I. EXECUTIVE SUMMARY

This proposal includes a phase 1b clinical trial of MRX-2843 and osimertinib in patients with advanced EGFRMT NSCLC and may lead to development of more effective and less toxic therapies to improve survival and quality of life for lung cancer patients. Correlative studies are included in the trial to identify potential biomarkers that could be used to monitor target inhibition and/or immune response in patients treated with the combination. Preclinical studies will also be conducted using animal models to expand our understanding of the direct and immune-mediated mechanisms by which MERTK contributes to tumorigenesis and resistance to EGFR inhibition in EGFRMT NSCLC.

II. PROJECT AIMS

Aim 1- Determine the effects of MERTK inhibition alone and in combination with EGFR TKIs in preclinical EGFRMT NSCLC models. Target inhibition mediated by shRNA, TKIs, or ligand traps and effects on downstream signaling, colony-forming potential, sensitivity to cytotoxic chemotherapies and EGFR TKIs, and induction of metastatic phenotypes will be determined in EGFRMT and osimertinib-resistant NSCLC cell cultures. Therapeutic effects of MERTK inhibition in combination with EGFR TKIs will be assessed in subcutaneous and orthotopic cell line and patient-derived xenograft models. Pharmacodynamic (PD) studies will be conducted to determine relevant biomarkers. A MERTK mutant that does not bind MRX-2843 will be used to evaluate off-target effects.

Aim 2- Determine the effects of MERTK inhibition on anti-tumor immunity in syngeneic EGFRMT NSCLC models. MERTK is expressed on tumor-associated macrophages and suppresses anti-tumor immunity. Induction of anti-tumor immunity (immune infiltrates in tumor and blood, immune function in tumor, cytokine and chemokine profiling) will be assessed in mice with syngeneic subcutaneous and orthotopic EGFRMT grafts after treatment with a TAM kinase inhibitor and immune biomarkers will be identified. Similar studies will be conducted in MERTK knock-out mice and mice with MERTK knock-out chimeric bone marrow. Depletion of immune cell subsets will be conducted to identify cellular mechanisms of anti-tumor immunity.
Aim 3- Systematically evaluate the safety, efficacy and biomarkers of activity of the combination of MRX-2843 and osimertinib in patients with advanced EGFRMT NSCLC. The safety and recommended phase II dose (RP2D) of combined MRX-2843 and osimertinib will be defined in a phase Ib study enrolling newly diagnosed patients with EGFRMT NSCLC. Escalating doses of MRX-2843 will be administered with the approved dose of osimertinib (80mg once daily). The starting dose of MRX-2843 will be 25% of the single agent RP2D to be established in a first-in-human multicenter study that will activate in April 2018. PD markers (MERTK expression and phosphorylation, downstream signaling readouts, and immune response biomarker modulation) will be interrogated in paired pre-and post-treatment biopsies obtained from parallel expansion cohorts of osimertinib-naive and osimertinib-resistant patients.

III. PROJECT DESCRIPTION

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related death in the US. EGFR tyrosine kinase inhibitors (TKIs) have improved outcomes for patients who have non-small cell lung cancer (NSCLC) with an activating EGFR mutation (EGFRMT), but many tumors do not respond and most that do will become resistant in 9-12 months. Osimertinib, a 3rd generation EGFR TKI, has recently advanced to frontline therapy for EGFRMT NSCLC, irrespective of T790M mutation, but treatment options remain limited for patients who develop resistant tumors. This proposal describes preclinical studies to evaluate inhibition of the MERTK receptor tyrosine kinase in combination with EGFR TKIs for treatment of EGFRMT NSCLC and includes a phase 1b clinical trial to test the combination in these patients. 70% of NSCLCs have abnormally high levels of MERTK and inhibition in tumor cells decreases tumor growth in mice. MERTK is also present in immune cells in the tumor microenvironment, where it suppresses the anti-tumor innate immune response. Our data suggest that inhibition of MERTK reprograms the immune system to attack the tumor. MERTK can also mediate resistance to EGFR TKIs, including osimertinib, suggesting that MERTK inhibition will sensitize EGFRMT tumors to treatment with EGFR TKIs and may decrease development of resistance. These data identify MERTK as a new target in NSCLC and implicates MERTK-targeted inhibitors as an unprecedented opportunity to provide a three-pronged therapeutic approach in a single drug, leading to (1) direct tumor cell killing, (2) activation of anti-tumor innate immunity, and (3) increased sensitivity to EGFR TKI therapy. To test this idea and generate drugs that can be used in humans, we developed MERTK-selective TKIs, including MRX-2843. MRX-2843 is effective as monotherapy in mice and increases sensitivity to EGFR TKIs in EGFRMT NSCLC cells. The proposed studies use MRX-2843 and other MERTK inhibitors to investigate the effects of combined MERTK and EGFR inhibition in cell culture and mouse models of EGFRMT NSCLC, including models with tumor cells implanted directly in the lung, models derived from fresh patient samples, and models of tumor cell metastasis. Mice with mertk knockout will also be used to determine the effects of MERTK inhibition in the tumor microenvironment and its impact on anti-tumor immunity. Additional studies will determine how MERTK inhibition in the immune system leads to tumor rejection. Finally, a highlight of this project is the dedicated clinical trial of MRX-2843 and osimertinib in patients with advanced EGFRMT NSCLC, a study that includes 2 expansion cohorts with paired collection of preand post-treatment tumor biopsies and blood samples to evaluate biomarkers of MERTK inhibition, including changes in immune function, following treatment with MRX-2843. The results from the clinical trial and associated studies will provide more effective and less toxic treatment options leading to optimized care and improved survival for patients with EGFRMT NSCLC.