Protocol Title: EA5152: A Randomized Phase II Trial of Nivolumab, Cabozantinib Plus Nivolumab, and Cabozantinib Plus Nivolumab Plus Ipilimumab in Patients with Previously Treated Non-Squamous NSCLC

Target Population: Previously Treated Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Summary: This partially randomized phase II trial studies how well Nivolumab, Cabozantinib S-Malate, and Ipilimumab work in treating patients with Recurrent Stage IV Non-Small Cell Lung Cancer.

Key Eligibility Criteria:
- Tumors with the following molecular alterations must submit testing results via Medidata Rave to determine eligibility to Arm T:
  - ROS1 gene rearrangement by FISH or DNA analysis (may have progressed on prior Crizotinib therapy)
  - MET exon 14 splice mutations on DNA analysis (may have progressed on prior Crizotinib therapy)
  - MET high amplification by FISH or DNA analysis or other MET mutations predicted to be sensitive to MET inhibitor (no prior targeted therapy allowed)
  - RET gene rearrangement by FISH or DNA analysis (no prior targeted therapy allowed)
- Pathologically confirmed non-squamous NSCLC that is Stage IV (includes M1a, M1b, or recurrent disease)
- Predominant non-squamous histology
- Tumors must be tested and known negative for EGFR TKI sensitizing mutations and ALK gene rearrangements by CLIA-certified clinical testing methods
- Must have progressed on first line platinum-based chemotherapy, no additional lines of therapy are permitted
  - Exception Arm T: At least one line of prior chemotherapy or targeted therapy is required, but there is no limit on number of prior treatments
- Must have measurable disease as defined by RECIST 1.1 criteria
- No prior anti-MET therapy such as Crizotinib or Cabozantinib, or PD-1/PD-L1 immune checkpoint inhibitor therapy (such as Nivolumab, Pembrolizumab, Atezolizumab) or CTLA4 inhibitor therapy (such as Ipilimumab)
  - Exception for targeted therapy sub-study (Arm T): Prior Crizotinib may be allowed depending on the gene alteration
- No prior radiation therapy for bone metastasis within 2 Weeks, any other radiation therapy within 4 Weeks prior to registration
- No known active or untreated brain metastasis
- Must have ECOG Performance Status 0-1 and anticipated life expectancy greater than 3 Months
- Adequate bone marrow, renal, and liver function
- No concomitant anticoagulation with oral anticoagulants (e.g., Warfarin, Direct Thrombin and Factor Xa Inhibitors) or Platelet Inhibitors (e.g., Clopidogrel)
- Must have corrected QT interval calculated by Fridericia formula ≤ 500 ms within 28 Days before registration
- No currently active other malignancies which require systemic treatment
- No known active autoimmune disease or known history of autoimmune disease for which recurrence may affect vital organ function or require immune suppressive treatment including systemic corticosteroids
- No ongoing major illness or psychosocial issues that would limit compliance with the protocol
- Women must not be pregnant or breast-feeding

Contacts:
  Principal Investigator: Suma Satti, MD
  Research Nurses (RN): Nicole Duffaut (nicole.duffaut@ochsner.org, ext. 23683)
  Amanda Woolery (amanda.woolery@ochsner.org, ext. 20275)

For additional information: https://clinicaltrials.gov/ct2/show/NCT03468985