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# VARIANT: A multicentre randomised feasibility trial of implementing a biomarker-guided personalised treatment in patients with advanced prostate cancer

**Submission date**
01/08/2019

**Recruitment status**
No longer recruiting

**Registration date**
12/08/2019

**Overall study status**
Completed

**Last Edited**
28/04/2023

**Condition category**
Cancer

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

## Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-a-blood-test-to-help-doctors-decide-the-best-treatment-for-advanced-prostate

Background and study aims
Prostate cancer is the most common male cancer in the UK, and is the second-highest cause of male cancer deaths. Prostate cancer in most cases is a slowly progressing diseases when detected early, however, 1 in 4 men present or develop to non-curable metastatic disease. Metastatic prostate cancer is non-curable, with less than one-third of patients surviving for 5 years or longer. The treatment pathway is evolving for metastatic prostate cancer, currently there are two approaches for treatment; (i) further hormonal treatment with abiraterone or enzalutamide or (ii) 'non-hormonal' treatment, typically chemotherapy or "drug delivered" internal radiotherapy (radium 223). Patients and clinicians often choose the first method, as it is less toxic. However, only 30-50% of men respond well to the treatment. The AR-V7 biomarker is found in the blood of some men who have received initial hormone treatment for prostate cancer. Recent studies have suggested that patients who have this biomarker in their blood may be less likely to respond well to advanced hormone therapy. Measuring the amount of this biomarker in the blood (which is not usually tested for), may be useful to help guide the choice of treatment for patients with advanced metastatic prostate cancer. It is hoped this will improve patient experience and outcome by spending less time on and experiencing side effects of treatments that might not work, starting a different treatment earlier, and potentially reduce the cost to the NHS. This study is a feasibility study in which the researchers will look at whether doctors and patients are willing to use the results of this blood test to decide on a treatment option.

Who can participate?
Men aged 18 and over with metastatic Castration-Resistant Prostate Cancer (mCRPC) clinically indicated to proceed to further hormonal therapy or chemotherapy

What does the study involve?
Participants are randomly allocated to receive either R-V7 biomarker-guided personalised clinical treatment or standard treatment for mCRPC. There are three visits, at the start of the study, after 12 weeks and 24 weeks. A blood sample, about 26 ml, is collected on all three visits. Some participants are randomly selected to give an additional 9 ml of blood for validation work during the first visit. On two of these visits, participants are asked to complete a short questionnaire about their quality of life. Information that is already collected as part of standard care is used, for example, their diagnosis, results of scans, blood tests and reports of physical health. Study visits take place during usual hospital visits for the participants. There are no additional visit or scans required. As part of the study, some blood samples collected from participants are stored in a biobank at the Northern Institute of Cancer Research and used for future prostate cancer research.

What are the possible benefits and risks of participating?
By taking part, participants will be helping researchers to gather information to learn about using the AR-V7 biomarker to guide treatment for patients with advanced metastatic prostate cancer. It is hope that this will improve the quality of life of patients in the future. For some patients, taking part in the study will mean that the doctor receives their AR-V7 biomarker result before deciding on a treatment. This may help to inform which treatment would be best after reviewing the participant's medical history. Taking blood samples may cause some discomfort and minor pain, and occasionally patients can feel faint during or after. Sometimes patients will have some bruising where the blood has been taken. Only trained members of staff will perform the blood tests and every effort will be made to prevent any discomfort.

Where is the study run from?
Patients will be recruited and treated in NHS Trusts in the United Kingdom. This is a multi-centre trial taking place in three secondary care sites including:
1. The Newcastle upon Tyne Hospitals NHS Foundation Trust
2. NHS Greater Glasgow and Clyde (The Beatson West of Scotland Cancer Centre)
3. Velindre University NHS Trust (Velindre Cancer Centre)

When is the study starting and how long is it expected to run for?
April 2018 to September 2020

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Shriya Sharma
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# Contact information

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Public

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Scientific

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## Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
PB-PG-0816-20043

## Study information

### Scientific Title
The Prostate Cancer Androgen Receptor Splice Variant 7 Biomarker Study - a multicentre randomised feasibility trial of biomarker-guided personalised treatment in patients with advanced prostate cancer

### Acronym
VARIANT

### Study objectives
The VARIANT Study is being undertaken to understand the feasibility of conducting a large-scale trial comparing AR-V7 bio-marker driven management with the current standard of care in patients with metastatic Castration-Resistant Prostate cancer.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Approved 02/01/2019, Wales Research Ethics Committee 2 (Tel: +44 (0)1792 606334, +44 (0) 2920785740/+44 (0)2920785738; Email: Wales.REC2@wales.nhs.uk), ref: 18/WA/0419

## Study design
Pragmatic multi-centre randomised trial

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Advanced metastatic prostate cancer

## Interventions
Patients who fulfil the eligibility criteria will be randomised (using a ratio of 1:1) to:
Intervention: AR-V7 biomarker-guided personalised clinical treatment (AR-V7+ve : chemotherapy or radium-223, AR-V7-ve : abiraterone or enzalutamide therapy)
Control: Standard care (chemotherapy, radium-223, abiraterone or enzalutamide therapy (as guided by doctor & agreeable to patient)) without biomarker-guided treatment

Patients will be approached about the trial during routine clinic appointments from urology or oncology clinical services. There are 3 visits for this trial, at the start of the study, after 12 weeks and 24 weeks. A blood sample, approximately 26 ml, will be collected on all three visits. Some patients will be randomly selected to give an additional 9 ml of blood for validation work during the first visit. On two of these visits, participants will be asked to complete a short questionnaire about their quality of life. Information that is already collected as part of standard care will be used, for example, their diagnosis, results of scans, blood tests and reports of physical health.

Study visits will take place during usual hospital visits for the participants. There is no additional visit or scans required.
As part of the study, some blood samples collected from participants will be stored in a biobank at the Northern Institute of Cancer Research and used for future prostate cancer research.

## Intervention Type
Other

## Primary outcome(s)
Current primary outcome measures as of 14/11/2019:
Primary outcome measures are related to feasibility (recruitment, retention and adherence) and will report the following;
1. The proportion of prostate cancer patients identified through clinics who meet the eligibility criteria
2. The number of patients accrued per site per month over the course of the trial
3. Baseline prevalence of AR-V7 expression in the participant cohort (this will be presented as a crude percentage of AR-V7 positivity of total participants, and in each arm)

4. The willingness of patients to be randomised (defined as the proportion of patients consenting to be randomised from all eligible patients approached about the study)
5. Compliance rate (this will be defined as the number of patients who start randomised treatment as a proportion of the number randomised)
6. The proportion of patients who: start AR-V7 recommended treatment; start treatment other than the recommended treatment; change treatment before disease progression; or withdraw. (This measure will capture information regarding patients who choose not to take recommended treatment because of strong preferences and patients who progress rapidly while waiting for treatment with a change in eligibility for treatment options).
7. The proportion of trial participants with assessable blood samples for biomarker status (which would affect treatment targeting)
8. The median time from the blood sample being drawn to:
8.1. AR-V7 result being sent back to the site
8.2. patient starting treatment (and compared with standard of care treatment)
9. The proportion of randomised patients for whom data is collected on each clinical and health economic outcome at baseline, 12 and 24 weeks.

Previous primary outcome measures:
Feasibility outcome measures:
1. The number of patients recruited per site per month over the course of the trial
2. The proportion of patients with prostate cancer identified who meet the eligibility criteria
3. The proportion of those meeting the eligibility criteria who agree to be randomised in the study
4. Baseline prevalence of AR-V7 expression in trial participants
5. The proportion of patients who: start AR-V7 recommended treatment; start treatment other than the recommended treatment; change treatment before disease progression; or withdraw. This measure will capture information regarding patients who choose not to take recommended treatment because of strong preferences and patients who progress rapidly while waiting for treatment with a change in eligibility for treatment options.
6. The proportion of trial participants with assessable blood samples for biomarker status (which would affect treatment targeting)
7. The proportion of randomised patients for whom data is collected on each clinical and health economic outcome at baseline, 12 and 24 weeks
8. The median time from drawing the blood sample for biomarker assessment to
8.1. AR-V7 result being sent back to site
8.2. Time taken to start treatment in both control and intervention arms

## Key secondary outcome(s))

Current secondary outcome measures as of 14/11/2019:
Standardised clinical assessment tools used in monitoring castration-resistant prostate cancer (CRPC) disease and progression on treatment will be reported and measured as secondary outcomes.
1. Time to PSA progression: Confirmed rising PSA more than 12 weeks after randomisation. (Where there has been a decline in PSA from baseline, progression will be a 25% or greater increase, and an absolute increase of at least 2 ng/ml, from the nadir, which is confirmed by a second value obtained three or more weeks later. Where no decline from baseline is documented, progression must be a 25% or greater increase from the baseline value along with an increase in absolute value of 2 ng/ml or more. In all cases, the initial rise in PSA must occur after a minimum of 12 weeks from randomisation).
2. Clinical progression and survival within 6 months:
2.1. Number of patients who have progressed clinically at 6 months (includes change of systemic

anti-cancer therapy and death from prostate cancer)
2.2. Cancer specific survival at 6 months
2.3. Overall survival at 6 months
3. Quality of life for patients with cancer assessed using EORTC QLQ-C30
4. Additional quality of life items patients with prostate cancer assessed using EORTC QLQ-PR25
5. Participant costs questionnaire measured with Health Services Questionnaire

Previous secondary outcome measures:
Clinical outcome measures:
1. Time to PSA progression: Confirmed rising PSA more than 12 weeks after randomisation. Where there has been a decline in PSA from baseline, progression will be a 25% or greater increase, and an absolute increase of at least 2ng/mL, from the nadir, which is confirmed by a second value obtained 3 or more weeks later. Where no decline from baseline is documented, progression must be a 25% or greater increase from the baseline value along with an increase in absolute value of 2 ng/mL or more. In all cases, the initial rise in PSA must occur after a minimum of 12 weeks from randomisation.
2. Clinical progression and survival within 6 months:
2.1. Number of patients who have progressed clinically at 6 months (includes change of systemic anti-cancer therapy and death from PC)
2.2. Cancer-specific survival at 6 months
2.3. Overall survival at 6 months
3. Quality of life for patients with cancer, measured using EORTC QLQ-C30 at baseline and 24 weeks after the first treatment
4. Additional quality of life items for patients with prostate cancer, measured using EORTC QLQ-PR25 at baseline and 24 weeks after the first treatment
5. Participant costs measured using Use of Health Services Questionnaire at 24 weeks after the first treatment

### Completion date
30/09/2020

# Eligibility

### Key inclusion criteria
1. Histologically or cytologically proven diagnosis of adenocarcinoma of the prostate
2. Radiographic and/or histological and/or cytological evidence of metastatic disease
3. Castrate levels of testosterone and documented ongoing medical or surgical castration. Testosterone level ≤50ng/dl /1.73 nmol/L and maintaining on androgen suppression therapy.
4. Disease progression since the last change in therapy defined by one or more of the following:
4.1. PSA progression as defined by the prostate cancer working group 3 (PCWG3) criteria. This must be based on a series of at least 3 readings, each at least 7 days apart demonstrating rising PSA. The 3rd reading must be ≥ 2ng/ml. In the event where an intermediate reading is lower than a previous reading, then the patient will still be eligible (i.e. the 3 readings do not need to be consecutive). The first of the three readings must have been obtained after commencing the previous systemic therapy, or, in the case of androgen receptor antagonists, after discontinuing
4.2. Bone disease progression as determined by the local radiology/ multidisciplinary team
4.3. Radiographic progression of nodal or visceral metastases as determined by the local radiology/ multidisciplinary team
5. Suitable for treatment with at least one novel hormonal treatment (with available treatments abiraterone acetate or enzalutamide) and one non-hormonal therapy (with available treatments docetaxel, cabazitaxel or radium-223). At least one of each type of treatment must be available

to the patient
6. At least two high risk features
6.1. Age <60 years at time of diagnosis of metastatic disease
6.2. Bone metastases present at time of initial metastatic prostate cancer diagnosis (although not mandated, it is considered good clinical practice to have up to date imaging within 8 weeks)
6.3. Gleason grade group 4 or 5 (Gleason score 8 to 10)
6.4. Presence of visceral metastases (e.g. liver or lung) at any time point. This does not include lymph node metastases (although not mandated, it is considered good clinical practice to have up to date imaging within 8 weeks).
6.5. PSA doubling time < 3 months
6.6. Elevated alkaline phosphatase above institutional upper limit of normal
6.7. ECOG Performance Status worse than or equal to 1
6.8. Previous treatment for castration-resistant prostate cancer with docetaxel chemotherapy
6.9. Previous treatment for castration-resistant prostate cancer with abiraterone and/or enzalutamide or equivalent agent
7. Estimated life expectancy > 6 months
8. Aged 18 years or over
9. Provision of written informed consent, including consent for bio-banking of blood samples at the NICR

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Adult

## Lower age limit
18 years

## Sex
Male

## Total final enrolment
12

## Key exclusion criteria
1. Histological variants of prostate cancers with small cell or neuroendocrine features
2. Prior or current malignancy (except adenocarcinoma of the prostate) with an estimated ≥ 30% chance of relapse/progression within next 2 years
3. Previously identified brain metastases or spinal cord compression unless treated with full functional recovery
4. Administration of an investigational agent within 30 days of first dose of trial medication

## Date of first enrolment
29/07/2019

## Date of final enrolment
18/03/2020

# Locations

### Countries of recruitment
United Kingdom

England

Scotland

Wales

### Study participating centre
**Sir Bobby Robson Cancer Trials Research Centre (Newcastle upon Tyne Hospitals NHS Foundation Trust)**
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

### Study participating centre
**Velindre Cancer Centre (Velindre University NHS Trust)**
Velindre Road,
Whitchurch,
Cardiff
Cardiff
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CF14 2TL

### Study participating centre
**The Beatson West of Scotland Cancer Centre (NHS Greater Glasgow and Clyde)**
1053 Great Western Road
Glasgow
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# Sponsor information

### Organisation

Newcastle upon Tyne Hospitals NHS Foundation Trust

**ROR**
https://ror.org/05p40t847

# Funder(s)

**Funder type**
Government

**Funder Name**
Research for Patient Benefit Programme

**Alternative Name(s)**
NIHR Research for Patient Benefit Programme, Research for Patient Benefit (RfPB), The NIHR Research for Patient Benefit (RfPB), RfPB

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**
The data collected in the study will be used to feed into a larger study. As this study is looking at the feasibility aspects of having a larger definitive trial, the participant level data will not be shared.

**IPD sharing plan summary**
Not expected to be made available

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 10/01/2023 | 28/04/2023 | Yes | No |
| Protocol article | protocol | 18/12/2019 | 23/12/2019 | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |
| Plain English results | | | 28/04/2023 | No | Yes |