

4. INTRODUCTION

4.1 Investigational Plan

Vical Inc. proposes a Phase I/II protocol to assess safety and efficacy of Leuvectin administration in patients with evidence of locally recurring prostate cancer following external beam radiation, radiation seed implants, or cryosurgery. It is postulated that the enhanced anti-tumor effect generated by treatment may prevent or delay the cancer spread. It is possible that locally activated anti-tumor lymphocytes will gain access to the circulation, and that these activated immune cells will detect and destroy micrometastases that otherwise would have escaped immune surveillance. This study is intended to provide a database to assess PSA values and slopes over time as impacted by the treatment as well as clinical manifestations. This database may constitute the rationale for the design of adequately powered, controlled, randomized future studies of Leuvectin in this patient population.

4.2 Overview

Prostate cancer is the most commonly diagnosed cancer, and the second leading cause of cancer-related death among men in the United States (1). The American Cancer Society estimates that in 1998, over 39,200 men will die from prostate cancer, and another 184,500 will be diagnosed with prostate cancer (2). With the advent of serum prostate-specific antigen (PSA) testing in 1988, and increased public awareness, the rate of diagnosis for prostate cancer has dramatically increased during the last decade (3). Earlier detection has resulted in a significant stage migration toward clinically organ-confined disease (3). Presently, approximately 60% of men newly diagnosed with prostate cancer are believed to have organ-confined disease (4). Despite this stage migration, approximately 40-60% of patients are found to have pathologically detected extracapsular disease after examination of prostatectomy specimens (5). Approximately 20-40% of patients treated with a radical prostatectomy or radiation eventually have disease progression. For this population, there is no curative treatment (6). The treatment options available to patients who have failed definitive radiation therapy are limited. Cryotherapy and salvage prostatectomy offer potential cures for select patients; however, they are associated with low cure rates and high complication rates.

Studies have shown that biochemical failure as determined by post-treatment PSA measurements, correlates with the development of clinically measurable disease for patients with prostate cancer treated with external beam radiation (7). Clinically significant differences have been seen in the 5-year actuarial rates of clinical local control, disease-free survival, distant metastases free survival, and cause-specific survival in patients that have been biochemically controlled, versus patients that have failed biochemically (7). Additionally, it has been demonstrated that biochemical control is the single most important predictor of outcome for disease-free survival, and distant metastases free survival (7).

For most patients who have rising PSA levels following radiation treatment, the only active treatment option is anti-androgen therapy to slow the rate of cancer growth and to palliate symptoms; however, this treatment has not been proven to prolong survival, and experts disagree as to when the treatment should be initiated. "Watchful waiting" without further immediate treatment, is often an appropriate option for men who are found to have less aggressive tumors, have a life expectancy of less than 10 years, are older than 70, have significant co-existing illnesses, or prefer the risk of disease progression to the risks associated with the more aggressive therapies.

Cytokine treatment has been shown to effectively alter several prostate cancer properties closely associated with tumor invasion and a metastatic phenotype (8). IL-2 has been shown to have the greatest bioactivity of all the cytokines studied so far. IL-2 can stimulate cytotoxic T cell reactions against tumors, and has shown a mild to moderate growth inhibition to prostate cancer cells (8). However, systemic treatment with IL-2 does not allow for adequate levels within the tumor without dose-limiting toxicities, and intralesional IL-2 protein therapy is limited by a short half-life and rapid renal clearance. Gene-based therapy offers a different approach to treating prostate cancer. Gene-based therapy with IL-2 potentially allows for a steady IL-2 production within the tumor, allowing for prolonged, elevated cytokine levels, while minimizing the side effects seen in patients who receive systemic therapy.