

A Phase II Trial of LEE011 in Combination with Everolimus in the Treatment of Advanced Well Differentiated Neuroendocrine Tumors of Foregut Origin

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Background: Changes in the retinoblastoma tumor suppressor pathway are believed to contribute to the development of well differentiated neuroendocrine tumors (WDNETs). Specifically, the downregulation of proteins that normally inhibit the cyclin dependent kinases Cdk4 and Cdk6 have been demonstrated to contribute to NET development. Separately, rigorous investigation of everolimus in WDNETs has unequivocally demonstrated a survival benefit in this patient population.

Pre-clinical data suggests that LEE011 (Cdk4/Cdk6 inhibitor) is synergistically active with everolimus. The aim of this study is to evaluate the antitumor efficacy of the combination of LEE011 and everolimus in subjects with advanced WDNETs of foregut origin (thymic, bronchopulmonary, gastric, duodenal, and pancreatic).

Methods: This is a multicenter, non-randomized, phase II clinical trial using a Simon two stage optimal design. Main inclusion criteria include: adult patients with well/moderately differentiated WDNET of foregut origin, low/intermediate grade, unresectable and/or metastatic, documented evidence of disease progression with measurable disease, ECOG PS 0-1. Between 15 and 43 patients will be enrolled from three sites. All subjects will receive the oral combination LEE011 (300 mg daily, 3 weeks on/1 week off) and everolimus (2.5 mg daily). Patients will receive therapy until progressive disease/death or unacceptable toxicity. All enrolled patients will be followed by telephone contact for overall survival until death/withdrawal consent. The primary endpoint, progression free survival (time from therapy initiation to progressive disease/death), will be assessed based on radiographic review using RECIST v1.1. Secondary endpoints include safety, objective response rate, clinical benefit rate, and overall survival. Correlative objectives include exploring the effect of this drug combination on biomarkers related to the retinoblastoma pathway and/or the pathogenesis of WDNETs. This trial is scheduled to begin enrollment in the summer of 2016.