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Testing the addition of new treatments to standard treatment in prostate cancer that has spread to other areas of the body

Submission date 20/04/2023	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 22/09/2023	**Overall study status** Ongoing	
Last Edited 10/02/2026	**Condition category** Cancer	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-new-ways-to-improve-treatment-for-prostate-cancer-that-has-spread-stampede2

Background and study aims
STAMPEDE2 is a clinical trial comparing two new treatments with standard of care in people with prostate cancer that has spread to other parts of the body and is responsive to hormone therapy. People from all backgrounds and ethnicities are encouraged to take part and multiple hospitals across the UK are involved. University College London is running the trial.

Who can participate?
Adult men aged over 18 years old with prostate cancer

What does the study involve?
Each comparison within the trial has its own control arm where people get the best standard of care (Arm A) versus a research arm where a new treatment is added to the standard of care.

Participants are allocated to an arm by a computerised system with a 50% chance of getting the research treatment.

Comparison S: Arm A(S) versus Arm S (Stereotactic Ablative Body Radiotherapy (SABR))
• Tests whether giving targeted doses of radiotherapy (SABR) to parts of the body where the cancer has spread slows the spread of the cancer and improves survival. 1920 people will be in this comparison.

Comparison P: Arm A(P) versus Arm P (PSMA-Lutetium (177Lu-PSMA-617))
• Tests whether giving a radioactive material (177Lu-PSMA-617) that targets prostate cancer cells slows the spread of cancer and improves survival. 1440 people will be in this comparison.

All participants will be followed up with scans and tests to monitor their cancer. Doctors will check for any side effects from the treatments. Treatments will be stopped if side effects are serious, or people no longer wish to take the treatments.

What are the possible benefits and risks of participating?
All participants will have been diagnosed with metastatic prostate cancer that requires treatment as part of SoC. The risks and burdens of taking part in STAMPEDE2 over and above their standard care are listed below. Sites will be trained in discussing all these issues with patients as part of the consent procedure for each comparison:
1. As for many clinical trials, participation can lead to an increased risk of toxicities with research treatments. For cancer trials, there are also toxicities associated with the cancer itself as well as the standard of care therapies. The Patient Information Sheet (PIS) documents the likelihood of toxicities associated with the new research therapies so that patients can decide if they wish to take part. Any emerging symptoms or toxicities for a participant will be managed by the site regardless of whether they are caused by the cancer, the standard therapies or research therapies.
2. Some patients will require more frequent visits to the hospital and this is explained in the PIS. For the majority of the time, patient follow-up visits for the trial will coincide with routine follow-up appointments that occur as a result of the patient receiving their SoC treatments.
3. A small number of additional fitness tests may be required to check eligibility but the majority of the tests will be done as part of routine care for their cancer. For the translational research blood samples, a small amount of additional blood will be taken whilst the patient is having blood collected for their routine care, thus no need for further venepuncture procedures.
4. For patients undergoing 177Lu-PSMA-617 treatment, there will be some restrictions on their lifestyle after each dose is administered. These are outlined in the patient discharge letter which is also uploaded in this submission and will be given to patients after each dose and when they are being consented to participation in Comparison P.
5. Patients participating in the Comparison P Imaging Sub-Study will require additional imaging requirements over standard care including whole-body MRI, PSMA PET/CT and dosimetry tests. These are important for the investigators to confirm that PSMA-Lu treatment is safe and acceptable in patients with hormone-sensitive disease and that toxicities are not substantially elevated over the SoC arm.
6. It is important that the trial participant is aware of the potential risks for any foetus should his partner become pregnant by him whilst he is receiving treatment. Pregnancy in this setting is extremely rare as the ADT hormonal control will make this very unlikely. However, full details have been provided in the PIS and protocol and should any partner become pregnant during the course of the trial we will be required to follow the mother and baby through to full term to record any complications.

Where is the study run from?
Medical Research Council Clinical Trials Unit (MRC CTU) at University College London (UK)

When is the study starting and how long is it expected to run for?
April 2023 to March 2032

Who is funding the study?
1. Advanced Accelerator Applications International S.A Novartis
2. Cancer Research UK
3. MRC UK Research and Innovation
4. Johnson and Johnson (during set-up phase)

Who is the main contact?
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Additional identifiers

ClinicalTrials.gov (NCT)
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Clinical Trials Information System (CTIS)
2025-522145-21-00

Integrated Research Application System (IRAS)
1006437

Central Portfolio Management System (CPMS)
57467

Protocol serial number
PR12

Study information

Scientific Title
Studying Treatments in patients receiving androgen deprivation therapy (ADT) for Metastatic Prostate Cancer: Evaluation of Drug and radiation Efficacy: A 2nd multi-arm multi-stage randomised controlled trial (STAMPEDE2)

Acronym
STAMPEDE2

Study objectives

Current study objectives as of 11/08/2025:
The main objective of the trial is to determine whether the addition of one of two new therapies (stereotactic ablative body radiotherapy [SABR] or PSMA-Lu) can slow down the progression of prostate cancer (PCa) and thus lengthen life for men. Slowing down the progression of PCa means it takes longer for existing sites of cancer in the body to get larger or for new sites of cancer to develop in the body away from the prostate. It is hypothesised that if the addition of these new treatments to the standard of care (SOC) can slow down the progression of PCa, this should lengthen the lives of those receiving these new treatments compared to those who are receiving SOC alone. A randomised control trial is proposed that randomly gives half of the participants the new treatment in addition to SOC whilst the other half gets the SOC alone. The participants are then followed to see if the cancer progresses more slowly with the new treatments and whether this means that the participants live longer.

The study will investigate if the new treatments are safe and tolerable for those who receive them. This is done by collecting data on side effects and seeing if these are unacceptably high in the group receiving the new treatments. Participants will be asked to complete quality-of-life questionnaires to understand the impact of any treatment side effects or the cancer itself. Data will also be collected on other kinds of PCa progression which might mean that the participant's cancer is becoming resistant to the therapies they are receiving. This can lead to hormone levels in the body such as testosterone or prostate-specific antigen (PSA) starting to rise and becoming difficult to control using standard hormone therapies. These often act as early indicators that the cancer is growing again. Collecting data on them is therefore important as it prompts clinicians to send participants for imaging to check for any changes in the cancer.

Previous study objectives:
The main objective of the trial is to determine whether the addition of one of 3 new therapies (stereotactic ablative body radiotherapy [SABR], PSMA-Lu or niraparib with abiraterone) can slow down the progression of prostate cancer (PCa) and thus lengthen life for men. Slowing down the progression of PCa means it takes longer for existing sites of cancer in the body to get larger or for new sites of cancer to develop in the body away from the prostate. It is hypothesised that if the addition of these new treatments to the standard of care (SOC) can slow down the progression of PCa, this should lengthen the lives of those receiving these new treatments compared to those who are receiving SOC alone. A randomised control trial is proposed that randomly gives half of the participants the new treatment in addition to SOC whilst the other half gets the SOC alone. The participants are then followed to see if the cancer progresses more slowly with the new treatments and whether this means that the participants live longer.

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Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 20/09/2023, London – Harrow Research Ethics Committee (Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8154; harrow.rec@hra.nhs.uk), ref: 23/LO/0415

Primary study design
Interventional

Study design
Randomized-controlled open-label parallel-group platform study

Study type(s)
Efficacy, Safety, Treatment

Health condition(s) or problem(s) studied
Metastatic hormone-sensitive prostate cancer

Interventions
Current interventions as of 11/08/2025:
STAMPEDE2 is a platform trial testing the addition of experimental treatments to Standard of Care (SoC) for metastatic hormone-sensitive prostate cancer (mHSPC). Each research question is called a “comparison” and within each comparison, there are two randomised arms. The STAMPEDE2 protocol includes two research comparisons with letter nomenclature based on the first letter of the research treatment:

Comparison S:
Stereotactic Ablative Body Radiotherapy (SABR) in men whose metastatic disease is eligible for SABR and receiving ADT + ARPI + radiotherapy (RT) to the primary +/- pelvic lymph nodes +/- docetaxel as SoC

Experimental Arm S: SoC + SABR
Active Comparator Arm A(S): SoC

Comparison P:
Prostate Specific Membrane Antigen–177 Lutetium (177Lu-PSMA-617) in men whose metastatic disease is ineligible for SABR (comparison S) and receiving ADT + ARPI +/- RT to the primary +/- pelvic lymph nodes +/- docetaxel as SoC

177Lu-PSMA-617 is an injectable therapy that directly kills cancer cells through radiation. It achieves targeted treatment to the cancer cells because once injected, it finds its way only to cells which display a protein called prostate-specific membrane antigens (PSMA). The amount of radiation is carefully selected to deliver damage and resulting death of the cancer cells whilst minimising damage to healthy tissue.

Experimental Arm P: SoC + 177Lu-PSMA-617
Active Comparator Arm A(P): SoC

Randomisation will be performed using a 1:1 allocation ratio using minimisation with a random element based upon various stratification factors. All men will be followed up over a number of years and will have imaging to determine whether their cancer has become worse or hormone levels have reached a point that other therapies might need to be considered.

Previous interventions:
STAMPEDE2 is a platform trial testing the addition of experimental treatments to Standard of Care (SoC) for metastatic hormone-sensitive prostate cancer (mHSPC). Each research question is called a “comparison” and within each comparison, there are 2 randomised arms. The STAMPEDE2 protocol includes 3 research comparisons with letter nomenclature based on the first letter of the research treatment:

Comparison S
Stereotactic Ablative Body Radiotherapy (SABR) in men whose metastatic disease is eligible for SABR and receiving ADT + ARSI + radiotherapy (RT) to the primary +/- pelvic lymph nodes +/- docetaxel as SoC

Experimental Arm S: SoC + SABR
Active Comparator Arm A: SoC

Comparison P
Prostate Specific Membrane Antigen–177 Lutetium (177Lu-PSMA-617) in men whose metastatic disease is ineligible for SABR (comparison S) and receiving ADT + ARSI +/- RT to the primary +/- pelvic lymph nodes +/- docetaxel as SoC

177Lu-PSMA-617 is an injectable therapy that directly kills cancer cells through radiation. It achieves targeted treatment to the cancer cells because once injected, it finds its way only to cells which display a protein called prostate-specific membrane antigens (PSMA). The amount of radiation is carefully selected to deliver damage and resulting death of the cancer cells whilst minimising damage to healthy tissue.

Experimental Arm P: SoC + 177Lu-PSMA-617
Active Comparator Arm A: SoC

Comparison N
Niraparib with abiraterone acetate plus prednisolone (Nira-AA+P) versus apalutamide in men with deleterious alterations in genes involved in homologous recombination repair and recently started long-term ADT +/- RT to the primary +/- pelvic lymph nodes +/- docetaxel +/- SABR +/- 177Lu-PSMA-617. Prior randomisation in comparisons S or P is permitted.

Experimental Arm N: SoC + Nira-AA+P
Active Comparator Arm A (N): SoC + Apalutamide

STAMPEDE2 allows co-enrolment into Comparison N for the 10-15% of men who test biomarker-positive and who are already randomised into either Comparison S or P. All the comparisons are unblinded and eligible men can choose to participate in just one comparison if preferred.

Randomisation will be performed using a 1:1 allocation ratio using minimisation with a random element based upon various stratification factors. All men will be followed up over a number of years and will have imaging to determine whether their cancer has become worse or hormone levels have reached a point that other therapies might need to be considered.

Intervention Type
Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)
Stereotactic ablative body radiotherapy (SABR), 177Lu-PSMA-617

Primary outcome(s)
Corrected 06/02/2026:
Current primary outcome measure as of 11/08/2025:
For both Comparisons S and P, the primary outcome is Overall Survival (OS) defined as time from randomisation to death from any cause.
2.1. Comparison S:
2.1.2. OS data maturity requires that 289 deaths have occurred in the control arm and this is expected to occur 79 months (6.6 years) after First Patient First Visit (FPFV).
2.2. Comparison P:
2.2.2. OS data maturity requires that 286 deaths have occurred in the control arm and this is expected to occur 59 months (5 years) from First Patient First Visit (FPFV).
If necessary, NHS Registry data will be used for events beyond trial closure.

Previous primary outcome measure:
All three comparisons will use dual-primary outcome measures of:
1. Radiological progression-free survival (rPFS), defined as the time from randomisation to metastatic cancer progression or death from any cause. The definition for rPFS requires at least one of the following four criteria to be met:
1.1. Progression of bone metastases as defined by PCWG3
1.2. Radiological metastatic progression by RECIST v1.1
1.3. Symptomatic skeletal-related events secondary to cancer progression
1.4. Death from any cause.

2. Overall survival (OS), defined as the time from randomisation to death from any cause.

2.1. Comparison S:
2.1.1. rPFS is expected to report when 231 rPFS events have occurred in the control arm ~4.8 years from FPFV
2.1.2. OS is expected to report after 341 deaths have occurred in the control arm ~7.8 years from FPFV

2.2. Comparison P:
2.2.1. rPFS is expected to report when 228 rPFS events have occurred in the control arm ~3.5 years from FPFV
2.2.2. OS is expected to report after 337 deaths have occurred in the control arm ~5.2 years from FPFV

2.3. Comparison N:
2.3.1. rPFS is expected to report when 86 rPFS events have occurred in the control arm ~5.4 years from FPFV
2.3.2. OS is expected to report when 210 deaths have occurred in the control arm ~14.8 years from FPFV

If necessary, NHS Registry data will be used for events beyond trial closure

Key secondary outcome(s)

Current secondary outcome measures as of 11/08/2025:
Analyses will also be undertaken for the following secondary outcomes:
1. Failure-free survival (FFS) reported alongside the primary outcome measures when those are mature enough for reporting
2. Radiographic Progression-Free-Survival (rPFS)
3. Prostate cancer-specific survival (PCSS) reported alongside the primary outcome measures when those are mature for reporting
4. Safety through reporting of SAEs reported as part of annual DSUR reports and in any publications for the primary and secondary outcomes
5. Toxicity using CTCAE classification data will be reviewed as part of closed IDMC meetings throughout the trial. Results for these outcomes will be reported alongside the primary outcome measures when those are mature for reporting
6. Compliance with randomised allocation data will be reviewed as part of closed IDMC meetings throughout the trial. Results for these outcomes will be reported alongside the primary outcome measures when those are mature for reporting.
7. Resource use for cost-effectiveness assessment
8. EQ-5D-5L questionnaire for cost-effectiveness assessment will be collected at baseline, 3 months and then 6-monthly until death or end of the trial. Reporting of these results will be specific to each comparison and likely to coincide with the reporting of the primary outcomes

Additional more detailed FACT-RNT Quality of life (QoL) questionnaires will be collected in patients taking part in the Imaging sub-study. Patient Reported Outcome Measures (PROMS) have not been included in this first version of the protocol but will be added later as a substantial amendment.

Previous secondary outcome measures:
Analyses will also be undertaken for the following secondary outcomes:
1. Failure-free survival (FFS) reported alongside the primary outcome measures when those are mature enough for reporting
2. Prostate cancer-specific survival (PCSS) reported alongside the primary outcome measures when those are mature for reporting
3. Safety through reporting of SAEs reported as part of annual DSUR reports and in any publications for the primary and secondary outcomes
4. Toxicity using CTCAE classification data will be reviewed as part of closed IDMC meetings throughout the trial. Results for these outcomes will be reported alongside the primary outcome measures when those are mature for reporting
5. Compliance with randomised allocation data will be reviewed as part of closed IDMC meetings throughout the trial. Results for these outcomes will be reported alongside the primary outcome measures when those are mature for reporting.
6. EQ-5D-5L questionnaire for cost-effectiveness assessment will be collected at baseline, 3 months and then 6-monthly until death or end of the trial. Reporting of these results will be specific to each comparison and likely to coincide with the reporting of the primary outcomes

Additional more detailed Quality of life (QoL) instruments as well as other Patient Reported Outcome Measures (PROMS) will be collected in a subset of patients. This is not included in this first version of the protocol but will be added later as a substantial amendment.

Completion date
01/03/2032

Eligibility

Key inclusion criteria

Current inclusion criteria as of 11/08/2025:
General Inclusion Criteria:
1. At least 18 years old.
2. Histological confirmation of prostate adenocarcinoma or a strong clinical suspicion of prostate cancer with a plan to confirm the diagnosis formally before any future randomisation.
3. Confirmation of metastatic site(s) on CT/MRI and either bone or PET scan. Patients with metastatic disease meeting any of the following criteria are eligible:
• Metastatic disease to the bone (in any distribution).
• Non-regional lymph node metastases of any size or distribution. Lymph nodes that are only visible on PET will not be eligible as sites of metastasis. Note: If lymph nodes are the only site of metastases, then at least one must be at least 1.5cm in short axis AND outside of the pelvis.
• Visceral metastases of any size or distribution.
4. Clinical presentation is:
A. de novo
OR
B. relapsed with:
(1) continuing hormone sensitivity in the opinion of the investigator, and;
(2) all hormone treatments (e.g., ADT and ARPI) will have been completed ≥2 years prior to any future randomisation into any of the comparisons, and;
(3) will have received ≤3 years total of ADT at the point of randomisation into any comparison.
Note: the dates will be checked again at randomisation. It is the responsibility of the investigator to account for the time between registration and randomisation into any comparison.
5. Long-term androgen deprivation therapy (ADT) has started or there is an intention to start for a minimum of 2 years.
6. WHO Performance Status 0-2 or, if WHO Performance Status 3, deemed to be due to metastatic burden and expected to improve with ADT. Note: Improvement to WHO status 0-2 will be checked again at randomisation into any subsequent comparison.
Note: For WHO performance status definitions see Appendix 1.
7. Willing and able to comply with trial treatments.
8. Patient has signed informed consent form for registration into the STAMPEDE2 Trial platform.

Eligibility Criteria For Comparison S Testing SABR:
Patients who meet the general eligibility criteria can be considered for the SABR comparison. Recruiting sites will assess metastatic disease burden using CT/MRI scans and baseline Tc-99m bone scan or PET scan to assess the number of metastatic bone and non-regional lymph node foci, and presence of visceral metastases. Patients will be classified as either ‘SABR-eligible’ or ‘SABR-ineligible’ using the following definition.

Definition of SABR-eligible disease:
Patients will be classified as SABR-eligible if they meet all the following criteria:
• 1-5 metastatic lesions (including either bone and/or non-regional lymph node sites).
• Clinician determination that metastatic lesions are considered suitable for SABR on technical grounds (such as proximity of dose-limiting normal tissue or tumour volume). Note: Clinical determination can consider next-generation imaging (e.g., PSMA PET-CT or WBMRI) where available. It is the investigator’s responsibility to consider the impact of any findings on the suitability of SABR for the patient. Any next-generation imaging used prior to randomisation should be declared at randomisation so that it can be used as a stratification factor.
• Absence of visceral metastases.

Otherwise, patients will be classified as SABR-ineligible.

In addition to the general registration eligibility criteria, they need to meet all the following criteria for entry into Comparison S:

1. Patient still meets all eligibility criteria for registration in Section 4.4.
2. Histological confirmation of prostate adenocarcinoma.
3. Newly diagnosed (de novo) metastatic disease that is considered eligible for SABR according to the above definition.
4. Patient has started ADT and randomisation is ≤12 weeks since the start of ADT.
5. WHO performance status 0-2 (see Appendix 1).
6. Patient has provided signed informed consent for participation in Comparison S.

Eligibility Criteria For Comparison P Testing 177LU-PSMA-617:
In addition to the general eligibility criteria, patients need to meet the following criteria for entry into Comparison P:

1. Patient still meets all eligibility criteria for registration.
2. Histological confirmation of prostate adenocarcinoma.
3. Patient meets the definition of SABR-ineligible disease.
4. Patients must have adequate organ function as indicated by blood tests within 4 weeks prior to randomisation:
Bone marrow function
a. ANC ≥1.5 x 109/L
b. Platelets ≥100 x 109/L
c. Haemoglobin ≥9g/dL, independent of transfusions for at least 28 days
Hepatic function
a. Total bilirubin ≤2 x ULN. For patients with Gilbert's Syndrome ≤3 x ULN is permitted.
b. AST and/or ALT performed with all results ≤3 × ULN or ≤5 x ULN for patients with liver metastasis
Renal Function
a. EGFR ≥50 mL/min/1.73m2 calculated using the MDRD formula
b. Albumin ≥25g/L
5. Patient has started ADT and randomisation is ≤12 weeks since the start of current ADT.
6. If relapsed disease, prior LHRH agonist/antagonist with or without first generation anti-androgen use in the adjuvant/neo-adjuvant setting, hormone treatment must have been discontinued ≥2 years prior to randomisation AND must not have exceeded a total of >3 years of therapy AND must not have shown disease progression within 12 months of completing adjuvant /neo-adjuvant therapy.
7. WHO performance status 0-2 (see Appendix 1).
8. Patient has provided signed informed consent for participation in Comparison P.

Previous inclusion criteria:
General inclusion criteria:
1. At least 18 years old
2. Histological confirmation of prostate adenocarcinoma on a biopsy of the prostate or metastases, or a strong clinical suspicion of prostate cancer with consent from the patient and a plan to undergo a confirmatory tissue biopsy.
3. Confirmation of metastatic site(s) on CT or bone scan. Patients with metastatic disease meeting the following criteria are eligible:
• Metastatic disease to the bone (in any distribution) visible on 99Tc-Bone Scan
AND/OR
• Non-regional lymph node metastases of any size or distribution. Lymph nodes that are only

visible on PET will not be eligible as sites of metastasis.
Note: If lymph nodes are the only site of metastases, then at least one must be at least 1.5cm in short axis AND outside of the pelvis
AND/OR
• Visceral metastases of any size or distribution
4. De novo presentation or, if relapsed, all hormonal treatments (ADT and ARSI) will have been completed ≥1 year prior to any future randomisation into any of the comparisons and have received ≤1 year total of ADT. This will be checked again at randomisation.
5. If not already started, there must be an intention to start long-term androgen deprivation therapy (ADT).
6. WHO performance status 0-2 (For WHO performance status definitions, see Appendix 1) or if WHO Performance Status 3, deemed to be due to metastatic burden and expected to improve with ADT.
7. Willing and able to comply with trial treatments.
8. Patient has signed informed consent form for registration into the STAMPEDE2 Trial platform.

Eligibility for Molecular Biomarker Testing
In addition to the general eligibility criteria patients need to meet the following criteria for biomarker testing:
1. If the patient has already commenced ADT, check that if there is adequate time for the biomarker test to be returned in time for randomisation into Comparison N no more than 6 months after starting ADT.
2. Have not yet commenced ARSI. If this has already started, patients will not be eligible for Comparison N or prospective biomarker testing, but they can still be considered for Comparisons S and P.
3. Have a tumour block that is available for testing and transferring to the central UCL biomarker lab. The location details for this block will be needed at the block request stage. Where patients have a confirmed alteration in one of the genes in the biomarker panel using a local regulatory cleared biomarker test, this can be used to assess biomarker status.
4. There are no contraindications to niraparib, abiraterone acetate, prednisolone or apalutamide according to the reference safety information.
5. Patient has provided signed informed consent for use of tissue for testing (if central testing is required).

Eligibility criteria for comparison S testing SABR
Patients who meet the general eligibility criteria can be considered for the SABR comparison. Recruiting sites will assess metastatic disease burden using conventional imaging (baseline Tc-99m bone scintigraphy and CT/MRI scans) to assess the number of metastatic bone and non-regional lymph node foci, and the presence of visceral metastases. Patients will be classified as either ‘SABR-eligible’ or ‘SABR-ineligible’ using the following definition.

Definition of SABR-eligible disease:
Patients will be classified as SABR-eligible if they meet all the following criteria:
• 1-5 metastatic lesions (including either bone and/or non-regional lymph node sites) using conventional imaging.
• Clinician determination that metastatic lesions are considered suitable for SABR on technical grounds (such as proximity of dose-limiting normal tissue or tumour volume).
• Absence of visceral metastases.
Otherwise, patients will be classified as SABR-ineligible.
In addition to the general registration eligibility criteria, they need to meet all the following criteria for entry into Comparison S:

Inclusion criteria
1. Patient still meets all eligibility criteria for registration
2. Newly diagnosed, synchronous (de novo) metastatic disease that is considered eligible for SABR according to the definition
3. Treatment naïve (de novo/synchronous) or minimal prior hormone treatment with:
3.1. If the patient has already started ADT, it must be ≤12 weeks since the start of the current ADT.
3.2. ≤12 weeks of luteinizing hormone-releasing hormone (LHRH) agonist/antagonists or bilateral orchiectomy, with or without first-generation anti-androgen (e.g., bicalutamide, flutamide), for metastatic prostate cancer is allowed prior to randomisation. If given, first-generation anti-androgen must be discontinued prior to the start of study therapy or after 28 days, whichever is earliest.
4. WHO performance status 0-2 (see Appendix 1)
5. Patient has provided signed informed consent for participation in Comparison S

Eligibility criteria for comparison P testing 177LU-PSMA-617
In addition to the general eligibility criteria, patients need to meet the following criteria for entry into Comparison P:

Inclusion criteria
1. Patient still meets all eligibility criteria for registration
2. Patient meets the definition of SABR-ineligible disease
3. Patients must have adequate organ function as indicated by blood tests within 8 weeks prior to randomisation:
3.1. Bone marrow function
3.1.1. ANC ≥1.5 x 10(9)/L
3.1.2. Platelets ≥100 x 10(9)/L
3.1.3. Haemoglobin ≥9g/dL, independent of transfusions for at least 28 days
3.2. Hepatic function
3.2.1. Total bilirubin ≤2 x ULN. For patients with Gilbert's Syndrome ≤3 x ULN is permitted.
3.2.2. ALT or AST ≤3 x ULN or ≤5 x ULN for patients with liver metastasis
3.3. Renal Function
3.3.1. EGFR ≥50 mL/min calculated using the MDRD formula
3.3.1. Albumin ≥25 g/L
4. Treatment naïve (de novo/synchronous) or minimal prior hormone treatment (metachronous) with:
4.1. If the patient has already started ADT, it must be ≤12 weeks since the start of the current ADT.
4.2. ≤12 weeks of luteinizing hormone-releasing hormone (LHRH) agonist/antagonists or bilateral orchiectomy, with or without first-generation anti-androgen (e.g., bicalutamide, flutamide), allowed prior to randomisation. If given, first-generation anti-androgen must be discontinued prior to start of study therapy or after 28 days, whichever is earliest.
4.3. If relapsed, prior LHRH agonist/antagonist with or without first-generation anti-androgen use in the adjuvant/neo-adjuvant setting, hormone treatment must have been discontinued >12 months prior to randomisation AND must not have exceeded 12 months of therapy AND must not have shown disease progression within 12 months of completing adjuvant/neo-adjuvant therapy.
4.4. WHO performance status 0-2 (see Appendix 1)
4.5. Patient has provided signed informed consent for participation in Comparison P

Eligibility criteria for comparison N testing NIRAPARIB-AA+P
In addition to the general registration eligibility criteria, patients need to meet the following criteria for randomisation into Comparison N:

Inclusion criteria
1. Patient still meets all eligibility criteria for registration
2. Biomarker-positive status as defined in Section 9.4.
3. Patient has not yet commenced ARSI therapy (including abiraterone acetate and prednisolone, enzalutamide, apalutamide or darolutamide).
4. Patients must have adequate organ function as indicated by blood tests within 8 weeks prior to randomisation:
4.1. Absolute neutrophil count ≥1.5 x 10(9)/L
4.2. Haemoglobin ≥9.0 g/dL, independent of transfusions for at least 28 days
4.3. Platelet count ≥100 x 10(9)/µL
4.4. Serum albumin ≥30 g/L
4.5. Creatinine ≤2 x upper limit of normal (ULN)
4.6. Serum potassium ≥3.5 mmol/L
4.7. Serum total bilirubin ≤1.5 × ULN or direct bilirubin ≤1 x ULN (Note: In participants with Gilbert's syndrome where total bilirubin is >1.5 × ULN, direct bilirubin of ≤1.5 × ULN is permitted
4.8. AST or ALT ≤3 × ULN
5. Participants who have received prior docetaxel treatment for prostate cancer must meet the following criteria:
5.1. Received ≤6 cycles of docetaxel therapy
5.2. Received the last dose of docetaxel ≥3 weeks prior to starting on IMP and ≤3 months prior to randomisation
5.3. Maintained a response to docetaxel of stable disease or better, by investigator assessment of imaging and/or PSA, prior to randomisation
6. WHO performance status 0-2 (see Appendix 1).
7. Able to swallow the trial treatment tablets whole (clinician determined).
8. Patient has provided signed informed consent for participation in Comparison N.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
Male

Total final enrolment
0

Key exclusion criteria

Current exclusion criteria as of 11/08/2025:
General Exclusion Criteria:
1. Clinically and pathologically overt small cell carcinoma.
2. Metastatic brain disease or leptomeningeal disease.
3. Any active malignancies (i.e., progressing or requiring any treatment in the previous 36 months) other than prostate cancer (except non-muscle invasive bladder cancer; non-melanomatous skin cancer or a malignancy that is considered cured with minimal risk of recurrence).
4. Any other medical condition that in the investigator's opinion means the participant is unfit or unsuitable for long-term ADT or the trial treatments in the comparison for which they are being considered.

Exclusion Criteria For Comparison S Testing SABR:
1. Patient has relapsed prostate cancer.
2. Prior radical treatment to the prostate (e.g., radical surgery and/or radiotherapy).
3. Intracranial metastatic disease.
4. Prior treatment to a metastatic site (e.g., radiotherapy, surgery or RFA).
5. Significant or progressive neurological deficit such that emergency (within 24 hours) surgery or radiation required (e.g., metastatic spinal cord compression, or impingement of the cord or any other clinical scenario whereby urgent radiotherapy to the spine is required).
6. Any condition or co-morbidities that, in the judgement of the clinician, preclude procedures required to facilitate radiotherapy delivery, e.g.:
a. Disease staging and follow-up.
b. Radiotherapy planning procedures.
7. Any condition or co-morbidities that, in the judgement of the clinician, preclude the safe delivery of radiotherapy to the prostate (± pelvic lymph nodes) and/or metastases, e.g., inflammatory bowel disease, significant systemic connective tissue disorder, radiological evidence of idiopathic pulmonary fibrosis).
8. Active malignancy other than prostate cancer within the last 36 months.

Exclusion Criteria For Comparison P Testing 177Lu-PSMA-617:
1. Prior treatment with any of the following:
a. Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223
b. PSMA-targeted radioligand therapy
2. Symptomatic cord compression, or clinical/radiological findings indicative of impending cord compression.
3. Any condition that precludes raised arms position.
4. Unmanageable bladder outflow obstruction or urinary incontinence. Note: bladder outflow obstruction or urinary incontinence which is manageable and controlled with best available standard of care (incl. drainage, pads) is permitted.
5. Imaging Sub-study only: Contraindication to MRI (e.g., pacemakers, except MRI-compatible pacemakers).

Previous exclusion criteria:
General exclusion criteria
1. Clinically and pathologically overt small cell carcinoma
2. Metastatic brain disease or leptomeningeal disease
3. Any active malignancies (i.e., progressing or requiring any treatment in the previous 36 months) other than prostate cancer (except non-muscle invasive bladder cancer; non-melanomatous skin cancer or a malignancy that is considered cured with minimal risk of

recurrence)
4. Any other medical condition that in the investigator's opinion means the participant is unfit or unsuitable for long-term ARSI or the trial treatments in the comparison for which they are being considered.

Exclusion criteria For comparison S testing SABR
1. Prior radical treatment to the prostate (e.g., radical surgery and/or radiotherapy).
2. Intracranial metastatic disease
3. Prior treatment to a metastatic site (e.g., radiotherapy, surgery or RFA)
4. Significant or progressive neurological deficit such that emergency (within 24 hours) surgery or radiation required (e.g., metastatic spinal cord compression, or impingement of the cord or any other clinical scenario whereby urgent radiotherapy to the spine is required)
5. Any condition or co-morbidities in the judgement of the clinician that precludes procedures required to facilitate radiotherapy delivery e.g.
5.1. Disease staging and follow-up
5.2. Radiotherapy planning procedures
6. Any condition or co-morbidities in the judgement of the clinician that precludes the safe delivery of radiotherapy to the prostate (+/- pelvic lymph nodes) and/or metastases e.g., inflammatory bowel disease, significant systemic connective tissue disorder, radiological evidence of idiopathic pulmonary fibrosis)
7. Active malignancy other than prostate cancer within the last 36 months
8. Contraindication to MRI (e.g., pacemakers, except MRI-compatible pacemakers)

Exclusion criteria For comparison P testing 177LU-PSMA-617
1. Prior treatment with any of the following:
1.1. Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223
1.2. PSMA-targeted radioligand therapy
2. Symptomatic cord compression, or clinical/radiological findings indicative of impending cord compression
3. Any condition that precludes raised arms position
4. Unmanageable bladder outflow obstruction or urinary incontinence. (Note: bladder outflow obstruction or urinary incontinence which is manageable and controlled with best available standard of care (incl. drainage, pads) is permitted)

Exclusion criteria For comparison N testing NIRAPARIB-AA+P
1. Prior treatment with a poly ADP ribose polymerase (PARP) inhibitor, radiopharmaceutical or any chemotherapy for prostate cancer other than docetaxel outside the STAMPEDE2 trial.
2. History of adrenal dysfunction.
3. History or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML).
4. Known allergies, hypersensitivity, or intolerance to the excipients of AA, or Nira-AA DAT (refer to the IBs for Nira-AA DAT and AA).
5. Current evidence of any medical condition that would make prednisolone use contraindicated.
6. Presence of sustained uncontrolled hypertension. At randomisation, sites will be asked to provide one blood pressure reading (systolic <160 mmHg and diastolic blood pressure reading <100 mmHg) recorded within the 8 weeks prior to randomisation.
7. Received an investigational intervention not related to the STAMPEDE2 trial (including investigational vaccines) or used an invasive investigational medical device within 30 days of randomisation.
8. >6 months from start of current ADT to randomisation.
9. Participants who have had the following ≤28 days prior to randomisation:
9.1. A transfusion (platelets or red blood cells);

9.2. Hematopoietic growth factors;
9.3. Surgery requiring general anaesthetic
10. Known active hepatitis B virus (e.g., hepatitis B surface antigen reactive) or active hepatitis C virus (HCV; e.g., HCV ribonucleic acid [RNA] [qualitative] is detected).
11. Known HIV infection and any one of the following:
11.1. AIDS-defining opportunistic infection within 6 months of randomisation
11.2. HAART or ART regimen non-compatible with the drugs of the study due to drug-drug interaction with Niraparib (e.g., Protease inhibitors, cobicistat, efavirenz, nevirapine, etravirine, doravirine and rilpivirine)
11.3. CD4 count below 300/mm3 within the 8 weeks prior to randomisation.
11.4. Detectable viral load within the 8 weeks prior to randomisation.

Date of first enrolment
11/06/2024

Date of final enrolment
31/12/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
England
NW1 2PG

Study participating centre
The Royal Marsden Hospital (london)
Fulham Road
London
England
SW3 6JJ

Study participating centre
The Royal Marsden Hospital (surrey)
Downs Road
Sutton
England
SM2 5PT

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
Exeter
England
EX2 5DW

Study participating centre
The James Cook University Hospital
Marton Road
Middlesbrough
England
TS4 3BW

Study participating centre
North Tees Health NHS Trust
North Tees General Hospital
Hardwick
Stockton-on-tees
England
TS19 8PE

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
80 Newark Street
London
England
E1 2ES

Study participating centre
Mount Vernon Hospital
Mount Vernon Road
Barnsley
England
S70 4DP

Study participating centre
Barking, Havering and Redbridge University Hospitals NHS Trust
Queens Hospital
Rom Valley Way
Romford
England
RM7 0AG

Study participating centre
Sherwood Forest Hospitals NHS Foundation Trust
Kings Mill Hospital
Mansfield Road
Sutton-in-ashfield
England
NG17 4JL

Study participating centre
University Hospitals Plymouth NHS Trust
Derriford Hospital
Derriford Road
Derriford
Plymouth
England
PL6 8DH

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Queen Alexandras Hospital
Southwick Hill Road
Cosham
Portsmouth
England
PO6 3LY

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
England
NW3 2QG

Study participating centre
The Princess Alexandra Hospital
Hamstel Road
Harlow
England
CM20 1QX

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Industry

Funder Name
Advanced Accelerator Applications, a Novartis company

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Johnson and Johnson (during set-up phase)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. A formal data-sharing process has been developed at the MRC CTU. Requests for sharing data will need to provide details on the specific requirements, proposed research, qualifications of researchers and publication plan. The requests will be reviewed by the appropriate STAMPEDE2 committees. A data transfer agreement will be signed prior to the transfer of any information. All patients will be consented for future data sharing and if data requests are approved, only anonymised data will be sent using appropriately encrypted methods for data transfer.

Access to the digital image repository from researchers outside of the MRC CTU will be obtained through a formal data-sharing application detailing the specific requirements, proposed research, investigator qualifications and publication plan if they are interested in using the images.

Access to use of the stored pathological tissue by researchers outside of the MRC CTU will be obtained through a formal tissue access application detailing the specific requirements, proposed research, investigator qualifications and publication plan. Applications for access to tissue are required separately from access to the shared clinical data.

Data will be shared according to the CTU's controlled access approach, based on the following principles:
• No data should be released that would compromise an ongoing trial or study.
• There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
• Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data before key trial data are made available to other researchers.
• The resources required to process requests should not be underestimated, particularly successful requests which lead to preparing data for release. Therefore, adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
• Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Data will be available for sharing and researchers wishing to access STAMPEDE2 data should contact the Trial Management Group via the CTU Trial team using the study mailbox in the first instance. Research data will be stored for a minimum of 25 years.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other publications		22/07/2023	10/02/2026	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes