

## 4. INTRODUCTION

### 4.1 Investigational Plan

Vical Inc. proposes a Phase II protocol to assess safety and efficacy of Leuvectin administration in patients with metastatic renal cell carcinoma. This treatment is intended to stimulate an immune response by expressing Interleukin-2 within the tumor, while limiting systemic side effects of the protein.

### 4.2 Overview

Renal cell carcinoma accounts for about 85% of all kidney tumors, and approximately 3% of all adult cancers (1,2). In 1999, the American Cancer Society estimates that there will be about 30,000 new cases of kidney cancer (17,800 in men and 12,200 in women) in the United States and about 11,900 deaths (7,200 men and 4,700 women) (2). The worldwide incidence of renal cell carcinoma is expected to exceed 150,000 in the year 1999 (3). Renal cell carcinoma is curable only in patients presenting with resectable, early stage disease; however, nearly one-third of patients present with metastatic disease and as many as 40% of all patients treated for local tumors will ultimately relapse with metastatic disease (4,5). The prognosis of untreated patients with metastatic disease is very poor, with a 3-year survival rate of less than 5% (6).

Immunotherapy is the only pharmacologic approach that has produced marginal results in metastatic renal cell carcinoma (3). The goal of immunotherapy is to stimulate the immune system to recognize and kill cancer cells. This may be achieved by modifying either the tumor cells or the host response causing various lymphocyte populations, particularly cytotoxic T lymphocytes (CTLs), to respond specifically to tumor cell antigens. Cancers such as renal cell carcinoma are sometimes responsive to immunotherapy because the immune system can be induced to recognize tumor-associated and tumor-specific antigens in these cells.

In some instances, the immune system appears to contribute to the surveillance and destruction of neoplastic cells by mobilization of either cellular or humoral immune effectors. Cellular mediators of antitumor activity include MHC-restricted cytotoxic T cells (CTLs), natural killer (NK) cells (7, 8) and lymphokine-activated killer (LAK) cells (9). Cytokines participate in the antitumor response by direct action on cell growth or by activating cellular immunity. IL-2 causes replication of antigen-stimulated CTLs (10). IL-2 also stimulates the growth of lymphokine-activating killer (LAK) cells and natural killer (NK) cells, as well as cytokines such as interferon- $\gamma$  (IFN- $\gamma$ ), which are tumoricidal at the site of metastases (3). LAK cells are capable of lysing autologous, syngeneic or allogeneic tumor cells but not normal cells (9, 11, 12). The LAK cells lyse tumor cells without preimmunization or MHC restriction (13). Systemic administration of IL-2 alone, or IL-2 with LAK cells has been shown to upregulate the immune system resulting in tumor regression; however, significant side effects result as well (14).

Recombinant interleukin-2 (rIL-2) is currently the only immunotherapeutic agent approved by the FDA for treatment of renal cell carcinoma in the United States (15). Cumulative experience with high-dose IV bolus rIL-2 regimens has demonstrated approximately a 15% objective response rate (complete and partial responses). The majority of the complete responses are durable for 3 or more years, significantly improving long-term survival (15).

### 4.3 Leuvectin

Scientists at Vical Inc. have developed a direct gene transfer method to transfect tumor cells with genes encoding immunomodulating proteins. The Vical approach introduces the recombinant gene encoding the IL-2 protein directly into malignant tumor cells *in vivo*, which eliminates the need to establish cell lines from each patient and minimizes delays in the time to treatment. Additionally, no viral vectors are contained in the formulation. The product, Leuvectin, is composed of plasmid DNA coding for IL-2 (VCL-1102) formulated in an injection vehicle with DMRJE/DOPE, a proprietary cationic lipid mixture (cytofectin). When introduced into the target tumor, the lipid facilitates transfection of the tumor cells. The IL-2 gene product is expressed and secreted at the tumor site. By local expression of cytokines at the site of the tumor, it is expected that lower levels of cytokine will be required for efficacy as compared to systemic administration. It is expected that these levels would be sufficiently low to avoid producing toxicity in the patient, but would be adequate to generate an antitumor response by stimulating the immune response.

In developing Leuvectin, Vical conducted pharmacology and toxicology studies to: 1) demonstrate that the plasmid/lipid complex results in transfection and the plasmid produces biologically active IL-2 protein in tumors, 2) demonstrate that VCL-1102 reduces tumor burden in a mouse tumor model, and 3) explore the effect of injecting the plasmid directly into normal mouse liver. Results of the studies showed that: 1) the IL-2 plasmid/lipid formulation produced a high level of IL-2 protein expression in injected tumors, 2) the direct intratumoral injection of a plasmid DNA expression vector encoding the human IL-2 gene into subcutaneous B16 melanoma or renal cell carcinoma tumors in mice significantly slowed tumor growth and reduced the incidence of palpable tumors, and 3) intrahepatic administration of Leuvectin in mice was well tolerated and there were no adverse effects associated with the drug; adverse effects that occurred were attributed to the injection procedure and not considered to be of biological significance. Details of these pharmacology and toxicology studies are contained in the Investigator's Brochure.