

M-I (1) Scientific Abstract. Each year, primary carcinoma of the lung affects more than 170,000 individuals in the United States, making it the leading cause of cancer death for both men and women. Histologically and biologically, lung cancer has been divided into 2 groups: small cell (20%) and non-small cell (80%). Non-small cell lung cancer (NSCLC) is a major health problem, with only slow advances in therapy over several decades. This phase I clinical study is directed towards augmenting host anti-tumor immunity by using gene transfer to activate dendritic cells (DC: cells of our immune system that play a central role in initiating immune responses) hosted by tumors in individuals with lung cancer. Based on extensive animal studies, this clinical study will evaluate the concept that transient modification of the genetic composition of tumors to express CD40 Ligand (CD40L; a potent activator of DC) will activate DC within the tumor, and the interaction of DC with tumor antigens will induce trafficking of activated DC to lymph nodes, with induction of tumor-specific immunity. To assess this concept, an adenovirus vector (Ad_{CU}CD40L) will be used to transfer and transiently express the human CD40L cDNA in tumors of individuals with NSCLC. The vector is an E1a-, partial E1b-, E3-adenovirus gene transfer vector expressing CD40 ligand under cytomegalovirus early/intermediate promoter/enhancer. The study will be carried out in two phases. First 12 individuals with inoperable stage IIIb or IV NSCLC will be used to assess safety/toxicity with ascending doses of the Ad_{CU}CD40L vector. Second, once the safety profile is determined, part B will assess the administration of the highest non-toxic dose (as identified in part A) of Ad_{CU}CD40L vector (or a placebo, in a randomized, blinded fashion) to stage I NSCLC tumors. A total of 20 individuals will be evaluated in part B with surgery for removal of the primary tumor 1, 3, 6 or 10 days after administration of the vector (n=5/timepoint, including n=4 receiving the Ad_{CU}DC40L vector and n=1 receiving placebo). There is no evidence that delay of surgery for solid tumors for 10 days following diagnosis alters the prognosis. Following administration of the vector into the lung tumor and its surgical removal, there will be an assessment of apoptosis, immunohistochemistry and the cytokine mRNA. At the conclusion of the study, the following objectives will be met: (1) to assess the hypothesis that it is safe to administer the Ad_{CU}CD40L vector to lung tumors; (2) to evaluate the hypothesis that intratumoral administration of the Ad_{CU}CD40L vector will result in the activation of DC in the tumor and accumulation of DC and other relevant immune cells in the tumor and regional lymph nodes, with the induction of tumor-specific immunity.