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:
    - reduction of circulating tumour DNA
    - 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 partiicpant, 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 is an unlicensed medicinal product manufactured by 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 NaCI, 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 1x109pfu/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®), leuprorelin 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:
- 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®), leuprorelin 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

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

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 spone which shwed 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 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	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. 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 nivolimab 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. The PIS RP was changed to reflect the changes above. The PIS mPCa was changed to reflect the changes above. The ICF RP was changed to reflect the reduction of nivolumab infusions. The changes to the GP Letter reflected the reduction in follow-up period for RP participants. The Diary Cards were changed to reflect the changes in dosing regimens. New Investigator's Brochure for MVA.5T4 The HRA schedule of events was changed to reflect the changes in the vaccines and nivolumab dosing regimens.
05 September 2018	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. 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 ADVANCE Protocol Version 3.0, 03Sep2018 was submitted.
29 November 2018	SA003 was submitted to the REC and the MHRA and modified the study protocol. 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 ADVANCE Protocol Version 4.0, 19Nov2018 was submitted.

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: