(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 October 2023 (12.10.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/194525 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 31/58* (2006.01)
A61K 31/4375 (2006.01) *A61P 35/00* (2006.01)
A61K 31/573 (2006.01) *A61P 35/04* (2006.01)

(21) International Application Number:
PCT/EP2023/059123

(22) International Filing Date:
06 April 2023 (06.04.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/362,614 07 April 2022 (07.04.2022) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT,

(54) Title: COMBINATION THERAPY FOR TREATING CANCER

(57) Abstract: The present disclosure includes methods, pharmaceutical compositions, and kits for the treatment of prostate cancer, wherein AZD5305 and abiraterone acetate are dosed in combination to a subject in need.

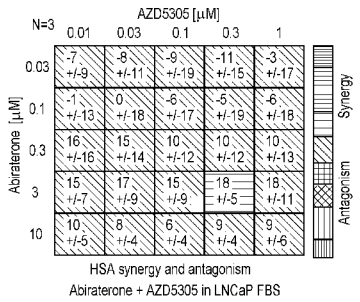

Fig. 1A

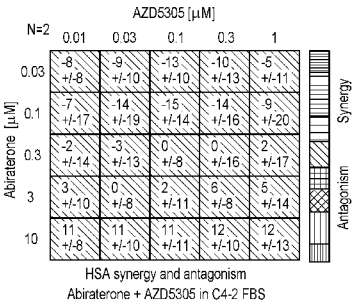

Fig. 1B

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LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

COMBINATION THERAPY FOR TREATING CANCER

The present disclosure relates to methods of treating metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) and castrate resistant prostate cancer (CRPC) in a patient in need thereof.

Background

Prostate cancer is the second most common cancer in men. With an estimated 375,304 deaths in 2020 worldwide, prostate cancer is the fifth leading cause of death from cancer in men and represents 6.8% of total cancer death in males (Sung 2021).

Treatment of prostate cancer with androgen deprivation therapy (ADT) such as luteinising hormone-releasing hormone (LHRH) analogues or orchidectomy is usually initially effective at controlling metastatic disease. However, patients inevitably progress from an androgen sensitive to a castration-resistant phenotype which is associated with 90% of overall mortality (Scher 2015).

The recent approval of several new hormonal agents (NHAs) has significantly altered the treatment landscape for patients with metastatic castrate resistant prostate cancer (mCRPC) and NHAs are now considered standard of care in both the mCRPC and metastatic hormone sensitive prostate cancer (mHSPC) settings (Mohler 2019, Parker 2020).

Both abiraterone acetate and enzalutamide in combination with ADT have demonstrated robust improvements in progression free survival (PFS) and overall survival (OS) and have shown a significantly prolonged time to initiation of cytotoxic chemotherapy in patients with CRPC (Beer 2014, Ryan 2013).

Additionally, recent data have demonstrated the benefit of NHAs in patients with mHSPC. Abiraterone acetate plus prednisone with ADT demonstrated significant survival benefits compared with ADT alone, by further prolonging OS and delaying initiation of chemotherapy and subsequent therapy (Fizazi 2019). Enzalutamide plus ADT significantly reduced the risk of radiographic progression or death versus placebo plus ADT as well as reduced risk of PSA progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and pain progression (Armstrong 2019)

A Phase III trial is ongoing to evaluate darolutamide in combination with standard ADT in patients with mHSPC (ARANOTE, NCT04736199).

The addition of Olaparib (a PARP1/PARP2 inhibitor) to abiraterone acetate plus ADT has demonstrated an improvement in radiographic progression-free survival (rPFS) compared with abiraterone acetate alone for both men with mCRPC who had previously received docetaxel (Clarke 2018), and those who had not received a prior line of systemic therapy, irrespective of homologous recombination repair gene mutation (HRRm) status (AstraZeneca Press Release 24 September 2021).

It is not expected that Olaparib (a PARP1/PARP2 inhibitor) could be successfully used in combination with enzalutamide as enzalutamide is a strong CYP3A4 inducer (Gibbons 2015) and Olaparib is a substrate of CYP3A4 (Dirix 2016), so co-administration of enzalutamide with Olaparib in a multiple dose setting would significantly reduce Olaparib exposure in patients.

While much progress has been made in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) and castrate resistant prostate cancer (CRPC), including metastatic hormone sensitive prostate cancer (mHSPC) and metastatic castrate resistant prostate cancer (mCRPC), many patients who have such cancers live with an incurable disease. Accordingly, it is important to continue to find new treatments for patients with incurable cancer.

Summary

In some embodiments, disclosed is a method of treating metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject in need thereof, comprising administering to the subject a first amount of AZD5305 or a pharmaceutically acceptable salt thereof, and a second amount of abiraterone acetate, and optionally prednisone or prednisolone. In the method, the first amount and the second amount together comprise a therapeutically effective amount.

In some embodiments, disclosed is AZD5305, or a pharmaceutically acceptable salt thereof, for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said AZD5305, or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate, and optionally prednisone or prednisolone, to said subject.

In some embodiments, disclosed is abiraterone acetate, and optionally prednisone or prednisolone, for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said abiraterone acetate, and optionally prednisone or prednisolone, and ii) AZD5305, or a pharmaceutically acceptable salt thereof, to said subject.

In some embodiments, disclosed is the use of AZD5305, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC), wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising AZD5305, or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate, and optionally prednisone or prednisolone, to said subject.

In the above embodiments, the metastatic prostate cancer may be metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).

In some embodiments, disclosed is a pharmaceutical product comprising i) AZD5305 or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate, and optionally prednisone or prednisolone.

In some embodiments, disclosed is a kit comprising: a first pharmaceutical composition comprising AZD5305, or a pharmaceutically acceptable salt thereof; a second pharmaceutical composition comprising abiraterone acetate, and optionally prednisone or prednisolone; and instructions for using the first and second pharmaceutical compositions in combination.

The combination of AZD5305 and abiraterone acetate, and optionally prednisone or prednisolone, may result in fewer side effects or be more effective than current monotherapies or combination therapies. This may result from AZD5305 being a selective PARP1 inhibitor. By 'selective PARP1 inhibitor' it is meant an inhibitor of the PARP enzyme having greater selectivity for PARP1 over other members of the PARP family, such as PARP2, PARP3, PARP5a, and PARP6. In some embodiments the selective PARP1 inhibitor has a selectivity for PARP1 over PARP2. In some embodiments, the selective PARP1 inhibitor has a selectivity for PARP1 over PARP2 which is greater than 5:1. In some

embodiments, the selective PARP1 inhibitor has a selectivity for PARP1 over PARP2 which is greater than 10:1. In some embodiments, the selective PARP1 inhibitor has a selectivity for PARP1 over PARP2 which is greater than 100:1.

In some embodiments, disclosed is a method of treating metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject in need thereof, comprising administering to the subject a first amount of a selective PARP1 inhibitor (such as AZD5305), or a pharmaceutically acceptable salt thereof, and a second amount of abiraterone acetate, and optionally prednisone or prednisolone. In the method, the first amount and the second amount together comprise a therapeutically effective amount.

In some embodiments, disclosed is a selective PARP1 inhibitor (such as AZD5305), or a pharmaceutically acceptable salt thereof, for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said selective PARP1 inhibitor (such as AZD5305), or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate, and optionally prednisone or prednisolone, to said subject.

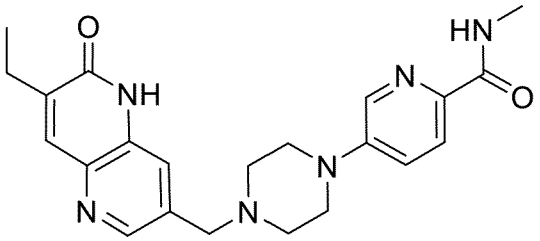
In some embodiments, disclosed is abiraterone acetate, and optionally prednisone or prednisolone, for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said abiraterone acetate, and optionally prednisone or prednisolone, and ii) a selective PARP1 inhibitor (such as AZD5305), or a pharmaceutically acceptable salt thereof, to said subject.

Brief Description of the Drawings

Figure 1 shows representative 6 × 6 synergy matrix heatmaps for AZD5305 and abiraterone treatment in LnCAP and C4-2 cells.

Detailed Description

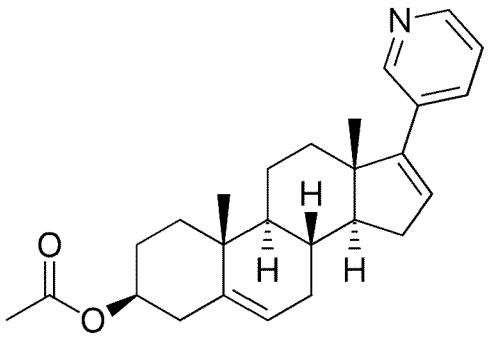
The term “AZD5305” refers to a compound with the chemical name 5-{4-[(7-ethyl-6-oxo-5,6-dihydro-1,5-naphthyridin-3-yl)methyl]piperazin-1-yl}-N-methylpyridine-2-carboxamide and structure shown below:



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, with reduced effects on human bone marrow progenitor cells *in vitro*.

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. 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 term "abiraterone acetate" refers to a compound with the chemical name [(3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-pyridin-3-yl-2,3,4,7,8,9,11,12,14,15-decahydro-1H-cyclopenta[a]phenanthren-3-yl] acetate and structure shown below:

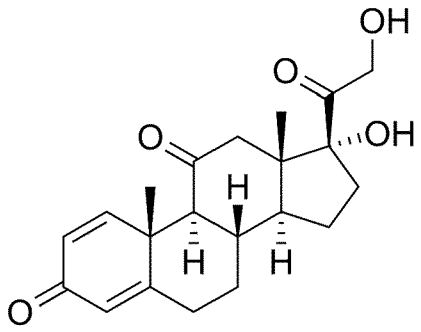


Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme CYP17. This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, dehydroepiandrosterone and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17-C20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals. Abiraterone acetate is indicated with prednisone or prednisolone, for the treatment of mCRPC in adult men who are

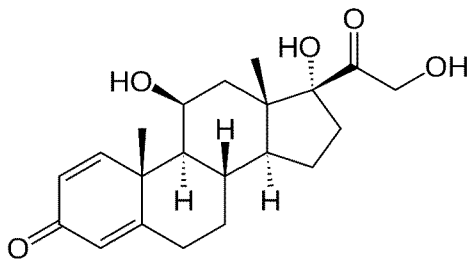
asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated, and for the treatment of patients with metastatic high-risk castration-sensitive prostate cancer.

The synthesis of abiraterone acetate is described in Potter 1995, the contents of which are hereby incorporated by reference in its entirety.

The term "prednisone" refers to a compound with the chemical name 17,21-dihydroxypregna-1,4-diene-3,11,20-trione and structure shown below:



The term "prednisolone" refers to a compound with the chemical name 11,17-Dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydrocyclopenta[a] phenanthren-3-one and structure shown below:



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, or abiraterone acetate, and optionally prednisone or prednisolone. 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, AR or metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, amelioration of one or more symptoms of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, or the slowing or delaying of progression of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) 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 metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC).

The language “therapeutically effective amount” includes that amount of AZD5305 and that amount of abiraterone acetate which together will elicit a biological or medical response in a subject, for example, the reduction or inhibition of enzyme or protein activity related to PARP1, AR, or cancer; amelioration of symptoms of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC); or the slowing or delaying of progression of metastatic prostate cancer, hormone sensitive prostate

cancer (HSPC) or castrate resistant prostate cancer (CRPC). In some embodiments, the language "therapeutically effective amount" includes the amount of AZD5305 and abiraterone acetate together that is effective to at least partially alleviate, inhibit, and/or ameliorate metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) or inhibit PARP1 or AR, and/or reduce or inhibit the growth of a tumor or proliferation of cancerous cells in a subject.

In some embodiments, disclosed is a method of treating metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject in need thereof, comprising administering to the subject a first amount of AZD5305 or a pharmaceutically acceptable salt thereof, and a second amount of abiraterone acetate, and optionally prednisone or prednisolone. In the method, the first amount and the second amount together comprise a therapeutically effective amount.

In some embodiments, disclosed is AZD5305, or a pharmaceutically acceptable salt thereof, for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said AZD5305, or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate, and optionally prednisone or prednisolone, to said subject.

In some embodiments, disclosed is abiraterone acetate, and optionally prednisone or prednisolone, for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said abiraterone acetate, and optionally prednisone or prednisolone, and ii) AZD5305, or a pharmaceutically acceptable salt thereof, to said subject.

In some embodiments, disclosed is the use of AZD5305, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising AZD5305, or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate, and optionally prednisone or prednisolone, to said subject.

In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof and abiraterone acetate, and optionally prednisone or prednisolone, are administered separately, sequentially or simultaneously in a treatment cycle. In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof is continuously administered in the treatment cycle and abiraterone acetate, and optionally prednisone or prednisolone, is also 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 combination 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 and abiraterone acetate are administered in a coordinated fashion. 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 and abiraterone acetate, and optionally prednisone or prednisolone, are 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, and abiraterone acetate, and

optionally prednisone or prednisolone, is administered for 28 days in the 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 up to about 60 mg (for example, up to about 5 mg, up to about 10 mg, up to about 15 mg, up to about 20 mg, up to about 25 mg, up to about 30 mg, up to about 35 mg, up to about 40 mg, up to about 45 mg, up to about 50 mg, up to about 55 mg, or up to about 60 mg AZD5305) per day. In some embodiments, AZD5305 is administered once a day (QD). In some embodiments, AZD5305 is administered in a dose of about 10 mg QD, about 15 mg QD, about 20 mg QD, about 25 mg QD, about 30 mg QD, about 35 mg QD, about 40 mg QD, about 45 mg QD, about 50 mg QD, about 55 mg QD or about 60 mg QD.

In some further embodiments, AZD5305 is administered in a dose of up to about 140 mg (for example, up to about 80 mg, up to about 90 mg, up to about 100 mg, up to about 110 mg, up to about 120 mg, or up to about 140 mg AZD5305) per day. In some further embodiments, AZD5305 is administered in a dose of about 80 mg QD, about 90 mg QD, about 100 mg QD, about 110 mg QD, about 120 mg QD, or about 140 mg QD.

In some embodiments, abiraterone acetate is administered orally. In some embodiments, abiraterone acetate is in tablet dosage form. In some embodiments, abiraterone acetate thereof is administered in a dose of about 1000 mg orally once a day (QD). In some embodiments, the 1000 mg dose comprise two 500 mg tablets or four 250 mg tablets. In some embodiments, prednisone or prednisolone is administered orally. In some embodiments, prednisone or prednisolone is in tablet dosage form. In some embodiments, prednisone or prednisolone is administered in a dose of about 5 mg orally once a day (QD). In some embodiments, prednisone or prednisolone thereof is administered in a dose of about 10 mg orally once a day (QD). In some embodiments, when treating mHSPC, prednisone or prednisolone thereof is administered in a dose of about 5 mg orally once a day (QD). In some embodiments, when treating mCRPC, prednisone or prednisolone thereof is administered in a dose of about 10 mg orally once a day (QD).

In some embodiments, AZD5305, abiraterone acetate, and optionally prednisone or prednisolone are taken together on an empty stomach, with no food two hours before, and one hour after.

In some embodiments, disclosed is a pharmaceutical product comprising i) AZD5305 or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate, and optionally prednisone or prednisolone. In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof, and abiraterone acetate, and optionally prednisone or prednisolone, are present in a single dosage form. In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof, and abiraterone acetate, and optionally prednisone or prednisolone, are present separate dosage forms.

In some embodiments, disclosed is a kit comprising: a first pharmaceutical composition comprising AZD5305, or a pharmaceutically acceptable salt thereof; a second pharmaceutical composition comprising abiraterone acetate, and optionally prednisone or prednisolone; and instructions for using the first and second pharmaceutical compositions in combination.

Metastatic prostate cancer refers to prostate cancer which has spread or metasised to another part of the body.

Hormone sensitive prostate cancer (HSPC) refers to prostate cancer whose growth is inhibited by a decrease in androgen levels or by inhibiting androgen action.

Castrate resistant prostate cancer (CRPC) refers to prostate cancer which continues to grow even when androgen levels in the body are extremely low or undetectable.

Metastatic hormone sensitive prostate cancer (mHSPC) refers to prostate cancer which has spread or metasised to another part of the body, and whose growth is inhibited by a decrease in androgen levels or by inhibiting androgen action.

Metastatic castrate resistant prostate cancer (mCRPC) refers to prostate cancer which has spread or metasised to another part of the body, and which continues to grow even when androgen levels in the body are extremely low or undetectable.

In some embodiments, treatment with a luteinising hormone-releasing hormone (LHRH) agonist or antagonist may be administered concurrently, especially if the patient has not undergone an orchidectomy or a subcapsular orchidectomy. LHRH agonists include leuprolide/leuprorelin, goserelin, triptorelin, histrelin, and buserelin. LHRH antagonists include degarelix, relugolix, bicalutamide, flutamide and cyproterone acetate. Such additional treatments may be dosed at the current standard of care.

Without wishing to be bound by theory, the combination of AZD5305 and abiraterone acetate may be beneficial as PARP1 is a positive co-regulator of the AR-driven gene expression of AR targets, in addition to its role in DNA repair. (Schiewer 2012; Schiewer and Knudsen 2014). As a result, AZD5305 should further inactivate the androgen receptor pathway, adding to the effect of abiraterone acetate.

In addition, New Hormonal Agents (NHAs) have been shown to induce an HRR-deficient phenotype through inhibition of AR signalling (Asim 2017; Goodwin 2013; Li 2017; Polkinghorn 2013; Tarish 2015). Homologous recombination repair gene transcripts and protein levels were found to be upregulated in response to enhanced AR signalling in prostate cancer, and increased radioresistance was observed in the presence of functional AR signalling while decreased HRR gene expression was seen in NHA-treated cells and tumour biopsies. As a result, without wishing to be bound by theory, the induction of an HRR-deficient phenotype by a NHA will lead to increased sensitivity to AZD5305, a selective PARP-1 inhibitor.

In some embodiments, the prostate 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 (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 factors such as EMSY (Hughes-Davies 2003). HR components are also described in Wood 2001.

A prostate 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 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 prostate cancer cells of an individual having a prostate

cancer which is 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 prostate cancer cells may have a BRCA1 and/or a BRCA2 deficient phenotype i.e. BRCA1 and/or BRCA2 activity is reduced or abolished in the prostate cancer cells. Prostate 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 prostate 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 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).
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.

Examples

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

Example 1. Efficacy of AZD5305 combined with abiraterone acetate in an *in vitro* assay

Cell lines

The following cell lines were originally obtained from ATCC:

Cell Lines	Source	AR status	AR variants	Reference
LnCAP	mHSPC	AR+, T877A	AR-FL	Cunningham and You 2015
C4-2	mCRPC	AR+, ARV7, AR8	AR-FL, ARV7	Cunningham and You 2015

Cell line identification was validated using the CellCheck assay (IDEXX Bioanalytics, Westbrook, ME, USA). All cell lines were validated free of virus Mycoplasma contamination using the MycoSEQ assay (Thermo Fisher Scientific, Waltham, MA, USA) or STAT-Myco assay (IDEXX Bioanalytics). All cell lines were grown RPMI-1640 growth media (Corning 17-105-CV) supplemented with 10% fetal bovine serum (FBS) or, when indicated, 10% charcoal stripped FBS (ThermoFisher Scientific, 12676029) and 2 mM glutamine.

Cell proliferation assay and combination benefit calculation

Cells in 384-well or 96-well plates were dosed using an Echo 555 (LabCyte, San Jose, CA, USA) or using the HP D300e Digital Dispenser (HP Life Science Dispensing), respectively. Live cell count pre- and post-treatment (7 days after treatment) was determined using CellTiter-Glo as per manufacturer's instructions (Promega, Madison, WI, USA; G7570).

Cell viability was determined with the Sytox Green assay as described in Davies 2012 and the AC_{50} calculated. The HSA (Highest Single Agent) Synergy Score was calculated according to Bernenbaum 1989.

Results

Cell Line	AZD5305, µM	Abiraterone, µM
	AC_{50}	**AC_{50}**
LnCAP	>1	4.94
C4-2	>1	2.81

Figure 1 shows representative 6 × 6 synergy matrix heatmaps for AZD5305 and abiraterone treatment in prostate cancer cells. Fig 1A shows the heatmap for the treatment of LnCAP cells and Fig 1B shows the heatmap for the treatment of C4-2 cells. HSA represents the calculated excess activity above that expected from an additive combination, based on the HSA additivity model.

Example 2. Efficacy of AZD5305 combined with abiraterone acetate in an *in vivo* pre-clinical model

LNCaP cells ($1x10^7$ cells 1:1 in Matrigel) will be implanted subcutaneously onto the flank of male NOD SCID mice (aged 5-8 weeks weighing approximately 25-30 g, supplied by Charles River) using a 23-gauge needle. When tumours reach approximately 150 mm^3, 40 mice with the most similar sized tumours will be randomly assigned to treatment groups as demonstrated in the table below.

Group	n	Treatment	Dose	Schedule
1	10	Vehicle		
2	10	Abiraterone acetate	200 mg/kg	QD
3	10	AZD5305	1 mg/kg	QD
4	10	Abiraterone% + AZD5305	200 mg/kg + 1 mg/kg	QD + QD

% - Abiraterone to be given 1h prior to the AZD5305 morning dose

Dosing formulations

	Formulation	Concentration
Abiraterone acetate	1% polysorbate 80 in pure water	20 mg/ml
AZD5305	sterile deionized water/HCl pH 3.5-4	0.1 mg/ml

Study

The mice will be dosed for 42 days, with the dose calculated for individual animals on day of dosing, and with a 10mg/kg dosing volume.

Tumour measurement

Tumours will be measured three times per week using digital calipers. The length and width of the tumour will be measured and volume calculated using the following formula:

$$\text{volume} = (\text{length} \times \text{width}^2)/2.$$

Bodyweight

The bodyweight of all mice in the study will be measured and recorded 3 times per week; this information will be used to calculate precise dosing for each animal.

Example 3. Clinical Study of combination of AZD5305 and abiraterone acetate to treat mCRPC and mHSPC

Inclusion Criteria

- Patients must have a histologically confirmed diagnosis of metastatic prostate cancer.
- Candidate for treatment with abiraterone acetate with documented current evidence of metastatic prostate cancer, where metastatic status is defined as at least one documented metastatic lesion on either bone scan or CT/MRI scan.
- Surgically or medically castrated, with serum testosterone levels ≤ 50 ng/dL (≤ 1.75 nmol/L) within (≤) 28 days before first dose of study treatment. Ongoing ADT with a GnRH agonist or antagonist for patients who have not undergone bilateral orchiectomy must be initiated at least 2 weeks before enrolment and must continue throughout the study.
- Patients must have either:

  (a) Metastatic Castrate Resistant Prostate Cancer.

  Patients with mCRPC should have documented prostate cancer progression at screening as assessed by the Investigator with at least one of the following:

  (i) PSA (prostate-specific antigen) 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 µg/L (1 ng/mL).

  (ii) Radiographic progression of soft tissue disease by RECIST criteria with or without PSA progression.

  (iii) Radiographic progression of bone metastasis with two or more documented new bone lesions on a bone scan with or without PSA progression.

Patients with mCRPC should be either first or second line in the castrate resistant setting (should have received ≤ 1 prior line of systemic therapy). Androgen deprivation therapy does not count as a line of therapy. Docetaxel that was previously used when the patient was in the hormone sensitive stage of their disease would not count as a line of therapy.

OR

(b) Metastatic Hormone Sensitive Prostate Cancer.

For patients with mHSPC, the following prior therapies are permitted:

(i) Prior treatment with oestrogens, cyproterone acetate, or first-generation antiandrogens are permitted so long as treatment is discontinued 3 weeks or 5 half-lives (whichever is shorter) prior to enrolment.

(ii) ≤ 6 months of ADT prior to enrolment is permitted. Androgen deprivation therapy treatment should continue on study.

(iii) Patients may have received disease-related radiation or surgery; which should have been completed at least 4 weeks prior to enrolment.

- Adequate organ and marrow function (in the absence of transfusions or growth factor support within 14 days prior to enrolment) as defined below :

Category	Parameter	Value
Haematological	Haemoglobin	≥ 10.0 g/dL
	Absolute neutrophil count	≥ 1.5 × 10^9/L
	Platelet count	≥ 100 × 10^9/L
Hepatic	Total bilirubin	≤ 1.5 × ULN; ≤ 3 × ULN if the patient has Gilbert's syndrome
	ALT and AST	≤ 2.5 × ULN in the absence of liver metastases
		≤ 5 × ULN[a] in presence of liver metastases
	Albumin	≥ 3 g/dL
	INR	≤ 1.5 Patient receiving non-Vitamin K antagonist oral anticoagulants may be enrolled with an INR of < 2
Renal	Calculated creatinine clearance by Cockcroft-Gault	≥ 45 mL/minute

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

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

- ECOG PS (Eastern Cooperative Oncology Group Performance Status): 0-1 with no deterioration over the previous 2 weeks.
- Life expectancy ≥ 16 weeks.

Abiraterone acetate, Prednisone and AZD5305 Dose Escalation

The starting dose of AZD5305 will be 60mg once daily (QD). Abiraterone acetate will be dosed at 1000mg once daily (QD), prednisone will be dosed at 5mg or 10mg once daily (QD), with concurrent dosing of AZD5305 in combination with abiraterone acetate and prednisone from day 1 of cycle 1.

The dose of prednisone corresponds to the indication:

- For mHSPC, abiraterone acetate will be dosed with 5 mg prednisone once daily
- For mCRPC, abiraterone acetate will be dosed with 10 mg prednisone once daily

In the study, the cycle length will be 28 days, with AZD5305 being dosed once daily, and abiraterone acetate being dosed once daily at 1000mg. AZD5305, abiraterone acetate and prednisone will be taken on an empty stomach with no food for 2 hours and 1 hour after. The 1000mg dose of abiraterone acetate will be taken as two 500mg film-coated tablets.

If the starting dose of AZD5305 of 60mg QD is tolerated, the dose may be escalated to 90 mg QD if required (whilst the abiraterone acetate dose will be maintained at 1000 mg QD, and the prednisone dose maintained at 5mg or 10mg OD), and if not tolerated, the AZD5305 dose will be de-escalated to 40 mg QD.

The dose of AZD5305 may be further escalated, up to no more than 140 mg QD.

The dose of AZD5305 may be de-escalated to 20 mg QD, either due to tolerability or if such dose is shown to be effective.

All potential dose escalation and/or de-escalation levels (including intermediate dose levels and exploration of alternative schedules of AZD5305) after the starting dose may be adjusted in light of emerging safety, tolerability and/or PK data.

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.

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Claims

1. A method of treating metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject in need thereof, comprising administering to the subject a first amount of AZD5305 or a pharmaceutically acceptable salt thereof, and a second amount of abiraterone acetate, wherein the first amount and the second amount together comprise a therapeutically effective amount.

2. The method according to claim 1, wherein prednisone or prednisolone are administered to the subject.

3. The method according to either claim 1 or claim 2, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).

4. The method according to any one of claims 1 to 3, wherein AZD5305 is administered once daily.

5. The method according to claim 4, wherein AZD5305 is administered in a dose of up to about 60 mg per day.

6. The method according to claim 5, wherein AZD5305 is administered in a dose of 60 mg per day.

7. The method according to claim 5, wherein AZD5305 is administered in a dose of 20 mg per day.

8. The method according to any one of claims 1 to 7, wherein abiraterone acetate is administered once daily.

9. The method according to claim 8, wherein abiraterone acetate is administered in a dose of 1000 mg once daily.

10. A method according to any one of claims 1 to 9, wherein AZD5305 and abiraterone acetate, are taken together, on an empty stomach, with no food two hours before.

11. AZD5305, or a pharmaceutically acceptable salt thereof, for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said AZD5305, or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate to said subject.

12. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 11, wherein said treatment also comprises the separate, sequential or simultaneous administration of prednisone or prednisolone.

13. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to either claim 11 or claim 12, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).

14. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 13, wherein AZD5305 is administered once daily.

15. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 14, wherein AZD5305 is administered in a dose of up to about 60 mg per day.

16. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 15, wherein AZD5305 is administered in a dose of 60 mg per day.

17. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 15, wherein AZD5305 is administered in a dose of 20 mg per day.

18. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 17, wherein abiraterone acetate thereof is administered twice daily.

19. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 18, wherein abiraterone acetate is administered in a dose of 1000 mg once daily.

20. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 11 to 19, wherein AZD5305 and abiraterone acetate are taken together on an empty stomach, with no food two hours before.

21. Abiraterone acetate for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said abiraterone acetate, and ii) AZD5305, or a pharmaceutically acceptable salt thereof, to said subject.

22. Abiraterone acetate for use according to claim 21, wherein said treatment also comprises the separate, sequential or simultaneous administration of prednisone or prednisolone.

23. Abiraterone acetate for use according to either claim 21 or claim 22, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).

24. Abiraterone acetate for use according to any one of claims 21 to 23, wherein AZD5305 is administered once daily.

25. Abiraterone acetate for use according to claim 24, wherein AZD5305 is administered in a dose of up to about 60 mg per day.

26. Abiraterone acetate for use according to claim 25, wherein AZD5305 is administered in a dose of 60 mg per day.

27. Abiraterone acetate for use according to claim 25, wherein AZD5305 is administered in a dose of 20 mg per day.

28. Abiraterone acetate for use according to any one of claims 21 to 27, wherein abiraterone acetate is administered once daily.

29. Abiraterone acetate for use according to claim 28, wherein abiraterone acetate is administered in a dose of 1000 mg once daily.

30. Abiraterone acetate for use according to any one of claims 21 to 29, wherein AZD5305 and abiraterone acetate are taken together on an empty stomach, with no food two hours before.

31. The use of AZD5305, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC), wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising AZD5305, or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate to said subject.

32. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 31, wherein said treatment also comprises the separate, sequential or simultaneous administration of prednisone or prednisolone.

33. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to either claim 31 or claim 32, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).

34. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 31 to 33, wherein AZD5305 is administered once daily.

35. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 34, wherein AZD5305 is administered in a dose of up to about 60 mg per day.

36. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 35, wherein AZD5305 is administered in a dose of 60 mg per day.

37. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 35, wherein AZD5305 is administered in a dose of 20 mg per day.

38. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 37, wherein abiraterone acetate is administered once daily.

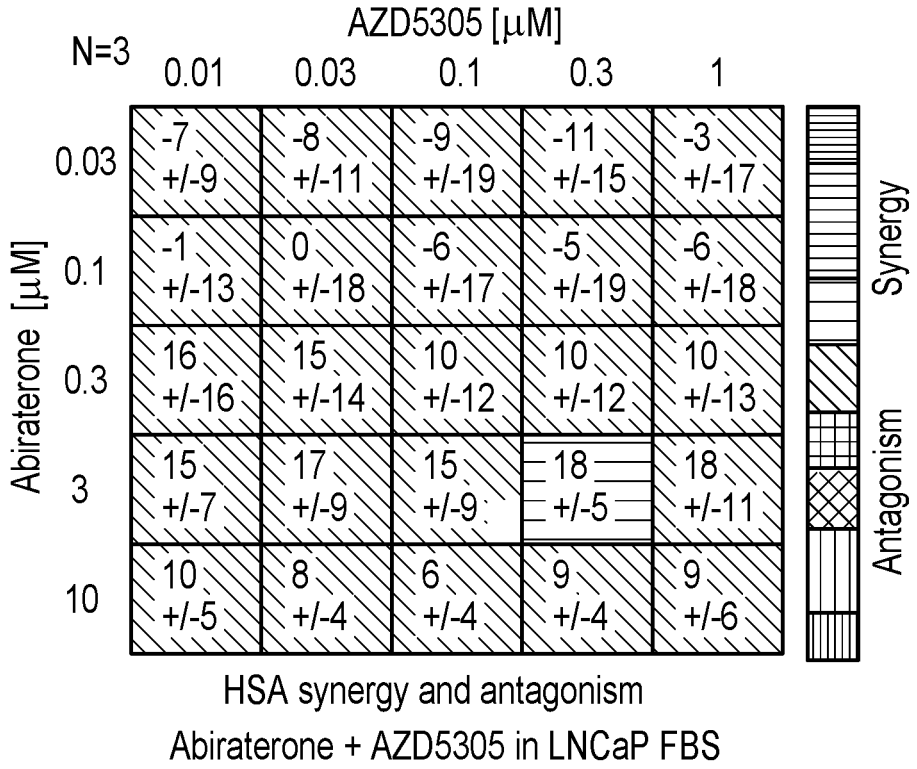
39. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 38, wherein abiraterone acetate is administered in a dose of 1000 mg once daily.

40. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 31 to 39, wherein AZD5305 and abiraterone acetate are taken together on an empty stomach, with no food two hours before.

41. A pharmaceutical product comprising i) AZD5305 or a pharmaceutically acceptable salt thereof, and ii) abiraterone acetate.

42. A kit comprising: a first pharmaceutical composition comprising AZD5305, or a pharmaceutically acceptable salt thereof; a second pharmaceutical composition comprising abiraterone acetate; and instructions for using the first and second pharmaceutical compositions in combination.

43. A method, compound, use, pharmaceutical product, or a kit according to any preceding claim, wherein AZD5305 is replaced by an alternative selective PARP1 inhibitor.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0.3
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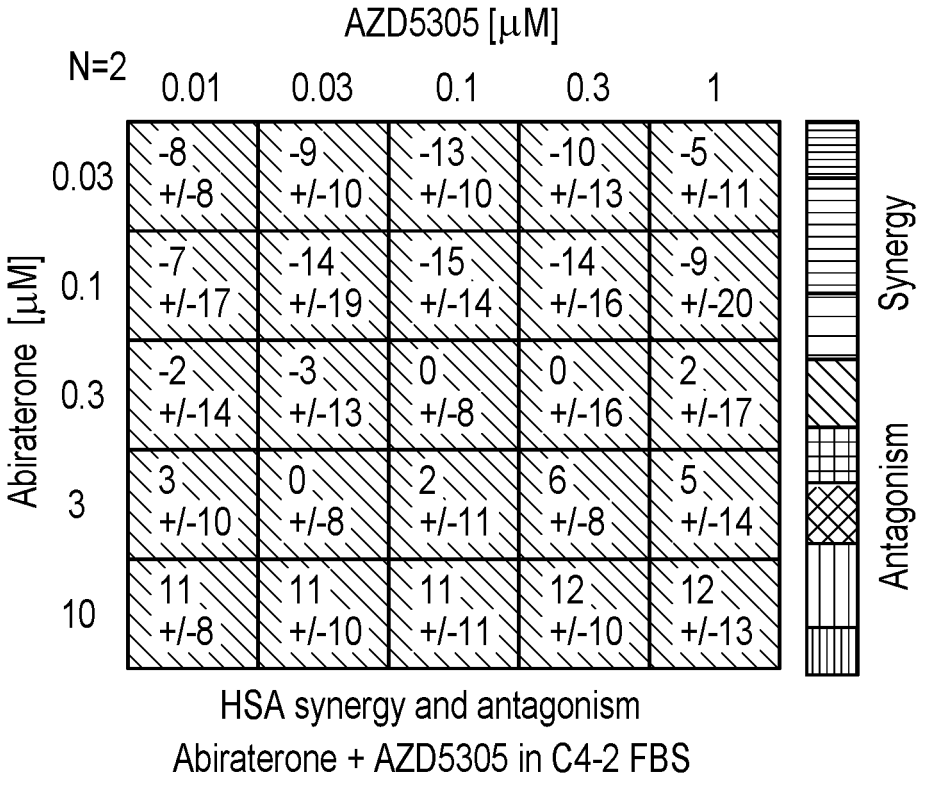
0.3
3
10
-7 +/-9
-8 +/-11
-9 +/-19
-11 +/-15
-3 +/-17
-1 +/-13
0 +/-18
-6 +/-17
-5 +/-19
-6 +/-18
16 +/-16
15 +/-14
10 +/-12
10 +/-12
10 +/-13
15 +/-7
17 +/-9
15 +/-9
18 +/-5
18 +/-11
10 +/-5
8 +/-4
6 +/-4
9 +/-4
9 +/-6
Synergy
Antagonism
HSA synergy and antagonism
Abiraterone + AZD5305 in LNCaP FBS

Fig. 1A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0.1
0.3
1
Abiraterone [µM]
0.03
0.1
0.3
3
10
-8 +/-8
-9 +/-10
-13 +/-10
-10 +/-13
-5 +/-11
-7 +/-17
-14 +/-19
-15 +/-14
-14 +/-16
-9 +/-20
-2 +/-14
-3 +/-13
0 +/-8
0 +/-16
2 +/-17
3 +/-10
0 +/-8
2 +/-11
6 +/-8
5 +/-14
11 +/-8
11 +/-10
11 +/-11
12 +/-10
12 +/-13
Synergy
Antagonism
HSA synergy and antagonism
Abiraterone + AZD5305 in C4-2 FBS

Fig. 1B