PANCREATIC NEUROENDOCRINE

Clinical Trial Name: ALLIANCE-A022001-PNETS Lutetium LU 177 Dotatate PRRT vs Capecitabine and Temozolomide in PNET

Study Design: This is a phase II randomized, prospective trial of Lutetium LU 177 Dotatate PRRT versus Capecitabine and Temozolomide in well-differentiated pancreatic neuroendocrine tumors.

NCT#:
NCT05247905

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Key Inclusion

- Histologic or pathologic documentation of well-differentiated pancreatic neuroendocrine tumor (G1, G2, or well-differentiated G3) confirmed by local histology and/or pathology. Functional or nonfunctional tumors are allowed.
- Stage: locally unresectable or metastatic disease.
- Tumor Site: neuroendocrine tumor of pancreatic primary site.
- Radiologic evaluation: tumor must have shown somatostatin receptor (SSTR) positivity on 68Ga-DOTATATE PET or other SSTR-PET scan in the 12 months prior to registration; however, documentation of SSTR positivity in the 6 months prior to registration is preferred. SSTR positivity is defined as uptake greater than background liver in all measurable lesions.
- Patients are eligible if they meet one of the following criteria:
  - Previously untreated patients with grade 2 or 3 disease AND with symptoms of either disease bulk causing pain, anorexia, early satiety, large effusions/ascites, abdominal pain, abdominal fullness due to hepatomegaly, dyspnea) OR incompletely controlled symptoms of hormone excess despite somatostatin analogue (SSA) and supportive care (including but not limited to: diarrhea, hypercalcemia, hypoglycemia, hyperglycemia, flushing, Cushing's syndrome). Patient may have been started on SSA for up to 2 months for attempted symptom control without disease progression prior to registration.
  - Patients previously treated with SSA only and with disease progression by RECIST in prior 12 months.
  - Patients previously treated with SSA and one or more prior systemic therapy must have received prior anti-vascular endothelial growth factor (VEGF) pathway therapy inhibitor OR have contraindication to anti-VEGF therapy (including but not limited to: uncontrolled hypertension [systolic blood pressure [SBP] > 150 and/or diastolic blood pressure [DBP] > 90 despite medical management], stage IIB or greater heart disease, angina pectoris, prior arterial [ATE] and venous thromboembolic [VTE] events in the past 6 months, gastrointestinal [GI] bleed in the last 6 months) and disease progression by RECIST in prior 12 months.
  - Patients previously treated with more than 2 lines of therapy, not including anti VEGF therapy, but with NET related symptoms as outlined in first bullet (pain, anorexia, early satiety, large effusions/ascites, abdominal pain, abdominal fullness due to hepatomegaly, anorexia, early satiety, dyspnea) OR incompletely controlled symptoms of hormone excess despite somatostatin analogue (SSA) and supportive care (including but not limited to: diarrhea, hypercalcemia, hypoglycemia, hyperglycemia, flushing, Cushing's syndrome).
  - Any patient with disease progression by RECIST criteria in < 4 months.
- Patients must have measurable disease per RECIST v1.1 by computer tomography (CT) scan or magnetic imaging (MRI). Any lesions which have undergone percutaneous therapies or radiotherapy after starting protocol therapy should not be considered measurable unless the lesion has clearly progressed since the procedure.
- Lesions must be accurately measured in at least one dimension (longest diameter to be recorded) as >= 1 cm with CT or MRI (or shortest diameter >= 1.5 cm for lymph nodes). Non-measurable disease includes disease smaller than these dimensions or lesions considered truly non- measurable including: leptomeningeal disease, bone metastases, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung.
- Prior treatment with tyrosine kinase inhibitors (TKIs) such as mammalian target of rapamycin (mTOR) inhibitors (e.g. everolimus, temsirolimus, etc.) or VEGF pathway inhibitors (e.g. sunitinib, pazopanib, cabozantinib, bevacizumab, etc.) are allowed.

	• Prior treatment with hepatic intra-arterial embolic therapies is allowed if there is recovery from all toxicities, measurable lesions do not include embolized liver unless there has been clear subsequent progression, all measurable lesions are somatostatin receptor avid, and treatment completed at least 2 months prior to registration. • Prior treatment with cryoablation or thermal/radiofrequency ablation of metastases is allowed if there is recovery from all toxicities, measurable lesions do not include treated metastases, and treatment completed at least 2 months prior to registration. • ECOG = 0-2. • Absolute neutrophil count (ANC) >= 1,500/mm^3, Platelet count >= 100,000/mm^3, Hemoglobin >= 9.0 g/dL, Creatinine =< 1.5 x upper limit of normal (ULN) OR calculated (calc.) creatinine clearance >= 30 mL/min (calculated by the Cockcroft-Gault equation), Total bilirubin =< 1.5 x ULN (in patients with liver metastases or known Gilbert's syndrome, total bilirubin must be =< 3.0 x ULN), Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) =< 3.0 x ULN, Albumin >= 3.0 g/dL. • Concurrent somatostatin analog use while on protocol therapy is allowed provided that the patient: ▪ Has a functional tumor (evidence of peptide hormones and/or bioactive substances associated with a clinical hormone syndrome such as carcinoid syndrome or Cushing's syndrome). ▪ Has been on a stable dose of somatostatin analog therapy for at least three months. ▪ Has previously demonstrated radiographic disease progression while on somatostatin analog therapy. For subjects receiving lutetium Lu 177 dotatate, there should be a minimum of 14 days between long-acting somatostatin analogue and lutetium Lu 177 dotatate dosing. Short-acting somatostatin analogs should not be administered within 24 hours of lutetium Lu 177 dotatate dosing. Following lutetium Lu 177 dotatate dosing, long-acting somatostatin analogs may be administered between 4 and 24 hours after each dose. ***Key Exclusion:*** • Patients with poorly differentiated neuroendocrine carcinoma (large cell histology or small cell histology) are not eligible. • No prior temozolomide, dacarbazine, capecitabine, 5-FU, or any PRRT for treatment of the pNET. • No uncontrolled congestive heart failure (New York Heart Association [NYHA] II, III, IV). • No "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy or are on adjuvant hormonal therapy and are free of disease for >= 3 years. • No known medical condition causing an inability to swallow and no known impairment of gastrointestinal function that may significantly alter the absorption of an oral agent.