

COMBINATION OF A WEE1 INHIBITOR AND A TOPOISOMERASE 1 INHIBITOR

FIELD OF THE INVENTION

- 5 The present invention generally relates to the combination of a WEE1 inhibitor and a topoisomerase 1 inhibitor, and to the combination of a WEE1 inhibitor and an antibody-drug conjugate (ADC) comprising a topoisomerase 1 inhibitor. More specifically, the present invention relates to the use of a combination of a WEE1 inhibitor and a topoisomerase 1 inhibitor, and to the use of a combination of a
- 10 WEE1 inhibitor and an ADC comprising a topoisomerase 1 inhibitor, to treat cancer in patients in need thereof.

BACKGROUND

- DNA is continuously subjected to both endogenous insults (e.g., stalled replication
- 15 forks, reactive oxygen species) and exogenous insults (UV, ionizing radiation, chemical) that can lead to DNA damage. As a result, cells have established sophisticated mechanisms to counteract these deleterious events that would otherwise compromise genomic integrity and lead to genomic instability diseases such as cancer. These mechanisms are collectively referred to as the DNA
- 20 damage response (DDR). One component of the overall DDR is the activation of various checkpoint pathways that modulate specific DNA-repair mechanisms throughout the various phases of the cell cycle, which includes the G1, S, G2 and Mitosis checkpoints. A majority of cancer cells have lost their G1 checkpoint owing to p53 mutations and as such, rely on the G2 checkpoint to make the necessary
- 25 DNA damage corrections prior to committing to enter mitosis and divide into 2 daughter cells.

- DNA damage repair inhibitors have been proposed as potentially useful therapeutic approaches. Nonetheless, there is still a need for improved cancer
- 30 treatment options. The present invention aims to provide such improved cancer therapies. In particular, it is an objective to provide cancer therapies exhibiting superior therapeutic efficacy and/or reduced side effects.

SUMMARY OF THE INVENTION

The present invention provides drug combinations, drugs for use in combination
5 therapies, pharmaceutical compositions and kits, as set forth in the appended
claims and as further described in the detailed description below.

The present invention relates to a combination of a WEE1 inhibitor and a
topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor. It is to be
10 understood that any reference to a WEE1 inhibitor, a topoisomerase 1
inhibitor/ADC comprising a topoisomerase 1 inhibitor also encompasses the
pharmaceutically acceptable salt thereof, even if not explicitly mentioned as such.

The present invention further relates to a combination of a WEE1 inhibitor and a
15 topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor for use as a
medicament.

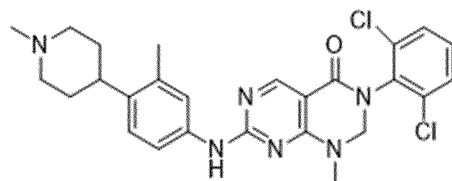
The present invention further relates to a combination of a WEE1 inhibitor and a
topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor for use in
20 treating cancer in a patient in need thereof.

The present invention further relates to a WEE1 inhibitor for use in treating cancer
in a patient in need thereof, wherein the WEE1 inhibitor is administered in
combination with a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1
25 inhibitor.

The present invention further relates to a topoisomerase 1 inhibitor/ADC
comprising a topoisomerase 1 inhibitor for use in treating cancer in a patient in
need thereof, wherein the topoisomerase 1 inhibitor/ADC comprising a
30 topoisomerase 1 inhibitor is administered in combination with a WEE1 inhibitor.

In some aspects of the present invention, the WEE1 inhibitor is a compound of
formula (I)

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(I),

or a pharmaceutically acceptable salt thereof.

In some aspects of the present invention, the WEE1 inhibitor is administered

- 5 a. on days 1 to 3 of a 21-day cycle,
- b. on days 1 to 3 and 8 to 10 of a 21-day cycle,
- c. on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle,
- d. on days 1 to 5 over 21-day cycle,
- e. on days 1 to 5 and 8 to 12 over a 21-day cycle,
- 10 f. on days 1 to 5, 8 to 12 and 15 to 19 of a 21-day cycle,
- g. on days 1 to 14 of a 21-day cycle,
- h. daily over a 21-day cycle,
- i. on days 1 to 5 and 8 to 10 of a 28-day cycle,
- j. on days 1 to 5, 8 to 10 and 15 to 17 of a 28-day cycle,
- 15 k. on days 1-3 of a 28-day cycle,
- l. on days 1-3 and 8-10 of a 28-day cycle,
- m. on days 1-3 and 15-17 of a 28-days cycle,
- n. on days 1-3, 8-10 and 15-17 of a 28-day cycle,
- o. on days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle,
- 20 p. on days 1-5 of a 28-day cycle,
- q. on days 1-5 and 8-12 of a 28-day cycle,
- r. on days 1-5 and 15-19 of a 28-day cycle,
- s. on days 1-5, 8-12 and 15-19 of a 28-day cycle,
- t. on days 1-5, 8-12, 15-19 and 22-26 of a 28-day cycle, or
- 25 u. daily over a 28-day cycle, or
- v. on days 1, 8, 15 and 22 of a 6-week cycle.

In some aspects of the present invention, the WEE1 inhibitor is administered

- a. at a dose ranging from about 30 to about 1000 mg per WEE1 inhibitor treatment day, preferably about 30 to about 720 mg per WEE1 inhibitor treatment day, and/or
- b. orally, and/or
- 5 c. as a single dose on a WEE1 inhibitor treatment day, and/or
- d. at approximately the same time on each WEE1 inhibitor treatment day.

10 In some aspects of the present invention, the topoisomerase 1 inhibitor is administered

- a. on days 1 and 15 of a 28-day cycle,
- b. on day 1 of a 21-day cycle,
- c. on days 1-5 of a 21-day cycle,
- d. on days 1-3 of a 21-day cycle,
- 15 e. on days 1, 8, 15 of a 28-day cycle,
- f. on days 1-5 of a 28-day cycle,
- g. on days 1-5 and 8-12 of a 28-day cycle,
- h. on days 1-5, 8-12 and 15-19 of a 28-days cycle,
- i. on days 1, 8, 15 and 22 of a 6-week cycle, or
- 20 j. on the same days as the WEE1 inhibitor treatment days, preferably as defined in any of aspects a to v defined in relation to the 21-day cycles, 28-day cycles or 6-week cycles of the WEE1 inhibitor above.

25 In some aspects of the present invention, the ADC comprising a topoisomerase 1 inhibitor is administered

- a. on days 1 and 8 of a 21-day cycle,
- b. on days 1 and 8 of a 28-day cycle,
- c. on days 1, 8 and 15 of a 21-day cycle,
- 30 d. on days 1, 8 and 15 of a 28-day cycle,
- e. on days 1, 8, 15 and 22 of a 28-day cycle,
- f. on day 1 of a 21-day cycle (once every three weeks), or
- g. on day 1 of a 28-day cycle (once every four weeks).

In some aspects of the present invention, the combination, the WEE1 inhibitor and/or the topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more 21-day cycles, over 1, 2, 3, 4, 5, 6 or
5 more 28-day cycles, or over 1, 2, 3, 4, 5, 6 or more 6-week cycles.

In some aspects of the present invention, the cancer is breast cancer, colorectal cancer, non-small-cell lung cancer (NSCLC), small cell lung cancer (SCLC), ovarian cancer, endometrial cancer, including uterine serous carcinoma (USC),
10 testicular cancer, penile cancer, anal cancer, stomach cancer, bladder cancer, cervical cancer, esophageal cancer, head and neck cancer, gallbladder cancer, pancreatic cancer, prostate cancer, gastric cancer, peritoneal cancer, hepatocarcinoma, renal cell carcinoma (RCC), melanoma, soft tissue sarcoma, lymphoma or glioma, including glioblastoma.

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In some aspects of the present invention, the cancer is characterized by reduced expression of HER2.

In some aspects of the present invention, the cancer is characterized by CCNE1 overexpression, WRN deficiency, ATRX deficiency, FBXW7 deficiency, PPP2R1A
20 inactivating mutation, or reduction or loss of histone H3K36 trimethylation (H3K36me3).

In some aspects of the present invention, the cancer is metastatic.

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In some aspects of the present invention, the metastatic cancer comprises brain metastases.

In some aspects of the present invention, the topoisomerase 1 inhibitor is
30 - camptothecin or a camptothecin derivative, preferably selected from topotecan, irinotecan, SN38, govitecan, deruxtecan (Dxd), exatecan, belotecan, silatecan, gimatecan, namitecan (ST1968), or a pharmaceutically acceptable salt thereof, or

- an indenisoquinoline, preferably selected from indenoisoquinoline NSC 314622, indotecan (LMP-400), indimitecan (LMP-776), or a pharmaceutically acceptable salt thereof, or
- a phenanthridine, an indolocarbazole, a β -carboline hybrid, a pyrazole-linked benzothiazole- β -naphthol derivative, a 4 β -[4'-(1-(aryl)ureido)benzamide]podophyllotoxin congener, a benzimidazole congener or a pharmaceutically acceptable salt thereof.

In some aspects of the present invention, an ADC comprising a topoisomerase 1 inhibitor is used, wherein the topoisomerase 1 inhibitor moiety in the ADC is selected from SN38, govitecan, deruxtecan (Dxd), exatecan, sesutecan, belotecan, tirumotecan, samrotecan or a pharmaceutically acceptable salt thereof.

In some aspects of the present invention, the ADC comprising a topoisomerase 1 inhibitor is selected from sacituzumab govitecan, datopotamab deruxtecan, sacituzumab tirumotecan, trastuzumab deruxtecan, patritumab deruxtecan, ifinatumab deruxtecan, puxitatug samrotecan, AZD-5335, rinatabart sesutecan, labetuzumab govitecan, PF-08046050, M9140, raludotatug deruxtecan, ABBV-400, DS-3939, ABBV-706, BAT-8007, ACR-246, ZW-220 or a pharmaceutically acceptable salt thereof.

The present invention further relates to a pharmaceutical composition comprising the combination as further specified herein, or comprising the WEE1 inhibitor as specified herein, or the topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor as specified herein, for use in treating cancer in a patient in need thereof, wherein the use is as described herein.

The present invention further relates to a kit comprising the combination as further specified herein, wherein the WEE1 inhibitor and topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor are provided in separate dosage forms and/or containers, optionally for use in treating cancer in a patient in need thereof, wherein the use is as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the in vitro cell proliferation results obtained in Example 1:
5 combination of Compound of Formula (I) with SN38 in 2 cell lines (Figure 1A),
combination of Formula (I) with topotecan in 3 cell lines (Figure 1B).

Figure 2 depicts the in vitro results obtained in Example 2: combination of
Compound of Formula (I) with sacituzumab govitecan in 4 breast cancer cell lines
10 including TROP2^{high} and TROP2^{low}.

Figure 3 depicts the in vitro results obtained in Example 2: combination of
Compound of Formula (I) with sacituzumab govitecan in 2 TROP2^{low} GBM cell
lines.
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Figure 4 depicts the in vitro results obtained in Example 2: combination of
Compound of Formula (I) with sacituzumab govitecan in 3 CRC cancer cell lines
including TROP2^{high} and TROP2^{low}.

20 Figure 5 depicts the in vivo results obtained in Example 3: combination of
Compound of formula (I) (30 mg/kg QD) with sacituzumab govitecan at 8 mg/kg
QWx2 (Figure 5A) or at 12.5 mg/kg QWx2 (Figure 5B) in a TROP2 high model of
breast cancer in mice.

25 Figure 6 depicts the in vivo results obtained in Example 4: combination of
Compound of formula (I) (30 mg/kg QD) with sacituzumab govitecan (12.5 mg/kg
QWx2) in a TROP2 low model of breast cancer in mice.

Figure 7 depicts the in vivo results obtained in Example 5: combination of
30 Compound of formula (I) (30 mg/kg QD) with datopotamab deruxtecan (6mg/kg
QWx2) in a TROP2 low PDX model of breast cancer.

Figure 8 depicts the in vivo results obtained in Example 6: combination of Compound of formula (I) (30 mg/kg QD) with datopotamab deruxtecan (6mg/kg QWx2) in a TROP2 moderate PDX model of colorectal cancer.

- 5 Figure 9 depicts the in vivo results obtained in Example 7: combination of Compound of formula (I) (30 mg/kg QD) with sacituzumab govitecan (12.5 mg/kg QWx4) in a TROP2 moderate PDX model of colorectal cancer.

- Figure 10 depicts the in vivo results obtained in Example 8: combination of
10 Compound of formula (I) (30 mg/kg QD) with sacituzumab govitecan (10mg/kg QWx4) in a TROP2 high PDX model of NSCLC cancer.

- Figure 11 depicts the in vivo results obtained in Example 9: combination of
Compound of formula (I) (30 mg/kg QD) with sacituzumab govitecan (10mg/kg
15 QWx2) in a TROP2 high PDX model of ovarian cancer.

DETAILED DESCRIPTION OF THE INVENTION

20 DEFINITIONS

So that the invention may be more readily understood, certain terms are specifically defined below. Unless explicitly defined elsewhere in this document, all other technical and scientific terms used herein have the meaning that would be
25 commonly understood by one of ordinary skill in the relevant art.

As used herein, including in the appended claims, the singular forms of words such as “a”, “an”, and “the”, include their corresponding plural references unless the context clearly indicates otherwise.

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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 term "and/or" as used herein in a phrase such as "A and/or B" herein is intended to include both "A and B," "A or B," "A," and "B." Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass
5 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).

As used herein, a "WEE1 inhibitor" refers to a compound that inhibits the activity of the WEE1 kinase, for example with an IC₅₀ of <10nM in an ADP-GLO kinase
10 assay or an IC₅₀ of <100nM in an enzyme profiling assay. The compound of formula (I) herein is an example of a WEE1 inhibitor.

In some aspects, a "brain penetrant" WEE1 inhibitor refers to a WEE1 inhibitor that is able to cross the blood brain barrier (whether impaired or not) and to distribute
15 into the brain. In some aspects, the ability of a compound to cross the blood brain barrier and distribute into the brain is reflected by its brain to plasma concentration ratio exceeding a certain threshold. For example, compound of formula (I) may exhibit a better ability to cross the blood brain barrier and distribute into the brain than AZD1775 and Zn-c3, as evidenced by its higher brain to plasma
20 concentration ratios. Compound of formula (I) may thus be referred to as a brain penetrant WEE1 inhibitor.

The term "topoisomerase 1" or "Topo1" or "TOP1", as used herein, refers to an enzyme catalyzing changes in DNA topology via single strand DNA cleavage. It
25 plays an essential role in controlling the topological structure of DNA during various cell processes including replication, transcription, recombination and repair, through transiently cutting one strand of DNA to form single-strand breaks, allowing supercoiled DNA to relax.

30 The term "topoisomerase 1 inhibitor" or "Topo1 inhibitor" or "TOP1 inhibitor", as used herein, represents a compound or composition that impedes the activity of topoisomerase 1 enzymes. Topoisomerase 1 inhibitors may be grouped in two types, (i) Topo1 poisons that covalently trap topoisomerases on DNA and (ii)

- Topo1 catalytic inhibitors, which prevent DNA cleavage (Pommier Y. DNA topoisomerase I inhibitors: chemistry, biology, and interfacial inhibition. Chem Rev. 2009 Jul;109(7):2894-902. doi: 10.1021/cr900097c. PMID: 19476377; PMCID: PMC2707511; Xu Y, Her C. Inhibition of Topoisomerase (DNA) I (TOP1): DNA
- 5 Damage Repair and Anticancer Therapy. Biomolecules. 2015 Jul 22;5(3):1652-70. doi: 10.3390/biom5031652). Topo1 activity (or inhibitory activity) may be measured e.g. by the conversion of supercoiled DNA to its relaxed form using known methods or kits, such as a topoisomerase I drug screening kit (Topogen), and using a known Topo1 poison such as camptothecin (CPT) as the positive
- 10 control. More specifically, Topo 1 inhibitory activity of a compound may be assessed following the procedure described in the Topoisomerase I Drug Screening Kit User Manual by Topogen, Protocol TG1018, Version 05202016, or following the “Basic Protocol 1: Assay of Topoisomerase I Activity” described in Nitiss, J. L., Kiianitsa, K., Sun, Y., Nitiss, K. C., & Maizels, N. (2021).
- 15 Topoisomerase assays. Current Protocols, 1, e250. doi: 10.1002/cpz1.250.

The term “topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor”, as used herein in connection with combinations of the invention, is to be understood as characterizing the respective combination to contain at least one

20 compound selected from topoisomerase 1 inhibitors and ADCs comprising a topoisomerase 1 inhibitor. The respective combination may thus comprise a single topoisomerase 1 inhibitor or a single ADC comprising a topoisomerase 1 inhibitor, or it may comprise two or more topoisomerase 1 inhibitors or it may comprise two or more ADCs comprising a topoisomerase 1 inhibitor, or it may comprise a

25 mixture of one or more topoisomerase 1 inhibitors and one or more ADCs comprising a topoisomerase 1 inhibitor. The same logic is applicable if the term “topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor” is used in connection with the description of therapeutic uses, methods, and the like. It is thus intended to have the same meaning as the wording “at least a drug selected

30 from a topoisomerase 1 inhibitor and an antibody-drug conjugate (ADC) comprising a topoisomerase 1 inhibitor”.

The term "antibody" means an immunoglobulin molecule that recognizes and specifically binds to a target antigen, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing through at least one antigen recognition site within the variable region of the immunoglobulin molecule. A target antigen generally has numerous possible binding sites, also called epitopes, that may be recognized by complementary-determining regions (CDRs) on multiple antibodies. Each antibody that specifically binds to a different epitope has a different structure. Thus, one antigen may have more than one corresponding antibody. An antibody includes a full-length immunoglobulin molecule or an immunologically active portion of a full-length immunoglobulin molecule. As used herein, the term "antibody" encompasses intact polyclonal antibodies, intact monoclonal antibodies, antibody fragments (such as Fab, Fab', F(ab')₂, and Fv fragments), single chain Fv (scFv) mutants, multispecific antibodies such as bispecific antibodies generated from at least two intact antibodies, chimeric antibodies, human antibodies, antibodies derived from another species, such as humanized antibodies, fusion proteins comprising an antigen determination portion of an antibody, and any other modified immunoglobulin molecule comprising an antigen recognition site so long as the antibodies exhibit the desired biological activity. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well-known subunit structures and three-dimensional configurations.

The term "antibody fragment" as used herein refers to a portion of a full-length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include, but are not limited to Fab, Fab', F(ab')₂, and Fv fragments, diabodies, linear antibodies, single chain antibodies, single domain antibodies and multispecific antibodies formed from antibody fragments.

The term "antibody-drug conjugate", "ADC" or "ADC format" as used herein refers to a compound designed for targeted disease therapy, comprising an antibody

moiety, a cytotoxic payload, and a linker. The antibody serves as the targeting agent, specifically binding to certain proteins or receptors predominantly expressed on the surface of target cells such as cancer cells. The cytotoxic payload is a potent therapeutic drug generally intended to eliminate these target cells upon delivery. The linker plays a critical role in securely attaching the drug to the antibody yet allowing its release once inside the target cell. The linker may be cleavable or non-cleavable. The ADC structure facilitates precise delivery of potent drugs directly to pathogenic cells while minimizing systemic exposure and thereby reducing potential adverse side effects.

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The term “compound”, as used herein, is intended to encompass both small molecules, such as topoisomerase 1 inhibitors like irinotecan, and conjugates such as the herein-mentioned antibody-drug conjugates.

15 As used herein, the term “biomarker”, also sometimes referred to as “biological marker”, is a measurable indicator of a biological state or condition. The biomarker refers to a molecule whose activity, conformation, localization and/or abundance can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or predictor of pharmacologic responses to therapeutic treatment. Biomarkers can be specific cells, molecules, genes, gene products, proteins, enzymes or hormones. They contribute to the understanding of disease mechanisms and the effect of drug treatment. Biomarkers may be measured and evaluated using blood, urine, cells or tissues.

25 In some aspects, the term “reduced expression” or “overexpression” as used herein refers to an abnormal expression level of a given biomarker in tumor cells compared to the expression level in corresponding (or comparable) healthy cells or tissue. The person of skill in the art would understand that the reference healthy cell or tissue for “normal” expression levels may vary depending on the solid tumor type considered. In some aspects, it may preferably be a healthy cell or tissue of the same origin. Gene expression (including reduced expression or overexpression) may be detected by known methods, including for example mass spectrometry proteomics, immunohistochemistry (IHC), western blot for protein

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levels, and/or by measuring mRNA expression level using whole transcriptome sequencing, microarray technology or qPCR.

The terms "HER2" and "erbB2" are used interchangeably herein. They refer to
5 erythroblastic oncogene B-2, which encodes the receptor tyrosine-protein kinase
erbB-2, a 185-kDa transmembrane glycoprotein belonging to the epidermal growth
factor receptor (EGFR) family. Cells having a reduced expression of HER2 are
cells that exhibit a lower activity of HER2 than cells normally expressing HER2.
The reduced expression of HER2 is for instance measured by identifying the gene
10 copy number or expression level of the gene product in a cell (e.g., HER2 mRNA
transcript count or HER2 protein level) and comparing the same with the gene
copy number or expression level of healthy cells or tissue. Reduced gene copy
numbers or HER2 loss may for example be assessed by in-situ-hybridization (ISH).
Reduced expression may be assessed by IHC.

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The terms "CCNE1" and "cyclin E1," are used interchangeably herein. They refer
to G1/S specific cyclin E1 (Gene name: CCNE1). A cell overexpressing CCNE1 is
a cell that exhibits a higher activity of CCNE1 than a cell normally expressing
CCNE1. CCNE1 amplification is present in a cell that exhibits a gene copy number
20 of at least 3 compared to a diploid normal cell with 2 copies. A CCNE1-
overexpressing cell may for instance be a cell that exhibits CCNE1 amplification. A
cell exhibiting a copy number greater than 3 of CCNE1 is therefore likely a cell
overexpressing CCNE1. CCNE1 expression levels can also be affected by
alterations in transcription or CCNE1 protein stability irrespective of copy number
25 variation. The CCNE1 overexpression is for instance measured by identifying the
expression level of the gene product in a tumor cell or tissue (e.g., CCNE1 mRNA
transcript count or CCNE1 protein level) and comparing the same with the
expression level of healthy (non-cycling) cell or tissue, or tumor tissue not known
for CCNE1 overexpression. For example, immunohistochemical (IHC) detection
30 and intensity scoring of tumor samples with at least 25% of tumor cells displaying
a moderate (intensity score of 2 or more) to strong staining (intensity score of 3 or
more) of CCNE1 can be considered as CCNE1 overexpressing tumors (equivalent
to an H-score ≥ 50). Methods for reproducible semi-quantitative protein detection in

tissue by IHC and pathologist-based scoring are described, for example, in Meyerholz and Beck, 2018, Principles and approaches for reproducible scoring of tissue stains in research, Laboratory Investigation, Volume 98, Issue 7, Pages 844-855, ISSN 0023-6837, <https://doi.org/10.1038/s41374-018-0057-0>
5 (<https://www.sciencedirect.com/science/article/pii/S0023683722010194>).

The term “WRN” as used herein refers to the gene encoding for the Werner syndrome ATP-dependent helicase, also referred to as DNA helicase, RecQ-like type 3. “WRN gene promoter” refers to the Werner syndrome gene promoter. WRN
10 is a member of the RecQ Helicase family. Helicase enzymes generally unwind and separate double-stranded DNA. The term “WRN-deficient” cancer or “WRN deficiency” as used herein means that the WRN gene in the cancer presents alterations such as promoter hypermethylation or mutations resulting in a dysfunctional protein and/or decrease or loss of protein expression. Promoter
15 hypermethylation can cause reduced protein expression of WRN. Cells expressing limited amounts of WRN protein have elevated mutation frequencies compared with wildtype cells. Mutations in the WRN gene lead to chromosomal instability. Gene expression (or decrease or loss thereof) may be detected by known methods, including for example mass spectrometry proteomics,
20 immunohistochemistry or western blot for protein levels and/or by measuring mRNA expression level using whole transcriptome sequencing or microarray technology. Mutations may for example be detected by Next Generation Sequencing (NGS).

25 The term “ATRX” as used herein refers to the alpha-thalassemia/mental retardation syndrome X-linked (ATRX) gene. The term “ATRX-deficient” or “ATRX deficiency” as used herein means that the ATRX gene in the cancer presents alterations such as nonsense or frameshift mutations resulting in a truncated protein and/or decrease or loss of protein expression (often consequent on gene
30 alteration). Such gene alterations may be detected by known methods, including for example whole exome sequencing. Gene expression (or decrease or loss thereof) may be detected by known methods, including for example mass spectrometry proteomics, immunohistochemistry, western blot, for protein levels

and/or by measuring mRNA expression level using whole transcriptome sequencing or microarray technology.

The term "FBXW7" is used hereinto refer to F-box/WD Repeat-Containing Protein
5 7 gene, transcript, or protein. An FBXW7-deficient gene has one or more alterations such as an inactivating mutation, a deletion or a promoter hypermethylation and thus fails to produce a functional FBXW7 protein or produces reduced quantities of FBXW7 protein in a cell. Mutations may for example be assessed by Next Generation Sequencing (NGS) and reduced
10 expression may be assessed by whole transcriptome sequencing, qPCR, western blot, mass spectrometry or IHC techniques.

The term "PPP2R1A" as used herein, refers to Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform, which is an enzyme
15 that is encoded by the PPP2R1A gene. This gene encodes a constant regulatory subunit of protein phosphatase 2. Protein phosphatase 2 is one of the four major Ser/Thr phosphatases and it is implicated in the control of cell growth and division. A PPP2R1A-mutated gene, sometimes referred to herein as an PPP2R1A gene having an inactivating mutation, is a gene, which fails to produce a functional
20 PPP2R1A protein or produces reduced quantities of PPP2R1A protein in a cell. Mutations may for example be assessed by Next Generation Sequencing (NGS) and reduced expression may be assessed by whole transcriptome sequencing, qPCR, western blot, mass spectrometry or IHC techniques.

25 The term "Histone H3K36 trimethylation" (H3K36me3) as used herein refers to a post-translational modification to the DNA packaging protein Histone H3. It indicates the trimethylation of the lysine residue at amino acid position 36 within the histone H3 protein. H3K36me3 is required for homologous recombinational repair of DNA damage such as double-strand breaks and facilitates transcriptional
30 activity.

The terms "reduced H3K36me3", "H3K36me3 reduction", "reduced level of histone H3K36 trimethylation", "reduced level of H3K36me3", "reduced degree of histone

H3K36 trimethylation”, “reduced degree of H3K36me3” and “low H3K36me3 levels” are used interchangeably herein, to refer to tumor cells having reduced levels or degrees of H3K36me3 compared to corresponding healthy cells such as tumor stromal cells. H3K36me3 reduction results in an alteration of the chromatin structure, affecting (reducing) transcriptional activity and the DNA damage response. A reduced H3K36me3 level is for instance measured using antibodies directed specifically against trimethylated lysine 36 of Histone H3, either by Western Blot, Immunohistochemistry or Immunofluorescence, in tumor cells and comparing that level to the level in corresponding healthy cells or tissue, such as tumor stromal cells, used as an internal control for normal H3K36me3 levels.

The terms “loss of H3K36me3” and “H3K36me3 loss” are used interchangeably herein to refer to tumor cells that exhibit no or substantially no H3K36me3. They include complete loss of H3K36me3. The H3K36me3 loss is for instance measured using antibodies directed specifically against trimethylated lysine 36 of Histone H3, either by Western Blot, Immunohistochemistry or Immunofluorescence, in tumor cells, and using corresponding healthy cells or tissue, such as tumor stromal cells, used as an internal control for normal H3K36me3 levels.

The term “Trop-2” or “TROP2” as used herein refers to the Trophoblast cell surface antigen 2, a type I transmembrane glycoprotein involved in Ca^{2+} signalling. It is encoded by the tumor-associated calcium signal transducer 2 (TACSTD2) gene. Overexpressed in a variety of human cancers, it has been identified as a potential therapeutic target due to its role in promoting tumor growth and progression. Trop-2 protein is found mainly on the surface of epithelial cells, where it can interact with other cells or extracellular matrix components, contributing to the invasive and metastatic characteristics of cancer cells.

Administration at “approximately the same time” refers to administration at a time that is the same as the time of administration of the reference day or a time that deviates from the time of administration of the reference date by no more than about one hour.

A "treatment cycle" of e.g. 21 days, 28 days, 6 weeks refers to a time period of e.g. 21 or 28 consecutive days, or 6 consecutive weeks, during which a drug of interest is administered at one or more days of the treatment cycle. As in the present invention a combination of at least two drugs of interest is administered, it is preferred to coordinate administration of the drugs such that the treatment cycles for the two drugs start on the same day and/or that the treatment cycles have the same duration. However, it is also conceivable to administer one drug according to a first treatment cycle, and the other drug according to a second treatment cycle, wherein the two treatment cycles may differ from each other in terms of duration and/or starting date.

As used herein, the expression "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic or organic acids. For example, acceptable salts derived from acids such as quaternary salt, acetate, carbonate, carbamate, sulfonate, strong inorganic acids and the like. In general, pharmaceutically acceptable salts may be used for modifying the solubility or hydrolysis characteristics of a compound, or in sustained release formulations. It will be understood that, as used herein, references to the WEE1 inhibitor or the topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor are meant to also include the pharmaceutically acceptable salts unless stated otherwise.

As used herein, 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.

"Combination", as used herein, refers to the presence of the combination partners, i.e. at least a WEE1 inhibitor and at least a drug selected from topoisomerase 1 inhibitors and ADCs comprising a topoisomerase 1 inhibitor. The combination partners may be provided in the same pharmaceutical composition, or they may be provided separately, for instance in two separate pharmaceutical compositions. Likewise, any references to administration "in combination" are to be understood

as administration of the combination partners to the same subject or patient such that the combination partners may be administered together or separately from each other. If they are administered separately from each other, administration includes simultaneous (concurrent) and consecutive administration in any order.

- 5 For instance, the WEE1 inhibitor and topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor may be administered in combination by administering the WEE1 inhibitor first and the topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor later, or vice versa.
- 10 As used herein, terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt or reverse progression or severity of a diagnosed pathologic condition, disorder or disease. Thus, those in need of treatment include those already diagnosed with or suspected of having the disorder. In certain
- 15 aspects, a subject is successfully "treated" for cancer according to the methods of the present invention if the subject or patient shows one or more of the following: a reduction in the number of or complete absence of cancer cells; a reduction in the tumor size or burden; inhibition of or an absence of cancer cell infiltration into peripheral organs; inhibition of or an absence of tumor metastasis; inhibition of or
- 20 an absence of tumor growth; relief of one or more symptoms associated with the specific cancer; reduced morbidity and mortality; improvement in quality of life; reduction in tumorigenicity, tumorigenic frequency, or tumorigenic capacity, of a tumor; reduction in the number or frequency of cancer stem cells in a tumor; differentiation of tumorigenic cells to a non-tumorigenic state; as well as increased
- 25 chances to have a complete response (CR), a partial response (PR), increased chances to have the disease under control (e.g. CR, PR, stable disease SD), to live longer without progression, and without disease, to live longer, decreased chances to have a progressive disease (PD) and to increase the time until progression. Collectively for groups or populations of patients, successful
- 30 treatment may result in endpoints such as increased Overall Response Rate (ORR), Best Overall Response (BOR), Duration of Response (DOR), Disease Control Rate (DCR), progression-free survival (PFS), overall survival (OS), time to progression (TTP) or any combination thereof.

As used herein when referring to cancer or to a subject or patient suffering therefrom, the terms "relapse", "to relapse", "recurrence", "to recur" mean a worsening of the disease and/or of the signs and symptoms of the disease after a
5 period of improvement, stabilization or disease absence.

As used herein when referring to cancer or to a subject or patient suffering therefrom, the terms "progression" or "to progress" means when the cancer becomes worse, either due to existing lesions that are growing and/or due to
10 appearance of new lesions.

As used herein, the term "WEE1 inhibitor treatment day" refers to a day on which the WEE1 inhibitor is administered according to the present invention.

15 As used herein, the term "topoisomerase 1 inhibitor treatment day" refers to a day on which the topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor is administered according to the present invention.

As used herein, the term "WEE1-topoisomerase 1 inhibitor combination treatment
20 day" or "combination treatment day" refers to a day on which the WEE1 inhibitor and the topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor are administered according to the present invention.

As used herein, the term "therapeutically effective amount" refers to an amount of
25 a drug effective to "treat" cancer in a subject or patient. In some aspects, the term "therapeutically effective amount" of a given drug when used in monotherapy, such as a "WEE1 therapeutically effective amount" or a "topoisomerase 1 inhibitor therapeutically effective amount", or a "combination therapeutically effective amount", refers to an amount of a drug or combination of drugs effective to "treat"
30 a cancer in a subject or patient, whilst keeping an acceptable safety profile. Said "combination therapeutically effective amount" thus characterizes any combination of any amount of WEE1 inhibitor with any amount of topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor that permits to "treat" a

cancer in a subject or patient, whilst keeping an acceptable safety profile. The "WEE1 therapeutically effective amount" when administered as monotherapy may be different from the amount of WEE1 inhibitor that is contained in the "combination therapeutically effective amount". The therapeutically effective amount of the drug or combination can reduce the number of cancer cells; reduce the tumor size or burden; inhibit (i.e., slow to some extent and in a certain aspect, stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and in a certain aspect, stop) tumor metastasis; inhibit, to some extent, tumor growth; relieve to some extent one or more of the symptoms associated with the cancer; and/or result in a favorable response such as increased Overall Response Rate (ORR), Best Overall Response (BOR), Duration of Response (DOR), Disease Control Rate (DCR), progression-free survival (PFS), overall survival (OS), complete response (CR) rate, partial response (PR) rate, or, in some cases, stable disease (SD) rate, a decrease in progressive disease (PD), an increased time to tumor progression (TTP) or any combination thereof. See the definition herein of "treating".

As used herein, "Overall Survival" (OS) in a clinical trial refers to the time from patient enrollment, first treatment administration or randomization to death from any cause or censored at the date last known alive. Improvement in OS includes a prolongation in life expectancy as compared to naive or untreated individuals or patients. Overall survival refers to the situation wherein a patient remains alive for a defined period of time, such as one year, five years, etc., e.g., from the time of randomization or first treatment.

As used herein, "RECIST v1.1" or "RECIST 1.1 criteria" refers to the "New response evaluation criteria in solid tumors, Revised RECIST guideline (version 1.1)" set out in Eisenhauer E.A. *et al.*, European Journal of Cancer 45 (2009) 228 – 247. In some embodiments, the RECIST guideline may evolve in the future and (a) new version(s) may be released and considered.

As used herein, the term "pharmaceutical formulation" or "pharmaceutical composition" refers to a preparation which is in such form as to permit the

biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

- 5 As used herein, the expression "oral dosage form" refers to any form of a pharmaceutical composition that is suitable for oral administration.

It is to be understood that any reference to a WEE1 inhibitor or a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor also encompasses the
10 pharmaceutically acceptable salt thereof, even if not explicitly mentioned as such.

Information introduced in the present disclosure by the wording „in some aspects“, „in specific aspects“, or the like, is to be understood such that it can be freely combined with any other information provided elsewhere in the present disclosure,
15 irrespective whether this is also introduced by the wording „in some aspects“, „in specific aspects“, or any other wording. An exception to this general rule applies however for those instances, where the information to be combined is no consistent or even contradictory or mutually exclusive, so that the resulting combined information would be inconsistent, unclear and/or not technically
20 meaningful.

COMBINATION

The present invention relates to a combination of a WEE1 inhibitor and a
25 topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor.

The present invention further relates to a combination of a WEE1 inhibitor and a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor for use as a medicament. The present invention also relates to a method of using a
30 combination of a WEE1 inhibitor and a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor as a medicament. The use or method can comprise administering a therapeutically effective amount of the WEE1 inhibitor, a therapeutically effective amount of the topoisomerase 1 inhibitor/ADC comprising

a topoisomerase 1 inhibitor, or a combination therapeutically effective amount of the WEE1 inhibitor and the topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor.

- 5 The present invention relates to a combination of a WEE1 inhibitor or a pharmaceutically acceptable salt thereof, and a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor or a pharmaceutically acceptable salt thereof for use in, or for use in the preparation of a medicament for, treating cancer in a patient in need thereof.

10

Any disclosure relating to a WEE1 inhibitor herein is understood to be combined with any disclosure relating to a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor herein.

- 15 In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and the topoisomerase 1

- 20 inhibitor or topoisomerase inhibitor moiety in the ADC is

- camptothecin or a camptothecin derivative, preferably selected from topotecan, irinotecan, SN38, govitecan, deruxtecan (Dxd), exatecan, belotecan, silatecan, gimatecan, namitecan (ST1968), or a pharmaceutically acceptable salt thereof, or
- 25 - an indenisoquinoline, preferably selected from indenoisoquinoline NSC 314622, indotecan (LMP-400), indimitecan (LMP-776), or a pharmaceutically acceptable salt thereof, or
- a phenanthridine, an indolocarbazole, a β -carboline hybrid, a pyrazole-linked benzothiazole- β -naphthol derivative, a 4 β -[4'-(1-(aryl)ureido)benzamide]podophyllotoxin congener, a benzimidazole
- 30 congener or a pharmaceutically acceptable salt thereof.

In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and the topoisomerase 1 inhibitor is irinotecan, topotecan, belotecan, gimatecan, silatecan or a pharmaceutically acceptable salt thereof.

5

In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and the topoisomerase 1 inhibitor used as an ADC payload is SN38, govitecan, deruxtecan (Dxd), exatecan, sesutecan, belotecan, tirumotecan, samrofecan, or a pharmaceutically acceptable salt thereof.

10

In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and the ADC comprising a topoisomerase 1 inhibitor is an ADC targeting TROP-2, an ADC targeting HER-2, an ADC targeting HER-3, an ADC targeting B7-H3, an ADC targeting B7-H4, an ADC targeting folate receptor alpha (FR α), an ADC targeting Cadherin-6 (CDH6), an ADC targeting carcinoembryonic antigen-related cell adhesion molecule (CEACAM), particularly CEACAM5, an ADC targeting cMET receptor tyrosine kinase, an ADC targeting tumor-associated mucin-1 (TA-MUC1), an ADC targeting seizure related 6 homolog (SEZ-6), an ADC targeting nectin-4, an ADC targeting 5T4 oncofoetal glycoprotein (5T4) or an ADC targeting NaPi2b (a cell surface sodium-dependent inorganic phosphate (Pi) transporter).

15

20

In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and the ADC comprising a topoisomerase 1 inhibitor is an ADC targeting TROP-2. Examples of such TROP2-targeting ADCs are provided herein. In specific aspects the TROP2-targeting ADC is selected from sacituzumab govitecan or datopotamab deruxtecan.

25

30

In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and the ADC comprising a topoisomerase 1 inhibitor is sacituzumab govitecan, datopotamab deruxtecan,

sacituzumab tirumotecan, trastuzumab deruxtecan, patritumab deruxtecan, ifinatumab deruxtecan, puxitatug samrotecan, AZD-5335, rinatabart sesutecan, labetuzumab govitecan, PF-08046050, M9140, raludotatug deruxtecan, ABBV-400, DS-3939, ABBV-706, BAT-8007, ACR-246, ZW-220, or a pharmaceutically acceptable salt thereof.

USES

The present invention relates to a WEE1 inhibitor for use in treating cancer in a patient in need thereof, wherein the WEE1 inhibitor is administered in combination with a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor.

The present invention relates to a topoisomerase 1 inhibitor or ADC comprising a topoisomerase 1 inhibitor for use in treating cancer in a patient in need thereof, wherein the topoisomerase 1 inhibitor or ADC comprising a topoisomerase 1 inhibitor is administered in combination with a WEE1 inhibitor.

It is to be understood that any reference to a compound or combination for use herein also encompasses the use of the respective compound or combination. For instance, any reference to a compound or combination for use in treating cancer is to be understood as also encompassing a use of the compound or combination for treating cancer, or method of treating cancer with the compound or combination. Hence, unless the context dictates otherwise, all disclosures provided herein with respect to the compounds or combinations for use according to the present invention equally apply to the uses of the present invention.

METHODS

The present invention also relates to a method for treatment of cancer in a patient in need thereof using a combination, a WEE1 inhibitor or a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor, as well as a method involving the combination treatments described herein. Any disclosure of a use of a combination, use of a WEE1 inhibitor, or use of a topoisomerase 1 inhibitor/ADC

comprising a topoisomerase 1 inhibitor in the treatment of cancer may be understood as relating to the method for treatment of cancer of the present invention, and vice versa.

- 5 It is to be understood that any reference to a compound or combination for use herein also encompasses the method of using the compound. For instance, any reference to a use of a compound or combination for treating cancer is to be understood as also encompassing a method of using the compound or combination for treating cancer, or method of treating cancer with the compound
10 or combination. Hence, unless the context dictates otherwise, all disclosures provided herein with respect to the compounds or combinations for use according to the present invention equally apply to the methods of the present invention.

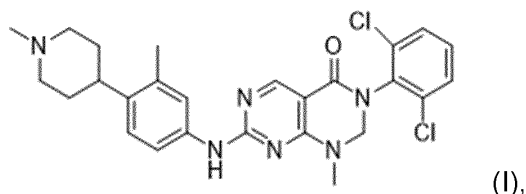
In some aspects of the uses or methods according to the present invention,
15 previous treatment in any setting or for any disease excludes treatment with a topoisomerase 1 inhibitor or an ADC comprising a topoisomerase 1 inhibitor. In more specific aspects, previous treatment in any setting or for any disease excludes treatment with a TROP2-directed ADC.

20 In some aspects of the uses or methods according to the present invention, previous treatment in any setting or for any disease excludes treatment with a WEE1 inhibitor.

SPECIFIC COMPOUNDS

25

In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I)

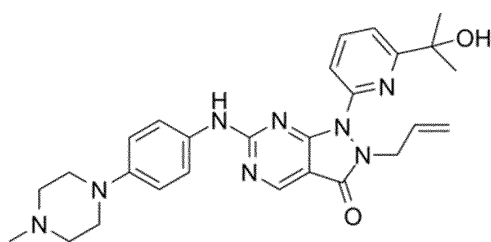


or a pharmaceutically acceptable salt thereof.

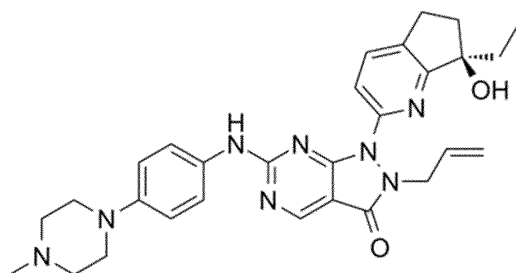
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The compound of formula (I) is a selective WEE1 inhibitor.

In some aspects, the WEE1 inhibitor is any compound described in the patent applications WO2018090939, WO2022155202, WO2022256680, 5 WO2013126656, WO2020192581 and WO2008153207, each of which is fully incorporated herein by reference. Specifically, the WEE1 inhibitor may be a compound of one of the following formulas, or a pharmaceutically acceptable salt thereof:

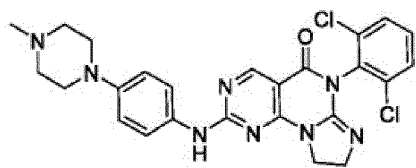


, also known as AZD-1775 (adavosertib);



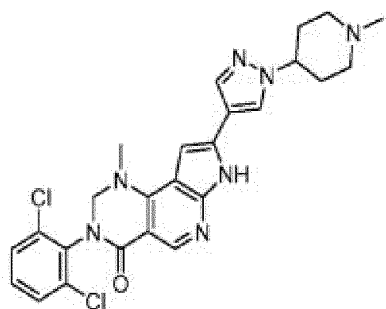
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, also known as Zn-C3 (azenosertib);

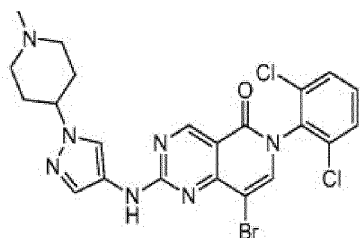


, also known as IMP7068 (as described in

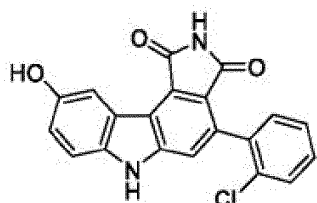
WO2018090939);



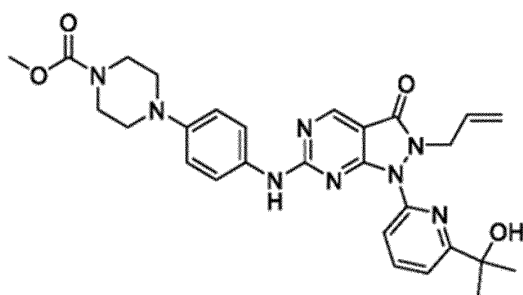
, also known as STC-8123 (as described in WO2022155202);



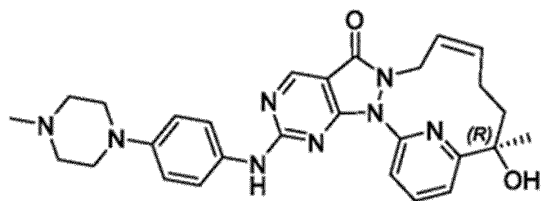
5 , also known as ATRN-W1051 (as described in WO2022256680);



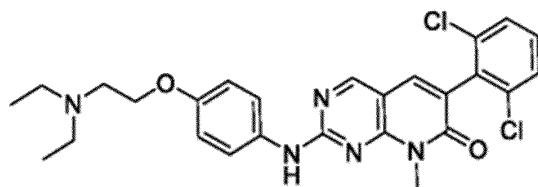
, also known as PD0407824;



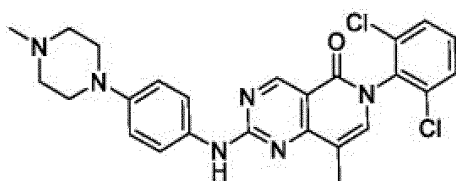
, also known as CJM061;



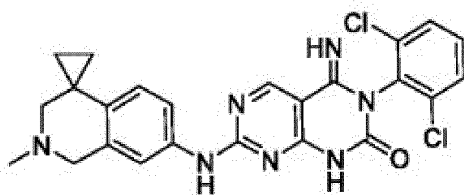
, also known as SC0191;



, also known as PD0166285;



(as described in WO2013126656), or



5

(as described in WO2008153207).

In some aspects, the WEE1 inhibitor is the compound SY-4835, or any compound described in patent application WO2020192581, especially the compounds disclosed in claims 3 and 6 of this document and the compound of Example 59 of
 10 CN111718348 identified as SY-4835 by Q. Ye et al., Bioorganic & Medicinal Chemistry, 2023, 87, 117312, <https://doi.org/10.1016/j.bmc.2023.117312>.

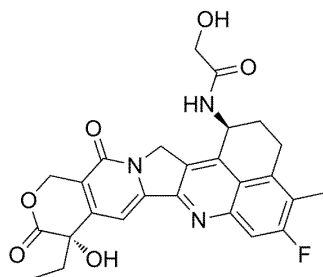
The topoisomerase 1 inhibitor or ADC comprising a topoisomerase 1 inhibitor may be any compound described in the literature as having inhibitory action against
 15 topoisomerase 1, including compounds described as having inhibitory action against topoisomerases 1 and 2 although compounds that are selective for topoisomerase 1 are preferred. This literature includes for instance K.E. Hevener et al., Acta Pharmaceutica Sinica B, 2018, 6, 844-861, <https://doi.org/10.1016/j.apsb.2018.07.008>; P.A. Yakkala et al., Pharmaceuticals
 20 2023, 16, 1456. <https://doi.org/10.3390/ph16101456>; K. Buzun et al., Journal of Enzyme Inhibition and Medicinal Chemistry, 2020, 35, 1781-1799,

<https://doi.org/10.1080/14756366.2020.1821676>; X. Liang, et al., Eur J Med Chem. 2019, 171, 129-168, doi: 10.1016/j.ejmech.2019.03.034; T. Agatsuma, Yakugaku Zasshi 2017, 137, 545-550, doi: 10.1248/yakushi.16-00255-4; T. Nakada et al., Chem Pharm Bull (Tokyo), 2019, 67, 173-185, doi: 10.1248/cpb.c18-00744; A. Bardia et al., Future Oncol. 2023, doi: 10.2217/fon-2023-0188; T. Grinda et al., Curr Treat Options Oncol. 2023, 24, 442-465, doi: 10.1007/s11864-023-01072-5; A. Dri et al., Cancer Treat Rev. 2024, 123, 102672, doi: 10.1016/j.ctrv.2023.102672; documents cited elsewhere in the present application and literature cited in any of these documents, each of which is fully incorporated herein by reference.

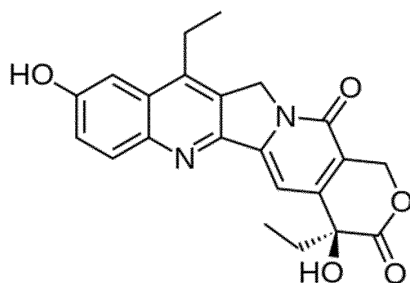
In further aspects, the topoisomerase 1 inhibitor or ADC comprising a topoisomerase 1 inhibitor may be any compound or conjugate described as having topoisomerase 1 inhibitor activity in the patent applications WO 2023/235716 A2, WO 2023/228095 A1, WO 2023/201268 A1, WO 2023/201267 A1, WO 2022/270524 A1, EP 4 086 284 A1, WO 2022/232808 A1, CN 114569739 A, EP 4 183 421 A1, CN 111454264 A, CN 107986951 A, US 10894044 B2, US 11090306 B2, US 10653689B2, JP 2016 196484 A, US 2014/378404A1, CN 102526731A, WO 2011/064152A1, KR 101121871B1, EP 2 391 364 A1, US 2010/166843A1, US 2005/187172A1, and documents cited therein, each of which is fully incorporated herein by reference.

In some aspects of the present invention, the topoisomerase 1 inhibitor or topoisomerase 1 inhibitor moiety in ADC is a compound selected from camptothecin, camptothecin derivatives, and pharmaceutically acceptable salts thereof.

The camptothecin derivatives are preferably selected from topotecan, irinotecan, SN38, govitecan, deruxtecan (Dxd), exatecan, belotecan, silatecan, gimatecan, namitecan (ST1968), and pharmaceutically acceptable salts thereof. The chemical structures of most of these drugs are shown for instance in P.A. Yakkala et al., Pharmaceuticals 2023, 16, 1456. <https://doi.org/10.3390/ph16101456>. The structure of deruxtecan (DxD) is as follows:



The structure of SN38 is as follows:



5

When used in an ADC, the topoisomerase inhibitor SN38 leads to an international non-proprietary name (INN) comprising "govitecan". This is the case for example in sacituzumab govitecan.

- 10 In some aspects of the present invention, the topoisomerase 1 inhibitor or topoisomerase 1 inhibitor moiety in ADC is a compound selected from indenisoquinolines and pharmaceutically acceptable salts thereof.

- The indenisoquinolines are preferably selected from indenoisoquinoline NSC
 15 314622, indotecan (LMP-400) and indimitecan (LMP-776) and pharmaceutically acceptable salts thereof. The structures of these compounds are also shown for instance in Yakkala et al.

- In some aspects of the present invention, the topoisomerase 1 inhibitor or
 20 topoisomerase 1 inhibitor moiety in ADC is a compound selected from phenanthridines and pharmaceutically acceptable salts thereof.

Phenanthridines capable of inhibiting topoisomerase 1 are described for instance in B. Ivanova and M. Spiteller, *Medicinal Chemistry Research*, 22, 5204-5217, 2013. <https://doi.org/10.1007/s00044-013-0515-6>, in D. Makhey et al., *Bioorganic and Medicinal Chemistry*, 11, 1809-1820, 2003, and in D. Li et al., *Bioorganic and Medicinal Chemistry*, 11, 3795-3805, 2003.

In some aspects of the present invention, the topoisomerase 1 inhibitor or topoisomerase 1 inhibitor moiety in ADC is selected from indolocarbazoles and pharmaceutically acceptable salts thereof. An example of an indolocarbazole is NB-506, described in Ren Jinsong, Bailly Christian and Chaires Jonathan B.(2000), NB-506, an indolocarbazole topoisomerase I inhibitor, binds preferentially to triplex DNA, *FEBS Letters*, 470, doi: 10.1016/S0014-5793(00)01335-1.

In some aspects of the present invention, the topoisomerase 1 inhibitor or topoisomerase 1 inhibitor moiety in ADC is a compound selected from β -carboline hybrids and pharmaceutically acceptable salts thereof.

The β -carboline hybrids are preferably selected from β -carboline chalcone hybrids, β -carboline pyrazole hybrids, β -carboline-bisindole analogs, as described in section 4.2 of Yakkala et al.

In some aspects of the present invention, the topoisomerase 1 inhibitor or topoisomerase 1 inhibitor moiety in ADC is a compound selected from pyrazole-linked benzothiazole- β -naphthol derivatives and pharmaceutically acceptable salts thereof.

The pyrazole-linked benzothiazole- β -naphthol derivatives are preferably the pyrazole-linked benzothiazole- β -naphthol derivatives described in section 4.4 of Yakkala et al.

In some aspects of the present invention, the topoisomerase 1 inhibitor or topoisomerase 1 inhibitor moiety in ADC is a compound selected from 4 β -[4'-(1-(aryl)ureido)benzamide]podophyllotoxin congeners and pharmaceutically acceptable salts thereof.

5

The 4 β -[4'-(1-(aryl)ureido)benzamide]podophyllotoxin congeners are preferably those described in section 4.5 of Yakkala et al.

In some aspects of the present invention, the topoisomerase 1 inhibitor or
10 topoisomerase 1 inhibitor moiety in ADC is a compound selected from benzimidazoles congeners and pharmaceutically acceptable salts thereof.

The benzimidazoles congeners are preferably bibenzimidazole and terbenzimidazole compounds as described in section 4.6 of Yakkala et al.

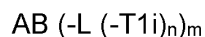
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In some aspects, the topoisomerase 1 inhibitor used in the combinations according to the present invention is the payload of an antibody drug conjugate (ADC). That is, in some aspects, an ADC comprising a topoisomerase 1 inhibitor is used in the combinations, therapeutic uses and methods of the present invention.

20

The ADC comprising a topoisomerase 1 inhibitor is a conjugate comprising an antibody moiety, which is covalently bonded to at least one linker, wherein the linker is covalently bonded to at least one topoisomerase 1 inhibitor moiety. This can be characterized by the following general formula:

25



wherein AB represents an antibody moiety as described herein, L represents a linker as described herein, T1i represents a topoisomerase 1 inhibitor moiety as
30 described herein, n and m are each independently selected from a range of from 1 to 12.

The antibody moiety is derived from an antibody, wherein the antibody can be any antibody used in or developed for cancer therapy, and especially an antibody targeting TROP-2, an antibody targeting HER-2, an antibody targeting HER-3, an antibody targeting B7-H3, an antibody targeting B7-H4, an antibody targeting
5 folate receptor alpha (FRalpha, FR α), an antibody targeting Cadherin-6 (CDH6), an antibody targeting carcinoembryonic antigen-related cell adhesion molecule (CEACAM), particularly CEACAM5, an antibody targeting cMET receptor tyrosine kinase, an antibody targeting tumor-associated mucin-1 (TA-MUC1), an antibody targeting seizure related 6 homolog (SEZ-6), an antibody targeting nectin-4, an
10 antibody targeting 5T4 oncofoetal glycoprotein (5T4), an antibody targeting NaPi2b (a cell surface sodium-dependent inorganic phosphate (Pi) transporter) or any other antibody contained in the ADCs described herein. Preferred antibodies are sacituzumab, datopotamab, trastuzumab, patritumab, ifinatamab, puxitatug, rinatabart, labetuzumab, raludotatug or gatipotuzumab.

15

The linker is not particularly restricted and has the function of covalently connecting antibody and topoisomerase 1 inhibitor. It may be stable or cleavable under physiologic conditions. In some aspects, the linker is cleaved under the conditions prevailing in a cancer cell. Typically, the linker contains at least one
20 continuous chain of atoms selected from C, N, O, P and S. Said continuous chain may contain any number of such atoms ranging from 2 to 1000, preferably 4 to 500 such as 8 to 400. In case of the linker containing cyclic elements, the above ranges refer to the shortest chain linking antibody and topoisomerase 1 inhibitor. The linker may for instance contain one or more amino acid or peptide units, one
25 or more polyethylene glycol units, linear, branched or cyclic other structural elements and any combination thereof. Cleavage may for instance be induced by changes in pH or presence of hydrolytic enzymes such as cathepsin B. There are various classes of linkers, including but not limited to disulfide-based linkers, acid-labile hydrazone or acetal-based linkers, peptide-based linkers, thioether-based
30 noncleavable linkers, enzyme-cleavable dipeptide-based VC (valine-citrulline) or PABC (para-amino benzyloxycarbonyl) linker systems. Suitable linker molecules include, for example, N-succinimidyl 3-(2-pyridyldithio) propionate (SPDP) (see, e.g., Carlsson et al., Biochem. J., 173: 723-737 (1978)), N-succinimidyl 4-(2-

- pyridyldithio)butanoate (SPDB) (see, e.g., U.S. Patent No. 4,563,304), N-succinimidyl 4-(2-pyridyldithio)2-sulfobutanoate (sulfo-SPDB) (see US Publication No. 20090274713), N-succinimidyl 4-(2-pyridyldithio) pentanoate (SPP) (see, e.g., CAS Registry number 341498-08-6), 2-iminothiolane, acetylsuccinic anhydride, or
- 5 linkers described in Zheng Su, Dian Xiao, Fei Xie, Lianqi Liu, Yanming Wang, Shiyong Fan, Xinbo Zhou, Song Li, Antibody–drug conjugates: Recent advances in linker chemistry, *Acta Pharmaceutica Sinica B*, Volume 11, Issue 12, 2021, Pages 3889-3907, <https://doi.org/10.1016/j.apsb.2021.03.042>.
- 10 The topoisomerase 1 inhibitor moiety contained in the ADC can be any moiety derived from any topoisomerase 1 inhibitor described herein. In some aspects, the topoisomerase 1 inhibitor moiety is derived from SN38, govitecan, deruxtecan, exatecan, sesutecan, belotecan, tirumotecan or samrotecan. ... For the avoidance of doubt, the present invention uses the expressions “ADC comprising a
- 15 topoisomerase 1 inhibitor moiety”, “ADC comprising a topoisomerase 1 inhibitor”, “topoisomerase 1 inhibitor being the payload of an ADC” and the like as having the same meaning. In each of these cases, a topoisomerase 1 inhibiting moiety is bonded via a linker to an antibody to form an ADC. If the linker is not cleavable, the topoisomerase 1 inhibitor payload must be able to exercise its inhibiting
- 20 function in the bonded state. By contrast, in case of a cleavable linker, it is sufficient that the molecule released upon cleavage exhibits topoisomerase 1 inhibiting function. Optionally, such a payload may also show inhibitory function before being cleaved.
- 25 In the context of the present application, the expression of a moiety being “derived from” a compound is meant to characterize a moiety that shows all structural characteristics of the underlying compound with the only exception being the structural modification required to form a covalent bond, e.g., a covalent bond to the linker of an ADC. This is typically an ester bond, thioester bond, disulfide bond,
- 30 amide bond or the like that is formed by reaction of a carboxyl group, hydroxyl group, thiol group or amino group with a suitable reaction partner. If covalent bond formation is accomplished by means of a cycloaddition reaction or the like, the

“derived from” expression is intended to permit also formation of such a new cyclic structure involving simultaneous formation of two covalent bonds.

For example, the topoisomerase 1 inhibitor-containing antibody drug conjugate
5 may be one of the following ADCs:

Topoisomerase 1 inhibitor-containing ADCs with antibodies targeting human trophoblast cell surface antigen 2 (TROP-2):

- 10 - Sacituzumab govitecan (anti-TROP-2 antibody conjugated with SN-38 as described in D.M. Goldenberg and R.M. Sharkey, mAbs, 11:6, 987-995, DOI: 10.1080/19420862.2019.1632115, also known as sacituzumab govitecan-hziy, IMMU-132, GS-0132, Trodelvy),
- Datopotamab deruxtecan (anti-TROP2-Ab linked to DXd with development code DS-1062 or DS-1062a as described in A. Spira et al. in Journal of Thoracic
15 Oncology, 16, S106-S107, 2021. <https://doi.org/10.1016/j.jtho.2021.01.280>; and D. Okajima et al., J Clin Oncol (Suppl). 2018;36 (abstract):e24206),
- Sacituzumab tirumotecan (SKB-264; MK-2870), an ADC comprising a third-generation antibody targeting TROP-2, conjugated to a potent topoisomerase I inhibitor derived from belotecan (KL610023), integrated via a sulfonyl pyrimidine-
20 CL2A-carbonate linker, under development by Klus Pharma for the treatment of solid tumours (Clinical trials: NCT04152499; NCT05351788, NCT06132958),
- BNT-325 (DB-1305), a Trop-2 targeting ADC with a novel topoisomerase I inhibitor P1021, under development by Duality Biologics using its DITAC platform technology for the treatment of solid tumours (Clinical trial: NCT05438329; The
25 Trop-2-targeting antibody drug conjugate DB-1305 has higher antitumor activity and a potentially better safety profile compared with DS1062, European Journal of Cancer 174S1 (2022) S3–S128, Abstract 253),
- ESG-401, a recombinant humanized anti-Trop2 Mab-SN38 conjugate, under development by Shanghai Escugen Biotech for the treatment of solid tumours.
30 (ClinicalTrial: NCT04892342),
- SHR-A1921, an antibody-drug conjugate with a TROP2-targeting antibody and a DNA topoisomerase I inhibitor payload, under development by Jiangsu Hengrui Pharmaceuticals for the treatment of solid tumours (Clinical trial: NCT05154604,

- China FDA, CTR20240254, Jie Wang, Lin Wu, Zhengbo Song, Xingya Li, Caigang Liu, Tianshu Liu, Yiwen Wu, Ze Zhang, Shuni Wang. A first-in-human (FIH) phase 1 study of SHR-A1921, a TROP-2 targeted antibody-drug conjugate (ADC), in patients with advanced solid tumors [abstract]. AACR 2023; Part 2 (Clinical Trials and Late-Breaking Research); Cancer Res 2023;83(8_Suppl):Abstract nr CT181.),
- 5 - BAT-8008, an antibody-drug conjugate (ADC) composed of a humanized TROP-2 antibody and a toxic small-molecule topoisomerase I inhibitor connected by a self-developed cleavable linker, under development by Bio-Thera Solutions for the treatment of solid tumours (Clinical trial: NCT05620017. Xingxing Mei, Weijia Tang, Xin Zhou, Xuekang Qi, Siqi Mai, Zhi Zhong, Shuoxu Li, Jianjun Fan, Jirong Gan, Binghua Tan, Yao Qi, Yanling Guo, Jin-Chen Yu, Shengfeng Li. BAT8008, a novel Trop-2 ADC with strong bystander effect, for the treatment of Trop-2 positive cancer [abstract]. In: Proceedings of the 2022 San Antonio Breast Cancer Symposium; 2022 Dec 6-10; San Antonio, TX. Philadelphia (PA): AACR; Cancer
- 10 Res 2023;83(5 Suppl):Abstract nr P4-01-32.),
- 15 - MHB-036C, an ADC under development by Shanghai Minghui Pharmaceutical for the treatment of solid tumours. It is composed of a humanized anti-TROP-2 monoclonal antibody conjugated to its proprietary DNA topoisomerase I inhibitor via a cleavable linker (Clinical trial: NCT05642949);
- 20 - BSI-04702, an ADC consisting of a TROP2-targeting antibody conjugated to a potent DNA topoisomerase I inhibitor, under development by Biosion in collaboration with OBI Pharma using its SynTracer platform for the treatment of solid tumours,
- HS-20105, an ADC formed by coupling humanized anti-Trop-2 monoclonal antibody of IgG1 subtype with cytotoxic payload (DNA topoisomerase I inhibitor),
- 25 under development by Jiangsu Hansoh Pharmaceutical for the treatment of advanced solid tumours (Clinical trial: NCT06144723).

- Topoisomerase 1 inhibitor-containing ADC with antibodies targeting human
- 30 epidermal growth factor receptor 2 (HER-2):
- Trastuzumab deruxtecan (anti-HER2-Ab conjugated with deruxtecan, also known as AZD 4552, DS-8201, Enhertu, as described in S. Vranić et al. in Bosn J Basic Med Sci. 21, 1-4, 2021),

- BNT-323 (DB-1303) is a HER2-targeting ADC with novel DNA topoisomerase I inhibitor P1003, under development by Duality Biologics using its DITAC platform technology for the treatment of breast cancer, endometrial cancer and solid tumours (Clinical trial: NCT05150691 in patients with advanced/unresectable, 5 recurrent, or metastatic HER2-expressing solid tumors),
- JSKN-003, a biparatopic HER2-targeting ADC, which comprises a topoisomerase I inhibitor linked to the N glycosylation site of the antibody KN026 via the glycosite-specific conjugation, under development by Alphamab Oncology by using its bispecific antibody conjugation (BADC) technology for the treatment of 10 solid tumours (Clinical trial: China FDA, CTR20232959, Antib Ther. 2023 Jul; 6(Suppl 1): tbad014.009. doi: 10.1093/abt/tbad014.009),
- Trastuzumab rezetecan (SHR-A1811), an anti-HER2 ADC with a Topoisomerase 1 inhibitor payload, under development by Jiangsu Hengrui Pharmaceuticals (previously known as Jiangsu Hengrui Medicine) for the treatment of solid tumours 15 (ClinicalTrials: NCT04446260, NCT04513223, NCT04818333, NCT05353361, NCT05896020; WHO INN List, List 127, 22 Jul 2022; AACR 2023, Cancer Res (2023) 83 (8_Supplement): LB031, <https://doi.org/10.1158/1538-7445.AM2023-LB031>),
- BAT-8010 is an ADC composed of a humanized HER2 antibody and a toxic 20 small-molecule topoisomerase I inhibitor connected by a self-developed cleavable linker, under development by Bio-Thera Solutions for the treatment of solid tumours (Clinical trial: NCT05848466, NIC thesaurus Code C188243),
- BL-M07D1, ADC consisting of trastuzumab, a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04, a derivative of the alkaloid 25 camptothecin), under development by SystImmune using the HIRE-ADC technology platform for the treatment of breast and gastric cancer (Weili Wan, Shuwen Zhao, Shi Zhuo, Yong Zhang, Lan Chen, Gangrui Li, Jahan Salar Khalili, Sa Xiao, Yongqi Yan, Xuejiao Shen, Yi Zhu. BL-M07D1, a novel HER2-targeting ADC, demonstrates potent anti-tumor efficacy in preclinical pharmacodynamic 30 models [abstract]. AACR 2023; Part 1 (Regular and Invited Abstracts); Cancer Res 2023;83(7_Suppl):Abstract nr 2643., Clinical trials: NCT05461768, NCT06031584, China FDA, CTR20233464, CTR20233640).

- TQB-2102, ADC comprised of a humanized antibody against (HER2), a enzyme-cleavable linker, and a topoisomerase I inhibitor payload, under development by Chia Tai Tianqing Pharmaceutical (subsidiary of Sino Biopharmaceutical) for the treatment of advanced malignant tumours (Clinical trial: NCT05735496, China FDA, CTR20233430),
- an anti-HER2 ADC composed of topoisomerase 1 (Topo1) inhibitor as payload, developed by Araris Biotech using its novel antibody-drug conjugate (ADC)-linker technology for the treatment of cancer (Isabella Attinger-Toller, Rachael Fay, Romain Bertrand, Philipp Probst, Ramona Stark, Roger Santimaria, Dragan Grabulovski, Bernd Schlereth, Philipp Rene Spycher. Inducing significant and efficient tumor growth inhibition vs trastuzumab deruxtecan with low drug-load topoisomerase 1 inhibitor ADC using novel peptide linkers for payload conjugation [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2023; Part 2 (Clinical Trials and Late-Breaking Research); 2023 Apr 14-19; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2023;83(8_Suppl):Abstract nr LB219).

Topoisomerase 1 inhibitor-containing ADC with antibodies targeting human epidermal growth factor receptor 3 (HER-3)

- Patritumab deruxtecan, or HER3-DXd, an ADC consisting of a fully human monoclonal antibody to human epidermal growth factor receptor 3 (HER3) attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker. (Yu HA, Goto Y, Hayashi H, Felip E, Chih-Hsin Yang J, Reck M, Yoh K, Lee SH, Paz-Ares L, Besse B, Bironzo P, Kim DW, Johnson ML, Wu YL, John T, Kao S, Kozuki T, Massarelli E, Patel J, Smit E, Reckamp KL, Dong Q, Shrestha P, Fan PD, Patel P, Sporchia A, Sternberg DW, Sellami D, Jänne PA. HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy. J Clin Oncol. 2023 Dec 10;41(35):5363-5375. doi: 10.1200/JCO.23.01476. Epub 2023 Sep 10.),
- BL-B01D1, a bispecific ADC which blocks EGFR and HER3 signals to cancer cells and inhibits topoisomerase 1 with its payload, under development by Biokin

Pharmaceutical using its HIRE-ADC platform for the treatment of solid tumours (ClinicalTrials: NCT05262491, NCT05393427, NCT05803018, NCT05924841, NCT05956587, NCT06008054, NCT06042894, NCT05990803),

5 - DB-1310, a HER3-targeting ADC composed of a novel humanized anti-Her3 immunoglobulin G1 (IgG1) monoclonal antibody covalently linked to a proprietary DNA topoisomerase 1 inhibitor payload via a maleimide tetrapeptide-based cleavable linker with a drug antibody ratio (DAR) of approximately eight, under development by Duality Biologics for the treatment of solid tumours (Cancer Res (2023) 83 (7_Supplement): 1884, <https://doi.org/10.1158/1538-7445.AM2023-1884>),

10 - YL-202 (BNT-326), an ADC composed of a human anti-HER3 antibody, protease-cleavable linker, and a novel topoisomerase I inhibitor, under development by Medilink Therapeutics (Suzhou) for the treatment of breast cancer and non-small cell lung cancer using its using its TMALIN (Tumour Microenvironment Activable Linker) technology (Clinical trials: NCT05653752, China FDA, CTR20233371),

15 - AMT-562, an anti-HER3 ADC comprising an Ab562 antibody and T800 (modified self-immolative PABC spacer) to conjugate exatecan, under development by Multitude Therapeutics for the treatment of colorectal carcinoma, gastrointestinal carcinoma and EGFR-resistant non-small cell cancer (Mol Cancer Ther, 5 Sep 2023, 22, 1013, <https://pubmed.ncbi.nlm.nih.gov/37302522/>; Clinical trial: NCT06199908),

20 - SHR-A2009, an ADC developed by Jiangsu Hengrui Pharmaceuticals, comprised of a fully humanized anti-HER3 IgG1 monoclonal antibody, an enzyme-cleavable linker, and a proprietary DNA topoisomerase I inhibitor for the treatment of advanced solid tumours (Clinical trial: NCT05114759, 658MO Phase I study of SHR-A2009, a HER3-targeted ADC, in advanced solid tumors, Q. Zhou et al. Annals of oncology Volume 34, Suppl 2, 2023, DOI:<https://doi.org/10.1016/j.annonc.2023.09.1844>).

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Topoisomerase 1 inhibitor-containing ADC with antibodies targeting B7-H3:

- Ifinatamab deruxtecan (MK-2400, DS-7300; DS-7300a), a humanized anti-B7-H3 monoclonal antibody conjugated to topoisomerase I inhibitor payload by a

- tetrapeptide-based linker, under development by Daiichi Sankyo utilizing DXd technology for the treatment of cancer (Clinical trial: NCT04145622, Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with advanced solid tumors: Updated clinical and biomarker results from a phase I/II study, Patel et al.
- 5 <https://doi.org/10.1016/j.annonc.2023.09.1876>),
- BNT-324 (DB-1311), an ADC comprised of a humanized B7-H3 antibody conjugated to a DNA topoisomerase I inhibitor P1021 via a cleavable linker (Li et al. AACR 2023. Preclinical development of a B7-H3-targeting ADC with a novel DNA topoisomerase I inhibitor for solid tumors, Clinical trial: NCT05914116),
 - 10 - HS-20093, a fully humanized IgG1 ADC that specifically binds to B7-H3 and has DAR4 topoisomerase 1 inhibitor payload, under development by Jiangsu Hansoh Pharmaceutical for the treatment of solid tumours (Clinical trials: NCT05276609, NCT05830123, NCT06001255, NCT06052423, NCT06112704 ; J Clin Oncol 41, 2023 (suppl 16; abstr 3017), https://doi.org/10.1200/JCO.2023.41.16_suppl.3017),
 - 15 - YL-201, an ADC comprised of an anti-B7-H3 human monoclonal antibody conjugated to a novel topoisomerase 1 inhibitor via a protease-cleavable linker, under development by Suzhou Medilink Therapeutics for the treatment of solid tumours using its using its TMALIN (Tumour Microenvironment Activable Linker) technology (Clinical trial: China FDA, CTR20240246, 26 Jan 2024, AACR 2023
 - 20 Abstract 6304: Preclinical development of a next generation antibody drug conjugate (ADC) targeting B7-H3 for treatment of solid tumors, Xu et al. Cancer Res (2023) 83 (7_Supplement): 6304, <https://doi.org/10.1158/1538-7445.AM2023-6304>),
 - BAT-8009, an ADC composed of a recombinant humanized anti-B7H3 antibody
 - 25 and a toxic small molecule topoisomerase I inhibitor, connected by a self-developed cleavable linker, under development by Bio-Thera Solutions for the treatment of solid tumours (Clinical trial: NCT05405621),
 - MHB-088C, an ADC under development by Shanghai Minghui Pharmaceutical for the treatment of advanced or metastatic solid tumours, composed of a
 - 30 humanized anti-B7-H3 monoclonal antibody conjugated to a proprietary DNA topoisomerase I inhibitor via a cleavable linker (Clinical trial: NCT05652855).

Topoisomerase 1 inhibitor-containing ADC with antibodies targeting B7-H4:

- Puxitatug samrotecan (AZD-8205), an ADC targeting B7-H4 conjugated to a topoisomerase I inhibitor payload, under development by AstraZeneca for the treatment of solid tumours (ClinicalTrial: NCT05123482; WHO INN List 90, Vol 37, No 3, 2023).

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Topoisomerase 1 inhibitor-containing ADC with antibodies targeting folate receptor alpha (FR α , FR α):

- AZD-5335, an FR α -targeting ADC comprising a topoisomerase I inhibitor payload, under development by AstraZeneca for the treatment of solid tumours (Clinical trial: NCT05797168, Marco Gymnopoulos, Tima Thomas, Diana Gasper, Judith Anderton, Ravinder Tammali, Ed Rosfjord, Nick Durham, Chris Ward, Claire Myers, Jixin Wang, Wenyan Zhong, Simon Christ, Lina Meinecke, Katharina Nekolla, Laura Sebastian Monasor, Roger Dodd, Neki Patel, Mark Albertella, Jorge Zeron-Medina, Paula Fraenkel, Puja Sapra. First disclosure of AZD5335, a TOP1i-ADC targeting low and high FR α -expressing ovarian cancer with superior preclinical activity vs FR α -MTI ADC [abstract]. AACR 2023; Part 2 (Clinical Trials and Late-Breaking Research); Cancer Res 2023;83(8_Suppl):Abstract nr LB025),
- Rinatabart sesutecan (PRO-1184), an ADC against folate receptor alpha, delivering exatecan to tumour cells, under development by ProfoundBio for the treatment of solid tumours (Clinical trial: NCT05579366, Call JA, Anderson I, Winer I, et al708 A phase 1/2 study of rinatabart sesutecan (PRO1184), a novel folate receptor alpha-directed antibody-drug conjugate, in patients with locally advanced and/or metastatic solid tumors, Journal for ImmunoTherapy of Cancer 2023;11:doi: 10.1136/jitc-2023-SITC2023.0708),
- BAT-8006, an ADC composed of a recombinant humanized anti-folate receptor alpha (FR α) antibody and a toxic small-molecule topoisomerase I inhibitor connected by a self-developed cleavable linker, under development by Bio-Thera Solutions for the treatment of solid tumours (siqi mai, xingxing Mei, weijia Tang, Xin Zhou, Xuekang qi, Zhi Zhong, Shuoxu Li, Jianjun fan, Jirong Gan, Binghua Tan, Yao Qi, Yanling Guo, Shengfeng li, Jin-Chen Yu. BAT8006, a novel FR α ADC with strong bystander effect, for the treatment of advanced solid tumor [abstract]. In: Proceedings of the 2022 San Antonio Breast Cancer Symposium;

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- 2022 Dec 6-10; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2023;83(5 Suppl):Abstract nr P4-01-12),
- MBK-103, an anti FR α -ADC, linked to exatecan, under development by Mablink Bioscience, using its PSARlink technology for the treatment of solid tumours
- 5 (Company pipeline, Mablink Bioscience, 8 Sep 2021 & 21 Jun 2022, <https://www.mablink.com/adc-pipeline/>; Company Web Page, Mablink Bioscience, 8 Sep 2021 & 21 Jun 2022, <https://www.mablink.com/about-adc/>). It also targets folate receptor alpha (FOLR1) (Press release, Mablink Bioscience, 14 Mar 2023, [https://www.globenewswire.com/news-release/2023/03/14/2627277/0/en/Mablink-](https://www.globenewswire.com/news-release/2023/03/14/2627277/0/en/Mablink-Bioscience-to-Present-Promising-Preclinical-Data-for-Lead-ADC-Candidate-MBK-103-at-the-AACR-Annual-Meeting-2023.html)
- 10 Bioscience-to-Present-Promising-Preclinical-Data-for-Lead-ADC-Candidate-MBK-103-at-the-AACR-Annual-Meeting-2023.html),
- ZW-191 under development by Zymeworks (Sam Lawn, Andrea Hernandez Rojas, Raffaele Colombo, Dayananda Siddappa, Jodi Wong, Kaylee Wu, Vincent Fung, Dunja Urosev, Luying Yang, Jamie R. Rich, Stuart D. Barnscher. ZW191, a
- 15 novel FR α -targeting antibody drug conjugate bearing a topoisomerase 1 inhibitor payload [abstract]. AACR 2023; Part 1 (Regular and Invited Abstracts); Cancer Res 2023;83(7_Suppl):Abstract nr 2641).

- Topoisomerase 1 inhibitor-containing ADCs with antibodies targeting
- 20 carcinoembryonic antigen-related cell adhesion molecule (CEACAM), particularly CEACAM5:
- Labetuzumab govitecan, an ADC directed to CEACAM5C and carrying an SN38 payload (Wenjuan Dong, Jianyou Shi, Ting Yuan, Baowen Qi, Jiying Yu, Jingying Dai, Lin He, Antibody-drug conjugates of 7-ethyl-10-hydroxycamptothecin: Sacituzumab govitecan and labetuzumab govitecan, European Journal of
- 25 Medicinal Chemistry, Volume 167, 2019, Pages 583-593, ISSN 0223-5234, <https://doi.org/10.1016/j.ejmech.2019.02.017>),
- PF-08046050 (SGN-CEACAM5C; SAR-445953), a novel topoisomerase I inhibitor ADC targeting CEACAM5, under development by Pfizer (Seagen before
- 30 acquisition) in collaboration with Sanofi for the treatment of solid tumours (Baudat et al. A novel topoisomerase I inhibitor antibody-drug conjugate targeting CEACAM5 has potent anti-tumor activity in colorectal cancer models, AACR 2023, Cancer Res (2023) 83 (7_Supplement): 4890.; Clinical trial: NCT06131840);

- M9140, an ADC targeting CEACAM5 and with a topoisomerase I payload, under development by Merck KGaA for the treatment of solid tumours (Clinical trial: NCT05464030).

5 Topoisomerase 1 inhibitor-containing ADCs with other targets:

- Raludotatug deruxtecan (MK-5909, DS-6000a, DS-6000) is an anti-cadherin-6 (CDH6) ADC, under development by Daiichi Sankyo for the treatment of renal and ovarian cancer (Clinical trial: NCT06161025, WHO INN List, List 127, 22 Jul 2022),
- ABBV-400, a cMET targeting ADC delivering an anti-topoisomerase 1 payload,
10 under development by AbbVie in advanced solid tumors. (ClinicalTrials: NCT05029882, Dose escalation results from a first-in-human study of ABBV-400, a novel c-Met–targeting antibody-drug conjugate, in advanced solid tumors, Sharma et al. Journal of Clinical Oncology, Volume 41, Number 16_suppl, June 2023, https://doi.org/10.1200/JCO.2023.41.16_suppl.3015),
- 15 - DS-3939 (GT-00A ADC), a gatipotuzumab ADC containing deruxtecan, under development by Daiichi Sankyo using its ADC technology, for the treatment of solid tumour. Gatipotuzumab is a humanized monoclonal antibody recognizing the carbohydrate-induced epitope of the tumor-associated mucin-1 (TA-MUC1) (Clinical trial: NCT05875168. The Journal of Precision Medicine, Volume 7, Issue
20 2, 15 June 2021, <https://www.thejournalofprecisionmedicine.com/wp-content/uploads/expanded-precision.pdf>),
- ABBV-706, a SEZ-6 targeting ADC delivering a topoisomerase-1 inhibitor, under development by AbbVie for the treatment of solid tumours such as small cell lung cancer (SCLC), high-grade central nervous system (CNS) tumours and high-grade
25 neuroendocrine carcinomas (NECs) (ClinicalTrial: NCT05599984),
- BAT-8007, an ADC composed of a humanized nectin-4 antibody and a toxic small-molecule topoisomerase I inhibitor connected by a self-developed cleavable linker, under development by Bio-Thera Solutions for the treatment of solid tumours (Clinical trial: NCT05879627),
- 30 - ACR-246, an ADC targeting 5T4 with a novel topoisomerase 1 inhibitor as its payload and a stable and tumour microenvironment (TME) cleavable linker, under development by Hangzhou Adcoris Biopharma for the treatment of solid tumours (Clinical trial: NCT06238401),

- ZW-220, ADC targeting NaPi2b under development by Zymeworks (Andrea Hernandez Rojas, Jodi Wong, Dunja Urosev, Sam Lawn, Kaylee Wu, Saki Konomura, Manuel Lasalle, Diego A. Alonzo, Luying Yang, Mark Petersen, Lemlem T. Degeffie, Araba P. Sagoe-Wagner, Sohyeong Kang, Chi Wing Cheng, Raffaele Colombo, Daya Siddappa, Stuart D. Barnscher, Jamie R. Rich. ZW220, a novel NaPi2b-targeting antibody drug conjugate bearing a topoisomerase 1 inhibitor payload [abstract]. AACR 2023; Part 1 (Regular and Invited Abstracts); Cancer Res 2023;83(7_Suppl):Abstract nr 1533.),
- 5 - AZD-9829, a CD123-targeting ADC comprising a topoisomerase I inhibitor payload, under development by AstraZeneca using its proprietary linker technology for the treatment of haematological malignancies. (ClinicalTrial: NCT06179511, ASH 2023, 616, Dutta et al. Blood (2023) 142 (Supplement 1): 5957, <https://doi.org/10.1182/blood-2023-187642>),
- 10 - PRO-1160, an ADC against CD70, delivering exatecan to tumour cells, under development by ProfoundBio (Suzhou) for the treatment of non-Hodgkin's lymphoma (NHL), nasopharyngeal carcinoma and renal cell carcinoma (RCC) (Lei Wang, Haidong Liu, Xiao Shang, Tae Han, Baiteng Zhao. PRO1160, a novel CD70-directed antibody-drug conjugate, demonstrates robust anti-tumor activity in mouse models of renal cell carcinoma and non-Hodgkin lymphoma [abstract]. AACR 2022; Cancer Res 2022;82(12_Suppl):Abstract nr 1759, clinical trial: NCT05721222),
- 15 - AMT-253 (MTX-253) is a MUC18-targeted ADC with an exatecan payload, under development by Multitude Therapeutics, for the treatment of melanoma and solid tumours (Clinical trials: NCT05906862; China FDA, CTR20234311, Cancer Res (2023) 83 (22): 3783–3795. <https://doi.org/10.1158/0008-5472.CAN-23-1356>),
- 20 - BGC-0222 is a peptide-drug conjugate comprising PEG-cRGD-conjugated irinotecan derivative, under development by BrightGene Bio-Medical for the treatment of breast cancer, colon cancer, gastric cancer, gliomas, pancreatic cancer, small cell lung cancer, and other solid tumours (Huang YQ, Yuan JD, Ding HF, Song YS, Qian G, Wang JL, Ji M, Zhang Y. Design, synthesis and pharmacological evaluation of a novel PEG-cRGD-conjugated irinotecan derivative as potential antitumor agent. Eur J Med Chem. 2018 Oct 5;158:82-90. doi: 10.1016/j.ejmech.2018.08.091. Epub 2018 Aug 31. PMID: 30199708.),
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- A claudin 18.2 targeting ADC comprised of a humanized anti-CLDN18.2 IgG1 monoclonal antibody, an enzyme-digestible linker, and a DNA topoisomerase I inhibitor for the treatment of gastric cancer, prostate cancer and solid tumours over-expressing Claudin 18.2, developed by Luzsana Biotechnology,
- 5 - HLX-43, an ADC targeting PD-L1 conjugated with a novel high potency DNA topoisomerase I inhibitor, under development by Shanghai Henlius Biotech for the treatment of solid tumours (Clinical trial: NCT06115642),
- JSKN-033 is a subcutaneous injection compound consisting of HER2 bispecific antibody-conjugated drug (JSKN-003, above-mentioned) and envafolimab, under
10 development by Alphamab Oncology using its bispecific antibody conjugation (BADC) platform for the treatment of solid tumours. JSKN-003 is a HER2 dual-epitope-targeting antibody-conjugated drug composed of three parts: bispecific antibodies targeting two non-overlapping epitopes of the HER2 extracellular domain, a cleavable linker, and a topoisomerase I inhibitor. Envafolimab is a Fc
15 fusion protein consisting of humanized anti-PD-L1 single domain antibody and human IgG1 Fc fragment (Clinical trial for JSKN-033: NCT06226766),
- SKB-315 (A-315) is a third-generation ADC targeting claudin 18.2 conjugated to highly potent topoisomerase I inhibitor, under development by Kelun Biotech (Klus Pharma) for the treatment of solid tumours (Clinical trial: NCT05367635),
- 20 - ZL-1310 (YL-212), a DLL3 ADC with a topoisomerase I inhibitor payload, under development by Zai Lab and MediLink Therapeutics using MediLink's TAMLIN platform for the treatment of small cell lung cancer and neuroendocrine tumours (Clinical trial: NCT06179069),
- AMB-101, an ADC targeting tissue factor (TF) with a proprietary next-generation
25 topoisomerase 1 inhibitor-based linker payload under development by AmMax Bio for the treatment of solid tumours (Clinical trial: NCT05349643),
- AMB-302 (GQ-1011), an ADC consisting of a topoisomerase 1 inhibitor conjugated to an FGFR3 targeting antibody, under development by AIMEDBIO for the treatment of bladder cancer and glioblastoma (Byeongkwi Min, Lily Shi, Hye
30 Jin Kim, Sangwoo Kim, Beibei Fan, Cao Lv, Yajun Sun, Nam-Gu Her, Paul Song, Gang Qin, Do-Hyun Nam. AMB302/GR1017, an antibody-drug conjugate (ADC) with topoisomerase 1 inhibitor shows therapeutic potency in orthotopic glioblastoma PDX and bladder cancer models with FGFR3-TACC3 fusion

- [abstract]. AACR 2023; Part 1 (Regular and Invited Abstracts); Cancer Res 2023;83(7_Suppl):Abstract nr 2634),
- CUSP-06 (AMT-707), an anti-CDH6 ADC with an exatecan payload, under development by OnCusp Therapeutics for the treatment of solid tumours (Clinical trial: NCT06234423),
 - HLX-42, an anti-EGFR ADC consisting of an anti-EGFR monoclonal antibody conjugated with a novel high potency DNA topoisomerase I (topo I) inhibitor, under development by Shanghai Henlius Biotech for the treatment of solid tumours (Clinical trial: NCT06210815),
 - MBK-101, MBK-102, MBK-104 or MBK-105, ADCs under development by Mablink Bioscience based on exatecan payload,
 - MGC-026, an ADC composed of topoisomerase inhibitor cytotoxic payload with undisclosed target, under development by MacroGenics for the treatment of solid tumours (Clinical trial: NCT06242470),
 - STRO-003, an ADC targeting ROR1, under development by Sutro Biopharma for the treatment of solid tumours & haematological cancers (Yam A, Hanson J, Bajjuri K, et al 1191 STRO-003 is a novel ROR1-targeted ADC for breast and lung cancer Journal for ImmunoTherapy of Cancer 2022;10:doi: 10.1136/jitc-2022-SITC2022.1191),
 - XB-033, an ADC composed of IL13R α 2 and topoisomerase 1 inhibitor, under development by Exelixis for the treatment of cancer,
 - ZW-251, ADC targeting glypican-3 under development by Zymeworks (Laurence Madera, Andrea Hernández Rojas, Raffaele Colombo, Alex Wu, Chayne L. Piscitelli, Dunja Urosev, Allysha Bissessur, Chi Wing Cheng, Renee Duan, Catrina Kim, Kevin Yin, Vincent Fung, Kaylee Wu, Winnie Cheung, Diego A. Alonzo, Mark E. Petersen, Stuart D. Barnscher, Jamie R. Rich. ZW251, a novel glypican-3-targeting antibody drug conjugate bearing a topoisomerase 1 inhibitor payload [abstract]. AACR 2023; Part 1 (Regular and Invited Abstracts); Cancer Res 2023;83(7_Suppl): Abstract nr 2658.).

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The topoisomerase 1-containing antibody drug conjugate is preferably selected from sacituzumab govitecan, datopotamab deruxtecan, sacituzumab tirumotecan, trastuzumab deruxtecan, patritumab deruxtecan, ifinatamab deruxtecan, puxitatumab

samrotercan, AZD-5335, rinatabart sesotecan, labetuzumab govitecan, PF-08046050, M9140, Raludotatug deruxtecan, ABBV-400, DS-3939, ABBV-706, BAT-8007, ACR-246 or ZW-220.

- 5 In some aspects, the topoisomerase 1 inhibitor is incorporated in the form of particles.

The topoisomerase 1 inhibitor-containing particles are preferably selected from CRLX101 (C. Young, et al., Curr Bioact Compd. 7, 8-14, 2011 and D.D. Gadade et
10 al., Adv. Pharm. Bull. 2020, 10, 166) and MM-398 (pegylated liposomal irinotecan, ONIVYDE®). Microparticle compositions of a topoisomerase 1 inhibitor are also described in WO 2007/017514 A1.

The compound of formula (I) is a WEE1 inhibitor. In some aspects, an N-oxide or
15 N-oxide derivative of the compound of formula (I) and/or of the topoisomerase 1 inhibitor may be used.

In specific aspects of the combinations, the uses and the methods according to the present invention, the WEE1 inhibitor is a compound of formula (I), or a
20 pharmaceutically acceptable salt thereof. All of the further information provided herein is to be understood as applying also in particular to the aspect of the WEE1 inhibitor being a compound of formula (I), or a pharmaceutically acceptable salt thereof.

25 In other specific aspects of the combinations, the uses and the methods according to the present invention, the WEE1 inhibitor is a compound of formula (I), or a pharmaceutically acceptable salt thereof and the topoisomerase 1 inhibitor or topoisomerase inhibitor moiety in the ADC is camptothecin or a camptothecin derivative, preferably selected from topotecan, irinotecan, SN38, govitecan,
30 deruxtecan (Dxd), exatecan, belotecan, silatecan, gimatecan, namitecan (ST1968), or a pharmaceutically acceptable salt thereof.

In other specific aspects of the combinations, the uses and the methods according to the present invention, the WEE1 inhibitor is a compound of formula (I), or a pharmaceutically acceptable salt thereof and the topoisomerase 1 inhibitor is irinotecan, topotecan, belotecan, gimatecan, silatecan, or a pharmaceutically acceptable salt thereof. All of the further information provided herein is to be understood as applying also in particular to the aspect of the WEE1 inhibitor being a compound of formula (I), or a pharmaceutically acceptable salt thereof and the topoisomerase 1 inhibitor being, especially irinotecan, topotecan, belotecan, gimatecan, silatecan or a pharmaceutically acceptable salt thereof.

10

In other specific aspects of the combinations, the uses and the methods according to the present invention, the WEE1 inhibitor is a compound of formula (I), or a pharmaceutically acceptable salt thereof and the topoisomerase 1 inhibitor is the payload of an ADC and is preferably selected from SN38, govitecan, deruxtecan (Dxd), exatecan, sesutecan, belotecan, tirumotecan, samrotercan or a pharmaceutically acceptable salt thereof. All of the further information provided herein is to be understood as applying also in particular to the aspect of the WEE1 inhibitor being a compound of formula (I), or a pharmaceutically acceptable salt thereof and the topoisomerase 1 inhibitor moiety in an ADC being especially SN38, govitecan, deruxtecan (Dxd), exatecan, sesutecan, belotecan, tirumotecan, samrotercan or a pharmaceutically acceptable salt thereof.

In other specific aspects of the combinations, the uses and the methods according to the present invention, the WEE1 inhibitor is a compound of formula (I), or a pharmaceutically acceptable salt thereof and the ADC comprising a topoisomerase 1 inhibitor is preferably selected from sacituzumab govitecan, datopotamab deruxtecan, sacituzumab tirumotecan, trastuzumab deruxtecan, patritumab deruxtecan, ifinatamab deruxtecan, puxitatug samrotercan, AZD-5335, rinatabart sesutecan, labetuzumab govitecan, PF-08046050, M9140, Raludotatug deruxtecan, ABBV-400, DS-3939, ABBV-706, BAT-8007, ACR-246, ZW-220 or a pharmaceutically acceptable salt thereof. All of the further information provided herein is to be understood as applying also in particular to the aspect of the WEE1 inhibitor being a compound of formula (I), or a pharmaceutically acceptable salt

thereof and the ADC comprising a topoisomerase 1 inhibitor being especially sacituzumab govitecan, datopotamab deruxtecan, sacituzumab tirumotecan, trastuzumab deruxtecan, patritumab deruxtecan, ifinatamab deruxtecan, puxitatum samrotecan, AZD-5335, rinatabart sesutecan, labetuzumab govitecan, PF-08046050, M9140, raludotatug deruxtecan, ABBV-400, DS-3939, ABBV-706, BAT-8007, ACR-246, ZW-220 or a pharmaceutically acceptable salt thereof. The combination of the WEE1 inhibitor being a compound of formula (I), or a pharmaceutically acceptable salt thereof and the ADC comprising a topoisomerase 1 inhibitor being sacituzumab govitecan is a specific embodiment of interest; all further disclosures provided herein apply particularly to this specific embodiment (as far as consistent and technically reasonable). The combination of the WEE1 inhibitor being a compound of formula (I), or a pharmaceutically acceptable salt thereof and the ADC comprising a topoisomerase 1 inhibitor being datopotamab deruxtecan is also a specific embodiment of interest; all further disclosures provided herein apply particularly to this specific embodiment (as far as consistent and technically reasonable).

DOSES, SCHEDULES AND ROUTES OF ADMINISTRATION

As used herein, the term “about” describes a deviation from the indicated value of $\pm 10\%$. The individual values are to be understood as describing ranges between any of the described values.

Dose indications provided herein are to be understood as characterizing the mass of the free base compound. If a pharmaceutically acceptable salt of the respective compound is used, the dose indication may need to be adjusted according to the molecular weight of the compound in said salt form.

In some aspects of the combinations, the uses or the methods according to the present invention, the combination, the WEE1 inhibitor and/or the topoisomerase 1 inhibitor described herein are administered orally. In other aspects, the WEE1 inhibitor is administered orally, and the topoisomerase 1 inhibitor is administered parenterally, such as i.v., s.c. or i.m.

In some aspects, the WEE1 inhibitor is administered according to a scheme selected from the following:

- a. on days 1 to 3 of a 21-day cycle,
- 5 b. on days 1 to 3 and 8 to 10 of a 21-day cycle,
- c. on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle,
- d. on days 1 to 5 over 21-day cycle,
- e. on days 1 to 5 and 8 to 12 over a 21-day cycle,
- f. on days 1 to 5, 8 to 12 and 15 to 19 of a 21-day cycle,
- 10 g. on days 1 to 14 of a 21-day cycle,
- h. daily over a 21-day cycle, or
- i. on days 1 to 5 and 8 to 10 of a 28-day cycle,
- j. on days 1 to 5, 8 to 10 and 15 to 17 of a 28-day cycle
- k. on days 1-3 of a 28-day cycle
- 15 l. on days 1-3 and 8-10 of a 28-day cycle,
- m. on days 1-3 and 15-17 of a 28-days cycle,
- n. on days 1-3, 8-10 and 15-17 of a 28-day cycle,
- o. on days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle,
- p. on days 1-5 of a 28-day cycle,
- 20 q. on days 1-5 and 8-12 of a 28-day cycle,
- r. on days 1-5 and 15-19 of a 28-day cycle,
- s. on days 1-5, 8-12 and 15-19 of a 28-day cycle,
- t. on days 1-5, 8-12, 15-19 and 22-26 of a 28-day cycle, or
- u. daily over a 28-day cycle, or
- 25 v. on days 1, 8, 15 and 22 of a 6-week cycle.

The above schemes a to v are also referred to as WEE1 inhibitor administration schemes.

In some aspects of the combinations, the uses or the methods according to the present invention, the WEE1 inhibitor is administered

- a. at a dose ranging from about 30 to about 1000 mg per WEE1 inhibitor treatment day, preferably about 30 to about 720 mg per WEE1 inhibitor treatment day, and/or

- b. orally, and/or
- c. as a single dose on a WEE1 inhibitor treatment day, and/or
- d. at approximately the same time on each WEE1 inhibitor treatment day.

5 In some aspects, the WEE1 inhibitor is administered at a dose ranging from about 30 to about 1000 mg per WEE1 inhibitor treatment day, preferably about 30 to about 720 mg, or about 60 to about 720 mg, per WEE1 inhibitor treatment day, and in some aspects about 90 to about 720 mg per WEE1 inhibitor treatment day or about 150 to about 720 mg per WEE1 inhibitor treatment day. For example, the
10 WEE1 inhibitor may be administered as a single dose on a WEE1 inhibitor treatment day.

In some aspects of the present invention, the WEE1 inhibitor is administered at approximately the same time on each WEE1 inhibitor treatment day, e.g. at the
15 same time $\pm$ about 60 min, preferably $\pm$ 60 min on each WEE1 inhibitor treatment day, for example in a given cycle. In more specific aspects, the compound of formula (I) is administered in the morning, for example between about 5 a.m and noon.

20 In some aspects of the uses or methods according to the present invention, the WEE1 inhibitor is administered irrespective of food status of the patient.

In some aspects of the combinations, the uses or the methods according to the present invention, on a WEE1 inhibitor treatment day, administration of the WEE1
25 inhibitor precedes administration of the topoisomerase 1 inhibitor. For example, on a WEE1 inhibitor treatment day, topoisomerase 1 inhibitor administration is initiated about 5 minutes or more, such as 30 minutes or more, and 4 hour or less, such as 1 hours or less, after WEE1 inhibitor administration.

30 In some aspects of the combinations, the uses or the methods according to the present invention, the WEE1 inhibitor and the topoisomerase 1 inhibitor are administered simultaneously, which can be in the form of separate pharmaceutical

compositions or in the form of a single pharmaceutical composition comprising both agents.

5 In some aspects of the combinations, the uses or the methods according to the present invention, the combination, the WEE1 inhibitor and/or the topoisomerase 1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more cycles. The number of cycles is not particularly limited other than by the occurrence of serious adverse effects or progression of the disease.

10 In some aspects of the combinations, the uses or the methods according to the present invention, the combination, the WEE1 inhibitor and/or the topoisomerase 1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more 21-day cycles or 28-day cycles or 6-week cycles. Typically, there are no breaks between any consecutive cycles, i.e. the day following a prior 21-day or 28-day cycle or 6-week cycle may
15 be the first day of the consecutive cycle.

In some aspects of the combinations, the uses or the methods according to the present invention, the topoisomerase 1 inhibitor is administered

- a. on days 1 and 15 of a 28-day cycle,
- 20 b. on day 1 of a 21-day cycle,
- c. on days 1-5 of a 21-day cycle,
- d. on days 1-3 of a 21-day cycle,
- e. on days 1, 8 and 15 of a 28-day cycle,
- f. on days 1-5 of a 28-day cycle,
- 25 g. on days 1-5 and 8-12 of a 28-day cycle,
- h. on days 1-5, 8-12 and 15-19 of a 28-days cycle,
- i. on days 1, 8, 15 and 22 of a 6-week cycle, or
- j. on the same days as the WEE1 inhibitor treatment days, preferably as defined in any of scheme aspects a to v described herein in relation to
30 the WEE1 inhibitor administration scheme.

The above schemes a to i are also referred to as topoisomerase 1 inhibitor administration schemes, in aspects where the topoisomerase 1 inhibitor is not in the form of an ADC and/or is a small molecule.

In some aspects of the combinations, the uses or the methods according to the present invention, the ADC comprising a topoisomerase 1 inhibitor is administered

- a. on days 1 and 8 of a 21-day cycle,
- 5 b. on days 1 and 8 of a 28-day cycle,
- c. on days 1, 8 and 15 of a 21-day cycle,
- d. on days 1, 8 and 15 of a 28-day cycle,
- e. on days 1, 8, 15 and 22 of a 28-day cycle,
- f. on day 1 of a 21-day cycle (once every three weeks), or
- 10 g. on day 1 of a 28-day cycle (once every four weeks).

The above schemes a to g may also be referred to as the administration schemes for an ADC comprising a topoisomerase 1 inhibitor.

In some aspects, the ADC comprising a topoisomerase 1 inhibitor is sacituzumab
15 govitecan, which is administered on days 1 and 8 of a 21-day cycle. Sacituzumab govitecan is generally administered via intravenous infusion. The WEE1 inhibitor may be administered according to any administration scheme having a 21-cycle, such as WEE1 inhibitor administration schemes a to h specified above, preferably on Days 1-3 and 8-10 of a 21-day cycle. Preferably, the dose of sacituzumab
20 govitecan is 10 mg/kg per administration. Preferably the WEE1 inhibitor is compound of formula (I), and the dose of compound of formula (I) ranges from 150 mg to 720 mg. Preferably the WEE1 inhibitor is compound of formula (I), and the dose of compound of formula (I) ranges from 150 mg to 720 mg per WEE1 inhibitor treatment day. For example, the dose of compound of formula (I) ranges
25 from 150 mg to 520 mg per WEE1 inhibitor treatment day, or from 200 mg to 520 mg per WEE1 inhibitor treatment day. For example, compound of formula (I) is administered orally, such as once a day.

In some aspects, the ADC comprising a topoisomerase 1 inhibitor is datopotamab
30 deruxtecan, which is administered on day 1 of a 21-day cycle. Datopotamab deruxtecan is generally administered via intravenous infusion. The WEE1 inhibitor may be administered according to any administration scheme having a 21-cycle, such as WEE1 inhibitor administration schemes a to h specified above, preferably

on Days 1-3 and 8-10 of a 21-day cycle. Preferably, the dose of datopotamab deruxtecan is 6 mg/kg per administration. For example, the dose of datopotamab deruxtecan is 6 mg/kg per administration up to a maximum of 540 mg for patients ≥ 90 kg. Preferably the WEE1 inhibitor is compound of formula (I), and the dose of compound of formula (I) ranges from 100 mg to 720 mg per WEE1 inhibitor treatment day. For example, the dose of compound of formula (I) ranges from 150 mg to 520 mg per WEE1 inhibitor treatment day, or from 200 mg to 520 mg per WEE1 inhibitor treatment day. For example, compound of formula (I) is administered orally, such as once a day.

10

In some aspects, the topoisomerase 1 inhibitor is irinotecan, which is administered either on day 1 of a 21-day cycle, or on days 1, 8, 15 and 22 of a 6-week cycle. The WEE1 inhibitor may be administered according to any administration scheme having a 21-cycle if the irinotecan is also administered according to a 21-day cycle, such as WEE1 inhibitor administration schemes a to h specified above. If irinotecan is administered according to a 6-week cycle, the WEE1 inhibitor may be administered according to any administration scheme with a 6-week cycle such as the above WEE1 inhibitor administration scheme v. Preferably, the dose of irinotecan is about 350 mg/m² per administration if the administration is according to a 21-day administration scheme and about 125 mg/m² per administration if the administration is according to a 6-week administration scheme. Irinotecan is generally administered via intravenous infusion, for example over 90 minutes.

In some aspects, the topoisomerase 1 inhibitor is nanoliposomal irinotecan, which is administered either on day 1 of a 21-day cycle, or on days 1 and 15 of a 28-day cycle. The WEE1 inhibitor may be administered according to any administration scheme having a 21-cycle if the nanoliposomal irinotecan is also administered according to a 21-day cycle, such as WEE1 inhibitor administration schemes a to h specified above. If nanoliposomal irinotecan is administered according to a 28-day cycle, the WEE1 inhibitor may be administered according to any administration scheme with a 28-day cycle such as the above WEE1 inhibitor administration schemes i to u. Preferably, the dose of nanoliposomal irinotecan is about 120 mg/m² per administration if the administration is according to a 21-day

administration scheme and about 70 mg/m² per administration if the administration is according to a 28-day administration scheme. Nanoliposomal irinotecan is generally administered via intravenous infusion, for example over 90 minutes.

- 5 In some aspects, the topoisomerase 1 inhibitor is topotecan, which is administered either on days 1-5 of a 21-day cycle, or on days 1, 2 and 3 of a 21-day cycle. The WEE1 inhibitor may be administered according to any administration scheme having a 21-cycle, such as WEE1 inhibitor administration schemes a to h specified above. Preferably, the dose of topotecan is
- 10 - about 1.5 mg/m² per administration if the administration is on days 1-5 of a 21-day administration scheme and the administration is via intravenous infusion,
- about 2.3 mg/m²/day if the administration is on days 1-5 of a 21-day administration scheme and the administration is oral, or
- 15 - about 0.75 mg/m² per administration if the administration is on days 1, 2, 3 of a 21-day administration scheme and the administration is via intravenous infusion.

An intravenous infusion of topotecan is usually done over 30 minutes.

- 20 In some aspects, the topoisomerase 1 inhibitor is belotecan, which is administered either on days 1-5 of a 21-day cycle, or on days 1, 2,3 and 4 of a 21-day cycle. The dose of belotecan may be between about 0.3 mg/m² and about 0.5 mg/m² per administration day. The WEE1 inhibitor may be administered according to any administration scheme having a 21-cycle, such as WEE1 inhibitor administration
- 25 schemes a to h specified above. Belotecan is generally administered via intravenously.

- In some aspects, the topoisomerase 1 inhibitor is gimatecan, which is administered on days 1-5 of a 28-day cycle, on days 1-5 and 8-12 of a 28-day
- 30 cycle, on days 1-5, 8-12 and 15-19 of a 28-days cycle, or on days 1, 8, 15 of a 28-day cycle. Gimatecan is orally administered. The dose of gimatecan may be about 0.8 mg/m² per administration day. The WEE1 inhibitor may be administered

according to any administration scheme having a 28-cycle, such as WEE1 inhibitor administration schemes i to u specified above.

5 In some aspects, the topoisomerase 1 inhibitor is silatecan, which is administered on days 1-5 of a 21-day cycle. The dose of silatecan may be about 7.5 mg/m² per administration days. The WEE1 inhibitor may be administered according to any administration scheme having a 21-cycle, such as WEE1 inhibitor administration schemes a to h specified above. Silatecan is generally administered via intravenously.

10

In some aspects of the combinations, the uses or the methods according to the present invention, administration of the WEE1 inhibitor is separate, simultaneous, concomitant or sequential to the administration of the topoisomerase 1 inhibitor.

15 In the combinations, uses and methods of the present invention, the WEE1 inhibitor may be administered at doses ranging from about 30 to about 1000 mg of free base, preferably ranging from about 30 to about 720 mg of free base per WEE1 inhibitor treatment day. In some aspects the compound of formula (I) may preferably be administered at doses from about 90 to about 720 mg of free base,
20 or from about 150 to about 720 mg of free base per WEE1 inhibitor treatment day.

For example, the WEE1 inhibitor may be administered at a dose of about 30, about 60, about 75, about 90, about 100, about 120, about 130, about 150, about 200, about 220, about 250, about 260, about 300, about 320, about 350, about
25 360, about 400, about 420, about 450, about 460, about 500, about 520, about 550, about 600, about 620, about 650, about 700, about 720, about 750, about 800, about 820, about 850, about 900, about 920, about 950 or about 1000 mg of free base per WEE1 inhibitor treatment day. In particular, the WEE1 inhibitor may be administered at a dose of 30, 60, 75, 90, 100, 120, 130, 150, 200, 220, 250,
30 260, 300, 320, 350, 360, 400, 420, 450, 460, 500, 520, 550, 600, 620, 650, 700, 720, 750, 800, 820, 850, 900, 920, 950 or 1000 mg of free base per WEE1 inhibitor treatment day.

In a more specific aspect, the WEE1 inhibitor may be administered at doses of about 30, about 60, about 75, about 90, about 100, about 120, about 150, about 200, about 250, about 260, about 300, about 350, about 360, about 400, about 450, about 460, about 500, about 520, about 550 or about 720 mg of free base per WEE1 inhibitor treatment day. For example, the WEE1 inhibitor may be administered at a dose of 30, 60, 75, 90, 100, 120, 150, 200, 250, 260, 300, 350, 360, 400, 450, 460, 500, 520, 550 or 720 mg of free base per WEE1 inhibitor treatment day.

10

In another specific aspect, the WEE1 inhibitor may be administered at doses of about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 520, about 550, about 600, about 620, about 650, about 700, about 720, about 750, about 800, about 820, about 850, about 900, about 920, about 950 or about 1000 mg of free base per WEE1 inhibitor treatment day. For example, compound of formula (I) may be administered at doses of about 100, about 130, about 150, about 200, about 300, about 400 or about 520 mg of free base per WEE1 inhibitor treatment day.

20 In another aspect of the present invention the WEE1 inhibitor may be administered at doses ranging from 100 to 1000 mg of free base, preferably ranging from 150 to 720 mg of free base, per WEE1 inhibitor treatment day. For example, compound of formula (I) may be administered at a dose of 100, 150, 200, 250, 300, 350, 400, 450, 500, 520, 550, 600, 620, 650, 700, 720, 750, 800, 820, 850, 900, 920, 950 or 1000 mg of free base per WEE1 inhibitor treatment day. In particular, compound of formula (I) may be administered at doses of 100, 150, 200, 300, 400, 520 or 720 mg of free base per WEE1 inhibitor treatment day.

30 In some aspects, a WEE1 therapeutically effective amount or an amount of WEE1 inhibitor resulting in a combination therapeutically effective amount may be administered.

In some aspects of the present invention, the WEE1 inhibitor is administered orally.

In some aspects of the present invention, the WEE1 inhibitor is administered as a
5 single dose per WEE1 inhibitor treatment day (QD), or in two doses per WEE1 inhibitor treatment day (BID).

In some aspects of the present invention, the WEE1 inhibitor is administered on Days 1, 2, 3 and 8, 9, 10 of a 21-day cycle. In some aspects, if the WEE1 inhibitor,
10 especially the compound of formula (I), is administered on days 1, 2, 3 and 8, 9, 10 of a 21-day cycle, it is optionally possible to administer the WEE1 inhibitor, especially the compound of formula (I), only on days 1, 2 and 3 of subsequent 21-day cycles. This change of the administration days may be advantageous especially if the patient develops side-effects upon administration on days 1, 2, 3
15 and 8, 9, 10. Similar changes of administration days may be considered, such as administering the WEE1 inhibitor daily during a first 21-day cycle, or more, and then administering the WEE1 inhibitor on a reduced number of days in subsequent 21-day cycles.

20 In these aspects, the WEE1 inhibitor may be administered over 1, 2, 3, 4, 5, 6 or more cycles. Typically, there are no breaks between any consecutive cycles, i.e. the day following a prior 21-day cycle may be the first day of the consecutive cycle. In some aspects, the treatment with the WEE1 inhibitor such as compound of formula (I) may continue until progression of disease, unacceptable toxicity,
25 patient's decision to stop, discontinuation as per physician's decision, initiation of subsequent antineoplastic treatment, the end of a clinical study, or death.

In some aspects of the methods of the present invention, the topoisomerase 1
30 inhibitor is used in a therapeutically effective amount for the intended purpose, particularly the indication to be treated.

In some aspects, a topoisomerase 1 inhibitor therapeutically effective amount, or an amount of topoisomerase 1 inhibitor resulting in a combination therapeutically effective amount is administered. For example, the topoisomerase 1 inhibitor may be administered at a dose ranging from about 0.1 mg/m² to about 500 mg/m² per administration day. Alternatively, in embodiments where an ADC comprising a topoisomerase 1 inhibitor is used, the ADC may be administered at a dose ranging from about 0.1 mg/kg to about 50 mg/kg of patient weight or more, or from about 0.5 to about 25 mg/kg of patient weight, such as about 10 mg/kg of patient weight, or about 6 mg/kg of patient weight (for example with a maximum of 540 mg for patients ≥90 kg).

In some aspects, the topoisomerase 1 inhibitor may be administered at least partly on the same days as the WEE1 inhibitor, such as on the same days of a 21-day cycle, 28-day or 6-week cycle, or in a different schedule.

In any aspects of the combinations herein, the WEE1 inhibitor may be compound of formula (I). In any aspects of the combinations with an ADC comprising a topoisomerase 1 inhibitor herein, the ADC may be a TROP2-targeting ADC. In particular, such combination of the present invention may advantageously achieve therapeutic activity against both TROP2^{low} and TROP2^{high} cancers.

In some specific aspects, the WEE1 inhibitor may be compound of formula (I) and the TROP2-targeting ADC comprising a topoisomerase 1 inhibitor is sacituzumab govitecan. The combination of compound of formula (I) with sacituzumab govitecan shows a synergistic effect in treating cancer, along with an acceptable safety profile. In particular, such specific combination of the present invention achieves therapeutic activity against both TROP2^{low} and TROP2^{high} cancers.

In other specific aspects, the WEE1 inhibitor may be compound of formula (I) and the TROP2-targeting ADC comprising a topoisomerase 1 inhibitor is datopotamab deruxtecan. The combination of compound of formula (I) with datopotamab deruxtecan shows a synergistic effect in treating cancer, along with an acceptable safety profile.

It is to be understood that any indication of an administration, dosage, schedule, regimen or indication for a WEE1 inhibitor herein applies in particular to the compound of formula (I).

5

INDICATIONS

In some aspects of the combinations, the uses or the methods according to the present invention, wherein a cancer is treated, the cancer is breast cancer, colorectal cancer (CRC), non-small-cell lung cancer (NSCLC), small cell lung cancer (SCLC), ovarian cancer, endometrial cancer, including uterine serous carcinoma (USC), testicular cancer, penile cancer, anal cancer, stomach cancer, bladder cancer, cervical cancer, esophageal cancer, head and neck cancer, gallbladder cancer, pancreatic cancer, prostate cancer, gastric cancer, peritoneal cancer, hepatocarcinoma, renal cell carcinoma (RCC), melanoma, soft tissue sarcoma, lymphoma or glioma, including glioblastoma.

In some aspects, the cancer is characterized by reduced expression of HER2.

20 In some aspects according to the present invention, a cancer is treated in a subject, wherein a therapeutically effective amount of the combination including WEE1 inhibitor and topoisomerase 1 inhibitor/ADC comprising topoisomerase 1 inhibitor is administered to the subject in need thereof, wherein the cancer has been previously identified as a cancer with reduced expression of HER2.

25

In some aspects according to the present invention, a cancer is treated in a subject, wherein a therapeutically effective amount of the combination including WEE1 inhibitor and topoisomerase 1 inhibitor/ADC comprising topoisomerase 1 inhibitor is administered to the subject, wherein the cancer is characterized by reduced expression of HER2.

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In some aspects according to the present invention, the combination including WEE1 inhibitor and topoisomerase 1 inhibitor/ADC comprising topoisomerase 1

inhibitor induces cell death in a cancer cell harboring reduced expression of HER2, comprising contacting the cell with an effective amount of the combination including WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising topoisomerase 1 inhibitor.

5

In some aspects, the cancer with reduced expression of HER2 is breast cancer, colorectal cancer, stomach cancer, lung cancer, including SCLC and NSCLC, or pancreatic cancer.

10 In some aspects, the cancer is triple negative breast cancer (TNBC) or Hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer. In some more specific aspects, the cancer is advanced or metastatic TNBC or HR+/HER2- breast cancer, relapsing after one or two lines of treatment.

15 In some aspects, the cancer, such as a breast cancer, has been previously treated with taxanes regardless of disease stage (adjuvant, neoadjuvant, or advanced), unless contraindicated for a given patient.

In some aspects, the cancer is a breast cancer characterized by one or more of
20 the following:

- i. the cancer is a histologically confirmed TNBC or HR+/HER2- breast cancer as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, such as the
25 Guideline Update” and/or
- ii. the cancer is an unresectable locally recurrent or metastatic breast cancer, documented by computerized tomography (CT) scan or magnetic resonance imaging (MRI), that is not amenable to resection with curative intent, and/or
- 30 iii. the cancer has been previously treated with taxanes regardless of disease stage (adjuvant, neoadjuvant, or advanced), unless contraindicated for a given patient, and /or

- iv. the breast cancer is refractory to at least one prior standard of care chemotherapy regimen for unresectable locally advanced or metastatic breast cancer. Earlier adjuvant or neoadjuvant therapy for more limited disease may be considered as one of such prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within a 12-month period after completion of chemotherapy, and/or
- v. the HR+/HER2– breast cancer is refractory to at least 1 prior anti-cancer hormonal treatment for advanced disease and has resistance to CDK4/6 (cyclin-dependent kinases 4 and 6) inhibitor, defined as:
- Disease progression while on, or within 12 months after the end of CDK4/6 inhibitor treatment in the (neo)adjuvant setting, or
 - Disease progression to CDK4/6 inhibitor treatment during advanced disease.

15

In some aspects according to item iv) above, the breast cancer is refractory to at least one, and no more than two, prior standard of care chemotherapy regimens for unresectable locally advanced or metastatic breast cancer. In some aspects, the breast cancer is refractory to at least two prior standard of care chemotherapy regimens for unresectable locally advanced or metastatic breast cancer. Earlier adjuvant or neoadjuvant therapy for more limited disease may be considered as one of such prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within a 12-month period after completion of chemotherapy.

25

In some aspects, which may be cumulative with any, some or all of items i) to v) above, the breast cancer patient has brain metastasis. In further aspects, such breast cancer patient may additionally receive low dose of corticosteroids, such as ≤ 20 mg prednisone or equivalent daily.

30

In some aspects, which may be cumulative with any, some or all of items i) to v) above, the breast cancer patient has a bone-only metastatic disease with at least

one measurable soft-tissue component of 10 mm or more in diameter, according to RECIST v1.1.

5 More generally, in some aspects, the cancer patient has a bone-only metastatic disease with at least one measurable soft-tissue component of 10 mm or more in diameter, according to RECIST v1.1. The cancer may be a cancer with a high prevalence of bone metastasis such as breast cancer or prostate cancer.

10 In some aspects, the cancer is characterized by CCNE1 overexpression and/or amplification.

In some aspects according to the present invention, a cancer is treated in a subject, wherein a therapeutically effective amount of the combination including WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising
15 topoisomerase 1 inhibitor is administered to the subject in need thereof, wherein the cancer has been previously identified as a cancer overexpressing CCNE1.

In some aspects according to the present invention, a cancer is treated in a subject, wherein a therapeutically effective amount of the combination including
20 WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising topoisomerase 1 inhibitor is administered to the subject, wherein the cancer is a cancer overexpressing CCNE1.

In some aspects according to the present invention, the combination including
25 WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising topoisomerase 1 inhibitor induces cell death in a cancer cell overexpressing CCNE1, comprising contacting the cell with an effective amount of the combination, WEE1 inhibitor and/or topoisomerase 1 inhibitor.

30 In some aspects, the cancer overexpressing CCNE1 is uterine cancer, ovarian cancer, breast cancer, stomach cancer, esophageal cancer, peritoneal cancer, colorectal cancer, bladder cancer, cervical cancer, lung cancer, including SCLC and NSCLC, sarcoma, or endometrial cancer, including USC.

In some aspects according to the present invention, a cancer is treated in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of the combination including WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising topoisomerase 1 inhibitor, wherein the cancer has been previously identified as a cancer having a deficiency in the FBXW7 gene, which may be an inactivating mutation in the FBXW7 gene.

In some aspects according to the present invention, a cancer is treated in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of the combination including WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising topoisomerase 1 inhibitor, wherein the cancer has a deficiency in the FBXW7 gene, which may an inactivating mutation in the FBXW7 gene.

In some aspects according to the present invention, cell death is induced in a FBXW7-deficient cancer cell, which may be an FBXW7-mutated cancer cell, comprising contacting the cell with an effective amount of the combination including WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising topoisomerase 1 inhibitor. In some aspects, the FBXW7-deficient or FBXW7-mutated cancer is uterine cancer, colorectal cancer, breast cancer, lung cancer, including SCLC and NSCLC, esophageal cancer, stomach cancer, cervical cancer, bladder cancer or sarcoma.

In some aspects, the cancer is characterized by ATRX deficiency, which may be an ATRX-inactivating mutation. In some aspects, the ATRX-deficient cancer is breast cancer, lung cancer, including SCLC and NSCLC, melanoma or glioma, including GBM.

In some aspects, the cancer is characterized by PPP2R1A deficiency, which may be a PPP2R1A-inactivating mutation. In some aspects, the PPP2R1A deficient cancer is uterine cancer, CRC, cervical cancer, sarcoma, lung cancer, including SCLC and NSCLC, or ovarian cancer.

In some aspects, the cancer is characterized by WRN deficiency. In some aspects, the WRN-deficient cancer is CRC or breast cancer.

- 5 In some aspects, the cancer is characterized by reduction or loss of histone H3K36 trimethylation (H3K36me3). In some aspects such cancer is breast cancer, in particular triple-negative breast cancer (TNBC), pancreatic cancer, renal cell carcinoma (RCC), lung cancer, including SCLC and NSCLC, prostate cancer or high-grade glioma.

10

In some aspects of the combinations, uses or methods according to the present invention, the cancer is newly diagnosed.

- 15 In some aspects of the combinations, uses or methods according to the present invention, the cancer has progressed or recurred after initial or prior cancer treatment.

- 20 In some aspects of the combinations, the uses or the methods according to the present invention the cancer is metastatic.

20

In some aspects of the combinations, the uses or the methods according to the present invention the metastatic cancer comprises brain metastases.

PHARMACEUTICAL COMPOSITIONS AND KITS

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- The present invention also relates to a pharmaceutical composition comprising the combination including the WEE1 inhibitor as described herein, and topoisomerase 1 inhibitor or the ADC comprising the topoisomerase 1 inhibitor as described herein, as well as its use in the preparation of a medicament for treating cancer in
30 a patient in need thereof. Likewise, the present invention also relates to a pharmaceutical composition comprising the WEE1 inhibitor as described herein for use in combination with the topoisomerase 1 inhibitor or the ADC comprising the topoisomerase 1 inhibitor as described herein. In further aspects, it relates to a

pharmaceutical composition comprising the topoisomerase 1 inhibitor or the ADC comprising the topoisomerase 1 inhibitor as described herein for use in combination with the WEE1 inhibitor as described herein. Unless specified otherwise, the following indications apply equally to pharmaceutical compositions comprising the WEE1 inhibitor only, pharmaceutical compositions comprising the topoisomerase 1 inhibitor or ADC comprising the topoisomerase 1 inhibitor only, and pharmaceutical compositions comprising both the WEE1 inhibitor and the topoisomerase 1 inhibitor or ADC comprising the topoisomerase 1 inhibitor. The possible presence of the WEE1 inhibitor, or the topoisomerase 1 inhibitor or ADC comprising the topoisomerase 1 inhibitor or both is jointly referred to as “the active ingredient(s)”.

Pharmaceutical compositions of the present invention that are suitable for oral administration (oral dosage forms) may be presented in solid or liquid form. Suitable solid oral dosage forms include capsules (which may comprise powders, granules and/or minitablets and which may be soft or hard capsules), tablets, powders or granules and the like, each containing a predetermined amount of the active ingredient(s). Suitable liquid oral dosage forms include solutions, emulsions or suspensions. Pharmaceutical compositions of the present invention may also be in the form of sustained release formulations.

Any inert ingredient that is commonly used as a carrier or diluent may be used as pharmaceutically acceptable excipient in the solid oral formulations of the present invention, such as for example, a gum, a starch, a sugar, a cellulosic material, an acrylate, or mixtures thereof. Preferred diluents include, for example, microcrystalline cellulose, anhydrous lactose. The compositions may further comprise a disintegrating agent (e.g., croscarmellose sodium, sodium starch glycolate) and a lubricant (e.g., magnesium stearate), and may additionally comprise one or more additives selected from a binder (e.g., hydroxypropylcellulose), a glidant (e.g., silicon dioxide), a buffer (e.g., citric acid), a surfactant (e.g., tween 80), a solubilizing agent (e.g., cyclodextrin), a plasticizer (e.g., triacetin), an emulsifier (e.g., sodium lauryl sulfate), a stabilizing agent (e.g., povidone, ascorbic acid), a viscosity increasing agent (e.g., hydroxypropyl

methycellulose), a sweetener (e.g., sucrose), a film forming agent (e.g., cellulose based systems, polymers), a colorant (e.g., iron oxide), a flavoring agent or any combination thereof.

- 5 The oral pharmaceutical compositions of the present invention may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient(s) with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely
10 divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder,
15 lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

WEE1 inhibitor

20

The pharmaceutical composition comprising the WEE1 inhibitor may for instance have a unit dose selected from the range 10 mg to 250 mg, or 20 mg to 200 mg, such as 20, 30, 60, 80, 100, 130, 140, 150, 200 and 240 mg of active ingredient (free base). Intermediate strengths may readily be produced to cover alternative
25 dose levels.

For example, the WEE1 inhibitor is formulated in capsules, such as hard gelatin capsules comprising minitabets, each minitabets containing 10 mg of active ingredient. In some aspects, the WEE1 inhibitor is a compound of formula (I). The
30 following capsule strengths may be available: 20, 30, 60, 100, 130, 150 and 200 mg of active ingredient (free base). Intermediate capsule strengths may readily be produced to cover alternative dose levels.

In some aspects, the solid oral dosage form is packaged in a blister and/or a bottle. In some aspects, one, two, three, four, five or six unit dosage forms are administered per intake of the WEE1 inhibitor. Preferably, one or two unit dosage form(s) is administered per intake of the WEE1 inhibitor.

5

For example, when formulated as capsules containing minitables, the excipients in each minitab,let may include microcrystalline cellulose, anhydrous lactose, hydroxypropylcellulose, sodium starch glycolate, anhydrous colloidal silica and magnesium stearate. Alternative excipients may be used in an oral dosage form.

10

Topoisomerase 1 inhibitor

The topoisomerase 1 inhibitor formulation may be a sterile formulation for injection, which comprises the topoisomerase 1 inhibitor as well as one or more excipients such as water for injection, D-sorbitol, lactic acid, tartaric acid, sodium hydroxide and/or hydrochloric acid. This type of pharmaceutical composition is particularly suitable for irinotecan.

For instance, in case of irinotecan, said solution may be a concentrate that contains 10-30 mg, and especially 17.33 mg, irinotecan per 1 mL of solution. It may be diluted prior to use with solutions of dextrose or sodium chloride to contain 0.05 - 5 mg irinotecan per 1 mL of solution. The pH of the solution may for example be in the range of 3 to 4.

For instance, in case of topotecan, the formulation may be a concentrate containing 0.5 to 1.5 mg topotecan per 1 mL of solution, which may be diluted prior to use. Dilution can be effected using a solution containing sodium chloride (0.9%) or glucose (5%) to reach a final topotecan concentration between 20 and 60 microgram per 1 mL.

30

In yet further aspects, the pharmaceutical formulation of the ADC comprising the topoisomerase 1 inhibitor may be a powder for reconstituting a solution for injection. Said powder may comprise the ADC, for instance sacituzumab

govitecan, as well as excipients such as 2-(N-morpholino)ethane sulfonic acid (MES), Polysorbate 80 (E433), and Trehalose dihydrate. In other formulations, for example in connection with trastuzumab deruxtecan, the excipients may be L-histidine, L-histidine hydrochloride monohydrate, sucrose, and polysorbate 80.

5

The formulation may be reconstituted by addition of sodium chloride solution (0.9%) to generate a solution that contains for example sacituzumab govitecan in a concentration of 5 to 20 mg/mL and typically 10 mg/mL. In another aspect, the formulation is reconstituted to contain 10 to 30 mg/mL and typically 20 mg/mL of

10 trastuzumab deruxtecan.

The formulation may be provided in a vial for single use or in a multiple use container with a rubber stopper.

15 In yet further aspects, the pharmaceutical formulation of the ADC comprising the topoisomerase 1 inhibitor may be a powder comprising datopotamab deruxtecan, for reconstitution and further dilution before administration via intravenous infusion. For example, the formulation may be provided as 100 mg lyophilized powder in single-dose vials. Each 100 mg vial may be reconstituted using a sterile syringe to

20 slowly inject 5 mL of Sterile Water for Injection to obtain a final concentration of 20 mg/mL datopotamab deruxtecan. The adequate volume of reconstituted formulation for the appropriate dose may then be diluted in an infusion bag containing 100 mL of 5% Dextrose Injection.

25

Kit

The present invention also relates to a kit comprising the combination of WEE1 inhibitor and topoisomerase 1 inhibitor and/or ADC comprising topoisomerase 1

30 inhibitor, wherein the kit contains a single pharmaceutical formulation of said components together with instructions for use. In another aspect, the kit may contain in separate containers the WEE1 inhibitor or a pharmaceutical formulation comprising the same, and the topoisomerase 1 inhibitor or ADC comprising a

topoisomerase 1 inhibitor, or a pharmaceutical composition comprising the same, and optionally instructions for use in treating cancer, in particular in accordance with the uses and methods described herein. In some aspects, the kit comprises a WEE1 inhibitor, in particular the compound of formula (I), and a topoisomerase 1
5 inhibitor or ADC comprising a topoisomerase 1 inhibitor, optionally in separate containers and optionally in form of pharmaceutical formulations, as well as instructions for use in treating cancer, in particular in accordance with the uses and methods described herein. Optionally, in specific aspects, the kit may comprise, in separate dosage forms or containers, the WEE1 inhibitor, in particular
10 the compound of formula (I), as well as topoisomerase 1 inhibitor or ADC comprising a topoisomerase 1 inhibitor, in particular a topoisomerase 1-containing antibody drug conjugate which may for instance be selected from sacituzumab govitecan, sacituzumab tirumotecan, datopotamab deruxtecan, trastuzumab deruxtecan, patritumab deruxtecan, ifinatamab deruxtecan, puxitatug deruxtecan,
15 rinatabart sesutecan, labetuzumab govitecan, and raludotatug deruxtecan.

In some aspects of the present invention, the combination of the WEE1 inhibitor
20 with topoisomerase 1 inhibitor/ADC comprising topoisomerase 1 inhibitor, shows a synergistic effect in treating cancer, such as in some instances synthetic lethality.

It has been found that a WEE1 inhibitor in combination with a topoisomerase 1 inhibitor/ADC comprising a topoisomerase 1 inhibitor *in vitro* leads to a significant
25 increase in the induction of cell death. *In vivo*, a combination of WEE1 inhibitor and ADC comprising a topoisomerase 1 inhibitor is efficacious in significantly improving tumor growth inhibition, improving survival, and inhibiting or reducing metastasis e.g., to lung and/or lymph nodes. The combination was also well tolerated *in vivo*.

30

The present invention may thus have several beneficial therapeutic effects including improving tumor growth inhibition and/or improving survival, and/or

inhibiting or reducing metastasis e.g., to lung and/or lymph nodes and/or brain metastasis.

The synthetic lethality effect of the combinations disclosed herein may be particularly useful in the treatment of a disease or condition, e.g., cancer, and, in particular, those diseases or conditions harboring certain alterations or biomarkers, e.g., cancers that harbor CCNE1 amplification/overexpression, FBXW7- deficient cancers, ATRX-deficient cancers, cancers harboring a PPP2R1A-inactivating mutation, WRN-deficient cancers or cancers harboring a reduction or loss of histone H3K36 trimethylation (H3K36me3).

Aspects of the present disclosure can be further defined and illustrated by reference to the following non-limiting examples. It will be apparent to those skilled in the art that many modifications or changes, e.g. to the materials and methods described, can be practiced without departing from the scope of the present disclosure.

20

EXPERIMENTAL SECTION

Example 1: Efficacy of Compound of formula (I) in combination with topoisomerase 1 isomerase inhibitors in vitro

Activity of Compound of formula (I) in combination with SN38 or topotecan was determined in Breast (JIMT-1 HER2-low), Colorectal (CRC) (LoVo) and/or NSCLC (A549) cancer cell lines in vitro. The optimal seeding density for each cell line was determined to ensure exponential growth for the duration of the experiment. All cells in the vehicle group were sub-confluent by the end of the treatment period, as determined by visual inspection. Cells were seeded at approximately 500-2,400 cells/90ul in 96 well plates. Cells were treated with:

- either compounds in monotherapy: Compound of formula (I) (10-fold serial dilutions starting at 10uM), SN38 (5 concentrations from 100-0.4nM), or topotecan (5 concentrations from 500-2nM), or
 - a combination of Compound of Formula (I) (300nM) with SN38 at 5 different
 - 5 doses (same concentrations used for SN38 monotherapy) for 120 hours, or
 - a combination of Compound of Formula (I) (300nM) with topotecan at 5 different doses (same concentrations used for topotecan monotherapy) for 120 hours.
- Cell proliferation was then assessed by Sulforhodamine B staining and IC50s determined.

10

The IC50 curves are shown in Figure 1A for the SN38 combinations in the above-mentioned breast HER2low and CRC cell lines, and in Figure 1B for the topotecan combinations in the above-mentioned breast HER2low, CRC and NSCLC cell lines.

15

Significant synergy was observed across all cell lines tested as indicated by a reduction in IC50 values of the combination treatment compared to either monotherapy.

20 Example 2: Efficacy of Compound of formula (I) in combination with Sacituzumab govitecan (SG) in vitro

Activity of Compound of formula (I) in combination with SG was determined in GBM (D54 and U87MG), breast (MDA-MB-231, HCC38, MDA-MB-468 and BT20)

25 and colorectal (Colo205, SW480 and HCT116) cell lines in vitro.

Trop-2 determination and monotherapy dose range finding

Trop2 expression for breast cancer cell lines has been previously reported (Goldenberg et al., 2015 Trop-2 is a novel target for solid cancer therapy with

30 sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC), Oncotarget. 2015; 6:22496-22512), with MDA-MB-231 and BT20 cells described as TROP2low and MDA-MB-468 and HCC38 cells described as TROP2high.

Each of the GBM and CRC cell lines was analyzed by flow cytometry using a Trop2 antibody to determine the percentage of Trop2+ cells and surface expression level of Trop2.

- 5 Harvested cells were washed in ice-cold DPBS by centrifugation. The cells were resuspended in DPBS and transferred to a deep 96-well plate. IR Viability dye and Human TruStain FcX™ Fc Block were added to 1.0E+06 cells. After a 15-minute incubation at ambient temperature protected from light, Cell Staining Buffer was added to bind the remaining dye and the stained cells were centrifuged. The cells
10 were resuspended in Cell Staining Buffer and transferred to a new 96-well plate containing pre-diluted antibodies. The samples were incubated for 30 minutes protected from light at 4°C. The stained cells were washed with Cell Staining Buffer, resuspended in ice-cold Cell Staining Buffer, and acquired on the CytoFLEX LX Cytometer in triplicate. Analysis of Trop-2 staining was determined
15 by a Trop-2+ gate, which was placed based on the isotype control. The mean fluorescence intensity (MFI) in the AF488 channel was reported in the live cell population.

- The COLO 205-Luc cell line had the highest percentage of Trop2+ cells (98%) and
20 an MFI of 1.39E+05 in the AF488 channel. The SW480 cell line had 71% Trop2+ cells and an MFI of 4.98E+04. There were trace amounts of Trop2+ cells in the HCT 116-Luc cell line (3%). However, the D54-Luc and U87-MG-Luc cell lines had similar expression levels compared to the isotype control. Thus, following this determination of TROP2 expression HCT-116, D54 and U87-MG cells were
25 denoted as TROP2low and SW480 and COLO 205 cells denoted as TROP2high.

- SG (sacituzumab govitecan-hziy) targets the Trop-2 receptor, which is expressed on various tumor cells, and delivers SN-38, a topoisomerase I inhibitor directly to the tumors, resulting in cell death. In monotherapy, SG showed cytotoxic efficacy
30 in vitro against the five tumor lines tested, with IC50 values ranging from 0.5 to 2.5 µM. Compound of formula (I) was supplied by Debiopharm International SA and was less efficacious at tumor cell killing in vitro than SG, with IC50 values ranging from 4.1 to > 10 µM across the five cell lines in monotherapy.

Combination study

SG and Compound of formula (I) concentrations were chosen based on the results of the individual test agent dose response results.

5

Cells were resuspended in fresh growth medium to a concentration of 30,000 cells/mL. For each cell line, one hundred microliters of the cell suspension were added to each interior well (3,000 cells/well) of black-walled 96-well plates and the cells were allowed to equilibrate under normal culture conditions overnight prior to the addition of test agents. Ten microliters of each test agent in growth medium were added to each well to give final concentrations of 0.13, 0.37, 1.1, 3.3, and 10 μ M for SG and 0.62, 1.9, 5.6, 17, and 50 μ M for Compound of formula (I). Vehicle and cell free wells were also included in the assay. The dosed cells were cultured under normal conditions for 96 hours. CellTiter-Glo® 2.0 reagent (Promega Corp., Madison, WI) was added (100 μ L/well), the plate was briefly shaken on a plate shaker, then allowed to equilibrate while protected from light for 10 min at ambient temperature. Luminescence was quantified using a Cytation3 Imaging Plate Reader (Biotek Instruments) and four parameter nonlinear regression curve fitting was done using Graphpad Prism software.

20

The results are shown in Figure 2 (Breast cancer cell lines), Figure 3 (GBM cell lines) and Figure 4 (CRC cell lines). Despite the differences in TROP2 expression, a clear synergy was observed across all cell lines tested with each cell line registering a Bliss synergy score >10 indicating strong synergy (e.g. Fouquier et al., 2015, *Pharma Res Per*, 3(3), 2015, e00149, doi: 10.1002/prp2.149; original reference Bliss C. I., *Annals of Applied Biology*, Volume 26, Issue 3, August 1939, Pages 585-615), at multiple low doses of both compounds in combination. Furthermore, a dose-response effect was evident through increasing doses of the combination.

30

Example 3: In vivo efficacy of Compound of formula (I) in combination with sacituzumab govitecan (SG) in TROP2 high model of breast cancer

NSG mice were immobilized and inoculated subcutaneously in the right flank region with MDA-MB-468 breast tumor cells at 5×10^6 in 0.2 mL of PBS solution (mixed with Matrigel, 1:1) for tumor development. The randomization was performed when mean tumor size reached approximately 75-150 mm³ and randomly allocated to 4 study groups based on "Matched distribution" method/ "Stratified" method (StudyDirectorTM software, version 3.1.399.19). Date of randomization noted as Day 0. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured 2 times a week in two dimensions using a caliper, and the volume will be expressed in mm³ using the formula: " $V = (L \times W \times W)/2$ ", where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L).

The treatment with Vehicle, Compound of formula (I) (30mg/kg QD), SG (8mg/kg QW x 2 for study A or 12.5mg/kg QW x 2 for study B) and combinations were initiated immediately after grouping per study design for up to 112 days.

Tumor growth inhibition (TGI): TGI% is an indication of antitumor activity, and expressed as: $TGI (\%) = 100 \times (1 - T/C)$. T and C are the mean tumor volume (or weight) of the treated and control groups, respectively, on a given day.

In all studies, the treatments of test agent Compound of formula (I) could be tolerated by test animals, after combining with SG no obvious treatment related mice body weight loss or adverse clinical sign was observed.

In study A (Figure 5A): statistical comparisons made vs vehicle control and Cpd of formula (I) groups were made when all animals remained on study (alive), day 112 and on day 127 for comparison to SG controls. The mean tumor volume of vehicle treated group reached 1750 mm³ at Day 112. Monotherapy of Compound of formula (I) at 30 mg/kg could only bring minor anti-tumor response, TGI was 26.7% ($p > 0.05$) when compared with vehicle control group. Treatment with SG at 8 mg/kg could produce a significant but non-durable (temporary) anti-tumor

activity, with 40% complete responses at day 94. Combination Compound of formula (I) and SG resulted in improved and excellent anti-tumor activity where 90% of tumors were designated as complete regressions (tumors below quantifiable lower limit of detection). Furthermore, at day 127, the combination of
5 Compound of formula (I) and SG elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy (tumors 60% smaller than SG monotherapy) ($p < 0.01$). At day 127 the combination group of compound of formula (I) + SG retained 1 complete response whereas no complete responses remained in any monotherapy or control groups.

10

In study B (Figure 5B): statistical comparisons made vs vehicle control and Cpd of formula (I) groups were made when all animals remained on study (alive), day 94 and on day 116 for comparison to SG controls. The mean tumor volume of vehicle treated group reached 1433mm³ at day 94. Monotherapy of Compound of formula
15 (I) at 30 mg/kg could only bring minor anti-tumor response, TGI and 24% ($p > 0.05$) when compared with vehicle control group. Treatment with SG at 12.5mg/kg could produce a significant anti-tumor activity, with 25% complete responses at day 116 at 12.5mg/kg. Combination Compound of formula (I) and SG resulted in improved and excellent anti-tumor activity where 100% of tumors were designated as
20 complete regressions (tumors below quantifiable lower limit of detection). Furthermore, at day 116 the combination of Compound of formula (I) and SG elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy (tumors 94% smaller for combination of compound of formula (I) + SG vs Cpd of formula (I) monotherapy and 88% smaller
25 than SG monotherapy) ($p < 0.01$). At day 116, a complete regression rate of 75% was observed for the combination group of compound of formula (I) + SG whereas a complete regression rate of only 25% was observed in the SG monotherapy group.

30 Example 4: In vivo efficacy of Compound of formula (I) in combination with sacituzumab govitecan (SG) in TROP2 low model of breast cancer

SCID beige mice were immobilized and inoculated subcutaneously in the right flank region with MDA-MB-231-Luc-D3H2LN breast tumor cells at 2×10^6 in 0.2 mL

of PBS solution (mixed with Matrigel, 1:1) for tumor development. The randomization was performed when mean tumor size reaches approximately 75-150 mm³ and randomly allocated to 4 study groups based on "Matched distribution" method/ "Stratified" method (StudyDirectorTM software, version 3.1.399.19). Date of randomization noted as Day 0. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured 2 times a week in two dimensions using a caliper, and the volume will be expressed in mm³ using the formula: " $V = (L \times W \times W)/2$ ", where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L). Animals were imaged to monitor tumor metastasis throughout the study using an In Vivo Imaging System (IVIS) once weekly, detecting tumor bioluminescence (BLI) in photons.

The treatment with Vehicle, Compound of formula (I) (30mg/kg QD), SG (12.5mg/kg QW x 2, i.e. once weekly for 2 weeks) and combinations were initiated immediately after grouping per study design for up to 64 days.

Tumor growth inhibition (TGI): TGI % is an indication of antitumor activity, and expressed as: $TGI (\%) = 100 \times (1 - T/C)$. T and C are the mean tumor volume (or weight) of the treated and control groups, respectively, on a given day.

The treatments of test agent Compound of formula (I) could be tolerated by test animals, after combining with SG no obvious treatment related mice body weight loss or adverse clinical sign was observed.

The results are shown on Figure 6.

(Figure 6A) The mean tumor volume of vehicle treated group reached 1866 mm³ at Day 43 after randomization. Monotherapy of Compound of formula (I) at 30 mg/kg could only bring minor anti-tumor response, TGI was 12% ($p > 0.05$) when compared with control group. Treatment with SG at 12.5 mg/kg could produce mild but non-significant anti-tumor activity, TGI 26% ($p > 0.05$). After combining Compound of formula (I) and SG, improved and significant anti-tumor activity was observed with TGI of 41% ($p < 0.01$).

(Figure 6B) Furthermore, the combination of Compound of formula (I) and SG elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy ($p < 0.01$). Additionally, Compound of formula (I) produced a minor reduction in metastatic tumor growth with 12% reduction in detectable nodules within the liver, lung and lymph nodes, SG monotherapy significantly reduced detectable metastases by 25% compared to vehicle controls and combination of compound of formula (1) reduced metastatic nodules by 62% vs vehicle controls.

(Figure 6C) Additionally, treatment with SG and compound of formula (I) each resulted in a minor increase in survival (time to progression) of 16.6% and 10% respectively ($p > 0.05$), whereas combination of compound of formula (I) with SG resulted in a significant 43.3% improvement in survival ($p < 0.01$).

Example 5: In vivo efficacy of Compound of formula (I) in combination with datopotamab deruxtecan (Dato-Dxd) in TROP2 low patient derived xenograft (PDX) model of breast cancer

Nu/Nu mice were immobilized and inoculated subcutaneously in the right flank region with patient-derived breast tumor cells expressing low levels of TROP2 (188 transcripts per million [TPM] measured by NGS) in PBS solution (mixed with Matrigel, 1:1) for tumor development. The randomization was performed when mean tumor size reached approximately 164 mm³ and randomly allocated to 4 study groups based on "Matched distribution" method / "Stratified" method. Date of randomization noted as Day 0. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured 2 times a week in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: " $V = (L \times W \times W)/2$ ", where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L). Animals were imaged to monitor tumor metastasis throughout the study using an In Vivo Imaging System (IVIS) once weekly, detecting tumor bioluminescence (BLI) in photons.

The treatment with Vehicle, Compound of formula (I) (30mg/kg QD), Dato-Dxd (6mg/kg QW x 2) and combinations were initiated immediately after grouping per study design for up to 35 days.

5 Tumor growth inhibition (TGI): TGI % is an indication of antitumor activity, and expressed as: $TGI (\%) = 100 \times (1 - T/C)$. T and C are the mean tumor volume (or weight) of the treated and control groups, respectively, on a given day.

The treatments of test agent Compound of formula (I) could be tolerated by test animals, after combining with Dato-Dxd no obvious treatment-related mice body weight loss or adverse clinical sign was observed.

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The results are shown on Figure 7.

The mean tumor volume of vehicle treated group reached 1285 mm³ at Day 35 after randomization. Monotherapy of Compound of formula (I) at 30 mg/kg could only bring non-significant anti-tumor response when compared with control group.

15 Treatment with Dato-Dxd at 6 mg/kg produced significant anti-tumor activity, with all tumors regressing (TGI >100%) and 1 out of 8 tumors achieving complete regression. After combining Compound of formula (I) and Dato-Dxd, improved and significant anti-tumor activity was observed with 8/8 tumors achieving a complete response.

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Example 6: In vivo efficacy of Compound of formula (I) in combination with datopotamab deruxtecan (Dato-Dxd) in TROP2 moderate PDX model of colorectal cancer

25 Nu/Nu mice were immobilized and inoculated subcutaneously in the right flank region with patient-derived colorectal cancer cells expressing moderate levels of TROP2 (367 transcripts per million [TPM] measured by NGS) in PBS solution (mixed with Matrigel, 1:1) for tumor development. The randomization was performed when mean tumor size reached approximately 145 mm³ and randomly allocated to 4 study groups based on "Matched distribution" method/ "Stratified" method. Date of randomization noted as Day 0. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured 2 times a week in two dimensions using a caliper, and the volume was

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expressed in mm³ using the formula: " $V = (L \times W \times W)/2$ ", where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L). Animals were imaged to monitor tumor metastasis throughout the study using an In Vivo Imaging System (IVIS)

5 once weekly, detecting tumor bioluminescence (BLI) in photons.

The treatment with Vehicle, Compound of formula (I) (30mg/kg QD), Dato-Dxd (6mg/kg QW x 2) and combinations were initiated immediately after grouping per study design for up to 28 days.

10 Tumor growth inhibition (TGI): TGI % is an indication of antitumor activity, and expressed as: $TGI (\%) = 100 \times (1 - T/C)$. T and C are the mean tumor volume (or weight) of the treated and control groups, respectively, on a given day.

The treatments of test agent Compound of formula (I) could be tolerated by test animals, after combining with Dato-Dxd no obvious treatment related mice body weight loss or adverse clinical sign was observed.

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The results are shown on Figure 8.

The mean tumor volume of vehicle treated group reached 1928 mm³ at Day 14 after randomization. Monotherapy of Compound of formula (I) at 30 mg/kg could only bring minor anti-tumor response with a TGI of 38% ($p < 0.05$) when compared
20 with control group. At Day 14, treatment with Dato-Dxd at 6 mg/kg could produce a significant anti-tumor activity, TGI 74% ($p < 0.01$) when compared with control group. After combining Compound of formula (I) and Dato-Dxd, an improved and significant anti-tumor activity was observed with TGI of 86% ($p < 0.01$) at Day 14 when compared with control group. Furthermore, the combination of Compound of
25 formula (I) and Dato-Dxd elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy at day 14 ($p < 0.01$). And after 28 days of treatment, the combination of Compound of formula (I) and Dato-Dxd resulted in a TGI of 76% when compared to Dato-Dxd monotherapy ($p < 0.01$).

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Example 7: In vivo efficacy of Compound of formula (I) in combination with SG in TROP2 moderate PDX model of colorectal cancer

Nu/nu mice were immobilized and inoculated subcutaneously in the right flank region with patient-derived colorectal cancer tumor cells expressing moderate levels of TROP2 (367 transcripts per million [TPM] measured by NGS) in PBS solution (mixed with Matrigel, 1:1) for tumor development. The randomization was performed when mean tumor size reached approximately 145 mm³ and randomly allocated to 4 study groups based on "Matched distribution" method/ "Stratified" method. Date of randomization noted as Day 0. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured 2 times a week in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: " $V = (L \times W \times W)/2$ ", where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L). Animals were imaged to monitor tumor metastasis throughout the study using an In Vivo Imaging System (IVIS) once weekly, detecting tumor bioluminescence (BLI) in photons.

The treatment with Vehicle, Compound of formula (I) (30mg/kg QD), SG (12.5mg/kg QW x 4) and combinations were initiated immediately after grouping per study design for up to 33 days.

Tumor growth inhibition (TGI): TGI % is an indication of antitumor activity, and expressed as: $TGI (\%) = 100 \times (1 - T/C)$. T and C are the mean tumor volume (or weight) of the treated and control groups, respectively, on a given day.

The treatments of test agent Compound of formula (I) could be tolerated by test animals, after combining with SG no obvious treatment related mice body weight loss or adverse clinical sign was observed.

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The results are shown on Figure 9.

The mean tumor volume of vehicle treated group reached 1928 mm³ at Day 14 after randomization. Monotherapy of Compound of formula (I) at 30 mg/kg could only bring minor anti-tumor response, TGI was 38% ($p > 0.05$) when compared with control group. At Day 14, treatment with SG at 12.5 mg/kg could produce significant anti-tumor activity, TGI 73% ($p > 0.05$) when compared with control group. After combining Compound of formula (I) and SG, improved and significant anti-tumor activity was observed with TGI of 83% ($p < 0.01$) at Day 14 when

compared with control group. Furthermore, the combination of Compound of formula (I) and SG elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy at day 14 ($p < 0.01$). And after 33 days of treatment, the combination of Compound of formula (I) and SG resulted in a TGI of 65% when compared to SG monotherapy ($p < 0.01$).

Example 8: In vivo efficacy of Compound of formula (I) in combination with SG in TROP2 high PDX model of Non-small cell lung cancer (NSCLC)

Athymic nude mice were immobilized and inoculated subcutaneously in the right flank region with patient derived NSCLC tumor cells expressing high levels of TROP2 (512 transcripts per million [TPM] measured by NGS) in PBS solution (mixed with Matrigel, 1:1) for tumor development. The randomization was performed when mean tumor size reached approximately 272 mm³ and randomly allocated to 4 study groups based on "Matched distribution" method / "Stratified" method. Date of randomization noted as Day 0. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured 2 times a week in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: " $V = (L \times W \times W)/2$ ", where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L). Animals were imaged to monitor tumor metastasis throughout the study using an In Vivo Imaging System (IVIS) once weekly, detecting tumor bioluminescence (BLI) in photons.

The treatment with Vehicle, Compound of formula (I) (30mg/kg QD), SG (10mg/kg QW x 4) and combinations were initiated immediately after grouping per study design for up to 35 days.

Tumor growth inhibition (TGI): TGI % is an indication of antitumor activity, and expressed as: $TGI (\%) = 100 \times (1 - T/C)$. T and C are the mean tumor volume (or weight) of the treated and control groups, respectively, on a given day.

The treatments of test agent Compound of formula (I) could be tolerated by test animals, after combining with SG no obvious treatment related mice body weight loss or adverse clinical sign was observed.

The results are shown on Figure 10.

The mean tumor volume of vehicle treated group reached 2070 mm³ at Day 24 after randomization. Monotherapy of Compound of formula (I) at 30 mg/kg could only bring minor insignificant anti-tumor response with a TGI of 26% (p>0.05) when compared with control group. At Day 24, treatment with SG at 10 mg/kg could produce a significant anti-tumor activity, TGI 67% (p<0.01) when compared with control group. After combining Compound of formula (I) and SG, an improved and significant anti-tumor activity was observed with TGI of 100% (p<0.01) at Day 24 when compared with control group. Furthermore, the combination of Compound of formula (I) and SG elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy at day 24 (p<0.01). And after 33 days of treatment, the combination of Compound of formula (I) and SG resulted in a TGI of 76% when compared to SG monotherapy (p<0.01).

Example 9: In vivo efficacy of Compound of formula (I) in combination with SG in TROP2 high PDX model of Ovarian cancer.

Nude mice were immobilized and inoculated subcutaneously in the right flank region with patient-derived ovarian tumor cells expressing high levels of TROP2 (417 transcripts per million [TPM] measured by NGS) in PBS solution (mixed with Matrigel, 1:1) for tumor development. The randomization was performed when mean tumor size reached approximately 183 mm³ and randomly allocated to 4 study groups based on "Matched distribution" method / "Stratified" method. Date of randomization noted as Day 0. After tumor cells inoculation, the animals were checked daily for morbidity and mortality. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured 2 times a week in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: "V = (L x W x W)/2", where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L). Animals were imaged to monitor tumor metastasis throughout the study using an In Vivo Imaging System (IVIS) once weekly, detecting tumor bioluminescence (BLI) in photons.

The treatment with Vehicle, Compound of formula (I) (30mg/kg QD), SG (10mg/kg QW x 2) and combinations were initiated immediately after grouping per study design for up to 64 days.

5 Tumor growth inhibition (TGI): TGI % is an indication of antitumor activity, and expressed as: $TGI (\%) = 100 \times (1 - T/C)$. T and C are the mean tumor volume (or weight) of the treated and control groups, respectively, on a given day.

The treatments of test agent Compound of formula (I) could be tolerated by test animals, after combining with SG no obvious treatment related mice body weight loss or adverse clinical sign was observed.

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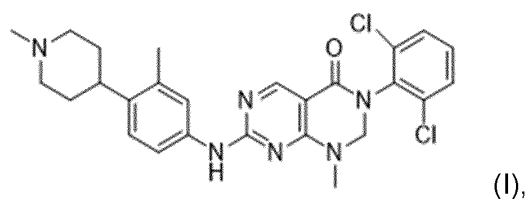
The results are shown on Figure 11.

The mean tumor volume of vehicle treated group reached 912 mm³ at Day 32 after randomization. Monotherapy of Compound of formula (I) at 30 mg/kg could only bring minor anti-tumor response, TGI was 39% ($p < 0.05$) when compared with control group. At Day 32, treatment with SG at 10 mg/kg could produce significant anti-tumor activity, TGI 76% ($p > 0.01$) when compared with control group. After combining Compound of formula (I) and SG, improved and significant anti-tumor activity was observed with TGI of 86% ($p < 0.01$) at Day 32 when compared with control group. Furthermore, the combination of Compound of formula (I) and SG elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy ($p < 0.05$) at Day 32. And after 56 days of treatment, the combination of Compound of formula (I) and SG resulted in a TGI of 68% vs SG monotherapy ($p < 0.01$).

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CLAIMS

1. Combination of a WEE1 inhibitor and at least a drug selected from a topoisomerase 1 inhibitor and an antibody-drug conjugate (ADC) comprising a topoisomerase 1 inhibitor.
2. Combination according to claim 1 for use as a medicament.
3. Combination according to claim 1 or 2 for use in treating cancer in a patient in need thereof.
4. WEE1 inhibitor for use in treating cancer in a patient in need thereof, wherein the WEE1 inhibitor is administered in combination with a topoisomerase 1 inhibitor or an ADC comprising a topoisomerase 1 inhibitor.
5. Topoisomerase 1 inhibitor for use in treating cancer in a patient in need thereof, wherein the topoisomerase 1 inhibitor is administered in combination with a WEE1 inhibitor.
6. ADC comprising a topoisomerase 1 inhibitor for use in treating cancer in a patient in need thereof, wherein the ADC is administered in combination with a WEE1 inhibitor.
7. Combination according to claim 1, combination for use according to claim 2 or 3, WEE1 inhibitor for use according to claim 4, topoisomerase 1 inhibitor for use according to claim 5, or ADC for use according to claim 6, wherein the WEE1 inhibitor is a compound of formula (I)



or a pharmaceutically acceptable salt thereof.

8. Combination according to claim 1 or 7, combination for use according to claim 2, 3 or 7, WEE1 inhibitor for use according to claim 4 or 7, topoisomerase 1 inhibitor for use according to claim 5 or 7, or ADC for use according to claim 6 or 7, wherein the topoisomerase 1 inhibitor or topoisomerase 1 inhibitor moiety in the ADC is selected from:

- camptothecin or a camptothecin derivative, preferably selected from topotecan, irinotecan, SN38, govitecan, deruxtecan (Dxd), exatecan, belotecan, silatecan, gimatecan, namitecan (ST1968), or a pharmaceutically acceptable salt thereof, or
 - 5 - an indenisoquinoline, preferably selected from indenoisoquinoline NSC 314622, indotecan (LMP-400), indimitecan (LMP-776), or a pharmaceutically acceptable salt thereof, or
 - 10 - a phenanthridine, an indolocarbazole, a β -carboline hybrid, a pyrazole-linked benzothiazole- β -naphthol derivative, a 4 β -[4'-(1-(aryl)ureido)benzamide]podophyllotoxin congener, a benzimidazole congener or a pharmaceutically acceptable salt thereof.
9. Combination according to claim 1 or 7, combination for use according to claim 2, 3 or 7, WEE1 inhibitor for use according to claim 4 or 7, or ADC for use according to claim 6 or 7, wherein the topoisomerase 1 inhibitor moiety in the ADC is selected from SN38, govitecan, deruxtecan (Dxd),
- 15 exatecan, sesutecan, belotecan, tirumotecan, samrotecan or a pharmaceutically acceptable salt thereof.
10. Combination according to any one of claims 1, 7 or 9, combination for use according to any one of claims 2, 3, 7 or 9, WEE1 inhibitor for use according to any one of claims 4, 7 or 9, or ADC for use according to any one of claims 6, 7 or 9, wherein the ADC is sacituzumab govitecan, datopotamab deruxtecan, sacituzumab tirumotecan, trastuzumab deruxtecan, patritumab deruxtecan, ifinatamab deruxtecan, puxitatug samrotecan, AZD-5335, rinatabart sesutecan, labetuzumab govitecan,
- 20 PF-08046050, M9140, raludotatug deruxtecan, ABBV-400, DS-3939, ABBV-706, BAT-8007, ACR-246, ZW-220 or a pharmaceutically acceptable salt thereof.
- 25 11. Combination for use according to any one of claims 2, 3 or 7 to 10, WEE1 inhibitor for use according to any one of claims 4 or 7 to 10, or topoisomerase 1 inhibitor for use according to any one of claims 5, 7 or 8, or ADC for use according to any one of claims 6 to 10, wherein the cancer is breast cancer, colorectal cancer, non-small-cell lung cancer (NSCLC), small cell lung cancer (SCLC), ovarian cancer, endometrial
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- 5 cancer, including uterine serous carcinoma (USC), testicular cancer, penile cancer, anal cancer, stomach cancer, bladder cancer, cervical cancer, esophageal cancer, head and neck cancer, gallbladder cancer, pancreatic cancer, prostate cancer, gastric cancer, peritoneal cancer, hepatocarcinoma, renal cell carcinoma (RCC), melanoma, soft tissue sarcoma, lymphoma or glioma, including glioblastoma.
- 10 12. Combination for use according to any one of claims 2, 3 or 7 to 11, WEE1 inhibitor for use according to any one of claims 4 or 7 to 11, or topoisomerase 1 inhibitor for use according to any one of claims 5, 7, 8 or 11, or ADC for use according to any one of claims 6 to 11, wherein the cancer is characterized by reduced expression of HER2.
- 15 13. Combination for use according to any one of claims 2, 3 or 7 to 12, WEE1 inhibitor for use according to any one of claims 4 or 7 to 12, topoisomerase 1 inhibitor for use according to any one of claims 5, 7, 8, 11 or 12, or ADC for use according to any one of claims 6 to 12, wherein the WEE1 inhibitor is administered
- 20 a. on days 1 to 3 of a 21-day cycle,
b. on days 1 to 3 and 8 to 10 of a 21-day cycle,
c. on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle,
d. on days 1 to 5 over 21-day cycle,
e. on days 1 to 5 and 8 to 12 over a 21-day cycle,
f. on days 1 to 5, 8 to 12 and 15 to 19 of a 21-day cycle,
g. on days 1 to 14 of a 21-day cycle,
h. daily over a 21-day cycle,
- 25 i. on days 1 to 5 and 8 to 10 of a 28-day cycle,
j. on days 1 to 5, 8 to 10 and 15 to 17 of a 28-day cycle
k. on days 1-3 of a 28-day cycle
l. on days 1-3 and 8-10 of a 28-day cycle,
m. on days 1-3 and 15-17 of a 28-days cycle,
- 30 n. on days 1-3, 8-10 and 15-17 of a 28-day cycle,
o. on days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle,
p. on days 1-5 of a 28-day cycle,
q. on days 1-5 and 8-12 of a 28-day cycle,

- r. on days 1-5 and 15-19 of a 28-day cycle,
 - s. on days 1-5, 8-12 and 15-19 of a 28-day cycle,
 - t. on days 1-5, 8-12, 15-19 and 22-26 of a 28-day cycle,
 - u. daily over a 28-day cycle, or
 - 5 v. on days 1, 8, 15 and 22 of a 6-week cycle.
14. Combination for use according to any one of claims 2, 3 or 7 to 13, WEE1 inhibitor for use according to any one of claims 4 or 7 to 13, topoisomerase 1 inhibitor for use according to any one of claims 5, 7, 8 or 11 to 13, or ADC for use according to any one of claims 6 to 13,
- 10 wherein the WEE1 inhibitor is administered
- a. at a dose ranging from about 30 to about 1000 mg per WEE1 inhibitor treatment day, preferably about 30 to about 720 mg per WEE1 inhibitor treatment day, and/or
 - b. orally, and/or
 - 15 c. as a single dose on a WEE1 inhibitor treatment day, and/or
 - d. at approximately the same time on each WEE1 inhibitor treatment day.
15. Combination for use according to any one of claims 2, 3, 7, 8 or 11 to 14, WEE1 inhibitor for use according to any one of claims 4, 7, 8 or 11 to
- 20 14, or topoisomerase 1 inhibitor for use according to any one of claims 5, 7, 8 or 11 to 14, wherein the topoisomerase 1 inhibitor is administered
- a. on days 1 and 15 of a 28-day cycle,
 - b. on day 1 of a 21-day cycle,
 - c. on days 1-5 of a 21-day cycle,
 - 25 d. on days 1-3 of a 21-day cycle,
 - e. on days 1, 8 and 15 of a 28-day cycle,
 - f. on days 1-5 of a 28-day cycle,
 - g. on days 1-5 and 8-12 of a 28-day cycle,
 - h. on days 1-5, 8-12 and 15-19 of a 28-days cycle,
 - 30 i. on days 1, 8, 15 and 22 of a 6-week cycle, or
 - j. on the same days as the WEE1 inhibitor treatment days, preferably as defined in claim 13.

16. Combination for use according to any one of claims 2, 3, 7 or 9 to 14, WEE1 inhibitor for use according to any one of claims 4, 7 or 9 to 14, or ADC for use according to any one of claims 6 to 14, wherein the ADC comprising a topoisomerase 1 inhibitor is administered
- 5 a. on days 1 and 8 of a 21-day cycle,
 b. on days 1 and 8 of a 28-day cycle,
 c. on days 1, 8 and 15 of a 21-day cycle,
 d. on days 1, 8 and 15 of a 28-day cycle,
 e. on days 1, 8, 15 and 22 of a 28-day cycle,
- 10 f. on day 1 of a 21-day cycle (once every three weeks), or
 g. on day 1 of a 28-day cycle (once every four weeks).
17. Combination for use according to any one of claims 2, 3 or 7 to 16, WEE1 inhibitor for use according to any one of claims 4 or 7 to 16, or topoisomerase 1 inhibitor for use according to any one of claims 5, 7, 8
- 15 or 11 to 15, or ADC for use according to any one of claims 6 to 14 or 16, wherein the combination, the WEE1 inhibitor and/or the topoisomerase 1 inhibitor and/or ADC comprising a topoisomerase 1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more 21-day cycles, over 1, 2, 3, 4, 5, 6 or more 28-day cycles, or over 1, 2, 3, 4, 5, 6 or more 6-week
- 20 cycles.
18. Combination for use according to any one of claims 2, 3 or 7 to 17, WEE1 inhibitor for use according to any one of claims 4 or 7 to 17, topoisomerase 1 inhibitor for use according to any one of claims 5, 7, 8, 11 to 15 or 17, or ADC for use according to any one of claims 6 to 14, 16
- 25 or 17, wherein the cancer is characterized by CCNE1 overexpression, WRN deficiency, ATRX deficiency, FBXW7 deficiency, PPP2R1A inactivating mutation, or reduction or loss of histone H3K36 trimethylation (H3K36me3).
19. Combination for use according to any one of claims 2, 3 or 7 to 18, WEE1 inhibitor for use according to any one of claims 4 or 7 to 18, or topoisomerase 1 inhibitor for use according to any one of claims 5, 7, 8, 11 to 15, 17 or 18, or ADC for use according to any one of claims 6 to 14, or 16 to 18, wherein the cancer is metastatic.
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20. Combination for use according to claim 19, WEE1 inhibitor for use according to claim 19, topoisomerase 1 inhibitor for use according to claim 19, or ADC for use according to claim 19, wherein the metastatic cancer comprises brain metastases.
- 5 21. Pharmaceutical composition comprising the combination according to claim 1, optionally as further specified in one or more of claims 7 to 10, or comprising the WEE1 inhibitor as specified in one or more of claims 4, 7 to 10, or the topoisomerase 1 inhibitor as specified in one or more of claims 5, 7 or 8, or the ADC as specified in one or more of claims 6, 7, 8,
- 10 9 or 10, for use in treating cancer in a patient in need thereof, wherein the use is as described in any of claims 11 to 20.
22. Kit comprising the combination according to claim 1 optionally as further specified in one or more of claims 7 to 10, wherein the WEE1 inhibitor and the at least one of topoisomerase 1 inhibitor or ADC comprising a
- 15 topoisomerase 1 inhibitor are provided in separate dosage forms and/or containers, optionally for use in treating cancer in a patient in need thereof, wherein the use is as described in any of claims 11 to 20.

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