

COMBINATION OF A WEE1 INHIBITOR AND A PKMYT1 INHIBITOR

FIELD OF THE INVENTION

The present invention generally relates to the combination of a WEE1 inhibitor and
5 a PKMYT1 inhibitor. More specifically, the present invention relates to the use of a
combination of a WEE1 inhibitor and a PKMYT1 inhibitor to treat cancer in patients
in need thereof.

BACKGROUND

10 DNA is continuously subjected to both endogenous insults (e.g., stalled replication
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
15 such as cancer. These mechanisms are collectively referred to as the DNA 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
20 mutations and as such, rely on the G2 checkpoint to make the necessary 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
25 approaches. Nonetheless, there is still a need for improved cancer 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.

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SUMMARY OF THE INVENTION

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

The present invention relates to a combination of a WEE1 inhibitor and a PKMYT1 inhibitor. It is to be understood that any reference to a WEE1 inhibitor or a PKMYT1 inhibitor also encompasses the pharmaceutically acceptable salt thereof, even if not
10 explicitly mentioned as such.

The present invention further relates to a combination of a WEE1 inhibitor and a PKMYT1 inhibitor for use as a medicament.

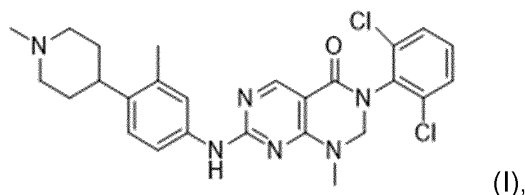
15 The present invention further relates to a combination of a WEE1 inhibitor and a PKMYT1 inhibitor for use in treating cancer in a patient in need thereof.

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
20 combination with a PKMYT1 inhibitor.

The present invention further relates to a PKMYT1 inhibitor for use in treating cancer in a patient in need thereof, wherein the PKMYT1 inhibitor is administered in combination with a WEE1 inhibitor.

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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 administered

- 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,
- i. on days 1 to 5, 8 to 10 and 15 to 17 of a 28-day cycle,
- j. on days 1 to 5 of a 28-day cycle,
- k. on days 1 to 5 and 8 to 10 of a 28-day cycle,
- 15 l. on days 1 to 5 and 8 to 12 of a 28-day cycle,
- m. on days 1 to 5, 8 to 12 and 15 to 19 of a 28-day cycle,
- n. on days 1 to 3, 8 to 10 and 15 to 17 of a 28-day cycle,
- o. on days 1 to 3 and 8 to 10 of a 28-day cycle, or
- p. on days 1 to 3 of a 28-day cycle.

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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
- 25 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.

30 In some aspects of the present invention, the PKMYT1 inhibitor is administered

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- a. for 7 consecutive or non-consecutive days or more, such as 14 consecutive or non-consecutive days or more or every day of a 21-day cycle, and/or
 - b. on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle, and/or
 - c. on the same days as the WEE1 inhibitor treatment days, preferably as defined in any of aspects (a) to (p) defined in relation to the 21-day cycles or 28-day cycles of the WEE1 inhibitor above, and/or
 - d. on days different from the WEE1 inhibitor treatment days of a 21-day or a 28-day cycle, wherein said WEE1 inhibitor treatment days of a 21-day or a 28-day cycle may in particular be the WEE1 inhibitor treatment days specified herein, e.g., under items (a) to (p) above, and/or
 - e. such that the PKMYT1 inhibitor and the WEE1 inhibitor are administered in an alternating manner wherein one of the drugs is administered for x days and then paused for y days and the other drug is paused during the x days and administered during the y days, followed by another period of x and y days, and so forth, wherein x and y are independently selected from 1, 2, 3, 4, 5, 6 and 7, such as 1, 2, 3 or 4, wherein in some aspects x and y are selected such that $x+y=7$, for instance an administration scheme consisting of three days administration of the WEE1 inhibitor and then four days administration of the PKMYT1 inhibitor and so forth (or vice versa); in other aspects x and y may be the same and both are jointly selected from 1, 2, 3, 4, 5, 6 and 7 and especially 1, 2 or 3, such as three days administration of the WEE1 inhibitor and then three days administration of the PKMYT1 inhibitor and so forth.

In some aspects of the present invention, the PKMYT1 inhibitor is administered

- 5 a. at a dose ranging from about 60 mg to about 400 mg, or about 100 mg to about 300 mg or at a dose of about 240 mg per PKMYT1 inhibitor treatment day, and/or
- b. once or twice a day per PKMYT1 inhibitor treatment day, and/or
- c. once or twice a day at a dose selected from about 30 to about 100 mg, or about 60 to about 100 mg, or about 80 to about 100 mg per administration and/or
- 10 d. at a dose ranging from about 80 to about 100 mg per administration, twice a day, per PKMYT1 inhibitor treatment day, and/or,
- e. daily at a dose of 240 mg per PKMYT1 inhibitor treatment day, and/or
- f. orally.

- 15 In some aspects of the present invention, the combination, the WEE1 inhibitor and/or the PKMYT1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more 21-day cycles, or over 1, 2, 3, 4, 5, 6 or more 28-day cycles.

- 20 In some aspects of the present invention, the cancer is ovarian cancer, primary peritoneal cancer, fallopian tube cancer, epithelial ovarian cancer (EOC) including serous EOC, endometrioid EOC, or clear cell EOC, stomach cancer, colorectal cancer, bladder cancer, cervical cancer, esophageal cancer, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), breast cancer, soft tissue sarcoma, glioma or endometrial cancer including uterine serous carcinoma (USC).

- 25 In some aspects of the present invention, the cancer is characterized by CCNE1 overexpression and/or CCNE1 amplification.

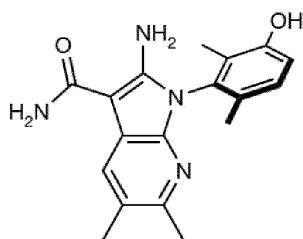
- 30 In some aspects of the present invention, the cancer is characterized by ATRX deficiency, FBXW7 inactivating mutation or PPP2R1A inactivating mutation.

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

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

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In some aspects of the present invention, the PKMYT1 inhibitor is a compound of formula (II),



(II),

or a pharmaceutically acceptable salt thereof.

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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 PKMYT1 inhibitor as specified herein, for use in treating cancer in a patient in need thereof, wherein the use is as described herein.

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The present invention further relates to a kit comprising the combination as further specified herein, wherein the WEE1 inhibitor and PKMYT1 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.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts results obtained in Example 1: bar graph showing relative PKMYT1 expression in A549 cells transfected with 25 nM, 50 nM or 100 nM PKMYT1 siRNA or scrambled siRNA.

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Figure 2 depicts results obtained in Example 2: (A) representative bright field pictures of cells 72h post-transfection of A549 WT cells or A549 WEE1 KO cells with 50 nM PKMYT1 siRNA or scrambled siRNA, and (B) graph showing quantification of live cells per well by flow cytometry 72h and 96h post-transfection.

Figure 3 depicts results obtained in Example 3 (cell line derived xenograft model of ovarian cancer): tumor volume over time for the various treatment groups (left graph), and mean body weight of the animals over time (right graph).

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Figure 4 depicts results obtained in Example 4 (cell line derived xenograft model of breast cancer): graph showing tumor volume over time for the various treatment groups.

15 Figure 5 depicts results obtained in Example 5 (PDX model of breast cancer): graph showing tumor volume over time for the various treatment groups.

Figure 6 depicts results obtained in Example 5 (PDX model of ovarian cancer): graph showing tumor volume over time for the various treatment groups.

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DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

25 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 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.

- 5 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.

10 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 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).

- 15 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 assay or an IC₅₀ of <100nM in an enzyme profiling assay. The compound of formula (I) herein is an example of a WEE1 inhibitor. The “WEE1 inhibitor” as used herein typically exhibits selectivity in the sense that it does not inhibit PKMYT1 to such an
20 extent that the compound might also be identified as a PKMYT1 inhibitor in accordance with the definition below.

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
25 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 concentration
30 ratios (see e.g. Example 1 of WO 2024/170480). Compound of formula (I) may thus be referred to as a brain penetrant WEE1 inhibitor.

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
5 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
10 measured and evaluated using blood, urine, cells or tissues.

It is to be noted that for some biomarkers used in the present invention (such as CCNE1, FBXW7 or PPP2R1A), the same name or acronym is used for the gene and the resulting gene product (e.g. mRNA and/or protein). The person of skill in the
15 art will understand that an amplification, a mutation or deletion of a given biomarker concerns the biomarker gene, while the mention of expression levels (e.g. reduced expression or overexpression) refers to a corresponding biomarker gene product.

The term “PKMYT1” or “Myt1,” as used herein, refers to membrane-associated tyrosine and threonine- specific cdc2-inhibitory kinase (Myt1) (Gene name PKMYT1).
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The term “PKMYT1 inhibitor” or “Myt1 inhibitor,” as used herein, represents a compound that upon contacting the enzyme Myt1, whether in vitro, in cell culture, or
25 in an animal, reduces the activity of Myt1, such that the measured Myt1 IC₅₀ is 100 nM or less (e.g., 30 nM or less, 10 nM or less, or 3 nM or less) and could be as low as 100 pM or 10 pM. More preferably, the Myt1 IC₅₀ is less than 20 nM (e.g., 1 nM to 20 nM). The Myt1 IC₅₀ value may be determined by means of the PKMYT1 cell-based activity assay as described in J. Szychowski et al. in J. Med. Chem. 2022,
30 65(15), 10251-10284, doi:10.1021/acs.jmedchem.2c00552. The PKMYT1 inhibitor may also be a dual inhibitor, which inhibits both WEE1 and PKMYT1.

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.

- 5 CCNE1 amplification is present in a cell that exhibits a copy number 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
- 10 CCNE1 protein stability irrespective of copy number 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.
- 15 For example, immunohistochemical (IHC) detection 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
- 20 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> (<https://www.sciencedirect.com/science/article/pii/S0023683722010194>).

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The term "FBXW7" is used hereinto refer to F-box/WD Repeat-Containing Protein 7 gene, transcript, or protein. An FBXW7-mutated gene, sometimes referred to herein as an FBXW7 gene having an inactivating mutation, is a gene, which fails to produce a functional FBXW7 protein or produces reduced quantities of FBXW7 protein in a

30 cell.

The term "PPP2R1A," as used herein, refers to Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform, which is an enzyme that in humans is encoded by the PPP2R1A gene. This gene encodes a constant regulatory subunit of protein phosphatase 2. Protein phosphatase 2 is one of the
5 four major Ser/Thr phosphatases, and it is implicated in the negative control of cell growth and division. It consists of a common heteromeric core enzyme, which is composed of a catalytic subunit and a constant regulatory subunit, that associates with a variety of regulatory subunits. The constant regulatory subunit A serves as a scaffolding molecule to coordinate the assembly of the catalytic subunit and a
10 variable regulatory B subunit. This gene encodes an alpha isoform of the constant regulatory subunit A. 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 PPP2R1A protein or produces reduced quantities of PPP2R1A protein in a cell.

15

Gene mutations or amplifications may for example be assessed by Next Generation Sequencing (NGS) and reduced expression or overexpression of a given gene product may be assessed by NGS, qPCR, western blot, or IHC techniques.

20 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.

25 A "treatment cycle" of e.g. 21 days refers to a time period of e.g. 21 consecutive days 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. However, it is also
30 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 PKMYT1 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, comprising at least the WEE1 inhibitor and PKMYT1 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 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. For instance, the WEE1 inhibitor and PKMYT1 inhibitor may be administered in combination by administering the WEE1 inhibitor first and the PKMYT1 inhibitor later, or vice versa.

- 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
- 5 those already diagnosed with or suspected of having the disorder. In certain aspects, a subject is successfully "treated" for cancer according to the methods of the present invention if the 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;
- 10 inhibition of or an absence of tumor metastasis; inhibition of or 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
- 15 non-tumorigenic state; as well as increased 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
- 20 patients, successful 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.
- 25 As used herein when referring to cancer or to a 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 period of improvement, stabilization or disease absence.

As used herein when referring to cancer or to a 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 appearance of new lesions.

- 5 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.

As used herein, the term "PKMYT1 inhibitor treatment day" refers to a day on which the PKMYT1 inhibitor is administered according to the present invention.

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As used herein, the term "WEE1-PKMYT1 combination treatment day" refers to a day on which the WEE1 inhibitor and the PKMYT1 inhibitor are administered according to the present invention.

- 15 As used herein, the term "therapeutically effective amount" refers to an amount of a drug effective to "treat" a disease or disorder in a subject or patient. In the case of cancer, the therapeutically effective amount of the drug 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.,
20 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),
25 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".

- 30 In some aspects, the term "therapeutically effective amount" of a given drug when used in monotherapy, such as a "WEE1 therapeutically effective amount", a

“PKMYT1 inhibitor therapeutically effective amount”, or a “combination therapeutically effective amount”, refers to an amount of a drug or combination of drugs effective to “treat” a disease or disorder in a subject or patient, whilst keeping an acceptable safety profile. In some aspects, when administering a WEE1 inhibitor and PKMYT1 inhibitor in combination, their respective therapeutically effective amounts may be referred to as the “WEE1-PKMYT1-combination therapeutically effective amount”. In cases where the WEE1 inhibitor is a compound of formula (I), the “WEE1 therapeutically effective amount” of the compound of formula (I) when administered as monotherapy may be different from the “WEE1-PKMYT1-combination therapeutically effective amount”. In the case of cancer, the therapeutically effective amount of the drug 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, 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
5 would be administered.

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

10 It is to be understood that any reference to a WEE1 inhibitor or a PKMYT1 inhibitor also encompasses the pharmaceutically acceptable salt thereof, even if not explicitly mentioned as such.

Information introduced in the present disclosure by the wording „in some aspects“,
15 “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, 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
20 or even contradictory or mutually exclusive, so that the resulting combined information would be inconsistent, unclear and/or not technically meaningful.

COMBINATION

25 The present invention relates to a combination of a WEE1 inhibitor and a PKMYT1 inhibitor.

The present invention further relates to a combination of a WEE1 inhibitor and a PKMYT1 inhibitor for use as a medicament. The present invention also relates to a
30 method of using a combination of a WEE1 inhibitor and a PKMYT1 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 PKMYT1 inhibitor, or a therapeutically effective amount of the WEE1 inhibitor and the PKMYT1 inhibitor.

- 5 The present invention relates to a combination of a WEE1 inhibitor or a pharmaceutically acceptable salt thereof, and a PKMYT1 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 PKMYT1 inhibitor herein.

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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In some aspects of the present invention, the WEE1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and the PKMYT1 inhibitor is a compound of formula (II) or a pharmaceutically acceptable salt thereof.

20 ***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 PKMYT1 inhibitor.

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The present invention relates to a PKMYT1 inhibitor for use in treating cancer in a patient in need thereof, wherein the PKMYT1 inhibitor is administered in combination with a WEE1 inhibitor.

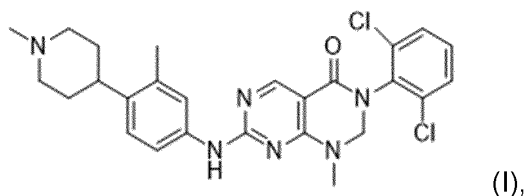
METHODS

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 PKMYT1 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 PKMYT1 inhibitor in the treatment of cancer may be understood as relating to the method for treatment of cancer, and vice versa.

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 or combination.

SPECIFIC COMPOUNDS

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

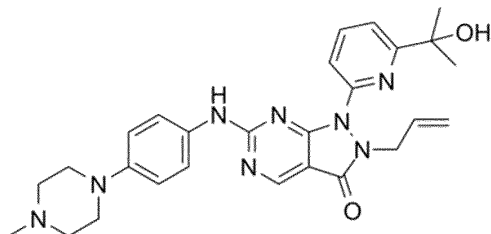


or a pharmaceutically acceptable salt thereof.

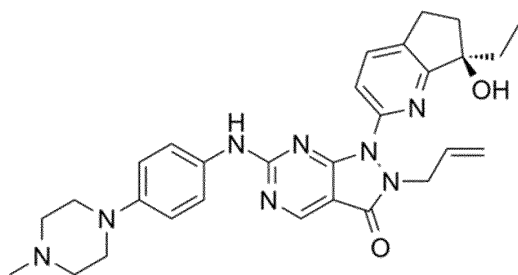
The compound of formula (I) is a selective WEE1 inhibitor.

In some aspects, the WEE1 inhibitor is any compound described in the patent applications WO2018090939, WO2022155202, WO2022256680, 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:

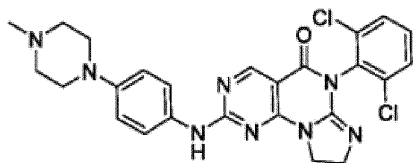


, also known as AZD-1775 (adavosertib);

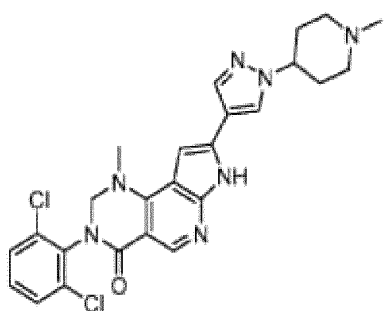


, also known as Zn-C3 (azenosertib);

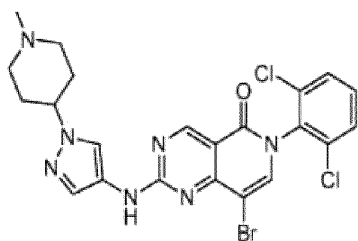
5



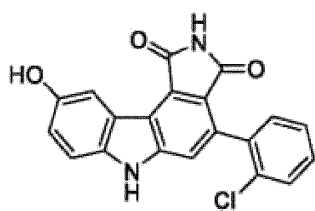
, also known as IMP7068 (as described in WO2018090939);



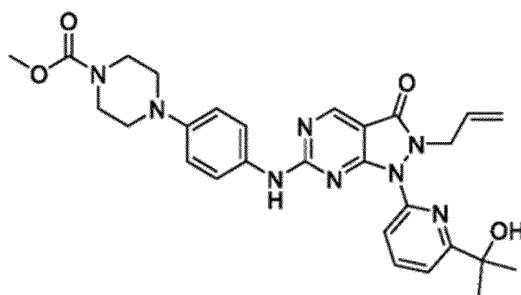
10 , also known as STC-8123 (as described in WO2022155202);



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

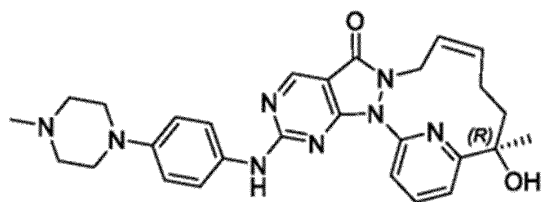


, also known as PD0407824;

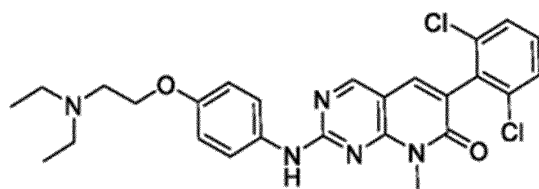


5

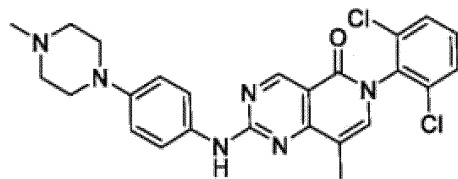
, also known as CJM061;



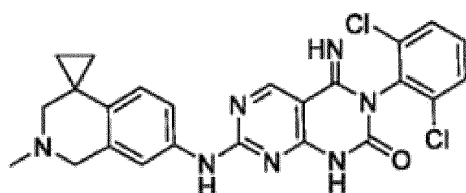
, also known as SC0191;



, also known as PD0166285;



(as described in WO2013126656), or

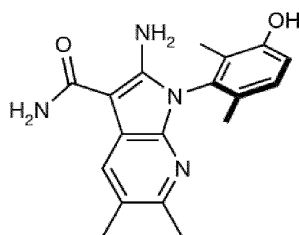


(as described in WO2008153207).

- 5 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 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>.

10

In some aspects of the present invention, the PKMYT1 inhibitor is a compound of formula (II)



(II),

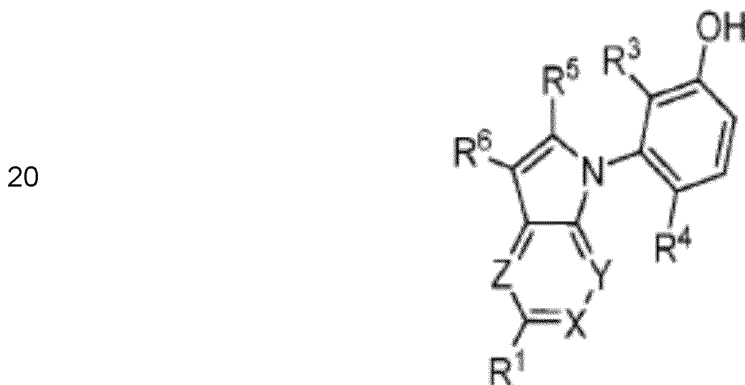
- or a pharmaceutically acceptable salt thereof. The compound of formula (II) may
15 also be referred to as lunresertib or RP-6306.

In some aspects, the PKMYT1 inhibitor is any compound described in J. Szychowski et al. in J. Med. Chem. 2022, 65(15), 10251-10284, doi:10.1021/acs.jmedchem.2c00552 and in patent application WO2021/195781 A1, each of which is fully incorporated herein by reference. In further aspects, the
5 PKMYT1 inhibitor is any compound described in the patent applications WO2023/022659 A1 (and especially the inhibitors described in the section "Therapeutic agents" and in claim 39 thereof), WO 2023/155892 A, WO 2023/155871 A, WO 2023/155870 A, WO 2024/112853 A1 or WO 2024/137671 A1, each of which is fully incorporated herein by reference. In further
10 aspects, the PKMYT1 inhibitor is AST-NS2301 of Allist Pharmaceuticals, ACR-2316 of Acrivon Therapeutics, EVT-0002518 of Evariste or XL495 of Exelixis.

In some aspects, the PKMYT1 inhibitor is as described in claim 1 of WO2021/195781 A1, which reads as follows:

15

A compound of the following formula



25

or a pharmaceutically acceptable salt thereof, wherein each of X, Y, and Z is independently N or CR²;

R¹ and each R² are independently hydrogen, optionally substituted C1-6 alkyl, optionally substituted C2-6 alkenyl, optionally substituted C2-6 alkynyl, optionally
30 substituted C3-8 cycloalkyl, optionally substituted C3-8 cycloalkenyl, optionally substituted C2-9 heterocyclyl, optionally substituted C2-9 heterocyclyl C1-6 alkyl,

optionally substituted C6-10 aryl, optionally substituted C1-9 heteroaryl, optionally substituted C1-9 heteroaryl C1-6 alkyl, halogen, cyano, $-N(R^7)_2$, $-OR^7$, $-C(O)N(R^8)_2$, $-SO_2N(R^8)_2$, $-SO_2R^{7A}$, or $-Q-R^{7B}$; or R^1 combines with one R^2 that is vicinal to R^1 to form an optionally substituted C3-6 alkylene;

5 each of R^3 and R^4 is independently optionally substituted C1-6 alkyl or halogen;

R^5 is H or $-N(R^7)_2$;

R^6 is $-C(O)NH(R^8)$, $-C(O)R^{7A}$, or $-SO_2R^{7A}$;

each R^7 is independently hydrogen, optionally substituted C1-6 alkyl, optionally substituted C6-10 aryl C1-6 alkyl, optionally substituted C3-8 cycloalkyl, optionally

10 substituted C6-10 aryl, optionally substituted C2-9 heterocyclyl, optionally substituted C1-9 heteroaryl, optionally substituted C1-9 heteroaryl C1-6 alkyl, or $-SO_2R^{7A}$; or two R^7 groups, together with the atom to which both are attached, combine to form an optionally substituted C2-9 heterocyclyl;

each R^{7A} is independently optionally substituted C1-6 alkyl, optionally substituted

15 C3-8 cycloalkyl, or optionally substituted C6-10 aryl;

each R^{7B} is independently hydroxyl, optionally substituted C1-6 alkyl, optionally substituted C6-10 aryl, optionally substituted C2-9 heterocyclyl, optionally substituted C1-9 heteroaryl, $-N(R^7)_2$, $-C(O)N(R^8)_2$, $-SO_2N(R^8)_2$, $-SO_2R^{7A}$, or optionally substituted alkoxy;

20 each R^8 is independently hydrogen, optionally substituted C1-6 alkyl, optionally substituted C2-6 alkoxyalkyl, optionally substituted C6-10 aryl C1-6 alkyl, optionally substituted C6-10 aryl, optionally substituted C3-8 cycloalkyl, or optionally substituted C1-9 heteroaryl; or two R^8 , together with the atom to which they are attached, combine to form an optionally substituted C2-9 heterocyclyl;

25 Q is optionally substituted C1-6 alkylene, optionally substituted C2-6 alkenylene, optionally substituted C2-6 alkynylene, optionally substituted C3-8 cycloalkylene, optionally substituted C3-8 cycloalkenylene optionally substituted C6-10 arylene, optionally substituted C2-9 heterocyclylene, or optionally substituted C1-9 heteroarylene.

30

The compound of formula (I) is a WEE1 inhibitor. The compound of formula (II) is a PKMYT1 inhibitor. In some aspects, an N-oxide or N-oxide derivative of the compound of formula (I) and/or formula (II) may be used.

5 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 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
10 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 PKMYT1 inhibitor is a compound
15 of formula (II), 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 PKMYT1 inhibitor being a compound of formula (II), or a pharmaceutically acceptable salt thereof.

20

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
25 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
30 molecular weight of the compound in said salt form. 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 salt form.

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 PKMYT1 inhibitor described herein are administered orally.

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

- 10 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,
- 15 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, 8 to 10 and 15 to 17 of a 28-day cycle,
- j. on days 1 to 5 of a 28-day cycle,
- 20 k. on days 1 to 5 and 8 to 10 of a 28-day cycle,
- l. on days 1 to 5 and 8 to 12 of a 28-day cycle,
- m. on days 1 to 5, 8 to 12 and 15 to 19 of a 28-day cycle,
- n. on days 1 to 3, 8 to 10 and 15 to 17 of a 28-day cycle,
- o. on days 1 to 3 and 8 to 10 of a 28-day cycle, or
- 25 p. on days 1 to 3 of a 28-day cycle.

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

- 30 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. daily, 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 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, such as at a dose of about 200 mg or about 150 mg per
10 WEE1 inhibitor treatment day. For example, the WEE1 inhibitor may be administered as a single dose on a WEE1 inhibitor treatment day.

In some aspects, the WEE1 inhibitor is administered at approximately the same time on each WEE1 inhibitor treatment day such as at the same time $\pm$ about 60 min,
15 preferably $\pm$ 60 min on each WEE1 inhibitor treatment day.

In some aspects, the WEE1 inhibitor and/or the PKMYT1 inhibitor is administered after fasting, preferably for 4 hours. In the same or other aspects, the combination, the WEE1 inhibitor and/or the PKMYT1 inhibitor administration may be followed by
20 fasting, preferably for 2 hours.

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 inhibitor precedes administration of the PKMYT1 inhibitor. For example, on a WEE1
25 inhibitor treatment day, PKMYT1 inhibitor administration is initiated about 5 minutes or more, such as 30 minutes or more, and 1 hour or less, such as 4 hours or less, after WEE1 inhibitor administration. In some aspects, the time period between WEE1 inhibitor administration and PKMYT1 inhibitor administration may be any of the periods from 5 min to 240 min, 15 min to 180 min, or 30 min to 120 min. In further
30 aspects, the two drugs may be administered approximately at the same time, for

example the time period between WEE1 inhibitor administration and PKMYT1 inhibitor administration may be 5 minutes to 30 minutes or 5 minutes to 15 minutes.

5 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 PKMYT1 inhibitor precedes administration of the WEE1 inhibitor. For example, on a WEE1 inhibitor treatment day, PKMYT1 inhibitor administration is initiated about 5 minutes or more, such as 30 minutes or more, and 1 hour or less, such as 4 hours or less, before WEE1 inhibitor administration. In some aspects, the time period between
10 WEE1 inhibitor administration and PKMYT1 inhibitor administration may be any of the periods from 5 min to 240 min, 15 min to 180 min, or 30 min to 120 min. In further aspects, the two drugs may be administered approximately at the same time, for example the time period between PKMYT1 inhibitor administration and WEE1 inhibitor administration may be 5 minutes to 30 minutes or 5 minutes to 15 minutes.

15

In some aspects of the combinations, the uses or the methods according to the present invention, the WEE1 inhibitor and the PKMYT1 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.

20

In some aspects of the combinations, the uses or the methods according to the present invention, the combination, the WEE1 inhibitor and/or the PKMYT1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more cycles.

25 In some aspects of the combinations, the uses or the methods according to the present invention, the combination, the WEE1 inhibitor and/or the PKMYT1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more 21-day cycles or 28-day cycles. Typically, there are no breaks between any consecutive cycles, i.e. the day following a prior 21-day or 28-day cycle may be the first day of the consecutive cycle.

30

In some aspects of the combinations, the uses or the methods according to the present invention, the PKMYT1 inhibitor is administered

- a. for 7 consecutive or non-consecutive days or more, such as 14 consecutive or non-consecutive days or more or every day of a 21-day cycle, and/or
- b. on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle, and/or
- c. on the same days as the WEE1 inhibitor treatment days, preferably as defined in any of scheme aspects (a) to (p) described herein in relation to the WEE1 inhibitor administration scheme and/or
- d. on days different from the WEE1 inhibitor treatment days of a 21-day or a 28-day cycle, wherein said WEE1 inhibitor treatment days of a 21-day or a 28-day cycle may in particular be the WEE1 inhibitor treatment days specified herein, e.g., under items (a) to (p) above, and/or
- e. such that the PKMYT1 inhibitor and the WEE1 inhibitor are administered in an alternating manner wherein one of the drugs is administered for x days and then paused for y days and the other drug is paused during the x days and administered during the y days, followed by another period of x and y days, and so forth, wherein x and y are independently selected from 1, 2, 3, 4, 5, 6 and 7, such as 1, 2, 3 or 4, wherein in some aspects x and y are selected such that $x+y=7$, for instance an administration scheme consisting of three days administration of the WEE1 inhibitor and then four days administration of the PKMYT1 inhibitor and so forth (or vice versa); in other aspects x and y may be the same and both are jointly selected from 1, 2, 3, 4, 5, 6 and 7 and especially 1, 2 or 3, such as three days administration of the WEE1 inhibitor and then three days administration of the PKMYT1 inhibitor and so forth.

In some aspects of the combinations, the uses or the methods according to the present invention, the PKMYT1 inhibitor is administered

- a. at a dose ranging from about 60 mg to about 400 mg, or about 100 mg to about 300 mg or at a dose of about 240 mg per PKMYT1 inhibitor treatment day, and/or
- b. once or twice a day per PKMYT1 inhibitor treatment day, and/or
- 5 c. once or twice a day at a dose selected from about 30 to about 100 mg, or about 60 to about 100 mg, or about 80 to about 100 mg per administration and/or
- d. at a dose ranging from about 80 to about 100 mg per administration, twice a day, per PKMYT1 inhibitor treatment day, and/or,
- 10 e. daily at a dose of 240 mg per PKMYT1 inhibitor treatment day, and/or
- f. orally.

In some aspects of the combinations, the uses or the methods according to the present invention, the PKMYT1 inhibitor is administered orally at a dose of about 40
15 mg, about 60 mg, about 80 mg or about 100 mg per administration, twice a day.

In a specific aspect, the WEE1 inhibitor and the PKMYT1 inhibitor are administered according to one of the following options:

- A. both the WEE1 inhibitor and the PKMYT1 inhibitor are administered on days
20 1-3, 8-10 and 15-17 of a 21-day cycle,
- B. both the WEE1 inhibitor and the PKMYT1 inhibitor are administered on days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle,
- C. the WEE1 inhibitor is administered daily and the PKMYT1 inhibitor is administered on days 1-3, 8-10 and 15-17 of a 21-day cycle,
- 25 D. the WEE1 inhibitor is administered daily and the PKMYT1 inhibitor is administered on days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle,
- E. the WEE1 inhibitor is administered on days 1-3 and 8-10 of a 21-day cycle and the PKMYT1 inhibitor is administered on days 1-3, 8-10 and 15-17 of a 21-day cycle, or
- 30 F. both the WEE1 inhibitor and the PKMYT1 inhibitor are administered on days 1-3 and 15-17 of a 28-day cycle.

In each of the above options A to F, the WEE1 inhibitor and the PKMYT1 inhibitor are each administered either once or twice per administration day. Once or twice administration per administration day may be selected independently for the WEE1 inhibitor and the PKMYT1 inhibitor. For instance, in a specific aspect in connection
5 with each of the above options A to F, the WEE1 inhibitor is administered once per WEE1 inhibitor treatment day while the PKMYT1 inhibitor is administered twice per PKMYT1 inhibitor treatment day.

In a further specific aspect, the WEE1 inhibitor and the PKMYT1 inhibitor are both
10 administered daily. The duration of this administration is not particularly limited other than by the occurrence of serious adverse effects. It can for instance be 1, 2, 3, 4, 5, 6 or more 21-day cycles, or 1, 2, 3, 4, 5, 6 or more 28-day cycles or any other duration.

15 In some aspects, the combination, the WEE1 inhibitor and/or the PKMYT1 inhibitor is administered on days 1, 2 and 3 of a 21-day cycle. The combination, the WEE1 inhibitor and/or the PKMYT1 inhibitor may also be administered on days 1, 2, 3 and 8, 9, 10 of a 21-day cycle.

20 In some aspects, the WEE1 inhibitor is administered daily and the PKMYT1 inhibitor is administered on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle.

In some aspects, the WEE1 inhibitor is administered on days 1 to 3 and 8 to 10 of a 21-day cycle and the PKMYT1 inhibitor is administered on days 1 to 3, 8 to 10 and
25 15 to 17 of a 21-day cycle.

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 PKMYT1 inhibitor.

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, 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 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, 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.

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 150, about 200, about 300, about 400 or about 520 mg of free base per WEE1 inhibitor treatment day.

5

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,
10 450, 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.

15 In some aspects, a WEE1 therapeutically effective amount or a WEE1 combination therapeutically effective amount may be administered.

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

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

In some aspects, the WEE1 inhibitor is administered on Days 1, 2 and 3 of a 21-day
25 cycle. In other 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, 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-
30 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 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.

- 5 In some aspects, the WEE1 inhibitor may be administered on Days 1, 2 and 3 of a 21-day cycle at the doses per WEE1 inhibitor treatment day indicated above. In some aspects, the WEE1 inhibitor may be administered on Days 1, 2, 3 and 8, 9, 10 of a 21-day cycle at the doses per WEE1 inhibitor treatment day indicated above.
- 10 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, patient's
- 15 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 present invention, the WEE1 inhibitor is administered at approximately the same time on each WEE1 inhibitor treatment day, e.g. at the
- 20 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 5 a.m and noon.

- In some aspects of the uses or methods according to the present invention, the
- 25 compound of WEE1 inhibitor administered after fasting, preferably after a fasting period of 4 hours. In the same or other aspects, the WEE1 inhibitor administration may be followed by fasting, preferably followed by 2 hours of fasting.

- In alternative aspects of the uses and methods according to the present invention,
- 30 the WEE1 inhibitor is administered in a fed state.

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

- 5 In some aspects of the methods of the present invention, the PKMYT1 inhibitor is used in a therapeutically effective amount for the intended purpose.

In some aspects, a PKMYT1 inhibitor therapeutically effective amount, or a PKMYT1 inhibitor combination therapeutically effective may be administered.

10

In some aspects, the PKMYT1 inhibitor may be administered on the same days as the WEE1 inhibitor, such as on the same days of a 21-day cycle or 28-day cycle, or in a different schedule, as defined below.

- 15 A PKMYT1 inhibitor can be administered to the patient in a single dose or in multiple doses. Said multiple doses may be administered with any time interval between administrations, ranging from 1-24 hours, 1-7 days, 1-4 weeks, or 1-12 months. The PKMYT1 inhibitor may be administered according to a schedule. In other aspects, the PKMYT1 inhibitor may be administered without a predetermined schedule. The
20 PKMYT1 inhibitor may for instance be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per day, every 2nd, 3rd, 4th, 5th, or 6th day, 1, 2, 3, 4, 5, 6, or 7 times per week, 1, 2, 3, 4, 5, or 6 times per month, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per year. In certain aspects, it is possible to administer specific dosage regimes specifically adjusted according to the individual patient's needs and the
25 professional judgment of the person administering or supervising the administration of the compositions.

- An effective amount of the PKMYT1 inhibitor may be, for example, a total daily dosage ranging from 0.05 mg to 3000 mg. More specific dose ranges may include,
30 for example, from 10 to 1000 mg (e.g., 50-800 mg). In some aspects, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or

1000 mg of the PKMYT1 inhibitor is administered. Alternatively, the dosage amount can be calculated using the body weight of the patient. Of course, the attending physician will determine the appropriate dosage having regard to the patient's condition, age, gender, body weight, etc.

5

There is no particular restriction regarding the time period during which multiple doses of a PKMYT1 inhibitor are administered to a patient. For example, doses of the PKMYT1 inhibitor can be administered to a patient over a time period that is 1-7 days or 1-12 weeks or 1-3 months. The time period of administration of the
10 PKMYT1 inhibitor may also be longer, such as 4-11 months or 1-30 years. The PKMYT1 inhibitor may be administered to a patient at the onset of symptoms. Generally, the amount of PKMYT1 inhibitor that is administered may vary during the time period of administration. When a PKMYT1 inhibitor is administered daily, administration may for instance take place 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times
15 per day.

In some aspects, the PKMYT1 inhibitor may be administered continuous daily as a single dose per PKMYT1 inhibitor treatment day (QD) or in two doses per PKMYT1 inhibitor treatment day (BID).

20

In some aspects, the PKMYT1 inhibitor may be administered at an intermittent or intermittent weekly regimen as a single dose per PKMYT1 inhibitor treatment day (QD) or in two doses per PKMYT1 inhibitor treatment day (BID).

25 In some aspects, the PKMYT1 inhibitor may be administered at doses of about 5 to about 600 mg, such as about 5, about 15, about 30, about 60, about 75, about 80 mg, about 90, about 100, about 120, about 140, about 150, about 200, about 240, about 250, about 260, about 300, about 350, about 360, about 400, about 450, about 460, about 500, about 520, about 550 or about 600 mg of free base per PKMYT1
30 inhibitor treatment day. In specific aspects the PKMYT1 inhibitor may be

administered at a dose of 60 mg, 80 mg, 100 mg, 140 mg, or 240 mg of free base per PKMYT1 inhibitor treatment day.

5 In further aspects, the PKMYT1 inhibitor may be administered continuously daily as a single dose per PKMYT1 inhibitor treatment day (QD) at a dose of 5 mg to 600 mg, preferably 240 mg of free base per PKMYT1 inhibitor treatment day.

10 In some aspects, the PKMYT1 inhibitor may be administered continuously daily in two doses per PKMYT1 inhibitor treatment day (BID) at a dose of 5 mg to 600 mg, preferably 60 mg or 80 mg of free base per PKMYT1 inhibitor treatment day.

15 In some aspects, the PKMYT1 inhibitor may be administered intermittent weekly in two doses per PKMYT1 inhibitor treatment day (BID) at a dose of 5 mg to 600 mg, preferably 60 mg to 140 mg of free base per PKMYT1 inhibitor treatment day.

In some aspects, the PKMYT1 inhibitor may be administered intermittent in two doses per PKMYT1 inhibitor treatment day (BID) at a dose of 5 mg to 600 mg, preferably 80 mg to 100 mg of free base per PKMYT1 inhibitor treatment day.

20 In any aspects of the combinations herein, the WEE1 inhibitor may be compound of formula (I). In any aspects of the combinations herein, the PKMYT1 inhibitor may be compound of formula (II). Particularly, in some aspects, the combination of compound of formula (I) with the compound formula (II) shows a synergistic effect in treating cancer, along with an acceptable safety profile.

25 It will be understood that any of the specific compounds, administrations, dosages, regimens and indications described herein can be used in any combination. For instance, the present disclosure provides for combinations, uses and methods, wherein the WEE1 inhibitor is administered at a dose ranging from about 30 to about 30 1000 mg per WEE1 inhibitor treatment day, preferably about 30 to about 720 mg per WEE1 inhibitor treatment day, and the PKMYT1 inhibitor is administered at a

dose ranging from about 100 mg to about 400 mg, such as about 200 mg to about 300 mg and more specifically a dose of about 240 mg per day. It will thus be understood that any of the doses, schedules and routes of administration described herein for either the WEE1 inhibitor or the PKMYT1 inhibitor can be combined with
5 the doses, schedules and routes of administration of the respective other.

For instance, any administration of the WEE1 inhibitor in a 21-day cycle may be combined with administration of the PKMYT1 inhibitor in the same 21-day cycle, or in a different cycle.

10

In any aspects of the combinations herein, the WEE1 inhibitor may be compound of formula (I). In any aspects of the combinations herein, the PKMYT1 inhibitor may be compound of formula (II). It will also be understood that any reference to a dosage, schedule or administration for a WEE1 inhibitor can be applied to the
15 compound of formula (I). Similarly any reference to a dosage, schedule or administration for a PKMYT1 inhibitor can be applied to the compound of formula (II). The compound of formula (I) and the compound of formula (II) can therefore be preferably used in the doses, schedules and routes of administrations described herein.

20

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

25 It is further to be understood that any indication of an administration, dosage, regimen or indication for a PKMYT1 inhibitor herein applies in particular to the compound of formula (II).

For instance, in some aspects of the combinations herein, the WEE1 inhibitor is
30 compound of formula (I), which is administered once daily at a dose ranging from about 100 mg to about 260 mg, such as at a dose of about 100 mg, about 120 mg,

about 150 mg, about 200 mg or about 260 mg per WEE1 inhibitor treatment day. In such aspects, the PKMYT1 inhibitor may be administered on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle at a dose of administered at a dose ranging from about 40 mg to about 100 mg, such as at a dose of about 40 mg, about 60 mg, about 80 mg or about 100 mg per administration, twice a day, preferably at a dose of 60 mg or 80 mg per administration, twice a day. Both compound of formula (I) and the PKMYT1 inhibitor may be administered orally. The PKMYT1 inhibitor may target a cancer characterized by CCNE1 overexpression and/or amplification, an inactivating mutation in the FBXW7 gene, and/or a PPP2R1A inactivating mutation.

10 The PKMYT1 inhibitor may be compound of formula (II).

In some aspects of the combinations herein, the WEE1 inhibitor is compound of formula (I), which is administered once daily on days 1 to 3 and 8 to 10 of a 21-day cycle at a dose ranging from about 200 mg to about 720 mg, such as at a dose of about 200 mg, about 300 mg, about 400 mg, about 520 mg or about 720 mg per WEE1 inhibitor treatment day. In such aspects, the PKMYT1 inhibitor may be administered on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle at a dose of administered at a dose ranging from about 40 mg to about 100 mg, such as at a dose of about 40 mg, about 60 mg, about 80 mg or about 100 mg per administration, twice a day, preferably 60 mg or 80 mg per administration, twice a day. Both compound of formula (I) and the PKMYT1 inhibitor may be administered orally. The PKMYT1 inhibitor may target a cancer characterized by CCNE1 overexpression and/or amplification, an inactivating mutation in the FBXW7 gene, and/or a PPP2R1A inactivating mutation. The PKMYT1 inhibitor may be compound of formula (II).

RADIOTHERAPY

In some aspects of the combinations, uses or methods according to the present invention, the WEE1 inhibitor is used in combination with the PKMYT1 inhibitor and radiotherapy.

The radiotherapy used may be any suitable type of radiation therapy, such as 3D conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT), focal radiotherapy or fractionated radiotherapy.

5

In some aspects, radiotherapy is fractionated radiotherapy.

In some aspects, the radiotherapy is fractionated radiotherapy and is administered in a regimen of 1 Gy to 100 Gy, preferably 2 Gy to 80 Gy, further preferably 10 Gy to 60 Gy, and even more preferably 60 Gy divided over 5 consecutive days per week until a total radiation dose has been administered.

10

In some aspects, radiotherapy is used in combination with the compound of formula (I) and compound of formula (II).

15

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 ovarian cancer, primary peritoneal cancer, fallopian tube cancer, epithelial ovarian cancer (EOC) including serous EOC, endometrioid EOC, or clear cell EOC, stomach cancer, colorectal cancer, bladder cancer, cervical cancer, esophageal cancer, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), breast cancer, soft tissue sarcoma, glioma or endometrial cancer including uterine serous carcinoma (USC).

20

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, WEE1 inhibitor

25

30

and/or PKMYT1 inhibitor is administered to the subject in need thereof, wherein the cancer has been previously identified as a cancer overexpressing CCNE1.

5 In some aspects according to the present invention, a cancer is treated in a subject, wherein a therapeutically effective amount of the combination, WEE1 inhibitor and/or PKMYT1 inhibitor is administered to the subject, wherein the cancer is a cancer overexpressing CCNE1.

10 In some aspects according to the present invention, the combination, WEE1 inhibitor and/or PKMYT1 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 PKMYT1 inhibitor.

15 In some aspects, the cancer overexpressing CCNE1 is uterine cancer, ovarian cancer, breast cancer, stomach cancer, esophageal cancer, lung cancer, or endometrial cancer.

20 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, WEE1 inhibitor and/or PKMYT1 inhibitor, wherein the cancer has been previously identified as a cancer having an inactivating mutation in the FBXW7 gene.

25 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, WEE1 inhibitor and/or PKMYT1 inhibitor, wherein the cancer has an inactivating mutation in the FBXW7 gene.

30 In some aspects according to the present invention, cell death is induced in an FBXW7-mutated cancer cell, comprising contacting the cell with an effective amount of the combination, WEE1 inhibitor and/or PKMYT1 inhibitor. In some aspects, the

FBXW7-mutated cancer is uterine cancer, colorectal cancer, breast cancer, lung cancer, or esophageal cancer.

5 In some aspects, the cancer is characterized by ATRX deficiency or PPP2R1A inactivating mutation.

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

10 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.

15 In some aspects of the combinations, uses or methods according to the present invention, the initial or prior cancer treatment comprises radiotherapy administration.

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

25 The present invention also relates to a pharmaceutical composition comprising the combination, the WEE1 inhibitor as described herein, or the PKMYT1 inhibitor as described herein, as well as its use in the preparation of a medicament for treating cancer in a patient in need thereof. Unless specified otherwise, the following indications apply equally to pharmaceutical compositions comprising the WEE1
30 inhibitor only, pharmaceutical compositions comprising the PKMYT1 inhibitor only, and pharmaceutical compositions comprising both the WEE1 inhibitor and the

PKMYT1 inhibitor. The possible presence of the WEE1 inhibitor, or the PKMYT1 inhibitor or both is jointly referred to as “the active ingredient(s)”.

Pharmaceutical compositions of the present invention that are suitable for oral
5 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
10 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
15 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
20 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
25 methylcellulose), 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.

The oral pharmaceutical compositions of the present invention may be prepared by
30 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 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,
5 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, 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
10 an inert liquid diluent.

WEE1 inhibitor

The pharmaceutical composition comprising the WEE1 inhibitor may for instance
15 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 dose levels.

20 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 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
25 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
30 administered per intake of the WEE1 inhibitor.

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.

5

PKMYT1 inhibitor

The pharmaceutical composition comprising the PKMYT1 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 dose levels.

10

Kit

15

The present invention also relates to a kit comprising the combination, the WEE1 inhibitor for use, or the PKMYT1 inhibitor for use in, or for use in the preparation of a medicament for, treating cancer in a patient in need thereof. In some aspects, the kit comprises a WEE1 inhibitor, in particular the compound of formula (I), and a PKMYT1 inhibitor, in particular the compound of formula (II), 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 the compound of formula (I), as well as PKMYT1 inhibitor, in particular the compound of formula (II).

20

In some aspects of the present invention, the combination of the WEE1 inhibitor with PKMYT1 inhibitor, shows a synergistic effect in treating cancer, such as synthetic lethality.

25

It has been found that a WEE1 inhibitor in combination with a PKMYT1 inhibitor *in vitro* leads to a significant increase in the induction of cell death (synthetic lethality). *In vivo*, the combination is efficacious in significantly improving tumor growth inhibition, which may even lead to complete regression. The combination was also
5 well tolerated *in vivo*.

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 (e.g., cancers that harbor CCNE1
10 amplification/overexpression or FBXW7- mutated cancers) which depend on the activity of membrane-associated tyrosine and threonine- specific cdc2-inhibitory kinase (Myt1) (Gene name PKMYT1).

Aspects of the present disclosure can be further defined and illustrated by reference
15 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: Efficient knock-down of PKMYT1 by siRNA

A549 cells (lung cancer cell line) were reverse-transfected with DharmaFECT 1 and
25 a PKMYT1 siRNA pool at various concentrations for 48hr prior to PKMYT1 mRNA analysis by RT-qPCR. PKMYT1 gene expression was normalized to the housekeeping gene GAPDH and the percentage of PKMYT1 relative expression and knockdown were reported relatively to cells transfected with a matched concentration of a scrambled siRNA (negative control). N=2 transfection replicates.
30 Values shown as mean +/- SD.

The results are illustrated in Figure 1. DharmaFECT combined with a PKMYT1 siRNA at a dose ranging from 25 to 100 nM mediates more than 90% PKMYT1 knock-down in A549 cells.

- 5 The confluency of the cells at 48h post-transfection was similar among the doses of siRNA. The dose selected for Example 2 was 50nM siRNA.

Example 2: Synthetic lethality of PKMYT1 knock-down by siRNA in WEE1 knock-out (KO) cells

10

A549 cells WT or WEE1 KO were reverse-transfected with DharmaFECT 1 and a PKMYT1 siRNA pool or a Scrambled siRNA at 50 nM. (A) Representative bright field pictures of cells 72h post-transfection (similar data at 96h, not shown) and (B) quantification of live cells per well by flow cytometry 72h and 96h post-transfection.

15

The results are illustrated in Figure 2. Transfection with PKMYT1 siRNA does reduce cell viability in A549 WT cells after 72h and 96h but viable cells remain. Transfection with PKMYT1 siRNA in A549 WEE1 KO cells was synthetically lethal leading to no detectable surviving cells.

20

Example 3: In vivo synthetic lethality of combining a PKMYT1 inhibitor and a WEE1 inhibitor (cell line derived xenograft model of ovarian cancer)

- 25 Balb/c nude mice were immobilized and inoculated subcutaneously in the right flank region with OVCAR-3 ovarian tumor cells at 1×10^7 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 150-200 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 was 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
- 30

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).

5

The treatment with Vehicle, compound of formula (I) (30mg/kg QD) (referred to as [Cpd of formula (I)]), RP6306 (10mg/kg or 20mg/kg BID) and combinations were initiated immediately after grouping per study design for 37 days.

- 10 Tumor growth inhibition (TGI): TGI% is an indication of antitumor activity, and is 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 results are illustrated in Figure 3. The treatments of test agent compound of formula (I) could be tolerated by test animals, after combining with RP-6306 no obvious treatment related mice body weight loss or adverse clinical sign was observed. The mean tumor volume of vehicle treated group (Group 1) reached 1387.86 mm³ at Day 37 after randomization. Monotherapy of compound of formula (I) at 30 mg/kg (Group 2) could only bring minor anti-tumor response, TGI was 17.18% ($p > 0.05$) when compared with control group. Treatment with RP-6306 at 20&10 mg/kg (Group 3&4) could produce mild but non-significant anti-tumor activity, TGIs were 38.9% and 42.26% ($p > 0.05$). After combining compound of formula (I) and RP-6306, improved and excellent anti-tumor activity was observed in Group 5&6 (RP6306 20mg/kg and 10mg/kg respectively), where all tumors were designated as complete regressions (TGIs of 94.23% and 82.54% ($p < 0.01$); all below the lower limit of quantification). Furthermore the combination of compound of formula (I) and RP6306 (at either dose) elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy ($p < 0.01$).

30

Example 4: In vivo efficacy of compound of formula (I) in combination with RP6306 in cell line derived xenograft model of breast cancer

Balb/c nude mice were immobilized and inoculated subcutaneously in the right flank region with SUM149PT breast tumor cells at 4×10^6 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 190 mm^3 and randomly allocated to 4 study groups based on "Matched distribution" method/ "Stratified" method (StudyDirector™ software, version 3.1.399.19). Date of randomization was 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 mm^3 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) (referred to as [Cpd of formula (I)]), RP6306 (20mg/kg BID) and combinations were initiated immediately after grouping per study design for 28 days.

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

The results are illustrated in Figure 4. The treatments of compound of formula (I) could be tolerated by test animals, after combining with RP-6306 no obvious treatment related mice body weight loss or adverse clinical sign was observed. The mean tumor volume of vehicle treated group (Group 1) reached 1471 mm^3 at Day 28 after randomization. Monotherapy of compound of formula (I) at 30 mg/kg (Group 2) could only bring minor anti-tumor response, TGI was 20.67% ($p < 0.05$) when compared with control group. Treatment with RP-6306 at 20mg/kg (Group 3) could

not produce any significant anti-tumor activity, TGIs were -10.17% ($p>0.05$). After combining compound of formula (I) and RP-6306, improved and excellent anti-tumor activity was observed in Group 4, where all tumors achieved regression by day 18 compared to starting tumor volumes and a TGI of 100.71% ($p<0.01$) at day 28.

- 5 Furthermore the combination of compound of formula (I) and RP6306 elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy ($p<0.01$).

- Example 5: In vivo efficacy of compound of formula (I) in combination with RP6306
10 in Patient Derived Xenograft (PDX) models of breast and ovarian cancer

- NCG mice were immobilized and inoculated subcutaneously in the right flank region with 3x3x3mm fragments of patient derived breast or ovarian tumor cells in Matrigel for tumor development. The randomization was performed when mean tumor size
15 reached approximately 185mm³ for the breast cancer PDX or 150mm³ for the ovarian PDX, and randomly allocated to 4 study groups based on "Matched distribution" method/ "Stratified" method. Date of randomization was 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
20 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).

- 25 The treatment with Vehicle, compound of formula (I) (30mg/kg QD) (referred to as [Cpd of formula (I)]), RP6306 (20mg/kg BID) and combinations were initiated immediately after grouping per study design for 28 days.

- Tumor growth inhibition (TGI): TGI% is an indication of antitumor activity, and is
30 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.

Breast LD1 model:

The LD1 model used was characterized as CCNE1 amplified (26 copies) and high CCNE1 mRNA expression (139 transcripts per million by RNAseq).

- 5 The results are illustrated in Figure 5. The treatments of compound of formula (I) could be tolerated by test animals, after combining with RP-6306 no obvious treatment related mice body weight loss or adverse clinical sign was observed. The mean tumor volume of vehicle treated group (Group 1) reached 1284mm³ at Day 35 after randomization. Monotherapy of compound of formula (I) at 30 mg/kg (Group 2)
- 10 could only bring minor anti-tumor response, TGI was 20% ($p < 0.05$) when compared with control group. Treatment with RP-6306 at 20mg/kg (Group 3) could not produce any significant anti-tumor activity. After combining compound of formula (I) and RP-6306, improved and excellent anti-tumor activity was observed in Group 4, where all tumors achieved complete regression by day 38 (no detectable tumors) which
- 15 regression was sustained until completion of study at day 52 ($p < 0.01$). Furthermore the combination of compound of formula (I) and RP6306 elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy ($p < 0.01$).

- 20 Ovarian PDX280 model:

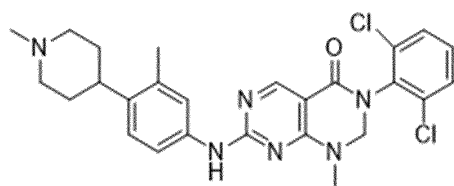
The results are illustrated in Figure 6. The treatments of compound of formula (I) could be tolerated by test animals, after combining with RP-6306 no obvious treatment related mice body weight loss or adverse clinical sign was observed.

- The mean tumor volume of vehicle treated group (Group 1) reached 471.5mm³ at
- 25 Day 28 after randomization. Monotherapy of compound of formula (I) at 30 mg/kg (Group 2) could only bring minor anti-tumor response, TGI was 2.8% ($p > 0.05$) when compared with control group. Treatment with RP-6306 at 20mg/kg (Group 3) could not produce any significant anti-tumor activity, TGIs were -2.5% ($p > 0.05$). After combining compound of formula (I) and RP-6306, improved and excellent
- 30 anti-tumor activity was observed in Group 4, where 7 out of 8 tumors were designated as complete regressions by day 28 compared to starting tumor

volumes with a TGI of 183% ($p < 0.01$) compared to vehicle control. Furthermore, the combination of compound of formula (I) and RP6306 elicited a significant tumor growth inhibition when compared to either single drug administration as a monotherapy ($p < 0.01$).

CLAIMS

1. Combination of a WEE1 inhibitor and a PKMYT1 inhibitor.
- 5 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
- 10 PKMYT1 inhibitor.
5. PKMYT1 inhibitor for use in treating cancer in a patient in need thereof, wherein the PKMYT1 inhibitor is administered in combination with a WEE1 inhibitor.
6. Combination according to any one of claims 1 to 3, WEE1 inhibitor for use
- 15 according to claim 4, or PKMYT1 inhibitor for use according to claim 5, wherein the WEE1 inhibitor is a compound of formula (I)



(I), or a pharmaceutically

- acceptable salt thereof.
7. Combination for use according to claims 3 or 6, WEE1 inhibitor for use
 - 20 according to claims 4 or 6, or PKMYT1 inhibitor for use according to claims 5 or 6, wherein the WEE1 inhibitor is administered
 - 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,
 - 25 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,
 - i. on days 1 to 5, 8 to 10 and 15 to 17 of a 28-day cycle,
 - j. on days 1 to 5 of a 28-day cycle,
 - k. on days 1 to 5 and 8 to 10 of a 28-day cycle,
 - 5 l. on days 1 to 5 and 8 to 12 of a 28-day cycle,
 - m. on days 1 to 5, 8 to 12 and 15 to 19 of a 28-day cycle,
 - n. on days 1 to 3, 8 to 10 and 15 to 17 of a 28-day cycle,
 - o. on days 1 to 3 and 8 to 10 of a 28-day cycle, or
 - p. on days 1 to 3 of a 28-day cycle.
- 10 8. Combination for use according to any one of claims 3, 6 or 7, WEE1 inhibitor for use according to any one of claims 4, 6 or 7, or PKMYT1 inhibitor for use according to any one of claims 5, 6 or 7, wherein the WEE1 inhibitor is administered
- 15 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
 - 20 day.
9. Combination for use according to any one of claims 3, 6, 7 or 8, WEE1 inhibitor for use according to any one of claims 4, 6, 7 or 8, or PKMYT1 inhibitor for use according to any one of claims 5, 6, 7 or 8, wherein the PKMYT1 inhibitor is administered
- 25 a. for 7 consecutive or non consecutive days or more, such as 14 consecutive or non consecutive days or more or every day of a 21-day cycle, and/or
 - b. on days 1 to 3, 8 to 10 and 15 to 17 of a 21-day cycle, and/or
 - c. on the same days as the WEE1 inhibitor treatment days, preferably
 - 30 as defined in claim 7, and/or

- d. on days different from the WEE1 inhibitor treatment days of a 21-day or a 28-day cycle, and/or
- e. such that the PKMYT1 inhibitor and the WEE1 inhibitor are administered in an alternating manner wherein one of the drugs is administered for x days and then paused for y days and the other drug is paused during the x days and administered during the y days, followed by another period of x and y days, and so forth, wherein x and y are independently selected from 1, 2, 3, 4, 5, 6 and 7.
10. Combination for use according to any one of claims 3 or 6 to 9, WEE1 inhibitor for use according to any one of claims 4 or 6 to 9, or PKMYT1 inhibitor for use according to any one of claims 5 or 6 to 9, wherein the PKMYT1 inhibitor is administered
- a. at a dose ranging from about 60 mg to about 400 mg, or about 100 mg to about 300 mg or at a dose of about 240 mg per PKMYT1 inhibitor treatment day, and/or
- b. once or twice a day per PKMYT1 inhibitor treatment day, and/or
- c. once or twice a day at a dose selected from about 30 to about 100 mg, or about 60 to about 100 mg, or about 80 to about 100 mg per administration and/or
- d. at a dose ranging from about 80 to about 100 mg per administration, twice a day, per PKMYT1 inhibitor treatment day, and/or,
- e. daily at a dose of 240 mg per PKMYT1 inhibitor treatment day, and/or
- f. orally.
11. Combination for use according to any one of claims 7 to 10, WEE1 inhibitor for use according to any one of claims 7 to 10, or PKMYT1 inhibitor for use according to any one of claims 7 to 10, wherein the WEE1 inhibitor and the PKMYT1 inhibitor are administered according to one of the following options:

- A. both the WEE1 inhibitor and the PKMYT1 inhibitor are administered on days 1-3, 8-10 and 15-17 of a 21-day cycle,
- B. both the WEE1 inhibitor and the PKMYT1 inhibitor are administered on days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle,
- 5 C. the WEE1 inhibitor is administered daily and the PKMYT1 inhibitor is administered on days 1-3, 8-10 and 15-17 of a 21-day cycle,
- D. the WEE1 inhibitor is administered daily and the PKMYT1 inhibitor is administered on days 1-3, 8-10, 15-17 and 22-24 of a 28-day cycle,
- E. the WEE1 inhibitor is administered on days 1-3 and 8-10 of a 21-day cycle and the PKMYT1 inhibitor is administered on days 1-3, 8-10 and 15-17 of a 21-day cycle, or
- 10 F. both the WEE1 inhibitor and the PKMYT1 inhibitor are administered on days 1-3 and 15-17 of a 28-day cycle.
12. Combination for use according to any one of claims 7 to 11, WEE1 inhibitor for use according to any one of claims 7 to 11, or PKMYT1 inhibitor for use according to any one of claims 7 to 11, wherein the combination, the WEE1 inhibitor and/or the PKMYT1 inhibitor is administered over 1, 2, 3, 4, 5, 6 or more 21-day cycles, or over 1, 2, 3, 4, 5, 6 or more 28-day cycles.
- 15
13. Combination for use according to any one of claims 3 or 6 to 12, WEE1 inhibitor for use according to any one of claims 4 or 6 to 12, or PKMYT1 inhibitor for use according to any one of claims 5 or 6 to 12, wherein the cancer is ovarian cancer, primary peritoneal cancer, fallopian tube cancer, epithelial ovarian cancer (EOC) including serous EOC, endometrioid EOC, or clear cell EOC, stomach cancer, colorectal cancer, bladder cancer, cervical cancer, esophageal cancer, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), breast cancer, soft tissue sarcoma, glioma or endometrial cancer including uterine serous carcinoma (USC).
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- 25
14. Combination for use according to any one of claims 3 or 6 to 13, WEE1 inhibitor for use according to any one of claims 4 or 6 to 13, or PKMYT1
- 30

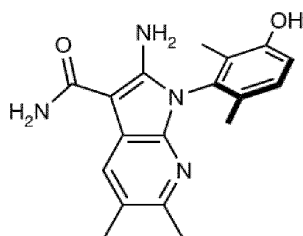
inhibitor for use according to any one of claims 5 or 6 to 13, wherein the cancer is characterized by CCNE1 overexpression and/or CCNE1 amplification.

5 15. Combination for use according to any one of claims 3 or 6 to 13, WEE1 inhibitor for use according to any one of claims 4 or 6 to 13, or PKMYT1 inhibitor for use according to any one of claims 5 or 6 to 13, wherein the cancer is characterized by ATRX deficiency, FBXW7 inactivating mutation or PPP2R1A inactivating mutation.

10 16. Combination for use according to any one of claims 3 or 6 to 15, WEE1 inhibitor for use according to any one of claims 4 or 6 to 15, or PKMYT1 inhibitor for use according to any one of claims 5 or 6 to 15, wherein the cancer is metastatic.

15 17. Combination for use according to claim 16, WEE1 inhibitor for use according to claim 15, or PKMYT1 inhibitor for use according to claim 15, wherein the metastatic cancer comprises brain metastases.

18. Combination for use according to any one of claims 1, 2, 3 or 6 to 17, WEE1 inhibitor for use according to any one of claims 4 or 6 to 17, or PKMYT1 inhibitor for use according to any one of claims 5 or 6 to 17, wherein the PKMYT1 inhibitor is a compound of formula (II),



20 (II) or a pharmaceutically acceptable salt thereof.

25 19. Pharmaceutical composition comprising the combination according to any one of claims 1 to 3 and/or as further specified in claims 6 and/or 18, or comprising the WEE1 inhibitor as specified in one or more of claims 4, 6 or 18, or the PKMYT1 inhibitor as specified in one or more of claims 5, 6

or 18, for use in treating cancer in a patient in need thereof, wherein the use is as described in any of claims 3-5, or 7-17.

- 5 20. Kit comprising the combination according to any one of claims 1 to 3 and/or as further specified in claims 6 and/or 18, wherein the WEE1 inhibitor and PKMYT1 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 3-5, or 7-17.

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