SCIENTIFIC ABSTRACT

Background and Rationale

The primary objective of this trial is to evaluate the safety of multiple courses of intratumoral injection of VCL-IM01 followed by electroporation in subjects with recurrent metastatic melanoma.

The VCL-IM01 product consists of the human IL-2-expressing pDNA VCL-1102 in phosphate-buffered saline (PBS). VCL-IM01 has been intralesionally administered to metastatic melanoma subjects followed by electroporation using the MedPulser® System. VCL-1102 has previously been administered intralesionally to cancer subjects as a pDNA/cationic lipid formulation (Leuvectin®) that was found to be safe and free of systemic toxicity.[1,2] The MedPulser® System has been tested clinically in the U.S. for intralesional administration of the chemotherapeutic agent bleomycin and was well-tolerated with minimal side effects.[3,4]

Electroporation enhances the delivery of pDNA to tumors[5] and enhances antitumor activity.[6] Preclinical studies performed at Vical have demonstrated 60% tumor regression following treatment of established murine tumors with IL-2 pDNA and electroporation (see response to question **II-B-2-b-(3), Appendix M**).

Recombinant IL-2 (i.e., Proleukin®) is an approved therapy for metastatic melanoma and can elicit durable clinical responses.[7] However, systemic administration of Proleukin® is associated with severe toxicities that limit its use and necessitate hospitalization. The proposed research seeks to determine if intralesionally administeredVCL-IM01 followed by electroporation will provide a safer therapy for treatment of metastatic melanoma.

For the IM01-101 trial, a standard half log dose-escalation format is being used to define either the maximum tolerated dose (MTD) or the highest achievable dose. Subjects start their treatment on this trial at the dose at which they completed the prior IM01-101 trial. The investigator will have the option to escalate the dose to the highest tolerated dose evaluated for safety on the IM01-101 trial. Dose escalations should be completed on a cycle-by-cycle stepwise fashion until the highest dose is reached. For example, if a subject enters this trial at the 0.5 mg dose and the highest tolerated dose is the 5.0 mg dose, the subject would receive the 0.5 mg dose for the first cycle and the 1.5 mg dose for the second cycle. Assuming the subject completes the treatment course and is eligible to continue on one more course of treatment, the 5.0 mg dose would be given for the next treatment course.

The investigator should contact Vical to confirm initial dose assignment and prior to potential dose changes.

Subjects will be allowed to undergo one dose de-escalation, if required. If a second dose de-escalation is required (e.g., secondary to an adverse event), the subject should be withdrawn from treatment.

1 Figlin R, Parker S, Horton H. Technology evaluation: interleukin-2 gene therapy for the treatment of renal cell carcinoma. Curr Opin Mol Ther 1999; 1:271-78.

2 Hoffman DMJ, Figlin RA. Intratumoral interleukin 2 for renal-cell carcinoma by direct gene transfer of a plasmid DNA/DMRIE/DOPE lipid complex. World J Urol 2000; 18:152-56.

3 Orr R. Technology evaluation: electroporation therapy, Genetronics Inc. Curr Opin Mol Ther 2000;2:205-10.

4 Hoffman G, Dev S, Dimmer S, Nanda GS. Electroporation therapy: a new approach for treatment of head-and-neck cancer. IEEE Trans Biomed Eng 1999; 46:752-59.

5 Lohr F, Lo DY, Zaharoff DA, Hu K, Zhang X, Li C-Y, et al. Effective tumor therapy with plasmid-encoded cytokines combined with *in vivo* electroporation. Cancer Res 2001 Apr 15; 61:3281-84.

6 Heller R. Delivery of plasmid DNA using *in vivo* electroporation. Preclinica 2003 Oct; 1 (4):198-208.

7 Tsao H, Atkins M, Sober A. Management of cutaneous melanoma. New Engl J Med 2004; 351:998-1012.