

Scientific Abstract

This phase I study is an open-label, multi-center, dose comparison trial of a multi-component immune based therapy, MKC1106-PP, consisting of a single dose of the DNA plasmid vector PRAME/PSMA (pPRA-PSM) with one dose each of the synthetic peptides PRAME (E-PRA) and PSMA (E-PSM), for the treatment of advanced solid malignancies. PRAME and PSMA are tumor-associated antigens. PRAME is preferentially expressed by melanoma and many carcinomas including lung, breast, ovarian, pancreatic, and colorectal. PSMA is expressed by prostate carcinoma, and by the vascular endothelium of a broad range of other solid tumors. The study's prime-boost treatment regimen is designed to stimulate anti-PRAME and PSMA immune responses in subjects with PRAME and PSMA expressing solid tumors. The primary objective of this study is to determine the immunologic response of subjects to pPRA-PSM plasmid DNA priming followed by peptide boosting, as measured by changes in the frequency of PRAME and PSMA specific T-lymphocytes following treatment. The secondary objectives are to determine the safety and adverse events profile of the MKC 1106-PP regimen, the blood levels of pPRA-PSM plasmid, the effects of MKC 1106-PP on circulating cytokine levels, and the objective response on tumor progression. The hypothesis of this trial is that MKC 1106-PP vaccination will generate anti-tumor responses in subjects with advanced PRAME and PSMA expressing tumors, and that the regimen will be safe and tolerable.

The population to be treated by the MKC1106-PP vaccine will include 24 subjects with advanced carcinoma or stage IV melanoma without brain metastases, whose diseases have failed standard therapy. Subjects must be HLA-A2 positive, as the epitopes encoded by the plasmid are restricted to HLA-A2, and tumors must express PRAME and PSMA. Eligible HLA-A2 positive patients will have a staging workup with CT scans of chest, abdomen, and pelvis to determine the extent of disease prior to initiation of study treatment.

The vaccine components will be administered separately to superficial inguinal lymph nodes by an ultrasound guided echogenic needle. All subjects will receive 1200 µg of the plasmid pPRA-PSM bilaterally on Days 1, 4, 15, and 18 of the treatment cycle. Subsequently, E-PRA and E-PSM peptides will be injected unilaterally on Days 29 and 32, with 12 subjects receiving low doses of peptides (30 µg each of E-PRA and E-PSM), and 12 receiving high doses (300 µg of each peptide). The treatment cycle will span 39 days, and successive cycles will be separated by 4 days. It is planned that all subjects will receive 2 cycles of therapy. Thereafter, patients whose disease has not progressed after 2 treatment cycles will be permitted to undergo 4 additional treatment cycles. The primary immunologic endpoint, i.e., changes in the frequency of PRAME and PSMA specific cytotoxic T-lymphocytes will be evaluated on Days 29 and 39 of each treatment cycle, using Tetramer and ELISPOT assays. Cytokine levels will be measured on Day 39. The extent of disease will be assessed on Day 39 of every other treatment cycle. Objective treatment response will be measured according to the RECIST method. Vital signs, clinical laboratory functions, and adverse events will be monitored throughout each treatment cycle.

Although assessment of the pPRA-PSM plasmid and E-PRA and E-PSM peptides in animal studies found little significant toxicity, treated subjects will be monitored closely for potential toxicities. Evaluation of previous vaccination approaches with peptides, tumor lysates, or peptide-pulsed dendritic cells delivered intranodally in subjects with metastatic melanoma, have reported no mortalities or life threatening adverse effects. Toxicities reported with parenteral administration of DNA vaccines include transient headache, fever, weakness, arthralgias, and rash. It is possible that vaccination of subjects with MKC1106-PP may result in vitiligo skin changes, as the PRAME antigen may be expressed on melanocytes; or prostatitis, since PSMA is expressed on normal prostate epithelial cells. Non-specific autoimmune manifestations such as arthritis, arthralgia, kidney or liver dysfunction, fatigue, or rash may occur. There may also be temporary infection, pain, bleeding, or edema of lymph nodes at the injection site, although these effects should be minimal with ultrasound guided echogenic needle administration. Though unlikely, more rapid tumor growth may occur, resulting from the development of immune tolerance to tumor antigens.