A Phase 1a/1b Study of FPA008 in Combination with Nivolumab in Patients with Selected Advanced Cancers

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Introduction: Tumor-associated macrophages (TAMs) are a major cellular component of human tumors, and actively suppress anti-tumor immune responses. Colony stimulating factor 1 receptor (CSF1R) signaling plays a major role in the differentiation and survival of TAMs. Programmed cell death 1 (PD-1) is expressed on exhausted lymphocytes in the tumor, and delivers a negative signal to suppress lymphocyte activation. FPA008 is a humanized IgG4 monoclonal antibody that binds to human CSF1R, and blocks the ability of IL34 and CSF1 to activate CSF1R expressed on macrophages. Nivolumab is a fully-human lgG4 PD-1 immune checkpoint inhibitor that blocks the interaction of PD-1 with its ligands (PD-L1 and PD-L2), thereby inhibiting the negative signal and promoting the host immune response. This immune response can then recognize and eliminate tumor cells. Blocking CSF1R with FPA008 treatment could alleviate the immunosuppressive tumor environment that is generated by TAMs and create an environment that is more conducive to immune-based anti-cancer therapies such as nivolumab.

Experimental Procedures: This open-label study is designed to evaluate the safety of FPA008 alone and in combination with nivolumab. Eligible patients (≥ 18 years) with advanced cancers will have an Eastern Cooperative Oncology Group performance status of 0 or 1. The Phase 1a dose escalation will include all advanced solid tumors and the Phase 1b expansion part of this study will focus on six tumor types: non-small cell lung cancer, melanoma, head and neck cancer, pancreatic cancer, colorectal cancer, and malignant glioma. For Phase 1a, the primary objectives are to assess the safety and tolerability of FPA008 alone and in combination with 3 mg/kg nivolumab, and to determine the maximum tolerated dose of FPA008 in this combination. Secondary objectives include an assessment of pharmacokinetics, objective response rate, overall survival, duration of response, and progression-free survival of FPA008 in combination with nivolumab. Pre- and on-treatment biopsies will be collected from patients to characterize the tumor microenvironment and examine pharmacodynamic responses to treatment. Additionally, post-progression biopsies in a subset of patients will be collected to study potential mechanisms of resistance. Exploratory objectives for Phase 1a and Phase 1b include an evaluation of biomarkers and their relationship to tumor response.

Summary: This is a Phase 1 study designed in two parts to assess the safety and tolerability of FPA008 alone and in combination with nivolumab. This study will also assess efficacy and correlate response with pharmacodynamic markers of activity for both drugs.

Conclusions: Emerging data elucidate the contribution TAMs make to immunosuppression in the tumor microenvironment. Inhibition of TAMs by FPA008 may reduce their immunosuppressive effects and increase T cell anti-tumor responses. This activity may be further enhanced by combining FPA008 with a PD-1 inhibitor, such as nivolumab. This study will evaluate the safety and preliminary efficacy of this novel combination in treating patients with advanced cancers. (NCT Number pending)