



Clinical trial results:

Phase II open label randomised safety and efficacy study of the viral vectored ChAd-MVA 5T4 vaccine in combination with PD-1 checkpoint blockade in low- or intermediate-risk localized or locally advanced prostate cancer and advanced metastatic prostate cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-001992-22 |
| Trial protocol | GB |
| Global end of trial date | 20 May 2022 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 04 August 2023 |
| First version publication date | 04 August 2023 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | ADVANCE |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03815942 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | RGEA, University of Oxford |
| Sponsor organisation address | Churchill hospital, Old Road, Headington, Oxford, United Kingdom, OX3 7LE |
| Public contact | Adrian Hill, The Jenner Institute, University of Oxford, +44 1865617610, adrian.hill@ndm.ox.ac.uk |
| Scientific contact | Adrian Hill, The Jenner Institute, University of Oxford, +44 1865617610, adrian.hill@ndm.ox.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 May 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 May 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 May 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy of ChAd-MVA 5T4 vaccination in combination with checkpoint inhibitor nivolumab when administered to early stage and advanced metastatic prostate cancer patients.

Low- or intermediate-risk localised or locally advanced prostate cancer patients:

- To assess safety of the viral vectored ChAd-MVA 5T4 vaccine when administered in combination with anti-PD-1 mAb
- To determine whether ChAd-MVA 5T4 vaccine in combination with anti-PD-1 will impact on the serum level of PSA

Metastatic prostate cancer patients

- To assess safety of the viral vectored ChAd-MVA 5T4 vaccine when administered in combination with anti-PD-1 mAb
- To assess efficacy of the viral vectored ChAd-MVA 5T4 vaccine when administered in combination with anti-PD-1 mAb as measured by composite response rate defined as one of the following:

- o reduction of circulating tumour DNA
- o serum PSA decrease

Protection of trial subjects:

All patients will sign and date the informed consent form before any study-specific procedures are performed. The information sheet will be made available to the patient at least 24 hours prior to the screening visit. The patient will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasised:

- Participation in the study is entirely voluntary
- Refusal to participate involves no penalty or loss of medical benefits
- The patient may withdraw from the study at any time
- The patient is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The study involves research of an investigational vaccine and checkpoint inhibitor
- The study involves delaying the patient's surgery by approximately 2 months
- There may be no direct benefit for participating

The aims of the study and all tests to be carried out will be explained. The patient will be given the opportunity to ask about details of the study, and will then have time to consider whether or not to participate. If they do decide to participate, they will sign and date the consent form, which will also be signed and dated by the investigator. One copy will be given to the participant, one copy will be placed in the study file, and the original will be placed in their medical notes.

Background therapy: -

Evidence for comparator:

N/A

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 23 |
| Worldwide total number of subjects | 23 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 2 |
| From 65 to 84 years | 21 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited into one of two cohorts within the study: those with operable localised or locally advanced prostate cancer who are planned to undergo radical prostatectomy, or those with metastatic prostate cancer who demonstrate disease progression on therapy with second generation anti-androgens (enzalutamide or abiraterone).

Pre-assignment

Screening details:

The subjects were men over 18 years old. 2 groups

Radical prostatectomy: Men with low- or intermediate-risk advanced prostate cancer and deemed operable and fit to undergo radical prostatectomy (0 recruited)

Metastatic prostate cancer: men with metastatic prostate cancer with demonstrated disease progression following anti-androgen treatment (23)

Period 1

| | |
|------------------------------|------------------------------|
| Period 1 title | Whole trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

N/A

Arms

| | |
|-----------|---------|
| Arm title | Group 2 |
|-----------|---------|

Arm description:

Participants with Metastatic Prostate Cancer

| | |
|--|-------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ChAdOx1.5T4 vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Injection , Intramuscular use |

Dosage and administration details:

ChAdOx1.5T4 vaccine is an unlicensed medicinal product manufactured by the University of Oxford Clinical Biomanufacturing Facility (CBF), Churchill Hospital, Oxford. It is formulated in formulation buffer at a nominal concentration of 1.1x10¹¹ vp/mL.

The formulation buffer consists of 10mM Histidine, 7.5% sucrose, 35mM NaCl, 1mM MgCl₂, 0.1% PS80, 0.1mM EDTA, 0.5% EtOH, pH 6.6. The fill volume is 0.5-1.0 mL.

The dose of ChAdOx1.5T4 used in this study is 2.5x10¹⁰ vp.

The vaccine was allowed to thaw to room temperature and were administered by intramuscular injection within 1 hour of removal from the freezer. The preferred site for vaccination was the vastus lateralis muscle of the thigh but the deltoid muscle of the arm was an acceptable alternative.

| | |
|--|-------------------------------|
| Investigational medicinal product name | MVA.5T4 vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Injection , Intramuscular use |

Dosage and administration details:

MVA.5T4 vaccine is an unlicensed medicinal product that has not been administered to humans before. It has been manufactured under Good Manufacturing Practice conditions by IDT Biologika GmbH, Germany.

MVA.5T4 was supplied as a frozen liquid formulation in 10mM Tris buffer 140 mM NaCl, pH 7.7 in 2.0 mL clear glass vials. The formulation titre is 2x10⁹ pfu/ml, the final drug product titre is 1x10⁹ pfu/ml. The fill volume is 0.55 mL.

The vaccine was allowed to thaw to room temperature and administered by intramuscular injection within 1 hour of removal from the freezer. The preferred site for vaccination was the vastus lateralis muscle of the thigh but the deltoid muscle of the arm was an acceptable alternative. It was planned to use a different thigh (arm) for each of the two MVA.5T4 immunisations.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Immune checkpoint inhibitor nivolumab |
| Investigational medicinal product code | |
| Other name | Opdivo® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Nivolumab 480mg, was prepared from 10mg/ml concentrate, diluted into sodium chloride 9mg/mL (0.9%) solution for injection and administered intravenously in a volume of 100ml to a final concentration of 4.8mg/ml. Preparation and handling adopted strict aseptic technique. In line with the manufacturer's instructions, nivolumab was administered intravenously over a period of 60 minutes using a volumetric pump, an infusion set and an in-line, sterile, nonpyrogenic, low protein binding filter of pore size of 0.2µm to 1.2µm. After administration the line was flushed with sodium chloride 9 mg/mL (0.9%) solution for injection.

| Number of subjects in period 1 | Group 2 |
|---------------------------------------|----------------|
| Started | 23 |
| Visit 1 | 23 |
| Visit 3 | 23 |
| Visit 5 | 21 |
| Visit 7 | 19 |
| Visit 9 | 17 |
| Visit 0 : Consenting / Screening | 23 |
| Enrolled | 23 |
| Completed | 6 |
| Not completed | 17 |
| Consent withdrawn by subject | 17 |

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | Group 2 |
| Reporting group description: | |
| Participants with Metastatic Prostate Cancer | |

| Reporting group values | Group 2 | Total | |
|------------------------|---------|-------|--|
| Number of subjects | 23 | 23 | |
| Age categorical | | | |
| Group 2 participants | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 2 | 2 | |
| From 65-84 years | 21 | 21 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 23 | 23 | |

Subject analysis sets

| | |
|----------------------------|-----------------|
| Subject analysis set title | Group 2 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The participant must satisfy all the following criteria to be eligible for the study:

- Histologically confirmed adenocarcinoma of the prostate cancer. Note, any Gleason grade or primary tumour staging at diagnosis is permitted.
- Evidence of at least one distant metastasis based on MRI, CT, PET or bone scintigraphy.
- Established on and suitable to continue with androgen deprivation therapy (ADT) using any luteinizing hormone releasing hormone (LHRH) agonist. LHRH agonist therapy may include goserelin (Zoladex®), leuporelin acetate (Prostap®) or any other licenced product in this class.
- On treatment with anti-androgen therapy using either abiraterone (Zytiga®) or enzalutamide (Xtandi®) and demonstrating evidence of disease progression at the time of enrolment, defined according Prostate Cancer Working Group 3 Criteria as either:
 - PSA progression as defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each assessment where the PSA value at screeni

| Reporting group values | Group 2 | | |
|------------------------|---------|--|--|
| Number of subjects | 23 | | |
| Age categorical | | | |
| Group 2 participants | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 2 | | |
| From 65-84 years | 21 | | |
| 85 years and over | 0 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | | |
| Male | 23 | | |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | Group 2 |
| Reporting group description: Participants with Metastatic Prostate Cancer | |
| Subject analysis set title | Group 2 |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The participant must satisfy all the following criteria to be eligible for the study: <ul style="list-style-type: none">- Histologically confirmed adenocarcinoma of the prostate cancer. Note, any Gleason grade or primary tumour staging at diagnosis is permitted.- Evidence of at least one distant metastasis based on MRI, CT, PET or bone scintigraphy.- Established on and suitable to continue with androgen deprivation therapy (ADT) using any luteinizing hormone releasing hormone (LHRH) agonist. LHRH agonist therapy may include goserelin (Zoladex®), leuporelin acetate (Prostap®) or any other licenced product in this class.- On treatment with anti-androgen therapy using either abiraterone (Zytiga®) or enzalutamide (Xtandi®) and demonstrating evidence of disease progression at the time of enrolment, defined according Prostate Cancer Working Group 3 Criteria as either:<ul style="list-style-type: none">• PSA progression as defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each assessment where the PSA value at screeni | |

Primary: Completed the study

| | |
|--|------------------------------------|
| End point title | Completed the study ^[1] |
| End point description: Those participants who completed the full study | |
| End point type | Primary |
| End point timeframe: Week 48 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Due to the confidential nature of this information, we have not provided this analysis at this time. The scientific paper can be uploaded following publication if required. | |

| End point values | Group 2 | Group 2 | | |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 23 | 23 | | |
| Units: 23 | | | | |
| Completed Study | 6 | 6 | | |
| Withdrew Week 36 | 2 | 2 | | |
| Withdrew Week 24 | 8 | 8 | | |
| Withdrew week 17 | 1 | 1 | | |
| Withdrew Week 16 | 1 | 1 | | |
| Withdrew Week 12 | 1 | 1 | | |
| Withdrew Week 9 | 1 | 1 | | |
| Withdrew Week 8 | 2 | 2 | | |
| Withdrew Week 4 | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Received Vaccination / Infusions

End point title Received Vaccination / Infusions^[2]

End point description:

How many had the dose(s) administered at each stage

End point type Primary

End point timeframe:

Progression of vaccinations / infusions through the trial

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the confidential nature of this information, we have not provided this analysis at this time. The scientific paper can be uploaded following publication if required.

| End point values | Group 2 | Group 2 | | |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 23 | 23 | | |
| Units: 23 | | | | |
| Day 0 - ChAdOx1.5T4 | 23 | 23 | | |
| Week 4 MVAA.5T4 | 23 | 23 | | |
| Week 4 Nivo | 23 | 23 | | |
| Week 8 Nivo | 20 | 20 | | |
| Week 12 ChAdOx1.5T4 | 19 | 19 | | |
| Week 12 Nivo | 18 | 18 | | |
| Week 16 MVA.5T4 | 17 | 17 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

From Enrolment until End of Study

Adverse event reporting additional description:

ADV-00118011

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 26 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group 2 |
|-----------------------|---------|

Reporting group description:

All of the participants in the trial (metastatic prostate cancer)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Due to the confidential nature of this information, we have not provided this analysis at this time. The scientific paper can be uploaded following publication if required.

| Serious adverse events | Group 2 | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 23 (34.78%) | | |
| number of deaths (all causes) | 21 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Spinal cord compression | Additional description: ADV00118007 was admitted with left lower limb weakness. Underwent MRI of the spine which showed metastatic spinal cord compression at T2. Had radiotherapy as an inpatient. This is related to disease progression. | | |
| subjects affected / exposed | 3 / 23 (13.04%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | Additional description: ADV00118001 Blood in urine for 3 weeks. Extreme fatigue, poor appetite, increased leg swelling, breathlessness. On admission had ultrasound of urinary tract to have bloods taken. Stent removed and replaced via nephrostomy | | |
| subjects affected / exposed | 1 / 23 (4.35%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | Additional description: ADV-00118002 Admitted with temperature of 37.7C and lower abdominal pain. Discharged after treatment | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed | 1 / 23 (4.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Pyrexia and rigors | Additional description: ADV-00118017 Participant admitted to triage due to pyrexia and rigors. On admission started on antibiotics for possible chest infection. Discharged 4 days later | | |
| subjects affected / exposed | 1 / 23 (4.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | Additional description: ADV099118103: Attended for a visit and was less well with multiple adverse events. Bloods showed raised calcium and acute kidney injury. Discharged following IV fluids and treatment for hypercalcemia | | |
| subjects affected / exposed | 1 / 23 (4.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | Additional description: ADV-00118019 lower back pain progressively worsened over a month. MRI demonstrated minor protrusion of the R L5 nerve root. Started on Dexamethasone. Discharged with new regime and outpatients radiotherapy | | |
| subjects affected / exposed | 1 / 23 (4.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Chest pain | Additional description: ADV00119105: Admitted with chest pain. Suspected pulmonary clots. CT pulmonary angiogram : no PE. Chest pain of unknown origin. Suspect infection | | |
| subjects affected / exposed | 1 / 23 (4.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| | | | |
|---|----------------|--|--|
| Non-serious adverse events | Group 2 | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 23 (0.00%) | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 08 June 2016 | <p>SA001 was REC-Only and included changes to the Protocol, the Participant Information Sheets (PIS RP and PIS mPCa), ICF(RP), Diary Cards and GP letter and provision of the new Investigator's Brochure for MVA.5T4 IMP.</p> <p>The changes to the Protocol were: 1) Removal of one recruiting site 2) Addition of one recruiting site 3) For radical prostatectomy patients (RP) reduction of the following: a) number of nivolumab infusions, b) intervals between study treatments, c) surgery delay, d) number of study visits, e) follow-up period. 4) for metastatic prostate cancer patients (mPCa): modification of the vaccines and nivolumab dosing regimes and clarification of study endpoints 5) New information regarding the MVA.5T4 vaccine.</p> <p>The PIS RP was changed to reflect the changes above.</p> <p>The PIS mPCa was changed to reflect the changes above.</p> <p>The ICF RP was changed to reflect the reduction of nivolumab infusions.</p> <p>The changes to the GP Letter reflected the reduction in follow-up period for RP participants.</p> <p>The Diary Cards were changed to reflect the changes in dosing regimens.</p> <p>New Investigator's Brochure for MVA.5T4</p> <p>The HRA schedule of events was changed to reflect the changes in the vaccines and nivolumab dosing regimens.</p> |
| 05 September 2018 | <p>SA002 was submitted to the REC and the MHRA and modified the study protocol and extended the shelf-life of the study IMP ChADOx1.5T4 to 15Jul2019 on the basis of stability test results.</p> <p>The changes to the protocol were 1) Removal of 3 recruiting sites 2) Addition of 1 recruiting site 3) Addition of Principal Investigator 4) Reduction in sample size from 60 to 36 participants 5) For Metastatic Prostate Cancer participants: a) removal of the control arm receiving Nivolumab only b) removal of randomisation c) reduction of the follow-up period to 12 months and reduction of the number of study visits</p> <p>ADVANCE Protocol Version 3.0, 03Sep2018 was submitted.</p> |
| 29 November 2018 | <p>SA003 was submitted to the REC and the MHRA and modified the study protocol.</p> <p>The changes in the protocol were in Appendix 1 (Schedule of events): 1) No collection of blood samples for exploratory biochemistry for Group 2 (mPCA) 2) Significant reduction in number of blood samples for ctDNA quantification but increase in blood volume 3) Small increase in blood volume for exploratory immunology at several timepoint</p> <p>ADVANCE Protocol Version 4.0, 19Nov2018 was submitted.</p> |

| | |
|------------------|---|
| 19 February 2019 | SA004 was submitted to the REC and the MHRA and modified the study protocol. The changes to the protocol were: 1) Two sites and their respective Principal Investigators were removed 2) Treatment with abiraterone and enzalutamide were discontinued after enrolment to the study 3) Participant confidentiality section was modified to comply with GDPR and Data Protection Act 4) Changes to the Schedule of events: a) Timeframe for phone call increased to 2+3 days b) Blood sample for HLA typing collected at visit 2 instead of 3 c) Timepoints for ctDNA and CTC modified to remove collection at week 48 and add collection at weeks 4, 8 and 12 for cdctDNA and week 8 for CTC sample. ADVANCE Protocol Version 5.0, 15Feb2019 was submitted. |
| 16 October 2019 | SA006 was submitted to the REC and the MHRA and constituted a temporary halt of the study following the identification of a potentially serious breach. |
| 19 November 2019 | SA007 was submitted to the REC and the MHRA and requested the re-start of the trial following the implementation of measures to rectify the situation. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|---|------------------|
| 16 October 2019 | a temporary halt of the study following the identification of a potentially serious breach. | 19 November 2019 |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No participants were recruited to Group 1 (Radical prostatectomy group)

Notes: