Cancer Research Consortium of West Michigan
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Fast Facts

S1403: A Randomized Phase II/III Trial of Afatinib Plus Cetuximab Versus Afatinib Alone in Treatment-Naive Patients with Advanced, EGFR Mutation Positive Non-Small Cell Lung Cancer (NSCLC) – Drugs provided

ARM 1: Diphenhydramine 50mg IV prior to first dose of cetuximab hydrochloride

Afatinib 40mg PO Daily

Cetuximab 500mg/m2 2 hr IV infusion Day 1 & 15, q 28 days

ARM 2: Afatinib 40mg PO Daily

ELIGIBILITY CRITERIA

Disease Related Criteria

1. Patients must have histologically or cytologically confirmed Stage IV (AJCC 7th Edition) or recurrent non-small cell lung cancer (NSCLC).
2. Patients must have documented presence of an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. T790M mutation or other molecular abnormality will be allowed as long as it accompanies one of the mutations listed above. EGFR testing must have been performed using a FDA-approved test or in a CLIA-certified laboratory.
3. Patients must have tissue available and must agree to submission of tissue and blood as outlined in Section 15.0. One to two paraffin-embedded tissue blocks or 15-20 unstained slides are requested (a minimum of 12 slides is required). Cytology (i.e. fine-needle aspirations, pleural effusion specimens) is acceptable if a cell block or sufficient unstained slides are available. Tumor material must be reviewed by a local pathologist who must confirm that at least 100 viable tumor cells are present in the sample and sign the **S1403** Pathology Review Form. Patients must also be willing to submit blood samples for correlative research at baseline, during treatment and at progression.
4. Patients enrolled at sites participating in the Repeat Biopsy Study must agree to submission of tissue obtained by a repeat biopsy performed at the time of disease progression.
5. Patients must not have received any prior systemic anticancer therapy for advanced or metastatic disease including chemotherapy or EGFR tyrosine kinase inhibitor therapy (including gefitinib, erlotinib, afatinib, or any experimental EGFR TKI agents). Prior chemotherapy for non-metastatic disease (i.e. adjuvant therapy or concurrent chemo-radiotherapy) is allowed as long as >12 months has passed since completion of therapy. Adjuvant EGFR-directed therapy is not allowed. Local therapy (i.e. palliative radiotherapy) is allowed as long as a period of 7 days has passed since the last dose was received and the patient has recovered from any associated toxicity at the time of registration.
6. Patients may have measurable or non-measurable disease (see Section 10.1) documented by CT or MRI within 42 days prior to registration. The CT from a combined PET/CT may be used only if it is of diagnostic quality as defined in Section 10.1a. Laboratory parameters are not acceptable as the only evidence of disease. In order to qualify as measurable per Section 10.1a, measurable disease must be outside previous radiation field. All disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).
7. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to registration. Patient must not have symptomatic brain metastases or evidence of leptomeningeal

carcinomatosis. Patients with asymptomatic brain metastases are eligible if off of steroids for at least 7 days prior to registration without development of symptoms.

8. Patients must not have any known clinically active interstitial lung disease.

Clinical/Laboratory Criteria

1. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500/mcL; platelets ≥ 75,000/mcL; and hemoglobin ≥ 9 g/dL. These results must be obtained within 28 days prior to registration.
2. Patients must have adequate liver function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN), and AST and ALT ≤ 2.5 x IULN (or ≤ 5 x IULN for patients with known liver metastases). These results must be obtained within 28 days prior to registration.
3. Patient must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ 1.5 x IULN OR measured or calculated creatinine clearance ≥ 60 mL/min. This result must have been obtained within 28 days prior to registration. Estimated creatinine clearance = (140 - age) x wt (kg) x 0.85 (if female) 72 x creatinine (mg/dl)
4. Patients must not have significant gastrointestinal disorders with diarrhea as a major symptom (e.g. Crohn's disease, malabsorption, etc).
5. Patients must be able to swallow medication by oral route.
6. Patients must not have a history of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3 (see Section 18.5), unstable angina or poorly controlled arrhythmia or myocardial infarction within 6 months prior to registration. If clinically indicated, echocardiogram or MUGA must be performed and cardiac ejection fraction must be ≥ 50%.
7. Patients must not have had major surgery within 28 days prior to registration or be scheduled for surgery during the projected course of protocol treatment. Tumor biopsy is allowed.
8. Patients must not have a known history of active hepatitis B infection (defined as presence of Hep B sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV seropositive.
9. Patients must not have any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the study drug.
10. Patients must not be planning to receive any other investigational agents during the course of protocol treatment.
11. Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to afatinib and/or cetuximab.
12. Prestudy history and physical must be obtained with 28 days prior to registration.
13. Patients must have Zubrod Performance Status of 0 - 2 (see Section 10.4).
14. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.
15. Patients must not be pregnant or nursing because of the risk of fetal harm including fetal death. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously

celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Regulatory Criteria

1. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
2. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

Pre-Study Parameters

- History and Physical, weight, PS, Disease assessment
- CBC/Diff/Platelets
- CMP
- Serum Creatinine/Calc Clearance
- INR
- PET scan
- CT of chest/abdomen
- Brain CT or MRI
- ECHO/MUGA
- ECG