18], wherein the cancer is ovarian cancer;

[33] the pharmaceutical product according to [18], wherein the cancer is prostate cancer;

[34] the pharmaceutical product according to [18], wherein the cancer is kidney cancer;

[35] a pharmaceutical product as defined in any one of [1] to [17], for use in treating cancer;

[36] the pharmaceutical product for the use according to [25], wherein the cancer is as defined in any one of [19] to [34];

[37] use of an anti-HER2 antibody-drug conjugate or a DNA-PK inhibitor in the manufacture of a medicament for administration of the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor in combination, wherein the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor are as defined in any one of [1] to [15], for treating cancer;

[38] the use according to [37], wherein the cancer is as defined in any one of [19] to [34];

[39] the use according to [37] or [38] wherein the medicament is a composition comprising the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor, for simultaneous administration;

[40] the use according to [37] or [38] wherein the medicament is a combined preparation comprising the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor, for sequential or simultaneous administration;

[41] an anti-HER2 antibody-drug conjugate for use, in combination with a DNA-PK inhibitor, in the treatment of cancer, wherein the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor are as defined in any one of [1] to [15];

[42] the anti-HER2 antibody-drug conjugate for the use according to [41], wherein the cancer is as defined in any one of [19] to [34];

[43] the anti-HER2 antibody-drug conjugate for the use according to [41] or [42], wherein the use comprises administration of the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor sequentially;

[44] the anti-HER2 antibody-drug conjugate for the use according to [41] or [42], wherein the use comprises administration of the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor simultaneously;

[45] a DNA-PK inhibitor for use, in combination with an anti-HER2 antibody-drug conjugate, in the treatment of cancer, wherein the anti-HER2 antibody-drug conjugate and

the DNA-PK inhibitor are as defined in any one of [1] to [15];

[46] the DNA-PK inhibitor for the use according to [45], wherein the cancer is as defined in any one of [19] to [34];

[47] the DNA-PK inhibitor for the use according to [45] or [46], wherein the use comprises administration of the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor sequentially;

[48] the DNA-PK inhibitor for the use according to [45] or [46], wherein the use comprises administration of the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor simultaneously;

[49] a method of treating cancer comprising administering an anti-HER2 antibody-drug conjugate and a DNA-PK inhibitor as defined in any one of [1] to [15] in combination to a subject in need thereof;

[50] the method according to [49], wherein the cancer is as defined in any one of [19] to [34];

[51] the method according to [49] or [50], wherein the method comprises administering the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor sequentially; and

[52] the method according to [49] or [50], wherein the method comprises administering the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor simultaneously.

[Advantageous Effects of Disclosure]

The present disclosure provides a pharmaceutical product wherein an anti-HER2 antibody-drug conjugate, having an antitumor drug conjugated to an anti-HER2 antibody via a linker structure, and a DNA-PK inhibitor are administered in combination, and a therapeutic use and method wherein the specific antibody-drug conjugate and the DNA-PK inhibitor are administered in combination to a subject. Thus, the present disclosure can provide a medicine and treatment which can obtain a superior antitumor effect in the treatment of cancers.

[Brief Description of Drawings]

[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 CDRH1 (SEQ ID NO: 3 [= amino acid residues 26 to 33 of SEQ ID NO: 1]).

[Figure 4] Figure 4 is a diagram showing the amino acid sequence of a heavy chain CDRH2 (SEQ ID NO: 4 [= amino acid residues 51 to 58 of SEQ ID NO: 1]).

[Figure 5] Figure 5 is a diagram showing the amino acid sequence of a heavy chain CDRH3 (SEQ ID NO: 5 [= amino acid residues 97 to 109 of SEQ ID NO: 1]).

[Figure 6] Figure 6 is a diagram showing the amino acid sequence of a light chain CDRL1 (SEQ ID NO: 6 [= amino acid residues 27 to 32 of SEQ ID NO: 2]).

[Figure 7] Figure 7 is a diagram showing an amino acid sequence comprising the amino acid sequence of a light chain CDRL2 (SAS) (SEQ ID NO: 7 [= amino acid residues 50 to 56 of SEQ ID NO: 2]).

[Figure 8] Figure 8 is a diagram showing the amino acid sequence of a light chain CDRL3 (SEQ ID NO: 8 [= amino acid residues 89 to 97 of SEQ ID NO: 2]).

[Figure 9] Figure 9 is a diagram showing the amino acid sequence of a heavy chain variable region (SEQ ID NO: 9 [= amino acid residues 1 to 120 of SEQ ID NO: 1]).

[Figure 10] Figure 10 is a diagram showing the amino acid sequence of a light chain variable region (SEQ ID NO: 10 [= amino acid residues 1 to 107 of SEQ ID NO: 2]).

[Figure 11] Figure 11 is a diagram showing the amino acid sequence of a heavy chain (SEQ ID NO: 11 [= amino acid residues 1 to 449 of SEQ ID NO: 1]).

[Figures 12A and 12 B] Figures 12A and 12B are diagrams showing combination matrices obtained with high-throughput screens combining DS-8201 with AZD7648 (AZ13880164; DNA-PK inhibitor) in breast cancer cell lines with diverse HER2 expression and one gastric cell line with high HER2 expression.

In order that the present disclosure can be more readily understood, certain terms are first defined.

Additional definitions are set forth throughout the detailed description.

Before describing the present disclosure in detail, it is to be understood that this disclosure is not limited to specific compositions or method steps, as such can vary. As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. The terms "a" (or "an"), as well as the terms "one or more," and "at least one" can be used interchangeably herein.

Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic

Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

It is understood that wherever aspects are described herein with the language "comprising", otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided. The terms "inhibit", "block", and "suppress" are used interchangeably herein and refer to any statistically significant decrease in biological activity, including full blocking of the activity. For example, "inhibition" can refer to a decrease of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% in biological activity. Cellular proliferation can be assayed using art recognized techniques which measure rate of cell division, and/or the fraction of cells within a cell population undergoing cell division, and/or rate of cell loss from a cell population due to terminal differentiation or cell death (*e.g.*, thymidine incorporation).

The term "subject" refers to any animal (*e.g.*, a mammal), including, but not limited to humans, non-human primates, rodents, and the like, which is to be the

recipient of a particular treatment. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject.

The term "pharmaceutical product" refers to a preparation which is in such form as to permit the biological activity of the active ingredients, either as a composition containing all the active ingredients (for simultaneous administration), or as a combination of separate compositions (a combined preparation) each containing at least one but not all of the active ingredients (for administration sequentially or simultaneously), and which contains no additional components which are unacceptably toxic to a subject to which the product would be administered. Such product can be sterile. By "simultaneous administration" is meant that the active ingredients are administered at the same time. By "sequential administration" is meant that the active ingredients are administered one after the other, in either order, at a time interval between the individual administrations. The time interval can be, for example, less than 24 hours, preferably less than 6 hours, more preferably less than 2 hours.

Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to both (1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and (2) prophylactic or preventative measures that prevent and/or slow the

development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented. In certain aspects, a subject is successfully "treated" for cancer according to the methods of the present disclosure if the patient shows, *e.g.*, total, partial, or transient remission of a certain type of cancer.

The terms "cancer", "tumor", "cancerous", and "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancers include but are not limited to, breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, head-and-neck cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, digestive tract stromal tumor, uterine cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma. Cancers include hematological malignancies such as acute myeloid leukemia, multiple myeloma, chronic lymphocytic leukemia, diffuse large B cell lymphoma,

Burkitt's lymphoma, follicular lymphoma and solid tumors such as breast cancer, lung cancer, neuroblastoma and colon cancer.

The term "cytotoxic agent" as used herein is defined broadly and refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells (cell death), and/or exerts anti-neoplastic/anti-proliferative effects. For example, a cytotoxic agent prevents directly or indirectly the development, maturation, or spread of neoplastic tumor cells. The term includes also such agents that cause a cytostatic effect only and not a mere cytotoxic effect. The term includes chemotherapeutic agents as specified below, as well as other HER2 antagonists, anti-angiogenic agents, tyrosine kinase inhibitors, protein kinase A inhibitors, members of the cytokine family, radioactive isotopes, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin.
The term "chemotherapeutic agent" is a subset of the term "cytotoxic agent" comprising natural or synthetic chemical compounds.

In accordance with the methods or uses of the present disclosure, compounds of the present disclosure may be administered to a patient to promote a positive therapeutic response with respect to cancer. The term "positive therapeutic response" with respect to cancer treatment refers to an improvement in the symptoms associated with the disease. For example, an improvement

in the disease can be characterized as a complete response. The term "complete response" refers to an absence of clinically detectable disease with normalization of any previous test results. Alternatively, an improvement in the disease can be categorized as being a partial response. A "positive therapeutic response" encompasses a reduction or inhibition of the progression and/or duration of cancer, the reduction or amelioration of the severity of cancer, and/or the amelioration of one or more symptoms thereof resulting from the administration of compounds of the present disclosure. In specific aspects, such terms refer to one, two or three or more results following the administration of compounds of the instant disclosure:

(1) a stabilization, reduction or elimination of the cancer cell population;

(2) a stabilization or reduction in cancer growth;

(3) an impairment in the formation of cancer;

(4) eradication, removal, or control of primary, regional and/or metastatic cancer;

(5) a reduction in mortality;

(6) an increase in disease-free, relapse-free, progression-free, and/or overall survival, duration, or rate;

(7) an increase in the response rate, the durability of response, or number of patients who respond or are in remission;

(8) a decrease in hospitalization rate,

(9) a decrease in hospitalization lengths,

(10) the size of the cancer is maintained and does not increase or increases by less than 10%, preferably less than 5%, preferably less than 4%, preferably less than 2%, and

(11) an increase in the number of patients in remission.

(12) a decrease in the number of adjuvant therapies (*e.g.*, chemotherapy or hormonal therapy) that would otherwise be required to treat the cancer.

Clinical response can be assessed using screening techniques such as PET, magnetic resonance imaging (MRI) scan, x-radiographic imaging, computed tomographic (CT) scan, flow cytometry or fluorescence-activated cell sorter (FACS) analysis, histology, gross pathology, and blood chemistry, including but not limited to changes detectable by ELISA, RIA, chromatography, and the like. In addition to these positive therapeutic responses, the subject undergoing therapy can experience the beneficial effect of an improvement in the symptoms associated with the disease.

As used herein, the phrase "effective amount" means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical product will vary with the particular condition being treated, the severity of the condition,

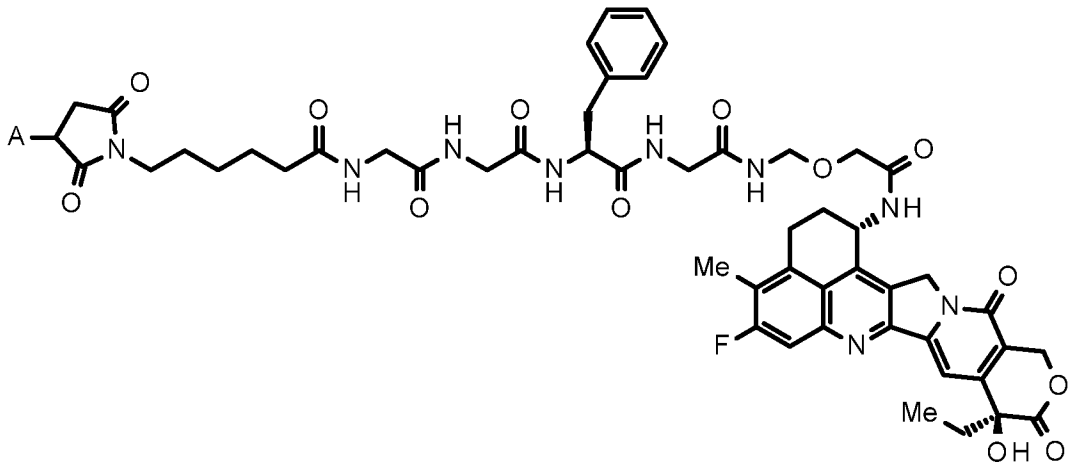
the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, and like factors within the knowledge and expertise of the attending physician. In particular, an effective amount of a compound for use in the treatment of cancer in combination with the antibody-drug conjugate is an amount such that the combination is sufficient to symptomatically relieve in a warm-blooded animal such as man, the symptoms of cancer, to slow the progression of cancer, or to reduce in patients with symptoms of cancer the risk of getting worse.

[Description of Embodiments]

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

1. Antibody-drug conjugate

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



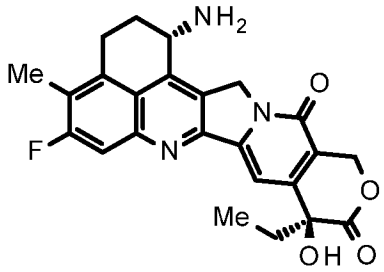
wherein A represents the connecting position to an antibody,

is conjugated to an anti-HER2 antibody via a thioether bond.

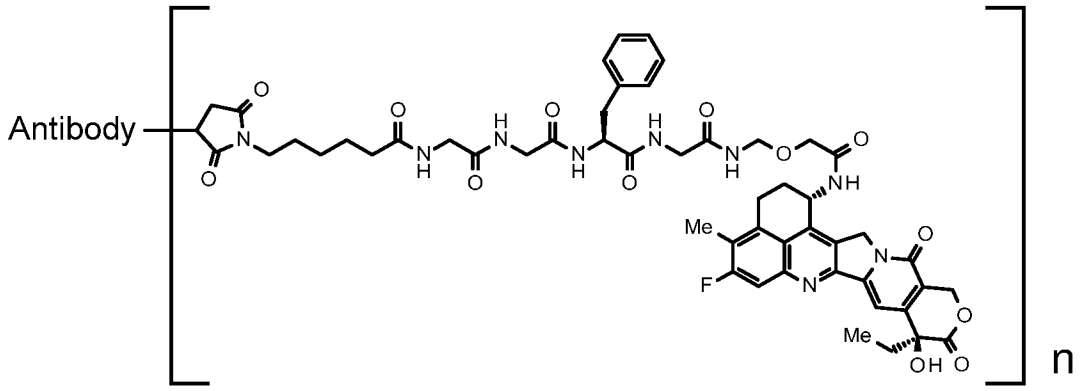
In the present disclosure, the partial structure consisting of a linker and a drug in the antibody-drug conjugate is referred to as a "drug-linker". The drug-linker is connected to a thiol group (in other words, the sulfur atom of a cysteine residue) formed at an interchain disulfide bond site (two sites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

The drug-linker of the present disclosure 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:

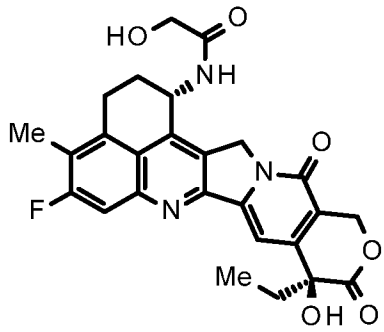


The anti-HER2 antibody-drug conjugate used in the present disclosure can be also represented by the following formula:



Here, the drug-linker is conjugated to an anti-HER2 antibody ('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.

After migrating into cancer cells, the anti-HER2 antibody-drug conjugate used in the present disclosure is cleaved at the linker portion to release a compound represented by the following formula:



This compound is inferred to be the original source of the antitumor activity of the antibody-drug conjugate used in the present disclosure, 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).

The anti-HER2 antibody-drug conjugate used in the present disclosure is known to have a bystander effect (Ogitani Y. et al., Cancer Science (2016) 107, 1039-1046). The bystander effect is exerted through a process whereby the antibody-drug conjugate used in the present disclosure is internalized in cancer cells expressing the target and the compound released then exerts an antitumor effect also on cancer cells which are present therearound and not expressing the target. This bystander effect is exerted as an excellent antitumor effect even when the anti-HER2 antibody-drug conjugate is used in combination

with a DNA-PK inhibitor according to the present disclosure.

2. Antibody in antibody-drug conjugate

The anti-HER2 antibody in the antibody-drug conjugate used in the present disclosure may be derived from any species, and is preferably an anti-HER2 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 anti-HER2 antibody may be a polyclonal antibody or a monoclonal antibody and is preferably a monoclonal antibody.

The antibody in the antibody-drug conjugate used in the present disclosure is an anti-HER2 antibody preferably having a characteristic of being capable of targeting cancer cells, and is preferably an antibody possessing, for example, a property of recognizing a cancer cell, a property of binding to a cancer cell, a property of internalizing in a cancer cell, and/or cytocidal activity against cancer cells.

The binding activity of the anti-HER2 antibody against cancer cells can be confirmed using flow cytometry. The internalization of the antibody into cancer 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.

The antitumor activity of the anti-HER2 antibody can be confirmed in vitro by determining inhibitory activity against cell growth. For example, a cancer cell line overexpressing HER2 as 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 change in the cancer cell.

Since the compound conjugated in the anti-HER2 antibody-drug conjugate exerts an antitumor effect, it is preferred but not essential that the anti-HER2 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 anti-HER2 antibody should have the property of internalizing to migrate into cancer cells.

The anti-HER2 antibody in the antibody-drug conjugate used in the present disclosure can be obtained by a procedure known in the art. For example, the antibody of the present disclosure 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.

Alternatively, antibody-producing cells which produce antibodies against the antigen are fused with myeloma cells according to a method known in the art (e.g., Kohler and Milstein, Nature (1975) 256, p. 495-497; and 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.

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.

The anti-HER2 antibody in the antibody-drug conjugate used the present disclosure 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.

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)).

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), and 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.

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 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.

In the present disclosure, modified variants of the anti-HER2 antibody in the antibody-drug conjugate used in the present disclosure are also included. The modified variant refers to a variant obtained by subjecting the

antibody according to the present disclosure 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 disclosure, 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 disclosure 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.

Further, by regulating the modification of a glycan which is linked to the antibody according to the present disclosure (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, those disclosed in WO99/54342, WO00/61739, WO02/31140, WO2007/133855, WO2013/120066, etc. are known. However, the technique is not limited thereto. In the anti-HER2 antibody according to the present disclosure, antibodies in which the modification of a glycan is regulated are also included.

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 (the activation of complement, antibody-dependent cellular cytotoxicity, etc.) of the antibody. Therefore, in the anti-HER2 antibody according to the present disclosure, 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 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 anti-HER2 antibody according to the present disclosure 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 disclosure 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 anti-HER2 antibody according to the present disclosure 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 disclosure can be exemplified as preferred.

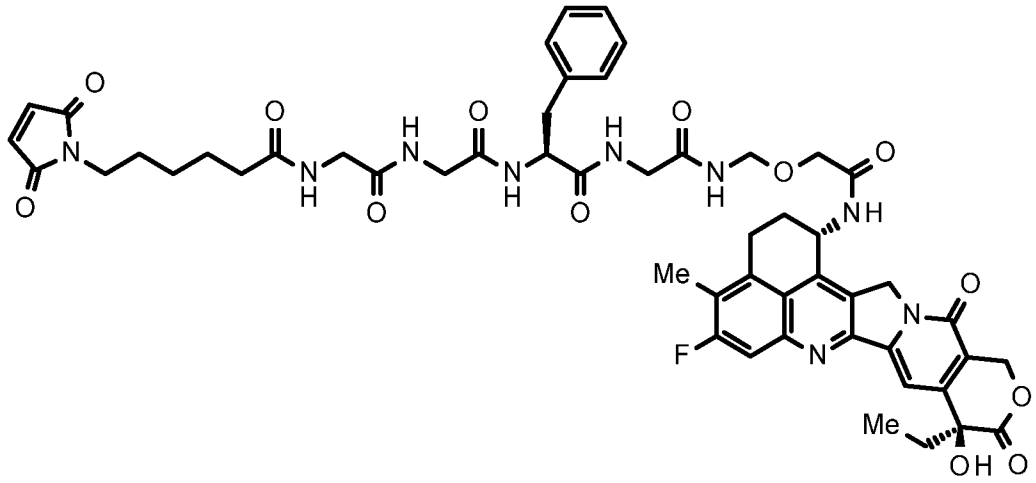
As isotypes of the anti-HER2 antibody according to the present disclosure, for example, IgG (IgG1, IgG2, IgG3, IgG4) can be exemplified, and IgG1 or IgG2 can be exemplified as preferred.

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

Examples of the anti-HER2 antibody include trastuzumab (U.S. Patent No. 5821337) and pertuzumab (WO01/00245), and trastuzumab can be exemplified as preferred.

3. Production of antibody-drug conjugate

A drug-linker intermediate for use in production of the anti-HER2 antibody-drug conjugate according to the present disclosure is represented by the following formula:



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 WO2014/057687, WO2015/098099, WO2015/115091, WO2015/155998, WO2019/044947 and so on.

The anti-HER2 antibody-drug conjugate used in the present disclosure can be produced by reacting the above-described drug-linker intermediate and an anti-HER2 antibody having a thiol group (also referred to as a sulfhydryl group).

The anti-HER2 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 anti-HER2 antibody having a sulfhydryl group with partially or completely reduced interchain disulfides within the antibody can be obtained.

Further, by using 2 to 20 molar equivalents of the drug-linker intermediate per anti-HER2 antibody having a sulfhydryl group, an anti-HER2 antibody-drug conjugate in which 2 to 8 drug molecules are conjugated per antibody molecule can be produced.

The average number of conjugated drug molecules per anti-HER2 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).

Conjugation between the anti-HER2 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 WO2014/057687, WO2015/098099, WO2015/115091, WO2015/155998, WO2017/002776, WO2018/212136, and so on.

In the present disclosure, 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 present disclosure is an anti-HER2 antibody.

The anti-HER2 antibody is preferably an antibody comprising a heavy chain comprising CDRH1 consisting of an amino acid sequence consisting of amino acid residues 26 to 33 of SEQ ID NO: 1, CDRH2 consisting of an amino acid sequence consisting of amino acid residues 51 to 58 of SEQ ID NO: 1 and CDRH3 consisting of an amino acid sequence consisting of amino acid residues 97 to 109 of SEQ ID NO: 1, and a light chain comprising CDRL1 consisting of an amino acid sequence consisting of amino acid residues 27 to 32 of SEQ ID NO: 2, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 50 to 52 of SEQ ID NO: 2 and CDRL3 consisting of

an amino acid sequence consisting of amino acid residues 89 to 97 of SEQ ID NO: 2, and 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 120 of SEQ ID NO: 1 and a light chain comprising a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 1 to 107 of SEQ ID NO: 2, and even more preferably an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 1 and a light chain consisting of the amino acid sequence represented by SEQ ID NO: 2, or an antibody comprising a heavy chain 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 all amino acid residues 1 to 214 of SEQ ID NO: 2.

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.

The anti-HER2 antibody-drug conjugate used in the present disclosure can be produced with reference to descriptions in WO2015/115091 and so on.

In preferred embodiments, the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan (DS-8201).

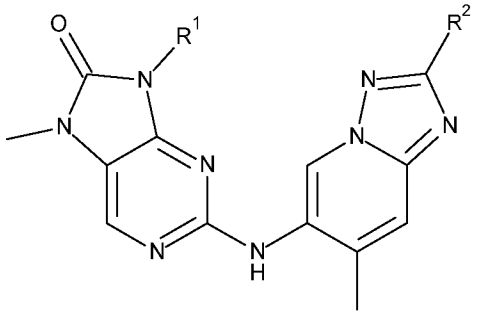
4. DNA-PK inhibitor

In the present disclosure, the term "DNA-PK inhibitor" refers to an agent that inhibits DNA-PK (nuclear serine/threonine protein kinase complex composed of the catalytic subunit DNA-PKcs and a heterodimer of Ku proteins (Ku70/Ku80)). The DNA-PK inhibitor in the present disclosure may selectively inhibit the kinase DNA-PK, or may non-selectively inhibit DNA-PK and inhibit also kinase(s) other than DNA-PK. The DNA-PK inhibitor in the present disclosure is not particularly limited as long as it is an agent that has the described characteristics, and preferred examples thereof can include those disclosed in WO2018/114999 and WO2019/238929.

Examples of DNA-PK inhibitors which may be used according to the present disclosure are selective inhibitors of DNA-PK including M3814/peposertib (Merck) and M9831 (Merck), and non-selective inhibitors of DNA-PK including BR-101801 (Boryung Pharma), SF-2523 (SignalRx Pharmaceuticals), BR-2002/BCN-005 (Boryung Pharma), and CC115 (Celgene).

Preferably, the DNA-PK inhibitor in the present disclosure inhibits DNA-PK selectively.

According to preferred embodiments of the DNA-PK inhibitor used in the present disclosure, the DNA-PK inhibitor is a compound represented by the following formula (I):



(I)

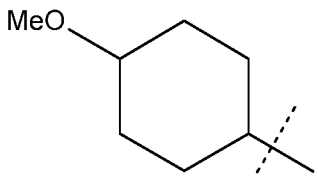
wherein:

R^1 is a cyclohexyl, tetrahydrofuranyl or oxanyl ring, each of which is optionally substituted by one or more groups selected from hydroxyl, methoxy and methyl; and

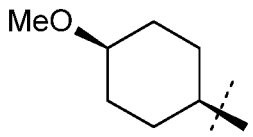
R^2 is hydrogen or methyl,

or a pharmaceutically acceptable salt thereof.

The term "cyclohexyl ring" refers to carbocyclic ring containing six carbon atoms and no heteroatoms. 1-methoxycyclohex-4-yl groups and 4-methoxycyclohex-1-yl groups have the same structure, as shown below.

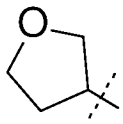


A *cis*-1-methoxy-cyclohex-4-yl group is equivalent to a *cis*-4-methoxy-cyclohex-1-yl and has the following structure:



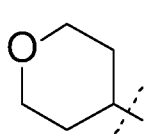
The same conventions apply to other cyclohexyl groups, for example 1-hydroxycyclohex-4-yl groups and 4-hydroxycyclohex-1-yl groups.

The term "tetrahydrofuranyl ring" includes tetrahydrofuran-3-yl, the structure of which is shown below.

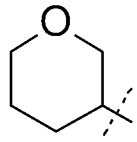


Tetrahydrofuran-3-yl

The term "oxanyl ring" includes oxan-3-yl and oxan-4-yl groups, the structures of which are shown below.



Oxan-4-yl



Oxan-3-yl

In the above structures the dashed line indicates the bonding position of the relevant group.

An oxanyl ring may also be referred to as a tetrahydropyranyl ring. Similarly, an oxan-4-yl ring may be referred to as a tetrahydropyran-4-yl ring, and an oxan-3-yl ring may be referred to as a tetrahydropyran-3-yl ring.

Values of variable groups in formula (I) are as follows. Such values may be used in combination with any of the definitions, claims, or embodiments defined herein

to provide further embodiments of compounds of formula (I):

a) $\mathbf{R^1}$ is a cyclohexyl ring which is optionally substituted by one or more groups selected from hydroxyl, methoxy and methyl, or $\mathbf{R^1}$ is a tetrahydrofuranyl or oxanyl ring.

b) $\mathbf{R^1}$ is a cyclohexyl ring which is optionally substituted by one or more groups selected from hydroxyl, methoxy and methyl.

c) $\mathbf{R^1}$ is a tetrahydrofuranyl or oxanyl ring.

d) $\mathbf{R^1}$ is a cyclohexyl ring which is optionally substituted by one hydroxyl or methoxy group.

e) $\mathbf{R^1}$ is a cyclohexyl ring which is optionally substituted by a hydroxyl and a methyl group.

f) $\mathbf{R^1}$ is 1-methoxy-cyclohex-4-yl, 1-hydroxy-cyclohex-4-yl, 1-hydroxy-1-methylhex-4yl or 1-hydroxy-4-methyl-cyclohex-4-yl.

g) $\mathbf{R^1}$ is 1-methoxy-cyclohex-4-yl, 1-hydroxy-cyclohex-4-yl or 1-hydroxy-1-methyl-cyclohex-4yl.

h) $\mathbf{R^1}$ is 1-hydroxy-1-methyl-cyclohex-4-yl.

i) $\mathbf{R^1}$ is *cis*-1-hydroxy-1-methyl-cyclohex-4-yl.

j) $\mathbf{R^1}$ is *cis*-1-methoxy-cyclobut-4-yl or *cis*-1-hydroxy-cyclohex-4-yl.

k) $\mathbf{R^1}$ is *cis*-1-hydroxy-cyclohex-4-yl.

l) $\mathbf{R^1}$ is an oxetanyl ring.

m) $\mathbf{R^1}$ is oxetan-3-yl.

n) $\mathbf{R^1}$ is an cyclohexyl ring.

o) $\mathbf{R^1}$ is a tetrahydrofuranyl ring.

p) R^1 is tetrahydrofuran-3-yl.

q) R^1 is an oxanyl ring.

r) R^1 is an oxan-3-yl.

s) R^1 is oxan-4-yl.

t) R^2 is hydrogen.

u) R^2 is methyl.

In one embodiment the compound of formula (I) is selected from the group consisting of:

9-((1r,4r)-4-hydroxycyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one;

9-((1s,4s)-4-hydroxycyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one;

7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one;

2-((2,7-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7-methyl-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one;

9-((1s,4s)-4-methoxycyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one;

9-((1r,4r)-4-methoxycyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one;

(S)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-3-yl)-7,9-dihydro-8H-purin-8-one;

(R)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-3-yl)-7,9-dihydro-8H-purin-8-one;

9-((1r,4r)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one;

9-((1s,4s)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one;

(S)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8H-purin-8-one;

9-((1s,4s)-4-hydroxy-1-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one; and

9-cyclohexyl-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one,

or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one;

9-((1r,4r)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one; and
9-((1s,4s)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one.

In another embodiment the compound of formula (I) is selected from the group consisting of:
7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one; and
9-((1s,4s)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one:
or a pharmaceutically acceptable salt thereof.

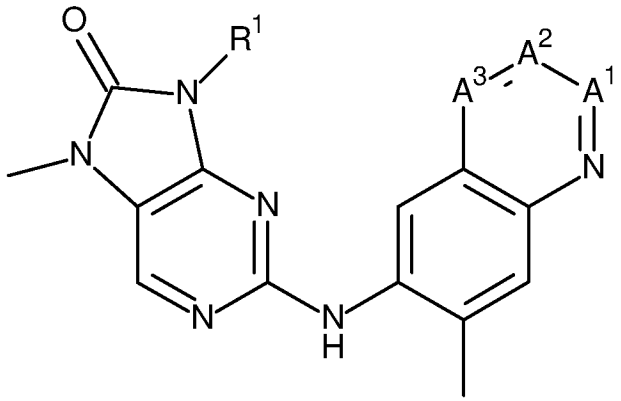
In another embodiment the compound of formula (I) is 7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one, or a pharmaceutically acceptable salt thereof.

In another embodiment the compound of formula (I) is 9-((1r,4r)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one, or a pharmaceutically acceptable salt thereof.

In another embodiment the compound of formula (I) is 9-((1s,4s)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-

dihydro-8H-purin-8-one, or a pharmaceutically acceptable salt thereof.

According to other embodiments of the DNA-PK inhibitor used in present disclosure, the DNA-PK inhibitor is a compound represented by the following formula (II):



(II)

or a pharmaceutically acceptable salt thereof,

wherein:

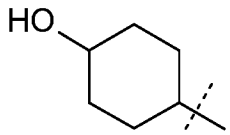
A^1 represents N or CR^{2A}, A^2 represents N or CR^{2B} and A^3 represents N or CR^{2C}, where no more than one of A^1, A^2 and A^3 represent N;

R^1 represents C_{4-6} cycloalkyl or a 4 to 6 membered heterocycloalkyl containing one heteroatom selected from O, S and N, wherein the C_{4-6} cycloalkyl or 4 to 6 membered heterocycloalkyl is optionally substituted with one or more groups selected from fluoro, C_{1-3} alkyl (optionally substituted with a group selected from hydroxyl and C_{1-2} alkoxy), cyclopropyl, hydroxyl, NH_2, dioxo, $C(O)C_{1-2}$ alkyl, azetidinyl and oxetanyl; and

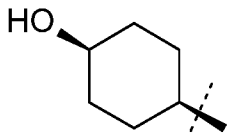
R^{2A}, R^{2B} and R^{2C} each independently represent hydrogen, methyl or methoxy.

C_{4-6} cycloalkyl is a saturated non-aromatic carbocyclic ring containing no heteroatoms. C_{4-6} cycloalkyl is any such carbocyclic ring containing 4 to 6 carbon atoms. C_{4-6} cycloalkyl groups include cyclobutyl, cyclopentyl and cyclohexanyl, for example cyclohexanyl.

The term "cyclohexanyl" refers to a carbocyclic ring containing six carbon atoms. 1-hydroxycyclohex-4-yl groups and 4-hydroxycyclohex-1-yl groups have the same structure, as shown below.



A *cis*-1-hydroxy-cyclohex-4-yl group is equivalent to a *cis*-4-hydroxy-cyclohex-1-yl and has the following structure:



In the above structures the dashed line indicates the bonding position of the relevant group.

A 4 to 6 membered heterocycloalkyl is a saturated non-aromatic ring comprising one heteroatom independently selected from nitrogen, oxygen or sulphur with the remaining ring members being carbon. 4 to 6 membered heterocycloalkyl groups include piperidinyl,

tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, azetidinyl and oxetanyl, for example piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxetanyl and pyrrolidinyl. For the avoidance of doubt, substituents on the heterocycloalkyl ring may be linked via either a carbon atom or a heteroatom.

The term "dioxo" means two oxo substituents which are attached to the same atom. Examples of dioxo substitution include instances where R^1 represents thianyl, which may also be referred to as tetrahydrothiopyranyl, where the sulphur ring atom is substituted with two oxo groups, i.e.tetrahydrothiopyran 1,1-dioxide.

The prefix C_{p-q} in C_{p-q}alkyl and other terms (where p and q are integers) indicates the range of carbon atoms that are present in the group and unless otherwise stated alkyl and alkoxy groups containing the requisite number of carbon atoms can be branched or unbranched. C_{1-3} alkyl groups include methyl (Me), ethyl (Et), n-propyl and i-propyl, for example methyl and ethyl.

The term C_{p-q}alkoxy comprises -O-C_{p-q}alkyl groups. C_{1-2} alkoxy groups include methoxy and ethoxy, for example methoxy.

In one embodiment, in formula (II), R^1 represents cyclohexanyl or a 4 to 6 membered heterocycloalkyl containing one heteroatom selected from O, N or S.

In another embodiment, in formula (II), R^1 represents a 4 to 6 membered heterocycloalkyl containing one heteroatom selected from O or N.

In another embodiment, in formula (II), R^1 represents a 4 to 6 membered heterocycloalkyl containing one N heteroatom.

In another embodiment, in formula (II), R^1 is selected from cyclohexanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl and tetrahydrothiopyranyl.

In another embodiment, in formula (II), R^1 is selected from pyrrolidinyl and piperidinyl.

In another embodiment, in formula (II), R^1 is selected from cyclohexanyl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, piperidin-4-yl and tetrahydrothiopyran-4-yl.

In another embodiment, in formula (II), R^1 is selected from pyrrolidin-3-yl and piperidin-4-yl.
In one embodiment, in formula (II), R^1 is optionally substituted with one or two substituents selected from fluoro, methyl, ethyl, hydroxyl, NH_2, dioxo, C(O)Me and oxetanyl, wherein the ethyl is optionally substituted with hydroxyl or methoxy. In one embodiment, R^1 is optionally substituted with fluoro, methyl, ethyl, hydroxyl, NH_2 and oxetanyl. In one embodiment, R^1 is optionally substituted with fluoro or methyl.

In another embodiment, in formula (II), R^1 represents pyrrolidinyl or piperidinyl and is optionally substituted with one or two substituents selected from fluoro, methyl, ethyl, hydroxyl, NH_2 and oxetanyl.

In another embodiment, in formula (II), R^1 represents cyclohexanyl optionally substituted with hydroxyl, methyl or NH_2.

In another embodiment, in formula (II), R^1 represents oxetan-3-yl.

In another embodiment, in formula (II), R^1 represents tetrahydrofuran-3-yl.

In another embodiment, in formula (II), R^1 represents tetrahydropyran-3-yl or tetrahydropyran-4-yl.

In another embodiment, in formula (II), R^1 represents pyrrolidin-3-yl optionally substituted with methyl. In another embodiment, in formula (II), R^1 represents pyrrolidin-3-yl optionally substituted with fluoro.

In another embodiment, in formula (II), R^1 represents 4-fluoropyrrolidin-3-yl.

In another embodiment, in formula (II), R^1 represents piperidin-4-yl optionally substituted with a group selected from methyl, ethyl (unsubstituted or substituted with methoxy or hydroxyl), C(O)Me and oxetan-3-yl. In another embodiment, in formula (II), R^1 represents piperidin-4-yl optionally substituted with methyl.

In another embodiment, in formula (II), R^1 represents 1-methylpiperidin-4-yl.

In another embodiment, in formula (II), R^1 represents dioxidotetrahydro-2H-thiopyran-4-yl.

In one embodiment, in formula (II), A^1 represents CR^{2A}, A^2 represents CR^{2B} and A^3 represents CR^{2C}.

In another embodiment, in formula (II), A^1 represents N, A^2 represents CR^{2B} and A^3 represents CR^{2C}.

In another embodiment, in formula (II), A^2 represents N, A^1 represents CR^{2A} and A^3 represents CR^{2C}.

In another embodiment, in formula (II), A^3 represents N, A^1 represents CR^{2A} and A^2 represents CR^{2C}.

In another embodiment, in formula (II), A^1 represents CR^{2A} or N, A^2 represents CR^{2B} and A^3 represents CR^{2C}.

In one embodiment, in formula (II), R^{2A} represents hydrogen. In one embodiment, in formula (II), R^{2B} represents hydrogen. In one embodiment, in formula (II), R^{2C} represents hydrogen.

In another embodiment, in formula (II), one, two or three groups selected from R^{2A}, R^{2B} and R^{2C} is/are independently selected from methyl and methoxy, and any remaining R^{2A}, R^{2B} and/or R^{2C} groups represent hydrogen.

In another embodiment, in formula (II), one, two or three groups selected from R^{2A}, R^{2B} and R^{2C} represent methyl.

In another embodiment, in formula (II), one, two or three groups selected from R^{2A}, R^{2B} and R^{2C} represent methoxy.

In another embodiment, in formula (II), one or two groups selected from R^{2A}, R^{2B} and R^{2C} are independently selected from methyl and methoxy.

In another embodiment, in formula (II), one or two groups selected from R^{2A}, R^{2B} and R^{2C} represent methyl.

In another embodiment, in formula (II), one or two groups selected from R^{2A}, R^{2B} and R^{2C} represent methoxy.

In another embodiment, in formula (II), one group selected from R^{2A}, R^{2B} and R^{2C} represents methyl.

In another embodiment, in formula (II), one group selected from R^{2A}, R^{2B} and R^{2C} represents methoxy.

In another embodiment, the DNA-PK inhibitor is a compound of formula (II), wherein:

A^1 represents N or CR^{2A}, A^2 represents N or CR^{2B} and A^3 represents N or CR^{2C}, wherein no more than one of A^1, A^2 and A^3 represents N;

R^1 represents cyclohexanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl or tetrahydrothiopyranyl and is optionally substituted with one or two groups selected from fluoro, methyl, ethyl, hydroxyl, NH_2, dioxo, C(O)Me and oxetanyl, wherein the ethyl is optionally substituted with hydroxyl or methoxy; and

R^{2A}, R^{2B} and R^{2C} each independently represent hydrogen, methyl or methoxy.

In another embodiment, the DNA-PK inhibitor is a compound of Formula (II), wherein:

A^1 represents N or CR^{2A}, A^2 represents N or CR^{2B} and A^3 represents N or CR^{2C}, wherein no more than one of A^1, A^2 and A^3 represents N;

R^1 represents pyrrolidinyl or piperidinyl and is optionally substituted with one or two groups selected from fluoro, methyl, ethyl, hydroxyl, NH_2, dioxo and oxetanyl, wherein the ethyl is optionally substituted with hydroxyl or methoxy; and

R^{2A}, R^{2B} and R^{2C} each independently represent hydrogen, methyl or methoxy.

In one embodiment, A^1 represents N or CR^{2A}, A^2 represents CR^{2B} and A^3 represents CR^{2C}; R^1 represents cyclohexanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl or tetrahydrothiopyranyl and is optionally substituted with one or two groups selected from fluoro, methyl, ethyl, hydroxyl, NH_2, dioxo, C(O)Me and oxetanyl, wherein the ethyl is optionally substituted with hydroxyl or methoxy; and R^{2A}, R^{2B} and R^{2C} each independently represent hydrogen, methyl or methoxy.

In one embodiment, A^1 represents CR^{2A} or N, A^2 represents CR^{2B} and A^3 represents CR^{2C}; R^1 represents pyrrolidinyl or piperidinyl and is optionally substituted with one or two groups selected from fluoro, methyl, ethyl, hydroxyl, NH_2, dioxo and oxetanyl, wherein the ethyl is optionally substituted with hydroxyl or methoxy;

and R^{2A}, R^{2B} and R^{2C} each independently represent hydrogen, methyl or methoxy.

In one embodiment, A^1 represents CR^{2A}, A^2 represents CR^{2B} and A^3 represents CR^{2C}; R^1 represents cyclohexanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl or tetrahydrothiopyranyl and is optionally substituted with one or two groups selected from fluoro, methyl, ethyl, hydroxyl, NH_2, dioxo, C(O)Me and oxetanyl, wherein the ethyl is optionally substituted with hydroxyl or methoxy; and R^{2A}, R^{2B} and R^{2C} each independently represent hydrogen, methyl or methoxy.

In one embodiment, A^1 represents CR^{2A}, A^2 represents CR^{2B} and A^3 represents CR^{2C}; R^1 represents pyrrolidinyl or piperidinyl and is optionally substituted with one or two groups selected from fluoro, methyl, ethyl, hydroxyl, NH_2, dioxo and oxetanyl, wherein the ethyl is optionally substituted with hydroxyl or methoxy; and R^{2A}, R^{2B} and R^{2C} each independently represent hydrogen, methyl or methoxy.

In one embodiment, A^1 and A^2 both represent CH and A^3 represents CR^{2C}; R^1 represents cyclohexanyl, oxetanyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl or tetrahydrothiopyranyl and is optionally substituted with one or two groups selected from fluoro, methyl, hydroxyl, NH_2, dioxo, C(O)Me and oxetanyl; and R^{2C} represents hydrogen, methyl or methoxy.

In another embodiment, A^1 represents N, and A^2 and A^3 both reperesnt CH; R^1 represents cyclohexanyl, tetrahydrofuranyl, tetrahydropyranyl or piperidinyl and

is optionally substituted with hydroxyl, methyl or C(O)Me.

In one embodiment, A^1 represents CH or N, and A^2 and A^3 both represent CH; and R^1 represents a 5 or 6 membered heterocycloalkyl containing one heteroatom selected from N or O optionally substituted with fluoro or methyl.

In another embodiment, A^1, A^2 and A^3 each represent CH; and R^1 represents piperidinyl substituted with methyl.

In another embodiment, A^1, A^2 and A^3 each represent CH; and R^1 represents pyrrolidinyl substituted with fluoro.

In another embodiment, A^1 represents N, and A^2 and A^3 represent CH; and R^1 represents tetrahydrofuranyl.

In one embodiment the compound of formula (II) is selected from the group consisting of:
9-(1-acetylpiperidin-4-yl)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;
9-(1-acetylpiperidin-4-yl)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;
9-(1-acetylpiperidin-4-yl)-7-methyl-2-((7-methylquinazolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;
9-(1-acetylpiperidin-4-yl)-2-((2,7-dimethylquinoxalin-6-yl)amino)-7-methyl-7,9-dihydro-8*H*-purin-8-one;
9-(1-acetylpiperidin-4-yl)-2-((3,7-dimethylquinoxalin-6-yl)amino)-7-methyl-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-hydroxycyclohexyl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-hydroxycyclohexyl)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

2-((4,7-dimethylquinolin-6-yl)amino)-9-((1*r*,4*r*)-4-hydroxycyclohexyl)-7-methyl-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-hydroxycyclohexyl)-2-((4-methoxy-7-methylquinolin-6-yl)amino)-7-methyl-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-hydroxycyclohexyl)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-hydroxycyclohexyl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-hydroxycyclohexyl)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-hydroxycyclohexyl)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-hydroxy-4-methylcyclohexyl)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-hydroxy-1-methylcyclohexyl)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

(*S*)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one;

(*S*)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one;

(*R*)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one;

(*R*)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one;

(*R*)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-3-yl)-7,9-dihydro-8*H*-purin-8-one;

(*R*)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-3-yl)-7,9-dihydro-8H-purin-8-one;

(*S*)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-3-yl)-7,9-dihydro-8*H*-purin-8-one;

(*S*)-7-methyl-2-((7-methylquinoxalin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-3-yl)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8H-purin-8-one;

7-methyl-2-((7-methylquinolin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-2-((7-methylquinoxalin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-2-((7-methylquinazolin-6-yl)amino)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one;

2-((2,7-dimethylquinoxalin-6-yl)amino)-7-methyl-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one;

2-((3,7-dimethylquinoxalin-6-yl)amino)-7-methyl-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one;

9-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-2-((7-methylquinolin-6-yl)amino)-9-(oxetan-3-yl)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-2-((7-methylquinolin-6-yl)amino)-9-(piperidin-4-yl)-7,9-dihydro-8*H*-purin-8-one;

9-((3*S*,4*R*)-3-fluoropiperidin-4-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*s*,4*s*)-4-amino-4-methylcyclohexyl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((1*r*,4*r*)-4-amino-4-methylcyclohexyl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

(*R*)-7-methyl-9-(1-methylpyrrolidin-3-yl)-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

(*S*)-7-methyl-9-(1-methylpyrrolidin-3-yl)-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(1-methylpiperidin-4-yl)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-9-(1-methylpiperidin-4-yl)-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-9-(1-methylpiperidin-4-yl)-2-((7-methylquinoxalin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-((3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

7-methyl-2-((7-methylquinolin-6-yl)amino)-9-(1-(oxetan-3-yl)piperidin-4-yl)-7,9-dihydro-8*H*-purin-8-one;

9-(1-(2-hydroxyethyl)piperidin-4-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-(1-(2-methoxyethyl)piperidin-4-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-(1-ethylpiperidin-4-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

9-(1-acetylpiperidin-4-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one; and

9-((3*R*,4*R*)-4-fluoropyrrolidin-3-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one,

or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound of formula (II), or a pharmaceutically acceptable salt thereof, is selected from the group consisting of:

7-methyl-9-(1-methylpiperidin-4-yl)-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one;

(*S*)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one; and

9-((3*R*,4*R*)-4-fluoropyrrolidin-3-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one.

In one embodiment there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein the compound is 7-methyl-9-(1-

methylpiperidin-4-yl)-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one, or a pharmaceutically acceptable salt thereof.

In another embodiment of a compound of formula (II), the compound is (*S*)-7-methyl-2-((7-methylcinnolin-6-yl)amino)-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one, or a pharmaceutically acceptable salt thereof.

In another embodiment of a compound of formula (II), the compound is 9-((3*R*,4*R*)-4-fluoropyrrolidin-3-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8*H*-purin-8-one, or a pharmaceutically acceptable salt thereof.

Where the term "optionally" is used, it is intended that the subsequent feature may or may not occur. As such, use of the term "optionally" includes instances where the feature is present, and also instances where the feature is not present. For example, a group "optionally substituted by one methoxy group" includes groups with and without a methoxy substituent.

The term "substituted" means that one or more hydrogens (for example 1 or 2 hydrogens, or alternatively 1 hydrogen) on the designated group is replaced by the indicated substituent(s) (for example 1 or 2 substituents, or alternatively 1 substituent), provided that any atom(s) bearing a substituent maintains a permitted valency. Substituent combinations encompass only stable compounds and stable synthetic intermediates.

"Stable" means that the relevant compound or intermediate is sufficiently robust to be isolated and have utility either as a synthetic intermediate or as an agent having potential therapeutic utility. If a group is not described as "substituted", or "optionally substituted", it is to be regarded as unsubstituted (*i.e.* that none of the hydrogens on the designated group have been replaced).

The term "pharmaceutically acceptable" is used to specify that an object (for example a salt, dosage form or excipient) is suitable for use in patients. An example list of pharmaceutically acceptable salts can be found in the *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, P. H. Stahl and C. G. Wermuth, editors, Weinheim/Zürich:Wiley-VCH/VHCA, 2002.

A suitable pharmaceutically acceptable salt of a compound of formula (I) is, for example, an acid-addition salt. An acid addition salt of a compound of formula (I) may be formed by bringing the compound into contact with a suitable inorganic or organic acid under conditions known to the skilled person. An acid addition salt may for example be formed using an inorganic acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid. An acid addition salt may also be formed using an organic acid selected from the group consisting of trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric

acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid and *para*-toluenesulfonic acid.

Therefore, in one embodiment there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid or *para*-toluenesulfonic acid salt. In another embodiment there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a trifluoroacetic acid, formic acid or methanesulfonic acid salt. In another embodiment there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a trifluoroacetic acid or methanesulfonic acid salt. In another embodiment there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a methanesulfonic acid salt. In another embodiment there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a *mono*-methanesulfonic acid salt, *i.e.*

the stoichiometry of the compound of formula (I) to methanesulfonic acid is 1:1.

Compounds and salts described in this specification may exist in solvated forms and unsolvated forms. For example, a solvated form may be a hydrated form, such as a hemi-hydrate, a mono-hydrate, a di-hydrate, a tri-hydrate or an alternative quantity thereof. The disclosure encompasses all such solvated and unsolvated forms of compounds of formula (I) or (II), particularly to the extent that such forms possess DNA-PK inhibitory activity.

Atoms of the compounds and salts described in this specification may exist as their isotopes. The disclosure encompasses all compounds of formula (I) or (II) where an atom is replaced by one or more of its isotopes (for example a compound of formula (I) or (II) where one or more carbon atom is an ^{11}C or ^{13}C carbon isotope, or where one or more hydrogen atoms is a ^{2}H or ^{3}H isotope, or where one or more nitrogen atoms is a ^{15}N isotope or where one of more oxygen atoms is an ^{17}O or ^{18}O isotope).

Compounds and salts described in this specification may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms. The disclosure includes any optically active or racemic form of a compound of formula (I) or (II) which possesses DNA-PK inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by

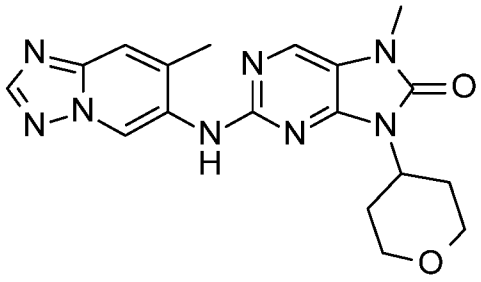
synthesis using optically active materials or by resolution of a racemic form.

Therefore, in one embodiment, a compound of formula (I) or (II), or a pharmaceutically acceptable salt thereof, is a single optical isomer being in an enantiomeric excess (%ee) of ≥ 95%, ≥ 98% or ≥ 99%. In another embodiment, the single optical isomer is present in an enantiomeric excess (%ee) of ≥ 99%.

Some of the compounds of formula (I) or (II) may be crystalline and may have more than one crystalline form. It is to be understood that the disclosure encompasses any crystalline or amorphous form, or mixtures thereof, which possess properties useful in DNA-PK inhibitory activity. It is well known how to determine the efficacy of a crystalline or amorphous form by standard tests.

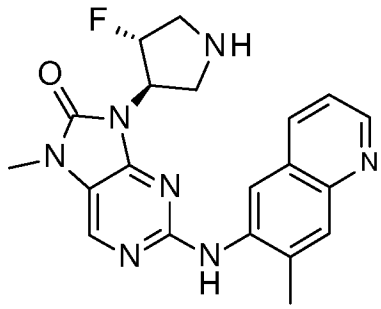
It is generally known that crystalline materials may be analysed using conventional techniques such as, for example, X-Ray Powder Diffraction (hereinafter XRPD) analysis and Differential Scanning Calorimetry (DSC).

In a preferred embodiment the DNA-PK inhibitor used in the disclosure is the compound AZD7648, 7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one represented by the following formula:



or a pharmaceutically acceptable salt thereof.

In another preferred embodiment the DNA-PK inhibitor used in the disclosure is the compound 9-((3R,4R)-4-fluoropyrrolidin-3-yl)-7-methyl-2-((7-methylquinolin-6-yl)amino)-7,9-dihydro-8H-purin-8-one, represented by the following formula:

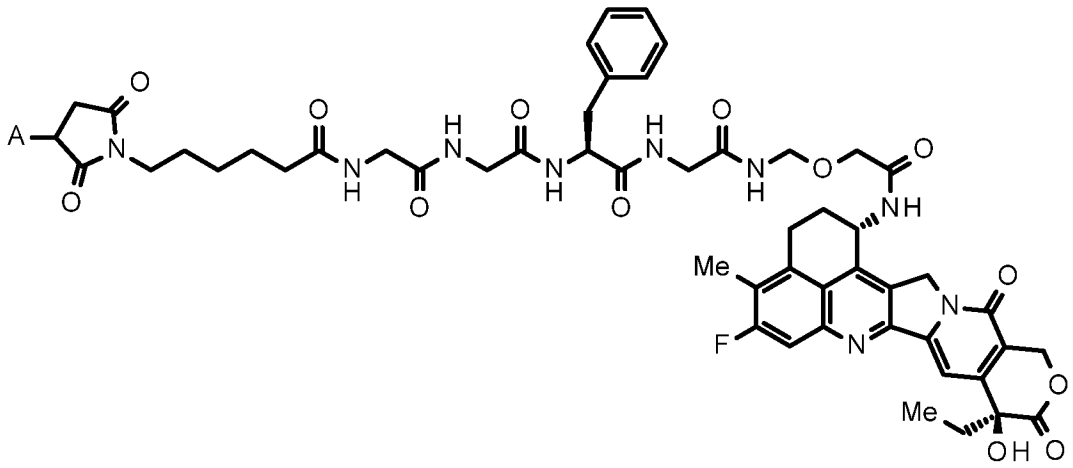


or a pharmaceutically acceptable salt thereof.

DNA-PK inhibitors such as compounds of formula (I), including AZD7648, may be prepared by methods known in the art such as disclosed in WO2018/114999 and compounds of formula (II) may be prepared by methods known in the art such as disclosed in WO2019/238929.

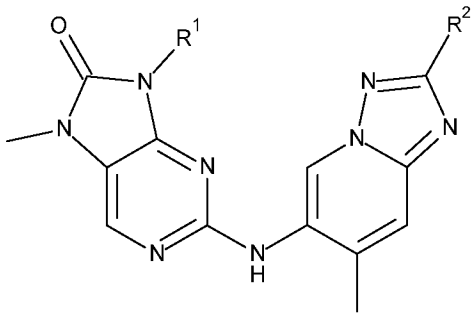
5. Combination of antibody-drug conjugate and DNA-PK inhibitor

In a first combination embodiment of the disclosure, the anti-HER2 antibody-drug conjugate which is combined with the DNA-PK inhibitor is an antibody-drug conjugate in which a drug-linker represented by the following formula:



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

In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above for the first combination embodiment is combined with a DNA-PK inhibitor which is a compound represented by the following formula (I):



(I)

wherein:

R^1 is a cyclohexyl, tetrahydrofuranyl or oxanyl ring, each of which is optionally substituted by one or more groups selected from hydroxyl, methoxy and methyl; and

R^2 is hydrogen or methyl,

or a pharmaceutically acceptable salt thereof.

In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above is combined with a DNA-PK inhibitor which is a compound represented by formula (I) as defined above wherein, in formula (I), R^1 is oxanyl.

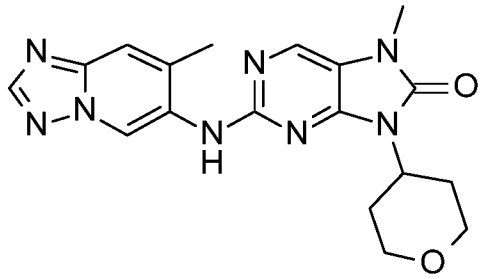
In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above is combined with a DNA-PK inhibitor as defined above wherein, in formula (I), R^1 is oxan-4-yl.

In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above is combined with a DNA-PK inhibitor as defined above wherein, in formula (I), R^1 is cyclohexyl.

In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above is combined with a DNA-PK inhibitor as defined above wherein, in formula (I), R^1 is 1-hydroxy-1-methyl-cyclohex-4-yl.

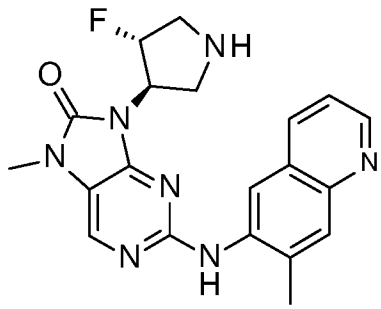
In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above is combined with a DNA-PK inhibitor as defined above wherein, in formula (I), R^2 is hydrogen.

In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above is combined with a DNA-PK inhibitor as defined above, wherein the DNA-PK inhibitor is AZD7648 represented by the following formula:



or a pharmaceutically acceptable salt thereof.

In another combination embodiment, the anti-HER2 antibody-drug conjugate as defined above is combined with a DNA-PK inhibitor as defined above, wherein the DNA-PK inhibitor is the compound represented by the following formula:

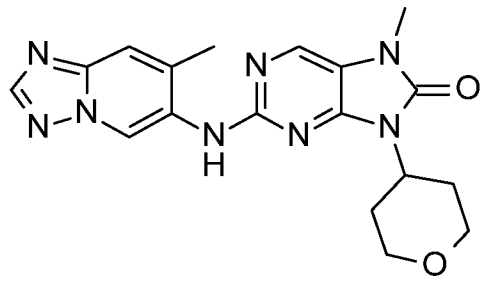


or a pharmaceutically acceptable salt thereof.

In an embodiment of each of the combination embodiments described above, the anti-HER2 antibody comprises a heavy chain comprising CDRH1 consisting of an amino acid sequence represented by SEQ ID NO: 3, CDRH2 consisting of an amino acid sequence represented by SEQ

ID NO: 4 and CDRH3 consisting of an amino acid sequence represented by SEQ ID NO: 5, and a light chain comprising CDRL1 consisting of an amino acid sequence represented by SEQ ID NO: 6, CDRL2 consisting of an amino acid sequence consisting of amino acid residues 1 to 3 of SEQ ID NO: 7 and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 8. In another embodiment of each of the combination embodiments described above, the anti-HER2 antibody comprises a heavy chain comprising a heavy chain variable region consisting of an amino acid sequence represented by SEQ ID NO: 9 and a light chain comprising a light chain variable region consisting of an amino acid sequence represented by SEQ ID NO: 10. In another embodiment of each of the combination embodiments described above, 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. In another embodiment of each of the combination embodiments described above, the anti-HER2 antibody comprises a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 11 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 2.

In a particularly preferred combination embodiment of the disclosure, the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan (DS-8201) and the DNA-PK inhibitor is the compound represented by the following formula:



also identified as AZD7648.

6. Therapeutic combined use and method

Described in the following are a pharmaceutical product and a therapeutic use and method wherein the anti-HER2 antibody-drug conjugate according to the present disclosure and a DNA-PK inhibitor are administered in combination.

The pharmaceutical product and therapeutic use and method of the present disclosure may be characterized in that the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor are separately contained as active components in different formulations, and are administered simultaneously or at different times, or characterized in that the antibody-drug conjugate and the DNA-PK inhibitor are contained as active components in a single formulation and administered.

In the pharmaceutical product and therapeutic method of the present disclosure, a single DNA-PK inhibitor used in the present disclosure can be administered in combination with the anti-HER2 antibody-drug conjugate, or two or more different DNA-PK inhibitors can be administered in combination with the antibody-drug conjugate.

The pharmaceutical product and therapeutic method of the present disclosure can be used for treating cancer, and can be preferably used for treating at least one cancer selected from the group consisting of breast cancer (including triple negative breast cancer and luminal 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 adenocarcinoma, 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, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma, and 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 (preferably non-small cell lung cancer), pancreatic cancer, ovarian cancer, prostate cancer, and kidney cancer.

The presence or absence of HER2 tumor markers can be determined, for example, by collecting tumor tissue from a cancer patient to prepare a formalin-fixed, paraffin-embedded (FFPE) specimen and subjecting the specimen to a test for gene products (proteins), for example, with an immunohistochemical (IHC) method, a flow cytometer, or Western blotting, or to a test for gene transcription, for example, with an in situ hybridization (ISH) method, a quantitative PCR method (q-PCR), or microarray analysis, or by collecting cell-free circulating tumor DNA (ctDNA) from a cancer patient and subjecting the ctDNA to a test with a method such as next-generation sequencing (NGS).

The pharmaceutical product and therapeutic method of the present disclosure can be used for HER2-expressing cancer, which may be HER2-overexpressing cancer (high or moderate) or may be HER2 low-expressing cancer.

In the present disclosure, the term "HER2-overexpressing cancer" is not particularly limited as long as it is recognized as HER2-overexpressing cancer by those skilled in the art. Preferred examples of the HER2-overexpressing cancer can include cancer given a score of 3+ for the expression of HER2 in an IHC method, and cancer given a score of 2+ for the expression of HER2 in an IHC method and determined as positive for the expression of HER2 in an in situ hybridization method (ISH). The in situ hybridization method of the present disclosure includes a fluorescence in situ hybridization

method (FISH) and a dual color in situ hybridization method (DISH).

In the present disclosure, the term "HER2 low-expressing cancer" is not particularly limited as long as it is recognized as HER2 low-expressing cancer by those skilled in the art. Preferred examples of the HER2 low-expressing cancer can include cancer given a score of 2+ for the expression of HER2 in an IHC method and determined as negative for the expression of HER2 in an in situ hybridization method, and cancer given a score of 1+ for the expression of HER2 in an IHC method.

The method for scoring the degree of HER2 expression by the IHC method, or the method for determining positivity or negativity to HER2 expression by the in situ hybridization method is not particularly limited as long as it is recognized by those skilled in the art. Examples of the method can include a method described in the 4th edition of the guidelines for HER2 testing, breast cancer (developed by the Japanese Pathology Board for Optimal Use of HER2 for Breast Cancer).

The cancer, particularly in regard to the treatment of breast cancer, may be HER2-overexpressing (high or moderate) or low-expressing breast cancer, or triple-negative breast cancer, and/or may have a HER2 status score of IHC 3+, IHC 2+, IHC 1+ or IHC >0 and <1+.

The pharmaceutical product and therapeutic method of the present disclosure can be preferably used for a mammal, but are more preferably used for a human.

The antitumor effect of the pharmaceutical product and therapeutic method of the present disclosure can be confirmed by transplanting cancer cells to a test subject animal to prepare a model and measuring reduction in tumor volume or life-prolonging effect by application of the pharmaceutical product and therapeutic method of the present disclosure. And then, the effect of combined use of the antibody-drug conjugate used in the present disclosure and a DNA-PK inhibitor can be confirmed by comparing antitumor effect with single administration of the antibody-drug conjugate used in the present disclosure and that of the DNA-PK inhibitor.

The antitumor effect of the pharmaceutical product and therapeutic method of the present disclosure can be confirmed in a clinical trial using any of an evaluation method with Response Evaluation Criteria in Solid Tumors (RECIST), a WHO evaluation method, a Macdonald evaluation method, body weight measurement, and other approaches, and can be determined on the basis of indexes of complete response (CR), partial response (PR); progressive disease (PD), objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and so on.

By using the above methods, the superiority in antitumor effect of the pharmaceutical product and therapeutic method of the present disclosure to existing pharmaceutical products and therapeutic methods for cancer treatment can be confirmed.

The pharmaceutical product and therapeutic method of the present disclosure can delay development of cancer cells, inhibit growth thereof, and further kill cancer cells. These effects can allow cancer patients to be free from symptoms caused by cancer or achieve improvement in quality of life (QOL) of cancer patients and attain a therapeutic effect by sustaining the lives of the cancer patients. Even if the pharmaceutical product and therapeutic method of the present disclosure do not accomplish killing cancer cells, they can achieve higher QOL of cancer patients while achieving longer-term survival, by inhibiting or controlling the growth of cancer cells.

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

The pharmaceutical product of the present disclosure can be administered containing at least one pharmaceutically suitable ingredient. Pharmaceutically suitable ingredients can be suitably selected and applied from formulation additives or the like that are generally used in the art, in accordance with the dosage, administration concentration, or the like of the antibody-drug conjugate used in the present disclosure and a DNA-PK inhibitor. The anti-HER2 antibody-drug conjugate used in the present disclosure can be administered, for example, as a pharmaceutical product

containing a buffer such as histidine buffer, a vehicle such as sucrose and trehalose, and a surfactant such as Polysorbates 80 and 20. The pharmaceutical product containing the antibody-drug conjugate used in the present disclosure 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.

In the case that the pharmaceutical product containing the anti-HER2 antibody-drug conjugate used in the present disclosure is an aqueous injection, the aqueous injection can be preferably diluted with a suitable diluent and then given as an intravenous infusion. Examples of the diluent can include dextrose solution and physiological saline, dextrose solution can be preferably exemplified, and 5% dextrose solution can be more preferably exemplified.

In the case that the pharmaceutical product of the present disclosure is a lyophilized injection, a required amount of the lyophilized injection dissolved in advance in water for injection can be preferably diluted with a suitable diluent and then given as an intravenous infusion. Examples of the diluent can include dextrose solution and physiological saline, dextrose solution can be preferably exemplified, and 5% dextrose solution can be more preferably exemplified.

Examples of the administration route applicable to administration of the pharmaceutical product of the

present disclosure can include intravenous, intradermal, subcutaneous, intramuscular, and intraperitoneal routes, and intravenous routes are preferred.

The anti-HER2 antibody-drug conjugate used in the present disclosure can be administered to a human with intervals of 1 to 180 days, can be preferably administered with intervals of a week, two weeks, three weeks, or four weeks, and can be more preferably administered with intervals of three weeks. The anti-HER2 antibody-drug conjugate used in the present disclosure can be administered in a dose of about 0.001 to 100 mg/kg per administration, and can be preferably administered in a dose of 0.8 to 12.4 mg/kg per administration. For example, the anti-HER2 antibody-drug conjugate can be administered once every three 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, and can be preferably administered once every three weeks at a dose of 5.4 mg/kg or 6.4 mg/kg.

The DNA-PK inhibitor according to the present disclosure can be orally administered to a human once or twice in each one to seven days, and can be preferably orally administered once a day or twice per day. The DNA-PK inhibitor used in the present disclosure can be orally administered in a dose of 0.1 mg to 4000 mg per administration, and can be preferably administered in a dose of 2.5 mg to 600 mg per administration. The DNA-PK inhibitor used in the present disclosure can be

administered to a human as an intravenous drip with intervals of 1 to 180 days, and can be preferably administered as an intravenous drip with intervals of a week, two weeks, three weeks, or four weeks. The DNA-PK inhibitor used in the present disclosure can be administered as an intravenous drip in a dose of 0.1 mg to 3000 mg per administration, and can be preferably administered as an intravenous drip in a dose of 10 mg to 100 mg per administration.

For example, a formulation of a DNA-PK inhibitor compound of formula (I) or (II) will normally be administered to a warm-blooded animal at a unit dose within the range 2.5-5000 mg/m^2 body area of the animal, or approximately 0.05-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 0.1-250 mg of active ingredient. For further information on Routes of Administration and Dosage Regimes, reference may be made to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose required for the therapeutic treatment of a particular disease state will necessarily be varied depending on the subject treated, the route of administration and the severity of the illness being treated.

The pharmaceutical product and therapeutic method of the present disclosure can be used as adjuvant

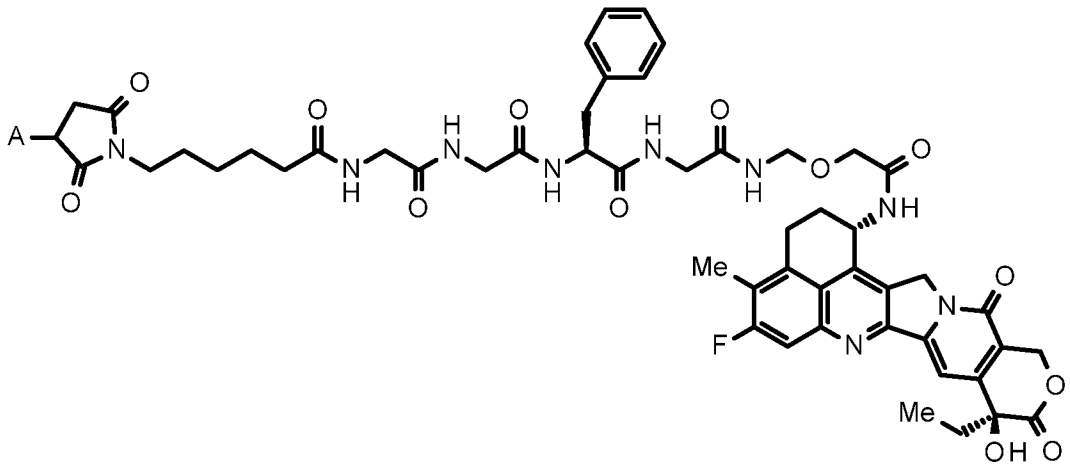
chemotherapy combined with surgery operation. The pharmaceutical product of the present disclosure may be administered for the purpose of reducing tumor size before surgical operation (referred to as preoperative adjuvant chemotherapy or neoadjuvant therapy), or may be administered for the purpose of preventing recurrence of tumor after surgical operation (referred to as postoperative adjuvant chemotherapy or adjuvant therapy).

[Examples]

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

Example 1: Production of antibody-drug conjugate

In accordance with a production method described in WO2015/115091 and using an anti-HER2 antibody (an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 11 (amino acid residues 1 to 449 of SEQ ID NO: 1) and a light chain consisting of an amino acid sequence consisting of all amino acid residues 1 to 214 of SEQ ID NO: 2), an anti-HER2 antibody-drug conjugate in which a drug-linker represented by the following formula:

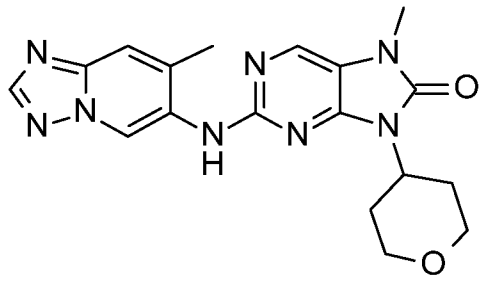


wherein A represents the connecting position to an antibody,

is conjugated to the anti-HER2 antibody via a thioether bond was produced (DS-8201: trastuzumab deruxtecan). The DAR of the antibody-drug conjugate is 7.7 or 7.8.

Example 2: Production of DNA-PK inhibitor

In accordance with a production method described in WO2018/114999, a DNA-PK inhibitor of formula (I) is prepared. Specifically, 7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one:



(AZD7648)

can be prepared according to Example 3 of WO2018/114999.

Example 3: Antitumor test

Combination of antibody-drug conjugate DS-8201 (trastuzumab deruxtecan) with DNA-PK inhibitor AZD7648 (7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one)

Method:

A high-throughput combination screen was run, in which breast cancer cell lines with diverse HER2 expression and one gastric cell line with high HER2 expression (Table 1) were treated with combinations of DS-8201 and AZD7648 (DNA-PK inhibitor).

Table 1

Cell line	HER2 expression	Cancer type
KPL4	High	Breast (HER2 +)
NCI-N87	High	Gastric
HCC1419	Amp/High	Breast (HER2 +)
T47D	Low	Breast (ER+)
HCC38	Amp/Low	Breast

The readout of the screen was a 7-day cell titer-glo cell viability assay, conducted as a 6 x 6 dose response matrix for each combination (5-point log serial dilution for DS-8201, and half log serial dilution for partners). In addition, trastuzumab and exatecan (DNA topoisomerase I inhibitor) were also screened in parallel with AZD7648.

Combination activity was assessed based on a combination of the ΔEmax and HSA synergy scores.

Results:

Results are shown in Figures 12A and 12B and Table 2.

Figure 12A shows matrices of measured cell viability signals. X axes represent drug A (DS-8201), and Y axes represent drug B (AZD7648). Values in the box represent the ratio of cells treated with drug A + B compared to DMSO control at day 7. All values are normalised to cell viability values at day 0. Values between 0 and 100 represent % growth inhibition and values above 100 represent cell death.

Figure 12B shows HSA excess matrices. Values in the box represent excess values calculated by the HSA (Highest Single Agent) model.

Table 2 shows HSA synergy and Loewe additivity scores:

Table 2

Cell line	KPL4	NCI-N87	HCC1419	T47D	HCC38
HSA synergy score	30.3	39.3	8.6	3.3	6.9
Loewe synergy score	29.6	38.6	8.6	3.3	5.9

Loewe Dose Additivity predicts the expected response if the two compounds act on the same molecular target by means of the same mechanism. It calculates additivity

based on the assumption of zero interaction between the compounds and it is independent from the nature of the dose-response relationship.

HSA (Highest Single Agent) [Berenbaum 1989] quantifies the higher of the two single compound effects at their corresponding concentrations. The combined effect is compared with the effect of each single agent at the concentration used in the combination. Excess over the highest single agent effect indicates cooperativity. HSA does not require the compounds to affect the same target.

Excess Matrix: For each well in the concentration matrix, the measured or fitted values are compared to the predicted non-synergistic values for each concentration pair. The predicted values are determined by the chosen model. Differences between the predicted and observed values may indicate synergy or antagonism, and are shown in the Excess Matrix. Excess Matrix values are summarized by the combination scores Excess Volume and Synergy Score.

As seen from Figures 12A and 12B and Table 2, AZD7648 (AZ13880164) interacted synergistically with DS-8201 and the combination also increased cell death at Emax (10 µM AZD7648 and 10 µg/ml (0.064 µM) DS-8201) in HER2 + cell lines KPL4, NCI-N87 and HCC1419. In HER2 + cell lines, combination activity was also observed at lower

concentrations. AZD7648 and DS-8201 also showed moderate combination activity in HER2 low/ER+ cell line T47D and in HER2 low cell line HCC38.

The results demonstrate that DNA-PK inhibition using AZD7648 enhances the antitumor efficacy of DS-8201 in both high and low HER2-expressing cell lines in vitro. AZD7648 showed synergistic combination activity and increased cell death in HER2 high cell lines. Beneficial combination activity was also observed in HER2 low cancer cell lines.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the embodiments. The foregoing description and Examples detail certain embodiments and describe the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the embodiments may be practiced in many ways and the claims include any equivalents thereof.

Free Text of Sequence Listing

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

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

SEQ ID NO: 3 – Amino acid sequence of a heavy chain CDRH1 [= amino acid residues 26 to 33 of SEQ ID NO: 1]

SEQ ID NO: 4 – Amino acid sequence of a heavy chain CDRH2 [= amino acid residues 51 to 58 of SEQ ID NO: 1]

SEQ ID NO: 5 – Amino acid sequence of a heavy chain CDRH3 [= amino acid residues 97 to 109 of SEQ ID NO: 1]

SEQ ID NO: 6 – Amino acid sequence of a light chain CDRL1 [= amino acid residues 27 to 32 of SEQ ID NO: 2]

SEQ ID NO: 7 – Amino acid sequence comprising an amino acid sequence of a light chain CDRL2 (SAS) [= amino acid residues 50 to 56 of SEQ ID NO: 2]

SEQ ID NO: 8 – Amino acid sequence of a light chain CDRL3 [= amino acid residues 89 to 97 of SEQ ID NO: 2]

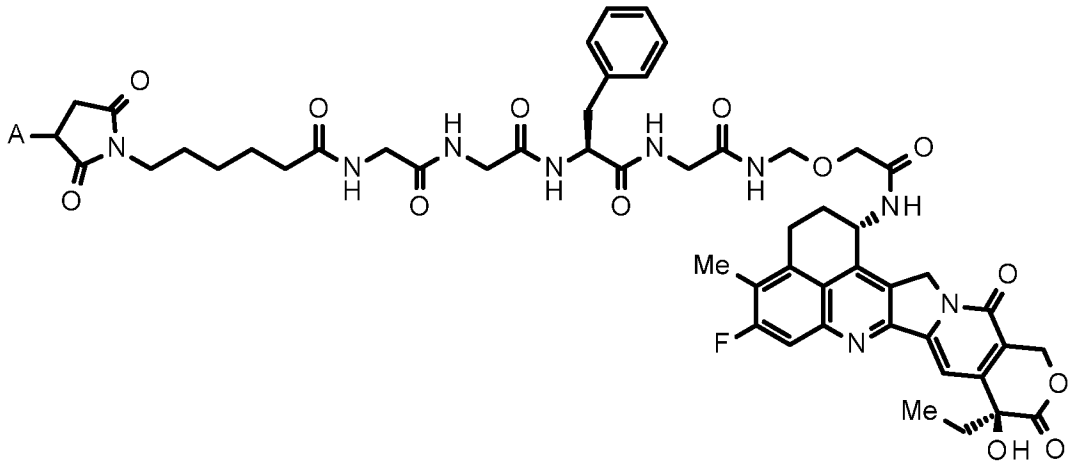
SEQ ID NO: 9 – Amino acid sequence of a heavy chain variable region [= amino acid residues 1 to 120 of SEQ ID NO: 1]

SEQ ID NO: 10 – Amino acid sequence of a light chain variable region [= amino acid residues 1 to 107 of SEQ ID NO: 2]

SEQ ID NO: 11 – Amino acid sequence of a heavy chain [= amino acid residues 1 to 449 of SEQ ID NO: 1]

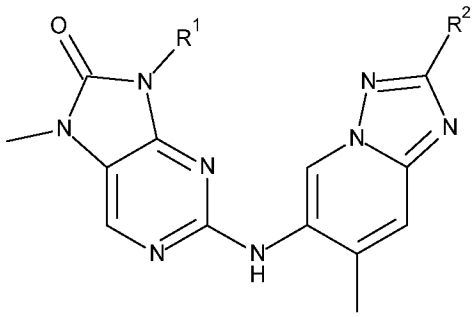
CLAIMS

1. A pharmaceutical product comprising an anti-HER2 antibody-drug conjugate and a DNA-PK inhibitor for administration in combination, wherein the anti-HER2 antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:



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

2. The pharmaceutical product according to claim 1, wherein the DNA-PK inhibitor is a compound represented by the following formula (I):



(I)

wherein:

R^1 is a cyclohexyl, tetrahydrofuranyl or oxanyl ring, each of which is optionally substituted by one or more groups selected from hydroxyl, methoxy and methyl; and

R^2 is hydrogen or methyl,

or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical product according to claim 2 wherein, in formula (I), R^1 is oxanyl.

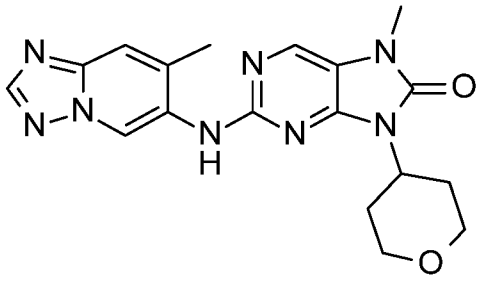
4. The pharmaceutical product according to claim 3 wherein, in formula (I), R^1 is oxan-4-yl.

5. The pharmaceutical product according to claim 2 wherein, in formula (I), R^1 is cyclohexyl.

6. The pharmaceutical product according to claim 5 wherein, in formula (I), R^1 is 1-hydroxy-1-methyl-cyclohex-4-yl.

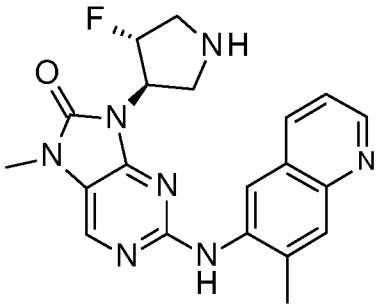
7. The pharmaceutical product according to any one of claims 2 to 6 wherein, in formula (I), R^2 is hydrogen.

8. The pharmaceutical product according to claim 2, wherein the DNA-PK inhibitor is AZD7648 represented by the following formula:



or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical product according to claim 1, wherein the DNA-PK inhibitor is the compound represented by the following formula:



or a pharmaceutically acceptable salt thereof.

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

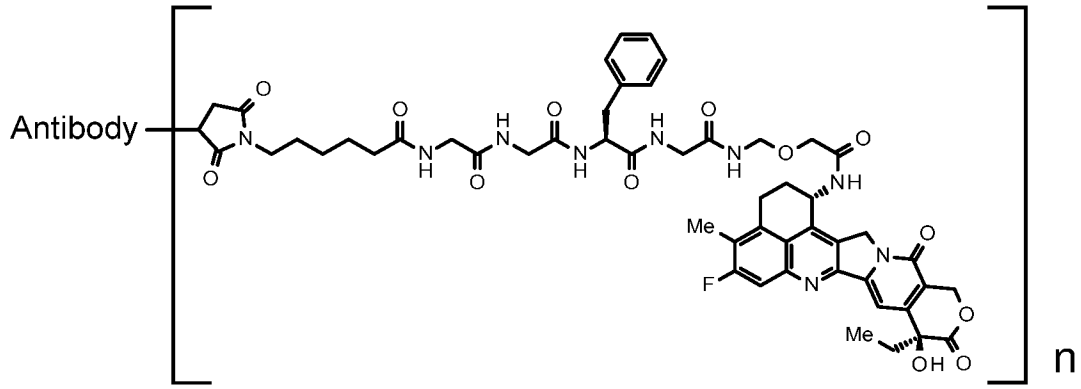
1 to 3 of SEQ ID NO: 7 and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 8.

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

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

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

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



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

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

16. The pharmaceutical product according to any one of claims 1 to 15, wherein the product is a composition comprising the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor, for simultaneous administration.

17. The pharmaceutical product according to any one of claims 1 to 15, wherein the product is a combined preparation comprising the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor, for sequential or simultaneous administration.

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

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

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

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

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

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

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

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

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

27. The pharmaceutical product according to claim 18, wherein the cancer is gastric cancer.

28. The pharmaceutical product according to claim 18, wherein the cancer is colorectal cancer.

29. The pharmaceutical product according to claim 18, wherein the cancer is lung cancer.

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

31. The pharmaceutical product according to claim 18, wherein the cancer is pancreatic cancer.

32. The pharmaceutical product according to claim 18, wherein the cancer is ovarian cancer.

33. The pharmaceutical product according to claim 18, wherein the cancer is prostate cancer.

34. The pharmaceutical product according to claim 18, wherein the cancer is kidney cancer.

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

36. The pharmaceutical product for the use according to claim 35, wherein the cancer is at least one selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, lung cancer, esophageal cancer, head-and-neck cancer, esophagogastric junction adenocarcinoma, biliary tract cancer, Paget's disease, pancreatic cancer, ovarian cancer, uterine carcinosarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, digestive

tract stromal tumor, uterine cervix cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, corpus uteri carcinoma, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

52. Use of an anti-HER2 antibody-drug conjugate or a DNA-PK inhibitor in the manufacture of a medicament for administration of the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor in combination, wherein the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor are as defined in any one of claims 1 to 15, for treating cancer.

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

myeloma, glioblastoma multiforme, osteosarcoma, sarcoma, and melanoma.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

70. The use according to any one of claims 52 to 68 wherein the medicament is a combined preparation

comprising the anti-HER2 antibody-drug conjugate and the DNA-PK inhibitor, for sequential or simultaneous administration.

71. A method of treating cancer comprising administering an anti-HER2 antibody-drug conjugate and a DNA-PK inhibitor as defined in any one of claims 1 to 15 in combination to a subject in need thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[Figure 1]

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

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVR
QAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSK
NTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[Figure 2]

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

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQ
KPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

[Figure 3]

SEQ ID NO: 3 - Amino acid sequence of heavy chain CDRH1

GFNIKDTY

[Figure 4]

SEQ ID NO: 4 - Amino acid sequence of heavy chain CDRH2

IYPTNGYT

[Figure 5]
SEQ ID NO: 5 - Amino acid sequence of heavy chain CDRH3
SRWGGDGFYAMDY

[Figure 6]
SEQ ID NO: 6 - Amino acid sequence of light chain CDRL1
QDVNTA

[Figure 7]
SEQ ID NO: 7 - Amino acid sequence comprising an amino acid sequence of light chain CDRL2 (SAS)
SASFLYS

[Figure 8]
SEQ ID NO: 8 - Amino acid sequence of light chain CDRL3
QQHYTTPPT

[Figure 9]
SEQ ID NO: 9 - Amino acid sequence of heavy chain variable region
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVR
QAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSK
NTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSS

[Figure 10]
SEQ ID NO: 10 - Amino acid sequence of light chain variable region
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQ
KPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

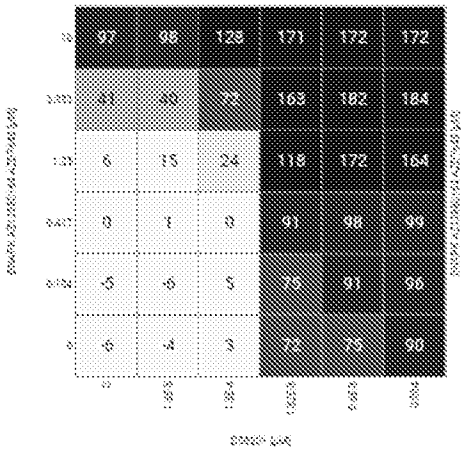
[Figure 11]

SEQ ID NO: 11 - Amino acid sequence of heavy chain

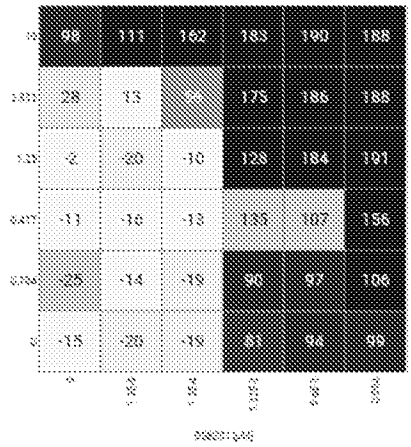
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVR
QAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSK
NTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[Figure 12A]

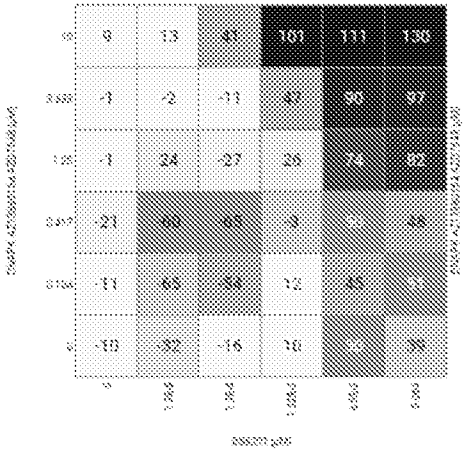
KPL4 (HER2 High)



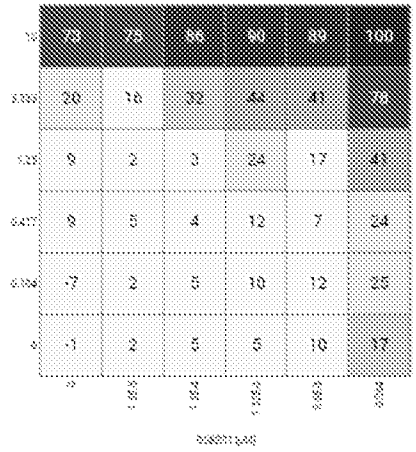
NCI-N87 (HER2 High)



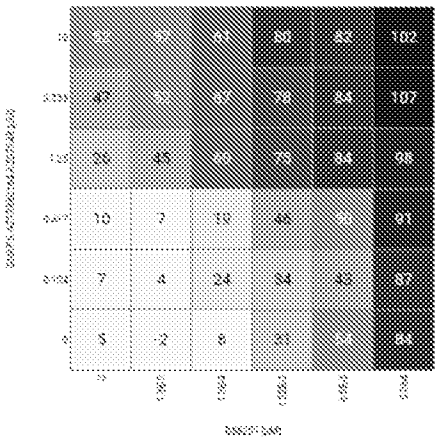
HCC1419 (HER2 High)



T47D (HER2 Low)

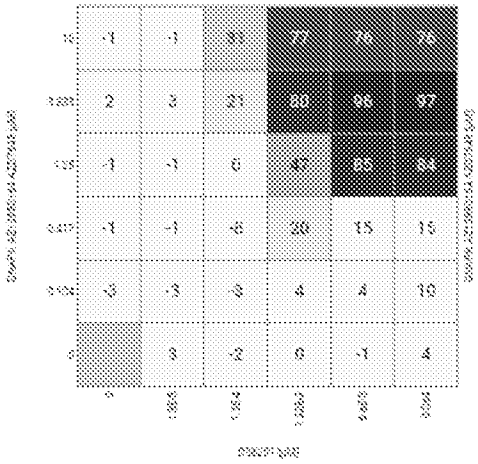


HCC38 (HER2 Low)

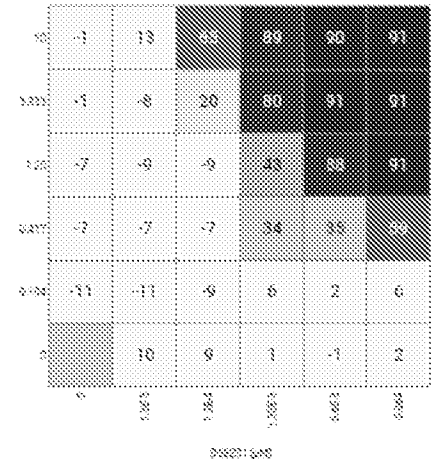


[Figure 12B]

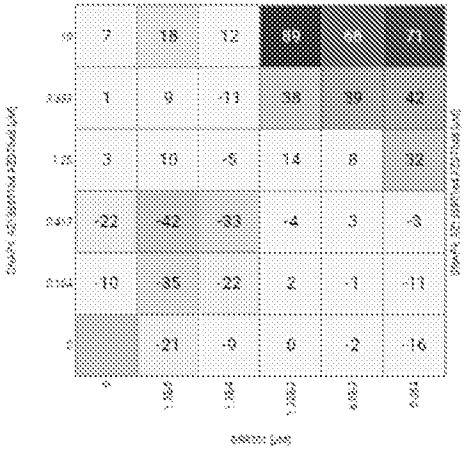
KPL4 (HER2 High)



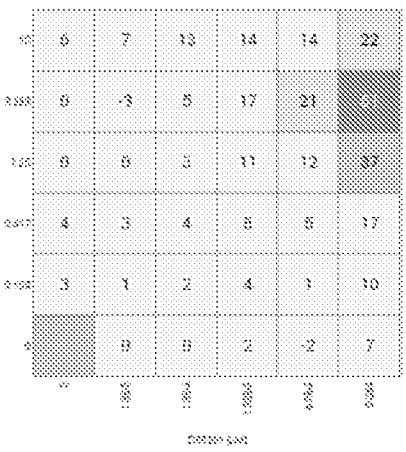
NCI-N87 (HER2 High)



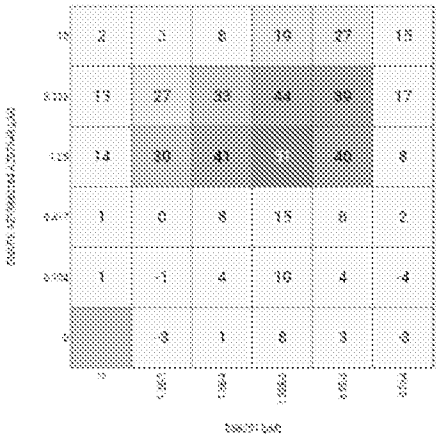
HCC1419 (HER2 High)



T47D (HER2 Low)



HCC38 (HER2 Low)



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/055552

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/68 A61K31/522 A61K45/06 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 3 101 032 A1 (DAIICHI SANKYO CO LTD [JP]) 7 December 2016 (2016-12-07) example 50 evaluation examples 5, 7-14 ----- -/--	1-89

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2021	07/10/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Monami, Amélie

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