Version 04/21/21 (Add. #2)

NCI National Clinical Trials Network

EA5191

ECOG-ACRIN cancer research group
Reshaping the future of patient care

For Patients with Non-Squamous NSCLC

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 chemo/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)

See protocol for additional eligibility for Arms A-C, Arm T, and Crossover Arm Z

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/m^2) and Ramucirumab (10 mg/kg) day 1; subsequent cycles dose may be modified/Ramucirumab may be held; OR
- Docetaxel IV (initial dosing 75 mg/m^2 day 1 or 35 mg/m^2 day 1 and 8)
- Gemcitabine IV (initial dosing 1000 mg/m^2 day 1 and 8)
- Paclitaxel IV (initial dosing 150 mg/m^2 day 1)
- Nab-paclitaxel IV (initial dosing 100 mg/m^2 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*

Study Chair:
Joel Neal, MD, PhD

Co-Chair:
Heather Wakelee, MD

Patient Enrollment

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

Protocol Information

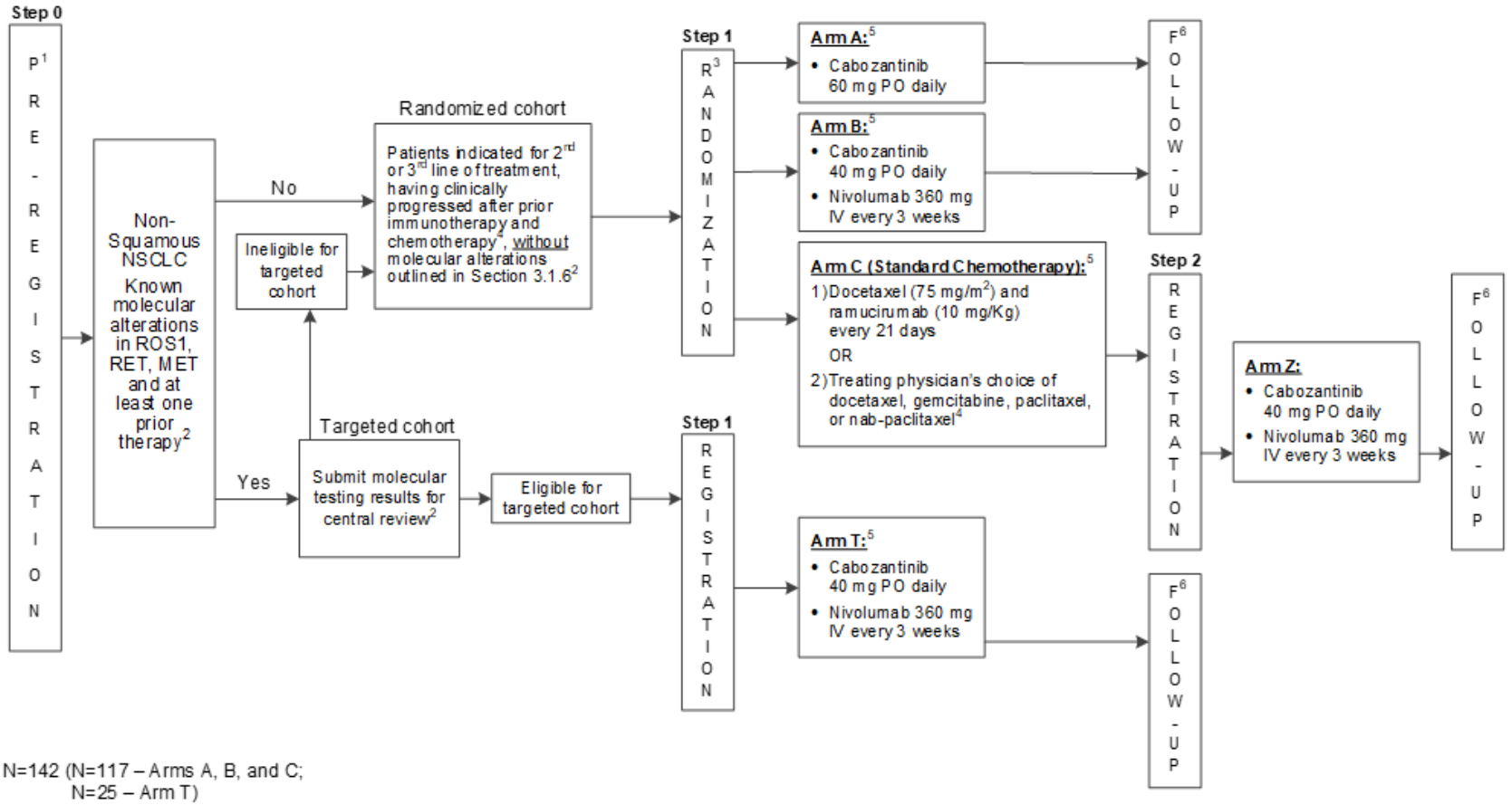
ECOG-ACRIN Operations-Boston: 857-504-2900, http://ecog-acrin.org (Member Login)

Please Enroll Your Eligible Patients!

Version 04/21/21 (Add. #2)

EA5191

Schema



N=142 (N=117 – Arms A, B, and C;
N=25 – Arm T)

Cycle = 3 weeks (21 days)

1. Pre – Registration (Step 0) is for the purpose of central review of patient's molecular testing to determine treatment assignment.
2. Tumors must be known to be negative for EGFR or ALK mutations for patients with or without eligible molecular alterations. Patients with molecular alterations (MET exon 14 mutation, MET amplification, ROS1 rearrangement, RET rearrangement) must submit testing results per Section 4.1.4.2.
3. Randomization is 1:1:1 across Arms A, B, and C
4. Please refer to Section 5.1.3 for specific dosing guidelines.
5. Patients will continue on study treatment until progressive disease or until an adverse event requiring discontinuation occurs at which time patient would proceed to follow-up.
6. Patients remain in follow-up for 3 years per Section 5.8.