

Phase II Study of Metastatic Cancer that Overexpresses p53 using Lymphodepleting Conditioning Followed by Infusion of Anti-p53 TCR-Gene Engineered Lymphocytes

Principal Investigator: Steven A. Rosenberg, M.D., Ph. D., Chief, Surgery Branch, NCI

M-I-A.3. Non-Technical Abstract:

This study will be performed in patients who have metastatic cancer with tumors that overexpress a normal gene called p53. Patients with metastatic renal cell cancer and melanoma will be in one group for analysis and patients with other tumor types will be in another group for analysis. Up to 41 patients will be enrolled in each group. The main purpose of this research study is to determine whether lymphocyte cells that we take from patients' blood, introduce genetic material called anti-cancer protein T-cell receptor retroviral vector (called anti-p53 TCR) and grow in the laboratory, and then give back to the patient, will improve the ability to fight the patients' cancer when we suppress their immune system from attacking these special tumor fighting cells. Patients will be given a p53 peptide immunization and interleukin-2 after the cell administration. The secondary objectives of this study are to determine the survival of infused cells that have been genetically engineered and to determine the toxicity of the treatment.

Initially patients will have lymphocytes harvested through leukapheresis. The lymphocytes will be grown in the laboratory. During the procedure to grow the cells in the laboratory, a piece of genetic material, the anti-cancer protein (p53) T-cell receptor (TCR) will be put into the cells using a process called "retroviral transduction". The retrovirus is made from a virus that has been inactivated or changed in a way that prevents it from reproducing and causing any type of illness. It serves only as a vehicle to deliver the anti-cancer protein TCR into the cells.

Once the cells are grown in the laboratory and the gene inserted, patients will be given chemotherapy, (cyclophosphamide and fludarabine) for seven days to suppress the immune system. On the eighth day, they will be given two injections of the p53 peptide, emulsified in an immune-stimulating adjuvant, Montanide ISA-51, in an effort to increase the immune response. These injections will be repeated for a total of five days

and then weekly for 3 more injections for a total of eight days of injections. Also on the eighth day, all patients will be given the cells intravenously, over 20-30 minutes, followed within 24 hours with intravenous Interleukin 2 (IL-2, a hormone that stimulates lymphocyte growth) at 720,000 IU/kg every 8 hours for up to 15 doses, depending on patient tolerance. Patients will be given appropriate medications to treat the side effects of this treatment regimen and to prevent infection secondary to the immune suppression caused by the chemotherapy.

Patients will return to NIH after four to six weeks to have their tumor(s) evaluated. If there is shrinkage of their tumor(s), the cell infusion will be repeated. If there is no response, patients will be taken off this study. In patients who are responding, up to one retreatment course may be given.