ABSTRACT 4172: Results from ADVANCE, a Phase I/II open-label non-randomised safety and efficacy study of the viral vectored ChAdOx1-MVA 5T4 (VTP-800) vaccine in combination with PD-1 checkpoint blockade in metastatic prostate cancer

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BACKGROUND

Based on encouraging safety and exceptional T cell immunogenicity of the ChAdOx1-MVA 5T4 (VTP-800) vaccine vectors in the VANCE study in localised prostate cancer (NCT02390063), the phase I/II ADVANCE (NCT03815942) trial was undertaken to test VTP-800 safety and efficacy in combination with PD-1 blockade (Nivolumab) in metastatic castrate resistant prostate cancer (mCRPC).

METHODS

Objectives: To describe the safety, efficacy and immunogenicity of VTP-800 (ChAdOx1.5T4 + MVA.5T4) and anti-PD-1 (Nivolumab) in patients with metastatic castrate resistant prostate cancer.

Study Design

Regimen: ChAdOx1.5T4 was administered intramuscularly in an extremity (e.g. thigh) at a dose of 2.5 x 10^{10} virus particles and MVA.5T4 administered via the same route at a dose of 2 x 10^{8} plaque forming units. Nivolumab was administered as a flat dose of 480 mg over approximately 60-minutes via I.V. infusion.

Primary endpoints

- 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 by a composite response rate defined as one of the following: - reduction of circulating tumour DNA, - serum PSA decrease

Secondary endpoints

- To assess the magnitude of immune responses in the periphery generated by ChAd-MVA 5T4 vaccine in combination with anti-PD-1 mAb
- Radiographic progression-free survival at 6 and 12 months post enrolment
- To evaluate overall survival at 6 and 12 months post enrolment

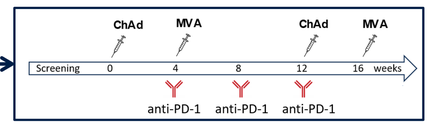
Statistical Methods

- Kaplan–Meier analyses are planned to perform time-to-event analyses
- ORRs with two-sided 90% confidence intervals (CIs) are planned

Figure 1: Study Design

Patients (N=23)

- ≥ 18 years of age
- Histologically confirmed prostate cancer
- ECOG Status of ≤1
- Evidence of at least one distant metastasis based on MRI, CT, PET or bone scintigraphy
- On treatment with anti-androgen therapy using either abiraterone (Zytiga®) or enzalutamide (Xtandi®)
- Disease progression at the time of enrolment according to the Prostate Cancer Working Group 3



RESULTS

23 out of a planned 24 patients with mCRPC were recruited between 21/02/19 and 01/10/19. Due to COVID-19, study recruitment was terminated early and the first-pre-planned analysis was performed after 6 months of follow up.

Table 1: Baseline Demographics and Disease Characteristics

Characteristics	VTP-800 with anti-PD-1 mAb
Median age, years (range)	71 (54-82)
ECOG performance status, n (%)	
0	64% (14/22)
1	36% (8/22)
Median Gleason scores (range)	9 (7- 10)
Median PSA (range)	78.5 (8.3-2462)

Figure 2: Efficacy – PSA waterfall plot

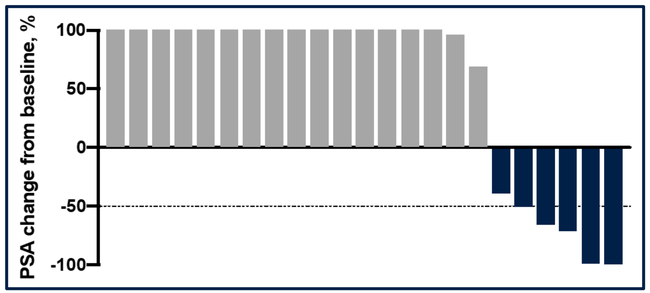


Figure 3: Efficacy – PSA Individual Responses

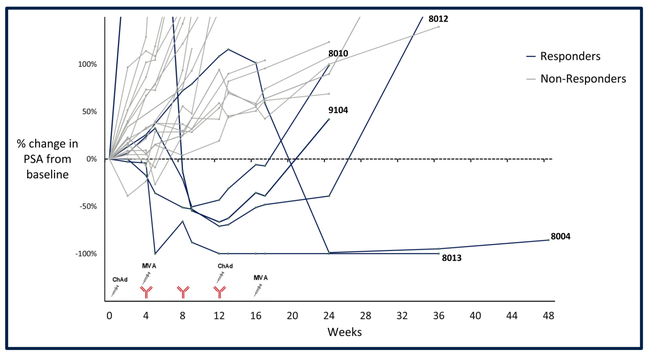


Figure 4: T cell immune responses

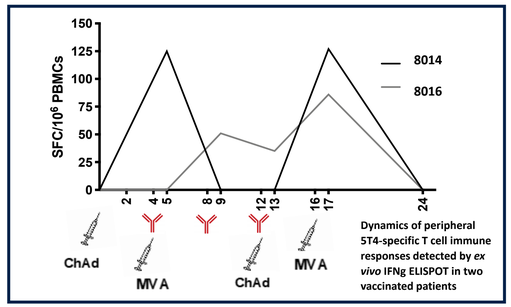


Table 2: Treatment emergent Adverse Events

AEs, n (%)	VTP-800 with anti-PD-1 mAb **N=23** Any grade	Grade ≥3
Any AE	22 (91)	1 (4)
Diarrhea	1 (4)	0
Asthenia	1(4)	0
Injection site pain	4(17)	0
Bone pain	8 (35)	0
Nausea	0	0
Fatigue	1 (1)	0
Constipation	4(17)	0
Vomiting	0	0
Liver function test changes	1 (4)	0
Stomatitis	4 (17)	0
Dry Mouth	2 (8)	0
Muscle Pain	4(17)	0
Chest infection	1(4)	1

- The most common AEs were mild and grade 1 or 2
- The only grade 3 adverse event was a chest infection which was not thought to be related to the study medicines. The most common adverse events were pain at injection sites, stomatitis (17%), muscle pain (17%) and constipation (17%)
- There were no grade 4 or 5 treatment related adverse events

Table 3: Radiological responses by RECIST 1.1

Patients		
Total Enrolled	23	
Withdrawn to date	15	3 – noncompliance 1 – lost to FU Other – disease progression
Withdrawn prior to w24 (CT Scan)	5	
Unmeasurable disease by RECIST	10	
Evaluable by RECIST	**8**	3– Partial response, 2 – Stable disease, 3 – Progressive Disease

Genetic Analysis of ADVANCE patients

Four of five PSA_{50} responder patients screened for tumour microsatellite instability by DNA-seq

- **8004** – negative
- **8013** – negative
- **8012** – negative
- **8010** – no tissue sample available
- **9104** – negative

The same five PSA_{50} responder patients screened for germline polymorphisms in 84 genes

- **8004** – variant of DNA repair gene MUTYH gene – likely pathogenic variant; but MUTYH gene not implicated in mismatch repair syndromes or enhanced anti-PD-1 response
- **8013** – variant of DNA repair gene NTHL1 – likely pathogenic variant of DNA repair gene, and DNA repair gene PMS2 of "uncertain significance"
- **8012** – no variant in any of the genes in the 84 gene panel
- **8010** – has variant in NTHL1 gene - of "uncertain significance"
- **9104** – has variants in CTNNA1 and RET genes - both of "uncertain significance"

Conclusion: no evidence that genetic factors are implicated in the high PSA_{50} response rate

A planned analysis of changes in circulating tumour DNA, progression free survival and overall survival has been delayed by laboratory closures and temporary suspension of study follow up due to COVID-19.

CONCLUSIONS

- VTP-800 and Nivolumab treatment led to a >50% reduction in PSA in 22% of patients in the ADVANCE trial
- ChAdOx1-MVA 5T4 (VTP-800) and Nivolumab were safe and well tolerated in this group of patients with advanced castrate resistant prostate cancer
- No evidence that genetic factors are implicated in the high PSA_{50} response rate
- Clinical studies of new therapeutic multi-antigen ChAdOx1/MVA vaccine vectors containing 5T4 are in development

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Presented by Dr Mark Tuthill at ESMO 2020: mark.tuthill@ouh.nhs.uk

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DISCLOSURES Dr Mark Tuthill: Consulting/advisor role for Vaccitech Limited, Pfizer, Novartis, Lilly, Janssen, Roche, BMS, and Oxford Vacmedix. Paid speaking engagements and education support Novartis, Pfizer, Roche, Janssen, BMS, Genomic Health, Astellas, Esai, Everything Genetic, Chugai. Adrian V. S. Hill is a co-founder of and shareholder in Vaccitech Ltd. The disclosures of other the co-authors are available on request.