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

I. Redchenko¹, F. Cappucci¹, E. Pollock¹, R. Bryant¹, L. Carter¹, C. Verrill¹, J. Hollidge¹, L. Goodwin², R. Harrop³, P. Romero⁴, S. Viganò⁴, T. Evans⁵, J. Catto⁵, 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 oncofoetal antigen 5T4 in early stage prostate cancer patients. The study arms are shown on the right.

Primary objectives:
- Safety and immunogenicity (ex vivo IFNγ 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
- Safety and immunogenicity
- Phenotype and functional profile of PBMCs
- T cell epitope mapping

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Study Results

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

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

Kinetics of vaccine-induce T cell response

Vaccination induces transient increase in serum PSA

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 vaccinated patients
- 5T4-specific CD4 and CD6 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

Illustrative patient VAN-010 results: ex vivo ELISPOT, flow cytometry of PBMCs and TILs, PSA kinetics and IHC

ST4-specific T-cell responses to vaccination measured by IFNy ELISPOT. Peak response, expressed as a number of the antigen-specific T cells secreting IFNy per one million of PBMCs, in each patient who mounted the ST4-specific T cell response following vaccination was compared to the ST4 response detected at baseline. Bars represent medians.

In the ELISPOT assay, the overlapping peptides spanning the entire ST4 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 ST4 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 ChAdOx5T4; B indicates boost with MVA5T4.

5T4-specific T-cell responses to vaccination measured by IFNy 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 ST4 peptide pools for 18 hours and and the numbers of the antigen-specific T cells secreting IFNy have been calculated per one million of PBMCs. The graphs represent an average number of ST4-specific T cells at each timepoint in two study arms.

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.

ST4-specific T cell response is detected ex vivo

ST4-specific CD8 T cells secreting IFNγ and TNF-α are expanded from the blood and prostate tissue

Level of serum PSA sub-forms is increased following vaccination

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

ST4-specific T cell response is detected ex vivo

VAN-010 was randomised to the accelerated regimen to receive the ChAdOx vaccine at week 0, MVA at week 1 and to undergo surgery at week 4. Blood samples were collected at each clinic visit for IFNy ELISPOT assay. The ST4-specific T cell response peaked one week after the boosting MVA5T4 immunisation.

PBMCs and prostate surgical specimens were cultured either in medium alone or in the presence of the total ST4 peptide pools to expand the relatively infrequent ST4-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 IFNy and TNF-α in response to ST4 peptide pool stimulation. Both samples were collected at week 4 on the study. R10-R10 denotes the ST4 antigen naïve T cells; 5T4-5T4 denotes the T cells expanded in the presence of ST4 peptide pool.

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.

Consecutive sections of the FFPE surgical specimen were stained for CD3, CD8, CD68 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 Definitions).