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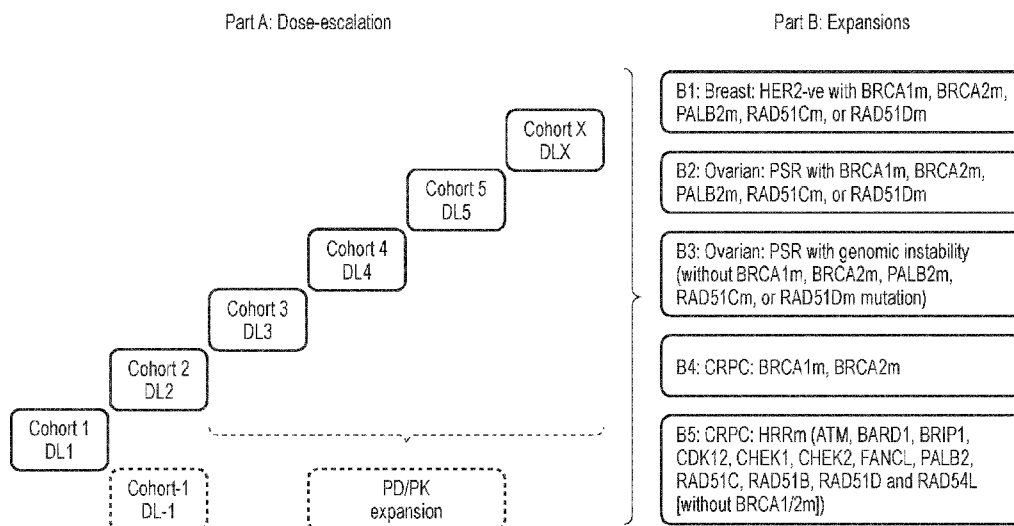


FIG. 1

(57) Abstract: A method of treatment or prophylaxis of diseases or conditions in which inhibition of PARP1 is beneficial, comprising administering to the subject AZD5305 in a daily dose of 10 to 140 mg, wherein AZD5305 may be in the form of a pharmaceutically acceptable salt.

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DOSING REGIMENT OF AZD5305

The present disclosure relates to methods of treatment or prophylaxis of diseases and conditions in which inhibition of PARP1 or PARP1 function is of therapeutic significance.

5 **Background**

PARP family of enzymes play an important role in a number of cellular processes, such as replication, recombination, chromatin remodeling, and DNA damage repair (O'Connor 2015).

Examples of PARP inhibitors and their mechanism of action are taught in e.g.

10 WO2004/080976.

PARP1 and PARP2 are the most extensively studied PARPs for their role in DNA damage repair. PARP1 is activated by DNA damage breaks and functions to catalyse the addition of poly (ADP-ribose) (PAR) chains to target proteins. This post-translational modification,
15 known as PARylation, mediates the recruitment of additional DNA repair factors to DNA lesions.

Following completion of this recruitment role, PARP auto-PARylation triggers the release of bound PARP from DNA to allow access to other DNA repair proteins to complete repair.

20 Thus, the binding of PARP to damaged sites, its catalytic activity, and its eventual release from DNA are all important steps for a cancer cell to respond to DNA damage caused by chemotherapeutic agents and radiation therapy (Bai 2015).

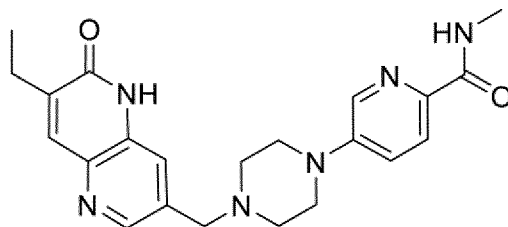
Inhibition of PARP family enzymes has been exploited as a strategy to selectively kill cancer
25 cells by inactivating complementary DNA repair pathways. A number of pre-clinical and clinical studies have demonstrated that tumour cells bearing deleterious alterations of BRCA1 or BRCA2, key tumour suppressor proteins involved in double-strand DNA break (DSB) repair by homologous recombination (HR), are selectively sensitive to small molecule inhibitors of the PARP family of DNA repair enzymes. Such tumours have deficient
30 homologous recombination repair (HRR) pathways and are dependent on PARP enzymes function for survival. Although PARP inhibitor therapy has predominantly targeted *BRCA*-mutated cancers, PARP inhibitors have been tested clinically in non-*BRCA*-mutant tumors, those which exhibit homologous recombination deficiency (HRD) (Turner 2004).

35 It is believed that PARP inhibitors having improved selectivity for PARP1 may possess improved efficacy and reduced toxicity compared to other clinical PARP1/2 inhibitors. It is

believed also that selective strong inhibition of PARP1 would lead to trapping of PARP1 on DNA, resulting in DNA double-strand breaks (DSBs) through collapse of replication forks in S-phase. It is believed also that PARP1-DNA trapping is an effective mechanism for selectively killing tumour cells having HRD.

5

“AZD5305” refers to a compound with the chemical name 5-{4-[(7-ethyl-6-oxo-5,6-dihydro-1,5-naphthyridin-3-yl)methyl]piperazin-1-yl}-N-methylpyridine-2-carboxamide and structure shown below:



10 AZD5305 is a potent and selective PARP1 inhibitor and PARP1-DNA trapper with excellent *in vivo* efficacy. AZD5305 is highly selective for PARP1 over other PARP family members, with good secondary pharmacology and physicochemical properties and excellent pharmacokinetics in preclinical species, and with reduced effects on human bone marrow progenitor cells *in vitro*.

15

The synthesis of AZD5305 is described in Johannes 2021 and in WO2021/013735, the contents of which are hereby incorporated by reference in their entirety.

To deliver AZD5305 to patients, safe and effective dosing regimens need to be developed
20 with the aim of providing a more efficacious and less toxic cancer treatment compared with currently approved PARP inhibitors.

Summary

In some embodiments, disclosed is a method of treatment or prophylaxis of diseases or
25 conditions in which inhibition of PARP1 is beneficial, comprising administering to the subject AZD5305 in a daily dose of 10 to 140 mg. AZD5305 may be administered as a pharmaceutically acceptable salt thereof, where the daily dosage is that of AZD5305 not in a salt form.

30 In some embodiments, disclosed is AZD5305, or a pharmaceutically acceptable salt thereof, for use in a method of treatment or prophylaxis of diseases or conditions in which inhibition

of PARP1 is beneficial, wherein said AZD5305 is administered in a daily dose of 10 to 140 mg.

In some embodiments, disclosed is the use of AZD5305, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treatment or prophylaxis of diseases or conditions in which inhibition of PARP1 is beneficial, wherein said treatment comprises the administration of said medicament comprising AZD5305 in a daily dose of 10 to 140 mg.

In some embodiments, disclosed is a pharmaceutical product comprising AZD5305 in a dose of 10 to 140 mg, where AZD5305 may be present as a pharmaceutically acceptable salt, and a pharmaceutically acceptable excipient, carrier or diluent.

In some embodiments, said disease or condition in which inhibition of PARP1 is beneficial is cancer. In some of these embodiments, the cancer is breast, ovary, pancreas, prostate, hematological, gastrointestinal such as gastric and colorectal, or lung cancer. In certain of these embodiments, the cancer is breast, ovary, pancreas or prostate cancer.

In some embodiments, the breast cancer is *BRCA1m* (*BRCA1* mutated), *BRCA2m* (*BRCA2* mutated), *PALB2m* (*PALB2* mutated), *RAD51Cm* (*RAD51C* mutated), or *RAD51Dm* (*RAD51D* mutated) HER2-negative breast cancer.

In some embodiments, the ovarian cancer is *BRCA1m* (*BRCA1* mutated), *BRCA2m* (*BRCA2* mutated), *PALB2m* (*PALB2* mutated), *RAD51Cm* (*RAD51C* mutated), or *RAD51Dm* (*RAD51D* mutated) ovarian cancer or ovarian cancer with high genomic instability.

In some embodiments, the prostate cancer is *BRCA1/2* mutated prostate cancer or HRRm (HRR mutated) non-*BRCA1/2* mutated prostate cancer.

Figures

Figure 1 is a flow chart of a clinical trial of AZD5305.

Figures 2A and 2B show the AZD5305 plasma concentration against the time after a single dose and after a dose during continuous dosing respectively.

Figure 3 shows residual activity of PARP1 after a single dose of AZD5305.

Figures 4 to 7 show the response of 46 patients treated with AZD5305 as best percentage change in target lesion size by dose, tumour type, mutation type and dependent on prior PARPi treatment.

Figure 8 shows the results of ctDNA measurements of 13 patients treated with AZD5305. Figure 9 shows the PSA₅₀ and ctDNA responses of a patient with prostate cancer treated with AZD5305.

Figures 10A and 10B are a baseline scan and second scan of the same patient treated with AZD5305 as in Figure 9.

Figures 11A to 11D show the PSA₅₀ and ctDNA responses of four patients with prostate cancer treated with AZD5305.

Figure 12 shows the CA15.3 response of a patient with breast cancer treated with AZD5305.

Figures 13A to 13C are baseline scans, first scans and second scans respectively of the same patient treated with AZD5305 as in Figure 12.

Figure 14 shows the CA125 response of a patient with ovarian cancer treated with AZD5305.

Figures 15A and 15B are baseline scans and third scans of the same patient treated with AZD5305 as in Figure 14.

Detailed Description

In some embodiments, a free base AZD5305 is administered to a subject. In some embodiments, a pharmaceutically acceptable salt of AZD5305 is administered to a subject.

In some embodiments, crystalline AZD5305 or a pharmaceutically acceptable salt of AZD5305 is administered to a subject.

The language “pharmaceutical composition” includes compositions comprising an active ingredient and a pharmaceutically acceptable excipient, carrier or diluent, wherein the active ingredient is AZD5305 or a pharmaceutically acceptable salt thereof. The language “pharmaceutically acceptable excipient, carrier or diluent” includes compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, as ascertained by one of skill in the art. In some embodiments, the pharmaceutical compositions are in solid dosage forms, such as capsules, tablets, granules, powders or sachets. In some embodiments, the pharmaceutical compositions are in the form of a sterile injectable solution in one or more aqueous or non-aqueous non-toxic parenterally acceptable buffer systems, diluents, solubilizing agents, co-solvents, or carriers. A sterile injectable preparation may also be a sterile injectable aqueous or oily suspension or suspension in a non-aqueous diluent, carrier or co-solvent, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents. The

pharmaceutical compositions could be a solution for iv bolus/infusion injection or a lyophilized system (either alone or with excipients) for reconstitution with a buffer system with or without other excipients. The lyophilized freeze-dried material may be prepared from non-aqueous solvents or aqueous solvents. The dosage form could also be a concentrate for further dilution for subsequent infusion.

The language "treat," "treating" and "treatment" includes the reduction or inhibition of enzyme or protein activity related to PARP-1 in a subject, amelioration of one or more symptoms of diseases or conditions in which inhibition of PARP1 is beneficial in a subject, or the slowing or delaying of progression of diseases or conditions in which inhibition of PARP1 is beneficial in a subject. The language "treat," "treating" and "treatment" also includes the reduction or inhibition of the growth of a tumor or proliferation of cancerous cells in a subject.

The language "inhibit", "inhibition" or "inhibiting" includes a decrease in the baseline activity of a biological activity or process.

The term "subject" includes warm-blooded mammals, for example, primates, dogs, cats, rabbits, rats, and mice. In some embodiments, the subject is a primate, for example, a human. In some embodiments, the subject is suffering from diseases or conditions in which inhibition of PARP1 is beneficial.

In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof are administered in a treatment cycle. In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof is continuously administered in the treatment cycle.

The term "continuous" or "continuously" refers to administration of a therapeutic agent, e.g. AZD5305, at regular intervals without stopping or interruption, i.e., no void day. By "void day", it is meant a day when a therapeutic agent is not administered.

A "cycle", "treatment cycle" or "dosing schedule", as used herein, refers to a period of treatment that is repeated on a regular schedule. For example, the treatment can be given for one week, two weeks, or three weeks wherein AZD5305 is administered. In some embodiments, a treatment cycle is about 1 week to about 3 months. In some embodiments, a treatment cycle is about 5 days to about 1 month. In some embodiments, a treatment cycle is about 1 week to about 3 weeks. In some embodiments, a treatment cycle is about 1 week, about 10 days, about 2 weeks, about 3 weeks, about 4 weeks, about 2 months, or about 3 months.

In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof is administered to the human subject in one or more treatment cycles, e.g., a treatment course. A "treatment course" comprises multiple treatment cycles, which can be repeated on a regular schedule, or adjusted as a tapered schedule as the patient's disease progression is monitored. For example, a patient's treatment cycles can have longer periods of treatment and/or shorter periods of rest at the beginning of a treatment course (e.g., when the patient is first diagnosed), and as the cancer enters remission, the rest period lengthens, thereby increasing the length of one treatment cycle. The period of time for treatment and rest in a treatment cycle, the number of treatment cycles, and the length of time for the treatment course can be determined and adjusted throughout the treatment course by the skilled artisan based on the patient's disease progression, treatment tolerance, and prognosis. In some embodiments, the method comprises 1 to 10 treatment cycles. In some embodiments, the method comprises 2 to 8 treatment cycles.

In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof is administered for 28 days in a 28-day treatment cycle.

In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof is administered orally. In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof is in tablet dosage form.

In some embodiments, AZD5305 is administered in a dose of 10 to 140 mg per day. The daily dose may be up to 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg. The daily dose may be at least 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg or 130 mg.

In some embodiments, AZD5305 is administered in a daily dose of 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg.

In some embodiments, AZD5305 is administered once a day (QD). In some embodiments, AZD5305 is administered in a dose of 10 to 140 mg QD. The once daily dose may be up to 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 130 mg. The once daily dose may be at least 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg or 130 mg.

In some embodiments, AZD5305 is administered in a once daily dose (QD) of 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg.

5 In some embodiments, the cancer treated may be deficient in Homologous Recombination (HR) dependent DNA DSB repair activity. The HR dependent DNA DSB repair pathway repairs double-strand breaks (DSBs) in DNA via homologous mechanisms to reform a continuous DNA helix (Khanna and Jackson 2001). The components of the HR dependent DNA DSB repair pathway include, but are not limited to, ATM (NM_000051), RAD51
10 (NM_002875), RAD51L1 (NM_002877), RAD51C (NM_002876), RAD51L3 (NM_002878), DMC1 (NM_007068), XRCC2 (NM_005431), XRCC3 (NM_005432), RAD52 (NM_002879), RAD54L (NM_003579), RAD54B (NM_012415), BRCA1 (NM_007295), BRCA2 (NM_000059), RAD50 (NM_005732), MRE11A (NM_005590) and NBS1 (NM_002485). Other proteins involved in the HR dependent DNA DSB repair pathway include regulatory
15 factors such as EMSY (Hughes-Davies 2003). HR components are also described in Wood 2001.

A cancer which is deficient in HR dependent DNA DSB repair may comprise or consist of one or more cancer cells which have a reduced or abrogated ability to repair DNA DSBs
20 through that pathway, relative to normal cells i.e. the activity of the HR dependent DNA DSB repair pathway may be reduced or abolished in the one or more cancer cells.

The activity of one or more components of the HR dependent DNA DSB repair pathway may be abolished in the one or more cancer cells of an individual having a cancer which is
25 deficient in HR dependent DNA DSB repair. Components of the HR dependent DNA DSB repair pathway are well characterised in the art (see for example, Wood 2001) and include the components listed above.

In some embodiments, the cancer cells may have a BRCA1 and/or a BRCA2 deficient
30 phenotype i.e. BRCA1 and/or BRCA2 activity is reduced or abolished in the cancer cells. Cancer cells with this phenotype may be deficient in BRCA1 and/or BRCA2, i.e. expression and/or activity of BRCA1 and/or BRCA2 may be reduced or abolished in the cancer cells, for example by means of mutation or polymorphism in the encoding nucleic acid, or by means of amplification, mutation or polymorphism in a gene encoding a regulatory factor, for example
35 the EMSY gene which encodes a BRCA2 regulatory factor (Hughes-Davies 2003).

BRCA1 and BRCA2 are known tumour suppressors whose wild-type alleles are frequently lost in tumours of heterozygous carriers (Jasin 2002; Tutt 2002). The association of BRCA1 and/or BRCA2 mutations with breast cancer is well-characterised in the art (Radice 2002). Amplification of the EMSY gene, which encodes a BRCA2 binding factor, is also known to be associated with breast and ovarian cancer. Carriers of mutations in BRCA1 and/or BRCA2 are also at elevated risk of certain cancers, including breast, ovary, pancreas, prostate, hematological, gastrointestinal and lung cancer.

In some embodiments, the individual is heterozygous for one or more variations, such as mutations and polymorphisms, in BRCA1 and/or BRCA2 or a regulator thereof. The detection of variation in BRCA1 and BRCA2 is well-known in the art and is described, for example in EP 699 754, EP 705 903, Neuhausen and Ostrander 1992; Chappuis and Foulkes 2002; Janatová 2003; Jancárková 2003). Determination of amplification of the BRCA2 binding factor EMSY is described in Hughes-Davies 2003.

Mutations and polymorphisms associated with cancer may be detected at the nucleic acid level by detecting the presence of a variant nucleic acid sequence or at the protein level by detecting the presence of a variant (i.e. a mutant or allelic variant) polypeptide.

In some embodiments, AZD5305 is administered as a monotherapy.

In some embodiments, AZD5305 is administered in combination with one or more other agents which can be used in treating diseases and conditions in which inhibition of PARP1 or PARP 1 function is of therapeutic significance.

Preclinical studies

Preclinical characterization of AZD5305 is reported in Illuzzi 2022.

AZD5305 was tested in vitro for PARylation inhibition, PARP-DNA trapping, and antiproliferative abilities. In vivo efficacy was determined in mouse xenograft and PDX models. The potential for hematologic toxicity was evaluated in rat models, as monotherapy and combination. It was reported that AZD5305 was a highly potent and selective inhibitor of PARP1 with 500-fold selectivity for PARP1 over PARP2. AZD5305 inhibits growth in cells with deficiencies in DNA repair, with minimal/no effects in other cells. Unlike first-generation PARPi, AZD5305 has minimal effects on hematologic parameters in a rat pre-clinical model at predicted clinically efficacious exposures. Animal models treated with AZD5305 at doses

≥0.1 mg/kg once daily achieved greater depth of tumor regression compared to olaparib 100 mg/kg once daily, and longer duration of response.

Examples

- 5 The compounds of the application will now be further explained by reference to the following non-limiting examples.

Example 1 – Clinical Trial

- 10 This study plans to investigate the safety and preliminary clinical efficacy of AZD5305 in patients with advanced/metastatic cancer and HRD.

- Part A is a dose-escalation study and will include patients with advanced/relapsed ovarian cancer, HER2 (human epidermal growth factor receptor 2)-negative breast cancer, CRPC (castration-resistant prostate cancer) or pancreatic cancer. All patients should have a loss of
15 function or predicted loss of function mutation in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C* or *RAD51D*.

Part B will have expansion cohorts in specific indications:

- 20 Cohort B1 - Advanced/relapsed HER2-negative breast cancer patients with *BRCA1m*, *BRCA2m*, *PALB2m*, *RAD51Cm* or *RAD51Dm*

Cohort B2 – PSR (platinum sensitive relapsed) high grade epithelial ovarian cancer patients with loss of function mutations in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C* or *RAD51D*.

- 25 Cohort B3 – PSR high grade epithelial ovarian cancer patients with high levels of genomic instability (and absence of loss of function mutations in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C* or *RAD51D*)

Cohort B4 – Histologically or cytologically confirmed advanced/metastatic CRPC and a qualifying loss of function mutation in *BRCA1* or *BRCA2*.

- 30 Cohort B5 – Histologically or cytologically confirmed advanced/metastatic CRPC and a qualifying loss of function alteration (in HRRm (*ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L* [without *BRCA1/2m*])).

For patients in Part A, up to one prior line of treatment with PARP inhibitor is allowed (either in the metastatic or treatment setting). For Part B, patients must be PARP inhibitor naïve.

The study flow chart is shown in Figure 1 (DL = dose level).

Objectives and Endpoints*Table 1 - Primary Objectives and Endpoints*

Primary/Safety Objective	Primary Endpoints/Variables
To assess the safety and tolerability of AZD5305 as monotherapy and in combination with anti-cancer agents in patients with advanced malignancies	• Incidence of Adverse Events (AEs)/ Serious Adverse Events (SAEs) • Dose-Limiting Toxicities (DLTs) • Maximum Tolerated Dose (MTD) • Changes from baseline in laboratory findings, physical examination, ECOG PS (Eastern Cooperative Oncology Group Performance Status), Electrocardiograms (ECGs) and vital signs

Table 2 - Secondary Objectives and Endpoints

Secondary Objective	Endpoints/Variables
To characterize the Pharmacokinetics (PK) of AZD5305 in plasma, following a single dose and at steady state after multiple dosing, when given orally	• Plasma concentrations of AZD5305 and plasma PK parameters, including but not limited to Area Under Curve (AUC), $C_{\max}$ (maximum plasma concentration of the drug) and $T_{\max}$ (the time taken to reach the maximum concentration) as data allow, of AZD5305 after single dose and multiple doses administration

To assess the preliminary anti-tumour activity of AZD5305	• Radiological response evaluated according to response evaluation criteria in solid tumours (RECIST v1.1; Response Evaluation Criteria In Solid Tumours version 1.1) ○ Best percentage change in target lesion ○ ORR (objective response rate), DoR (duration of response), PFS (progression-free survival), TTR (time to response) • For ovarian cancer patients, CA125 (Cancer antigen 125) response evaluated according to the GCIG (Gynecologic Cancer InterGroup) criteria • Specifically, for prostate cancer patients (in addition to what is in the core protocol): ○ ORR and rPFS using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria ○ Proportion of subjects achieving a $\geq 50\%$ decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA₅₀ response)
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To evaluate pharmacodynamics (PD) of AZD5305 in tumour tissue when given orally as monotherapy	Includes, but is not limited to assessment pH2AX - Ser139 (phospho-histone 2AX - Serine 139) PD biomarker modulations at baseline visit 1 and during treatment.
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Table 3 - Exploratory Objectives and Endpoints

Exploratory Objective	Endpoints/Variables
To investigate the presence and/or identify (in plasma and urine) drug metabolites of AZD5305 and, if appropriate, characterise PK	Metabolite identification
To understand the CYP3A4 induction potential of AZD5305	Pre-dose to post-dose 4-β-hydroxy cholesterol ratio
To explore relationship between PK concentration or parameters and selected endpoints (which may include PD parameters, efficacy, and/or safety), where deemed appropriate	Correlation of PK with other primary/secondary/exploratory endpoints in patients treated with AZD5305.
To characterise the PD of AZD5305, following a single dose and at steady state after multiple dosing, when given orally	- Assessment of modulation from baseline (Visit 1) or pre-treatment in PD biomarkers from PBMC (peripheral blood mononuclear cell), and/or tumoural samples - Analysis of PARP1 inhibition including, but not limited to PAR (poly adenosine diphosphate-ribose), PARP-DNA trapping and pH2AX (Ser139)
To investigate predictive markers of response and acquired resistance to AZD5305 that may be observed in tumour and ctDNA (circulating tumour DNA) from patients treated with AZD5305	Assessment of association of biomarkers including but not limited to gene mutations, genomic alterations, mRNA, proteins, <i>RAD51</i> foci with observed response or resistance to AZD5305

To determine the efficacy of AZD5305 according to biomarker subgroups defined from the blood, tumour or ctDNA	Clinical efficacy associated with biomarkers including but not limited to: ○ <i>tBRCAm</i> (tumour <i>BRCA</i> mutation), <i>gBRCAm</i> (germline <i>BRCA</i> mutation), <i>sBRCAm</i> (somatic <i>BRCA</i> mutation) <i>BRCA</i> methylation, <i>non-BRCAm</i> (patients without <i>BRCA</i> or HRR mutations HRRm - individually and as a panel) ○ Genomic instability status ○ <i>RAD51</i> foci
To explore the impact of the study treatment on ctDNA levels in patients by exploring the relationship between ctDNA kinetics and clinical response/ progression, clonal evolution of disease, predictive biomarkers of response and resistance	● Correlation of percentage change in ctDNA mutation frequency with PFS and other clinical and translational endpoints
To collect and store germline DNA to assess CHIP (Clonal Haematopoiesis of Indeterminate Potential) to aid interpretation of ctDNA mutation monitoring	● Presence or absence of CHIP mutations ● Germline DNA may also be used for possible exploration of genetic factors associated with drug response and tolerability
To collect and store plasma, serum blood or tissue samples for companion diagnostics development and exploratory analysis	● This may include analysis of tumour specific and circulating biomarkers, such as tumour DNA, genes/ genetic variations, mRNA, proteins, cytokines or metabolites. ● Exploratory biomarkers ● Pharmacogenomics (genomics initiative)
To assess the overall survival when treated by AZD5305	● Overall Survival (OS)

To assess the preliminary anti-tumour activity of AZD5305	Proportion of subjects achieving a decline in the number of CTCs from ≥ 5 cells/7.5mL to < 5 cells/7.5 mL blood (CTC conversion rate)
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Number of patients

Part A will require approximately 45 patients (n=3 to 6 per cohort). This number of patients is expected to provide a model-based estimate of MTD with a target toxicity of 25%. Doses and/or schedules of AZD5305 will be defined by taking the Bayesian adaptive design scheme and PK into consideration. Dose-escalation will stop at the MTD, MFD, or the RP2D.

Part A, dose-escalation cohorts may be expanded to evaluate further the safety, tolerability, PK, PD, and biological activity of AZD5305, provided the dose has already been declared as tolerated. Patients with specific tumour types and prior treatment status (within the current eligibility criteria) may be enrolled in these Part A expansion cohorts based on emerging data. Dose-escalation will continue in parallel. Patients recruited for tumour PD analysis will be required to have paired biopsies.

In Part B, expansion cohorts may be initiated to investigate preliminary efficacy and build on safety data in specific patient populations. Expansions may be initiated at more than one dose level depending on emerging data. A sample size of approximately 30 evaluable patients per Part B expansion cohort is sufficient for preliminary detection of an efficacy signal. A mean of 2 cohorts for each of the 4 patient populations in B1-B4 is estimated plus 1 cohort for B5. Thus, in total, approximately 270 patients are planned.

These are summarised in the study flow chart shown in Figure 1.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule.

Core Inclusion Criteria

For inclusion in the study, patients must fulfil all the following criteria:

- Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses. If a patient declines to participate in any voluntary

exploratory research and/or optional genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

2. Age ≥ 18 at the time of screening
- 5 3. Patients must have histological or cytological confirmation of advanced malignancy considered to be suitable for study treatment.
4. Eastern Cooperative Oncology Group Performance status (ECOG PS: 0-2) with no deterioration over the previous 2 weeks
5. Life expectancy ≥ 12 weeks
- 10 6. Progressive cancer at the time of study entry
7. Patients must have evaluable disease as defined in module-specific criteria for Part A and Part B
8. Female subjects of childbearing potential:
 - 15 (a) Must have a negative pregnancy test result at screening and prior to each cycle of study treatment
 - (b) If sexually active with a non-sterilized male partner, must use at least one highly effective method of birth control from screening to approximately 6 months after the last dose of study treatment in combination with one effective method (male condom plus spermicide) from screening until approximately 6 months after the last
 - 20 dose of study treatment.
9. Female subjects must not breastfeed and must not donate or retrieve ova for their own use from screening to approximately 6 months after the last dose of study treatment.
10. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to
- 25 approximately 6 months after the last dose of study treatment (Note: Male condoms are not reliable as a sole contraception method. In countries where spermicide is not approved, use of male condoms without spermicide is permitted). It is strongly recommended that female partners of male patients also use at least one highly effective method of contraception throughout this period. In addition, male patients must
- 30 refrain from fathering a child or donating sperm during the study and for approximately 6 months after the last dose of study treatment.
11. Adequate organ and marrow function (in the absence of transfusions or growth factor support within 14 days prior to enrolment) as defined below in Table 4:

Table 4 - Criteria for adequate organ and marrow function

Category	Parameter	Value
Hematological	Hemoglobin	≥ 9.0 g/dL (5.59 mmol/L)
	Absolute neutrophil count	$\geq 1.5 \times 10^9/L$ (1,500 per mm^3)
	Platelet count	$\geq 100 \times 10^9/L$ (100,000 per mm^3)
	INR	≤ 1.5
Hepatic	Total bilirubin	$\leq 1.5 \times ULN$ in the absence of Gilbert's syndrome
		$\leq 3 \times ULN$ if the subject has Gilbert's syndrome
	ALT and AST	$\leq 2.5 \times ULN$ in the absence of liver metastases
		$\leq 5 \times ULN$ in presence of liver metastases ^a
Renal	Calculated creatinine clearance by modified Cockcroft-Gault (Rostoker 2007)	≥ 45 mL/minute

ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; ULN = upper limit normal

^a In the presence of liver metastases and raised ALT/AST between 2.5-5 $\times$ ULN, patients can only be enrolled if total bilirubin level is $< 1.5 \times ULN$.

12. For Part B expansion cohorts: Provision of formalin-fixed and paraffin embedded (FFPE) tumour specimen is mandatory, where available, except if stated that it is optional in a specific Module. An archival tissue specimen is preferred but a new tissue sample may be used (if, for example, it is routine at a site to undertake biopsy of metastatic lesions).

Core Exclusion Criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Treatment with any of the following:

- (a) Nitrosourea or mitomycin C within 6 weeks of the first dose of study treatment
 (b) Any investigational agents or study drugs from a previous clinical study within 5 half-lives or 3 weeks (whichever is shorter) of the first dose of study treatment

- (c) Any other anti-cancer treatment within the following time periods prior to the first dose of study treatment:
- (i) Cytotoxic and non-cytotoxic treatment: 3 weeks or 5 half-lives (whichever is shorter)
 - 5 (ii) Biological products including immuno-oncology agents: 4 weeks before enrolment
- (d) Any live virus or bacterial vaccine within 28 days of the first dose of study treatment
2. Concomitant use of medications or herbal supplements known to be cytochrome P450 3A4 (CYP3A4) strong and moderate inhibitors or inducers, or inability to stop use at
10 least 21 days or at least 5 half-lives (whichever is shorter) before the first dose of study treatment until 30 days after the last dose of study treatment.
 3. Concomitant use of drugs that are known to prolong or shorten QT and have a known risk of Torsades de Pointes.
 4. During the 4 weeks prior to the first dose, receiving continuous corticosteroids at a dose
15 of >10 mg prednisone/day or equivalent for any reason.
 5. Major surgery within 4 weeks of the first dose of study treatment.
 6. Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 2 weeks of the first dose of study treatment.
 7. With the exception of alopecia, any unresolved toxicities from prior therapy greater than
20 Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment.
 8. Any history of persisting (>2 weeks) severe pancytopenia due to any cause (absolute neutrophil count [ANC] <0.5 × 10⁹/L or platelets <50 × 10⁹/L)
 9. Spinal cord compression or brain metastases unless asymptomatic, treated and stable
25 and not requiring continuous corticosteroids at a dose of >10 mg prednisone/day or equivalent for at least 4 weeks prior to start of study treatment
 10. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is
30 not required.
 11. Patients with any known predisposition to bleeding (e.g., active peptic ulceration, recent [within 6 months] haemorrhagic stroke, proliferative diabetic retinopathy).
 12. Any of the following cardiac criteria:
 - (a) Mean resting corrected QT interval (QTcF) >450 milliseconds or QTcF<340
35 milliseconds obtained from triplicate electrocardiograms (ECGs) and averaged, recorded within 5 minutes

- (b) Any factors that increase the risk of QT prolongation, shortening or risk of arrhythmic events such as hypokalaemia, congenital long or short QT syndrome, family history of long QT syndrome, familial short QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong or shorten the QT interval.
- (c) Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g., complete left bundle branch block, second or third degree atrioventricular (AV) block and clinically significant sinus node dysfunction not treated with pacemaker.
13. Other cardiovascular diseases as defined by any of the following:
- (a) Symptomatic heart failure (as defined by New York Heart Association [NYHA] class ≥ 2),
- (b) uncontrolled hypertension,
- (c) hypertensive heart disease with significant left ventricular hypertrophy
- (d) acute coronary syndrome (ACS)/acute myocardial infarction (AMI), unstable angina pectoris, coronary intervention procedure with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 6 months.
- (e) cardiomyopathy of any etiology
- (f) presence of clinically significant valvular heart disease
- (g) history of atrial or ventricular arrhythmia requiring treatment; subjects with atrial fibrillation and optimally controlled ventricular rate are permitted
- (h) transient ischaemic attack, or stroke within 6 months prior to screening
- (i) patients with symptomatic hypotension at screening
14. Patients with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML.
15. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD5305
16. Known allergy or hypersensitivity to investigational product(s) or any of the excipients of the investigational product(s)
17. Any concurrent anti-cancer therapy
18. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements
19. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the study treatment or interpretation of subject safety or study results

20. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
21. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
22. Previous study treatment assignment in the present study (i.e., dosing with AZD5305 previously initiated in this study)
23. Uncontrolled intercurrent illness within the last 12 months, including but not limited to, active interstitial lung disease, serious chronic GI conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

In addition, the following are considered criteria for exclusion from the exploratory genetic research:

Previous allogeneic bone marrow transplant

Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection

Specific Inclusion Criteria

For inclusion in the different Parts, they must also meet the following inclusion criteria. If the criteria in the different Parts is different from that in the core criteria, the specific criteria should be followed.

In Part A (monotherapy dose-escalation):

1. Patients must have one of the following:

(a) Histologically or cytologically confirmed relapsed advanced ovarian*, fallopian tube or primary peritoneal cancer and evidence of a predicted loss of function germline or tumour mutation in one of the following homologous recombination repair genes: *BRCA1*, *BRCA2*, *PALB2*, *RAD51C* or *RAD51D*

NOTE: *Patients with stromal, sex cord or germ cell tumours are excluded. Patients with carcinosarcoma are eligible.

(b) Histologically or cytologically confirmed HER2-negative carcinoma of the breast with recurrent locally advanced or metastatic disease and evidence of a predicted loss of function germline or tumour mutation in one of the following homologous recombination repair genes: *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, or *RAD51D*

(c) Histologically or cytologically confirmed advanced/metastatic CRPC and evidence of a predicted loss of function germline or tumour mutation in one of the following homologous recombination repair genes: *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, or *RAD51D*

(d) Histologically or cytologically confirmed advanced/metastatic pancreatic cancer and evidence of a predicted loss of function germline or tumour mutation in one of the following homologous recombination repair genes: *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, or *RAD51D*

2. Patients must have evaluable disease:

(a) At least one measurable and/or non-measurable lesions per RECIST v1.1 that can be accurately assessed at baseline and suitable for repeated assessments by CT or MRI scans; and/or

(b) Patients with ovarian cancer will be eligible if their disease is assessable by Gynecologic Cancer InterGroup (GCIg) CA125 response criteria (pre-treatment sample must be at least twice the ULN within 2 weeks prior to starting treatment); and/or

(c) Patients with prostate cancer will be eligible if they have PSA evaluable disease as defined by PSA levels $\geq 1\text{ng/ml}$.

3. Patients may have received up to one prior line of therapy with a PARPi-based regimen (either as a treatment or as maintenance)

4. In the opinion of the Investigator, patients must be suitable for treatment with a PARPi.

5. Patients receiving non-Vitamin K antagonist oral anticoagulants may be enrolled with an international normalized ratio (INR) <2 ; patients with other clinical causes of INR increase (such as bleeding disorders, impaired hepatic synthesis) should be excluded.

Part A dose-escalation cohorts may be expanded to evaluate further the safety, PK, PD, and biological efficacy of AZD5305.

1. Patients recruited specifically for PD evaluation must have at least 1 tumour suitable for paired biopsies and be willing to consent to pre and on-treatment biopsies.

In Part B expansions:

1. Patients must not have received prior therapy with a PARPi-based regimen (either as a treatment or as maintenance).

2. Patients must have at least one lesion, not previously irradiated (or with evidence of disease progression following radiation), that can be accurately measured at baseline as $\geq 10\text{ mm}$ in the longest diameter (except lymph nodes which must have short axis $\geq 15\text{ mm}$) with CT or MRI and which is suitable for accurate repeated assessment as per RECIST v1.1; and/or

For patients with ovarian cancer; disease that is assessable by GCIG CA125 response criteria (pre-treatment sample must be at least twice the ULN within 2 weeks prior to starting treatment); and/or

Patients with prostate cancer will be eligible if they have PSA evaluable disease as defined by PSA levels $\geq 1\text{ng/ml}$.

3. Patients receiving non-Vitamin K antagonist oral anticoagulants may be enrolled with an INR < 2 ; patients with other clinical causes of INR increase (such as bleeding disorders, impaired hepatic synthesis) should be excluded.

10 In Part B1 expansion (*BRCA1m*, *BRCA2m*, *PALB2m*, *RAD51Cm* or *RAD51Dm* HER2-negative breast cancer):

1. Patients must have metastatic or recurrent locally advanced histologically or cytologically confirmed HER2-negative carcinoma of the breast and evidence of a predicted loss of function germline or tumour mutation in either *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, or *RAD51D*.

2. Patients who have received platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer are eligible to enter the study provided there has been no evidence of disease progression during the platinum chemotherapy.

3. Patients who have received prior platinum based chemotherapy as neo-adjuvant/adjuvant treatment are eligible provided at least 12 months has elapsed between the last dose of platinum-based treatment and study treatment.

In Part B2 expansion (*BRCA1m*, *BRCA2m*, *PALB2m*, *RAD51Cm*, or *RAD51Dm* ovarian cancer):

25 1. Patients must have histologically or cytologically confirmed relapsed advanced ovarian*, fallopian tube or primary peritoneal cancer and evidence of a predicted loss of function, germline or tumour mutation in either *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, or *RAD51D*

NOTE: *Patients with stromal, sex cord or germ cell tumours are excluded. Patients with carcinosarcoma are eligible.

2. Patients must have received at least one prior line of platinum-containing chemotherapy for advanced disease.

3. Subjects must be partially-platinum-sensitive (defined as progression 6 to 12 months after the end of the last platinum-based chemotherapy) or platinum-sensitive (defined as progression >12 months after the end of the last platinum-based chemotherapy);

In Part B3 expansion (ovarian cancer with high genomic instability):

1. Patients must have histologically or cytologically confirmed relapsed advanced ovarian*, fallopian tube or primary peritoneal cancer and evidence of HRD as determined by either:

- A Myriad genomic instability score (GIS) score ≥ 42
- An FMI global loss of heterozygosity (LoH) score $\geq 16\%$

*Patients with stromal, sex cord or germ cell tumours are excluded. Patients with carcinosarcoma are eligible.

2. Patients must not have a known predicted loss of function germline or tumour mutation in either *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, or *RAD51D*.

3. Patients must have received at least one prior line of platinum-containing chemotherapy for advanced disease.

4. Patients must be partially-platinum-sensitive (defined as progression 6 to 12 months after the end of the last platinum-based chemotherapy) or platinum-sensitive (defined as progression >12 months after the end of the last platinum-based chemotherapy).

In Part B4 expansion (*BRCA1/2* mutated prostate cancer):

1. Patients must have histologically or cytologically confirmed metastatic castrate-resistant prostate cancer where metastatic status is defined as at least one documented metastatic lesion on either bone scan or CT/MRI scan. Subjects whose disease spread is limited to regional pelvic lymph nodes or local recurrence (e.g., bladder, rectum) are not eligible.

2. Patients must have a known predicted loss of function germline or somatic mutation in either *BRCA1* or *BRCA2*.

3. Subjects must have progressed on prior next-generation hormonal agent (NHA) (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC. Determination of progression is done per local investigator.

4. Serum testosterone levels ≤ 50 ng/dL (≤ 1.75 nmol/L) within ($\leq$) 28 days before treatment allocation). If the patient is being treated with luteinising hormone-releasing hormone (LHRH) agonists (patients who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to Cycle 0 Day 1 and must be continued throughout the study. Subjects without prior surgical castration must be currently taking and willing to continue LHRH analogue (agonist or antagonist) therapy throughout the duration of study treatment.

5. Documented prostate cancer progression as assessed by the investigator with one of the following:

- PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 1 $\mu\text{g/L}$ (1 ng/ml).
- Radiographic progression of soft tissue disease by RECIST criteria with or without PSA progression.
- Radiographic progression of bone metastasis with two or more documented new bone lesions on a bone scan with or without PSA progression.

6. Patients should not have received prior treatment with DNA-damaging cytotoxic chemotherapy, except if for a non-prostate cancer indication and last dose > 5 years prior to treatment allocation. For example, subjects who have received prior mitoxantrone or platinum-based chemotherapy for prostate cancer are excluded. Prior estramustine therapy and prior use of taxanes are allowed.

In Part B5 expansion (HRRm, non-BRCA1/2 mutated prostate cancer):

1. Patients must have histologically or cytologically confirmed metastatic castrate-resistant prostate cancer where metastatic status is defined as at least one documented metastatic lesion on either bone scan or CT/MRI scan. Subjects whose disease spread is limited to regional pelvic lymph nodes or local recurrence (e.g., bladder, rectum) are not eligible.
2. Patients must have a known predicted loss of function germline or somatic mutation in one of the HRRm genes (ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L [without BRCA1/2m]).
3. Subjects must have progressed on prior NHA (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC. Determination of progression is done per local investigator.
4. Serum testosterone levels ≤ 50 ng/dL (≤ 1.75 nmol/L) within ($\leq$) 28 days before treatment allocation). If the patient is being treated with LHRH agonists (patients who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to Cycle 0 Day 1 and must be continued throughout the study. Subjects without prior surgical castration must be currently taking and willing to continue LHRH analogue (agonist or antagonist) therapy throughout the duration of study treatment.
5. Documented prostate cancer progression as assessed by the investigator with one of the following:
 - PSA progression defined by a minimum of three rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 1 $\mu\text{g/L}$ (1 ng/ml).

- Radiographic progression of soft tissue disease by modified RECIST v1.1 criteria with or without PSA progression.
- Radiographic progression of bone metastasis with two or more documented new bone lesions on a bone scan with or without PSA progression.

5 6. Patients should not have received prior treatment with DNA-damaging cytotoxic chemotherapy, except if for a non-prostate cancer indication and last dose > 5 years prior to treatment allocation. For example, subjects who have received prior mitoxantrone or platinum-based chemotherapy for prostate cancer are excluded. Prior estramustine therapy and prior use of taxanes are allowed.

10

Starting Dose and Schedule

Studies with AZD5305, as well as clinically approved PARP inhibitors, have shown maintaining free plasma concentrations above the DLD-1 *BRCA*^{-/-} cell growth inhibition assay IC₉₅ achieves maximal pre-clinical efficacy in vivo in a mouse xenograft model (MDA-MB-436).

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AZD5305 was well-tolerated in pre-clinical toxicology experiments. Based on international guidance for starting dose selection for agents in cancer patients (ICH S9), which recommends that the starting dose should be set at a dose of 1/10 of the Severely Toxic Dose in 10% of the animals (STD 10) in rodent toxicity studies, 50 mg/daily is considered a safe starting dose of AZD5305.

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A dose of 10 mg/daily is predicted to give a steady state free C_{max} and AUC of 0.080 µM and 0.87 µM.h respectively (equivalent to 350 ng/mL and 3800 ng.h.mL⁻¹ total).

25 Each cycle will be 28 days.

Study Treatment (AZD5305)

AZD5305 will be administered as a film-coated tablet with a unit-dose strength of 0.5 to 100 mg.

30

Dose-escalation

The dose-escalation study flow chart is presented in Figure 1 and Table 5 and shows an example dose-escalation scheme. After the first DLT has been observed (at any dose), a Bayesian logistic regression model will be used to inform subsequent dose selections. On the basis of the pre-clinical toxicology data, allowing a start dose of up to 50 mg, rapid dose-

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escalation from 10 mg to 40 mg may be considered, following review of early PK and safety data.

All potential dose-escalation and de-escalation doses and schedules after the starting dose may be adjusted in light of emerging safety, tolerability, and/or PK data. A minimum of 3 patients will be recruited per cohort. Part A dose-escalation cohorts may be expanded at to evaluate further the safety, tolerability, PK, PD, and biological activity of AZD5305, provided the dose has already been declared as tolerated. Patients with specific tumour types and prior treatment status (within the current eligibility criteria) may be enrolled in these Part A expansion cohorts based on emerging data. Dose-escalation will continue in parallel. Patients recruited for tumour PD analysis will be required to have paired biopsies.

Sentinel dosing will be applied with a single patient exposed for a minimum of 24 hours before further patients are enrolled at that dose level. In the absence of any significant toxicities in the first patient as confirmed by the treating physician, the patients for the remainder of the cohort may be enrolled, concurrently or sequentially. If significant toxicities are observed during the first 24 hours of observation in the first patient of the cohort, further enrolment into the cohort will be halted until the all the safety and PK data related to that patient (if relevant) and cumulative data from all trial patients has been reviewed to determine the appropriate action.

Table 5 - Example of dose-escalation scheme

Cohort	AZD5305 (mg/daily)
1	10
2	20
3	40
4	80
5	160
Cohort n (escalate to MTD or MFD)	No more than 100% increment

MFD = maximum feasible dose: MTD = maximum tolerated dose;

There will not be any pause awaiting the assessment of Part A PD/PK expansion cohorts. Dose-escalation and de-escalation will follow the Bayesian adaptive design scheme below:

- If no DLT at any dose has been observed, then dose-escalation may occur without modelling.

- After the first DLT has been observed (at any dose), a Bayesian logistic regression model will be used to inform subsequent dose selections. After each cohort, cumulative data on the evaluable patients will be used to estimate the predicted probability of a DLT at each potential next dose.
- 5 • The recommendation for the next dose will be based on the following principles:
- The recommendation for the next dose will be chosen to target a DLT of 25% for monotherapy but ignoring any dose for which the model suggests the probability of a DLT exceeds 33%. This will allow efficient identification of the MTD whilst restricting the risk of overdosing.

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Dose-escalation and de-escalation will be completed when any of the following occur:

- The target toxicity of 25% (for monotherapy) is reached and the required precision of the estimated MTD is achieved (i.e., the ratio of the upper/lower 95% credible interval limits for the estimated MTD <5.0).
- 15 • The maximum number of evaluable patients for the dose-escalation cohort has been reached.
- The MFD is achieved.
- Decision made to stop dose-escalation.

20

Prior established dose toxicity relationship at doses at which 10% and 50% (or similar) of patients experience DLTs will be used to inform the Bayesian model.

1. There is no minimum time period required between completion of dosing in the last evaluable patient from 1 cohort and the start of dosing in the subsequent cohort.
2. Intermediate dose levels, dosing intervals and/or frequency, and/or schedules may be evaluated prior to declaring the RP2D, which will be guided by the evolving safety, preliminary efficacy, PK and PD data.

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Dose-limiting Toxicity

DLTs will be evaluated during Cycle 0 and Cycle 1 of treatment. Toxicity will be graded according to the CTCAE National Cancer Institute (NCI) v5.0.

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A DLT is defined as any toxicity that occurs from the first dose of study treatment up to and including the planned end of Cycle 1 (the DLT assessment period) that is assessed as unrelated to the disease or disease-related processes under investigation and which includes:

Haematological toxicities including:

- Grade 4 neutropenia ($\text{ANC} < 500 \text{ cells/mm}^3$) lasting > 4 days; Grade 3 or above neutropenia ($\text{ANC} < 1000 \text{ cells/mm}^3$) of any duration accompanied with a single temperature of $> 38.3^\circ\text{C}$ or a sustained temperature of $\geq 38.0^\circ\text{C}$ (for more than one hour) and/or systemic infection.
- 5 • Grade 4 thrombocytopenia ($< 25,000/\text{mm}^3$) lasting > 1 day or Grade 3 or above thrombocytopenia ($< 50,000/\text{mm}^3$) with clinically significant bleeding attributable to thrombocytopenia.
- Any other confirmed haematological toxicity $\geq$ CTCAE Grade 4 (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).
- 10 • Haematological AEs requiring dose interruption for ≥ 14 days

Cardiac DLTs including:

- symptomatic tachycardia or tachycardia with resting supine heart rate of > 125 beats per minute persisting for at least 10 minutes
- 15 • hypotension requiring medical intervention e.g., IV fluids
- any other cardiac toxicity of CTCAE $>$ Grade 2
- QTcF interval value < 340 milliseconds confirmed on at least 2 separate ECGs, recorded 5 minutes apart
- 20 • QTcF prolongation > 500 milliseconds or QTcF prolongation from baseline by > 60 milliseconds confirmed on at least 2 separate ECGs, recorded 5 minutes apart

Non-haematological toxicities (CTCAE Grade ≥ 3) including:

- Nausea, vomiting or diarrhoea lasting for ≥ 72 hours despite administration of maximal supportive therapy.
- 25 • Any treatment-related event, including significant dose reductions, omissions or delays, judged to be a DLT. Examples may include confirmed laboratory abnormalities (CTCAE Grade ≥ 3 or above), CTCAE Grade 2 toxicities that are clinically significant and/or unacceptable according to the Investigator, toxicities that result in an inability to administer at least 75% of study treatment during Cycle 1 or delay the administration of study treatment in the subsequent cycle by ≥ 7 consecutive days.
- 30 • Any death not clearly due to the underlying disease or extraneous causes

35 DLTs will not include the following:

- Transient isolated laboratory abnormalities which are not considered clinically significant and resolve to baseline within 72 hours without any intervention.
- Alopecia
- CTCAE Grade ≥ 3 nausea, vomiting or diarrhoea lasting < 72 hours in the absence of maximum supportive therapy
- Grade 3 fatigue < 5 days.
- Grade 3 hypertension in the absence of maximal medical therapy
- Grade 3 electrolyte abnormalities that resolve to Grade ≤ 1 within 48 hours spontaneously or with conventional medical intervention and that are not clinically complicated.
- Grade 3 rash that resolves to Grade ≤ 1 within 3 weeks.
- Grade 3 or Grade 4 elevation in serum amylase and/or lipase that are not associated with clinical or radiographic evidence of pancreatitis

15 In order to define a DLT, patients should not be prophylactically prescribed growth factor support, blood products, antiemetics, anti-diarrhoeals or antipyretics during Cycle 1 of therapy, unless this is part of the standard supportive medications required for combination agents.

20 *Definition of DLT-evaluable Patients*

For decisions on dose-escalation (Part A), an evaluable patient is defined as a patient that has received AZD5305 and either:

- Has completed the safety follow-up and has received at least 75% of the total amount of the planned dose of AZD5305 through the DLT assessment period; or
- Has experienced a DLT during the DLT assessment period.

Definition of MTD

The MTD is defined as the highest dose at which the predicted probability of a DLT is less than or equal to 25% (for monotherapy) or 30% (for combinations). At least 6 evaluable patients are required to determine the MTD.

Definition of Maximum Feasible Dose (MFD)

A dose and schedule will be considered non-feasible and escalation will cease where PK parameters determine that a maximum absorbable dose has been reached, or where the maximum dose permitted based on the Chemistry Manufacturing and Controls (CMC) quality

specifications (currently set against a maximum daily dose of 320 mg) has been reached, whichever is the lower dose.

Definition of Predicted Effective Dose

- 5 Determination of the predicted effective dose (PED) will be based on pre-clinical PK/PD modelling and human PK. It is defined as the AZD5305 dose required to achieve a minimum steady-state plasma drug concentration ($C_{\min,ss}$) above 28 ng/mL (total plasma, IC₉₅ DLD-1 *BRCA2*^{-/-}) in the majority of patients. If $C_{\min,ss}$ is not available, other PK parameters including area under the curve (AUC) and maximum plasma drug concentration ($C_{\max}$) could
10 be used based on emerging clinical data; additionally, alternate dosing schedules that achieve similar target engagement may also be evaluated.

Definition of Recommended Phase 2 Dose (RP2D)

- The RP2D will take into account the MTD (or alternative doses/schedules in the absence of
15 MTD), MFD, PED, PK, and biological/clinical activity (PD data), as well as data beyond Cycle 1 during dose-escalations. The RP2D will not exceed the maximum tolerated dose.

Collection of Plasma Samples for ctDNA

A peripheral blood sample will be collected to provide plasma for ctDNA.

- 20 Testing may include (but is not limited to):
- Whether there is sufficient ctDNA in plasma for mutational testing
 - Correlation of baseline ctDNA levels and kinetics of ctDNA changes with clinical outcome measures
 - Correlation between tumour and plasma mutational status
 - 25 • Genetic alterations as potential mechanisms of sensitivity or resistance to AZD5305 treatment
 - Future diagnostic development

Efficacy Assessments

30 *RECIST v1.1 Assessments of Tumour*

The RECIST v1.1 guidelines for measurable and non-measurable TLs and non-target lesions (NTLs) and the objective tumour response criteria can be found in Eisenhauer 2009.

- At baseline, the imaging modalities used for assessment should be contrast enhanced
35 computer tomography (CT) (magnetic resonance imaging [MRI] where CT is contraindicated) scans of the chest, abdomen and pelvis (including liver and adrenal glands)

and should encompass all areas of known predilection for metastases in the disease under evaluation, and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Brain imaging (either with CT or MRI) is only required at baseline in patients with known or suspected brain metastases. Follow-up CT or MRI assessments will cover chest, abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites at which new disease is suspected should also be appropriately imaged. Radiological examinations performed in the conduct of this study should be retained at site as source data. All treatment decisions will be based on site assessment of scans.

Baseline radiological assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Scans obtained as part of standard clinical practice, prior to informed consent, but within the 28-day period are acceptable. The radiological confirmatory scans should be performed no less than 4 weeks after the prior assessment of tumour and preferably at the next scheduled visit (in the absence of clinically significant deterioration). The methods of assessment used at baseline should be used at each subsequent follow-up assessment through to objective confirmed radiological disease progression, as defined by Investigator assessed RECIST v1.1 or PCWG3 for patients with prostate cancer. Tumour assessments should be performed every 8 weeks from Cycle 1 Day 1 (± 1 week) or earlier, if disease progression is suspected. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should continue to be followed (unless they withdraw consent) until objective disease progression, as defined by RECIST v1.1 or PCWG3 for patients with prostate cancer. Scans confirming progression should not be conducted within 1 week after a progression biopsy to allow for reduction in inflammation.

If scans are performed outside of scheduled visit window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled visits whilst the patient remains on study treatment. If the patient interrupts treatment or incurs a treatment delay, scans should continue to occur at the protocol-defined frequency.

It is important to follow the schedule of assessments as closely as possible.

Bone scans

Patients with breast cancer should have a baseline bone scan performed in the screening period (28 days) prior to first dose of study treatment (AZD5305) and as close as possible to study treatment start. At follow-up, additional bone scans may be performed, if clinically indicated and should be performed at disease progression.

All prostate cancer patients should have a baseline bone scan in the screening period (28 days) prior to first dose. Follow-up bone scans should then be performed 8-weekly until disease progression for all prostate cancer patients.

Tumour Evaluation by RECIST v1.1

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR, PR, and stable disease (SD). The CR and PR will need to be confirmed. Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumour response will be calculated in comparison to the pre-dose tumour measurements obtained before starting treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment until the Investigator reassesses the patient's status at the next scheduled assessment (confirmation) or sooner if clinically indicated.

To achieve 'unequivocal progression' based on non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

Bone Lesion Assessment by PCWG3 (Applicable to Prostate Cancer Patients Only)

In patients with prostate cancer, disease progression will be deemed to have occurred if one or more of the following criteria is met:

- Soft tissue disease progression as defined by RECIST v1.1 (Table 6)
- Bone lesion progression by Prostate Cancer Working Group 3 (PCWG3) (Table 6)
- Death

In patients with prostate cancer, categorisation of tumour progression of bone lesions will be based on the PCWG3 criteria. Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions. When the bone scan is the sole indicator of progression, radiographic progression based on the appearance of new bone lesions is defined as:

At least two new lesions observed at the first post-baseline bone scan, with at least two additional new lesions observed at a subsequent bone scan (2 + 2 rule), or
Following the first post-baseline bone scan, at least 2 new lesions relative to the first post-baseline scan confirmed on a subsequent scan at least 6 weeks apart, as specified in PCWG3 criteria (Scher 2016). In situations where the scan findings are suggestive of a flare reaction, or apparent new lesion(s) may represent trauma, confirmation with other imaging modalities such as MRI (magnetic resonance imaging) or fine-cut CT (computer tomography) is required. The exception to this requirement occurs if multiple new areas of uptake are observed.

The requirements for determination and confirmation of radiographic progression by either bone scan (bone progression) or CT/MRI (soft tissue progression) are summarised in Table 6:

Table 6 Requirements for Documentation of Disease Progression in Patients with Prostate Cancer

Visit date	Criteria for bone progression (PCWG3)	Criteria for soft tissue progression (RECIST v1.1)
Week 8	3. 2 or more new lesions compared to baseline bone scan	5. Progressive disease on CT or MRI by RECIST v1.1
	4. <u>Requires confirmation scan</u> at least 6 weeks later with ≥ 2 additional lesions compared to Week 8 scan	6. No confirmation scan required

Visit date	Criteria for bone progression (PCWG3)	Criteria for soft tissue progression (RECIST v1.1)
Week 16 or later	7. 2 or more new lesions compared to Week 8 bone scan 8. <u>Requires confirmation scan</u> at least 6 weeks later for persistence or increase in number of lesions	9. Progressive disease on CT or MRI by RECIST v1.1 10. No confirmation scan required

Safety

All safety analyses will be performed on the safety analysis set. At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

- 5 Data from all cycles of initial treatment will be combined in the presentation of safety data. Graphical presentations of safety data may be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots may also be considered to investigate trends in parameters compared to baseline.

10

Exposure

Exposure to each study treatment, i.e., total amount of study treatment received will be listed for all patients. Total treatment duration and actual treatment duration (=total treatment duration excluding dose interruptions not in accordance with the protocol) will be

15 summarised for each study treatment and cohort by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least 1 non-protocolled dose interruption and at least 1 dose reduction will be presented.

20 Adverse events

AEs will be listed individually by patient and cohort. For patients who have a dose modification, all AEs (due to study treatment or otherwise) will be assigned to the initial dose group.

- 25 The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE Grade. The number and percentage of patients with AEs in different categories

(e.g., causally related, CTCAE Grade ≥ 3 etc.) will be summarised by dose regimen, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. SAEs will be summarised separately.

- 5 Any AE occurring before the first dose of study treatment (i.e., before study Day 1) will be included in the data listings but will not be included in the summary tables of AEs. Treatment-emergent AEs occurring prior to first dose of study treatment (i.e., before study Day 1) which subsequently worsen in severity following dosing will be included in the summary tables.

10

Any AE occurring within the defined 28-day follow-up period after discontinuation of study treatment will be included in the AE summaries. Any AEs in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings. AEs occurring after the 28-day follow-up period after
15 discontinuation of study treatment will be listed separately, but not included in the summaries.

Other safety data

- Hematology, clinical chemistry, vital signs, ECG data, ECOG PS, physical examination,
20 demographic data, medical histories and concomitant medications will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE Grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used for continuous variables. Categorical variables will be summarised by frequency counts and
25 percentages for each category (n [%]).

Details of any deaths will be listed for all patients.

Efficacy

30 Tumour Response Data

Tumour response data will be summarised for dosed patients with measurable disease at baseline, except for PFS that will be summarised for dosed patients.

Data will be listed and summarised by cohort using the following response categories: CR, PR, SD, disease progression and not evaluable (NE).

35

Waterfall plots (bar charts) indicating the percentage best change from baseline in sum of the diameters of TLs may be produced by cohort.

Tumour response includes the following variables:

- 5 • Percentage best change in TL
- DoR
- PFS
- ORR
- TTR

10

Additional tumour response criteria based on tumour markers may be considered for sensitivity analyses.

Derivation of Tumour Response Variables

15 Every 8 weeks ($\pm$ 1 week), or earlier if disease progression is suspected, patients will be programmatically assigned a RECIST v1.1 visit response of CR, PR, SD, and disease progression depending on the status of their disease compared to baseline and previous assessments.

20 Progression of TLs will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded during the study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

25 If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a response of NE unless there is evidence of progression in which case the response will be assigned as disease progression.

Percentage Best Change in TL

30 Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs.

Duration of Response (DoR)

35 Duration of response is defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the

absence of disease progression (PD) (i.e., date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

5

Time to Response (TTR)

The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was PR or CR that was subsequently confirmed.

10 **Progression-Free Survival (PFS)**

PFS is defined as the time from Cycle 1 Day 1 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression (i.e., date of PFS event or censoring – date of first dose +1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST v1.1 assessment prior to the 2 missed visits.

20 **Objective Response Rate (ORR)**

ORR will be assessed per RECIST v1.1. ORR is defined as the percentage of patients who have a confirmed visit response of CR or PR prior to any evidence of progression (as defined by RECIST v1.1).

25 For the analysis of ORR, the response evaluable set will be derived and will exclude patients who do not have measurable disease at baseline. Note that responses that occur after the start of subsequent anti-cancer therapy must be excluded from the derivation of ORR.

A visit response of CR is defined when all TLs and NTLs present at baseline have disappeared (with the exception of lymph nodes which must be <10 mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

35 In the case of SD, measurements should have met the SD criteria at least once after the study start.

When the Investigator reassesses the progression of the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

5 CA125 Response (Ovarian Cancer Patients)

The endpoint CA125 response is defined as at least a 50% reduction in CA125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA125 only if they have a pre-treatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

Pharmacokinetics

Following single dose and following multiple dose administration, plasma concentrations of AZD5305 and the following PK parameters may be determined (including but not limited to): AUC, C_{max}, and T_{max} as data allow.

PK analysis of plasma concentration data for AZD5305 will be performed using actual elapsed sampling times and standard non compartmental methods.

Venous blood samples (2.0 mL each) for determination of concentrations of AZD5305 in plasma will be taken at the times presented in Table 7. Time points post-dose are relative to the timing of AZD5305 dose.

Urine samples (10 mL) for the determination of concentrations of AZD5305 will be taken from the total urine sample provided during each of the collection intervals presented in Table 7. The date and time of collection and the date and time of freezing of each sample will be recorded. Additionally, the total volume/weight of each urine collection will be recorded.

Table 7 Blood and urine sampling schedule for AZD5305

Cycle and Day	Time for Blood samples	Collection of intervals for urine samples
Cycle 0 Day 1 & Cycle 1 Day 15	Pre dose	Pre-dose (spot urine)
Cycle 0 Day 1 & Cycle 1 Day 15	30 min post-dose	0 to 4 h

Table 7 **Blood and urine sampling schedule for AZD5305**

Cycle and Day	Time for Blood samples	Collection of intervals for urine samples
Cycle 0 Day 1 & Cycle 1 Day 15	1 h post-dose	
Cycle 0 Day 1 & Cycle 1 Day 15	1.5 h post-dose	
Cycle 0 Day 1 & Cycle 1 Day 15	2 h post-dose	
Cycle 0 Day 1 & Cycle 1 Day 15	3 h post-dose	
Cycle 0 Day 1 & Cycle 1 Day 15	4 h post-dose	4 to 8 h
Cycle 0 Day 1 & Cycle 1 Day 15	6 h post-dose	
Cycle 0 Day 1 & Cycle 1 Day 15	8 h post-dose	8 to 24 h ^a
Cycle 0 Day 2 & Cycle 1 Day 16	24 h post-dose	
Cycle 0 Day 3	48 h post-dose	24 to 48 h ^a
Cycle 1 Day 1, Cycle 1 Day 8 , Cycle 2 Day 1 and Cycle 3 Day 1	Pre dose and 1 to 4 h post- dose	None
Cycle 1 Day 8-15	24 h post-dose (to match biopsy collection) ^b	None
Discontinuation /EoT	Discontinuation/EoT visit	None

EoT = end of treatment; h = hour(s)

^a Urine collected at home^b Sample only collected if biopsy is performed**Pharmacodynamics**

The change from baseline in PD biomarkers, for example poly-ADP-ribosylation (PAR) will be assessed, as well as other PD parameters, as data allow, and will be described on the

5 PD analysis set.

The collection of blood-based PD biomarker samples is mandatory to obtain a preliminary assessment of PARP1 target inhibition in patients. Peripheral blood samples will be collected as detailed in Table 8. In addition, there will be PK samples collected at the same time as PD samples to allow exploration of the exposure/PD relationships. The exact time of PD sample collection will be noted. The collection of the PD samples may be adjusted during the study and according to local regulatory approval, dependent on emerging data, in order to ensure appropriate characteristics of the plasma concentration-time profile.

Table 8 Pharmacodynamic blood sample collection

Cycle and Day	Time for Blood samples for PD (PAR/PARP)	Time for Blood samples for PD (Immune markers, proteomics)	Time for Blood samples for ctDNA
Screening	Post-consent	None	Post-consent
Cycle 0 Day 1 & Cycle 1 Day 15	Pre-dose	Pre-dose	None
Cycle 0 Day 1 & Cycle 1 Day 15	1 h post-dose	None	None
Cycle 0 Day 1 & Cycle 1 Day 15	4 h post-dose	None	None
Cycle 0 Day 2, Cycle 1 Day 16	24 h post-dose	None	None
Cycle 0 Day 3	48 h post-dose	None	None
Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15	Pre-dose & 1-4 h post-dose	Pre-dose at Cycle 1 Day 1 and Cycle 1 Day 15	Pre-dose at Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 1 Day 15
Cycle 2 Day 1	Pre-dose & 1-4 h post-dose	Pre-dose	Pre-dose
Cycle 2 Day 15	None	None	Pre-dose
Cycle 3 Day 1	Pre-dose & 1-4 h post-dose	Pre dose	Pre-dose

Table 8 Pharmacodynamic blood sample collection

Cycle and Day	Time for Blood samples for PD (PAR/PARP)	Time for Blood samples for PD (Immune markers, proteomics)	Time for Blood samples for ctDNA
Cycle 4 onwards	None	Pre-dose Day 1, Pre-dose up to Cycle 5 Day 1	At each radiological assessment
Cycle 1 Day 8-15	24 h post-dose (to match PK collection) ^a	None	None
Discontinuation (EoT)	At discontinuation/EoT visit	None	At discontinuation/EoT visit

ctDNA = circulating tumour deoxyribonucleic acid; EoT = end of treatment; h = hour(s); PAR = poly adenosine diphosphate-ribose; PARP = poly adenosine diphosphate-ribose (ADP-ribose) polymerase; PD = pharmacodynamic; PK = pharmacokinetic

^a Sample only collected if biopsy is performed

Exploratory Analyses

Where appropriate, tumour markers will be collected e.g., CA125, prostate specific antigen (PSA), CA19.9 and CA15.3 from patients with ovarian, prostate, pancreatic and breast cancer, respectively.

The efficacy analysis (ORR, TTR, PFS, DoR) will be repeated for various biomarker subgroups defined at baseline: *tBRCA*, *gBRCA*, *sBRCA*, BRCA methylation, *non-BRCAm*, HRR (individually and as a panel), genomic instability status, *RAD51* nuclear foci.

Exploratory analyses will be described in the SAP or in dedicated analysis plans according to the exploratory endpoints. The results of exploratory analyses may be reported separately from the CSR.

Collection of PBMCs

PBMCs will be assessed for PD changes in biomarkers that may include but are not limited to protein/gene levels and post-translational modifications such as poly (ADP-ribose).

Peripheral whole blood subpopulations may also be enumerated to determine any PD

- 5 effects of potential immunological relevance, such as changes in the number of B-lymphocytes or regulatory T-lymphocytes or evaluated for T-cell receptor clonality or gene expression changes.

The number of samples taken, as well as the volume required for each analysis, may be

- 10 changed during the study as new data on AZD5305 becomes available.

Collection of Plasma Samples for ctDNA and other Soluble Analytes

A peripheral blood sample will be collected to provide plasma for ctDNA to assess clinical response and to interrogate changes in genetic alterations as potential mechanisms of

- 15 sensitivity/ resistance to AZD5305 treatment. Blood samples for ctDNA are to be collected as detailed in Table 8. Other soluble analytes in plasma such as proteins, cytokines may be analysed for downstream effects of PARP1 inhibition.

Collection of Tumour Samples for PD Assessment

Paired fresh tumour biopsies for PD assessment are optional for all patients in Module 1 except for patients recruited to a Part A cohort expansion for PD assessment, in which case they are mandatory. Paired biopsies will be collected within 15 days prior to Cycle 0 Day 1 and during the on-treatment period (any time in Cycle 1 between Days 8 and 15 at 24 hours post dose).

25

Accessible lesions are defined as tumour lesions which are amenable to repeat biopsy, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

30

Blood samples for PK will also be taken at the time of any on-treatment biopsy sample.

Biopsy samples will be analysed for the effects of PARP1 inhibition in tumour and may include but is not limited to the assessment of the following biomarkers: poly (ADP-ribose), PARP-DNA trapping, pH2AX (Ser139) and RAD51 foci. On-treatment biopsy timing may be

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refined with emerging PK and/or PD data during the course of the study.

Results

The following results are derived from the above studies carried out on 61 patients dosed from 10 mg to 140 mg QD. The data cut-off date is 22 February 2022.

5

The patients can be characterised as follows:

Characteristics	Total (N=61)
Median age (range), yrs	56.0 (25, 78)
Age ≥65 years, n (%)	16 (26.2)
Male / female, n (%)	20 (32.8) / 41 (67.2)
Race, n (%)	
White	40 (65.6)
Asian	11 (18.0)
Black/African American	3 (4.9)
Other	4 (6.6)
<i>Pending</i>	3 (4.9)
ECOG PS 0 / 1, n (%)	25 (41.0) / 36 (59.0)
Tumor type, n (%)	
Ovarian	19 (31.1)
Platinum sensitive (PD ≥ 6 mos post-platinum)	4 (21.1)
Platinum Resistant/Refractory	14 (73.7)
<i>Pending</i>	1 (5.3)
Breast	18 (29.5)
TNBC (triple-negative breast cancer)	5 (27.8)
HR+	12 (66.7)
<i>Pending</i>	1 (5.6)
Pancreatic	12 (19.7)
Prostate	10 (16.4)
<i>Pending</i> ¹	2 (3.3)
Alteration for eligibility (by eCRF), n (%)	
BRCA1	21 (34.4)
BRCA2	29 (47.5)
PALB2	7 (11.5)
RAD51C	1 (1.6)

<i>RAD51D</i>	0
<i>Pending</i>	3 (4.9)
Median number of prior lines of therapy (range)	3 (0, 8)
Prior PARPi / platinum therapy status, n (%)	
PARPi and/or platinum	44 (72.1)
Both PARPi and platinum	18 (40.9)
Platinum only	20 (45.5)
PARPi only	6 (13.6)
No PARPi or platinum	17 (27.9)

eCRF, electronic case report form; HR, hormone receptor

Dose	Number of Patients
10mg	8
20mg	19
40mg	17
60mg	10
90mg	3
140mg	4

5 Plasma concentration

Figure 2A shows the AZD5305 plasma concentration against the time after a single dose.

Figure 2B shows the AZD5305 plasma concentration against the time after a dose during continuous dosing (cycle 1 Day 15).

Dose	Symbol	Dose	Symbol
10mg		60mg	
20mg		90mg	
40mg		140mg	

- 10 Dose proportional increase in exposure (C_{max} and AUC) was observed with increasing dose (10 – 140 mg QD). There was quick onset (T_{max} 0.5-3 h) with mean terminal elimination half-life 13.1 - 16.4 hours across the different cohorts. Steady state C_{min} above target effective concentration (TEC) was achieved in all patients with mean fold C_{min}/TEC 7.12 and 55.88 at 10 mg and 140 mg QD, respectively

TEC, target effective concentration; TEC: IC₉₅ in DLD-1 BRAC2-/-

Safety summary

AE category, n (%)	AZD5305 10 mg QD (n=8)	AZD5305 20 mg QD (n=19)	AZD5305 40 mg QD (n=17)	AZD5305 60 mg QD (n=10)
Duration of therapy (months), median (range)	4.8 (1.8- 14.9)	2.8 (0.9- 11.5)	2.0 (0.4- 9.6)	1.95 (0- 3.8)
All TEAEs	8 (100.0)	19 (100.0)	17 (100.0)	8 (80.0)
Grade ≥3 AEs	3 (37.5)	10 (52.6)	6 (35.3)	3 (30.0)
Serious TEAEs	0	9 (47.4)	5 (29.4)	2 (20.0)
Discontinuations	0	0	0	1 (10.0)
Dose reductions	1 (12.5)	0	1 (5.9)	0
AZD5305-related TEAEs	5 (62.5)	11 (57.9)	9 (52.9)	4 (40.0)
Grade ≥3 AEs	3 (37.5)	3 (15.8)	1 (5.9)	0
Serious TEAEs	0	0	0	0
Discontinuations	0	0	0	0
Dose reductions	1 (12.5)	0	1 (5.9)	0

5

AE category, n (%)	AZD5305 90 mg QD (n=3)	AZD5305 140 mg QD (n=4)	Total (N=61)
Duration of therapy (months), median (range)	4.8 (4.6- 4.9)	0.7 (0.6- 1.6)	2.1 (0- 14.9)
All TEAEs	3 (100.0)	0	55 (90.2)
Grade ≥3 AEs	2 (66.7)	0	24 (39.3)
Serious TEAEs	0	0	16 (26.2)
Discontinuations	0	0	1 (1.6)
Dose reductions	0	0	2 (3.3)
AZD5305-related TEAEs	3 (100.0)	0	32 (52.5)
Grade ≥3 AEs	2 (66.7)	0	9 (14.8)
Serious TEAEs	0	0	0
Discontinuations	0	0	0
Dose reductions	0	0	2 (3.3)

AZD5305 was well tolerated across all doses, with only 2 patients (3.3%) having dose reductions (for grade 3 neutropenia and grade 1 thrombocytopenia related to AZD5305). At the data cut-off, there had been no DLTs and no AZD5305-related serious AEs or treatment discontinuations.

PARP1 inhibition

Pharmacodynamic analyses were carried out on PBMCs to measure PARP1 inhibition by the loss of signal from poly(ADP-ribose) after a single dose of AZD5305. PARylation inhibition has been a useful measure of target engagement for first generation PARP inhibitors. The results are shown in Figure 3, in which:

Dose	n	Symbol
10mg	2	●
20mg	3	■
40mg	2	▲
60mg	2	▼

C1D1 was median 1 day after C0D3 (max 4 days post C0D3)

Durable PARylation inhibition $\geq 90\%$ was observed at all tested doses (10, 20, 40, and 60 mg) in PBMCs of 9 patients after a single dose of AZD5305

Efficacy Assessments

46 patients were included in the interim response analysis set, which represents all dosed subjects who had measurable disease at baseline and who received their first dose at least 13 weeks prior to data extract. 6 patients were not evaluable for RECIST v1.1 assessment – 5 did not have a follow up scan and 1 had SD < 7 weeks. Of 40 evaluable patients, by RECIST v1.1, observed were:

- 10 Partial Responses (PR) (7 confirmed; 3 unconfirmed)
- 11 Stable Disease (SD), and
- 19 Progressive Disease (PD)

Figures 4 to 7 show the response (Best % change in target lesions size by dose) across:

- Doses (Figure 4)
- Tumour Types (Figure 5)
- Mutation types (Figure 6) and
- Independent of prior treatment with a PARP inhibitor (Figure 7).

In each figure, the symbols have the following meanings:

◆	GCIG CA125 response
▼	PCWG3 PSA ₅₀ response
*	Patients with 0% change from baseline
•	Percent change >100 was cut at 100

ctDNA responses

5 Figure 8 shows the results of ctDNA measurements on 13 patients.

8 out of 13 patients showed a ctDNA decrease (mean variant allele frequency (mVAF) of all somatic variants detected with at least 0.3% allele frequency; % change was calculated from baseline to C2D1 (Guardant Health OMNI at screening and GH360 thereafter including 5/5 prostate cancer patients

In patients with no measurable disease the PCWG3 PSA₅₀ response (confirmed and unconfirmed) only is represented, using the following abbreviations:

cPR, confirmed Partial Response;

15 SD, stable disease;

PD, progressive disease;

PSAR, PCWG3 PSA₅₀ response;

PSA↓, PSA decrease 0-49%

20 *Individual Patient results*

Case 1 - 66-year-old man with a *BRCA2m* prostate cancer (AZD5305 20 mg)

The patient had been treated with 3 prior lines of therapy: ADT; docetaxel; abiraterone

Figure 9 shows the PSA₅₀ (◆) and ctDNA (■) responses. A PSA₅₀ partial response (-38.6%) was observed using RECIST, which was confirmed at second scan, and a -58% PCWG3

25 PSA₅₀ response was observed at C3D1.

Figure 10A is the baseline scan (28 June 2021) and Figure 10B is the second scan (22 October 2021) – the white arrows in Figure 10A indicate three tumours.

30 *Cases 2 to 5*

Figures 11A to 11D show the PSA₅₀ (◆) and ctDNA (■) responses of the following 4 prostate cancer patients:

- Case #2: 56 y/o; *BRCA2m*; AZD5305 10 mg; 2 prior lines of therapy ADT/abiraterone, and docetaxel
- Case #3: 55 y/o; *BRCA2m*; AZD5305 20 mg; 3 prior lines of therapy: bicalutamide, ADT, abiraterone, and docetaxel
- 5 • Case #4: 60 y/o; *BRCA2m*; AZD5305 20 mg; 3 prior lines of therapy: docetaxel, enzalutamide, and cabazitaxel
- Case #5: 60 y/o; *BRCA2m*; AZD5305 40 mg; 3 prior lines of therapy: bicalutamide, docetaxel, and enzalutamide

10 These results provide preliminary evidence of early ctDNA responses and association with clinical responses.

Case 6 – 43 year old woman with gRAD51Cm HR+ breast cancer (AZD5305 40 mg)

The patient had been treated with 6 prior lines of therapy:

15 doxorubicin/cyclophosphamide/paclitaxel; tamoxifen; letrozole/palbociclib;
fulvestrant/Palbociclib; capecitabine/tesataxel; and everolimus/exemestane.

Figure 12 shows the CA15.3 (U/mL) response, and Figure 13 shows patient scans. Figure 13A shows the baseline scans on 11 November 2021, Figure 13B shows the scans on 18
20 January 2022, and Figure 13C shows the scans on 15 March 2022.

A RECIST v1.1 partial response was noted (-83%), which was confirmed at second scan (-86.8%).

The white arrow in Figure 13A indicates a tumour.

25 Case 7 - 53 year old woman with *BRCA1m* platinum resistant ovarian cancer (AZD5305 20 mg)

The patient had been treated with 3 prior lines of therapy: carboplatin/paclitaxel, LPD/carboplatin followed by olaparib maintenance (given for 1.6 months, but discontinued for nausea), carboplatin/gemcitabine.

30

Figure 14 shows the CA125 (U/mL) response and Figure 14 shows patient scans. Figure 15A shows the baseline scans on 18 January 2021, and Figure 15B shows the third scan on 29 July 2021. A RECIST v1.1 partial response (-75.0%) was confirmed at the third scan.

The white arrows in Figure 15A indicates a tumour.

References

A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. The entirety of each of these references is incorporated herein.

5

	Reference	Doi
Bai 2015	Bai P. Mol Cell 2015; 58: 947-958	10.1016/j.molcel.2015.01.034
Chappuis and Foulkes 2002	Chappuis PO and Foulkes WD, <i>Cancer Treat Res</i> , 107, 29-59 (2002)	10.1007/978-1-4757-3587-1_2
Eisenhauer 2009	Eisenhauer EA, <i>et al.</i> , European Journal of Cancer, 45, 228-247 (2009)	10.1016/j.ejca.2008.10.026
Hughes-Davies 2003	Hughes-Davies, et al., Cell, 115, 523-535 (2003)	10.1016/s0092-8674(03)00930-9
Illuzzi 2022	Illuzzi G, et al., Clin Cancer Res 2022; 28:4724-4736	10.1158/1078-0432.CCR-22-0301
Janatová 2003	Janatová M, et al., Neoplasma, 50(4), 246-50 (2003)	PMID: 12937835
Jancarkova 2003	Jancárková, N, Ceska Gynekol., 68(1), 11-6 (2003)	PMID: 12708108
Jasin 2002	Jasin M., Oncogene, 21(58), 8981-93 (2002)	10.1038/sj.onc.1206176
Johannes 2021	Johannes, JW, et al., <i>J Med Chem</i> 2021, 64, 14498-14512	10.1021/acs.jmedchem.1c01012
Khanna and Jackson 2001	Khanna KK and Jackson SP, Nat. Genet. 27(3): 247-254 (2001)	10.1038/85798
Neuhausen and Ostrander 1992	Neuhausen SL and Ostrander EA, <i>Genet. Test</i> , 1, 75-83 (1992)	10.1089/gte.1997.1.75
O'Connor 2015	O'Connor MJ, Mol Cell (2015) 60(4):547-560	10.1016/j.molcel.2015.10.040
Radice 2002	Radice, P.J., Exp Clin Cancer Res., 21(3 Suppl), 9-12 (2002)	PMID: 12585647
Rostoker 2007	Rostoker G, et al., J Nephrol. 2007; 20(5):576-585	PMID: 17918143

Scher 2016	Scher HI, et al., J Clin Oncol. 2016; 34(12):1402-1418	10.1200/JCO.2015.64.2702
Tutt 2002	Tutt, et al., Trends Mol Med., 8(12), 571-576, (2002)	10.1016/s1471-4914(02)02434-6
Turner 2004	Turner N, et al., Nat Rev Cancer, 2004; 4: 814-819	10.1038/nrc1457
Wood 2001	Wood, et al., Science, 291, 1284- 1289 (2001)	10.1126/science.1056154

Claims

1. A method of treatment or prophylaxis of diseases or conditions in which inhibition of PARP1 is beneficial, comprising administering to the subject AZD5305 in a daily dose of 10 to 140 mg, wherein AZD5305 may be in the form of a pharmaceutically acceptable salt.
5
2. The method according to claim 1, wherein the disease or condition in which inhibition of PARP1 is beneficial is cancer.
3. The method according to claim 2, wherein the cancer is breast, ovary, pancreas,
10 prostate, hematological, gastrointestinal such as gastric and colorectal, or lung cancer.
4. The method according to any one of claims 1 to 3, wherein AZD5305 is administered in a dose of up to 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg per day.
15
5. The method according to any one of claims 1 to 4, wherein AZD5305 is administered in a dose of at least 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg or 130 mg per day.
- 20 6. The method according to any one of claims 1 to 3, wherein AZD5305 is administered in a dose of 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg per day.
7. The method according to any one of claims 1 to 6, wherein AZD5305 is administered
25 once daily.
8. The method according to any one of claims 1 to 7, wherein AZD5305 is administered for 28 days in a 28-day treatment cycle.
- 30 9. The method according to any one of claims 1 to 8, wherein AZD5305 is administered orally.
10. The method according to claim 9, wherein AZD5305 is in tablet dosage form.
- 35 11. AZD5305, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or conditions in which inhibition of PARP1 is beneficial in a subject,

wherein said treatment comprises the administration of said AZD5305 in a daily dose of 10 to 140 mg to said subject.

12. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 11, wherein the disease or condition in which inhibition of PARP1 is beneficial is cancer.

13. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 12, wherein the cancer is breast, ovary, pancreas, prostate, hematological, gastrointestinal such as gastric and colorectal, or lung cancer.

14. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 13, wherein AZD5305 is administered in a dose of up to 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg per day.

15. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 14, wherein AZD5305 is administered in a dose of at least 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg or 130 mg per day.

16. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 13, wherein AZD5305 is administered in a dose of 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg per day.

17. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 16, wherein AZD5305 is administered once daily.

18. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 17, wherein AZD5305 is administered for 28 days in a 28-day treatment cycle.

19. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 18, wherein AZD5305 is administered orally.

20. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 19, wherein AZD5305 is in tablet dosage form.

21. The use of AZD5305, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of or prophylaxis of diseases or conditions in which inhibition of PARP1 is beneficial, wherein said treatment administering to the subject AZD5305 in a daily dose of 10 to 140 mg.

22. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 21, wherein the disease or condition in which inhibition of PARP1 is beneficial is cancer.

23. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 22, wherein the cancer is breast, ovary, pancreas, prostate, hematological, gastrointestinal such as gastric and colorectal, or lung cancer.

24. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 21 to 23, wherein AZD5305 is administered in a dose of up to 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg per day.

25. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 21 to 24, wherein AZD5305 is administered in a dose of at least 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg or 130 mg per day.

26. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 21 to 23, wherein AZD5305 is administered in a dose of 10 mg, 20 mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg or 140 mg per day.

27. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 21 to 26, wherein AZD5305 is administered once daily.

28. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 21 to 27, wherein AZD5305 is administered for 28 days in a 28-day treatment cycle.

29. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 21 to 28, wherein AZD5305 is administered orally.

30. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to
5 claim 29, wherein AZD5305 is in tablet dosage form.

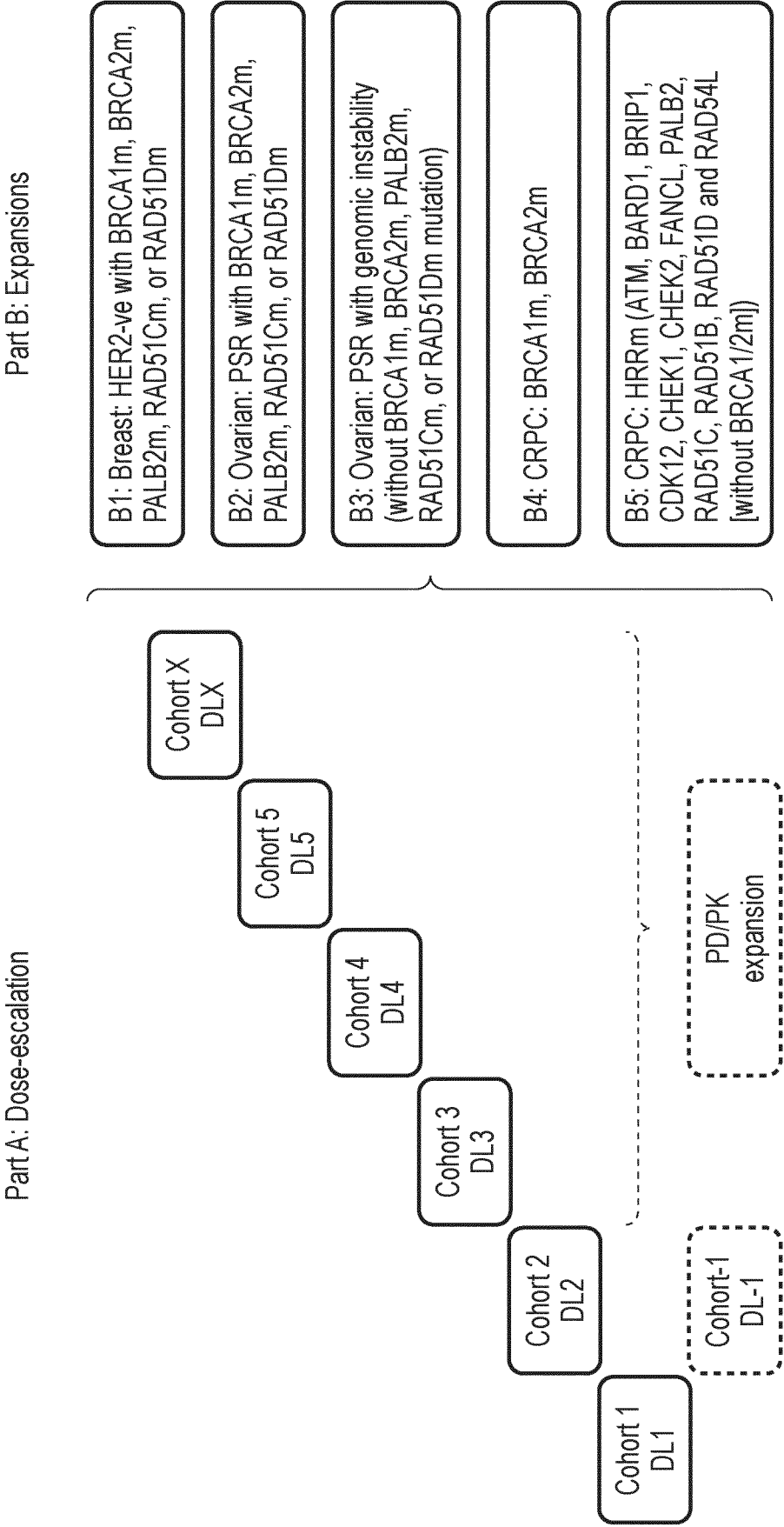


FIG. 1

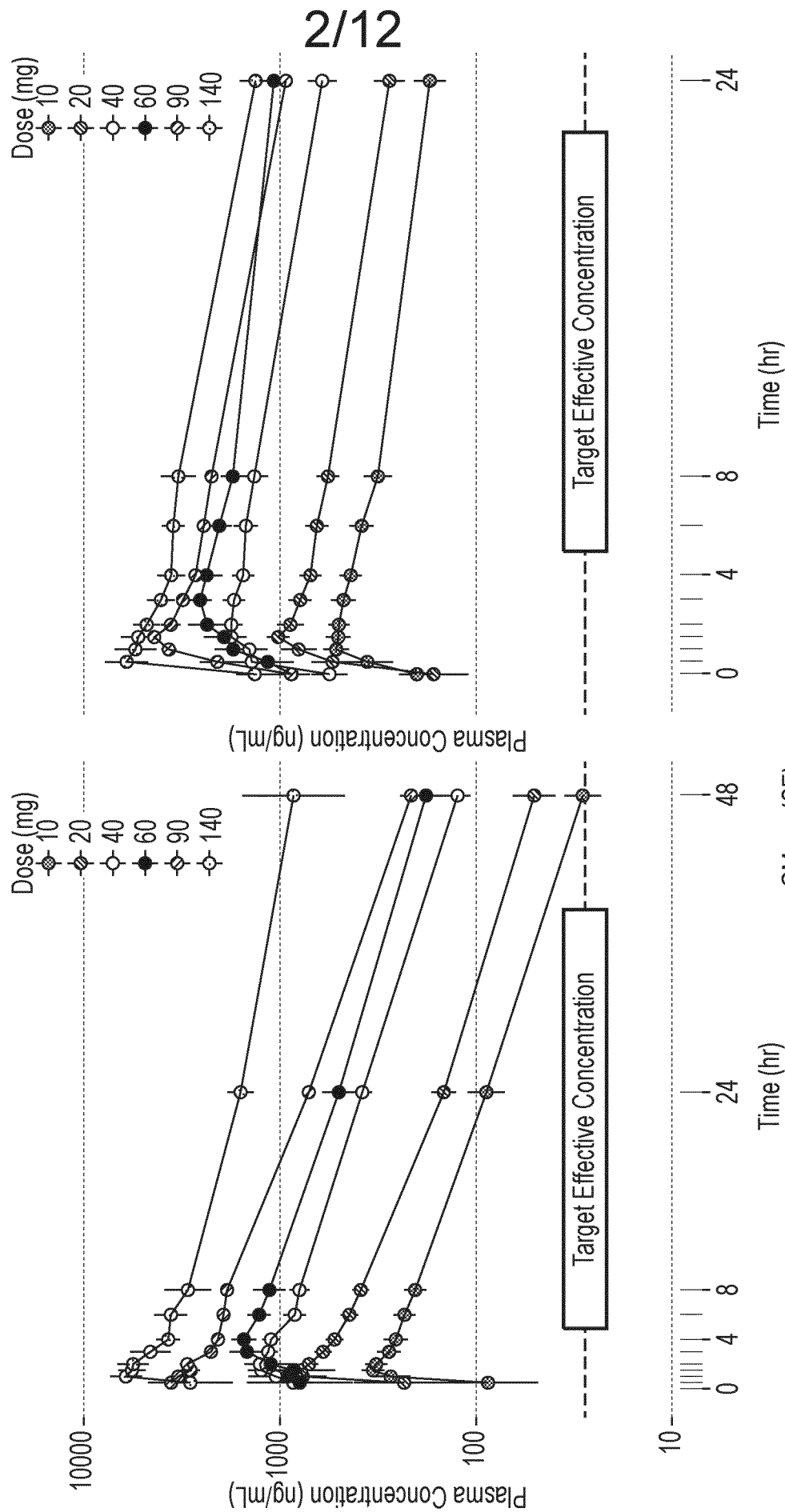


FIG. 2B

FIG. 2A

3/12

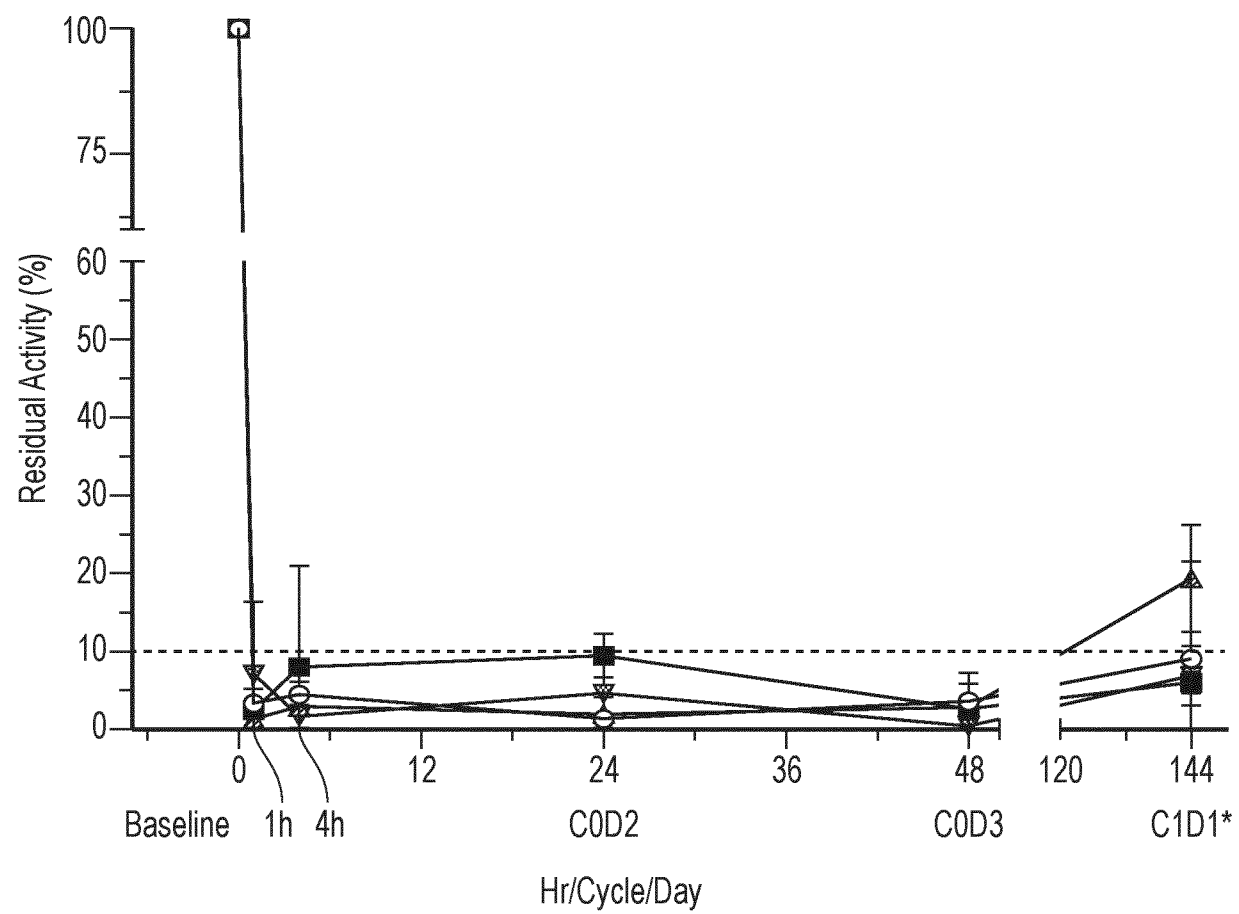


FIG. 3

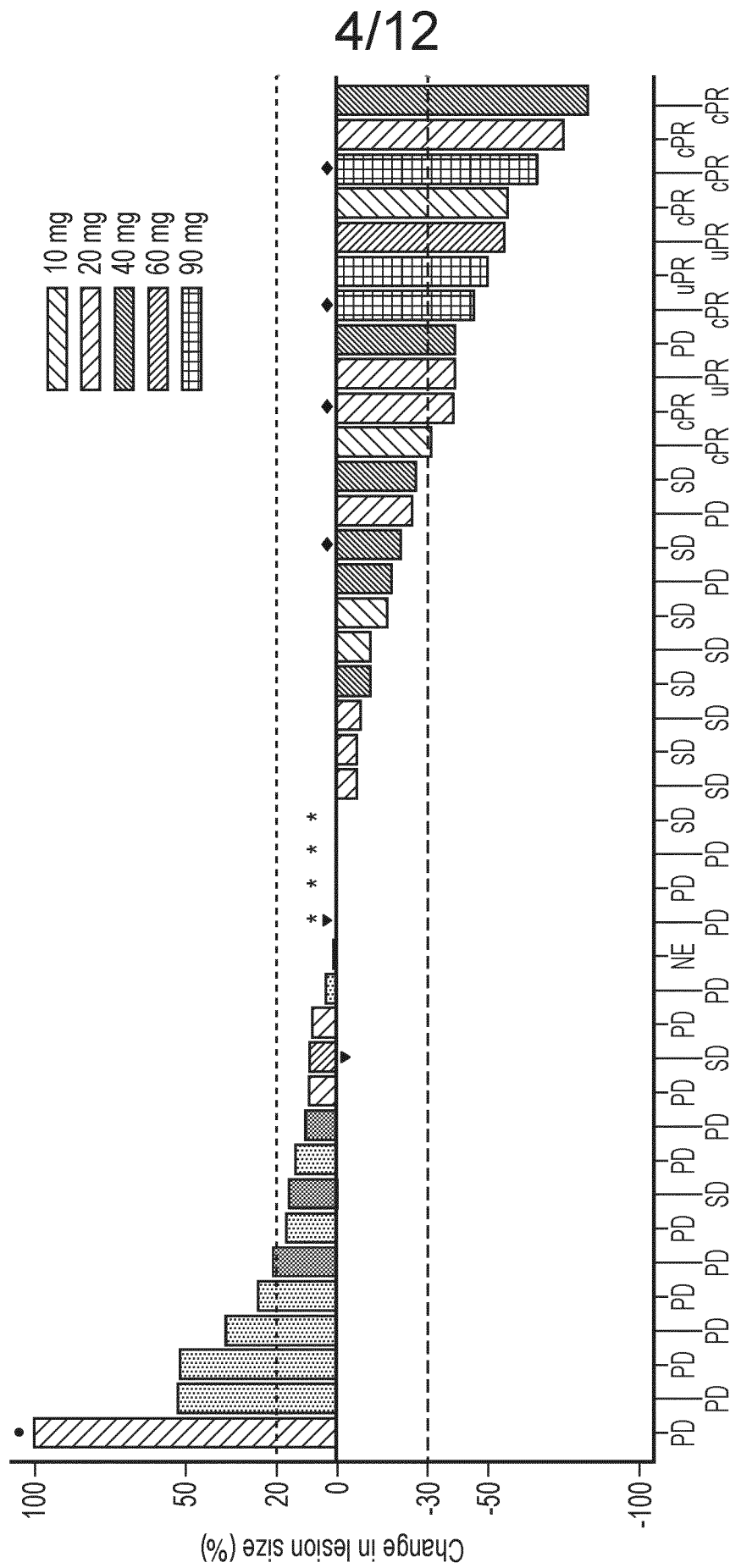
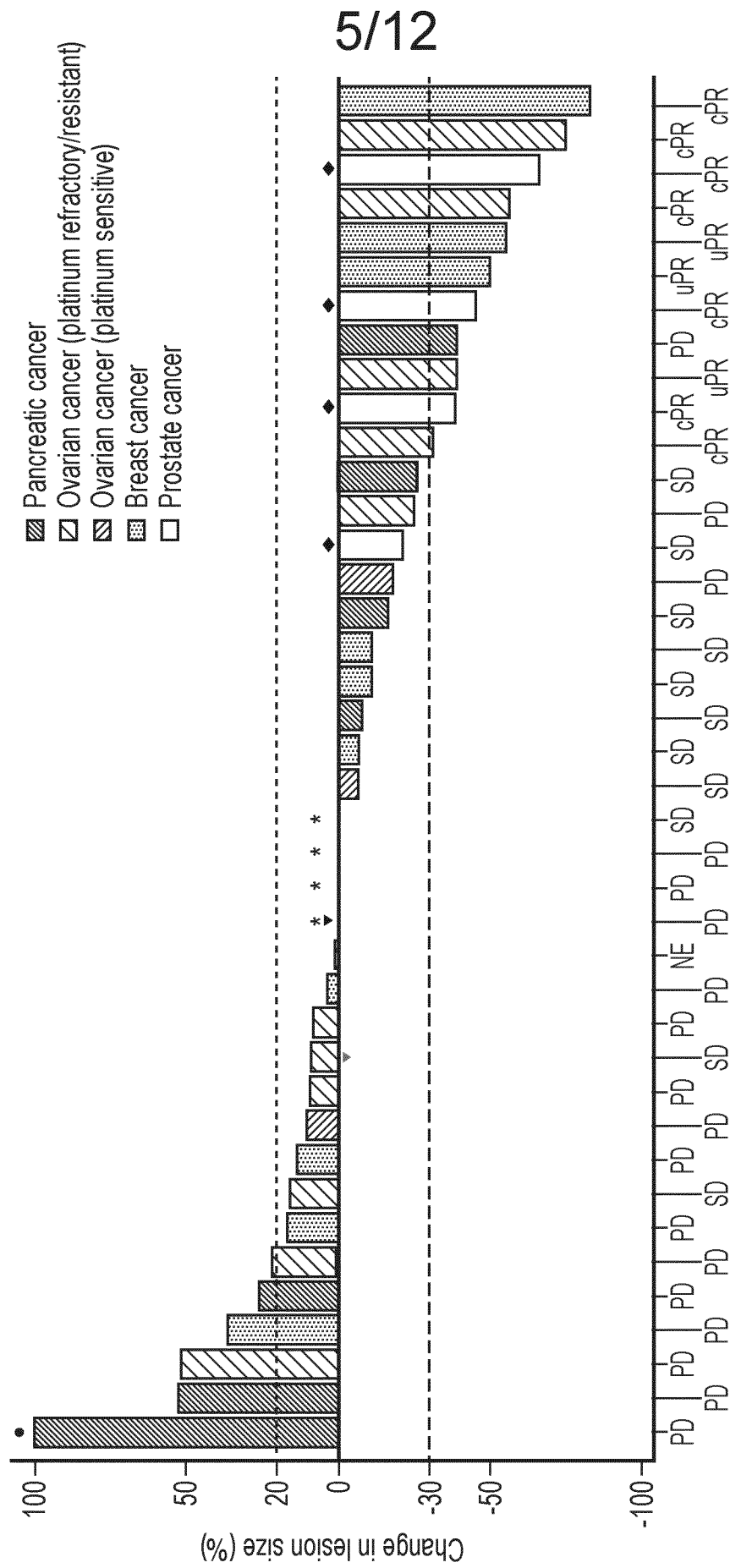
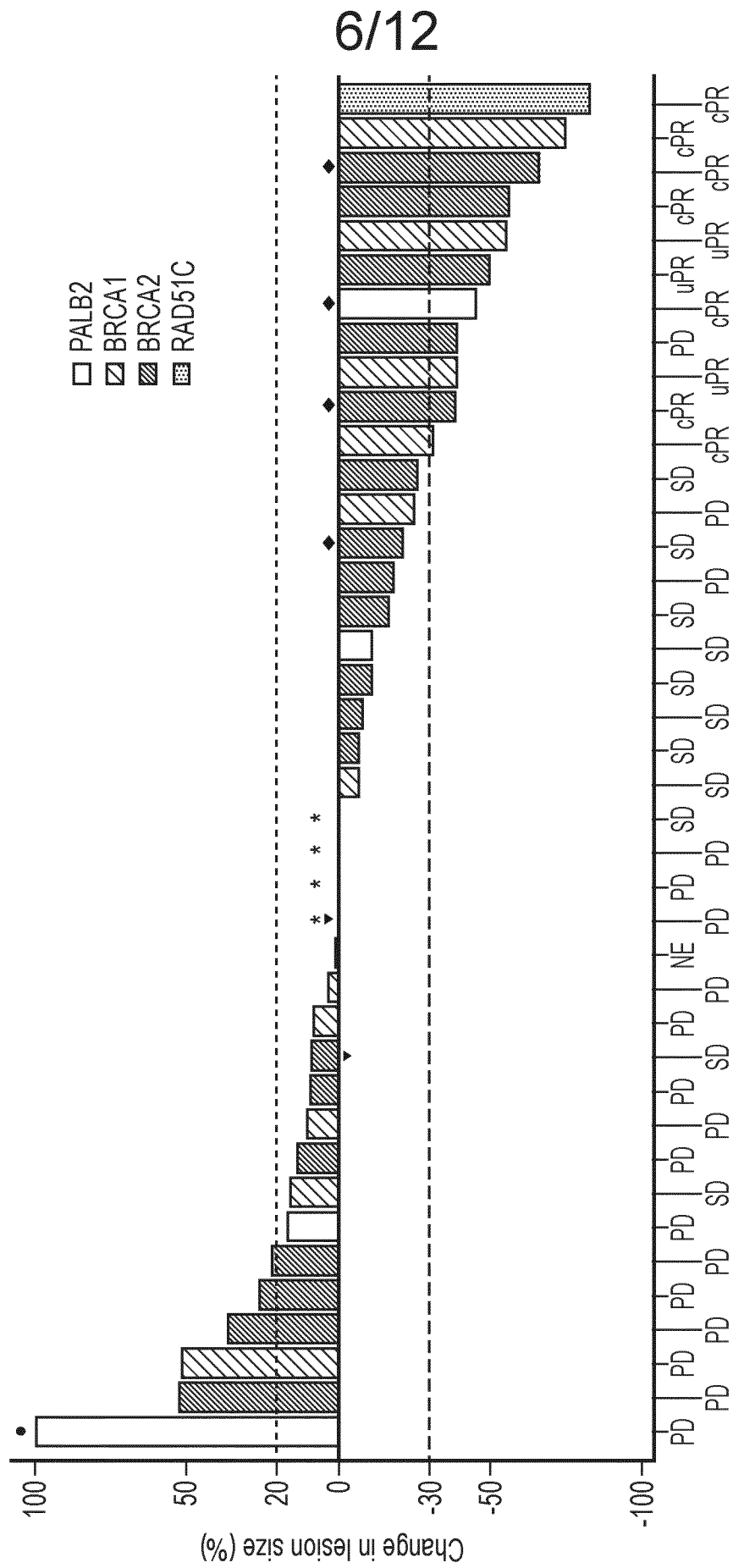


FIG. 4



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6. 6.1

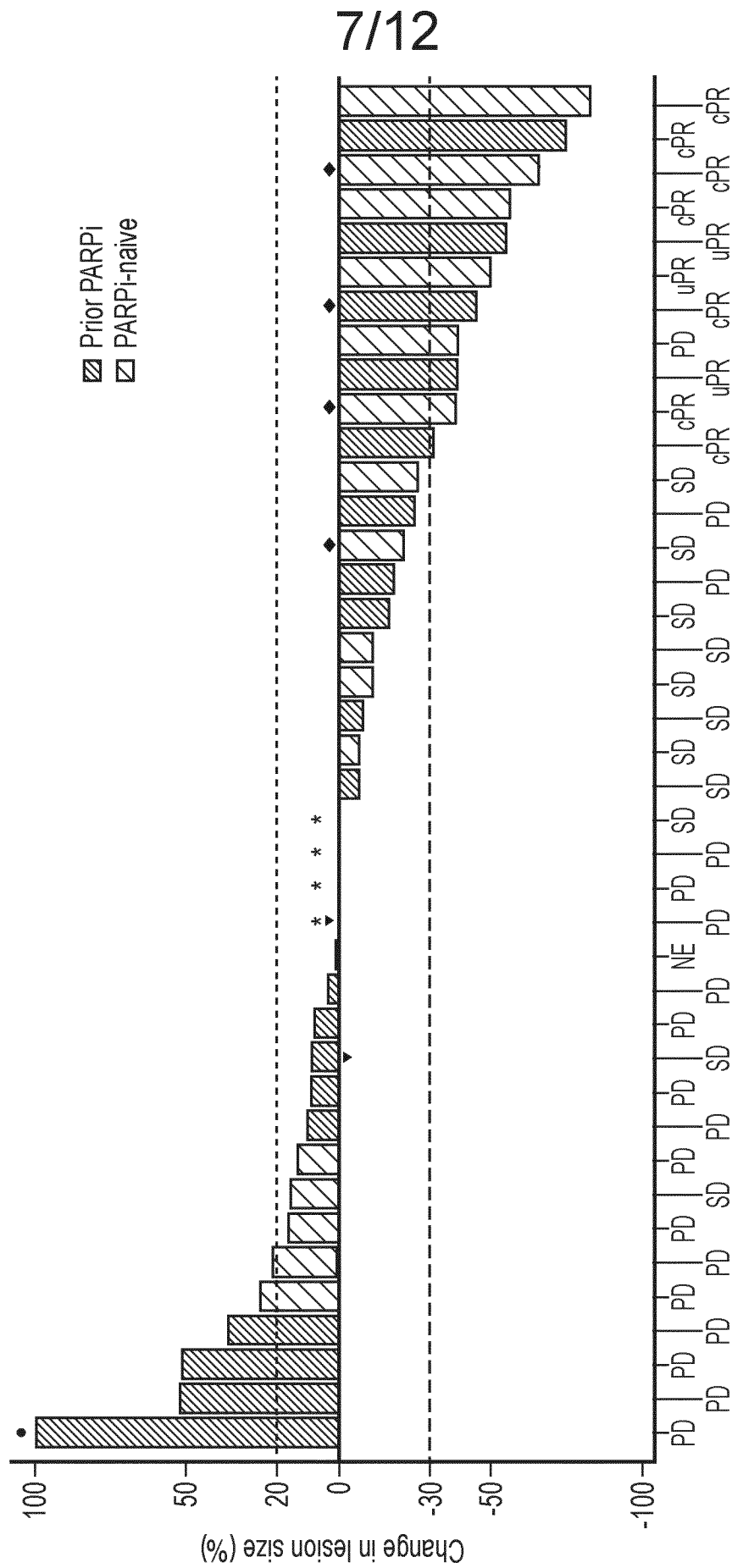


FIG. 7

8/12

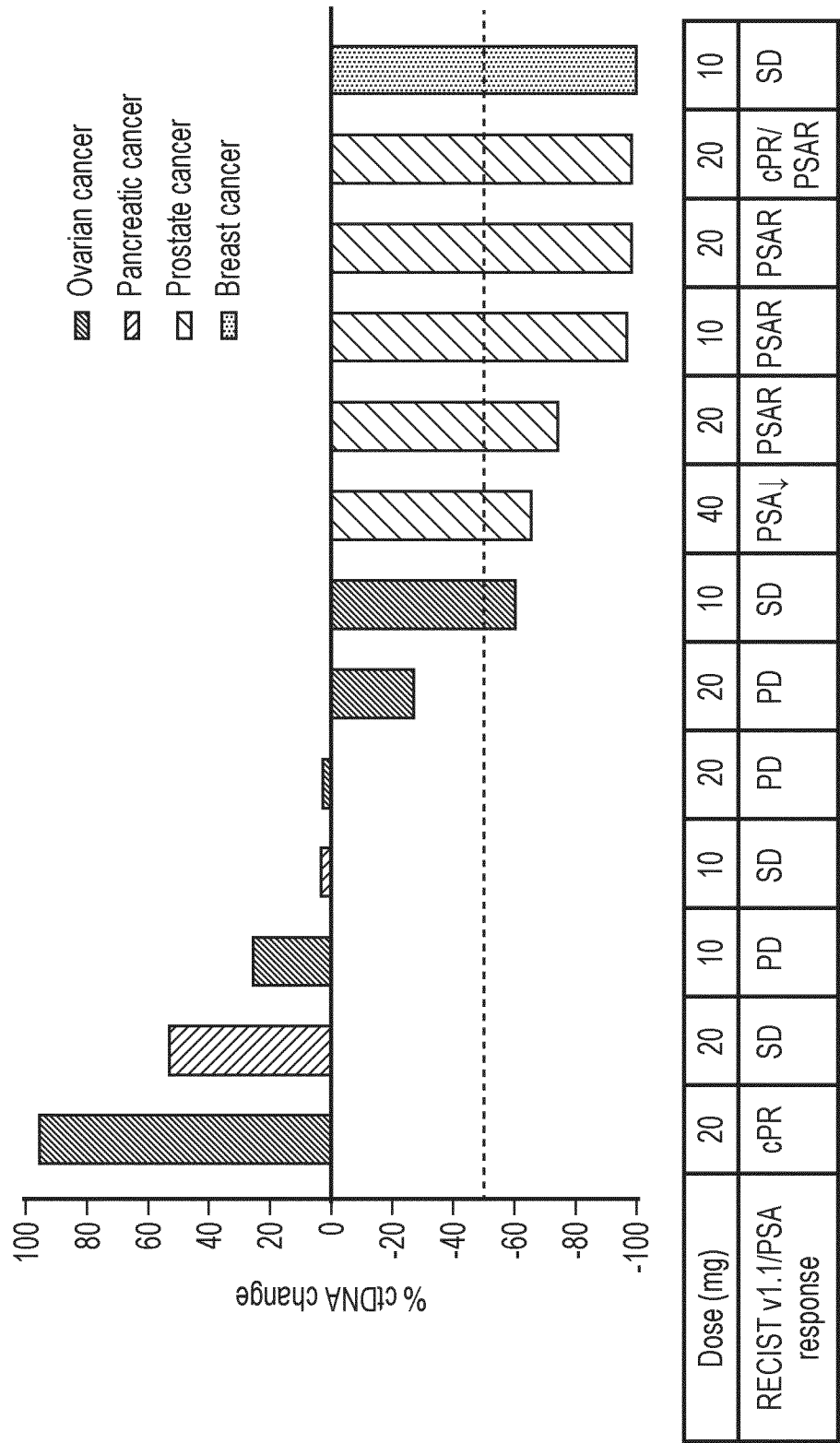


FIG. 8

9/12

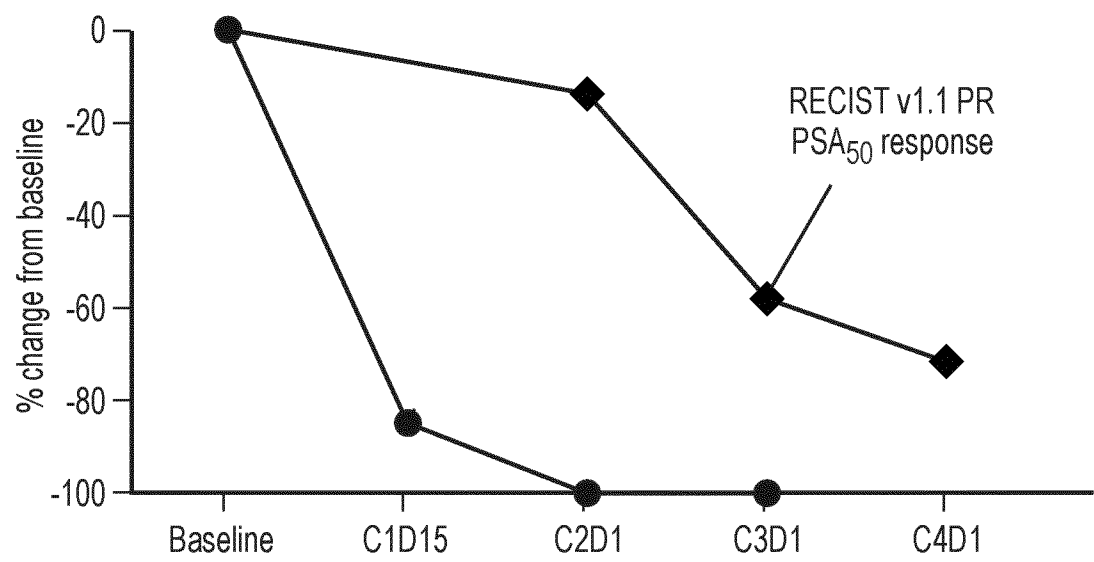


FIG. 9

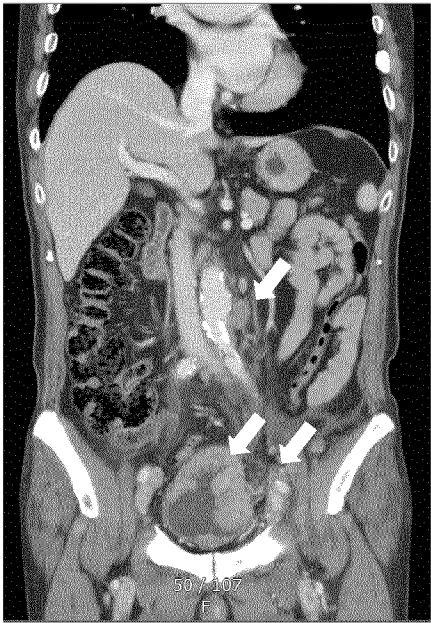


FIG. 10A

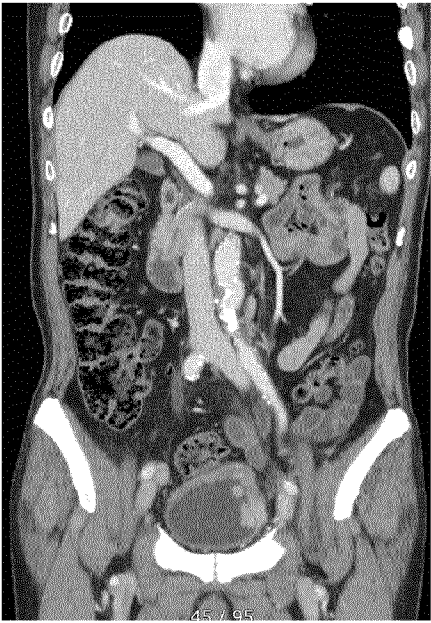


FIG. 10B

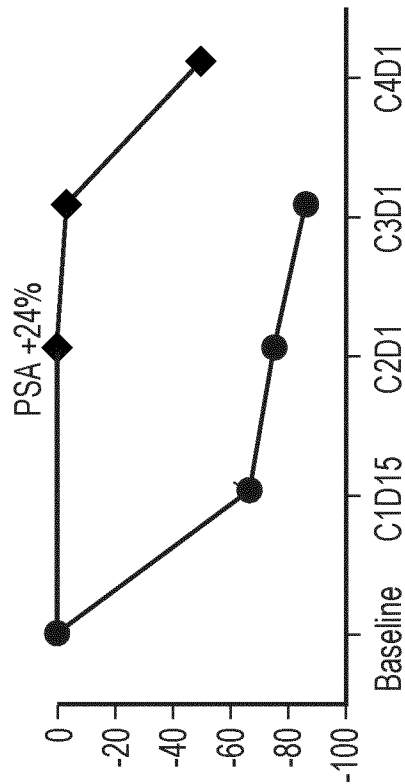


FIG. 11B

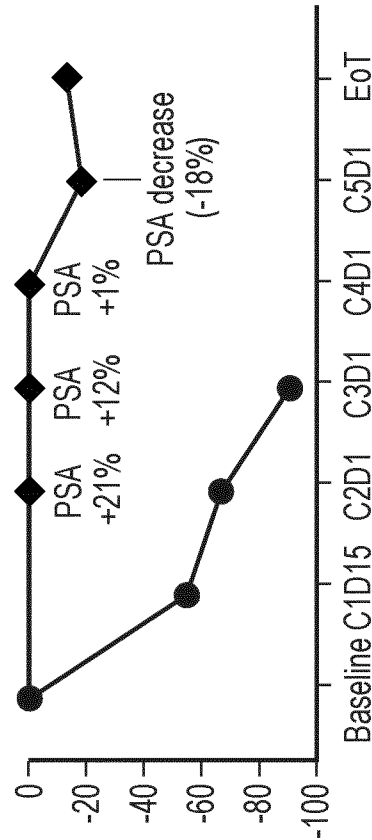


FIG. 11D

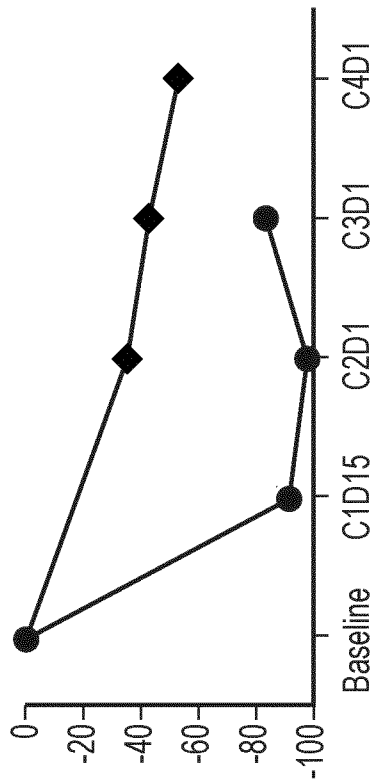


FIG. 11A

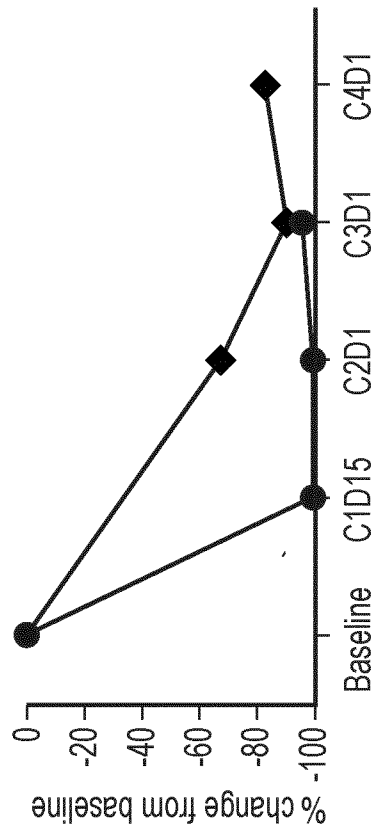


FIG. 11C

11/12

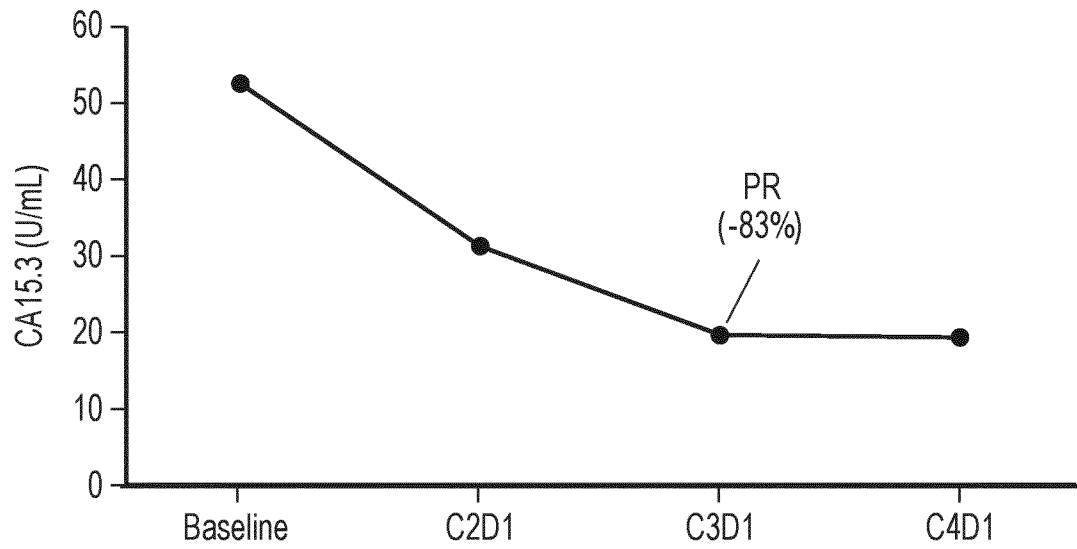
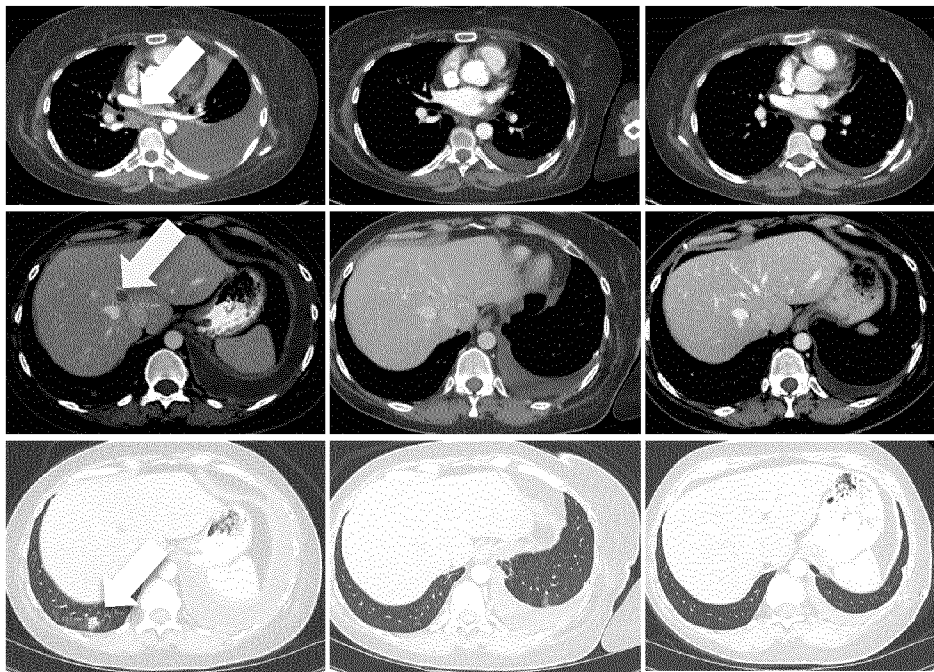


FIG. 12



12/12

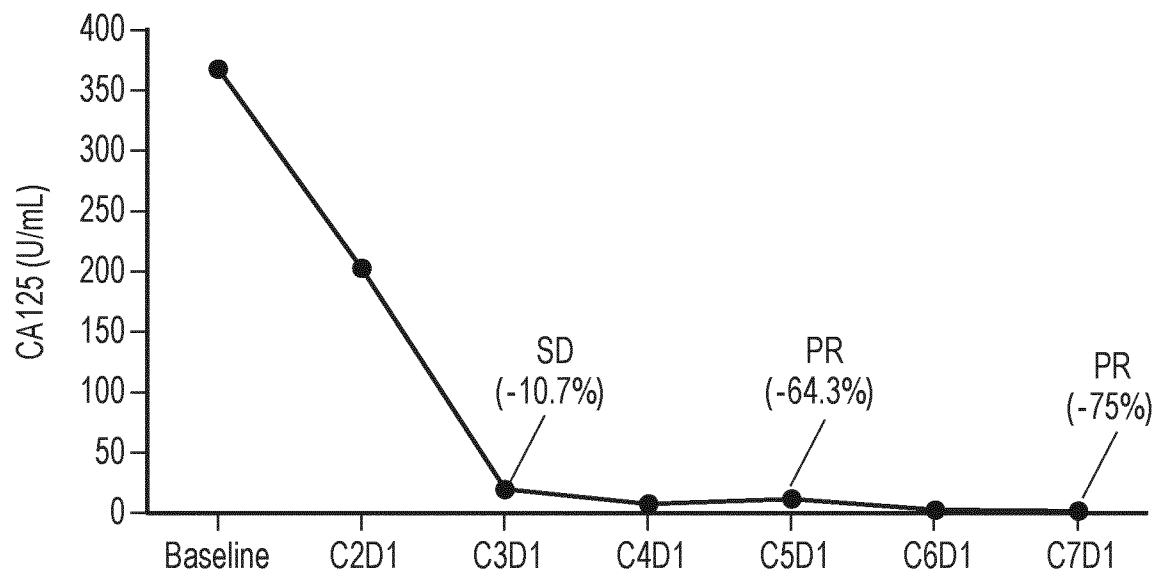


FIG. 14

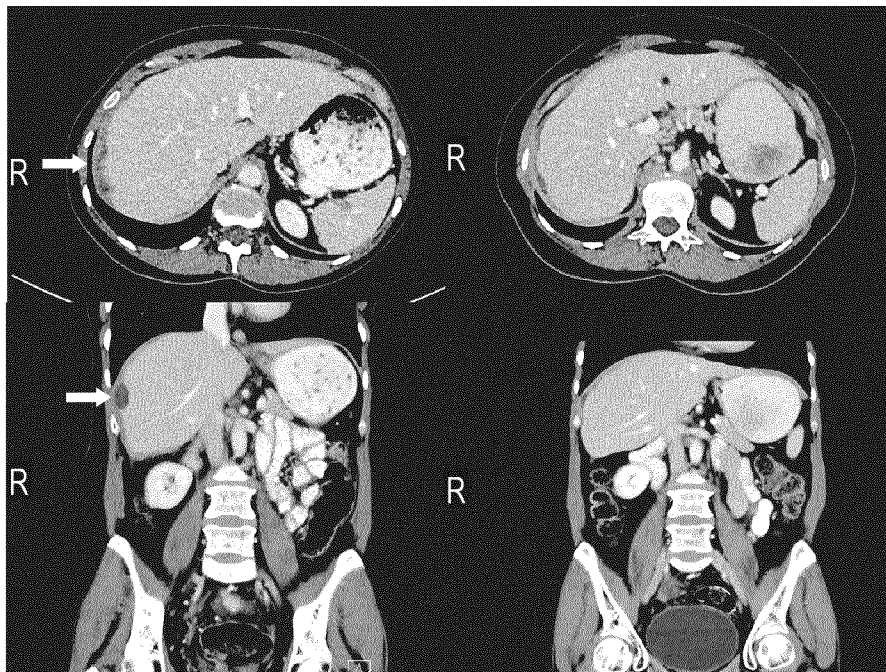


FIG. 15A

FIG. 15B

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/058465

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/496 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DIDOMENICO NATALIE: "AZD5305 More Tolerable than Earlier PARP Agents", CANCER DISCOVERY, vol. 12, no. 7, 6 July 2022 (2022-07-06), pages 1602-1602, XP093088498, US ISSN: 2159-8274, DOI: 10.1158/2159-8290.CD-NB2022-0039 INTERNET Retrieved from the Internet: URL:https://aacrjournals.org/cancerdiscove ry/article-pdf/12/7/1602/3176548/1602.pdf> [retrieved on 2023-10-03] page 1602 ----- -/--	1-30

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

5 October 2023

Date of mailing of the international search report

12/10/2023

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European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Opravz, Petra

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/058465

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Yap Timothy A. ET AL: "CT007- PETRA: First in class, first in human trial of the next generation PARP1-selective inhibitor AZD5305 in patients (pts) with BRCA1/2, PALB2 or RAD51C/D mutations", , 10 April 2022 (2022-04-10), XP093088494, Retrieved from the Internet: URL:https://www.abstractsonline.com/pp8/#!/10517/presentation/20149 [retrieved on 2023-10-04] the whole document -----	1-30
X	Killmurray Conor: "Next-Generation PARP Inhibitor AZD5305 Shows Promising Safety Profile and Clinical Activity in Several Cancer Types", , 14 April 2022 (2022-04-14), XP093088496, Retrieved from the Internet: URL:https://web.archive.org/web/20220414140537/https://www.targetedonc.com/view/next-generation-parp-inhibitor-azd5305-shows-promising-safety-profile-and-clinical-activity-in-several-cancer-types [retrieved on 2023-10-04] the whole document -----	1-30
T	Anonymous: "History of Changes for Study: NCT04644068: Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies (PETRA)", , 10 March 2023 (2023-03-10), XP93089003, Retrieved from the Internet: URL:https://classic.clinicaltrials.gov/ct2/history/NCT04644068?V_24=View#StudyPageToP [retrieved on 2023-10-05] the whole document -----	