Cabozantinib Plus Telgaglenstat (CB-839): A Phase II Combination in Patients with Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors (WD-GEP NETs)

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Background: Patients with well-differentiated gastroenteropancreatic neuroendocrine tumors (WD-GEP NETs) possess limited cytoreductive treatment options outside of capecitabine plus temozolimide and peptide receptor radionuclide therapy. Even after these treatments, many patients are left with extensive disease, and remain in need of further cytotoxic treatments. Although several FDA-approved single-agents such as everolimus or sunitinib are utilized in later-line settings for patients with WD-GEP NETs, they are largely cytostatic, with limited effectiveness in patients with bulky disease. A therapeutic option which has demonstrated cytotoxic potential is cabozantinib, a tyrosine kinase inhibitor which inhibits vascular endothelial growth factor (VEGF) receptor 2, among other targets. Cabozantinib demonstrated an objective response rate (ORR) of 15% in heavily pretreated patients with WD-GEP NETs in an earlier phase II study. An opportunity to build on the apparent cytotoxicity of cabozantinib is through inhibiting glutamine metabolism and glutamate generation through targeting glutaminase. GEP NET tumors along with renal cell carcinoma (RCC) are VEGF driven, creating a dependence on glutamate to fuel oncogenesis. CB-839 is a potent glutaminase inhibitor which has demonstrated synergy in combination with cabozantinib in cell line and xenograft models of RCC and early clinical efficacy in a phase I study in RCC patients. Our proposed single-arm phase II trial tests cabozantinib plus CB-839 in patients with progressive WD GEP-NETs and will serve as the platform to perform to perform correlatives which may identify the patients who derive optimal benefit from the study combination.

Methods and Experimental Approach: The primary objective of this study is to assess the anti-tumor effect of cabozantinib plus CB-839. This will be measured by ORR, progression-free survival and overall survival. The study is powered by ORR and based on a target ORR of 30%, we will need 37 patients to conduct the trial. The study follows a Simon's two-stage minimax design where in stage I, 18 patients will be recruited. If 3 or more patients experience a response by RECIST 1.1, 19 further patients will be recruited. Otherwise, accrual will stop for lack of efficacy. The secondary objectives of the study are to establish a recommended phase 2 dose (RP2D) and to assess the general safety and tolerability of the treatment as the two drugs have not been combined in NET patients. Dose-limiting toxicities will be used to define the RP2D during a 6-12 patient safety lead-in period in stage I of the study while adverse event data will be collected throughout the trial. The exploratory objectives of the study are to identify a metabolic tumor signature, by tissue biopsy, predictive of response to cabozantinib plus CB-839. Pretreatment tumor biopsies will be obtained in 7 patients in stage I of the study and glutamine metabolism gene expression signatures will be analyzed by RNA sequencing and correlated with response endpoints.

Results: We have written the study protocol and are in the process of submitting it to our Institutional Review Board and Scientific Review Committee for approval. We have obtained study funding from Exelixis and drug provision from Calithera.

Conclusions/Next Steps: We anticipate a study activation date within the next 2-3 months.