**EA5191 Available Through ECOG-ACRIN Cancer Research Group**

A Randomized Phase II Trial of Cabozantinib and Cabozantinib plus Nivolumab versus Standard Chemotherapy in Patients with Previously Treated Non-Squamous NSCLC

### Patient Population

**See Section 3.0 for Complete Eligibility Details**

**Step 0 Eligibility (Pre-registration):**
- ≥ 18 years old; ECOG PS 0-1; pathologically confirmed non-squamous NSCLC
- Must have Stage IV disease (includes M1a, M1b, or recurrent earlier stage disease) (AJCC 8th ed.)
- Must have predominant non-squamous histology (NSCLC NOS is eligible; if small cell elements are present the patient is ineligible)
- Patient’s tumor(s) must be tested and known negative for EGFR TKI sensitizing mutations and ALK gene rearrangements (see protocol for details)
- Patients without tumors with known molecular alterations in ROS1, MET, RET must have progressed radiographically following only 1 line of platinum-based chemotherapy AND only 1 line of prior immunotherapy. Patient must have received at least 2 prior doses of checkpoint inhibitor therapy; OR patients with tumors with known molecular alterations in ROS1, MET, RET must have progressed radiographically on at least 1 line of prior chemotherapy or targeted therapy (no limit; immunotherapy allowed but not required); see protocol for details

**Step 1 Eligibility (Randomization/Registration):**
- Must have measurable disease (RECIST 1.1); adequate lab values; anticipated life expectancy greater than 3 months
- Any prior chemotherapy or RT must be completed in greater than or equal to the time periods per protocol
- Patients are not permitted to have history of the list of items in protocol section 3.2.9
- Must not receive concomitant anticoagulation with oral anticoagulants/platelet inhibitors, or concomitant treatment of strong CYP3A4 inhibitors within 7 days of randomization (see protocol for allowed anticoagulants)
- Patients with brain metastases are eligible per protocol
- No known active autoimmune disease (see protocol)

### Treatment Plan

**See Section 5.0 for Complete Treatment Details**

Cycle length = 21 days; patients will continue treatment until disease progression or an AE requiring discontinuation occurs

**Arm A:**
- Cabozantinib 60 mg by mouth daily

**Arm B:**
- Cabozantinib 40 mg by mouth daily
- Nivolumab 360 mg IV over 30 mins every 21 days

**Arm C (standard chemotherapy, see protocol):**
- Initial dosing is Docetaxel (75 mg/m²) and Ramucirumab (10 mg/kg) day 1; subsequent cycles dose may be modified/Ramucirumab may be held; OR
- Docetaxel IV (initial dosing 75 mg/m² day 1 or 35 mg/m² day 1 and 8)
- Gemcitabine IV (initial dosing 1000 mg/m² day 1 and 8)
- Paclitaxel IV (initial dosing 150 mg/m² day 1)
- Nab-paclitaxel IV (initial dosing 100 mg/m² day 1, 8, and 15)

**Arm T (ongoing):**
- Cabozantinib 40 mg by mouth daily
- Nivolumab 360 mg IV over 30 mins every 21 days

**Arm Z (crossover arm):**
- Cabozantinib 40 mg by mouth daily
- Nivolumab 360 mg IV over 30 mins every 21 days

### Notes:
- Cabozantinib should be taken on an empty stomach, whole. Do not take missed dose within 12 hours of the next dose
- All therapy should start on the same day, but cabozantinib may start the morning following infusion therapy

### Patient Enrollment

All Sites: Oncology Patient Enrollment Network (OPEN) [https://open.ctsu.org](https://open.ctsu.org)

### Protocol Information

ECOG-ACRIN Operations-Boston: 857-504-2900, [http://ecog-acrin.org](http://ecog-acrin.org) (Member Login)

Please Enroll Your Eligible Patients!