

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

The incidence of renal cell carcinoma has increased 54% from 1975 to 1990. In 1996, approximately 30,000 new cases were diagnosed in the United States (1). In the same year, an estimated 12,000 renal cell carcinoma-related deaths occurred in the United States (2). Nearly half of all renal cell carcinoma patients present with localized disease, one-quarter present with stage II disease, and nearly one-third of patients present with metastatic disease (1). In addition, as many as 40% of all patients treated for local tumors will ultimately relapse with metastatic disease (3). The prognosis of untreated patients with metastatic disease is very poor, with a 3-year survival rate of less than 5% (4).

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 (5). Cumulative experience with high-dose IV bolus rIL-2 regimens has demonstrated approximately a 15% objective response rate (complete and partial responses) (5). The majority of the complete responses are durable for 3 or more years, significantly improving long-term survival (5).

Immunotherapy has shown promise as an approach to the treatment of malignancy. 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 (6, 7) and lymphokine-activated killer (LAK) cells (8). Cytotoxic T cells which infiltrate tumors have been isolated and characterized (9). These tumor infiltrating lymphocytes (TIL) selectively lyse cells of the tumors from which they have been derived (10,11). Macrophages can also kill neoplastic cells

through antibody-dependent mechanisms (12,13), or by activation induced by substances such as Bacillus Calmette-Guerin (BCG) (14).

Cytokines also participate in the antitumor response by direct action on cell growth or by activating cellular immunity. The cytostatic effects of tumor necrosis factor- α (TNF- α), interferon- α (IFN- α), interferon- γ (IFN- γ) and lymphotoxin can result in neoplastic cell death (15,16). Interferon- γ markedly increases class I and II MHC cell surface expression (17,18) and synergizes with TNF- α in producing this effect (19). Colony stimulating factors such as G-CSF and GM-CSF activate neutrophils and macrophages to lyse tumor cells directly (20), and interleukin-2 (IL-2) activates Leu-19+ NK cells to generate lymphokine activated killer cells (LAK) capable of lysing autologous, syngeneic or allogeneic tumor cells but not normal cells (8, 21, 22). The LAK cells lyse tumor cells without preimmunization or MHC restriction (23). Interleukin-4 (IL-4) also generates LAK cells and acts synergistically with IL-2 in the generation of tumor-specific killer cells (24).

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 (25). Recently, several studies have examined the tumor suppressive effect of lymphokine production by genetically altered tumor cells.