Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

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 Randomization (Step 1)

1. 3.2.1 Patient must have met all eligibility requirements for Step 1 (see Section 3.1) at time of registration to Step 1 to be eligible for Step 2.
2. 3.2.2 Patient must have radiographic progressive disease per RECIST criteria (see Section 6.1.4) after ≥ 2 cycles of therapy on Arm C. The scan showing progression must be completed within 6 weeks prior to Step 2 registration.
3. 3.2.3 Patient must not have intervening anticancer treatment or major surgical procedure(s) between Step 1 and Step 2, except palliative radiation which was completed ≥ 1 week prior to registration to Step 2.
4. Patient may not have central nervous system progression, but patients with stable CNS disease are allowed.
5. Patient must have an ECOG performance status 0-2 (see Appendix V)
6. Patient must have recovered to equal to or less than grade 1 toxicities related to prior treatment, unless the adverse event(s) are clinically nonsignificant and/or stable on supportive therapy (as determined by the treating physician).
7. Patient must have acceptable bone marrow, renal, hepatic, and coagulation function, obtained within 2 weeks prior to registration to Step 2 as defined below:

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

- Absolute neutrophil count ≥ 1,500/mcL
- Absolute neutrophil count: _____ Date of Test_____
- Platelets ≥ 100,000/mcL
- Platelets: _____ Date of Test_____
- Hemoglobin ≥ 9 g/dL
- Hemoglobin: _____ Date of Test_____
- Total bilirubin ≤ 1.5 x institutional ULN (for patients with Gilbert's disease total bilirubin must be ≤ 3x ULN)
- Total bilirubin: _____ ULN: _____ Date of Test_____
- Gilbert's disease: _____(Yes or No)
- AST(SGOT) and ALT(SGPT) ≤ 2.5 × ULN
- AST (SGOT): _____ ULN: _____ Date of Test_____
- ALT (SGPT): _____ ULN: _____ Date of Test_____
- Creatinine ≤ 1.5 x ULN
  OR
- Calculated (Crockoft-Gault formula) or measured creatinine clearance ≥ 50 mL/min/1.73m2 (normalized to BSA) for patients with creatinine levels greater than 1.5 times the institutional normal Creatinine ≤ 1.5 X ULN or creatinine clearance ≥ 50ml/min/1.73m2
- Creatinine: _____ ULN: _____ Date of Test _____
- Creatinine clearance: _____ Date of Test: _____

8. Patient must have corrected QT interval calculated by the Fridericia formula (QTcF) ≤ 500 ms within 28 days prior to Step 2 registration.

9. Patient must not have any intercurrent illness or disease complication that the investigator believes would limit the ability to safely tolerate the combination of cabozantinib and nivolumab.
10. Patient 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.
11. All patients of childbearing potential must have a blood test or urine study within 14 days prior to registration to Step 2 to rule out pregnancy.

12. A patient of childbearing potential is anyone, 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).
    Patient of childbearing potential? _____ (Yes or No)
    Date of blood test or urine study: _____

13. Patients 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 6 months after completion of treatment on the study.

Eligibility Criteria for Step 2 (Crossover Arm Z)

1. Patient must have met all eligibility requirements for Step 1 (see Section 3.1) at time of registration to Step 1 to be eligible for Step 2.
2. Patient must have radiographic progressive disease per RECIST criteria (see Section 6.1.4) after ≥ 2 cycles of therapy on Arm C. The scan showing progression must be completed within 6 weeks prior toStep 2 registration.
3. Patient must not have intervening anticancer treatment or major surgical procedure(s) between Step 1 and Step 2, except palliative radiation which was completed ≥ 1 week prior to registration to Step 2.
4. Patient may not have central nervous system progression, butpatients with stable CNS disease are allowed.
5. Patient must have an ECOG performance status 0-2 (see AppendixV)
6. Patient must have recovered to equal to or less than grade 1 toxicitiesrelated to prior treatment, unless the adverse event(s) are clinically nonsignificant and/or stable on supportive therapy (as determined by the treating physician).
7. Patient must have acceptable bone marrow, renal, hepatic, and coagulation function, obtained within 2 weeks prior to registration toStep 2 as defined below:
    - ULN = institutional upper limit of normal; LLN = institutional lower limitof normal
    - Absolute neutrophil count ≥ 1,500/mcL
    - Absolute neutrophil count:_____

      Date of Test_____

      Platelets ≥ 100,000/mcL
    - Platelets:_____

Date of Test_____

Hemoglobin ≥ 9 g/dL

- Hemoglobin:_____
  Date of Test_____
- Total bilirubin ≤ 1.5 x institutional ULN (for patients with Gilbert'sdisease total bilirubin must be ≤ 3x ULN)
- Total bilirubin:___ULN:___Date of Test___
- Gilbert's disease:___(Yes or No)

AST(SGOT) and ALT(SGPT) ≤ 2.5 × ULN

- AST (SGOT):_____ULN:_____

  Date of Test_____
- ALT (SGPT):_____ULN:_____

  Date of Test_____
- Creatinine ≤ 1.5 x ULNOR
- Calculated (Crockoft-Gault formula) or measured creatinine clearance
- ≥ 50 mL/min/1.73m^2 (normalized to BSA) for patients with creatininelevels greater than 1.5 times the institutional normal Creatinine ≤ 1.5 X ULN or creatinine clearance
- ≥ 50ml/min/1.73m^2
- Creatinine:_____ULN:_____

  Date of Test _____
- Creatinine clearance:_____

  Date of Test: _____

8. Patient must have corrected QT interval calculated by the Fridericiaformula (QTcF) ≤ 500 ms within 28 days prior to Step 2 registration.
9. Patient must not have any intercurrent illness or disease complicationthat the investigator believes would limit the ability to safely tolerate the combination of cabozantinib and nivolumab.
10. Patient must not be pregnant or breast-feeding due to the unknown effects of cabozantinib and nivolumab on human development and forthe potential risk for adverse events in nursing infants with the treatment regimens being used.
    - All patients of childbearing potential must have a blood test or urinestudy within 14 days prior to registration to Step 2 to rule out pregnancy.
    - A patient of childbearing potential is anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meetsthe following criteria: 1) has achieved menarche at some point, 2) hasnot 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

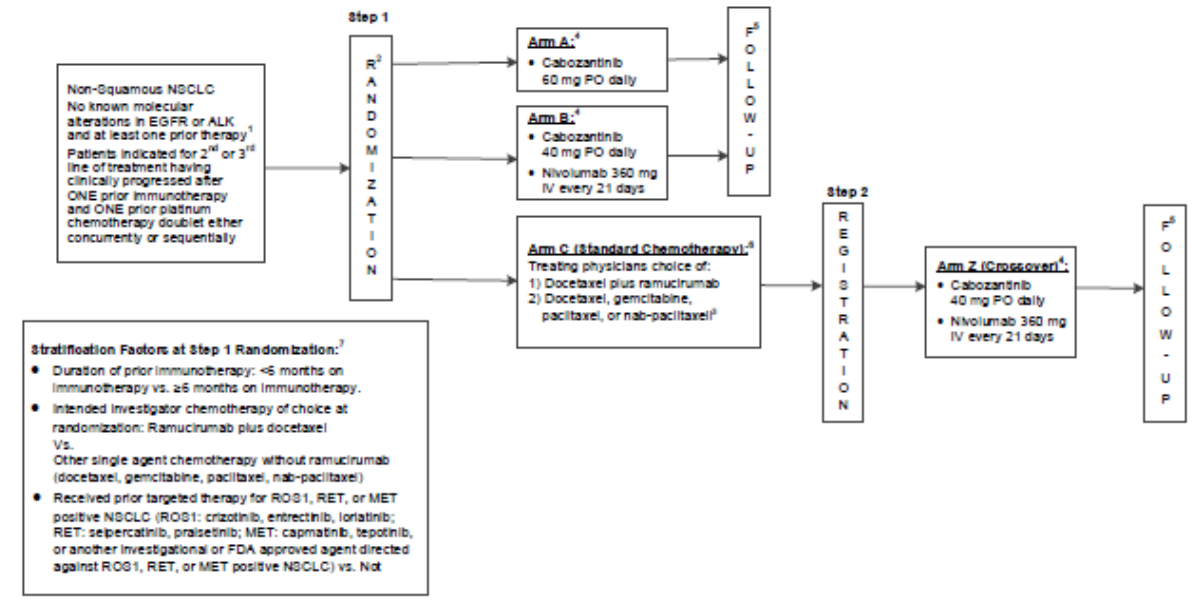
menses at any time in the preceding 24 consecutive months).

- Patient of childbearing potential?_____(Yes or No)

  Date of blood test or urine study: _____

11. Patients must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstainingfrom sexual intercourse for the duration of their participation in the study and for 6 months after completion of treatment on the study.

Schema



N=117 (Arms A, B, and C)

1 Cycle = 3 weeks (21 days)

1. Tumors must be known to be negative for EGFR or ALK mutations.
2. Randomization is 1:1:1 across Arms A, B, and C.
3. Please refer to Section 5.1.3 for specific dosing guidelines.
4. Patients will continue on study treatment until progressive disease or until an adverse event requiring discontinuation occus at which time patient would proceed to follow-up.
5. Patients remain in follow-up for 3 years per Section 5.7.
6. Patients will continue Arm C treatment until progressive disease, at which point the patient may proceed to Step 2 registration for crossover Arm Z (if eligible, see Section 3.2).
7. If patients have not received prior targeted therapy for ROS1/RET/MET, randomization will be stratified. Patients who have received prior targeted therapy will be randomized directly.