

RAC APPENDIX M TEMPLATE

REQUIREMENTS FOR PROTOCOL SUBMISSION, REVIEW AND REPORTING -HUMAN GENE TRANSFER EXPERIMENTS

M.I.A. Requirements for Protocol Submission

Scientific abstract

OncoVEX^{GM-CSF} is a selectively replication competent herpes simplex type-1 virus (HSV1) for the treatment of solid tumours by intra-tumoural injection. The virus selectively replicates in tumours while sparing normal tissue – i.e. it is “oncolytic”. The virus also expresses the gene for human granulocyte macrophage colony stimulating factor (hGM-CSF), a cytokine involved in the stimulation of T-cells intended to boost the immune response to tumour associated antigens released following oncolytic virus replication. The aim is therefore to treat locally injected tumours by a combination of oncolytic and immune effects, and to treat metastatic disease through the generation of an anti-tumour immune response.

There has been considerable previous clinical work with oncolytic viruses including versions of adenovirus and HSV. In all cases a good safety profile has been seen, and in some cases there has been evidence of a therapeutic effect. HSV has advantages over other viruses which might be used for oncolytic therapy in that it is able to infect a wide variety of cell types, has a rapid replication cycle resulting in cell lysis, has the capacity to deliver single or multiple transgenes which may improve the oncolytic anti-tumour effect and is relatively easy to produce to high titre in quantities sufficient for clinical use.

OncoVEX^{GM-CSF} aims to build on the promising previous clinical work with oncolytic viruses, including with HSV, to combine the potential benefits of oncolytic tumour therapy with those of anti-tumour vaccines which similarly in a number of cases have given evidence of a beneficial clinical effect. In this regard, tumour cells engineered to secrete GM-CSF have given particular promise when used for vaccination, hence the inclusion of GM-CSF in OncoVEX^{GM-CSF}.

OncoVEX^{GM-CSF} was constructed using a new strain of HSV1 (strain JS1; ECACC Accession Number 01010209) and has been fully sequenced. To produce OncoVEX^{GM-CSF} two previously well characterized gene deletions were introduced into the virus. The first deletion is that of the gene encoding ICP34.5, the so-called neurovirulence factor. Deletion of ICP34.5 provides the greatest attenuation of any HSV gene which still allows the virus to replicate in culture and renders the virus non-pathogenic. The function of ICP34.5, and the properties of ICP34.5 deletion mutants, have been the subject of many studies and therefore considerable literature is available supporting this point. As well as generating a non-pathogenic virus, deletion of ICP34.5 provides the property of tumour selective replication, i.e. as required for an oncolytic virus. The second deletion is that of the gene encoding ICP47. Deletion of ICP47 alone has again been shown to render HSV non-pathogenic, and so OncoVEX^{GM-CSF} contains two separate mutations which individually attenuate the virus. The role of ICP47 is to block antigen presentation to MHC class I and II molecules by blocking the transporters associated with antigen processing (TAP1 and TAP2). As the intention is to generate an anti-tumour immune response following injection of OncoVEX^{GM-CSF}, this deletion would be anticipated to be beneficial in maximizing such an effect. The deletion of ICP47 also allows the increased expression of the HSV US11 gene. It has been shown previously that such

increased expression boosts the replication of ICP34.5 deleted HSV in tumour cells without affecting the level of attenuation of the virus and tumour selectivity. The gene for human GM-CSF expression is inserted so as to completely replace the coding sequences for ICP34.5 and is under the control of the human cytomegalovirus immediate early promoter (hCMV IE). The construction of OncoVEX^{GM-CSF} is described in Lui et al. 2003¹.

BioVex has conducted an extensive pre-clinical program with OncoVEX^{GM-CSF} showing it to have properties typical of an ICP34.5 deleted version of HSV. This includes multiple dose toxicology and bio-distribution in rodents and efficacy studies showing the improved anti-tumour properties of the product, including the protection of previously treated animals from tumour cell re-challenge.¹

Previous oncolytic versions of HSV have been tested in clinical studies in both the UK and the US. As indicated above, these have demonstrated a good safety profile when used for direct intra-tumoral injection in glioma patients (UK and US) or melanoma patients (UK), or by hepatic artery infusion in liver cancer patients in the US. In addition, BioVex has conducted a Phase I clinical trial with OncoVEX^{GM-CSF} in the UK in 30 patients where cutaneous or sub-cutaneous deposits of a number of tumour types (mainly breast cancer, melanoma and head and neck cancer) were injected with single or multiple doses of OncoVEX^{GM-CSF}. A good safety profile was seen, combined with evidence of an anti-tumour effect. This trial informed an approach to dosing in which a low dose of virus is used to seroconvert and render seronegative patients tolerant of the virus before escalation of the dose to potentially therapeutic levels.

Two phase II studies with OncoVEX have just commenced dosing. In the United States an OncoVEX trial in melanoma (OncoVEX^{GM-CSF}/002/03) is underway after approval from RAC and the FDA and in Britain an OncoVEX trial in head and neck cancer (OncoVEX^{GM-CSF}/004/04) in combination with both radiotherapy and chemotherapy is underway after approval from GTAC and the MHRA.

Following on from the Phase I study described above, the current proposal describes a Phase I/II study in up to 18 evaluable patients with locally advanced or metastatic adenocarcinoma of the pancreas. Four dosing regimens will be tested. Each dosing regimen involves the administration of 3 consecutive doses of OncoVEX^{GM-CSF} separated by a period of 3 weeks. OncoVEX^{GM-CSF} will be administered by direct injection into the tumour using endoscopic ultrasound guided (EUS) fine needle injection (FNI). Patients will be observed for safety, tolerability and for evidence of efficacy primarily by assessing tumour response, survival time and pain relief. This is an open label upward titration study and will be conducted at a small number of selected sites within the US and possibly the EU.

¹ Lui BL, Robinson M, Han ZQ, Branston RH, English C, Reay P, McGrath Y, Thomas SK, Thornton M, Bullock P, Love CA, Coffin RS *Gene Ther.* 2003 Feb;10(4):292-303 ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties