

VANCE: first in human phase I study of a novel ChAdOx1-MVA 5T4 vaccine in low and intermediate risk prostate cancer

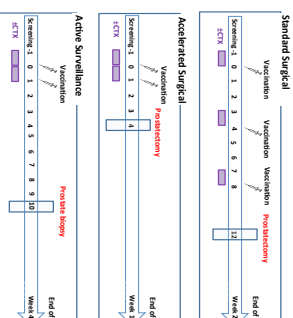
I. Redchenko¹, F. Cappuccini¹, E. Pollock¹, R. Bryant¹, L. Carter¹, C. Verrill¹, J. Hollidge¹, L. Goodwin², R. Harrop³, P. Romero⁴, S. Viganò⁴, T. Evans⁵, J. Catto³, F. Hamdy¹, A.V.S. Hill¹

¹University of Oxford, Oxford, UK, ²Royal Hallamshire Hospital, Sheffield, UK, ³Oxford Biomedica plc, Oxford, UK, ⁴Lausanne University Hospital, Lausanne, Switzerland, ⁵Vaccitech Ltd, Oxford, UK

Study Design and Objectives

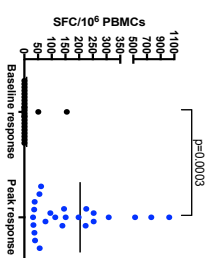
We evaluated a novel vaccination platform based on two replication-deficient viruses, chimpanzee adenovirus ChAdOx1 and MVA, targeting the oncofetal antigen 5T4 in early stage prostate cancer patients. The study arms are shown on the right.

- Primary objectives:**
- Safety and immunogenicity (ex vivo IFN γ ELISPOT)
- Secondary objectives:**
- Tumour immune infiltration into the prostate (IHC of FFPE tissue, flow cytometry of fresh tissue)
 - Serum PSA level change secondary to vaccination
 - Phenotype and functional profile of PBMCs
- Exploratory objectives:**
- T cell epitope mapping



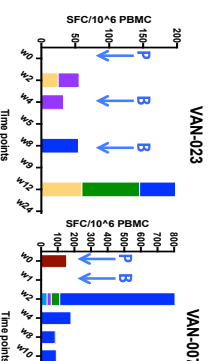
Study Results

Vaccination induces ex vivo 5T4 T cell response in the majority of patients



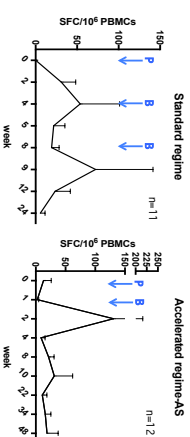
5T4-specific T-cell response to vaccination measured by IFN γ ELISPOT. Peak response, expressed as a number of the antigen-specific T cells secreting IFN γ per one million of PBMCs, in each patient who mounted the 5T4-specific T cell response following vaccination was compared to the 5T4 response detected at baseline. Bars represent medians.

Vaccination induces T cell response to a broad range of 5T4 T cell epitopes



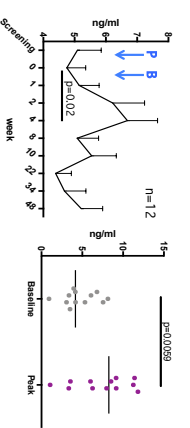
In the ELISPOT assay, the overlapping peptides spanning the entire 5T4 protein have been split into 8 pools (10 peptides per pool). The response to each individual pool is shown in a different colour. The magnitude and kinetics of the 5T4 T cell response are shown in 2 illustrative patients: one patient (VAN-023) was randomised to the standard vaccination regimen, another (VAN-007) – to the accelerated immunisation schedule. P indicates prime with ChAdOx1-5T4, B indicates boost with MVA-5T4.

Kinetics of vaccine-induced T cell response



5T4-specific T-cell responses to vaccination measured by IFN γ ELISPOT. Blood samples from vaccinated patients have been collected on the day of each vaccination, 7-14 days after each vaccination and at the follow-up visits up to week 48. The PBMCs have been exposed to the 5T4 peptide pools for 18 hours and the numbers of the antigen-specific T cells secreting IFN γ have been calculated per one million of PBMCs. The graphs represent an average number of 5T4-specific T cells at each timepoint in two study arms.

Vaccination induces transient increase in serum PSA

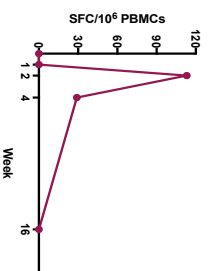


A PSA level kinetics averaged for 12 vaccinated patients in the active surveillance (AS) arm during the study period is shown on the left. There is a statistically significant transient increase in PSA at week 4 compared to baseline. The graph on the right shows a maximum PSA level at any timepoint compared to baseline for each AS patient.

Conclusions

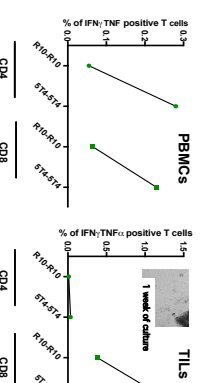
- Both ChAd and MVA vaccines were well tolerated in all subjects
- Clear evidence of breaking tolerance
- Ex vivo 5T4-specific CD8 and CD4 T cell responses were induced in the majority of vaccinees
- 5T4-specific CD4 and CD8 T cells were expanded from fresh prostate tissue of immunised subjects
- CD8 T cell infiltration was detected in the FFPE surgical specimens of the vaccinated patients
- Intriguing transient increase in PSA in the majority of the vaccinated patients

5T4-specific T cell response is detected ex vivo



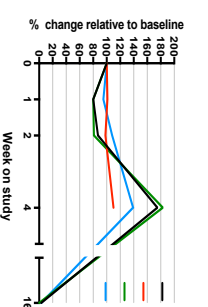
VAN-010 was randomised to the accelerated regimen to receive the ChAd vaccine at week 0, MVA at week 1 and to undergo surgery at week 4. Blood samples were collected at each clinic visit for IFN γ ELISPOT assay. The 5T4-specific T cell response peaked one week after the boosting MVA-5T4 immunisation.

5T4-specific CD8 T cells secreting IFN- γ and TNF- α are expanded from the blood and prostate tissue



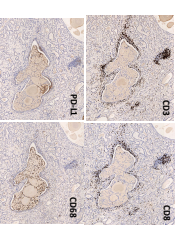
PBMCs and prostate surgical specimens were cultured either in medium alone or in the presence of the total 5T4 peptide pool to expand the relatively infrequent 5T4-specific T cells for further analysis by cytokine flow cytometry. ~0.2% of CD8 T cells in the blood and ~1% in the prostate secreted IFN γ and TNF α in response to 5T4 peptide pool stimulation. Both samples were collected at week 4 on the study. R10-R10 denotes the 5T4 antigen naive T cells. 5T4-5T4 denotes the T cells expanded in the presence of 5T4 peptide pool.

Level of serum PSA sub-forms is increased following vaccination



Free PSA (PSA_f) and intact PSA (PSA_i) have more rapid elimination kinetics compared to the total PSA (PSA_T). Therefore, these sub-forms could be a more sensitive readout of the vaccine effect on the target organ. As shown on the graph, there was an 80% increase over the baseline in the level of both intact and free PSA sub-forms following vaccination.

Immune cell infiltration including CD8 T cells is detected in prostate tissue by IHC



Consecutive sections of the FFPE surgical specimen were stained for CD3, CD8, CD88 and PD-L1 expression. The staining of paired pre-treatment biopsy samples is underway to quantify densities of immune cell subsets by digital image analysis (to be performed by Definiens).

ADVANCE trial of ChAdOx1-MVA 5T4 vaccine in combination with Nivolumab will commence in the summer 2018