

1.0 INTRODUCTION

Vical Inc. is currently conducting a multicenter, Phase II trial with Allovectin-7 in patients with metastatic disease in five tumor types: melanoma, non-Hodgkin's lymphoma, breast adenocarcinoma, renal cell carcinoma and colorectal adenocarcinoma. Allovectin-7 is a plasmid DNA agent encoding both the heavy and light chains of the class I MHC (major histocompatibility complex) antigen, HLA-B7, formulated with a cationic lipid mixture. The agent is administered intralesionally in HLA-B7 negative patients. The rationale for the Phase II trial was developed from the preclinical and Phase I/II clinical observations indicating that gene transfer and gene product expression inducing a cell-mediated immune response could be safely and reproducibly accomplished (1). Clinical benefit was observed in several patients with advanced melanoma in the Phase I/II trials. Allovectin-7's product concept is based on the observation that tumor cells often lose their ability to present cell surface HLA antigens due to quantitative or qualitative deficiencies in MHC class I expression (2). Gene transfer of HLA-B7 to tumor cells represents a form of "substitution therapy" to restore deficient antigen expression and induce an antitumor immune response. HLA-B7 was chosen because it is a relatively infrequent haplotype and an allogeneic immune response would be triggered independently of tumor antigens in HLA-B7 negative patients.

In parallel with the U.S. Phase I/II clinical trials, Dr. Hulbert Silver at the British Columbia Cancer Agency evaluated the administration of Allovectin-7 in seven patients with advanced melanoma without pre-selecting the HLA haplotype. Three of the seven treated patients were HLA-B7 positive. A significant tumor response was observed in three patients. Two of the responses qualified as partial, clinical remissions. Intriguingly, two of the three responders were HLA-B7 positive. This observation raises the possibility that Allovectin-7 may be an active immunotherapeutic irrespective of the allogeneic immune activation. This corresponds with preclinical animal models that show an inverse relationship between tumor aggressivity and MHC class I expression (3). To further explore this possibility, Vical is proposing an additional, Phase II protocol to determine the safety and efficacy of Allovectin-7 in both HLA-B7 positive and negative melanoma patients. The study design is similar to the ongoing Phase II protocol except for the dosing regimen which parallels the study conducted by Dr. Silver at the British Columbia Cancer Agency.

2.0 BACKGROUND AND RATIONALE

2.1 Overview

The management of malignant melanoma remains unsatisfactory. Of greater concern is the fact that in recent years the incidence of malignant melanoma has been doubling approximately every ten years (4). Although relatively low risk, "thin" lesions have a

higher rate of cure with limited surgical margins, the optimal surgical management for high risk, "thick" melanomas remains unclear. Even with generous surgical margins and regional lymphadenectomy, many lesions will recur (5,6). Levamisole may be useful as a surgical adjuvant, but this is not universally accepted. High dose interferon α can reduce recurrence in Stage I and II melanoma by about 40%, but it is highly toxic and difficult to administer (7). There is continuing effort to identify other approaches, such as immunotherapy, that might lend themselves to adjuvant use.

Dimethyl triazeno imidazole carboxamide (DTIC) is the best, single chemotherapy agent with a response rate in systemic, metastatic disease of about 20% (8). Significantly increased response rates can be expected by newer combination programs such as tamoxifen, BCNU, cis-platinum and DTIC (9), but this is at the cost of increased toxicity. There is no consensus on second line treatment and no treatment after front-line therapy for Stage III and IV disease has been shown to be effective. At this point, consideration is often given to the use of cytokines or other experimental approaches.

The role of the immune system in malignant melanoma has been an area of intense interest. Melanoma antigens have been well studied in the past, as has evidence of a host immune response (9-11). Agents that can stimulate non-HLA-restricted cellular cytotoxicity, such as interferons and interleukin-2, have produced sustained regressions in some patients (12).

It is now possible to trigger an immune response through gene transfer. Numerous models have been developed and have led to several clinical trials exploring the possibility of manipulating either tumor cells or host lymphocytes transfected with a variety of cytokine genes (13). Other specific gene therapy strategies have sought to directly influence the interaction between immunocyte and antigen presenting cell by enhancement of HLA-restricted immunity.