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Systemic therapy in advanced or metastatic prostate cancer: evaluation of drug efficacy

Submission date 02/02/2004	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 03/08/2004	**Overall study status** Ongoing	[_] Statistical analysis plan [X] Results
Last Edited 20/08/2025	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-hormone-therapy-with-zoledronic-acid-docetaxel-or-celecoxib-for-prostate-cancer

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Public

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Additional identifiers

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PR08

Study information

Scientific Title
Systemic therapy in advanced or metastatic prostate cancer: evaluation of drug efficacy

Acronym
STAMPEDE

Study objectives
Current hypothesis as of 15/01/2018:
Original Comparisons: Research interventions will improve survival over standard-of-care (SOC)
Abiraterone Comparison: Addition of abiraterone to SOC will improve survival over SOC alone
M1/RT Comparison: Addition of radiotherapy to SOC will improve survival over SOC alone
Enzalutamide and Abiraterone Comparison: Addition of enzalutamide, in combination with abiraterone, to SOC will improve survival over SOC alone
Metformin Comparison: Addition of metformin to SOC will improve survival over SOC alone
Transdermal Oestradiol Comparison: Transdermal oestrdiol will be non-inferior to standard hormone therapy, while having fewer side-effects and improved quality of life

Previous hypothesis:
Updated 11/09/2008:
Prostate cancer accounts for around one fifth of all cancers among men. In the UK there are around 25,000 new cases of prostate cancer each year, and around 10,000 deaths. Most men are given hormone therapy if their prostate cancer has spread (metastasised), or if the cancer is very likely to spread. This usually stops the tumour from growing for a while. However, in most cases over time the tumour will start to grow again. The trial is testing how well three new drugs work to prevent the tumour from growing again. The drugs are called celecoxib, docetaxel and zoledronic acid and are used with the hormone therapy.

Updated 23/01/2013:
Recruitment to the celecoxib arms (D and F) is now closed. An additional arm containing abiraterone was added in protocol version 8.0. A further comparison arm involving prostate radiotherapy for patients with metastatic disease is added in the current protocol version 9.0. The trial has multiple arms; the control arm of the trial is androgen deprivation therapy (ADT) only, achieved through the use of luteinising hormone releasing hormone (LHRH) analogues or LHRH antagonists, or bilateral orchidectomy according to local practice.

Updated 29/07/2014:
Recruitment to the zoledronic acid, docetaxel and abiraterone arms (B, C, E and G) have completed recruitment. Protocol version 12.0 was released on 29/07/2014. This includes the addition of arm J which adds abiraterone and enzalutamide to androgen deprivation therapy (ADT).

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 04/10/2004, West Midlands Edgbaston REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)207 104 8155; edgbaston.rec@hra.nhs.uk), ref: 04/MRE07/35

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Prostate adenocarcinoma

Interventions
Interventions as of 14/11/2018:
Currently recruiting interventions as of 19/10/2017
Arm A = Standard of Care - control
Arm K = ADT + Metformin (included from protocol version 15.0)
Arm L = Transdermal Oestradiol therapy (included from protocol version 16.0)

Standard-of-Care as of xx/xx/2018:
Androgen deprivation therapy (ADT) as per local practice. For some participant groups, this should now be supplemented with SOC Radiotherapy. From protocol v14.0 onwards the SOC permits docetaxel for all suitable participants. From protocol v19.0 onwards, where accessible SOC abiraterone may also be permited as an alternative to docetaxel.
In summary, SOC treatment is defined as being one of the following combinations:
1. ADT alone
2. ADT + Prostate Radiotherapy (RT) +/- nodal
3. ADT + Docetaxel
4. ADT + Docetaxel + RT
5. ADT + Abiraterone*
6. ADT + Abiraterone + RT*
*Note not all forms of SOC treatment are permitted in all comparisons. SOC abiraterone is only permitted within the metformin comparison.

Standard-of-Care: Standard forms of background treatment permitted as part of the STAMPEDE protocol which include licensed androgen deprivation therapy (e.g. LHRH analogues) given in the setting of hormone-naïve prostate cancer and first-line use of docetaxel.
Metformin: This anti-diabetic medication is proposed to have both anti-cancer effects and may help prevent the adverse metabolic effects of long-term ADT.
Transdermal Oestradiol: This form of hormone treatment which can suppress testosterone as effectively as standard ADT and has been shown to avoid some of the side-effects. For example, treatment with transdermal oestradiol does not appear to cause the bone to thin which is a common problem with standard forms of ADT. It may also help to avoid some of the side effects and therefore improve overall quality of life compared with standard forms of ADT.

Interventions closed to recruitment as of 19/10/2017
Arm B = ADT + zoledronic acid

Arm C = ADT + docetaxel
Arm D = ADT + celecoxib
Arm E = ADT + zoledronic acid + docetaxel
Arm F = ADT + zoledronic acid + celecoxib
Arm G = ADT + abiraterone
Arm H = ADT + radiotherapy to the prostate
Arm J = ADT + abiraterone + enzalutamide

Zoledronic acid: Prostate cancer cells can spread to bones and weaken them. Zoledronic acid is a drug that reduces bone destruction and hardens bones. This may make them more resistant to attack by cancer cells.
Docetaxel & Prednisolone: A drug that stops cells replicating that is currently being used to treat a range of cancers including lung, breast and ovarian cancer as well as prostate cancer. Docetaxel prolongs survival in men with relapsed metastatic prostate cancer.
Celecoxib: An aspirin-like drug that is used to treat arthritis. It slows down the growth of cancer cells in the laboratory. We wished to see if it had the same effect on cancer cells in patients. Recruitment to new patients for the evaluation of this drug is finished as a planned interim analysis failed to demonstrate sufficient activity.
Abiraterone Acetate & Prednisolone: An inhibitor of steroid hormone synthesis that blocks prostate cancer cells from generating their own male hormones. This is thought to be a major way in which prostate cancer cells resume growth following castration based therapies. The agent prolongs survival when given to men following failure of docetaxel chemotherapy.
Prostate radiotherapy: A treatment with high-energy x-rays targeted to the prostate gland. This treatment is now mandatory for patients with cancer that is confined to the prostate gland as large trials have shown it improves survival times. We are not certain whether we should give radiotherapy to the prostate if the cancer has already spread.
Enzalutamide: An androgen receptor signaling inhibitor and has gained recent approval for use on its own in the treatment of advanced CRPC, and there is evidence of activity for hormone-naïve prostate cancer.

Interventions as of 15/01/2018:
Currently recruiting interventions as of 19/10/2017
Arm A = Standard of Care - control
Arm K = ADT + Metformin (included from protocol version 15.0)
Arm L = Transdermal Oestradiol therapy (included from protocol version 16.0)

Standard-of-Care: Standard forms of background treatment permitted as part of the STAMPEDE protocol which include licensed androgen deprivation therapy (e.g. LHRH analogues) given in the setting of hormone-naïve prostate cancer and first-line use of docetaxel.
Metformin: This anti-diabetic medication is proposed to have both anti-cancer effects and may help prevent the adverse metabolic effects of long-term ADT.
Transdermal Oestradiol: This form of hormone treatment which can suppress testosterone as effectively as standard ADT and has been shown to avoid some of the side-effects. For example, treatment with transdermal oestradiol does not appear to cause the bone to thin which is a common problem with standard forms of ADT. It may also help to avoid some of the side effects and therefore improve overall quality of life compared with standard forms of ADT.

Interventions closed to recruitment as of 19/10/2017
Arm B = ADT + zoledronic acid
Arm C = ADT + docetaxel
Arm D = ADT + celecoxib
Arm E = ADT + zoledronic acid + docetaxel

Arm F = ADT + zoledronic acid + celecoxib
Arm G = ADT + abiraterone
Arm H = ADT + radiotherapy to the prostate
Arm J = ADT + abiraterone + enzalutamide

Zoledronic acid: Prostate cancer cells can spread to bones and weaken them. Zoledronic acid is a drug that reduces bone destruction and hardens bones. This may make them more resistant to attack by cancer cells.
Docetaxel & Prednisolone: A drug that stops cells replicating that is currently being used to treat a range of cancers including lung, breast and ovarian cancer as well as prostate cancer. Docetaxel prolongs survival in men with relapsed metastatic prostate cancer.
Celecoxib: An aspirin-like drug that is used to treat arthritis. It slows down the growth of cancer cells in the laboratory. We wished to see if it had the same effect on cancer cells in patients. Recruitment to new patients for the evaluation of this drug is finished as a planned interim analysis failed to demonstrate sufficient activity.
Abiraterone Acetate & Prednisolone: An inhibitor of steroid hormone synthesis that blocks prostate cancer cells from generating their own male hormones. This is thought to be a major way in which prostate cancer cells resume growth following castration based therapies. The agent prolongs survival when given to men following failure of docetaxel chemotherapy.
Prostate radiotherapy: A treatment with high-energy x-rays targeted to the prostate gland. This treatment is now mandatory for patients with cancer that is confined to the prostate gland as large trials have shown it improves survival times. We are not certain whether we should give radiotherapy to the prostate if the cancer has already spread.
Enzalutamide: An androgen receptor signaling inhibitor and has gained recent approval for use on its own in the treatment of advanced CRPC, and there is evidence of activity for hormone-naïve prostate cancer.

Current interventions as of 29/07/2014:
Arm A = Androgen deprivation therapy (ADT) - control
Arm H = ADT + radiotherapy to the prostate (included from protocol version 9.0)
Arm J = ADT + abiraterone + enzalutamide (included from protocol version 12.0)

1. Prostate radiotherapy (included from protocol version 9.0): treatment with high-energy x-rays targeted to the prostate gland. This treatment is now mandatory for patients with cancer that is confined to the prostate gland as large trials have shown it improves survival times. We are not certain whether we should give radiotherapy to the prostate if the cancer has already spread.
2. Abiraterone (included from protocol version 8.0): An inhibitor of steroid hormone synthesis that blocks prostate cancer cells from generating their own male hormones. This is thought to be a major way in which prostate cancer cells resume growth following castration based therapies. The agent prolongs survival when given to men following failure of docetaxel chemotherapy.
3. Enzalutamide is a androgen receptor signalling inhibitor and has gained recent approval for use on its own in the treatment of advanced CRPC,(50) and there is evidence of activity for hormone-naïve prostate cancer.

Previous interventions from 23/01/2013 to 29/07/2014:
Arm A = Androgen deprivation therapy (ADT) - control
Arm B = ADT + zoledronic acid
Arm C = ADT + docetaxel
Arm D = ADT + celecoxib
Arm E = ADT + zoledronic acid + docetaxel (NOW CLOSED)
Arm F = ADT + zoledronic acid + celecoxib (NOW CLOSED)

Arm G = ADT + abiraterone (included from protocol version 8.0):
Arm H = ADT + radiotherapy to the prostate (included from protocol version 9.0)

1. Zoledronic acid: Prostate cancer cells can spread to bones and weaken them. Zoledronic acid is a drug that reduces bone destruction and hardens bones. This may make them more resistant to attack by cancer cells.
2. Docetaxel: A drug that stops cells replicating that is currently being used to treat a range of cancers including lung, breast and ovarian cancer as well as prostate cancer. Docetaxel prolongs survival in men with relapsed metastatic prostate cancer.
3. Celecoxib: An aspirin-like drug that is used to treat arthritis. It slows down the growth of cancer cells in the laboratory. We wished to see if it had the same effect on cancer cells in patients. Recruitment to new patients for the evaluation of this drug is finished as a planned interim analysis failed to demonstrate sufficient activity.
4. Abiraterone (included from protocol version 8.0): An inhibitor of steroid hormone synthesis that blocks prostate cancer cells from generating their own male hormones. This is thought to be a major way in which prostate cancer cells resume growth following castration based therapies. The agent prolongs survival when given to men following failure of docetaxel chemotherapy.
5. Prostate radiotherapy (included from protocol version 9.0): treatment with high-energy x-rays targeted to the prostate gland. This treatment is now mandatory for patients with cancer that is confined to the prostate gland as large trials have shown it improves survival times. We are not certain whether we should give radiotherapy to the prostate if the cancer has already spread.

Previous interventions until 23/01/2013:
Patients will be randomised to the control arm (Arm A) or one of the five investigational arms. All patients will receive androgen suppression (AS) to
castration level. The method of AS is a local choice but must be specified for each patient prior to randomisation. All trial treatments should commence as soon as practically possible after randomisation. Patients
having a bilateral orchidectomy should commence any additional treatment within four weeks of the operation unless there is a strong clinical reason not
to do so.

Arm A = Androgen suppression (AS) - control
Arm B = AS + zoledronic acid
Arm C = AS + docetaxel
Arm D = AS + celecoxib
Arm E = AS + zoledronic acid + docetaxel
Arm F = AS + zoledronic acid + celecoxib

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Abiraterone acetate, prednisolone, enzalutamide, metformin, transdermal oestradiol

Primary outcome(s)

Current primary outcome measures as of 15/01/2018:
Pilot phase: Safety
Efficacy Stage I-III: Failure-free survival (FFS)
Efficacy Stage IV: Overall survival

Previous as of 11/09/2008:
Pilot phase: Safety
Efficacy Stage I-III: Failure-free survival (FFS)
Efficacy Stage IV: Overall survival

Key secondary outcome(s))

Current secondary outcome measures as of 15/01/2018:
Pilot phase:
Feasibility

Efficacy Stage I-III:
1. Overall survival (OS)
2. Toxicity
3. Skeletal-related events

Efficacy Stage IV:
1. Quality of life
2. Cost effectiveness
3. Failure-free survival
4. Toxicity
5. Skeletal-related events

Previous as of 11/09/2008:
Pilot phase:
1. Feasibility

Efficacy Stage I-III:
2. Overall survival (OS)
3. Toxicity
4. Skeletal-related events

Efficacy Stage IV:
1. Quality of life
2. Cost effectiveness
3. Failure-free survival
4. Toxicity
5. Skeletal-related events

Completion date

31/03/2026

Eligibility

Key inclusion criteria

Participant inclusion criteria as of 14/11/2018:
Participants must fulfil all the criteria in one of the following three categories:

1. HIGH-RISK NEWLY DIAGNOSED NON-METASTATIC NODE-NEGATIVE DISEASE - Both:
1.1. At least two of: Stage T3/4, PSA ≥ 40 ng/ml or Gleason sum score 8-10
1.2. Intention to treat with radical radiotherapy (unless there is a contra-indication; exemption can sought in advance of consent, after discussion with MRC CTU)

OR
2. NEWLY DIAGNOSED METASTATIC OR NODE-POSITIVE DISEASE - At least one of:
2.1. Stage Tany N+ M0
2.2. Stage Tany Nany M+

OR
3. PREVIOUSLY TREATED WITH RADICAL SURGERY AND/OR RADIOTHERAPY, NOW RELAPSING - At least one of:
3.1. PSA ≥ 4 ng/ml and rising with doubling time less than 6 months
3.2. PSA ≥ 20 ng/ml
3.3. N+
3.4. M+

AND
4. FOR ALL PATIENTS
4.1. Histologically confirmed prostate adenocarcinoma
4.2. Intention to treat with long-term androgen deprivation therapy
4.3. Treating clinician and participant should have decided if additional systemic therapy with docetaxel or abiraterone is to be used as part of the standard-of-care prior to randomisation
4.4 Fit for all protocol treatment2 and follow-up, WHO performance status 0-23
4.5 Have completed the appropriate investigations prior to randomisation
4.6. Adequate haematological function: neutrophil count >1.5x109/l and platelets >100x109/l
4.7. Estimated creatinine clearance >30ml/min
4.8. Written informed consent
4.9. Willing and expected to comply with follow-up schedule
4.10. Using effective contraceptive method if applicable

Participant inclusion criteria as of 23/01/2013:
Patients must fulfil both of the criteria in Section 1 or one criterion in Section 2 or at least one criteria in Section 3. Additionally, all patients must fulfil the criteria in Section 4.

1. HIGH-RISK NEWLY DIAGNOSED NON-METASTATIC NODE-NEGATIVE DISEASE - Both:
1.1. At least two of: Stage T3/4, PSA ≥ 40 ng/ml or Gleason sum score 8-10
1.2. Intention to treat with radical radiotherapy (unless there is a contra-indication; exemption can sought in advance of consent, after discussion with MRC CTU)

OR
2. NEWLY DIAGNOSED METASTATIC OR NODE-POSITIVE DISEASE - At least one of:
2.1. Stage Tany N+ M0
2.2. Stage Tany Nany M+

OR
3. PREVIOUSLY TREATED WITH RADICAL SURGERY AND/OR RADIOTHERAPY, NOW RELAPSING - At least one of:
3.1. PSA ≥ 4 ng/ml and rising with doubling time less than 6 months

3.2. PSA ≥ 20 ng/ml
3.3. N+
3.4. M+

AND
4. FOR ALL PATIENTS
4.1. Histologically confirmed prostate adenocarcinoma
4.2. Intention to treat with long-term androgen deprivation therapy
4.3. Fit for all protocol treatment2 and follow-up, WHO performance status 0-23
4.4 Have completed the appropriate investigations prior to randomisation
4.5. Adequate haematological function: neutrophil count >1.5x109/l and platelets >100x109/l
4.6. Estimated creatinine clearance >30ml/min
4.7. Serum potassium ≥3.5mmol/L
4.8. Written informed consent
4.9. Willing and expected to comply with follow-up schedule
4.10. Using effective contraceptive method if applicable

Previous inclusion criteria until 23/01/2013:
Patients must fulfil one of the inclusion criteria in section one or one of the inclusion criteria in section two. Additionally, all patients must fulfil the inclusion criteria in section three:

Section one - high risk newly diagnosed patients must fulfil one of the following criteria:
1. Stage T3/4 N0 M0 histologically confirmed prostate adenocarcinoma with Prostate Specific Antigen (PSA) = 40 ng/ml or Gleason sum score eight to ten
2. Stage Tany N + M0 or Tany Nany M + histologically confirmed prostate adenocarcinoma
3. Multiple sclerotic bone metastases with a PSA = 100 ng/ml

Section two - patients with histologically confirmed prostate adenocarcinoma previously treated with radical surgery or radiotherapy that are now relapsing. (Please note that prior hormone therapy for localised disease must have been completed 12 months previously, have been no longer than 12 months in duration and given as adjuvant or neoadjuvant therap:
1. PSA = 4 ng/ml and rising with doubling time less than six months
2. PSA = 20 ng/ml

Section three - for all patients:
1. Intention to treat with long-term androgen suppression
2. Fit for all protocol treatment and follow-up, World Health Organisation (WHO) performance status zero to two
3. Have completed the appropriate investigations prior to randomisation
4. Adequate haematological function: neutrophil count more than 1.5 x 10^9 l and platelets more than 100 x 10^9 l
5. Adequate renal function: Serum creatinine less than 1.5 Upper Limit of Normal (ULN)
6. Adequate liver function: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) less than 1.5 ULN, bilirubin less than ULN
7. Normal testosterone level prior to treatment
8. Written informed consent
9. Willing and expected to comply with follow-up schedule

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
Male

Total final enrolment
11992

Key exclusion criteria
Participant exclusion criteria as of 14/11/2018:
1. Prior systemic therapy for locally-advanced or metastatic prostate cancer
2. Metastatic brain disease or leptomeningeal disease
3. Abnormal liver functions consisting of any of the following:
3.1. Serum bilirubin ≥1.5 x ULN (except for participants with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3µmol/l or 3mg/dl)
3.2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN
4. Any other previous or current malignant disease which, in the judgement of the responsible clinician, is likely to interfere with STAMPEDE treatment or assessment
5. Any surgery (e.g. TURP) performed within the past 4 weeks
6. Participants with significant cardiovascular disease, including:
6.1. Severe/unstable angina
6.2. Myocardial infarction less than 6 months prior to randomisation
6.3. Arterial thrombotic events less than 6 months prior to randomisation
6.4. Clinically significant cardiac failure requiring treatment, defined as New York Heart Association (NYHA) class II or above1
6.5. Cerebrovascular disease (e.g. stroke or transient ischaemic episode) less than 6 months prior to randomisation
6.6. Or any other significant cardiovascular disease that in the investigator's opinion means the participant is unfit for any of the study treatments.
7. Prior chemotherapy for prostate cancer2
8. Prior exposure to long-term hormone therapy before randomisation
9. Prior exposure to systemic treatment for prostate cancer (excluding ADT or participants receiving abiraterone as part of SOC)

Comparison-Specific Selection Criteria
In addition to the general inclusion and exclusion criteria, the following comparison-specific eligibility criteria apply.
Metformin Comparison
In addition to the general inclusion and general exclusion criteria the following comparison-specific inclusion criteria must be met to be eligible for randomisation to the "metformin comparison":
1. Hb A1c <48mmol/mol (equivalent to <6.5%)1
2. Adequate renal function, defined as GFR ≥45ml/min/1.73m2 (except for Switzerland 2)

3. No history of lactic acidosis or predisposing conditions
4. No current or previous treatment with metformin
5. No contraindications to metformin

The method used to determine glomerular filtration rate may vary according to local practice. Equations that either estimate glomerular filtration rate (eGFR) or creatinine clearance (CrCl) may be used and the same threshold value applies. Where possible, HbA1c should be performed prior to commencing SOC docetaxel to reduce the likelihood of corticosteroid-related hyperglycaemia impacting on eligibility. All participants with abnormal baseline HbA1c (i.e. 6.5% or higher) should be informed and referred to their GP for further management.

Transdermal Oestradiol Comparison
In addition to the general inclusion and exclusion criteria, participants fulfilling all of the following are eligible for the "transdermal oestradiol comparison":
1. ≤8 weeks of anti-androgen (AR-antagonists) use
2. ≤1 dose of monthly or 4-weekly LHRH agonist/antagonist
3. No prior LHRH agonist injection with a stated duration of effect greater than 1 month
4. ≤12 weeks since first dose of any hormone therapy
5. Not had a bilateral orchidectomy
6. No use of cyproterone acetate (77) prior to randomisation
7. No known porphyria
8. No known history of deep vein thrombosis or pulmonary embolism confirmed radiologically
9. No known thrombophilic disorder (e.g. Protein C, Protein S, antithrombin deficiency)
10. Not planned to receive SOC abiraterone

Participant exclusion criteria as of 16/01/2018:
Patients must not fulfil any of the criteria, below.
1. Prior systemic therapy for locally-advanced or metastatic prostate cancer except as listed in 1.3
2. Metastatic brain disease or leptomeningeal disease
3. Abnormal liver functions consisting of any of the following:
3.1. Serum bilirubin ≥1.5 x ULN (except for patients with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3µmol/l or 3mg/dl
3.2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN
4. Any other previous or current malignant disease which, in the judgement of the responsible clinician, is likely to interfere with STAMPEDE treatment or assessment
5. Any surgery (e.g. TURP) performed within the past 4 weeks
6. Patients with significant cardiovascular disease, including:
6.1. Severe/unstable angina
6.2. Myocardial infarction less than 6 months prior to randomisation
6.3. Arterial thrombotic events less than 6 months prior to randomisation
6.4. Clinically significant cardiac failure requiring treatment (NYHA II-IV)[3]
6.5. Cerebrovascular disease (e.g. stroke or transient ischemic episode) less than 6 months prior to randomisation
6.6. Patients with uncontrolled hypertension defined as systolic BP greater or equal than 160mmHg or diastolic BP greater or equal than 95mmHg[4]
6.7. Or any other significant cardiovascular disease that in the investigator's opinion means the patient is unfit for any of the study treatments
7. Prior chemotherapy for prostate cancer (excluding patients receiving docetaxel as part of the new SOC)

8. Prior exposure to long-term hormone therapy before randomisation
9. Prior exposure to systemic treatment for prostate cancer (excluding hormone therapy) e.g. abiraterone and enzalutamide

Comparison-Specific Selection Criteria
Metformin Comparison
1. Patients with known diabetes mellitus are not eligible for randomisation. All non-diabetic patients require an HbA1c to be performed prior to randomisation (ideal timeline: within 8 weeks prior to randomisation), to confirm their non-diabetic status.
2. HbA1c <48mmol/mol (equivalent to <6.5%)
3. Adequate renal function, defined as GFR ≥45ml/min/1.73m²
4. No history of lactic acidosis or pre-disposing conditions
5. Not current or previous treatment with metformin
6. No contra-indications to metformin

Transdermal Oestradiol Comparison
Patients who have any of the following are not eligible for the transdermal oestradiol comparison
1. >8 weeks of anti-androgen use
2. >1 dose of monthly or 4 weekly LHRH agonist/antagonist
3. Prior LHRH agonist injection with a stated duration of effect greater than 1 month
4. >12 weeks since first dose of any hormone therapy
5. Bilateral orchidectomy
6. Cyproterone acetate started prior to randomisation
7. Known porphyria
8. Any history of deep vein thrombosis or pulmonary embolism confirmed radiologically
Known thrombophilic disorder (e.g. Protein C, Protein S, antithrombin deficiency)

Current exclusion criteria as of 29/07/2014:
1. Prior systemic therapy for locally advanced or metastatic prostate cancer except as listed in Section 4.1.3
2. Metastatic brain disease or leptomeningeal disease
3. Abnormal liver functions consisting of any of the following:
3.1. Serum bilirubin ≥1.5 x ULN (except for patients with Gilberts disease, for whom the upper limit of serum bilirubin is 51.3µmol/l or 3mg/dl)
3.2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN
4. Any other previous or current malignant disease which, in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment
5. Patients with contra-indications to prednisolone, including active peptic ulceration or a history of gastrointestinal bleeding
6. Patients with active inflammatory bowel disease
7. Symptomatic peripheral neuropathy grade 2 (NCI CTC)5
8. Any surgery (e.g. TURP) performed within the past 4 weeks
9. Patients with significant cardiovascular disease such that, in the investigator's opinion, the patient is unfit for any of the study treatments. This might include:
9.1. Severe/unstable angina
9.2. Myocardial infarction less than 6 months prior to randomisation
9.3. Arterial thrombotic events less than 6 months prior to randomisation
9.4. Clinically significant cardiac failure requiring treatment (NYHA II-IV)6
9.5. Cerebrovascular disease (e.g. stroke or transient ischaemic episode) less than 2 years prior to randomisation
9.6. Patients with uncontrolled hypertension defined as systolic BP greater or equal than 160

mmHg or diastolic BP greater or equal than 95 mmHg
10. Patients receiving treatment with drugs known to induce CYP3A4 (including phenytoin, carbamazepine, Phenobarbital)7
11. Prior exposure to abiraterone
12. Prior exposure to enzalutamide
13. Prior chemotherapy for prostate cancer
14. Prior therapy with zoledronic acid or other bisphosphonates other than treatment for hypercalcaemia or low bone density
15. Prior exposure to policy of long-term hormone therapy before randomisation (unless as described in Section 4.4.2)
16. History of seizure including any febrile seizure, loss of consciousness, or transient ischaemic attack within 12 months of randomisation or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization)
17. Unexplained history of loss of consciousness within 12 months of randomisation
18. Operation of heavy machinery during treatment

SELECTION CRITERIA FOR COMPARISON OF RESEARCH (M1) RT FOR METASTATIC DISEASE
All patients meeting criteria the above criteria are eligible for the trial, but not all can be allocated to the research (M1) radiotherapy arm. The selection criteria for this 'RT to the prostate' comparison are:
1. Newly-diagnosed prostate cancer
2. Demonstrable M1 disease
3. No contraindication to radiotherapy e.g. no previous pelvic radiotherapy and no history of inflammatory bowel disease
4. No previous radical prostatectomy

Any patients meeting these criteria will have a chance to be allocated to Arm H.

Previous exclusion criteria from 23/01/2013 to 29/07/2014:
1. Prior systemic therapy for locally advanced or metastatic prostate cancer except as listed in Section 4.1.3.
2. Metastatic brain disease or leptomeningeal disease
3. Abnormal liver functions consisting of any of the following:
3.1. Serum bilirubin ≥1.5 x ULN (except for patients with Gilberts disease, for whom the upper limit of serum bilirubin is 51.3µmol/l or 3mg/dl)
3.2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN
4. Any other previous or current malignant disease which, in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment
5. Patients with active peptic ulceration, gastrointestinal bleeding, inflammatory bowel disease
6. Symptomatic peripheral neuropathy grade 2 (NCI CTC)5
7. Any surgery (e.g. TURP) performed within the past 4 weeks
8. Patients with significant cardiovascular disease such that, in the investigator's opinion, the patient is unfit for any of the study treatments. This might include:
8.1. Severe/unstable angina
8.2. Myocardial infarction less than 6 months prior to randomisation
8.3. Arterial thrombotic events less than 6 months prior to randomisation
8.4. Clinically significant cardiac failure requiring treatment (NYHA II-IV)6
8.5. Cerebrovascular disease (e.g. stroke or transient ischaemic episode) less than 2 years prior to randomisation
8.6. Patients with uncontrolled hypertension defined as systolic BP greater or equal than 160 mmHg or diastolic BP greater or equal than 95 mmHg

9. Patients who have been scheduled to have major dental extractions within the next 2 years
10. Patients receiving treatment with drugs known to induce CYP3A4 (including phenytoin, carbamazepine, Phenobarbital)7
11. Prior exposure to abiraterone
12. Prior chemotherapy for prostate cancer
13. Prior therapy with zoledronic acid other than short-term treatment for hypercalcaemia
14. Prior exposure to policy of long-term hormone therapy before randomisation (unless as described in Section 4.4.2 of the protocol)

SELECTION CRITERIA FOR COMPARISON OF RESEARCH (M1) RT FOR METASTATIC DISEASE
All patients meeting criteria above are eligible for the trial, but not all can be allocated to the research (M1) radiotherapy arm. The selection criteria for this RT to the prostate comparison are:
1. Newly diagnosed prostate cancer
2. Demonstrable M1 disease
3. No contraindication to radiotherapy e.g. no previous pelvic radiotherapy,
4. No previous radical prostatectomy
Patients meeting these criteria will have a chance to be allocated to Arms A and H.

Previous exclusion criteria until 23/01/2013:
1. Prior systemic therapy for locally advanced or metastatic prostate cancer except as listed in section two
2. Metastatic brain disease or leptomeningeal disease
3. Any other previous or current malignant disease which, in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment
4. Symptomatic peripheral neuropathy grade two (National Cancer Institute Common Toxicity Criteria [NCI CTC])
5. Any surgery (e.g. transurethral resection of the prostate [TURP]) performed within the past four weeks

Date of first enrolment
17/10/2005

Date of final enrolment
31/03/2023

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Switzerland

Study participating centre
CRUK Institute for Cancer Studies
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Research organisation

Funder Name
Cancer Research UK (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

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	03/09/2008		Yes	No
Results article	results	11/06/2009		Yes	No
Results article	results	01/05/2012		Yes	No
Results article	results	15/09/2012		Yes	No
Results article	results	01/05/2013		Yes	No
Results article	results	01/11/2014		Yes	No
Results article	results	01/06/2015		Yes	No
Results article	results	01/02/2016		Yes	No
Results article	results	01/03/2016		Yes	No
Results article	results	19/03/2016		Yes	No
Results article	results	01/12/2016		Yes	No
Results article	results	10/05/2017		Yes	No
Results article	results	27/07/2017		Yes	No
Results article		07/06/2022	08/06/2022	Yes	No
Results article	Metformin for patients with metastatic prostate cancer starting androgen deprivation therapy: a randomised phase 3 trial of the STAMPEDE platform protocol	07/07/2025	11/07/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results		31/01/2019	08/11/2021	No	Yes
Plain English results		13/01/2022	13/01/2022	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes