NCI Protocol #: N/A

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TITLE: A Phase 2 Study of EGF816 and gefitinib in TKI-naïve EGFR-mutant Non-Small Cell Lung Cancer

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Other Agent(s): Gefitinib, commercial

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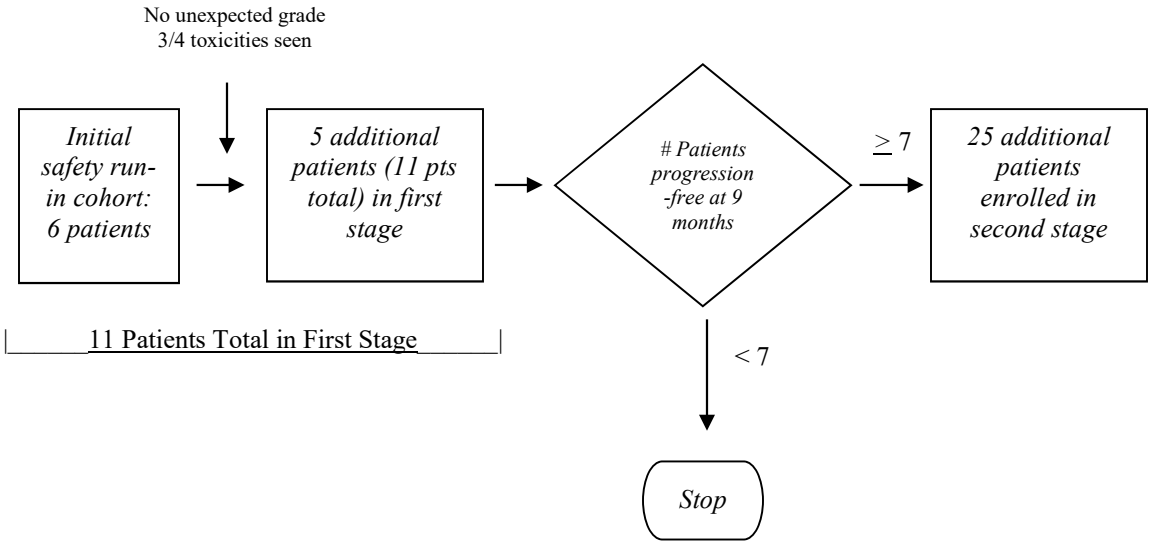
SCHEMA


No unexpected grade 3/4 toxicities seen
Initial safety run-in cohort: 6 patients
5 additional patients (11 pts total) in first stage
Patients progression -free at 9 months
≥ 7
25 additional patients enrolled in second stage
11 Patients Total in First Stage
< 7
Stop

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1. OBJECTIVES

1.1 Study Design

This is a single arm, open-label phase II study evaluating the safety and efficacy of the combination of the third-generation EGFR inhibitor EGF816 with the first-generation EGFR inhibitor gefitinib in the treatment of TKI-naïve *EGFR*-mutant non-small cell lung cancer. The study will have a Simon two-stage design with eleven patients enrolled in the first stage and a plan to enroll a total of 36 patients (25 patients in the second stage) if at least seven patients remain progression-free at nine months in the first stage. The first six patients enrolled in the study will constitute a safety run-in evaluating the safety of the combination of EGF816 at the recommended phase II dose of 150mg QD and gefitinib at a standard dose of 250mg QD. If unexpected toxicities are observed among the first six patients, expansion cohorts will be added to explore different doses and/or schedules of the combination.

1.2 Primary Objectives

The primary objective of the study is to evaluate the efficacy of EGF816 in combination with gefitinib in the treatment of TKI-naïve EGFR-mutant NSCLC. Efficacy will be measured as proportion that are progression-free at 39 weeks.

1.3 Secondary Objectives

The secondary objectives of the study will include:

- To describe the median progression free and overall survival of patients treated with EGF816 and gefitinib.
- To evaluate the safety and tolerability of the EGF816/gefitinib combination.

1.4 Exploratory Objectives

- To characterize the pharmacokinetic interactions between gefitinib and EGF816.
- To evaluate resistance mechanisms to EGF816 and gefitinib.
- To characterize the molecular response to treatment in on-treatment tumor biopsies and in circulating tumor DNA.

2. BACKGROUND

2.1 Study Disease(s)

Non small cell lung cancer (NSCLC) is a heterogeneous entity which affects over 220,000 people in the US each year, and is the leading cause of cancer-related mortality in the world[2]. Over half of NSCLC patients have advanced or metastatic disease at presentation. Unfortunately, metastatic disease is not curable, and current chemotherapy offers only modest improvements in survival. Recently, genetic alterations leading to an "oncogene-addicted" biology have been shown to occur

in a subset of NSCLC patients and confer sensitivity to specific tyrosine kinase inhibitors (TKI's.)[3] These biologically targeted agents have had a significant impact on the survival of patients carrying such genetic alterations, but their efficacy is limited and the discovery of novel ways to prolong the disease course remains a top research priority.

The epidermal growth factor receptor (EGFR) receptor signaling pathway plays a central role in the neoplastic transformation of NSCLC and promotes cancer cell survival, metastasis and angiogenesis[4]. Somatic mutations in the EGFR gene in NSCLC tumors have been well-described. EGFR mutations are present in about 10% of unselected US patients with NSCLC, but in up to 50% of never-smoking NSCLC patients[5]. Although a variety of mutations within EGFR have been described, the most common of these mutations include exon 19 deletion and the L858R mutation in exon 21, both of which sensitize NSCLC tumors to treatment with EGFR TKIs such as gefitinib and erlotinib. Erlotinib and gefitinib have now been shown to improve both response rates and progression-free survival in patients with EGFR-mutant NSCLC in multiple randomized trials[6-8].

Although remarkable response rates are seen in patients with EGFR mutations that are treated with EGFR TKIs (~ 80%), the responses are of limited duration because eventually patients develop "acquired resistance". Several resistance mechanisms have been identified, the most common being a secondary mutation at the threonine gatekeeper residue at position 790, T790M, which develops in up to 50% of NSCLC patients harboring a primary EGFR mutation treated with first generation EGFR TKIs[9,10].

Third generation EGFR inhibitors targeting T790M and activating EGFR mutations with relative sparing of wild-type EGFR have now been developed. One such drug, osimertinib, received FDA approval based on objective response rate of ~60% among patients with T790M-mediated acquired resistance to initial EGFR inhibitor[11]. Several other third-generation EGFR inhibitors, including EGF816, are in clinical development and have shown equally promising activity. Unfortunately, the activity of these new drugs is also limited by the eventual development of acquired resistance, with current PFS estimates of about 9-13 months on osimertinib and other third-generation EGFR inhibitors[11,12].

Recent reports show that resistance to osimertinib, olmutinib and rociletinib can be mediated by the development of a new tertiary resistance mutation, C797S[13-15], which occurs at the site of covalent binding of all irreversible EGFR inhibitors, and has previously been identified as a putative resistance mechanism to this class of drugs in in vitro models[16]. Other resistance mechanisms, including MET amplification, Her2 amplification, BRAF mutations and SCLC transformation have also been identified in individual cases treated with third-generation EGFR inhibitors[17-19], and there is growing evidence that resistance to these novel agents may develop in the setting of increasing molecular heterogeneity and that multiple resistance mechanisms can co-exist in cancers progressing on third-generation EGFR TKIs[15].

Since cancers treated with sequential single-agent EGFR inhibitors have repeatedly demonstrated the ability to overcome such drugs through eventual development of resistance mechanisms including T790M and C797S, we hypothesize that using combinations of a first- and third-generation EGFR inhibitor in the first-line setting may delay the development of acquired resistance as neither resistance mutation alone would be sufficient to overcome the combination.

2.2 EGF816

2.2.1 Overview and non-clinical experience

EGF816 is a targeted covalent epidermal growth factor receptor (EGFR) inhibitor that selectively inhibits activating and resistance mutants (L858R, Exon 19 deletion mutation(s) of EGFR (ex19del), and T790M) while sparing wild type (WT) EGFR. First and second generation inhibitors of EGFR, which target activating mutations as well as WT EGFR, have been validated as therapeutic agents in specific scenarios; however, the narrow therapeutic window of these EGFR inhibitors, by inhibiting both mutant EGFR within the tumor and WT EGFR within normal tissues, significantly limits the maximum potential of this class of drugs. By sparing WT EGFR, while inhibiting mutant EGFR, EGF816 has the potential to improve upon the first and second generation EGFR inhibitors. Additionally, by inhibiting EGFR T790M, EGF816 offers a therapeutic option for patients harboring that mutation. EGF816 demonstrated efficacy in several EGFR-mutant non-small cell lung cancer (NSCLC) cell lines and xenograft models, including in vivo tumor regression in the H1975 model, which harbors EGFR L858R/T790M. In *in vivo* models, EGF816 also demonstrated a pharmacokinetic (PK)-tumor pharmacodynamic (PD) relationship, with PD outlasting PK, consistent with the irreversible binding of EGF816 to EGFR. Dose-dependent anti-tumor efficacy was observed in several xenograft models, and EGF816 was well tolerated with no body weight loss observed at efficacious doses.

In preclinical toxicology studies conducted in rats and dogs, EGF816 was overall well tolerated at plasma concentrations that resulted in anti-tumor activity in rodent efficacy models. One of the off-targets of EGF816 is Tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases. The results of a T-cell Dependent Antigen Response (TDAR) assay in rats indicated a trend for a dose-response effect of EGF816 on inhibiting the generation of antigen-specific antibodies to a foreign antigen; this effect was reversible following withdrawal of EGF816. In the first-in-human study of EGF816 in patients with EGFR-T790M NSCLC, preliminary PK data demonstrated that the EGF816 exposure increased largely in proportion to dose 75 mg to 350 mg, quaque die/ daily (q.d.) and the terminal half-life (T1/2) ranged from 13 hours (h) to 18h EGF816 appears to be efficacious at doses of 75 mg q.d. and above, and preliminary exposure-response analyses showed a flat relationship between EGF816 steady state trough concentration and overall response rate (RR). Preliminary population PK analysis indicated similar exposures from the matched doses in capsule and tablet formulations.

2.2.2 Clinical Experience

CEGF816X2101 is the first-in-human Phase I/II study of single-agent oral EGF816, and is currently ongoing. As of the data cut-off date (18-Dec-2015), 148 patients have been treated with EGF816 capsules or tablets at seven dose levels: 75 mg q.d. (N=7), 100 mg q.d. (N=29), 150 mg q.d. (N=64), 200 mg q.d. (N=8), 225 mg q.d. (N=24), 300 mg q.d. (N=5) and 350 mg q.d. (N=11). Eighty-four patients (56.8%) were still receiving treatment and 64 patients (43.2%) had discontinued treatment. Of these 64 patients, 53 (35.8%) discontinued treatment due to progressive disease, three (2.0%) discontinued treatment due to AEs, and 3 (2.0%) discontinued treatment due to death. Of the three patients who discontinued treatment due to

AE, one patient at the 350 mg q.d. reported Grade 3 maculopapular rash, one patient at the 150 mg daily dose reported Grade 3 interstitial lung disease, and one patient at the 300 mg daily dose reported Grade 3 pulmonary oedema. Of the three patients who discontinued treatment due to death, one patient died due to sepsis (considered not related to study treatment), one patient died due to hepatitis B virus (HBV) reactivation (considered related to study treatment), and one patient died due to pneumonia (considered not related to study treatment).

As of 18-Dec-2015, dose-limiting toxicities (DLT) were reported in five patients: one patient at the dose level of 150 mg capsule reported Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 225 mg capsule reported Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 350 mg capsule reported Grade 3 acute kidney failure and Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 350 mg capsule reported Grade 3 maculopapular rash that resulted in permanent discontinuation of treatment, and one patient at the dose level of 350 mg capsule reported. Grade 3 enteritis and Grade 3 dehydration that resulted in temporary treatment interruption.

As of the data cutoff date of 18-Dec-2015, 142 patients (95.9%) who were treated with EGF816 capsules or tablets experienced at least one AE of any grade, regardless of relationship to the study drug. The most frequent AEs (all CTCAE grades, >10% of patients) regardless of study drug relationship at the seven dose levels specified below were rash (group term) (56.1%), diarrhea (41.9%), maculopapular rash , pruritus (36.5%), fatigue (27.0%), stomatitis (27.0%), dry skin (24.3%), nausea (23.6%), cough (20.9%), decreased appetite (20.3%), vomiting (14.9%), constipation (14.2%), headache (12.8%), anemia (12.2%), paronychia (11.5%), pyrexia (11.5%), dyspnea (10.8%), edema peripheral (10.8%), back pain (10.1%), and upper respiratory tract infection (10.1%)

One-hundred thirty-four (90.5%) patients experienced AEs of any grade that were suspected to be related to EGF816. The most frequent (>10% of patients) AEs of any CTCAE grade suspected to be related to EGF816 were rash (group term) (52%), diarrhea (36.5%), pruritus (33.8%), dry skin (24.3%), stomatitis (24.3%), fatigue (16.2%), nausea (15.5%), decreased appetite (12.2%), and vomiting (10.1%)

Seventy (47.3%) patients who were treated with EGF816 capsules or tablets at the dose levels specified below experienced Grade 3 or Grade 4 AEs regardless of relationship to the study drug. Grade 3/4 AEs occurring in ≥ 2% of patients were rash (grouped term) (15.5%), anemia (5.4%), pneumonia (5.4%), diarrhea (4.7%), fatigue (2.7%), dyspnea (2.7%), urticaria (2.7%),hypertension (2.7%), stomatitis (2.0%), decreased appetite (2.0%), hyperuricemia (2.0%), and seizure (2.0%) .

Forty-four patients (29.7%) experienced Grade 3/4 AEs that were suspected to be related to EGF816. Those occurring in ≥ 1% of patients were rash (group term) (15.5%), anemia (2.7%), urticaria (2.7%), diarrhea (2.0%), fatigue (2.0%), stomatitis (2.0%), HBV (1.4%), and increased lipase (1.4%).

As of the data cutoff date (18-Dec-2015), SAEs, regardless of study drug relationship, were

reported in 48 patients (32.4%) who received at least one dose of single agent EGF816 capsules or tablets (at seven dose levels: 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg and 350 mg) (Table 5-9). Of these 48 patients, 15 experienced SAEs that were suspected to be related to study drug or study procedures: one patient at the 350 mg capsule daily dose was reported to have Grade 3 acute kidney injury that resulted in temporary drug interruption, one patient at the 350 mg capsule daily dose was reported to have Grade 3 dehydration and enteritis that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 hepatitis B reactivation and Grade 3 hepatic failure that resulted in permanent treatment discontinuation and death, one patient at the 225 mg capsule daily dose was reported to have Grade 3 purpura that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 hepatitis B reactivation that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 maculopapular rash that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 diarrhea that resulted in temporary drug interruption, two patients at the 150 mg capsule daily dose reported Grade 2 dyspnea that resulted in no action taken with study drug, one patient at the 150 mg capsule daily dose was reported to have Grade 1 acute renal failure that resulted in temporary drug interruption, one patient at the 150 mg capsule daily dose reported Grade 2 diarrhea that resulted in temporary drug interruption, one patient at the 150 mg capsule daily dose was reported to have Grade 3 interstitial lung disease that resulted in temporary drug interruption, one patient at the 150 mg capsule daily dose was reported to have Grade 3 pneumothorax that was related to a study-associated procedure that occurred after the patient had discontinued study drug, one patient at the 150 mg tablet daily dose was reported to have Grade 3 diarrhea that resulted in temporary drug interruption, and one patient at the 150 mg tablet daily dose was reported to have Grade 3 upper gastrointestinal hemorrhage that resulted in temporary drug interruption and was reported to have Grade 3 anemia (the SAEs of gastrointestinal hemorrhage and anemia were updated to not suspected related to study treatment in the safety database, but have not been updated in the clinical database).

As of 18-Dec-2015, the outcome of SAEs suspected to be related to study treatment was recovered or recovering in 12 of 15 patients. One patient died due to hepatic failure secondary to HBV reactivation, one patient was reported as not recovered from Grade 3 maculopapular rash, and one patient was reported as not recovered from Grade 3 anemia.

As of 18-Dec-2015, 2 SAEs of HBV reactivation have been reported in 2 patients participating in the CEGF816X2101 study. One case had a fatal outcome, and the second case (Patient 9001-012) was considered medically significant. The fatal case involved a patient who received EGF816 at 225 mg q.d., had a history of HBV infection and was not on antiviral treatment at study entry. The patient developed HBV reactivation during the study and died due to hepatic failure despite initiation of antiviral treatment after HBV reactivation had been confirmed. The second patient also received EGF816 at 225 mg q.d., had a history of HBV and was not on antiviral treatment at the time of joining the study, HBV reactivation was detected after the patient had been on study for approximately 10 weeks. Antiviral treatment was immediately initiated, EGF816 was interrupted and the HBV infection was brought under control. The patient later resumed EGF816 at the same dose of 225 mg q.d. while continuing on antiviral medication. The viral reactivation in these two patients was likely due to immunosuppression related to EGF816. Reactivation of HBV and hepatitis C virus (HCV) has been reported with anticancer therapies that suppress the immune

system.

The preliminary efficacy results showed an overall response rate (ORR) of 59.5% by Investigator assessment in 25 (11 confirmed and 14 awaiting confirmation) out of 42 evaluable patients treated at all dose levels. Note: evaluable patients include those who were ongoing and had at least one post-baseline tumor assessment or who discontinued study treatment as of the data cut-off date. The antitumor activity of EGF816 is in line with the antitumor activity observed with other 3rd-generation EGFR TKIs including AZD9291and CO-1686. To minimize the risk to all trial subjects and to manage the potential risk of severe liver toxicity associated with hepatitis reactivation, Novartis has amended the protocols for all clinical trials involving EGF816 to provide guidance for patients with evidence of current or prior hepatitis B or hepatitis C infection.

Please refer to the current Investigator's Brochure for more details.

2.3 Gefitinib

Gefitinib is an oral first-generation EGFR inhibitor which reversibly inhibits the kinase activity of wild-type and certain activating mutations of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signaling and blocking EGFR-dependent proliferation. Gefitinib's binding affinity for EGFR exon 19 deletion or exon 21 point mutation L858R mutations is higher than its affinity for the wild-type EGFR. Gefitinib also inhibits IGF and PDGF-mediated signaling at clinically relevant concentrations; inhibition of other tyrosine kinase receptors has not been fully characterized.

Gefitinib is approved for the first-line treatment of EGFR-mutant NSCLC in the United States, Europe and Asia. The IPASS study was a randomized, multicenter, open-label trial conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment[8]. Patients were randomized (1:1) to receive gefitinib 250 mg orally once daily or up to 6 cycles of carboplatin/paclitaxel. The efficacy outcomes included progression-free survival (PFS) and objective response rate (ORR) as assessed by BICR.

The subset population consisted of 186 of 1217 patients (15%) determined to be EGFR positive and had radiographic scans available for a retrospective assessment by BICR. In this subset, there were 88 gefitinib-treated patients and 98 carboplatin/paclitaxel-treated patients. Demographic and baseline characteristics of this subset were a median age of 59 years, age 75 years or older (7%), age less than 65 (70%), Asian (100%), female (83%), never smokers (96%), adenocarcinoma histology (100%), and PS 0-1 (94%).

The median duration of treatment for gefitinib-treated patients was 9.8 months. The hazard ratio for PFS favored the gefitinib-treated patients [HR of 0.54 (95% CI: 0.38, 0.79)] with a median PFS of 10.9 months for the gefitinib-treated patients and 7.4 months for the carboplatin/paclitaxel-treated patients as assessed by BICR. In addition, the objective response rate was 67% (95% CI: 56, 77) for gefitinib-treated patients and 41% (95% CI: 31, 51) for carboplatin/paclitaxel-treated patients based on BICR assessment. The median duration of response was 9.6 months for gefitinib-treated patients and 5.5 months for carboplatin/paclitaxel-treated patients.

Gefitinib is generally well-tolerated, with common side effects including rash and diarrhea. Rare but serious side effects including interstitial lung disease, hepatotoxicity and ocular disorders including keratitis can be seen.

Please see the gefitinib package insert and latest version of the investigator's brochure for further details.

2.4 Rationale for the combination of EGF816 and gefitinib

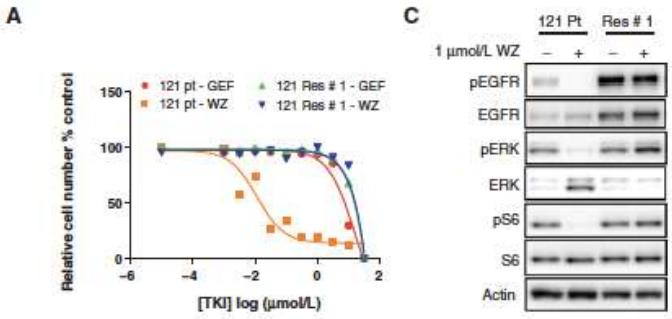

Figure 1. A WZ4002-resistant patient-derived cell line (121 Res) acquires a C797S mutation and maintains EGFR activity in the presence of TKI, while the parental (121 pt) cell line is sensitive to WZ4002[1].

It is well-known that resistance to first generation EGFR inhibitors is mediated in a majority of cases by the development of a secondary mutation in EGFR exon 20, T790M. The development of T790M restores the receptor's affinity for ATP and prevents first-generation EGFR TKIs from effectively inhibiting EGFR[20]. T790M can be successfully overcome with third-generation EGFR inhibitors, which bind covalently to EGFR and have activity against both T790M and the original founder EGFR mutations[11,12]. We have now seen that resistance to third-generation EGFR TKIs is frequently mediated by the development of a tertiary resistance mutation in EGFR, C797S, which occurs at the site of covalent binding of all irreversible EGFR inhibitors[14-16,21]. Indeed, using in vitro models, C797S renders cancers resistant to all tested third-generation EGFR inhibitors[1]. Interestingly, cell lines bearing C797S alone, in the absence of T790M, retain sensitivity to first-generation EGFR inhibitors (erlotinib and gefitinib) which do not rely on C797 to engage in the drug pocket.

In vitro models suggest that the genetic context of the C797S mutation is important to its therapeutic implications. C797S which arises on the same allele (in *cis* configuration) with T790M renders the cells resistant to all currently available EGFR inhibitors; none are able to overcome the combination of both resistance mutations on the same DNA strand[1,22]. However, in cell line models where T790M and C797S are on different alleles (in a *trans* configuration) retain sensitivity to combination of a first-generation and a third-generation EGFR inhibitor. This data suggests that upfront use of a combination of a 1st and 3rd generation EGFR inhibitor could not be overcome by development of either resistance mutation alone. Resistance to the combination would require the simultaneous development of C797S and T790M in a cis configuration, an event which is statistically unlikely. Thus, we hypothesize that the combination of a first and third-

generation EGFR inhibitor given together in the first-line setting may have the potential to induce highly durable remissions, as the development of both mutations in a cis configuration would be required to drive resistance. We therefore propose a phase II trial to test the efficacy and safety of EGF816 in combination with gefitinib for the first-line treatment of EGFR-mutant NSCLC

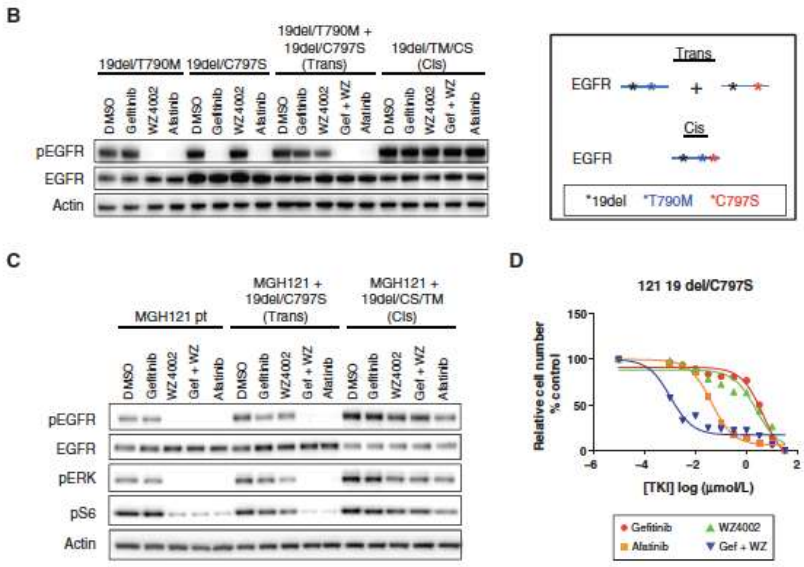

Figure 2. EGFR C797S located in cis or trans with T790M alters drug sensitivity[1].

2.5 Correlative Studies Background

2.5.1 Pre-treatment, on-treatment and resistant tumor biopsies

Mandatory tumor biopsies will be required at the start of treatment and at the time of disease progression. These samples will be analyzed via next-generation sequencing at Novartis to characterize mechanisms of resistance to the EGF816/gefitinib combination.

In addition, an on-treatment biopsy will be obtained after about 2-3 weeks of treatment. These samples will allow for characterization of the response to treatment. Biopsies will be submitted for single-cell sorting and transcriptional profiling to study the direct effect of the TKI combination on tumor cells, and to identify potential early signs of eventual resistance to the combination. These exploratory analyses will be performed at Massachusetts General Hospital and at Novartis Pharmaceuticals.

2.5.2 Plasma-based circulating tumor DNA (ctDNA) analysis

The characterization of circulating tumor DNA (ctDNA) in patient plasma samples is now widely utilized on both a research and clinical basis. ctDNA has several advantages over tissue-based testing, and can serve as an key complement to traditional tumor biopsies. Tumor DNA is shed by cancer cells into the plasma from multiple disease sites; as our understanding of the intra and intertumoral heterogeneity which can exist within an individual patient grows, there is growing evidence that ctDNA can more fully capture the heterogeneity of disease present within the patient[23,24]. In addition, ctDNA allows for easier sampling and facilitates longitudinal analyses

over time. We and others have demonstrated that longitudinal plasma assessments can be used to track response to treatment and that emerging resistance can be detected on the molecular level in the ctDNA prior to the development of radiographic disease progression[14,18].

In this study, longitudinal plasma samples will be obtained at the start of treatment, on D3, D8 and D15 of cycle 1,and at the start of each cycle and at the time of progression. Samples will be analyzed by ddPCR and next-generation sequencing to quantify molecular response to treatment, detect early signs of emerging resistant clones and to more fully characterize resistance mechanisms via NGS at the time of progression.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Patients may be entered in the study only if they meet all of the following criteria:

3.1.1 Participants must have a pathologically-confirmed diagnosis of non-small cell lung cancer (NSCLC).

3.1.2 Participants must have advanced disease - either stage IV disease, stage IIIB disease not amenable to definitive multi-modality therapy, or recurrent disease after a prior diagnosis of stage I-III disease. All staging is via the American Joint Committee on Cancer (AJCC)/IASLC 7th edition proposed staging criteria (see appendix 2)

3.1.3 An EGFR sensitizing mutation must be detected in tumor tissue. Specifically, patients harboring the most common mutations, deletions in exon 19 or the L858R mutation in exon 21 are eligible. Other EGFR sensitizing mutations may be eligible after discussion with the principal investigator. Patients may be enrolled in the study based on an activating EGFR mutation detected by a CLIA-certified tissue or plasma-based assay, but will be required to undergo a mandatory tumor biopsy during study screening.

3.1.4 Participants must have measurable disease, per RECIST 1.1. See Section 11 for the evaluation of measurable disease.

3.1.5 Patients in the six patient safety run-in cohort may have had a prior EGFR TKI in the metastatic setting (to allow for patients who started initial therapy at an outside hospital), but treatment duration must have been less than three months. After the initial six-patient safety run-in, no prior EGFR TKI therapy in the metastatic setting is allowed. An EGFR TKI given in the adjuvant setting (i.e. with no measurable disease at the time of administration) is allowable provided the subject has been off of EGFR TKI therapy for at least six months at the time of enrollment.

3.1.6 Patients may have had no more than one prior line of chemotherapy or immunotherapy in the metastatic setting. At least 14 days must have elapsed from the last chemo/immunotherapy administration until the start of protocol treatment, and patients must have recovered from the side effects of any of these agents.

3.1.7 Patients must be screened for HBV. Patients who are either HBsAg positive or HBV-DNA positive must be willing and able to take antiviral therapy 1-2 weeks prior to 1st dose of study treatment and continue on antiviral therapy for at least 4 weeks after the last dose of EGF816. Additional management of the patients would be provided by a physician with expertise in management of HBV, if needed. Patients must have negative hepatitis C antibody (HCV-Ab) or positive HCV-Ab but undetectable level of HCV-RNA. Note: patients with detectable HCV-RNA are not eligible for the study.

3.1.8 Patients must receive insurance approval for or be willing to pay for commercial gefitinib.

3.1.9 Age ≥ 18 years.

3.1.10 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

3.1.11 Life expectancy of greater than 12 weeks.

3.1.12 Participants must have normal organ and marrow function as defined below:

- Leukocytes ≥3,000/mcL
- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥100,000/mcL
- Total bilirubin <1.5 x upper limit of normal (ULN) **For patients with Gilbert's syndrome total bilirubin <3.0 x ULN*
- AST(SGOT)/ALT(SGPT) ≤3 × institutional upper limit of normal; for patients with known hepatic metastases AST and/or ALT > 5x ULN
- Creatinine ≤1.5 × institutional upper limit of normal

3.1.13 The effects of EGF816 and gefitinib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use highly effective contraception during the study and for 3 months after stopping the study treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptomthermal, postovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male Partner: male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- **Combination** of any **two** of the following (a+b or a+c, or b+c):
    - A. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    - B. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    - C. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
    - D. In case of use of oral contraception women should have been stable on the same pill for a minimum of 30 days before taking study treatment.
- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.
- Sexually active males must agree to use a condom during intercourse while taking drug and for 3 months after stopping treatment; men should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Written informed consent must be obtained prior to any screening procedures.

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be eligible to enter in the study:

3.2.1 Participants with clinically active or symptomatic interstitial lung disease or interstitial pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention) and patients with history of clinically significant interstitial lung disease or radiation pneumonitis.

3.2.2 Patients with clinically symptomatic brain metastases or leptomeningeal disease. Patients may be on a stable dose of corticosteroids to control brain metastases if they have been on a stable dose for two weeks prior to study treatment and are clinically asymptomatic.

3.2.3 Patients who have had radiation to the lung fields within four weeks of starting treatment. For patients receiving palliative radiation to thoracic vertebrae, ribs or other sites where the radiation field includes the lungs, radiation must be completed at least two weeks before starting treatment. For all palliative radiation to all other sites, at least 7 days must have elapsed prior to starting to treatment. At least six months must have elapsed from radiation given with curative intent.

3.2.4 Patients who have had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 2 weeks prior to starting study drug or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥1 week after the procedure.

3.2.5 Patients unable or unwilling to undergo a biopsy for research during the screening period, 2-3 weeks into the course of therapy and at the time of progression.

3.2.6 Patients with a second, clinically active, cancer. Patients with second cancers which have been treated with curative intent and/or are currently inactive are allowed.

3.2.7 Patients who have undergone a bone marrow or solid organ transplant.

3.2.8 Known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory).

3.2.9 Participants who are receiving any other investigational agents. Patients previously treated with investigational agents must complete a washout period of at least one week or five half-lives, whichever is longer, before starting treatment.

3.2.10 Patients receiving concomitant immunosuppressive agents or chronic corticosteroid use, except those on steroid to control brain metastases, those on topical or inhaled steroids, or steroids given via local injection.

3.2.11 Patients with clinically significant, uncontrolled cardiovascular disease, such as:

- Unstable angina within 6 months prior to screening
- Myocardial infarction within 6 months prior to screening
- Patients with a history of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Peripheral vascular disease
- Patients with uncontrolled hypertension defined as a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
- Ventricular arrhythmias
- Supraventricular and nodal arrhythmias not controlled with medication
- Other cardiac arrhythmia not controlled with medication
- Patients with corrected QT (QTc) ≥450 ms (male patients) or ≥460 ms (female patients) using Fridericia correction (QTcF) on the screening ECG
- Patients with history of congenital long QT syndrome or history of torsade de pointes

3.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition to EGF816 or gefitinib.

3.2.13 Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A4 are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.14 Unable or unwilling to swallow tablets or capsules.

3.2.15 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.16 Pregnant women are excluded from this study because the effects of EGF816 and gefitinib on a developing fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with EGF816 or gefitinib, breastfeeding should be discontinued if the mother is treated with EGF816 and gefitinib.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

All patients will receive combination therapy with EGF816 and gefitinib in an open-label fashion. A treatment cycle will be defined as 28 days. After completing 1 year of study treatment, visits will occur every 6 weeks.

The first six patients enrolled in the study will constitute a safety run-in; if severe unexpected toxicities are observed during cycle 1 among these six patients, further expansion cohorts at lower dose levels will be explored. Severe unexpected toxicities will be defined as any grade 3or higher adverse event assessed to be treatment-related by the treating physician occurring in > 1/6 patients during the safety run-in. Rash will be excluded as grade 3 rash during the 1st cycle has occured with each drug individually and is typically responsive to dose hold. If >1 patient has a grade 3 or higher treatment-related adverse event during cycle 1 of treatment, we will de-escalate treatment to gefitinib 250 mg QD and EGF816 100 mg QD.

EGF816 will be supplied by Novartis to the investigational drug pharmacy at all participating sites. Gefitinib will be supplied directly to the patient through prescription as a commercial product. As stated in the eligibility criteria, only patients with insurance approval to obtain gefitinib or who agree to self-pay for gefitinib will be able to participate in this study. Upon signing of the study ICF and confirmation of eligibility, participants will be prescribed a 30-day (one 28-day cycle; with two additional pills in case of lost, dropped pills) supply of gefitinib. C1D1 will begin only once the supply of gefitinib is in the patient's possession.

All patients will receive gefitinib 250 mg orally once daily and EGF816 100 mg orally once daily without interruption, unless an interruption is required to manage treatment-related toxicity (as outlined in Tables 6-1 and 6-2). Patients will be monitored at the start of each 28-day treatment cycle. Treatment will be administered on an outpatient basis. The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-Treatment Criteria

Prior to any study related testing, patients will sign the informed consent form and undergo medical evaluation to establish their baseline condition and determine eligibility. Imaging and all other studies will be obtained within 28 days of enrollment for the purpose of baseline assessment:

- Complete medical history and physical examination including:
- Complete medical history
- Documentation of disease status
- Documentation of prior systemic therapies for advanced disease treatment
- Documentation of current medications and all medications used within 30 days prior to enrollment.
- Complete physical examination, including vital signs (pulse, blood pressure, weight, and height) and assessment of ECOG performance status (See Appendix A)
- Pre-existing conditions will be assessed and evaluated according to the NCI CTCAE v4.0 to establish the patient's baseline condition

The following screening laboratory tests will be performed within 28 days prior to Day 1 of treatment:

- CBC with differential
- Chemistries: sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin

- Urinalysis
- Urine or serum pregnancy test (for premenopausal women)
- ECG

Disease-specific testing:

- Baseline CT scans of the chest, abdomen and pelvis and baseline imaging of the brain by MRI (or CT with contrast if MRI is contraindicated.) Repeat tumor assessments (CT chest, abdomen and pelvis) will be performed every 8 weeks thereafter to assess response and disease progression. Brain imaging (MRI, or CT with contrast in patients with contraindications to MRI) should be obtained every 8 weeks for patients with known brain metastases at the start of treatment. For patients without known history of brain metastases, CNS imaging should be obtained if clinically indicated based on symptoms.
- Mandatory pre-treatment tumor biopsy will be obtained within 28 days of Cycle 1, Day 1. Processing of tumor biopsy specimens will be performed as outlined in section 8.3.1.1

5.2.1 Cycle 1, Day 1

Patients who have signed the informed consent form, completed the screening process, and met the criteria for enrollment will be entered into the trial and assigned an identification number. In addition the following will be performed:

- Certification that patient meets all inclusion and exclusion criteria and is able to comply with all requirements of the clinical trial
- Review concomitant medications since screening
- Perform physical examination with vital signs and ECOG performance status
- Blood investigations – to be done if screening labs were done more than 7 days prior to day 1.
- Blood investigations performed on C1D1 must be reviewed before starting treatment to ensure that there are no clinically significant abnormalities. However, C1D1 laboratory studies do not have to re-meet eligibility criteria to begin treatment.
- Blood for correlative ctDNA analyses

5.2.2 Subsequent Cycles

The following studies will be obtained at the start of each new treatment cycle:

- Complete medical history
- Complete physical examination, including vital signs (pulse, blood pressure, weight, and height) and assessment of ECOG performance status (See Appendix A)
- Documentation of all current medications
- Laboratory studies including:
  - CBC with differential
  - Chemistries: sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin

Blood for correlative ctDNA analyses will be collected at baseline, on C1D3, C1D8, C1D15 and at the start of each new cycle.

Before beginning each cycle, any treatment related toxicities requiring treatment delay must have resolved to grade 1 or pre-therapy baseline. If toxicities have not resolved to grade 1 on the scheduled day of retreatment, treatment may be delayed for up to 28 days from the time of the last daily dose of EGF816 and gefitinib.

For patients who require drug holds to manage toxicities, the cycle day count should continue during the hold and the dosing and assessment schedule should not change.

5.3 Agent Administration

5.3.1 EGF816

Investigational Product: EGF816
Pharmaceutical Form: Tablets
Source: Novartis
Procurement: Provided via sponsor, dispensed from research pharmacy.
Unit Strength: 150mg tablets
Daily Dose: 100 mg once daily
Duration of Use: Continuous daily dosing without interruption
Administration Route: Oral (swallowed)
Schedule: Once daily, with or without food

Missed Doses/Vomited Doses: If a patient inadvertently does not take the EGF816 dose at their usual time, he or she may take the dose up to 6 hours later; in other words, they may continue as long as it is at least 6 hours before the next dose of gefitinib is due to be taken. The daily treatment schedule will be resumed the next day with the patient taking the scheduled dose at the usual time. If an entire daily dose is skipped, the patient should

resume treatment the following day with their regular dose. No "make-up dose" or increased dosing should occur. If a dose is vomited within 1 hour of administration, medications to control nausea and vomiting should be used, and the dose can be repeated. Patients should report all vomited, missed or delayed doses to the study staff and will be provided with a medication diary which should be turned in at every visit (see appendix 5.)

Tablets should be swallowed whole and not chewed or opened. Patients should be instructed to take their dose of each drug at approximately the same time of day. **Drugs should be separated by approximately 12 hours (e.g, gefitinib taken in the morning and EGF816 in the evening.)** The time of drug administration should be recorded by the patient in the study-provided drug diary. On days when blood for PK samples need to be collected in clinic, the patient should hold their morning gefitinib until arrival, and take the dose in the clinic after clearance to do so from the care team.

Grapefruit or grapefruit juice, seville orange (and juice), pummelos, star citrus fruits and hybrids of these mentioned fruits should be avoided during study treatment.

5.3.2 Gefitinib

Commercial Product: Gefitinib
Pharmaceutical Form: Tablets
Source: Commercial pharmacy
Procurement: Obtained directly from commercial pharmacy, delivered to patient.
Unit Strength: 250 mg tablets
Daily Dose: 250 mg once daily
Duration of Use: Continuous daily dosing without interruption
Administration Route: Oral (swallowed)
Schedule: Once daily, with or without food

If a patient inadvertently does not take the gefitinib dose at their usual time, he or she may take the dose up to 6 hours later, in other words, they may continue as long as it is at least 6 hours before the next dose of EGF816 is due to be taken. The daily treatment schedule will be resumed the next day with the patient taking the scheduled dose at the usual time. If an entire daily dose is skipped, the patient should resume treatment the following day with their regular dose. No "make-up dose" or increased dosing should occur. If a dose is vomited within 1 hour of administration, medications to control nausea and vomiting should be used, and the dose can be repeated. Patients should report all vomited, missed or delayed doses to the study staff and will be provided with a medication diary which should be turned in at every visit (see appendix 5.)

Tablets should be swallowed whole and not chewed or opened. However, gefitinib may be dissolved in 4-8 oz of water if patients have difficulty swallowing the tablets. **Drugs should be separated by 12 hours (e.g, gefitnib taken in the morning and EGF816 in the evening.)** Patients should be instructed to take their dose of each drug consistently at approximately the same time each day. Time of drug administration should be recorded by

the patient in the study-provided drug diary. On days when blood for PK samples need to be collected, the patient should take the dose in the clinic.

5.4 General Concomitant Medication and Supportive Care Guidelines

Information about concomitant medications will be collected as part of this study. This will be collected during screening, at the start of each cycle, and at the time of study discontinuation. Patients are allowed to receive full supportive care therapies concomitantly during the study. No other chemotherapy, immunotherapy, hormonal cancer therapy or experimental medications will be permitted while the patients are receiving study therapy.

5.4.1 Permitted Concomitant Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g., such as anti-emetics, anti-diarrhea) and safety of the patient are allowed. Anticoagulation treatment is also allowed if INR has been established within the therapeutic range prior to study entry. PT and PTT $\geq$ 1.5x ULN are permitted in these cases. The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. All medications (other than study treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered within 28 days prior to the administration of study treatment and during the study must be listed on the Prior and Concomitant Medications or the Surgical and Medical procedures eCRF.

Patients who develop a solitary site of disease progression may undergo locally ablative therapy (LAT; including radiotherapy, ablation or surgical resection) to the site of progression and remain on study. Note that if the solitary site of progression is within a target lesion, the tumor response will be categorized as progression at the time LAT begins. EGF816 and gefitinib should be held for at least 5 days prior to LAT. EGF816 and gefitinib may be resumed >3 days after completing local therapy if all procedure related toxicities have resolved to $\leq$ Grade 1. No other concomitant anti-neoplastic therapy will be allowed.

5.4.2 Permitted Concomitant Therapy Requiring Caution and/or Action

Based on the in vitro studies, both EGF816 and gefitinib are metabolized by CYP3A4. Moderate inhibitors and inducers of CYP3A4 should be used with caution and strong inhibitors and strong inducers of CYP3A4 should not be used concomitantly with either drug. Grapefruit juice is a CYP3A4 inhibitor, therefore, consumption of grapefruit or grapefruit juice should be avoided during study treatment.

EGF816 is a P-gp substrate. Co-administration of EGF816 with P-gp inhibitors may increase systemic exposure and/or alter tissue uptake of EGF816. EGF816 is a moderate inhibitor of BCRP with IC50 value of 4 μM. The exposure of BCRP substrate may increase when coadministered with EGF816. EGF816 is an inhibitor of the human multidrug and toxin extrusion transporter 1 and 2-K (MATE1 and MATE2-K) with an IC50 of 0.70 and 4.6 μM respectively. As a result EGF816 has potential to increase the exposure of co-medications whose clearance is significantly

mediated by MATE. In the absence of data confirming whether such an interaction occurs in patients, caution should be exercised when potent P-gp inhibitors and MATE or BCRP substrates are concurrently used. The patient and the Investigator should be aware of potential signs of overdose of the concomitant medication. In the event of suspected toxicity, administration of either EGF816 or concomitant drugs should be discontinued according to Investigator judgment. Refer to Appendix B, Table 13-1, for permitted medications that require caution and Appendix B, Table 13-2 for a list of prohibited medications.

Live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) should not be administered while a patient is dosed with EGF816 and for 30 days after the last dose of EGF86. Refer to Appendix B, Table 13-1, for permitted medications that require caution and Appendix B, Table 13-2 for a list of prohibited medications. If a patient must use a drug in Appendix B, Table 13-2, the patient must be discontinued from the study.

Drugs that elevate gastric pH (e.g., proton pump inhibitors, histamine H2-receptor antagonists, and antacids) may reduce plasma concentrations of gefitinib. Avoid concomitant use of gefitinib with proton pump inhibitors, if possible. If treatment with a proton-pump inhibitor is required, take gefitinib 12 hours after the last dose or 12 hours before the next dose of the proton-pump inhibitor. Take gefitinib 6 hours after or 6 hours before an H2-receptor antagonist or antacid.

5.5 Criteria for Taking a Participant Off Protocol Therapy

The duration of treatment will depend on response and tolerance. In the absence of treatment delays due to adverse events, EGF816 and gefitinib may be continued until there is disease progression by RECIST 1.1. Patients may continue treatment beyond disease progression determined by RECIST if they are deemed to be deriving ongoing clinical benefit from treatment by the treating investigator.

Participants will also be removed from the study if any of the following criteria apply:

- Clinically significant disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the DF/HCC website at http://www.dfhcc.harvard.edu/research/clinical-research-support/document-library-forms-sops-etc/.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Zofia Piotrowska at 617-724-4000.

5.6 Duration of Follow Up

Participants will be followed for 30 days (+/- 7) after removal from study for adverse event assessment, or until all AEs present at end of treatment have resolved or stabilized. Patients will then be monitored every 3 months until death for survival follow up.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

EGF816 and gefitinib are both EGFR tyrosine kinase inhibitors and have both overlapping and distinct toxicities. Guidelines for the management of potentially drug-related toxicities, including dose interruptions and dose reductions of each drug, are provided in section 6.1.

When possible, toxicities should be managed with appropriate medical treatment (including anti-emetics, anti-diarrheals, etc.) Other contributing factors, including concomitant medications which may be contributing to the toxicity, should be identified and discontinued or dose reduced if appropriate. The following sections provide guidelines for dose modification and dose interruption (i.e., interruption and re-initiation criteria for EGF816 and gefitinib treatment). All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.0). If, due to study drug related toxicity, a patient requires a dose interruption of >28 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study treatment.

Each patient is allowed no more than two dose reductions of each study drug. In addition, a patient must discontinue treatment with EGF816 and gefitinib if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity.

Exceptions can be made on a case by case basis after discussion with the Principal Investigator. In exceptional cases, after discussion with the PI, patients may be allowed to continue treatment or resume treatment with only one of the investigational drugs. All interruptions or modifications must be recorded on the Dosage Administration Record CRF.

In case of study treatment interruption, visit schedule should still be followed and assessments performed as per Table 10-1 (study calendar.)

6.1 Conditions requiring dose modification:

The dose modification levels for EGF816 are as follows:

Table 6-1: EGF816 dose reduction

Dose Level	EGF816 Dose
0	100 mg once daily
-1	75 mg once daily
-2	50 mg once daily

The dose modification levels for gefitinib are as follows:

Table 6-2: Gefitinib dose reduction

Dose Level	Gefitinib Dose
0	250 mg once daily
-1	250 mg every other day

General guidelines for dose of modifications of EGF816 and gefitinib for all toxicities that are at least possibly related to study drug are listed in table 6-3. Please see sections 6.1.1-6.1.6 for detailed guidelines for management of specific toxicities including pneumonitis/interstitial lung disease, liver function abnormalities, diarrhea, rash and cardiac toxicities. Modifications to these recommended guidelines may be made individual cases based on the clinical judgment of the treating investigator.

Table 6-3: Criteria for interruption, re-initiation and dose-reduction of study treatment

Recommended Dose Modifications	
Worst toxicity *CTCAE Grade*	*Action*
Grade 1	Maintain dose level of both drugs
Grade 2	Maintain dose level of both drugs
Grade 3	Omit both EGF816 and gefitinib until resolved to ≤ Grade 1. When the toxicity has resolved to grade

	1 or less, reintroduce drugs one at a time with one dose-level reduction in each drug. EGF816 should be reintroduced first[a] and the patient should then be monitored closely for recurrence of the AE for at least 7 days; if there is no recurrence of > grade 1 AE, gefitinib can then be reintroduced.
Grade 4	Permanently discontinue treatment.

A. *The order of drug reintroduction can be changed in clinical circumstances where the treating investigator feels it would be indicated to reintroduce gefitinib first.*

6.1.1 Management of Pneumonitis/Interstitial Lung Disease

CTCAE Grade	**Required investigations**	**Management of pneumonitis**	**Action and dose modification**
Grade 1 Asymptomatic, radiographic findings only	CT Chest; repeat at least every 2 cycles until radiographic abnormalities resolve.	No specific therapy required.	Continue both drugs with close monitoring for the development of symptoms.
Grade 2 Symptomatic, not interfering with activities of daily living (ADLs)	CT Chest Consider PFTs[a] Repeat scan at least every other cycle until radiographic abnormalities resolve. Consider bronchoscopy with biopsy and /or bronchoalveolar lavage (BAL)[c].	Symptomatic only. Consider corticosteroids[b] if symptoms are clinically significant.	Interrupt both drugs until improvement to ≤ Grade 1. If symptoms resolve to ≤ Grade 1 in ≤ 7 days, reduce both gefitinib and EGF816 by 1 dose level and reintroduce one at a time as above. If symptoms fail to resolve within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue both study drugs.
Grade 3 Symptomatic, interfering with ADL; O2 indicated	CT Chest and Pulmonary Function Testing (PFTs) Repeat scan at least every cycle until radiographic	Short course of corticosteroids[b] to be considered if infective origin is ruled out.	Permanently discontinue both study drugs.

	abnormalities resolve. Bronchoscopy with biopsy and/or BAL[c] is recommended.		
Grade 4 Life threatening; ventilator support indicated	CT Chest and required PFTs, if possible (including spirometry, DLCO, and room air O2 saturation at rest.) Repeat scan at least every cycle until return to within normal limits. Bronchoscopy with biopsy and / or BAL[c] is recommended, if possible.	Short course of corticosteroids[b] to be considered if infective origin is ruled out.	Permanently discontinue both study drugs.
A PFT (Pulmonary function tests) to include: diffusing capacity corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation. Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O2 saturation ≤ 88% at rest on room air. B Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. C If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.			

6.1.2 Management of liver function abnormalities (bilirubin, AST, ALT)

Table 6-4: Guidelines for management of abnormal LFTs:

Investigations (Hepatic)[a]	
Total Bilirubin *(for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)*	
Grade 1 (>ULN and ≤1.5 x ULN)	Maintain dose level with liver function test (LFTs) monitored as per protocol
Grade 2 (>1.5 and ≤3.0 x ULN) with ALT or AST ≤3.0 x ULN	Omit both drugs until resolved to ≤ grade 1, then: If resolved in ≤7 days, then resume EGF816 at the original dose level with close LFT monitoring. Resume gefitinib at the original dose level if LFTs remain ≤ grade 1 after 7 days of EGF816. If resolved in >7 days, then resume drugs one at a

	time (as above) with one level dose reduction in each drug.
Grade 3 (>3.0 and ≤10.0 x ULN) with ALT or AST ≤3.0 x ULN	Omit both drugs until resolved to ≤ grade 1, then: If resolved in ≤7 days, resume EGF816 with one level dose reduction and close LFT monitoring. Resume gefitinib with one level dose reduction if LFTs remain ≤ grade 1 after 7 days of EGF816. If resolved in □7 days discontinue patient from study treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilized over 4 weeks.
Grade 4 (>10.0 x ULN)	Permanently discontinue study treatment. The patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilized over 4 weeks.
AST or ALT	
Grade 1 (>ULN and ≤3.0 x ULN)	Maintain dose level with LFTs monitored per protocol
Grade 2 (>3.0 and ≤5.0 x ULN) without total bilirubin elevation to >2.0 x ULN	Maintain dose level with LFTs monitored per protocol
Grade 3 (>5.0 and ≤20.0 x ULN) without total bilirubin elevation to >2.0 x ULN	Omit both drugs until resolved to ≤ Grade 1 (or to baseline), then resume EGF816 with one level dose reduction and close LFT monitoring. Resume gefitinib with one level dose reduction if LFTs remain ≤ grade 1 after 7 days of EGF816. Permanently discontinue study treatment if ≥ Grade 3 elevation recurs. If AST or ALT > 5 x ULN in patients with baseline AST or ALT ≤ 3 x ULN, or if AST or ALT > 8 x ULN in patients with baseline AST or ALT > 3 x ULN but ≤ 5 x ULN, **immediate testing for viral hepatitis infection or reactivation should be performed**, see Section 6.1.3. Patients who have HBV-DNA monitoring during the study should be re-tested immediately.
Grade 4 (>20.0 x ULN) without total bilirubin elevation to >2.0 x ULN	Omit both drugs until resolved to ≤ Grade 1 (or to baseline), then resume EGF816 with one level dose reduction and close LFT monitoring. Resume gefitinib with one level dose reduction if

	LFTs remain ≤ grade 1 after 7 days of EGF816. However, permanently discontinue study treatment if the elevation of Grade 4 recurs. If AST or ALT>20.0 x ULN **immediate testing for viral hepatitis infection or reactivation should be performed**, see Section 6.1.3. Patients who have HBV-DNA monitoring during the study should be retested immediately.
Combined[b] elevation of AST or ALT and concurrent total bilirubin[c]	
For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[d] OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0xULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin >2x baseline AND >2.0xULN]	Discontinue study treatment permanently in the absence of signs of cholestasis, hemolysis, and if alternative causes of the liver injury have been excluded (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, viral hepatitis etc.) Repeat LFTs as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilized over 4 weeks. Testing for viral hepatitis infection or reactivation should be performed, see Section 6.1.3 and Table 6-5.

a. If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., Review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.
b. "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold
c. If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction
d. "Cholestasis" defined as: ALP elevation (>2xULN and R value< 2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis
Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury

6.1.3 Guidelines for screening, monitoring and management of HBV/HCV reactivation

HBV screening tests, on study monitoring, and management of HBV reactivation:

1. All patients must be screened with HBV serologic markers: HBsAg, HBsAb, and HBcAb.

2. If HBsAg and/or HBcAb are positive, test for HBV-DNA.
3. Refer to Table 6-5 for actions to be taken based on screening HBV results.
4. If a patient is HBsAg positive or HBV-DNA positive BUT is not on antiviral therapy:
   a. Consult a physician with expertise in managing HBV
   b. Initiate antiviral therapy with entecavir 0.5mg QD 1-2 weeks prior to first dose of EGF816 treatment.
   c. If a patient cannot take entecavir, contact the principal investigator to select an appropriate antiviral therapy.
   d. If antiviral therapy cannot be given, the patient is not eligible for the study.
   e. During the study, monitor HBV-DNA every 12 weeks (or more frequently if clinically indicated). (Refer to Table 6-6 if there is evidence of viral reactivation on study)
   f. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816.

5. Patients who are HBsAg positive or HBV-DNA positive at screening and already have been receiving antiviral therapy are eligible provided the patient remains on antiviral treatment.
   a. Identify a consulting physician with expertise in managing HBV who can provide treatment guidance, if required, while the patient is on study.
   b. HBV-DNA should be monitored every 12 weeks (or more frequently if clinically indicated).
   c. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816.

6. Refer to Table 6-6 for guidelines of management for HBV reactivation.

Table 6-5: Actions to be taken based on hepatitis B results screening

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	- or + with prior HBV vaccination	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-

Test	Result	Result	Result	Result	Result
Required actions	* Consult a physician with expertise in managing HBV. After the consultation, antiviral therapy should be started 1-2 weeks prior to 1st dose of EGF816 treatment. Recommended antiviral therapy is entecavir 0.5mg QD. Contact the study PI if a patient cannot take entecavir. Monitor HBV-DNA every 12 weeks (or more frequently if clinically indicated). Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816.		No antiviral therapy. . Monitor HBV-DNA every 4 weeks.		No antiviral therapy. HBV-DNA screening not required unless HBsAg and/or HBcAb are positive

Table 6-6 Guidelines for management of HBV reactivation

HBV reactivation (with or without clinical signs and symptoms)*		
Screening test results	**Monitoring test results that define HBV reactivation**	**Actions to be taken**
Positive HBV-DNA OR Positive HBsAg	Increase of 1 log in HBV-DNA relative to screening HBV-DNA value OR New appearance of measurable HBV-DNA	Interrupt EGF816 and gefitinib treatment. Assess patient compliance with antiviral therapy. Consult a physician with expertise in managing HBV and consider changing antiviral therapy. While patient is on antiviral therapy, continue interruption of EGF816 administration until resolution to: • ≤ screening HBV-DNA levels and • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed If resolution occurs within ≤ 21 days EGF816 and gefitinib should be re-started, one at a time, at the same dose level unless dose reduction/interruption is indicated due to any other reason. Resume EGF816 first with close LFT monitoring. Resume gefitinib if LFTs remain ≤ grade 1 after at least 7 days of EGF816. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816. If resolution occurs > 21 days, contact study PI for approval of restarting of EGF816. • If restarting of EGF816 and gefitinib is approved: follow the same guidelines as above. • If restarting of EGF816 and gefitinib is NOT approved: discontinue study treatment. Continue antiviral therapy for at least 4 weeks after the last dose of EGF816 • Monitor HBV-DNA every 12 weeks (or more frequently if clinically indicated).

HBV reactivation (with or without clinical signs and symptoms)*		
Screening test results	**Monitoring test results that define HBV reactivation**	**Actions to be taken**
Negative HBV-DNA AND Negative HBsAg	New appearance of measurable HBV-DNA	Interrupt EGF816 and gefitinib treatment. Consult a physician with expertise in managing HBV. After the consultation, start antiviral therapy. While patient is on antiviral therapy, continue interruption of EGF816 and gefitinib administration until resolution to: • ≤ baseline HBV-DNA levels and • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed If resolution occurs within ≤ 21 days EGF816 and gefitinib should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. Reintroduce EGF816 first; if LFT remains ≤ grade 1 after at least 7 days on EGF816, resume gefitinib. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816. If resolution occurs > 21 days Contact study PI for approval of restarting of EGF816. If restarting of EGF816 and gefitinib is approved: follow the same guidelines as above. If restarting of EGF816 and gefitinib is NOT approved: discontinue EGF816 treatment. Continue antiviral therapy for at least 4 weeks after the last dose of EGF816. Monitor HBV-DNA every 12 weeks (or more frequently if clinically indicated).
** All reactivations of HBV are to be recorded as serious adverse event (SAE). Date of viral reactivation is the date on which the defined lab results for reactivation were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-15 and whose ALT reached > 5 × ULN on 01-APR-15, the date of viral reactivation is 01-APR-15).*		

HCV screening tests, on study monitoring, and management of HCV reactivation

1. Screen all new patients for HCV-Ab. If HCV-Ab is detected then check HCV-RNA.
2. Only patients with negative HCV-Ab or with positive HCV-Ab but **undetectable** level of HCV-RNA are eligible to be enrolled in the study (assuming all other eligibility criteria are met). Patients with detectable HCV-RNA are not eligible to be enrolled in the study.

3. Patients with known history of HCV infection and undetectable HCV-RNA at screening should be monitored every 8 weeks (or more frequently if clinically indicated) with HCV RNA-PCR for HCV reactivation.
4. Refer to Table 6-7 for definition of HCV reactivation and the management guidelines.

Table 6-7 Guidelines for management of HCV reactivation

HCV reactivation (with or without clinical signs and symptoms)[1]		
Screening test results	**Monitoring test results that define HCV reactivation**	**Action to be taken**
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA	Interrupt EGF816 and gefitinib treatment. Consult a physician with expertise in managing HCV. After the consultation, start antiviral therapy. While patient is on antiviral therapy, continue interruption of EGF816 and gefitinib administration until resolution to: • no detectable HCV-RNA and • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed. If resolution occurs within ≤ 21 days EGF816 should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. Reintroduce EGF816 first; if LFT remains < grade 1 after at least 7 days on EGF816, resume gefitinib. If resolution occurs > 21 days Contact study PI for approval of restarting of EGF816. • If restarting of EGF816 and gefitinib is approved: follow the same guidelines as above. • If restarting of EGF816 and gefitinib is NOT approved: permanently discontinue the patient from EGF816 treatment Monitor HCV-RNA every 8 weeks (or more frequently if clinically indicated)

[1] All reactivations of HCV are to be recorded as serious adverse event (SAE). Date of viral reactivation is the date on which the defined lab results for reactivation were met (e.g., for a patient whose HCV-RNA was detectable on 01-JAN-15 and ALT reached > 5 x ULN on 22-JAN-15, the date of viral reactivation is 22-JAN-15).

On study monitoring of liver function test (LFT) for all patients

LFTs should be monitored for all patients as per protocol, or more frequently if clinically indicated.

At any time during the study, if ALT > 5 x ULN in patients with baseline ALT ≤ 3 x ULN, or if ALT > 8 x ULN in patients with baseline ALT > 3 x ULN but ≤ 5 x ULN: immediately

1. Perform test(s) for viral hepatitis infection or reactivation: all patients should be screened with viral hepatitis panel (HAV-Ab-IgM, HBsAg, HBcAb-IgM, and HCV-Ab). In addition:
   a. Patients who have HBV-DNA monitoring during the study should be re-tested for HBV-DNA immediately; refer to Table 6-6 for definition and management of HBV reactivation.
   b. Patients who have HCV-RNA monitoring during the study should be re-tested for HCV-RNA immediately; refer to Table 6-7 for definition and management of HCV reactivation.
2. If any of the above tests indicate:
   a. HBV reactivation: refer to Table 6-6 for management guidelines.
   b. HCV reactivation: refer to Table 6-7 for management guidelines.
   c. New viral infection: immediately interrupt EGF816 and gefitinib dosing, consult a physician with expertise in managing viral hepatitis and contact study PI for further discussion.
3. Perform other relevant tests/procedures as clinically indicated.
4. Follow the dosing modification for ALT elevation according to guidelines in Table 6-4.

6.1.4 Management of diarrhea

Table 6-8: Guidelines for management of diarrhea

Diarrhea[a]	
Grade 1	Maintain dose level but adjust anti-diarrheal treatment
Grade 2 (despite maximal antidiarrheal medication)	Omit gefitinib and EGF816 until resolved to ≤ Grade 1, then reintroduce EGF816 same dose level; if diarrhea remains < grade 1 after at least a week on EGF816, resume gefitinib. If diarrhea returns as ≥ Grade 2, then omit both drugs until resolved to ≤ Grade 1, then decrease both drugs by one dose level and reintroduce one at a time as above.
Grade 3 (despite maximal antidiarrheal medication)	Omit both drugs until resolved to ≤ Grade 1, then decrease EGF816 and gefitinib by 1 dose level and reintroduce one at a time (as above) if diarrhea is grade ≤ 1 after at least one week on EGF816.
Grade 4 (despite maximal antidiarrheal medication)	Omit both drugs until resolved to ≤ Grade 1, then decrease EGF816 and gefitinib by 1 dose level and reintroduce one at a

	time (as above) if diarrhea is grade ≤ 1 after at least one week on EGF816.

a. Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

Grade 1-2 diarrhea should be managed with Loperamide (4mg at first onset, followed by 2mg every 2-4 hours until diarrhea free for 12 hours with maximum daily dose of 16 mg per 24 hours.) If loperamide is ineffective, consider adding Lomotil (5 mg, four times a day), or tincture of opium (15-20 drops orally every 4 hours) or octreotide (150 to 300 mcg SQ twice daily).

6.1.5 Management of rash

Both EGF816 and gefitinib are known to cause rash, but the rash typically associated with each drug is distinct. Gefitinib-associated rash is generally an acneiform, papular rash while that associated with EGF816 is more commonly maculopapular, pruritic and without true acneiform lesions. The management of each type of rash is different, and both are outlined below.

Table 6-9: Guidelines for prevention and symptomatic care of rash/skin toxicities

Type of care	**Action**
Prevention/Prophylaxis Starting from Day 1 for all patients	Avoid unnecessary exposure to sunlight Apply broad-spectrum sunscreen with SPF≥15 at least twice daily Use thick, alcohol-free emollient cream (e.g. glycerin and cetomacrogol cream) on dry areas of the body at least twice daily
Symptomatic lesions	Pruritic lesions: cool compresses and oral antihistamine therapies Desquamation: thick, alcohol-free emollient cream and mild soap Paronychia: antiseptic bath and topical antibiotics; if no improvement, consult dermatologist Infected lesions: appropriate topical or systemic antibiotics
Patients who develop rash/skin toxicities should be evaluated by a qualified physician and receive symptomatic and supportive care management.	

Table 6-10. Guidelines for management of maculopapular rash

CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	Initiate appropriate symptomatic care (Refer to Table 6-9) Use mild-strength topical steroid (e.g. 1% hydrocortisone cream) on	Continue both study drugs at same dose level

	affected areas Re-assess after 1 week	
Grade 2	Initiate appropriate symptomatic care (Refer to Table 6-9) Use moderate-strength topical steroid (e.g. 2.5% hydrocortisone cream or 0.5% fluticasone cream) on affected areas PLUS low-dose oral steroid (e.g. 5mg-10mg PO QD for 1 week) with taper Re-assess after 1 week	Continue both study drugs at same dose level If no recovery or worsened within 1 week, interrupt EGF816 and gefitinib until recovery to ≤ Grade 1. Once rash has recovered to ≤ Grade 1, restart EGF816 at one level reduced from the previous dose level[3]. Drugs should be reintroduced one at a time; if no recurrent rash occurs with introduction of EGF816, gefitinib can be resumed at the original dose level.
Grade ≥ 3	Initiate appropriate symptomatic care (Refer to Table 6-9) Use moderate-strength topical steroid on affected areas PLUS mid-dose oral steroid (e.g. 20-40mg PO QD for 1 week) with taper over 1-2 weeks or IV steroid (e.g. methylprednisolone 20-30mg IV BID for 3 days) if clinically indicated Consult dermatologist	Interrupt both study drugs until rash recovers to ≤ Grade 1. Once recovers to ≤ Grade 1, restart EGF816 at one level reduced from the previous dose level. Drugs should be reintroduced one at a time; EGF816 should be resumed first and, if no recurrent rash occurs within a week, gefitinib can be resumed at original dose level. Oral antihistamine therapies (e.g. levocetirizine 5mg QD, desloratadine 5mg QD, or fexofenadine 180 mg QD) should be given concurrently with study drugs for 4 weeks when restarting treatment. If no recovery to ≤ Grade 2 within 3 weeks, permanently discontinue EGF816. Gefitinib can be continued. Patients who develop more than 1 episode of Grade ≥ 3 rash will be permanently discontinued from EGF816.
1. Maculopapular rash includes macular rash, papular rash, and maculopapular rash.		

2. *For all grades of maculopapular rash, consider skin biopsy for pathologic evaluation.*

Table 6-11. Guidelines for management and dose modification of other rashes including acneiform rash.

	Adverse Event Management	**Adverse Event Management**
Grade 1	Monitor for change in severity and consider symptomatic and/or topical treatment (Refer to Table 6-9) Re-assess after 2 weeks	Continue study drug at same dose level
Grade 2	Initiate appropriate symptomatic care (Refer to Table 6-9) Depending on the type of rash, a variety of agents can be used including mild to moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, and retinoid creams. Re-assess after 2 weeks	Continue study drugs at same dose level If no recovery or worsened within 2 weeks, interrupt both study drugs until rash recovers to ≤ Grade 1 Once rash recovers to ≤ Grade 1, then restart gefitinib at one reduced dose level and continue same EGF816 dose.
Grade 3	Initiate appropriate symptomatic care (Refer to Table 6-9) Depending on the type of rash, a variety of agents can be used including mild to moderate strength steroid creams, low-dose oral steroids, topical or systemic antibiotics, topical or systemic antihistamines, and retinoid creams. Consult dermatologist	Interrupt both study drugs until rash recovers to ≤ Grade 1. Once rash recovers to ≤ Grade 2, restart gefitinib at one reduced dose level. If no rash ≥ grade 1 recurs after at least 7 days on gefitinib, EGF816 can be then be resumed at the original dose level. If rash ≥ grade 1 recurs within 1 week, interrupt both drugs again until rash recovers to ≤ Grade 1, then resume gefitinib at the reduced dose level, monitor for recurrence and then resume EGF816 reduced by one dose level.

		If no recovery to ≤ Grade 2 within 3 weeks, permanently discontinue study drugs. Patients who develop more than 1 episode of Grade ≥3 rash will be permanently discontinued from study treatment

6.1.6 Management of Cardiac Toxicities

Cardiac Investigations	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms)	Maintain dose level.
Grade 2 (QTc 481-500 ms)	Maintain dose level.
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Omit EGF816 and gefitinib until QTc is less than 481 ms and then decrease EGF816 by one dose level; monitor QTc after 48 hours and 1 week on EGF816, if it remains ≤ grade 1 after 7 days of EGF816, resume gefitinib with one level dose-reduction and continue to monitor QTc closely. - Perform an analysis of serum potassium and, if below lower limit of normal, correct with supplements to within normal limits.- Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc <481 ms - Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms.
Bradycardia	
Grade 1 or 2	Omit EGF816 until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm. Continue gefitinib. Evaluate concomitant medications known to cause bradycardia and adjust the dose of EGF816
Grade 3 or Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit EGF816 and gefitinib until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm If grade with a concomitant medication-- if the concomitant medication can be adjusted or discontinued, resume EGF816 with a decrease by one dose level with frequent monitoring, if no recurrent bradycardia after 7 days on treatment, resume gefitinib.

Grade 4 (in patients who are *not* taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Permanently discontinue EGF816. If bradycardia resolved, continue gefitinib.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Event Characteristics

Expected Adverse Events

Adverse events can be 'Expected' or 'Unexpected'. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Investigator's Brochure

Unexpected Adverse Events

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the Investigator's Brochure.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2 Expedited Adverse Event Reporting

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Abnormal lab values that do not require treatment
- treatment planned before signing informed consent for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

7.2.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.2.2 <u>DF/HCC Expedited Reporting Guidelines</u>

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for

Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.2.3 Reporting to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739).

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 EGF816

The investigator or responsible site personnel must instruct the patient or caregiver to take EGF816 as per protocol. EGF816 will be dispensed to the patient by authorized site personnel only. Dose strength and treatment schedule are described in Table 6-1 and 6-2 and sections 5.3.1 and 5.3.2. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF. Study treatment including instructions for administration is dispensed by study personnel. Patients will be provided with adequate supply of EGF816.

8.1.1 EGF816 packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. All information on labels will be included in the pharmacy reversibility record. Medication labels will be in compliance with the US legal requirements. They will include storage conditions for the drug and the medication number but no information about the patient.

8.1.2 EGF816 Supply and storage

EGF816 must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

8.1.3 EGF816 Compliance and Accountability

8.1.3.1 EGF816 Compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

8.1.3.2 EGF816 Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

8.1.4 EGF816 Disposal and Destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. . IP returned by participants and expired medications will be destroyed at the investigational site.

8.2 Gefitinib

Gefitinib will be obtained by each patient through a commercial pharmacy. Patients will be required to bring gefitinib supply in at the start of each treatment cycle for verification by study staff.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Tumor biopsies

9.1.1 Pre-treatment biopsy:

Patients will undergo a mandatory fresh core needle or excisional pre-treatment biopsy within 28 days of starting treatment. The site of biopsy will be selected by the treating investigator; cytology specimens and FNA specimens will not be accepted. Cell blocks made from pleural or pericardial fluid are acceptable.At least six cores will be obtained; one fresh sample for single-cell sorting and RNA sequencing, one each for patient-derived cell line and patient-derived xenograft establishment, one core snapfrozen and one core fixed in formalin and embedded in paraffin for subsequent DNA and protein-based studies. An FNA or core sample will be sent for clinical testing to confirm non-small cell histology. Any additional cores will be transported to the MGH Center for Cancer Research at the Charlestown Navy Yard campus.

Although the results of local testing will be used to confirm EGFR mutation status for study screening and registration, all samples will be analyzed centrally post-hoc by NGS for confirmation of pre-treatment EGFR status.

9.1.2 On-treatment biopsy

A mandatory on-treatment core needle or excisional biopsy will be obtained between D15 and 21 of cycle 1. The site of biopsy will be selected by the treating investigator, preferably the same site as the pre-treatment biopsy, however if this is not possible, a biopsy of a different site is allowed; cytology specimens and FNA specimens will not be accepted. Cell blocks made from pleural or pericardial fluid are acceptable. At least four cores will be obtained. One fresh core will be saved in media for single-cell sorting and RNA analysis, one snapfrozen and two cores fixed in formalin and embedded in paraffin for subsequent DNA and protein-based studies. Any additional cores will be sent to the MGH Center for Cancer Research at the Charlestown Navy Yard campus.

9.1.3 Post-progression tumor biopsy

A post-treatment core needle or excisional biopsy will be obtained at the time of disease progression. The exact timing of this biopsy will be at the discretion of the treating investigator, but must occur at or after the patient reaches PD by RECIST. The site of biopsy will be selected by the treating investigator; cytology specimens and FNA specimens will not be accepted. Cell blocks made from pleural or pericardial fluid are acceptable. At least six cores will be obtained; one fresh sample for single-cell sorting and RNA sequencing, one each for patient-derived cell line and patient-derived xenograft establishment, one core snapfrozen and one core fixed in formalin and embedded in paraffin for subsequent DNA and protein-based studies. An FNA or core sample will be sent for clinical testing to confirm non-small cell histology. Any additional cores will be transported to the MGH Center for Cancer Research at the Charlestown Navy Yard campus.

9.1.4 Analysis of pre-treatment, on-treatment and post-treatment tumor biopsies

Pre-treatment and progression biopsies will be used to establish patient-derived cell lines as has been previously described (Crystal, et al, Science 2015.) Next-generation sequencing will be performed at Novartis. Because the scientific assays used to interrogate tumor specimens are constantly evolving, additional tumor samples may be used for research purposes in exploratory studies. These studies may include DNA sequencing (including gene-specific, whole exome, and whole genome sequencing), RNA sequencing (including RT-PCR, Q-PCR, and whole transcriptome sequencing), DNA methylation studies (including CHIP-sequencing), and proteomics assays. Live tissue may also be cultured in vitro and/or implanted into immunodeficient mice to generate xenograft models. Any exploratory research studies will be performed at the MGH Center for Cancer Research at the Charlestown Navy Yard Campus or at the Novartis Institute for Biomedical Research.

9.2 Longitudinal circulating tumor DNA analyses

Blood samples will be collected for circulating tumor DNA analyses at screening, C1D1, C1D3 (as close to 48 hours after the first dose as possible), C1D8, C1D15 and on the first day of each subsequent cycle (every 28 days) until the end of treatment. Two Streck tubes (a total of 20 cc of blood) will be collected at each time point. Samples will be sent to the Charlestown Navy Yard via US Ground courier for isolation of plasma within 8 hours of sample collection. Plasma will be isolated from each tube according to the protocol in Appendix C. Plasma will be stored frozen at -80 degrees until ctDNA extraction. The remaining whole blood will be used to extract peripheral blood mononuclear cells for germline analyses.

Next-generation sequencing will be used to analyze pre-treatment ctDNA sample and the one obtained at progression to identify mechanisms of resistance to the EGF816/gefitinib combination. The intervening samples will then be studied via ddPCR or next-generation sequencing to further characterize dynamic molecular changes occurring in ctDNA over time. Because the scientific assays used to interrogate ctDNA specimens are constantly evolving, additional samples may be used for research purposes in exploratory studies.

Please Note:
Sam Bilton (sbilton@mgh.harvard.edu) should be alerted 24hrs prior to each sample being drawn if possible (or as soon as it is determined that a sample will be drawn).
561-901-5369

Samples Shipped To:
MGH Charlestown Navy Yard Facility
Hata Laboratory
149 13th Street, Room 7316
Charlestown, MA 02129

9.3 Pharmacokinetic studies:

A pre-EGF816 dose blood sample will be obtained at baseline on C1D1 and on C1D15 for pharmacokinetic analysis to establish steady state levels of EGF816 and gefitinib. For each timepoint, at least two 2mL of blood will be collected in a properly labelled plastic lavender top K2-EDTA-tube. Immediately after each tube of blood is drawn, it should be inverted gently

several times to ensure the mixing of tube contents. Avoid prolonged sample contact with the rubber stopper. Place the tube upright in a test tube rack surrounded by ice until centrifugation. Within 30 minutes, centrifuge the sample at between 3-5 degrees Celsius for 10 minutes at approximately 2000g (or centrifuge the sample at room temperature if tubes placed on ice quickly after processing). Immediately after centrifugation, aliquot the collected plasma into two uniquely labeled tubes (PK plasma A and B). The tubes will be frozen immediately over solid carbon dioxide (dry ice) then kept frozen at -70 degrees Celsius or colder pending analysis, which will be performed in collaboration with WuXi AppTec.

Samples will be shipped frozen at -70 to:

Li Li
288 Fute Zhong Road,
Waigaoqiao Free Trade Zone
Shanghai 200131
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10. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Table 10-1 Study Calendar

	Pre-Study	C1D1	C1D3	C1D8	C1D15	C2D1 and D1 of all subsequent cycles[n]	Disease Progression	Off Study[k]
EGF816		X----------					X[a]	
Gefitinib		X----------					X[a]	
Informed consent*	X							
Medical history	X	X		X	X	X		X
Concurrent meds	X	X		X	X	X	X	X
Physical exam (including VS, weight)	X	X		X	X	X	X	X
Performance status	X	X		X	X	X	X	X
CBC w/diff	X	X[l]		X	X	X	X	X
Serum chemistry[b]	X	X		X	X	X	X	X
Hepatitis serologies[c]	X							
Urinalysis[d]	X							
ECG	X	X[m]				X[m]		
PK Sampling		X[j]			X[j]			
Adverse event evaluation		X		X	X	X	X	
Radiologic evaluation (CT C/A/P, +/- brain imaging) [e]	X					X		
B-HCG (serum or urine)	X	X				X		
Tumor biopsy	X[f]				X[g]		X[h]	
Plasma for ctDNA analysis	X	X	X[i]	X	X	X	X	X

* Re-consent is required if treatment starts more than 28 days after the original consent.

a. Treatment with EGF816 and gefitinib can be continued beyond progression at the discretion of the treating investigator (see section 5.5)
b. Sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]. If screening chemistry is drawn > 7 days before C1D1, chemistry should be redrawn on C1D1. These do not need to re-meet eligibility.
c. Screening labs should include HBsAg, HBsAb, HCV-Ab, and HBcAb. Check HBV-DNA if HBsAg and/or HBcAb are positive (see section 6.1.3). In addition, HBV DNA and/or HCV RNA monitoring will be required for some patients based on initial screening (see section 6.1.3)
d. Urinalysis should be performed at baseline and then only if clinically indicated.
e. Radiologic evaluation (CT chest, abdomen and pelvis) should be performed every 8 weeks of treatment. After completing 1 year of treatment, radiologic evaluations should be performed every 12 weeks. Brain imaging (MRI, or CT with contrast in patients with contraindications to MRI) should be obtained every 8 weeks for patients with known brain metastases at the start of treatment. For patients without known baseline brain metastases, CNS imaging should be obtained if clinically indicated based on symptoms.
f. Pre-treatment core needle or excisional should be done within 28 days of start of treatment
g. On-treatment biopsy should be performed between D15 and D21 of cycle 1. On the day of the on-treatment biopsy, patients should take both study drugs. Their morning gefitinib dose can be taken with sips of water.
h. Post-treatment core needle biopsy should be obtained at the time of disease progression. The exact timing of this biopsy will be at the discretion of the treating investigator, but must occur at or after the patient reaches PD by RECIST.
i. Cycle 1, Day 3 ctDNA blood draw should be performed as close to 48 hours after first dose as possible.
j. Pre-dose steady state levels of EGF816 and gefitinib will obtained on C1D1 and C1D15.
k. The duration of EGF816 and gefitinib administration will be determined as specified in section 5.5. Follow up for survival will be performed by telephone contact or clinic visits every 3 months (+/-1 month) after exit visit until the participant is deceased or lost to follow up.
l. If screening CBC with differental is done > 7 days from C1D1, CBC with differental should be repeated on C1D1. These do not have to remeet eligibility.
m. ECGs at each cycle visit should be captured pre-dose
n. After completing 1 year of treatment, visits should be performed every 6 weeks.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response 8 weeks. After completing one year of treatment, re-evaluation should occur every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained *4* (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions

(longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

11.2 Response Criteria

11.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.2.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or

flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response

CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.2.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.2.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase II study designed to evaluate the efficacy of the combination of EGF816 and gefitinib in the first-line treatment of EGFR-mutant non-small cell lung cancer. The primary end-point is proportion of patients free from progression at 9 months. The study is designed as a Simon two-stage study. The null hypothesis is that EGF816 does not add any benefit to gefitinib monotherapy, with the assumption that the median PFS for gefitinib monotherapy is 9 mo, in other words 50% of patients will be free from progression at 9 months. The study is designed to have 80% power at the 0.05 significance level to show that the combination regimen of gefitinib plus EGF816 increases the proportion of progression-free patients at 9 months to 73% using a

one-sided binomial test. The total study size is 36 patients. 11 patients will be enrolled in the first stage of the study, with a planned second stage of 25 patients if at least 7 patients in the first-stage are progression-free at nine month. The rejection criteria for the null would be having 23 patients who are progression-free by 9 months. Based on our prior experience with first-line treatment of pateints with EGFR mutant NSCLC, we do not expect any patients to be lost to follow-up or unevaluable prior to the 9 month timepoint.

13.2 Sample Size, Accrual Rate and Study Duration

As stated above, 11 patients will be enrolled in the first stage of the study, with a planned second stage of 25 patients if at least 7 patients in the first-stage are progression-free at nine months. The null will be rejected and the study deemed positive if at least 23 total patients are progression-free at 9 months.

We expect to accrue approximately 10-15 patients/year, therefore assuming the study advances to the second stage and that there may be a brief pause in enrollment between the first and second stage (to allow for patients to reach the 9 month endpoint), will complete accrual for the study within 3 years. Final data for the primary endpoint will be mature within 4 years.

13.3 Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- A definition of patient enrollment
- A summary of data regarding patient discontinuation of study treatment
- A summary of data regarding patient inclusion and exclusion in efficacy and safety analyses

13.4 Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Baseline tumor molecular characteristics
- Significant medical history and co-morbidities
- Concomitant therapies
- Other characteristics as appropriate

13.5 Interim Monitoring Plan- N/A

13.6 Analysis of Primary Endpoints

The primary end-point is proportion of patients free from objective disease progression or death at 9 months. Progression will be defined by RECIST 1.1

13.7 Analysis of Secondary Endpoints

Response rate will be assessed as per RECIST, see Section 9.1. Results will be reported with 95% confidence intervals. All patients will be evaluable for response rate. Progression-Free Survival (PFS) will be defined as the duration of time from start of treatment to time of objective disease progression or death. Overall survival (OS) will be defined as the duration of time from start of treatment until death. Analysis will be performed using the Kaplan-Meier method. All patients will be evaluable for survival endpoints.

A summary of the adverse events, grading according to CTCAE and their attributed relatedness to treatment will be provided as a measure of patient safety and tolerability. All patients will be included in the safety analyses.

The first six patients in the study will constitute a safety cohort as outlined in section 5.1. If >1 patient has a grade 3 or higher treatment-related adverse event during cycle 1 of treatment, the dose will be de-escalated as outlined. Six additional patients will be treated at the lower dose to establish safety prior to proceeding to open enrolment of the remainder of the trial. The probability of stopping at the initial dose in order to dose de-escalate and the probability of stopping the trial after the safety run in at the lower dose based on assumptions about the associated underlying toxicity rates are as follows:

True toxicity rate	Probability of reducing the starting dose	Probability of stopping the trial
0.05	0.265	0.033
0.1	0.468	0.114
0.2	0.738	0.345
0.3	0.883	0.580
0.4	0.954	0.767
0.5	0.985	0.890

Biopsies from pre, post and on-treatment will be obtained to facilitate comparative analysis by next-generation sequencing, single-cell RNA sequencing, transcriptional profiling and an evaluation of the emergent resistance mechanisms at the time of progression. Analyses for these outcomes may include the Cox proportional Hazard models for the examination of the relationship between changes in sequencing parameters and time to progression, Sign-Rank test to compare pre and post measurements of gene expression for genes of interest and other correlation tests such as linear regression to examine relationship between relevant outcomes.

The feasibility of single-cell sorting and transcriptional analysis of on-treatment biopsies will be assessed based on the rate of interpretable results. The lower-bound of the 95% CI will be provided for this rate and will serve as an indication of the ability to use such methods in an expanded setting.

The results of longitudinal ctDNA analysis before, during and after treatment are exploratory and will be evaluated in a descriptive manner.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B **INFORMATION ON USE OF CONCOMITANT MEDICATIONS**

Table 13-1**: Permitted Concomitant Medications Requiring Caution.**

Mechanism of Interaction	**Drug Name**
Moderate CYP3A4 inhibitor	Antibiotics: ciprofloxacin, erythromycin Protease Inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir Antifungals: fluconazole Antiviral: faldaprevir Calcium Channel Blockers: diltiazem, verapamil Other: aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, lomitapide netupitant, schisandra sphenanthera, tofisopam
Moderate CYP3A4 inducer	bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, [semagacestat], [talviraline], thioridazine, lersivirine
BCRP substrate	methotrexate, mitoxantrone, rosuvastatin, sulfasalazine
MATE substrate	Metformin, tenofovir
Potent P-gp inhibitor	quinidine, dronedarone, valspodar (PSC 833), elacridar (GF120918)
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: Apr2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. Please note that this list may not be exhaustive. For the latest information, please refer to the above mentioned database. Drugs between brackets are not marketed in US. Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor. Potent P-gp inhibitor, which results in AUC ratio>2-fold.	

Table 12-3 Prohibited concomitant medications

Mechanism of interaction	**Drug name**
Strong CYP3A4 inhibitor	Antibiotics: clarithromycin, telithromycin, troleandomycin Protease Inhibitors: indinavir, lopinavir, nelfinavir, ritonavir saquinavir, tipranavir Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole Antivirals: boceprevir, telaprevir, danoprevir/ritonavir Others: cobicistat, conivaptan, elvitegravir, mibefradil nefazodone, grapefruit or grapefruit juice, seville orange (and juice), pummelos, star citrus fruits, and hybrids of these mentioned fruits
Strong CYP3A4 inducer	avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
Live vaccines	e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines

NTI: narrow therapeutic index

Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: Apr2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. Please note that this list may not be exhaustive. For the latest information, please refer to the above mentioned database.

APPENDIX C PLASMA ISOLATION PROTOCOL FOR CTDNA ANALYSIS

Preparation of plasma for the isolation of circulating DNA

Purpose

These instructions describe how to collect whole blood samples and prepare plasmafor the isolation of cell-free circulating tumor DNA.

Materials and Equipment

- Two Streck tubes
- Vacutainer needles or butterfly needles, 20G/21G (Becton Dickinson, # 367344/364815 or equivalent)
- 2 ml cryogenic vial, round bottom, self-standing (Corning, # 430659 or equivalent)
- 10 ml and 5 ml serological disposable pipettes (Corning, # 4487 or #4488 or equivalent)
- 15 ml polypropylene centrifuge tubes (Fisher, # 3208303 or equivalent)
- Freezer storage boxes for 2 ml cryogenic vials (Fisher, # 3468196 or equivalent)
- Centrifuge, capable of ~3000 g with a swing bucket rotor (e.g. Eppendorf, 5702; # 5702 000.019 or equivalent)
- Pipetting aid (e.g. Eppendorf, Easypet; #4421 000.013 or equivalent)
- Ultra-Low Temperature Freezer (e.g. Thermo Electron, Revco Ultima PLUS; ULT1786-10 or equivalent)

Health and safety

In accordance with the site's policies and guidelines, use personal protective equipment to prevent exposure to blood borne pathogens or other potentially infectious materials, and dispose of all clinical waste appropriately. Before starting to work under this protocol all staff should review the guidelines for working with blood borne pathogens and have been vaccinated.

Procedure

Blood Draw (in Clinic)

· Confirm subject's ID and write subject's name or subject ID and DOB on the sample sheet and EDTA tube.
· Prepare subject for blood draw.
· Obtain venous blood (~1 to 2 times10 ml) by any standard phlebotomy technique from a peripheral access point or from a central line by trained personnel into EDTA tubes.

For special instructions, see Streck tube product information.

· Gently invert tubes about 10 times immediately after collection.
· Record date and time of blood draw on samples sheet and Streck tube.
· Prepare sample for the transportation to the laboratory or processing side.

CRITICAL STEP

Time between blood collection and plasma/blood cell processing is recommended to be <4-5 h. Experiments have shown that extended storage at room temperature ≥ 5 h can affect the detection of cell-free circulating tumor DNA in plasma. Plasma Processing (in Laboratory)

· Upon arrival in the laboratory, centrifuge Streck tubes at room temperature for 10 min at 1600 (±150) g.

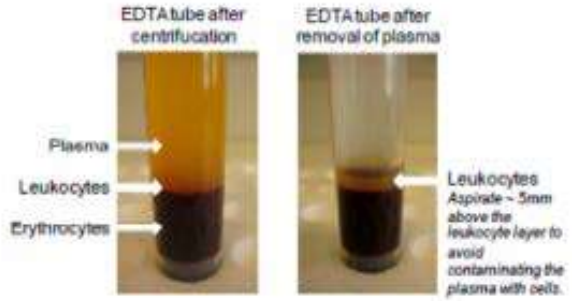
If centrifuge uses rpm (revolutions per minute), see centrifuge instructions for the conversion.

Ensure that brake switch is off in order to prevent disruption of the cell layer.

· Record plasma processing start time at start of first centrifugation.
· After centrifugation remove tubes from centrifuge.
· Transfer supernatant of the two Streck tubes to one fresh 15 ml centrifuge tube without disturbing the cellular layer using a disposable 10 ml serological pipette or disposable bulb pipette.

CRITICAL STEP

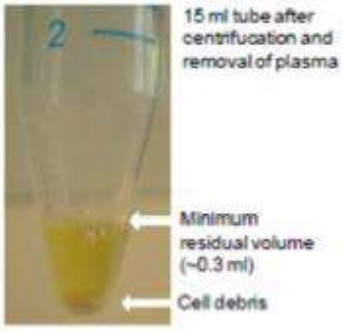
Centrifugation separates plasma from leukocytes and erythrocytes as shown in the figure below (left). Leaving sufficient residual plasma in the tubes after the centrifugation and not disturbing the leukocyte layer (see image) when pipetting is a critical step in the sample preparation process (right). Be careful not to disturb leukocyte layer in the tubes.



After transferring the plasma to a 15 ml centrifuge tube as described, discard Streck tube in biohazard trash.
· Centrifuge the plasma in the 15 ml centrifuge tube at room temperature for 10 min at 3000 (±150) g.

CRITICAL STEP
The 2nd centrifugation is intended to remove any residual intact blood cells carried over from the 1st centrifugation step. Tests have shown that speeds slower than 3000g do not completely remove blood cells from the supernatant. Centrifugation speeds higher than 3000 g are preferred.
· After centrifugation remove tubes from centrifuge.
· Transfer supernatant to a fresh 15 ml centrifuge tube without disturbing the cellular layer using a disposable 5 ml or 10 ml serological pipette or disposable bulb pipette.

CRITICAL STEP
Leave a residual volume of about 0.3 ml (~7 mm) on the bottom of the 15 ml tube to avoid contaminating the plasma with cells (see image).



After transferring the plasma to a new 15 ml centrifuge tube as described, gently mix plasma and record total plasma volume (~8-10 ml plasma per 20 ml blood).
· Transfer 1 ml plasma aliquots with a pipette to 2 ml pre-labeled cryogenic vials.

Confirm that the sample tube ID matches the subject's ID.

Suggested information on tube:
Plasma
Subject/patient ID or subject/patient name
DOB
Plasma collection date and time
Study or protocol code

Place plasma tubes into storage box and freeze plasma in freezer upright in storage box at -70°C or colder.
Short time storage at -20°C is possible.

Specimen Storage Instructions
· Once frozen, maintain samples continuously at -70°C or colder.
· When outside the freezer, such as when transferring to a different freezer in another location or preparing for shipment, boxes containing tubes should be covered with dry ice.
· Freezer or dry ice specimen storage container temperature must be checked and documented at least once each workday. Document any deviation from protocol.
· The freezer or dry ice storage box containing the specimens should either be locked or in a secure area accessible only to authorized site staff.
· A backup storage plan should be in place in the event of freezer failure.

APPENDIX D SOP For Tumor Biopsy Sample Collection

Contacts:
Zosia Piotrowska, MD – pager 16423 (PI)
Aaron Hata, MD, PhD - 615 838-3607 (Primary lab collaborator)
Mandeep Banwait- pager 29830 (Research Assistant)
Sam Bilton - 561 901-5369 (Primary contact in Hata Lab)

For each biopsy, cores should be processed in the following order and stored as outlined:

1. Pre-Treatment Biopsy (within 28 days of treatment start)

1) Snapfrozen
2) Fresh- cell line/PDX (media)
3) Fresh- cell line/PDX (media)
4) Snapfrozen
5) Formalin
6) MGH path
7) Any extras- snapfrozen

Cores 1-4 (and any extra snapfrozen specimens) to be sent to Hata lab at CNY via courier.
Core 5 to be stored in research path by Marina Kem/Mari Mino-Kenudson

Clinical testing- Snapshot, MET and EGFR FISH

2. On-Treatment (C1D15-21)

1) Snapfrozen
2) Snapfrozen
3) Formalin
4) Formalin
5) Any extra- snapfrozen

Cores 1-2 (and any extra snapfrozen specimens) to be sent to Hata lab at CNY via courier.
Cores 3-4 to be stored in research path by Marina Kem/Mari Mino-Kenudson

Note- no MGH path/clinical sample submitted form on-treatment biopsy

3. Post-Progression (at/after RECIST progression)

1) Snapfrozen
2) Fresh- cell line/PDX
3) Fresh- cell line/PDX
4) Snapfrozen

5) Formalin
6) MGH path
7) Any extras- snapfrozen

Cores 1-4 (and any extra snapfrozen specimens) to be sent to Hata lab at CNY via courier. Core 5 to be stored in research path by Marina Kem/Mari Mino-Kenudson

Clinical testing- Snapshot, MET and EGFR FISH on pre and post-treatment biopsies (none for on-treatment bx)