Appendix:

Appendix 1: Complete Eligiblity Criteria

Eligibility

- Cytologically or histologically confirmed non-small cell lung carcinoma (NSCLC).
- Predominant non-squamous histology (patients with NSCLC NOS were eligible). Mixed tumors were categorized by the predominant cell type. If small cell elements were present the patient was ineligible.
- Stage IV disease (includes M1a, M1b, or recurrent disease), according to the 7th edition of the lung cancer TNM classification system.
- The tumor must not have had a sensitizing mutation in *EGFR*, defined as follows: (1) *EGFR* mutation testing of tumor was performed and did not demonstrate an EGFR tyrosine kinase inhibitor sensitizing mutation. At minimum, testing for *EGFR* Exon 19 deletion and Exon 21 L858R mutations must have been included. OR (2) *EGFR* mutation testing was attempted and was inconclusive (for example, due to lack of sufficient DNA yield). OR (3) *EGFR* mutation status was unknown but tumor was positive for at least one alternative driver mutation, i.e: KRAS mutation, BRAF mutation, HER2 mutation, RET rearrangement/fusion, or one not listed following approval by the study chair prior to registration.
- Patients must have had measurable disease as defined by RECIST v1.1 criteria. Baseline measurements and evaluation of ALL sites of disease must have been obtained within 4 weeks prior to registration.
- Prior to registration, the investigator/site must have confirmed that sufficient pathology material representative of patient's cancer was available for submission for MET immunohistochemical testing. Patients for whom there was not sufficient pathology material representative of the patients cancer (tumor block or 10 unstained slides) were not eligible to participate in this study.
- Patients must have received one or two lines of prior chemotherapy (first line platinum-doublet based chemotherapy plus switch maintenance chemotherapy counted as one line of therapy). Prior adjuvant chemotherapy for early stage disease did not count as one line of therapy if 12 months or greater elapsed between completion of adjuvant therapy and initiation of first-line systemic therapy. If less than 12 months elapsed, adjuvant chemotherapy counted as one line of therapy.
- No prior erlotinib, other EGFR tyrosine kinase inhibitor therapy, VEGFR tyrosine kinase inhibitor therapy, Met tyrosine kinase inhibitor therapy, or MetMAb. Prior antibody therapy such as bevacizumab or cetuximab was allowed with a washout period depending on dosing interval and investigational nature (see following two eligibility criteria below).
- Any prior chemotherapy (based on administration schedule) must have been completed in greater than or equal to the time frames specified in the protocol.
- Patients must have discontinued treatment with any other type of investigational agent 24 weeks prior to registration.
- Patients must have recovered to baseline or CTCAE v4.0 : Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs.
- Patients with no known brain metastasis at baseline must have had baseline brain imaging within 12 weeks prior to study registration not demonstrating brain metastases. Patients with brain metastases at baseline must have had baseline brain imaging within 4 weeks prior to study registration and meet all of the specific treatment criteria for brain mets listed in the protocol.
- Radiation related toxicities must have resolved to : Grade 1 prior to registration.
- Patients must not have received radiation therapy to the thoracic cavity, abdomen or pelvis within 3 months prior to registration, to the bone or brain within 14 days prior, or to any other site within 28 days or registration.
- Patients must have had an ECOG performance status between 0-2.
- Patients must have had an anticipated life expectancy greater than 3 months.

- Patients must have had acceptable bone marrow, renal and hepatic function within 2 weeks prior to registration as defined in the protocol.
- No history of the following: Clinically-significant gastrointestinal bleeding within 6 months prior to registration; Hemoptysis of 2 0.5 teaspoon (2.5 mL) of red blood within 3 months prior to registration; Any other signs indicative of pulmonary hemorrhage within 3 months prior to registration.
- No radiographic or other evidence of the following within 28 days prior to registration: Tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor; Cavitating pulmonary lesion(s);Tumor in contact with, invading or encasing any major blood vessels.
- No patients with psychiatric illness/social situations that would limit compliance with study requirements.
- No history of major thrombotic events (DVT or PE) within 6 months prior to registration.
- No concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, low molecular weight heparin (LMWH), thrombin or Factor Xa inhibitors, or antiplatelet agents (e.g., clopidogrel). (Low dose aspirin (: 81 mg/day) and prophylactic LMWH was permitted.)
- No concomitant treatment of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. Johns Wort).
- No cardiovascular disorders including: Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening; Concurrent uncontrolled hypertension; No history of congenital long QT syndrome; None of the following within 6 months prior to registration: unstable angina pectoris,clinically-significant cardiac arrhythmia; No gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation.
- No uncontrolled, significant, intercurrent or recent illness.
- Patients must have had corrected QT interval calculated by the Fridericia formula (QTcF) : 500 ms within 28 days before registration.
- Patients must have been able to swallow tablets.
- No prior malignancy within 2 years prior to registration which required systemic treatment or was currently active.
- Age 2 18 years on day of consent.
- Women must not have been pregnant or breast-feeding.
- Patients with known HIV disease taking antiretroviral therapy were excluded.

Appendix 2: All treatment-related adverse events

Toxicity Type	Treatment Arm											
	A (n=40)				B (n=40)				C (n=39)			
	Grade				Grade				Grade			
	1,2	3	4	5	1,2	3	4	5	1,2	3	4	5
	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)
Anemia	5	1	-	-	11	1	-	-	13	1	-	-
Blood and lymphatic system disorders - Other, specify	-	-	-	-	-	-	-	-	1	-	-	-
Atrial fibrillation	-	-	-	-	2	1	-	-	-	-	-	-
Cardiac disorders - Other, specify	-	-	-	-	-	-	-	-	1	-	-	-
Chest pain - cardiac	-	-	-	-	1	-	-	-	-	-	-	-
Heart failure	-	-	-	-	1	-	-	-	-	-	-	-
Myocardial infarction	-	-	-	-	-	1	-	-	-	-	-	-
Sinus tachycardia	-	-	-	-	-	1	-	-	-	-	-	-
Chills	1	-	-	-	2	-	-	-	-	-	-	-
Edema face	-	-	-	-	1	-	-	-	1	-	-	-
Fatigue	18	5	-	-	22	6	-	-	27	6	-	-
Fever	-	-	-	-	2	-	-	-	-	-	-	-
Flu like symptoms	1	-	-	-	1	-	-	-	-	-	-	-
General disorders and administration site conditions - Other, specify	-	-	-	-	-	-	-	-	1	-	-	-
Malaise	-	-	-	-	1	-	-	-	1	-	-	-
Pain	-	-	-	-	2	-	-	-	-	-	-	-
Edema limbs	-	-	-	-	4	-	-	-	1	-	-	-
Non-cardiac chest pain	-	-	-	-	1	-	-	-	-	-	-	-
Alopecia	1	-	-	-	2	-	-	-	2	-	-	-
Dry skin	9	-	-	-	9	-	-	-	10	-	-	-
Erythroderma	-	-	-	-	1	-	-	-	-	-	-	-
Hirsutism	-	-	-	-	1	-	-	-	-	-	-	-
Nail discoloration	-	-	-	-	1	-	-	-	-	-	-	-
Pain of skin	-	-	-	-	-	-	-	-	1	-	-	-
Pruritus	5	-	-	-	2	-	-	-	7	-	-	-
Rash acneiform	22	1	-	-	6	1	-	-	23	2	-	-
Rash maculo-papular	3	-	-	-	4	-	-	-	6	1	-	-
Skin and subcutaneous tissue disorders - Other, specify	-	-	-	-	4	-	-	-	3	-	1	-
Skin hypopigmentation	-	-	-	-	2	-	-	-	-	-	-	-
Skin ulceration	-	-	-	-	1	-	-	-	-	-	-	-
Nail loss	1	-	-	-	-	-	-	-	-	-	-	-
Palmar-plantar	3	-	-	-	6	1	-	-	6	-	-	-

erythrodysesthesia syndrome												
Endocrine disorders - Other, specify	-	-	-	-	1	-	-	-	2	-	-	-
Hyperthyroidism	-	-	-	-	5	-	-	-	1	-	-	-
Hypothyroidism	-	-	-	-	10	-	-	-	2	-	-	-
Abdominal pain	4	-	-	-	4	1	-	-	4	-	-	-
Bloating	-	-	-	-	2	-	-	-	-	-	-	-
Colitis	1	-	-	-	-	-	-	-	-	-	-	-
Constipation	1	-	-	-	6	-	-	-	4	-	-	-
Diarrhea	21	3	-	-	20	3	-	-	25	11	-	-
Dry mouth	3	-	-	-	3	-	-	-	6	-	-	-
Dyspepsia	2	-	-	-	4	-	-	-	5	-	-	-
Dysphagia	3	-	-	-	2	-	-	-	-	-	-	-
Esophageal pain	-	-	-	-	-	-	-	-	1	-	-	-
Esophagitis	-	-	-	-	1	-	-	-	-	-	-	-
Flatulence	-	-	-	-	3	-	-	-	1	-	-	-
Gastrointestinal disorders - Other, specify	-	-	-	-	2	-	-	-	-	-	-	-
Hemorrhoids	-	-	-	-	-	-	-	-	1	-	-	-
Mucositis oral	2	-	-	-	13	4	-	-	8	1	-	-
Nausea	8	1	-	-	18	2	-	-	17	1	-	-
Oral hemorrhage	-	-	-	-	-	-	-	-	1	-	-	-
Oral pain	-	-	-	-	2	-	-	-	4	-	-	-
Pancreatitis	-	-	-	-	-	1	-	-	-	-	-	-
Rectal hemorrhage	-	-	-	-	1	-	-	-	2	-	-	-
Rectal pain	-	-	-	-	1	-	-	-	-	-	-	-
Stomach pain	-	-	-	-	1	-	-	-	-	-	-	-
Vomiting	4	1	-	-	5	1	-	-	10	1	-	-
Oral dysesthesia	-	-	-	-	1	-	-	-	-	-	-	-
Esophageal fistula	1	-	-	-	-	-	-	-	-	-	-	-
Gastroesophageal reflux disease	-	-	-	-	2	-	-	-	-	-	-	-
Hepatobiliary disorders - Other, specify	-	-	-	-	-	-	-	-	1	-	-	-
Portal vein thrombosis	-	-	-	-	-	1	-	-	-	-	-	-
Infections and infestations - Other, specify	-	-	-	-	1	-	-	-	-	-	-	-
Paronychia	-	-	-	-	-	-	-	-	2	-	-	-
Skin infection	1	-	-	-	1	1	-	-	-	-	-	-
Urinary tract infection	-	-	-	-	1	1	-	-	-	-	-	-
Vaginal infection	-	-	-	-	1	-	-	-	-	-	-	-
Lung infection	-	-	-	-	-	2	-	-	-	-	-	-
Scrotal infection	-	-	-	-	-	-	-	-	1	-	-	-

Papulopustular rash	1	-	-	-	-	-	-	-	-	-	-	-
Bruising	-	-	-	-	1	-	-	-	-	-	-	-
Fall	-	-	-	-	-	1	-	-	-	-	-	-
Activated partial thromboplastin time prolonged	-	-	-	-	-	-	-	-	1	-	-	-
Alanine aminotransferase increased	4	-	-	-	21	-	-	-	13	-	-	-
Alkaline phosphatase increased	2	-	-	-	8	-	-	-	3	-	-	-
Aspartate aminotransferase increased	8	-	-	-	26	-	-	-	17	-	-	-
Blood bilirubin increased	5	1	-	-	5	-	-	-	4	1	-	-
Creatinine increased	1	-	-	-	5	-	-	-	3	-	-	-
Investigations - Other, specify	1	-	-	-	1	-	-	-	1	-	-	-
Lipase increased	2	1	-	-	-	2	-	-	3	-	-	-
Lymphocyte count decreased	1	-	-	-	5	1	-	-	5	1	-	-
Neutrophil count decreased	-	-	-	-	1	1	-	-	2	-	-	-
Platelet count decreased	1	-	-	-	14	-	-	-	8	-	1	-
Weight loss	6	-	-	-	12	1	-	-	13	-	-	-
White blood cell decreased	1	-	-	-	9	-	-	-	5	-	-	-
Anorexia	10	2	-	-	15	1	-	-	17	3	-	-
Dehydration	2	1	-	-	2	-	-	-	5	1	-	-
Hypercalcemia	2	-	-	-	-	-	-	-	1	-	-	-
Hyperglycemia	1	-	-	-	3	-	-	-	2	-	-	-
Hyperkalemia	-	-	-	-	2	-	-	-	-	-	-	-
Hypoalbuminemia	2	-	-	-	9	-	-	-	4	-	-	-
Hypocalcemia	1	-	-	-	4	1	-	-	7	-	-	-
Hypoglycemia	-	-	-	-	1	-	-	-	-	-	-	-
Hypokalemia	4	1	-	-	4	-	-	-	7	-	-	-
Hypomagnesemia	6	-	-	-	12	1	-	-	13	-	-	-
Hyponatremia	3	-	-	-	3	1	-	-	2	3	-	-
Hypophosphatemia	-	-	-	-	1	-	-	-	1	-	-	-
Metabolism and nutrition disorders - Other, specify	1	-	-	-	-	-	-	-	-	-	-	-
Arthralgia	-	-	-	-	1	-	-	-	-	-	-	-
Bone pain	-	-	-	-	-	-	-	-	-	1	-	-
Musculoskeletal and connective tissue disorder - Other, specify	-	-	-	-	1	-	-	-	-	-	-	-
Myalgia	2	-	-	-	1	-	-	-	1	-	-	-
Pain in extremity	-	-	-	-	1	-	-	-	-	-	-	-
Buttock pain	-	-	-	-	1	-	-	-	-	-	-	-

Generalized muscle weakness	-	-	-	-	2	1	-	-	4	-	-	-
Muscle weakness lower limb	-	-	-	-	1	1	-	-	1	-	-	-
Cognitive disturbance	-	-	-	-	-	1	-	-	-	-	-	-
Dizziness	1	-	-	-	3	-	-	-	5	-	-	-
Dysgeusia	6	-	-	-	12	-	-	-	11	-	-	-
Dysphasia	-	-	-	-	-	1	-	-	-	-	-	-
Headache	1	-	-	-	2	-	-	-	1	-	-	-
Intracranial hemorrhage	-	-	-	-	-	-	1	-	-	-	-	-
Lethargy	-	-	-	-	2	-	-	-	-	-	-	-
Nervous system disorders - Other, specify	-	-	-	-	1	-	-	-	-	-	-	-
Peripheral sensory neuropathy	-	-	-	-	4	1	-	-	1	-	-	-
Presyncope	-	-	-	-	1	-	-	-	-	-	-	-
Syncope	-	-	-	-	-	-	-	-	-	3	-	-
Blurred vision	-	-	-	-	1	-	-	-	1	-	-	-
Conjunctivitis	3	-	-	-	-	-	-	-	-	-	-	-
Dry eye	2	-	-	-	2	-	-	-	2	-	-	-
Eye disorders - Other, specify	-	-	-	-	-	-	-	-	1	-	-	-
Watering eyes	1	-	-	-	1	-	-	-	2	-	-	-
Anxiety	-	-	-	-	-	-	-	-	2	-	-	-
Confusion	-	-	-	-	1	1	-	-	-	-	-	-
Depression	1	-	-	-	-	-	-	-	1	-	-	-
Hallucinations	-	-	-	-	1	-	-	-	-	-	-	-
Insomnia	1	1	-	-	1	-	-	-	-	-	-	-
Allergic rhinitis	-	-	-	-	1	-	-	-	-	-	-	-
Cough	2	-	-	-	2	-	-	-	3	-	-	-
Dyspnea	1	-	-	-	3	2	-	-	6	1	-	-
Epistaxis	1	-	-	-	2	-	-	-	1	-	-	-
Hoarseness	-	-	-	-	2	-	-	-	2	-	-	-
Pneumonitis	1	-	-	-	-	-	-	-	-	-	-	1
Respiratory failure	-	-	-	-	-	-	-	1	-	-	-	-
Respiratory, thoracic and mediastinal disorders - Other, specify	-	-	-	-	1	-	-	-	-	-	-	-
Sore throat	1	-	-	-	3	-	-	-	-	-	-	-
Voice alteration	1	-	-	-	3	-	-	-	3	-	-	-
Bronchopulmonary hemorrhage	1	-	-	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	2	-	-	-	-	-	-	-
Proteinuria	1	-	-	-	12	2	-	-	18	-	-	-

Renal and urinary disorders - Other, specify	-	-	-	-	1	-	-	-	-	-	-	-
Urinary tract pain	-	-	-	-	1	-	-	-	-	-	-	-
Chronic kidney disease	-	-	-	-	2	-	-	-	1	-	-	-
Vaginal fistula	-	-	-	-	-	1	-	-	-	-	-	-
Hypertension	4	-	-	-	8	10	-	-	17	1	-	-
Hypotension	-	-	-	-	1	1	-	-	1	-	-	-
Superior vena cava syndrome	-	-	-	-	-	-	-	-	1	-	-	-
Thromboembolic event	2	-	-	-	1	3	-	-	-	1	1	-
WORST DEGREE	23	13	-	-	12	26	1	1	11	24	3	1

Appendix 3: Lethal Adverse Events

Treatment group	Adverse Event	Attribution
Erlotinib	Hepatic failure	Definitely related to lung cancer
Erlotinib	Respiratory failure	Definitely related to lung cancer
Erlotinib	Neoplasms -Other	Possibly related to lung cancer
Erlotinib	Respiratory failure	Definitely related to lung cancer
Erlotinib	Neoplasms -Other	Probably related to lung cancer
Erlotinib	Respiratory failure	Definitely related to lung cancer
Erlotinib	Neoplasms -Other	Definitely related to lung cancer
Cabozantinib	Neoplasms -Other	Definitely related to lung cancer
Cabozantinib	Neoplasms -Other	Definitely related to lung cancer
Cabozantinib	Respiratory failure	Treatment-related
Erlotinib + Cabozantinib	Pneumonitis	Treatment-related
Erlotinib + Cabozantinib	Dyspnea	Definitely related to lung cancer
Erlotinib + Cabozantinib	Neoplasms –Other	Definitely related to lung cancer
Erlotinib + Cabozantinib	Neoplasms –Other	Definitely related to lung cancer
Erlotinib + Cabozantinib	Neoplasms –Other	Probably related to lung cancer
Erlotinib + Cabozantinib	Respiratory thoracic mediastinal - Other	Probably related to lung cancer
Erlotinib + Cabozantinib	Neoplasms –Other	Probably related to lung cancer
Erlotinib + Cabozantinib (Crossover arm)	Neoplasms –Other	Definitely related to lung cancer

Appendix 4: Accrual by Institution

Stanford Cancer Institute	11	8.8%
Metro-Minnesota CCOP	11	8.8%
Central Illinois CCOP	7	5.6%
Emory University/Winship Cancer Institute	6	4.8%
University of Pittsburgh Cancer Institute (UPCI)	6	4.8%
Michigan Ca Res Consortium CCOP	6	4.8%
University of Wisconsin Hospital and Clinics	5	4.0%
Mayo Clinic	5	4.0%
Thomas Jefferson University Hospital	5	4.0%
Indiana Univ/Melvin and Bren Simon Cancer Center	5	4.0%
Albert Einstein College of Medicine	5	4.0%
Main Line Health CCOP	4	3.2%
Ill ORA CCOP	4	3.2%
Sanford Community CA Consortium-SD	4	3.2%
Northwestern University	4	3.2%
CWRU - MetroHealth Medical Center	3	2.4%
St. Vincent Hosp Reg Ca Ctr CCOP	3	2.4%
Christiana Care CCOP	3	2.4%
Fox Chase Cancer Center	2	1.6%
University of Pennsylvania/Abramson Cancer Center	2	1.6%
Columbus CCOP	2	1.6%
Carle Clinic CCOP	2	1.6%
University of Miami Miller Schl Med-SylvesterCaCtr	2	1.6%
Colorado CA Research Program CCOP	2	1.6%
Northern Indiana CRC CCOP	2	1.6%
Sanford Comm CA Consortium-Fargo	2	1.6%
Johns Hopkins Univ/Sidney Kimmel Cancer Center	2	1.6%
Case Western Reserve University	1	0.8%
Missouri Valley CA Consortium CCOP	1	0.8%
Cedar Rapids CCOP	1	0.8%
Kalamazoo CCOP	1	0.8%
LewisCa and ResPvln@StJoseph's/Candler	1	0.8%
Evanston NW Healthcare CCOP	1	0.8%
Geisinger CCOP	1	0.8%
University of Texas Hlth Science Ctr @ San Antonio	1	0.8%
Wichita CCOP	1	0.8%
University of Alabama at Birmingham Cancer Center	1	0.8%

Note: Because of the organisational structure of ECOG-ACRIN, the principal investigator at many sites may not have recruited patients, so this information is not provided.