Clinical Study Protocol	
Study Intervention	Saruparib (AZD5305)
Study Code	D9727C00001
Version	2.0
Date	10 April 2025
EU CT Number	2024-513586-39
IND Number	165861

A Randomised, Double-blind, Placebo-controlled, Phase III Study of Adjuvant Saruparib (AZD5305) in Patients with BRCAm Localised High-Risk Prostate Cancer Receiving Radiotherapy with Androgen Deprivation Therapy (EvoPAR-Prostate02)

Sponsor Name: AstraZeneca

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Regulatory Agency Identifier Number(s):

Registry	ID
EU CT Number	2024-513586-39
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This protocol has been subject to a peer review according to AstraZeneca Standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Version Scope: Global

Brief Title: A study to evaluate the impact on metastases-free survival with the addition of saruparib versus placebo to a standard radiotherapy/androgen deprivation regimen in men with high-risk prostate cancer with a *BRCA* mutation.

Study Phase: Phase III

Acronym: EvoPAR-Prostate02

Study Clinical Lead and Contact Information will be provided separately.

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5 STUDY POPULATION

The target populations of interest in this study are participants with high-risk and very high-risk (localised/locally advanced) prostate cancer and participants with a high-risk BCR with a *BRCA*m status.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply.

*Criteria relevant to pre-screening (*BRCA*m biomarker testing).

Age

1 Participant must be male and ≥ 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place), at the time of signing the ICF.

Type of Participant and Disease Characteristics

2 Participant must have a histologically documented diagnosis of prostate adenocarcinoma. Participants with pathologic features of small cell, neuroendocrine, sarcomatoid, spindle cell, or signet cell histology **are not** eligible.*

3 Participants with newly diagnosed high-risk and very high-risk (localised/locally advanced) prostate cancer or participants with a high-risk BCR following radical prostatectomy, as defined by one of the following disease criteria:*

(a) High-risk (localised) prostate cancer (as defined by one of the following):

(i) N0 with cT3a.

(ii) N0 with Gleason score of 8.

(iii) N0 with PSA ≥ 20 ng/mL.

OR

(b) Very high-risk (locally advanced) prostate cancer (as defined by one of the following):

(i) N0 with cT3b-T4.

(ii) N0 with Gleason score 9-10.

(iii) N0 with ≥ 2 high-risk features (see above).

(iv) N1 disease

OR

(c) Participants with high-risk BCR following a radical prostatectomy (< 365 days).

PSA that rises to ≥ 0.2 ng/mL with a second measurement also ≥ 0.2 ng/mL and at least one of the following high-risk disease or PSA characteristics:

(i) Primary disease with T3-T4.

(ii) Primary disease with Gleason score 8-10.

(iii) Primary disease with PSA ≥ 20 ng/mL.

(iv) Primary disease with N1.

(v) PSA doubling time < 9 months.

ORPSA persistence (defined as detectable PSA measurement obtained 8 weeks following a radical prostatectomy).

4 Provision of a FFPE tumour tissue sample as specified in the Laboratory Manual and designated Diagnostic Testing Manuals (refer to Section 8.8.1.1).

5 Confirmed *BRCA*1 or *BRCA*2 mutation status by central tumour tissue is required for enrolment.

*BRCA*m results obtained through local germline testing cannot be used for eligibility. If a participant has a confirmed local germline testing result, a confirmed *BRCA*m will still be required by a centrally confirmed tumour tissue result.

6 All participants will be required to have a CT or MRI and a bone scan following the completion of their planned RT. This screening scan must confirm no evidence of disease or evidence of disease confined to the pelvis (M0), as assessed by a central reader (see Section 8.2).

7 All participants will be required to have a PSMA-PET following the completion of their planned RT. This screening scan must confirm no evidence of disease or evidence of disease confined to the pelvis (M0), as assessed by a central reader (see Section 8.2).

8 Participants experiencing RT-associated AEs must have resolution of their conditions to CTCAE Grade 1 or baseline values.

9 ECOG performance status of 0 or 1 with no deterioration over the 2 weeks prior to randomisation.

10 Minimum life expectancy of 12 months.*

11 Adequate organ and bone marrow function as follows:*

(a) Haemoglobin ≥ 10.0 g/dL with no blood transfusion in the 14 days prior to randomisation.

(b) Absolute neutrophil count ≥ 1.5×10^9/L with no growth factor support in the 28 days prior to randomisation.

(c) Platelet count ≥ 100×10^9/L.

(d) Serum albumin ≥ 3 g/dL.

(e) INR ≤ 1.5. Participants receiving oral anticoagulants may be enrolled with an INR < 2. Participants with other causes of INR increase, such as haematologic disorders or impaired hepatic synthesis should be excluded.

(f) TBL ≤ 1.5 × ULN or ≤ 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).

(g) ALT and AST ≤ 2.5 × ULN (see Appendix E 6 and Appendix E 4.2).

(h) eGFR of ≥ 45 mL/min/1.73 m^2 as determined by CKD-EPI formula (Inker et al 2021):

(i) For participants with SCr ≤ 0.9 mg/dL (≤ 79.56 µmol/L), use the following formula:

$142 \times (SCr/0.9)^{-0.302} \times 0.9938^{Age\ (years)}$

(ii) For participants with SCr > 0.9 mg/dL (> 79.56 µmol/L), use the following formula:

$142 \times (SCr/0.9)^{-1.200} \times 0.9938^{Age\ (years)}$

Pre-study Radiotherapy and Treatment Requirements

12 All participants will have received either primary or salvage RT; participants must be eligible for randomisation within 10 months of initial diagnosis (*de novo* or BCR).

(a) Radiotherapy administered to the prostate (± pelvis) either in the primary or salvage setting must be delivered with curative intent. Use of metastases-directed therapy, as part of the RT radiation plan, is permitted as localised RT treatment for a metastatic lesion(s) outside the pelvis.

13 All participants will have received a planned regimen of ADT with a GnRH analogue (investigator choice).

14 If applicable, participants entering the study on an ADT + abiraterone regimen must be receiving an abiraterone regimen of 1000 mg/day (with prednisone 5 mg or equivalent) and this regimen will be continued at the time of study entry.

Sex and Contraceptive/Barrier Requirements

15 Male participants:

(a) Must not father children or donate sperm from signing ICF, during the study intervention and for 6 months after the last dose of study intervention. For participants wishing to father children, arrangement of donation of sperm prior to signing ICF must be made. Male participants may be rejected as a sperm donor after the study.

(b) Must use a condom (with spermicide – where permitted) from signing ICF, during study intervention, and for 6 months after the last dose of study drug, with all sexual

partners. Female partners who are women of childbearing potential should use a highly effective method of contraception for the same period (Appendix G).

Informed Consent

16 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.

17 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports the Genomic Initiative (see Appendix D 2).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

*Criteria relevant to pre-screening (*BRCA*m biomarker testing).

Medical Conditions*

1 Participants with a history of MDS/AML or with features suggestive of MDS/AML (as determined by prior diagnostic investigation). In case there is no clinical MDS/AML suspicion, no specific screening for MDS/AML (by bone marrow/bone biopsy) is required.

2 Participants with any known predisposition to bleeding (eg, active peptic ulceration, recent [within 6 months] haemorrhagic stroke, proliferative diabetic retinopathy).

3 Any history of persisting (> 2 weeks) severe cytopenia due to any cause (eg, absolute neutrophil count $< 0.5 \times 10^9$/L or platelets $< 50 \times 10^9$/L).

4 Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of saruparib and/or abiraterone.

5 History of another primary malignancy, with the following exceptions:

(a) Adequately resected non-melanoma skin cancer.

(b) Curatively treated in situ disease.

(c) Malignancy treated with curative intent ≥ 3 years before the first dose of study intervention, and with no known active disease during the intervening time period.

6 Persistent toxicities (CTCAE Grade ≥ 2) caused by previous anticancer therapy. Participants with side effects that are not reasonably expected to affect the safety of the participant on study intervention in the opinion of the investigator (eg, ADT-related side effects) may be included if agreed with the Study Clinical Lead.

7 Any of the following cardiac criteria:

(a) Mean resting corrected QT interval (QTcF) > 470 milliseconds obtained from triplicate ECGs and averaged, recorded 5 minutes apart.

(b) Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.

8 History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted if deemed medically safe by the investigator.

9 Evidence of active and uncontrolled hepatitis B and/or hepatitis C. Screening for hepatitis B and hepatitis C is not required. Participants previously exposed to hepatitis B or hepatitis C are eligible if they meet one of the following criteria:

(a) Are negative for HBsAg and anti-HBc; or

(b) Are HBsAg+ and anti-HBc+ (chronic hepatitis B), and meet conditions i to iii below:

(i) HBV DNA viral load < 2000 IU/mL.

(ii) Have normal aminotransferase values.

(iii) Start antiviral treatment at least 2 weeks prior to the first dose of study intervention and maintain antiviral treatment during the interventional period. For permitted concomitant therapies, see Appendix I.

(c) Are anti-HBc positive, HBsAg negative, and have HBV DNA < 2000 IU/mL.

(d) Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

NOTE: Inclusion of this group of participants should be carefully considered if participant has no access to hepatology service and/or is currently in need of antiviral treatments.

10 Evidence of active and uncontrolled HIV infection. Participants with controlled HIV need to meet the following criteria: undetectable viral RNA load less than 400 copies/mL in the last 4 weeks prior to first dose of study intervention, CD4+ count of ≥ 350 cells/μL, no history of AIDS-defining opportunistic infection within the past 12 months, and stable on the same anti-HIV medications (as permitted in Appendix I) for at least 6 months. Screening for HIV is not required.

NOTE: Inclusion of this group of participants should be carefully considered if participant has no access to specialist service and/or is not stabilised on antiviral treatments.

11 Active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).

12 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 4 weeks of the first dose of study intervention or an anticipated

need for major surgery during the study. Participants should have fully recovered from any clinically significant AEs.

13 As judged by the investigator, any other evidence of diseases, such as severe or uncontrolled systemic diseases or active uncontrolled infections, including but not limited to uncontrolled major seizure disorder, active bleeding diseases, superior vena cava syndrome, or history of allogenic organ transplant, which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or would jeopardise compliance with the protocol.

Prior/Concomitant Therapy

14 Any prior chemotherapy (ie, docetaxel) or immunotherapy; any prior treatment with a PARP inhibitor.*

15 Prior treatment within 14 days with blood product support or growth factor support.

16 Concomitant use of the following types of medications or herbal supplements within 21 days or at least 5 half-lives (whichever is longer), of randomisation:

(a) Strong inducers and inhibitors of CYP3A4 (applies to saruparib and abiraterone).

The above includes, but may not be limited to, the prohibited medications and herbal supplements listed in Table 6 and Appendix I.

17 Concomitant use of drugs that are known to prolong QT and have a known risk of TdP (Appendix I).

Prior/Concurrent Clinical Study Experience

18 Concurrent enrolment in another clinical study (unless the study is non-interventional, or the participant is in the follow-up period of an interventional study).

Other Exclusions

19 Participants with a known hypersensitivity to saruparib or any excipients of these products.

20 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the site).

21 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

22 Previous randomisation in the present study.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

- Participants must follow the contraception requirements outlined in Appendix G.

- Participants should not donate blood or blood components while participating in this study and through 7 days after the last dose of study intervention.

Restrictions relating to concomitant therapies are described in Appendix I.

5.3.1 Meals and Dietary Restrictions

Participants should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL], half a grapefruit, or one to 2 teaspoons [15 g] of Seville orange marmalade daily). Please also see the prohibited concomitant medications (Section 5.2 and Appendix I).

On C1D1 and C3D1 visits (when PK samples will be taken), participants must take saruparib/placebo on an empty stomach (no food or drink other than water for 2 hours prior to dosing and for at least one hour after dosing) at the site.