

FAST FACTS

EA5191 - A Randomized Phase II Trial of Cabozantinib and Cabozantinib Plus Nivolumab Versus Standard Chemotherapy in Patients with Previously Treated Non-Squamous NSCLC

Eligibility Criteria for Step 0 (Pre-Registration)

1. Patient must be ≥ 18 years of age on day of consent.
2. Patient must have pathologically confirmed non-squamous non-small cell lung carcinoma (NSCLC)
3. Patient must have Stage IV disease (includes M1a, M1b, or recurrent earlier stage disease), according to the 8th edition of the lung cancer TNM classification system.
4. Patient must have predominant non-squamous histology (patients with NSCLC NOS are eligible). Mixed tumors will be categorized by the predominant cell type. If small cell elements are present the patient is ineligible.
5. Patient's tumor(s) must be tested and known negative for EGFR TKI sensitizing mutations (EGFR Exon 19 deletions, L858R, L861Q, G719X) and ALK gene rearrangements (by FISH, NGS, or IHC) by routine CLIA-certified clinical testing methods. Negative circulating tumor DNA results alone are not acceptable. Prior testing for tumor PD-L1 status is not required.
6. Patients WITHOUT tumors with known molecular alterations in ROS1, MET, RET (see below), or must have progressed radiographically (per local investigator assessment) following one, but only one, line of platinum-based chemotherapy AND one, but only one, line of prior immunotherapy. Lines of therapy are defined by clinical or radiographic progression. Patients may have received chemotherapy and immunotherapy either concurrently or sequentially in either order. (See note in Section 3.2 for patients who received prior adjuvant chemotherapy or chemoradiation.) Patient must have received at least 2 prior doses of checkpoint inhibitor therapy in an every 2, 3, or 4 week schedule. No submission of molecular testing is required and patients may be registered for Step 0 then proceed directly to Step 1 screening.

–OR–

Patients with tumors with known molecular alterations in ROS1, MET, and RET must have progressed radiographically (per local investigator clinical assessment) on at least one line of prior chemotherapy or targeted therapy, but there is no limit on number of prior number of therapies. Receipt of prior immunotherapy is allowed but not required. See note in Section 3.2 for patients who received prior adjuvant chemotherapy or chemoradiation.

- Known molecular alterations in ROS1, MET, and RET are defined as below ROS1 gene rearrangement by FISH or DNA analysis. In addition to above requirements, these patients must have progressed on at least one prior ROS1 TKI therapy
- MET exon 14 splice mutations on DNA analysis. In addition to above requirements, prior MET directed TKI therapy is optional.
- MET mutations predicted to be sensitive to MET inhibitor. In addition to above requirements, prior MET directed TKI therapy is optional.
- High MET amplification by FISH (characterized by a fluorescence in situ hybridization MET/CEP7 ratio of 5 or greater); OR MET amplification by DNA NGS CLIA certified assay. In addition to above requirements, prior MET directed TKI therapy is optional.
- RET gene rearrangement by FISH or DNA analysis. In addition to above requirements, prior RET directed TKI therapy is optional.

NOTE: During Step 0 screening, CLIA reports of the testing results must be submitted via Medidata Rave for central review (see section 4.2.4) for instructions. The central review will be performed by the Study Chair, Co-Chair, Biology Co-Chair, and/or a delegate to determine that the results indicate a patient's eligibility for targeted therapy. CLIA reports that contain information pertaining to any of the above mutations will be uploaded to Medidata Rave for central review of documentation for determination of patient eligibility for targeted therapy (Arm T). Central testing of tissue will not be performed. Institutions will be notified of the patient's eligibility status for Arm T within two (2) business days of submission of the molecular testing reports. Patients with tumors with the above known molecular alterations are eligible for cohort Arm Z following Step 1 eligibility review.

Patients without tumors with the above known molecular alterations are eligible for randomization to Arm A, B or C following Step 1 eligibility review.

7. **NOTE:** Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen (in the opinion of the treating physician) are eligible for this trial.
8. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents (such as anthracycline or HER2-directed antibody therapy, but not prior checkpoint inhibitor therapy), must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients must be class 2B or better. ([Appendix XI](#))
9. Patient must have ECOG performance status 0-1

Eligibility Criteria for Step 1 (Randomization/Registration) for All Treatment Arms

1. Patient must have met the eligibility criteria outlined in Section [3.1](#)
2. Patient must have measurable disease as defined by RECIST v1.1 criteria in Section [6](#). Measurements must be obtained within 4 weeks prior to randomization/registration.
3. Patient must have an anticipated life expectancy greater than 3 months.
4. Any prior chemotherapy (based on administration schedule) must have been completed in greater than or equal to the following times prior to randomization/registration:
 - a. Chemotherapy/targeted oral therapy administered in a daily or weekly schedule must be completed ≥ 1 week prior to randomization/registration
 - b. Any chemotherapy administered in an every 2 week or greater schedule must be completed ≥ 2 weeks prior to randomization/registration.
 - c. Additionally, patient should be recovered to equal to or less than grade 1 toxicities related to any prior treatment, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy (as determined by the treating physician).
5. Patient must not have had any prior radiation therapy for bone metastasis within 2 weeks, or any other radiation therapy within 4 weeks prior to randomization/registration.

6. Patient must have acceptable bone marrow, renal, hepatic, and coagulation function, obtained within 2 weeks prior to randomization/registration as defined below:

ULN = institutional upper limit of normal; LLN = institutional lower limit of normal

- Leukocytes $\geq 3,000/\text{mcl}$
Leukocytes: _____ Date of Test _____
- Absolute neutrophil count $\geq 1,500/\text{mcl}$
Absolute neutrophil count: _____ Date of Test _____
- Platelets $\geq 100,000/\text{mcl}$
Platelets: _____ Date of Test _____
- Hemoglobin $\geq 9 \text{ g/dL}$
Hemoglobin: _____ Date of Test _____
- Total bilirubin $\leq 1.5 \times \text{institutional ULN}$
Total bilirubin: _____ ULN: _____ Date of Test _____
- AST(SGOT) and ALT(SGPT) $\leq 2.5 \times \text{ULN}$
AST (SGOT): _____ ULN: _____ Date of Test _____
ALT (SGPT): _____ ULN: _____ Date of Test _____
- Creatinine $\leq 1.5 \times \text{ULN}$

OR

Calculated (Cockcroft-Gault formula) or measured creatinine clearance $\geq 50 \text{ mL/min/1.73m}^2$ (normalized to BSA) for patients with creatinine levels greater than 1.5 times the institutional normal Creatinine $\leq 1.5 \times \text{ULN}$ or creatinine clearance $\geq 50\text{ml/min/1.73m}^2$

Creatinine: _____ ULN: _____ Date of Test _____

Creatinine clearance: _____ Date of Test: _____

7. Women must not be pregnant or breast-feeding due to the unknown effects of cabozantinib and nivolumab on human development and for the potential risk for adverse events in nursing infants with the treatment regimens being used. All females of childbearing potential must have a blood test or urine study within 14 days prior to randomization/registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Female of childbearing potential? _____ (Yes or No)
Date of blood test or urine study: _____
8. Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and for up to 7 months after completion of treatment on the study (see [Appendix VI](#)).
9. Patient must not have history of the following:
- a. Clinically significant gastrointestinal bleeding within 6 months prior to randomization/registration.

- b. Pulmonary hemorrhage or hemoptysis of ≥ 0.5 teaspoon (2.5 mL) of red blood within 3 months prior to randomization/registration.
 - c. Any grade drug induced pneumonitis within 3 months prior to randomization/registration. Prior immune mediated pneumonitis of grade 3 or 4 are not eligible regardless of time window.
 - d. Current radiographic evidence of cavitating pulmonary lesion(s).
 - e. Current radiographic evidence of tumor invading any major blood vessels.
 - f. Evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or mainstem endobronchial tumor within 28 days prior to randomization/registration.
 - g. Peptic ulcer disease, inflammatory bowel, known malabsorption syndrome, bowel obstruction or gastric outlet obstruction (PEG tube placement) within 3 months prior to randomization/registration.
 - h. Abdominal fistula, GI perforation, intra-abdominal abscess within 6 months prior to randomization/registration.
 - i. Grade 3 or greater infection, or infection requiring intravenous systemic treatment within 28 days prior to randomization/registration. Patients should be off antibiotics at the time of randomization/registration.
 - j. Serious non-healing wound/ulcer/bone fracture within 28 days prior to randomization/registration.
 - k. History of organ transplant.
 - l. Concurrent symptomatic untreated hypothyroidism within 7 days prior to randomization/registration.
 - m. History of major surgery (within 3 months, with wound healing within 28 days, prior to randomization/registration), minor surgery (within 28 days prior to randomization/registration), other minor procedures (within 7 days prior to randomization/registration) or clinically relevant ongoing complications from prior surgery.
 - n. Concurrent uncontrolled hypertension defined as sustained BP > 140 mm Hg systolic, or > 90 mm Hg diastolic within 7 days of registration despite optimal antihypertensive treatment
 - o. History of the following within 6 months prior to therapy:
 - Unstable angina pectoris
 - Clinically-significant cardiac arrhythmias
 - Stroke (including TIA, or other ischemic event)
 - Myocardial infarction
 - Thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose.

NOTE: Subjects with a diagnosis of DVT (but not PE) within 6 months are allowed if stable, asymptomatic, and treated with LMWH for at least 2 weeks before first dose
10. Patient must not receive concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel) within 7 days prior to randomization/registration. Allowed anticoagulants are the following:
- a. Low-dose aspirin (100 mg po daily or less) is permitted.
 - b. Anticoagulation with therapeutic doses of LMWH is allowed in patients who are on a stable dose of LMWH for at least 6 weeks prior to study randomization/registration, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor within this time period.

11. Patient must not receive concomitant treatment of strong CYP3A4 inducers (e.g., dexamethasone (> 1 mg daily dosing), phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) within 7 days prior to randomization/registration.
12. Patient must have corrected QT interval calculated by the Fridericia formula (QTcF) \leq 500 ms within 28 days prior to randomization/registration.
13. Patient must be able to swallow tablets.
14. Patient must not be on systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to randomization/registration, with the following exceptions:
 - a. Inhaled or topical steroids and adrenal replacement doses \leq 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
 - b. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
 - c. Physiologic replacement doses of systemic corticosteroids are permitted, if < 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
15. Patients with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression.
16. Patients with new or progressive brain metastases (active brain metastases) are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of study treatment.
 - a. Patient must meet one of the following criteria with respect to brain metastases:

Patients with no known brain metastasis must have baseline brain imaging within 12 weeks prior to study randomization/registration not demonstrating brain metastases

OR

Patients with known brain metastases must have baseline brain imaging and completed treatment to all symptomatic brain metastases (with whole brain radiation or radiosurgery; or complete neurosurgical resection \geq 3 months prior to randomization/registration) \geq 4 weeks prior to randomization/registration. They must be clinically stable. Known leptomeningeal disease is not allowed.
17. Patient must not have 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 (e.g., immune-related neurologic disease, multiple sclerosis, autoimmune neuropathy, Guillian-Barre syndrome, etc.).
18. Known human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial.
19. For patients with known history of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy at time of registration/randomization, if indicated.
20. Patients with a known history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load at time of registration/randomization.
21. Additional Eligibility Criteria for Step 1 (Randomization) Arms A-C
 - a. Patient must not be eligible for the targeted therapy arm (Arm T) per one of the following criteria

- i. Patient did not have a known molecular alteration in ROS1, RET, or MET and did not have central review of tissue
 - ii. Central review report the patient is not eligible for Arm T based on molecular report.
 - b. Patient must have progressed radiographically (per local investigator clinical assessment) following one, and only one, line of platinum-based chemotherapy AND one, and only one, line of prior immunotherapy. Patients may have received these lines of treatment together or sequentially. Patient must have received at least 2 prior doses of checkpoint inhibitor therapy (of only one type), in an every 2, 3, or 4 week schedule.
NOTE: The requirement for prior chemotherapy will be met if patients have recurrence within 6 months after prior adjuvant platinum based chemotherapy for early stage disease, or recurrence within 6 months after prior radiotherapy plus platinum based chemotherapy for locally advanced disease.
NOTE: Patients with unresectable stage III A/B NSCLC who have received chemo and radiation then consolidation durvalumab, followed by progression pts are eligible if progression happens while on after >2 doses of durvalumab. Prior bevacizumab with chemo is also allowed.
 - c. Patient must not have had any prior anti-MET therapy, such as crizotinib or cabozantinib.
 - d. Patient must not have had any prior allergic reaction or hypersensitivity to study drug components or related drugs (multitargeted small molecule tyrosine kinase inhibitors or checkpoint inhibitor monoclonal antibodies).
 - e. Patients must not have had history of life-threatening toxicity related to prior immune therapy (eg.anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g., hypo/hyperthyroidism)
22. Additional Eligibility Criteria for Step 1 (Registration) Targeted Arm T
- a. Patient was registered to Step 0, Targeted Arm and central review results report the patient is eligible for Arm T
 - b. Patients with ROS1 gene rearrangements must have progressed on at least one prior ROS1 targeted therapy such as crizotinib.
 - c. Patient must have progressed radiographically (per local investigator clinical assessment) on at least one line of prior chemotherapy or targeted therapy, but there is no limit on number of prior number. Prior immunotherapy is allowed but not required. Prior bevacizumab with chemo is allowed.
NOTE: The requirement for prior chemotherapy will be met if patients have recurrence within 6 months after prior adjuvant platinum based chemotherapy for early stage disease, or recurrence within 6 months after prior radiotherapy plus platinum based chemotherapy for locally advanced disease.
NOTE: Patients with unresectable stage III NSCLC who have received chemo and radiation then consolidation durvalumab, followed by progression are eligible if progression happens after >2 doses of durvalumab. Prior bevacizumab with chemo is also allowed.

Section 3.3 STEP 2 Eligibility Criteria (Crossover Arm Z)

- 1. Patients must have met all eligibility requirements for Step 1 (see Section 3.2) at time of registration to Step 1 to be eligible for Step 2.

2. Patients must have radiographic progressive disease per RECIST criteria (see Section 6.1.4) after ≥ 2 cycles of therapy on Arm C.
3. Patients must not have intervening anticancer treatment or major surgical procedure(s) between Step 1 and Step 2, except palliative radiation to the bone finishing ≥ 1 week prior to registration to Step 2.
4. Patients may not have central nervous system progression, but patients with stable CNS disease are allowed.
5. Patients must be registered to Step 2 within 4 weeks of the last dose of treatment administration from Step 1.
6. Patients must have an ECOG performance status between 0-2 (see Appendix V)
7. Patients must have recovered to baseline (pre-Step 1) or CTCAE v.5.0 \leq Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs.
8. Patient must have acceptable bone marrow, renal, hepatic, and coagulation function, obtained within 2 weeks prior to randomization/registration as defined below:
 - a. ULN = institutional upper limit of normal; LLN = institutional lower limit of normal
 - b. Leukocytes $\geq 3,000/\text{mcl}$
Leukocytes: _____ Date of Test _____
 - c. Absolute neutrophil count $\geq 1,500/\text{mcl}$
Absolute neutrophil count: _____ Date of Test _____
 - d. Platelets $\geq 100,000/\text{mcl}$
Platelets: _____ Date of Test _____
 - e. Hemoglobin $\geq 9 \text{ g/dL}$
Hemoglobin: _____ Date of Test _____
 - f. Total bilirubin $\leq 1.5 \times$ institutional ULN
Total bilirubin: _____ ULN: _____ Date of Test _____
 - g. AST(SGOT) and ALT(SGPT) $\leq 2.5 \times$ ULN
AST (SGOT): _____ ULN: _____ Date of Test _____
ALT (SGPT): _____ ULN: _____ Date of Test _____
 - h. Creatinine $\leq 1.5 \times$ ULN
OR
Calculated (Cockcroft-Gault formula) or measured creatinine clearance $\geq 50 \text{ mL/min/1.73m}^2$ (normalized to BSA) for patients with creatinine levels greater than 1.5 times the institutional normal Creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50\text{ml/min/1.73m}^2$
Creatinine: _____ ULN: _____ Date of Test _____
Creatinine clearance: _____ Date of Test: _____
9. Patients must have corrected QT interval calculated by the Fridericia formula (QTcF) $\leq 500 \text{ ms}$ within 28 days before registration.
10. No intercurrent illness or disease complication that the investigator believes would limit the ability to safely tolerate the combination of cabozantinib and nivolumab.

Schema

