

## Appendix 2 Scientific Abstract

### Appendix M-I-A Requirements for Protocol Submission

TroVax is an immunotherapeutic vaccine, based on the modified vaccinia virus, Ankara (MVA), which is replication incompetent and encodes the oncofoetal antigen 5T4. TroVax is designed as an expression vector that can stimulate a potent immune response against the 5T4 antigen, when expressed on tumour cells. The vaccine is administered as an intramuscular injection, but is designed to have a short-term effect in the target cell. Briefly, the vector enters cells at the site of injection and expresses its own genes and the therapeutic gene, 5T4. Cellular protein synthesis is shut down, and expression of vector encoded 5T4 protein is initiated at very high levels, and the 5T4 antigen is expressed on the surface of the target cell. The surface expression in the context of MHC Class II presentation induces a potent immune response. However, the expression is transient and the target cell short lived.

MVA has an excellent safety profile and is a well- tested expression vector, that cannot replicate to produce infectious virus in any primary human cell type tested to date. 5T4 is a protein that is normally expressed at high levels in the placenta, specifically on trophoblasts and at low levels on a restricted number of non-essential normal tissues. Many human tumours express significant levels of 5T4 on the tumour cell surface and /or in the surrounding stroma. In colorectal and renal cancer the appearance of tumours bearing 5T4 is correlated with a poor prognosis and it is commonly found that metastatic tumours are positive for 5T4. Similarly, in separate studies we have shown high levels of 5T4 expression on the surface of prostate carcinoma cells, which indicates that prostate cancer should provide an appropriate target for immunotherapy with TroVax.

TroVax has demonstrated a good safety profile in both pre-clinical and clinical studies. To date, TroVax has been administered to > 90 patients with either colorectal or renal cancer at a dose of  $1 \times 10^9$ TCID<sub>50</sub>/ml ( $5 \times 10^8$ pfu/ml) and was found to be safe and well tolerated. Furthermore, the vaccine was shown to induce both humoral and cell mediated immune responses to the 5T4 antigen 2-8 weeks after the start of vaccination in the majority of patients treated.

The proposed trial will be of intra-muscular administrations of TroVax ( $5 \times 10^8$ pfu/ml dose strength) in men with androgen resistant prostate cancer, who have received at least one prior taxane chemotherapy or who has refused chemotherapy.. The main aims of the trial are summarised as follows:

#### Primary

- To assess the safety and tolerability of TroVax alone and in combination with GM-CSF
- To evaluate whether GM-CSF markedly increases the cellular or humoral anti-5T4 responses to TroVax

#### Secondary

- To evaluate the objective response frequency of TroVax alone and in combination with GM-CSF

Provided that the first two criteria are met in that TroVax is safe and induces immune responses in combination with GM-CSF, we will seek permission to undertake a larger randomised study to establish statistically significant data on clinical efficacy.