

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.

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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).

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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).

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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).

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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).

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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)

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

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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
5 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
10 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.

15 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 of these patients who have such cancers live with an incurable disease. Accordingly, it is important to continue to find new treatments for
20 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
25 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 darolutamide or a pharmaceutically acceptable salt thereof. In the method, the first amount and the second amount together comprise a therapeutically effective amount.

30 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) darolutamide, or a pharmaceutically
35 acceptable salt thereof, to said subject.

In some embodiments, disclosed is darolutamide, 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
5 darolutamide, or a pharmaceutically acceptable salt thereof, 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
10 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) darolutamide, or a pharmaceutically acceptable salt thereof, to said subject.

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

20 In some embodiments, disclosed is a pharmaceutical product comprising i) AZD5305 or a pharmaceutically acceptable salt thereof, and ii) darolutamide or a pharmaceutically acceptable salt thereof.

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

30 The combination of AZD5305 and darolutamide 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
35 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.

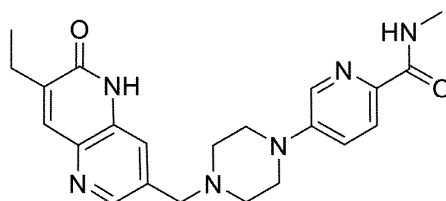
In some embodiments, disclosed is a method of treating metastatic prostate cancer, hormone sensitive prostate cancer (HSPC) or castrate resistant prostate cancer (CRPC) in a subject in need thereof, comprising administering to the subject a first amount of a selective PARP1 inhibitor (such as AZD5305),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

In some embodiments, disclosed is darolutamide, 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 darolutamide, or a pharmaceutically acceptable salt thereof, and ii) a selective PARP1 inhibitor (such as AZD5305), or a pharmaceutically acceptable salt thereof, to said subject.

Detailed Description

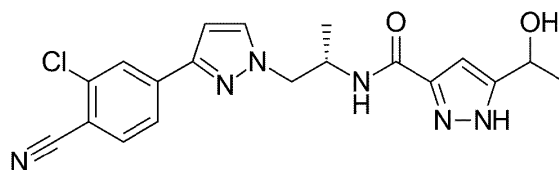
The term "AZD5305" refers to a compound with the chemical name 5-{4-[(7-ethyl-6-oxo-5,6-dihydro-1,5-naphthyridin-3-yl)methyl]piperazin-1-yl}-N-methylpyridine-2-carboxamide and structure shown below:



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, and 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 "darolutamide" refers to a compound with the chemical name *N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide* and structure shown below:



Darolutamide is an AR antagonist specifically inhibiting AR nuclear translocation. Darolutamide and the active metabolite (ORM-15341) each inhibit wild-type AR as well as clinically relevant AR mutations AR (F876L), which trigger enzalutamide and apalutamide antagonist to agonist switch, as well as AR (W742L) and AR (T877A) which cause bicalutamide agonist switch (Moilanen 2015). Darolutamide has a low potential for drug-drug interaction (Shore 2019) and provides promising reductions in brain penetrance, as well as effectively inhibiting all known AR mutations (Fizazi 2015). Darolutamide was approved by the FDA on 30 July 2019 for use in non-metastatic CRPC, based on performance in the ARAMIS trial (NCT02200614) (Fizazi 2019) which showed metastasis free survival was 40.4 months in darolutamide treated patients compared to 18.5 months in placebo treated patients.

The synthesis of darolutamide is described in WO2011/051540, the contents of which are hereby incorporated by reference in its entirety. In some embodiments, a free base

darolutamide is administered to a subject. In some embodiments, a pharmaceutically acceptable salt of darolutamide is administered to a subject.

5 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 darolutamide 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
10 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-
15 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
20 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.

25 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
30 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.

35 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,
5 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 darolutamide 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
10 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
15 darolutamide 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.

20 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 darolutamide or a pharmaceutically acceptable salt thereof. In the method, the first amount and the second
25 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
30 comprises the separate, sequential or simultaneous administration of i) said AZD5305, or a pharmaceutically acceptable salt thereof, and ii) darolutamide, or a pharmaceutically acceptable salt thereof, to said subject.

In some embodiments, disclosed is darolutamide, 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
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darolutamide, or a pharmaceutically acceptable salt thereof, and ii) AZD5305, or a pharmaceutically acceptable salt thereof, to said subject.

5 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) darolutamide, or a pharmaceutically acceptable salt thereof, to said subject.

10 In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof and darolutamide or a pharmaceutically acceptable salt thereof 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 darolutamide or a pharmaceutically acceptable salt is also continuously administered in the treatment cycle.

20 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.

25 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 darolutamide 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.

30 In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof and darolutamide or a pharmaceutically acceptable salt thereof 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

5 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.

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

15 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
20 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.

25 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.
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In some embodiments, darolutamide or a pharmaceutically acceptable salt thereof is administered orally. In some embodiments, darolutamide or a pharmaceutically acceptable salt thereof is in tablet dosage form. In some embodiments, darolutamide or a
35 pharmaceutically acceptable salt thereof is administered in a dose of about 600 mg orally twice per day (BID). In some embodiments, the 600 mg dose comprise two 300 mg tablets.

In some embodiments, AZD5305 and darolutamide are taken separately, where a dose of AZD5305 is taken on an empty stomach, with no food two hours before, and a dose of darolutamide is taken at least one hour after AZD5305 with food.

- 5 In some embodiments, disclosed is a pharmaceutical product comprising i) AZD5305 or a pharmaceutically acceptable salt thereof, and ii) darolutamide or a pharmaceutically acceptable salt thereof. In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof, and darolutamide or a pharmaceutically acceptable salt thereof are present in a single dosage form. In some embodiments, AZD5305 or a pharmaceutically acceptable salt thereof, and darolutamide or a pharmaceutically acceptable salt thereof are present separate
10 dosage forms.

- In some embodiments, disclosed is a kit comprising: a first pharmaceutical composition comprising AZD5305, or a pharmaceutically acceptable salt thereof; a second
15 pharmaceutical composition comprising darolutamide, or a pharmaceutically acceptable salt thereof; and instructions for using the first and second pharmaceutical compositions in combination.

- Metastatic prostate cancer refers to prostate cancer which has spread or metastasised to
20 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.

- 25 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 metastasised to another part of the body, and whose growth is inhibited by a
30 decrease in androgen levels or by inhibiting androgen action.

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

- 35 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.

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Without wishing to be bound by theory, the combination of AZD5305 and darolutamide 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 darolutamide.

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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 et al 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.

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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.

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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.

5 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.

10 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
15 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
20 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
25 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
30 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
35 non-limiting examples.

Example 1. Efficacy of AZD5305 combined with darolutamide in an *in vitro* assayCell 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
LnCAP 95	mCRPC	AR+	AR-FL, ARV7	Cunningham and You 2015
CWR22Pc-R1-AD1	mCRPC	AR+	AR-FL, ARV8	Nyquist 2013

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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.

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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).

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Cell viability was determined with the Sytox Green assay as described in Davies 2012 and the AC₅₀ calculated. The HSA (Highest Single Agent) Synergy Score was calculated according to Bernenbaum 1989.

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Results

Cell Line	AZD5305, M		Darolutamide, M		Synergy score	
	AC ₅₀	±SD	AC ₅₀	±SD	HSA	±SD

LnCAP	2.85E-07	1.91E-07	3.63E-06	9.98E-07	1.328	0.1915
LnCAP 95	7E-07	2.71E-07	0.0000175	3.54E-06	1.019	0.3456
CWR22Pc-R1-AD1	5.66E-09	3.30E-09	6.55E-08	1.31E-08	2.625	0.49

Monotherapy agent's potency is expressed in M concentrations; values are the mean of two independent experiments each performed in triplicate. HSA (Highest Single Agent) is the synergy score mean of three independent experiments each performed in triplicate. SD indicate standard deviation error, where not indicated only one experiment was performed.

These results show that the combination of AZD5305 and darolutamide showed synergy in the LnCAP, LnCAP 95 and CWR22Pc-R1-AD1 cell lines.

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

ST1273PDX model (~70 mg tumour fragments) will be implanted subcutaneously onto the flank of athymic nude male mice (aged 6-12 weeks). When tumours reach approximately 150-300 mm³, 32 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	8	Vehicle		
2	8	Darolutamide	50 mg/kg	BID
3	8	AZD5305	1 mg/kg	QD
5	8	Darolutamide ^{&} + AZD5305	50 mg/kg + 1 mg/kg	BID + QD

& - Darolutamide to be given 1h prior to the AZD5305 morning dose

Dosing formulations

	Formulation	Concentration
Darolutamide	PEG400:propylene glycol:5% glucose (50:30:20)	5.0 mg/ml
AZD5305	sterile deionized water/HCl pH 3.5-4	0.1 mg/ml

Study

The mice will be dosed for 28 days, with the dose calculated for individual animals on day of dosing, and with a 10mg/kg dosing volume.

5 *Tumour measurement*

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

$$\text{volume} = (\text{length} \times \text{width}^2) \pi / 6.$$

10 *Bodyweight*

The bodyweight of all mice in the study will be measured and recorded 2 times per week; this information will be used to calculate precise dosing for each animal.

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

Inclusion Criteria

- Patients must have a histologically confirmed diagnosis of metastatic prostate cancer.
- Candidate for treatment with darolutamide 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 ($\leq$) 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 $\mu\text{g/L}$ (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.

5 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

10 (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.

15 (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.

20 • 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	$\geq 1.5 \times 10^9/L$
	Platelet count	$\geq 100 \times 10^9/L$
Hepatic	Total bilirubin	$\leq 1.5 \times ULN$; $\leq 3 \times ULN$ if the patient has Gilbert's syndrome
	ALT and AST	$\leq 2.5 \times ULN$ in the absence of liver metastases
		$\leq 5 \times ULN^a$ 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
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^a In the presence of liver metastases and raised ALT/AST between $2.5\text{--}5 \times \text{ULN}$, patients can only be enrolled if total bilirubin level is $< 1.5 \times \text{ULN}$.

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

- 5
 - ECOG PS (Eastern Cooperative Oncology Group Performance Status): 0-1 with no deterioration over the previous 2 weeks.
 - Life expectancy ≥ 16 weeks.

Darolutamide and AZD5305 Dose Escalation

- 10 The starting dose of AZD5305 will be 60 mg once daily (QD). Darolutamide will be dosed at 600 mg twice daily (BD) with concurrent dosing of AZD5305 in combination with darolutamide from day 1 of cycle 1.

- 15 In the study, the cycle length will be 28 days, with AZD5305 being dosed once daily, and darolutamide being dosed twice daily at 600 mg. AZD5305 will be taken on an empty stomach with no food for 2 hours and 1 hour after, with darolutamide being taken with food at least one hour after the daily dose of AZD5305. The 600mg dose of darolutamide will be taken as two 300 mg film-coated tablets.

- 20 If the starting dose of AZD5305 of 60 mg QD is tolerated, the dose may be escalated to 90 mg QD if required (whilst the darolutamide dose will be maintained at 600 mg BD), and if not tolerated, the AZD5305 dose will be de-escalated to 40 mg QD.

- 25 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.

- 30 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.

	Reference	Doi
Armstrong 2019	Armstrong AJ, et al., J Clin Oncol. 2019 Nov 10; 37(32): 2974-2986	10.1200/JCO.2019.37.7_suppl.687
Asim 2017	Asim M, et al., Nat Commun. 2017 Aug 29;8(1):374	10.1038/s41467-017-00393-y
Beer 2014	Beer TM, et al., N Engl J Med. 2014 July 31; 371(5):424-433	10.1056/NEJMoa1405095
Berenbaum 1989	Berenbaum MC, Pharmacol Rev, 41 (1989), pp. 93-141	PMID: 2692037
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
Clarke 2018	Clarke N, et al. <i>Lancet Oncol</i> 2018; 19: 975-986	10.1016/S1470-2045(18)30365-6
Cunningham and You 2015	Cunningham D and You Z., J Biol Methods 2015;2(1):e17	10.14440/jbm.2015.63
Davies 2012	Davies BR, et al., Mol Cancer Ther (2012) 11(4): 873-887	10.1158/1535-7163.MCT-11-0824-T
Dirix 2016	Dirix L, et al., Clin Therapeutics (2016) 38(10): 2286-2299	10.1016/j.clinthera.2016.08.010
Fizazi 2015	Fizazi K, et al., Expert Rev Anticancer Ther. 2015 15(9):1007-17	10.1586/14737140.2015.1081566
Fizazi 2019	Fizazi K, et al., N Engl J Med. 2019 Mar 28; 380(13):1235-46	10.1056/NEJMoa1815671
Gibbons 2015	Gibbons J, et al., Clin Pharmacokinet (2015) 54:1057–1069	10.1007/s40262-015-0283-1
Goodwin 2013	Goodwin JF, et al., Cancer Discov. 3, 1254–1271 (2013)	10.1158/2159-8290.CD-13-0108

Hughes-Davies 2003	Hughes-Davies, et al., <i>Cell</i> , 115, 523-535 (2003)	10.1016/s0092-8674(03)00930-9
Janatová 2003	Janatová M, et al., <i>Neoplasma</i> , 50(4), 246-50 (2003)	PMID: 12937835
Jancarkova 2003	Jancárková, N, <i>Ceska Gynekol.</i> , 68(1), 11-6 (2003)	PMID: 12708108
Jasmin 2002	Jasin M., <i>Oncogene</i> , 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, <i>Nat. Genet.</i> 27(3): 247-254 (2001)	10.1038/85798
Li 2017	Li L, et al. <i>Sci Signal.</i> 2017 May 23;10(480):eaam7479	10.1126/scisignal.aam7479
Moilanen 2015	Moilanen A-M et al., <i>Sci Rep.</i> 2015 Jul 3; 5:12007	10.1038/srep12007
Mohler 2019	Mohler JL, et al., <i>J Natl Compr Canc Netw.</i> 2019 May 1;17(5):479-505	10.6004/jnccn.2019.0023
Neuhausen and Ostrander 1992	Neuhausen SL and Ostrander EA, <i>Genet. Test</i> , 1, 75-83 (1992)	10.1089/gte.1997.1.75
Nyquist 2013	Nyquist MD, et al., 2013 <i>PNAS</i> 110(43), 17492–17497	10.1073/pnas.1308587110
Parker 2020	Parker C, et al., <i>Ann Oncol.</i> 2020 Sep;31(9):1119-1134	10.1016/j.annonc.2020.06.011
Polkinghorn 2013	Polkinghorn WR, et al., <i>Cancer Discov.</i> 2013 Nov;3(11):1245-53	10.1158/2159-8290.CD-13-0172
Potter 1995	Potter GA, et al., <i>J. Med. Chem.</i> 1995, 38, 13, 2463-2471	10.1021/jm00013a022
Ryan 2013	Ryan CJ, et al., <i>N Engl J Med.</i> 2013 Jan 10; 368(2):138-148	10.1056/NEJMoa1209096
Scher 2015	Scher HI, et al., <i>PLoS One.</i> 2015 Oct 13; 10(10):e039440	10.1371/journal.pone.0139440
Schiewer 2012	Schiewer MJ, et al. <i>Cancer Discov.</i> 2012 Dec; 2(12):1134-1149	10.1158/2159-8290.CD-12-0120

Schiewer and Knudsen 2014	Schiewer MJ and Knudsen KE, Mol Cancer Res. 2014 Aug;12(8):1069-1080	10.1158/1541-7786.MCR-13-0672
Shore 2019	Shore N, et al., Targeted Oncology (2019) 14:527-539	10.1007/s11523-019-00674-0
Sung 2021	Sung H, et al., CA Cancer J Clin. 2021 May; 71(3):209–249	10.3322/caac.21660
Tarish 2015	Tarish FL, et al., Sci Transl Med. 2015 Nov 4;7(312):312re11	10.1126/scitranslmed.aac5671
Tutt 2002	Tutt, et al., Trends Mol Med., 8(12), 571-576, (2002)	10.1016/s1471-4914(02)02434-6
Wood 2001	Wood, et al., Science, 291, 1284-1289 (2001)	10.1126/science.1056154

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 darolutamide or a pharmaceutically acceptable salt thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount.
5
2. The method according to claim 1, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).
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3. The method according to either claim 1 or claim 2, wherein AZD5305 is administered once daily.
15
4. The method according to claim 3, wherein AZD5305 is administered in a dose of up to about 60 mg per day.
5. The method according to claim 4, wherein AZD5305 is administered in a dose of 60 mg per day.
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6. The method according to claim 4, wherein AZD5305 is administered in a dose of 20 mg per day.
7. The method according to any one of claims 1 to 6, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered twice daily.
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8. The method according to claim 7, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered in a dose of 600 mg twice daily.
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9. A method according to any one of claims 1 to 8, wherein AZD5305 and darolutamide are taken separately, where a dose of AZD5305 is taken on an empty stomach, with no food two hours before, and a dose of darolutamide is taken at least one hour after AZD5305 with food.
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10. 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) darolutamide, or a pharmaceutically acceptable salt thereof, to said subject.
11. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 10, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).
12. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to either claim 10 or claim 11, wherein AZD5305 is administered once daily.
13. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 12, wherein AZD5305 is administered in a dose of up to about 60 mg per day.
14. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 13, wherein AZD5305 is administered in a dose of 60 mg per day.
15. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 13, wherein AZD5305 is administered in a dose of 20 mg per day.
16. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 10 to 15, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered twice daily.
17. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to claim 16, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered in a dose of 600 mg twice daily.
18. AZD5305, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 10 to 17, wherein AZD5305 and darolutamide are taken separately, where a dose of AZD5305 is taken on an empty stomach, with no food two hours before, and a dose of darolutamide is taken at least one hour after AZD5305 with food.

19. Darolutamide, 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 darolutamide, or a pharmaceutically acceptable salt thereof, and ii) AZD5305, or a pharmaceutically acceptable salt thereof, to said subject.
20. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to claim 19, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).
21. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to either claim 19 or claim 20, wherein AZD5305 is administered once daily.
22. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to claim 21, wherein AZD5305 is administered in a dose of up to about 60 mg per day.
23. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to claim 22, wherein AZD5305 is administered in a dose of 60 mg per day.
24. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to claim 22, wherein AZD5305 is administered in a dose of 20 mg per day.
25. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 19 to 24, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered twice daily.
26. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to claim 25, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered in a dose of 600 mg twice daily.
27. Darolutamide, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 19 to 26, wherein AZD5305 and darolutamide are taken separately, where a dose of AZD5305 is taken on an empty stomach, with no food two hours before, and a dose of darolutamide is taken at least one hour after AZD5305 with food.

28. 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
5 i) said medicament comprising AZD5305, or a pharmaceutically acceptable salt thereof, and
ii) darolutamide, or a pharmaceutically acceptable salt thereof, to said subject.

29. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 28, wherein the metastatic prostate cancer is metastatic hormone sensitive prostate
10 cancer (mHSPC) or metastatic castrate resistant prostate cancer (mCRPC).

30. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to either claim 28 or claim 29, wherein AZD5305 is administered once daily.

15 31. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 30, wherein AZD5305 is administered in a dose of up to about 60 mg per day.

32. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 31, wherein AZD5305 is administered in a dose of 60 mg per day.
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33. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 31, wherein AZD5305 is administered in a dose of 20 mg per day.

34. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any
25 one of claims 1 to 33, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered twice daily.

35. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to claim 34, wherein darolutamide or a pharmaceutically acceptable salt thereof is administered
30 in a dose of 600 mg twice daily.

36. The use of AZD5305, or a pharmaceutically acceptable salt thereof, according to any one of claims 28 to 35, wherein AZD5305 and darolutamide are taken separately, where a dose of AZD5305 is taken on an empty stomach, with no food two hours before, and a dose
35 of darolutamide is taken at least one hour after AZD5305 with food.

37. A pharmaceutical product comprising i) AZD5305 or a pharmaceutically acceptable salt thereof, and ii) darolutamide or a pharmaceutically acceptable salt thereof.
38. A kit comprising: a first pharmaceutical composition comprising AZD5305, or a pharmaceutically acceptable salt thereof; a second pharmaceutical composition comprising darolutamide, or a pharmaceutically acceptable salt thereof; and instructions for using the first and second pharmaceutical compositions in combination.
39. A method, compound, use, pharmaceutical product, or a kit according to any preceding claim, wherein AZD5305 is replaced by an alternative selective PARP1 inhibitor.