

## Scientific Abstract

**TRIST: An international, randomised double blind, placebo controlled, parallel group study to investigate whether TroVax<sup>®</sup> added to first-line standard of care therapy, prolongs the survival of patients with locally advanced or metastatic renal clear cell adenocarcinoma**

TroVax<sup>®</sup> is a cancer vaccine derived from a replication incompetent vaccinia virus called modified vaccinia Ankara (MVA), that was developed as a safe vaccine for smallpox. The expression vector is designed to deliver a human gene encoding the 5T4 oncofoetal antigen. Poxvirus vaccines work by entering human cells, expressing genes that are processed via the antigen presentation system and then killing the cell to release the cocktail of expressed proteins (cytolysis). In the case of MVA only the initial cells that take up the vector are killed, the cytolytic effect does not spread because the vector cannot replicate. The damage to the cells is essential to generating a strong immune response and is thought to be the reason for the potency of this class of vectors.

A cancer vaccine, such as TroVax is intended to prolong survival by inducing an immune response to a tumour associated antigen (5T4). Preclinical models indicate that cancer vaccines may delay tumour growth and reduce the number of new metastases. It is not yet known whether a cancer vaccine must produce a high objective tumour response rate (by RECIST) in order to have clinically useful effect on prolonging survival. This will only be determined by a randomised survival study in patients receiving adequate vaccination to reliably induce an efficacious immune response. To date, both disease stabilisation and late tumour responses have been reported with various cancer vaccines. Several Phase I/II clinical studies have demonstrated that patients with advanced stage disease including renal cancer can be immunized against specific targeted tumor antigens such as 5T4 and thus, generate an immune response against their tumor. In these studies induction of a measurable vaccine-specific DTH response, a well characterized in vivo surrogate of systemic antigen-specific immunologic memory and/or T cell responsiveness was associated with a trend toward improved clinical response. To date, TroVax has been administered to >100 patients receiving a total of > 400 doses and has been shown to be safe and well tolerated at all doses, with no serious adverse events being reported as related to the vaccine.

Thus, it appears that vaccination offers a potential therapeutic strategy to prevent the relapse of disease by establishing an effective memory response targeting specific cancer antigens.

The proposed study is a Phase III trial planned in patients with metastatic renal cancer. It is an international, randomised, double blind, placebo controlled, parallel group study to investigate whether a minimum of three doses of TroVax<sup>®</sup> added to first-line standard of care therapy prolongs the survival of patients with locally advanced or metastatic renal clear cell adenocarcinoma.

The primary endpoint is survival. The study is designed to be pragmatic, limiting additional study related investigations to a minimum. Protocol mandated scans and X-rays are limited to two time points (baseline and week 26) to permit comparison of the percentage of patients with progressive disease at 6 months as a secondary efficacy endpoint. This period was selected based on a review of the published literature which indicated that progressive disease was commonly observed by 26 weeks in patients with renal cancer. Endpoints such as tumour response by RECIST are considered of secondary importance to survival and will be determined by radiological examinations ordered at the discretion of the investigator based on

the clinical status of the patient and will be based the interpretation of the patient's care-team (investigator and local radiologist).

Patients will be assigned by the investigator (their physician) to one of the following defined first-line standard of care regimens:

1. subcutaneous low dose IL-2
2. interferon-a (excluding pegylated IFN $\alpha$ )
3. sunitinib

Randomisation to TroVax<sup>®</sup> or placebo will be stratified based on the standard of care chosen by the investigator, study prognostic indicators (Motzer score) and geography.

TroVax<sup>®</sup> is administered at a dose of  $1 \times 10^9$  TCID<sub>50</sub>/ml in 1ml by injection into the deltoid muscle of the upper arm at regular intervals up to 8 weeks apart up to a maximum of 13 doses.

An independent Data Safety Monitoring Board (DSMB) will be responsible for preparing the formal monitoring rules for this study. This parallel-designed study contains a series of planned interim assessments for futility, and to ensure that the planning elements relative to attrition and the primary endpoint remain consistent. A frequentist monitoring approach will be used for evaluating the event rate ratio to ensure that the assumptions are accurate and the sample size continues to be appropriate for assessing superiority. The DSMB may recommend changes to the enrollment target if pretrial assumptions prove inaccurate.